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ADVERSE DRUG REACTION PROFILE OF ANTIRETROVIRAL THERAPY IN AN ART CENTRE

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Abstract

Antiretroviral therapy has turned HIV infection into a manageable chronic condition, but adverse drug reactions still lead to regimen changes, poor adherence and loss to follow-up. This review summarises published evidence on the adverse reaction profile of antiretroviral drugs as encountered in routine ART centre practice, with attention to national programme regimens. It covers the main reaction types by organ system, risk factors, causality and severity assessment tools, and management by monitoring, substitution and counselling. Published cohorts show broadly consistent patterns, yet definitions, follow-up and reporting differ widely. The review reports no new patient data and notes the need for standardised, prospectively collected pharmacovigilance data from centre-based programmes.

1. INTRODUCTION

Combination antiretroviral therapy has changed the outlook for people living with HIV. Mortality fell sharply in the late 1990s once potent regimens became available, and later programmes in low- and middle-income countries extended treatment to millions of people through public clinics [1, 2]. Most of these patients now take treatment for decades, not months. That shift raises the importance of tolerability: a drug that is merely irritating in the first year may be unacceptable by the tenth, and cumulative toxicity becomes as relevant as short-term side effects [3, 4]. In low-income settings the same change has been slower, but even there the median patient on treatment is now years rather than weeks into therapy.

In India, treatment is delivered mainly through ART centres run under the national programme, where patients collect medicines monthly and are seen by a medical officer, a counsellor and often a pharmacist. These centres hold a large volume of routine clinical information, including reasons for switching regimens, and they are a natural place to monitor adverse reactions [5, 6]. Yet the information is not always recorded in a form that supports analysis, and published reports differ in how they define a reaction, how long they follow patients and how they attribute causality [6, 7].

This review gathers published literature on the adverse reaction profile of antiretroviral drugs, and reads it with the ART centre setting in mind. It describes the regimens in use, the reactions reported by organ system, the factors that make some patients more susceptible, the tools used to judge causality and severity, and the usual management responses. It also comments on limits of the evidence. The work is a narrative synthesis of published studies, trials, guidelines and reviews. No patient records from any centre were analysed, and no new incidence figures are reported.

The terminology used in the field is worth fixing at the start. An adverse drug reaction is a harmful and unintended response to a medicine at doses normally used, which separates it from an adverse event that merely occurs during treatment and may have nothing to do with the drug. Many centre-based studies blur this distinction, and so incidence estimates differ between papers largely because different things are being counted [8, 9]. Reviewers who want to compare studies should therefore check the denominator, the follow-up period and the definition used before comparing any two percentages. A drug-related reaction in one paper may be called a side effect, a toxicity or an adverse event in another, and the three words are not always interchangeable.

2. REGIMENS USED IN NATIONAL PROGRAMMES

The World Health Organization recommends a public health approach with a limited number of standard regimens, so that drugs can be procured in bulk and clinicians in busy centres can apply simple rules [10, 11]. For several years the preferred first-line option in many countries was a non-nucleoside reverse transcriptase inhibitor, usually efavirenz or nevirapine, combined with two nucleoside analogues such as tenofovir and lamivudine or zidovudine and lamivudine. Older stavudine-containing regimens were phased out because of lipodystrophy, neuropathy and lactic acidosis [3, 10, 12]. Each of these combinations has its own pattern of adverse reactions.

Dolutegravir, an integrase strand transfer inhibitor, has since become the preferred anchor drug in WHO guidance, and national guidance in India has moved in the same direction with a fixed-dose tenofovir, lamivudine and dolutegravir combination [5, 11]. Trials showed that dolutegravir-based treatment suppressed virus at least as well as efavirenz-based regimens and was less likely to be stopped for adverse events, including in a pragmatic trial using low-dose efavirenz as comparator [13, 14]. These trials changed practice, but they were conducted in specific populations, and the reaction profile in everyday centre use may differ.

Protease inhibitors, usually boosted with ritonavir or cobicistat, are used in second-line therapy and for patients who cannot take other classes. They are associated with gastrointestinal intolerance and with metabolic effects, namely raised lipids and altered glucose handling [15, 16, 17]. Abacavir appears in alternative first-line regimens, particularly for children and patients with renal problems, and carries a well-defined hypersensitivity risk [18, 19]. Anyone reading a centre report should therefore check which combinations were being given, since the mix of regimens largely determines the mix of reactions. Switching among these regimens also changes which laboratory tests are needed, so monitoring plans must be updated each time.

