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ORIGINAL PAPER

The Longitudinal Effects of Non-injection Substance Use on Sustained HIV Viral Load Undetectability Among MSM and Heterosexual Men in Brazil and Thailand: The Role of ART Adherence and Depressive Symptoms (HPTN 063)

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Abstract
The effect of non-injection substance use on HIV viral load (VL) is understudied in international settings. Data are from HPTN063, a longitudinal observational study of HIV-infected individuals in Brazil, Thailand, and Zambia, with focus on men with VL data (Brazil = 146; Thailand = 159). Generalized linear mixed models (GLMM) assessed whether non-injection substance use (stimulants, cannabis, alcohol, polysubstance) was associated with VL undetectability. ART adherence and depressive symptoms were examined as mediators of the association. *In Thailand,* substance use was not significantly associated with VL undetectability or ART adherence, but alcohol misuse among MSM was associated with increased odds of depression (AOR = 2.75; 95% CI 1.20, 6.32, p = 0.02). *In Brazil,* alcohol misuse by MSM was associated with decreased odds of undetectable VL (AOR = 0.34; 95% CI 0.13, 0.92, p = 0.03). Polysubstance use by heterosexual men in Brazil was associated with decreased odds of ART adherence (AOR = 0.25; 95% CI 0.08, 0.78, p = 0.02). VL suppression appears attainable among non-injection substance users. Substance use interventions among HIV-positive men should address depression, adherence, and VL undetectability.

Keywords Substance use · HIV · Depression · Adherence · Undetectable viral load

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Introduction

Over time, improvements in antiretroviral therapy (ART) have lengthened lifespan and reduced HIV transmission among people living with HIV (PLH) [1–3]. Findings that ART adherence can suppress viral load (VL) and reduce HIV transmissibility during condomless sex have led to prioritizing treatment as prevention (TasP) as a key strategy to prevent HIV transmission by PLH [4]. However, high rates of substance use and depression among PLH remain key barriers to successful implementation of TasP in the U.S. and other similar settings [1]. However, empirical studies on the associations of substance use, depression, and achieving undetectable VL have not been adequately assessed in low- and middle-income settings.

Non-injection substance use is the most common form of substance use among PLH, with 40–70% reporting the use of alcohol, cannabis, non-injection stimulants (e.g., cocaine, amphetamines), and/or opioids [5, 6]. In general, PLH who use substances are less likely to access ART [7–10], are found to have lower ART adherence [11–13], are less likely to achieve viral suppression [8, 9, 11, 14], and are more likely to have faster disease progression [15–18] compared to non-substance using PLH. Moreover, this population may be the most likely to engage in condomless sex [19, 20], making it critical to understand how to improve their HIV care outcomes. Aside from behavioral risk, and the reduced ART adherence associated with substance use, emerging research indicates that substance use may have pathophysiological effects on HIV disease progression [21]. For example, stimulants have been linked to increased HIV replication—in peripheral blood mononuclear cells [22–24] and in mouse models [25].

When examining the effects of substance use on VL or other HIV outcomes, it is also important to investigate the contribution of depression as it is a highly prevalent comorbid condition. Depression is a more common comorbidity to substance use among PLH than the general population [26], and is the most common psychiatric health condition among PLH—affecting 20–33% of adults in HIV care [27, 28]. In terms of HIV clinical outcomes, depression is thought to lower ART adherence [29] and reduce the likelihood of sustained viral suppression [30]. Studies indicate that depressive symptoms may also affect HIV disease progression above and beyond sub-optimal ART adherence by reducing individuals' responsiveness to ART, decreasing CD4+ count, and increasing HIV VL [16, 31]. Depressive symptoms and substance use are prevalent among PLH and likely contribute substantially to the lack of sustained viral suppression. Despite the high prevalence of substance use and depressive symptoms among PLH, most research examining depression, substance use, and HIV disease outcomes has been conducted in the U.S. [5].

