Ther Adv Drug Saf
2022, Vol. 13: 1–14
DOI: 10.1177/20420986221080795

Prevalence and global trends of polypharmacy among people living with HIV: a systematic review and meta-analysis

Mohammed I. Danjuma, Oyelola A. Adegboye, Ahmed Aboughalia, Nada Soliman, Ruba Almishal, Haseeb Abdul, Mohamad Faisal Hamad Mohamed, Mohamed Nabil Elshafie, Abdulatif AlKhal, Abdelnaser Elzouki, Arwa Al-Saud, Mas Chaponda and Mubarak Arriyo Bidmos

***Abstract*:**

Background: There has been a rising prevalence of polypharmacy among people living with HIV (PLWH). Uncertainty however remains regarding the exact estimates of polypharmacy among these cohorts of patients.

Methods: We conducted a systematic search of PubMed; EMBASE, CROI, Cochrane Database of Systematic Reviews; Science Citation Index and Database of Abstracts of Reviews of Effects for studies between 1 January 2000 and 30 June 2021 that reported on the prevalence of polypharmacy (ingestion of >5 non-ART medications) among PLWH on antiretroviral therapy regimen (ART). Prevalence of polypharmacy among HIV-positive patients on ART with Clopper–Pearson 95% confidence intervals were presented. The heterogeneity between studies was evaluated using I^2 and τ^2 statistics.

Results: One hundred ninety-seven studies were initially identified, 23 met the inclusion criteria enrolling 55,988 PLWH, of which 76.7% [95% confidence interval (CI): 76.4–77.1] were male. The overall pooled prevalence of polypharmacy among PLWH was 33% (95% CI: 25–42%) ($I^2 = 100\%$, $\tau^2 = 0.9170$, $p < 0.0001$). Prevalence of polypharmacy is higher in the Americas (44%, 95% CI: 27–63%) ($I^2 = 100\%$, $\tau^2 = 1.0886$, $p < 0.01$) than Europe (29%, 95% CI: 20–40%) ($I^2 = 100\%$, $\tau^2 = 0.7944$, $p < 0.01$).

Conclusion: The pooled prevalence estimates from this synthesis established that polypharmacy is a significant and rising problem among PLWH. The exact interventions that are likely to significantly mitigate its effect remain uncertain and will need exploration by future prospective and systematic studies.

Registration: PROSPERO: CRD42020170071

Plain Language Summary

Background: In people living with HIV (PLWH), what is the prevalence of polypharmacy and is this influenced by sociodemographic factors?

Methods and Results: In this systematic review and meta-analysis of 23 studies comprising 55,988 participants, we have for the first time found an estimated polypharmacy pooled prevalence of 33% among PLWH. There was a relatively higher pooled prevalence of polypharmacy among the America's compared with European cohorts of PLWH.

Conclusion: Polypharmacy among PLWH is a rising morbidity that needs urgent intervention both at policy and patient levels of care.

Keywords: ART, HIV, PLWH, polypharmacy, prevalence

Received: 24 August 2021; revised manuscript accepted: 26 January 2022.

Correspondence to:
Mohammed I. Danjuma
Department of Internal Medicine, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar
College of Medicine, QU Health, Qatar University, Doha, Qatar
mdanjuma@hamad.qa

Oyelola A. Adegboye, Evolution Equations Research Group, Ton Duc Thang University, Ho Chi Minh City, Vietnam

Faculty of Mathematics and Statistics, Ton Duc Thang University, Ho Chi Minh City, Vietnam

Ahmed Aboughalia
Nada Soliman
Ruba Almishal
Haseeb Abdul
Mubarak Arriyo Bidmos
College of Medicine, QU Health, Qatar University, Doha, Qatar

Mohamad Faisal Hamad Mohamed
Mohamed Nabil Elshafie
Abdelnaser Elzouki
Arwa Al-Saud
Department of Internal Medicine, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar

Abdulatif AlKhal
College of Medicine, QU Health, Qatar University, Doha, Qatar

Centre for Disease Control, Hamad Medical Corporation, Doha, Qatar

Mas Chaponda
Department of Molecular & Clinical Pharmacology, University of Liverpool, Liverpool, UK

Centre for Disease Control, Hamad Medical Corporation, Doha, Qatar

Introduction

An increasing proportion of multimorbidities has been associated with people living with HIV (PLWH).[1–3] This is principally as a result of increasing survival of this cohort of patients since the advent of antiretroviral therapy (ART) drugs.[2] It is estimated that almost 50% of all PLWH are over 50 years of age in the United States.[1] However, this salutary survival benefit is often complicated by a demonstrable rise in number of comorbidities in these patients and at times excess mortality, some of which is attributable to therapeutics-associated multimorbidity.[4–6] One area of increasing concern is polypharmacy associated with non-HIV therapeutics, often against a background of decreasing burden of HIV-related medications.[7]

While there is still no consensus on the exact definition of polypharmacy in both PLWH and the general population,[8–10] its reported burden on both populations continues to rise.[11,12] Among these includes the risk of drug–drug interactions,[13,14] drug–food interactions, drug–alcohol interactions, adverse drug reactions, pharmacogenetic interaction,[15] as well as noncompliance due to rising pill burden.[16] Despite uncertainty with regard to outcomes of studies exploring this, a rising pill burden regardless of its aetiology (whether HIV or non-HIV related) is associated with increased risk of nonadherence to therapy.[17,18] The most validated definition of polypharmacy is taking more than five non-HIV medications.[8] The overall prevalence of polypharmacy among PLWH is variable, but it is estimated to range between 18% and 33%.[19–21] Among the range of patient- and/or system-related factors reported to account for this variability includes differences in study design, patient populations, as well as case definition of polypharmacy.[22,22–24]

Determining the exact burden of polypharmacy among PLWH is crucial in understanding and devising therapeutic interventions aimed at addressing it. This will also have additional benefit in informing decisions regarding medicines commissioning, as well as inform policy and practice around polypharmacy in PLWH. Despite studies specifically designed to address the exact phenotype and prevalence of polypharmacy among this population, a systematic synthesis of the overall prevalence estimates has remained unexplored. The most recent attempt is a narrative which examined the varied phenotypes of polypharmacy among PLWH, factors impacting on them, as well as expert opinion on measures that are likely to mitigate them.[25] A systematic examination of studies investigating the prevalence as well as the global trend of polypharmacy among PLWH (by way of a meta-analysis) is long overdue.

In this study, we have for the first time carried out a synthesis of studies exploring the burden of polypharmacy among PLWH through a systematic review and meta-analysis with the aim of ascertaining the exact prevalence of this morbidity among these cohorts of patients. We additionally explored the global trends of factors driving any apparent variability in prevalence estimates. This is with the view to identifying areas of intervention for both physicians as well as policy makers.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) procedure for the study selection as shown in Figure 1. This systematic review and meta-analysis was registered in the PROSPERO database (CRD42020170071).

