Is expanded HIV treatment preventing new infections? Impact of antiretroviral therapy on sexual risk behaviors in the developing world

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There have been dramatic increases in access to antiretroviral therapy (ART) across the developing world, and growing public health attention has focused on the possibility of utilizing ART as a means of slowing the global HIV epidemic. The preventive impact of ART will likely depend on decreasing levels of sexual risk behaviors following treatment initiation. The current review study examines the impact of wider access to ART on sexual risk behaviors among HIV-infected individuals in the developing world. The observational studies to date demonstrate that ART is associated with a significant reduction in unprotected sex following treatment initiation. Although data on the impact of ART on possible risk compensation are rapidly expanding across the developing world, more evidence is still needed before we can safely conclude expanded treatment will result in durable decreases in sexual risk behaviors.

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Introduction

Over the past decade, there has been a dramatic increase in the number of HIV-infected individuals who are receiving antiretroviral therapy (ART) across the developing world [1]. It is currently estimated that of the 15 million individuals living with HIV in these regions, 5.2 million have access to ART [2]. However, the sobering reality is that the global epidemic continues to grow with over 2.5 million new infections each year [3], and for each individual receiving treatment, an estimated four additional individuals require treatment [2]. Beyond the individual clinical benefits accrued from treatment [4,5], ART has dramatically decreased mother-to-child HIV transmission (MTCT) [6], and recent evidence, most notably from the HIV Prevention Trials Network (HPTN052), suggests that treatment can decrease the sexual transmission of HIV within serodiscordant couples by suppressing viral levels in the genital tract in the HIV-infected partner and by decreasing the risk of transmission by 96% [7–9]. Because behavioral interventions alone have not consistently resulted in durable declines in HIV incidence, and it will be many more years before an efficacious HIV prevention vaccine is available [10], increasing attention has focused on the impact of ART in slowing the global epidemic.

Current 'test and treat' hypotheses regarding HIV prevention assume that all individuals in a given population are regularly tested for HIV and those found to be infected

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are promptly linked to treatment and care, regardless of immunological status [11], and that sexual risk behaviors among those found to be HIV-infected do not increase over time [12]. Hence, the premise that ART may decrease HIV transmission rests on the assumption that treatment decreases infectivity, but does not increase sexual risk behaviors that potentiate the continued spread of the epidemic [13]. Based on studies in the developed world, individuals who learn that they are HIV-infected tend to decrease their sexual risk behaviors [14]. However, most of the developed world cohorts were conducted among high-risk populations [15–17]. The dynamics of sexual transmission in settings where HIV spread is predominantly through heterosexual contact have not been studied in as much detail [18]. It is plausible that the impact of ART on sexual risk behaviors may vary in the developing world due to difficulties in accessing and maintaining long-term clinical care, differences in cultural and gender norms, and family planning.

The impact of growing access to ART on sexual risk behaviors remains an ongoing debate. It is possible that with increasing access to ART, HIV-infected individuals may be more likely to engage in sexual risk behaviors referred to as 'behavioral disinhibition' or 'risk compensation' sparked by decreases in the perceived risk of HIV transmission, but increased access to care and ART with multiple HIV medical encounters could also encourage declines in sexual risk behaviors [19–23]. The current review study examines the impact of wider access to ART on sexual risk behaviors among HIV-infected individuals in the developing world. We first summarize recent observational data showing consistent decreases in unprotected sex following ART initiation in the developing world and then assess implications of these findings and key mediating factors.

Assessing the relationship between antiretroviral therapy use and sexual risk behaviors

The sexual transmission of HIV involves a complex interplay of both biological and behavioral factors (Fig. 1) [24]. The sexual transmission of HIV in the absence of ART remains a low probability but high consequence event, occurring in less than one out of every 100 contacts on average [25]. ART itself reduces the risk of HIV transmission through its effect of lowering both plasma and genital tract viral load [26–28]. However, potential HIV prevention modalities, including ART, may inhibit the uptake of safer behaviors by reducing individuals' perceptions of their risk of infection [20]. Though condom use can be associated with over a 90% reduction in HIV risk, they must be used consistently and correctly to be efficacious [20,22]. The risk of HIV transmission depends on who one has sex with, such as with a primary partner in a steady monogamous relationship compared to multiple partners over a short period of time, and of course, partner HIV status.

Early mathematical models suggested that even modest increases in sexual risk behaviors resulting from the increased use of ART could offset the potential protective benefits of wider treatment access [29–33]. More recent models promoting 'test and treat' strategies also assume that sexual risk behaviors do not increase with ART coverage [34]. However, some recent models suggest that a test and treat strategy in the United States may be beneficial in terms of life expectancy but may have only modest impact on transmission [35]. In the developed world, the early availability of tolerable ART regimens was associated with upswings in sexual risk behaviors among MSM and injecting drug users (IDUs) [36–39].

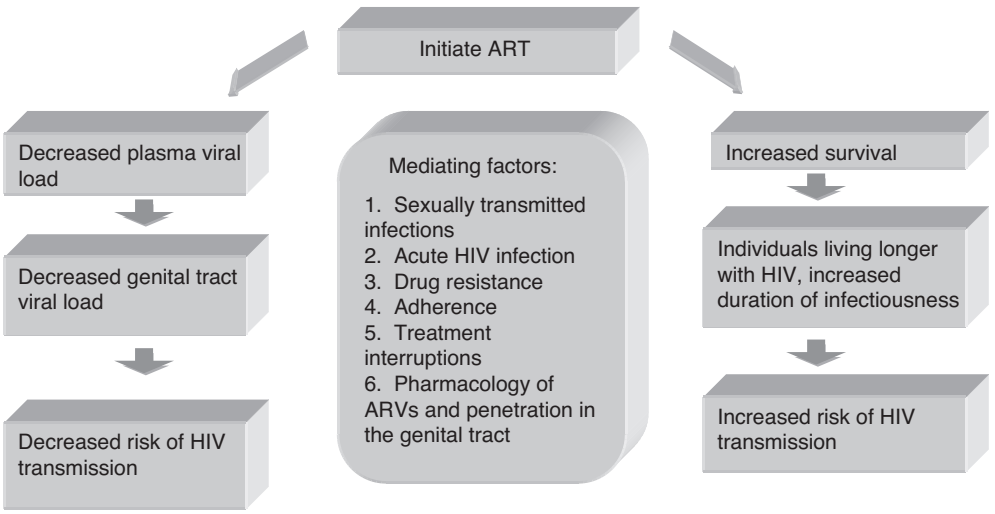

Fig. 1. Biological factors that mediate how antiretroviral therapy alters HIV sexual transmission. ART, antiretroviral therapy. Figure adapted from [24].

Although a meta-analysis assessing the impact of ART on sexual behavior concluded that rates of unprotected sex did not differ between those receiving treatment compared to those who were not, those who perceived that treatment might reduce the risk of HIV transmission had significantly higher levels of sexual risk behaviors [16]. Data on the impact of ART on sexual risk behaviors are gradually emerging from developing world settings. Although most of the early studies were cross-sectional in design, increasingly observational cohorts have assessed changing patterns of sexual risk behaviors before and after ART initiation (Table 1) [40–56].

