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Pharmacology supports "on-demand" PrEP

David V. Glidden, PhD[a] **[Prof.]**, **Peter L. Anderson, Pharm D**[b] **[Prof.]**, and **Robert M. Grant, MD**[b,c,d] **[Prof.]**

[a]University of California San Francisco, San Francisco, California, United States

[b]University of Colorado Denver, Anschutz Medical Campus, United States

[c]Gladstone Institutes of Virology, San Francisco, California, United States

[d]San Francisco AIDS Foundation, San Francisco, California, United States

Several clinical trials have demonstrated that tenofovir-based oral pre-exposure prophylaxis (PrEP) prevents HIV acquisition from sexual and injection drug use exposures to the virus. The original PrEP regimen used oral daily dosing regardless of the timing of possible HIV exposures. The rationale for daily dosing is that HIV exposures may be unanticipated or unpredictable and daily dosing ensures continuous therapeutic drug concentrations.

Recently, Molina et al (1) reported the results of the placebo-controlled IPERGAY trial in 400 HIV- men who have sex with men (MSM) in France and Canada. IPERGAY evaluated an "on demand" PrEP regimen consisting of a loading double tablet dose of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) 2 to 24 hours before sex, with single tablets at 24 and 48 hours after sex. The intent-to-treat efficacy was 86% (95% CI 40 to 98) with 14 infections on the placebo arm versus 2 on TDF/FTC - both of whom were non-adherent by pill counts and drug level testing. While only a single study, this strong data has led to the regimen's endorsement in France and Canada. Here, we highlight pharmacologic evidence that supports the high efficacy of this regimen even for infrequent HIV exposures.

The IPERGAY results are consistent with drug concentration analyses conducted as a part of the iPrEx trial (2) in 2499 MSM and transgender women (TW). iPrEx investigators modeled the gradient in HIV risk-reduction associated with tenofovir diphosphate levels (TFV-DP) by comparing levels in HIV seroconverters to HIV- controls (3) and estimated the TFV-DP level associated with a 90% reduction in HIV risk (EC_{90}). They applied the model to TFV-DP concentrations in the STRAND study (4) of directly observed dosing in 21 participants taking 2, 4 and 7 tenofovir tablets per week and inferred HIV risk reductions of 76%, 96% and 99% for these dosing patterns, respectively. Data from the iPrEx OLE (5) and PrEP-DEMO (6) studies in MSM/TW supported this; none of the combined 30 HIV seroconversions had TFV-DP levels were consistent with ≧ 4 pills per week at the time of infection.

Correspondence to: Prof. Robert M. Grant, Gladstone Institutes of Virology, 1650 Owen Street, San Francisco, CA 94158, robert.grant@ucsf.edu.

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Parsing the protection in IPERGAY is complicated by the regimen's frequent use. Participants reported using a median of 15 tablets per month (IQR: 9 to 21) – nearly 4 tablets/week. The iPrEx model suggests this dosing pattern alone would be highly protective. How efficacious, then, would event-driven dosing be for infrequent fewer sexual encounters? The Cell-PrEP study (7) provides useful guidance.

Cell PrEP was a prospective, observational pharmacokinetic study that included 21 HIV-uninfected volunteers. Participants were naive to TDF/FTC and initiated it daily for 30 days with TFV-DP levels measured at days 1 (first dose), 3, 7, 20, and 30 after the first dose. Table 1 lists the estimated proportion of people who achieved the EC_{90} and the population-level risk reduction with each additional dose after initiation. The risk reduction was 98% (95% CI: 67%–100%) after 4 doses. Hence, drug level modeling based on pharmacology studies suggests that the event-driven 4-tablet regimen (2-tablet loading dose, 2 post-exposure doses) can confer high protection for MSM/TW even for infrequent sexual exposures.

While modeling studies indicate that women require more frequent dosing compared with men to achieve the same effect, recent work finds protective levels can be achieved in the rectal and female genital compartment with 3 daily TDF/FTC doses (9); however, therapeutic drug concentration may decline more rapidly in vaginal tissue, indicating that controlled studies are needed for event driven dosing strategies in women.(9) A caveat for event driven dosing is adherence may also require anticipation of sex and offer less forgiveness for a missed tablet than daily use. Cell PrEP (7) found nearly 16% of people don't achieve the estimated EC_{90} after 4 doses and 29% do not reach it after 3 doses. IPERGAY found that 28% of participants did not use PrEP during the most recent sexual intercourse suggesting that individuals may make PrEP decisions based on perceived risk of a partner. This strategic use may not reflect actual risk. There may further be variation in drug absorption, endogenous nucleotides, clearance, transport, and activation leading to greater sensitivity to mistimed or missed doses.

Daily dosing avoids many of these issues; however, many candidates for PrEP are unwilling to commit to continuous daily therapy. A primary reason for their hesitation may be because they have infrequent potential exposures to HIV. Pharmacology indicates substantial protection for MSM/TW using IPERGAY dosing even with periodic use. For these individuals, "on demand" dosing is a plausibly effective and acceptable regimen. One that is clearly preferable to no PrEP at all.

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Table 1

Proportion protected and average efficacy for men who have sex with men.

Tablets Taken	% of participants Reaching Effective Concentration for reducing HIV risk by 90%	Estimated HIV risk reduction	95% Confidence Interval
1	17%	77%	40% to 93%
2	44%	89%	51% to 98%
3	71%	96%	60% to 100%
4	84%	98%	67% to 100%
7	90%	99%	70% to 100%