Module 4: Introduction to Antiretroviral Therapy

Session 1: Introduction to Antiretroviral Therapy

Total Session Time: 15 minutes

Learning Objectives

At the end of this session, participants will be able to:
- Describe the goal of ARV therapy in children
- Explain the immunological and virological responses to ART
- Explain the general principles of ARV therapy in children

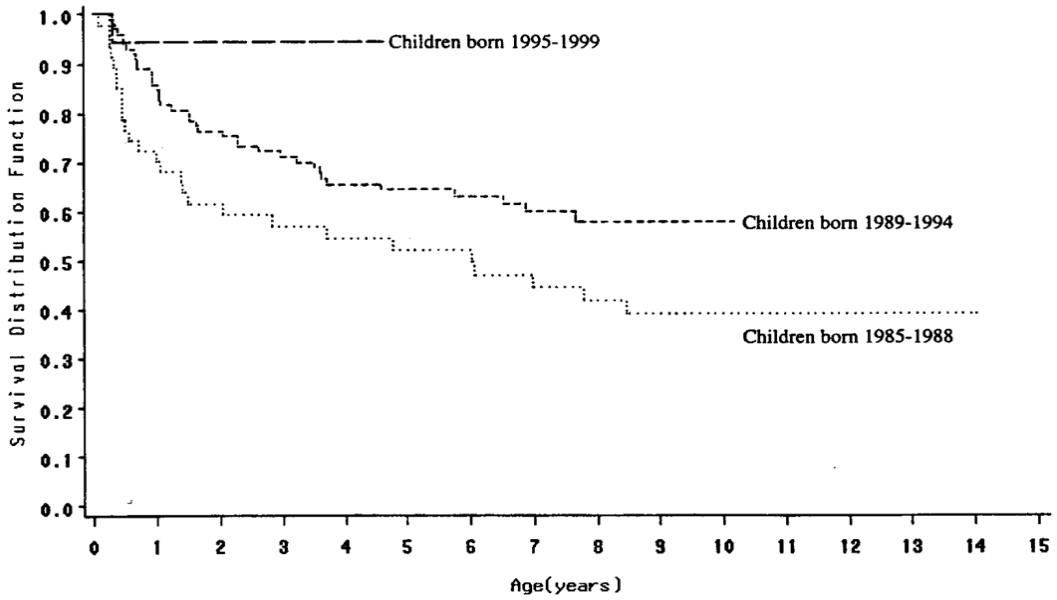
Goals of ARV Therapy in Children & Immunological and Virological Responses to ART

Goals of ARV Therapy in Children
Paediatric ART is more difficult in children due to high initial set point–this is a challenge to achieving the goals of paediatric ART. Thus the goals of ARV in children are to:
- Promote optimal growth and development
- Preserve, enhance, or reconstitute the immune system therefore reducing OIs
- Suppress HIV-replication and prevent disease progression
- Reduce morbidity and improve quality of life
- Reduce mortality
- Reduce HIV transmission

Generally, the goals of antiretroviral treatment are to:
- Prevent the multiplication (replication) of HIV and thereby suppress the viral load and keep it suppressed. This will stop the progression of the disease.
- Protect or restore the immune function by increasing the CD4 count. This will improve the quality of life and general health.

Remember that: Many of these goals are consistent with adult and adolescent ART goals.

Estimated Progression to Serious Disease or Death

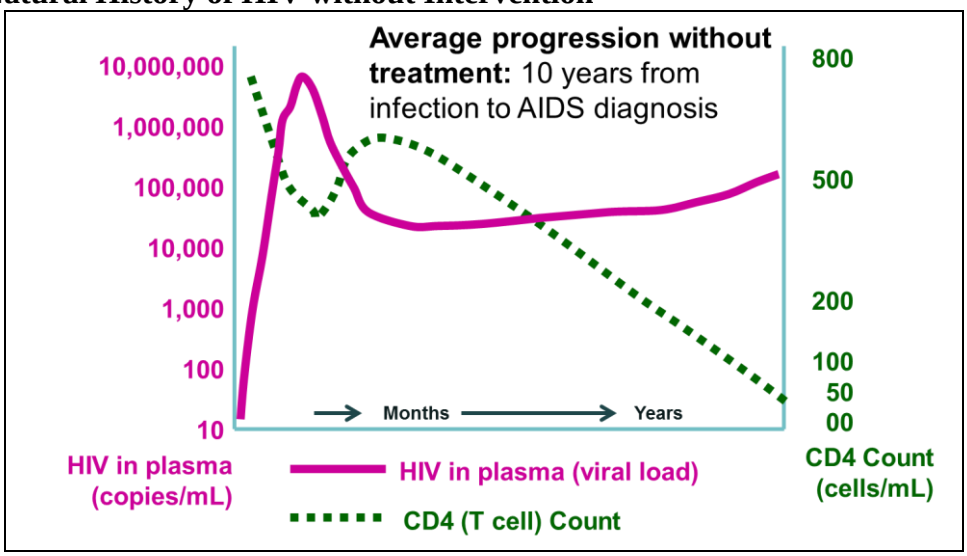


Prior to antiretroviral therapy many HIV infected children were dying mainly in infancy. However, there is an increased survival rate in the era of ARVs, which this graphic represents

HIV RNA in Children

HIV viral load (VL) is initially very high, but then as the body starts to fight the infections it reaches a lower VL ('set point'). VL in children is usually higher than Adults, which is due to inability of the infant's immature immune system to contain viral replication. There is also a greater number of HIV susceptible (CD4) cells thus provide opportunity for faster replication of viral copies

Natural History of HIV without Intervention



For adults infected with HIV, the HIV viral load is initially high, and then reaches its "set point". The CD4 count falls rapidly with acute infection, and then rises as the viral load approaches the set point. Over the next 5-10 years the CD4 count will gradually decline.

General Principles of ARV Therapy in Children

General Principles of ART

- ART works best when the other components of comprehensive HIV care and treatment are maximized.
- Use combination of ARVs (minimum of 3);
  - Use drugs from more than one class
- Use a combination demonstrated to have durable treatment success (e.g. national first line)
- Avoid overlapping toxicities and drug-drug interactions
- Always consider and treat co-morbidities as a priority; e.g. TB, Hepatitis B or C or chronic renal/liver disease, severe anaemia. Co-morbidities may influence the choice of ARVs to treat HIV infection.
- Preserve future treatment options;
  - Start with default regimen as per national guidelines
- Starting ART is not an emergency:
  - Patient preparation is key to maximum adherence
  - Caregivers should undergo adherence counseling prior to initiation of treatment to the child

'Other components' of paediatric HIV care and treatment include:

- Early diagnosis of HIV infection
- Growth and development monitoring
- Routine immunization and de-worming
- Nutrition supplementation
- Treatment of acute infections
- Treatment and prevention of OIs
- Psychosocial support and palliative care
- Adolescent care and support
- Mother and family care (PMTCT and MTCT plus)

A child's best chance for long-term success is with the 1st line ARV regimen, so make sure the patient and caregiver understands the importance of adherence and has good support in place prior to starting ARVs.

Key Points

- ART reduces morbidity, mortality and improves quality of life
- Emphasis should be to maintain the 1st line regimen for the best treatment outcome
- Mono-or dual therapy are not recommended in ART

Sources/Bibliography

- *ECS-Pediatrics 108, July 2001*

Session 2: Antiretroviral Medications

Total Session Time: 1 hour 30 minutes

Learning Objectives

At the end of this session, participants will be able to:
- Describe the different classes of ARVs and their sites and modes of action
- Explain ARV medicines dosages and formulations available for children in Tanzania
- Explain the management of common adverse effects of ARV medicines
- Outline the interactions of ARVs with other medicines and food

Classification of ARVs

Classification of ARVs
Three major classes of ARVs:
- **NRTIs:** Nucleoside Reverse Transcriptase Inhibitors
- **NNRTIs:** Non-Nucleoside Reverse Transcriptase Inhibitors
- **PIs:** Protease Inhibitors

*Refer to **Handout 4.2.1: Classes of ARVs** on **page 187** for more details on the classes of ARVs.*

NRTIs (Reverse Transcriptase Inhibitors)
Block reverse transcriptase enzyme and prevents HIV taking control over the CD4 cells. Oldest known ARVs belong to this class. Form the 'backbone' of ART.

