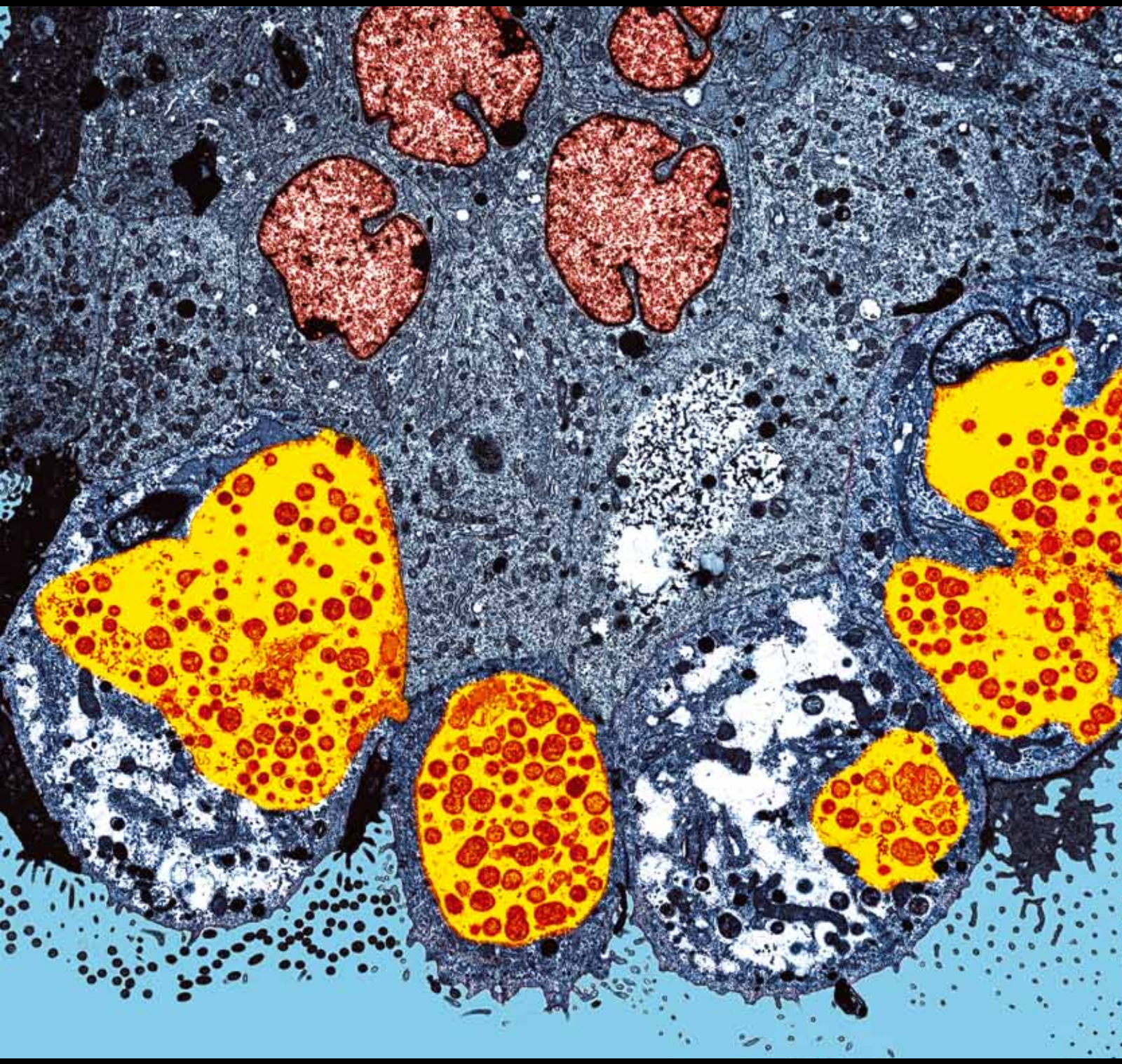
Journal of Sexually Transmitted Diseases

Combination Prevention for HIV

Guest Editors: Mark R. Dybul, Peter Piot, and Kevin O'Reilly



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Editorial Board

Contents

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Research Article

Investigating Recent Testing among MSM: Results from Community-Based HIV Rapid Testing Attendees in France

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Background. We aimed to identify factors associated with recent HIV testing in MSM who attended two experimental community-based and nonmedicalized voluntary counselling and testing programmes (CB-VCT) targeting MSM in France. *Methods*. This analysis was based on data collected in 2009–2011 through a self-administered pretesting questionnaire. An index measuring the level of participants' sexual orientation disclosure was built: the higher the index, the greater the disclosure. Factors associated with recent HIV testing (last test ≤ 1 year) were identified using a multivariate logistic regression model adjusted for the CB-VCT programme of enrolment. *Results*. 716 MSM provided data on testing history. Overall, 49% were recently tested for HIV and 51% were not. Recently tested MSM had a higher homosexuality disclosure index (adjusted OR [95% confidence interval]: aOR = 1.2 [1.1–1.4]), reported more inconsistent condom use during anal sex with men (aOR = 1.6 [1.2–2.1]), and were less likely to have sex under the influence of club drugs (aOR = 0.6 [0.4–1.0]). *Conclusion*. New testing strategies should focus on those who live their homosexuality relatively secretly and those who use club drugs before sex. Governments should develop policies which encourage improved social acceptance of homosexuality as concealment of sexual orientation represents a major barrier to testing.

1. Introduction

In resource-rich countries, men who have sex with men (MSM) are greatly affected by the HIV burden [1–7], including France where they account for 40% of the annual new diagnoses [8]. The French HIV incidence in MSM is 60 times higher than that in the overall population [2]. Although a large proportion of MSM have already been tested for HIV in France [7, 9, 10], it is estimated that they account for 31% of the hidden epidemic [11] and for 19% of the diagnoses made at an advanced disease stage in 2011 (CD4 < 200/mm^3, [8]).

HIV testing has now become a tool to limit the HIV epidemic [12] and is a recognized element of combination prevention based on biomedical (preexposure prophylaxis, treatment as prevention) and behavioural (mainly serosorting and positioning) tools [13–17]. Indeed, knowledge of HIV

serostatus is the cornerstone of successful combination prevention, as the latter's implementation is adapted according to the individual's serological status.

In France, just as in the USA, guidelines encourage the extension of HIV testing and recommend annual testing of certain population groups at high risk of acquiring HIV, in particular MSM [18–20]. Early detection of HIV leads to adequate linkage to care and treatment initiation, which in turn reduce viral load and limit onward transmission [13, 14, 21]. Furthermore, it has been demonstrated that half of new HIV contaminations are due to people who are unaware of their HIV infection [22].

Barriers to HIV testing have been highlighted in MSM as well as in the general population. These include the individual's perception of low or no risk of being infected, the fear of testing positive, and concerns about confidentiality and structural barriers, such as the time needed to take the test [23–25]. In addition, inappropriate counselling and moralistic attitudes regarding MSM sexual practices and regarding their testing habits were reported by the gay community as reasons for not testing [26].

The first step taken to overcome such barriers was to bring new HIV testing offers to MSM living in France through two community-based and nonmedicalized voluntary counselling and testing (CB-VCT) programmes: ANRS-COM'TEST [27] and ANRS-DRAG [28]. Testing was included in a comprehensive strategy of HIV exposure risk reduction where sexuality was openly addressed with peers. Among MSM who participated in the ANRS-COM'TEST, roughly 30% had not been tested for at least two years and reported HIV at-risk behaviours [27]. In order to increase repeat testing, the next step was to understand what leads MSM to go for testing or not. This study aimed to identify factors associated with recent testing in MSM who attended the two CB-VCT programmes (ANRS-COM'TEST and ANRS-DRAG) in France.

2. Methods

2.1. Intervention and Population. This analysis is based on data from two French CB-VCT programmes using rapid HIV tests exclusively targeting MSM: ANRS-COM'TEST and ANRS-DRAG, reported in detail elsewhere [27, 28].

In brief, both studies were cross-sectional and assessed a nonmedicalized voluntary counselling and testing offer implemented by community members from the French NGO *AIDES*, a community-based organization that focuses on outreach and prevention services for HIV-exposed populations, including MSM. Although they are not professional healthcare workers, *AIDES* staff members performed the entire testing procedure using HIV rapid tests and provided specific counselling based on the motivational interview method which they were trained in [29]. The studies were carried out during dedicated weekend or evening sessions once or twice a week. MSM were informed about the availability of the CB-VCT through communication campaigns in gay venues and on the Internet (posters, flyers, web banners, and ads). Eligibility criteria were as follows: being older than 18, being a man, and reporting to have sex with other men.

The ANRS-COM'TEST study was conducted from February 2009 to June 2010 in four French cities: Paris, Lille, Montpellier, and Bordeaux. The study was implemented at various *AIDES* premises, where potential participants came to be tested following the communication campaign [27]. The ANRS-DRAG study was conducted from March 2010 to April 2011 in free and anonymous VCT centres based in three French cities (Paris, Marseille, and Nice), outside of opening hours. The centres were only open during these hours to MSM who came to be tested using the CB-VCT offer and not to their usual attendees [28].

Both studies were approved by the French comité de protection des personnes (ANRS-COM'TEST: Nord-Ouest III, ANRS-DRAG: Sud-Est III) and the Agence française de sécurité sanitaire des produits de santé (AFSSAPS). All participants had to provide written informed consent before enrolment, and the studies were anonymous.

2.2. Data Collection. All participants had to fill in self-administered questionnaires during the testing procedure. The present analysis was based on data from the pre-testing questionnaire that collected sociodemographic characteristics, risk perceptions, HIV testing history, and sexual behaviour in the previous six months. Similar questionnaires were used in both studies, allowing us to merge databases.

2.3. Main Outcome and Explanatory Variables. Participants were asked when their last HIV test had been. This variable was then dichotomised into "recently tested" (i.e., the most recent HIV test performed in the 12 months prior to the CB-VCT) versus "not recently tested" (i.e., the most recent HIV test performed more than 12 months prior to the CB-VCT or having never been tested). This 12-month cutoff was chosen in accordance with French testing guidelines which recommend a test every year for MSM [18].

Several potential explanatory variables were computed using one or more questions. We built an index of sexual orientation disclosure, measuring the level of disclosure of one's sexual orientation with the question: "Is your homo-, bisexuality known to your ..." and broken down for each of the following categories: father, mother, brother(s) or sister(s), colleagues, and heterosexual friends. The higher the index, the greater the participant's disclosure of his sexual orientation.

Participants were asked to answer several questions about anal sex and condom use with their casual and/or steady partners. We then computed a risk proxy variable of inconsistent condom use (ICU): participants who reported that they had not systematically used condoms during anal intercourse in the previous six months, irrespective of the type of partner, were classified as having ICU.

The questionnaire also collected information about sex under the influence of psychoactive products. The following potential explanatory variables were therefore considered: alcohol, poppers, cannabis, and club drugs grouped together (ecstasy, MDMA, cocaine, and crack).

2.4. Statistical Analysis. A logistic regression model was built to determine factors associated with the outcome, that is, with

the fact of having been tested in the last 12 months. This model was adjusted for the specific study in which participants were enrolled (ANRS-COM'TEST or ANRS-DRAG) in order to take into account the possible recruitment biases in both studies. Potential explanatory variables of recent testing were individually screened in univariate analyses. Variables achieving a significance level of ≤0.25 were considered eligible for inclusion in the multivariate model. A backward method based on the log-likelihood ratio test (entry threshold P-value ≤ 0.05) was then used to select factors independently associated with the outcome. A sensitivity analysis was performed: two additional multivariate models were built using different cut-off points for the outcome variable (11 and 13 months versus 12 in the base-case analysis).

Statistical analyses were performed using SPSS-17 software (SPSS, Inc., Chicago, Illinois, USA) and STATA 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

3. Results

3.1. Study Population. Overall, 743 MSM participated in the ANRS-COM'TEST and the ANRS-DRAG studies. Complete data on the most recent HIV test were available for 716 MSM (our study group). The other 27 were excluded from this analysis: 5 men gave no information about history of HIV testing and 22 reported having been previously tested but did not specify the date of the most recent test.

Among the 716 MSM included in this analysis, 517 (71%) and 199 (28%) were enrolled in the ANRS-COM'TEST and ANRS-DRAG studies, respectively. Median age was 31 (interquartile range, IQR = [25–39]); 81% defined themselves as homosexual. Regarding the main outcome, 349 MSM (49%) were recently tested, that is, reported at least one test in the 12 months previous to the study. Among the 367 MSM (51%) not recently tested, 146 (40%) had been tested more than one year but less than two years previously. For the 221 (60%) not tested within the previous two years, the median time since their last test was 46 months (IQR = [33–64]).

3.2. Comparison of MSM Regarding the Outcome. MSM characteristics according to recent and not recent HIV testing are shown in Table 1. Compared with their not recently tested counterparts, univariate analyses showed that MSM recently tested were younger (median age: 30 versus 32 years, P = 0.03), defined themselves more often as homosexual (86% versus 77%, P = 0.06), and were more often victims of verbal abuse because of their sexual orientation (24% versus 16%, P = 0.005).

Interestingly, the MSM recently tested had disclosed their homosexuality more than those not tested recently with, respectively, a median sexual orientation disclosure index of 5/5 (i.e., disclosed to all categories outlined above) and 4/5 (i.e., had not disclosed to at least one of those categories, P < 0.001). Among those not recently tested, 68% had not disclosed their homosexuality to their father.

Recently tested MSM were also more likely to report having had casual male partners (87% versus 82%, P = 0.06) or steady male partners (82% versus 73%, P = 0.002) in the previous 6 months and to report ICU with male partners (62% versus 50%, P = 0.001) than their not recently tested counterparts. However, the total number of sexual male partners in the previous six months was not different between both MSM groups (overall median [IQR] = 11 [4–24]). Those recently tested tended to report less sex with women (10% versus 14%, P = 0.13) than those not recently tested.

Both groups often reported sex under the influence of alcohol (62%). Those recently tested were more likely to report sex using poppers (46% versus 38%, P = 0.04) and, to a lesser extent, when they smoked cannabis (27% versus 22%, P = 0.18). However, they tended to report less sex under the influence of club drugs (9% versus 12%, P = 0.22) compared with not recently tested MSM.

3.3. Factors Associated with Recent HIV Testing. After adjustment for the specific study, factors independently associated with recent HIV testing were as follows: the index of sexual orientation disclosure to relatives and friends (adjusted odds ratio, aOR = 1.2; 95% confidence interval, CI = [1.1–1.4]), ICU (aOR = 1.6; 95% CI = [1.2–2.1]), and sex under the influence of club drugs (aOR = 0.6, 95% CI = [0.4–1.0]) (Table 2).

In the sensitivity analysis (Table 3), the model remained nearly unchanged when the 11 and 13 months cut-off points were used to define recent testing.

4. Discussion

This is the first study investigating recent HIV testing among MSM living in France. Our analysis showed that approximately half of the study group (49%) had been tested for HIV in the 12 months previous to their participation in the CB-VCT programmes. These men were more likely to be out to all their relatives and friends and to report inconsistent condom use (ICU), but they were less likely to have had sex under the influence of club drugs when compared with those not tested for over one year or who had never been tested.

The two CB-VCT programmes reported here reached a significant proportion of MSM who had been recently tested for HIV as well as those who had not. However, our analysis was restricted to a convenience sample of the specific population of MSM who felt the need to be tested for HIV, so we did not provide information about men who were unwilling to be tested. It is important to underline that this study was based on MSM who decided to participate in an alternative HIV testing offer and who may have been reluctant to be tested using conventional HIV testing offers, or who experienced more discrimination based on the sexual orientation.

The French context regarding HIV testing has changed: the government recently decided to authorize the use of HIV rapid tests by nonmedical staff [30]. Currently, many HIV tests are performed by community members. It would be interesting to reconduct such study in a few months in order to verify whether the level of recent testing increased or not and whether the factors influencing the fact of being recently tested remain unchanged.

The sensitivity analysis showed that using different cut-off points for the outcome variable (i.e., tested within the past 11, 12, and 13 months) did not drastically change the base-case model. Thus, the final multivariate model is stable and

Table 1: Comparison of participants regarding the outcome: recently versus not recently tested (univariate analyses, $n = 716$).

Variables	Items	Whole sample ($n = 716$)	Recently tested ($n = 349$)	Not recently tested ($n = 367$)	P^*
		n (%)	n (%)	n (%)	
Study enrolment	ANRS-DRAG	199 (27.8)	103 (29.5)	96 (26.2)	
	ANRS-COM'TEST	517 (70.5)	246 (70.5)	271 (73.8)	0.32
Demographics					
Age[§]	Median [IQR]	31 [25–39]	30 [25–38]	32 [25–40]	0.03
Education	<Secondary school certificate	93 (13)	44 (12.6)	49 (13.4)	
	≤2 years after secondary school	238 (33.2)	119 (34.1)	119 (32.4)	0.66
	>2 years after secondary school	374 (52.2)	179 (51.3)	195 (53.1)	0.92
Being in active employment	No	142 (19.8)	72 (20.6)	70 (19.1)	
	Yes	563 (78.6)	272 (77.9)	291 (79.3)	0.61
Being single	No	208 (29.1)	94 (26.9)	114 (31.1)	
	Yes	506 (70.7)	255 (73.1)	251 (68.4)	0.21
Sexual orientation, disclosure, and victim of verbal abuse or aggression					
Sexual orientation	Homosexual	582 (81.3)	299 (85.7)	283 (77.1)	
	Bisexual	94 (13.1)	38 (10.9)	56 (15.3)	0.05
	Heterosexual	9 (1.3)	0 (0)	9 (2.5)	na
	Other	27 (3.8)	10 (2.9)	17 (4.6)	0.15
Index of sexual orientation disclosure[§]	Median [IQR]	4 [2–5]	5 [3–5]	4 [1–5]	<0.001
Victim of verbal abuse because of sexual orientation	No	570 (79.6)	263 (75.4)	307 (83.7)	
	Yes	143 (20.0)	85 (24.4)	58 (15.8)	0.005
Victim of aggression because of sexual orientation	No	682 (95.3)	331 (94.8)	351 (95.6)	
	Yes	22 (3.1)	11 (3.2)	11 (3.0)	0.89
Sexual life (previous 6 months)					
Total no. of sex male partners[§]	Median [IQR]	11 [4–24]	11 [5–30]	10 [3–22]	0.48
Having casual male partners	No	111 (15.5)	45 (12.9)	66 (18.0)	
	Yes	605 (84.5)	304 (87.1)	301 (82.0)	0.06
No. of casual male partners[§]	Median [IQR]	8 [3–20]	10 [3–22]	7 [2–20]	0.53
Having steady male partners	No	163 (22.7)	62 (17.8)	101 (27.5)	
	Yes	553 (77.2)	287 (82.2)	266 (72.5)	0.002
No. of steady male partner(s)[§]	Median [IQR]	2 [1–4]	2 [1–4]	2 [0–4]	0.58
ICU	No	293 (40.9)	121 (34.7)	172 (46.9)	
	Yes	401 (56.0)	216 (61.9)	185 (50.4)	0.001
Sex with women	No	592 (82.7)	297 (85.1)	295 (80.4)	
	Yes	87 (12.2)	36 (10.3)	51 (13.9)	0.13
Sex under the influence of drugs (previous 6 months)					
Alcohol	No	275 (38.4)	127 (36.4)	148 (40.3)	
	Yes	441 (61.6)	222 (63.6)	219 (59.7)	0.28
Poppers	No	418 (58.4)	190 (54.4)	228 (62.1)	
	Yes	298 (41.6)	159 (45.6)	139 (37.9)	0.04
Cannabis	No	541 (75.6)	256 (73.4)	285 (77.7)	
	Yes	175 (24.4)	93 (26.6)	82 (22.3)	0.18
Club drugs[**]	No	640 (89.4)	317 (90.8)	323 (88.0)	
	Yes	76 (10.6)	32 (9.2)	44 (12.0)	0.22

[*] This column displays P values for each variable tested in univariate logistic regression, showing whether differences between recently tested and not recently tested MSM are significant or not; [**] Ecstasy, MDMA, cocaine, or crack.
[§] Medians were used because these variables did not follow a normal distribution.
IQR: interquartile range; ICU: inconsistent condom use with casual and/or steady male partners; na: not applicable.