Renal safety guidance makes clear how regimen choice interacts with comorbidity. Patients with existing kidney disease, diabetes or hypertension are at greater risk of progression when exposed to tenofovir disoproxil, and the HIV Medicine Association

guideline advises alternatives or dose adjustment in those with reduced clearance [20, 21, 22]. National programmes with limited drug choices face a real dilemma here, since the alternatives may be less convenient or costlier. The practical compromise is to screen for renal function before starting, to repeat tests regularly, and to switch early when decline is first noticed instead of waiting for overt failure [5, 20].

3. SPECTRUM OF ADVERSE REACTIONS

Reported reactions can be grouped by organ system and by the drug most often implicated, as summarised in table 1. Early reactions, appearing within the first weeks or months, include skin rash, hypersensitivity, gastrointestinal upset, headache, dizziness, and hepatitis. Later reactions include renal impairment, bone loss, lipid disturbances, weight gain, neuropathy and lipodystrophy [3, 4, 23]. The Swiss HIV Cohort Study found that a large share of patients experienced at least one treatment-limiting event, with most occurring in the first months [23]. Cohorts in developing countries report a similar pattern of early toxicity followed by a slower accumulation of metabolic problems [6, 7].

Central nervous system effects are the best-known problem of efavirenz. Vivid dreams, dizziness, insomnia and mood disturbance appear in a substantial minority of patients, usually settle within weeks, but occasionally persist or become severe [24, 25]. A meta-analysis of randomised trials confirmed an excess of neuropsychiatric events relative to comparators, and plasma concentration studies linked higher exposure to a greater risk, which is relevant in populations where slow metabolisers of CYP2B6 are common [24, 25]. Neuropsychiatric effects have also been reported with dolutegravir, notably insomnia and mood symptoms, with higher discontinuation rates described in women and older patients [26].

Boosted protease inhibitors bring a different kind of problem, which is interaction. Ritonavir inhibits cytochrome P450 3A4 strongly, so it raises levels of many co-administered drugs, including some statins, calcium channel blockers, corticosteroids and sedatives, occasionally to toxic concentrations [3, 4]. Rifampicin reduces protease inhibitor and nevirapine levels. A reaction in a patient on several medicines may therefore be a pharmacokinetic interaction and not an intrinsic effect of an antiretroviral, which is one reason why the full medication history, including over-the-counter and traditional preparations, should be recorded at each visit [4, 10].

Table 1: Principal adverse reactions of antiretroviral drugs reported in the published literature, by organ system

Drug / class	Principal reported reaction	Ref.
Efavirenz NNRTI	Excess of neuropsychiatric events compared with other first-line agents	[24]
Efavirenz plasma level	Higher drug concentrations linked to greater neuropsychiatric risk	[25]
Dolutegravir INSTI	Neuropsychiatric discontinuations reported more often in women and older patients	[26]
Tenofovir DF NtRTI	Small renal function loss; proximal tubulopathy in a minority	[21, 22]
Tenofovir DF vs TAF NtRTI	Alafenamide gave smaller changes in renal and bone markers	[27]
Antiretroviral therapy general	Loss of bone mineral density after starting treatment	[28]
Abacavir NRTI	Hypersensitivity linked to HLA-B*5701, prevented by screening	[19]
Nevirapine NNRTI	Rash and hepatotoxicity, more frequent in women and with co-infection	[29, 30]
Zidovudine NRTI	Anaemia and neutropenia, especially in advanced disease	[31]
Stavudine and older NRTIs mitochondrial	Mitochondrial toxicity with lactic acidosis and neuropathy	[12]
Protease inhibitors early	Lipodystrophy, hyperlipidaemia and insulin resistance	[17]
INSTI + TAF weight	Weight gain, more marked in women	[32]

Hepatic and cutaneous reactions are associated mainly with nevirapine. Rash is common in the first weeks, and a small number of patients develop severe forms, including Stevens–Johnson syndrome, while hepatotoxicity can appear at any time and is more frequent in patients with higher CD4 counts at initiation and in those with hepatitis co-infection [29, 30]. Abacavir hypersensitivity is a multi-organ syndrome that mostly appears in the first six weeks and is strongly linked to HLA-B*5701. The association was first reported in 2002, and screening before treatment is advised where the test is available [19].

