

HIV/AIDS

Learning objectives

Upon completion of the chapter, the students will be able to:

1. Explain the routes of transmission for HIV and its natural disease progression.
2. Identify typical and atypical signs and symptoms of acute and chronic HIV infection.
3. Identify the desired therapeutic outcomes for patients with HIV infection.
4. Recommend appropriate first-line pharmacotherapy interventions for patients with HIV infection.
5. Recommend appropriate second-line pharmacotherapy interventions for patients with HIV infection.
6. Describe the components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for HIV infection.
7. Educate patients about the disease state, appropriate lifestyle modifications, and drug therapy required for effective treatment.

Introduction

- AIDS was first recognized in **1981** in young homosexual men with significant immune deficiency.
- Since then, **HIV-1** has been clearly identified as the major cause of AIDS.
- **HIV-2** is much less prevalent than HIV-1, but also causes AIDS.
- HIV primarily targets **CD4+ lymphocytes**, which are critical to proper immune system function

- If left untreated, patients experience a prolonged asymptomatic period followed by rapid, progressive immunodeficiency.
- Therefore, most complications experienced by patients with AIDS involve **opportunistic infections** and **cancers**.

- Several risk behaviors for the acquisition of HIV infection have been identified in the United States, most notably the practice of **anorectal intercourse** and the sharing of **blood-contaminated needles** by injection-drug users.
- In many resource-limited countries, the majority of HIV transmission occurs via **heterosexual intercourse** (70 to 80% of HIV infections) and from child bearing women to their offspring

Etiology and pathogenesis

- HIV-1 is a **retrovirus** and member of the genus ***Lentivirus***.
- These viruses have a characteristically prolonged latency period.
- There are two molecularly and serologically distinct but related types of HIV: **HIV-1 and HIV-2**.
- HIV-2 is a less common cause of the epidemic and is found primarily in **West Africa**.

Transmission

- HIV infection occurs through **three primary modes of transmission:**
 - ✓ By Sexual contact
 - ✓ By contact with blood or blood products (Parenteral) and
 - ✓ From mother to child during gestation, delivery, or breast-feeding (Perinatal)

Risk factors for transmission

- high viral load in the source patient
 - whether the individual is taking antiretroviral therapy (ART) and the stage of HIV disease
 - higher during acute than chronic infection
- sexually transmitted infections (STIs)
- Sexual behavior
- lack of circumcision
 - circumcision reduces the risk of female-to-male HIV transmission by 50 to 60 percent
 - However, male circumcision of HIV-infected men does not appear to decrease the risk of HIV transmission to the female partner
- host and genetic factors

Sexual Transmission

- The highest risk appears to be from **receptive anorectal intercourse** at about **1.4 transmissions per 100 sexual acts**
- Transmission risk is lower for receptive vaginal intercourse
- Insertive sex acts have lower risk than receptive acts.
- Factors that affect the probability of infection include
 - ✓ the stage of HIV disease and viral load in the index partner
 - ✓ Individuals with genital ulcers or STDs are at high risk
 - ✓ compromised mucosal surfaces, or
 - ✓ in the case of men, has not been circumcised(Male circumcision reduce risk of male acquisition of HIV approximately by 50%)
- **Appropriate Condom** use reduces the risk of transmission by more than 90%.

Parenteral Transmission

- Primarily occurs through injection-related supplies or sharing of needles.
- Health care workers have a risk of acquiring HIV infection through percutaneous **needle stick injury** (0.3% percutaneous and 0.1% from mucocutaneous).

Perinatal infection

- Also known as **vertical transmission** or mother-to-child transmission [**MTCT**].
- The risk of MTCT is approximately **35%** in the absence of ART
- It can occur during **gestation** (rare), during labor and **delivery**, and during **breast-feeding**.
- Risk of Transmission
 - ✓ Labor and delivery $\approx 20\%$
 - ✓ Breast feeding $\approx 15\%$

- Factors that increase the likelihood of vertical transmission include
 - prolonged rupture of membranes,
 - chorioamnionitis,
 - genital infection during pregnancy,
 - preterm delivery,
 - vaginal delivery,
 - birth weight less than 2.5 kg,
 - high maternal viral load

Pathogenesis

- Once HIV enters the body, an outer viral glycoprotein called **gp120 binds** to CD4 receptors found on the surface of monocytes, T lymphocytes, macrophages and dendritic cells.
- This allows further binding to other **chemokine receptors** on the cell surface called **CCR5** and **CXCR4**.

- After the virus has attached to CD4 and chemokine receptors, another viral glycoprotein (**gp41**) assists with **viral fusion** to the cell and internalization of the **viral contents**.
- The viral contents include single-stranded RNA, **reverse transcriptase** & other enzymes.
- Using the single-stranded viral RNA as a template, reverse transcriptase synthesizes double-stranded DNA.

- The single-stranded viral RNA is removed from the newly formed DNA strand by **ribonuclease H**, and reverse transcriptase completes the synthesis of double-stranded DNA.
- The viral reverse transcriptase enzyme is highly **error-prone**, and many **mutations** occur in the conversion of RNA to DNA.
- This inefficient reverse transcription activity is responsible for HIV's ability to rapidly mutate and develop drug **resistance**.

- A chronic infection is established when the double stranded DNA migrates to the host cell nucleus and is integrated into the host cell chromosome by an HIV enzyme called **integrase**.
- Once the cell becomes activated by antigens or cytokines, HIV replication starts:
- Host DNA polymerase transcribes viral DNA into messenger RNA, and messenger RNA is translated into viral proteins.

- These proteins assemble beneath the bilayer of the host cell, a nucleocapsid forms containing these proteins, and the virus buds from the cell.
- After budding, the virus matures when an HIV **protease enzyme** cleaves large polypeptides into smaller functional proteins.
- Without this process, the virus is unable to infect other cells.

Clinical Presentation

TABLE 40-3 Clinical Presentation of Primary HIV Infection in Adults

Symptoms

Fever, sore throat, fatigue, weight loss, and myalgia

40–80% of patients will also exhibit a morbilliform or maculopapular rash usually involving the trunk

Diarrhea, nausea, and vomiting

Lymphadenopathy, night sweats

Aseptic meningitis (fever, headache, photophobia, and stiff neck) may be present in a one-fourth of presenting cases

Other

High viral load (exceeding 50,000 copies/mL in the adult or 500,000 copies/mL in the child)

Persistent decrease in CD4 lymphocytes

Diagnosis

- Screening method for HIV is an enzyme-linked immunosorbent assay (**ELISA**), which detects antibodies against HIV-1 and is both highly sensitive and specific.
- Positive ELISA are repeated in duplicate and if one or both tests are reactive, a confirmatory test is performed for final diagnosis.
- Rapid tests are also available for diagnosis.

HIV severity is determined by following:

- **Viral load** can be used as a prognostic factor to monitor disease progression and the effects of treatment.
- **CD4** lymphocytes count in the blood is a surrogate marker of **disease progression**.
- Normal adult CD4 lymphocyte count: 500 - 1,600 cells/ μ L, (40% - 70% of all lymphocytes)

Staging

- Ethiopia uses the WHO Staging System(developed in 1990 and revised in 2006)
- emphasized the use of **clinical parameters** to guide the management of HIV/AIDS patients.
- CD4 count not necessarily required
- Is a tool used to guide management of HIV patient in resource limited settings.
- Simple, flexible and widely used.
- Utilizes **4 clinical stages** based on the degree of immunocompromisation and prognosis.

