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ORIGINAL ARTICLE

Treatment and comorbidity burden among people living with HIV: a review of systematic literature reviews

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ABSTRACT

Background: As the human immunodeficiency virus (HIV) treatment landscape continues to evolve, the prolonged life expectancy and long-term exposure to antiretroviral drugs have modified the burden associated with living with HIV.

Objective: To better understand the current treatment and comorbidity burden in people living with HIV (PLWH).

Methods: Peer-reviewed systematic literature reviews (SLRs) between 2017 and 2020 that included US studies and examined drug adherence/pill burden, resistance burden, or comorbidities in PLWH were identified. Methods and findings were extracted for the overall studies and examined in the subset of US studies.

Results: Among 665 publications identified, 47 met the inclusion criteria (drug adherence/pill burden: 5; resistance: 3; comorbidities: 40). While antiretroviral drug adherence levels varied across SLRs, single-tablet regimens (STR) were associated with higher adherence versus multiple-tablet regimens. STRs were also associated with lower risk of treatment discontinuation, higher cost-effectiveness, and lower risk of hospitalization. Longer survival resulted in a high comorbidity burden, with non-AIDS causes accounting for 47% of deaths among PLWH in the US. HIV doubled the risk of cardiovascular disease and was associated with other health problems, including bone and muscle diseases, depression, and cancers. Several antiretroviral regimens were associated with chronic diseases, including cardiometabolic conditions. Lifetime HIV costs are substantially increasing, driven by antiretroviral, adverse event, and comorbidity treatment costs cumulated due to longer survival times.

Conclusions: There is a considerable burden associated with HIV and antiretroviral treatment, highlighting the benefits of less complex and safer regimens, and the unmet need for effective preventative interventions.

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KEYWORDS
Adherence; antiretrovirals; comorbidities; human immunodeficiency virus; treatment resistance

1. Introduction

In 2018, an estimated 1,173,900 individuals of 13 years of age and older were living with human immunodeficiency virus (HIV) in the United States (US), with 37,515 newly-diagnosed cases[1].

Treatment for HIV was revolutionized with the introduction of combination antiretroviral therapy (ART), which is effective at suppressing HIV replication, but is not curative[2,3]. Nonetheless, effective combination ART has increased viral suppression rates, thereby decreasing HIV-related morbidity and mortality, and reducing the risk of sexual transmission of HIV[4]. Combination ART regimens have historically comprised three active agents, including a backbone of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and an additional drug from another drug class, such as non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), or protease inhibitors (PIs)[4]. Selected two-drug regimens are now part of the treatment armamentarium[5], and the use of single-tablet regimens (STRs) has been shown to improve adherence to treatment compared to multiple-tablet regimens (MTRs)[4,6]. Nevertheless, as a chronic disease that is incurable with ART, HIV is associated with a substantial burden, including the requirement for lifelong treatment and the risk of treatment resistance[2,7,8]. In addition, with the increased life expectancy and the long-term use of ART among people living with HIV (PLWH), the lifetime risk of developing non-AIDS comorbidities is on the rise[7].

While previous systematic literature reviews (SLRs) included publications on the burden associated with medication adherence and complexity[9–11], treatment resistance[12,13], and comorbidities[14,15] among PLWH, none have comprehensively covered all these aspects of the disease and treatment

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burden in this population. Therefore, this SLR of SLRs was conducted to provide a comprehensive summary of the ART adherence and pill burden, antiretroviral resistance burden, and comorbidity burden in PLWH based on SLRs that included the US as one of the countries of interest.

2. Methods

2.1. Search strategy

A systematic search was conducted on 8 December 2020 through MEDLINE, MEDLINE In Process, and EMBASE. The search used a combination of terms relating to HIV and the outcomes of interest (see Table 1 for the full search strategy).

2.2. Study selection

Two researchers independently conducted the selection process (RB and KM), and discrepancies were resolved through discussion with a third researcher (HR). Included studies met the following selection criteria: peer-reviewed SLRs (with or without meta-analysis), included patients diagnosed with HIV-1, evaluated at least one of the outcomes of interest (i.e. ART adherence and pill burden, antiretroviral resistance burden, or comorbidity burden), included studies on patients aged $\geq$ 9 years, and were published in English in 2017 or later. SLRs were excluded if the US was not part of the countries considered or if the regions covered were not specified. Conference abstracts, articles with data not reported or where the full text could not be found were excluded.

2.3. Data extraction

The following characteristics of the selected articles were extracted: study type (SLR or SLR in combination with meta-analysis), type of studies included in the SLR (e.g. retrospective, randomized controlled trial [RCT]), publication period covered, population(s) considered, and outcome(s) of interest assessed. In addition, the main findings related to the outcomes of interest were extracted. If available, study-level findings from the US studies included in each SLR were also reviewed. Data were compiled into an electronic spreadsheet and a narrative synthesis of the included studies was conducted. In this paper, the results from the SLRs were reported for the overall studies included. The findings of the US studies were reported when noteworthy or generally inconsistent with those of the overall studies.

3. Results

3.1. Study characteristics

The electronic database search identified 665 review abstracts. After the 2-level screening, 47 review articles were included in the final analysis (Figure 1).

