Centers for Disease Control and Prevention

Effectiveness of Prevention Strategies to Reduce the Risk of Acquiring or Transmitting HIV

There are now more options than ever before to reduce the risk of acquiring or transmitting HIV. Using medicines to treat HIV, using medicines to prevent HIV, using condoms, having only low-risk sex, only having partners with the same HIV status, and not having sex can all effectively reduce risk. Some options are more effective than others. Combining prevention strategies may be even more effective. But in order for any option to work, it must be used correctly and consistently.

The following tables provide the **best estimates** of effectiveness for various strategies to prevent HIV acquisition or transmission. Each estimate was identified from the published scientific literature and represents the effectiveness of each strategy **when used optimally**. Available measures of optimal use vary by strategy. The principles for prioritizing measures and findings that were most relevant can be found here. A description of each prevention strategy, corresponding effectiveness estimate, and a summary of the evidence is provided below.

Antiretroviral Therapy (ART) for HIV-Positive Persons to Prevent Sexual Transmission

Population	Effectiveness Estimate	Source	Interpretation
"Optimal Use" (Taking ART daily as prescribed and achieving and maintaining viral suppression)			
Heterosexual Men and Women	100%	Cohen, 2016 Rodger, 2016	For HIV-positive heterosexual men and women, taking ART regularly greatly reduces the risk of HIV transmission to an HIV–negative partner. For persons who achieve and maintain viral suppression, there is *effectively no risk* of transmitting HIV to their HIV–negative sexual partner. This translates to an effectiveness estimate of 100%[†] for taking ART regularly as prescribed and achieving and maintaining viral suppression. Effectiveness is lower, and there is a risk of transmitting HIV, when persons do not take ART as prescribed or stop taking ART, if viral suppression is not achieved, or if viral suppression is not maintained.
Men who have sex with men (MSM)	100%	Rodger, 2016 Bavinton, 2018 Rodger, 2019	For HIV-positive MSM, taking ART regularly greatly reduces the risk of HIV transmission to a negative partner. For persons who achieve and maintain viral suppression, there is *effectively no risk* of transmitting HIV to their HIV-negative sexual partner. This translates to an effectiveness estimate of 100%[†] for taking ART regularly as prescribed and achieving and maintaining viral suppression. Effectiveness is lower, and there is a risk of transmitting HIV, when persons do not take ART as prescribed or stop taking ART, if viral suppression is not achieved, or if viral suppression is not maintained.

[†] Data are not available from these studies to calculate a combined confidence interval for the effectiveness estimate of 100%; however, confidence intervals for transmission rate estimates from each study are presented below. A recent review of many studies, including these, reported a combined HIV transmission risk estimate, across populations, while the HIV-positive person was virally suppressed of 0.00 (95% CI: 0.00 – 0.07) per 100 couple-years (Vernazza, 2019).

Evidence Supporting Effectiveness Estimates:

- **Effectiveness estimates based on suppressive ART ("Optimal Use" of ART) as indicated by achieving and maintaining viral suppression:**
    - Optimal use of ART is defined as taking ART daily as prescribed and achieving and maintaining a suppressed viral load (or viral suppression).
    - Four key studies provide evidence for the effectiveness of ART, *when used optimally*, on preventing the sexual transmission of HIV. These studies – HPTN052 (Cohen, 2016), PARTNER (Rodger, 2016), Opposites Attract (Bavinton, 2018), and PARTNER2 (Rodger, 2018) – observed zero linked sexual transmissions among HIV-discordant couples with viral suppression.
        - Each of these studies followed HIV-discordant couples while the HIV-positive partners were treated with ART with the intent of suppressing HIV replication. The follow-up assessments, at frequencies typical of what experts recommend for clinical care, included regular measurement of plasma HIV RNA concentrations and HIV testing of the HIV-negative partner. In each study, new HIV infections in the uninfected partners were assessed phylogenetically to determine whether they were genetically linked to their HIV-positive partner in the study.
        - The **HPTN052 study (Cohen, 2016)** followed 1,763 HIV-discordant couples (97% heterosexual; 3% MSM) for a median of 5.5 years. Zero genetically linked transmissions were observed while the HIV-positive partner was virally suppressed, defined as <400 copies/mL of plasma, resulting in a transmission rate estimate of 0.00 per 100 couple-years and an effectiveness estimate of 100%, if calculated (not reported in study). The confidence intervals for the effectiveness and transmission rate estimates were not reported and could not be calculated from data reported. The authors reported six partner infections that occurred during the study period where linkage could not be determined due to the inability to amplify HIV RNA; these infections were excluded from all analyses. Although linked infection could not be definitively ruled out, epidemiologic investigation strongly suggested most were not linked (Eshleman, 2017). Reported condom use was high (93%) among couples (Cohen, 2011) and likely contributed to the observed reduction in HIV transmission risk.
        - The **PARTNER study (Rodger, 2016)** followed 1,166 HIV-discordant couples (62% heterosexual; 38% MSM) for a median of 1.3 years while the HIV-positive partner was treated with ART and virally suppressed at baseline. During the 1,238 couple-years of follow-up time included in the analysis, where nearly 900 couples engaged in over 58,000 condomless sex acts, the HIV-negative partner did not use PrEP or PEP, and the HIV-positive partner was virally suppressed, defined as VL <200 copies/mL of plasma, zero genetically linked transmissions were observed. The resulting transmission rate estimate per 100 couple-years was 0.00, with a 95% confidence interval (CI) = (0.00, 0.30). The upper 95% confidence limit varied by risk group and sexual behavior due to the range of couple-years observed across the subgroups. For example, the estimate for the sexual transmission rate of HIV among discordant couples while the HIV-positive partner was virally suppressed was:
            - 0.00 (0.0 – 0.46) per 100 couple-years during **any condomless sex** among **heterosexual men and women**
            - 0.00 (0.0 – 0.89) per 100 couple-years during **condomless anal sex** among **MSM**
        - The **Opposites Attract study (Bavinton, 2018)** followed 343 HIV-discordant male-male couples for a median of 1.7 years while the HIV-positive partner was treated with ART, with most taking ART at baseline (80%). During the 232 couple-years of follow-up time included in the analysis, where the HIV-positive partner was virally suppressed (defined as <200 copies/mLof plasma) and couples reported over 12,000 episodes of any condomless anal sex acts and no PrEP use, there were zero genetically linked transmissions observed. This translates to a transmission rate estimate of:
            - 0.00 (0.00 – 1.59) per 100 couple-years during **condomless anal sex** among **MSM**
        - The **PARTNER2 study (Rodger, 2019)** was an extension of the PARTNER study that recruited more HIV-discordant male-male couples and extending the follow-up time for those enrolled in the PARTNER study, totaling 972 HIV-discordant male-male couples enrolled in PARTNER2. The final analysis included almost 800 couples followed for a median of 2.0 years. Over nearly 1,600 couple-years of follow-up while the HIV-positive partner was on ART and virally suppressed, defined as <200 copies/mL of plasma, and couples reported no PrEP use and over 76,000 episodes of condomless anal sex, zero genetically linked transmissions were observed. This translates to a transmission rate estimate of:
            - 0.00 (0.00 – 0.23) per 100 couple-years during **condomless anal sex** among **MSM**
    - Additional supporting evidence beyond the four individual studies includes:
        - Combining over 2,600 couple-years of follow-up and more than 125,000 episodes of sex without a condom

