Systematic Review/Meta-analysis

ANNALS OF MEDICINE & SURGERY

OPEN

Antiretroviral drug use and the risk of falls in people living with HIV: a systematic review and meta-analysis

Pratik Lamichhane, MBBS[a,*], Michail Koutentakis, MS[h], Sushma Rathi, MBBS[g], Ayomide D. Ode, MD[d], Hirak Trivedi, MS[e], Summiya Zafar, MBBS[f], Pratima Lamichhane, MS[c], Prahlad Gupta, MS[a], Rakesh Ghimire, MD[b]

Objective: The risk of falls in people living with HIV (PLHIVs) on antiretroviral therapy (ART) has received little attention in the literature. The aim of the meta-analysis is to quantify the association between fall risk and various categories of drugs used in ART.

Material and Methods: PubMed, Google Scholar, Embase, and the Cochrane Central Register of Controlled Trials were systematically searched from inception to January 2023. Any observational study or controlled trial that reported on the relationship of at least one antiretroviral drug with falls in PLHIVs was included. Data on the frequency of single fallers, multiple fallers (≥2 falls), and non-fallers were extracted and studied for each drug and drug category. The pooled results were reported as an odds ratio (OR) with a 95% confidence interval (CI).

Results: A total of five observational studies (51 675 participants) were included out of 414 articles obtained through a literature review. Stavudine use was found to be associated with an increased risk of single falls in PLHIVs (OR: 1.69, 95% CI: 1.08–2.66, $P = 0.02$). However, efavirenz (OR: 0.82, 95% CI = 0.76–0.89, $P < 0.001$) and zidovudine (OR: 0.82, 95% CI = 0.77–0.92, $P < 0.001$) were found protective against the single falls. Didanosine had no significant association with fall risk (OR: 1.23, 95% CI: 0.78–1.93, $P = 0.37$). Likewise, protease inhibitors, integrase inhibitors, nucleoside reverse transcriptase inhibitors, and non-nucleoside reverse transcriptase inhibitors were discovered to have no significant association with fall risk.

Conclusion: Most drug categories of ART have no significant association with the risk of falls in PLHIVs. However, certain drugs, such as didanosine and stavudine, which have the inherent effect of causing balance deficits and neuropathy, should be used cautiously.

Keywords: accidental falls, AIDS, antiretroviral therapy, HIV, people living with HIV

Introduction

The human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) continues to be a key global health issue in today's world. In 2019, there were 36.9 million new HIV/AIDS infections, 863.8 thousand deaths, and 47.6 million disability-adjusted life years, which were the highest in Southern Sub-Saharan Africa[1]. Similar to the huge number of medical complications that can occur in HIV, the rates of injuries and accidents in people living with HIV (PLHIV) are also considerable. The crude incidence rate of unintentional injury was 18.56 per 1000 person-years among PLHIVs, which was significantly higher than the incidence rate in the general population. Furthermore, injury-related deaths were also more than twice as common among PLHIVs as among the noninfected population[2].

Antiretroviral therapy (ART) is highly efficacious in maintaining undetectable viral loads, allowing PLHIVs to live a near-normal life[3,4]. Strict adherence to ART is mandatory if viral suppression is to remain optimal. A systematic review from Africa reported that the level of adherence to ART ranged from 44.6 to 72.9% among the patients[5,6]. Nevertheless, ART is not free of adverse reactions, and these adverse reactions are identified as one of the causes of nonadherence to the treatment. One of the

HIGHLIGHTS

- Most classes of currently used antiretroviral drugs do not increase the risk of falls in users.
- Stavudine use was found to be associated with an increased risk of single falls in users.
- Efavirenz and zidovudine were found to protect against the risk of a single fall episode.

[a]Maharajgunj Medical Campus, Institute of Medicine, Kathmandu, Nepal, [b]Department of Clinical Pharmacology, Maharajgunj Medical Campus, Institute of Medicine, Kathmandu, Nepal, [c]Manipal College of Medical Sciences, Kaski, Nepal, [d]Mainland Hospital, Yaba, Lagos, Nigeria, [e]Washington University of Health and Science, San Pedro, Belize, [f]Jinnah Sindh Medical University, [g]Dow University of Health Sciences, Karachi, Pakistan and [h]Medical University of Warsaw, Warsaw, Poland

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Maharajgunj Medical Campus, Institute of Medicine, Maharajgunj, Kathmandu 44600, Nepal. E-mail: pratiklamichhane@iom.edu.np (P. Lamichhane).

Annals of Medicine & Surgery (2023) 85:6105–6114

Received 15 June 2023; Accepted 9 October 2023

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/annals-of-medicine-and-surgery.

Published online 17 October 2023

http://dx.doi.org/10.1097/MS9.0000000000001411

less studied yet significant adverse reactions of ART in PLHIVs is falls. The incidence of falls in middle-aged PLHIVs on ART is about 30%, of which 18% are recurrent fallers. Falls are one of the most prevalent reasons for emergency department visits and loss of independence among patients[7]. Several factors, like multiple comorbidities, use of multiple medications, frailty, and functional impairments, are implicated in falls in PLHIVs[7,8].

Generally, patients who are nonadherent to ART are more likely to fall than adherent patients[9]. However, the association of ART medications with the risk of falls has been inconsistent throughout the studies. Therefore, we conducted a systematic review and meta-analysis to quantify the association between the use of different ART medications and the risk of falls in PLHIVs.