Cross-sectional studies

Studies conducted in clinic populations of HIV-infected Africans have documented relatively high levels of unprotected sex and multiple sex partnerships prior to access to ART [57,58], as well when waiting to start ART [40], emphasizing the importance of prevention messages before treatment initiation. In the era of expanding access to ART, early cross-sectional studies conducted among samples of men and women enrolled in care and prevention programs in sub-Saharan Africa reported decreased sexual risk behaviors, generally measured as sexual abstinence and unprotected sex over the past 6 months, following treatment initiation [41–44]. These clinic-based studies suggested that a sizeable number of patients reported being sexually abstinent (>50%) at the time of receiving ART [42,43]. In order to fully understand the level of potential risk taking in these populations, these studies only analyzed sexual risk behaviors among those who were not sexually abstinent. Among those who had sex (generally around 50% of all participants), a substantial number reported unprotected sex (>40%) [43–45], suggesting that the potential for HIV transmission may persist among a subset of patients. Some of these early studies were later summarized in a systematic review on the impact of ART on sexual risk behavior [59]. A study conducted among HIV-infected Indians in care documented an association between ART and sexual abstinence, as well as an association between desire for having children and unprotected sex [46,60]. A national survey in the Cameroon found that not being on ART was associated with an over two-fold higher rate of inconsistent condom use [47], which also held for those who reported a partner who was HIV-uninfected or of unknown status [48]. A recent study conducted in South Africa assessed whether sexual risk behaviors differed by self-reported partner HIV status and found that although patients on ART demonstrated consistent decreases in sexual risk behaviors, those patients who reported having a HIV-negative or status unknown partner had similar levels of sexual risk behaviors compared to those with a HIV-positive partner [49].

It should be noted that most of these studies took place within clinic-based samples and hence may not be generalizable to HIV-infected individuals who did not enter care or who did not follow up once enrolled in a treatment program. Additionally, cross-sectional studies are limited by being unable to detect causal and temporal associations between pre and post-ART changes in sexual risk behaviors. These studies were also conducted soon after treatment initiation, and it is possible that the impact of treatment on sexual risk behavior could vary over longer periods of follow-up.

Cohort studies

One of the first longitudinal studies conducted among HIV-infected men and women enrolled in a care program in Uganda noted a 70% reduction in unprotected sex following 6 months of treatment [45]. An important finding was that most unprotected sex (>80%) occurred among married couples. A later study by the same group following individuals for 3 years after ART initiation also found a decrease in unprotected sex, but an increase in not being sexually abstinent [50]. A study conducted among female Kenyan sex-workers showed consistent decreases in unprotected sex, but not multiple sex partners, following access to ART [51]. Among women with more advanced immunosuppression (CD4 cell counts below 200 cells/μl), ART was associated with reductions in both frequency of sex and number of sex partners. A recent study conducted among over 6000 South African men and women in urban and rural primary care programs found robust and sustained reductions in reporting unprotected sex and multiple sex partners following ART initiation, which remained after adjustment for CD4 cell count [52]. Other clinic-based observational studies conducted among HIV-infected individuals in sub-Saharan Africa have also similarly noted a decrease in unprotected sex for up to 12 months after ART initiation compared to pretreatment baseline [53–55,61]. Unlike the previous data, a cohort study from the Ivory Coast showed that unsafe sex increased among those receiving ART 6 months after treatment initiation [56], which the authors speculated could have been linked to the inadequate provision of prevention messages in this treatment program.

Differing results in these settings highlight the complexity of measuring the association between ART use and sexual risk behaviors and variations in study populations and treatment program characteristics. Future studies will need to examine whether early reductions in sexual risk behaviors following ART initiation persist over time, particularly after individuals have fully regained their health and quality of life.

Ecological studies

In addition to ART use decreasing the risk of HIV transmission from already infected individuals, it is possible that wider access to treatment may be associated with changes in sexual behaviors among the population of susceptible and undiagnosed individuals, especially in settings of high HIV prevalence. As at-risk uninfected

Table 1. Observational studies assessing the impact of antiretroviral therapy on sexual risk behaviors in the developing world.

Study, author name	Country	Study period	Study design	Sample size	Outcome measure[a,b]	Adjusted effect size[c,d]	Significant decrease in unprotected sex with ART[e]
Cross-sectional studies							
Moatti *et al.* [43]	Ivory coast	1999–2000	Cross-sectional	711 adults; 164 initiated ART	Unprotected sex	0.52 (0.29–0.93)	Yes
Bateganya *et al.* [44]	Uganda	2003	Cross-sectional	723 adults; 369 initiated ART	Being sexually active; consistent condom use	2.0 (0.3–9.9); 2.82 (1.74–4.60)	Yes
Sarna *et al.* [42]	Kenya	2003–2005	Cross-sectional	322 adults; 179 initiated ART	Unprotected sex with regular partners; associated with not using ART[b]	4.26 (1.90–9.58)	Yes
Dia *et al.* [48]	Cameroon	2006–2007	Cross-sectional; National multicenter study	907 sexually active adults who reported sex with a partner of either HIV-uninfected or unknown status; 691 received ART	Inconsistent condom use associated with not using ART[b]	2.28 (1.64–3.18)	Yes
Marcellin *et al.* [47]	Cameroon	2006–2007	Cross-sectional; National survey	3151 adults; 2458 initiated ART	Inconsistent condom use	0.50 (0.34–0.74)	Yes
Venkatesh *et al.* [46]	India	2008	Cross-sectional	247 men and women; 198 initiated ART	Being sexually active; unprotected sex	0.31 (0.13–0.74); 2.70 (0.48–15.15)	Yes
Kaida *et al.* [41]	Brazil, South Africa, Uganda	2008	Cross-sectional	179 women; 116 initiated ART	Recent sexual intercourse; protected sex	0.76 (0.34–1.72); 3.64 (1.41–9.38)	Yes
Venkatesh *et al.* [49]	South Africa	2009–2010	Cross-sectional	1163 men and women; 182 initiated ART	>2 coital acts in the last 2 weeks; unprotected sex; >1 sex partner	0.53 (0.30–0.93); 0.64 (0.38–1.08); 0.11 (0.01–0.89)	Yes
Cohort studies							
Bunnell *et al.* [45]	Uganda	2003–2004	Cohort; 6 months of follow-up	926 adults who initiated ART; 882 had follow-up	Being sexually active; unprotected sex	1.2 (1.0–1.5); 0.5 (0.3–0.8)	Yes
Wanyama *et al.* [55]	Uganda	2004–2005	Cohort; follow-up at 6 and 12 months	492 patients initiated ART	Being sexually active; condom use at last sex	55.2–70% ($P<0.05$)[d]; 50.6–79.9% ($P<0.05$)[d]	Yes
Luchters *et al.* [54]	Kenya	2003–2004	Cohort; 12 months of follow-up	234 adults; all initiated on ART	Sex in last 12 months[a]; unprotected sex in past year with a partner of either HIV-uninfected or unknown status[a]; unprotected sex at last sex act	1.30 (0.86–1.96); 0.52 (0.32–0.87); 0.16 (0.08–0.32)	Yes
Diabaté *et al.* [56]	Ivory Coast	2005	Cohort; 6 months of follow-up	615 adults; 303 initiated ART	Unprotected sex	1.40 (1.21–1.61)[f]	No
Eisele *et al.* [40]	South Africa	2006–2007	Cohort; 12 months of follow-up	913 adults; 512 initiated ART	Unprotected sex	0.46 ($P=0.0121$)[g]	Yes
McClelland *et al.* [51]	Kenya	1993–2008	Cohort; median >2 years of follow-up post-ART	819 female sex workers; 129 initiated ART	Unprotected sex; abstinence; 100% condom use	0.86 (0.62–1.19); 0.81 (0.65–1.01); 1.54 (1.07–2.20)	Yes
Bunnell *et al.* [50]	Uganda	2003–2007	Cohort; follow-up for 3 years	928 adults initiated ART	Being sexually active; unprotected sex	28–41% ($P<0.001$)[d]; 22–8% ($P<0.001$)[d]	Yes
Peltzer and Ramlagan [53]	South Africa	2007–2008	Cohort; follow-up at 6 and 12 months	735 adults, all initiated on ART	Being sexually active; sex without a condom; no condom with last sex partner whose HIV status was not disclosed	49.8–50.1% ($P=0.311$)[d]; 24.1–16.0% ($P=0.001$); 5.9–0.9% ($P=0.003$)	Yes
Venkatesh *et al.* [52]	South Africa	2003–2010	Cohort; mean number of 2.6 pre-ART visits and 2.6 post-ART visits (with visits 6 months apart)	6263 adults; 2330 initiated ART	Being sexually active; unprotected sex; >1 sex partner	0.86 (0.78–0.95); 0.40 (0.34–0.46); 0.20 (0.14–0.29)	Yes

