Published in final edited form as:

Stat Commun Infect Dis. 2019 January ; 11(1): . doi:10.1515/scid-2019-0011.

Advancing Novel PrEP Products – Alternatives to Non-Inferiority

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Abstract

With the scale-up of HIV pre-exposure prophylaxis (PrEP) with tenofovir (TDF) with or without emtricitabine (FTC), we have entered an era of highly effective HIV prevention with a growing pipeline of potential products to be studied. These studies are likely to be randomized trials with an oral TDF/FTC control arm. These studies require comparison of incident infections and can be time and resource intensive. Conventional approaches for design and analysis active controlled trial can lead to very large sample sizes. We demonstrate the importance of assumptions about background infections for interpreting trial results and suggest alternative criteria for demonstrating the efficacy and effectiveness of potential PrEP agents.

Keywords

active controlled; non-inferiority; hiv prevention; pre-exposure prophylaxis

1 Introduction

1.1 HIV Pre-Exposure Prophylaxis

Pre-exposure prophylaxis (PrEP) using daily co-formulated oral tenofovir disoproxil fumarate with emtricitabine (TDF/FTC) launched a revolution in HIV prevention. It was shown to be safe and effective for preventing HIV infection in a broad range of populations (Fonner et al., 2016). Credible estimates of efficacy, the effect when taken daily, were greater than 90% (Anderson et al., 2012, Donnell et al., 2014). However, adherence was highly variable across randomized trials and the effectiveness of providing PrEP in preventing HIV infection was correspondingly variable (Fig 1). The trials' results demonstrated there can be a large gap between TDF/FTC's biological efficacy and its population level effectiveness.

Implementation of PrEP has encountered structural barriers including medication costs, leading to a lack of access to TDF/FTC in some populations. There is also the issue of the acceptability of PrEP to potential users; many people at substantial HIV risk will decline an offer of PrEP or indicate interest without taking steps to initiate (Mayer et al., 2018, Rolle et al., 2017, Serota et al., 2018); high proportions who initiate will discontinue within a matter of months (Serota et al., 2018, Chan et al., 2016). Many people don't find a daily oral medication acceptable and would prefer an alternative delivery method (e.g., an implant, a

microbicide or an injectable) (Greene et al., 2017, Meyers et al., 2017). The United States leads the world in the number of people taking TDF/FTC for PrEP (AIDS Vaccine Advocacy Coalition, 2019) yet the overwhelming majority of those in the United States who might benefit from PrEP are not using it (Smith et al., 2018, Sullivan et al., 2018). It has become clear that a person's decision to use TDF/FTC for PrEP depends heavily on a person's preferences for how they wish to avoid HIV infection and that a daily oral medication is not a desirable method for many potential users.

Hence, if the objective is to expand the reach of highly effective biomedical HIV prevention, then ease of use, acceptability and user preference should be important considerations in the development of a preference-sensitive product like PrEP. Alternatives, particularly, non-daily and/or non-oral formulations may be required to realize the potential of PrEP. Many such products are in pre-clinical development and will require rigorous trials to evaluate if they are safe, effective and, hopefully, acceptable. We term such non-daily/non-oral products "novel PrEP methods" (NPM). Trials of NPM we must allow for access to the standard of care (daily TDF/FTC) for those who are currently at risk, deal with the gap between self-reported and actual use of TDF/FTC (Amico et al., 2016), and handle the uncertain population level effects of an offer of TDF/FTC. This paper reviews the implications of these issues on the design of trials for the evaluation of NPMs. We argue that non-inferiority is not a useful concept for a NPM and introduce an alternative concept, mosaic effectiveness. We show how this quantity depends on the PrEP choice/preference distribution in the population and argue that in addition to large scale trials, we require smaller more focused studies which interrogate potential user's preferences for a PrEP product.

1.2 Studies of Alternate PrEP strategies

To date, three studies have been launched of two agents for antiretroviral-based PrEP. HPTN083 and HPTN084 (HPTN 083 Protocol Team, 2016, HPTN 084 Protocol Team, 2017) evaluate cabotegravir long-acting injections (CAB-LAI) and the DISCOVER study (DISCOVER Protocol Team, 2016) evaluates co-formulated tenofovir alafenamide with emtricitabine (TAF/FTC). Two of these, HPTN083 and DISCOVER, are non-inferiority studies in a population of men who have sex with men and transgender women (MSM/TW). Their sample sizes are strikingly large.

Fig 2 compares planned person years of follow-up for HPTN083, DISCOVER and the achieved follow-up for the primary analysis of iPrEx study (Grant et al., 2010). The iPrEx trial randomized 2499 MSM/TW to daily oral placebo or TDF/FTC; it was the trial which first established the effectiveness of TDF/FTC PrEP in the MSM/TW population. Note, it followed a similar population to HPTN083 and DISCOVER with a heuristically similar objective (establishing effectiveness of a PrEP agent) but the resource requirements, which tend to track with total follow-up, are 2–3 times larger for DISCOVER and HPTN 083 than for iPrEx.

This difference arises from the fact that the latter two are active controlled non-inferiority studies and iPrEx was a placebo-controlled superiority study. The active controlled studies required a large number of participants and longer duration because they were powered to show non-inferiority under the 95/95 (Hung et al., 2005) method. The approach has two

parts: an assumption (discussed in Sect 3) and a standard (discussed in Sect 4). We review how each of these are a poor fit for HIV PrEP trials and discuss alternative assumptions and standards.

This paper is careful to distinguish between the related terms efficacy and effectiveness. “Efficacy” should be construed to refer to a PrEP product’s ability to reduce the risk of infection (compared to background/no PrEP risk) when taken under ideal conditions (e.g., daily for TDF/FTC). “Effectiveness” will refer to a PrEP products’ ability to reduce the risk of infection (compared to background/no PrEP risk) when taken under typical conditions. Effectiveness is generally known as the intent to treat effect and HIV infections ascribable to non-adherence diminish effectiveness even if the product could have biologically prevented those infections. These concepts have been long recognized in the clinical trials literature but the gulf between them (and the heterogeneity of effectiveness in different populations) is a prominent feature of TDF/FTC for PrEP.

The resource requirements for DISCOVER and HPTN 083, which were powered under 95/95, are formidable. These ambitious trials can cost hundreds of millions of US dollars. Such a high resource barrier to the clinical development of a NPM may cause sponsors to abandon the idea of launching trials even with an agent which may hold promise for HIV prevention. The objective of this paper is to consider trials designs and criteria for a NPM which may be rigorous but less resource intensive than active controlled trial using the 95/95 approach.