Data Sources and Searches

All publications between 1 January 2000 and 30 June 2021 were searched from the following databases: PubMed; EMBASE, CROI, Cochrane Database of Systematic Reviews; Science Citation Index and Database of Abstracts of Reviews of Effects. The following medical subject headings (MESH) terms were used: HIV [tiab] OR antiretroviral [tiab] AND polypharmacy [tiab]. We included all studies (irrespective of design) that reported on the prevalence of polypharmacy among PLWH on ART regimen. Other studies involving PLWH on antiretroviral drugs in addition to some other drugs (for associated comorbidities) were also included.

Study Selection

Following an initial literature search from the databases, we removed duplicates and then carried out study eligibility assessment from the resultant abstract. For those studies where this

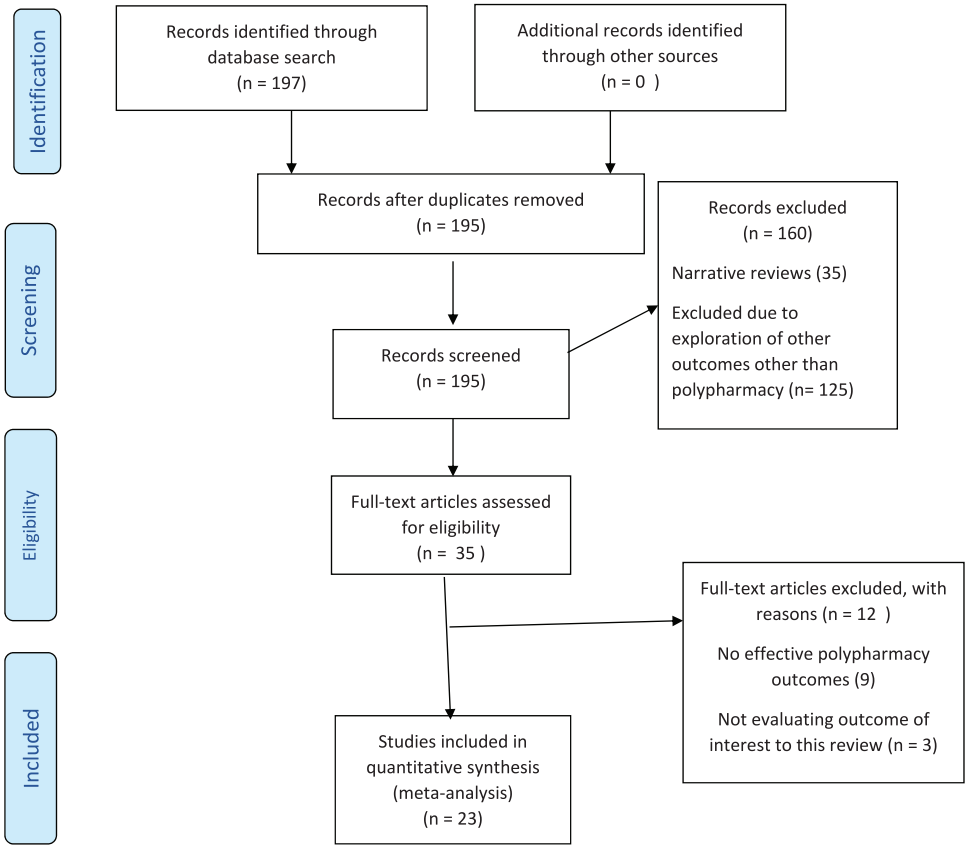


Figure 1. PRISMA flow chart for study selection.

was not possible, we retrieved the full text version to ascertain eligibility and inclusion in the review. Two reviewers (MID and MAB) independently assessed each study for the possibility of inclusion in this review based on the predetermined inclusion criteria. However, in cases where a disagreement occurred, this was resolved either by consensus or by adjudication by a third reviewer (AA). Thereafter, we combined an agreed final list of all studies that meet the following eligibility criteria: Studies published in English Language between 1 January 2000 and 30 June 2021; age of patients more than 18 years; PLWH; patients must be on ART regimen and on more than five other drugs. All studies that failed to meet the inclusion criteria were excluded from this systematic review.

Data Extraction and Study Quality Assessment

All studies that comprised PLWH on any of the ART drug combinations as part of a treatment regimen and on more than five non-HIV medications (polypharmacy) published between 1 January 2000 and 30 June 2020 were included. Two reviewers (MID and MAB) developed a data collection form for the extraction of data from included studies. The following variables were extracted from each study: Last name of the first author and the year of publication; study centre/location; number of PLWH; number of polypharmacy patients; statistics on number of medications and age; median CD4 count and viral load; ART type; median comorbidities; median co-medications; percentage of chronic comorbidities; median time since ART initiation; median since HIV diagnosis and Hepatitis B/Hepatitis C coinfection.

Quality and risk of bias assessment was carried out using the Loney criteria to assess the quality of the included prevalence studies.[26] The Loney criteria comprise eight critical appraisal checklists. These include sample size, sampling adequacy, unbiased sampling frame, measures of outcomes, unbiased assessors, response rate with refusals described, prevalence with confidence intervals and by relevant subgroups, and appropriate description of study subjects for the

research question. One point was allocated for each criterion met. Scores range between zero to eight, with higher scores denoting good study quality. For each study, methodological scoring system were used to rate the quality of each study on the prevalence of polypharmacy. Two independent reviewers carried out screening for methodological quality of the included studies utilizing this tool. In the unlikely event of disagreement, this was resolved by consensus or by the third reviewer (AIA).

Statistical Analysis

Descriptive statistics such as median and interquartile range were calculated for age and sample size, frequencies and percentages were reported for categorical data. For the included studies in the meta-analysis, we quantified the pooled estimates (with inverse-variance weights) of prevalence of polypharmacy among PLWH on ART using random effects meta-regression analysis[27] with Clopper–Pearson[28] confidence limits for binomial proportion. We assessed the heterogeneity between studies with I^2 statistic and τ^2 statistic.[29] The I^2 thresholds of 25%, 50% and 75% represent low, moderate and high between-study variances, respectively, while a τ^2 value of zero is an indicative of no heterogeneity.[30] We visualized the small-study effect and publication bias with funnel plots[31] and inference was made using Egger *et al.*'s test.[32] Subanalysis included prevalence of polypharmacy by geographical location, and we estimated the pooled median of number of medications across studies. Also, as a sensitivity analysis, we recalculated the pooled estimates based on risk of bias threshold. Statistical analysis of the proportion of polypharmacy was conducted in 'R'[33] package 'meta'[34] while pooled median estimate was implemented in 'metamedian'.[35]

Results

Characteristics of included studies

One hundred ninety-seven studies were identified from the initial literature search. We excluded 160 studies following the screening of titles and abstracts. The reasons for exclusion are laid out in Figure 1. Thereafter, 35 potentially relevant studies were selected for full text review, of which 23[21,36–57] studies satisfied the inclusion for the network meta-analysis. The source of data for the selected studies ranged from HIV outpatient clinics and University/Tertiary hospital pharmacies to multicentre AIDS cohort studies (Table 1). All included studies were published between 2014 and 2021, with most of the studies conducted in Europe (13, 56.5%) and America (7, 30.4%). See Map figure.

