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.

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.

Treatment for HIV was revolutionized with the introduction of combination antiretroviral therapy (ART), which is effective at suppressing HIV replication, but is not curative. 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. 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). Selected two-drug regimens are now part of the treatment armamentarium, and the use of single-tablet regimens (STRs) has been shown to improve adherence to treatment compared to multiple-tablet regimens (MTRs). 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. 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.

While previous systematic literature reviews (SLRs) included publications on the burden associated with medication adherence and complexity, treatment resistance, and comorbidities among PLWH, none have comprehensively covered all these aspects of the disease and treatment...
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 ≥ 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 PLWH9–12,16, three SLRs covered treatment resistance in PLWH12,13,17, and 40 SLRs focused on the HIV and/or ART-associated comorbidity burden14,15,18–55 (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 children19; 13–18 years; ≥15 years27,32; ≥16 years53; young people [age not specified]69), one was conducted in children and adolescents (<18 years)26, and two in older adults (≥50 years)14,21.

In addition, some of the SLRs focused on specific subpopulations of PLWH, such as prison inmates11, veterans36, pregnant women43,47,54, premenopausal women95, men33, 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 | (HIV or "human immunodeficiency virus").ti,ab or exp HIV/ | 787,208 |
| Study type | 1 and ((review* and systematic) or meta-analys* or "meta analysis" or "meta analyses" or "meta review" or "meta-review").ti,ab | 11,036 |
| | 2 not animal*.mp | 10,849 |
| Outcomes | 3 and (exp Drug Resistance/ or ((treatment or medication or drug) adj3 (resistance or resistant)).ti,ab) | 500 |
| | 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 |
| | 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 | 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.
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 count16, and 53–99% based on self-report12. The individual studies included in these SLRs included various subpopulations, such as ART-naïve 56 and homeless and marginally housed individuals57. In the specific population of prison inmates, the proportion of patients with ART adherence ≥ 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 ART9,16, although some of the studies included in one SLR reported a non-significant association10. 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 = 2.53, p = .02), separately16. 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 MTRs16. Higher levels of adherence were associated with greater viral suppression9 and lower percentages of treatment failure and treatment resistance12.

3.3. Antiretroviral drug resistance in PLWH

The prevalence of drug resistance mutations in PLWH receiving ART varied between 1% and 13% in the US12, and the prevalence of resistance acquired after virological failure was 23% for NRTI and 19% for NNRTI resistance mutations in North America13. 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 |
|                  | 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 | Prison inmates living with HIV receiving ART |
|                  | Dakum et al. (2019)¹⁹ | 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) | PLWH |
| **Antiretroviral resistance burden** | Altice et al. (2019)⁹ | SLR and meta-analysis | RCTs and observational studies | 2006–2016 | Individuals receiving STRs or MTRs for HIV treatment |
|                  | Mbunkah et al. (2020)¹⁷ | SLR | RCTs, cohort studies, and longitudinal studies | 2001–2019 | PLWH initiating ART |
|                  | 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)¹⁰ | SLR and meta-analysis | Cross-sectional, case-control, and cohort studies | January 2007–24 October 2018 | PLWH (age restriction: > 18 years) |
|                  | Chou et al. (2019)¹⁵ | SLR and meta-analysis | RCTs, cohort studies, and case-control studies | October 2012–June 2018 | PLWH (adolescents [13 to < 18 years] and adults) |
|                  | Vannappagari et al. (2019)¹³ | SLR and meta-analysis | Observational studies | None specified for original search (update search date range: January 2015–25 May 2018) | Elderly PLWH (age restriction: ≥ 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 (≤ 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: ≥ 18 years) |
|                  | Ekrisko et al. (2018)²⁶ | SLR and meta-analysis | Observational studies and clinical trials | 1982–September 2016 | PLWH (age restriction: ≥ 18 years) |
|                  | Erquou et al. (2019)²⁷ | SLR and meta-analysis | No study type specified | 1990–May 2018 | PLWH (age restriction: ≥ 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 coinfection (age restriction: ≥ 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: ≥ 18 years) |

(continued)
Among the 40 SLRs that covered comorbidities in PLWH, 21 articles focused on cardiovascular and metabolic diseases\textsuperscript{13},\textsuperscript{14,15,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39}, nine on mental health disorders\textsuperscript{14,15,24,30,45,48,49,52,54}, five on bone and muscle diseases\textsuperscript{14,15,31,34,40}, four on liver diseases\textsuperscript{5,29,37,42}, four on renal diseases\textsuperscript{15,26,29,41}, and six on other comorbidities\textsuperscript{14,15,29,33,35,50}. Additionally, one SLR assessed hearing loss in children with HIV\textsuperscript{22}, and another one assessed the economic burden of HIV management and comorbidities in the US\textsuperscript{51}.

