Factors Increasing the Risk of Acquiring or Transmitting HIV

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The following tables provide estimates for key risk factors that increase risk of acquiring or transmitting HIV as identified in the published scientific literature.

Ulcerative STD Infection of HIV-Negative Persons

Population	HIV Risk Estimate	Source	Interpretation
Heterosexual Men and Women	2.65	Hughes 2012	Having an STD more than doubles the risk of an HIV-negative heterosexual person of acquiring HIV during sex with an HIV-positive heterosexual partner.
MSM	2.65	Hughes 2012	There are no empirical data providing a direct estimate for MSM. Biological and epidemiological theories provide indirect evidence that ulcerative STD infection has similar effects on HIV risk in MSM.

Strengths and Limitations of Risk Estimates:

- Hughes, 2012 is a longitudinal cohort study of 3,297 discordant heterosexual African couples, with 86 confirmed linked HIV transmissions. This risk estimate for ulcerative STDs is specific to genital ulcer disease among HIV-negative partners, where genital ulcer disease includes genital herpes (due to HSV-1 or HSV-2), syphilis, and chancroid.
- The evidence supports an increased risk of HIV acquisition when the uninfected partner has an STD. It is unclear, however, what the most appropriate estimates are for each population, behavior, and type of STD given the observational nature of these kinds of studies. Several studies have found that ulcerative STDs may confer higher risk (e.g., risk ratio ranges from 2.2 to 11.3) than non-ulcerative, inflammatory STDs (e.g. risk ratio ranges from 3 to 4) (Fleming, 1999; Galvin, 2004; Berman, 2006). However, an updated systematic review of the published literature is needed for more accurate risk estimates by population, behavior, and type of STD.
- Although no direct empirical evidence has been identified for MSM at this time, it is biologically and epidemiologically plausible for STDs to also increase the risk of HIV acquisition among HIV-negative MSM. The estimate for heterosexual men and women is the best proxy estimate for MSM until more direct evidence is available.

Source:

- Hughes JP, Baeten JM, Lingappa JR, et al. Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples. J Inf Dis 2012;205(3):358-65.
- Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Trans Infect 1999; 75(1):3–17.
- Galvin SR & Cohen MS. The role of sexually transmitted diseases in HIV transmission. Nature Reviews: Microbiology 2004;2(1):33-42.
- Berman SM & Cohen MS. STD treatment: How can it improve HIV prevention in the South? Sex Trans Dis 2006;33:S50-S57.

Ulcerative STD Infection of HIV-Positive Persons

Population	HIV Risk Estimate	Source	Interpretation
Heterosexual Men and Women	2.58	Gray 2001	Having an STD more than doubles the risk of an HIV-positive heterosexual man or women to transmit HIV during sex to his/her uninfected heterosexual partner.
MSM	2.58	Gray 2001	There are no empirical data providing a direct estimate for MSM. Biological and epidemiological theories provide indirect evidence that ulcerative STD infection has similar effects on HIV risk among MSM.

Strengths and Limitations of Risk Estimates:

- Gray, 2001 is a longitudinal cohort study of 174 monogamous discordant heterosexual couples, with 38 HIV transmissions to uninfected partners, from a larger Rakai (Uganda) community-randomized trial of STD control for AIDS prevention. This risk estimate for ulcerative STDs is specific to the presence of genital ulceration.
- The evidence suggests an increased risk of HIV transmission due to the HIV-positive partner having an STD. It is unclear, however, what the most appropriate estimates are for each population, behavior, and type of STD given the observational nature of these kinds of studies. Indirect evidence of STDs increasing the infectiousness of HIV exist. Ulcerative STDs generally increase HIV shedding in the genital tract and inflammatory STDs increase the concentration of HIV in the urethra, semen, and cervical fluid (Galvin, 2004). An updated systematic review of the published literature is needed for more accurate risk estimates by population, behavior, and type of STD.
- Although no direct empirical evidence has been identified for MSM at this time, it is biologically and epidemiologically plausible for STDs to also increase the risk of HIV transmission among HIV-positive MSM. The estimate for heterosexual men and women is the best proxy estimate for MSM until more direct evidence is available.

Source:

- Galvin SR & Cohen MS. The role of sexually transmitted diseases in HIV transmission. Nature Reviews: Microbiology 2004;2(1):33-42.
- Gray RH, Wawer MJ, Brookmeyer R, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. Lancet 2001;357:1149-53.

Acute HIV Infection

Population	HIV Risk Estimate	Source	Interpretation
Heterosexual Men and Women	7.25	Wawer, 2015	The risk of HIV transmission during acute infection is about 7.25 times the risk during the middle stage of HIV disease among heterosexual men and women.
MSM	7.25	Wawer, 2015	There are no empirical data providing a direct estimate for MSM. It is biologically plausible for acute infection to have a similar effect on HIV transmission among MSM.

Strengths and Limitations of Risk Estimates:

- Wawer, 2015 estimates the increased risk of HIV transmission due to acute HIV infection from a retrospective sub-sample of 235 monogamous, HIV-discordant heterosexual couples with follow up time from a larger Rakai (Uganda) community-randomized trial of STD control for AIDS prevention. This study looked at early-stage infection (defined as up to 5 months after seroconversion, a 2.5-month midpoint), established infection or "middle" stage of infection (>6 months after seroconversion), and late-stage infection (6 to 25 months before death).
- No other published study of empirical data on increased risk of HIV transmission during acute infection exists.

Acute HIV Infection

- Acute HIV infection is clinically defined as the time between viral infection and development of detectable antibodies against HIV-1. During this time, concentrations of HIV in blood and semen are highest and transmission risk is therefore greatest; this period typically last a few weeks (Cohen, 2005; Pilcher, 2004). Pilcher, 2007 estimated that viral load reaches its peak at 17 days after seroconversion in blood and around 4 weeks after seroconversion in semen. A modeling paper (Pilcher, 2004) estimated the probability of heterosexual transmission of HIV during acute infection is ~8 to10 times the probability during later stage of infection, where the viral load peak in semen was modeled at about day 20 after infection.
- Although no direct empirical evidence has been identified for MSM at this time, acute infection is likely to also be associated with increased HIV transmission risk among MSM. The estimate for heterosexual men and women is the best proxy estimate for MSM until more direct evidence is available.

Source:

- Cohen MS & Pilcher CD. Amplified HIV transmission and new approaches to HIV prevention. J Infect Dis 2005;191:1391-3.
- Pilcher CD, Tien HC, Eron JJ Jr, et al. Quest Study, Duke-UNC-Emory Acute HIV Consortium. Brief but efficient: acute HIV infection and the sexual transmission of HIV. J Infect Dis 2004; 189(10):1785–92.
- Pilcher CD, Joaki G, Hoffman IF, et al. Amplified transmission of HIV-1: comparison of HIV-1 concentrations in semen and blood during acute and chronic infection. AIDS 2007;21(13):1723-30.
- Wawer MJ, Gray RH, Sewankambo NK, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis 2005;191:1403-9.

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)