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Our Issues, Our Drugs, Our Patients

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Baseline HIV drug resistance: **Can we prevent it?**

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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

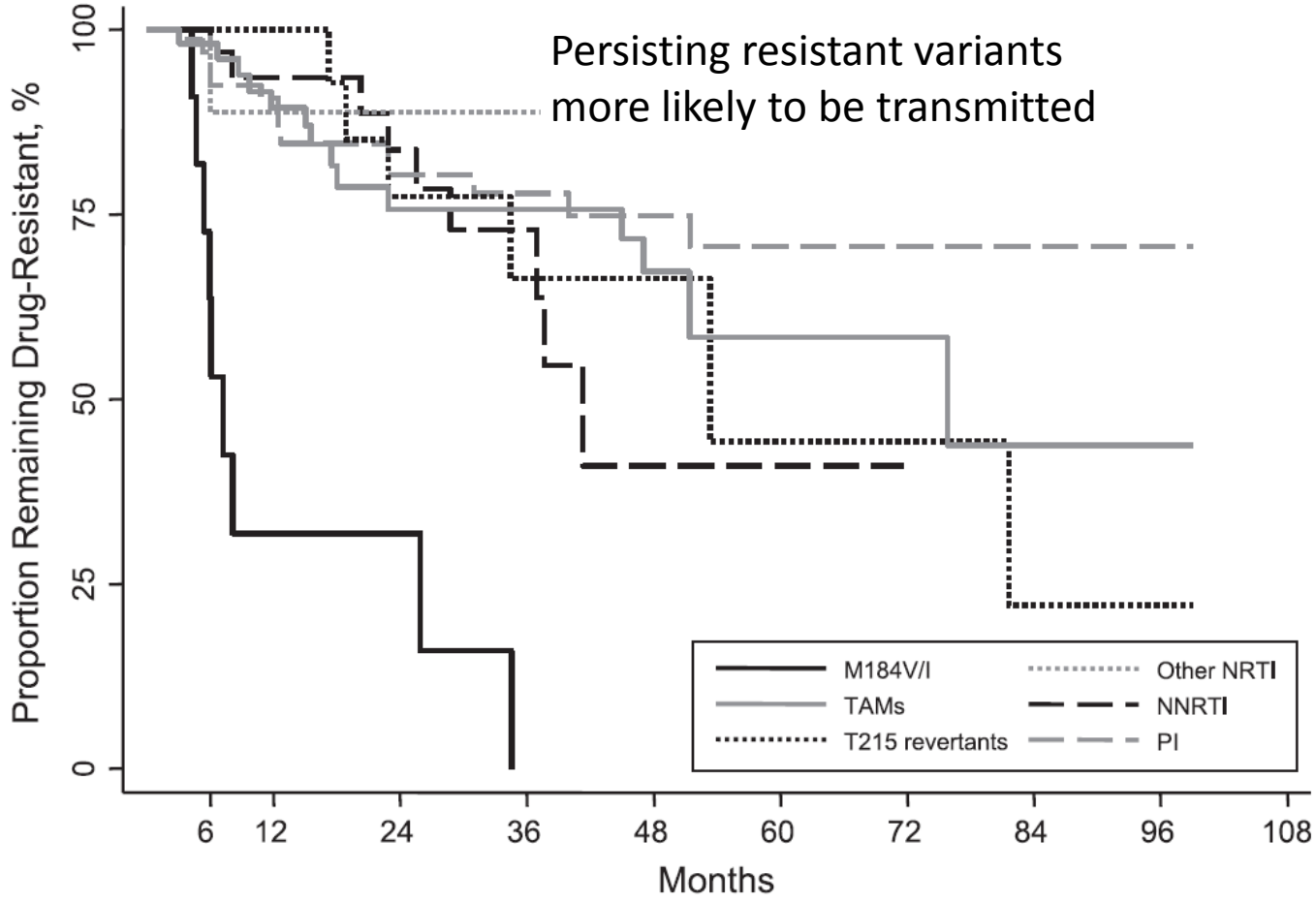
WHO drug resistance surveillance

- 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

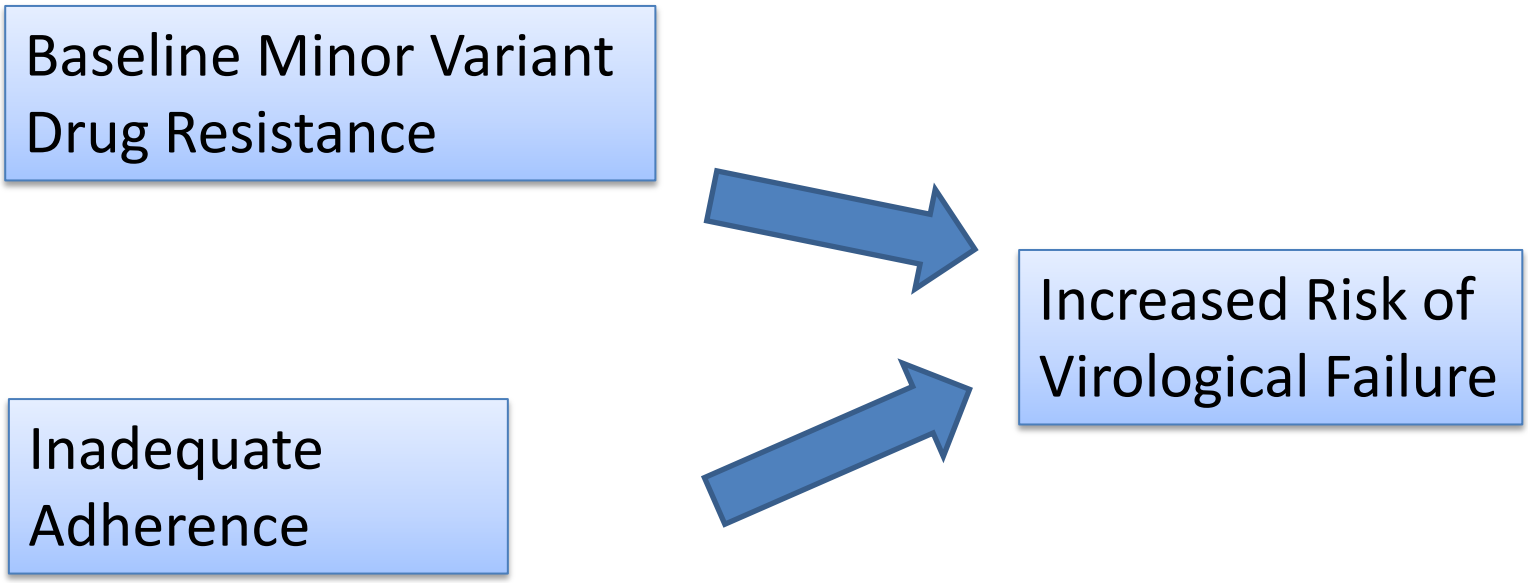
- Fitness price: M184V and K65R reverts faster than other NRTI or NNRTI mutations
- TDR: Most often only one variant is transmitted – random specific mutation events resulting in reversion: SLOW
- In cases of acquired drug resistance with therapy interruption: **pre-existing** wild-type displace less fit resistant strains: ***FAST***

Mutations: Different reversion rates



Jain V, Sucupira MC, Bacchetti P, Hartogensis W, Diaz RS, Kallas EG, et al. Differential persistence of transmitted HIV-1 drug resistance mutation classes. J Infect Dis. 2011 Apr 15;203(8):1174–81.