Methods

Ethical compliance and research registration

All data collected for the meta-analysis were extracted from primary published studies, and hence, there is no ethical issue. The current meta-analysis was conducted in accordance with the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplemental Digital Content 1, http://links.lww.com/MS9/A281)[10]. The AMSTAR2 (A Measurement Tool to Assess Systematic Reviews 2) checklist was used to assess the quality of our review, which showed our review being of moderate quality. The details of the AMSTAR2 checklist are provided in the Supplementary File (Supplemental Digital Content 2, http://links.lww.com/MS9/A282).

Search strategy and selection criteria

The electronic medical databases, PubMed, Google Scholar, Embase, and the Cochrane Central Register of Controlled Trials, were systematically searched from inception to January 2023 for potentially eligible studies. Boolean logic was used for conducting the database search, and Boolean search operators "AND" and "OR" were used to link the search terms. The detailed search strategy used in the literature review has been provided in Appendix 1 of the Supplementary File (Supplemental Digital Content 3, http://links.lww.com/MS9/A283). For advanced PubMed search, the medical subject headings (MeSH) database was used to find corresponding MeSH terms for the search terms. Similarly, for advanced Embase search, corresponding Emtree terms were used as the search terms. All shortlisted studies were then imported to the Endnote library, and duplicates were removed appropriately. A subsequent manual check was also done with the removal of the remaining duplicates wherever applicable. Two reviewers independently reviewed the titles and abstracts for all the identified references for inclusion and verified them with another reviewer.

Eligibility criteria

Any observational study or a controlled trial that reported on the relationship of at least one antiretroviral drug or antiretroviral class [nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTI), integrase inhibitors (II), and protease inhibitors (PI)] with falls in PLHIVs was included. Studies without distinction between separate antiretroviral drugs, case reports and series, reviews, meta-analyses, letters, and editorials were excluded. Further, the articles with insufficient information and those which did not meet the eligibility criteria were also excluded.

Data extraction and quality assessment

Data extraction was performed independently by two researchers into a standardized data collection form in the Microsoft Excel 2019 spreadsheet program. Data on the first author, study design, site of study, year of publication, sample size, mean age of patients in the study, gender of patients in the study, presence of comorbidities, frequency of single fallers, multiple fallers ($\geq$2 falls), and non-fallers were extracted and studied for each ART drug and drug class. The quality of observational studies was evaluated with respect to bias using the Newcastle–Ottawa Scale (https://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf). The scale was used to assess study quality under three headings: selection, comparability, and exposure. Studies with scores of five or more qualified for inclusion, and studies with more than seven were labeled high-quality studies. Any discrepancies during data extraction and quality assessment were resolved by discussion with all the authors.

Statistical analysis

We performed separate meta-analyses to determine the association between the fall risk and use of each ART drug and drug category. Odds ratios (ORs) were used as the common measure of association across studies. Statistical heterogeneity was examined by I^2 statistics. The I^2 value threshold of 25%, 50%, or $>$75% were considered as low, moderate, or substantial heterogeneity, respectively[11]. The fixed-effects and random-effects models were utilized to pool the extracted data according to statistical heterogeneity. If moderate or substantial heterogeneity was identified, we used random-effects models (DerSimonian and Laird) to pool the outcomes[12]. Otherwise, a fixed-effects model was used. The pooled results were reported as OR with a 95% confidence interval (CI). The cumulative pooling of different classes of ART was avoided due to major differences in their known mechanism of actions and adverse events profile. Additional sensitivity analysis was performed to assess the influence of a single study on the pooled OR using the leave-one-out method. All analyses were performed with the STATA version 16.0 (StataCorp, College Station, Texas, USA).

Results

Study characteristics

A total of 414 studies were identified through systematic database searches. First, we removed 159 duplicate articles, and the titles and abstracts of the remaining articles were screened. The 16 remaining articles with full text after screening were assessed per the eligibility criteria. Finally, five full-text articles (51 675 participants) were included in the systematic review and meta-analysis[7,13–16]. A flowchart demonstrating the details of study selection according to the PRISMA guidelines is presented in Figure 1. All five studies were observational studies with the sample size ranging from 279 to 26 373 participants. All the studies were conducted in the PLHIVs from the USA, and the majority of the patients included in the analysis were males (48 699, 94.24%). Two studies each exclusively studied male and female patients. The different classes of ARTs studied in these

