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REVIEW

HIV: how to manage heavily treatment-experienced patients

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Abstract

Although decreasing in prevalence, heavily treatment-experienced (HTE) persons with limited options for HIV treatment present unique complexities, even amongst experienced providers, as there is no single approach to successful management. HTE patients are described as those having two or less antiretroviral (ARV) classes available for use with limited fully active ARV agents within each class. A detailed understanding of the underlying processes that caused previous treatment failures, diagnostics to define resistance, resistance mechanisms and ARV pharmacology should all function in tandem to determine the next steps of clinical care. This narrative review provides an overview of the clinician approach to care, including diagnostics, approaches to regimen creation, relevant resources, and a broad array of both currently available and upcoming ARVs that may be used in regimens for HTE patients.

Keywords: antiretroviral therapy, HIV, HIV resistance, treatment experienced.

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Introduction

Treatment of HIV has made significant progress since the US Centers for Disease Control and Prevention first drew attention to the burgeoning AIDS epidemic in June 1981. Currently, many persons with HIV (PWH) can maintain virological suppression with regimens consisting of a single tablet taken once daily with minimal adverse effects. Despite these advancements, certain patient populations remain who require regimens of increased complexity due to viral resistance.

Although the definition of heavily treatment-experienced (HTE) patients is not standard, HTE patients can be described as having two or less antiretroviral (ARV) classes available for use with limited fully active ARV agents within each class. Given the potency, availability and tolerability of new generation ARVs, the prevalence of HTE PWH with limited treatment options has declined. Between January 2000 through December 2017, the Center for AIDS Research Network of Integrated Clinical Systems followed 27,133 PWH in care at their seven sites. Prior to the introduction of the integrase strand inhibitor (INSTI) class in 2007, prevalence of PWH with limited treatment options increased from 5.2% in the year 2000 to 7.5% in the year 2006. Prevalence of HTE patients then notably declined to 1.8% in 2007 after INSTIs were introduced and has since decreased to less than 1% in 2012; this rate remained so through 2017.[1]

HTE patients with limited treatment options can be complex to manage, even amongst experienced providers. A detailed understanding of the underlying processes that caused the treatment failure, diagnostics to define resistance, resistance mechanisms and ARV pharmacology should all function in tandem to determine the next steps in clinical management.

Approaches to a patient who is failing

Amongst patients with viral loads suggestive of treatment failure, an initial examination into adherence should be conducted. Barriers to ARV adherence may be multifactorial and may consist of a combination of medication-related adverse effects, issues related to medication procurement, pill burden, difficulty swallowing or overall treatment fatigue, amongst others.[2] If present, these factors should be addressed prior to treatment re-initiation.

Once adherence has been established and associated barriers resolved, treatment issues related to pharmacokinetics should be ruled out. Pharmacokinetics, generally subdivided into the absorptive, distributive, metabolic and eliminative properties of a medication may be pre-empted by drug–drug interactions. A direct example of prevented absorption exists between the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine or the protease inhibitor (PI)

atazanavir and acid-suppressing medications (e.g. proton pump inhibitors, H_2 receptor antagonists and other antacids) given their acid-dependent absorption. Additionally, INSTIs (e.g. bictegravir, cabotegravir, dolutegravir, elvitegravir and raltegravir) may exhibit chelation when co-administered with divalent or polyvalent cations. Medication interactions that reduce overall drug concentrations may be additionally attributed to the induction of the cytochrome P450 metabolic pathway. Although ARVs do not solely utilize this pathway for metabolism, many agents across the NNRTI, PI and INSTI classes are major substrates of cytochrome P450*3A4. Therefore, medications that significantly induce this pathway (e.g. carbamazepine and rifamycins) are generally contraindicated for coadministration with these ARVs given clinically significant reduction of ARV levels and risk for loss of virological control.[3] Clinician resources for drug–drug interactions can be found in Appendix B of the Department of Health and Human Services guidelines for the use of ARV agents in adults and adolescents living with HIV[3] as well as the HIV drug interaction database from the University of Liverpool.[4]

Resistance screening

Multiple types of resistance tests are available to the clinician, including circulating genotypes, phenotypes, proviral DNA screenings and tropism assessments. Circulating genotypes and phenotypes generally require an HIV viral load of over 200 copies to be completed; however, this is dependent on the laboratory utilized.