[a]Outcomes generally measured using either 3-month or 6-month recall periods. If recall period was greater than 12 months, noted with variable.
[b]Antiretroviral therapy (ART) exposure measured as sexual risk behavior associated with being on ART. Otherwise, in a few cases as noted measured as 'not being on ART'.
[c]Estimates taken from adjusted multivariable models. Effect sizes represent adjusted odds ratios (AORs) unless noted otherwise.
[d]Univariate finding presented due to lack of access to multivariable effect size.
[e]'Unprotected sex' defined as increased condom use or increased sexual abstinence. Based on statistically significant result ($P<0.05$).
[f]Measures relative risk.
[g]Confidence interval not provided.

individuals have access to HIV prevention services, stigma may decrease and there may be an increase in willingness to be tested, leading to greater access to care [62]. A population-based survey in Kenya suggested that individuals who reported higher risk compensation (that is increased sexual risk taking now that ART was available) and a belief that ART cures HIV were more likely to be infected with HIV [63], perhaps suggesting therapeutic optimism. A study conducted among HIV-uninfected nonspousal household members of adults taking ART in Uganda found that perceiving HIV as curable and lower AIDS-related anxiety were independently associated with risky sex [64]. Despite expanding access to ART and HIV prevention services in hyperendemic settings, uptake of HIV testing remains relatively low and a substantial proportion of at-risk individuals continue to engage in unprotected sex [65,66]. The community impact of wider access to ART on sexual behavior remains an area for further studies and it is likely behavioral responses to treatment will vary in different socio-cultural settings.

In summary, of the eight cross-sectional and nine cohort studies that assessed the impact of ART on sexual risk behaviors in the developing world, all but one study noted a significant reduction in unprotected sex measured as increased condom use or sexual abstinence following access to ART. These findings have important implications for how decreases in risky sexual behavior may synergize with a reduced biological risk of HIV transmission following access to ART.

Implications of decreased sexual risk behavior following antiretroviral therapy initiation

Although most studies conducted in the developing world have failed to demonstrate an increase in risk compensation following access to ART, the specific factors in the clinical encounter that may be the most important in facilitating behavior change remain difficult to disentangle [67]. Figure 2 summarizes individual, dyadic (i.e., within the sexual relationship), and community level factors that could impact engaging in sexual risk behaviors following wider treatment access. Although epidemiological studies can examine whether individuals on treatment engage in sexual risk behaviors, qualitative data are needed to understand specific reasons for why treated individuals may change their behavioral practices. It is not known whether individuals starting ART seek to protect others from being infected through an enhanced awareness of their infectiousness or whether other specific prevention messages coupled with treatment initiation are responsible for durable risk reduction. Important variables that may mediate the association between ART and sexual

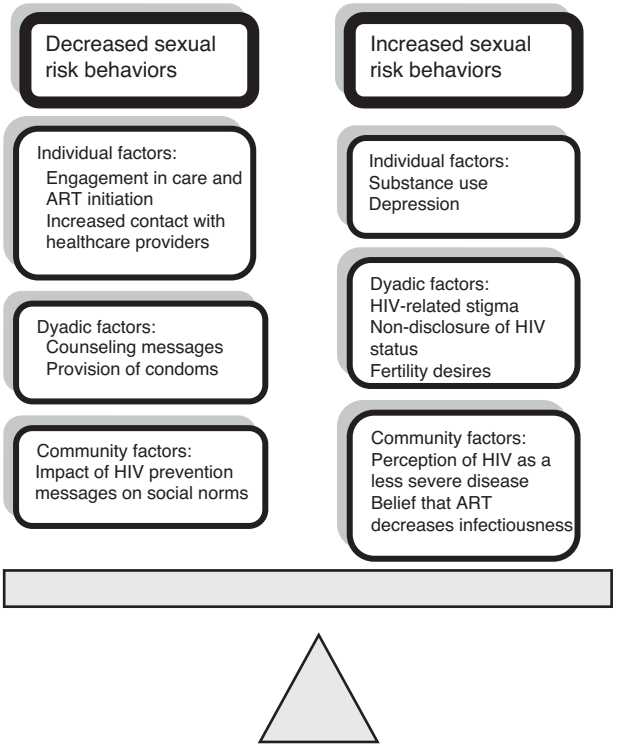

Fig. 2. Individual, dyadic, and community level factors associated with increased relative to decreased sexual risk behaviors following wider access to antiretroviral therapy. ART, antiretroviral therapy.

risk behaviors include partner seroconcordance, reproductive health, access to HIV prevention services, and psychosocial factors.

Partner characteristics

The risk of HIV transmission and the preventive impact of ART depend on the type of partner (primary vs. casual sex partner) and HIV seroconcordance [68]. The practice of selectively engaging in sexual risk behaviors with partners of the same HIV status (i.e., serosorting) has been well documented among high-risk groups, such as MSM and IDUs in the developed world [69,70]. In contrast, serostatus knowledge may play less of a role in sub-Saharan Africa where studies conducted among ART-experienced individuals demonstrate that unprotected sex occurs mainly within primary partnerships [42,43], and it is estimated that nearly half of cohabiting HIV-infected individuals may be in a serodiscordant relationship [71,72].

To date, most observational studies assessing ART use and sexual risk behaviors have not measured partner HIV status other than by enquiring about multiple partnerships. A few studies have asked participants whether they knew that their primary sex partner was HIV-positive, HIV-negative, or of unknown status, and a large proportion of participants (>30%) have reported not knowing their partner's HIV status, suggesting the

need for more robust partner HIV testing [42,46,48]. Interventions to promote HIV counseling and testing of partners have resulted in substantial increases in condom use among couples [73,74]. Further data are needed to understand whether sexual risk behaviors differ by knowledge of partner's HIV status in order to target secondary prevention on subgroups of HIV-infected individuals.

Reproductive health

In many societies that value fertility, ART-experienced individuals may continue to engage in unprotected sex in order to procreate [75]. Unprotected sex to procreate remains an important limitation of condom-based HIV prevention interventions for couples trying to fulfill their reproductive goals. Given the close link between heterosexual HIV transmission and the incidence of pregnancy, there is a need for further studies to examine safe ways for HIV-infected individuals in serodiscordant relationships to procreate, including prompt initiation of ART for the infected partner [76], assisted reproduction [77], and possibly antiretroviral chemoprophylaxis for the uninfected at-risk partner [78,79].

