

Medication errors in anti-retroviral therapy among people living with HIV and the impact of stewardship interventions: study protocol for a systematic review and meta-analysis

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Abstract

Background: Medication errors involving antiretroviral therapy (ART) in people living with HIV (PLHIV) are frequent, particularly in general hospitals and during care transitions, and may lead to preventable toxicity, virological failure and drug resistance. Several stewardship interventions have been implemented to reduce these errors, but the available evidence remains fragmented and heterogeneous. **Material and methods:** We will conduct a systematic review and meta-analysis of observational studies and intervention studies reporting ART-related medication errors in adults (≥ 18 years) with HIV in any clinical setting. We will search MEDLINE, Embase, CINAHL, Web of Science, CENTRAL and grey literature without language or date restrictions. Two reviewers will independently screen records, extract data and assess risk of bias using design-specific tools (RoB-2, ROBINS-I, Newcastle-Ottawa Scale and EPOC). We will perform random-effects meta-analyses when appropriate and synthesize implementation outcomes narratively. Certainty of evidence for key outcomes will be assessed with GRADE. **Conclusions:** This review will provide up-to-date, quantitatively synthesized estimates of the burden and clinical impact of ART-related medication errors and will evaluate the effectiveness of antiretroviral stewardship and related interventions. Its findings will inform HIV units, antimicrobial stewardship programmes and policy-makers aiming to improve the safety of ART. **Study registration:** PROSPERO CRD420251233303.

Keywords: HIV • patient safety • medication errors • antiretroviral therapy • stewardship

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Introduction

Medication errors involving anti-retroviral therapy (ART) in people living with HIV represent a persistent patient-safety issue that is often underestimated in routine clinical care. Although current ART regimens are highly effective, they remain pharmacologically complex. Fixed-dose combinations, strong inhibition (or induction) of metabolic pathways, relevant transporter effects and the need for dose adjustment in renal or hepatic impairment all increase the potential for error. In clinical practice, small prescribing or administration changes can have disproportionate clinical consequences [1-5].

These problems are particularly visible in hospital settings. During inpatient care, ART is frequently prescribed or modified by clinicians who do not routinely manage HIV treatment, often under time pressure and with limited access to specialist advice. The reported prevalence of ART-related medication errors varies widely, but rates above 20% (and in some settings substantially higher) are repeatedly described [1, 3, 6-8]. Typical errors include incomplete regimens, unintended treatment interruptions, inappropriate substitutions between non-equivalent agents, dosing mistakes and clinically significant drug-drug interactions, particularly at admission and discharge.

The clinical impact of such errors goes beyond theoretical concern. Unplanned interruptions or incomplete ART regimens may lead to virological rebound and facilitate the selection of resistance mutations. Conversely, failure to account for organ dysfunction or drug interactions can result in avoidable toxicity and adverse drug events [1-2, 4, 6]. At a population level, these individual failures matter because sustained viral suppression is central not only to individual prognosis but also to public-health objectives, including the UNAIDS 95-95-95 targets [9].

Several factors contribute to the occurrence of ART-related medication errors. Many reports highlight limited familiarity with ART among non-specialist prescribers, electronic prescribing systems that inadequately reflect ART-specific constraints, variable involvement of clinical pharmacists, and the absence of standardised processes to validate or reconcile ART prescriptions [2, 4, 8, 10]. In parallel, the demographic profile of people living with HIV is changing. Increasing age, multimorbidity and polypharmacy further amplify the risk of errors and drug-drug interactions in everyday practice.

In addition to prescriber- and system-level determinants, patient-related and structural factors may modify the risk and consequences of ART-related medication errors. Substance use disorders, mental health comorbidity, unstable housing, stigma, privacy concerns and avoidance of healthcare services can impair adherence to ART and clinic attendance, and may increase vulnerability to treatment interruptions, incomplete medication reconciliation or delayed recognition of prescribing

errors. These factors are not medication errors, but they may influence both the likelihood that errors occur and their clinical impact, particularly during hospital admission, discharge and transitions of care.

In response to these challenges, a range of interventions has been developed over the last decade. These include pharmacist-led medication reviews, dedicated antiretroviral stewardship programmes, predefined order sets, structured reconciliation workflows and electronic decision-support tools. Many single-centre studies report reductions in error rates or faster correction of errors after implementation of such strategies. However, interpretation is difficult because definitions of “medication error,” outcome measures and study designs differ substantially across reports [1, 3-4, 6-7, 11].

