

HIV Treatment Guidelines: 2010

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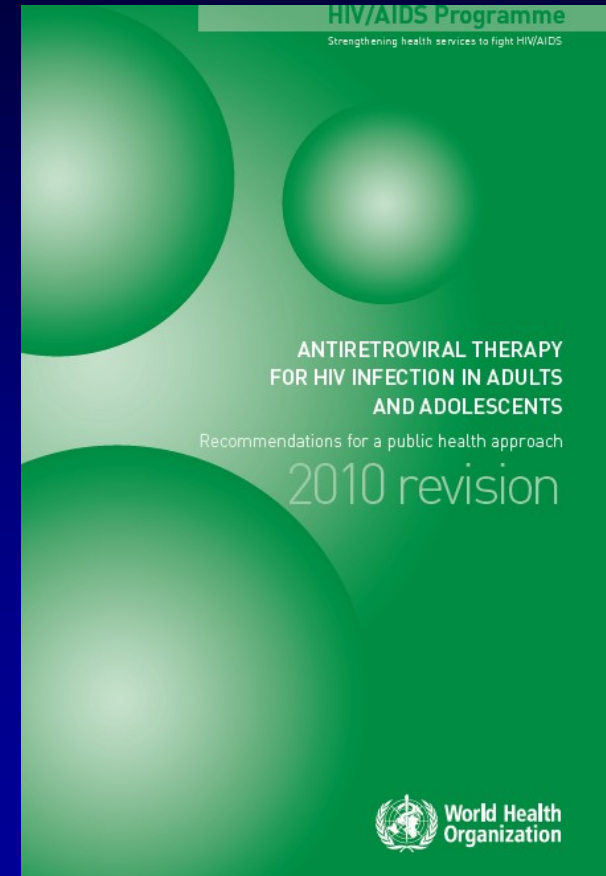


Case

- 29 yo M with 8 weeks of cough and fever.
- Diagnosed with smear-positive pulmonary TB.
- HIV-1 antibody positive.
- CD4 count 361. HIV-1 RNA 23,000 c/mL. HBsAg negative.
- Started on antituberculous therapy, with rapid improvement in his symptoms.
- What do you do next?
 1. Recommend initiation of ART
 2. Monitor CD4 count; start ART when <250

WHO Guidelines

- First published 2002, updated 2006
 - ART recommended when CD4 cell count <200
- Revision: July 2010
 - Antiretroviral therapy for HIV infection in adults & adolescents (today)
 - Antiretroviral drugs for treating pregnant women & preventing HIV infection in infants (V. Black, tomorrow)
 - Antiretroviral therapy for HIV infection in infants & children (M. Archary, tomorrow)



WHO Guidelines

- “Public health approach to the delivery of ART . . . in settings with limited health systems capacity and resources”
- Consider in context of countries’ health systems and resources
 - Avoid undermining current treatment programmes
 - Protect access for the most at-risk populations
 - Achieve greatest impact for the greatest number of people
 - Ensure sustainability
- Evidence weighted using the “GRADE” evidence profile methodology



Key Recommendations

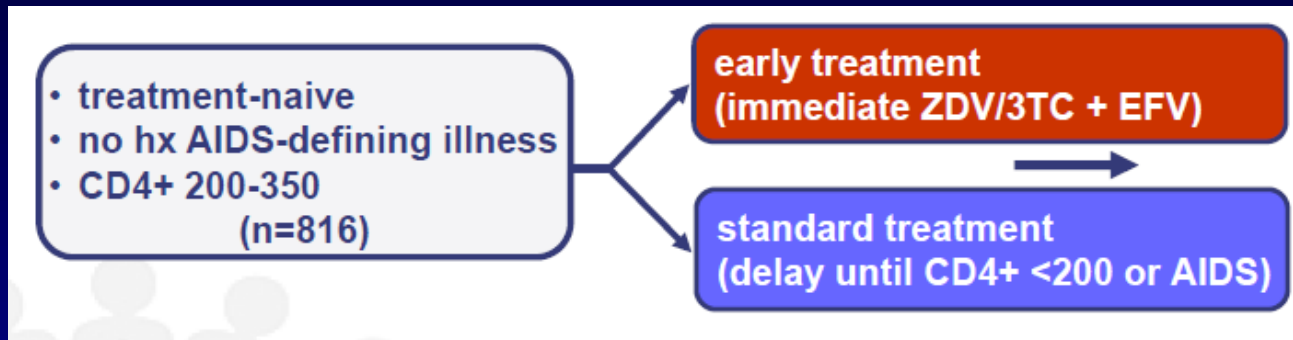
- When to start
- What to start
- ART for HIV/TB coinfection
- ART for HIV/HBV coinfection
- ART for pregnant women
- When to switch ART
- Second-line ART
- Third-line regimens

