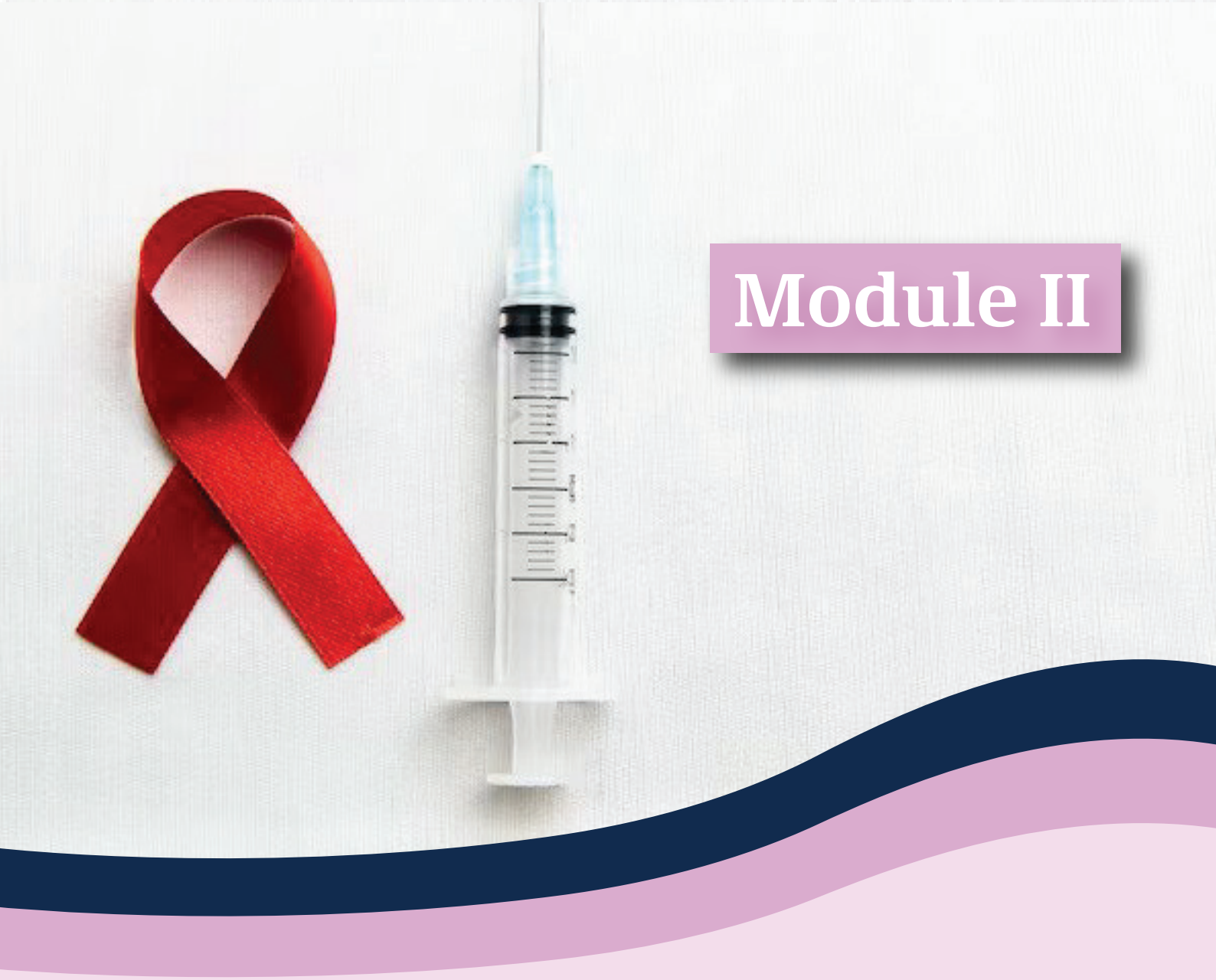
Module on Advances in HIV management



Module II

Management of treatment failure and HIV drug resistance.

CONTENT

Introduction

In 2014, the Joint United Nations AIDS Programme established global targets such that 90% of people living with HIV will be diagnosed, 90% of those diagnosed will be on antiretroviral therapy (ART), and 90% of those on ART will be virally suppressed by 2020. However, in the United States, 20% of people living with HIV who have linked to care or are on ART still remain virologically unsuppressed. Thus, optimal management of treatment failure plays a critical role in our ability to improve viral suppression rates and to achieve epidemic control.

Identifying Virologic Failure

Terminology regarding levels of HIV-1 viremia and virologic suppression are presented in Table 1.4 In the United States, virologic suppression is typically defined as a confirmed HIV-1 RNA that is below the lower limit of detection for the assay, while virologic failure is defined as failure to achieve or sustain suppression of viral replication to a HIV-1 RNA level < 200 copies/mL Modern polymerase chain reaction assays for HIV-1 RNA will quantify detectable viral load less than 200 copies/mL. However, the clinical significance of low-level viremia and viral blips as well as their optimal management remain uncertain, with data from various sources demonstrating both increased risk of future virologic failure and that blips are of little clinical consequence. For those with viral load less than 200 copies/mL, current treatment guidelines suggest that the current ART regimen should be continued, along with frequent viral load monitoring.

Resistance Testing

After identifying virologic failure, or in cases in which there is concern for incomplete virologic response, providers should obtain resistance testing to guide the next steps in management. Table 2 summarizes the literature regarding the clinical efficacy of resistance testing, stratified by testing method and time point. Most studies support the use of resistance testing, both to guide initial therapy and for selection of an optimal ART regimen following treatment failure. Cost-effectiveness analyses of resistance testing are summarized in Table 3. Overall, these studies conclude that standard genotypic resistance testing is cost-effective both prior to ART initiation and at the time of virologic failure. One notable exception is that pre-treatment integrase gene sequencing for individuals taking integrase strand transfer inhibitors (INSTIs) is expected to increase costs and lead to poorer clinical outcomes, as results could lead providers away from selecting dolutegravir (DTG) or bictegravir (BIC)-based regimens that retain activity.

