Journal of
Addiction Research & Therapy
ISSN: 2155-6105

Nduka et al., J Addict Res Ther 2015, 6:4
DOI: 10.4172/2155-6105.1000255

Research Article Open Access

Drug Abuse in People Living with HIV in the Era of Highly Active Antiretroviral Therapy: A Systematic Review and Meta-Analysis

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Received date: Nov 1, 2015; **Accepted date:** Dec 23, 2015; **Published date:** Dec 31, 2015

Abstract

Objective: Little is known about the epidemiology of drug abuse in HIV-infected populations. Therefore, we aimed to estimate the prevalence of drug abuse among people living with HIV. We also sought to examine factors potentially associated with drug abuse in this high-risk population subgroup.

Methods: We searched EMBASE and PubMed databases from 1997 to September 2015 for studies that reported crude prevalence estimates of drug abuse in people living with HIV. Using random-effects meta-analysis, we pooled prevalence estimates of all forms of drug abuse, including alcohol, crack/cocaine, methamphetamine, heroin, over-the-counter, tobacco/nicotine, and prescription drugs. We defined drug abuse strictly in terms of its accompanying self-damaging effects. Random-effects meta-regression analysis was performed on all study-level characteristics to identify factors that may be associated with drug abuse in HIV-infected persons.

Results: Seventy two studies, comprising 153,711 HIV-infected participants, met our inclusion criteria. Majority (87%) of the study population was resident in the United States (US). Overall, the prevalence of drug abuse was 33.6% (95% confidence interval [CI] 28.2 to 39.3, I^2=99.7%, 31 studies, 28,238 participants), with prescription drugs identified as the most abused (42.7%, 95% CI 25.7 to 60.6, I^2=99.7%, 14 studies, 1775 participants). While HIV infection duration (coefficient 0.03, 95% CI 0.0003 to 0.05, P=0.49, explained variance [R^2]=51.3%) and ethnicity (Hispanic/Latino) (coefficient 0.006, 95% CI 0.001 to 0.01, P=0.012, R^2=23.2%) may be determinants of drug abuse in people living with HIV, exposure to antiretroviral treatment was a strong deterrent (coefficient -0.004, 95% CI -0.01 to -0.0001, P=0.048, R^2=10.1%).

Conclusion: One in three HIV-infected persons may be affected by drug abuse, with HIV infection duration and ethnicity (Hispanic) identified as predictors of this disorder. However, most of the available evidence comes from US studies. More studies originating from low- and middle-income countries are needed to obtain more precise estimates.

Keywords: Drug abuse; HIV; Prevalence; Highly active antiretroviral therapy

Introduction

Drug abuse, as opposed to mere substance use, entails the illicit and self-damaging use of recreational or prescription drugs [1,2]. Although drug abuse is a well-established risk factor for HIV infection [1-3], the potential for reverse causation in this association may also be high, with evidence suggesting substantially higher rates of alcohol and other forms of substance abuse among people living with HIV, compared with the general population [1]. Of note, people living with HIV may use recreational drugs as coping mechanisms for relieving psychologically stressful events often associated with chronic diseases [4,5]. Given that HIV infection is an immunosuppressive disease, often requiring pharmacological treatment, the effects of drug abuse may also be more severe among HIV-infected patients, compared with the general population. For instance, studies show that HIV-infected drug abusers are likely to have inadequate antiretroviral adherence levels, which may lead to treatment failure and progression to more advanced clinical stages of HIV infection, marked by a high occurrence of opportunistic infections, non-AIDS-defining illnesses and HIV-related deaths [6,7].

However, without a comprehensive assessment of drug abuse prevalence in people living HIV, it would be impossible to accurately estimate or predict its burden in this high-risk group. While prevalence estimates of HIV infection in drug abusers have been reported to vary widely between 0.01% and 72.1% depending on geographical location [8], the epidemiology of drug abuse among people living with HIV remains largely unknown. Previous systematic reviews have either provided global estimates of HIV prevalence in substance abusers [8] or estimated the prevalence of drug use in the general population [9]. Given these gaps in the available literature, we aimed to provide estimates of drug abuse prevalence in people living with HIV. We also

sought to identify factors that may be associated with drug abuse in HIV-infected populations.

Methods

Eligibility criteria

We included studies that reported prevalence estimates of drug abuse among HIV-infected patients. Of note, studies without clear characterization of drug use as abuse, in which case, drug abuse was not defined in terms of its accompanying self-damaging effects, were not eligible for inclusion [1,2] (see Box 1 for eligibility criteria).

	Inclusion	Exclusion
Population	HIV-infected	HIV-sero negative
	Adolescents and Adults	Children
Outcome	Any drug abuse including:	Drug or substance use not associated with any self-damaging effect.
	Alcohol	
	Crack cocaine	
	Methamphetamine	
	Heroin	
	Inhalants e.g. amyl nitrite	
	Prescription drugs	
	*Over-the-counter medications	
	Tobacco/Nicotine	
Study types	Any study design including:	Expert reviews
	Cross-sectional	Policy reports
	Case-control	
	Cohort	
	Randomized trials	
	Population-based studies	
	Hospital-based studies	
	Full-texts	
	Conference abstracts	

Box 1: Eligibility Criteria,*: Over-the-counter medications e.g., cough and cold medicines, non-steroidal anti-inflammatory drugs.

Search strategy and study selection

We sought for eligible studies from PubMed (1997 to 10 September 2015) and EMBASE (1997 to 11 September 2015) databases using the following medical subject heading (MeSH) terms and keywords: *drug abuse/, *illicit drug/, *cocaine/, heroin.mp./, *diamorphine/, *methamphetamine/, *amyl nitirite/, *alcohol abuse/, *prevalence/, HIV.mp./ (Appendices 1 and 2). We also scanned bibliographies of relevant articles identified by the electronic search. The electronic search was limited to studies published after 1996, the year marking the onset of the highly active antiretroviral therapy (HAART) era [10], so as to assess the influence of antiretroviral treatment on drug use behaviour. All articles obtained from the search were screened by their titles and abstracts initially, and by the full texts subsequently. CUN and OAU independently evaluated the eligibility of studies yielded by the search, and SS resolved any disparities.