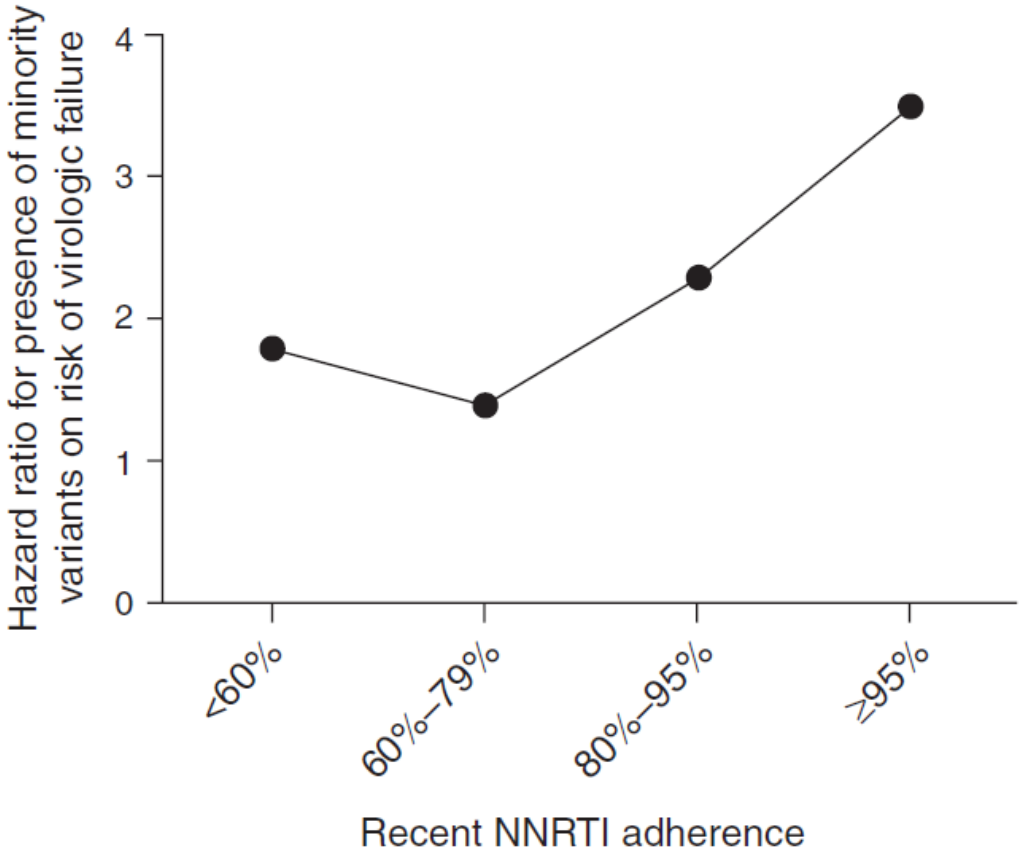
Baseline drug resistance and first-line therapy outcomes



1. Li JZ, Paredes R, Ribaudo HJ, Svarovskaia ES, Kozal MJ, Hullsiek KH, et al. Relationship between minority nonnucleoside reverse transcriptase inhibitor resistance mutations, adherence, and the risk of virologic failure. AIDS. 2012 Jan 14;26(2):185–92.

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 are predictors of failure and modify each other's effect



Poor adherence; **Baseline drug** resistance; or **BOTH** result in failure

Li JZ, Paredes R, Ribaudo HJ, Svarovskaia ES, Kozal MJ, Hullsiek KH, et al. Relationship between minority nonnucleoside reverse transcriptase inhibitor resistance mutations, adherence, and the risk of virologic failure. AIDS. 2012 Jan 14;26(2):185–92.

