RESEARCH PAPER

Adverse Drug Reactions to Antiretroviral Therapy in Adults Living With HIV: A Systematic Review and Meta-Analysis Across Settings, Regimens, and Treatment Eras

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Abstract

Background: ART has substantially extended survival for people living with HIV, but adverse drug reactions (ADRs) can affect tolerability and continuity of care. As treatment combinations have changed, including wider use of dolutegravir, the frequency and pattern of reported reactions remain important to assess.

Objective: To synthesise evidence on ADR prevalence among adults receiving ART and explore variation by geography, study design, regimen category, and treatment period.

Methods: We conducted a systematic review and meta-analysis guided by PRISMA 2020. PubMed/MEDLINE, Embase, Scopus, Web of Science, Google Scholar, ClinicalTrials.gov, grey literature, organisational sources, and reference lists were searched. Eligible studies involved adults aged 18 years or older receiving ART and reported ADR outcomes. Random-effects analyses using the DerSimonian–Laird method and subgroup analyses were reported; heterogeneity and possible small-study effects were assessed using statistical and graphical approaches.

Results: Sixty studies with more than 30,000 participants were included; study-level ADR prevalence ranged from 7.9% to 62.8%. The source outputs contain two different overall pooled estimates—42% (95% CI 36%–48%; I^2=99.5%) and 38% (95% CI 37%–39%; I^2=76.5%)—which require verification before publication. Reported subgroup estimates were 36% in India, 40% in Ethiopia, and 40% in Kenya. Estimates by study design ranged from 35% to 40%. Regimen-category estimates ranged from 21% for DTG to 44% for mixed regimens, but do not establish comparative safety. The difference between pre-DTG and DTG-era estimates was not statistically significant (40% versus 45%; p=0.5174). Publication-bias tests suggested possible small-study effects; certainty was rated low.

Conclusion: ADRs remain an important consideration in long-term ART, although reported prevalence differs substantially across studies. The subgroup findings are descriptive and cannot establish causal differences in regimen safety. Harmonised outcome definitions, continued pharmacovigilance, and stronger comparative studies are needed. The inconsistent pooled estimates must be reconciled with the original analysis before submission.

Keywords: HIV; antiretroviral therapy; adverse drug reactions; prevalence; systematic review; meta-analysis; pharmacovigilance; dolutegravir

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Introduction

The expansion of antiretroviral therapy (ART) has markedly changed the natural history of human immunodeficiency virus (HIV), allowing many people to live with the infection as a long-term condition. India has made substantial progress in widening access to treatment through the National AIDS Control Organization (NACO); its 2023 report estimated that 84% of diagnosed people were receiving treatment, compared with fewer than one in five in the mid-2000s (1). Maintaining these gains requires attention to treatment safety as well as access. Adverse drug reactions (ADRs) can affect day-to-day wellbeing, reduce adherence, prompt regimen changes, and sometimes lead to treatment cessation. These issues are especially relevant where patients receive different combinations over time, coexisting illnesses are common, and routine toxicity monitoring may be uneven.

ART prescribing in India has evolved over the past decade. Earlier first-line combinations frequently included non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as efavirenz or nevirapine, alongside nucleoside reverse transcriptase inhibitors (NRTIs), including zidovudine, stavudine, and lamivudine (2). Although these combinations achieved virological control, reported toxicities included anaemia, neuropathy, altered fat distribution, liver injury, and neuropsychiatric symptoms (3). One

prospective Indian investigation found that over 90% of participants receiving older first-line treatment experienced at least one ADR within six months; severe events led to withdrawal of treatment in almost 18% (4). Subsequent regimen changes included wider use of tenofovir disoproxil fumarate and, more recently, dolutegravir-containing combinations recommended in treatment guidance (5). These developments have changed the toxicity profile rather than removed the need for surveillance: weight gain, metabolic changes, gastrointestinal symptoms, and neuropsychiatric complaints have also been described with dolutegravir-based treatment (6,7).

Indian studies continue to report clinically relevant reactions with both established and newer ART combinations. In a longitudinal hospital-based study in western India, approximately 78% of participants experienced an ADR during six months of observation; frequently noted findings included raised alkaline phosphatase, dyslipidaemia, and nephrotoxicity (8). In a phase IV study of a fixed-dose tenofovir/lamivudine/dolutegravir combination among treatment-naïve adults, adverse events were reported by more than half of participants during the first 24 weeks, although most were classified as mild or moderate (9). Real-world observations following a switch to generic dolutegravir/lamivudine have also described weight gain, hyperglycaemia, and dyslipidaemia, with some concerns among older patients and those with existing comorbidities (10). Thus, the adverse-effect profile remains relevant across successive generations of ART.

Differences in patient characteristics and clinical context may influence the likelihood of an ADR being observed. Indian reports have identified sex, low body mass index, tuberculosis co-infection, and socioeconomic disadvantage among factors associated with greater susceptibility (11). When ART is used alongside anti-tuberculosis medicines, overlapping toxicity profiles may complicate the assessment of liver-related events; undernutrition may also increase vulnerability to haematological effects such as anaemia (12). Toxicities described in paediatric cohorts include effects on growth, neuropsychiatric symptoms, and metabolic changes (13). Taken together, these observations suggest that drug choice alone does not determine treatment tolerability; patient-level factors, concurrent illnesses, other medicines, and access to monitoring also matter.

ADRs can interfere with consistent ART use and may contribute to switching or stopping treatment. Published estimates indicate that as many as one-quarter of people living with HIV may change or discontinue a regimen during the first year because of toxicity (14). Treatment interruptions can have wider consequences, including loss of virological control and the development or transmission of resistant virus (15). These risks may be harder to manage where alternative regimens and laboratory monitoring are limited. Although pharmacovigilance activities have expanded, incomplete reporting remains a barrier to estimating the frequency and consequences of ART-associated ADRs in India (16).