There is little information on the type and patterns of non-injection substance use, on the prevalence of depression, and on how these common comorbidities affect viral suppression among PLH in low- and middle-income settings. There is reason to think that the association between substance use and viral load detectability may operate through decreased ART adherence and increased co-morbidity with depression among PLH. Previous research have linked substance use—including alcohol, cocaine, heroin, methamphetamines, and other stimulants—to decreased ART adherence, although these studies took place in the U.S. [32, 33]. A recent systematic review focused on ART adherence among those who engaged in substance use in low- and middle-income countries found sub-optimal adherence to treatment [34], however this review solely focused on injection drug use. In addition, a study that examined active drug use on ART adherence and viral suppression found that depression appeared to mediate the association, although the finding was only significant for HIV-infected women and not HIV-infected men [11]. Moreover, based on the *minority stress theory*—which posits that sexual minorities have adverse health outcomes as a result of heightened stress from prejudice and stigma based on their sexual minority status—it is thought that men who have sex with men (MSM) may have greater substance use and depressive symptoms than heterosexual men [35]. This greater comorbidity prevalence is hypothesized to magnify the association between substance use, depression, and viral load detectability. This is likely the case for men in low- and middle-income settings, such as Thailand and Brazil, where HIV prevalence is much greater among MSM compared to the general adult population at 9.2% (vs. 1.1% adult) and 10.5% (vs. 0.6% adult), respectively [36, 37]. Although less research has been conducted among men who identify as heterosexual in international contexts, in Brazil they comprise the largest proportion of men infected with HIV [38] and as many as 70% receive late HIV-diagnosis [39]. Furthermore, non-injection substance use often affects MSM and heterosexual men at greater rates than women [40, 41], potentially exacerbating the effects of substance use on HIV outcomes via ART adherence and depression in low- and middle-income settings.

This study aims to address this gap in research by conducting a secondary data analysis focused on MSM and heterosexual men using HPTN 063 data, a longitudinal observational study of HIV-positive individuals in HIV care in Zambia, Thailand, and Brazil [42]. First, we described the type and pattern of non-injection substance use and prevalence of depressive symptoms among men infected with HIV at baseline. Second, we examined the effect of non-injection substance use on ART adherence and HIV VL undetectability, testing ART adherence as a mediator of the association

between substance use and HIV VL undetectability. Third, we examined the effect of non-injection substance use on depressive symptoms and VL undetectability, testing depressive symptoms as a mediator of the association between substance use and HIV VL undetectability. Then, we tested whether there was evidence of effect modification due to sexual orientation, on the association between substance use, mediators (e.g., ART adherence, depressive symptoms), and HIV outcomes. For all analyses, we stratified by unique country context.

Methods

Data were collected via HPTN 063, a multi-site, longitudinal observational cohort study of people living with HIV at high risk for sexual transmission in HIV care in Africa (Lusaka, Zambia), Asia (Chiang Mai, Thailand), and South America (Rio de Janeiro, Brazil). Recruited participants included HIV-infected heterosexual men, heterosexual women, and men who have sex with men (MSM). Structured interviews were conducted every 3 months over the course of 12 months, collecting data on socio-demographics, behavioral risk, substance use, mental health, and ARV adherence. HIV clinical variables (e.g., plasma RNA [VL], CD4 + count) were extracted from patient files. All procedures were approved at each site (Thailand—Chiang Mai University; and the Johns Hopkins Bloomberg School of Public Health, Brazil—the Evandro Chagas Clinical Research Institute; and the National Committee for Ethics in Research) and each participant provided written informed consent. The HPTN063 study design has been described in detail in previous publications [42, 43].

Sample

This study reports findings using the data collected from HPTN 063 focused on heterosexual men and MSM in Thailand (n = 159) and Brazil (Brazil = 146) as VL data was not available in Zambia. Men were considered MSM regardless if they reported having sex with women as well. In order to have sufficient observed data to characterize patterns of ART adherence and VL, we included participants who completed at least two of five assessments with information on substance use, depressive symptoms, ART adherence, and VL detectability. There were an average of 2.7 VL observations per individual.

Measures

Plasma HIV-RNA VL was extracted from medical records at baseline and each follow-up visit and recorded if a current VL was documented. VL was then dichotomized (0: VL ≥ 200 copies/ml and 1: VL < 200 copies/ml).

Non-injection substance use was measured as the number of self-reported use days and included stimulants, cannabis, and alcohol. *Stimulant use* was measured as the number of days that non-injection cocaine (powder and crack), methamphetamine, and ecstasy use were reported in the prior 3 months. *Cannabis* was measured as the number of days that marijuana and hashish were reported in the prior three months. *Alcohol misuse* was measured using the 10-item alcohol use disorders identification test (AUDIT). Example items include how many drinks containing alcohol one has on a typical day and how often one is not able to stop drinking once started. AUDIT score was dichotomized into alcohol misuse (AUDIT score ≥ 8) versus no alcohol misuse (AUDIT score 0–7) [44].

Polysubstance use was measured as the total number of non-injection substances reported used in the past 3 months (yes/no), including stimulants, cannabis, and alcohol misuse, and was treated as a continuous variable (range 0–4).