2 Design Approaches

A clinical trial of a novel PrEP agent (NPM) must deal with the fact that oral TDF/FTC has established efficacy for PrEP. Researchers are then ethically obligated to make a meaningful offer and/or provide TDF/FTC to HIV negative persons at substantial risk. A number of designs are possible but they all present a mix of practical and scientific complications (Donnell et al., 2013, Cutrell et al., 2017).

2.1 “Add-on” Designs

In the “add-on” design, the standard treatment (TDF/FTC) is provided to all participants in the trial and they are then randomized to combine TDF/FTC with either the experimental treatment (NPM) or a matching placebo. This design has important strengths: all participants receive access to the established standard. Hence, there is no chance someone will receive a level of HIV protection which would be lower than if they did not participate in the trial.

The add-on design would be well attuned to the setting that effectiveness (compared to placebo) for the standard agent is incomplete and concomitant use of an experimental therapy could boost effectiveness. Such a design answers the question: “is it better to provide the standard alone (TDF/FTC) as PrEP or would it be better to combine the standard with an additional agent?”.

The design is simple to implement – all participants receive open-label TDF/FTC and are randomized to the addition of the NPM or a matching NPM placebo. All HIV infections

would be blinded to randomized treatment. The design is intriguing because it provides TDF/FTC to all participants, but it is not well aligned with the PrEP context. First, there is substantial evidence that TDF/FTC's efficacy as PrEP is near complete with rare failures. Hence, if someone is an adherent user of TDF/FTC, there is no advantage to adding another medication to their PrEP. There is a disadvantage; combination treatment, particularly with other antiretrovirals (ARV), would make PrEP more medically complex and expensive.

The real value of providing the NPM would be in those who refuse TDF/FTC or are poorly adherent. If these individuals truly do not want to take a daily oral pill, then the design of the study may not appeal to them because it calls for taking daily oral TDF/FTC in addition to the blinded NPM. Further, the ITT estimate will be highly dependent on the pattern of TDF/FTC adherence in the trial. Among those highly adherent to TDF/FTC, there are likely to be few HIV infections in either randomized arm. Any evidence of difference will come from the effect of the NPM in persons who are not effectively using TDF/FTC.

This design is ethically compelling, but it does not reflect how NPMs would be deployed in practice. Rather than offering people combination PrEP with TDF/FTC and a NPM, the objective is to offer a choice between two effective products.

2.2 Enrolling Refusers and Those with Contraindications

In the PrEP context, the need for a NPM arises because largely because people choose not to use TDF/FTC or are incompletely adherent. It is in that population that a NPM would be beneficial. Hence, a seemingly promising approach for this context would be to screen a population for the need for PrEP and enroll those who decline an offer of TDF/FTC and/or have medical contraindications to TDF/FTC.

Such a trial would enroll those who do not desire PrEP in a placebo controlled trial. Scientifically, this trial answers the question: "If a person does not desire TDF/FTC, is the NPM an effective alternative regimen for HIV PrEP?" This alignment of design, and context allows such a trial to yield the most directly interpretable results. Despite its straightforwardness, none of the second-generation PrEP trials have yet adopted this design. This design presents an ethical dilemma — it would create an apparent tension between enrolling participants and encouraging TDF/FTC use among people at risk for HIV. Even if participants make an informed decision to decline TDF/FTC, the investigators can appear complicit in providing a lower standard of prevention. Hence, such a trial calls for ethical safeguards to ensure that the choice not to use TDF/FTC is an informed one and requires that study staff regularly reengage participants on their desire not to use TDF/FTC. Participants should be able to change their minds and initiate TDF/FTC while continuing in the trial.

Notably, this design could be operationally very similar to the add-on design in a population with a low propensity to use TDF/FTC. It is an advantageous design because it answers a compelling scientific question; however, it has not been adopted by any trials of NPMs; in part, because of the fraught ethical issues of failing to provide TDF/FTC in a population who may need it.

2.3 Active Controlled Studies

To date, all three second-generation PrEP studies have chosen an active controlled design. These studies have randomized participants to daily oral TDF/FTC v. the NPM. All have been double blind and double dummy with a matching placebo to either TDF/FTC or the NPM. It is best for assessing whether the NPM has non-inferior (or even superior) effectiveness compared to daily oral TDF/FTC. It addresses “Is a NPM is a useful alternate PrEP regimen for those who would use either TDF/FTC or the NPM?” rather than “Is the NPM is an effective option for those who decline TDF/FTC?”.

This design has multiple advantages; the active controlled design avoids multiple (possibly redundant) antiretroviral drug exposure and it also avoids an at-risk person from being assigned to a non-PrEP arm as a part of study participation, although it does not guarantee that enrollee will have access to TDF/FTC. It also does not require that a person declare a preference to use or not use TDF/FTC as a condition of enrollment. It is likely to be adopted by many future PrEP trials and may be the design that the field will need to work within.

2.4 Design Implications

Any design must allow for meaningful access to TDF/FTC to participants at risk. The discussed designs differ substantially in practical, scientific, and ethical considerations. It is notable that, to date, of the 3 second-generation PrEP trials, all chose the active control design. While it is not ideally suited to the question, it has a compelling practicality. Hence, we consider inference from active controlled trials for the rest of the paper.

3 The Importance of Background HIV Incidence

A central problem is that active controlled trials lack key information for interpretation — a concurrent non-PrEP control group. We show how for any active controlled trial, interpretation requires making assumptions about how the NPM would compare to a counterfactual placebo arm. We review the current approach (95/95) for inferring background incidence and argue that other approaches are needed which will be more attuned to trials of NPMs.

3.1 Notation

Consider an active control trial which randomizes between a TDF/FTC arm (C, denoting “control”) and an experimental arm, E, (a NPM). Let λ_1^E and λ_1^C denote the (average) rates of infection among those assigned to E and C, respectively. Denote, λ_1^P as the counterfactual placebo HIV rate if the placebo condition could be observed in the trial which randomized between C and E.

