HIV Resistance Strategy for clinical management

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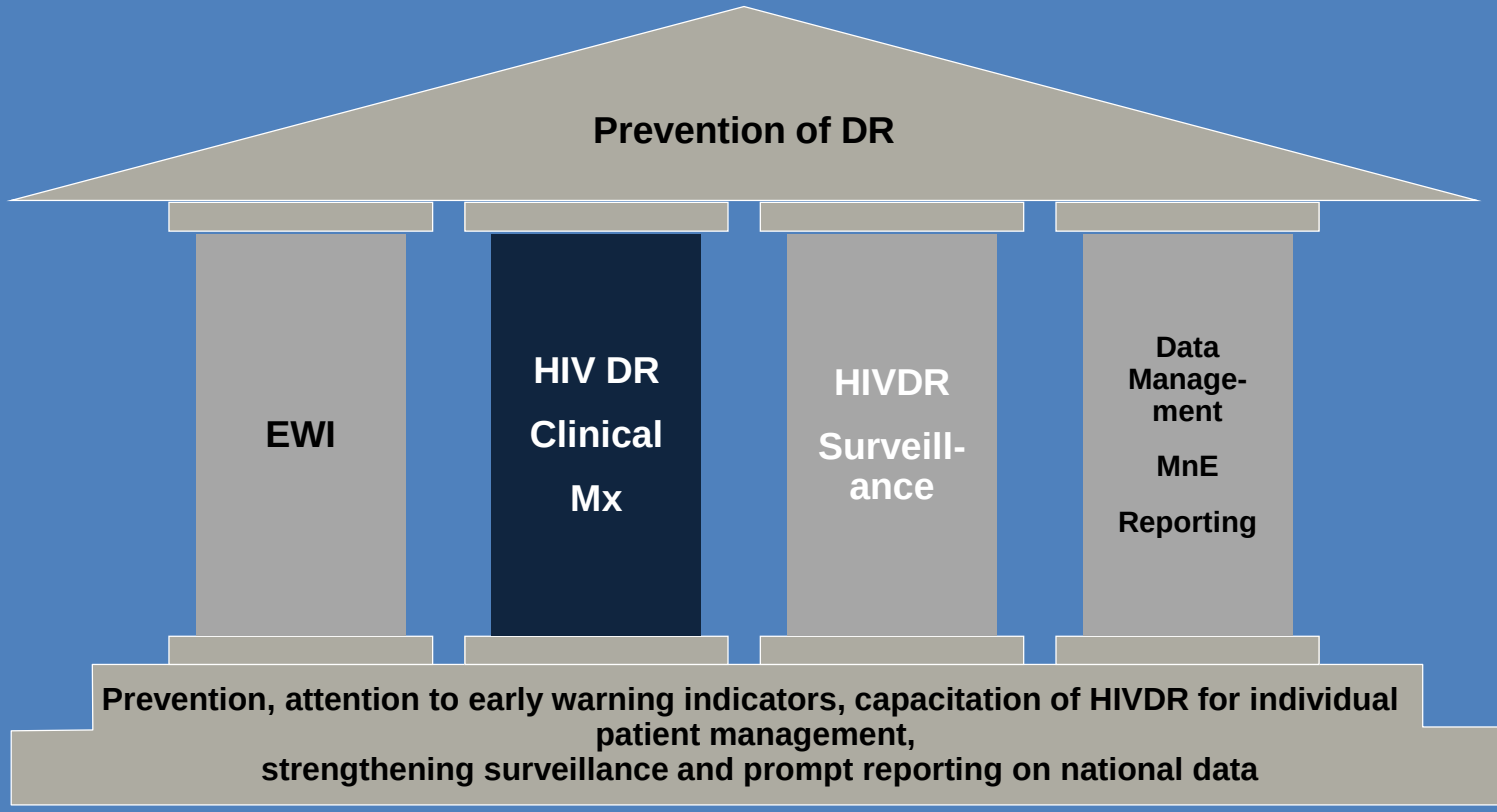
The strategy rests on 4 key pillars:



First regimen

1st Line		
All new patients needing treatment, including pregnant women	TDF + FTC or 3TC +EFV FDC preferred.	NVP: In patients with significant psychiatric comorbidity or .intolerance to EFV and where the neuro-psychiatric toxicity of EFV may impair daily functioning, e.g. shift workers.