Genotypes screen for mutations on the three major HIV enzymes: reverse transcriptase, protease and integrase. Results from genotypes will generally report which medications will be active or inactive; however, whilst individual mutations may have individual effects on medication activity, combinations of mutations may be synergistic or negating, and knowledge of resistance mechanisms may be required to interpret complex results.[5,6] Available resources that may help clinicians can be found through the Stanford HIV Drug Resistance Database[7] or through resistance resources available through the International Antiviral Society – USA.[8]

Phenotypic resistance testing will report the concentration needed to inhibit 50% of viral growth. This screening may prove particularly useful when many mutations are present as these results will not only report if resistance is present but will also report the degree of resistance to individual agents. Given procedures needed to conduct HIV phenotyping, this test requires a longer time to result and is more expensive than a genotype. Ideally, resistance testing should be performed when a patient is either on the failing regimen or within 4 weeks of regimen discontinuation to maximize the expression of all resistance mutations present. If a patient has not taken their ARV regimen for more than 4 weeks, current guideline recommendations are to restart the failing regimen prior to resistance screening.[5]

Proviral DNA genotypic testing does not require circulating virus; therefore, it presents utility amongst patients that are unable to provide a full treatment history or who are currently virally suppressed. Despite the advantages of this testing, the sensitivity and predictive values of the proviral DNA genotypic screening have not been reliably established, and results should be interpreted with caution.[9]

Tropism screening is used to determine which coreceptor the virus uses during the viral entry process: whether CCR5 only, CXCR4 only or both. As maraviroc is a CCR5-coreceptor antagonist, it is only useful amongst viruses using CCR5 for viral entry alone. Maraviroc should not be initiated amongst patients who have not had a favourable tropism test.[10]

Choosing a new regimen

Regimen selection should incorporate a complete review of the patient's prior ARV history as well as all prior resistance results. The presence of a complete record of historical resistance testing is ideal, as all mutations may not result from currently circulating virus (archived mutations). Viruses containing these archived mutations may express and replicate and become dominant species if an ARV is initiated to which the virus has previously become resistant.[3]

In addition to resistance and medication history, the presence or likelihood of medication interactions should be considered, whether it be between two different ARVs (e.g. etravirine and dolutegravir) or between medications for other disease states and the selected ARV (e.g. phenytoin and dolutegravir). The presence of coinfection with hepatitis B virus may affect regimen selection, as tenofovir, emtricitabine and lamivudine all have activity against hepatitis B, even if they may not have activity against the patient's HIV; discontinuing these agents may lead to an acute hepatitis flare.[3]

The ultimate goal of ARV therapy is to create a regimen that will suppress a patient's virus to below the limit of detection. Should a patient be failing their current regimen, it is not recommended to add one fully active agent to the failing regimen, nor to place the patient on a 'treatment interruption'. Regimen selection goals should be to create a combination of ARVs with at least two known fully active agents based on resistance testing.[3] For example, one might use a cytosine analogue nucleoside reverse transcriptase inhibitor (NRTI) (e.g. lamivudine or emtricitabine) in the presence of an M184V mutation to reduce overall viral fitness and to increase the activity of other agents such as tenofovir. Neither lamivudine nor emtricitabine would be considered active in this example. An example of ARV use with partial activity would be darunavir in the presence of several darunavir-associated mutations, such as the I54L/M or the I84V (the presence of these mutations would warrant a dosing adjustment of the darunavir to 600 mg twice daily). Practitioners may use a resistance scoring system to assess ARV activity in which agents are assigned scores between 0 and 1. In the examples above, emtricitabine would have a

score of 0 in the presence of M184V and darunavir would have a score of 0.5 in the presence of the darunavir mutations.

Primary agents should be selected from the PI and INSTI classes if available.[11,12] If agents from both classes are fully active, this would be considered a fully active regimen.[13] If only one such class is fully active, other partially active agents may be used to complete the regimen.[3,14]

In cases where neither a fully active PI nor INSTI is available for use, other ARVs with novel mechanisms of action may be initiated. These ARVs may include older agents such as maraviroc or enfuvirtide, or newer agents such as ibalizumab or fostemsavir.[15–18] Regardless of the agent(s) used, the general goal is to complete a regimen to an overall activity score of 2. In the absence of previous resistance testing to guide activity assessments, the patient's medication history may guide treatment decisions as patterns of ARV use may suggest common resistance to those agents; caution and careful monitoring is recommended.[3]

In rare cases, or in resource-limited settings, a fully suppressive regimen is not possible with all available ARVs. In an example where only one remaining active agent may be available (including those with the novel mechanisms of actions described above), it is not recommended to add that agent to a failing regimen. Instead, the agent should be saved until another new fully active agent becomes available, either through FDA approval, clinical trial or compassionate use mechanism. Practitioners may keep the patient on a boosted PI and two NRTIs. In these rare cases, NNRTIs, INSTIs and enfuvirtide may be discontinued in the setting of this failing regimen as more resistance may develop and preclude future agents within those classes.[3]

Medications that may be implemented in regimens for HTE PWH

A summary of the medications described in this section can be found in Table 1.