Five SLRs covered the ART adherence and pill burden in PLWH[9–12,16], three SLRs covered treatment resistance in PLWH[12,13,17], and 40 SLRs focused on the HIV and/or ART-associated comorbidity burden[14,15,18–55] (Table 2). These SLRs covered a range of study types, including observational studies in general, RCTs, prospective and retrospective studies, and cross-sectional and longitudinal studies. Publication periods covered in these SLRs varied across studies, including some that did not impose any publication period, and spanned up to 2020 (Table 2). While the retained SLRs mostly focused on adult PLWH, six also included adolescents (<18 years, excluding children[19]; 13–18 years[15]; $\geq$15 years[27,32]; $\geq$16 years[53]; young people [age not specified][49]), one was conducted in children and adolescents ($\leq$18 years)[22], and two in older adults ($\geq$50 years)[14,21], In addition, some of the SLRs focused on specific subpopulations of PLWH, such as prison inmates[11], veterans[36], pregnant women[43,47,54], premenopausal women[35], men[33], and men who have sex with men (MSM)[52]. The main findings of the included SLRs are detailed in Figure 2.

3.2. Art adherence and pill burden

Different types of measures were used to report adherence to ART, including self-report, pill count, medication event

Table 1. Search strategy.

	Search term	Number of publications
HIV		
1	(HIV or "human immunodeficiency virus").ti,ab or exp HIV/	787,208
Study type		
2	1 and ((review* and systematic) or meta-analys* or "meta analysis" or "meta analyses" or "meta review" or "meta-review").ti,ab	11,036
3	2 not animal*.mp	10,849
Outcomes		
4	3 and (exp Drug Resistance/ or ((treatment or medication or drug) adj3 (resistance or resistant)).ti,ab)	500
5	3 and ((burden adj2 (pill or drug or treatment or medication or therapy or regimen)) or ((patient or drug or treatment or medication or therapy or regimen) adj2 (complian* or non?complian* or adheren* or non?adheren* or "proportion of days covered" or PDC))).ti,ab	606
6	3 and (comorbid* or weight gain or obesity or bmi or "body mass index" or diabet* or hypertens* or cardiovascular or hyperlipid* or anxiety or depressi* or fatigue or headache or insomnia or dizziness or "poor concentration" or suicid*).ti,ab	1,597
Combinations		
7	4 or 5 or 6	2,470
Language and time period		
8	limit 7 to (English language and yr = "2017–Current")	1,074
9	remove duplicates from 8	665

Abbreviations: HIV, human immunodeficiency virus; SLR, systematic literature review; US, United States.

