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The management of treatment-experienced HIV patients (including virologic failure and switches)

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***Abstract*:** Significant advances in the potency and tolerability of antiretroviral therapy (ART) have led to very high rates of virologic success for most who remain adherent to therapy. As a result, the life expectancy of people living with HIV (PLWH) has increased significantly. PLWH do, however, continue to experience a significantly higher risk of noninfectious comorbidities and chronic age-related complications, including cardiovascular disease and malignancies, which are now the biggest drivers of this excess morbidity and mortality. Therefore, in addition to virologic failure, the management of the treatment-experienced patient increasingly requires optimization of ART to enhance tolerability, avoid drug–drug interactions, and mitigate non-AIDS complications and comorbid conditions. This article will present principles of the management of virologic failure, poor immunologic recovery, and strategies for optimizing ART in the setting of virologic suppression.

Keywords: adherence, comorbidities, HIV, virologic failure

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Introduction

Modern antiretroviral regimens achieve a very high level of virologic success, and rates of virologic failure have declined significantly over the past decade. As a result, the life expectancy of people living with human immunodeficiency virus (HIV) (PLWH) has increased significantly in the modern antiretroviral therapy (ART) era, and the survival gap between PLWH and the general population has decreased significantly.[1] The remaining excess morbidity and mortality are now driven mostly by noninfectious comorbidities, including cardiovascular and metabolic complications, liver disease, including chronic hepatitis C, and non-AIDS malignancies.[2] These occur at much higher rates in people living with HIV than in the general population, and their pathogenesis likely involves patient factors (sociodemographic and behavioral), viral factors [HIV-associated chronic inflammation and immune activation, as well as likely viral copathogens such as hepatitis C virus (HCV) and cytomegalovirus (CMV)] and treatment factors (potential toxicities from antiretroviral drugs and other concomitant medications).

Given these trends, the management of treatment-experienced patients has shifted from a focus on the management of virologic failure in patients receiving ART towards more focus on optimization of ART to enhance tolerability and avoid drug–drug interactions, and identification of potential non-AIDS complications and comorbid conditions that might require modification of antiretroviral regimens in the setting of virologic suppression.

In this article, we will first review the management of virologic failure and poor immunologic recovery on ART. Then, we will discuss the rationale, general principles, and recommended strategies for optimization of ART in the setting of virologic suppression.

Management of patients with virologic failure

The risk of virologic failure has declined significantly in the past decade. This is likely due to a combination of more potent antiretroviral

Table 1. Virologic response definitions.

Virologic response definitions (adapted from DHHS HIV guidelines)
Virologic suppression: Confirmed HIV-1 RNA level below LLOD of available clinical assays.
Virologic failure: Failure to achieve or maintain HIV-1 RNA level <200 copies/ml.
Incomplete virologic response: Two consecutive HIV-1 RNA levels ⩾200 copies/ml after 24 weeks on an ART regimen in a patient who has not yet achieved virologic suppression.
Virologic rebound: Confirmed HIV-1 RNA level ⩾200 copies/ml after virologic suppression.
Virologic blip: After virologic suppression, an isolated detectable HIV-1 RNA level <200 copies/ml that is immediately followed by virologic suppression again.
Low-level viremia: Confirmed (repeated) detectable HIV-1 RNA level <200 copies/ml.

ART, antiretroviral therapy; HIV, human immunodeficiency virus; LLOD, Lower limit of detection.

regimens and ease of their administration with multiple single-tablet regimen (STR) options.

We propose the following steps in the assessment and management of patients with virologic failure:

(1) define the problem: operational definition of virologic failure;
(2) analyze the cause(s), consider patient and viral factors;
(3) establish goals;
(4) determine strategy.

Definition of virologic failure

The goal of ART is to achieve and maintain HIV-1 plasma RNA levels below lower limits of detection (LLOD) with the assays currently used in clinical settings (between 20 and 50 copies/ml).[3] Virologic suppression below these levels prevents drug resistance emergence,[4] and is strongly predictive of lower rates of progression to acquired immunodeficiency syndrome (AIDS) and death.[5] Common terminology and definitions used in defining virologic suppression and failure in HIV treatment guidelines and literature are shown in Table 1.

