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Author Manuscript

AIDS. Author manuscript; available in PMC 2013 February 28.

Published in final edited form as:

AIDS. 2012 November 28; 26(18): 2267–2273. doi:10.1097/QAD.0b013e328355713d.

Does ART prevent HIV transmission among MSM?

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Keywords

HIV; sexually transmitted diseases; Highly Active Antiretroviral Therapy; men who have sex with men; MSM; treatment as prevention

One randomized controlled trial [1] and numerous observational studies [2–6] provide strong evidence that antiretroviral therapy (ART) can reduce or prevent the sexual transmission of HIV-1 within serodiscordant heterosexual couples. A key question remains: does ART reduce HIV transmission among men who have sex with men (MSM), where the primary mode of transmission is via condomless anal intercourse? New WHO guidelines for earlier initiation of ART among serodiscordant couples were released in April 2012 [7] and some countries, such as China, have already embraced treatment as prevention (TasP) for heterosexual couples. In the process of reevaluating current ART guidelines, we anticipate that for some countries, the issue of whether to recommend TasP for MSM will be under debate. The evidence supporting TasP for MSM is promising, but major gaps in our knowledge remain. To identify priority areas for research, in this paper we synthesize evidence of (a) the biological plausibility that virally suppressive ART reduces HIV infectiousness via anal intercourse and (b) epidemiologic evidence of whether ART has played a role in attenuating HIV incidence among MSM.

Some biological and epidemiological evidence suggests that ART for preventing transmission via anal intercourse may have more limited efficacy than via vaginal intercourse. Without ART, the probability of HIV transmission is estimated as 1 infection for every 20 to 300 acts of condomless anal intercourse, as compared to 1 in 200 to 1 in 2,000 for penile-vaginal exposure [8–13]. Additionally, a higher median number of HIV

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AUTHOR CONTRIBUTIONS: Myron S. Cohen, Ying-Ru Lo and David Burns conceived of the primary idea for this article. Kathryn E. Muessig and M. Kumi Smith completed the literature review, data analysis, and crafted the first draft. All authors identified additional relevant literature and studies and contributed substantively throughout the subsequent development of the manuscript.

Conflicts of Interest: We have no conflicts of interests to declare.

variants are transmitted in MSM couples as compared to heterosexual couples [14–16] potentially posing greater challenges for drug resistance [17].

The pharmacology of antiretroviral (ARV) agents also differs between the urogenital tract (vaginal intercourse) and the gastrointestinal (GI) tract (anal intercourse). ARVs can reduce—but not eliminate—the amount of HIV recovered from the genital tract [18–20] and GI tract [21–23]. Higher levels of HIV DNA and RNA have been found in the GI tract (duodenum, ileum, ascending colon, and rectum) as compared to the blood [24,25] and semen [23] irrespective of ART use, although these levels may be positively correlated [21,26,27]. Some ARVs such as tenofovir, tenofovir diphosphate, and maraviroc have been shown to penetrate rectal tissue with greater efficiency than blood or seminal plasma [28,29] but the durability of this penetration and required levels for prevention are not yet established. Furthermore, paired blood and rectal biopsy samples tested for resistance to ARVs have shown different mutation profiles in the virus recovered from each site [30]. This would suggest that replication can persist in the rectum even if a patient appears otherwise virally suppressed. While the results of HPTN 052 demonstrated the capacity of ARVs to markedly reduce the risk of penile-vaginal transmission despite similar biological and pharmacokinetic uncertainties, we cannot be certain that this will be the case for anal intercourse given the much higher transmission probability in the absence of ART.

In addition, we do not know the extent to which sexual risk behaviors might offset the potential prevention benefits of ART. Increases in bacterial sexually transmitted infections (STIs) are compelling evidence of ongoing high-risk behaviors among MSM [31–35] and these co-infections amplify HIV transmission [36–41]. Globally, there is evidence of increases in STIs among MSM including rectal gonorrhea [31,33,34,42], urethral gonorrhea [43], and syphilis [33,34,44–46]. Other behaviors such as serosorting (limiting sexual partners to those thought to be the same HIV serostatus) [47] and rectal douching [48] also alter the risk of HIV transmission among MSM.

