BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057094
Article Type:	Protocol
Date Submitted by the Author:	03-Sep-2021
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Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adverse events < THERAPEUTICS, CLINICAL PHARMACOLOGY

Adverse drug reactions to antiretrovirals in women living with HIV/AIDS: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction: Antiretroviral therapy (ART) for HIV/AIDS has adverse drug reactions (ADR) documented, ranging from mild to fatal and from short to long term. However, little is known about differences between ADR in women and men living with HIV/AIDS. The aim of this study is to assess the incidence of ADR to ART in people living with HIV/AIDS associated with age or/and sex.

Methods and Analysis: We will consider for inclusion randomized controlled trials evaluating ART in people living with HIV/AIDS, describing any ADR, with any complexities and classes of regimens combination, and with any ART initiation or duration. Searches will be conducted in Medline, Embase, Cochrane Library, Epistemonikos, Lilacs, clinical trial registration portals and gray literature databases, without restriction on publication status, follow-up duration, conduction period of the study, and language. The primary outcome will be occurrence of serious ADR. Secondary outcomes include total number of ADR, ART discontinuation due to ADR, cardiovascular, neuropsychiatric, cutaneous, musculoskeletal, gastrointestinal, hepatic, hematological, immunological, respiratory, renal, reproductive, endocrine, ophthalmological events, and fever. Selection, data extraction and quality assessment will be performed in pairs and disagreements will be resolved by consensus or by a third reviewer. Cochrane Collaboration tools will be used to assess the risk of bias and methodological quality. If appropriate, a meta-analysis will be conducted to synthesize results. The overall quality of the evidence for each outcome will be determined by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE).

Ethics and Dissemination: We expect that the results help to assist in the formulation of public policies aimed at the management and monitoring of ADR of ART in people living with HIV/AIDS. A Deliberative Dialogue will be scheduled with the Department of Chronic Conditions and Sexually Transmitted Infections of Brazil's Ministry of Health during the project, to align it with policymakers' interests.

Protocol Registration: PROSPERO – CRD42021251051

Keywords: HIV & AIDS. Health policy. Adverse events. Clinical Pharmachology.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review will be potentially the best evidence available about de incidence of ADR to antiretroviral therapy in people living with HIV/AIDS.
- This review can contribute to the formulation of public policies, development of guidelines and clinical practice about the management and follow-up of people living with HIV/AIDS in the use of antiretrovirals.
- Most primary studies about antiretrovirals used for HIV/AIDS do not assess ADR considering gender and age. This review possibly will not find ADR to all antiretrovirals used in the clinical practice.

INTRODUCTION

The human immunodeficiency virus (HIV) remains a major global public health problem. In 2020, 37.6 million people were living with HIV [1]. About 16% of them were unaware of being infected by the virus [2]. Most of these people are in low-middle-income countries [3].

Although a decrease in HIV diagnosis is observed, women still account for almost 50% of adults living with HIV worldwide [4]. In the United States, in 2019, 51% of new HIV diagnoses were in women aged between 25 and 44 years old and 14%, between 13 and 24 years old [5]. In sub-Saharan Africa, young women (15-24 years old) are twice as likely to acquire HIV than men of the same age [2].

HIV affects women in a unique way. In addition to HIV itself and possible adverse drug reactions (ADR) to antiretroviral therapy (ART), women need to live with hormonal changes and unique health problems [6]. Gender inequalities in response to the combination of antiretrovirals have been reported in several studies summarized in a meta-analysis [7]. ART was evaluated for at least 48 weeks, between the years 2000 and 2008, finding several significant differences related to gender, in addition to demonstrating that there was better effectiveness of ART in men than in women.

ART has now been recommended for all patients, regardless of CD4 lymphocyte count, to decrease the transmissibility of the disease and to reduce long-term complications, such as HIV-related dementia [8]. Currently, around 27.4 million people in the world use ART [2]. Since therapy must be continued indefinitely, the focus of patient management should evolve towards the identification and management of early toxicities related to pharmacological treatment [9]. Viral suppression sustained throughout life must be accompanied by individualized management and adjustments in advance to overcome the toxicities and ADR of ART, both in the short and long term [10].

The use of ART has made HIV infection a chronic condition rather than a life-limiting disease [11]. With the increase in life expectancy of people living with HIV/AIDS, more elderly people started to be monitored. It is estimated that by 2030, 40% of the population with HIV will be people over 60 years of age [12]. However, the impact of the use of ART in the elderly, including ADR, is still not fully known, as this age group is generally unrepresented in studies [11].

Brazil is considered a vanguard country in terms of care policy for patients living with HIV/acquired immunodeficiency syndrome (AIDS), especially regarding access to medication [13]. Discontinuation due to ADR, however, remains one of the central problems, even when access to the service is made available [14]. Despite the general benefits of viral suppression and improved immune function because of ART far outweighing the risks associated with ADR, in general, it appears that women are more susceptible than men to the development of toxicity associated with ART, and this can affect outcomes, care and treatment [15]. In addition to the possible differences in gender, the elderly also seems to be more subject to the toxicity of drugs used for HIV/AIDS, such as nephrotoxicity, bone fractures and peripheral neuropathy [ref] [11]. The known effect of ART on carbohydrate and lipid metabolism may impact the cardiovascular risk of older people [16], with an increase in the occurrence of myocardial infarction [11] and the need for a different look at their care.

Clinical studies on HIV rarely focus only on outcomes in women, with data on gender analysis often scarce and controversial [17-19]. It is worth mentioning that the long-term complications of ART can be underestimated since most clinical trials use highly specific inclusion criteria for recruiting patients and the duration of patient follow-up is relatively short [7,20].

Understanding the occurrence of ADR in women is important to assess the need to define public policies that can adapt the treatment to minimize the damage, improve adherence and guarantee the success of the therapy and, consequently, the reduction in disease transmission [21].

Likewise, it is important to know the ADR in the elderly, who tend to be more susceptible due to possible age-related pharmacokinetic and pharmacodynamic changes, added to polypharmacy and the greater number of comorbidities, with higher risk for drug-drug and drug-disease interactions [12]. It may be necessary to monitor the occurrence of certain types of adverse reactions more frequently, depending on the ART regimen used [11].

ADR to antiretrovirals have been reported with the use of all drugs and are the main reason for discontinuing or exchanging therapy and non-adherence to treatment [22]. Changes in the immune system, common in people with HIV, also affect female hormones, causing problems in the menstrual period, uterine fibroids, genital tract infections and early menopause [23].

A systematic review that included six studies, between 1980 and 2012, revealed that current data on the effect of ART on the age of onset of menopause and the influence of menopause on the response to therapy in women infected by HIV are conflicting. Part of the challenge is that the existing studies presented a series of confounders, coming from small and poorly designed cohorts [24]. Some antiretrovirals can increase the risk of osteoporosis, but it is not yet determined to what extent this affects women more than men [25]. In general, existing systematic reviews that specifically assess ADR in women living with HIV, focus only on pregnant women and those experiencing the perinatal period [26-28].

In a preliminary search conducted on May 16th, 2021, with the terms ("Anti-Retroviral Agents" OR "Antiretroviral Agents" OR "anti-HIV Agents") in the International Prospective Register of Systematic Reviews (Prospero), Open Science Framework (OSF), Cochrane Protocols; and search for (Adverse AND Protocol) in the title at the British Medical Journal Open (BMJ Open) identified 66 records of systematic review protocols, but none intended to study the ADR related to sex or age.

In assessing the incidence of ADR considering gender and age, it intends to contribute to improving the management of patients living with HIV/AIDS and to support the Health System. We hope that, when completed, this review can represent the best available evidence on the relative incidence of ADR to ART in people and can be used to guide the development of specific public policies.

METHODS AND ANALYSIS

Study design, protocol, and registration

This systematic review study will be performed according to the recommendations found in the Cochrane Handbook for Intervention Reviews [29]. This protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [30] (**Supplementary Material 1**). The systematic review was also registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under registration no. CRD42021251051.

Patient and Public Involvement

We plan on having a Deliberative Dialogue [31] with decision-makers, health professionals and users of the health system living with HIV/AIDS. We will present the results and get suggestions on how to implement, monitor and manage ADR in women living with HIV/AIDS using Dialogue Deliberative approach.

Eligibility criteria

The research question was structured using Population, Intervention, Comparison and Outcomes (PICO), which guides the eligibility criteria.

Inclusion criteria

Type of studies

Randomized controlled trials, which are the gold standard of design for intervention studies when comparing efficacy and safety. Although cohort and case-control studies may have larger samples and longer follow-up times than clinical trials, providing information on rarer or longer-term ADR, non-randomized studies will be excluded due to the greater likelihood of bias and

factors of confusion. The inclusion of these other types of study would tend to bring uncertain results since it is intended to compare genders and the occurrence of ADR in different age groups.

Type of participants

Studies that describe ADR in people living with HIV on antiretroviral therapy without age restriction.

Type of interventions

1. Any ART;
2. Any complexities of ART regimens (monotherapy, dual therapy, highly active antiretroviral therapy (HAART));
3. Any classes of ART regimens (Nucleoside Reverse Transcriptase Inhibitor (NRTI)-based, Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-based, Protease Inhibitor (PI)-based, Integrase Strand Transfer Inhibitor (INSTI)-based, integrase inhibitors, fusion inhibitors, CCR5 Inhibitors);
4. Any specific ART drugs;
5. Any timings of ART initiation;
6. Any combinations of complexities and classes of ART regimens and specific ART drugs and timings of ART initiation.

Types of comparators

1. Placebo;
2. Any ART;
3. Any complexities of ART regimens (monotherapy, dual therapy, HAART);
4. Any classes of ART regimens (NRTI-based, NNRTI-based, PI-based, INSTI-based, integrase inhibitors, fusion inhibitors, CCR5 Inhibitors);
5. Any specific ART drugs;
6. Any timings of ART initiation;

7. Any combinations of complexities and classes of ART regimens and specific ART drugs and timings of ART initiation.

Types of outcome measures

PRIMARY OUTCOMES

Serious ADR of ART, as defined by the U. S. Food & Drug Administration (FDA) [32]. Such effects include:

1. Death;
2. Life-threatening event;
3. Hospitalization;
4. Disability.

The definition of serious ADR is any ADR associated with death, life-threat, hospitalization, disability or, adverse reactions requiring intervention to prevent disability or permanent damage.

If any of the primary studies do not show the total number of serious ADR, we will consider the number of participants with at least one serious effect, as defined in the study for this outcome.

SECONDARY OUTCOMES

1. Discontinuation of ART due to ADR;
2. Total number of ADR;
3. The number of:
    a. Cardiovascular ADR: these included the presence of any diagnoses of arrhythmia, endocarditis, heart failure, myocardial infarction, or any exacerbation. Some studies do not specify the cardiovascular ADR but present grouped data as cardiac, cardiopulmonary, or circulatory ADR;
    b. Neuropsychiatric ADR: these include any diagnoses of headache, insomnia, drowsiness, asthenia, dizziness, mental confusion, vivid dreams, feeling intoxicated, difficulty concentrating, peripheral neuropathy, cerebellar ataxia, stroke, convulsion, anxiety, depression, psychotic disorders, suicide;
    c. Skin ADR: pruritus, rash, rash, hyperpigmentation, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis and/or any exacerbation will be included;

d. Musculoskeletal ADR: these include arthralgia, low back pain, myalgia, myositis, rhabdomyolysis, decreased bone mineral density and diagnoses of osteopenia and/or osteoporosis;
e. Respiratory ADR: presence of cough, runny nose, rhinitis, pneumonia will be included;
f. Reproductive ADR: presence of gynecomastia will be included;
g. Gastrointestinal and liver ADR: these include abdominal pain, diarrhea, nausea, vomiting, heartburn, loss of appetite, jaundice and/or diagnoses of cholestatic jaundice syndrome, cholelithiasis, hepatomegaly, hepatitis, cirrhosis, portal vein thrombosis, non-cirrhotic portal hypertension, pancreatitis;
h. Hematologic ADR: these include new diagnoses of anemia, thrombocytopenia, neutropenia, pancytopenia, hemorrhage;
i. Renal ADR: increased creatinine, decreased glomerular filtration rate or creatinine clearance, renal failure, Fanconi syndrome, nephrogenic diabetes insipidus, hematuria, nephrolithiasis will be included;
j. Endocrine and metabolic ADR: diagnoses of hypercholesterolemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes, diabetic ketoacidosis, lactic acidosis will be included;
k. Immunological ADR: if reported the presence of hypersensitivity reaction, anaphylaxis, immune reconstitution syndrome or any exacerbation will be included.
l. Ophthalmic ADR: new diagnoses of optic neuritis will be included; and
m. Other ADR: such as reports of fever.

If any of the primary studies do not show the total number of ADR, we will consider the number of participants with at least one adverse reaction, as defined in the study for this outcome.

Exclusion criteria

Studies evaluating ART regimens for HIV pre-exposure (PREP) and post-exposure (PEP) prophylaxis will be excluded; studies focusing on pregnant, breastfeeding, or perinatal women and those that analyze the use of ART in the presence of co-infections, such as viral hepatitis B and C and tuberculosis.

Search methods for identification of studies

The search strategy will use DeCS/MeSH descriptors and synonyms, being adapted according to each database searched (**Supplementary Material 2**). The searches will be conducted by an experienced librarian and will be reviewed by another professional librarian, according to the Peer Review of Electronic Search Strategies (Press) [33]. No limitations will be imposed on the status of publication (e.g., unpublished studies are eligible for inclusion), duration of follow-up, year of publication of the study, and language).

Electronic searches

A structured search for potential primary studies will be done in the main electronic databases: Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed; Excerpt Medical data BASE (Embase) via Elsevier; Cochrane Central Register of Controlled Trials (Central); Epistemonikos; Latin American and Caribbean Health Sciences Literature (Lilacs).

Searching other resources

A manual search will be conducted in the references of the included studies. We will adapt a specific structured search strategy for the gray literature, including dissertations databases (ProQuest Dissertations and Theses Database), records of clinical trials (Global Index Medicus of World Health Organization - WHO; Brazilian Registry of Clinical Trials - Rebec; ClinicalTrials.gov), summaries of selected international symposium conferences on HIV, websites of government agencies and non-governmental organizations that conduct research or implement relevant programs.

Data collection and analysis

The data collection and analysis will be performed based on the recommendations found in the Cochrane Handbook for Intervention Reviews [29].

Selection of studies

The reviewers will work in pairs and will independently assess whether titles and abstracts meet the eligibility criteria. A similar process will be used to track full texts. The reviewers will be calibrated for each stage of study selection. The differences between the assessments will be resolved by consensus or by a third reviewer. In case of duplicate publication, we will use the article with the most complete data. In addition, secondary publications from the same study will be consulted to verify the results of ADR. We will examine the included manuscripts to ensure that they contain unique patients whose data is not used in another included study. Subsequently, two team members will independently examine the references for each full-text article included to identify potentially relevant studies.