Available medicines in Tanzania include:
- **Zidovudine**
- **Lamivudine**
- **Tenofovir**
- **Abacavir**
- **Emtricitabine**

NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors)
Block the same enzyme as NRTIs but their method of action is different. Available medicines in this class in Tanzania include:
- Nevirapine
- Efavirenz

Resistance to these medicines develops rapidly, especially when used alone.

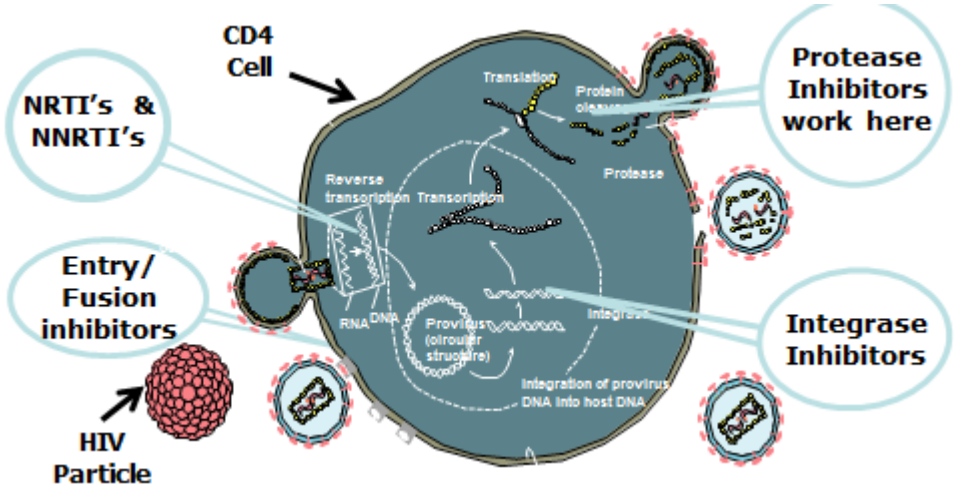
PIs (Protease Inhibitors)
These prevent HIV-infected CD4 lymphocytes from building and releasing new mature viruses. Generally most expensive ARVs, and reserved for 2nd line treatment.

Available medicines in Tanzania include:

- Lopinavir
- Ritonavir
- Atazanavir

Target Sites of ARV Drugs

HIV destroys CD4 cells in the process of multiplication/replication as follow:



All Antiretroviral Drugs (ARVS) work by preventing multiplication of the HIV virus at the various stages of replication and that they do so by either blocking certain processes or inhibiting certain enzyme activity.

The main enzymes activity inhibited include reverse transcriptase, integrase, and protease enzymes. Stopping/reducing replication in turn stops/reduces CD4 cell destruction.

*Refer to **Handout 4.2.2: Target and Mode of Action for ARVs** on **page 189** for more information on how ARV medicines work.*

Fixed Dose Combinations (FDC)

Many fixed dose combinations are becoming available, making it easier for patients to take their medicines by reducing the pill burden.

FDCs available in Tanzania include:

- **Duovir-N:** Zidovudine + Lamivudine + Nevirapine
- **Combivir:** Lamivudine + Zidovudine
- **Abacavir + Lamivudine**
- **TLE:** Tenofovir + Lamivudine + Efavirenz
- **Atripla:** Tenofovir + Emricitabine + Efavirenz
- **Truvada:** Tenofovir + Emtricitabine
- **Atanazavir/Ritonavir**

Paediatric FDCs are available including:

- Duovir-N has paediatric formulations namely Duovir-N Baby-AZT+3TC+NVP (60/30/50mg).
- Combivir Baby – AZT+3TC (60/30mg).
- Abacavir + Lamivudine.

General Guidelines

ART usually involves a combination of **three** antiretroviral medicines from different classes:

- The 'backbone' of ART is typically 2 NRTIs
- The third medicine is either NNRTI or PI

The following combinations are preferred:

- 2 NRTIs + PI/r (RTV boosted PI)
- 2 NRTIs + 1 NNRTI

Less desirable:

- 2 NRTIs + 1 PI
- 3 NRTIs including Abacavir

Criteria Used to Select ARV Combination Selection

- Recommended regimen from the national guidelines
- Proven potency/efficacy
- Safety, tolerability, favourable side-effects profile
- Cost and availability
- Ease of dosing, anticipated adherence
- Preserving future treatment options
- Availability of fixed-dose combinations
- Co-existent health conditions (such as tuberculosis, HBV, HCV, pregnancy or potential thereof
- Access to proper storage
- Public health approach;
    - HIV care services should:
    - Benefit for the majority
    - Delivered by trained health care providers
    - Be facilitated by availability of a wide range of ARVs including availability of suitable second-line regimens
    - Individualized to meet the patient's specific needs
    - Age

In developing a public-health ART approach, the key conceptual shift is the move from an individual-based approach to a population-based approach to make ART rapidly accessible to the many people in need and enhancing equity.

- For syrups and suspensions:
    - Availability (not all ARVs have paediatric formulations)
    - Cost (generally more expensive)
    - Storage requirements
    - Shelf life
    - Palatability (e.g. ritonavir suspension is extremely unpalatable)

ARV Regimens for Children

Default first line ARV for Children under 3 years: ABC/3TC + LPV/r

First line ART Regimen for children younger than 3 years:	
Default 1st line ARV Regimen	**ABC + 3TC + LPV/r**
Alternative 1st line ARV Regimen	**AZT + 3TC + LPV/r**
	AZT + 3TC + NVP

Default first line ARV for Children ***over*** 3 years: **ABC/3TC + EFV**

First line ART Regimen for children over 3 years to adolescents less than 35 kg:	
Default 1st line ARV Regimen	**ABC + 3TC + EFV**
Alternative Regimen	**AZT + 3TC + EFV**
Alternative Regimen	**ABC + 3TC + NVP**

Special Cases: TB/HIV Co-Infection

- Children < 3 years preferred: triple NRTI 1st line regimen such as **ABC + 3TC + AZT.**
- Alternative: ABC + 3TC + LPV/r
- Children > 3 years:
  - preferred: standard ABC + 3TC + EFV
  - Alternative AZT+3TC+EFV

REMEMBER that: For the children <3 alternative regimen ABC + 3TC + LPV/r the dose of ritonavir should be increased to a one to one ratio. Harmonize national guidelines on the management of TB HIV /AIDS.

ARV Medicines Dosages and Formulations Available for Children in Tanzania & Management of Common Adverse Effects of ARV Medicines

Paediatric Dosing

As part of preparation for ART the weight, height/length of the child must be taken. Paediatric dosages are **most accurate** if calculated using the Body Surface Area (BSA) i.e. $mg/m^{2.}$

*Refer to **Handout 4.2.3: Paediatric dosing charts for ARVs** on **page 191** for more information*

ARV Medicines Adverse Events

Common "mild" side effects include:

- Significant to patient
- Patient/caregiver needs to be prepared for predictable side effects that are often self limiting
- Supportive/symptomatic treatment if needed
- Treatment discontinuation or change rarely required

Serious and/or life threatening side effects:

- Less common (e.g. severe rash, pancreatitis, lactic acidosis)
- Treatment change often required

These side effects are not specific to children, when a child presents with a new symptom, it can be difficult to know what is causing it.
The criteria that might help to identify adverse events include:

- Timing of the symptom: rash occurs early in therapy while lipodystrophy occurs over time
- The signs and symptoms that the child presents with, could be due to either other illnesses or else immune reconstitution

Some of the criteria that might help to identify the cause of the new symptoms or toxicity include:

- Occurs within the first week while rash due to Nevirapine can occurs 2-6 weeks after initiation (but usually within the first 2 weeks)
- Other medications that the child is taking: "Could newly prescribed medications be responsible for the problem?
- Is child taking alternative remedies such as vitamins, herbs (these may cause side effects or drug interactions with prescribed ARVs)
- Rash due to Cotrimoxazole

It is important to educate caregiver about the possibility of side effects prior to ART initiation. If they are not prepared, they may not be adherent to the regimen. Mild side effects include headache, fatigue, GI symptoms, diarrhoea. These mild side effects occur early in treatment and often wear off and should be treated symptomatically.

*Refer to **Handout 4.2.4: Common Side Effects of First Line Antiretroviral Therapy** on **page 195** for more information on side effects.*

NRTI Class Toxicities
NRTI toxicities are less common in children than in adults.

