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SYSTEMATIC REVIEW

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Developing an HIV-specific falls risk prediction model with a novel clinical index: a systematic review and meta-analysis method

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Abstract

Background Falls are a common problem experienced by people living with HIV yet predictive models specific to this population remain underdeveloped. We aimed to identify, assess and stratify the predictive strength of various physiological, behavioral, and HIV-specific factors associated with falls among people living with HIV and inform a predictive model for fall prevention.

Methods Systematic review and meta-analysis were conducted to explore predictors of falls in people living with HIV. Data was sourced, screened, extracted, and analyzed by two independent reviewers from eight databases up to January 2nd, 2024, following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocol. Evidence quality and bias were assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) and the Mixed Method Appraisal Tool (MMAT), respectively. Pooled odds ratios (OR) with 95% confidence intervals (CI) were computed using random-effects models to establish associations between predictors and falls risk. We applied established criteria (Bradford Hill's criteria, Rothman's and Nweke's viewpoints) to stratify risk factors and create a weighted predictive algorithm.

Results This review included 12 studies on falls/balance dysfunction in 117,638 participants (54,513 people living with HIV), with varying ages (45–50 years), sample sizes (32 – 26,373), study durations (6 months to 15 years), disease stages (CD4 + counts 347.2 cells/mm^3 to ≥ 500 cells/μL) and fall definitions (self-reported histories to real-time reporting). Some predictors of falls in people living with HIV including depression, cannabis use, cognitive impairment/neurocognitive adverse effects (NCAE), hypertension, and stavudine—showed perfect risk responsiveness (Ri = 1), indicating their strong association with falls. Notably, cannabis use demonstrated the highest risk weight (Rw = 3.0, $p < 0.05$, 95%CI:1.51–5.82), followed by NCAE (Rw = 2.3, $p < 0.05$, 95%CI:1.66–3.21) and frailty with a broad confidence interval (Rw = 2.2, $p < 0.05$, 95%CI:0.73–14.40). Other significant predictors included hypertension (Rw = 1.8, $p < 0.05$, 95%CI:1.33–2.33), depression (Rw = 1.6, $p < 0.05$, 95%CI:1.22–2.18), stavudine use (Rw = 1.5, $p < 0.05$, 95%CI: 0.95–2.25), neuropathy (Rw = 1.3, $p < 0.05$, 95%CI:1.26–2.11), and polypharmacy (Rw = 1.2, $p < 0.05$, 95%CI:1.16–1.96). The fall risk threshold score was 12.8, representing the 76th percentile of the specific and sufficient risk weight.

Conclusion Our meta-analysis identifies predictors of falls in people living with HIV, emphasizing physiological, behavioral, and HIV-specific factors. Integrating these into clinical practice could mitigate falls-related sequelae. We propose a novel approach to falls risk prediction using a novel clinical index, resulting in a HIV-specific falls risk assessment tool.

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Trial registration The study protocol is registered with PROSPERO ID: CRD42023453556.

Keywords Falls predictive models, People living with HIV, Physiological, Behavioral, HIV-specific fall risk factors

Introduction

Background to the study

Living with HIV is associated with polypharmacy as well as the development of peripheral neuropathy and cognitive impairment [1–3]. These conditions increase the risk of falls by impairing balance [4, 5]. Falls are a significant public health concern as they often result in severe consequences including fracture, head injury and death, especially among older people [6, 7]. HIV has become a treatable condition and people living with HIV are experiencing different sequelae including falls [8]. In people living with HIV, falls tend to occur at a younger age compared to the general population [7]. Given the morbidity associated with falls, it is important to implement strategies to percent falls in people living with HIV as well as investigating and managing those who are falling [8].

Amidst the growing recognition of the unique challenges faced by people living with HIV in relation to falls, there is a need to promote falls risk assessment in people living with HIV [9]. An effective way to prevent and identify falls is through regular risk assessments which are often built around the casual factors otherwise known as predictors. Hence, there is a need to identify the predictors of falls in people living with HIV. A recent study has implicated central nervous system (CNS) and peripheral nervous system (PNS) factors such as temporal volumes, two-point pedal discrimination and compromised sensory perception, as independent contributors to postural instability and falls in people living with HIV [10]. This phenomenon may be attributed to the damage HIV inflicts on both the central and peripheral nervous systems, coupled with the intricate process of integrating various sensory inputs [10]. These inputs, processed by peripheral systems and brain networks, are crucial for coordinating sensory and musculoskeletal information to maintain balance [10]. The complex nature of this integration is fundamental for upholding postural stability [10]. Additionally, HIV is commonly associated with reduced bone mineral density [11] and increased risk of fracture [12] which may contribute to balance problems and falls. Similarly, frailty [7, 8, 13] and polypharmacy [14, 15] have been associated with falls in people living with HIV. The diversity of predictors for falls in people living with HIV necessitates a systematic review to elucidate the underlying relationships and synthesize the collective evidence. Additionally, the variable contributions of these factors to falls risk in people living with HIV warrant a comprehensive examination of the mechanistic pathways and effect size estimates, which provide a basis for falls risk stratification.

Therefore, this study aimed to address knowledge gaps in falls prediction amongst people living with HIV by conducting a systematic review and meta-analysis. We sought to identify and stratify predictors of falls using a clinically relevant index, and inform the development of a multivariate predictive model and sustainable multipronged falls prevention and treatment strategies. The research question was: What are the predictors of falls in people living with HIV, to what extent do the identified predictors predict falls in people living with HIV, and how can they be stratified based on clinical relevance?

Methods

This is a systematic review and meta-analysis of the predictors of falls in people living with HIV. The study was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16]. The review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42023453556).

Eligibility criteria

We included studies if they were (1) peer-reviewed studies, (2) examined predictors of falls in people living with HIV, (3) reported both the predictor and corresponding risk estimates (Odds ratio) or, provide sufficient information for the risk estimate to be calculated and transformed into odds ratios, (4) To be included in the meta-analysis part of the study, a risk factor has to be reported by at least two studies. There was no restriction regarding publication country, ethnicity, and gender.

Exclusion criteria

Studies were excluded if (1) determined to possess high risk of bias. A quality score $\leq$ 40% on the mixed method appraisal tool was defined as high risk of bias [17] and (2) if the frequency of predictors of falls were reported without documenting the corresponding risk estimate (Odds ratio or its equivalent) or providing sufficient information to allow their computation.

Outcome measures

In the context of people living with HIV, various risk factors were associated with an increased likelihood of falls. These predictors include CD4, frailty,

multimorbidity, neuropathy, hypertension, obesity, cognitive impairment, depression, NCAE, stavudine, cannabis use. Both laboratory-based and non-laboratory outcome measures were evaluated.

Frailty

A multifaceted concept describing increased vulnerability and reduced physiological reserve, often associated with aging and chronic health conditions [18–21]. Key components include:

i. *Physical Weakness*: Assessed through grip strength, gait speed, and chair stands.
ii. *Exhaustion*: Persistent fatigue or lack of energy, captured through self-reported questionnaires.
iii. *Weight Loss:* Monitoring unintentional weight loss over a specific period.
iv. *Low Physical Activity*: Evaluating the person's level of physical activity.
v. *Slow Walking Speed*: Measuring the time to walk a specific distance.
vi. *Cognitive Impairment*: Assessing cognitive function.
vii. *Nutritional Status*: Evaluating nutritional intake and deficiencies.
viii. *Social Isolation*: Considering social support networks and social engagement.
ix. *Multimorbidity*: Accounting for the presence of multiple chronic conditions.
x. *Overall, Health Status*: Considering chronic conditions, functional limitations, and quality of life.

Neuropathy

Neuropathy refers to conditions affecting peripheral nerves, leading to dysfunction or damage [22]. Key components include:

i. *Symptoms Assessment:* Evaluating symptoms such as numbness, tingling, burning, pain, weakness, muscle cramps, or loss of coordination.
ii. *Objective Measures:*

- *Nerve Conduction Studies (NCS):* Measuring the speed and strength of electrical signals along the nerves.
- *Electromyography (EMG):* Assessing muscle response to nerve stimulation.
- *Quantitative Sensory Testing (QST):* Evaluating sensory perception thresholds (e.g., temperature, vibration, pressure) to detect neuropathic changes.

CD4+ count

The CD4+ count is a key marker for immune health in people living with HIV [23]. It measures the number of CD4+-positive T cells per microliter of blood, critical for immune function. Categories based on clinical characterization [24] include:

i. *Severely Immunocompromised (CD4+ count < 200 cells/μL):* High risk of opportunistic infections and severe immunosuppression.
ii. *Moderately Immunocompromised (CD4+ count 200-349 cells/μL):* Moderate immune suppression; increased infection risk.
iii. *Mildly Immunocompromised (CD4+ count 350-499 cells/μL):* Mild immune suppression; better immune function but still requires precautions.
iv. *Normal Immune Function (CD4+ count ≥ 500 cells/μL):* Robust immune system with low risk of infection.

Obesity

Obesity is a complex condition characterized by excessive body fat accumulation. A comprehensive approach considers both objective measures and individual context:

a *Body Mass Index (BMI):* Calculated as weight (kg) divided by height (m^2) [25]. Categories:

- Underweight: BMI < 18.5
- Normal weight: BMI 18.5-24.9
- Overweight: BMI 25-29.9
- Obesity Class I: BMI 30-34.9
- Obesity Class II: BMI 35-39.9
- Severe Obesity Class III: BMI ≥ 40

b *Waist Circumference:* Assesses abdominal obesity. Cut-off values:

- Low risk: < 94 cm
- High risk: 94-102 cm
- Very high risk: > 102 cm [26, 27]

c *Body Fat Percentage:* Provides a more accurate measure of obesity. General adiposity is defined as ≥ 25% body fat [28]. Methods include DEXA, bioelectrical impedance, and skinfold thickness measurements.

d *Waist-to-Hip Ratio (WHR):* Measures fat distribution. Central obesity is indicated by WHR ≥ 0.85. Categories:

- Healthy Range: Men ≤ 0.90, Women ≤ 0.85
- Increased Risk: Men > 0.90, Women > 0.85 [29]

e *Health Risks and Comorbidities:* Includes cardiovascular disease, diabetes, and sleep apnea [30].
f *Lifestyle Factors:* Evaluates dietary habits, physical activity, and sedentary behavior [31, 32].
g *Psychosocial Impact:* Assesses effects on self-esteem, quality of life, and stigma.

Polypharmacy

Polypharmacy is defined as the concurrent use of five or more medications. It can lead to drug interactions, adverse effects, and complicate health management [33]. Monitoring and assessing the total number of medications a person uses is essential in clinical practice. Polypharmacy occurs when an individual takes five or more medications simultaneously.

Depression

Depression is a complex mental health condition affecting millions, including people living with HIV [6, 34] It involves emotional, cognitive, and physical symptoms and requires thorough assessment for proper intervention. Key components include:

i. *Symptoms Assessment*: Evaluating persistent sadness, anhedonia, changes in appetite or weight, sleep disturbances, fatigue, and feelings of worthlessness or guilt. Severity is assessed using standardized scales (e.g., PHQ-9, Beck Depression Inventory) [35].
ii. *Duration and Persistence*: Symptoms typically last at least two weeks and may be persistent or recurrent.
iii. *Functional Impairment*: Assessing impact on daily functioning, including work, relationships, and self-care.
iv. *Psychosocial Impact*: Evaluating emotional and social consequences, such as withdrawal from activities and relationships.
v. *Diagnostic Criteria*: Applying established criteria (e.g., DSM-5) for diagnosing major depressive disorder (MDD).
vi. *Comorbidity*: Considering the presence of other mental health conditions (e.g., anxiety, substance use disorders).
vii. *Severity Grading*: Classifying severity (e.g., mild, moderate, severe) based on symptom intensity and functional impairment.

Multimorbidity

Multimorbidity refers to the presence of two or more concurrent health conditions in an individual [36]. These conditions can be chronic, acute, or a combination of both. Key components include:

i. Types of Comorbidities:

- *Physical-Physical*: Coexistence of multiple physical health conditions (e.g., diabetes and hypertension).
- *Physical-Mental*: Simultaneous presence of physical and mental health conditions (e.g., depression and heart disease).
- *Mental-Mental*: Presence of multiple mental health conditions (e.g., anxiety and substance use disorder).

ii. Impact:

- *Health Outcomes*: Comorbidities often worsen health outcomes and lead to more severe symptoms and complications.
- *Treatment*: Treatment decisions must consider interactions between conditions and potential side effects.

Cannabis use

Cannabis is a psychoactive substance used for recreational or medicinal purposes [37]. The extent to which it constitutes a risk for falls may vary depending one or more of the following: frequency and duration of use, mode of consumption and purpose of consumption [37]. Neurocognitive-Adverse Effects (NCAE) Drugs: Identify medications known to cause neurocognitive adverse effects, which can include drugs for pain management, psychiatric disorders, or chronic illnesses associated with HIV [38].

