ORIGINAL ARTICLE

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# The PrEP Failures at CROI 2013

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One of the exciting if controversial advance in HIV medicine is the use of antiretroviral medications to prevent the infection ( pre-exposure prophylaxis - short PrEP). The previous iPrEx, TDF2, and PARTNERS studies (1,2) established the beachhead of the tenofovir/emtricitabine (TDF/FTC, Truvada), TDF-only PrEP in adherent patients, as well as TDF vaginal gel (3), leading to the U.S. Food and Drug Administration approval of tenofovir/emtricitabine for PrEP in 2012.

In late 2010 iPrEx, which evaluated daily oral emtricitabine/tenofovir (FTC/TDF) among 2499 men who have sex with men and transgender woman from six countries, reported that oral PrEP reduced HIV risk by 44% (p=0.005) (4). In 2011 three PrEP trials released results and findings were published in 2012. The Partners PrEP Study involved 4747 HIV serodiscordant couples from Uganda and Kenya and evaluated oral TDF and an oral FTC/TDF treatment. PrEP significantly reduced HIV incidence heterosexual women and men who were exposed to a high risk of infection due to their respective HIV-infected partner (TDF 67%, p<0.001 and FTC/TDF 75%, p<0.001) (5). The TDF2 study, which tested daily oral FTC/TDF in a study of 1200 young heterosexuals from Botswana, demonstrated high efficacy for PrEP (63%, p=0.01) (6).

However, not all PrEP trials found such positive results. The FEM-PrEP Study (7) failed to show HIV protection using daily oral FTC/TDF treatment among 2120 African women. The principal reason for the failure of efficacy in FEM-PrEP has been determined to be the lack of adherence to the study medication - less than 30% of the participants blood samples, taken in a lapse of time, showed tenofovir traces.

The scientific world is still treating this issue. A couple of oral abstracts focused on the subject, were exposed also at CROI which celebrates its 20th anniversary this year, arising a lot of interest.

In the VOICE study (8) presented by Dr Marrazzo, none of the treatments worked, not oral TDF, oral TDF/FTC, or vaginal TDF gel. Particularly in the VOICE study over 5,000 HIV-uninfected women were treated randomly with oral TDF, oral TDF/FTC, oral placebo, vaginal TDF gel or vaginal gel placebo. The data safety monitoring board had previously halted the oral TDF and vaginal TDF gel arms due to an inability to demonstrate a reduction in the acquisition of HIV but the Truvada PrEP and placebo-pill arms, however, were continued.. None of the 3 preventive methods resulted in fewer HIV infections than placebo. In the women using the tenofovir-gel microbicide there were 15% fewer infections versus placebo, but this was not statistically significant. In the oral PrEP arms there were more infections in women taking PrEP compared to placebo. Women taking Truvada were 4% more likely and women taking tenofovir alone 49% more likely to become HIV positive than women taking placebo and in the latter case this was almost statistically significant (95% confidence interval 0.97-2.29; P = 0.07).Adherence to the pills or microbicide, according to the 2 different methods of self-report, was 90%. However analysis of drug levels in the blood and in the case of the microbicide in vaginal fluids, showed a very different story, and one that is starting to be familiar in PrEP and microbicide studies: only 28-29% of women taking tenofovir or Truvada PrEP had measurable drug levels in their blood, and only 22% of women using tenofovir microbicide.

Then it appears that poor adherence was the explanation for the overall treatment failure; while more than

90% of participants reported adherence to the regimens, TDF was detected in only 25% to 30% of the samples, and 50% to 58% of the participants never had detectable TDF plasma levels.

Women who were married, were aged over 25 or who had a primary partner aged over 28, were more likely to have detectable drug levels. Particularly married women were 2.6 times more likely to have detectable drug. The results of VOICE complete a long and challenging course for PrEP for HIV prevention. PrEP, particularly oral PrEP, for which there are multiple studies demonstrating efficacy, works for preventing HIV, but only if it is taken. Understanding determinants of PrEP taking is a challenge for the field - it is not likely as simple as being young (iPrEx average age was also <25 years), or young and from southern Africa (given the efficacy in TDF2).