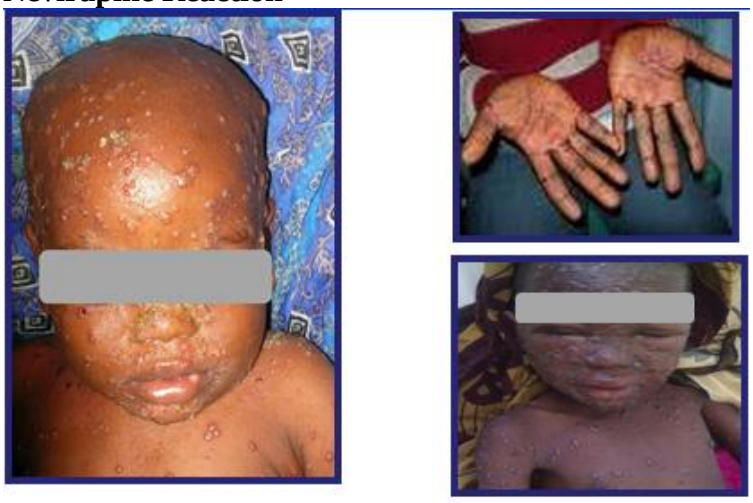
- Lactic acidosis;
  - Excessive lactic acid in the body presenting with deep and rapid breathing, vomiting, and abdominal pain
- Hepatic steatosis;
  - Excessive collection of triglycerides and other fats in liver cells. Present with pain under the rib cage on the right side
- Pancreatitis;
  - Present with gradual or sudden pain in the upper abdomen. Other symptoms are Swollen and tender abdomen Nausea and vomiting Fever and Rapid pulse
- Myopathy;
  - Present with muscle weakness, cramps, and spasms due to a primary defect of the muscle fiber
- Cardiomyopathy;
  - Present with breathlessness, swelling of the legs, ankles and feet, orthopnoea, fatigue and chest pain
- Lipodystrophy;
  - A disorder of adipose (fatty) tissue characterized by a selective loss of body fat.
- Rapidly ascending muscular weakness related lactic acidosis
- Rash; a rash is a common symptom but can be distressing and difficult to manage. Usually maculopapular, pruritic, and mild to moderate in severity and rarely requires drug discontinuation

- Stevens Johnson Syndrome (rare)
- Other reported adverse events include diarrhoea, nausea, and increased aminotransferase levels

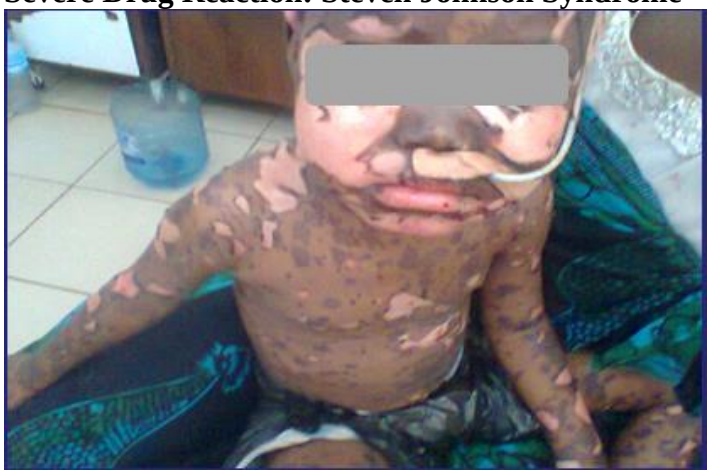
Hypersensitivity reactions can be graded as either mild or severe. The grading helps to determine how the rash is managed (whether to stop the offending drug). This mild to moderate rash is managed by reassuring the patient, and close follow up until resolved.

Note that: it is necessary to counsel family to return to clinic if rash develops.

Nevirapine Reaction



Severe Drug Reaction: Steven Johnson Syndrome



PI Class Toxicities

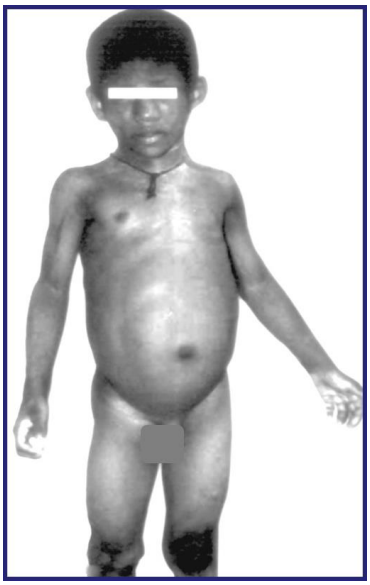
Known to cause most ART metabolic disorders such as dyslipidaemia , lipodystrophy syndrome and hyperlipidaemia, nephrolithiasis. Also new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus & hyperglycaemia.

Increased bleeding, including spontaneous skin hematomas and haemarthrosis, in patients with hemophilia A and B treated with protease inhibitors.

Haematoma is a localized swelling that is filled with blood caused by a break in the wall of a blood vessel. Haemathrosis is accumulation of blood in a joint or joint cavity.

Hemophilia is a hereditary disorder presenting with a profound deficiency in the activity of clotting factor VIII. Affected individuals suffer hemorrhage into joints and muscles, easy bruising, and prolonged bleeding from wounds. The disease is inherited as an X-linked trait, so males are affected and females carry the gene.

PI Lipodystrophy (Fat Accumulation)



Guiding Principles in Management of Side Effects
Side effects can be managed under the following guiding principles:

- Determine the seriousness of the toxicity
- Determine whether the side effect is due to ARVs or other medications
- Consider other disease processes (e.g. a child who develops jaundice may have hepatitis), because not all problems during treatment are due to ARVs
- Manage according to severity
- Try and establish the ARV medicine responsible for the adverse effect
- Consider duration of ARV use, other disease processes, other treatments (including self administered)

Refer to ***Handout 4.2.5: Severe toxicities of ARVs in infants and children, and potential drug substitutions*** *on* ***page 197***

In NNRTI containing regimens, stopping all 3 drugs at once may allow for development of drug resistance. It is therefore recommended that the NRTI backbone should be continued for 1 week if possible to reduce the likelihood of NNRTI resistance developing

Minimizing Adverse Events can be through:

- Appropriate drug and regimen selection
- Dose titration
- Monitoring and reassuring for effects that are transient
- Appropriate timing of administration
- Pharmacological interventions
- Withdrawal of the offending medicine(s)

Other guiding principles in management of side effects include:

- Grade 4: Severe life-threatening conditions:
  - Immediately discontinue all ARVs and manage the medical event
  - Reintroduce ARVs when the patient is stable, *substitute* the offending medicine
- Grade 3: Serious SE:
  - *Substitute the offending* medicine without stopping ARVs
- Grade 2: Moderate reaction:
  - Consider continuing ARVs as long as feasible
  - May consider substitution if no changes
- Grade 1: Mild reactions
  - Bothersome but do not merit changes in therapy

NOTE: Because ARV combinations are limited, premature switching to completely new regimens should be limited.

Laboratory Indications for Changing ARVs Due to Adverse Effects

Parameter	Grade 3 Toxicity
Haemoglobin	**≤ 7.0 g/dL**
Absolute Neutrophil Count	**≤ 250 mm^3**
Bilirubin	**≥ 3.0 – 7.5 × upper limits of normal**
Creatnine	**≥ 1.2 – 1.5 (<2 yrs); 1.7 – 2.0 (2 yrs)**
AST (SGOT)	**≥ 5 × upper limits of normal or rapidly increasing**
ALT (SGPT)	**≥ 10 upper limits of normal or rapidly increasing**
Amylase, Lipase	**≥ 2 – 3 × upper limits of normal**

Hepatotoxicity

- NVP most common cause
- EFV, PIs, NRTIs can also cause hepatitis
- Check ALT/SGPT if any hepatic symptoms

Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune reconstitution inflammatory syndrome (also known as "Immune recovery syndrome") is a condition seen in some cases of AIDS or immunosuppression, in which the immune system begins to recover after initiation of ARVs, but then responds to a previously acquired opportunistic infection with an overwhelming inflammatory response that paradoxically makes the symptoms of infection worse.

This is an unexpected clinical deterioration which occurs soon (usually within 4 to 12 weeks) after antiretroviral treatment is begun. After initially improving, the child becomes ill once again. Usually observed in adults, less frequent in children, but especially among those starting treatment with very low CD4. Development of symptoms of OI associated with concurrent rapid rise in CD4 usually days to weeks (~6) after initiation of effective ART. Its clinical presentations vary depending on causative organism and the organ system that is colonized.