Hypertension

Hypertension is defined by persistently elevated blood pressure, typically with systolic $\geq$ 140 mm Hg and/or diastolic $\geq$ 90 mm Hg [39]. It is a major risk factor for cardiovascular diseases and requires regular monitoring and management. Hypertension is accurately diagnosed based on blood pressure measurements, and classified into stages (e.g., stage 1 or stage 2) to guide treatment decisions [40].

Cognitive Impairment

Refers to decline in cognitive abilities, including memory loss and impaired decision-making, due to aging, neurological conditions, or other health issues [41]. Early detection and intervention are crucial.

Stavudine

Stavudine (d4T), an antiretroviral medication used in HIV/AIDS treatment, belongs to nucleoside analog reverse-transcriptase inhibitors (NRTIs) [42]. It is used in combination with other antiretrovirals for treatment.

Sources of information

The databases searched included: Medline, PubMed, AMED, CINAHL, PsycINFO and SCOPUS from 1966 to April 2024. A draft PubMed search strategy developed and pilot-tested is attached (Appendix A).

Search strategy

The search strategy was crafted using a combination of medical subject headings (MeSH) and keywords. Boolean operators "AND" and "OR" were used to combine terms relevant to each concept:

i. Concept 1: HIV positive patients, HIV-1, HIV Infections, people living with HIV, HIV seropositive patients
ii. Concept 2: Motor dysfunction, balance impairment, postural instability, balance disorders, unsteadiness, vertigo, gait disturbances
iii. Concept 3: Accidental falls, slip, stumble, topple

The search terms for each concept were combined with "OR," and the concepts were combined using "AND." The search was restricted to papers published from June 1983 to January 2024. Additionally, reference lists of identified documents were manually reviewed to find further relevant studies, which were then subjected to the same screening process as the initial papers.

Data management

Duplicate results were removed from the literature search and managed using EndNote 20. Titles and abstracts were screened after duplicates were eliminated. Articles were included and excluded based on predefined criteria, and data was organized in EndNote 20 to create the PRISMA flow chart and for in-text citations.

Study selection and data extraction

The principal investigator (SCI) and EOO initially screened titles and abstracts, resolving discrepancies through discussion. EOO's training was overseen by SCI. Data extraction was performed by EOO and verified by MN. Discrepancies were resolved through discussion between EOO and MN. Full-text authors were not contacted as all required information was available in the texts. The PRISMA diagram detailed the research flow and reasons for exclusion.

Data items

Primary data included predictors of falls and their estimations (odds ratios or event proportions for OR calculation). Derived data comprised risk responsiveness, weight, and critical risk points. Clinically minimum important differences (CMID) were defined as a 50% or greater increase in risk. Secondary data encompassed study characteristics such as location, design, and sample size.

Assessment of risk of bias

The quality of included studies was assessed independently using Mixed method appraisal tool (MMAT) Version 2011 [43]. Risk of bias was categorized as low (80–100% quality score), moderate (40–60% quality score), or high (below 40% quality score). This assessment aimed to validate findings and inform stakeholders for effective treatment strategies in people living with HIV.

Evidence statement and quality assessment

Each evidence statement underwent rigorous quality rating:

a. *High Quality*: Implies that further research is unlikely to alter effect estimates.
b. *Moderate Quality*: Suggests that additional research could significantly impact effect estimates.
c. *Low Quality*: Indicates that further research is very likely to alter or significantly change the estimate.

The study's grade of evidence was determined using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [44].

1. Risk of Bias:
   Risk of bias was assessed using MMAT. According to Guyatt et al. [45], substantial concerns about bias could lead to downgrading certainty by one level for high risk and by two levels for moderate risk.
2. Inconsistency:
   Inconsistency reflects variation in study results' treatment effects [46]. Higher I^2 values indicate greater inconsistency (e.g., < 40% low, 30-60% moderate, 50-90% substantial, 75-100% significant) [47]. Evidence was downgraded by one level in the presence of significant heterogeneity.
3. Indirectness:
   Indirectness arises from differences in patients, interventions, comparisons, or outcomes compared to

available evidence. Significant differences may lead to downgrading evidence certainty by one level [48].

4. Imprecision:
   Imprecision results from small sample sizes, few events observed, or wide confidence intervals. A study is deemed imprecise if confidence intervals exceed thresholds or fail to reach optimal information size. Relative risks of 0.75 and 1.25 serve as rough benchmarks for assessing result precision [49].
5. Publication Bias:
   Publication bias occurs when studies are selectively reported in literature, potentially biasing systematic reviews or guidelines. Its presence may downgrade evidence quality by one level [50].
6. Risk Estimate:
   Relative risk measures, such as odds ratios, were used in this study to assess effects. Evidence quality was upgraded by one level for at least a two-fold risk reduction or increase, and by two levels for at least a five-fold change [51].

Rating quality of evidence and strength of recommendation

Assessment of evidence strength

We evaluated recommendation strength using the GRADE approach [52–56] , which considers study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Process

Two independent reviewers (SCI and EOO) assessed evidence for each identified risk factor. To ensure objectivity, both reviewers applied GRADE criteria independently. Disagreements were resolved through discussion and consensus.

GRADE criteria and evidence grading

Evidence was categorized as:

- *High (++++):* Further research is very unlikely to change confidence in the effect estimate.
- *Moderate (+++):* Further research may have an important impact on confidence in the effect estimate and could alter it.
- *Low (++):* Further research is likely to significantly impact confidence in the effect estimate and is likely to change it.
- *Very Low (+):* Estimates are very uncertain.

Tools and software

We used GRADEpro software to streamline the assessment and ensure thorough documentation and presentation of the evidence. This tool facilitated a systematic and transparent evaluation process. By applying the GRADE methodology, we aimed to provide a robust and transparent assessment of the strength of evidence for each risk factor, enhancing the reliability and credibility of our conclusions.

Summary of findings

A Summary of Findings (SoF) table was prepared to summarize evidence for each outcome, considering risk of bias, indirectness, imprecision, and publication bias, alongside relative risk or odds ratio and evidence strength.

Application of SoF in the systematic review

The SoF table was used to succinctly summarize evidence in the systematic review:

i. *Identification of Outcomes:* Outcomes were selected based on research objectives.
ii. *Study Selection:* Studies reporting on selected outcomes were included.
iii. *Risk of Bias Assessment:* MMAT assessed bias in each study.
iv. *Indirectness Assessment:* Considered study population, intervention, and outcomes.
v. *Imprecision Assessment:* Evaluated based on sample size and effect size.
vi. *Publication Bias Assessment:* Utilized funnel plots and Egger's test.
vii. *Evidence Grading:* GRADE approach applied for each outcome.
viii. SoF Table Preparation: Summarized evidence, including risk of bias, indirectness, imprecision, publication bias, and effect measures.

Using the SoF table facilitated clear, concise evidence summaries for decision-making and future research guidance.

Data items

Data from included studies are author references, participant characteristics, inclusion/exclusion criteria, sample size, and outcome measures: Frailty, Neuropathy, CD4+count, Obesity, Polypharmacy, Depression, Comorbidity, Cannabis use, NCAE, Hypertension, Cognitive impairment, and Stavudine use.

Data synthesis and analysis

Initially, we focused on identifying predictors of falls in people living with HIV. Quantitative study results were compiled and compared in an evidence table. Descriptive statistics (mean, standard deviation) characterized

study subjects, and gender distribution was presented as percentages. Predictive factors were assessed using odds ratios (OR), with transformations applied when OR < 1 to ensure consistency [57]. Confidence intervals were calculated using reciprocal transformations (1/OR^2) [57]. Pooled odds ratios, heterogeneity indices (e.g., I^2), and publication bias were analyzed using random-effects meta-analysis. Critical risk points and relative risk weights were identified in the highest quartile. Meta-analysis utilized Statistical Package for the Social Sciences (SPSS) and Comprehensive Meta-Analysis (CMA, version 4), with significance set at $\alpha = 0.05$.

Heterogeneity and sensitivity analysis

We computed the I^2 to assess heterogeneity. The I^2 were interpreted as follows: 0–40%: might not be important; 30–60%: may represent moderate heterogeneity, 50–90%: may represent substantial heterogeneity and 75–100%: considerable heterogeneity [58]. To conduct sensitivity analysis, we removed the outlying studies with significant deviations in odds ratios.

Establishing fall risk metrics in PLWH: a methodological framework

Risk weight and using Clinical Minimum Important Difference (CMID)

In our study, risk weight denotes the relative impact of a specific risk factor on predicting falls in people living with HIV. It quantifies the strength of a risk factor's contribution to the occurrence of the outcome. A higher risk weight indicates a stronger association with the outcome. We determined critical risk points for fall predictors using principles from Bradford Hill's criteria [59, 60], Rothman's sufficient cause model [61, 62], and Nweke's viewpoints [63, 64]. We defined a clinically significant difference as a 50% change in the strength of association (odds ratio, OR) between predictors and falls.

Calculation of risk responsiveness We assessed the consistency of association across studies using risk responsiveness (Ri). This measure is calculated as the ratio of the number of studies reporting statistically significant and clinically important associations for a given risk factor (Fs) to the total number of well-controlled studies (ΣF). According to Nweke et al. [5], Ri reflects how consistently a specific factor is identified as a risk factor in the literature:

$$\text{Risk Responsiveness (Ri)} = \frac{\text{Fs}}{\Sigma \text{F}}$$

Calculation of risk weight The risk weight (Rw) also known as Nweke's (N) factor for a factor is calculated by multiplying its strength of association (odds ratio, OR) with its risk responsiveness (Ri) [63, 64]. This approach integrates both the magnitude and consistency of the association. Risk Weight (Rw)= $\text{OR} \times \text{R}_i$

Determination of critical risk point The critical risk point signifies the threshold at which the risk of a specific outcome (e.g., falls in people living with HIV, people living with HIV) becomes significant. It is typically identified as the 76th percentile of risk weights associated with relevant risk factors. This percentile is chosen based on the premise that it represents a sufficient cause for the outcome [5, 65]. The critical risk point guides interventions or preventive measures by identifying levels of risk warranting attention.

Results

Study selection and characteristics

We initially identified 1,600 records. After removing duplicates and screening titles and abstracts, 22 records underwent full-text review. Ten publications were subsequently excluded, resulting in 12 articles included in our review. These comprised 1 case-control study, 2 longitudinal studies, 1 cross-sectional study, and 8 cohort studies, involving a total of 117,638 participants, with 54,513 being people living with HIV. The majority of studies (75%) were conducted in the United States, with one study (8.3%) in Indonesia and two (16.7%) multisite studies. Eleven studies (91.7%) investigated falls, while one examined balance dysfunction, and was excluded from the meta-analysis due to insufficient data (Fig. 1).

Most studies [8, 13, 66–71] focused on individuals aged approximately 45–50 years. Study durations ranged from 6 months [7, 68] to 15 years [72]. Sample sizes varied widely, with the smallest study including 32 participants [71] and the largest 26,373 [72]. Female representation varied significantly, from 0% [72] to 100% [68, 69]. Attrition rates ranged from 1.3% [73] to 48.8% [13], though many studies did not report attrition rates. Definitions of falls varied from self-reported histories [8, 13, 66, 68, 69, 71, 73] to real-time reporting [67, 70, 72, 74].

Participants of included studies

This review involved 112,676 participants aged 45–50 years, with participant numbers ranging from 32 [71] to 80,590 [72] across the studies. Regarding disease stage, the lowest current CD4 + count reported was 347.2 cells/mm^3 [71], while the highest was ≥ 500 cells/μL [72, 73]. Nadir CD4 + counts ranged from 71.5 cells/mm^3 [7] to < 200 cells/μL [72, 74]. Viral loads varied from undetectable in some studies [8, 73] to a mean of 31,379 copies/ml [69]. Most of the study participants (84.8%) were receiving antiretroviral therapy (ART) [7, 8, 13, 66, 67, 69–74].

