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Drug-Related Problems (DRPs) in the Use of Antiretroviral Drugs (ARV/ART): A Scoping Review

Masalah-Masalah Terkait Obat (DRPs) pada Penggunaan Obat Antiretroviral (ARV/ART): Sebuah Tinjauan Cakupan

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Abstract

Background: Antiretroviral therapy (ART) has transformed HIV infection into a manageable chronic disease. However, lifelong ART use and rising comorbidity burdens are associated with various drug-related problems (DRPs) that can lead to virological failure, drug resistance, hospitalization, and increased healthcare costs. **Objective:** This scoping review aimed to identify and map the types, prevalence, and risk factors of DRPs associated with antiretroviral drug use based on literature published between January 1, 2015, and May 29, 2026, reflecting the modern integrase inhibitor and dual-therapy era. **Methods:** We conducted a scoping review using the Population, Concept, and Context (PCC) framework. We searched PubMed, Scopus, and the Cochrane Library for articles published from January 1, 2015, to May 29, 2026 (final search on May 29, 2026). Two reviewers independently selected studies and charted data using Mendeley in accordance with the PRISMA-ScR guideline, and appraised primary observational studies using the Newcastle-Ottawa Scale (NOS). **Results:** Of the 3,298 articles initially identified, 18 articles met the inclusion criteria, encompassing 12,981 participants across 11 primary observational studies and >60,900 cumulative participants synthesized across 7 review and meta-analysis articles. The main DRPs identified included drug-drug interactions (DDIs), adverse drug reactions (ADRs), polypharmacy, medication non-adherence, medication errors, and inappropriate regimens. The prevalence of DDIs ranged from 7.0% for contraindicated interactions to 65.5% for interactions across all severity levels (with 47.5% to 77.0% of identified clinically significant interactions being potentially clinically relevant). A meta-analysis in Ethiopia reported a pooled prevalence of ART-related ADRs of 36.7%, while polypharmacy was reported in a pooled global prevalence of 33.0% among people living with HIV. **Conclusion:** DRPs associated with ART use are multidimensional and driven by regimen-, patient-, and health system-related factors. Integrating clinical pharmacists, routine DDI screening, and regimen simplification are key strategies to optimize ART pharmacotherapy. Future studies are also needed to establish a standardized HIV-specific DRP classification and expand real-world evidence in low- and middle-income countries, including Indonesia.

Keywords: Drug-related problems; antiretroviral therapy; HIV; drug interactions; polypharmacy; scoping review

Abstrak

Latar Belakang: Terapi antiretroviral (ART) telah mengubah infeksi HIV menjadi penyakit kronis yang dapat dikelola. Namun, penggunaan ART seumur hidup dan meningkatnya komorbiditas dikaitkan dengan berbagai *Drug-Related Problems* (DRPs) yang berisiko menyebabkan kegagalan virologis, resistensi obat, rawat inap, serta peningkatan biaya pelayanan kesehatan. **Tujuan:** Mengidentifikasi dan memetakan jenis, prevalensi, serta faktor risiko DRPs yang terkait dengan penggunaan obat ARV/ART berdasarkan literatur yang dipublikasikan antara 1 Januari 2015 dan 29 Mei 2026, yang mencerminkan era inhibitor integrase dan terapi dual modern. **Metode:** *Scoping review* menggunakan kerangka PCC (*Population, Concept, Context*) dengan pencarian pada database *PubMed, Scopus,* dan *Cochrane Library* untuk artikel periode 1 Januari 2015 – 29 Mei 2026 (pencarian terakhir pada 29 Mei 2026). Seleksi studi dan ekstraksi data dilakukan secara independen oleh dua *reviewer* menggunakan Mendeley sesuai pedoman PRISMA-ScR, serta penilaian kualitas studi observasional primer dilakukan menggunakan *Newcastle-Ottawa Scale* (NOS). **Hasil:** Dari 3.298 artikel yang teridentifikasi, 18 artikel memenuhi kriteria inklusi, mencakup 12.981 partisipan dari 11 studi observasional primer serta >60.900 partisipan kumulatif yang dirangkum dalam 7 artikel tinjauan sistematis dan meta-analisis. DRPs utama meliputi interaksi obat (*drug-drug interactions*/DDIs), reaksi obat yang tidak dikehendaki (*adverse drug reactions*/ADRs), polifarmasi, ketidakpatuhan (*non-adherence*), kesalahan pengobatan (*medication errors*), dan ketidaktepatan regimen. Prevalensi DDI berkisar antara 7,0% untuk interaksi kontraindikasi hingga 65,5% untuk seluruh tingkat keparahan (dengan 47,5%–77,0% interaksi yang signifikan secara klinis dan berpotensi relevan secara klinis). Studi meta-analisis di Ethiopia melaporkan prevalensi gabungan (*pooled prevalence*) ADRs terkait ART sebesar 36,7%, sedangkan polifarmasi ditemukan pada 33,0% ODHA secara global. **Kesimpulan:** DRPs dalam penggunaan ARV/ART bersifat multidimensional dan dipengaruhi oleh faktor regimen, pasien, serta sistem kesehatan. Integrasi apoteker klinis, skrining DDI rutin, dan penyederhanaan regimen merupakan strategi utama untuk mengoptimalkan farmakoterapi ART, disertai perlunya penelitian lebih lanjut terkait klasifikasi DRP spesifik HIV serta penguatan bukti di negara berkembang, termasuk di Indonesia.

Kata Kunci: Drug-Related Problems, antiretroviral, HIV, interaksi obat, polifarmasi, scoping review

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Introduction

Since the introduction of combination antiretroviral therapy (cART) in the mid-1990s, the life expectancy of people living with HIV/AIDS (PLWHA) has increased dramatically and has approached that of the general population. [1,2]. Globally, an estimated 39 million people are living with HIV, and most have gained access to antiretroviral therapy (ART) [3]. The success of ART in suppressing viral replication and restoring immune function has transformed HIV from a fatal disease into a manageable chronic condition. [4–6].

However, this success has introduced new clinical challenges. The aging population of PLWHA faces an increasing prevalence of age-related comorbidities, including cardiovascular disease, diabetes, dyslipidemia, kidney disease, and osteoporosis. [1,2,7]. According to epidemiological surveillance cited by Ballard et al. [1]approximately 45% of PLWHA in the United States were aged ≥50 years by the end of 2015, and demographic modeling by Smit et al. [8] projects that PLWHA aged ≥60 years will represent more than 40% of the HIV population by 2030 [2,7,8]. The increasing burden of comorbidities has led to greater use of non-antiretroviral medications, thereby increasing the risk of polypharmacy [2,7,9].

Polypharmacy, commonly defined as the concurrent use of ≥5 non-ART medications, has been reported to have a pooled global prevalence of 33% among PLWHA. [9]. This prevalence is even higher among older populations, ranging from 15% to 94% among PLWHA aged ≥50 years. [2,7]. Polypharmacy increases the risk of drug-drug interactions (DDIs), adverse drug reactions (ADRs), reduced medication adherence, hospitalization, and healthcare expenditures. [2,10–13].

In this review, drug-related problems (DRPs) are defined according to the Pharmaceutical Care Network Europe (PCNE) classification as events or circumstances involving drug therapy that actually or potentially interfere with the achievement of desired health outcomes. [1,14,15]. In the context of ART, DRPs cover a broad spectrum, including DDIs, ADRs, medication non-adherence, inappropriate dosing, therapeutic duplication, prescribing errors, and inappropriate polypharmacy. [1,14,15]. Compared with pharmacotherapy for other chronic diseases, ART represents a unique pharmacological case because it requires lifelong daily adherence to maintain viral suppression, involves multi-agent regimens with complex pharmacokinetics—particularly protease inhibitors (PIs) and integrase inhibitors boosted with ritonavir or cobicistat that strongly inhibit or induce cytochrome P450 (CYP450) enzymes and drug transporters—and is increasingly co-prescribed alongside multiple chronic disease medications, making PLWHA a population at exceptionally high risk for DRPs [7,16–18].