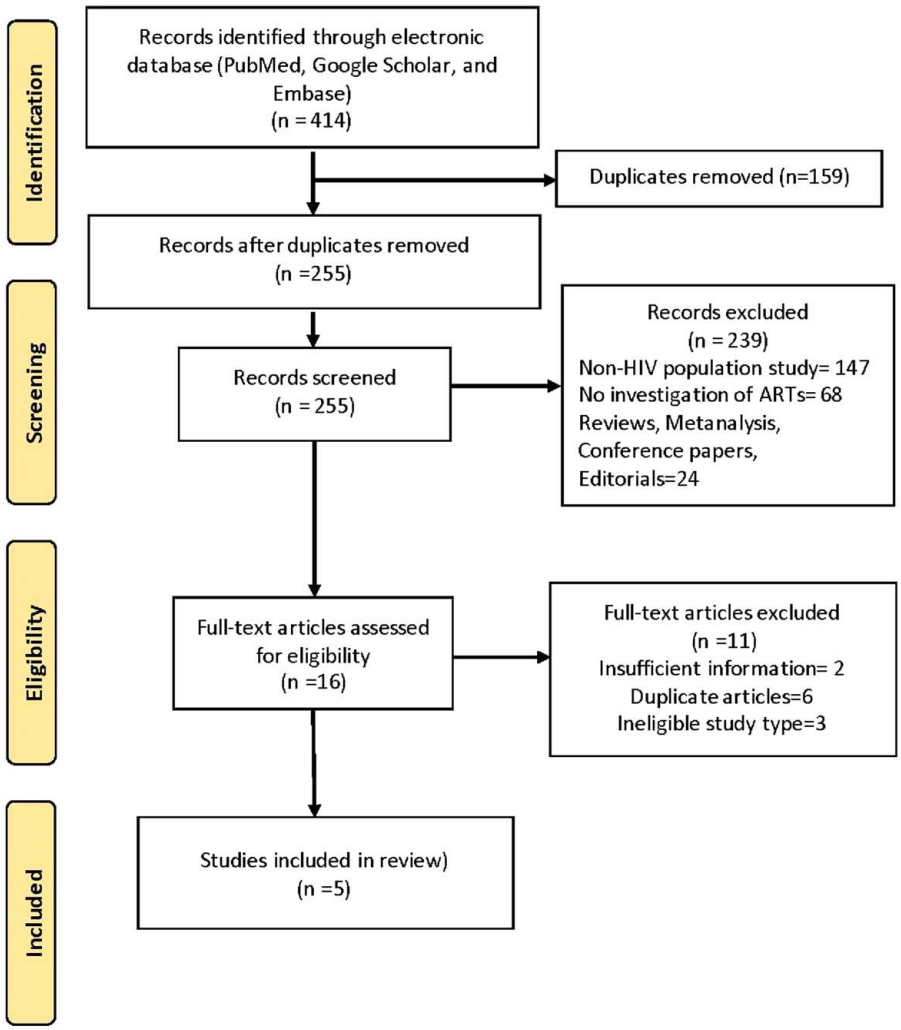


Figure 1. PRISMA flow diagram.

studies were NRTIs, NNRTIs, PIs, and IIs. Additionally, the risk of falls with the use of single drugs such as stavudine, didanosine, efavirenz, and zidovudine was studied. The details of the studies included in the review are presented in Table 1.

The quality assessment of the studies is provided in Appendix 2 of the Supplementary File (Supplemental Digital Content 3, http://links.lww.com/MS9/A283). According to quality assessment tools, the methodological quality score ranged from 7 to 8. None of the studies were of low quality. All the studies were included in the systematic review and meta-analysis.

Risk of falls with different classes of ARTs

None of the different classes of ARTs (NRTIs, NNRTIs, PIs, and IIs) had a statistically significant association with the risk of falls among PLHIVs (Fig. 2). The cumulative pooling of different classes of ART was avoided due to major differences in their known mechanism of actions and adverse events profile. The use of NRTIs was not statistically associated with the risk of falls (OR = 0.89, 95% CI = 0.73–1.07, $P = 0.21$, $I^2 = 67.22\%$). Likewise, NNRTI use was also not associated with an increased risk of falls (OR = 0.90, 95% CI = 0.79–1.03, $P = 0.12$, $I^2 = 87.67\%$). The use of PIs was not found to be associated with the significantly increased risk of falls either (OR = 1.06, 95% CI = 0.87–1.29, $P = 0.59$, $I^2 = 90.65\%$). Similarly, II users were also spared of the increased risk of falls (OR = 0.81, 95% CI = 0.38–1.69, $P = 0.57$, $I^2 = 98.12\%$).

Risk of fall with stavudine use

The risk of a single episode of a fall was significantly higher in stavudine users than non-users (OR = 1.69, 95% CI = 1.08–2.66, $P = 0.02$, $I^2 = 0\%$). However, the risk of multiple falls was not significantly higher in stavudine users (OR = 1.21, 95% CI = 0.81–1.82, $P = 0.34$, $I^2 = 35.41\%$) (Fig. 3).

Risk of fall with didanosine use

The risk of a single episode of a fall was not significantly higher in didanosine users than non-users (OR = 1.23, 95% CI = 0.78–1.93, $P = 0.37$, $I^2 = 4.04\%$). Likewise, the risk of multiple falls was not associated with the use of didanosine (OR = 1.17, 95% CI = 0.54–2.54, $P = 0.69$, $I^2 = 57.28\%$) (Fig. 4).

Table 1
Characteristics of studies included in the review.

References	Study site	Study design	Sample	Male (%)	Total fallers	Non-fallers	ART classes investigated	ART drug investigated
Womack *et al.*[13]	USA	Case–control study	23 252	22 322 (96%)	3919	19 333	NRTI, NNRTI, PIs, IIs	Efavirenz, zidovudine
Womack *et al.*[14]	USA	Cohort study	26 373	25 793 (97.8%)	5673	20 700	NRTI, NNRTI, PIs, IIs	N/A
Erlandson *et al.*[16]	USA	Cohort study	279	279 (100%)	114	165	PIs, IIs	Stavudine, efavirenz, didanosine
Sharma *et al.*[15]	USA	Cohort study	1412	0 (0%)	263	1149	N/A	Stavudine, zidovudine, efavirenz, didanosine
Erlandson *et al.*[7]	USA	Case–control study	359	305 (85%)	109	250	N/A	Stavudine, efavirenz, didanosine

IIs, intergrase inhibitors; N/A, not available; NNRTIs, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; USA, United States of America.