Table 2: Factors independently associated with recent testing, adjusted for the study (multivariate analysis, $n = 685^{*}$).

Variables	Items	Recently tested % ($n = 336$)	Not recently tested % ($n = 349$)	OR [95% CI]	P	aOR [95% CI]	P
Index of sexual orientation disclosure[§]	Median [IQR]	5 [3–5]	4 [1–5]	1.2 [1.1–1.4]	<0.001	1.2 [1.1–1.4]	<0.001
ICU	No	36	48	1		1	
	Yes	64	52	1.7 [1.2–2.3]	0.001	1.6 [1.2–2.1]	0.005
Club drugs[**]	No	91	87	1		1	
	Yes	10	13	0.7 [0.5–1.2]	0.22	0.6 [0.4–1.0]	0.05
Study enrolment	ANRS-COM'TEST	70	74	1		1	
	ANRS DRAG	30	26	1.2 [0.9–1.6]	0.32	1.1 [0.8–1.6]	0.43

[*] Valid dataset for all variables of the model; [**] Ecstasy, MDMA, cocaine, or crack.
[§] Median was used because this variable did not follow a normal distribution.
OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval; IQR: interquartile range; ICU: inconsistent condom use with casual and/or steady male partners. Log-likelihood = −456.01.

Table 3: Sensitivity analysis: factors independently associated with recent testing, adjusted for the study and using different cut-off points for the outcome (multivariate analysis, $n = 685^{*}$).

(Recently tested/not recently tested)		12-month cutoff (base-case analysis) (49%/51%)		11-month cutoff (46%/54%)		13-month cutoff (51%/49%)	
Variables	Items	aOR [95% CI]	P	aOR [95% CI]	P	aOR [95% CI]	P
Index of sexual orientation disclosure[§]	Median [IQR]	1.2 [1.1–1.4]	<0.001	1.2 [1.1–1.3]	<0.001	1.2 [1.1–1.3]	<0.001
ICU	No	1		1		1	
	Yes	1.6 [1.2–2.1]	0.005	1.7 [1.2–2.3]	0.001	1.5 [1.1–2.1]	0.008
Club drugs[**]	No	1		1		1	
	Yes	0.6 [0.4–1.0]	0.05	0.6 [0.4–1.0]	0.05	0.6 [0.4–1.0]	0.05
Study enrolment	ANRS-COM'TEST	1		1		1	
	ANRS DRAG	1.1 [0.8–1.6]	0.43	1.3 [0.9–1.9]	0.12	1.17 [0.8–1.7]	0.35

[*] Valid dataset for all variables of the model; [**] Ecstasy, MDMA, cocaine, or crack.
[§] Median was used because this variable did not follow a normal distribution.
aOR: adjusted odds ratio; CI: confidence interval; IQR: interquartile range; ICU: inconsistent condom use with casual and/or steady male partners.

robust; the associations between the explanatory variables and the outcome are not exclusively due to the large size of our sample.

Our results should be interpreted carefully as we cannot exclude recruitment bias arising from differences between the CB-VCT programmes in terms of study period and setting (*AIDES*' premises versus free and anonymous testing centres). However, the model was adjusted for the specific study in which men were enrolled, and no significant differences were found between both. In addition, the two programmes were carried out in large urban areas. Consequently, results cannot be extrapolated to MSM living in small towns or in the countryside, where living one's homosexuality openly is more complicated due to the fear of being recognized, the fear of outing and being labelled as gay and/or HIV positive.

The present study shows that half of the MSM involved had not been tested for HIV for more than one year. The current situation is far from adhering to French guidelines which recommend annual HIV testing for MSM [18]. Our rate of recent testing is comparable with those in many other studies among MSM conducted in resource-rich countries, from 43% in the UK to 54% in the USA [31–35]. However, one French study conducted among MSM attending gay venues in Paris (the Prevagay study) showed that 63% of participants had been tested within the previous 12 months [7]. These men reported attending various gay venues quite frequently, where HIV prevention is very present. It has been shown elsewhere that recent testing is associated with exposure to HIV prevention [36]; this may explain the higher rate of recently tested MSM in PREVAGAY compared with our study. Furthermore, attending such venues—identified as gay venues—requires the individual to be at least a little comfortable with his homosexuality in order to overcome the fear of outing.

In our study, recently tested MSM had a higher index of sexual orientation disclosure (5/5) that is, they lived their homosexuality openly with all their relatives and friends, compared with nonrecently tested MSM (4/5). This finding has also been highlighted in a large US study among young MSM [33] and more recently in the European MSM Internet

Survey (the EMIS study) [10, 37], where being out sexually to many people was positively associated with recent testing. In a recent French Internet survey on MSM, men who accessed—or who were interested in accessing—self-tests were also more likely to not have been tested recently and to live their sexual lives with men in absolute secrecy [38, 39].

Our results confirm that nondisclosure of sexual orientation is a major barrier to testing, and therefore to repeat testing among MSM. Nonrecently tested MSM were significantly less likely to be out; they were also more likely to define themselves as nonhomosexual and to report that they had sex with women compared with their recently tested counterparts. Interestingly, in a US study conducted among MSM, the desire to be perceived by others as heterosexual was negatively associated with recent testing, their belief being that "HIV testing is so gay" [35]. In Lebanon, a recent study highlighted that MSM who had disclosed their homosexuality to family and parents were more likely to have been tested for HIV [40]. In France, homosexuality is no longer criminalized and seems to be better accepted than in Lebanon for example, but many MSM do not live their homosexuality openly, probably because of quite widespread discrimination on the grounds of sexual orientation [41].

Unlike other studies which showed that a higher number of sex partners were associated with higher odds of recent testing [32, 35], we found no difference between recently and not recently tested MSM regarding the number of sex partners (high in both groups). On the other hand, those reporting ICU were significantly more likely to be recently tested. Not perceiving oneself to be at risk of acquiring HIV is a well-known barrier to HIV testing and is common in MSM as well as in the general population [23, 25, 42]. It is thus important to increase the self-perception of being at risk among those not recently tested and reporting ICU.

The use of psychoactive products is associated with sexual risk behaviours and with a higher prevalence of HIV and other sexually transmitted diseases in MSM [43–46]. In our study, not recently tested MSM were significantly more likely to report sex under the influence of club drugs than their recently tested counterparts. The homosexuality disclosure variable seemed to play the role of what is known as a "suppressor variable" [47]: introducing the latter increased the explanatory significance of club drug use and consequently the quality of the model (i.e., log-likelihood (LL) was significantly higher when the homosexuality disclosure variable was introduced; $LL_{\text{with revelation variable}} = -456.01$ versus $LL_{\text{without revelation variable}} = -474.05$). This is not such a striking result in social science research, and particularly in behavioural studies [48]. The phenomenon suggests that club drugs use and homosexuality disclosure share important information and should be interpreted as a composite. Further qualitative research is needed to better identify behaviours, beliefs, and attitudes which mediate the relationship between club drug use, disclosure of homosexuality, and HIV testing.

Although repeating HIV testing is being promoted in MSM who engage in at-risk sexual behaviour, prevention efforts to reach MSM who are tested less frequently should be focused on those who use club drugs, particularly before sex, and those who live their homosexuality in relative secrecy. Increasing self-perception of risk among MSM should be an intervention included in a comprehensive and understandable prevention message for all MSM. In addition, governments should develop policies which encourage improved social acceptance of homosexuality, as concealment of sexual orientation represents a major barrier to testing and might impede health and well-being of sexual minorities.

Authors' Contribution

NL, KC, BS and YY conceived and designed the study. KC, JMLG and YY implemented the ANRS-COM'TEST study. NL, MM, MP, MSM and BS implemented the ANRS-DRAG study. JB, LF and LST performed the statistical analysis. All authors contributed to the results' interpretation. KC and NL wrote the manuscript. All authors critically revised the manuscript, and approved the final version. NL and KC contributed equally to this work.

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Clinical Study

High-Risk Sexual Behavior Is Associated with Postexposure Prophylaxis Nonadherence among Men Who Have Sex with Men Enrolled in a Combination Prevention Intervention

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Methamphetamine use among men who have sex with men (MSM) is associated with increased HIV prevalence, due to increased engagement in high-risk sexual behavior. Fifty-three HIV-negative, methamphetamine-using MSM were enrolled in a biobehavioral combination prevention intervention in Los Angeles, CA, to assess the feasibility of administering postexposure prophylaxis (PEP) in combination with contingency management (CM) to prevent HIV seroconversion. The study combined a CM behavioral intervention targeting reductions in methamphetamine use with a PEP biomedical intervention for HIV prevention. Those who reported recent exposure to HIV were initiated on tenofovir/emtricitabine- (Truvada-) based PEP ($n = 35$). This secondary analysis sought to determine whether sexual risk taking was associated with PEP adherence. Regression analyses controlling for participant sociodemographics demonstrated that, at baseline, increased number of lifetime sexually transmitted diseases (STDs; Coef. = −0.07; 95% CI= (−0.12) – (−0.01)) and recent episodes of unprotected anal intercourse (UAI; Coef. = −0.01; 95% CI= (−.01) – (−0.002)) were associated with reductions in medication adherence. Given these associations between baseline sexual risk and PEP adherence, providers working with high-risk MSM may look to target reductions in sexual risk taking; this will reduce direct risk of HIV infection and may work to optimize medication adherence in the case of PEP initiation.

1. Introduction

In the United States, men who have sex with men (MSM) exhibit disproportionately high incidence and prevalence of HIV infection. MSM represent an estimated 4.7–9.2% of the total United States (US) population [1] yet, in 2009, accounted for 61% of all new HIV infections in the US [2]. Risk factors for HIV infection have been widely documented and among MSM in the US include unprotected anal intercourse, high number of male partners [3], and methamphetamine use [4, 5]. Postexposure prophylaxis (PEP) is a biomedical intervention intended to reduce the likelihood of HIV seroconversion after exposure to the virus. Combination prevention approaches combine biomedical interventions like PEP with behavioral (e.g., cognitive behavioral therapy, motivational interviewing) and/or structural (e.g., needle exchange, condom distribution) interventions, thereby optimizing the likelihood of proper adherence to the PEP medication while also reducing the risk factors placing participants at risk for HIV seroconversion.

1.1. Combination Prevention Interventions. Combination prevention interventions integrate behavioral, biomedical, and/or structural intervention strategies in the attempt to maximize the likelihood of intervention success and optimize intervention outcomes [6]. The increasing application of combination prevention interventions in the US represents the impact of the National HIV/AIDS Strategy

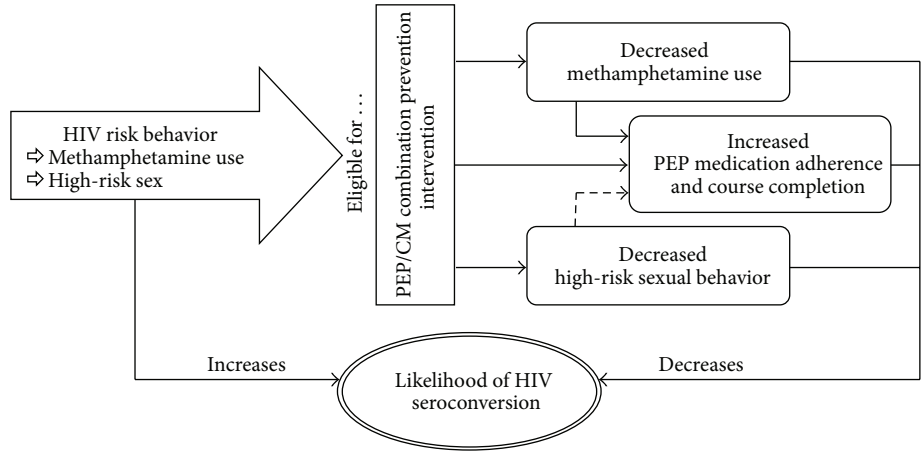

Figure 1: Proposed causation model.

(NHAS) [7], which highlighted the importance of combination approaches in successfully reducing HIV transmission. Recent disease epidemic models have demonstrated that movement away from purely behavioral interventions towards combination efforts may reduce the long-term costs of care as well as the overall number of persons living with HIV in the US [8, 9]. In addition, such efforts may be most cost effective when targeted for communities or populations at highest risk for HIV transmission.

1.2. Methamphetamine Use and HIV Sexual Risk among MSM. Methamphetamine is the most frequently used substance among MSM, following alcohol and marijuana, particularly in urban centers along the western US [10]. Among MSM, methamphetamine use has been associated with increased high-risk sexual behaviors [11–14]. Results have shown an ecological association between intensity of methamphetamine use and HIV infection; as the intensity of methamphetamine use increases, so does the likelihood of an observed HIV-positive status [5].

1.3. Postexposure Prophylaxis. Postexposure prophylaxis is the preventative strategy of taking 28 days of antiretroviral therapy (ART), initiated rapidly after an exposure to HIV, to reduce the odds of HIV acquisition [15]. Though there is currently limited clinical data for nonoccupational use [16], PEP is currently recommended for use after high-risk sexual exposures and/or needle sharing [15]. Failure to properly adhere to a prescribed PEP treatment regimen may not only fail to deter HIV seroconversion, but may also result in viral resistance which would make subsequent treatment of the disease with ART more difficult [16]. As such, difficult to treat populations (e.g., substance users, the homeless) may require additional intervention support in order to ensure proper adherence to a prescribed PEP regimen.

1.4. The Efficacy and Feasibility of PEP for High-Risk MSM. In a randomized noninferiority trial conducted in San Francisco [17], PEP-related adherence outcomes were contrasted across groups of low- and high-sexual risk-taking MSM. Though noninferiority was corroborated in the group of low risk-taking MSM, the high-risk MSM required more counseling support to achieve comparable results. Those that did not receive enhanced counseling displayed marginally lower rates of PEP course completion; evidence from animal models suggests that truncated courses of PEP severely compromise the efficacy of the intervention [18].

Sexual risk-taking MSM prescribed PEP may thus require additional motivation and support, such as that provided by combination prevention methods, to optimize levels of medication adherence and to maximize likelihood of course completion. Preliminary pilot data from a behavioral/biomedical combination prevention intervention in Los Angeles demonstrated that high-risk, methamphetamine-using MSM receiving PEP and undergoing a contingency management intervention to reduce methamphetamine use produced levels of medication adherence and rates of course completion comparable to historical cohorts [19–21]. The behavioral component of the intervention (i.e., contingency management to reduce methamphetamine use) was associated with reductions in participant methamphetamine use; it was also demonstrated that years of heavy methamphetamine use at baseline, and ongoing methamphetamine use during the course of the study were both associated with suboptimal PEP medication adherence and/or course completion.

MSM with multiple risk factors for HIV infection, such as high-risk sexual behaviors and methamphetamine use, may represent a prime target population for combination prevention interventions designed to simultaneously reduce HIV risk behavior and incident HIV infection. A causation model illustrating the proposed linkages between methamphetamine use, high-risk sexual behaviors, the PEP/CM combination prevention intervention, and likelihood of HIV seroconversion is provided in Figure 1. This secondary analysis sought to determine if lifetime and/or recent levels of high-risk sexual behavior were associated with poorer medication adherence and/or course completion among a sample of high-risk HIV negative, methamphetamine-using MSM. It was hypothesized that both recent and lifetime

sexual risk taking would be associated with reductions in PEP medication adherence and odds of course completion. This hypothesized association would corroborate the dashed arrow in Figure 1.

2. Materials and Methods

The Institutional Review Boards for UCLA and Friends Research Institute provided oversight for all study activities and approved all study-related documents, materials, and procedures. Exact procedures of the contingency management behavioral intervention (including payout schedules) are published elsewhere [21].

2.1. Participants. Participants were recruited between March 2009 and August 2010 using targeted ads posted in local gay magazines and the distribution of flyers and club cards in the settings where methamphetamine-using MSM congregate (e.g., dance clubs, bathhouses, coffee houses, and gyms). Potential participants were eligible if they self-identified as MSM, were at least 18 years of age, HIV uninfected on rapid HIV ELISA testing, self-reported methamphetamine use within the previous 30 days, and reported unprotected anal intercourse (UAI) with an HIV-positive or HIV-serostatus-unknown partner in the previous 90 days.

2.2. Study Procedures. All study procedures were conducted at a community research site in Los Angeles, CA. At a baseline visit, all eligible participants underwent informed consent, completed baseline assessments, received rapid HIV testing (OraQuick Advance, OraSure technologies, Bethlehem, PA), provided specimens for syphilis, Neisseria gonorrhoeae, and Chlamydia testing, and received a medical examination. Those who reported a high-risk sexual or drug exposure episode with an HIV-positive or serostatus-unknown source within the preceding 72 hours immediately initiated tenofovir isoproxil fumarate + emtricitabine (Truvada, Gilead Sciences), one tablet daily, for 28 days. All other participants received a 4-day "starter pack" of Truvada to be initiated only in the future case of a high-risk exposure to HIV. Thirty-five participants initiated PEP during the study period and comprise the analytic sample. One incident of HIV seroconversion was observed in a participant who reported medication nonadherence and multiple subsequent sexual exposures. Further study procedures and information on the incident seroconversion are described in detail elsewhere [21].