or PrEP while the HIV-positive partner was virally suppressed, from the PARTNER, PARTNER2, and Opposites Attract studies, results in a combined HIV transmission risk estimate for condomless and PrEP-less sex

among heterosexual or MSM couples of 0.00 (0.00 – 0.14) per 100 couple-years (https://www.cdc.gov/hiv/pdf/risk/art/cdc-hiv-art-viral-suppression.pdf [PDF – 160 KB]).

- A recent review at the 2019 CROI conference combined the four studies above along with several previous observational studies, accumulating over 4,000 couple-years of follow-up, and reported a combined HIV transmission risk estimate while the HIV-positive person was virally suppressed, excluding unconfirmed viral loads, of 0.00 (0.00 – 0.07) per 100 couple-years (Vernazza, 2019).
- No cases of linked HIV transmission to sexual partners when the person with HIV was virally suppressed have been documented.

- **Earlier effectiveness estimates based on original RCT study:**
  - Cohen (2011) was the first published RCT examining the protective benefits of ART for reducing HIV transmission. This paper reported the interim analysis of the HPTN 052 study, a randomized controlled trial (RCT) of providing early ART, compared with delayed ART, among 1,763 mostly heterosexual, serodiscordant couples followed for a median of 1.7 years. The effectiveness estimate for ART was 96%, based on the ITT results using verified linked cases of HIV.
    - Typically, findings from the primary analysis within an RCT include many participants assigned to the intervention strategy but not necessarily using the strategy. In this study, however, most participants in the "early ART" arm were ***taking ART consistently*** as evidenced by a high level of adherence to ART (79% had at least 95% adherence via pill count) and a high rate of viral suppression (89% were virally suppressed by 3 months). Given that this ITT analysis included time periods where the HIV-positive person was not taking ART or not virally suppressed, this effectiveness estimate for consistent use of ART is not an accurate estimate for optimal use of ART, where the HIV-positive person would be taking ART as prescribed and would have achieved viral suppression.
    - The 96% effectiveness of taking early ART, as well as a significant reduction in morbidity and mortality among HIV-positive participants, led to ending the RCT and offering all couples ART. Cohen and colleagues have continued to follow participants from this original study and offer ART to participants in both arms (thereby turning the study from an RCT to an observational design, although they continue also to analyze participants per their original random assignment) (Cohen, 2016). By the end of the study, 96% of HIV-positive persons in the "delayed ART" arm had started ART. The final HPTN 052 study ITT effectiveness estimate, including more than 5 years of follow-up, was 93% comparing "early ART" vs "delayed ART" (Cohen, 2016). Given that essentially all participants in both arms has started ART by the end of the study, this finding is not a better estimate of the effectiveness of taking ART (versus not taking ART) on reducing HIV transmission.
    - Based on the HPTN 052 RCT (Cohen, 2011), the best estimate for the overall effectiveness of ***taking ART consistently*** among heterosexuals is 96%. There are no comparable RCTs for MSM or PWID.