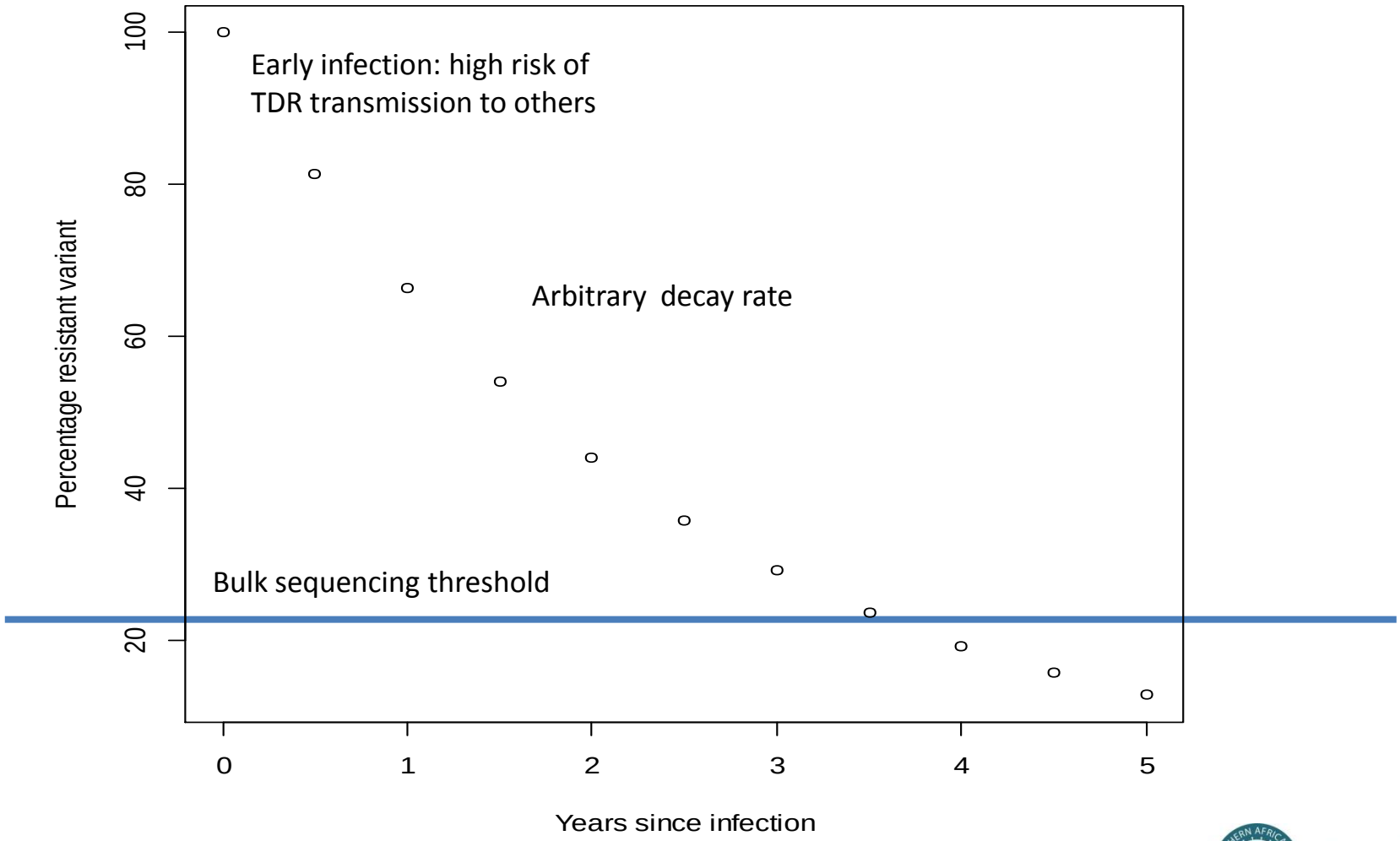
Higher K103N load associated with higher risk of failure

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

Goodman DD, Zhou Y, Margot NA, McColl DJ, Zhong L, Borroto-Esoda K, et al. Low level of the K103N HIV-1 above a threshold is associated with virological failure in treatment-naive individuals undergoing efavirenz-containing therapy. AIDS. 2011 Jan 28;25(3):325–33.