2.3. Assessments. Baseline assessments included demographics, methamphetamine use (DSM-IV-TR), sexual risk behaviors (Behavioral Questionnaire-Amphetamine [BQA-II]), medication adherence, HIV serostatus, and sexually transmitted diseases (STDs, urine sample, self-performed rectal swab for nucleic acid amplification [NAAT] for *N. gonorrhoeae* and C. trachomatis and pharyngeal swab for *N. gonorrhoeae*, and syphilis testing via serum rapid plasma reagin [RPR] assay). HIV and STD testing were performed at three-month followup; HIV RNA testing was performed only in the event of suspicion of acute HIV seroconversion. Further specifics regarding biologic testing and monitoring are provided elsewhere [21].

To determine medication adherence, participants were asked to report if they had missed any doses of the Truvada medication each time they came on site for a scheduled study appointment or to pick up additional medication. Proportional PEP adherence is defined as the number of doses taken divided by the total number of doses prescribed (e.g., X/28). If a participant missed more than 3 consecutive doses at any point during the 28-day regimen, they were discontinued from the medication and were considered to have not achieved course completion. Thus, course completion was a dichotomous (0/1) variable that indicates that a participant never missed more than three consecutive doses and was thus able to continue taking the prescribed medication through to the last dose.

There were two measures of high-risk sexual behaviors in this study. Recent high-risk sexual behavior was operationalized as the self-reported number of episodes of UAI during past six months at baseline. Lifetime high-risk sexual behavior was operationalized as the self-reported number of STDs acquired over the life course at baseline.

2.4. Statistical Analysis. For descriptive analyses, counts and percentages were provided for nominal variables, while means and standard deviations were provided for continuous or count variables. Multivariate analyses included both ordinary least squares (OLS) regressions (for analyses of proportional medication adherence) and logistic regressions (for analyses of course completion; 0 = did not complete course, 1 = completed course). All multivariate analyses included participants' race/ethnicity and sexual identity as statistical controls. In no case were participants' race/ethnicity or sexual identity significantly associated with PEP-related outcomes, and thus their coefficient estimates were omitted. Three participants were unwilling to disclose sexual risk behaviors at baseline. Due to the small sample sizes, results are reported as significant beginning at $P \leq 0.1$. All analyses were carried out using Stata version 10SE (StataCorp, College Station, TX).

3. Results

Participant sociodemographics are presented in Table 1. Most participants (60%) identified as white, with most nonwhite participants identifying as Hispanic/Latino ($n = 9$; 25.7%). Most participants identified as gay (85.7%), and most reported having a high school diploma or GED equivalent (60.0%). Self-reported annual income in the sample was low, with nearly half (48.6%) of the sample reporting yearly earnings of less than or equal to $15,000, and nearly three-quarters of the sample (74.3%) reporting earning less than or equal to $30,000 a year. Most participants reported renting or owning a house/apartment (54.3%), though a sizable minority reported being homeless (11.4%). Self-reported lifetime history of STDs was common ($M_{\text{STD}} = 1.8$; SD = 2.2), as were counts of recent episodes of UAI ($M_{\text{UAI}} = 11.9$; SD = 26.5).

Table 2 presents overall proportional PEP adherence rates; nearly half (48.6%) of all participants who initiated

Table 1: PEP-initiator sociodemographic characteristics ($N = 35$).

Characteristic	N (%) or mean (SD)
Age	34.1 (7.4)
Race/ethnicity	
Caucasian/white	21 (60.0%)
Non-White	14 (40%)
Sexual identity	
Gay	30 (85.7%)
Non-gay	5 (14.3%)
Educational attainment	
Less than HS	1 (2.9%)
HS Diploma/GED	21 (60.0%)
BA/BS	9 (25.7%)
Post graduate	4 (11.4%)
Annual income	
≤$15,000	17 (48.6%)
$15,001–$30,000	9 (25.7%)
$30,001–$60,000	6 (17.1%)
>$60,000	3 (8.6%)
Housing status	
Own/Rent House/Apt.	19 (54.3%)
Group Housing/Sober Living	3 (8.6%)
With Family/Friends	9 (25.7%)
Homeless	4 (11.4%)
Sexually transmitted diseases	
Lifetime	1.8 (2.2)
# Times unprotected anal intercourse[a]	
Past 6 months	11.9 (26.5)

[a]$n = 32$.

Table 2: Adherence to post-exposure prophylaxis medication regimen.

Proportional adherence	Freq.	Percent	Cumulative
0.04	3	8.6	8.6
0.07	2	5.7	14.3
0.14	1	2.9	17.1
0.25	1	2.9	20.0
0.46	1	2.9	22.9
0.57	2	5.7	28.6
0.77	1	2.9	31.4
0.82	1	2.9	34.3
0.89	1	2.9	37.1
0.93	1	2.9	40.0
0.96	4	11.4	51.4
1.00	17	48.6	100.0
Total	35	100	

PEP took all 28 doses of the Truvada medication. Another five (14.3%) participants were at least 90% adherent to the medication regimen, meaning 62.9% of the PEP-initiators were ≥90% adherent. Eight PEP-initiators (22.9%) failed to complete half of the 28-day treatment regimen. Of the 35 PEP initiators, 25 (71.4%) continued taking the medication with sufficient frequency to avoid discontinuation and completed the prescribed course (i.e., course completion).

Table 3 provides the results of six separate multivariate regressions, three models for each of the two PEP-related outcomes (medication adherence, course completion). Results included under Model 1 provide associations between participants' lifetime number of STDs and medication adherence/course completion. When controlling for covariates, participants' lifetime number of STDs was significantly associated with both PEP adherence and course completion. For each additional STD reported at baseline, participants' estimated proportional medication adherence reduced by 0.07 (approximately 2 of the 28 total doses), and their odds of course completion reduced by an estimated 31%.

Results appearing under Model 2 provide associations between recent episodes of UAI and medication adherence/course completion. Participants' self-reported count of recent UAI was significantly associated with both participants' PEP adherence and odds of course completion. For each additional episode of UAI in the past six months, participants' estimated proportional medication adherence reduced by 0.01 and their odds of completing the PEP course reduced by an estimated 6%. Analyses appearing under Model 3 regress PEP outcomes on STDs and episodes of UAI simultaneously. Results revealed that only the number of recent episodes of UAI remains significantly associated with PEP outcomes when all cofactors are included simultaneously. However, an examination of the coefficients of determination (i.e., R^2, Pseudo-R^2) revealed a nontrivial increase in the amount of variance explained in each model when including both factors simultaneously. This indicates that the significance test on the coefficient for STDs is likely being influenced by the small sample size ($n = 32$) and relatively large number of factors ($k = 4$) included in the model and may represent a type II hypothesis testing error rather than a genuine lack of statistical association. Additional factors tested for inclusion in the analysis included self-reported methamphetamine use (or methamphetamine and an other substance use) during sex, current relationship status, and total number of recent nonprimary sexual partners. In no case were these factors significantly associated with PEP adherence, and were thus omitted from the final models.

4. Discussion

Given the associations between methamphetamine use, high-risk sexual behaviors, and HIV infection/transmission among MSM, there is a need to develop effective interventions to prevent the acquisition and transmission of HIV among this extremely high-risk population [14]. At baseline, participants reported an average of almost two prior STDs and 12 recent episodes of UAI in the past six months. This was commensurate with the eligibility criteria of the study, one of which was self-report UAI (either receptive or insertive) with an HIV-positive or serostatus-unknown partner in the past three months. Given the well-documented association between methamphetamine use and high-risk sexual behaviors among MSM, as well as the urgency to

Table 3: Multivariate analyses of PEP adherence and course completion.

Outcome variable	Factor(s)	Model 1 ($N = 35$)		Model 2 ($n = 32$)		Model 3 ($n = 32$)	
		Coef.	95% CI	Coef.	95% CI	Coef.	95% CI
PEP adherence	STDs	-0.07^{*}	(−0.12)–(−0.01)	—	—	−0.04	(−0.10)–0.03
	UAI	—	—	-0.01^{**}	(−0.01)–(−0.002)	-0.01^{**}	(−0.01)–(−0.002)
		$R^2 = 0.17$		$R^2 = 0.28$		$R^2 = 0.32$	
		AOR	95% CI	AOR	95% CI	AOR	95% CI
Course completion	STDs	$0.69^{\dagger}$	0.46–1.01	—	—	0.71	0.42–1.21
	UAI	—	—	0.94°	0.87–1.01	0.94°	0.87–1.01
		Pseudo $R^2 = 0.12$		Pseudo $R^2 = 0.22$		Pseudo $R^2 = 0.27$	

$^{\circ}P \leq 0.1$; $^{\dagger}P = 0.058$; $^{*}P \leq 0.05$; $^{**}P \leq 0.01$.
Controls: Race/Ethnicity, Sexual Identity.
STDs: Sexually Transmitted Diseases (Lifetime).
UAI: Unprotected Anal Intercourse (past 6 months).

target sexual risk behaviors among MSM in HIV prevention efforts, it is important to determine whether sexual risk taking impacted medication adherence rates and/or the likelihood of course completion among this sample of high-risk, methamphetamine-using MSM.

Findings demonstrated that medication adherence was comparable with other, nonsubstance using populations [19, 20, 22], with 63% of all participants who initiated PEP achieving a minimum of 90% adherence to the 28-day medication regimen. When controlling for participant race/ethnicity and sexual identity, separate analytical models revealed that increased numbers of lifetime STDs and recent episodes of UAI were both associated with reductions in PEP medication adherence and course completion. When both factors (and the aforementioned controls) were estimated simultaneously, only recent episodes of UAI remained significantly associated with the PEP-related outcomes, though the likelihood of a type II hypothesis testing error for the coefficient on STDs is high. When all factors were included simultaneously, analytic models succeeded at explaining a third of all variance in medication adherence and a quarter of all variation in course completion.

Individuals undertaking high levels of sexual risk are prime candidates for efficacious HIV prevention strategies, including administration of biomedical interventions such as PEP. However, insofar as these same individuals are empirically less likely to properly adhere to such interventions, there is potential for the development of drug-resistant strains of HIV or other risks associated with suboptimal medication adherence. As such, the acceptability of PEP among populations unlikely to adhere to prescribed regimens may be drawn sharply into question. Any evidence revealing associations between past behavior and estimated PEP-adherence must, then, be closely attended.

The intention of combination prevention interventions is to provide, through the integration of multimodal intervention techniques, additional support and motivation to those at highest risk for intervention noncompliance to complete their assigned medication regimen and maximize the likelihood of HIV nonseroconversion. The PEP/CM combination prevention intervention described here was designed in part to reduce methamphetamine use among participants; prior results indicated that the intervention was associated with reductions in methamphetamine use and high-risk sexual behavior [21]. Reduction of high-risk sexual behaviors was not a direct targeted outcome of the CM behavioral intervention, though previous research has also demonstrated that reductions in methamphetamine use among MSM were accompanied by reductions in high-risk sexual behaviors [23]. Given the results presented here, combination prevention interventions that provide PEP to high-risk MSM should consider the inclusion of behavioral interventions explicitly designed to reduce substance use and concomitant high-risk sexual behaviors. In this way, sexual risk taking may be preemptively targeted for reduction, increasing the likelihood that a PEP regimen will be adhered to and/or completed.

Such reductions in high-risk sexual behaviors would benefit high-risk MSM in multiple ways, including reducing the need for PEP, lowering risk of infection with HIV and STDs, and maximizing adherence and likelihood of course completion if PEP is initiated. The direct reductions in the need for PEP initiation as well as decreased risk for infection with HIV or other STDs are of primary interest. However, for those who reduce but do not eliminate high-risk behaviors and still require PEP initiation, results presented here also indicate that PEP-related outcomes may be maximized, further decreasing the likelihood of HIV seroconversion. Perhaps most promisingly, given the intersecting and reinforcing nature of methamphetamine use and high-risk sexual behaviors among MSM, combination prevention interventions designed to reduce both while simultaneously providing biomedical interventions to avoid seroconversion would provide a more holistic, syndemic approach to HIV-prevention among high-risk MSM.

This study was limited by the face-to-face, self-reported nature of the sexual risk data collected at baseline. Furthermore, given the highly specialized nature of the sample (methamphetamine-using MSM living in Los Angeles county engaged in at least one high-risk sexual behavior in the past three months), results presented here may not be generalizable to other populations. Lastly, the small sample size and use of multivariate inferential statistics necessitated

the use of relaxed statistical reporting standards, increasing the risk of both type I and type II hypothesis testing errors. However, in spite of these limitations, the results presented here provide evidence that both recent and lifetime high-risk sexual behaviors are associated with PEP-related outcomes. Given that high-risk, methamphetamine-using MSM are often targeted for HIV-prevention interventions, including PEP combination prevention interventions, the results presented here provide important evidence to researchers looking to develop combination prevention interventions to this and similar high-risk populations.

High-risk sexual behavior is a serious public health concern among MSM communities across the US. As indicated by the recently implemented NHAS, combination prevention interventions are being tested for their efficacy in augmenting purely biomedical means of preventing HIV transmission in this and other populations disproportionately affected by the HIV epidemic. The ability to effectively determine factors endemic to such high-risk populations that may prevent proper implementation and adherence to prescribed biomedical interventions is crucial to this effort. The results presented here indicate that self-reported sexual risk taking is associated with reduced rates of medication adherence and likelihood of course completion among methamphetamine-using MSM. Thus, future combination prevention interventions targeting high-risk MSM should include behavioral intervention components specifically designed to reduce high-risk sexual behaviors that can, thereby, serve to optimize biobehavioral outcomes.

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Research Article

Access to Basic HIV-Related Services and PrEP Acceptability among Men Who Have sex with Men Worldwide: Barriers, Facilitators, and Implications for Combination Prevention

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Introduction. Men who have sex with men (MSM) are disproportionately impacted by HIV globally. Easily accessible combination HIV prevention strategies, tailored to the needs of MSM, are needed to effectively address the AIDS pandemic. *Methods and Materials*. We conducted a cross-sectional study among MSM ($n = 3748$) from 145 countries from April to August 2012. Using multivariable random effects models, we examined factors associated with acceptability of preexposure prophylaxis (PrEP) and access to condoms, lubricants, HIV testing, and HIV treatment. *Results*. Condoms and lubricants were accessible to 35% and 22% of all respondents, respectively. HIV testing was accessible to 35% of HIV-negative respondents. Forty-three percent of all HIV-positive respondents reported that antiretroviral therapy was easily accessible. Homophobia, outness, and service provider stigma were significantly associated with reduced access to services. Conversely, community engagement, connection to gay community, and comfort with service providers were associated with increased access. PrEP acceptability was associated with lower PrEP-related stigma, less knowledge about PrEP, less outness, higher service provider stigma, and having experienced violence for being MSM. *Conclusions*. Ensuring HIV service access among MSM will be critical in maximizing the potential effectiveness of combination approaches, especially given the interdependence of both basic and newer interventions like PrEP. Barriers and facilitators of HIV service access for MSM should be better understood and addressed.

1. Introduction

HIV surveillance studies show that men who have sex with men (MSM) continue to shoulder a disproportionate HIV disease burden compared with the general population in virtually every country for which there is reliable surveillance data [1]. This fact has been true since the epidemic began in the early 1980s [2].

In many high-income countries, incidence of HIV among MSM continues to climb even while overall HIV incidence is in decline. In the United States, the number of new HIV infections among MSM has been increasing at a rate of 8% per year since 2001 [3, 4]. HIV prevalence across North, South, and Central America, South and Southeast Asia, and Sub-Saharan African ranges consistently between 14 and 18% [2].

Due to stigma, discrimination, and criminalization, the HIV epidemic among MSM continues to go largely unaddressed in many parts of the world. As of December 2011, 93 countries had failed to report any data on HIV prevalence among MSM over the previous 5 years [5], and recent reports indicate that less than 2% of global HIV prevention funding is directed toward MSM [6].

These troubling trends are taking place against the backdrop of a shifting HIV prevention and treatment landscape. Randomized controlled trials have shown the prevention potential of biomedical interventions like preexposure prophylaxis (PrEP) among MSM and early initiation of antiretroviral treatment to prevent forward transmission between serodiscordant heterosexual couples [7, 8]. Trial findings are consistent with observational and ecologic studies that have noted the association between HIV treatment and reductions in new HIV infections [9, 10].

Recent advances underscore the need to develop and implement carefully planned combination prevention approaches tailored to the needs and concerns of MSM in a wide range of contexts to reduce new HIV infections in this population [11–14]. However, if MSM are to benefit from approaches that combine new and existing biomedical, behavioral, and structural interventions, factors that impact access to and acceptability of these interventions for MSM must be clearly described and addressed.

In 2012, the Global Forum on MSM and HIV (MSMGF) developed and implemented the Global Men's Health and Rights Survey (GMHR), an international multilingual online questionnaire designed to identify and examine barriers and facilitators that affect HIV service access for MSM around the world. We were particularly interested in understanding access to and acceptability of various service components that could comprise combination HIV prevention, with the aim of encouraging more effective AIDS responses tailored to the specific needs of MSM at the country level.

Our study evaluated the impact of social factors such as homophobia, service provider stigma, violence, community engagement, connection to gay community, comfort with service provider, and outness on access to condoms, lubricants, HIV testing, and HIV treatment. We also examined the relationship of these factors to PrEP acceptability.

We hypothesized a priori that access to condoms, lubricants, HIV testing, and HIV treatment, and PrEP acceptability would be:

(1) negatively associated with homophobia, violence toward MSM, violence toward men living with HIV, and service provider stigma;

(2) positively associated with community engagement, connection to gay community, comfort with service provider, and being out as gay or MSM; and

(3) positively associated with living in a high-income country compared to living in a low, lower-middle or upper-middle income country.

In addition, we hypothesized that PrEP acceptability would be

(4) positively associated with PrEP knowledge; and

(5) negatively associated with perceived stigma associated with PrEP.