WHO Staging of HIV/AIDS

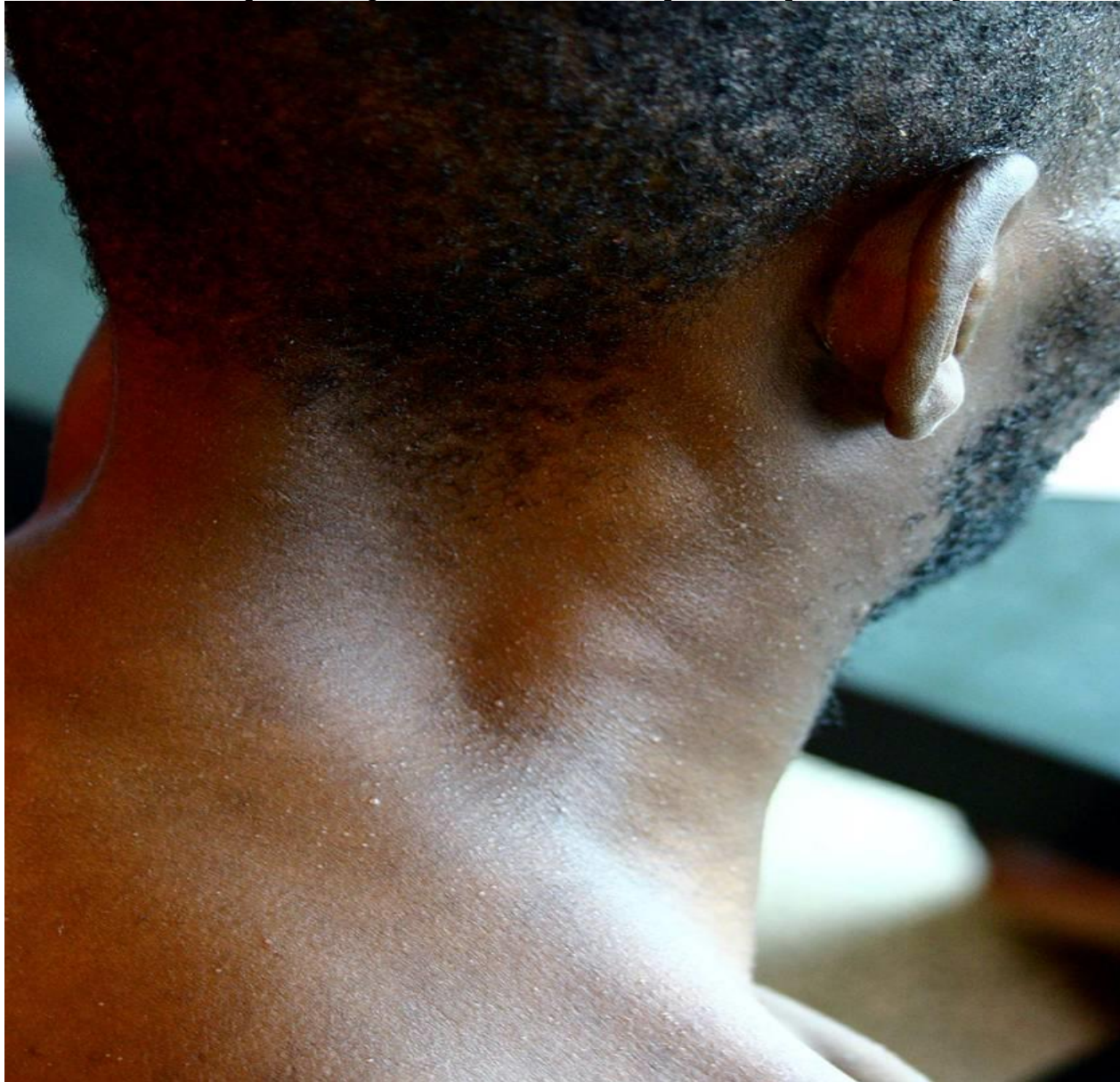
- Stage I - Asymptomatic
- Stage II - Mild disease
- Stage III - Moderate disease
- Stage IV - Advanced immunosuppression

WHO Clinical Stage I

- Asymptomatic or
- Persistent generalized lymphadenopathy (PGL)
 - Swollen lymph nodes will present bilaterally in the cervical area, under the arm, or groin.
 - Usually not painful.
 - [Rule of 1, 2, 3: > 1cm, 2 or more sites, and > 3 months].

Performance scale 1: able to carry on normal activity.

Persistent Generalized



Courtesy of Charles Steinberg MD

WHO Clinical Stage II

- Moderate unexplained weight loss (>5 and $<10\%$ of presumed or measured body weight)
- Recurrent upper respiratory tract infections [e.g. sinusitis, otitis media, tonsillitis, pharyngitis];
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulcerations

WHO Clinical Stage II (2)

- Papular pruritic eruptions [PPE]
- Seborrheic dermatitis
- Fungal fingernail infections

And/or

- **Performance scale 2:** symptomatic, able to carryout normal activity with effort but unable to do active work, requires occasional assistance

Pruritic Papular Eruption (2)



Seborrheic Dermatitis (Dandruff)



Apthous Ulcer



Dermatomal Herpes (Varicella) Zoster



Image courtesy of Tom Thacher, MD

Dermatomal Herpes (Varicella) Zoster



WHO Stage III

- Severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhoea for longer than one month
- Unexplained persistent fever (intermittent or constant for longer than one month)
- Persistent Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (TB)
- Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, ...)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

WHO Stage III (2)

- Conditions where confirmatory diagnostic testing is necessary:
 - Unexplained anaemia (<8 g/dl), and or
 - Neutropenia ($<500/\text{mm}^3$) and or
 - Thrombocytopenia ($<50\,000/\text{mm}^3$) for more than one month

Performance scale 3: bedridden $< 50\%$ of the day during last month.

Oral Candidiasis



Oral Hairy Leukoplakia



WHO Stage IV

- HIV wasting syndrome (>10%, involuntary, associated with chronic diarrhea or weakness and fever for more than 1 month)
- Pneumocystis pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)
- Oesophageal candidiasis (or candidiasis of trachea, bronchi or lung)
- Extrapulmonary TB
- Kaposi's sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)

WHO Stage IV (2)

- Central nervous system (CNS) toxoplasmosis
- HIV encephalopathy
- Extra pulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacteria infection
- Progressive multifocal leukoencephalopathy (PML)
- Disseminated mycosis (extra-pulmonary Histoplasmosis etc)
- Chronic Cryptosporidiosis
- Chronic Isosporiasis

WHO Stage IV (3)

- Recurrent septicemia
- Lymphoma (cerebral or B cell nonHodgkins)
- Invasive cervical cancers
- Atypical disseminated Leishmaniasis
- Symptomatic HIV associated nephropathy or cardiomyopathy

Performance Scale 4: bedridden > 50% of the day during the last month

Wasting Syndrome



Kaposi's Sarcoma (KS)

- Usually, multiple dark raised lesions
- Lesions themselves are not itchy and are rarely painful



Courtesy of Tom Thacher, MD

Kaposi's Sarcoma



Courtesy of Toby A. Maurer, MD, Timothy G. Berger, MD,
From [HIV InSite Knowledge Base](#)



Courtesy of CDC, Dr. Steve Kraus

Oral Kaposi's Sarcoma



Severe Chronic Herpes Simplex Ulcers



Molluscum Contagiosum and Cryptococcus



HIV Web Study (www.HIVwebstudy.org)

Supported by HRSA

Esophageal Candidiasis

- HIV infected patient with oral candidiasis and chest (sub-sternal) pain with swallowing has presumed Candida esophagitis
- Endoscopy would prove the diagnosis but is unnecessary if the patient responds to antifungal therapy



HIV Web Study (www.HIVwebstudy.org)

Supported by HRSA

T staging

- Staging while on ART to assess progress
 - uses the same clinical parameters as WHO clinical staging
 - used for monitoring of ARV treatment success or failure after six months of therapy
 - Up and down staging is possible
 - Guides when to change treatment clinically and with laboratory tests

When to Start Anti-Retroviral Therapy (ART)

- The optimal time to initiate therapy in chronic HIV infection has been a matter of debate for decades.
- The main arguments for postponing therapy were the concern for **cumulative drug toxicity** and trepidation for **drug resistance** and loss of therapeutic options.
- Today, the availability of newer medications with different mechanisms of action (eg, InSTI and attachment inhibitors) and significantly improved adverse event profiles helps mitigate these issues.

- An additional issue, until recently, was the lack of high-quality evidence of clinical benefits for initiating therapy at higher versus lower CD4 counts.
- This issue was addressed in 2015 with results from two large randomized controlled trials.
 - resulted in significantly fewer serious AIDS events and non-AIDS events as compared with delaying ART.
- In addition to these important studies, immediate ART is also known to prevent **ongoing HIV transmissions** by as much as 96% compared with delayed 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.

Treatment

Goals of Treatment

- To decrease morbidity and mortality,
- To improve quality of life,
- To restore and preserve immune function, and
- prevent further transmission

***Elimination of HIV is not possible with currently available therapies*

- **Maximal suppression of viral replication:**
 - is defined as HIV RNA concentrations undetectable (usually less than 50 copies/mL) by the most sensitive assay available.
 - After the initiation of therapy, a decline to undetectable HIV RNA in **4-6 months** is a predictor of improved clinical outcomes.
- **Degree of immune function preservation**
 - also correlates with decreased viral replication, and is measured by CD4+ T-cell counts.
 - CD4 measures are the best predictor of progression to AIDS, and help decide when to initiate treatment.

- At CD4+ T-cell counts of 200 cells/mm³ ($200 \times 10^6/L$) and lower, patients require drug prophylaxis for opportunistic infections.
- In addition to these parameters,
 - basic blood chemistry tests,
 - liver function tests,
 - complete blood counts, and
 - lipid profiles should be monitored every 3 to 6 months in patients receiving antiretroviral therapy.