Risk of fall with efavirenz use

The risk of a single episode of a fall was significantly lower in efavirenz users than non-users (OR = 0.82, 95% CI = 0.76–0.89, $P < 0.001$, $I^2 = 45.73\%$). However, no such association was observed between the use of efavirenz and the risk of multiple falls (OR = 1.20, 95% CI = 0.70–2.05, $P = 0.52$, $I^2 = 58.86\%$) (Fig. 5).

Risk of fall with zidovudine use

The risk of a single episode of a fall was significantly lower in zidovudine users than non-users (OR = 0.82, 95% CI = 0.74–0.92, $P < 0.001$, $I^2 = 34.57\%$) (Fig. 6). The risk of multiple episodes of falls could not be determined due to a lack of data in the included studies.

Sensitivity analysis

Sensitivity analysis was performed using the leave-one-out method in a total of four studies that reported on the association between stavudine and the risk of falls. No studies had a major influence on the pooled OR except for a study by Erlandson *et al.*[16]. On the omission of this study, the risk of falls with stavudine was changed significantly (OR = 0.88, 95% CI = 0.7–1.1, $P < 0.001$). The same study also had a significant influence on pooled OR of risk of fall with the use of efavirenz. On the omission of the study, the risk of falls with efavirenz changed significantly (OR = 0.82, 95% CI = 0.76–0.89, $P < 0.001$). However, none of the studies had a major influence on the pooled OR of risk of falls with the use of protease inhibitors and didanosine. The details of all sensitivity analyses are provided in Appendix 3 of the Supplementary File (Supplemental Digital Content 3, http://links.lww.com/MS9/A283).

Association of comorbidities with falls in PLHIVs

Apart from the associations observed between ART drugs and the risk of falls in PLHIVs, factors such as comorbidities can also have a significant influence on the risk of falls. All five studies included in this systematic review have reported on the association of comorbidities and the risk of falls in PLHIVs. However, a quantitative assessment of the association between comorbidities and fall risk could not be performed due to heterogeneity in the data of selected studies.

The prevalence of comorbidities was found to be higher among fall cases than the controls by Womack *et al.*[13]. The common comorbidities studied in the included studies were diabetes mellitus (DM), hypertension, peripheral neuropathy, psychiatric disorders, and neurological impairment. Womack *et al.*[14] also reported that an increase in the count of physical comorbidities increased the likelihood of falls in PLHIVs by 1.13 times.

The presence of DM in a PLHIV increased the risk of falls by 1.48[16] to up to 6.2[7] times when compared to the patients without DM. Likewise, HIV patients with hypertension had an increased fall risk of 1.35[16] to 1.8 times[7]. Another important comorbidity, psychiatric disorders, was associated with an increased risk of falls in PLHIVs. A patient with at least one mental health diagnosis was 1.22 times more likely to experience falls, according to Womack *et al.*[14]. Likewise, the presence of a psychiatric illness increased fall risk by 3.6 times in HIV-1-infected patients[7]. Depression alone can increase the fall risk by 1.49 times in these patients[15]. Similarly, the association of