Data extraction

CUN and OAU independently extracted data from each included study using a piloted data extraction form and any disparities were resolved by consensus with SS. Data extracted included: citation, study design, sample size, country, geographical region, country income group, mean age, sex distribution, proportion with a history of incarceration, proportion with same sex partners, duration of HIV-infection, HAART status, housing, educational status, and occupational grade. Crude prevalence of drug abuse in any form was the primary outcome; however, we also extracted data on prevalence

estimates with regard to specific drugs of abuse, such as alcohol, crack/cocaine, methamphetamine, heroin, marijuana, over-the-counter, and prescription drugs.

Assessment of risk of bias

Using a domain-based checklist adapted from the Newcastle-Ottawa scale, we investigated potential sources of bias in each included study: selection of participants, sample size justification, outcome assessment and statistical test [11] (Appendix 3).

Statistical analysis

First, we stabilized the raw proportions of participants with drug abuse from each study using the Freeman-Turkey variant of the arcsine square root transformed proportion [12] (Appendix 4). For each drug reported, we performed random-effects meta-analyses to obtain overall prevalence estimates of drug abuse. Heterogeneity across the included studies was assessed by inspecting forest plots using the I2 statistic, for which a value greater than 75% indicated considerable heterogeneity [13]. Subgroup analysis was also performed using the random-effects model to assess for any differential impact of country income group, geographical region and study design on drug abuse prevalence. We performed leave-one-out sensitivity analysis by omitting the included studies one at a time in order to determine whether any of the individual studies had an undue influence on the overall prevalence of drug abuse. To examine for predictors of drug abuse in people living with HIV, we performed univariate random-effects meta-regression analyses on a number of study-level variables: age, sex, ethnicity, educational status, occupational status, housing, sexual orientation, history of incarceration, duration of HIV infection and HAART status. We also examined for evidence of secular trend in drug abuse prevalence by performing meta-regression analysis on the year of publication. Publication bias was assessed by funnel plot inspection and using Egger's regression test for funnel plot asymmetry. Where publication bias was present, we ascertained its effect on the overall results using the 'trim and fill' analysis of Duval and Tweedie [14]. Prevalence estimates were reported with 95% confidence intervals (CI) and $P<0.05$ was considered statistically significant for meta-regression analysis. All analyses were conducted using Stata version 14 for Windows (Stata Corp, College Station, Texas).

Results

Search strategy and study selection

From 553 records yielded by the literature research, 357 articles were excluded by abstracts and 8 duplicate records were withdrawn, leaving 188 articles assessed to determine eligibility for inclusion. We excluded an additional 116 articles after reviewing the full texts, leaving 72 studies [15-86] eligible for inclusion in the systematic review and meta-analyses. The details of the study selection process are illustrated in Figure 1.