Define the (counterfactual) log hazard ratio between C compared to P as $\beta_1^{PC} = \log(\lambda_1^C/\lambda_1^P)$, where the superscript denotes the arm/comparison and the subscript denotes the study in which the comparison is made (1 for the active controlled study). Define also the percent efficacy for the above as

$$\theta_1^{PC} = 100 \left\{ 1 - \exp(\beta_1^{PC}) \right\} = \frac{100(\lambda_1^P - \lambda_1^C)}{\lambda_1^P}$$

Further, define

$$\theta_1^{PE} = 100 \left\{ 1 - \exp(\beta_1^{PE}) \right\} = 100(\lambda_1^P - \lambda_1^E)/\lambda_1^P$$

They are the effectiveness of TDF/FTC and the NPM compared to the counterfactual placebo HIV rate in the active controlled study, respectively.

3.2 Interpretation

Active-controlled studies compare TDF/FTC to the NPM and, thus, provide information to estimate λ_1^C , λ_1^E and $\beta_1^{CE} = \log(\lambda_1^E/\lambda_1^C)$. They are inherently ambiguous for interpreting both efficacy and effectiveness (relative to a non-PrEP control arm). This can be illustrated in a table of the hypothetical result of a randomized, active controlled NPM trial with a TDF/FTC control group (Table 1). The data show substantial similarity in seroconversion rates between the NPM and TDF/FTC. The incidence rate ratio (IRR), $\exp(\beta_1^{CE})$, for NPM v. TDF/FTC can be calculated in the trial population (IRR: 1.12, 95% CI: 0.83 to 1.53). This hypothetical data is meant to mimic the HPTN 083 trial (HPTN 083 Protocol Team, 2016) which is powered to observe 172 HIV seroconversions. Using the 95/95 method (Fleming et al., 2011, Hung et al., 2005), they derive a non-inferiority margin of 1.23. By that standard, the IRR upper confidence bound (1.53) is far above 1.23 - a clear failure to show non inferiority of the effectiveness of the NPM.

The data is consistent with at least two scenarios. One where both regimens have moderate effectiveness, $\theta_1^{PC} = 60\%$ and $\theta_1^{PE} = 55\%$, against a high background risk of HIV infection ($\lambda_1^P = 0.04$, 4 per 100 person years) or both yield low effectiveness, $\theta_1^{PC} = 19\%$ and $\theta_1^{PE} = 9\%$, with a moderate background risk of HIV infection ($\lambda_1^P = 0.02$, 2 per 100 person years).

Despite abundant data in an active controlled trial (172 endpoints), there would be substantial uncertainty about efficacy and effectiveness of the NPM compared to a hypothetical placebo. The different effectiveness, or equivalently non-PrEP incidence rates λ_1^P , lead to different conclusions about the number of averted HIV infections - the expected difference between the number of infections under the no PrEP condition Δ_1^P compared with the observed number of infections each arm (Δ_1^E and Δ_1^C , respectively). Define

$$\bar{\Delta}_1^E = E(\Delta_1^P | - \Delta_1^E) = \frac{\exp(\hat{\beta}_1^{CE}) \Delta_1^E \{1 - (1 - \theta_1^{PC}) \exp(\hat{\beta}_1^{CE})\}}{1 - \theta_1^{PC}} = \tau_1(\lambda_1^P - \lambda_1^E) \quad (1)$$

$$\bar{\Delta}_1^C = E(\Delta_1^P - \Delta_1^C) = \frac{\theta_1^{PC} \Delta_1^C}{1 - \theta_1^{PC}} = \tau_1(\lambda_1^P - \lambda_1^C)$$

as the expected number of averted infections on the TDF/FTC and NPM arm, where τ_1 denotes the total follow-up time (in person years) in the active controlled study. Note (1), can be calculated by either specifying θ_1^{PC} or λ_1^P . The predicted number of averted infections would be $\bar{\Delta}_1^C = 19$ and $\bar{\Delta}_1^E = 9$ under $\lambda_1^P = 0.02$ and $\bar{\Delta}_1^C = 119$ and $\bar{\Delta}_1^E = 109$ under $\lambda_1^P = 0.04$. Note, $\bar{\Delta}_1^E - \bar{\Delta}_1^C = -(\Delta_1^E - \Delta_1^C) = -10 - 10$ fewer averted infections on NPM than TDF/FTC under any assumption about the background incidence; however, the interpretation of this is very different in the two scenarios.

Thus, the stakes are high in aligning the assumed TDF/FTC effectiveness (θ_1^{PC}), or equivalently background incidence λ_1^P , with the truth. If they are too high, we overstate the NPM effectiveness. If they are too low, then the analysis of the NPM is excessively skeptical and stringent. That skeptical assumption costs power and compels larger studies. The major approach for postulating a working value of θ_1^{PC} , relies on summarizing completed trials of TDF/FTC v. placebo (Table 2, Fig 1). The variability in these results makes specification of this working value both important and difficult.

3.3 The 95 Assumption

The typical approach to inferring θ_1^{PC} is known as the 95/95 approach. Both HPTN083 and DISCOVER were powered using the 95/95 method; it is an approach used in many pivotal regulatory non-inferiority studies. A meta analysis of studies comparing the standard therapy (e.g., oral TDF/FTC) versus placebo is calculated. Its log relative risk is denoted by $\hat{\beta}_{0.}^{PC}$.

This value is then “discounted” to yield

$$\beta_*^{PC} = \hat{\beta}_{0.}^{PC} + 1.96 * SE\{\hat{\beta}_{0.}^{PC}\} \quad (2)$$

and this β_*^{PC} is used as the working specification of β_1^{PC} for the analysis of the active controlled trial. The log relative risk of the experimental treatment compared to the imputed placebo arm in the active control trial is then estimated by

$$\hat{\beta}_1^{PE} = \beta_*^{PC} + \hat{\beta}_1^{CE} = \hat{\beta}_{0.}^{PC} + 1.96 * SE\{\hat{\beta}_{0.}^{PC}\} + \hat{\beta}_1^{CE} \quad (3)$$

In (3), there is a single source of statistical variability, the estimate of $C v. E$ in the active controlled trial.

This discounting has been justified as a hedge against selection of a non-optimal control therapy, changes in background treatment, and publication bias in the meta analysis (Fleming et al., 2011). Each of these are less applicable in the PrEP context. There is currently a single biomedical therapy (TDF/FTC); all randomized trials are known and published; and there is no known background preventative that would plausibly diminish the efficacy or effectiveness of TDF/FTC. These considerations may be relevant in chronic diseases with many plausible control comparators, but they are implausible with TDF/FTC. Discounting here has a less compelling rationale.

