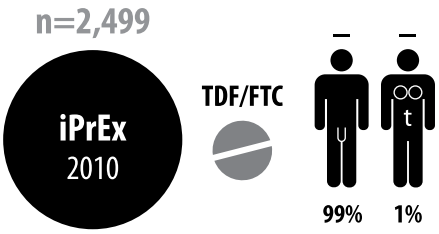
iPrEx Study



STUDY DESIGN | **The iPrEx (*Initiativa Profilaxis Pre-Exposición*) study started in 2007 and results were presented in November 2010.**

This randomized, double-blind, placebo controlled trial studied the safety and efficacy of taking Truvada (emtricitabine/tenofovir disoproxil fumarate) to prevent HIV infection.

One group of 1,251 people was assigned to take Truvada daily, while the other group of 1,248 was assigned to take a placebo daily. The pills looked alike so no one knew what they were taking. Everyone was counseled on using other prevention methods, including condoms. Everyone received risk reduction counseling, condoms and HIV and STD testing.

STUDY PARTICIPANTS | **2,499 HIV-negative men and transgender women who have sex with men at 11 sites in 6 countries: Brazil, Ecuador, Peru, South Africa, Thailand and US.**

At study entry, everyone was interviewed on sexual activity, risk of HIV, and use condoms. All had blood work done to confirm HIV status as well as liver, kidney and other tests. Everyone received 30-day supplies of pills, requiring them to return monthly for adherence interviews and blood work (HIV test; drug blood level test; and liver, kidney and other tests). Average age was 27 and participants were followed for about 21 months.

STUDY RESULTS | **Final results showed that a total of 131 people became infected: 48 in the Truvada group and 83 people in the placebo group.**

Overall, Truvada reduced the rate of new infections by 42%. This includes those who took their doses every day as well as anyone who took them less often. Although participants reported their pill-taking and condom use, blood samples were also taken monthly to detect how much drug was present. Participants with better adherence to Truvada saw higher rates of protection:

- Those *who reported taking Truvada* >50% of the time, the efficacy was 50%.
- Those *who reported taking Truvada* >90% of the time, the efficacy was 73%.
- Those *with blood levels of drug* equal to 4 days of dosing per week, the efficacy was 96%.
- Those *with blood levels of drug* equal to 7 days of dosing per week, the efficacy was 99%.

ADDITIONAL INFORMATION

>>
10 people who started the study were actually HIV-positive.

>>
At study start, the average number of sexual partners reported in past 3 months was 18. 60% reported unprotected anal intercourse in past 3 months while 78% reported it with a partner of unknown HIV status in past 6 months. 54% of participants stated they had more than five alcoholic drinks per day.

>>
93% of participants stated they took the pills correctly, but only 51% actually did according to tests that detect drug levels in blood.

>>
Hair samples found 90% adherence in the US.

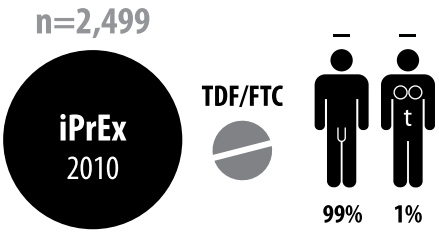
>>
In general, participants reported slightly more condom use as the study continued.

>>
The amount of condom use, as reported by participants, was the same between the two study groups.

>>
Resistance to emtricitabine was only seen in two of those who had undiagnosed HIV infection at study entry. No resistance to tenofovir disoproxil fumarate was seen.

>>
Kidney dysfunction occurred in <1% of those on Truvada. Kidney health returned to normal to in those who stopped the drug.

iPrEx Study



Adverse events reported in iPrEx, n (%)

SYMPTOM	TDF / FTC	PLACEBO	p VALUE
Depression	43 (3%)	62 (5%)	0.07
Grade 3/4 events	151 (12%)	164 (13%)	0.51
Death	1 (<1%)	4 (<1%)	0.18
Serious AE	60 (5%)	67 (5%)	0.57
Diarrhea	46 (4%)	56 (4%)	0.36
Headache	56 (4%)	41 (3%)	0.10
Nausea	20 (2%)	9 (<1%)	0.04
Weight decrease	27 (2%)	14 (1%)	0.04
Creatinine elevation	25 (2%)	14 (1%)	0.08
Confirmed Cr increase (0.4%)	5	0	0.06

