

KITSO AIDS Training Program

Lecture 4:

Principles of ARV Therapy
in the
Botswana National ARV Program

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Learning Objectives

- The goals of ARV therapy
- When to start ARV therapy in Botswana
- HAART regimens in Botswana
- How to monitor ARV therapy in Botswana
- Definitions of treatment failure
- Treatment of TB/HIV co-infection

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Accepted Abbreviations for the Same Therapeutic Intervention to Treat HIV Infection:

- ARV: Antiretroviral
- ART: Antiretroviral Therapy
- HAART: Highly Active Antiretroviral Therapy

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Goals of ARV Therapy:

- **Clinical:** prolong life, improve quality of life, and sustain productivity. With proper therapy and excellent adherence, *HAART can increase life expectancy of HIV-infected patients to that of uninfected patients.*
- **Virologic:** achieve maximal suppression of HIV. *Viral load should fall to < 400 copies/mL by 6 months after HAART initiation, and should remain there indefinitely.*
- **Immunologic:** Reverse immune system damage, i.e., increase CD4 count/% and decrease non-specific, uncoordinated immune activation.

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Principle 1

The most effective way to suppress HIV replication is the simultaneous initiation of combinations of at least three effective ARV drugs (HAART).

The use of at least three ARV drugs for ARV treatment is mandatory under the Botswana National ARV Program.

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Principle 2

Drugs used in ARV therapy regimens should be used according to the Botswana National ARV Guidelines in the most effective and tolerable pattern that a patient can manage.

However, the Guidelines are not a substitute for good clinical decision making, and may be deviated from, but *only after consultation with an HIV Specialist.*

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Principle 3

Disease progression differs among HIV-infected persons. The decision to begin treatment should be individualized and based upon three major factors:

1. The degree of HIV-related disease—i.e., the patient's clinical condition.
2. The degree of HIV-related immune suppression—i.e., the CD4 count/%.
3. A solid adherence plan and a working relationship with the healthcare system.

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HAART Eligibility Criteria for Adults (Non-Pregnant and Pregnant)

- WHO clinical stage 3 or 4, regardless of CD4 count, or
- CD4 count less than **250** cells/μL (previously < 200 cells/μL)
 - The increase in CD4 threshold for HAART reflects WHO and other international guidelines recommending HAART initiation before the CD4 count drops below 200 cells/μL.

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Pediatric Eligibility Criteria for HAART

- All infants < 12 months of age.
- Children > 1 year of age with:
 - WHO clinical stage 3 (“advanced”) or 4 (“severe”) signs or symptoms, or
 - “Advanced” or “Severe” immune suppression by WHO age-related CD4- CD4%-based criteria:

WHO CD4-Based Criteria for Commencement of HAART in Children:

WHO stage	<1 year	1-<3 years	3-<5 years	≥5 years
Mild	Treat	No HAART	No HAART	No HAART
Advanced	Treat	20-24%	15-19%	200-349 cells/μL
Severe	Treat	<20% or <750 cells/μL	<15% or <350 cells/μL	< 15% or <200 cells/μL

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HAART Initiation (2)

- If an HIV-infected patient of any age has an active WHO clinical stage 3 or 4 condition, the patient's clinical condition is poor, and the CD4 cell count or % is pending, *do not wait for the CD4 count or % to return*: begin the patient on HAART on the basis of the patient's having an active WHO clinical stage 3 or 4 condition and being in poor clinical condition. Likewise, do not delay CTX prophylaxis.
- Before beginning HAART in an adult/adolescent patient without a CD4 count, as above, the possibility that the patient might have a high baseline CD4 count requires LPV/r-based or EFV-based HAART and not NVP, because of risk of NVP-induced hepatotoxicity with high baseline CD4 counts (see below).

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HAART Initiation (3)

- There may arise other HIV-related conditions which may justify HAART in certain patients, as well as instances when severe WHO stage 2 conditions, e.g., severe dermatitis, merit HAART.
 - A disproportionately low CD4% (< 15%) in an adult with absolute CD4 count > 250 cells/ μ L may also justify HAART.
 - Although acute HIV infection is not, in and of itself, an indication for HAART initiation, a patient with severe symptoms of the acute retroviral syndrome should be discussed with an HIV Specialist for possible HAART initiation.
 - In all such patients, an HIV Specialist should be consulted for possible HAART initiation.