Genotypic resistance tests involve direct sequencing of the viral genome and remain the preferred resistance testing method. Currently available commercial assays utilize Sanger sequencing to sequence the HIV-1 reverse transcriptase (RT) and protease (PR)-producing region of the pol gene, which typically detects resistance mutations occurring in at least 20% of the viral population. In the US, turnaround time for these tests is approximately 7-14 days. Of note, the integrase protein (IN) region sequencing is usually not included as part of standard testing and must be requested separately as another assay. Similarly, HIV-1 viral tropism assays and sequencing of the env gene to assess susceptibility to maraviroc and enfurvitide, respectively, are also not included as part of standard resistance testing.

In contrast, phenotypic tests culture clinical HIV-1 virus in the presence of various antiretroviral agents and directly measure drug activity. These assays are less commonly utilized given higher costs and a longer turnaround time.

Thus, phenotypic tests are only recommended for new or investigational agents or for individuals with extensive ART exposure (especially involving protease inhibitors) and/or complex resistance profiles.

Finally, next generation sequencing (NGS) is a newer technology for genotypic resistance testing. NGS differs from Sanger sequencing in that it utilizes high-throughput methods, which require less specialized personnel and lowers costs per specimen. In addition, NGS can detect minority variants at thresholds as low as 1%, thus capturing significantly more drug resistance mutations than traditional Sanger sequencing. An important unresolved challenge for the field is to determine the optimal threshold for detection of mutations by NGS that correlates with clinically significant resistance.

Use of Resistance Tests in Clinical Practice

The most clinically useful resistance testing results will be yielded if resistance testing is performed while individuals are taking ART or within four weeks of treatment cessation.4 If an individual has spent a longer duration without selective pressure from a failing ART regimen, it is possible that mutations in the HIV-1 viral population would revert to wild-type, while resistant strains could be circulating in lower numbers and/or archived, and therefore not detected. However, relevant mutations (particularly to NNRTIs) can still be frequently identified even in those who have stopped their ART.
Interpreting genotypic resistance test results can be complex. Algorithms that incorporate evidence from the literature and expert opinion to derive scores for predicted susceptibility to each of the antiretroviral agents are available to aid with interpretation. The Stanford HIV Drug Resistance Database, French National Agency for AIDS Research (ANRS), HIV Genotypic Resistance-Algorithm Deutschland (HIV-GRADE), and Rega are all widely recognized algorithms for this purpose.

Finally, it is important to consider current and past resistance tests results when choosing a new ART regimen. If selective pressure from a prior agent is no longer present, resistance to that drug may not manifest on a current HIV genotype. However, if a mutation was present on a prior genotypic resistance test result, the mutation should still be considered as part of a cumulative genotype result.

Virologic Failure Without Resistance

Etiologies of Virologic Failure without Resistance

Some individuals with virologic failure have detectable viremia in the absence of detectable resistance mutations by standard genotype testing. Virologic failure without resistance is most often the result of inadequate drug levels due to non-adherence. Other possible contributors may include limited gastrointestinal absorption and drug-drug interactions.

Non-adherence to ART is a complex, multidimensional challenge. Psychosocial factors such as concurrent substance abuse, unstable housing or homelessness, financial challenges, and issues related to stigma and non-disclosure of HIV status should all be considered. Medical comorbidities including concurrent mental illness may also increase risk of non-adherence to ART. In addition, regimen factors may represent barriers to adherence, particularly if there is a high pill burden or if the regimen is poorly tolerated due to side effects. Finally, system-level factors can also contribute to non-adherence, which is often most-pronounced in resource-limited settings where medication stock-outs are common.

Nearly all patients taking modern ART regimens are virologically suppressed. As a result, virologic failure without resistance mutations in the setting of high-level ART adherence is rare. Potential causes include drug interactions and errors either in pharmacy dispensing or patient misunderstanding of how to take ART correctly. In these settings, pharmacy refill records can be utilized to ensure accuracy and frequency of drug dispensing. Drug-drug interactions may be assessed with the assistance of online or other interaction review tools. Furthermore, some antiretroviral medications, including atazanavir, darunavir, and rilpivirine, should be taken with food to achieve appropriate drug concentrations. Medical and anatomical disorders of impaired absorption may also lead to decreased drug levels; thus, providers should carefully assess patient symptoms and review medical and surgical history in the evaluation of virologic failure.

In scenarios of either non-adherence or poor drug absorption, genotypic resistance tests may fail to identify extant resistance-conferring mutations, if there is insufficient exposure to ART to create selective pressure on the sequenced viral population. Consequently, it is important to repeat viral load testing in two to four weeks after adherence has improved or absorption issues have resolved to ensure response to ART.

Management of Virologic Failure without Resistance

The core management principles for treatment failure without resistance involve interventions to improve patient adherence to ART and to ensure therapeutic drug levels. These typically include patient-centered strategies to target barriers to adherence. Providers can often address regimen-specific barriers through simplification of the ART regimen, regimens without a requirement for co-administration with food, and fixed dosed combinations to decrease pill burden and scheduling complexity. Providers may also need to substitute components of the ART regimen for agents with better side effect profiles if symptoms are responsible for poor adherence and cannot be otherwise managed. Pill-boxes and text-message reminders have also proven effective at improving ART adherence in cases where mnemonic aids are needed. Interventions to address more complex factors, such as substance use disorders, concurrent mental illness, food, transportation or housing insecurity, and economic hardship, have also been shown to improve adherence to ART. Finally, one-on-one individualized patient education, adherence assessment, and adherence counseling should be prioritized at every clinical visit for patients with or at risk for drug adherence challenges.