Non-pharmacologic Interventions

- ❖ *Patient adherence is a key component in treatment success.*
- Counsel all patients initially and repeatedly on ways to prevent viral transmission.
- Preventing the spread of resistant virus is particularly important.
- Patients receiving antiretroviral therapy can still transmit virus to sexual partners and to those with whom they share needles or other drug equipment.

- Where both partners are HIV-positive, safe sex using condom and safe needle practices reduce the risk of super infection with differing strains of HIV and the transmission of other sexually transmitted diseases.
- Treating other sexually transmitted infections (STIs), particularly genital herpes, in HIV-infected patients may help to prevent HIV transmission.
- The presence of STIs increases genital tract HIV viral load and, correspondingly, the risk of HIV transmission to sexual partners.

❖ ***Nutrition and dietary counseling should also be included in the care of the HIV patient, as poor nutrition leads to poorer outcomes and complicates treatment.***

- Antiretroviral therapy itself introduces a host of nutritional issues, including drug–food interactions, GI adverse effects that may affect appetite and limit dietary intake, lipid abnormalities, and fat redistribution.

Pharmacologic Therapy

- The following classes of drugs are used to treat HIV infection:
 1. **Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs),**
 2. **Nonnucleoside reverse transcriptase inhibitors (NNRTIs),**
 3. **Protease inhibitors (PIs),**
 4. **Integrase inhibitors. (INSTIs)**
 5. Fusion inhibitors (Enfuvirtide)*,
 6. CCR5 receptor antagonists (Maraviroc)*, and
 7. Maturation inhibitors*

** are not available in Ethiopia.*

Current Antiretroviral Medications

NRTI

- **Abacavir**
- **Didanosine***
- **Emtricitabine**
- **Lamivudine**
- **Stavudine***
- **Tenofovir**
- **Zidovudine**
- Zalcitabine (DDC) *

NNRTI

- **Delavirdine****
- **Efavirenz**
- **Etravirine****
- **Nevirapine**

PI

- **Atazanavir*****
- **Darunavir*****
- **Fosamprenavir**
- **Indinavir**
- **Lopinavir*****
- **Nelfinavir**
- **Ritonavir**
- **Saquinavir**
- **Tipranavir**

Fusion Inhibitor

- **Enfuvirtide**

CCR5 Antagonist

- **Maraviroc**

Integrase Inhibitor

- **Raltegravir**
- **Dolutegravir**

*are phased out due to toxicity

** not available in Ethiopia

*** available in Ethiopia

Classes of Antiretrovirals

- **Fusion inhibitors: Enfuvirtide, Maraviroc**
 - Prevents fusion of the virus into a CD4 cell by preventing conformational change needed to allow virus to enter a CD4 cell
- **Nucleoside/tide reverse transcriptase inhibitors (NRTIs) or nukes**
 - Mimic naturally occurring nucleosides
 - Block viral DNA construction as they deceive reverse transcriptase

Classes of Antiretrovirals (2)

- **Non- nucleoside reverse transcriptase inhibitors (NNRTIs) or non-nukes (Nevirapine or Efavirenz)**
 - Bind to the reverse transcriptase enzyme
- **Integrase inhibitors (Raltegravir, Elvitegravir)**
 - Inhibit integration of proviral DNA into the host DNA
- **Protease inhibitors (PIs) (Lopinavir)**
 - Prevents cleavage of the protease chain

Pharmacologic Therapy for ARV-Naïve Patients

- The preferred first-line regimen for adults and adolescents is
 - **TDF+3TC+DTG** or
 - **TDF+3TC+EFV** as a once-daily dose.
- Upon its availability, use **TDF+3TC+DTG** is the preferred regimen for newly identified HIV positive adult and adolescent patients
- For adult and adolescent patients with TB/HIV co-infections, give TDF+3TC as once daily dose and DTG 50mg twice daily.

- For pregnant and breast-feeding mothers, the preferred first-line regimen is TDF+3TC+EFV as once daily dose
- In patients with depression, suicidal ideation, and previous history of acute psychosis, use alternative regimen and avoid EFV

- However, this class also has a low threshold for drug resistance (mutation causes high level cross-class resistance), and patient adherence is a critical consideration.
- In patients who cannot tolerate the above preferred first-line therapies, or have a compelling reason to choose a different agent, alternative first-line therapies are recommended.
- More complex and have higher pill burdens.

Note:

- If abacavir is included in a regimen, patients should undergo HLA-B*5701 testing prior to initiation to reduce the risk of abacavir hypersensitivity.
- Patients who test positive for the allele are at high risk (approximately 61%) of developing this reaction and should not be given abacavir.

- An abacavir allergy should also be documented in the patient's medical record to prevent future administration.
- Those patients with a negative test may receive abacavir, but should still be monitored for the development of hypersensitivity.

- **Triple NRTI therapy** is recommended *only when a first line* or alternative first-line therapy with either an NNRTI based or PI-based regimen cannot be used.
- **Abacavir + zidovudine + lamivudine** is the only regimen approved.

❖ Therapies *not recommended for initial treatment due to poor potency or significant toxicity* include:

- ✓ Nevirapine in patients with moderate to high CD4+ T-cell counts
- ✓ Ritonavir used without another protease inhibitor
- ✓ Tenofovir plus didanosine with an NNRTI

❖ **Drugs that should *not be combined due to overlapping toxicities* include:**

- ✓ Two NNRTIs
- ✓ Didanosine and stavudine
- ✓ Emtricitabine and lamivudine should not be combined because of their similar chemical structures
- ✓ Antagonism can result when stavudine is combined with zidovudine

Antiretroviral Therapy (ART)

- Combination of at least 3 drugs,
 - Usually:
 - 2 NRTIs**
 - +**
 - 1 NNRTI, or 1 Int Is or 1-2 PIs**
 - Rarely Triple NRTIs
- Therapy with only one or two agents allows HIV to overcome therapy through resistance mutations

Summary of 1st-line ART regimens for adults & adolescents

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
Adolescents (10 to 19 years) ≥35 kg (including those with TB/HIV ^b coinfection.)		AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC + NVP ABC + 3TC + EFV
Pregnant and breastfeeding women	TDF + 3TC + EFV (FDC)	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC + NVP
Children 3 years to less than 10 years and adolescents <35 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

- The decision to choose a NNRTI-based or PI-based regimen as initial therapy is based on many patient- and clinician-specific factors.
- NNRTI-based regimens have low pill burdens and may have decreased incidences of long-term adverse effects (e.g., dyslipidemia) in comparison to some PI-based regimens.

Second line regimens

Preferred 2nd line regimens for adults and adolescents (≥10 years)