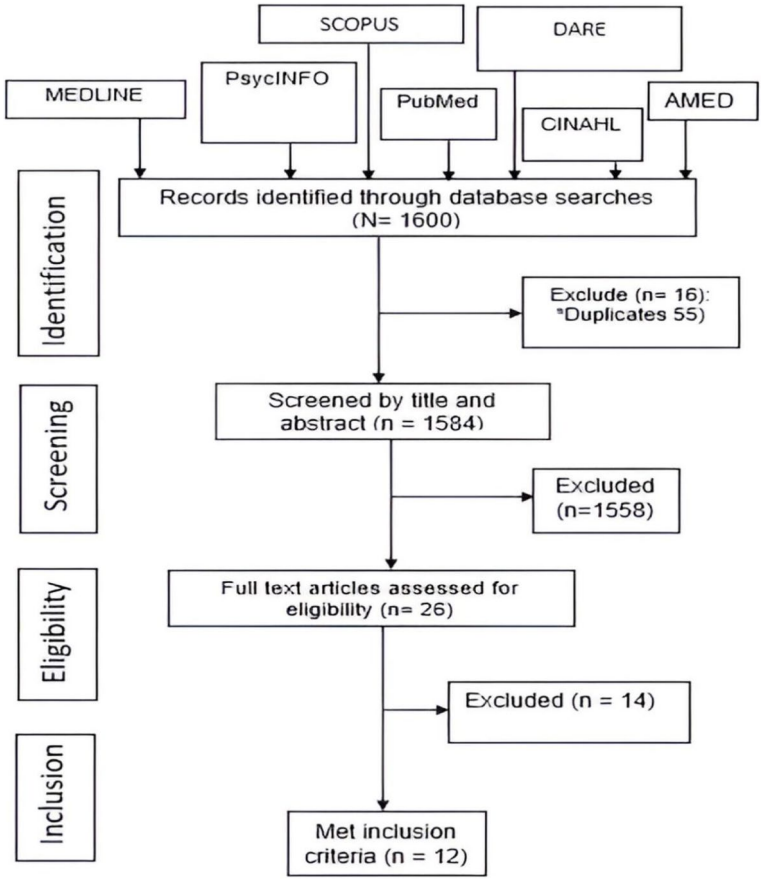


Fig. 1 PRISMA flow diagram for a systematic review of predictors of falls in people living with HIV

Assessment of risk of bias

Outcome measurement diversity in studies analyzing balance dysfunction and falls in PLWH

Our systematic review of twelve studies revealed significant variability in assessing balance dysfunction and falls in people living with HIV, affecting the consistency of findings. Five studies [7, 8, 65–67] investigated polypharmacy as a predictor of falls. Three of these studies [7, 8, 66] did not classify the types of falls. Psomas et al. [67] included patients with both single and multiple falls, while Erlandson et al. [71] focused on single, injurious, and multiple falls. Chronic distal sensory polyneuropathy (cDSPN) was identified by Sakabumi et al. [66] as a predictor of balance dysfunction in people living with HIV. Different measurement tools were used across studies: Wahyudi et al. [7] employed the Jamar Hydraulic Hand Dynamometer, Sharma et al. [13] used a handheld dynamometer, and Erlandson et al. [8] utilized the Lafayette dynamometer. Sharma et al. [16] and Erlandson et al. [73] identified several predictors of falls, including behavioral factors, comorbidities, obesity, and clinical imbalance. This heterogeneity in outcome measurement, arising from different assessment tools and specific outcomes evaluated, complicates the comparison of findings and may affect the reliability and validity of the systematic review's conclusions. We observed a wide range of approaches to assessing balance dysfunction and falls in people living with HIV. This diversity in outcome measurement could impact the consistency of findings across studies.

Quality of the included studies

Table 2 summarizes the risk of bias assessment for each of the included studies using the GRADE tool. Further details are provided below:

1. *Research Objective Clearly Stated:* All twelve included studies [7, 8, 13, 59–67] explicitly stated their research objectives, minimizing bias related to objective clarity.

2. *Study Population Clearly Specified and Defined:* Eleven studies (91.67 %) [7, 8, 13, 66–74] clearly specified and defined their study populations, resulting in a low risk of bias.
3. *Participation Rate of Eligible Persons at Least 50 %:* Eleven studies (91.67 %) [7, 8, 13, 66–70, 72–74] achieved a participation rate of at least 50 % among eligible persons, minimizing bias related to recruitment.
4. *Population Uniformity in Recruitment and Eligibility Criteria:* Only four studies [8, 63–65] (33.33 %) recruited all subjects from similar populations with uniformly applied eligibility criteria. The majority of studies (eight or 66.67 %) [7, 13, 66–69, 73, 74] did not adhere to this practice, posing a high risk of bias.
5. *Sample Size Justification:* Only one study [7] (8.33 %) justified its sample size, while the majority (eleven out of twelve studies, 91.67 %) [8, 13, 66–74] lacked such justification, indicating a high risk of bias.
6. *Exposure Measurement Timing:* Half of the included studies (50 %) [7, 13, 67, 68, 70] measured exposure prior to the outcome, contributing to a moderate risk of bias.
7. *Adequate Time Frame for Exposure-Outcome Association:* Ten studies [8, 13, 67–74] (83.33 %) had a sufficient time frame to observe associations between exposure and outcome, minimizing bias. However, two studies (16.67 %) did not meet this criterion.
8. *Different Levels of Exposure Measured:* All twelve included studies [7, 8, 13, 59–67] measured different levels of exposure related to the outcome, indicating a low risk of bias.
9. *Clear and Consistent Exposure Measures:* Nine studies [7, 8, 13, 66, 69–72, 74] (75 %) had clearly defined, valid, and reliable exposure measures, reducing bias. However, three studies (25 %) [67, 68, 73] lacked consistency in implementing these measures.
10. *Longitudinal Assessment of Exposure:* Eight studies [13, 66–70, 72, 74] (66.67 %) assessed exposure more than once over time, indicating a low risk of bias. However, four studies [7, 8, 71, 73] (33.33 %) did not follow this practice.

Overall summary

Among the included studies, eleven [7, 8, 13, 66–70, 72–74] demonstrate higher methodological quality, adhering to rigorous standards. However, the study by Ruiz et al. [71] has limitations related to population specification and exposure measurement.

Association between risk factors and falls in people living with HIV

The meta-analysis explored predictors of falls in people living with HIV. While some risk factors showed significant associations, others did not. Further context and specific findings would enhance understanding and are presented below:

Predictors with significant association with falls

Significant associations were found between certain factors and the risk of falls, including.

i. Cannabis Use:
Cannabis use was significantly associated. with an increased risk of falls (OR: 2.54, 95 % CI: 1.79, 3.61). Strong evidence (Fig. 2) against the null hypothesis was supported by a Z-value of 5.20 (p=0.0001) with no heterogeneity (I^2 = 0.00 %). This finding was based on two high-quality prospective cohort studies [13, 73]. (Table 1) involving 3926 participants (Table 2).
ii. Depression symptoms:
Depressive symptoms were significantly associated with an increased risk of falls (OR: 1.63, 95 % CI: 1.22, 2.18). This finding is supported by strong evidence against the null hypothesis, indicated by a Z-value of 3.62 (p=0.001), with no heterogeneity (I^2 = 0.00 %) (Fig. 3). The association was observed in two studies [7, 62] involving 1,966 participants (Table 2), employing different study designs (prospective cross-sectional and prospective cohort). One high-quality study [62] supports the association, while another [7] found no link.
iii. Hypertension:
Hypertension was significantly associated with an increased risk of falls (OR: 1.76, 95 % CI: 1.33, 2.33). This finding is supported by strong evidence against the null hypothesis, with a Z-value of 3.93 (p=0.0001), with no heterogeneity (I^2 = 0.00 %) (Fig. 4). The association was observed in two high-quality prospective cohort studies (Table 1) [13, 66] involving 5,437 participants (Table 2).
iv. Cognitive impairments:
Cognitive impairments were significantly associated with an increased risk of falls (OR: 2.31, 95 % CI: 1.66, 3.21). This finding is supported by strong evidence against the null hypothesis, with a Z-value of 5.00 (p=0.0001), and no heterogeneity (I^2 = 0.00 %) (Fig. 5). The association was observed in two studies

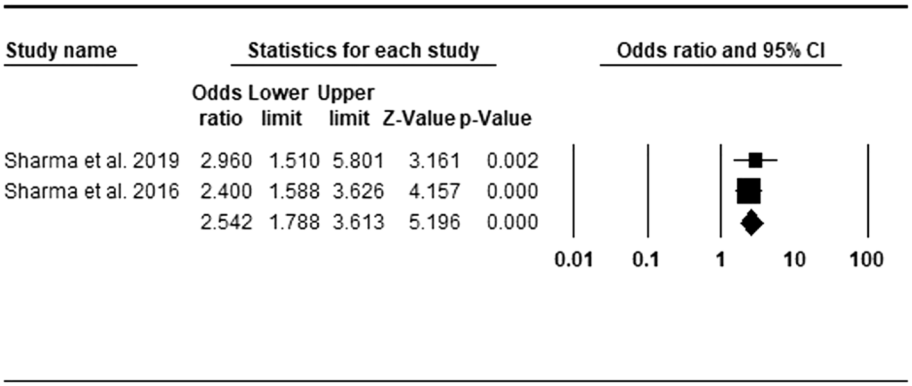


Fig. 2 Association between cannabis use and falls in people living with HIV

[7, 71] involving 1,966 participants (Table 2), utilizing different prospective cross-sectional and prospective cohort study designs (Table 1). Both studies were of high quality and consistently supported the association.

v. Polypharmacy:
Polypharmacy was significantly associated with an increased risk of falls (OR: 1.50, 95 % CI: 1.16, 1.96). This finding is supported by strong evidence against the null hypothesis, with a Z-value of 3.03 (p=0.002), despite high heterogeneity ($I^2 = 89.36$ %) (Fig. 6). The association was observed in five studies [7, 8, 67, 69, 73] involving 4,447 participants (Table 2), utilizing various study designs including prospective cross-sectional, longitudinal, retrospective cohort, prospective case-control, and prospective cohort (Table 1). While several high-quality studies support this association [8, 67, 69, 73], one study did not find a link [7].

vi. The primary meta-analysis (Fig. 7). investigated the association between neuropathy and falls risk in PLWH, revealing an odds ratio of 1.628 (; 95% CI = 1.259, 2.105; Z = 3.714; p = 0.000; I2 = 0.00 %, 3 studies; 4028.participants), indicating a higher likelihood of falls with neuropathy among PLWH. The Z value suggests stronger evidence against the null hypothesis, and the narrower confidence interval (1.259 to 2.105) and significant p-value further support this association. Two high-quality studies [13, 62] supported the association, while one high-quality study [7] (Table 2) found no link. Notably, the studies utilized different research designs (prospective cross-sectional, and prospective cohort) (Table 1) to explore this relationship.

Table 2 Risk of bias assessment

Study	Domains					Score
	Sampling strategy relevant?	Is the sample representative?	Measurements appropriate?	Is the risk of nonresponse bias low?	Statistical analysis appropriate?	
Sakabumi et al. 2019 [65]	Yes	No	Yes	Yes	Yes	3: Moderate Risk
Ruiz et al. 2013 [70]	No	No	Yes	Yes	Yes	3: Moderate Risk
Womack et al. 2019 [69]	Yes	No	Yes	Yes	Yes	4: Low risk
Sharma et al. 2019 [14]	Yes	No	Yes	Yes	Yes	4: Low risk
Womack et al. 2019 [69]	Yes	No	Yes	Yes	Yes	4: Low risk
Wahyudi et al. 2022 [7]	Yes	No	Yes	Yes	Yes	4: Low risk
Sharma et al. 2016 [67]	Yes	No	Yes	Yes	Yes	4: Low risk
Kim et al. 2018 [66]	Yes	No	Yes	Yes	Yes	4: Low risk
Erlandson et al. 2016 [72]	Yes	Yes	Yes	Yes	Yes	5: Low risk
Erlandson et al. 2019 [73]	Yes	Yes	Yes	Yes	Yes	5: Low risk
Psoma et al. 2022 [68]	Yes	No	Yes	Yes	Yes	4: Low risk
Womack et al. 2021 [71]	Yes	No	Yes	Yes	Yes	4: Low risk

Table 1 Characteristics of the studies included in the review

Authors	Design	Method of data collection	Outcome predicted	Sample size	Country	Region
Wahyudi et al. 2022 [7]	Cross-sectional	Prospective	Falls	102	Indonesia	Southeast Asia
Sharma et al. 2016 [67]	Cohort	Prospective	Falls	2062	United States	North America
Sharma et al. 2019 [14]	Cohort	Prospective	Falls	1864	United States	North America
Erlandson et al. 2012 [8]	Cohort	Retrospective	Falls	359	United States	North America
Sakabumi et al. 2019 [65]	Cohort	Prospective	Balance dysfunction	3375	United States	North America
Erlandson et al. 2016 [72]	Cohort	Retrospective	Falls	536	United States	North America
Erlandson et al. 2019 [73]	Longitudinal	Prospective	Falls	221	United States	North America
Psoma et al. 2022 [68]	Case control	Prospective	Falls	1872	United States	North America
Womack et al. 2019 [69]	Cohort	Prospective	Falls	80,590	Different countries	Different regions
Womack et al. 2021 [71]	Cohort	Prospective	Falls	26,373	Different Countries	Different regions
Ruiz et al. 2013 [70]	Cohort	Retrospective	Falls	32	United States	North America
Kim et al. 2018 [66]	longitudinal	Prospective	Falls	250	United States	North America

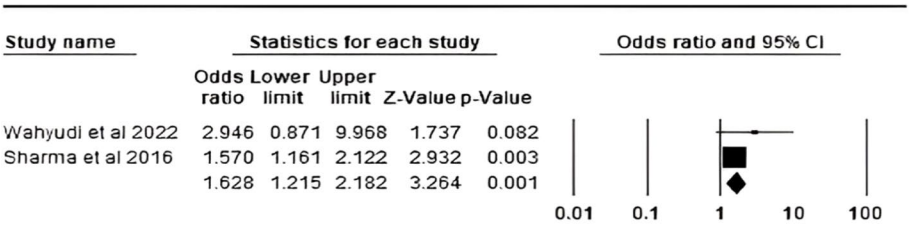


Fig. 3 Association between symptoms of depression and falls inpeople living with HIV