The most important clinical question is what threshold of low-level viremia is predictive of worse clinical outcomes, whether future risk of virologic failure or development of AIDS or non-AIDS complications. Large retrospective HIV cohorts shed some light on this question. Virologic blips, defined as isolated detectable viremia between 20 and 200 copies/ml followed by a return to viral suppression, have not been demonstrated to predict subsequent virologic failure.[6] Conversely, multiple recent studies show that persistent low-level viremia, less than 500 copies/ml, particularly in the range between 200 and 500 copies/ml, is strongly predictive of development of AIDS event, death, or subsequent virologic failure, but a low-level viremia of <200 copies/ml is not strongly predictive of worse outcomes.[7–9] Based on this data, the United States Department of Health and Human Services (DHHS) guidelines adopted a definition of virologic failure as 'confirmed' viral load above 200 copies/ml, which should be confirmed in two consecutive assays.[3] However, even patients with persistent detectable viremia below the 200 copies/ml threshold should be counseled on adherence and monitored closely, since this has been shown in some studies to be associated with future virologic failure.[10,11]

Analyzing the causes of virologic failure

Virologic failure could be assessed as resulting from one or a combination of three groups of factors: patient factors; viral factors; and drug-related factors (Figure 1).

Patient factors: challenges to treatment adherence. The most common cause of virologic failure is suboptimal adherence to ART. Before considering other causes, a thorough investigation of barriers to ART adherence should be undertaken. Potential barriers may include comorbid mental health disorders or active substance abuse; psychosocial factors, such as housing instability, poor access to care, or issues related to drug adverse effects; tolerability; costs; pill burden; or dosing frequency. Evidence-based guidelines for improving retention in HIV care and antiretroviral adherence for PLWH are available,[12] and specific strategies for optimizing ART adherence will be discussed in more detail below.

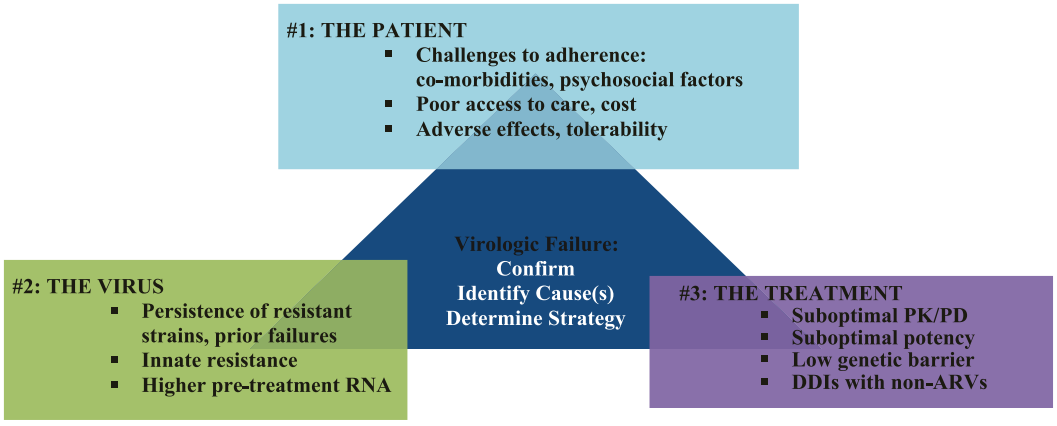

Figure 1. Analyzing the causes of virologic failure.
ARV, antiretroviral; DDI, drug–drug interactions; PK/PD, pharmacokinetics/pharmacodynamics.

Viral factors: drug resistance. A second important cause of virologic failure is the development of drug resistance mutations. The HIV-1 reverse transcriptase (RT) is inherently error-prone, and lacks proof-reading in its activity, leading to high mutation rates and likelihood of evolution of drug-resistant viral strains if viral replication is ongoing.[13] In newly acquired infections, there is also the possibility of transmitted drug resistance at the time of infection, which has been reported in up to 16% of treatment-naïve patients.[3] In treatment-experienced patients, ongoing replication leading to drug resistance is more likely, due to either suboptimal drug exposure from poor adherence (see patient factors above) or failure of the ART regimen to achieve viral suppression despite good adherence (see treatment factors below). An example of the latter was seen in the SWITCHMRK 1 and 2 clinical trials, in which patients with a history of prior virologic failure were more likely to experience virologic failure when switched to a raltegravir (RAL)-based regimen than continuation of a boosted protease inhibitor (PI) regimen, likely from unmasking of pre-existing drug resistance.[14]

Risk factors associated with virologic failure due to drug resistance include higher pretreatment viral loads, and, in some cases, lower pretreatment CD4 counts, especially for certain less potent regimens.[3] Innate resistance to certain ART classes based on viral tropism (e.g. CCR5 antagonists in patients with X4 or dual tropic virus) or HIV-2 coinfection may also explain virologic failure. In treatment-experienced patients, inadequate accounting for prior ART history, resistance testing, or archived drug resistance mutations can lead to a switch to a regimen that fails to suppress viral replication and leads to more resistance.