Haematological toxicity is characteristic of zidovudine. Anaemia and neutropenia were prominent in the early trials of the drug, particularly in patients with advanced disease, and remain a common reason for switching in programme cohorts that use zidovudine-based regimens [31, 33]. Monitoring of haemoglobin during the first months of therapy is a standard recommendation. In settings where anaemia is already common because of nutritional deficiency or chronic infection, distinguishing drug effects from the underlying condition is difficult, and this uncertainty complicates any causality assessment [7, 33]. Reports of renal loss are strongest for the disoproxil salt of tenofovir.

Renal and bone effects have been linked to tenofovir disoproxil fumarate. A meta-analysis found a statistically significant but small loss of renal function in treated patients compared with controls, with proximal tubular injury in a minority, and large cohort data associated greater cumulative exposure with chronic kidney disease [21, 22]. Reduced bone mineral density occurs after starting antiretroviral therapy, with a greater effect from tenofovir-containing regimens [28]. The alafenamide prodrug produced smaller changes in renal and bone markers in a randomised comparison, though it is associated with greater weight gain and lipid changes [27, 32].

Metabolic effects are now of great concern because patients live long. Older protease inhibitors and thymidine analogues were linked to lipodystrophy, hyperlipidaemia and insulin resistance, and mitochondrial toxicity was proposed as a common mechanism for several nucleoside reactions, including lactic acidosis and neuropathy [12, 17]. More recently, weight gain has emerged with integrase inhibitors, especially in combination with tenofovir alafenamide, and is more marked in women and in people with low CD4 counts at the start [14, 32]. Diabetes risk rose with cumulative exposure in a large cohort [16], and the D:A:D study linked some protease inhibitors and abacavir to myocardial infarction [15].

Cardiovascular and lipid effects have attracted attention as the population on treatment ages. The D:A:D cohort found that cumulative exposure to some protease inhibitors was associated with a higher risk of myocardial infarction, and recent abacavir use was also implicated, though the mechanism remains uncertain [15, 18]. Part of the excess risk is attributable to lipid changes and the rest to other factors, among them smoking and inflammation from HIV itself. For centres this means that cardiovascular risk assessment, including blood pressure, lipids and smoking status, belongs in routine HIV care, and that drug choice should take baseline risk into account [4, 15].

Immune reconstitution inflammatory syndrome belongs in any list although it is a consequence of immune recovery rather than a direct drug effect. It occurs when treatment is started in people with advanced disease and a co-existing opportunistic infection such as tuberculosis, and a meta-analysis estimated that it affects roughly one in six patients starting therapy, with a higher risk when CD4 counts are very low [34]. In an ART centre, it is easily mistaken for treatment failure or a drug reaction, and the distinction matters because the right response is usually to continue antiretroviral therapy and treat the infection [34].

The distribution of the evidence is itself informative. Entries in table 1 are not evenly spread across organ systems, with neuropsychiatric, renal and bone, metabolic, hypersensitivity and haematological themes all represented (fig. 1). Some reactions are well studied because they are frequent, such as efavirenz neurotoxicity; others are well

studied because they are dangerous, such as abacavir hypersensitivity. Moderate but common symptoms like nausea or fatigue receive less attention, although they influence adherence considerably [35]. Studies of generic regimens in southern India described many modifications for these reasons, which suggests that the underlying risk is real in routine practice and not an artefact of trial design [7].