WHO Guidelines: When to Start

- CD4 count <350, irrespective of symptoms
- WHO stage 3 or 4, irrespective of CD4 count
 - Unexplained weight loss, chronic diarrhea, pulmonary TB, severe bacterial infections, unexplained cytopenias, opportunistic infection or malignancy, HIV-associated nephropathy or cardiomyopathy
- CD4 testing required to identify if patients with WHO stage 1 and 2 disease need to start ART
 - >50% stage 1 and 2 patients have CD4 count <350

CIPRA HT001

- Randomized controlled trial in Haiti of early vs. deferred therapy in HIV-infected patients with CD4 count 200-350

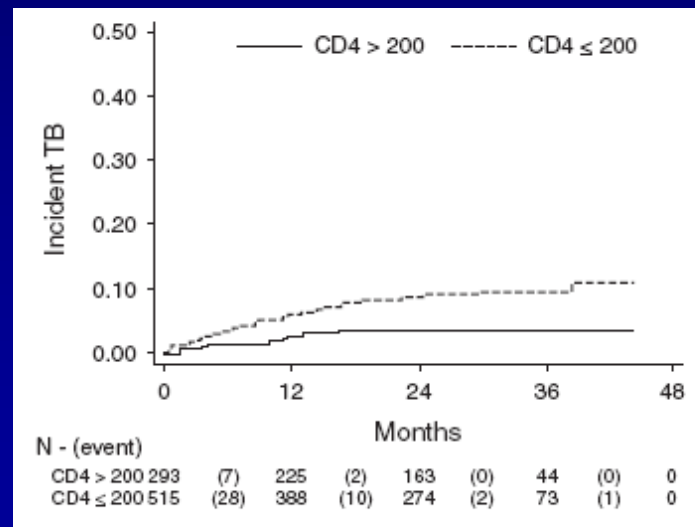
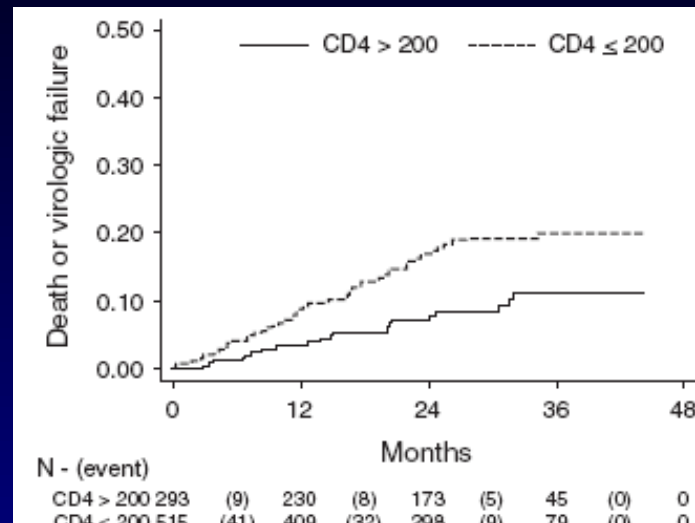


- DSMB stopped trial after median follow-up of 21 months because of excess mortality in the standard of care arm

	Early	Standard	HR (p-value)
Death	6	23	4.0 (0.0011)
Incident TB	18	36	2.0 (0.0125)

CIPRA-SA

- Observational cohort study within a randomized study of doctor- vs. nurse-monitored ART
- 812 patients in Jo'burg and Cape Town with CD4 cell count <350
- Compared with patients who started ART when CD4 cell count <200, those who started when CD4 cell count >200 had:
 - Lower risk of virologic failure (6.8% vs. 12%)
 - Lower risk of death (0.7% vs. 3.7%)
 - Lower risk of incident TB



WHO Guidelines: Benefits and Risks

15 million people eligible for ART, up from 10 million. Only 5.2 million currently on treatment