Table 1. Summary of medications that may be implemented in regimens for heavily treatment-experienced patients with HIV.

Medication	Class	Mechanism of action	Key resistance mutations	Administration route	Trials of note
Tenofovir alafenamide (TAF)	Nucleotide reverse transcriptase inhibitor	Inhibits reverse transcription by incorporating into HIV DNA and causing chain termination	K65R	Oral	
Etravirine (ETR)	Non-nucleoside reverse transcriptase inhibitor	Inhibits reverse transcription by binding reverse transcriptase	L100I, K101P, V106A, E138A, V179F, Y181I/C/V, G190C, M230L	Oral	DUET 1 and 2
Doravirine (DOR)	Non-nucleoside reverse transcriptase inhibitor	Inhibits reverse transcription by binding reverse transcriptase	V106A, E138K, P225H F227C	Oral	DRIVE FORWARD; DRIVE AHEAD; ILLUMINATE
Darunavir/ritonavir (DRV/r)	Protease inhibitor	Prevents cleavage of proteins after transcription by binding protease	V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, L89V	Oral	POWER 1, 2, 3
Dolutegravir (DTG)	Integrase strand inhibitor	Prevents viral DNA from incorporating with host DNA by blocking integrase	G118R, Q148H/K/R, R263K	Oral	SAILING; VIKING-3
Fostemsavir (FTR)	Attachment inhibitor	Prevents HIV attachment to CD4 cells by binding to glycoprotein 120 on viral envelope	No commercially available resistance test	Oral	BRIGHTE

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Table 1. (*Continued*)

Medication	Class	Mechanism of action	Key resistance mutations	Administration route	Trials of note
Ibalizumab (IBA)	Post-attachment inhibitor	Monoclonal antibody; binds CD4 receptor after HIV attachment and prevents fusion	No commercially available resistance test	Intravenous	TMB-301
Enfuvurtide (T-20)	Fusion inhibitor	Prevents viral fusion by binding glycoprotein 41 on viral envelope	G36D/E/S, I37T/N/V, V38A/E/M, Q39R, Q40H, N42T, N43D/K/S	Subcutaneous	TORO 1 and 2
Maraviroc (MVC)	CCR5 coreceptor antagonist	Binds CCR5 coreceptor on CD4 cells and prevents viral entry	CXCR4 or dual tropic virus	Oral	MOTIVATE 1 and 2
Islatravir (ISL)[a]	Nucleoside reverse transcriptase translocation inhibitor	Inhibits translocation of viral RNA into DNA via multiple mechanisms	Data under development	Oral	Protocol 011; ILLUMINATE
Lenacapavir (LEN)[a]	Capsid inhibitor	Inhibits viral assembly, disassembly and transport through p24 protein binding	No commercially available resistance test	Subcutaneous/ oral	CALIBRATE; CAPELLA

[a]These medications have not yet been approved by the FDA. Information is subject to change.

Role of cytosine analogues

The cytosine analogue NRTIs include both emtricitabine (FTC) and lamivudine (3TC). Both FTC and 3TC select for the M184V mutation conferring complete resistance to these two ARVs. Although these agents are generally considered to have a low genetic barrier to resistance and this mutation is common amongst patients with resistance overall, FTC and 3TC do retain a role in the treatment of HTE regimens. Expression of an M184V mutation reduces viral fitness to a clinically significant degree and increases sensitivity to other agents within the class (e.g. tenofovir). Presence of the M184V mutation additionally delays the appearance of thymidine analogue mutations.[19,20]

Tenofovir alafenamide

Tenofovir alafenamide (TAF) is a prodrug of the nucleotide reverse transcriptase inhibitor tenofovir. Comparing TAF to its predecessor tenofovir disoproxil fumarate (TDF), TAF achieves approximately four-fold higher intracellular concentrations and lower serum levels, which may in turn provide a higher genetic barrier to resistance.[21] Additional advantages of TAF are lower rates of renal dysfunction and bone mineral density loss than TDF as assessed in clinical study[21]; however, in recent years, TAF has been associated with weight gain amongst PWH.[21,22]