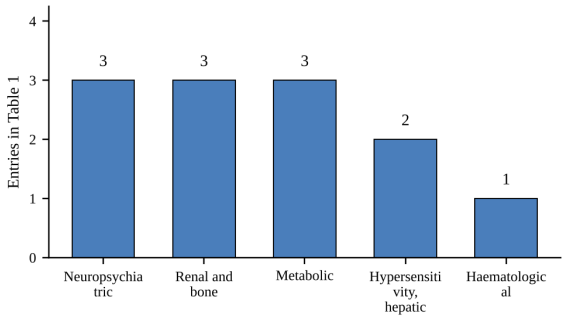


Fig. 1: Number of entries in table 1 by organ-system theme

Peripheral neuropathy, once a feature of stavudine and didanosine, still appears in reports from centres where those drugs remain in older patients, and it is slow to resolve after withdrawal. Switching earlier, before neuropathic pain becomes established, gives better recovery, which is one argument for regular symptom enquiry at each visit [3, 12]. Peripheral neuropathy, once a feature of stavudine and didanosine, still appears in reports from centres where those drugs remain in use for older patients, and it is slow to resolve after withdrawal. Patients typically describe burning or numbness in the feet and hands, sometimes severe enough to interfere with walking and sleep, and these symptoms can be mistaken for diabetic neuropathy or the effect of HIV itself. Because the damage is more reversible if caught early, structured enquiry about foot symptoms at every visit is more useful than waiting for the patient to volunteer them. Switching earlier, before pain becomes established, gives better recovery [3, 12].

4. RISK FACTORS AND PREDICTORS

Several patient characteristics recur as predictors of adverse reactions in published cohorts. Female sex is associated with a higher risk of nevirapine rash and hepatotoxicity, and with greater weight gain on integrase inhibitor regimens [26, 30, 32]. Low body weight raises the risk of anaemia and lactic acidosis with some nucleoside drugs, and advanced disease at initiation increases the chance of haematological toxicity and immune reconstitution syndrome [31, 33, 34]. Older age, pre-existing kidney disease and diabetes predispose to tenofovir nephrotoxicity and metabolic complications [16, 21, 22]. These associations come from cohort data in which confounding cannot be excluded.

Co-infection and co-medication are other well-recognised risks. Hepatitis B or C increases the likelihood of liver enzyme elevations with nevirapine and with several protease inhibitors, and antituberculosis drugs add their own hepatotoxicity and interactions, particularly with rifampicin, which lowers levels of many antiretrovirals [29, 30]. In India, where tuberculosis co-infection is common, the overlap of two treatments with similar toxicities makes attribution of a hepatic or cutaneous reaction especially difficult, and clinicians often have to withdraw both drugs and reintroduce them in sequence [5, 7]. Time since starting treatment also matters, as some risks fall with time while others accumulate.

Pregnancy and breastfeeding add a particular set of concerns. Efavirenz was long viewed with caution in the first trimester because of animal data, but a systematic review of the human evidence found no increase in overall birth defect risk [36]. Early observational data from Botswana linked dolutegravir at conception to neural tube defects, which prompted precautionary advice for women of childbearing potential; as more pregnancies were followed, the estimated excess shrank towards that seen with other agents [37]. The episode illustrates how an early safety signal can shift policy before confirmation, and why registries of exposed pregnancies are an essential part of pharmacovigilance for new antiretroviral drugs.

Genetic factors have been studied for some reactions. HLA-B*5701 is the best-validated example, and its screening is among the few pharmacogenetic tests that have entered routine practice [19]. Variants in CYP2B6 influence efavirenz exposure and

neuropsychiatric risk, and they differ in frequency between populations, with higher prevalence of slow-metabolising alleles in people of African and some Asian ancestry [25]. Using such markers in a resource-limited centre is not yet practical for most patients, but they help explain why reaction rates in one population cannot be assumed to apply to another.

Nutritional status, alcohol use and concurrent traditional or herbal products are additional contributors that centre-based studies seldom measure. These factors may modify drug exposure or add hepatic stress. They are best recorded at enrolment and reviewed at follow-up, even if only as brief structured questions asked by the pharmacist or counsellor [6, 7]. Studies seldom measure these factors, even though they plausibly modify risk. A brief structured form completed by the pharmacist or counsellor at enrolment, asking about alcohol, herbal products, tobacco and diet, would cost little and permit later analysis. Such records would also help to separate drug-related liver injury from other causes, a distinction that is often unresolved in retrospective reviews [6, 7].