The meta analysis approach for PrEP has the limitation that it is based on a heterogeneous and modest knowledge base. The HPTN 083 protocol (HPTN 083 Protocol Team, 2016) presents an excellent summary. For women, it is not possible to show non-null TDF/FTC effectiveness after applying the 95% discount to a meta analysis restricted to female participants. For MSM/TW, the HPTN083 analysis estimated 34% efficacy after discounting. However, DISCOVER (by excluding those who did not report condomless receptive anal intercourse at enrollment and weighting trials equally) justified a 1.62 non-inferiority margin (DISCOVER Protocol Team, 2016) using the same set of trials. This illustrates the importance of subtle assumptions made in the meta analysis. For instance, there is some subjectivity about which studies to include - neither PROUD nor ipergay are placebo controlled studies of daily oral TDF/FTC. The 34% effectiveness assumed in the design (and analysis) of HPTN 038 is a particularly skeptical value and lower than that observed in any of the MSM/TW studies. Note, the data in Table 1 fails to show non inferiority for the NPM at the 1.23 margin (used as the NI margin for HPTN083) but would demonstrate non inferiority at the 1.62 margin (used as the NI margin for DISCOVER).

Alternatives should be encouraged to either: estimate the background incidence λ_1^P in the trial cohort or credibly estimate TDF/FTC effectiveness θ_1^{PC} in the cohort. Either one will disambiguate the TDF/FTC vs. NPM comparison. A variety of methods have been proposed by (Hanscom et al., 2018, Adimora et al., 2017, Mullick and Murray, 2019, Baeten et al., 2016). All of the methods have advantages and disadvantages. Most are likely to give a more credible estimate of the TDF effectiveness in the trial/background HIV incidence rate than 95% discounting.

4 Study Objectives

The 95/95 method has two parts: the 95 assumption discussed in Sect. 3.3 and a standard for effect preservation. In this section we critique effect preservation as a study objective and present an alternative approach.

4.1 Non-Inferiority/Preservation of Effect

The HPTN083 and DISCOVER trials were designed as non-inferiority studies. Specifically, they used standards for non-inferiority that required that the investigational PrEP agent

demonstrate that it preserves at least 50% of effectiveness of TDF/FTC. This standard was implicit in the NI margin these studies derived.

Effect preservation is a major part of why the second-generation studies are so large. The HPTN083 trial would be considerably smaller if it were powered on establishing effectiveness relative to placebo. Snapinn and Jiang (2008) gave an insightful critique of preservation of effect criteria (e.g., non-inferiority margins) and illustrated scenarios where an experimental therapy had stronger results than the standard. The standard was compared to placebo and “passed” while the experimental therapy (even with stronger results) could not exclude the non-inferiority margin and “failed”. Simply by being second, the experimental therapy was judged to be a failure. Hence, under effect preservation, the new agent is held to a higher standard. DISCOVER and HPTN083 require far larger sample sizes than iPrEx (Grant et al., 2010) because, in large part, because the new agents must meet a higher bar than was applied to TDF/FTC.

The rationale for effect preservation is compelling in some situations (Fleming et al., 2011) – for instance, if the relevant clinical question is “should the standard of care change from use of the TDF/FTC as the recommended PrEP agent to use of the NPM as the recommended PrEP agent?”. That is a setting in which the objective is substitution of one therapy for another. If so, it is sensible to demand more from the new drug. Substituting a new drug implies losing some benefits (demonstrated long term safety, drug costs) and it is prudent to require an additional assurance that not much efficacy is lost. An example of this would be a daily oral anti-retroviral compared to daily oral TDF/FTC (e.g., TAF/FTC as in the DISCOVER trial). Here TAF/FTC would be a daily oral substitute for daily oral TDF/FTC and effect preservation should be established.

4.2 Abandoning Effect Preservation

We contend that in many PrEP agents - particularly, non-oral delivery agents should not be required to demonstrate non-inferiority to TDF/FTC. That standard misses the rationale for their development. While oral TDF/FTC for PrEP is still scaling up, adoption of PrEP in the United States is only meeting a fraction of the need (Sullivan et al., 2018). Many people at risk are aware of PrEP but choose not to use TDF/FTC; further, there is data that some people prefer a non-oral alternative (Greene et al., 2017). The working assumption, in analogy with contraception, is that additional delivery options will increase the population willing to use a form of PrEP (Ross and Stover, 2013, Delany-Moretlwe et al., 2016).

In short, PrEP use and, in particular, delivery method is a preference-sensitive decision. That consideration compels the development of an alternative (e.g., long acting injections) rather than a substitute for oral TDF/FTC. It is not an attempt to prevent infections by getting oral TDF/FTC users to switch to a new PrEP regimen but by engaging non TDF/FTC users in some form of PrEP. Non-inferiority, with its criterion of effect preservation, is a poor match for preference-sensitive decisions.

4.3 Standards for a Preference Sensitive Decision

Consider the following standard for a NPM

- i. i The product is very safe and well-tolerated.
- ii. The product shows evidence of high efficacy (effectiveness when used as directed). An ideal NPM would be 90% or higher effective when used as directed. The as-treated estimate of efficacy would ideally be compared to the background incidence rate (discussed in Sec 3) and should be able to rule out low to moderate efficacy. This was a similar standard was used to power first generation PrEP trials v. placebo.
- iii. Evidence of a substantial proportion of those who do not take TDF/FTC adequately will, in fact, take the NPM as directed.

Safety (i) for prophylaxis remains paramount. The criterion (ii) ensures that we are confident that the product works if used. Criterion (iii) ensures that the product is engaging people not already using TDF/FTC.

In the preference sensitive scenario, let's think about how the NPM would be delivered. One would not assign people at random to receive the NPM or TDF/FTC or even switch TDF/FTC users to NPM. Instead, providers would hope to match people to the delivery method which fits with their preference - one they are likely to adopt, sustain and use as directed.

