Supplementary Note 5: Long-term PrEP efficacy (module V)

A number of clinical trials were performed to estimate the effectiveness of pre-exposure prophylaxis (PrEP) in preventing HIV-1 infections. The outcomes of these assessments were highly variable. In this note, we will show that an estimate of PrEP efficacy based on a clinical trial is confounded by various factors and we will derive an explicit formula that relates the *true* PrEP efficacy, i.e. the probability to prevent an infection after a single virus challenge, to a corresponding estimate from a clinical trial of particular duration, incl. risk behavior (e.g. including risk compensation). This formula allows therefore to assess potential confounders upfront or to correct the clinical estimate *a posteriori*. This module can take results from modules III and IV as input (see **Supplementary Notes 3-4**).

SN4.1 Trial efficacy estimates

A clinical trial consists typically of two arms, –a treatment arm and a placebo arm–, which are followed for the trials' duration. At the end of the trial, based on the results of two arms (proportion infected; rate of infections) the efficacy of the intervention S is stated, e.g. [1,2,3,4]:

$$1-\omega_T \approx \left(\frac{\#\text{inf}_S}{T_{F,S}}\right)\cdot\left(\frac{\#\text{inf}_\emptyset}{T_{F,\emptyset}}\right)^{-1} \qquad \text{(trial efficacy)} \tag{SN5.1}$$

where $\#\text{inf}_S$, $\#\text{inf}_\emptyset$ denote the number of infections in the intervention S and placebo/untreated $\emptyset$ arm and $T_{F,S}$, $T_{F,\emptyset}$ denote the follow-up duration in e.g. person-years.
We will show that the quantity stated above does not reflect the efficacy of the intervention itself, since, among other factors, the duration of the trial affects this estimate, making efficacy estimates from trials not readily comparable. In the following we will highlight the dependence of a trial efficacy estimate on different variables.
However, first let us derive a mathematically *exact* trial efficacy estimate (unlike eq. (SN5.1) which is a sample estimate). Let us consider a clinical trial for PrEP conducted with HIV-1 uninfected persons at risk. There are two arms, –a placebo arm and a treatment arm. Given a particular individual k is followed T_k months, the probability that a particular individual becomes infected in the placebo or -treatment $\emptyset/S$ arm are

$$P_{\emptyset/S,k}(\text{inf}) \quad = \quad 1-\prod_{t_j}\left(1-P_{\emptyset/S,t_j,k}(\text{inf})\right) \tag{SN5.2}$$

respectively, where t_j denotes the jth time when the individual k was exposed to virus through e.g. unprotected intercourse with an infected individual. Obviously, the expected number of individuals infected in either arm is simply $\mathbb{E}(\#\text{inf}) = \sum_{k=1}^{K} P_k(\text{inf})$ and $\mathbb{E}(\#\text{inf})/T_F$ is the *true* incidence rate. Consequently,

$$1-\omega_T = \left(\frac{\mathbb{E}_S(\#\text{inf})}{T_{F,S}}\right)\cdot\left(\frac{\mathbb{E}_\emptyset(\#\text{inf})}{T_{F,\emptyset}}\right)^{-1} \tag{SN5.3}$$

would be the *exact* trial efficacy estimate.
Typically, we have $T_{F,S} \approx T_{F,\emptyset}$ in clinical trials (follow-up durations are approximately equal in the two arms) and approximately the same number of individuals $K_{\emptyset/S}$ in each arm, in which case the equation simplifies accordingly

$$1-\omega_T = \left(\frac{\mathbb{E}_S(\#\text{inf})}{T_{F,S}}\right)\cdot\left(\frac{\mathbb{E}_\emptyset(\#\text{inf})}{T_{F,\emptyset}}\right)^{-1} = \frac{\mathbb{E}_S(\#\text{inf})}{\mathbb{E}_\emptyset(\#\text{inf})} = \frac{\bar{P}_{S,T}(\text{inf})}{\bar{P}_{\emptyset,T}(\text{inf})}. \tag{SN5.4}$$

