National Comprehensive HIV Prevention, Care, and Treatment Training for Pharmacy Professionals

Participant Manual

Ministry of Health, Ethiopia

May 2018

Foreword

In line with its decentralization principle, the Ethiopian Health Policy has achieved great progress in improving access to comprehensive HIV/AIDS services to the majority of the population. Both quality and coverage of services have improved significantly since the initiation of the free ART program in 2005. The role of health workforce in general and that of pharmacy professionals assumes a central position in these achievements.

To further enhance accessibility and quality of services, capacity building of health cadres is critical. Therefore, this comprehensive HIV prevention, care and treatment training material is prepared with the primarily intention to build the capacity of pharmacy professionals at all levels so that they can contribute to the provision of HIV services. The Federal Ministry of Health and stakeholders are committed to coordinating and supporting this endeavor achieve its goals.

Finally, I would like to acknowledge all governmental and non-governmental organizations and development partners as well as their respective experts who contributed to the realization of this training material. It is my belief that pharmacy professionals, managers and trainers will benefit from this document immensely

Dr. Kebede Worku (MD, MPH)
State Minister
Federal Ministry of Health (FMOH)

APPROVAL STATEMENT OF THE MINISTRY

The Federal Ministry of health of Ethiopia has been working towards standardization and institutionalization of In-Service Trainings (IST) at national level. As part of this initiative the ministry developed a national in-service training directive and implementation guide for the health sector. The directive requires all in-service training materials fulfill the standards set in the implementation Guide to ensure the quality of in-service training materials. Accordingly, the ministry reviews and approves existing training materials based on the IST standardization checklist annexed on the IST implementation guide.

As part of the national IST quality control process, this national Comprehensive HIV Prevention, Care, and Treatment Training for Pharmacy Professionals has been reviewed based on the standardization checklist and approved by the ministry in August, 2018.

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Acknowledgement

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The Ministry extends its appreciation for the following individuals (alphabetically listed) and their organizations who were actively involved in the revision of this training manual.

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Acronyms and Abbreviations

3TC	Lamivudine
ABC	Abacavir
ADE	Adverse Drug Event
AIDS	Acquired Immune Deficiency Syndrome
ARV	Antiretroviral
ART	Antiretroviral Therapy
AZT/ZDV	Zidovudine
CBC	Complete Blood Count
CD4 cells	Cluster of Differentiation 4, type of T-lymphocyte, white blood cells
CMV	Cytomegalovirus
CPD	Continuous Professional Development
CPT	Cotrimoxazole Preventive Therapy
DHS	Demographic and Health Survey
DNA	Deoxyribonucleic acid
DTG	Dolutegravir
EFV	Efavirenz, also abbreviated as EFZ
FBOs	Faith-based organizations
FDC	Fixed dose combination
FHAPCO	Federal HIV/AIDS Prevention and Control Office
FMOH	Federal Ministry of Health
GFR	Glomerular Filtration Rate
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HSV	Herpes simplex virus
IP	Infection Prevention
IPT	INH Preventive Therapy
IRIS or IRS	Immune Reconstitution Inflammatory Syndrome also called Immune Reconstitution Syndrome (IRS)
IST	Institutional and Standardization Team
I-TECH	International Training and Education Center on HIV/AIDS
LFT	Liver Function Test
LPV	Lopinavir
MTCT	Mother-To-Child Transmission (of HIV)
NAC	National AIDS Council
NGO	Non-governmental Organization
NNRTI	Non-nucleoside reverse transcriptase inhibitor

NRTI	Nucleoside Analogue Reverse Transcriptase Inhibitor
NVP	Nevirapine
OIs	Opportunistic Infections
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PI	Protease Inhibitor
PLHIV	People living with HIV
PMTCT	Prevention of mother-to-child transmission (of HIV)
RNA	Ribonucleic acid
RTV, r	Ritonavir
PI/r	Ritonavir boosted Protease Inhibitor
RT	Reverse transcriptase
STI	Sexually Transmitted Illnesses
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
TLC	Total Lymphocyte Count
UNAIDS	The Joint United Nations Program on HIV/AIDS
VCT	Voluntary Counseling & Testing
WHO	World Health Organization

Table of Content

Introduction to the training manual

Ethiopia started its free Antiretroviral Treatment (ART) program in early 2005 and since then many lives have been saved due to the concerted efforts of the government and its partners. The country has seen large HIV/AIDS service scale up programs that resulted in making the service more accessible to the community. As a result, the number of sites that provide ART services has reached more than 1230 in 2017. At the end of 2017, 415,578 adults and 21,385 children under the age of 15 were on ART, which shows the country needs to do more to reach the remaining target. It is estimated that the national HIV prevalence in 2017 is 1.16%.

In conjunction with its scale up programs, the government has also been engaged in large scale capacity building activities to enhance the knowledge and skills of healthcare professionals to properly provide the HIV prevention, care and treatment in a sustainable manner. Many off-site and on-site in-service trainings, pre-service trainings, mentoring, and supportive supervision activities were carried out towards that end. To sustain these efforts, institutionalizing of training activities at public universities is also underway. This move is believed to create ownership of programs and has huge cost containment benefits.

The role of the pharmacy professional in the multidisciplinary ART team is very crucial. Besides managing the supply of antiretroviral drugs, OI medicines and related medical supplies, pharmacists are engaged in promoting the rational use of these medicines by providing pharmaceutical care. Promoting the rational use of medicines involves critical activities such as adherence preparation and promotion, medicines use counselling, side effect identification and management, managing drug interactions, and similar interventions that improve the patients' treatment success.

To carry out these activities appropriately, pharmacy professional must be knowledgeable about current treatment practices and emerging needs in managing the proper care and treatment of HIV patients. It is to be noted that without properly planned and coordinated trainings, the pharmacy professional cannot provide the level of professional support expected from them and it would eventually affect the quality of care and outcomes of treatment for HIV patients. Hence, there is a need to keep these professionals abreast with developments in the practice.

In line with the WHO and national HIV prevention, care and treatment consolidated guidelines revision, this syllabus and training materials for pharmacy professionals were revised in 2017. The syllabus is designed to enhance pharmacy professionals' knowledge, skills and attitude in critical area of competencies so that they can meaningfully contribute to HIV treatment and care. The training materials contain Participant's Manual, Trainers' Guide and PowerPoint presentation. The curriculum considers participants as the focus of the learning process and activities in the sessions are designed to be more trainee-focused using a modular approach. Moreover, to give the trainees better practical exposure, expert patient trainers (EPT) and hospital visits are included.

This course needs training of trainers (TOT) and basic trainings in all regions of the country. The training will be given in selected training centers with proper infrastructure and facility. Furthermore, the centers should have appropriate attachment facilities. The course has the following outline to be given for seven (7) days.

Outline

Session 1. Overview of HIV/AIDS Situation in Ethiopia
Session 2. Pathogenesis of HIV Disease and Natural History of HIV Infection
Session 3. Staging of HIV/AIDS Disease and Initiating Therapy
Session 4.1 Basic Pharmacology of Antiretroviral Drugs (ARVs)
Session 4.2 Monitoring and Management of ARV Drug Toxicities
Session 4.3 Significant Drug Interactions with Antiretroviral Drugs
Session 4.4 HIV Resistance to Antiretroviral Drugs
Session 5. Monitoring and Changing Antiretroviral Therapy
Session 6.1 Management of HIV in Women, and PMTCT
Session 6.2 Management of HIV in Children
Session 7.1 Prophylaxis and Treatment of Opportunistic Infections
Session 7.2 Sexually Transmitted Infections
Session 8.1 Adherence Support to ART
Session 8.2 Communication skills for Pharmacy professionals
Session 9. Standard Precautions and Post Exposure Prophylaxis (PEP)
Session 10. HIV and Nutrition

Session 11. Palliative Care in HIV/AIDS

Session 12. Overview of Supply Management of ARVs and related medicines

Session 13. SOPs for managing information on ARV Drugs Dispensing & Patient Medication Records

Session 14. Skill Station with Expert Patient Trainers (EPT)

Session 15. Hospital Visit

Core Competencies

The core competencies that the trainees are expected to attain after going through this course are:

1. Prepare and promote patient adherence on treatment
2. Dispense ARVs, OI drugs and related medicines properly
3. Monitor treatment outcomes
4. Manage ADEs and drug interactions
5. Provide drug information to the staff and patients.
6. Manage the supply chain of ARVs, OI drugs, and related medicines and supplies
7. Assist in nutritional support and palliative care activities
8. Manage information on ARV drug dispensing and patient medication records
9. Practice standard precautions and infection prevention activities

Course Syllabus

Course description

The *National Comprehensive HIV Prevention, Care, and Treatment Training course for Pharmacy Professionals* is designed to enhance the role of pharmacy professionals on the management of HIV/AIDS and related OIs. It is designed to enable pharmacy professionals' play their specific roles on ART in a more effective way. The course contains the global and national context of the disease, pathogenesis of HIV infection, staging of disease, initiation of therapy, clinical pharmacology of ARVs, adherence to treatment, management of HV/AIDS in women and children, management of comorbidities, and care to HIV/AIDS patients. The course is competency based and employs adult learning methodologies.

Course Goal

This training material is prepared with the intention of delivering basic knowledge, skills and attitude required by pharmacy professionals to provide comprehensive HIV prevention, care, and treatment services at all level of the health care system. Especially, the course prepares the professional to provide individualized pharmaceutical care to promote the rational use of ARVs and related medicines.

Course objectives

After completion of this course, the trainees will be able to:

- Describe the epidemiology of HIV/AIDS and the national response for prevention and control of HIV/AIDS.
- Describe the pathogenesis and natural history to HIV/AIDS.
- Discuss the WHO clinical staging of HIV/AIDS
- Grade the severity of ARV toxicities
- Manage of common side effects
- Manage common ARV drug interactions
- Take part in prevention of HIV resistance to ARV drugs
- Monitor treatment outcome of ARV drugs

- Describe special considerations in the management of HIV/AIDS in women, exposed infants, and HIV infected children.
- Describe the prophylaxis and treatment of common opportunistic infections
- Promote patient adherence on ART
- Apply communication skills for interacting with patients and health care providers.
- Counsel patients on the rational use of ARVs and OI medicines
- Make use of standard precautions and post exposure prophylaxis
- Discuss the nutrition care and support needed for HIV positive individuals.
- Apply the principles of palliative care in the management of HIV
- Improve the supply chain of ARVs, OI drugs, and related medicines and supplies
- Manage information on ARV drug dispensing and patient medication records

Training Methods

This course adopts participatory and interactive training approaches and is designed to maximize the involvement of all participants in the learning process. The course employs the following methodologies:

- Interactive presentation
- Individual reading and reflection
- Brainstorming
- Group discussions
- Think-pair-share
- Individual and group exercises
- Role-plays
- Expert Patient Training (EPT)
- Site visit
- Case studies

Learning Materials

This course requires the following materials:

- National Comprehensive HIV Prevention, Care, and Treatment Training for Pharmacy Professionals
  - Participant's manual
  - Facilitator's guide
  - PowerPoint presentation
  - SOP exercise package
  - Pre-and posttest
  - OI banner (1mx3m)
- Other materials, supplies and equipment required (see below in the 'Course Facilitator Preparation for this training' section).

Participant selection criteria

The target groups for this course are pharmacists, druggists and pharmacy technicians who will be involved in the care of HIV infected adults, adolescents, women and children and their families at all levels of the healthcare delivery system. Additionally, pharmacy and pharmaceutical supply chain professionals working at FMOH, RHBs/ZHD/WoHO, PFSA, universities, private drug retail outlets, etc. are target audiences of this training.

Trainer selection criteria

Trainer of this course shall fulfill the following criteria:

- Trainers who have a basic a TOT certificate on National Comprehensive HIV Prevention, Care, and Treatment Training for Pharmacy professionals. OR
- Trainers who have a TOT certificate on National Comprehensive HIV Prevention, Care, and Treatment Training for Healthcare Providers.

Methods of Evaluation:

Course Evaluation:

The course will be evaluated by:

- Daily feedback filled by the participants
- End of course evaluation filled by the participants
- Oral feedback by the participants

Participant Evaluation:

Participants of this course will be evaluated by:

- Pretest and post test
- Mid-course evaluation using expert patients
- ADR and drug interaction home take assignments

Certification Criteria

Certification for this course will be based on the following criteria.

- Full attendance of the course
- Knowledge assessment using post-test (50%)
- Mid-course evaluation using expert patients (30%)

- ADR and drug interaction home take assignments (20%)

Overall/aggregate score of 70% and above

Duration of the training

- Total duration for the course is 7 days.

Suggested class size and number of trainers

- Suggested training class size shall not be more than 25 participants per classroom
- 4 trainers shall be assigned per one training event.
- 12 Expert Patient Trainers (EPT) shall be assigned per training event (1 EPT for 2 trainees).

Training Venue

The training will be conducted at selected national and regional IST centers/CPD providers having appropriate facilities, trainers, and attachment health facilities.

Schedule for National Comprehensive HIV Prevention, Care, and Treatment Training for Pharmacy Professionals

Day	Time	Topic/session	Responsible
Day One	8:30-9:00AM	Registration	
	9:00-9:10AM	Welcoming Speech	
	9:10-9:55AM	Introduction to course	
	9:55-10:15AM	Pretest	
	10:15-10:30AM	Tea Break	
	10:30-11:30AM	Session 1. Overview of HIV/AIDS Situation in Ethiopia	
	11:30-12:30PM	Session 2. Pathogenesis of HIV Disease and Natural History of HIV Infection	
	12:30-2:00PM	Lunch break	
	2:00-2:30PM	Session 2. Pathogenesis of HIV Disease and Natural History of HIV Infection	
	2:30-3:30PM	Session 3. Staging of HIV/AIDS Disease and Initiating Therapy	
	3:30-3:45PM	Tea Break	
	3:45-5:00PM	Session 3. Staging of HIV/AIDS Disease & Initiating Therapy	
	5:15-5:30PM	Daily feedback	
End of Day One			
Day Two	8:30-8:45AM	Recap	
	8:45-10:30AM	Session 4.1 Pharmacology of Antiretroviral Drugs (ARVs)	

	10:30-10:45AM	Tea Break	
	10:45-12:00PM	Session 4.1 Pharmacology of Antiretroviral Drugs (ARVs)	
	12:00-12:30PM	Session 4.2 Monitoring and Management of ARV Drug Toxicities (ADR/SEs)	
	12:30-2:00PM	Lunch break	
	2:00-3:30PM	Session 4.2 Monitoring and Management of ARV Drug Toxicities (ADR/SEs)	`
	3:30-3:45PM	Tea Break	
	3:45-4:30PM	Session 4.2 Monitoring and Management of ARV Drug Toxicities (ADR/SEs)	
	4:30-5:15PM	Session 4.3 Significant Drug Interactions with Antiretroviral Drugs	
	5:15-5:30PM	Daily feedback	
End of Day Two			
Day Three	8:30-8:45AM	Recap of Day Two	
	8:45-10:15AM	Session 4.3 Significant Drug Interactions with Antiretroviral Drugs	
	10:15-10:30AM	Tea Break	
	10:30-12:00PM	Session 4.4 HIV Resistance to Antiretroviral Drugs	
	12:00-12:30PM	Session 5. Monitoring and Changing Antiretroviral Therapy	
	12:30-2:00PM	Lunch break	
	2:00-3:30PM	Session 5. Monitoring and Changing Antiretroviral Therapy	
	3:30-3:45PM	Tea Break	
	3:45-5:15PM	Session 6. Management of HIV in Women and Children	
	5:15-5:30PM	Daily feedback	
End of Day Three			
Day Four	8:30-8:45PM	Recap of Day Three	
	8:45-10:15PM	Session 6. Management of HIV in Women and Children	
	10:15-10:30AM	Tea Break	
	10:30-12:30PM	Session 7.1 Prophylaxis and Treatment of Opportunistic Infections	
	12:30-2:00PM	Lunch break	
	2:00-2:45PM	Session 7.1 Prophylaxis and Treatment of Opportunistic Infections	
	2:30-3:30PM	Session 7.2 Sexually Transmitted Infections	
	3:30-3:45PM	Tea Break	
	3:45-4:15PM	Session 7.2 Sexually Transmitted Infections	
	4:15-5:15PM	Session 9. Standard Precautions and Post Exposure Prophylaxis (PEP)	
	5:15-5:30PM	Daily feedback	
End of Day Four			
Day Five	8:30-8:45AM	Recap of Day Four	
	8:45-9:15AM	Session 9. Standard Precautions and Post Exposure Prophylaxis	

		(PEP)	
	9:15-10:30AM	Session 10. HIV and Nutrition	
	10:30-10:45AM	Tea Break	
	10:45-11:45AM	Session 11. Palliative Care in HIV/AIDS	
	11:45-12:30PM	Session 8.1 Adherence Support to ART	
	12:30-2:00PM	Lunch break	
	2:00-3:00PM	Session 8.1 Adherence Support to ART	
	3:00-3:30PM	Session 8.2 Communication skills for Pharmacy professionals	
	3:30-3:45PM	Tea Break	
	3:45-4:45PM	Session 8.2 Communication skills for Pharmacy professionals	
	4:45-5:15PM	Session 12. Overview of Supply Management of ARVs and Related medicines	
	5:15-5:30PM	Daily feedback	
End of Day Five			
Day Six	8:30-8:45AM	Recap of Day Five	
	8:45-9:30AM	Session 12. Overview of Supply Management of ARVs and Related medicines	
	9:30-10:30AM	Session 13. SOPs for Managing Information on ARV Drugs Dispensing and Patient Medication Records	
	10:30-10:45AM	Tea Break	
	10:45-12:30AM	Session 13. SOPs for Managing Information on ARV Drugs Dispensing and Patient Medication Records	
	12:30-2:00PM	Lunch break	
	2:00-3:00PM	Session 13. SOPs for Managing Information on ARV Drugs Dispensing and Patient Medication Records	
	3:00-3:30PM	Skill Station with Expert Patient Trainers (EPT)	
	3:30-3:45PM	Tea Break	
	3:45-5:15PM	Skill Station with Expert Patient Trainers (EPT)	
	5:15-5:30PM	Daily feedback	
End of Day Six			
Day Seven	8:00-8:30AM	Arrive at assigned hospital	
	8:30-10:30AM	Health facility practical attachment	
	10:30-10:45AM	Tea Break	
	10:45-12:30PM	Health facility practical attachment	
	12:30-2:00PM	Lunch break	
	2:00-2:30PM	Post test	
	2:30-3:00PM	Certification and closing Speech	
	3:15-3:30PM	Tea Break	
End of Program			

Session 1: Overview of HIV/AIDS in Ethiopia

Session Description

This session provides an overview of HIV/AIDS epidemic in Ethiopia. It starts by explaining the epidemiology of the disease. The economic, health, and psycho-social impacts of HIV/AIDS are discussed. The session continues by describing the national response for HIV/AIDS.

Primary Objective:

The primary objective of this session is to describe the epidemiology of HIV/AIDS and the national response for prevention and control of HIV/AIDS.

Enabling Objectives

By the end of this session, participants will be able to:

- Describe the epidemiology of HIV/AIDS
- Discuss impact of HIV /AIDS in Ethiopia
- Discuss the national response to HIV/AIDS
- Describe the national strategic plan for HIV/AIDS
- Explain the 90-90-90 targets set

Session outline

- Epidemiology of HIV/AIDS
- Impact of HIV /AIDS in Ethiopia
- The national response to HIV/AIDS epidemic
  - National AIDS Policy
  - National ART program
  - National strategic plan and targets for HIV/AIDS
- Session Summary

1.1 Epidemiology of HIV/AIDS

Brainstorming

Describe the prevalence and mortality of HIV/AIDS?

Global Epidemiology

At the end of 2015, 36.7 million people were living with HIV. In the same year, 2.1 million people became newly infected with HIV and 1.1 million people died from HIV-related causes globally. New HIV infections have fallen by 35% since 2000 and AIDS-related deaths have fallen by 42% since the peak in 2004. The world has exceeded the AIDS targets of Millennium Development Goal (MDG) 6, halting and reversing the spread of HIV, and increasingly countries are getting on the Fast-Track to end the AIDS epidemic by 2030 as part of the Sustainable Development Goals (SDGs).

Sub-Saharan Epidemiology

Sub-Saharan Africa is the most affected region, with 25.6 million people living with HIV and accounts for two-thirds ($2/3^{rd}$) of the global total of new HIV infections. Nearly 1 in every 20 adults living with HIV and accounting for nearly 70% of the people living with HIV worldwide.

National Epidemiology

Currently the data source for HIV prevalence estimations in Ethiopia are Antenatal Care (ANC) sentinel surveillances and national demographic and health surveys (DHS). From these data sources, estimated prevalence and other indicators of HIV/AIDS of the country are synthesized.

According to the Ethiopian Public Health Institute (EPHI) HIV Related Estimates and Projections for Ethiopia for 2018, the national HIV prevalence is 0.96%. According to the same estimate for 2018, there are a total of 610,335 people living with HIV, of which 62 % are females. Besides, there are an estimated 13,488 people newly infected, of whom 61.5% are females. Annual estimated AIDS related death for 2018 is 13,556.

Variations in HIV prevalence were also observed among regions. According to the 2018 EPHI estimates, Gambella has the highest prevalence (4.06%) followed by Addis Ababa and Dire Dawa with prevalence of 3.58% and 3.03%, respectively, while it is lowest in SNNPR and Ethiopia Somali regional states with HIV prevalence of 0.42% and 0.16%, respectively (Figure

1). However, due to their large population size, Amhara and Oromia regions have the largest People Living with HIV (PLHIV). Although these regions have a lower HIV prevalence, they still bear a significant proportion of the epidemic burden. Overall, the HIV epidemic in Ethiopia can be explained as both generalized and heterogeneous.

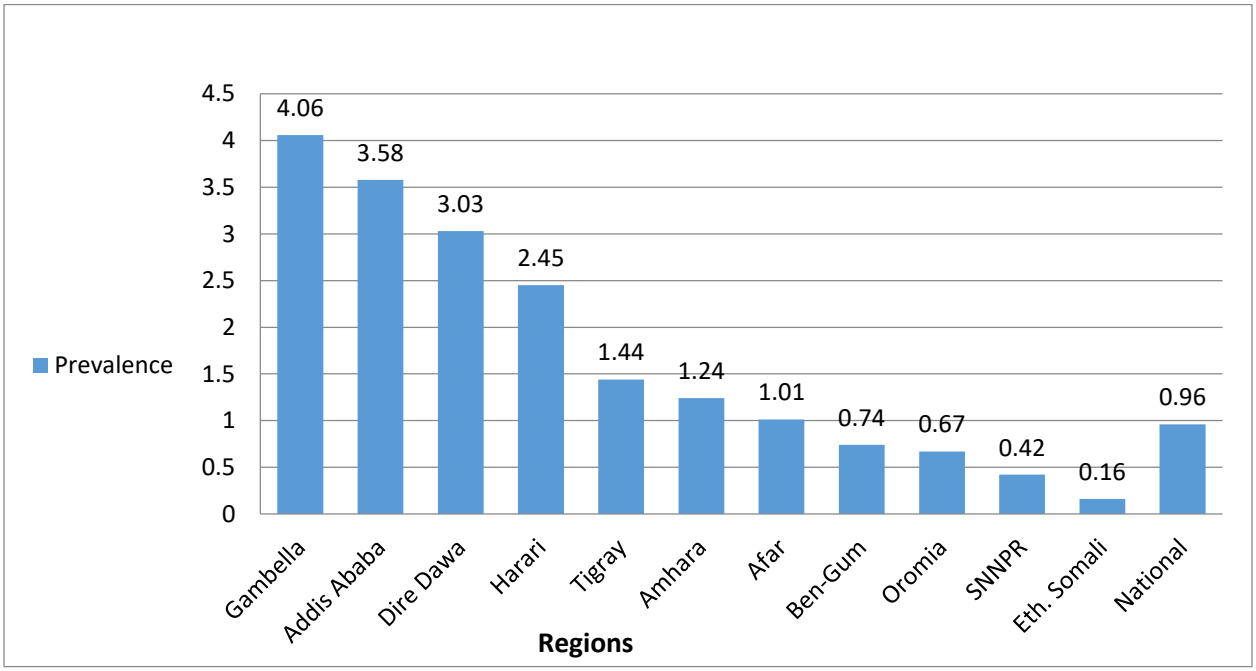


Figure 1: HIV Prevalence by Region in 2018

Previously, Ethiopia was one of the countries with the highest number of new HIV infections in the continent. But recent reports show a remarkable decline in the number of new infections (Figure 2).

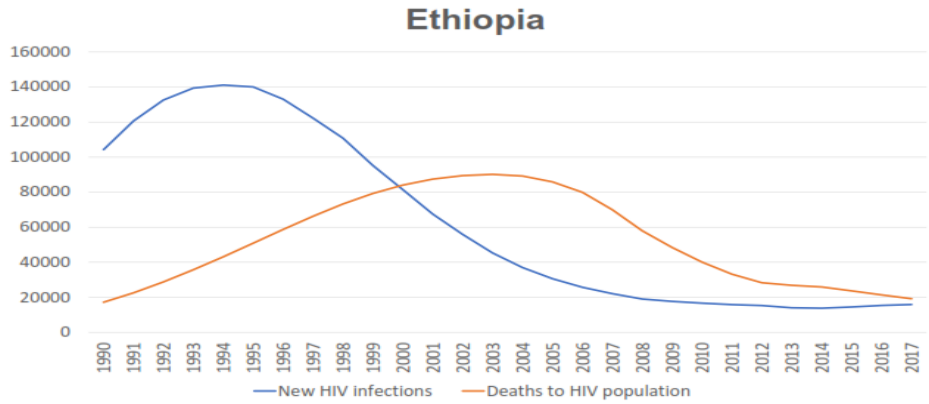


Figure 2: Trends of HIV incidence and mortality in Ethiopia, 1990-2017

Ethiopia has achieved exemplary successes in terms of HIV service expansion and uptake, which impacted to a 95% decline of new HIV infection from 1994 to 2012 and 73 % reduction of AIDS deaths compared to the periods 2006 to 2016 respectively (Figure 3).

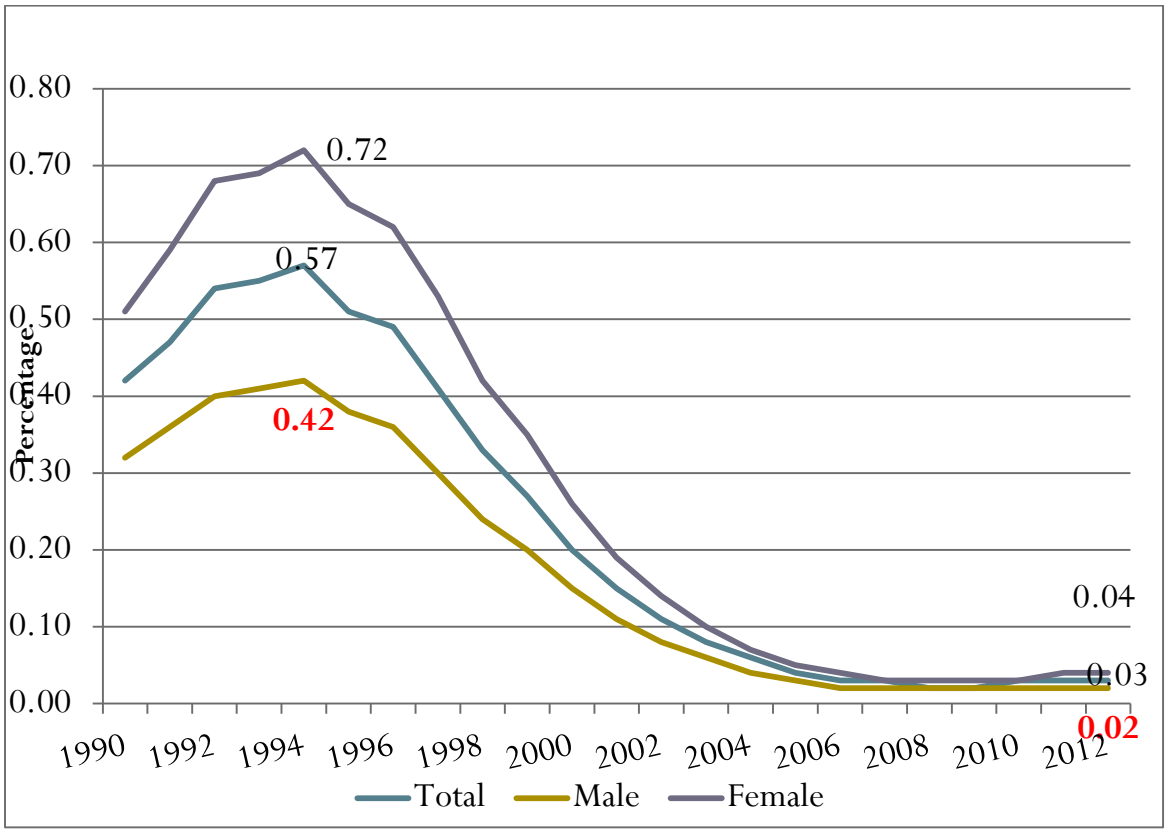


Figure 3: HIV incidence rate, 1990-2012, FMOH, Ethiopia

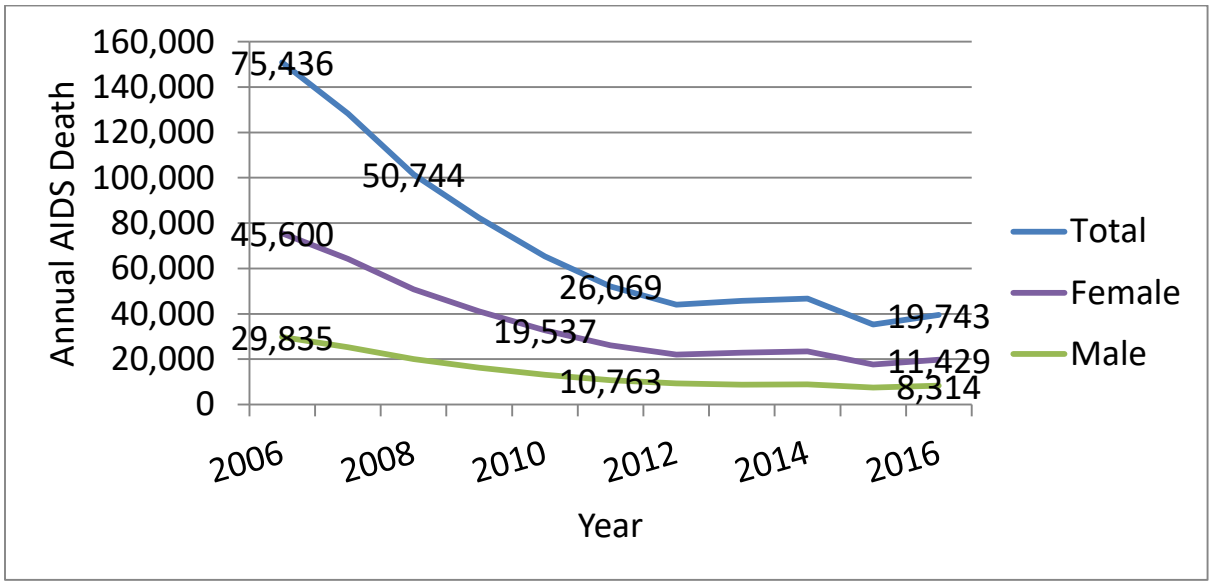


Figure 4:Trend of AIDS related deaths per year, 2006-2016

1.2 Impact of HIV/AIDS in Ethiopia

From your experience, what are the impacts of HIV/AIDS in Ethiopia?

HIV/AIDS has a negative economic, psycho-social and health related impact at national, household, and individual level.

1. Economic impact

- Expenses for medical treatment
- Resource shift for HIV/AIDS program which could have been used for other development programs.

2. Health Related

- Suffering from OIs and other diseases
- Decrease life expectancy at birth

3. Psycho-Social

- Increased number of orphans
- Stigma and discrimination

1.3 National Response to HIV/AIDS Epidemic

1.3.1 National AIDS Policy

Individual reading

Read the National HIV/AIDS policy of Ethiopia

Soon after the report of the first two confirmed cases of HIV in 1984, Ethiopia responded to the HIV epidemic promptly by establishing a taskforce in 1985. Two years later, in 1987, the national taskforce was upgraded to a department level under FMOH. The department had the responsibility of coordinating the national prevention and control program. Subsequently, short- and medium-term plans were prepared and implemented in collaboration with national and international partners. However, the National AIDS Policy was issued only a decade later (1998).

Further, in 1999, the Strategic Framework for the National Response against HIV was prepared. Both documents served as the basis for the expanded and multi-sectoral response against HIV.

Despite the prompt initial response, the national progress was evaluated to be slow and interrupted. As a result, further restructuring in the response mechanism was required. In April 2000, the National AIDS Council (NAC) was established with secretariat offices from federal down to kebele levels. This further evolved into an office, the HIV/AIDS Prevention, and Control Office (HAPCO), in 2002. The 1998 Ethiopian HIV Policy and the Strategic Plan on Multi-sectorial response have guiding principles including: multi-sectoralism, shared sense of urgency, ownership and active involvement of the community, leadership commitment, partnership, gender sensitivity, public health approach, promotion and protection of human rights, greater involvement of PLHIV, and best use of resources, equitable and universal access, sustainability, and coordination.

1.3.2 National ART Program

Ethiopia introduced ART in 2003 in selected health facilities following the issuance of the national antiretroviral (ARVs) drugs supply and use policy in 2002. The first adult treatment guideline was issued in 2003, and revised in 2005, 2007, 2014 and 2017. A pediatrics treatment guideline was also developed in 2007 and after that it was consolidated with the adult guidelines. Free ARV service was launched in 2005 in public hospitals and in 2006 in health centers. At the end of 2017, 415,578 adults and 21,385 children under the age of 15 were on ART, which shows the country needs to do more to reach the remaining target.

1.3.3 National Strategic Plan for Prevention and Control of HIV/AIDS

Pair Reading Activity

Read paragraph 1 in pairs and discuss in five minutes

Ethiopia has now developed HIV/AIDS prevention care and treatment strategic plan in an investment case approach which is being implemented from 2015-2020. This strategic plan aims to pave the path for ending AIDS by 2030 through averting 70,000- 80,000 new HIV infections and saving about half a million lives till 2020. The targets set in this plan are in line with the

three 90's (90-90-90) targets set by UNAIDS to help end the AIDS epidemic. The 90-90-90 targets to be reached by 2020 are:

- 90% of all people living with HIV will know their HIV status.
- 90% of all people with diagnosed HIV infection will receive sustained ARV therapy.
- 90% of all people receiving antiretroviral therapy will have viral suppression

Strategic objectives:

The 2015-2020 strategic plan has **four strategic objectives** to achieve the goals and targets.

1. **Strategic Objective-I:** Implement high impact and targeted prevention program
    1. This strategic objective has 4 priority programs: Behavior change communication, condom distribution and use, prevention and control of sexually transmitted infections and blood safety.
2. **Strategic Objective-II:** Intensify targeted HIV testing and counseling services
    2. This strategic objective focuses to raise the proportion of PLHIV who know their HIV status to 90% by 2020 through intensifying targeted HIV testing and counselling. This is being implemented through provider initiated testing and counseling (PITC) and voluntary counseling and testing (VCT).
3. **Strategic Objective-III:** Attain virtual elimination of mother to child transmission (MTCT)
    3. This objective aims at providing ART for 95% of HIV positive pregnant women, ARV prophylaxis for 95% of HIV exposed children & reduce the vertical transmission to 1% by 2020.
4. **Strategic Objective-IV:** Optimize and sustain quality care and treatment
    4. This strategic objective aims to put and retain 90% of all people diagnosed with HIV on ART and achieve 95% viral suppression (< 1000 copies/ml) in care by 2020.

Critical enablers

There are four critical enablers identified as necessary for optimum implementation of the prioritized interventions and achieving the expected results.

1. **Critical enabler 1:** Health Management Information System/Monitoring and Evaluation, Pharmaceuticals, and Health Products Management system (PHPM) & Laboratory services.
2. **Critical enabler 2:** Enhance Partnership, Coordination, and Leadership
3. **Critical enabler 3:** Increase domestic resources for HIV response
4. **Critical enabler 4:** Gender equality and equity: Address gender related barriers to HIV and sexual and reproductive health (SRH) needs of girls and boys, and women and men.

Appointment Spacing Model (ASM)

To achieve the three 90 targets, Ethiopia is implementing the new treatment recommendations of WHO (test and treat). In line with this, the country adopted Appointment Spacing Model (ASM) of differentiated HIV service delivery to accommodate the growing number of stable individuals on ART and improve retention in care and health outcomes. In this model, stable clients will be appointed every six months for clinical visit and medication refill.

Stable individuals are those who have received ART for at least one year, have no adverse drug reactions that require regular monitoring, have good understanding of lifelong adherence, and evidence of treatment success (i.e. two consecutive viral load measurements below 1000 copies/ml) with no current illnesses excluding adults on third and second line treatment, children, adolescents, pregnant and lactating women.

In this model, the benefits of multiple month dispensing are to:

- Improve adherence by reducing the frequency of visits to health facilities
- Enable health facilities to manage higher number of patients expected from test and start
- Reduce patient travel time and costs to visit health facilities

1.4 Session Summary

- Even though new HIV infection has decreased globally, there are significant number of PLHIV. The Sub-Saharan Africa region is the most severely affected part of the world.
- In Ethiopia, the prevalence of HIV is 1.16%.
- HIV/AIDS has economic, health related, and psycho-social impacts.
- Ethiopia has achieved exemplary success in terms of HIV service expansion and uptake.
- Ethiopia is striving to achieve the 90-90-90 global target through its 5-year strategic plan

Session 2: Pathogenesis and Natural History of HIV Infection

Session Description:

This session describes the pathogenesis and natural history of HIV infection. The session starts by describing the characteristics and mode of transmission of HIV. Then, the mechanism of HIV replication and the virus' attack on the body is dealt with. Also, life cycle of HIV, natural history and progression of HIV infection will also be addressed.

Primary Objective:

The primary objective of this session is to describe the pathogenesis, natural history, and the body`s immunologic response to HIV/AIDS.

Enabling objectives:

Upon completion of this session, participants will be able to:

- Describe the characteristics and mode of transmission of HIV
- Discuss the mechanism of HIV attack on the body's immune system and its replication
- Explain the natural history of HIV and its clinical implications

Session Outline

- Characteristics and mode of transmission of HIV
- Pathogenesis and mechanism of HIV replication
- Natural history of HIV infection and its clinical implications
- Session Summary

2.1 Characteristics and mode of transmission of HIV

HIV stands for human immune deficiency virus that belongs to special family of virus called retrovirus thus uses RNA as a genetic material. Viruses are simple in structure and cannot replicate by itself and thus require the components of other cells for replication (require host cells to replicate) (figure 5). HIV, like all virus, must therefore enter into other cells if they are to replicate and survive (obligate microorganisms). HIV infections leads to AIDS over time. HIV primarily affects the CD4 cells and impair body's immune activity leading to development of opportunistic infections. HIV infection does not have cure.

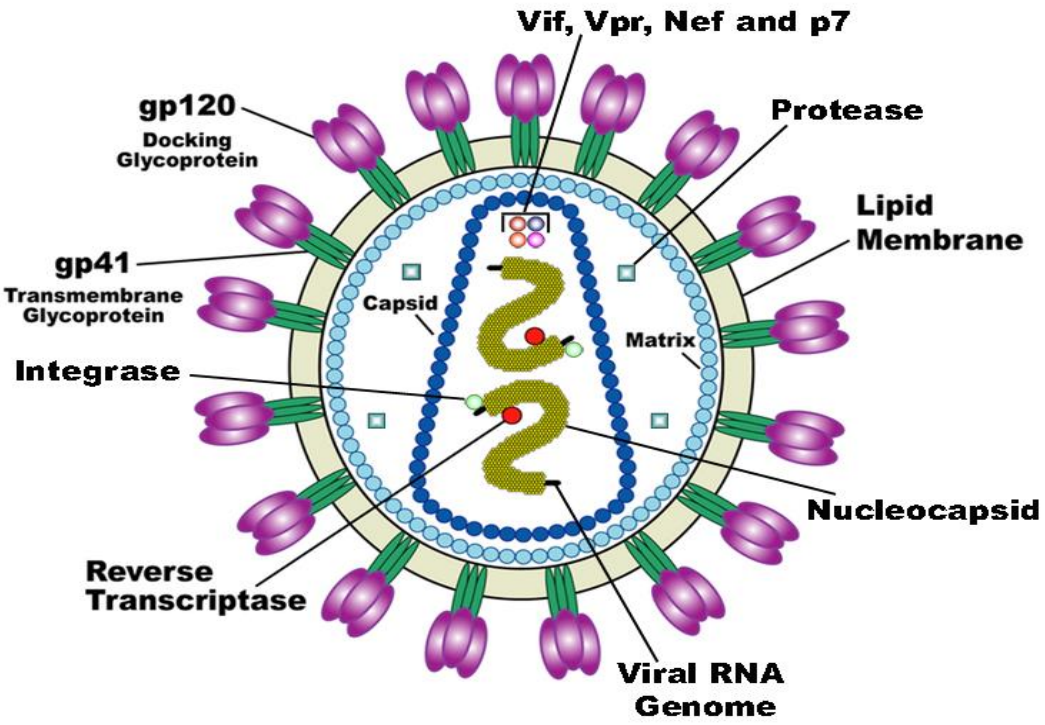


Figure 5: HIV cell structure

Brainstorming

What are the modes of HIV transmission?

HIV can be transmitted from one person to another through:

- Sexual contact (vaginal, anal and oral intercourse), vaginal secretions, semen
- Blood and body fluids
- Mother to child (during pregnancy, birth and breastfeeding)
- Percutaneous exposure

HIV is **NOT** transmitted by:

- Other body fluids like tears, saliva, sweat and urine.
- Personal contacts: kisses on the mouth, hugging, handshakes.
- Social contacts: during the work, in school, cinema, restaurant, and sauna.
- Air or water: sneezing, coughing, swimming pool, swimming in the sea.
- Contact with common items: pens, toilets, towels, sheets, soap.
- Insects: mosquito bites or other insects.

2.2 Pathogenesis and mechanism of HIV replication

Paired Reading Activity

Read the pathogenesis of HIV in pairs for 10 minutes

Q: How does HIV cause damage to human body?

Pathogenesis

HIV affects the human immune system extensively and in a complex manner, resulting in both depletion and dysfunction of all elements of the immune system. The white blood cells play an important role to defend the body against infection. The CD4 cell is a special type of lymphocyte (type of white blood cell) with a marker on its surface called CD4.

Viruses need a receptor on the cell surface in order to attach themselves and get access to go inside the cell. For a cell to be infected by HIV, there has to be a CD4 receptor molecules. These receptors are shown on T-cells and other cells in the monocot-macrophage cell lines. Besides, fusion co-receptor called CXCR4 or CCR5 are needed for virus entry. Thus, HIV infects these cells and uses them for its multiplications. In the process the infected cells are killed and consequently the body becomes defenseless.

Indirect and direct mechanisms of injury can describe the pathogenesis HIV infection. The indirect injury is associated immune suppression leading to opportunistic infections. HIV affects all elements of immune system. CD4 depletion occurs due to elimination of HIV-infected cells by virus-specific immune responses, loss of plasma membrane integrity because of viral budding and interference with cellular RNA processing. CD4 depletion also occurs indirectly through syncytium formation, apoptosis and autoimmunity. CD4 cells may undergo apoptosis (programmed cell death) in the presence of HIV infection.

Not only does the virus destroys and disrupts the immune system, the virus can also manipulate the immune system to its own replicative advantage. This is achieved by immune activation. Clinically, this is demonstrated by the observation that viral load transiently increases in the presence of inter-current illnesses, such as TB.

Decline in immune status parallels the decline in CD4 number and function which limits the immunity to respond to intracellular infections and malignancy resulting in occurrence of mycobacteria, Salmonella, Legionella, leishmania, Toxoplasma, Cryptosporidium,

Microsporidium, Pneumopsystic carnimonia plasmoxis (PCP), Histoplamosis, Herpes Simplex Virus (HSV), Varisola Zoster Virus (VZV), John Cunningham (JC) virus, pox viruses and Epstein-Barr Virus (EBV)-related lymphomas.

In addition to its effect on CD4 cells, HIV also causes a direct injury to different parts of the body by attacking different target cells. In the nervous system, it causes encephalopathy and peripheral neuropathy; to the kidney it causes HIV-associated nephropathy; to the heart it causes HIV cardiomyopathy; to the endocrine it causes hypogonadism in both sexes and to the GI tract it causes dysmotility and malabsorption. In addition, numerous organ systems are infected by HIV:

- Brain: macrophages and glial cells
- Lymph nodes and thymus: lymphocytes and dendritic cells
- Blood, semen, vaginal fluids: macrophages
- Bone marrow: lymphocytes
- Skin: Langerhans cells
- Colon, duodenum, rectum: chromaffin cells
- Lung: alveolar macrophages

The extent of immune damage inflicted by HIV is assessed by the CD4 count and tells us how strong the immune system is. A CD4 count between 450-1500 cells/mm3 indicates the immune system is coping well and managing to remain high despite HIV. However, over time, the CD4 cells are progressively destroyed and the CD4 count falls. A low CD4 count tells us the immune system is weak. The viral load indicates the activity of HIV infection and hence Viral Load is an important blood test to tell us how much HIV is in the blood. Over time the Viral Load increases as more and more viruses are produced resulting in rapid progression to AIDS.

HIV life cycle

HIV needs gp-120 and gp-41 (glycoprotein layer that we saw on the diagram of the AIDS virus) for entry into the CD4 cell (or another cell). HIV enters the factory and starts replicating, using the CD4 cell's machinery. Millions of new viruses are released from the factory (CD4 cell). These new viruses then move on to infect other CD4 cells which also become factories for HIV.

There are 6 stages in the HIV life cycle (Figure 6)

- HIV attaches to the CD4 cell & releases RNA & enzymes.

- The enzyme Reverse Transcriptase makes a DNA copy of the viral RNA.
- New viral DNA is then integrated using the enzyme integrase into the CD4 cell nucleus.
- New viral components are then produced, using the cell's "machinery"
- These are assembled together using the enzyme protease
- Then released as new viruses.

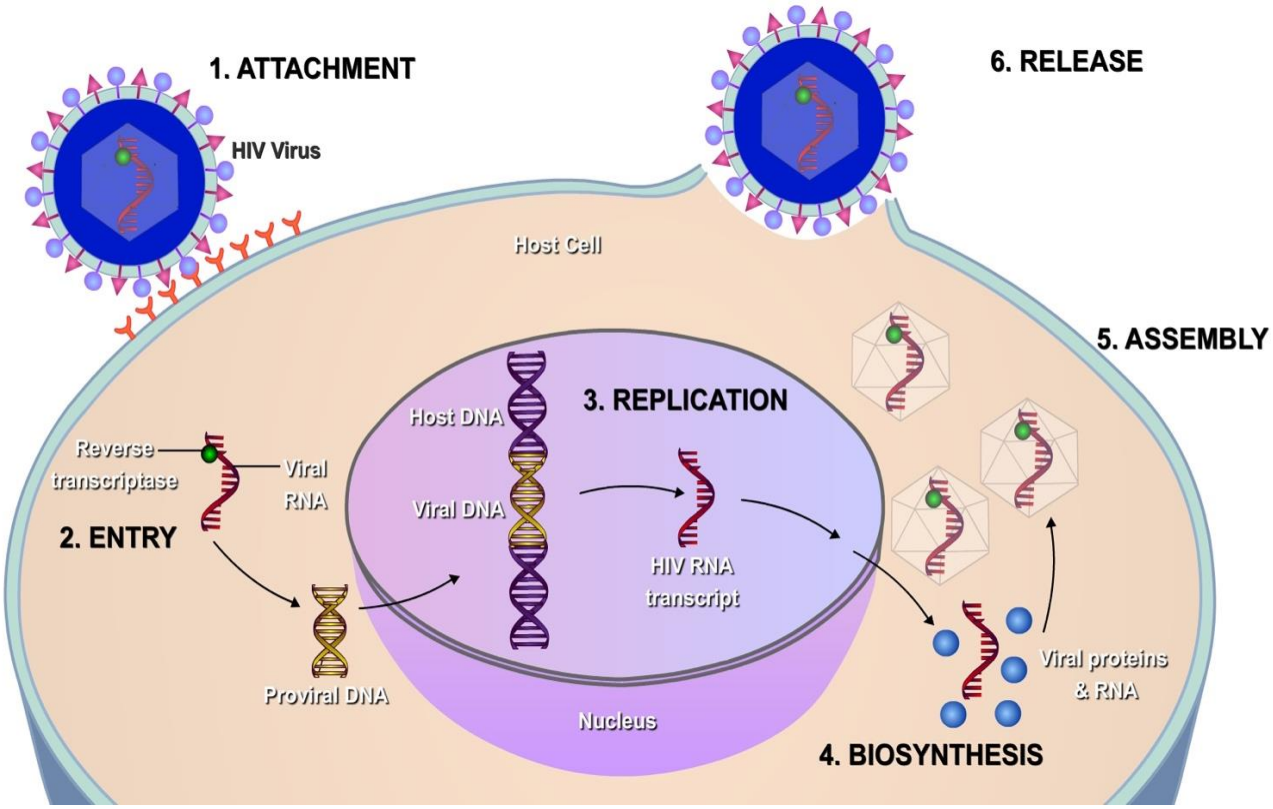


Figure 6: Life Cycle of HIV

2.3 Natural history of HIV infection and its clinical implications

The clinical course of HIV infection has the following stages: primary HIV infection, asymptomatic stage/clinical latent stage, and AIDS stage.

a. Primary HIV infection

The initial stage following HIV infection is called primary HIV infection. Patients develop non-specific 'flu-like' symptoms, which do not lead directly to the diagnosis of HIV infection because the symptoms are nonspecific. These symptoms include fever, fatigue, pharyngitis, lymphadenopathy, rash etc.

During primary infection, the patient could be negative for HIV specific antibodies despite the presence of infection. Thus, repeat antibody testing should be advised 3 months later. This stage is called window period and is characterized by very high viral load signifying extreme infectiousness despite false negative antibody result. The switch from antibody negative to antibody positive is called sero-conversion and most patients' sero-convert within three months after exposure to the virus.

Clinical management of patients during this time includes symptomatic treatment, counseling for risk reduction and repeat antibody testing. Patients are most likely to transmit HIV during the early stage of infection.

HIV establishes infection across the skin or mucosal surfaces like the cervix or urethra within in 72 hours of its introduction. This information suggests that PEP (post-exposure prophylaxis with antiretroviral drugs after high-risk blood or sexual contacts) and PMTCT should be immediate. For process of early infection, see the figure 7.

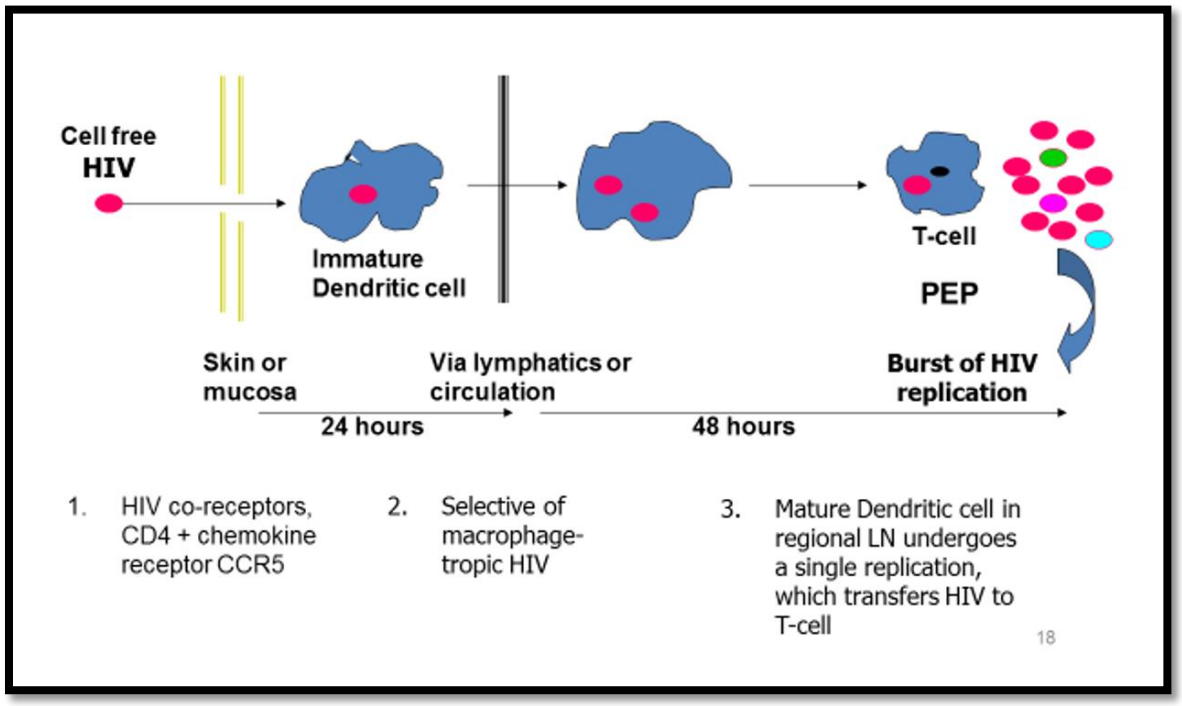


Figure 7: Early phases of HIV infection

b. Asymptomatic stage/ latent infection

- When a person gets infected with HIV, the virus starts to attack the immune system. During the first years of infection, the immune system although weakened a bit by the HIV virus, it

still functions quite well. The infected person may have no symptoms or only minor symptoms like skin diseases, loss of weight, or repeated sinusitis. A lot of people do not know they are HIV+ at this stage. The clinical latency stage lasts an average of 10 years, but some people may progress faster.

c. AIDS

- After several years, the person's immune system becomes very weak hence; they are vulnerable to diseases that they could normally fight off. These diseases are called opportunistic infections (OIs) named so because they take advantage of a weakened immune system to cause disease. In general, as the number of CD4 has decreased, the person will start to have some OIs. When the CD4 has decreased < 200 cells /mm^3, the person will have very serious opportunistic infections.
- Figure 8 further explains HIV disease progression. Soon after infection, there is a rapid burst of replication peaking at 2-4 weeks, with ≥10^9 cells becoming infected. This peak is associated with a transient drip in the number of peripheral CD4+ (helper) T-lymphocytes.

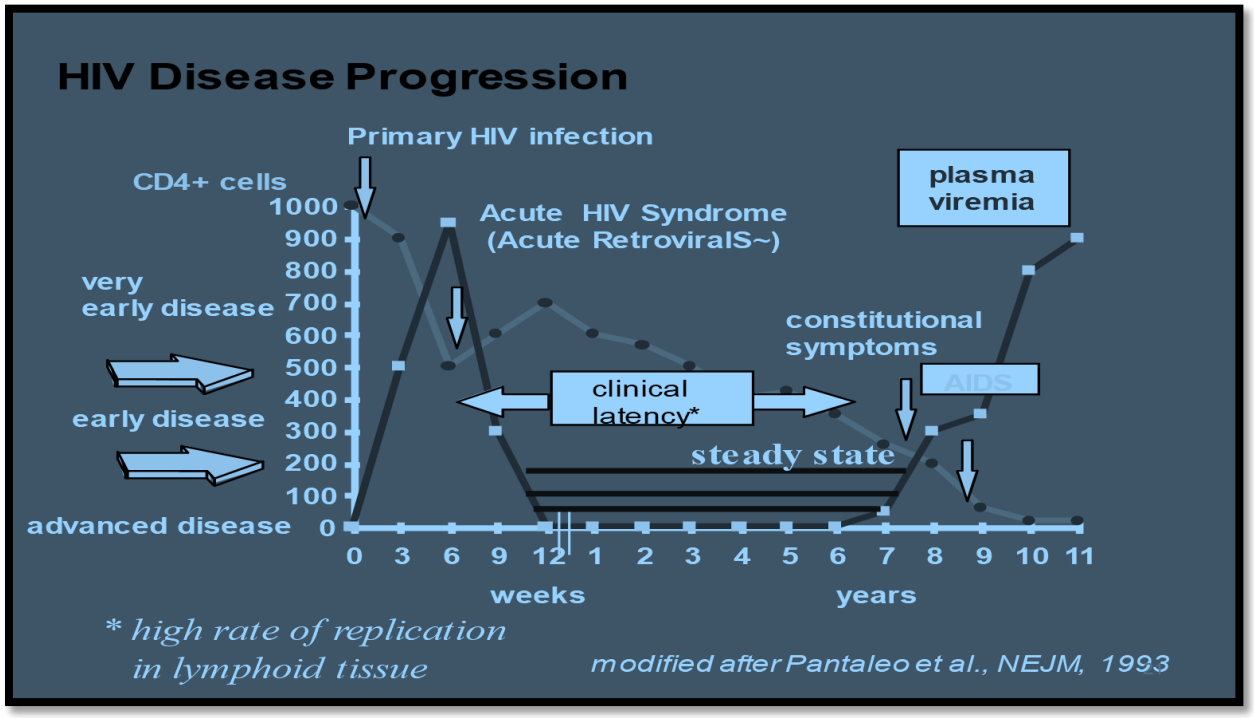


Figure 8: HIV disease progression

- Because of new host immune responses and target cell depletion, the number of infectious virions (also known as viral load) declines. Within 6 months, the host's immune response can control the infection to a point where the number of virus particles produced per day equals

the number of particles destroyed per day. This steady-state is often referred to as the patient's viral "set point." This viral set point reflects the interplay between host immunity and the pathogenicity of the infecting virus.

- Patterns of HIV disease progression varies among patients because of the viral set point (serum viral load level 6 months to one year after aquisition of HIV infection) following seroconversion. Accordingly, three types of progression are noted in adults.
  - Typical progressors account for 90% of individuals who can stay for 8-10 years before developing symptoms. The viral set point is medium in this group.
  - 5% of individuals are called rapid progressors because they develop AIDS within 3years. Often this group of patients has high viral set point.
  - Up to 10% individuals will have stable CD4 count for more than 8 years and are called long term non-progressors. This group has remarkably low viral set point. See figure 9 below.

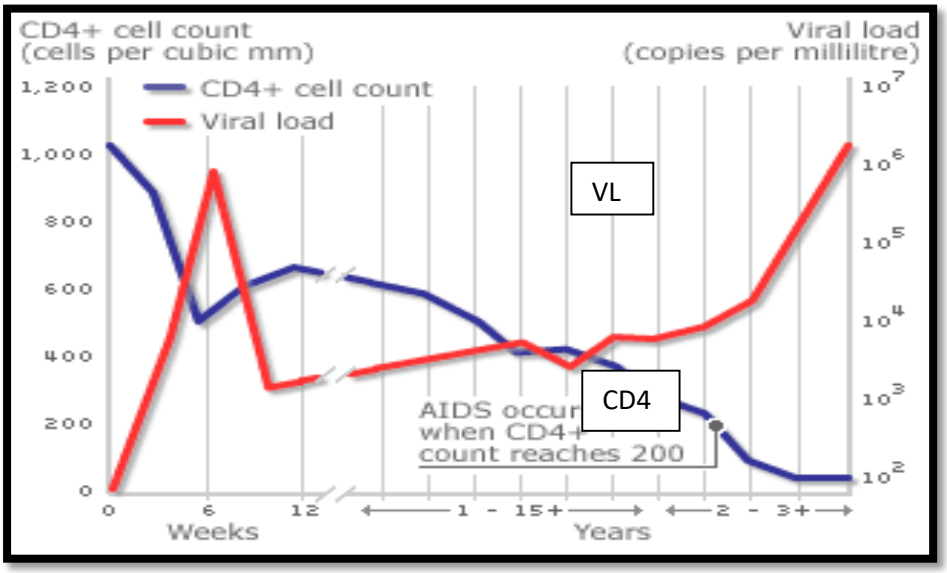


Figure 9: Pattern of disease progression among adults

- On the other hand, for Paediatric HIV infected populations, the following patterns are usually observed.
  - **Category 1 (25–30%):** Rapid progressors, who die by the age of one and who are thought to have acquired the infection *in utero* or during the early perinatal period.
  - **Category 2 (50–60%):** Children who develop symptoms early in life, followed by a downhill course and death by the age of three to five.