Treatment (drug-related) factors. The final cause of virologic failure are drug-related or pharmacologic factors. Often, this category of failure is caused by suboptimal pharmacokinetics of the ART regimen related to drug–drug interactions or drug–food interactions that prevent adequate serum concentrations of the antiretroviral agent (See resources in Table 2). Genetic polymorphisms have been shown to affect antiretroviral drug metabolism (e.g. cytochrome P450 isoenzymes) or drug transport (e.g. P-glycoproteins), leading to altered drug concentrations that compromise ART efficacy and safety.[15] Examples of how to assess and optimize these drug-related factors are discussed in detail below (see Table 2 for additional HIV pharmacologic resources). Medical conditions, such as chronic diarrhea or intestinal malabsorption, can also impact treatment efficacy. Errors in medication prescribing or administration, especially during transitions of care, can jeopardize virologic suppression. Finally, certain antiretroviral medications may require fewer mutations before resistance can occur, often referred to as a 'low genetic barrier to resistance,' which might jeopardize future treatment options.[16] Examples of such medications include lamivudine (3TC), emtricitabine (FTC), raltegavir (RAL), Elvitegravir (EVG), and efavirenz (EFV). Fortunately, the development of well-tolerated,

single-tablet or once-daily, ART regimens, based mostly on integrase inhibitors (INSTI) with a higher genetic barrier to resistance can help mitigate some of these treatment-related factors contributing to virologic failure.[17]

Establishing the goals of antiretroviral therapy in a patient with virologic failure

Once the factors underlying virologic failure have been investigated, the provider and patient must establish the goals of ART moving forward. In the modern ART era, the vast majority of patients will achieve virologic suppression if adherent to their medications. The current guidelines recommend that, in designing a new ART regimen for a patient with virologic failure, the goal is to include at least two, and preferably three, medications predicted to be fully active based on prior ART history, resistance testing, and mechanisms of action.[3] In some cases, drugs with partial activity against the patient's virus, such as nucleoside RT inhibitors (NRTI) or PI, may be retained in the regimen in order to provide immunologic and virologic benefits associated with maintaining a viral population that has reduced replicative capacity.[18] However, there will be rare patients who are not able to achieve maximal virologic suppression with currently available agents due to toxicities or acquired resistance to most available drugs. In these patients, the goals are to prevent clinical progression of HIV disease, preserve immunologic function, and minimize development of further resistance that could compromise future ART.[3] Cohort studies in this patient population with multidrug ART resistance demonstrate that even modest reductions in HIV RNA levels may translate into meaningful clinical benefits,[19,20] although at the risk of potential further resistance.

Determining the antiretroviral treatment strategy moving forward

The final step in addressing virologic failure is to identify the best antiretroviral treatment strategy moving forward. The factors considered in choosing a future ART regimen include assessment of adherence as above, consideration of prior ART treatment history, and, importantly, HIV drug-resistance testing results at present and in the past. Another important factor is the patient's hepatitis B virus (HBV) coinfection status because drugs active against HBV must be continued in the new regimen to avoid HBV reactivation, which can result in fulminant hepatic failure.[21] Figure 2 outlines a suggested management approach to selecting a new ART regimen.

Performing HIV drug-resistance testing. All patients with virologic failure with HIV RNA levels >1000 copies/ml should have drug resistance testing performed, while resistance testing can be considered between 500 and 1000 copies/ml though it may be unsuccessful. Drug resistance ideally is performed while the patient is still on the failing ART regimen, or within 4 weeks of discontinuation of the regimen. Resistance testing done after a longer period off therapy may still provide useful information, but drug-resistant virus strains can decline rapidly below the LLOD as the wild-type virus returns as the dominant virus off ART.[22] These archived drug-resistant strains can still re-emerge once ART is reintroduced.

Drug-resistance testing is divided into genotypic and phenotypic assays. Genotypic assays typically use Sanger sequencing to detect mutations in the RT, protease (PR), and integrase (IN) genes. IN resistance testing may be included in standard assays, or may require separate testing depending on the commercial assay used. Currently available commercial assays will generally detect mutations present in >10–20% of the circulating virus population. The International AIDS-USA society maintains an updated list of clinically significant resistance mutations in the RT, PR, and IN genes. Other resources, such as the online Stanford University HIV Drug Resistance Database (https://hivdb.stanford.edu/) provide guidance on how to interpret genotype resistance data. Phenotypic assays evaluate the ability of a patient's virus to grow in different concentrations of ART drugs compared with a reference HIV strain. The drug concentration that inhibits viral replication by 50% (IC_{50}) is calculated, and the ratio of IC_{50} for the patient and reference viruses is reported to give a relative fold increase in IC_{50} or fold resistance.

Genotypic assays are preferred in first- and second-line regimen failure when resistance profile is not expected to be complex due to more widespread availability, quicker turnaround time, lower cost, and generally clearer interpretation of results.