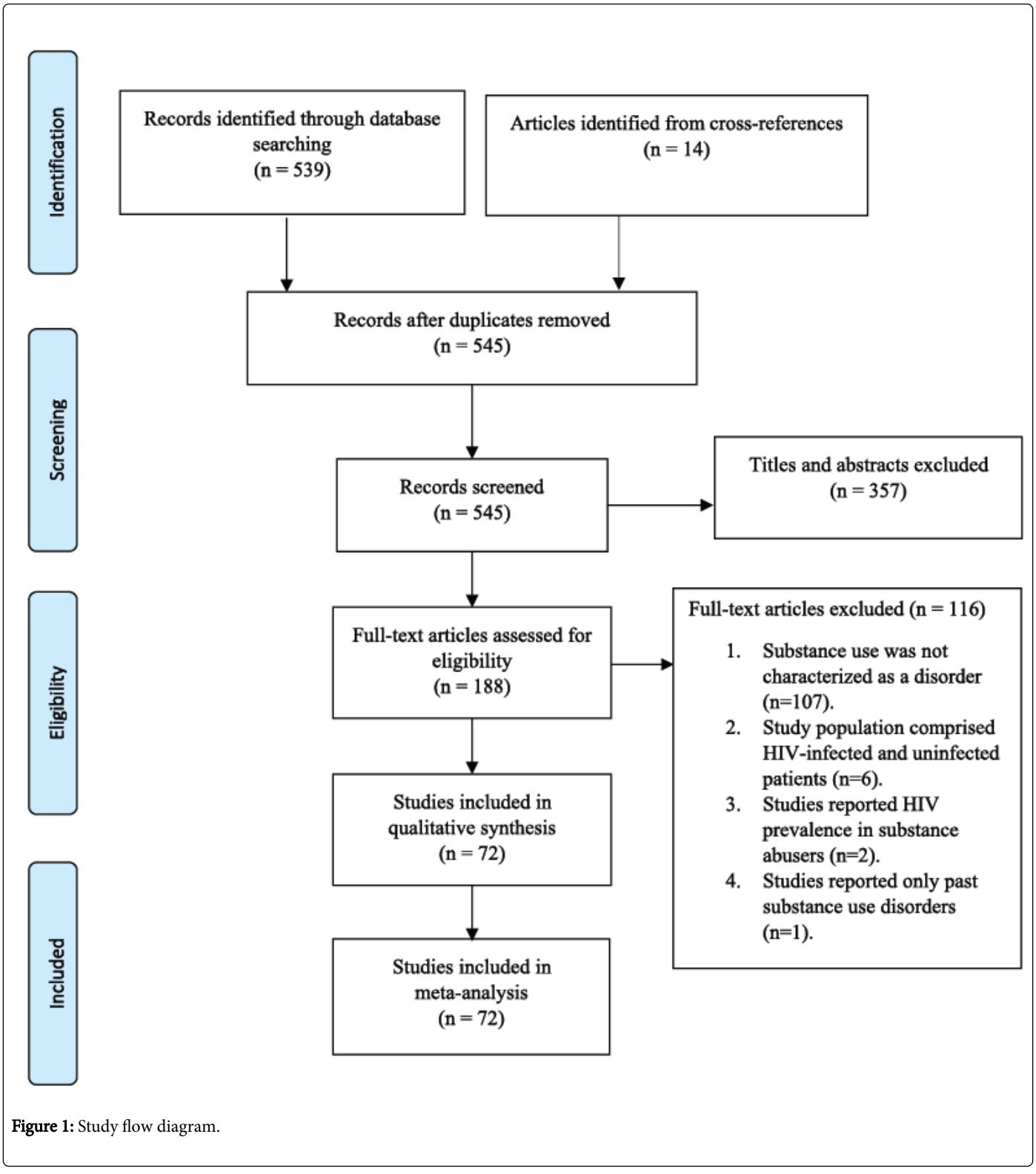

Figure 1: Study flow diagram.

Characteristics of the included studies

We obtained data from 153,711 HIV-infected participants in studies conducted across 21 countries, with males accounting for more than 80% of the total study population. Table 1 summarizes the characteristics of the study participants in all 72 included studies. Most of the studies (n=60 studies; 149,074 participants) were conducted in high-income countries, including a substantial majority originating from the United States of America (n=44 studies; 133,865 participants). The total mean age was 43.0 ± 9.1 years, and participants from high-income countries (mean age 43.4 ± 8.7 years) were much older than those from low- and middle-income countries (mean age

38.2 ± 13.0 years). There were more participants of African descent (47.9%), compared with Caucasians (39.9%) and Hispanics (19.6%). The average duration of HIV infection was 8.1 ± 5.3 years, with 64% of patients exposed to HAART. More than one in three (34.7%) had a history of incarceration, and sexual orientation was homosexual in 37%. About half (46.9%) of the included participants had received less than 12 years of formal education, 60% were unemployed at the time, and the proportion of study participants who were homeless was 30%.

Author	Year	Study design	Country	Income group	Region	Number analyzed	M (%)	Age (years)	HIV duration (years)	ART (%)	Incarcerated (%)	Homosexual (%)	Homeless (%)	Education<12 years (%)	Unemployed (%)
Ajuoga	2009	Cross-sectional	USA	High	America	215	69	45 ± 8.3						50.2	71.2
Altice	2011	Cohort	USA	High	America	295	68.1	45.2 ± 8.2		59.7		19	24.7		
Belloso	2010	Cohort	Multiple	LMIC	America	520			5.5 ± 4.4	80					
Berg	2009	RCT	USA	High	America	77	53	47 ± 6.9	13 ± 4	100				75	97
Bertolaccini	2008	Cohort	Italy	High	Europe	26	85	39 ± 6.1		85		23			
Buchacz	2008	Cohort	USA	High	America	7155	80.5					58.5			
Castellares	2008	Cross-sectional	Spain	High	Europe	2168	76.2	42 ± 6				34			
Chander	2006	Cohort	USA	High	America	1957	63.7			73.2		23.6			
Chao	2012	Cohort	USA	High	America	12872	90	40.1 ± 9.8	2.8 ± 4.1	21.1		61.6			
Fuster	2014	Cohort	USA	High	America	400	74.7	43 ± 7.4		62					
Fuster	2013	Cross-sectional	USA	High	America	308	73.1	42.8 ± 7.3		60.4					
Goar	2011	Cross-sectional	Nigeria	LMIC	Africa	160	35.6							73.8	
Goh	2007	Cross-sectional	Singapore	High	W/Pacific	96	89.6	40.2 ± 7.3				22			
Green	2010	Cohort	USA	High	America	3160	97.5	49.4 ± 8.8					8.1	40.7	
Grzeszczuk	2015	Cross-sectional	Poland	LMIC	Europe	457	76.6	38 ± 6.1	10 ± 3.3		23.4	8.8			
Hayashi	2015	Cross-sectional	Thailand	LMIC	W/Pacific	128	80.4			54.7	93.3			43.6	
Helleberg	2013	Cohort	Denmark	High	Europe	2921	77.5	43.3 ± 6.6	7 ± 2.6	77.4		52.9			
Hsu	2013	Cohort	USA	High	America	30533	95.5	50.3 ± 11							
Ibrahim	2014	Cross-sectional	Nigeria	LMIC	Africa	250	47.6							11.2	
Ikeda	2013	Cross-sectional	Brazil	LMIC	America	1240	50.6	39.1 ± 10		65.7					
Josephs	2010	Cross-sectional	USA	High	America	951	68			69		34		26	10

