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iPrEx Fact Sheet: Key Results

- iPrEx is the first efficacy study to report results on oral pre-exposure prophylaxis (PrEP); the first HIV prevention study focused on men and transgender women who have sex with men (MSM) to take place in Africa or Asia; and the first study to demonstrate efficacy for a biomedical HIV prevention intervention in MSM.

- The iPrEx study enrolled participants at 11 sites in 6 countries (Brazil, Ecuador, Peru, South Africa, Thailand and the United States) on 4 continents.

- Participants in the study were randomly assigned to receive oral co-formulated emtricitabine 200 mg/tenofovir 300 mg (FTC/TDF), also known as Truvada®, or placebo. All study participants also received a comprehensive package of HIV prevention services including HIV testing, risk reduction counseling, condoms and screening for and management of sexually transmitted infections. The sexual partners of participants were also offered treatment for sexually transmitted infections. In addition, all study participants who were found to be susceptible were offered vaccination against HBV infection.

- iPrEx enrolled 2,499 participants; 1,251 were assigned to FTC/TDF and 1,248 were assigned to take a placebo tablet. Participants were followed for a median of 14 months.

- The iPrEx study involved:
  - 43,248 participant visits
  - 39,754 visits for HIV testing and counseling
  - 650,000 pages of data faxed to the data management center
  - 1,184,400 tablets of study drug dispensed
  - 4,533 HBV vaccination doses given
  - 1,019 syphilis cases diagnosed and treated
  - ~500,000 condoms distributed to participants

Efficacy

- iPrEx found that a daily dose of oral co-formulated emtricitabine 200 mg/tenofovir 300 mg (FTC/TDF), also known as Truvada®, reduced HIV infection risk among men and transgender women who have sex with men (MSM) by an average of 43.8% overall. This is a statistically significant level of efficacy and an important step forward for HIV prevention research.

  - iPrEx found 36 HIV infections among participants who received FTC/TDF and 64 infections among participants receiving placebo – a reduction of 43.8% (p=0.005) in the study arm that received FTC/TDF and comprehensive prevention services versus those that received placebo plus comprehensive prevention services.

- PrEP prevented 28 infections in the active drug arm. Dividing the 64 infections recorded in the placebo arm by the 28 fewer infections recorded in the active drug arm produces a net reduction in infections of 43.8% among study participants who received FTC/TDF. The 95% confidence interval for this effect is 15.4 to 62.6% (P=0.005)

    - ***P-value*** *measures how likely it is that these differences could have arisen by chance. The P-value of the modified intent-to-treat analysis in iPrEx is 0.005, indicating that there is only a 5 in 1,000 chance that the difference between infections in the study arm could have arisen by chance.*

    - ***Confidence interval*** *is the range of effectiveness that the intervention could have, given the amount of evidence in hand. The modified intent-to-treat analysis of iPrEx indicates that it can be determined with 95% confidence that the efficacy of PrEP with FTC/TDF, which is estimated at 43.8%, could be as high as 62.6% or as low as 15.4% among all those who received active drug in the study, regardless of whether they used the pill or not.*

- This result includes available data on all participants who were HIV-negative at the time of enrollment -- even if the participant was not taking the study pill for any reason.

- A variety of measures and analyses found that PrEP was more protective in people at higher risk for HIV and among those who took the pill more consistently.

    - PrEP efficacy was higher among participants at particularly high risk for HIV, as measured by their reports of unprotected receptive anal intercourse (URAI) at the time of enrollment in the study (efficacy 58%, 95% CI 32-74%).

    - Among study participants who used PrEP on 50% or more of days, as measured by pill counts, dispensation and self-report, risk of HIV infection fell by 50.2% (95% CI 17.9-69.7%; P=0.006). Those who reported using PrEP on 90% or more of the days had 72.8% efficacy (95% CI 40.7-87.5%; P=0.001).

        - It should be noted that these pill-taking measures rely on self-reports and are not objective. Self-reported pill use was significantly higher than pill use measured by blood testing.
        - The optimal timing and frequency of PrEP dosing is not known and requires further study.
        - The next generation of PrEP research should focus on ways to improve the use of PrEP as well as the reliability of pill use reporting.

- An additional analysis of PrEP drug levels among a sub-set of study participants who received FTC/TDF in the study indicates a strong connection between use of the PrEP drug and the level of protection against infection achieved.

    - Only 3 of the 34 people (9%) who became HIV-positive in the group receiving FTC/TDF had any detectable level of the PrEP drug in their systems. By

- comparison, 22 of 43 participants (51%) who remained seronegative in the group that received FTC/TDF PrEP, and whose blood was tested to determine whether they were taking the drug, had detectable levels of drug in their systems.