Although phenotypic assays are more costly and labor-intensive, they can augment the results of

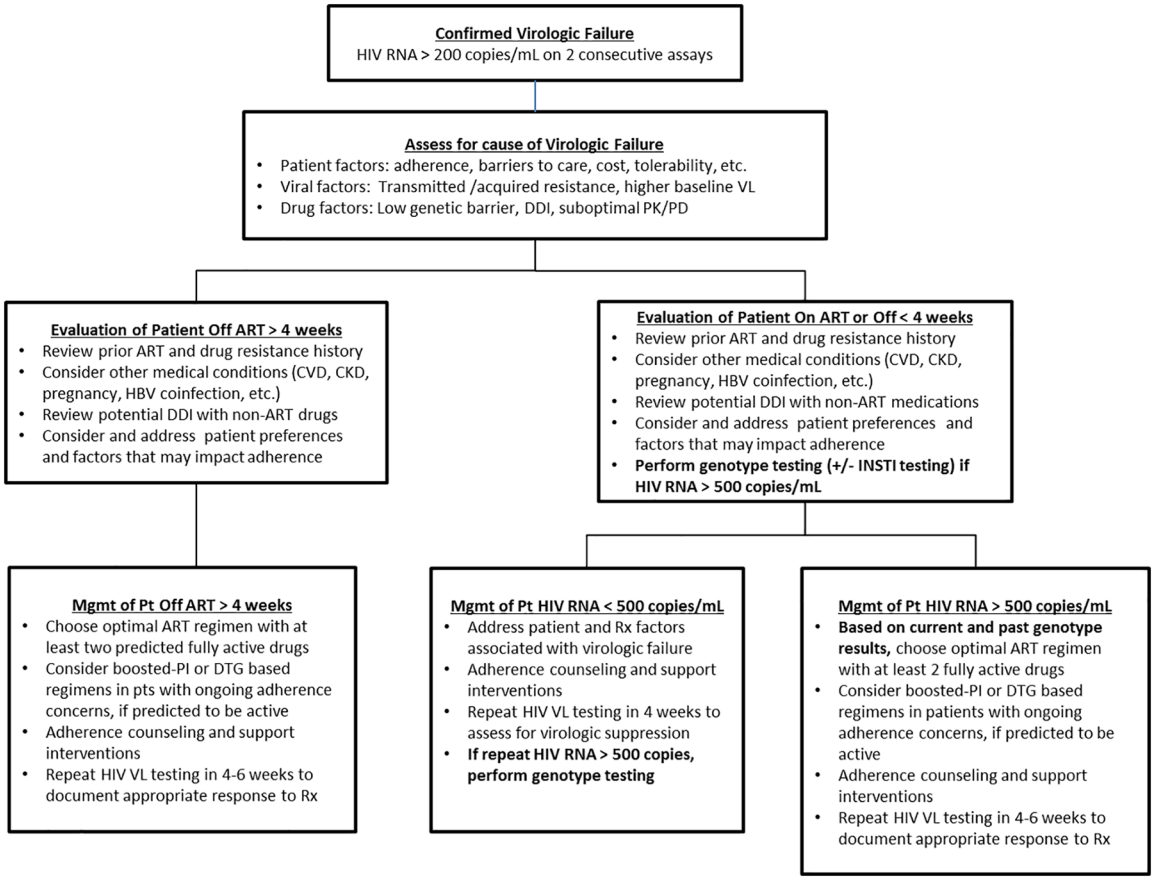

Figure 2. Suggested management approach to selecting a new ART regimen.
For more details, please refer to Department of Health and Human Services ART guidelines (https://aidsinfo.nih.gov/guidelines/) or European AIDS Clinical Society guidelines (http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html).
AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CKD, chronic kidney disease; CVD, cardiovascular disease; DDI, drug–drug interactions; DTG, Dolutegravir; HBV, hepatitis B virus; HIV, human immunodeficiency virus; INSTI, integrase inhibitors; Mgmt, management; PK/PD, pharmacokinetics/pharmacodynamics; Pt, patient; Rx, prescribed regimen; VL, viral load.

Table 2. HIV drug interaction resources.

General	Disease specific
Micromedex (version 2.0) (https://www.micromedexsolutions.com/home/dispatch)	University of Liverpool (https://www.hiv-druginteractions.org/)
Epocrates (https://www.epocrates.com/)	HIV In Site (UCSF) (http://hivinsite.ucsf.edu/)
Clinical Pharmacology https://www.clinicalpharmacology.com/	Toronto HIV Clinic (https://hivclinic.ca/)
Medscape Drug Reference https://reference.medscape.com/	
Facts and Comparisons 4.0/Lexicomp https://fco.factsandcomparisons.com/lco/action/home https://online.lexi.com/lco/action/login	

HIV, human immunodeficiency virus.

genotypic resistance testing in the setting of known or suspected complex or extensive genotypic drug resistance mutations in patients with multiple treatment failures. Randomized clinical trials have demonstrated a consistent clinical benefit to resistance testing over expert clinician judgment without resistance testing in patients with virologic failure,[23,24] although the best scenario is resistance testing combined with expert physician interpretation.