- **Category 3 (5–25%):** Long-term survivors, who live beyond the age of eight.

2.4 Session Summary

- HIV is a retrovirus, capable of integrating into host genome for replication and survival. HIV mainly attacks the host CD4 cells.
- The important steps in the lifecycle of HIV include cell entry, reverse transcription, integration, and maturation/assembly
- Primary HIV infection, asymptomatic stage and AIDS are clinical courses of HIV infection. As HIV replicate the CD4 count declines by both direct and indirect mechanisms

Review Question (paired Exercise)

1 Explain that HIV causing immunosuppression induces immune activation in early infection.

2 Describe how HIV gets access in to the cell and gets replicated.

3 Explain what happens over the clinical course of HIV infection.

Session 3: Stages of Disease and Initiating Therapy

Session Description:

The session explains WHO clinical staging system for HIV/AIDS and it discusses T-staging for follow-up of patients on ART. It further elaborates the initiation of antiretroviral therapy under which the goals and factors for initiation of ART as well as when and what ART regimen to start.

Primary Objective:

The primary objective of this session is to describe the WHO clinical staging of HIV/AIDS and to familiarize participants with considerations and national recommendations for initiating ART.

Enabling Objectives:

By the end of this session, participants will be able to:

- Briefly explain HIV testing and diagnosis
- Recognize WHO clinical staging system and T-staging
- Discuss the goals of ART
- Identify the factors and issues to discuss before initiation
- Explain when to start ART
- Identify what ART regimen to start
- Discuss the role of the pharmacy professionals in initiation of ART

Session Outline

- HIV testing and diagnosis
- WHO clinical staging system and T-staging
- Initiation of ART
    - Goals of ART
    - Factors to consider during initiation of ART
    - Retesting before initiation of ART
    - When to start ART
    - What ART regimen to start
- Role of the pharmacy professional in initiation of ART
- Session Summary

Introductory case

HG is a 30 years old lady who is neither pregnant nor breast feeding diagnosed with HIV just today. She has white patches on her tongue. She also has crops of multiple painful fluid containing lesions on one side of her chest. She seems willing to start a treatment. Up on counseling and discussion with the provider, she well understood the importance of ART and found to have no adherence barrier for life long treatment.

Which of the following statement is **false** about this patient?

1. Her WHO clinical stage is stage 2.
2. HG is eligible to start ART.
3. The preferred first line regimen for HG is TDF+3TC+ EFV.
4. HIV retesting before initiation is recommended.

3.1 HIV testing and diagnosis

- Before dealing with disease staging and ART initiation, it is natural to deal with HIV testing and diagnosis. However, since pharmacy professionals are not engaged in diagnosis of disease, only a brief concept of HIV testing and diagnosis will be presented here so that they will be able to closely work with prescribers on availability and quality of the required test kits.
- Currently, HIV testing services (HTS) includes the full range of services that should be provided together with HIV testing. There are two HTS models in Ethiopia:
  1. Health facility based HTS model and
  2. Community based HTS model.
- There are also two HTS approaches which are being implemented in Ethiopian health facilities:
  1. Voluntary Counselling and Testing (VCT) approach and
  2. Provider Initiated Testing and Counselling (PITC) approach

- HIV testing must be done using the nationally accepted antibody based rapid diagnostic tests (RDTs) or rapid test kits (RTKs) following the latest national HIV testing algorithm (Fig. 10).

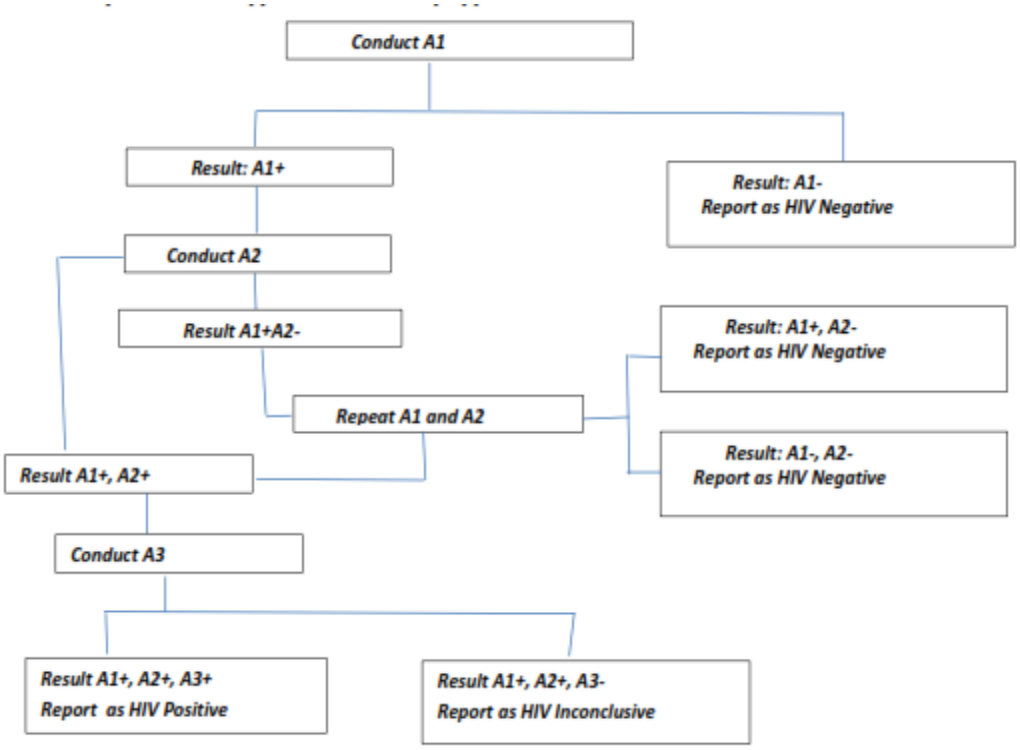


Figure 10: The national HIV testing algorithm

The three RTKs currently in use are:

1. HIV ½ STAT-PAK™ (A1) 20 tests per kit
2. ABON™ HIV 1/2/o (A2) - 40 tests per kit
3. SD BIOLINE HIV-1/2 v3.0 (A3) – 25 tests per kit

3.2 WHO clinical staging system and T-staging

- WHO clinical staging system utilizes 4 clinical stages based on the degree of immunosuppression and prognosis. The purpose of staging HIV patients is to monitor them while on treatment and for initiation of cotrimoxazole preventive therapy (CPT).
- There is also T-staging which uses the same clinical parameters as WHO clinical staging and used for monitoring of ARV treatment success or failure after 6 months of therapy. If treatment is successful, the T-stage is expected to decrease but in those whose treatment is

failing it begins to increase as they develop new OIs. In T-staging, up and down staging is possible.

- There are 4 WHO clinical stages, and these are:

  Stage I - Asymptomatic
  Stage II - Mild disease
  Stage III - Moderate disease
  Stage IV - Advanced Immunosuppression

Table 1: WHO clinical staging for children and adults

Adults and adolescents	Children
Clinical Stage 1: ***Performance scale 1 (able to carry on normal activity)***	
○ Asymptomatic ○ Persistent generalized lymphadenopathy ✓ Swollen or enlarged lymph nodes >1 cm, in two or more non-contiguous sites, excluding inguinal nodes, lasting for at least 3 months in absence of known cause.	○ Asymptomatic ○ Persistent generalized lymphadenopathy
Clinical stage 2: ***Performance scale 2 (symptomatic, able to carry out normal activity)***	
○ Moderate unexplained weight loss (>5 and <10% of presumed or measured body weight) ○ Recurrent upper respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) ○ Herpes zoster ○ Angular cheilitis ○ Recurrent oral ulceration ○ Papular pruritic eruption ○ Fungal nail infections ○ Seborrhoeic dermatitis	○ Unexplained persistent hepato-splenomegaly ○ Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) ○ Herpes zoster ○ Lineal gingival erythema ○ Recurrent oral ulceration ○ Papular pruritic eruption ○ Fungal nail infections ○ Extensive wart virus infection ○ Extensive molluscum contagiosum ○ Unexplained persistent parotid enlargement
Clinical stage 3: ***Performance scale 3 (bedridden < 50% of the day during last month)***	
○ Unexplained severe weight loss (>10% of presumed or measured body weight) ○ Unexplained chronic diarrhea for > 1 month ○ Unexplained persistent fever (intermittent or constant for > 1 month) ○ Persistent oral candidiasis ○ Oral hairy leukoplakia ○ Pulmonary tuberculosis	○ Unexplained moderate malnutrition not adequately responding to standard therapy[a] ○ Unexplained persistent diarrhea (≥14 days) ○ Unexplained persistent fever (above 37.5°C, intermittent or constant, for > one 1 month) ○ Persistent oral candidiasis (after first 6 weeks of life) ○ Oral hairy leukoplakia ○ Lymph node tuberculosis

○ Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) ○ Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis ○ Unexplained anemia (<8g/dl), neutropenia (<500cell/mm^3) or chronic thrombocytopenia (<50,000 cells/ mm^3).	○ Pulmonary tuberculosis ○ Severe recurrent bacterial pneumonia ○ Acute necrotizing ulcerative gingivitis or periodontitis ○ Unexplained anemia (<8g/dl), neutropenia (<500cell/mm^3) or chronic thrombocytopenia (<50,000 cells/ mm^3). ○ Symptomatic lymphoid interstitial pneumonitis ○ Chronic HIV-associated lung disease, including bronchiectasis
Clinical Stage 4: ***Performance Scale 4 (bedridden > 50% of the day during the last month)***	
○ **HIV wasting syndrome** ✓ Unexplained weight loss greater than 10% of body weight and visible thinning of Face, waist and extremities; plus ✓ either unexplained chronic diarrhoea (lasting more than one month) or unexplained prolonged or intermittent fever for one month or more. ○ Pneumocystis (jirovecii) pneumonia ○ Recurrent severe bacterial pneumonia ○ Chronic herpes simplex infection (orolabial, genital or anorectal of >1 month duration or visceral at any site) ○ Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs) ○ Extra pulmonary tuberculosis ○ Kaposi sarcoma ○ Cytomegalovirus infection (retinitis or infection of other organs) ○ Central nervous system toxoplasmosis ○ HIV encephalopathy ○ Extra pulmonary cryptococcosis, including meningitis ○ Disseminated non-tuberculous mycobacterial infection	○ Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy[b] ○ Pneumocystis (jirovecii) pneumonia ○ Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) ○ Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site) ○ Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs) ○ Extra pulmonary tuberculosis ○ Kaposi sarcoma ○ Cytomegalovirus infection (retinitis or infection of other organs with onset at age > 1 month) ○ Central nervous system toxoplasmosis (after the neonatal period) ○ HIV encephalopathy ○ Extra pulmonary cryptococcosis, including meningitis ○ Disseminated non-tuberculosis myco-bacterial infection ○ Progressive multifocal leuko-encephalopathy ○ Chronic cryptosporidiosis (with diarrhea) ○ Chronic isosporiasis ○ Disseminated endemic mycosis (extra pulmonary histoplasmosis, coccidioidomycosis, penicilliosis)

○ Progressive multifocal leukoencephalopathy ○ Chronic cryptosporidiosis ○ Chronic isosporiasis ○ Disseminated mycosis (extra-pulmonary histoplasmosis, coccidioidomycosis) ○ Lymphoma (cerebral or B-cell non-Hodgkin) ○ Symptomatic HIV-associated nephropathy or cardiomyopathy ○ Recurrent septicemia (including Non-typhoidal Salmonella) ○ Invasive cervical carcinoma ○ Atypical disseminated leishmaniasis	○ Cerebral or B-cell non-Hodgkin lymphoma ○ HIV-associated nephropathy or cardiomyopathy

[a] Documented loss of body weight of -2 SD, failure to gain weight on standard management and no other cause identified during investigation. [b] Confirmed by documented weight loss of >-3 SD +/- oedema.

3.3 Initiation of Antiretroviral Therapy

1. What are the goals of ART?
2. When should we start ART?

3.3.1 Goals of ART

- ***Clinical goals***: prolongation of life and improvement in quality of life.
- ***Virologic goals***: maximal and durable viral load reduction as much as possible (preferably to undetectable) to prevent, delay or halt progression, and prevent/reduce resistant variants.
- ***Immunologic goals***: immune reconstitution (the immune status improvement) that is both quantitative (CD4 cell count) and qualitative (pathogen specific immune response).
- ***Therapeutic goals****:* rational sequencing of drugs in a fashion that achieves clinical, virologic, and immunologic goals while maintaining future treatment options, free of drug toxicity and realistic in terms of probability of drug adherence.
- ***Epidemiologic goals***: reduce HIV transmission.

3.3.2 When to Start ART

- All HIV positives are eligible for ART. The ideal time for ART initiation depends on the clinical condition and readiness of the client. But, it is critical for people living with HIV to initiate ART as early as possible. This enables to shorten the time between HIV diagnosis and ART initiation, which significantly reduces HIV related morbidity and mortality, and transmission of HIV including MTCT.
- Clients understanding about HIV and the importance of life long treatment adherence need to be emphasized. All adherence barriers should be exhaustively assessed and addressed before considering ART initiation. For those HIV positive clients, who understand the importance and benefits of life long adherence and are ready for early initiation, start ART as early as possible including same day.

ART should be initiated for all individuals (children, adolescents, and adults) living with HIV immediately after confirming HIV diagnosis, regardless of WHO clinical stage and CD4 count.

3.3.3 Factors to consider in initiating ART

Before people start ART, it is important to have a detailed discussion with them about their willingness and readiness to initiate ART.

The following issues should be addressed during the preparation to initiate ART:

- The benefits of ART
- Detailed adherence counseling including information regarding lifelong treatment
- Possible adverse effects of ARVs & OI medications
- The required follow-up and monitoring visits
- Education on safer sex practice, STI and screening of family members
- Ensure readiness of patient for ARV therapy
    - Patient understands benefits of treatment and committed for lifelong adherence, possible side effects, adherence schedule and wants treatment.
    - Patient interested and actively involved in own care.
    - No recent non-adherence to care or other medication (when applicable).
    - Barriers to adherence have been addressed such as highly unstable social situation, heavy alcohol or substances dependence, serious psychiatric illness, or other severe comorbidities.

- The health care provider should also consider the following factors while initiating therapy.
  - Latest national HIV prevention, care, and treatment guidelines; Potential side effects, drug interactions and antiretroviral resistance; Concurrent health conditions including abnormal laboratory values; Future treatment options and Potential barriers to adherence.

3.3.4 Retesting before initiation of ART

- It is required that all HIV positive clients linked to care and treatment services need to be retested before treatment is initiated. Retesting aims to rule out possible technical or clerical errors; including specimen mix-up through mislabeling and transcription errors, as well as random error either due to the provider or the test device.
- Retesting people on ART is not recommended. The effect of ART in suppressing viral replication may extend to suppression of the immune response and therefore reduction of antibody production will be there. Once a person is started on ART, low antibody titers make it challenge to discern whether an individual is indeed HIV positive and will lead to potential risks of incorrect diagnosis.

3.3.5 What ART regimen to start with (first-line ART)?

Using simplified, less toxic, more effective and convenient regimens as fixed-dose combination is recommended for first-line ART. The preferred first-line regimen for adults and adolescents is TDF+3TC+DTG or TDF+3TC+EFV as a once-daily dose. Upon availability of the FDC DTG containing regimen, it will be the preferred first line regimen for adult and adolescent HIV patients. In case of TB-HIV coinfections in adults and adolescents, the dose of DTG should be 50mg BID.

For pregnant and breast-feeding mothers and women of child bearing age, the preferred first-line regimen is TDF+3TC+EFV as once daily dose. Although there is no clear pattern of abnormalities emerged with DTG during pregnancy, more data are needed on maternal safety and tolerability and adverse outcomes to the fetus exposed in utero and on the safety of infants exposed during breastfeeding.

For children younger than three years a protease inhibitor (PI)-based regimen is the preferred approach.

In older patients with long-term diabetes, uncontrolled hypertension, and renal failure, select appropriate drug from the alternative regimen.

In patients with depression, suicidal ideation, and previous history of acute psychosis, use alternative regimen and avoid EFV.

Table 2: Summary of first-line ART regimens for adults, pregnant & breastfeeding women, adolescents and children

Population	**Preferred first-line regimens**	**Alternative first-line regimens[a]**
Adults (including those with TB/ HIV[b]-coinfection.)	TDF + 3TC + DTG (FDC)* OR TDF + 3TC + EFV (FDC)**	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC + NVP
Pregnant and breastfeeding mothers and women of childbearing age	TDF + 3TC + EFV (FDC)	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC + NVP
Adolescents (10 to 19 years) weight ≥30 kg (including those with TB/HIV[b]-coinfection.)	TDF + 3TC + DTG (FDC)* OR TDF + 3TC + EFV (FDC)**	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC + NVP ABC + 3TC + EFV
Children 3 years to less than 10 years and adolescents weight <30 kg	AZT/ABC + 3TC + EFV	AZT + 3TC + NVP TDF + 3TC + EFV TDF + 3TC + NVP ABC + 3TC + NVP***
Children <3 years	ABC/AZT + 3TC + LPV/r	ABC + 3TC + NVP AZT + 3TC + NVP

[a] ABC or boosted PIs (ATV/r, LPV/r) can be used in special circumstances.

[b] In case of TB-HIV coinfection, the dose of DTG should be 50mg BID.

*If available as triple FDC, TDF+3TC+DTG is the preferred regimen for HIV positive adult and adolescent patients.

**TDF+3TC+EFV400 (FDC) will replace the TDF+3TC+EFV600 (FDC) for adults and adolescents (except for pregnant mothers and TB/HIV co-infected patients as there is no adequate data for this groups) up on availability.
*** Caution: co-administration of ABC with NVP in pediatric patients will increase the risk of hypersensitivity reaction and requires extreme precaution.

3.4 Role of pharmacy professionals during initiation of ART

- Address medication side effects and their management to patients and providers.
- Discuss potential drug-drug, drug-food, or drug-alternative medicines interactions.
- Explain medication dosing and how to handle missed doses.
- Educate patient on handling and storage of medications.
- Discuss importance of lifelong treatment adherence and identify adherence barriers.
- Ensure patients readiness and willingness for ARV therapy.
- Discuss importance of regular follow-up and schedule follow-up appointment for refills.
- Provide written drug information, when appropriate and possible.
- Discuss treatment regimen properties and selection with other health care providers, considering efficacy, safety, convenience, and availability.

Case studies

Case 1. HM is a 40 years old man. Recently he started to notice change in his weight and lost 7 kg over 3 months' time (from 69 to 62) and had diarrhea for the last 1 month. He spends most of his time in bed for the last 1 month. Today he is diagnosed as HIV positive. But HM's wife is found to be HIV negative with repeated tests (discordant couples).

1. What is his WHO clinical stage? Why?
2. What management does HM require before ART?
3. Do you recommend ART to HM? If HM starts ART, what is the benefit to his wife?
4. What counseling point do you provide for this couple in addition to the ART?

Case 2. SA is a 16 years old boy who was brought by his mother to be tested for HIV as the mother was found to be HIV positive. SA's antibody test turned out to be positive. He had no past medical illness and no current complaint.

1. What is his WHO clinical stage?
2. Does SA need ART?
3. What should be done before initiating ART?
4. If ART is to be started, which regimen do you prefer?

3.5 Session Summary

- WHO clinical staging system utilizes 4 clinical stages based on the degree of immunosuppression and prognosis.
- Currently, the purpose of staging HIV patients is to monitor patients on treatment and for initiation of CPT.
- T-staging is used to monitor response to therapy after 6 months of ART using the same clinical parameters to WHO clinical staging.
- ART should be initiated for all individuals living with HIV immediately after confirming HIV diagnosis, regardless of WHO clinical stage and CD4 cell count.
- The preferred first line ART for adults and adolescents is TDF+3TC+DTG or

TDF+3TC+EFV. For women of childbearing age including pregnant and breast-feeding mothers, the preferred first-line regimen is TDF+3TC+EFV instead of TDF+ 3TC + DTG.

- Before initiating ART, it is important to have a discussion with patients to ensure their willingness and readiness to initiate ART.
- It is very critical to discuss with patients about the importance of lifelong treatment adherence, and identify and solve any adherence barriers.

Session 4: Clinical Pharmacology of Antiretroviral Drugs

Session 4.1: Pharmacology of Antiretroviral Drugs

Session Description

This session deals with basic pharmacology of antiretroviral drugs. Targets for therapeutic drug interventions based on HIV life cycle are discussed. It then describes the mechanisms of action of the different classes of antiretroviral drugs. The dose, pharmacokinetics, side effects and pregnancy category of each antiretroviral drug are discussed in detail.

Primary Objective:

The purpose of this session is to introduce participants to the basic pharmacology of antiretroviral drugs available in Ethiopia

Enabling Objectives:

By the end of this session, participants will be able to:

- Identify classes of antiretroviral drugs
- Describe the mechanism of action for ARV classes
- Discuss the pharmacology of ARV drugs currently available in Ethiopia
- Identify ARV class side effects
- Describe ARV dosing
- List the role of the pharmacy professional

Session outline

- Classes of antiretroviral drugs
- Mechanism of action for ARV classes
- Pharmacology of ARV drugs currently available in Ethiopia
- ARV class side effects
- ARV dosing and reasons for dose modifications
- The role of the pharmacy professional

Introductory Case

TW, a 32-year-old woman, presents to the ART pharmacy for her 1month follow-up after starting ART (Zidovudinne, Lamivudine and Efavirenz). She appears tired and feels fatigue. When you ask her how she is doing on her medication, she replies that she is feeling worse after starting ART. She occasionally feels nauseated. Also, she has trouble falling asleep, and during the night she is awoken with nightmares.

1. In which class of ARVs do TW's medicines belong?
2. What are the adult doses of TW's ARVs medicines?
3. Which agent(s) is/are mainly associated for tiredness and fatigue in TW?
4. Which agent(s) is/are causing insomnia and nightmares in TW?

4.1.1 Introduction to Antiretroviral Therapy (ART)

1. What are benefits of ART?
2. What are the benefits of ART?

HAART or simply ART is the use of a combination of three or more antiretroviral to achieve durable suppression of viral replication. The term HAART or ART stands for:

HAART: **H**ighly **A**ctive **A**nti-**R**etroviral **T**herapy

ART: **A**nti-**R**etroviral **T**herapy

Since the introduction of the first agent, Zidovudine in 1987, substantial advances have been made in ART. At that time Zidovudine was prescribed as monotherapy for only patients with advanced, symptomatic disease in five times daily dose. In mid-1996, it was discovered that these drugs are far more effective when three or more are taken at the same time. This combination therapy with

maximally potent agents (comprising at least three ARV Agents) reduces viral replication to the lowest possible level and decreases the likelihood of emergence of resistance.

With the advent of HAART, HIV-1 infection is now manageable as a chronic disease in patients who have access to medication and who achieve durable virologic suppression. ART is effective in reducing HIV viremia and in improving CD4+ counts. In addition, ART is important to prolong life and improve quality of life, to significantly decrease morbidity and mortality and to reduce mother-to-child transmission of HIV.

4.1.2 Targets for therapeutic drug intervention in HIV

- Currently available drugs do not kill the virus but only inhibit the replication of HIV by interfering its life cycle. ARVs act on different targets of the viral life cycle when the virus infects a CD4+ T lymphocyte or other cells.

There are six classes of antiretroviral agents currently available for use. These include:

- **Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs),**
- **Nonnucleoside reverse transcriptase inhibitors (NNRTIs),**
- **Protease inhibitors (PIs),**
- **Integrase inhibitors. (INSTIs)**
- Fusion inhibitors (Enfuvirtide)*,
- CCR5 receptor antagonists (Maraviroc)*, and
- Maturation inhibitors*

* *are not available in Ethiopia.*

- HIV enters the host cell by binding to CCR-5 and CXCR4 receptors on CD4 cells. Fusion inhibitors and CCR5 receptor antagonists are the best classes of ARVs that can act on this stage to inhibit binding and fusion of the virus.
- Reverse transcriptase (RT) is major target for ARV drugs in HIV treatment. The class of ARVs that inhibit transcription of viral RNA to DNA are Nucleoside and Nonnucleoside reverse transcriptase inhibitors.

- New viral DNA is then integrated using the **enzyme integrase** into host DNA in the CD4 cell nucleus. Integrase inhibitors are the agents that act on this stage of the virus life cycle.
- Protease inhibitors are the agents that act on the protease enzyme which cleaves the longer precursor proteins into smaller core proteins for the generation of infectious viral particles

4.1.3 Classes of Antiretroviral and Specific drugs

I. Nucleoside/-tide Reverse Transcriptase Inhibitors (NRTIs)/Nukes

NRTIs are key components of ART regimens, and are often referred to as the **"backbone"/Nukes** of HIV treatment. NRTIs exhibit activity against HIV-1 and HIV-2.

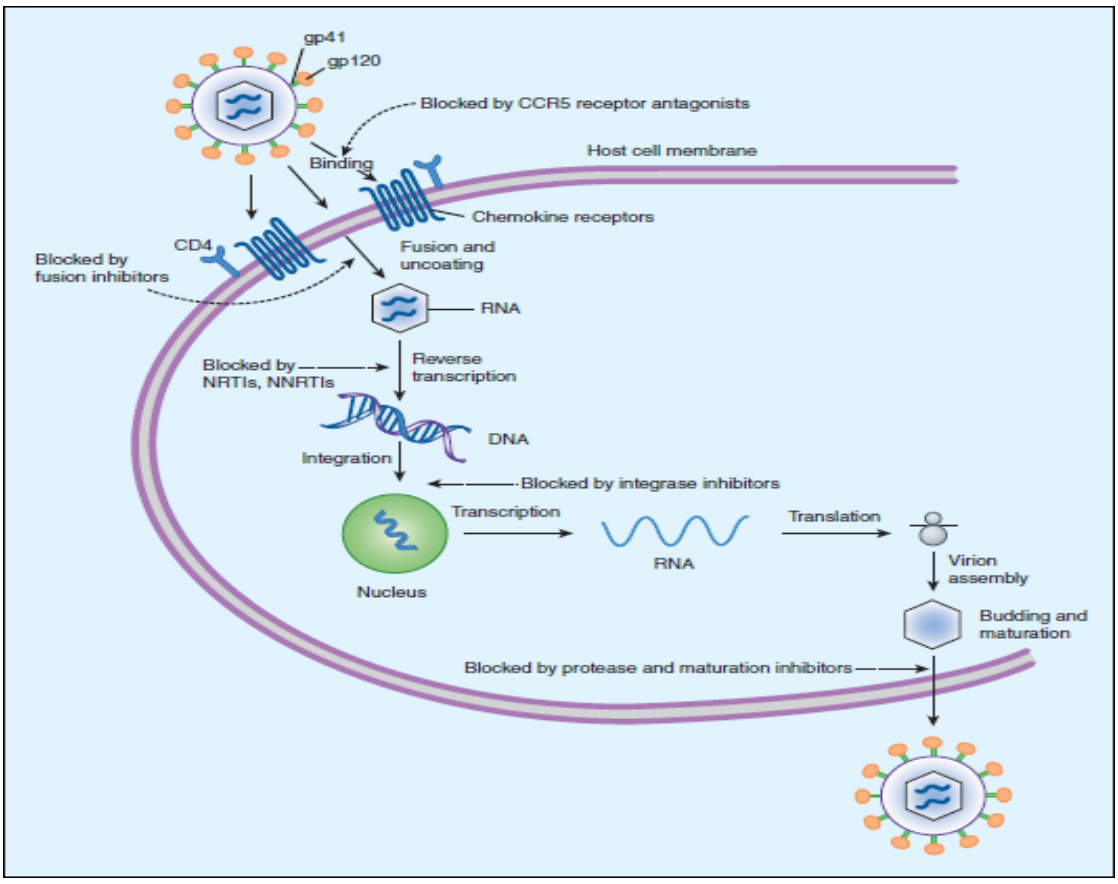


Figure 11: Life cycle of HIV and the targets for ARV agents

The NRTI class includes:

- Zidovudine (ZDV);
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtracitabine (FTC)
- Tenofovir Disoproxil Fumarate (TDF)
- Didanosine (DDI)*
- Stavudine (D4T)*
- Zalcitabine (DDC) *

  *are phased out due to toxicity

Mechanism of action of NRTIs

All NRTIs are prodrugs, they require intracellular phosphorylation to exert their antiviral effects. The pharmacologic active moiety for all NRTIs is an **intracellular 5'-triphosphate compound.** Intracellular phosphorylation is mediated by several host enzymes (cytoplasmic or mitochondrial kinases and phosphotransferases), which sequentially transform the parent drug to the monophosphate, diphosphate and finally the active triphosphate forms.

The active NRTI triphosphate inhibits viral replication through **competitive binding** to the viral enzyme, reverse transcriptase; after incorporation of the NRTI triphosphate, **DNA chain elongation is terminated.** Structurally, all the NRTIs are "nucleosides", while tenofovir, which contains one phosphate group within the parent molecule, is a nucleotide. Thus, Tenofovir requires only two phosphorylation steps.

Zidovudine (AZT or ZDV)

Zidovudine is a deoxythymidine analog which the first approved ARV and is still commonly used as a component of ARV regimens. It has potent *in vitro* activity against a broad spectrum of retroviruses including HIV-1, HIV-2, and human T-cell lymphotropic viruses (HTLV) I and II.

AZT Dosing and Key Pharmacokinetics

- **Adult dosing:** 300mg BID oral

- Bioavailability (F): 64%
- **Food interaction:** Drug can be administered regardless of food intake**.** Food decreases ZDV-related nausea.
- $T_{1/2}$: 1 hour; Intracellular $T_{1/2}$*: 3-4 hours
- Elimination: metabolized by liver to 5'-glucuronyl zidovudine that is renally excreted

Note: *NRTIs work in the cell, duration of action is based on intracellular $t_{1/2}$

Side Effects of AZT

- Common side effects headache, malaise, nausea, anorexia and vomiting (incidence ≥15%).
- Bone marrow suppression resulting in **anemia** (1-7%; Hgb <7% in 1-4% patient) within 2-4 weeks**, neutropenia** (1-2%) occurs after 6 to 8 weeks and thrombocytopenia.
- Myalgias (muscle pains) are rare
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases

Pregnancy category C: crosses the placenta. No increased risk of overall birth defects.

Drug interactions of AZT

- Probenecid, fluconazole, atovaquone, and valproic acid may increase plasma concentrations of AZT probably through inhibition of glucuronosyl transferase.
- Bone marrow-suppressive drugs such as ganciclovir, dapsone, pyrimethamine, sulfadiazine, amphotericin B increases AZT-induced bone suppression.

Lamivudine (3TC)

Lamivudine is a synthetic cytidine analogue active against HIV-1, HIV-2, and hepatitis B virus. 3TC is a potent inhibitor of HBV, good for patients with HIV and HBV co-infection.

3TC Dosing and key Pharmacokinetics

- Adult Dosing: 150mg BID or 300mg QD
- Bioavailability (F): 86%
- Food Interactions: No food interactions (can be taken with or without meals
- $T_{1/2}$: 3-6 hours Intracellular $T_{1/2}$: 12 hours
- **Elimination:**3TCis 71% renally excreted

Side Effects of 3TC:

Lamivudine (3TC) is best tolerated of all ARVs. Side effects associated with 3TC include:

- Headache, nausea, malaise and fatigue, nasal signs and symptoms, diarrhea and cough.
- Lactic acidosis and severe hepatomegaly with steatosis
- Exacerbations of hepatitis have occurred after discontinuation in patients with HIV-1 and Hepatitis B Virus Co-infection.

Pregnancy Category C: crosses the human placenta but use in pregnancy is safe, well established and effective.

Drug Interaction: 3TC has no significant interactions

Paired discussion

Discuss on TDF and ABC in Pairs in 15 minutes and present to large group (*focus on adult doses, bio availability, food interaction, elimination, and side effects)****.***

Tenofovir Disoproxil Fumarate (TDF)

Tenofovir is an acyclic nucleoside phosphonate (i.e, nucleotide) analog of adenosine. Like 3TC, TDF also is active against HIV-1, HIV-2, and HBV.

TDF Dosing and Pharmacokinetics

- Adult Dosing: 1 x 300mg tablet QD for ≥10 years old
- Bioavailability**:** fasted state 25% and increases to 39% after a high-fat meal.
- Food interaction: Can be taken with or without food
- $T_{1/2}$: 12 to 18 hours
- Intracellular $T_{1/2}$: 10 to 50 hours
- **Elimination:** Renally excreted

Side effects:

TDF is very well tolerated and has minimal side effects such as:

- Headache, nausea and diarrhea
- Renal insufficiency: rare episodes of acute renal failure and Fanconi's syndrome
- TDF-related decreases in bone mineral density have been observed in children
- Lactic acidosis and severe hepatomegaly with steatosis

Pregnancy Category B: Crosses placenta. No increased risk of overall birth defects

Drug interactions:

- **Protease inhibitors**: co-administration decreases atazanavir concentrations and increases tenofovir concentrations.

Abacavir (ABC)

ABC is a dideoxy-guanosine analogue. The safety and effectiveness of ABC have been established in pediatric patients aged 3 months and older.

ABC Dosing and Key Pharmacokinetics

- Adult Oral dosage: 300 mg tablet BID or 600 mg tablet QD
- Bioavailability (F): 83%,
- Food interaction: Can be administered with or without food.
- $T_{1/2}$: 1.5 hours
- Intracellular $T_{1/2}$: > 21 hours, thus making ABC daily dose possible.
- Elimination: 81% metabolized by alcohol dehydrogenase and glucouronyl transferase (5′-glucuronide) with renal excretion of metabolites; 16% recovered in stool, and 1% unchanged in urine.

Side effects:

Abacavir is generally well tolerated. The reported side effects include:

- ✓ nausea, headache, malaise and fatigue, nausea and vomiting and dreams/sleep disorder.

- ✓ Abacavir hypersensitivity reaction (HSR) (5-8%)
- ✓ Increased risk of myocardial infarction (MI)

Pregnancy category C: Abacavir crosses the human placenta. No increased risk of overall birth defects has been observed

Drug Interaction: Alcohol affects the metabolism of ABC

Class Side Effects of NRTIs

- The hallmark toxicity of the **NRTI class is mitochondrial toxicity**, which may manifest as peripheral neuropathy, pancreatitis, lipoatrophy, hepatic steatosis, and myopathy. However, the risk of mitochondrial toxicity depends on the affinity of the individual NRTI for mammalian mitochondrial DNA polymerase gamma. The rank of NRTIs based on their affinity to this enzyme:
  - ddC* >> ddI* > d4T*> ZDV >>> TDF = 3TC = FTC = ABC.

* The dideoxynucleosides or d-drugs such as ddC, ddI and d4T are no longer recommended for use due to their high risk of mitochondrial toxicity. Since, ZDV>>>TDF, TDF is much safer than ZDV with respect to this toxicity.

- **Lactic acidosis and severe hepatomegaly with steatosis,** including fatal cases, have been reported with the use of nucleoside analogues alone or in combination. Most of these cases have been in women. Obesity and prolonged exposure to NRTI analogues may be risk factors. All NRTIs have warnings in their product labeling regarding the possibility of **lactic acidosis.**
- **Peripheral neuropathy and pancreatitis** are most noted with the "D" drugs – D4T, DDI.

II. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

NNRTIs are a class of potent ARV drugs that are very effective and recommended as first line agents for HIV-1-infected, antiretroviral-naïve patients. They are only active against HIV-1.

The drugs under NNRTI class include:

Nevirapine (NVP)	Delavirdine*
Efavirenz (EFV)	Etravirine * (ETV) ------2nd generation

Rilpivirine* --------2nd generation

**Not available in Ethiopia*

Mechanisms of Action:

NNRTIs include chemical substrates that bind to a hydrophobic pocket in the p66 subunit of the HIV-1 RT. These compounds induce a conformational change in the three-dimensional structure of the enzyme that greatly reduces its activity, and thus they act as ***noncompetitive inhibitors of RT***.

Unlike NRTIs, these compounds do not require intracellular phosphorylation to attain activity. NNRTIs are active against HIV-1 but no effect on HIV-2 or other retroviruses. They also have no activity against host cell DNA polymerases.

Nevirapine (NVP)

NVP is a dipyridodiazepinone NNRTI with potent activity against HIV-1.

NVP Dosing and Key Pharmacokinetics

- Adult Dosing: 200 mg QD x 2 weeks (lead-in dosing period), then 200 mg BID
- Bioavailability (F): well absorbed, 93%
- Food interaction: neither food nor antacid affects the absorption
- $T_{1/2}$: 25-30 hours at steady state.
- Elimination: Metabolized by cytochrome P450 3A4 (CYP3A4) to hydroxylated metabolites, 80% of metabolites are excreted in the urine.

Side effects of NVP:

- **Rash** (up to15%, with Grade 3/4 rash occurring in 2%)
  - Mild rash or Severe, life-threatening skin reactions such as Steven-Jonson syndrome (SJS), toxic epidermal necrosis and HSR
  - Commonly occur in first 6-18 weeks of therapy
  - **The 14-day lead-in period** with NVP 200 mg daily dosing has been demonstrated to reduce the frequency of rash, thus should be strictly followed.

- **Hepatitis** (up to 14% but symptomatic only in 4%). Hepatitis most commonly occur in the first 6 weeks, but it can occur at any time during treatment.

Why lead-in dosing of NVP is required?

Pregnancy Category C: Crosses placenta.

Drug Interactions: NVP induces CYP3A4 and lowers C_P of co-administered CYP3A4 substrates

- NVP decreases concentration of combined oral contraceptives, ketoconazole, praziquantel, lumefantrine and PIs
- NVP also induces its own metabolism, which decreases the $t_{1/2}$ from 45 hours following the first dose to 25-30 hours after 2 weeks. To compensate for this, a lead-in period is recommended.

Efavirenz (EFV)

EFV is a 1, 4-dihydro-2H-3, 1-benzoxazin-2-one. It is the preferred agent for use in combination therapy for treatment-naive patients

EFV Dosing and Key Pharmacokinetic

- **Adult Dosing**: 600mg tablet at bed time (QHS)
- **Bioavailability:** EFV is moderately absorbed (45%) and reaches peak plasma concentrations within 5 hours. High-fat meals increase absorption by 50% and should be avoided. Administer on an empty stomach; however, it can be taken with a low-fat meal
- **$T_{1/2}$**: 40-55 hours
- **Elimination**: EFV is cleared via oxidative metabolism by CYP **2B6** and to a lesser extent by CYP3A4. About 14% to 34% is excreted in urine as glucuronide metabolites and 16% to 61% in stool as unchanged drug.

Side Effects of EFV:

- **CNS side effects** (Up to 53%, but <5% result in discontinuation). These include dizziness, impaired concentration, dysphoria, vivid or disturbing dreams, and insomnia. CNS symptoms may occur with the first dose and last for hours; more severe symptoms may require weeks to resolve (2-4 weeks).
- **Psychiatric side effects** such as depression, hallucinations, and/or mania)
- **Rash (**mild 27%, severe like SJS in 0.1%) occurs in the first 2 weeks of initiation but resolves spontaneously (within a month)
- **Hepatotoxicity:** The rate is less frequent and less severe than seen with NVP

Efavirenz in pregnancy: Safe

Drug interactions: EFV is a moderate inducer of CYP3A4, but weak to moderate inhibitor of CYP 2C9 and CYP 2C19.

- ✓ EFV decreases level of phenobarbital, phenytoin, carbamazepine
- ✓ Rifampin level is unchanged by EFV, but rifampin may reduce EFV level slightly. EFV reduces the rifabutin AUC by 38% on average (increase rifabutin dose to 450mg QD or 600mg 3x/week).
- ✓ EFV increase warfarin level by inhibiting CYP 2C9, monitor carefully

What are the class side effects of NNRTIs?

NNRTI Class Side Effects

- Common side effects associated with NNRTIs are **Rash** and **liver toxicity**.
- **Rate of Rash:** EFV (27%) > NVP (15%). Rate of rash that requires discontinuation of the causative agent: NVP (5%) > EFV (1.7%).
- **Rate of hepatotoxicity:** NVP (8-18%; 4% symptomatic and 9% asymptomatic with LFTs increase >5 x ULN)> EFV (2-8%).

III. Protease inhibitors (PIs)

HIV protease inhibitors are peptide-like chemicals that competitively inhibit the action of the virus aspartyl protease. Antiretroviral drugs under this class include:

- **Lopinavir ***
- **Atazanavir ***
- *Darunavir*
- *Nelfinavir (NFV)*
- *Indinavir*
- *Saquinavir-SGC*
- *Tipranavir*
- *Ritonavir*
- *Saquinavir-HGC*
- *Amprenavir*
- *Fosamprenavir*

***** available in Ethiopia – Lopinavir + Ritonavir, Atazanavir + Ritonavir. But, Darunavir is included in the national ART guideline.

Mechanism of actions:

These drugs prevent proteolytic cleavage of HIV Gag and Gag-pol precursor polypeptides. The pharmacokinetic properties of PIs are characterized by high inter-individual variability, which may reflect differential activity of intestinal and hepatic CYPs.

Lopinavir/ritonavir (LPV/r)

Lopinavir (LPV) is a peptidomimetic PI that is structurally similar to ritonavir but is 3- to 10-fold more potent against HIV-1 *in vitro*. LPV is active against both HIV-1 and HIV-2 and currently used for the treatment of HIV-1 infection in adults and pediatric patients (14days and older). LPV is available only in co-formulation with low doses of ritonavir (Lopinavir/Ritonavir). The ritonavir component is required to inhibit the CYP3A4 metabolism of lopinavir, allowing increased plasma levels of lopinavir (pharmacokinetic boosting).

What is pharmacokinetic boosting?

Dosing and key pharmacokinetics

- **Adult Dosing:**400mg/100mg BID
- **Bioavailability (F):** ~80% with food and 48% on an empty stomach,
  - Tablet may be taken with or without food, swallowed whole and not chewed, broken, or crushed.
  - Oral solution must be taken with food.
- **$T_{1/2}$:** 5 to 6 hours (when LPV + RTV)
- **Elimination:** Metabolized primarily by CYP450 3A4 enzymes. Less than 3% is excreted unchanged in urine.

Side effects of LPV/r*:* It is well tolerated. The most common adverse events reported

- GI side effects**:** diarrhea (7-28%), vomiting (children 21%, adult 2-6%), nausea (5-16%), abdominal pain (1-11%), dyspepsia (<6%)
- Dermatologic**:** Rash (children 12%, adult ≤5%),
- Endocrine & Metabolic: Hypercholesterolemia (3-39%), triglyceride increase (3%-36%), hyperglycemia (<5%), hyperuricemia (<5%),
- Hepatic: increase in GGT, ALT, AST, bilirubin
- Altered cardiac conduction: QT and PR interval prolongation
- Fat redistribution (lipodystrophy): (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).

Pregnancy Category C: Crosses placenta. No increase in risk of teratogenic effects

Drug Interaction: is mainly due to inhibition of CYP3A4 by RTV**.** This effect is less than seen with full doses of RTV.

LPV/r with other antiretroviral drugs:

- LPV/r may decrease the C_P of Abacavir.
- NVP reduces C_{min} of LPV by 55%: NVP standard + LPV/r 533/133 mg bid.
- Efavirenz: may decrease the C_P of Lopinavir. Avoid once daily use of LPV/r with EFV. Avoid use of this combination in patients less than 6 months of age.

LPV/r with non-ARV drugs

- Avoid combination with Amiodarone, Cisapride, Calcium Channel Blockers (if impossible frequently monitor),
- Contraceptives (Estrogens): PIs may decrease the C_P of Contraceptives. Ketoconazole may increase the C_P of LPV $w_h$ile LPV may increase the level of Ketoconazole.

Atazanavir/ritonavir (ATV/r)

Atazanavir is an azapeptide PI that is active against both HIV-1 and HIV-2.

Dosing and Key Pharmacokinetics

- **Adult Dosing**: ATV/r 300/100 mg once-daily
- **Bioavailability: ATV** is absorbed rapidly after oral administration, but its absorption is sensitive with food. Absorption is pH dependent**;** itrequires an acidic gastric pH for absorption.
- **$T_{1/2}$**: Unboosted therapy: 7-8 hours; Boosted therapy (with ritonavir): 9-18 hours
- **Elimination:** Hepatically metabolized by CYP3A4. Excreted via Feces (79%, 20% of total dose as unchanged drug); urine (13%, 7% of total dose as unchanged drug)

Side Effects: ATV is generally well tolerated. However; the following side effects are reported:

- GI side effects: diarrhea and nausea mainly during the first few weeks of therapy.
- Indirect hyperbilirubinemia (Jaundice),
- Fat redistribution: may cause redistribution of fat (eg, buffalo hump, peripheral wasting with increased abdominal girth, cushingoid appearance).
- Cholecystitis, cholelithiasis, cholestasis, and other hepatic function abnormalities.
- It has minimal effect on lipid profile and does not induce insulin resistance unlike other PIs.

Pregnancy Category B: It is not known whether ATZ is present in breast milk or crosses placenta. ATZ use in pregnancy may potentially cause hyperbilirubinemia in neonates or young infants.

Drug Interaction: ATV inhibits 3A4, 1A2, 2C9, and UGT. It is metabolized by CYP3A4.

- TDF decreases ATV levels: Combine ATV with RTV when dosed with TDF
- EFV and NVP decrease ATV levels: use boosted ATZ when dosed with NNRTIs
- Oral contraceptives: increase estradiol AUC by 48% and norethindrone AUC 110%
- H2 receptor antagonists and antacids
- Concomitant administration of agents that induce CYP3A4 enzyme (e.g., rifampicin) is contraindicated.

Darunavir (DRV)

Darunavir is used as an adjunct therapy with low dose Ritonavir. It is used in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.

DRV Dosing and Key Pharmacokinetics

- **Adult dosing:**
  - Darunavir 800 mg plus ritonavir 100 mg orally once a day with food if no Darunavir resistance associated substitutions
  - Darunavir 600 mg plus ritonavir 100 mg orally twice a day with food for therapy-experienced patients with at least 1 darunavir resistance associated substitution:
- Bioavailability (F): the absolute oral bioavailability of a single 600 mg dose of darunavir alone and after co-administration with 100 mg ritonavir twice daily was 37% and **82%,** respectively.
- **Food interaction:** taken with food - better absorption (+30%).
- $T_{1/2}$: approximately 15 hours when combined with ritonavir
- Elimination: primarily metabolized by CYP3A. Approximately 79.5% and 13.9% of administered dose of darunavir is recovered in feces and urine, respectively.

Side Effects of DRV

- Dark-colored urine, yellowing of your skin or the whites of your eyes (jaundice), pale-colored bowel movements, diabetes
- Nausea, vomiting, pain or tenderness on the right side below your ribs, loss of appetite, tiredness

- Hypersensitivity reactions with fever, tiredness, muscle or joint pain, blisters or skin lesions, mouth sores or ulcers, and conjunctivitis (redness or swelling of the eyes).

Pregnancy category: C

Drug interactions:

DRV is primarily metabolized by CYP3A; and a lot of interactions are expected with agents like Lovastatin, Simvastatin, Artemether/lumefantrine, Caffeine/ergotamine, Alfentanil, Colchicine , Isoniazid/rifampin, Phenobarbital, Phenytoin, Sildenafil

Class Side Effects of PIs

What are Class side effects of PIs?

- **Gl Intolerance:** the most important side effect of this class is gastrointestinal intolerance. Nausea and vomiting can be treatment-limiting. These side effects are seen with all of the protease inhibitors, but were most significant with full dosing of ritonavir (600 mg BID), which is no longer used.
- **Hepatitis:** All PIs can cause liver inflammation, though RTV has been more frequently associated with severe liver toxicity. Elevated liver enzymes can occur at any time during PI treatment.
- **Insulin resistance/ diabetes.** Insulin resistance occurs in up to 40% of patients treated with PIs, hyperglycaemia (high blood sugar), new cases of type 2 diabetes mellitus and worsening of pre-existing diabetes mellitus have also been reported.
- **Lipodystrophy**: is a long-term complication of PI therapy, which includes metabolic (hyperglycemia and hyperlipidemia) and morphologic abnormalities (fat atrophy and fat deposition). Changes in body fat distribution have been reported in as many as 80% of patients receiving PIs
- **Lipid abnormalities:** Most of the protease inhibitors, with the exception of unboosted atazanavir, are associated with significant lipid abnormalities, such as hypertriglyceridemia and hypercholesterolemia. This is particularly true of lopinavir/ritonavir.
- **Bleeding:** increased bleeding episodes have been reported in haemophilia type A and type B patients who are receiving PIs.

- **Electrocardiographic changes**: significant prolongation of PR interval and minimal QT interval prolongation and torsades de pointes have be reported with use of PI.
- **Bone disorders:** osteopenia, osteoporosis and osteonecrosis have been reported in adults and children on ART.However, it is not clearly associated with PIs.

IV. Integrase Inhibitors (INSTIs)

Antiretroviral under this class include:

- Dolutegravir(DTG) *****
- Raltegravir(RAL) *****
- Elvitegravir

** Included in the national ART guideline.*

Mechanism of action:

Integrase strand transfer inhibitors (INSTIs) block integrase (an HIV enzyme). Blocking integrase prevents HIV from replicating.

Dolutegravir (DTG)

Dolutegravir is included into the national comprehensive HIV prevention care and treatment guideline as the preferred first line ARV for adults and adolescents from the age of 10 and above except for women of childbearing age (<50 years) including pregnant and breast feeding women because of potential risk to the fetus. DTG is equivalent or superior to existing treatment regimens in both treatment-naïve and treatment-experienced patients including those with previous raltegravir or elvitegravir failure.

DTG Dosing and Key Pharmacokinetics

- **Adult dosing:** 50 mg once daily
- Bioavailability (F): absolute bioavailability of dolutegravir has not been established
- **Food interaction:** administered without regard to food.
- $T_{1/2}$: 13 to 14 hours
- Elimination: DTG is primarily metabolized via UGT1A1 with CYP3A4 as a secondary metabolic pathway. 53% percent of the total oral dose is excreted as unchanged DTG in feces. 31% of the total oral dose is excreted in urine.

Side Effects of DTG

- Common adverse events include headache, nausea, and diarrhea, trouble sleeping, tiredness, but the proportion with severe reactions (grade III or IV) is 1%.
- Serious side effects of dolutegravir include allergic reactions and liver problems.
- Changes in liver test results.
- Changes in body fat (including gain or loss of fat).
- Immune reconstitution inflammatory syndrome (IRIS)

Pregnancy category: B. Currently WHO doesn't recommend use of DTG for women of child bearing age (<50 years) including pregnant mothers because of potential risks to the fetus during pregnancy.

Drug interactions: DTG has drug interactions with other medications and nutritional products.

- Efavirenz and Nevirapine
- Antacids, calcium, iron supplements, Rifampin, Rifabutin

Class side effect of INSTIs

- Diarrhea, nausea, fatigue, headache, insomnia (common but mild)
- Skin reaction (rare but serious)

Raltegravir (RAL)

RAL is a potent and generally well tolerated ARV that plays an important role in the treatment of patients harboring resistance to other ARV and is recommended as potential 3rd-line option.

RAL Dosing and Key Pharmacokinetics

- **Adult dosing:** 400mg BID oral (no dose adjustment is required in renal and hepatic impairment)
- Bioavailability (F): absolute bioavailability has not been established
- **Food interaction:** may be taken without regard to meals
- $T_{1/2}$: approximately 7 to 12 hours
- Elimination: metabolized away via glucuronidation

Side Effects of RAL

- Diarrhea, nausea, and headache
- Dizziness, sleep problems (insomnia),
- Unexplained muscle pain, tenderness, or weakness. This may be a sign of a rare but serious muscle problem that can lead to kidney problems.
- Changes in the shape or location of body fat (especially in arms, legs, face, neck, breasts, and trunk).
- Serious side effects of raltegravir include skin reactions, allergic reactions, and liver problems.
- Immune reconstitution inflammatory syndrome (IRIS)

Pregnancy category: C

Drug interactions:

- RAL does not have the substantial drug-drug interaction potential of many other antiretroviral because it is metabolized by glucuronidation.
- Interactions have been reported with the following agents: Omeprazole, Rifampin, Tenofovir, Efavirenz, Atazanavir, Atazanavir/r, Darunavir/r, and Lopinavir/r

4.1.4 ARV drugs dose modification

Dosing recommendations for antiretroviral agents in patients with renal and hepatic impairment are often extrapolated from information about the structure, chemical characteristics, metabolism, and elimination of the drug in patients with normal organ function. Refer to the table below for dosing recommendations for renal or hepatic insufficiency.

Table 3: ART dosing recommendations for renal or hepatic insufficiency

ARV drug	**Dosing in renal impairment**		**Dosing in hepatic impairment**
CrCl(mL/min) Normal value – 75 – 125			
Nucleoside/-tide reverse transcriptase inhibitors			
Zidovudine (ZDV)	CrCl (mL/min)	Dose	No dosage recommendation
	<15 or HD	100 mg three times per day or 300 mg once daily	

<table>
<tr><td rowspan="6">Lamivudine (3TC)/</td><td>CrCl (mL/min)</td><td>Dose</td><td colspan="2" rowspan="6">No dosage adjustment necessary</td></tr>
<tr><td>30-49</td><td>150 mg Q 24 h</td></tr>
<tr><td>15-29</td><td>1 x 150 mg, then 100 mg Q 24 h</td></tr>
<tr><td>5-14</td><td>1 x 150 mg, then 50 mg Q 24 h</td></tr>
<tr><td><5 or HD</td><td>1 x 50 mg, then 25 mg Q 24 h</td></tr>
<tr><td colspan="2">Take dose after hemodialysis (HD) session on dialysis days</td></tr>
<tr><td rowspan="6">Tenofovir (TDF)</td><td>CrCl (mL/min)</td><td>Dose</td><td colspan="2" rowspan="6">No dosage adjustment necessary</td></tr>
<tr><td>30-49</td><td>300 mg Q 48 h</td></tr>
<tr><td>10-29</td><td>300 mg twice weekly</td></tr>
<tr><td><10 not on HD</td><td>No recommendation</td></tr>
<tr><td>HD</td><td>300 mg every 7 days</td></tr>
<tr><td colspan="2">Take dose after HD session on dialysis days</td></tr>
<tr><td rowspan="3">Abacavir (ABC)</td><td colspan="2" rowspan="3">No dosage adjustment necessary</td><td>Child-Pugh score</td><td>Dose</td></tr>
<tr><td>5-6</td><td>200 mg twice per day (use oral solution)</td></tr>
<tr><td>>6</td><td>Contraindicated</td></tr>
<tr><td colspan="5">Non-nucleoside reverse transcriptase inhibitors</td></tr>
<tr><td>Nevirapine (NVP)</td><td colspan="2">HD patients: limited data; no dosage recommendation</td><td colspan="2">Child-Pugh Class A: no dosage adjustment

Child-Pugh Class B or C: contraindicated</td></tr>
<tr><td>Efavirenz (EFV)</td><td colspan="2">No dosage adjustment necessary</td><td colspan="2">No dosage recommendation; use with caution in patients with hepatic impairment</td></tr>
</table>

<table>
<tr><td colspan="4">Protease inhibitors (PIs)</td></tr>
<tr><td>Lopinavir/ritonavir(LPV/r)</td><td>Avoid once daily dosing in patients on HD</td><td colspan="2">No dosage recommendation; use with caution in patients with hepatic impairment</td></tr>
<tr><td rowspan="4">Atazanavir(ATV)</td><td rowspan="4">No dosage adjustment for patients with renal dysfunction not requiring HD

ARV-naïve patients on HD: (ATV 300 mg + RTV 100 mg) once daily

ARV-experienced patients on HD: ATV or RTV-boosted ATV not recommended</td><td>Child-Pugh score</td><td>Dose</td></tr>
<tr><td>7-9</td><td>300 mg once daily</td></tr>
<tr><td>>9</td><td>Not recommended</td></tr>
<tr><td colspan="2">RTV boosting is not recommended in patients with hepatic impairment (Child-Pugh score ≥7)</td></tr>
<tr><td>Ritonavir(RTV)</td><td>No dosage adjustment necessary</td><td colspan="2">Refer to recommendations for the primary PI</td></tr>
<tr><td>Darunavir (DRV)</td><td>No dose adjustment for CrCl >30 ml/mi

Data not available for CrCl< 30ml/min</td><td colspan="2">No dose adjustment mild to moderate liver disease (Child-Pugh A and B).
Not recommended for severe liver disease (Child-Pugh C)</td></tr>
<tr><td colspan="4">Integrase inhibitors (INSTIs)</td></tr>
<tr><td>Raltegravir (RAL)</td><td>No dosage adjustment necessary</td><td colspan="2">No dosage adjustment necessary</td></tr>
<tr><td>Dolutegravir (DTG)</td><td>No dose adjustment</td><td colspan="2">No dose adjustment in mild to moderate liver disease (Child-Pugh A and B).
Not recommended for severe liver disease (Child-Pugh C).</td></tr>
</table>

Individual side effect drill exercise

- *Attach the side effect cards given to you on ARV medicines posted on the wall that most probably causing it.*

4.1.5 Role of Pharmacy Professionals

- Effectively manage and optimize pharmacotherapy for HIV-infected individuals.
- Provide medicines information on clinically oriented questions for both Health care providers and patients regarding ARVs
- Advise patients on appropriate dosing of ARVs regarding food.
- Counsel patients during initiation of ART on potential side effects and how to cope with them
- Monitors and identifying potential drug–drug interactions, and recommend for dose adjustment or prevent co-administration of contraindicated medications,
- Monitoring for the ART outcomes and potential side effects of ARV medicines.
- Pharmacist should involve in HIV treatment of key patient populations such as women (counsel patient on interactions between ART and contraceptives use), children (consider pharmacokinetic differences and antiretroviral agent–specific dosing recommendations), and selection of ARVs for patients with co morbid conditions or co infections (HBV, HCV).

4.1.6 Session Summary

- Antiretroviral cannot kill the existing virus; they can only prevent the production of new virus by blocking its replication.
- The classes of antiretroviral drugs are: (1) nucleoside reverse transcriptase inhibitors (NRTI), (2) non-nucleoside reverse transcriptase inhibitors (NNRTI), (3) protease inhibitors (PI), (4) fusion inhibitors (FI), (5) integrase inhibitors (INSTIs), (6) CCR5 inhibitors (MIs)
- ART may be associated with individual medicine induce or class related side effects
- Modification of ARV dosing is considered in patients with renal or hepatic impairment.

Case Studies

Case Study 1

A.B, a 25-year-old man, was tested for HIV because his wife tested positive in a prenatal clinic. He has seborrheic dermatitis and enlarged bilateral posterior cervical lymph nodes. He weighs 72 kg. He has felt well, and his physical exam is otherwise normal. His HIV antibody test was positive, and his CD4+ count was 140cells/mm^3. Other baseline laboratory tests were normal, and he was counseled to start antiretroviral therapy. He started cotrimoxazole prophylaxis six weeks ago and ART with ZDV, 3TC and NVP two weeks ago. This is his first follow-up visit and he reported perfect adherence and some itching of his skin. On his exam, he had mild diffuse erythematous macules on his torso, arms and legs.

1. What do you think is going on with A.B?
2. Which medicine (s) is most likely causing mild diffuse erythematous macules on his torso, arms and legs?

He was maintained on NVP based regimen but returned one week later due to worsening of rash. The rash has spread onto his palms and soles. Now he has developed life threatening rash.

3. What would you recommend this time for A.B.?

Three weeks later the fever resolved following discontinuation of NVP, rash and mucous membrane disease have healed.

4. How do you initiate ART for A.B at this time?

Case Study 2

A.R is 28-year-old HIV-infected man on first line ART (AZT/3TC/EFV) regimen for 4 years. The patient is admitted hospital for pneumonia. Now, his CD4 count of 266 cells/mm^3 and an HIV-1 RNA level of 92,000 copies/ml. Treatment failure was suspected, and he was started on the regimen ABC/3TC/LPV/r. Ten days later he calls complaining of mild flu-like symptoms. After discussing the situation with the patient, the medication is continued with a plan for close follow-up. During the next few days, the patient develops fever, malaise, nausea, and vomiting. He states that the symptoms are most prominent several hours after day after taking the medication in the morning and each day the symptoms seem to be getting progressively worse. Of note, the patient did not have an Human leukocyte antigen type B (HLA-B*5701) test performed prior to starting abacavir.

1. What is going on of therapy for A.R?
2. How the abacavir induced hypersensitivity reactions manifest?
3. Can we reuse ABC after the HSR have been corrected? If no, what are the potential problems following the re-challenging of ABC?