References:

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Oral Daily Pre-Exposure Prophylaxis (PrEP)[†] for HIV-Negative Persons

Population	Effectiveness Estimate	Source	Interpretation
"Optimal or Consistent Use"[a] (Taking PrEP daily or at least 4 times per week)			
Men who have sex with men (MSM)	~99%	Grant, 2014 Liu, 2015 McCormack, 2015 Volk, 2015 Marcus, 2017	When taking PrEP daily or consistently (*at least 4 times per week*), the risk of acquiring HIV is reduced by about 99% among MSM. While daily use is recommended in the U.S., taking PrEP consistently (*at least 4 times per week*) appears to provide similar levels of protection among MSM. The effectiveness of oral PrEP is highly dependent on PrEP adherence. When taking oral PrEP daily or consistently, HIV acquisition is extremely rare and has not been observed in any of the studies described below. In clinical practice, a few cases of new HIV infections have been confirmed while HIV-negative individuals were on PrEP with verified adherence.
Heterosexual Men and Women	~99%	*N/A*	There is evidence for the effectiveness of PrEP when used recently[b] (based on detecting TFV in plasma), which is estimated to be 88 – 90% as described below. There is no effectiveness estimate of PrEP when taken daily or consistently among heterosexuals; however, it is likely to be greater than the estimates corresponding to recent use and similar to what has been observed for MSM. The effectiveness of oral daily PrEP is highly dependent on PrEP adherence, with maximum effectiveness when taking PrEP daily and lower effectiveness when not taken consistently.
Persons Who Inject Drugs (PWIDs)	74 – 84%	Choopanya, 2013 Martin, 2015	PWID face HIV risks from both injecting and sex behaviors. Studies on the effectiveness of PrEP when taken daily among PWID are limited. However, when taking PrEP consistently, the risk of acquiring HIV is reduced by an estimated 74 – 84% among PWID. These estimates are based on tenofovir alone and among a subset of PWID taking PrEP consistently, as verified by directly observed therapy or daily diary plus monthly pill count. The effectiveness of two-drug oral therapy has not been assessed among PWID but may be higher. The effectiveness of oral daily PrEP is highly dependent on PrEP adherence, with maximum effectiveness when taking PrEP daily and lower effectiveness when missing doses.

[†] The guidelines for PrEP use in the U.S. recommends daily oral PrEP (https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf [PDF – 2 MB]) and daily dosing is the only Food and Drug Administration (FDA)-approved schedule for taking PrEP to prevent HIV. Therefore, this summary evidence table refers to the science behind optimal or consistent use of daily PrEP and does not currently include on-demand PrEP. Although not included above, evidence also demonstrates that on-demand PrEP provides effective protection during sex for MSM as described below in the IPERGAY Trial and IPERGAY OLE.

[a] Optimal use of oral daily PrEP is defined as taking PrEP daily. In studies, optimal or daily PrEP use has been determined by levels of TFV-DP detected in dried blood spots equivalent to 7 pills/week. Consistent use is defined as taking PrEP at least 4 pills/week, and has been measured in studies by levels of TFV-DP detected in dried blood spots or other objective adherence measures, consistent with at least 4 pills/week.

[b] Recent use of oral PrEP is determined by detecting any amount of TFV in plasma.

Evidence Supporting Effectiveness Estimates[c]:

- **Effectiveness estimates based on "Optimal or Consistent Use" of oral daily PrEP.**
    - The effectiveness of oral daily PrEP is highly dependent on PrEP adherence (Riddell, 2018). The effectiveness estimate of PrEP, when taken daily or consistently, is presented here. The effectiveness estimates of PrEP as assigned within a trial or when used recently are presented below.
    - When taking oral PrEP daily or consistently, it is extremely effective in preventing HIV and HIV acquisition is extremely rare. Only three cases of seroconversion have been confirmed to date worldwide, while HIV-negative individuals were on PrEP with verified adherence (http://www.thebody.com/content/80972/has-anyone-gotten-hiv-when-they-were-on-prep.html)
    - The US Preventive Services Task Force (USPSTF) provides a Grade A recommendation for oral daily PrEP in preventing HIV acquisition in persons at high risk. The USPSTF also concludes with high certainty that the benefit of oral PrEP is substantial, but that adherence to PrEP is central to maximizing its benefit (USPSTF, 2019).
    - **MSM:** Several studies evaluated the effectiveness of PrEP use among MSM. These studies vary in study design methods (e.g. RCT, observational) as well as how PrEP adherence is measured; but all provide evidence for the effectiveness of PrEP when taken daily or consistently.
        - **iPrEx OLE Study** (Grant, 2014). This open-label extension (OLE) cohort study enrolled 1,603 MSM and transgender women previously enrolled in three PrEP trials (ATN 082; iPrEx; and US Safety Study) and followed participants for 72 weeks. All were offered free daily oral PrEP (TDF/FTC or *Truvada*), and 1,225 elected to take PrEP. PrEP adherence was measured by drug concentration of TFV-DP in dried blood spots. No new HIV infections were observed among MSM taking PrEP where drug levels indicated they had taken 4 or more doses per week.
            - Among those with the highest drug concentrations indicating daily PrEP use, as verified by drug level of TFV-DP in dried blood spots of ≥1250 fmol/punch (equivalent to ~7 pills/week), there were no new HIV infections. This resulted in a risk reduction estimate of 100% when compared to the previous placebo group from the iPrEx trial or the concurrent group of participants not on PrEP.
            - In addition, among those with drug concentration levels indicating at least 4 pills/week (>700 fmol/punch), there were no new HIV infections, which resulted in a risk reduction estimate of 100% when compared to either comparison group.
        - **DEMO Project** (Liu, 2015). This open-label observational study enrolled 557 MSM and transgender women in 2 STI clinics and a community health center in 3 U.S. cities and offered free daily oral PrEP (TDF/FTC) for 48 weeks. PrEP adherence was measured by drug concentration of TFV-DP in dried blood spots in a large sample of participants at all follow-up visits. At the end of follow-up, 527 had at least 1 follow-up visit, providing a total of 481 person-years of follow-up. Most of the participants (ranging from 80% to 86% of participants across the follow-up visits) of those assessed for PrEP adherence had drug levels considered protective (consistent with ≥4 pills/week). At the end of the study, 2 participants acquired HIV infection; however, both participants had drug levels indicative of < 2 doses/week or BLQ (below the limit of quantification) throughout the study. This means no new HIV infections were observed among those with protective levels of PrEP use.
        - **PROUD Study** (McCormack, 2015). The PROUD study was a randomized-control trial (RCT) evaluating immediate daily oral PrEP (TDF/FTC) vs delayed PrEP among HIV-negative MSM patients in 13 clinics in England from 2012-2014. A total of 554 MSM were randomized, 275 to immediate PrEP and 269 to the delayed group. After an interim analysis, the trial stopped early and all deferred patients were offered PrEP. More than 90% of the patients in each group were retained at the end of the study, providing ~500 person-years of follow up. The mITT results from the trial are reported below. Although there were 3 new HIV infections among those assigned to the immediate PrEP group, there were no HIV infections observed among those actually taking PrEP. All 3 new HIV infections in the immediate PrEP group, based on clinical indications, attendance, and prescription info, were not taking PrEP near the time of seroconversion – 2 never started taking PrEP and 1 infection was identified over 40 weeks after last clinic visit (where 90 PrEP pills were provided).
        - **Kaiser Permanente Observational Study** (Volk, 2015; Marcus, 2017). This observational study followed 1,045 Kaiser Permanente (KP) patients, mostly MSM (98-99%), who were referred to a specialized PrEP program in KP San Francisco during 2012-2015, and then later extended through February 2017. PrEP use was measured based on pharmacy refill data. Among the 2,107 patients never starting PrEP, there were 22 new HIV infections. Among the 4,991 who started PrEP, although we don't know how many were always taking PrEP daily, there were no new HIV infections while PrEP prescriptions were filled (over 12.4 months; 5,104 person-years on PrEP). Of the 1,303 patients who stopped PrEP (prescription not re-filled), 11 new HIV infections were later observed after stopping PrEP, by the end of the follow-up.