Clinically significant drug interactions (CSDIs) have been reported in up to 47.5% of patients with HIV, with the total number of medications used and duration since HIV diagnosis serving as independent predictors. [19]. In addition, DDIs between antiretroviral drugs and illicit drugs represent an important clinical concern, with 51.1% of PLWHA who used illicit substances experiencing potentially significant DDIs [20].

In Southeast Asia, and particularly in Indonesia, the clinical management of HIV presents distinct pharmacological challenges. Under the Indonesian Ministry of Health guidelines (Permenkes RI No. 23 of 2022) [21], the decentralization of Care, Support, and Treatment (Perawatan, Dukungan, dan Pengobatan [PDP]) services to primary healthcare centers and referral hospitals has expanded access to first-line fixed-dose combination regimens, notably tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) and tenofovir/lamivudine/dolutegravir (TDF/3TC/DTG). Nevertheless, high rates of opportunistic co-infections—especially tuberculosis-HIV (TB-HIV) co-infection—alongside growing cardiometabolic comorbidities

frequently necessitate complex concomitant therapy [3,7,9]. Recent clinical studies from Indonesian referral hospitals report that 64.9% of TB-HIV patients experience three or more DRPs, predominantly pharmacokinetic DDIs reducing therapeutic efficacy (97.3%) or increasing toxicity (62.2%) and medication non-adherence (34.2%) [22,23].

Despite growing primary literature on individual medication issues, a comprehensive synthesis mapping the multidimensional spectrum of DRPs across evolving ART regimens remains lacking. The period from 2015 to 2026 was specifically selected for this review because it captures the modern treatment era initiated by the 2015 World Health Organization (WHO) 'Treat All' recommendation, the global transition from boosted PIs and NNRTIs toward second-generation integrase strand transfer inhibitors (INSTIs), and the clinical adoption of dual ART regimens (such as dolutegravir/lamivudine). Using the Population, Concept, and Context (PCC) framework, this scoping review aimed to systematically identify and map the types, prevalence, risk factors, and clinical management of DRPs associated with antiretroviral drug use published between January 1, 2015, and May 29, 2026.

Method

Study Design and Reporting Standard

This study employed a scoping review design following the methodological framework proposed by Arksey and O'Malley. [24], strengthened by the updated recommendations of the Joanna Briggs Institute (JBI) [25]. The reporting of this review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guideline. [26]. Although the review protocol was not prospectively registered in public registries such as PROSPERO or the Open Science Framework (OSF), the a priori protocol and standardized data charting templates were developed before literature retrieval and are available from the corresponding author upon reasonable request.

Eligibility Criteria

Eligibility criteria were defined a priori using a PCC (Population, Concept, Context) framework adapted for scoping reviews (Box 1) [25].

Box 1. Population, Concept, and Context (PCC) eligibility framework

Component	Description
Population	Adults aged ≥18 years living with HIV/AIDS and receiving antiretroviral therapy (ART).
Concept	Drug-related problems (DRPs), including drug-drug interactions (DDIs), adverse drug reactions (ADRs), non-adherence, inappropriate dosing, therapeutic duplication, prescribing errors, polypharmacy, and other medication-related problems.
Context	All healthcare settings worldwide, including outpatient care, inpatient care, intensive care units, and community settings.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) original research articles (including retrospective and prospective cohort studies, cross-sectional studies, and clinical demonstration projects) as well as systematic reviews, meta-analyses, and scoping reviews; (2) studies that investigated the concept, prevalence, types, risk factors, clinical impact, or pharmacist-led management of drug-related problems (DRPs)—including DDIs, ADRs, polypharmacy, medication non-adherence, prescribing/medication errors, and inappropriate regimens—associated with antiretroviral therapy; (3) studies involving adult populations aged ≥18 years living with HIV/AIDS and receiving ART; (4) articles published in English or Indonesian between January 1, 2015, and May 29, 2026; and (5) articles available in full text.

The exclusion criteria were defined explicitly as follows: (1) studies involving pediatric or adolescent populations aged <18 years, or mixed-age cohorts without separate adult data; (2) studies assessing medication adherence in isolation without evaluating DRPs or medication therapy issues; (3) in vitro, animal, or basic preclinical pharmacological studies lacking clinical DRP outcomes; (4) studies focusing exclusively on pre-exposure prophylaxis (PrEP), which were excluded because PrEP is prescribed to HIV-negative individuals for prevention rather than therapeutic ART management in PLWHA, thus falling outside the PCC population criteria; and (5) conference abstracts, editorials, commentaries, or records without full-text availability.

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Information Sources and Search Strategy

The literature search covered three major international electronic databases—PubMed/MEDLINE, Scopus, and the Cochrane Library—from January 1, 2015, to May 29, 2026, with the final database search conducted on May 29, 2026. We selected these three databases for their comprehensive biomedical coverage, standardized MeSH/Emtree indexing, and rigorous peer-review standards. Because the Cochrane Library primarily indexes controlled trials and systematic reviews, its sensitivity for retrieving observational DRP studies is inherently lower than that of PubMed and Scopus. Regional databases (such as Garuda and Neliti) and grey literature repositories (such as programmatic WHO or national health ministry reports) were not searched during primary database retrieval to maintain uniform indexing and reproducibility; however, relevant Indonesian guidelines and clinical studies were incorporated to contextualize the findings, and the omission of regional/grey databases is acknowledged in the study limitations.

The search string using Boolean operators was as follows:

PubMed:

("drug-related problems" OR "drug related problems" OR "medication-related problems" OR "drug interactions" OR "adverse drug reactions" OR "adverse drug events" OR "medication errors" OR "prescribing errors" OR "inappropriate prescribing" OR "polypharmacy" OR "non-adherence" OR "nonadherence" OR "drug therapy problems") AND ("antiretroviral" OR "antiretroviral therapy" OR "ART" OR "ARV" OR "HAART" OR "cART" OR "HIV treatment" OR "anti-HIV agents") AND ("HIV" OR "human immunodeficiency virus" OR "AIDS" OR "acquired immunodeficiency syndrome" OR "people living with HIV" OR "PLWH")

Scopus:

TITLE-ABS-KEY (("drug-related problems" OR "drug interactions" OR "adverse drug reactions" OR "medication errors" OR "polypharmacy" OR "non-adherence") AND ("antiretroviral" OR "ART" OR "ARV" OR "HIV treatment") AND ("HIV" OR "AIDS" OR "people living with HIV")) AND (LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "PHAR") OR LIMIT-TO (SUBJAREA , "IMMU")) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re")) AND (LIMIT-TO (LANGUAGE , "English") OR LIMIT-TO (LANGUAGE , "Indonesian")) AND (LIMIT-TO (EXACTKEYWORD , "Human") OR LIMIT-TO (EXACTKEYWORD , "Humans")) AND (LIMIT-TO (PUBSTAGE , "final")) AND PUBYEAR > 2014 AND PUBYEAR < 2027

Cochrane Library:

("drug-related problems" OR "drug related problems" OR "medication-related problems" OR "drug interactions" OR "adverse drug reactions" OR "medication errors" OR "prescribing errors" OR "polypharmacy" OR "non-adherence") AND ("antiretroviral" OR "antiretroviral therapy" OR "ART" OR "ARV" OR "cART" OR "HIV treatment") AND ("HIV" OR "human immunodeficiency virus" OR "AIDS" OR "people living with HIV")

Selection of Sources of Evidence

All records retrieved from the electronic databases were imported into Mendeley reference management software for automated and manual deduplication. Before formal screening, we conducted a pilot calibration exercise on a random sample of 20 titles and abstracts to ensure high inter-reviewer agreement on the PCC eligibility criteria. Two reviewers (AFA and BHS) then selected studies independently in two stages: first, title and abstract screening, and second, full-text eligibility assessment. The reviewers resolved any discrepancies or disagreements at either stage through structured consensus discussion with the third reviewer (MF).