Depression symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CESD) [45]. Example items ask how often during the past week participants had a poor appetite or felt depressed. CESD score was dichotomized into severe depressive symptoms (CESD score ≥ 16) versus not severe depressive symptoms (CESD score < 16).

ART adherence was measured using the self-reported question on adherence ability, "in the last 3 months, on average, how would you rate your ability to take all your antiretroviral drugs as your doctor prescribed?" [46]. Instructions provided prior to the interview normalized ART non-adherence. Participants were provided with a response card with Likert response options, ranging from very poor to excellent. This single-item, self-report adherence measure has been found as valid and reliable in prior research [47]. Due to small cell size, ART adherence ability in Thailand was recoded into two levels (very poor/poor/fair vs. good/very good/excellent). For Brazil, ART adherence ability was missing on too many participants (n = 43; 30%) to warrant inclusion in this analysis and the dichotomized variable of taking ARTs was used in place. The self-reported measure asked, "In the last 3 months, have you taken antiretroviral drugs?"

Socio-demographic variables included in our analysis were age group (18–24, 25–44, and ≥ 45 years) and education (primary, secondary, and technical/college).

Statistical Analysis

Data analysis began with descriptive statistics at baseline of the total sample and of heterosexual men versus men who have sex with men (MSM) on non-injection substance use,

depression, HIV outcomes, and socio-demographics. The Chi square statistic test was used for categorical variables, and t-statistic test for continuous variables, to detect statistically significant differences between groups (Table 1). Next, we described the type and number of self-reported non-injection substances used in the prior 3 months at baseline stratified by country and sub-group to understand poly-substance use in our sample (Fig. 1). Then, generalized linear mixed models (GLMMs) were applied with the logit link function for longitudinal binary outcomes to estimate the odds ratios of non-injection substance use on having an undetectable HIV VL adjusting for covariates, age and education (Tables 2, 3). The mediators, ART adherence and depression, were also estimated as an outcome of non-injection substance use using GLMM (Table 2 and 3, respectively) and mediation was controlled for when estimating the effects of non-injection substance use on undetectable HIV VL. GLMMs with the logistic link function with a random intercept and compound-symmetric covariance were used to account the correlations of observations between visits within individuals [48]. All analyses were stratified by country. For each model, an interaction term of substance use and sub-group (MSM and heterosexual men) was included to test for statistically significant differences between MSM and heterosexual men in the associations between substance use and ART adherence, depressive symptoms, and undetectable VL.

Results

Table 1 shows the baseline characteristics of participants in the total sample stratified by study site and heterosexual men versus MSM. *In Thailand*, 43% of the total sample reported alcohol misuse. In the past 3 months, individuals, on average, reported using stimulants for zero days (range 0–30 days), cannabis one day (range 0-90 days), and used one non-injection substance (range 0–3 substances), with no significant difference by sub-group. Twenty-two percent of the total sample had severe depressive symptoms, with no significant difference by sub-group. In terms of HIV outcomes (adherence and VL), 82.4% reported good/very good/excellent adherence ability, with MSM reporting significantly better adherence ability than heterosexual men (89% vs. 77%, p value = 0.051). Seventy-seven percent of the total sample presented an undetectable VL at baseline, with no significant differences by sub-group. The median CD4+ count at baseline was significantly lower among heterosexual men compared to MSM (397.0 vs. 511.0, p-value = 0.002).

In Brazil, 34% of the total sample reported alcohol misuse. In the past 3 months, individuals, on average, reported using stimulants for 4 days (range 0–90 days), cannabis for 5 days (range 0–90 days), and used one non-injection substance (range 0–4 substances), with no significant difference by sub-group. About half of the sample in Brazil had severe depressive symptoms, with no significant difference by sub-group. Seventy-one percent of the total sample reported taking ART in the past 3 months, with significantly more heterosexual men reporting taking ARTs than MSM (86% vs. 61%, p-value = 0.002). Only 53% of the total sample presented an undetectable VL at baseline, with significantly more heterosexual men presenting an undetectable VL than MSM (67% vs. 43%, p-value = 0.003). The median CD4 + count at baseline was also significantly lower among heterosexual men than MSM (462 vs. 648, p-value 0.004). In both sites, heterosexual men were significantly older and had lower education than MSM.