As the immune system recovers, the body may develop an inflammatory response to any of the following:

1. Hidden or mild infections which have been missed clinically (i.e. unmask unrecognised infection). An example would be silent TB.
2. Worsen existing infections. An example would be TB which has only been treated for a few weeks.

The suppression of CD4 T cells by HIV causes a decrease in the body's normal response to certain infections. Not only does this make it more difficult to fight the infection; it may mean that a level of infection that would normally produce symptoms is instead undetected (subclinical infection). If the CD4 count rapidly increases (due to effective treatment of HIV), a sudden increase in the inflammatory response produces nonspecific symptoms such as fever, and in some cases a worsening of damage to the infected tissue.

NOTE: During the initial stages of antiretroviral therapy many children with advanced HIV infection are still severely immunosuppressed and are thus susceptible to new opportunistic infections. Therefore differentiating classic IRIS from new infection associated with ongoing immune suppression during the first 6 months of antiretroviral treatment may be difficult.

Management includes specific antimicrobial therapy. In severe reactions or where CNS or eyes involved, adjunctive steroid therapy may be necessary.

Activity on ARVs, side effects, and toxicity.

*Refer to **Worksheet 4.2.1: Case Studies** on **page 199** for the case studies on ARVs, side effects, and toxicity.*

Interactions of ARVs with other Medicines and Food

Interactions between ARVs and other medicines

Many antiretroviral medications used to treat HIV infection, particularly certain protease inhibitors and nonnucleoside reverse transcriptase inhibitors, interact with other antiretroviral agents. These interactions are usually due to effects on hepatic drug metabolism and can cause clinically significant alterations in serum medicine concentrations. Certain antiretroviral agents require dosage adjustment (or pharmacokinetic enhancement) when co-administered, and some combinations are contraindicated.

ARVs – Rifampicin Interactions

Decrease in serum concentration of some commonly used ARVs when given with Rifampicin. Because of interactions between Rifampicin and PIs/NVP (with the serum levels of former reducing the later increasing), treatment for HIV positive patients with TB may have to be modified.

PIs	**Decrease**
Ritonavir	35%
NNRTIs	**Decrease**
Nevirapine	37% (not usually used, double the dose if used)
Efavirenz	26% (give standard dose)

Common Overlapping Adverse Effects are:

Bone Marrow Suppresion: • AZT • Ganciclovir • Cotrimoxazole	**Peripheral Neuropathy:** • Isoniazid
Nephrotoxicity: • Aminoglycosides	**Diarrhea:** • RTV • Cotrimoxazole
Rash: • ABC, EFV, NVP, Dapsone • Cotrimoxazole	**Pancreatitis:** • 3TC in children • RTV
Hepatotoxicity: • EFV, NVP, NRTIs • Rifampicin/Rifabutin • Isoniazid • Fluconazole	**Ocular Effects:** • Rifabutin • Ethambutol

Concomitant use of drugs with overlapping toxicities is not recommended. Where suitable alternatives are not available, close monitoring should be done and appropriate measures e.g. administering the medicines at different intervals.

Management of ARV Toxicities/ Adverse Medicine Reactions (ADR)
Patient and their Caregiver should be reminded that:

- All medications have side effects.
- Some side effects will disappear with time as the body adjusts.
- Most side effects can be managed if detected early and/or without changing ARV therapy.
- Very rarely, side effects can be life threatening and patients should seek medical attention

Also;

- ADR should be anticipated and if possible avoided
- Depends on grade of ADR (grades 1-4; 4 the most severe)
- Management depends on specific medicine and grade of ADR
- Supportive care may be needed

Patient and caregiver should be encouraged to:

- Talk to their health care providers about the side effects experienced.
- Attend all clinic appointments.
- Detect and manage their ARV side effects before they become severe.
- Not to stop or change their ARVs without first consulting with their doctor.
- Not to take other medicines (including traditional medicines) without consulting their doctor first**.**

Strategies to Management of ARV Toxicities/ ADR
These strategies to manage ARV toxicities include:

- Appropriate medicine and regimen selection
- Dose titration

- Monitoring and reassuring for effects that are transient
- Appropriate timing of administration
- Pharmacological interventions
- Withdrawal of the offending medicine(s)

Providers should remind the patients/caretakers the warning signals that need to be reported to the health care provider. These include:

- Difficulty breathing.
- Severe Abdominal pain.
- Yellow skin/ eyes.
- Red rash that is intensifying and may occur with fever, blistering and mucous membrane involvement.
- Persistent vomiting.
- Persistent diarrhoea.
- Moderate to severe numbness/tingling/burning in hands and feet
- Severe Fatigue/ Weakness

Reporting of Severe Adverse Drug/ Medicine Effects

Adverse effects should be reported using tools provided for this purpose if it warrants any of the following:

- A change to a patient's drug regimen
- Cessation of ART
- Significant disability
- Death

All severe adverse drug effects should be reported to TFDA using special form (Yellow form).

Medicine-Food Interaction

As the effect of food on the efficacy of a medicine is food and medicine specific, the counselor should help the client draw up a food and medicine timetable. This timetable should take into account both the food and medicine interactions of each medicine to be taken and the client's eating habits to ensure the greatest efficacy of the treatment.

Food enhances or inhibits the absorption or metabolism of some ARVs. A high-fat meal increases the bioavailability of the nucleoside analogue. A high-calorie, high-fat, high-protein meal decreases absorption of the protease inhibitor Indinavir and reduces the absorption of the nucleoside reverse transcriptase inhibitor Zidovudine; Zidovudine should therefore not to be taken with high-fat meals (>40g of fat).

Activity correct regimen & dose for each patient

*Refer to **Worksheet 4.2.2: Exercise on Regimens and Dosages** on **page 201** for more exercise on correct regimen & dose for the patient.*

Key Points

- There are 3 main classes of ARVs in Tanzania, NRTIs form the backbone of ART
- Adhere to the National guidelines when initiating/changing ARVs
- Paediatric ARV dosing is based on BSA (most accurate) and body weight
- Adhere to principles of managing side effects caused by ARVs for all mild to serious ones
- Observe medicine -medicine and food-medicine interactions when treating HIV positive children

Sources/Bibliography

- *Tenofovir, Pronsky, Meyer, and Fields-Gardner 2001*

Handout 4.2.1: Classes of ARVs

Types of Antiretroviral Drugs Available in Tanzania

The currently existing and commercially available antiretroviral drugs in Tanzania fall into the following four main categories:

- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Nucleotide reverse transcriptase inhibitors (Nucleotide analogues)
- Protease inhibitors (Pls)

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

This group of drugs is the mainstay of antiretroviral therapy in the country. The primary mechanism of action of this class is inhibition of viral RNA-dependent DNA polymerase (reverse transcriptase) enzyme by forming faulty versions of building blocks that HIV needs to make more copies of itself. When HIV uses an NRTI instead of a normal building block, reproduction of the virus is stalled. The drugs available are:

- Zidovudine (AZT),
- Lamivudine (3TC),
- Emtricitabine (FTC)
- Abacavir (ABC).

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Similar to the NRTIs, NNRTIs bind to the reverse transcriptase and disrupt the reverse transcription of viral RNA into DNA that is then incorporated in the cell's nucleus. However, unlike the NRTIs, they are not directly incorporated into the viral DNA; instead they inhibit replication directly by binding to the enzyme reverse transcriptase. Drugs under this class that are available in Tanzania are:

- Nevirapine (NVP)
- Efavirenz (EFV).

Nucleotide Reverse Transcriptase Inhibitors (Nucleotide analogues)

Nucleotide analogues resemble NRTIs and an example of this relatively new class of antiretroviral drugs is:

- Tenofovir (TDF).

Protease Inhibitors (PIs)

PIs competitively inhibit the HIV protease enzyme whose activity is critical for the terminal maturation of infectious virions. This inhibition prevents the maturation of virions capable of infecting other cells. Drugs available in Tanzania are:

- Atazanavir (ATV).
- Lopinavir (LPV),

Ritonavir (usually used as a booster with above mentioned PIs).

