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REVIEW

A Review of Long-Term Toxicity of Antiretroviral Treatment Regimens and Implications for an Aging Population

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ABSTRACT

Human immunodeficiency virus (HIV) is a chronic infectious disease currently requiring lifelong antiretroviral therapy (ART). People living with HIV (PLWH) face an increased risk of comorbidities associated with aging, chronic HIV, and the toxicity arising from long-term ART. A literature review was conducted to identify the most recent evidence documenting toxicities associated with long-term ART, particularly among aging PLWH. In general, PLWH are at a greater risk of developing fractures, osteoporosis, renal and metabolic disorders, central nervous system disorders, cardiovascular disease, and liver disease. There remains limited evidence describing the economic burden of long-term ART. Overall, an aging HIV population treated with long-term ART presents a scenario in which the clinical, humanistic, and economic burden for healthcare systems will demand thoughtful policy solutions that preserve access to treatment. Newer treatment regimens with fewer drugs may mitigate some of the cumulative toxicity burden of long-term ART.

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Keywords: Aging; Antiretroviral therapy; HIV/AIDS; Toxicity; Two-drug regimen

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INTRODUCTION

Antiretroviral therapy (ART) has led to substantial improvements in the life expectancy of patients infected with human immunodeficiency virus (HIV), which is now treated as a chronic disease requiring life-long ART treatment [1–3]. Current ART regimens are generally well tolerated with fewer associated severe adverse events (AEs) that are life-threatening or that lead to disability or permanent damage in the short term compared with older regimens; AE profiles that have been documented across all classes of ART are reported in Table 1 [4, 5].

Table 1 Frequent and severe AEs associated with ART by class. Adapted from EACS October 2017 guidelines [4]

Class	Frequent AEs (≥ 10% of patients)	Severe AEs
NRTI	Steatosis, peripheral neuropathy, lipoatrophy, dyslipidemia	Ischemic heart disease, systemic hypersensitivity syndrome, rhabdomyolysis, hyperlactatemia, pancreatitis, increased fracture risk, Fanconi syndrome
NNRTI	Depression, sleep disturbances, headache, dyslipidemia, lower plasma 25(OH) vitamin D	Suicidal ideation, systemic hypersensitivity, rash
PI	Dry skin, nausea and diarrhea, hyperbilirubinemia, nephrolithiasis, increase of abdominal fat, dyslipidemia	Hepatitis, ischemic heart disease, intracranial hemorrhage, dyslipidemia
Boosting	Lowering of eGFR	None
FI	None	Injection nodules
INSTI	Nausea, lowering of eGFR, sleep disturbance, headache	Rhabdomyolysis, systemic hypersensitivity syndrome (< 1%)
CCR5i	None	None

AE adverse event, *CCR5i* C–C chemokine receptor 5 inhibitor, *eGFR* estimated glomerular filtration rate, *FI* fusion inhibitor, *INSTI* integrase strand transfer inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleos(t)ide reverse transcriptase inhibitor, *PI* protease inhibitor

There has been a decrease in the proportion of patients switching or discontinuing treatment, and fewer patients now discontinue ART compared with a decade ago [6]. This decrease can be attributed to factors including fewer AEs or intolerance with newer ART regimens as well as research showing that continuous use of ART is superior to episodic use [6, 7].

Advances in ART have also led to significant increases in survival among people living with HIV (PLWH) [8]; however, the corollary of a longer lifespan is that PLWH are now faced with an increased risk of developing comorbidities and chronic diseases associated with aging in addition to chronic HIV. Approximately 45% of PLWH are aged ≥ 50 years, and by 2020 an estimated 70% of Americans with HIV are projected to be in this age group [9, 10]. Furthermore, PLWH are now using ART over a much longer period of time, and the resulting potential cumulative toxicity that can emerge is not fully understood. Not only could such long-term toxicity lead to poor health status and a diminished quality of life but ART-related AEs that ultimately result in increases in morbidity and mortality risk may contribute significantly to healthcare resource utilization and costs associated with HIV treatment. Reducing the number of ART agents that PLWH require may have the potential to reduce cumulative toxicities as well as the economic burden associated with long-term treatment. Novel ART strategies, such as two-drug regimens, are currently being explored. While not all two-drug regimens studied to date have demonstrated efficacy and safety results indicative of an alternative to current regimens [11], certain regimens have been shown to provide non-inferior viral suppression along with reduced toxicity in virologically stable patients compared with three-drug regimens that are currently considered to be standard of care [12–16].