SOURCES

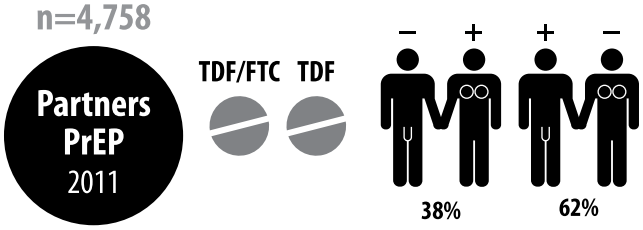
Grant RM, et al; "Preexposure chemoprophylaxis for HIV prevention in men who have sex with men". NEJM 2010;363 (27):2587-99. (*http://www.nejm.org/doi/full/10.1056/NEJMoa1011205*)

"Completed observation of the randomized placebo-controlled phase of iPrEx: daily oral FTC/TDF pre-exposure HIV prophylaxis among men and trans women who have sex with men", 6th IAS Conference, Rome, Italy, 2011 (*http://pag.ias2011.org/abstracts.aspx?aid=4800*)

"Hair as a biological marker of daily oral pre-exposure prophylaxis (PrEP) adherence and tenofovir/emtricitabine (TFV/FTC) exposure in the Global iPrEx Study", 6th IAS Conference, Rome, Italy, 2011 (*http://pag.ias2011.org/abstracts.aspx?aid=4692*)

i-Base: *http://i-base.info/htb/14833.*

Partners PrEP



STUDY DESIGN | The Partners PrEP study started in 2008 and its results were presented in July 2011.

This randomized, double-blind, placebo controlled trial studied the safety and efficacy of taking the Truvada (emtricitabine/tenofovir disoproxil fumarate) or Viread (tenofovir disoproxil fumarate) to prevent HIV infection.

Three groups were assigned a different pill: one-third (1,579) was assigned to take Truvada daily, one-third (1,584) Viread daily, and one-third (1,584) placebo daily. The pills looked alike so no one knew what they were taking. Everyone was counseled on using condoms and other prevention methods both individually and as couples. Condoms and treatment for STDs were provided. Couples were followed for 2–3 years.

STUDY PARTICIPANTS | 4,758 mixed-status heterosexual couples at 9 sites in 2 African countries: Kenya and Uganda.

62% of the women were HIV-negative while 38% of the men were HIV-negative. The HIV-positive partners were in good health with CD4 counts >250 but not on HIV treatment per national guidelines. All couples were in stable relationships, >95% were married, and none of the women were pregnant.

At study entry, everyone was interviewed on sexual activity, risk of HIV, and use condoms. HIV-negative partners received 30-day supplies of pills, requiring them to return monthly for adherence interviews and ongoing blood work (HIV test; drug blood level test; and pregnancy, liver, kidney and other tests). Any women who became pregnant stopped the medication.

STUDY RESULTS | Through July 2011, a total of 82 people became infected: 13 in the Truvada group, 17 in the Viread group, and 52 people in the placebo group. Most infections were in women.

Overall, Truvada reduced the rate of new infections by 75% while Viread lowered it 67%. These results include those who took their doses every day as well as anyone who took them less often. Blood samples were taken monthly to detect how much drug was actually present. Participants with better adherence to Truvada saw higher rates of protection:

- Those *with detectable blood levels of drug*, the efficacy was 90%.

ADDITIONAL INFORMATION

>>
12 "HIV-negative" partners who started the study actually had undiagnosed HIV infection.

>>
No evidence of drug resistance occurred among those on PrEP who became HIV-infected during the study.

>>
The HIV-negative women on Truvada or Viread who became pregnant stopped taking PrEP.

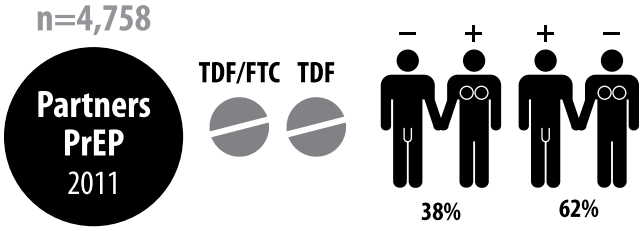
>>
Condomless sex, as reported in the previous month, decreased from 27% to 10% by the end of the study.

>>
There was no statistical difference in efficacy of PrEP in men or women for either PrEP regimen.

>>
The placebo arm was stopped early after an interim review of the data found a highly significant reduction of HIV infection from PrEP.