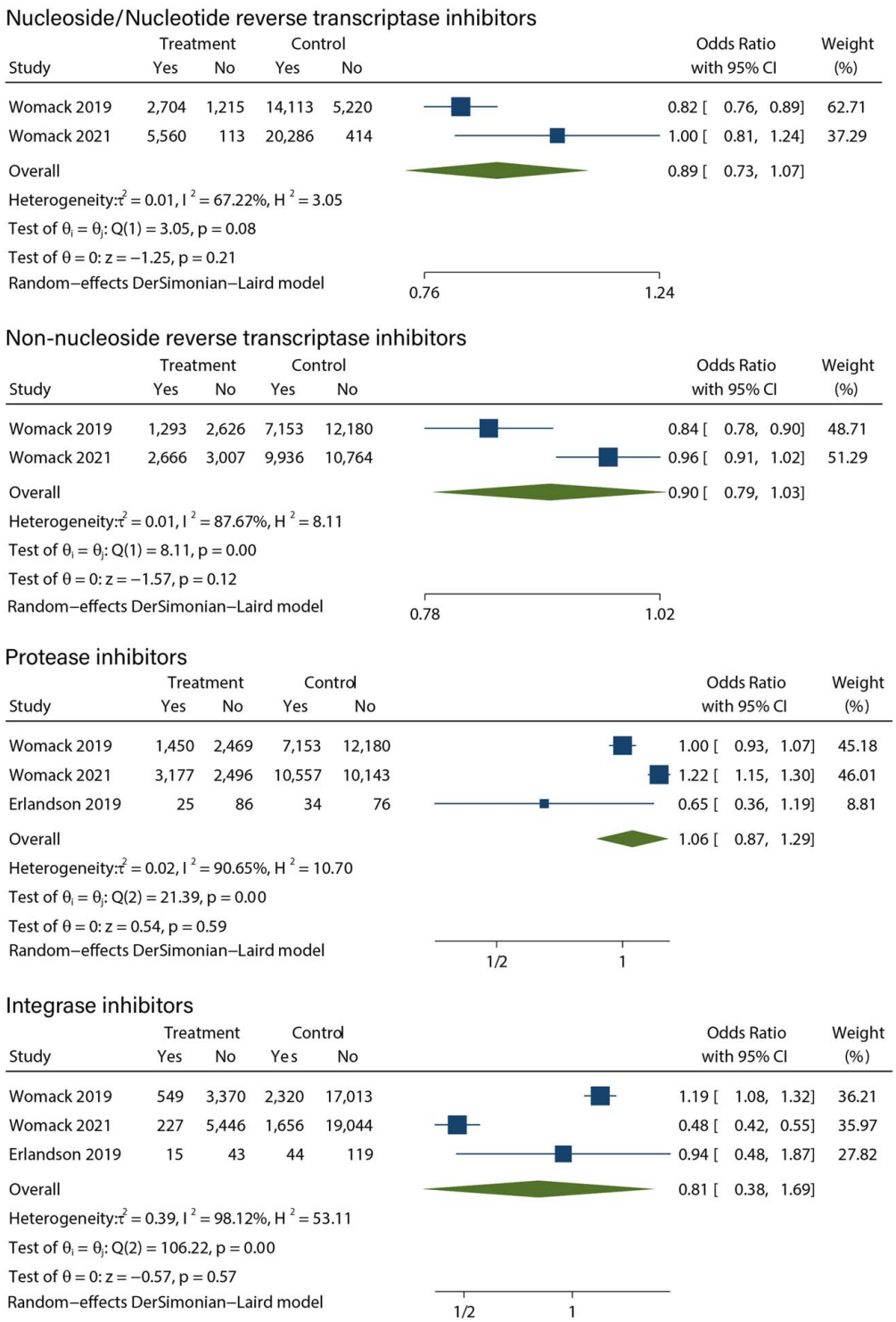
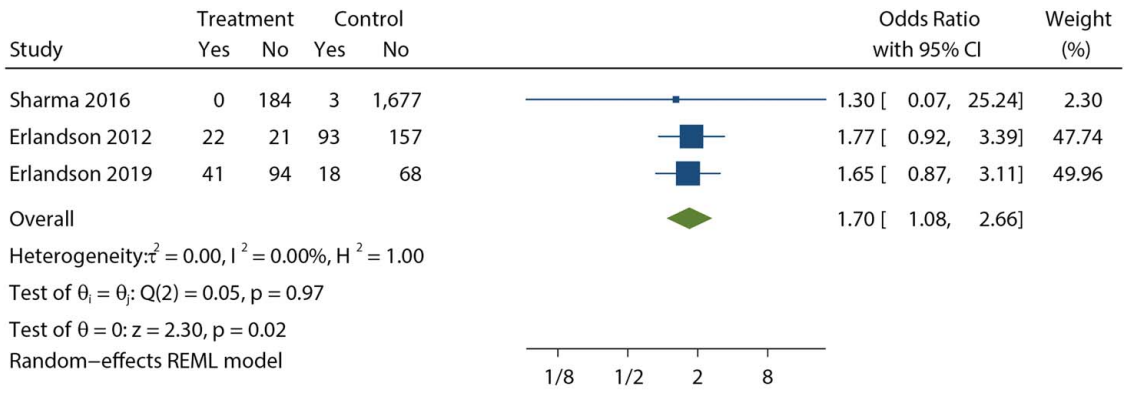


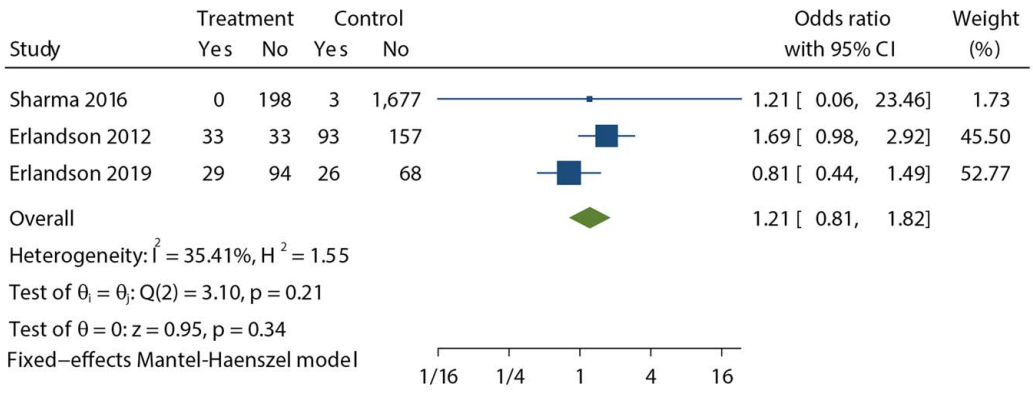
Figure 2. Forest plot of meta-analysis of the risk of falls with the use of different classes of ARTs (antiretroviral therapies).

peripheral neuropathy with falls has been reported in three out of five studies[7,15,16]. The presence of peripheral neuropathy in patients could increase the risk of a single episode of falls by 2.17[15] times to 3.3 times[7].

Other patient attributes, like illicit drug use, were reported in four studies. The use of illicit drugs by PLHIVs increased the likelihood of falls event by 1.14[14] to 1.94 times[16]. Heavy alcohol use was the strongest predictor of falls, with an OR of 7.28, according to Sharma *et al.*[15]. The details on the association of comorbidities and substance use with the fall risk in PLHIVs have been provided in Appendix 4 of the Supplementary File (Supplemental Digital Content 3, http://links.lww.com/MS9/A283).