If AZT was used in first-line ART

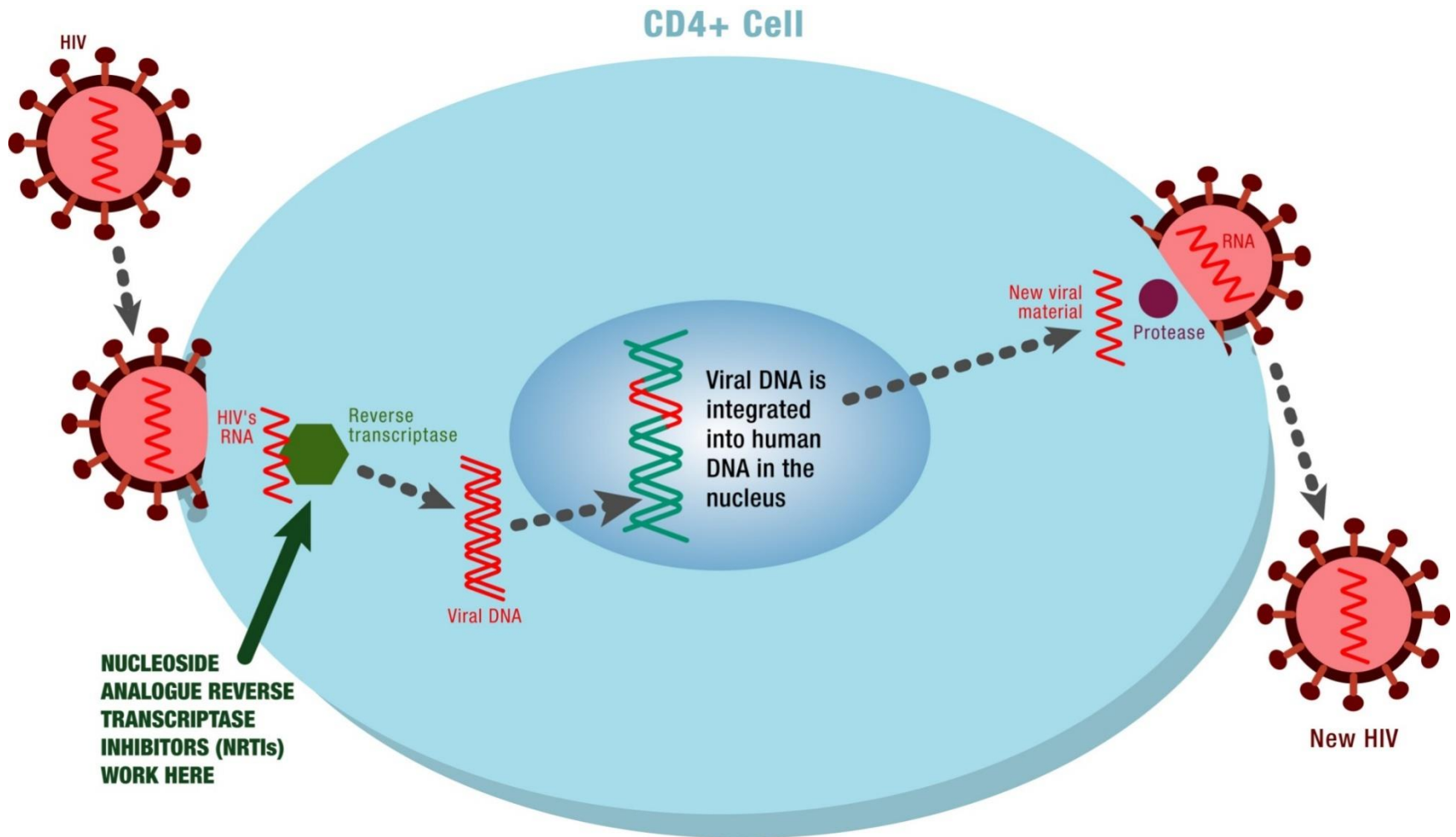
TDF + 3TC + LPV/r or ATV/r

If TDF was used in first line ART

AZT + 3TC + LPV/r or ATV/r

NRTI

Mechanism of Action



Zidovudine (AZT or ZDV)

- Dosing: **300mg** BID
- Reduce ZDV dose for patients with renal compromise and hepatic failure
- Food Interactions
 - None – with or without food is ok
 - Food decreases ZDV-related nausea
- Drug interactions
 - Avoid use with other bone marrow suppressing drugs
 - TMP/SMX
 - Pyrimethamine

Zidovudine (3)

- Toxicity
 - Nausea
 - Bone Marrow Suppression
 - Anemia (fatigue)
 - Monitor Hgb
 - Thrombocytopenia (low platelet count)
 - Neutropenia (low white blood cell [neutrophils] count)
 - Headache

Zidovudine (4)

- Toxicity cont.
 - Myalgia
 - Myopathy
 - Insomnia
 - Pigmentation of nail beds
 - Lactic acidosis, fatty liver

Lamivudine (3TC)

- Dosing: 150mg BID or 300mg QD
 - Reduce dose with renal compromise
- Can be used for Hep B.
 - 3TC is a potent inhibitor of HBV, good for patients with co-infection
- Food Interactions: no food interactions
- Toxicity: very rare
 - Headache
 - Occasional nausea
 - Lactic acidosis, fatty liver

Tenofovir Disoproxil Fumarate (TDF)

- Actually, a nucleo**TIDE**
- Dosing: 1 x 300mg tablet QD for >10 years old
 - Reduce dose with renal compromise
- Also has activity against Hepatitis B
 - Dosed 300mg QD
- Food Interactions: Can be taken with or without food

Tenofovir Disoproxil Fumarate (2)

- Drug interactions:
 - TDF increases ddl levels
 - TDF reduces ATZ levels
- Toxicity
 - Headache
 - Nausea, diarrhea
 - Lactic acidosis, fatty liver
 - Renal insufficiency (rare episodes of acute renal failure and Fanconi's syndrome)
 - TDF-related decreases in bone mineral density have been observed in children

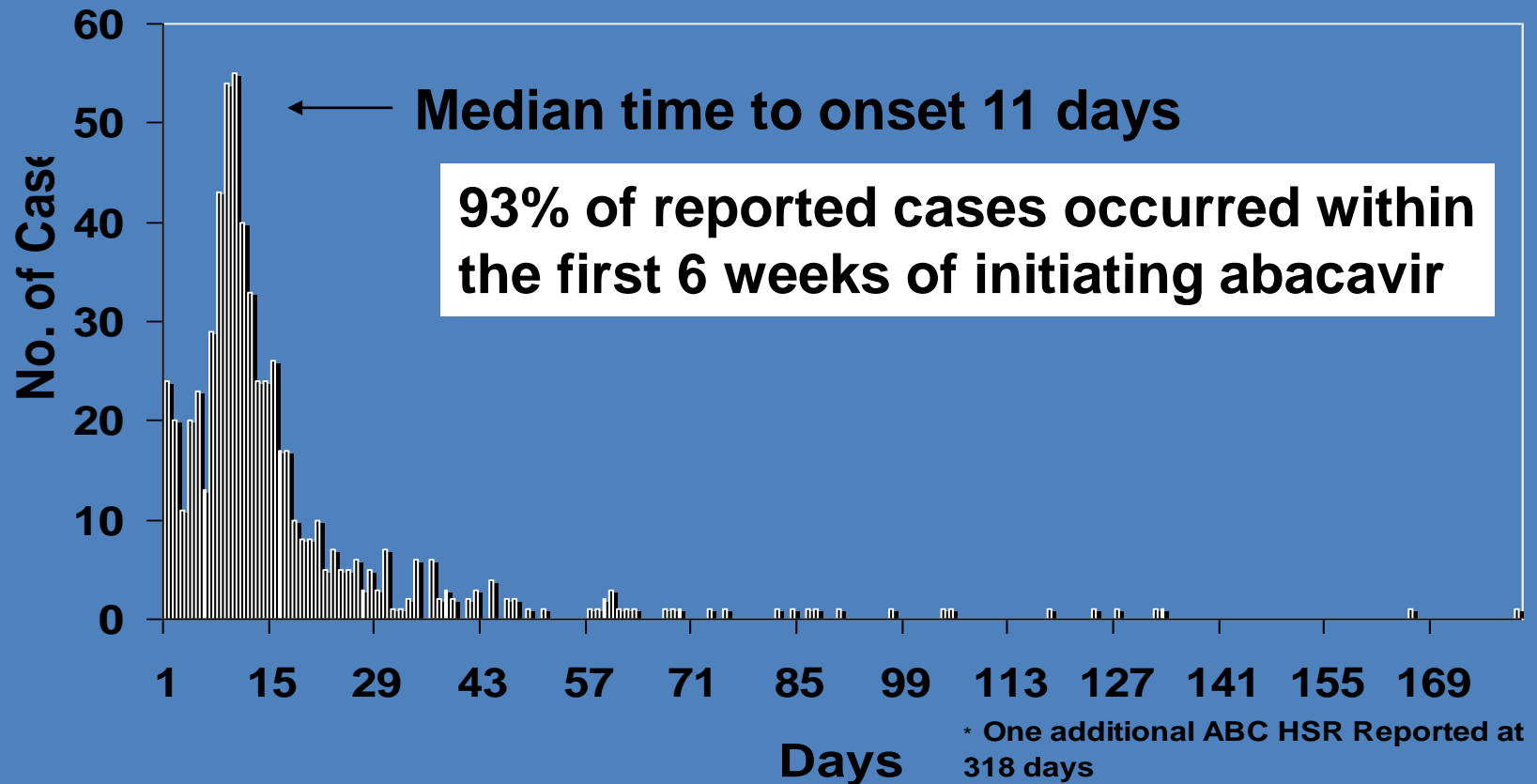
Abacavir (ABC)

- Dosing: 1 x 300mg tablet BID or 600 mg QD
- Food Interactions: no food interactions
- No dose adjustment for renal failure
- Toxicity
 - Hypersensitivity
 - Occurs within first 6 weeks of therapy
 - GI intolerance
 - Rash
 - Flu-like symptoms

Hypersensitivity to Abacavir

- Observed in approximately 5-8 % of all patients receiving abacavir
- Multi-organ system involvement
- **NEVER** rechallenge – May be fatal
- Most common signs and symptoms:
 - Fever (>80%)
 - Rash (maculopapular or urticarial) (70%)
 - Fatigue (>70%)
 - Flu-like symptoms (50%)
 - GI (nausea, vomiting, diarrhea, abdominal pain) (50%)

Time to Onset of 636 Cases



Hetherington S et al. In: Abstracts of the 7th Conference of Retroviruses and Opportunistic Infections. San Francisco, CA. January 30- February 2, 2000, Poster No. 60.