Case Study 3

K.W 35-year-old HIV-infected man with a CD4 count of 265 cells/mm^3 is started on his first antiretroviral regimen consisting of tenofovir-emtricitabine-efavirenz. His past history is notable for polysubstance abuse (in remission for the past year) and chronic hepatitis C virus infection. He takes his antiretroviral medication on an empty stomach at night before going to bed. One week after starting this regimen, he calls to complain that he is feeling dizzy and is having difficulty concentrating at work.

1. Which ARV medicine is causing dizziness and difficulty of concentrating in K.W?
2. Why was K.W taking ARV medications at night and empty stomach?
3. What information should be provided for K.W regarding these side effects?

Session 4.2: Monitoring and Management of ARV Drug Toxicities

Session Description:

This session starts by defining terminologies used in the management of ARV drug toxicities. It continues to explain the major types of ARV drug toxicities and the clinical as well as laboratory monitoring of toxicities and the management of these toxicities based on the human body organ system classification. Finally, the session concludes by pointing out the reporting requirements of adverse drug events related to ARVs.

Primary Objective:

The objective of this session is to introduce participants with grading the severity of ARV toxicities and the management of common side effects (and ADRs) of ARV drugs.

Enabling Objectives:

After completing this session, participants will be able to:

- List the types of ARVs drug toxicities
- Describe monitoring strategies for common drug toxicities
- Explain the management for the common drug toxicities
- Discuss what, when, by whom, and to whom to report adverse drug events (ADEs)
- List the role of pharmacy professional in monitoring and management of ADEs

Session Outline

- Introductory case and Learning objectives
- Types of ARV drug toxicities
- Clinical and laboratory monitoring for drug toxicities
- Management of common ARV toxicities
- ADE reporting
- Role of pharmacy professional
- Case studies
- Session Summary

Introductory case

S.M is a 32-year-old male who has been on AZT, 3TC, LPV/r and Cotrimoxazole 960 mg for the past 3 years. Six months ago, he began noticing body shape changes such as belly has gotten bigger, arms and legs are skinnier and his area on his upper back is starting to poke up. He believes that the changes are due to ARV medicines. Consequently, he started missing doses frequently. Four months ago, his CD4 count began dropping and his viral load went from undetectable to 45,000. Despite 3 months of enhanced adherence support and continuation of the regimen, his viral load has remained at 20,000. Therefore, his provider suspected treatment failure and switched to the following third line regimen two weeks ago. S.M began the following medications:

- Darunavir 600 mg plus ritonavir 100 mg orally twice a day
- Lamivudine 150mg BID
- Abacavir 300mg BID

Today he comes to the pharmacy with a rash on his extremities, back and trunk that started 3 days ago.

1. Which drug(s) would most likely cause lipodystrophy in S.M?
2. Which drug(s) might be responsible for the rash?
3. What management strategy would you suggest for the rash?

4.2.1 Introduction

Adverse effects have been reported with the use of all ARVs. Toxicities result in about 25% of patients discounting therapy in the first year and about 25% of patients also do not adhere to their regimen.

Operational definition of terminologies

Side effect

- Any unintended effect occurring at doses normally used in man and is related to the pharmacological properties of the drug.

Adverse reaction

- A noxious and unintended effect which occurs in doses normally used in man and may not be related to its pharmacological properties.

ARV toxicities:

- Indicate both the side effects and ADRS (not related to over dose of drugs)

4.2.2 Types of ARV drug toxicities

Large group discussion

How do you classify of ARV medicines toxicities?

The ARV drug toxicities are classified in to three types based on their onset, prevalence and severity

1. **Early Side Effects that are Uncomfortable for the Patient, But Not Dangerous**

(a) Common side effects, but do not cause danger to the health of the patient. These include nausea, headache, dizziness, diarrhea, feeling tired and muscle pain. Usually they occur when treatment begins and then improve within two to four weeks. The patient should be reassured that this will go away after some weeks. For example; efavirenz induced CNS toxicities will often resolve within the first 2 weeks after initiation of treatment.

(b) Less common and not serious side effects: It is not necessary (or advisable) to warn patients about these side effects. For example: AZT may cause blue nails.

2. **Early and Potentially Serious Side Effects:** These require emergency consultation. The patient needs to be warned about these potential side effects. For some, the patients need to seek care urgently if they occur. Examples are pallor (anemia—can occur with AZT),yellow eyes due to sick liver (hepatitis—can occur with NVP or EFV), severe abdominal pain and rash.
3. **Side Effects Occurring Later During Treatment:** These occur after the patient has been taking ARV drugs for several months or even years. Examples include abnormal distribution of body fat (lipodystrophy) and lactic acidosis.

4.2.3 Clinical and Laboratory Monitoring of ARV Drugs Toxicities

Monitoring of treatment is recommended more often at the beginning of a new HAART. Standard clinical evaluations include a thorough history of allergies, physical examination, measurement of vital signs and body weight. Routine laboratory investigations include a full blood count, liver, pancreas and renal function tests, electrolytes (plus phosphate in patients on tenofovir) as well as fasting cholesterol, triglycerides, and glucose levels.

Guiding principles of ARV toxicities:

- Establish whether the adverse event is due to ARV drugs, other drugs, or clinical illness.
- Try to identify the responsible ARV drugs
- Assess the severity using ACTG (AIDS Clinical Trial Group) grading system

Table 4: Clinical Grading of ARV toxicities

Item	**Grade 1** **Mild toxicity**	**Grade 2** **Moderate toxicity**	**Grade 3** **Severe toxicity**	**Grade 4: Severe life-threatening toxicity**
Cutaneous/Rash/ Dermatitis*	Erythema, pruritus	Diffuse, maculopapular rash or dry desquamation	Vesiculation or moist desquamation or ulceration*	Erythema multiforme or suspected SJS or Toxic Epidermal Necrolysis (TEN)
Diarrhea	3-4 loose stools a day or mild diarrhea lasting less than one week	5-7 loose stool a day or diarrhea lasting more than one week	Bloody diarrhea or over 7 loose stools a day or needing IV treatment or feeling dizzy when standing	Hospitalization required (possible also for grade 3)
Fatigue	Normal activity reduced by less than 25%	Normal activity reduced by reduced by 25-50%	Normal activity reduced by over 50%. Cannot work	Unable to care for yourself
Nausea	Mild or transient reasonable food intake	Moderate discomfort or intake decreased for less than 3	Severe discomfort or intake decreased for minimal food intake for more than 3 days	Hospitalization required

		days		
Vomiting	2-3 episodes a day or mild vomiting for less than one week	4-5 episodes a day or mild vomiting for more than one week	Severe vomiting of all food and fluids over 24 hours or needing IV treatment or feeling dizzy when standing	Hospitalization for IV treatment (possibly also for grade 3)
Mood disturbance	Mild anxiety, able to continue daily tasks	Moderate anxiety/disturbance, interfering with ability to work, etc	Severe mood changes requiring medical treatment. Unable to work	Acute psychosis, suicidal thoughts
MANAGEMENT	**Continue ARV** **Provide careful clinical monitoring** **Consider change of a single drug if condition worsens**		**substitute responsible drug**	**Stop ARV and consult experienced physician**

Table 5: Laboratory Grading of ARV Toxicities

Laboratory test abnormalities item	**Reference Range**	**Grade 1 toxicity**	**Grade 2 toxicity**	**Grade 3 toxicity**	**Grade 4 toxicity**
Hemoglobin	14 – 18 g/dL 12 – 16 g/dL	8.0-9.4 g/dL	7.0-7.9 g/dL	6.5-6.9 g/dL	<6.5 g/dL
Absolute Neutrophil Count		1,000-1,500 mm3	750-990 mm3	500-749 mm3	<500 mm3
Platelets	130,000 – 400,000	75,000- 99,000	50,000-74,999	20,000-49,999 mm3	<20,000
ALT	0 - 35 Unit	1.25-2.5 X ULN	2.5-5 X ULN	5.0-10 X ULN	>10 X ULN
Bilirubin	0.3 – 1.1m g/dl.	1-1.5XULN	1.5-2.5 X ULN	2.5-5 x ULN	>5 x ULN
Amylase/lipase	35 – 120 Unit	1-1.5XULN	1.5-2 X ULN	2-5 x ULN	>5x ULN
Triglycerides *	<160 mg/dL	200-399mg/dL	400-750 mg/dL	751-1200mg/dL	>1200mg/dL

Cholesterol (total)*	<200 mg/dL	1.0–1.3 X ULN	1.3-1.6 X ULN	1.6-2.0 X ULN	>2.0 X ULN
MANAGEMENT		**Continue ARV** **Repeat test 2 weeks after initial test and reassess**		**substitute responsible drug**	**Stop ARV and consult experienced physician**
		Lipid imbalances could be managed with diet, exercise and pharmacologically with the use of fibrates. **ALWAYS SEEK EXPERT ADVICE IN CASE OF DOUBT**			

Grade 1 (Mild reaction): are bothersome but do not require changes in therapy

Grade 2 (Moderate reaction): consider continuation of ART if feasible. If the patient does not improve in symptomatic therapy, consider single-drug substitution.

Grade 3 (Severe reaction): Substitute offending drug without stopping ART. Closely monitor using laboratory and clinical parameters.

Grade 4 (Severe life-threatening reaction): Immediately discontinue all ARV drugs, manage the medical event with symptomatic and supportive therapy, and reintroduce ARV drugs using a modified regimen (i.e. with an ARV substitution for the offending drug) when the patient is stabilized. Life-threatening toxicity includes severe hepatitis, pancreatitis, lactic acidosis or Steven-Johnson syndrome.

* For a patient on nevirapine, rash with mucosal involvement or associated with fever and/or systemic symptoms, and/or derangement in liver functions should be treated as Grade 4 toxicity.

4.2.4 Management of Common ARV Drug Toxicities

Small Group discussion and presentation

Discuss on the side effect assigned to your group and take note of main points on flip chart for large group discussion

1. Management of Gastrointestinal Related Side Effects

Gastrointestinal (GI) problems are the most common side effects of almost all ARVs drugs. These include **nausea, vomiting, diarrhea, abdominal discomfort, loss of appetite**. They are mainly associated with **NRTIs and most PIs** especially during initiation of ART. Patients should be informed that these side effects usually resolve after four to six weeks of treatment.

a. ***Nausea and Vomiting*****:** Nausea is a common symptom associated with AZT. Treatment with AZT rarely leads to a severe form of gastric pain, nausea and vomiting in the early phase of therapy, in which case it should be discontinued.

- Non-pharmacologic management includes
  - Taking AZT with meal reduces the risk of nausea and vomiting
  - Ginger, peppermint or chamomile teas or sweets may also be helpful, as well as frequent small meals.
  - Care should be taken with fatty foods and dairy products.
  - Coffee, smoking, alcohol, aspirin and very spicy foods should be avoided if possible
- Pharmacologic management
  - For symptomatic treatment, metoclopramide is useful.
  - Dimenhydrinate or ondansetron can also be used.
- If nausea persists for more than two months, a change of treatment should be considered.

b. **Diarrhea:** Diarrhea occurs frequently with AZT and all PIs, particularly with lopinavir and nelfinavir. Other causes such as gastrointestinal infections or lactose intolerance should be excluded.

- Non-pharmacologic management
  - The priority is to treat dehydration and loss of electrolytes.
  - Difficult to digest foodstuffs (particularly those rich in fats or glucose) should be avoided and those that are easy to digest (e.g. potatoes, rice, noodles) are recommended.
  - Avoid spicy, fatty, starchy, or processed foods, caffeine, alcohol, dairy products, and foods that give you gas.
- Pharmacologic management
  - PI-associated diarrhea can also be managed by calcium, taking calcium carbonate, at a dosage of 500 mg bid (taken 2 hours apart from ARVs)
  - Symptomatic treatment consists of loperamide (initially 2 - 4 mg, followed by 2 mg, up to a maximum of 16 mg daily).

2. Management of Hepatotoxicity

Hepatotoxicity is common and is associated with most antiretroviral agents. Severe hepatotoxicity occurs in up to 6% of patients on ART, but liver failure is rare. It is commonly associated with NRTIs (D4T and DDI), **NNRTIs (**NVP >efavirenz), **PIs** (Full-dose ritonavir), and **INSTIs** (DTG). The patients may present with signs or symptoms of hepatitis (anorexia,

malaise, jaundice, nausea, vomiting, bilirubinemia, hepatomegaly, and hepatic tenderness). Other constitutional symptoms may include fever, arthralgia, fatigue, and other findings or generalized organ dysfunction.

Who are at higher risk for ARV- induced hepatotoxicity?

- Baseline elevated serum aminotransferases,
- Chronic hepatitis B or C co-infection
- Concomitant hepatotoxic medication,
- History of alcohol abuse
- Protease inhibitor therapy,
- Thrombocytopenia and renal insufficiency.
- Female gender and baseline High CD4 count (NVP induced hepatotoxicity)
    - Women with CD4 count >250 cells/dl
    - Men with CD4 count>400cells/dl

When is hepatotoxicity expected?

- **NNRTIs** especially nevirapine often cause hypersensitivity reaction within the first 12 weeks**.**
- **NRTIs** lead to hepatic steatosis; which occurs after more than 6 months on treatment.
- **PIs** cause hepatotoxicity at any stage of treatment
- **INSTIs** – One of serious DTG adverse effects is abnormal liver function, particularly in patients with HBV or HCV coinfection.

a. Monitoring and Managing NVP-induced hepatotoxicity

Liver toxicity occurs usually early during therapy with greatest risk in the first 6 weeks of therapy. However, monitor closely for the first 18 weeks of treatment. Asymptomatic elevated AST/ALT > 5x ULN occurs in up to 8.8% but symptoms are observed in 4% of patients taking NVP. About half of these cases were associated with rash.

Monitoring for Hepatitis involves checking LFTs at baseline, 2 weeks, 4 weeks, 3 months and every 6 months. Check for HBV or HCV at baseline. Check LFTs if a patient presents with

hypersensitivity reaction. If severe skin reactions or other hypersensitivity signs occur with hepatotoxicity, then discontinue NVP and seek medical attention immediately.

b. Management of Atazanavir induced Hepatotoxicity

Atazanavir causes hyperbilirubinemia due to inhibition of hepatic enzyme UDP-glucuronosyl transferase. However, the levels of bilirubin return to normal following discontinuation of the drug. If bilirubin is mildly elevated (< 3X ULN) and the serum liver enzyme levels are normal, treatment change is not mandatory. If the bilirubin is constantly elevated, the drug should be discontinued.

3. Management of Renal problems (nephrotoxicity)

Tenofovir use has been associated with renal insufficiency, particularly in older patients with underlying renal disease, long-term diabetes, or uncontrolled hypertension. Renal toxicity occurs after some months, rarely at the beginning of therapy. Other risk factors include relatively high TDF exposure, low body weight, and co-administration of nephrotoxic drugs.

- Do not initiate TDF when the estimated GFR <50 ml/min, or in long-term diabetes, uncontrolled hypertension, and renal failure.
- Renal function tests including serum creatinine, urea or Blood urea nitrogen, creatinine clearance (CrCl), proteinuria, glycosuria, blood and urine phosphate should be checked.
- In case of renal dysfunction, especially in patients with low body weight, avoid tenofovir if possible, or made dose adjustment based on CrCl.

4. Management of AZT Induced Hematological toxicities

AZT is myelosuppressive causing neutropenia and macrocytic anemia. Anemia generally occurs during the first 6 months of AZT therapy and may be completely asymptomatic or symptomatic with fatigue or dyspnea. Risk factors include advanced HIV infection, pre-existing myelosuppression, chemotherapy or co-medication with other myelotoxic drugs such as pyrimethamine, amphotericin B, ribavirin, and interferon.

- Zidovudine should be discontinued in severe cases and a **blood transfusion** may be necessary.
- Change AZT to less myelotoxic drugs

- If there are no options to change, **erythropoietin is an option**, but should be avoided as a long-term option if possible, due to the associated high costs.
- Due to **drug-induced neutropenia**, despite viral suppression, the CD4+ T-cell count may remain low after an initial rise.
    - Change the treatment to less myelotoxic ARVs such as TDF, ABC & 3TC, most of the PI and all NNRTIs.
    - AZT should be avoided.

5. Management of Hypersensitivity Reactions

Although virtually any drug can cause a hypersensitivity syndrome, it is common with

- **NRTIs**: Abacavir (5-8%),
- **NNRTI:** Nevirapine (15 to 20 %, discontinuation in 5 to 10 %) and less frequently on efavirenz therapy, where only 2 % of the patients discontinue the drug.
- **PIs:** Atazanavir (6 % in patients and is usually mild)
- **INSTIs:** Raltegravir (4.3% discontinuation of therapy). Doultegravir (3.6% discontinuation of therapy)

a. Management of NNRTIs induced HSR

Approximately 50 % of NNRTI allergies resolve despite continuation of therapy. Treatment should be discontinued immediately in cases with:

- mucous membrane involvement, blisters and exfoliation
- Hepatic dysfunction (transaminases > 5 times ULN) or fever > 39°C.

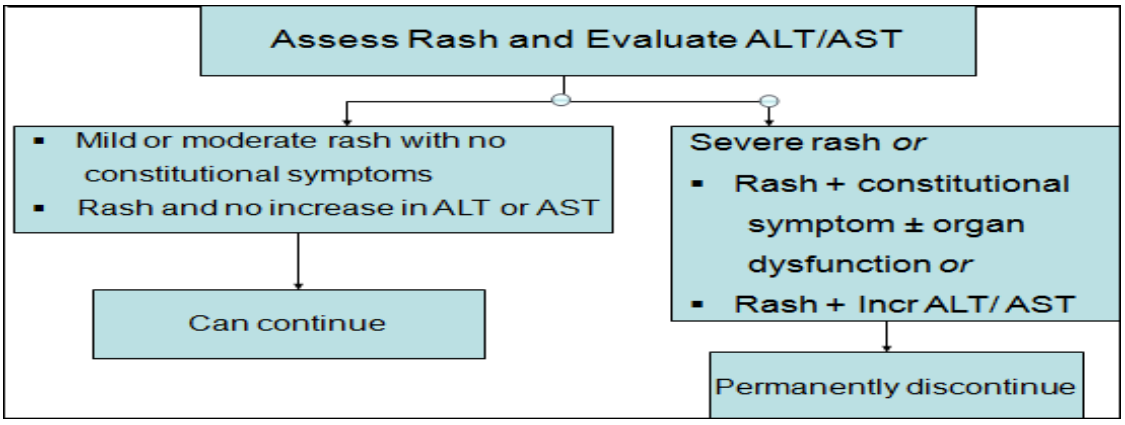


Figure 12: Management algorithm for NVP-induced hypersensitivity reaction

- If patients present with a suspected NVP -associated rash, hepatotoxicity should be looked for and LFTs should be performed. Patients with rash-associated AST or ALT elevations should permanently discontinue NVP.
- **Antihistamines** may be helpful. However, prophylactic treatment with glucocorticosteroids or antihistamines has been shown to be of no benefit for the prevention of nevirapine HSR.

b. Management of ABC induced HSR

- ABC induced HSR typically presents with a combination of symptoms including **fever** (which is almost always present), **constitutional symptoms** (eg, malaise, dizziness, and headache), and **gastrointestinal disturbances** (eg, nausea, vomiting, diarrhea). Respiratory symptoms (eg, dyspnea, cough, sore throat) occurred in approximately one-third of patients.
- Rash is often a late symptom that is absent in up to 30% of patients. Most HSR (90%) occur within the first 6 weeks and the median onset is 7-8 days.
- Exclusion of Human leukocyte antigen type B (HLA-B*5701) individuals from ABC treatment could largely prevent HSR.
- If ABC is discontinued in time, the HSR is completely reversible within a few days.
- Following discontinuation of ABC, further supportive treatment includes, intravenous hydration and possibly steroids therapy
- **NEVER re-challenge ABC again.** Re-challenge to abacavir after an initial HSR can result in a more rapid, severe, and potentially life-threatening anaphylactic reaction
- Treatment with abacavir requires detailed counseling (and documentation) on the possible occurrence and symptoms of the HSR.
- It is difficult to differentiate HSR due to ABC or NNRTIs. Therefore, synchronous initiation of ABC and NNRTIs should generally be avoided if possible.

c. Management of RAL induced HSR

- Advice patients to immediately stop taking RAL and contact health care provider right away if they develop a rash with any of the following symptoms. Fever, general ill feeling, extreme tiredness, muscle or joint aches, blisters or sores in mouth, blisters or peeling of skin, redness or swelling of eye, face or mouth swelling, trouble breathing.

6. Management of neurological side effect

CNS toxicities such as dizziness, insomnia, nightmares, mood fluctuations, depression, depersonalization, paranoid delusions, confusion, and suicidal ideation are mainly associated with EFV in first days and weeks of treatment. They can occur rarely with 3TC and ABC.

- Reassure the patient that they will go away with continued EFV therapy
- Avoid administration of EFV with fatty meal
- Discontinuation of therapy becomes necessary in only 3 % of patients. If the CNS side effects persist for more than two to four weeks,
  - The dose of Efavirenz can be divided into a 400 mg at night and a 200 mg in morning.
  - Lorazepam can diminish the CNS side effects, and haloperidol can be given for panic attacks and nightmares. But lorazepam and haloperidol should be restricted to severe cases, because of their side effects and addictive potency.
  - Give due attention to mental health on patients taking ARVs

7. Management of Mitochondrial Toxicity

- The clinical presentation of mitochondrial toxicity depends on the target organ that is involved.
- Mitochondrial toxicity is the major cause of NRTIs induced myopathy, neuropathy, lipoatrophy, and lactic acidosis.

NRTI induced Lactic Acidosis:

- Lactic acidosis mostly occurs with stavudine and didanosine but less often with zidovudine, abacavir and lamivudine.
- Lactic acidosis usually follows a minimum of six months of treatment. Nowadays lactic acidosis is not a clinical problem since d-drugs are no longer in use.
- If incase it occurs, management of hyperlactatemia and lactic acidosis involves discontinuation of NRTI treatment and initiating supportive treatment such as correction of the acidosis.
- Mortality of patients with lactate levels above 10 mmol/l is approximately 80%.
- Agents used for treatment of congenital mitochondrial disorders may hasten recovery (thiamine, riboflavin, coenzyme Q, L-carnitine).

Lipodystrophy:

- Is characterized by peripheral, subcutaneous lipoatrophy in the face, arms, legs and buttocks and central fat accumulation in the neck, breasts, and abdomen (referred to as lipohypertrophy). It results in body shape abnormalities (abdominal girth & buffalo hump).
- Risk factors include increasing age, female sex, amount of body fat, and longer duration of ART (which may be a surrogate for longer duration of HIV infection. Weight-bearing exercise to maintain muscle mass and diet can be beneficial to prevent and treat lipodystrophy.

8. Management of insulin resistance

- Insulin resistance is mostly associated with PIs (40%). Hyperglycemia (3-17%), new cases of diabetes mellitus (1%) and worsening of preexisting diabetes has also been reported.
- Therefore, patients receiving PIs should be advised about the warning signs of hyperglycemia, such as excessive thirst, excessive urination, and excessive appetite. Hyperglycemia resolves in some but not all patients after the discontinuation of PI based therapy.
- Switching from PI-based regimens often allows improvement however, most experts, would continue ART with supportive therapy (oral hypoglycemic drugs or insulin) in the absence of severe diabetes.

9. Management of lipid abnormalities

It has been linked to treatment with all the **PIs** (higher with ritonavir). Rises in cholesterol and triglycerides may put someone at increased risk of heart disease particularly if they smoke or overweight or have high blood pressure. Lipid abnormalities are generally **treated with fibrates and/or statins.** However, beware of drug interactions between ART, statins, and fibrates that may lead to risk of myositis.

10. Management of bone disorders

a. Avascular necrosis

- Avascular necrosis is death of bone tissue due to a lack of blood supply. Avascular necrosis most often affects the head of the thighbone (femur), causing hip pain.

- Risk factors for avascular necrosis are alcohol abuse, hyperlipidemia, steroid treatment, hypercoagulability, hemoglobinopathy, trauma, nicotine abuse and chronic pancreatitis.
- Identify risk factors and take measure to eliminate. Once the diagnosis is confirmed, refer patients to an orthopedic surgeon.
    - Physiotherapy, rest and sometimes surgery are recommended.
    - Bisphosphonate medications, such as alendronate and
    - Nonsteroidal anti-inflammatory drugs (e.g. ibuprofen) are the treatment of choice for analgesia.

b. Osteopenia/Osteoporosis

- Treatment with PIs (boosted) and NRTIs lower bone density in patients in addition to HIV infection itself.
- Other factors such as malnutrition, diminished fat tissues, steroid treatment, hypogonadism, and immobilization can induce osteopenia/osteoporosis.
- Osteopenia and osteoporosis are often asymptomatic. Thus, it is reasonable to screen patients with numerous risk factors for osteopenia with Dual Energy X-ray absorptionometry.
- Preventive measures (such as physical exercise, sufficient ingestion of calcium and vitamin D) and elimination of risk factors (such as alcohol, tobacco, and poor diet) are warranted.
- Osteopenia should be treated with vitamin D daily and a calcium-rich diet or calcium tablets with a dose of 1200 mg/day.
- In cases with osteoporosis, Bisphosphonates such as alendronate treatment for 48 weeks increased bone mass density
    - ✓ Tablets should be taken on an empty stomach 30 min before breakfast, and an upright position should be maintained for at least 30 min.
    - ✓ No calcium should be taken on this day.
- Since testosterone suppresses osteoclasts, hypogonadism should be treated.

Table 6: Types of toxicities associated with first-, second- and third-line ARV drugs

ARV drug	**Major types of toxicity**	**Risk factors**	**Suggested management**
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 allele	Do not use ABC in the presence of HLA-B*5701 allele.

			Substitute with AZT or TDF.
ATV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome	Use with caution in people with pre-existing conduction disease or who are on concomitant drugs that may prolong the PR or QRS intervals.
	Indirect hyperbilirubinaemia (clinical jaundice)	Presence of uridine diphosphate (UDP)-glucuronosyltransferase 1A1*28 (UGT1A1*28) allele	This phenomenon is clinically benign but potentially stigmatizing. Substitute only if adherence is compromised.
	Nephrolithiasis	History of nephrolithiasis	Substitute with LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider substituting with integrase inhibitors.
AZT	Severe anaemia, neutropaenia	CD4 cell count of ≤200 cells/ mm3	Substitute with TDF or ABC. Consider use of low-dose zidovudine *(405)*.
	Lactic acidosis or severe hepatomegaly with steatosis Lipoatrophy Lipodystrophy Myopathy	BMI >25 (or body weight >75 kg) Prolonged exposure to NRTIs	Substitute with TDF or ABC.
DTG	Hepatotoxicity Hypersensitivity reactions	Hepatitis B or C coinfection Liver disease	If DTG is used in first-line ART, and there are hypersensitivity reactions, substitute with another therapeutic class (EFV or boosted PIs).
DRV/r	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	Substitute with ATV/r or LPV/r. When it is used in third-line ART, limited options are available. For hypersensitivity reactions, substitute with another therapeutic class.
	Severe skin and hypersensitivity reactions	Sulfonamide allergy	

EFV	Persistent central nervous system toxicity (such as dizziness, insomnia, abnormal dreams) or mental symptoms (anxiety, depression, mental confusion)	Depression or other mental disorder (previous or at baseline)	For CNS symptoms, dose at night-time. Consider using EFV at a lower dose (400 mg/ day) or substitute with NVP or integrase inhibitor (DTG) if EFV 400 mg is not effective in reducing symptoms. For severe hepatotoxicity or hypersensitivity reactions, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
	Convulsions	History of seizure	
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	
	Severe skin and hypersensitivity reactions	Risk factor(s) unknown	
	Gynaecomastia	Risk factor(s) unknown	Substitute with NVP or another therapeutic class (integrase inhibitors or boosted PIs).
LPV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome Hypokalaemia	Use with caution in people with pre-existing conduction disease or those on concomitant drugs that may prolong the PR or QRS intervals
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	If LPV/r is used in first-line ART for children, substitute with NVP or RAL for children younger than 3 years and EFV for children 3 years and older. ATV can be used for children older than 6 years. If LPV/r is used in second-line ART for adults, and the person has treatment failure with NNRTI in first-line ART, consider integrase inhibitors.

	Pancreatitis	Advanced HIV disease, alcohol misuse	
	Dyslipidaemia	Cardiovascular risk factors such as obesity and diabetes	Substitute with another therapeutic class (integrase inhibitors).
	Diarrhoea		Substitute with ATV/r, DRV/r or integrase inhibitors.
NVP	Hepatotoxicity Severe skin rash and hypersensitivity reaction, including Stevens-Johnson syndrome	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs High baseline CD4 cell count (CD4 count >250 cells/mm3 in women or >400 cells/mm3 in men)	If hepatotoxicity is mild, consider substitution with EFV, including in children 3 years and older. For severe hepatotoxicity and hypersensitivity, and in children under the age of 3 years, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
RAL	Rhabdomyolysis, myopathy, myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis, including statins	Substitute with another therapeutic class (etravirine, boosted PIs).
	Hepatitis and hepatic failure Severe skin rash and hypersensitivity reaction	Risk factors unknown	
TDF	Chronic kidney disease Acute kidney injury and Fanconi syndrome	Underlying renal disease Older than 50 years of age BMI <18.5 or low body weight (<50 kg) notably in females Untreated diabetes Untreated hypertension Concomitant use of nephrotoxic drugs or a	Substitute with AZT or ABC. Do not initiate TDF at eGFR <50 mL/min, uncontrolled hypertension, untreated diabetes, or presence of renal failure.

		boosted PI	
	Decreases in bone mineral density	History of osteomalacia (in adults) and rickets (in children) and pathological fracture Risk factors for osteoporosis or bone mineral density loss Vitamin D deficiency	
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity Liver disease	

ABC abacavir, ATV atazanavir, AZT zidovudine, CNS central nervous system, DRV darunavir, DTG dolutegravir, EFV efavirenz, eGFR estimated glomerular filtration rate, HBV hepatitis B virus, HCV hepatitis C virus, LPV lopinavir, NNRTI non-nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r ritonavir, RAL raltegravir, TDF tenofovir.

4.2.5 Adverse Drug Event Reporting

What, when, why, by whom, and to whom should adverse drug events be reported?

Demonstration of FMHACA ADE reporting Forms (annex 4.2.1)

Spontaneous reporting is a system whereby case reports of adverse drug events are voluntarily submitted by health professionals and pharmaceutical manufacturers to the national regulatory authority/ pharmacovigilance center **(FMHACA).**

To promote medicines safety, any suspected ADRs, medication errors or quality defects should be reported as **soon as possible** after all relevant information is compiled. Reports can be sent either via:

- The yellow, prepaid report form available at the facility **(Annex 3)**
- Telephone 01115523142 (direct) or 0115524122 (via operator) or 8482 (toll free line)
- Download report form from website www.fmhaca.gov.et. and send via email regulatory@fmhaca.gov.et.

Adverse drug events to be reported

- The direct pharmacological mechanism of a medicine
- An individual's particular vulnerability
- Drug interactions
- Unexpected therapeutic ineffectiveness (e.g. resulting from drug interactions, product quality problems or antimicrobial resistance)
- Medication errors
- Product quality defects
- A malfunction or deterioration in the characteristics or performance of in-vitro diagnostic device
- False positive or false negative test result falling outside the declared performance of the test.

The reporter does not need to prove that there is a causal association between drug and adverse reaction. Therefore, uncertainty of the cause and effect relationship should not be a reason for not reporting

Why should we report ADEs? Advantages of ADE reporting

In clinical trials medicines will only have been tested for short-term safety and efficacy on a limited number of carefully selected individuals (not more than 5000 people). Therefore, it is essential that new treatments are monitored for their effectiveness and safety under real-life conditions post release in large general population. Spontaneous ADE reporting is inexpensive method for addressing safety and efficacy in general population. In addition, ADE monitoring and reporting is important to determine safety and efficacy:

- in specific populations (elderly, pregnant women and children)
- with chronic use
- in combination with other medicines and food

4.2.6 Role of Pharmacy Professionals

- Pharmacist plays a significant role monitoring and managing ARV toxicities with MDT.

- Advise patients about medication toxicities, how to prevent or control them and when to seek medical assistance.
- Provide drug information on the ARVs medicines toxicities to patients and health care providers.
- Involve in the management of encountered toxicities with MDT. Recommends the appropriate care to patients suffering from toxicities.
- Recommend dosage adjustment in renal and hepatic dysfunction
- Handle and dispense medications for management of ARVs drug toxicities
- Monitor and report any adverse drug events associated with ARVs and related medicines to regulatory body (FMHACA).

4.2.7 Session Summary

- Side effects are among the most common reasons cited for switching or discontinuing ART and for medication non-adherence. Toxicities result in about 25% of patients discounting therapy in the first year and about 25% of patients also do not adhere to their regimen.
- ARV drug side effects are classified in to three: (1) early side effects that are uncomfortable for the patient, but not dangerous. (2) Early and potentially serious side effects. (3) Side effects occurring later during treatment.
- The management of ARV side effects is categorized into: gastrointestinal, hepatic, renal, neurological, CNS, hematologic, hypersensitivity, mitochondrial, insulin resistance, lipid abnormalities, and bone disorders.
- ARV toxicities are managed based on ACTG grades of severities. The side effects of some ARVs will go away with continuation of therapy, while others may require a dose modification or a change in the antiretroviral regimen
- Adverse drug events due to ARVs should be recorded and reported to the regulatory authority in a timely manner.
- Pharmacist plays a significant role in identifying and managing ARV toxicities.

Case studies

Case study 1

Y.M is a 38-year-old male who has been on NVP+ZDV+3TC combination tablet for 5 months. Today he came to your ART pharmacy for refill. When you asked him how he is doing with treatment, he reports that he has become very tired in the last two weeks. In fact, he has missed 4 days of work in the past 2 weeks because he just couldn't get out of bed. He also has felt nauseated on and off ever since he started the medications. He believes these changes are a result of his antiretroviral medications; therefore, he has begun missing doses.

1. What do you think is going on with Y.M.?
2. What drug(s) might be responsible for his fatigue?
3. Do you need any additional information to know the cause of the problem(s)?

Based on the assumption you discussed with physician to order hematologic tests, the result was Hgb = 7.2 and his Hct = 20%. He says that he eats food before some of his doses, but not all the time. Usually he takes the dose with a piece of injera. He hasn't tried anything else to control the nausea.

4. How severe (grade of severity) is Y. M's anemia?
5. What management strategy would you suggest?

Case study 2:

HD is 40-year-old HIV-infected man with chronic hepatitis B virus infection on first line regimen for 3 years, currently his CD4 count dropped to of 180 cells/mm^3, and an HIV-1 RNA level raised to 91,630 copies/ml. hence he was changed to TDF/3TC/ATV/r regimen. One month after starting the new regimen, he returns and states that he feels well, but has noticed that his eyes are look yellow. The physical examination shows jaundice and scleral icterus. Laboratory studies show a hematocrit of 41%, normal lactate dehydrogenase (LDH), normal haptoglobin, and no significant changes in chemistry panel, except for an increase in the baseline total bilirubin of 1.1 to 4.8 mg/dl.

1. Which drug (s) is/are mainly associated with hyperbilirubinemia?
2. At what grade of severity is his hyperbilirubinemia?

3. How do you manage this patient's hyperbilirubinemia?

Case study 3

A 59-year-old Ethiopian HIV-infected woman presents for a routine follow-up visit. She started antiretroviral therapy three years ago with tenofovir-lamivudine-efavirenz. She smokes cigarettes, has a body mass index (BMI) of 19, and has coinfection with hepatitis C. On routine laboratory testing on sixth month of therapy, her HIV RNA is undetectable, serum creatinine has increased from 0.9 to 2.4, and urinalysis demonstrates new proteinuria (Hint: Normal Serum Cr is 0.6 - 1.2)

1. Which drug (s) is potentially causing her renal test abnormalities?
2. What are the risk factors for developing nephrotoxicity in this patient?
3. What is the recommend management for this patient?

Session 4.3: Significant Drug Interactions with ART

Session Description

This session deals with significant drug interactions with antiretroviral therapy. It starts with definition of drug interaction and its mechanism. It then discusses significant drug interactions with individual ARVs and their management in detail.

Primary objective:

The purpose of this session is to introduce participants to common ART drugs interactions and their management.

Enabling Objectives:

By the end of this session trainees should be able to:

- Explain basic drug interaction concepts
- Describe mechanisms of interactions
- Identify significant drug interactions commonly encountered with antiretroviral drugs
- Discuss the management of known drug interactions
- List the role of pharmacy professionals in managing drug interaction

Session outline

- Introductory case
- Introduction to concepts of Drug Interactions
- Significant drug interactions with ARVs and their Management
- Systematic approach to manage drug interactions
- The Role of a Pharmacy professional in Drug Interactions
- Case studies
- Session Summary

Introductory Case (Paired Reading)

AT, a 25-year-old HIV + woman comes to your pharmacy with prescriptions for her routine therapy of Phenytoin and Co-trimoxazole. Her recent lab results indicate that her CD_4 level is 250 and she is going to begin treatment with ART. Today she is given prescriptions for the first line regimen: Tenofovir, Lamivudine and Efavirenz. Which of the following statements is true about possible interactions between these medications?

A. There is no interaction between ART and phenytoin. They can safely be administered together.
B. An interaction exists between phenytoin and Efavirenz. The dose of Efavirenz must be increased to account for increased metabolism due to phenytoin.
C. Efavirenz may increase phenytoin levels and therefore the dose of phenytoin may need to be decreased to avoid toxicity.
D. An interaction exists between phenytoin and Co-trimoxazole. They should not be administered together.

i. Introduction to concepts of drug interactions

Individual Reading and Q&A

1. What is a drug interaction?
2. Why are HIV/AIDS patients at risk to drug interactions?
3. What are the two most common mechanisms of drug interactions?
4. Have you encountered a drug interaction? What type of interaction happened? What were the clinical consequences of the interaction?

A **drug interaction** is a change of activity of one drug arising from the concomitant application of another drug or from the concomitant intake of food or herbs. ARV drugs used in the treatment of HIV are often prone to drug interactions because many of them are metabolized through the CYP450 system. Increased longevity in HIV positive patients and the fact that many HIV positive patients are on concurrent non-antiretroviral treatments for co-morbid conditions puts ART patients at risk of drug interactions.

In general, beware that: A drug interaction can occur: • Whenever a new medication is started • Whenever a medication is discontinued • Whenever a dose is changed	ATTENTION: • Inducing interactions o Gradual onset/offset • Inhibiting interactions o Quick onset/offset

Drug-drug interactions can result in a therapeutically desired effect, a negative drug-interaction, a new side effect of a drug, or no consequence at all.

1. Some interactions increase beneficial effects (eg. ritonavir + lopinavir). NB: All first line and second line treatment regimens are combined to give beneficial effect
2. Some interactions increase harmful effects (eg. ritonavir + simvastatin)
3. Some interactions decrease therapeutic effects (eg, rifampicin + protease inhibitors, rifampicin + coumadin anticoagulant).
4. Some interactions may result in a new effect not previously observed with either drug alone (e.g. ritonavir + amitriptyline; the interaction can possibly cause a new side effect: cardiac arrhythmia.
5. Some interactions have unclear clinical significance (e.g. TDF & ritonavir)

Mechanism of drug Interactions:

The mechanism of the drug interaction may be pharmacokinetic (PK) or pharmacodynamic (PD) in nature.

Pharmacokinetic interaction:

Pharmacokinetic interactions occur when one drug alter the absorption, distribution, metabolism, or excretion of another, thus increasing or reducing the amount of drug available to produce its pharmacological effects.

The most common mechanisms of **PK interactions** are:

1. PK Interactions Affecting Drug Absorption: The extent of oral absorption of drugs can be affected by changes in gastric pH, complexation or chelation,

2. PK Interactions Affecting Hepatic Metabolism: Two major enzyme systems namely the cytochrome P450 enzyme system and Uridine diphosphate (UDP)-glucuronosyltransferase (UGT) enzyme system are most frequently responsible for clinically significant drug interactions.

Pharmacodynamic Interactions:

PD drug interactions result in:-

- Additive effects or synergistic interactions: It may be **desired**: e.g. sulfonamides and trimethoprim; NRTIs plus PIs or NNRTIs; or **not desired**: e.g. bone marrow toxicity caused by ganciclovir and AZT.
- Antagonistic effects: Concurrent therapy leads to reduced drug effect for both drugs, e.g. salbutamol and B-blockers.

4.3.2 Significant drug interactions with ARVs and their management

NRTIs Drug Interactions

In this class both PD (mainly additive and antagonistic effect) and PK (predominantly absorption and elimination) interactions occur.

1. **Zidovudine (AZT)**: if it is combined with agents that cause bone marrow suppression (i.e. flucytosine, ganciclovir, ribavirin and peg-interferon alfa-2a,), there will be additive bone marrow toxicity. WHO recommends substituting AZT with TDF if these agents are going to be used.

- Drugs that may increase AZT concentrations as a result of glucuronosyltransferase (UGT) inhibition (and therefore potential toxicity) are probenecid, atovaquone, methadone, valproic acid, Phenytoin and fluconazole. The recommendation is to monitor for signs of zidovudine toxicity.
- Clarithromycin, Rifampicin, and Phenobarbital may reduce AZT concentration.

2. **Abacavir (ABC)** is metabolized by alcohol dehydrogenase, therefore alcohol can increase abacavir levels and toxicity. No disulfiram reaction noted, no change in alcohol pharmacokinetics, but 41% increase in ABC AUC (not clinically significant).
3. **Tenofovir (TDF):** Use of TDF should be avoided with concurrent or recent use of a nephrotoxic drugs. Some examples include, but are not limited to, aminoglycosides,

amphotericin B, ganciclovir, pentamidine, vancomycin or interleukin-2. Closely monitor renal function for patients taking TDF and a ritonavir boosted protease inhibitor.

NNRTIs and PIs drug interaction

Drug interactions in these classes of drugs are very common problem and interactions occur mainly during metabolism by CYP450 system.

NNRTIs and PIs (particularly RTV, even at low doses) interact with the cytochrome P450 enzyme system, resulting either in the inhibition or induction of these enzymes.

Remember: Inducing interactions have gradual onset/offset and inhibiting interactions have quick onset/offset.

NNRTIs	**Efavirenz (EFV)**	**Nevirapine (NVP)**
Substrate	• CYP3A4, CYP2B6	• CYP3A4, CYP2B6
Inducer	• CYP3A4 (moderate), CYP2B6, CYP2C9/19, UGT1A1	• CYP3A4(strong), CYP2B6, CYP2C9
Inhibitor	• CYP 3A4, CYP1A2, CYP2C9/19	

PIs

Protease Inhibitors (PIs) are often complicated by drug interactions because each is a strong inhibitor of the CYP3A4.

The strongest inhibitor of CYP3A4 is Ritonavir (RTV), followed by amprenavir, atazanavir, lopinavir, indinaivr, nelfinavir and saquinavir. ritonavir also exhibits inhibition of CYP2D6.

Pharmacokinetics Enhancement (Boosting): Pharmacokinetic rationale for dual PI therapy

Pharmacokinetic (PK) enhancement is the concept of combining agents to improve ARV pharmacokinetics, instead of high peaks and low troughs, allows lower peak concentrations to protect against toxicity and higher trough concentrations to maintain efficacy.

(e.g RTV alone at the approved 600 mg bid dose is the least well tolerated PI than RTV 100mg when used as booster with LPV 400mg).

Table 7: Common NNRTIs/PI drug interactions with HIV-related medications classification

Definite drug interactions	**Probable drug interactions**	**Possible drug interactions**
• Rifampicin • Statins • Erectile dysfunction agents • Methadone	• Antidepressants • Oral contraceptives • Warfarin • Proton pump inhibitors or H-2 blockers & ATV • Macrolids	• Herbal products (except in the case of St. John's wort) • Antifungal agents • Anticonvulsants • Benzodiazepines
Comment • High Level of Evidence • Well understood clinical significance • Consensus exists regarding the management strategy	*Comment* • Limited Level of Evidence • Significance not clearly established • Management strategy based on clinical judgment	*Comment* • Theoretical evidence is available • Significance not clearly established • Management strategy based on clinical judgment

1. NNRTI/PI and Anticonvulsants

	Substrate	**Inducer**
Carbamazepine	CYP3A4	CYP3A4 (**strong**), CYP2C9/19
Phenytoin	CYP2C9(70%)>2C19(minor)	CYP3A4(**strong**), UGT
Phenobarbital	CYP2C9/19	CYP3A4 (**strong**), CYP2C9/19

There is a potential to decrease PIs and NNRTI levels when co-administered with Carbamazepine, Phenytoin, and Phenobarbital, which may impact viral efficacy. If these drugs are used the patient must be monitored for virologic failure or anticonvulsant failure. Safer anti-convulsant alternatives are valproic acid, gabapentin, and levetiracetam.

Efavirenz may increase phenytoin level and therefore need to monitor for phenytoin related toxicity (drowsiness, nervousness, bleeding of the gum, and swelling etc.).

2. NNRTI/PI and Antidepressants

Depression in HIV is a significant contributor to the morbidity of HIV itself. It can decrease quality of life for these patients, decrease adherence with HIV medications, and it has shown to decrease overall positive outcomes.

Antidepressant	Potential for Interaction	Management
Amitriptyline Substrate: CYP2D6, CYP2C19, 3A4>UGT	ritonavir, lopinavir/r,	Start with lower dose (50%) of amitriptyline, adjust dose when adding ritonavir. Monitor for side effects
Fluoxetine Substrate: CYP2D6 Inhibitor: CYP2D6	ritonavir, lopinavir/r, all other PIs	As above

Small Group discussion

Discuss on the NNRTI/PI interaction with other two classes of drugs assigned to your group for 15 minutes and take notes on provided flip chart for large group presentation.

3. NNRTI/ PI/ and Rifampicin

Rifampicin is a strong inducer of cytochrome P450 enzyme activity (CYP3A4, 1A2, 2C19. 2D6) as well as of P-gp and phase 2 enzyme activities.

If rifampicin is used, careful consideration must be made to the choice of ARV and dosage:

- EFV AUC reduced by 26%. No dosage adjustment currently recommended.
- NVP AUC reduced by 20%–58%. Efavirenz is preferred, but if it must be used, coadministration should be done with careful monitoring of virologic responses and toxicities.
- Rifampicin can dramatically lower the levels of LPV/r. Current national guideline recommend, adjusted dose of LPV/r (LPV 800 mg +RTV 200 mg twice daily or LPV 400 mg + RTV 400 mg twice daily) with close monitoring of liver functions.
- Avoid concurrent use with atazanavir/r as dose adjustment not established.

4. NNRTI/ PI/ and Azole Antifungals

CYP3A4 Inhibition: Ketoconazole, Itraconazole,> fluconazole **CYP3A4 Substrate**: Ketoconazole and Itraconazole; Fluconazole (11% by P450, P-gp)

In general, Fluconazole and concurrent ARV therapy have demonstrated drug interactions of minimal clinical significance and therefore, it is the preferred antifungal drug of choice for treating systemic and severe topical fungal infections but Ketoconazole and Itraconazole are not recommended.

5. NNRTI/ PI/ and Hormonal Contraceptives

NVP, LPV/r and ATV/r decrease the level of ethynyl estradiol in hormonal contraceptive. But current WHO contraception guidelines conclude that none of these drug interactions are significant enough to prevent their use together.

Counsel clients to regularly use condom additionally.

If women receiving ART decide to initiate or continue using hormonal contraceptives, consistent use of condoms is recommended both to prevent HIV transmission and to compensate for any possible reduction in the effectiveness of the hormonal contraception.

6. NNRTI/ PI/ and statins

Most of the statins undergo significant metabolism via the cytochrome P450 isozymes: Pravastatin is the safest drug for treating hyperlipidemia during concurrent PI therapy. Do not co-administer Lovastatin or Simvastatin due to an increased risk of myopathy including rhabdomyolysis. If possible avoid combination of Atorvastatin or Rosuvastatin.

7. NNRTI/ PI/ and Benzodiazipines (BZD)

Benzodiazipines (BZD) : substrat, CYP 3A4

- when given orally, alprazaolam, midazolam and triazolam undergo extensive first pass metabolism by CYP3A4 in the gut wall and liver. **These benzodiazepines are contraindicated with all PIs.** Avoid combinati**on of diazepam or clonazepam** with all PIs.
- Lorazepam, oxazepam or temazepam are safer alternatives.

- If these alternatives are not available, midazolam single dose parenteral administration may be used with caution.

NVP + BZD: monitor for benzodiazepine efficacy and withdrawal symptoms. Increase the dose as necessary.

8. NNRTI/ PI/ and Ergot Alkaloids

Ergot Alkaloids : Substrate, CYP 3A4

PIs + Ergot Alkaloids: The co-administration of PIs and ergot derivatives such as ergotamine and ergometrine is contraindicated due to the potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by nausea, vomiting, peripheral vasospasm and ischemia of the extremities and other tissues. The onset of reaction is rapid.

EFV + Ergot Alkaloids: Co-administration is contraindicated as it could inhibit the metabolism of ergot alkaloids and create the potential for serious and/or life-threatening reactions such as acute ergot toxicity.

NVP: Theoretically nevirapine may reduce effects of ergot derivatives. Monitor response.
When treating migraines, a safer choice of medication to use with PIs or EFV is sumatriptan. Paracetamol, or narcotic analgesics can be used as alternative.

9. NNRTI/ PI/ and Macrolide antibiotics

Macrolide antibiotics : **Substrate: CYP3A4**: Erythromycin and Clarithromycin **Inhibitor: CYP3A4;** Erythromycine>>Clarithromycin.

Erythromycin and Clarithromycin have strong DDI with NNRTIs and PIs. Therefore it's not recommended to use those macrolide unless there is no alternative.

Azithromycin, has a minimal effect on CYP450 enzymes and may be a suitable alternative.

10. Atazanavir/r with Acid-reducing Agents

Atazanavir (ATV) requires an acidic gastric environment to be absorbed.

In addition, combining ATV with TDF may put a patient at risk of treatment failure since TDF can reduce ATV level (mechanism of interaction is not known).

- **Antacids and buffered medications:** ATV/r should be taken 2 hours before or 1 hour after these medications.
- **H2-receptor antagonist**: Temporal separation of 2 hours before and at least 10 hours following the administration of H2-receptor antagonist.
- **Proton pump inhibitors (PPIs):** if possible avoid using PPIs. If unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir.

NB: Administration of ATV (as sulfate)/RTV 300 mg/100mg tablets in combination with TDF and an H2-receptor antagonist/PPI should be avoided.

11. Miscellaneous Agents and ARVs drug Interactions

Warfarin consists of a racemic mixture of two isomers that include S-warfarin and R-warfarin. S-warfarin is more potent than R-warfarin, with the S isomer being metabolized via CYP2C9 and the R-isomer via CYP1A2 and CYP3A4. Several case reports have evidenced significant drug interactions between warfarin and PIs or NNRTIs due to their inhibition or induction of CYP450 enzymes. Therefore, current guidelines recommend closely monitoring the international normalized ratio (INR) when initiating or discontinuing a PI or NNRTI in patients on a stable warfarin dosage, since INR can increase or decrease.

Management of Food and ARVs Interaction

The following table summarizes drug-food interactions of commonly used ARVs in Ethiopia and recommendations for the management of expected interaction.

NRTIs	
ARVs	**Recommendation**
Tenofovir (TDF)	Should be taken with food
Lamivudine (3TC)	Can be taken with OR without Food
Zidovudine (AZT)	Can be taken with OR without food, but if it causes nausea or stomach

	problems, take with a low-fat meal.
Abacavir (ABC)	Can be taken with OR without food
NNRTIs	
ARVs	**Recommendation**
Efavirenz (EFV)	Should be taken on an empty stomach
Nevirapine (NVP)	Can be taken with OR without food
PIs	
ARVs	**Recommendation**
Atazanavir/r	Should be taken with food
Lopinavir/r	Can be taken with OR without food
Ritonavir (RTV)	Should be taken with or after food
Fixed Dose Combinations	
ARVs	**Recommendation**
TDF/FTC,or3TC/EFV	Take an hour before food or an empty stomach
AZT/3TC	Can be taken with or without food
AZT/3TC+NVP	Can be taken with or without food
TDF/3TC	Take with or after food

Interactions of herbal medicines with HIV Medications

Some alternative medicine or herbal therapies have been shown to interact with ART. The interactions may increase or decrease ART levels leading to either an increase in toxicity or loss of efficacy. Therefore, pharmacy professionals and providers must be aware of the potential interaction should their patient wish to take alternative medicine.

Recreational Drugs

Drug interactions involving drugs of abuse are of particular concern due to an increased risk of life threatening side effects. However, not surprisingly, data in this area are sparse. We do not know the interaction of Chat with ARV; yet more studies are needed. Alcohol should be avoided.

Individual exercise

Attempt the following Exercise question

Exercise 4.3.1

1. Proton Pump Inhibitors (PPIs) are not recommended in patients taking ATV/r based regimen because of the risk of treatment failure.
2. Cotrimoxazole and AZT may have additive bone marrow suppression effect when used concurrently. They should not be administered together.
3. Lopinavir-ritonavir will not impact ethinyl estradiol and norethindrone levels.
4. Protease inhibitors (PIs) are inhibitors of CYP3A4 isoenzyme. Among which RTV is a strongest inhibitor of CYP3A4.
5. Rifampicin can dramatically lower the levels of LPV/r. Therefore, ifa patient is being treated for tuberculosis with rifampicin, LPV/r should be avoided completely.
6. Fluconazole and concurrent ARV therapy have demonstrated drug interactions of minimal clinical significance and therefore, it is the preferred antifungal drug of choice for treating fungal infection.
7. Oral midazolam is a safer choice of benzodiazepine in patients taking ART.
8. Pravastatin is the best choice of statin in HIV patients taking ART with hypercholesterolemia since itdoes not undergo any major metabolism via CYP450 pathways.
9. When using macrolide antibiotics, unlike clarithromycin and erythromycin, azithromycin has a minimal effect on CYP3A4 and is a safer choice.

4.3.3 Systematic approach to manage drug interactions

With new therapeutic agents continually being developed, keeping abreast with potential interactions is extremely challenging. In such situations, familiarity with the basic pharmacokinetic and pharmacodynamics characteristics of the involved agents may help pharmacists predict the likelihood of interactions.

The following steps would help pharmacists to predict and manage drug interaction before happening.

1. Obtain complete medication history
    - including prescription, OTC, herbals, vitamins, recreational
    - categorize drugs by pharmacokinetic/dynamic properties
2. Identify potential conflicting combinations

- different absorption requirements

- opposing/overlapping metabolic characteristics: CYP450 substrate, induction/inhibition

3. Assess data in literature, reference books

- WHO publications, national guidelines, national medicine Formulary

4. Assess clinical significance

Once the potential for a significant interaction has been identified, the clinical significance must be determined. The clinical significance of an interaction will depend upon several factors, including:

  - the magnitude of change in pharmacokinetic parameters
  - the efficacy and toxicity of the affected agent(s)

5. Evaluate Therapeutic Alternatives

Management options may vary depending upon a number of factors, including the mechanism and clinical consequences of the interaction, availability of therapeutic alternatives, patient convenience, and cost. Options may include:

- *Space dosing times* (eg, separate ketoconazole and antacid by 2 hour). Can this be done in a practical and/or convenient way for the patient?
- *Change drug dose*. The potential impact of dosage manipulation on patient adherence should be carefully considered. This in turn may depend upon the drug formulations available, existing pill burden and dosing schedule, and cost. For instance, to adequately adjust for the interaction between lopinavir/r and rifampicin, lopinavir/r should be increased to 800mg/200mg every 12 hours. This can be done with no additional dosing times and minimal increase in pill burden.
- *Change agent* (eg, change Fluconazole to ketoconazole for treatment of fungal infection). What are the comparative efficacy, side effects, cost, availability, compliance issues, and drug interactions associated with the new agent?

Take no action. In certain situations (e.g. low likelihood of an interaction occurring, minor or insignificant clinical impact of a potential interaction) the pharmacist may wish to maintain the patient's current regimen and monitor the patient's condition.

4.3.4 Role of pharmacy professionals in preventing DDI in clinical practice

Pharmacy Professionals:

- Must be knowledgeable about potential drug-drug, drug-food interactions

- Should question a patient about their current medications whenever filling a prescription that is new for them
- Should educate patients that drug interactions can also occur if they stop or receive a change in dose of their medications
- Should ask patients about their use of herbal preparations and other recreational drugs as they can interact with ARV therapy
- Should educate healthcare team members on ARV drug interactions, and its management.
- Should have excellent coordination with multidisciplinary team to avoid/manage drug interactions or to monitor patients for treatment failure or toxicity.

4.3.5 Session Summary

- A drug interaction is a change of activity of one drug arising from the concomitant application of another drug or from the concomitant intake of food or herbs.
- Consequences of drug interactions range from drug toxicities to therapeutic failures.
- The mechanism of the drug interaction may be pharmacokinetic or pharmacodynamic
- Drug interactions in NRTI class are very rare, both PK (predominantly absorption and elimination) and PD (mainly antagonistic) interactions may occur.
- Drug interactions in NNRTI and PI classes of drugs are very common problem and interactions occur mainly during metabolism by CYP450 system.
- Pharmacy professionals should question a patient about their current medications whenever filling a prescription that is new for them, when a dose is changing or when a medication is being discontinued.
- Patients should be educated that drug interactions can also occur if they stop or receive a change in dose of their medications.

Case Studies: Small Group discussion

Case Study 1

ET, a 45-year-old HIV+ male presenting for routine follow-up who is on HAART for the past two years. CD4 count: 480 cells/mm^3 HIV RNA < 50 copies/mL. He comes into your pharmacy

after having seen a physician for his migraine. He is glad to try a new medication as his headaches have been a problem for him for years. He is so distraught about them that he has begun taking an herbal product to help with his mood.

You ask him his current medication regimen, which is:

- Nevirapine 200 mg bid
- Zidovudine 300 mg + Lamivudine 150mg tab bid
- And herbal medicine when he feels "down"
- New medications prescribed today: Ergotamine + caffeine

1. Which of the following combinations represents a potential drug-drug interaction?
   A. Nevirapine and herbal medicine
   B. Zidovudine and ergotamine
   C. Ergotamine and nevirapine
   D. Caffeine and zidovudine
2. What would you recommend to ET for his depression?
3. What would you recommend to him for his migraines?

Case Study 2

LA, a 50-year-old male HIV + for 5 years, stable on therapy presenting to the clinic to get more medication to treat his thrush. He has been taking his brother's medication which seemed to help at first and then stopped working. He would like to get some more to clear the white plaques on his tongue. His current ARV regimen is:

- Nevirapine 200 mg bid
- Zidovidine 300 mg + Lamivudine 150 mg Tablet bid

He has one pill of the medication left from his brother and the physician brings it to your pharmacy to determine what medication this is.

You identify the tablet as ketoconazole 200 mg.

1. Is this an appropriate medication to use with his current ARV regimen?
2. What are some counseling points for this patient?

Case Study 3

FT, a 30-year-old female patient who has just completed 6 months of TB therapy (regimen was rifampicin and isoniazid along with pyridoxine) 3 weeks ago. She has also been on the following ARVs (EFV 600 mg + 3TC 150 mg + TDF 300 mg tablet qhs) during this time. She presents to the OPD with a bloody nose and bruises on her arm.

- Other current medications include
- coumadin for atrial fibrillation
- atenolol for blood pressure
- Oral contraceptive (ethinyl estradiol and norethindrone)

1. What do you suspect has happened?
2. How should this patient have been counseled before the TB medication was discontinued?

Case Study 4

ST, a 48-year-old HIV-infected man, well-controlled hyperlipidemia presents to the clinic complaining of a 4-day history of diarrhea, fatigue, leg weakness, total body aches, and muscle pain. He has noticed his urine has been darker than normal. Three weeks prior, he started a new antiretroviral regimen (see below) after having virologic breakthrough on a regimen consisting of tenofovir-lamivudine-efavirenz. His physical examination shows a T = 38.4°C, HR = 110, and diffuse muscle tenderness. Laboratory result show a serum creatinine of 3.2 mg/dL, serum urea nitrogen = 67 mg/dL, AST level of 632 U/L, ALT level of 400 U/L, and creatine kinase = 9700 U/L

Current Medications:

- Zidovudine + Lamivudine
- Lopinavir/r
- Trimethoprim-Sulfamethoxazole
- Lovastatin: 20 mg PO daily

- What do you suspect has happened?
- Possible Interactions? Mechanism?
- What would you recommend to him as an alternative?

