WHO and U.S. NIH Working Group Meeting on
Treatment for HIV Prevention among MSM:
What Additional Evidence is Required?
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CONCLUSIONS

Introduction
Recent results from the HPTN 052 trial have clearly demonstrated the effectiveness of antiretroviral therapy (ART) as prevention in serodiscordant couples. HPTN 052 results were announced in May 2011, four years ahead of schedule, after an efficacy rate of 96% was shown for early ART initiation to prevent sexual transmission of HIV in a randomized controlled clinical trial of 1763 serodiscordant couples at 13 sites in nine countries (Cohen M et al 2011). This confirmed similar results from multiple observational studies (Anglemyer A et al 2011). However the fact that only 37 of the couples in the HPTN 052 trial were MSM raises the question about the external validity of the results in MSM, transgender persons, and others who engage in anal intercourse. New HIV diagnoses are emerging or continuing to rise in these populations (WHO 2008).

This consultation, convened by WHO and the U.S. National Institutes of Health (NIH) brought together key investigators, selected public health experts, HIV programme managers and civil society representatives to assess whether additional evidence may be required before earlier initiation of ART for HIV prevention among MSM, transgender individuals and women who engage in anal sex can be recommended.

Evidence Reviewed
Although it is believed that ART will reduce the risk of penile-rectal transmission of HIV, the magnitude of this effect may differ from that observed for penile-vaginal transmission. Multiple studies indicate that the per-act rate of transmission associated with anal intercourse is an order of magnitude greater than the rate associated with penile-vaginal intercourse (Baggaley R et al 2010, Vittinghoff E et al 1999). On the other hand, the levels of some antiretrovirals have been found to be up to 10 to 100 times greater in rectal than cervicovaginal tissue (Smith K et al 2011). Shedding of HIV viral particles has been repeatedly detected in the semen, rectum and cervicovaginal secretions, even when viral load (VL) is undetectable in the plasma, but it is unclear whether this virus is capable of transmission (Smith K et al 2011).

The limited data currently available give a somewhat mixed picture regarding the impact of ART on HIV transmission during anal intercourse. Ecologic data from San Francisco, where 86% of all new HIV infections between 2004 and 2008 were among MSM, are supportive. The number of newly diagnosed HIV cases steadily declined at the same time that a progressive reduction in the mean 'community' VL was observed (Das-Douglas M et al 2010).

On the other hand, Jin et al. found that the per-contact probability of transmission among a cohort of men followed in Sydney from 2001 to 2007 was essentially unchanged from the early 1990s, prior to ART (Jin F et al 2010; Vittinghoff E et al 1999). Moreover, cohort data from the Netherlands suggest that between 2000 and 2008 new infections among MSM increased from approximately 382 to 840 annually (van Sighem Al et al 2011). These investigators did not use 'community' VL but 'community' infectiousness, taking into account the relationship between VL and infectiousness observed in discordant couples (Hollingsworth TD et al 2008). They concluded, as have others, that a majority of new infections resulted from persons unaware of their HIV positive status (Marks G et al 2005; Fisher M et al 2010).

Finally, a study combining epidemiologic, phylogenetic, and clinical cohort data collected between 2000-2006 at a sexual health clinic in southern England, found that ongoing transmission among MSM was associated with higher VL, younger
age, recent HIV infection, and recent sexually transmitted infection (STI) diagnosis (Fisher M et al 2010). Effective ART was highly associated with lower VL and decreased risk of transmission. A limitation of this analysis was that findings were based on only 41 of the 159 incident infections that occurred during this time period; the other incident cases’ viral sequences could not be linked to a single most likely transmission source, frequently because the index case was undiagnosed or was from a different region and no sequence data were available.

**Ongoing Studies**

Ongoing and planned observational studies may be able to provide valid estimates of the magnitude of the prevention effect of ART in MSM. The PARTNER study is enrolling HIV serodiscordant persons who have had condomless penetrative anal or vaginal intercourse together in the past month and who expect to have sex together in the coming months. The index partner must be on ART and both members of the partnership must agree to 4-6 monthly visits for testing and assessment of HIV risk behaviors. In cases in which the HIV-negative person becomes infected, anonymized data will be analyzed to determine whether the transmission was linked. Thus far, approximately one-third of the couples enrolled at sites throughout Europe are MSM.