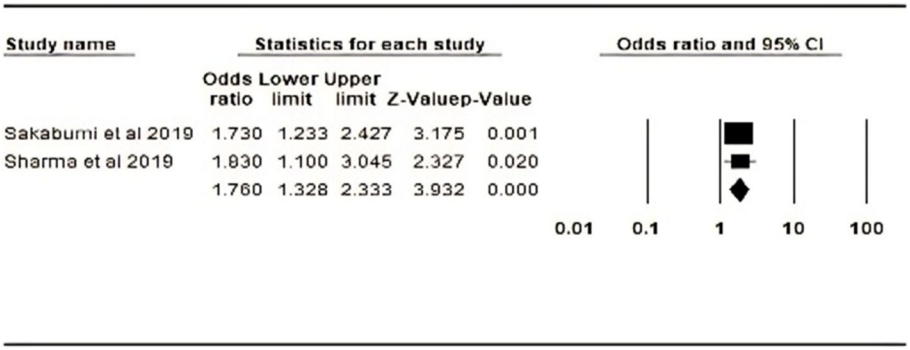


Fig. 4 Association between hypertension and risks of falls in people living with HIV

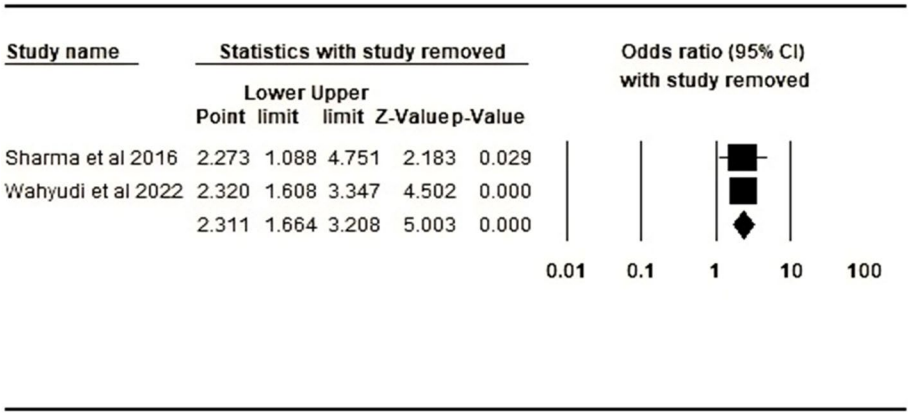


Fig. 5 Association between cognitive impairment and falls in people living with HIV

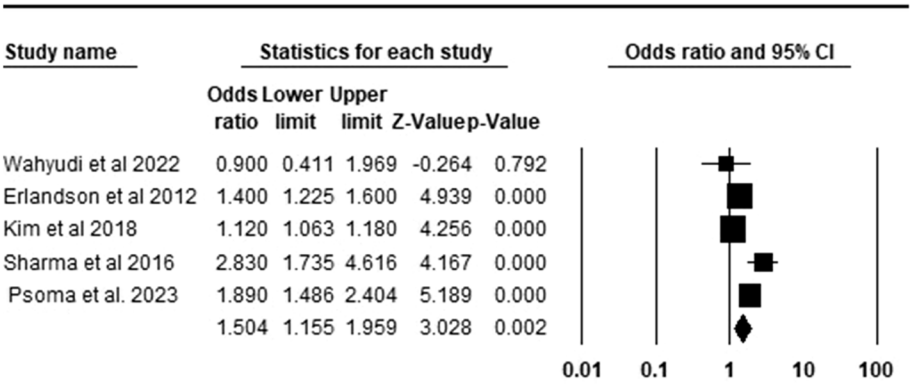


Fig. 6 Association between polypharmacy and falls in people living with HIV

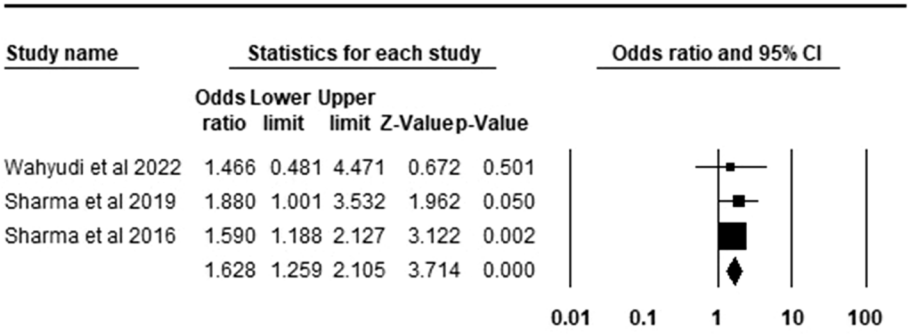


Fig. 7 Association between neuropathy and falls in people living with HIV

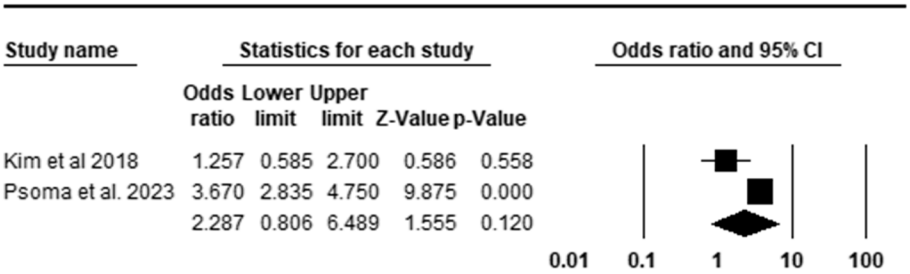


Fig. 8 Association between NCAE and falls in people living with HIV

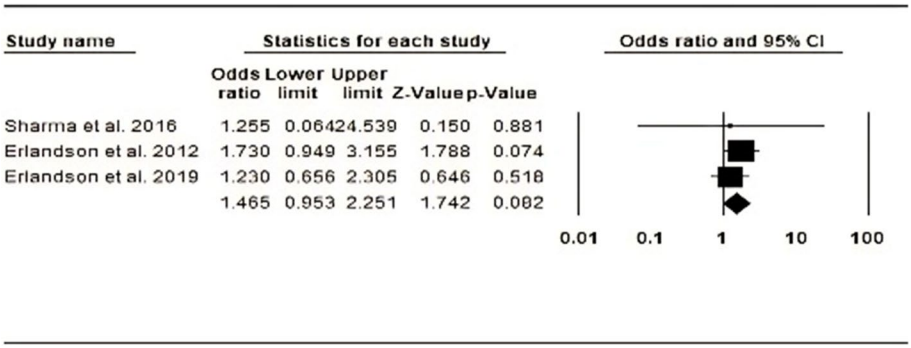


Fig. 9 Association between stavudine use and falls in people living with HIV

Predictors with no significant association with falls

Several factors showed non-significant associations with falls risk including:

vii. NCAE drugs:
The use of NCAE drugs was associated with a higher likelihood of falls among people living with HIV. The odds ratio (OR) was 2.29 (95 % CI: 0.81–6.49). A substantial heterogeneity was observed (I^2 = 85.24 %) (Fig. 8). This analysis included two studies [66, 67], using prospective case-control and prospective longitudinal designs (Table 1) with 2122 participants (Table 2). One study [66], supported the association, while one [67], found no link between use of NCAE and falls.

viii. Stavudine:
There was no significant association between stavudine and falls among people living with HIV with an odds ratio (OR) of 1.47 (95 % CI: 0.95–2.25). There was no substantial heterogeneity (I^2 = 0.00 %) (Fig. 9). This analysis included three studies with a total of 2621 participants, employing both prospective and retrospective cohort designs (Table 1). Two high-quality studies [8, 73] and one moderate-quality study [72] found no significant association between stavudine use and falls.

ix. Frailty:
Frailty is associated with a higher likelihood of falls among people living with HIV, with an odds ratio (OR) of 3.23 (95 % CI: 0.73–14.40). However, the wide confidence interval, non-significant Z-value (1.538), indicate that this result is not statistically significant (Fig. 10). This analysis included three studies with a total of 2523 participants, using prospective cross-sectional, retrospective cohort, and prospective cohort designs (Table 1). One high-quality study [8] supported the association, while two studies [7, 13] found no significant link.

x. CD4+ count:
The association between CD4+ count and falls risk among people living with HIV was non-significant, with an odds ratio (OR) of 1.01 (95 % CI: 0.84–1.20), a Z-value of 0.06) (Fig. 11). The wide confidence interval and non-significant *p*-value prevent a confident conclusion of statistical significance. This analysis included three studies with a total of

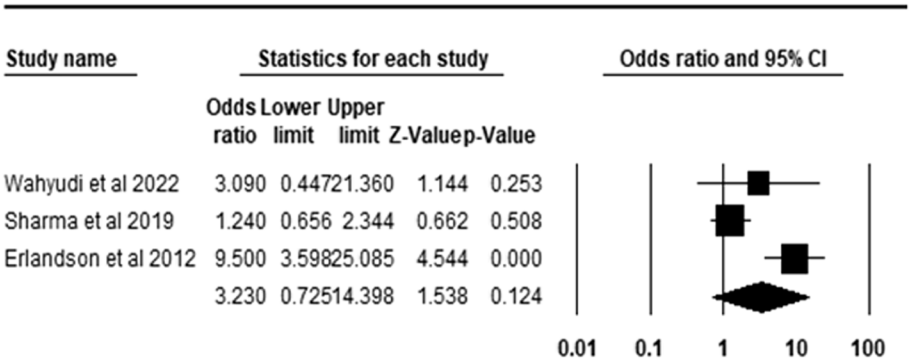


Fig. 10 Association between frailty and falls in people living with HIV

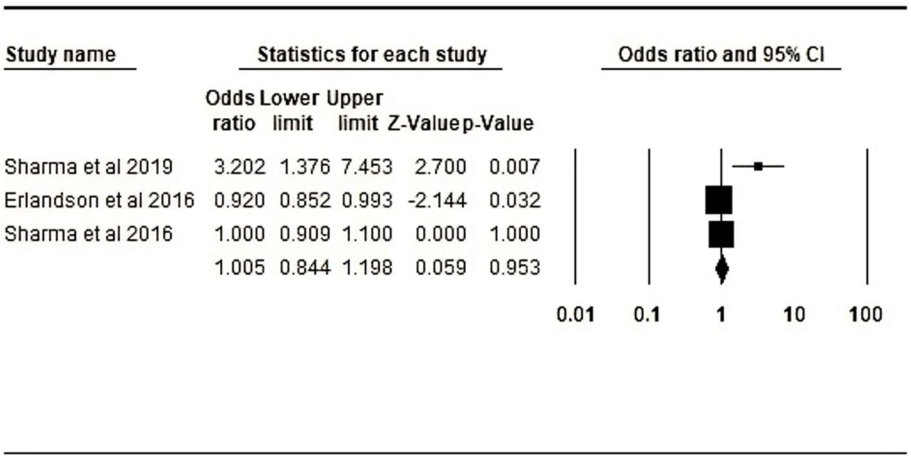


Fig. 11 Association between CD4+ count and falls in people living with HIV

4462 participants, using prospective cohort and retrospective cohort designs (Table 1). One high-quality study [13] and one moderate-quality study [68] supported the association, while another high-quality study [73] found no significant link.

xi. Multimorbidity:
Multimorbidity is associated with a higher likelihood of falls among people living with HIV, with an odds ratio (OR) of 1.42 (95 % CI: 0.83–2.43). However, the Z-value of 1.29 and a *p*-value of 0.196 indicate that this result is not statistically significant. The moderate heterogeneity ($I^2 = 52.68$ %) (Fig. 12) also suggests variability in the study outcomes. This analysis included two studies with a total of 461 participants, using prospective cross-sectional and retrospective cohort designs (Table 1). One high-quality study [7] and one moderate-quality study [68] found no significant link between comorbidity and falls.

xii. Obesity:
Obesity shows a non-significant association with falls risk among people living with HIV, with an odds ratio (OR) of 1.32 (95 % CI: 0.92–1.88). The Z-value of 1.52 suggests insufficient evidence to conclude a significant association (Fig. 13). This analysis included three studies with a total of 4462 participants, using prospective cohort and retrospective cohort designs (Table 1). Two high-quality studies supported the association [13, 68], while one study [71] found no significant link between obesity and falls.