Data extraction and management

A pre-piloted and standardized form will be used to extract data from the included studies. The reviewers will be calibrated by extracting at least three articles and, afterward, they will carry out consensus, in pairs and independently. This process will take place until the standardization of the extracted data. The overlap of two articles in all teams of reviewers will be adopted to assess the reliability between reviewers in extracting data between the different teams.

After this stage, two reviewers will extract the data independently, and any discrepancies will be identified and resolved (with a third author, when necessary). The data collected will be characteristics of studies(country, ID, number of sites, duration of study, timing of outcome measurement (in weeks or months), bibliometric information), patients [inclusion, exclusion criteria, age, comorbidities, antiretroviral therapy (ART) exposure (naive versus experienced), numbers in each arm, drug regimen, cointerventions others to treat comorbidities];, reported ADR (number of participants who experienced an event for dichotomous outcomes; means and standard deviations for normally distributed continuous outcomes. We will standardize continuous data not reported on the same scale and report with standard errors). We will also check the method of adverse event assessment: did the researchers actively monitor for AEs (low risk of bias), or did they simply provide spontaneous reporting of AEs that arose (high risk of bias)? For studies

identified only in clinical trial registry websites, we will check the same data and check if they are ongoing.

When two or more papers are found for the same study, we will report it using only one ID and will extract the data of all the studies to provide the most complete report. No secondary or post hoc analysis will be performed. We will also not use an open-label extension.

Assessment of methodological quality and risk of bias

The quality of individual studies will be assessed using Cochrane's Risk of Bias Tool version 2.0 for randomized trials on bias arising from the randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. The reviewers will assign independently as answer alternatives "definitely yes", "probably yes", "probably not", "definitely not" or "not informed" for each of the domains, classifying, according to the answers, as “low risk of bias”, “some concern about the risk of bias” or “high risk of bias”. Reviewers will resolve disagreements through discussion, and a third person will judge unresolved disagreements. Publication bias will be assessed using the funnel graph [34] for each outcome.

Data synthesis and analysis

For the synthesis of the dichotomous results, the relative risk and the absolute risk will be estimated, with a 95% confidence interval (95% CI). The risk difference will be calculated to obtain the number necessary to cause damage. We will calculate the weighted mean difference (WMD) for continuous data measured on the same scale, and the standard mean difference (SMD) for continuous data measured on different scales. We will present these results with 95% confidence interval (CI) values. The existence of statistical significance will be considered when the p value is less than or equal to 0.05.

Meta-analyses of fixed and random effects will be conducted [35,36] separately for the outcomes. The summary estimates will be presented together with their 95% CI. Differences between estimates of fixed and random effects suggest that there are differences between the estimated effects of the treatment of small and large studies [37]. Such differences will be examined using funnel charts and the Harbord test for asymmetry of the funnel chart [38] when ten or more

studies are included in the meta-analysis. Asymmetry will be explored by examining the clinical and methodological characteristics of the discrepant studies.

Data on missing participants for dichotomous outcomes will be addressed according to a systematic review guide developed for this purpose [39]. This approach will only be applied to results that satisfy the following criteria: present a significant treatment effect and report sufficient data from missing participants to potentially introduce clinically important bias [40].

Heterogeneity

Statistical, clinical, and methodological heterogeneities will be examined before performing meta-analyses. The magnitude of the statistical heterogeneity will be estimated using the Qprofile method to estimate the 95% CI. The proportion of variability that is due to heterogeneity, rather than sampling error, will also be quantified using measure I^2 [41]. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity.

The total number of covariables to be tested in the meta-regression will be limited so that it is equal to 1/10 of the number of studies. Meta-analyses and meta-regressions will be conducted using the Comprehensive MetaAnalysis STATA software (version 16).

Some aspects will be observed as possible causes of heterogeneity, if it is significantly present, such as the location of the population participating in the study, immunological status (CD4 level), length of follow-up, presence of comorbidities and concomitant use of other drugs besides ART.

If the meta-analysis is not appropriate due to the excessive heterogeneity of the population, intervention, comparator, result, or method, summary tables will be made, and the narrative synthesis will be provided.

Subgroup analysis or sensitivity analysis

When appropriate, subgroup analysis will be employed. The subgroup that will be used includes age groups, type of drugs associated with ADR, factors associated with ADR occurrence, location of the population of the study, immunological status (CD4 level), time of follow-up, presence of comorbidities, concomitant use of drugs other than ART; combined versus single antiretroviral therapy; risk of bias; doses and ART combinations. The robustness of the results

found can be examined through sensitivity analyzes based on factors such as the risk of bias, as well as doses and combinations in the ART.

Assessment of the certainty of the evidence and the strength of the recommendation

After the results are grouped, two reviewers will independently assess the overall certainty of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [42]. The main results of the review will be presented in outcome tables (Summary of Findings - SoF), as recommended by The Cochrane Collaboration [43]. The SoF table includes a general classification of the evidence related to each of the main outcomes, using the GRADE approach [44]. This table will be built with the aid of the GRADEpro software program.

The use of the GRADE allows evaluating the certainty of the evidence for each result considering the methodological quality, the objectivity of the evidence, the heterogeneity, the precision of the effect estimates and the risk of publication bias [43]. If the analysis of an outcome is not possible, for example, due to the lack of data, we will present the reasons for this in the SoF table in a footnote.

ETHICS AND DISSEMINATION

This research project will yield two publications. One that will compare the incidence of ADR of ART in women or men considering the proportion of them. Another that will assess the occurrence of these ADR in people considering different ages.

It is hoped that the results will serve to assist in the formulation of public policies, aimed at guiding professionals on the management and monitoring of the ADR of ART in people living with HIV/AIDS. For this purpose, meetings are scheduled with the Department of Chronic Conditions and Sexually Transmitted Infections of the Ministry of Health of Brazil during the project, seeking to align it with the interests of policymakers. We will also present the results and discuss the implementation, monitoring and management of ADR in women living with HIV/Aids in a deliberative dialogue with stakeholders, policymakers, and other researchers.

AUTHOR CONTRIBUTIONS

Study concept and design: LCL.

Methodology: LCL.

Drafting of the manuscript: JCO, LCL and MRA.

Review and editing of the manuscript: LCL, MRA, CCB, SBF, JCO, RSI, FRM, TVP, MTS, AI, JMB, DLS, DSL, LGM, RDD.

ACKNOWLEDGEMENTS

The authors would like to thank Genevieve Gore and Mabel Figueiro, experienced librarians, for their collaboration with the review and definition of the final search strategy for the present study. The authors would like to thank Filipe Perini as well, for his contributions to the search questions, choice of medicines to be included and the functioning of the current Brazilian public policies for HIV.

FUNDING

This research received funding from the São Paulo Research Foundation (FAPESP), grant n°. 2018/16893-8.

COMPETING INTERESTS

None to declare.

WORD COUNT: 3510

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SUPPLEMENTARY MATERIAL 1 - PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	15-16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	16
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Suppl. Material

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12-13
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11-12
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11-12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	12-13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	13
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	13-14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	14
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	15
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	15

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

SUPPLEMENTARY MATERIAL 2 – Search strategies

PubMed	(HIV infections [MeSH] OR HIV [MeSH] OR Acquired Immunodeficiency Syndrome [MeSH] OR HIV Seropositivity [MeSH] OR HIV OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR HIV/AIDS) AND (Anti-retroviral agents [Mesh] OR antiretroviral therapy, highly active [Mesh] OR Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)) OR Saquinavir [tiab] OR Lopinavir [tiab] OR Indinavir [tiab] OR Ritonavir [Tiab] OR Nelfinavir [tiab] OR Amprenavir [tiab] OR Fosamprenavir [tiab] OR Atazanavir [Tiab] OR Tipranavir [tiab] OR Darunavir [tiab] OR Cobicistat [Tiab] OR Emtricitabine [Tiab] OR Zidovudine [Tiab] OR Didanosine [tiab] OR Stavudine [tiab] OR Lamivudine [Tiab] OR Abacavir [Tiab] OR Nevirapine [tiab] OR Darunavir [Tiab] OR Etravirine [Tiab] OR Elvitegravir [Tiab] OR Alafenamide [Tiab] OR "Tenofovir disoproxil fumarate" [Tiab] OR "Tenofovir Alafenamide" [Tiab] OR Tenofovir [Tiab] OR Efavirenz [Tiab] OR Enfuvirtide [Tiab] OR Raltegravir [tiab] OR Maraviroc [tiab] OR Dolutegravir [tiab] OR Bictegravir [tiab]) AND (("abnormalities, drug-induced"[mesh] OR "drug hypersensitivity"[mesh] OR "drug monitoring"[mesh] OR "drug recalls"[mesh] OR "poisoning"[mesh] OR "safety-based drug withdrawals"[mesh] OR "substance-related disorders"[mesh] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "Long Term Adverse Effects"[Mesh] OR "product surveillance, postmarketing"[mesh] OR "adverse effects"[sh] OR "complications"[sh] OR "drug effects"[sh] OR "safe"[tw] OR "safety"[tw] OR "side effect*"[tw] OR "undesirable effect*"[tw] OR "treatment emergent"[tw] OR "tolerability"[tw] OR "toxicity"[tw] OR "adverse drug reaction*"[tw] OR "adrs"[tw] OR "adverse effect*"[tw] OR "adverse drug effect*"[tw] OR "adverse reaction*"[tw] OR "adverse event*"[tw] OR "adverse drug event*"[tw] OR "adverse outcome*"[tw] OR "complication*"[tw] OR "harm"[tw] OR "harmful"[tw] OR "harms"[tw] OR "risk"[tw] OR (adverse[tw] AND (effect[tw] OR effects[tw] OR reaction[tw] OR reactions[tw] OR event[tw] OR events[tw] OR outcome[tw] OR outcomes[tw]))))

	AND ((((((randomized controlled trial [pt]) OR controlled clinical trial [pt]) OR randomized [tiab]) OR placebo [tiab]) OR clinical trials as topic [mesh: noexp] OR randomly [tiab]) OR trial [tiab]) NOT (animals [MeSH] NOT humans [MeSH])
Embase	No. Query Results 11,308 #6 #1 AND #2 AND #3 AND #4 NOT #5 5,615,547 #5 'animal'/exp NOT 'human'/exp 1,832,252 #4 'randomized controlled trial':it OR 'controlled clinical trial':it OR randomized:ab,ti OR placebo:ab,ti OR ('clinical trial'/de AND topic) OR randomly:ab,ti OR trial:ab,ti 10,788,807 #3 'adverse drug reaction'/exp OR 'drug hypersensitivity'/exp OR 'drug monitoring'/exp OR 'drug recall'/exp OR 'drug intoxication'/exp OR 'side effect'/exp OR 'postmarketing surveillance'/exp OR 'drug safety'/exp OR 'drug surveillance program'/exp OR 'drug toxicity'/exp OR 'adverse event'/exp OR 'complication'/exp OR 'drug effect'/exp OR safe OR safety OR 'side effect*' OR 'undesirable effect*' OR 'treatment emergent' OR 'tolerability' OR 'toxicity' OR 'adverse drug reaction*' OR 'adrs' OR 'adverse effect*' OR 'adverse drug effect*' OR 'adverse reaction*' OR 'adverse event*' OR 'adverse drug event*' OR 'adverse outcome*' OR 'complication*' OR 'harm' OR 'harmful' OR 'harms' OR 'risk' OR (adverse AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)) 522,768 #2 'antiretrovirus agent'/exp OR 'highly active antiretroviral therapy'/exp OR antiretroviral* OR (anti AND retroviral*) OR arv OR art OR 'antiretroviral therapy' OR haart OR (highly AND active AND antiretroviral* AND therap*) OR (anti

	AND hiv) OR (anti AND acquired AND immunodeficiency) OR (anti AND acquired AND immuno-deficiency) OR (anti AND acquired AND immune-deficiency) OR (anti AND acquired AND immun* AND deficienc*) OR saquinavir:ab,ti OR lopinavir:ab,ti OR indinavir:ab,ti OR ritonavir:ab,ti OR nelfinavir:ab,ti OR amprenavir:ab,ti OR fosamprenavir:ab,ti OR atazanavir:ab,ti OR tipranavir:ab,ti OR cobicistat:ab,ti OR emtricitabine:ab,ti OR zidovudine:ab,ti OR didanosine:ab,ti OR stavudine:ab,ti OR lamivudine:ab,ti OR abacavir:ab,ti OR nevirapine:ab,ti OR darunavir:ab,ti OR etravirine:ab,ti OR elvitegravir:ab,ti OR alafenamide:ab,ti OR 'tenofovir disoproxil fumarate':ab,ti OR 'tenofovir alafenamide':ab,ti OR tenofovir:ab,ti OR efavirenz:ab,ti OR enfuvirtide:ab,ti OR raltegravir:ab,ti OR maraviroc:ab,ti OR dolutegravir:ab,ti OR bictegravir:ab,ti 610,204 #1 'human immunodeficiency virus infection'/exp OR 'acquired immune deficiency syndrome'/exp OR 'human immunodeficiency virus 1'/exp OR 'human immunodeficiency virus 1 infection'/exp OR 'human immunodeficiency virus 2'/exp OR 'human immunodeficiency virus 2 infection'/exp OR 'hiv aids'/exp OR hiv OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR (hiv AND infect*) OR (human AND immunodeficiency AND virus) OR (human AND immune AND deficiency AND virus) OR (human AND immuno-deficiency AND virus) OR (human AND immune-deficiency AND virus) OR (human AND immun* AND deficiency AND virus) OR (acquired AND immunodeficiency AND syndromes) OR (acquired AND immune AND deficiency AND syndrome) OR (acquired AND immuno-deficiency AND syndrome) OR (acquired AND immune-deficiency AND syndrome) OR (acquired AND immun* AND deficiency AND syndrome)
Cochrane Central	Search Name: Cochrane RADAR Last Saved: 25/05/2021 20:49:52 Comment: ID Search #1 MeSH descriptor: [HIV Infections] explode all trees #2 MeSH descriptor: [HIV] explode all trees #3 MeSH descriptor: [Acquired Immunodeficiency Syndrome] explode all trees #4 MeSH descriptor: [HIV Seropositivity] explode all trees #5 (HIV OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR

	acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS):ti,ab,kw #6 #1 OR #2 OR #3 OR #4 OR #5 #7 MeSH descriptor: [Anti-Retroviral Agents] explode all trees #8 MeSH descriptor: [Antiretroviral Therapy, Highly Active] explode all trees #9 (Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*))):ti,ab,kw #10 (Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir):ti,ab #11 #7 OR #8 OR #9 OR #10 #12 MeSH descriptor: [Abnormalities, Drug-Induced] explode all trees #13 MeSH descriptor: [Drug Hypersensitivity] explode all trees #14 MeSH descriptor: [Drug Monitoring] explode all trees #15 MeSH descriptor: [Drug Recalls] explode all trees #16 MeSH descriptor: [Poisoning] explode all trees #17 MeSH descriptor: [Safety-Based Drug Withdrawals] explode all trees #18 MeSH descriptor: [Substance-Related Disorders] explode all trees #19 MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees #20 MeSH descriptor: [Long Term Adverse Effects] explode all trees #21 MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees #22 MeSH descriptor: [] explode all trees and with qualifier(s): [adverse effects - AE] #23 MeSH descriptor: [] explode all trees and with qualifier(s): [complications - CO] #24 MeSH descriptor: [] explode all trees and with qualifier(s): [drug effects - DE] #25 ("safe" OR "safety" OR "side effect*" OR "undesirable effect*" OR "treatment emergent" OR "tolerability" OR "toxicity" OR "adverse drug reaction*" OR "adrs" OR "adverse effect*" OR "adverse drug effect*" OR "adverse

	reaction*" OR "adverse event*" OR "adverse drug event*" OR "adverse outcome*" OR "complication*" OR "harm" OR "harmful" OR "harms" OR "risk" OR (adverse AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))) #26 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 #27 #22 OR #23 OR #24 #28 #25 OR #26 OR #27 #29 #6 AND #11 AND #28
Biblioteca Virtual em Saúde (BVS)	((mh:(HIV infections)) OR (mh:(HIV)) OR (mh:(Acquired Immunodeficiency Syndrome)) OR (mh:(HIV Seropositivity)) OR ((HIV OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS))) AND ((mh:(Anti-Retroviral Agents)) OR (mh:(Antiretroviral Therapy, Highly Active)) OR ((Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)))) OR (ti:((Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir))) OR (ab:((Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir)))) AND ((mh:(Abnormalities, Drug-Induced)) OR (mh:(Drug Hypersensitivity)) OR (mh:(Drug Monitoring)) OR (mh:(Drug Recalls)) OR (mh:(Poisoning)) OR (mh:(Safety-Based Drug Withdrawals)) OR (mh:(Substance-Related Disorders)) OR (mh:(Drug-Related Side Effects and Adverse Reactions)) OR (mh:(Long Term Adverse Effects)) OR (mh:(Product Surveillance, Postmarketing)) OR ("adverse effect" OR "adverse effects" OR "drug effects" OR safe OR safety OR "side effect" OR "side effects" OR

	"undesirable effect" OR "undesirable effects" OR "treatment emergent" OR tolerability OR toxicity OR "adverse drug reaction" OR "adverse drug reactions" OR adrs OR "adverse drug effect" OR "adverse drug effects" OR "adverse reaction" OR "adverse reactions" OR "adverse event" OR "adverse events" OR "adverse drug event" OR "adverse drug events" OR "adverse outcome" OR "adverse outcomes" OR complication OR complications OR harm OR harmful OR harms OR risk OR ((adverse) AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)))) AND ((mh:(clinical trials)) OR (randomized controlled trial) OR (controlled clinical trial) OR randomized OR placebo OR randomly OR trial)
Epistemonikos	((HIV infections) OR HIV OR (Acquired Immunodeficiency Syndrome) OR (HIV Seropositivity) OR (hiv-1) OR (hiv-2) OR hiv1 OR hiv2 OR (hiv infect*) OR (human immunodeficiency virus) OR (human immune deficiency virus) OR (human immuno-deficiency virus) OR (human immune-deficiency virus) OR ((human immun*) AND (deficiency virus)) OR (acquired immunodeficiency syndromes) OR (acquired immune deficiency syndrome) OR (acquired immuno-deficiency syndrome) OR (acquired immune-deficiency syndrome) OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS) AND ((Anti-retroviral agents) OR (antiretroviral therapy, highly active) OR Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)) OR Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir) AND ("abnormalities, drug-induced" OR "drug hypersensitivity" OR "drug monitoring" OR "drug recalls" OR "poisoning" OR "safety-based drug withdrawals" OR "substance-related disorders" OR "Drug-Related Side Effects and Adverse Reactions" OR "Long Term Adverse Effects" OR "product surveillance, postmarketing" OR "adverse effects" OR "complications" OR "drug effects" OR "safe" OR "safety" OR "side effect*" OR "undesirable effect*" OR "treatment emergent" OR "tolerability" OR "toxicity" OR "adverse drug reaction*" OR "adrs" OR "adverse effect*" OR "adverse drug effect*" OR "adverse reaction*" OR "adverse event*" OR "adverse drug event*" OR "adverse outcome*" OR "complication*" OR "harm" OR "harmful" OR "harms" OR "risk" OR (adverse AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))) AND ((randomized controlled trial) OR (controlled clinical trial) OR randomized OR placebo OR randomly OR trial)

ClinicalTrials.gov	((HIV infections) OR HIV OR (Acquired Immunodeficiency Syndrome) OR (HIV Seropositivity) OR (hiv-1) OR (hiv-2) OR hiv1 OR hiv2 OR (hiv infect*) OR (human immunodeficiency virus) OR (human immune deficiency virus) OR (human immuno-deficiency virus) OR (human immune-deficiency virus) OR ((human immun*) AND (deficiency virus)) OR (acquired immunodeficiency syndromes) OR (acquired immune deficiency syndrome) OR (acquired immuno-deficiency syndrome) OR (acquired immune-deficiency syndrome) OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS) AND ((Anti-retroviral agents) OR (antiretroviral therapy, highly active) OR Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)) OR Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir) AND ("abnormalities, drug-induced" OR "drug hypersensitivity" OR "drug monitoring" OR "drug recalls" OR "poisoning" OR "safety-based drug withdrawals" OR "substance-related disorders" OR "Drug-Related Side Effects and Adverse Reactions" OR "Long Term Adverse Effects" OR "product surveillance, postmarketing" OR "adverse effects" OR "complications" OR "drug effects" OR "safe" OR "safety" OR "side effect*" OR "undesirable effect*" OR "treatment emergent" OR "tolerability" OR "toxicity" OR "adverse drug reaction*" OR "adrs" OR "adverse effect*" OR "adverse drug effect*" OR "adverse reaction*" OR "adverse event*" OR "adverse drug event*" OR "adverse outcome*" OR "complication*" OR "harm" OR "harmful" OR "harms" OR "risk" OR (adverse AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))) Filters: Interventional (Clinical Trial)
Global Index Medicus	((mh:(HIV infections)) OR (mh:(HIV)) OR (mh:(Acquired Immunodeficiency Syndrome)) OR (mh:(HIV Seropositivity)) OR ((HIV OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS))) AND ((mh:(Anti-Retroviral Agents)) OR (mh:(Antiretroviral Therapy, Highly Active)) OR ((Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly)

	AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)))) OR (ti:((Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir))) OR (ab:((Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir)))) AND ((mh:(Abnormalities, Drug-Induced)) OR (mh:(Drug Hypersensitivity)) OR (mh:(Drug Monitoring)) OR (mh:(Drug Recalls)) OR (mh:(Poisoning)) OR (mh:(Safety-Based Drug Withdrawals)) OR (mh:(Substance-Related Disorders)) OR (mh:(Drug-Related Side Effects and Adverse Reactions)) OR (mh:(Long Term Adverse Effects)) OR (mh:(Product Surveillance, Postmarketing)) OR ("adverse effect" OR "adverse effects" OR "drug effects" OR safe OR safety OR "side effect" OR "side effects" OR "undesirable effect" OR "undesirable effects" OR "treatment emergent" OR tolerability OR toxicity OR "adverse drug reaction" OR "adverse drug reactions" OR adrs OR "adverse drug effect" OR "adverse drug effects" OR "adverse reaction" OR "adverse reactions" OR "adverse event" OR "adverse events" OR "adverse drug event" OR "adverse drug events" OR "adverse outcome" OR "adverse outcomes" OR complication OR complications OR harm OR harmful OR harms OR risk OR ((adverse) AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)))) AND ((mh:(clinical trials)) OR (randomized controlled trial) OR (controlled clinical trial) OR randomized OR placebo OR randomly OR trial)

BMJ Open

Sex differences and adverse events of antiretrovirals in people living with HIV/AIDS: a systematic review and meta-analysis protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057094.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Dec-2021
Complete List of Authors:	de Oliveira, Jardel; Secretaria Municipal de Saúde, Médico de Família e Comunidade, Especialista em Saúde da Família, Geriatria e Gerontologia Alves, Maíra; Universidade de Sorocaba, Pharmaceutical Science Iwami, Rodrigo ; Universidade da Sorocaba Motter, Fabiane; University of Sorocaba, Programa de Pós-graduação em Ciências Farmacêuticas Bergamaschi, Cristiane; Universidade de Sorocaba, Pharmaceutical Science Silva, Marcus; Federal University of Amazonas, Faculty Medicine; Universidade de Sorocaba, Post-Graduate Program of Pharmaceutical Science Itria, Alexander; UFSCAR, Department of Economics Scalco, Diogo; Florianópolis Family Medicine Residency Program Lucio, Donavan; Florianópolis Family Medicine Residency Program Mazzei, Lauren; Universidade da Sorocaba Derech, Rodrigo; Florianópolis City Hall Pereira, Tiago; St Michael's Hospital Li Ka Shing Knowledge Institute, Health Research Centre Barreto , Jorge ; Oswaldo Cruz Foundation, Fiocruz Brasilia Lopes, Luciane; Universidade de Sorocaba, Pharmaceutical Science
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Epidemiology, HIV/AIDS, Pharmacology and therapeutics
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adverse events < THERAPEUTICS, CLINICAL PHARMACOLOGY

Sex differences and adverse events of antiretrovirals in people living with HIV/AIDS: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction: Antiretroviral therapy (ART) for HIV/AIDS is associated with adverse events (AE). However, little is known about the differences in the risk of AEs between women and men living with HIV/AIDS. This study aims to determine whether there is evidence indicating sex differences in AE incidence among people with HIV/AIDS treated with ART and determine the prevalence in women.

Methods and Analysis: We will include randomized trials evaluating ART in people living with HIV/AIDS with at least 12 weeks of duration follow up. Searches will be conducted in Medline, Embase, Cochrane Library, Epistemonikos, Lilacs, trial registries, and gray literature databases, without restriction on publication status, year of publication, and language. The primary outcome will be the risk of discontinuation or dropouts/withdrawals of ART due to AE and number of any treatment-emergent AE. The secondary outcome are the incidence of serious clinic or laboratory (grade 3 and/or 4) treatment-emergent AE, the incidence of hospitalization and death due to AE. We also will check specific AE that matter to women. Selection, data extraction, and quality assessment will be performed by pairs of reviewers, and disagreements will be resolved by consensus or adjudication by a third reviewer. Cochrane Collaboration tools will be used to assess the risk of bias. If appropriate, a meta-analysis will be conducted to synthesize results. The overall quality of the evidence for each outcome will be determined by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE).

Ethics and Dissemination: The results of the present systematic review will assist the formulation of public policies aimed at the management and monitoring of AE of ART in people living with HIV/AIDS. A deliberative dialogue will be scheduled with the Department of Chronic Conditions and Sexually Transmitted Infections of Brazil's Ministry of Health to align the project with policymakers' interests further.

Protocol Registration: PROSPERO – CRD42021251051

Keywords: HIV & AIDS. Health policy. Adverse events. Clinical Pharmachology.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review holds the potential to offer a comprehensive panorama on differences between men and women regarding the risk of adverse events during antiretroviral therapy.
- Our systematic review may have limited generalizability due to the reduced availability of data on within-study sex-by-treatment interaction effects and the possibility of aggregation bias.
- The primary studies could bring limitations to this review considering the confusion between the report of AE and signs and symptoms of HIV/AIDS.

INTRODUCTION

The human immunodeficiency virus (HIV) remains a major global public health problem. In 2020, 37.6 million people were living with HIV [1]. About 16% of them were unaware of being infected by the virus [2]. Most of these people are in low-middle-income countries [3].

Sex, here defined as biological, physiological, and genetic attributes that normally differentiate female individuals from males, can affect the incidence of adverse events (AE) [4]. In addition to HIV itself and possible AE to antiretroviral therapy (ART), women need to live with hormonal changes and unique health problems [5]. Sex inequalities in response to the combination of antiretrovirals have been reported in several studies summarized in a meta-analysis [6]. ART was evaluated for at least 48 weeks, between the years 2000 and 2008, finding several significant differences related to sex, in addition to demonstrating that there was better effectiveness of ART in men than in women.

ART has now been recommended for all patients, regardless of CD4 lymphocyte count, to decrease the transmissibility of the disease and to reduce long-term complications, such as HIV-related dementia [7]. Currently, around 27.4 million people in the world use ART [2]. Since therapy must be continued indefinitely, the focus of patient management should evolve towards the identification and management of early toxicities related to pharmacological treatment [8]. Viral suppression sustained

throughout life must be accompanied by individualized management and adjustments in advance to overcome the toxicities and AE of ART, both in the short and long term [9].

The use of ART has made HIV infection a chronic condition rather than a life-limiting disease [10]. With the increase in life expectancy of people living with HIV/AIDS, more elderly people started to be monitored. It is estimated that by 2030, 40% of the population with HIV will be people over 60 years of age [11]. However, the impact of the use of ART in the elderly, including AE, is still not fully known, as this age group is generally unrepresented in studies [10].

Brazil is considered a vanguard country in terms of care policy for patients living with HIV/acquired immunodeficiency syndrome (AIDS), especially regarding access to medication [12]. Discontinuation due to AE, however, remains one of the central problems, even when access to the service is made available [13]. Despite the general benefits of viral suppression and improved immune function because of ART far outweighing the risks associated with AE, in general, it appears that women are more susceptible than men to the development of toxicity associated with ART, and this can affect outcomes, care, and treatment [14]. In addition to the possible differences in sex, the elderly also seem to be more subject to the toxicity of drugs used for HIV/AIDS, such as nephrotoxicity, bone fractures, and peripheral neuropathy [10]. The known effect of ART on carbohydrate and lipid metabolism may impact the cardiovascular risk of older people [15], with an increase in the occurrence of myocardial infarction [10] and the need for a different look at their care.

Clinical studies on HIV rarely focus only on outcomes in women, with data on sex analysis often scarce and controversial [16-18]. It is worth mentioning that the long-term complications of ART can be underestimated since most clinical trials use highly specific inclusion criteria for recruiting patients and the duration of patient follow-up is relatively short [6, 19].

Understanding the occurrence of AE associated with sex, either women or men are important to assess the need to define public policies that can adapt the treatment to minimize the damage, improve adherence, and guarantee the success of the therapy. Consequently, this could also help reduce disease transmission [20].

Likewise, it is important to know the AE in the elderly, who tend to be more susceptible due to possible age-related pharmacokinetic and pharmacodynamic changes, added to polypharmacy and the greater number of comorbidities, with higher risk for drug-drug and drug-disease interactions [11]. It may be necessary to monitor the

occurrence of certain types of adverse reactions more frequently, depending on the ART regimen used [10].