- There are several caveats that should be considered in looking at this data on the biological activity of PrEP:

  - Measurement of drug levels were taken at the first clinic visit after a person became HIV-positive, and do not indicate what their blood drug levels were at the exact moment of infection.
  - It is possible that there are links between the behavioral characteristics that would make a person more or less able to take PrEP regularly and the characteristics that could decrease or increase their risk of HIV infection (e.g., a person who is better able to take PrEP more regularly may also be more cautious about their HIV risk behavior)
    - An additional analysis that adjusted for the high risk sexual behavior of unprotected receptive anal intercourse, however, continued to find a very high level of protection among those with detectable levels of drug in their systems.

- Data on the biological activity of the PrEP drug must be confirmed through additional studies.

- Oral PrEP does not prevent STIs such as gonorrhea, chlamydia, syphilis, herpes, warts, or chancroid. PrEP does not prevent hepatitis C infection, which may be sexually transmitted in MSM. All MSM, whether they use PrEP or not, should have regular medical attention including periodic screening for STIs. Vaccination for HBV infection is important. Vaccination of MSM for human papilloma virus (HPV) may be effective for prevention of warts and anal cancer. Condoms are effective for decreasing the transmission of many of these infections. MSM should communicate with partners about HIV test results and other aspects of sexual health.

<u>Safety</u>

- iPrEx found that PrEP with FTC/TDF is safe and well tolerated.

  - This finding is consistent with other safety studies (of TDF for PrEP by Family Health International among women in West Africa; of TDF for PrEP by the U.S. CDC among MSM in the United States), and with extensive experience with FTC/TDF as an approved therapy for HIV.

- On the placebo arm 164 participants developed a moderate or severe adverse event compared to 151 participants on FTC/TDF.

- There was no statistically significant difference between the two study groups in a wide variety of laboratory tests including tests related to liver function, pancreatitis, electrolytes, glucose, phosphate, complete blood count and absolute neutrophil count.

- Side effects related to use of the PrEP pill were mild:
    - Nine percent (9%) of individuals who received the PrEP pill reported nausea in the first month, compared to 5% of those who received placebo. After the first month there was no excess nausea among those who received the active pill. Similar rates of nausea are also reported by HIV infected people starting antiretroviral treatment. As with treatment, providing reassurance that the nausea resolves after the first few weeks may help encourage longer term use of PrEP.
    - The drugs used in this study are known to cause small increases in serum creatinine, a naturally occurring molecule filtered by the kidneys. In this study, 5 of 1251 participants (0.3%) who received the PrEP pill experienced mild increases in serum creatinine that persisted until the next test. All creatinine elevations resolved with discontinuation of the pill. Four of the 5 participants restarted PrEP without recurrence of the creatinine increase. Investigators monitored renal function throughout the study and found no serious kidney problems.
    - Unintentional weight loss of more than 5% was reported in 2.2% of people using PrEP compared with 1.1% of placebo users (P=0.04).
    - Sixty-six (66) headache events were reported by 56 (4.5%) of participants in the FTC/TDF group, as compared to 55 headache events among 41 (3.3%) of the placebo group (p=0.10).
- More information is needed to evaluate any possible subclinical effects of FTC/TDF PrEP, including those that may affect bone, low-level drug resistance or kidney function. HBV hepatic flares after stopping PrEP were not observed in the study of TDF PrEP in West Africa. More information will come from iPrEx as HBV infected participants stop taking PrEP. These issues are also being investigated in sub-studies of iPrEx and in other PrEP trials.
- The reported numbers of partners decreased and condom use increased among participants in both arms of the iPrEx study, as was observed during previous studies of PrEP. Whether HIV risk behavior will increase or decrease in PrEP users in the future is unknown.
- Overall, low drug levels and pill taking among the study participants likely diminished both the efficacy of PrEP and he study's power to assess safety. More information will come from other studies in the field.

For more information, please see *iPrEx Fact Sheet: Safety*

Resistance

- No resistance mutations for TDF were found among iPrEx participants.
- Three cases of resistance to FTC were found. Of these, one was in a participant in the placebo arm, and two were participants in the FTC/TDF arm.
    - All three participants with FTC resistance mutations were found to be HIV-infected at the time of study enrollment.
    - FTC resistance limits the activity of HIV treatment using FTC (emtricitabine, Emtriva) and 3TC (lamivudine, Epivir). However, the FTC resistant infections that appeared in the PrEP arm of this study were fully susceptible to nonnucleoside reverse transcriptase inhibitors such as Nevirapine and Efavirenz; all protease inhibitors such as Lopinavir, Atazanavir and Daurunavir; integrase inhibitors; and entry inhibitors. The two FTC resistant viruses that appeared in the PrEP arm exhibited increased susceptibility to zidovudine (AZT).