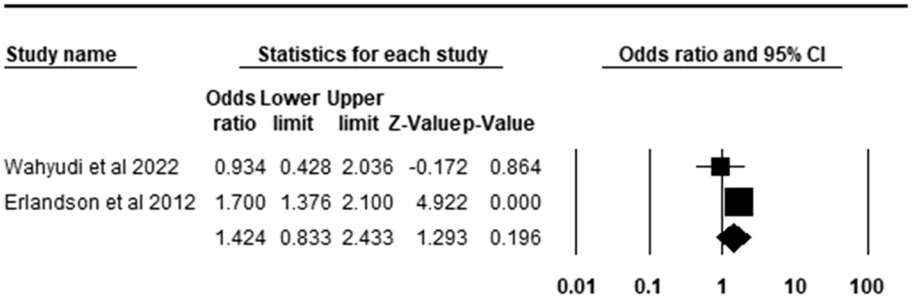


Fig. 12 Association between having a comorbidity and falls in people living with HIV

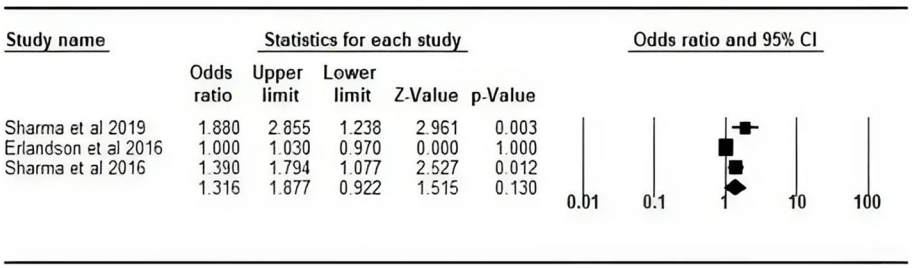


Fig. 13 Association between Obesity and falls in people living with HIV

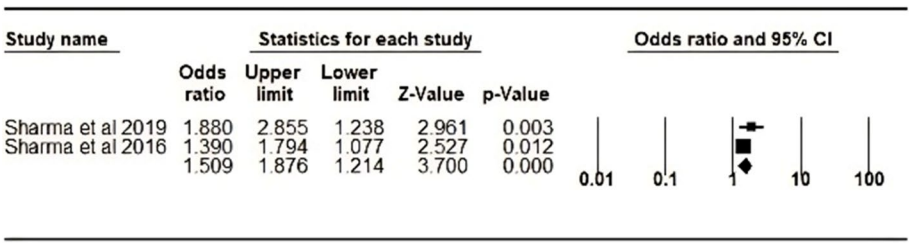


Fig. 14 Association between Obesity and falls in people living with HIV

Sensitivity analysis

A sensitivity analysis was conducted to assess the robustness of the primary meta-analysis results and to explore sources of heterogeneity. Outlying studies with significant deviations in odds ratios were excluded from the analysis. The results of the sensitivity analysis are summarized below:

Obesity

The sensitivity analysis revealed that excluding Erlandson et al. [73] reduced heterogeneity substantially, from 86.58 to 31.53% (Q = 1.460, $p = 0.227$) indicating non-significant heterogeneity. As a result, the meta-analysis showed a statistically significant association between obesity and falls among people living with HIV (OR = 1.51, $p = 0.0001$) (Fig. 14). This highlights the influence of Erlandson et al. [73] on the variability observed in the primary meta-analysis. The non-significant association reported by Erlandson may not be unconnected to the retrospective data collection method and relatively small sample size, compared with Sharma et al. [66] and Sharma et al. [13].

Frailty

The inclusion of Sharma et al. [13] with its large sample size significantly influenced heterogeneity in the

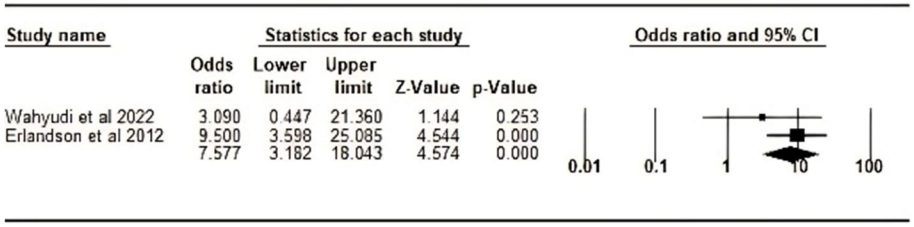


Fig. 15 Association between frailty and falls in people living with HIV

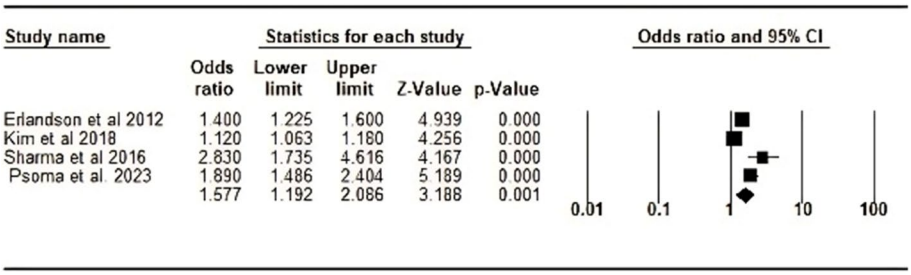


Fig. 16 Association between polypharmacy and falls inpeople living with HIV

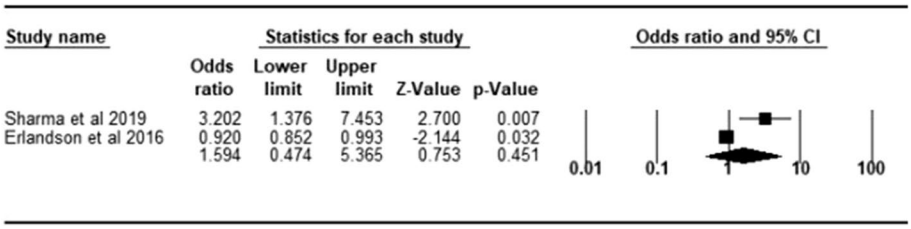


Fig. 17 Association between CD4+ *Count* and falls inpeople living with HIV

meta-analysis for frailty as a risk factor for falls. Excluding this study reduced the I^2 value from 83.20 to 3.40% and the Q statistic to 1.04 ($p=0.31$, indicating non-significant heterogeneity (Fig. 15). The odds ratio increased to 7.57 (95% CI: 3.18–18.03), reinforcing a stronger, significant association. This suggests that Sharma et al.'s methodology or population notably impacted the overall analysis. Unlike Wahyudi et al. [17] a cross-sectional study with sample size of 102, and Erlandson et al. [8], a retrospective cohort with samples size 359, Sharma et al. [13] was a prospective cohort with a sample size well above 1864.

Polypharmacy

Excluding Wahyudi et al. [7] from the meta-analysis increased heterogeneity substantially (I^2 = 91.92%; Q=37.118, $p<0.001$) (Fig. 16). The significant Q statistic indicates remaining heterogeneity is beyond chance. This change highlighted a significant association between polypharmacy and falls (OR=1.58, $p=0.001$). The study by Wahyudi et al. likely contributed to the observed variability due to its unique study design, sample size, and geographic location. Specifically, unlike the rest of the study, Wahyudi et al. [7] utilized a cross-sectional design and employed 102 participants and was conducted in Southeast Asia.

CD4 + count

In a sensitivity analysis examining CD4 + count's impact on falls in people living with HIV, excluding Sharma et al. [66] increased heterogeneity substantially (I^2 = 87.96%; Q=8.305, $p=0.004$) (Fig. 17). The meta-analysis then showed a non-significant trend towards higher fall risk with higher CD4 + counts (OR=1.59, $p=0.45$). Although Sharma et al. [68] contributed to the observed variability, it shares similar characteristics as Sharma et a [13]. in being both North American studies, utilized prospective design and employed sample of middle-aged women, Sharma [68] utilized fewer samples (1864) compared to Sharma et al. [13].

Factors contributing to heterogeneity in study outcomes

The heterogeneity observed in the studies presented in Table 1 can be attributed to several factors inherent to their methodologies and contexts.

Study design variability

The studies included in Table 1 employ diverse approaches, including cross-sectional [7, 64], cohort [8, 13, 68, 70–74], case-control [69], and longitudinal [67] designs. Each design introduces unique biases or confounding factors due to differences in data collection methods, follow-up durations, and control of variables, contributing to heterogeneity in study outcomes.

Geographic factors

Studies vary significantly by geographical location, encompassing both high-income countries and low-income countries, contributing to diverse contexts in the study of falls and balance dysfunction [7, 8, 13, 66–74]. Geographic variation plays a crucial role, with studies originating from diverse regions like the United States and Indonesia.

Sample size variation

There is considerable variation in sample sizes across studies (ranging from 32 to 80,590 participants), which contributes to heterogeneity [69, 70]. Larger sample sizes [13, 66, 68–70, 72, 73] generally offer greater statistical power to detect effects, influencing the precision and variability of study outcomes.

Outcome measurement diversity

Variability in outcome measurement is a critical factor influencing heterogeneity in the included studies. Differences in outcome definitions, assessment tools, and measurement methods among studies can impact the consistency of findings. For example, some studies focused on predicting outcomes such as falls or balance dysfunction, each with its own set of measurement challenges and implications for study outcomes. Five studies [7, 8, 67–69] examined polypharmacy as a predictor of falls. Three studies did not classify fall types, while Psomas et al. [69] included both single and multiple falls, and Erlandson et al. [73] focused on single, injurious, and multiple falls. Sakabumi et al. [66] identified chronic distal sensory polyneuropathy (cDSPN) as a predictor of balance dysfunction. Various tools were used, including the Jamar Hydraulic Hand Dynamometer [7], a hand-held dynamometer [13], and the Lafayette dynamometer [8].

Sampling strategies and representativeness

Disparities in sampling strategies and representativeness of the target population are evident among the studies. Studies with rigorous sampling methodologies and high representativeness [8, 66] tend to yield more generalizable findings, whereas studies with less rigorous approaches [7, 13, 66–74] may introduce biases that contribute to heterogeneity in results.

Risk of nonresponse bias

Moreover, the risk of nonresponse bias varies across studies, influencing the validity and reliability of findings. Studies with low [7, 13, 66–74] or moderate risk [66, 70] of nonresponse bias are likely to provide more accurate estimates of associations, whereas studies with higher risks may introduce uncertainties that contribute to heterogeneity.

Statistical analysis methods

While all the studies demonstrated appropriateness of statistical analysis methods applied across studies which otherwise could lead to variability in results, varied analytical approaches, including differences in adjustment for confounding variables, handling of missing data, or choice of statistical models, can impact the magnitude and direction of observed associations and contribute to heterogeneity. For instance, in studies examining balance dysfunction and falls among people living with HIV, diverse statistical analysis methods were employed: Kim et al. [67] used logistic regression, Erlandson et al. [73] applied PROC LOGISTIC, Wahyudi et al. [7] employed Poisson regression, Sakabumi et al. [66] utilized Fisher's Exact Test, and Sharma et al. [13] employed stepwise logistic regression models. In our review of statistical adjustments in data analysis across studies, we found considerable diversity in the factors considered for adjustment: Wahyudi et al., [7] did not specify the adjustments made. Sharma et al., [13] adjusted for cannabis use and hypertension. Kim et al., [67] accounted for socio-demographics, comorbidities, and behavioral factors. Erlandson et al., [73] adjusted for age, gender, ethnicity, and body mass index. Sharma et al., [68] adjusted for study site and age. Ruiz et al., [71] adjusted for socio-demographics, comorbidities, and HIV-related factors. Erlandson et al., [8] adjusted for age, gender, and CD4+ lymphocyte count. This diversity in statistical analysis and adjustment factors highlights the complexity and variability in controlling potential confounders across studies. The diversity

Table 3 Stratification of predictors of falls in people living with HIV

Predictors	Reference Category	Number of studies	Risk responsiveness	Odds ratio	I^2	Egger's *t*-value; *p* value	Risk weight (*N*-factor)
Frailty	Yes	3	0.67	3.23(0.73–14.40)	83.20	0.59; 0.66	2.16[a]
Neuropathy	Yes	3	0.67	1.68 (1.26–2.11)	0.00	0.26; 0.84	1.13[a]
CD4 + count	< 200 cells/mm^3	3	0.33	1.01 (0.84–1.20)	79.37	3.58; 0.73	0.33
Obesity	Yes	3	0.67	1.32 (0.92–1.88)	86.58	18.46; 0.03*	0.88
Polypharmacy	Yes	5	0.80	1.50 (1.16–1.96)	89.36	0.26; 0.73	1.20[a]
Depression	Yes	2	1.0	1.63 (1.22–2.18)	0.00	NA	1.63[a]
Comorbidity	Yes	2	0.5	1.42 (0.83–2.43)	52.68	NA	0.71
Cannabis use	Yes	2	1.0	2.96 (1.510–5.82)	0.00	NA	2.96[a]
NCAE	Yes	2	1.0	2.287 (0.81–6.49)	85.24	NA	2.29[a]
Hypertension	Yes	2	1.0	1.76 (1.33–2.33)	0.00	NA	1.76[a]
Cognitive impairment	Yes	2	1.0	2.311 (1.66–3.21)	0.00	NA	2.31[a]
Stavudine	Yes	3	1.0	1.465 (0.95–2.25)	0.00	0.17; 0.89	1.47[a]

NCAE Drugs with neurocognitive-adverse effects

[a] Met the clinically importance difference (CMID) defined as increase in risk by at least 50%

Table 4 Predictive model/tool for falls in people living with HIV

Factors	Risk status & assigned score	
Frailty	Yes = 2.0	No = 0
Neuropathy	Yes = 1.1	No = 0
Polypharmacy	Yes = 1.2	No = 0
Depression	Yes = 1.6	No = 0
Cannabis use	Yes = 3.0	No = 0
NCAE	Yes = 2.3	No = 0
Hypertension	Yes = 1.8	No = 0
Cognitive impairment	Yes = 2.3	No = 0
Stavudine use	Yes = 1.5	No = 0
Total possible score	16.8	
Cut-off	Cut-off = 12.8	

NCAE Drugs with neurocognitive-adverse effects

in statistical analysis methods and adjustment factors introduces heterogeneity by influencing how associations are measured, controlled for potential confounders, and interpreted across studies.

