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NEW DATA SHOW THE PROTECTIVE BENEFIT OF PRE-EXPOSURE PROPHYLAXIS TO PREVENT HIV INFECTION IS DURABLE AT 144 WEEKS

Six New Analyses from the iPrEx Study Presented at the 18th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston

(Boston, MA) – New data from the iPrEx study of pre-exposure prophylaxis (PrEP) to prevent HIV infection shows that the protective effect of daily use of the antiretroviral combination drug emtricitabine and tenofovir disoproxil fumarate (FTC/TDF or Truvada®) against HIV infection remains highly significant at 144 weeks. iPrEx is the first clinical trial to establish the effectiveness of PrEP to prevent HIV infection in people.

A primary analysis of iPrEx published in the *New England Journal of Medicine* November 23, 2010, included data from July of 2007 to May 1st, 2010. In a special session here on "Advances in PrEP," iPrEx Protocol Chair Robert Grant, MD, MPH of the Gladstone Institutes and the University of California at San Francisco presented data from seven additional months of follow up of iPrEx participants, through November, 2010.

The new data show that the daily use of the FTC/TDF coformulation decreased HIV acquisition by 42% (95% CI 18 – 60, P= 0.002) among study participants, with no moderate or severe toxicity. There were 83 HIV seroconversions among the 1248 participants in the placebo arm and 48 among the 1251 in the FTC/TDF arm, meaning that the use of FTC/TDF PrEP prevented 35 HIV infections among participants in the FTC/TDF arm. As with the interim iPrEx safety and efficacy analysis, more consistent use of PrEP was highly correlated with levels of protection against HIV infection.

A total of 2499 men who have sex with men (MSM) and transgender women participated in the six-country iPrEx study. All study participants received a comprehensive package of prevention services designed to reduce their risk of HIV infection throughout the trial, including HIV testing, intensive safer sex counseling, condoms and treatment and care for sexually transmitted infections. Half of study participants also received FTC/TDF, while the other half received a placebo.

An 18-month "open label" continuation of the iPrEx study, which will provide FTC/TDF PrEP to all interested HIV uninfected participants from the original study, will begin in the coming months. The open label study is designed to provide additional information on the efficacy and safety of FTC/TDF PrEP, as well as on pill-taking and any other behavioral impact of PrEP.

"With 2.6 million new HIV infections last year, there is no question that the world urgently needs new ways to stop the spread of HIV – especially for young people, men who have sex with men, and people in geographic regions such as Africa, Asia and South America, where HIV is having

its most devastating impact," said Dr. Grant. "PrEP represents an important HIV prevention option for MSM, who carry a heavy burden of the epidemic worldwide. "

"Other PrEP studies now underway will show whether and to what degree PrEP may reduce HIV infections in other populations at risk," added Dr. Grant. "The open-label extension of iPrEx will help us determine how much people will use PrEP in a study without a placebo arm, after they receive clear information about safety and efficacy of PrEP."

Other iPrEx-related analyses presented here examined the circumstances that led to more or less consistent use of FTC/TDF PrEP, the relative predictive values of different measures of pill use, the impact of FTC/TDF PrEP on bone mineral density, PrEP-associated drug resistance and the impact of PrEP on acquisition of herpes (HSV-2).

Adherence

Two CROI presentations focused on multiple measures of adherence in the iPrEx study and how these correlated to participants' study drug levels: 95LB. Adherence Indicators and PrEP Drug Levels in the iPrEx Study (Rivet Amico, PhD); and 96LB. Interpreting Detection Rates of Intracellular FTC-TP and TFV-DP: The iPrEx Trial (Peter Anderson, PharmD)). The findings illustrate the complexity of predicting adherence to PrEP in the iPrEx study, an observation that has been echoed in many other clinical trials of therapies and preventive agents in HIV and other disease areas. The authors conclude that enhanced communication is key to improving adherence to PrEP, and note that the iPrEx open-label extension study will gather important information that may help improve PrEP adherence rates moving forward.

Data presented here also show that the drug detection rate among participants at the San Francisco and Boston iPrEx study sites who received the study drug was 97%, indicating that very high adherence to the study medication is achievable. iPrEx study data published in November 2010 found that PrEP was more protective among those who reported taking the pill more regularly. Among participants who used the tablet sufficiently to have a detectable level of drugs in the body, the protective effect of FTC/TDF PrEP was 92%.