Fixed dose combination

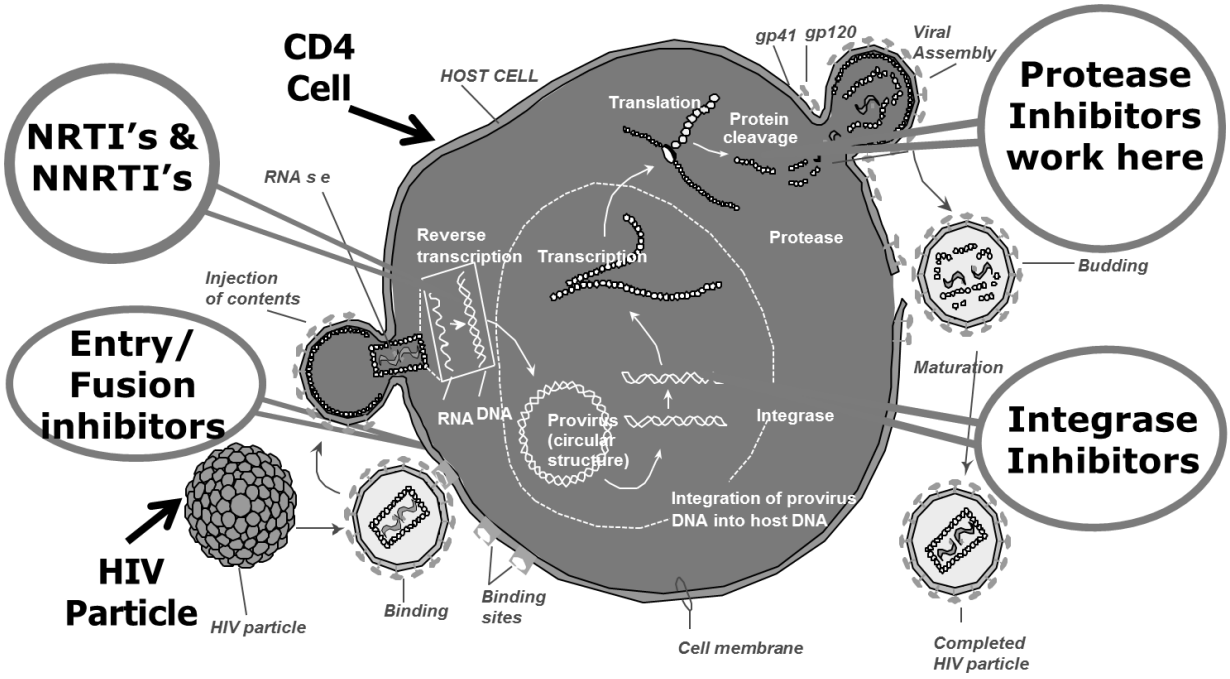
The following FDC are available in Tanzania

- Aluvia: Lopinavir + Ritonavir
- Combivir: Lamivudine + Zidovudine
- Duovir-N: Zidovudine + Lamivudine + Nevirapine
- Atripla: Tenofovir + Emricitabine + Efavirenz
- Truvada: Tenofovir + Emtricitabine
- Abacavir + Lamivudune

Handout 4.2.2: Target and Modes of Action of ARV Drugs

HIV infects CD4 cells and takes over the machinery of that cell to replicate or copy itself. The ARV drugs work by interfering with the process of HIV replication. Different ARV classes target different steps in the replication process. The NRTIs and NNRTIs interfere with the activity of the reverse transcriptase enzyme. This makes the HIV unable to copy its RNA into DNA. The PIs interfere with the activity of the protease enzyme. This makes the HIV unable to cut its viral proteins so they can be packaged into a new virus. Other classes of drugs that are not available in Tanzania are fusion inhibitors and integrase inhibitors. Fusion inhibitors block the entry of HIV into the CD4 cell. Integrase inhibitors don't allow the copy of the viral DNA to incorporate into the host cell genome for replication.

Targets and Modes of Action of ARV Drugs:



Handout 4.2.3: Paediatric Dosing Charts for ARVs

Number of tablets of child-friendly solid formulations for morning and evening dosing

Drug	Strength of paediatric tab (mg)	Children 6 weeks of age and above										Strength of adult tb(mg)	Number of tablets by weight-band	
		Number of tablets by weight-band morning and evening											25-34.9	
		3-5.9kg		6-9.9kg		10-13.9		14-19.9		20-24.9				
		am	pm	am	pm	am	pm	am	pm	am	pm		am	pm
SINGLE DRUGS														
AZT	60	1	2	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
ABC	60	1	2	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
NVP	50	1	2	1.5	1.5	2	2	2.5	2.5	3	3	200	1	1
COMBINATIONS														
AZT/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150	1	1
AZT/3TC/NVP	60/30/50	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150/200	1	1
ABC/AZT/3TC	60/30/30	1	2	1.5	1.5	2	2	2.5	2.5	3	3	300/150/150	1	1
ABC/3TC	60/30	1	1	1.5	1.5	2	2	2.5	2.5	3	3	b		
LPV/r[C]	100/50	NR	NR	2	1	2	2	2	2	2	2	100/25	3	3

Notes:
a. See ABC/3TC FDC closing table.
b. Higher doses of LPV/r may be required when co-administered with enzymes-inducing drugs such as NVP, EFV, Los-ampernavie (FPV), Rifampicin

Ml of liquid formulation and number of tablets or capsules of adult solid formulation for morning and evening dosing

Drug	Strength of pediatric syrup/ tab(mg)	Children 6 weeks of age and above									
		Number of tablets by weight-band morning and evening									
		3-5.9 kg		6-9.9 kg		10-13.9kg		14-19.9 kg		20-24.9 kg	
		am	pm	am	pm	am	pm	am	pm	am	pm
AZT	10 mg/ml 300 mg	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	0.5	0.5	1	0.5
ABC	20 mg/ml 300 mg	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	0.5	0.5	1	0.5
3TC	10 mg/ml 150 mg	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	0.5	0.5	1	0.5
NVP	10mg/ml; 15mgor20mg	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	1	0.5	1	0.5
LPV/r	80/20 mg/ml	1or1.5mlb	1or1.5mlb	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml

Notes:
b LPV/r liquid for 3-3.9 kg, use 1 ml a.m and 1 ml p.m; for 4-5.59 kg use 1.5 ml p.m. In addition, higher doses of LPV/r may be required when co-administered with enzymes- inducing drugs such as NVP, EFV, FPV or Rifampicin.

Drug	Strength	Number of tablets or capsules by weight-band once daily					Strength of tab.cap (mg)	Number of tab/cap by wt band once daily
		3-5.9kg	6-9.9kg	10-13.9	14-19.9	20-24.9		24-34.9
		Once daily	Once daily	Once daily	Once daily	Once daily		Once daily
SINGLE DRUGS								
EFV[a]	200mg	NR	NR	1	1.5	1.5	200	2
a. EFV is not recommended for children below 3 years and weighing less than 10kg								
NR=not recommended EC=enteric coated								

WHO DOSING RECOMMENDATIONS FOR EXISTING PEDIATRICS FDCS

Dosing Schedules: AZT/3TC/NVP (50/60/30mg) |AZT/3TC (60/30mg)

Weight range (kg)	< 5.9 kg 6	6-9.9 kg	10-13.9 kg	14-19.9 kg	20-24.9 kg	25 kg and Above
INDUCTION DOSE AZT/3TC/NVP (50/60/30mg) Tablet AZT/3TC(60/30mg)Tablet	1A.M	1.5A.M	2A.M	2.5 A.M	3A.M	4A.M or 1 tab OD of 200/300/150mg (Adult formulation)
	1P.M	1.5P.M	2P.M	2.5 P.M	3 P.M	4 P.M or 1 tab OD of 300/150mg (Adult formulation)
MAINTANANCE DOSE AZT/3TC/NVP (50/60/30mg) Tablet	1 BD	1.5 BD	2 BD	2.5 BD	3 BD	4 BD or 1 tab BD of 200/300/150mg (Adult formulation)
	0.5 P.M	0.5 P.M	1 P.M	1 P.M	1.5 P.M	2 P.M or 1 tab OD of 30/150mg (Adult formulation)

Handout 4.2.4: Common Side Effects of First-Line Antiretroviral Therapy

ARV Side Effects

Many of the ARV medicines have side effects. Some of these side effects (i.e. nausea) are mild and will improve over time without changing the medication. However, other side effects may be more severe (i.e. peripheral neuropathy) or even life threatening (i.e. Steven's Johnson Syndrome) requiring change of the drug.

