

The case *for* GDRT and third-line therapy in the state sector

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Disclosure: Conflict of interest

- I am paid to interpret GDRT “sign out tests” – NHLS employed
- I do research on the prevalence ARV GDR and factors associated with it



My case is *for*

- ***Conservative criteria*** for GDRT
- Continued research
 - Differentiate poor adherence x resistance
- A cost-effective strategy to identify patients with the need for third-line therapy
- Access to third-line therapy only for those who require it as the only long-term solution



The playing field

- Public sector paediatric and adult regimens
- Our patient population is very heterogeneous –interventions should be ‘targeted’ to the group at the highest risk
- ‘Clues’ to determine who would benefit most from GDRT (highest cost-benefit) are not well-researched



GDRT after first-line NNRTI failure?

- Article by Rosen et al. (JIAS, 2011) – modelling shows that GDRT in patients with confirmed failure (2 x consecutive viral loads > 1000 copies) could detect about 16.8% of patients without resistance
 - Possible marginal cost-saving by **not switching** the non-resistant patients to ‘expensive’ second-line (2.4x more than first-line)
 - Study based on ‘old’ SA regimens before TDF was introduced in first-line
 - Future generic PIs?; economy of scale?
- Further benefits: selecting the best second-line regimen (NRTI backbone)



GDRT after first-line NNRTI failure?(2)

- **Costly** – even if prices reduced to R1500 - R1800 from the current R2300 for the public sector.
- “Unfortunately” GDRT is the best **current** way to discriminate between
 - first-line failure due to resistance
 - failure due to poor adherence
- Neither CD4, VL, or concurrent drug levels* could be used to discriminate adherence x resistance during NNRTI regimen failure
 - *Low genetic barrier – short period of non adherence –select resistance



Second-line NNRTIs

- Children who were switched after failure of PI to NNRTI – poor outcomes
- For third-line one ideally needs an archived specimen/ GDRT result after first-line failure and second-line failure



What do we need after first-line failure?

- Affordable test that will differentiate 3 categories
 - (1) Not failing 😊
 - Failing 😞
 - (2) Resistance - Need switch to second line
 - (3) Poor adherence - Need adherence
- Point of care
- Competitive price < R 500
- **Concept in development!!**



Is there a need for resistance testing after boosted PI regimen failure?

- Adult patients: Low probability of PI resistance **in absence of un-boosted PI exposure**
- **Most adult** patients failing a boosted PI regimen fail due to **poor adherence** (van Zyl. JAIDS, 2011)



Prevalence of major PI resistance in adults after PI regimen failure

RCTs:

- Dlamini et al. JAIDS, 2011 (0/38) mean time to rebound *17.1 months*
- Firnhaber et al. PloS ONE, 2011 (1/53) mean follow up *72 weeks*

Real life:

- Wallis et al. AIDS research and Treatment, 2011 – 5/75 (7%)
- van Zyl et al. JAIDS 2011 (2/37) (5%)



Why do we need to worry about PI resistance in adults?