Overall, there were 55988 PLWH included in this meta-analysis, of which 76.7% [95% confidence interval (CI): 76.4–77.1] were male (Table 2). The median age of patients ranged from 31 years [interquartile range (IQR): 26–36] to 70 years (IQR: 68–74). The range of median CD4 count and undetectable viral load were 350–659 cells/μl and 50.9–96.9%, respectively (Table 2). Patients in the studies were on various combinations of ART with most of the studies reporting a combination of nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI) (Table 2). The median time since diagnosis of HIV in the included studies ranged between 4 and 19 years (Table 2). Patients in the selected studies were also on treatment for a variety of chronic medical conditions. The most common reported comorbidities for each study are presented in Table 2. In most studies, hypertension, ischemic heart disease, type II diabetes mellitus and dyslipidaemia appeared to be the most common comorbidities in patients (Table 2). The prevalence of Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infections were also reported in several studies and the range were 5–13.8% and 10–66.2%, respectively (Table 2).

Prevalence of polypharmacy

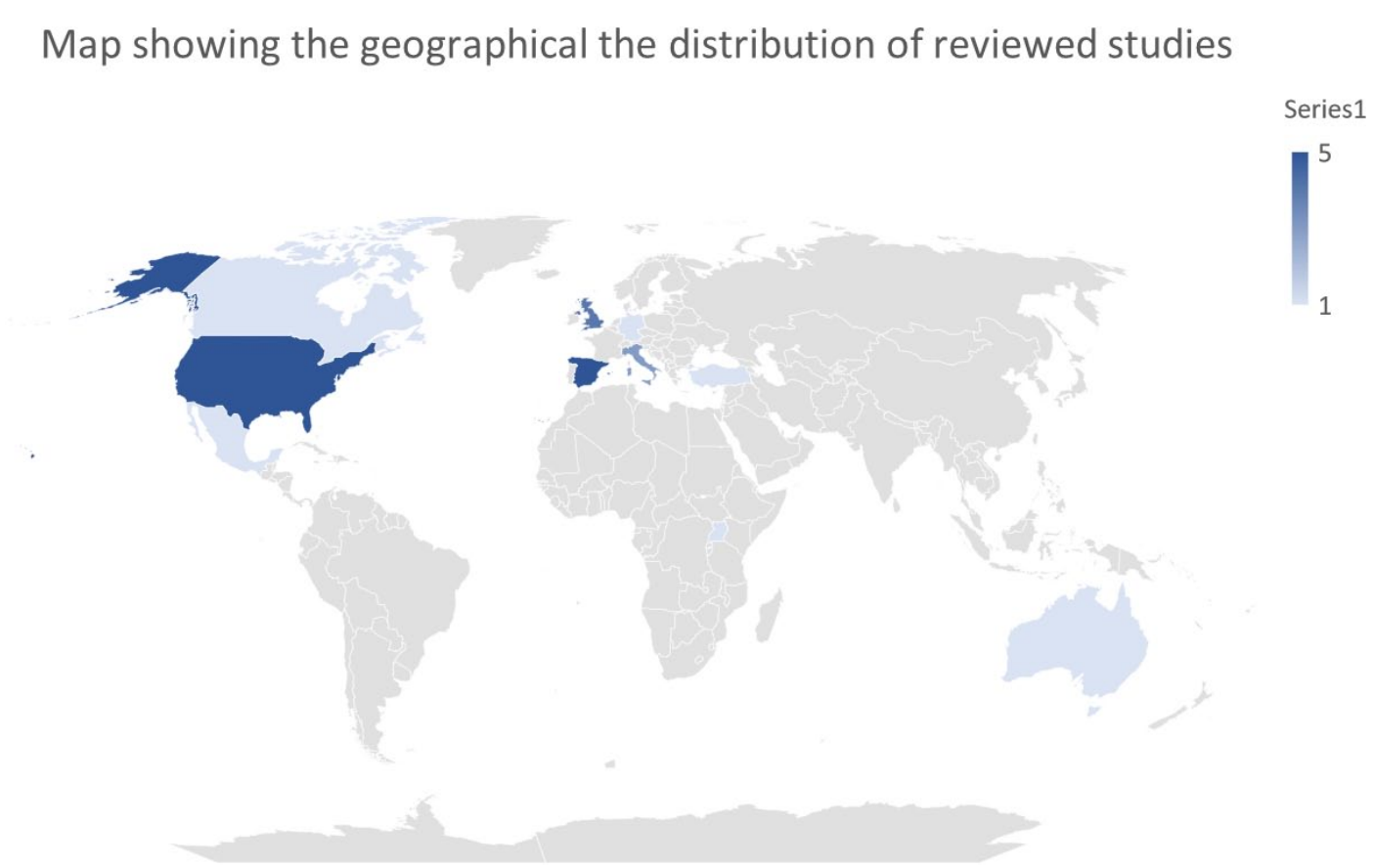
For inclusion in this review, we determined that studies must have a score of >5 (suggesting robust methodological quality on the Loney criteria).[26] Figure 2 presents the contour-enhanced funnel plot of the included studies with different significant levels. The plot did not show a sign of publication bias (Figure 1), which was confirmed with egger's test for small-study effects (−0.93, p value = 0.7631). Detailed results of the meta-analyses are presented in Figures 2 and 3. The overall pooled prevalence of polypharmacy among PLWH was 33% (95% CI: 25–42%) (Figure 2). The subgroup meta-regression showed a higher pooled prevalence of polypharmacy of 44% (95%

Table 1. Characteristics of selected studies.

Study	Year[a]	Country	Data source	Risk of bias[b]
Cantudo-Cuenca *et al.*[36]	2002–2011	Spain	Pharmaceutical care office of a hospital pharmacy service	5
Gimeno-Gracia *et al.*[47]	2011	Spain	University hospital pharmacy	6
Gimeno-Gracia *et al.*[51]	2014	Spain	University hospital pharmacy	5
Guaraldi *et al.*[52]	2006–2018	Italy	Modena HIV Metabolic Clinic Cohort Study	5
Guaraldi *et al.*[53]	2015–2016	Italy	GEPPO	7
Halloran *et al.*[54]	2013–2016	UK/Ireland	POPPY	6
Holtzman *et al.*[55]	2006–2010	USA	HIV Outpatient Study (HOPS) cohort	4
Justice *et al.*[56]	2010–2015	USA	N/A	6
Kara *et al.*[57]	2015–2016	Turkey	N/A	5
Kim *et al.*[37]	2012–2014	USA	Safety-net HIV clinics.	5
Krentz *et al.*[38]	2011–2013	Canada	Southern Alberta Clinic Cohort (SAC),	5
Lopes *et al.*[39]	2016	Germany	German health insurance claims database (InGef)	4
Lopez-Centeno *et al.*[40]	2017	Spain	Madrid Health Service	4
Mata-Marín *et al.*[41]	2015	Mexico	"La Raza" National Medical Center	7
Mazzitelli *et al.*[42]	2009–2019	UK	Chelsea and Westminster Hospital NHS Foundation Trust	4
Morillo-Verdugo *et al.*[43]	2014	Spain	Tertiary Hospital	7
Nozza *et al.*[44]	2015–2016	Italy	GEPPO	5
Okoli *et al.*[45]	2019	Multiple	Multiple	8
Patel *et al.*[46]	2008–2010	UK	HIV outpatient clinic	6
Siefried *et al.*[48]	2013–2015	Australia	Australian sexual health clinics	8
Ssonko *et al.*[49]	2015	Uganda	Mildmay Uganda outpatient HIV/AIDS care centre	5
Ware *et al.*[21]	2004–2016	USA	Multicenter AIDS Cohort Study (MACS)	8
Ware *et al.*[50]	2004–2016	USA	MACS	8