The objective of this review is to provide a synthesis of evidence documenting the toxicity implications arising from long-term ART use in high-income settings, particularly as it relates to an aging population of PLWH. The economic burden of AEs resulting from long-term ART use is also assessed.

METHODS

In this literature review, a combined approach of targeted searches of published literature for pre-specified topics of interest was supplemented with searches to identify additional major studies and clinical guidelines. Searches were conducted in MEDLINE (via PubMed) using keywords to identify studies reporting data on the AEs associated with long-term use of ART. Searches incorporated HIV-, AIDS-, treatment-, and economic-based terms (see supplementary material Table S1 and Table S2 for complete search strings). Identified studies were assessed by the authors and those relevant to the objectives of this review were included. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

For PLWH, long-term ART use has the potential to increase the underlying risk of conditions or diseases associated with both aging and chronic HIV infection. Nearly half of PLWH aged $\geq$ 50 years have at least one major medical comorbidity, and PLWH have more age-associated non-communicable comorbidities (AANCCs) than age-matched non-infected individuals [mean $\pm$ standard deviation (SD) number AANCCs: 1.3 ± 1.14 vs. 1.0 ± 0.95, respectively; $P < 0.001$] [17, 18]. Furthermore, the prevalence of comorbid conditions such as cardiovascular disease (CVD), diabetes mellitus (DM), and osteoporosis among PLWH significantly increases as PLWH age [19].

Chronic comorbidities also contribute to a greater pill burden, often resulting in additional complications [20, 21]. In an analysis of the Swiss HIV Cohort Study, the proportion of PLWH who were taking at least four non-HIV co-medications was 5.2% among those aged 50–64 years compared with 14.2% for those aged $\geq$ 64 [19]. In a separate retrospective chart review of 89 older ($\geq$ 60 years) PLWH, the median number of concomitant medications was 13 (range 9–17) compared with only 6 for their uninfected peers; of these 13 medications, only 4 were ART agents [22]. Several harmful effects of polypharmacy in older patients have been documented; these include drug–drug interactions (DDIs) between ART and therapies prescribed to manage non-HIV conditions, with Category D (consider therapy modification) DDIs reported in 70% of patients and Category X (avoid combination) DDIs reported in 11% of patients older than 60 years [22]. Additionally, a loss of treatment efficacy can often result from polypharmacy [23–25].

Common comorbidities that have known associations with long-term ART use and chronic HIV infection in older patients include fracture risk and osteoporosis, renal and metabolic disorders, central nervous system (CNS) disorders, cardiovascular disease, and liver disease.

Bone Disease

As PLWH age, they are at an increased risk for osteoporosis and fragility fractures, independent of long-term ART use [25–31]. In a cross-sectional study of 202 drug-naïve and drug-experienced PLWH, age was associated with the risk of fractures [odds ratio (OR) for each year = 1.18; 95% confidence interval (CI): 1.03–1.25; $P = 0.01$]. Additionally, vertebral fracture was more prevalent among those aged 50–67 years compared with those aged 31–50 (32% vs. 13%; $P = 0.008$) [32]. A stronger association between HIV infection and major fractures in patients $\geq$ 59 years [hazard ratio (HR) = 2.11; 95% CI 1.05–4.22; $P = 0.035$] compared with patients < 59 (HR = 1.35; 95% CI 0.88–2.07; $P = 0.17$) has similarly been reported based on an analysis of medical records of Spanish PLWH ($n = 2489$) [30]. Additionally, the prevalence of fractures was higher among PLWH compared with HIV-uninfected peers for both men ($P < 0.001$) and women ($P = 0.002$) in a population-based study conducted at a large US healthcare system ($n = 8525$ PLWH; $n = 2{,}208{,}792$ HIV-uninfected), and the differences widened with increasing age [27].