Forest plot of meta-analysis of risk of single fall with use of stavudine



Forest plot of meta-analysis of risk of multiple falls with use of stavudine

Figure 3. Forest plot of meta-analysis of the risk of falls with the use of stavudine. REML, restricted maximum likelihood.

Discussion

This is the first systematic review and meta-analysis to summarize the association between the risk of falls with the use of ART in PLHIVs. Our study found that the major classes of ARTs – NRTIs, NNRTIs, PIs, and IIs – were not associated with an increased risk of falls. However, stavudine use was associated with a significantly increased risk of falls. On the contrary, efavirenz and zidovudine use significantly reduced the risk of falls in the patients.

The risk of falls in elderly patients is commonly discussed in the literature since falls are a significant component of geriatric syndrome. Around one-third of people aged 65 years or older experience a fall each year[7]. Falls in non-elderly people, though less reported, can contribute to significant morbidity. PLHIVs are identified as a vulnerable population with an increased risk of falls and poor bone mineral metabolism and quality. Multiple comorbidities, the use of multiple medications (≥ 5) known as polypharmacy, frailty, disability, and functional impairments are implicated in falls in PLHIVs[7,8]. Since the commencement of ART in HIV patients, life expectancy, morbidity, mortality, and quality of life have improved. This has led to a change in the demographics of the existing global cohort of HIV patients. There has been an increase in the number of aging people with HIV, defined as PLHIVs, who are 50 years of age or older. These patients face an increased risk of aging-related issues such as the existence of multiple comorbidities, polypharmacy, and frailty[17,18]. Hence, the assessment of fall risk and its prevention should receive increased importance in the management of elderly patients with HIV/AIDS.

Comorbidities like cardiovascular diseases, diabetes, hypertension, dementia, neuropathy, arthritis, chronic pain, and psychiatric diseases are found to increase the risk of falls in PLHIV[7]. Likewise, impairments of vision and cognition, neuropathy, strength, and gait are also associated with falls in PLHIV[8]. Elderly PLHIVs who are pre-frail and frail are much more likely to fall, which can be worsened if conditions such as peripheral neuropathy co-exist in the patient[19]. Sharma *et al.*[15] suggested that falls in PLHIVs were associated with factors affecting cognition rather than HIV status.

Polypharmacy has also been identified as one of the most important risk factors for falls among HIV patients by a multitude of studies[7,20]. Apart from a standard three-drug ART regimen, patients receive non-ART drugs to alleviate additional symptoms, adverse drug reactions, or comorbidities[21]. More than two-thirds of HIV patients receive at least one more prescription medication in addition to ART. Furthermore, these prescriptions are more likely to be drugs acting on the central nervous system or cardiovascular system, which increases the fall risk in the patients[22,23]. The use of non-ART medications like beta blockers, antidepressants, antipsychotics, sedatives like benzodiazepines, muscle relaxants, insulin, and opiates is also independently associated with an increased risk of falling in PLHIVs[7]. As per our study, the risk of a single episode of fall was significantly higher in stavudine users than non-users. Stavudine