Virological Failure with Resistance

Virologic failure with drug resistance mutations can arise as a result of two scenarios: pretreatment HIV drug resistance and/or acquired drug resistance.

Pretreatment HIV Drug Resistance

Transmitted drug resistance (TDR) occurs when a treatment naive individual is infected with a resistant strain of virus.33 Globally, the term pretreatment drug resistance (PDR) refers to TDR, as well as any resistance mutations present prior to initiating or re-initiating first-line ART, including acquired mutations which resulted from prior treatment exposure or prevention of mother to child transmission practices. With increasing numbers of people with HIV now on ART, rates of PDR are rising worldwide with the prevalence of PDR reaching 10% or greater in many regions. PDR is driven primarily by resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs), whereas PDR to other classes remains much less common. PDR to INSTIs is extremely rare, with transmitted major INSTI mutations occurring in 0 – 0.8% in cohort studies from the US and Europe or in isolated case reports.

Acquired HIV Drug Resistance

Acquired drug resistance refers to drug resistance mutations that are selected in individuals who are receiving ART. The high rate of HIV-1 viral replication, combined with the high error rate of reverse transcriptase, allows for emergence of viral strains with resistance-conferring mutations, when ART is used imperfectly. Without selective pressure from ART, mutant strains typically comprise a minority of the viral population because many non-polymorphic viral mutations lead to a reduction in viral fitness and replication capacity. However, under selective pressure of ART, mutant strains can emerge as the dominant viral population if ART is not sufficiently potent for viral suppression, with potency being a factor of both susceptibility of the mutant virus to the ART regimen, as well as the necessary therapeutic drug levels. Imperfect adherence to ART is the most likely etiology for ongoing viral replication. Other possible explanations include incorrect dosing, poor absorption, or reduced drug levels due to drug-drug interactions. In addition, some regimens may be particularly susceptible to selecting for drug resistance due to differences in the half lives of component drugs, leading to unplanned monotherapy sometimes referred to as a pharmacokinetic "tail". With continued viral replication in the face of ART, emergence of resistant mutants is also related to the genetic barrier to resistance of the ART regimen, which is a factor of the number of mutations required to reduce viral susceptibility. Thus, while NRTIs, NNRTIs, and early generation INSTIs are considered to have a low genetic barrier to resistance, PIs and later generation INSTIs require multiple mutations before drug susceptibility is impacted. Finally, mutations can continue to accumulate over time, leading to worsening resistance. This particularly occurs when mutations appear on the same virus through recombination, rather than being distributed throughout the quasi species.

HIV Drug Resistance Mutations

Table 4 summarizes drug susceptibility information adapted from the Stanford HIV db algorithm for common resistance mutations for the NRTIs, NNRTIs, PIs, and INSTIs, though it is not meant to be a comprehensive list. The World Health Organization and IAS-USA also maintain a list of relevant mutations which are freely available online.

NRTI mutations (Table 4)

NRTIs are nucleoside analogues, which lead to chain termination when incorporated into viral DNA by the viral reverse transcriptase enzyme. This drug class has a relatively low genetic barrier to resistance, which occurs by one of two mechanisms: 1) decreasing the rate of NRTI binding versus natural nucleotides or 2) increasing the rate of NRTI excision. M184V/I, K65R, K70E and L74V are examples of mutations in the discriminatory pathway, which require only single mutations to cause resistance and lead to a substantial reduction in viral fitness. M184V is often the first mutation to arise and causes high-level resistance to lamivudine (3TC) and emtricitabine (FTC). This mutation also causes increased susceptibility to zidovudine (AZT) and tenofovir (TDF), which can act in opposition to thymidine analogue mutations (TAMs), discussed below (Table 4). In clinical practice, either 3TC or FTC is typically maintained as part of ART regimens, even when M184V is present, to intentionally select for a less-fit virus. K65R, the signature mutation for TDF, also leads to a reduction in viral fitness and causes hyper susceptibiity to AZT (Table 4).

In contrast, TAMs are selected by AZT and stavudine (d4T), and function through the excisional pathway. These mutations confer less of a viral fitness cost than discriminatory NRTI mutations. Single TAMs have little impact on NRTI susceptibility; however, the fold-change level, or decreased activity of the drug, is directly correlated with an increasing number of TAMs. In addition, while all TAMs confer resistance to AZT and d4T, the type I TAM pathway has a greater negative impact on tenofovir susceptibility than the type 2 TAM pathway (Table 4).

NNRTI mutations (Table 4)

NNRTIs bind to the hydrophobic pocket of RT, thus inhibiting viral replication.83 Mutations conferring resistance to NNRTIs cause changes in the hydrophobic pocket, which decrease the ability of NNRTIs to bind. Compared to the PIs and INSTIs, NNRTIs generally have a lower barrier to resistance. Cross resistance amongst drugs within this class occurs with most NNRTI mutations. However, etravirine (ETR) retains activity against isolates with K103N, allowing for its use in salvage regimens (Table 5b). Rilpivirine is also active in vitro against virus with the K103N mutation, and was effective in maintaining viral suppression in study participants who switched from boosted PI regimens and harbored this mutation. In addition, doravirine (DOR), the newest agent in this class, is active against viral strains with K103N or Y181C, (Table 4). Data on use of doravirine in patients with NNRTI resistance are limited.

