

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

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There are now more options than ever before to reduce the risk of acquiring or transmitting HIV. Using medications that treat 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 can 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 consistently. Available measures of consistent use vary by strategy. A description and rationale for each prevention strategy and corresponding effectiveness estimate is provided within a separate table for each strategy. Lower or higher levels of adherence to each strategy would increase or decrease effectiveness from the estimate provided.

ART for HIV-Positive Individuals

Population	Effectiveness Estimate	Source	Interpretation
Heterosexual Men and Women	96%	Cohen, 2011	Providing HIV-positive heterosexual men and women with ART reduces the risk of HIV transmission to a negative partner by 96%. Effectiveness is lower for persons who take ART and do not maintain viral suppression. Effectiveness may be higher among persons who achieve and maintain viral suppression.
MSM	96%	Cohen, 2011	<p>There is no direct evidence (i.e., from an RCT or other valid study) for effectiveness of ART in reducing HIV transmission risk among MSM. Because there is no biologic or other reason to believe the effectiveness of ART would be lower for MSM, the heterosexual estimate should be used for this population until direct evidence is available.</p> <p>Providing HIV-positive MSM with ART may reduce the risk of HIV transmission to a negative partner by 96%. Effectiveness is lower for persons who take ART and do not maintain viral suppression. Effectiveness may be higher among persons who achieve and maintain viral suppression.</p>

Strengths and Limitations of Effectiveness Estimates:

- The Cohen, 2011 (HPTN 052) study was an RCT of providing early ART, compared to delayed ART, among mostly heterosexual HIV-discordant couples. The estimate is based on the ITT results using verified linked cases of HIV. Most subjects in the treatment group were virally suppressed (89%) by 3 months and most had high adherence via pill count (79% had at least 95% adherence).
- No published study provides subset analyses of persons with evidence of ART use based on biologic, objective measures (e.g., detectable drug), so we have selected the Cohen RCT ITT results as the best estimate to represent consistent use. Since most participants were virally suppressed and reported high adherence levels, therefore results based on evidence of drug use are likely to be similar to these results.
- Without direct empirical evidence at this time for MSM, the estimate for heterosexual men and women is the best estimate until more direct evidence is available.

Source:

- Cohen MS et al. Prevention of HIV-1 with early antiretroviral therapy. *N Engl J Med* 2011;365(6):493-505.

Daily Pre-Exposure Prophylaxis (PrEP) for HIV-Negative Persons

Population	Effectiveness Estimate	Source	Interpretation
MSM	92%	Grant, 2010	When taking PrEP, with adherence indicated by laboratory-detected presence of drug, the risk of acquiring HIV is reduced by 92% for HIV-negative MSM. Missed doses result in lower effectiveness. Very high levels of adherence may increase effectiveness.
Heterosexual Men and Women	90%	Baeten, 2012	When taking PrEP, with adherence indicated by laboratory-detected presence of drug, the risk of acquiring HIV is reduced by 90% for HIV-negative heterosexual men or women. Missed doses result in lower effectiveness. Very high levels of adherence may increase effectiveness.
Persons Who Inject Drugs (PWIDs)	70%	Choopanya, 2013	When taking PrEP, with adherence indicated by laboratory-detected presence of drug, the risk of acquiring HIV is reduced by 70% for HIV-negative PWIDs. Missed doses result in lower effectiveness. Very high levels of adherence may increase effectiveness.

Strengths and Limitations of Effectiveness Estimates:

- The Grant, 2010 (iPrEx) study was an RCT evaluating daily PrEP use (TDF/FTC) against placebo among MSM. This effectiveness estimate comes from the case/control sub-analysis looking at new HIV infection associated with any drug detected, as measured by levels of FTC or TFV in plasma or levels of FTC-TP or TFV-DP in PBMC.
- The Baeten, 2012 (Partners PrEP) study was an RCT evaluating daily PrEP use (TDF/FTC) against placebo among heterosexual men and women. This effectiveness estimate comes from a case/control sub-analysis looking at new HIV infection associated with any drug detected, as measured by TFV plasma levels.
- The Choopanya, 2013 (Bangkok Tenofovir Study, BTS) study was an RCT evaluating daily PrEP use (TDF) against placebo among PWID. This effectiveness estimate comes from a case/control sub-analysis looking at new HIV infections associated with any drug detected, as measured by TFV plasma levels.
- All effectiveness estimates are selected from subset analyses within the larger RCTs evaluating PrEP, where PrEP use is defined as “any drug detected” and based on a biologic, objective measure for detecting the presence of drug. This is the only consistent objective measure of actual PrEP use across all populations at present. The estimates do not, however, reflect optimal adherence, which would likely yield even greater effectiveness.