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Adult WHO Clinical Staging

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Clinical Stage 1

“Asymptomatic” and/or persistent generalized lymphadenopathy

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Clinical Stage 2: “Mild” disease

- Unexplained moderate weight loss < 10% of baseline weight
- Recurrent upper respiratory infections (sinusitis, otitis media, tonsillitis, pharyngitis)
- Mono-dermatomal VZV
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrheic dermatitis
- Fungal nail infections

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Clinical Stage 3: “Advanced” Disease

- Unexplained weight loss > 10% of baseline
- Unexplained chronic diarrhea for more than one month
- Unexplained persistent fever (> 37.5C, intermittent or constant) for more than one month
- Persistent oral candidiasis
- Oral hairy leukoplakia
- Pulmonary TB
- Severe bacterial infections (e.g., pneumonia, meningitis, PID,* bone/joint infection, bacteremia)
- Multi-dermatomal, recurrent mono-dermatomal, or ophthalmic VZV*
- Necrotizing ulcerative gingivitis, periodontitis, stomatitis
- Unexplained anemia (< 8 gm/dL), neutropenia (< 500/ μ L), and/or thrombocytopenia (< 50,000/ μ L)

*Not part of international WHO staging, but added as a frequent Botswana-specific HIV-related “advanced” condition meriting HAART.

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Clinical Stage 4: “Severe” Disease

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe bacterial pneumonia
- Chronic HSV infection (orolabial, genital, rectal *for more than one month* or visceral at any site)
- Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)
- Extra-pulmonary TB
- KS
- CMV (retinitis or infection of other organs)
- CNS toxoplasmosis
- HIV encephalopathy (continued)

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Clinical Stage 4: “Severe” Disease (cont)

- Clinical Stage 4: “Severe” disease (continued)
 - Extrapulmonary cryptococcosis, including meningitis
 - Disseminated non-TB mycobacterial infection
 - Progressive multifocal leukoencephalopathy
 - Chronic cryptosporidiosis, isosporiasis
 - Disseminated mycosis
 - Recurrent septicemia
 - Lymphoma (cerebral or non-Hodgkin's)
 - Invasive cervical carcinoma
 - Atypical disseminated leishmaniasis
 - Symptomatic HIV-associated nephropathy and cardiomyopathy

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Before Therapy is Initiated

All Patients:

- History and physical, including IPT/TB history and history of HIV-related illnesses
- Baseline laboratories

ARV-Experienced Patients:

- Obtain full treatment history.
 - What prior regimen/s has the patient taken?
 - What was the duration of the therapy?
 - If switched, why?
 - How was adherence?
 - Obtain all old CD4 and VL results.

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Longitudinal Monitoring

- Monitoring Adherence
 - Discuss at each visit
- Monitoring tolerability of ART
 - Direct questioning, with follow-up of any patient complaints or concerns
 - Clinical assessment and laboratory tests
- Monitoring efficacy of ART
 - Clinical indicators (weight, hemoglobin)
 - CD4 and viral load measurements

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Principle 4

**ARV Therapy is a
life-long
commitment.**

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Before initiating HAART, clinicians must assess a patient's understanding and readiness to make a life-long commitment to taking ARV medications.

Delay HAART initiation until any acute opportunistic infection(s) or other medical complications have been stabilized, and the patient has been discharged from the hospital, e.g., cryptococcal meningitis, PCP.

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Principle 5

The more treatment-experienced a patient is, the less likely that subsequent ARV regimens will be effective. The best chance of success with ARV therapy is with the first regimen—thus, *the primal importance of excellent adherence from the very start of therapy.*

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ARVs in the Botswana National Program

<i>NRTIs</i>	<i>NNRTIs</i>	<i>PIs</i>
<small>Nucleoside Reverse Transcriptase Inhibitors</small>	<small>Non-Nucleoside Reverse Transcriptase Inhibitors</small>	<small>Protease Inhibitors</small>
AZT (zidovudine) 3TC (lamivudine) FTC (emtricitabine) d4T (stavudine) ddl (didanosine) ABC (Abacavir); <u>pediatrics only</u>	EFV (efavirenz) NVP (nevirapine)	LPV/r (RTV-boosted lopinavir; "Kaletra," "Aluvia") Special Order PIs: SQV (saquinavir) RTV (ritonavir) NFV* (nefinavir)
<small>NtRTIs: Nucleoside Reverse Transcriptase Inhibitors</small> TDF (tenofovir)		
		<small>* Patients on NFV should be switched to LPV/r.</small>

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ARVs in the Botswana National Program (2)

- **FTC** (emtricitabine) is identical in efficacy, resistance patterns, and side-effects as **3TC**. However, it has a longer half-life, which permits once daily dosing (200mg OD). (However, 3TC may also be dosed 300mg OD). Whether FTC or 3TC is available will depend upon supply and cost issues.
- **ABC** is a "special order" drug for adults, but not pediatric patients.
- Co-formulated ARVs, which improve medication adherence:
 - **AZT + 3TC** ("Combivir" or "Lamzid")
 - **TDF + FTC** ("Truvada")
 - **TDF + FTC + EFV** ("Atripla"): the "once a day pill"
 - Availability of Truvada and Atripla will depend upon supply and cost as the ARV program moves forward.

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Mechanism of Action of ARVs

- NRTIs, NtRTIs, and NNRTIs block HIV replication early in its life-cycle by inhibiting reverse transcription.
- PIs block HIV replication late in its life-cycle by inhibiting protease-catalyzed assembly of the virus.