Side effects can be classified according to severity (Grade 1-4) and the action needed is determined by the grade.

Grade	Effects	Action Needed
Grade 1 (Mild)	Transient or mild discomfort, no limitation in activity, no medical intervention needed	Does not require change in therapy, symptomatic treatment may be given
Grade 2 (Moderate)	Limitation in activity, some assistance may be needed; no or minimal medical intervention/ therapy required	Continue ART if possible; if no improvement consider substitution with medicine in same class but with different toxicity profile
Grade 3 (Severe)	Marked limitation in activity, some assistance usually required, medical intervention required, possible hospitalization	Substitute offending agent without stopping therapy
Grade 4 (Severe, life-threatening)	Extreme limitation in activity, significant assistance required, significant medical intervention/ therapy required, hospitalization or hospice care	Discontinue all ARV medicines, manage medical event until patient stable and toxicity resolved

Handout 4.2.5: Severe toxicities of ARVs in infants and children, and potential drug substitutions

Toxicity Events	Responsible ARV	Suggested first-line ARV drug substitution
Acute symptomatic hepatitis	NVP	EFV If the patient cannot tolerate either NNRTI, use boosted PI
Severe or life-threatening rash (Stevens-Johnson syndrome)		Boosted PI
Hypersensitivity reaction	ABC	AZT
Lipoatrophy/metabolic syndrome	LPV/r	If LPV/r is used in first line ART for children, use an age appropriate NNRTI (NVP for children younger than 3 years and EFV for children 3 years and older) ATV/r can be used for children older than 6 years
Severe anaemia or neutropenia	AZT	Substitute with ABC if < 35 kg Substitute with TDF if ≥ 35 kg
Severe gastrointestinal intolerance		
Persistent and severe central nervous system toxicity	EFV	NVP
Tubular renal dysfunction	TDF	If TDF is being used in first line ART, substitute with AZT or ABC If TDF is being used in second line ART, substitute with ABC

Worksheet 4.2.1: Case Studies

Instructions:

- In small groups, read the case studies below and answer the questions.
- You will have approximately 15 minutes to complete the worksheet.
- Be prepared to share and discuss your responses in plenary.

Case Study 1: Rash

A 13 year old child has been commenced on AZT+3TC (BD) and NVP (OD). She returns after 2 weeks with a dry, itchy rash over her entire body.

1A. What grade is her rash?

1B. What action should be taken?

Case Study 2: Hepatotoxicity

A 10 year old boy has been taking ABC/3TC/NVP twice a day for 6 weeks. He presents with abdominal pain, nausea and malaise. He has marked RUQ tenderness, but is not clinically jaundiced.

2A. What test should be performed urgently?

An ALT is performed urgently and the result comes back at **462 IU** (Normal range 0-40 U/L)

2B. What grade hepatitis is this?

2C. What is the most likely cause?

2D. What action should be taken?

Case Study 3: Haematological Toxicity

A 6 year old girl before starting ART has a baseline Haemoglobin of 12.4gm/dL. She is started on AZT/3TC + EFV. Routine Hb check at 1 month is 6.8 – an urgent repeat Hb confirms the result.

3A. What is the grade of adverse drug reaction?

3B. What drug is the most likely cause?

3C. What action should be taken?

Continued on next page

Case Study 4: TB Symptoms

A child develops symptomatic TB disease or worsening of signs and symptoms of TB not caused by TB-treatment failure or another infection/illness soon after initiation of HAART. Clinically you find new infiltrations, lymphadenopathy, fever, neurologic symptoms (peripheral neuropathy).

4A. What is the diagnosis?

4B. What should you do?

Worksheet 4.2.2: Determining Regimens and Dosages

Instructions:

- In small groups, determine the regimen and dose for each patient listed below.
- Refer to the dosage chart as needed.
- Be prepared to share and discuss your responses in plenary.

1. **Patient is 3 years of age, Hb 9.9g/l, 12 kg, 87cm ready to start on 1st line ARVs.**

What is your recommended regimen & dose:

2. **Patient is 5 years old, Hb 11.3 g/l, 14 kg, 108 cm, on Anti-TB maintenance is to start on first line ART.**

What is your recommended regimen & dose:

3. **Patient is 6 years old, Hb 7.0 gm/dl, 15 kg, 110 cm, on Fe SO4 is to start first line ART.**

What is your recommended regimen & dose:

4. **Patient is 13 years old Hb 10.6gm/dL, 29 kg, 132 cm, has numbness in legs and has to start first line ART.**

What is your recommended regimen & dose:

5. **Patient is 9months, Hb 8.8 gm/dl, 6.5 kg, 62 cm has to start first line ART.**

What is your recommended regimen & dose:

Session 3: Initiating and Monitoring ART in Children

Total Session Time: 45 minutes

Learning Objectives

By the end of this session, participants will be able to:
- Describe the eligibility criteria for initiating ART in children
- Explain the social and biological aspects to be assessed prior to initiating ART
- Explain appropriate regimens for ART initiation in children
- Explain outcomes of ART in children

Eligibility Criteria for Initiating ART in Children

Eligibility Criteria for Initiation of ART to HIV Positive Children Under 15 yrs
All children below 15 years of age who have a confirmed diagnosis of HIV, regardless of WHO clinical stage or CD4 cell count. All HIV exposed children aged less than 18 months with a presumptive HIV infection; such as a child who have a positive rapid antibody test and meets WHO criteria for severe HIV disease.

Age	When to Start ART
Children 0-15	Initiate ART to all regardless of WHO clinical stage or CD4 cell count
Children below 18 months who qualify for presumptive diagnosis	Start ART while awaiting virological confirmation

Presumptive Diagnosis of Severe HIV Disease is when:
- Infant is confirmed HIV antibody positive **AND**
- Diagnosis of any AIDS- indicator condition can be made **OR**
- The child is symptomatic with two or more of the following:
  - Oral thrush
  - Severe pneumonia
  - Severe sepsis

Continue cotrimoxazole prophylaxis, begin ART and do confirmatory testing as soon as possible.

Other factors that support presumptive diagnosis of severe HIV disease include:
- Recent HIV-related maternal death
- Advanced HIV disease in the mother
- CD4< 25%

Presumptive diagnosis applies only to children <18 months who are HIV antibody test positive but PCR is not available. If children meet the criteria for presumptive diagnosis they

should be started on ART. When PCR becomes available the test should be done. If the result is positive continue ART but if the result is negative and there is no risk of HIV transmission (stopped breastfeeding for more than 6 weeks), stop ART. If the child is breastfeeding, the breastfeeding guidelines should be consulted.

Social and Biological Aspects to be Assessed before Starting ART, Appropriate Regimens for ART Initiation in Children & Outcomes of ART in Children

Social and Biological Aspects to be Assessed before Starting ART

Social Aspects

The following social criteria should be met before starting antiretroviral treatment:

- Infants and children depend on their caregivers
- A clearly defined and committed caregiver is necessary for the successful treatment of young children
- Child's, caregiver's and family's readiness to initiate ART
- Access to social support services
- Disclosure status

In the case of HIV infected children the caregiver, who may be either a parent or other family member or a guardian, needs to be involved fully in the care and treatment. Counseling on the prognosis and the demands of ART is vital from the outset. Family and social support is important for the success of ART.

Biological Factors

These include:

Age:

- The risk of disease progression is inversely correlated with age
- Criteria distinguish children <15 years of age and older children
- Medication recommendations vary with age and co-morbidities

Patient Assessment Prior to ART Initiation

Before ART initiation, a patient should be assessed based on:

- **History taking:**
  - Confirm HIV exposure status and/or HIV infection status if not previously done or documented
  - Review previous ARV exposure (e.g. for PMTCT prophylaxis)
  - Review concomitant medications
- **Evaluate for existing co-infections:**
  - Screen all patients for tuberculosis
  - STI screening indicated for sexually active adolescents
- Neuro-developmental assessment;
  - Assess developmental milestones
- Nutritional assessment:
  - Measure weight, length/height, and head circumference
  - Use Growth Charts interpret the measurements
- Perform complete physical examination
- Perform WHO Clinical Staging

- **Laboratory:**
  - Complete blood count: in the areas where complete blood count is unavailable check hemoglobin levels"
  - Liver function tests (ALT/SGPT)
  - CD4 count or percentage
  - Viral load (where available)
  - Other tests as indicated by presenting symptoms

Patient and Family Readiness

Patient readiness means that the family has been fully prepared for ART. This needs to:

- Confirm availability of family and social support services
- Identifying a primary committed caregiver and provide adherence counseling
- Encourage primary caregiver to identify and include a 'treatment supporter'
- Age-appropriate disclosure to child prior to initiation
- Reinforce importance of excellent adherence
- Ensure access to primary care and treatment services

If this preparation is not correctly planned and done properly, then antiretroviral treatment is unlikely to be successful due to poor adherence. Therefore, patient readiness is very important and is needed before antiretroviral treatment can be started.

