Mosaic effectiveness: measuring the impact of novel PrEP methods

David V Glidden, Megha L Mehrotra, David T Dunn, Elvin H Geng

Lancet HIV 2019; 6: e800–06

Published Online
September 27, 2019
https://doi.org/10.1016/S2352-3018(19)30227-9

Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA (Prof D V Glidden PhD, M L Mehrotra MPH); **Department of Medicine, Washington University, St Louis, MO, USA** (E H Geng MD); **and MRC Clinical Trials Unit at University College London, London, UK** (Prof D T Dunn PhD)

Correspondence to:
Prof David Glidden, Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA 94158, USA
david.glidden@ucsf.edu

Various ongoing trials seek to evaluate long-acting pre-exposure prophylaxis (PrEP) agents by showing that they are non-inferior to daily oral tenofovir disoproxil fumarate and emtricitabine. Trials comparing oral PrEP to new methods examine effectiveness in a setting where only one or the other is provided; however, a new product will probably be delivered in a context where oral PrEP is also available. The effectiveness of a new PrEP product is best measured by its potential effect in a context that also includes oral tenofovir disoproxil fumarate and emtricitabine as an option. We offer an alternative standard for long-acting products—a measure of the effectiveness of the new product in addition to oral tenofovir disoproxil fumarate and emtricitabine as compared with oral PrEP alone. We term this measure mosaic effectiveness. We illustrate scenarios where a novel product can fail to show non-inferiority but show substantial mosaic effectiveness, thus implying the public health value of the novel product even if it is less effective than oral PrEP. Regulatory standards should consider mosaic effectiveness, not just comparative effectiveness. We assert that measurements that combine rigor with public health relevance can accelerate progress against the HIV epidemic.

The promise of pre-exposure prophylaxis

Oral co-formulated tenofovir disoproxil fumarate and emtricitabine is highly efficacious for HIV pre-exposure prophylaxis (PrEP) with an excellent safety profile.[1] The scale-up to translate PrEP efficacy to public health effectiveness has been challenging. In the USA in 2015, the global leader in the number of PrEP initiations,[2] only 18% of individuals with indications for PrEP received it.[3] The proportion is lower in key populations within the country. African Americans make up 45% of the US population with indications for PrEP[4] but only 1% of these individuals have been started on the regimen.[5]

Most individuals with substantial HIV risk will either decline an offer of PrEP, indicate interest without initiation, or discontinue use shortly after starting.[6,7] Surveys of potential PrEP users suggest that many people do not find a daily oral medication acceptable and would prefer an alternative PrEP delivery method (eg, an implant, a microbicide, or an injectable).[8,9] This finding implies that the use of, and delivery method for, PrEP is a preference-sensitive decision. A variety of non-oral PrEP products are being developed. Communities and the public health sector hope that a broader variety of options will engage a greater percentage of the at-risk population in effective biomedical HIV prevention, and thereby curb the HIV epidemic, especially in populations with the greatest need.

Currently, the roadmap for the development of new PrEP products involves showing non-inferiority to oral tenofovir disoproxil fumarate and emtricitabine in randomised trials. Non-inferiority is a natural criterion for proving that a new product is an adequate substitute. However, the public health effect of long-acting PrEP will stem from retaining and engaging a new population, non-users of oral PrEP, in another effective prevention method, increasing the reach of biomedical HIV prevention. Therefore, we seek an alternative product for oral PrEP non-users rather than a replacement product for existing users. We propose a novel measure, mosaic effectiveness, as an alternative index of effectiveness because it is more aligned with this objective. Heuristically, the index measures the reductions in HIV infections between a context in which oral tenofovir disoproxil fumarate and emtricitabine is the only available PrEP product and one in which this and long-acting PrEP are both available as options. To have added effectiveness, long-acting PrEP will require a new delivery modality (eg, injection, ring, or douche) to be likely to engage a new set of users for which oral PrEP is not acceptable.

Trials for long-acting PrEP products: non-inferiority

Three phase 3 clinical trials have been launched to evaluate next-generation agents for antiretroviral-based PrEP. HPTN083 (NCT02720094)[10] and HPTN084 (NCT03164564)[11] are evaluating cabotegravir long-acting injections, and the DISCOVER[12] study (NCT02842086) evaluates co-formulated tenofovir alafenamide with emtricitabine.

The HPTN083 and DISCOVER trials are designed as non-inferiority studies with the hypothesis that a long-acting PrEP preserves at least 50% of the effectiveness of tenofovir disoproxil fumarate and emtricitabine at the 95% confidence level.[13,14] This standard is typical in non-inferiority studies and conceptually compelling if the new product is designed as a replacement for the control treatment.

However, Snappin and Jiang[15] render an insightful critique of the preservation of effect criteria. They show that effect preservation translates into a higher standard for the new product than the initial criterion (better than placebo) that placebo-controlled trials typically apply to the control product (eg, tenofovir disoproxil fumarate and emtricitabine). We compare the planned years of follow-up for the HPTN083 and DISCOVER trials with the achieved follow-up in the primary analysis of iPrEx

study[16] (figure 1). The studies enrolled participants from similar populations with a similar objective but the planned follow-up, which tends to track cost and resource requirements, are 2–3 times larger for DISCOVER and HPTN083 than for iPrEx. The preservation of effect criterion is a high-cost resource-intensive standard for a long-acting PrEP to reach.