[a]Year of data collection.
[b]Higher scores suggest better study quality[26]: 'likely unbiased' (7–8), 'some suggestion of bias' (5–6) and 'substantial suggestion of bias' (<4).
GEPPO: GEriatric Patients living with HIV/AIDS: a Prospective Multidimensional cOhort (GEPPO), Italy; POPPY: Pharmacokinetic and Clinical Observations in People Over 50 (POPPY) study, England and Ireland.

CI: 27%–63%) in North and South America compared with 29% (95% CI: 20–40%) in European countries (Figure 3). The overall heterogeneity was significant for both overall analysis ($I^2 = 100\%$, $p < 0.0001$) and subgroup analyses ($I^2 = 100\%$, $p < 0.01$) and ($I^2 = 100\%$, $p < 0.01$) for the Americas and European studies, respectively. The reported median number of medications used reported in the studies varied from 2.8 (IQR: 0–4) to 8 (IQR: 5–11). The pooled median number of medications was estimated to be 4 (95% CI: 4–6.48) (Figure S2).



Map.

We also performed a sensitivity analysis by categorizing the studies by risk of bias 'likely unbiased' (7–8), 'some suggestion of bias' (5–6) and 'substantial suggestion of bias' (<4). Based on this categorisation, the estimated pooled prevalence of polypharmacy ranged from 30% (95% CI: 17–46%) in studies with medium bias to 44% (95% CI: 35–46%) for studies with high risk of bias (Figure S1).

Discussion

To the best of our knowledge, this study represents the first systematic evaluation of the prevalence of polypharmacy among PLWH as well as the global trend of factors associated with its variability. We explored the longitudinal data of over 55,988 patients from over 24 countries and territories. We found the overall pooled prevalence of polypharmacy among PLWH was about 33%. There was a proportionately higher prevalence of polypharmacy in the Americas (44%) compared with European countries (29%) (Figure 4). Despite significant heterogeneity across all studies included in the review, we found reliable certainty with regard to the overall pooled estimate of the period prevalence. The prevalence estimates reported from this systematic review and meta-analysis consolidates on the overall burden reported by recent studies exploring the case burden of polypharmacy among PLWH cohorts.[21,58]

Our findings underscore the gravity of the rising burden of polypharmacy among PLWH and the pressing need to adopt some of the interventions that have been proven to reduce the burden of polypharmacy in the general non-HIV population. Among these include timely drug prioritization, drug reconciliation and statutory review of all medications with every opportunity provided by patient contact.[59] The most recent study to evaluate the prevalence of polypharmacy in PLWH reported an estimate of about 33.1%, a prevalence rate comparatively higher than non-HIV positive patient cohorts in the study.[21] Their prevalence estimates were consistent with

Table 2. Summaries of HIV and therapeutic parameters of the included studies.

Study	*N*	CD4 (Median-cells/μl)	Undetectable viral load	ART drug class	Chronic comorbidities (%)	Time (years) since HIV diagnosis: Median	HBV coinfection (%)	HCV coinfection (%)
Cantudo-Cuenca *et al.*[36]	594	514	69.40%	NRTI, NNRTI, PI	Hyperlipidaemia (18.9%) Ischaemic heart disease (18.5%) Hypertension (12.1%)	NR	7.7	66.2
Gimeno-Gracia *et al.*[47]	118	NR	88.00%	PI/r-based: 53.4%, NNRTI-based: 41.5%	NR	13.4	NR	28
Gimeno-Gracia *et al.*[51]	199	659	91.90%	PI: 52.7%, NNRTI: 47.7%, NRTI: 73.4%, integrase inhibitor: 19.6%, CCR5 receptor antagonist: 1.5%	NR	18	NR	NR
Guaraldi *et al.*[52]	2944	NR	96.90%	NRTI, NNRTI, PI	NR	19	NR	NR
Guaraldi *et al.*[53]	1258	644.5	NR	Triple/M ART: 31.91%, Mono/dual ART: 68.09%	Hypertension (60.83%) Type II DM (27.54%) CVD (16.88%)	NR	9.8	12.5
Halloran *et al.*[54]	1072	628	NR	NRTI PI	NR	NR	NR	NR
Holtzman *et al.*[55]	3810	432	NR	PI, NNRTI, Integrase inhibitor, Fusion inhibitor	NR	NR	9.5	24.9
Justice *et al.*[56]	9473	515	NR	60% Protease Inhibitor based, 40% nonnucleoside reverse transcriptase inhibitors, and $<0.1\%$ on an Integrase inhibitor	Hypertension (38.1%) Diabetes (21.7%) Hyperlipidaemia (39.1%)	NR	NR	
Kara *et al.*[57]	181	586	80.10%	NRTI, Integrase inhibitors, Protease inhibitors, NNRTI, Entry inhibitors	Hypertension (12.7%) Dyslipidemia (9.4%) Major depression (7.7%)	4	NR	NR
Kim *et al.*[37]	250	NR	NR	NR	NR	NR	NR	NR
Krentz *et al.*[38]	1329	NR	NR	NR	NR	7.5	NR	NR
Lopes *et al.*[39]	2680	NR	NR	NR	CNS disorder: (27%) Hypertension: (27%) Dyslipidemia: 517 (19%)	NR	5	10
Lopez-Centeno *et al.*[40]	22945	NR	NR	Boosted Pis NNRTIs, Boosted INSTIs Nonboosted INSTIs nRTIs CCR5 inhibitors (MVC)	NR	NR	NR	NR

(*Continued*)

Table 2. (Continued)