As survival improves, long-term treatment effects have become increasingly important alongside short-term tolerability. Metabolic outcomes such as insulin resistance, dyslipidaemia, weight change, and cardiovascular risk are relevant to people receiving ART over many years (17). Dolutegravir and other newer agents are often considered better tolerated than some earlier drugs, but reports of weight gain and metabolic changes mean that ongoing evaluation is warranted. This is particularly pertinent in populations where diabetes and cardiovascular disease are already important public health concerns (18).

Individual studies provide useful but not always directly comparable estimates because they differ in design, sample size, participant profiles, treatment combinations, follow-up, and ADR definitions. A systematic review can bring these findings together, estimate the proportion of adults affected where pooling is appropriate, describe commonly reported reactions, and examine whether results vary across regions, study designs, regimens, and treatment periods. Such synthesis may also identify evidence gaps, including limited representation of rural communities, pregnant people, and those receiving second- or third-line treatment.

Reliable safety estimates are relevant to clinical services and programme planning. Health systems need evidence to plan toxicity monitoring, laboratory testing, and supportive care, while clinicians must consider both treatment effectiveness and tolerability when discussing regimens with patients. The evidence may also help identify priorities for pharmacovigilance and future economic evaluation. Findings from Indian settings can contribute to the wider ART-safety literature, while differences in patient characteristics, healthcare access, and local prescribing practices should be considered when interpreting results across countries.

Against this background, the present systematic review and meta-analysis brings together published evidence on ART-associated ADRs in adults. Its objectives were to summarise reported prevalence and patterns, examine variation by geographical setting, study design, regimen, and treatment era, and describe the evidence on severity and causality where reported. The findings are intended to support a more consistent approach to safety monitoring and to identify priorities for better-designed research.

2. Methodology

2.1 Study design and methodological framework

We undertook a systematic review and meta-analysis of published studies reporting adverse drug reactions (ADRs) among adults living with HIV who were receiving antiretroviral therapy (ART). The review considered the frequency of reactions as well as their reported manifestations, severity, and causality assessments. Evidence from different countries, clinical settings, populations, and ART combinations was synthesised, and subgroup analyses were used to explore variation in reported prevalence. Reporting was guided by the PRISMA 2020 statement [1].

The methodology documents state that the protocol was developed prospectively and registered with PROSPERO. The registration identifier was not available in the supplied materials and must be confirmed from the original registration record before submission.

2.2 Research question and eligibility criteria

Eligibility criteria were framed around the population, intervention, comparator, outcomes, and study-design elements (PICOS). The review addressed adults receiving ART and sought data on ADR occurrence, clinical presentation, severity, causality assessment, and factors associated with reactions.

Eligible participants were adults aged 18 years or older with HIV/AIDS who were receiving ART. Treatment exposures included NRTIs, NNRTIs, protease inhibitors, integrase inhibitors, fusion inhibitors, and CCR5 antagonists. Where available, comparator groups included alternative ART combinations or placebo; studies without a comparator could still be included if ADR data were extractable. The primary outcomes were ADR prevalence, type, severity, and causality assessment, while associated patient or clinical factors were treated as secondary outcomes.

Eligible designs included prospective or retrospective cohorts, cross-sectional and longitudinal studies, pharmacovigilance analyses, and randomised trials reporting relevant safety outcomes. The protocol materials specify English-language publications from 2013 to 2024. The results file describes included studies from 2014 to 2024, so the final date range should be checked against the search log.

We excluded case reports, reviews, editorials, letters, animal studies, and reports without sufficient data on clinical ADR outcomes. Studies restricted to children and laboratory-only investigations without relevant clinical outcomes were also excluded.

2.3 Information sources and search strategy

Searches were reported for PubMed/MEDLINE, Embase, Scopus, Web of Science, Google Scholar, and ClinicalTrials.gov. The search was supplemented by grey-literature sources, relevant organisational websites, and citation checking of potentially eligible articles.

Search terms combined concepts for HIV, antiretroviral treatment, and adverse reactions. Medical Subject Headings were used where supported, alongside free-text terms; Boolean logic and database-specific syntax were applied to adapt the strategy to each source.

The recorded PubMed strategy included terms relating to antiretroviral medicines and adherence, adverse drug reactions, adverse drug events, and reaction monitoring. For reproducibility, the exact search strings for each database should be provided in supplementary material, using the original search records rather than reconstructing missing syntax.

The methodology file gives 2013–2024 as the publication window, while the results file describes included papers dated 2014–2024. This difference should be resolved by checking the original search dates and eligibility log.

2.4 Study selection process

The selection process followed a two-stage screening approach consistent with PRISMA 2020. Retrieved citations were imported into reference-management software, and duplicate records were identified and removed before screening.

At title-and-abstract screening, two reviewers independently assessed each record against the eligibility criteria. Records were excluded when they did not concern HIV, ART, or ADR outcomes, focused only on paediatric populations, described laboratory work without clinical outcomes, or lacked relevant safety data.

Full texts of potentially eligible reports were then assessed independently by two reviewers, with exclusion reasons recorded. Differences in judgement were discussed and, when required, referred to a third reviewer for resolution.

The results file records 782 database/register records and 34 additional records from supplementary sources. It then reports 646 records screened, 352 excluded, 294 reports sought, 218 full texts assessed from database-derived records, and 19 supplementary reports assessed. Sixty studies were ultimately listed as included. These counts need to be reconciled with the screening log before the PRISMA diagram and manuscript are finalised.

2.5 Data extraction

Information was extracted using a structured form. The methodology describes independent extraction by two reviewers, with disagreements resolved through discussion or a third reviewer. Recorded study characteristics included author, year, country, design, sample size, participant profile, and ART regimen. Extracted outcomes included the number of participants with ADRs, prevalence, reaction types, severity, causality methods, and reported associated factors.

For causality, the review recorded the approach used in each original study, including the WHO-Uppsala Monitoring Centre (WHO-UMC) system where applicable. This allowed the synthesis to describe the basis on which investigators judged a suspected reaction to be related to ART.

2.6 Risk-of-bias assessment

Risk of bias was to be evaluated with design-appropriate instruments: RoB 2 for randomised trials and the Newcastle–Ottawa Scale for observational studies. The domains considered included selection, confounding, outcome measurement, missing data, and selective reporting. These judgements should inform interpretation of both individual study estimates and the overall body of evidence.