Data Charting Process

Two reviewers (AFA and BHS) conducted data extraction (charting) independently using a standardized, pre-piloted charting form in Microsoft Excel, and the third reviewer (MF) cross-verified it for completeness and accuracy. The extracted variables included: first author, year of publication, country/setting, study design, sample size, target population, operational DRP definitions, main types of DRPs identified, reported prevalence or frequency, independent risk factors, and key clinical outcomes.

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Quality Assessment

Although formal critical appraisal is optional in scoping reviews [25,26]We conducted methodological quality and risk-of-bias assessments for all included primary observational studies (cohort, prospective, and cross-sectional designs; n = 11) using the Newcastle-Ottawa Scale (NOS). The NOS was selected to provide an objective evaluation of internal validity across three domains: selection (maximum 4 points), comparability (maximum 2 points), and outcome/exposure assessment (maximum 3 points), categorized as Very Good (9/9), Good (7–8/9), or Fair (5–6/9). Secondary review articles (systematic reviews, meta-analyses, scoping reviews, and narrative reviews; n = 7) were not evaluated using the NOS because the instrument is validated specifically for primary non-randomized observational studies. No studies were excluded based on NOS scores; instead, the quality ratings were used to contextualize evidence strength and generalizability during narrative synthesis.

Data Synthesis

Findings were synthesized narratively using an inductive and deductive thematic approach, organizing the mapped evidence into six core DRP categories: (1) drug-drug interactions (DDIs), (2) adverse drug reactions (ADRs), (3) polypharmacy, (4) medication non-adherence, (5) prescribing and medication errors, and (6) inappropriate regimen selection. Because the included studies employed varying operational definitions of DRPs and polypharmacy (e.g., ≥5 non-ART medications vs. ≥5 total medications) as well as different DDI screening databases (e.g., Liverpool HIV Drug Interactions, Lexicomp, or Micromedex), we extracted the exact definitions and databases used in each study. We mapped the reported problems into standardized domains aligned with the PCNE classification framework where possible. We summarized quantitative prevalence ranges and subgroup comparisons by geographic region and ARV drug class descriptively, without pooling data in a single meta-analysis because of substantial clinical and methodological heterogeneity ($I^2 > 95\%$).

Result

The search across the three databases identified 3,298 records (PubMed: n = 896; Scopus: n = 1,415; Cochrane Library: n = 987). After removing duplicates using Mendeley (n = 2,363), 935 unique articles remained for title and abstract screening. Of these, 847 articles were excluded based on the eligibility criteria, leaving 88 articles for full-text assessment. Following full-text review, 70 articles were excluded, and 18 articles met the final inclusion criteria and were included in this scoping review. [1,2,19,20,27–32,9–11,13–15,17,18].

Collectively, the 18 included articles encompassed 12,981 participants across 11 primary observational studies. [10,11,32,13,17–20,27,28,30] and more than 60,900 cumulative participants synthesized across 7 review and meta-analysis articles [1,2,9,14,15,29,31]. Regarding publication trends, the majority of the included studies (15 of 18 studies; 83.3%) were published between 2020 and 2025 (with 3 studies in 2016–2019, 13 studies in 2020–2023, and 2 studies in 2025), reflecting rapidly growing clinical and research attention toward multimorbidity, polypharmacy, and DRP management in the modern INSTI era.

Assessment of Bias and Study Quality

Cohort and Cross-sectional Studies: Newcastle-Ottawa Scale (NOS)

Of the 18 included studies, 11 primary observational studies (comprising retrospective/prospective cohorts, demonstration projects, and cross-sectional studies) [10,11,32,13,17–20,27,28,30] were evaluated for methodological quality using the Newcastle-Ottawa Scale (NOS). The remaining 7 included studies were secondary syntheses—comprising systematic reviews and meta-analyses [1,2,9,15,29], a scoping review [31], and a narrative review [14]—and were therefore not assessed with the observational NOS instrument.

NOS Interpretation:

1. Selection: Most studies had good sample representativeness. However, several single-center studies, such as those by İnkaya [27] and Emerole [13]had limitations in terms of generalizability.
2. Comparability: Studies that controlled for key confounding factors, such as age and number of medications, received higher scores. Emerole et al. [13] had limitations because of its small sample size (n = 59) and the absence of a control group.
3. Outcome: Studies that used validated drug interaction databases, such as the Liverpool HIV Drug Interactions database, received higher scores than studies that relied on a single source.

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Table 2. Bias Assessment of Cohort and Cross-sectional Studies Using the Newcastle-Ottawa Scale

No.	Study	Selection (Max 4)	Comparability (Max 2)	Outcome / Exposure (Max 3)	Total Score (Max 9)	Quality	Ref.
1	Al Sayed et al., 2022	3/4 (+++)	2/2 (++)	2/3 (++)	7/9	Good	[19]
2	Krentz & Gill, 2016	4/4 (++++)	2/2 (++)	3/3 (+++)	9/9	Very Good	[10]
3	İnkaya et al., 2023	3/4 (+++)	1/2 (+)	2/3 (++)	6/9	Fair	[27]
4	Emerole et al., 2022	2/4 (++)	1/2 (+)	2/3 (++)	5/9	Fair	[13]
5	Xia et al., 2020	4/4 (++++)	2/2 (++)	2/3 (++)	8/9	Good	[17]
6	Lopez Delhoulle et al., 2025	3/4 (+++)	2/2 (++)	3/3 (+++)	8/9	Good	[28]
7	Hazen et al., 2021	3/4 (+++)	1/2 (+)	2/3 (++)	6/9	Fair	[30]
8	Khawcharoenporn & Tanslaruk, 2020	3/4 (+++)	2/2 (++)	3/3 (+++)	8/9	Good	[32]
9	Jakeman et al., 2017	4/4 (++++)	2/2 (++)	2/3 (++)	8/9	Good	[18]
10	da Silva et al., 2023	4/4 (++++)	2/2 (++)	2/3 (++)	8/9	Good	[11]
11	Castro-Granell et al., 2021	3/4 (+++)	1/2 (+)	2/3 (++)	6/9	Fair	[20]

Note: Each plus symbol (+) represents 1 point awarded under the Newcastle-Ottawa Scale criteria (Selection: 0–4 points; Comparability: 0–2 points; Outcome/Exposure: 0–3 points). Quality classification: Very Good (9/9), Good (7–8/9), Fair (5–6/9).

