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Choosing a metric for measurement of pre-exposure prophylaxis

As the results of HIV prevention trials transition to public health practice, Susan Buchbinder and colleagues¹ have provided a timely exploration of how to prioritise the targeting of pre-exposure prophylaxis (PrEP) to men who have sex with men (MSM). They have drawn attention to the need to examine the efficiency of PrEP in seroconversion prevention and the effect on the HIV epidemic that could be achieved through targeting potential subgroups of the MSM population. Buchbinder and colleagues used the efficiency metric number needed to treat and the effect metric of population-attributable fraction (PAF). However, in the context of PrEP delivery, PAF might not be the ideal metric for evaluation and interpretation of the effect of the intervention.

Kenneth Rothman and colleagues² provide a common definition of the PAF as “the reduction in incidence that would be achieved if the population had been entirely unexposed, compared to its current (actual) exposure pattern”. The PAF can be useful when assessing the effect of an intervention that modifies an exposure and potentially reduces the risk in the

exposed subgroup to the level in the remaining unexposed individuals. As noted by Buchbinder and colleagues, the PAFs of modifiable traits and behaviours were previously assessed for MSM subgroups in Australia.³

The interpretation of PAF is less meaningful in a PrEP setting because the subgroups are defined according to risk factors that we do not plan to modify, but merely to use in targeting PrEP; and treatment with PrEP might be more or less efficacious than reducing the risk to the level in the non-targeted population. We suggest that the fraction of population incident cases that arise in each subgroup is more relevant and interpretable than is the PAF for judging the contribution of each subgroup to overall population incidence. An assessment of the potential effect of PrEP might then be obtained by multiplying each subgroup's fraction of population incident cases by PrEP efficacy within that subgroup. Our suggested metric is thus given by:

Fraction of incident cases averted by PrEP = (incident cases in targeted subgroup/incident cases in total population) × PrEP efficacy

By contrast with the PAF, which assumes that only the excess infections in a particular subgroup can be averted, our proposed metric would assess the fraction of total infections potentially averted by targeting each subgroup. Using this metric in conjunction with the number needed to treat would allow a more direct assessment of the cost-benefit tradeoffs for targeting different subgroups of the population.

We declare no competing interests.

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We read with interest Susan Buchbinder and colleagues' report about HIV pre-exposure prophylaxis (PrEP) in men who have sex with men (MSM) and male-to-female transgender women.¹ WHO recommends that in countries where HIV transmission occurs in men and transgender women who have sex with men, daily oral PrEP is a possible additional intervention for HIV prevention.² Buchbinder and colleagues noted that 53% of the risk of HIV seroconversion came from unprotected receptive anal intercourse with partners of unknown serostatus. Those results are important to identify priority populations for PrEP implementation. However, where do we find those priority populations?

We are doing a clinic-based longitudinal cohort study in Lima, Peru, in high-risk MSM and transgender women to better understand HIV and sexually transmitted infections. In our study, trained behavioural interviewers gathered information in a survey about sociodemographic characteristics and recent sexual behaviour, including unprotected receptive anal intercourse and venues where participants engaged in anal sex. We assessed unprotected receptive anal intercourse in this cohort and incident HIV infection to find out who in our study population should be targeted for PrEP as suggested by Buchbinder and colleagues and to identify the types of venues that can be used to find PrEP candidates.

Of the 400 participants, 214 (54%) reported any unprotected receptive anal intercourse and 76 (19%) reported transactional sex in the past

3 months. The overall incidence of HIV in this cohort was 8.5 cases per 100 person-years. The incidence of HIV in participants who reported unprotected receptive anal intercourse was 14.5 per 100 person years versus 2.0 per 100 person-years in those reporting no unprotected receptive anal intercourse. Using the population-attributable fraction like Buchbinder and colleagues, based on the above rate ratios and the prevalence of exposure, we calculated that unprotected receptive anal intercourse accounted for 77% of infections.

In addition to calculating the prevalence of unprotected receptive anal intercourse and its association with HIV incidence, we identified where participants were having anal intercourse outside of the home. Participants reported anal intercourse primarily at hotels or hostels (68%), in public places (eg, parks; 18%), night clubs (14%), and bathhouses (13%).

The results of our analysis can inform evidence-based public health action. Population-specific HIV prevention efforts for MSM and transgender women in Lima should target those who engage in risk behaviours including unprotected receptive anal intercourse. The venues identified in our analysis in Lima should be prioritised for outreach, education, and PrEP promotion efforts. Additionally, other prevention programmes should identify sites, venues, and subpopulations associated with high-risk sexual behaviour.

This study is funded by the US National Institutes of Health (NIH) through NIH/National Institute of Allergy and Infectious Diseases the R-01 study (grant number 1R01AI099727-01). We thank the study programme staff and research participants.

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Barriers to simplified HIV treatment in low-resource settings

Pedro Cahn and colleagues¹ reported the results of the GARDEL trial, which showed non-inferiority of dual antiretroviral therapy (ART; consisting of lopinavir/r plus lamivudine) compared with the standard regimen of triple antiretroviral therapy (lopinavir/r plus two nucleoside reverse transcriptase inhibitors [NRTI]) with respect to treatment efficacy in patients with HIV not previously treated with ART. However, in this study 54% of the control group used a combination of zidovudine and lamivudine (old fixed-NRTIs), which might have restricted the study results and the generalisation of the findings from this study.

Present guidelines, by the International Antiviral Society-USA panel and the Department of Health and Human Services (USA), for initiation of HIV treatment recommend the use of tenofovir disoproxil fumarate and emtricitabine as the preferred NRTI combination.² Furthermore, Joel Gallant and colleagues³ showed that the tenofovir combination is better in terms of virological suppression, immunological response, and fewer adverse events than is a fixed-dose combination of zidovudine and lamivudine. Thereby, the efficacy outcome noted and the high toxicity-related discontinuations in the control group of standard triple ART could be partly attributed to the use of inferior NRTI combinations.

Despite these restrictions the role of this simplified strategy for

treatment cannot be underestimated, particularly in resource-limited settings where issues related to drug costs and laboratory monitoring are crucial. Nevertheless, even in those regions, I believe that appropriate selection of patients for this strategy might be troublesome. In low-resource countries, where hepatitis B virus is endemic, the burden of the co-infection of HIV and hepatitis B virus is higher than in developed countries with more available resources.⁴ For instance, in a prospective observational study⁵ of adult inpatients with HIV in Malawi in 2004, co-infection of HIV and hepatitis B virus was 20.4%. Conversely, a seroprevalence study⁶ done in Iran during 2004-05, co-infection of these viruses was 44.3%. Thus, a substantial proportion of candidates were excluded for dual ART. Additionally, because of widespread ART-roll out programmes in those countries, transmitted drug-resistance is increasing in patients who are ART-naïve.⁷ M184V mutations might have accounted for 1.2% of resistance-associated mutation patterns, but the pretreatment genotypic test for resistance are rarely done in developing countries, compromising the efficacy of this simplified strategy.

Although the use of dual ART with lopinavir/r plus lamivudine seems an exciting strategy, further research is needed to confirm the GARDEL findings¹ in a real-world setting.

I declare no competing interests.

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For the International Antiviral Society USA panel guidelines see <https://www.iasusa.org/guidelines>

For guidelines by the Department of Health and Human Services see <http://www.guideline.gov/browse/by-organization.aspx?orgid=937>