Study	*N*	CD4 (Median-cells/μl)	Undetectable viral load	ART drug class	Chronic comorbidities (%)	Time (years) since HIV diagnosis: Median	HBV coinfection (%)	HCV coinfection (%)
Mata-Marín *et al.*[41]	125	447	72%	NR	Hypertension (33%) Diabetes mellitus (18.3%) Hyperlipidaemia (8.17%)	NR	13.8	NR
Mazzitelli *et al.*[42]	790	661	NR	cART (46 on ritonavir, six on cobicistat)	NR	15.4	NR	NR
Morillo-Verdugo *et al.*[43]	223	NR	84.40%	2 NRTI + 1 NNRTI (36.2% pateints) 2 NRTI + protease inhibitor (18.8%) 2 NRTI + INSTI (12.6%) Other combinations (31.4%, like monotherapy-20%, 40% dual ART)	Viral liver disease (67.3%) CVD/HTN (25.0%) CNS disease (20.5%)	NR	NR	NR
Nozza *et al.*[44]	1222	645	94.31%	Triple therapy (66.4%) Dual therapy (25.3%) Monotherapy (6.5%) Mega ART (> 3 drugs)= (1.64%)	Dyslipidemia (71.12%) HTN (63.55%) T2DM (28.45%)	17.2	9.8	12.6
Okoli *et al.*[45]	2112	NR	NR	NR	NR	NR	NR	NR
Patel *et al.*[46]	299	NR	NR	NR	NR	11.9	NR	NR
Siefried *et al.*[48]	522	399	NR	NR	Hypertension (18%) Heart disease (10.9%) DM (5.9%)	NR	13 HBV and HCV	
Ssonko *et al.*[49]	411	350	NR	NR	NR	NR	NR	NR
Ware *et al.*[21]	1715	NR	50.90%	Monotherapy = 7 Combination therapy = 110 ART = 1073	Hypertension (17.8%) DM (4.9%) Dyslipidemia (30.0%)	NR	NR	NR
Ware *et al.*[50]	1716	NR	57.70%	Monotherapy = 144 Combination therapy = 1125 HAART = 21161	NR	NR	NR	NR
Overall	55988							

ART, antiretroviral therapy regimen ; CCR5, C-C chemokine receptor type 5; CNS, central nervous system; CVD, cardiovascular disease; HTN, hypertension; DM, Diabetes Mellitus; HAART, highly active antiretroviral therapy; HBV, Hepatitis B virus; HCV, Hepatitis C virus; INSTI, Integrase strand transfer inhibitors; MVC, Maraviroc; NR, not reported; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

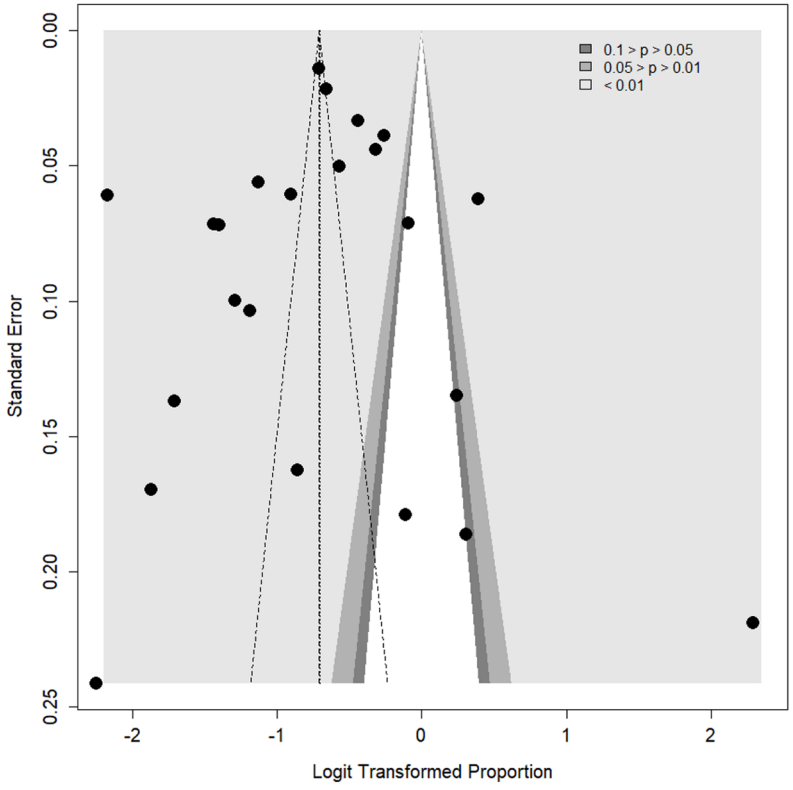


Figure 2. Contour-enhance funnel plot of the 23 included studies in the meta-analysis. The vertical and the diagonal dashed lines represent the overall estimated effect size and its 95% CI while the shaded area represent different significance levels for the effect sizes, respectively.

findings from our review.[16] Where uncertainty exists from polypharmacy prevalence studies in PLWH, this has principally revolved around the initial lack of consensus regarding the exact definition of polypharmacy.[60] Intake of greater than five non-HIV medications is generally defined as polypharmacy, although there remains lack of a unifying consensus around this.

The significant heterogeneity in the prevalence estimates we observed among the studies included in this review may be due to several factors. Some of these include differences in the methods of adjudication of polypharmacy, study design, as well as the geographical disposition of areas where the studies were carried out. In addition, the difference in the mean age of the constituent studies appears to stratify the point prevalence of polypharmacy. Studies with a higher median age of 69 years (66.7–72.0) such as the recent report by Gimeno-Gracia *et al.*[58] showed a higher overall pooled prevalence compared with those reporting on a younger population cohort. The median age of patients in our review ranged between 31 years (IQR: 26–36) and 70 years (IQR: 68–74) and perhaps accounts for the relatively lower overall prevalence of 33% in this synthesis. Furthermore, stratifying studies included in the review based on the risk of bias resulted in different prevalence estimates. Studies with medium risks had polypharmacy rates of about 30%, whereas those with high risk reported prevalence estimates of about 44%. The 33% overall prevalence of polypharmacy reported in this review therefore appears closer to the estimate with a reasonably low risk of bias.

The phenotype of polypharmacy in the PLWH has long been reported to contrast with that of the general population.[16,45] PLWH cohorts with polypharmacy have been suggested to be younger and therefore more likely to live longer with both the epidemiological as well as the therapeutic consequences of polypharmacy.[16] This observation is consistent with a recent longitudinal series reported by Krentz and Gill[38] which found that nearly one in every four patients in that study