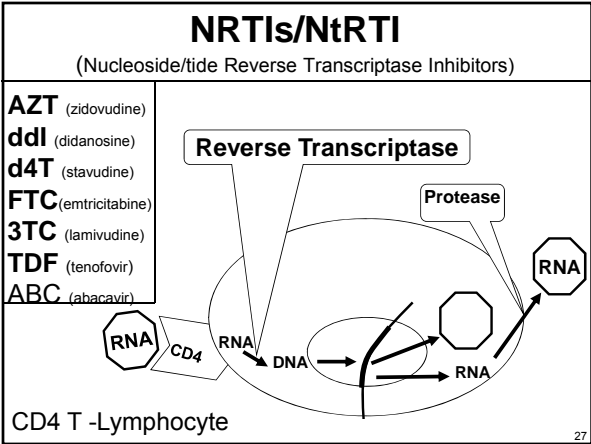
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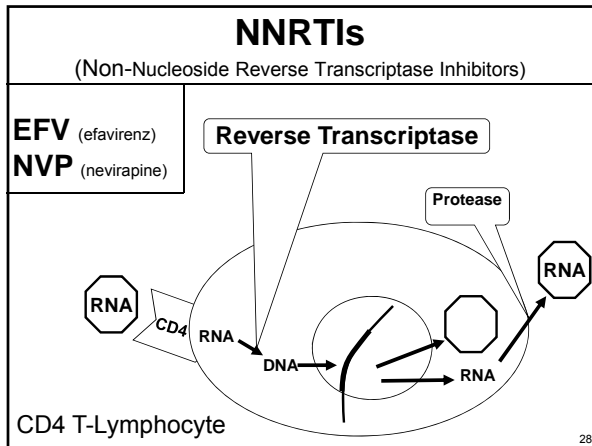
Mechanisms of Action NRTIs/NtRTIs & NNRTIs

NRTIs/NtRTIs and **NNRTIs** inhibit reverse transcriptase by different mechanisms:

- **NRTIs** and **NtRTIs** are “false nucleotides” and, once incorporated into the growing DNA chain, terminate further elongation of the DNA chain, stopping the HIV life cycle.
- **NNRTIs** directly inhibit the enzymatic function of reverse transcriptase by binding near the catalytic site.

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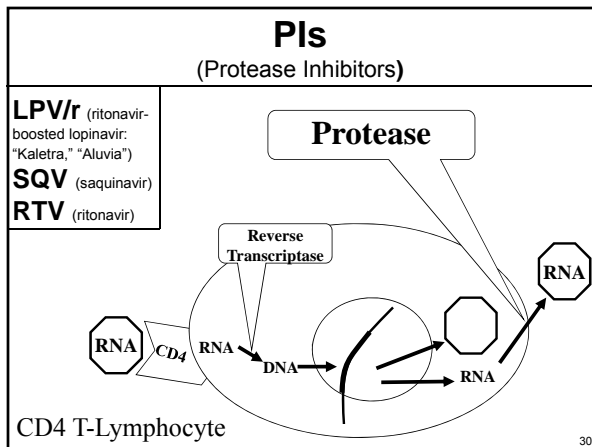




Mechanism of Action: PIs

- Protease inhibitors inhibit protease by binding at the catalytic site of protease.
- Assembly of the various components of the HIV particle cannot take place, and non-functional, non-infectious virions are produced.

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HAART Regimens Under the 2008 Guidelines: General Principles

- Under the 2008 Guidelines, the general structures of first and second line regimens for all ages remain the same:

First line regimen	2 N[t]RTIs	EFV or NVP
Second line regimen	2 N[t]RTIs	LPV/r

- Both first and second line regimens always contain two reverse transcriptase inhibitors:
- First line regimen is NNRTI-based (EFV or NVP).
- Second line regimen is PI-based (LPV/r).

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HAART Regimens Under the 2008 Guidelines: General Principles (2)

- The major changes in the 2008 regimens achieve important clinical goals:
 - Avoidance of AZT in first line HAART (except for pregnancy, as below), because of increased risk of AZT-induced anemia in AIDS patients. However, patients who are stable on the AZT-based 2005 first line regimen should continue this regimen under the 2008 Guidelines.
 - Avoidance of d4T in adolescents and adults, because of increased d4T-related toxicities. (Pediatric patients have fewer d4T/ddI side effects). Patients on any d4T/3TC- and d4T/ddI-containing regimens will be switched to TDF/FTC (or 3TC)-containing HAART under the 2008 Guidelines.

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**2008 Botswana Guidelines:
 New Adult & Adolescent Patients (Non-Pregnant)**

	NRTI/NtRTIs	NNRTIs	PIs
1 st Line	TDF + FTC or TDF + 3TC	NVP* or EFV	(Exceptions below)*
2 nd Line	AZT + 3TC		LPV/r
3 rd Line	Resistance assay and consultation with HIV Specialist		

*NVP if woman has reproductive potential
 *LPV/r if sd-NVP < 6 months prior.
 *If baseline CD4 count > 250 cells/μL (women) or > 400 cells/μL (men), use either EFV or LPV/r.