For these reasons, a comprehensive and methodologically rigorous synthesis of the available evidence is warranted. This protocol describes a systematic review and meta-analysis designed to quantify the burden and nature of ART-related medication errors, explore associated clinical consequences and assess the observed impact of stewardship-type interventions. It describes applying design-specific risk-of-bias tools and grading the certainty of evidence using the GRADE methodology. In this systematic review and meta-analysis we aim to provide results that are both transparent and directly applicable to clinical practice and healthcare organisation.

Material and methods

Study design and registration

This manuscript describes the protocol for a prospectively registered systematic review and meta-analysis. The protocol was developed in accordance with PRISMA-P recommendations and registered in the PROSPERO registry (CRD4202512-33303) before study selection began. The completed review will be reported in accordance with the PRISMA 2020 guidance [12].

From the outset, this systematic review was planned to address 2 closely related questions. First, how frequent are medication errors involving antiretroviral therapy in adults living with HIV and how do these errors differ across various healthcare settings. Second, whether antiretroviral stewardship interventions are associated with measurable reductions in such errors. Key methodological decisions, including eligibility criteria, outcomes of interest and analytical approaches, were specified a priori to minimise selective reporting and analytical flexibility.

Objectives

The primary objective of this systematic review is to identify and characterise the full spectrum of medication errors related to antiretroviral therapy and HIV treatment stewardship in adults living with HIV, across different clinical contexts. This will include errors during prescribing, medication reconciliation, dispensing, administration, treatment interruption, regimen substitution and transitions of care. A second primary objective is to evaluate the effect of interventions designed to prevent or correct these errors, including pharmacist-led programmes, stewardship initiatives and system-level strategies.

Secondary objectives include summarising reported clinical consequences of ART-related medication errors (e.g. virological outcomes, drug-related toxicity and preventable adverse events) as well as organisational outcomes when available (e.g. length of hospital stay or time to error correction). Where data permit, this review will also explore sources of heterogeneity, including healthcare setting, study design and type of intervention implemented.

Eligibility criteria

We will include studies that report medication errors related to antiretroviral therapy in adults (≥ 18 years) living with HIV, as well as studies evaluating interventions intended to reduce such errors. Eligible study designs will comprise observational studies (cross-sectional, cohort and case-control) and interventional studies (including randomised trials), quasi-experimental designs and before-after evaluations. Case reports and case series with < 10 participants will be considered when they provide sufficient methodological and clinical detail to identify uncommon, severe or potentially preventable ART-related medication errors. These reports will be included only in the qualitative synthesis and will not contribute to pooled prevalence estimates or quantitative analyses of intervention effects. Larger case series, observational studies and interventional studies will be considered for quantitative synthesis when appropriate.

We will include studies conducted in any healthcare setting, including inpatient wards, emergency departments, outpatient clinics and transitional care environments. No restrictions will be applied based on country, healthcare system or language of publication. Studies focusing exclusively on paediatric populations will be excluded because paediatric ART formulations, dosing strategies and prescribing processes differ substantially from those used in adults. We will also exclude case reports, narrative reviews, editorials and conference abstracts that do not provide sufficient methodological detail.

The primary outcomes of interest are the prevalence and types of ART-related medication errors and for

interventional studies, also changes in error frequency following implementation of a stewardship-type intervention. Secondary outcomes include reported clinical consequences (e.g. virological failure, drug toxicity or preventable adverse events) and organisational or process-related outcomes (e.g. time to error detection or length of hospital stay), when these data are available.

Information sources and search strategy

We will perform comprehensive searches in MEDLINE (via PubMed), Embase, CINAHL, Web of Science Core Collection and the Cochrane Central Register of Controlled Trials (CENTRAL). Searches will not be restricted by language or publication date (from database inception to the present). Grey literature will be explicitly included in the search strategy in order to minimise publication bias and capture relevant unpublished or difficult-to-index evidence. Sources will include OpenGrey, ProQuest Dissertations and Theses, conference proceedings and other relevant institutional or professional sources when sufficient information is available to assess eligibility. In addition, we will screen reference lists of included studies and perform forward citation tracking using Google Scholar. If clarification or additional data are required, we will contact study authors.