For more information, please see *iPrEx Fact Sheet: Drug Resistance*.

Pill-taking (Adherence)

- PrEP with FTC/TDF was most effective when the participants took PrEP consistently.
- iPrEx participants received intensive adherence counseling, including monthly counseling and aids such as pill boxes. Pill taking in the study was measured in multiple ways, including through computer assisted self interviews (CASI), interviewer-administered interviews, pill counts, bottle returns and measurements of drug concentrations in blood.
- Although self-reported pill use was high in both study arms, actual pill use and drug exposure may have been substantially lower, and this appears to have impacted the overall efficacy of PrEP in the study.
    - The drugs used in the iPrEx study would generally be detectable in blood cells if the PrEP pill had been taken within 7 to 14 days of testing.
    - Only 51% (22/43) of the participants in the active drug arm who remained seronegative, and whose blood was tested to determine whether they were taking the drug, had detectable levels of the PrEP drugs in their systems.
    - Only 9% (3/34) of participants in the active drug arm who became HIV-positive during the study had detectable levels of the PrEP drugs in their systems at the time the infection was found. All had drug levels far lower than those of the participants in the PrEP arm who remained seronegative.
- The low drug levels indicate the promise and challenges of PrEP. While PrEP appears to provide protection when used, many participants in the study did not take the drug

consistently – pointing out the need for greatly enhanced support and information to enable consistent use of the pill.

  - Studies in a number of disease areas and populations show that tracking and accurately reporting on adherence is very difficult for individuals to do. Over-reporting adherence can be due to multiple factors, including a participant simply forgetting whether or not they took their pill on a certain day and the desire to fulfill the goals of full participation in the study.

- A complete analysis of participant characteristics that were associated with having a drug level in this study is underway.

For more information, please see *iPrEx Fact Sheet: Adherence*.

Next steps

- Whether iPrEx data alone are sufficient to warrant approval of PrEP is a decision to be made by regulatory authorities after careful review of the data and discussion with experts and people impacted by the epidemic.

  - The iPrEx investigators urge WHO, UNAIDS and other global and national HIV policymaking bodies, especially those in the countries in which the iPrEx study was conducted, to meet promptly to review these findings and develop clear recommendations for next steps in the study of PrEP.

- In addition to data on efficacy, iPrEx provides important information in a number of areas that can help authorities develop the best and most effective access strategies for PrEP, now or in the future. Specifically, iPrEx showed that:

  - Drug resistance did not occur among the 100 persons who became infected after starting PrEP; drug resistance was seen, however, in three persons (two in the active drug arm, one on the placebo arm) who started PrEP who were in the RNA positive/Antibody negative window period at enrollment. Signs and symptoms of acute HIV infection should be checked before starting PrEP, to help avoid resistance. RNA testing could be used as well.

  - Side effects from PrEP were mild and manageable. Most elevations in creatinine were mild and resolved without interruption of PrEP.

- iPrEx results cannot be extrapolated beyond MSM. Other PrEP studies are underway in different communities at risk and should continue.

- Risk reduction counseling, condoms, and periodic testing for HIV and other STIs should be provided as part of any PrEP trial and program.

- An “open label” phase of iPrEx, in which all HIV-negative iPrEx participants who wish to participate will receive the PrEP treatment for almost 18 months, is scheduled to begin next year and should provide additional information on efficacy, safety, behavior and pill

taking.

  - The ethical conduct of efficacy trials requires that people be informed that the pill they are taking could be a placebo, and that the active drug has no proven benefit. Now that PrEP is known to offer some protection to MSM, open-label PrEP studies can provide clearer information to prospective users, which might increase their use of the pill.

- Additional data from the iPrEx study will be collected, analyzed and released in the coming year. This will include analyses of:

  - Bone mineral density of participants in both study arms
  - Drug resistance using more sensitive investigational assays
  - Urine analysis for evidence of low level kidney effects
  - Drug levels in hair to assess patterns of drug exposure over time
  - Sexually transmitted infections, including herpes, in the trial
  - Additional safety and efficacy data
  - A better understanding of pill taking during iPrEx

For more information, please see *iPrEx Fact Sheet: Rollover Study and Next Steps*

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