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Adult Patients Currently on Prior 1st and 2nd Line Regimens (2005 Guidelines)

- Adult patients currently on **AZT + 3TC + EFV/NVP** should continue this regimen as long as VL has been < 400 copies/mL and there are no **AZT**-associated side effects (e.g., anemia, lipoatrophy, neuropathy).
- Adult patients currently on either **d4T + 3TC + EFV/NVP** or **d4T + ddl + EFV/NVP** must be switched *as soon as possible* to the new 1st line regimen of **TDF + FTC (or 3TC) +EFV/NVP**, in order to avoid **d4T/ddl** toxicities.

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**2008 Botswana Guidelines:
 New Pregnant Patients Eligible for HAART**

For pregnant women who are eligible for HAART, AZT-based HAART is recommended for its PMTCT effects (see also lecture 12). The AZT-based regimen should be continued after delivery if there have been no side effects. If this first line regimen fails during pregnancy, discuss use of TDF in second line regimen with an HIV Specialist.

	N[t]RTIs	NNRTIs	PIs
1st Line	AZT + 3TC	NVP	
2 nd Line	TDF + FTC (or 3TC)		LPV/r
3 rd Line	Consultation with HIV Specialist		

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**Standard 1st line HAART:
 New Adult Patients (Non-Pregnant)**

2 NRTI/NtRTIs + 1 NNRTI

- **TDF+FTC (or 3TC) + EFV**
- **TDF+ FTC (or 3TC) + NVP**
- Give **NVP** to women with reproductive potential.
- In adults, **EFV** is usually given to all males and to women without reproductive potential.

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**Standard Dosages of 1st Line Therapy:
New Adult Patients**

- **(TDF + FTC):*** 1 tablet OD
- **TDF + 3TC:**
 - TDF 300mg OD
 - 3TC 150mg BD, or 300mg OD
- **EFV** (200mg capsules and 600mg tablets):** 600 mg nocte

*Co-formulated TDF/FTC ("Truvada"): 300mg TDF + 200mg FTC
**Co-formulated TDF/FTC/EFV ("Atripla"): 300mg TDF+
200mg FTC+600mg EFV₃₇

**Standard Dosages of 1st Line Therapy:
New Adult Patients (2)**

- Nevirapine: 200 mg BD
 - Begin NVP, 200 mg OD for 2 weeks.
 - After 2 weeks, evaluate the patient for rash or symptoms of hepatitis, draw AST/ALT, and, if patient is without symptoms of rash or hepatitis, increase NVP to 200 mg BD.
 - Dose escalation will reduce the incidence of side effects.

**NVP Hepatotoxicity
with High Baseline CD4 Counts**

- Because of increased risk of hepatotoxicity, avoid **NVP** in patients with high baseline CD4 counts, e.g., patients who qualify for HAART because of WHO stage 3 or 4 conditions, as follows:
 - Women with baseline CD4>250 cells/ μ L
 - Men with baseline CD4>400 cells/ μ L

**Standard 2nd Line HAART for Adults:
 2 N[t]RTIs + LPV/r**

Second line regimen will depend upon what the failing first line regimen has been:

Failure of this first line regimen:	Switch to this second line regimen:
AZT + 3TC + EFV or NVP	TDF + 3TC + LPV/r
TDF + FTC/3TC + EFV or NVP	AZT + 3TC + LPV/r

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Standard Doses: New 2nd Line Regimen for Patients Failing the 2008 1st Line Regimen

- AZT 300mg BD
- 3TC 150mg BD (or 3TC 300mg OD)
- LPV/r 400mg/RTV 100mg BD:
 - “Kaletra” (LPV 133mg/RTV 33mg): 3 capsules BD, preferably with food
 - “Aluvia” (LPV 200mg/RTV 50mg): 2 tablets BD
 - Unlike Kaletra, Aluvia is heat-stable and not food-dependent.

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Patients on Prior Second Line Regimen d4T + ddl + LPV/r

- Adult patients on prior second line regimen of **d4T + ddl + LPV/r** must be switched to **TDF + FTC (or 3TC) + LPV/r**, to avoid d4T/ddl toxicities.
 - Prior to switch, it is essential to determine that viral load within the previous 6 months was < 400 copies/mL.
 - If viral load not done within prior 6 months, then first obtain *priority* viral load, and if < 400 copies/mL, proceed with switch. If not < 400 copies/mL, then defer switch and address possible treatment failure.
 - Obtain follow-up *priority* viral load 6 weeks after the switch. If full viral suppression is not maintained, an HIV Specialist must be consulted.