Impact of HIV prevention services

Most studies conducted in the developing world have taken place within treatment and care programs in which patients received ongoing risk-reduction counseling, as well as free male condoms. Although in some studies the prevention services were the same before and after receiving ART, in other studies individuals who received ART had access to more robust HIV prevention programs and counseling compared to those who were ART-naive [42,48]. Hence, it remains difficult to compare individuals who are treated compared to those who are not. Additionally, individuals on treatment may have access to greater psychosocial support, adherence counseling, and other favorable clinical conditions that may potentiate changes in risk behaviors [80]. Recent data suggest that an integrated behavioral intervention to improve ART adherence could also decrease reported unprotected sex and minimize risk compensation beliefs [81].

Psychosocial factors related to sexual risk behavior

Psychosocial factors, including substance use and depression, can alter both treatment access and adherence and engaging in sexual risk behaviors. Repeated studies conducted in African and Asian settings have demonstrated an association between alcohol use and HIV infection [82,83]. Individuals may still be at risk for depression even after receiving ART, despite an increase in CD4 cell count and a decrease in HIV-related symptoms [84,85], suggesting the need for assessing and treating depression as part of ART treatment programs. Nondisclosure of HIV status has been shown to be strongly associated with sexual risk behaviors in African settings [86,87] and may be most apparent with partners of unknown HIV status [88,89]. Additionally, studies conducted in African settings have also documented demographic factors, such as educational level, rural compared to urban area of habitation, and migration, as important parameters that affect patterns of sexual risk behavior among HIV-infected individuals [57,90,91].

High-risk subpopulations

Although most studies in the developing world assessing the impact of ART on sexual risk behaviors have focused primarily on heterosexual individuals, it is important to note that MSM and IDUs have a greater risk of being HIV infected compared to the general population in these settings [92,93]. Understanding patterns of sexual risk behaviors and increasing access to ART in these communities may be hampered by still fragmentary data, lack of visibility due to social stigma, and governmental sanctions [94]. MSM may serve as 'bridge populations' in which they are unaware of their own infection and may continue to engage in unprotected sex with their wives, resulting in further transmission to female partners and possibly offspring [95]. The decreased engagement of high-risk populations in HIV prevention and care due to human rights remains cause for concern, and further nuanced and sensitive public health interventions coupled with ART roll-out are warranted.

Challenges in evaluating the impact of access to antiretroviral therapy in decreasing sexual risk behaviors

There are important limitations of the currently available data on the impact of treatment on sexual behavior in the developing world, including adequate plasma viral suppression as well as other mediating biological factors, and bias associated with the measurement of sexual behaviors.

Plasma viral load data determine HIV transmission risk

Studies assessing risk compensation following ART access in the developing world have generally not presented data on plasma HIV-1 RNA as measurement has generally not been a part of standard of care in these settings. The strong association between plasma viral load and the risk of HIV transmission has been consistently demonstrated in the pre and post-ART eras [28,96–99] and has been recently shown among serodiscordant couples in sub-Saharan Africa [9,98]. Ecological data from North America have revealed a link between treatment coverage, population viral load, and HIV incidence [100,101]. However, there may be sufficient subpopulations of HIV-infected individuals not linked to treatment as well as a subset of those in care engaging in sexual risk

behaviors to allow for the continued growth of the epidemic in some regional settings [37,102]. The durability of ART on plasma viral load suppression may change over time if treatment-experienced individuals are not fully adherent to their treatment regimens and develop treatment failure and/or acquire drug resistance.

Mediating biological factors affecting HIV transmission

Though the primary determinant of predicting the impact of ART on decreasing the sexual transmission of HIV is the level of plasma HIV-1 RNA, other important mediating biological factors include the acute phase of infection, the relative penetration of different antiretrovirals in the genital tract, acquired drug resistance, and intercurrent sexually transmitted infections (STIs; Fig. 1). It has been estimated that nearly half of new HIV transmission events result from recently infected individuals [103,104]. A recent mixed-methods study conducted in southern Africa noted a reduction in HIV risk behavior following diagnosis of acute HIV infection [105]. Though there are now 25 antiretroviral agents available for the treatment of HIV infection, not all drug combinations of ART may be equally effective in the genital and systemic compartments [26,106], which may be a function of protein binding and other pharmacodynamic properties [107]. STIs and HIV act in synergy with STIs amplifying the risk of HIV transmission and acquisition, especially in developing world settings with high co-prevalence [108]. It is possible that the efficacy of early initiation of ART may be mitigated by the residual effects of untreated STIs and the chronic inflammatory milieu that they potentiate. Although it is biologically plausible that antiretrovirals will make HIV-infected individuals less infectious, it is clear that there are a variety of mediating biological factors that may influence the general trend toward HIV-1 RNA suppression in the genital tract following ART initiation.

Measurement of sexual risk behaviors

The measure of sexual risk behaviors utilizing self-report is ever open to recall and social desirability bias [109,110]. In HIV care programs with regular prevention counseling, participants may have a greater incentive to misreport sexual risk behaviors compared to HIV-infected individuals not enrolled in preventive care. Some studies have tried to address social desirability bias by providing cultural and gender sensitivity training to clinic and research staff, but achieving adequate control over this bias can be difficult in settings in which sexuality is not openly discussed and/or specific sexual behaviors are stigmatized. Several studies have questioned the validity of using self-reported measures of sexual risk behavior among HIV-infected populations and have instead recommended utilizing audio computer-assisted self-interview (ACASI) [111,112]. Although none of the studies assessing ART and sexual risk behaviors in the developing world used ACASI, some used STIs as epidemiological biomarkers of sexual risk behavior by correlating reports of unprotected sex with incident STI diagnoses [42,51].

Optimal utilization of a limited resource

There are multiple ways in which antiretrovirals could be possibly used as means of primary and secondary HIV prevention, including pre-exposure prophylaxis (PrEP) and postexposure prophylaxis (PEP) [24,113,114], as well as by expanding treatment access to decrease the onward sexual transmission from infected individuals [115–117]. The recent expansion of WHO treatment guidelines to initiate ART at a higher CD4 cell count of 350 cells/μl rather than 200 cells/μl will mean that a larger pool of HIV-infected individuals will be in need of treatment to improve their own clinical status [1]. Recent results from HPTN 052 support the preventive impact of earlier access to ART in stopping HIV transmission among serodiscordant couples [8]. In an era of limited donor commitment and fiscal austerity, developing nations face limited budgets for HIV treatment, and thus will have to carefully decide how to make best use of limited clinical resources in order to also decrease the number of new infections.

Conclusion

The optimal preventive impact of ART on the spread of the HIV epidemic across the developing world will partially depend on decreasing levels of sexual risk behaviors following treatment initiation. Of the eight cross-sectional and nine observational cohort studies conducted in the developing world that were included in this review, all but one study noted a significant reduction in unprotected sex following access to ART. Although current data suggest access to ART has not led to significant risk compensation in the developing world, careful ongoing observation will be needed before we can safely assume expanded treatment will invariably be a successful long-term strategy to prevent the spread of HIV. The observational studies to date confirm the assumptions of current 'test and treat' strategies that the widespread provision of ART is not undermined by upswings in sexual risk behaviors. However, a subset of participants are still engaged in unprotected intercourse, and hence the potential risk for HIV transmission persists. It is important that HIV clinical care programs continue to emphasize behavioral prevention even after initiating therapy. In the years ahead, there will likely be more studies on the topic of ART and sexual risk behaviors tracking both individuals newly initiating therapy and those with more prolonged treatment exposure.