We contend that active controlled trial designs will not address the public health impact of a new PrEP product. Specifically, a comparative effectiveness trial with a non-inferiority design shows the effectiveness of either the oral PrEP alone or the novel agent alone. The ultimate impact of the new product will depend, not on its effect alone, but on its ability to add to a milieu of biomedical preventions by engaging at-risk populations that do not use or desire oral PrEP. A non-inferiority analysis does not address this ability and is poorly aligned to reveal the value of novel products. It would be a natural criterion for a similar, presumably replacement, product. Daily oral tenofovir alafenamide with emtricitabine has the same regimen and delivery as tenofovir disoproxil fumarate and emtricitabine, is not a long-acting PrEP, and should be required to meet conventional non-inferiority through showing preservation of effectiveness.

Consider a randomised, active controlled trial of a long-acting PrEP with an oral tenofovir disoproxil fumarate and emtricitabine control group. Using standard methods,[13,14] a non-inferiority margin of about 1·23 can be justified[10], leading to a sample size of approximately 172 incident HIV seroconversions. Here we present data that mimics the potential results of a trial with that sample size (table 1). Note, the upper limit of the 95% CI for the rate ratio of 1·53 is outside the non-inferiority margin and thus the long-acting PrEP does not show non-inferiority. Therefore, the product would fail its primary objective and probably not be licensed for use. Accordingly, should the long-acting PrEP be abandoned? We consider alternative perspectives on the evaluation of this question.

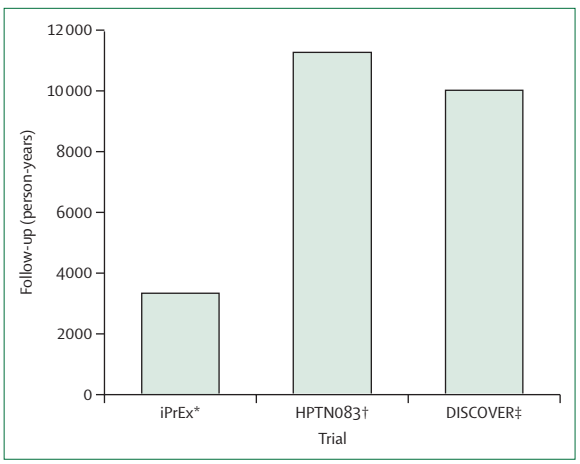


Figure 1: **Person-years of follow-up in three HIV PrEP trials**
*Tenofovir disoproxil fumarate and emtricitabine versus placebo superiority study. †Tenofovir disoproxil fumarate and emtricitabine versus injectable cabotegravir non-inferiority study. ‡Tenofovir disoproxil fumarate and emtricitabine versus tenofovir alafenamide with emtricitabine non-inferiority study.

	Participants (N)	Person-years	HIV-positive participants (N)	Rate per 100 person-years follow-up
TDF-FTC*	2500	5000	81	1·62
Long-acting PrEP†	2500	5000	91	1·82

PrEP=pre-exposure prophylaxis. TDF-FTC=tenofovir disoproxil fumarate and emtricitabine. *Daily oral TDF-FTC. †Non-daily, oral or non-oral PrEP agent.

Table 1: **Hypothetical results from an active controlled trial of a novel prevention method**

Standards for a preference sensitive decision

We imagine that a candidate agent would be evaluated in a double-blind or double dummy randomised active controlled trial of tenofovir disoproxil fumarate and emtricitabine versus a long-acting PrEP. We propose the following three criteria for a candidate agent to fulfil. First, safety—ie, the product is very safe and well tolerated. Second, efficacy—ie, the long-acting PrEP shows high efficacy or effectiveness when used as directed. An ideal long-acting PrEP would have an efficacy of 90% or higher when used as directed (like oral tenofovir disoproxil fumarate and emtricitabine). The efficacy estimation should be done using principled causal methods[17,18] based on the trial data when compared with the inferred background HIV incidence rate. This efficacy estimate should then be used to rule out products with low to moderate efficacy. Finally, effectiveness—ie, evidence of a public health impact after the introduction of the long-acting PrEP within the set of available prevention options. This standard will require evidence of effective use of the long-acting PrEP in a population that either declines to use or does not effectively use oral PrEP.

