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Assessing the utility of the tipping point ratio to monitor HIV treatment programmes in the era of universal access to ART

Simon de Montigny [a, b, *], Marie-Claude Boily [c], Benoît R. Mâsse [a, b], Kate M. Mitchell [c], Dobromir T. Dimitrov [d]

[a] CHU Sainte-Justine Research Center, Montreal, QC, Canada
[b] School of Public Health, University of Montreal, Montreal, QC, Canada
[c] Department of Infectious Disease Epidemiology, Imperial College, London, United Kingdom
[d] Fred Hutchinson Cancer Research Center, Seattle, WA, United States

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ABSTRACT

Background: The epidemiological tipping point ratio (TPR) has been suggested as a useful indicator to monitor the scale-up of antiretroviral treatment (ART) programmes and determine when scale-up is sufficient to control the epidemic. TPR has been defined as the ratio of yearly number of new HIV infections to the yearly number of new ART initiations or to the yearly net increase in the number of people on ART. It has been used to rank the progress of treatment programmes across countries, with the objective of reaching a TPR value under 1. Our study aims to assess if TPR alone can be used as an indicator of ART success across settings by comparing the expected changes in HIV incidence and ART coverage when TPR is maintained constant over time. In particular, we focus on the effect of ART initiation timing (emphasis on ART being initiated early or late during HIV progression) on the interpretation of the TPR.

Methods: We used a dynamic model of HIV transmission in South Africa representing ART rollout leading to universal treatment in 2017. The model is calibrated to HIV incidence, HIV prevalence and ART coverage in 2012 in South Africa, and 1000 simulations are selected for the base-case scenario. To measure the effect of TPR, we simulate TPR-preserving interventions, maintaining TPR (yearly number of new ART initiations denominator) at the value observed in 2019 (between 0.65 and 1.25) for 15 years. We compare ART coverage and HIV incidence across TPR values and across strategies in which ART access is prioritized differently. In a secondary analysis, we illustrate the sensitivity of new ART initiations to ART retention, and we compare both definitions of the TPR.

Results: Our analysis shows that HIV incidence reduction is weakly correlated to TPR: the same reduction in HIV incidence (15%) can be achieved by implementing the same strategy with a wide range of TPR maintained (0.65–1.12). Assuming high retention in ART, TPR-preserving strategies prioritizing early ART initiation yield greater reduction in HIV incidence than strategies where most individuals initiate ART late. High ART coverage is associated with low HIV incidence and it can be reached with a TPR below or equal to one with strategies favoring early ART initiation. Low ART retention over time results in higher HIV incidence even if TPR is maintained low. If ART retention is low, strategies prioritizing late ART initiation are associated with lower HIV incidence than

* Corresponding author. CHU Sainte-Justine Research Center, 3175 chemin de la Côte-Sainte-Catherine, Montreal, Quebec, H3T 1C5, Canada
E-mail address: simon.de.montigny@umontreal.ca (S. de Montigny).
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strategies where ART is initiated early. Maintaining a fixed TPR value based on the net increase in people on ART gives higher HIV incidence reduction and requires fast ART scale-up.

Conclusion: Our analysis suggests that the TPR is not an adequate indicator of ART programme impact, without information on ART coverage and retention. Achieving early initiation and adherence to treatment to improve ART coverage might be as important as attaining a specific TPR target. Comparisons of TPR in different settings should account for differences in epidemic conditions.

1. Introduction

The epidemiological tipping point ratio (TPR) has been defined as the ratio of the number of annual new HIV infections to the number of annual new antiretroviral treatment (ART) initiations or to the annual net increase in the number of people on ART. This statistic has been suggested as a useful indicator to monitor the scale-up of ART programmes and determine when a programme is likely to have reached a level sufficient to successfully control the HIV epidemic (US PEPFAR, 2012). Intuitively, reducing the TPR below 1 appears desirable as it implies that more infected individuals initiate treatment than become infected. Therefore, fewer infected individuals should remain untreated over time, increasing coverage. Proponents of TPR as an indicator of ART progress say that TPR values maintained less than 1 show "a country getting ahead of its epidemic" (US PEPFAR, 2012). Still, to control the epidemic, the timing of ART initiation might be as important as the number of HIV+ persons initiating treatment due to the increased opportunities for HIV transmission prior to ART initiation at a later stage of infection.

One problem with the applicability of the TPR as an independent metric comes from the fact that alternative definitions are used in the literature with respect to how the denominator of the ratio is estimated. Even though first mentions of the TPR (US PEPFAR, 2012) suggest to use the net increase of in the number of people on ART as denominator, many research publications and even some PEPFAR country reports use the denominator defined or approximated by the number of new ART initiations, number of new people placed on ART, new people initiating or enrolled in ART or becoming suppressed (Coggin, 2014; Granich et al., 2015; Hall, Espinoza, Harris, Tang, & Mermin, 2015; Henry, 2015; ONE, 2016; PAHO, 2013; Tanzania Third National Multi-Sectorial Strategic Framework for HIV and AIDS, 2013; US PEPFAR, 2015). This definition has been widely used which is the reason we use it in our main analysis (we refer to this definition as the TPR). We refer to the definition using the net ART increase as the "net TPR" and investigate its performance in a secondary analysis. Different versions of these two definitions have been used interchangeably even within single documents which often creates confusion and the false sense that they have the same meaning.

There is no clear recommendation on how to use the TPR in monitoring ART programmes. It has been suggested that the TPR should only be derived once ART coverage exceeds 67% (Bass, de Lacy Donaldson, Fisher, & Warren, 2014). It also has been pointed out that if ART coverage gets very high, the TPR may be uninformative with few HIV-infected persons not already on treatment (US PEPFAR, 2013). Thus, once 67% ART coverage is achieved, the TPR can be used to track progress towards the targets of 90% and 95% coverage (90-90-90 and 95-95-95 WHO initiatives). However, the 67% threshold for TPR interpretation has been disregarded in some TPR rankings of countries or US states (Granich et al., 2015; Hall et al., 2015). It remains an open question if TPR values are comparable between settings with different trends in the timing of ART initiation. Moreover, ART retention, a key factor for effective ART scale-up, is not reflected by the TPR using ART initiation as denominator.

Mathematical models are invaluable tools in evaluating the effectiveness of biomedical interventions for HIV prevention (Dimitrov et al., 2010, 2015; Hallett et al., 2011; Vickerman et al., 2006; van de Vijver et al., 2013). In this study, we use a mathematical model to assess the validity of the TPR as an indicator of an ART programme's progress. The model reproduces the dynamics of HIV transmission in South Africa and represents ART rollout starting in 2002 with progressive expansion of eligibility criteria (based on CD4 count) until universal treatment is introduced in 2017.

In our main analysis, we simulate different treatment strategies, introduced in 2020 to maintain the TPR at the value observed in 2019. These strategies have different ART access priorities based on CD4 count categories (>200, 200–350, 350–500 and >500). Maintaining the TPR constant over a prolonged period of time enables us to clearly see how the TPR relates to HIV incidence without the relationship being obscured by changes in TPR over time. Our objective is to verify if lower TPR values and if particular strategies are associated with larger reduction in HIV incidence and greater increase in ART coverage. This analysis informs the validity of the TPR as a measure of ART progress by investigating the importance of lowering the TPR value and helps determine the merit in ranking ART progress in different settings by TPR value only. We emphasize the importance of the distribution of ART initiations across different HIV-infected subgroups and demonstrate that it deserves more attention when ART programmes are planned or implemented.