Study-level ratings were not included in the supplied methodology text. The manuscript should report the completed assessments from the original worksheets; individual ratings should not be inferred from study design or prevalence results.

2.7 Statistical analysis

The meta-analysis aimed to estimate the pooled proportion of participants reported to have experienced an ART-associated ADR. For each study, the proportion was based on the number of affected participants divided by the relevant study denominator. A DerSimonian–Laird random-effects model was specified to allow for variation in underlying prevalence across studies and settings.

Between-study variability was evaluated with Cochran's Q and quantified using I^2. The source methodology treats I^2 above 75% as considerable heterogeneity; the results report values reaching 99.5%. Subgroup analyses were organised by geography, study design, ART regimen (including AZT, TDF, EFV, DTG, and mixed categories), and publication period: pre-DTG (2014–2018) versus DTG implementation (2019–2024).

A leave-one-out analysis was specified to examine whether individual studies materially influenced the pooled results. The supplied documents do not identify the statistical package, its version, or the transformation used to pool proportions. Those details should be added only after checking the analysis files.

2.8 Publication bias and certainty of evidence

Possible small-study effects were explored through funnel-plot inspection and the reported Egger, Begg, and Harbord tests. The Duval–Tweedie trim-and-fill procedure was also used. According to the results file, six studies were imputed and the pooled proportion changed from 0.375 to 0.370. These tests and plots are indirect indicators and should be interpreted in the context of the substantial heterogeneity.

The source methodology grades the overall certainty of evidence as low, citing methodological limitations, inconsistency between studies, and possible publication bias. The final report should ensure that this rating is supported by the completed certainty assessment.

2.9 Ethical considerations

Because this review synthesised previously published data and did not recruit participants or collect new identifiable information, the source methodology states that separate ethical approval was not required.

3. Results

3.1 Study selection

The database and register search yielded 782 records: PubMed (82), Embase (128), Scopus (85), Web of Science (42), Google Scholar (201), ClinicalTrials.gov (242), and two further register records. Supplementary searching identified another 34 records (13 from websites, nine from organisations, and 12 through citation searching). The source file records 136 removals before screening—95 duplicates, 26 automation exclusions, and 15 for other reasons—and states that 646 records proceeded to title-and-abstract review; 352 were excluded at this stage. Of 294 database-derived reports sought for retrieval, 76 were unavailable and 218 full texts were assessed. The source then records 163 full-text exclusions: 100 for failure to meet PICOT criteria and 63 because full text was unavailable.

Among the 34 supplementary records, 15 could not be retrieved and 19 underwent full-text review. Fourteen were excluded (six for ineligibility and eight because full text was unavailable). The results file reports 60 studies included overall. However, the screening arithmetic is internally inconsistent: 782 plus 34, less 136 removals, does not equal 646. (Figure 1)

3.2 Characteristics of the included studies

The 60 studies were conducted in India, Ethiopia, Kenya, Ghana, Nigeria, South Africa, Tanzania, Iran, Egypt, Uganda, Iraq, and the United Kingdom. Designs included prospective and retrospective cohorts, cross-sectional and longitudinal studies, and pharmacovigilance analyses. The combined sample exceeded 30,000 participants; individual studies ranged from fewer than 100 participants to more than 12,000. The regimens examined included AZT-, TDF-, EFV-, NNRTI-, DTG-, and mixed-regimen groups.

The main outcome was whether a participant experienced at least one ART-associated ADR. Across studies, the reported proportion ranged from about 7.9% to 62.8%. Studies differed in follow-up, treatment exposure, design, and ascertainment methods, which included participant reports, clinical assessment, laboratory results, medical records, and pharmacovigilance databases.

3.3 Overall pooled prevalence of ART-associated ADRs

The principal pooled analysis reported an ADR prevalence of 38% (95% confidence interval [CI]:

36%-48%) using a random-effects model. The analysis demonstrated substantial between-study heterogeneity (I^2 = 99.5%, p < 0.0001), indicating considerable variability in the reported prevalence estimates. The prediction interval ranged from 4% to 87%, further reflecting the wide variation in prevalence across study settings.

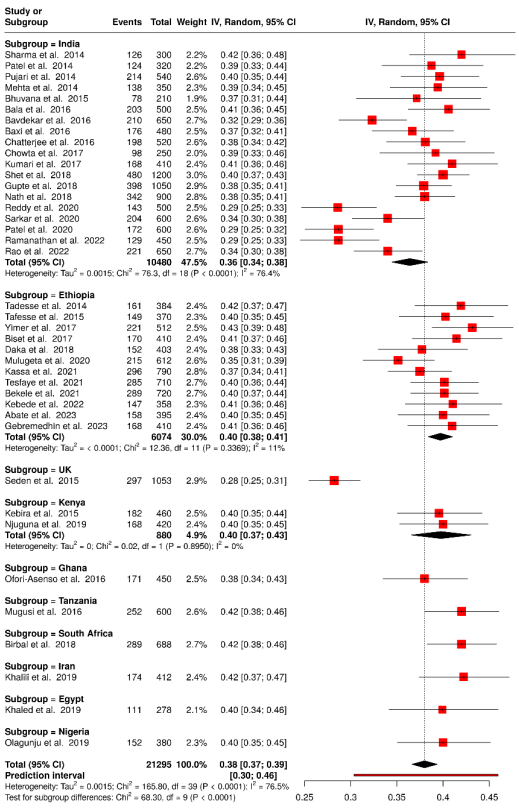
However, the geographical and study-design forest-plot analyses in the same results file reported an overall pooled prevalence of 38% (95% CI: 37%-39%), with I^2 = 76.5% (p < 0.0001) and a prediction interval of 30%-46%. These estimates differ from those in the principal analysis and require reconciliation with the original statistical outputs before a single definitive pooled estimate is reported in the final manuscript.

