HIV-1 prevention with ART and PrEP: mathematical modeling insights into resistance, effectiveness and public health impact

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The development of, and global access to, effective antiretroviral medications revolutionized HIV-1 care. In addition to their important life-saving treatment benefits, antiretrovirals have recently been demonstrated to be highly efficacious for HIV-1 prevention as well, when used as antiretroviral therapy (ART) to reduce the infectiousness of HIV-1 infected persons and pre-exposure prophylaxis (PrEP) for uninfected persons who have ongoing HIV-1 exposure. Antiretroviral-based prevention, both ART and PrEP, are among the most promising strategies for reducing the number of new HIV-1 infections globally. Consequently, policymakers are weighing the costs, benefits, and risks of public health implementation of ART and PrEP for HIV-1 prevention. One potential risk of both ART and PrEP is the selection and transmission of HIV-1 variants that are resistant to one or more antiretroviral medications, which can result in HIV-1 treatment failure with associated morbidity and mortality and increased costs (of more complex second- and third-line treatment regimens); thus, there has been considerable speculation about the potential risks of resistance from both ART and PrEP.

In this issue of the Journal, Abbas et al. present a mathematical model to estimate the number of HIV-1 infections averted and the number of acquired and transmitted HIV-1 cases of resistance in a setting similar to South Africa and under several scenarios about coverage of ART and PrEP [1]. For PrEP, the authors assumed use of combination emtricitabine-tenofovir, for which efficacy has been demonstrated [2-4]. For ART, the authors modeled first-line regimens containing the same antiretrovirals and assumed that second-line drugs were not available, given limited availability of second-line medications in many resource-limited settings. A number of additional scenarios were analyzed, including having ART initiation at CD4 counts at either <200 or <350 cells/µL, reflecting evolving international guidelines on clinical benefits of earlier ART initiation, and allowing for "inappropriate" PrEP use by persons that are already infected with HIV-1, either through PrEP initiation occurring during unrecognized seronegative acute HIV-1 infection or PrEP initiation by persons with undocumented, chronic HIV-1 infection,

which could occur if HIV-1 testing is not conducted prior to initiation or through 'black market'

availability of PrEP. The authors used optimistic scenarios for ART retention and PrEP

effectiveness; notably, the model assumed general distribution of PrEP, rather than risk-

targeted delivery.

      Not surprisingly, the results of this mathematical modeling article underscore that

population-level coverage and effectiveness (which is dependent on adherence) are the main

determinants of the number of infections averted with both ART and PrEP and that

implementation of a combination of ART and PrEP prevents more infections in a population than

a program that delivers exclusively either ART or PrEP. More interestingly, the model analysis

also suggests that HIV-1 drug resistance in a population would be largely driven by ART, not

PrEP, in all scenarios modeled, as a result of insufficient ART adherence or lack of viral load

monitoring in ART programs, leading to selection of resistant variants during incomplete viral

suppression. The model also finds that the population prevalence of resistance directly as a

result of PrEP may be very low and that the greatest resistance risks related to PrEP would be

from inappropriate use by persons already HIV-1 infected, rather than from PrEP being

prescribed for HIV-1 prevention, even anticipating inadvertent prescribing for persons with

unrecognized acute HIV-1 infection.

      What do these findings mean for potential implementation of PrEP for HIV-1 prevention?

First, these results directly address the often-voiced concern that PrEP will lead to substantial

HIV resistance in populations. Instead, because high PrEP adherence prevents most HIV-1

infections, and although low PrEP adherence does not prevent infection, it is unlikely to select

for resistant variants, the model presented by Abbas et al. suggests substantial population-level

resistance is unlikely. Moreover, even with optimistic assumptions about ART continuation

rates, the amount of resistance generated from ART failure greatly exceeds the resistance

selected by PrEP. Indeed, emerging evidence from Africa has demonstrated increasing

resistance accompanying ART roll-out over the past decade.[5-7] Nevertheless, if persons on

PrEP alternated between periods of good and poor adherence in patterns that increased the risk of them becoming HIV-1 infected and then taking PrEP, the risk of resistance could be greater than predicted in this model. Implementation of PrEP will require ongoing complementary strategies to ensure high quality HIV-1 testing, reduce HIV-1 risk, and maximize PrEP taking.