HSV-2 Acquisition

In presentation 1002, "Oral TDF and Its Impact in HSV-2 Acquisition and Clinical Expression," iPrEx protocol co-chair Javier Lama, MD, MPH reported that, contrary to a finding of the CAPRISA 004 trial, in which the use of 1% coitally-dependent vaginal gel formulation of tenofovir was associated with a decreased incidence of Herpes Simplex Virus Type-2 (HSV-2) infection among women, daily-oral PrEP with FTC/TDF did not reduce HSV-2 acquisition among MSM. This suggests that the concentrations of TDF in the rectal or penile tissues after oral dosing appear to be insufficient to decrease the acquisition of HSV-2 infection. However, FTC/TDF may decrease the clinical expression of herpes in the perianal area, based on the finding that fewer HSV-2 infected participants assigned to the FTC/TDF arm had one or more perianal ulcers (RR: 0.4, 95%CI: 0.22-0.85, P=0.01).

Bone mineral density

Additional data presented here showed a statistically significant loss of bone mineral density (BMD) of less than 1% among iPrEx participants who received FTC/TDF. Use of antiretroviral

therapy for the treatment of HIV infection is known to decrease bone mineral density (BMD), usually by 2 to 4% on average. The change in BMD during therapy for HIV typically occurs in the first 6 to 12 months of treatment and does not progress afterward. The loss of bone mineral density among participants in the active arm of the iPrEx study was not associated with any clinical harm: reported bone fractures occurred at comparable rates in the placebo and FTC/TDF arms of the study

Commenting on the finding, study author Kathleen Mulligan, PhD of the University of California, San Francisco added, "We know from other studies that vitamin D supplementation, and possibly lifestyle-related measures, may offset the loss in bone mineral density associated with the use of antiretroviral agents. Additional research is needed to determine what people using antiretrovirals for HIV treatment or prevention may do to help keep bones healthy. With longer periods of follow-up we hope to be able to see if this bone loss is reversed or stabilizes."

Resistance

In CROI abstract 97LB, "Drug Resistance and Minor Drug Resistant Variants in iPrEx," Teri Liegler, PhD of the University of California, San Francisco presented data on drug resistance based on the analysis of virus from 91 participants who became infected in the iPrEx study, using standard and ultrasensitive diagnostic methods. None of the participants (0/33) randomized to the active study arm showed resistance to FTC or TDF, including 3 participants with measurable but low drug levels. Two individuals in the placebo arm (2/58) showed very low levels of drug resistant virus (~1%), one to TDF and another to FTC, which likely arise due to transmission from a treated partner or natural variation in the evolving virus population. Two seronegative participants enrolled in the study during early infection and randomized to the active arm showed drug resistance to FTC at seroconversion, which waned to undetectable levels (less than 0.5%) within 6 months after discontinuing PrEP. Antiretroviral treatment is expected to be fully effective after drug resistant variants wane below 1% of the infection, based on information from women treated with antiretroviral therapy for prevention of mother to child HIV transmission during pregnancy.

The iPrEx Study

The iPrEx study (Iniciativa Profilaxis Preexposicion or Prexposure Prophylaxis Initiative http://www.globaliprex.com) is a double blind, placebo controlled Phase III clinical trial, that was sponsored by the U.S. National Institutes of Health (NIH) through a grant to the Gladstone Institutes, a non-profit independent research organization affiliated with the University of California at San Francisco. Additional support for iPrEx was provided by the Bill & Melinda Gates Foundation. Study medication was donated by Gilead Sciences, Inc. The medication is available from Gilead and from generic manufacturers in many of the poorest countries of the world.

iPrEx abstracts presented at the 18th CROI

Following are the abstracts of new iPrEx study data presented at the 18th Conference on Retroviruses and Opportunistic Infections. A webcast of the study presentations will be available at the conference website (http://www.retroconference.org) beginning at approximately 8 p.m. EST on Tuesday, March 1, 2011.