In addition to expanding the use of ART for prevention, successful approaches to change behavior, including maximizing the use of existing risk-reduction programs

and technologies, should be studied, adapted, and applied simultaneously. Positive prevention efforts that aim to decrease the risk of HIV transmission from already infected individuals through behavioral and biomedical interventions have yet to be widely implemented in the developing world [17,118]. The use of ART as a critical tool for HIV prevention will need to be part of a larger toolbox to reduce the number of new infections globally, including circumcision, PrEP and PEP, prevention of MTCT, behavioral change, and treatment of STIs, that are culturally tailored to the factors that potentiate regional epidemics [119,120]. Further studies in pharmacology, virology, and behavioral science will be needed to best understand the intended, and unintended, clinical consequences of increasingly using ART as a means of prevention. Decreases in sexual risk behaviors following wider access to ART may operate synergistically with the impact of ART in reducing HIV transmission in the developing world.

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Conflict of interest

There are no conflicts of interest.

References

1. World Health Organization. Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents; 2009. website. http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf. [Accessed 21 July 2011].
2. World Health Organization. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector; 2008. http://www.who.int/hiv/mediacentre/2008progressreport/en/index.html. [Accessed 3 February 2009].
3. UNAIDS. UNAIDS/WHO AIDS epidemic update. UNAIDS/WHO; 2010. http://www.unaids.org/epidemic-update/. [Accessed 26 January 2011].
4. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, *et al*. **EuroSIDA study group. Decline in the AIDS and death rates in the EuroSIDA study: an observational study.** *Lancet* 2003; **362**:22–29.
5. Palella F, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, *et al*. **Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators.** *N Engl J Med* 1998; **338**:853–860.
6. De Cock K, Fowler MG, Mercier E, de Vincenzi I, Saba J, Hoff E, *et al*. **Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice.** *JAMA* 2000; **283**:1175–1182.
7. Baeten J, Kahle E, Lingappa JR, Coombs RW, Delany-Moretlwe S, Nakku-Joloba E, *et al*. **Genital HIV-1 RNA predicts risk of heterosexual HIV-1 transmission.** *Sci Transl Med* 2011; **3**:77ra29.
8. Cohen MS, Chen YQ, McCauley M, Gamble T, Hossemipon MC, Kumavasamy N, *et al*. **Prevention of HIV-1 infection with early antiretroviral therapy.** *N Engl J Med* 2011; **356**:493–505.
9. Donnell D, Baeten JM, Kiarie J, Thomas KK, Stevens W, Cohen CR, *et al*. **Partners in Prevention HSV/HIV Transmission Study Team. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis.** *Lancet* 2010; **375**:2092–2098.
10. Johnston M, Fauci AS. **An HIV vaccine: evolving concepts.** *N Engl J Med* 2007; **356**:2073–2081.
11. Cohen M, Gay CL. **Treatment to prevent transmission of HIV-1.** *Clin Infect Dis* 2010; **50**:S85–S95.
12. Granich R, Crowley S, Vitoria M, Lo YR, Souteyrand Y, Dye C, *et al*. **Highly active antiretroviral treatment for the prevention of HIV transmission.** *J Int AIDS Soc* 2010; **12**:1.
13. Hogben M, Liddon N. **Disinhibition and risk compensation: scope, definitions, and perspective.** *Sex Transm Dis* 2008; **35**:1009–1010.
14. Marks G, Crepaz N, Senterfitt W, Janssen RS. **Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States.** *J Acquir Immune Defic Syndr* 2005; **39**:446–453.
15. Crepaz N, Hart TA, Marks G. **Highly active antiretroviral therapy and sexual risk behavior.** *JAMA* 2006; **292**:224–236.
16. Crepaz N, Hart TA, Marks G. **Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review.** *JAMA* 2004; **292**:224–236.
17. Fisher J, Smith L. **Secondary prevention of HIV infection: the current state of prevention for positives.** *Curr Opin HIV AIDS* 2009; **4**:279–287.
18. Attia S, Egger M, Müller M, Zwahlen M, Low N. **Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis.** *AIDS* 2009; **23**:1397–1404.
19. Salomon J, Hogan DR, Stover J, Stanecki KA, Walker N, Ghys PD, Schwartländer B. **Integrating HIV prevention and treatment: from slogans to impact.** *PLoS Med* 2005; **2**:e16.
20. Cassell M, Halperin DT, Shelton JD, Stanton D. **Risk compensation: the Achilles' heel of innovations in HIV prevention?** *BMJ* 2006; **332**:605–607.
21. Kelly J, Otto-Salaj LL, Sikkema KJ, Pinkerton SD, Bloom FR. **Implications of HIV treatment advances for behavioral research on AIDS: protease inhibitors and new challenges in HIV secondary prevention.** *Health Psychol* 1998; **17**:310–319.
22. Eaton L, Kalichman S. **Risk compensation in HIV prevention: implications for vaccines, microbicides, and other biomedical HIV prevention technologies.** *Curr HIV/AIDS Rep* 2007; **4**:165–172.
23. Lalani T, Hicks C. **Does antiretroviral therapy prevent HIV transmission to sexual partners?** *Curr Infect Dis Rep* 2008; **10**:140–145.
24. Mayer K, Venkatesh KK. **Antiretroviral therapy for HIV prevention: current status and future prospects.** *Am J Public Health* 2010; **100**:1867–1876.
25. Boily M, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, Alary M. **Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies.** *Lancet Infect Dis* 2009; **9**:118–129.
26. Cu-Uvin S, Caliendo AM, Reinert S, Chang A, Juliano-Remollino C, Flanigan TP, *et al*. **Effect of highly active antiretroviral therapy on cervicovaginal HIV-1 RNA.** *AIDS* 2000; **14**:415–421.
27. Vernazza P, Gilliam BL, Flepp M, Dyer JR, Frank AC, Fiscus SA, *et al*. **Effect of antiviral treatment on the shedding of HIV-1 in semen.** *AIDS* 1997; **11**:1249–1254.
28. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, *et al*. **Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group.** *N Engl J Med* 2000; **342**:921–929.
29. Blower S, Gershengorn HB, Grant RM. **A tale of two futures: HIV and antiretroviral therapy in San Francisco.** *Science* 2000; **287**:650–654.