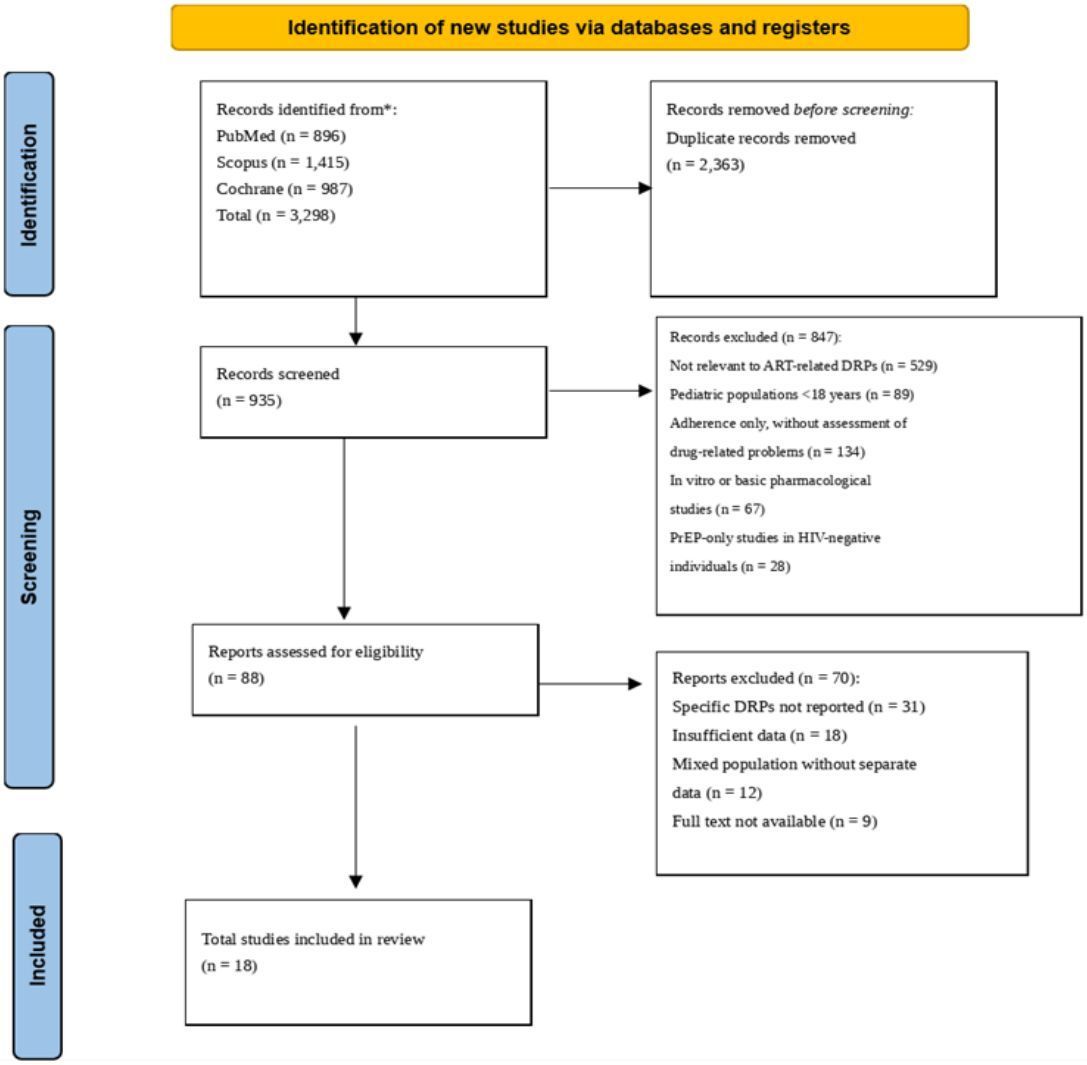


Figure 1. PRISMA 2020 flow diagram of the study selection process.

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Table 1. Characteristics of included studies on drug-related problems associated with antiretroviral therapy

No	Author, Year	Country	Study Design	Sample	Population	Main Types of DRPs	Prevalence of DRPs	Main Risk Factors	Key Findings
1	Ballard et al., 2019 [1]	United States (Multicountry)	Systematic review	Multiple cohorts (incl. Brazil outpatient cohort, n = 140)	Adult people living with HIV/AIDS	DDIs, ADRs, non-adherence, inappropriate regimen	Varied. Pharmacist interventions reduced DRPs by 38.4%	Polypharmacy, older age, PI-based regimen	Clinical pharmacists significantly reduced DRPs. Their role expanded to comorbidity management, DDI monitoring, and optimization of care transitions.
2	Sarma et al., 2023 [2]	Multicountry, mostly United States	Systematic review	79 studies (n = 1,947 in DDI sub-analysis)	People living with HIV/AIDS aged ≥50 years	DDIs, ADRs, polypharmacy, medication burden	Up to 2,552 potential DDIs among 1,947 participants	Older age, comorbidities, polypharmacy	Comorbidities, quality of life, polypharmacy, DDIs, ADRs, adherence, and medication burden influenced medication-related needs in older people living with HIV/AIDS.
3	Al Sayed et al., 2022 [19]	United Arab Emirates	Retrospective cohort	181	Adult outpatients living with HIV/AIDS	DDIs, clinically significant drug interactions	47.5% of patients had CSDIs. A total of 140 CSDIs were identified	Number of medications, OR 1.165. Duration since HIV diagnosis, OR 1.156	A total of 77% of CSDIs were potentially clinically relevant. Interactions between ARV drugs accounted for 37.14%, while ARV and non-ARV interactions accounted for 62.85%.
4	Krentz & Gill, 2016 [10]	Canada	Retrospective cohort	1,190	Adult people living with HIV/AIDS receiving ART	Polypharmacy, non-adherence, non-continuous ART	32.2% experienced polypharmacy	Polypharmacy, ART pill burden, older age	Polypharmacy increased the risk of non-continuous ART, 36.8% versus 30.0%, $p<0.01$. Non-adherence and adverse effects were the main causes.
5	Ahmed et al., 2023 [15]	Multicountry	Systematic review	21 studies, 2,998 people living with HIV/AIDS	Adult people living with HIV/AIDS	Incomplete regimen, DDIs, inappropriate dosing, therapeutic	Varied across studies	Hospitalization, complex regimen	Pharmacist interventions significantly reduced incomplete regimens, DDIs, inappropriate dosing, therapeutic

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						duplication, polypharmacy, ADRs, prescribing errors			duplication, polypharmacy, administration errors, ADRs, and prescribing errors.
6	Michienzi et al., 2020 [14]	United States	Review	6 studies	Hospitalized adults living with HIV/AIDS	Medication errors	Medication errors decreased significantly after implementing an ARV stewardship program.	Hospitalization, lack of HIV expertise	All six studies reported a significant reduction in medication errors after implementation of an antiretroviral stewardship program.
7	İnkaya et al., 2023 [27]	Turkey	Retrospective study	75	Adult people living with HIV/AIDS receiving comedications	DDIs, polypharmacy	DDIs ranged from 55% to 64%, depending on the database. Polypharmacy was 79%	Boosted ARV regimen, number of comedications	The dual regimen DTG/3TC significantly reduced DDIs compared with standard triple therapy, p=0.029.
8	Castro-Granell et al., 2021 [20]	Spain	Cross-sectional study	694	People living with HIV/AIDS who used illicit drugs	Interactions between ARV drugs and illicit drugs	51.1% had significant DDIs. The mean was 2.1 ± 1.7 DDIs per patient	PI regimen, boosted INSTI regimen, NNRTI regimen	Cocaine, cannabis, MDMA, and nitrates were the most frequently involved substances. Awareness of DDIs was positively associated with intentional non-adherence.
9	Emerole et al., 2022 [13]	Russia	Retrospective study	59	People living with HIV/AIDS admitted to the ICU	DDIs, polypharmacy, organ dysfunction	100% experienced polypharmacy. A total of 65.5% had DDIs. The mean number of concomitant drugs was 15	ICU care, number of medications	The most common DDIs were TDF/vancomycin (49.2%) and LPV/RTV/ciprofloxacin (30.3%). The TDF/vancomycin interaction group showed a significant difference in creatinine level.
10	Xia et al., 2020 [17]	China	Multicenter cross-sectional study	600	Adult people living with HIV/AIDS receiving ARV therapy	DDIs	We identified 2,566 DDIs. Contraindicated DDIs accounted for 0.43%, while	Boosted PI, boosted INSTI, NNRTI, systemic anti-infective drugs,	A total of 85.2% of patients had at least one non-HIV comedication. Boosted PI regimens had the highest risk of DDIs.