Figure 1 illustrates the type and pattern of non-injection substance use. *In Thailand*, of men who reported using non-injection substances in the past 3 months at baseline (n = 118), 91% (n = 107) used one drug and 9% (n = 11) used two drugs simultaneously. *In Thailand*, among heterosexual men who reported using non-injection substances (n = 71), 89% (n = 63) reported using one substance (predominantly alcohol misuse) and 11% (n = 8) reported using two substances (predominately alcohol misuse in combination with methamphetamines). *In Thailand*, among MSM who reported using non-injection substances (n = 47), 94% (n = 44) reported using one substance (predominantly alcohol misuse) and 6% (n = 3) reported using two substances (predominately alcohol misuse in combination with methamphetamines).

In Brazil, of men who reported using non-injection substances (n = 112), 67% (n = 75) used one drug, 22% (n = 30) used two drugs, 5% (n = 5) used three drugs, and 2% (n = 2) used four drugs. *In Brazil*, among heterosexual men who reported using non-injection substances (n = 41), 63% (n = 26) reported using one substance (predominantly alcohol misuse), 32% (n = 13) reported using two substances (predominately alcohol misuse in combination with cocaine), and 5% (n = 2) reported using three substances (both alcohol misuse in combination with cocaine and cannabis). *In Brazil*, among MSM who reported using non-injection substances (n = 71), 69% (n = 49) reported using one substance (all alcohol misuse), 24% (n = 17) reported using two substances (predominately alcohol misuse in combination with either cocaine or cannabis), 4% (n = 3) reported using three substances (alcohol misuse in combination with cannabis and either cocaine or ecstasy), and 6% (n = 4) reported using four substances (alcohol misuse in combination with cannabis, cocaine, and ecstasy). For MSM in Brazil, the proportion of ecstasy users increased with the number of substances an individual reported to have taken in the past 3 months.

Table 1 Baseline characteristics of HIV-infected men in Thailand and Brazil, HPTN 063

	Thailand							Brazil						
	Heterosexual (n = 93)		MSM (n = 66)		p-value	Total (n = 159)		Heterosexual (n = 58)		MSM (n = 88)		p-value	Total (n = 146)	
	n	%	n	%		n	%	n	%	n	%		n	%
Non-injection substance use[a]														
Alcohol misuse (AUDIT score 8)	44	47.3	25	37.9	*0.237*	69	43.4	19	32.8	31	35.2	*0.611*	50	34.2
Stimulants (days used, past 3 mos.) (M, SD)	1.0	3.2	0.0	0.7	*0.298*	0.0	2.5	5.0	14.0	3.0	13.1	*0.476*	4.0	13.4
Marijuana (days used, past 3 mos.) (M, SD)	2.0	11.2	0.0	0.9	*0.245*	1.0	8.6	2.0	12.5	6.0	20.1	*0.209*	5.0	17.5
# of substances used (past 3 mos.) (M, SD)	1.0	0.6	1.0	0.5	*0.293*	1.0	0.5	1.0	0.8	1.0	0.8	*0.291*	1.0	0.8
Depression														
Severe depressive symptoms (CESD 16)	19	20.4	17	25.8	*0.429*	36	22.6	27	46.6	43	48.9	*0.685*	70	47.9
HIV outcomes														
Adherence ability														
Very poor, poor, or fair	21	22.6	7	10.6	*0.051*	28	17.6	6	10.3	9	10.2		15	10.3
Good, very good, or excellent	72	77.4	59	89.4		131	82.4	44	75.9	44	50		88	60.3
Took ARTs in past 3 mos.	93	100	66	100		159	100	50	86.2	54	61.4	*0.002*	104	71.2
Detectable viral load	14	15.1	10	15.2	*0.956*	24	15.1	13	22.4	40	45.5	*0.003*	53	36.3
Undetectable viral load	71	76.3	52	78.8		123	77.4	39	67.2	38	43.2	*0.003*	77	52.7
Viral load missing at baseline	8	8.6	4	6.1	*0.550*	12	7.5	6	10.3	10	11.3	*0.847*	16	11.0
CD4+ count (cells/mm^3) (M, SD)	397.0	158.0	511.0	289.1	*0.002*	444.0	227.8	462.0	263.2	648.0	416.6	*0.004*	572.0	372.4
CD4+ count (cells/mm^3) (range)	(30, , 413)		(47, 1413)			(30, , 1413)		(126, 1508)		(13, 2614)			(13, 2614)	
Socio-demographics														
Age (M, SD)	41.0	7.3	38.0	8.6	*0.019*	40.0	8.0	40.0	9.3	35.0	8.7	*0.001*	37.0	9.3
Age (range)	(21, 60)		(22, 62)			(21, 62)		(21, 60)		(19, 57)			(19, 60)	
18–24	1	1.1	4	6.1		5	3.1	2	3.4	11	12.5		13	8.9
25–44	64	68.8	45	68.2		109	68.6	36	62.1	64	72.7		100	68.5
45 or older		30.1	17	25.8		45	28.3	20	34.5	13	14.8		33	22.6
Education														
Primary school or less	46	49.5	13	19.7	*< 0.0001*	59	37.1	20	34.4	23	26.2	*0.033*	43	29.5
Secondary school (not/complete)	32	34.4	26	39.4		58	36.5	31	53.5	38	43.2		69	47.2
Technical training or college (not/complete)	15	16.1	27	40.9		42	26.3	7	12.1	27	30.7		34	23.4