Detected baseline resistance: Ears of the hippo

Transmitted resistant variant: 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

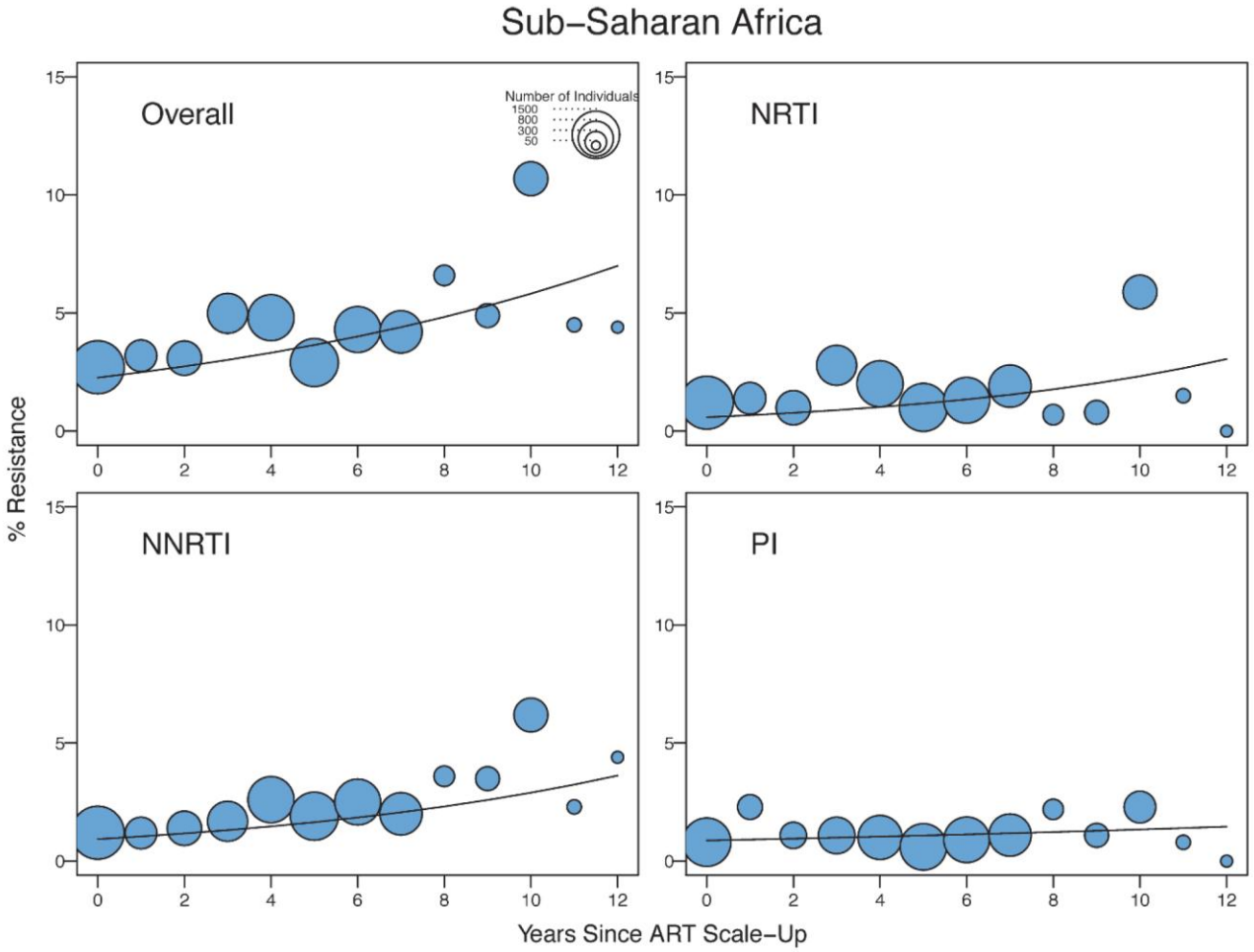
- Older 'naïve' patients more likely to have drug resistance: Contrary to reversion model (likely to be infected for longer)
- Evidence of ARV exposure
  - ARVs detected
  - suppressed viral loads
- Patients screening for a microbicide trial were more likely to have drug resistance if:
  - They had a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

Kasang C, Kalluvya S, Majinge C, et al. HIV drug resistance (HIVDR) in antiretroviral therapy-naïve patients in Tanzania not eligible for WHO threshold HIVDR survey is dramatically high. *PLoS One*. 2011;6(8):e23091. doi:10.1371/journal.pone.0023091.

