Resistance testing for Third Line

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Third-line ART

- Third-line ART is used when a patient has experienced virological failure on drugs from the NRTI, NNRTI and PI classes (with documented PI resistance).
- Adherence interventions should be intensified



When to Use Resistance Testing

	IAS-USA ^[1]	DHHS ^[2]	European ^[3]
Primary/acute	Recommend	Recommend	Recommend
Postexposure prophylaxis			Recommend*
Chronic, Rx naive	Recommend	Recommend	Recommend
Failure	Recommend	Recommend	Recommend
Pregnancy	Recommend	Recommend	Recommend
Pediatric		Recommend	Recommend

*Test source patient especially if treated with antiretroviral drugs.

1. Hirsch MS, et al. Clin Infect Dis. 2008;47:266-285.

2. November 2008 DHHS Guidelines. Available at: http://www.aidsinfo.nih.gov.

Accessed November 10, 2008.

3. EACS Guidelines Version 3. Available at: http://www.eacs.eu/guide/index.htm.

Accessed October 24, 2008.

Southern African HIV Clinicians Society

Failure of a boosted PI-based regimen		
Adults and children with two VL measurements >1 000 RNA copies/ml [†] and/or a <2 log ₁₀ drop in VL while on PI-based ART (measurements 3 - 6 months apart)	Recommended	Failure on PI regimens is almost always due to poor adherence. Adherence [‡] issues should be addressed comprehensively between the 2 measurements. Resistance testing should be performed while the patient is on the failing regimen or within 4 weeks of discontinuation.

What information can we get?

- Resistance tests serve two purposes:
 - Adherence test.
 - If resistance mutations are present, ability to chose a regimen.

What information can we not get?

- NRTI mutations that are present only represent the current regimen.
 - Presume all first generations will not work
- NNRTI mutation are usually archived

Requirements for resistance testing

- Patient must be on ART at the time or stopped within the last 4 weeks.
- Should not be done on the first detectable viral load
- No rush between 3-6 months.

Measures of adherence

- Self-reported, short-term adherence
- Dispensing-based long-term adherence
- Consistency of visit attendance
- Pill count-based medium-term adherence
- Electronic cap monitoring

Adherence support

- Inadequate treatment literacy
- Side effects
- Depression and other mental illnesses
- Poverty and food insecurity
- Work related issues
- Substance use
- Social problems
- Denial
- Pill burden
- Altered fertility intentions
- Conflict of opinions

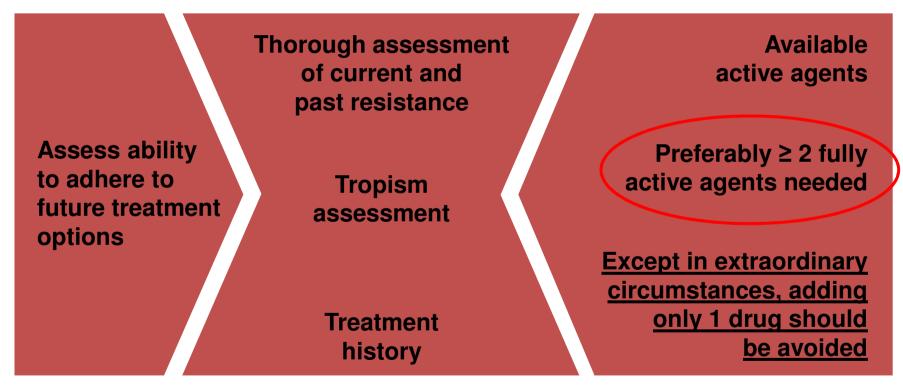
Principles

- First-generation NNRTIs have no place in thirdline therapy
- A boosted PI with the broadest resistance profile should be selected
- No double ritonavir-boosted PIs.
- The addition of 3TC (or FTC) is recommended
- Consideration of the addition of other salvage drugs (e.g. RAL and/or ETV) will depend on genotype resistance test result