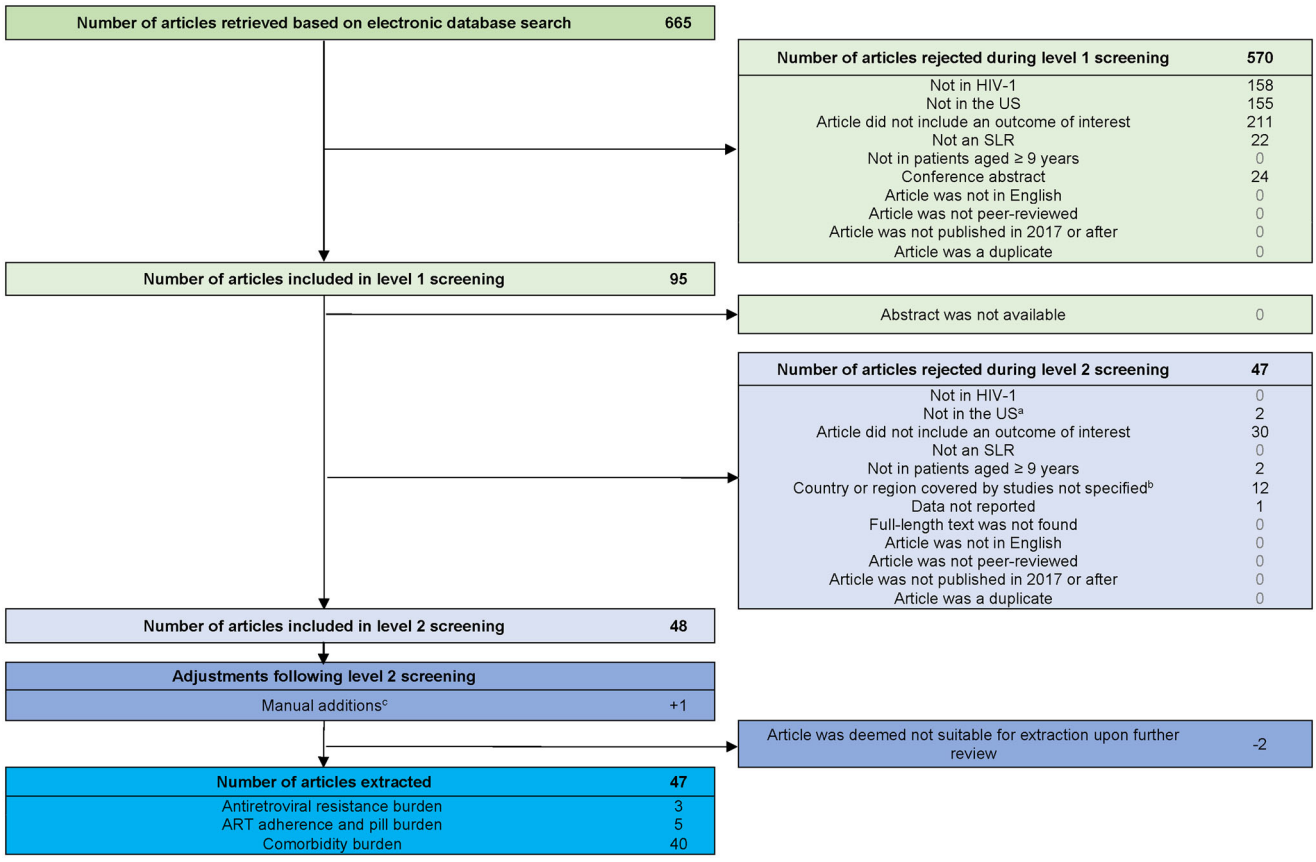

Figure 1. PRISMA diagram of study selection.
Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis; SLR, systematic literature review. US, United States.
[a]SLRs that included both non-US and US studies, with results at the study level presented (for the US studies), were not excluded.
[b]SLRs where the country was not specified overall or at the study level were excluded.
[c]One scoping review included a US study in children aged 7–17 years. It was manually added to include potentially relevant information, despite the study population including children less than 9 years of age.

monitoring system, medication possession ratio, proportion of days covered, and pharmacy/prescription refill rates. In addition, the threshold to determine adequate adherence levels varied across studies and was mostly either 90% or 95%[9,11,12].

Among the individual US studies included in the SLRs, ART adherence level estimates ranged between 74% and 98% based on pill count[16], and 53–99% based on self-report[12]. The individual studies included in these SLRs included various subpopulations, such as ART-naïve[56] and homeless and marginally housed individuals[57]. In the specific population of prison inmates, the proportion of patients with ART adherence $\geq$ 95% was ~54% (overall and in North America)[11], which the authors contrasted to other high-risk subgroups identified in literature outside of the SLR, such as drug users living with HIV (60%), female sex workers living with HIV (76%), and adolescents living with HIV (62%)[11].

PLWH using MTRs versus STRs were more likely to have lower adherence to ART[9,16], although some of the studies included in one SLR reported a non-significant association[10]. Odds ratios (ORs) for better adherence in patients using STRs versus MTRs ranged from 1.43 [9] to 1.96 [16] ($p < .001$ for both). This finding remained true when comparing STRs to once-daily MTRs (OR = 1.66, $p = .002$]) and to twice-daily MTRs (OR = 2.53, $p = .02$), separately[16]. STRs were also reported to be associated with a lower risk of ART discontinuation (relative risk [RR] = 0.69, $p = .05$), incremental cost-effectiveness ratio for initial treatment of $26,383 per quality-adjusted life year, lower risk of hospitalization (HR = .71; 95% CI = .59–.86), extended time to hospitalization (median: 1,508 vs. 1,032 days; $p = .004$), and better patient satisfaction, symptom control, and overall health status, as compared to MTRs[16]. Higher levels of adherence were associated with greater viral suppression[9] and lower percentages of treatment failure and treatment resistance[12].

3.3. Antiretroviral drug resistance in PLWH

The prevalence of drug resistance mutations in PLWH receiving ART varied between 1% and 13% in the US[12], and the prevalence of resistance acquired after virological failure was 23% for NRTI and 19% for NNRTI resistance mutations in North America[13]. The most frequent drug resistance mutation acquired after virological failure was at position M184 for NRTI (49% in North America) and at position Y181 for NNRTI (8% in North America)[13]. In addition, the prevalence of pretreatment resistance in North America was estimated to be 6% for NRTI and 8% for NNRTI resistance mutations,

Table 2. Publication details of the included reviews.