- **Benefits**

- 49% increase in # of people on ART; 20% reduction in mortality by 2010-2015
- Reduces costs of hospitalizations for OIs, other complications
- Reduces transmission
- Reduces TB (54-92%)



- **Risks**

- Increased ART costs by ~50%
 - Additional \$2 b over the next 5 yr
- Longer exposure to ART (~1-2 yrs more)
- May displace sicker patients if not all eligible patients can be treated

WHO Guidelines: What to Start

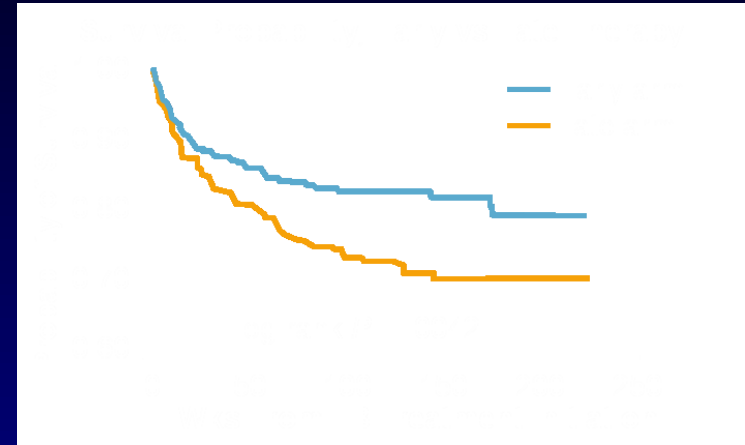
- AZT + 3TC+ EFV
 - AZT + 3TC + NVP
 - TDF + 3TC or FTC + EFV
 - TDF + 3TC or FTC + NVP
-
- Panel placed “high value on avoiding the disfiguring, unpleasant and potentially life-threatening toxicity of d4T”
 - Countries should move towards AZT- or TDF-based first-line regimens, based on an assessment of cost and feasibility
 - If d4T use is continued, it should be dosed at 30 mg BID for all individuals, irrespective of body weight

ART for HIV/TB Coinfection

- Start ART in all HIV-infected patients with active TB, irrespective of CD4 count
 - ART reduces TB rates and TB recurrence rates
 - Modeling suggests TB mortality and transmission at the population level also decreased by ART
- Start TB treatment first, followed by ART as soon as possible (and within the first 8 wks)
- Use EFV as the preferred NNRTI
 - Less interaction with rifampicin compared with NVP

CAMELIA (Cambodian Early vs Late Introduction of Antiretroviral Drugs)

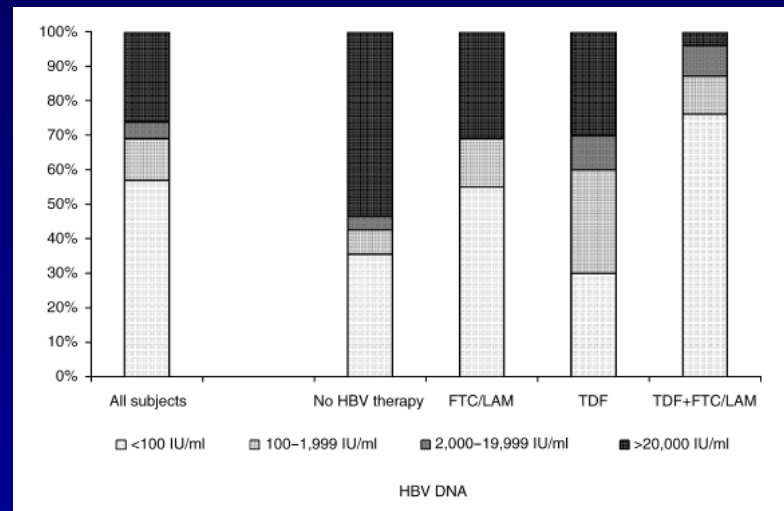
- 661 HIV+ pts with CD4 count <200 and newly diagnosed TB
 - Median CD4 count 25
 - 2/3 pulmonary TB, 22% pulm and extra-pulm TB
- All patients started TB treatment
- Randomized to begin ART either 2 or 8 wks later (d4T/3TC/EFV)
- Significantly lower mortality rate in the early arm
 - 8.28/100 pyr vs 13.77/100 pyr
 - 33% difference
- Higher incidence of IRIS in early gp: 4.03 vs. 1.44/100 person-mo.
- VL UD in 96.5%



