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

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Abstract

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 paper 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. While data on the impact of ART on possible risk compensation is 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.

Keywords

HIV; AIDS; sexual risk behaviors; ART; treatment

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 4 additional individuals require treatment [4]. Beyond the individual clinical benefits accrued from treatment [5, 6], ART has dramatically decreased

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mother-to-child HIV transmission (MTCT) [7], and recent evidence, most notably 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% [8–10]. 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 [11], 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 are promptly linked to treatment and care, regardless of immunological status [12], and that sexual risk behaviors among those found to be HIV-infected do not increase over time [13]. 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 [14]. Based on studies in the developed world, individuals who learn that they are HIV-infected tend to decrease their sexual risk behaviors [15]. However, most of the developed world cohorts were conducted among high-risk populations [16–18]. The dynamics of sexual transmission in settings where HIV spread is predominantly through heterosexual contact have not been studied in as much detail [19]. It is plausible that the impact of ART on sexual risk behaviors may vary in the developing world due to difficulties 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 [20–24]. The current review paper 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 ART use and sexual risk behaviors

The sexual transmission of HIV involves a complex interplay of both biological and behavioral factors. The sexual transmission of HIV in the absence of ART remains a low probability but high consequence event, occurring in less than 1 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 [21]. Though condom use can be associated with over a 90% reduction in HIV risk, they must be used consistently and correctly to be efficacious [21, 23]. 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 US 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]. While 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 [17]. Data on the impact of ART on sexual risk behaviors is 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 (See Table 1).

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 [40, 41], as well when waiting to start ART [42], 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 [43–46]. These clinic-based studies suggested that a sizeable number of patients reported being sexually abstinent (>50%) at the time of receiving ART [44, 45]. 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%) [45–47], 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 [48]. 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 [49, 50]. 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 [51], which also held for those who reported a partner who was HIV-uninfected or of unknown status [52]. A recent study conducted in South Africa assessed whether sexual risk behaviors differed by self-reported partner HIV status, and found that while 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 [53].

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 [47]. An important finding was that most unprotected sex (>80%) occurred among married couples. A later study by the same group following individuals for three years after ART initiation also found a decrease in unprotected sex, but an increase in not being sexually abstinent [54]. A study conducted among female Kenyan sex-workers showed consistent decreases in unprotected sex, but not multiple sex partners, following access to ART [55]. Among women with more advanced immunosuppression (CD4 cell counts below 200 cells/ul), 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 [56]. 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 pre-treatment baseline [57–60]. Unlike the previous data, a cohort study from the Ivory Coast showed that unsafe sex increased among those receiving ART six months after treatment initiation [61], 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 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 (i.e. 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 8 cross-sectional and 9 cohort studies that assessed the impact of ART on sexual risk behaviors in the developing world, all but 1 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 ART 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. While 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 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 [44, 45], 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 inquiring about multiple partnerships. A few studies have asked participants whether they knew if 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 [44, 50, 52]. 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 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 fulfill their reproductive goals [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 ARV 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. While 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-naïve [44, 52]. 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. Non-disclosure 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 [40, 90, 91].

High-risk sub-populations:

While 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 ART 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 determines 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 [10, 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 (ARVs) in the genital tract, acquired drug resistance, and intercurrent sexually

transmitted infections (STIs) (See Figure 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 ARV 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 ARVs 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 towards 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]. While 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 [44, 55].

Optimal utilization of a limited resource:

There are multiple ways in which ARVs could be possibly used as means of primary and secondary HIV prevention, including PrEP and PEP [113–115], as well as by expanding treatment access to decrease the onward sexual transmission from infected individuals [116–118]. The recent expansion of World Health Organization (WHO) treatment guidelines to initiate ART at a higher CD4 cell count of 350 cells/ul rather than 200 cells/ul 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 [9]. 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.

Conclusions

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 8 cross-sectional and 9 observational cohort studies conducted in the developing world that were included in this review, all but 1 study noted a significant reduction in unprotected sex following access to ART. While 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 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 as well as 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 [18, 119]. 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 [120, 121]. 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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Figure 1. Biological factors that mediate how ART alters HIV sexual transmission

Note: Figure adapted from Mayer and Venkatesh, *American Journal of Public Health*, 2010.

Figure 2.

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

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

Study, first author	Country	Study period	Study design	Sample size	Outcome measure $\frac{f}{f_{**}}$	Adjusted Effect size $^{*}\%$	Significant decrease in unprotected sex with ART †
<i>Cross-sectional studies</i>							
Moatti [45]	Ivory coast	1999–2000	Cross-sectional	711 adults; 164 initiated ART	Unprotected sex	0.52 (0.29–0.93)	Yes
Bateganya [46]	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
Sama [44]	Kenya	2003–2005	Cross-sectional	322 adults; 179 initiated ART	Unprotected sex with regular partners associated with not using ART $\frac{f}{f_{**}}$	4.26 (1.90–9.58)	Yes
Dia [52]	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 $\frac{f}{f_{**}}$	2.28 (1.64–3.18)	Yes
Marcellin [51]	Cameroon	2006–2007	Cross-sectional; National survey	3151 adults; 2458 initiated ART	Inconsistent condom use	0.50 (0.34–0.74)	Yes
Venkatesh [50]	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 [43]	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 [53]	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
<i>Cohort studies</i>							
Bunnell [47]	Uganda	2003–2004	Cohort; 6 months 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 2010	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% to 70% ($p<0.05$) [*] 50.6% to 79.9% ($p<0.05$) [*]	Yes
Luchters [58]	Kenya	2003–2004	Cohort; 12 months of follow-up	234 adults; all initiated on ART	Sex in last 12 months ** Unprotected sex in past year with partner a partner of either HIV-	1.30 (0.86–1.96) 0.52 (0.32–0.87) 0.16 (0.08–0.32)	Yes

Study, first author	Country	Study period	Study design	Sample size	Outcome measure f^{**}	Adjusted Effect size **	Significant decrease in unprotected sex with ART f
					uninfected or unknown status Unprotected sex at last sex act		
Diabate [61]	Ivory Coast	2005	Cohort; 6 months follow-up	615 adults; 303 initiated ART	Unprotected sex	1.40 (1.21–1.61) $^{\#}$	No
Eisele [42]	South Africa	2006–2007	Cohort; 12 months follow-up	913 adults; 512 initiated ART	Unprotected sex	0.46 (p=0.0121) †	Yes
McClelland [55]	Kenya	1993–2008	Cohort; Median >2 years 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 [54]	Uganda	2003–2007	Cohort; Follow-up for 3 years	928 adults initiated ART	Being sexually active Unprotected sex	28 to 41% (p<0.001) * 22% to 8% (p<0.001) *	Yes
Peltzer 2010 [57]	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 whom HIV status was not disclosed	49.8% to 50.1% (p=0.311) * 24.1% to 16.0% (p=0.001) 5.9% to 0.9% (p=0.003)	Yes
Venkatesh [56]	South Africa	2003–2010	Cohort; Mean number of 2.6 preART 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

† Estimates taken from adjusted multivariable models. Effect sizes represent adjusted odds ratios (AOR) unless noted otherwise.

* Univariate finding presented due to lack of access to multivariable effect size.

** Outcomes generally measured using either 3 or 6 month recall periods. If recall period was greater than 12 months, noted with variable.

f „Unprotected sex” defined as increased condom use or increased sexual abstinence. Based on statistically significant result (p<0.05).

† 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”.

$^{\#}$ Measures relative risk.

† Confidence interval not provided.