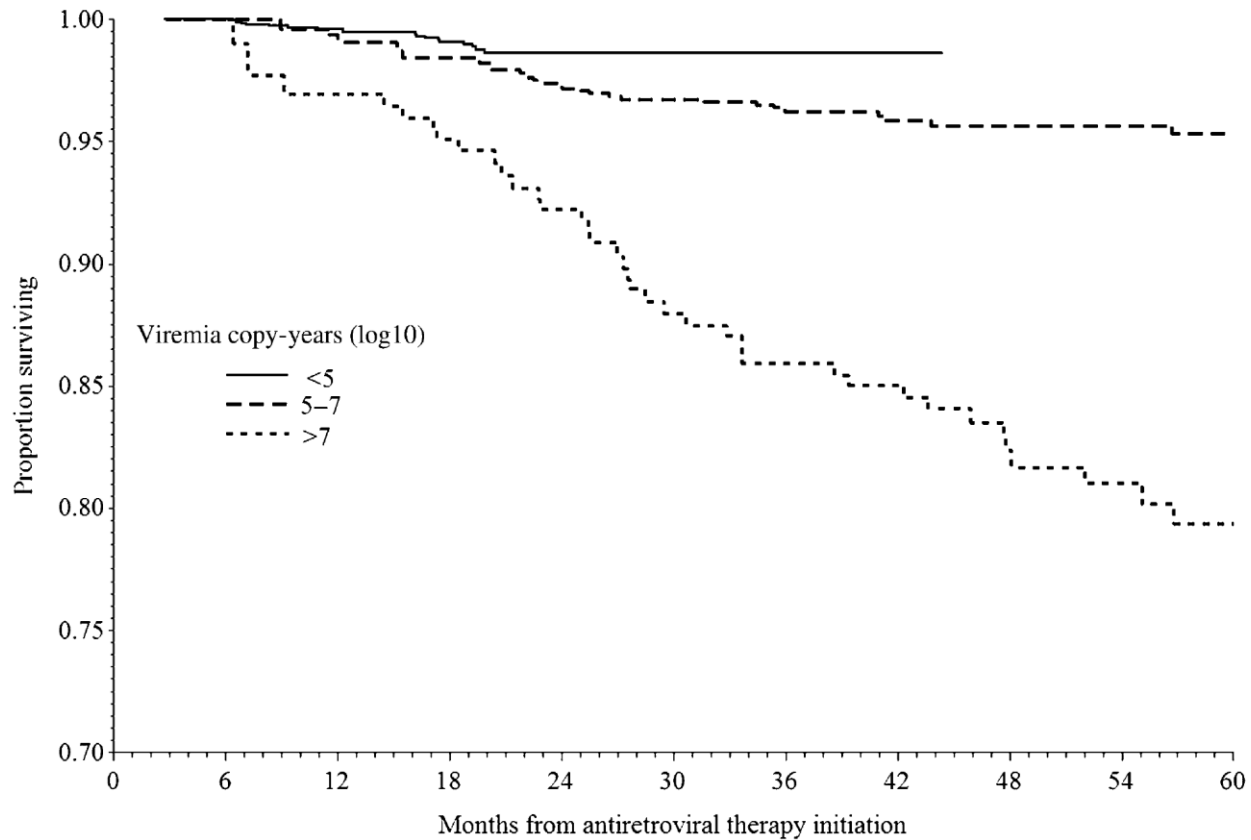
- 5% to 7% prevalence in a real-life setting is not negligible
- Why the difference with RCT?
 - Likely a survival bias!
 - Patients who have poor adherence are likely to die, being lost to follow-up and are removed from ‘natural cohorts’
 - LPV/r still fairly active in patients with intermediate resistance – slow CD4 decline, relative low viral loads
 - Therefore those with sufficient adherence to select resistance will survive along with those who remain virologically suppressed



More on survival...

- Viraemia copy years predict survival on ART (Mugavero et al, CID 2011)
 - Hazard ratio: 1.44 per log copy years
 - That means someone with a viral load of 100 000 is 6 times more likely to die/ year of failure than someone with a viral load < 50 copies
- Second-line is our last-line:
 - survivors are those with good or intermediate resistance –highest likelihood of PI resistance