5. DETECTION, CAUSALITY AND SEVERITY ASSESSMENT

Detection depends on how actively reactions are sought. Spontaneous reporting captures only a fraction of events, and WHO guidance on pharmacovigilance promotes active monitoring where a population is on long-term treatment [9, 38]. In ART centres this can be built into visits: structured symptom enquiry, laboratory monitoring of haemoglobin, liver and renal function, and lipid and glucose testing at defined intervals, as set out in national guidelines [5, 10]. Where laboratory tests are unavailable, clinical vigilance carries more weight, which probably leads to under-detection of silent problems such as early tubulopathy or hyperlipidaemia.

Laboratory monitoring is the backbone of detection for silent reactions. National and international guidelines recommend baseline assessment of haemoglobin, liver function, creatinine and urinalysis, followed by repeat tests at defined intervals depending on the regimen, and added lipid and glucose testing for patients on protease inhibitors or with other risk factors [5, 10, 20]. The kidney disease guidance for people with HIV recommends regular checks of creatinine and proteinuria in those on tenofovir and avoidance of the drug where function is already poor [20, 21]. Where a centre cannot run all tests, a risk-based approach that targets the patients most likely to be affected is preferable to monitoring nobody.

Causality assessment answers the question of whether the drug caused the event. Two tools dominate the literature. The Naranjo algorithm, one of several published methods that have been compared and found to classify the same events differently, uses ten weighted questions covering temporal relation, response to withdrawal and rechallenge, alternative causes and objective confirmation, and gives a score that classifies reactions from doubtful to definite [39]. The WHO–UMC system relies on structured judgement and classifies reactions as certain, probable, possible, unlikely, conditional or unassessable [40]. The two tools do not give identical classifications, since their categories are not equivalent, and so papers should name the tool used [39, 40].

Severity and preventability are assessed separately. The DAIDS grading table assigns severity on an ordinal scale, from mild events that need no change in therapy to potentially life-threatening ones, with death recorded as a separate grade, and some centres add a judgement of whether the event could have been prevented [41]. Preventability is relevant for centres, because a share of reactions follow a recognisable error, such as giving nevirapine to a patient with a high CD4 count and liver disease, or prescribing tenofovir to a patient with known renal impairment [4]. Such events are valuable teaching cases for audit.

Reporting systems then pass information upwards. Pharmacovigilance programmes depend on standard reporting forms, trained staff and feedback to those who report. Evaluations of such programmes have repeatedly noted under-reporting and incomplete forms, with a lack of time and of feedback cited by health workers [9, 38].

Centres that appoint a named focal person and review reactions in regular meetings produce more and better reports. Linking reaction data with prescription and laboratory records would enable a proper estimate of incidence per patient-year, which is rarely available [6, 38]. Those who work in resource-limited settings may prefer to start with the simpler of the two.

6. MANAGEMENT AND REGIMEN CHANGE

Management follows a stepwise logic. Mild reactions are often managed by reassurance and symptomatic treatment, for example advice to take efavirenz at bedtime, antiemetics for nausea or antihistamines for mild rash. Moderate reactions call for closer follow-up, and severe or life-threatening reactions require stopping the suspected drug, supportive care and a considered switch [4, 5, 10]. Counselling before treatment starts, which explains which symptoms are expected and likely to ease, reduces unnecessary discontinuation and improves adherence, as patients who are told what to expect tolerate early symptoms better [35].

When a switch is needed, substitution within the same class is sometimes sufficient. Studies of switching between nevirapine and efavirenz after toxicity found that cross-reactivity is limited for hepatic reactions, but a patient with a severe nevirapine rash should not receive another non-nucleoside agent without caution [30]. Replacing zidovudine with tenofovir resolves anaemia in most patients. Replacing tenofovir disoproxil with abacavir or alafenamide is possible when renal or bone problems arise, although each change has trade-offs and needs HLA-B*5701 testing or attention to metabolic risk [18, 19, 27]. The choice also depends on what the next line of therapy will be if the first substitution fails.

Co-treatment with antituberculosis drugs requires planned handling. When a hepatic or cutaneous reaction occurs in a patient taking both treatments, the usual approach is to stop all suspected drugs, wait for recovery, and reintroduce them one at a time under observation, beginning with the least likely culprit. Antiretroviral therapy is generally started within weeks of starting tuberculosis treatment, which increases the chance of overlap [5, 10, 34]. The sequential rechallenge procedure is slow and anxiety-provoking for patients, but it avoids the permanent loss of a first-line drug on the basis of an uncertain attribution [7, 30].