Author and Date	Study Type	Type of Studies Included in the SLR (e.g. Retrospective, RCT)	Publication Period Covered in the SLR	Population(s) Included
ART adherence and pill burden				
Altice et al. (2019)[9]	SLR and meta-analysis	RCTs and observational studies	2006–2016	Individuals receiving STRs or MTRs for HIV treatment
Clay et al. (2018)[16]	SLR and meta-analysis	RCTs (single-blind or open-label) and observational studies	2005–2017	Individuals receiving STRs or MTRs for HIV treatment
Diallo et al. (2020)[12]	SLR	RCTs, cohort studies, and longitudinal studies	2001–2019	PLWH initiating ART
Pantuzza et al. (2017)[10]	SLR	Cross-sectional, prospective, and retrospective (includes observational and experimental designs)	All articles published up until March 2016	Individuals or patients living with HIV and chronic conditions
Uthman et al. (2017)[11]	SLR and meta-analysis	Cross-sectional and cohort studies that reported ART adherence rates as primary or secondary outcome	All articles (no publication date restriction was imposed)	Prison inmates living with HIV receiving ART
Antiretroviral resistance burden				
Diallo et al. (2020)[12]	SLR	RCTs, cohort studies, and longitudinal studies	2001–2019	PLWH initiating ART
Mbunkah et al. (2020)[17]	SLR	No explicit inclusion criteria outlined; however, reviews, brief communications, conference proceedings, abstracts, and posters were excluded	All published articles through May 2019	PLWH who are ART-naïve
Vannappagari et al. (2019)[13]	SLR and meta-analysis	No explicit exclusion criteria outlined	All published articles through July 2018	PLWH
Comorbidity burden				
Bhatta et al. (2020)[14]	SLR and meta-analysis	No study type specified	January 2000–December 2018	Elderly population (age restriction: $>$ 50 years)
Biadgo et al. (2019)[18]	SLR and meta-analysis	No study type restriction	All studies published up until April 2018	Pregnant women living with HIV
Bigna et al. (2019)[19]	SLR and meta-analysis	Cross-sectional, case-control, and cohort studies	All studies published up until 4 November 2015	PLWH (adolescents and adults)
Bigna et al. (2020)[20]	SLR and meta-analysis	Cross-sectional, case-control, and cohort studies	January 2007–24 October 2018	PLWH (age restriction: $\geq$ 18 years)
Chou et al. (2019)[15]	SLR	RCTs, cohort studies, and case-control studies	2012–June 2018	PLWH (adolescents [13 to $<$ 18 years] and adults)
Dakum et al. (2019)[21]	SLR and meta-analysis	Observational studies	None specified for original search (update search date range: January 2015–25 May 2018)	Elderly PLWH (age restriction: $\geq$ 50 years old)
Dawood et al. (2020)[22]	Scoping review	All study types except reviews, opinions/commentaries, non-peer reviewed articles, any sources of grey literature, and conference proceedings	January 2000 through June 2019	Children living with HIV ($\leq$ 18 years)
Dorjee et al. (2018)[23]	SLR and meta-analysis	RCTs, cohort studies, and case-control studies	All studies published up until May 2018	Patients living with HIV receiving abacavir or abacavir-based regimens
Duko et al. (2019)[24]	SLR and meta-analysis	Cross-sectional and other observational studies	No publication period restriction	PLWH or AIDS
Echecopar et al. (2018)[25]	SLR and meta-analysis	Prospective and retrospective cohort studies, case-control studies, and RCTs	All studies published up until November 2015	PLWH receiving PI treatment (age restriction: $\geq$ 18 years)
Ekrikpo et al. (2018)[26]	SLR and meta-analysis	Observational studies and clinical trials	1982–September 2016	PLWH (age restriction: $\geq$ 18 years)
Erqou et al. (2019)[27]	SLR and meta-analysis	No study type specified	1990–May 2018	PLWH (age restriction: $\geq$ 15 years old)
Eyawo et al. (2019)[28]	SLR and meta-analysis	Observational studies and RCTs	2000–18 July 2018	PLWH (excluding children – no age specified)
Farahani et al. (2017)[29]	SLR and meta-analysis	Prospective and retrospective studies	All articles published after 1 January 2005 (study end date required to be after 2005)	PLWH receiving ART
Fialho et al. (2017)[30]	SLR and meta-analysis	Prospective and retrospective studies	All articles published up until December 2014	Individuals with HCV, HIV, or HIV/HCV co-infection (age restriction: $\geq$ 18 years)
Goh et al. (2018)[31]	SLR and meta-analysis	Cross-sectional and longitudinal studies	1989–May 2015	PLWH and PLWH who have been treated with either ART, PI, tenofovir (control populations were included for each group; age restriction: $\geq$ 18 years)

(*continued*)

Table 2. Continued.