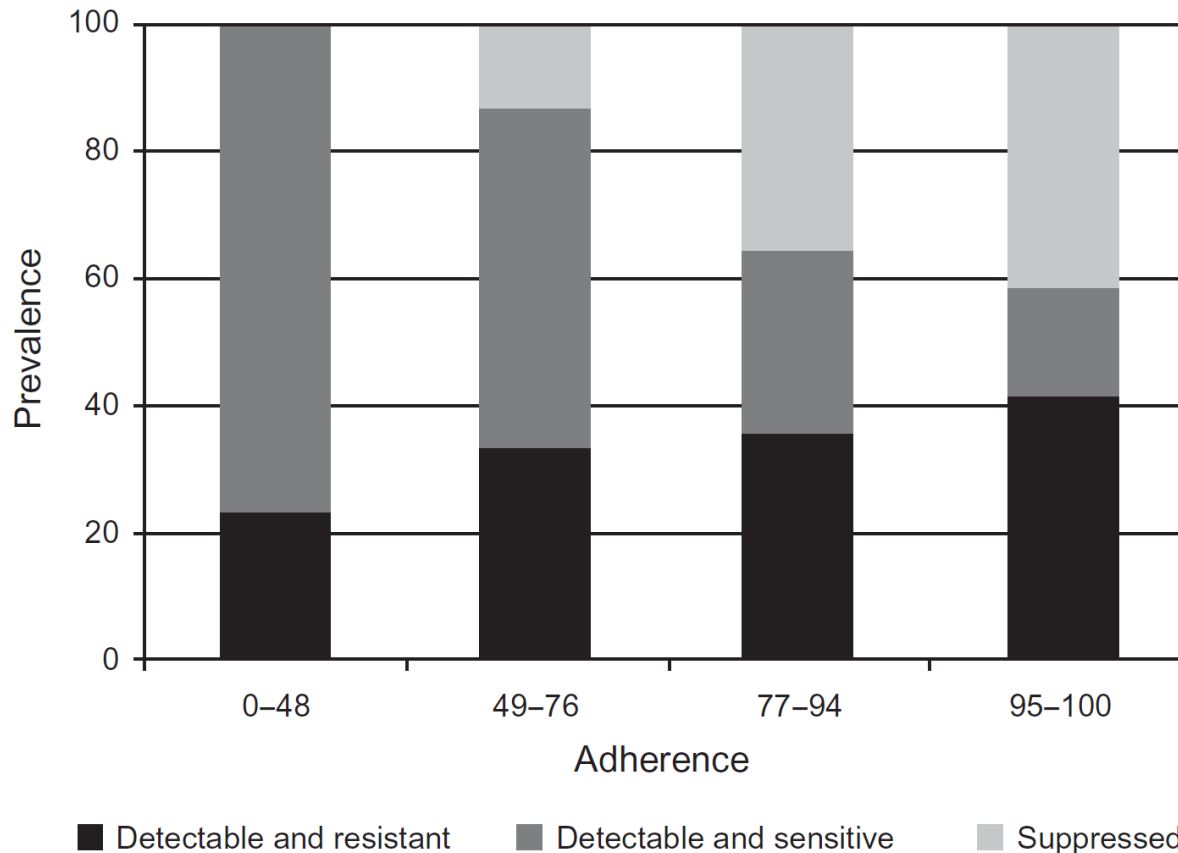




Viremia copy-years (log ₁₀)	Number at risk									
	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	42 mo	48 mo	54 mo	60 mo
<5	1692	1414	1105	317	79	18	2			
5-7	245	289	332	833	851	727	606	509	414	316
>7	90	135	181	192	183	169	152	132	122	108

Mugavero et al, CID 2011

Patients with viraemia but good levels of adherence are more likely to have PI resistance



Gardner et al. AIDS, 2009

Paediatrics – a different landscape

- High baseline viral loads
- Exposure to un-boosted regimens (RTV)
 - <6-months of age (prior to 2007)
 - rifampicin co-administered (prior to 2008)
- Frequent dose adjustments, initial liquid formulations (being spit out), growth, adolescence!!



Resistance prevalence in Paeds on PI therapy

- Limited data – regularly absence of therapy denominator



SA PI resistance	Location	Source
14/32 exposed to RTV sPI versus 0/7 receiving only LPV/r	JHB	Taylor et al., AIDS Res Hum Retroviruses, 2011
12/17 who were RTV sPI exposed versus 1/13 who only received boosted PI therapy (LPV/r)	CPT	Van Zyl, et al., PIDJ, 2009
6/93 of failures have major PI resistance on LPV/r, mean 700 days after therapy start	JHB	Lee Fairlee, Shobna Sawry - unpublished
4/9 failing (RTV exposure unknown)	JHB	Wallis et al., PIDJ 2009
16/49 after average time on therapy: 1,083 days (RTV exposure unknown)	PTA	Theresa Rossouw - unpublished



When to do GDRT in patients failing boosted PI regimens?

- Low threshold to test children with previous exposure to RTV sPI
- First exclude patients with inadequate LPV concentrations (plasma and or hair) [van Zyl et al, JAIDS 2011]
 - LPV concentrations would identify most patients who fail with poor adherence and is much cheaper than genotypic resistance testing – and therefore cost-saving and informative (\$ 20 to \$ 40 versus \$ 300)
 - Resistance testing on the rest would be able to identify patients who require third-line therapy