Consider an example of how preferences in a population might map to the impact of introducing a NPM along side TDF/FTC. Suppose that, simplistically, 40% of the population will adhere to TDF/FTC on a daily basis, that 30% of the population will adhere to the NPM as directed but their intersection is unclear. Assume that the HIV risk is a homogeneous 2.5 per 100 person years across the adherence strata (no HIV/adherence confounding) and that both TDF/FTC and the NPM reduce HIV infection risk by 90% when used as directed - 90% efficacy of each. This can lead to the data given in Table 1. This data does not meet standards for non-inferiority. However, the compelling question is not the relative effectiveness of the two strategies in competition but rather their impact working in synergy - since the rationale is that people will be choosing between them. The comparison is the public health benefit effect of TDF/FTC alone versus the choice of NPM or TDF/FTC.

4.4 An Alternative Index of Effectiveness: Mosaic Effectiveness

We propose a criterion which maps to public health impact of the introduction of the NPM when TDF/FTC is an existing option. It could be defined as comparing HIV incidence in a population under the scenario that TDF/FTC is the only PrEP option, λ^C , to the HIV incidence in which the same population is offered their choice of use of TDF/FTC or the NPM (denoted λ^M). We term the comparison of control and choice effectiveness (θ^{PC} and θ^{PM} , respectively) conditions as “mosaic effectiveness”. A NPM will demonstrate mosaic effectiveness only if then population includes TDF/FTC non-users at risk of HIV who elect to adopt the NPM. We define mosaic effectiveness as the ratio of the effectiveness measures, θ^{PM}/θ^{PC} . This is equivalent to the averted infections ratio (AIR) – a measure previously proposed for active controlled trials (Dunn et al., 2018).

Choice effectiveness (θ^{PM}), and thus mosaic effectiveness, are not directly identifiable from the effectiveness observed in an active controlled trial randomizing to TDF/FTC vs. NPM. Both choice and mosaic effectiveness measures depend intimately on the acceptability of, and adherence to, the NPM among TDF/FTC non-users which requires additional information in order to estimate θ^{PM} .

Define A_i^C and A_i^E as binary time-fixed variables which indicate, respectively, whether the i th person would adopt and adhere to the control (TDF/FTC) and experimental (NPM) PrEP regimens in the active controlled trial. In an active controlled trial, the randomization would determine which of these we would observe. We cannot estimate the joint distribution (A_i^C, A_i^E) directly in a clinical trial, since each person is assigned only to C or E, but it is required to estimate λ^M – the rate of the HIV infections in choice scenario.

Suppose, counter to fact, we could observe $\mathcal{S}_i = (A_i^C, A_i^E)$ for each person in the active controlled trial. This would require that we know the adoption/adherence to both PrEP methods for each person, including the one they were not randomized to. The stratification is critical for defining the rate of HIV infections under the choice scenario. Assume, under choice, that individuals choose a PrEP regimen x if $A^x = 1$. If $\mathcal{S} = (1, 1)$, then assume they'll adopt the more efficacious of C and E. Define $\lambda^x(\mathcal{S} = s)$ as the rate of HIV infections if offered regimen x given stratum membership $\mathcal{S} = s$. The rate of HIV infection under choice is

$$\lambda^M \approx \min\{\lambda^C(1, 1), \lambda^E(1, 1)\} \text{pr}\{\mathcal{S} = (1, 1)\} + \lambda^C(1, 0) \text{pr}\{\mathcal{S} = (1, 0)\} + \lambda^E(0, 1) \text{pr}\{\mathcal{S} = (0, 1)\} + \lambda^P(0, 0) \text{pr}\{\mathcal{S} = (0, 0)\} \quad (4)$$

where we make the restriction assumption that $\lambda^E(0, 0) = \lambda^C(0, 0) = \lambda^P(0, 0)$. This assumption means that the stratum $\mathcal{S} = (0, 0)$ will not experience risk reduction from an offer of C or E. The (equation 4) is not exact because the marginal hazards is not equal to the mean of the conditional hazard functions. It is approximately correct when the HIV rate is low (less 10 per 100 person years), as is often seen in HIV negative cohorts. However, (4) will be exact if we replace hazard functions with cumulative probabilities of HIV infection to a fixed time.

The choice risk, λ^M is only estimable if $\mathcal{S}_i$ is known, or estimable, for each person in the active controlled trial. In a typical trial, only the marginal distributions of A^C or A^E and the marginal rates λ^C and λ^E are available. However, similar marginal distributions can give rise to very different estimates of λ^M , and hence, θ^{PM}/θ^{PC} as we illustrate.

4.5 Hypothetical and Illustrative Example

4.5.1 Redundant Preferences Scenario—Let's return to a scenario given in Sect 4.3 that 40% of the population will adhere to TDF/FTC on a daily basis and that 30% of the

population will adhere to the NPM as directed with both TDF/FTC and the NPM has 90% efficacy. This would yield the hypothetical head-to-head data in Table 1. An adherence based analysis of NPM would hopefully show (correctly) that the NPM is a safe and shows 90% efficacy — thus, criteria (i) and (ii) are met. However, suppose that all of those adherent to the NPM are also adherent to TDF/FTC. Then, the $\text{pr}\{\mathcal{S} = (1, 1)\}$ equals 0.3 (users of both TDF/FTC and NPM); the probability equals 0.10 for (1,0) – TDF/FTC users but NPM non-users, and the probability equals 0.60 for (0,0) — non users of both NPM and TDF/FTC. We can use these strata to estimate the effect of the choice of TDF/FTC alone vs. TDF/FTC/NPM. The results appear in Table 3. Under both TDF/FTC and choice, the expected number of averted infections is 45 of the 125 infections which would occur without any PrEP.

Hence, the estimate control effectiveness (of TDF/FTC alone), $\hat{\theta}^{PC}$, and estimated choice effectiveness, $\hat{\theta}^{PM}$, (of offering a choice of TDF/FTC or NPM) are both 35%, 95% CI (14% to 52%). The difference in effectiveness, $\hat{\theta}^{PM} - \hat{\theta}^{PC}$, is 0.00, 95% CI (−0.20 to +0.20), $p=1.00$. The ratio of the effectiveness, $\hat{\theta}^{PM}/\hat{\theta}^{PC}$, the AIR (Dunn et al., 2018); its value here is 1.00, 95% CI (0.57 to 1.76).

In this preference configuration, while the NPM has high efficacy, a public health strategy of matching people with their preferred method between PrEP and NPM yields no fewer infections than an offer of TDF/FTC alone. All the infections which are averted by the addition of the NPM would be averted by the use of TDF/FTC alone.