Session 4.4: HIV Resistance to Antiretroviral Drugs

Session Description:

The session highlights the mechanisms and factors that influence the development of antiretroviral drug resistance. The session continues explaining methods of resistance identification and considerations for choosing the next regimen during treatment failure. The session also discusses the strategies to reduce the risk of resistance and the role of pharmacy professionals in preventing HIV resistance.

Primary Objective:

The objective of this session is to enable participants prevent HIV resistance to ARV drugs.

Enabling Objectives:

By the end of this session, participants will be able to:

- Explain the mechanism of HIV drug resistance (HIVDR)
- Describe the various methods of identifying drug resistance
- List basic considerations for choosing the next regimen after treatment failure
- Identify the factors that increase the risk of developing HIV resistance
- Discuss strategies for minimizing development of drug resistance
- Identify role of pharmacy personnel in reducing the risk of HIVDR

Session Outline

- Introduction to the session
- Mechanism, type, and consequences of antiretroviral resistance
- Methods of resistance identification
- Basic considerations for choosing the next regimen (including cross resistance)
- Factors that influence development of drug resistance
- Strategies for minimizing development of drug resistance
- The role of the pharmacy personnel
- Case studies
- Session Summary

Introductory Case: Think- Pair-Share

ST, a 45-year-old man with a baseline CD4 count of 310 cells/mm^3 and HIV RNA level of 45,000 copies/ml initiates antiretroviral therapy with a once-daily regimen of TDF/3TC/EFV. Within 6 months, he has an undetectable HIV RNA. 2 years later, he has intermittent problems with adherence. The patient then returns after being lost to follow up for approximately 5 months and states intermittently took treatment. You have access to viral load (HIV-1 RNA) and resistance testing:

- CD4 count is 295 cells/mm^3
- The viral load is 15,000 copies/ml
- The genotype test shows mutations at K103N

Questions:

A. How could you know if ST has developed HIV drug resistance?
B. How do you relate treatment failure and drug resistance?
C. In the case of ST, what factors contribute to resistance to occur?
D. How does resistance occur?
E. Do you recommend new regimen for ST?
F. Which class should not be included in ST's new regimen? Why?

4.4.1 Introduction

HIV drug resistance emerges when HIV replicates in the presence of ARVs. ARV resistance is a major challenge to ART program. Transmission of drug-resistant HIV strains is documented and is associated with a suboptimal virologic response to initial ART.

With the rapid expansion of ART using the public health approach, emergence of HIVDR is a threat for the national ART program. However, testing for resistance to ARVs is a challenge in Ethiopia. Hence, principles of population-based therapies will be useful when choosing a first and second line regimen.

4.4.2 Mechanism, type, and consequence of antiretroviral resistance

Mechanism of resistance

HIV replicates very quickly, making millions of new viruses copies every day. Viruses which

can replicate in the presence of ARVs are said to be resistant strains. When ARV drug levels in the patient are not high enough to completely suppress HIV replication, then the resistant strain which typically has a selective advantage over the wild type virus (non-resistant) may eventually become one of the dominant circulating strains of HIV. Therefore, missing a dose of medication can allow the blood drug level to fall below the level needed to fully suppress replication, which ultimately may lead to drug resistance (figure 13).

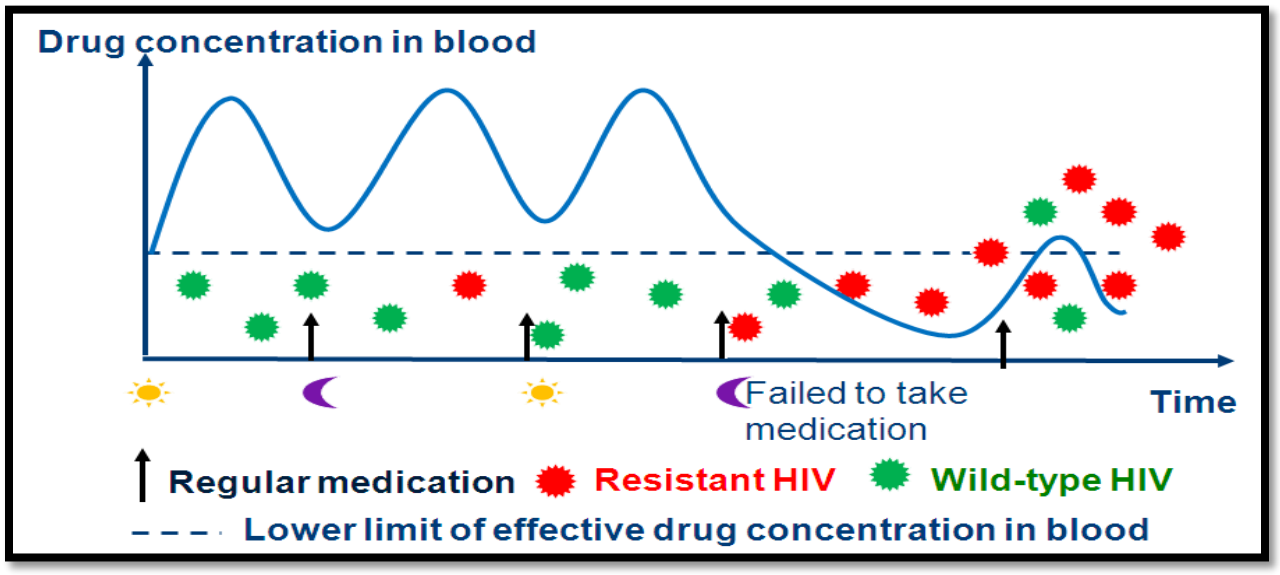


Figure 13: Changes of drug concentration in blood during treatment

Types of resistance

HIV drug resistance can be either primary (transmitted) or acquired. If HIVDR occurred before treatment in treatment-naïve patients, it is called primary resistance or transmitted drug resistance (TDR). This might reflect direct infection from drug experienced individuals. When HIVDR develops in treatment-experienced persons, it is called acquired resistance.

Resistance Terminologies

1. **Genetic Barrier:** Genetic barrier is a measure of how many mutations are needed to develop resistance to an ARV drug. DTG and PIs have a greater genetic barrier to resistance compared to NNRTIs and NRTIs. If individuals with TDR start ART with ARVs having lower genetic barrier to resistance, it will result in a higher risk of virologic failure and a higher risk of developing drug resistance even to other ARVs in the regimen that were originally fully active.

Low genetic barrier	High genetic barrier

• High level resistance with one mutation:
  • NVP, EFV: K103N
  • 3TC: M184V
	• DTG has the highest genetic barrier
	• ≥3 mutations needed to develop high level resistance to most PIs

2. **Cross-Resistance:** Mutations that are associated with resistance to one drug can also have resistance to similar drugs in the same family, this is called cross-resistance.
3. **Viral fitness** is defined as the overall capacity of a virus to infect, replicate, and produce mature infectious progeny in a defined host environment. Some resistant mutations may revert to more fit than the wild-type but in general most resistant mutations cause a significant loss in fitness, i.e. the virus becomes weaker after mutation.

Consequences of HIV drug Resistance

HIV drug resistance has the potential to seriously compromise the effectiveness and impact of ART. The consequences of HIV drug resistance include;

- Treatment failure
- Spread of drug resistant HIV
- Cross resistance
- Limit current drug regimen effectiveness and future option.

Methods of resistance identification

How can resistance be identified?

There are two main ways to measure and describe drug resistance. These are

1. **GENOTYPIC testing** – look for specific mutations that could cause drug resistance.

A combination of letters and numbers describe mutations. For example, **M184V = 3TC resistance**

- **M** (Methionine): name for the amino acid in the wild type virus

- **184**: identifies the position of the codon
- **V** (Valine): name for the "changed" amino acid in the mutant sample

A mutation, or change in the nucleotide, will change the codon and the amino acid coded for by the codon.

2. **PHENOTYPIC testing** – measure ability of a patient's virus to grow in different concentrations of ARV.

As ART program in Ethiopia continue to expand, individuals on ART should be closely monitored for the emergence of drug resistance. Unfortunately, drug resistance testing is still not readily accessible at health facility level in Ethiopia. If treatment failure is witnessed by elevated viral load or clinical failure or immunologic failure, then the presence of drug resistant mutations can be suspected. In general, most of the failure in the first 24 weeks of treatment using recommended HAART regimens is due to lack of adherence or lack of potency, and most late failures that follow good virologic response are due to resistance.

4.4.4 Basic considerations for choosing the next regimen

Mutations Associated with Resistance to NRTIs

A good knowledge of NRTI-resistance pathways is a key aspect of HIV-1-treatment strategies as it allows anticipation of the evolution of the virus. A high mutation rate occurs during the reverse transcription process, predominantly because HIV reverse transcriptase fails to correct erroneously incorporated nucleotides during the reverse transcription process. The altered nucleotide sequences can result in amino acids substitutions during translation, with the potential formation of a mutated protein. The NRTI resistance mutations include:

1. **M184V**: It is selected by 3TC and FTC. It delays the appearance of TAMs and increases the susceptibility to ZDV and TDF. More than any other reverse transcriptase mutation, M184V reduces viral fitness.
2. **Thymidine analogue mutations (TAMs)**: These are selected by the thymidine analogs ZDV. TAMs decrease susceptibility to ZDV and d4T and to ABC, and TDF (depending on TAMs accumulate).
3. **Mutations selected by regimens lacking thymidine analogs** (**Non-TAMs**). These include M184V alone or M184V + K65R or L74V+ K65R causes intermediate resistance to TDF, ABC, ddI, 3TC, and FTC, low-level resistance to d4T, and increased susceptibility to ZDV.

Table **Error! Use the Home tab to apply 0 to the text that you want to appear here.**8: Mutations associated with NRTIs

Mutations	TAMs (41, 67, 70, 210, 215, 219)	M184V	K65R+ L74V	M184V + K65R
Selected By	*AZT*	*3TC*	*TDF, ABC*	*3TC and TDF*
Susceptibility	*Reduce activity of all NRTIs*	*Reduces activity of, FTC, 3TC;*	*Intermediate resistance to TDF, ABC, 3TC, and FTC*	
		Increases activity of AZT and TDF	*Increases activity of AZT; Protects against TAMS;*	*Increases activity of TDF and AZT*
Cross-resistance	*To all NRTIs*	*FTC*	*TDF, ABC*	-
Viral fitness	*Mixed effect*	*Decreased*	*Decreased*	*Decrease (clinically relevant)*
Evolution of resistance (quick, intermediate, delayed)	*Delayed (but if AZT based regimen is being used in a failing regimen, develop more quickly)*	*Quick*	*Delayed*	*Delayed*
Utility of the drug after resistance developed	*None*	*Great*	*Intermediate*	*Great*
Option in class	*None*	*None (but still useful)*	*None, AZT*	*AZT, TDF-still useful*

Which antiretroviral drugs could be effective to use if there are M184V and TAMs?

Mutations Associated with Resistance to NNRTIs

The NNRTIs have a low genetic barrier to resistance. High-level resistance to nevirapine generally requires one mutation and high-level resistance to efavirenz generally requires one to two mutations.

There is a high level of cross-resistance within the NNRTI class because of two mechanisms: (1) most NNRTI resistance mutations reduce susceptibility to two or more NNRTIs; and (2) the low genetic barrier to NNRTI resistance makes it possible for multiple independent NNRTI-resistant lineages to emerge.

NNRTI resistance mutations – primarily **K103N** and **Y181C –**are the most common mutations associated with virologic failure.

Table 9: Mutations associated with NNRTIs

Mutations	K103N/Y181C
Selected By	*NVP, EFV*
Susceptibility	*Reduce activity of all NNRTIs (EFV and NVP)*
Cross-resistance	*To all NNRTIs*
Viral fitness	*No change*
Evolution of resistance (quick, intermediate, delayed)	*Emerges quickly due to point mutation*
Persistence of mutations	*May persist for years*
Utility of the drug	*None*
Option in class	*None*

Evolution of resistance for AZT/3TC+NVP regimen

Resistance mutations to NVP and 3TC often are selected at a faster rate compared with resistance mutations to AZT. In patients receiving the AZT/3TC/NVP regimen, **ZDV and 3TC in combination**, accumulation of TAMS occurs slowly over time and in a step-wise manner. A direct antagonistic effect of M184V on the emergence of TAMs has been proposed.

However, the longer a patient stays on a failing AZT-based regimen, the more TAMs accumulate. Multiple TAMs reduce the susceptibility of the virus to TDF or ABC, and thus may impact the success of future second-line therapy. By contrast, resistance to TDF or ABC does not

result in resistance to thymidine analogues and one important advantage of TDF or ABC as a first-line drug is that AZT will remain active in second-line.

Which antiretroviral drugs could be effective to use if there are M184V and TAMS and NNRTI mutations?

Evolution of resistance for TDF/3TC/EFV regimen

Among approved NRTIs, tenofovir selects for K65R as its preferred mutational pathway. It was also noted to emerge with abacavir. Mutation to TDF arises after the emergence of 3TC and NNRTI resistance mutations.

Study results demonstrate that the combination of TDF plus 3TC and EFV is a potent and well tolerated regimen for treatment-naïve patients. However, resistance to NNRTIs emerges rapidly due to point mutations in Reverse Transcriptase and K103N mutation confers cross resistance to NVP **if adherence to ART is compromised**. Because of its high genetic barrier, DTG is recommended to substitute EFV as preferred first line ARV.

Mutations Associated with Resistance to PIs

The development of PI resistance is believed to be a stepwise process: -

- **Primary mutations**- these often have only a small effect on resistance.
- **Secondary mutations:** during continuous PI therapy, additional mutations emerge in the proteases, and lead to high-level PI resistance.

Table 10: Mutations associated with PIs

Mutations	**Primary mutations and Secondary mutations**
Selected By	*PIs*
Susceptibility	*Primary or secondary mutations individually often have only a minor effect on drug susceptibility.* *In the presence of both 1^0 and 2^0 mutations can lead to a*

	drastic increase in resistance
Evolution of resistance (quick, intermediate, delayed)	*Delayed*
Continued use with failure	*Increasing PI mutations*
Option in class	*Many*

Table 11: Comparison between Resistances on NNRTIs and PIs

	NNRTI	**PI**
Effectiveness	Excellent	Excellent
Failure	Single mutation leads to class resistance	Requires multiple mutations
Options in class	None (Etravirine could be an option but not available in Ethiopia)	Many
Continued use with failure	No benefit	Increasing PI mutations

NNRTI-based and boosted PI-based combinations are similar in potency and duration of response. However, the use of PI regimens offered the benefit of delayed resistance that may in turn preserve active therapeutic options in the event of failure of the first regimen.

Which antiretroviral drugs could be effective to use if there are M184V and TAMS and NNRTI mutations and PI mutations?

ARV Drug Resistance and ARV Drug Sequencing

What do we mean by ARV drug sequencing?

Drug sequencing refers to the preferred use of a specific ARV drug (or drug class) in initial therapy with an assumption that virologic failure and drug resistance might later develop that could then be overcome using a second drug (of the same class or a different class). Sequencing

strategies might offer more benefit to drug-naive patients than to drug-experienced patients. Therefore, the selection of first-line therapies could consider the amenability of therapeutic regimens for drug sequencing, in addition to issues of tolerability and toxicity.

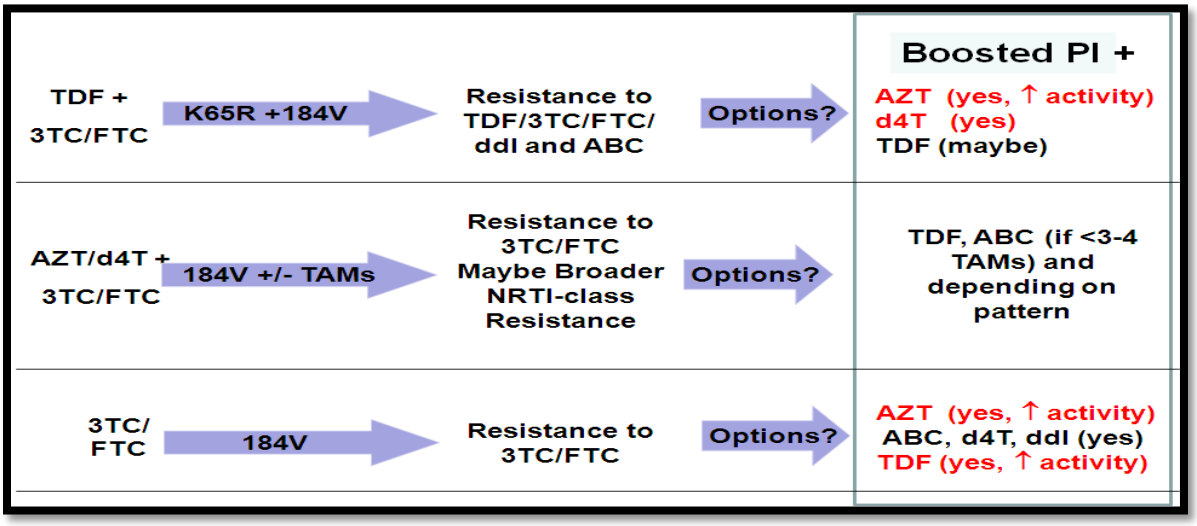


Figure 14: ART sequencing options

Factors that influence development of drug resistance

Individual reading and Large group discussion

1. What Regimen- and drug-specific factors influence drug resistance? What about virus factors?
2. What patient factors influence drug resistance?
3. What system (program) factors influence drug resistance?

Efforts to minimize HIVDR should be focused on these factors.

- Virus Factors
- Regimen-and drug-specific Factors
- Programmatic Factors
- Patient Factors

- **Virus Factors**:
  - Prevent tranmission of resistant (mutant) virus from one patient to another.
  - Identifying mutations and select treatment accordingly
- **Regimen-and drug-specific Factors:**

- Treat all patients with 3 or more drugs
- Use of appropriate drug regimens
- Can reliably suppress HIV replication to levels of <50 copies/ml
- Use of fixed-dose combinations to support adherence
- Don't continue treatment with a failing regimen – change to other regimen.
- Avoid adding one drug to a failing regimen – change the full regimen.

- **Programmatic Factors:** Program-level factors,
  - Limited human resources,
  - Inadequate infrastructure
  - Weak supply management systems,
  - Limited number of regimens
  - Lack of adequate lab service
- **Patient Factors:**
  - Adherence to treatment regimen
  - Avoiding interruption of treatment, even if only a few days
  - Regular follow-up (going to clinic)
  - Staying on uninterrupted first-line ART as long as possible

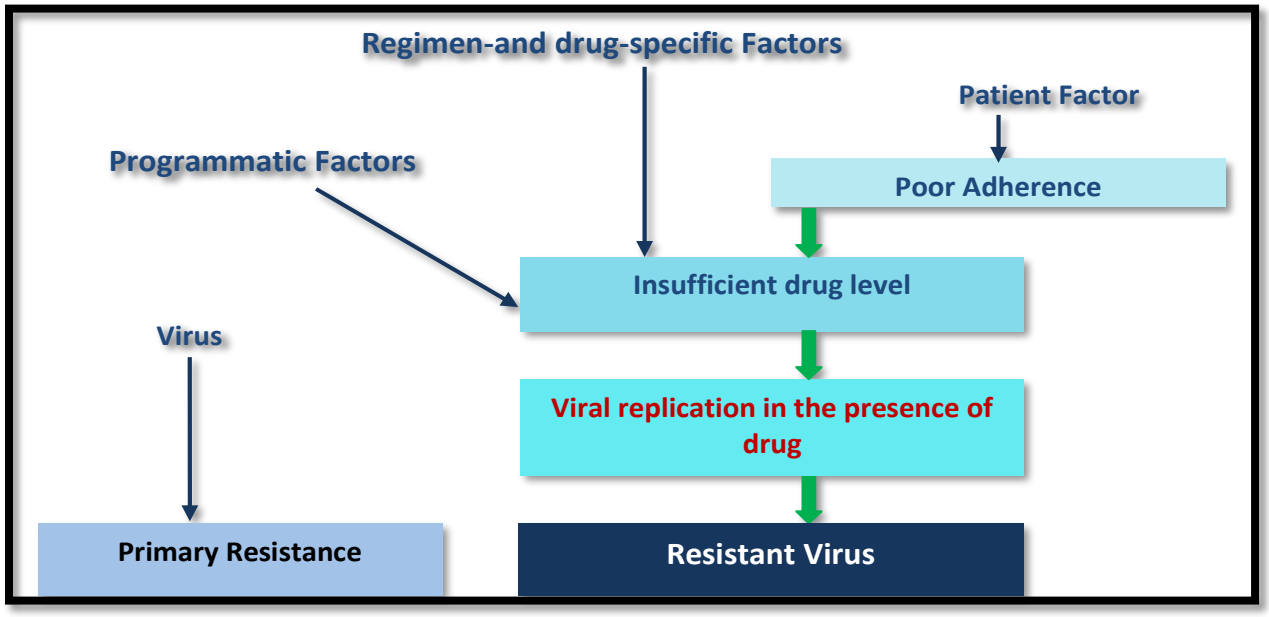


Figure 15: Summary of factors that influence development of drug resistance

4.4.7 Strategies for minimizing development of drug resistance

HIVDR Early Warning Indicators (EWI): are quality of care indicators which specifically assess ART sites and program factors potentially associated with HIVDR at individual ART clinics. Utilizing data routinely collected in patients' medical and pharmacy records. Figure 16 summarizes the five EWIs.

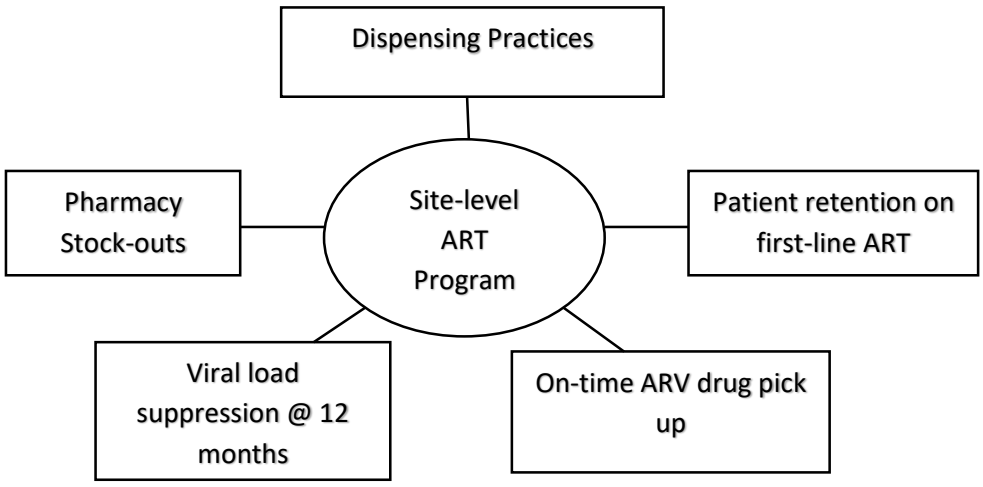
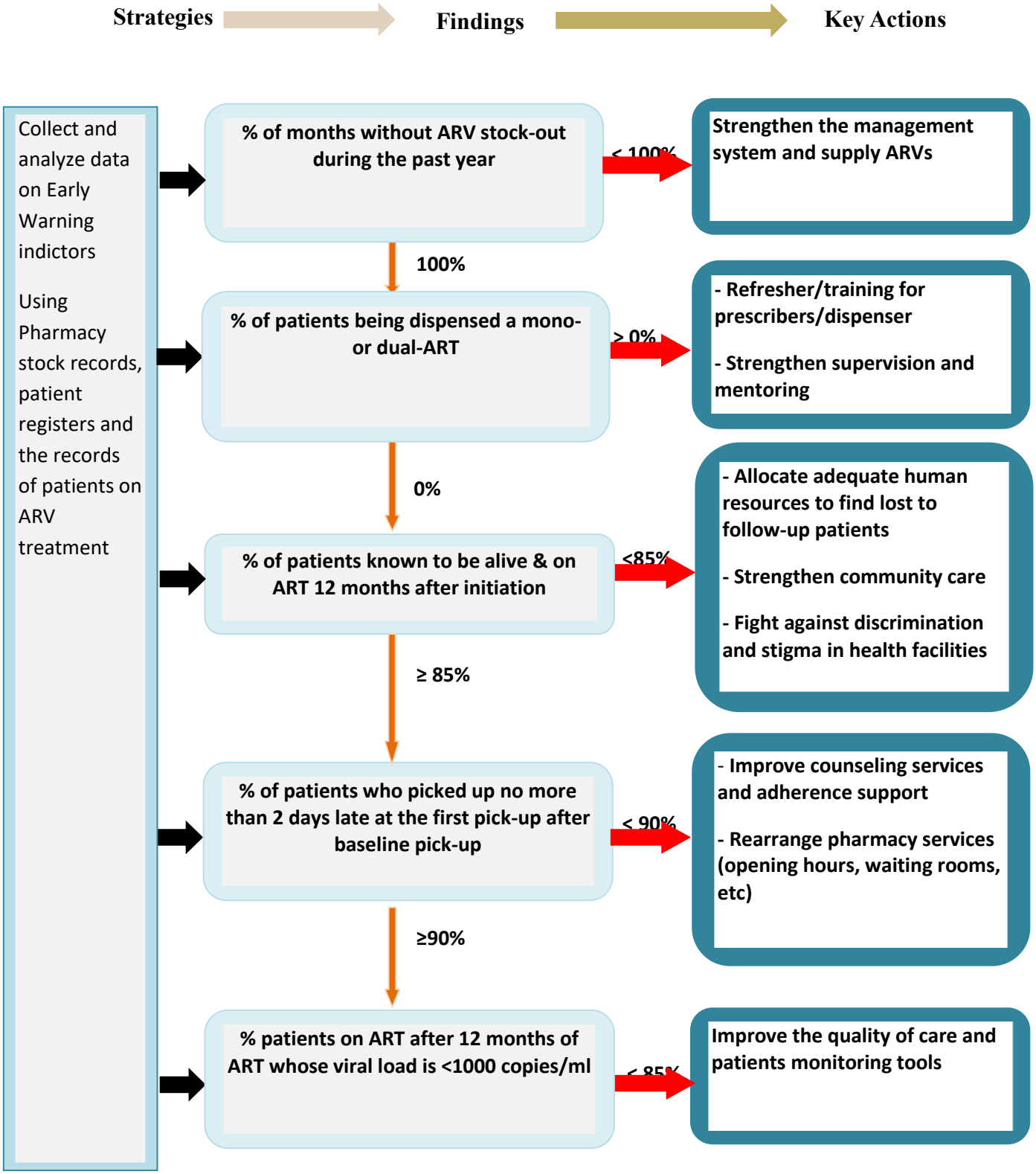


Figure 16: The five early warning indicators

The following algorithm (Figure 17) contains an excellent description of strategies to reduce risks of HIV drug resistance at the ART site. It describes the investigations recommended to identify gaps, possible findings following the investigation and actions needed in ART sites.

Figure 17: Algorithm to reduce risks of HIV drug resistance at the ART site



4.4.8 Role of pharmacy professionals in preventing HIV Resistance

Pharmacy professionals play an important role in preventing the occurrence of HIV resistance by assisting patients in remaining adherent to their regimens:

- Identify possible barriers to adherence prior to starting medication.
- Involve patients and their families as an active participant in their adherence plan.
- Educate patients on the importance of adherence in the prevention of resistance.
- Provide medication counseling and act as a resource to assist patients with side effects to prevent discontinuation of therapy.
- Keep accurate data to be used for EWI assessment
- Strengthen supervision and mentoring
- Strengthen the management system and supply of ARV
- Improve the quality of care and patient monitoring tools

4.4.9 Session Summary

- Resistance develops when HIV mutants emerge and reproduce in the presence of ARV drugs
- HIV drug resistance can be either primary (transmitted) or acquired
- HIV drug resistance seriously compromise the effectiveness and impact of ART leading to treatment failure, spread of drug resistant HIV, cross resistance and limit future drug option.
- The selection of first-line therapies could consider the amenability of therapeutic regimens for drug sequencing, in addition to issues of tolerability and toxicity.
- Factors that influence development of drug resistance can be categorized it to virus Factors, regimen-and drug-specific Factors, programmatic Factors and patient Factors
- HIVDR Early Warning Indicators (EWI) are quality indictors used to assess ART sites and program factors potentially associated with HIVDR and design strategies to reduce HIVDR at specific ART Clinics.
- Pharmacists play important role in prevention and early detection of HIV resistance

Case Studies

Case Study 1

MA, A 38-year-old man has been on Zidovudine, Lamivudine and Nevirapine for the past five years. He had history of frequent treatment interruption and has not disclosed his status to his wife or his family. On his last visit, the CD4 count had fallen from 200 cell/ml to 130 cells/ml and the viral load had risen from undetectable levels to 50,000 copies/ml.

Questions

1. What do you think is happening to the patient?
2. What regimen would have the best chance of success for viral suppression in this patient?
3. What are the key issues need to be addressed prior to restarting treatment?

Case Study 2

DT, A 35-year-old man was diagnosed HIV-1-antibody positive in 2013 after presenting with recurrent episodes of oral candidiasis. At the time of diagnosis, the CD4 count was 20 cells/ml and the plasma viral load was greater than 500,000 copies/ml. Antiretroviral therapy was started 2 weeks after diagnosis with TDF/3TC/EFV. On the 24^{th} week of treatment, viral load was suppressed to <50 copies/ml, accompanied by a rise in CD4 count to 230 cells/ml. However, the viral load rebound to 3650 copies/ml at week 32. On week 44 of treatment, although DT reported **optimal adherence,** he was diagnosed with bacterial pneumonia and persistent viremia that led to change of therapy to AZT/3TC and NVP.

Questions:

1. What do you think the reason for quick failure to the first treatment regimen? Based on current knowledge, would the management have been different?
2. Based on your current knowledge, would you recommend AZT/3TC and NVP as a change of therapy for this patient? Why?
3. What should be done now? What should the next step be?

Session 5: Monitoring and Changing Therapy

Session Description

This session describes in detail about monitoring and changing antiretroviral therapy. It starts with description of treatment monitoring and concepts & management of IRIS and then reasons for changing antiretroviral therapy. It then discusses the factors for failure of ART and the approaches to change ART following treatment failure, drug toxicity, comorbidities, or drug interaction. Finally, the factors that need to be considered before changing ART are discussed.

Primary Objective:

This session will enable participants to monitor response and identify the reasons for ART failure and to change therapy whenever indicated.

Enabling objectives

Upon completion of this session, participants will be able to:

- Describe treatment monitoring of ART
- Discuss the reasons for changing ART
- Explain factors that contribute to ART failure
- Identify ART regimen to switch to
- Discuss the necessary considerations before changing ART
- List the roles of pharmacy professionals in monitoring and changing ART

Session Outline

- Treatment monitoring Changing therapy
- Factors for ART failure
- How to change in ART
- Factors to consider before changing therapy
- The role of the pharmacy personnel
- Case studies
- Session Summary

Introductory Case

Mr. M. is a 28 year- old male who started triple ART regimen one year ago. At the time of ART initiation, he had PCP pneumonia and oral thrush which were treated effectively. As the result of regular and effective treatment with ART, his clinical condition was very good until his appointment two months ago. Today Mr. M. is diagnosed with toxoplasmosis and is hospitalized for treatment with pyrimethamine + sulfadiazine and folinic acid. CD4/TLC and VL monitoring is not available in his facility. What should be the next step to manage this patient? Choose the right answer from the following options.

A. Continue with the current ART regimen for unlimited length of time until VL test is available.
B. Continue ART therapy because this patient is not experiencing side effects
C. Change ART therapy because the new opportunistic infection implies clinical failure.
D. Continue ART therapy as there is no proof for decline of CD4 count.

5.1 Treatment monitoring

Large group Discussion

What are you going to monitor in the first 6 months of ART initiation?

Monitoring people on ART is important to ensure successful treatment, identify adherence problems and determine whether ART regimens should be switched in case of treatment failure. Monitoring of patients on ART should start from the day of initiation. Although taking ART is a lifelong commitment, the first six months of therapy are especially important. Complications are commonest when the people starting ART already have advanced HIV disease with severe immunodeficiency and existing co-infections and/or co-morbidities, severely low hemoglobin, low body mass index and very low CD4 counts or are severely malnourished.

Scenarios to look for with in first 6 months:

- Clinical and immunological improvement and virologic suppression
- Opportunistic infections and/or immune reconstitution inflammatory syndrome (IRIS)

- Early adverse drug reactions, such as drug hypersensitivity, especially in the first three months of ART.

Note: ART significantly decreases mortality and HIV related illnesses, however mortality can be higher in the first three to six months of ART initiation among people who started ART with advanced HIV disease with existing co-infections and/or co-morbidities, severely low hemoglobin, low body mass index (severe malnutrition) and/or very low CD4 counts.

Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS is a spectrum of clinical signs and symptoms thought to be associated with immune recovery brought about by a response to ART. It is a widely recognized phenomenon that occurs among 10–30% of the people initiating ART, usually within the first 4–8 weeks after initiating therapy. It may present in two different ways: **paradoxical IRIS**, when an opportunistic infection or tumor diagnosed before ART initially responds to treatment but then deteriorates after ART starts; or **unmasking IRIS**, in which initiating ART triggers disease that is not clinically apparent before ART. It should be considered only when the presentation cannot be explained by a new infection, expected course of a known infection or drug toxicity.

The clinical spectrum is diverse, and IRIS has been reported for many different infections, tumors and non-infectious conditions. The most serious and life-threatening forms of paradoxical IRIS are for TB, cryptococcosis, Kaposi's sarcoma and hepatitis. BCG vaccine–associated IRIS (localized and systemic) may occur in infants infected with HIV in settings where BCG immunization is routine. A low CD4+ cell count (<50 cells/mm3) at ART initiation, disseminated opportunistic infections or tumors and a shorter duration of therapy for opportunistic infections before ART starts are the main risk factors.

Management of IRIS

IRIS is not indicative of treatment failure or drug side effect. It is a transient and self-limiting phenomenon and is not a reason to stop ART or change regimen. Management of IRIS involves***:***

- Treating the underlying OI as soon as possible using standard guidelines.
- Continuation of ART when IRIS occurs
- In critically sick patients short course of corticosteroid might be indicated to control severe symptoms**.**

Clinical and laboratory monitoring

Clinical assessment and laboratory tests play a key role in assessing comorbidities, response to treatment and possible toxicity of ARV drugs.

Before initiating antiretroviral therapy, patients shall be thoroughly evaluated at baseline and periodically for the rest of their lives to monitor toxicity, intolerance, poor response or failure to treatment.

Table 12: Baseline and Follow up Assessment

Baseline assessment, week 0 **Objective: To conduct initial assessment**	
Activities	**Intervention**
• Check confirmatory HIV test is done and documented • Adherence counseling and ensure readiness • Clinical assessment: socio-economic status, any HIV related illnesses in the past, symptom screen for TB, other OIs, co-morbidities, pregnancy, past and current medication. • Determine WHO staging • Register, fill intake format • Counselling and education: adherence, treatment readiness, disclosure, address adherence barriers • Lab assessment: o base line CD4[1], o CBC, ALT, creatinine (if available). o If presumptive TB diagnosis, do GeneXpert. o Pregnancy and other tests as necessary.	• Develop impression on treatment readiness • Start CPT and IPT if clinically indicated. • Treat OI • Manage co-morbidities/ refer if necessary • Continue ART for transfer-ins • Start ART for those who are ready and have no adherence barriers; and give appointment to return after two weeks. If ART not started, give appointment to return after 1 week • Refer if necessary

[1]ART initiation shouldn't be delayed for the CD4 test; however, do the CD4 test to assess severity of immunosuppression.	
2nd Visit, 1 week after baseline visit Objective: To decide on ART initiation for those who didn't start ART during the first visit.	
• Review clinical and lab data • Adherence counselling and ensure readiness • Counseling and education on ART and preventive therapies • Encourage disclosure and discuss on treatment support.	• Determine ART treatment readiness • Start CPT (as indicated) and IPT if not started • Treat OI, Initiate TB treatment if indicated • Manage any drug toxicity and intolerance • Decide on regimen and initiate ART if ready. • Provide adherence counselling and patient education • Appointment to return after 2 weeks if ART initiated • Give appointment for those patients who defer early initiation after 1 week for 3rd session. **NB**: Continue the same session & counseling until the patient is ready & initiated on ART,
3rd visit, 2 weeks after initiation To determine toxicity/intolerance, adherence, and IRIS	
• Clinical assessment for: IRIS, toxicity etc. • Assess and support adherence addressing barriers • Provide counseling and education including prevention • Lab tests if necessary	• Increase/Adjust dose of nevirapine if patient is on NVP regimen. • Manage toxicity as indicated • Provide adherence support and patient education including HIV prevention • Treat OI if diagnosed • Give appointment to return in 2 weeks

• Support disclosure if not done	
4th visit 4 weeks after initiation Same as third visit	
• Same as 3rd visit • Hgb test if patient is on AZT • Assess and support adherence	• Refill ART and other medicine as necessary for one month • Treatment of OI if identified • Manage drug toxicity and intolerance • Provide adherence support and patient education including HIV prevention • Refer if necessary • Appointment to return after 4 weeks
5th visit 8 weeks after initiation	
Same as 4th visit	• Refill ART and other drugs as necessary for 1 month • Treatment of OI & co-morbidities. • Manage toxicity and intolerance • Provide adherence support and patient education including HIV prevention • Refer if necessary • Appointment to return after 4 weeks
6th visit 12 weeks after initiation	
Same as 5th visit	• Refill ART and other drugs as necessary for 1 month • Treatment of OI • Manage toxicity and intolerance • Provide adherence support and patient education including HIV prevention • Refer if necessary • Appointment to return after 4 weeks
7th visit 16weeks after initiation	
Same as 6thvisit	• Refill ART and other drugs as necessary for 2 months • Treatment of OI

	• Manage toxicity and intolerance • Provide adherence support and patient education including HIV prevention • Refer if necessary • Appointment to return after 8 weeks
8th visit 24 weeks after initiation	
Same as 7thvisit	• Determine CD4 if viral load testing is not available or patient is on CPT • Determine Viral load • Refill ART and other drugs as necessary for 3 months • Treatment of OI • Manage toxicity and intolerance • Refer if necessary • Appointment to return after 12 weeks

NB:

- CD4 testing may be used to determine discontinuation of OI prophylaxis.
- After the 24th week of initiation of antiretroviral therapy patients are scheduled to return every twelve weeks. At each visit antiretroviral drugs and CPT for three months are given, counseling of positive living, safe sexual practice, adherence assessment and support are done. Lab tests including ALT are requested when indicated.
- Patients should be encouraged to come at any time if they have concerns. Clients may be seen out of the above schedule whenever necessary.
- At every visit conduct screening for TB.

Table 13: Summary of recommended laboratory tests for HIV screening and monitoring, as well as approaches to screen for co-infections and non-communicable diseases

Population	1st line regimens	2nd line regimens	3rd line regimens
Adults, adolescents, pregnant &breastfeeding women	AZT+3TC + EFV/NVP	TDF+3TC + ATV/r or LPV/r	DRV/r [a] + DTG[b] + AZT+3TC
	TDF+3TC+EFV/NVP	AZT+3TC + ATV/r or LPV/r	DRV/r + DTG + TDF+3TC
	ABC+3TC+EFV/NVP	AZT+3TC + ATV/r or LPV/r	DRV/r + DTG + TDF + 3TC
Adults and adolescents 10 years & older with body weight≥30kg	TDF + 3TC + DTG[g]	AZT+3TC+ATV/r or LPV/r	DRV/r+ABC+3TC+EFVor NVP
Children younger than 3 years	ABC + 3TC + LPV/r	Maintain the 1st line regimen	RAL [c] + AZT + 3TC
	AZT + 3TC + LPV/r		RAL + ABC + 3TC
Children older than 3 years, and adolescents 10 years & older with body weight < 30kg	AZT + 3TC + EFV	ABC + 3TC + LPV/r	DRV/r + RAL + ABC +3TC
	ABC or TDF[d] + 3TC + EFV	AZT + 3TC + LPV/r	DRV/r + RAL + AZT + 3TC
All children (0 – 10)	AZT or ABC or TDF + 3TC + LPV/r[e]	AZT or ABC or TDF + 3TC + EFV or NVP	DRV/r[a,f] + RAL[g] + ABC +3TC or RAL[g] + ABC + 3TC (for < 3yrs)
			DRV/r[a,f] + RAL + TDF +3TC or RAL + TDF + 3TC (for < 3yrs)
			DRV/r + RAL [g] + AZT + 3TC RAL [g] + AZT + 3TC (for < 3yrs)

[a] In PI-experienced patients, the recommended DRV/r dose should be 600mg/100 mg twice daily.

[b] For women of childbearing age using DTG requires strict use of family planning.

[c] If RAL is not available, no change is recommended unless in the presence of advanced clinical disease progression or lack of adherence specifically because of poor palatability of LPV/r.

[d] TDF may only be given to children >2 years.

[e] ATV/r can be used as an alternative to LPV/r in children older than three months of age, however the limited availability of suitable formulations for children younger than six years of age, the lack of a fixed-dose formulation and the need for separate administration of RTV booster should be considered when choosing this regimen.

[f] DRV/r should not be used in children younger than three years of age.

[g] RAL can be used in children failing PI-based second-line treatment when DTG is not available and when RAL has not been not used in a previous regimen. DTG is currently only approved for children 6 years and older (>30kg of weight), however studies are ongoing to determine dosing in younger children and approval to lower age groups is expected in the near future. DTG containing regimens are not approved for pregnant and breast feeding mothers. For HIV/TB co-infected adults & adolescents, the recommended dose of DTG is 50 mg twice daily.

Table 14: Summary of recommended laboratory tests for HIV screening and monitoring, as well as approaches to screen for co-infections and non-communicable diseases

Management	Recommended	Desirable (if feasible)
At HIV diagnosis	• HIV testing (serology for adults and children 18 months or older; EID for children younger than 18 months) • Cryptococcus antigen if CD4 cell count ≤100 cells/mm3[b] • CD4 cell count • TB symptom screening	• HBV (HBsAg) serology[1a] • HCV serology • Pregnancy test to assess if ART initiation should be prioritized to prevent HIV transmission to the child • Assessment for major non-communicable chronic diseases and comorbidities
Follow-up for clients who differed ART initiation	• CD4 cell count (every 6 months in circumstances where ART initiation is differed)	
ART initiation		• Hemoglobin test for starting AZT[d] • Pregnancy test • Blood pressure measurement • Serum creatinine and estimated glomerular filtration rate (eGFR) for starting TDF[e] • Alanine aminotransferase for NVP[f] • Baseline CD4 cell count
Receiving ART	1. HIV viral load (at 6 months and 12	• Serum creatinine and eGFR for TDF[e] • Pregnancy test, especially for women

	months after initiating ART and every 12 months thereafter) 2. Viral load testing for pregnant mothers: o Newly diagnosed mother: after 3 months followed by the routine at 6, 12 month and then every 12 months. o For those who are already on ART and their VL test is longer than 6 months back do VL soon after pregnancy is known; the routine VL testing should continue as is. 3. CD4 cell count if indicated	of child bearing age not receiving family planning.

[a]If feasible, HBsAg testing should be performed at baseline to identify people with HIV and HBV coinfection and who should therefore initiate TDF-containing ART.

[b]Can be considered in settings with a high prevalence of Cryptococci antigenemia (>3%).

[c]Consider assessing for the presence of chronic conditions that can influence ART management, such as hypertension and other cardiovascular diseases, diabetes and TB according to the WHO Package of Essential NCD interventions (PEN), mental health Gap Action Programme (mhGAP) or national standard protocols. Monitoring may include a range of tests, including serum creatinine and estimated glomerular filtration rate (eGFR), serum phosphate and urine dipsticks for proteinuria and glycosuria.

[d]Among children and adults with a high risk of adverse events associated with AZT (low CD4 or low BMI).

[e]Among people with a high risk of adverse events associated with TDF: underlying renal disease, older age group, low body mass index (BMI), diabetes, hypertension and concomitant use of a boosted PI or potential nephrotoxic drugs.

[f]Among people with a high risk of adverse events associated with NVP, such as being ART-naive, women with HIV with a CD4 count >250 cells/mm3 and hepatitis C virus (HCV) coinfection. However, liver enzymes have low predictive value for monitoring NVP toxicity.

a. Changing Therapy

Large Group discussion

1. What are the reasons for changing ART?
2. What is the difference between clinical failure and IRIS?
3. What are the factors that cause treatment failure?

Once antiretroviral therapy (ART) is initiated, patients generally remain on medications indefinitely. The approach to change ART will differ depending on a number of issues, including the reason for change, the amount of prior antiretroviral treatment experience, and the available treatment options. ART should not be changed unless necessary!

5.2.1. Reasons for changing ART

Treatment failure and drug toxicity are the main reasons for switching ARV medications. The occurrence of active tuberculosis may also be indication for switching antiretroviral regimens.

1. Treatment Failure

Treatment failure is classified as Clinical failure, Immunologic failure; and Virologic failure. Viral load testing is the preferred monitoring approach to diagnose and confirm ARV treatment failure. Compared to clinical or immunological monitoring, viral load provides an early and more accurate indication of treatment failure and the need to switch from first-line to second-line drugs, reducing the accumulation of drug resistance mutations and improving clinical outcomes. If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure.

The three types of treatment failure may happen alone or together. In general, virologic failure happens first, followed by immunologic failure, and then clinical progression. They may happen months to years apart. Viral load testing should be used a side from the routine testing schedule whenever there is clinical or immunologic suspicion of treatment failure.

Table **Error! Use the Home tab to apply 0 to the text that you want to appear here.**15: Definitions of clinical, immunological and virologic failure for the decision to switch ART regimens

Failure	Definition	Remark

Clinical failure	**Adults and adolescents** New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition and certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure) after 6 months of effective treatment **Children** New or recurrent clinical event indicating advanced or severe immunodefiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6months of effective treatment.	It is the late presentation that comes after immunological & virological failures. The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART.
Immunologic failure	**Adults and adolescents** • CD4 count at or below 250 cells/mm3 following clinical failure Or • Persistent CD4 levels below 100 cells/mm3	Without concomitant or recent infection to cause a transient decline in the CD4 cell count. Persistent is to mean at least 2 CD4 measurements below the threshold. Current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virologic failure.
	Children **Younger than 5 years**: Persistent CD4 levels below 200 cells/mm3 or <10% **Older than 5 years**: Persistent CD4 levels below 100 cells/mm3	
Virologic failure	Viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months, with adherence support following the first viral load test	This is the early sign of failure before manifesting any of the clinical or immunological failure. An individual must be taking ART for at least

		6 months before it can be determined that a regimen has failed. VL testing should not be done when there is an acute infection/fever as there can be blips of VL. See guidance above.

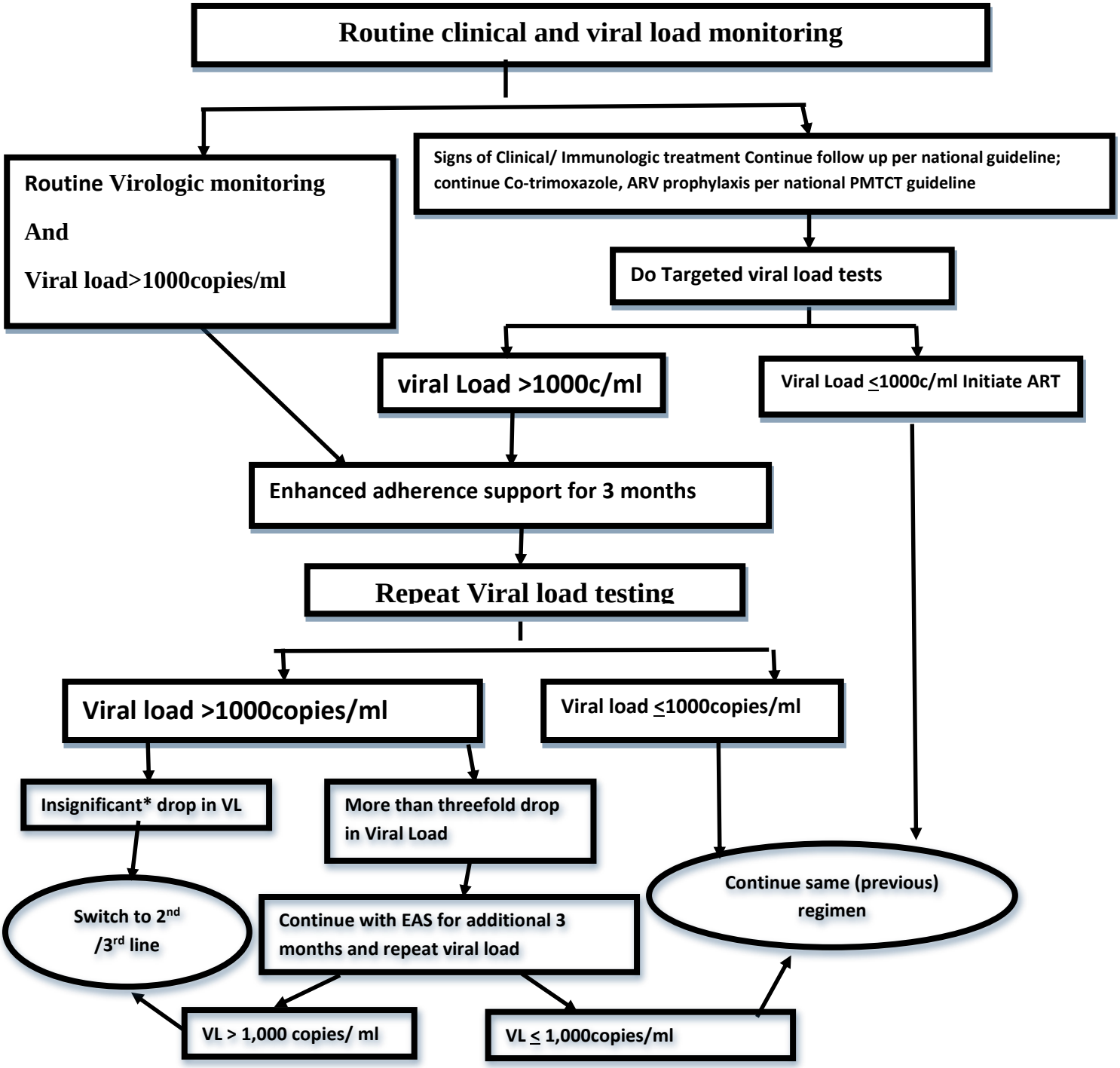


Figure 178: Algorithm for routine clinical and viral load monitoring

Factors contributing for treatment failure

There are many potential causes of ART failure. Some causes may be addressed ahead of time for example by preventing potential drug-drug interactions. Other causes may not be able to be identified upfront for example a pre-existing resistance. Each visit is an opportunity to identify any new factor that may cause treatment to failure.

Non-adherence: Adherence is critical to successful treatment. Therapeutic failure is most commonly associated with non-adherence. Evidence suggests that ART success rates decrease dramatically when adherence falls even slightly down to 95% (resistance rates increase by 20-30%). It is critical to evaluate adherence to ART prior to changing ART for presumed therapeutic failure and to try and make an intervention to improve adherence. If the patient cannot adhere to their regimen, you may need to try to change to an easier regimen.

Resistance: In the cases of treatment failure, resistance should be suspected. In the absence of resistance testing, regimen will be changed based on viral load and immunologic tests.

Adverse effects: Adverse effects of ARVs limit a patient's ability to take the medication properly. This may lead to the development of resistance as the levels of the drug in the body are not maintained adequate. This gives the virus a chance to make mutant strains.

Drug-drug interaction: Despite taking their medication properly, HIV patients might be at risk of treatment failure due to drug-drug, drug -herbal or drug-food interactions as the interactions may lead to diminished efficacy. Hence, when initiating or changing therapy, it is important to look for or ask about other medications and herbal medicines to avoid potential drug interaction.

2. Drug Toxicity

In some patients, antiretroviral drugs can have toxic side effects that can be life threatening. For example, liver damage and nerve damage can be so serious that a patient must stop ART. Some are potentially fatal like lactic acidosis, pancreatitis and hyperlipidemia which may cause a substantial long-term risk of cardiovascular disease could also be indications for change in therapy. A single drug substitution can be done for common side effects of ARVs (e.g. anemia due to AZT); this is not true treatment failure but a toxicity.

3. Co- morbidities (Active tuberculosis)

A change in clinical status may mandate switching ART. In occurrence of active TB, if patient was on NVP-based regimen that must be changed to EFV-based ART regimen.

5.2.2. How to change ART (Approaches to change ART)

Approaches to change ART following treatment failure

WHO recommends that if a switch in antiretroviral regimen is needed because of treatment failure, an entirely new regimen should be used.

- If 3 new drugs are not available, it is necessary to change at least one of the NRTI drugs and then change the NNRTI to a PI regimen.
- It is important to distinguish between the need to change therapy due to drug failure versus drug toxicity. In the latter case, it is appropriate to substitute one or more alternative drugs of the same potency and from the same class of agents as the agent suspected to be causing the toxicity.
- If the failure is due to non-adherence, it is inappropriate to start a second ARV regimen without solving the problem of adherence and proving that it no longer is a problem. Some people use adherence to visits and other medication as a marker like multivitamin or co-trimoxazole. When you are reasonably sure that the patient will be able to adhere, then prescribe a new regimen.

Table 16: Changing ART regimen during treatment failure.

Population	***1st line regimens***	***2nd line regimens***	***3rd line regimens***
Adults, adolescents, pregnant &breastfeeding women	*AZT+3TC + EFV/NVP*	*TDF+3TC + ATV/r or LPV/r*	*DRV/r [a] + DTG[b] + AZT+3TC*
	TDF+3TC+EFV/NVP	*AZT+3TC + ATV/r or LPV/r*	*DRV/r + DTG + TDF+3TC*
	ABC+3TC+EFV/NVP	*AZT+3TC + ATV/r or LPV/r*	*DRV/r + DTG + TDF + 3TC*
Adults and adolescents 10 years & older with body weight≥30kg	*TDF + 3TC + DTG[g]*	*AZT+3TC+ATV/r or LPV/r*	*DRV/r+ABC+3TC+EFVor NVP*

Children younger than 3 years	*ABC + 3TC + LPV/r*	*Maintain the 1st line regimen*	*RAL [c] + AZT + 3TC*
	AZT + 3TC + LPV/r		*RAL + ABC + 3TC*
Children older than 3 years, and adolescents 10 years & older with body weight < 30kg	*AZT + 3TC + EFV*	*ABC + 3TC + LPV/r*	*DRV/r + RAL + ABC +3TC*
	ABC or TDF[d] + 3TC + EFV	*AZT + 3TC + LPV/r*	*DRV/r + RAL + AZT + 3TC*
All children (0 – 10)	*AZT or ABC or TDF + 3TC + LPV/r[e]*	*AZT or ABC or TDF + 3TC + EFV or NVP*	*DRV/r[a,f] + RAL[g] + ABC +3TC or RAL[g] + ABC + 3TC (for < 3yrs)*
			DRV/r[a,f] + RAL + TDF +3TC or RAL + TDF + 3TC (for < 3yrs)
			DRV/r + RAL [g] + AZT + 3TC *RAL [g] + AZT + 3TC (for < 3yrs)*

[a] In PI-experienced patients, the recommended DRV/r dose should be 600mg/100 mg twice daily.

[b] For women of childbearing age using DTG requires strict use of family planning.

[c] If RAL is not available, no change is recommended unless in the presence of advanced clinical disease progression or lack of adherence specifically because of poor palatability of LPV/r.

[d] TDF may only be given to children >2 years.

[e] ATV/r can be used as an alternative to LPV/r in children older than three months of age, however the limited availability of suitable formulations for children younger than six years of age, the lack of a fixed-dose formulation and the need for separate administration of RTV booster should be considered when choosing this regimen.

[f] DRV/r should not be used in children younger than three years of age.

[g] RAL can be used in children failing PI-based second-line treatment when DTG is not available and when RAL has not been not used in a previous regimen. DTG is currently only approved for children 6 years and older (>30kg of weight), however studies are ongoing to determine dosing in younger children and approval to lower age groups is expected in the near future. DTG containing regimens are not approved for pregnant and breast feeding mothers. For HIV/TB co-infected adults & adolescents, the recommended dose of DTG is 50 mg twice daily.

Approaches to change ART following drug toxicity

Change in therapy is considered in Grade 3 drug toxicity and treatment should be stopped if there is a Grade 4 toxicity. Clinical and laboratory monitoring is required for identifying and grading adverse effects. For toxicities without symptoms laboratory monitoring is important to make sure that the ART is not causing any harm to organs (e.g., liver, kidneys, pancreas) or the blood.

Some of ARV toxicities that require change of therapy are listed in tables below. Refer grading of toxicities in session 4.2.

Table 17: Clinical indication to change ART due to toxicity

Symptom	**Clinical indication**
Nausea	Severe discomfort or minimal intake of food
Vomiting	Severe vomiting of all foods/fluids in 24hrs, orthostatic hypotension or need of IV fluids
Diarrhea	Bloody diarrhea, orthostatic hypotension or need of IV fluids
Fever	Unexplained fever of $\geq$ 39.6 C
Headache	Sever or requires narcotics
Allergic Reaction	Generalized urticarial, angioedema or anaphylaxis
Peripheral Neuropathy	Severe discomfort, objective weakness, loss of 2 - 3 previously present reflexes or sensory dermatomes
Fatigue	Normal activity reduced $\geq$ 50 %

If the adverse effects can be pinned to one drug in the regimen, it may be possible to change the offending drug. In situations where the toxicity cannot be pinned to one single drug, it may be necessary to switch the entire regimen. It is the right decision to stop all the 3 ARVs and then resume when patient is well again.

Table 18: Toxicity of ART and suggested alternative during ART change

Regimen	**Toxicity**	**Drug Substitution**
TDF/3TC/EFV	• EFV-related persistent CNS toxicity	• Switch EFV to DTG or NVP
TDF/3TC/NVP	• NVP related severe hepatotoxicity • NVP-related severe rash (but not life threatening) • Steven-Johnson's Syndrome	• Switch NVP to integrase inhibitors or lopinavir/ritonavir. EFV is also an option if the NVP related hepatotoxicity is mild. • Switch to Lopinavir/ ritonavir • Consult expert

Approaches to change ART during certain clinical conditions

- Atazanavir induced hyperbilirubinemia is a theoretical risk for the new born. Therefore, change to LPV/r regimen.
- In TB patients using rifampicin and on NVP based 1st line ART, change NVP to EFV or use NVP with adjusted dose.
- Substitution of rifabutin for rifampicin in the presence of protease inhibitors.

5.3. Factors that need to be considered before changing ART

When changing ART, many factors must be considered in order to choose a regimen that the patient can be successful with for the long term. The following must be considered when changing regimens:

- Obtain prior antiretroviral history to determine previous toxicities and/or response to therapy,
- Be aware of previous adverse effects and of the adverse effect profile of the suggested new regimen
- Identify barriers to adherence and help the patient to resolve adherence issues,
- Ascertain their ability to follow-up in clinic for lab monitoring,
- Identify and avoid potential drug interactions, identify other disease states which may impact success of therapy, cost and sustainability.

5.4. Role of pharmacy professionals in monitoring and changing therapy

- Discuss with patients about importance of regular follow-up to assess and identify clinical efficacy or treatment failure and to detect drug related toxicity.
- Regularly promote and reinforce adherence to ART during each visit.
- Educate patients about the potential side effects of ART regimen during and beyond initiation.
- Provide advice in preventing and managing potential side effects.
- Provide information to other healthcare providers about the next regimens to be used after switching or changing of therapy.
- Provide information for other healthcare provider on regimen selection, the availability of different options, dosage forms and consult on drug-drug interaction.
- Discuss with professionals and patients on general issues related to treatment failure and potential prevention strategies.

Case studies

Case No. 1

A 33 year-old female patient who has been on ART for about 3 weeks appears to emergency OPD with severe global headache and high grade fever. On examination, her temperature is 38.6 degrees. Neurological examination revealed meningeal signs are positive and she is confused. On investigation, her CD4 count turned out to be 56. The physician at the OPD is entertaining the diagnosis as probable cryptococcal meningitis. Is it clinical failure (new OI on ART) or IRIS? Why? Do you recommend stopping treatment?