Justice	2010	Cohort	USA	High	America	9784	97.9	45							
Kabali	2011	Cohort	USA	High	America	462	77								
Kagimu	2012	Case-control	Uganda	LMIC	Africa	106	18							79	
Kellerman	2003	Cohort	USA	High	America	16248	70.8			47.1		38.4			
Kellinghaus	2008	Cross-sectional	Germany	High	Europe	51	74.5	37 ± 2.5		72.6					
Kim	2006	Cohort	USA	High	America	349	89.3	40.7 ± 7.2		31.8	17.8		28.9	67.3	
Korthuis	2015	Cohort	USA	High	America	3038	97.5	49 ± 8.8		83.9			41.5	40.5	
Korthuis	2012	Cross-sectional	USA	High	America	3410	97.4	49.1 ± 8.8		83.2			42.1	41.3	
Krupitsky	2005	Cross-sectional	Russia	High	Europe	201	62	26.6 ± 8.2							
Lim	2014	Cross-sectional	USA	High	America	2111	97.7	48.5 ± 2.5		82.6					
Luo	2013	Cross-sectional	China	LMIC	W/Pacific	551	66.2			67.5	9.3				
Mayer	2010	Cross-sectional	USA	High	America	398	100	41.5 ± 8.4	8.6 ± 6.7	66.1		100		13.6	
Mayer	2012	Cohort	USA	High	America	557	78.6	42 ± 2.8	4.9 ± 1.5	78		65.5		12	40
McGinnis	2013	Cohort	USA	High	America	444		50 ± 8.4							
Merlin	2012	Cohort	USA	High	America	1521	42.3	43.7				54.9			
Merlin	2013	Cross-sectional	USA	High	America	1903	77.4	43.6				52.7			
Metsch	2009	Cross-sectional	USA	High	America	1038	62			42	31.4		19	40	
Miaskowski	2011	Cross-sectional	USA	High	America	296	70.7	48.2 ± 7.3		74.4			100	29.3	
Mijch	2006	Cohort	Australia	High	W/Pacific	2981	93.5					4.3			
Moore	2012	Cross-sectional	USA	High	America	117	87.5	43.7 ± 7.8							
Nahvi	2012	RCT	USA	High	America	77	53	47 ± 7		100				75	97
Nakimuli-Mpungu	2011	Cross-sectional	Uganda	LMIC	Africa	500	30.2							82.6	
Newville	2015	Cross-sectional	USA	High	America	295	67.8	47.5 ± 9.7	11.5	100				59.1	
Nicolleti	2007	Cross-sectional	Brazil	LMIC	America	385	70	37.5 ± 8.6		70				55	

Nunes	2006	Cross-sectional	USA	High	America	401	73			59	23		28		
Obel	2011	Cohort	Denmark	High	Europe	2267	73.9	40.8 ± 3.6	5.3			38.5			
Omland	2010	Cohort	Denmark	High	Europe	392	59.5	39 ± 2.6	6.5 ± 3	37.5					
Pace	2012	Cross-sectional	Russia	High	Europe	682	60	30 ± 5.2		17.2	38.1	2.1		42.7	27
Pakkala	2012	Cohort	USA	High	America	80	80	52		70		19			
Pintado	2001	Cross-sectional	Spain	High	Europe	80	80					7.5			
Robinson-Papp	2012	Cohort	USA	High	America	636	77	41							
Ruan	2007	Cohort	China	LMIC	W/Pacific	229	82.1								60
Ryan	2004	Cross-sectional	USA	High	America	107	81.3	43.5 ± 7.2							
Salmon-Ceron	2009	Cohort	France	High	Europe	898	75	46	11.8	88		26			
Sambamoorthi	2000	Cross-sectional	USA	High	America	5559	54.2			58.8					
Scribner	2000	Case-control	USA	High	America	75	89.3	39.5				61			
Siemieniuk	2012	Cross-sectional	Canada	High	America	687		45 ± 10.2			10.5		1.1		
Silverberg	2013	Cohort	USA	High	America	4137	87.6	47.2 ± 8.8	10 ± 5.9	81.1		61.6			
Sullivan	2006	RCT	USA	High	America	16	94	47.2 ± 8.5						19	81
Surrat	2013	Cross-sectional	USA	High	America	503	59.5	46.1 ± 7.8	13.3 ± 7.3				39.2		
Tabarsi	2012	Cross-sectional	Iran	LMIC	E/Mediterranean	111	96.4	38 ± 9		26.1	88.1	0.9			
Tetrault	2012	Cohort	USA	High	America	114	97	49		52					
Towner	2012	Cohort	USA	High	America	20775	91	41	3.5	33		59			
Tsui	2012	Cohort	USA	High	America	397	74.8	42.5 ± 7.5							
Tyurina	2013	Cohort	Russia	High	Europe	700	59.3	30.1 ± 5.2		17.3					
Vagenas	2014	RCT	USA	High	America	85	78.8	46		81.2			24.7		
Vallecillo	2013	Cross-sectional	Spain	High	Europe	91	63.7	44.5 ± 8		74.7					
Van der Werf	2006	Cross-sectional	Ukraine	High	Europe	968	73.6				12.1		5.8		

Vergara-Rodriguez	2011	Cohort	USA	High	America	303				60					
Vidrine	2006	RCT	USA	High	America	95	77.9	42.9 ± 8.1				37.9			
Whetten	2012	Cross-sectional	USA	High	America	611	68.7	40.1 ± 25				44.5		54.5	

Table 1: Characteristics of eligible studies, ART: antiretroviral therapy; E/Mediterranean: eastern mediterranean; LMIC: low- and middle-income country; M: males; W/Pacific

Methodological quality in the included studies

eTable 1 summarizes the quality assessment of the included studies. Sampling bias was low in only 13 studies [18,20–23,32,56,57,61,69,70,78,85]; sample size was justified and satisfactory in 15 studies [17,18,20–23,28,32,34,35,38,39,70,78]; respondents to questionnaires were no less than 70% of the study population and comparable in baseline characteristics to non-respondents in 18 studies [18,20–22,27,31,33–35,38,39,46,50,51,53,57,63,85]; and drug abuse was assessed using a validated instrument in 39 studies [15–17,23–26,28,33,34,41–45,49–51,53–58,61,63,66,68,70,73–75,79–82,84–86]. Nonetheless, statistical tests were described and appropriate in all 72 studies.

Overall prevalence of drug abuse in people living with HIV

Prevalence estimates of drug abuse in any form were reported in 31 studies (n=101,023 participants), and widely varied between 2.9% [54] and 93.7% [76]. The pooled prevalence of drug abuse was 33.6% (95% CI 28.2 to 39.3, 28,238 participants) (Figure 2). Heterogeneity across the 31 studies was considerable and statistically significant (I^2 statistic=99.7%, P<0.001). Funnel plot asymmetry was absent, suggesting no evidence of publication bias (P=0.46 for Egger's regression test for funnel plot asymmetry) (eFigure 1). Leave-one-out sensitivity analysis showed than no study included in the meta-analysis had an undue influence on the pooled prevalence of drug abuse as to change the confidence interval significantly (eFigure 2).