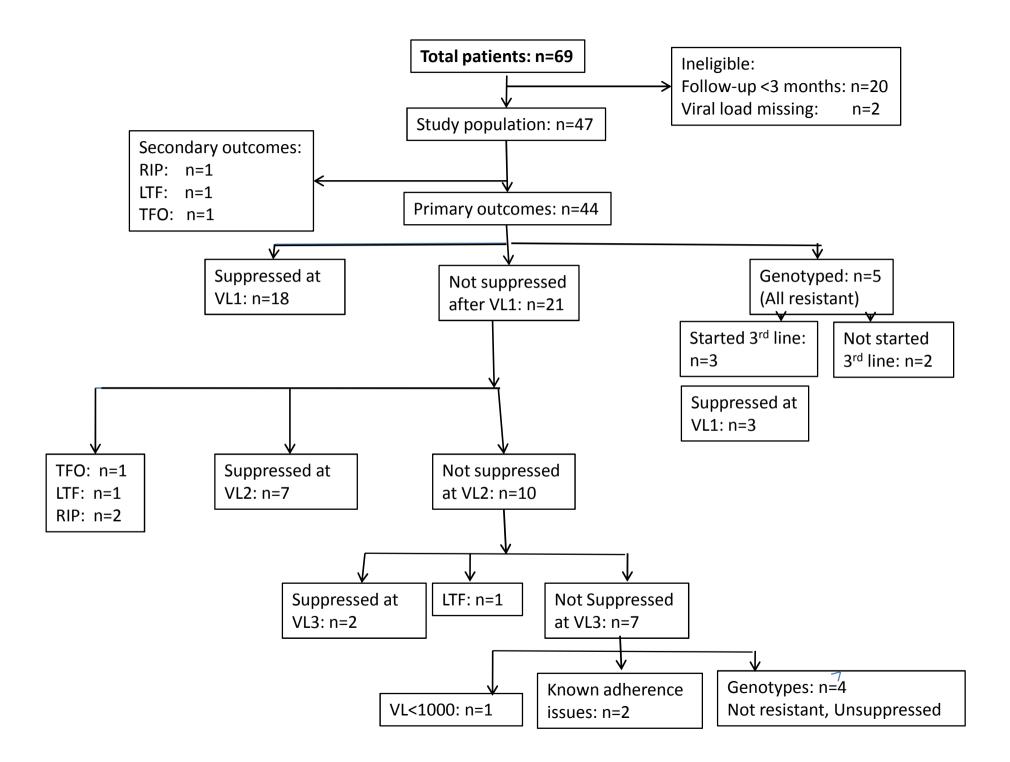
Patients who return after defaulting therapy

- Restart the same regimen and repeat HIV viral load measurements after 3 months
- Switching to a second-line regimen should be considered if the viral load is not suppressed at this point.
- AZT could be substituted for D4T.
- Do not substitute TDF

Is VL < 50 copies/mL Achievable in Tx-Experienced Patients With MDR HIV?



• Consider emerging treatment options and need for immediate enhancement of current regimen (ie, risk of clinical progression)



- All effort should be made to address adherence problems
- "understand the failure"
- Once adherence problems are solved, resuppresion if often possible under the same treatment.
- Request a Hep B sAg for patients failing a TDF base regimen. If Hepatitis B is positive, TDF should be included in the new regimen. (TDF is active against Hepatitis B virus)

PROTEASE INHIBITOR RESISTANCE IN SOUTH AFRICAN CHILDREN WITH VIROLOGIC FAILURE

Background:

- First-line ART for children < 3 years, PI + NRTI
- Children failing ritonavir or ritonavir-boosted lopinavir (LPV/r
- Major PI resistance mutations (MPIRM)

PROTEASE INHIBITOR RESISTANCE IN SOUTH AFRICAN CHILDREN WITH VIROLOGIC FAILURE

Materials and Methods:

Pediatric HIV patients at Tygerberg Academic Hospital with virologic failure on a PI regimen.