Treatment of ARV-Exposed Patients

Infants and children <2 years with NVP exposure as a component of PMTCT should receive a PI-based regimen (LPV/r) for treatment.

Selection of an appropriate regimen for a patient who has already been exposed to ARVs is complex, therefore, review:

- Previous exposure and reason – PEP, PMTCT, ART therapy
- Reason for discontinuation – toxicity, poor adherence, failure, defaulting from care

NOTE: Discuss with more experienced clinician or refer.

Monitoring Children on ART

Close monitoring of therapy is important. Checking on resolution of clinical signs or appearance of new symptoms is crucial for determining if a regimen is working or if side-effects are being experienced.

- Clinical
- Laboratory: Laboratory parameters help document response and toxicities to ART.
- Side effects/toxicity
- Treatment adherence
- Appointment adherence
- Psychological: Psychological effect of HIV and ART needs to be closely followed up and addressed. Taking of drugs on a daily basis may be an indirect disclosure of the HIV diagnosis.

Anthropometric measurements must be noted at each follow-up visit. Severe side effects should be reported immediately to the clinic.

Monitoring Schedule
Every 2 weeks for the first 4 weeks thereafter Monthly for clinical evaluation and refill

The main reason for follow up is to assess progress and detect side effects and treatment failure; which can be clinical, immunological and/or virological. New symptoms may indicate immune reconstitution or treatment failure.

NOTE that growth, development and nutrition should be monitored monthly.

It is essential to:
- Take patient history and physical exam at each visit
- Ensure that the lab results are well-interpreted
- Provide on-going counselling on adherence (including pill-counting and discussing any problems)

Other follow up activities such as:
- Re-assessing the patient's health status
- Prescribing **Cotrimoxazole** prophylaxis for WHO clinical stage 2,3 and 4
- Order laboratory investigations as needed (see handout on lab schedules)
- Treat new conditions (OIs, other HIV-related conditions)-look out for IRIS
- Assessing mental status; treat depression (medication, counselling) and referring to mental health clinic if needed

Clinical Monitoring
Monthly monitoring:
- Interval medical history and symptom check
- Weight, height, and head circumference for children <2 years, physical exam
- Nutritional assessment
- Developmental milestones
- Neurologic symptoms
- Side effects/toxicity
- Immune reconstitution the first six months

Assess adherence; Ask for demonstration of dose and administration of medication at each visit, and recalculate dose and dispense more doses.

Laboratory Monitoring
- Check CD4 count/percentage every 6 months;
  - Measure more frequently based on clinical presentation or disease progression
- Monitor hemoglobin at baseline, at initiation of ART and as required
- Other investigations as indicated clinically for intercurrent illnesses or signs of toxicity
- Where available measure viral load as required

CD4 monitoring
1. Measure CD4 if new clinical staging events develop, including growth faltering and neuro-developmental delay.
2. Where capacity for CD4 measurement is limited, target the use of CD4 monitoring to assess the significance of clinical events.

Viral load monitoring

3. Viral Load determination is desirable, but not essential, prior to initiating ART.
4. Viral Load should be assessed to confirm clinical or immunological failure, prior to switching a treatment regimen.

Routine clinical and laboratory monitoring

5. For infants and children, measure haemoglobin at week 8 after initiation of AZT-containing regimens, or more frequently if symptoms indicate.
6. Laboratory monitoring for toxicity should be symptom directed.

Refer to ***Handout 4.3.1: Laboratory Parameters for monitoring infants and children at baseline, before and during ART*** *on page* ***209****.*

Adherence Monitoring

Adherence strategies are as important as any choice of ARV drugs. Hence adherence should be assessed at each visit:

- Subjective – dose recall
- Objective – pill counts or syrup volume: Pill boxes/ calendars/diaries or other practical tools should be used to support adherence.

Good appointment adherence does not necessarily correlate with good medication adherence. Detailed information on adherence will be covered in the coming module.

Psychological Monitoring

Psychological monitoring can be assessed by asking about school attendance record and performance and enquire about relationship with other groups of people and stigmatization at school such as:

- Progress at school
- Relationships with family members, friends
- Attitude to daily medicine taking, adherence
- Progress with disclosure: disclosure issues become more important as the child grows and begins to question more and more.
- Development into adolescence – sexual awareness, behavioural issues

Older children should be allowed to take charge of their medicine-taking which can only be achieved after full disclosure and counseling. Tailor-made regimens to suit teen-agers may be considered.

Key Points

- Biological factors and social factors are important in determining when to initiate ART
- Choice of ARV medicines should always be guided by the National ARV Guidelines

Handout 4.3.1: Laboratory Parameters for Monitoring Infants and Children at Baseline, Before and During ART

Laboratory Tests for Diagnosis and Monitoring	Baseline (at entry into care)	At initiation of first-line or second-line ART regimen	Every six months	As required or symptom-directed
HIV diagnostic testing	✓			
Haemoglobin[a]	✓	✓		✓
WBC and differential count				✓
%CD4+ or absolute CD4 cell count[b]	✓	✓	✓	✓
Pregnancy testing in adolescent girls		✓		✓
Full chemistry (including but not restricted to, liver enzymes, renal function, glucose, lipids, amylase, lipase, and serum electrolytes)[c]				✓
HIV VL measurement[de]				✓
OI screening (where possible)	✓			✓

Notes:

a. Haemoglobin monitoring at week 8 after initiation of ART is recommended if AZT is used.
b. HIV-infected children not yet eligible for ART should be monitored with CD4 count every six months. For infants and children who develop new or recurrent WHO stage 2 or 3 events or whose CD4 count approaches threshold values, the frequency of CD4 measurement can be increased. % CD4+ is preferred in children <5 years.
c. Routine monitoring (every six months) of full chemistry, particular lipid levels, liver enzyme and renal function should be considered for infants and children on second-line drugs
d. At present, VL measurement is not a prerequisite for initiation or regular monitoring of ART in resource-limited settings. VL can be used to diagnose HIV infection and confirm clinical or immunological failure prior to switching treatment regimen.
e. VL should be assessed in infants on NNRTI-based regimens who are known to have been exposed to NNRTIs intrapartum or through breastfeeding.

Session 4: When to Stop or Change ART

Total Session Time: 45 minutes

Learning Objectives

By the end of this session, participants will be able to:
- Explain the criteria for treatment response
- Explain the indications for changing or stopping an ARV regimen
- Describe the medicine regimen recommended in Tanzania for second line treatment in children

Criteria for Treatment Response & Indications for Changing or Stopping an ARV Regimen

Clinical Response to ART

These are important signs and symptoms of clinical response on ART:
- Improvement in growth in children who were previously failing to grow
- Improvement in neurological symptoms and development in children with delayed milestones or encephalopathy
- Decreased incidence of infections (bacterial, thrush, and other OIs)

Immunological Response to ART

In most children CD4 rise with the initiation of therapy and immune recovery. CD4 should rise during the first year of treatment.

In children with severe immunosuppression, immune recovery may take longer; the lower the CD4 at the start of ART, the slower the recovery.

Virological Response to ART

The initial ARV regimen will be expected to achieve
- A one-log decline in HIV RNA by one to two weeks,
- A two log decline by four weeks and
- Undetectable viral load by 8 to 24 weeks, regardless of prior treatment experience

Viral load reductions may be more rapid in patients who are treatment-naïve, have higher CD4 cell counts, and/or lower levels of baseline viremia.

Being "naïve" to ARV medicines means the patient has never been exposed to ARVs before. An undetectable viral load means that the level of HIV in your blood is below the threshold needed for detection by this test, usually less than 50 copies/mL.

Indications of Changing or Stopping ART

Regimen may need to be changed due to medicine-medicine interactions e.g. patient starting therapy for TB, would change NVP to EFV.