[a]Mean and standard deviation reported for continuous variables

M mean, SD standard deviation; p-value for difference between heterosexual and MSM using χ^2 for comparisons among categorical variables and Student's t-test for comparison of means among continuous variables

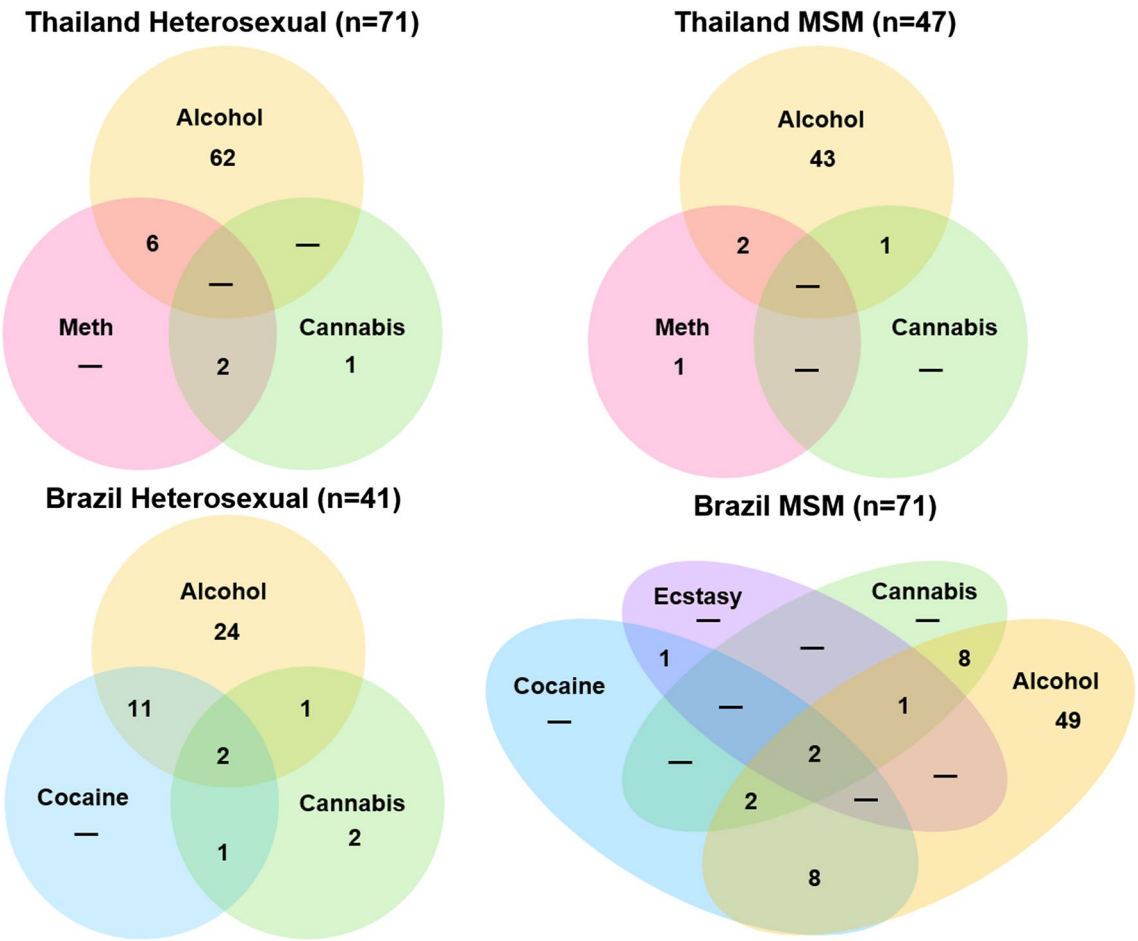

Fig. 1 Type and number of sell-reported non-injection substances used in prior 3 months at baseline among HIV-positive men in Thailand and Brazil