A second message from the Abbas et al. model is the importance of HIV-1 testing before PrEP initiation to avoid inadvertent exposure for an HIV-1 infected person to what is effectively sub-optimal mono- or dual-agent ART. The model assumed that 2.5% of persons with undiagnosed chronic HIV-1 infection would initiate PrEP each year, which is arguably very high. Nevertheless, the model alerts us to the importance of strategies to monitor quality HIV-1 testing and PrEP pharmacovigilance during this period where PrEP is moving from efficacy trials to implementation.

Third, a highly intuitive finding of the model is that less drug resistance could result if ART and PrEP regimens were used that did not include the same antiretroviral agents. The completed, first-generation PrEP trials used tenofovir, alone or in combination with emtricitabine, resting on the substantial body of clinical safety and experience with these agents for testing PrEP as a novel HIV-1 prevention strategy. New PrEP agents are in development but their use would not be routine for several years.   While, hypothetically, it is preferable to utilize PrEP regimens that do not overlap with antiretrovirals used for treatment, there is also a cost of inaction – missing the opportunity to prevent new HIV-1 infections with demonstrated effective tenofovir-based PrEP while waiting for new safe and effective PrEP regimens to be identified.

While providing some new insights, there are also limitations to the Abbas et al. model. For ART, the key benefit that was not included in this model was its health-impact in terms of saving lives. As the primary benefit of ART is to prolong life, and the primary problem of resistance is the loss of efficacy of ART, this is an important gap in the model. For PrEP, a critical operational factor for maximizing impact in terms of infections averted will be

'prioritization', in which age, gender and risk behaviors are incorporated into risk assessments for potential PrEP users to maximize the likelihood that PrEP is provided to those most at risk of HIV-1 infection. To optimally use resources for PrEP, programs will need to prioritize those who are at highest risk of HIV-1 acquisition and are motivated to take PrEP. Whereas the authors of the present model used a coverage level of 30% of the general population and includes those that do not adhere to PrEP well, other models have suggested that if PrEP delivery programs can target delivery to those at greater HIV-1 risk and achieve higher adherence in a prioritized population, by reducing the total number of new HIV-1 infections, PrEP could even reduce the prevalence of drug resistance [8]. Thus, the complex mathematical model developed by Abbas et al. helps identify some of the next steps for mathematical models and needs for empiric data to clarify policy considerations and implementation priorities for antiretroviral-based HIV-1 prevention through ART and PrEP.

For both PrEP and ART for HIV-1 prevention, adherence is key to effectiveness. For ART, the result is adherence over a lifetime, or until a cure is available. Expanding implementation of ART for HIV-1 prevention will include persons initiating at higher CD4 counts and earlier in their disease course before they have experienced symptoms, and they may face heightened adherence challenges. PrEP adherence has different challenges than ART, namely requiring persons without HIV-1 to perceive their own risk sufficiently to initiate and adhere to PrEP. Thus, PrEP needs to be delivered in a different model than ART, as it is not a commitment to life-long medications, but specially directed to individuals during life periods of highest risk.

While much can be learned from the Abbas et al. model about the potential for generation and spread of HIV-1 antiretroviral resistance related to ART and PrEP, equally important is what this model can teach us about the public health impact of these prevention strategies. The authors have moved the discussions about PrEP forward from modeling simply the number of drug resistance cases with their public health perspective in which they present

the ratio of cumulative HIV-1 infections averted to prevalent HIV-1 drug resistance, which puts

deleterious effect of drug resistance into context with the benefits of HIV-1 infection prevention.

This model clearly demonstrates that both ART and PrEP, particularly when rolled out together,

offer the potential for substantial HIV-1 prevention. Recognizing the potential risks of PrEP and

ART, including antiretroviral resistance, is critical for developing mitigating strategies, since the

potential benefits of these new prevention strategies are substantial and there is real public

health risk in not implementing tools that we know work.

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