Second regimens

2nd line		
Failing on a TDF-based 1st line regimen	AZT+3TC+ LPV/r	Patient with anaemia and renal failure switch to ABC
Failing on a d4T -based 1st line regimen	TDF+3TC (or FTC) and LPV/r	
Dyslipidaemia or diarrhoea associated with LPV/r	Switch LPV/r to ATV/r	

Third regimens

Third line		
Genotype driven	All get DRV/r Best choice NRTI Raltegravir Etravirine	Usually no first line genotype data available.

When to Use HIV 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.

These guidelines consider best international and local practice, but take into account the financial constraints in the Southern African region

GUIDELINES

The 2012 southern African ARV drug resistance testing guidelines

by the Southern African HIV Clinicians Society

F Conradie, D Wilson (Chairpersons of the Resistance Testing Guidelines Committee), **A Basson, T de Oliveira, G Hunt, D Joel, M Papathanasopoulos, W Preiser, J Klausner, D Spencer, W Stevens, F Venter, C van Vuuren** (Expert Panel Members), **L Levin, G Meintjes, C Orrell, H Sunpath, T Rossouw, G van Zyl** (Reviewers)

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Following the rapid scale-up of the programme for universal access to antiretroviral therapy (ART) in southern Africa, resistance to antiretroviral medications will occur. A detectable viral load must be treated as an emergency and should trigger intensive patient tracking and adherence counselling. In contrast to the developed world, the incidence of transmitted resistance is still low in most areas in the region. Therefore, in this consensus statement we do not recommend resistance testing in HIV-infected adults upon diagnosis or ART initiation. However, baseline resistance testing is recommended for children who have been exposed to ART for prevention of mother-to-child-transmission therapy and subsequently become HIV-infected. Resistance testing is also recommended after virological failure of first- and second-line ART regimens.

S Afr J HIV Med 2012;13(4):162-167. DOI:10.7196/SAJHIVMED.874

HIV Clinicians Society guidelines:

Patient group	Recommendation for HIV resistance testing	Comments
Recent infection		
Infants under the age of two years or within two years of stopping daily NVP	Recommended	As soon as HIV is diagnosed.
Documented recent infection	Recommended	
HIV diagnosis		
Patients without documented seroconversion presenting for routine clinical care	Not recommended	
ARV initiation		
Children above the age of 2 years about to start first-line ART	Not recommended	Unless within 2 years of stopping daily NVP
Pregnant women about to start first-line ART	Not recommended	Pregnant women should have a viral load measured three months after ARV initiation .Detectable >1000 copies/ml viraemia should be treated as a medical emergency (see below)
Adults about to start first-line ART	Not recommended	
Failure of NNRTI-based ART		
Adults and children with two viral load measurements>1,000** copies per ml and a <2 logs drop in viral load (at least 4-weeks apart) while taking NNRTI-based ART	Recommended	Adherence# issues should be comprehensively addressed between the two measurements. Resistance testing should be done while the patient is taking the failing regimen, or within 4 weeks of discontinuation.
Failure of a boosted protease-inhibitor based regimen		
Adults and children with two viral load measurements >1,000** copies/ ml and a < 2 log drop in viral load, > 4weeks apart while taking PI-based ART	Recommended	Adherence# issues should be comprehensively addressed between the two measurements. Resistance testing should be done while the patient is taking the failing regimen, or within 4 weeks of discontinuation

	SAHIVSoc	IAS-USA[1]	DHHS[2]	European[3]
Primary/acute	Recommend	Recommend	Recommend	Recommend
Postexposure prophylaxis				Recommend*
Chronic, Rx naive		Recommend	Recommend	Recommend
Failure (1^{st},2^{nd})	Recommend	Recommend	Recommend	Recommend
Pregnancy	Increase monitoring	Recommend	Recommend	Recommend
Pediatric			Recommend	Recommend