3.4 Geographical subgroup analysis

The pooled prevalence of ADRs varied across geographical subgroups. Studies conducted in India reported a pooled prevalence of 36% (95% CI: 34%-38%), with substantial heterogeneity (I^2 = 76.4%). Ethiopian studies reported a pooled prevalence of 40% (95% CI: 38%-41%), with low heterogeneity (I^2 = 11%). Studies from Kenya also yielded a pooled prevalence of 40% (95% CI: 37%-43%), with no observed heterogeneity (I^2 = 0%).

Single-study subgroups from the United Kingdom, Ghana, Tanzania, South Africa, Iran, Egypt, and Nigeria reported prevalence estimates ranging from 28% to 42%. The test for subgroup differences was statistically significant (p < 0.0001), indicating variation across the geographical categories in the reported analysis. The single-study estimates, however, should not be interpreted as pooled country-specific prevalence estimates. (Figure 2)

Figure 2: Pooled prevalence of antiretroviral therapy (ART) - associated adverse drug reactions (ADRs) across multiple countries



3.5 Subgroup analysis by study design

Pooled prevalence estimates differed across study designs. Prospective studies reported a prevalence of 39% (95% CI: 37%-42%), with moderate heterogeneity (I^2 = 63.8%). Cross-sectional studies yielded a prevalence of 40% (95% CI: 38%-42%), with no observed heterogeneity (I^2 = 0%). Retrospective studies reported a pooled prevalence of 37% (95% CI: 34%-41%), with substantial heterogeneity (I^2 = 80.8%). Pharmacovigilance studies showed a pooled prevalence of 35% (95% CI: 32%-38%), with low-to-moderate heterogeneity (I^2 = 38.8%). Longitudinal studies reported a pooled prevalence of 39% (95% CI: 37%-41%), with minimal heterogeneity according to the source analysis. The test for subgroup differences was statistically significant (p < 0.0001). Although most estimates fell within a relatively narrow range of 35%-40%, heterogeneity differed considerably between study-design categories. (Figure 3)

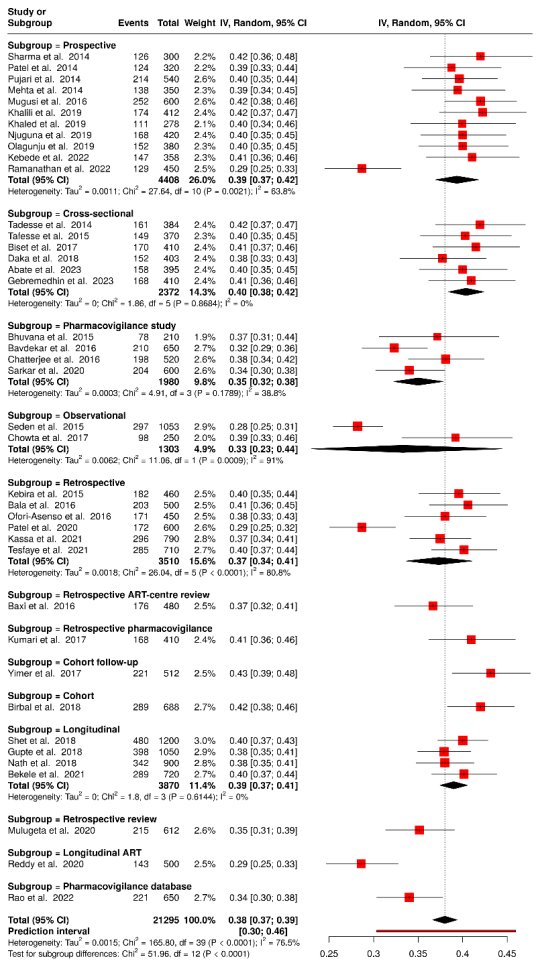


Figure 3: Forest Plot presentation of Subgroup analysis by study design

3.6 Comparison between pre-DTG and DTG implementation eras

The temporal subgroup analysis compared studies published during the pre-DTG era (2014-2018) with those from the DTG implementation era (2019-2024). The pooled prevalence of ADRs was 40% (95% CI: 33%-48%) in the pre-DTG subgroup and 45% (95% CI: 34%-55%) in the DTG-era subgroup. Although the estimate was numerically higher in the DTG-era subgroup, the difference was not statistically significant (χ^2 = 0.42, df = 1, p = 0.5174). Heterogeneity was extremely high in both subgroups, with I^2 = 99.4% in the pre-DTG era and I^2 = 99.5% in the DTG era. These findings do not demonstrate a statistically significant difference in overall ADR prevalence between the two periods. (Figure 4)

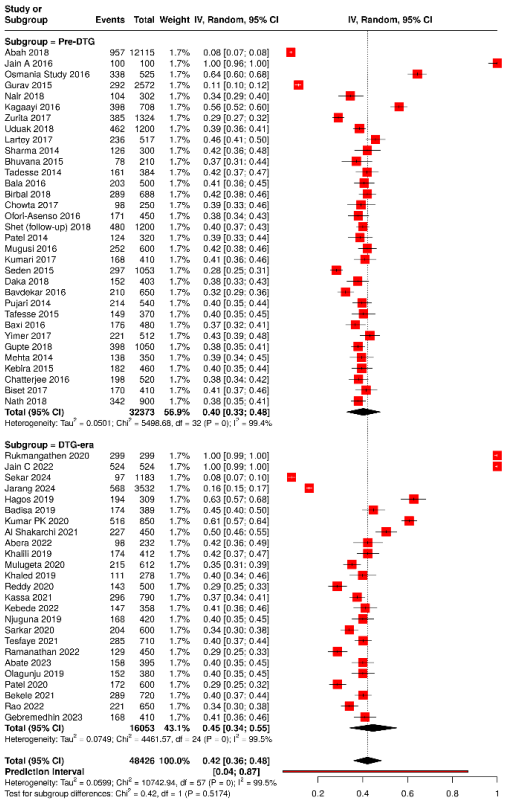


Figure 4: Forest Plot presentation of Comparison between pre-DTG and DTG implementation eras

3.7 Subgroup analysis by ART regimen

The regimen-specific analysis identified statistically significant differences between the reported categories (χ^2 = 292.88, df = 6, p < 0.0001). DTG-based regimens had the lowest reported pooled prevalence, at 21% (95% CI: 14%-30%), although heterogeneity was substantial (I^2 = 98.1%). TDF-based regimens showed a pooled prevalence of 40% (95% CI: 38%-42%; I^2 = 0%), while AZT-based regimens had a pooled prevalence of 40% (95% CI: 37%-42%; I^2 = 0%).