Using HIV drug-resistance results. Failure to detect drug resistance in the context of virologic failure on ART almost always indicates poor adherence. The focus should be directed to identifying and mitigating the patient and treatment factors related to adherence discussed above. Any available efforts to reduce toxicity, simplify dosing, or address behavioral barriers to adherence should be pursued, which may require modifications in the ART regimen. If suboptimal adherence remains a concern, choosing a regimen with a higher barrier to resistance, such as one containing either a boosted PI or Dolutegravir (DTG), can reduce the likelihood of selection for drug resistance.

In patients with virologic failure with detected resistance, a change in the ART regimen will be required, with the goal of constructing a new regimen with at least two, and preferably three, fully active drugs based on the patient's ART history and current and past drug-resistance testing.[3] The addition of a single new active drug to a failing regimen is not recommended due to the risk of resistance development and loss of that agent as a part of future treatment regimens. Decisions regarding whether to continue or stop specific drugs should be based on resistance testing results, but some general principles apply. Drugs from the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, and the early generation INSTI RAL and EVG, should generally be discontinued to avoid further resistance that may jeopardize future options in the same class. However, drugs from the NRTI class and boosted PIs may retain partial activity and could be continued. For example, in patients with the M184V mutation, continuation of 3TC or FTC has proven beneficial in partial virologic suppression, likely by selecting for drug-resistant strains that are less fit or replication competent than wild-type strains and are hypersusceptible to other agents such as tenofovir and zidovudine.[25] Finally, some specific drugs such as DTG and boosted darunavir (DRV) may be started or continued in the presence of known or suspected INSTI or PI class resistance, but these agents should be given twice daily rather than daily.[26,27]

Strategy based on failure of initial ART regimen. For patients who develop virologic failure on their initial ART regimen, the nature of the failed regimen can provide some clues as to potentially effective salvage regimens.

Patients failing an initial regimen of NNRTI + NRTIs often develop resistance-associated mutations to the NNRTI class (such as K103N) and to 3TC/FTC (M184V). Recommended second-line regimens shown to be efficacious in clinical trials (such as the Second Line, EARNEST, and the DAWNING trials) include a boosted PI + NRTIs or an INSTI + NRTIs.[28–31]

Patients failing an initial regimen of boosted PI + NRTIs often have no drug resistance or only isolated M184V/I resistance. The most common reasons for virologic failure in this scenario are poor adherence, drug–drug interactions, or poor tolerability.[3] If well-tolerated, the same regimen can be continued with concerted efforts to improve adherence and close virologic monitoring. However, if drug–drug interactions or poor tolerability are a concern, a change to a different boosted PI + two NRTIs or to an INSTI + two NRTIs is warranted.

Patients failing an initial regimen of INSTI + NRTIs often develop 3TC/FTC resistance, but resistance to the INSTI is more variable. Patients who fail RAL- or EVG-containing regimens may develop resistance to these drugs, but remain susceptible to DTG.[32] Conversely, patients who fail DTG or bictegravir (BIC)-containing regimens rarely develop resistance to these drugs.[33,34] Although there is a paucity of clinical trial evidence, the preferred second-line regimens in this scenario include either a boosted PI or DTG-based regimen.[3] For those patients with INSTI resistance, the recommended DTG dose is 50 mg twice daily.

Strategy based on failure of multiple ART regimens. For patients who have failed multiple ART regimens, the construction of a new ART regimen should be done in consultation with an expert in managing treatment-experienced patients.[3] In general, the anchor of the ART regimen, if available, should include either a fully active INSTI,

such as DTG, or a fully active boosted PI, such as DRV, paired with two NRTIs, at least one of which is fully active. If no active NRTI exists, then an INSTI plus a boosted PI regimen can be considered. In some of these cases, additional drugs could include the NNRTI etravirine, the fusion inhibitor T-20, or a CCR5 antagonist if an assay confirms CCR5 viral tropism. Careful attention to drug–drug interactions and appropriate dosing of agents is paramount as the complexity of ART regimens increases. The monoclonal antibody ibalizumab is a recently approved CD4 postattachment inhibitor that can be considered in heavily treatment-experienced patients without other options, and is administered by intravenous infusions every 2 weeks.[35] Finally, the first-in-class, investigational gp120 attachment inhibitor fostemsavir has phase III efficacy and safety data at 48 weeks in heavily treatment-experienced patients, and could be a treatment option if it receives regulatory approval.[36] Such patients should also be considered for inclusion into trials of other new and investigational agents.