Search strategies will combine controlled vocabulary terms (MeSH and Emtree) with free-text keywords related to HIV, antiretroviral therapy, medication errors and stewardship-type interventions. Strategies will be adapted for each database and developed with input from an experienced medical librarian. Where possible, search strategies will be peer reviewed using the PRESS framework. Full search strings for all databases will be provided in the supplementary materials.

Study selection

All records retrieved from the searches will be imported into Rayyan for de-duplication and screening [13]. Two reviewers will independently screen titles and abstracts against the predefined eligibility criteria. Full texts of potentially relevant articles will then be assessed independently by the same reviewers. Any disagreements will be resolved through discussion and, when necessary, consultation with a third reviewer.

Reasons for exclusion at the full-text stage will be documented, and the overall study selection process will be summarised in a PRISMA flow diagram. If multiple publications report data from the same underlying study population, these reports will be linked and treated as a single study, with data extracted from the most complete and informative source.

Data extraction

Data extraction will be performed independently by 2 reviewers using a standardised extraction form that will be piloted on a small sample of included studies and refined if necessary. For each study, we will collect information on study design, setting, country, study period and participant characteristics. Definitions and methods of detecting medication errors vary widely across the literature, therefore we will also record how they were defined and identified in the included studies.

For descriptive studies, we will extract data on the number and types of ART-related medication errors, prevalence estimates and any reported clinical or organisational consequences. For interventional studies, we will additionally collect detailed information on the intervention itself (e.g. its main components, duration, implementation context and comparator conditions). If outcome data are incomplete or unclear, we will attempt to contact the corresponding authors for clarification. If numerical results are presented only graphically, we will do our best to extract approximate values using digital measurement tools. Equivocal situations will be resolved through discussion or by involving a third reviewer.

When reported, we will also extract patient-related and structural risk modifiers that may influence ART safety, e.g. substance use disorders, mental health comorbidity, housing instability, stigma/privacy concerns, history of poor adherence, retention in care and use of long-acting injectable antiretroviral agents. These variables will be summarised descriptively and, if sufficiently reported across studies, explored as potential sources of heterogeneity or effect modification.

Risk of bias assessment

The risk of bias will be assessed independently by two reviewers, using tools appropriate for each study design. Randomized controlled trials will be assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [14]. Non-randomized interventional studies will be assessed using ROBINS-I, paying particular attention to confounding factors and deviations from planned interventions [15]. Observational studies will be assessed using the Newcastle-Ottawa scale, adapted pragmatically where necessary to reflect the specific challenges of medication error research [16].

For studies evaluating healthcare system or educational interventions, the criteria of the Cochrane Effective Practice and Organization of Care (EPoC) group will also be considered. Disagreements in risk of bias assessments will be discussed until consensus is reached, with the involvement of a third reviewer when necessary. Risk of bias assessments will inform sensitivity analyses and interpretation of results,

but studies will not be excluded solely on the basis of these assessments.

Data synthesis and statistical analysis

First, we will summarise the characteristics and results of the included studies descriptively, grouping them by study design, context, and outcome. When studies present with enough comparable results, we will perform a meta-analysis using random-effects models to account for the expected clinical and methodological heterogeneity. For prevalence estimates, appropriate transformations will be applied when necessary to stabilize variances prior to pooling.

In interventional studies, effect estimates will be synthesized using risk ratios, odds ratios, or mean differences, depending on the type of outcome and the form of reporting. Statistical heterogeneity will be quantified using the I^2 statistic and explored using prespecified subgroup analyses, such as healthcare setting, type of intervention, and study design, provided that an adequate number of studies are available. Sensitivity analyses will be performed by excluding studies considered to be at high risk of bias. When at least 10 studies contribute to a given meta-analysis, we will assess potential publication bias using funnel plots and formal statistical tests. All statistical analyses will be performed using Stata (StataCorp LLC, College Station, TX, USA).

Certainty of evidence

The certainty of evidence for key outcomes will be evaluated using the GRADE framework [17]. For each outcome, we will consider risk of bias, inconsistency, diffuseness, imprecision and potential publication bias. When the systematic review is feasible, GRADE assessments will be presented in table format. If quantitative synthesis is not possible, the same principles will be applied in a narrative review in order to ensure transparency in the reliability with which evidence is assessed. These assessments are intended to help readers distinguish between outcomes supported by evidence and those where conclusions remain uncertain.