30. Velasco-Hernandez J, Gershengorn HB, Blower SM. **Could widespread use of combination antiretroviral therapy eradicate HIV epidemics?** *Lancet Infect Dis* 2002; **2**:487–493.
31. Gray R, Li X, Wawer MJ, Gange SJ, Serwadda D, Sewankambo NK, *et al*. **Rakai Project Group. Stochastic simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission; Rakai, Uganda.** *AIDS* 2003; **17**:1941–1951.
32. Law M, Prestage G, Grulich A, Van de Ven P, Kippax S. **Modelling the effect of combination antiretroviral treatments on HIV incidence.** *AIDS* 2001; **15**:1287–1294.
33. Abbas U, Anderson RM, Mellors JW. **Potential impact of antiretroviral chemoprophylaxis on HIV-1 transmission in resource-limited settings.** *PLoS One* 2007; **2**:e875.
34. Granich R, Gilks CF, Dye C, De Cock KM, Williams BG. **Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model.** *Lancet* 2009; **373**:48–57.
35. Walensky R, Paltiel AD, Losina E, Morris BL, Scott CA, Rhode ER, *et al*. **CEPAC Investigators. Test and treat DC: forecasting the impact of a comprehensive HIV strategy in Washington DC.** *Clin Infect Dis* 2010; **51**:392–400.
36. Stolte I, Dukers NH, Geskus RB, Coutinho RA, de Wit JB. **Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study.** *AIDS* 2004; **18**:303–309.
37. Dukers N, Goudsmit J, de Wit JB, Prins M, Weverling GJ, Coutinho RA. **Sexual risk behaviour relates to the virological and immunological improvements during highly active antiretroviral therapy in HIV-1 infection.** *AIDS* 2001; **15**:369–378.
38. Ostrow D, Fox KJ, Chmiel JS, Silvestre A, Visscher BR, Vanable PA, *et al*. **Attitudes towards highly active antiretroviral therapy are associated with sexual risk taking among HIV-infected and uninfected homosexual men.** *AIDS* 2002; **16**:775–780.
39. Tun W, Gange SJ, Vlahov D, Strathdee SA, Celentano DD. **Increase in sexual risk behavior associated with immunologic response to highly active antiretroviral therapy among HIV-infected injection drug users.** *Clin Infect Dis* 2004; **38**:1167–1174.
40. Eisele T, Mathews C, Chopra M, Brown L, Silvestre E, Daries V, Kendall C. **High levels of risk behavior among people living with HIV initiating and waiting to start antiretroviral therapy in Cape Town South Africa.** *AIDS Behav* 2008; **12**:570–577.
41. Kaida A, Gray G, Bastos FI, Andia I, Maier M, McIntyre J, *et al*. **The relationship between HAART use and sexual activity among HIV-positive women of reproductive age in Brazil, South Africa, and Uganda.** *AIDS Care* 2008; **20**:21–25.
42. Sarna A, Luchters SM, Geibel S, Kaai S, Munyao P, Shikely KS, *et al*. **Sexual risk behaviour and HAART: a comparative study of HIV-infected persons on HAART and on preventive therapy in Kenya.** *Int J STD AIDS* 2008; **19**:85–89.
43. Moatti J, Prudhomme J, Traore DC, Juillet-Amari A, Akribi HA, Msellati P. **Côte d'Ivoire HIV Drug Access Initiative Socio-Behavioural Evaluation Group. Access to antiretroviral treatment and sexual behaviours of HIV-infected patients aware of their serostatus in Côte d'Ivoire.** *AIDS* 2003; **17**:S69–S77.
44. Bateganya M, Colfax G, Shafer LA, Kityo C, Mugyenyi P, Serwadda D, *et al*. **Antiretroviral therapy and sexual behavior: a comparative study between antiretroviral- naive and -experienced patients at an urban HIV/AIDS care and research center in Kampala, Uganda.** *AIDS Patient Care STDs* 2005; **19**:760–768.
45. Bunnell R, Ekwaru JP, Solberg P, Wamai N, Bikaako-Kajura W, Were W, *et al*. **Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda.** *AIDS* 2006; **20**:85–92.
46. Venkatesh KK, Srikrishnan AK, Safren SA, Triche EW, Thamburaj E, Prasad L, *et al*. **Sexual risk behaviors among HIV-infected South Indian couples in the HAART era: implications for reproductive health and HIV care delivery.** *AIDS* Care 2011; **23**:722–733.
47. Marcellin F, Bonono CR, Blache J, Carrieri MP, Spire B, Koulla-Shiro S. **EVAL Study Group Higher risk of unsafe sex and impaired quality of life among patients not receiving antiretroviral therapy in Cameroon: results from the EVAL survey (ANRS 12-116).** *AIDS* 2010; **24**:S17–S25.
48. Dia A, Marcellin F, Bonono R-C, Boyer S, Bouhnik A-D, Protopopescu C, *et al*. **the EVAL Study Group. Prevalence of unsafe sex with one's steady partner either HIV-negative or of unknown HIV status and associated determinants in Cameroon (EVAL ANRS12-16 survey).** *Sex Transm Infect* 2010; **86**:148–154.
49. Venkatesh K, de Bruyn G, Lurie MN, Modisenyane T, Triche EW, Gray GE, *et al*. **Sexual risk behaviors among HIV-infected South African men and women with their partners in a primary care program: implications for couples-based prevention**. *AIDS Behav* 2011 (in press).
50. Bunnell R, Ekwaru J, King R, Bechange S, Moore D, Khana K, *et al*. **3-Year follow-up of sexual behavior and HIV transmission risk of persons taking ART in rural Uganda**. *15th Conference on Retroviruses and Opportunistic Infections*. Boston; 2008.
51. McClelland R, Graham SM, Richardson BA, Peshu N, Masese LN, Wanje GH, *et al*. **Treatment with antiretroviral therapy is not associated with increased sexual risk behavior in Kenyan female sex workers**. *AIDS* 2010; **24**:891–897.
52. Venkatesh K, de Bruyn G, Lurie MN, Mohapi L, Pronyk P, Moshabela M, *et al*. **Decreased sexual risk behavior in the era of HAART among HIV-infected urban and rural South Africans attending primary care clinics.** *AIDS* 2010; **24**:2687–2696.
53. Peltzer K, Ramlagan S. **Safer sexual behaviours after 1 year of antiretroviral treatment in KwaZulu-Natal, South Africa: a prospective cohort study.** *Sexual Health* 2010; **7**:135–141.
54. Luchters S, Sarna A, Geibel S, Chersich MF, Munyao P, Kaai S, *et al*. **Safer sexual behaviors after 12 months of antiretroviral treatment in Mombasa, Kenya: a prospective cohort.** *AIDS Patient Care STDs* 2008; **22**:587–594.
55. Wanyama J, Kasibante D, Kayiira P, Wandera B, Kambugu A. **Sexual behavior of HIV+ persons before and after 1 year of ART at the Infectious Diseases Clinic, Kampala, Uganda**. *17th Conference on Retroviruses and Opportunistic Infections*. San Francisco; 2010.
56. Diabaté S, Alary M, Koffi CK. **Short-term increase in unsafe sexual behaviour after initiation of HAART in Côte d'Ivoire.** *AIDS* 2008; **22**:154–156.
57. Lurie M, Pronyk P, de Moor E, Heyer A, de Bruyn G, Struthers H, *et al*. **Sexual behavior and reproductive health among HIV-infected patients in urban and rural South Africa.** *J Acquir Immune Defic Syndr* 2008; **47**:484–493.
58. Kiene S, Christie S, Cornman DH, Fisher WA, Shuper PA, Pillay S, *et al*. **Sexual risk behaviour among HIV-positive individuals in clinical care in urban KwaZulu-Natal, South Africa.** *AIDS* 2006; **20**:1781–1784.
59. Kennedy C, O'Reilly K, Medley A, Sweat M. **The impact of HIV treatment on risk behaviour in developing countries: a systematic review.** *AIDS Care* 2007; **19**:707–720.
60. Venkatesh K, Srikrishnan AK, Mayer KH, Kumarasamy N, Raminani S, Thamburaj E, *et al*. **Predictors of nonadherence to HAART among HIV-infected South Indians in clinical care: implications for developing adherence interventions in resource-limited settings.** *AIDS Patient Care STDs* 2010; **24**:795–803.
61. Eisele T, Mathews C, Chopra M, Lurie MN, Brown L, Dewing S, Kendall C. **Changes in risk behavior among HIV-positive patients during their first year of antiretroviral therapy in Cape Town South Africa.** *AIDS Behav* 2008; **13**:1097–1105.
62. Kalichman S, Simbayi LC. **HIV testing attitudes, AIDS stigma, and voluntary HIV counseling and testing in a black township in Cape Town, South Africa.** *Sex Transm Infect* 2003; **9**:442–447.
63. Cohen C, Montandon M, Carrico AW, Shiboski S, Bostrom A, Obure A, *et al*. **Association of attitudes and beliefs towards antiretroviral therapy with HIV-seroprevalence in the general population of Kisumu, Kenya.** *PLoS One* 2009; **4**:e4573.
64. Bechange S, Bunnell R, Awor A, Moore D, King R, Mermin J, *et al*. **Two-year follow-up of sexual behavior among HIV-uninfected household members of adults taking antiretroviral therapy in Uganda: no evidence of disinhibition.** *AIDS Behav* 2010; **14**:816–823.
65. Boulle A, Hilderbrand K, Menten J, Coetzee D, Ford N, Matthys F, *et al*. **Exploring HIV risk perception and behaviour in the context of antiretroviral treatment: results from a township household survey.** *AIDS Care* 2008; **20**:771–781.