Predictors of falls

Predictors of falls

Stratification of predictors of falls and critical risk point In our analysis of 12 predictors included in the meta-analysis (Table 3), CD4 + count (Ri = 0.33) and comorbidity (Ri = 0.5) were classified as clinically non-responsive with Ri values below 0.5 (Table 4). Conversely, depression, cannabis use, NCAE, hypertension, cognitive impairment, and stavudine were identified as the most clinically responsive predictors, each with a perfect risk responsiveness (Ri = 1.0) (Table 4). Cannabis use (Rw = 2.96, Ri = 1.0), cognitive impairment (Rw = 2.29, Ri = 1.0), NCAE (Rw = 2.29, Ri = 1.0), and frailty (Rw = 2.16, Ri = 0.67) emerged as particularly significant predictors for falls (Table 3). We determined the critical risk point to be at the 76th percentile, with a cumulative risk weight of 12.8 (Table 4). Subsequently, we developed a predictive model for falls incorporating frailty, neuropathy, depression, polypharmacy, cannabis use, NCAE, cognitive impairment, and hypertension as constituent factors (Table 4).

Publication bias assessment using egger's test

The publication bias was assessed using Egger's test (Table 3) to evaluate potential bias in meta-analyses of factors associated with falls in people living with HIV. For CD4 + count (Fig. 18; t = 3.58, $p = 0.73$), stavudine (Fig. 19; t = 0.17, $p = 0.89$), polypharmacy (Fig. 20; t = 0.26, $p = 0.84$), frailty (Fig. 21; t = 0.26, $p = 0.84$), and neuropathy (Fig. 22; t = 0.27, $p = 0.84$), no significant publication bias was found, indicating robust and reliable evidence. However, the funnel plot for obesity and falls (Fig. 23) showed asymmetry and significant publication bias (t = 18.46, $p = 0.034$), suggesting caution in interpreting the evidence that found no link between obesity and increased risk of falls in people living with HIV people living with HIV窗体顶端 people living with HIVpeople living with HIV.

Strength of evidence for risk factors associated with falls

Table 5 presents a meta-analysis evaluating risk factors for falls in people living with HIV, categorizing them based

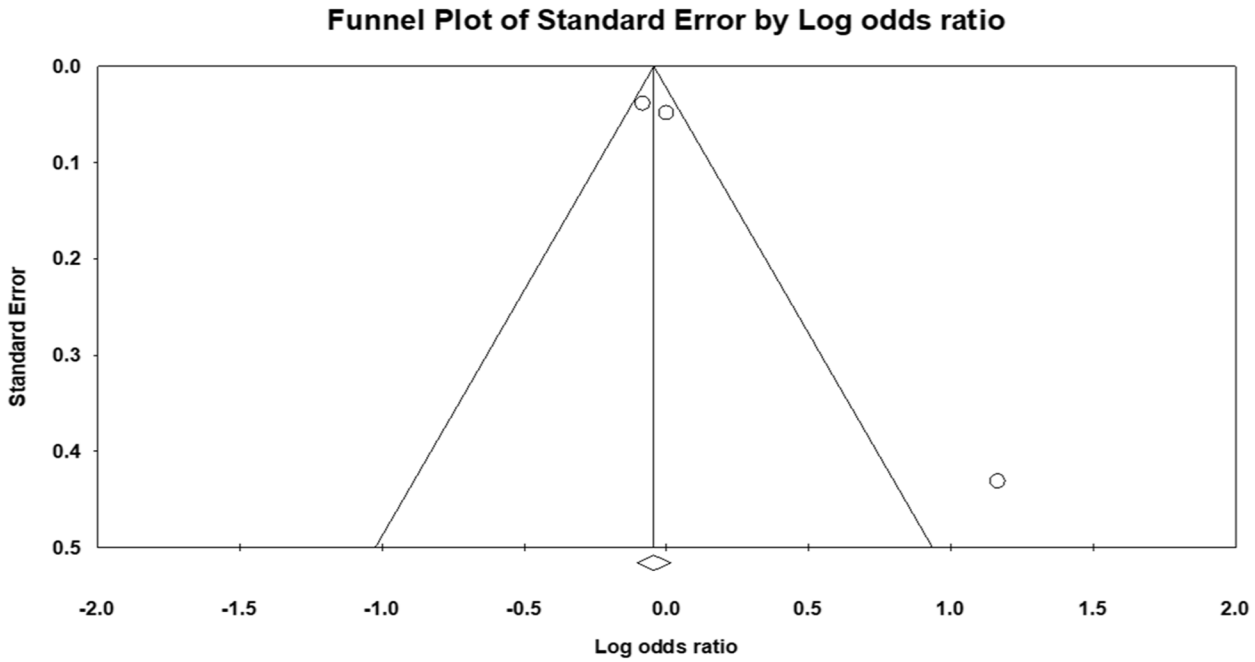


Fig. 18 Funnel Plot for CD4+ count and Falls in people living with HIV people living with HIV people living with HIV people living with HIVpeople living with HIV

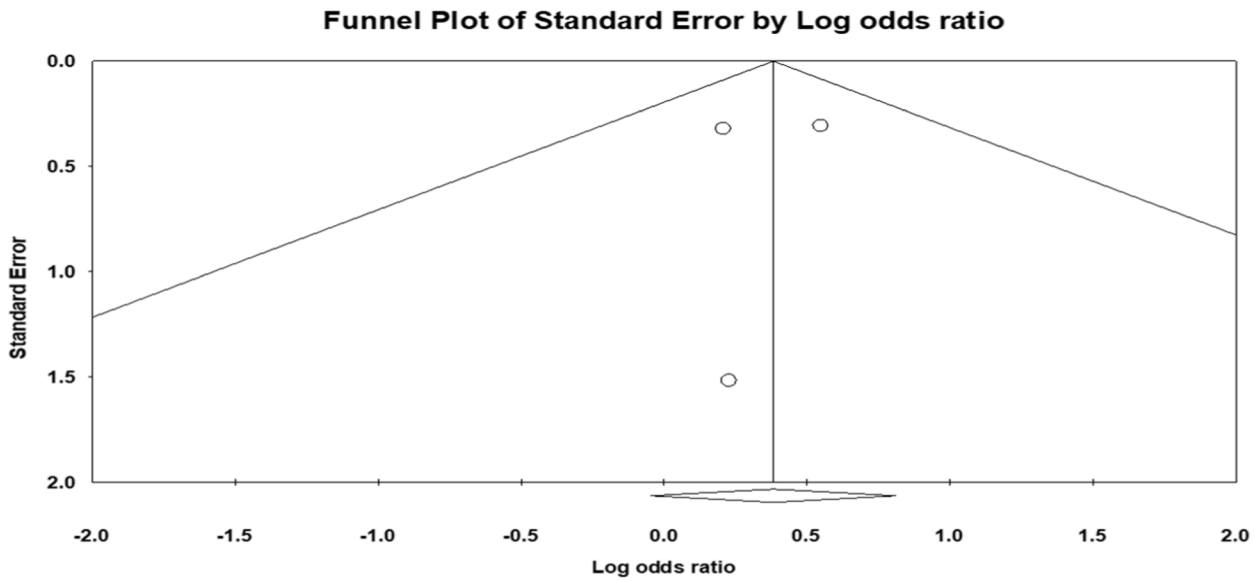


Fig. 19 Funnel Plot for stavudine and Falls in people living with HIV

on evidence strength ranging from strong to limited (+++ to +). The assessment considers factors such as bias risk, consistency, indirectness, precision, and publication bias.

Summary of findings (SoF)

The meta-analysis highlights several risk factors significantly associated with increased falls risk in people living with HIV, each varying in evidence strength.

Strong evidence (++++)

Cognitive impairment, neuropathy, cannabis use, and polypharmacy emerged as risk factors with robust evidence (++++) for their association with falls. Cognitive impairment and neuropathy consistently show increased falls risk across studies, with high confidence in these findings unlikely to change with further research. Cannabis use is also strongly correlated with falls due to

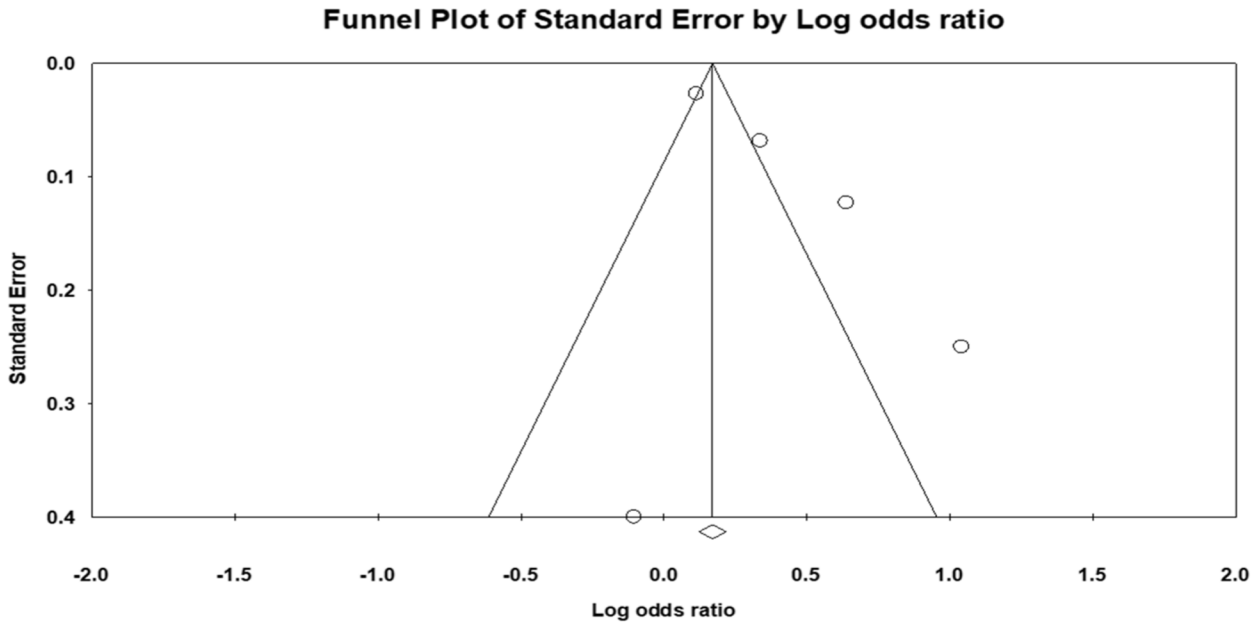


Fig. 20 Funnel Plot for polypharmacy and Falls in people living with HIV

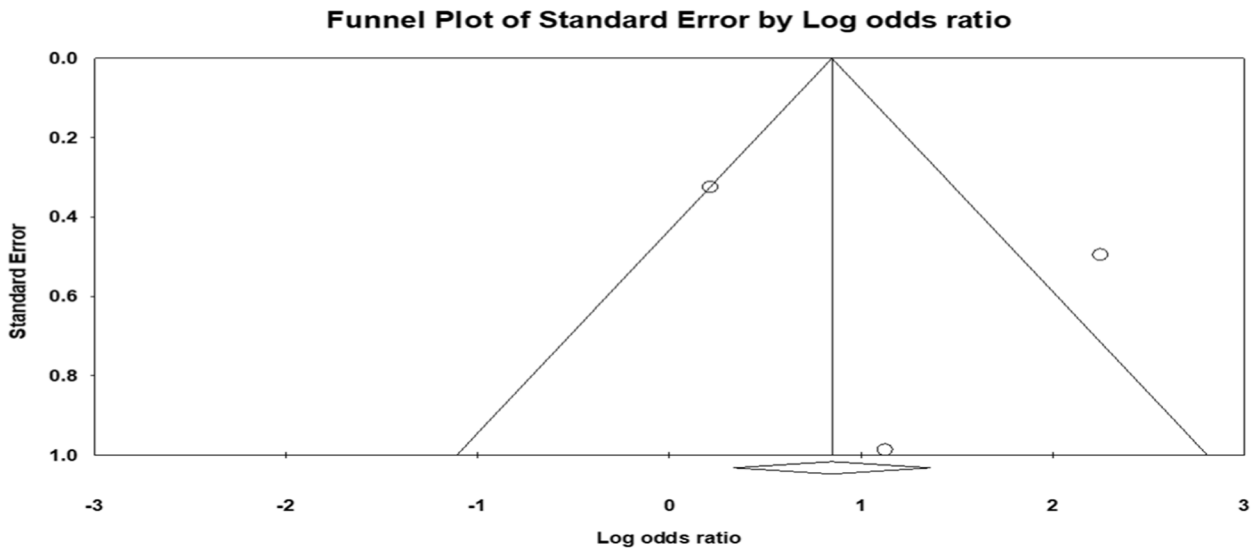


Fig. 21 Funnel Plot for frailty and Falls in people living with HIV

impaired coordination and judgment, supported by multiple studies. Polypharmacy, involving multiple medications, contributes to falls risk through complex interactions and side effects. The evidence supporting these factors is comprehensive and conclusive.