Management of patients with poor CD4 count recovery

Most patients who achieve sustained virologic suppression with ART will experience a steady increase in peripheral blood CD4 cell recovery, usually into the normal range (>500 cells/mm^3). However, about 15–20% of patients who start at very low CD4 counts (<200 cells/mm^3) will fail to have the desired immunologic recovery but will plateau at a lower CD4 count, usually defined as either <200 or <350 cells/mm^3.[37,38] The major risk factors for poor CD4 cell recovery include older age, lower nadir CD4 count, and lower CD4 count at ART initiation.[39,40] Conversely, earlier ART initiation can enhance maximal CD4 cell recovery.[41]

Unfortunately, those who have poor CD4 recovery, sometimes called 'immunologic nonresponders,' have increased risk of mortality and morbidity. For example, Engsig and colleagues found a 2.6-fold increased mortality in those whose CD4 counts remained <200 cells/mm^3 despite at least 3 years of suppressive ART, compared with their counterparts with immunologic recovery.[40] PLWH with poor immunologic response despite virologic suppression have been found to be at increased risk for cardiovascular events, osteoporotic fractures, chronic liver disease-related mortality, and infection-related non-AIDS malignancies in observational studies.[42–45] While these increased mortality and morbidity risks are most apparent at CD4 cell counts <500 cells/mm^3, there is likely a mortality benefit to higher CD4 cell recovery across the full spectrum of normal values.[46]

Despite the strong prognostic importance of CD4 cell count recovery, no adjunctive therapies that increase CD4 cell recovery beyond what is achieved with suppressive ART have succeeded at mitigating these mortality and morbidity risks. ART intensification (adding additional ART drugs), or ART class switching in patients who already are virologically suppressed, do not improve outcomes and are not recommended.[47,48] Two large randomized controlled trials of interleukin-2 adjunctive therapy demonstrated increased CD4 cell counts but no discernible clinical benefit to warrant its use.[49] Additional clinical trials are ongoing to evaluate other immune-based therapies to increase CD4 cell counts (such as interleukin-7), but none are proven to be beneficial, and they should not be used outside a clinical trial setting.

Therefore, at present, clinicians' approach to immunologic nonresponse should focus on prevention (early initiation of ART before significant CD4 decline); ruling out alternative causes of lymphopenia (drug toxicities, viral coinfections, malignancies); and mitigation of downstream consequences of immunosuppression. Fortunately, emerging consensus based on large observational studies also shows that primary prophylaxis against *Pneumocystis jirovecii* pneumonia can be safely stopped in patients with a CD4 cell count between 101 and 200 cells/mm^3 who were virologically suppressed on ART.[50]

Optimizing antiretroviral therapy in setting of virologic suppression

Rationale for optimizing antiretroviral therapy in the setting of virologic suppression

Simplification of antiretroviral therapy to enhance adherence. Since 2006, the advent of STRs has allowed a significant simplification of ART regimens in most treatment-naïve and -experienced patients[51]; their use has increased significantly in recent years and has been associated with increased adherence and a trend toward lower

rates of discontinuation.[52,53] However, disadvantages of STRs may include lack of flexibility with dosing of individual components if adjustment is required due to renal function or drug–drug interactions.[51] Additionally, as most STRs are available only as brand products, cost may be a limiting factor, which will be discussed below.

Novel strategies, including long-acting HIV parenteral drugs or implants, will likely soon further improve simplification of ART administration.[54] Monthly injections of two long-acting agents Cabotegravir (an INSTI) and Rilpivirine (RPV; an INSTI) have been shown to be safe, effective, and well tolerated (despite a high rate of mild injection site reactions) in trials.[55,56]

Improvement of tolerability. Adverse effects are possible with all antiretroviral agents, and are one of the leading reasons for switching regimens. Newer ARVs are associated with fewer serious and intolerable adverse effects, as noted by low discontinuation rates in randomized clinical trials, but long-term or rare side effects in special populations will likely not be evident until years into clinical practice, requiring continued vigilance by the healthcare providers, patients, industry, and regulators. Examples of ARV switches to newer agents within the same class or to a different class of ARV for improved tolerability are presented below. As ART is now recommended in all PLWH and needs to be continued indefinitely, the major focus has shifted from common, short-term adverse effects, such as gastrointestinal upset, to increased attention on the mitigation of long-term effects such as renal, bone, and cardiovascular toxicities. DHHS guidelines include comprehensive tables of adverse effects and their recommended management.[3]

Prevention or mitigation of drug–drug interactions. ARV agents may interact with a number of medications, necessitating change in therapy to avoid toxicities or impact on the therapeutic response. Whether to alter the ARV or the non-ARV agent will often depend on clinical stability of the patient's condition and available alternatives. Care should be taken to review potential interactions with non-ARVs when adding or switching to a new ARV. The interactions may occur during absorption, distribution, metabolism, or elimination, and should be considered carefully when readjusting ARV regimens.[57]