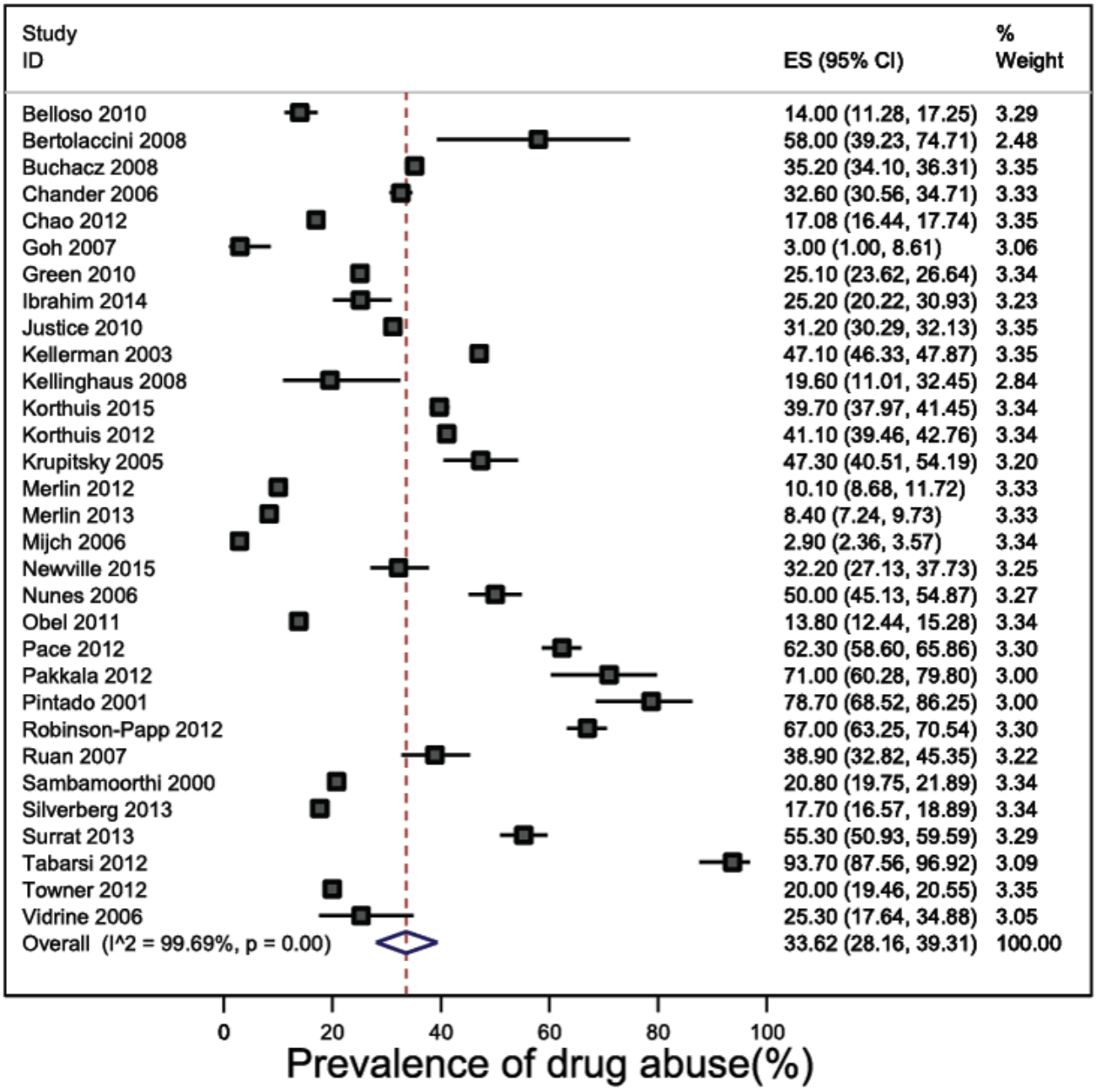

Figure 2: Forest plot showing pooled prevalence of drug abuse in people living with HIV.

Figure 3 summarizes the prevalence estimates regarding specific drugs of abuse. For instance, alcohol abuse was found in 29% of the included study population (95% CI 24.8 to 33.5, I^2=99.6%, 52 studies, 18,331 participants) (eFigure 3); prevalence of crack/cocaine abuse was 35.9% (95% CI 27.1 to 45.2, I^2=98.8%, 10 studies, 2439 participants) (eFigure 4); methamphetamine abuse prevalence was 14.4% (95% CI 6.9 to 24.0, I^2=98.9%, 8 studies, 629 participants) (eFigure 5); 42% (95% CI 16.7 to 68.9, I^2=98.7%, 4 studies, 372 participants) abused Heroin (eFigure 6); 20.4% (95% CI 13.0 to 28.9, I^2=98.3%, 7 studies, 2135 participants) abused marijuana (eFigure 7); and 42.7% (95% CI 25.7 to 60.6, I^2=99.7%, 14 studies, 1775 participants) abused prescription drugs (eFigure 8).