2. Materials and Methods

2.1. Recruitment and Implementation. From 23 April to 20 August 2012, we recruited a global convenience sample of MSM to complete the 30-minute online survey. Survey participants were recruited via the MSMGF's networks of community-based organizations focused on advocacy, health, and social services for MSM. The MSMGF sent E-mail blasts advertising the survey to its nearly 3500 online members representing more than 1500 organizations in over 150 countries. Partnering organizations also disseminated information about the survey through their respective regional and global networks, as well as to local MSM through word of mouth. In addition, the MSMGF recruited participants from online social networking sites popular with MSM in Africa, Asia, Europe, and Latin America. Participation in the survey was completely voluntary and anonymous.

2.2. Measures. The MSMGF designed and implemented the multilingual online survey to identify and explore factors that affect access to HIV services for MSM. The survey also evaluated hypothetical acceptability of PrEP consistent with prior intervention acceptability research [15] and explored correlates of acceptability.

Based on prior literature reviewed, we identified structural, community, and individual-level factors of significant importance to MSM health and hypothesized their mechanism of action (i.e., barrier or facilitator) on access to and acceptability of components of combination HIV prevention. We developed domain categories, adapted validated scales and items to measure these factors, and then tested our hypotheses. Barrier and facilitator variables were measured using multiple-item scales. All scales ranged from 1 to 5 except *service provider stigma*, which ranged from 0 to 1.

To assess reliability of these scales, we calculated Cronbach alphas overall. Cronbach alphas were also calculated by survey language and by participants' region of residence. As shown in Table 1, overall reliability of scales used in the analyses was acceptable (alpha levels ranged from 0.71 to 0.85).

The four accessibility outcomes of interest were measured using 5-level variables, with the lowest level indicating complete inaccessibility and the highest level indicating complete accessibility. For analysis, these variables were dichotomized so that respondents were considered to have access if they reported the highest level of accessibility.

The relationships between PrEP acceptability and hypothesized barriers and facilitators were also examined. PrEP knowledge was measured by asking two yes/no questions about PrEP and assigning a score depending on the respondent's answers to both questions.

Individual-level sociodemographic information and HIV-related clinical characteristics were collected. These included country of residence (used to determine region of residence and country income), age, sexual orientation, education, housing status, personal income, minority status (i.e., belonging to a racial or ethnic minority group in one's country), time since last HIV test, HIV status, and CD4

Table 1: Reliability scores for survey scales by region.

	Asia	Caribbean	E. Europe and Central Asia	Latin America	Middle East and N. Africa	Oceania	S-Saharan Africa	W N Europe N America	Overall
Homophobia: perceptions of homophobia in participant's country (e.g., in your country, how many people believe that a person who is gay/MSM cannot be trusted?)	0.77	0.76	0.69	0.73	0.79	0.81	0.83	0.77	**0.85**
Provider stigma: experiences of stigma from health providers (e.g., in your country, has a health provider ever treated you poorly because of your sexuality?)	0.74	0.61	0.71	0.80	0.69	0.66	0.69	0.68	**0.72**
Violence-MSM: experiences of violence for being perceived to be MSM (e.g., in the past 12 months, how often were you physically assaulted (slapped, punched, pushed, hit, or beaten) for being gay/MSM?)	0.74	0.81	0.83	0.75	0.84	0.64	0.88	0.64	**0.81**
*Violence-HIV**: experiences of violence for being HIV positive (e.g., in the past 12 months, how often were you physically assaulted (slapped, punched, pushed, hit, or beaten) for being HIV positive?)	0.77	0.79	0.73	0.64	0.85	0.44	0.89	0.53	**0.75**
Negative consequences for outness: negative experiences because the participant's sexuality is known to others (e.g., how often have you experienced negative consequences as a result of coworkers knowing that you are attracted to men?)	0.74	0.80	0.68	0.69	0.83	0.65	0.72	0.64	**0.71**
*PrEP stigma**: perceptions of stigma associated with taking PrEP (e.g., if you thought other people would find out that you were taking PrEP drugs to avoid being infected with HIV, how likely is it that you would use PrEP?)	0.79	0.68	0.76	0.74	0.77	0.64	0.73	0.67	**0.74**
Community engagement: level of engagement in social activities with other MSM (e.g., during the past 12 months, how often have you participated in gay social groups or in activities such as a book or cooking club?)	0.75	0.78	0.71	0.78	0.59	0.71	0.82	0.76	**0.76**
Connection to gay community: the degree to which the participant feels connected to a community of MSM (e.g., how connected do you feel to the gay community where you live?)	0.78	0.75	0.69	0.80	0.69	0.80	0.84	0.79	**0.78**

Table 1: Continued.

	Asia	Caribbean	E. Europe and Central Asia	Latin America	Middle East and N. Africa	Oceania	S-Saharan Africa	W N Europe N America	Overall
Comfort with provider: degree of comfort with health provider (e.g., in your country, how comfortable would you feel discussing HIV with your health care provider?)	0.77	0.76	0.73	0.70	0.83	0.72	0.71	0.76	**0.81**
Outness: to what degree the participant's sexuality is known to others (e.g., how many of your coworkers know that you are attracted to men?)	0.81	0.86	0.76	0.80	0.83	0.79	0.82	0.76	**0.84**
PrEP knowledge[*]: (e.g., do you know what PrEP is? Have you ever heard of taking HIV medications to avoid being infected with HIV?)	0.61	0.60	0.69	0.69	0.85	0.72	0.73	0.69	**0.72**
PrEP acceptability[*]: (e.g., how comfortable are you with the idea of using HIV medications to avoid becoming infected with HIV?)	0.78	0.78	0.79	0.77	0.85	0.85	0.84	0.84	**0.82**

[*]The scales for PrEP knowledge, stigma, and acceptability were only measured among respondents who reported being HIV negative or being unsure of their HIV status. Violence-HIV was only measured among respondents who reported living with HIV.

count (among survey participants who reported being HIV positive).

Country income was also investigated for its potential impact on access to services and PrEP acceptability. The country income variable was derived from World Bank classifications of country income [16].

The survey was originally developed in English and then translated into Chinese, French, Georgian, Russian, and Spanish, then quality-checked by key informants at the country-level utilizing back translation techniques [17]. A final draft of the survey was then pilot tested in English, Spanish, and French with key informants in an effort to increase its face validity among prospective respondents for whom the survey was intended [18].

2.3. Data Analysis. For this analysis, we excluded participants with missing or incomplete responses and participants who self-identified as heterosexual or "straight." We dichotomized our primary outcomes of interests on service access as reporting the highest level of accessibility (i.e., "easily accessible") versus otherwise.

Because access to HIV services is partially dependent on contextual variables (e.g., the state of the health system), it is likely that observations within countries are correlated with each other. Similarly, observations of PrEP acceptability might be correlated within countries since detailed information on PrEP might be differentially available across countries.

We used two different approaches for analyzing the data while accounting for this within-country correlation. These approaches were each consistent with the different goals of bivariate and multivariable analyses, respectively [19].

In bivariate analysis, we fitted regression models estimated using general estimating equations (GEE) with exchangeable correlation structure. Clusters were defined by country of residence. This approach allowed us to calculate the crude associations between the predictors and outcomes of interest; that is, the approach allowed us to calculate odds ratios that were not adjusted for potential confounders or unmeasured contextual factors. We used Wald tests to determine the statistical significance of predictors. Those variables that were statistically significant (with $P < 0.2$) were included in the multivariable model.

In multivariable analysis, we fitted logistic random effects regression models with random intercepts for respondents' country of residence. These models evaluated the relationship between our independent variables of interest and reporting of the highest level of access to condoms, lubricants, HIV testing, and HIV treatment, while adjusting for potential confounders (age, HIV status, education, housing status, personal income, and minority status) and also controlling for unmeasured contextual variables that occur at the country level. The continuous outcome for PrEP acceptability was modeled using multivariable linear random effects regression.

All data analysis was carried out using the statistical package, R.

3. Results

3.1. Respondent Characteristics. Of the 5779 men who accessed the survey, 3748 participants met the criteria for inclusion in this analysis. The majority of surveys were completed in English (58%, $N = 2190$), followed by Spanish (17%, $N = 654$), Russian (12%, $N = 434$), Chinese (9%, $N = 339$), French (3%, $N = 117$), and Georgian (<1%, $N = 14$). The mean age of participants was 35 (range: 12–90 years old). Participants described themselves as "gay" (89%, $N = 3328$) and "bisexual" (11%, $N = 420$).

A total of 145 countries were represented in the sample analyzed. Twenty-one percent of respondents were from low or lower-middle income countries. The sample contained a high degree of diversity by region. The sample was also diverse in regard to individual-level demographic variables, including age, education level, housing status, and personal income level (see Table 2).

Fifty-five percent of HIV-negative respondents ($N = 1709$) reported having been tested for HIV in the last 12 months, and 21% indicated having never been tested for HIV. Eighteen percent of respondents reported that they were living with HIV ($N = 669$). Of these respondents, the majority (83%) reported that they were taking antiretroviral medication. Forty-four percent of men living with HIV also reported a CD4 count of 500 or above. Among study participants living with HIV whose CD4 count was lower than 350, 21% reported not taking antiretroviral medications.

A low percentage of respondents reported that condoms, lubricant, and HIV testing were easily accessible (see Figure 1).

Nearly half of HIV-negative respondents reported low levels of knowledge about PrEP (48%), with the remaining participants split between medium (23%) and high (29%) levels of PrEP knowledge.

3.2. Bivariate Analyses: Factors Associated with Service Access and PrEP Acceptability. In bivariate analyses, homophobia and experiences of violence for being MSM were significantly associated with lower odds of having easy access to condoms, lubricants, HIV testing, and HIV treatment. Increased service provider stigma was significantly associated with lower odds of having easy access to condoms, lubricants, and HIV testing but was not associated with access to HIV treatment. Among respondents living with HIV, having experienced violence for being HIV positive was significantly associated with lower access to HIV treatment.

Conversely, community engagement, connection to gay community, and comfort with service provider were each significantly associated with higher odds of having easy access to condoms, lubricants, HIV testing, and HIV treatment. Bivariate associations were also found between country income, age, housing status, minority status, and easy access to HIV service types assessed. The odds ratio for each of these associations is shown in Table 3 below.

Homophobia ($\beta = 0.20$; 95% CI: 0.15–0.25, $P = 0.000$), service provider stigma ($\beta = 0.18$; 95% CI = 0.07–0.30, $P = 0.002$), and having experienced violence for being MSM ($\beta = 0.17$; 95% CI = 0.12–0.22, $P = 0.000$) were significantly and positively associated with greater PrEP acceptability, whereas outness ($\beta = -0.11$; 95% CI: −0.13 to −0.08, $P = 0.000$) and community engagement ($\beta = -0.09$; 95% CI: −0.17 to −0.02, $P = 0.018$) were significantly and negatively associated. PrEP knowledge ($\beta = -0.18$; 95% CI: −0.23 to −0.14) and PrEP stigma ($\beta = -0.42$; 95% CI: −0.45 to −0.39, $P = 0.000$) were also negatively associated with PrEP acceptability. Finally, compared to participants in high-income countries, participants expressed higher acceptability of PrEP in low income ($\beta = 0.84$; 95% CI: 0.59–1.11), lower-middle income ($\beta = 0.59$; 95% CI: 0.48–0.69), and upper-middle income ($\beta = 0.37$; 95% CI: 0.29–0.45) countries.

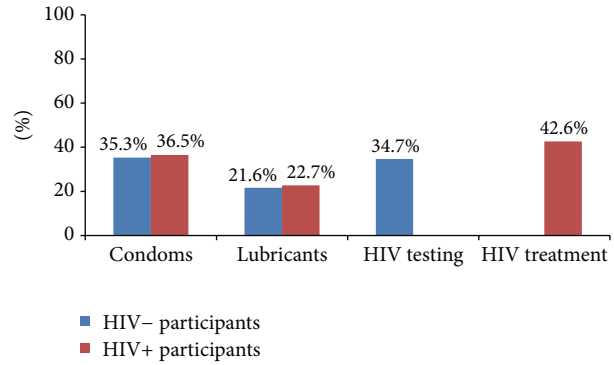

Figure 1: Percent of respondents who reported easy access to services.

3.3. Adjusted Multivariable Analyses. As summarized in Table 4, the highest level of access to condoms was independently associated with lower homophobia, fewer experiences of service provider stigma, more community engagement, greater connection to gay community, more comfort with service provider, and less outness, while adjusting for having experienced violence for being MSM, country income, and demographic variables.

The highest level of access to lubricants was independently associated with lower homophobia, more community engagement, greater connection to gay community, more comfort with service provider, and less outness, while adjusting for service provider stigma, having experienced violence for being MSM, country income, and demographic characteristics.

The highest level of access to HIV testing was independently associated with lower homophobia, greater connection to gay community, and more comfort with service provider, while adjusting for provider stigma, outness, having experienced violence for being MSM, country income and demographic characteristics.

Among participants living with HIV, the highest level of access to HIV treatment was independently associated with lower homophobia and higher comfort with service provider, while adjusting for outness, having experienced violence for being MSM, community engagement, connection to gay community, country income, and demographic characteristics.

Table 2: Respondent sociodemographic and clinical characteristics.

	All participants		Included in analysis	
	n	%	*n*	%
Total	**5779**		**3748**	
Region				
Asia	1635	28%	980	26%
Caribbean	126	2%	89	2%
Eastern Europe and Central Asia	966	17%	629	17%
Latin America	880	15%	567	15%
Middle East and North Africa	129	2%	67	2%
Oceania	288	5%	226	6%
Sub-Saharan Africa	380	7%	202	5%
Western and Northern Europe and North America	1375	24%	988	26%
Age category				
<18	72	1%	35	1%
18–25	1221	22%	699	19%
26–30	1194	22%	772	21%
31–40	1426	26%	989	26%
41–50	839	15%	626	17%
51–60	511	9%	414	11%
>60	242	4%	212	6%
Sexual orientation				
Other	81	2%	0	0%
Homosexual/gay	4459	84%	3328	89%
Bisexual	676	13%	420	11%
Heterosexual/straight	102	2%	0	0%
Education				
No postsecondary	1034	19%	652	17%
Postsecondary	4358	81%	3096	83%
Housing status				
Stable place to live	4160	77%	2990	80%
Unstable or no place to live	1232	23%	758	20%
Personal income				
None	561	10%	310	8%
Low/impoverished	433	8%	288	8%
Low middle	1713	32%	1202	32%
Middle	2379	44%	1725	46%
High	306	6%	223	6%
Time since last HIV test (HIV-negative participants)				
<6 months	1195	37%	1142	37%
6–12 months	590	18%	567	18%
1–3 years	482	15%	459	15%
>4 years	282	9%	273	9%
I have never been tested in HIV	679	21%	638	21%
Time since last HIV test (HIV-positive participants)				
In the last 6 months	259	37%	248	37%
Between last 6 months and 1 year ago	56	8%	50	7%
1–3 years ago	71	10%	64	10%
More than 3 years ago	316	45%	306	46%
I have never been tested in HIV	1	0	1	0

Table 2: Continued.

	All participants		Included in analysis	
	n	%	*n*	%
HIV status				
HIV negative or status unknown	3228	82%	3079	82%
HIV positive	703	18%	669	18%
CD4 count				
<500	386	56%	373	56%
>500	309	44%	296	44%

Results of the multivariable linear random effects regression model indicate that higher acceptability of PrEP was independently associated with lower PrEP stigma ($\beta = -0.51$; 95% CI: −0.55 to −0.48, $P = 0.000$), less outness ($\beta = -0.15$; 95% CI: −0.18 to −0.12, $P = 0.000$), more service provider stigma ($\beta = 0.12$; 95% CI: 0.02 to 0.23, $P = 0.021$), and less knowledge about PrEP ($\beta = -0.14$; 95% CI: −0.18 to −0.10, $P = 0.000$), while adjusting for homophobia, having experienced violence for being MSM, community engagement, country income level, and demographic characteristics. In this model, respondents in high-income countries reported less acceptability of PrEP than respondents in low-income ($\beta = 0.55$; 95% CI: 0.27 to 0.82, $P = 0.000$), lower-middle-income ($\beta = 0.43$; 95% CI: 0.25 to 0.61, $P = 0.000$), and upper-middle-income countries ($\beta = -0.19$; 95% CI: 0.02 to 0.35, $P = 0.031$).

4. Discussion

For combination prevention to be successful among MSM, we must ensure access to basic HIV services while promoting acceptability of new biomedical interventions. Our survey findings show that MSM worldwide have unacceptably poor access to the most essential HIV prevention tools. Just more than a third of MSM surveyed reported that condoms and HIV testing were easily accessible, and even fewer (21%) reported easy access to lubricants. Forty-three percent of MSM living with HIV reported that treatment was easily accessible, and these men had significantly less access to condoms or lubricants than they did to HIV treatment. Furthermore, our study found that among MSM homophobia functioned as a consistent barrier to accessing HIV services. We observed that higher levels of homophobia were significantly associated with lower odds of having easy access to condoms, lubricants, HIV testing, and HIV treatment.

These findings corroborate previous research indicating that structural barriers at the policy and social levels play a central role in hindering access to condoms, lubricants, HIV testing, and HIV treatment for MSM around the world [20–22]. Similarly, in a separate qualitative study of MSM and sexual health conducted by the MSMGF, focus group participants in Kenya, Nigeria, and South Africa described how criminalization and social stigma negatively affected both health seeking behavior and access to services [23]. Criminalization and stigma often lead to social alienation, poor health and mental health outcomes, and further declines in access to services and health seeking behavior among MSM [24–33]. Our findings call attention to the urgency of addressing structural barriers to HIV service access for MSM. Within efforts to implement combination prevention, structural level interventions that combat homophobia should be prioritized.

Our data also revealed facilitators of HIV service access for MSM. Specifically, we found that greater levels of community engagement, connection to gay community, and comfort with service providers were consistently and significantly associated with greater access to condoms, with greater access to condoms, lubricants, HIV testing, and HIV treatment. This finding is in line with other studies which have documented the importance of local community-based organizations as safe spaces for MSM to meet other men like themselves and to receive health services from knowledgeable, nonjudgmental service providers who understand the health needs of MSM from a holistic perspective [34]. Strong relationships with family and community were noted in these reports as facilitators of health and wellbeing, as was the ability to access stable educational and employment opportunities [23].

In addition, we found that acceptability of PrEP was independently associated with lower PrEP stigma. However, individuals who exhibited high knowledge of PrEP reported lower acceptability for PrEP. Prior research has shown similar findings among MSM [35, 36]. Other potential barriers to PrEP acceptability among MSM documented in previous research include the intervention's costs, its moderate efficacy, and potential side effects [37, 38]. It is possible that MSM with high PrEP knowledge also have high levels of awareness of these limitations [39, 40]. Thus, MSM with high knowledge of PrEP may be more cautious of the application of this intervention, especially if local and in-country efforts to increase access to more established HIV prevention and treatment interventions have not been fully realized.