Factor	Multivariate Adjusted HR (95% CI)	P
Late therapy	1.52 (1.12-2.05)	.007
BMI ≤ 16	1.68 (1.07-2.63)	.01
Karnofsky score ≤ 40	4.96 (2.42-10.16)	< .001
Pulmonary + extrapulmonary TB	2.26 (1.62-3.16)	< .001
NTM	2.84 (1.13-7.13)	< .001
MDR-TB	8.02 (4.00-16.07)	< .001

ART for HIV/HBV Coinfection

- TDF, 3TC, FTC active against HBV
- However, HBV resistance to 3TC: 25%/yr
- Use TDF + 3TC or FTC-containing regimens
 - Among 122 HIV/HBV, most with prior 3TC use, those on TDF + FTC/3TC more likely to have undetectable HBV DNA than those on TDF or 3TC monotherapy



Matthews GV,
AIDS, 2009

- Start ART in HIV/HBV+ who require treatment for HBV, irrespective of CD4 count or WHO stage
 - Global definition of chronic active hepatitis for RLS under discussion

ART for Pregnant Women



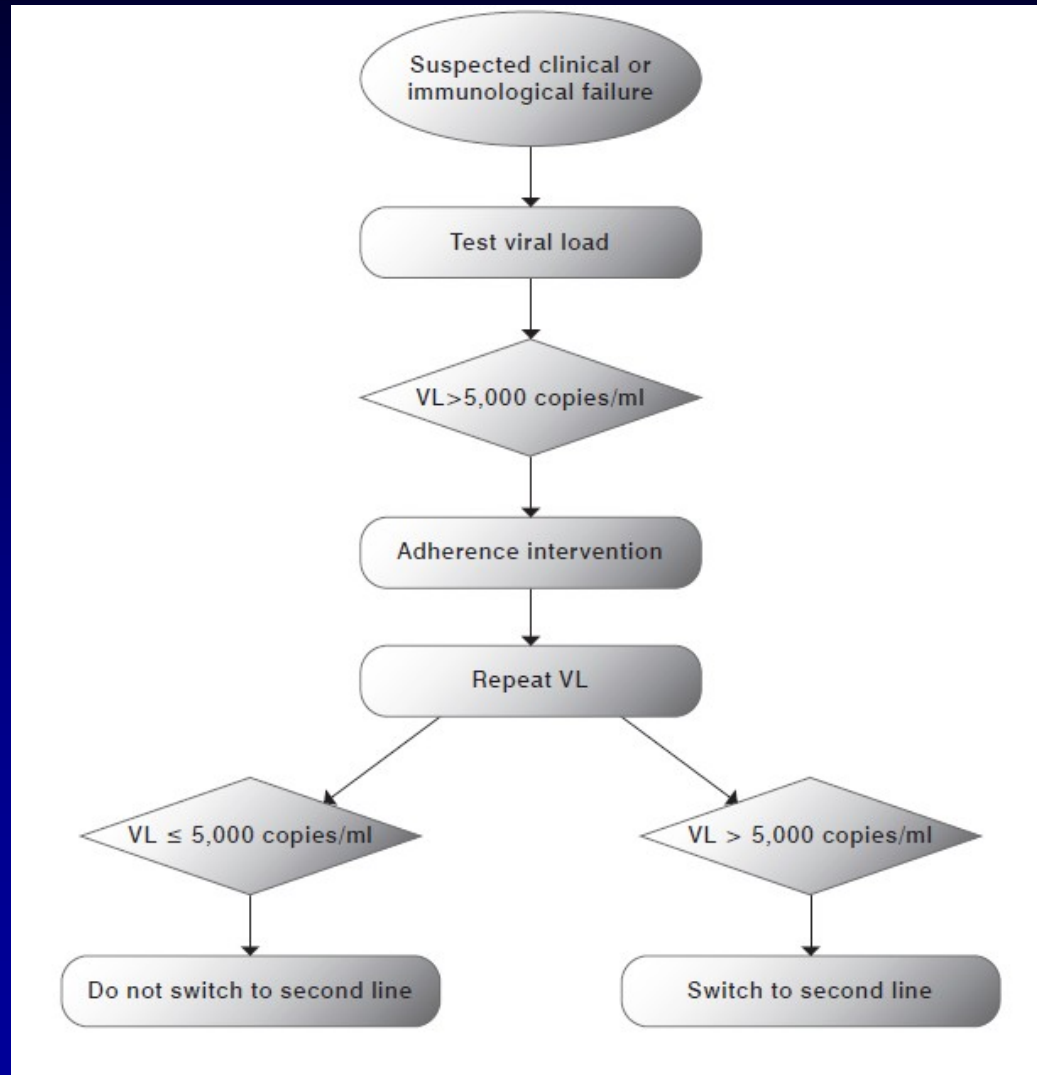
- Start ART in all pregnant women with CD4 count <350 or stage 3 or 4 disease
- CD4 count testing required to identify if pregnant women with stage 1 and 2 disease need to start ART and prophylaxis
- Start one of the following:
 - AZT + 3TC + EFV
 - AZT + 3TC + NVP
 - TDF + 3TC or FTC + EFV
 - TDF + 3TC or FTC + NVP
- Do not start EFV during the 1st trimester
- Stay tuned for Vivian Black's talk tomorrow