92. Pre-exposure Chemoprophylaxis for Prevention of HIV among Trans-women and MSM: iPREx

Study

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Background: Peri-exposure dosing of antiretroviral agents decreases maternal to child HIV transmission, and is an emerging concept for prevention of sexual transmission. Trans women and men and who have sex with men (MSM) bear a disproportionate burden of the HIV epidemic.
Methods: The iPrEx study is a double-blinded randomized trial of daily oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) vs placebo for prevention of HIV acquisition in MSM also receiving a comprehensive package of prevention services. The primary analysis published on November 23, 2010, was based on visits conducted through May 1, 2010. Participants continued on blinded study medication through August 2010, and were followed for 8 to 24 weeks after stopping study medication.
Results: We randomized 2499 participants between July 2007 and December 2009, and were followed for 3324 person-years. Prior to May 1, 2010, there were 110 seroconversion events, including 10 infections retrospectively found to have acute (RNA present, but seronegative) infection at baseline, and 100 emergent infections. Of the 100 emergent infections, 64 occurred in the placebo arm and 36 occurred in the FTC/TDF arm, representing a 44% decrease in HIV incidence (95%CI 15 to 63%; p = 0.005) in the modified intention to treat analysis. Overall efficacy was 47% (95%CI 22 to 64%; p = 0.001) in the intention to treat analysis that included the baseline infections. All infections in the active arm of the study were associated with undetectable (91%) or low (9%) PrEP drug levels in blood, indicating no recent PrEP use. There was no viral suppression or drug resistance among emergent infections in the active arm, commensurate with low or absent drug exposure. Drug detection was strongly associated with HIV (HR 12.9; 95%CI 1.7 to 99.3; p <0.001) in a nested case–control study, providing a surrogate marker for the prophylactic effect of oral FTC/TDF PrEP. This marker provides powerful insights into adherence, safety, tolerance, patterns of use, and protection from HIV acquisition.
Conclusions: Oral FTC/TDF decreased HIV acquisition in MSM. More information from extended follow-up is becoming available regarding the durability of the protective effect and markers associated with protection.

94LB. Effects of FTC/TDF on Bone Mineral Density in Seronegative Men from 4 Continents: DEXA Results of the Global iPrEx Study

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Background: Oral emtricitabine/tenofovir (FTC/TDF) pre-exposure prophylaxis (PrEP) decreases HIV acquisition among men who have sex with men (MSM). Initiation of TDF has been associated with decreases in bone mineral density in HIV+ people. HIV infection itself, host response to HIV, and other antiretroviral drugs may also contribute to bone loss in HIV- populations. The effect of the combination of FTC/TDF on bone mineral density in the absence of HIV infection is not known.
Methods: DEXA scans of the hip and spine were performed at baseline and 24-week intervals in a substudy of iPrEx, an international randomized, double-blind, placebo-controlled trial of FTC/TDF PrEP in MSM. Data are reported as the mean (SE) difference of change since enrollment in the FTC/TDF vs placebo groups; p values were based on a linear mixed model.
Results: We enrolled 503 participants (247 randomized to FTC/TDF and 256 to placebo) in this optional substudy (Peru n - 221, Thailand n - 95, US n - 71, South Africa n - 61, Brazil n - 55) with variable periods of follow–up. Mean body mass index was 23.5 (0.2) kg/m2; 18% were Caucasian, 13% black, 20% Asian, 49% mixed race; 52% were of Hispanic or Latino; 48% of subjects were age 18 to 24 years and likely still accruing bone mass. At baseline, 36% had low bone mineral density (Z-score <–1) in the spine and 18%

in the hip. There were no differences between randomization groups in baseline bone mineral density or percentage with low bone mineral density. Percentage changes in bone mineral density at weeks 24 (n - 418), 48 (n - 268), and 72 (n - 126) are shown below. Bone mineral density tended to increase in the placebo arm and decrease in the FTC/TDF arm, resulting in modest (–0.7 to –1.0%) but statistically significant differences between the groups by week 24. There were no differences between the groups in bone fractures (p = 0.56) or the incidence of low bone mineral density using WHO or International Society for Clinical Densitometry criteria.
Conclusions: In this large, diverse group of HIV- MSM, there were small but significant decreases in bone mineral density in those randomized to FTC/TDF relative to placebo, suggesting an effect of FTC/TDF on bone mass in the absence of HIV infection.