The progression of bone disease among aging PLWH is further complicated by long-term

toxicity concerns observed among patients treated with certain ART regimens. There is evidence that certain nucleos(t)ide reverse transcriptase inhibitors (NRTIs) are associated with declines in bone mineral density (BMD) and an increased risk of fractures in some studies; however, the issue remains controversial [33–36]. In an evaluation of HIV-infected patients in the Veterans Health Administration's (VHA) Clinical Case Registry ($n = 56,660$), extended use of tenofovir disoproxil fumarate was associated with an increased risk of osteoporotic fractures (yearly HR = 1.08; $P < 0.001$), although this finding was no longer significant after multivariate adjustment for age, race, tobacco use, diabetes, chronic kidney disease (CKD), hepatitis C virus (HCV), and body mass index (HR = 1.06; $P = 0.079$) [35]. Recent results from the EuroSIDA study ($n = 20,854$) showed that ever (vs. never), current (vs. no current use), and cumulative tenofovir disoproxil fumarate use was associated with increased fracture risk among PLWH in a univariate analysis; however, there was no association for any other ART investigated [36]. After multivariate adjustment, the association between ever and current tenofovir disoproxil fumarate use remained significant [adjusted incidence rate ratio (IRR) = 1.40; 95% CI 1.15–1.70; $P = 0.0008$ and adjusted IRR = 1.25; 95% CI 1.05–1.49; $P = 0.012$, respectively], while cumulative tenofovir disoproxil fumarate use (per 5 years additional exposure) did not remain significant (adjusted IRR = 1.08; 95% CI 0.94–1.25; $P = 0.027$) [36]. Recently, tenofovir alafenamide has been used in place of tenofovir disoproxil fumarate in ART regimens and has demonstrated smaller reductions in hip and lumbar spine BMD compared with tenofovir disoproxil fumarate ($P < 0.0001$) [4, 37]. However, long-term data on potential toxicity associated with tenofovir alafenamide-containing regimens are lacking [4].

Renal and Metabolic Disorders

Older PLWH are at an increased risk of developing premature renal failure and DM compared with the general population [29]. A cross-sectional retrospective case–control study found that PLWH had a higher prevalence of both renal failure and DM compared with HIV-uninfected controls, especially among those aged > 60 years (24.26% vs. 0.49% and 38.97% vs. 15.93%, respectively; both $P < 0.001$) [29]. Among PLWH in the John Hopkins HIV Clinical Cohort who developed CKD ($n = 284$), the adjusted IRRs were 3.47 (95% CI 2.07–5.81; $P < 0.001$) and 1.45 (95% CI 1.01–2.09; $P = 0.044$) for those > 55 years and 45–55 years old, respectively, relative to PLWH < 45 years of age [38].

Toxicity resulting from long-term ART use that affects renal and metabolic health may further compound the overall disease burden in aging PLWH. Long-term use of ART has been linked to an increased risk of CKD and DM. In particular, an analysis of over 10,000 patients demonstrated a 33% increased risk of CKD for each additional year of tenofovir disoproxil fumarate use (HR = 1.33; 95% CI 1.18–1.51; $P < 0.0001$) [39]. A similar analysis of 21,590 HIV-infected men found that the overall 5-year event rate of CKD in tenofovir disoproxil fumarate users compared with non-users was 7.7% versus 3.8%, respectively (overall adjusted HR = 2.0; 95% CI 1.8–2.2) [40]. Based on findings from the EuroSIDA study, higher rates of CKD have also been associated with a more frequent use of atazanavir (annual IRR = 1.21, $P = 0.003$) and lopinavir/ritonavir (annual IRR = 1.08; $P = 0.030$) [41]. Finally, in a prospective study of 1524 HIV-infected women with no evidence of DM, longer cumulative use of NRTIs was associated with an increased incidence of DM over the study period (October 2000 to March 2006) compared with no use of NRTIs (0–3 years NRTI use relative HR = 1.81; 95% CI 0.83–3.93; ≥ 3 years NRTI use relative HR = 2.64; 95% CI 1.11–6.32) [42].