The pooled prevalence was 42% for NNRTI-based regimens (95% CI: 38%-46%; I^2 = 88.1%) and 42% for EFV-based regimens (95% CI: 40%-45%; I^2 = 0%). Mixed-regimen studies showed a pooled prevalence of 44% (95% CI: 33%-55%), with very high heterogeneity (I^2 = 99.7%). A separate AZT/TDF subgroup represented by a single study reported a prevalence of 100%; this isolated estimate does not provide a reliable basis for comparison.

The significant subgroup test indicates variation among the regimen categories in the reported analysis. Nevertheless, the high heterogeneity in several groups and differences between study populations limit direct comparisons of the safety of individual regimens.

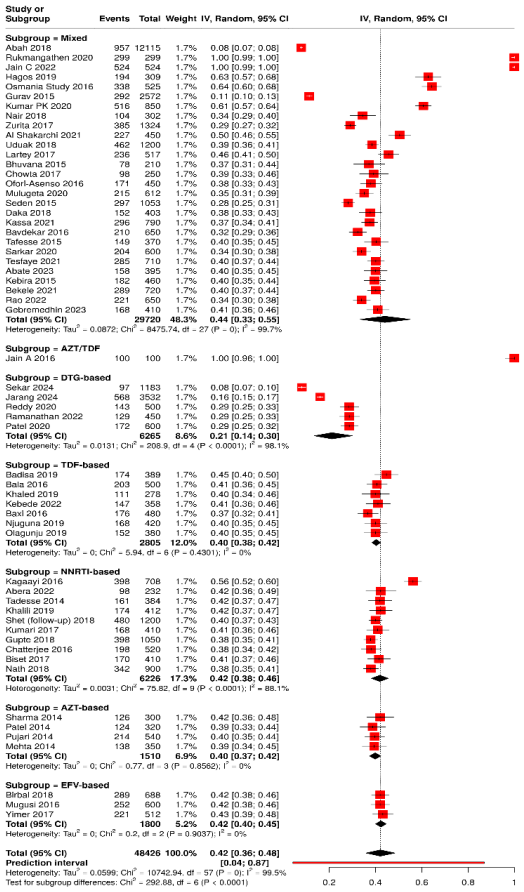


Figure 5: Forest Plot showing Subgroup analysis by ART regimen

3.8 Publication bias and small-study effects

The funnel plot (Figure 6) showed asymmetry, with a relative paucity of smaller studies reporting lower ADR proportions and several studies outside the pseudo-95% confidence limits. Egger's regression test indicated significant asymmetry (intercept $\beta_0 = 4.01$, slope $\beta_1 = 0.293$; $p < 0.001$). Begg's rank correlation test was also statistically significant (Kendall's tau = 0.242, $p = 0.029$). The Harbord test similarly indicated asymmetry (intercept = 31.91, $p < 0.001$).

The Duval and Tweedie trim-and-fill analysis imputed six potentially missing studies on the left side of the funnel plot. The reported pooled proportion decreased from 0.375 to 0.370 after adjustment. Although the numerical difference was small, the findings indicate possible small-study effects and warrant cautious interpretation of the pooled estimates.

Figure 6: Funnel Plot

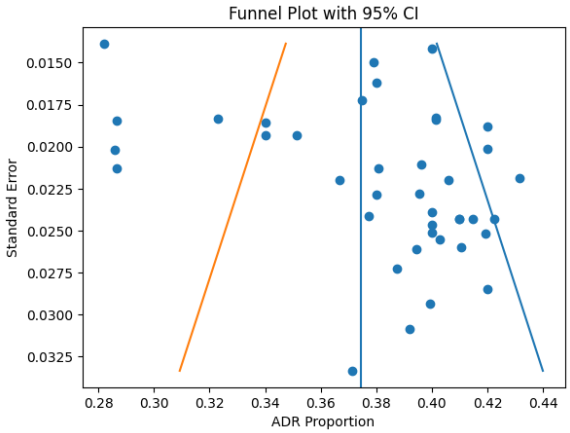
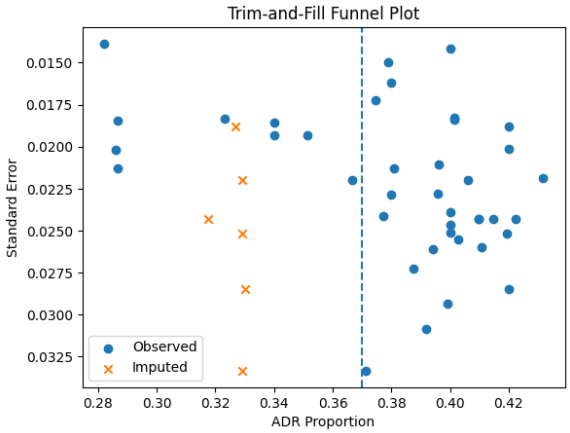


Figure 7: Trim and fill Funnel Plot



3.9 Risk of bias and certainty of evidence

The risk-of-bias assessment indicated a predominantly moderate risk-of-bias profile, with variation across studies and assessment domains. Confounding was a recurring concern, particularly in studies with limited adjustment for demographic, socioeconomic, or clinical characteristics. Additional concerns involved participant selection, outcome measurement, missing data, and selective reporting. Several studies demonstrated low risk in individual domains, whereas a smaller number were assessed as having high risk, particularly for selection and confounding.

Using the GRADE framework, the overall certainty of evidence was rated as low. This judgement reflected methodological limitations, substantial inconsistency in reported ADR prevalence, and potential publication bias. Indirectness and imprecision were not considered serious concerns in the supplied assessment, given the relevance of the included populations and the reported cumulative sample size exceeding 30,000 participants.