- In summary, the effectiveness of PrEP among MSM when used daily or consistently is estimated to be 100% in studies. However, a few cases of new HIV infections have been reported with PrEP verified adherence,

  indicating that the risk has not been completely eliminated and that the effectiveness of PrEP cannot be exactly 100%. Given the number of persons on PrEP worldwide (prepwatch.org), the risk reduction (or effectiveness of PrEP) would likely need to be very high and close to100% to observe only three confirmed cases of PrEP failure (new HIV infection despite taking PrEP daily or consistently) to date. To represent the protective value of PrEP while also acknowledging the small number of failures, we indicate the effectiveness of PrEP is about 99%.

- **Transgender women:** The **iPrEx OLE** cohort study (Grant, 2014) enrolled mostly MSM, but included 175 transgender women previously enrolled in three PrEP trials (ATN 082; iPrEx; and US Safety Study) and offered free daily oral PrEP (TDF/FTC or *Truvada*) for 72 weeks. PrEP adherence was measured by drug concentration of TFV-DP in dried blood spots. One transgender woman seroconverted while receiving PrEP and one seroconversion occurred in a woman who elected not to use PrEP. No new HIV infections were observed among transgender women who were taking PrEP where drug levels indicated they had taken 4 or more doses per week. However, the iPrEx trial results described below show no benefit of PrEP among transgender women, likely due to low PrEP adherence (Deutsch, 2015).
- **Heterosexual men and women:** There is no effectiveness estimate of PrEP when taken daily or consistently among heterosexuals. There is evidence for the effectiveness of PrEP when used recently, which is estimated to be 88 – 90%, as described below. These estimates come from subset analyses among heterosexual men or women with evidence of taking PrEP recently (based on detecting TFV in plasma). These subset analyses likely include people who vary in PrEP adherence, including those who used PrEP recently but not consistently, used PrEP consistently but not daily (e.g. ~4 times/week), or used PrEP daily. Given that the effectiveness of PrEP is highly dependent on PrEP adherence, the effectiveness of PrEP when taking PrEP daily or consistently is likely to be greater than when taking PrEP recently; therefore, likely to be greater than 90% and similar to what is observed for MSM. Data show that it takes longer (~13 days longer) to reach a maximum drug level of PrEP in vaginal tissue as compared to rectal tissue (CDC, 2018), but once maximum drug levels are reached, the effectiveness of PrEP in preventing acquisition during sex should be similar for vaginal or anal sex, and for men or women.
- **PWID:** The **Bangkok Tenofovir Study (BTS)** (Choopanya, 2013) was an RCT evaluating oral daily PrEP use (TDF alone) against placebo among HIV-negative persons who inject drugs (PWID).
  - When taking PrEP (TDF) nearly daily, as verified by TFV detected in plasma and directly observed therapy (DOT) (with at least 70% of days were DOT, with no gaps of >2 days without DOT; equivalent to ~5 days/week), the risk of HIV acquisition was reduced by 74% among HIV-uninfected injecting drug users (subset analysis; BTS; Choopanya, 2013).
  - When taking PrEP (TDF) nearly daily, when defined as 97.5% adherence, based on daily diary (most often confirmed daily by DOT staff) and monthly pill count, the risk of HIV acquisition was reduced by about 84% (subset analysis; BTS; Martin, 2015). This study also showed a dose-response between adherence and protection from PrEP, with greater adherence resulting in a greater effectiveness estimate for PrEP.
  - This BTS study evaluated TDF (Tenofovir) rather than the combination drug TDF/FTC (Truvada). The effectiveness of two-drug oral therapy has not been assessed among PWID but may be higher than TDF alone. TDF alone had been shown to have a slightly lower efficacy than TDF/FTC, although not statistically different, among heterosexual HIV-discordant couples in the Partners PrEP study (Baeten, 2012; Baeten, 2014). In addition, since the measures used in the BTS study for assessing PrEP adherence included those taking PrEP nearly daily but not daily, the effectiveness of daily PrEP use may in fact be greater.
  - Note that TDF (Tenofovir) is recommended in the U.S. as an alternative to TDF/FTC (Truvada) among PWID (https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf [PDF – 2 MB])