Case No. 2

A 28-year-old male diabetic patient was started ART with AZT/3TC/NVP regimen. After a few weeks later, he was brought to medical OPD with severe generalized body weakness. On examination, he appeared weak, had pale conjunctiva. On investigation of CBC, his hemoglobin is turned out to be 4.8 gm/dl. What is the next step management in the care of this patient?

Session Summary

- Ongoing laboratory monitoring is necessary to detect all side effects and to monitor success or failure of therapy. Patients need critical follow up on the first six month of therapy
- Treatment failure occurs because of preexisting resistance, limited regimen potency, imperfect adherence, poor absorption, rapid elimination, or drug-drug interactions.
- Therapy should not be changed unless absolutely necessary.
- The main reasons for changing ART are treatment failure and drug toxicity.
- Other reasons for changing ART include problems with adherence or other medical conditions or illnesses that may impact choice of therapy.
- Pharmacy professionals play critical role in the process of changing therapy by

providing information pertaining adherence, side effects, drug-drug interactions, available dosage form and selection of drugs

Session 6: Management of HIV/AIDS in Women and Children

Session Description

This Session deals with special issues during the management of HIV/AIDS in women and children. Because common issues are addressed in the other sessions. First it provides an overview of HIV/AIDS in women and children. Then it describes the prevention of mother to child transmission of HIV and the national PMTCT guidelines and strategies. It further explains transmission, diagnosis, and treatment of HIV in infants and children. Finally, it shows different pediatric ARV drugs formulations.

Primary Objective:

The primary objective of this session is to describe special considerations in the management of HIV/AIDS in women, exposed infants, and HIV infected children.

Enabling Objectives

By the end of this session participants will be able to:

- Describe the epidemiology of HIV in women and children
- Discuss the effect of gender differences regarding ART
- Discuss the unique considerations for the management of HIV infection in pediatrics
- List risk factors for maternal to child transmission and the interventions
- Explain management of HIV in pediatric patients
- Describe available pediatrics ARV formulations
- Discuss the adherence and feeding issues in pediatrics
- Discuss the role of the pharmacy professional in management of HIV in women and children

Session Outline

- Epidemiology of HIV/AIDS in women and children
- Gender differences between men and women regarding ART
- Unique considerations for diagnosis and barriers to management pediatric ART
- Risk factors for maternal to child transmission
- Intervention to reduce MTCT
- Management of HIV in pediatric patients

- Available pediatrics ARV formulations
- Adherence issues in pediatric patients
- Feeding issues in pediatric patients
- Role of the pharmacy professionals in management of HIV in women and children
- Session Summary

Session 6.1: Management of HIV/AIDS in Women

Case study: Paired discussion

Introductory Case

AM is 30 years old lady who is amenorrhoeic for the last 2 months. During her first ANC visit, she was tested for HIV and was found to be HIV positive. She has no illness in the past and her CD4 count is 800cells/mm3.The practitioner decided to start her on ART after adherence counseling. Today she came with prescription to your pharmacy with a regimen TDF, 3TC and EFV. Which of the following statement/s is/are true?

1. Efavirenz is contraindicated in pregnancy.
2. Risk of ART toxicity is high in women.
3. Adherence issues are more complicated in women
4. Mixed feeding should be avoided to decrease MTCT.

6.1.1 Epidemiology of HIV/AIDS in women

According to the 2018 Ethiopian Public Health institute (EPHI) estimates, there are about 379,251 women infected with HIV (about 62.1% of the total adult and adolescent HIV cases) in Ethiopia. Despite a decreasing trend in the incidence of new infections, this figure is projected to be about 375,311 in 2021 without significant change in the proportion of HIV prevalence in women.

6.1.2 Gender differences between men and women regarding HIV and ART

Paired discussion and summary Q & A:

Participants discuss in pairs about 10 minutes on the differences between man and female regarding HIV/AIDS and ART.

Summary Questions

1. Women with similar CD4 counts as men usually tend to have more viral loads than men. (True/False)
2. Given same doses, women are at higher risk of developing toxicities because of the medicines they are taking than men. (True/False)
3. Why do we worry about pharmacokinetic differences between men & women?
4. Do you agree women need a stronger support than men to attain a better adherence? Why?

Vulnerability

- Women and young girls are disproportionately vulnerable to HIV. Their physiological susceptibility – at least 2 to 4 times greater than men's – is compounded by social, cultural, economic, and legal forms of discrimination.
- Infection in women and girls is fueled by:
  - Poverty, low status, and unequal economic rights and educational opportunities that can place women and girls at greater risk of sexual exploitation, trafficking and abuse.
  - Gender power relations that limit women's ability to negotiate safe sex or refuse unwanted sex. Many women are powerless in their societies to encourage or insist upon condom use by their male partners.
  - Exploitation such as rape and abuse of young women and girls, especially in emergency and conflict situations.
  - Older men who often seek younger sexual partners. Even in marriage this age discrepancy can increase a girl's risk of infection.
  - Certain gender norms such as those that encourage men and boys to engage in risky, early, or aggressive sexual behavior increase the vulnerability of both men and women.
  - Cultural practices that deprive women of a means of protecting themselves from HIV infection, including early and forced marriages.

Viral Load and Disease Progression

- Women tend to have lower viral loads than men at similar CD4 counts, but women and men progress at similar rates. The presence of the lower viral load may be misleading and give the physician a false sense of security about the woman's disease. Use the CD4 count along with the viral load for accurate assessment. There is no advantage to be a woman in terms of the progression of this disease.

Drug interaction and Pharmacokinetics

- On average, men are larger than women, resulting in larger distribution volumes and altered clearance. Women have higher body fat content. Hepatic metabolism differs between men and women.
- The need for greater attention to PK differences is the fact that women have a 1.5-1.7 –fold greater risk of having an adverse drug reaction compared with men. PK studies have shown that women experience higher drug levels, which may put them at greater risk for toxicities.
- Some PIs may decrease estrogen (women hormone) levels, while atazanavir and efavirenz may increase estrogen levels. Reduction in natural levels of estrogen may be associated with other complications, such as the onset of early menopause or loss of bone density. Despite the differences in terms of drug toxicity and interactions, the efficacy of ARV drugs in men and women are comparable.
- NNRTIs and PIs interfere with blood levels of combination oral contraceptives and are associated with decreased levels of ethinyl estradiol, resulting in decreased contraceptive effectiveness. So, it is recommended to use additional or alternate method of contraception.

Women and Adherence

- Adherence issues are more complicated for women who need special attention and support: The reasons include failure to disclose HIV status due to stigma, feeling isolated, having responsibility as caregiver and challenges in accessing and maintaining care.
- Helping a woman to adhere to her care and treatment is very important because without good adherence, a woman will experience disease progression, be at higher risk for opportunistic infections, and be more likely to transmit HIV to her partner(s) and unborn baby.

ARV toxicity in Women

- Women are at increased risk of ART side effects including rash (5.5-7.3 times more), hepatotoxicity (3 times more), lactic acidosis (even though it is rare, it occurs more commonly in women especially those with higher CD4 count), mitochondrial toxicity, dysmenorrhea Lipodystrophy/Hyperlipidemia osteoporosis and renal compromise.
- Fat accumulation is more common in women, but fat depletion is more common in men. Accumulation and depletion in different body areas of same person occurs equally in men and women. Lipid abnormalities like triglyceride and cholesterol level elevations more common in men.

6.1.3 When and what ART to start in Pregnant and Breastfeeding women

- Start ART as early as possible to all pregnant and breastfeeding women living with HIV regardless of their WHO clinical stages and CD4 counts.
- For women identified at labor and delivery, provide ART the same hour with brief counseling and provide detailed counseling on ARV and adherence after delivery.
- Remember that TDF+3TC+EFV is the preferred regimen for pregnant and breastfeeding mothers.

Session 6.2: Management of HIV infection in Children and PMTC

Introductory Case

YB is a 2 years old female child who was diagnosed to be HIV positive one week ago. She had no illness in the past and no current medical complaint. Her CD4 count is 1000cells/mm3. The mother is concerned that YB may refuse to take drugs if she has to be on treatment. Which of the following statement/s is/are true?

1. There is no need to start ART as she has WHO clinical stage 1 disease.
2. Preferred first line ART regimen for YB is ABC, 3TC and LPV/r.
3.There are many strategies to assist with adherence in the pediatric population

6.2.1 Epidemiology of HIV/AIDS in children

Global

According to the UNAIDS, there were about 2.1 million children less than 15 years old in 2016 globally living with HIV; 160,000 children became newly infected with HIV and about 120,000 children died of AIDS in the same year. Estimated number of children (aged 0-14years) living with HIV and receiving ART was 43% in 2016.

National

According to the Ethiopian Public Health Institute (EPHI) HIV related estimates and projections for Ethiopia, in 2018 there are 56,514 HIV infected children younger than 15 years who are also eligible for ART. The 2018 total estimated number of new HIV infections among children younger than 15 years is 2,994 and estimated annual death is 3,181.

6.2.2 HIV transmission in children

Majority of children (90%) are infected through mother to child transmission during pregnancy, labor, and delivery, or whilst breastfeeding.

- The overall risk of MTCT is 35% where the estimated risk of becoming infected during pregnancy, labor and delivery is about 20% and post-natal (after delivery), through breastfeeding is about 15%.
- The risk of transmission during pregnancy is low, as the placenta protects the developing baby. During labor and delivery, the risk is increased through sucking, absorbing or aspirating blood or cervical fluid.

Risk factors for MTCT

There are several risk factors influencing MTCT of HIV. Some of the major factors are:

Maternal factors	**Infant factors**
• High viral load • Low CD4 count with advanced disease • Labor & delivery factors (prolonged rupture of membrane, chorioamnionitis, injury to birth canal, instrumental delivery, delayed infant cleaning & eye care, routine infant suctioning)	• Prematurity • Oral thrush and ulcer • Birth order (first twin) in twin pregnancies • Invasive fetal monitoring during labor and delivery

• HIV infection during pregnancy/ breast feeding • Mixed feeding • Crackled nipples and breast abscess • Viral or parasitic placental infection (especially malaria) • Maternal malnutrition	• Instrumental delivery

Other ways in which children can get HIV are:

- Sexual abuse
- Unsafe injections/injection by local healer
- Blood transfusion from HIV infected blood products
- Wet nursing by untested woman (breastfeeding by a woman rather that the mother may cause infection to the infant if that woman is not tested for HIV and necessary precautions are not taken).
- Manipulation by local healer (uvula cutting, milk teeth extraction, tonsillectomy),
- Feeding children by chewed food by the mother / adult care taker,
- using sharp object contaminated with HIV infected blood

6.2.3 Prevention of mother to child transmission of HIV

There are four prongs to prevent **m**other-**t**o-**c**hild **t**ransmission of HIV infection (PMTCT):

Prong 1: Primary prevention of HIV infection - focuses on keeping parents-to-be HIV negative.

Prong 2: Prevention of unintended pregnancies among women infected with HIV**.**

Prong 3: Prevention of HIV transmission from women infected with HIV to their infants – addresses care for infants born to HIV-positive women and their mothers during pregnancy, labor and childbirth, and the postpartum period**.**

Prong 4: Provision of treatment, care, and support for women infected with HIV, their infants, and their families**.**

- Access to quality and comprehensive maternal and newborn health services (i.e., antenatal, labor and childbirth, postpartum and newborn care services) which integrate access to HIV testing and counseling is central to any effort to prevent mother-to-child transmission of HIV.

- The current national recommendation for PMTCT is option B+ which is to start all pregnant and breast-feeding women on lifelong ART. The preferred ART regimen is TDF, 3TC and EFV (See the table below).

Table 19: Summary of maternal & infant ARV prophylaxis for different clinical scenarios

Scenario	**Maternal ARV a**	**Infant ARV Prophylaxis b**	**Duration of infant ARV prophylaxis**
Mother diagnosed with HIV during pregnancy	Initiate maternal ART	NVP Or AZT+NVP based on risk	NVP for 6 weeks. If mother took ART for <4 weeks, NVP+AZT for the first 6 weeks and continue NVP for additional 6 weeks **OR** extended NVP alone for 12 weeks.
Mother diagnosed with HIV during labor or immediately postpartum and plans to breastfeed	Initiate maternal ART	NVP+AZT OR NVP	NVP+AZT for the first 6 weeks and continue NVP for additional 6 weeks **OR** extended NVP alone for 12 weeks.
Mother diagnosed with HIV during labour or immediately postpartum and plans replacement feeding	Initiate maternal ART	NVP+AZT OR NVP	NVP+AZT for the first 6 weeks **OR** NVP alone for 6 weeks.
Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) and is on breastfeeding	Initiate maternal ART	NVP+AZT OR NVP	NVP+AZT for the first 6 weeks and continue NVP for additional 6 weeks or extended NVP alone for 12 weeks. plus take DBS specimen for DNA PCR for EID same day if infant older than 4weeks
Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) within 72 hours and is not breastfeeding	Initiate maternal ART	NVP+AZT OR NVP	NVP+AZT for the first 6 weeks **OR** NVP alone for 6 weeks.

Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) after 72 hours and is not breastfeeding	Initiate maternal ART	No ARV prophylaxis	Take DBS, do DNA PCR test, initiate treatment if the infant is infected
Mother receiving ART but interrupts ART regimen while breastfeeding (such as toxicity, stock-outs or refusal to continue)	Determine an alternative ART regimen; counsel regarding continuing ART without interruption	NVP	Until 6 weeks after maternal ART is restarted or until 1-week after breastfeeding has ended

a. If there is documented maternal viral suppression near delivery for a mother receiving ART and using replacement feeding, four weeks of infant ARV prophylaxis may be considered.

b. If infant AZT or NVP cause toxicity or not available, 3TC can be substituted.

Table 20: Dosage of AZT and NVP syrup for infant prophylaxis for different age groups

Infant age	Dosing of NVP	Dosing of AZT
Birth to 6 weeks		
Birth weight 2000−2499g [a]	10 mg once daily (1 ml of syrup once daily)	10 mg twice daily (1 ml of syrup twice daily)
Birth weight ≥2500 g	15 mg once daily (1.5 ml of syrup once daily)	15 mg twice daily (1.5 ml of syrup twice daily)
>6 weeks to 12 weeks		
	20 mg once daily (2 ml of syrup once daily or half a 50 mg tablet	No dose established for prophylaxis; use treatment dose 60 mg twice daily 6 ml of syrup twice daily or a 60 mg tablet twice

a For infants weighing <2000 g and older than 35 weeks of gestational age, the suggested doses are: NVP 2 mg/kg per dose once daily and AZT 4 mg/kg per dose twice daily. Premature infants younger than 35 weeks of gestational age should be dosed using expert guidance.

Note:

- AZT and NVP concentration is 50mg/5ml.
- Follow the manufacturer's instruction for the duration of use following opening. The bottle should be labeled with the date on which it was 1st opened.
- Infant dosing: The oral syringe should not be placed directly into the bottle. Infant dose should be measured by pouring a small amount of NVP syrup into a cup, and then draw the actual dose with oral syringe. Discard the leftover suspension in the cup.

6.2.4 Diagnosis of HIV in infants and children

- Early recognition of HIV infection in infants and children is crucial since there is fast progression of illness with 50% mortality by two years of age. Virologic tests are used to diagnose HIV infection in infants less than 18 months of age. Rapid HIV antibody test is used for infants ≥18 months of age.
- It is currently recommended that HIV testing, and counseling should be offered to all under five children visiting health facilities. Diagnosis of HIV infection in a child implies potential HIV infected case among family members. Hence, HIV counseling and testing should be offered to family members of HIV infected child.

Laboratory Diagnosis of HIV Infection in Infants and children

Specialized tests are required for infant diagnosis. These include DNA PCR, RNA PCR, and P24 antigen. PCR tests are the most widely available. The sensitivity of PCR tests increases during the first few weeks of life from 38% at birth to 96% at 4 weeks.

Table 21: Antibody versus virologic tests

Antibodies tests, including rapid test	Virologic assays such as RNA or DNA PCR
• These tests detect antibodies made by immune cells in response to the virus • Antibodies from the mother pass on to child and most have gone by 12 months of age, but in some instances, they do not disappear until the child is 18months of age • This means that a positive antibody test in children under the age of 18 months is not a reliable way to check for infection of the child	• These tests directly detect the presence of the HIV virus or products of the virus in the blood • Positive virologic test can therefore reliably detect HIV infection at any age, even before the child is 18 months old • If the tests are negative and the child has been breast-feeding, this does not rule out infection as the baby may have just become infected. • Tests done six weeks or more after completely stopping breast feeding are thought reliably rule out infection

Interpretation of HIV Test Results

The breast milk of an HIV-positive mother can transmit HIV infection. The main point that you need to remember is a positive virologic (DNA PCR) test at any age implies that the baby is HIV infected (two tests), and a positive ANTIBODY test at 18 months or more implies the child is HIV infected.

6.2.5 Care of HIV exposed infants

Infants born to HIV positive pregnant women are HIV exposed (HEI) by definition and these infants can be infected with HIV during pregnancy, labor, delivery or after birth by breast feeding.

Components of care for HEI:

1. **History**
2. **Physical examination**
3. **Growth assessment**

- Growth is the most sensitive clinical indicator of HIV infection in infants and young children.
- Children with HIV infection are at high risk for poor growth.
- Growth should be monitored closely for all HIV exposed and infected infants.

4. **Developmental assessment**: Use developmental check list to assess growth & development.
5. **Infant feeding:** Nutrition and feeding history should be assessed regularly.
6. **Immunization**: All HEI should be immunized according to expanded program on immunization (EPI) recommendations.
7. **ARV prophylaxis**

- For infants born to HIV infected mothers and on breastfeeding
  - Initiate ART for the mother
  - Infants of mothers who are receiving ART and are breastfeeding should receive 6 weeks of infant prophylaxis with daily NVP. If the infant is considered at high risk, provide enhanced AZT+NVP for the first 6 weeks followed by NVP alone for additional 6 weeks. If AZT is not available, provide extended NVP alone for 12 weeks. Refer Table 19.
  - Collect specimen for DNA PCR testing at 6 weeks of age.
- For infants born to HIV infected mothers but not breast feeding:
  - Initiate ART for the mother
  - If the infant is brought within 72 hours of birth provide NVP prophylaxis for 6 weeks; otherwise there is no need to provide NVP syrup for the infant.
  - If the infant is considered at high risk, provide enhanced AZT+NVP for 6 weeks. Refer Table 19.
  - Collect specimen for DNA PCR testing at 6 weeks of age.
- High-risk infants are defined as those infants:
  - Born to women with established HIV infection who have received less than four weeks of ART at the time of delivery; OR
  - Born to women with established HIV infection with viral load >1000 copies/ml in the four weeks before delivery, if viral load measurement available; OR
  - Born to women with incident HIV infection during pregnancy or breastfeeding (incident HIV infection is new HIV diagnosis in pregnancy or breastfeeding woman with a prior negative HIV test during pregnancy); OR

- Identified for the first time during the postpartum period, with or without a negative HIV test prenatally.

8. Co-trimoxazole preventive therapy (CPT)

- Using pediatric co-trimoxazole in ALL HIV EXPOSED INFANTS significantly reduces the rate of PCP and other bacterial infections and in turn reduces infant morbidity and mortality rates. Start co-trimoxazole to all HEI from 6 weeks of age and continue until the child is confirmed not to have HIV infection using antibody test after 18 months of age. Refer to table 22 below which is also presented in Session seven.

Table 22: Dosage of CPT in Adults, Adolescents, Children & Infants

Age (weight)	Suspension (240mg/5ml cotrimoxazole)	Single strength tab (480 mg of Co-trimoxazole)	Double strength tab (960 mg of Co-trimoxazole)
Up to 6 months (5 Kg)	2.5 ml/day	1/4 tab/day	-
6 months to 5 years (5-15 Kg)	5 ml/day	1/2 tab/day	-
6-14 years (15-30 Kg)	10 ml/day	1 tab/day	1/2 tab/day
>14 years (>30 Kg)	-	2 tab/day	1 tab/day

9. TB risk assessment

At each visit the infant should be evaluated for Tuberculosis. We need to ask for household exposure with an adult who has tuberculosis and symptoms suggestive of the disease and chest radiograph if clinically indicated.

10. Determination and evaluation of infection status

One of the goals of follow-up of HEI is to identify and treat the HIV infected ones early. All HEI should have virologic testing at 6 weeks of age or at earliest opportunity thereafter.

11. Current assessment and plan

At each visit based on the findings on history, physical examination (that includes growth and development assessment) and/or laboratory investigations, we need to have the assessment of the infant and we should plan our next steps in their management and follow-up.

12. Follow-up visits and schedule

Follow-up of HEI is recommended to be done monthly for the first six months of life then every 3 months until infection status is determined.

6.2.6 Care of HIV-Infected child

- All children who have confirmed HIV infection should be put on ART soon. Management of the HIV-infected child (HIC) is best achieved through integrated HIV services and primary health care. A multidisciplinary, family-centered approach to care is effective in engaging children and their families into long-term care. Comprehensive care and support for the HIV-infected child should be provided in a care and treatment center, preferably where the parent/caregiver receives treatment.
- Close regular follow-up is essential since these children are at risk of morbidity and mortality. Mortality estimates in Africa show that without treatment 35.2% of HIV-infected children will die in their first year and 52.5% by age two. This underscores the importance of timely antiretroviral treatment care and support.
- The goal of ART in children are to restore immune; maintain maximal suppression of viral replication; reduce HIV-related morbidity and mortality; and improve quality of life and prolong survival.

Components of care for HIV infected children (HIC)

Clinical assessment of the HIV-infected child should focus on the following:

- History with emphasis on previous AIDS defining conditions, history of ARV exposure (PMTCT or previous antiretroviral therapy), family members who are aware of the diagnosis, parental concerns, inter-current illness.
- Nutrition & growth assessment-plot weight, height & head circumference on growth chart.
- Developmental assessment using reference provided.
- Detailed physical exam looking for symptoms and signs suggestive of severe HIV infection.
- Clinical staging using WHO clinical staging.
- Immunological evaluation
- TB risk assessment – ask about history of TB contact and chest radiograph if clinically indicated.
- Co-trimoxazole preventive therapy – check eligibility based on clinical stage and/ or CD4

- Immunizations according to the National Expanded Program on Immunization.
- Nutrition counseling on provision of adequate nutrition, offer support as necessary.
- ART should be started after adequate assessment and adherence preparation.
- Adherence to care and co-trimoxazole preventive therapy should be reinforced at each visit.
- Disclosure of HIV status to a child should be discussed with the caregiver. Disclosure should be introduced early on in a neutral way, and should be tailored to the developmental maturity of the child. It is particularly important that adolescents be informed of their status, so they can become active participants in their own care.
- M & E: all intake and follow up forms should be completed and documented.

6.2.7 Special Considerations for pediatric ART

Dosing of ARV drugs:

There are special considerations with dosing of ARV drugs in HIV-infected children compared to adults, including dependence on chronologic age and/or body parameters (e.g., height, weight). Ongoing growth requires continuous reassessment of dosing of ARV drugs in order to avoid low drug exposure and development of viral resistance and virologic failure. Developmental differences in drug absorption, distribution, metabolism, and elimination contribute to high variability and a greater frequency of suboptimal exposure to multiple therapeutic agents including ARV drugs in children (particularly very young children) and adolescents compared to adults. Suboptimal exposure to selected ARV agents with recommended dosing has been demonstrated in pediatric patients, especially in young children.

Pediatric ARV drug recommendations are often based on extrapolation of efficacy results from large clinical trials in adults, and dosing recommendations for ARV drugs at the time of pediatric drug approval are frequently derived from a limited number of patients and pharmacokinetic (PK) modeling, and may be revised as newer PK data become available.

For simplification, doses are provided in ranges based on children's weights. Although weight and height can both be measured, it may be impractical to expect providers in many settings to accurately calculate body surface area (BSA).

Generally, for most drugs in 1st and 2nd line, in terms of weight band dosing, would prefer over- rather than under-dosing, to avoid development of resistance (exception might be for drug with significant toxicity known to be dose-associated, e.g., anemia and ZDV).

Drug pharmacokinetic varies by age. Younger children may need higher doses of drug to achieve same levels as with lower doses in older children. Yet pharmacokinetic in younger children not available for some of the WHO recommended drugs (e.g., EFV under age 3 years), thus choice of drugs in 1st or 2nd line regimens may differ depending on child's age.

Issues Related to Pediatric ARV drug formulations

- Not all tablets/capsules available in low enough doses for children.
- When child formulations are not available, splitting of adult tablets may be required to treat children. However, not all tablets are breakable. For example, LPV/r (100mg/25mg) tablet should not be split because it is formulated as melt-extrusion matrix tablet.
- When using adult formulations for children, be aware of potential under- or over-dosing because of inaccurate splitting.
- For NVP, children in certain weight categories would need FDC plus an additional dose of NVP; NVP also has issue of dose escalation. Implication: Must have ability to have liquid or tablet formulation of NVP alone available in addition to FDC.
- Opening capsules and mixing in liquid or food has been done to administer to children.

Challenges to pediatric ART

- Diagnostic challenges:

✓ Identification of HIV-exposed infants

✓ Need for virologic testing of infants <18 months

✓ Barriers to HIV testing of children (stigma, consent, etc)

- Complexity of ART administration:
  - ✓ Procurement of paediatric formulations
  - ✓ Weight-based dosing
  - ✓ Paediatric adherence
- Infrastructure & human resource requirements:

✓ PMTCT follow-up

- ✓ Systems for chronic care (appointments, medical records, community outreach)
- ✓ TrainingLimited availability of pediatric formulations

6.2.8 Individual Paediatric ARV drugs information

Paired Discussion

Discuss the individual Paediatric ARV drug in pairs for 30 minutes

Abacavir (ABC)

Formulations

Pediatric Oral Solution: 20 mg/mL

Tablets: 60mg (Dispersible)

Tablets: 300 mg (scored)

Fixed-Dose Combination Tablets:

With Lamivudine:

- Tablet: Abacavir 60mg plus lamivudine 30 mg

Dosing Recommendations

Please see dosage Chart

Neonate/Infant Dose:

- Not approved for infants aged <3 months.

For children who cannot swallow the *Dispersible Tablet* whole, advice care givers to do:-

1. Take 2 teaspoons (10ml) water in a small and clean container and add the required dose
2. Swirl the container until tablet disperses, and administer the entire mixture immediately
3. Rinse the container with an additional 10ml of water and get the child drink this water

Selected Adverse Events

- Hypersensitivity reactions
- Increased risk of myocardial infarction in adults; there are no data in children.

Special Instructions

- Warn patients and parents about risk of serious, potentially fatal hypersensitivity reactions. Occurrence of hypersensitivity reactions requires **immediate and permanent discontinuation** of abacavir. Do not re-challenge.
- Abacavir can be given without regard to food. Oral solution does not require refrigeration.

Zidovudine (AZT)

Formulations

Pediatric Oral Solution: 10 mg/mL

Tablets: 300mg

Fixed-Dose Combination Tablets:

With lamivudine*:*

- Tablet: 60 mg Zidovudine plus 30 mg Lamivudine
- Tablet: 300 mg Zidovudine plus 150 mg Lamivudine

With lamivudine and Nevirapine

- Tablet: 60 mg Zidovudine plus 30 mg Lamivudine plus 50mg Nevirapine

Dosing Recommendations	**Selected Adverse Events**
Please see dosage Chart Administration – tablets • 60 mg tablets are scored and can be split. • 300 mg tablets are often not scored – may be cut in half with a tablet cutter in a pharmacy. • Tablets may be crushed and combined with a small amount of food or water and immediately ingested.	• Bone marrow suppression: anemia, neutropenia • Nausea, vomiting, headache • Lactic acidosis/severe hepatomegaly with hepatic steatosis • Lipoatrophy • Myopathy **Special Instructions** • Give zidovudine without regard to food. • If substantial anemia develops, it may be necessary to discontinue therapy until bone marrow recovery is observed.

Lamivudine (3TC)

Formulations

Pediatric Oral Solution: 10 mg/mL

Tablets: 150mg

Fixed-Dose Combination Tablets:

With Zidovudine*:*

- Tablet: 60 mg Zidovudine plus 30 mg Lamivudine
- Tablet: 300 mg Zidovudine plus 150 mg Lamivudine

With Zidovudine and Nevirapine

- Tablet: 60 mg Zidovudine plus 30 mg Lamivudine plus 50mg Nevirapine

With Abacavir*:*

- Tablet: Abacavir 60mg plus lamivudine 30 mg

With TDF

- Tablet: 300mg Lamivudine plus 300mg TDF

With TDF and Efavirenz

- Tablet : 300mg Lamivudine plus 300mg TDF plus 600mg Efavirenz

Dosing Recommendations	**Selected Adverse Events**
Please see dosage Chart Note: Once-daily dosing is not yet approved for children but encouraging pharmacokinetic data are available for children switching to once-daily dosing once viral suppression occurs on ART. Administration – adult tablets(150mg) • Tablets are scored and can be easily divided; may be crushed and mixed with a small amount of water or food and ingested immediately	Minimal toxicity • Exacerbation of hepatitis after discontinuation of lamivudine in the setting of chronic Hepatitis B virus infection. **Special Instructions** • No food restrictions, oral solution may be stored at room temperature. • Screen patients for Hepatitis B virus infection before administering lamivudine.

Tenofovir Disoproxil Fumarate (TDF)

Formulations:

Fixed-Dose Combination Tablets:

With Lamivudine*:*

- Tablet: 300 mg Tenofovir plus 300mg Lamivudine
- Tablet: 75 mg Tenofovir plus 75mg Lamivudine *

With Lamivudine and Efavirenz

- Tablet: 300 mg Tenofovir plus 300 mg Lamivudine plus 600mg Efavirenz *(For >10 years and >35 kg)* (scored)
- Tablet: 75 mg Tenofovir plus 75 mg Lamivudine plus 150mg Efavirenz *

(currently not available in Ethiopia)*

Dosing Recommendations	**Selected Adverse Events**
Please see dosage	• *More common:* Nausea, diarrhea, vomiting, and flatulence. • *Less common (more severe):* TDF caused bone toxicity (osteomalacia

Chart **Neonate/Infant Dose:** Not FDA approved or recommended for use in neonates/infants aged <2 years.	and reduced bone mineral density [BMD]) in animals when given in high doses. Renal toxicity and lactic acidosis have been reported. **Special Instructions** • Do not crush tablets • Although TDF can be administered without regard to food, food requirements vary depending on the other antiretroviral (ARV) drugs contained in a combination tablet.

Efavirenz (EFV)

Formulations:

Capsule: 50mg

Capsule: 200mg

Tablet: 600mg

NB: Efavirenz Capsule (50 mg and 200 mg) are being replaced with 200 mg tablet, double scored so address different Weight/age bands.

Fixed-Dose Combination Tablets:

With Tenofovir and lamivudine

- Tablet: 300 mg Tenofovir plus 300 mg Lamivudine plus 600mg Efavirenz

Dosing Recommendations *Please see dosage Chart* **Neonatal Dose:** Efavirenz is not approved for use in neonates.	**Selected Adverse Events** • Rash • Central nervous system symptoms such as dizziness, somnolence, insomnia, abnormal dreams, impaired concentration, psychosis, seizures, suicidality **Special Instructions** • Efavirenz can be swallowed as a whole capsule or tablet or administered by sprinkling the contents of an opened capsule on food as described below. (Capsules or tablet have very peppery

	taste). • Avoid administration with a high-fat meal because of potential for increased absorption and hence CNS toxicity. • Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of central nervous system side effects. **Instructions for Use of Capsule as a Sprinkle Preparation with Food or Formula:** • Hold capsule horizontally over a small container and carefully twist to open to avoid spillage. • Gently mix capsule contents with 1–2 teaspoons of an age-appropriate soft food (e.g. yogurt or banana), or reconstituted infant formula at room temperature. • Administer infant formula mixture using a 10-mL syringe. • After administration, an additional 2 teaspoons of food or infant formula must be added to the container, stirred, and dispensed to the patient. • Administer within 30 minutes of mixing and do not consume additional food or formula for 2 hours after administration.

Nevirapine (NVP)

Formulations:

Pediatric Oral Suspension: 10mg/1mL

Tablet: 200mg

- Tablet: 60 mg Zidovudine plus 30 mg Lamivudine plus 50mg Nevirapine

Fixed-Dose Combination Tablets:

With Zidovudine and Lamivudine

Dosing Recommendations	**Selected Adverse Events**
Please see dosage Chart	• Rash, including Stevens-Johnson syndrome **Special Instructions**

Neonate/Infant Dose (≤14 Days) for Prevention	• Shake suspension well before administering • Can be given without regard to food. • Tablets can be crushed and mixed with a small amount of water or food and immediately ingested

Lopinavir/Ritonavir (LPV/r)

Formulations:

Pediatric Oral Solution: 80 mg/20 mg LPV/r per mL

Film-Coated Tablets: 100 mg/25 mg LPV/r, 200 mg/50 mg LPV/r

NB: LPV/r 80mg/20mg/ml oral syrup is being replaced by LPV/r (40/10mg) oral pellet. Unlike LPV/r 80mg/20mg/ml oral syrup, the pellet form does not require refrigeration, has no unpleasant taste and is easy to calculate and administer dose.

Dosing Recommendations	**Selected Adverse Events**
Please see dosage Chart **Neonatal Dose (<14 Days):** No data on appropriate dose or safety in this age group. Do not administer to neonates before a post-menstrual age of 42 weeks and a postnatal age of at least 14 days because of potential toxicities. **Formulations** *Palatability* The poor palatability-bitter taste. Numbing of the taste buds with ice chips before or after administration of the solution, masking of the taste by administration with sweet or tangy foods, or peanut butter can be used to manage the poor palatability of Lpv/r. Alternative pediatric formulations are currently being developed. *Do Not Use Crushed Tablets* Lopinavir/ritonavir tablets must be swallowed whole. Crushed tablets are slowly and erratically absorbed, and result in significantly reduce AUC, Cmax, and C_{trough} compared with swallowing the whole tablet.	• Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, taste alteration • Fat maldistribution • Risk of toxicity—including life-threatening cardiotoxicity—is increased in premature infants **Special Instructions** • Lopinavir/ritonavir tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability. • Lopinavir/ritonavir tablets must be swallowed whole. Do not crush or split tablets. • Lopinavir/ritonavir oral solution should be administered with food because a high-fat meal increases absorption. • Lopinavir/ritonavir oral solution can be kept at room temperature up to 77o F (25^{o} C) if used within 2 months. If kept refrigerated (2^{o} to 8^{o} C) lopinavir/ritonavir oral solution remains stable until the expiration date printed on the label. • Once-daily dosing is not recommended because of considerable variability in plasma concentrations in children aged <18 years and higher incidence of diarrhea.

	• Higher doses of LPV/r may be required when co-administered with enzyme-inducing drug, rifampicin.

Ritonavir (RTV)

Formulations:

Oral Solution: 80 mg/mL

Capsules: 100 mg

Dosing Recommendations	**Selected Adverse Events**
Ritonavir as a Pharmacokinetic (PK) Enhancer: Only recommended use at present is as a booster for lopinavir/ritonavir when co-administered with rifampicin-containing TB treatment	• Gastrointestinal intolerance, nausea, vomiting, • diarrhea • Taste perversion • Fat maldistribution **Special Instructions** Do **not** refrigerate ritonavir oral solution; store at 20°C to 25°C. Shake the solution well before use. Ritonavir oral solution has limited shelf life; use within 6 months. • Refrigerate ritonavir capsules only if the capsules will not be used within 30 days or cannot be stored below 25°C. • May need to use techniques described for LPV/r to improve tolerance of bitter taste.

Table 23: Management of issues related to administration of ARVs in pediatric patients

Issue	**Management**
Adherence	• Educate family with counseling and home-based support • Use fixed dose combinations when available • Replace large volumes of suspensions with tablets or capsules, if possible (age >3 years) • Try to administer same drugs across HIV infected family members on ART, if possible • Encourage older children (>8 years) to take responsibility for taking medications • Choose time(s) compatible with child's daily routine / activities; avoid administering medications during school hours
Refrigeration requirements	• Refrigerate (2-8°C) suspensions of LPV/r. If unable to refrigerate, use within 60 days • AZT, ABC, NVP suspensions do NOT require refrigeration
Taste/flavor	• Protease-inhibitor suspensions have a very strong, bitter taste. May have to be given with milk, fruit jam, cheese, butter, or juice to improve adherence, if it is nutritionally age-appropriate to do so. May give with a small amount of formula in infants.

	• EFV can have a peppery taste that can be reduced if given with something with sugar or a small amount of milk or formula
Nausea	• Symptoms resolve with time (usually first month) • May give with small amount of formula, milk, or food
Timing	• 30 minutes before or after meals, except EFV which is given at bedtime.
Dosing	• Use FMOH consolidated guidelines to calculate ARV doses for individual children by weight
Dose Adjustments	• NVP induction therapy per FMOH guidelines • Increase ritonavir level to LPV by administering LPV/r during rifampicin TB treatment
Splitting Tablets	• Avoid splitting combination tablets, unless scored. • Do NOT split tablets by more than ½. • Do NOT split LPV/r tablets
Pill Size Burden	• Administer smallest pill first and then progress to larger pills. • Capsules, except LPV/r, can be opened and sprinkled over food or drink

Paediatric Dosage Exercise

Table 24: Lists of ARV formulations for children

Drug class (fixed-dose combination)	Product	Formulation	Strength	Best to be used for (consider weight range, age group or its special use)
NNRTI	EFV	Capsule	200 mg	
NNRTI	EFV	Capsule	50mg	
NNRTI	NVP	Oral liquid	50 mg/5 ml	
Protease inhibitor	LPV/r	Tablet (heat-stable)	100 mg/25 mg	
Protease inhibitor	LPV/r	Oral liquid	80 mg/20 ml	
Fixed-dose combination	AZT + 3TC	Tablet (dispersible, scored)	60/30 mg	
Fixed-dose combination	AZT + 3TC + NVP	Tablet (dispersible, scored)	60/30/50 mg	
Fixed-dose combination	ABC + 3TC	Tablet (dispersible, scored)	60/30 mg	

Scenario One

4-year-old HIV positive child whose weight is 16 kg come to ART pharmacy with a prescription of AZT+3TC (60mg+30mg) 2 tablets BID and EFV 200 mg tablet, OD.

- Comment on the dosage in the prescription

- Dispense the best formulations to the care giver/parent. Which formulation/strength do dispense for the best child adherence?

Scenario Two

The care giver of 19-month-old HIV positive child whose weight is 6 kg comes with a prescription ABC+3TC (60mg+30mg) tablets, 2 tablets in morning and 1 tablet at night, and LPV/r Syrup 80/20 mg/ml, 2ml in morning and 1 ml at night

- Comment on the dosage in the prescription.
- Dispense the best formulations to the care giver/parent. Which formulation/strength do dispense for the best child adherence?
- Discuss on important counseling points need to be given to the care giver.

NB: ABC 60mg/3TC 30mg dual FDC is replaced by ABC 120mg/3TC 60mg dual FDC because it reduces pill burden for older/heavier children and less expensive compared to ABC 60mg/3TC 30mg.

Table 25: Simplified dosing of solid and oral liquid formulations **for twice-daily dosing** for infants and children 4 weeks of age and older

Drug	Formulations (tablet, capsule or oral liquid) and strength (mg/tab. or mg/ml for liquids)	Dose as number of tablets or ml by weight band, morning(AM) and evening (PM)										Adult tablets and their strength in mg	Dose as number of tablets by weight band			
		3 – 5.9Kg		6-9.9kg		10-13.9kg		14-19.9kg		20-24.9kg			25-29.9		30-34.9	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM	AM	PM
Solid formulations																
ABC/3TC	120mg/60mg (scored, dispersible tab)	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5	600mg/300mg tab	0.5	0.5	0.5	0.5
ABC/3TC	60mg/30mg (scored, dispersible tab)	1	1	1.5	1.5	2	2	2.5	2.5	3	3	600mg/300mg tab	0.5	0.5	0.5	0.5
ABC	60mg(dispersible tablet)	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300mg tab	1	1	1	1
AZT/3TC	60mg/30mg (scored, dispersible tab)	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300mg/150mg tab	1	1	1	1
AZT/3TC/NVP	60mg/30mg/50mg (scored, dispersible	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300mg/150mg/200mg tab	1	1	1	1
AZT	60mg (dispersible	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300mg tab	1	1	1	1
DRV [a]	75mg tablet	-	-	-	-	3	3	5	5	5	5					
LPV/r [b, c]	40mg/10mg oral pellets per capsule	2	2	3	3	4	4	5	5	6	6	200mg/50mg tab	2	1	2	1
	100mg/25mg tablet	-	-	-	-	2	1	2	2	2	2		2	1	2	1
NVP [d]	50mg (scored, dispersible	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200mg tab	1	1	1	1
RAL	100 mg, chewable tablet	-	-	-	-	-	-	1	1	1.5	1.5	400mg tab	1	1	1	1
	25mg, chewable tablet	-	-	-	-	3	3	4	4	6	6		1	1	1	1
	100 mg granules per sachet	0.25	0.25	0.5	0.5	-	-	-	-	-	-		1	1	1	1
Liquid formulations																
ABC	20mg/ml	3ml	3ml	4ml	4ml	6ml	6ml	-	-	-	-		-	-	-	-
AZT	10mg/ml	6ml	6ml	9ml	9ml	12ml	12ml	-	-	-	-		-	-	-	-

3TC	10mg/ml	3ml	3ml	4ml	4ml	6ml	6ml	-	-	-	-		-	-	-	-
NVP [d]	10mg/ml	5ml	5ml	8ml	8ml	10ml	10ml	-	-	-	-		-	-	-	-
LPV/r [e]	80mg/20mg/ml	1ml	1ml	1.5ml	1.5ml	2ml	2ml	2.5ml	2.5ml	3ml	3ml		-	-	-	-
DRV [a]	100mg/ml	-	-	-	-	2.5ml	2.5ml	3.5ml	3.5ml	-	-		-	-	-	-
RTV [f]	25mg tablet	-	-	-	-	2	2	2	2	2	2		2	2	2	2
	80mg/ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	-	-	-	-		-	-	-	-

[a] DRV must be administered with 0.5ml of RTV 80mg/mL oral suspension if the child weighs less than 15kg and with RTV 50mg solid formulation for children weighing 15–30kg. DRV/r should not be used in children younger than 3 years of age.

[b] LPV/r heat-stable oral pellets (presented in a capsule) must be administered by **opening the capsule and pouring the pellets over a small soft food** at room temperature and swallowed without chewing. The pellets **MUST NOT** be stirred, crushed, dissolved/dispersed in food. The capsules containing LPV/r oral pellets **must not** be swallowed whole.

[c] The LPV/r heat-stable tablet must be swallowed whole and should not be split, chewed, dissolved or crushed.

[d] NVP dose escalation with half dose for 2 weeks when initiating ART is still recommended to avoid toxicity from high initial NVP levels.

[e] LPV/r liquid requires a cold chain during transport and storage.

[f] RTV is a booster for other protease inhibitors such as LPV, ATV and DRV.

ABC=Abacavir; AZT=Zidovudine; 3TC= Lamivudine; DRV=Darunavir; LPV/r= Lopinavir combined with ritonavir; NVP=Nevirapine; RAL=Raltegravir; RTV=Ritonavir; ATV=Atazanavir.

Table 26: Simplified dosing of solid and oral liquid formulations for **once-daily dosing** for infants and children 4 weeks of age and older

Drug	Formulations (tablet, capsule or oral liquid) and strength (mg/tab. or mg/ml for liquids)	Dose as number of tablets or ml by weight band					Adult tablets and their strength in mg	Dose as number of tablets by weight band	
		3 – 5.9Kg	6-9.9kg	10-13.9kg	14-19.9kg	20-24.9kg		25-29.9kg	30-34.9kg
EFV [a]	200mg tablet	-	-	1	1.5	1.5	200 tab	2	2
	50mg capsule	-	-	4	6	6	600mg		
ABC/3TC	120mg/60mg (scored, dispersible tablet)	1	1.5	2	2.5	3	600mg/300mg	1	1

ABC/3TC	60mg/30mg (scored, dispersible tablet)	2	3	4	5	6	600mg/300mg	1	1
ATV [b]	100mg capsule	-	-	1	2	2		2 capsules of 100mg	1 tablet of 300mg
TDF [c]	Oral powder (40mg TDF per scoop of powder)	-	-	3	-	-		1 tablet of 200mg	1 tablet of 300mg
	150mg tablet	-	-	-	1	-			
	200mg tablet	-	-	-	-	1			
TDF/3TC	75mg/75mg tablet	-	-	1.5	2	2.5		3	3.5
TDF/3TC	300mg/300mg tablet	-	-	One third	One half	Two third		1	1
TDF/3TC/EFV	300mg/300mg/600mg tablet	-	-	One third	One half	Two third		1	1

[a] Two EFV 50mg capsules is administered in combination with EFV 200mg tablet for children weighing 14-24.9KG.

b ATV is only approved for use for children 3 months and older. ATV single-strength capsules should be administered with RTV 100 mg for all weight bands. The ATV powder formulation enables administration of ATV to infants and children as young as 3 months. Infants and children weighing 5–10 kg should be administered 200 mg of ATV with 80 mg of RTV oral solution (5 ml).

c TDF is only approved for use for children 2 years and older. Target dose: 8 mg/kg or 200mg/m^2 (maximum 300mg). A child would not receive more than 25% above the maximum target dose or more than 5% below the minimum target dose.

EFV=Efavirenz; TDF=Tenofovir disoproxil fumarate.

6.2.9 Role of Pharmacy professionals

- Manages the supply of Pediatric antiretroviral and HIV/AIDS related medicines and supplies
- Participate in the selection of appropriate medicines for HIV infected children
- Monitor and support adherence in children taking ART
- Provide medicines use information for patients and providers and conduct patient education
- Involve in monitoring of clinical outcomes
- Identify, manage, and report ADE including drug interaction
- Involve in changing treatment regimens
- Manages the supply of antiretroviral and HIV/AIDS related medicines and supplies for pregnant and lactating mothers
- Participate in the selection of appropriate medicines for pregnant and lactating mothers
- Involve in the management of pregnant and lactating mothers as part of MDT
- Provide ongoing adherence support
- Explain, monitor, identify and manage ART toxicities in women
- Anticipate and manage drug interactions

6.2.10 Session Summary

- More than 90% of children acquire through MTCT
- Virologic tests should be done to confirm HIV in infants & children <18 months of age
- All HIV infected children < 15 years of age should be started on ART irrespective of their clinical stage or CD4 count
- Pharmacy professionals have to be part of drug selection, monitoring of adherence and drug toxicities
- HIV prevalence is higher in females compared to males
- Women are at increased risk of ART side effects including rash, hepatotoxicity, lactic acidosis
- Pharmacy professionals have integral role in the management of pregnant and lactating mothers with HIV

Case studies

Case 1.

MA is a 22 years old lady who delivered her baby and came for 6th week vaccination. The health worker offered her HIV test and she was found to be HIV positive. She has no complaint and she is mostly breast feeding her baby but sometimes gives him formula feeding. Her CD4 count is 650cells/mm3.

-How do you manage her & her baby?

-What advise do you give her?

Case 2.

ZN is a 32 years old woman who had no ANC follow up but came 2 days after she delivered her baby at home. The health worker offered her HIV test which turned out to be positive. She is exclusively breast feeding her baby. She has no complaints and her CD4 count is 700cells/mm3.

-How do you manage her and her baby?

-What advise do you give her?

Case 3.

LM is a 3 months old infant born to HIV infected mother. The baby is clinically stable but her DNA PCR sent at 6 weeks came to be positive. Her CD4 percent is 35% indicating no evidence of immunosuppression.

1. What do you next?
2. Do you recommend ART to LM? Why?

Case 4.

AU is a 14 years old HIV infected child who was on ART for the last 5 years. She was clinically stable but Since a year back she is refusing to take the both cotrimoxazole and ART and asks her mother why she takes the drugs. Today she came to the clinic for she had diarrhea for the last 1month and lost significant weight. Her recent CD4 count is 90cells/mm3. Her viral load is 120,000copies/mm3.

1. What is AU's problem?
2. How do you manage her?

Session 7: Opportunistic Diseases

Session 7.1: Prophylaxis and Treatment of Opportunistic Infections

Session Description

This session explores the prophylaxis and treatment of common opportunistic infections (OIs) that occur due to HIV infection. First it provides a brief background on opportunistic infections and their association with the decline in immunity. Then, it discusses Cotrimoxazole, Isonizide and Fluconazole preventive therapy. In addition, the session describes the clinical manifestations and management of opportunistic diseases of the respiratory, gastrointestinal, nervous and cutaneous system.

Primary Objective:

The primary objective of this session is to equip participants with the necessary knowledge and skills to identify common OIs and provide the necessary prophylaxis and treatment.

Enabling Objectives:

By the end of this session, participants will be able to:

- Describe opportunistic infections and their association with the decline in immunity
- Explain the prophylaxis of common opportunistic infections
- Discuss the management of common opportunistic diseases in patients with HIV
- Identify the roles of pharmacy professionals in the prophylaxis and treatment of OIs

Session Outline

- Introduction on opportunistic infections
- Prophylaxis of common opportunistic infections
- Management of common opportunistic diseases in patients with HIV
- Role of pharmacy professionals in the prophylaxis and treatment of OIs
- Session Summary

Introductory case

Individual Exercise - 5 minutes

KH is a 45-year-old female HIV patient who never had any regular follow up. Over the last month, she has experienced progressive shortness of breath associated with dry cough. This has gotten to the point where she is unable to walk across the room without becoming short of breath. She comes to clinic to be evaluated. She states that she has fever. On examination, temperature= 38.5^{o}C, RR= 32bpm. CXR is consistent with PCP.

Which one is the appropriate treatment option for KH?

A. Co-trimoxazole 15 mg/kg/day based on TMP oral or IV divided q6-8h x 21 days + Prednisolone 40 mg bid for 5 days, 40 mg qd for 5 days, 20 mg qd for 11 days
B. Co-trimoxazole one SS tablet po TID X 21 days
C. Co-trimoxazole two DS tablets po TID X 21 days
D. Co-trimoxazole one DS tablet po TID X 21 days + prednisone as above

7.1.1 Introduction to opportunistic infections

Opportunistic infections (OIs) occur when a patient's immune system is impaired. OIs are the predominant causes of morbidity and mortality among HIV-infected patients. But, most of the common OIs are preventable as well as treatable. Hence, when patients present particularly at late clinical stages, screening and management of OI is critical.

The level of immunity determines the occurrence and type of opportunistic infections. In general, milder infections, such as herpes zoster and other skin infections, occur early whereas serious life- threatening infections such as CNS toxoplasmosis and cryptococcal meningitis occur later with severe immune-suppression. Some life-threatening infections, such as pneumonia and TB, may occur early as well as later. Figure 7.1 shows the relationship between the level of the patient's immunity status in terms of CD4 count and the type of OIs associated.

The common causative agents of the OIs in HIV are bacteria, fungi, viruses and protozoa. The main systems of the body affected are the nervous system, gastro-intestinal system, respiratory system and the skin. The general strategies to prevent OIs include reduction of

exposure (personal and environmental hygiene, safe sexual practices, chemoprophylaxis (primary/secondary), and starting HAART.

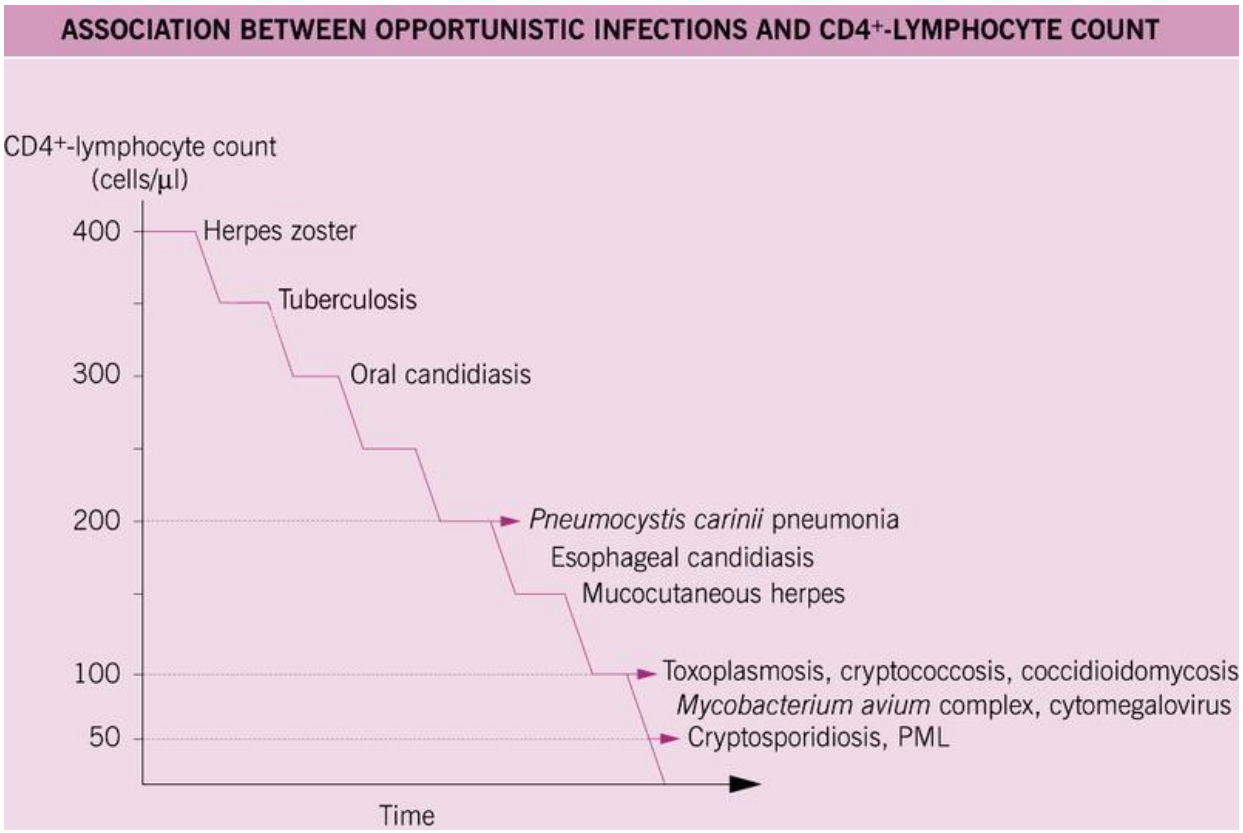


Figure 19: Association between opportunistic infections and CD4 count

7.1.2 Prophylaxis of common OIs

Co-trimoxazole Preventive Therapy (CPT)

Co-trimoxazole preventive therapy (CPT) should be implemented as an integral component of a package of HIV-related services. Existing recommendations cover initiation of CPT among adults, adolescents, pregnant women and children for prevention of pneumocystis pneumonia, toxoplasmosis, bacterial infections & diarrhea (caused by Isospora belli or Cyclospora species), as well as benefits for malaria prophylaxis.

Table 27: CPT Indication for primary prophylaxis

Age	Criteria for initiation	Criteria for discontinuation	Monitoring approach
HIV exposed infants	In all, starting at 6 weeks after birth irrespective of CD4 level.	Until the risk of HIV transmission ends and HIV infection is excluded.	Clinical at 3-monthly intervals with advice to report immediately if side effects appear.
HIV infected children < 5 year of age.	In all	Continue until 5 years of age regardless of CD4% or clinical symptom.	
Children ≥5 years of age, and Adults with HIV infection.	Any WHO stage and CD4 count <=350 cells/mm3 WHO stage 3 or 4 irrespective of CD4 level.	Discontinued in those who are clinically stable (those individuals on ART for at least one year without any new WHO clinical stage 2, 3 or 4 events) with ▪ Evidence of immune recovery and/or viral suppression (CD4 count >350 cells/mm3, with viral load suppression) or ▪ Two consecutive CD4 count > 350 cells/mm3 if no VL result	

Remarks:

- In addition to the criteria above the drug must be discontinued if the person develops Steven-Johnson's Syndrome (SJS), severe liver disease, severe anemia, severe pancytopenia or negative HIV status in HIV exposed infants.
- Contraindications to CPT: severe allergy to sulfa drugs (including Fansidar); severe liver disease, severe renal disease and glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- Because of high prevalence of bacterial infectious diseases, co-trimoxazole should be given regardless of CD4 percentage or clinical stage for children under five years of age.
- Because of high prevalence of bacterial infections or malaria, CPT may be continued longer for children.

Table 28: Dosage of CPT in adults, adolescents, children and infants

Age (weight)	**Suspension (240mg/5ml cotrimoxazol)**	**Single strength tab (480 mg of Co-trimoxazole)**	**Double strength tab (960 mg of Co-trimoxazole)**
Up to 6 months (5 Kg)	2.5 ml/day	1/4 tab/day	-
6 months to 5 years (5-15 Kg)	5 ml/day	1/2 tab/day	-
6-14 years (15-30 Kg)	10 ml/day	1 tab/day	1/2 tab/day
>14 years (>30 Kg)	-	2 tab/day	1 tab/day

Table 29: Adverse Effects of CPT and Management

Toxicity	**Clinical description**	**Recommendation**
Grade 1	Erythema, pruritus	Give Anti-histamine and continue CPT & close Follow-up.
Grade 2	Diffuse maculopapular rash, dry desquamation	Give Anti-histamine and continue CPT & close Follow-up.
Grade 3	Vesiculation, minor mucosal ulceration	STOP CPT, manage. Re-introduce after 2 weeks with observation
Grade 4	Exfoliative dermatitis, SJS or erythema multiform, moist desquamation	STOP CPT. NEVER RESTART CO-TRIMOXAZOL.

NB: If the patient is hypersensitive to co-trimoxazole and there are no alternatives, it is possible to desensitize the patient under supervision (see table below).

Table 30: Desensitization protocol for co-trimoxazole hypersensitivity

Step	Dose	Remark
	Adult and adolescent	Use co-trimoxazole oral suspension 40 mg trimethoprime + 200mg sulphamethoxazole per 5ml.
Day 1	2 ml	
Day 2	4 ml	
Day 3	6 ml	
Day 4	8 ml	
Day 5	480 mg tablet	
Day 6	960 mg tablet	

Dapsone as an alternative for CPT toxicity

In situations of severe allergy to co-trimoxazole or when desensitization is not successful, dapsone can be used instead. It is primarily effective as prophylaxis against PCP but does not have the other prophylactic benefits of cotrimoxazole. Dapsone will contribute to anemia in most

patients, and causes hemolytic anemia in some patients, so patients should have a baseline hemoglobin (Hgb) before starting dapsone and Hgb monitored every 1-2 weeks for the first couple of months. Dapsone is not recommended during breastfeeding. When dapsone is substituted for PCP prophylaxis, it is only recommended for patients in WHO Stage 4 and/or absolute CD4 count < 200 cells/mm3 (Or CD4 % < 25% for children <= 5 years old), and should be discontinued once a patient achieves a sustained CD4 count of > 200 cells/mm (Or> 25% for children <=5 years old) for at least 6 months. Dose of Dapsone for Adults is 100 mg once daily. Children 2 mg/kg once daily (maximum: 100 mg) Or 4 mg/kg once weekly (maximum 200 mg).

Isoniazid Preventive Therapy

LARGE GROUP EXERCISE

What are the contraindications of IPT?

Isoniazid Preventive Therapy (IPT) is the use of Isoniazid to sterilize latent TB infection. Thus, isoniazid is given to individuals with latent infection with Mycobacterium tuberculosis in order to prevent reactivation to active disease. Screening for exclusion of active TB in HIV infected persons is the single most important step that should precede the decision to initiate IPT. So far, evidences strongly favor the benefit of IPT in eligible individuals. Studies have shown that providing IPT to people living with HIV does not increase the risk of developing INH-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT. The dose of INH is 300mg/day for adults and 10mg/kg for children. The duration of IPT is for six months. It is also desirable to provide vitamin B6 (25mg/day) to prevent INH-induced peripheral neuropathy.

Table 31: INH dosage for Children and Adolescents

Weight Ranges for Children (kg)	**Number of 100 mg tablets of INH to be administered per dose**	**Dose given (mg)**
< 5	½ tablet	50
5.1-9.9	1 tablet	100
10-13.9	1 ½ tablet or ½ adult tablet	150
14 -19.9	2 tablets	200

20 -24.9	2 ½ tablets	250
>25	3 tablets or one adult tablet	300

Contraindications of IPT

Individuals with any one or more of the following conditions should not receive IPT.

