Antiretroviral Treatment, Preexposure Prophylaxis, and Drug Resistance in Sub-Saharan Africa: A Consensus Among Mathematical Models

To the Editor—Mathematical modeling is a powerful tool for analysis of problems in infectious diseases. However, differences in key modeling assumptions may lead to disparate predictions [1]. Nevertheless, the principal outcomes of the Botswana model by Supervie et al [2] are qualitatively similar to those of our South Africa model [3]. Despite substantial differences in the 2 models’ structural and parameter assumptions, the analyses we describe below confirm that, in both models, antiretroviral therapy (ART) plus preexposure prophylaxis (PrEP) will increase the prevalence of drug-resistant human immunodeficiency virus (HIV), with the major driver of resistance being...
ART, not PrEP. The discrepancies noted by Okano and Blower [4] in the predictions of the 2 models are primarily due to differences in the articulation of the results and in several optimistic assumptions made by Supervie et al [2].

Supervie et al [2] use the phrase “prevalence of transmitted resistance” instead of the incident of transmitted resistance, whereas Okano and Blower [4] refer to prevalent cases of resistance as “prevalence of resistance.” In a mature HIV epidemic, the incidence is likely to exceed the prevalence of transmitted resistance as a result of expanding ART rollout. In addition, changes in resistance prevalence and prevalent resistance cases may be nonparallel.

At PrEP rollout in the South Africa model, the incidence of transmitted resistance is approximately 7% (with prevalence at 1%). Thus, our initial conditions with respect to resistance are not only in agreement with empirical data from South Africa [5], but actually exceed the level (5%) assumed for the Botswana model and, thus, serve as an unlikely explanation for the different model outcomes, as posited by Okano and Blower [4].

The predicted prevalence of drug resistance has been reported for the South Africa model but not for the Botswana model [2]. In addition, the large decrease predicted in the prevalent resistance cases from overlapping ART plus PrEP is at odds with our model prediction. To address these 2 differences, we developed and analyzed de novo the Botswana model, using published methods [2]. Next, we calculated standardized median output metrics to enable comparison with our South Africa model. Both models agree qualitatively: the Botswana model predicts that HIV prevalence will decrease (Figure 1A) and that drug resistance prevalence will increase from ART plus PrEP, compared with ART alone, reaching 40% at 20 years (Figure 1B), and that only 2.4% of drug-resistant infections will be due to PrEP use (Figure 1C).

We then scrutinized the assumptions of the Botswana model to understand the reported decline in prevalent resistance cases [2, 4]. Several optimistic and potentially unrealistic assumptions likely led to the predicted decrease in prevalent resistance cases, including no infectiousness of persons receiving suppressive ART, significantly reduced infectiousness of persons receiving nonsuppressive ART, no drop out from ART, high PrEP coverage (75% of the general population), nonintuitive relationships between PrEP adherence and resistance, similar treatment outcomes for persons with wild-type and resistant virus acquired during PrEP, aggregation of persons with different viral variants into single compartments of transmitted and acquired ART resistance, and homogenous sexual mixing leading to an unrealistically small \( R_0 \) and a low threshold for epidemic elimination [6] (70% of our simulations of the Botswana model led to epidemic elimination). Finally, we reparameterized and reanalyzed the Botswana model, using antiretroviral-related inputs comparable to those of the South Africa model. Figure 1D compares the percentage decrease in prevalent cases of acquired ART resistance with increasing HIV prevention from ART plus PrEP, compared with ART alone, as predicted by the South Africa model (small decrease), the reparameterized Botswana model (intermediate decrease), and the original Botswana model (large decrease). This result shows that structural assumptions, in addition to model parameters, contribute to different model predictions.

Of note, a comparative study [7] has examined standardized outcomes from 3 independent mathematical models, including ours, that determined the influence of PrEP on HIV transmission and drug resistance in sub-Saharan Africa. All 3 models predict that the use of ART plus PrEP will decrease HIV prevalence, compared with ART alone. All 3 models also show that drug resistance will increase over the next 20 years, primarily because of ART. PrEP is predicted to increase the absolute prevalence of resistance in the total population by <0.5% and, among the infected individuals, by at most 7%. Twenty years after PrEP rollout, the majority of drug-resistant infections (50%–63% across models) will be due to ART, 40%–50% will be due to transmission of resistance, and <4% will be due to PrEP use. Thus, there is a consensus among mathematical models that ART plus PrEP will prevent more infections than ART alone but will increase the prevalence of drug resistance, with most resistance arising from ART. Optimized delivery of nonoverlapping PrEP and ART should be a public health priority [3].

Notes

Disclaimer. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Financial support. This work was supported by the Bill and Melinda Gates Foundation (grant OPP1005974 to U. L. A. and J. W. M.).

Potential conflicts of interest. J. W. M. is a member of the scientific advisory board of Gilead Sciences, has share options of RFS Pharmaceuticals, and acknowledges grant support from the AIDS Clinical Trials Group (National Institute of Allergy and Infectious Diseases [NIH] U01AI38858), the Microbicide Trials Network (NIH U01AI068633), the National Cancer Institute (Science Applications International Corporation [SAIC] contract 20XS190A). The other authors certify no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Ume L. Abbas, Robert Glaubius, Gregory Hood, and John W. Mellors

1Departments of Infectious Diseases and Quantitative Health Sciences, Cleveland Clinic, Ohio; and 2Pittsburgh Supercomputing Center and 3Division of Infectious Diseases, School of Medicine, University of Pittsburgh, Pennsylvania

References