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**Patients Referred on
 Non-Standard Regimens**

- Patients referred on HAART regimens containing d4T and/or ddI should be switched to a **TDF**-based regimen, while retaining either the NNRTI or PI component of the original regimen:

Original NRTIs:	Switch to:
d4T + 3TC	TDF + FTC (or 3TC)
ddI + 3TC	TDF + FTC (or 3TC)
d4T + ddI	TDF + FTC (or 3TC)

- Prior to switch, it is essential to determine that viral load within the previous 6 months was < 400 copies/mL. Obtain *priority* 6 week viral load after switch, to confirm continued virologic suppression.

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**HAART in Women with
 Past History of Single-Dose NVP**

- Single-dose NVP (sd-NVP) given to a woman at delivery can affect success of future NVP-based HAART, if initiated within 6 months of the sd-NVP. In such instances, LPV/r should be used instead of NVP.
- Women starting HAART must be evaluated for any past history of sd-NVP for PMTCT.
- First line regimen for women who received sd-NVP for PMTCT:
 - sd-NVP < 6 mos ago: **TDF + FTC (or 3TC) + LPV/r**
 - sd-NVP > 6 mos ago: **TDF + FTC (or 3TC) + NVP/EFV**

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**Summary:
 HAART Under the 2008 Guidelines**

- Key points to consider before initiating first line HAART:
 - Whether a woman has received sd-NVP within the prior 6 months
 - Whether a woman is pregnant, in which case AZT-based HAART is recommended
 - Whether the *baseline* CD4 count is > 250 cells/μL (women) or > 400 cells/μL (men) re: NVP hepatotoxicity

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Summary: HAART Under the 2008 Guidelines (2)

- Patients who are stable on the prior AZT-based first line regimen should continue this regimen.
- For adults/adolescents, d4T must be switched to **TDF**.
- Second line regimen will depend upon which particular first line regimen the patient has failed.

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Laboratory Monitoring of Patients on HAART

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Chemistry and Hematology

- Before start of HAART: full blood count, full chemistry (including AST/ALT, glucose, urea, creatinine), RPR, total cholesterol and triglycerides
- Monitoring labs post-HAART initiation:
 - FBC:
 - AZT-based HAART: at 1, 3, and 12 months, **then annually only**, and as clinically indicated
 - If not on AZT-based HAART: **annually only**, and as clinically indicated
 - AST/ALT:
 - NVP-based HAART: at 2, 4, and 12 weeks, thereafter **only as clinically indicated**
 - EFV-based HAART: at 4 and 12 weeks, thereafter **only as clinically indicated**
 - PI-based HAART: only as clinically indicated
 - Glucose and total cholesterol/triglycerides annually **only if on PI-based HAART**

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KITSO AIDS Training Program
 AIDS CLINICAL CARE FUNDAMENTALS

2008 Adult 1 st Line HAART (Non-Pregnant): TDF+FTC (3TC)+NVP/EFV							
	Baseline	2 weeks	1 month	3 months	6 months	12 months	Thereafter
CD4 count	✓			✓	✓	✓	q 6 months
Viral load	NONE			✓	✓	✓	q 6 months
FBC	✓					✓	q 12 months
Chemistry	✓						As indicated
AST/ALT	✓	✓ (NVP)	✓	✓			As indicated
Creatinine, C _{creat}	✓			✓	✓		q 6 months
RPR	✓						As indicated ⁴⁹

**Creatinine Clearance
for TDF-Based HAART**

- Renal function must be monitored for all TDF-containing HAART.
- Blood urea and creatinine are not acceptable measures of renal function, and can still be in normal range in spite of significant renal impairment.
- Creatinine clearance must be calculated at baseline, at 3 and 6 months post-initiation, and thereafter every 6 months for all patients on TDF. The following equations should be used to calculate creatinine clearance using serum creatinine, weight (kgs), and age in years:
 - Males: $1.22 \times [(140 - \text{age in yrs}) \times \text{wt (kg)}] / [\text{serum creat.}]$
 - Females: $1.037 \times [(140 - \text{age in yrs}) \times \text{wt (kg)}] / [\text{serum creat.}]$
- If baseline C_{creat} < 60cc/min, then do not use TDF. If on-treatment the C_{creat} becomes < 50cc/min, then consult HIV Specialist for guidance.

**Use of TDF When
Baseline C_{Creat} is < 60 cc/minute**

- Recalculate the creatinine clearance 2-3 days later, repeating the serum creatinine and patient weight, which should be verified with another set of scales. If the repeat clearance is still < 60cc/minute:
 - Initiate HAART with AZT, or, if there is significant baseline anemia, d4T. If already on d4T, continue d4T and do not switch to TDF.
 - Patients initiated on AZT should continue this ARV indefinitely, as long as there are no AZT side effects.
 - For patients on d4T, monitor the creatinine clearance every 3 months, until it is > 60cc/minute, at which time switch to TDF can be done. Also, monitor the patient at every visit for any adverse effects of d4T.
 - If side effects from either AZT or d4T develop, and creatinine clearance remains < 60cc/minute, then consult an HIV Specialist for use of ABC.