If the long-acting PrEP is safe, the safety criterion is satisfied. The efficacy criterion ensures confidence that the product works if used properly; as-treated analysis of trial data could be used to infer this. The effectiveness criterion is a novel requirement, which maps the public health impact of the deployment of the long-acting PrEP in a context in which oral PrEP is already an existing option. The measure could be defined as a comparison of the HIV incidence in a trial population where oral PrEP is the only PrEP option with the HIV incidence in the same trial population where users are offered both oral PrEP and the long-acting PrEP as options. We term control effectiveness as the effectiveness (relative to background HIV incidence) in a population provided with oral PrEP. We define choice effectiveness as the effectiveness (relative to background incidence) when the user or provider can choose between the oral PrEP and the long-acting PrEP. We term the comparison of control and choice effectiveness conditions as mosaic effectiveness. The long-acting PrEP will show mosaic effectiveness only if members of the population who are oral PrEP non-users at risk for HIV adopt the effective use of the

	TDF-FTC*	Long-acting PrEP†
Person-years	5000	5000
Background HIV rate per 100 person-years of follow-up PY	2·5	2·5
Efficacy (%)	90%	90%
Proportion adherent (%)	40% (1000/2500)	30% (750/2500)
Effectiveness (%)	36%	27%
Observed HIV-positive participants (N)	81	91
Averted HIV-positive participants (N)	44	34

PrEP=pre-exposure prophylaxis. TDF-FTC=tenofovir disoproxil fumarate and emtricitabine. *Daily oral TDF-FTC. †Non-daily, oral or non-oral PrEP agent.

Table 2: **Scenario underlying the results of the trial of a novel PrEP agent**

		TDF-FTC (N=125)*	
		Averted (n=44)	Observed (n=81)
Long-acting PrEP (N=125)†	Averted (n=34)	Flexible stratum‡ Δ_1	Long-acting PrEP adopter stratum¶ Δ_3
	Observed (n=91)	Pill-preferring stratum§ Δ_2	Unreached stratum‖ Δ_4

Figure 2: **Number of infections in the hypothetical trial distributed by the four strata of infections defined by whether HIV infections would occur or not between the TDF-FTC only stratum or novel PrEP agent only**
Distribution of the 125 individuals who would become HIV-positive in the absence of any PrEP in four principal strata. The numbers in each cell are latent number of infections. The shaded cells indicate strata in which infections could be prevented by the offer of either PrEP regimen. The numbers in these cells are latent. PrEP=pre-exposure prophylaxis. TDF-FTC=tenofovir disoproxil fumarate and emtricitabine. *Daily oral TDF-FTC. †Non-daily, oral or non-oral PrEP agent. ‡Individuals with infections prevented by offer of either TDF-FTC or long-acting PrEP, number of infections = Δ_1. §Individuals with infections prevented if offered TDF-FTC but not prevented if offered the long-acting PrEP, number of infections = Δ_2. ¶Individuals infected if offered TDF-FTC but prevented with an offer of long-acting PrEP, number of infections = Δ_3. ‖Individuals infected if provided with TDF-FTC or long-acting PrEP, number of infections = Δ_4.

long-acting PrEP. This situation would be unlikely to occur if the new product is similar in its delivery system—for instance, a daily oral tablet (eg, tenofovir alafenamide with emtricitabine).

Choice effectiveness, and thus mosaic effectiveness, is not directly identifiable from the effectiveness observed in a randomised active controlled trial of oral tenofovir disoproxil fumarate and emtricitabine versus a long-acting PrEP. Both mosaic and choice effectiveness measures depend intimately on the acceptability of and adherence to the long-acting PrEP among oral PrEP non-users (table 1).

Illustrating mosaic effectiveness

Illustrative scenario

We further elaborate (table 2) on the scenario that underlies the mock trial data (table 1). Let 40% of the population adhere to daily oral tenofovir disoproxil fumarate and emtricitabine, 30% adhere to the long-acting PrEP regimen, and both oral PrEP and the long-acting PrEP reduce HIV infection risk by 90% when used as directed (ie, efficacy is shown). Here, we treat adherence to both products as binary and fixed for an individual.

The impact of implementation is not established using the relative effectiveness of the two strategies in competition but rather using the effectiveness of the two combined as options—since the rationale is that individuals and providers (and other stakeholders) will probably be choosing between them. Mosaic effectiveness depends on the relative adherence to long-acting PrEP and oral PrEP—an idea intimately connected with choice and preference.

Considering the 5000-person cohort in the hypothetical scenario presented here (table 2). We expect approximately 125 HIV infections in the absence of any PrEP product (figure 2). Depending on the individual's assignment, some of these infections will be observed (because of non-adherence or imperfect efficacy) and others will be prevented (averted) by the PrEP method. Within these 125 infections, consider four latent strata,[19] defined by whether their infections will be prevented by the use of oral PrEP or the long-acting PrEP, if offered. First, a flexible stratum in which infections will be prevented by either method offered to them. Second, a pill-preferring stratum in which infections will be prevented if the oral PrEP is provided but not if the long-acting PrEP is offered. Individuals in this stratum do not benefit from the addition of a long-acting PrEP in the clinical milieu, rather these individuals will be harmed by its addition. Third, a stratum of long-acting PrEP adopters who would become infected if only oral PrEP is offered but not if long-acting PrEP is available. This population will allow the reach of PrEP to be increased and one that the long-acting PrEP is designed to engage. The final, unreached, stratum includes individuals who will become infected irrespective of whether they are offered oral PrEP or the long-acting PrEP, and, hence, will remain in need of additional HIV prevention options.