PI mutations (Table 4)

PIs bind competitively to the active site of PR, which prevents necessary cleaving of viral polypeptides required for formation of new HIV virions as well as maturation and cell budding. At present, the most commonly used agents in this class include lopinavir (LPV), ATV, and DRV. LPV and DRV must be given with pharmacologic boosters, while doing so with ATV improves drug exposure and is generally recommended. Mutations conferring resistance to these PIs confer changes such that the PIs are unable to bind to the active site. Unlike NRTIs and NNRTIs, pharmacologically boosted PIs have a higher barrier to resistance and usually require more than one major mutation to cause a reduction in susceptibility. Thus, failure on PI-based regimens, particularly when given as part of initial therapy, is more often due to non-adherence rather than to resistance. Cross resistance within this class is variable. For example, I50L causes resistance to ATV alone, while other PIs retain full activity. By contrast, mutations selected by unboosted indinavir, saquinavir, and sometimes nelfinavir can lead to broad resistance within this class. Similarly, prolonged failure on LPV/r in treatment-experienced patients can select for resistance to other PIs. In this setting, only DRV and tipranavir reliably retain activity. (Table 5b). Fosamprenavir (and its earlier formulation amprenavir) are structurally similar to DRV, and hence may compromise activity of DRV in future regimens. As a result, fosamprenavir is no longer recommended.

INSTI mutations (Table 4)

INSTIs bind the active site of IN, preventing viral DNA strand transfer. Mutations conferring resistance to INSTIs cause changes in the active site, which prevent binding of the drug. Early generation INSTIs, raltegravir (RAL) and elvitegravir (EVG), have a much lower genetic barrier to resistance than the later generation INSTIs DTG and BIC, which require multiple mutations to lower susceptibility to a clinically significant degree.

Resistance to RAL and EVG can develop quickly in the setting of suboptimal adherence. There is also significant cross resistance between RAL and EVG, which prevents sequential use of these earlier generation INSTIs. Resistance to RAL can occur through any of three main pathways: 1) Y143C, 2) Q148H/K/R or 3) N155H.97 EVG shares the Q148 and N155 pathways, but resistance to EVG can also develop with presence of T66A/I/K and E92Q. Of these pathways, Q148 is the most significant INSTI mutation and reduces activity of DTG and BIC, especially when combined with additional mutations.

While DTG is active against many strains which are resistant to RAL and EVG, resistance to DTG has been documented. Clinical trial data have shown emergence of DTG resistance through the Q148 pathway when other INSTI mutations are also present. DTG resistance also emerges when DTG is used as monotherapy. Though rare, additional DTG resistance pathways have been identified, which include G118R, R263K, and S230R. Resistance patterns for BIC are considered to be similar; however, there are currently no data for its use in treatment-experienced patients with INSTI resistance, and is not included in US guidelines for this population.

Management of HIV Drug Resistance

Many resistance mutations have important interactions with other mutations, and so it is vital to consider the resistance genotype as a whole. Many commercial resistance test reports will have accompanying drug susceptibility summaries that can assist providers in selecting the best treatment regimen. In addition, rule-based algorithms such as the Stanford University HIV Database as mentioned above allow users to input resistance data or sequences and will provide interpretation of results. Providers should also consider an individual's entire resistance genotype history to construct a cumulative resistance profile, particularly for patients who are very treatment-experienced. This is due to the potential presence of archived and minority drug resistance viruses as previously discussed.

When selecting active drugs for a new ART regimen, providers may select a new drug class and/or drugs from a class to which the individual has been exposed but has no evidence of cross-resistance on resistance test results. Regimens should include at least two active agents when possible, though three are preferred. If two active drugs are not available, ART should still be continued, with inclusion of NRTIs as resistance to this class has been most clearly associated with reduced viral fitness, a phenomenon further discussed below. Guidelines recommend against the addition of only one active agent to a failing regimen due to the risk of failure with functional monotherapy.
While resistance to NRTIs may be present, there is evidence that there may still be clinical benefit from residual activity. Numerous studies have shown a paradoxical outcome in which rates of viral suppression are inversely correlated with the number of active NRTIs, when used with both PIs and DTG. However, NRTI-containing regimens still lead to better viral suppression rates than PI or DTG monotherapy. Thus, NRTIs should be continued in salvage regimens when possible. Furthermore, as discussed above, 3TC or FTC are often continued despite the presence of M184V in order to select for a less fit virus. M184V has also been shown to delay (but not prevent) emergence of TAMs. In addition, K65R and TAMs function via antagonistic pathways. Thus continuation of NRTIs to maintain K65R or TAMs can help to prevent new mutations of the opposing type.

Second-line Regimens

Table 5a summarizes the results of clinical trials for second-line ART regimens.Current US guidelines offer recommendations for second-line regimens based on the failed first-line regimen. For those failing an NNRTI-based first-line regimen, second-line options include two NRTIs (at least one of which should be active) with either a boosted PI or DTG, or a boosted PI combined with an INSTI. The same strategy is recommended for those failing a PI-based first-line regimen with PI resistance, though substituting a different PI. If an individual is failing a regimen containing early generation INSTIs RAL or EVG, a regimen containing twice-daily DTG may be used in second-line with either a boosted PI or two NRTIs (at least one active) if DTG remains susceptible. A boosted PI with two NRTIs is also a reasonable option. Of note, there are no published data at present regarding optimal choice of second-line therapy for those failing DTG or BIC-based first-line regimens.