Parikh, U.M., Kiepiela, P., Ganesh, S., Gomez, K., Horn, S., Eskay, K., Kelly, C., Mensch, B., Gorbach, P., Soto-Torres, L., Ramjee, G., Mellors, J.W., 2013. Prevalence of HIV-1 drug resistance among women screening for HIV prevention trials in KwaZulu-Natal, South Africa (MTN-009). PLoS One

Mensch BS, Gorbach PM, Kelly C, et al. Characteristics Associated with HIV Drug Resistance Among Women Screening for an HIV Prevention Trial in KwaZulu-Natal, South Africa. *AIDS Behav*. 2015. doi:10.1007/s10461-015-1056-4.

What is happening with baseline resistance in the region?



Rhee S-Y, Blanco JL, Jordan MR, Taylor J, Lemey P, Varghese V, et al. Geographic and temporal trends in the molecular epidemiology and genetic mechanisms of transmitted HIV-1 drug resistance: an individual-patient- and sequence-level meta-analysis. PLoS Med. 2015 Apr;12(4):e1001810.

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

K. Steegen, S. Carmona, M. Bronze, M.A.Papathanasopoulos, G. Van Zyl, D. Goedhals, W. Macleod, I. Sanne, W.S. Stevens. *Moderate levels of pre-treatment HIV-1 antiretroviral drug resistance observed in a national survey in South Africa.* IAS 2015. Vancouver, Canada.

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?

Vardavas, R., Blower, S., 2007. The emergence of HIV transmitted resistance in Botswana: "when will the WHO detection threshold be exceeded?". PLoS One 2, e152. doi:10.1371/journal.pone.0000152

Hoffmann CJ, Maritz J, van Zyl GU. *CD4 count based failure criteria combined with viral load monitoring may trigger worse switch decisions than viral load monitoring alone.* Trop Med Int Health. 2015. doi:10.1111/tmi.12639.

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)

Orrell C, Harling G, Lawn SD, Kaplan R, McNally M, Bekker L-G, et al. *Conservation of first-line antiretroviral treatment regimen where therapeutic options are limited.* Antivir Ther. 2007 Jan;12(1):83–8.

Hoffmann CJ, Maritz J, van Zyl GU. *CD4 count based failure criteria combined with viral load monitoring may trigger worse switch decisions than viral load monitoring alone.* Trop Med Int Health. 2015. doi:10.1111/tmi.12639.

Hoffmann CJ, Charalambous S, Sim J, Ledwaba J, Schwikkard G, Chaisson RE, et al. *Viremia, resuppression, and time to resistance in human immunodeficiency virus (HIV) subtype C during first-line antiretroviral therapy in South Africa*. Clin Infect Dis. 2009 Dec 15;49(12):1928–35.

K. Steegen, M. Bronze, M.A. Papathanasopoulos, G. Van Zyl, D. Goedhals, W. Macleod, I. Sanne, W.S. Stevens, S. Carmona. *HIV-1 antiretroviral resistance patterns in patients failing NNRTI-based 1st-line treatment: results from a national survey in South Africa.* IAS 2015. Vancouver, Canada

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?

Phillips AN, Cambiano V, Miners A, et al. Effectiveness and cost-effectiveness of potential responses to future high levels of transmitted HIV drug resistance in antiretroviral drug-naive populations beginning treatment: modelling study and economic analysis. lancet HIV. 2014;1(2):e85-93. doi:10.1016/S2352-3018(14)70021-9.

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

Acknowledgements

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