### 3.4. Burden associated with comorbidities

Among the 40 SLRs that covered comorbidities in PLWH, 21 articles focused on cardiovascular and metabolic diseases\textsuperscript{13},\textsuperscript{14,15,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39}, nine on mental health disorders\textsuperscript{14,15,24,30,45,48,49,52,54}, five on bone and muscle diseases\textsuperscript{14,15,31,34,40}, four on liver diseases\textsuperscript{5,29,37,42}, four on renal diseases\textsuperscript{15,26,29,41}, and six on other comorbidities\textsuperscript{14,15,29,33,35,50}. Additionally, one SLR assessed hearing loss in children with HIV\textsuperscript{22}, and another one assessed the economic burden of HIV management and comorbidities in the US\textsuperscript{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\textsuperscript{46}. In the US, 29% of PLWH were estimated to have moderate-to-high cardiovascular risk\textsuperscript{32}, and 19% of non-AIDS
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)\(^{45}\), increased odds of hypertensive disorders of pregnancy (OR range \(= 1.27–8.90\))\(^{48}\), 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\(^{33,28}\). 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 nevirapine 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\(^{79}\). 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/osteooporosis 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); vertebral fractures: OR = 2.33; 95% CI = 1.37–3.85). ARTs in general and PIs in particular have been associated with higher prevalence of osteopenia/osteoporosis, tenofovir disoproxil fumarate (TDF) was associated with increased risk of fracture, and bone mineral density was reported to decrease during the first 2 years of ART.

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, and it was estimated that 6% of non-AIDS deaths among PLWH receiving ART in the US were due to liver diseases (11% globally).

3.4.5. Renal diseases
The prevalence of chronic kidney disease (CKD) in PLWH varied between 4.8% and 12.8%, 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. 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).

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). A higher prevalence of amenorrhea in premenopausal women living with HIV compared to HIV-negative controls was also reported. 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. Additionally, it was found that older age (> 50 years) and each added year on ART may lead to polyopathy (defined as the simultaneous occurrence of two or more defined diseases) and polypharmacy (defined as the use of four or more medications). 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.

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.

The total costs of HIV treatment and disease management ranged from $254 to $6,608 (in 2017 USD) per-patient-per-month (PPPMP). 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 $4,363, respectively.

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. 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. Evidence from outside of the SLR has additionally demonstrated an association between multiple comorbidities and decreased ART adherence, with patients citing poor understanding of health conditions, concern regarding comorbidities, and complex regimens as barriers to treatment adherence. Relatively, MTRs were shown to be associated with lower adherence and worse clinical and economic outcomes, including higher rates of treatment resistance and treatment failure. 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. Indeed, the prevalence of treatment resistance observed in PLWH was non-negligible. Given the potential for cross-resistance and the important associated clinical burden, less complex ART regimens containing agents with higher resistance barriers are important to improve adherence and reduce the chances of treatment failure.

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. HIV was reported to double the risk of CVD and to be associated with several other comorbidities, including bone and muscle diseases and depression. In older patients, HIV was additionally associated with severe weight loss, low physical activity, and non-HIV-related cancers. The long-term use of ART was shown to further increase the risk of developing cardiovascular, metabolic, bone, liver, and renal diseases. 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. 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. 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.

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 resistance to PIs and INSTIs relative to NRTIs and NNRTIs, 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. 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 ≥ 40 years of age in the US. 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. Notably, non-AIDS-defining cancers are now the most common tumors in PLWH in the Veterans Healthcare System, and younger ages at cancer diagnosis were observed in PLWH compared with the general population in North America. Additionally, recent studies reported that INSTIs were associated with higher weight gain than NNRTI or PI agents, and with an increased incidence of DM diagnoses following treatment initiation and cumulative use of ritonavir-boosted darunavir has been found to be associated with progressively increasing risk of CVD. 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. 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, and higher risk of cardiovascular and metabolic diseases and coinfection. 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.

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. 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.

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

Declaration of funding

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Declaration of financial/other relationships

BOT has served as a paid consultant to ViiV Healthcare, GSK, Gilead, Merck, and JSA. HR and MHL are employees of Analysis Group, Inc., a consulting company that has provided paid consulting services to JSA, which funded the development and conduct of this study and manuscript. RB and KM were employees of Analysis Group, Inc. at the time of study conduct.

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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