- **Effectiveness estimates based on "Recent Use" of oral daily PrEP.**
  - Recent use of oral PrEP is measured based on drug detected, typically detecting FTC or TFV, in plasma. All effectiveness estimates presented here come from subset analyses within larger RCTs restricting to participants with drug detected in plasma indicating recent use of PrEP. These estimates do not reflect optimal or consistent use of PrEP, which resulted in greater effectiveness estimates among MSM and PWID as described above.
  - **MSM:** The **iPrEx Trial** (Grant, 2010) was an RCT evaluating oral daily PrEP use (TDF/FTC) against placebo among MSM. The findings from a case/control sub-analysis show that effectiveness of PrEP, when recently used, was estimated to be 92%. This measure of recent use of PrEP was based on detecting FTC or TFV in plasma or detecting FTC-TP or TFV-DP in PBMC.
  - **Heterosexual men and women:** The **Partners PrEP Study** (Baeten, 2012) was an RCT with three arms, evaluating

oral daily PrEP use as TDF/FTC and as TDF alone against a placebo arm, among HIV-discordant heterosexual men and women.

- The effectiveness of PrEP (TDF/FTC), when used recently, was estimated to be 88% – 90%, which comes from two separate sub-analyses from the Partners PrEP Study.
- A case/control sub-analysis reported the effectiveness of PrEP, when used recently (based on detecting TFV in plasma), was estimated to be 90% among HIV-uninfected heterosexual men and women (Baeten, 2012).
- Another restricted analysis of the same study was based on TFV drug levels in plasma. When taking PrEP (TDF/FTC) recently, as defined by >40 ng/ml of TFV in plasma (unknown equivalent pills/week), the risk of HIV acquisition was reduced by 88% among HIV-uninfected heterosexual men and women (Donnell, 2014). Given these levels of TFV in plasma do not translate to a known level of PrEP adherence or known number of pills/week, this finding more accurately corresponds to those taking PrEP recently rather than daily or consistently.

◦ **PWID:** The **Bangkok Tenofovir Study (BTS)** (Choopanya, 2013) was an RCT evaluating oral daily PrEP use (TDF alone) against placebo among HIV-negative persons who inject drugs (PWID).

- A case/control sub-analysis reported the effectiveness of PrEP (TDF), when used recently (based on detecting TFV in plasma), was estimated to be 70% among PWID.
- This BTS study evaluated TDF (Tenofovir) rather than the combination drug TDF/FTC (Truvada). The effectiveness of two-drug oral therapy has not been assessed among PWID but may be higher than TDF alone. TDF alone has been shown to have a slightly lower efficacy than TDF/FTC when compared to placebo, although not statistically different, among heterosexual HIV-discordant couples in the Partners PrEP study (Baeten, 2012; Baeten, 2014).
- Note that TDF (Tenofovir) is recommended in the U.S. as an alternative to TDF/FTC (Truvada) among PWID (https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf [PDF – 2 MB])