95LB. Adherence Indicators and PrEP Drug Levels in the iPrEx Study
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Background: Monitoring adherence is a critical challenge in trials of self-administered prevention methods, like oral and topical pre-exposure prophylaxis (PrEP). Self-reported use typically exceeds objective measures of use, sometimes by a large margin. Validation of indicators of PrEP use using direct measurement of drug concentration is needed.
Methods: Seronegative, active-arm (daily oral emtricitabine [FTC]/tenofovir [TDF]) participants from the iPrEx study were randomly selected for intracellular drug level analysis using their week-24 peripheral blood mononuclear cell (PBMC) specimen (detection limits: 0.1 pmol and 2.5 fmol per sample for FTC-TP and TFV-DP, respectively). Associations between adherence indicators, including self-report, pill count, and refill-based assessments and drug detection were examined individually and in a multivariable logistic model.
Results: Specimens from 179 participants were analyzed; either drug was detected in 54%. Indicators of adherence were significantly related (R = 0.34 to 0.69). Self-report and pill count–based adherence were associated with drug detection (see the table for positive predictive values), with self-report of missing 50% or more of doses having stronger negative predictive value (83%). Refill-based assessments of pills dispensed over days between visits were most predictive of drug detection (p<0.001), 0% detection in those who had drug available for ≤50% of the days between visits; 39% if drug was available for 50 to 100% of days; 57% if drug was available for 100 to 150% of days; and 79% if drug was available for more than 150% of days. Having more pills than days reflects strict compliance with protocol visit schedules. Returning all previously dispensed bottles and on-time visits were also predictive of drug detection (each p <0.001). In a multivariate model, refill assessment was the only significant independent predictor of drug detection (OR 5.2, p = 0.01). Percentage of both drugs detected by adherence indicator.
Conclusions: None of the indicators were fully concordant with drug detection. Refill assessment is objectively measured and less susceptible to social desirability reporting bias. Direct drug measurements are costly, assess PrEP use at only one time, and provide no direct insights into patterns of intended PrEP use. Use of validated indicators will improve overall adherence assessments that are required for PrEP research and programs.

96LB. Interpreting Detection Rates of Intracellular FTC-TP and TFV-DP: The iPrEx Trial
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Background: The presence of quantifiable drug in viably cryopreserved peripheral blood mononuclear cells (PBMC) was a powerful predictor of HIV acquisition in the iPrEx HIV pre-exposure prophylaxis (PrEP) trial. This study defined an expected detection rate for emtricitabine-triphosphate (FTC-TP) and tenofovir-diphosphate (TFV-DP) in viably cryopreserved PBMC with consistent daily dosing, and examined drug detection in randomly selected iPrEx participants with no previous drug level assessment.
Methods: To define an expected detection rate in viably cryopreserved PBMC with daily dosing, a study separate from iPrEx evaluated 28 viably cryopreserved PBMC samples from 10 HIV-infected subjects with suppressed HIV-RNA. Drug detection was then evaluated in week 24 viably cryopreserved PBMC from randomly selected HIV- active arm participants among 7 iPrEx study sites (2 US, 4 South American, 1 South African). All viably cryopreserved PBMC were processed and analyzed in the same way. We assayed 2 million cells using LC-MS/MS. Detection was defined as above the limit of quantification for FTC-TP and TFV-DP of 0.1 pmol and 2.5 fmol per sample, respectively. Results were normalized to number of viable cells assayed.
Results: FTC-TP and TFV-DP were detectable in 100% of the viably cryopreserved PBMC from those with suppressed HIV RNA, with median (IQR) values of 3.3 (1.8 to 3.8) pmol/106 and 25.1 (18.0 to 46.9) fmol/106 cells, respectively. Viably cryopreserved PBMC specimens from 179 iPrEx participants were analyzed. FTC-TP and TFV-DP were detected in 54% and 45% of specimens, with values of 2.3 (1.2 to 3.5) pmol/106 and 18.0 (9.0 to 31.3) fmol/106 cells. Of the total, 8% had detectable FTC-TP, but not TFV-DP, suggestive of dosing just before the clinic visit. Participant characteristics independently associated with detectable drug ($p < 0.05$) included age ≥25 years (66% vs 37%), enrollment at a US site (97% vs ≤ 60%), and report of receptive anal intercourse without a condom in the previous 12 weeks vs no sex (71% vs 30%). Height, weight, creatinine clearance, and race/ethnicity did not independently correlate with detection rate. The reported half-lives for FTC-TP (39 hours) and TFV-DP (150 hours) suggest that both should be detectable for 7 to 14 days if dosing is consistent.
Conclusions: A 100% detection rate is expected in viably cryopreserved PBMC with consistent daily dosing. The 54% detection rate in randomly selected viably preserved PBMC specimens from iPrEx is suggestive of no recent tablet use. Higher detection rates in older participants and at US sites were not explained by biological differences. Episodic PrEP triggered by clinic visits or receptive anal intercourse may explain some drug detection patterns in iPrEx.