Salvage Regimens

Herein, we refer to salvage regimens as ART regimens that are used in ART-experienced individuals with limited treatment options. Virologic failure occurring on second-line and salvage regimens presents a challenge due to the amount of ART exposure and extensive resistance that is often present. Table 5b summarizes the results of clinical trials for salvage ART regimens. Dosing may differ for agents used in the setting of resistance. For example, both DRV/r and DTG are advised to be given twice daily when certain PI and INSTI mutations are present, respectively. For individuals who are extremely treatment-experienced, additional agents including maraviroc (a CCR5 antagonist), enfurvitide (a fusion inhibitor), and ibalizumab have shown benefit when added to an optimized background regimen. Importantly, maraviroc may only be used in individuals who are found to have CCR5-tropic virus by tropism testing. Recently, ibalizumab (IBA), a monoclonal antibody, has shown efficacy in treatment experienced mutations with extensive multi-class resistance, and is now approved for use in this patient population. IBA is a novel drug, which is classified as a post-attachment inhibitor that prevents viral entry. Still, reduced susceptibility to this agent leading to virologic failure was shown to occur in a phase 3 clinical trial. In addition, IBA must be administered via IV infusion, which may be challenging in some settings. We note that the treatment of patients with extensive drug resistance is a rapidly evolving field, owing to the pipeline of new HIV drugs and classes, such as nucleoside reverse transcriptase translocation inhibitors, maturation inhibitors, and attachment inhibitors.

Managing Virologic Failure in Special Populations

Women of Child-bearing Potential

There are preliminary data linking DTG use during conception and an increased risk of neural tube defects in babies born to these mothers. As a result, treatment guidelines have recommended counseling women of childbearing potential about this risk, and strong consideration for use of alternative agents whenever possible. In the settings where DTG is required for maintaining or achieving viral suppression, however, we would advocate use of this agent despite these preliminary data. Virologic failure could worsen maternal outcomes and increase the risk of viral transmission to the newborn.

Co-infection with Tuberculosis

For individuals presenting concurrently with virologic failure and newly diagnosed active tuberculosis (TB), we favor an approach in which TB treatment initiation and ART regimen switch do not occur simultaneously, to avoid occurrence of toxicity without a clear cause. TB treatment should be initiated immediately. Although current guidelines do not offer recommendations regarding the optimal timing of regimen switch relative to initiation of TB treatment., we favor waiting approximately two weeks to start a new HIV treatment, as is done for people presenting with co-occurring new diagnoses of HIV and pulmonary TB.

ART regimens in this scenario should be selected to achieve viral suppression, minimize side effects, and avoid drug-drug interactions with the TB treatment regimen. Particular attention must be paid to the rifamycin component of standard TB treatment regimens. Rifamycins are strong inducers of CYP3A4 enzymes (with the exception of rifabutin, a less potent inducer) and can lead to increased metabolism and decreased systemic levels of some antiretroviral agents. Thus, when selecting ART regimens for individuals with treatment failure, drug interaction review is particularly important. Generally, rifabutin leads to fewer interactions than rifampin. However, rifabutin is often unavailable in many resource-limited settings with a high prevalence of TB.

NRTIs can be safely included in second-line and salvage regimens with rifamycin-containing TB treatment regimens without dose adjustment. As an exception, current guidelines do not recommend coadministration of tenofovir alafenamide (TAF) with any of the rifamycins given the potential for decreased plasma concentrations of TAF. However, recent data show high intracellular concentrations of tenofovir diphosphate with coadministration of TAF and rifampin, which were actually greater than intracellular levels achieved with administration of TDF alone. Thus, while not currently recommended due to an absence of more robust outcomes data, coadministration of TAF and rifamycins still may prove efficacious.

Earlier generation NNRTIs, EFV and nevirapine (NVP), are the most studied agents for use in TB/HIV co-infection. However, these agents are not often used in second-line and salvage regimens due to the high prevalence of drug resistance mutations. ETR is more often utilized in salvage regimens and may be co-administered with rifabutin. However, ETR should not be co-administered with rifampin due to inability to achieve appropriate drug levels. DOR, a newly approved NNRTI in 2018, is not yet discussed in US guidelines for TB/HIV co-infection. However, studies have shown that it can be co-administered at a double dose with rifabutin but should not be used with rifampin.

If a boosted PI is used in the second-line or salvage ART regimen, rifabutin is the preferred rifamycin, given that dose adjustments of the boosted PI are not required. However, all PIs increase drug levels of rifabutin, requiring downward dose adjustment of the rifabutin to avoid drug toxicities. If rifampin must be used with a PI due to lack of access to rifabutin, a dose increase in the boosted PI is required to achieve therapeutic levels. LPV/r is the only PI which has been well-studied for concurrent administration with rifampin. Dosing options include either doubling the dose of LPV/r or increasing the dose of the ritonavir booster. Still, both of these strategies lead to markedly increased pill burden, risk of hepatoxicity, and significant GI side effects.

If an INSTI is chosen as part of the second-line or salvage ART regimen, dose adjustments are also required to achieve therapeutic INSTI levels. Specifically, DTG should be administered twice daily. RAL should be double-dosed when co-administered with rifampin, though no adjustment is necessary when co-administered with rifabutin.150-153 Co-administration of rifamycins with either BIC or EVG/c should be avoided.

Finally, enfurvitide and rifamycins can be co-administered without dose adjustment. However, drug interactions do exist with maraviroc and rifamycins, and there are no clinical studies to guide use of this combination.

Co-infection with Hepatitis B

For all patients co-infected with HIV-1 and hepatitis B virus (HBV), it is important to maintain agents with activity against HBV as part of the ART regimen. While 3TC and FTC have activity against HBV, these agents readily select for HBV resistance and as a result are not recommended as the only agent with activity against HBV. Even in the setting of HIV-1 drug resistance mutations to tenofovir, TDF or TAF should be included as part of the second-line or salvage ART regimen given that it is the first-line drug for HBV, has a high barrier to resistance, and is active against 3TC-resistant HBV strains. In addition, patients are at risk of HBV DNA rebound and hepatitis flare if agents active against HBV are discontinued. If a patient with HBV coinfection otherwise has contraindications to tenofovir, such as renal failure, entecavir can be added to a fully active ART regimen.