Also contrary to the expectations of the research team, results from the analysis indicated that outness served as a barrier to condom and lubricant access, while controlling for all other variables examined in the survey (including homophobia and connection to the gay community). Furthermore, we learned that respondents who were less out about their sexual orientation and respondents who reported having experienced violence as a result of being MSM were more likely to find PrEP acceptable. This may be due to the fact that outness can result in further stigmatization of MSM in some country contexts, increasing the impact of homophobia [41].

Table 3: Bivariate associations between hypothesized predictor variables and highest access to HIV services.

	Condoms			Lubricants			HIV testing*			HIV treatment*		
	OR	CI	*P*	OR	CI	*P*	OR	CI	*P*	OR	CI	*P*
Homophobia	**0.53**	**0.48–0.59**	**0.000**	**0.39**	**0.35–0.44**	**0.000**	**0.38**	**0.33–0.42**	**0.000**	**0.38**	**0.29–0.49**	**0.000**
Violence-MSM	**0.84**	**0.76–0.93**	**0.001**	**0.67**	**0.58–0.78**	**0.000**	**0.73**	**0.65–0.83**	**0.000**	**0.64**	**0.51–0.80**	**0.000**
Violence-HIV*										**0.60**	**0.43–0.84**	**0.003**
Provider stigma	**0.57**	**0.46–0.70**	**0.000**	**0.69**	**0.53–0.91**	**0.007**	**0.61**	**0.47–0.80**	**0.000**	0.77	0.54–1.10	0.152
PrEP stigma												
Outness	**1.20**	**1.14–1.26**	**0.000**	**1.22**	**1.15–1.30**	**0.000**	**1.37**	**1.29–1.46**	**0.000**	**1.28**	**1.08–1.51**	**0.005**
Community Engagement	**1.59**	**1.40–1.79**	**0.000**	**1.53**	**1.34–1.75**	**0.000**	**1.72**	**1.49–1.98**	**0.000**	**1.33**	**1.03–1.72**	**0.032**
Connection to gay community	**1.41**	**1.29–1.53**	**0.000**	**1.41**	**1.27–1.56**	**0.000**	**1.54**	**1.40–1.69**	**0.000**	**1.26**	**1.05–1.53**	**0.014**
Comfort with provider	**1.72**	**1.59–1.86**	**0.000**	**1.97**	**1.78–2.19**	**0.000**	**2.40**	**2.17–2.66**	**0.000**	**1.74**	**1.45–2.09**	**0.000**
PrEP knowledge												
Age (measured in decades)	**1.08**	**1.03–1.14**	**0.004**	**1.23**	**1.16–1.30**	**0.000**	**1.41**	**1.32–1.50**	**0.000**	**1.18**	**1.02–1.36**	**0.027**
Country income			**0.000**			**0.000**			**0.000**			**0.000**
High income (referent)												
Low income	**0.60**	**0.38–0.93**		**0.15**	**0.07–0.34**		**0.43**	**0.27–0.70**		**0.19**	**0.06–0.63**	
Lower-middle income	**0.55**	**0.45–0.68**		**0.30**	**0.23–0.39**		**0.26**	**0.20–0.32**		**0.38**	**0.21–0.67**	
Upper-middle income	**0.49**	**0.42–0.57**		**0.32**	**0.27–0.39**		**0.29**	**0.24–0.35**		**0.56**	**0.38–0.83**	
HIV status			0.565			0.542						
No HIV positive (referent)												
HIV positive	1.05	0.88–1.25		1.07	0.87–1.31							
Education			0.514			0.078			0.985			0.381
No postsecondary (referent)												
Postsecondary	0.94	0.79–1.13		0.83	0.67–1.02		1.00	0.82–1.22		0.83	0.55–1.25	
Personal income			0.026			0.020			0.000			0.246
None (referent)												
Low income/impoverished	1.22	0.88–1.71		1.17	0.79–1.72		1.40	0.95–2.06		1.13	0.40–3.16	
Low-middle	0.93	0.72–1.21		0.97	0.71–1.31		1.06	0.79–1.41		0.96	0.37–2.44	
Middle	1.19	0.92–1.53		1.24	0.92–1.67		1.32	1.01–1.73		0.83	0.33–2.13	
High	1.24	0.87–1.77		1.54	1.03–2.29		2.00	1.37–2.93		1.93	0.59–6.26	
Housing status			**0.000**			**0.000**			**0.000**			0.078
Stable place to live (referent)												
Unstable or no place	**0.67**	**0.56–0.80**		**0.60**	**0.47–0.75**		**0.56**	**0.46–0.69**		0.70	0.47–1.04	
Minority status			**0.001**			**0.025**			**0.030**			0.127
Not minority (referent)												
Minority	**1.30**	**1.11–1.52**		**1.22**	**1.02–1.45**		**1.21**	**1.02–1.44**		0.78	0.57–1.07	

*Violence-HIV and HIV treatment access were only measured among participants who reported being HIV positive. Bivariate associations with HIV testing access were calculated among HIV negative participants.

Because homophobia is a barrier to HIV service access, MSM may be concealing their sexual orientation to secure easier access to condoms and lubricants, especially if outness is viewed with disdain by the mainstream public and therefore stigmatizing [42, 43]. Likewise, MSM who have experienced violence or are living in more difficult country contexts may be more open to prevention options that they perceive as less stigmatizing and/or options which they know less about. More research is needed to better understand these associations.

In summary, findings from our study indicate an urgent need to scale up access to basic proven prevention tools and

Table 4: Multivariable logistics random effects modeling of factors associated with access to HIV prevention and treatment services.

	Condoms			Lubricants			HIV testing*			HIV treatment*		
	OR	CI	*P*	OR	CI	*P*	OR	CI	*P*	OR	CI	*P*
Homophobia	**0.65**	**0.56–0.75**	**0.000**	**0.54**	**0.46–0.65**	**0.000**	**0.64**	**0.54–0.76**	**0.000**	**0.52**	**0.36–0.76**	**0.001**
Violence-MSM	0.98	0.87–1.12	0.806	0.91	0.77–1.08	0.289	0.90	0.77–1.06	0.200	1.14	0.77–1.67	0.518
Violence-HIV*										0.71	0.42–1.19	0.191
Provider stigma	**0.72**	**0.57–0.91**	**0.007**	1.12	0.84–1.48	0.445	1.14	0.84–1.55	0.408			
Outness	**0.93**	**0.87–0.99**	**0.034**	**0.87**	**0.80–0.95**	**0.002**	0.99	0.91–1.07	0.719	1.13	0.92–1.38	0.238
Community engagement	**1.26**	**1.09–1.47**	**0.002**	**1.25**	**1.04–1.48**	**0.014**	1.18	0.98–1.42	0.081	1.14	0.80–1.62	0.465
Connection to gay community	**1.18**	**1.06–1.30**	**0.002**	**1.18**	**1.05–1.34**	**0.008**	**1.21**	**1.06–1.36**	**0.003**	1.10	0.85–1.42	0.483
Comfort with provider	**1.40**	**1.27–1.54**	**0.000**	**1.53**	**1.36–1.72**	**0.000**	**1.85**	**1.65–2.08**	**0.000**	**1.82**	**1.40–2.38**	**0.000**

*Violence-HIV and HIV treatment access were only measured among participants who reported being HIV positive. The model for HIV testing included only HIV negative participants.

services with the development and rollout of combination prevention for MSM. This is especially critical when considering the interdependent nature of different prevention interventions in maximizing the potential effectiveness of combination approaches. For example, minimizing condom slippage and breakage during anal sex can be aided by proper use of condom-compatible lubricants [44], which is only possible if lubricants are easily accessible. Similarly, the success of PrEP will be contingent upon the success of HIV-testing programs [45]. Challenges accessing any one intervention will likely set off a domino effect, undermining the overall potential of combination prevention approaches for MSM.

4.1. Limitations. This study had several limitations that are important to note. First, the survey data was gathered using a convenience sample, creating the possibility of selection bias for MSM who are more socially connected to MSM organizations or online MSM communication infrastructure, as well as those who have web and E-mail access. As a likely result, levels of participation were limited among MSM in regions where internet access is generally difficult, including Sub-Saharan Africa and the Pacific Islands. On the other hand, levels of participation may have been greater among MSM with higher levels of community involvement with MSM organizations. Hence, our findings may not be generalizable to all MSM.

It is striking that, among a sample of MSM, most of whom are linked to MSM organizations from which we recruited and to MSM-focused websites where the study was advertised, the proportion of MSM with easy access to condoms, lubricants, testing, and treatment is low. It is possible that among MSM who are not connected with MSM organizations or who do not have access to the internet, access to HIV services is even lower. Moreover, there may also be selection bias for MSM who are particularly motivated to participate. Thus, it is conceivable that data from our sample may be overestimating levels of access and knowledge.

In addition, our analyses explored the relationship between understudied social and structural factors and access to HIV services, testing multiple *a priori* hypotheses informed by the literature. Given the exploratory nature of these analyses, we did not formally adjust for multiple comparisons; thus, findings of nominal significance should be interpreted with caution [46].

Finally, the cross-sectional design of this study limits our ability to make causal inferences from our findings.

5. Conclusion

The study findings underscore the need to improve access to basic HIV prevention and treatment services among MSM before we can fully realize the potential of well-planned, locally relevant combination prevention. Structural, community, and individual-level barriers and facilitators to service access must be addressed on multiple fronts. Interventions must both disrupt the negative effects of barriers *and* support the protective effects of facilitators [47]. Given the positive impact of community engagement and comfort with service providers on access to services, supporting MSM-led community-based organizations to provide a safe space for MSM to access services and connect with the local gay community may be a highly effective strategy for addressing these issues [48]. Finally, when considering the implementation of combination prevention, study findings indicate a need for the dissemination of more and better information about PrEP. Adequately addressing knowledge, perceptions and concerns MSM have about HIV prevention interventions, including but not limited to PrEP, may be critical to their acceptance as part of combination prevention approaches.

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Review Article

The Role of Sexually Transmitted Infections in HIV-1 Progression: A Comprehensive Review of the Literature

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Due to shared routes of infection, HIV-infected persons are frequently coinfected with other sexually transmitted infections (STIs). Studies have demonstrated the bidirectional relationships between HIV and several STIs, including herpes simplex virus-2 (HSV-2), hepatitis B and C viruses, human papilloma virus, syphilis, gonorrhea, chlamydia, and trichomonas. HIV-1 may affect the clinical presentation, treatment outcome, and progression of STIs, such as syphilis, HSV-2, and hepatitis B and C viruses. Likewise, the presence of an STI may increase both genital and plasma HIV-1 RNA levels, enhancing the transmissibility of HIV-1, with important public health implications. Regarding the effect of STIs on HIV-1 progression, the most studied interrelationship has been with HIV-1/HSV-2 coinfection, with recent studies showing that antiherpetic medications slow the time to CD4 <200 cells/μL and antiretroviral therapy among coinfected patients. The impact of other chronic STIs (hepatitis B and C) on HIV-1 progression requires further study, but some studies have shown increased mortality rates. Treatable, nonchronic STIs (i.e., syphilis, gonorrhea, chlamydia, and trichomonas) typically have no or transient impacts on plasma HIV RNA levels that resolve with antimicrobial therapy; no long-term effects on outcomes have been shown. Future studies are advocated to continue investigating the complex interplay between HIV-1 and other STIs.

1. Introduction

Individuals infected with human immunodeficiency virus-1 (HIV-1) are often coinfected with other sexually transmitted infections (STIs) due to shared routes of transmission. Over the past decade, there has been mounting evidence of the bidirectional relationship between HIV-1 and other STIs. Initially, studies showed that HIV-1-infected persons may be at risk for more frequent and severe forms of STIs as well as poorer treatment outcomes, especially in cases of concurrent herpes simplex virus-2 (HSV-2) and syphilis infection. More recent data have demonstrated that certain concomitant STIs directly affect HIV-1 transmissibility and may alter HIV-1 control and increase progression to AIDS. This review summarizes the current literature regarding the most common STIs (HSV-2, hepatitis B virus, hepatitis C virus, human papilloma virus, syphilis, gonorrhea, chlamydia, and trichomonas) and their impact on HIV-1 progression.

2. Herpes Simplex Virus Type-2

Most persons who are infected with HIV-1 are also infected with HSV-2, with published seropositivity rates of 50–90% [1, 2]. Globally, HSV-2 is the most common cause of genital ulcer disease (GUD), and studies indicate a strong, synergistic relationship between the dual epidemics of HIV-1 and HSV-2 [3]. HSV-2 has been shown to play an important role in the spread of HIV-1 (a 3-fold higher risk of acquisition) [4] and has been estimated to contribute over 25% of incident HIV-1 infections in areas of high HSV-2 prevalence (e.g., Africa) [5]. This increased risk likely occurs through multiple

mechanisms, including the presence of mucosal disruption and the influx of cells expressing chemokine receptor 5 (CCR5) [6, 7]. Additionally, there is increased HIV-1 shedding in genital secretions [8] due to local inflammation and the interactions between HSV-2 proteins and the HIV-1 long terminal repeat (LTR) genes and *Tat* protein [9–11]. HSV-2 and HIV-1 can infect the same cells, and HSV-2 proteins ICP-10, ICP-27, and ICP-4 have been shown to upregulate HIV-1 replication by their interactions with the HIV-1 LTR region. Further, HSV-2 protein 16 interacts with the HIV-1 *Tat* protein and increases HIV-1 transcription [9–13]. As a result, HSV-2 may not only enhance HIV-1 transmission, but it may also have a significant impact on HIV-1 viral control and disease progression among coinfected patients.

Regarding the impact of HSV-2 on the HIV-1 coinfected patient, studies have demonstrated that HSV-2 increases both genital and plasma HIV-1 RNA levels. Initial studies demonstrated that HSV-2 reactivation, with the presence of clinical lesions, was associated with transient increases in genital shedding and levels of plasma HIV-1 RNA [14, 25]. Additionally, HSV-2 replication and shedding occur in the absence of symptoms, suggesting that the impact of HSV-2 extends beyond the timing of clinical HSV-2 lesions. Several studies have demonstrated that asymptomatic HSV-2 shedding significantly increases mean genital and plasma HIV-1 RNA levels and results in higher HIV-1 viral load set points [8, 14, 26, 27]. These findings suggest that HSV-2 coinfection may have important implications for both the spread of HIV-1 and HIV-1 virologic control of the coinfected patient.

Given the potential role of HSV-2 on HIV-1 infection, several studies have evaluated the impact of antiherpetic medications on genital and plasma HIV-1 RNA levels in HIV-1/HSV-2 coinfected persons (Table 1) [8, 14–24]. A small study by Schacker et al. ($n = 12$) showed that acyclovir reduced plasma HIV-1 RNA levels among coinfected persons, with an average reduction of 48% [14].

Eight randomized studies subsequently examined the impact of antiherpetic suppressive treatment on plasma HIV-1 RNA levels among HIV-1/HSV-2 coinfected persons not receiving combination antiretroviral therapy (CART) (Table 1). The first study found that valacyclovir 500 mg twice daily versus placebo in a cohort of 136 women in Burkina Faso with HIV-1/HSV-2 coinfection reduced both cervical (−0.29 $\log_{10}$ copy/mL, 95% confidence interval [CI]: −0.44, −0.15) and plasma (−0.53 $\log_{10}$ copy/mL, 95% CI: −0.72, −0.35) HIV-1 RNA levels [8]. Additional studies involving diverse HIV-1 populations are shown in Table 1. In the largest study to date, Celum et al. examined the effect of long-term acyclovir use in a study designed to determine if HIV-1 transmission rates among discordant couples could be reduced with acyclovir [19]. A randomized, placebo-controlled trial of acyclovir (400 mg twice daily for 102 weeks) among 3,408 African heterosexual couples reported a reduction in the mean plasma concentration of HIV-1 by $-0.25\log_{10}$ copies/mL (95% CI: −0.29, −0.22; $P < 0.001$) in men and women, although the study failed to show a reduction in HIV-1 transmission rates. Mugwanya et al. evaluated whether higher doses of antiherpetic medications were more effective at reducing HIV-1 RNA levels [21]. A randomized, crossover trial of two types and doses of antiherpetic medications was evaluated (valacyclovir 1.5 g versus acyclovir 400 mg twice daily for 12 weeks) in 32 HIV-1/HSV-2 dually infected Kenyan individuals with CD4 cell counts >250 cells/mL and not on CART. Mean plasma HIV-1 levels were significantly lower in the valacyclovir compared with the acyclovir arm: −0.62 $\log_{10}$ copies/mL (95% CI: −0.68, −0.55; $P < 0.001$, a 76% decrease), and valacyclovir decreased the viral load by >1 log compared with baseline pretreatment values. This study suggested that higher doses of antiherpetic medications may offer greater benefit in reducing HIV-1 RNA levels and revealed no increase in adverse events using the higher dose.

In summary, these studies examined both male and female HIV-1/HSV-2 coinfected patients from a variety of geographic locations and demonstrated that antiherpetic medications (typically using 400–800 mg of acyclovir twice daily or valacyclovir 500 mg twice daily) for 1–3 months reduced the plasma HIV-1 levels by 0.26 to 0.47 $\log_{10}$ copies/mL among HIV-1 patients not receiving CART.

A meta-analysis recently summarized the randomized evidence (2000–2009) regarding the association between antiherpetic medications and plasma HIV-1 RNA levels [28], with a summary effect estimate of −0.33 (95% CI: −0.56, −0.10) $\log_{10}$ copies, an approximate halving of HIV-1 plasma viral load. Of note, characteristics associated with a larger decrease in HIV-1 viral load included older median age, valacyclovir use, and higher compliance rates [28]. These randomized studies clearly show the benefit of antiherpetic medications in reducing HIV RNA levels in the setting of asymptomatic HSV-2 coinfection. The reduction in HIV-1 RNA loads by these agents is due to suppression of HSV-2 replication and its interaction with the HIV-1 virus, as described above, as well as the potential direct antiretroviral effects of acyclovir [29–31].

Unlike prior studies that examined the impact of antiherpetic therapy among HIV-1 patients not receiving CART, a randomized, double-blind, and placebo-controlled trial of valacyclovir 500 mg twice a day in HIV-1/HSV-2-infected women on CART, with a similar design as the study by Nagot et al. [8], showed no significant impact on the frequency or quantity of genital HIV-1 RNA [22]. The plasma HIV-1 RNA was reduced ($-0.41\log_{10}$ copy/mL), although this did not reach statistical significance, perhaps due to small sample size. Further studies are needed to examine the benefit of antiherpetic medication on systemic HIV-1 control in this setting.

