Interruption of Antiretroviral Therapy

Updated: September 24, 2026
Reviewed: September 24, 2026

Discontinuation or interruption of antiretroviral therapy (ART) may result in viral rebound, increased risk of HIV transmission, immune decompensation, and/or clinical progression.[1-5] Discontinuation **is not recommended** outside the context of a clinical trial **(AI).** However, interruption of ART may occur under certain circumstances, as discussed below. For discussion on the discontinuation of ART in the context of end-of-life palliative care, see HIV and the Older Person. Additionally, for guidance on ART interruptions due to nonadherence, see Adherence to the Continuum of Care.

Management considerations for ART interruptions will depend on regimen type (i.e., oral [PO], long-acting [LA] injectable, or a combination) and factors such as interruption duration, whether interruption is anticipated, and whether effective PO bridging was used for those on LA ART. If interruption of tenofovir (TFV)-containing ART is necessary in people with hepatitis B virus (HBV) and HIV, they should be carefully monitored, because discontinuation of TFV may lead to HBV reactivation and subsequent serious hepatocellular injury (see HBV/HIV Coinfection).

Unplanned Interruption of Oral Antiretroviral Medications

Reasons for short-term interruption (days to weeks) of PO ART vary and may include intercurrent illnesses that preclude oral intake (e.g., gastroenteritis, pancreatitis), surgical procedures, drug toxicity, or interrupted access to antiretroviral (ARV) drugs. Stopping PO ART for a short time (i.e., less than 1–2 days) usually can be done by holding all drugs in the regimen. Whether unplanned interruptions occur by accident (e.g., due to lost medications or interruptions during travel) or by necessity (e.g., due to drug toxicities), all efforts should be made to minimize interruption duration. Recommendations for some specific scenarios are listed below.

When PO ART is interrupted for more than a few days, viral load monitoring should be performed before and after ART resumption as is recommended in people who initiate or modify ART (see Laboratory Testing for Initial Assessment and Monitoring of People With HIV). If viral suppression is not achieved after resuming ART, drug-resistance testing should be performed to assess for emergence of drug resistance and to guide future therapy (see Drug-Resistance Testing).

Unexpected Difficulty Swallowing or Inability to Take Solid Oral Medications

For people with HIV who have difficulty swallowing or require enteral feeding, some ARV drugs are available in liquid or PO powder formulations, and some pills may be crushed. The Oral Antiretroviral/HCV DAA Administration provides information on crushing pills and formulating liquid ARV drugs. Enteral feeds contain polyvalent cations, which may bind and decrease absorption of integrase strand transfer inhibitors (INSTIs)[6]; see the Liverpool HIV Drug Interaction Checker for guidance. Additional information also may be available in drug product labels. Clinicians should consult an HIV specialist and/or pharmacist to assess the best way to continue an effective ARV regimen.

In cases where a person is unable to take medications by any enteral route (e.g., in the context of severe gastrointestinal disease), all components of the PO drug regimen should be stopped simultaneously **(AIII);** after resolution, all components of the ARV regimen should be restarted simultaneously **(AIII).**

Several ARV drugs are available as parenteral formulations; these include intramuscular (IM) cabotegravir plus rilpivirine (CAB/RPV), subcutaneous (SQ) lenacapavir (LEN), intravenous (IV) ibalizumab (IBA), and IV zidovudine (ZDV). The combination of CAB/RPV is approved as a complete regimen for the treatment of HIV (see Optimizing Antiretroviral Therapy in the Setting of Viral Suppression). There is limited experience with this regimen as an alternative for people who cannot take PO medications.[7] LEN is not suitable as a bridging option for people who unexpectedly cannot take PO medications because the injectable formulation (without the PO loading doses) would take approximately 4 weeks to reach target concentrations.[8] No data exist on the role of IBA and ZDV in these situations. Clinicians should consult with an HIV specialist before prescribing any of these medications.

Severe or Life-Threatening Toxicity to an Antiretroviral Medication

In the setting of a severe or life-threatening toxicity to an ARV, all components of the ARV drug regimen should be stopped simultaneously **(AIII).** After resolution, a complete regimen that does not include the toxic medication should be started **(AIII).**

Planned or Unplanned Interruption of Long-Acting Injectable Antiretroviral Medications

There may be circumstances in which people who are receiving LA injectable ARV medications (such as CAB/RPV, IBA, or LEN) have delayed or missed injection visits (e.g., due to hospitalization or unexpected travel). Because these agents have extended half-lives, treatment interruptions increase the risk of virologic failure with the development of drug resistance. For anticipated interruptions, PO bridging with suppressive ART should be implemented, and individuals should have a supply of PO ART on hand. Clinical assessment should be performed for unexpected interruptions that occur without PO bridging and/or for people without fully suppressive PO ART options. Some individuals may be receiving a regimen that contains both PO and LA injectable ARVs; if an interruption in the PO components of the ARV regimen occurs, see Unplanned Interruption of Oral Antiretroviral Medications above.