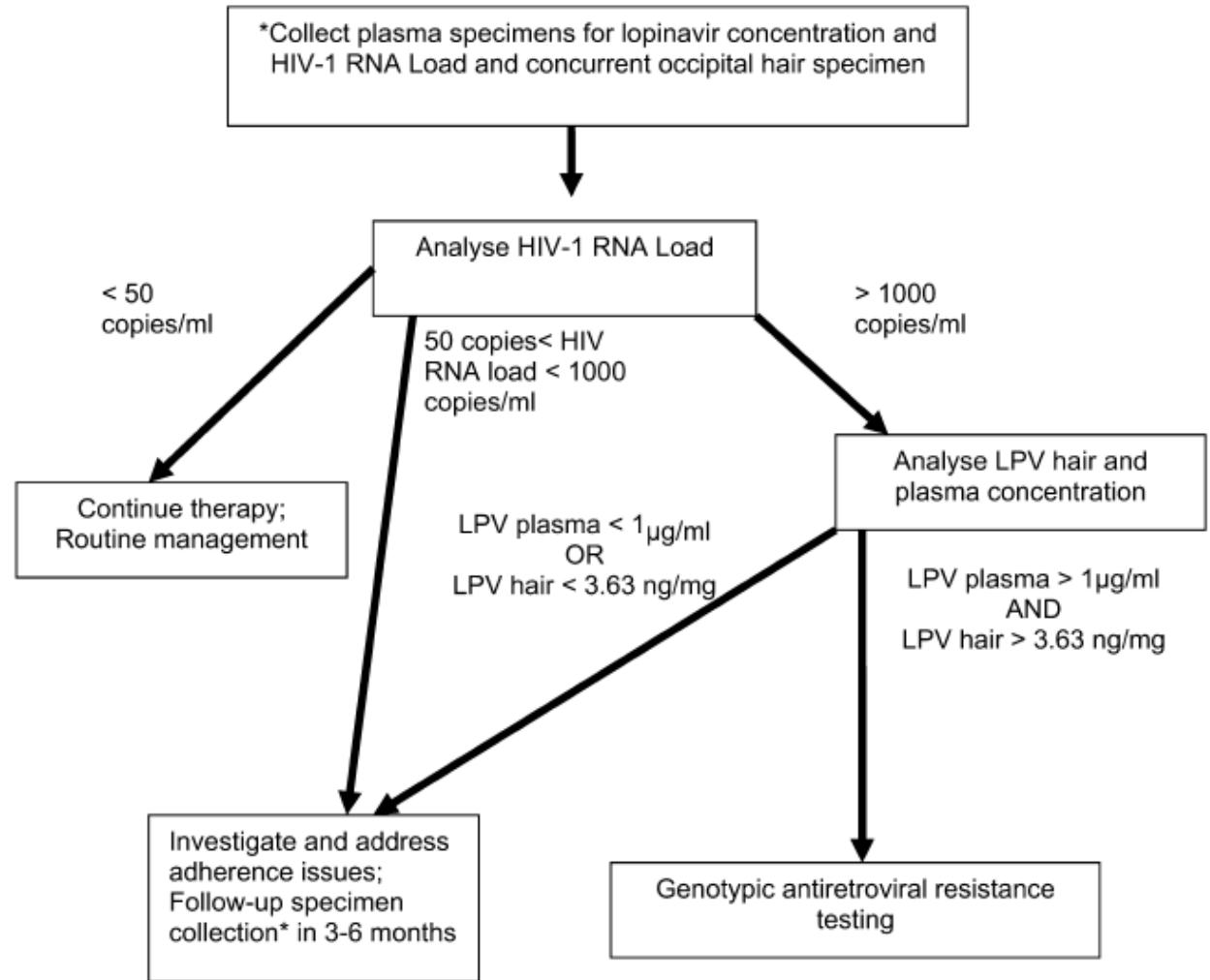


FIGURE 2. Proposed algorithm to investigate the cause of virologic failure of a Lopinavir boosted with low-dose ritonavir (LPV/r) containing second-line regimen in resource-limited settings. LPV concentrations in plasma and hair will only be analyzed when the viral load is >1000. This would allow the differentiation of patients who are failing due to poor adherence versus probable genotypic resistance. *Indicating the tests that are done at the “viral load” visit.

Sub-optimal alternatives

- Recycling: Evidence?
 - When, what and how?- dependent on mutation pattern in individual whether resistance is cross-class or limited
 - EFV& NVP: Unlikely as suggested PMTCT resistance survival (Lockman et al. 2011 NEJM)
- 3TC mono-therapy and NRTI-only regimens – lack of evidence!!



If we do not test patients failing on second line...

- Lose the benefits of virologic suppression
- Viraemia per se a risk factor for opportunistic infection and death
- Do not identify those with adherence problems (drug levels)
- Chronic immune activation
- Risk of transmitting resistance
- Third-line therapy for a minority may be less expensive than the complications of unsuccessful therapy



Conclusion

- The cost effectiveness of GDRT after first-line failure depends on underlying cost of testing and therapy (moving targets)
- In patients failing boosted PIs it is feasible to screen out patients with probable poor adherence and limit GDRT to those with the highest pre-test probability of having ARV GDR [longitudinal data may be helpful]
- Motivation for third-line therapy in these patients are likely to be life saving – especially in terms of QALY gained for children
- The current high price of third-line regimens are a constraint
- Collective negotiating may be needed for resource-limited countries!





Is it time to demand access to
third-line regimens?

We need researchers AND
Activists!!



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