While these studies demonstrated that antiherpetic therapy reduces genital and plasma HIV-1 RNA levels among patients not receiving CART [8, 14–21], whether this therapy could slow HIV-1 clinical progression was not specifically examined. Since higher plasma HIV-1 RNA levels are associated with faster HIV-1 disease progression [32], it was hypothesized that HSV-2 suppression may slow HIV-1 progression. A recent review noted that a reduction in HIV-1 viral load of 0.3 $\log_{10}$ or 0.5 $\log_{10}$ may slow HIV-1 clinical progression by 25% to 44%, respectively [33]. Additionally, during early trials of antiretroviral therapy (ART), acyclovir was associated with increased survival [34]. Hence, clinical trials

Table 1: Studies evaluating the impact of HSV-2 suppressive treatment on HIV-1 plasma RNA levels and progression.

First author and reference	Publication year	Sample size	Study	Location	Intervention	Genital HIV-1 RNA change (log_{10} copy/mL)	Plasma HIV-1 RNA change (log_{10} copy/mL)	Clinical outcomes
Studies examining the impact on plasma and/or genital viral load coinfected patients off CART								
Schacker [14]	2002	12 (no CART); 1 patient on dual therapy	Single-arm study	USA	Acyclovir 800 mg three times daily for 8 weeks; no treatment during the preceding and subsequent 8-week periods	NR	48% reduction in RNA levels	NR
Nagot [8]	2007	136 women (no CART)	Randomized study	Burkina Faso	Valacyclovir 500 mg twice daily versus placebo for 12 weeks	Cervical: −0.53 (95% CI: −0.72, −0.35)	−0.29 (95% CI: −0.44, −0.15)	NR
Zuckerman [15]	2007	20 MSM (no CART)	Placebo-controlled crossover	Lima, Peru	Valacyclovir 500 mg twice daily versus placebo (8 weeks for each arm)	Rectal levels: −0.16 (95% CI: −0.07, −0.25; $P = 0.0008$), 33% decrease	−0.33 (95% CI: −0.23, −0.42; $P < 0.0001$), 53% decrease	NR
Dunne [16]	2008	67 women (no CART)	Placebo-controlled crossover	Chiang Rai, Thailand	Acyclovir 800 mg twice daily versus placebo (1 month each phase)	Cervicovaginal levels: −0.3, $P < 0.01$	−0.47, $P < 0.01$	NR
Baeten [17]	2008	20 women (no CART)	Placebo-controlled crossover	Peru	Valacyclovir 500 mg twice daily versus placebo (8-week treatment)	Cervical levels: −0.35, a 55% decrease, and $P < 0.001$	−0.26, a 45% decrease [$P < 0.001$]	NR
Delany [18]	2009	300 women (no CART)	Randomized study	South Africa	Acyclovir 400 mg twice daily versus placebo (3 months)	Cervicovaginal levels: 0.13 (95% CI: −0.14, 0.39)	−0.34 (95% CI: −0.15, −0.54)	NR
Celum* [19]	2010	3,360 heterosexual men and women (no CART)	Randomized study	South and East Africa	Acyclovir 400 mg twice daily for up to 102 weeks	NR	−0.25 (95% CI: −0.29, −0.22), $P < 0.001$	NR
Tanton [20]	2010	484 women (no CART)	Randomized study	Tanzania	Acyclovir 400 mg twice daily versus placebo for 6 months	Cervicovaginal levels: −0.01 (95% CI: −0.20, 0.19)	0.04 (95% CI: −0.07, 0.15)	NR
Mugwanya [21]	2011	32 men and women (no CART)	Placebo-controlled crossover	Kenya	Valacyclovir 1.5 g twice daily versus acyclovir 400 twice daily (12 weeks)	NR	−0.62 (95% CI: −0.68, −0.55, $P < 0.001$)	NR
Studies examining the impact on plasma and/or genital viral load coinfected patients on CART								
Ouedraogo [22]	2006	60 women (on CART)	Randomized study	Burkina Faso	Valacyclovir 500 mg twice daily versus placebo for 12 weeks	Cervicovaginal levels: −0.41 (95% CI: −1.35, 0.53)	−0.33 (95% CI: −0.81, 0.16)	NR

Table 1: Continued.

First author and reference	Publication year	Sample size	Study	Location	Intervention	Genital HIV-1 RNA change (log_{10} copy/mL)	Plasma HIV-1 RNA change (log_{10} copy/mL)	Clinical outcomes
Studies examining the impact on clinical HIV-1 progression								
Lingappa* [23]	2010	3,381 heterosexual men and women (no CART)	Randomized study	East and Southern Africa	Acyclovir 400 mg twice daily versus placebo for 24 months	NR	*	16% reduction in HIV-1 progression (HR 0.84, 95% CI: 0.71, 0.98)
Reynolds [24]	2012	440 (no CART)	Randomized study	Uganda	Acyclovir 400 mg twice daily versus placebo for 24 months	NR	NR	25% reduction in progression (HR: 0.75, 95% CI: 0.59, 0.99)

*Utilized same study population.
CART: combination antiretroviral therapy; CI: confidence interval; HR: hazard ratio; NR: not reported.

were undertaken to determine if the use of acyclovir could slow HIV-1 progression.

Lingappa et al. [23] randomized 3,381 HIV-1/HSV-2 dually infected heterosexuals to acyclovir 400 mg twice daily or placebo for 24 months (Table 1). All participants had a CD4 cell count ≥250 cells/μL and were not receiving CART. HIV-1 progression was defined as a CD4 cell count <200 cells/μL, CART initiation, or a nontrauma-related death. The receipt of acyclovir was associated with a 16% reduction in HIV-1 progression (hazard ratio [HR] = 0.84, 95% CI: 0.71, 0.98, and $P = 0.03$), as well as with a delayed risk of reaching a CD4 cell count <350 cells/μL (HR = 0.81, 95% CI: 0.71, 0.93, and $P = 0.002$). Assuming that the incidence of endpoints remained constant over time, acyclovir would have delayed the median time to an endpoint by estimated 10.7 months. A second study on HIV-1 progression [24] investigated the effect of daily suppressive acyclovir on HIV-1 disease progression in patients with CD4 cell counts of 300–400 cells/μL who were not receiving CART. Participants were randomized to acyclovir 400 mg twice daily or placebo and followed for 24 months. The treatment group had a 25% reduced risk of developing a CD4 cell count <250 cells/μL or initiating of CART for WHO stage 4 disease. In addition to these studies [23, 24], one study evaluated the impact of acyclovir (400 mg twice daily) versus placebo on the viral load set point during early HIV-1 infection ($n = 76$) but found no significant effect [35].

Overall, these studies provide strong evidence that antiherpetic medications reduce both plasma and genital HIV-1 RNA levels among chronically infected HIV-1 patients who are coinfected with HSV-2. Antiherpetic medication may offer an important and viable strategy to reduce HIV-1 progression in the setting of limited CART availability or among patients wishing to remain off CART. Advantages of antiherpetic medication use in these settings include its low cost (i.e., available as a generic medication), excellent tolerability, lack of need for specific laboratory monitoring, and low frequency of adverse events. Therapy is most advantageous when utilized continuously, since the interruption of therapy is associated with viral rebound [21]. The effect of antiherpetic medication on plasma HIV-1 concentrations can be seen within a week of initiation [21], with no reduction in efficacy noted over time [23]. The added value of antiherpetic medications concurrently with CART or in other clinical scenarios (at time of seroconversion or among HIV-2 patients) requires further evaluation.

3. Hepatitis B Virus

Hepatitis B virus (HBV) is more common in HIV-1-infected individuals than in the general population due to shared risk factors for acquisition [36–39], with published rates of 6–14% having concurrent chronic HBV [40]. Current evidence suggests that HIV-1 infection modifies the course of HBV with an adverse impact on HBV-related liver disease progression, including higher serum HBV DNA polymerase activity; lower rates of loss of serum hepatitis B e antigen (HBeAg); and increased risk of cirrhosis, liver-related mortality, and hepatocellular carcinoma, especially among patients with lower CD4 cell counts [36, 41–46]. HBV infection is also more likely to become chronic in those coinfected with HIV-1 [43].

Overall, studies evaluating the influence of HBV/HIV coinfection on HIV RNA suppression, immunologic CD4 cell count recovery, and clinical outcomes in individuals on HAART have been limited and conflicting, with several studies finding no substantial impact of HBV coinfection on immunologic or HIV virologic responses to ART [46–53]. Other studies, however, have shown a significant impact on ART outcomes [54–56]. Conflicting findings from these studies may be attributable to the inconsistent choice of viral markers for study eligibility [46, 55], being observational versus prospective studies, having limited follow-up time [46, 55], small numbers of HIV/HBV coinfected patients, limited mortality data [57], varying HBV disease characteristics (HBeAg status, HBV DNA), varying endemicity of HBV, HCV coinfection, lack of data on opportunistic infections [53], and lack of data to specify if patients were receiving HBV-active ART. Clinical studies prior to the general availability of CART evaluating the impact of HBV on HIV-1 progression have also shown inconsistent results [48, 49, 51, 54, 56, 58–60]. Some studies found no differences in HIV-1 progression between those with and without chronic HBV [36, 53, 59, 61], while other studies have shown that chronic HBV may negatively impact HIV-1 progression with a significant increased risk of AIDS or death [55, 62–64]. HBV is thought to mediate destruction of CD4 cells through T-cell activation or splenic sequestration seen in advanced liver disease [53].

Studies on CD4 cell counts at and after ART initiation are conflicting. Some have shown that HIV-1/HBV coinfected patients have significantly lower CD4 cell counts at ART initiation compared with individuals infected with HIV-1 alone [46, 48, 53, 55, 65, 66]. In a study from China, HBeAg positivity, rather than HBV DNA level, was associated with lower cell counts in chronic HIV-1/HBV coinfected patients [65]. Other studies have not detected differences in CD4 cell counts prior to ART initiation [49, 54, 67]. In one study, individuals with occult hepatitis B (HBV DNA present in the absence of hepatitis B surface antigen) demonstrated lower CD4 cell counts as compared to individuals without occult hepatitis B [68].

Some studies evaluating CD4 cell count responses in coinfected individuals after ART found no differences in CD4 gains in HIV-1/HBV coinfected versus HIV-1 monoinfected individuals [54, 57, 69], while other studies have shown a negative impact of HBV on CD4 cell count recovery. However, the studies by Law and Hawkins showed no difference by 48 weeks and borderline significance at 12 months, respectively [46, 55, 56, 67]. Individuals with HBeAg-positive status at ART initiation and HBV DNA ≥20,000 IU/mL were significantly associated with lower CD4 cell counts, but HBV status and HBV DNA level were not shown to affect CD4 cell count rise [53]. One hypothesis why lower CD4 cell counts may be observed with HBeAg and higher HBV DNA is the possibility that HBV replication increases HIV-1 replication, in turn lowering CD4 cell counts based on in vitro data showing HBV X protein acting as a transactivator of HIV-1

transcription, but these data have not been demonstrated in vivo [70–72]. An alternative explanation is that HBV leads to increased apoptosis of CD4 cells through increased T-cell activation or an alternation in cytokines that leads to decreased production or destruction of CD4+ T cells [53].

In addition to the potential effects on CD4 cell counts, several studies have examined the impact of coinfection on the plasma HIV-1 viral load. Evaluation of HIV-1 viral load at ART initiation has not shown any differences, but there are conflicting data on virologic suppression, with some studies showing no differences in the proportion of individuals achieving virologic suppression over time [55, 57, 65–67]. For example, a lower proportion of HBeAg-positive individuals achieved VS (HIV-1 VL ≤400 copies/mL) at 24 weeks compared with HBeAg-negative or HIV-1 monoinfected individuals, but no differences were observed by 48 weeks [53]. Additionally, in this study from Nigeria, the proportion of patients with virologic suppression (HIV-1 VL ≤400 copies/mL) at 6 months was 67% versus 70% in the HIV-1/HBV coinfected and HIV-1 monoinfected groups, respectively [53]. Finally, one study showed a higher rate of virologic failure in HBV/HIV-1 coinfected patients, although the cause for the higher rate was not clear [54].

There have been no reported differences in the incidence of new AIDS-defining events among HBV/HIV-1 coinfected compared with HIV-1 monoinfected individuals [46, 54, 73]. Nevertheless, all-cause mortality has been shown to be higher, most commonly attributable to liver-related deaths [42, 46, 73]. A meta-analysis (including 11 studies with 12,382 patients) showed a significantly increased risk for all-cause mortality in coinfected patients [73]. Studies evaluating the impact of HBV-active ART on mortality are limited. One study conducted in an urban Tanzanian cohort showed a significantly higher risk of mortality (HR = 1.28, 95% CI: 1.02–1.61, and $P < 0.03$) in coinfected patients compared with monoinfected HIV-1 patients on ART regimens that did not contain tenofovir (TDF), but no difference in mortality among the two groups with the use of TDF-containing regimens [55].

Given the findings from a recent multinational cohort showing HIV-1/HBV coinfected individuals have significantly lower CD4 cell counts than monoinfected patients, determining the HBV status at HIV diagnosis and prior to CART initiation should be a priority [66]. Despite the dramatic reductions in morbidity and mortality in the CART era, lower survival rates in HBV/HIV-1 coinfected individuals are seen, with death attributable to chronic hepatic complications assuming more prominence in the era of CART [54]. Given the differences in findings from the studies described above, further evaluations of the long-term immunologic and virologic responses to ART in HBV/HIV-1 coinfected individuals compared with HIV-1 monoinfected individuals are needed to further our understanding of the effect of HBV on HIV-1 and ART response and long-term outcomes.

4. Hepatitis C Virus

Hepatitis C virus (HCV) is a common blood-borne pathogen among HIV-1-positive intravenous drug users, with recent increasing rates via sexual transmission among men who have sex with men (MSM) [74–76]. The negative impact of HIV-1 infection on the natural history of HCV infection is well established; HCV-associated liver disease, including fibrosis, cirrhosis, and end-stage liver disease, is accelerated among HIV-1-infected populations. For example, progression to cirrhosis is 2-3 times higher in coinfected than monoinfected individuals, with a third of coninfected patients estimated to progress to cirrhosis in less than 20 years [77]. An increased risk of liver-related deaths among coinfected compared with HCV monoinfected drug users despite CART use has also been reported from a recent 20-year prospective study [78].

While the mechanism to explain the adverse impact of HIV-1 on liver disease in HCV-infected individuals is not clear to date, it likely includes immune activation, apoptosis, and diminished HCV-specific T-cell responses [79–81]. Increased tissue damage in coinfected populations may be due to the accumulation of cytotoxic CD8 cells in the liver that may increase inflammatory mediators [82, 83]. HIV-1 replication has been noted in hepatocytes and hepatic stellate cells [81, 84, 85], with promotion of collagen expression and secretion of proinflammatory cytokines [85]. Insulin resistance appears to be critical in liver steatosis and liver disease progression, although the data are not definitive if it is more prevalent among coinfected [86] or monoinfected individuals [87].

The debate as to whether HCV has a negative impact on HIV-1 disease progression continues. While many studies have shown higher mortality among HIV-1/HCV coinfected individuals compared with those with mono-infection, a meta-analysis conducted in 2009 that included 100,000 patients across 30 studies found no increase in mortality in coinfected patients prior to the CART era. After CART, this study found an increased risk for overall mortality but not for AIDS-defining conditions [88]. However, some studies have found an increased risk of AIDS and AIDS-related infections; data from a cohort in Italy reported a twofold increase in AIDS risk among coinfected participants [89], with increases in bacterial and mycotic infections. Similarly, a US cohort of HIV-1-positive women also found an almost twofold increase in risk of AIDS for those never on CART [90].

Coinfected patients have been found to have high levels of T-cell activation even following CART compared with monoinfected patients [90–92]. Chronic immune activation may cause immune dysfunction and cytokine production, leading to enhanced HIV-1 and HCV replication and lower CD4 cell counts [91]. In one study of HIV-1-infected women, HCV-viremic compared with HCV-uninfected women had high levels of activated CD8 T cells associated with incident AIDS, and AIDS in both groups was associated with CD4 activation [90, 91], while suppression of HCV with therapy reduces activation [92]. HCV coinfection may increase immune activation, leading to CD4 cell apoptosis in HIV-1-untreated patients and more rapid progression to severe immunodeficiency [93]. However, the impact of HCV infection on CD4 cell recovery following CART is conflicting; some reports note a poorer CD4 response in coinfected compared with monoinfected patients [94], while others do not [93–98].

It is important to consider the timing of CART initiation relative to anti-HCV therapy for coinfected patients. CART may slow liver disease progression and might therefore be initiated earlier in coinfected than in HIV-1 monoinfected patients [99, 100]. Conversely, CART may increase fibrosis in coinfected patients through cumulative hepatotoxicity [99, 101]. Recent guidelines recommend that CART generally be initiated first to slow liver disease progression and increase CD4 cell count, bearing in mind that some drugs should be avoided while others should be monitored for hepatotoxicity [102].

5. Human Papilloma Virus

Human papilloma virus (HPV) is known to be the causative agent for urogenital warts, oropharyngeal cancer, cervical dysplasia and cancer in women, and anal dysplasia and cancer in men and women [103–106]. Cervical and anal cancers develop from cervical intraepithelial neoplasia (CIN) and anal intraepithelial neoplasia (AIN), respectively. Most studies in the medical literature demonstrate adverse effects of HIV-1 infection on HPV disease and its progression. In fact, HIV-1-infected persons tend to have larger and multicentric venereal warts, have more anal and cervical dysplasia, and tend to be infected with multiple HPV subtypes [107–110].

HIV-1-infected persons are also at higher risk for intraepithelial neoplasia and cancers. Women with HIV-1 infection are approximately 30 times more likely to develop CIN (compared with HIV-1-uninfected women) [107], and MSM with HIV-1 infection are approximately 6–9 times more likely to develop AIN (compared to HIV-1-negative MSM) [111]. Of note, anal sex is not a prerequisite for AIN. Conley et al. found the following AIN prevalence among their HIV-1-infected cohort: 9–31% in MSM, 3–17% in women, and 1–9% in men who have sex with women [112], while another study of HIV-1-infected women found an AIN prevalence of 33% over 3 years of follow-up [113]. HIV-1-infected persons are also at higher risk of developing anal cancer compared with their HIV-1-uninfected counterparts. Crum-Cianflone et al. found anal cancer incidence rate of 128/100,000 among a large cohort of HIV-1-infected persons compared with 1.4/100,000 for men in the general US population [114].