LA CAB/RPV is approved as a complete regimen given once monthly or every 2 months for the treatment of HIV. If LA CAB/RPV injections will be missed or delayed by >7 days, suppressive PO bridging ART should be started within 1 week (+/- 7 days) of the next scheduled injection. PO bridging may be comprised of PO CAB plus PO RPV, or another fully suppressive ARV regimen (e.g., dolutegravir/RPV or a prior well-tolerated and effective regimen). PO bridging should be continued until LA CAB/RPV injections are restarted. If the injections are missed or delayed by >7 days without PO bridging, the person with HIV should be clinically assessed to determine whether resumption is appropriate. See the prescribing information for dosing guidance after missed or delayed injections.[9] If discontinuing LA CAB/RPV, transition to a suppressive PO ARV regimen should occur within 1 to 2 months of the last IM doses, depending on the dosing schedule. Plasma viral load testing should be performed before the transition, and drug-resistance testing should be considered if plasma viremia is present.

People with drug-resistant HIV may receive IBA or LEN as a component of a subsequent regimen. People who have interruptions of the LA agent and/or PO background regimen should be assessed to determine whether resumption is appropriate. Plasma viral load testing should be performed; see Drug-Resistance Testing for information regarding IBA and LEN resistance testing. The recommended reinitiation strategies are described below.

IBA is initiated with a 2,000-mg IV loading dose, followed by 800 mg IV every 14 days as maintenance therapy. If a dose is missed by ≥3 days, a repeat loading dose of 2,000 mg IV is recommended as soon as possible before resumption of maintenance therapy.[10]

After an initial PO and SQ loading phase, LEN is given as two SQ injections every 6 months (26 weeks). If a dose is missed by >2 weeks (i.e., >28 weeks from the last injection), PO LEN 300 mg once weekly should be given for up to 6 months until the injections can be resumed. If a lapse of >28 weeks occurs between injections without LEN PO bridging, individuals should be reassessed clinically for appropriateness of continuation. If LEN is to be continued, therapy should be reinitiated with PO and SQ loading doses as recommended in the prescribing information.[11]

Analytical Treatment Interruption of Antiretroviral Medications in a Research Setting

Several research studies are evaluating approaches to achieve sustained ART-free viral remission or a functional cure for HIV.[12] Viral eradication (i.e., elimination of HIV entirely from an individual) remains a more challenging, longer-term goal. Currently, the only way to reliably test the effectiveness of these strategies is to interrupt ART and closely monitor for viral rebound in the setting of a clinical trial, an approach referred to as "analytical treatment interruption" or ATI.[13] The duration of treatment interruption, the dynamics of viral rebound, and the criteria for restarting ART are part of ATI clinical trial designs, with the goal of conducting these clinical trials safely.[14] To date, ATI trials have only enrolled people who received daily PO ART. Currently, no published data exist on strategies for ATI in people receiving LA injectable ARV medications.

Before ART is interrupted, participants in ATI trials should be made aware of and understand the risks of viral rebound,[15] acute retroviral syndrome, increased HIV transmission risk, CD4 T lymphocyte cell count decline, HIV disease progression, minor HIV-associated manifestations (e.g., oral thrush) or serious non-AIDS complications (e.g., renal, cardiac, hepatic, or neurologic complications), drug resistance development, and potential psychosocial effects of ATI.[14] Participants should be counseled about the need for close clinical and laboratory monitoring during ART interruptions and provided counseling and linkage to pre-exposure prophylaxis services, should they wish to refer sexual partners at risk for acquiring HIV.

When the ARV regimen contains PO drugs with different half-lives, stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life. However, limited to no data exist on optimal discontinuation strategies in the context of contemporary ART, including with nucleoside reverse transcriptase inhibitors that have longer intracellular half-lives (e.g., TFV, emtricitabine),[16,17] ARV medications with higher genetic barriers to resistance, or currently available coformulated regimens.

Knowledge Gaps

- Research is needed to identify optimal parenteral ARV regimens to use in people with difficulty swallowing or who are unable to take medications by any enteral route.
- Research is needed on best practices for supporting PO bridging of LA injectable ART during treatment delays or interruptions.
- Research is needed on the safety and risks of ATIs, including safe interruption of LA injectable ARVs and contemporary ART.

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