Author and Date	Study Type	Type of Studies Included in the SLR (e.g. Retrospective, RCT)	Publication Period Covered in the SLR	Population(s) Included
Grand et al. (2020)[32]	SLR and meta-analysis	Cross-sectional and longitudinal studies	All articles published up until July 2018	PLWH (age restriction: > 15 years)
Huntingdon et al. (2020)[33]	SLR	All study types except reviews, conference proceedings, brief reports, non-peer reviewed work	All articles published since 1997	Male PLWH
Ilha et al. (2018)[34]	SLR and meta-analysis	RCTs, cohort studies, cross-sectional studies, and case-control studies	All studies published up until 27 September 2017	PLWH (age restriction: ≥ 18 years)
King et al. (2019)[35]	SLR and meta-analysis	Prospective observational studies	No publication period specified	Premenopausal female PLWH
Masenga et al. (2019)[36]	SLR	Published articles in peer-reviewed journals	No publication period specified	PLWH (Veterans)
Maurice et al. (2017)[37]	SLR and meta-analysis	Prospective and retrospective observational or interventional studies, RCTs, and SLRs	All articles published up until September 2016	Individuals with HIV-monoinfection (age restriction: ≥ 16 years)
Mulè et al. (2020)[55]	SLR and meta-analysis	Observational studies	All studies published up until 31 December 2018	PLWH
Nansseu et al. (2018)[38]	SLR and meta-analysis	Cohort studies	January 2000–April 2017	PLWH exposed to ART (age restriction: ≥ 18 years)
Olawepo et al. (2020)[39]	SLR and meta-analysis	All study types except cross-sectional studies	All articles published through February 2018	Treatment-naïve PLWH (age restriction: ≥ 18 years) who started highly active ART and remained on treatment for at least 6 months
Oliveira et al. (2020)[40]	SLR and meta-analysis	Observational studies	All articles published up until 1 August 2019	PLWH (adults – no age specified)
Park et al. (2018)[41]	SLR	All study types except SLRs/meta-analyses, reviews or editorials	January 2010–August 2016	PLWH (age restriction: > 21 years)
Pires et al. (2020)[42]	SLR	Cross-sectional studies	2006–2018	PLWH
Premkumar et al. (2019)[43]	SLR	RCTs and observational studies	January 1997–October 2017	Pregnant PLWH
Rao et al. (2019)[44]	SLR and meta-analysis	Longitudinal studies	All articles published prior to January 2017	PLWH (age restriction: ≥ 18 years)
Rezaei et al. (2019)[45]	SLR and meta-analysis	Observational studies	January 2000–October 2018	PLWH or AIDS
Shah et al. (2018)[46]	SLR and meta-analysis	Longitudinal studies	1948–August 2016	PLWH
Soepnel et al. (2017)[47]	SLR and meta-analysis	All study types except for case report studies	All articles published up until October 2015	Pregnant PLWH (no age restriction)
Tao et al. (2018)[48]	SLR and meta-analysis	No study type restriction	1996–15 December 2015	PLWH receiving ART
Tsegay et al. (2020)[49]	SLR and meta-analysis	All study types except commentaries, reviews, case reports, case series studies, studies done on animals, books, editorials, letters, and conference papers	All published articles up until May 2020	Young PLWH or AIDS (no age specified)
Vancampfort et al. (2017)[50]	SLR and meta-analysis	Prospective and cross-sectional studies	All articles published up until 11 May 2016	PLWH or AIDS
Ward et al. (2020)[51]	Targeted literature review	No study type specified	January 2012–November 2017	PLWH (US; adults)
Xiao et al. (2020)[52]	SLR and meta-analysis	Cross-sectional, case-control, and cohort studies	All studies published through January 2020	Men having sex with men with HIV
Xu et al. (2017)[53]	SLR and meta-analysis	Cross-sectional and longitudinal studies	January 2011 through December 2016	PLWH (age restriction: ≥ 16 years)
Zhu et al. (2019)[54]	SLR and meta-analysis	No study type restriction	All studies published up until 3 August 2019	Pregnant PLWH

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MTR, multi-tablet regimen; PI, protease inhibitor; PLWH, people living with HIV; RCT, randomized controlled trial; SLR, systematic literature review; STR, single-tablet regimen; US, United States.

based on studies with study periods spanning from 1995 to 2016[13].

3.4. Burden associated with comorbidities

Among the 40 SLRs that covered comorbidities in PLWH, 21 articles focused on cardiovascular and metabolic diseases[15,18–21,23,25,27–29,32,36–39,43,44,46,47,53,55], nine on mental health disorders[14,15,24,30,45,48,49,52,54], five on bone and muscle diseases[14,15,31,34,40], four on liver diseases[15,29,37,42], four on renal diseases[15,26,29,41], and six on other comorbidities[14,15,29,33,35,50]. Additionally, one SLR assessed hearing loss in children with HIV[22], and another one assessed the economic burden of HIV management and comorbidities in the US[51].

3.4.1. Cardiovascular and metabolic diseases

The global burden of HIV-associated cardiovascular disease (CVD) has tripled over the last two decades and is now responsible for 2.6 million disability-adjusted life years per annum[46]. In the US, 29% of PLWH were estimated to have moderate-to-high cardiovascular risk[32], and 19% of non-AIDS