Where for the last identity we used $\mathbb{E}_{\emptyset/S}(\#\text{inf}) = K_{\emptyset/S}\cdot\bar{P}_{\emptyset/S,T}(\text{inf})$ with $\bar{P}_{\emptyset/S,T}(\text{inf})$ being the *average* probability of infection for a trial of length T (person-years) in placebo/untreated $\emptyset$ or PrEP arm S.
Let $\text{N}_{c,\emptyset}$ and N_S be the average number of unprotected sex acts with an infected person per month in the placebo- and treatment arm respectively. Given a trial duration of T months, the proportion of infected people in the placebo and treatment arm are $\bar{P}_{\emptyset,T}(\text{inf}) = 1-\left(1-\bar{P}_\emptyset(\text{inf})\right)^{T\cdot\text{N}_\emptyset}$ and $\bar{P}_{S,T}(\text{inf}) = 1-\left(1-\bar{P}_S(\text{inf})\right)^{T\cdot\text{N}_S}$ respectively, where

$\bar{P}_{\emptyset/S}(\text{inf})$ is the average *per challenge* probability of infection, as stated in the main manuscript. The ratio of these infection probabilities can be used to quantify the clinical trial efficacy (ω_T) as shown below:

$$1-\omega_T = \frac{1-\left(1-\bar{P}_S(\text{inf})\right)^{T\cdot \mathrm{N}_S}}{1-\left(1-\bar{P}_\emptyset(\text{inf})\right)^{T\cdot \mathrm{N}_\emptyset}} \tag{SN5.5}$$

Previously, we have derived the average PrEP efficacy *per typical challenge* (ψ), see **Supplementary Note 3** and eq. (3) (main manuscript):

$$\bar{P}_S(\text{inf}) \approx (1-\psi)\cdot \bar{P}_\emptyset(\text{inf}). \tag{SN5.6}$$

Using eq. (SN5.6) we can rewrite eq. (SN5.5) as

$$1-\omega_T = \frac{1-\left(1-\bar{P}_\emptyset(\text{inf})\cdot(1-\psi)\right)^{T\cdot \mathrm{N}_S}}{1-\left(1-\bar{P}_\emptyset(\text{inf})\right)^{T\cdot \mathrm{N}_\emptyset}}, \tag{SN5.7}$$

which shows the dependence of clinical trial efficacy (ω_T) on the duration of the clinical trial (T), the prophylactic efficacy of the intervention after a *typical* exposure (ψ) and the number of unprotected sex acts with an infected individual in the treatment arm (N_S) and the placebo arm ($\mathrm{N}_\emptyset$) respectively.

Eq. (SN5.7) can be used to assess the influence of **risk compensation** on the long-term efficacy, i.e. when the number of risky sex acts in the treatment arm is higher than in the placebo arm $\mathrm{N}_S > \mathrm{N}_\emptyset$. Another important implication from eq. (SN5.7) is the dependence of the trial efficacy on the trial duration. For instance, two trials using the same treatment PrEP strategy (i.e. same treatment efficacy ψ) evaluated over different trial durations (or alternatively evaluated in different risk groups) would result in different trial efficacy estimates. Thus, for an unbiased comparison, it is advisable to compute the treatment efficacy ψ from the clinical trial efficacy ω_T estimate.

SN4.2 Computation of PrEP efficacy from trial efficacy estimate

To compute the treatment efficacy ψ from a clinical trial estimate ω_T by rearranging eq. (SN5.7):

$$\begin{aligned}
1-\omega_T &= \frac{1-\left(1-\bar{P}_\emptyset(\text{inf})\cdot(1-\psi)\right)^{\mathrm{N}_S\cdot T}}{1-\left(1-\bar{P}_\emptyset(\text{inf})\right)^{\mathrm{N}_\emptyset\cdot T}},\\
\cancel{1}-\left(1-\bar{P}_\emptyset(\text{inf})\right)^{\mathrm{N}_\emptyset\cdot T}-\omega_T+\omega_T\cdot\left(1-\bar{P}_\emptyset(\text{inf})\right)^{\mathrm{N}_\emptyset\cdot T} &= \cancel{1}-\left(1-\bar{P}_\emptyset(\text{inf})\cdot(1-\psi)\right)^{\mathrm{N}_S\cdot T},\\
\left(1-\bar{P}_\emptyset(\text{inf})\cdot(1-\psi)\right)^{\mathrm{N}_S\cdot T} &= \left(1-\bar{P}_\emptyset(\text{inf})\right)^{\mathrm{N}_\emptyset\cdot T}+\omega_T-\omega_T\cdot\left(1-\bar{P}_\emptyset(\text{inf})\right)^{\mathrm{N}_\emptyset\cdot T},\\
1-\bar{P}_\emptyset(\text{inf})\cdot(1-\psi) &= \sqrt[\mathrm{N}_S\cdot T]{\left(1-\bar{P}_\emptyset(\text{inf})\right)^{\mathrm{N}_\emptyset\cdot T}+\omega_T-\omega_T\cdot\left(1-\bar{P}_\emptyset(\text{inf})\right)^{\mathrm{N}_\emptyset\cdot T}}.
\end{aligned}$$