Moderate evidence (+++)

The meta-analysis identifies several risk factors with moderate evidence (+++) for increased fall risk in people living with HIV. The NCAE shows a potential association with falls, though the evidence is less robust than for stronger risk factors such as cognitive impairment and neuropathy (++++). Stavudine use is linked to falls, likely due to its known side effects, with moderate confidence in the current findings. Hypertension is associated with falls, potentially due to effects like orthostatic hypotension or medication-related issues, but the evidence, while supportive, is not definitive. Frailty increases

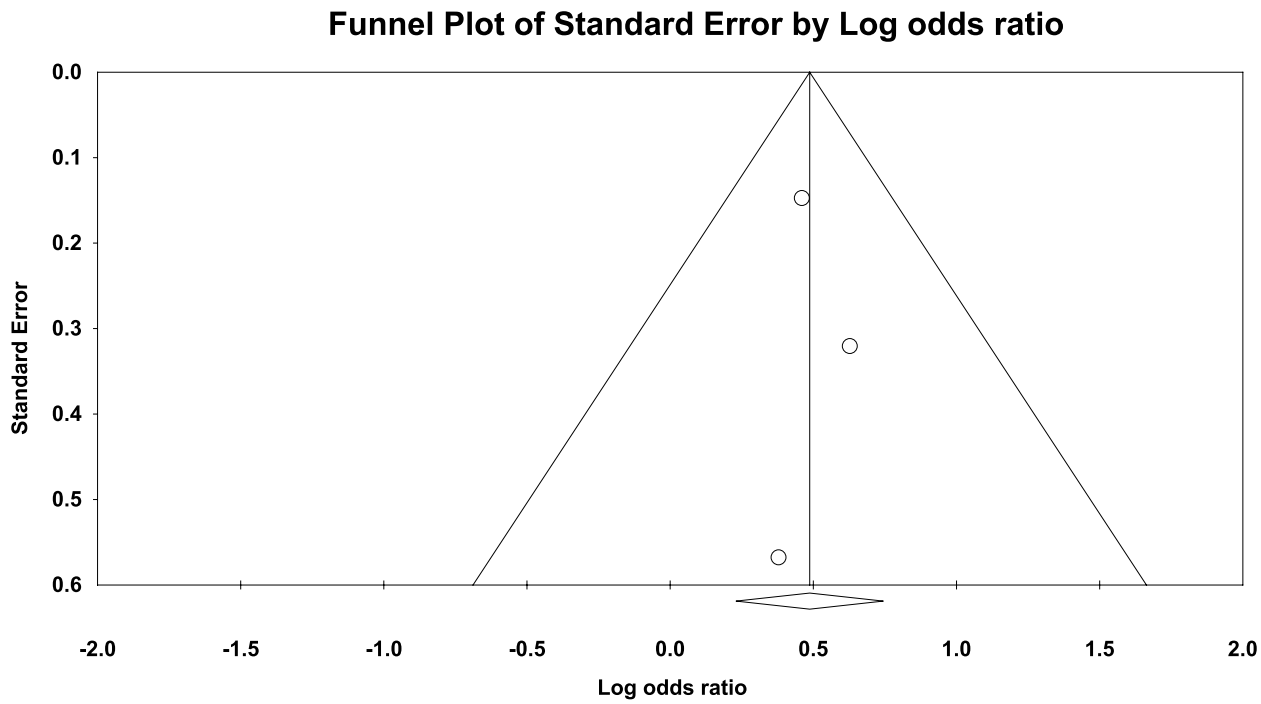


Fig. 22 Funnel Plot for neuropathy and Falls in people living with HIV

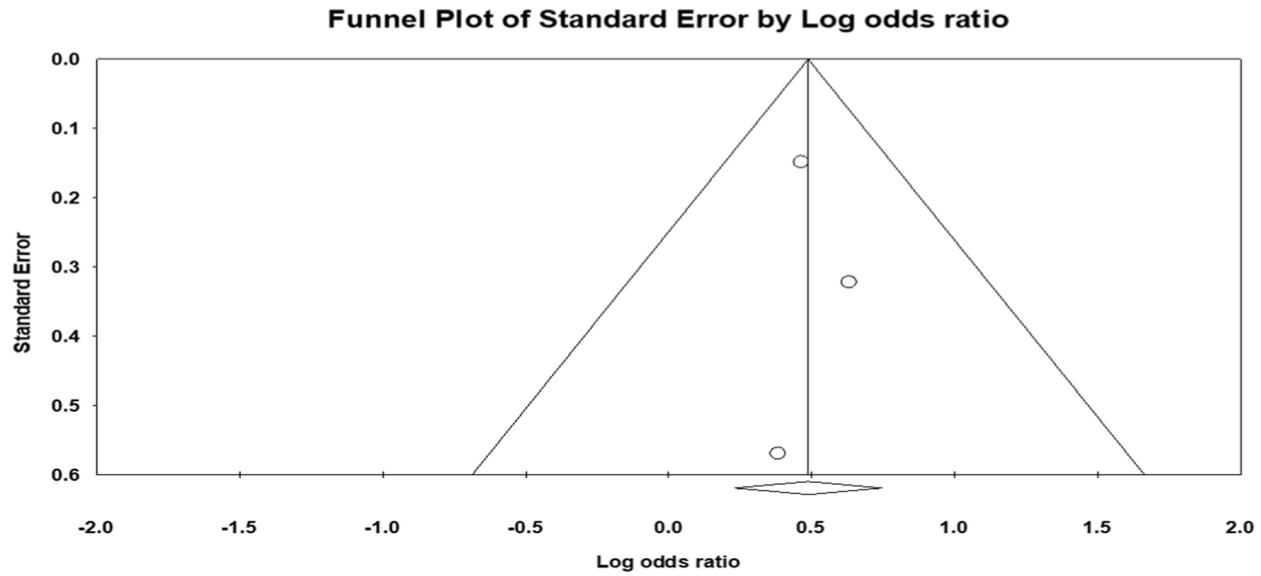


Fig. 23 Funnel Plot for Obesity and Falls in people living with HIV

vulnerability to falls, supported by moderate quality evidence, indicating that further research could refine the estimate. Comorbidity, reflecting multiple health conditions, contributes to higher fall risk. Obesity shows a correlation with fall risk, though the evidence is less consistent, warranting additional studies for confirmation.

Limited evidence (+)

CD4 + count was downgraded to limited evidence (+) from moderate evidence (+++) primarily due to imprecision, indicated by a wide confidence interval (0.84–1.20) for the relative risk (1.01) of CD4 + count and falls in people living with HIV. CD4 + count stands as the only

Table 5 Strength of evidence for risk factors associated with falls in people living with HIV

Meta-analysis of risk factors	Risk of bias	Inconsistent?	Indirectness	Imprecise?	Publication bias	Relative Risk (Odds ratio)	Strength of evidence
Drugs with neurocognitive-adverse effects (NCAE) and falls in PLWH	Low risk	Likely	Unlikely	Yes	-	2.287 (0.81–6.49)	++++
Association between cannabis use and falls in PLWH	Low risk	Unlikely	Unlikely	No	-	2.96 (1.510–5.82)	+++++
Symptoms of depression and risk of falls in PLWH	Low risk	Unlikely	Unlikely	Yes	-	1.63 (1.22–2.18)	++++
Stavudine use and risk of falls in PLWH:	Low risk	Unlikely	Unlikely	Yes	No	1.465 (0.95–2.25)	+++++
Hypertension and risk of falls in PLWH:	Low risk	Unlikely	Unlikely	No	-	1.76 (1.33–2.33)	+++++
Cognitive impairments and risk of falls in PLWH	Low risk	Unlikely	Unlikely	No	-	2.311 (1.66–3.21)	++++++
Association between polypharmacy and falls in PLWH	Low risk	Likely	Unlikely	Yes	No	1.50 (1.16–1.96)	+++++
Association between frailty and falls in PLWH	Low risk	Likely	Unlikely	Yes	No	3.23(0.73–14.40)	+++++
Association between neuropathy and falls in PLWH	Low risk	Unlikely	Unlikely	No	No	1.68 (1.26–2.11)	++++++
Association between CD4 + count and falls in PLWH	Low risk	Likely	Unlikely	Yes	No	1.01 (0.84–1.20)	++++
Association between having a comorbidity and falls in PLWH	Low risk	Unlikely	Unlikely	Yes	-	1.42 (0.83–2.43)	++++
Association between obesity and falls in PLWH	Low risk	Likely	Unlikely	Yes	Yes	1.32 (0.92–1.88)	+++

PLWH people living with HIV

risk factor with limited evidence, suggesting that current data do not strongly support an association between CD4 + count and falls in people living with HIV.

Overall, the evidence strength for risk factors associated with falls in people living with HIV ranges from strong (++++) to limited (+), with most risk factors demonstrating moderate to strong evidence (+++ to ++++). Interventions targeting these primary risk factors hold promise for mitigating falls among people living with HIV, thereby enhancing their safety and quality of life.

Discussion

Study characteristics

The diverse methodologies in HIV balance and fall research, such as differences in participant characteristics, treatment status, disease progression, study duration, and fall definitions, significantly affect the analysis of balance problems and fall predictors [75–78]. While larger studies provide robust data, smaller ones offer comprehensive insights [79]. Variations in treatment, disease stages, age, and sex necessitate targeted analyses. Study duration differences influence the temporal relevance of findings, and inconsistent fall definitions and attrition rates may bias results [80, 81]. To address this heterogeneity, our review's meta-analysis employed random-effects models [82]. Addressing these variations is essential for developing clinically relevant predictors to guide personalized interventions and enhance patient outcomes.

Developing an HIV-specific fall risk assessment model

Current fall risk assessment models for people living with HIV are limited by narrow sample frames, reliance on statistical significance for stratification, and lack of specificity [83, 84]. A new HIV-specific fall risk model (Table 4) was created to reduce false negatives and positives by identifying predictor combinations that meet the threshold score. While further validation is needed, results suggest recalibrating several existing models. This study provides a prioritized list of physiological, behavioral, traditional, and HIV-specific fall predictors for people living with HIV, aiding targeted prevention strategies. Accurate fall prediction in people living with HIV could improve patient outcomes by reducing fall-related consequences [85].

Predictors of falls and falls prevention

Cannabis use was identified as a significant predictor of falls among people living with HIV, with a risk weight of

3.0 and perfect risk responsiveness. The meta-analysis included two studies reporting significantly higher odds of falls among cannabis users compared to non-users [13, 73], indicating that cannabis users are approximately three times more likely to experience falls. Despite its predictive power and ease of assessment, cannabis use is not included in current predictive models for falls in people living with HIV. The mechanism by which cannabis use precipitates falls among people living with HIV is not well understood, as cannabis use reportedly does not induce balance disturbances [86]. As people living with HIV exhibit fall patterns similar to those of older adults, resulting from a combination of intrinsic, pharmacologic, environmental, behavioral, and activity-related factors [87], an ideal predictive tool should integrate multiple risk factor domains, including cannabis use, to effectively assess fall risk in people living with HIV.

Cognitive impairment and falls in people living with HIV

Cognitive impairment and the use of drugs with NCAE were identified as significant fall predictors in people living with HIV, each with a risk weight of 2.3 and perfect risk responsiveness. Cognitive impairment is an established independent fall predictor among older adults [88–90]. Although no prior systematic review links cognitive impairment to falls in people living with HIV, similar aging patterns support the finding that cognitive impairment or its proxy (NCAE) is a key fall determinant in people living with HIV. NCAE medication use significantly increased fall odds among women with HIV, independent of polypharmacy [69]. Recurrent falls were also linked to the use of beta-blockers, antidepressants, antipsychotics, and sedatives/hypnotics in another people living with HIV cohort [74]. Non-cannabis-related substances impair cognitive function, especially executive function, reducing attention to balance and gait and the ability to navigate environmental obstacles, thus increasing fall risk [91]. Both cognitive impairment and NCAE status should be included in predictive models for HIV-related falls due to their ease of measurement and their inclusion in some existing models [92, 93], supporting the conclusion that both cognitive impairment and NCAE use are vital fall predictors in people living with HIV.