Use of artificial intelligence

Artificial intelligence (AI) tools were used to assist with language review during writing of the manuscript and the translation to English. Decisions regarding study design, eligibility criteria, data extraction, risk-of-bias assessment, statistical analysis and interpretation were made by the authors. The final version of the manuscript was reviewed and edited by the authors to ensure accuracy, consistency and alignment with the study objectives.

AI tools will not replace independent human judgement while conducting this systematic review. Study selection, data extraction, risk-of-bias assessment, statistical analysis and interpretation will be performed and verified by the authors according to the methods described above.

Results

This article describes the study protocol, therefore results are not yet available and are not presented here. This document highlights the methods that will be used in study selection, data collection and synthesis. The systematic review will be conducted after the publication of this protocol, following the procedure described earlier.

Discussion

Despite the availability of well-established clinical guidelines and simplified therapeutic regimes, medication errors involving antiretroviral therapy (ART) continue to happen in standard hospital practices. The problem is more frequent during admissions and care transitions, when ART is usually managed by a non-specialist practitioner outside office hours. Multiple studies have addressed this issue, but the literature lacks in quality and is difficult to translate across healthcare settings [1, 3-4, 6-7, 11]. This protocol describes a structured approach via systematic review of the published evidence surrounding this issue with the objective of assessing the burden of ART-related medication errors and the observed impact of stewardship-type interventions.

The key strength of this systematic review is the inclusion of observational and interventional studies within a single analytical framework. Descriptive studies inform on how often these errors occur and what kind of them are, while interventional studies address whether the efficacy of targeted strategies in reducing the error frequency. Previous data suggest that reviews led by pharmacists, stewardship programmes and computer-level interventions can lead to significant reduction in the quantity and quality of errors, although the extent to which these reduction can be extrapolated to different healthcare settings remains unknown [1, 3-4, 7]. By integrating risk-of-bias reductions tools in the design and implementation of a grading system to measure the certainty of evidence (GRADE), we aim to clarify how much confidence can be placed in these estimates.

Several challenges are anticipated. There is not a consensus on the definition of “medication error” and the methods used to identify and categorize those errors are considera-

bly different in the literature. These differences are likely to account for part of the expected heterogeneity of data. Interventions described as “stewardship” also differ greatly in method and type, ranging from single-component pharmacist review to multidisciplinary and multi-approach programmes that combines education, restrictions of prescription and computer-supported decision-making [3-4, 6-7]. Such variability can be a limitation of this study, via diminishing the precision of the quantitative pooling for particular outcomes and confound direct comparison between different strategies.

The emergence of long-acting injectable ART also deserves specific consideration in the context of medication safety. Long-acting cabotegravir + rilpivirine may reduce some risks associated with daily oral dosing, pill burden, dispensing complexity and inadvertent treatment interruptions, particularly in selected people with adherence challenges. However, these regimens do not eliminate medication-safety risks, but rather they shift part of the risk toward scheduling of injections, management of missed or delayed doses, oral bridging strategies, documentation across care settings and prevention of functional monotherapy or resistance in the setting of prolonged subtherapeutic drug exposure. For this reason, stewardship interventions may need to adapt to long-acting ART by incorporating injection tracking, structured recall systems and clear protocols for missed doses or hospital admissions.

Despite these limitations, the planned systematic review and meta-analysis is expected to be clinically informative. By quantifying the frequency and nature of ART-related medication errors and summarising which intervention components appear most consistently associated with error reduction, this review can support decision-making in infectious diseases units, hospitals and antimicrobial stewardship programmes. Ultimately, improving the safety and continuity of ART prescriptions requires interventions that are not only effective but also feasible in real-world clinical environments, especially outside specialist HIV units.

Conclusions

This protocol describes the methodology of a systematic review and meta-analysis on medication errors associated with ART and its impact of stewardship interventions. The review will take into consideration how often these mistakes happen, how they are reported across different healthcare settings and whether structured stewardship interventions can be associated with a reduction in error frequency. It is expected that our results can potentially guide efforts to improve safety and ensure continuity of the ART prescription in both specialist and general care.

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