HIV Treatment, Preexposure Prophylaxis, and Drug Resistance: Reconciling Conflicting Predictions From Mathematical Models

TO THE EDITOR—We read with interest the article by Abbas et al, in which they model the potential impact of preexposure prophylaxis (PrEP) on human immunodeficiency virus (HIV) transmission and drug resistance in South Africa [1]. They predict that rolling out Truvada-based PrEP will increase the transmission and prevalence of resistance. Notably, their results conflict with those from 2 previous modeling studies [2, 3]. In one study, Supervie et al [2] predict that rolling out Truvada-based PrEP in San Francisco will decrease both the transmission and prevalence of resistance. In the other study, they predict that rolling out Truvada-based PrEP in Botswana will increase the transmission and decrease the prevalence of resistance [3]. The conflicting predictions regarding PrEP and resistance are illustrated in Figure 1A.

Mathematical models can be useful health policy tools. However, they can, as in this case, cause confusion. To reconcile the results from the 3 studies, we examine their underlying assumptions. They all assume that PrEP can lead to the development and transmission of resistance—in other words, they assume that (1) resistance can develop if HIV-infected individuals begin taking PrEP and/or uninfected individuals become infected while receiving PrEP, and (2) these drug-resistant strains could be transmitted. In addition, they all assume that (3) HIV treatment programs are in place when PrEP is rolled out and (4) HIV treatment can lead to the development and transmission of resistance. Resistance due to HIV treatment has been observed in resource-rich countries since 1987 and has reached moderate-to-high levels [4]. In contrast, resistance in resource-constrained countries is fairly low, because treatment has only recently become available [5, 6].

Each of the modeling studies predicts the potential effect of PrEP on the transmission and prevalence of resistance [1–3]. The important difference between the 3 studies is that each study makes different assumptions—which drive their results—regarding the initial level of resistance when PrEP is rolled out.

Abbas et al make the intuitive prediction that rolling out Truvada-based PrEP in South Africa (where HIV treatment is available) will increase resistance (Figure 1A) [1]. Notably, this result will only hold true

Figure 1. A, Diagram of the impact predicted by 3 modeling studies [1–3] of rolling out preexposure prophylaxis (PrEP) on the transmission and prevalence of resistance in both resource-rich (San Francisco; gold) and resource-constrained (Botswana and South Africa; green and pink, respectively) settings. The change in resistance is very dependent on the level of resistance when the rollout of PrEP is initiated. B, The functional relationship identified by Supervie et al [3] between the percentage of infections prevented and the reduction in the prevalence of resistance after PrEP is rolled out in the presence of treatment programs.
under certain assumptions. Specifically, if (1) the transmission and (2) the prevalence of resistance will be close to zero when the rollout begins. Under these conditions, the transmission and prevalence of resistance can only increase (at least over the short term) if PrEP generates resistance.

Supervie et al, in their modeling study for Botswana, assume that transmitted resistance will be fairly low (approximately 4%) and that the prevalence of resistance will be low to moderate when PrEP is rolled out [3]. These assumptions reflect current conditions in Botswana [7]. They predict that rolling out PrEP will cause a moderate (but transient) increase in transmitted resistance and decrease the prevalence of resistant HIV (Figure 1A). Transmitted resistance will transiently increase because the effect of PrEP on generating resistance will initially be greater than the effect on reducing transmission. Prevalence will decrease because (1) PrEP (by decreasing transmission) will reduce the number of individuals needing treatment and (2) the major source of resistance is treatment, rather than PrEP. Supervie et al identify a quantitative relationship between the effectiveness of PrEP in reducing transmission and the reduction in the prevalence of resistance (Figure 1B) [3].

Supervie et al have also predicted the potential impact of widespread use of PrEP in San Francisco [2]. PrEP is available in this city, but current coverage is low. Their assumptions about resistance reflect current conditions in San Francisco, namely, that the prevalence and transmission of resistance is fairly high [8, 9]. They predict that widespread use of PrEP will substantially decrease both the transmission and prevalence of resistance (Figure 1A). Transmitted resistance will decrease (rather than increase, as in Botswana) because (1) transmission in San Francisco is greater than in Botswana and (2) the effectiveness of PrEP depends on the transmission rate. Specifically, the higher the transmission rate, the greater the effectiveness. Prevalence will decrease for the same reasons as for Botswana.

By comparing 3 modeling studies [1–3], we have shown that predictions are extremely sensitive to the assumptions that are made about the initial levels of resistance when the rollout begins. We caution that the predictions made by Abbas et al [1] (ie, that rolling out PrEP will increase resistance) are only applicable for resource-constrained countries where resistance is close to zero. Their predictions do not apply to South Africa, where resistance has already risen to fairly high levels [5, 10]. The predictions made by Supervie et al for Botswana are more relevant [3]. Consequently, we predict that rolling out PrEP in South Africa could decrease, rather than increase, resistance.

Notes

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