AE to antiretrovirals have been reported with the use of all drugs and are the main reasons for discontinuing or exchanging therapy and non-adherence to treatment [21]. Changes in the immune system, common in people with HIV, also affect female hormones, causing problems in the menstrual period, uterine fibroids, genital tract infections, and early menopause [22].

In a preliminary search conducted on May 16th, 2021, with the terms ("Anti-Retroviral Agents" OR "Antiretroviral Agents" OR "anti-HIV Agents") in the International Prospective Register of Systematic Reviews (Prospero), Open Science Framework (OSF), Cochrane Protocols; and search for (Adverse AND Protocol) in the title at the British Medical Journal Open (BMJ Open) identified 66 records of systematic review protocols, but none intended to study the AE related to sex or age.

This systematic review has two objectives. The objective 1 is to determine whether there are sex differences in the risk of adverse events in people with HIV/AIDS treated with ART and the objective 2 is related to the prevalence of AE to reproductive system and bone mineral density (osteoporosis, osteopenia, and fractures) in women.

METHODS AND ANALYSIS

Study design, protocol, and registration

This systematic review study will be performed according to the recommendations found in the Cochrane Handbook for Intervention Reviews [23]. This protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [24] (**Supplementary Material 1**). The systematic review was also registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under registration no. CRD42021251051.

Patient and Public Involvement

We will conduct a deliberative dialogue, involving relevant decision-makers, healthcare professionals, and users of the Brazilian public health system living with

HIV/AIDS. We will present the results and get suggestions on implementing, monitoring, and managing AE in women living with HIV/AIDS using the DD approach.

Eligibility criteria

The research question was structured using the Population, Intervention, Comparison, and Outcomes (PICO) structure.

Objective 1

Inclusion criteria

Type of studies

We will include only randomized controlled trials (RCTs) with at least 12 weeks of follow up duration. For cross-over RCT studies, we will include the first period of data only. Although observational studies may have larger samples and longer follow-up times than RCTs, providing information on rarer or longer-term AE, non-randomized studies will be excluded due to the higher risk of bias compared to RCTs.

Type of participants

Individuals of both sexes living with HIV/AIDS and receiving antiretroviral – regardless of age. We opted to analyze sex and not gender differences for considering that our study's outcomes address biological, genetic, and physiological aspects that usually distinguish females from males instead of social attributes designated to women, men, and people with other gender identities [4].

Type of interventions

1. Any combinations of complexities and classes of ART regimens and specific ART drugs and timings of ART initiation.

Types of comparators

1. Oral placebo;
2. Any combinations of complexities and classes of ART regimens and specific ART drugs and timings of ART initiation.

*Types of outcome measures*PRIMARY OUTCOMES

1. Incidence of discontinuation or dropouts/withdrawals of ART due to AE
2. Total number of any AE
3. Total number of treatment-related AE.

If any of the primary studies do not show the total number of AE, we will consider the number of participants with at least one adverse reaction, as defined in the study for this outcome.

SECONDARY OUTCOMES

1. Incidence of any serious clinic or laboratory AE (grade 3 and/or 4)
2. We will extract this AE as reported or defined by studies (serious, separate AE grade 3, separate grade 4, grade 3, and 4). We adopted AE grades 3 and 4 as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.
3. Incidence of treatment-related serious clinic or laboratory AE (grade 3 and/or 4)
4. We will extract this AE as reported or defined by studies (serious, separate AE grade 3, separate grade 4, grade 3, and 4). We adopted AE grades 3 and 4 as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.
5. Incidence of osteoporosis (bone mineral density or fracture)
6. Incidence of hospitalization
7. Death due to AE.

If any of the primary studies do not show the total number of serious AE, we will consider the number of participants with at least one serious effect, as defined in the study for this outcome.

Objective 2

Inclusion criteria

Type of studies

We will include only randomized controlled trials (RCTs) with at least 12 weeks of follow up duration. For cross-over RCT studies, we will include the first period of data only. Although observational studies may have larger samples and longer follow-up times than RCTs, providing information on rarer or longer-term AE, non-randomized studies will be excluded due to the higher risk of bias compared to RCTs.

Type of participants

Women living with HIV/AIDS and receiving antiretroviral – regardless of age.

1. Any combinations of complexities and classes of ART regimens and specific ART drugs and timings of ART initiation.

Types of comparators

1. Any combinations of complexities and classes of ART regimens and specific ART drugs and timings of ART initiation.

Types of outcome measures

PRIMARY OUTCOMES

1. Incidence of discontinuation or dropouts/withdrawals of ART due to AE
2. Total number of any AE
3. Total number of treatment-related AE.

If any of the primary studies do not show the total number of AE, we will consider the number of participants with at least one adverse reaction, as defined in the study for this outcome.

SECONDARY OUTCOMES

2. Prevalence of women with:

1. Delayed puberty

   It means the absence of breast development by age 12 to 13 years in girls [25].

2. Amenorrhea

   Amenorrhea was defined as the absence of menses for more than 3 to months [26, 27].

3. Other menstrual irregularities are considered present when the participant reported any of five variations from normal menstruation including changes in regularity, frequency, volume, duration, and intermenstrual bleeding as defined by FIGO.

4. Early menopause

   Premature ovarian failure is considered when it occurs in women under the age of 40 years [27].

5. Vasomotor symptoms of menopause (hot flushes)

   Presence of hot flushes.

   Frequency of hot flushes by severity [28].

6. Osteopenia

   It's defined as bone mineral density (BMD) t-score -2.5 to -1 in women with 30 years or more and as BMD z-score -2 to -1 in those under 30 years [29].

7. Osteoporosis

   It's defined as bone mineral density (BMD) t-score < -2.5 in women with 30 years or more and as BMD z-score < -2 in those under 30 years [29].

8. Osteoporosis fractures

   Vertebral, non-vertebral, wrist, spine, and hip fractures will be considered.

Exclusion criteria

Studies evaluating ART regimens for HIV pre-exposure (PREP) and post-exposure (PEP) prophylaxis will be excluded. We will exclude studies focusing on pregnant, breastfeeding, or perinatal women and those that examined the use of ART in the presence of co-infections, such as viral hepatitis B and C and tuberculosis, secondary or post hoc analysis, and open-label extension. We will also exclude studies with antiretrovirals, or ART doses no longer used in clinical practice and with ART in the study phase, not yet utilized.

Search methods for identification of trials

The search strategy will use DeCS/MeSH descriptors and synonyms, being adapted according to each database searched (**Supplementary Material 2**). The searches will be conducted by an experienced librarian and will be reviewed by another professional librarian, according to the Peer Review of Electronic Search Strategies (Press) [30]. No limitations will be imposed on the publication status, duration of follow-up, year of publication, and language.

Electronic searches

A structured search for eligible primary studies will be conducted in the main electronic databases: MEDLINE via PubMed; Embase via Elsevier; Cochrane Central Register of Controlled Trials (Central); Epistemonikos; and Latin American and Caribbean Health Sciences Literature (Lilacs).

Searching other resources

A manual search will be conducted in the references of the included trials. We will adapt a specific structured search strategy for the gray literature, including dissertations databases (ProQuest Dissertations and Theses Database), records of clinical trials (Global Index Medicus of World Health Organization - WHO; Brazilian Registry of Clinical Trials - Rebec; ClinicalTrials.gov), summaries of selected international symposium conferences on HIV, websites of government agencies and non-governmental organizations that conduct research or implement relevant programs.

Data collection and analysis

Selection of studies

Trial selection and data extraction will be performed based on the Cochrane Handbook for Intervention Reviews [23]. More specifically, reviewers will work in pairs and independently assess titles and abstracts to verify if trials meet the eligibility criteria. A similar process will be used to track full texts. Discrepancies between the assessments will be resolved by consensus or adjudication by a third reviewer. In case of duplicate publication, we will use the article with the most complete data. Secondary publications from the same trial will also be used as supplementary information. We will perform

detailed assessments of each eligible trial to minimize the possibility of overlapping trials (i.e., trials that report data from the same participants). Subsequently, two team members will independently examine the references for each full-text article to identify additional relevant studies.

Data extraction and management

A pre-piloted and standardized form will be used to extract data from the included studies. The reviewers will be calibrated by extracting at least three articles and, afterward, they will carry out consensus, in pairs and independently. This process will take place until the standardization of the extracted data. The overlap of two articles in all teams of reviewers will be adopted to assess the reliability between reviewers in extracting data between the different teams.

After this stage, two reviewers will extract the data independently, and any discrepancies will be identified and resolved (with a third author, when necessary). The data collected will be characteristics of studies (sponsorship, country, registered number, number of sites, duration of study, timing of outcome measurement (in weeks or months), bibliometric information, patients [inclusion, exclusion criteria, age, antiretroviral therapy (ART) exposure (naive versus experienced), CD4 level, numbers in each arm, drug regimen,]; reported AE as specified in the section outcomes (number of participants who experienced an event) for dichotomous outcomes. We will also check the method of adverse event assessment: did the researchers actively monitor for AEs (low risk of bias), or did they simply provide spontaneous reporting of AEs that arose (high risk of bias)? For studies identified only in clinical trial registry websites, we will check the same data and check if they are ongoing.

When two or more papers are found for the same study, we will report it using only one ID and will extract the data of all the studies to provide the most complete report.

Assessment of methodological quality and risk of bias

The quality of individual studies will be assessed using Cochrane's Risk of Bias Tool version 2.0 for randomized trials on bias arising from the randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. The reviewers will assign independently as

answer alternatives "definitely yes", "probably yes", "probably not", "definitely not" or "not informed" for each of the domains, classifying, according to the answers, as “low risk of bias”, “some concern about the risk of bias” or “high risk of bias”. Reviewers will resolve disagreements through discussion, and a third person will judge unresolved disagreements. Publication bias will be assessed using the funnel graph [31] for each outcome.

Statistical analysis

Objective 1

The statistical approach to summarize trial results will depend vastly on the type of available data. Differences between sexes in the risk of an event after treatment with antiretrovirals can be considered covariate-by-treatment interactions. Hence, we will attempt to employ statistical techniques that explicitly disentangle within-trial interactions effects from between-trial interaction effects, thereby minimizing the risk of ecological bias [32].

We anticipate that some trials may report information sufficient to reconstruct individual-participant data (IPD) (e.g., the number of events by treatment group stratified by sex). In contrast, other trials may report information adequate to calculate only the odds ratio of the event and the proportion of women in each arm (i.e., aggregate data only). Thus, our primary analysis model will be based on an adaption of the model by Saramago et al. [33]. Specifically, we will use a Bayesian IPD-AD pair-wise random-effects model that separates the within-trial interaction effects from between-trial interaction effects.

However, if only aggregate data is available (e.g., odds ratio estimates and proportion of female by treatment group), we will perform a "daft" approach, combining across-trial interactions alone [32]. More specifically, we will conduct a Bayesian random-effects meta-regression to assess the association between the log-odds of the event and the proportion of women in the trial. We will graphically display these results using bubble plots and prediction lines with 95% credible intervals.

If only aggregate data is available, but it is possible to estimate the odds ratio by sex separately, we will perform the "deft" approach, combining within-trial interactions only. This approach eliminates the risk of ecological bias seen in the daft approach [32].

The log ratio of odds ratios will be used as a metric, and the summary estimate will be obtained by a Bayesian random-effects model [34].

All primary analyses will employ uninformative priors. However, for the between-trial variances, we will use informative prior distributions in sensitivity analyses [35]. We will estimate the between-trial heterogeneity from the median between-trial variance, τ2, observed in the posterior distribution. A τ^2 of up to 0.04 was prespecified to denote low heterogeneity, 0.16 to denote moderate, and 0.36 to denote high statistical heterogeneity among trial estimates [36].

Ninety-five percent credible intervals (95% Crls) will be calculated from the 2.5 and 97.5 percentiles of the posterior distributions. Bayesian models will be implemented in the BUGS language, and estimates will be obtained via Markov chain Monte Carlo (MCMC) methods (Gibbs sampling). Convergence will be checked graphically by running three chains and using the Gelman-Rubin statistic. An R statistic > 1.1 will be considered evidence of non-convergence [37]. The burning-in period will have 100,000 simulations, and three different chains with 166,667 simulations each will be used (500,000 simulations in total). Starting values were manually selected to guarantee very different random draws for the three chains. Results were summarized using posterior medians with 95% Crls. The autocorrelation and density of the estimates were checked graphically.Funnel plot asymmetry will be examined by contour-enhanced plots using frequentist estimates of log-odds ratio on the horizontal axis and their corresponding standard error estimates on the vertical axis. We will also investigate funnel plot asymmetry with Habord's test. For the latter, a $P < 0.10$ will be considered statistically significant.

For all analyses, we will use Stata 16 (College Station, TX, USA) and MultiBUGS 2.0 (Cambridge, UK).

Objective 2

We will meta-analyze proportions using a random-effects Bayesian model. Specifically, the model uses the binomial likelihood and the logit transformation of the proportions. The proportions are considered a random variable, and the mean of the logit proportions is assumed to follow a normal distribution [38]. We will use a non-informative prior for the mean of the logit-transformed study-specific proportions and the between-study variance. The burning-in period will have 50,000 simulations, and three

different chains with 50,000 simulations each will be used (150,000 simulations in total). Starting values were manually selected to guarantee very different random draws for the three chains. Results were summarized using posterior medians with 95% Crls. All model diagnostics will be performed as described above.

Subgroup analysis or sensitivity analysis

When appropriate, subgroup analysis will be employed. The subgroup that will be used includes age groups (<18 years *vs* 18-60 years *vs* >60 years); level of economic development of the study setting (low or lower-middle-income country *vs* middle or high-income country, as defined by the World Bank [39]); immunological status (CD4 <250 *vs* CD4 ≥250 cells/µl); time of follow-up (≤ 24 weeks *vs* 25 to 48 weeks *vs* ≥ 48 weeks); industry-independent funding (no *vs* yes); ITT analysis of AE (no *vs* yes); attribution of AEs to drugs (no *vs* yes); combined versus single antiretroviral therapy; risk of bias (high *vs* moderated and low; blinded *vs* open-label; adequate allocation concealment *vs* unclear allocation concealment).

Assessment of the certainty of the evidence and the strength of the recommendation

After the results are grouped, two reviewers will independently assess the overall certainty of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [40]. The main results of the review will be presented in outcome tables (Summary of Findings - SoF), as recommended by The Cochrane Collaboration [41]. The SoF table includes a general classification of the evidence related to each of the main outcomes, using the GRADE approach [42]. This table will be built with the aid of the GRADEpro software program.

The use of the GRADE allows evaluating the certainty of the evidence for each result considering the methodological quality, the objectivity of the evidence, the heterogeneity, the precision of the effect estimates, and the risk of publication bias [41]. If the analysis of an outcome is not possible, for example, due to the lack of data, we will present the reasons for this in the SoF table in a footnote.