>>
Although Viread showed 62% reduction in HIV infection, the medication is not currently being used as PrEP.

Partners PrEP



Adverse events reported in Partners PrEP; (%)

SYMPTOM	TDF	FTC/TDF	PLACEBO	TDF VS. PO	FTC/TDF vs. Po
Nausea	1.6%	1.7%	1.5%	0.23	0.18
Diarrhea	1.6%	1.8%	1.4%	0.18	0.02

Adverse events reported in Partners PrEP; n=

SAFETY EVENT	TOTAL	TDF	FTC/TDF	PLACEBO
Death	24	8	7	9
Serious adverse event	320	108	107	105
Creatinine AE	49	17	20	12
Phosphorus AE	403	138	133	132

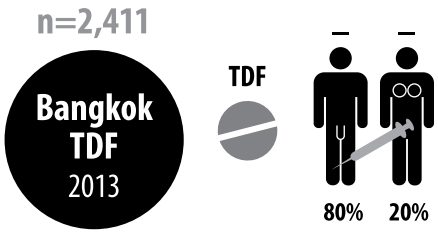
SOURCES

Baeten JM, et al. "Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women", NEJM 2012; 367:399-410. (*http://www.nejm.org/doi/full/10.1056/NEJMoa1108524*)

Baeten JM, et al. "ARV PrEP for HIV-1 Prevention among Heterosexual Men and Women". 19th Conference on Retroviruses and Opportunistic Infections, Seattle, WA. March 2012." (*source no longer available online*)

"Partners PrEP Study Demonstrates that PrEP Significantly Reduces HIV risk: Key Messages" (*http://depts.washington.edu/uwicrc/research/studies/files/PrEP_ResultsKeyMessages.pdf*)

Bangkok TDF study



STUDY DESIGN | **The Bangkok TDF study started in 2005 and results were presented in June 2013.**

This randomized, double-blind, placebo controlled trial studied the safety and efficacy of taking the HIV medication Viread (tenofovir disoproxil fumarate, TDF) to prevent HIV infection in injection drug users.

One group of 1,204 people was assigned TDF daily, while the other group of 1,207 was assigned to take a placebo daily. The pills looked alike so no one knew what they were taking. Everyone was counseled on using other prevention methods, including safer injection drug behavior and provision of bleach and condoms. Directly observed therapy (DOT) and financial incentives were also offered and nearly 90% of participants chose DOT.

STUDY PARTICIPANTS | **2,411 HIV-negative injection drug users at 17 drug treatment program sites in Bangkok, Thailand.**

80% of the participants were men. At study start and within the previous 12 weeks, 63% had injected drugs and 9% injected daily. About 20% reported sharing needles. 22% of participants had had >1 sexual partner, and 5% of men reported sex with another man. Participants were followed on average about 5 years. Average age was 31 while ages ranged from 20–60 years.

STUDY RESULTS | **A total of 50 people became infected: 17 in the TDF group and 33 people in the placebo group.**

Overall, TDF decreased the rate of new infections by 49%. In a separate analysis, the HIV infection rate decreased 74% among those known to be taking TDF consistently. Specifically, these were participants who chose DOT, took TDF at least 71% of days while missing no more than 2 consecutive doses, and had detectable blood levels of TDF. Further, those who had drug blood levels equal to >97.5% adherence had an 84% lower risk of infection.

Adherence was high overall: participants were on DOT 87% of the time, participants took study drug an average of 84% of days, and adherence did not differ between the two groups.

ADDITIONAL INFORMATION

>>
2 people had undiagnosed HIV infection at study entry.

>>
No resistance to tenofovir was seen in those who became HIV-positive during the study.

>>
The study did not see significant safety concerns with daily TDF.

>>
Participants who took TDF were more likely to initially experience nausea and/or vomiting than placebo, though reports of this greatly decreased after the first 2 months.

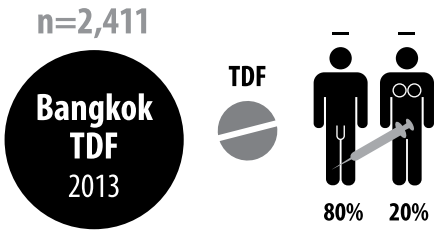
>>
Women and those over 40 years old had better adherence and higher rates of efficacy.