This gives the following relation:

$$(1-\psi) = \frac{1-\sqrt[T\cdot \mathrm{N}_S]{\left(1-\bar{P}_\emptyset(\text{inf})\right)^{\mathrm{N}_\emptyset\cdot T}+\omega_T-\omega_T\cdot\left(1-\bar{P}_\emptyset(\text{inf})\right)^{\mathrm{N}_\emptyset\cdot T}}}{\bar{P}_\emptyset(\text{inf})}. \tag{SN5.8}$$

SN4.2.1 Examples

Let us hypothetically consider the case where there is exactly one risky sex act per person in both intervention arms. In this case

$$\mathrm{N}_\emptyset\cdot T = \mathrm{N}_S\cdot T = 1$$

and the identity

$$1-\psi = 1-\omega_T$$

follows from eq. (SN5.8).

In all other cases, where $\mathrm{N}_S\cdot T \geq \mathrm{N}_\emptyset\cdot T \geq 1$, we have $\omega_T \leq \psi$, i.e. the trial efficacy may under predict the PrEP efficacy *per coitus* or stated inversely, the PrEP efficacy *per coitus* over predicts risk prevention following multiple viral challenges, and in the case of risk compensation.

SN4.2.2 Clinical trial simulation

For illustration and verification, we predicted clinical trial outcomes by stochastic simulations. Stochastic simulations were motivated by the well-known Gillespie Algorithm[5], where the time to the next event τ (intercourse with an infected individual) was drawn randomly from an exponential distribution with mean and variance $r_0 = \left(\sum_k r_k\right)^{-1}$, where r_k is the contact rate ((number of risky contacts per month)$^{-1}$) for the uninfected individual k, (See Gillespie et al.[5]). That is for ξ_1 in uniform distribution $[0, 1)$:

$$\tau = \frac{1}{r_0} \ln\left(\frac{1}{\xi_1}\right). \tag{SN5.9}$$

The exposed individual m was drawn randomly in proportion to his/her sexual activity and infected (removed from the population of uninfected individuals) proportionally to the probability of infection after exposure $P(\text{inf}\,|V_0 = n)$. I.e.

$$m \quad = \quad \text{smallest integer satisfying} \sum_{k'=1}^{k} r_{k'} > \xi_2 \cdot r_0 \tag{SN5.10}$$

$$m \text{ infected if:} \qquad \xi_3 \leq P(\text{inf}\,|V_0 = n). \tag{SN5.11}$$

with $\xi_1, ...\xi_3$ being independent uniform random numbers from the unit interval.
Parameterizations for the simulations (Fig. SN5.1 below) were largely based on data provided in the IPERGAY study[3,6]: Roughly 7 condom-less anal sex acts per month with different sexual partners among MSM were reported in the IPERGAY study[6]. The prevalence of HIV-1 in the particular MSM group was reported to be around 17 %[7]. Thus, the average number of risky sex acts of an exposed individual per month with a potential donor was fixed to 1.19 (7×0.17). We consider the same risk behaviour in both arms i.e. $N_\emptyset = N_S = 1.19$. The prophylactic efficacy of the PrEP treatment ψ was set to 80%. The *average* infection probabilities per coitus $\bar{P}_\emptyset(\text{inf})$ for homosexual- and heterosexual transmission were assumed to be 0.03 and 0.003 respectively[8,9,10].