ETHICS AND DISSEMINATION

It is hoped that the results will serve to assist in the formulation of public policies, aimed at guiding professionals on the management, and monitoring of the AE of ART in people living with HIV/AIDS. For this purpose, meetings are scheduled with the Department of Chronic Conditions and Sexually Transmitted Infections of the Ministry of Health of Brazil during the project, seeking to align it with the interests of policymakers.

We will also present the results and discuss the implementation, monitoring, and management of AE in people living with HIV/Aids in a DD with stakeholders, policymakers, and other researchers. This protocol will be submitted for approval to the ethics committee before the conduction of the DD.

DISCUSSION

Our future results could impact public policies for people living with HIV/AIDS by offering evidence that can highlight challenges and areas of improvement, with a special view over the diversity of people and their contexts. However, there are potential limitations.

The primary studies could bring limitations to this review considering the confusion between the report of AE and signs and symptoms of HIV/AIDS; some trials do not report the time of initiation of ART and do not separate the outcomes by sex.

Although the observational studies could give more information about AE for a long-time follow-up, this type of design could introduce more biases in the final analysis due to confounders.

The results of this systematic review could highlight important findings to decision-making, considering the management of AE in the different age ranges of women.

AUTHOR CONTRIBUTIONS

Study concept and design: LCL.

Methodology: LCL.

Drafting of the manuscript: JCO, LCL, and MRA.

Review and editing of the manuscript: LCL, MRA, CCB, SBF, JCO, RSI, FRM, TVP, MTS, AI, JMB, DLS, DSL, LGM, RDD.

ACKNOWLEDGEMENTS

The authors would like to thank Genevieve Gore and Mabel Figueiro, experienced librarians, for their collaboration with the review and definition of the final search strategy for the present study. The authors would like to thank Filipe Perini as well, for his contributions to the search questions, choice of medicines to be included, and the functioning of the current Brazilian public policies for HIV.

FUNDING

This research received funding from the São Paulo Research Foundation (FAPESP), grant n°. 2018/16893-8.

COMPETING INTERESTS

None to declare.

WORD COUNT: 3808

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SUPPLEMENTARY MATERIAL 1 - PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	15-16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	16
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Suppl. Material

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12-13
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11-12
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11-12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	12-13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	13
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	13-14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	14
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	15
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	15

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

SUPPLEMENTARY MATERIAL 2 – Search strategies

PubMed	(HIV infections [MeSH] OR HIV [MeSH] OR Acquired Immunodeficiency Syndrome [MeSH] OR HIV Seropositivity [MeSH] OR HIV OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR HIV/AIDS) AND (Anti-retroviral agents [Mesh] OR antiretroviral therapy, highly active [Mesh] OR Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)) OR Saquinavir [tiab] OR Lopinavir [tiab] OR Indinavir [tiab] OR Ritonavir [Tiab] OR Nelfinavir [tiab] OR Amprenavir [tiab] OR Fosamprenavir [tiab] OR Atazanavir [Tiab] OR Tipranavir [tiab] OR Darunavir [tiab] OR Cobicistat [Tiab] OR Emtricitabine [Tiab] OR Zidovudine [Tiab] OR Didanosine [tiab] OR Stavudine [tiab] OR Lamivudine [Tiab] OR Abacavir [Tiab] OR Nevirapine [tiab] OR Darunavir [Tiab] OR Etravirine [Tiab] OR Elvitegravir [Tiab] OR Alafenamide [Tiab] OR "Tenofovir disoproxil fumarate" [Tiab] OR "Tenofovir Alafenamide" [Tiab] OR Tenofovir [Tiab] OR Efavirenz [Tiab] OR Enfuvirtide [Tiab] OR Raltegravir [tiab] OR Maraviroc [tiab] OR Dolutegravir [tiab] OR Bictegravir [tiab]) AND (("abnormalities, drug-induced"[mesh] OR "drug hypersensitivity"[mesh] OR "drug monitoring"[mesh] OR "drug recalls"[mesh] OR "poisoning"[mesh] OR "safety-based drug withdrawals"[mesh] OR "substance-related disorders"[mesh] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "Long Term Adverse Effects"[Mesh] OR "product surveillance, postmarketing"[mesh] OR "adverse effects"[sh] OR "complications"[sh] OR "drug effects"[sh] OR "safe"[tw] OR "safety"[tw] OR "side effect*"[tw] OR "undesirable effect*"[tw] OR "treatment emergent"[tw] OR "tolerability"[tw] OR "toxicity"[tw] OR "adverse drug reaction*"[tw] OR "adrs"[tw] OR "adverse effect*"[tw] OR "adverse drug effect*"[tw] OR "adverse reaction*"[tw] OR "adverse event*"[tw] OR "adverse drug event*"[tw] OR "adverse outcome*"[tw] OR "complication*"[tw] OR "harm"[tw] OR "harmful"[tw] OR "harms"[tw] OR "risk"[tw] OR (adverse[tw] AND (effect[tw] OR effects[tw] OR reaction[tw] OR reactions[tw] OR event[tw] OR events[tw] OR outcome[tw] OR outcomes[tw]))))

	AND ((((((randomized controlled trial [pt]) OR controlled clinical trial [pt]) OR randomized [tiab]) OR placebo [tiab]) OR clinical trials as topic [mesh: noexp] OR randomly [tiab]) OR trial [tiab]) NOT (animals [MeSH] NOT humans [MeSH])
Embase	No. Query Results 11,308 #6 #1 AND #2 AND #3 AND #4 NOT #5 5,615,547 #5 'animal'/exp NOT 'human'/exp 1,832,252 #4 'randomized controlled trial':it OR 'controlled clinical trial':it OR randomized:ab,ti OR placebo:ab,ti OR ('clinical trial'/de AND topic) OR randomly:ab,ti OR trial:ab,ti 10,788,807 #3 'adverse drug reaction'/exp OR 'drug hypersensitivity'/exp OR 'drug monitoring'/exp OR 'drug recall'/exp OR 'drug intoxication'/exp OR 'side effect'/exp OR 'postmarketing surveillance'/exp OR 'drug safety'/exp OR 'drug surveillance program'/exp OR 'drug toxicity'/exp OR 'adverse event'/exp OR 'complication'/exp OR 'drug effect'/exp OR safe OR safety OR 'side effect*' OR 'undesirable effect*' OR 'treatment emergent' OR 'tolerability' OR 'toxicity' OR 'adverse drug reaction*' OR 'adrs' OR 'adverse effect*' OR 'adverse drug effect*' OR 'adverse reaction*' OR 'adverse event*' OR 'adverse drug event*' OR 'adverse outcome*' OR 'complication*' OR 'harm' OR 'harmful' OR 'harms' OR 'risk' OR (adverse AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)) 522,768 #2 'antiretrovirus agent'/exp OR 'highly active antiretroviral therapy'/exp OR antiretroviral* OR (anti AND retroviral*) OR arv OR art OR 'antiretroviral therapy' OR haart OR (highly AND active AND antiretroviral* AND therap*) OR (anti

	AND hiv) OR (anti AND acquired AND immunodeficiency) OR (anti AND acquired AND immuno-deficiency) OR (anti AND acquired AND immune-deficiency) OR (anti AND acquired AND immun* AND deficienc*) OR saquinavir:ab,ti OR lopinavir:ab,ti OR indinavir:ab,ti OR ritonavir:ab,ti OR nelfinavir:ab,ti OR amprenavir:ab,ti OR fosamprenavir:ab,ti OR atazanavir:ab,ti OR tipranavir:ab,ti OR cobicistat:ab,ti OR emtricitabine:ab,ti OR zidovudine:ab,ti OR didanosine:ab,ti OR stavudine:ab,ti OR lamivudine:ab,ti OR abacavir:ab,ti OR nevirapine:ab,ti OR darunavir:ab,ti OR etravirine:ab,ti OR elvitegravir:ab,ti OR alafenamide:ab,ti OR 'tenofovir disoproxil fumarate':ab,ti OR 'tenofovir alafenamide':ab,ti OR tenofovir:ab,ti OR efavirenz:ab,ti OR enfuvirtide:ab,ti OR raltegravir:ab,ti OR maraviroc:ab,ti OR dolutegravir:ab,ti OR bictegravir:ab,ti 610,204 #1 'human immunodeficiency virus infection'/exp OR 'acquired immune deficiency syndrome'/exp OR 'human immunodeficiency virus 1'/exp OR 'human immunodeficiency virus 1 infection'/exp OR 'human immunodeficiency virus 2'/exp OR 'human immunodeficiency virus 2 infection'/exp OR 'hiv aids'/exp OR hiv OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR (hiv AND infect*) OR (human AND immunodeficiency AND virus) OR (human AND immune AND deficiency AND virus) OR (human AND immuno-deficiency AND virus) OR (human AND immune-deficiency AND virus) OR (human AND immun* AND deficiency AND virus) OR (acquired AND immunodeficiency AND syndromes) OR (acquired AND immune AND deficiency AND syndrome) OR (acquired AND immuno-deficiency AND syndrome) OR (acquired AND immune-deficiency AND syndrome) OR (acquired AND immun* AND deficiency AND syndrome)
Cochrane Central	Search Name: Cochrane RADAR Last Saved: 25/05/2021 20:49:52 Comment: ID Search #1 MeSH descriptor: [HIV Infections] explode all trees #2 MeSH descriptor: [HIV] explode all trees #3 MeSH descriptor: [Acquired Immunodeficiency Syndrome] explode all trees #4 MeSH descriptor: [HIV Seropositivity] explode all trees #5 (HIV OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR

	acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS):ti,ab,kw #6 #1 OR #2 OR #3 OR #4 OR #5 #7 MeSH descriptor: [Anti-Retroviral Agents] explode all trees #8 MeSH descriptor: [Antiretroviral Therapy, Highly Active] explode all trees #9 (Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*))):ti,ab,kw #10 (Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir):ti,ab #11 #7 OR #8 OR #9 OR #10 #12 MeSH descriptor: [Abnormalities, Drug-Induced] explode all trees #13 MeSH descriptor: [Drug Hypersensitivity] explode all trees #14 MeSH descriptor: [Drug Monitoring] explode all trees #15 MeSH descriptor: [Drug Recalls] explode all trees #16 MeSH descriptor: [Poisoning] explode all trees #17 MeSH descriptor: [Safety-Based Drug Withdrawals] explode all trees #18 MeSH descriptor: [Substance-Related Disorders] explode all trees #19 MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees #20 MeSH descriptor: [Long Term Adverse Effects] explode all trees #21 MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees #22 MeSH descriptor: [] explode all trees and with qualifier(s): [adverse effects - AE] #23 MeSH descriptor: [] explode all trees and with qualifier(s): [complications - CO] #24 MeSH descriptor: [] explode all trees and with qualifier(s): [drug effects - DE] #25 ("safe" OR "safety" OR "side effect*" OR "undesirable effect*" OR "treatment emergent" OR "tolerability" OR "toxicity" OR "adverse drug reaction*" OR "adrs" OR "adverse effect*" OR "adverse drug effect*" OR "adverse

	reaction*" OR "adverse event*" OR "adverse drug event*" OR "adverse outcome*" OR "complication*" OR "harm" OR "harmful" OR "harms" OR "risk" OR (adverse AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))) #26 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 #27 #22 OR #23 OR #24 #28 #25 OR #26 OR #27 #29 #6 AND #11 AND #28
Biblioteca Virtual em Saúde (BVS)	((mh:(HIV infections)) OR (mh:(HIV)) OR (mh:(Acquired Immunodeficiency Syndrome)) OR (mh:(HIV Seropositivity)) OR ((HIV OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS))) AND ((mh:(Anti-Retroviral Agents)) OR (mh:(Antiretroviral Therapy, Highly Active)) OR ((Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)))) OR (ti:((Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir))) OR (ab:((Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir)))) AND ((mh:(Abnormalities, Drug-Induced)) OR (mh:(Drug Hypersensitivity)) OR (mh:(Drug Monitoring)) OR (mh:(Drug Recalls)) OR (mh:(Poisoning)) OR (mh:(Safety-Based Drug Withdrawals)) OR (mh:(Substance-Related Disorders)) OR (mh:(Drug-Related Side Effects and Adverse Reactions)) OR (mh:(Long Term Adverse Effects)) OR (mh:(Product Surveillance, Postmarketing)) OR ("adverse effect" OR "adverse effects" OR "drug effects" OR safe OR safety OR "side effect" OR "side effects" OR

	"undesirable effect" OR "undesirable effects" OR "treatment emergent" OR tolerability OR toxicity OR "adverse drug reaction" OR "adverse drug reactions" OR adrs OR "adverse drug effect" OR "adverse drug effects" OR "adverse reaction" OR "adverse reactions" OR "adverse event" OR "adverse events" OR "adverse drug event" OR "adverse drug events" OR "adverse outcome" OR "adverse outcomes" OR complication OR complications OR harm OR harmful OR harms OR risk OR ((adverse) AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)))) AND ((mh:(clinical trials)) OR (randomized controlled trial) OR (controlled clinical trial) OR randomized OR placebo OR randomly OR trial)
Epistemonikos	((HIV infections) OR HIV OR (Acquired Immunodeficiency Syndrome) OR (HIV Seropositivity) OR (hiv-1) OR (hiv-2) OR hiv1 OR hiv2 OR (hiv infect*) OR (human immunodeficiency virus) OR (human immune deficiency virus) OR (human immuno-deficiency virus) OR (human immune-deficiency virus) OR ((human immun*) AND (deficiency virus)) OR (acquired immunodeficiency syndromes) OR (acquired immune deficiency syndrome) OR (acquired immuno-deficiency syndrome) OR (acquired immune-deficiency syndrome) OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS) AND ((Anti-retroviral agents) OR (antiretroviral therapy, highly active) OR Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)) OR Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir) AND ("abnormalities, drug-induced" OR "drug hypersensitivity" OR "drug monitoring" OR "drug recalls" OR "poisoning" OR "safety-based drug withdrawals" OR "substance-related disorders" OR "Drug-Related Side Effects and Adverse Reactions" OR "Long Term Adverse Effects" OR "product surveillance, postmarketing" OR "adverse effects" OR "complications" OR "drug effects" OR "safe" OR "safety" OR "side effect*" OR "undesirable effect*" OR "treatment emergent" OR "tolerability" OR "toxicity" OR "adverse drug reaction*" OR "adrs" OR "adverse effect*" OR "adverse drug effect*" OR "adverse reaction*" OR "adverse event*" OR "adverse drug event*" OR "adverse outcome*" OR "complication*" OR "harm" OR "harmful" OR "harms" OR "risk" OR (adverse AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))) AND ((randomized controlled trial) OR (controlled clinical trial) OR randomized OR placebo OR randomly OR trial)