NRTI Class Side Effects

- Nausea
- Headache
- Peripheral Neuropathy (d4T/ddI)
- Lipoatrophy
- Pancreatitis (ddI > d4T)
- Lactic Acidosis, fatty liver
 - d4T > ddI > ZDV
 - Rare with ABC, TDF, 3TC and FTC

NRTI Mitochondrial Toxicity

- Inhibition of mitochondrial DNA polymerase- γ
 - \downarrow oxidative metabolism
 \rightarrow \downarrow ATP generation
- Implicated in lactic acidosis with hepatic steatosis
- Other possible manifestations:
 - Neuropathy (d4T, ddI)
 - Lipoatrophy (d4T)
 - Pancreatitis (ddI)
 - Myopathy (ZDV)
 - Cardiomyopathy (d4T, ZDV)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Nevirapine (NVP)
- Efavirenz (EFV)
- Delavirdine* (DLV)
- Etravirine * (ETV)-*New drug*

*Not available in Ethiopia

NNRTIs Mechanism 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***.

Nevirapine (NVP)

- Dosing: 200 mg QD x 2 weeks, then 200 mg BID
- Food Interactions: None
- Pregnancy
 - Prevention of perinatal transmission
- Drug interactions (induces liver enzymes)
 - Reduces plasma level of certain drugs (ethinyl estradiol, ketoconazole, PIs, etc)
- Toxicity
 - Rash (up to 15%, with Grade 3/4 rash occurring in 2%)
 - Hepatitis (up to 14% but symptomatic only in 4%)

Nevirapine-Induced Rash



Courtesy of HIV Web Study, www.hivwebstudy.org

Moderate Rash



Severe Rash



Efavirenz (EFV)

- Dosing: 600mg tablet QHS
- Food Interactions
 - Take with low-fat meal - High-fat meals increase absorption 50% → increases side effects
- Drug interactions (induces liver enzymes)
 - Changing from EFV to PI, may need to increase dose of PI for first two weeks
- **Efavirenz in pregnancy: Safe**

Efavirenz (2)

- Toxicity
 - CNS Changes (53%) only 5% needs discontinuation
 - Insomnia, nightmares, poor concentration, mood change, dizziness, dysequilibrium, depression, psychosis
 - Rash (mild 27%, severe like SJS in 0.1%)
 - Nausea

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 increase warfarin level by inhibiting CYP 2C9, monitor carefully

NNRTI Class Effects

- Side effects
 - Rash
 - EFV > DLV > NVP
 - Hepatotoxicity manifested by elevated transaminase
- Cross resistance across entire class
 - Essentially a one chance class of drugs

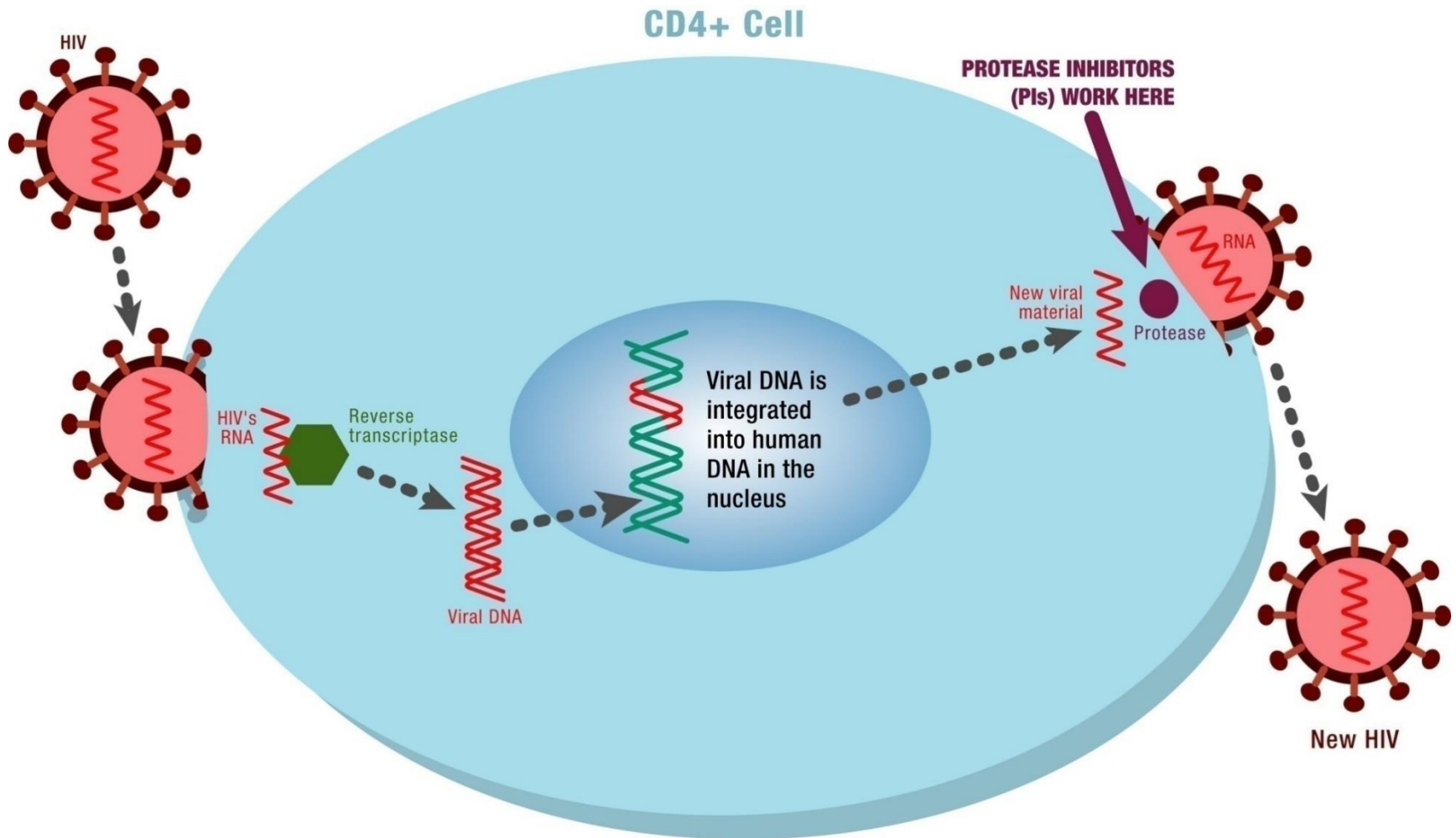
Protease Inhibitors (PI)

- Lopinavir + Ritonavir
- Atazanavir + Ritonavir
- Darunavir + Ritonavir
- Nelfinavir*
- Indinavir*
- Saquinavir-SGC*
- Ritonavir*
- Saquinavir-HGC*
- Amprenavir*
- Fosamprenavir*
- Tipranavir*

*Currently not available in Ethiopia

The ritonavir component is required to inhibit the CYP3A4 metabolism, allowing increased plasma levels (pharmacokinetic boosting).

PIs Mechanism of Action



These drugs prevent proteolytic cleavage of HIV Gag and Gag-pol precursor polypeptides

Lopinavir/ritonavir (LPV/r)

- Dosing: 250mg tabs BID and 500mg BID
 - Each tablet contains LPV 200 mg/RTV 50 mg
 - pediatric patients --- (14 days and older)
- Food Interactions:
 - The tablet can be taken with or without food
 - Oral solution must be taken with food.
- Bioavailability: 80% with food and 48% on an empty stomach
- Toxicity
 - Vomiting (children-21%, adult -2-6%), diarrhea (7-28%)
 - Dermatologic: Rash (children 12%, adult $\leq 5\%$)
 - Lipid abnormalities,
 - Fat redistribution (lipodystrophy):
 - Hyperglycemia
- ⁹⁹ Tablets can be stored at room temperature

Lopinavir/ritonavir (2)

- Interactions with other ARVs(it is b/c RTV is liver enzyme inhibitor)
 - **EFV** and **NVP** decrease LPV/r levels by 55%
 - Increase LPV/r to 4 caps bid
- LPV/r may decrease the C_P of Abacavir
 - This combination is not recommended
- 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 while LPV may increase the level of Ketoconazole.

Atazanavir/ritonavir (ATZ/r)

- Dosing: 2 x 200mg capsules **QD**
 - Dosed with ritonavir 100mg QD, ATZ dose = 2 x 150mg QD
- Food Interactions: Take with food (It requires an acidic gastric pH for absorption)
- Toxicity:
 - Nausea
 - Diarrhea
 - Elevated bilirubin (indirect hyperbilirubinemia)
 - Fat redistribution
 - ❖ It has minimal effect on lipid profile and does not induce insulin resistance unlike other PIs.