4.5.2 Complementary Preferences Scenario—Let's maintain the constraint that 40% of the population will adhere to TDF/FTC on a daily basis and that 30% of the population will adhere to the NPM as directed and that both TDF/FTC and the NPM have reduced HIV infection risk by 90% when used as directed. However, suppose that all of those adherent to the NPM are non TDF/FTC users. This yield a distribution for $\text{pr}\{\mathcal{S}\} = (0, 0.40, 0.30, 0.30)$ for $\{(1, 1), (1, 0), (0, 1), (0, 0)\}$.

While the head to head data is the same as Table 1, the effectiveness of offering the choice between TDF/FTC and NPM is higher (see Table 4). The population effectiveness of TDF/FTC alone, $\hat{\theta}^{PC}$, (35%) is unchanged from Tables 1 and 3; however, the population effectiveness of the preference-based delivery of TDF/FTC and the NPM, $\hat{\theta}^{PM}$, is 62%, 95% CI (47% to 74%). There is higher choice effectiveness in this setting because the NPM will be used by 50% = (750/1500) of those would not use TDF/FTC. The additive mosaic effectiveness, $\hat{\theta}^{PM} - \hat{\theta}^{PC}$, is $(44+34)/125 - 44/125 = 0.27$, 95% CI (+0.09 to +0.45), $p=0.003$. Thus, 27% all background infections in the population would be prevented solely by the introduction of the NMP as an option. The averted infections ratio, $\hat{\theta}^{PM}/\hat{\theta}^{PC}$, would be 1.77, 95% CI (1.09 to 2.89).

It is critical to note that both redundant preference and synergy scenario arise from the same (marginal) results of a head to head comparison of effectiveness in a randomized active control trial. This type of trial is likely to be conducted in the future; however, it is

uninformative about a key effectiveness question. The joint (not marginal) distribution of preferences leads to the large differences in mosaic effectiveness in the two scenarios.

4.6 Aligning Objectives

Our focus is on novel PrEP products (NPMs)- ones which are non-daily (e.g., pills that could be taken monthly, or quarterly) or long-acting injectable/implant products. The search for NPMs is motivated by the fact that a major barrier to the uptake of PrEP is that many people who are at risk for HIV do not find a daily oral medication to be a desirable prevention option (Serota et al., 2018). Some people directly refuse oral TDF/FTC; others do not initiate even after multiple offers. For NPMs, their effectiveness relative to TDF/FTC, specifically through measures of effect preservation, misses the point. The search for a product requires something which is safe with high efficacy. But also, something which can motivate use among those at risk for HIV but who not use oral TDF/FTC. This paper proposes “mosaic effectiveness” as an index of effectiveness (for an already efficacious product) to describe the population level impact of an NPM. This quantity depends both of the product’s efficacy but also its ability to engage not users of TDF/FTC – this preference structure is captured in the latent distribution of $\mathcal{S}$. Unfortunately, active controlled trials, which we believe are likely to be the dominant design for future NPMs, do not allow us to directly estimate $\mathcal{S}$ and, thus, mosaic effectiveness. This paper strongly advocates that statisticians and trialists collaborate with social science colleagues on strategies to collect/measure product preference data both within clinical trial participants and in population-based studies. For instance, studying “trial use” of various delivery methods (Montgomery et al., 2019) and/or discrete choice experiments (Ryan et al., 2001) can be ways that estimates of $\mathcal{S}$ could be derived for populations. Through our example, we hope to motivate the idea that a product may fail non inferiority criteria but show public health impact. The key driver is the proportion of TDF/FTC non users in a given population who would sustain use of a NPM.

5 Discussion

Currently, there is a single safe and effective product for PrEP — oral TDF/FTC. It is clear that it is not fully satisfactory for all who could benefit for it. The hope is that new products can build a patchwork of options which might expand the number of people who benefit from biomedical HIV prevention.

Many studies of new PrEP agents are designed as active controlled non-inferiority studies. Non-inferiority based on the 95/95 method produces a stringent assessment of effectiveness of a new agent, leading to large studies. The size and scope of these studies can be a barrier to innovation. This paper critiques both aspects of the 95/95 method. The method is meant to achieve two goals: yield an assumption about the counterfactual placebo rate and give a standard for a NPM to show it has value in the context of the established efficacy of TDF/FTC.

We have argued that the interpretation of the value of a NPM is intimately tied to assumptions of about the background placebo incidence either directly (through inferring λ_1^P)

or, indirectly, through the assumed TDF/FTC effectiveness (θ_1^{PC}). The 95/95 method does the latter indirectly based on 95% discounting from historical trials. This is likely to produce an excessively conservative assessment of new agents. We argue that use of either external controls and/or observed pharmacology is more likely to give a more transparent and flexible approach; one more likely to be attuned to the observed risk behaviors and TDF/FTC observed in the trial.

We have also argued that in many settings, particularly when the intervention is preference sensitive, that the emphasis on non-inferiority is not clinically compelling. Instead, we propose an alternative index of effectiveness. This effectiveness is meant to capture the public health impact of introducing a new choice into the PrEP context. Calculating this quantity requires knowing the joint distribution of adherence to possible PrEP agents – a quantity intimately connected to preference and choice. This information would be external to trials. This paper argues that such information should be collected in a more systematic way through preference surveys and discrete choice experiments. Statistical approaches to estimating mosaic effectiveness are a work in progress.

Overall, this paper finds the 95/95 approach to be a poor fit for the HIV PrEP context and hopes to encourage alternative approaches to inferring background placebo rates with principled and transparent assumptions and standards for novel products which have a clear connection to public health impact.