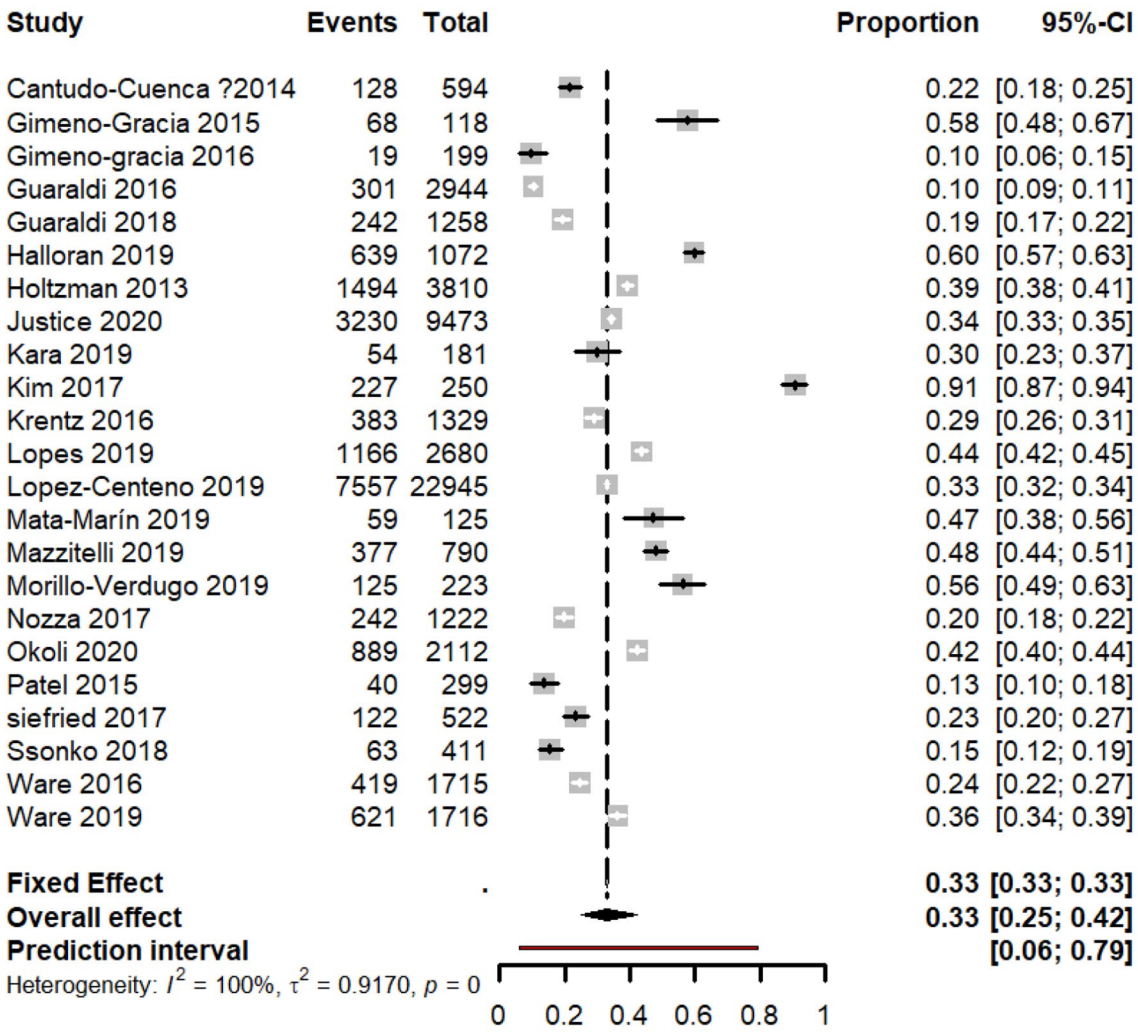


Figure 3. Meta-analysis of the proportion/prevalence of polypharmacy among HIV positive.

between the ages of 31 and 45 years experienced polypharmacy. Since the advent of ART and the increasing survival of PLWH, the therapeutic challenge in the overall scheme of their management has long been predicted to shift to polypharmacy. And this is likely to remain so for the foreseeable future, considering the frantic sustained search for optimal treatment for ever ballooning comorbidities.

The multiclass ART regimen on their own are typified by complex pharmacokinetics, which provides a setting for potential serious drug–drug interactions. What has been studied and reported thus far are predominantly bidirectional interactions. However, other permutations such as drug–food, drug–alcohol and pharmacogenetic interactions[15] have increasingly been reported lately. The spectre of potential permutations and combinations of interactions that could possibly occur when a rising census of medications taken together remains unexplored and continues to be subjects of ongoing therapeutic concerns.

Strength

The principal strength of this synthesis lies in its novelty at estimating the overall pooled prevalence of polypharmacy among PLWH. It has for the first time provided physicians and policy makers a systematic synthesis of the true burden of polypharmacy among this cohort of patients.

Limitations

The high proportion of heterogeneity between studies included in our review accounted for

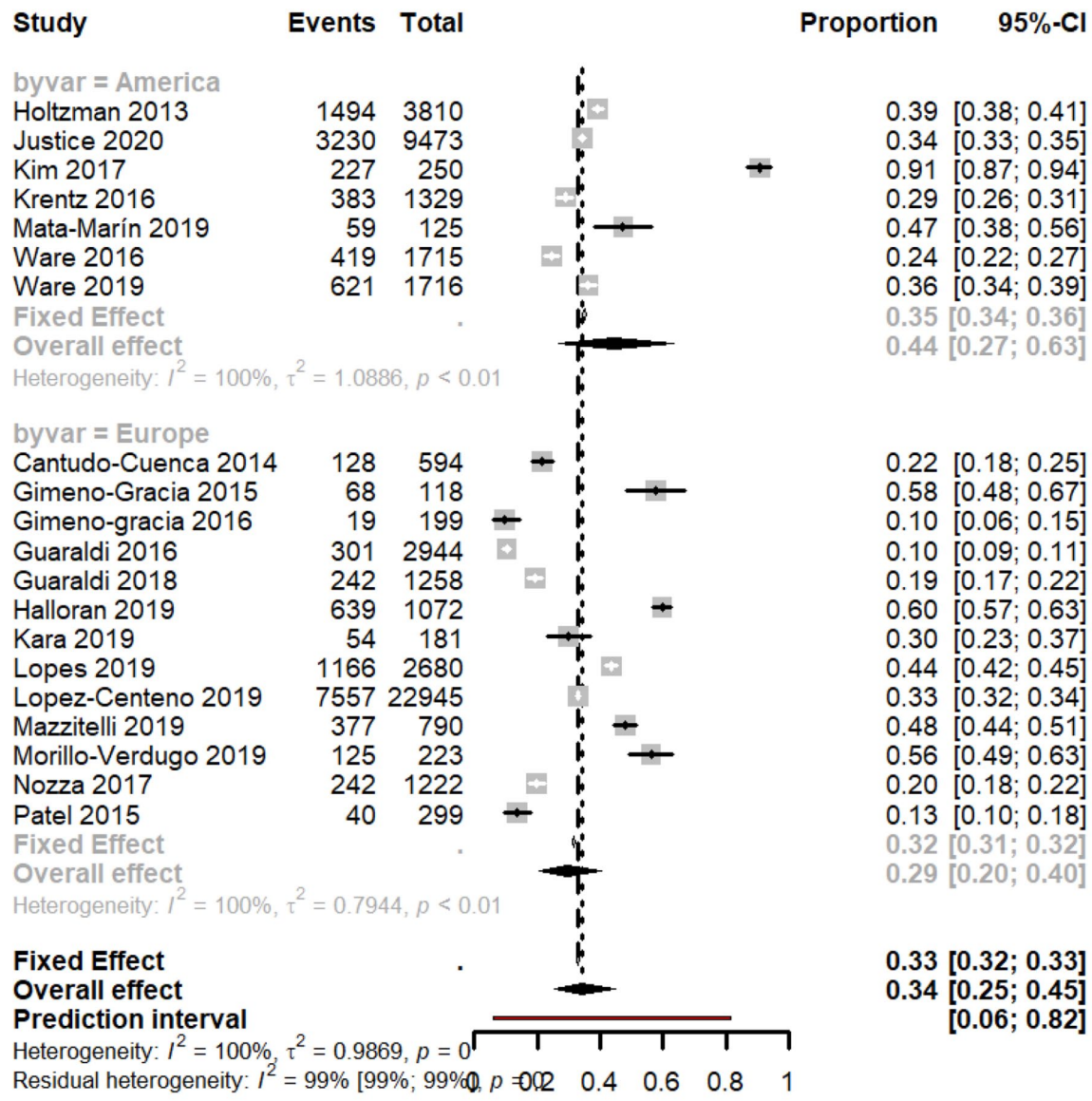


Figure 4. Meta-analysis of the proportion/prevalence of polypharmacy among HIV positive, by world region (America and Europe).

some of the imprecise point estimates, but this is unlikely to significantly influence the reported prevalence as the rate of 33% is within the ballpark reported from recent studies. In addition, this review has not examined the impact of polypharmacy on health-related quality of life, perhaps by far one of the most important real-life consequences of this morbidity.