3.10 Causality assessment

Six studies using the WHO-Uppsala Monitoring Centre (WHO-UMC) causality assessment system contributed a total of 588 reported ADRs to the causality synthesis. The proportion classified as "probable" ranged from 37.3% to 47.1% across the

individual studies. Acharya et al. reported 22 probable reactions among 59 ADRs (37.3%); Raut et al. reported 52 of 120 (43.3%); Patel et al. reported 39 of 84 (46.4%); Jose et al. reported 48 of 102 (47.1%); Singh et al. reported 67 of 150 (44.7%); and Gupta et al. reported 33 of 73 (45.2%).

These findings describe the proportions classified as probable by the individual studies. They do not establish that all reported reactions were caused by ART, and the study-level proportions should be distinguished from any pooled causality estimate.

4. Discussion

4.1. Principal findings

This review brought together 60 studies with more than 30,000 adults receiving ART. Across the included reports, the proportion experiencing an ADR ranged from 7.9% to 62.8%. The analyses also showed variation by country, study design, treatment category, and publication period. Because the reported pooled estimates are inconsistent across the source outputs and heterogeneity is substantial, the results should be interpreted as evidence of a common safety concern with variable reported frequency, rather than as one universally applicable prevalence figure.

The pattern of findings is broadly compatible with the Indian prospective cohort reported by Shet et al. [18]. In that study, 90.0% of 321 adults starting first-line ART experienced at least one adverse reaction over two years, 26.5% had a severe reaction, and zidovudine-associated anaemia was reported in 37.1%. The cohort reflects treatment with older first-line regimens and illustrates how estimates depend on the drugs used, the length of observation, and the way events are captured.

A count of all ADRs does not, by itself, describe their clinical importance. A transient symptom, an abnormal laboratory result, a serious reaction, and an event that forces a regimen change have different implications. Interpretation of the evidence therefore requires information on severity, persistence, management, and treatment consequences in addition to the proportion affected.

The overall prevalence remains unresolved in the source material. One section reports 42% (95% CI 36–48%; I^2=99.5%), another reports 38% (95% CI 37–39%; I^2=76.5%), and the trim-and-fill analysis starts from 37.5% before adjustment to 37.0%. These values should not be combined or selected by preference. The original model output, study inclusion set, and calculation settings must be checked before a definitive pooled estimate is stated.

4.2. Magnitude and variability of ADR occurrence

The spread of study-level estimates may reflect differences in the populations and treatments studied, but methodological variation is also likely to contribute. For example, prospective follow-up can capture symptoms and laboratory changes as they arise, while retrospective studies depend on what clinicians recorded. Studies also differ in follow-up length, definitions of an ADR, and whether outcomes are patient-reported, clinically assessed, or drawn from routine records.

A related evidence synthesis by Endalamew et al. [19] estimated an ADR incidence rate of 5.09 per 100 person-years in ten Ethiopian studies (95% CI 3.86–6.71; I^2=96.4%). Because that review reports incidence per person-time, its result is not directly comparable with a prevalence proportion. It nevertheless reinforces the need to account for substantial between-study variability when summarizing ART safety.

The very high heterogeneity in the current analysis means that an overall average may not describe the experience of a particular clinic or population well. Age, sex, co-infections, other medicines, ART duration, and the specific combination prescribed may all influence the observed proportion. Differences in how investigators seek and classify reactions may be equally important.

Future studies should define the denominator and outcome consistently. In particular, reports should distinguish the percentage of participants with at least one reaction from the total number of events, and should separately present serious events, laboratory-confirmed toxicities, and reactions that lead to treatment modification or cessation.

4.3. Geographical and study-design differences

The country-level analysis reported proportions of 36% for India and 40% for both Ethiopia and Kenya; countries represented by one study had estimates between about 28% and 42%. Although the source analysis indicates a statistically significant subgroup test, the result may reflect differences in treatment mix, participant characteristics, service delivery, monitoring, and reporting as well as geography. Estimates from single studies should not be treated as stable national rates.

Endalamew et al. [19] reported an incidence rate of 5.09 ADRs per 100 person-years for Ethiopia. Since incidence and prevalence measure different quantities, this finding should be used as contextual evidence of ongoing safety concerns, not as a direct validation or contradiction of the 40% prevalence estimate in this review.

Reported proportions by design were 39% in prospective studies, 40% in cross-sectional studies, 37% in retrospective studies, and 35% in pharmacovigilance studies. The approach used to identify events may help explain these differences: prospective observation permits structured follow-up, retrospective work relies on existing records, and pharmacovigilance datasets depend on reporting

practices. These mechanisms can affect the number of reactions detected.

The statistically significant design subgroup test does not show that study design itself caused the differences. The categories may contain different populations, drug combinations, follow-up periods, and numbers of studies. The findings are best understood as variation between the available groups rather than a ranking of study designs by their ability to detect ADRs.

4.4. Differences across ART regimens

The reported pooled proportions were 21% for DTG-based regimens, 40% for TDF, 40% for AZT, 42% for NNRTI-based regimens, 42% for EFV, and 44% for mixed regimens. The subgroup test was statistically significant, but these are not head-to-head estimates from comparable populations. The observed differences therefore cannot establish that one regimen is safer than another.

Evidence from drug-specific comparisons also shows that adverse-event profiles differ across antiretroviral agents. In their systematic review and meta-analysis, Shubber et al. [20] found that nevirapine-based first-line treatment was associated with more discontinuations due to adverse events than efavirenz-based treatment; severe liver, skin, and hypersensitivity reactions were also more frequent with nevirapine, while severe central nervous system events were more frequent with efavirenz.

The present synthesis extends the scope to a wider set of regimen categories, but it measures a different outcome from the comparative analysis by Shubber et al. [20]. Their review evaluated relative risks for particular adverse outcomes, whereas the current analysis pooled the proportion of participants reported to have any ADR across heterogeneous studies. The results should therefore be considered alongside one another, not as directly equivalent estimates.