We break down the anticipated number of HIV infections within each of the strata (figure 2). The numbers of HIV infections by treatment group are set using the mock data from the hypothetical trial (table 1). The control effectiveness of the delivery of oral PrEP alone is defined as $(\Delta_1+\Delta_2)/125$, where Δ_1 is the number of HIV infections that would occur in the flexible stratum in absence of any PrEP and Δ_2 is the number of HIV infections that would occur in the pill-preferring stratum. In our scenario, control effectiveness=$(\Delta_1+\Delta_2)/125=44/125=0\cdot35$ (35%)

The choice effectiveness is defined as $(\Delta_1+\Delta_2+\Delta_3)/125$, where, Δ_3 is the number of infections that would be preventable by offering long-acting PrEP to the long-acting PrEP adopter stratum who would not use oral PrEP. The number of these infections cannot be known although

some constraints (eg, $\Delta_1+\Delta_3=34$) are apparent (figure 2). Δ_3 depends on scenarios of product preference. Let us consider two scenarios: a high efficacy, low effectiveness scenario and a high efficacy, high effectiveness scenario.

The high efficacy, low effectiveness scenario: redundant preferences

Suppose all individuals who are adherent to the long-acting PrEP are also adherent to oral tenofovir disoproxil fumarate and emtricitabine. From our mock scenario (table 2), the population then sub-stratifies into the following: 30% long-acting PrEP and oral PrEP users (who will adopt or adhere to either), 10% oral PrEP but not long-acting PrEP users, and 60% non-users of both long-acting PrEP and oral PrEP. None is adherent to long-acting PrEP but not to oral PrEP. This scenario is evident from the number of individuals for whom infections have been averted using oral PrEP (figure 3A [in blue]) or using the long-acting PrEP (figure 3B [in red]), which overlap considerably. The combination of these outcomes (ie, choice effectiveness; figure 3C [in purple]) yields the situation where the long-acting PrEP adopters have zero infections (Δ_3=0), and the number of of observed infections (figure 3 [in black]) is not less in the combined scenario than in the oral PrEP but not long-acting PrEP users alone (figure 3A). Hence, the control effectiveness (of oral PrEP alone) and choice effectiveness (of offering a choice between oral PrEP and long-acting PrEP) are both 35% (95% CI 14–52). Mosaic effectiveness can be defined as the difference or the ratio between the choice and control effectiveness estimates. The difference in effectiveness would be 0·00 (95% CI –0·20 to 0·20; p=1·00). The ratio of the effectiveness is equivalent to the averted infections ratio (AIR), a measure previously proposed for active controlled trials;[20] the AIR in this scenario is 1·00 (95% CI 0·57–1·76).

In this setting, all individuals who use the long-acting PrEP would use oral PrEP anyway; hence, any infections that are averted because individuals choose the long-acting PrEP would be averted by offering oral PrEP (figure 3C [in purple]). Therefore, long-acting PrEP does not have a role in preventing infections against a background of oral PrEP, and mosaic effectiveness is null. However, a different preference configuration can yield very different results.