Central Nervous System

Data on the effect of aging on CNS function among PLWH are mixed, and are complicated by potential synergistic effects of comorbid conditions including mental illness, the natural aging process, and HIV infection, each of which

may contribute to decline in cognitive function [43–46]. Furthermore, while there are various screening tools available, there is a lack of clear consensus among care providers on how to diagnose and manage HIV-associated neurocognitive disorder [47, 48]. In a longitudinal case–control study including 54 PLWH and 30 HIV-uninfected individuals, the interaction of HIV and age significantly predicted longitudinal decline in verbal memory performance, suggesting that older age was associated with a greater decline in the HIV-positive group [43]. Additionally, in a prospective study of 146 PLWH with normal neurocognitive function at baseline, PLWH were nearly five times as likely to have a neurocognitive disorder after 14 months follow-up than patients without HIV; however, a logistic regression analysis found no effect of age ($\leq$ 40 or $\geq$ 50 years) among PLWH on incident neurocognitive disorders over the same follow-up period ($P = 0.410$) [44]. In contrast, in a cross-sectional study ($n = 392$), older PLWH were at a higher risk of exhibiting cognitive impairment compared with younger PLWH (OR = 2.28; 95% CI 1.35–3.82; $P = 0.002$), although the extent to which the cognitive impairment is attributable solely to HIV or to an interaction between HIV infection and other age-related diseases is not fully understood [45].

The potentially increased risk for impaired CNS function among older PLWH is further complicated by evidence of an association between long-term ART and neurocognitive functioning. An analysis of neurocognitive functioning in patients from the CNS HIV Antiretroviral Therapy Effects Research cohort found that patients with long-term (median 17.9 months) use of efavirenz had worse speed of information processing ($P = 0.04$), verbal fluency ($P = 0.03$), and working memory ($P = 0.03$) relative to patients using ritonavir-boosted lopinavir [49]. Additionally, efavirenz has been shown to contribute to other serious long-term effects; a pre-specified retrospective analysis of four AIDS Clinical Trial Group studies reported a higher risk of suicidality (HR = 2.28; 95% CI 1.27–4.10; $P = 0.006$), defined as suicide ideation, attempted or completed suicide, or a numerically higher risk of attempted or completed suicide (HR = 2.58; 95% CI 0.94–7.06; $P = 0.065$) with efavirenz use compared with non-efavirenz regimens [50]. However, there is conflicting evidence to support this association; a retrospective analysis of data from the US Food and Drug Administration Adverse Event Reporting System found that disproportionality scores for efavirenz were below the pre-determined threshold for a potential association for increased suicidality [51]. The AEs associated with efavirenz may be related to the dose of the drug; results from the ENCORE-1 trial showed that a dose of 400 mg efavirenz provided non-inferior efficacy and had fewer AEs than the standard dose of 600 mg efavirenz when combined with tenofovir plus emtricitabine in ART-naïve patients [52]. Rilpivirine has been studied as an alternative treatment to efavirenz in combination with two background NRTIs; this combination demonstrated a significantly lower incidence of neurological AEs compared with efavirenz in HIV-1 treatment-naïve patients enrolled in the ECHO and THRIVE trials [53, 54]. Improved neurological tolerability outcomes were also observed in a study of patients switching from an efavirenz-containing regimen to one containing rilpivirine [55].

In addition to efavirenz-related toxicity, a retrospective analysis evaluating patients with HIV who were treated with dolutegravir, raltegravir, and elvitegravir showed rates of neuropsychiatric AEs leading to discontinuation at 12/24 months of 5.6/6.7%, 0.7/1.5%, and 1.9/2.3%, respectively. In patients older than 60 years, the discontinuation rate due to neuropsychiatric AEs for dolutegravir was nearly three-fold higher compared with younger patients [56]. However, a recent analysis of five phase 3 clinical trials involving patients treated with dolutegravir-based regimens found that psychiatric symptoms were reported with low frequencies, were generally mild to moderate in intensity, and rarely necessitated dolutegravir discontinuation, similar to other commonly prescribed anchor drugs, including efavirenz, raltegravir, and darunavir [57].