When to Switch ART

- Where available, use VL to confirm treatment failure
 - Immunological failure not good predictor of virologic failure: 8-40% of patients with immunologic failure have virologic suppression
- Where available, use VL every 6 months to detect HIV replication
- Persistent VL $>5,000$ confirms treatment failure
- When VL not available, use immunologic criteria to confirm clinical failure
 - Fall of CD4 count to baseline or below or
 - 50% fall from on-treatment peak value or
 - Persistent CD4 <100

When to Switch ART



Second-line ART

- Boosted PI (PI/r) + 2 NRTIs
- **Which boosted PI?** ATV/r and LPV/r preferred
- **Which NRTI?**
 - If d4T or AZT used in 1st-line, use TDF + 3TC or FTC
 - If TDF was used in 1st-line, use AZT + 3TC in 2nd line
- Important that monitoring and early switching take place to avoid resistance to 2nd line NRTI

Third-line ART

- National programmes should develop policies for 3rd line ART that “consider funding, sustainability and provision of equitable access”
- 3rd-line regimens should include new drugs, such as integrase inhibitors and 2nd generation NNRTIs and PIs
- Patients on a failing 2nd-line regimen with no new ARV options should continue with a tolerated regimen
- “It was recognized that many countries have financial constraints that may limit adoption of 3rd-line regimens”

Comparison of WHO and US Guidelines

	WHO	U.S. DHHS
When to start?	CD4 count <350	CD4 count <500 Consider: CD4 count >500
What to start?	EFV + AZT/3TC or TDF/3TC, FTC NVP + AZT/3TC or TDF/3TC, FTC	EFV or ATV/r or DRV/r or RAL + TDF/FTC
When to switch?	Persistent VL above 5,000	Persistent VL above 50

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Implementing the WHO Guidelines

- Guiding principles for implementation
 - Do no harm: preserve access for sickest, most in need.
 - Accessibility: ensure eligible people can receive treatment
 - Quality of care
 - Equity of access
 - Efficiency in resource use (human and financial)
 - Ensure sustainability

Implementing the WHO Guidelines

- In implementing the new WHO guidelines, must be sure not to displace those who are most in need
 - How best to achieve this goal must be determined
 - Where resources not available to implement these guidelines immediately, high-risk population (TB, pregnancy) or CD4-based prioritization needed
 - A U.S. study showed that prioritizing patients with CD4 counts <250 lowered mortality and time to 1st OI compared with a first-come first-served approach. [Linac, JAIDS, 2009](#)

WHO Guidelines: Final Words

- In the “Rapid Advice” document, a remarkable statement: “In this context, the individual rights of PLHIV should not be forfeited in the course of a public health approach”
- “Act in such a way that you treat humanity, whether in your own person or in the person of any other, never merely as a means to an end, but always at the same time as an end”--Immanuel Kant



