Country-level drivers of NNRTI resistance in Southern Africa

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IeDEA Southern Africa — International epidemiologic Databases to Evaluate AIDS

#1506

Background

The rise of HIV-1 drug resistance to **non-nucleoside reverse-transcriptase inhibitors** (NNRTI) threatens the success of antiretroviral therapy (ART) in southern Africa:

- low genetic barrier to resistance
- poor adherence, bad prescription practices, supply chains...

It is generally assessed by monitoring **pretreatment drug resistance** (PDR): the proportion of resistance mutations among ART-naïve individuals.

Increasing PDR in the region

Systematic review of PDR surveys in adults **by region** until 2016:

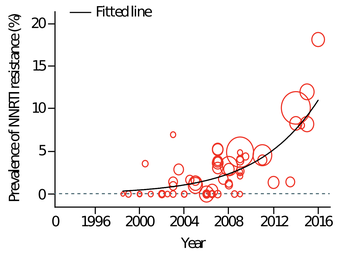


Figure 1: NNRTI PDR from surveys conducted in the **southern Africa region** (Gupta et al., 2018).

Objectives

1. **Estimate** the emergence of NNRTI resistance across countries accounting for the local dynamics of HIV-1 transmission, treatment and mortality.

2. Conduct between-country **comparisons**.

3. Identify **potential drivers** at the country level.

⇒ *at the crossroads of statistical inference and infectious disease modelling*

Modelling strategy

We want a **multivariate model** able to fit jointly, in each country, the local dynamics of:

- adult HIV-1 prevalence
- HIV-infected adults under ART
- adult AIDS-related mortality
- adult population size

UNAIDS data (2000-2018)

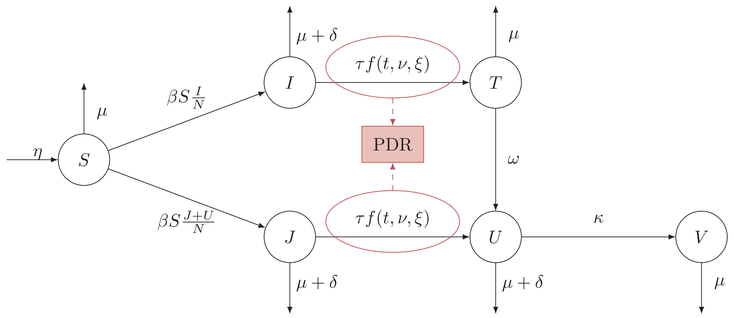
- survey data on NNRTI PDR in adults

Systematic review (2000-2018)

Figure 2: Model fit (median posterior and 95% credible interval) for the Republic of South Africa (2000-2018).

Model description

We propose the following compartmental model:



S	Susceptible adults	β	Transmission rate
I	Drug-sensitive HIV-1, untreated	τ	Maximal treatment rate
T	Drug-sensitive HIV-1, on first-line ART	$f(t, \nu, \xi)$	Time-dependent ART roll-out (logistic function)
J	NNRTI-resistant HIV-1, untreated	ω	Rate of treatment failure with NNRTI resistance
U	NNRTI-resistant HIV-1, on first-line ART	κ	Rate of switching to second-line ART
V	NNRTI-resistant HIV-1, on second-line ART	μ	Background mortality rate
$t_0 = 1999$	Starting date of the model	δ	AIDS-related mortality rate
$J(t_0) = \iota$	Initial prevalence of NNRTI resistance	η	Population growth rate

We imposed a **hierarchical structure** on the parameters related to NNRTI resistance (ω and ι). The other parameters were independently estimated for each country. The model was considered in a Bayesian framework and implemented in `Stan` (Carpenter et al., 2017).

Results

The model is able to describe the rise of NNRTI PDR in each country over 2000-2018, accounting for the local dynamics of HIV-1 transmission, of ART roll-out and of AIDS-related mortality:

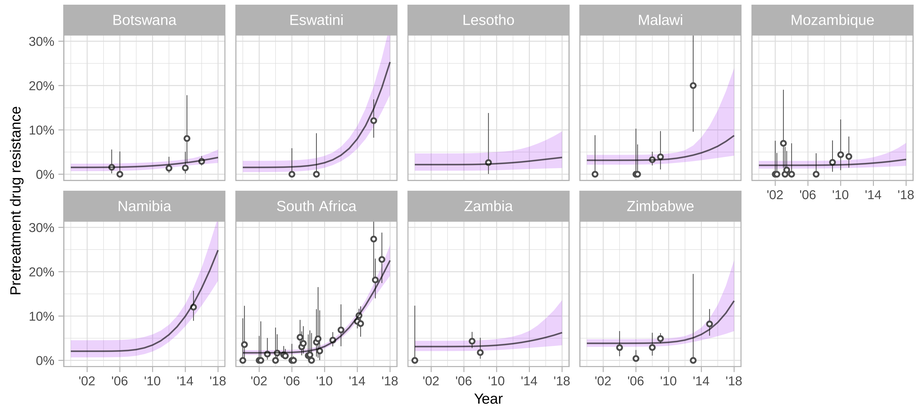


Figure 3: Model fit (median posterior and 95% credible interval) of NNTI PDR for southern Africa (2000-2018).

Predicted levels of NNRTI PDR in 2018 ranged between 3.3% (95% credible interval 1.9 to 7.1%) in Mozambique and 25.3% (17.9 to 33.8%) in Eswatini. **The main driver of NNRTI PDR was the conjunction of high ART coverage with a high rate of treatment failure associated with NNRTI resistance**. The rate of treatment failure associated with NNRTI resistance ranged from 0.0009 per year (0 to 0.13) in Botswana to 0.22 per year (0.12 to 0.55) in the Republic of South Africa.

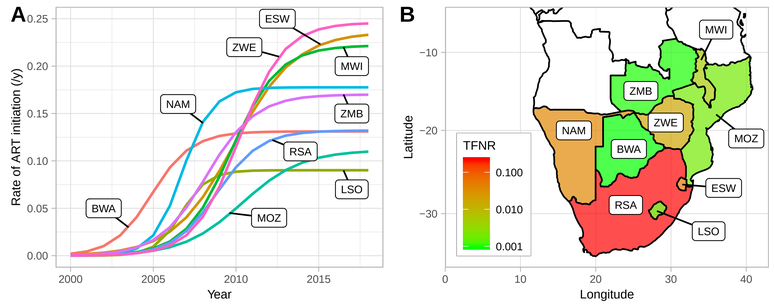


Figure 4: (A) Estimated timing and intensity of ART roll-out by country. (B) Median estimate of the rate of treatment failure associated with NNRTI resistance per year (TNFR, corresponding to parameter ω).

Conclusion

Even with the introduction of dolutegravir, NNRTIs will remain a central component of first-line regimen in southern Africa. Between-country comparison shows that **NNRTI resistance can be controlled despite high levels of ART coverage, as has been shown in Botswana**, likely because of better patient management and lower exposure to ART before treatment initiation. Additional data on NNRT PDR and ART management is urgently needed in some countries of southern Africa.

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