There are limited data implicating HPV infection as a risk factor for acquiring HIV-1 infection [115, 116] with a systematic review in 2012 (examining six studies in women and two in men) showing a twofold increased risk of HIV-1 acquisition in women, with similar trends in the men [115]. However, regarding the potential direct effect of HPV on HIV-1 infection control (e.g., HIV RNA levels) or noncancer-related clinical progression (e.g., time to AIDS), our review did not identify any published studies to date.

6. Syphilis

Syphilis represents the second most common cause of GUD among HIV-1-infected persons, with documented increasing rates of syphilis among HIV-1-infected persons over the past decade, especially among MSM [117–119]. Multiple studies have confirmed that syphilis infection is associated with an increased risk of acquiring and transmitting HIV-1 [120, 121], with mechanisms including the disruption of the mucosa and the influx of CCR5+ cells. Regarding the impact of HIV-1 infection on syphilis, studies have shown that it adversely affects the serologic response to syphilis treatment, especially at lower CD4 cell counts <200 cells/μL, but that CART reduces the failure rate [122, 123].

Several studies have evaluated the impact of syphilis on the natural history of HIV-1 infection. Initial studies focused on the effect of syphilis coinfection on CD4 cell counts and HIV-1 RNA plasma levels. The first published report demonstrated small changes in HIV-1 RNA levels and CD4 counts associated with syphilis infection; Buchacz et al. showed that among 52 HIV-1-infected men in California with primary or secondary syphilis, within-person changes in viral loads were slightly higher during versus prior to the syphilis infections (mean $0.22\log_{10}$ copies/mL, $P = 0.02$) that decreased after therapy ($-0.10\log_{10}$ copies/mL, $P = 0.52$) [124]. A small decrease in CD4 cell counts was also noted during infection (−62 cells/μL, $P = 0.04$), with recovery after treatment (+33 cells/μL, $P = 0.23$).

A second study was conducted in Denmark among 41 HIV-1-infected persons with primary or secondary syphilis. This study found an increase in HIV-1 RNA levels and a reduction in CD4 cell counts among those with an initial CD4 count of >500 cells/μL [125], which improved after the treatment of syphilis. Additionally, a study from Spain demonstrated that, among 118 coinfected patients, syphilis resulted in similar CD4 cell and viral load effects among one-third of patients [126]. Specifically, among those with a detectable viral load before syphilis, infection resulted in an increase in HIV-1 viral load of $1.03\log_{10}$ (IQR 0.64–1.32), and 25% of those initially suppressed had viral load detection during syphilis infection. Mean CD4 counts were lower during syphilis than before (496 versus 590 cells/μL, $P < 0.001$) and increased after treatment (597 versus 509 cells/μL, $P < 0.001$) [126]. Of note, >50% of patients in each of these studies [124–126] were on ART. Although most studies have shown that syphilis adversely impacts HIV-1 control, some studies have shown no effect, including a study of 38 coinfected persons from Italy [127]. Further, a study examining 63 coinfected persons and a group of controls (without an STI) from London showed no major impact on HIV-1 RNA levels in the blood or semen, but it did show changes in CD4 cell counts among early latent syphilis cases [128].

The most recent study examined a cohort of HIV-1 patients 1998–2006 and compared 282 coinfected patients with 1,233 syphilis-free matched HIV-1 controls [129]. This study showed that plasma HIV-1 RNA increases (adjusted odds ratio = 1.87, 95% CI: 1.40–2.49) and CD4 cell decreases (−28 cells/μL, $P = 0.001$) were more likely among those with syphilis infection. Further, this study demonstrated the association between syphilis and viral rebound among patients who were receiving effective CART regimens. These findings were independent of the syphilis stage or initial CD4 cell count. The potential mechanism of these effects has been hypothesized to be a result of immune activation of host

cells, increase in cytokine secretion, and upregulation of chemokine coreceptors [126, 130].

In order to evaluate the potential effect of syphilis on HIV-1 progression (time to AIDS or death), a study by Weintrob et al. prospectively evaluated 2,239 HIV-1 seroconverters not receiving ART with confirmed (9.2%) and probable (2.9%) syphilis [131]. This study, with 7,827 person-years of follow-up, however, found no impact of syphilis on HIV-1 disease progression (HR = 0.99, 95% CI: 0.73–1.33). Overall, syphilis increases the risk of HIV-1 transmission and leads to transient increases in HIV-1 RNA plasma levels and decreases in CD4 counts among a subset of patients regardless of the receipt of ART. Treatment of syphilis leads to resolution of the viral load and CD4 cell changes with no apparent long-term impact on HIV-1 progression.

7. Gonorrhea and Chlamydia Infections

Neisseria gonorrhoeae (GC) and *Chlamydia trachomatis* (CT) are bacteria that may be sexually transmitted from person to person and cause pharyngitis, cervicitis/urethritis, epididymitis, proctitis, and pelvic inflammatory disease. Both men (including MSM) and women often harbor asymptomatic infection [132]. The interrelationships of these bacteria and HIV-1 are complex, but exacerbation of either infection and facilitation of HIV-1 transmission have been demonstrated at some, but not all, mucosal surfaces. HIV-1-infected persons may have reduced clearance of these infections at mucosal sites. For example, interferon gamma (IFN-γ) is thought to be important for the clearance of CT infection [133–135]; however, studies suggest that HIV-1-infected persons secrete significantly less (IFN-γ) [136], suggesting impaired elimination of these infections.

Concurrent bacterial STIs have been shown to increase HIV-1 shedding at mucosal sites, with subsequent treatment resulting in a decrease in the amount of HIV-1 present in genital fluids [137–140]. A study comparing seminal HIV-1 levels among HIV-1 patients (not on CART) with GC/CT, nonspecific urethritis, or no STI found that the presence of GC or CT resulted in a fivefold increase in seminal HIV-1 RNA levels that were not observed in the other groups [138]. Following antibiotic therapy, HIV-1 RNA levels decreased in the GC/CT group. In a second study, the effects of GC/CT were evaluated among an HIV-1 cohort on ART, finding that most patients with undetectable plasma HIV-1 viral loads maintained no detection of HIV-1 in seminal fluid after acquiring GC/CT [139]. Similarly, a study of MSM receiving CART who had a bacterial STI showed that the plasma HIV-1 RNA level was the only significant correlate of rectal viral load in a model that included concurrent GC and CT infection [141]. However, presence of GC or CT infection strengthened the correlation between plasma and rectal viral load; thus these coinfections may enhance rectal shedding in setting ongoing viral replication. These data suggest that the impact of GC/CT urethritis on changes in genital HIV-1 RNA levels is limited in the setting of effective ART, but substantial in patients not receiving CART and who have detectable plasma HIV-1 viral loads, potentially enhancing HIV-1 infectivity.

Regarding the effect of GC/CT on HIV-1 plasma viral load, Nkengasong et al. studied HIV-1-infected female sex workers in Africa and found that STIs, specifically ulcerative disease and GC, caused a 2.5-fold rise in HIV-1 plasma viral load [142]. They also found that those with STIs tended to demonstrate more CD4 cell activation and increased proinflammatory cytokines, but they did not reach statistical significance. Anzala et al. also studied female sex workers in Africa [143] and found that acute infection with GC caused transient increases ininterleukin- (IL-) 4, IL-6, IL-10, soluble tumor necrosis factor- (TNF-) α, and HIV-1 plasma viral load and a decline in CD4 cell counts, which returned to baseline after the acute bacterial infection was treated. They also observed similar changes in women with acute pelvic inflammatory disease.

These data suggest that coinfection with bacterial STIs may acutely impact HIV-1 control and increase transmissibility of the virus. To date, there are no data to suggest that GC/CT infections impact the long-term progression of HIV-1 disease.

8. Trichomoniasis

Trichomoniasis, caused by the protozoan parasite, *Trichomonas vaginalis,* is the most common curable, nonviral STI worldwide [144–147], with over 170 million cases per year [148]. *T. vaginalis* is a highly prevalent STI among HIV-1-infected patients [149, 150], and there is a high frequency of asymptomatic or subclinical infection [151–153]. *T. vaginalis* infections are not currently reported to state agencies in the United States, limiting available prevalence data. The advent of polymerase chain reaction (PCR) testing, as a much more sensitive diagnostic technique, has allowed for a greater understanding of the global epidemiology of *T. vaginalis* and has heightened the awareness of the potential impact trichomoniasis has on HIV-1 transmission and female reproductive health [145].

Data have demonstrated that *T. vaginalis* infection enhances HIV-1 transmission [151, 154–156], with risk increased up to threefold [148, 154, 155, 157–159]. One recent study using mathematical modeling found 23% of HIV-1 transmission events from HIV-1-infected women may be attributable to *T. vaginalis* infection [160]. Proposed mechanisms by which *T. vaginalis* infection may increase HIV-1 infection include inducing the inflammatory response of vaginal, exocervix, and urethral epithelia; disrupting mucosal barrier function; recruitment of CD4 lymphocytes and macrophages; development of microhemorrhages; degrading secretory leukocyte protease inhibitors; and enhancing susceptibility to bacterial vaginosis or other abnormal vaginal flora that may increase the risk of HIV-1 acquisition [161–164].

The hemorrhages and inflammation produced by *T. vaginalis* infection in an HIV-1-infected individual can increase the level of virus-laden body fluids and/or the numbers of HIV-1-infected macrophages and lymphocytes in genital areas, thereby amplifying the probability of HIV-1 exposure and transmission [161]. Increased cervical shedding of HIV-1 has been shown to be associated with cervical inflammation

[165, 166]. Similarly, studies have shown that men with urethritis have higher HIV-1 RNA concentrations in semen if infected with *T. vaginalis* than those with urethritis of an unidentified cause [167]. Data regarding HIV-1 patients receiving ART have shown that detection of vaginal HIV-1 RNA was not different before or during a *T. vaginalis* infection, suggesting that CART generally maintains low or undetectable genital HIV-1 levels, even in the presence of this STI [168].

Studies have shown that treatment for trichomoniasis significantly reduces HIV-1 RNA genital shedding [169–171]. These data have important implications for the importance of screening and early treatment of trichomoniasis to decrease viral shedding and possibly decrease HIV-1 transmission risk [170].

The impact of *T. vaginalis* infection on HIV-1 outcomes (immunologic, virologic, and clinical [AIDS or death]) is less well defined. Given the impact of both HIV-1 and *T. vaginalis* on immune activation locally and systemically, it can be hypothesized that coinfection alters immune responses and may alter either CD4 cell count or HIV-1 viral load, but there are no data to support this. Similarly, the coinfection's interaction with the immune system and the enhanced or altered susceptibility to other infections that impact HIV-1 outcomes are plausible.

Despite the limited data on the impact of *T. vaginalis* infection on HIV-1 progression, it is clear that *T. vaginalis* has a substantial impact on the spread of HIV-1. The potentially large reservoir of asymptomatic carriers, the availability of treatment for trichomoniasis, and the overlap of HIV-1 epidemics throughout communities and the world should prompt policy makers to consider screening and treatment programs for *T. vaginalis* and prompt greater research in understanding the impact trichomoniasis has on HIV-1 outcomes.

9. Summary

Complex bidirectional relationships exist between HIV-1 and other STIs. While the impact of HIV-1 infection on the clinical presentations and treatment outcomes of STIs is well known, fewer data exist regarding the impact of concurrent STIs on HIV-1 progression (virologic, immunologic, and clinical) and acquisition, with most studies focusing on HIV-1 shedding at genital mucosal sites. Studies have shown that the presence of some STIs, both ulcerative and nonulcerative, increases genital HIV-1 RNA levels and enhances the transmissibility of HIV-1, with important public health implications. Studies have also shown that these effects are substantially limited among HIV-1 patients receiving effective ART, suggesting an important role for early ART initiation. Additionally, safe-sex counseling, routine STI screening, and early treatment are critically important.

Regarding the effect of STIs on HIV-1 progression, the most studied interrelationship has been HIV-1/HSV-2 coinfection. Studies have shown that HSV-2 increases genital and plasma HIV-1 RNA levels and that the use of antiherpetic medications reduces these effects and reduces HIV-1 progression among coinfected patients not receiving CART. The impact of other STIs on HIV-1 progression is less clear, but those coinfected with HBV or HCV appear to have higher mortality rates (predominantly HBV/HCV related), during the CART era, but not necessarily higher rates of AIDS progression. For other treatable, nonchronic STIs (i.e., syphilis, gonorrhea, and chlamydia), their impact on HIV-1 RNA levels and CD4 cell counts are typically transient and resolve with antimicrobial therapy. Future studies are needed to continue to define the rates of coinfections in various HIV-1 populations, the pathogenesis and impact of STIs on HIV-1 outcomes, and the role of STI therapy on reducing HIV-1 progression.

Conflict of Interests

The authors have no financial interest in this work. All authors contributed to the content of the paper and concurred with the decision to submit it for paper. The content and views expressed in this publication are the sole responsibility of the authors and do not necessarily reflect the views, policies of the NIH, the Department of Health and Human Services, US Army, Navy, Air Force, Department of Defense, or the US Government. Mention of trade names, commercial products, or organizations does not imply endorsement by the US Government.

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Research Article

Dual Protection and Dual Methods in Women Living with HIV: The Brazilian Context

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The cooccurrence of HIV and unintended pregnancy has prompted a body of work on dual protection, the simultaneous protection against HIV and unintended pregnancy. This study examines dual protection and dual methods as a risk-reduction strategy for women living with HIV. Data are from a cross-sectional sample of HIV-positive women attended in Specialized STI/AIDS Public Health Service Clinics in 13 municipalities from all five regions of Brazil 2003-2004 ($N = 834$). Descriptive techniques and logistic regression were used to examine dual protection among women living with HIV. We expand the definition of dual protection to include consistent condom use and reversible/irreversible contraceptive methods, we test the dual methods hypothesis that women who use dual methods will use condoms less consistently than women who use only condoms, and we identify predictors of dual protection. Dual protection is common in our sample. Women who use dual methods have lower odds of consistent condom use than women who only use condoms. Among dual method users, we find that women who use an irreversible method use condoms more consistently than women who use a reversible method. Women on ART and with an HIV-serodiscordant partner have greater odds of consistent condom use than their counterparts.

1. Introduction

The cooccurrence of HIV and unintended pregnancy has prompted a relatively recent body of work on dual protection, the simultaneous protection against HIV and unintended pregnancy [1]. Dual protection can be achieved through *single method use* (condoms) or *dual method use* (condoms + another contraceptive method). Most studies measure dual protection with condom use, but dual protection definitions must expand to capture condom use consistency and a wider variety of contraceptive methods [1]. Thus far, dual protection studies have focused on samples of women from the general population, have concentrated on developed or African countries, and have not considered HIV-related factors as influential in dual protection behavior. Studies that have considered the benefits of dual protection for people living with HIV show that dual protection can be an effective strategy to prevent HIV transmission to partners and to promote safe childbearing [2–5], which warrants more research in this population. This paper aims to describe dual protection among women living with HIV in Brazil.

Worldwide, HIV is the leading cause of death for women of childbearing age, and up to 64% of all pregnancies are unintended [6, 7]. Brazil has over a third of all people living with HIV in Latin America and the Caribbean [6]. Although the epidemic has become stabilized in Brazil (at 0.5% prevalence) [8], the male to female ratio of new HIV infections fell from 27 to 1 in 1985 to 1.4 to 1 in 2010 [9]. Women represent 35% of the 608,230 people living with HIV/AIDS, and most female infections are in women of childbearing age (83%) and via heterosexual transmission (96%) [9]. Little is known about the dual protection behavior of women living with HIV in Brazil.

Although a substantial proportion of women living with HIV have children after being diagnosed with HIV, women living with HIV in Brazil report lower reproductive intentions than women in the general population [10, 11]. Access to and provision of family planning to these women are essential to enable fertility control and to prevent unintended pregnancy. Although no global estimates exist for unintended pregnancy among women living with HIV, an estimated 30 to 64% of all pregnancies are unintended, with women in South America enduring the greatest burden worldwide [7]. Some studies indicate that the incidence of induced abortion in women living with HIV may be greater than that found in the general population [12]. Other studies find that women living with HIV are often exclusively offered condoms, because they provide dual protection, to the exclusion of being offered a complete basket of contraceptive options [8, 13]. For almost a decade, studies report an unmet need for family planning among women living with HIV in Brazil [12, 14, 15]. Although dual protection is not explicitly promoted in Brazil, most adults in the general population and women living with HIV make clear distinctions between contraceptive methods and the dual protection offered by condoms [16, 17].

Given these distinctions it is critical that we better understand dual method use, a much less studied form of dual protection that grants women greater control over their fertility than condom use alone. From a public health perspective, there is resistance to promoting dual methods due to a notion that we call the *dual method hypothesis*, which purports that women who use dual methods for dual protection will use either method or both methods more inconsistently than if they just used one sole method. Several studies provide support for this hypothesis but test it among the general population of women [18, 19]. This study tests the dual method hypothesis and reveals how the dual method hypothesis plays out in a sample of women living with HIV in Brazil.

We also explore how HIV-related factors like antiretroviral therapy (ART) and partner's HIV status affect sexual behavior, condom use, and contraception. People living with HIV may be more sexually active than originally thought. A study in Africa found that, within a three-month period, most people living with HIV (89%) had more than one sexual partner and some (36%) had acquired a new sexual partner [20]. Although the overall effect of ART on sexual behavior and dual protection is relatively unexplored [21], we know that ART lowers viral load, that ART together with condoms helps to prevent HIV transmission to a sexual partner [22], and that ART together with family planning is the most effective way to reduce the vertical transmission of HIV [23].

Since 1996, the Brazilian National HIV program has offered universal access to ART and HIV care to people living with HIV. Clinical status and CD4+ count are used to determine when to initiate ART. Generally, ART is initiated when CD4+ count $\leq 500\,\text{cells/m}^3$ or when the person is symptomatic, coinfected with hepatitis B, at high risk for (or has) cardiovascular disease, being treated for cancer, or pregnant [24]. HAART is offered to all people in HIV-serodiscordant partnerships [24]. Brazil also has protocols in place to prevent vertical transmission, which has resulted in a rapid decline in infants with HIV. Despite the availability of ART, a study in São Paulo, Brazil, finds that less than half of the women living with HIV report using condoms [15].