Frailty and falls in people living with HIV

Our study identifies frailty as a critical predictor of falls in people living with HIV, with a risk weight of 2.2 and a risk responsiveness of 0.67. A meta-analysis of three studies reveals that frail individuals have higher odds of falling compared to non-frail individuals [7, 8, 13], with frail people living with HIV being roughly twice as likely to fall as their non-frail peers. Factors contributing to frailty in people living with HIV include viral replication, antiretroviral therapy (ART), malnutrition, immunosuppression, and chronic inflammation [94]. ART can cause metabolic side effects [95], such as fat distribution changes, insulin resistance, and metabolic abnormalities, leading to frailty [96]. HIV weakens the immune system, increasing infection risk [97], resulting in muscle wasting and physical decline, contributing to frailty [98]. HIV also affects appetite and nutrient absorption, causing malnutrition [99], which exacerbates muscle wasting, bone weakening, and frailty, heightening fall risk [100]. The significant role of frailty in predicting falls among people living with HIV justifies its inclusion in our proposed model (Table 3), despite its exclusion from existing HIV-specific models.

Polypharmacy and falls in people living with HIV

Polypharmacy significantly predicts falls in people living with HIV, with a risk weight of 1.2 and a risk responsiveness of 0.8 [97]. A meta-analysis of five studies reveals higher odds of falls among those exposed to polypharmacy [7, 8, 67, 69, 73], highlighting its crucial role in fall prediction [101] and cost-effectiveness in predictive models. Polypharmacy, the use of five or more medications, is increasingly common among people living with HIV [102], with an estimated 15–39% experiencing it [103]. ART usually involves three medications, while additional non-ART drugs manage symptoms and comorbidities [102], raising the risk of drug interactions, adverse effects [102], and medication-related falls due to physiological vulnerabilities like frailty [91]. Recognizing polypharmacy's predictive value has led to its inclusion in HIV-specific predictive models [92].

Neuropathy and falls in people living with HIV

Neuropathy is a significant predictor of falls in people living with HIV, corroborating the hypothesis that neuropathic conditions elevate fall risk [104]. This meta-analysis synthesized findings from three studies demonstrating increased fall odds in individuals with neuropathy compared to those without [7, 13, 73]. HIV-related neurological dysfunction, caused by active viral replication in neurons and chronic inflammation, disrupts nerve physiology [104], decreasing sensation in extremities, impairing hazard detection and footing stability [105], and consequently increasing fall risk. Despite its predictive value, neuropathy is frequently omitted from standard fall prediction models in people living with HIV, possibly due to the complexity and cost of assessment.

Depression and falls in people living with HIV

Depression significantly predicts falls in people living with HIV, aligning with systematic reviews among older

adults [106, 107]. Laboni and Flint [108] found a fourfold increase in fall risk among older adults with major depressive disorder, while Stubbs et al. [109] noted higher fall risk compared to those with subthreshold depressive symptoms. The mechanism linking depression to falls is unclear, though postural abnormalities and altered gait patterns may contribute [108]. Depression-related cognitive deficits in attention, executive functions, and processing speed also elevate fall risk [109]. In people living with HIV, depression often coincides with frailty, similar to geriatric populations [109]. Despite its predictive potential, depression is absent from current fall prediction models for people living with HIV. Some models include antidepressant use as NCAE predictors, but this does not directly indicate depression status. Underdiagnosis and lack of treatment for depression, especially in resource-limited settings [110, 111], highlight the need to incorporate depression assessment into fall prediction models for people living with HIV.

Hypertension and falls in people living with HIV

Hypertension predicts falls in people living with HIV, consistent with findings in older adults, who exhibit a 250% higher fall risk with systolic hypertension [112]. The people living with HIV demonstrated twice the odds of falls compared to HIV-negative controls, emphasizing hypertension's significant role and perfect risk responsiveness in the complex interplay of factors contributing to falls. Although the precise physiological mechanisms remain unclear [112], aging and hypertension correlate with impaired baroreflex-mediated cardio-acceleration, renal function, and cerebral blood flow regulation, potentially causing orthostatic hypotension and falls [113, 114]. Despite its simplicity in diagnosis, hypertension is often omitted from predictive models for HIV-related falls. Incorporating hypertension into these models may improve their effectiveness, considering its prevalence among people living with HIV and potential impact on fall prevention strategies.

Stavudine use and falls in people living with HIV

Stavudine use was identified as a significant predictor of falls in people living with HIV, with a cumulative odds ratio of approximately 1.5 and perfect risk responsiveness, indicating that people living with HIV on stavudine are about twice as likely to experience falls compared to those on other antiretroviral therapies, consistent with the existing literature [99]. The central nervous system side effects of stavudine, such as neuropathy, lipoatrophy, and dizziness, have been linked to increased fall risk [68, 115], as confirmed by a recent systematic review and meta-analysis (OR: 1.69, 95% CI: 1.08–2.66, $P=0.02$) [99]. These effects stem from mitochondrial toxicity, often manifesting as peripheral neuropathy [116]. Despite these known risks, stavudine use was not considered in the existing HIV-specific fall predictive model [92]. Integrating stavudine into such models could enhance their accuracy and utility, considering its significant impact on fall risk among people living with HIV and the contrasting protective effects of other antiretroviral drugs, such as Efavirenz and Zidovudine [99].

Addressing key challenges and enhancing prediction accuracy

A multifactorial model with nine domains (Table 3) is proposed to improve prediction accuracy for HIV-related falls while avoiding overfitting and complex assessments. Each factor uniquely contributes to falls, and their interrelatedness suggests internal consistency. Meta-analysis and combined indices are used to estimate clinical relevance and stratify predictors, but limitations include involvement of cross-sectional studies and heterogeneity in some pooled estimates. The model requires validation, and subjectivity in determining the critical risk point is a potential weakness. Immediate validation is crucial. Stratifying HIV-related fall predictors, integrating risk weights, and the CIMD proxy could innovate high-performing predictive models for falls among people living with HIV.

Strengths of the study

This study stands out for its comprehensive synthesis of relevant falls predictors, stratification based on risk weight and clinical importance, and the development of an HIV-specific falls predictive model. These strengths facilitate tailored falls prevention strategies for people living with HIV, offering a holistic understanding of falls by exploring physiological, psychosocial, and treatment-related factors. Focused on people living with HIV, it addresses a critical gap with its HIV-specific model, supported by meta-analysis to enhance validity and generalizability. Novel predictors like cannabis and stavudine use expand insights, while its multifactorial predictive model across nine domains promises effective interventions.

Limitations of the study

The study's limitations include reliance on cross-sectional designs and heterogeneous pooled estimates, necessitating cautious interpretation. While sensitivity analyses addressed variability, subgroup analyses were constrained by limited study numbers. Cross-sectional data hinder establishing causality, underscoring the need for longitudinal and comparative effectiveness research. Subjectivity in adjudicating critical risk point for may impact model reliability. This represents a trade-off between sensitivity and specificity. The optimum critical

risk point established in the validation phase of our project. Transparent reporting and sensitivity analyses can mitigate bias. Validation in independent cohorts is essential to confirm clinical applicability and predictive accuracy. Practical considerations, like the potential costliness of measuring predictors such as neuropathy, must be addressed for widespread model adoption in research and clinical practice. Future studies should prioritize cost-effectiveness and practical implementation.

Conclusion

The study illuminates diverse predictors of falls among people living with HIV, offering valuable insights for clinical practice and research. The significant predictors were cannabis use, cognitive impairment, frailty, polypharmacy, neuropathy, depression, hypertension, and stavudine use across physiological, psychosocial, and treatment domains. The HIV-specific predictive model developed here represents a significant advancement, and may have addressed previous study limitations like small sample sizes and lack of specificity to people living with HIV. The framework utilized in the study may enhance falls risk assessment and informs targeted interventions by emphasizing the need for comprehensive approaches in both clinical practice and future research to optimize HIV-related falls prevention strategies. Noteworthy, the evidence underlying the conclusions could change with further research.

Implications for practice

The study's findings offer practical implications for managing people living with HIV:

1. Tailored Falls Assessment: Integrate HIV-specific risk factors (e.g., cannabis use, stavudine use, cognitive impairment, frailty) into falls assessment tools for targeted interventions.
2. Multidisciplinary Approach: Engage a team of physical therapists, nurses, occupational therapists, physicians, pharmacists, and social workers to address the multifactorial nature of falls in people living with HIV.
3. Medication Review: Regularly review medications, especially those with neurocognitive adverse effects, to minimize falls risk associated with antiretroviral therapies like stavudine.
4. Screening for Depression: Integrate routine depression screening into people living with HIV care to manage associated risks contributing to falls.
5. Frailty Assessment and Management: Prioritize frailty assessment and management through nutritional support, exercise, and medication adjustments to mitigate falls risk.
6. Education and Counseling: Educate people living with HIV on modifiable risk factors (e.g., cannabis use, medication adherence) and lifestyle changes to empower self-management.
7. Continuous Monitoring and Follow-Up: Regularly monitor and follow up with people living with HIV at risk of falls to adjust interventions and reinforce preventive measures.

These strategies aim to reduce falls and improve overall quality of life for people living with HIV through targeted, comprehensive care approaches.

Implications for research

The study identifies key areas for future research in HIV-related falls:

1. Validation of Predictive Models: Validate the multifactorial predictive model across diverse people living with HIV populations to assess its generalizability and clinical utility.
2. Longitudinal Studies: Conduct longitudinal studies to explore temporal relationships between HIV-specific predictors and falls, identifying modifiable risk factors for targeted interventions.
3. Mechanistic Studies: Investigate underlying mechanisms linking HIV-specific factors (e.g., stavudine use, cognitive impairment) to falls, informing targeted intervention development.
4. Comparative Studies: Conduct comparative effectiveness research comparing HIV-specific and generic falls predictive models to guide clinical practice.
5. Intervention Studies: Implement randomized controlled trials to assess tailored fall prevention interventions targeting identified HIV-specific risk factors.
6. Health Equity and Social Determinants: Address social determinants of falls risk among people living with HIV to inform equitable interventions and policies.
7. Implementation Science: Conduct implementation science research to integrate evidence-based fall prevention strategies into diverse healthcare settings effectively.

This study advances understanding of HIV-related falls, providing a framework for assessing falls risk and guiding tailored interventions. Integrating HIV-specific predictors into falls management strategies and prioritizing validation, mechanistic insights, comparative effectiveness, health equity, and implementation science will enhance care for people living with HIV and reduce falls burden effectively.

Abbreviations

MMAT	Mixed method appraisal tool
OR	Odds ratios
CI	Confidence intervals
Rw	Risk weights
Ri	Risk responsiveness
PLWH	People living with HIV
NCAE	Neurocognitive-adverse effects
CMID	Clinical minimum important difference
CNS	Central nervous system
PNS	Peripheral nervous system
HIV	Human Immunodeficiency Virus
WHO	World Health Organisation
LMICs	Lower-Middle income countries
PROSPERO	International platform of Registered Systematic Prospective Register of Systematic Reviews
NCS	Nerve Conduction Studies
EMG	Electromyography
QST	Quantitative Sensory Testing
DEXA	Dual-energy X-ray absorptiometry
WHR	Waist-to-hip ratio
WC	Waist circumference
HC	Hip circumference
MDD	Major depressive disorder
NRTIs	Reverse-transcriptase inhibitors
MeSH	Medical subject headings
GRADEpro	GRADE profiler software
SoF	Summary of Findings
SPSS	Statistical program for the social sciences
ART	Antiretroviral therapy
CMA	Comprehensive Meta-Analysis
ARV	Antiretroviral
AZT	Zidovudine
ddI	Didanosine
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
MeSH	Medical Subject Heading
NIHR	National Institute of Health Research
PRISMA	Preferred Reporting items for systematic Reviews and Meta-analysis
GRADE	Grading of Recommendations Assessment, Development and Evaluation
BMI	Body mass index
WC	Waist circumference

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Authors' contributions
SCI and EOO conceived the study, designed the methodology, conducted the literature search and review, performed data extraction and statistical analysis, and drafted the manuscript. MN contributed significantly to data extraction, statistical analysis, and manuscript drafting. GCI participated in data extraction, served as the Ethics Advisor, and assisted in drafting the manuscript. SCI, EOO, MN, and GCI collaborated on the study design and coordination. All authors have read and approved the final manuscript.

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Data availability
The datasets supporting the conclusions of this article are available in the institutional University of Nigeria repository and will be made easily available on request when required. All requests for the study data should be addressed to the first author via email: sam.ibeneme@unn.edu.ng.

Declarations

Competing interests
The authors declare no competing interests.

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