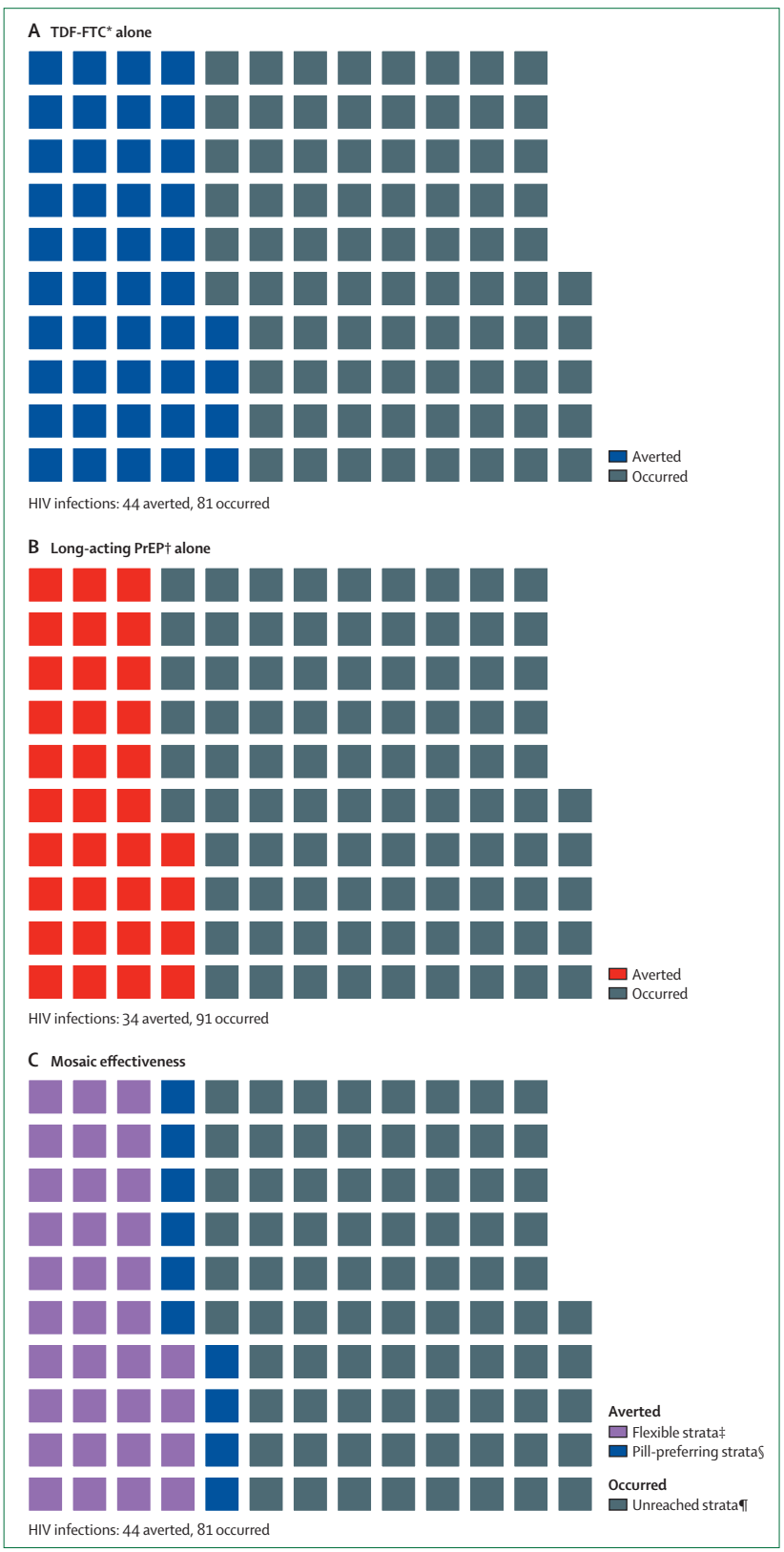
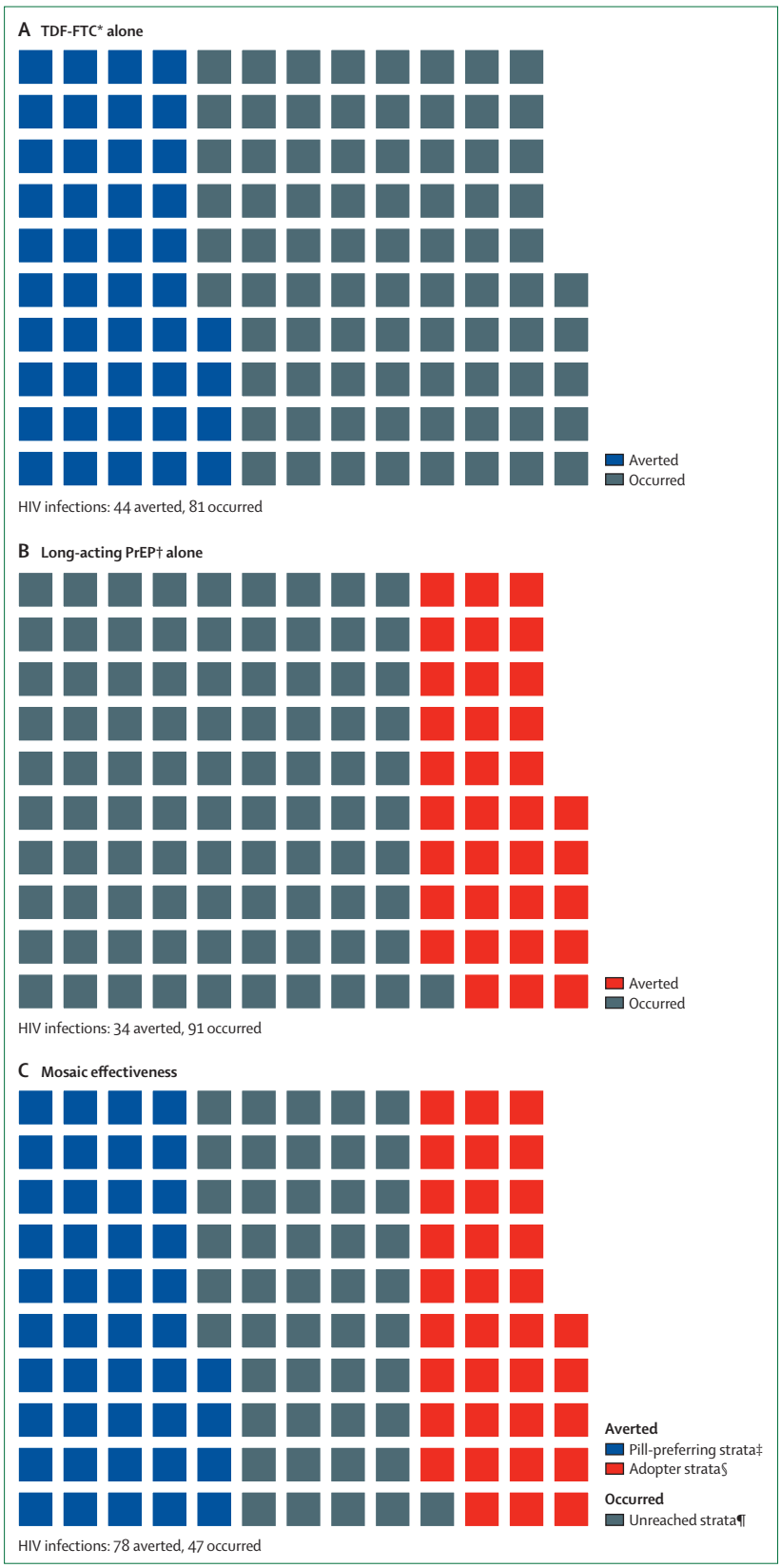