Table 2 reports the odds ratio of ART adherence ability (Thailand) or taking ARTs in the past 3 months (Brazil) and having an undetectable VL on non-injection substance use, adjusting for covariates such as age and education in the model. ART adherence ability (Thailand) or taking ARTs in the past 3 months (Brazil) was further adjusted in the VL analyses. *In Thailand*, non-injection substance use was not significantly associated with ART adherence ability or undetectable VL in each risk group. There were no differences between risk groups demonstrated by non-significant interaction terms. Furthermore, ART adherence did not mediate the association between substance use and undetectable VL. *In Brazil*, drug and alcohol misuse was associated with an overall lower likelihood of ART adherence ability and a lower likelihood of an undetectable VL, although this association was only significant in a few models. There were no differences between risk groups demonstrated by non-significant interaction terms. Furthermore, ART adherence did not mediate the association between substance use and undetectable VL. Alcohol misuse, although not significantly associated with having taken ARTs in the past 3 months, was significantly associated with decreased in odds of having an undetectable VL over 12 months in Brazilian MSM (AOR = 0.34; 95% CI 0.13, 0.92; p-value = 0.03). Additionally, the number of non-injection substances used was significantly associated with decreased in odds of having taken ARTs in the past 3 months over 12 months in Brazilian heterosexual men (AOR = 0.25; 95% CI 0.08, 0.78; p-value = 0.02).

Table 3 reports the odds ratio of non-injection substance use on depressive symptoms and an undetectable VL using generalized linear mixed effects models. Depression was further adjusted in the undetectable VL analysis. *In Thailand*, non-injection substance use was associated with an overall greater likelihood of reporting severe depressive symptoms and lower likelihood of having an undetectable VL. Reporting alcohol misuse was significantly associated with an increase in reporting severe depressive symptoms in MSM (AOR: 2.75, 95% CI 1.20, 6.32; p-value = 0.02). There were no differences between risk groups demonstrated by

Table 2 The association of non-injection substance use with ART adherence and viral load (< 200 copies/mL vs. 200 copies/mL) among men in Thailand and Brazil over 12 months, HPTN063

Outcomes	Thailand (n = 159)						Brazil (n = 146)					
	Adherence ability (good)			Undetectable viral load[a]			Took ART (past 3mos.)			Undetectable viral load[c]		
Predictors	HM (n = 93)	MSM (n = 66)	Group diff.[b]	HM (n = 93)	MSM (n = 66)	Group diff.	HM (n = 52)	MSM (n = 78)	Group diff.	HM (n = 50)	MSM (n = 54)	Group diff.
	AOR (95% C1)	AOR (95% C1)	p-value	AOR (95% C1)	AOR (95% C1)	p-value	AOR (95% C1)	AOR (95% C1)		AOR (95% C1)	AOR (95% C1)	p-value
Stimulants	0.96 (0.89, 1.03)	0.83 (0.48, 1.42)		0.94 (0.85, 1.04)	0.90 (0.34, 2.33)		0.97 (0.92, 1.02)	1.00 (0.95, 1.04)		1.00 (0.94, 1.05)	0.99 (0.96, 1.03)	
p-value	0.24	0.49	0.61	0.25	0.82	0.92	0.17	0.86	0.36	0.89	0.77	0.96
Marijuana	–			–			1.01 (0.95, 1.07)	1.00 (0.98, 1.03)		0.98 (0.94, 1.02)	1.00 (0.97, 1.03)	
p-value							0.80	0.89	0.86	0.35	0.83	0.53
Alcohol misuse	0.79 (0.37, 1.72)	0.59 (0.23, 1.51)		1.09 (0.38, 3.15)	1.28 (0.37, 4.45)		0.21 (0.04, 1.14)	0.67 (0.23, 1.99)		0.57 (0.15, 2.08)	0.34 (0.13, 0.92)	
p-value	0.56	0.27	0.63	0.87	0.70	0.85	0.07	0.48	0.25	0.39	0.03	0.54
# of substances	0.92 (0.47, 1.81)	0.85 (0.41, 1.74)		0.68 (0.26, 1.77)	1.81 (0.55, 5.99)		0.25 (0.08, 0.78)	0.70 (0.38, 1.30)		0.88 (0.37, 2.11)	1.20 (0.64, 2.25)	
p-value	0.82	0.66	0.87	0.43	0.33	0.20	0.02	0.26	0.12	0.42	0.71	0.83

All models adjusted for age and education

HM heterosexual men, *MSM* men who have sex with men

[a]Models estimating undetectable viral load in Thailand are adjusted for adherence ability

