ASSESSING THE UTILITY OF THE TIPPING POINT RATIO FOR MONITORING ART PROGRAM SUCCESS

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BACKGROUND

The tipping point ratio (i.e. theoretical TPR), defined as the yearly ratio of new HIV infections to the net increase in HIV+ individuals on antiretroviral therapy (ART), has been used to compare ART scale-up efforts across countries and measure their progress toward HIV elimination. However, in the literature, estimates of TPR are often based on a definition, using new ART initiations as the denominator (i.e. practical TPR), which is easier to estimate.

OBJECTIVE

To analyze and compare the utility of two TPR indicators used in the literature, theoretical and practical, for monitoring the progress of ART rollout under various epidemic conditions.

METHODOLOGY

Model structure

- Deterministic compartmental model of HIV transmission and ART rollout in South Africa (2002-2024) w/ expansion to universal treatment in 2017
- Adult population (15-49 years old) stratified by HIV status (HIV-, acute HIV, CD4 count >500, 350-500, 200-350, <200) and stage of care (undiagnosed, diagnosed, on ART, failing ART) – see Fig.1
- Force of infection determined by rate of partnership acquisition, HIV prevalence, infectiousness of HIV+ partner, number of sex acts per year, fraction of protected sex acts, protection efficacy per sex act

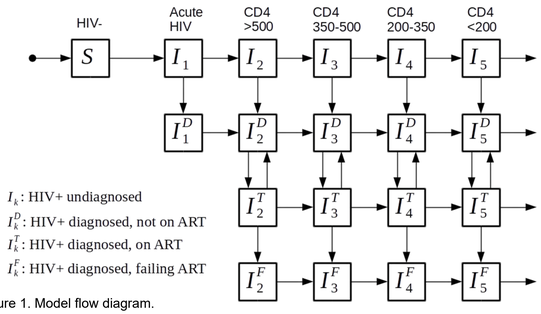

Figure 1. Model flow diagram.

Key model parameters

Parameter		Calibration range
Reduction of HIV transmission risk on ART		73% - 99%
ART initiation rates*	CD4 <200: years 2002 to 2009	0.8 - 1
	CD4 <200: years 2010 to 2019	1.5 - 2
	CD4 200-350: years 2010 and 2011	0.2 - 0.3
	CD4 200-350: years 2012 to 2019 CD4 350-500: years 2015 to 2019 CD4 350-500: years 2017 to 2019	0.6 - 0.8

*Rates expressed as # ART initiations per person-year

Calibration

We used Monte Carlo filtering to select 1000 simulations calibrated to epidemiological data as of 2012 (HIV incidence, HIV prevalence, ART coverage, population size, undiagnosed HIV+) as shown in Fig.2.

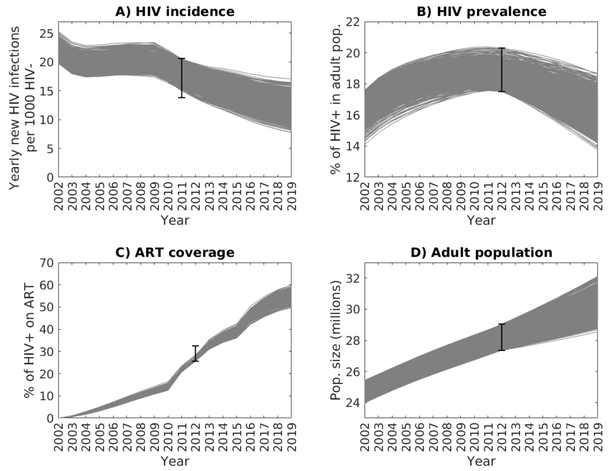

Figure 2. Calibrated simulations in 2002-2019 period (grey curves). We generated random parameter sets and selected epidemic curves hitting all calibration bars.

Scenarios

- Base-case (**BC**): 2002-2019 ART initiation rates maintained up to 2024
- ART scale-up (**AS**): theoretical TPR targeting a fixed value (random in range 0.6-1.8) up to 2024 with yearly compensation for losses of individuals on ART during the previous year
- AS scenario: two options for ART access priority
  - **Early** ART: HIV+ diagnosed individuals move to treatment before HIV+ undiagnosed individuals following the distribution of CD4 count among HIV+ diagnosed individuals not on ART
  - **Late** ART: individuals in low CD4 count compartments move to treatment before individuals in higher CD4 count compartments

Outcomes

- HIV incidence = $\frac{\text{Yearly new HIV infections}}{\text{\# HIV- individuals @ mid-year}}$
- HIV incidence reduction = $100\% \left(\frac{\text{BC incidence} - \text{AS incidence}}{\text{BC incidence}}\right)$
- ART coverage = $\frac{\text{\# HIV+ individuals on ART}}{\text{\# HIV+ individuals}}$
- Theoretical TPR = $\frac{\text{Yearly new HIV infections}}{\text{Yearly net increase in HIV+ individuals on ART}}$
- Practical TPR = $\frac{\text{Yearly new HIV infections}}{\text{Yearly new ART initiations}}$

RESULTS

We measured HIV incidence and ART coverage under BC / AS scenarios (Fig.3). We compared theoretical TPR, practical TPR and ART coverage as indicators of HIV incidence reduction (Fig.4). In particular, we illustrate the TPR threshold value of 1 which has been proposed as a target for the scale-up of ART programs.