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ORIGINAL ARTICLE

Assessment of Second-Line Antiretroviral Regimens for HIV Therapy in Africa

Nicholas I. Paton, M.D., Cissy Kityo, M.Sc., Anne Hoppe, Ph.D., Andrew Reid, M.R.C.P., Andrew Kambugu, M.Med., Abbas Lugemwa, M.D., Joep J. van Oosterhout, Ph.D., Mary Kiconco, M.P.H., Abraham Siika, M.Med., Raymond Mwebaze, M.Med., Mary Abwola, M.Med., George Abongomera, M.Sc., Aggrey Mweemba, M.Med., Hillary Alima, M.P.H., Dickens Atwongyeire, M.B., Ch.B., Rose Nyirenda, M.Sc., Justine Boles, M.Sc., Jennifer Thompson, M.Sc., Dinah Tumukunde, M.P.H., Ennie Chidziva, Dipl.G.N., Ivan Mambule, M.B., Ch.B., Jose R. Arribas, M.D., Philippa J. Easterbrook, M.D., James Hakim, F.R.C.P., A. Sarah Walker, Ph.D., and Peter Mugyenyi, F.R.C.P., for the EARNEST Trial Team*

BACKGROUND

The efficacy and toxic effects of nucleoside reverse-transcriptase inhibitors (NRTIs) are uncertain when these agents are used with a protease inhibitor in second-line therapy for human immunodeficiency virus (HIV) infection in resource-limited settings. Removing the NRTIs or replacing them with raltegravir may provide a benefit.

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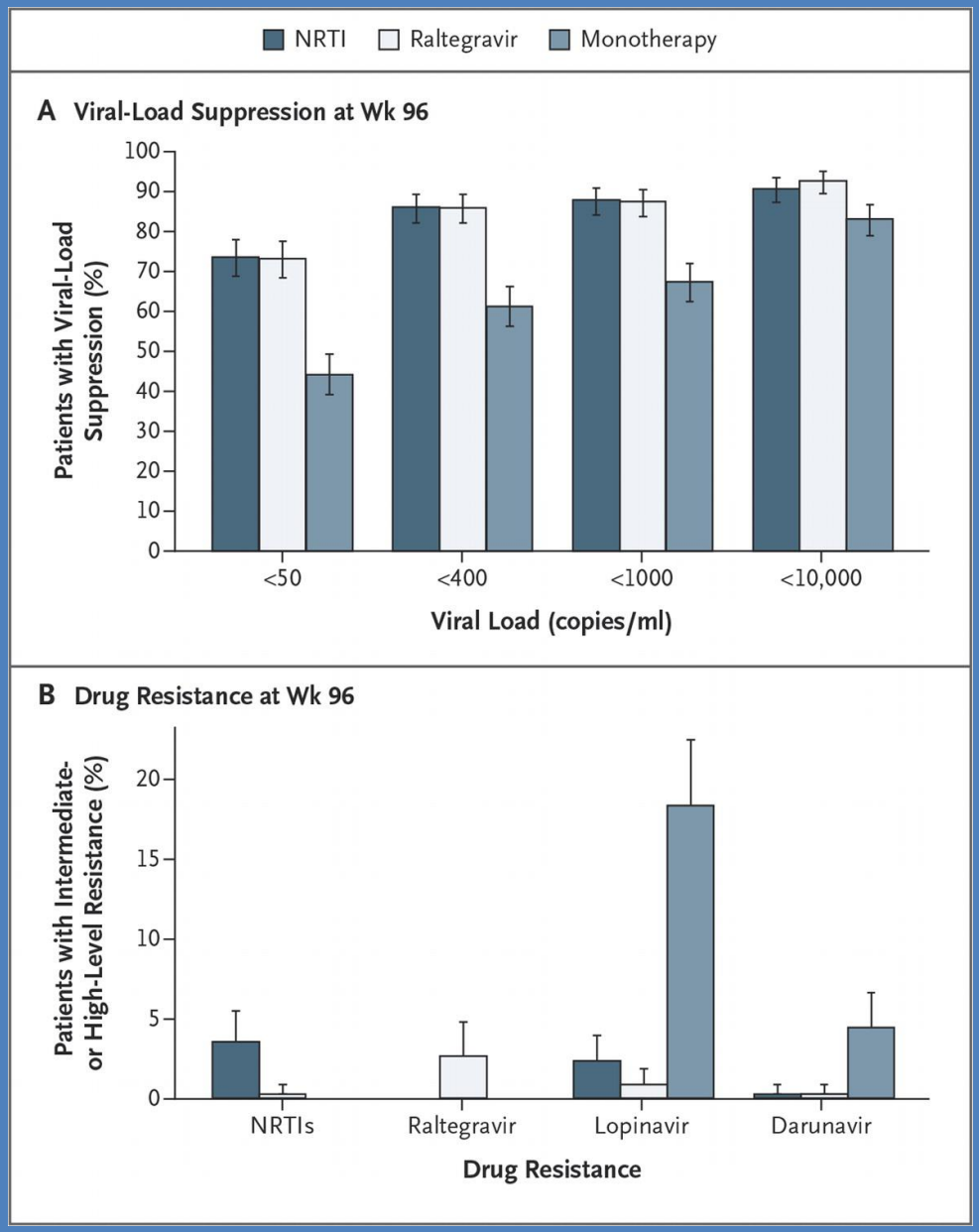
RESULTS