97LB. Drug Resistance and Minor Drug Resistant Variants in iPrEx

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Background: The iPrEx study showed that pre–exposure prophylaxis (PrEP) with oral emtricitabine/ tenofovir disoproxyl fumarate (FTC/TDF) provides additional protection against HIV–1 infection among men who have sex with men (MSM) receiving standard prevention methods. Selection for drug resistance may occur if PrEP is used inconsistently. Viral population based drug resistance assays, used in previous reports from iPrEx, are not sensitive for the detection of minor sequence variants.
Methods: Among iPrEx participants with HIV-1 seroconversion, reverse transcription mutations K65R, K70E, M184V, and M184I were interrogated in plasma samples obtained at first evidence of seroconversion using a quantitative minor variant assay based on allele-specific PCR (lower limit of quantitation 0.5%). Seronegative participants with pre-existing infection at enrollment were monitored longitudinally for drug resistance using population-based sequencing (TRUGENE).
Results: Control of primer-binding site heterogeneity proved to be essential for the specificity of the minor variant assay. Of the 100 post-enrollment infections, none showed FTC or TDF resistance by population sequencing. Plasma RNA from 91 subjects were analyzed for minor variant drug resistance. None of the 33 in the active arm showed evidence of minor variant drug resistance, including the 3 active arm seroconverters who had detectable (albeit low) drug levels. Of 58 in the placebo arm, 2 showed minor variant drug resistance, 1 subject at K65R (0.69%), and 1 at M184V (1.26%). Both were infected with

subtype B virus. Plasma viral load was high and comparable in the 2 arms (active arm median 5.31 log10 copies/mL, IQR 4.96 to 5.75; placebo arm median 5.22 log10 copies/mL, IQR 4.71 to 5.62). Among those who enrolled with pre-existing HIV-1 infection (RNA positive, seronegative), M184V or I mutants that were detectable at seroconversion became undetectable by population sequencing 9 and 12 weeks after stopping FTC/TDF, and 36 weeks after stopping placebo.
Conclusions: Minor variant drug resistance was not detected in the active arm of the iPrEx study, consistent with low drug exposure in FTC/TDF PrEP failures. FTC resistance among those who started FTC/TDF with pre-existing infection waned rapidly after FTC/TDF was stopped.

1002. Oral TDF and Its Impact in HSV-2 Acquisition and Clinical Expression

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Background: Use of 1% vaginal gel formulation of tenofovir was associated with a decreased incidence of herpes simplex virus type-2 (HSV-2) infection among high-risk women. The effectiveness of oral tenofovir disoproxil fumarate (TDF) to prevent HSV-2 acquisition or clinical expression remains unclear.
Methods: To assess the impact of oral TDF on HSV-2 acquisition among high-risk men who have sex with men (MSM) participating in the iPrEx study (oral pre-exposure prophylaxis trial of a co-formulation of TDF and emtricitabine [FTC/TDF] to prevent HIV-1 infection among MSM receiving standard prevention methods), we compared incidence of seroconversion to HSV-2 (defined as a reactive EIA with an IR ≥ 3.5 by Focus Technology) between randomized groups of HSV-2 seronegative (a reactive EIA with an IR <0.9 observed at baseline) participants. Participants with indeterminate HSV-2 test results were excluded from analyses. Additional analyses investigated between-group differences in HSV-2-related clinical manifestations, and also include participants with prevalent HSV-2 infection.
Results: At baseline, 891 (38.6%) out of 2,307 iPrEx participants with valid tests were HSV-2 seropositive. Among 1416 (61.4%) HSV-2 seronegative participants at baseline, HSV-2 seroconversion occurred in 88: 43 in the FTC/TDF arm (incidence rate 6.2/100 person-years; 95%CI 4.6 to 8.3) and 45 in the placebo arm (incidence rate 5.8/100 person-years; 95%CI 4.3 to 7.9), p = 0.76. Analyses restricted to incident HSV-2 seroconversions occurring before subsequent HIV seroconversions yielded similar results. In the FTC/TDF arm, 13 participants experienced herpes genital ulcer-defined adverse events (grade 2+) compared to 24 in the placebo arm (p = 0.06). Among prevalent or incident HSV-2 seropositive participants, there were no differences in the proportion of participants developing ≥1 ulcers classified either as sexually transmitted infection-related or placed the genital area, but fewer participants with ≥1 perianal ulcers (RR 0.4, 95%CI 0.22 to 0.85, p = 0.01) were observed among those assigned to the FTC/TDF arm.
Conclusions: Daily oral TDF (in co-formulation with FTC) did not reduce HSV-2 acquisition among high-risk MSM. The concentrations of TDF in the rectal or penile tissues after oral dosing appear to be insufficient to decrease the acquisition of HSV-2 infection, but seems to marginally decrease its clinical expression in the perianal area.

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