Figure 3: **Redundant preferences scenario**
(A) TDF-FTC alone. (B) Long-acting PrEP alone. (C) TDF-FTC and long-acting PrEP offered as a choice in a redundant scenario. The same 125 individuals are displayed in squares in the three scenarios. Squares in the same position across the graphs identify the same individual. PrEP=pre-exposure prophylaxis. TDF-FTC=tenofovir disoproxil fumarate and emtricitabine. *Daily oral TDF-FTC. †Non-daily and either oral or non-oral PrEP agent. ‡Infections prevented by use of either TDF-FTC or long-acting PrEP (n=33). §Infections averted by TDF-FTC but not by long-acting PrEP (n=11). ¶Infected if provided with TDF-FTC or long-acting PrEP (n=81).



The high efficacy, high effectiveness scenario: synergy of choices

Suppose, instead, that the long-acting PrEP and daily oral tenofovir disoproxil fumarate and emtricitabine represent distinct choices and that individuals strongly prefer one and would not use the other. The population would then stratify to: 0% of individuals adherent to both the long-acting PrEP or oral PrEP, 40% users of oral PrEP but not long-acting PrEP, 30% users of long-acting PrEP but not oral PrEP, and 30% non-users of either regimen. These strata totals are also consistent with our hypothetical trial results (figure 1) and the underlying scenario (figure 3). Estimations of the population that would seroconvert without PrEP (figure 4A, figure 4B) show that the averted infections for oral PrEP (figure 4A [in blue]) and the long-acting PrEP (figure 4B [in red]) are non-overlapping. Hence, in the combined scenario, 34 HIV infections occur among the adopters (figure 4C [in red]; Δ_3=34)—ie, infections that could be averted by the delivery of long-acting PrEP, but not by delivery of oral PrEP to individuals in this stratum.

Here the control effectiveness remains 36%, whereas the choice effectiveness increases to (44+34)/125=0·62 (62%), due to the availability of the long-acting PrEP. A higher choice effectiveness exists in this setting because the long-acting PrEP will be used by 50% of individuals (750/1500) who would not use oral PrEP. The additive mosaic effectiveness comparison would be (44+34)/125−44/125=0·27 (95% CI 0·09–0·45; p=0·003). Thus, 27% of all background infections in the population would be prevented solely by the introduction of the long-acting PrEP as an option. The AIR would be [(44+34)/125]/(44/125)=1·77 (95% CI 1·09–2·89). This outcome suggests that the introduction of the choice of using long-acting PrEP into the synergy scenario will increase the number of averted infections by 1·77 times. Defining the additive rate is possible by standardising to person-years, [(44+34)−44]/5000=0·7 HIV infections avoided per 100 person-years. Such a measure could be helpful in estimating the absolute number of infections prevented by incorporating the long-acting PrEP.

Our head-to-head analysis (table 1) suggests that long-acting PrEP is a marginal product, presumably with no public health benefit. However, the mosaic framework addresses the question of whether introduction of long-acting PrEP as an option prevents infections against a

Figure 4: **Synergy of choices scenario**
(A) TDF-FTC alone. (B) Long-acting PrEP alone. (C) TDF-FTC and long-acting PrEP offered as a choice in a synergistic scenario. The same 125 individuals are displayed in squares in the three scenarios. Squares in the same position across the graphs identify the same individual. PrEP=pre-exposure prophylaxis. TDF-FTC=tenofovir disoproxil fumarate and emtricitabine. *Daily oral TDF-FTC. †Non-daily and either oral or non-oral PrEP agent. ‡Infections averted by TDF-FTC but not by long-acting PrEP (n=44). §Infections averted by long-acting PrEP but not by TDF-FTC (n=34). ¶Infected if provided with TDF-FTC or long-acting PrEP (n=47).

background of oral PrEP alone (or any other existing standard of care) and that the answer depends on long-acting PrEP use in oral PrEP non-users. The example illustrates that mosaic effectiveness is shown when the long-acting PrEP expands the pool of PrEP users by the adoption of the long-acting PrEP among oral PrEP non-users. For instance, a new daily oral PrEP tablet (eg, tenofovir alafenamide with emtricitabine) would not be expected to show mosaic effectiveness.

Discussion

A new PrEP agent should be safe, efficacious, and effective. Efficacy is vital because motivating users will require messaging that conveys that the new PrEP product is highly protective if taken as directed. Even if a novel product is proven effective, it will be difficult for any normative agency to license the product without the confidence that it provides very high protection if used as directed. Efficacy estimates might be biased by confounding variables, but this is considerably reduced if principled methods[17,18] are combined with a thorough sensitivity analysis. Any evaluation of a new prevention product requires the complimentary perspective of effectiveness, shown by intention-to-treat analysis, and efficacy, inferred though adherence analyses. Our novel criterion replaces proof-of-effect preservation tests. We believe that effect preservation as a standard is misaligned with the objectives of developing novel PrEP products.