Good HIV disease control was achieved in 60% of the patients (mean, 255 patients) in the NRTI group, 64% of the patients (mean, 277) in the raltegravir group (P=0.21 for the comparison with the NRTI group; superiority of raltegravir not shown), and 55% of the patients (mean, 232) in the monotherapy group (noninferiority of monotherapy not shown, based on a 10-percentage-point margin). There was no significant difference in rates of grade 3 or 4 adverse events among the three groups (P=0.82). The viral load was less than 400 copies per milliliter in 86% of patients in the NRTI group, 86% in the raltegravir group (P=0.97), and 61% in the monotherapy group (P<0.001).


NRTI
Raltegravir
Monotherapy
A Viral-Load Suppression at Wk 96
Patients with Viral-Load Suppression (%)
100
90
80
70
60
50
40
30
20
10
0
<50
<400
<1000
<10,000
Viral Load (copies/ml)
B Drug Resistance at Wk 96
Patients with Intermediate- or High-Level Resistance (%)
20
15
10
5
0
NRTIs
Raltegravir
Lopinavir
Darunavir
Drug Resistance

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CONCLUSIONS

When given with a protease inhibitor in second-line therapy, NRTIs retained substantial virologic activity without evidence of increased toxicity, and there was no advantage to replacing them with raltegravir. Virologic control was inferior with protease-inhibitor monotherapy. (Funded by European and Developing Countries Clinical Trials Partnership and others; EARNEST Current Controlled Trials number, ISRCTN 37737787, and ClinicalTrials.gov number, NCT00988039.)

Prevention of resistance

- Compliance with adherence support guidelines
- Compliance with VL testing algorithm
- What are the barriers to switching patients failing first line
- Referral system and level of expertise across the spectrum of health facilities

Prevention of resistance

- Training of clinicians on resistance testing (testing algorithm, test results interpretation)
- Ongoing mentorship or quality management to ensure clinicians comply with guidelines
- Patient education materials
- Test result delivery mechanism and notification system to patients