Cardiovascular Disease

Rates of CVD mortality, acute MI risk, and ischemic stroke risk increase with age among PLWH, and the absolute risk for CVD is expected to increase in parallel with age [58–61]. A large US population-based cohort study showed that proportionate CVD mortality in PLWH increased from 1.95% in 1999 to 4.62% in 2013 ($P < 0.0001$) [59]. By comparison, the general population saw a decrease in proportionate CVD mortality over the same 15-year time period [59]. An analyses of male veterans ($n = 76,835$) found a higher risk for ischemic stroke among HIV-infected versus HIV-uninfected veterans (adjusted HR = 1.17, 95% CI 1.01–1.36; $P < 0.04$) [60]. A separate analysis of 82,459 participants in the same cohort found that HIV-positive veterans had an increased risk of incident acute MI compared with uninfected veterans (adjusted HR = 1.48, 95% CI 1.27–1.72) [61]. In addition, the mean (95% CI) rate of acute MI events per 1000 person-years increased with age in HIV-infected veterans compared with uninfected veterans [2.0 (1.6–2.4) vs. 1.5 (1.3–1.7) for those aged 40–-49 years; 3.9 (3.3–4.5) vs. 2.2 (1.9–2.5) for those aged 50–59; and 5.0 (3.8–6.7) vs. 3.3 (2.6–4.2) for those aged 60–69, respectively; $P < 0.05$ for all] [61]. However, it is difficult to discern to what extent the survival effect is leading to high rates of CVD in the aging HIV population.

The increased risk for CVD among older PLWH may be exacerbated by cumulative toxicity associated with ART. One study ($n = 23,437$) of PLWH showed that the incidence of MI over more than 6 years of follow-up was higher in patients treated with PIs than those not treated with PIs (6.01 per 1000 person-years vs. 1.53 per 1000 person years, respectively) [62]. After multivariate adjustment, the relative rate of MI per year of PI use was 1.16 (95% CI 1.10–1.23) [62]. The data regarding any association between abacavir and CVD risk are very mixed and the issue remains controversial [63–69]. Recently updated data from the D:A:D cohort ($n = 49,717$) found that current abacavir use was associated with a 98% increase in the rate of MI among PLWH compared with PLWH not currently on abacavir treatment (adjusted RR = 1.98, 95% CI 1.72–2.29) [65, 69].

Liver Disease

Liver-related morbidity and mortality are major concerns for PLWH, with liver disease accounting for approximately 13% of all deaths among PLWH [70]. As a person ages, the regenerative capacity of the liver declines. In addition, accelerated fibrogenesis has been observed in patients with HIV/HCV co-infection, although direct acting antivirals have now been shown to effectively treat and cure HCV infection in patients with HIV/HCV co-infection at rates similar to patients without HIV co-infection [71, 72]. However, there are limited data indicating that curing HCV in HIV/HCV co-infected patients reverses hepatic damage. Older age is also associated with increased risk of mitochondrial dysfunction, increased polypharmacy, worse prognosis of alcoholic liver disease, greater severity of non-alcoholic fatty liver disease, and an increased risk of liver cancer [73]. Although nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD) are frequently observed in PLWH, use of specific ART agents and duration of ART have not been established as risk factors [74]. NASH and NAFLD may be emerging comorbidities in this population based on the association between HIV and metabolic syndrome, which has a reported prevalence in patients with HIV from 11.2% up to 45.4% [75].

While the increased risk of liver disease among older PLWH is established, evidence describing the association between long-term ART use and liver-related toxicity is variable. In a study of 23,441 patients treated with NRTI-based ART, increased liver-related mortality has been observed with continuing use (annual relative risk = 1.11; 95% CI 1.02–1.12, $P = 0.02$) [76]. However, a large study of 22,910 patients without hepatitis virus co-infection over 114,478 person-years of follow-up (D.A.D. cohort) found that there were 12 liver-related deaths resulting in an incidence of 0.10/1000 person-years [77]. Seven deaths were due to severe alcohol use and five were due to

established ART-related toxicity, the latter of which resulted in an ART-related mortality incidence of 0.04/1000 person-years. The increased risk of liver-related AEs, including liver fibrosis, with use of specific NRTIs such as didanosine is well known [78]. As a result of these known AEs, current treatment guidelines no longer recommend the use of didanosine [5, 79].