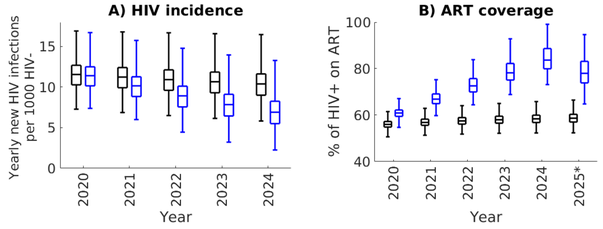

Figure 3. Box plots (over 1000 calibrated simulations) of HIV incidence and ART coverage for BC scenario (**black**) and AS scenario with Early ART access (**blue**). Boxes and whiskers show the minimum, 1st quartile, median, 3rd quartile and maximum of yearly data.

*Panel B): Data for 2025 is the ART coverage achieved after 2020-2024 ART scale-up with no compensation for ART drop-out during 2024.

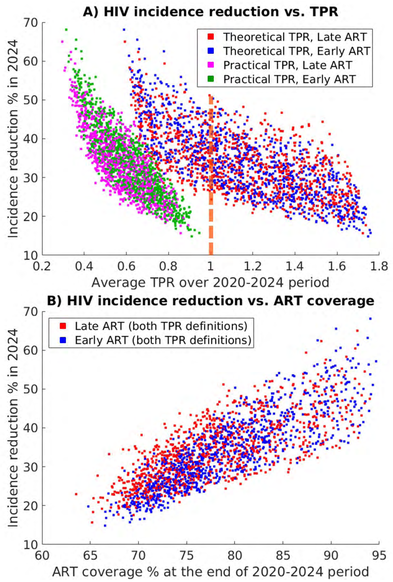

Figure 4. Scatterplots (over 1000 calibrated simulations) of HIV incidence reduction vs. TPR and ART coverage. *There is a large difference in Theoretical and Practical TPR values (Practical TPR <1 in all simulations, Theoretical TPR >1 in most simulations).* Simulated ART coverage achieved in 2024 is a better predictor of incidence reduction (with Pearson's r = 0.85) than Theoretical TPR (Pearson's r = -0.79).

Results show that the same HIV incidence reduction (35%) can be achieved with a wide range of TPR (theoretical TPRs 0.68-1.58; practical TPRs 0.42-0.72). Practical TPR which counts ART compensation as new initiations yields lower incidence reduction for the same value as the theoretical TPR, e.g. TPR = 0.8 has 19-30% incidence reduction under the practical definition and 29-54% under the theoretical definition.

Under the AS scenario, there is no significant difference in HIV incidence reduction between Late and Early ART access.

- Mean (sd) of differences = 0.04 (2.54) percent point
- 95% CI = [-0.12, 0.20] percent point

These ART access priorities are more constrasted if losses of individuals on ART are not compensated (see Fig.5). The difference in HIV incidence reduction is then more pronounced (and statistically significant).

- Mean (sd) of differences = 1.86 (1.59) percent point
- 95% CI = [1.85, 1.86] percent point

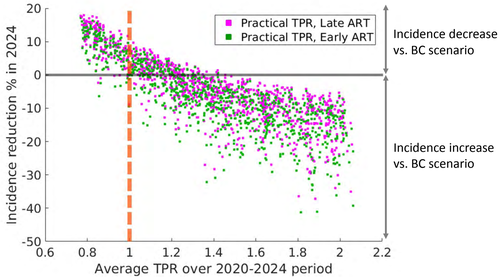

Figure 5. Scatterplot (over 1000 calibrated simulations) of HIV incidence reduction vs. Practical TPR when there is no compensation for the loss of individuals on ART in AS scenario. Note that without compensation, Theoretical TPR can be negative and difficult to interpret. Negative incidence reduction means that HIV incidence is increasing relatively to BC scenario. The slight advantage of Late ART is due to the focus of treatment on individuals with CD4 count <200 which are more infectious. This effect could be difficult to maintain over time since individuals with CD4 <200 do not stay on ART as long as individuals with higher CD4 counts.

KEY FINDINGS

- Practical TPR definition yields a much lower indicator value than the Theoretical TPR definition
- HIV incidence is greatly reduced under ART scale-up with theoretical TPR <1 and high ART coverage
- Calibrated simulations yield a variety of epidemic conditions under which a single TPR indicator value reflects notably different progress of ART
- ART access priorities have a small effect on ART progress over 5 years

CONCLUSION

Our analysis suggests that a clear definition of the TPR indicator needs to be used in the literature. The practical TPR likely overestimates the progress of ART programs and often produces TPR values below 1. Although a more reasonable indicator, the theoretical TPR is technically more difficult to estimate and should be supplemented with ART coverage data to monitor the progress of ART programs.

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