Atazanavir/r (2)

- Pregnancy
 - Potential for ATZ to cause hyperbilirubinemia in neonates
- Drug interactions
 - Inhibits liver enzymes
 - If used with RTV, decrease dose to 300 mg qd + RTV 100 mg qd
 - TDF decreases ATZ levels
 - Use boosted ATZ with TDF
 - Use boosted ATZ with any NNRTI
 - **Oral contraceptives:** increase estradiol AUC by 48% and norethindrone AUC 110%
 - Concomitant administration of agents that induce CYP3A4 enzyme (e.g., rifampicin) is contraindicated.

PI Class Side Effects

- Metabolic Disorders
 - Hepatotoxicities
 - Hyperglycemia, insulin resistance
 - Lipid abnormalities
 - Fat redistribution
- Bone Disorders
 - Avascular necrosis
 - Osteoporosis and Osteopenia
- GI intolerance
- Drug interactions
 - Due to CYP450 3A4 Inhibition

PIs induced Hepatotoxicity

- RTV use linked to increased risk of severe hepatotoxicity
- Increased LFT's observed with all PI's
 - More common in patients with chronic viral hepatitis (HBV, HCV)
- Data do not, however, support withholding PI's from patients co-infected with HBV or HCV

Treatment in Special Populations

Pregnant and Breast feeding Mothers

- 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.

Children

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

Risk factors for MTCT

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

Risk factors for MTCT...

Infant factors

- Prematurity
- Oral thrush and ulcer
- Birth order (first twin) in twin pregnancies
- Invasive fetal monitoring

Prevention of mother to child transmission of HIV

- There are four prongs to eliminate **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

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

National PMTCT guideline and Strategy

- 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 + EFV**.

Summary of National PMTCT recommendation

PMTCT program	Pregnant and breast feeding women with HIV	HIV exposed infant	
Use lifelong ART for all pregnant and breastfeeding women (“Option B+”)	Initiate lifelong ART Regardless of WHO clinical stage or CD4 cell count	Breast feeding	Replacement Feeding
		6 weeks of infant prophylaxis with once-daily NVP	4–6 weeks of infant prophylaxis with once-daily NVP

Summary of maternal and infant ARV prophylaxis for different clinical scenarios.

Scenario	Maternal ARV prophylaxis ^a	Infant ARV prophylaxis	Duration of infant ARV prophylaxis
Mother diagnosed with HIV during pregnancy	Initiate maternal ART	NVP	6 weeks; assuming that the mother has been on ART for more than 4 weeks.
Mother diagnosed with HIV during labor, within one month of delivery or postpartum within 72 hours regardless of feeding plan	Initiate maternal ART	NVP + AZT or NVP only	NVP+AZT for 6 weeks and NVP for additional 6 weeks OR NVP for 12 weeks
Infant identified as HIV exposed <u>after birth</u>	Initiate maternal ART	NVP	Perform infant PCR early infant diagnosis test and then immediately
(through infant or maternal HIV antibody testing) and is breastfeeding			initiate 6 weeks of NVP – strongly consider extending this to 12 weeks

Summary of maternal and infant cont'd

<p>Infant identified as HIV exposed after 72 hours after birth (through infant or maternal HIV antibody testing) and is not breastfeeding</p>	<p>Initiate maternal ART</p>	<p>No prophylaxis needed</p>	<p>Do HIV PCR test in accordance with national recommendations on early infant diagnosis; no infant ARV prophylaxis; initiate treatment if the infant is infected</p>
<p>Mother receiving ART but interrupts ART regimen while breastfeeding (such as toxicity, stock-outs or refusal to continue)</p>	<p>Determine an alternative ART regimen or solution; counsel regarding continuing ART without interruption</p>	<p>NVP</p>	<p>Until 6 weeks after maternal ART is restarted or until 1 week after breastfeeding has ended</p>

Summary of maternal and infant cont'd

- a. Ideally, obtain the mother's CD4 cell count at the time of initiating or soon after initiating ART
- b. If infant NVP causes toxicity or NVP is not available, 3TC can be substituted.
- c. If the mother is using replacement feeding, infant AZT can be substituted for infant NVP; 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.
- d. If it is known that the mother has initiated ART less than 4 weeks before delivery, consider extending infant NVP for infants who are breastfeeding to 12 weeks.

Dosage of NVP syrup for different age groups

Infant age	NVP daily dosing	Dose in ml
Birth to 6 weeks <ul style="list-style-type: none"> • Birth weight 2000-2499 g • Birth weight ≥ 2500 g 	10mg once daily 15 mg once daily	1ml 1.5ml
Age 6 weeks to 6 months	20 mg once daily	2ml
Age 6 months to 9 months	30 mg once daily	3ml
Age > 9 months	40 mg once daily	4ml

Diagnosis of HIV in infants and children

- Early recognition of HIV infection in infants and children is crucial as there is **fast progression** of illness.
 - without treatment **35.2%** of HIV-infected children will die in their first year and **52.5%** by age two.
- Diagnosis is by virologic test for those <18 months and antibody test for >18 months.
- All < 5 children visiting health facility should be tested for HIV.

- Specialized tests are required for infant diagnosis
 - DNA PCR, RNA PCR, 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**

Antibody versus virological tests

Antibodies tests, including rapid test	Virological assays such as RNA or DNA PCR
<ul style="list-style-type: none"> • 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 18 months 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 	<ul style="list-style-type: none"> • These test directly detect the presence of the HIV virus or products of the virus in the blood • Positive virological 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.
1. A positive **virologic (DNA PCR) test** at any age implies that the baby is HIV infected (two tests), and
 2. A positive **ANTIBODY test** at 18 months or more implies the child is HIV infected.

Dosage of Anti-retroviral Drugs in Children...

Regimen	Drugs in Regimen	Dosage Form	Strength	Unit	3-5.9kg		6-9.9kg		10-13.9 kg		14-19.9 kg		20-24.9 kg		25-29.9 kg		30-34.9 kg	
					AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
ABC-3TC-ATV/r	ABC/3TC	FDC tab	600/300mg	tab											1	-	1	-
	+														+	+	+	+
	ATV/r	FDC tablet	300/100mg	tab											1	-	1	-
ZDV-3TC-NVP	ZDV/3TC/NVP	FDC tab	60/30/50mg	tab	1	1	2	1	2	2	3	2	3	3				
ZDV-3TC-NVP	ZDV/3TC/NVP	FDC tab	300/150/200mg	tab											1	1	1	1
ZDV-3TC-EFV	ZDV/3TC	FDC tab	60/30mg	tab					2	2	3	2	3	3				
	+								+	+	+	+	+	+				
	EFV	Loose capsules	50mg,200mg	caps					•	1x200mg tab	•	1x200mg & 1x50mg	•	1x200mg & 2x50mg				
ZDV-3TC-EFV	ZDV/3TC	FDC tab	300/150mg	tab											1	1	1	1
	+														+	+	+	+
	EFV	Loose capsules	50mg,200mg	caps											•	1x200mg &3x50mg	•	2x200mg
ZDV-3TC-Lop/r	ZDV/3TC	FDC tab	60/30mg	tab	1	1	2	1										
	+				+	+	+	+										
	Lop/r	FDC suspension	80/20mg per ml	ml	1ml	1ml	2ml	1ml										
ZDV-3TC-Lop/r	ZDV/3TC	FDC tab	60/30mg	tab					2	2	3	2	3	3				
	+								+	+	+	+						
	Lop/r	FDC tab	100/25mg	tab					2	1	2	2	3	2				
ZDV-3TC-Lop/r	ZDV/3TC	FDC tab	300/150mg	tab											1	1	1	1
	+														+	+	+	+
	Lop/r	FDC tab	200/50mg	tab											2	1	2	2
ZDV-3TC-ATV/r	ZDV/3TC	FDC tab	300/150mg	tab											1	1	1	1
	+														+	+	+	+
	ATV/r	FDC tab	300/100mg	tab											1	-	1	-
TDF-3TC-EFV	TDF/3TC/EFV	Adult FDC tab,scored	300/300/600mg	tab					-	1/3 tab	-	1/2 tab	-	2/3 tab	-	1tab	-	1tab
TDF-3TC-NVP	TDF/3TC	Adult FDC tab,scored	300/300mg	tab							1/2 tab	-	2/3 tab	-	1tab	-	1tab	-
	+										+	+	+	+	+	+	+	+
	NVP	Loose tablet	200mg	tab							1	1/2 tab	1	1/2 tab	1	1	1	1

POSTEXPOSURE PROPHYLAXIS (PEP)

- PEP with a triple-drug regimen consisting of two NRTIs and a boosted-PI is recommended for percutaneous blood exposure involving **significant risk** (i.e., large-bore needle or large volume of blood or blood from patients with advanced AIDS).
- Two NtRTIs may be offered to healthcare workers with **lower risk** of exposure such as that involving the mucous membrane.