ClinicalTrials.gov	((HIV infections) OR HIV OR (Acquired Immunodeficiency Syndrome) OR (HIV Seropositivity) OR (hiv-1) OR (hiv-2) OR hiv1 OR hiv2 OR (hiv infect*) OR (human immunodeficiency virus) OR (human immune deficiency virus) OR (human immuno-deficiency virus) OR (human immune-deficiency virus) OR ((human immun*) AND (deficiency virus)) OR (acquired immunodeficiency syndromes) OR (acquired immune deficiency syndrome) OR (acquired immuno-deficiency syndrome) OR (acquired immune-deficiency syndrome) OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS) AND ((Anti-retroviral agents) OR (antiretroviral therapy, highly active) OR Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)) OR Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir) AND ("abnormalities, drug-induced" OR "drug hypersensitivity" OR "drug monitoring" OR "drug recalls" OR "poisoning" OR "safety-based drug withdrawals" OR "substance-related disorders" OR "Drug-Related Side Effects and Adverse Reactions" OR "Long Term Adverse Effects" OR "product surveillance, postmarketing" OR "adverse effects" OR "complications" OR "drug effects" OR "safe" OR "safety" OR "side effect*" OR "undesirable effect*" OR "treatment emergent" OR "tolerability" OR "toxicity" OR "adverse drug reaction*" OR "adrs" OR "adverse effect*" OR "adverse drug effect*" OR "adverse reaction*" OR "adverse event*" OR "adverse drug event*" OR "adverse outcome*" OR "complication*" OR "harm" OR "harmful" OR "harms" OR "risk" OR (adverse AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))) Filters: Interventional (Clinical Trial)
Global Index Medicus	((mh:(HIV infections)) OR (mh:(HIV)) OR (mh:(Acquired Immunodeficiency Syndrome)) OR (mh:(HIV Seropositivity)) OR ((HIV OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS))) AND ((mh:(Anti-Retroviral Agents)) OR (mh:(Antiretroviral Therapy, Highly Active)) OR ((Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly)

	AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)))) OR (ti:((Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir))) OR (ab:((Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir)))) AND ((mh:(Abnormalities, Drug-Induced)) OR (mh:(Drug Hypersensitivity)) OR (mh:(Drug Monitoring)) OR (mh:(Drug Recalls)) OR (mh:(Poisoning)) OR (mh:(Safety-Based Drug Withdrawals)) OR (mh:(Substance-Related Disorders)) OR (mh:(Drug-Related Side Effects and Adverse Reactions)) OR (mh:(Long Term Adverse Effects)) OR (mh:(Product Surveillance, Postmarketing)) OR ("adverse effect" OR "adverse effects" OR "drug effects" OR safe OR safety OR "side effect" OR "side effects" OR "undesirable effect" OR "undesirable effects" OR "treatment emergent" OR tolerability OR toxicity OR "adverse drug reaction" OR "adverse drug reactions" OR adrs OR "adverse drug effect" OR "adverse drug effects" OR "adverse reaction" OR "adverse reactions" OR "adverse event" OR "adverse events" OR "adverse drug event" OR "adverse drug events" OR "adverse outcome" OR "adverse outcomes" OR complication OR complications OR harm OR harmful OR harms OR risk OR ((adverse) AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)))) AND ((mh:(clinical trials)) OR (randomized controlled trial) OR (controlled clinical trial) OR randomized OR placebo OR randomly OR trial)

BMJ Open

Sex differences and adverse events of antiretrovirals in people living with HIV/AIDS: a systematic review and meta-analysis protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057094.R2
Article Type:	Protocol
Date Submitted by the Author:	03-Jan-2022
Complete List of Authors:	de Oliveira, Jardel; Secretaria Municipal de Saúde, Médico de Família e Comunidade, Especialista em Saúde da Família, Geriatria e Gerontologia Alves, Maíra; Universidade de Sorocaba, Pharmaceutical Science Lopes, Luis; Federal University of Rio de Janeiro Iwami, Rodrigo ; Universidade da Sorocaba Motter, Fabiane; University of Sorocaba, Programa de Pós-graduação em Ciências Farmacêuticas Bergamaschi, Cristiane; Universidade de Sorocaba, Pharmaceutical Science Silva, Marcus; Federal University of Amazonas, Faculty Medicine; Universidade de Sorocaba, Post-Graduate Program of Pharmaceutical Science Itria, Alexander; UFSCAR, Department of Economics Scalco, Diogo; Florianópolis Family Medicine Residency Program Lucio, Donavan; Florianópolis Family Medicine Residency Program Mazzei, Lauren; Universidade da Sorocaba Derech, Rodrigo; Florianópolis City Hall Pereira, Tiago; St Michael's Hospital Li Ka Shing Knowledge Institute, Health Research Centre Barreto , Jorge ; Oswaldo Cruz Foundation, Fiocruz Brasilia Lopes, Luciane; Universidade de Sorocaba, Pharmaceutical Science
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Epidemiology, HIV/AIDS, Pharmacology and therapeutics
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adverse events < THERAPEUTICS, CLINICAL PHARMACOLOGY

Sex differences and adverse events of antiretrovirals in people living with HIV/AIDS: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction: Antiretroviral therapy (ART) for HIV/AIDS is associated with adverse events (AEs). However, little is known about the differences in the risk of AEs between women and men living with HIV/AIDS. This study aims to determine (i) whether there are sex differences in the risk of AE in people with HIV/AIDS treated with ART and (ii) the prevalence of AEs to the reproductive system and bone mineral density in women.

Methods and Analysis: This Systematic Review (SR) will include randomized trials evaluating ART in people living with HIV/AIDS with at least 12 weeks of duration follow-up. Searches will be conducted in Medline, Embase, Cochrane Library, Epistemonikos, Lilacs, trial registries, and gray literature databases, without restriction on publication status, year of publication, and language. The primary outcome will be the risk of ART discontinuation or dropouts/withdrawals of ART due to AE and the number of any treatment-emergent AE. The secondary outcomes are the incidence of serious clinic or laboratory (grade 3 and/or 4) treatment-emergent AEs, hospitalization, death, and AE specific to the reproductive system and bone mineral density (osteoporosis, osteopenia, and fractures) of women. Selection, data extraction, and quality assessment will be performed by pairs of reviewers. Cochrane Collaboration tools will be used to assess the risk of bias. If appropriate, a meta-analysis will be conducted to synthesize results. The overall quality of the evidence for each outcome will be determined by the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE).

Ethics and Dissemination: The results of this SR will assist the formulation of public policies aimed at the management and monitoring of AE of ART in people living with HIV/AIDS. A deliberative dialogue will be scheduled with the Department of Chronic Conditions and Sexually Transmitted Infections of Brazil's Ministry of Health to align the project with policymakers' interests.

Protocol Registration: PROSPERO – CRD42021251051

Keywords: HIV & AIDS. Health policy. Adverse events. Clinical Pharmacology.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review, in addition to studying the differences between the sexes, it will scrutinize the literature to estimate the prevalence of adverse events specific to women, about which the existing literature is quite conflicting.
- This study will use the key stakeholders (e.g., policymakers, opinion leader health care professional, community representative of patients, etc.) through deliberative dialogue, to overcome barriers to implement the evidence summarized.
- Our systematic review may have limited generalizability due to the reduced availability of data on within-study sex-by-treatment interaction effects and the possibility of aggregation bias.
- The primary studies could bring limitations to this review considering the confusion between the report of adverse events and signs and symptoms of HIV/AIDS.

INTRODUCTION

The human immunodeficiency virus (HIV) remains a major global public health problem. In 2020, 37.6 million people were living with HIV [1]. About 16% of them were unaware of being infected by the virus [2]. Most of these people are in low-middle-income countries [3].

Antiretroviral therapy (ART) has now been recommended for all patients, regardless of CD4 lymphocyte count, to decrease the transmissibility of the disease and to reduce long-term complications, such as HIV-related dementia [4]. Currently, around 27.4 million people in the world use ART [2]. Since therapy must be continued indefinitely, the focus of patient management should evolve towards the identification and management of early toxicities related to pharmacological treatment [5]. Viral suppression sustained throughout life must be accompanied by individualized management and adjustments in advance, to overcome toxicities and adverse events (AEs) in ART, both in the short and long term [6].

In addition to HIV itself and possible AEs to ART, women need to live with hormonal changes and unique health problems [7]. Sex inequalities in response to the combination of antiretrovirals have been reported in several studies summarized in a

meta-analysis [8]. ART was evaluated for at least 48 weeks, between the years 2000 and 2008, finding several significant differences related to sex, in addition to demonstrating that there was better effectiveness of ART in men than in women.

AEs to antiretrovirals have been reported with the use of all drugs and are the main reason for discontinuation, exchanges in therapy, and non-adherence to treatment [9]. Changes in the immune system, common in people with HIV, also affect female hormones, causing problems in the menstrual period, uterine fibroids, genital tract infections, and early menopause [10].

Ovarian function in women with HIV is reportedly shorter than in women uninfected by the virus, which leads to an increase in the burden of the disease as menopause impacts on the onset and progression of chronic diseases and bone mineral density (BMD) [11]. Observational studies are controversial regarding the influence of ART on menstrual abnormalities. A retrospective cohort [12] was not associated with ART, while a cross-sectional study [13] showed increased abnormal menstruation in women using ART compared to treatment-naïve women (AOR 2.36, 95% CI 1.25– 4.45). A systematic review [14] that combined six observational studies showed an increase in amenorrhea in women with HIV, which may be associated with low bone mineral density. The authors reinforce the need to assess the reproductive health and last menstrual period of women with the virus.

Studies suggest an increased bone mineral loss in women with HIV, but its relationship with the disease or the use of antiretroviral therapy is uncertain. A systematic review [15] with one clinical trial and four cross-sectional studies showed a difference greater than 3% in bone mineral density of the femoral neck in women using regimens containing protease inhibitors, but failed to conclude on the risk of fractures. Another review [16], also based mainly on cross-sectional studies, points out that HIV infection reduces bone density in postmenopausal women, but that additional studies are needed to understand the mechanism of this effect and whether ART has an impact on bone mineral density.

Brazil is considered a vanguard country in terms of healthcare policy for patients living with HIV/AIDS, especially regarding access to medication [17]. Discontinuation due to AEs, however, remains one of the central problems, even when access to the service is available [18]. Despite the general benefits of viral suppression and improved immune function due to ART far outweigh the risks associated with AEs, in general, it

appears that women are more susceptible than men to develop toxicities associated with ART, and this can affect outcomes, care, and treatment [19].

Clinical studies on HIV rarely focus only on outcomes in women, with data on sex analysis often scarce and controversial [20-22]. It is worth mentioning that the long-term complications of ART can be underestimated since most clinical trials use highly specific inclusion criteria for recruiting patients and the duration of patient follow-up is relatively short [8, 23].

Understanding the occurrence of AEs associated with sex is important to assess the need to define public policies that can adapt ART to minimize the damage, improve adherence, and guarantee the success of the therapy. Consequently, this could also help reduce disease transmission [24].

In a preliminary search conducted on May 16th, 2021, with the terms ("Anti-Retroviral Agents" OR "Antiretroviral Agents" OR "anti-HIV Agents") in the International Prospective Register of Systematic Reviews (Prospero), Open Science Framework (OSF), Cochrane Protocols; and with the title terms (Adverse AND Protocol) in the journals that publish SR protocols (e.g., Systematic Reviews, BMJ Open, Plos One, Medicine, etc.) we identified 66 records of systematic review protocols, but none intended to study AEs related to sex.

This systematic review has two objectives. Objective 1 is to determine whether there are sex differences in the risk of adverse events in people with HIV/AIDS treated with ART and objective 2 is to determine the prevalence of AEs to the reproductive system and bone mineral density (osteoporosis, osteopenia, and fractures) in women.

METHODS AND ANALYSIS

Study design, protocol, and registration

This systematic review study will be performed according to the recommendations of the Cochrane Handbook for Intervention Reviews [25]. This protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [26] (**Supplementary Material 1**). This systematic review was also registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under registration no. CRD42021251051.

Patient and Public Involvement

We will conduct a deliberative dialogue (DD), involving relevant decision-makers, healthcare professionals, and users of the Brazilian public health system living with HIV/AIDS. We will present the results and get suggestions on implementation, monitoring, and management of AEs in women living with HIV/AIDS using the DD approach.

Eligibility criteria

The research question was structured using the Population, Intervention, Comparison, and Outcomes (PICO) structure.

Objective 1

Inclusion criteria

Type of studies

We will include only randomized controlled trials (RCTs) with at least 12 weeks of follow-up duration. For cross-over RCTs, we will include the first period of data only. Although observational studies may have larger samples and longer follow-up times than RCTs, providing information on rarer or longer-term AEs, non-randomized studies will be excluded due to the higher risk of bias compared to RCTs. In an RCT, we have more monitored/controlled, standardized, and reported diagnoses of AEs compared to observational studies.

Type of participants

Individuals of both sexes living with HIV/AIDS and receiving antiretroviral – regardless of age. Our study intends to analyze sex differences according to their biological definition, not the distinction between females and males by the choice of gender identity [27].

Type of interventions

1. Any combinations of complexities and classes of ART regimens, specific ART drugs, and timings of ART initiation.

Types of comparators

1. Oral placebo;
2. Any combinations of complexities and classes of ART regimens, specific ART drugs, and timings of ART initiation.

Types of outcome measures

PRIMARY OUTCOMES

1. Risk of discontinuation or dropouts/withdrawals of ART due to AEs
2. Risk of any AE
3. Risk of treatment-related AE.

SECONDARY OUTCOMES

1. Risk of any serious clinic or laboratory AE (grade 3 and/or 4)
   We will extract the AE as reported or defined by studies (serious, separate AE grade 3, separate grade 4, grade 3, and 4). We adopted AE grades 3 and 4 as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events [28].
2. Risk of treatment-related serious clinic or laboratory AE (grade 3 and/or 4)
   We will extract the AE as reported or defined by studies (serious, separate AE grade 3, separate grade 4, grade 3, and 4). We adopted AE grades 3 and 4 as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events [28].
3. Risk of osteoporosis (bone mineral density or fracture)
4. Risk of hospitalization
5. Risk of death due to AE.

Objective 2

Inclusion criteria

Type of studies

We will include only randomized controlled trials (RCTs) with at least 12 weeks of follow-up duration. For cross-over RCTs, we will include the first period of data only. Although observational studies may have larger samples and longer follow-up times than RCTs, providing information on rarer or longer-term AE, non-randomized studies will be excluded due to the higher risk of bias compared to RCTs.

Type of participants

Women living with HIV/AIDS and receiving ART – regardless of age.