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							12.89% required dose adjustment or monitoring.	cardiovascular drugs.	
11	Lopez Delhoulle et al., 2025 [28]	Belgium	Retrospective cohort	812 (Liège cohort, 2017–2022; n = 543 longitudinal subgroup)	Adult people living with HIV/AIDS	Red-flag DDIs, polypharmacy	Red-flag DDIs decreased after 2017, while polypharmacy continued to increase.	Boosted ARV regimen, topical corticosteroids, PPIs	The use of non-ARV medications increased significantly and continuously. Contraindicated DDIs decreased following the transition to unboosted regimens.
12	Zewdu et al., 2025 [29]	Ethiopia	Systematic review and meta-analysis	29 studies	Adult people living with HIV/AIDS receiving ART	ADRs	The pooled prevalence of ADRs was 36.7%, 95% CI: 26.6–46.9	Female sex, advanced disease, comorbidities, malnutrition, tuberculosis treatment, poor adherence	ART-related ADRs remained a significant health problem. Close monitoring is required.
13	Hazen et al., 2021 [30]	United States	Prospective demonstration project	765 (PCHCM demonstration cohort)	Adult people living with HIV/AIDS	ART-related and non-ART-related therapy problems	The mean number of problems was 4.2 for ART and 6.4 for non-ART therapy per patient.	Younger age, Black race, number of medications	Adherence problems were the most common issue (57%). The proportion of days covered was 89% in patients with no ART-related problems and 73% in patients with ≥3 ART-related problems.
14	He et al., 2023 [31]	Multicountry	Scoping review	29 studies	Adult people living with HIV/AIDS with polypharmacy	Barriers and facilitators of adherence in polypharmacy	A total of 80 specific factors were identified	Individual factors, medication-related factors, condition-related factors, healthcare provider factors, socioeconomic factors	Non-ART medications affected ART adherence, and ART also affected adherence to non-ART medications. Both individual and overall medication assessments are needed.
15	Danjuma et al., 2022 [9]	Multicountry	Systematic review and meta-analysis	23 studies, 55,988 people living with HIV/AIDS	Adult people living with HIV/AIDS receiving ART	Polypharmacy	The pooled prevalence of polypharmacy	Geographic region, 44% in the Americas and 29% in Europe	Polypharmacy is a significant and growing issue. Effective

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							was 33%, 95% CI: 25–42%		interventions require further investigation.
16	Khawcharoenporn & Tanslaruk, 2020 [32]	Thailand	Prospective study	248	People living with HIV/AIDS initiating ART	Polypharmacy, DDIs, ADRs	Polypharmacy was 9%. Virological suppression was similar	HIV-related hospitalization, aOR 11.63. Low adherence score, aOR 0.49	Polypharmacy did not affect virological outcomes in a comprehensive multidisciplinary care setting
17	Jakeman et al., 2017 [18]	United States	Cross-sectional study	3,810	Adult people living with HIV/AIDS receiving ARV therapy	Contraindicated DDIs	Contraindicated DDIs were found in 7% of patients. Moderate-to-high severity interactions were found in 33%	Older age, aOR 1.17 per 10 years, anxiety, dyslipidemia, non-ARV medication burden, PI regimen	The probability of contraindicated DDIs varied according to ART regimen, age, and number of non-HIV medications.
18	da Silva et al., 2023 [11]	Brazil	Cross-sectional study	4,547	Adult people living with HIV/AIDS receiving ARV therapy	Polypharmacy	50.6%, 95% CI: 49.2–52.1	Older age, cisgender female sex, lower education level, longer duration since HIV diagnosis	Nervous system drugs, anti-infective agents, and cardiovascular drugs were the most commonly prescribed concomitant medications, at 64.8%, 60.0%, and 40.0%, respectively.

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Synthesis of Findings: Types of DRPs in ARV Use

Based on the analysis of 18 included articles, DRPs in ARV use fall into six main categories.

1. Drug-Drug Interactions (DDIs)

DDIs were the most frequently reported and investigated DRPs. The prevalence of DDIs varied substantially by population, ARV regimen, and identification database.

Prevalence of DDIs:

a) Among the general outpatient PLWHA population: 47.5% in the UAE [19] and 55%–64% in Turkey [27].
b) Among PLWHA in China: 2,566 DDIs were identified in 600 patients, with 0.43% classified as contraindicated and 12.89% requiring dose or timing adjustment [17].
c) Among PLWHA who used illicit drugs in Spain: 51.1% [20].
d) Among PLWHA admitted to ICUs in Russia: 65.5% of patients receiving ARVs had DDIs [13].
e) In a United States cohort: 7% had contraindicated interactions, and 33% had moderate or high-severity interactions [18].

Risk factors for DDIs:

Multivariate analyses across several studies consistently identified the following factors as independent predictors of DDIs [17–19]:

a) Use of protease inhibitors (PIs), particularly ritonavir-boosted regimens.
b) Number of medications used.
c) Older age.
d) Longer duration since HIV diagnosis.
e) Specific comorbidities, including dyslipidemia and anxiety.

Drug classes most commonly involved [17,19,20,28]**:**

a) ARVs: PIs, especially LPV/RTV, ATV/RTV, and DRV/RTV; NNRTIs, particularly efavirenz; and boosted INSTIs, especially EVG/COBI.
b) Non-ARVs: cardiovascular drugs, statins, benzodiazepines, NSAIDs, corticosteroids, antithrombotic agents, proton pump inhibitors (PPIs), and antibiotics.
c) Illicit drugs: cocaine, cannabis, MDMA, and nitrates.

An important finding from İnkaya et al. [27] showed that dual regimens, particularly DTG/3TC, significantly reduced DDIs compared with standard triple regimens ($p = 0.029$ based on the Liverpool database). This suggests that simplifying ARV regimens may help reduce DDIs. Delhoulle et al. support this finding. [28], who reported a reduction in red-flag DDIs following the transition from boosted to unboosted regimens in Belgium.

2. Adverse Drug Reactions (ADRs)

The systematic review and meta-analysis by Zewdu et al. [29]which synthesized 29 primary studies conducted in Ethiopia, reported a pooled national prevalence of ART-related ADRs of 36.7% (95% CI: 26.6–46.9%; $I^2 = 99.64\%$), representing a setting-specific pooled estimate in a resource-limited country rather than a global prevalence. Independent predictors of ADRs included female sex, advanced WHO clinical disease stage, comorbidities, malnutrition, concomitant tuberculosis treatment, and poor adherence. [29].

Commonly reported ADRs associated with ARV use included gastrointestinal disorders, such as diarrhea and nausea; neuropsychiatric symptoms, such as insomnia, fatigue, and headache; and weight gain associated with second-generation INSTIs [1,2]. Emerole et al. [13] reported that the TDF/vancomycin DDI in ICU patients was associated with a significant difference in creatinine levels ($p < 0.05$), indicating a clinically relevant impact of DDIs on organ function.

3. Polypharmacy

Polypharmacy is a DRP with an increasing prevalence as the population of PLWHA continues to age—as reported in the meta-analysis by Danjuma et al. [9] reported a pooled prevalence of polypharmacy of 33% (95% CI: 25–42%) from 23 studies involving 55,988 PLWHA. The prevalence was higher in the Americas (44%) than in Europe (29%).