Co-infection with Hepatitis C

With the introduction of direct-acting antivirals, there are many options for the treatment of hepatitis C virus (HCV). However, it is important to be aware of the drug-drug interactions between anti-HCV and ART regimens.

Drug-drug interactions between HCV and HIV drugs have been published previously and are available online. If an ART regimen change is required during the course of HCV treatment due to HIV virologic failure, providers should consult a drug interaction resource. If virologic failure is diagnosed prior to the start of HCV treatment, then the ART regimen should be appropriately adjusted and viral suppression achieved prior to beginning the HCV treatment regimen.

Infection with HIV-2

In contrast to HIV-1, there are currently no standard genotypic resistance tests available for HIV-2 to guide treatment decisions at the time of virologic failure. However, knowledge of key features of HIV-2 can aid in the empiric selection of ART regimens at the time of treatment failure. In particular, HIV-2 is intrinsically resistant to both NNRTIs and to enfurvitide. NRTIs have activity against HIV-2, but as in HIV-1, they should be used in combination with another drug class. Select boosted PIs have demonstrated activity against HIV-2, including DRV, LPV, and saquinavir; however, other PIs do not show equivalent activity and should be avoided. All currently available INSTIs demonstrate potent activity against HIV-2 though development of resistance has been demonstrated, particularly with earlier generation INSTIs. While CCR5 antagonists may have activity against HIV-2, there are currently no standardized tropism assays for HIV-2.

Managing Virologic Failure In Resource-limited Settings

In resource-limited settings, virologic failure is defined as two consecutive HIV-1 RNA levels >1,000 copies/mL despite interval intensive adherence counseling. This higher HIV-1 RNA cutoff has been selected due to the widespread use of viral load monitoring using dried blood spots in many regions, and as a public health approach to minimize unnecessary switching to more costly and burdensome HIV regimens. Notably, genotypic resistance testing is not routinely available or recommended for pretreatment resistance testing or resistance testing at the time of virologic failure on first-line ART. Rather, empiric first-line regimens recommended by WHO are based on results of national pre-treatment drug resistance surveillance studies. Given increasing rate of PDR to NNRTIs as discussed above, ART programs are advised to now utilize a DTG-based regimen as preferred first-line treatment, with the exception of women of child-bearing age, for whom assessment of contraception access and risk-based stratification is recommended. Similarly, empiric second-line regimens are recommended based on the first-line regimen that an individual has failed. Specifically, WHO recommends a boosted PI-containing regimen following failure on DTG-based first-line regimens and a DTG-containing regimen following failure on NNRTI-based first-line regimens. The NRTI component of second-line regimens is also empirically recommended based upon most likely resistance mutations that would have been selected by the first-line regimen, thus requiring a switched NRTI backbone. For example, an individual failing a TDF-containing first-line regimen should be switched to an AZT-containing second-line regimen, given presumed presence of K65R, with the caveat that TDF should also be continued in the setting of chronic HBV coinfection. An individual failing an AZT-containing first-line regimen should be switched to a TDF-containing second-line regimen, given presumed presence of TAMs.

In contrast to first-line treatment failure, WHO now recommends the use of genotypic resistance testing when feasible at the time of virologic failure on second-line ART. Both boosted PIs and DTG have higher barriers to resistance than NNRTIs.Thus, resistance testing allows for identification of individuals with second-line failure due to poor adherence alone, as well as treatment optimization in those who are found to have second-line failure due to drug resistance. In those who do require a switch to third-line ART, WHO currently recommends that salvage regimens include DRV/r, DTG, and an optimized NRTI background when possible. Many countries employ use of an expert panel or committee to review resistance results and approve use of third-line regimens to ensure appropriate use and stewardship of these agents. For individuals with no active drugs available or in settings without access to salvage regimens, WHO recommends continuation rather than cessation of ART.

Summary

Though virologic failure can be a complex and clinically significant complication of HIV infection, advances in diagnostics and novel therapeutics have expanded treatment options even for those patients with extensive exposure to ART and multidrug resistant virus. Principles of management for virologic failure include 1) conduct of genotypic resistance testing; 2) differentiating between adherence and resistance driven failure, which are not mutually exclusive; and 3) selection of optimized regimens with a minimum of two active drugs from two separate classes. As with treatment initiation, the goal of therapy after treatment failure is to select a regimen that is well-tolerated, minimally burdensome, and rapidly and durably yields virologic suppression. Achieving this goal will improve health for people with HIV and prevent viral transmission.

KEY POINTS

- Virologic failure can occur with or without drug resistance mutations, the latter being due to poor adherence or low exposure to ART.
- Genotypic resistance testing is recommended as the preferred test to guide regimen choice following virologic failure and should be performed while the individual is on ART.
- Rule-based algorithms are available to aid in the interpretation of genotypic resistance results.
- ART regimens should include at least 2-3 active drugs when possible.
- ART should be continued, even if no active drugs are available.

Figures

Table 1.

Virologic Response

Viral suppression	HIV-1 RNA < 200 copies/mL
Virologic failure	HIV-1 RNA ≧ 200 copies/mL
Incomplete virologic response	Failure to achieve viral suppression to <200 copies/mL on two measurements after 24 weeks on antiretroviral therapy
Virologic rebound	Sustained HIV-1 RNA ≧ 200 copies/mL on at least two HIV-1 RNA measurements after a previous period of viral suppression
Viral blips	Brief, isolated episode of detectable HIV-1 RNA, between two suppressed HIV-1 RNA measurements

Data from DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Accessed December 5, 2018.