Additional Estimates:

- **Effectiveness Estimates (from trials, regardless of level of Prep use):**
 - **MSM:** In an RCT, the risk of HIV acquisition was reduced by 44% among HIV-uninfected MSM assigned to daily PrEP (TDF/FTC) (mITT analysis; Grant, 2010). This estimate includes all participants assigned to take daily PrEP, regardless of actual use.
 - **Heterosexual men and women:** In an RCT, the risk of HIV acquisition was reduced by 75% among HIV-uninfected heterosexual men and women assigned to daily PrEP (TDF/FTC) (mITT analysis; Baeten, 2012). This estimate includes all participants assigned to take daily PrEP, regardless of actual use.
 - **PWIDs:** In an RCT, the risk of HIV acquisition was reduced by 49% among HIV-uninfected injecting drug users assigned to daily PrEP (TDF) (mITT analysis; Choopanya, 2013). This estimate includes all participants assigned to take daily PrEP, regardless of actual use.

Daily Pre-Exposure Prophylaxis (PrEP) for HIV-Negative Persons

- **Effectiveness Estimates (based on “Optimal Use” of PrEP indicated by objective adherence measures):**
 - **MSM:** When taking PrEP (TDF/FTC) daily, as verified by highest drug level of TFV-DP in dried blood spots (>1250 fmol/punch; ~7 pills/week), the risk of HIV acquisition is reduced by an estimated 100% among HIV-uninfected MSM (subset analysis; iPrEx OLE; Grant, 2014).
 - **Heterosexual men and women:** When taking PrEP (TDF/FTC), as verified by a high drug level of TFV in plasma (>40 ng/ml; unknown equivalent pills/week), the risk of HIV acquisition is reduced by 88% among HIV-uninfected heterosexual men and women (subset analysis; Partners PrEP; Donnell, 2014). It is noted that blood plasma level detects more recent use, so may not be the best objective measure for optimal use.
 - **PWIDs:** When taking PrEP (TDF) nearly daily, as verified by DOT (at least 70% of days were DOT, with no gaps of >2 days without DOT; equivalent to ~5 days/week) and TFV drug detected in plasma, the risk of HIV acquisition is reduced by 73.5% among HIV-uninfected injecting drug users (subset analysis; BTS; Choopanya, 2013). When taking PrEP (TDF) nearly daily, defined as 97.5% adherence based on daily diary (most often confirmed daily by staff), the risk of HIV acquisition is reduced by 83.5% (subset analysis; BTS; Martin, 2015).

Source:

- Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012;367(5):399-410.
- Choopanya K, Martin M, Suntharasamai P, 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;381:2083-90.
- Donnell D, Baeten JM, Bumpus NN, et al. HIV protective efficacy and correlates of tenofovir blood concentrations in a clinical trial of PrEP for HIV prevention. *J Acquir Immun Defic Syndr* 2014(3);66:340.
- Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010;363(27):2587-99.
- Grant RM, Anderson PL, McMahan V, 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* 2014;14:820-9.
- Martin M, Vanichseni S, Suntharasamai P, et al. The impact of adherence to preexposure prophylaxis on the risk of HIV infection among people who inject drugs. *AIDS* 2015;29:819-24.

Male Condom Use

Population	Effectiveness Estimate	Source	Interpretation
MSM, Insertive Anal Sex	63%	Smith, 2015	Always using condoms, based on self-report, during insertive anal sex with an HIV-positive partner reduces the risk of HIV acquisition by 63% among MSM. Self-report may not be entirely accurate. Condom effectiveness is likely to be higher when condoms are used correctly every time during anal sex.
MSM, Receptive Anal Sex	72%	Smith, 2015	Always using condoms, based on self-report, during receptive anal sex with an HIV-positive partner reduces the risk of HIV acquisition by 72% among MSM. Self-report may not be entirely accurate. Condom effectiveness is likely to be higher when condoms are used correctly every time during anal sex.
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 80% among heterosexual men and women. Self-report may not be entirely accurate. Condom effectiveness is likely to be higher when condoms are used correctly every time during vaginal sex.