References

- Adimora AA, Cole SR, and Eron JJ (2017): “US black women and human immunodeficiency virus prevention: time for new approaches to clinical trials,” *Clinical Infectious Diseases*, 65, 324–327. [PubMed: 28383649]
- AIDS Vaccine Advocacy Coalition (2019): “PrEP watch country updates,” <https://www.prepwatch.org>, accessed 15 March 2019.
- Amico KR, Mehrotra M, Avelino-Silva VI, McMahan V, Veloso VG, Anderson P, Guanira J, Grant R, iPrEx Study Team, et al. (2016): “Self-reported recent PrEP dosing and drug detection in an open label PrEP study,” *AIDS and Behavior*, 20, 1535–1540. [PubMed: 26992393]
- Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, McMahan V, Bushman LR, Casapia M, Montoya-Herrera O, Veloso VG, Mayer KH, Charialertsak S, Schechter M, Bekker LG, Kallas EG, Grant RM, and the iPrEx Study Team (2012): “Emtricitabine-Tenofovir Concentrations and Pre-Exposure Prophylaxis Efficacy in Men Who Have Sex with Men,” *Science Translational Medicine*, 4, 151ra125–151ra125.
- Baeten JM, Heffron R, Kidoguchi L, Mugo NR, Katabira E, Bukusi EA, Asimwe S, Haberer JE, Morton J, Ngunjiri K, et al. (2016): “Integrated delivery of antiretroviral treatment and pre-exposure prophylaxis to HIV –1-serodiscordant couples: a prospective implementation study in Kenya and Uganda,” *PLoS Medicine*, 13, e1002099. [PubMed: 27552090]
- Chan PA, Mena L, Patel R, Oldenburg CE, Beauchamps L, Perez-Brumer AG, Parker S, Mayer KH, Mimiaga MJ, and Nunn A (2016): “Retention in care outcomes for HIV pre-exposure prophylaxis implementation programmes among men who have sex with men in three US cities,” *Journal of the International AIDS Society*, 19, 20903. [PubMed: 27302837]
- Cutrell A, Donnell D, Dunn DT, Glidden DV, Grobler A, Hanscom B, Stancil BS, Meyer RD, Wang R, and Cuffe RL (2017): “HIV prevention trial design in an era of effective pre-exposure prophylaxis,” *HIV clinical trials*, 18, 177–188. [PubMed: 29039265]

- Delany-Moretlwe S, Mullick S, Eakle R, and Rees H (2016): "Planning for HIV preexposure prophylaxis introduction: lessons learned from contraception," *Current Opinion in HIV and AIDS*, 11, 87–93. [PubMed: 26575146]
- DISCOVER Protocol Team (2016): "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)." <https://clinicaltrials.gov/ct2/show/NCT02842086>, accessed 15 March 2019.
- Donnell D, Baeten JM, Bumpus NN, Brantley J, Bangsberg DR, Haberer JE, Mujugira A, Mugo N, Ndase P, Hendrix C, et al. (2014): "HIV protective efficacy and correlates of tenofovir blood concentrations in a clinical trial of PrEP for HIV prevention," *Journal of Acquired Immune Deficiency Syndromes*, 66, 340. [PubMed: 24784763]
- Donnell D, Hughes JP, Wang L, Chen YQ, and Fleming TR (2013): "Study design considerations for evaluating efficacy of systemic pre-exposure prophylaxis interventions," *Journal of Acquired Immune Deficiency Syndromes*, 63, S130–S134. [PubMed: 23764624]
- Dunn DT, Glidden DV, Stirrup OT, and McCormack S (2018): "The averted infections ratio: a novel measure of effectiveness of experimental HIV pre-exposure prophylaxis agents," *The Lancet HIV*, 5, e329–e334. [PubMed: 29893246]
- Fleming TR, Odem-Davis K, Rothmann MD, and Li Shen Y (2011): "Some essential considerations in the design and conduct of non-inferiority trials," *Clinical Trials*, 8, 432–439. [PubMed: 21835862]
- Fonner VA, Dalglisch SL, Kennedy CE, Baggaley R, Oreilly KR, Koechlin FM, Rodolph M, Hodges-Mameletzis I, and Grant RM (2016): "Effectiveness and safety of oral HIV preexposure prophylaxis for all populations," *AIDS*, 30, 1973–1983. [PubMed: 27149090]
- Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, Goicochea P, Casapía M, Guanira-Carranza JV, Ramirez-Cardich ME, et al. (2010): "Preexposure chemoprophylaxis for HIV prevention in men who have sex with men," *New England Journal of Medicine*, 363, 2587–2599. [PubMed: 21091279]
- Greene GJ, Swann G, Fought AJ, Carballo-Diéguez A, Hope TJ, Kiser PF, Mustanski B, and Richard T (2017): "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 and Behavior*, 21, 1336–1349. [PubMed: 27770215]
- Hanscom B, Hughes JP, Williamson BD, and Donnell D (2018): "Adaptive non-inferiority margins under observable non-constancy," *Statistical Methods in Medical Research*.
- HPTN 083 Protocol Team (2016): "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," <https://www.hptn.org/research/studies/hptn083>, accessed 15 March 2019.
- HPTN 084 Protocol Team (2017): "A phase 3 double blind safety and efficacy study of long-acting injectable cabotegravir compared to daily oral tdf/ftc for preexposure prophylaxis in HIV -uninfected women." <https://www.hptn.org/research/studies/hptn084>, accessed 15 March 2019.
- Hung HJ, Wang S-J, and O'Neill R (2005): "A regulatory perspective on choice of margin and statistical inference issue in non-inferiority trials," *Biometrical Journal: Journal of Mathematical Methods in Biosciences*, 47, 28–36.
- Mayer K, Grasso C, Levine K, et al. (2018): "Increasing PrEP uptake, persistent disparities in at-risk patients in a Boston center," in *Conference on Retroviruses and Opportunistic Infections Boston*.
- McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, Sullivan AK, Clarke A, Reeves I, Schembri G, Mackie N, Bowman C, Lacey CJ, Apea V, Brady M, Fox J, Taylor S, Antonucci S, Khoo SH, Rooney J, and Nardone A (2016): "Pre-exposure prophylaxis to prevent the acquisition of HIV –1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial," *The Lancet*, 387, 53–60.
- Meyers K, Rodriguez K, Brill AL, Wu Y, La Mar M, Dunbar D, Koblin B, Margolis D, Sobieszczyk ME, Van Tieu H, et al. (2017): "Lessons for patient education around long-acting injectable prep: findings from a mixed-method study of phase ii trial participants," *AIDS and Behavior*, 1–8.