Results: MPIRM were found in

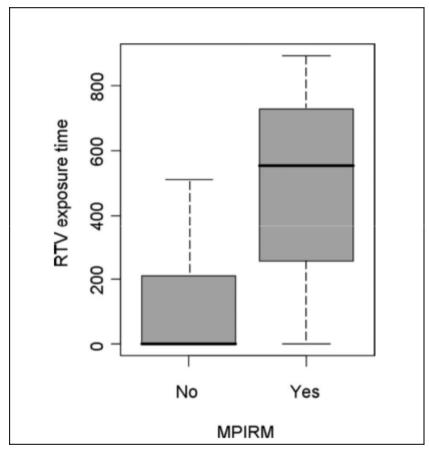
12 of 17 patients exposed to RTV-sPI

1 of 13 patients treated with LPV/r.

- Conclusions: RTV-sPI in infants and children poses a significant risk of MPIRM
- van Zyl, G.U. et al., 2009

Variable	$\begin{array}{l} LPV\!/r \\ (n=13) \end{array}$	$\begin{array}{l} RTV\text{-}sPI\\ (n=8) \end{array}$	RTV-sPI Followed by LPV/r (n = 9)	$\begin{array}{l} Total \\ (n=30) \end{array}$
Age at first study				
visit (mo) Median	27	20	33	28
Range	11-65	6-91	26-53	6-91
MPIRM (%)	1 (8%)	7 (88%)	5 (55%)	13 (43%)
Concurrent TB	5 (38%)	7 (88%)	7 (78%)	19 (63%)
therapy (number [%])				

van Zyl, G.U. et al., 2009. Protease inhibitor resistance in South African children with virologic failure. *The Pediatric infectious disease journal*, 28(12), pp.1125–7. 12, 2011].



• van Zyl, G.U. et al., 2009

HIV-1-resistance-associated mutations after failure of first-line antiretroviral treatment among children in resource-poor

regions: a systematic review.

- Resistance rates and patterns among children in developing countries in whom antiretroviral treatment has failed.
- Outcomes in 3241 children were eligible.

• Sigaloff KC et 2011

HIV-1-resistance-associated mutations after failure of first-line antiretroviral treatment among children in resource-poor regions: a systematic review.

- Viruses with resistance-associated mutations were isolated from 90% (95% CI 88-93%) of children.
- The prevalence of mutations associated with
 - NRTI 80%,
 - NNRTI -88%
 - PI- 54%.

Protease Inhibitor Resistance Is Uncommon in HIV-1 Subtype C Infected Patients on Failing Second-Line Lopinavir/r-Containing Antiretroviral Therapy in South Africa

Variable	Median (inter quartile range)		
	Median (inter quartile range)	No PI major mutations (n = 70)	PI major mutations $(n = 5)$
Age (years)	34 (29–40)		
CD4+ T-cells/mm ³	141 (75–245)	138 (80–229)	246 (194–254)
HIV-1 RNA (copies/mL)	184,779 (8790–166,300)	61000 (15000–155000)	3260 (2200–33000)
Time on second-line (months)	16 (7–18)		

• Wallis, C.L. et al., 2011.

Resistance Mutations	n (%)
NRTI mutations	26 (35%)
M184V	15 (20%)
K65R	o (0%)
Q151M	1 (1%)
TAMs	10 (13%)
NNRTI mutations	39 (52%)
K103N	16 (21%)
V106M	9 (12%)
Any PR mutations (major and minor)	67 (89%)
MajorLPV mutations	5 (7%)
M46I, L76V	1
M46I	1
L33F, I54S, V82A, I84V	1
L33F, M46I, I54V, I84V, L90M	1
M46I, I54V, L76V	1

Major lopinavir resistance mutations were infrequent (5 of 75; 7%), indicating that drug resistance is not the main barrier to future viral suppression.

Wallis, C.L. et al., 2011. Protease Inhibitor Resistance Is Uncommon in HIV-1 Subtype C Infected Patients on Failing Second-Line Lopinavir/r-Containing Antiretroviral Therapy in South Africa. *AIDS research and treatment*, 2011, p.769627.