Use of TDF When Serum Creatinine Cannot be Done

- Proceed with TDF initiation or switch, *unless* 1) the patient is over 60 years of age, 2) the patient has a history of renal disease (insufficiency, chronic infection, stones), 3) there is greater than trace proteinuria on urinalysis, 4) serum urea is above the upper limit of normal range, or 5) the patient has conditions such as diabetes or uncontrolled hypertension, which might impair renal function. When serum creatinine can eventually be done, monitor C_{creat} per laboratory schedules.
- For patients who fall into one or more of the above five clinical situations, initiate HAART with AZT (or d4T, if there is anemia). If already on d4T, continue d4T and do not switch to TDF.
 - Once serum creatinine can be done, monitor clearance every 3 months for patients on d4T, until it is > 60cc/minute, at which time switch to TDF can be done. Monitor at every visit for any adverse effects of d4T.
 - Patients initiated on AZT should continue this ARV indefinitely, as long as there are no AZT side effects.
 - If side effects from either AZT or d4T develop, then consult an HIV Specialist for use of ABC.

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**1st Line HAART for Eligible Pregnant Women:
 AZT + 3TC + NVP**

	Baseline	2 weeks	1 month	3 months	6 months	12 months	Thereafter
CD4 count	✓			✓	✓	✓	q 6 months
Viral load	NONE			✓	✓	✓	q 6 months
FBC	✓		✓	✓		✓	q 12 months
Chemistry	✓						As indicated
AST/ALT	✓	✓	✓	✓			As indicated
RPR	✓						As indicated

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2008 Adult 2nd Line HAART: AZT+3TC+LPV/r

	At switch	1 month	3 months	6 months	12 months	Thereafter
CD4 count			✓	✓	✓	q 6 months
Viral load			✓	✓	✓	q 6 months
FBC	If not done at baseline	✓	✓		✓	q 12 months
Chemistry	As above					As indicated
AST/ALT	As above					As indicated
Glucose, TG/chol	If not done in prior 12 months				✓	q 12 months

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KITSO AIDS Training Program

AIDS CLINICAL CARE FUNDAMENTALS

Previous Adult 1st Line Regimen (AZT+3TC+NVP/EFV):
Continue if no AZT side effects
 Start this schedule at whatever post-initiation stage the patient is at when 2008 guidelines are released. Also, use this schedule for new pregnant patients.

	2 weeks	1 month	3 months	6 months	12 months	Thereafter
CD4 count			✓	✓	✓	q 6 months
Viral load			✓	✓	✓	q 6 months
FBC		✓	✓		✓	q 12 months
Chemistry						As indicated
AST/ALT (NVP)	✓	✓	✓			As indicated
RPR						As indicated

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Prior Adult 1st Line d4T+3TC+NVP/EFV or d4T+ddI+NVP/EFV:
Change to TDF+FTC/3TC+ NVP/EFV.
Prior Adult 2nd Line d4T + ddI + LPV/r: Change to TDF+FTC/3TC + LPV/r

	At time of switch	6 weeks	3 months	6 months	12 months	Thereafter
Viral load	If not done within prior 6 months and < 400 copies	✓		✓	✓	q 6 months
CD4 count	As above			✓	✓	q 6 months
FBC	If not done at baseline				✓	q 12 months
Chemistry	If not done at baseline					As indicated
AST/ALT	If not done at baseline					As indicated
Glucose, chol/TG	If not done in prior 12 months				✓	q 12 months (LPV/r only)
Creatinine, C _{creat}	✓		✓	✓	✓	q 6 months

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Notes on 2008 Laboratory Schedule

- “Chemistry” testing should include electrolytes, urea, creatinine, glucose.
- “As indicated” means that these tests should not be done routinely; rather, they should only be done when specifically indicated in individual patients.
- CD4 cell count/% measurements should return to every three month determinations (or more frequently as clinically indicated) whenever any of the following situations arises:
 - Any new WHO stage 3 or 4 clinical condition
 - Whenever a previously suppressed viral load becomes detectable
 - Any time the patient’s HAART regimen is changed, either for failure, toxicity, or side effects
 - When viral load results are not available
 - Once any of the above situations becomes stable for 6 months, then CD4 cell count/% determinations may return to every 6 months.

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Notes on 2008 Laboratory Schedule (2)

- Once a patient's CD4 cell count/% has been > 300 cells/ μ L/30%, respectively, for one year (i.e., two consecutive six-month determinations), then CD4 cell counts/% should be done every 12 months.
- Any change in HAART regimen for treatment failure requires repeat viral load 3 and 6 months after the switch. If < 400 copies/mL, then viral load monitoring can resume every 6 months.
- When a regimen has previously been fully suppressive, switching ARVs for toxicity (or to avoid d4T and ddI as required in 2008 guidelines) requires follow-up priority viral load 6 weeks after the switch, to verify that viral suppression has been maintained.