Adverse drug events/Toxicities:
- Intolerable side effects
- Medicine interactions
- Pregnancy

Treatment Failure:
- Clinical Failure
- Immunological Failure
- Virological Failure

Women who become pregnant on ART should be changed to TLE(Tenofovir+ lamivudine and Efavirenz)"

Sometimes you have to stop/change ARV therapy in cases of:
- New clinical data/review of guidelines
- Patients refusal

For patients whom ARV therapy has been stopped, other medical, palliative and psychosocial support continues to provide.

Clinical Criteria defining Treatment Failure
Clinical conditions indicating a need to change to 2nd line therapy include:
- Poor growth (failure to gain weight, declining or stationary weight) over a 6 months period, after excluding other causes such as TB, food insecurity
- No improvement on neuro-developmental milestones
- Development of HIV encephalopathy
- Recurrent infections, such as oral candidiasis, persistent diarrhea, recurrent severe bacteria pneumonia etc
- Advancement from one clinical stage to another or new evidence of new WHO clinical stage 3 or 4 disease

ARVs should not be changed prematurely. Worsening of disease after initial clinical improvement or the development of a new or recurrent OI soon after initiating ART in a child does not necessarily indicate treatment failure and is not always an indication to stop or switch ART. Assess for good adherence and think of IRIS.

Development of TB may not be an indicator of clinical failure, and should not require consideration for second line therapy.

Immunological Criteria defining Treatment Failure
Immunological failure indicating a need to change to 2^{nd} line therapy is recognized as developing or returning to the following age related immunological thresholds after at least 24 weeks on ART, in a treatment adherent child:

Children <5 years of age	CD4 count of <200 cells/mm^3 or <10%
Children ≥5 years of age	CD4 count of <100 cells/mm^3

Preferably, at least two CD4 measurements should be available. Use of %CD4+ in children <5 years and absolute CD4 counts in those ≥5 years of age is preferred. If serial CD4 values are available, the rate of decline should be taken into consideration.

According to the WHO Consolidated Guidelines on the use of Antiretroviral drugs for treating and preventing HIV infection 2013 pg. 134.
Immunological Failure: Immunological treatment failure can be identified by examining baseline CD4 and the initial immunological response to ART. Treatment failure is characterized by a drop in the CD4 to values at or below their age-related CD4 threshold for the initiation of treatment after initial immune recovery following the initiation of ART. Thus recognition of treatment failure on the basis of immunological values relies on comparison with previous CD4 values.

TLC, while useful to guide when to initiate therapy in the absence of CD4, it is a poor indicator of treatment success and should not be used for the evaluation of response to ART therapy.

Virological Criteria defining Treatment Failure
Virological failure is recognized if the child is adherent to the ART regimen, more than 6 months from ART initiation. Virological conditions indicating a need to change to 2nd line therapy include:

- Plasma viral load >1000 copies/ml based on two consecutive viral load measurements after 3 months for an individual with 6 months of therapy, with adherence support

Reasons for ARV Regimen failure
Poor adherence is the most common reason for failure of ART. Hence some other reasons can include:

- Poor adherence; Always check adherence since this is the most common reason for treatment failure.
- Problems of medicine administration and availability
- Pharmacokinetic reasons: medicine-medicine interactions; food-ARVs interaction
- Tolerability: taste, vomiting, food interaction
- Resistance

Poorly tasting or difficult to take medications and formulations are difficult to take on long-term basis. When resistance is suspected and facilities for testing are available this should be used to guide the change in regimen.

Considerations for Changing ART in Treatment Failure
When changing ART caused by treatment failure, the following should be considered:

- Assess and review adherence;
  - Review patient medications
- Change all the ARVs in the regimen if possible
- Consider overlap in resistance
- Consider and discuss quality of life issues especially if complex new regimens are to be used

*Refer to **Handout 4.4.1: General Information on Changing ARV Therapy** on **page 215** for more information.*

Treatment Failure Protocol
Procedures to follow in treatment failure include:

- Prescribe second line:
  - Review all medications for medicine-medicine interactions
  - Consider quality of life issues
- Counsel child & caregiver on new medicines
- Schedule further adherence counseling and more frequent follow up appointments

For adolescents >12 years of age with hepatitis B, who had been on Tenofovir disoproxil fumarate (TDF) + Emtricitabine (FTC) + NNRTI as first line, the preferred second line is Boosted PI + 2NRTI.

Actions to be taken in Poor Adherence

- Refer for comprehensive and adherence counseling
- Schedule regular appointments to assess adherence
- If child/caregiver commitment to continuation of ART is still in doubt decisions need to be made about discontinuing ART altogether;
  - e.g. in multidisciplinary team meeting

Paediatric Second-Line Regimens

First line regimen	Second line regimen:
If client is below 3 years & started on LPV/r based 1st Line regimen	**Continue with same regimen**
If client is below 3 years & started on AZT/3TC/NVP	**ABC/3TC+LPV/r**
If client is above 3 years & started on ABC based 1st Line regimen	**AZT/3TC+LPV/r**
If client is above 3 years & started on AZT based 1st Line regimen	**ABC/3TC+LPV/r**

*Refer to **Worksheet 4.4.1: Case Studies** on **page 217** for the case studies.*

Key Points

- Treatment failure is assessed using WHO clinical, immunological and virological criteria
- Give enough time before changing a regimen
- Always check adherence first when suspecting treatment failure
- In case of treatment failure, change at least 2 medicines according to national guidelines

Sources/Bibliography

- *National guidelines for the management of HIV and AIDS. Fifth Ed. May 2015*

Handout 4.4.1: General Information on Changing ARV Therapy

- Although the efficacy of different combination ARVs in children probably can be extrapolated from clinical trial data obtained for adults, data are limited regarding the pharmacokinetics, appropriate dosing, and short- and long-term safety of various combinations in children.

- The choice of a new ARV regimen is dictated by the indications that warranted the change in therapy (e.g. toxicity/intolerance vs. drug resistance vs. poor adherence) and the available alternative ARV agents.

- A decision to change therapy and the proposed new regimen to be chosen should partly take into account the impact of the changes on future treatment options.

- When changing therapy because of treatment failure, assess adherence to therapy as a potential cause of failure.

- If the patient is adherent to the prescribed drug regimen, assume the development of drug resistance and, if possible, change to at least two new ARVs. Change in one drug or addition of a drug to a failing regimen is suboptimal. The new regimen should include at least three drugs, if possible. Consider the potential for cross-resistance between ARVs when choosing new drugs.

- A change to a new regimen, especially one containing PIs or NNRTIs, must include a discussion of treatment adherence issues by the healthcare provider with the patient, when appropriate, and caregivers of the infected child. Recognize that certain medications are difficult to take in combination because of exacting and often conflicting requirements e.g. with/without food and other ARVs. Palatability, pill size, number and dosing frequency are part of the considerations when choosing the new regimen and should be discussed with the child, and when appropriate, with the child's caregivers.

- When considering changing therapy because of disease progression in a patient with advanced disease, consider the patient's quality of life.

Worksheet 4.4.1: Case Study

Directions: In groups of 4 or 5, have participants read the case studies below (found in their participant manual) and answer the questions which follow. Provide them 20 minutes to complete the activity. After 20 minutes they will share answers with the rest of the group.

Case study 1

A 28 yr. old mother brings her vertically-infected (presumed), 7 yr. old child in for routine follow up. The child is on the national first line HAART regimen of AZT, 3TC and NVP but her CD4 count has been decreasing over the last two visits (from 599 to 457).

- What is your next step?

You ask the mother if she is giving the medicine to the child and she says "yes." You then ask the child if she is taking the medicine and she replies "no." The child is unaware of her status. The mother is also unaware of her own status and has refused to be tested for HIV despite being counseled numerous times to do so. When she is asked to test again she replies, "I am thinking about it."

Case study 2

Rehema 9 yrs old, is on d4T, 3TC and NVP for 18 months. She gained 6kg in the first 6 months and 7 cm. For the last 6 months there is neither weight gain nor growth. The CD4 count at start was 192/ml, 356/ml at 6 months, 423/ml at 12 months and now 273/ml. Last month she had a pneumonia which responded to Amoxicillin.
O/E she has a new tineacapitis and on auscultation signs of a pneumonia. Her father who is very concerned about her, got a VL done at a private Hospital, showing 70,390 copies/ ml.

- What steps are you taking?