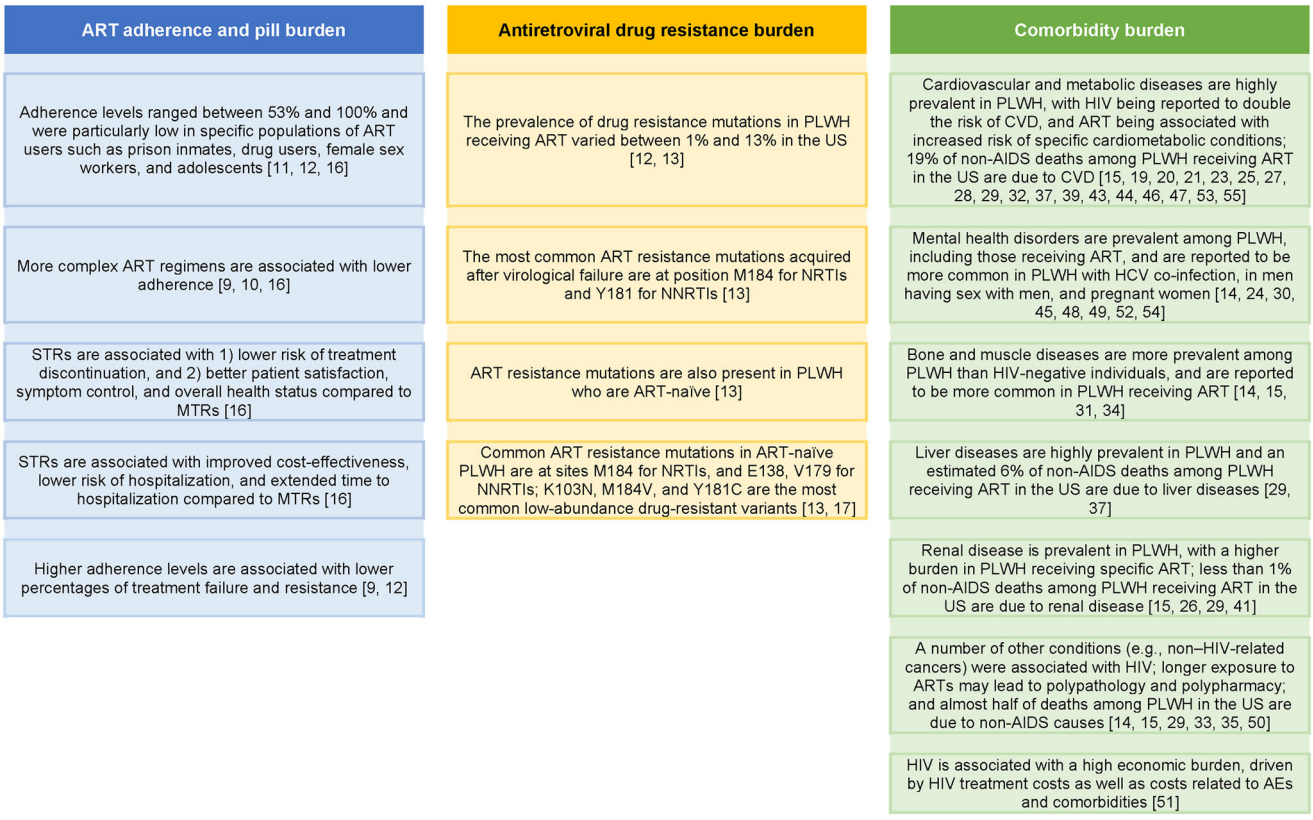

Figure 2. Main findings related to HIV ART adherence and pill burden, antiretroviral resistance burden, and comorbidity burden.
Abbreviations: AE, adverse event; AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CVD, cardiovascular disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MTR, multiple-tablet regimen; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PLWH, people living with HIV; STR, single-tablet regimen.

deaths among PLWH receiving ART were attributable to CVD (13% globally)[29].

The prevalence of hypertension in PLWH varied between 20% and 25% globally[20,32,53], with a prevalence of 42% in PLWH aged 50 and over[21] and of 30% among PLWH in the Americas WHO region[20]. The prevalence of diabetes in PLWH varied between 6%[44] and 7.24%[32], and of dyslipidemia between 22%[44] and 39.5%[32].

HIV was found to roughly double the risk of CVD[46], with greater odds of having acute myocardial infarction (AMI; OR = 1.87; 95% CI = 1.42–2.47)[44] and higher risk of myocardial infarction (MI; RR = 1.73; 95% CI = 1.44–2.08)[28], AMI (RR = 1.96; 95% CI = 1.48–2.57)[44], heart failure (RR = 1.7; 95% CI = 1.4–2.0), or any grade of diastolic dysfunction (RR = 3.0; 95% CI = 1.8–5.1)[27], compared to no HIV.

In addition, ART was reported to be associated with a higher prevalence of hypertension (34.7% in ART-experienced vs. 12.7% in ART-naïve PLWH)[53], increased odds of hypertensive disorders of pregnancy (OR range = 1.27–8.90)[43], increased risk of MI (RR = 1.80; 95% CI = 1.17–2.77)[28], and increased body mass index (BMI; effect size = 1.58 kg/m^2; 95% CI = 1.36–1.81)[39]. In some studies, recent exposure to abacavir was associated with an increased risk of developing CVD in general and AMI/MI in particular[23,28]. However, another SLR reported that while one observational study found that abacavir was associated with increased risk of MI, one meta-analysis of 26 trials found no association between abacavir use and risk of MI[15]. Exposure to PIs as a class was reported to be associated with increased risk of MI[28], although the association was inconsistent across individual PI agents, with no association being found between atazanavir, saquinavir, or nelfinavir exposure and MI risk in the SLRs included in this study[15,28]. PI exposure was also reported to be associated with increased risk of developing metabolic syndrome, but with a non-significant increase in risk of diabetes[25]. PIs were also associated with a non-significant increase in risk of gestational diabetes mellitus (GDM) in pregnant women, except for studies that solely investigated the exposure to older PIs (i.e. those no longer widely used in the US), which reported a significant association with GDM[47]. While efavirenz was associated with increased risk of cardiovascular events[15], exposure to efavirenz or nevirapine was not associated with a higher risk of MI[28].