- **Effectiveness estimates based on modified intent-to-treat (mITT) analyses in trials, regardless of level of PrEP use:**
  - **MSM:**
    - **The iPrEx Trial** (Grant, 2010) was an RCT designed to evaluate the efficacy of oral daily PrEP (TDF/FTC) versus placebo in preventing HIV acquisition among 2,499 HIV-uninfected MSM and transgender women. After a median of 1.2 years of follow-up, the risk of HIV acquisition was reduced by 44% among HIV-uninfected MSM assigned to daily PrEP (TDF/FTC) (mITT analysis). This estimate includes all participants assigned to take daily PrEP, regardless of actual use.
    - The **PROUD Study** (McCormack, 2015) was an RCT evaluating immediate daily oral PrEP (TDF/FTC) versus delayed PrEP among HIV-negative patients in 13 clinics in England from 2012-2014. A total of 554 MSM were randomized, 275 to immediate PrEP and 269 to the delayed group. After an interim analysis, the trial stopped early and all deferred patients were offered PrEP. More than 90% of the patients in each group were retained at the end of the study, providing ~500 person-years of follow-up.
      - RCT results (mITT analysis) – At the end of interim analysis, 3 new HIV infections were observed in the immediate PrEP group and 20 in delayed group, resulting in a risk reduction estimate of 86%.
      - There were no HIV infections observed among those taking PrEP. All 3 new HIV infections in immediate PrEP group, based on clinical indications, attendance, and prescription information, were not taking PrEP near the time of seroconversion – 2 never started taking PrEP and 1 infection was identified over 40 weeks after last clinic visit (where 90 PrEP pills were provided).
    - The **IPERGAY Trial** (Molina, 2015) was an RCT evaluating the efficacy of "on-demand" PrEP (TDF/FTC) regimen (defined as taking 2 pills 2-24 hours before sex, 1 pill 24 hours later, and a 4th pill 24 hours after the 3rd) versus placebo among 400 MSM. At the interim analysis of the trial, after 1 year of follow-up, the efficacy of "on-demand" PrEP was estimated to be 86% in the mITT analysis and 82% in the ITT analysis. By measured plasma drug levels in a subset of those randomized to TDF/FTC, 86% had TDF levels consistent with having taken the drug during the previous week.
      - The **IPERGAY OLE** (Molina, 2017) study. Following the interim analysis where the efficacy of "on-demand" PrEP was determined, the placebo group was discontinued, all study participants were offered TDF/FTC in an OLE phase of the study, and 361 enrolled. Although not part of the trial, the **IPERGAY OLE** study reported the risk of HIV acquisition was reduced by 97% when comparing the MSM taking PrEP as part of the OLE cohort to the placebo arm of the IPERGAY trial (Molina, 2017). Seventy-one percent of those in the OLE cohort had TDF levels consistent with having taken the drug during the previous week.
      - Two participants in the "on-demand" PrEP arm of the RCT seroconverted after enrollment and 1 participant in the OLE cohort seroconverted during follow-up. In all three cases, study records showed

participant in the OLE cohort seroconverted during follow-up. In all three cases, study records showed that the participants were not taking PrEP at the time of the diagnosis (no drug detected in plasma and

all had returned all or most of their PrEP pills at the most recent visit). No new HIV infections were observed among participants taking PrEP.

- A small sub-study of the IPERGAY trial reported high effectiveness of on-demand PrEP among those MSM participants with less frequent sexual intercourse (Antoni, 2017). This subset analysis reported an estimated 100% reduction in HIV incidence among a subset of participants reporting less frequent sexual intercourse (median of 5 sex acts/month) when reportedly taking on-demand PrEP, about 9.5 pills/month (or ~2-3 pills/week), compared to placebo.
- Daily dosing is the only Food and Drug Administration (FDA)-approved schedule for taking PrEP to prevent HIV. However, the International Antiviral Society-USA supports the "off-label" but evidence-based use of on-demand PrEP, as an alternative to daily PrEP, for gay, bisexual and other men who have sex with men with infrequent sexual exposures (Saag, 2018). Given limited data on the effectiveness of on-demand PrEP for heterosexual men and women, PWID, and transgender persons, IAS-USA does not currently recommend on-demand PrEP for these populations. Several health departments have developed guidance on off label use of on demand PrEP for MSM, including the New York City Department of Health (https://www1.nyc.gov/assets/doh/downloads/pdf/ah/prep-on-demand-dosing-guidance.pdf) and the San Francisco Department of Public Health (http://www.gettingtozerosf.org/wp-content/uploads/2018/11/HIVUpdate_02122019_v2.pdf)
  - **Transgender women:** A follow-up sub-analysis of the **iPrEx Trial** evaluated the effectiveness of PrEP (TDF/FTC) versus placebo among 339 transgender women (Deutsch, 2015). No benefit of PrEP was identified (HR=1.1, 95% CI: 0.5 – 2.7); however the transgender women appeared to have lower PrEP adherence than MSM within iPrEx.
  - **Heterosexual men and women:**
    - The **Partners PrEP study** was an RCT among 4747 HIV-discordant heterosexual couples assessing the efficacy of oral daily PrEP by comparing three treatment arms – TDF/FTC (Truvada), TDF alone, and placebo. The risk of HIV acquisition was reduced by 75% among HIV-uninfected heterosexual men and women assigned to TDF/FTC (Truvada) compared to placebo (mITT analysis; Baeten, 2012). This estimate included all participants assigned to take daily PrEP, regardless of actual use.
    - The **TDF2 study** was an RCT among 1219 HIV-negative heterosexual men and women comparing TDF/FTC (Truvada) to placebo and found the risk of HIV acquisition was reduced by 62% (mITT analysis; Thigpen, 2012). This estimate included all participants assigned to take daily PrEP, regardless of actual use. An as-treated analysis, restricting to those participants taking PrEP recently based on self-reported PrEP use in last 30 days, found the risk of HIV acquisition was reduced by 78%. This, however, was based on self-report and not an objective measure of recent use.
    - There are additional PrEP trials among women reported in the literature not summarized here. Riddell (2018) and the USPSTF (2019) reviewed the trial findings for PrEP and described additional trials among women showing no significant effects of PrEP, primarily due to extremely low adherence among women in the studies.
  - **PWIDs:** The **Bangkok Tenofovir Study (BTS)** was an RCT evaluating oral daily PrEP use (TDF alone) against placebo among HIV-negative persons who inject drugs. This trial showed the risk of HIV acquisition was reduced by 49% among HIV-uninfected injecting drug users assigned to oral daily PrEP (TDF) (mITT analysis; Choopanya, 2013). This estimate included all participants assigned to take daily PrEP, regardless of actual use.

c The effectiveness estimate for PrEP is estimating the percentage reduction in HIV risk due to PrEP. It is not estimating the risk of HIV acquisition among those on PrEP, but is estimating the relative reduction in that risk due to PrEP. An effectiveness estimate of "about 99%" results in an extremely small estimated risk of HIV acquisition for those taking oral PrEP daily or consistently.