[b]Significance of ratio of AORs between HM and MSM

[c]Models estimating undetectable viral load in Brazil only includes observations where men reported taking ARTs in the last 3 months

Table 3 The association of non-injection substance use with severe depressive symptoms and HIV viral load (<200 copies/mL vs. 200 copies/mL) among men in Thailand and Brazil over 12 months, HPTN063

Outcomes	Thailand (n = 159)						Brazil (n = 146)					
	Severe depressive symptoms			Undetectable viral load[a]			Severe depressive symptoms			Undetectable viral load[c]		
Predictors	HM (n = 93)	MSM (n = 66)	Group diff.[b]	HM (n = 93)	MSM (n = 66)	Group Diff.	HM (n = 52)	MSM (n = 78)	Group diff.	HM (n = 50)	MSM (n = 54)	Group diff.
	AOR (95% C1)	AOR (95% C1)	p-value	AOR (95% C1)	AOR (95% C1)	p-value	AOR (95% C1)	AOR (95% C1)		AOR (95% C1)	AOR (95% C1)	p-value
Stimulants	1.03 (0.96, 1.12)	1.47 (0.82, 2.67)		0.93 (0.84, 1.03)	0.79 (0.30, 2.09)		1.00 (0.96, 1.04)	1.01 (0.98, 1.04)		1.00 (0.94, 1.05)	0.99 (0.96, 1.03)	
p-value	0.40	0.20	0.25	0.17	0.63	0.74	0.96	0.53	0.75	0.89	0.76	0.95
Marijuana	–			–			1.00 (0.97, 1.03)	1.02 (1.00, 1.04)		0.98 (0.94, 1.02)	1.00 (0.97, 1.03)	
p-value							0.99	0.12	0.43	0.33	0.82	0.51
Alcohol misuse	1.01 (0.48, 2.11)	2.75 (1.20, 6.32)		1.10 (0.38, 3.16)	1.14 (0.32, 4.09)		2.06 (0.71, 5.94)	0.73 (0.35, 1.51)		0.57 (0.15, 2.11)	0.34 (0.13, 0.92)	
p-value	0.99	0.02	0.08	0.86	0.83	0.96	0.18	0.40	0.11	0.40	0.03	0.53
#Substances	1.42 (0.73, 2.77)	1.30 (0.65, 2.58)		0.66 (0.26, 1.69)	1.68 (0.51, 5.58)		1.19 (0.64, 2.20)	1.24 (0.81, 1.88)		0.88 (0.35, 2.11)	1.20 (0.64, 2.25)	
p-value	0.30	0.46	0.85	0.38	0.40	0.22	0.59	0.32	0.91	0.77	0.57	0.57

All models adjusted for age and education

HM heterosexual men, *MSM* men who have sex with men

[a]Models estimating undetectable viral load in Thailand are adjusted for depression and adherence ability

[b]Ratio of ORs between HM and MSM

[c]Models estimating undetectable viral load in Brazil are adjusted for depression and only include observations where men reported taking ARTs in the last 3 months

non-significant interaction terms. Severe depressive symptoms did not mediate the association between substance use and undetectable VL. *In Brazil*, non-injection substance use was generally not significantly associated with reporting depressive symptoms. Alcohol misuse, although not significantly associated with reporting severe depressive symptoms, was significantly associated with decreased odds of having an undetectable VL over 12 months in MSM (AOR = 0.34; 95% CI 0.13, 0.92; p-value = 0.03). There were no differences between risk groups demonstrated by non-significant interaction terms. Severe depressive symptoms did not mediate the association between substance use and undetectable VL.

Discussion

This exploratory study examined the overlap between reported non-injection substance use, severity of depressive symptoms, ART adherence, and HIV VL undetectability among men living with HIV in Rio de Janeiro (Brazil) and Chiang Mai (Thailand) over 12 months. We found varying types and patterns of non-injection substance use between countries and sub-groups. One key finding is that alcohol misuse, although not associated with reported ART adherence ability in Thailand or with taking ARTs in Brazil, was associated with significantly lower odds of achieving undetectable VL among MSM in Brazil. Another key finding is that the number of non-injection substances used was associated with lower odds of taking ARTs in the past 3 months among heterosexual men in Brazil, but not in Thailand. Lastly, alcohol misuse was associated with significantly greater odds of having depressive symptoms among MSM in Thailand, although not significantly associated with HIV VL.