>>
Risk behaviors for injecting drugs decreased significantly over the first year (63% to 23%), sharing needles (18% to 2%), and multiple sexual partners (22% to 11%), and remained lower throughout the study than at study entry. These rates were similar in both groups.

>>
It is unknown how many infections were due to injection drug use or to sexual exposure.

>>
There was no indication of elevated creatinine or renal failure among participants in the TDF group.

Bangkok TDF study



Adverse events reported in Bangkok TDF; n, (%)

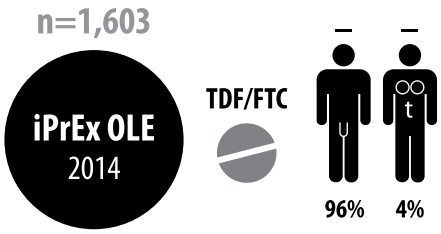
SYMPTOM	TDF	PLACEBO	p VALUE
Any adverse event	1,098	1,083	0.455
Any serious adverse event	227	246	0.352
Death	49	58	0.369
Nausea/vomiting	96	59	0.002
Renal disease	13	11	0.689
Creatinine: grade 1	37	28	0.268
Creatinine: grade 2	2	0	0.249
Creatinine: grade 3 or 4	3	3	0.996

SOURCES

Choopanya K, et al; "Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial". Lancet 2013;381(9883):2083-90. (*http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)61127-7/fulltext*)

"The Bangkok Tenofovir Study, an HIV pre-exposure prophylaxis trial in Thailand: participant adherence and study results", 6th IAS Conference, Rome, Italy, 2011 (*http://pag.ias2013.org/Abstracts.aspx?SID=73&AID=3124*)

iPrEx OLE study



STUDY DESIGN | The iPrEx OLE (*Open Label Extension*) study started in 2010 and its results were presented in July 2014.

Extension clinical trial recruited participants from 3 other PrEP trials and studied the continued safety, adherence and efficacy of taking Truvada (emtricitabine/tenofovir disoproxil fumarate) to prevent HIV.

Enrolled participants could choose to start and/or stop PrEP at any time within the first 48 weeks. Scheduled site visits included those at weeks 0, 4, 8, 12 and then every 12 weeks for up to 72 weeks. Everyone received risk reduction counseling while those on PrEP also were counseled on adherence.

STUDY PARTICIPANTS | 1,603 HIV-negative men and transgender women who have sex with men at 11 sites in 6 countries: Brazil, Ecuador, Peru, South Africa, Thailand and US.

A total of 1,225 participants chose to continue on PrEP. A higher proportion was transgender women (4%) than in the original iPrEx. About 1 in 5 participants enrolled from the US. Average age was 31, while one-fifth was under 24 years old and one-fifth were over 40 years old.

About one-third of the participants reported receptive anal sex without a condom before study start. 11% reported an HIV-positive partner, and more than one-fifth had had an STD.

STUDY RESULTS | A total of 41 people became infected: 28 in the Truvada group and 13 people in the other group.

Overall, Truvada reduced the rate of new infections by 49%. Of the 28 in the Truvada group who became positive, 7 had stopped taking Truvada more than 2 months before infection. Participants with better adherence to Truvada saw higher rates of protection:

- Those *with blood levels of drug* equal to <2 days of dosing per week, the efficacy was 44%.
- Those *with blood levels of drug* equal to 2–3 days of dosing per week, the efficacy was 84%.
- Those *with blood levels of drug* equal to 4–7 days of dosing per week, the efficacy was 100%.

ADDITIONAL INFORMATION

>>
Those who reported receptive anal intercourse without condoms were more likely to ask for PrEP.

>>
The reasons for not asking for PrEP included concerns about side effects (50%), don't like taking pills or taking pills every day (29%), and other prevention methods (14%).

>>
Higher educational levels and older age were associated with better adherence.

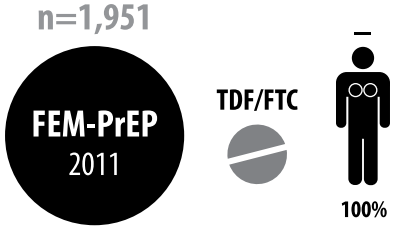
>>
A significant drop-out rate occurred, primarly among young participants, which occurred early on and despite people being at continued risk of HIV.