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Notes on 2008 Laboratory Schedule (3)

- When HAART has been restarted or continued after completed interventions for treatment failure due to nonadherence, drug interactions, gastroenteritis, or incorrect ARV dose, obtain follow-up *priority* viral loads after 6 weeks, to determine if the intervention has been successful (see Lecture 9).
- If ATT is being administered with HAART, AST/ALT should be monitored monthly for the first 3 months, or more frequently as indicated.
- For pediatric and adolescent patients: viral load every 3 months until age 20 years.

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2008 Guidelines Testing Schedule

- **Baseline viral load must not be done!!!!**
- Once viral load is < 400 copies/mL 6 months after HAART initiation, it should be measured only every 6 months **for adults.**
- **Pediatric and adolescent patients (under 20 years of age) must have every 3 month viral load monitoring.**
- CD4 count/%: monitor only every 6 months for all ages, once 3 and 6 month post-initiation monitoring has passed.
- Frequency of FBC and ALT/AST monitoring has been decreased, and is determined by the specific HAART regimen (see prior slides). **CLINICIANS MUST NOT ROUTINELY ORDER EVERY THREE MONTH FBC, AST/ALT, CD4%, AND VIRAL LOAD.**

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3rd Line or “Salvage” Therapy

- There are limited options for 3rd line regimen in the Botswana National Program
- A patient who has failed two regimens will need a regimen that takes into account the previous drug history.
- Adherence assessment and interventions are crucial.
- Genotypic resistance assay *must* be performed *while the patient is still on the failing regimen*, or no later than 4 weeks after discontinuation of the failing regimen.
- *Do not wait for more than 4 weeks for the resistance assay to return* before changing to an empiric third line regimen, under Specialist guidance.

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3rd Line or “Salvage” Therapy (2)

- By late 2008, two new, highly potent ARVs will be available for use as “salvage” therapy for patients who have failed multiple ARV regimens. Darunavir (DRV) is a potent protease inhibitor, and raltegravir (RAL) is an integrase inhibitor.
- “Salvage” therapy of both DRV and RAL (plus optimized background therapy), if used properly, should result in full virologic suppression in the majority of cases. A patient who may require such “salvage” HAART should be referred to an HIV Specialist.
- DRV dosing (300mg tablets): 600mg BD *with 100mg RTV BD*, taken with food. Major side effects: diarrhea, hepatitis, rash (rare SJS). Metabolized by CYP450 3A4, and drug interactions are anticipated.
- RAL dosing (400mg tablets): 400mg BD. No significant side effects or drug interactions have been reported to date.

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Changing Regimens

In the course of therapy there are two reasons to change regimens:

1. Toxicity or Severe Side Effects: for any serious and/or persistent adverse reaction to a particular ARV drug in the regimen, **CHANGE ONLY THE OFFENDING DRUG, RETAINING THE OTHER ARV DRUGS.**
OR
2. Therapy Failure: when the HAART regimen fails to suppress viral replication to < 400 copies/mL (either by 6 months after initiation or, after initial suppression, at anytime in the future), **CHANGE ENTIRE REGIMEN.**

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Principle 6

- **Therapy failure *MUST* be addressed promptly, and the patient must not be kept on a failing regimen for more than a month.**
- **Every ARV clinic *must* have an ongoing procedure for reviewing lab tests, including viral loads, as soon as they return, for any abnormalities requiring action.**
 - Because baseline viral loads have been abolished, any returning viral load *not* < 400 copies/mL will be from a patient on HAART, and thus *must* be promptly followed up.

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Principle 7

- Decisions about changing a patient to third line regimen should be reviewed with an HIV Specialist as soon as possible. Resistance assay must be performed on patients failing second line regimen, for review with the Specialist.
 - If the assay does not return within 4 weeks, begin on empiric 3rd line regimen, under Specialist guidance.
 - An HIV Specialist Panel has been established as a resource for practitioners to contact any time clinical questions arise. Contact numbers of individual Specialists are listed in the 2008 guidelines and at www.moh.gov.bw.

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Treatment Failure

- **Virologic**: failure to suppress HIV replication to < 400 copies/mL, either by 6 months after HAART initiation, or, after initial suppression to < 400 copies/mL, any time afterwards.
- **Immunologic**: 1) failure to increase CD4 count by 25-50 cells/ μ L by 1 year after HAART initiation, 2) a decrease in CD4 count below baseline, or 3) a 50% decrease in CD4 count from the highest CD4 count on HAART.
- **Clinical**: occurrence of an OI or other AIDS-defining event more than 3-6 months after initiation of HAART.
- All cases of immunologic and/or clinical failure when viral load is < 400 copies/mL *must* be reviewed with an HIV Specialist before changing regimens. Such patients may not require regimen switch.