- Molina J-M, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, Tremblay C, Le Gall J-M, Cua E, Pasquet A, et al. (2015): "On-demand preexposure prophylaxis in men at high risk for HIV –1 infection," *New England Journal of Medicine*, 373, 2237–2246. [PubMed: 26624850]
- Montgomery ET, Beksinska M, Mgodhi N, Schwartz J, Weinrib R, Browne EN, Mphili N, Musara P, Jaggernath M, Ju S, et al. (2019): "End-user preference for and choice of four vaginally delivered HIV prevention methods among young women in South Africa and Zimbabwe: the Quatro Clinical Crossover Study," *Journal of the International AIDS Society*, 22, e25283. [PubMed: 31069957]
- Mullick C and Murray J (2019): "Correlations between HIV infection and rectal gonorrhea incidence in men who have sex with men: Implications for future HIV pre-exposure prophylaxis trials," *The Journal of Infectious Diseases*.
- Rolle C-P, Rosenberg ES, Luisi N, Grey J, Sanchez T, del Rio C, Peterson JL, Frew PM, Sullivan PS, and Kelley CF (2017): "Willingness to use pre-exposure prophylaxis among black and white men who have sex with men in Atlanta, Georgia," *International Journal of STD & AIDS*, 28, 849–857. [PubMed: 28632468]
- Ross J and Stover J (2013): "Use of modern contraception increases when more methods become available: analysis of evidence from 1982–2009," *Global Health: Science and Practice*, 1, 203–212.
- Ryan M, Bate A, Eastmond C, and Ludbrook A (2001): "Use of discrete choice experiments to elicit preferences," *BMJ Quality & Safety*, 10, i55–i60.
- Serota DP, Rosenberg ES, Lockard AM, Rolle C-PM, Luisi N, Cutro S, del Rio C, Siegler AJ, Sanchez TH, Sullivan PS, et al. (2018): "Beyond the biomedical: preexposure prophylaxis failures in a cohort of young black men who have sex with men in Atlanta, Georgia," *Clinical Infectious Diseases*, 67, 965–970. [PubMed: 29635415]
- Smith DK, Van Handel M, and Grey J (2018): "Estimates of adults with indications for HIV pre-exposure prophylaxis by jurisdiction, transmission risk group, and race/ethnicity, United States, 2015," *Annals of Epidemiology*, 28, 850–857. [PubMed: 29941379]
- Snapinn S and Jiang Q (2008): "Preservation of effect and the regulatory approval of new treatments on the basis of non-inferiority trials," *Statistics in Medicine*, 27, 382–391. [PubMed: 17914712]
- Sullivan PS, Giler RM, Mouhanna F, Pembleton ES, Guest JL, Jones J, Castel AD, Yeung H, Kramer M, McCallister S, et al. (2018): "Trends in the use of oral emtricitabine/tenofovir disoproxil fumarate for pre-exposure prophylaxis against HIV infection, United States, 2012–2017," *Annals of Epidemiology*, 28, 833–840. [PubMed: 30037634]

Figure 1:
Meta Analysis of TDF/FTC Efficacy Across Placebo Controlled PrEP Trials

Figure 2:
Planned Person Years for DISCOVER and HPTN083 Compared to Follow-Up in iPrEx

Table 1:
Hypothetical Non-Inferiority Study of a Novel PrEP Method (NPM) v. Oral TDF/FTC

	Person Years	Number HIV+	Rate (100 PY)
TDF/FTC	5000	81	1.62
NPM	5000	91	1.82

NPM v. TDF/FTC Relative Rate = 1.12 (0.83 to 1.53)

Randomized Controlled PrEP Trials in Men Who Have Sex with Men and/or Transgender Women

Table 2:

Study Name	TDF/FTC		Placebo		% Risk Reduction 95% CI
	Person Years	HIV+ (Rate [*])	Person Years	HIV+ (Rate [*])	
ipergay ¹	220	2 (0.9)	212	14(6.6)	86 (40 to 98)
PROUD ²	243	3(1.2)	222	20 (9.0)	86 (54 to 96)
iPrEx ³	2124	48 (2.3)	2113	83 (3.9)	44 (17 to 63)
Pooled					55 (34–69)

¹ Molina et al. (2015)
² McCormack et al. (2016)
³ Grant et al. (2010)
^{*} Rate per 100 person years

Table 3:

Mosaic Effectiveness: Redundancy of Choices Scenario

TDF/FTC Alone TDF/FTC						
Stratum	$\mathcal{S}$	N.	Person Years	Background HIV+	Observed HIV+	Averted HIV+
TDF/FTC+/NPM+	(1,1)	750	1500	38	5	33
TDF/FTC+/NPM-	(1,0)	250	500	12	1	11
TDF/FTC-/NPM+	(0,1)	0	0	0	0	0
TDF/FTC-/NPM-	(0,0)	1500	3000	75	75	0
Overall		2500	5000	125	81	44
TDF/FTC v. NPM Choice						
Stratum	$\mathcal{S}$	N.	Person Years	Background HIV+	Observed HIV+	Averted HIV+
TDF/FTC+/NPM+	(1,1)	750	1500	38	5	33
TDF/FTC+/NPM-	(1,0)	250	500	12	1	11
TDF/FTC-/NPM+	(0,1)	0	0	0	0	0
TDF/FTC-/NPM-	(0,0)	1500	3000	75	75	0
Overall		2500	5000	125	81	44

 $\theta^{PC} = 35\%$, 95% CI (14% to 52%)

 $\theta^{PM} = 35\%$, 95% CI (14% to 52%)

TDF/FTC: co-formulated tenofovir disoproxil fumarate/emtricitabine) NPM: Novel PrEP Method

Table 4:

Mosaic Effectiveness: Synergy of Choices Scenario

TDF/FTC Alone TDF/FTC						
Stratum	$\mathcal{S}$	N.	Person Years	Background HIV+	Observed HIV+	Averted HIV+
TDF/FTC+/NPM+	(1,1)	0	0	0	0	0
TDF/FTC+/NPM-	(1,0)	1000	2000	50	6	44
TDF/FTC-/NPM+	(0,1)	750	1500	38	38	0
TDF/FTC-/NPM-	(0,0)	750	1500	37	37	0
Overall		2500	5000	125	81	44
TDF/FTC v. NPM Choice						
Stratum	$\mathcal{S}$	N.	Person Years	Background HIV+	Observed HIV+	Averted HIV+
TDF/FTC+/NPM+	(1,1)	0	0	0	0	0
TDF/FTC+/NPM-	(1,0)	1000	2000	50	6	44
TDF/FTC-/NPM+	(0,1)	750	1500	38	4	34
TDF/FTC-/NPM-	(0,0)	750	1500	37	37	0
Overall		2500	5000	125	47	78

 $\theta^{PC} = 35\%$, 95% CI (14% to 52%) $\theta^{PM} = 62\%$, 95% CI (47% to 74%)

TDF/FTC: co-formulated tenofovir disoproxil fumarate/emtricitabine NPM: Novel PrEP Method