Conclusion

The pooled prevalence estimates from this synthesis established that polypharmacy is a significant and rising problem among PLWH. The exact interventions that are likely to significantly mitigate its effect remain uncertain and will need exploration by future prospective and systematic studies.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Mohammed I. Danjuma: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

Oyelola A. Adegboye: Data curation; Formal analysis; Methodology.

Ahmed Aboughalia: Data curation; Methodology; Validation; Writing – review & editing.

Nada Soliman: Data curation; Validation; Writing – review & editing.

Ruba Almishal: Data curation; Methodology; Writing – review & editing.

Haseeb Abdul: Data curation; Validation; Writing – review & editing.

Mohamad Faisal Hamad Mohamed: Data curation; Formal analysis; Methodology; Writing – review & editing.

Mohamed Nabil Elshafie: Data curation; Formal analysis; Methodology; Writing – review & editing.

Abdulatif AlKhal: Data curation; Methodology.

Abdelnaser Elzouki: Formal analysis; Methodology; Validation; Writing – review & editing.

Arwa Al-Saud: Data curation; Resources; Validation; Writing – review & editing.

Mas Chaponda: Data curation; Formal analysis; Methodology; Validation; Writing – review & editing.

Mubarak Arriyo Bidmos: Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Acknowledgements

None.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by the Qatar National Library.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Not applicable.

ORCID iD

Mohammed I. Danjuma https://orcid.org/0000-0003-2198-5278

References

1. Justice AC. HIV and aging: time for a new paradigm. *Curr HIV/AIDS Rep* 2010; 7: 69–76.
2. Gueler A, Moser A, Calmy A, *et al*. Life expectancy in HIV-positive persons in Switzerland: matched comparison with general population. *AIDS* 2017; 31: 427–436.
3. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *Lancet HIV* 2017; 4: e349–e356.
4. Farahani M, Mulinder H, Farahani A, *et al*. Prevalence and distribution of non-AIDS causes of death among HIV-infected individuals receiving antiretroviral therapy: a systematic review and meta-analysis. *Int J STD AIDS* 2017; 28: 636–650.
5. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390(10100): 1151–1210.
6. Okoli C, Schwenk A, Radford M, *et al*. Polypharmacy and potential drug-drug interactions for people with HIV in the UK from the Climate-HIV database. *HIV Med* 2020; 21: 471–480.
7. Patel R, Moore T, Cooper V, *et al*. An observational study of comorbidity and healthcare utilisation among HIV-positive patients aged 50 years and over. *Int J STD AIDS* 2015; 27: 628–637.
8. Bjerrum L, Søgaard J, Hallas J, *et al*. Polypharmacy: correlations with sex, age and drug regimen. *Eur J Clin Pharmacol* 1998; 54: 197–202.
9. Viktil KK, Blix HS, Moger TA, *et al*. Polypharmacy as commonly defined is an indicator of limited value in the assessment of drug-related problems. *Br J Clin Pharmacol* 2007; 63: 187–195.
10. Gnjidic D, Hilmer SN, Blyth FM, *et al*. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol* 2012; 65: 989–995.
11. Fried TR, O'Leary J, Towle V, *et al*. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. *J Am Geriatr Soc* 2014; 62: 2261–2272.
12. Rawle MJ, Cooper R, Kuh D, *et al*. Associations between polypharmacy and cognitive and

physical capability: a British birth cohort study. *J Am Geriatr Soc* 2018; 66: 916–923.

13. Danjuma MI, Mohiuddin A, Pirmohamed M, *et al.* Tenofovir disoproxil fumarate and the kidney in HIV-infected patients: the evidence thus far. *HIV Ther* 2010; 4(3): 345–359.
14. Danjuma MI, Mohamad-Fadzillah NH and Khoo S. An investigation of the pattern of kidney injury in HIV-positive persons exposed to tenofovir disoproxil fumarate: an examination of a large population database (MHRA database). *Int J STD AIDS* 2014; 25: 273–279.
15. Danjuma MI, Egan D, Abubeker IY, *et al.* Polymorphisms of tenofovir disoproxil fumarate transporters and risk of kidney tubular dysfunction in HIV-positive patients: genetics of tenofovir transporters. *Int J Std Aids*. Epub ahead of print 2 August 2018. DOI: 10.1177/0956462418786562.
16. Edelman EJ, Gordon KS, Glover J, *et al.* The next therapeutic challenge in HIV: polypharmacy. *Drug Aging* 2013; 30: 613–628.
17. Shalansky SJ and Levy AR. Effect of number of medications on cardiovascular therapy adherence. *Ann Pharmacother* 2002; 36: 1532–1539.
18. Grant RW, Devita NG, Singer DE, *et al.* Polypharmacy and medication adherence in patients with type 2 diabetes. *Diabetes Care* 2003; 26: 1408–1412.
19. Rasmussen LD, Kronborg G, Larsen CS, *et al.* Use of non-antiretroviral drugs among individuals with and without HIV-infection: a Danish nationwide study. *Infect Dis* 2017; 49: 42–54.
20. López-Centeno B, Badenes-Olmedo C, Mataix-Sanjuan McAllister ÁK, *et al.* Polypharmacy and drug-drug interactions in HIV-infected subjects in the region of Madrid, Spain: a population-based study. *Clin Infect Dis an Off Publ Infect Dis Soc Am* 2020; 71: 353–362.
21. Ware D, Palella FJ Jr, Chew KW, *et al.* Prevalence and trends of polypharmacy among HIV-positive and -negative men in the Multicenter AIDS Cohort Study from 2004 to 2016. *PLOS ONE* 2018; 13: e0203890.
22. Hasse B, Ledergerber B, Furrer H, *et al.* Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis an Off Publ Infect Dis Soc Am* 2011; 53: 1130–1139.
23. Greene M, Steinman MA, McNicholl IR, *et al.* Polypharmacy, drug-drug interactions, and potentially inappropriate medications in older adults with human immunodeficiency virus infection. *J Am Geriatr Soc* 2014; 62: 447–453.
24. Kantor ED, Rehm CD, Haas JS, *et al.* Trends in prescription drug use among adults in the United States from 1999-2012. *JAMA* 2015; 314: 1818–1831.
25. Back D and Marzolini C. The challenge of HIV treatment in an era of polypharmacy. *J Int AIDS Soc* 2020; 23: e25449.
26. Loney PL, Chambers LW, Bennett KJ, *et al.* Critical appraisal of the health research literature: prevalence or incidence of a health problem. *Chronic Dis Can* 1998; 19: 170–176.
27. DerSimonian R and Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 2015; 45: 139–145.
28. Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934; 26: 404–413.
29. Higgins JPT, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003; 327(7414): 557–560.
30. Quintana DS. From pre-registration to publication: a non-technical primer for conducting a meta-analysis to synthesize correlational data. *Front Psychol* 2015; 6: 1549.
31. Egger M, Juni P, Bartlett C, *et al.* How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. *Health Technol Assess* 2003; 7: 1–76.
32. Egger M, Davey Smith G, Schneider M, *et al.* Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315(7109): 629–634.
33. Core Team R. *R: A language and environment for statistical computing*. Vienna: R Foundation for Statistical Computing (2013), Suppl Fig S 2015; 2.
34. Schwarzer G. meta: an R package for meta-analysis. *R News* 2007; 7: 40–45.
35. McGrath S, Zhao X, Steele R, *et al. Metamedian: meta-analysis of medians* (R Package Version 01) 2019; 4.
36. Cantudo-Cuenca MR, Jiménez-Galán R, Almeida-Gonzalez CV, *et al.* Concurrent use of comedications reduces adherence to antiretroviral therapy among HIV-infected patients. *J Manag Care Spec Pharm* 2014; 20: 844–850.
37. Kim TW, Walley AY, Heeren TC, *et al.* Polypharmacy and risk of non-fatal overdose for patients with HIV infection and substance dependence. *J Subst Abuse Treat* 2017; 81: 1–10.
38. Krentz HB and Gill MJ. The impact of non-antiretroviral polypharmacy on the continuity of antiretroviral therapy (ART) among HIV