Cohort data show that substitutions for toxicity are common in the first years of treatment. In a large South African cohort, a sizeable minority of patients had substituted a drug within three years, most often because of the nucleoside component, while studies from southern India reported similar reasons for modification, with zidovudine anaemia and nevirapine reactions prominent [7, 33]. Rates of change depend heavily on the regimen mix, so they fall as the programme moves towards dolutegravir-based therapy, though new patterns such as weight gain are likely to take their place [14, 32]. Monitoring should therefore adapt along with the regimens.

Adherence and toxicity are bound together, and the relationship runs in both directions. Patients who experience side effects are more likely to skip doses, and skipped doses selectively expose the virus to sub-therapeutic drug levels, encouraging resistance [35]. A cohort study of first-line discontinuation found that drug-related adverse events were a leading reason for stopping the initial regimen, and that predictors could be identified at baseline [38]. A change prompted by a minor reaction can preserve adherence at the price of a more complex or costly regimen, so decisions should be made together with the patient, explaining the alternatives and recording the reasoning [5, 38].

7. LIMITATIONS AND FUTURE DIRECTIONS

The literature has recurring weaknesses. Retrospective record reviews dominate, with differing definitions of an adverse reaction, little laboratory data, short follow-up and no comparison group, which means that rates cannot be compared across studies [6, 7]. Many do not state the causality tool or severity scale used, and some count laboratory abnormalities with no clinical significance. Results from trials do not

necessarily apply to routine care. Evidence for newer drugs such as dolutegravir is accumulating quickly, so any summary risks being dated within a short time [13, 14, 37]. Put simply, these limits mean that any pooled estimate of reaction rates would be difficult to defend.

Better evidence would come from prospective cohort studies that enrol consecutive patients in ART centres, use a common reaction dictionary and a named causality method, record regimen changes with reasons, and follow patients for several years. Linking centre data to national pharmacovigilance reports would add value, as would reporting of pregnancy outcomes, since early signals about dolutegravir and neural tube defects were later revised as more data accrued [14, 37]. Such work is within the reach of well-organised centres and would give programme managers practical information on which patients need closer monitoring.

Under-reporting for social reasons is a further limit that numbers cannot show. Stigma still shapes how patients use HIV services, and patients who fear disclosure may avoid mentioning symptoms that could draw attention, or may stop collecting medicines rather than return with a complaint [35, 38]. A centre that offers private consultations, a welcoming counsellor and confidentiality will probably record more reactions than one that does not, even if the drugs are identical. Comparing reaction rates between centres without considering such differences in reporting climate can therefore mislead, and any future cross-centre analysis should record basic features of service organisation alongside clinical data [6, 7].

8. CONCLUSION

The published record shows a fairly stable picture. Efavirenz and dolutegravir are linked to neuropsychiatric symptoms, nevirapine and abacavir to hypersensitivity and liver injury, zidovudine to anaemia, tenofovir disoproxil to renal and bone effects, and older nucleosides and protease inhibitors to metabolic and mitochondrial toxicity [12, 19, 22, 24, 30, 31]. The mix seen in an individual ART centre will depend on which regimens it prescribes and on how carefully reactions are sought and recorded.

Practical lessons follow. Patients benefit from counselling before treatment starts, structured symptom enquiry at each visit, risk-based laboratory monitoring, HLA-B*5701 testing where possible, and a clear policy for causality and severity grading [5, 19, 39]. Researchers should publish prospective, well-defined data from centres, with the regimen, the assessment tool and the reason for change stated. Without these, programmes will continue to learn about toxicity slowly, and often only after it has already affected patients [6, 7, 38].

9. ABBREVIATIONS

ART-Antiretroviral therapy, CD4-Cluster of differentiation 4 lymphocytes, CYP2B6-Cytochrome P450 2B6, HLA-Human leucocyte antigen, INSTI-Integrase strand transfer inhibitor, NNRTI-Non-nucleoside reverse transcriptase inhibitor, NRTI-Nucleoside reverse transcriptase inhibitor, TAF-Tenofovir alafenamide, UMC-Uppsala Monitoring Centre, WHO-World Health Organization

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11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

13. REFERENCES

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