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Treatment Failure (2)

- For the patient not yet on treatment, decisions about when to initiate HAART focus on immunologic (i.e., CD4 count) and clinical factors (WHO Clinical Stages 3 or 4 conditions and/or symptoms).
- Once the patient starts HAART, *the focus of attention changes*: decisions about therapy success or failure center primarily on the virologic response (i.e., whether or not viral load is < 400 copies/mL by 6 months). The CD4 and clinical responses usually follow the virologic response.

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Treatment Failure (3)

- Usually virologic failure occurs first, followed by immunologic failure, and then clinical deterioration.
- Only rarely will a patient have immunological or clinical failure without virologic failure. Such patients must be reviewed with an HIV Specialist before changing regimens.
- In general, “therapy failure” means virologic failure, and the two terms are usually used interchangeably.

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Definition of Treatment (i.e. Virologic) Failure

- The ARV regimen initially fails to suppress replication—i.e., the viral load does not fall to < 400 copies/mL no later than 6 months after HAART initiation.
- or*
- The regimen initially suppressed replication (viral load <400 copies/ml), but at a later date (months or years after successful HAART initiation) the viral load now becomes detectable (i.e., >400 copies/ml).

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TB/HIV Co-Infection and HAART

- Patients with newly diagnosed TB and not on HAART should be treated for TB first, and HAART should be delayed.
- Timing of HAART initiation after ATT initiation for active TB depends upon both the CD4 count and the clinical condition of the patient.
- Patients already on HAART and who develop active TB should continue HAART while ATT is initiated, but with close clinical and laboratory monitoring for hepatotoxicity and with attention to any drug interactions, e.g., RIF and LPV/r.

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TB/HIV Co-Infection and HAART (2)

TB/HIV Co-infected Patients not yet on HAART:

- **CD4 > 250** Treat TB first, then evaluate for HAART
- **CD4 100-250** Treat TB first, and begin ART 2-4 weeks later, depending upon severity of HIV-related disease. Patients in good clinical condition can defer ART until 2 months post-ATT initiation.
- **CD4 < 100** ART may be started as early as 1-2 weeks post-ATT initiation, only if patient's condition is desperate. Closely monitor LFTs!

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TB/HIV Co-Infection and HAART (3)

- Early initiation of HAART in active TB infection will not enhance ATT, but will protect against other O.I.s. However, early HAART may transiently *worsen* TB symptoms, due to immune reconstitution inflammatory syndrome (see Lecture 10).
- Patients on ATT and **NVP**- or **EFV**-based HAART do *not* require dose adjustment of either **NVP** or **EFV**.
- Because of significant drug-drug interactions between rifampicin and protease inhibitors, patients who develop TB while on LPV/r-based regimens require major modifications to their ARV regimen, since rifampicin lowers **LPV** levels profoundly, and treatment failure will result (see Lecture 7).

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Nutrition

- ARVs control the virus. Good nutrition supports immune reconstitution.
- Daily multiple vitamins in patients with poor food intake or wasting
- Use of good hygiene with food preparation
- High-protein diets with a minimum of five portions of vegetables and fruit every day
- Thorough cooking of meat, avoidance of raw/under-cooked meat, eggs, and seafood

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Nutrition (2)

Nutritional Strategies for HIV Complications:

- Weight loss:
 - Energy-/protein-rich diets and drinks
 - Frequent snacks
- Anorexia:
 - Small frequent meals and snacks
- Nausea:
 - Avoid cooking smells
 - Ginger or peppermint additives
- Diarrhea:
 - Increased fiber
 - Decreased lactose (milk products)
 - Decreased fat intake if malabsorption suspected

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Nutrition (3)

- Avoidance of *ingested* traditional medicines, which may adversely affect appetite and cause adverse drug interactions. Spiritual healing and other non-parenteral, noninvasive practices should not be discouraged, since such “healing” may provide important cultural and spiritual support to patients.
- Practitioners must identify and treat any conditions which might interfere with proper nutrition, such as oro-esophageal candidiasis, oral or esophageal ulcers, dental disease, and gastroenteritis.
- Patients must be discouraged from using so-called “immune boosters,” which are of unproven benefit and are often very expensive.

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Principle 8

Being “naïve” to a class of drugs is the single most important factor in predicting response to future salvage therapy. Any salvage regimen should ideally contain at least two active ARVs.

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Principle 9

Adherence strategies between patient and clinician are as important
or
more important
than any choice of ARV drugs.

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Principle 10

All HIV-infected persons, even those taking ARV medications with viral loads below detectable limits, still remain infectious. Safer sex counseling must occur at every patient visit, as well as discussion of family planning and reproductive choices.

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Final Summary

- ARV choices are limited, and must be protected:
 - Use 3 ARVs simultaneously.
 - Always discuss adherence at *every* visit.
 - Closely monitor for evidence of treatment failure by *prompt review of returning viral loads*.
- For any drug change make sure the reasons are clearly documented.
- If in doubt, ask the most experienced HIV physician, or consult an HIV Specialist.

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