66. Venkatesh K, Madiba P, De Bruyn G, Lurie MN, Coates TJ, Gray GE. **Who gets tested for HIV in a South African Urban township? Implications for test and treat and gender-based prevention interventions.** *J Acquir Immune Defic Syndr* 2010; **56**:151–165.
67. Gregson S, Garnett GP. **Antiretroviral treatment is a behavioural intervention: but why?** *AIDS* 2010; **24**:2739–2740.
68. Garnett G, Gazzard B. **Risk of HIV transmission in discordant couples.** *Lancet* 2008; **372**:270–271.
69. Eaton L, Kalichman SC, O'Connell DA, Karchner WD. **A strategy for selecting sexual partners believed to pose little/no risks for HIV: serosorting and its implications for HIV transmission.** *AIDS Care* 2009; **21**:1279–1288.
70. Suarez T, Kelly JA, Pinkerton SD, Stevenson YL, Hayat M, Smith MD, Erti T. **Influence of a partner's HIV serostatus, use of highly active antiretroviral therapy, and viral load on perceptions of sexual risk behavior in a community sample of men who have sex with men.** *J Acquir Immune Defic Syndr* 2001; **28**:471–477.
71. Dunkle K, Stephenson R, Karita E, Chomba E, Kayitenkore K, Vwalika C, *et al*. **New heterosexually transmitted HIV infections in married or cohabiting couples in urban Zambia and Rwanda: an analysis of survey and clinical data.** *Lancet* 2008; **371**:2183–2191.
72. Hugonnet S, Mosha F, Todd J, Mugeye K, Klokke A, Ndeki L, *et al*. **Incidence of HIV infection in stable sexual partnerships: a retrospective cohort study of 1802 couples in Mwanza Region, Tanzania.** *J Acquir Immune Defic Syndr* 2002; **30**:73–80.
73. Allen S, Meinzen-Derr J, Kautzman M, Zulu I, Trask S, Fideli U, *et al*. **Sexual behavior of HIV discordant couples after HIV counseling and testing.** *AIDS* 2003; **17**:733–740.
74. Guthrie B, de Bruyn G, Farquhar C. **HIV-1-discordant couples in sub-Saharan Africa: explanations and implications for high rates of discordancy.** *Curr HIV Res* 2007; **5**:416–429.
75. Maier M, Andia I, Emenyonu N, Guzman D, Kaida A, Pepper L, *et al*. **Antiretroviral therapy is associated with increased fertility desire, but not pregnancy or live birth, among HIV+ women in an early HIV treatment program in rural Uganda.** *AIDS Behav* 2008; **13**:28–37.
76. Barreiro P, del Romero J, Leal M, Hernando V, Asencio R, de Mendoza C, *et al*. **Spanish HIV-Discordant Study Group. Natural pregnancies in HIV-serodiscordant couples receiving successful antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2006; **43**:324–326.
77. Savasi V, Parrilla B, Ratti M, Ferrazzi E. **Reproductive assistance in HIV-1 discordant couples.** *Curr Opin Obstet Gynecol* 2008; **20**:205–210.
78. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, *et al*.; the CAPRISA 004 Trial Group. **Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women.** *Science* 2010; **329**:1168–1174.
79. Grant R, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, *et al*., iPrEx Study Team. **Preexposure chemoprophylaxis for HIV prevention in men who have sex with men.** *N Engl J Med* 2010; **363**:2587–2599.
80. Kalichman S. **Co-occurrence of treatment nonadherence and continued HIV transmission risk behaviors: implications for positive prevention interventions.** *Psychosom Med* 2008; **70**:593–597.
81. Kalichman S, Cherry C, Kalichman MO, Amaral CM, White D, Pope H, *et al*. **Integrated behavioral intervention to improve HIV/AIDS treatment adherence and reduce HIV transmission.** *Am J Public Health* 2011; **101**:531–538.
82. Fisher J, Bang H, Kapiga SH. **The association between HIV infection and alcohol use: a systematic review and meta-analysis of African studies.** *Sex Transm Dis* 2007; **34**:856–863.
83. Kalichman S, Simbayi LC, Kaufman M, Cain D, Jooste S. **Alcohol use and sexual risks for HIV/AIDS in sub-Saharan Africa: systematic review of empirical findings.** *Prev Sci* 2007; **8**:141–151.
84. Peltzer K, Ramlagan S. **Perceived stigma among patients receiving antiretroviral therapy: a prospective study in KwaZulu-Natal, South Africa.** *AIDS Care* 2011; **23**:60–68.
85. Pearson C, Micek MA, Pfeiffer J, Montoya P, Matediane E, Jonasse T, *et al*. **One year after ART initiation: psychosocial factors associated with stigma among HIV-positive Mozambicans.** *AIDS Behav* 2009; **13**:1189–1196.
86. Kairania R, Gray RH, Kiwanuka N, Makumbi F, Sewankambo NK, Serwadda D, *et al*. **Disclosure of HIV results among discordant couples in Rakai, Uganda: a facilitated couple counselling approach.** *AIDS Care* 2010; **22**:1041–1051.
87. Wong L, Rooyen HV, Modiba P, Richter L, Gray G, McIntyre JA, *et al*. **Test and tell: correlates and consequences of testing and disclosure of HIV status in South Africa (HPTN 043 Project Accept).** *J Acquir Immune Defic Syndr* 2009; **50**:215–222.
88. Simbayi L, Kalichman SC, Strebel A, Cloete A, Henda N, Mqeketo A. **Disclosure of HIV status to sex partners and sexual risk behaviours among HIV-positive men and women, Cape Town, South Africa.** *Sex Transm Infect* 2007; **83**:29–34.
89. Crepaz N, Lyles CM, Wolitski RJ, Passin WF, Rama SM, Herbst JH, *et al*. **HIV/AIDS Prevention Research Synthesis (PRS) Team. Do prevention interventions reduce HIV risk behaviours among people living with HIV? A meta-analytic review of controlled trials.** *AIDS* 2006; **20**:143–157.
90. Kalichman S, Ntseane D, Nthomang K, Segwabe M, Phorano O, Simbayi LC. **Recent multiple sexual partners and HIV transmission risks among people living with HIV/AIDS in Botswana.** *Sex Transm Infect* 2007; **83**:371–375.
91. Protopopescu C, Marcellin F, Préau M, Gabillard D, Moh R, Minga A, *et al*. **Psychosocial correlates of inconsistent condom use among HIV-infected patients enrolled in a structured ART interruptions trial in Côte d'Ivoire: results from the TRIVACAN trial (ANRS 1269).** *Trop Med Int Health* 2010; **15**:706–712.
92. Baral S, Sifakis F, Cleghorn F, Beyrer C. **Elevated risk for HIV infection among men who have sex with men in low- and middle-income countries 2000–2006: a systematic review.** *PLoS Med* 2007; **4**:e339.
93. van Griensven F, de Lind van Wijngaarden JW, Baral S, Grulich A. **The global epidemic of HIV infection among men who have sex with men.** *Curr Opin HIV AIDS* 2009; **4**:300–307.
94. Mayer K, Mimiaga MJ, Safren SA. **Out of the closet and into public health focus: HIV and STDs in men who have sex with men in middle income and resource-limited countries.** *Sex Transm Dis* 2009; **37**:205–206.
95. Kumta S, Lurie M, Weitzen S, Jerajani H, Gogate A, Row-kavi A, *et al*. **Bisexuality, sexual risk taking, and HIV prevalence among men who have sex with men accessing voluntary counseling and testing services in Mumbai, India.** *J Acquir Immune Defic Syndr* 2010; **53**:227–233.
96. Fideli U, Allen SA, Musonda R, Trask S, Hahn BH, Weiss H, *et al*. **Virologic and immunologic determinants of heterosexual transmission of human immunodeficiency virus type 1 in Africa.** *AIDS Res Hum Retroviruses* 2001; **17**:901–910.
97. Tovanabutra S, Robison V, Wongtrakul J, Sennum S, Suriyanon V, Kingkeow D, *et al*. **Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand.** *J Acquir Immune Defic Syndr* 2002; **29**:275–283.
98. Sullivan P, Kayitenkore K, Chomba E, Karita E, Mwananyanda L, Vwalika C, *et al*. **Reduction of HIV transmission risk and high risk sex while prescribed ART: results from discordant couples in Rwanda and Zambia.** *16th Conference on Retroviruses and Opportunistic Infections (CROI)*. Montreal; 2009.
99. Fang C, Hsu HM, Twu SJ, Chen MY, Chang YY, Hwang JS, *et al*. **Division of AIDS and STD, Center for Disease Control, Department of Health, Executive Yuan. Decreased HIV transmission after a policy of providing free access to highly active antiretroviral therapy in Taiwan.** *J Infect Dis* 2004; **190**:879–885.
100. Montaner J, Lima VD, Barrios R, Yip B, Wood E, Kerr T, *et al*. **Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study.** *Lancet* 2010; **376**:532–539.
101. Das M, Chu PL, Santos GM, Scheer S, Vittinghoff E, McFarland W, Colfax GN. **Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco.** *PLoS One* 2010; **5**:e11068.
102. Jansen I, Geskus R, Davidovich U, Coutinho R, Prins M, Stolte I. **Increasing trend in HIV-1 incidence among young men who have sex with men in Amsterdam: a 25-year prospective cohort study.** *17th Conference on Retroviruses and Opportunistic Infections*. San Francisco; 27 February to 2 March 2010.