3.4.2. Mental health disorders

Depression was reported in 31% of PLWH[45] and 41% of those receiving ART[48], and was more common in the subpopulations of PLWH with hepatitis C virus (HCV) co-infection[30], MSM[52], and pregnant women[54]. The prevalence of lifetime suicidal ideation and suicidal attempt in young PLWH was estimated to be 24% and 13%, respectively[49]. Alcohol use disorders were reported in 30% of PLWH, with a higher prevalence in developed (42%) versus developing countries (25%)[24]. Additionally, approximately half of older PLWH were found to experience some degree of cognitive loss, with some progressing to dementia[14].

3.4.3. Bone and muscle diseases

Bone and muscle diseases were reported to be significantly more prevalent in PLWH than HIV-negative individuals (osteopenia/osteoporosis at the lumbar spine: OR = 2.4; 95% CI = 2.0–2.8, and at the hip: OR = 2.6; 95% CI = 2.2–3.0[31]; vertebral fractures: OR = 2.33; 95% CI = 1.37–3.85[34]). ARTs in general and PIs in particular have been associated with higher prevalence of osteopenia/osteoporosis[31], tenofovir disoproxil fumarate (TDF) was associated with increased risk of fracture[15], and bone mineral density was reported to decrease during the first 2 years of ART[14].

3.4.4. Liver diseases

The estimated prevalence of nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and significant fibrosis in mono-infected PLWH is 35.3%, 41.7%, and 21.7%, respectively[37], and it was estimated that 6% of non-AIDS deaths among PLWH receiving ART in the US were due to liver diseases (11% globally)[29].

3.4.5. Renal diseases

The prevalence of chronic kidney disease (CKD) in PLWH varied between 4.8% and 12.8%[26,41], and it was estimated that less than 1% of non-AIDS deaths among PLWH receiving ART in the US (and globally) were due to renal disease[29]. TDF and ritonavir-boosted atazanavir were associated with increased risk of CKD and the use of TDF and PIs was associated with increased risk of renal adverse events (AEs)[15].

3.4.6. Other comorbidities

HIV was associated with various additional conditions. Higher rates of non-HIV-related cancers and more frequent severe weight loss, exhaustion, and low physical activity were reported in older PLWH (aged > 50 years) compared with non-infected older people (aged > 50 years)[14]. A higher prevalence of amenorrhea in premenopausal women living with HIV compared to HIV-negative controls was also reported[35]. While longer exposure to ART was associated with lower risk of AIDS-defining cancers, use of PIs was associated with higher risk of non-AIDS-defining cancers[15]. Additionally, it was found that older age (> 50 years) and each added year on ART may lead to polypathology (defined as the simultaneous occurrence of two or more defined diseases) and polypharmacy (defined as the use of four or more medications)[14]. Finally, the overall proportion of non-AIDS causes of death in PLWH was estimated to be equal to 35% globally and 47% in the US[29].

3.4.7. Economic burden of HIV management and comorbidities

The estimated total lifetime cost of HIV in the US (in 2017 USD) increased from $1,246,810 in 1996 to $1,673,510 in 2018, driven by antiretroviral drug and AE costs (35% increase) and comorbidity treatment costs (e.g. 180% increase for CVD and 174% for CKD). However, costs of HIV management, including costs of inpatient care, emergency department and outpatient visits, opportunistic infections prophylaxis, HIV testing, and non-HIV medication, decreased as HIV patients approached general population survival rates[51].

The total costs of HIV treatment and disease management ranged from $254 to $6,608 (in 2017 USD) per-patient-per-month (PPPM)[51]. The mean per-event costs for AEs ranged up to $31,545 for MI. The mean per-event costs for opportunistic infections ranged between $8,495 and $13,036. Lastly, the mean PPPM costs for CVD management, CKD management, and fracture/osteoporosis were $5,898, $6,108, and $4,365, respectively[51].

4. Discussion

This SLR summarized the burden associated with ART adherence and complexity, treatment resistance, and comorbidities among PLWH based on SLRs that included the US as part of the countries of interest.

Achieving adequate adherence was shown to be especially challenging in certain subpopulations, such as prison inmates, sex workers, drug users, and adolescents[11]. Poorer adherence has also been associated in the literature with other patient factors such as female gender, Black/non-white race, low education, poverty, and unemployment[58,59]. Evidence from outside of the SLR has additionally demonstrated an association between multiple comorbidities and decreased ART adherence[60], with patients citing poor understanding of health conditions, concern regarding comorbidities, and complex regimens as barriers to treatment adherence[61]. Relatedly, MTRs were shown to be associated with lower adherence and worse clinical and economic outcomes, including higher rates of treatment resistance and treatment failure[9,12,16]. These associations are all the more plausible because MTRs are more prone to adherence patterns that may increase the risk of failure with resistance, such as variable adherence to different components of an ART regimen[62]. Indeed, the prevalence of treatment resistance observed in PLWH was non-negligible. Given the potential for cross-resistance[63,64] and the important associated clinical burden[65], less complex ART regimens containing agents with higher resistance barriers are important to improve adherence and reduce the chances of treatment failure[63].