At CROI 2013 a poster (2) presented HIV protection efficacy for a number of higher-risk subgroups from the Partners PrEP Study, including groups limited to women, to younger persons, to those whose partners had high plasma HIV viral loads, and to those for whom placebo arm incidence was ≥5 per 100 person-years. In all groups, PrPE efficacy was high - suggesting that, in population in which PrEP adherence can be motivated, PrEP is highly efficacious for HIV prevention

Another oral abstract, presented by Dr Grant (1), with a title declarative about the result ( "No Excess in HIV Incidence after Stopping Oral Emtricitabine/Tenofovir Pre-exposure Prophylaxis: The iPrExTrial"), showed no excess in HIV incidence or high risk behavior after stopping PrEP in the iPrEx study. The randomization phase of the iPrEx study ended in November 2010, and from June 2011 to June 2012 the iPrEx OLE (open-label extension) study enrolled former trial participants to gather further data on the safety of PrEP and the behavior of PrEP users over a longer period. For a number of reasons (including safety and funding protocols), PrEP was not made available to former study participants during this period. This seven-to-nineteen-month gap, explained Grant, offers important insights into how interruptions in PrEP access may contribute—or not—to HIV acquisitions.

During the gap in access to PrEP, 78 new HIV infections occurred. Among those who had taken placebo pills during iPrEx, HIV incidence during the gap was 4.1 infection events per person-year, (PY ) compared with 3.3 new infections per PY in those who had taken Truvada during iPrEx. (This difference did not reach statistical significance.) demonstrating both 1) no increased HIV risk (suggesting delayed HIV seroconversion) in those who had received PrEP and 2) ongoing HIV risk for study participants after PrEP was discontinued. Risk factors for HIV included lack of condom use, younger age, and herpes simplex virus type 2 (HSV-2) infection.

By participant self-report of behavior collected over time, it appeared that participants moved in and out of periods of higher HIV risk. HIV incidence in the now-ongoing iPrEx OLE cohort - with access to open-label PrEP - will be important as well as PrEP adherence, particularly during "seasons" of HIV risk.

"There was no excess incidence after stopping PrEP, even in the case of protective PrEP as observed in iPrEx," Grant concluded.

Two oral abstracts in this same session described potential new, long-acting PrEP agents, which may avert some of the adherence challenges faced by daily oral/vaginal PrEP.

**GSK744 long-acting** (9). GSK744 is a potent integrase inhibitor being formulated as a long-acting nanosuspension (GSK744LAP) for injectable use as PrEP. In human volunteers, the half-life of GSK744LAP is on the order of ≥3 weeks, supporting the concept of monthly to quarterly injections for regular use. Andrews et al. reported the result of an 8-week macaque model weekly rectal challenge SHIV study using GSK744LAP, given at baseline and week 3. All 8 placebo macaques became infected (after a median of 2 challenges) compared with none of the 8 animals receiving GSK744LAP ($p<0.001$). Can the GSK744LAP be the answer to PreEP adherence issues? Further work on agents like GSK744LAP will be important, as long-acting, user-independent PrEP agents offer opportunities to overcome adherence challenges seen in some of the trials of tenofovir-based daily oral PrEP.

**Tenofovir vaginal ring** (10). Intravaginal, slow-release rings containing antiretrovirals for PrEP offer a potentially powerful opportunity to prevent HIV while minimizing systemic medication exposure and also overcome some challenges to PrEP adherence. A tenofovir intravaginal ring containing 120 mg of TDF, releasing 2.4-2.7 mg/day in vitro and in macaques and resulting in high tissue concentrations of the medication, was developed. In a macaque low-dose vaginal challenge study, 11 of 12 control animals became infected, after a median of 4 exposures. In contrast, full protection was seen in 6 animals receiving the TDF intravaginal ring. This study represents the first study demonstrating 100% protection against vaginal SHIV challenges with an antiretroviral intravaginal ring.

In conclusion, long-acting antiretrovirals have great potential in improving adherence and health benefits in both treatment and prevention. The energy devoted recently in developing delivery technologies (nanosuspensions for injection, slow-release rings, etc.) is encouraging, because PreP efficacy=adherence.

These results are consistent with the previously reported FEM-PrEP study and highlight the requirements (and unmet needs) of adherence to PrEP regimens

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