SOURCES

Grant RM, et al. "Results of the iPrEx open-label extension (iPrEx OLE) in men and transgender women who have sex with men: PrEP uptake, sexual practices, and HIV incidence", 20th IAC, Melbourne, Australia, 2014. (*http://pag.aids2014.org/Abstracts.aspx?SID=1106&AID=11143*)

Grant RM, et al. "Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study", Lancet Infectious Diseases. (*http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(14)70847-3/abstract*)

FEM-PrEP study



STUDY DESIGN | **The FEM-PrEP study started in 2009; results were presented in April 2011. The study was stopped early due to futility.**

This randomized, double-blind, placebo controlled trial studied the safety and efficacy of taking Truvada (emtricitabine/tenofovir disoproxil fumarate) to prevent HIV infection in women.

Women took Truvada daily for 12 months and attended monthly study visits over 14 months. One group was assigned to take Truvada daily, while the other group was assigned a placebo daily. The pills looked alike so no one knew what they were taking. Only hormonal contraception was used, so those who were using barrier methods or none at all had to switch to injected or oral contraception. Everyone was counseled on using other HIV prevention methods, including condoms. Pregnancy and STD tests and condoms were provided. Anyone who became pregnant stopped the study drug.

STUDY PARTICIPANTS | **1,951 HIV-negative non-pregnant women aged 18–35 at 4 sites in 3 African countries: South Africa, Kenya and Tanzania.**

The annual incidence of HIV infection near these study sites was 5 infections per 100 women, although 70% of the women thought they were not at high risk of HIV.

STUDY RESULTS | **A total of 68 women became infected: 33 in the Truvada group and 35 in the placebo group.**

Overall, Truvada did not reduce the rate of new infections in HIV-negative women. However, this was due to very poor adherence.

On the one hand, self-reported adherence was 95% while pill/bottle count adherence was 86%. On the other hand, according to drug blood level tests, <40% of the women had taken any drug within the 48 hours before a blood test, and only 26% of those who *did not* get HIV actually took it as prescribed.

The overall pregnancy rate was 8% per year and more women who took Truvada became pregnant — other indicators of poor adherence in this study.

Over the course of the study, participants reported fewer sexual partners, less condomless sex, and less vaginal intercourse.

ADDITIONAL INFORMATION

>>

22% of the women stated that joining FEM-PrEP meant there was free medical health testing available to them.

>>

In a survey of 5% of the participants, it appears that the women may have enrolled for reasons other than PrEP. They valued getting a monthly HIV test to ease their minds on their status.

>>

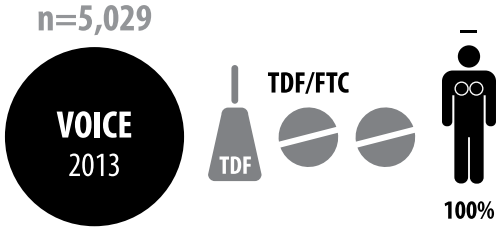
In women who started oral birth control at study start, the risk of HIV infection was 80% higher than average. However, in women who already were using injected contraception, the risk of HIV infection was 53% lower than average. This difference approached but was not clinically significant.

SOURCES

Van Damme L, et al. "Preexposure Prophylaxis for HIV Infection among African Women". NEJM 2012 (*http://www.nejm.org/doi/pdf/10.1056/NEJMoa1202614*)

"Final results of FEM-PrEP HIV-prevention study indicate great attention to adherence will be required in PrEP programs." (*http://www.fhi360.org/final-results-fem-prep-hiv-prevention-study-indicate-great-attention-adherence-will-be-required-prep*)

VOICE study



STUDY DESIGN | The VOICE (*Vaginal and Oral Interventions to Control the Epidemic*) study started in 2009 and results were presented in March 2013. Three study arms were stopped early due to futility in 2011.

This randomized, double-blind, placebo controlled trial studied the safety and efficacy of taking Truvada (emtricitabine/tenofovir dosporoxil fumarate) or Viread (tenofovir disoproxil fumarate) or a tenofovir vaginal gel to prevent HIV infection in women.

Five groups took various PrEP products: 1) assigned to take Truvada daily, 2) take Viread daily, 3) a placebo pill daily, 4) tenofovir vaginal gel applied daily, and 5) placebo gel daily. Adherence was measured by pill bottle count, gel applicator count and online questionnaire as well as by drug blood levels. Everyone was followed for 14–36 months, and everyone received risk reduction counseling, condoms, and HIV, STD and pregnancy tests.