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Individual studies reported varying prevalence rates:

a) 32.2% in Canada [10].
b) 50.6% in Brazil [11].
c) 79% in Turkey among patients with comedications [27].
d) 100% in ICUs in Russia [13].
e) 9.0% in Thailand [32].

This wide variation in reported polypharmacy prevalence (ranging from 9.0% to 100%) reflects substantial differences in operational definitions (concurrent use of ≥5 non-ART medications versus ≥5 total medications), clinical care settings (outpatient ART initiation clinics in Thailand. [32] versus intensive care units in Russia [13] or pre-selected comedicated cohorts in Turkey [27]), and population characteristics (younger treatment-naive cohorts versus older PLWHA with multimorbidity). Polypharmacy was associated with several negative outcomes, including non-continuous ART use. [10], increased DDIs [17,18]and reduced quality of life [2]. However, a study from Thailand [32] showed that, in a comprehensive multidisciplinary care setting, polypharmacy did not significantly affect virological outcomes.

4. Non-adherence

Non-adherence was one of the most commonly reported ART-related problems. Hazen et al. [30] reported that 57% of ART-related therapy problems were associated with adherence. The Proportion of Days Covered (PDC) decreased from 89% among patients without ART-related problems to 73% among patients with three or more ART-related problems. [30].

He et al. [31] identified 80 specific factors affecting polypharmacy adherence among PLWHA. They grouped these factors into five categories: individual factors, medication-related factors, condition-related factors, healthcare provider-related factors, and socioeconomic factors. An important finding was that non-ART medications affected ART adherence and vice versa, indicating a bidirectional interaction between different types of DRPs [31].

Castro-Granell et al. [20] reported a unique finding that awareness of DDIs and beliefs about potential toxicity were positively correlated with intentional non-adherence ($p < 0.0001$). This suggests that inappropriate or poorly framed information about DDIs may reduce adherence.

5. Medication Errors

Michienzi et al. [14] reported that all six studies evaluating inpatient ARV stewardship programs found a significant reduction in medication errors after implementation. Medication errors among hospitalized PLWHA included incomplete regimens, incorrect doses, wrong formulations, and omitted medications.

Ahmed et al. [15]In their systematic review, they reported that pharmacist-led interventions significantly reduced various types of medication errors, including incomplete or inappropriate ARV regimens, incorrect dosing, therapeutic duplication, administration errors, and prescribing errors.

6. Inappropriate Regimens

Inappropriate ARV regimen selection, including regimens that do not align with the patient's resistance profile, comorbidities, or comedications, represents a significant DRP. Ballard et al. [1] emphasized that initial ART selection should consider regimen potency, potential adverse effects, potential DDIs, genetic barriers to resistance, patient comorbidities, and compatibility with the patient's lifestyle.

Table 3 presents a structured synthesis of the six DRP categories, including the number of contributing studies, prevalence ranges, primary risk factors, and clinical impacts.

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Table 3. Structured synthesis of drug-related problem (DRP) categories associated with antiretroviral therapy

DRP Category	No. of Studies [Refs]	Reported Prevalence / Frequency Range	Main Risk Factors	Key Clinical Impacts
1. Drug-Drug Interactions (DDIs)	11 studies [1,2,32,13,15,17–20,27,28]	7.0% (contraindicated DDIs) to 65.5% (all-severity DDIs in ICU); 47.5%–77.0% clinically significant/relevant DDIs in outpatients	Ritonavir- or cobicistat-boosted PI/INSTI regimens, number of comedications, older age, longer HIV duration, dyslipidemia, anxiety, illicit drug use	Altered ARV or comedication plasma concentrations, nephrotoxicity (e.g., TDF/vancomycin creatinine elevation), treatment toxicity, or intentional non-adherence
2. Adverse Drug Reactions (ADRs)	6 studies [1,2,13,15,29,32]	36.7% pooled prevalence (95% CI: 26.6–46.9%) in Ethiopian meta-analysis	Female sex, advanced WHO clinical stage, malnutrition, concomitant TB therapy, poor adherence, second-generation INSTI or EFV use	Gastrointestinal disturbances, neuropsychiatric symptoms, INSTI-associated weight gain, organ dysfunction, and regimen discontinuation
3. Polypharmacy (≥5 non-ART drugs)	11 studies [1,2,32,9–11,13,15,27,28,31]	33.0% pooled global prevalence (95% CI: 25–42%); 9.0% (Thailand) to 79.0% (Turkey comedicated) and 100% (Russia ICU)	Older age (≥50 years), multimorbidity (cardiovascular, CNS, metabolic disorders), female sex, lower educational attainment, ICU admission	Increased DDI exposure, non-continuous ART (36.8% vs. 30.0%, $p < 0.01$), higher pill burden, falls, and reduced health-related quality of life
4. Medication Non-adherence	6 studies [1,2,10,20,30,31]	57.0% of all ART-related therapy problems; PDC declined from 89% (0 problems) to 73% (≥3 problems)	High pill burden, complex multi-tablet regimens, fear/beliefs regarding DDI toxicity, socioeconomic barriers, bidirectional non-ART burden	Suboptimal antiretroviral exposure, non-continuous ART, increased risk of virological failure, and emergence of drug resistance
5. Prescribing and Medication Errors	3 studies [1,14,15]	Reported across all 6 inpatient ARV stewardship studies and 21 pharmacist-intervention studies	Inpatient hospitalization, care transitions, complex multi-drug regimens, and prescribers lacking specialized HIV pharmacotherapy training	Incomplete ART regimens, incorrect dosing or renal adjustment, wrong formulations, omitted doses, and therapeutic duplication
6. Inappropriate Regimen Selection	3 studies [1,15,27]	Reduced by 38.4% (overall DRPs) via clinical pharmacist intervention; dual DTG/3TC significantly lowered DDIs vs. triple ART ($p = 0.029$)	Failure to account for baseline viral resistance, organ dysfunction, comedication DDI profiles, or patient lifestyle	Preventable DDI exposure, suboptimal virological suppression, avoidable metabolic toxicity, and higher treatment burden

Quantitative Prevalence Range and Subgroup Synthesis

Based on available data from studies reporting DDI prevalence with 95% confidence intervals (CIs), we conducted a quantitative subgroup synthesis to evaluate the distribution of DDIs among PLWHA. Across individual cohorts, Al Sayed et al. reported an overall DDI prevalence of 47.5% (95% CI: 40.1–54.9%). [19]55.0% (95% CI: 43.5–66.0%) by İnkaya et al. [27]51.1% (95% CI: 47.2–55.0%) by Castro-Granell et al. [20]and 65.5% (95% CI: 52.3–77.3%) by Emerole et al. [13]. When stratified by interaction severity, Xia et al. [17] identified red-flag (contraindicated) interactions in 0.4% (95% CI: 0.2–0.8%) and orange-flag (potential dose adjustment or close monitoring required) interactions in 12.9% (95% CI: 11.6–14.3%) of evaluated drug pairs, whereas Jakeman et al. [18] reported patient-level prevalences of 7.0% (95% CI: 6.2–7.9%) for contraindicated DDIs and 33.0% (95% CI: 31.5–34.5%) for moderate-to-high severity interactions. Because heterogeneity was very high across studies ($I^2 > 95\%$)—reflecting substantial differences in DDI definitions, interaction databases used, study populations, and ARV regimens—we did not calculate a single pooled estimate, as it would not be

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clinically meaningful; instead, we performed a narrative subgroup synthesis. Subgroup analysis by ARV regimen type demonstrated that PI-boosted regimens were consistently associated with the highest prevalence of DDIs. [17–19]Unboosted INSTI-based regimens were associated with the lowest prevalence of DDIs. [27,28], and dual regimens (DTG/3TC) showed a significant reduction in DDIs compared with standard triple regimens [27].