Type of interventions

1. Any combinations of complexities and classes of ART regimens, specific ART drugs, and timings of ART initiation.

Types of comparators

1. Any combinations of complexities and classes of ART regimens, specific ART drugs, and timings of ART initiation.

Types of outcome measures

Prevalence of women with:

1. Delayed puberty
   It means the absence of breast development by age 12 to 13 years in girls [29].
2. Amenorrhea
   Amenorrhea was defined as the absence of menses for more than three months [14, 30].
3. Other menstrual irregularities will be considered present whenever the participant reports any of the five variations from normal menstruation including changes in

regularity, frequency, volume, duration, and intermenstrual bleeding as defined by the International Federation of Gynecology and Obstetrics (FIGO).

4. Early menopause

   Premature ovarian failure is considered when it occurs in women under the age of 40 years [30].

5. Vasomotor symptoms of menopause (hot flushes)

   Presence of hot flushes.

   Frequency of hot flushes by severity [31].

6. Osteopenia

   It is defined as bone mineral density (BMD) t-score -2.5 to -1 in women with 30 years or more and as BMD z-score -2 to -1 in those under 30 years [28].

7. Osteoporosis

   It is defined as bone mineral density (BMD) t-score < -2.5 in women with 30 years or more and as BMD z-score < -2 in those under 30 years [28].

8. Osteoporosis fractures

   Vertebral, non-vertebral, wrist, spine, and hip fractures will be considered.

Exclusion criteria

Studies evaluating ART regimens for HIV pre-exposure (PREP) and post-exposure (PEP) prophylaxis will be excluded. We will exclude studies focusing on pregnant, breastfeeding, or perinatal women; studies that examined the use of ART in the presence of co-infections, such as viral hepatitis B and C and tuberculosis; secondary or *post hoc* analysis; and open-label extensions. We will also exclude studies with antiretrovirals, or ART doses no longer used in clinical practice, and with ART in the study phase, not yet utilized.

Search methods for identification of trials

The search strategy will use DeCS/MeSH descriptors and synonyms, being adapted according to each database searched (**Supplementary Material 2**). The searches will be conducted by an experienced librarian and will be reviewed by another professional librarian, according to the Peer Review of Electronic Search Strategies

(Press) [32]. No limitations will be imposed on the publication status, duration of follow-up, year of publication, and language (we will be using a professional translation service)

Electronic searches

A structured search for eligible primary studies will be conducted in the main electronic databases: MEDLINE via PubMed; Embase via Elsevier; Cochrane Central Register of Controlled Trials (Central); Epistemonikos; and Latin American and Caribbean Health Sciences Literature (Lilacs).

Searching other resources

A manual search will be conducted in the references of the included trials. We will adapt a specific structured search strategy for the gray literature, including dissertations databases (ProQuest Dissertations and Theses Database), records of clinical trials (Global Index Medicus of World Health Organization - WHO; Brazilian Registry of Clinical Trials - Rebec; ClinicalTrials.gov), summaries of selected international symposium conferences on HIV, websites of government agencies and non-governmental organizations that conduct research or implement relevant programs.

Data collection and analysis

Selection of studies

Trial selection and data extraction will be performed based on the Cochrane Handbook for Intervention Reviews [25]. More specifically, reviewers will work in pairs and independently to assess the eligibility of titles and abstracts. A similar process will be used to track full texts. Discrepancies between the assessments will be resolved by consensus or adjudication by a third reviewer. In case of duplicate publication, we will use the article with the most complete data. Secondary publications from the same trial will also be used as supplementary information. We will perform detailed assessments of each eligible trial to minimize the possibility of overlapping trials (i.e., trials that report data from the same participants). Subsequently, two team members will independently examine the references for each full-text article to identify additional relevant studies.

Data extraction and management

A pre-piloted and standardized form will be used to extract data from the included studies. The reviewers will be calibrated by extracting at least three articles, in pairs and independently, and, afterward, they will carry out consensus. This process will take place until the standardization of the extracted data. The overlap of two articles in all teams of reviewers will be adopted to assess the reliability between reviewers in extracting data in the different teams.

After this stage, two reviewers will extract the data independently, and any discrepancies will be identified and resolved (with a third author, when necessary). The data collected will be characteristics of studies (sponsorship, country, registered number, number of sites, duration of the study, timing of outcome measurement (in weeks or months); bibliometric information; information about patients (inclusion, exclusion criteria, age, ART exposure (naive versus experienced), CD4 level, numbers in each arm, drug regimen); and if the study reported AE as specified in the section outcomes (number of participants who experienced an event) for dichotomous outcomes. We will also check the method of AE assessment: did the researchers actively monitor for AEs (low risk of bias), or did they simply provide spontaneous reporting of AEs that arose (high risk of bias)? For studies identified only in clinical trial registry websites, we will check the same data and check if they are ongoing.

When two or more papers are found for the same study, we will report it using only one ID and will extract the data of all the studies to provide the most complete report.

Assessment of methodological quality and risk of bias

The quality of individual studies will be assessed using Cochrane's Risk of Bias (RoB) Tool version 2.0 for randomized trials on bias arising from the randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. The reviewers will independently assign "definitely yes", "probably yes", "probably not", "definitely not" or "not informed" for each of the domains, classifying, according to the answers, as “low risk of bias”, “some concern about the risk of bias” or “high risk of bias”. Reviewers will resolve disagreements through discussion, and a third person will judge unresolved

disagreements. Publication bias will be assessed using the funnel graph [33] for each outcome.

Statistical analysis

Objective 1

The statistical approach to summarize trial results will depend vastly on the type of available data. Differences between sexes in the risk of an event after treatment with antiretrovirals can be considered covariate-by-treatment interactions. Hence, we will attempt to employ statistical techniques that explicitly disentangle within-trial interactions effects from between-trial interaction effects, thereby minimizing the risk of ecological bias [34].

We anticipate that some trials may report information sufficient to reconstruct individual-participant data (IPD) (e.g., the number of events by treatment group stratified by sex). In contrast, other trials may report information adequate to calculate only the odds ratio of the event and the proportion of women in each arm (i.e., aggregate data only). Thus, our primary analysis model will be based on an adaption of the model by Saramago et al. [35]. Specifically, we will use a Bayesian IPD-AD pair-wise random-effects model that separates the within-trial interaction effects from between-trial interaction effects.

However, if only aggregate data is available (e.g., odds ratio estimates and proportion of female by treatment group), we will perform a "daft" approach, combining across-trial interactions alone [34]. More specifically, we will conduct a Bayesian random-effects meta-regression to assess the association between the log-odds of the event and the proportion of women in the trial. We will graphically display these results using bubble plots and prediction lines with 95% credible intervals.

If only aggregate data is available, but it is possible to estimate the odds ratio by sex separately, we will perform the "deft" approach, combining within-trial interactions only. This approach eliminates the risk of ecological bias seen in the daft approach [34]. The log ratio of odds ratios will be used as a metric, and the summary estimate will be obtained by a Bayesian random-effects model [36].

All primary analyses will employ uninformative priors. However, for the between-trial variances, we will use informative prior distributions in sensitivity analyses [37]. We will estimate the between-trial heterogeneity from the median between-trial variance, $\tau 2$,

observed in the posterior distribution. A τ^2 of up to 0.04 was prespecified to denote low heterogeneity, 0.16 to denote moderate, and 0.36 to denote high statistical heterogeneity among trial estimates [38].

Ninety-five percent credible intervals (95% Crls) will be calculated from the 2.5 and 97.5 percentiles of the posterior distributions. Bayesian models will be implemented in the BUGS language, and estimates will be obtained via Markov chain Monte Carlo (MCMC) methods (Gibbs sampling). Convergence will be checked graphically by running three chains and using the Gelman-Rubin statistic. An R statistic > 1.1 will be considered evidence of non-convergence [39]. The burning-in period will have 100,000 simulations, and three different chains with 166,667 simulations each will be used (500,000 simulations in total). Starting values were manually selected to guarantee very different random draws for the three chains. Results were summarized using posterior medians with 95% Crls. The autocorrelation and density of the estimates were checked graphically. Funnel plot asymmetry will be examined by contour-enhanced plots using frequentist estimates of log-odds ratio on the horizontal axis and their corresponding standard error estimates on the vertical axis. We will also investigate funnel plot asymmetry with Habord's test. For the latter, a $P < 0.10$ will be considered statistically significant.

For all analyses, we will use Stata 16 (College Station, TX, USA) and MultiBUGS 2.0 (Cambridge, UK).

Objective 2

We will meta-analyze proportions using a random-effects Bayesian model. Specifically, the model uses the binomial likelihood and the logit transformation of the proportions. The proportions are considered a random variable, and the mean of the logit proportions is assumed to follow a normal distribution [40]. We will use a non-informative prior for the mean of the logit-transformed study-specific proportions and the between-study variance. The burning-in period will have 50,000 simulations, and three different chains with 50,000 simulations each will be used (150,000 simulations in total). Starting values were manually selected to guarantee very different random draws for the three chains. Results were summarized using posterior medians with 95% Crls. All model diagnostics will be performed as described above.

Subgroup analysis or sensitivity analysis

When appropriate, subgroup analysis will be employed. The subgroup that will be used includes age groups (<18 years *vs* 18-60 years *vs* >60 years); level of economic development of the study setting (low or lower-middle-income country *vs* middle or high-income country, as defined by the World Bank [41]); immunological status (CD4 <250 *vs* CD4 ≥250 cells/µl); time of follow-up (≤ 24 weeks *vs* 25 to 48 weeks *vs* ≥ 48 weeks); industry-independent funding (no *vs* yes); ITT analysis of AE (no *vs* yes); attribution of AEs to drugs (no *vs* yes); combined versus single antiretroviral therapy; risk of bias (high *vs* moderated and low; blinded *vs* open-label; adequate allocation concealment *vs* unclear allocation concealment).

Assessment of the certainty of the evidence and the strength of the recommendation

After the results are grouped, two reviewers will independently assess the overall certainty of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [42]. The main results of the review will be presented in outcome tables (Summary of Findings - SoF), as recommended by The Cochrane Collaboration [43]. The SoF table includes a general classification of the evidence related to each of the main outcomes, using the GRADE approach [44]. This table will be built with the aid of the GRADEpro software program.

The use of the GRADE allows evaluating the certainty of the evidence for each result considering the methodological quality, the objectivity of the evidence, the heterogeneity, the precision of the effect estimates, and the risk of publication bias [43]. If the analysis of an outcome is not possible, for example, due to the lack of data, we will present the reasons for this in the SoF table as a footnote.

ETHICS AND DISSEMINATION

We plan on sharing our results through publication in scientific journals of high impact, peer-reviewed, and presenting it at national and international conferences. We hope that the results will serve to assist in the formulation of public policies aimed at guiding professionals on the management and monitoring of the AEs of ART in people living with HIV/AIDS. For this purpose, meetings are scheduled with the Department of

Chronic Conditions and Sexually Transmitted Infections of Brazil's Ministry of Health during the project, seeking to align it with the interests of policymakers.

We will also present the results and discuss the implementation, monitoring, and management of AE in people living with HIV/Aids in a DD with stakeholders, policymakers, and other researchers. Considering that the results of the DD can make adjustments in the recommendations of the SR, the stakeholders have to disclaim their potential conflicts of interest. For this reason, this protocol will be submitted for approval to the ethics committee before the conduction of the DD.

DISCUSSION

The results of this systematic review could highlight important findings to decision-making, considering the management of AE in the different age ranges of women.

Our future results could impact public policies for people living with HIV/AIDS by offering evidence that can highlight challenges and areas of improvement, with a special view over the diversity of people and their contexts. However, there are potential limitations.

The primary studies could bring limitations to this review considering the confusion between the report of AEs and signs and symptoms of HIV/AIDS; some trials do not report the time of initiation of ART and do not separate the outcomes by sex. To overcome this limitation, we will extract the information of all trials that report the time of initiation of ART and if possible, we will meta-analyze this result.

Antiretroviral drugs also are usually given in combination, being difficult to ascertain which agent causes the AE, this could be another potential limitation of this systematic review.

This study did not include real-world studies that reported adverse drug reactions in patients receiving antiretrovirals because we consider that RCTs provide a more accurate diagnosis of AEs as they can be better monitored/controlled, standardized, and reported compared to real-world studies.

AUTHOR CONTRIBUTIONS

Study concept and design: LCL.

Methodology: LCL.

Drafting of the manuscript: JCO, LCL, and MRA.

Review and editing of the manuscript: LCL, MRA, LPNL, CCB, SBF, JCO, RSI, FRM, TVP, MTS, AI, JMB, DLS, DSL, LGM, RDD.

ACKNOWLEDGEMENTS

The authors would like to thank Genevieve Gore and Mabel Figueiro, experienced librarians, for their collaboration with the review and definition of the final search strategy for the present study. The authors would like to thank Filipe Perini as well, for his contributions to the search questions, choice of medicines to be included, and the functioning of the current Brazilian public policies for HIV.

FUNDING

This research received funding from the São Paulo Research Foundation (FAPESP), grant n°. 2018/16893-8.

COMPETING INTERESTS

None to declare.