Figure SN5.1 shows Kaplan-Meier estimates of the proportion of individuals becoming infected during the course of the stochastically simulated (see eqs. above) clinical trial in the untreated/placebo (panel **A**) and the PrEP-treated arm (panel **B**) respectively, for 400 individuals (200 in each arm) belonging to homosexual- vs. heterosexual risk groups. The superimposed solid yellow- and blue lines indicate the computed proportions using the analytical formula (eq. (SN5.7)). Panel **C** of Figure SN5.1 depicts the clinical trial efficacy estimate ω_T (computed from the analytical Eqn (SN5.5)) as a function of the trial duration T for the homosexual- (yellow), and the heterosexual target group (blue). Note that the clinical trial efficacy estimates ω_T decrease with increasing trial duration, relative to the *actual* PrEP efficacy (dashed horizontal line). However, bias is much stronger for the homosexual target group, which only differs in the simulations with respect to $\bar{P}_\emptyset(\text{inf})$, which is 10-times larger than for the heterosexual target group. All in all, this bias is a consequence of many individuals becoming infected in the homosexual target group. Note that in the heterosexual target group, the number of individuals becoming infected is very low. The latter indicates, that although the PrEP efficacy estimate ω_T may be very accurate when the overall proportion infected is low, such a result is hardly evaluable: That is: in the PrEP treated arm almost no individual becomes infected after an average follow-up time of ≈ 12 month. Thus, an estimate of the incidence rate would be highly unreliable in a statistical sense.
The evaluations in simulations in Figure SN5.1 highlight two important caveats to be considered when designing and evaluating a clinical trial:

- short trial durations with few people infected deliver estimates that almost accurately reflect PrEP efficacy *in theory*, but are statistically very unreliable *in practice* (estimates of incidence rates are heavily confounded by chance events).

- long trial durations with many people infected deliver estimates of PrEP efficacy ω_T that heavily under predict the true PrEP efficacy *per challenge* ψ, but the underlying incidence rate estimates are statistically reliable.

Taking these considerations into account, we strongly recommend to conduct a trial with a long-as-possible follow-up to ensure statistical certainty in the incidence rate prediction and then to convert the trials efficacy estimate ω_T to an actual PrEP efficacy estimate ψ using eq. (SN5.8).

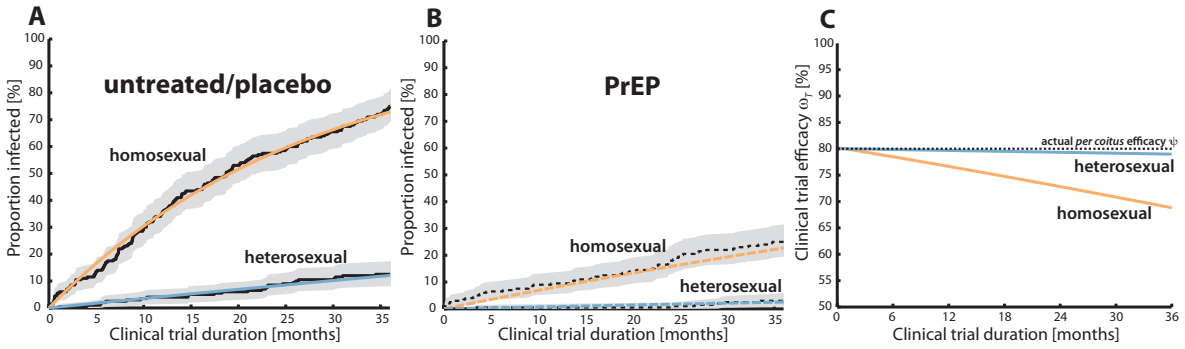

Figure SN5.1: **Simulated PrEP clinical trials for homosexual- and heterosexual transmission modes.** A: Proportion of infected individuals in the placebo arm. The yellow and blue solid lines represent the proportion of infected in the homosexual and heterosexual transmission groups computed from eq. (SN5.5). The solid black lines represents the Kaplan-Meier estimate of a stochastic simulation with 200 individuals. The gray area marks the region between the upper and lower bounds of the Kaplan-Meier estimate. The infection probability *per coitus* $\bar{P}(\text{inf})$ for homosexual and heterosexual transmission were fixed to 3% and 0.3 % respectively. B: Proportion of infected individuals in the treated arm with prophylactic efficacy of ψ =80% *per coitus*. The yellow and blue dashes lines denote the homosexual- and heterosexual target group. The black dash lines denotes the Kaplan-Meier estimate and the gray region denotes the area between the upper and lower bound of the Kaplan-Meier estimate for a stochastic simulation with 200 individuals. Panel C compares the trial efficacies ω_T for the homosexual- and heterosexual target. The horizontal black dashed line marks the prophylactic efficacy of PrEP per viral challenge ψ.

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