patients. *AIDS Patient Care STDS* 2016; 30: 11–17.

39. Lopes S, O'Day K, Meyer K, *et al*. Comedication prescription patterns and potential for drug-drug interactions with antiretroviral therapy in people living with human immunodeficiency virus type 1 infection in Germany. *Pharmacoepidemiol Drug Saf* 2020; 29: 270–278.
40. López-Centeno B, Badenes-Olmedo C, Mataix-Sanjuan McAllister ÁK, *et al*. Polypharmacy and drug–drug interactions in people living with human immunodeficiency virus in the region of Madrid, Spain: a population-based study. *Clin Infect Dis* 2020; 71: 353–362.
41. Mata-Marín JA, Martínez-Osio MH, Arroyo-Anduiza CI, *et al*. Comorbidities and polypharmacy among HIV-positive patients aged 50 years and over: a case–control study. *BMC Res Notes* 2019; 12: 1–6.
42. Mazzitelli M, Milinkovic A, Pereira B, *et al*. Polypharmacy and evaluation of anticholinergic risk in a cohort of elderly people living with HIV. *Aids* 2019; 33: 2439–2441.
43. Morillo-Verdugo R, Robustillo-Corté MA, Abdel-Kader Martín L, *et al*. Determination of a cutoff value for medication regimen complexity index to predict polypharmacy in HIV+ older patient. *Rev Esp Quimioter* 2019; 32: 458–464.
44. Nozza S, Malagoli A, Maia L, *et al*. Antiretroviral therapy in geriatric HIV patients: the GEPPO cohort study. *J Antimicrob Chemother* 2017; 72: 2879–2886.
45. Okoli C, de Los Rios P, Eremin A, *et al*. Relationship between polypharmacy and quality of life among people in 24 countries living with HIV. *Prev Chronic Dis* 2020; 17: E22–E22.
46. Patel R, Moore T, Cooper V, *et al*. An observational study of comorbidity and healthcare utilisation among HIV-positive patients aged 50 years and over. *Int J STD AIDS* 2016; 27: 628–637.
47. Gimeno-Gracia M, Crusells-Canales MJ, Javier Armesto-Gomez F, *et al*. Prevalence of concomitant medications in older HIV+ patients and comparison with general population. *HIV Clin Trials* 2015; 16: 117–124.
48. Siefried KJ, Mao L, Cysique LA, *et al*. Concomitant medication polypharmacy, interactions and imperfect adherence are common in Australian adults on suppressive antiretroviral therapy. *AIDS* 2018; 32: 35.
49. Ssonko M, Stanaway F, Mayanja HK, *et al*. Polypharmacy among HIV positive older adults on anti-retroviral therapy attending an urban clinic in Uganda. *BMC Geriatr* 2018; 18: 125.
50. Ware D, Palella FJ, Chew KW, *et al*. Examination of polypharmacy trajectories among HIV-positive and HIV-negative men in an ongoing longitudinal cohort from 2004 to 2016. *AIDS Patient Care STDS* 2019; 33: 354–365.
51. Gimeno-Gracia M, Crusells-Canales MJ, Armesto-Gómez FJ, *et al*. Polypharmacy in older adults with human immunodeficiency virus infection compared with the general population. *Clin Interv Aging* 2016; 11: 1149–1157.
52. Guaraldi G, Menozzi M, Zona S, *et al*. Impact of polypharmacy on antiretroviral prescription in people living with HIV. *J Antimicrob Chemother* 2017; 72: 511–514.
53. Guaraldi G, Malagoli A, Calcagno A, *et al*. The increasing burden and complexity of multi-morbidity and polypharmacy in geriatric HIV patients: a cross sectional study of people aged 65–74 years and more than 75 years. *BMC Geriatr* 2018; 18: 99.
54. Halloran MO, Boyle C, Kehoe B, *et al*. Polypharmacy and drug–drug interactions in older and younger people living with HIV: the POPPY study. *Antivir Ther* 2019; 24(3):193–201.
55. Holtzman C, Armon C, Tedaldi E, *et al*. Polypharmacy and risk of antiretroviral drug interactions among the aging HIV-infected population. *J Gen Intern Med* 2013; 28: 1302–1310.
56. Justice AC, Gordon KS, Skanderson M, *et al*. Nonantiretroviral polypharmacy and adverse health outcomes among HIV-infected and uninfected individuals. *AIDS* 2018; 32: 739.
57. Kara E, Inkaya AÇ, Hakli DA, *et al*. Polypharmacy and drug-related problems among people living with HIV/AIDS: a single-center experience. *Turkish J Med Sci* 2019; 49: 222–229.
58. Gimeno-Gracia M, Sánchez-Rubio-Ferrández J, Robustillo-Cortés M, *et al*. Prevalence of polypharmacy and pharmacotherapy complexity in elderly people living with HIV in Spain. POINT study. *Farm Hosp* 2020; 44: 127–134.
59. Scott IA, Hilmer SN, Reeve E, *et al*. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med* 2015; 175: 827–834.
60. Gleason LJ, Luque AE and Shah K. Polypharmacy in the HIV-infected older adult population. *Clin Interv Aging* 2013; 8: 749–763.