WORD COUNT: 3791

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SUPPLEMENTARY MATERIAL 1 - PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page No
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1-2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	15-16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	16
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	11
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Suppl. Material

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12-13
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11-12
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11-12
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	12-13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	13
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	13-14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	14
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	15
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	15

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

SUPPLEMENTARY MATERIAL 2 – Search strategies

PubMed	(HIV infections [MeSH] OR HIV [MeSH] OR Acquired Immunodeficiency Syndrome [MeSH] OR HIV Seropositivity [MeSH] OR HIV OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR HIV/AIDS) AND (Anti-retroviral agents [Mesh] OR antiretroviral therapy, highly active [Mesh] OR Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)) OR Saquinavir [tiab] OR Lopinavir [tiab] OR Indinavir [tiab] OR Ritonavir [Tiab] OR Nelfinavir [tiab] OR Amprenavir [tiab] OR Fosamprenavir [tiab] OR Atazanavir [Tiab] OR Tipranavir [tiab] OR Darunavir [tiab] OR Cobicistat [Tiab] OR Emtricitabine [Tiab] OR Zidovudine [Tiab] OR Didanosine [tiab] OR Stavudine [tiab] OR Lamivudine [Tiab] OR Abacavir [Tiab] OR Nevirapine [tiab] OR Darunavir [Tiab] OR Etravirine [Tiab] OR Elvitegravir [Tiab] OR Alafenamide [Tiab] OR "Tenofovir disoproxil fumarate" [Tiab] OR "Tenofovir Alafenamide" [Tiab] OR Tenofovir [Tiab] OR Efavirenz [Tiab] OR Enfuvirtide [Tiab] OR Raltegravir [tiab] OR Maraviroc [tiab] OR Dolutegravir [tiab] OR Bictegravir [tiab]) AND (("abnormalities, drug-induced"[mesh] OR "drug hypersensitivity"[mesh] OR "drug monitoring"[mesh] OR "drug recalls"[mesh] OR "poisoning"[mesh] OR "safety-based drug withdrawals"[mesh] OR "substance-related disorders"[mesh] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "Long Term Adverse Effects"[Mesh] OR "product surveillance, postmarketing"[mesh] OR "adverse effects"[sh] OR "complications"[sh] OR "drug effects"[sh] OR "safe"[tw] OR "safety"[tw] OR "side effect*"[tw] OR "undesirable effect*"[tw] OR "treatment emergent"[tw] OR "tolerability"[tw] OR "toxicity"[tw] OR "adverse drug reaction*"[tw] OR "adrs"[tw] OR "adverse effect*"[tw] OR "adverse drug effect*"[tw] OR "adverse reaction*"[tw] OR "adverse event*"[tw] OR "adverse drug event*"[tw] OR "adverse outcome*"[tw] OR "complication*"[tw] OR "harm"[tw] OR "harmful"[tw] OR "harms"[tw] OR "risk"[tw] OR (adverse[tw] AND (effect[tw] OR effects[tw] OR reaction[tw] OR reactions[tw] OR event[tw] OR events[tw] OR outcome[tw] OR outcomes[tw]))))

	AND ((((((randomized controlled trial [pt]) OR controlled clinical trial [pt]) OR randomized [tiab]) OR placebo [tiab]) OR clinical trials as topic [mesh: noexp] OR randomly [tiab]) OR trial [tiab]) NOT (animals [MeSH] NOT humans [MeSH])
Embase	No. Query Results 11,308 #6 #1 AND #2 AND #3 AND #4 NOT #5 5,615,547 #5 'animal'/exp NOT 'human'/exp 1,832,252 #4 'randomized controlled trial':it OR 'controlled clinical trial':it OR randomized:ab,ti OR placebo:ab,ti OR ('clinical trial'/de AND topic) OR randomly:ab,ti OR trial:ab,ti 10,788,807 #3 'adverse drug reaction'/exp OR 'drug hypersensitivity'/exp OR 'drug monitoring'/exp OR 'drug recall'/exp OR 'drug intoxication'/exp OR 'side effect'/exp OR 'postmarketing surveillance'/exp OR 'drug safety'/exp OR 'drug surveillance program'/exp OR 'drug toxicity'/exp OR 'adverse event'/exp OR 'complication'/exp OR 'drug effect'/exp OR safe OR safety OR 'side effect*' OR 'undesirable effect*' OR 'treatment emergent' OR 'tolerability' OR 'toxicity' OR 'adverse drug reaction*' OR 'adrs' OR 'adverse effect*' OR 'adverse drug effect*' OR 'adverse reaction*' OR 'adverse event*' OR 'adverse drug event*' OR 'adverse outcome*' OR 'complication*' OR 'harm' OR 'harmful' OR 'harms' OR 'risk' OR (adverse AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)) 522,768 #2 'antiretrovirus agent'/exp OR 'highly active antiretroviral therapy'/exp OR antiretroviral* OR (anti AND retroviral*) OR arv OR art OR 'antiretroviral therapy' OR haart OR (highly AND active AND antiretroviral* AND therap*) OR (anti

	AND hiv) OR (anti AND acquired AND immunodeficiency) OR (anti AND acquired AND immuno-deficiency) OR (anti AND acquired AND immune-deficiency) OR (anti AND acquired AND immun* AND deficienc*) OR saquinavir:ab,ti OR lopinavir:ab,ti OR indinavir:ab,ti OR ritonavir:ab,ti OR nelfinavir:ab,ti OR amprenavir:ab,ti OR fosamprenavir:ab,ti OR atazanavir:ab,ti OR tipranavir:ab,ti OR cobicistat:ab,ti OR emtricitabine:ab,ti OR zidovudine:ab,ti OR didanosine:ab,ti OR stavudine:ab,ti OR lamivudine:ab,ti OR abacavir:ab,ti OR nevirapine:ab,ti OR darunavir:ab,ti OR etravirine:ab,ti OR elvitegravir:ab,ti OR alafenamide:ab,ti OR 'tenofovir disoproxil fumarate':ab,ti OR 'tenofovir alafenamide':ab,ti OR tenofovir:ab,ti OR efavirenz:ab,ti OR enfuvirtide:ab,ti OR raltegravir:ab,ti OR maraviroc:ab,ti OR dolutegravir:ab,ti OR bictegravir:ab,ti 610,204 #1 'human immunodeficiency virus infection'/exp OR 'acquired immune deficiency syndrome'/exp OR 'human immunodeficiency virus 1'/exp OR 'human immunodeficiency virus 1 infection'/exp OR 'human immunodeficiency virus 2'/exp OR 'human immunodeficiency virus 2 infection'/exp OR 'hiv aids'/exp OR hiv OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR (hiv AND infect*) OR (human AND immunodeficiency AND virus) OR (human AND immune AND deficiency AND virus) OR (human AND immuno-deficiency AND virus) OR (human AND immune-deficiency AND virus) OR (human AND immun* AND deficiency AND virus) OR (acquired AND immunodeficiency AND syndromes) OR (acquired AND immune AND deficiency AND syndrome) OR (acquired AND immuno-deficiency AND syndrome) OR (acquired AND immune-deficiency AND syndrome) OR (acquired AND immun* AND deficiency AND syndrome)
Cochrane Central	Search Name: Cochrane RADAR Last Saved: 25/05/2021 20:49:52 Comment: ID Search #1 MeSH descriptor: [HIV Infections] explode all trees #2 MeSH descriptor: [HIV] explode all trees #3 MeSH descriptor: [Acquired Immunodeficiency Syndrome] explode all trees #4 MeSH descriptor: [HIV Seropositivity] explode all trees #5 (HIV OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR

	acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS):ti,ab,kw #6 #1 OR #2 OR #3 OR #4 OR #5 #7 MeSH descriptor: [Anti-Retroviral Agents] explode all trees #8 MeSH descriptor: [Antiretroviral Therapy, Highly Active] explode all trees #9 (Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*))):ti,ab,kw #10 (Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir):ti,ab #11 #7 OR #8 OR #9 OR #10 #12 MeSH descriptor: [Abnormalities, Drug-Induced] explode all trees #13 MeSH descriptor: [Drug Hypersensitivity] explode all trees #14 MeSH descriptor: [Drug Monitoring] explode all trees #15 MeSH descriptor: [Drug Recalls] explode all trees #16 MeSH descriptor: [Poisoning] explode all trees #17 MeSH descriptor: [Safety-Based Drug Withdrawals] explode all trees #18 MeSH descriptor: [Substance-Related Disorders] explode all trees #19 MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees #20 MeSH descriptor: [Long Term Adverse Effects] explode all trees #21 MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees #22 MeSH descriptor: [] explode all trees and with qualifier(s): [adverse effects - AE] #23 MeSH descriptor: [] explode all trees and with qualifier(s): [complications - CO] #24 MeSH descriptor: [] explode all trees and with qualifier(s): [drug effects - DE] #25 ("safe" OR "safety" OR "side effect*" OR "undesirable effect*" OR "treatment emergent" OR "tolerability" OR "toxicity" OR "adverse drug reaction*" OR "adrs" OR "adverse effect*" OR "adverse drug effect*" OR "adverse

	reaction*" OR "adverse event*" OR "adverse drug event*" OR "adverse outcome*" OR "complication*" OR "harm" OR "harmful" OR "harms" OR "risk" OR (adverse AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))) #26 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 #27 #22 OR #23 OR #24 #28 #25 OR #26 OR #27 #29 #6 AND #11 AND #28
Biblioteca Virtual em Saúde (BVS)	((mh:(HIV infections)) OR (mh:(HIV)) OR (mh:(Acquired Immunodeficiency Syndrome)) OR (mh:(HIV Seropositivity)) OR ((HIV OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS))) AND ((mh:(Anti-Retroviral Agents)) OR (mh:(Antiretroviral Therapy, Highly Active)) OR ((Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)))) OR (ti:((Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir))) OR (ab:((Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir)))) AND ((mh:(Abnormalities, Drug-Induced)) OR (mh:(Drug Hypersensitivity)) OR (mh:(Drug Monitoring)) OR (mh:(Drug Recalls)) OR (mh:(Poisoning)) OR (mh:(Safety-Based Drug Withdrawals)) OR (mh:(Substance-Related Disorders)) OR (mh:(Drug-Related Side Effects and Adverse Reactions)) OR (mh:(Long Term Adverse Effects)) OR (mh:(Product Surveillance, Postmarketing)) OR ("adverse effect" OR "adverse effects" OR "drug effects" OR safe OR safety OR "side effect" OR "side effects" OR

	"undesirable effect" OR "undesirable effects" OR "treatment emergent" OR tolerability OR toxicity OR "adverse drug reaction" OR "adverse drug reactions" OR adrs OR "adverse drug effect" OR "adverse drug effects" OR "adverse reaction" OR "adverse reactions" OR "adverse event" OR "adverse events" OR "adverse drug event" OR "adverse drug events" OR "adverse outcome" OR "adverse outcomes" OR complication OR complications OR harm OR harmful OR harms OR risk OR ((adverse) AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)))) AND ((mh:(clinical trials)) OR (randomized controlled trial) OR (controlled clinical trial) OR randomized OR placebo OR randomly OR trial)
Epistemonikos	((HIV infections) OR HIV OR (Acquired Immunodeficiency Syndrome) OR (HIV Seropositivity) OR (hiv-1) OR (hiv-2) OR hiv1 OR hiv2 OR (hiv infect*) OR (human immunodeficiency virus) OR (human immune deficiency virus) OR (human immuno-deficiency virus) OR (human immune-deficiency virus) OR ((human immun*) AND (deficiency virus)) OR (acquired immunodeficiency syndromes) OR (acquired immune deficiency syndrome) OR (acquired immuno-deficiency syndrome) OR (acquired immune-deficiency syndrome) OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS) AND ((Anti-retroviral agents) OR (antiretroviral therapy, highly active) OR Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)) OR Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir) AND ("abnormalities, drug-induced" OR "drug hypersensitivity" OR "drug monitoring" OR "drug recalls" OR "poisoning" OR "safety-based drug withdrawals" OR "substance-related disorders" OR "Drug-Related Side Effects and Adverse Reactions" OR "Long Term Adverse Effects" OR "product surveillance, postmarketing" OR "adverse effects" OR "complications" OR "drug effects" OR "safe" OR "safety" OR "side effect*" OR "undesirable effect*" OR "treatment emergent" OR "tolerability" OR "toxicity" OR "adverse drug reaction*" OR "adrs" OR "adverse effect*" OR "adverse drug effect*" OR "adverse reaction*" OR "adverse event*" OR "adverse drug event*" OR "adverse outcome*" OR "complication*" OR "harm" OR "harmful" OR "harms" OR "risk" OR (adverse AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))) AND ((randomized controlled trial) OR (controlled clinical trial) OR randomized OR placebo OR randomly OR trial)

ClinicalTrials.gov	((HIV infections) OR HIV OR (Acquired Immunodeficiency Syndrome) OR (HIV Seropositivity) OR (hiv-1) OR (hiv-2) OR hiv1 OR hiv2 OR (hiv infect*) OR (human immunodeficiency virus) OR (human immune deficiency virus) OR (human immuno-deficiency virus) OR (human immune-deficiency virus) OR ((human immun*) AND (deficiency virus)) OR (acquired immunodeficiency syndromes) OR (acquired immune deficiency syndrome) OR (acquired immuno-deficiency syndrome) OR (acquired immune-deficiency syndrome) OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS) AND ((Anti-retroviral agents) OR (antiretroviral therapy, highly active) OR Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)) OR Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir) AND ("abnormalities, drug-induced" OR "drug hypersensitivity" OR "drug monitoring" OR "drug recalls" OR "poisoning" OR "safety-based drug withdrawals" OR "substance-related disorders" OR "Drug-Related Side Effects and Adverse Reactions" OR "Long Term Adverse Effects" OR "product surveillance, postmarketing" OR "adverse effects" OR "complications" OR "drug effects" OR "safe" OR "safety" OR "side effect*" OR "undesirable effect*" OR "treatment emergent" OR "tolerability" OR "toxicity" OR "adverse drug reaction*" OR "adrs" OR "adverse effect*" OR "adverse drug effect*" OR "adverse reaction*" OR "adverse event*" OR "adverse drug event*" OR "adverse outcome*" OR "complication*" OR "harm" OR "harmful" OR "harms" OR "risk" OR (adverse AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))) Filters: Interventional (Clinical Trial)
Global Index Medicus	((mh:(HIV infections)) OR (mh:(HIV)) OR (mh:(Acquired Immunodeficiency Syndrome)) OR (mh:(HIV Seropositivity)) OR ((HIV OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR AIDS))) AND ((mh:(Anti-Retroviral Agents)) OR (mh:(Antiretroviral Therapy, Highly Active)) OR ((Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV OR ART OR "antiretroviral therapy" OR HAART OR ((highly)

	AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR (anti AND (acquired immune-deficiency)) OR (anti AND (acquired immun*) AND (deficienc*)))) OR (ti:((Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir))) OR (ab:((Saquinavir OR Lopinavir OR Indinavir OR Ritonavir OR Nelfinavir OR Amprenavir OR Fosamprenavir OR Atazanavir OR Tipranavir OR Darunavir OR Cobicistat OR Emtricitabine OR Zidovudine OR Didanosine OR Stavudine OR Lamivudine OR Abacavir OR Nevirapine OR Darunavir OR Etravirine OR Elvitegravir OR Alafenamide OR "Tenofovir disoproxil fumarate" OR "Tenofovir Alafenamide" OR Tenofovir OR Efavirenz OR Enfuvirtide OR Raltegravir OR Maraviroc OR Dolutegravir OR Bictegravir)))) AND ((mh:(Abnormalities, Drug-Induced)) OR (mh:(Drug Hypersensitivity)) OR (mh:(Drug Monitoring)) OR (mh:(Drug Recalls)) OR (mh:(Poisoning)) OR (mh:(Safety-Based Drug Withdrawals)) OR (mh:(Substance-Related Disorders)) OR (mh:(Drug-Related Side Effects and Adverse Reactions)) OR (mh:(Long Term Adverse Effects)) OR (mh:(Product Surveillance, Postmarketing)) OR ("adverse effect" OR "adverse effects" OR "drug effects" OR safe OR safety OR "side effect" OR "side effects" OR "undesirable effect" OR "undesirable effects" OR "treatment emergent" OR tolerability OR toxicity OR "adverse drug reaction" OR "adverse drug reactions" OR adrs OR "adverse drug effect" OR "adverse drug effects" OR "adverse reaction" OR "adverse reactions" OR "adverse event" OR "adverse events" OR "adverse drug event" OR "adverse drug events" OR "adverse outcome" OR "adverse outcomes" OR complication OR complications OR harm OR harmful OR harms OR risk OR ((adverse) AND (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)))) AND ((mh:(clinical trials)) OR (randomized controlled trial) OR (controlled clinical trial) OR randomized OR placebo OR randomly OR trial)