Successful prevention of HIV in a population with individuals at risk requires matching individuals with PrEP technologies that fit their preferences, needs, desires and, therefore, methods that they will use. Active controlled trials examine relative overall effectiveness but make no account of choice or preference and might attract populations that are amenable to both products being compared. We have numerically illustrated a case where a product could fail the non-inferiority test but still have a strong public health impact. Adopting the new criteria will increase power for detecting products that fit a similar profile. The increase in power can translate into more efficient trials. Here, we have focused on trials in HIV prevention; however, this framework is relevant in trials that compare any technology with preference sensitivity in adoption or adherence.

Research about desires, preference, fit, and, therefore, use, require new kinds of data on the acceptability and suitability of the long-acting PrEP among individuals who will not initiate or sustain the use of daily oral tenofovir disoproxil fumarate and emtricitabine. The fulfilment of our criteria (safety, efficacy, and effectiveness) could possibly be evaluated in a single trial but effectiveness might be best evaluated in a study that focuses on user preferences. Fortunately, study designs exist that can obtain this information. These studies are typically focused, small, and done outside of pivotal randomised trials. Qualitative research using inductive methods can bring the complexities and nuances of preference into clear focus and direct efforts towards the development of such medications. Discrete choice experiments are widely used in marketing and have been used to examine PrEP method preference.[21,22] This approach offers the respondent a series of comparisons between two goods or services in which the attributes are repeatedly varied. By indicating their desired product iteratively, the respondent reveals a quantifiable metric for the strength of their preferences. Quantifying desire can help understand the kinds of trade-offs patients are willing to make to get what they want. Other approaches could mimic the TRIO study,[23] which had participants without HIV try a variety of delivery systems (delivering placebo rather than antiretrovirals) and asked them to rate their preferences and experiences. To date, acceptability and preference are sometimes considered to be problems to defer because they are distal in the translational pipeline (ie, in the domain of implementation science) but we feel these considerations should be incorporated into the earliest phases of product development and phase 3 trial design.

Mosaic effectiveness requires counterfactual estimation of the HIV background incidence in the trial population and estimation of the HIV incidence when participants are matched to the product (oral tenofovir disoproxil fumarate and emtricitabine *vs* long-acting PrEP) to which they would be adherent. Estimation approaches could use the transportability framework[24] on the markers of product use. This is a framework similar to one that has been proposed for HIV vaccine bridging studies.[25] Formal theoretical development of this framework is an area of open research. In our hypothetical scenarios, we also treat adherence as being static. But methods must be developed for handling time-varying adherences. This approach will be particularly difficult for so-called on-demand products, where documenting product use at the time of HIV exposure might be difficult. The statistical details for incorporating preference data to estimate the counterfactual scenario where participants are matched with a PrEP product are a work in progress. In addition, the example considered a scenario in which a perfect match could be made between an individual and the product they would adhere to. This preference might be unknown at the time of PrEP initiation; therefore, statistical methods should elucidate a choice process that will be guided by pre-PrEP characteristics and the attitudes of participants.

The impact of new products will depend on engaging and sustaining PrEP users and motivating health systems to offer and promote them. Tenofovir disoproxil fumarate and emtricitabine PrEP efficacy trials vividly showed this effect when the trials were reported and the gap between stated adherence and documented adherence was apparent.[26] Thus, we advocate greater emphasis on the study of product preference and choice (on the part of users and other stakeholders), particularly revealed preferences, and

the incorporation of this information into the interpretation of trials of next-generation PrEP agents.

Contributors

DVG developed the approach and took the lead in drafting the manuscript. Critical insights were provided by discussions with MLM, DTD, and EHG. All co-authors contributed substantially to the revision of the manuscript content and text.

Declaration of interests

DTD reports personal fees from Gilead Sciences, outside of the submitted work. DVG has accepted fees from Gilead Sciences and Merck. MLM and EHG have no competing interests.

Acknowledgments

Authors were supported by US National Institutes of Health grants R03 AI120819, R03 AI122908, and R01 AI143357 (to DVG); and F31 MH111346 (to MLM) and K24 AI134413 (to EHG). DTD was supported by UK Medical Research Council grant MRC_UU_12023/23. We thank Holly Janes for her insights and support. A version of this work was presented at the International AIDS Conference 2018 and the HIV Prevention Efficacy Trial Designs of the Future symposium, Seattle WA, 2018.

References

1 Fonner VA, Dalglish SL, Kennedy CE et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. *AIDS* 2016; **30:** 1973–83.

2 PrEP Watch. Country updates. https://www.prepwatch.org/country-updates/ (accessed June 15, 2019).

3 Smith DK, Van Handel M, Wolitsky RJ, et al. Estimated percentages and numbers of adults with indications for preexposure prophylaxis to prevent HIV acquisition—United States, 2015. *MMWR Morb Mortal Wkly Rep* 2015; **64:** 1291–95.

4 Smith DK, Van Handel M, Grey J. Estimates of adults with indications for HIV pre-exposure prophylaxis by jurisdiction, transmission risk group, and race/ethnicity, United States, 2015. *Ann Epidemiol* 2018; **28:** 850–57.