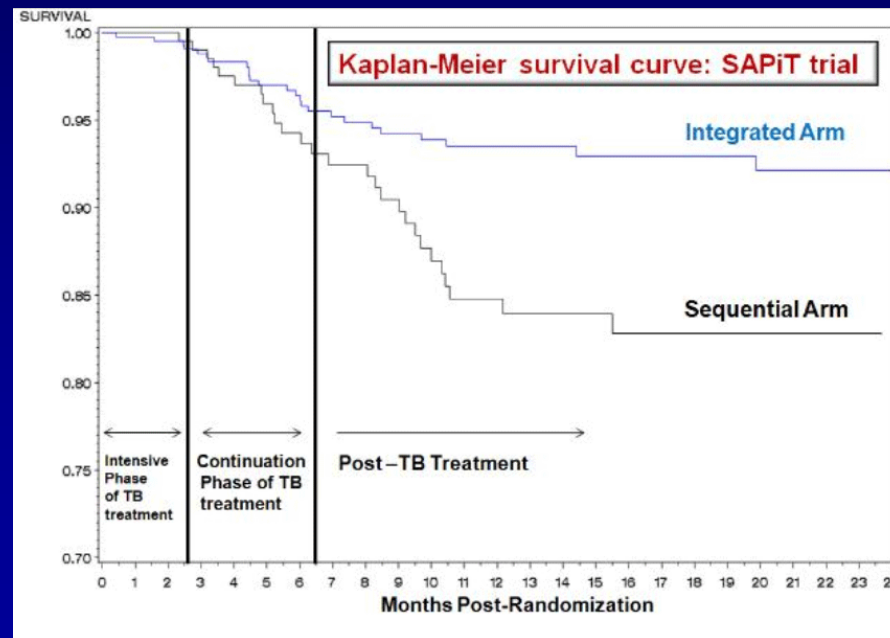
Extra Slides

WHO Guidelines: What to Start

- Panel placed “high value on avoiding the disfiguring, unpleasant and potentially life-threatening toxicity of d4T”
- Countries should move towards AZT- or TDF-based first-line regimens, based on an assessment of cost and feasibility
- “WHO will develop tools to assist countries/programs in the transition to and implementation of these recommendations”

SAPIT

- HIV+, CD4 count <500, smear + or – TB
- Integrated arms: ART initiated during TB therapy;
Sequential arm: ART started after TB therapy completed
- 56% lower mortality with earlier therapy, in both the CD4 <200 and >200 strata



DHHS Guidelines: When to Start

- **CD4 count-based criteria**
 - <350
 - CD4 count 350-500: 55% voted for strong recommendation; 45% voted for moderate recommendation
 - CD4 count >500: 50% favor, 50% view starting ART as optional
- **Irrespective of CD4 count**
 - AIDS-defining illness
 - Pregnancy
 - HIV associated nephropathy
 - HBV coinfection, when HBV therapy indicated

NA-ACCORD

- Collaboration of 22 HIV research cohorts in the US and Canada, representing more than 60 sites
- 17,517 asymptomatic treatment-naïve HIV+ patients who received medical care during 1996 to 2005
- Patients stratified by CD4 count: 350-500 or >500
- Compared the relative risk of death for patients who started ART when CD4 count was above the threshold vs. those who deferred therapy until the CD4 count was below the threshold

NA-ACCORD

- Two parallel analysis:
 - 1st analysis
 - 8362 patients with CD4 count 351-500
 - 2084 initiated therapy at CD4 count 351-500 and 6278 deferred therapy
 - 2nd analysis
 - 9155 patients with CD4 count >500
 - 2220 initiated therapy at CD4 count >500 and 6935 deferred therapy.

NA-ACCORD

- Risk of death associated with deferral of ART, according to CD4 count at baseline, with adjustment for VL, age, sex

	CD4 count 351-500		CD4 count >500	
	Relative risk	P-value	Relative risk	P-value
Deferral of therapy	1.69 (1.26-2.26)	<0.001	1.94 (1.37-2.79)	<0.001

DHHS Guidelines: What to Start

- EFV + TDF + FTC
- ATV/r + TDF + FTC
- DRV/r + TDF + FTC
- Raltegravir + TDF + FTC

- Pregnant women: LPV/r (twice daily) + AZT/3TC

DHHS Guidelines: When to switch

- Optimal virologic response to therapy:
 - VL < 400 after 24 weeks
 - VL < 50 after 48 weeks

DHHS Guidelines: Resistance Testing

- In patients with sub-optimal VL reduction, perform drug-resistance testing while the patient is taking ARVs
- Genotypic testing is preferred in patients with suboptimal virologic responses or virologic failure while on 1st or 2nd line regimens
- Add phenotypic testing to genotypic testing in persons with known or suspected complex drug resistance mutations, particularly to PIs