Table 2.

Studies of the Clinical Impact of Resistance Testing at the Time of Virologic Failure

Study	Citation	Sample size	Population	Outcome	Results
Randomized Controlled Trials Comparing Genotype to No Resistance Test					
VIRADAPT	Durant, Lancet 1999	108	HIV-1 RNA >10,000 copies/mL; Exposure to PIs	Change in VL	Favors use of resistance testing
CPCRA 046	Baxter, AIDS 2000	153	Three-fold rise in HIV-1 RNA; Exposure to PIs	Change in VL	Favors use of resistance testing
ARGENTA	Cingolani, AIDS 2002	174	HIV-1 RNA >2,000 copies/mL x2 or incomplete virologic response to combination ART	Virologic suppression	Does not favor resistance testing
Havana	Tural, AIDS 2002	326	HIV-1 RNA >1,000 copies/mL; On combination ART	Virologic suppression	Favors use of resistance testing
PENTA 8	Green, Antivir Ther 2006	170	Children with HIV-1 RNA >2,000 copies/mL; On combination ART	Virologic suppression	Does not favor resistance testing
Randomized Controlled Trials Comparing Phenotype to No Resistance Test					
VIRA3001	Cohen, AIDS 2002	272	HIV-1 RNA >2,000 copies/mL; Exposure to PIs	Virologic suppression	Favors use of resistance testing
CCTG 575	Haubrich, AIDS 2005	256	HIV-1 RNA >400 copies/mL; On combination ART	Virologic suppression	Does not favor resistance testing
Randomized Controlled Trials Comparing Genotype, Phenotype, and No Resistance Test					
NARVAL	Meynard, AIDS 2002	591	HV RNA>1,000 copies/mL; History of exposure to PIs	Virologic suppression	Does not favor resistance testing
CERT	Wegner, CID 2004	450	On combination ART	Time to persistent treatment failure despite change in regimen	Favors resistance testing, but only for those with extensive treatment experience
Randomized Controlled Trials Comparing Modes of Resistance Tests					
GenPheRev	Mazzotta, JAIDS 2003	201	Virologic failure; Exposure to at least 6 ART agents	Virologic suppression	No difference between real versus virtual phenotype
Realvirfen	Perez-Elias, Antivir Ther 2003	276	Virologic failure	Virologic suppression	Favors virtual phenotype over real phenotype
ERA	Dunn, JAIDS 2005	311	Virologic failure	Virologic response	Favors genotype over genotype + phenotype

Abbreviations: PI = protease inhibitor; VL = viral load; ART = antiretroviral therapy; NNRTI = non-nucleoside reverse transcriptase inhibitor

Table 3.

Modelling Studies Evaluating Cost Effectiveness of Genotypic Resistance Testing

Study	Setting	Favors Pre-ART Resistance Testing	Favors Resistance Testing at Virologic Failure
Weinstein, Ann Int Med 2001	US, Europe	Yes	Yes
Corzillius, Antiviral Therapy 2004	Central Europe	Yes	Yes
Sax, CID 2005	US	Yes	Not addressed
Yazdanpanah, Antiviral Therapy 2007	Europe	Not addressed	Yes
Sendi, PLOS One 2007	Switzerland	Not addressed	Yes
Rosen, JIAS 2011	South Africa	Not addressed	Yes
Levison, CID 2013	South Africa	Not addressed	Yes
Phillips, PLOS One 2014	Zimbabwe	Not addressed	No
Luz, JAIDS 2015	Brazil	Yes	Not addressed
Koullias, CID 2017	US	Pre-ART INSTI testing not favored	Not addressed
Phillips, Lancet HIV 2018	Sub-Saharan Africa	Yes (though less effective than a policy change to INSTI-based first-line ART)	Not addressed

Abbreviations: ART = antiretroviral therapy; US = United States; INSTI = integrase strand transfer inhibitor

Mutation	Agents leading to mutation selection	Reduced Susceptibility	Increased Susceptibility	Notes for use
Y188L	EFV, NVP	High-level resistance: EFV, NVP, RPV, DOR Potential low-level resistance: ETR		
G190A	EFV, NVP	High-level resistance: NVP Intermediate resistance: EFV		
G190S	EFV, NVP	High-level resistance: EFV, NVP Intermediate resistance: DOR		
G190E	EFV, ETR	High-level resistance: EFV, NVP, RPV, DOR Intermediate resistance: ETR		
		Protease inhibitor mutations		
V32I	IDV, FPV, LPV, DRV	Low-level resistance: ATV/r, LPV/r, DRV/r		DRV/r should be given twice daily
I47V	IDV, FPV, LPV, DRV	Low-level resistance: LPV/r Potential low-level resistance: ATV/r, DRV/r		
G48V/M	SQV, IDV, LPV	Intermediate resistance: ATV/r Low-level resistance: LPV/r		
I50L	ATV	High-level resistance: ATV/r	LPV/r, DRV/r	
I50V	DRV, LPV, FPV	Intermediate resistance: LPV/r Low-level resistance: DRV/r		DRV/r should be given twice daily
I54M/L	DRV, FPV	Low-level resistance: ATV/r, LPV/r, DRV/r		DRV/r should be given twice daily
L76V	IDV, LPV, DRV	Intermediate resistance: LPV/r Low-level resistance: DRV/r	ATV	DRV/r should be given twice daily
V82A	IDV, LPV	Intermediate resistance: LPV/r Low-level resistance: ATV/r		
V82F	IDV, LPV	Intermediate resistance: LPV/r Low-level resistance: ATV/r, DRV/r		DRV/r should be given twice daily
V82T/S	ATV, IDV, LPV, TPV	Intermediate resistance: LPV/r, ATV/r		
I84V/C	All PIs	High-level resistance: ATV/r Intermediate resistance: LPV/r Low-level resistance: DRV/r		DRV/r should be given twice daily
I84A	All PIs	High-level resistance: ATVr, LPV/r Intermediate resistance: DRV/r		DRV/r should be given twice daily
N88S	ATV, NFV, IDV	High-level resistance: ATV/r	DRV/r	
		Integrase strand transfer inhibitor mutations		
T66A	EVG, RAL	High-level resistance: EVG Low-level resistance: RAL		
T66I	EVG, RAL, DTG	High-level resistance: EVG Low-level resistance: RAL		
T66K	EVG, RAL	High-level resistance: EVG, RAL		DTG should be given twice daily