- Symptoms compatible with tuberculosis even if the diagnosis isn't yet confirmed.
- Active hepatitis (chronic or acute).
- Regular and heavy alcohol consumptions.
- Prior allergy or intolerance to isoniazid.
- Symptoms of peripheral neuropathy.

NB: History of TB and current pregnancy should not be contraindications for starting IPT.

National Policy on IPT
• *IPT should be administered at enrolment to HIV care after ruling out active TB.* • *IPT is to be administered once and should not be repeated unless there is strong indication on its benefits which is to be decided by senior physician.* • *IPT should be administered only for six months.* • *IPT should not be administered right after completing full course of TB treatment.* • *IPT can be administered for patients who had history of TB treatment before three years.*

Follow-up of patients on IPT

Patients should be given monthly supply of Isoniazid for the first three months and three months' supply for the remaining three months. They will be assessed at each follow-up visit to:

- Evaluate adherence to treatment and to educate client.
- Evaluate for drug toxicity.
- Evaluate for signs and symptoms of active tuberculosis or other OIs (HIV clinic).
  - Stop IPT if active TB is diagnosed and immediately start anti-TB (HIV clinic).

Treatment interruption management

If a patient has interrupted IPT without the medical personnel advice, the client should be traced (by adherence case managers/adherence supporters, HEW or through the index person) and treatment must be resumed after identifying and addressing the adherence barriers.

IPT is said to be completed if a patient completed the full course of therapy within nine months period (i.e. the six months doses should be finished in nine months' time).

If the client discontinues treatment for a period of less than three months:

- Resume the same course by adding for the missed doses at the end.

If the client discontinues treatment for a period of more than three months:

- Re-initiate new course of IPT for six months.

Fluconazole Preemptive Therapy (FPT)

According to the pilot study conducted by MOH in collaboration with CHAI and ICAP-CU from June 2015 to July 2016, in 22 high case load facilities in all regions, the proportion of newly enrolled clients with CD4 count less than 100 was 25.88%. In the same study the prevalence of clients screened positive for cryptococcal antigenemia was high (9.9%).

The use of routine serum or plasma CrAg screening in ART-naive adults followed by pre-emptive antifungal therapy if CrAg positive to reduce the development of cryptococcal disease, should be considered prior to ART initiation in patients with a CD4 count < 100 cells/mm_3 and where this population also has a high prevalence (>3%) of cryptococcal antigenemia.

If the CrAg screening is positive and the patient is symptomatic, LP will be performed. If the LP result is positive, the patient will be treated for cryptococcal meningitis. If the LP result is negative in this symptomatic patient and for those asymptomatic patients with CD4 <100, give Fluconazole 800mg daily for two weeks. Then, initiate ART after two weeks of therapy. Fluconazole 400mg daily for 8 weeks, then 200 mg daily until CD4 > 200 for at least 6 months on ART will be given.

7.1.3 Management of Opportunistic Diseases in patients with HIV

Management of Opportunistic Diseases of the Respiratory System

Respiratory problems with HIV infection are caused by several infectious and non-infectious etiologies, but the most common are pneumonia, tuberculosis, and PCP.

Bacterial Pneumonia

Bacterial pneumonia can occur in immune-competent individuals, however, in HIV-infected patients particularly in those infected with S. pneumonia, the incidence of bacteremia is higher. Bacterial pneumonia occurs during the whole spectrum of HIV disease, but tends to be more severe and recurrent as the CD4 counts drops significantly. Streptococcus pneumonia and *Hemophilus influenza* are the most common etiologies of community acquired pneumonia. Getting children vaccinated with *PCV* and *hemophilus influenza* vaccines is useful to prevent the occurrence of bacterial pneumonia.

In general, HIV positive patients with bacterial pneumonia present similar to HIV uninfected individuals. Typically the patient presents with sudden onset of cough, sputum production, chest pain, fever and/or shortness of breath. If not treated promptly, extra pulmonary complications like empyema, meningitis, pericarditis, hepatitis and arthritis can follow.

Treatment:

For non-severe pneumonia:

- Amoxicillin 500mg BID or TID for seven days. For children, 50mg/kg per day in three divided doses for seven days.
- In patients with penicillin allergy use Erythromycin 500mg QID for the same duration.
- Alternative, Azithromycin 500 mg PO per day for three days,
- Clarithromycin 500 mg twice daily for seven days or
- Doxycycline 100 mg BID for seven days. Avoid Doxycycline in pregnancy.

If not improving after three days and if patient is adherent to the antibiotic, review and consider switching to IV regimen.

- Ceftriaxone, 1g I.V. OR I.M every 12-24 hours for 7 days *PLUS* Azithromycin, 500mg on day 1 followed by 250mg/day on days 2 – 5
- For children ceftriaxone 75-100 mg per kg IV/IM once a day or equally divided twice per day for 7 to 10 days. Maximum dose 2-4 gm per day for seven days.

Pneumocystis Carini Pneumonia (PCP)

Pneumocystis pneumonia is caused by Pneumocystis jiroveci formerly known as pneumocystis carini pneumonia (PCP), a ubiquitous organism that is classified as a fungus

but also shares biologic characteristics with protozoa. It commonly occurs when patients have significant immune suppression (CD4<200cells/mm3 or CD4 % <14%). The incidence of PCP has declined substantially with widespread use of prophylaxis and HAART.

The clinical manifestation includes subacute onset of progressive dyspnea, fever, non-productive cough, and chest discomfort that worsens within days to weeks. Diagnosis is mainly clinical when patients have severe and advanced immunosuppression (CD4<200/mm3) in resource limited settings.

Treatment:

- Trimethoprim 15-25 mg/Kg and sulphamethoxazole 75-125mg/kg, three or four times daily for 21 days (parenteral route may be considered in patients who present with severe illness or those with GI side effects).
- In severely ill adults, prednisolone 80mg for the first five days, 40 mg until 11 days and 20 mg until 21 days has to be given simultaneously.
- For severe cases of PCP in children, provide prednisolone 2mg/kg per day for the first 7-10 days followed by a tapering regimen for the next 10-14 days.

Alternative regimens for mild to moderate cases of PCP include:

- Clindamycin 600 mg po qid plus Primaquine 15 mg po BID or
- Clindamycin 600 mg qid plus Dapsone 100 mg po daily

The following regimens are used for PCP prophylaxis:

Preferred:

- Cotrimoxazole 1 DS QD
- Cotrimoxazole 1 SS QD

Alternatives:

- Cotrimoxazole 1 DS TIW
- Dapsone
- Aerosolized Pentamidine
- Atovaquone

TB-HIV Co-infection

TB is the most frequent life-threatening OI and a leading cause of death in PLHIV. Only 5-10% of TB infected persons (primary infection) develop active disease. Following primary infection, rapid progression to disease is more common in children less than 5 years of age. However, HIV positive people with latent TB infection have a 10% annual and 50% lifetime

risk of developing active TB disease. Latest WHO reports shows TB-HIV co-infection rate in Ethiopia is 8%.

HIV care settings should implement WHO's three 'I' strategy. These are intensified TB case-finding, isoniazid preventive therapy (IPT) and infection control at all clinical encounters. The two programs must collaborate to provide better service for the co-infected patients. The rationale for the integration is that TB and HIV prevention and control programs share mutual challenge of high impact of TB on HIV and vice versa.

Reflections

- What percent of individuals with primary TB infection develop clinical TB?
- What proportion of HIV infected people are at risk of developing active TB?
- What are the three WHO 3 I's strategies for TB/HIV treatment?

Clinical features of TB

- Cough, weight loss, fatigue, malaise, fever, night sweats, loss of appetite.
- Poor weight gain/weight loss, cough, fever, and reduced playfulness in children.
- Patients may have few symptoms or have symptoms that are even less specific.

Risk factors for TB disease

- Infection with HIV
- Recent TB infection (<1year)
- Co-morbid conditions (malignancy etc)
- Age less than five years, Malnutrition
- Close contact with a known TB or chronically coughing patient, especially in young children.

Diagnosis of TB in HIV infected people

Diagnosis of TB is challenging in HIV positive individuals, especially when the stage of the disease is advanced. The following are tests recommended to diagnose TB in PLHIV.

- **XPert MTB/RIF Test (GeneXpert Test)**: The GeneXpert system is a fully automated PCR system, which detects MTB complex DNA in sputum and other sample types. It

simultaneously identifies rifampicin resistance. It is recommended as an initial diagnostic test for all presumptive TB cases (individuals with TB symptoms) among HIV infected people.

- **AFB Microscopy:** AFB Microscopy is indicated for HIV infected presumptive TB cases when access to GeneXpert test is limited.
- **Chest Radiography:** Chest X-ray plays a significant role in shortening delays in diagnosis of TB in PLHIV. It can be an entry point to diagnose non-TB chest diseases, which are common among PLHIV.
- **Sputum Culture:** In patients with XPert negative results, sputum culture may be indicated as part of the diagnostic procedure for PLHIV if clinical suspicion persists. Sputum culture is the gold standard for the diagnosis of TB in general.

Management of TB in HIV patients

There are issues related to the treatment of TB in HIV patients and the treatment of HIV in TB patients. These include response to TB treatment, drug-drug interactions, immune reconstitution syndrome, overlapping ARV & TB drug side effects and non-adherence with multi-drug therapy.

When TB is diagnosed in patients already receiving ART, anti-TB treatment should be started immediately. There are two issues to consider for such patients:

(1) Is modification of the ART regimen needed due to drug-drug interactions or to decrease the potential of overlapping toxicities and

(2) Does this presentation of active TB in a patient on ART constitute ART failure requiring a change in the ART regimen?

Drug regimens for TB treatment in HIV

The drug regimens used to treat TB in an HIV-infected patient are the same as those for the HIV-negative patients. Therefore,

- *New patients*: New TB Patients will be treated with 2(RHZE)/4(RH). This means these patients will be treated with four drugs (Rifampicin, Isonizide, Pyrazinamide and Ethambutol) for the first 2 months and then they will continue with Rifampicin and Isonizide for 4 months.
- *Previously treated*: will have two options based on Drug susceptibility test (DST).
    - If DST is positive - previously treated TB cases will be re-treated with 2(RHZE)/4(RH). The same as new cases

- If DST is negative and shows drug resistance. The patient will be treated using Drug Resistance TB Regimen. The regimen to be used will depend on the resistance pattern.
- Majority of the patients will be treated using short term regimen (9-12 months).
    - For initiation phase (4-6 months); Kanamycin, Moxifloxacin, Clofazimine, Ethambutol, Isoniazide, Pyrizinamide, Prothionamide, Pyridoxine.
    - Continuation Phase (5 months); Moxifloxacin, Clofazimine, Ethambutol, Pyrizinamide.

- Extra pulmonary TB
    - Treat patient with extra-pulmonary TB involving any site for six-month with standardized first-line regimen with the exception of CNS TB(meningitis, tuberculoma) and Osteoarticular TB (including vertebral bones, joint and osteomyelitis), which require prolongation of the continuation phase for 10 months: 2RHZE/10RH
    - An initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8weeks should be used for patients with Tuberculosis meningitis and/or pericarditis to improve outcome and reduce complications.

Table 32: Principles of TB Management in HIV Patients

Patients with TB found to be HIV Positive	HIV positive patients taking ART diagnosed with TB
• ART should be started in all TB patients, including those with drug-resistant TB (both MDR and XDR TB), irrespective of their CD4 cell count. • Anti-TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of TB treatment. • HIV-positive TB patients with profound immune-suppression (such as CD4 counts < 50 cells/mm3) should receive ART immediately within the first two weeks of initiating TB treatment.	• Start anti-TB immediately. • Modify ART regimen to avoid drug-drug interactions such as between NVP and Rifampicin. • Ensure optimum NVP dose is being given (200mg/m^2). • Evaluate for treatment failure.

<table>
<tr><td colspan="2">Start CPT for all TB-HIV co-infected patients regardless of their CD4 Count.
ART should be started in any child with active TB disease as soon as possible within 8 weeks following the initiation of anti-TB treatment irrespective of the CD4 count and clinical stage.
Efavirenz should be used as the preferred drug in patients starting ART while on anti-TB treatment.
When second line is initiated, LPV/r is preferable.</td><td></td></tr>
<tr><td colspan="3">Recommended regimens for children and adolescents initiating ART while on TB treatment</td></tr>
<tr><td colspan="2">Younger than 3 years</td><td>Two NRTIs + NVP, ensuring that dose is 200 mg/m2
or
Triple NRTI (AZT + 3TC + ABC) c</td></tr>
<tr><td colspan="2">3 years and older</td><td>Two NRTIs + EFV
or
Triple NRTI (AZT + 3TC + ABC) c</td></tr>
<tr><td colspan="3">Recommended regimen for children and infants initiating TB treatment while receiving ART</td></tr>
<tr><td rowspan="2">Child on standard NNRTI-based regimen (two NRTIs + EFV or NVP)</td><td>Younger than 3 years</td><td>Continue NVP, ensuring that dose is 200 mg/m2
Or Triple NRTI (AZT + 3TC + ABC)c</td></tr>
<tr><td>3 years and older</td><td>If the child is receiving EFV, continue the same regimen
If the child is receiving NVP, substitute with EFV
or
Triple NRTI (AZT + 3TC + ABC)c</td></tr>
<tr><td>Child on standard PI based</td><td>Younger than 3 years</td><td>Triple NRTI (AZT + 3TC + ABC) c
or
Substitute NVP for LPV/r, ensuring that dose is 200 mg/m2</td></tr>
</table>

regimen (two NRTIs + LPV/r)	3 years and older	If the child has no history of failure of an NNRTI-based regimen: Substitute with EFVe or Triple NRTI (AZT + 3TC + ABC)c or Continue LPV/r; consider adding RTV to achieve the full therapeutic dosed If the child has a history of failure of an NNRTI-based regimen: Triple NRTI (AZT + 3TC + ABC)c Consider consultation with experts for constructing a second line regimen

Multidrug-resistant TB (MDR-TB): Patients with both HIV & MDR-TB face complicated clinical management, fewer treatment options and poor treatment outcomes. The complexity of ARV regimens and second-line TB treatment, each with its own toxicity profiles and some of which may be potentiated by concomitant therapy, demands rigorous clinical monitoring, and early recognition and management of adverse drug reactions. PLHIV with DR-TB should receive both second-line anti-TB and ART in DR-TB treatment initiating centers (TIC).

Management of Opportunistic Diseases of the Gastrointestinal System

There are several opportunistic and pathogenic organisms causing GI disease in patients infected with HIV. Most common ones are isospora belli, cryptosporidium, shigella, salmonella, CMV etc. The GI OI diseases commonly manifest with diarrhea, nausea and vomiting, dysphagia and odynophagia among others. The general principle of managing GI OIS is identifying and treating the specific offending agent and providing supportive care to monitor situations such as fluid loss. A number of drugs can cause adverse effects that

present with clinical manifestations which are similar to OIs of the GI, posing challenges in differential diagnosis.

Dysphagia and Odynophagia

Dysphagia (difficulty in swallowing) and Odynophagia (painful swallowing) are symptoms of esophagitis occurring at advanced stages of AIDS. They are usually caused by candida, HSV, CMV, and aphthous ulcers. In addition to be a sign of severe immunodeficiency, esophagitis seriously impairs the patient's nutritional status. Therefore, prompt diagnosis and treatment are mandatory to avert nutritional complications and inability to swallow prescribed medications. Children may present with reluctance to eat, excessive salivation, or crying while feeding. If thrush is associated with dysphagia, odynophagia, and retrosternal pain, consider esophageal candidiasis as it may occur in the absence of oral thrush. Thrush or oropharyngeal candida is characterized by white, painless, plaque-like lesions on the buccal surface and/or tongue.

Diagnosis is frequently made on clinical grounds, but when facilities are available upper GI endoscopy with or without biopsy or contrast imaging may be done.

Treatment:

- Systemic
    - Fluconazole 200 mg (6mg/kg/day in children) PO daily for 14-21 days. Alternatively,
    - Itraconazole capsule 200mg daily with food
    - Itraconazole suspension 10 mg/ml 100-200 mg daily without food
    - Ketoconazole 200 mg (3-6mg/kg/day daily in children) twice daily for 4 weeks.
    - If diagnosis suggests HSV esophagitis, use acyclovir 400mg orally five times a day for 14 to 21 days.
    - HAART
- Topical
    - Miconazole oral gel
    - Nystatin oral suspension 500,000 units 5x day
    - Nystatin pastilles 100,000 units:1 to 2 pastilles (200,000 to 400,000 units) 4 to 5x daily

- Clotrimazole 1% cream

Diarrhea

Diarrhea is among the most frequent symptoms of HIV disease. Delay in treatment can result in fluid loss and hemodynamic instability. Chronic diarrhea may also lead to nutritional deficiencies and wasting.

Diarrhea is caused by opportunistic or pathogenic organisms, such as viruses (including HIV), bacteria, protozoa, fungi, helminthes, non-infectious causes and drugs. Patient work up: Stool microscopy including modified acid fast stain, and Stool culture when indicated.

The most important first step in management of diarrheal disease is correction of fluid loss. Depending on the severity of dehydration, ORS or IV fluid therapy can be given. Patients with severe dehydration are admitted for IV fluid administration. In children, zinc 20mg per day for 10-14 days (10mg per day for infants < 6 months of age) should be added even diarrhea stops.

In patients with bloody diarrhea with repeat negative stool results, empirical treatment with ciprofloxacin or norfloxacin (co-trimoxazole in children) can be given, especially when patient has constitutional symptoms such as fever. In adults use of anti-diarrheal agents, Loperamide 4mg stat then 2mg after each bowel motion up to 16mg/day or Diphenoxylate 5mg QID, may help reduce diarrhea. Necessary caution should be taken to avoid anti-diarrheal agents in bacterial or parasitic infectious colitis or enteritis, since toxic mega colon may occur. Patients with chronic diarrhea develop nutritional deficiencies of variable severity; therefore proper nutritional assessment and support are helpful.

Table 33: Summary of the diagnosis and drug treatment of diarrheal diseases

Agent	**CD4**	**Symptom**	**Diagnosis**	**Treatment**
E. hystolytica	any	Bloody stool, colitis	Stool microscopy	Metronidazole
Giardia	Any	Watery diarrhea	Stool microscopy	Metronidazole
Cryptosporidium	<150	Watery diarrhea	Modified AFB	HAART*
Isospora belli	<100	Watery diarrhea	Modified AFB	TMP-SMX
Microsporidium	< 50	Watery diarrhea	Giemsa stain	Albendazole
CMV	<50	Watery/bloody diarrhea, Colitis	Tissue biopsy	Ganciclovir

**No specific treatment for Cryptosporidium but it improves with immune restoration following ART.*

Peri-anal and genital herpes

A number of chronic or acute peri-anal problems commonly occur in patients with HIV disease, particularly in advanced stages of immunodeficiency. These include recurrent peri-anal abscesses, chronic peri-anal fistula, peri-anal herpes (severe, persistent and extensive), and peri-anal warts (sometimes large with obstructive problems). Genital herpes is treated by Acyclovir 400mg five times a day for 10-14 days. There is a risk of recurrence with severe immunodeficiency. In such cases repeat treatment and put patients on chronic HIV care including ART. Herpetic oro-labial infection is treated the same way as ano-genital herpes.

HCV/HIV and HBV/HIV Co-infection Management

HCV/HIV Co-infection Management

HIV patients are among high risk groups for Hepatitis C Virus (HCV) and should be given priority for screening. Therefore all HIV patients should be screened using Anti-HCV rapid diagnostic test (RDT) or immunoassay (IA) and confirmation viral load test should be done for HCV screened positives using either quantitative or qualitative PCR.

All chronic HCV infected individuals should be treated to eradicate the virus and achieve cure so that complications can be avoided. Follow up quantitative or qualitative HCV RNA viral load is required to confirm if the patient has achieved Sustained Virologic Response (SVR). This should be performed 12 weeks after the completion of therapy. Treatment of HCV in HIV infected individuals is not different from non-HIV infected. All combination of direct acting antiviral (DAA) including SOF/LDV, SOF/RIB and SOF/DCV can safely be used. However, attention should be given to drug-drug interactions and shared side effects like headache, fatigue and anemia. According to the national viral hepatitis prevention and control guidelines, the following are treatment options:

- *Sofosbuvir 400 mg oral once daily + Daclatasvir 60mg oral once daily for 12 weeks (dose of DCV be adjusted to 90 mg with Efavirenz and 30 mg with Atazanavir/r).*
- *Sofosbuvir 400mg oral once daily + Ledipasvir 90mg oral once daily for 12 weeks.*
- *For cirrhotic patients' treatment duration will be extended to 24 weeks for the above options.*
- *Sofosbuvir 400mg oral once daily + Ribavirin 1000mg (weight < 75kg), 1200mg (weight ≥ 75Kg) twice on divided doses for 24 weeks.*

It is recommended to thoroughly evaluate chronic HCV infected person with cirrhosis and treatment duration be decided according to the genotype, type of drug and addition of ribavirin.

HBV/ HIV Co-infection Management

HIV co-infection has been shown to have a profound impact on almost every aspect of the natural history of HBV infection and includes more rapid progression to cirrhosis and hepatocellular carcinoma (HCC), higher liver-related mortality, and decreased treatment response compared with persons without HIV coinfection.

HIV/HBV-co-infected persons also demonstrated more rapid HIV disease progression compared to those who were HIV-infected alone, and had an impaired recovery of CD4 cells. HIV patients are among the high risk groups for HBV and should be given priority for screening. All HIV patients should get screened for HBV and evaluated for chronic infection as per the national Viral Hepatitis prevention and control guidelines. After test result, vaccination or treatment and care for reactive patients are recommended when resources permit.

Treatment options for patients with HIV/HBV Co-infection:

- During HBV/HIV co-infection if treatment is indicated for HBV, combination ART should be initiated with drugs containing TDF+3TC+EFV as a preferred regimen.
- Oral drug therapy is first line for these patients with at least 2 of the drugs having activity against HBV like combination of Tenofovir, Emtricitabine/ lamuvidine and Efavirenz.
- The use of lamivudine as mono-therapy in any of these diseases is contraindicated due to high viral resistance to the drug.
- When switching treatment in patients with HIV on ART failure, the regimen that will continue should have two of the drugs having activity against HBV.
- If tenofovir-associated renal toxicity occurs, the dose of tenofovir should be adjusted according to the renal clearance.

Management of Opportunistic Diseases of the Nervous System

Neurological manifestations of HIV can occur at any time from viral acquisition to the late stages of AIDS. It affects the nervous system in 70-80% of infected patients. They are varied and

may affect any part of the nervous system including the brain, spinal cord, autonomic nervous system and the peripheral nerves. The effect may be due to direct effect of the virus, OIs and/or malignancies. Neurological conditions in HIV patients may be due to HIV (HIV encephalopathy), OIs (toxoplasmosis, crypotococcal meningitis, neurosyphilis, malignancies (primary CNS lymphoma)) and drugs like EFV. Diagnosis of neurological disorders in HIV depends on the patient history, standard neurological examinations and imaging results.

Cryptococcal infection

Cryptococcal meningitis is one of the most important opportunistic infections and a major contributor to high mortality before and after ART is initiated. The main reasons for this high death rate include delayed presentation, together with poor availability and high cost of treatment. Most HIV-associated cryptococcal infections are caused by Cryptococcus neoformans. The clinical manifestation includes subacute meningitis or meningoencephalitis with fever, malaise, and headache, neck stiffness and photophobia. Some patients experience encephalopathic symptoms, such as lethargy, altered mentation, personality changes, and memory loss that are usually a result of increased intracranial pressure, thought to result from impaired cerebrospinal fluid (CSF) absorption.

Treatment option A: Induction phase (2 weeks)-give high dose of Fluconazole 600 mg twice daily alone (In children 12mg/kg/day) and Consolidation phase (8 weeks)-Fluconazole 800 mg/day (In children 12mg/kg/day). Then, Maintenance treatment (secondary prophylaxis) - Fluconazole 200 mg daily (In children 6mg/kg/day).

Treatment Option B: Induction phase (2 weeks) - Amphotericin B + Fluconazole: Amphotericin 0.7-1 mg/kg/day + Fluconazole 800 mg/day. Consolidation phase (8 weeks)-Fluconazole 400-800 mg/day. Then, Maintenance treatment (secondary prophylaxis) - Fluconazole 200 mg daily (In children 6mg/kg/day). It can be discontinued if patients are stable and adherent to ART and anti-fungal maintenance treatment for at least one year and have a CD4 cell count of >= 200 cells/mm3 (two measurements six months apart).

Timing of ART initiation

- Immediate ART initiation is not recommended in HIV-infected patients with cryptococcal meningitis due to the high risk of IRIS, which may be life-threatening.

- ART initiation should be deferred until there is evidence of a sustained clinical response to anti-fungal therapy, and
- After 2-4 weeks of induction and consolidation treatment with amphotericin B-containing regimens combined with fluconazole, or
- After 4-6 weeks of induction and consolidation treatment with high-dose oral fluconazole.

Tuberculosis Meningitis

Tuberculosis meningitis is one of the neurological manifestations in HIV infected patients. About 10% of AIDS patients who present with TB will show signs of meningial involvement. Symptoms include: fever, confusion, headache, meningismus, and focal neurological deficit (20%) especially cranial nerve palsy. Sometimes seizure and loss of consciousness seen. For diagnosis, LP is mostly safe and reveals characteristic results but AFB is seldom positive (10-40%). The management is according to the national TB treatment protocol. For all patients, in addition to the Anti-TB, start prednisolone 1mg/kg for 2-4 weeks then taper off over 4-8 weeks.

CNS Toxoplasmosis [Toxo-encephalitis]

Toxoplasma encephalitis (TE) is caused by the protozoan Toxoplasma gondii. Disease appears to occur almost exclusively because of reactivation of latent tissue cysts. Primary infection occasionally is associated with acute cerebral or disseminated disease. The most common clinical presentation of T. gondii infection is focal encephalitis with headache, confusion, or motor weakness and fever. Patients may also present with non-focal manifestations, including only non-specific headache and psychiatric symptoms.

HIV-infected patients with TE are almost uniformly seropositive for anti-toxoplasma immunoglobulin G (IgG) antibodies. Definitive diagnosis of CNS toxoplasmosis requires a compatible clinical syndrome, identification of one or more mass lesions by CT, MRI, or other radiographic testing and detection of the organism in a clinical sample. In the absence of imaging support, empirical treatment is justified when patients present with focal neurological findings and the CD4 count is < 200 cells/μL. Failure to respond to conventional therapy, based on presumptive clinical diagnosis within a week or two of initiation of therapy, suggests the diagnosis to be unlikely. With empirical treatment for toxoplasmosis, nearly 90% of patients will

demonstrate clinical improvement within days of starting therapy. In the absence of treatment, disease progression results in seizures, stupor, and coma.

Trimethoprim/sulfamethoxazole is used to treat toxoplasmosis 80/400, oral, 4 tablets 12 hourly for 28 days, followed by 2 tablets 12 hourly for 3 months in adults. In children 10mg of trimethoprim + 50mg of sulfamethoxazole per kg per dose every 12 hours for 28 days followed by maintenance therapy at 50% reduced dosage for three months. For secondary prophylaxis, co-trimoxazole 960mg daily for adults is used till the CD4 picks above 350 cells/mm3 for three months. Refer to the session on Pediatric ART for dose in children.

Management of Opportunistic Diseases of the Cutaneous System

The skin is an organ frequently affected by OIs; early manifestations of HIV infections frequently occur in the skin. Different kinds of OIs, such as herpes zoster, and other viral, fungal and bacterial infections occur in the skin. Manifestations of adverse drug reactions and non-infectious conditions also can occur in the skin. In most patients, diagnosis can be established by examining the cutaneous lesions.

Pruritus is the most common dermatological symptoms in HIV infected patients. The most common skin conditions associated with pruritus in patients with AIDS include:

1. Papular pruritic eruption (PPE)
2. Excessive dryness of the skin (Xerosis cutis)
3. Eczemas like seborrheic dermatitis or contact dermatitis
4. Folliculitis that may include infections by Staph aureus or hypersensitivity to insects
5. Drug eruptions
6. Scabies
7. Intertrigo (candida, tinea, herpes simplex)

The following table (Table 7.1.8) describes the common skin problems in HIV infected individuals which are caused by viral, bacterial, fungal and parasitic infections.

Table 34: Common skin problems in HIV infected individuals

Infections	Diseases	Clinical Presentation	Treatment	Remark
Viral	Herpes zoster	Painful and vesicular eruptions with dermatomal distribution. When healed, scar will remain.	Acyclovir (800mg po five times per day for 7 days OR 10 mg/kg/dose every 8 hours. Give pain relief.	Monitor renal function. When it involves the eyes it is a medical emergency. Do not give Acyclovir* if duration is >72 hours.
	Herpes simplex	Painful vesicular lesion or sores, involving lips, mouth and genitalia. Recurrent and extensive, difficult to eradicate during advanced immune deficiency. Can become extensive with serious mouth ulcerations.	If severe ulceration, give acyclovir 400mg TID for 10 days. In children 20 mg/kg/dose 4X/d.	If Chronic (> one month) patient will benefit from immediate ART initiation if not on ART
	Warts/ Verrucae	Painless flat to raised warts over fingers or genitalia. In advanced immune deficiency, they tend to be multiple and exophytic.	Treat with Podophyllin or extensive lesions refer for Cryotherapy.	Genital lesions can be a risk for cervical cancer.
	Molluscum Contagiosum	Umbilicated and raised facial lesions that tend to be very big during immunodeficiency state.	May not require therapy;	Contagious
Bacterial	Cellulitis	Poorly defined erythema. Pus and crust at the site plus signs of inflammation.	Amoxicillin 500mg tid for 10-14 days or erythromycin 500mg qid if allergic to penicillin.	Mostly occur in lower extremities and often unilateral.
	Impetigo or Folliculitis	Erythematous small papules usually limited to few lesions coalescing in to crusted plaques.	Use topical antibiotics. use like Mupirocin Or Fusidic acid. If extensive use cloxacillin or Amoxicillin. If allergic to	Usually a superficial lesion.

			cloxacillin, use erythromycin.	
	Carbuncle	Nodular Lesion with extensions to the deeper Structure. Signs of Inflammation present.	Use Cloxacillin 500mg qid for ten days.	Involves the trunk as well as extremities.
	Papular itching rash (prurigo)	Itching rash with small papules and scratch marks.	Give topical steroid	A clinical stage 2 disease.
	Eczema	highly pruritic inflammatory skin disease, associated with remitting and flaring course	Short-term: use topical steroid cream (not on face). Treat itching with Antihistamine.	
Fungal	Dermatophytosis (tinea)	Superficial fungal infections usually affect all parts of the skin from head to toes.	Topical antifungal cream for limited skin infection.	
	Thrush	White plaques on the buccal mucosa including the tongue that can be scraped off leaving red base. Can be associated with candida.	Apply Miconazole gel 2% bid or Fluconazole PO100 mg daily for ten days for recurrent or oropharyngeal thrush.	
	Deep Fungal infection	Presentation varies from fungating nodules and tumors to ulcers and diffuse papulonodular disease.	Disseminated Cryptococcus can be confused for Molluscum contagiosum. Treat with amphotericin induction and/or fluconazole maintenance.	
Parasitc	Scabies	Pruritic lesions ranging from pinpointed erythematous papules involving interdigital and gluteal places to varying degrees of hyperkeratotic plaques associated with significant skin thickening and crusting.	BBL, lindane or permethrin to be applied to whole body. Ivermectin 200 microgram/kg stat orally.	May manifest as crusted scabies in HIV infected children

7.1.4 The role of pharmacy professionals in prophylaxis and treatment of OIs

With foundation knowledge in recognizing the common OIs in HIV patients, pharmacy professionals are expected to play significant roles in the care of HIV patients with OIs through:

- Recommending drugs for the prophylaxis and treatment of common OIs.
- Providing technical expertise in anticipating, detecting and managing common drug interactions and adverse effects of drugs used for the prophylaxis and treatment of OIs.
- Continuously avail required medicines for prophylaxis and treatment of OIs.
- Dispense and provide medication use counseling to patients who are taking drugs for OIs.
- Support patients on adherence to OI treatment.
- Provide adequate education and counseling on common OIs prevention and treatment.
- Closely work and collaborate with prescribers in prevention and treatment of OIs.

Case studies

Case 1: Mr. Z is a 50 years-old male who is being discharged from the hospital after completing treatment for PCP. His CD4 is 32, VL is 500,000. The physician decides to initiate HAART to Mr. Z. The physician then asks you to recommend an appropriate therapy for PCP prophylaxis. Based on the guidelines, which option below do you consider to be the best option for Mr. Z? And Why?

1. Atovaquone 750 mg po qd
2. Cotrimoxazole DS po qd
3. Dapsone 100mg po qd
4. Cotrimoxazole DS once weekly

Case 2: A is 25-year-old woman and presented to the ART clinic. She was referred from the testing center with a positive HIV test. She has white patches in her mouth and weight loss. Does she need co-trimoxazole prophylaxis? If so, how many pills will you give to the patient? What will you explain to the patient?

Case 3: NS is a 34 year-old man who comes to the ART clinic for his ART refill. He was diagnosed to have HIV two years ago. At presentation, he complains of seborrhoea and recurrent mouth ulcers. He had history of facial herpes zoster infection two years ago. He does not have any signs of stage 3 or 4 in HIV staging.

How would you respond to his request? What can be offered?

Case 4: HA is a 36 years old HIV patient who is diagnosed with TB lymphadenitis. While doing a routine HIV test the patient is found to be positive. CD4 was done and it is 250/mm3. The physician decided to start treatment for both HIV and TB. As a pharmacist, what do you advise in terms of what to treat first and when to start ART? Which ART regimen do you recommend and why?

7.1.5 Session Summary

- As immunosuppression progresses the overall incidence of OIs increases.
- The most common OIs encountered in Ethiopia include oropharyngeal candida, PCP, TB, CNS toxoplasmosis and cryptococosis, herpes zoster & pneumonia.
- OIs may be bacterial, viral, fungal, parasitic or non-infectious.
- CPT should be considered for HIV patients with CD4 < 350 or WHO stage 3 and 4.
- FPT shall be considered for those HIV patients with CD4 count < 100.
- Beware of drug interactions and overlapping toxicities in management of co-infections.
- IPT should be provided to all HIV infected individuals without active TB provided that they don't have contraindications.
- The type of OIs, severity of disease, drug interactions & toxicities affect choice of therapy.

Session 7.2: Sexually Transmitted Infections

Session Description:

The session starts with the definition and classification of STIs and the association between HIV and STIs. Further, interventions to reduce transmission are discussed. Then, the session describes the approaches to STI case management, i.e., syndromic approach.

Primary Objective:

The primary objective of this session is to describe about STI and syndromic management of commonly encountered STIs in the context of HIV/AIDS.

Enabling Objectives:

By the end of this session participants will be able to:

- Differentiate STIs and STD
- Describe the association between STIs and HIV
- Discuss syndromic management of commonly encountered STIs
- Identify the role of the pharmacy personnel in the management of STIs

Session Outline

- Introduction STIs in HIV/AIDS
- The association between STIs and HIV/AIDS
- Syndromic approach of STI management
- The role of the pharmacy personnel
- Session Summary

7.2.1 Introduction to STIs in HIV/AIDS

Large Group Discussion

Share your experience in the management of STIs

Sexually transmitted infections (STIs) are among the most common causes of illness in the world and have far reaching health, social and economic consequences. STIs have public health importance because of their magnitude, potential complications and their interaction with HIV/AIDS.As their name implies, the main mode of transmission of STI is through unprotected sexual intercourse. Other modes of transmission include: mother-to-child, blood transfusions, or other contact with blood or blood products.

Some people use the terms STI &STD interchangeably, but they actually have different meaning.

- **STI** – Infections acquired through sexual intercourse (may be symptomatic or asymptomatic)
- **STD** – Symptomatic disease acquired through sexual intercourse
- STI is most commonly used because it applies to both symptomatic and asymptomatic infections

STIs are caused by more than 30 different pathogens including bacteria, viruses, protozoa, fungus and ecto-parasites. Most of the STIs are curable but resistance to many of the older antibiotics is a current challenge; while other STIs are incurable.

The common classical STIs include:

- Gonorrhea,
- Syphilis,
- Chancroid,
- Lymphogranuloma venerum
- Chlamydial infections and
- Trichomoniasis
- Human immunodeficiency virus,
- Human papilloma virus,
- Hepatitis B virus, and
- Herpes simplex virus

Note: *Bacterial vaginosis and candidiasis are also common causes of reproductive tract infections (vaginal discharge), but are not sexually transmitted.*

7.2.2 The Association between STIs & HIV/AIDS

The relationship between STIs and HIV/transmission has been described as an epidemiological synergy.

STIs and HIV infection share similar epidemiologic determinants

- Result from risky sexual behavior, however other routes transmission for both include blood, blood products, donated organs or tissue and vertical transmission from an infected mother to her fetus or newborn infant.
- Affect similar group of society (youth, mobile population and individuals who frequently change partners are commonly affected.

STIs facilitate transmission HIV and acquisition through:

- The presence of genital ulcers is known to increase the risk of HIV transmission (five folds) by disrupting the integrity of the skin.
- STIs that primarily cause inflammation such as gonorrhea, trichomoniasis, and chlamydial infections present a weak barrier to HIV.
- STIs Increase viral shedding (reported in genital fluids of patients with STIs) and increase susceptibility to HIV.

HIV affects the clinical presentation and management of STIs

- HIV alters susceptibility of STI pathogens to antibiotics (be more resistant to treatment)
- Increased susceptibility to STIs among immune suppressed individuals
- Clinical features of STIs are influenced by HIV co-infection. This can be demonstrated well in the following examples:
    - Syphilis has atypical presentation with a tendency to rapidly progress to neurosyphilis.
    - Recurrent or persistent genital ulcers caused by Herpes simplex virus are common in patients with HIV and they are often multiple and extensive. Extra-genital or perianal ulceration could as well occur.
- The treatment of conventional STIs is also affected when infection with HIV coexist.

- Risk of treatment failure following single injection of benzathine penicillin is increased among patient with primary syphilis.
- Topical anti-fungals are less effective and hence oral antifungals like ketoconazole may be indicated for patients with candidiasis.
- Severe genital herpes may require treatment of primary episode or suppression of recurrence with acyclovir. However, resistance to acyclovir may subsequently develop.

Interventions to Reduce Transmission

All STIs, including HIV, are preventable. The prevention and control of STIs involves:

- Decreasing duration of infectivity (early diagnosis and treatment of index cases and partners)
- Decreasing transmission (promotion of safer sexual behavior)
- Promotion of health care-seeking behavior, and targeting vulnerable groups.

7.2.3 Syndromic approach to STI Case Management

There are three approaches **etiologic approach, clinical approach** and **syndromic approach** such can be used for case management of STI patients. These approaches have their advantages and disadvantages.

Management of STI in Ethiopia follows syndrome approach. A syndrome is simply a group of the symptoms a patient complains about and the clinical signs you observe during the exam. Implementing syndromic STI management will contribute to successful STI control.

STI treatment (antimicrobial) regimens are chosen to cover the major pathogens responsible for the syndromes in the specific geographic area. In order to make this determination, a laboratory analysis of the syndromes is made and the pathogens for each syndrome are identified. This means that, afterwards, the management of individual patients will not depend on laboratory investigation.

Components of syndromic management of STI

1. Drug treatment and follow-up
2. Partner notification and management

3. Health education and risk reduction
4. Condom provision and education
5. PITC
6. Abstinence from sex till all symptoms resolve
7. Recording and reporting

Small group Discussion (Jigsaw Method):

Discuss two syndromes in small groups focusing on the common causes, sign and symptoms, and management points and share what you discussed to other group members and learn other syndromes from other group members (30 minutes)

Table 35: Summary of Syndromic Management of Common STIs

Syndrome	**Common causes**	**Sign and Symptom**	**Management**	**Remark**
Urethral discharge	Gonorrhoia (Neisseria Gonnorrhea- 81%)**,** *Chlamydia* ***(****Chlamydia trachomatis*-36.8%) **Others:** *Mycoplasma genitalium, Trichomonas vaginalis, and Ureaplasma urealyticum.*	Urethral discharge (purulent or mucoid, white) Dysuria (burning sensation during micturition) Urgency and frequent urination	Ceftriaxone 250mg IM stat/ Spectinomycin 2 gm IM stat **Plus** Azithromycin 1gm po stat/ Doxycycline 100 mg po bid for 7 days/ Tetracycline 500 mg po qid for 7 days/ Erythromycin 500 mg po qid for 7 days in cases of contraindications for Tetracycline (children and pregnancy) **Note: The preferred regimen is Ceftriaxone 250mg IM stat plus Azithromycin 1gm po stat**	For recurrent Urethral discharge **Re-treat with initial regimen:** If non-compliant or re-exposure occurs If compliant with the initial regimen and re-exposure can be excluded ▪ Metronidazole 2 gm po. stat/Tinidazole 1gm po once for 3 days (Avoid Alcohol!) **PLUS** ▪ Azithromycin 1 g orally in a single dose (only if not used during the initial episode to address

				doxycycline resistant M.genitalium) **Referral:** If men require treatment with a new antibiotic regimen and a sexually transmitted agent is the suspected cause, all partners in the past 3 months before
Genital Ulcer	Syphilis *(Treponema Pallidum*), Chancroid (*Haemophililus ducreyla)*, Genital herpes (HSV-1 & HSV 2), Chlamydia and Klebsiella granulomatis (donovanosis)	Genital open sore or break, Constitutional symptoms (fever, headache, malaise and muscular pain), Recurrent painful vesicles and irritations	**Vesicular, multiple or recurrent genital ulcer**: Acyclovir 400mg po tid for seven days OR Acyclovir 200mg five times daily for 10 days **Non-vesicular:** Bezanthine Peniciline 2.4 mIU IM stat / Doxicycline 100mg po bid for 14 days (for Penicillin allergy) **Plus** Ciprofloxacillin 500mg po bid for 3 days/Erythromycin 500 mg po QID for 7 days **plus** Acyclovir 400mg po tid/10 days	

Vaginal Discharge	**Cervicitis:** Gonorrhea, Chlamydia, **Vaginitis:** Trichomonas vaginalis, Gardnerella vaginalis (Polymicrobial) Candida albicans	Abnormal vaginal discharge, vaginal itching, dysuria, dyspareuria (pain during sexual intercourse)	**Vaginal Discharge with STI risk assessment positive** Ceftriaxone 250mg IM stat/ Spectinomycin 2 gm IM stat **Plus** Azithromycin 1gm po stat/ Doxycycline100 mg po bid for 7 days **Plus** Metronidazole 500 mg bid for 7 days NB:If discharge is white or curd-like **add** Clotrimazole vaginal pessary 200 mg at bed time for 3 days **Note:** The preferred regimen is Ceftriaxone 250mg IM stat **plus** Azithromycin 1gm po stat **plus** Metronidazole 500 mg bid for 7days **Vaginal discharge with negative STI risk assessment** Metronidazole 500mg po bid for 7 days Plus Clotrimazol 200mg vaginal tabs at bed time for 3 days If discharge is white or curd-like **add** Clotrimazole vaginal pessary 200 mg at bed time for 3 days	**Risks of STI** One or more of the following risks: • age <25, • new partner within the last three months, • multiple partner within the last three months, • Ever traded sex

Lower abdominal pain	PID is frequently poly-microbial. **STIs:** Gonorrhea and Chlamydia **Non-STI:***M. genitalium, Bacteroides species, E. coli, H. influenza, Streptococcus*	Lower abdominal pain, dyspareuria, lower abdominal tenderness, vaginal discharge, Fever, nausea and vomiting	**OPD** Ceftriaxone 250 mg IM stat / Spectinomycin 2gm i.m stat **Plus** Azithromycin 1gm po stat/ Doxycycline 100 mg po b.i.d for 14 days **Plus** Metronidazole 500 mg po b.i.d for 14 days **Note :** *The preferred regimen is Ceftriaxone 250mg IM stat* **plus** *Azithromycin 1gm po stat* **plus** *Metronidazole 500 mg bid for 14 days* **Inpatient** Ceftriaxone 250 mg i.m/i.v/ Spectinomycin 2 gm i.m bid **Plus** Azithromycin 1gm po/ Doxycycline 100 mg po b.i.d for 14 days **Plus** Metronidazole 500 mg po b.i.d for 14 days	***Note:*** *For inpatient PID, ceftriaxone, spectinomycin or azithromycin should continue for 24hrs after the patientremain clinically improved, after which doxycycline and metronidazole should continue for a total of 14 days*
Scrotal	**STIs:** Gonorrhea and	Scrotal pain &	Ceftriaxone 250mg i.m	***Note :****The preferred*

Swelling Photo-7B	Chlamydia syphilis, **Non-STIs:***M. tuberculosis, Mumps virus P. aeruginosa, Filarial diseases*	swelling; Edema & erythema of the scrotum Dysuria	stat/Spectinomycin 2gms i.m stat. **Plus** Azithromycin 1gm po stat/Doxycycline 100mg po bid for 7 days/ Tetracycline 500mg qid for 7 days	*regimen is Ceftriaxone 250mg IM stat **plus** Azithromycin 1gm po stat*
Inguinal bubo	Chlamydia, Klebsiella granulomatis (donovanosis), syphilis, Chanchroid	Painful swelling of inguinal lymph nodes, Fever, Headache, Fluctuant abscess formation which forms coalesce mass (bubo)	Ciprofloxacin 500mg bid orally for 3 days **Plus** Doxycycline 100 mg bid orally for 14 days / Erythromycin 500mg po qid for 14 days If patient have genital ulcer,**add** Acyclovir 400mg tid orally for 10 days(or 200mg fve times per day for 10 days)	**Note:** surgical incisions are contraindicated; aspirate pus with hypodermic needle through the healthy skin
Neonatal conjunctivitis	**STIs:** N. gonorrhea, C. trachomatis, **Non-STIs:** S. pneumonia, H. influenza, S. aureus.	ocular redness, swelling and drainage, baby can't open eyes	Ceftriaxone 50mg/Kg) Max of 125mg IM stat Spectinomycin 25mg/kg IM stat (Maximum of 75mg) **Plus** Erythromycine 50mg/kg in four divided doses for 14 days	

NB: For detailed guidance on management of specific sexually transmitted infection syndrome refer to the national syndromic STI management guideline.

7.2.4 STIs in Children and Adolescents

The occurrence of STIs in children except for neonatal infections and congenital syphilis invariably indicates sexual abuse. Pharmacy professionals therefore, should arrange for emotional as well as legal support for the child as part of the comprehensive management (See Annex 3).

7.2.5 Kiting of STI medicines

STI management through pre-packed treatment kits has been an approach to strengthen the syndromic approach of STI treatment. In addition to the recommended drugs for the specific syndrome, the package comprises condoms, partner referral card, information sheet on adherence and illustrative pictures.

Currently, three types of Pre-Packed STI treatment kits (PPST), namely: Addis Cure, Addis Cure Plus and Ul-cure are in use in Ethiopia for the treatment of urethral discharge, vaginal discharge and genital ulcer syndromes, respectively (Refer Annex 4).

7.2.6 Role of Pharmacy Professional in STI Management

- Ensure the sustainable availability of STI management kits.
- Encourages the notification and management of sexual partners
- Counsels patients on importance of Voluntary counseling and testing of HIV when they present with STIs
- Dispense medications for management of STIs and supply condom to the patient after appropriate counseling on the prevention of STIs and HIV.

7.2.7 Session Summary

- STIs are among the most common causes of illness in the world
- Conventional STI and HIV infection share similar risk factors.
- STIs increase the acquisition and transmission of HIV
- HIV infection alters the clinical features and response to therapy of STIs
- The syndromic approach to STIs management is simple, rapid and inexpensive and thus recommended by WHO and is adopted in Ethiopia

- Effective management of STI can reduce HIV infection.

Case Studies

Case Study 1

GR and JA met at college and dated during their senior year. They made plans to marry after graduation. A few weeks after his bachelor party, GR noticed a white discharge from his penis and felt pain when he urinated. He was really concerned about it and calls JA if she was having any symptoms. She said, "I do not have any symptoms!" and he presented to clinic seeking for treatment.

1. What do you think is happening in GR?
2. What are the possible causes of his penile discharge and dysuria?
3. What treatments are recommended for GR? Does JA need treatment?
4. What are you going to counsel GR and JA?

Case Study 2

M.G is 23-year-old woman presented to clinic to be examined by a gynecologist. She complains of whitish vaginal discharge. When gynecologist asked her sexual history she was shy and responded she had changed 3 sexual partners and occasionally use condom. Up on examination the gynecologist notices cervicitis. The physician ordered pregnancy test and the result was positive.

1. What is happening in MG?
2. What are the common causes of her problem? What are the risk factors in MG for having STI?
3. Can her pregnancy affect the choice of drug therapy?
4. How do you treat MG?

Session 8.1: Adherence support to ART

Session Description:

In this session, adherence support to ART is described. The session starts with the definition and importance of optimal adherence to ART. Then it explores the consequences of poor adherence, barriers to ART adherence, strategies, and interventions to promote and optimize adherence to ART. It also discusses the different methods of assessing adherence to ART.

Primary Objective:

The purpose of this section is to introduce participants the importance of adherence to care and adherence to ART medications.

Enabling Objectives:

By the end of this session trainees should be able to:

- Explain the concept of adherence to ART
- Identify barriers for adherence to ART
- Explain strategies to promote adherence
- Identify methods of adherence assessment and/or monitoring
- List the role of pharmacy personnel in supporting adherence to ART

Session Outline

- Introduction to Adherence
- Barriers to adherence
- Strategies to promote adherence
- Methods of adherence assessment
- The role of the pharmacy personnel
- Session Summary

Introductory Case

Pair Discussion

TR is a 38-year-old broker who lives in Adama diagnosed HIV positive three years ago in Debrezeit Health center. He did not want to think about it, so he has not returned to the clinic for checkups as advised, and has been well—until last week. Today he wants to see a doctor because for the past week, he has been having difficulty swallowing and he noticed that there are sores in his mouth. He is feeling anxious, but he wants help. He fears he will have to take many pills, something he has never liked to do and something that might mean he will have to tell his wife he is HIV positive.

He travels to Zewditu Hospital, Addis Ababa and the doctor prescribed him fluconazole for the oral/esophageal candidiasis and paracetamol for his pain, confirmed that HIV test is positive and counseled him and prescribed TDF/3TC/EFV. The patient presented to your pharmacy with prescription to start ART. You dispense Fluconazole and Paracetamol to him and told him to take paracetamol now and come back after 10 minutes for adherence counseling.

Group Discussion:

You prepare the following list of questions to explain to him:

1. What is medicines adherence?
2. What are you going to assess this patient before dispensing ART medications?
3. What are the barriers for adherence for this patient?
4. How can you reduce adherence barriers this patient to make the treatment successful?

8.1.1. Introduction to adherence

World Health Organization defines treatment adherence as; *"the extent to which a person's behavior – taking medications, following a diet, and/or executing lifestyle changes – corresponds*

*with **agreed** recommendations from a health care provider"*. Adherence involves a mutual decision-making process between patient and health care provider.

Why is Adherence to ART Important?

Adherence to ART is the major factor in ensuring the success of an initial regimen and is a significant determinant of survival. Adherence is second only to the CD4 cell count as a predictor of progression to AIDS and death.

For ART, a high level (Optimal adherence rate of ≥95%) of **sustained** adherence is necessary to:

1. suppress viral replication and improve immunological and clinical outcomes;
2. decrease the risk of developing ARV drug resistance; and
3. reduce the risk of transmitting HIV.

Achieving >= 95% adherence significantly reduces the likelihood of virologic failure and drug resistance, which provides, by far, the best chance for long term clinical success. If the adherence is less than 80%, the treatment WILL NOT WORK in half the cases!!!

	%	**(of 30 doses)**	**(of 60 doses)**
Good (optimal)	≥ 95 %	≤2 doses	≤ 3 doses
Fair	85-94%	3-5 doses	3-9 doses
Poor	<85%	≥ 6 does	>9 doses

Adherence rate is calculated by using brief survey of missed doses in the last 3 days, 7 days or two weeks can be used.

$$\% \text{ Adherence} = \frac{\text{\# Doses should have been taken - \# Missed doses}}{\text{\# Doses should have been taken}} * 100$$

Challenges of Adherence to ART

Adherence to ART is a unique challenge in health care because....

- No immediate "reward" to ART as it does not cure HIV infection.
- Life- long treatment,

- Pill burden: Triple ART regimen and medications for OIs causes pill burden on the patient
- Medication related issues & side effects.
- Access to health care
- Behavioural change may be required
- Confidentiality concerns

Consequences of poor adherence: Non-adherence has enormous negative consequences on individual patient, public health, and economy.

- **For the individual**: -poor adherence can lead to inadequate suppression of viral replication, progressive decline in immune function (continued destruction of CD4 cells) and disease progression. Poor adherence is also an important reason for the emergence of viral resistance to one or more antiretroviral medications.
- **From a public health perspective:** - Transmission of resistant virus (subsequent ART failure), increased morbidity and mortality
- **From a health economics perspective**: - increased health care cost on individual patient and health care system

8.1.2. Barriers to ART Adherence

Adherence rates vary not just between individuals, but within the same individual over time. Adherence is therefore best thought of as a variable behavior rather than as a stable characteristic of an individual – most people will exhibit low adherence some of the time. Generally, factors that affect adherence can be categorized into patient variables, treatment regimen, disease characteristics, patient-provider relationship, and contextual factors (table 8.2.1).

Table 8.2.1: Factors that Affect Adherence

Factors	Description of Barriers
Patient Variables	**Socio-demographic factors**: gender, ethnicity, age, employment status, income, education, and literacy: - do not significantly predict adherence **Psychosocial factors**- consistent associations • Forgetting doses; being away from home; changes in daily routines

Factors	Description of Barriers
	• Active alcohol and/or drug use • Depression/psychiatric illness • Lack of social support • Nondisclosure of HIV status, with accompanying stigma and isolation • General health – if people do not feel ill, may be less motivated to take medicines • Lack of perceived efficacy of ART • Lack of knowledge of the disease • Lack of transport, shortage of food, use of traditional medicine, fear of stigma and discrimination **Physical Factors:** Visual impairment, Hearing impairment, Cognitive impairment, Impaired mobility, and Swallowing problems
Patient-Provider Relationship	• A poor patient-provider relationship will decrease a patient's adherence success • Factors that might contribute to a poor relationship include: o 'Superiority' attitude of care provider o Contradicting information from doctor, nurse, pharmacist o Lack of trust and confidence of PLHIV in their care providers o Poor support by care providers
Therapy Related Factors	• Complexity of medication regimen (Dose frequency, Pill burden, dietary requirements), • Medication adverse effects • Treatment requires mastery of certain techniques (especially pediatric formulations) • Frequent changes in medication regimen • Lack of immediate benefit of therapy • Treatment interferes with lifestyle or requires significant behavioral changes

Factors	Description of Barriers
Disease Related factors	• The stage and duration of HIV infection • Associated opportunistic infections • HIV-related symptoms **N.B. Reported predictors of poor adherence include:** • Lack of advanced disease and prior experience with OIs
Contextual Factors	**Health Services factors** • Travelling long distances to reach health services • Bearing the direct and indirect costs of care. • Stock-outs of ARV drugs and Poor access to medications or care, • Shortage of staff at clinics or pharmacy • Lack of a system for monitoring retention in care **Life Situation Issues:** Homelessness, lack of steady financial income, and no coverage for medical care services are some of these situational issues that cross the boundaries between individual and systemic concerns

Question from the Introductory Case

What are the potential barriers that could influence TR's adherence to treatment (introductory case)?

8.1.3 Strategies to Promote ART Adherence

GROUP WORK

1. What does it mean a multidisciplinary team (MDT) approach? Why is it important to use it as a strategy to promote Adherence?
2. What strategies need to be in place to improve adherence before initiation of therapy?
3. What factors would be assessed before initiation before initiation of ART?
4. What should be pharmacy professionals counsel and educate the patient before initiation for promote adherence before initiation?

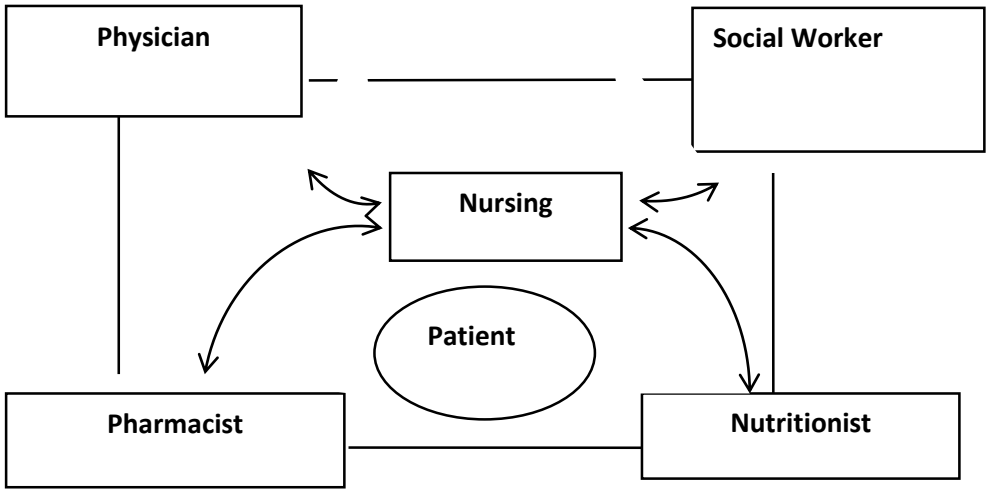
2. Improve adherence before initiation
    i. Establish a trusting relationship with the patient
    ii. Assess readiness to start antiretroviral therapy (ART)
    iii. Educate and Counsel patients
    iv. Involve the patient in treatment plan development
    v. Simplify treatment regimens
3. Ongoing monitoring and adherence support
    - Identify the type of and reasons for non-adherence at every clinic visit
    - Using interventions to improve adherence
    - Reminder and engagement tools like

1. Use a multidisciplinary team approach

A multidisciplinary approach is the best approach for improving adherence. **The "Adherence Team"** should involve physicians, nurses, pharmacists, other health care providers, and family/friends of the patient as possible.

All disciplines should address adherence with patients at every visit in a **non-judgmental fashion**

ART Care Model (Adherence Protocol) Multidisciplinary (Team) effort:



Ongoing education with the **same messages** from pharmacist, nurse, counselor, physician

Role of the pharmacy professional as key member of the multidisciplinary team:

- Identifying barriers to adherence before a patient begins therapy and suggest possible solutions with the patient and /or other health care workers
- Assessing patient adherence and follow up
- Developing strategies to promote adherence
- Monitoring adherence for patient's overtime
- Dispensing of medications and Counseling patients

2. Improving Adherence: before ART Initiation

i. Establish a trusting relationship with the patient

ii. Assess readiness to start antiretroviral therapy

It is extremely important to take time to assess and prepare the patient for initiation of ART. Initial assessment should include the following points:

- Assess the **patient's health** through a detailed medical history.
- Assess the **patient's beliefs and attitudes** about HIV and treatment.
- Assess the **sources of social support**.
- Assess the **socio-economic situation** of the patient.
- Assess the **prior use of antiretroviral** and other medications.
- Assess the **patient's current state of physical health**.

iii. Educate and Counsel patients:

Most effective adherence interventions for ART involve dedicated time with patients to plan for and support medication adherence. The following points should be addressed before initiation of therapy to improving adherence:

Make sure that the patient is involved in the decision to start therapy: the success of therapy is dependent on the patients' agreement and motivation to start therapy. Discuss with the patient to determine the regimen and time for taking medication that best fits with their routine activities. Before initiating ARV therapy, establish that the patient/care giver is willing, motivated and agrees to treatment

Take time to educate the patient on the benefits and goals of therapy, necessity of adherence to regimen, potential adverse drug effects and potential drug interactions (with other drugs, natural medicines, or food)

In addition, provide written information to supplement the counseling points addressed (especially time to take their medication and adherence).

While counseling and educating the patient use **medication use counseling checklist** (Annex 8.1.1.) and **5 A's (Assess, Advise, Agree, Assist, and Arrange)** for chronic HIV/AIDS care (*refer session 8.2; table 8.2.1*).

Develop strategies for handling adverse effects, missed doses, change in routine (carry an extra dose of ARVs), travel (time zones), storage of medications and fear of taking medications in front others.

iv. **Use of Simple Regimens*:*** Fixed-dose combinations have greatly reduced the pill burden and hence improve adherence.

v. **Establish a treatment plan**: determine the frequency of visits to pharmacy and fix new appointments or change appointments if s/he cannot come for a scheduled visit.