Regarding the prevalence of polypharmacy among PLWHA, the meta-analysis by Danjuma et al. [9] across 23 studies established a pooled global prevalence of 33% (95% CI: 25–42%; $I^2 = 100\%$, $\tau^2 = 0.9170$, $p < 0.0001$), with regional subgroup analyses showing a higher prevalence in the Americas at 44% (95% CI: 27–63%) compared with Europe at 29% (95% CI: 20–40%). Similarly, individual studies included in this review reported varying polypharmacy prevalence rates, including 32.2% by Krentz & Gill [10], 50.6% (95% CI: 49.2–52.1%) by da Silva et al. [11], 79.0% by İnkaya et al. [27], 100% in ICU patients by Emerole et al. [13], and 9.0% by Khawcharoenporn & Tanslaruk [32]. This wide variation reflects differences in polypharmacy definitions, clinical care settings, and healthcare access across countries.

Analysis

The prevalence of DDIs and polypharmacy varied markedly across the included literature. Studies conducted in high-income countries (such as the United States, Canada, and European nations) generally reported higher prevalences of DDIs and medication burden compared with studies from middle-income countries (such as Thailand and China) [9,10,17,18,28,32]. This disparity is likely attributable to better access to non-ARV medications in high-income countries that increases polypharmacy, a larger proportion of older PLWHA with age-related comorbidities in high-income settings. [1,2,7], and regional differences in the antiretroviral regimens prescribed.

A clear distinction in DRP profiles was also evident across different antiretroviral drug classes. Boosted PI regimens (ritonavir- or cobicistat-boosted) were consistently associated with a very high risk of DDIs [17–19], moderate-to-high rates of ADRs, and moderate regimen complexity. NNRTI-based regimens, particularly efavirenz, exhibited a moderate risk of DDIs [17,18] and low regimen complexity, but carried a high risk of neuropsychiatric ADRs [1,6,29]. Conversely, unboosted INSTI-based regimens demonstrated a low risk of DDIs [27,28], low-to-moderate ADR rates (primarily weight gain) [1,2]and low regimen complexity, whereas dual ART regimens (DTG/3TC) achieved the lowest risk of DDIs [27], low ADR rates, and the lowest overall regimen complexity.

Furthermore, studies evaluating clinical pharmacist interventions consistently demonstrated positive clinical and therapeutic outcomes across care settings. Pharmacist-led interventions achieved a 38.4% reduction in DRPs in Brazil. [1], a significant reduction in medication errors across all six inpatient antiretroviral stewardship program (ARVSP) studies [14], physician acceptance rates exceeding 90% for pharmacist recommendations [15]and a significant reduction in drug interaction scores following pharmacist-guided ART simplification [1,2].

Discussion

Spectrum of DRPs in ARV Use

This scoping review confirms that DRPs in ARV use are multidimensional and interrelated. The six main categories of DRPs identified, namely DDIs, ADRs, polypharmacy, non-adherence, medication errors, and inappropriate regimens, do not occur independently. Instead, they form a complex causal network. Polypharmacy increases the risk of DDIs [17,18]DDIs and ADRs reduce adherence. [10,20,29]and non-adherence subsequently increases the risk of virological failure and drug resistance [1,30].

Our in-depth analysis shows that DDIs are the most frequently investigated DRP and have the broadest clinical implications. The prevalence of DDIs, ranging from 7.0% for contraindicated interactions to 65.5% for interactions of all severity levels (and up to 77.0% of identified CSDIs being potentially clinically relevant in outpatient cohorts), reflects the pharmacokinetic complexity of ARV drugs, particularly those metabolized through the CYP450 system. The finding that PI-boosted regimens are consistently associated with the highest risk of DDIs has important implications for regimen selection, especially among aging people living with HIV/AIDS who have multiple comorbidities [17–19].

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Evolution of DRP Profiles Alongside Changes in the ART Landscape

One of the most significant findings of this review is evidence from recent studies published between 2023 and 2025 showing that DRP profiles change as ARV regimens evolve. [2,11,15,27–29,31]. In a 2025 longitudinal cohort of 812 patients in Belgium, Lopez Delhoulle et al. [28] demonstrated that while non-ARV comedication use rose from 81.7% in 2017 to 88.6% in 2022 (and polypharmacy increased from 20.7% to 28.9%), the total number of contraindicated red-flag DDIs decreased by 50% ($p = 0.044$) as dual therapy adoption rose from 3.2% to 35.0% and boosted regimens declined. Similarly, İnkaya et al. [27] provided direct comparative evidence in 2023 that dual regimens, particularly DTG/3TC, significantly reduced DDIs compared with standard triple regimens ($p = 0.029$).

This shift reflects advances in ARV development, particularly second-generation INSTIs, such as dolutegravir and bictegravir, which have a more favorable DDI profile than PI-boosted regimens [27,28]. However, recent systematic reviews and meta-analyses from 2023–2025 emphasize that second-generation INSTIs are associated with clinically significant weight gain and cardiometabolic changes, while ADR burdens in resource-limited settings remain high at 36.7% [1,2,29]. This indicates that although pharmacokinetic DDIs may decrease with modern regimens, metabolic ADRs and non-ARV polypharmacy challenges continue to emerge.

Polypharmacy as a Major Driver of DRPs

The meta-analysis by Danjuma et al. [9]which reported a pooled polypharmacy prevalence of 33% among people living with HIV/AIDS, highlights the magnitude of this problem. More concerningly, Delhoulle et al. [28] reported a significant and continuous increase in the use of non-ARV medications from 2017 to 2022, indicating that the problem of polypharmacy may worsen as the population of people living with HIV/AIDS continues to age.

The 2023 cohort study by da Silva et al. [11] in Brazil ($n = 4,547$), which showed a 50.6% polypharmacy prevalence with nervous system drugs (64.8%), anti-infective agents (60.0%), and cardiovascular drugs (40.0%) as the most frequently prescribed comedications, provides specific targets for clinical intervention. These drug classes have considerable potential for DDIs with ARVs, particularly through CYP3A4 and P-glycoprotein pathways. [7,17,19].

However, the findings of Khawcharoenporn and Tanslaruk [32] in Thailand, which showed that polypharmacy did not affect virological outcomes in a comprehensive multidisciplinary care setting, provide an important perspective. This suggests that the negative impact of polypharmacy can be mitigated through a structured care approach, including close DDI monitoring, adherence counseling, and multidisciplinary collaboration.

Non-adherence: A Complex Interaction with Other DRPs

The finding that 57% of ART-related therapy problems were associated with adherence [30] confirms that non-adherence remains a major challenge in HIV management. Interestingly, He et al. [31] identified that non-ART medications affected ART adherence and vice versa, indicating that strategies to improve adherence should be holistic and should not focus solely on ART.

The counterintuitive finding by Castro-Granell et al. [20], which showed that awareness of DDIs was positively correlated with intentional non-adherence, has important implications for patient education. Information about DDIs should be delivered in a way that empowers patients to manage their treatment safely, rather than creating fear that may reduce adherence.

Role of Pharmacists and Evidence-based Interventions

Consistent evidence from various studies shows that pharmacist-led interventions significantly reduce DRPs among people living with HIV/AIDS. [1,14,15]. Notably, Ballard et al. [1] highlighted a clinical pharmacy cohort study in an outpatient HIV clinic in Brazil ($n = 140$; 70 intervention vs. 70 control patients) in which clinical pharmacist consultations achieved a statistically significant 38.4% reduction in DRPs, alongside improved CD4+ T-cell counts. Furthermore, physician acceptance of pharmacist recommendations exceeding 90% in systematic reviews confirms that integrating pharmacists into HIV care teams is an effective and well-accepted strategy [1,14,15].