We do not know the extent to which sexual risk behaviors among MSM are changing due to the increasing availability of ART. Positive beliefs about the protective ability of ART (treatment optimism) [49–51] and being on ART itself [51–54], irrespective of actual viral suppression, have been associated with increased condomless anal intercourse. A meta-analytic review of studies published between 1996 and 2003 found a non-significant association between taking ART and increased condomless anal intercourse among MSM (OR 1.38, 95% CI, 0.62–3.07); however, the *belief* that being on ART protects against transmission was associated with an almost two-fold increase in condomless anal intercourse (OR 1.84, 95% CI, 1.53–2.20) [55]. The number of studies on these impacts of ART on behavior has more than doubled since this review and an updated meta-analysis has been commissioned by the WHO with results anticipated in 2012. Changes in transmission risk behaviors are also being assessed as a secondary outcome in the randomized controlled START trial (Strategic Timing of Antiretroviral Treatment), a study among treatment naïve HIV-positive persons recruited from over 200 sites worldwide comparing initiation of ART at CD4 >500 cells/mm³ to initiation at <350 cells/mm³ [56].

Observational evidence to support the idea that ART reduces HIV transmission among MSM is mixed. Surveillance data and longitudinal cohort studies suggest that HIV incidence among MSM has fluctuated, in some cases increasing, in spite of widespread availability of ART [42–44,57–63]. To estimate how ART has affected HIV transmission among MSM, some studies have calculated a per-partner or per-act transmission risk and compared these rates pre and post-HAART [13,64]. For example, the Health in Men Australian cohort (2001–2007) used behavioral risk data and annual HIV incident infections to estimate per-contact HIV transmission risk. In Sydney—with overall stable incidence of HIV and

increasing uptake of ART—the authors conclude that the overall per-contact risk of transmission has not changed in spite of increased ART coverage and more effective regimens [13].

Other studies have combined HIV surveillance and/or cohort data from communities with high ART coverage to compare trends in ART use and transmission (Table 1) [43,57,65–67]. For instance, one older study in San Francisco (1995–1999) using community surveillance and clinic data concluded that any decrease in HIV infectivity gained by widespread use of ART may have been offset by increases in condomless anal intercourse and/or STIs [57]. A more recent San Francisco study using HIV surveillance data (2004–2008) described a significant correlation between decreased annual mean community viral load (CVL, an aggregate measure of the total known viral load among a particular population) and decreases in newly diagnosed cases of HIV; however the association with HIV incidence measured with the BED assay was not statistically significant [65]. A similar study using surveillance data (2004–2008) from Washington DC found a decrease in mean CVL and an increase in the proportion of known HIV-positive persons virally suppressed, but a statistically significant increase in newly diagnosed cases of HIV [67]. In these data, MSM had the highest proportion of individuals with undetectable viral load compared with other risk groups; however, black MSM were less likely to have undetectable viral load compared to white MSM [67]. A study conducted in Vancouver reported similar associations between decreases in CVL and new HIV diagnoses [43]; however, the role of injection drug use in driving these trends is unclear [68,69] and government surveillance reports show fluctuations in new HIV diagnoses among MSM in British Columbia with no overall change compared to 2003 [63]. Among Vancouver MSM specifically, HIV prevalence is steady and slightly rising, likely reflecting increases in survival as well as new diagnoses [70]. In contrast, a report from Denmark using national HIV surveillance and clinic data showed that rising proportions of HIV-infected MSM on suppressive treatment were correlated with stable rates of new HIV diagnoses in spite of increasing proportions of MSM reporting condomless anal intercourse [66].

Due to their reliance on aggregate data and on new diagnosis reports rather than on new incident infections, these ecological studies are unable to draw causal inferences about the individual-level processes driving transmission. Their mixed results suggest that characteristics of specific geographic epidemics as well as behavioral patterns likely contribute to the population-level impact of ART on HIV transmission among MSM.

The majority of data available for the impact of ART among MSM are from developed countries in North America, Western Europe and Australia. As a result, what we know about ART's effect on HIV transmission comes from a small subset of MSM, limiting the generalizability of these results within other social, cultural and epidemic settings. While recognizing the barriers of stigma, discrimination and legal repercussions, it is clear that more research is needed in this regard among MSM populations in South America, Africa, Central Europe and Asia. In order to inform optimal ART recommendations, we also need to better understand the social and cultural environments in which new sexual behavioral trends are evolving.