Mutation	Agents leading to mutation selection	Reduced Susceptibility	Increased Susceptibility	Notes for use
		Low-level resistance: DTG, BIC		
E92G	EVG, RAL	Intermediate resistance: EVG Low-level resistance: RAL		
E92Q	EVG, RAL, DTG	High-level resistance: EVG Intermediate resistance: RAL Potential low-level resistance: DTG		
G118R	DTG	Intermediate resistance: EVG, RAL Low-level resistance: DTG, BIC		DTG should be given twice daily
Y143C/R	RAL	High-level resistance: RAL		Synergistic with T97A; reduces EVG susceptibility with L74M, T97A, G163R, S230R
Y143A/G/K/S	RAL	High-level resistance: RAL		Reduces EVG susceptibility with accessory INSTI mutations
Q148H/R	EVG, RAL, DTG	High-level resistance: EVG, RAL Low-level resistance: DTG, BIC		When combined with E138K and/or G140SA, susceptibility to DTG and BIC are affected. Effect is more pronounced with N155H, L74M, or T97A. DTG should be given twice daily
Q148K	EVG, RAL, DTG	High-level resistance: EVG, RAL Intermediate resistance: DTG, BIC		When combined with E138 and G140 mutations, can lead to high-level resistance to DTG and BIC. DTG should be given twice daily
N155H	EVG, RAL, DTG	High-level resistance: EVG, RAL Potential low-level resistance: DTG, BIC		
S230R	EVG, RAL, DTG	Low-level resistance: EVG, RAL, DTG Potential low-level resistance: BIC		DTG should be given twice daily
R263K	EVG, DTG, BIC	Intermediate resistance: EVG Low-level resistance: RAL, DTG, BIC		DTG should be given twice daily

Abbreviations: TDF = tenofovir disoproxil fumarate; TAF = tenofovir alafenamide; ABC = abacavir; d4T = stavudine; ddI = didanosine; 3TC = lamivudine; FTC = emtricitabine; AZT = zidovudine; TAM = thymidine analog mutation; EFV = efavirenz; NVP = nevirapine; RPV = rilpivirine; ETR = etravirine; DOR = doravirine; IDV = indinavir; FPV = fosamprenavir; LPV = lopinavir; DRV = darunavir; ATV = atazanavir; r = ritonavir; SQV = saquinavir; TPV = tipranavir; PI = protease inhibitor; NFV = nelfinavir; EVG = elvitegravir; RAL = raltegravir; DTG = dolutegravir; BIC = bictegravir

Common HIV Drug Resistance Mutations and Impact on Antiretroviral Susceptibility

Mutation	Agents leading to mutation selection	Reduced Susceptibility	Increased Susceptibility	Notes for use
Nucleoside reverse transcriptase inhibitors mutations				
K65R	TDF/TAF, ABC, d4T, ddI	High-level resistance: TDF/TAF. Intermediate resistance: ABC, 3TC, FTC	AZT	
K70E	TDF/TAF, ABC, d4T	Low-level resistance: TDF/TAF, ABC Potential low-level resistance: 3TC, FTC	AZT	
L74V	ABC, ddI	Intermediate resistance: ABC		
M184V/I	3TC, FTC	High-level resistance: 3TC and FTC Low-level resistance: ABC	TDF/TAF, AZT	Leads to reduced viral fitness; 3TC or FTC usually continued
Type 1 TAMs	AZT, d4T			Resistance to AZT increases with additional TAMs; Greater negative impact on TDF and ABC than Type 2 TAMs
M41L	AZT, d4T	Low-level resistance: AZT		
L210W	AZT, d4T	Low-level resistance: AZT		
T215Y	AZT, d4T	Intermediate resistance: AZT Potential low-level resistance: ABC, TDF		
Type 2 TAMs	AZT, d4T			Resistance increases with additional TAMs
D67N	AZT, d4T	Low-level resistance: AZT		
K70R	AZT, d4T	Intermediate resistance: AZT		
T215F	AZT, d4T	Intermediate resistance: AZT Potential low-level resistance: ABC, TDF		
K219Q/E	AZT, d4T	Potential low-level resistance: AZT		
Non-nucleoside reverse transcriptase inhibitor mutations				
L100I	EFV, RPV, ETR	High-level resistance: EFV, NVP, RPV Intermediate resistance: ETR		When K103N is present, leads to reduced DOR susceptibility
K101E	EFV, NVP, RPV, ETR	Intermediate resistance: EFV, RPV Low-level resistance: NVP, ETR, DOR		
K101P	EFV, NVP, RPV, ETR	High-level resistance: EFV, NVP, ETR, RPV		
K103N/S	EFV, NVP	High-level resistance: EFV, NVP		
Y181C	EFV, NVP, RPV	High-level resistance: NVP Intermediate resistance: EFV, ETR, RPV		
Y181I/V	NVP, ETR	High-level resistance: NVP, ETR, RPV Intermediate resistance: EFV		
Y188C/H	EFV, NVP	High-level resistance: NVP, EFV		

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