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Our Issues, Our Drugs, Our Patients

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Baseline HIV drug resistance: Can we prevent it?

Gert van Zyl
Stellenbosch University, Faculty of Medicine and Health Sciences and NHLS, Tygerberg
Talk Overview

• Difference between ‘baseline’ and WHO defined ‘transmitted’ HIV drug resistance
• Pre-cART resistance and the impact on first-line cART
• Baseline resistance: measuring the tip of the iceberg or overestimation?
• Is it on the increase?
• Factors affecting transmitted HIV drug resistance
• Can we prevent it?
Definitions

• Baseline HIV drug resistance = Pre-Therapy Drug Resistance

• Transmitted HIV drug resistance (TDR):
  – Drug resistance in a newly infected individual
  – WHO specific criteria for TDR surveillance
WHO drug resistance surveillance

- Include recently infected individuals
  - Asymptomatic
  - Under 25 years-of-age
  - Recent HIV diagnosis

- Purpose is to find recently infected individuals in whom transmitted drug resistance would be detectable before it reversed
Different rates of reversion; reversion vs displacement

• Fitness price: M184V and K65R reverts faster than other NRTI or NNRTI mutations

• TDR: Most often only one variant is transmitted – random specific mutation events resulting in reversion: SLOW

• In cases of acquired drug resistance with therapy interruption: **pre-existing** wild-type displace less fit resistant strains: **FAST**
Mutations: Different reversion rates

Persisting resistant variants more likely to be transmitted

Baseline drug resistance and first-line therapy outcomes


2. Li JZ. Low-Frequency HIV-1 Drug Resistance Mutations and Risk of NNRTI-Based Antiretroviral Treatment Failure. JAMA. 2011 Apr 6;305(13):1327.
Minor variant drug resistance and adherence are predictors of failure and modify each other’s effect.

Higher K103N load associated with higher risk of failure

- K103N load $> 2000$ copies/ml associated with a 47.4 odds ratio of failure (95% confidence interval 5.2–429.2)

Detected baseline resistance: Ears of the hippo
Transmitted resistant variant: bulk sequencing threshold

Early infection: high risk of TDR transmission to others

Arbitrary decay rate

Bulk sequencing threshold
Detected baseline drug resistance may be tip of the iceberg

- Patients tested long after infection
- Reversion of transmitted drug resistance over time – undetectable or low frequency variants
- Bulk Sequencing = standard HIV drug resistance test insensitive to minor variant resistance
Real-life “Baseline resistance” may include patients who are not therapy naïve

- Older ‘naïve’ patients more likely to have drug resistance: Contrary to reversion model (likely to be infected for longer)
- Evidence of ARV exposure
  - ARVs detected
  - suppressed viral loads
- Patients screening for a microbicide trial were more likely to have drug resistance if:
  - They had a high perceived risk of being infected
  - Previously participated in a microbicide trial


What is happening with baseline resistance in the region?

Recent data from South Africa

2013-2014:

• 25/277 (9%) Surveillance drug resistance mutations (SDRM)
• 23/277 (8.3%) NNRTI SDRM
• 7/277 (2.5%) NRTI SDRM (all 2 class resistance)
• 2/277 (0.7%) PI SDRM

Factors resulting in increased transmitted drug resistance

• Duration since scale up
• Contribution of acute/early infections in transmission (series)
• cART coverage (infections transmitted from therapy experienced individuals)
• Time spent failing on a regimen
  – Viral load monitoring may be protective
  – Do not wait for CD4 count to fall; patients with sustained CD4 counts are more likely to have drug resistance and require therapy switches
• Low genetic barrier regimens?

Rapid response to first-line failure may help to protect first-line regimens

• Adherence intensification most successful in first year after therapy initiation
  – Orrell et al. ~ 70%
  – Hoffmann et al. ~ 41%

• Later after failure a large proportion (~ 90%) of patients have drug resistance (Steegen et al. 2015); resuppression would be less likely

• CD4 decline slow in patients with resistance relative to those without (Hoffman et al. 2016)


Rapid response to first-line failure may help to protect first-line regimens

- Adherence intensification = trial of adherence
- Old guidelines said if adherence > 80% and viral load remains > 1000 copies/ml a switch is indicated
- Considering 1) the high proportion of patients failing first-line with drug resistance and 2) the public health benefits of definitive therapy for these patients: ACTIVE failure management is a priority
Managing patients in the context of an increased prevalence of baseline drug resistance

• Early viral load monitoring (before 6 months)
• The end of NNRTI regimens as first line?
  – Replacement with PIs (Phillips et al 2014)
  – New Integrase Strand Transfer Inhibitors (ISTIs): in fixed dose combinations
• Baseline HIV drug resistance testing
  – Feasibility dependent on a test cost reduction?

Conclusions

• When would first-line therapy lose its success? **Unknown**

• An increase in transmitted drug resistance need not be inevitable!

• Failing patients and early infections may fuel transmitted resistance

• **PLEASE HELP SAVE** first-line therapy
  1) Early 4-6 months viral load testing
  2) Active failure management throughout therapy
  3) Focus on getting early infections on therapy
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