Going forward, there are great opportunities to further our understanding of the individual- and population-level transmission dynamics of HIV and ART among MSM. For example, applying the tools of phylogenetic analysis, researchers may be able to identify the most likely source of an individual's HIV infection, describe the size and distribution of clusters of new cases in the population, and assess the relative contributions to new transmissions by persons at various stages of infection. For example, a phylogenetic transmission cluster analysis with matched epidemiological and clinical data among MSM in the UK found that

those who are recently infected, are untreated, and have a concomitant STI may be contributing disproportionately to secondary transmission [71]. While an individual-level randomized clinical trial to directly evaluate the efficacy of ART for prevention in MSM may not be feasible or ethical (Cohen et al., in press CLIN Trials), well-designed observational studies of seroconcordant and discordant couples—as reported with heterosexual subjects [3,4]—allow researchers to measure both the risk of acquiring as well as transmitting HIV. Two such studies involving MSM couples are currently enrolling or planned in Europe and Australia [72,73].

The benefits of TasP for MSM are highly plausible, but not certain. The results of HPTN 052 have generated great urgency for maximizing the prevention benefit of ART. The impact of ART on HIV transmission via anal intercourse requires further evaluation, however, given the inconclusive observational data currently available for MSM and the challenging biological and behavioral risk factors that may be present. If TasP becomes part of prevention policy for MSM, implementation of early treatment in combination with other prevention methods including promotion of condom use to prevent other STIs, expanded STI treatment, structural and behavioral interventions, and earlier diagnosis will be critical.

Acknowledgments

Source of Funding: Kathryn E. Muessig and M. Kumi Smith are supported by an NIH institutional training grant (5T32AI007001-35). Kimberly A. Powers is supported by the NIH (R01 AI083059, R01 DA025885). Myron S. Cohen is supported by the Center for AIDS Research (CFAR) and the NIH HIV Prevention Trials Network (HPTN-052). The views expressed herein do not reflect the official stance of any funding agencies.

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Table 1

Ecological studies of ART and new diagnoses of HIV.

Citation Location	Data Source	Estimation of Suppressive ART	Estimation of HIV Incidence	Interpretation of Results
Castel et al. (2012); Washington DC; USA [67]	District health department HIV/AIDS case surveillance system	Annual mean and total of most recent viral load test, proportion of virally suppressed	Number of new HIV diagnoses as reported through the District HIV/AIDS surveillance system	No association was found between trends in the mean CVL and newly diagnosed HIV/AIDS cases. MSM had a higher proportion of virally suppressed cases
Das M et al. (2010); San Francisco, USA [65]	City health department HIV/AIDS case surveillance system	Annual measures of mean and total CVL	Newly reported HIV diagnoses and HIV incidence estimated using the STARHS method	Reductions in CVL were significantly associated with fewer annual HIV diagnoses, though not with estimated HIV incidence using the STARHS method
Katz M et al. (2002); San Francisco, USA [57]	City health department AIDS registry, stored samples from VCT and STD clinics, and behavioral surveys of MSM	Numbers of HIV infected individuals receiving HAART, reported sexual risk behaviors	Trends in HIV incidence as determined by STARHS method	Any decrease in per contact risk of HIV transmission due to HAART use appears to have been countered or overwhelmed by increases UAI
Montaner JSG et al. (2010); British Columbia, Canada [43]	Provincial disease surveillance database; provincial treatment center database	Numbers of HIV infected individuals receiving HAART	New HIV positive tests per 100 population.	Rising numbers of individuals receiving HAART and rising proportions of treated individuals with VL < 500 copies/mL were strongly associated with decreased number of HIV diagnoses per year
Cowan S et al. (2010); Denmark (national) [66]	National HIV surveillance data and behavioral studies of MSM	Estimated prevalence of HIV-positive MSM receiving HAART, sexual risk behaviors	Annual numbers of MSM notified as HIV infected via serologic testing, used as proxy for incidence	Increasing numbers of treated MSM coincides with stable numbers of newly notified HIV positive MSM and increasing STI diagnoses, suggesting reduced infectiousness among HIV infected MSM