103. Wawer M, Gray R H, Sewankambo N K, Serwadda D, Li X, Laeyendecker O, *et al*. **Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda.** *J Infect Dis* 2005; **191**:1403–1409.
104. Brenner B, Roger M, Routy JP, Moisi D, Ntemgwa M, Matte C, *et al*. **Quebec Primary HIV Infection Study Group. High rates of forward transmission events after acute/early HIV-1 infection.** *J Infect Dis* 2007; **195**:951–959.
105. Pettifor A, Macphail C, Corneli A, Sibeko J, Kamanga G, Rosenberg N, *et al*.; **NIAID Center for HIV/AIDS Vaccine Immunology. Continued high risk sexual behavior following diagnosis with acute HIV infection in South Africa and Malawi: implications for prevention.** *AIDS Behav* 2010; **15**:1243–1250.
106. Eron J, Vernazza PL, Johnston DM, Seillier-Moiseiwitsch F, Alcorn TM, Fiscus SA, Cohen MS. **Resistance of HIV-1 to antiretroviral agents in blood and seminal plasma: implications for transmission.** *AIDS* 1998; **12**:F181–F191.
107. Taylor S, Pereira AS. **Antiretroviral drug concentrations in semen of HIV-1 infected men.** *Sex Transm Infect* 2001; **77**:4–11.
108. Ward H, Rönn M. **Contribution of sexually transmitted infections to the sexual transmission of HIV.** *Curr Opin HIV AIDS* 2010; **5**:305–310.
109. Schroder K, Carey MP, Vanable PA. **Methodological challenges in research on sexual risk behavior: II. Accuracy of self-reports.** *Ann Behav Med* 2003; **26**:104–123.
110. Buvé A, Lagarde E, Caraël M, Rutenberg N, Ferry B, Glynn JR, *et al*. **Study Group on Heterogeneity of HIV Epidemics in African Cities. Interpreting sexual behaviour data: validity issues in the multicentre study on factors determining the differential spread of HIV in four African cities.** *AIDS* 2001; **15**:S117–S126.
111. Langhaug L, Sherr L, Cowan FM. **How to improve the validity of sexual behaviour reporting: systematic review of questionnaire delivery modes in developing countries.** *Trop Med Int Health* 2010; **15**:362–381.
112. Langhaug L, Cheung YB, Pascoe SJ, Chirawu P, Woelk G, Hayes RJ, Cowan FM. **How you ask really matters: randomised comparison of four sexual behaviour questionnaire delivery modes in Zimbabwean youth.** *Sex Transm Dis* 2010; **87**:165–173.
113. Cohen M, Gay C, Kashuba AD, Blower S, Paxton L. **Narrative review: antiretroviral therapy to prevent the sexual transmission of HIV-1.** *Ann Intern Med* 2007; **146**:591–601.
114. Mayer K, Venkatesh, KK. **Chemoprophylaxis for HIV prevention: new opportunities and new questions.** *J Acquir Immune Defic Syndr* 2010; **55 (Suppl 2)**:S122–S127.
115. Venkatesh K, Lurie MN, Mayer KH. **How HIV treatment could result in effective prevention.** *Future Virol* 2010; **5**:405–415.
116. Montaner J, Hogg R, Wood E, Kerr T, Tyndall M, Levy AR, Harrigan PR. **The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic.** *Lancet* 2006; **368**:531–536.
117. Cohen M, Kaleebu P, Coates T. **Prevention of the sexual transmission of HIV-1: preparing for success.** *J Int AIDS Soc* 2008; **11**:4.
118. Janssen RS, Holtgrave DR, Valdiserri RO, Shepherd M, Gayle HD, De Cock KM. **The serostatus approach to fighting the HIV epidemic: prevention strategies for infected individuals.** *Am J Public Health* 2001; **19**:1019–1024.
119. Kurth A, Celum C, Baeten JM, Vermund SH, Wasserheit JN. **Combination HIV prevention: significance, challenges, and opportunities.** *Curr HIV/AIDS Rep* 2010; **8**:62–72.
120. Coates T, Richter L, Caceres C. **Behavioural strategies to reduce HIV transmission: how to make them work better.** *Lancet* 2008; **372**:669–684.