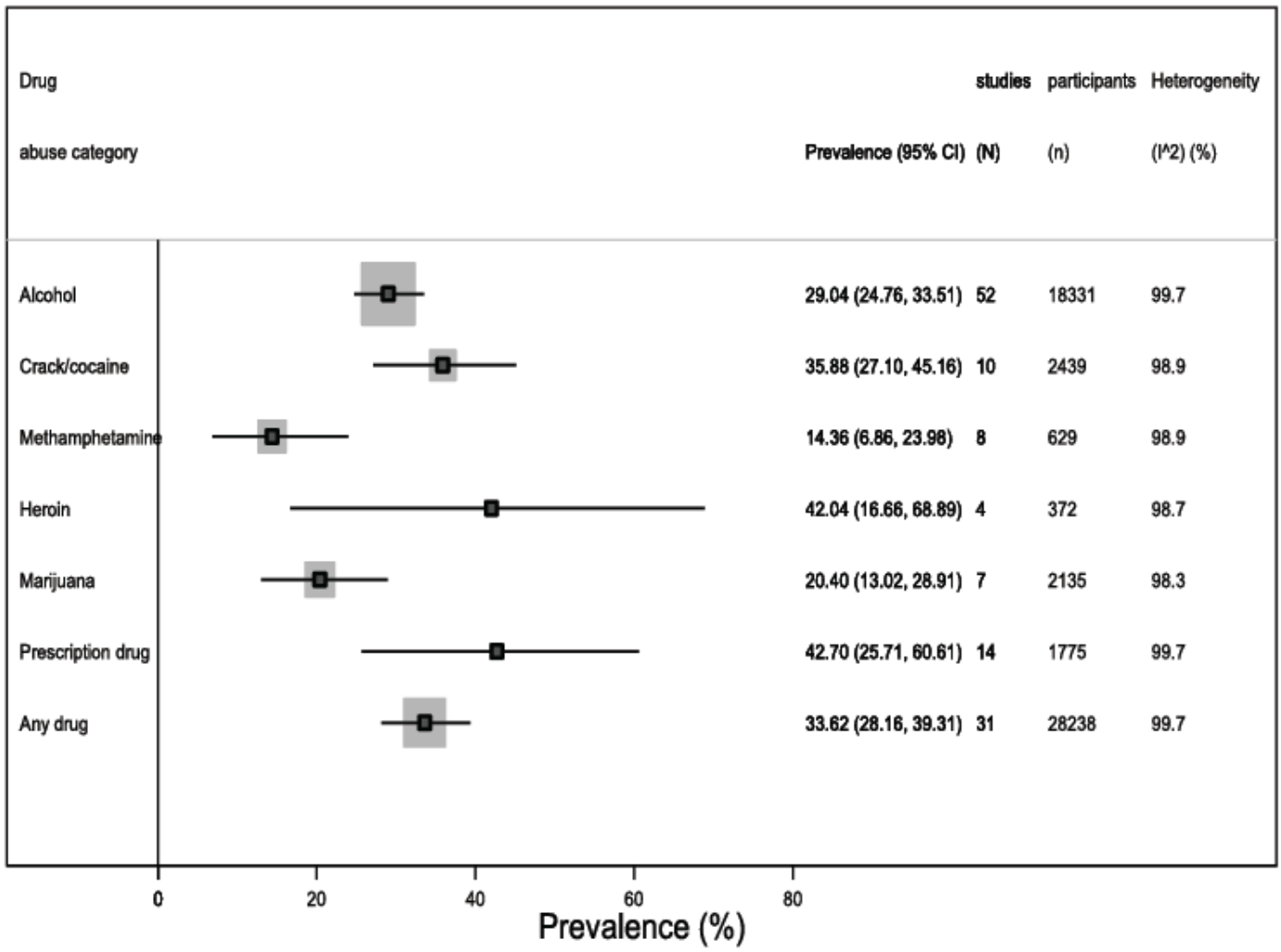

Figure 3: Forest plot summarizing pooled prevalence estimates of drugs abused in people living with HIV.

Subgroup estimates of drug abuse prevalence in people living with HIV

Among studies reporting any form of drug abuse in people living with HIV in high income countries, the pooled prevalence was 32.3% (95% CI 26.6 to 38.3, I^2=99.7%, 27 studies, 99,913 participants). Although drug abuse prevalence was higher among people living with HIV in low- and middle-income countries (pooled prevalence 43.6%, 95% CI 14.9 to 74.9, I^2=99.1%, 4 studies, 1110 participants), the difference was not statistically significant (Figure 4; eTable 2).

In general, studies conducted in European countries reported higher prevalence estimates of drug abuse, compared with other regions (pooled prevalence 45.7%, 95% CI 19.9 to 72.8, I^2=99.3%, 6 studies, 3307 participants) (Figure 4). Although, we observed a 93.7% prevalence of drug abuse among HIV-infected patients resident in the Middle-East, this estimate was based on evidence from one study only, which comprised a highly selected population. Nonetheless, the difference in drug abuse prevalence in people living with HIV was not statistically significant across geographical regions (eTable 2).