STUDY PARTICIPANTS | 5,029 HIV-negative non-pregnant women aged 18 to 45 at 15 sites in 3 African countries: South Africa, Uganda and Zimbabwe.

Average age was 25 and most women were unmarried (79%). Retention was good (only 9% dropped out). Before study start, self-reported condom use at last vaginal sex was very high (85%). 22% reported >1 male partner in previous 3 months, and 17% reported anal sex in the past 3 months. 71% used injected contraception while 23% took oral birth control.

STUDY RESULTS | A total of 312 women became infected: 61 in Truvada group, 60 in Viread group, 60 in placebo pill group, 61 people in tenofovir gel group, and 70 in placebo gel group.

None of the PrEP products used in this study showed any reduction of HIV infection. However, this was due to very poor adherence. Self-reported adherence occurred in about 90% of the women on pills or applicators. However, drug blood level tests showed that only about one-third were taking Truvada (29%) or Viread (28%) as prescribed and only 23% used tenofovir gel as prescribed. Between 50–58% had no detectable drug levels at any study visit.

ADDITIONAL INFORMATION

>>

22 women started the study with undiagnosed HIV infection.

>>

Factors that increased adherence included: married women, being 26 years or older, or having a primary partner over 28 years old.

>>

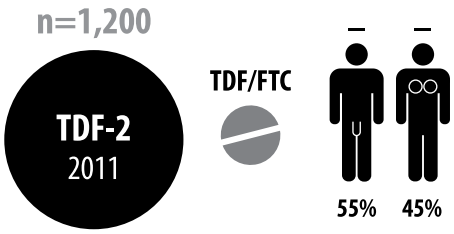
The annual pregnancy rate was 8%, suggesting that a high proportion of women – especially those using non-injectable methods – were not using contraception.

SOURCES

J Marrazzo, et al. "Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine or vaginal tenofovir gel in the VOICE study (MTN 003)". 20th Conference on Retroviruses and Opportunistic Infections. Atlanta, GA, March 3-6, 2013. (*source no longer available online*)

VOICE Backgrounder. (*www.mtnstopshiv.org/news/studies/mtn003/backgrounder*)

TDF-2 study



STUDY DESIGN | The TDF-2 study started in March 2007 and its results were presented in July 2011.

This randomized, double-blind, placebo controlled trial studied the safety and efficacy of taking Truvada (emtricitabine/tenofovir disoproxil fumarate) to prevent HIV infection. The study was stopped early due to low retention.

One group of 601 people was assigned to take Truvada daily, while the other group of 599 was assigned a placebo daily. The pills looked alike so no one knew what they were taking. Everyone received risk reduction counseling, condoms and HIV and STD testing. The women received pregnancy testing and family planning counseling.

STUDY PARTICIPANTS | 1,200 HIV-negative heterosexual men and women aged 18–39 years at 2 sites in 1 African country: Botswana.

54% of the participants were men, 46% were women, and >93% were single. All had monthly site visits for routine blood work to confirm HIV status as well as pregnancy, liver, kidney and other tests. Participants were followed for a minimum of 12 months. In both groups, 14% stated having >1 sexual partner within the past month while 81% reported consistent condom use.

STUDY RESULTS | A total of 33 people became infected: 9 in the Truvada group and 24 in the placebo group.

Overall, Truvada reduced the rate of new infections by 63%. However, when also excluding those who became infected because they ran out of Truvada for at least 30 days, the pill reduced the rate by 78%.

Adherence was 84% from pill counts and 94% from self-reports. However, half of those who became infected had no detectable drug in their blood.

Adverse events reported in Partners PrEP, (%)

SYMPTOM	TRUVADA	PLACEBO
Nausea	19%	7%
Vomiting	12%	7%
Diarrhea	15%	11%

ADDITIONAL INFORMATION

>>
1 participant started the study with undiagnosed HIV infection.

>>
Participants reported fewer sex partners over the course of the study although the amount of condomless sex stayed stable.

>>
Participants reported fewer sex partners over the course of the study although the amount of condomless sex stayed stable.

SOURCES

Thigpen MC, et al; "Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana". NEJM 2012;367(5):423-34. (*http://www.nejm.org/doi/full/10.1056/NEJMoa1110711*)

Thigpen MC, et al; "Daily oral antiretroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana: results from the TDF2 study". 6th IAS Conference, Rome, Italy, 2011. (*http://pag.ias2011.org/Abstracts.aspx?SID=98&AID=4631*)