The following are examples of drug–drug interactions between ARVs and non-ARVs that should be considered:

(1) Polyvalent cations (aluminum, magnesium and calcium containing drugs): they decrease INSTI exposure. It is therefore recommended to temporally space their administration from that of the INSTI. Avoid coadministration of magnesium/aluminum hydroxide-containing antacids with once-daily RAL.[58]
(2) Direct-acting anticoagulants: exercise caution as their exposure can be increased by coadministration with EVG/cobicistat.
(3) Anti-seizure medications: Carbamazepine and Phenytoin could decrease INSTI exposure; twice daily DTG can be used with Carbamazepine
(4) Metformin: BIC and DTG administration blocks metformin excretion, increasing metformin exposure. Monitor for metformin adverse effects and when initiating metformin start at lower dose and titrate based on glycemic control.
(5) Rifamycins: they decrease INSTI exposure. It is OK to use Rifabutin with DTG.
(6) Steroids: PIs and EVG/c can increase their serum levels. This can occur even with inhaled formulations (inhaled Beclomethasone appears to be safe).
(7) Proton pump inhibitors: they decrease exposure to Atazanavir (ATV) and RPV.
(8) HMG CoA reductase inhibitors (statins): their metabolism can be impaired by PIs leading to significantly increased serum levels.

Accommodating food requirements. Several ARVs require coadministration with food for optimal absorption; it is therefore imperative to assess each patient for food insecurity when selecting a regimen. Examples include RPV and DRV: RPV exposure is lower in fasted state, requiring administration with a protein-rich meal or drink.[59] DRV exposure is significantly increased when DRV/cobicistat is given with a high fat meal.[60]

Occasionally, patients are unable to take oral medications, requiring the use of enteral feeding tubes. This may be due to opportunistic infections (i.e. *Candida* esophagitis), or medical conditions such as small bowel obstruction, need for

surgery, or dysphagia from a stroke. As most ARV are available as a tablet or a capsule, it is important to explore which drugs can be safely crushed (for example for administration with a feeding tube) and which have an available liquid formulation. The data in this area is limited but emerging.[61–63] Providers should consult with their clinical pharmacists and the manufacturer, or perform a literature search for the most recent data. The University of Toronto also maintains a summary of data on their website, which may be a useful resource (https://hivclinic.ca/).

Pregnancy-related concerns. ART is recommended in all PLWH, including those planning a pregnancy or who are pregnant.

Certain agents should be avoided in PLWH who are pregnant or contemplating pregnancy due to potential fetal toxicity, or because of altered pharmacokinetics, especially in the second or third trimester, leading to subtherapeutic levels. Several commonly prescribed antiretrovirals have no safety data in pregnancy and should be avoided.

At this time, and pending additional data, the DHHS guidelines recommend against the use of DTG in females contemplating pregnancy, or those who are in the first trimester, due to the early signal of increased neural tube defects from a Botswana cohort.[64] The current preferred regimens, if no contraindications exist, include abacavir/lamivudine or tenofovir disoproxil fumarate (TDF) with either lamivudine or emtricitabine as the backbone, with one of the following: twice daily RAL, DTG after the first trimester, ritonavir-boosted ATV, or twice daily boosted DRV.

Cost considerations. ARV cost remains a controversial and dynamic topic due to variability in medical coverage, insurance plans, or pharmacy benefits, which may include hidden rebates, discounts, or reimbursements. Often, such practices are confidential, and, therefore, difficult to evaluate or compare. Nevertheless, despite the generally high cost of ARVs, cost-effectiveness of HIV treatment has been well established.[65,66] One mechanism for potential cost reduction is the introduction of generic medications that can drive down cost and expand access.[66,67] This advantage might have to be balanced against the use of older drugs that are available in generic formulations but have higher rates of toxicity (such as EFV or TDF).

General principles for antiretroviral therapy optimization

Regardless of the reasons for antiretroviral therapy changes, it is important to remember that the primary objective for all patients remains maintenance of virologic suppression. Incorporating antiretrovirals in the new regimen that had been part of a previously failing regimen could potentially jeopardize the success of the new regimen, as 'archived' resistance mutations might resurface. It is therefore important to account for prior ART history, and results of prior resistance testing before any antiretroviral switch. In the absence of resistance testing, it is safe to assume resistance to EFV, 3TC, FTC, RAL, or EVG, if these agents were part of a previously failing regimen since they have a relatively low genetic barrier to resistance. In virologically suppressed patients with a history of multiple failures or prior regimens, proviral DNA genotypic testing may be useful.