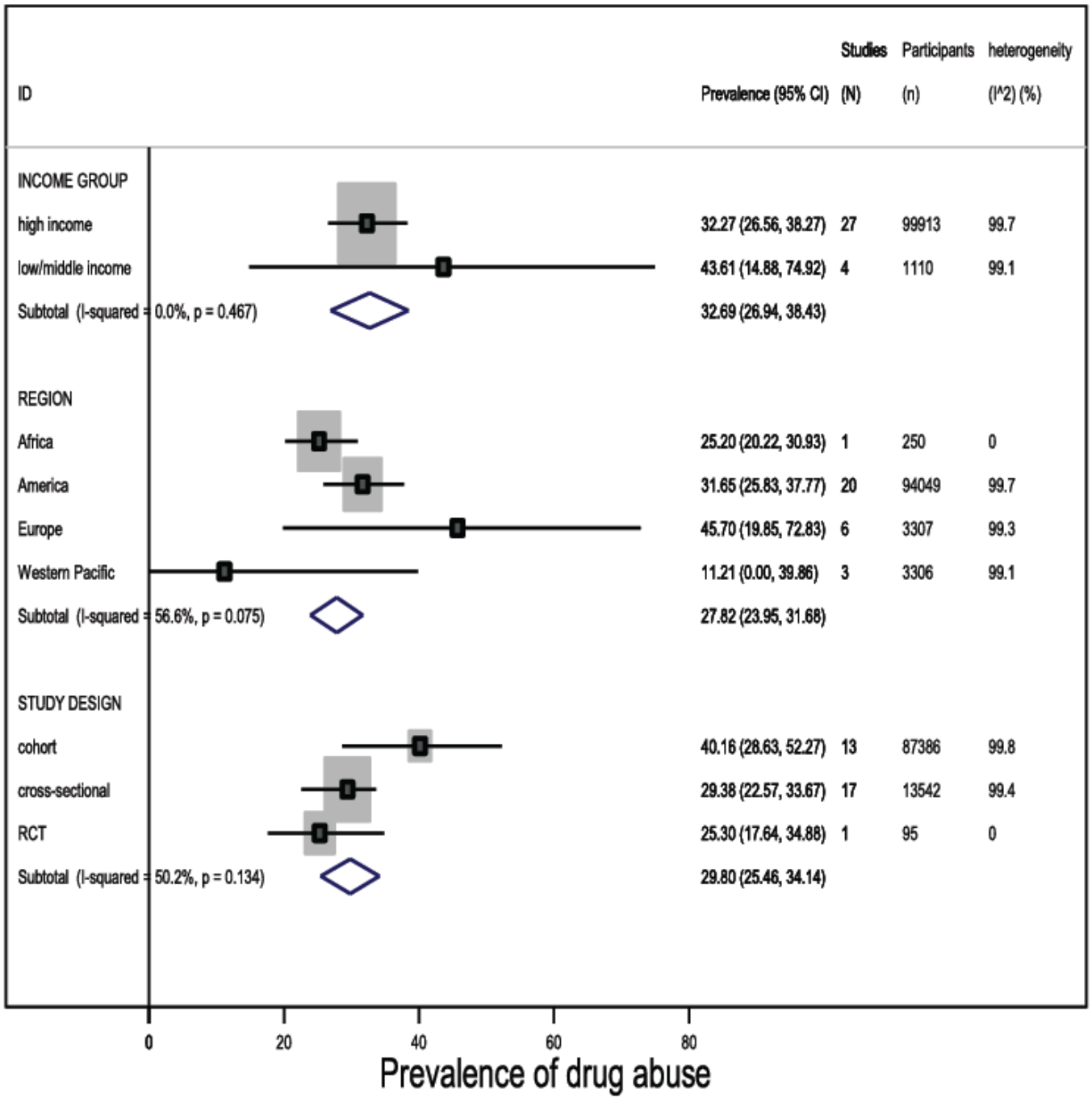

Figure 4: Forest plot showing subgroup estimates of drug abuse prevalence in people living with HIV.

Prevalence estimates of drug abuse in HIV-infected subjects were higher (P=0.05) in cross-sectional studies (pooled prevalence 40.2%, 95% CI 28.6 to 52.3, I^2=99.8%, 13 studies, 13,542 participants), compared with cohort studies (pooled prevalence 29.4%, 95% CI 22.6 to 33.7, I^2=99.4%, 17 studies, 87,386 participants), but the difference was also not statistically significant at P<0.05 (Figure 4).

Furthermore, we observed that most of the included studies did not consider alcohol abuse to be a form of drug abuse. Therefore, it was additionally important to perform a subgroup analysis of the prevalence of alcohol abuse. Prevalence of alcohol abuse was higher among people living with HIV in high income countries (pooled prevalence 30.6%, 95% CI 26.0 to 35.5, I2=99.6%, 42 studies, 17,515 participants), compared with those in low- and middle-income countries (pooled prevalence 24.8%, 95% CI 9.3 to 44.7, I^2=99.4%. 10 studies, 2923 participants). However, there was no statistically significant difference between both subgroup estimates. By region,

alcohol abuse prevalence was highest among people living with HIV in the Western Pacific (pooled prevalence 74.4%, 95% CI 71.0 to 77.6, I^2=99.4%, 2 studies, 501 participants); whereas, HIV-infected subjects in the Africa region had the lowest prevalence of alcohol abuse (pooled prevalence 20.2%, 95% CI 1.0 to 53.9, I^2=96.7%, 3 studies, 106 participants).

Factors associated with drug abuse in people living with HIV

The results of meta-regression analyses showed a significant direct association between the duration of HIV infection and drug abuse of any form in people living with HIV (coefficient 0.03, 95% CI 0.0003 to 0.05, P=0.048) (Figure 5). In fact, variations in the mean duration of HIV infection between the included studies accounted for more than half of the heterogeneity in the pooled prevalence of drug abuse (explained variance R^2=51.3%) (eTable 2). We also found a significant association between ethnicity (Hispanic/Latino) and alcohol abuse in people living with HIV (coefficient 0.006, 95% CI 0.001 to 0.01, P=0.012, R^2=23.2%) (eTable 3). In contrast, HIV-infected persons exposed to HAART (coefficient -0.004, 95% CI -0.01 to -0.0001, P=0.048) and those with same sex partners were significantly less likely to abuse drugs (coefficient -0.007, 95% CI -0.01 to -0.001, P=0.019) (eTable 3). Meta-regression analysis performed on publication year revealed no evidence of a secular trend in the prevalence of drug abuse in people living with HIV (coefficient -0.002, 95% CI -0.02 to 0.19, P=0.847) (eTable 2).

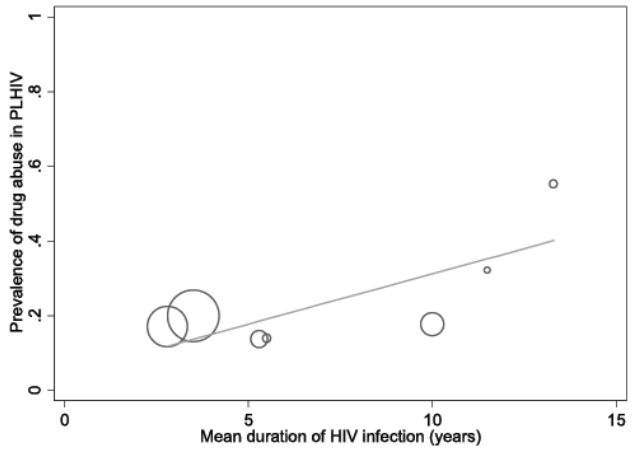

Figure 5: Bubble plot showing significant direct association between the duration of HIV infection and drug abuse.