The “Opposites Attract” study will enroll serodiscordant dyads comprised of men in an ongoing sexual relationship that involves anal intercourse. Recruitment will focus on dyads at early stages in their relationships; those that break up will be replaced. Study visits will revolve around the routine clinical management schedule of the HIV positive partner, which must include at least two clinic visits per year at which a viral load measurement is performed. Visits of the HIV negative partner will be linked to those of his partner.

In addition, demonstration projects such as a proposed Test-and-Treat study among MSM in Thailand to assess the acceptability, feasibility and adherence to HIV testing and re-testing and immediate ART may provide important information for programme implementation. Given the very high HIV incidence among MSM in Kenya, up to 20.7 per 100 person-years among male sex workers (who report sex with men only), it has been proposed that both ART as prevention and pre-exposure prophylaxis (PrEP) be offered as part of a high-impact combination prevention package (Sanders E et al 2011).

**Discussion and Main Consensus Points**

There is reason to believe that early initiation of ART for HIV prevention will benefit MSM, transgender women, and others who have anal intercourse, although the magnitude of the effect may be different from that observed in serodiscordant heterosexual couples. It was felt that an additional individual randomized clinical trial in MSM was not warranted. However, it was recognized that additional evidence is required to inform scale up. This is necessary, first because the HPTN 052 trial and other serodiscordant couples studies lacked participants in early stages of infection when transmissibility is highest (Hollingsworth T et al, 2008). Second, exposure to other potentially infectious partners may be more common given that frequency of sex outside primary relationships may be greater in many MSM and transgender communities (van de Ven P et al 1998, Guadamuz T et al 2011). This may be because many MSM and transgender people do or cannot (due to stigma or legal barriers) have steady partnerships or due to involvement in sex work. Offering earlier HIV testing and ART to all sexually active individuals might be necessary to overcome these realities.

Hypothetical limitations to the prevention benefit of ART in MSM that will be examined in the new and ongoing studies include a potential reduction in the use of condoms and other increased risk taking (also called risk compensation), and a possible increase in rectal STIs. Other research may also need to consider the possible impact of anorectal inflammation and micro- (and macro-) trauma.

Factors that likely contributed to the success of the HPTN 052 trial were 3-monthly visits that included VL measurements, adherence reminders that were intensified when HIV RNA was detectable, and promotion of condom use. Only a small number of participants required second line regimens, which were quickly provided. These measures may be achievable in resource-rich settings, but may not be elsewhere unless additional resources are made available.

Participants in the consultation also noted that motivation will be a key element in the effectiveness of ART as prevention among MSM, just as it is for all prevention efforts. One factor that likely contributed to the success of HPTN 052 trial was the index participant’s desire to not transmit to their partner (so called “adherence altruism”).

Among MSM, frequent seroadaptive behaviours by the HIV-positive partner in some settings suggests similar desire and altruism (Jin F et al 2009), but it is
known that these behaviours are less protective than condom use (WHO 2011). The emergence of sexual sub-cultures around drug use to increase sexual pleasure and intentional condomless sex (Jin F et al 2009) are emerging factors that may also affect the effectiveness of early ART among MSM and transgender individuals. Ongoing sociocultural research on evolving sexual practices across the globe and their implications for new prevention strategies is warranted.

**Next Steps and Challenges**

Brazil, China, Kenya and the United States have announced guidance on early ART among serodiscordant couples, potentially including MSM. Early experience from implementing those programmes will provide important information, e.g. whether viral load suppression is sustained when implementing ART as prevention in the field.

Important challenges remain, such as low HIV testing rates and infrequent disclosure of positive status to partners (Guadamuz T et al 2011), and, especially, the stigma, discrimination, and violence against MSM and transgender people that continue to severely restrict or completely block access to prevention, HIV testing, care, treatment and support (WHO 2011). These socio-structural factors undermine the resilience of sexual partnerships and harm the overall sexual health of MSM and transgender people. Unless and until structural interventions are applied to address these barriers ART as prevention for these communities will remain elusive.

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**These conclusions do not necessarily represent the decisions or policies of the World Health Organization.**

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**References**