Don't make assumptions about patient adherence: ask questions and discuss solutions for the following **simple and specific questions to assess the patient's /care giver's understanding**:

- What are the benefits of ART?
- Does ART cure patients from HIV?
- How long do you have to take ART?
- What is the effect of ART on the body's defense?
- Why is it important to come regularly to the health center when you are taking ART?
- What do you know about side effects of ART?
- Why is it important not to miss a dose when you take ART?
- What happens if you do not take ART correctly?
- Why is not good to combine ART with other drugs without consulting the health provider?

3. Ongoing Monitoring and Adherence Support

Adherence is a dynamic behavior that is affected by factors that change throughout a person's life. The reasons for missing doses change over time due to *lifestyle changes, pill fatigue, improved health and intermittent hospital admissions for non-HIV-related issues*. Therefore, pharmacist should assess patient's medication taking behavior, barriers and facilitators to treatment adherence at each visit to pharmacy continually and regularly. This would be more practical if it is done in conjunction with the provision of information on the results of viral load and CD4 count.

How to ask about adherence:

Useful:

- Majority of patients really miss doses, what happens to you when you do it?
- It's practically impossible not to miss medication dose at least once. Tell me how it was with you.
- I know that you try hard to be adherent, tell me about your problems in this respect and we will try to solve them together

Not effective:

- You don't miss doses, do you?
- You take all the prescribed pills, is that right?
- You know that you should not miss doses, don't you?
- You never miss your ARV dose, do you?

How many pills did you forget yesterday, last three days, and last month?

Interventions to improve adherence

Based on identified adherence problems during monitoring of the patient, effective interventions will be used to improve adherence. No single adherence intervention or package of interventions is effective for all populations and all settings.

Program-level interventions for improving adherence to ART include:

- avoid imposing out-of-pocket payments at the point of care,

- using fixed-dose combination regimens for ART and
- Strengthening drug supply management systems to reliably forecast, procure, and deliver ARV drugs and prevent stock-outs.

***The individual-level adherence intervention*:**

- Nutritional support, peer support, management of depression and substance use disorders and patient education are vital components of routine health and HIV care.

Reminder and Engagement Tools

1. Pillboxes

Pillboxes are containers for storing medication with dividers for each day and each dose within the day. This makes it easy for patients to take doses correctly. A possible disadvantage of the pillbox may be its visibility in situations where patients need to hide medications from others due to confidentiality reasons. Patients who are illiterate or very sick may need help to fill the pillboxes correctly.

2. Electronic devices:

Devices range from beepers to alarm watches that remind patients to take medications on time. Electronic devices can be used both to measure adherence as well as a reminder tool for patients.

3. Mobile phone text messages:

Mobile phone text messages could be considered as a reminder tool for promoting adherence to ART as part of a package of adherence interventions (WHO 2013 recommendation).

4. Medication diaries

These are diaries in which patients record the time and date of medication intake, missed doses and reasons for missed doses. These can serve as useful records of side effects or other problems patients may experience. This is a useful tool to identify patterns of use and reasons for missing doses.

5. 'Buddy' system

The buddy system relies on a friend or family member to help the patient to take medications regularly—reminding the patient to take his medication on time, offering encouragement to keep going, helping to keep hospital appointments, providing support etc.

6. Pill charts

Pill charts are used to visually display pills (color and shape), names and dosage for each medication and are used by the pharmacists or health provider during counseling. This is a very useful tool for patients with literacy problems.

7. Directly Observed Therapy (DOT)

It is not practical to observe all doses as most HAART regimens have multiple doses and treatment is life-long. Therefore, only some doses are observed for a fixed period (a few months) for specific type of patients who require special attention. This is called ***modified DOT*** or ***directly administered antiretroviral therapy (DAART).***

Table 36: The common reasons for missing doses, possible barriers, and suggested solution

Reasons for missing doses	***Possible barriers***	***WHAT WE CAN DO***
Forgot to take pills	Patient forgot because: • Traveling • Alcohol/active drug use • Depression/psychiatric illness • Living alone and sick • Homeless, no family support	• Plan before travel, take extra pills • Use reminder cues • Address addiction (alcohol and drugs) • Enlist family support • Treat depression • Use PLHA support groups
Pills do not help	• Inadequate knowledge	• Enhanced counseling • Provide scientific information and examples • Enlist family support
Felt better so did not continue	• Incorrect beliefs and attitudes	
Family said no to Medications	• Inadequate knowledge • Incorrect beliefs and attitudes	• Family counseling • Provide scientific information and examples
Instructions were not clear Did not understand how to take medications	• Literacy levels • Depression/psychiatric illness • Alcohol/active drug use • Insufficient time to counsel	• Use literacy materials • Use dummy pills and repeat instructions • Ask patient to repeat instructions • Enlist family support • Treat depression • Address addiction (alcohol and drugs)
Unable to care for Self	• Living alone	• Use PLHA support groups

	• No employment • AIDS dementia/mental illness	• Register with the home-based care program • Link with FBO food donation programs • Locate family and enlist support • Identify a friend who could help
Did not want others to see patient taking medications	• Stigma at place of work • Non-disclosure in the family	• Provide counseling support to help with disclosure • Identify a friend who could help keep medications
Fear of toxicity	• Insufficient preparation • Inadequate knowledge	• Provide scientific information on what to expect and how to manage it • Counsel on risks of non-adherence

8.1.4. Methods of ART Adherence Assessment

Objective monitoring of adherence to ARV drugs is necessary for effective and efficient treatment planning and ongoing support. Each facility visit brings opportunity for assessing and supporting treatment adherence. Effectively monitoring adherence requires a combination of approaches based on human and financial resource capacity, acceptability to people living with HIV and to health workers and the local context.

Table 37: Common Methods Used to Measure Adherence: Advantages and Disadvantages

Method	**Advantages**	**Disadvantages**
Self-report: Pharmacists can ask: "How many pills did you miss in the last 3 days?"	• Easily completed using patient interview or questionnaire (report of nonadherence is more reliable than report of adherence). • Inexpensive. • Patient may feel that she or he has more hands-on involvement in health care decisions.	• Overestimates adherence. • Correlation is dependent on patient's relationship with staff. Patients may tell prescribers what they perceive as socially desirable or "right" responses.
Pill counts:	• Useful adjunct to self-report. • Unannounced pill counts may be more accurate. • Direct costs are minimal.	• Tends to overestimate adherence as a result of pills being "dumped" prior to visit. • Casts pharmacy personnel in

		the role of medication monitor and not ally or advocate • Does not prove that patient actually took medication.
Pharmacy refill monitoring	• Easy, minimal time commitment. • Timely refilling of prescriptions correlates well with adherence. • Most successful when limited to patient using one pharmacist. • Is a useful adjunct to self-report	• Does not equate with taking medication. • Patients may use more than one pharmacy. • Medication may be shared or sold.
Viral load	• Can correlate with adherence. • Although poor adherence is associated with virologic failure, not all patients with virologic failure will be poor adherers.	• Does not necessarily indicate nonadherence. • May overestimate adherence. • Virologic failure can be indicative of drug resistance.
Directly observed therapy	• 100 % adherence, in theory. • Ideal method for institutional settings (e.g., prisons, nursing homes).	• Labor intensive. • Concern for development of resistance if plan not followed.
Health care provider estimation	• None.	• Provider estimation is more poorly correlated with actual adherence.

8.1.5 Roles of the Pharmacy personnel

- Assesses patient readiness for initiation to ART
- Identifies barriers to adherence and suggest possible solutions with the patient and /or other health care workers
- Educate and counsel the patient about optimal medication use
- Discuss with and develop plan on medication regimen to accommodate the patient's lifestyle
- Encourage the use of adherence aids/reminder devices (e.g. alarms)

- Monitors and supports patient adherence regularly at each visit
- Developing strategies to promote adherence
- Dispensing of medications and counseling patients on appropriate use

8.1.6 Session Summary

- Antiretroviral (ARV) regimens are complex and have multiple barriers to adherence exist
- Serious potential consequences can result from non-adherence
- Patient/family education and involvement is critical for successful treatment of HIV infection
- Pharmacist is key member of the multidisciplinary adherence team.
- The medical team (provider, pharmacist, nurse) and the patient must work together to promote optimal adherence to both HIV care and ARV regimens
- The pharmacist plays a vital role in promoting adherence and offering techniques for improvement of adherence

Session 8.2: Effective Communication with health care providers and patients

Session Description:

Definition of communication and the need for effective communication in HIV/AIDS practice are discussed as introduction of the session. Importance of team approach in ART and effective communication with providers is discussed. Then the approaches and reasons for communicating patients are explained. Furthermore, the 5A's for effective communication in the chronic management of HIV/AIDS is addressed in this session.

Primary Objective:

The objective of this session is to equip participants with communication skills for interacting with patients and health care providers

Enabling Objectives:

By the end of this session participants will be able to:

- Demonstrate the principles of communication. Explain basic principles and behaviors of ART counseling
- Describe the team approach to HIV care and treatment
- Practice communication with patient and provider

Session Outline

- Introduction to communication
- Effective communication with health care providers
- Effective communication with patients
- Practice communication with patient and provider
- Session Summary

8.2.1 Introduction to Communication

Communication is sharing of information, ideas, thoughts and feelings which are meaningful to those involved. It is the process in which messages are generated and sent by one person and received and translated by another person. However, the meaning generated by the receiver can be different from the sender's intended message.

There are five steps in the communication process:

1. The **Sender** has an idea to communicate: what the sender intended to say
2. The Sender encodes the idea in **a message:** what the sender actually said
3. The message travels **over a channel:** Media of communication (verbal, written, non-verbal or electronic)
4. The **receiver decodes** the message: What the receiver understood
5. The receiver understands and sends **feedback to** sender

Why effective communication is needed?

Effective communication is required for effectively sharing information between health care providers and patients and within health care providers themselves.

Pharmacists need to be able to share information in order to work effectively with patients, and the MDT members. Effective communication also ensures the confidentiality of patient. The effective communication should be:

- on a professional level with the multidisciplinary team (MDT)
- With an individual patient on a level that he/she can understand

Non-verbal communications

Effective two-way communication requires continual observation and assessment of how the other person is communicating. Body language and gestures provide important clues for the pharmacist, as well as the patient and health care provider. Nonverbal communications includes body movements, gestures, facial expressions and gaze pattern. These behaviors convey information that words alone often do not. They provide a clue to a person's inner thoughts and

feelings. They can enhance or interfere with the verbal messages that are delivered. There must be congruency, or consistency, between the verbal and nonverbal messages.

Note!

Verbal Communication conveys 10% of the message

90% of the message is transmitted by non-verbal communication

(40% how it is said and 50% body language)

The following non-verbal messages are important in effectively communicating a patient and to demonstrate caring relationship, empathy and interest to the patient.

- Keep the chest area open and arms unfolded to avoid setting up a perceived barrier between you and the patient (no arms across the chest or tightly clutched chart or X-rays).
- Maintain a relaxed and open body position, whether standing or sitting helps to appear confident as it will enhance trust.
- Make eye contact; look at the patient directly (have face to face interaction).
- Sit at eye level
- Lean slightly forward when speaking.
- Keep an appropriate distance from the patient. For most people, 2–4 feet will be comfortable for the patient and also convey your engagement in the conversation.
- Avoid looking over the rim of your glasses at the patient, a gesture that strikes an authoritarian, superior pose. On the other hand, taking off your glasses while the patient is speaking conveys a caring, empathic response to what you are hearing.
- Remain still and focused on the patient who is telling you something that is clearly important to him or her. Use facial expressions in response to the patient's comments as a way of letting the patient know you are listening attentively. Nod your head at key points in the patient's statements.
- Some form of touch involves in caring for patient. All touch should be conscious and by mutual agreement between provider and patient

8.2.2 Effective communication with health care providers

Think-pair- share

Be in pairs and think-pair- share for 5 minutes on effective communication with healthcare providers focusing on team approach (MDT) and what needs to be done by the pharmacy personnel to have an effective communication with the health care providers.

Comprehensive care for HIV/AIDS patients involves multidisciplinary team or clinical team. A "**clinical team**" is a team of health workers that collaborate in the clinical care of a patient. Each member of the clinical team may have different roles and be concerned with different aspects of the care of the patient, but they discuss each case and decide together on the treatment plan. The members are medical Doctor, Health officer, Pharmacist /Druggist, Laboratory head, Nurse, Case manager, Data clerk/HIT in MDT.

Effective communication between pharmacists and physicians, nurses, and other pharmacists is essential. Poor communication not only leads to frustration and lack of respect among professionals but also may compromise patient care if important information is misunderstood, ineffectively conveyed, or left out.

When communicating with other health care provider use the following steps:

- Begin by identifying yourself
- Identify the patient whom you are to discuss
- Present the issue or concern that you have identified
- Do not be judgmental
- Use professional rapport to gain respect
    - Be prepared to discuss the issue at a professional level
    - Propose a solution or recommendation
- Await feedback

Note that:

- ✓ You may not always have all the answers to the questions that follow
- ✓ Be comfortable saying that you do not know the answer now, that you will look into it and get back to the provider as soon as you can

- ✓ The provider will respect that you provide only information about which you are confident
- ✓ Over time, you will build a working relationship with the healthcare team members that you work with.

8.2.3 Effective Communicating with Patients

Effective communication between pharmacists and patients or family members is extremely important. Ineffective communication leads to confusion and misunderstanding and may contribute to inappropriate decisions regarding medication therapy. The communication process between you and your patients serves two primary functions:

- It establishes the ongoing relationship between you and your patients; and
- It provides the exchange of information necessary to assess your patients' health conditions, reach decisions on treatment plans, implement the plans, and evaluate the plan

The pharmacy professional must be empathic to patient**,** perceive each patient's experience as unique**,** foster a more open relationship with patients, and build a therapeutic relationship with patients to meet mutually understood goals of therapy**.**

In national health promotion and communication strategy 2016-2020, **Ethiopia** has developed health service delivery strategy that strengthen the relationships between health service providers and their clients to create friendliness and welcoming health facility environment through **caring, respectful and compassionate (CRC)** health professionals.

Individual Reading on the Characteristics of CRC

Caring, Respectful and Compassionate (CRC) health professionals are having the following four essential characteristics:

1. Consider patients as human beings with complex psychological, social and economic needs and provide person centered care with empathy
2. effective communication with health care teams and interactions with patients and other health professionals over time, and across settings

3. Respect for and facilitation of patients' and families' participation in decision and care; and
4. Take pride in the health profession they are in and get satisfied by serving the people and the country

Behavioral checklist for effective communication with patient

- Be relaxed, confident, and comfortable.
- Show interest in the patient.
- Maintain objectivity
- Do not be judgmental.
- Be sincere and honest.
- Maintain control of the communication process.

Checklist for Pharmacist-Patient Communication Skills

1. Provide clear instructions regarding the structure of the interview and expectations for the patient.
2. Use a balance of open-ended and closed-ended questions.
3. Use vocabulary geared to the patient (avoid medical jargons).
4. Use nonbiased questions.
5. Give the patient time to respond.
6. Interrupt or redirect as necessary but do not interrupt when the patient is on track.
7. Listen to the patient; do not cut off the patient.
8. Discuss one topic at a time.
9. Move from general to specific topics.
10. Pursue unclear answers to questions until they are clarified.
11. Ask simple questions.
12. Identify and recognize patient feelings. Verbally acknowledge inappropriate or hostile feelings.
13. Give feedback to the patient. Ask, "Is this what you mean?"
14. Obtain feedback from the patient.
15. Attend to patient cues (posture, tone of voice, affect).

16. Invite the patient to ask questions.
17. Answer patient questions.
18. Use transitional statements and summarization.
19. Close the communication.

Reasons for Communicating Patients

Readiness preparation for ART Initiation

Before patients start ART, it is important to have a detailed discussion with them about their willingness and readiness to initiate ART, the ARV regimen, dosage and scheduling, the likely benefits and possible adverse effects and the required follow-up and monitoring visits. Tell the patient how to handle missed dose.

Patient counseling

Effective patient counseling is not simply the provision of information. As a pharmacist you are the expert on medication therapy, but patients are experts on their daily routines, how they understand their illness and its treatment, and whether they anticipate any problems taking the medicine as prescribed. Each of these points needs to be assessed if counseling is to be effective. For effective patient counseling follow **medicines use counseling checklist** (see annex: 2).

Providing Medication Information

Pharmacy professionals are responsible for provision of medication information for patients and providers. Particularly ART pharmacist, should give information on the medicines dosage, treatment regimen, common toxicities and how to manage toxicities. The information may be provided verbally or in written form. In the provision of information to the patient:

- Identify whether the patient has any learning barriers such as low literacy for written information,
- Ensure information is provided in a language the patient understands
- Use pictures to communicate information,
- Indicate colors of the pills to familiarize patients with their regimen, ask patient to tell you how they will use the medication and correct misunderstandings before they leave.

- Give patients specific examples of how to remember to take their doses: for example, when they brush their teeth or when they wake up their children
- Assist patients in preparing for changes in their routine: for example, vacation or visiting family
- Appropriately label all the patient medications and make sure the patient's understanding
- Advise the patient on how to appropriately store his/her medications
- In cases when it is obligatory to dispense medications with different expiry dates, appropriately label medications and make sure that clients understand it. Help clients to take their medicines orderly in accordance with their expiry dates.

Adherence support

The pharmacy professional should communicate the necessity of strict (near-perfect) adherence for treatment success, prevention of resistance and treatment failure. Assess adherence each time patients refill their ART. Ask a question like *"When did you last miss a dose?"* rather than, *"Have you missed any doses?"* Congratulate the adherent patient.

- Assess adherence each time patients refill their ART. Ask a question like ***"When did you last miss a dose?"*** rather than, ***"Have you missed any doses?"*** Congratulate the adherent patient.
- Identify the reason for missed doses and provide possible solution to prevent missing of doses in the future.

Communication and Chronic Care of HIV/AIDS

Good chronic care recognizes the fact that the patient and family/care taker should understand and learn to manage the patient's chronic condition. The following principles can be used in managing chronic care of HIV/AIDS.

1. Develop a treatment partnership with your patient to achieve agreed goal
2. Focus on your patient's concerns and priorities
3. Use the **5 A's**—Assess, Advise, Agree, Assist and Arrange
4. Support patient self-management
5. Organize proactive follow-up
6. Involve "expert patients," peer educators and support staff in your health facility

7. Link the patient to community-based resources and support
8. Use written information
9. Work as a multidisciplinary clinical team
10. Assure continuity of care

5 A's—Assess, Advise, Agree, Assist, Arrange

The 5 A's are a key part of good chronic care. They are a series of steps to use in caring for patients.

Table 38: 5-A's in HIV/AIDS care

ASSESS:	• Patient's goals for the ART pharmacy visit • Understanding of HIV/AIDS and ARV therapy • Readiness for initiation of therapy • Potential barriers to adherence, such as: o Financial problems o Unstable housing o Substance abuse o Mental health problems o Lack of social support
ADVISE ON:	• Benefits of ARV therapy • How to take medications (dose, frequency, duration and interactions with food and other drugs) • Importance of adherence • Possibility of side effects (common and serious) • Management side effects, if they happen • Seeking of care for any treatment concerns • Importance of adherence especially for patients initiation ART and for stable patients on appointment spacing model (ASM) scheme • Proper medication storage conditions • Importance of disclosure of HIV status Importance of notifying his/her ART regimen while seeking care from health care providers

AGREE:	Establish that the patient agrees and is motivated to take ART Has the patient agreed to keep appointments and to adhere to treatments Has the patient disclosed his or her HIV status? If not, encourage him/her to do so. Confirm the patients understanding and willingness to start treatment
ASSIST:	Help the patient develop the resources and support needed for good adherence • to come for required scheduled follow-up • Home and work situation that allows for taking medications without stigma • linking with treatment supporters (adherence supporter, associations, family or friends) Develop a plan for the specific ARV regimen. • Provide the names and show medicines in the regimen • describe the number of pills, dosing schedule, and duration of treatment • Provide aids for adherence, such as a pillbox or pill chart. • Prepare patient and treatment supporter for possible common side effects and what to do if they occur and when to seek care. Provide psychosocial and emotional support
ARRANGE:	When the patient is ready for ARV therapy • Work in MDT to develop treatment plan • Arrange next follow-up appointment

8.2.4 Practice communication with patient and provider

Role Plays **Demonstrating an effective communication with patient and health care provider using role plays**

Role Play Scenario – 1

MA is 27 years old woman who was tested HIV positive recently. The clinical team has decided that she needs ART and she come to your pharmacy with prescription of TDF/3TC/EFV for

initiation. The pharmacy professional is going to counsel the patient and assure readiness to ART using the 5A's.

The rest of the group should watch the role play and comment on the advice given and any difficulties faced by both the pharmacy personnel and women during the consultation.

Role Play Scenario-2

Treatment naïve patient brings a prescription to the ART pharmacy with AZT/3TC/NVP fixed dose combination to be taken twice daily for one month. While reviewing the prescription, pharmacy personnel recognized the overlapping that nevirapine should be given once daily for the first two weeks. In addition, this regimen is not the preferred first line regimen for initiation. Then, he goes to contact the prescriber to alert the issue and recommend initiating preferred first line ART regimen.

8.2.5 Session Summary

- A team approach to HIV care and treatment is an effective way to care for HIV-positive patients.
- Good communication with providers and patients is essential for successful HIV care and treatment.
- Pharmacists need to counsel patients on ART readiness, ART information, and the importance of adherence and ongoing monitoring.
- Use the principle of 5 A's when communicating with patients.

Session 9: Standard Precaution (SP) and Post Exposure Prophylaxis (PEP)

Session Description:

This session starts by defining and outlining components of standard precautions. Then, concepts occupational exposure and risk of transmission of viral Infections and the management of occupational exposure are discussed.

Primary Objective:

The objective of this session is to introduce the participants with universal precautions and post exposure prophylaxis

Enabling Objectives:

By the end of this session, participants will be able to:

- Describe the basic principles and procedures of standard precautions
- Explain the occupational exposure and risk of transmission of viral infections
- List the management steps of occupational exposure
- Describe the principles of HIV post-exposure prophylaxis (PEP)
- Identify the role of pharmacy personnel in SP and PEP

Session outline

- Basic Principles and Procedures of Standard Precautions
- Occupational Exposure and Risk of Transmission of Viral Infections
- Management of occupational exposure
- Role of pharmacy professional
- Session Summary

9.1 Basic Principles and Procedures of Standard Precautions

Activity

- **Share your/your colleagues' real-life experiences about occupational exposure for 3-5 minutes (if any).**
- **How occupational exposure can be reduced?**

Standard precaution (formerly called Universal Precaution) is a set of standards of infection control developed to prevent exposure and transmission of blood-borne pathogens (HIV, HBV, and HCV). It should be implemented and practiced at all times by all health care providers and caregivers in all settings (hospital, clinic, community settings, and patient homes).

Components of Standard Precautions include the following:

- Increased attention for the correct handling of sharps and all contaminated materials: Safe disposal of sharps material like needles, scalpels, and suture materials
- Safe disposal of waste contaminated with blood or body fluids**:** bandages, dressings, linens, or materials contaminated with blood or body fluids must be handled with gloved hands and placed in containers for safe disposal.
- Hand washing with soap and water before and after all procedures: The single most important step that the healthcare worker can take to ensure the safety of their patients and himself is by using recommended antiseptics solutions.
- Use of protective barriers, such as gloves, gowns, masks, goggles when in direct contact with potentially infected body fluids. Glove use results in 50% decrease in volume of blood transmitted.
- Proper disinfection of instruments and other contaminated equipment**:** Immunization**:** against hepatitis A and B are recommended for all health care workers as a component of standard precautions

Refer Annex 8 for details on components of standard precautions

9.2 Occupational Exposure and Risk of Viral Transmission

Health care providers (HCPs) and support staff have a low but measurable risk of HIV infection after accidental exposure to infected blood or body fluid. The seroconversion rate of HIV infection per occupational needle stick injury is much lower than seroconversion rate of HBV in unvaccinated HCP (0.3% Vs 30%) and HCV (0.3% Vs 1.8%).

The risk of transmission of HIV infection following inadvertent exposure varies widely depending upon the type and severity of exposure. Most injuries in the healthcare workplace are due to contaminated sharp injuries. The risk of HIV transmission is highest with **percutaneous exposure (0.3%)** followed by mucous membrane exposure (0.09%) and cutaneous exposure is less likely to transmit HIV.

Factors that increase the risk of transmission are:

- exposure to large volume fluid,
- deep (intramuscular) injury,
- injury with hallow bore IV- needle than solid suture materials,
- source patient with high viral load and exposure to open wound.
- the type of body fluids exposed exposure to blood has the highest risk.

Table 39: Infectious and Non-Infectious Body Fluids for HIV

Infectious Body Fluids	**Non-Infectious Body Fluids**
• blood • body fluids containing visible blood • Vaginal secretions • Semen • Pericardial fluid • Pleural fluid • Cerebrospinal fluid • Amniotic fluid • Peritoneal fluid • Synovial fluid	• Tears • Feces • Urine • Saliva • Nasal secretions • Sputum • Vomit • Sweat

9.3. Management of Occupational Exposure

Management of occupational exposure comprises a set of services that are provided to manage the specific aspect of exposure to HIV and to help prevent HIV infection in a person exposed to the risk of getting infected by HIV. These services comprises of first aid, counseling including the assessment of risk of exposure to the infection, HIV testing, and ARVs for PEP.

First Aid

Individual Reading

Read First Aid actions to be taken immediately following exposure to potentially infections fluids and Counseling of Exposed Client for 5-7 minutes

Take the following first aid steps for the following condition:
following an injury with a used needle or other sharp instrument, Wash the injury immediately, using soap (don't scrub vigorously).

- Encourage the puncture wound to bleed freely under running water for several minutes or until bleeding ceases.
- If running water is not available, clean site with a gel or hand cleaning solution.
- **Do not** use any strong solutions, such as alcohol, bleach or iodine, as they may irritate the wound and make the injury worse.
- **Do not** squeeze or rub the injury site.
- **Do not** suck a puncture wound.
- Irrigate exposed mucosal surfaces with sterile saline

After a splash of blood or body fluids,

- ***for a splash on unbroken skin:***
  - ♦ wash the area immediately;
  - ♦ if running water is not available, clean the area with a gel or hand rub solution;
  - ♦ **do not** use any strong solutions, such as alcohol, bleach or iodine, as they may irritate the affected area;
  - ♦ use mild disinfectants, such as Chlorhexidine gluconate 2–4%;
  - ♦ **do not** rub or scrub area;

- **do not** use a dressing.

- ***for a splash in the eye:***
  - irrigate the exposed eye immediately with water or normal saline. Sit in a chair, tilt the head back and have a colleague gently pour water or normal saline over the eye, gently pulling the eyelids up and down to make sure the eye is cleaned thoroughly;
  - if wearing contact lenses, leave them in place while irrigating, as they form a barrier over the eye and will help protect it; once the eye has been cleaned, remove the contact lenses and clean them in the normal manner, which will make them safe to wear again;
  - **do not** use soap or disinfectant on the eye.
- ***for a splash in the mouth:***
  - spit the fluid out immediately;
  - rinse the mouth thoroughly, using water or saline, and spit out again. Repeat this process several times.
  - **do not** use soap or disinfectant in the mouth.

Counseling an exposed person

Counseling for exposed person on risk-reduction behaviors should be provided to reduce the risk of future exposures. Psychological support should be an integral part of counseling and include appropriate referrals as needed. When it is occupational exposure address standard precaution measures for those at risk of workplace exposure. For non-occupational exposure (such as sexual assault) address STIs and provide contraceptive and condom.

ARVs for Post Exposure Prophylaxis

The rationale for recommending PEP include:

1. The pathogenesis of HIV infection, particularly the time course of early infection; systemic infection does not occur immediately, **leaving a brief window of opportunity** during which post exposure ARVs intervention might modify or prevent viral replication.
2. The biological plausibility that infection can be prevented or ameliorated by using ARV drugs;

3. Direct or indirect evidence of the efficacy of specific agents used for prophylaxis; and
4. The risk and benefit of PEP to exposed HCP

Exposures that may warrant PEP include:

- Parenteral or mucous membrane exposure (splashes to the eye, nose or oral cavity) to body fluids with risk of transmitting HIV. The potentially exposed individual is not infected or not known to be infected with HIV; The source is HIV-infected or the HIV status is unknown

PEP is not indicated

- when the exposed individual is already HIV positive;
- exposure to bodily fluids that does not pose a significant risk
- Exposure to body fluids from a person known to be HIV- negative, unless is risky and likely to be within the window period
- If the exposure occurred before 72 hours

Assessment of exposure risk: Low-risk exposure:

- Exposure to small volume of blood or blood contaminated fluids
- Following injury with a solid needle
- Asymptomatic source patient

High-risk exposure:

- Exposure to a large volume of blood or potentially infectious fluids
- Exposure to blood or potentially infectious fluids from a patient with clinical AIDS or acute HIV infection
- Injury with a hollow needle
- Needle used in source patient artery or vein
- Visible blood on device
- Deep and extensive injury

Table 40: Interpretation of exposure code (Severity of Exposure)

Exposure Code	Type of exposure
EC 1	Is a minor mucocutanous exposure to small volume of blood for short period (Few Seconds to minutes)
EC 2	Is a Major mucocutanous exposure to large volume of blood for longer duration (Several minutes) or Mild Percutaneous exposure (with Solid needle or superficial scratch or injury)
EC 3	Severe Percutaneous exposure (Large bore hollow needle , Deep puncture,Visible blood on devise , Needle used in patient artery/vein)

Evaluating exposure source: If an exposure source is known and available, testing the source person for HIV is recommended as soon as possible, or testing the suspected exposure material (blood, tissue, etc) if the person is not available. The exposure source should also be tested for hepatitis C and B viruses (HCV and HBV).

Table 41: Interpretation of the HIV status of the source patient

HIV Source code (SC)	The HIV Status and Severity of the illness in the source patients
HIV SC 1	The Source patient is HIV Positive but is asymptomatic and has reasonably good immune status
HIV SC 2	The Source patient is HIV Positive and is symptomatic, may have AIDS or has other evidence of advanced illness (Low CD4 or High viral load)
HIV SC unknown	The HIV status of the source patients is unknown (either the patient has refused HIV testing or died or discharged before HIV testing) or The source patient is unknown (e/g Unlabeled blood sample in a laboratory)

Recommendation of PEP based on Risk assessment

Table 42: Recommended PEP for Percutaneous injuries and Mucous membrane or non-intact skin exposure

Status code	Exposure code		
	EC 1	**EC 2**	**EC 3**
SC 1	basic 2 drug PEP	basic 2 drug PEP	expanded 3 drug PEP
SC 2	basic 2 drug PEP	expanded 3 drug PEP	expanded 3 drug PEP
SC unknown			
	Consider basic 2-drugs PEP for source with HIV risk factors		
HIV negative	No PEP warranted	No PEP warranted	No PEP warranted

Recommended ARV regimens for PEP

The two types of regimens for PEP are basic regimen (2-drug combination) and expanded regimen (3-drug combination). The decision to initiate the type of regimen depends on the type of exposure and HIV sero status of the source person.

- TDF + 3TC is recommended as the preferred backbone regimen PEP.
- LPV/r or ATV/r is recommended as the preferred third drug for adults and adolescents.

ARV regimen	Dose	Duration
2-Drug Regimen	TDF 300mg/3TC 300mg Once daily AZT 300mg/3TC 150mg twice a day	28 days
3-Drug Regimen	Triple FDC (TDF 300mg/3TC 300mg/EFV 600mg) QD AZT 300mg / 3TC 150mg BID **plus** EFV 600mg QD **or** LPV/r 400mg/100mg BID **or** ATV/r 300mg/100mg QD	

Important Notes:

- *Provision of PEP is an emergency and the set up should be organized to provide the drugs within hours (preferably the first 2hrs). Remember to initiate PEP immediately after*

exposure until test result confirms the HIV status of the victim. Stop PEP if the health worker is positive for HIV antibodies.

- Testing of health care worker: HIV serology should be performed immediately after exposure. If result is positive there is no need for PEP, but if negative you should administer PEP as soon as possible as outlined above and then repeat serology at 6 weeks, 3 months, and 6 months.
- *Do not use NVP containing regimen for PEP, as there is high risk of* hepatotoxicity *at higher CD4.*
  - ABC should not be used for PEP due to high risk of potentially life-threatening hypersensitivity reaction.

Monitoring and Management of PEP Toxicity

- Exposed clients should be reassessed within 3-5 days for medication tolerability and toxicity. If further details about the source become available, a risk assessment re-evaluation may also be appropriate.
- Clients taking PEP should be monitored for drug toxicity by testing at baseline and again 2 weeks after starting PEP. The scope of testing should be based on medical conditions in the exposed person and the toxicity of drugs included in the PEP regimen.
- Minimally, lab monitoring for toxicity should include a complete blood count and liver function tests.
- If toxicity is noted, modification of the regimen should be considered.

9.4 The Role of Pharmacy Professionals

- Participate in evaluation of exposure to consider PEP after occupational injury or sexual assault.
- Provide psychological support and reassure the exposed person if PEP is not warranted
- Avail, dilute and distribute antiseptics and disinfectants
- Educate the health care providers how to use antiseptics and disinfectants
- Select the appropriate regimen for PEP based on the risk.
- Counsel the exposed patient on the need for proper adherence to the regimen
- Advise and monitor the common adverse effects that may be experienced while taking PEP

- Discontinuing PEP medication if their initial HIV test is positive
- Documenting & reporting the use of ARVs for PEP

9.5 Session Summary

- SPs should be implemented and practiced at all times by all health care providers and caregivers in all settings (hospital, clinic, community settings, and patient homes).
- The most effective infection control measure that can be performed by health care workers is hand washing with soap and water before and after patient contact.
- Risk factors for seroconversion vary according to the type of injury, viral load of source patient, glove use, type of needle, and drying conditions.
- PEP is the use of therapeutic agents to prevent infection following exposure to a pathogen
- PEP should be initiated as soon as possible (within hours) and continued for four weeks.
- Consider resistance potential of source patient
- Basic PEP regimen involves 2 NRTIs while the expanded regimen includes an NNRTI or PI.

Case studies

Case study-1

MG is 30 years –old female nurse presents to your pharmacy requesting PEP for needle stick injury 2 days ago from a diabetic lancet. The source patient (SP) was 35-year-old male diabetic who was known HIV + patient on AZT/3TC/NVP regimens for past one year in the HIV clinic of the hospital. At the time of ART initiation, the SP was in clinical stage II, and currently the patient is in good health. On further assessment of SP; it was found that most recent CD4 count was 200, baseline CD4+ during ART initiation was 180. Viral load 2 months ago was 60,000.

Discussion questions:

1. What is her risk of contracting HIV?
2. What are the risk factors that influence the transmission of HIV to M.G?

3. What additional test is recommended for M.G?
4. Would you offer PEP? If so, which agents considering risk assessment for both the SP's response to ART?
5. Which regimen(s) should be considered for M.G?
6. What follow- up should be arranged?

Case study 2

KS is 24-year-old dental technician splashed in the eye during dental procedure 3 hours ago. She is too stresses since she is 8 weeks pregnant. Now she appears to your pharmacy looking for PEP. The source patient was 33-year-old HIV known HIV positive. Splashed saliva was visibly and mostly bloody. She rinsed out her eye immediately. Source patient was co-operative and given a lot of information. Source patient has ever taken antiretroviral with recent CD4 count of "about 500" and his recent viral load of 20,000.

- What else do you need to know?
- Can the pregnancy may affect our selection of ARV.
- What are your PEP recommendations?

Session 10: HIV and Nutrition

Session Description

This session starts by defining malnutrition and describes the effects of HIV/AIDS on nutrition and vice versa. The nutritional requirements of PLHIV, nutrition assessment and classification of patients based on their nutrition status including the management approaches are discussed in detail. Finally, the roles of pharmacy professional in the nutrition care are summarized.

Primary Objective:

The primary objective of this session is to describe the effect of nutrition on HIV/AIDS and vice versa and to discuss the nutrition care and support needed for HIV positive individuals.

Learning objectives

By the end of this session, participants will be able to:

- Define malnutrition
- Describe the vicious cycles of HIV and Nutrition
- Explain the Nutrition Assessment, Counselling & Support (NACS) detailing its components
- Identify the roles of the pharmacy professionals in HIV and Nutrition

Session Outline

- Introduction to malnutrition
- Effect of nutrition on HIV and vice versa
- Nutritional Assessment, Counseling and Support (NACS)
- Role of the pharmacy professionals in HIV and Nutrition
- Session Summary

10.1 Introduction to Malnutrition

Maintaining a healthy diet makes it possible for the HIV-infected individuals to remain productive, and improve or prolong their quality of life. Thus, the role of nutrition care and support plays an important part in the overall care of people living with HIV. Nutrition care should be part of a comprehensive program to provide healthcare, emotional, psychological, and spiritual support for the HIV-infected individual and their family.

Malnutrition includes under nutrition and over nutrition. Under nutrition impairs growth, leads to wasting and stunting and ultimately death due to infectious and metabolic complications. Patients with over nutrition are getting more energy and nutrients than the body needs over time, hence they need to be counseled on dietary and life style management.

Malnutrition is common in Ethiopia and can be manifested as wasting (acute malnutrition), stunting (chronic malnutrition), underweight and/or deficiencies of essential vitamins and minerals. In the developing world, because of the high prevalence of under nutrition, malnutrition often denotes under nutrition and the associated complications.

a. Effect of nutrition on HIV and vice versa

Malnutrition and HIV/AIDS exacerbate one another. Malnutrition is very common in HIV infected individuals. HIV can lead to malnutrition by multiple mechanisms. HIV affects nutrition in the following ways, sometimes overlapping:

1. HIV reduces amount of food intake resulting from appetite loss, difficulty of eating, possibly because of infection, side effects of medication and depression.
    - HIV, OI, or medicines induce anorexia and nausea and OIs of mouth and esophagus bring about painful swallowing.
    - Depression results in reduced motivation and ability to access, prepare, and consume foods.
    - Family instability or poverty leads to reduced access to food.
2. HIV interferes with the digestion and absorption of nutrients
    - This occurs due to recurrent or chronic diarrheal disease and damage to intestinal mucosa.
3. HIV alters metabolism of nutrients/food

- HIV and OIs increase catabolism and energy needs.

4. HIV increases energy needs because of virus replication, changes in metabolism caused by HIV and OIs. WHO does not recommend increasing protein, fat or micronutrient intake over the recommended dietary allowance (RDA) since there is no increment in such nutritional requirement.

Malnutrition contributes to immune system impairment, making the body vulnerable to frequent illness and increasing its energy and nutrient demand, thereby accelerating disease progression.

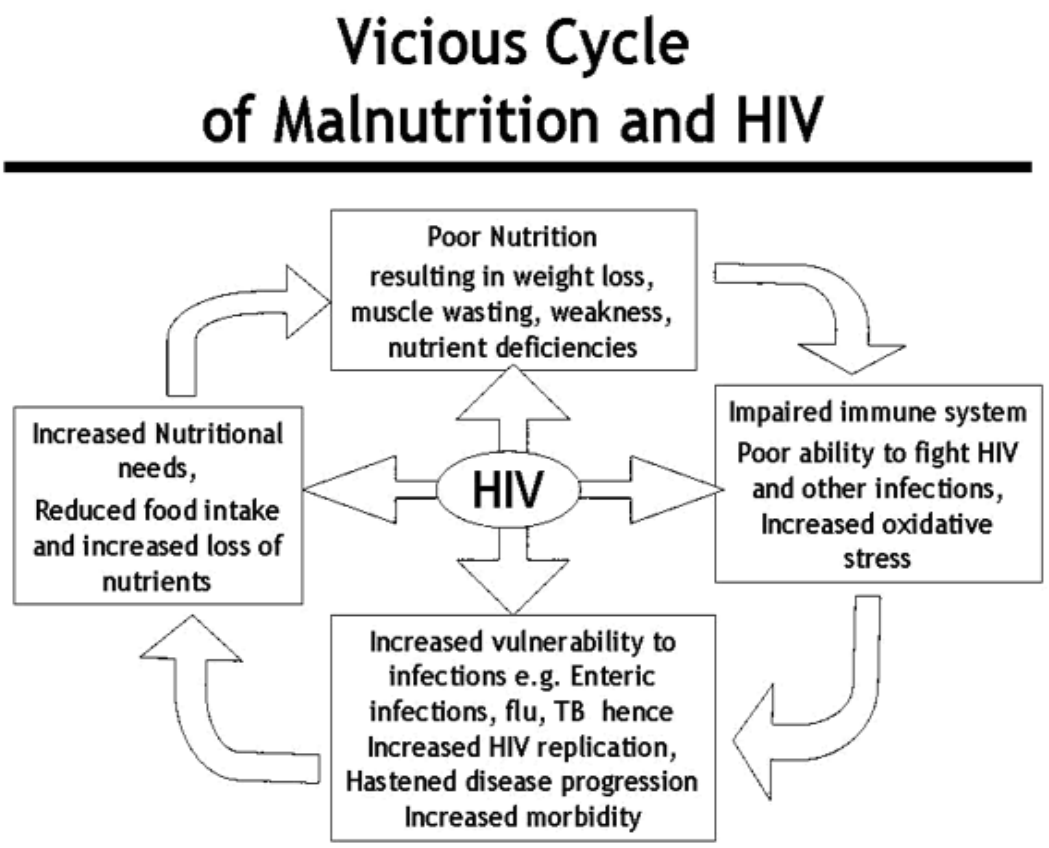


Figure 20: The vicious cycle of malnutrition and HIV

Table 43: Additional Energy Requirements for PLHIV

Category		Additional energy requirement in %
Adult	Asymptomatic	10%
	Symptomatic	20 % to 30 %
Children	Asymptomatic	10%
	Symptomatic losing weight	50% to 100%
	Symptomatic not losing weight	20% to 30%

Table 44: Average Daily Energy Requirements in Calories (*Source*: WHO, 1993)

Group	HIV negative	HIV positive		
	Energy (kcal/day)	**Asymptomatic (not displaying symptoms) (kcal/day)**	**Symptomatic (displaying symptoms) (kcal/day)**	**Protein (g/day)**
Men				
Average active	2430	2670	2910–3160	57
Women				
Average active	2170	2400	2600–2820	48
Pregnant	2460	2710	2950–3200	55
Lactating	2570	2830	3080–3340	68
Children				
6–11 months old	730	800	880–950	10
1–3 years old	1250	1380	1500–1630	25
2–5 years old	1500	1650	1800–1950	26
5–10 years old	1800	1980	2160–2340	35
Boys				
10–14 years old	2360	2600	2830–3070	64
15–18 years old	2800	3080	3360–3640	84
Girls				
10–14 years old	2040	2240	2450–2650	62
15–18 years old	2100	2310	2520–2730	65

10.3 Nutritional Assessment, Counseling, and Support (NACS)

Large Group Discussion

- **What are the goals of nutrition care and support in HIV infected individuals?**

Goals of Nutrition Care and Support

The goals of nutrition care and support are:

- Improve eating habits and diet to-maintain weight, prevent weight loss, preserve muscle mass and build stores of essential nutrients

- Prevent food-borne illnesses by promoting hygiene, food and water safety.
- Manage symptoms affecting food intake by treating opportunistic infections and pain.

Components of nutritional assessment, counseling, and support (NACS)

The components of nutritional assessment, counseling, and support (NACS) are:

Assessment

- Anthropometry (BMI, MUAC, Wt/Ht, Growth monitoring)
- Clinical
- Dietary
- Household food

Counseling

- Clinical (including adherence)
- Dietary (water, sanitation, and hygiene (WASH) and food safety)
- Psychosocial
- Referral to social services including economic strengthening, livelihood & food security support

Support

- Therapeutic/supplementary food support (Food by Prescription)
- Safe Water Treatment
- Multi-micronutrient supplements

1.3.1 Nutritional Assessment and Classification

Weight of HIV patients should be regularly measured and recorded in every visit. For adults, height should be recorded once at entry however adolescents may require repeated measurement.

Body Mass Index (BMI)

BMI is a reliable indicator of body fatness for people. BMI can't be used for pregnant and lactating mothers and adults with edema, rather MUAC can be used for these groups. It should be also noted that MUAC can also be problematic for individuals with changes in body composition due to ART, e.g. lipoatrophy. BMI is calculated as the weight of the client in kilograms divided by the square of the height in meters.

BMI= Weight in kg ÷ Height in m^2

Table 45: Classification of nutritional status based on BMI for adults.

BMI	**Nutritional Status**
BMI < 16 kg/m2	Severely malnourished
BMI = 16 -16.99 kg/m2	Moderately malnourished
BMI = 17 - 18.49 kg/m2	Mildly malnourished
BMI = 18.5 - 24.99 kg/m2	Normal weight
BMI = 25 - 29.99 kg/m2	Overweight
BMI > 30 kg/m2	Obese

BMI-for-Age

Children are in a dynamic growth process and will show varying weight and height at different ages. Therefore, for children between the ages of 5-17 years, the computed BMI shall be compared against a BMI-for-Age reference to decide whether the computed BMI indicates malnutrition or not (table 10.4).

Table 46: Classification of nutritional status based on BMI -for-Age for children 5-17 years old

BMI -for-Age	**Nutritional Status**
BMI-for-Age < -3 SD	Severely malnourished
BMI-for-Age -2 to -3 SD	Moderately malnourished
BMI-for-Age -1 to -2 SD	Mildly malnourished
BMI-for-Age > -1 SD	Normal

Middle Upper Arm Circumference (MUAC)

MUAC can be used to assess the nutritional status of pregnant and lactating mothers and children. Besides, MUAC can be used for adults who have edema or difficulty to measure height or weight for different reasons. Classification of nutritional status based on MUAC measurement is depicted in the table below.

Table 47: Nutritional classification in relation to MUAC measurement

MUAC	Classification
Children 6–11 months old: <11 cm Children 12–59 months old: <11 cm Children 5–9 years old: <13.5 cm Children 10–14 years old: <16 cm Adult < 18 cm Pregnant and lactating <19cm	Severe malnutrition
Infants 6–11 months old: 11–12 cm Children 12–59 months old: 11–13 cm Children 5–9 years old: 13.5–14.5 cm Children 10–14 years old: 16–18 cm Adults: 18–21 cm Pregnant and lactating 19-23cm	Moderate malnutrition
Infants 6 – 11 month old : > 12 cm Children 12 -59 months old : > 13 cm Children 5 -9 years old : > 14.5 cm Children 10 – 14 years old > 18 cm Adults: > 21 cm Pregnant and lactating >23cm	Normal

1.3.2 Nutrition Counseling

It is integral part of the care and support of HIV infected individuals and help individuals understand the need for maintaining an adequate diet, how to handle food safely and how to manage the nutritional complications of the disease. Counseling on hygiene can help prevent infections, infections that cause diarrhea, which is a common cause of HIV disease progression. Proper hygiene is especially important because the immune system of a person infected with HIV is weakened, making the individual more susceptible to other infections.

The health worker must counsel PLHIV to improve their eating behavior and get proper nutrition on the following points.

- Eat small, frequent meals throughout the day (5-6 meals/d)

- "Make every bite count"
- Drink plenty of liquids
- Take the medication with food to decrease nausea, when appropriate
- Take walks before meals as the fresh air helps to stimulate appetite
- Have family or friends assist with food preparation
- Mouth care
- Avoid citrus fruits, and acidic or spicy foods
- Eat foods at room temperature or cold
- Eat soft and moist foods
- Avoid caffeine and alcohol
- Provide psychological advice and refer if complicated

Foods to avoid

- Raw egg
- Raw or undercooked meat
- Water that is not boiled or juice that is made from water that is not boiled.
- "Junk" foods such as chips, biscuits, and sweets with little nutritional value
- Foods that aggravate symptoms related to diarrhea, nausea/vomiting, bloating, loss of appetite, and mouth sores

1.3.3 Nutrition Support

Management of malnutrition in PLHIVs

Nutrition management of PLHIV depends on a classification of the nutritional status of the patient, age, other medical conditions and the available therapeutic or supplementary food products. Nutrition care plans are interventions determined based on PLHIV clients' nutritional status and health conditions that affect their nutritional needs and utilization.

There are three nutrition care plans for treatment of malnutrition in PLHIV:

Nutritional Care Plan C

Clients classified as Severe Acute Malnutrition (SAM) with Medical Complication and/or failed appetite test and those classified as Moderate Acute Malnutrition (MAM) with Medical Complication and/or failed appetite test will be managed at inpatient/stabilization center according to the national SAM management guideline. Therefore, they should be referred to those facilities as identified. Management of SAM and MAM in the inpatient has 3 phases.

- **Phase 1:** Give F75 only, amounts based strictly on weight.

- **Transition phase *and Phase 2:*** Replace F75 with F100 and gradually introduce RUTF in small amounts until patient can take RUTF instead of F100.

Clients classified as SAM without Medical Complication and passed appetite test will be managed at Outpatient Therapeutic Program (OTP) or ART unit with Ready-to-Use-Therapeutic Food (RUTF) (Plumpynut). RUTF, mainly Plumpynut, is high-energy, nutrient-dense therapeutic food that is used to treat patients with severe malnutrition in OTP. It is similar in composition to F100 (except plumpynut contains iron and is about five times more energy nutrient dense). Dose and duration of plumpynut prescription for outpatient is as follows.

Adults: 4 sachets per day; maximum for 3 months. Then, transition the patient to care plan B.
Children: Dosage is based on their weight in kg as indicated below.
Table: RUTF reference table for outpatients

Weight (kg)	RUTF Paste		PLUMPY'NUT®	
	Grams per day	Grams per week	Sachet per day	sachet per week
3.0 - 3.4	105	750	1 ¼	9
3.5 - 4.9	130	900	1 ½	10
5.0 – 6.9	200	1400	2	14
7.0 – 9.9	260	1800	3	21
10.0 - 14.9	400	2800	4	28
15.0 – 19.9	450	3200	5	35
20.0 – 29.9	500	3500	6	42
30.0 - 39.9	650	4500	7	49
40 - 60	700	5000	8	56

Nutritional Care Plan B

Clients classified with MAM and without Medical Complication and those transitioned from care plan C will be managed with a Ready to Use Supplementary Food (RUSF) called PlumpySup. RUSF, mainly Plumpy Sup, is energy dense supplementary food that is used to treat patients with moderate malnutrition in OTP. Dose and duration of PlumpySup prescription is as follows.
Adults: 2 sachets per day; maximum for 3 months.

Children: Dosage is based on their age as indicated on the national guideline.

Both plumpy nut and plumpy sup are packed in sachets of 92 gm, 500 Kcal/sachet and with the shelf life of 24 months. They are much less likely to support the growth of bacteria because of their low moisture content. They do not require cooking.

Nutritional Care Plan A

No need of treatment but counsel the patients about healthy diet and life style.

How to use Plumpy nut and Plumpy Sup
• Gently mix by pressing the sachet for 30 seconds and make a small opening in the corner of the sachet. The patient should eat directly from the sachet. • For children, always offer plenty of breast milk and/or safe drinking water after eating Plumpy Sup as it can make children thirsty. • Continue breastfeeding and consuming other meals during the treatment. • Both Plumpynut & Plumpysup are ready to be used and should NOT be mixed with other foods • When a child has diarrhea, NEVER stop feeding. Continue to breastfeed and give extra food and clean water. • Once opened, the sachet should be stored in a clean and cool place and should be finished within 24 hours.

10.4. Nutrition and medication

- Medications used to treat HIV opportunistic infections may cause drug-nutrient interactions or side effects.
- Vitamin B6 supplementation should be administered with isoniazid therapy
- Iron- and zinc-containing supplements should not be taken with ciprofloxacin
- Antiretroviral drugs may have: Dietary requirements (e.g., with or without food), side effects with nutritional consequences such as diarrhea or nausea/vomiting. Identify those interactions and counsel patients accordingly.

10.5. Role of the pharmacy professionals in HIV and Nutrition

- Manage the supply of nutrition products.

- Involve in quantification of nutrition products
- Dispense Plumpy nut and Plumpy sup and counsel patients on their proper use
- Provide adherence counseling and monitor the adherence towards these products.

10.5 Session Summary

- Malnutrition includes both under nutrition and over nutrition; however, in developing world, malnutrition usually denotes under nutrition.
- HIV and Malnutrition have a vicious circle in that one fuels the other.
- Individuals infected with HIV require more energy than uninfected individual of the same status to meet the increased nutritional needs that result from the infections.
- Nutrition management of PLHIVs depends on a classification of their nutritional status, age of the patient, other medical conditions and the available therapeutic or supplementary food products.
- RUTF and RUSF also called Plumpynut & Plumpysup respectively, are the common nutrition products for the treatment of severe and moderate malnutrition in PLHIVs in outpatient setting.
- F-75 and F-100 are nutrition products which are used for the management of SAM in the inpatient setting.

Session 11: Palliative care in HIV/AIDS

Session Description:

This session starts with the definition of palliative care and its role in the management of HIV. Then the components of palliative care are described. Finally, the challenges of palliative care are discussed.

Primary Objective

This session is intended to equip participants with essential concepts of palliative care and its role in the management of HIV and help them identify drugs used in pain management

Learning Objectives:

Upon completion of this chapter, participants will be able to:

- Define palliative care and its role in the management of HIV
- Describe components of palliative care
- Describe the three-step-ladder in pain management and identify the drugs used in pain management
- Discuss challenges of palliative care in Ethiopian setting and explore the roles of pharmacy professionals in addressing the challenges

session Outline

- Introduction to palliative care
- Components of palliative care
- Challenges and Role pharmacy of palliative care
- Session Summary

Allocated Time: 60 minutes

11.1 Introduction to palliative care

What is palliative care and what is the relevance of the topic for your role as pharmacy professional while being engaged in HIV care?

Palliative care is interventions that improve the quality of life of patients and their families facing problem associated with life-threatening chronic illness such as AIDS, Diabetics or cancer. It is also important for those with a curable illness who may have symptoms for many months before they are cured. It is prevention and relief of suffering, pain and other physical problems as well as psychosocial and spiritual issues.

It is an integral part of a comprehensive care and support framework. In the framework of a continuum of care from the time of diagnosis until the end of life and regards dying as a normal process and affirms life. It also offers support to help the patient and family cope during the patient's illness and in the bereavement period.

The palliative care needs of patients increase with time, particularly in a situation where the underlying disease is getting worse rather than better. In areas where patients present late for a medical care the need for palliative care is immense.

Why is palliative care important in HIV/AIDS care?

- Chronic disease that requires lifelong treatment
- Presence of adverse drug reaction and toxicity
- The need for holistic approach (psychosocial, spiritual)
- Helps to improve adherence, retention and quality of life
- Contribute for effective and well-functioning health system.
- Palliative care is an important component of care for any medical condition. Palliative care includes the management of symptoms such as fatigue, dyspnea, and neuropathic pain, and treatment of drug side effects such as nausea, vomiting, and diarrhea. Palliative care also addresses psychosocial needs, for example depression and therefore by addressing these issues, the role of palliative care may extend beyond the individual to reach the community by reducing the emergence of drug resistance.

11.2 Components of palliative care

Palliative care encompasses symptomatic management, preventive care, psycho-social and spiritual support, and end of life care.

Symptomatic management

Clinical care includes assessing and managing common symptoms associated with HIV/AIDS and side effects of ARVs. See table 11.1 below for the symptoms that occurs as a result of opportunistic infections and ARV adverse effects that needs palliative care.

Table 48: Symptoms to be managed as a result of complication of HIV, OIs and ARVs

Managing complications from HIV/AIDS OIs	**Managing ARV side effects and complications**
- Pain - Dyspnoea - GI problems - Skin and mouth problems - Fever - Neurological disorders - Anxiety, fatigue	- Nausea and vomiting - Diarrhoea - Peripheral neuropathy etc.

*For further reading on symptom management refer to national palliative care guideline, 2016.

Pain management

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. This highlights that pain is not just a physical sensation but an emotional experience too. In simple words pain is what patient says, hurts, which gives emphasis on the patient's experience and is graded for management purpose. See below

Grading of pain

Numerical Scale**:** It has 0 at one end meaning no pain and 10 at the other end meaning worst imaginable pain (No pain) **0** 1 2 3 4 5 6 7 8 9 **10** (Worst possible pain)

Grading of pain in children

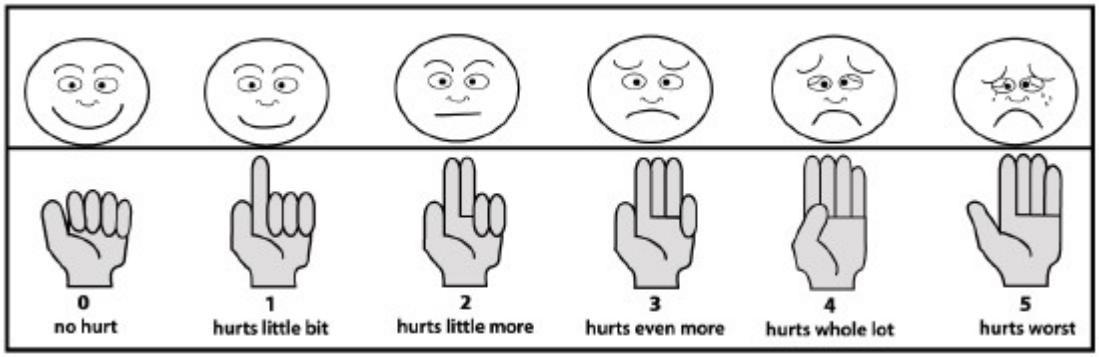


Figure 21: Grading of pain in children

Three-step analgesic ladder

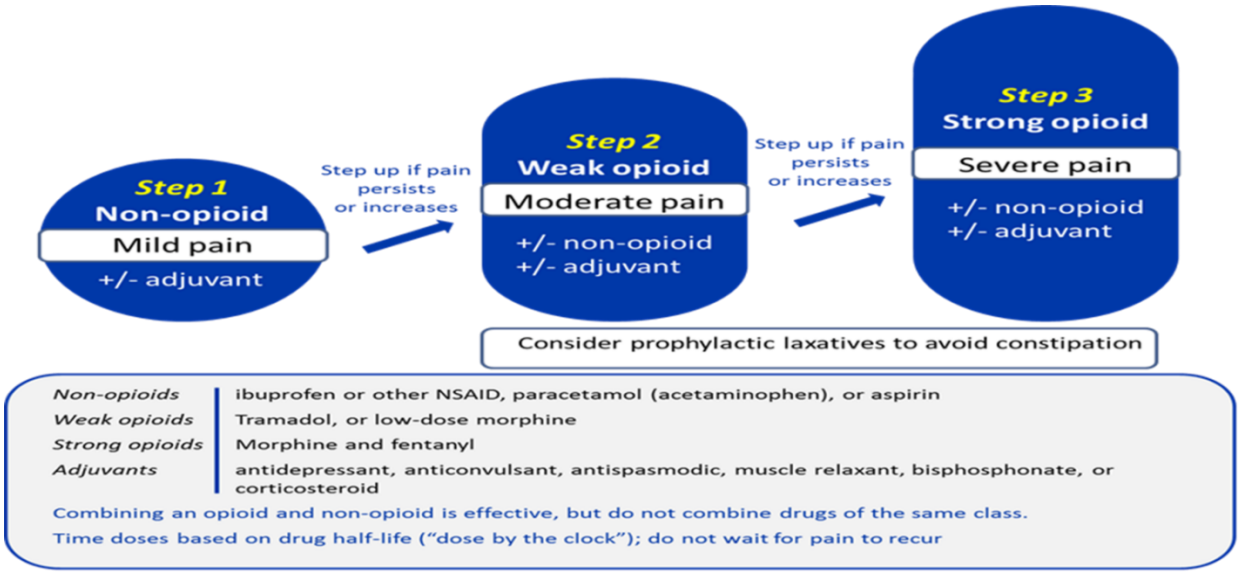


Figure 22: Three-step analgesic ladder

Table 49: summary of analgesic drugs use for step-by-step

	Usual Adult Dose	Pediatric Dose
Step1 Acetaminophen	PO 500-1000mg q 6 hr	PO 10-15 mg/kg /dose q 4-6hr (max. dose 90mg/kg/24 hr.)
Step1 Aspirin	PO 300-600 mg q 4-6 hr	Not recommended

Step1 Diclofenac	-PO 50 mg q 8hrs -Suppository 100mg once/day (extended release) - Im 75mg 12 hourly	Children: 25mg suppository eg 2-3mg/kg in 2-4 divided doses (max 200mg/day)
Step1 Ibuprofen	400 mg q 4-6 hr PO	5-10mg/kg/dose q 6-8 hr (max. dose 40mg/kg/24 hr)
Step1 Indomethacin	-PO 50-200 mg/daily divided 8-12hrly -suppository 100mg 12 hrly	Not recommended for children
Step 2-Codeine	-PO 30-60mg q 4 hr Max. dose 240mg/d-IM 30-60 mg q 4 hr	Not recommended for children
Step 2 – Tramadol	-PO 50-100mg q 6 hrs Max 400 mg/day -IM/IV 50-100 mg q 4-6 hrs. Max. 400mg/day	Not recommended for children
Step 3-Morphine[a]	2.5-5mg every 4 hours (dose can be increased by 1.5 or doubled after 24 hours if pain persists)	• < 1 year 0.1mg/kg Q6hrs • 1-12 yrs 0.2-0.4mg/kgQ4hrs • >12 yrs. use adult dose -

[a] Reduce morphine once pain is controlled; if used for weeks reduce it gradually to avoid withdrawal symptoms

Preventive care

Palliative care also includes preventive care aimed to keep people healthy as long as they live. This is consistent with the new definition of palliative care that rejects the notion of terminal care alone and embraces the concept of care from the time of diagnosis and continuing to end of life and death. The following are the essential preventive care packages in HIV palliative care:

- Active TB screening
- Co-trimoxazole prophylaxis
- Malaria prevention
- Safe water supply
- Positive living and prevention with positives
- Nutritional counseling and supplementation
- FTP

Psychosocial and spiritual support

In addition to curative and preventive care, palliative care also includes psycho-social and spiritual care for patients and their family members/caretakers throughout the continuum of

care. Because HIV patients have needs beyond physical when living with such a chronic illness, patients need to be supported with managing anxiety, grief and depression. The following are strategies in creating psychosocial and spiritual support:

- Counseling for parents and family members on positive living, dealing with stigma, adhering to care and treatment
- Support for caretakers
- Linkage to financial and food support
- Helping the patient and family prepare for death
- Support at the end of life and death

End of life care

Health care providers have a key role to play in helping patients and their families prepare for and deal with death. Facility-based staff should work with community health workers and spiritual leaders to ensure that quality end of life care are provided. The following are services that need to be provided in end of life care:

- Psychosocial and spiritual support
- Preparing for death and advanced care planning
- Providing comfort near end of life, including pain management
- Preparing the body for burial or cremation
- Helping family and friends deal with loss and grief

11.3 Challenges and Role of Pharmacy Professionals in palliative care

Group Discussion

- **What are the challenges in palliative care for HIV patients in Ethiopia?**
- **What roles can pharmacy professionals play in promoting HIV palliative care?**

Challenges

The challenges of palliative care include late disease presentation, inadequate diagnostic facilities, poor assessment skills, unavailability of chemotherapy and absence of drugs to alleviate pain particularly opioids due to regulatory issues, pricing obstacles and ignorance as well as false beliefs about its use.