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Male Condom Use

Population	Effectiveness Estimate	Source	Interpretation
"Optimal Use" (Used consistently and correctly during every sex act)			

Population	Effectiveness Estimate	Source	Interpretation
MSM or Heterosexual Men and Women	Not Avail	Not Avail	Condoms provide an impermeable barrier to HIV. FDA quality control standards and laboratory studies indicate leaks due to product failure are extremely rare. In practice, it is difficult, *if not impossible*, to measure optimal use of condoms during sex. No studies have been able to provide accurate estimates for the effectiveness of condoms in preventing HIV, when used consistently and correctly, in practice. However, such an estimate is likely to be greater than the estimates provided in studies where participants self-reported consistent condom use during sex.
"Consistent Use" (Always used during sex per self-report)			
Heterosexual Men and Women	80%	Weller, 2002	Always using condoms, based on self-report, during sex with an HIV-positive partner reduces the risk of HIV acquisition by an estimated 80% among heterosexual men and women. Self-report may not be entirely accurate, resulting in an underestimate of the true effectiveness for consistent condom use. Condom effectiveness is also likely to be higher when condoms are used correctly every time during sex.
MSM, Receptive Anal Sex	72-91%	Smith, 2015 Johnson, 2018	Always using condoms, based on self-report, during receptive anal sex with HIV-positive partners reduces the risk of HIV acquisition by an estimated 72% (Smith, 2015) and an estimated 91% (Johnson, 2018) among HIV-negative MSM. Self-report may not be entirely accurate, resulting in an underestimate of the true effectiveness for consistent condom use. Condom effectiveness is also likely to be higher when condoms are used correctly every time during sex.
MSM, Insertive Anal Sex	63%	Smith, 2015	Always using condoms, based on self-report, during insertive anal sex with HIV-positive partners reduces the risk of HIV acquisition by an estimated 63% among HIV-negative MSM. Self-report may not be entirely accurate, resulting in an underestimate of the true effectiveness for consistent condom use. Condom effectiveness is also likely to be higher when condoms are used correctly every time during sex.

Evidence Supporting Effectiveness Estimates:

- **Effectiveness Estimates based on "Optimal Use" of Condoms.**
  - Optimal use of condoms is defined here as both consistent and correct use during every sex act.
  - Laboratory studies show that (latex-based, polyurethane, or other synthetic material-based) condoms provide an impermeable barrier to passage of HIV. Even during optimal use, however, condoms may not offer complete protection all the time due to the rare chance of product failure.
  - Measures are in place to ensure high quality control on product development. Condoms are regulated as class II medical devices by the U.S. Food and Drug Administration (FDA). FDA requires every condom to be tested electronically for holes and weak spots before it is packaged and released for sale. In addition, samples of condoms undergo a series of additional laboratory tests for leakage, strength, and other factors. Condom samples must be at least 99.6% effective in laboratory "water leak" tests, which means that at least 996 out of every 1000 condoms sampled must pass the test. (Warner, 2018; FDA link below)
  - Other laboratory testing has estimated that the worst-case product failure would lead to less than 0.01% of volume leakage during sex. In other words, the worst-case scenario would still eliminate about 99.99% of volume exposure during sex, in the event of product failure. (Carey, 1992)
- **Effectiveness Estimates based on "Consistent Use" of Condoms.**
  - *Although rare, and not easily measured, condoms may break, slip, or leak during use, even if used correctly. In*

addition, not using condoms correctly (user failure) increases the risk of breakage, slippage, leakage, or incomplete coverage which can increase exposure to HIV and, thus, may decrease condom effectiveness.

Because male condoms are applied by the user during sex, user error or failure is an ongoing risk during each sexual episode. User error is difficult to eliminate; however, over time, as the user becomes more experienced, it is minimized. In addition, not using condoms consistently, meaning during every sex act, may further increase potential exposure to HIV and decrease effectiveness even more. Below are effectiveness estimates for consistently using condoms in practice as measured in observational studies.