Discussion

We present the first comprehensive systematic review examining the epidemiology of drug abuse in HIV-infected populations. Overall, our findings suggest that drug abuse in people living with HIV is a global public health problem, with one in three HIV-infected persons affected, and no evidence suggesting substantial regional, or socio-economic variation in the occurrence of this disorder. Although, in absolute terms, alcohol abuse may be more common among people living with HIV, compared with other drugs of abuse, we observe that prescription drug abuse, notably opioids, may be most prevalent, with approximately one in two HIV-infected persons affected. Interestingly, our analyses suggest that the likelihood for drug abuse among people living with HIV increases substantially as the duration of HIV infection increases. As is the case with other chronic diseases, we speculate that the increased life-expectancy of people living with HIV since the onset of the HAART era may be accompanied by increased levels of psychosocial stress, for which substance use may be a coping mechanism [5,87,88]. Our analyses also suggest that there might be an ethnic predilection for alcohol abuse among people living with HIV, specifically those of Hispanic origins. However, taking into account the occurrence of drug abuse of all forms, there was no evidence of ethnic variation.

Our findings may have important clinical and public health implications for HIV-infected populations worldwide. For instance, beyond the baseline assessment of recreational drug use among HIV-infected persons newly enrolled into care, our results support the inclusion of comprehensive routine screening and on-going assessment for substance users as part of care and treatment guidelines for HIV-infected patients [89]. Drug abusers may constitute a higher-risk subgroup within HIV-infected populations, emphasizing the importance of early identification in the clinic setting, especially as the duration of infection progresses.

In addition to differences in the duration of HIV infection, other factors accounting for some of the observed heterogeneity in the prevalence estimates of drug abuse include varying proportions of participants exposed to ART, and those with same sex partners. We observed that exposure to ART may deter drug abuse among HIV-infected patients, and this may be linked to an increased likelihood to quit the illicit use of drugs following the initiation of ART [89]. Similarly, while previous studies identify homosexuality to be associated with drug abuse in the general population [90,91], we find that the reverse may be the case among people living with HIV: our results suggest that homosexuality may also deter drug abuse among people living with HIV. However, while we hypothesize those HIV-infected persons with same sex partners may quit the illicit use of recreational substances and other drugs of abuse due to the underlying HIV infection; it is equally plausible that this proposed scenario may also apply to HIV-infected persons with heterosexual partners [89].

Strengths and limitations

Our findings must be interpreted with caution given that the population samples across the included studies were mostly limited to people living with HIV in the Americas, predominantly within the United States. In fact, less than 5% of the total population sample was resident in low-and middle-income countries - where the burden of HIV infection is most severe - potentially reducing generalizability of our findings across different geographic and socio-economic settings. In order to obtain a more comprehensive estimate of the prevalence of drug abuse among people living with HIV, studies originating from low- and middle-income countries in the Africa, Middle-East and South-East Asia regions need to be adequately represented. Secondly, the methodological quality across the included studies was moderate at best, with only 18% (n=13) of the studies assessed as having a low risk of sampling bias. Nonetheless, using meta-regression analysis, we affirm that sampling bias had no significant impact (P=0.121) on the pooled prevalence of drug abuse [13]. Furthermore, alcohol abuse was not considered in estimating the prevalence of drug abuse in some of the included studies. In fact, 16 of the 31 studies reporting prevalence estimates of drug abuse assessed alcohol abuse separately [17,22,23,28,36,39,42–44,58,60,63,66,73,76,85], which may potentially

suggest that the pooled prevalence of drug abuse in our study population of HIV-infected patients is likely to be underestimated. The dearth of studies reporting abuse of nicotine and over-the-counter medications (such as non-steroidal anti-inflammatory drugs and cold and cough medicines) precluded estimates of the prevalence of these potential drugs of abuse among people living with HIV. Although study-level analyses such as meta-regression allow multiple factors to be examined simultaneously, regression analyses using individual participant data (IPD) would be considered to be more robust in examining factors that may potentially influence drug abuse in persons living with HIV [92]. However, we did not have access to data recorded for each patient in each study.

Nonetheless, the strengths of our study should also be highlighted. For instance, we present the most comprehensive evidence and first pooled analyses investigating the prevalence, patterns and predictors of drug abuse including prevalence estimates of specific recreational drugs and controlled substances -among people living with HIV. Secondly, by identifying HIV infection duration as a potential predictor of drug abuse, we contribute a novel finding which strategically fills an important gap in the literature on a potentially neglected issue affecting people living with HIV worldwide [8,9]. Furthermore, the absence of small-study effects, and any undue influence on the overall prevalence of drug abuse by any of the included studies are also important strengths of our study.

Conclusion

This meta-analysis of over 150,000 subjects is the first of its kind to provide contemporary and up-to-date estimates that reflect the potential burden of drug abuse among people living with HIV worldwide. On average, one in three HIV-infected persons are affected by this disorder, which occurs more commonly as the duration of HIV infection increases. Although our findings may be limited by a high risk of sampling bias and considerable differences in the prevalence estimates of drug abuse between studies included in the meta-analysis, all analyses were performed using the random-effects model and meta-regression revealed that sampling bias had no significant impact on the pooled prevalence of drug abuse. However, future studies could employ IPD meta-analysis to investigate potential predictors of drug abuse in persons living with HIV. More prevalence studies originating from low- and middle-income countries are also needed to obtain more precise estimates across different geographic regions and socio-economic settings, as well as to accurately predict future trends of the global prevalence of drug abuse in people living with HIV.

Authorship

CUN conceived of the study, and participated in designing the study, data extraction, analysis and interpretation, and drafted the manuscript. OAU participated in designing the study, data extraction, analysis and interpretation. PKK participated in data analysis and interpretation. SS participated in designing the study and interpretation of the data. All authors critically revised the manuscript and approved submission of final draft.

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