- Treatment is not necessary if the source of exposure is **urine or saliva**.
- The optimal duration of treatment is unknown, but at least **4 weeks** of therapy is advocated.
- Ideally, treatment should be initiated within 1 to 2 hours of exposure, but treatment is recommended for up to **72 hours** postexposure.

Changing Therapy

Treatment Failure and IRIS

- Must differentiate treatment failure from IRIS
 - Clinical manifestation of a sub - clinical infection present at baseline.
 - Brought on by ART – induced reconstitution of the immune system
 - Typically seen within several weeks of initiating ART

IRIS

- Occurs in 10–30% of people initiating ART
- Usually happens within the first 4–8 weeks after initiating therapy
- It may present as **paradoxical** IRIS or **unmasking** IRIS
 - **unmasking** IRIS: in which initiating ART triggers disease that is not clinically apparent before ART.
 - **paradoxical** IRIS: when an OI or tumor diagnosed before ART initially responds to treatment but then deteriorates after ART starts;

Reasons for Changing ART

- ART should not be changed unless absolutely necessary!
- ART may be changed because of:
 - Treatment Failure
 - Toxicity or intolerance
 - Co - morbid conditions
 - Non - adherence/compromised quality of life

Treatment Failure

- Treatment failure is defined by
 - Clinical failure
 - Immunologic failure
 - Virology failure

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 immunodeficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment.

Immunological Failure

Adults and adolescents

- CD4 count at or below 250 cells/mm³ following clinical failure Or
- Persistent CD4 levels below 100 cells/mm³

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

Note:

- 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.

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.

Algorithm for Routine Clinical and Viral Load Monitoring

Look for other causes

Rapid test at ≥ 12 months of age or > 6 weeks after complete cessation of breastfeeding

Routine Virologic monitoring
And Viral load > 1000 copies/ml

Signs of Clinical/ Immunologic treatment Continue follow up per national guideline; continue Co-trimoxazole, ARV prophylaxis per national PMTCT guideline

Do Targeted viral load tests

viral Load > 1000 c/ml

viral Load ≤ 1000 c/ml Initiate ART

Enhanced adherence support for 3 months

Repeat Viral load testing

Viral load > 1000 copies/ml

Viral load ≤ 1000 copies/ml

Insignificant* drop in VL

More than threefold drop in Viral Load

Switch to 2nd /3rd line regimen

Continue with EAS for additional 3 months and repeat viral load

Continue same (previous) regimen

VL $> 1,000$ copies/ ml

VL $\leq 1,000$ copies/ml

Reasons for Treatment Failure

- Non-adherence
 - ART success rates decrease dramatically when adherence falls even slightly down to 95% (resistance rates increase by 20-30%)
- Resistance
- Adverse effects
- Drug-drug interactions

Changing Regimen

- When changing regimen due to treatment failure:
 - ✓ Evaluate for resistance through resistance testing or
 - ✓ Empiric decision- making based on clinical history
 - ✓ **Change to an entirely new regimen, with at least one drug from a new class**
 - ✓ Anticipate some cross - resistance (e.g. EFV-NVP)
 - ✓ Try to determine and correct reasons for failure of the first regimen (e.g. adherence issues)

What to Change?

Population	1 st line regimens	2 nd line regimens	3 rd line regimens
Adults, adolescents, Pregnant/breast feeding women	AZT+3TC + EFV/NVP	TDF+3TC + ATV/r or LPV/r	DRV/r ^a + DTG (or RAL) ± ABC
	TDF+3TC+EFV/NVP	AZT+3TC + ATV/r or LPV/r	DRV/r ^a + DTG (or RAL) ± ABC
	ABC+3TC+EFV/NVP	AZT+3TC + ATV/r or LPV/r	DRV/r ^a + DTG (or RAL) ± TDF
Children	d4t/AZT+3TC + LPV/r	If older than 3 years: ABC+3TC + EFV TDF+3TC + EFV	DTG/RAL/DRV/r + AZT+3TC
	ABC+3TC+LPV/r	AZT+3TC + EFV	DRV/r /RAL/DTG ^d + TDF+3TC
	ABC+3TC + EFV/NVP AZT+3TC + EFV/NVP	2 NRTIs + ATV/r ^c or LPV/r	DRV/r + DTG ^e ± 1-2 NRTIs RAL (or DTG) ^f + 2 NRTIs

Toxicity

- ARV toxicity can be detected from patient reports on their symptoms, physical exam, and laboratory tests.
- Certain laboratory abnormalities signal the need for a change in ART regimen.
- One should consider changing ART in **Grade 3** reactions and treatment should be stopped if there is a **Grade 4** adverse event.
- Therefore, it is crucial that patients get their scheduled follow-up laboratory monitoring tests (blood tests) to make sure that the ART is not causing any harm to organs (e.g., liver, kidneys, pancreas) or the blood.

Clinical Indications to Change ART Due to Toxicity

Symptom	Clinical indication
Nausea	Severe discomfort or minimal intake for 24hrs
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 $\geq 39.6^{\circ}\text{C}$
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 $\geq 50\%$

Toxicity: Changing One Drug

- **Regimen: TDF/3TC/NVP**
 - TDF - related renal problem: switch TDF to ABC/ZDV
 - NVP - related rash or hepatotoxicity
 - Switch NVP to EFZ ???
 - Switch NVP to PIs (in cases of pregnancy or severe adverse effect)
- **Regimen: TDF/3TC/EFV**
 - EFV - related persistent CNS toxicity: Switch EFV to NVP
- **Regimen: ZDV/3TC/EFV**
 - ZDV - related anemia or neutropenia : Switch ZDV to TDF/ABC

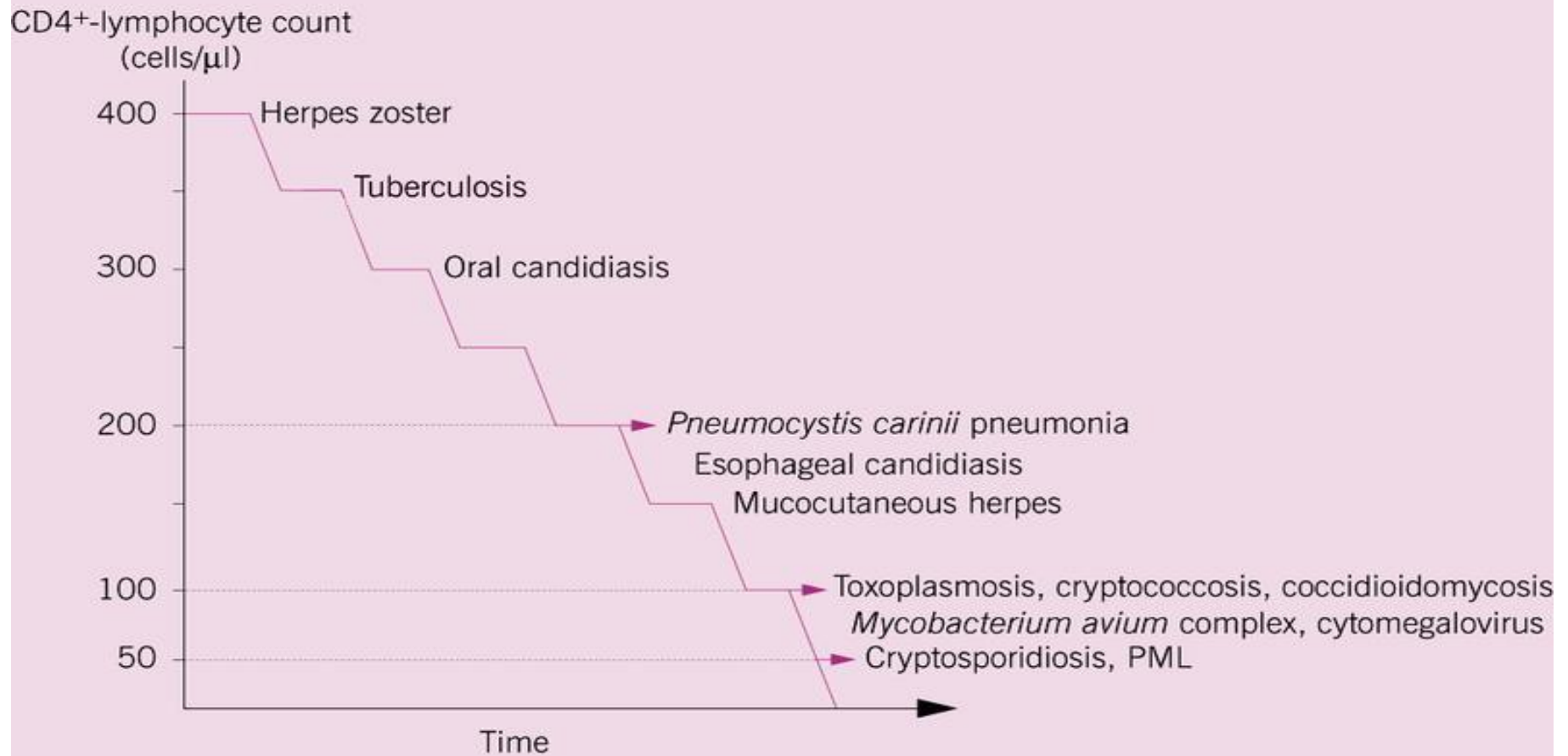
Prophylaxis and treatment of Opportunistic Infections