- **Heterosexual Men and Women:** The Weller 2002 Cochrane review of 13 longitudinal cohort studies among HIV discordant heterosexual couples reported results comparing those reporting "Always" vs "Never" using condoms during vaginal sex from 5 of the 13 studies with data available at the longest follow-up. Vaginal versus anal and insertive versus receptive sex were not distinguished in these analyses. Always using condoms, based on self-report, during sex with an HIV-positive partner reduces the risk of HIV acquisition per person-year of follow-up by an estimated 80% among heterosexual men and women. This measure does not account for the possibility of different numbers of sex acts over time between condom users and non-users.
- **MSM:** Two recent studies have estimated the effectiveness of consistent condom use on HIV risk among HIV-negative MSM having sex with HIV-positive men.
  - The Smith 2015 study combined data from two longitudinal studies among MSM (EXPLORE & Vax004) and compared HIV-negative MSM who reported "Always" vs "Never" using condoms during receptive anal sex, during insertive anal sex, and during any anal sex, with HIV-positive partners.
    - **MSM, Receptive Anal Sex —** Always using condoms, based on self-report, during receptive anal sex with HIV-positive partners reduced the risk of HIV acquisition per person-year by an estimated 72% among MSM.
    - **MSM, Insertive Anal Sex** — Always using condoms, based on self-report, during insertive anal sex with HIV-positive partners reduced the risk of HIV acquisition per person-year by an estimated 63% among MSM. This analysis does not take into account whether HIV-negative MSM also engaged in receptive anal sex, with or without condoms, which could affect this estimate.
    - **MSM, Any Anal Sex —** Always using condoms, based on self-report, during any (insertive or receptive) anal sex with HIV-positive partners reduced the risk of HIV acquisition per person-year by an estimated 70% among MSM.
    - These measures do not account for the possibility of different numbers of sex acts over time between condom users and non-users.
  - The Johnson 2018 study examined condom effectiveness per partner in four cohorts of MSM (EXPLORE, Vaxx004, JumpStart, and Vaccine Preparedness Study) by comparing those "Always" using condoms versus "Not always" using condoms, based on self-report, throughout the sexual partnerships. Among HIV-uninfected MSM engaging in receptive anal sex with their HIV-positive partner, always using condoms during receptive anal sex throughout the partnership reduced the risk of HIV acquisition per partner by an estimated 91%. This measure does not account for the possibility of different numbers of sex acts per partner between condom users and non-users.
- The estimates provided here likely underestimate the effectiveness of condoms when used consistently and correctly in practice due to measurement error regarding both aspects of condom use – *consistent use and correct use*.
  - These estimates for "*consistent use*" are based on observational cohort studies because no RCTs exist, due to ethical and feasibility concerns with assigning a no condom use arm. In addition, only subjective measures of condom use (*self-report*) are available in studies with HIV as an outcome, which may overestimate actual condom use, resulting in underestimating condom effectiveness. Therefore, the effectiveness of consistent condom use is likely greater.
  - These studies also did not measure whether condoms were used *correctly*. If used incorrectly, condoms may break, slip, leak, or not provide complete coverage, which may increase exposure to HIV. The studies among MSM, however, did ask MSM to count "breakage" and "slippage" as "not using a condom" in an attempt to account for user failure – but this relies on knowledge of failure and self-report and likely underestimates true failure. If these analyses included any data where condoms were used incorrectly but misclassified as consistent and correct use, then these estimates are likely underestimating condom effectiveness when used correctly, and the effectiveness of correct condom use is likely greater.

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Circumcision of Adult Males

Population	Effectiveness Estimate	Source	Interpretation
MSM, Insertive Anal Sex	Inconclusive	Wiysonge, 2011; Sanchez, 2011; Doerner, 2013	Based on observational studies of circumcision among adult males, there is insufficient evidence at this time to conclude that male circumcision reduces the risk of the insertive partner acquiring HIV during anal sex among MSM.
MSM, Receptive Anal Sex	Inconclusive	Wiysonge, 2011; Schneider, 2012	Based on observational studies of circumcision among adult males, there is insufficient evidence at this time to conclude that male circumcision (*of the insertive partne*r) reduces the risk of the receptive partner acquiring HIV during anal sex among MSM.
Heterosexual Men	50%	Siegfried, 2009	Based on trials of circumcision among adult males, male circumcision reduces the risk of heterosexual men acquiring HIV during sex by 50%.
Heterosexual Women	Inconclusive	Wawer, 2009; Weiss, 2009; Baeten, 2010	Based on several trials and observational studies of circumcision among adult males, there is insufficient evidence at this time to conclude that male circumcision reduces the risk of heterosexual women acquiring HIV during sex.

Strengths and Limitations of Effectiveness Estimates:

- Most of the evidence is based on observational studies and circumcision status is primarily based on self-report; only some studies are based on medical exam (objective measure of exposure).
- MSM Insertive Anal Sex – A Cochrane review of 7 observational studies among MSM reporting mainly or only "insertive" sex reports a significant protective effect of circumcision on acquiring HIV through insertive anal sex, 73% risk reduction (Wiysonge 2011). Exposure (circumcision) was primarily measured via self-report (subjective measure), although genital exams occurred in some studies. Two more recently published observational studies show non-significant effects of circumcision on HIV acquisition during insertive anal sex (Sanchez, 2011; Doerner, 2013). With conflicting results, the evidence is inconclusive and an updated meta-analysis is needed.
- MSM Receptive Anal Sex – A Cochrane review of 3 observational studies among MSM reporting primarily "receptive" sex reports a non-significant effect estimate for circumcision (*of the insertive partner*) on HIV acquisition during receptive anal sex, with exposure measured by self-report (Wiysonge 2011). A more recently published observational study reports a significant effect of circumcision (based on self-report) on HIV acquisition during receptive anal sex among MSM (Schneider, 2012). With conflicting results, the evidence is inconclusive, and an updated meta-analysis is needed.
- Heterosexual Men – A Cochrane review of 3 RCTs synthesizes ITT results on the effects of circumcision on risk of HIV acquisition during sex among HIV-negative heterosexual men (Siegfried, 2009).
- Heterosexual Women – A meta-analysis (including one RCT and several observational studies) reports that there is

insufficient evidence to conclude that male circumcision reduces the risk of HIV acquisition during sex among HIV-negative heterosexual women (Weiss, 2009). Two more recent reports, 1 RCT and 1 observational study, also show

non-significant effects of male circumcision (confirmed by medical exam) on HIV acquisition in women among HIV-discordant heterosexual couples (Baeten, 2010; Wawer, 2009). The evidence is inconclusive, and an updated meta-analysis is needed.

Source:

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