The lower estimate in the DTG category merits further investigation but should not be read as proof of superior safety. Heterogeneity in this subgroup was high (I^2=98.1%), and the contributing studies differed substantially. In addition, the categories are not mutually exclusive in pharmacological terms: EFV is an NNRTI, and AZT or TDF may be used within multidrug combinations. Variation in patient mix, exposure duration, study methods, and event ascertainment may explain part of the apparent contrast.

The AZT/TDF category's 100% estimate came from a single study and is therefore highly dependent on that study's design and participants. It cannot be generalised to all people receiving this combination or taken to mean that an ADR is inevitable.

4.5. Pre-DTG and DTG-era comparison

The pooled proportion was 40% (95% CI 33–48%) for studies in 2014–2018 and 45% (95% CI 34–55%) for studies in 2019–2024. The difference was not statistically significant (χ^2=0.42, df=1, p=0.5174), so the analysis did not demonstrate a clear change between these publication periods.

Randomised trials provide a different type of evidence about regimen safety. In ADVANCE, Venter et al. [21] compared DTG-based treatment with an EFV-based combination in adults initiating ART and reported differences in weight gain by treatment group at week 96. The NAMSAL trial, reported by Calmy et al. [22], also compared DTG-based therapy with low-dose EFV and provides controlled comparative evidence on treatment outcomes and safety.

Trial results highlight the importance of examining specific outcomes rather than relying only on an aggregate ADR proportion. Weight gain and metabolic changes, for example, may require separate measurement and longer follow-up. These controlled trials are not directly comparable with the present time-period subgroup, which groups studies by publication year rather than comparing otherwise similar individuals assigned to different treatments.

The non-significant result should not be interpreted as equivalence between the two eras. Heterogeneity was extremely high in both groups, and the comparison was not an adjusted comparison of participants receiving different regimens under comparable conditions. Differences in patient mix, treatment duration, monitoring, and regimen distribution may have influenced the estimates.

4.6. Causality assessment

Six studies used the WHO-UMC framework to classify causality. The source results list 588 assessments or cases, with study-level proportions rated 'probable' between 37.3% and 47.1%. These percentages describe how the included investigators classified suspected reactions; they do not establish that every event was caused by ART.

A 'probable' category indicates a judgement based on the available clinical evidence, not absolute proof of causation. Timing, the course after treatment changes, alternative explanations, co-infections, underlying HIV-related illness, and concomitant medicines can all affect that judgement.

Before an overall causality proportion is calculated, the reported counts require verification. The six denominators sum to 588 and the probable counts to 261, but it is unclear whether these values represent unique patients, individual ADR events, or assessments. Because one patient may experience more than one reaction, the unit of analysis must be confirmed from each original report.

4.7. Publication bias, risk of bias, and certainty of evidence

Asymmetry was observed in the funnel plot, and Egger, Begg, and Harbord tests were statistically significant. The trim-and-fill procedure imputed six studies and changed the pooled proportion from 37.5% to 37.0%. Together, these results raise the possibility of small-study effects, but they do not prove that publication bias is the only explanation; genuine clinical and methodological differences can also produce asymmetry.

The small change after trim-and-fill does not rule out bias. This adjustment relies on assumptions about the missing-study pattern and cannot correct every source of funnel-plot asymmetry. It should be interpreted alongside the high heterogeneity and the limitations of the included evidence.

The risk-of-bias assessment raised concerns about selection, confounding, outcome measurement, missing data, and selective reporting. Confounding is especially important for regimen comparisons because treatment groups may differ in illness severity, prior ART exposure, concomitant medication, comorbidity, and follow-up. Observed differences in ADR proportions may therefore reflect more than the pharmacological effects of the regimen itself.

The overall certainty was judged low because of risk-of-bias concerns, inconsistency, and possible publication bias. Although more than 30,000 participants were represented, sample size alone cannot correct systematic error or make differing ADR definitions comparable. The estimates should be viewed as a synthesis of the available studies, with uncertainty about how well they apply to any specific treatment setting.

4.8. Clinical and public health implications

Routine HIV care should include a structured process for identifying and documenting suspected ADRs. Clinical assessment should record when a reaction began, its severity and consequences, whether it required treatment, and whether other explanations are plausible. Review of concomitant medicines and underlying conditions is important before attributing symptoms or laboratory changes to ART.

Regimen-specific results should be interpreted together with established drug safety evidence, treatment effectiveness, resistance considerations, comorbidities, contraindications, and patient preferences. The lower pooled proportion in the DTG subgroup alone is not a sufficient basis for selecting a regimen.

At programme level, pharmacovigilance records would be more informative if they consistently reported the number of people exposed, the number experiencing an ADR, serious and treatment-limiting events, regimen changes, and the causality method used. Harmonised definitions and denominators would improve comparisons across clinics and studies.

4.9. Strengths and limitations

The review included 60 studies from several countries and study designs and examined reported ADR proportions across regimen groups and treatment periods. The analyses also considered risk of bias, sensitivity to individual studies, and potential small-study effects, providing several perspectives on the available evidence.

The findings have important limitations. High heterogeneity restricts the meaning of a single pooled value, while variation in ADR definitions, ascertainment, follow-up, and participant characteristics reduces comparability. Subgroup analyses may be confounded, and some categories contain limited evidence; the single-study AZT/TDF estimate is particularly unstable. The evidence base also includes possible publication bias and predominantly moderate risk-of-bias concerns.

Two data-quality issues must be resolved before submission: the overall pooled prevalence differs between sections of the results file, and the record-screening counts do not reconcile arithmetically. The reported causality denominators and analysis unit also require checking. These uncertainties should be resolved from the original statistical outputs and screening records, not by choosing one estimate without verification.

4.10. Recommendations for future research

Further studies should use explicit, consistent definitions for suspected, serious, and treatment-limiting ADRs. Multicentre prospective cohorts with a common follow-up schedule and structured clinical and laboratory monitoring would make estimates more comparable across settings.