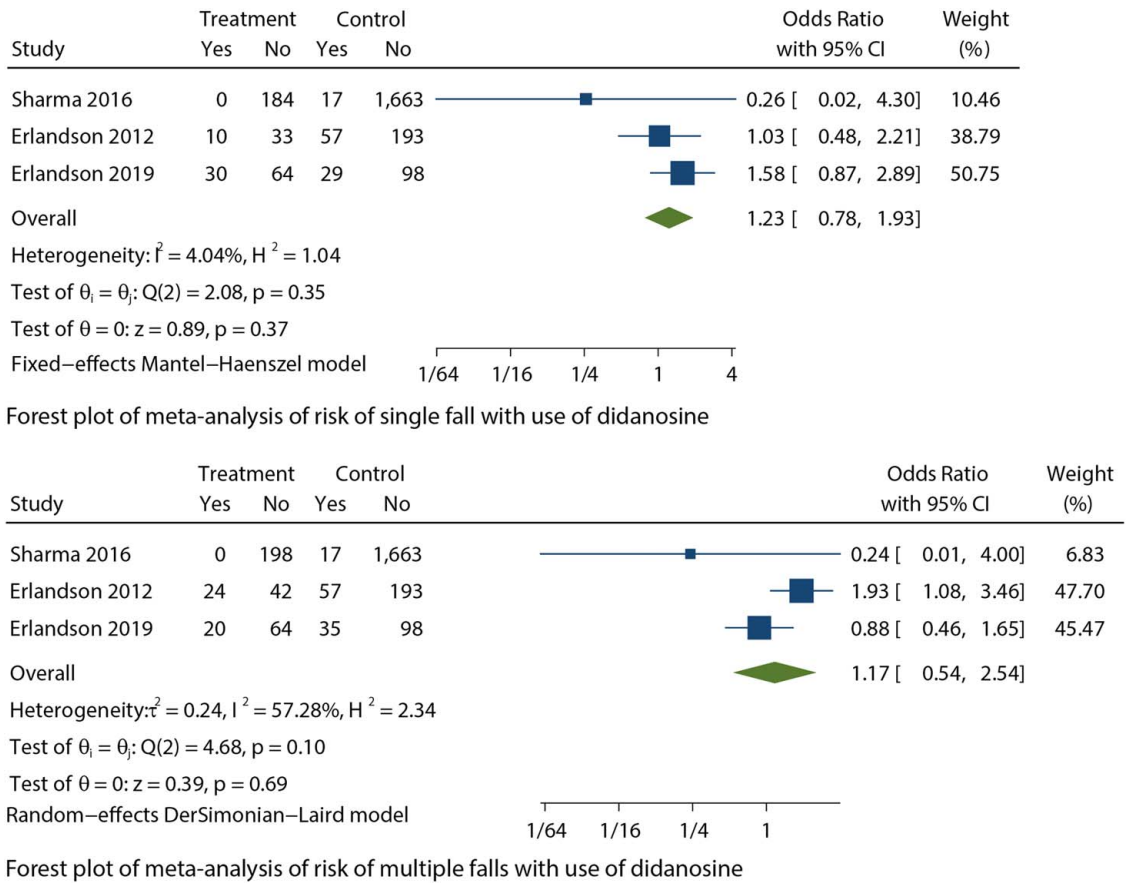


Figure 4. Forest plot of meta-analysis of the risk of falls with the use of didanosine.

is known to cause central nervous system side effects such as neuropathy or lipoatrophy, which might increase the risk of falling in patients[15]. Additionally, peripheral neuropathy is the major dose-limiting adverse event associated with stavudine use, which has been attributed to mitochondrial toxicity of the drug[24]. Peripheral neuropathy was observed more frequently with stavudine use in up to 23% of treated patients when compared to other ART drugs[25]. Other ART drugs, such as didanosine and efavirenz, are believed to increase fall risk through a similar mechanism of action. However, zidovudine, a drug belonging to the same class as stavudine, has not been reported to cause adverse events such as peripheral neuropathy or balance disturbances. Hence, the risk of falls was not increased risk with the use of zidovudine in ART.

Studies suggest that the presence of dizziness in older adults is associated with a markedly greater fear of falling and an increased risk of falls[26]. Dizziness was also frequently reported among HIV-infected participants in a study by Zingmond *et al.*[27]. The underlying etiologies of dizziness in HIV are multifactorial. As a side effect of ART, dizziness occurs in about 28% of efavirenz users[28]. However, some studies could not find an increased risk of falls among participants using efavirenz[29]. Our study has also shown a significantly lower risk of single episodes of falls in efavirenz and zidovudine users than non-users. The reason behind the apparent protective nature of these drugs against falls is less likely to be an innate protective effect. Rather, these drugs, which are now commonly used as a part of most ART regimens, represent the overall protective effect of ART against falls. Prior studies have shown that longer-term ART use was protective, whereas current efavirenz use is linked to an increased risk of injury[16]. Despite this, a multitude of studies suggests a decreased risk of falls in PLHIVs who are well adherent to ART[15,16,30]. Better virological control with ART means a decreased risk of complications from HIV and improved balance, mobility, physical activity, and quality of life.

PLHIVs with imbalance symptoms could ultimately result in a greater fear of falling and further activity restriction. Such activity restriction in these patients can contribute to poor bone density and quality. According to a systematic review and meta-analysis, the prevalence of osteoporosis among PLHIVs is threefold greater than that of noninfected individuals[31,32]. The risk factors for osteopenia in PLHIV are the use of ART (particularly protease inhibitors), low CD4 count, and the presence of chronic inflammation[33]. A higher fracture rate has been observed in the first 2 years following the start of ART. Nevertheless, continuing ART was not linked to rising fracture rates in young HIV-positive people[34].

Early identification of at-risk PLHIVs and targeted interventions can help decrease the frequency of falls. ART drugs such as efavirenz, didanosine, and stavudine should be used cautiously in PLHIVs, especially in those with pre-existing risk factors for falls such as neuropathy, illicit drug use, multiple comorbidities, frailty, etc. Other potential interventions, such as increasing