TAF has not been directly studied in HTE patients; however, it is commercially available both independently and in multiple combination products and expresses favourable distributive pharmacokinetics.[21] Historically, the primary resistance mutation to tenofovir is the K65R mutation; TAF should generally be avoided when this mutation is present. Of note, the concurrent expression of both the M184V and the K65R mutations may return partial activity to tenofovir; thus, it may be used in combination with other active agents.[23] Amongst patients expressing thymidine analogue mutations, limited in vitro data have suggested partial activity of TAF, and it may be considered in cases where treatment options are heavily limited.[24]

Etravirine

Etravirine (ETR), a second-generation NNRTI, has only been studied for use amongst treatment-experienced patients. ETR activity and utility were established in the DUET 1 and 2 trials in which all patients received an optimized background regimen, darunavir boosted with ritonavir, and then either ETR or placebo. Patients who received ETR were twice as likely to achieve an undetectable HIV PCR. ETR has a high genetic barrier to resistance with more than one mutation required for failure. Although over 15 mutations are known to affect ETR activity, these do not all reduce ETR activity to the same extent. The ETR resistance scoring system was developed to grade these mutations and categorize their ability to reduce ETR activity; a combined score of 4 or higher denotes significantly decreased efficacy.[25,26]

Doravirine

The NNRTI doravirine (DOR) is both commercially available independently as well as in a combination product with TDF

and 3TC. Patients included in DOR approval trials (DRIVE FORWARD and DRIVE AHEAD) were either treatment naive or suppressed on a stable regimen with no history of treatment failure; these trials established non-inferiority to darunavir/ritonavir or efavirenz-based regimens amongst these patient populations.[27,28] Although no currently available data have established the utility of DOR amongst HTE patients, DOR presents a unique advantage amongst the class due to its novel resistance pathway. DOR retains activity against HIV strains expressing the K103N, Y181C and G190A reverse transcriptase mutations, which otherwise confer resistance to most other agents within the class. Amongst in vitro trials, DOR expressed higher inhibitory quotients than either efavirenz or rilpivirine to the 11 most common NNRTI mutations with the exception of the Y188L. Of note, viruses that have developed resistance to DOR via the V106A or F227C mutations did not show resistance to either efavirenz or rilpivirine. Only two significant mutation examples exist for cross resistance between DOR and other NNRTIs: the E138K mutation is selected amongst patients receiving rilpivirine, and the P225H mutation is selected amongst patients receiving efavirenz; both mutations additionally reduce susceptibility to DOR.[29,30] The upcoming ILLUMINATE HTE phase III clinical trial (NCT04233216) is currently studying treatment response in HTE patients receiving a DOR/islatravir fixed-dose combination tablet.[31]

Boosted darunavir

Boosted darunavir (DRV) has two approved dosing recommendations: either 800 mg daily amongst treatment-naive patients, or 600 mg twice daily in patients who are treatment experienced or have a DRV-associated mutation (V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V and L89V).[32] Boosted DRV, when compared to earlier agents within the PI class, has both a higher binding affinity for, and fits tighter within the active site, giving it a high genetic barrier to resistance.[31] Generally, when patients fail a DRV-containing regimen, primary resistance mutations do not readily develop; therefore, it is an attractive treatment option amongst HTE patients. The POWER 1, 2 and 3 trials studied patients with an elevated HIV viral load or at least one PI mutation and assigned an optimized background regimen plus either boosted DRV or an investigator-selected PI. Results from these trials demonstrated that patients who were given twice daily boosted DRV in combination with the optimized background regimen had double the rates of sustained virological suppression at 96 weeks.[33,34] Given both the resistance and efficacy profiles of DRV, it is generally a cornerstone of HTE patient regimens.

Dolutegravir

Building upon earlier data demonstrating the high efficacy and safety of the first INSTI raltegravir to treat HTE patients who had never received an INSTI, dolutegravir (DTG), a second-generation INSTI, too showed activity/efficacy amongst patients who had early treatment failure and were INSTI naive in the SAILING trial.[11,35,36] Currently, given the widespread use of the INSTI class, HTE patients are likely to both be INSTI experienced as well as to have INSTI-associated mutations. In the VIKING-3 trial, patients with at least one active medication were given DTG twice daily; 69% of patients achieved an undetectable HIV viral load at 24 weeks.[14] Despite this positive data, the VIKING trial group demonstrated reduced efficacy of DTG in the presence of the Q148H/K/N/R mutation alongside two other mutations. Given the high genetic barrier to resistance of DTG alongside demonstrated efficacy in the presence of other INSTI mutations, DTG should be considered an important agent in patients who are HTE and dosed accordingly; if the patient is either treatment naive or does not have INSTI-based mutations, DTG is dosed at 50 mg once daily. In patients who have INSTI-based mutations, DTG is dosed 50 mg twice daily.