Comparative studies of DTG and alternative regimens should account for baseline clinical status, prior treatment, co-infections, concomitant medicines, and duration of exposure. Longer observation is needed for delayed or cumulative effects. Causality reports should specify the assessment framework and distinguish the number of patients from the number of events.

Future evidence syntheses would be strengthened by transparent study-level data, consistent outcome definitions, clear subgroup rules, and complete statistical reporting. Authors should provide numerators and denominators, identify the pooling model and proportion transformation, and explain how single-study subgroups were handled.

4.11. Conclusion

This review found that ADRs are commonly reported among adults receiving ART, but their reported frequency varied across countries, study designs, treatment categories, and publication periods. The findings underline that newer treatment options do not remove the need for systematic safety monitoring. Because the source analyses provide conflicting

overall pooled estimates and show substantial heterogeneity, a single definitive prevalence figure should not be reported until the underlying outputs have been reconciled.

Continued pharmacovigilance, consistent ADR definitions, and patient-centred clinical monitoring remain important throughout ART. Better-designed comparative studies with transparent outcome reporting and sufficient follow-up are needed to clarify regimen-specific and long-term safety. The final interpretation should be updated after the pooled estimate and study-selection counts have been verified.

References

1. National AIDS Control Organization. Annual Report 2023. Ministry of Health and Family Welfare, Government of India. New Delhi; 2023.
2. Mehta K, Shinde S, Sinha A, et al. Adverse drug reactions to antiretroviral therapy: Experience at a tertiary care teaching hospital in India. *Indian J Pharmacol*. 2011;43(3):258-61.
3. Sharma A, Vora R, Modi M, et al. Adverse effects of antiretroviral treatment in HIV patients at a tertiary care centre of Gujarat. *Indian J Sex Transm Dis*. 2010;31(1):24-8.
4. Kumar S, Jindal A, Singh G, et al. Adverse drug reactions to Antiretroviral Therapy in AIDS Patients at a Tertiary Care Hospital in India: A Prospective Observational Study. *Indian J Pharmacol*. 2012;44(3):293-7.
5. World Health Organization. Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring. Geneva: WHO; 2021.
6. Hill A, Venter WDF, Delpech V, et al. Progressive weight gain with dolutegravir: a concern for global HIV treatment. *AIDS*. 2021;35(1):105-14.
7. Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: Risk factors in randomized controlled trials. *Clin Infect Dis*. 2020;71(6):1379-89.
8. Sekar VD, Mandal J, Prabhu J, Mehta P, Kumar R. ADRsand Prescription Patterns of Antiretroviral Drugs: A Longitudinal Observational Study from a Tertiary Care Hospital in Western India. *Cureus*. 2024;16(3):e38638708.
9. Dravid A, Panandikar S, Gupte N, et al. Safety, tolerability, and efficacy of tenofovir/lamivudine/dolutegravir in treatment-naïve Indian adults: Results from a Phase IV study. *J Int Assoc Provid AIDS Care*. 2022;21:23259582221111514.
10. Patel A, Shah R, Jariwala P, et al. Metabolic outcomes and weight changes after switch to generic dolutegravir/lamivudine in Indian patients: A real-world study. *Indian J HIV Med*. 2023;25(2):145-52.
11. Patel K, Kshirsagar N, Gharat M, et al. Gender differences in Adverse drug reactions to antiretroviral therapy: Evidence from India. *Int J Clin Pharmacol Ther*. 2020;58(5):256-63.
12. Swaminathan S, Padmapriyadarsini C, Narendran G. HIV-associated tuberculosis: Clinical update. *Clin Infect Dis*. 2010;50(10):1377-86.
13. Shah I, Katira B. Adverse effects of antiretroviral therapy in HIV-infected children. *Indian Pediatr*. 2011;48(3):233-8.
14. Murphy RA, Sunpath H, Lu Z, et al. Outcomes after virologic failure of first-line ART in South Africa. *J Acquir Immune Defic Syndr*. 2010;55(3):303-10.
15. Gupta RK, Gregson J, Parkin N, et al. HIV drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: A systematic review and meta-regression. *Lancet Infect Dis*. 2018;18(3):346-55.
16. Suke SG, Kosta P, Negi H. Pharmacovigilance of antiretroviral therapy in India: Current status and challenges. *Perspect Clin Res*. 2015;6(4):169-74.
17. Negin J, Cumming RG. HIV infection in older adults in sub-Saharan Africa: Extrapolating prevalence from existing data. *Bull World Health Organ*. 2010;88(11):847-53.
18. Erlandson KM, Lake JE. The metabolic consequences of HIV treatment. *Curr Opin HIV AIDS*. 2016;11(1):50-9.
19. Shet A, Antony J, Arumugam K, Kumar Dodderi S, Rodrigues R, DeCosta A. Influence of adverse drug reactions on treatment success: prospective cohort analysis of HIV-infected individuals initiating first-line antiretroviral therapy in India. PLoS One. 2014;9(3):e91028. https://doi.org/10.1371/journal.pone.0091028
20. Endalamew SG, Assefa SK, Getachew MS, Arage FG, Asgedom DK, Terefe B, et al. Incidence of adverse drug reactions among HIV patients on antiretroviral drugs in Ethiopia: a systematic review and meta-analysis. AIDS Res Treat.

2025;2025:8820274. https://doi.org/10.1155/arat/8820274

21. Shubber Z, Calmy A, Andrieux-Meyer I, Vitoria M, Renaud-Théry F, Shaffer N, et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. AIDS. 2013;27(9):1403-1412. https://doi.org/10.1097/QAD.0b013e32835f1db0
22. Venter WDF, Sokhela S, Simmons B, Moorhouse M, Fairlie L, Mashabane N, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. Lancet HIV. 2020;7(10):e666-e676. https://doi.org/10.1016/S2352-3018(20)30241-1
23. Calmy A, Tovar Sanchez T, Kouanfack C, Mpoudi-Etame M, Leroy S, Perrineau S, et al. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open-label, phase 3 non-inferiority trial in Cameroon. Lancet HIV. 2020;7(10):e677-e687. https://doi.org/10.1016/S2352-3018(20)30238-1