- The development of certain opportunistic infections is directly or indirectly related to the level of **CD4 lymphocytes**.
- The most common opportunistic diseases include *Pneumocystis carinii pneumonia (PCP)*, *Mycobacterium avium complex (MAC)*, and *cytomegalovirus (CMV)* disease.

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/mm ³ Or 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 <ul style="list-style-type: none"> ▪ 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 	

ASSOCIATION BETWEEN OPPORTUNISTIC INFECTIONS AND CD4⁺-LYMPHOCYTE COUNT



Pneumocystis Carini Pneumonia (PCP)

- Caused by *Pneumocystis jirovecii* (formerly known as *pneumocystis carini pneumonia* (PCP)).
- Classified as a fungus (but also shares biologic characteristics with protozoa)
- Most people exposed to PCP early in life
- Disease is likely reactivation of latent infection
 - Can be transferred from person to person
- Risk greatly increased at CD4 count < 200 or CD4 percentage $< 14\%$
- Symptoms: sub acute onset of progressive dyspnea , fever, non-productive cough and chest discomfort that worsens with in days to weeks

PCP diagnosis

- Diagnosis is mainly clinical when patients have severe and advanced immunosuppression ($CD4 < 200/mm^3$) in resource limited settings.

Treatment Regimens for Acute PCP

Drug	Dose	Side Effects/Special Considerations
Cotrimoxazole	15mg/kg/day (based on TMP component) + (sulfamethoxazole 75 mg/kg/day) PO or IV divided q6h to q8h for 21 days (Typical oral dose is 2 DS tablets TID).	Rash, neutropenia, anemia, increased transaminases, hepatitis, pancreatitis, GI toxicity; monitor renal function
Dapsone + Trimethoprim	TMP 15mg/kg/day PO/IV divided q6h to q8h + Dapsone 100 mg po qd for 21 days	Dapsone can cause rash & hemolytic anemia; screen for G-6PD deficiency

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Source: Johns Hopkins AIDS Service - Medical Management of HIV Infection. www.hopkins-aids.edu

Treatment Regimens for Acute PCP (2)

Drug	Dose	Side Effects/Special Considerations
Pentamidine	3-4 mg/kg/day IV once daily for 21 days	Nephrotoxicity, hypotension, hypoglycemia, leukopenia, thrombocytopenia, GI intolerance, pancreatitis; keep patient hydrated & closely monitor renal function, electrolytes, and blood sugar
Clindamycin + Primaquine	Clindamycin 300 - 600 mg po q6h (600 -900 mg IV q6 -8h) + Primaquine base po 15 -30mg per day for 21 days	Primaquine can cause nausea, vomiting & epigastric pain which may be limited by administering with meals. Screen patients for G-6PD deficiency to avoid hemolytic anemia. Clindamycin can cause GI intolerance and diarrhea.

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Source: Johns Hopkins AIDS Service

- Medical Management of HIV Infection.

www.hopkins-aids.edu

PCP Treatment: Adjunctive Corticosteroids

- Indicated in patients with o_2 saturation < 80 or $\text{PaO}_2 < 70$
- Prednisolone 40 mg bid x5 days, then 40 mg qd x 11 days then 20 mg qd x 5 days (total prednisone course is 21 days)
- 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.

PCP Prophylaxis Regimens

Preferred:

- Cotrimoxazole 1 DS QD
- Cotrimoxazole 1 SS QD

Alternatives:

- Cotrimoxazole 1 DS TIW
- Dapsone
- Aerosolized Pentamidine
- Atovaquone

Candidiasis

- Of candidiasis infections
 - ✓ 75% are oral (thrush)
 - ✓ 20 - 40% are esophageal
 - ✓ 30 - 40% are vulvo - vaginal
- Recurrence is common (~30%)

Oropharyngeal Candidiasis : Treatment Principles

- **Mild to moderate disease:** topical therapy
 - Nystatin 500,000 units (4 – 6 mL) gargled 4 - 5x day
 - Clinical response occurs in 90 - 100% of patients within 7 days
 - Miconazole oral gel
- **Moderate to severe disease:** systemic therapies
 - Fluconazole 100 mg/day, Itraconazole 200 mg/day, Ketoconazole 200 mg/day
 - Continue antifungal therapy for two weeks until symptoms resolve

Candidiasis Treatment - Esophageal

- Duration: 2 - 3 weeks for all regimens

Systemic therapy:

- **Fluconazole** 200 -400 mg daily
- Itraconazole capsule 200mg daily with food
- Itraconazole suspension 100 - 200 mg daily without food
- Amphotericin B - IV 0.3 - 0.6 mg/kg/day
- Ketoconazole 200mg twice daily for 4wks

HIV Associated Cryptococcal Meningitis

Clinical presentation:

- Occurs in advanced immune damage CD4 <100
- Characterized by subtle clinical manifestations; headache, fever, malaise. Meningeal signs are not always present. Symptoms such as stiff neck, photophobia, and vomiting are only seen in a minority of patients
- Altered sensorium in 25% cases; and focal signs in 5%

Treatment

- Phase of treatment

Option A. (preferred in Ethiopian situation)

- ✓ Induction phase (2 weeks)

- Fluconazole 600 mg po bid daily alone (In children 12mg/kg/day in two divided doses):

- ✓ Consolidation phase (8 weeks)

- Fluconazole 800 mg/day, (in children 12mg/kg/day)

- ✓ Maintenance treatment (or secondary prophylaxis)- Fluconazole 200 mg daily(in children

- 6mg/kg/day)

- Management of intracranial pressure: CSF drainage

Toxoplasmosis Encephalitis (TE)

- **Caused by** the protozoan *Toxoplasma gondii*
- **Clinical presentation:** CNS; headache, confusion, lethargy, low - grade fever, seizures (~25%), hemiparesis and speech abnormalities
- **Diagnosis:**
 - Ring -enhancing lesions on CT scan or MRI
 - *Toxoplasma* IgG antibodies are usually present but may be negative in 5 - 10% patients with TE

Acute Toxoplasmosis Treatment

- 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.

Acute Toxoplasmosis Treatment

1st line regimen in the Ethiopian context :

- ✓ Co-trimoxazole 2DS or 4SS po bid, for 28 days, followed by 1DS or 2SS po bid for 3 months in adults.
- ✓ In children, 10mg of trimethoprim + 50mg of sulfamethoxazole/kg per dose every 12 hours for 28 days followed by maintenance therapy at 50%reduced dosage for three months.

Acute Toxoplasmosis Treatment

- **Alternative regimen:**
 - Sulfadiazine, 1-2 gm p.o.q 6h for six weeks or 3 weeks after resolution of lesion. Dosage/form: 500 mg tablets **PLUS** Pyrimethamine Loading dose of 200 mg once, followed by: Pyrimethamine 50-75 mg/day **PLUS** Folinic acid (Leucovorin): 10-20 mg/d **OR**
 - Pyrimethamine and Folinic Acid (Leucovorin): (standard dose) **PLUS** Clindamycin: 600 mg q 6 hrs .
- **Secondary prophylaxis:** use co-trimoxazole 960mg daily for adults

Toxoplasmosis Primary Prophylaxis

- Indications:
 - Patient who has never had toxoplasmosis
plus
 - Positive toxoplasma IgG serology
plus
 - CD4 count less than 100 cells/mm³

Toxoplasmosis Primary Prophylaxis

- Preferred Regimens:

- ❖ TMP/SMX DS daily

- ✓ co-trimoxazole 960mg daily for adults is used till the CD4 picks above 350/mm³ for three months.

- ❖ TMP/SMX DS three times/week

- ❖ TMP/SMX SS daily

Thank You