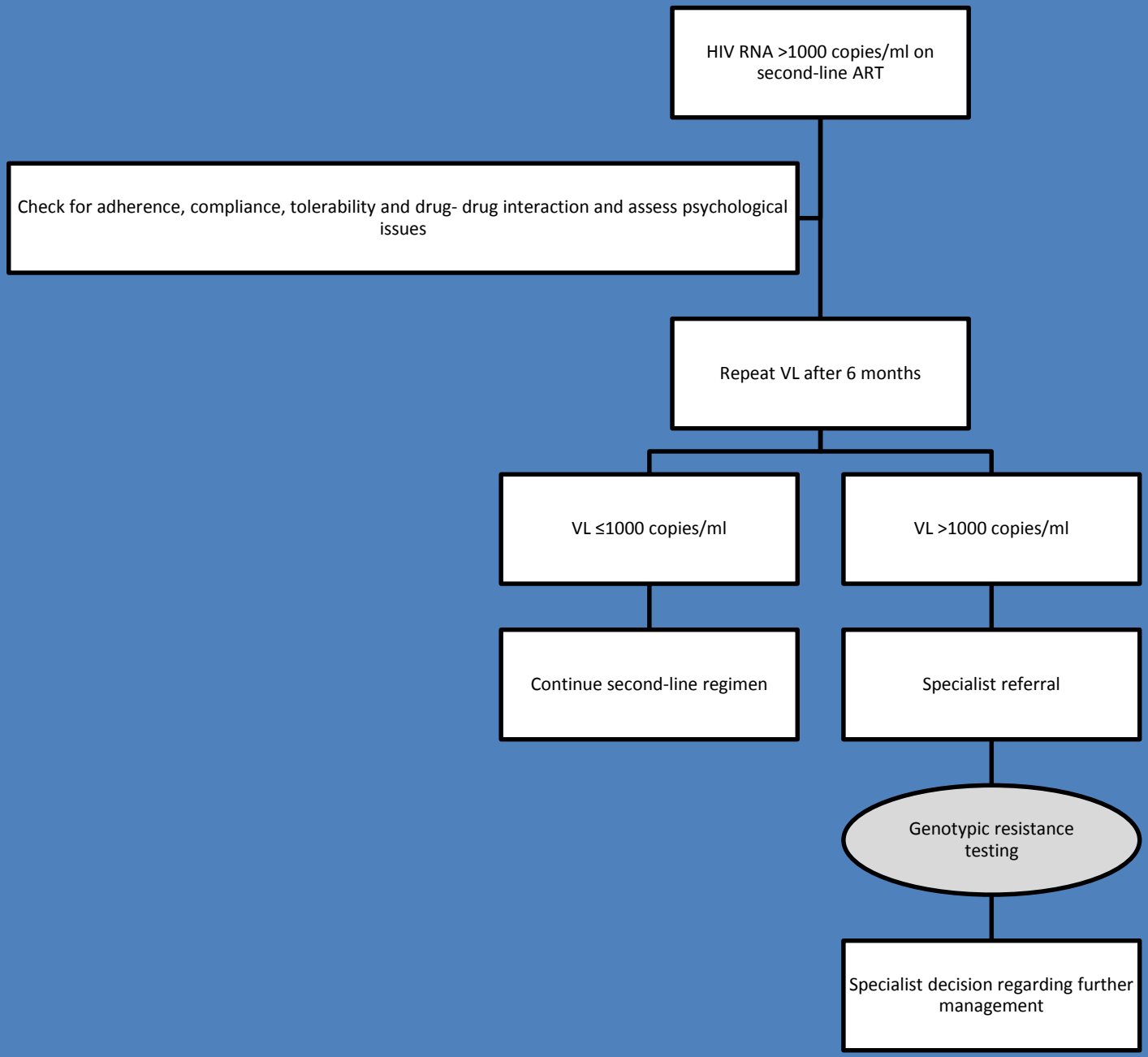
Training of clinicians

- Who can order a genotype ?

- When should a genotype test ?
  - Confirmed VL increase on second line (PI)
  - Check adherence
  - Drug history and toxicities

HIV DR testing strategy

- **Group 1:**
  - All patients on a PI regimen with virologic failure (2 consecutive VL above 1,000 cp/ml
  - **Group 2:**
  - All children < 5 years diagnosed positive: this will cover both infants diagnosed through EID and children diagnosed later through RT


HIV RNA >1000 copies/ml on second-line ART
Check for adherence, compliance, tolerability and drug- drug interaction and assess psychological issues
Repeat VL after 6 months
VL ≤1000 copies/ml
VL >1000 copies/ml
Continue second-line regimen
Specialist referral
Genotypic resistance testing
Specialist decision regarding further management