A structured inpatient ARV stewardship program, as proposed by Michienzi et al. [14]offers a practical framework that can be adapted to various healthcare settings. Its core elements include medication reconciliation at admission and discharge, routine DDI monitoring, renal/hepatic dose optimization, and

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interdisciplinary education. In addition, real-time DDI screening tools, electronic health record (EHR)-integrated medication reconciliation, and artificial intelligence (AI)-based clinical decision-support systems should be explored in future implementation studies to automate interaction alerts and prioritize high-risk patients for clinical pharmacist review [1,28,31].

Economic Burden and Pharmacovigilance in Long-Term ART

Beyond direct clinical morbidity, DRPs and polypharmacy are associated with substantial economic burdens, driven by preventable hospitalizations, emergency department visits, intensive care admissions, and the management of iatrogenic organ toxicity (such as TDF/vancomycin-associated nephrotoxicity) [2,10,13]. Conversely, collaborative pharmacist-led care models (such as the Patient-Centered HIV Care Model [30]) and pharmacist-guided regimen optimization are cost-saving by preventing treatment interruptions and averting downstream opportunistic complications; nevertheless, formal cost-effectiveness studies of pharmacist-led DRP interventions in resource-limited settings remain scarce and are urgently needed. Concurrently, strengthening active pharmacovigilance systems—including standardized ADR reporting and post-marketing safety surveillance—is essential to capture the real-world safety profile of modern ART, particularly INSTI-associated weight gain, cardiometabolic disturbances, and adverse events in patients receiving concomitant tuberculosis or chronic disease therapies [1,2,29].

Relevance to Clinical Practice and National ART Programs in Indonesia

In Indonesia, where ART is provided through a decentralized national program across referral hospitals and community health centers (Puskesmas PDP) under Ministry of Health regulations [21]Integrating clinical pharmacists and routine DDI screening could significantly reduce DRPs. Following the national transition toward TDF/3TC/DTG (TLD) alongside continued use of TDF/3TC/EFV, Indonesian practitioners frequently encounter complex pharmacokinetic DDIs—particularly rifampicin co-administration in TB-HIV co-infection requiring dolutegravir dose adjustment—and rising polypharmacy among aging PLWHA [21–23]. Recent studies in Indonesian referral hospitals confirm high rates of potential DDIs (62.2%–97.3%) and non-adherence (34.2%) [22,23]. However, limited clinical pharmacist human resources, high patient-to-pharmacist ratios, uneven access to validated DDI screening software, and fragmented electronic medical record infrastructure remain major implementation challenges across Indonesian healthcare facilities that require targeted policy and educational investment.

Strengths and Limitations

This scoping review has several strengths, including adherence to the JBI and PRISMA-ScR guidelines, a comprehensive 2015–2026 timeframe capturing the modern INSTI and dual-therapy era, and formal quality appraisal of primary observational studies using the NOS. However, eight methodological limitations must be considered when interpreting these findings: (1) the primary literature search was restricted to three international databases (PubMed, Scopus, and the Cochrane Library), which may have omitted studies indexed exclusively in Embase, Web of Science, or regional databases (such as Garuda and Neliti); (2) grey literature, programmatic WHO/UNAIDS reports, and unpublished dissertations were not included in the primary database screening; (3) substantial heterogeneity existed across included studies regarding operational definitions of DRPs and polypharmacy, as well as the drug interaction databases utilized (e.g., Liverpool HIV Drug Interactions vs. Lexicomp); (4) due to high statistical and clinical heterogeneity ($I^2 > 95\%$), a single pooled quantitative meta-analysis across all DRP categories could not be performed; (5) restricting eligibility to English and Indonesian publications may have introduced language bias; (6) publication bias could not be formally ruled out, as studies reporting high DRP prevalence or positive pharmacist interventions may be more likely to be published; (7) the NOS quality assessment could only be applied to the 11 primary observational studies, whereas the remaining 7 secondary review articles were not evaluated with a separate review appraisal tool (such as AMSTAR-2); and (8) none of the 18 studies meeting the strict primary inclusion criteria from the three international databases originated from Indonesia, although national Indonesian studies. [22,23] and regulations [21] were integrated to provide local clinical context.

Implications for Clinical Practice

Based on the synthesis of findings, several practical recommendations can be formulated. [1,14,15,18,27,28]:

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1. ARV regimen selection: Unboosted INSTI-based regimens should be prioritized in patients with high DDI risk or polypharmacy, while carefully considering individual viral resistance profiles, cardiometabolic comorbidities (including weight-gain risk), concomitant rifampicin-based tuberculosis therapy, and local formulary availability.
2. Routine DDI screening and digital decision support: The use of validated drug interaction databases, such as Liverpool HIV Drug Interactions, integrated where feasible with EHR alert systems and active pharmacovigilance reporting, should become a standard component of care.
3. Pharmacist integration: Clinical pharmacists should be integrated into HIV care teams to conduct regular medication reviews and manage DRPs.
4. Holistic approach: DRP assessment should include the patient's entire medication regimen, not only ARVs.
5. Regimen simplification: Dual regimens and long-acting injectable ARVs should be considered as strategies to reduce polypharmacy and DDIs.

Conclusion and Future Directions

This scoping review demonstrates that drug-related problems (DRPs) in antiretroviral therapy (ART) form a complex, interrelated clinical network encompassing drug-drug interactions (DDIs), adverse drug reactions (ADRs), polypharmacy, non-adherence, medication errors, and inappropriate regimen selection. Rather than occurring in isolation, multimorbidity-driven polypharmacy amplifies pharmacokinetic DDIs and ADRs, which in turn compromise medication adherence, increase healthcare costs, and threaten long-term treatment continuity. While the global transition from boosted protease inhibitors to unboosted second-generation INSTIs and dual therapy regimens (such as dolutegravir/lamivudine) has substantially reduced contraindicated DDIs, rising comedication burdens in aging PLWHA and emerging metabolic toxicities underscore the need for ongoing pharmacovigilance.

Evidence across outpatient, inpatient, and critical care settings consistently confirms that pharmacist-led medication therapy management, structured antiretroviral stewardship programs, and targeted regimen simplification effectively reduce DRPs and medication errors while maintaining virological suppression. From a health policy and educational perspective, policymakers should consider integrating clinical pharmacists into multidisciplinary HIV care teams and mandating routine DDI screening in national ART guidelines. [21]while strengthening training and continuing professional education programs for pharmacists, physicians, and nurses on DDI screening, pharmacovigilance, and DRP management. To address remaining evidence gaps, future research should: (1) develop and validate a standardized DRP classification framework specific to the HIV context; (2) evaluate the real-world DRP profile of long-acting injectable regimens, particularly cabotegravir/rilpivirine; (3) conduct mixed-methods studies in Indonesia to explore the prevalence and management of DRPs in both urban referral hospitals and rural primary HIV care (PDP) settings, including the perspectives of healthcare providers and patients. [21–23](4) investigate the bidirectional interactions among polypharmacy, DDIs, ADRs, and adherence using longitudinal study designs; (5) develop and evaluate real-time EHR- and AI-based clinical decision-support interventions for DRP detection and management; and (6) evaluate the cost-effectiveness of pharmacist-led DRP management and antiretroviral stewardship interventions in resource-limited settings.

Conflict of Interest

The authors declare no conflict of interest.

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