Male Condom Use

Strengths and Limitations of Effectiveness Estimates:

- The Smith 2015 study combined data from 2 longitudinal studies among MSM (EXPLORE & Vax004) and compared HIV-negative MSM who reported “Always” versus “Never” using condoms during insertive and receptive anal sex with an HIV-positive partner.
- The Weller 2002 Cochrane review of 13 longitudinal cohort studies among HIV discordant heterosexual couples reported results comparing those reporting “Always” versus “Never” using condoms during vaginal sex from among 5 studies with longest follow-up. Vaginal versus anal and insertive versus receptive sex were not distinguished in these analyses.
- Estimates are based on longitudinal cohort studies because no RCTs exist. No publications report condom effectiveness based on an objective measure of condom use; instead only subjective measures (self-report) are available. Since self-report tends to overestimate actual condom use, “Always” using condoms versus “Never” using condoms is the comparison selected.
- Theoretically, based on laboratory studies, condoms can be as high as 95-98% effective, if used consistently and correctly.

Source:

- Smith DK et al. Condom effectiveness for HIV prevention by consistency of use among men who have sex with men in the United States. *J Acquir Immune Defic Syndr.* 2015;68(3):337-44.
- Weller SC and David-Beatty K. Condom effectiveness in reducing heterosexual HIV transmission (Review). *Cochrane Database Syst Rev* 1. (2002): CD003255. Available at <http://apps.who.int/whl/reviews/langs/CD003255.pdf>

Serosorting for HIV-Negative Persons

Population	Effectiveness Estimate	Source	Interpretation
MSM	54%	Kennedy, 2013	When compared to condomless anal sex with either HIV-positive or unknown status partners, HIV-negative MSM who self-report serosorting reduce their risk of HIV acquisition by 54%. When compared to no condomless anal sex, serosorting results in increased risk of acquiring HIV.
Heterosexual Men and Women	54%	Kennedy, 2013	<p>There is no direct evidence for effectiveness of serosorting in reducing the risk of acquiring HIV among HIV-negative heterosexual men and women. There is no reason, however, to believe serosorting wouldn't also be effective in heterosexual men and women.</p> <p>When compared to condomless sex with either HIV-positive or unknown status partners, HIV-negative heterosexual men and women who self-report serosorting may reduce their risk of HIV acquisition by 54%. When compared to no condomless sex, serosorting may result in increased risk of acquiring HIV.</p>

Serosorting is typically defined as engaging in condomless sex *only* with HIV-negative partners.

Strengths and Limitations of Effectiveness Estimates:

- Kennedy 2013 systematic review and meta-analysis combines 3 observational studies comparing the risk of HIV infection among MSM who self-report serosorting behavior and MSM who reported condomless anal sex with either HIV-positive or unknown status partners.
- This same review also reports that serosorting when compared to no condomless anal sex (consistent condom use during anal sex or no anal sex) has an increased risk of HIV acquisition (RR=1.80).
- Estimates are based on longitudinal cohort studies because no RCTs exist. No publications report effectiveness based on an objective measure of serosorting; instead only subjective measures (self-reported behaviors or intentions to serosort) are available.

Serosorting for HIV-Negative Persons

- Given no direct empirical evidence at this time for HIV-negative heterosexual men and women, the estimate for MSM is the best estimate until more direct evidence is available.
- Serosorting, which is a known HIV-negative person having condomless sex only with a known HIV-negative partner, is theoretically 100% effective. The practice of serosorting, however, is less effective because it is difficult for both participants to know with certainty each other's HIV serostatus.

Source:

- Kennedy CE, Bernard LJ, Muessig KE, et al. Serosorting and HIV/STI infection among HIV-negative MSM and transgender people: A systematic review and meta-analysis to inform WHO guidelines. J STD 2013; <http://dx.doi.org/10.1155/2013/583627>

Circumcision of Adult Males

Population	Effectiveness Estimate	Source	Interpretation
MSM Insertive Anal Sex	Inconclusive	Wiysonge, 2011; Sanchez, 2011;	When compared to condomless anal sex with either HIV-positive or unknown status partners, HIV-negative MSM who self-report serosorting reduce their risk of HIV acquisition by 54%. When compared to no condomless anal sex, serosorting results in increased risk of acquiring HIV.
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 partner) 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	Wiysonge, 2011; Schneider, 2012	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.

Circumcision of Adult Males

- 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 at this time, and an updated meta-analysis is needed.