Economic Burden Associated with ART-Related Cumulative Toxicity

There is limited evidence describing the economic burden associated with cumulative toxicity that results from long-term ART use in older PLWH. Nevertheless, short-term toxicity-related costs among PLWH who are treated with ART have been documented, and there is an expectation that healthcare costs will increase commensurately as PLWH age. In a retrospective Medicaid claims analysis of PLWH treated with ATV or darunavir ($n = 2426$), the mean ± SD per-patient per-month costs of all medically attended AEs were US$3879 ± $6635 and $5354 ± $8127, respectively [80]. In another US claims analysis of PLWH treated with NNRTIs ($n = 2548$), mean total healthcare costs (12 months) were estimated to be $27,299 ± $37,170, and annual AE-associated costs were $608 ± $3897 [81]. Costs varied from $586 for lipid disorders to $4434 for nausea/vomiting. A retrospective US case–control study found that for patients who had initiated ART within the last 12 months, the median difference (episode with event of interest vs. without event of interest) in total all-cause healthcare costs was $3310 for managing diabetes/insulin resistance, $2792 for lipid disorders, $1389 for a renal disorder event, $390 for rash, $357 for a somnolence/sleep event, and $212 for a hepatic disorder event [82]. Aging in the population of PLWH is likely to add to the cost of HIV management; between 1999 and 2011, the proportion of older PLWH increased from 9.6 to 25.4%, and proportional costs increased from 25 to 31% [83].

Potential for New Therapies to Improve Long-Term Outcomes

Among PLWH, shifting from targeting an acute infection to managing a chronic disease requires new approaches to treatment and drug regimens that ultimately achieve viral suppression while minimizing cumulative toxicities. While continued improvements in ART cannot fully address issues related to chronic inflammation and other comorbidities associated with HIV and long-term ART in aging patients, such regimens have the potential to improve patient adherence, reduce pill burden, and ultimately lower the economic impact of cumulative toxicities. Novel approaches to treatment in certain patient populations include ART regimens taken 4 days per week compared with continuous ART 7 days per week (QUATUOR trial) [84], the use of long-acting injectable formulations [85], and two-drug regimens [13, 16, 85–87].

Assuming viral loads can be controlled with fewer drugs in a treatment regimen, the risk of toxicity associated with long-term ART may be lowered. Recent head-to-head studies of two-drug regimens comparing either atazanavir–ritonavir plus lamivudine or rilpivirine plus boosted darunavir to currently recommended three- or four-drug ART in virologically stable patients have shown non-inferior efficacy and favorable AE profiles for two-drug regimens [13, 16]. Studies investigating treatment switching from three- or four-drug regimens to two- or one-drug regimens in virologically stable patients have also demonstrated non-inferior efficacy and comparable or a more favorable AE profile associated with regimens that include fewer drugs [12, 14, 15, 85–87]; several switch studies are ongoing [88–91]. These recent head-to-head trials and switch studies are generally limited to a duration of 1 year or less, and may therefore underestimate the benefits of initiating or switching to simplified regimens that potentially have fewer cumulative long-term toxicities.

LIMITATIONS

The findings reported in this literature review are subject to several limitations. The review

was non-systematic and thus did not identify literature from a broad set of databases or undergo dual-reviewer study screening and evaluation. Additionally, while we attempted to include impactful and meaningful studies, we did not conduct a formal quality assessment and thus the quality of data reported may vary. Furthermore, not all included studies were case–control studies and caution should be used when interpreting findings of excess comorbidities among PLWH. Indeed, while not the focus of this review, lifestyle factors that affect patients without HIV as well as PLWH and that lead to age-related comorbidities may also complicate treatment outcomes among PLWH. Finally, the apparent lack of literature focusing on the economic burden of long-term ART toxicities may be a result of the non-systematic nature of the review, but may also highlight an important evidence gap and area of potential future research.

CONCLUSION

Potential cumulative toxicity remains a concern as more patients experience long-term treatment and are at greater risk for chronic diseases associated with aging, despite recent advances in ART that have significantly increased the life expectancy of PLWH and offer better safety profiles. Newer treatment regimens with fewer drugs may help mitigate the clinical, humanistic, and economic burden of cumulative toxicity that emerges because of long-term use of ART. Together, aging and long-term treatment of HIV as a chronic disease imply the risk of greater economic burden for healthcare systems, which will demand thoughtful policy solutions that preserve access to innovative ART.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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