HIV patients living longer due to successful ART resulted in a high comorbidity burden, with the proportion of non-AIDS causes of death in PLWH estimated to be equal to 35% globally and 47% in the US[29]. HIV was reported to double the risk of CVD and to be associated with several other comorbidities, including bone and muscle diseases and depression[34,40,45,46]. In older patients, HIV was additionally associated with severe weight loss, low physical activity, and non-HIV-related cancers[14]. The long-term use of ART was shown to further increase the risk of developing cardiovascular, metabolic, bone, liver, and renal diseases[15,28,31,39]. Each of these comorbidities may ultimately impact quality-of-life (QoL) negatively, so much so that QoL has been proposed as a "fourth 90" target in the Joint United Nations Program on

HIV/AIDS (UNAIDS) 90-90-90 goals for HIV testing and treatment, specifically that 90% of PLWH with viral suppression have good health-related QoL[66]. As the HIV population continues to live longer and with more comorbidities, equalization of QoL with persons without HIV will be essential, in addition to closure of the current gaps in comorbidity-free years of life[67]. In this regard, the establishment of specialized HIV clinics may be one way to help improve management of the aging HIV population, among other treatment-related initiatives. Indeed, implementation of a clinic dedicated to PLWH older than 50 years has led to the initiation of specialized care pathways and new joint HIV/specialty clinics, with ongoing research activities to evaluate and improve issues related to polypharmacy and comorbidities among the elderly population[68–71].

As an SLR of SLRs, more recent articles were not covered by the SLRs included. Indeed, other studies in the literature reported lower prevalence rates of drug resistance to PIs and INSTIs relative to NRTIs and NNRTIs[72,73], and suggested that starting with regimens with higher genetic barriers to resistance in the first line may help to improve the long-term success of ART[74]. Furthermore, some studies in the literature reported a few additional findings on the comorbidity burden related to HIV and ART. For example, frailty and neurocognitive impairment were recently shown to be prevalent in PLWH and to strongly predict poor health outcomes in PLWH $\geq$ 40 years of age in the US[75]. The burden of cancer among PLWH in the US was reported to shift from AIDS-defining cancers to non-AIDS-defining cancers, such as prostate and lung cancer, regardless of ART received[76]. Notably, non-AIDS-defining cancers are now the most common tumors in PLWH in the Veterans Healthcare System[77], and younger ages at cancer diagnosis were observed in PLWH compared with the general population in North America[78]. Additionally, recent studies reported that INSTIs were associated with higher weight gain than NNRTI or PI agents[79–81], and with an increased incidence of DM diagnoses following treatment initiation[82,83] and cumulative use of ritonavir-boosted darunavir has been found to be associated with progressively increasing risk of CVD[84]. MSM of all races and ethnicities, Blacks, Latinx, people who inject drugs, and transgender individuals have been identified by the Centers for Disease Control and Prevention as populations of greatest risk of HIV infection[85]. These high-risk groups are also associated with a higher HIV burden, such as higher barriers to HIV care, stigma, and lack of social support[86], and higher risk of cardiovascular and metabolic diseases[87] and coinfection[88]. Moreover, there are gender differences in the prevalence of some comorbidities, possibly mediated by differences in systemic immune activation and inflammation, that need to be better understood[89,90].

Taken together, the current findings show the substantial burden of HIV and long-term use of ART, including the risk of treatment resistance and development of comorbidities, which highlights the benefits of ART agents with lower toxicity as well as the need for a preventative intervention for HIV-1. Indeed, significant progress has been made in the use of antiretroviral drugs for HIV prevention, but major challenges remain[91]. An effective HIV-1 vaccine would further alleviate the clinical and economic burden of HIV, especially in the subpopulations experiencing a higher burden of disease; however, the quest for an effective HIV vaccine has achieved little success so far[92].

4.1. Limitations

The current findings should be interpreted in the context of some limitations. Differences in study selection criteria, countries/regions covered, and methods used at the SLR level, along with differences in designs, subpopulations of PLWH, and ARTs considered across the studies included in the SLRs may have influenced the conclusions drawn. This review is also subject to any limitations of the included SLRs, including if inclusion and exclusion criteria were poorly specified, if some studies were missed, or if there were any errors in the extraction, analysis, and synthesis of the findings. Additionally, despite a thorough search strategy, some relevant SLRs may have been missed. The search was limited to articles published in English, potentially excluding some that are relevant to the global population of PLWH. Recent findings that were not yet summarized in an SLR may have been missed as well. Also, findings from this study reporting a relationship between ART and specific comorbidities or medical events should not be interpreted as a causal relationship, but as an association. Causality would need to be further evaluated on a case-by-case basis. Lastly, the included SLRs may have covered overlapping studies.

5. Conclusions

This SLR of SLRs reveals substantial burden associated with HIV and long-term use of ART, highlighting the benefits of antiretroviral agents with lower toxicity and higher resistance barriers, less complex regimens, as well as ways to bridge current gaps in HIV prevention strategies. Further research is needed to assess the potential impact of the use of a preventative HIV vaccine on the clinical and economic burden of HIV and its related comorbidities.

Transparency

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PD is an employee of JSA and stockholder of Johnson & Johnson.

Author contributions

HR, MHL, RB, and KM contributed to study conception and design, literature search, and data analysis and interpretation. BOT and PD contributed to study conception and design, and data analysis and interpretation. All authors reviewed and approved the final content of this manuscript.

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Data availability statement

All data included in the study are publicly available or available for purchase through the journal or publisher.

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