

OBJECTIVE

To predict the epidemiological impact of pre-exposure prophylaxis (PrEP) interventions in the Men-who-have-Sex-with-Men (MSM) community in San Francisco in terms of infections prevented and increases in transmitted drug resistance (TDR).

BACKGROUND

✓ The administration of antiretroviral drugs (ARVs) prior to HIV exposure (PrEP) has gained considerable attention as a potential biomedical intervention to protect high-risk HIV-negative people against infection.

✓ Several efficacy trials of daily PrEP with tenofovir (TDF) or TDF with emtricitabine (FTC) are now ongoing among high-risk populations.

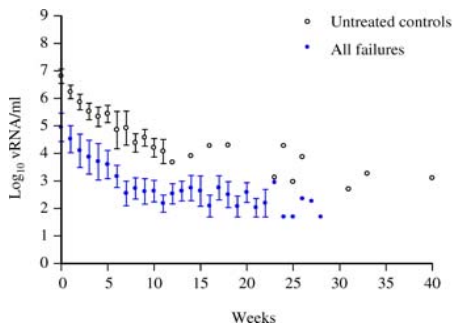
✓ A major concern is that drug resistance may develop in individuals who become infected with HIV while on PrEP. These individuals could then potentially transmit drug-resistant strains.

✓ PrEP could soon be used among high-risk populations, such as MSM, in resource-rich countries where HIV prevalence is high. In these countries therapeutic treatment, based on ARVs, has been available for 20 years. This has led to moderate to high levels of TDR in certain communities. There is therefore a concern that an intervention based on PrEP could substantially increase current levels of TDR.

✓ The macaque model of SHIV infection has provided important information regarding the effect of daily PrEP with FTC and TDF, alone or in combination as Truvada. These studies have shown:

- PrEP could protect against infection with wild-type strains (and potentially against drug-resistant strains);
- PrEP may blunt acute viremia. This has been observed in macaques (and also reported in humans) failing PrEP with FTC, Truvada, or a CCR5 inhibitor (Figure 1). Substantial reductions in acute viremia may attenuate the course of HIV infection and decrease HIV transmissibility.

Figure 1: Blunted peak viremia and decreased viral set points in macaques failing prophylaxis with FTC or FTC/TDF [1]



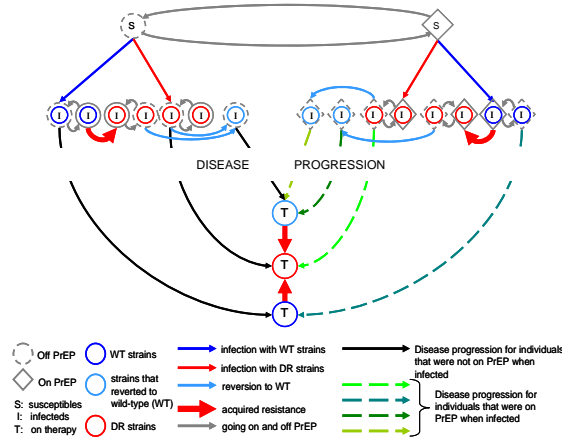
Mean viral load (bars show the standard error of the mean) in treated (n=6) and untreated control (n=10) macaques versus time. Time 0 indicates the peak plasma viral load.

METHODS

We constructed a complex mathematical model to predict the effects of PrEP on preventing infections and increasing levels of TDR in a MSM community in a resource-rich country.

Our model tracks 4 stages: primary infection, infected but not yet eligible for therapy, eligible for therapy, and on treatment. The model also tracks the acquisition and transmission of resistance due to the use of treatment, as well as the potential epidemiological effects of PrEP (Fig. 2).

Figure 2: Simplified Flow diagram of the PrEP model



We assumed that PrEP could differentially protect susceptible individuals against infection with wild-type or drug-resistant strains, reduce acute viremia, slow disease progression, and potentially lead to acquired resistance.

Our model was parameterized using clinical, behavioral and epidemiological data from San Francisco. It was calibrated to reflect HIV epidemiology in the MSM community in San Francisco. Currently, 26% of this community are infected [2] and levels of TDR are ~13% [3]; TDR is defined as the proportion of new infections that are due to drug-resistant strains.

To make predictions we used uncertainty analyses to investigate a wide range of parameter values [4]. We varied efficacy of PrEP against wild-type strains from 30 to 90%, efficacy against drug-resistant strains from 0 to 45%, reduction in acute viremia from 0.5 to 2.0 log₁₀, percentage of infected individuals who acquire resistance after one year on PrEP from 10 to 100%, and reversion time (once an individual goes off PrEP) for drug-resistant strains from 1 to 6 months (assuming resistance is selected when on PrEP).

10,000 Monte Carlo simulations were used to make predictions. Nonlinear response hypersurfaces [5] were fitted to our data to assess the impact of PrEP on : the percentage of infections prevented and the level of TDR.

REFERENCES

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RESULTS

Figure 3 shows that over 10 years PrEP could reduce incidence by 20% to 80% in the MSM community in San Francisco. The specific reduction in incidence will be determined by coverage and efficacy (Fig. 3).

Paradoxically, we found increasing PrEP efficacy increases both the number of infections prevented (Fig. 3) and the level of TDR (Fig. 4).

Figure 3: Response surface - color coding for the % infections prevented over the ten years after the introduction of PrEP

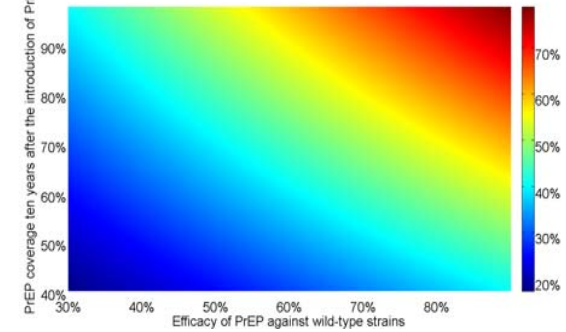
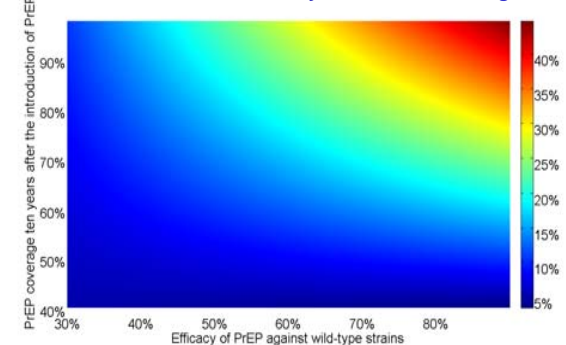


Figure 4: Response surface - color coding for the %-point increase in the levels of TDR ten years after introducing PrEP



This paradox occurs because increasing PrEP efficacy reduces wild-type strains more than resistant strains. Hence the proportion of new infections due to resistant strains increases (i.e., levels of TDR rise). Notably, the number of infections due to resistant strains does not increase (data not shown).

CONCLUSION

✓ PrEP regimens could substantially reduce HIV incidence in the community of MSM in San Francisco.

✓ By preferentially reducing wild-type strains PrEP regimens could increase the observed proportion, but not the absolute number, of resistant strains.

✓ Over time, the effectiveness of PrEP in San Francisco may decrease as the population of resistant strains is enriched.

✓ Findings suggest that it will be essential to develop new PrEP regimens that have increased effectiveness against resistant strains.

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