5 Smith DK, Van Handel M, Grey J. By race/ethnicity, blacks have highest number needing PrEP in the United States. Congress of Retroviruses and Opportunistic Infections; Boston, MA; March 4–7, 2018 (abstr 86).

6 Mayer KH, Grasso C, Levine K, et al. Increasing PrEP uptake, persistent disparities in at-risk patients in a Boston center. Congress of Retroviruses and Opportunistic Infections; Boston, MA; March 4–7, 2018 (abstr 1014).

7 Rolle CP, Onwubiko U, Jo J, Sheth AN, Kelley CF, Holland DP. PrEP implementation and persistence in a county health department setting in Atlanta, GA. *AIDS Behav* 2019; published online Aug 29. DOI:10.1007/s10461-019-02654-x.

8 Meyers K, Rodriguez K, Brill AL, et al. Lessons for patient education around long-acting injectable prep: findings from a mixed-method study of phase II trial participants. *AIDS Behav* 2018; **22:** 1209–16.

9 Greene GJ, Swann G, Fought AJ, et al. Preferences for long-acting pre-exposure prophylaxis (PrEP), daily oral PrEP, or condoms for HIV prevention among US men who have sex with men. *AIDS Behav* 2017; **21:** 1336–49.

10 HIV Prevention Trials Network. HPTN083: a phase 2b/3 double blind safety and efficacy study of injectable cabotegravir compared to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), for pre-exposure prophylaxis in HIV-uninfected cisgender men and transgender women who have sex with men. HIV Prevention Trials Network. https://www.hptn.org/research/studies/hptn083 (accessed June 15, 2019).

11 HIV Prevention Trials Network. HPTN084: a phase 3 double blind safety and efficacy study of long-acting injectable cabotegravir compared to daily oral TDF/FTC for pre-exposure prophylaxis in HIV-uninfected women. HIV Prevention Trials Network. https://www.hptn.org/research/studies/hptn084 (accessed June 15, 2019).

12 ClinicalTrials.gov. Safety and efficacy of emtricitabine and tenofovir alafenamide (F/TAF) fixed-dose combination once daily for pre-exposure prophylaxis in men and transgender women who have sex with men and are at risk of HIV-1 infection (DISCOVER). US National Library of Medicine. July 22, 2016. https://clinicaltrials.gov/ct2/show/NCT02842086 (accessed June 15, 2019).

13 Hung HMJ, Wang S-J, O'Neill RA. Regulatory perspective on choice of margin and statistical inference issue in non-inferiority trials. *Biom J* 2005; **47:** 28–36.

14 Fleming T R, Odem-Davis K, Rothmann MD, Li Shen Y. Some essential considerations in the design and conduct of non-inferiority trials. *Clin Trials* 2011; **8:** 432–39.

15 Snapinn S, Jiang Q. Preservation of effect and the regulatory approval of new treatments on the basis of non-inferiority trials. *Stat Med* 2008; **27:** 382–91.

16 Grant RM, Lama JR, Anderson PL, et la. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363:** 2587–99.

17 Hernán MA, Hernández-Díaz S. Beyond the intention-to-treat in comparative effectiveness research. *Clin Trials* 2012; **9:** 48–55.

18 Dai JY, Gilbert PB, Hughes JP, Brown ER. Estimating the efficacy of preexposure prophylaxis for HIV prevention among participants with a threshold level of drug concentration. *Am J Epidemiol* 2013; **77:** 256–63.

19 Frangakis CE, Rubin DB. Principal stratification in causal inference. *Biometrics* 2002; **58:** 21–29.

20 Dunn DT, Glidden DV, Stirrup OT, McCormack S. The averted infections ratio: a novel measure of effectiveness of experimental HIV pre-exposure prophylaxis agents. *Lancet HIV* 2018; **5:** e329–34.

21 Tan DHS, Rana J, Fowler S, Hart TA, Wilton J, Bayoum A. Preferences regarding emerging HIV prevention technologies among Toronto men who have sex with men. International AIDS Society Meeting; Paris; July 23–26, 2017 (abstr 2252).

22 Quaife M, Eakle R, Cabrera Escobar MA, et al. Divergent preferences for HIV prevention: a discrete choice experiment for multipurpose HIV prevention products in South Africa. *Med Decis Making* 2018; **38:** 120–33.

23 van der Straten A, Agot K, Ahmed K, et al. The Tablets, Ring, Injections as Options (TRIO) study: what young African women chose and used for future HIV and pregnancy prevention. *J Int AIDS Soc* 2018; **21:** e25094.

24 Dahabreh IJ, Robertson SE, Tchetgen EJ, Stuart EA, Hernán MA. Generalizing causal inferences from individuals in randomized trials to all trial-eligible individual. *Biometrics* 2019; **75:** 685–94.

25 Gilbert PB, Huang Y. Predicting overall vaccine efficacy in a new setting by re-calibrating baseline covariate and intermediate response endpoint effect modifiers of type-specific vaccine efficacy. *Epidemiol Methods* 2016; **5:** 93–112.

26 Amico KR, Marcus JL, McMahan V, et al. Study product adherence measurement in the iPrEx placebo-controlled trial: concordance with drug detection. *J Acquir Immune Defic Syndr* 2014; **66:** 530–37.