Finally, in patients with HIV/HBV coinfection, it is important to maintain two HBV-active drugs in new regimen. The use of 3TC or FTC as sole HBV-active drug is NOT recommended, as HBV resistance to these will likely develop rapidly.[68]

Examples of recommended ARV switch strategies

Based on results of previously published trials, the following are examples of antiretroviral therapy changes that could achieve simplification, improve tolerability, address drug–drug or drug–food interactions or be optimal in special situations such as pregnancy are presented below.

Switches within the same ARV class:

(1) EFV to RPV or doravirine (DOR): switching from EFV/FTC/TDF to RPV/FTC/TDF might mitigate EFV intolerance, including neuropsychiatric side effects.[69] The newly approved NNRTI DOR, either in the fixed drug combination of DOR/3TC/TDF, or paired with another NRTI backbone, can also avoid the neuropsychiatric side effects of EFV or food–drug interactions with RPV.[70]
(2) TDF to TAF: switches from TDF/FTC to TAF/FTC with any third agent,[71] or with RPV as third agent,[72] have been associated

with improved bone mineral density and markers of renal dysfunction.

(3) ABC to TAF: this switch was associated with no difference in renal or bone safety profile.[73] It could be considered in patients with high cardiovascular disease risk.

(4) RAL to EVG/cobicistat. A twice-daily RAL was simplified to a once-daily EVG/cobicistat regimen.[74] While a once-daily RAL option now does exist, one could consider that a switch from RAL to DTG or BIC might offer additional benefit of higher genetic barrier to resistance of the latter two INSTIs.

Switches to different ARV classes:

(1) Boosted PI to INSTI (BIC, DTG, or EVG/c).[75–77] Switch from PI to INSTI has been associated with improved GI tolerability and metabolic profiles, including lower lipid levels with switch to DTG in patients with high cardiovascular risk.[75] However, recent concerns emerge that the switch might also be associated with increased weight.[78]

(2) Boosted PI to RPV: this switch has been associated with improved lipid profiles.[79]

Switches from triple ARV to dual ARV therapy:

(1) DTG/RPV: Switch to a coformulated DTG/RPV has been shown to be safe and effective.[80] This can be considered in patients in whom NRTI exposure needs to be avoided (e.g. with significant renal impairment and high cardiovascular risk rendering administration of TDF, TAF, and ABC difficult).

(2) DTG/3TC: a switch to the two-drug combination DTG/3TC, a regimen shown to be effective as initial therapy,[81] was also recently shown to be non-inferior to continuing a TAF-based three-drug regimen in maintaining virologic suppression in HIV-1-infected ART-experienced adults.[82] This regimen may be considered for patients with significant metabolic comorbidities, such as cardiovascular, renal, or bone disease.

(3) Boosted PI + 3TC: switch to LPV/ritonavir + 3TC,[83] boosted ATV + 3TC,[84] or boosted DRV + 3TC,[85] have also been shown to be safe and effective. These could also be considered if there is a need to avoid NRTI exposure.

Discontinuation or interruption of antiretroviral therapy

The planned discontinuation or interruption of antiviral therapy is not recommended.[3] The Strategies for Management of Antiretroviral Therapy (SMART) study showed CD4-guided interruption of ART is associated with increased risk of AIDS and non-AIDS complications.[86]

Short-term, unanticipated treatment interruptions due to acute medical issues or drug availability can occur, but should be avoided or minimized when possible. Even in these cases, antivirals should be resumed as soon as medically practical.[3]

Conclusion

As we have reviewed, the current era of modern ART has introduced both great advances in the care of PLWH, but also new challenges, with the increasing life expectancy and accumulation of comorbid medical conditions in this population. The overarching goal of ART is still to achieve and maintain virologic suppression in all patients, but simplification, especially with potent single tablet regimens, and optimization of ART to reduce toxicities and ensure long-term tolerability has become a more important focal point in ongoing HIV management. The prospects of long-acting injectable HIV ARVs soon to be available represent the next horizon in the maintenance of virologic suppression in PLWH. As has been the case since the advent of ART, experienced HIV clinicians, working in multidisciplinary, collaborative teams with clinical pharmacists and other healthcare workers, can significantly impact the survival and quality of life of their patients by expertly deploying these treatment strategies in a patient-centered approach.

Author contributions

Roger Bedimo was responsible for the conception and overall organization of the manuscript, and also wrote substantial portions of the manuscript. Tomasz Jodlowski and James Cutrell contributed substantial portions of the manuscript.

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Conflict of interest statement

Roger Bedimo has received research funding from ViiV Healthcare and Merck and Co. He has also served in *ad hoc* scientific advisory boards for ViiV Healthcare and Merck and Co.

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Ethical statement

Our study did not require ethical board approval because it did not contain human or animal trials.

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