The effects of partner's HIV status on condom use is mixed depending on the sampled population. Studies find that condom use is typically more consistent among HIV-serodiscordant than seroconcordant couples [21, 25], but one study reports that serodiscordant partners have greater odds of changing sexual partners than seroconcordant partners [20]. Although statistics for Brazil are unavailable, one study reports that serodiscordant partnerships are on the rise and may make up 60% of all relationships [26]. Condom nonuse by HIV-seroconcordant couples may pose a risk for coinfection with other sexually transmitted diseases (STDs) which is linked to decreased CD4+ count and increased viral load [27, 28].

This study first describes the characteristics of our sample of women living with HIV in Brazil. Second, we test the dual methods hypothesis that women who use dual methods will do so less consistently than women who use only condoms. Third, we identify important predictors of dual protection in our sample.

2. Materials and Methods

Data are from a cross-sectional sample of HIV-positive women attended in Specialized STI/AIDS Public Health Service Clinics in 13 municipalities from all five regions of Brazil between 2003 and 2004 [29]. These clinics provide nearly all ART in Brazil. Women were eligible for the study if they could read and write, were over 18 years, and were HIV positive. A total of 1,777 women completed a self-administered questionnaire and deposited it anonymously into a secure ballot box. The self-administered ballot box technique is associated with fewer refusals, nonresponses, and false responses to sensitive questions and is associated with a greater frequency of reporting socially sanctioned behavior than face-to-face interviews and at times ACASI [30, 31]. The ballot box is a preferred technique to survey sexual behavior in Brazil because it is associated with the confidentiality of political elections, is a validated method in Brazil [31, 32], and is recommended for low-literacy populations (28% of our sample has an elementary school or less education) [33].

Our sample includes HIV-positive women who are bi-/heterosexual, of reproductive age, who report at least one sexual partner in the past six months, and with condom use data ($n = 1,087$). We conducted a sensitivity analysis, removing bisexual women, and results did not differ with the exception that sexual violence became a statistically nonsignificant predictor of consistent condom use. We used listwise deletion to include only cases with complete data. Further, only women who reported using condoms ($n = 834$) were included in our analysis of consistent condom use. We also conducted a missing data analysis and used multiple imputation to ascertain that omitted cases were not significantly different than those included. The research protocol was approved by the IRB of the São Paulo STI/HIV Reference and Training Center.

The outcome, dual protection, is measured with *consistent condom use*. The consistent condom use measure asked, "*In the last six months, you used condoms: Never, always, or sometimes?*" Respondents who said they *always* used condoms were coded as using consistent condoms, whereas respondents who marked *sometimes* used condoms were coded as using inconsistent condoms. *Sexual and reproductive health* variables include *method of contraception, desire to have children*, *number of live children*, *stable partner*, *history of STD in last six months*, and *lifetime history of sexual violence*. *Method of contraception* comprises three categories (excluding condom use): no method, irreversible method, and reversible method. Irreversible methods include tubal ligation and vasectomized partners. Reversible methods include birth control pills, intrauterine device (IUD), hormonal injection, and diaphragm. The few respondents who use traditional methods were coded as using no method. We classified contraceptive method based on a hierarchy where female-controlled methods took precedence over vasectomy and irreversible methods took precedence over reversible methods. Desire to have children is a binary variable in which the responses "*Yes*" and "*Do not know*" were collapsed into one category. Number of live children includes the number of children a woman had before and after testing positive for HIV. Women were categorized as having a stable partner if they responded positively to having a husband, fiancée, or steady boyfriend. Lifetime history of sexual violence measured any experience of being forced to engage in sexual relations. HIV-related variables include HIV status of sexual partner and currently taking *ART*. We used stepwise logistic regression to select dual protection predictor variables related to sociodemographic characteristics, sexual and reproductive health, fertility, and HIV-related variables.

We employed descriptive and logistic regression techniques to describe dual protection and to identify important predictors of dual protection in our sample. Our first set of analyses uses the chi-square coefficient to assess significant differences related to consistent condom use. Our second set of analyses uses logistic regression to examine the bivariate and adjusted associations between consistent condom use and predictors. Prior to entering each variable into an adjusted model, we conducted a bivariate analysis to assess the association between each independent variable and dual protection. Results for significant predictors of dual protection are displayed in the logistic models, but all independent variables are included in adjusted models. STATA 12 was the software used to conduct all analyses.

3. Results and Discussion

3.1. Results. Table 1 describes the characteristics of our sample. Women averaged 32 years old and most had a junior high school education or more (73%). Most women either used no method of contraception (51%) or an irreversible method (34%), did not desire to have children (58%), had 2.11 children on average, and were in a stable relationship (87%). The majority of women had no history of STDs in the past six months (81%) and had no history of sexual violence (78%). Most women were in an HIV-serodiscordant relationship (47%) and were taking ART (72%).

Table 1: Sociodemographic, sexual and reproductive, and HIV-related characteristics of women living with HIV/AIDS of reproductive age in Brazil, 2003-2004.

Total *N* (%)	834 (100%)[†]
SOCIODEMOGRAPHIC VARIABLES	
Age (mean (std. dev))	32.0 (6.86)
Education	
Elementary school or less	230 (28%)
Junior high school	308 (37%)
Some high school or more	296 (36%)
SEXUAL AND REPRODUCTIVE VARIABLES	
Method of contraception	
No method	424 (51%)
Irreversible method	285 (34%)
Reversible method	125 (15%)
Desire to have children	
No	483 (58%)
Yes/don't know	351 (42%)
Number of live children (mean (std. dev))	2.11 (1.63)
Stable partner	
No	113 (14%)
Yes	721 (87%)
History STD in last 6 months	
No	675 (81%)
Yes	159 (19%)
Lifetime history sexual violence	
No	647 (78%)
Yes	187 (22%)
HIV-RELATED VARIABLES	
HIV status of partner	
HIV positive	324 (39%)
Does not know	119 (14%)
HIV negative	391 (47%)
Woman on ART	
Yes	603 (72%)
No	231 (28%)

STD: sexually transmitted disease.
ART: antiretroviral therapy.
[†]Column percentages may not sum to 100% due to rounding.

Table 2 presents the distribution of consistent condom use by independent variables. Dual protection was prevalent in our sample with most women using condoms consistently (77%). Women who used only condoms for dual protection reported more consistent condom use (82%) than women who used dual methods (condoms + another method) for dual protection (72%). Among dual method users, 74% of the women who use an irreversible method report using condoms consistently versus only 66% of women who use a reversible method. Women not using dual protection (13%) either used no contraceptive method (42%), an irreversible method (37%), or a reversible method (22%). Women who

Table 2: Distribution of sociodemographic, sexual and reproductive, and HIV-related variables by consistent condom use among women living with HIV/AIDS of reproductive age in Brazil, 2003-2004.

	Consistent condom use (N = 834)	
	No	Yes
Total N (%)	192 (23%)	642 (77%)
SOCIODEMOGRAPHIC VARIABLES		
Age (mean (std. dev))	P = 0.020	
	31.1 (6.94)	32.2 (6.83)
Education	P = 0.020	
Elementary school or less	58 (25%)	172 (75%)
Junior high school	82 (27%)	226 (73%)
Some high school or more	52 (18%)	244 (82%)
SEXUAL AND REPRODUCTIVE VARIABLES		
Method of contraception	P = 0.001	
No method	77 (18%)	347 (82%)
Irreversible method	73 (26%)	212 (74%)
Reversible method	42 (34%)	83 (66%)
Desire to have children	P = 0.042	
No	99 (21%)	384 (80%)
Yes/don't know	93 (27%)	258 (74%)
Number of live children (mean (std. dev))	P = 0.544	
	2.17 (1.71)	2.09 (1.55)
Stable partner	P = 0.148	
No	20 (18%)	93 (82%)
Yes	172 (24%)	549 (76%)
History STD in last 6 months	P = 0.357	
No	151 (22%)	524 (78%)
Yes	41 (26%)	118 (74%)
Lifetime history sexual violence	P = 0.031	
No	138 (21%)	509 (79%)
Yes	54 (29%)	133 (71%)
HIV-RELATED VARIABLES		
HIV status of partner	P < 0.001	
HIV positive	103 (32%)	221 (68%)
Does not know	35 (29%)	84 (71%)
HIV negative	54 (14%)	337 (86%)
Woman on ART	P < 0.001	
Yes	119 (20%)	484 (80%)
No	73 (32%)	158 (68%)

STD: sexually transmitted disease.
ART: antiretroviral therapy.

use consistent condoms are slightly older and more educated than women who do not. Women who do not desire to have children report more consistent condom use (80%) than women who desire to have children (74%). Women with no lifetime history of sexual violence report more consistent condom use (79%) than women with a history of sexual violence (71%). Women with an HIV-negative partner report more consistent condom use (86%) than women who do not know their partners' HIV status (71%) and women with HIV-positive partners (68%). Women on ART report more consistent condom use (80%) than women who are not on ART (68%).

Table 3 presents the bivariate and adjusted models of independent variables on the odds of consistent condom use. Women who use irreversible methods have 0.59 times the odds and women who use reversible methods have 0.48 times the odds, of using consistent condoms than women who use only condoms for dual protection, net of other factors. Women who desire to have children have 0.63 times the odds of using consistent condoms than women who do not desire children, net of other factors. Women with a lifetime history of sexual violence have 0.64 times the odds of using consistent condoms than women without a history, net of other factors. Women with HIV-negative partners have 3.23 times the odds of using consistent condoms than women with HIV-positive partners, net of other factors. Women not on ART have 0.56 times the odds of using consistent condoms than women on ART, net of other factors.

3.2. Discussion. Our study finds a high prevalence of dual protection among women living with HIV. Consistent condom use (77%) was much greater in our sample of women living with HIV than women in the general population at the time (34% in steady relationships and 66% in casual relationships) [34]. One study in Brazil suggests that women increase consistent condom use from prediagnosis (71%) to postdiagnosis (86%) [14]. High levels of condom use in women living with HIV may be the result of the Brazilian government's extensive effort to promote condom use in populations most vulnerable for HIV infection. Despite high levels of condom use, 23% of our sample used no dual protection and 9% of our sample used no dual protection and no form of contraception. The lack of condom and contraception may reflect a desire to conceive [35, 36]. However, a closer look at our data reveals that only 60% of the women who do not use condoms or contraception report fertility desires, highlighting a need for intervention.

Our study provides some support for the dual methods hypothesis and adds a caveat to the hypothesis. The dual methods hypothesis argues that women who use dual methods for dual protection will use either one method or both methods inconsistently; some studies indicate that the more effective the contraceptive method, the more inconsistent the condom use [17, 37]. We find that women who use only condoms use them more consistently than women who use dual methods; this finding is also supported by Whiteman et al. [5]. Other studies that consider dual method use among women living with HIV demonstrate that dual method use is a viable option for dual protection but do not measure condom use consistency [2–4]. Mark et al. [2] finds the adoption of a nonbarrier contraceptive method does not lead to a decline in condom use or an increase in pregnancy.

Table 3: Binomial logistic regression estimates of sexual and reproductive and HIV-related variables on the odds of consistent condom use among women living with HIV/AIDS of reproductive age in Brazil, 2003-2004[†].

	Consistent condom use (N = 834)	
	Bivariate model	Adjusted model
	OR (CI)	OR (CI)
SEXUAL AND REPRODUCTIVE VARIABLES		
Method of contraception		
No method	ref.	ref.
Irreversible method	0.64	0.59
	(0.45, 0.93)	(0.39, 0.90)
	P = 0.018	P = 0.013
Reversible method	0.44	0.48
	(0.28, 0.68)	(0.30, 0.77)
	P < 0.000	P = 0.002
Desire to have children		
No	ref.	ref.
Yes/don't know	0.72	0.63
	(0.52, 0.99)	(0.44, 0.92)
	P = 0.043	P = 0.018
Lifetime history sexual violence		
No	ref.	ref.
Yes	0.67	0.64
	(0.46, 0.96)	(0.43, 0.96)
	P = 0.031	P = 0.030
HIV-RELATED VARIABLES		
HIV status of partner		
HIV positive	ref.	ref.
Does not know	1.12	1.30
	(0.71, 1.77)	(0.81, 2.11)
	P = 0.632	P = 0.282
HIV negative	2.91	3.23
	(2.01, 4.21)	(2.08, 5.02)
	P < 0.000	P < 0.000
Woman on ART		
Yes	ref.	ref.
No	0.53	0.56
	(0.38, 0.75)	(0.39, 0.81)
	P < 0.000	P = 0.002

Logistic regression; OR: odds ratio; CI = 95% confidence interval.
[†]Adjusted models are controlled for by number of children, stable partner, history of STD in last 6 months, age, and education.
ART: antiretroviral therapy.

Ngure et al. [3] find that women living with HIV can successfully uptake dual methods with appropriate intervention. However, Heffron et al. [4] use data from a multinational prospective study of HIV-serodiscordant couples in Africa to show modest declines in condom use with the uptake of another contraceptive method. Mixed findings likely result from differences in samples, interventions, and contexts. However, these studies highlight the promise of promoting dual methods for dual protection in this population.

Our study elaborates on the dual methods hypothesis. Our findings are contrary to the belief that the more effective the contraceptive method, the more inconsistent the condom use [17]. We find that, among dual method users, women who use an irreversible method use condoms more consistently than women who use a reversible method. A possible explanation for this finding may be the triple burden faced by women living with HIV where, on a daily basis, women must manage ART protocols, prevent HIV transmission, and prevent unintended pregnancy. A closer look at our data reveals a pattern in which condom use consistency is greatest among women who use a long-term contraceptive method (sterilization, IUD, and hormonal injection) followed by women who use contraceptive methods that require daily attention (contraceptive pill). Female sterilization may serve to alleviate women from the daily burden of contraception, allowing them to focus on consistent condom use. Moreover, for women on ART, taking the oral contraceptive pill adds yet another pill to their daily medication regimens, could cause undesirable side-effects, and could interact with ART to become a less effective method of contraception [38]. In light of these factors, future research should consider how consistency of condom use, consistency of reversible contraceptive use, and ART adherence interact; an analysis is not permitted with our data.

We find dual protection is determined by partner's HIV status. There is a growing body of literature that links the ability of women living with HIV to use condoms and contraception to a positive relationship context (i.e., quality of relationship, partner dynamics, and communication) [39–41]. Our study finds that women with HIV-serodiscordant partners report the most consistent condom use, followed (in order) by women who do not know their partners' HIV status, and women with HIV-seroconcordant partners. Our findings are supported by other studies that find the most consistent condom use is among HIV-serodiscordant couples [21, 25]. Women in HIV-serodiscordant relationships are likely to use more consistent condoms because they have disclosed their HIV status to their partners and are in "known" discordant relationships. These women are therefore clearer with their partners about the risks involved in having unprotected sex and more compelled to protect the health of their partners [42–44]. It is also possible that women who do not know their partners' status are likely to be in less committed relationships and, therefore, are not compelled to disclose their HIV-positive status to their sexual partner, are less able to negotiate condom use, and are not as concerned for their sexual partners' health to use consistent condoms [42, 44–46].

Women with HIV-seroconcordant couples had the lowest consistent condom use in our study, with over 30% not using consistent condoms. Relationship factors, like communication between HIV-seroconcordant partners, may lead

to decisions to discontinue condoms due to the lack of perceived risk and the desire for sensation and intimacy [39, 47]. However, unprotected sex among HIV-seroconcordant partners could expose women to coinfection with other STDs, which has been linked to decreases in CD4+ count and increases in HIV viral load [27, 28]. In addition, condom nonuse in HIV-seroconcordant couples may put them at risk of reinfection with other variants of HIV, including drug-resistant viral strains, which could hasten seroconversion to AIDS and potentially complicate ART protocols [48]. Although this phenomenon is not well understood, the potential repercussions are especially disconcerting for a context like Brazil, where ART is freely provided by the government. In fact, there is so much growing concern of the emergence and transmission of antiretroviral drug resistance (ADR) in Brazil that the Ministry of Health has started to monitor ADR in the most populated state capitals. Several studies have reported the prevalence of ADR in Brazil to vary from 1.4 to 12.7% [49–51], and one study in a national sample of MSM found the prevalence to be as high as 21–36% [52].

ART is positively related to consistent condom use in our sample, a finding supported by other studies [21, 53, 54]. Data from the Swiss HIV Cohort Study indicate that people living with HIV who are on ART have lower odds of engaging in unsafe sex than those who are not on ART [21]. This finding is also supported by several literature reviews [53, 54]. ART requires frequent visits to healthcare centers which may be linked to greater exposure to safe sex counseling, greater access to healthcare and to condoms, and health care seeking behavior. Other studies find that safer sexual behavior is related to ART adherence [2, 42] and that some people living with HIV believe condom use is essential for ART to be effective [55]. Evidence suggests that those who care for themselves by adhering to ART regimens may have greater odds of also protecting their sexual partners by using condoms consistently. On the contrary, we find that women who are not on ART have lower odds of consistent condom use. Condom nonuse may occur in women who are not on ART because they feel healthy and do not perceive the need to use, or cannot negotiate, condoms. Lack of condom use may also result from a limited knowledge of HIV transmission and disease dynamics and insufficient exposure to condom messaging. In any case, women living with HIV who are not on ART are also not likely to be connected with HIV services and may not know their HIV viral load, the most important determinant of HIV transmission risk in HIV-serodiscordant partners [56]. This finding highlights the need to counsel women, upon HIV-positive diagnosis, about transmission risk and to address barriers to condom use.

Several limitations of this study should be considered. First, data are from a convenient sample of women living with HIV in Brazil. Although this limits the generalizability of our findings, the Specialized STI/AIDS Health Service Clinics provide care to most HIV cases in each municipal; there is no reason to assume our sample is different than the greater population. Second, data are from a cross-sectional survey and employ questions that require the respondent to recall sexual behavior. This caveat may have introduced a recall bias that could have led the respondent to inaccurately recall information. However, the secret ballot box technique used for survey collection has been associated with a more accurate response rate to sensitive questions regarding sexual behavior than other modes of survey administration [30–33].

4. Conclusions

Our study has three main findings. First, dual protection is a common practice among our sample of women living with HIV in Brazil. Second, we test the dual methods hypothesis and find that women who use dual methods have lower odds of consistent condom use than women who use a single method (condoms). Of dual method users, we find women who use irreversible methods use consistent condoms more than women who use reversible methods. Third, we find that women who are on ART and who have HIV-serodiscordant partners have greater odds of consistent condom use than their counterparts. This study highlights dual method use as a promising form risk-reduction strategy for women living with HIV.

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