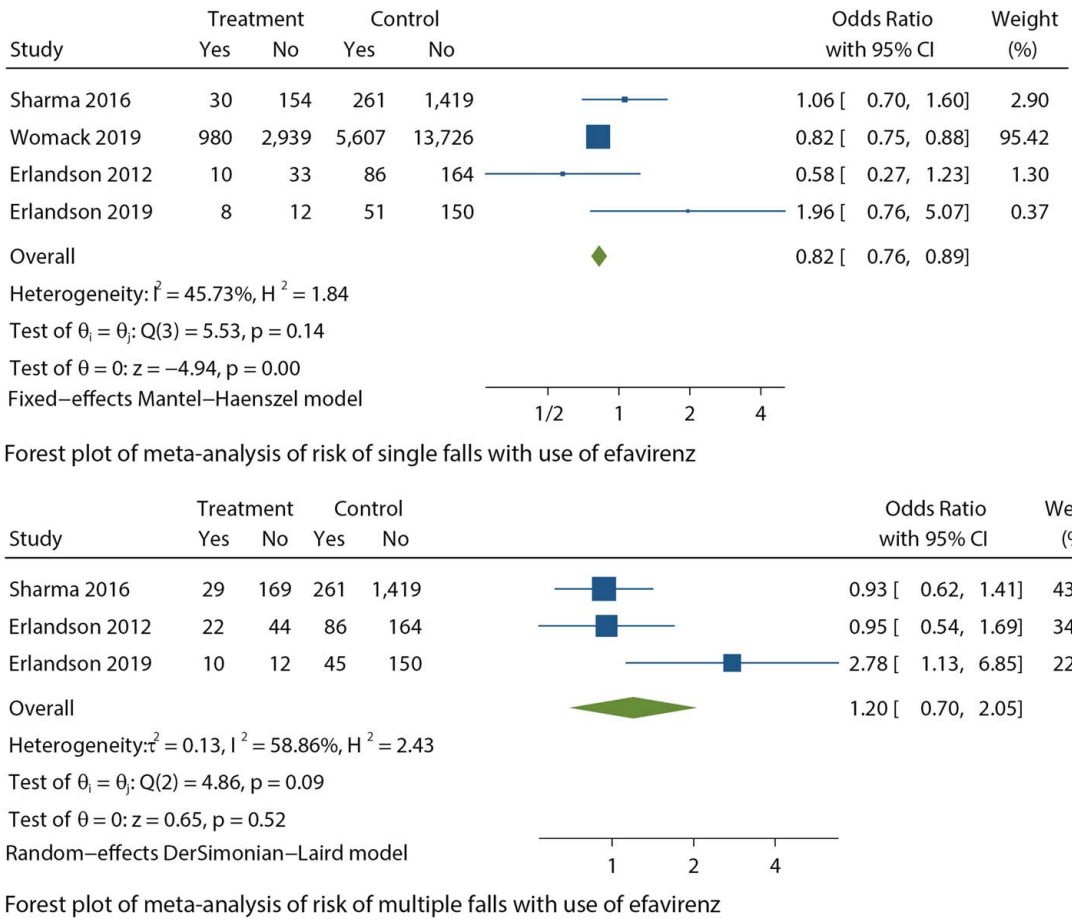


Figure 5. Forest plot of meta-analysis of the risk of falls with the use of efavirenz.

physical activity, improving physical function, and counseling regarding household and occupational hazards, can be useful.

The major strength of our study is that this is the only meta-analysis to quantify the risk of falls with the different classes of ARTs as well as individual drugs. The major limitation of our analysis is that the included studies are observational studies without randomized controlled trials, which would have yielded better results. Another major limitation is the limited number of studies and the limited data in the studies, which has restricted the subgroup analysis and meta-regression analysis. Since meta-regression could not be performed, the effect of covariates that represent the sociodemographic, clinical, and treatment characteristics of the subjects on the falls risk could not be studied in depth. Likewise, the potential ART drugs that can cause falls, like stavudine and didanosine, are now being replaced by novel drugs with a lower risk of such adverse events. Overall, these could limit the applicability and generalizability of the findings of our study.

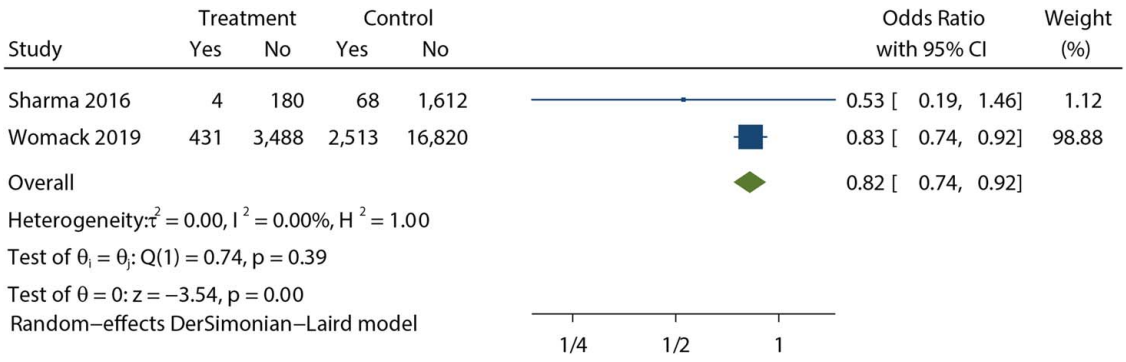


Figure 6. Forest plot of meta-analysis of the risk of falls with the use of zidovudine.

Conclusions

Most classes of ART drugs do not increase the risk of falls in PLHIVs. However, some drugs such as stavudine might increase the risk of falls owing to its inherent adverse neurological profile. Appropriate assessment of PLHIVs to identify the risk of falls should be done along with the initiation and continuation of ART to minimize the fall episodes.

Ethical approval

Not applicable due to the nature of the review article.

Consent

Not applicable for review article.

Sources of funding

The authors received no funding to conduct the research work.

Author contribution

Pratik L.L., M.K., S.R., and Pratima L.L.: study conception, data analysis, software, and manuscript writing; M.K., S.R., A.D.O., H.T., P.G., S.Z.,.: data acquisition, and manuscript writing and editing; Pratik L.L., P.G., S.Z., and H.T.: manuscript writing and editing; R.G.: manuscript writing and editing and supervision.

Conflicts of interest disclosure

The authors have no conflicts of interest to declare.

Research registration unique identifying number (UIN)

1. Name of the registry: PROSPERO.
2. Unique identifying number or registration ID: CRD420234 16150.
3. Hyperlink to your specific registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=416150.

Guarantor

Dr Pratik Lamichhane.

Data availability statement

The data used in the meta-analysis are available with the primary researchers.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Acknowledgements

None.

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