Reported alcohol misuse was prevalent in this sample and was associated with significantly lower odds of achieving an undetectable VL among MSM in Brazil. Alcohol misuse was detected in 35.2% (MSM in Brazil) and 47.3% (heterosexual men in Thailand) in our of HIV-infected men. This high prevalence of alcohol misuse is consistent with one review documenting that alcohol use disorders (AUDs) can be up to two to four times more prevalent among PLH than the general population in U.S. populations [49]. Factors that might explain lack of HIV suppression in our sample could range from biological factors to the diminished cognitive function and dysfunctional behaviors caused by alcohol misuse that may lead to poor self-regulation. Alcohol misuse might directly affect HIV control by inhibiting ART metabolism [50], enhancing HIV disease progression by lowering CD4 + T-cell count [51], and/or increasing HIV replication in peripheral blood mononuclear cells (PBMCs) [52]. These biological mechanisms deserve further research in human subjects, as the current knowledge base is largely limited to animal models. Regardless of the mechanism, our findings support the rationale for investing resources into alcohol misuse screening and prevention interventions among men with HIV/AIDS in middle-income countries, such as Brazil and Thailand.

Another key finding is that each additional substance used was associated with lower odds of taking ART among heterosexual men in Brazil. Polysubstance use among heterosexual men in Brazil involved reporting a combination of alcohol misuse, powder cocaine use, and/or cannabis use. Substance use, powder cocaine in particular, has been previously associated with poor ART adherence ability and faster HIV disease progression [8, 12, 21]. Specifically, cocaine may increase HIV disease progression by increasing HIV replication in PBMCs (in vitro) [23] and increasing circulating HIV-1 RNA (mouse models) [25]. There are fewer studies on the effect of cannabis on ART adherence ability and HIV VL with mixed findings [53]. Interestingly, non-injection substance use was associated with decreased odds of taking ART only among heterosexual men in Brazil. Previous studies that examined non-injection substance use among individuals with HIV have primarily focused on MSM [54, 55]. As there is limited research on non-injection substance use and ART adherence among HIV-infected heterosexual men, future research should examine this relationship to elucidate the contributing factors. Blips in HIV VL exams are also more frequent among people who misuse alcohol and drugs. Additional studies of ART adherence with biomarkers would enhance the understanding of how polysubstance use, ART, and HIV VL interact physiologically.

Lastly, we found that alcohol misuse was associated with significantly greater odds of having depressive symptoms among MSM in Thailand. Although our study found that depressive symptoms were not significantly associated with undetectable HIV VL, depression severity is consistently associated with inconsistent ART adherence and discontinuation [16]. Future research is needed to evaluate the efficacy of psychological and psychiatric interventions in mitigating the deleterious effects of substance use and depression on HIV disease progression. A recent critical literature review highlights some promising cognitive and behavioral and motivational interview interventions conducted among HIV-infected substance using MSM in the US [56]. Such interventions need to be adapted and evaluated in other countries and socio-cultural contexts.

The current findings should be considered in light of several limitations and strengths. First, non-injection substance use and ART adherence ability were self-reported and subject to potential biases based on recall bias or social desirability, the intentional under-reporting of sensitive or socially undesirable outcomes. There was

likely under-reporting of alcohol misuse, non-injection drug use, and ART non-adherence. Future studies should include more comprehensive measurements of substance use and ART adherence. For example, physiological biomarkers of substance use and ART adherence provide a more objective measure of chronicity and extent of substance use. Likewise, future studies would benefit from using instruments that assess substance misuse (e.g., ASI, DAST, DUDIT), as the current study assessed the number of days of non-injection drug use rather than misuse. Second, under-reporting, small sample size, and truncated variability could have decreased our statistical power to detect a significant association between key variables like stimulants, cannabis, polysubstance use, and HIV outcomes. Furthermore, it is important to highlight that significant associations were found in only one of the four sub-groups. Inconsistent findings could reflect distinct substance use and HIV care characteristics across countries and sub-groups, but could also be due to type 1 error. Third, our findings are not generalizable to populations of HIV-infected men in Thailand and in Brazil as this study focused on men engaged in care in select clinics and cities in each country.

Despite these limitations, this study contributes to evidence that achieving an undetectable VL is possible among male, non-injection substance users in low- and middle- income countries. Our results suggest TasP may be attainable among PLH who use non-injection substances. However, among MSM in Thailand and Brazil who misuse alcohol and among heterosexual men in Brazil who use multiple non-injection substances, interventions that address substance use may aim to lift mood, boost ART adherence and reduce HIV VL.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval Ethical considerations reviewed and approved by institutional review boards (IRB) within each recruitment country. Informed consent was obtained from all individual participants included in the study prior to interview.

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