Symptom management is more effectively accomplished when started early, however, because of limited access to care, and long travel distances, palliative care in Ethiopia may be challenging. Moreover, inadequate medical equipment and lack of trained personnel make accurate assessment of palliative care needs very difficult.

Role of pharmacy professionals

Pharmacy professionals may work towards and advocate for the need for pain management, for inclusion of certain medications like opioids through working with regulatory body, for improving the supply management system of essential pain medications.

11.4 Session Summary

- Palliative care is an integral part of a comprehensive care and support framework.
- Palliative care encompasses symptomatic management, preventive care, psycho-social and spiritual support and end of life care.
- Pain is managed by the three steps WHO analgesic ladder.

Session 12: Supply Chain Management of HIV/AIDS Pharmaceuticals

Session Description:

This session describes the supply chain management of ARVs and related pharmaceuticals in relation to ARV drugs supply and use policy. It also deals with the factors that influence the logistics management of ARVs.

Primary Objective:

This session will enable pharmacy professionals to be equipped with the basic knowledge on the supply chain management of ARV medicines and related pharmaceuticals so as to ensure uninterrupted supply of ARVs.

Enabling objectives:

By the end of this session participants will be able to:

- Describe the national policy on ARVs
- Discuss basic ARV medicines supply chain management
- Discuss program updates requiring logistics management considerations
- Discuss the factors that influence logistics management of ARVs

Session Outline

- National policy on ARVs
- ARV Medicines Supply Chain Management
- Program updates requiring logistics management considerations
- Factors that affect logistics management of ARVs
- Role of pharmacy professionals on HIV/AIDS SCM commodities
- Session Summary

12.1. National policy on ARVs

Group Discussion

Why the government formulated ARV drug supply and use policy and the rationale behind it?

"Antiretroviral Drugs Supply and Use Policy", which is aligned with the national health policy, national AIDS policy, and national drug policy, have been formulated to ensure sustainable availability, effective management and rational use of ARV drugs and related pharmaceuticals following the intensive advocacy campaign from associations of PLHIV and other organizations, and in appreciation of the gravity of the problem. The government adopted the policy on July 2003, paving the way for more initiatives towards facilitating access to free and low-cost ARV medicines. The general strategies of the ARV drugs supply and use policy mainly focuses on selection and supply of ARV medicines.

12.2 ARV Medicines Supply Chain Management

Reflections

i. **What is supply chain management?**
ii. **What is the goal of public health logistics system?**

Supply chain management (SCM) is the process of planning, implementing, managing, and controlling all activities involved in sourcing, procurement, conversion, and logistics management, with the aim of satisfying the end users as efficiently as possible. Importantly, it also includes coordination and collaboration with middle-level actors who serve as a link to the end users.

Pharmaceutical supply chain management (PSCM) follows these principles with the addition of public health concept and the sensitivity of pharmaceuticals. PSCM typically include selection, quantification, procurement, inventory management and serving customers. The goal of every public health supply chain management system is to ensure that every customer can obtain and use quality essential health supplies whenever he or she needs them.

Successful HIV programs are only possible if all health facilities providing ART are equipped with an uninterrupted and sustained supply of high-quality ARV medicines. Ensuring adequate and continuous availability of other pharmaceuticals that are needed to support ART services such as medicines to prevent or treat opportunistic infections, laboratory reagents, supplies and equipment to test and diagnose HIV and related infections, monitor the progression of HIV

infection, treatment follow up and detect adverse drug reactions at health facilities is a critical role of supply chain management system.

ARV treatment requires an effective supply chain to ensure that ARVs are available always so as not to cause treatment interruptions. Therefore, ARV supply chain management must take the following issues into consideration:

- Special distribution requirements for ARVs and diagnostics
- Constant stock availability (shortages can interrupt treatment and lead to drug resistance)
- ARVs are high-value, high-demand products which require extra security

ARV drug regimens are complicated; require high degree of adherence. Ensuring adequate and continuous availability of quality and affordable essential medicines, diagnostics and other consumables at service delivery sites is a critical role of supply chain management systems. The increasing number of people who need chronic HIV care, especially in settings with a high burden of HIV infection necessitates an uninterrupted supply of ARVs and related health products. This can be achieved only if strong ARV supply chain management system is designed and implemented at all levels of the health system.

National Pharmaceutical Supply Chain Management System

The Federal Ministry of Health (FMOH) through Pharmaceuticals Fund and Supply Agency (PFSA) started implementing Integrated Pharmaceuticals Logistics System (IPLS) since 2009. IPLS is the term applied to the single pharmaceuticals reporting and distribution system based on the overall mandate and scope of PFSA. Before the existence of IPLS, there were so many problems in the management of pharmaceuticals that lead to frequent stock out and wastage. IPLS is developed in response to the problems that Ethiopia had been suffering from lack of an integrated supply chain management system.

IPLS integrates the management of essential pharmaceuticals including those that were used to be managed vertically by programs; HIV/AIDS, Malaria, TB and Leprosy, EPI, MCH and purchased essential drugs. It is the primary mechanism through which all public health facilities obtain essential and vital pharmaceuticals. This system ensures that all Ethiopians receive pharmaceuticals they need when they are visiting health service delivery units by ensuring the six rights of supply chain management system are fulfilled.

Group Discussion

- **Form five groups composed of five participants, and select chairperson and secretary. The secretary will present your discussion to the large group after 10-minute discussion.**
- G-1 selection, quantification
- G-2 procurement and inventory control system
- G-3 LMIS, and record and reports
- G-4 data quality.
- G-5 discuss on storage and distribution

The main components of PSCM system are selection, Quantification, procurement, inventory management, storage and distribution, and customer use. Management support is also an integral to each component of the cycle. A brief description of each function is presented below.

1. Selection

Selection of ARV pharmaceuticals is done at national level considering their safety, efficacy, quality and cost. Accordingly, the National Essential Medicines List (EML) is updated whenever new ARVs are included.

Criterial for ARV products selection

- Epidemiological profile (category mix: morbidity and drug resistance)
- Evidence based medicine/Proven efficacy and safety
- Level of health facility and its capacity (eg. diagnostic facilities, STG)
- Financial resources
- Genetic, demographic and environmental factors
- Treatment guideline for first line, second line and third line therapy
- Marketing approval/registration
- Advocating fixed dose combination (FDC)

2. Quantification:

National quantification of ARV pharmaceuticals is conducted by PFSA in collaboration with FMOH and other stakeholders. It is done every two years which is revised every year based on changes in guidelines at national level and the data obtained from ART sites. It is important to

have detail report on number of clients currently on ART, disaggregated by regimen and patient type, attrition rate, and logistics data. Most of the data required emanates from health facilities and it is crucial to ensure the accuracy and completeness of logistics data to conduct a successful quantification. The goal of quantification is to maintain the most cost-effective balance between service levels and inventory costs.

3. **Procurement:**

The procurement of ARVs and related pharmaceuticals is executed by PFSA. The procurement process follows the national and international procurement regulation.

4. **Inventory control system**

The purpose of an inventory control system is to inform personnel when and how much of a pharmaceutical to order and to maintain an appropriate stock level so as to ensure commodity security. A well designed and well operated inventory control system helps to prevent shortages, oversupply, and expiry of pharmaceuticals.

The inventory control system for the IPLS is a Forced Ordering Maximum/Minimum inventory control system. This system is designed to ensure that quantities of stock in health facilities fall within an established maximum and minimum range and facilities are required to report on a fixed schedule. All products are re-supplied each time a report is completed. In emergencies, an emergency order can be placed. Health centres and hospitals calculate their own order sufficient quantities of ARVs along with other programs to bring stock levels up to the maximum level, and required to report and order every two months.

5. **Pharmaceuticals management information system (PMIS)**

Information is the engine that drives the entire PSCM cycle. We collect information to make decisions; the better information we have, the better decisions we can make. The purpose of PMIS is to collect, organize, and report information to other levels in the system to make decisions that govern the logistics system and ensure that all the six rights are fulfilled.

Records and reports

Keeping good records helps everyone to understand the flow of supplies into and out of the facility. Bin Cards and Stock Record Cards are used to account for products held in storage,

including their receipt and issue. Internal facility report and resupply form (IFRR) should be appropriately documented. Valuable information used to make re-supply decisions is recorded on the Bin Card, Stock Record Card and IFRR; data from these records are used in reporting, calculating reorder quantities and for monitoring stock levels.

Data quality

Data is generally considered high quality if it is "fit for its intended uses in operation, decision-making and planning. In relation to essential data items in IPLS, it refers to the timeliness, completeness and accuracy of IFRR and HPMRR submitted to main stores in a facility and RRF reported to PFSA hubs for making sound decision in resupplying products.

- Timeliness for DUs indicates reporting at the agreed day and within days in the schedule set for IFRR and HPMRR reporting; whereas within the specified period (1-10th days) for RRF reporting.
- Completeness refers to the degree of transferring the essential data items to all products (i.e. pharmaceuticals list on RRF and list specific to each DU).
- Data accuracy is the degree in which the transferring of the real situation of the stock to the reports for the essential data items.

Points contributing to poor data quality

The following issues can contribute for challenge in acquisition of quality reports and needs to be sought as areas of intervention for improving data quality

- Sources of delay in reporting timely
    - Lack of awareness on the benefits of timely reporting
    - Forgetfulness
    - Low staffs' commitment and
    - Low enforcement by the management
- Sources of challenges related to completeness
    - Lack of due attention,
    - Knowledge gaps (program items)
    - Organizing products as per the sequences in the reporting format, etc.…processes are subjected to compromise the quality of reports
- Sources of Data Inaccuracy

- Not maintaining bin card for all products
- Lack of regular bin card updating
- Error created while transferring data from bin card to reports
- Data manipulation

Since health facilities have a huge role on the success of IPLS. They must make sure the data reported is of the required quality.

6. Storage and Distribution:

Proper storage of ARVs, including refrigeration, is critical to maintain the quality of the medicines and related supplies. Central PFSA will deliver the pharmaceuticals to hubs; subsequently the hubs distribute the pharmaceuticals to health facilities every two months based on orders placed by the health facilities to PFSA hubs. Health facilities are expected to follow consumptions and keep record regularly. They get ARV medicines and related supplies except Rapid Test Kits (RTKs) if they submit their report and order, using Report and Requisition Form (RRF) with accurate data and in a timely manner. The logistics data for the RRF should always come from bin cards and IFRR. The quality of this data is very crucial as it will be used for quantifying future consumption.

RTKs distribution plan is done centrally for each region, federal hospital, and police and military health facilities taking the target set for each region every quarter. Then PFSA hubs in collaboration with regional health bureaus distribute the RTKs to testing sites. The target is taken from HIV/AIDS strategic plan investment case approach (2015-2020).

12.3 Program updates implications on ARV supply chain management

Test and treat

Ethiopia started the implementation of test and start strategy since August 2016. For HIV positive clients who understand and accept the importance of early initiation, ART will be initiated as early as possible. To do this the health facility is required to hold sufficient stock of medicine to be able to initiate ART starting from the day the patient is ready to initiation.

ASM implementation

Implementation of ASM will have a significant implication on the current SCM practice specially on storage, inventory control system, and reporting and requisition system.

- Significantly increases ARV volumes as it requires to maintain additional stock of commodities for high consumption periods, during the periods when higher number of clients on ASM are going to be refilled which in turn demands more storage space at health facility level.
- The current inventory control system which dictate hospitals and health centers to stock a maximum of 4 month and a minimum of 2 month will not go along with ASM implementation. Health facilities are required to stock a minimum of six-month stock to resupply stable patients.
- Transitioning all stable patients in to the appointment spacing model unevenly across the months will have implications on existing reporting and requisition system. The usual historical consumption based resupply decision might not work well as the consumption of ARV commodities will vary in accordance with the ASM enrolment pattern of stable clients

Suggested interventions include

- Maximize the existing storage space through dejunking and reorganizing for facilities with storage space constraint. This can be done both at pharmacy store and ART dispensary.
- Securing additional and relatively spacious room for storage at the facilities level to offset the increased volume during peak consumption periods.
- Store improvement with appropriate shelving and palletizing can be considered
- ART facilities will prepare and send their RRF as usual and annexing ASM enrollment data with RRF. So that PFSA hubs adjust the consumption taking in to consideration a six-month resupply to stable patients.

Guideline updates and new medicines introduction

- HIV/AIDS treatment and care guideline is being revised regularly. During revision, addition of a new medicine and new regimen, omission of a previously used medicine and adoption of a new strategy can be there. The PSCM system is required to be dynamic enough to incorporate these changes.

Diagnostic technology clock speed

- The speed by which technology of diagnostics facilities change will affect the PSCM system. The system should always consult the national direction to deliver the required equipment, reagents and chemicals to testing and diagnostic sites.

12.4 Factors affecting the supply chain management of ARVs

Large Group Exercise

- **What are the factors that affect supply chain management of ARVs?**

Poor quality of data reported from health facilities

Failing to meet the three data quality requirements (timeliness, completeness, and accuracy) will ultimately lead to the following situations;

- The required products can't reach or be received timely
- Frequent stock outs
- Accumulation of excess stock leading to expiry and disposal cost
- Compromise the stocks kept at supplying source

Weak supply chain infrastructure

Ensuring availability of ARV medicines and related pharmaceuticals requires the presence of storage facilities with appropriate storage condition, shelves, material handling equipments, trucks, road… etc. The gaps in this area include

- Poor storage facilities
- Lack of proper shelving and palletization
- Difficult to reach topographies
- Shortage of trucks
- Lack of road infrastructure and accessibility

Lack of human capacity

- Shortage of pharmacy professionals at health facility level and as a country as a whole

12.5 Role of pharmacy professionals in HIV/AIDS PSCM

- Regularly updating yellow sheet and Electronic Dispensing Tool (EDT)
- Setting a feasible schedule with pharmacy store for resupply

- Filling and submitting IFRR to pharmacy store as per the agreed schedule
- Regularly following the stock status of ARVs and supplies to avoid overage or stock out
- Sending RRF timely to PFSA for resupply
- Ensure that ARVs and related supplies are appropriately stored to maintain their quality and safety as well as easy access.

12.6 Session Summary

- Supply Chain Management encompasses the planning and management of all logistics management activities. Pharmaceutical supply chain management follows the same principle with the addition of public health concept and the sensitivity of pharmaceuticals.
- The goal of every public health logistics system is to ensure that every customer is able to obtain and use quality essential health supplies whenever he or she needs them.
- Successful HIV programs are only possible if all health facilities providing ART are equipped with an uninterrupted and sustained supply of high-quality ARV medicines
- ARV medicines, medicines to prevent or treat opportunistic infections, laboratory reagents, supplies and equipment to diagnose HIV and opportunistic infections, monitor the progression of HIV infection and treatment response and detect adverse drug reactions are managed through IPLS

Session 13: SOPs for managing information on ARVs dispensing and patient medication records

(Please note that there is a separate SOP manual for session 13)

Session Description:

This session introduces participants to the standard operating procedures for managing information in the ART pharmacy. It starts by describing the forms used for recording and documenting transactions. Then the procedures for recording and filing are explained. Finally, the steps for compiling monthly reports and tracing of patients is discussed.

Primary Objective:

The objective of the session is to introduce participants with the management of pharmaceutical information on ARV drugs dispensed and patient medication records.

Enabling Objectives:

By the end of the session participants will be able to:

- Describe forms for recording and documenting ARV drug transactions
- Identify the procedures for recording and filing confidential patient information
- Determine methods of tracing patients to ensure and support ART adherence
- Describe methods of compiling and preparing monthly pharmacy ART activity reports

Session Outline

- Learning Objectives and Introduction
- Formats and Main Procedures
- Practicum
- Session Summary

Annexes

Annex 1: Pregnancy category description

Pregnancy Category	Description
A	**No risk in controlled human studies:** Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	**No risk in other studies:** Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.
C	**Risk not ruled out:** Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	**Positive evidence of risk:** There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	**Contraindicated in pregnancy:** Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.
N	FDA has not yet classified the drug into a specified pregnancy category.

Annex 2: Medicines Use counseling Checklist

Medicines Use Counseling Guide

1. Check for any allergies in general and this medicine in particular:
    - Ask for any allergies
    - Obtain past medicines use history
2. Tell name and indication of the medicine:
    - Name is important in case of emergency and visit to more than one provider
    - Indication reinforces diagnosis and creates confidence
3. Tell route and frequency of administration:
    - Prevents taking by the wrong route
    - Inform if first time or reinforce what they know.
    - Note: "Take one tablet after meals" may not work since not everyone eats three meals a day
4. Tell the client how long to take the medicine:
    - helps to eliminate unrealistic expectations
    - Ensures reaching treatment goals
    - Prevents emergence of microbial resistance
5. Tailor medicine regimen to daily routine:
    - Ask the daily routine before suggesting a plan
    - Link taking a dose with regular daily task and effect of the medicine
    - Should not assume a common routine (e.g., eating three meals a day; sleeping night times, etc.)
6. Ask if the client has problem taking this medicine:
    - Complexity of the dosage regimen affects adherence
    - Is there special preference for a dosage form?
    - Consider total cost of care, not just the cost of the drug alone
7. Tell how long it will take for the medicine to show an effect:
    - If not told, the client may believe the medicine is not working and may stop taking, or increase dose with subsequent toxicity
8. Tell how many times and when to refill:
    - Number of refills. Check if there is inconvenience.
9. Emphasize benefits of the medicine:
    - Discuss benefits before potential side-effects
10. Discuss major side effects of the medicine:
    - Side effects that are common and how long they will stay
    - Measures to recognize, prevent, or manage side effects and adverse effects
    - Tell what to do if side effects don't go away or become intolerable
    - Encourage the patient to report side/adverse effects of the drugs
11. Discuss drug-drug, drug-food, drug-disease, drug-herb interactions:

- Ask if client is taking other medicines; discuss interference of other drugs, food or condition with current medicine and/or condition being treated

12. Discuss precautions and measures to improve treatment outcome:
    - Decreased salt intake, dietary requirements, self-monitoring, recommended exercises, activities to avoid, etc.
    - Don't assume the client may have prior information; it is good to repeat and discuss precautions
13. Discuss storage recommendations, supplementary instructions:
    - Shake well, refrigerate, avoid heat and humidity, etc.
    - Duration of use after opening container
14. Discuss religious and cultural issues that may affect medicines use:
    - Fasting and holy water, dosage forms preferences, etc.
15. Demonstrate and provide adequate information about special dosage forms:
    - Metered dose inhalers, suppositories, eye drops, ear drops, topical, transdermal patches, injections, sublingual tablets, nasal sprays, sustained-release tablets/capsules, etc.
16. Educate techniques for self-monitoring:
    - Diabetes: signs and symptoms of hypo- and hyper-glycemia; use of blood glucose monitoring devices
    - Hypertension: use of blood pressure monitors
17. Ask if there are any additional concerns or questions: listen respectfully and carefully
18. Ask client to repeat key information to check how instructions are understood:
    - Could you tell me how you are going to take your medicine?
    - Praising has been shown to reinforce adherence
19. Provide your telephone number and encourage to contact you, if the need arises

Annex 3: Management of STIs in children and adolescents

Syndrome	Infectious Agent	Regimen
Urethral Discharge	N. gonorrhea C. trachomatis M.genitalium	**Adolescents**: Ceftriaxone 125 mg IM stat **Plus** Azithromycin 1gm po stat/Doxycycline 100mg bid for 7 days **Children**: Ceftriaxone 125mg IM stat **Plus** Erythromycin 10mg/kg qid for 7 days **Note:** Use metronidazole 10 mg/kg bid for 7 days for persistent symptoms and 500mg bid for 7days in Adolescents:
Vaginal Discharge	N. gonorrhoeae C. Trachomatis T. vaginalis Bacterial vaginosis(BV) Vulvovaginal candidiasis (VVC)	**Adolescents**: Ceftriaxone 125 mg IM stat **Plus** Azithromycin 1gm po stat/Doxycycline 100mg bid for 7 days **Plus** metronidazole 500mg bid for 7 days **Children**: Ceftriaxone 125mg IM stat **Plus** Erythromycin 10mg/kg qid for 7 days **Plus** metronidazole 10 mg/kg bid for 7 days
Genital Ulcer	H SV type 2 T. pallidum H. ducreyia	**Adolescents**: Acyclovir 400mg tid for 10 days **Plus** Benzathine penicillin 2.4 million units IM stat **Plus** Erythromycin 500mg qid for 7 days **Children**: Acyclovir 10 mg/kg tid for 7 days **Plus** B. penicillin G 100,000 units/kg IM single dose **Plus** Erythromycin 10mg/kg qid for 7 days

PID	N. gonorrhoeae C. Trachomatis Anaerobics	**Adolescents**: Ceftriaxone 125mg stat **Plus** Azithromycin 1gm po stat/Doxycycline 100mg bid for 14 days/ Erythromycin 500mg qid for 14 days **Plus** Metronidazole 500mg bid for 14 days

Annex 4: Different types of STI kits and their components

Types of STI Kit	STI	Components of the KIt
Addis Cure	**Urethral Discharge**	**Ceftriaxone 250mg**
		Azithromycin 1gm
		Water for injection 10ml
		Syringe 5ml
Addis Cure+	**Vaginal Discharge**	Ceftriaxone250mg
		Azithromycin 1gm
		Water for injection 10ml
		Syringe 5ml
		Metronidazole 250mg (28)
Ulcure	**Genital Ulcer**	Benzathine Penicillin 2.4 MIU
		Syringe 5ml (2)
		Ciprofloxacin 500mg (6)
		Acyclovir 400mg PO (30)
		Water for injection 10ml

Annex 5: Definition of EWIs and their respective performance targets.

EWI and title	Definition	Numerator	Denominator	Target
EWI_1: On-time pill pick-up.	Proportion of patients (adult or children) that pick-up ART no more than two days late at the first pick-up after the baseline pick-up.	Number of patients picking-up their ART "on time" at the first drug pick-up after baseline pick-up date.	Number of patients who picked-up ARV drugs on or after the designated EWI sample start date.	Desirable performance (green): >90%; fair performance (amber): 80–90%; poor performance (red): <80%.
EWI_2: Retention in care.	Percentage of adults and children known to be alive and on ART 12 months after initiation.	Number of adults (or children) who are still alive and on ART 12 months after initiating treatment.	Total number of adults or children (excluding transfers out) who initiated ART and were expected to achieve 12-month outcomes within the reporting period.	Desirable performance (green): >85%; fair performance (amber): 75–85%; poor performance (red): <75%.

EWI$_3$: Pharmacy stock-outs.	Percentage of months in a designated year in which there were no ARV drug stock-outs (both for adult and pediatric patients).	Number of months in the designated year in which there were no stock-out days of any ARV drug routinely used at the site.	12 months of the reporting period.	Desirable performance (green): 100%; poor performance (red):<100%.
EWI$_4$: Pharmacy dispensing practice.	Percentage of patients (adults or children) being dispensed a mono- or dual-ART.	Number of patients who pick up from the pharmacy, a regimen consisting of one or two ARVs.	Number of patients picking up ART on or after the designated EWI sample start date	Desirable performance (green) defined as 0% patients picking-up a mono- or dual-ART; poor performance (red) defined as >0% patients picking-up a mono- or dual-ART.
EWI$_5$:Virological suppression.	Percentage of patients (adult or children) receiving ART at the site after the first 12 months of ART whose viral load is <1000 copies/ml.	Number of patients receiving ART at the site after the first 12 months of ART whose viral load is <1000 copies/ml.	Number of patients at the site who by national policy should have had a viral load performed 12 months after ART initiation.	Desirable performance (green): >85%; fair performance (amber): 70–85%; poor performance (red): <70%.

EWI, early warning indicator
EWI$_4$ is cross sectional in nature and is intended to assess pharmacy dispensing practices for populations on ART after any period of time on ART.

Annex 6: Summary of EWIs as per health facilities in 2013/14

The following selected facilities (see table) providing ART service for 153,549 patients were surveyed in the 2013/14 by the Ethiopian Public Health Institute. The site specific finding of the three EWIs (***On-time pill pick-up, retention in care, and pharmacy stock-outs)*** was presented in table below, and the score or achievement is also indicated as WHO 2012 recommendations.

EWI-1: On time pill pick-up			EWI-2: Retention in care			EWI-3: Pharmacy stock-out	
>90%	80-90%	<80%	>85%	75-85%	<75%	100%	<100%

No	Facility name	Level	Region	EWI-1	EWI-2	EWI-3
1	Adama Hospital	Hospital	Oromia	92.38	74.74	83
2	Addis Zemen Health center	H/C	Amhara	86.02	76.92	83
3	Adigrat Hospital	Hospital	Tigray	77.14	88.07	75
4	Agaro Hospital	Hospital	Oromia	93.60	93.83	100
5	Akaki Health center	H/C	AA	74.09	70.43	100
6	Alamata Hospital	Hospital	Tigray	77.21	79.20	100
7	ALERT Hospital	Hospital	AA	81.25	95.65	67
8	Ambo Hospital	Hospital	Oromia	92.92	91.43	100
9	Arbamich Hospial	Hospital	SNNPR	86.12	98.26	58
10	Asella Hospital	Hospital	Oromia	88.75	100.00	92
11	Asossa Hospital	Hospital	BG	84.76	80.49	92
12	Attat Hospital	Hospital	SNNPR	64.88	95.12	67
13	Awash Health center	H/C	Afar	88.46	99.38	92
14	Axum Hospital	Hospital	Tigray	86.19	81.90	42
15	Babasi Health center	H/C	BG	82.50	90.00	83
16	Bedele Health center	H/C	Oromia	88.17	100.00	100
17	Betezata General Hospital	Hospital	AA	93.45	97.83	67
18	Bisidimo Hospital	Hospital	Harari	88.33	99.16	92
19	Bole Health center	H/C	AA	88.00	85.71	67
20	Bonga Hospital	Hospital	Oromia	78.16	83.13	100
21	Burie Health center	H/C	Amhara	78.57	85.22	42
22	Bushlo Health center	H/C	SNNPR	85.71	91.94	58

23	Butajira Hospital	Hospital	SNNPR	95.33	83.70	42
24	Chencha Hospital	Hospital	SNNPR	75.64	90.24	25
25	Chiro Hospital	Hospital	Oromia	77.62	100.00	100
26	Dangla Health center	H/C	Amhara	73.17	83.53	75
27	Debark Hospital	Hospital	Amhara	82.38	76.70	75
28	Debre Markos Hospital	Hospital	Amhara	89.17	84.83	42
29	Debre tabor Hospital	Hospital	Amhara	83.80	74.77	100
30	Debrebirhan Hospital	Hospital	Amhara	91.08	75.00	17
31	Dessie Hospital	Hospital	Amhara	96.08	86.30	100
32	Dilchora Hospital	Hospital	DD	94.17	100.00	75
33	Dilla Hospital	Hospital	SNNPR	87.50	100.00	25
34	Durit Hospital	Hospital	Oromia	80.48	100.00	75
35	Estie Health Center	H/C	Amhara	90.86	84.62	75
36	Felege Hiwot Hospital	Hospital	Amhara	85.66	76.65	33
37	Finote Selam Hospital	Hospital	Amhara	86.11	77.27	42
38	Gambella Hospital	Hospital	Gambella	95.24	79.70	100
39	Gandi Hospital	Hospital	AA	92.62	98.68	100
40	Gelemso Hospital	Hospital	Oromia	34.48	100.00	92
41	Gobba Hospital	Hospital	Oromia	92.92	100.00	83
42	Gonder Hospital	Hospital	Amhara	86.67	85.81	100
43	Hawassa Hospital	Hospital	SNNPR	82.45	92.75	42
44	Hirna Health center	H/C	Oromia	83.33	100.00	83
45	Hiwot Fana Hospital	Hospital	Harari	66.67	100.00	92
46	Hossana Hospital	Hospital	SNNPR	88.05	85.84	100
47	Jigel Hospital	Hospital	Oromia	81.90	100.00	92
48	Jimma Hospital	Hospital	Oromia	89.29	82.07	100
49	Karamara Hospital	Hospital	Somali	93.81	100.00	83
50	Kazanchis Health center	H/C	AA	94.39	60.71	100
51	Kemissie |Health center	H/C	Amhara	84.62	86.08	42
52	Kombolcha Health center	H/C	Amhara	93.33	96.69	100
53	Kotebe Health Center	H/C	AA	90.61	95.49	83
54	Kuyu Hospital	Hospital	Oromia	88.17	66.25	50
55	Lalibela Hospital	Hospital	Amhara	83.65	85.02	58
56	Legehare Health center	H/C	Oromia	100.00	100.00	100
57	Mauchew Hospital	Hospital	Tigray	90.00	84.55	8
58	Mekele Health center	H/C	Tigray	84.29	84.72	50
59	Mekele Hospital	Hospital	Tigray	92.92	84.14	17
60	Meshualekia Health center	H/C	AA	92.31	92.13	83
61	Metema Hospital	Hospital	Amhara	86.02	61.34	75
62	Metukarl Hospital	Hospital	Oromia	85.71	90.09	83
63	Minilik Hospital	Hospital	AA	89.30	87.43	50
64	Mizan Aman Hospital	Hospital	Oromia	80.83	84.68	100
65	Moajo Hospital	Hospital	Oromia	87.96	92.43	92

Annex 7: Food, Medicine and Health Care Administration and Control Authority of Ethiopia (FMHACA)

Adverse Drug Event reporting form

Patient Name (abbreviation) ----------	Card No ----------	Age, Date of birth ----------	Sex ----------	Weight ----------	Height ----------
Ethnic group ----------		Substance of abuse ----------			

Information on suspected drug/vaccine S=suspected drug C=concomitantly used drugs

Drug name(write all information including brand name batch no and manufacturer	S/C	Dose/dosage form, route, frequency	Date drug taking was started (D/M/Y)	Date drug reaction started (D/M/Y)	Date drug taking was stopped (D/M/Y)	Indication (Reason for drug use)

Adverse drug event description (include all available laboratory test results)

Reaction necessitated Discontinuation of drug/s ☐ YES ☐ No Hospitalization prolonged ☐ YES ☐ No	Reaction subside after D/C of suspected drug ☐ YES ☐ No ☐ Information not available Reaction reappear after restart of suspected drug ☐ YES ☐ No ☐ Information not available

Treatment of reaction

_____

_____

_____

Outcome: ☐ Died due to the adverse event ☐ Died, drug may be contributory ☐ Not yet recovered ☐ Recovered without sequelae ☐ Recovered with sequelae ☐ Unknown

Sequelae

Relevant medical conditions such as allergies, renal disease, liver disease, other chronic diseases, pregnancy etc_____

Reported by: Name ----------	Profession: ----------	Email address: ----------	Telephone ----------

Name of health institution Date

Product quality problem: Color change, separating of components, powdering, crumbling, caking, molding, change of odor, incomplete pack, suspected contamination, poor packaging/poor labeling, etc (Write if anything different than given above)

Drug trade name	Batch No	Registration no	Dosage form and strength	Size /type of package
For office use only				
Received on:			Registration no:	
Key: D/M/Y; Date /Month/Year D/C; Discontinue treatment Y;YES N;NO				

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This ADE reporting form was prepared by FMHACA in collaboration with MSH/SPS and the financial support from USAID

What to report

All suspected reactions to drugs
Unknown or unexpected reactions
Serious adverse drug reactions
Unexpected therapeutic effects
All suspected drug interactions
Product quality problems
Treatment failures
Medication errors

NB. Drugs includes

Conventional drugs
Herbal drugs
Traditional medicines
Biologicals
Medical supplies
Medicated cosmetics

ቀጥሎ እዚህ ላይ እጠፍ----------

From ----------

የጉዳይ መስጫ አገልግሎት ፈቃድ ቁጥር HQ2
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Food, Medicine and Health Care Administration and Control Authority of Ethiopia

Regulatory Information Development and Dissemination Team

P.O.Box 5681-Tel.0115-523142

Addis Ababa, Ethiopia

Annex 8: Recommendations for the Application of Standard Precautions for the Care of All Patients in All Healthcare Settings.

Component	**Recommendations**
Hand Hygiene	• After touching blood, body fluids, secretions, excretions & contaminated items • Immediately after removing gloves • Between patient contacts • Between tasks and procedures on the same patient. • Alcohol based hand rubs/gels should only be used if hands are visibly clean.
Personal Protective Equipment (PPE)	
Gloves	• When touching blood, body fluids, secretions, excretions & contaminated items • For touching mucous membranes and non-intact skin. • Change gloves between tasks on the same patient after contact with material, which may contain a high concentration of microorganisms. • Change gloves before going to another patient. Always conduct hand hygiene to avoid transfer of microorganisms to other patients. • During procedures and patient-care activities when contact of clothing/exposed skin with blood/body fluids, secretions, and excretions is anticipated.
Mask, eye protection, goggles, face shield	• During procedures and patient care activities likely to generate splashes or sprays of blood, body fluids, secretions, especially suctioning, endotracheal intubation
Gown	• During procedures and patient care activities when contact of clothing/exposed skin with blood/body fluids, secretions and excretions is anticipated. • Select a gown that is appropriate for the activity and amount of fluid likely to be encountered.

	• Remove soiled gown as promptly as possible. • Hand Hygiene: Wash hands or use Alcohol based hand rubs/gels if hands are visibly clean.
Soiled patient-care equipment	• Handle in a manner that prevents transfer of microorganisms to other and to the environment; wear gloves if visibly contaminated; perform hand hygiene. • Ensure medical devices labeled as “Single Use Only” are not reprocessed or reused. • This symbol means “Single Use Only” • Ensure “Reusable Equipment” is appropriately decontaminated between patients.
Environmental Control	• Develop procedures for routine care, cleaning and disinfection of environmental surfaces, especially frequently touched surfaces in patient-care areas.
Textiles & laundry	• Handle, transport and process linen in a manner that prevents transfer of micro-organisms to others and to the environment
Needles & other sharps	• Do not recap, bend, break, or hand manipulate used needles. • Use safety features when available. • Place used sharps in an approved sharps container.
Patient Resuscitation	• Use mouthpiece, resuscitation bag other ventilation devices to prevent contact with mouth and oral secretions.
Patient Placement	• Priorities for single-patient room if patient is at increased risk of transmission, is likely to contaminate the environment, does not maintain appropriate hygiene, or is at increased risk of acquiring infection or developing adverse outcomes following infection. • If a private room is unavailable, consult with the Infection Control Team regarding patient placement or other alternatives.
Respiratory hygiene/cough etiquette	• Instruct symptomatic persons to cover mouth/nose when sneezing/coughing; use tissues and dispose in non-touch

(source containment of infectious respiratory secretions in symptomatic patients, beginning at initial point of encounter e.g., triage and reception areas in emergency departments and physician offices)	receptacle; observe hand hygiene after soiling of hands with respiratory secretions; wear surgical mask if necessary or maintain spatial separation > 3 feet if possible.

Annex 9. Grading of adverse events in children

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Severe Life-threatening
Diarrhoea ≥1 year of age <1 year of age	Transient or intermittent episodes of unformed stools OR increase of ≤3 stools over baseline per day. Liquid stools (more unformed than usual) but usual in number.	Persistent episodes of unformed to watery stools or increase of 4-6 stools over baseline per day. Liquid stools with increased number of stools or mild dehydration.	Grossly bloody diarrhoea or increase of ≥7 stools per day or IV fluid replacement indicated. Liquid stools with moderate dehydration.	Life-threatening consequences (e.g. hypotensive shock). Liquid stools resulting in severe dehydration with aggressive rehydration indicated or hypotensive shock.
Nausea	Transient (<24 hours) or intermittent nausea with no or minimal interference with oral intake.	Persistent nausea resulting in decreased oral intake for 24-48 hours.	Persistent nausea resulting in minimal oral intake for >48 hours or aggressive rehydration indicated (e.g. IV fluids).	Persistent nausea with no or minimal oral intake resulting in dehydration with aggressive rehydration indicated.
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake.	Frequent episodes of vomiting with no or mild dehydration.	Persistent vomiting resulting in orthostatic hypotension or aggressive rehydration indicated (e.g. IV fluids).	Life threatening consequences (e.g. hypotensive shock).
Acute systemic allergic	Localized urticaria (wheals) lasting	Localized urticaria with medical	Generalized urticaria or angio oedema with	Acute anaphylaxis or life- threatening bronchospasm or

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Severe Life-threatening
reaction	a few hours.	intervention indicated or mild angio oedema.	medical intervention indicated or symptomatic mild bronchospasm.	laryngeal oedema.
Pancreatitis	NA	Symptomatic and hospitalization not indicated (other than emergency treatment).	Symptomatic and hospitalization not indicated (other than emergency treatment).	Life-threatening consequences (e.g. Circulatory failure, haemorrhage, sepsis).
Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash or target lesions.	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site.	Extensive or generalized bullous lesions or Stevens-Johnson syndrome or ulceration of mucous membrane involving two or more distinct mucosal sites or Toxic Epidermal Necrolysis.
Alteration in personality-behaviour or mood	Alteration causing no or minimal interference with usual social and functional activities	Alteration causing greater than minimal interference with usual social and functional activities.	Alteration causing inability to perform usual social and functional activities and intervention indicated.	Behaviour potentially harmful to self or others or with life-threatening consequences.
Altered Mental	Changes causing no or minimal interference with usual social	Mild lethargy or somnolence causing greater than minimal interference with	Onset of confusion, memory impairment, lethargy, or	Onset of delirium, obtundation, or

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Severe Life-threatening
Status	and functional activities	usual social and functional activities.	somnolence causing inability to perform usual social and functional activities.	coma.
Source: Antiretroviral therapy of HIV infection in infants and children in resource-limited settings. WHO 2006				

Annex 10: Drug Interactions between ARVs and other drugs

Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs			
Concomitant Drug Class/Name	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulants/Antiplatelets			
Warfarin	EFV, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	EFV	Carbamazepine plus EFV: Carbamazepine AUC ↓ 27% EFV AUC ↓ 36% Phenytoin plus EFV: ↓ EFV ↓ phenytoin possible	Monitor anticonvulsant and EFV levels or, if possible, use alternative anticonvulsant to those listed.
	NVP	↓ anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses or consider alternative anticonvulsant.
Antifungals			
Fluconazole	EFV	No significant effect	No dosage adjustment necessary.
	NVP	NVP AUC ↑ 110%	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative ARV agent.
Itraconazole	EFV	Itraconazole and OH-itraconazole AUC, C_{max}, and C_{min} ↓ 35% to 44%	Failure to achieve therapeutic itraconazole concentrations has been reported. Avoid this combination if possible. If co-administered, closely monitor itraconazole concentration and adjust dose accordingly.
	NVP	↓ itraconazole possible ↑ NVP possible	Avoid combination if possible. If co-administered, monitor itraconazole concentration and adjust dose accordingly.
Ketoconazole	EFV	ketoconazole AUC ↓by	Avoid combination if possible. No data are

Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs			
Concomitant Drug Class/Name	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
		72% and Cmax ↓by 44%	available to make a dose recommendation.
	NVP	↓ Ketoconazole ↑ Nevirapine	It is not recommended to co-administer ketoconazole and NVP
Antimalarials			
Artemether/Lumefantrine	EFV	Artemether AUC ↓ 79% DHA AUC ↓ 75% Lumefantrine AUC ↓ 56%	Clinical significance of the reduced antimalarial drug concentrations unknown. If used in combination with EFV, monitor closely for anti-malarial efficacy.
	NVP	Artemether AUC ↓ 72% DHA AUC ↓ 37% Lumefantrine: AUC ↓ 25% in one study but ↑ 55.6% in another.	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy and lumefantrine toxicity.
Antimycobacterials			
Clarithromycin	EFV	Clarithromycin AUC ↓ 39%	Monitor for effectiveness or consider alternative agent, such as azithromycin, for MAC treatment.
	NVP	Clarithromycin AUC ↓ 31%	Monitor for effectiveness or use alternative agent, such as azithromycin, for MAC treatment.
Rifampicin	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600 mg once daily and monitor for virologic response.
	NVP	NVP ↓ 20% to 58%	Do not coadminister. BUT Child<3yrs TB co-infected, the recommendation is to continue NVP, ensuring that dose is 200 mg/m2
Benzodiazepines			
Lorazepam	EFV	Lorazepam C_{max} ↑ 16%, AUC ↔	No dosage adjustment necessary.
Midazolam	EFV	Significant ↑ midazolam expected	Do not coadminister with oral midazolam. Parenteral midazolam can be used with caution

Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs			
Concomitant Drug Class/Name	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
			as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	EFV	Significant ↑ triazolam expected	Do not coadminister.
Cardiac Medications			
Dihydropyridine CCBs	EFV, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Corticosteroids			
Dexamethasone	EFV, NVP	↓ EFV, NVP possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
Hormonal Contraceptives			
Hormonal Contraceptives	EFV	Ethinyl estradiol ↔ Levonorgestrel AUC ↓ 83% Norelgestromin AUC ↓ 64% Etonogestrel (implant) AUC ↓63%	Use alternative or additional contraceptive methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate.
	NVP	Ethinyl estradiol AUC ↓ 20% Norethindrone AUC ↓ 19%	Use alternative or additional contraceptive methods.
Levonorgestrel For emergency contraception	EFV	Levonorgestrel AUC ↓ 58%	Effectiveness of emergency post-coital contraception may be diminished.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV	Atorvastatin AUC ↓ 32% to 43%	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
Lovastatin	EFV	Simvastatin AUC ↓	Adjust simvastatin dose according to lipid

Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs			
Concomitant Drug Class/Name	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Simvastatin		68%	responses, not to exceed the maximum recommended dose. If EFV is used with a RTV-boosted PI, simvastatin and lovastatin should be avoided.
	NVP	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If NVP is used with a RTV-boosted PI, simvastatin and lovastatin should be avoided.
Rosuvastatin	EFV	Rosuvatatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
Methadone	EFV	Methadone AUC ↓ 52%	Opioid withdrawal common; increased methadone dose often necessary.
	NVP	Methadone AUC ↓ 37% to 51% NVP: no significant effect	Opioid withdrawal common; increased methadone dose often necessary.

Drug Interactions Between Protease Inhibitors and Other Drugs			
Concomitant Drug	**PI**	**Effect on PI and/or Concomitant Drug Concentrations**	**Dosing Recommendations and Clinical Comments**
Acid Reducers			
Antacids	ATV/r	When given simultaneously, ↓ ATV expected	Give ATV at least 2 hours before or 1 to 2 hours after antacids or buffered medications.
H2 Receptor Antagonists	ATV/r	↓ ATV	H2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40 mg BID in ART-naive patients or 20 mg BID in ART-experienced patients. Do not co-administer If using TDF based regimen.

Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs			
Concomitant Drug Class/Name	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
PPIs	ATV/r	↓ ATV	**PPIs are not recommended in patients taking ATV/r based regimen.**
Anticoagulants and Antiplatelets			
Warfarin	PI/r	↓ warfarin possible	Monitor INR closely when stopping or starting PI/r and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine	ATV/r, LPV/r,	↑ carbamazepine possible May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
Phenobarbital	All PIs	May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily, or unboosted ATV**
Phenytoin	ATV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	LPV/r	phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
Valproic Acid	LPV/r	↓ or ↔ VPA possible LPV AUC ↑ 75%	Monitor VPA levels and virologic response. Monitor for LPV-related toxicities.
Antidepressants, Anxiolytics, and Antipsychotics (Also see Sedative/Hypnotics section below.)			

Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs			
Concomitant Drug Class/Name	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Fluvoxamine	All PIs	↑ or ↓ PI possible	Consider alternative therapeutic agent.
Other Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. fluoxetine, paroxetine, sertraline)	ATV/r, LPV/r,	No data	Titrate SSRI dose based on clinical response.
Tricyclic Antidepressants Amitriptyline, Imipramine,	All RTV-boosted PIs,	↑ TCA expected	Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels.
Antifungals			
Fluconazole	ATV/r	No significant effect observed or expected	No dosage adjustment necessary.
Itraconazole	All PIs	↑ itraconazole possible ↑ PI possible	Doses >200 mg/day are not recommended with RTV-boosted PIs, unless dosing is guided by itraconazole levels.
Ketoconazole	All PIs	↑ ketoconazole possible ↑ PI possible	High doses of ketoconazole (> 200 mg/day) are not recommended.
Antimalarials			
Artemether/Lumefantrine	LPV/r	artemether AUC ↓ 40% lumefantrine AUC ↑ 470%	Clinical significance unknown. If used, monitor closely for anti-malarial efficacy and lumefantrine toxicity.

Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs			
Concomitant Drug Class/Name	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Atovaquone/Proguanil	ATV/r, LPV/r	ATV/r ↓ atovaquone AUC 46% and ↓ proguanil AUC 41% LPV/r ↓ atovaquone AUC 74% and ↓ proguanil AUC 38%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.
Antimycobacterials (for treatment of *Mycobacterium tuberculosis* and non-tuberculosis mycobacterial infections)			
Clarithromycin	LPV/r	clarithromycin AUC ↑	For patients with renal impairment (CrCL < 30 ml/min) dose reduction of clarithromycin should be considered. Caution should be exercised in administering clarithromycin with LPV/r to patients with impaired hepatic or renal function.
	ATV/r	clarithromycin AUC may be increased	No data
Erythromycin	LPV/r, ATV/r	could increaseconcentrations of erythromycin	Use with caution and if possible an alternative antibiotic should be used
Rifampicin	All PIs	↓ PI concentration by >75%	**Do not coadminister rifampicin and PIs**. If used consider dose adjustment based on the FMOH guideline.
Cardiac Medications			
Amiodarone	All PIs (except SQV/r)	↑ both amiodarone and PI possible	Use with caution. Monitor for amiodarone toxicity and consider ECG and amiodarone drug level monitoring
Calcium Channel Blockers (CCBs)	All PIs	↑ dihydropyridine possible	Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB

Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs			
Concomitant Drug Class/Name	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
		↑ verapamil possible	used with ATV
Digoxin	PI/r	RTV (200 mg BID) ↑ digoxin AUC 29% and ↑ half-life 43%	Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased. Titrate initial digoxin dose.
Corticosteroids			
Fluticasone, Mometasone Inhaled or Intranasal	All RTV-boosted PIs	↑ glucocorticoids possible RTV 100 mg BID ↑ fluticasone AUC 350-fold and ↑ C_{max} 25-fold	Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of inhaled or intranasal corticosteroid outweigh the risks of systemic corticosteroid adverse effects.** Consider alternative corticosteroid (e.g., beclomethasone).
Dexamethasone Systemic	All PIs	↓ PI levels possible	Use systemic dexamethasone with caution. Consider alternative corticosteroid for long-term use.
Prednisone	LPV/r	↑ prednisolone AUC 31%	Use with caution. Coadministration can result in adrenal insufficiency and Cushing's syndrome. **Do not coadminister unless potential benefits of prednisone outweigh the risks of systemic corticosteroid adverse effects.**
	All PIs	↑ prednisolone possible	
Methylprednisolone, Prednisolone, Triamcinolone (local injections, including intra-articular, epidural, intra-orbital)	All RTV-boosted PIs	↑ glucocorticoids expected	**Do not coadminister.** Coadministration can result in adrenal insufficiency and Cushing's syndrome.

Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs			
Concomitant Drug Class/Name	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Contraceptives			
Hormonal Contraceptives(oral)	ATV/r	ethinyl estradiol AUC ↓ 19% and C_{min} ↓ 37% norgestimate ↑ 85%	Recommend alternative or additional contraceptive method
	LPV/r,	ethinyl estradiol AUC ↓ 37% to 48% norethindrone AUC ↓ 14% to 34%	Recommend alternative or additional contraceptive method
Transdermal ethinyl estradiol/norelgestromin	LPV/r	LPV ↔ ethinyl estradiol AUC ↓ 45%, norelgestromin AUC ↑ 83%	Use standard dose.
	All other PIs	No data	Recommend alternative or additional contraceptive method
HMG-CoA Reductase Inhibitors			
Atorvastatin	ATV/r	↑ atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary.
	LPV/r	LPV/r ↑ atorvastatin AUC 488%	Use with caution and use the lowest atorvastatin dose necessary.
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated. Do not coadminister.**
Pravastatin	ATV/r	No data	Use lowest starting dose of pravastatin and monitor for efficacy and adverse effects.

Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs			
Concomitant Drug Class/Name	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
	LPV/r	pravastatin AUC ↑ 33%	No dose adjustment necessary.
Rosuvastatin	ATV/r, LPV/r	ATV/r ↑ rosuvastatin AUC 3-fold and C_{max}↑ 7-fold LPV/r ↑ rosuvastatin AUC 108% and C_{max} ↑ 366%	Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed 10 mg rosuvastatin daily.
Simvastatin	All PIs	Significant ↑ simvastatin level	**Contraindicated. Do not coadminister.**
Narcotics and Treatment for Opioid Dependence			
Buprenorphine	ATV/r	buprenorphine AUC ↑ 66% norbuprenorphine[d] AUC ↑ 105%	Monitor for sedation. Buprenorphine dose reduction may be necessary.
	LPV/r	No significant effect	No dosage adjustment necessary.
Methadone	RTV-boosted PIs	ATV/r ↓ R-methadone[e] AUC 16% to 18% LPV/r ↓ methadone AUC 26% to 53%	Opioid withdrawal unlikely but may occur. Dosage adjustment of methadone is not usually required, but monitor for opioid withdrawal and increase methadone dose as clinically indicated.
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Sildenafil	All PIs	RTV 500 mg BID ↑ sildenafil AUC 1,000%	For Treatment of Erectile Dysfunction: • Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil.

Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs			
Concomitant Drug Class/Name	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Tadalafil	All PIs	RTV 200 mg BID ↑ tadalafil AUC 124%	For Treatment of Erectile Dysfunction: • Start with tadalafil 5-mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil.
Vardenafil	All PIs	RTV 600 mg BID ↑ vardenafil AUC 49-fold	Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil.
Sedative/Hypnotics			
Alprazolam **Diazepam**	All PIs	↑ benzodiazepine possible RTV (200 mg BID for 2 days) ↑ alprazolam half-life 222% and AUC 248%	Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam.
Lorazepam **Oxazepam** **Temazepam**	All PIs	No data	These benzodiazepines are metabolized via non-CYP450 pathways; thus, there is less interaction potential than with other benzodiazepines.
Midazolam	All PIs	↑ midazolam expected	**Do not coadminister oral midazolam and PIs.** Parenteral midazolam can be used with caution when given as a single dose in a monitored situation for procedural sedation.
Triazolam	All PIs	↑ triazolam expected	**Do not coadminister.**
Miscellaneous Drugs			
Salmeterol	All PIs	↑ salmeterol possible	**Do not co-administer** because of potential increased risk of salmeterol-associated cardiovascular events.
Key to Symbols: ↑ = increase, ↓ = decrease, ↔ = no change **Key to Acronyms**: 17-BMP = beclomethasone 17-monopropionate; APV = amprenavir; ART = antiretroviral therapy;			

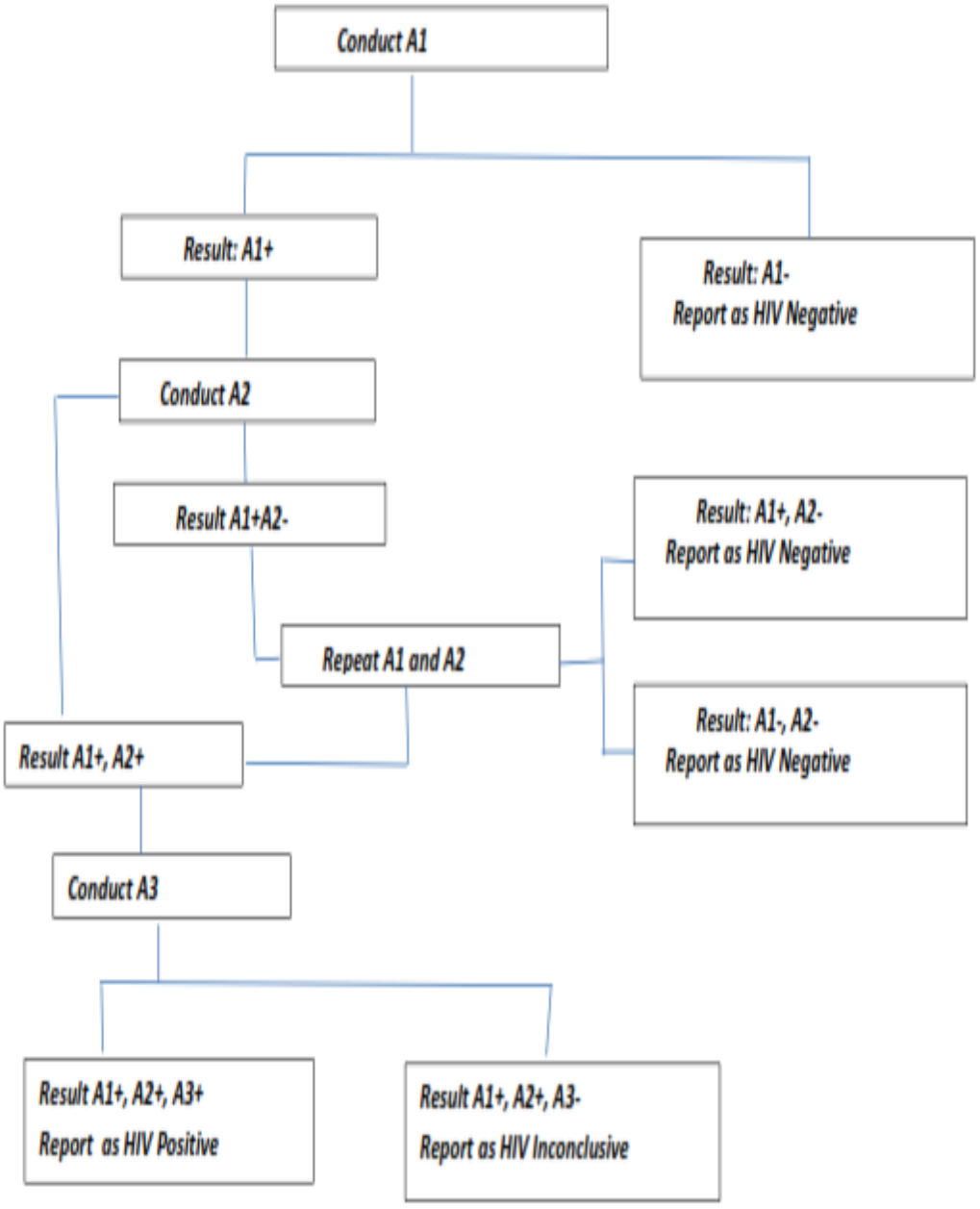
Drug Interactions Between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs			
Concomitant Drug Class/Name	NNRTI	Effect on NNRTI and/or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments

ARV = antiretroviral; ATV = atazanavir; ATV/r = ritonavir-boosted atazanavir; AUC = area under the curve; BID = twice daily; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; CNS = central nervous system; CrCl = creatinine clearance; CYP = cytochrome P; DHA = dihydroartemisinin; ECG = electrocardiogram; INR = international normalized ratio; LPV/r = ritonavir-boosted lopinavir; PAH = pulmonary arterial hypertension; PI = protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; QTc = QT corrected for heart rate; RTV = ritonavir; TCA = tricyclic antidepressants; TDF = tenofovir disoproxil fumarate; VPA = valproic acid

Key to Symbols: ↑ = increase, ↓ = decrease, ↔ = no change

Key to Acronyms: ARV = antiretroviral; AUC = area under the curve; BID = twice daily; CCB = calcium channel blockers; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; DAAs = direct-acting antivirals; DHA = dihydroartemisinin; EFV = efavirenz; FDA = Food and Drug Administration; HMG-CoA = hydroxy-methylglutaryl-coenzyme A; INR = international normalized ratio; MAC = *Mycobacterium avium* complex; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; OH-itraconazole = active metabolite of itraconazole; PDE5 = phosphodiesterase type 5; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RTV = ritonavir

Annex 11: The national HIV testing algorithm



Annex 12: ADR competency exercise

S. No.	Drug 's Generic Name	Two most common Side effect	Counseling or Management to avoid or minimize side effects	Possible substitutes in case of severe ADR (if it is G3 or G4)
1	Zudovudine Daily Adult Dose:			
2	Nevirapine Daily Adult Dose:			

S. No.	Drug 's Generic Name	Two most common Side effect	Counseling or Management to avoid or minimize side effects	Possible substitutes in case of severe ADR (if it is G3 or G4)
3	Efavirenz Daily Adult Dose:			
4.	Tenofovir Adult Dose:			
5.	Atazanavir/r Adult dose			

S. No.	Drug 's Generic Name	Two most common Side effect	Counseling or Management to avoid or minimize side effects	Possible substitutes in case of severe ADR (if it is G3 or G4)
	_____			

Error! Use the Home tab to apply 0 to the text that you want to appear here. Annex 13: competency test on ARVs interaction with other drugs

SN	ARVs		COC_s	Rifampicin	Cotrimoxazole	Diazepam	Phenytoin	Ketoconazole
1	Zudovudine	Interact (Y or N)						
		Consequence of Interaction						
		Advice (Management)						
2	Nevirapine	Interact (Y or N)						
		Consequence of Interaction						
		Advice (Management)						
3	Efavirenz	Interact (Y or N)						
		Consequence of Interaction						
		Advice (Management)						
4	Lopinavir/r	Interact (Y or N)						
		Consequence of Interaction						

SN	ARVs		COCs	Rifampicin	Cotrimoxazole	Diazepam	Phenytoin	Ketoconazole
		Advice (Management)						
5	Tenofovir	Interact (Y or N)						
		Consequence of Interaction						
		Advice (Management)						

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