Source:

- Baeten JM, Donnell D, Kapiga SH, et al. Male circumcision and risk of male-to-female HIV-1 transmission: a multinational prospective study in African HIV-1-serodiscordant couples. *AIDS* 2010;24(5):737-44.
- Doerner R, McKeown E, Nelson S, Anderson J, Low N, Elford J. Circumcision and HIV infection among men who have sex with men in Britain: The insertive sexual role. *Archives of sexual behavior*. 2013; 42:1319–1326.
- Sanchez J, Sal YRVG, Hughes JP, et al. Male circumcision and risk of HIV acquisition among MSM. *AIDS* 2011;25:519-23.
- Schneider JA, Michaels S, Gandham SR, et al. A protective effect of circumcision among receptive male sex partners of Indian men who have sex with men. *AIDS and Behav* 2012;16:(2)350-9.
- Siegfried N, Muller M, Deeks JJ, Volmink J. Male circumcision for prevention of heterosexual acquisition of HIV in men (Review). *Cochrane database of systematic reviews*. 2009(2):CD003362.
- Wawer MJ, Makumbi F, Kigozi G, et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomized controlled trial. *Lancet* 2009;374(9685):229-37.
- Weiss HA, Hankins CA, Dickson K. Male circumcision and risk of HIV infection in women: a systematic review and meta-analysis. *Lancet Infect Dis* 2009;9:669–77.
- Wiysonge CS, Kongnyuy EJ, Shey M, et al. Male circumcision for prevention of homosexual acquisition of HIV in men. *Cochrane database of systematic reviews*. 2011(6):CD007496.

Principles for Selecting Estimates

Given different states of the science for the different prevention strategies reviewed, with a range of study designs (e.g., RCT, observational) and measurement methods used (e.g., self-report, blood levels of drug) in the literature, decision rules were made to be applied across strategies in an effort to select effectiveness estimates that were most closely aligned with each other and that most accurately represented effectiveness if the prevention strategy was actually used. More detailed principles are listed below, and the rationale for each specific estimate that was chosen is provided within the tables.

The choice of estimate was prioritized based on the following criteria:

- Only evidence based on peer-reviewed published reports was considered. Unpublished data, including conference abstracts, were not considered to be reliable because results may change as more data become available and data are re-analyzed or methods adjusted based on peer-review feedback. Additionally, the amount of information available for unpublished studies does not allow us to adequately assess methods and quality of data and analysis.
- Only evidence regarding HIV transmission (e.g., HIV outcomes) was considered. Data for non-HIV outcomes (e.g., pregnancy prevention, STD prevention) were considered not to be good proxies for HIV transmission because modeling or other methods that require complex assumptions would be required to equate proxies with HIV transmission rates and introduce additional uncertainty.
- For the consensus estimates, a hierarchy was established for prioritizing the type of estimate to select.
- The greatest priority was given to estimates based on “verified use” of the strategy or interventions that were based on the most objective measure available for determining “verified use” (not selecting highest or optimal use but instead selecting based on any evidence of actual use).
- If an objective measure for “verified use” was not available, then we chose the best subjective measure available (e.g., self-report) and prioritized the highest level of use reported based on subjective measure (e.g., consistent use or always using) recognizing that self-report may overestimate actual use.
- If no analysis based on actual or level of use was available, then the mITT/ITT comparison of “assigned” versus “not assigned” was selected.
- An estimate from a published meta-analysis was used if available and relevant for the strategy/risk factor in question; otherwise the most appropriate estimate from an RCT or observational study was used.

Acronyms

ART	Anti-Retroviral Therapy	MSM	Men Who Have Sex with Men
BTS	Bangkok Tenofovir Study	OLE	Open-Label Extension
DOT	Directly Observed Therapy	PrEP	Pre-Exposure Prophylaxis
TDF/FTC	Drug combination of Tenofovir Disoproxil Fumarate and Emtricitabine	PBMC	Peripheral Blood Mononuclear Cells
FTC	Emtricitabine	PWID	Persons Who Inject Drugs
HPTN	HIV Prevention Trials Network	RCT	Randomized Controlled Trial
FTC-TP	Emtricitabine Triphosphate (active intracellular metabolite of FTC)	STD	Sexually Transmitted Disease
iPREX	Derived from the Spanish "Iniciativa Profilaxis Pre-Exposicion" meaning "PrEP initiative"	TDF	Tenofovir Disoproxil Fumarate
ITT	Intention To Treat	TFV	Tenofovir
mITT	Modified Intention-to-Treat	TFV-DP	Tenofovir Diphosphate (active intracellular metabolite of TFV)