Fostemsavir

The attachment inhibitor fostemsavir (FTR) has high utility for HTE patients given its unique mechanism of action. FTR is a prodrug that is converted into the active drug temsavir after hydrolysis. Temsavir binds to glycoprotein 120 (gp120) located on the HIV envelope, locking it into the closed position and thus preventing HIV attachment. The BRIGHTE trial was composed of two types of patients: those with one or two remaining active classes (although unable to construct a fully active regimen amongst remaining agents), and those with no remaining active classes; when FTR was added to an optimized background regimen, 60% of the former patient group and 37% of the latter were able to achieve an undetectable viral load at week 96. Several mutations on gp120 have been described in the medical literature causing resistance to fostemsavir; however, commercial gp120 resistance testing is not available.[18,37]

Ibalizumab

The CD4-directed post-attachment inhibitor ibalizumab-uiyk (IBA) is an IgG4 monoclonal antibody that non-competitively binds the CD4 receptor after HIV attachment, preventing viral fusion and entry. IBA's activity is coreceptor non-dependent; thus, it is active amongst viruses using either coreceptor CCR5 or CXCR4 trophic viruses. In addition to an optimized background regimen, IBA is uniquely administered as an intravenous infusion every 14 days.[38,39] Studied in the TMB-301 trial, IBA was given to adults who had multiple regimen failures, had resistance to at least one drug in three different classes, and had an elevated viral load. Patients were given IBA along with an optimized background regimen containing at least one fully active agent. Approximately half of the patients achieved an undetectable viral load after 24 weeks, which was then maintained up to 96 weeks in an expanded access protocol. Amongst patients who failed the IBA-containing regimen, evidence of reduced susceptibility to IBA was present, demonstrating that resistance to IBA can develop under selected circumstances.[17] As with FTR described earlier, there is

no commercially available resistance testing for IBA; resistance should be suspected if there is a clinical failure whilst receiving the drug.

Enfuvirtide

Enfuvirtide (T-20) binds to glycoprotein 41 and is considered the only HIV fusion inhibitor. The TORO 1 and 2 trials demonstrated significant reductions in viral loads amongst T-20 receiving patients combined with a resistance-guided ARV regimen compared to a resistance-guided ARV regimen alone. Despite T-20's efficacy and unique mechanism of action, this medication is not regularly used in clinical practice even amongst HTE patients as it requires a twice daily subcutaneous injection that the patient is required to reconstitute prior to administration. Administration of T-20 is well documented to cause irritation and subcutaneous nodules at the injection site.[16,40]

Maraviroc

Maraviroc (MVC) is the only CCR5 coreceptor antagonist able to prevent HIV viral entry. Notable for MVC use is the requirement of a viral tropism assay to determine if the virus uses CXCR4 or CCR5 coreceptors (or a combination of both) for entry. MVC can only be used with R5-tropic HIV. Amongst treatment-naive patients, approximately 80–90% of all circulating HIV is R5-tropic; however, amongst later stages of HIV infection after long-term exposure to ART, only 50% of HIV may be R5-tropic; the remaining 50% of the virus is either X4 or dual/mixed-tropic.[41] The MOTIVATE 1 and 2 trials enrolled patients who had previously received at least three different classes of ARVs and given an optimized background regimen plus either MVC or placebo. Patients in the maraviroc group had significantly greater reductions in viral loads, were more likely to achieve an undetectable viral load and had a greater increase in CD4 cells than patients in the placebo group.[15]

Islatravir

Islatravir (ISL) is an investigational nucleoside reverse transcriptase translocation inhibitor currently under development. Using this novel mechanism, ISL inhibits the translocation of viral RNA into DNA by blocking the nucleotide-binding site of the reverse transcriptase enzyme as well as changing the structure of viral DNA to prevent nucleotides from binding. Early data have suggested that these multiple mechanisms have conferred both high potency and a high genetic barrier to resistance.[42] ISL has not been directly studied in HTE patients; however, the efficacy of the medication has been established amongst treatment-naive patients. In the phase IIb study protocol 011, ISL was combined with DOR and 3TC as a complete regimen. After 24 weeks of treatment, patients receiving ISL with viral loads less than 50 copies/mL were switched to the two-drug regimen of ISL and DOR. These patients maintained virological suppression at 96 weeks.[43] Phase III trials, including the aforementioned ILLUMINATE HTE trial in combination with DOR, are presently ongoing.[31] Despite the lack of data thus far in HTE patients, it is proving a promising option based on its novel mechanism of action.

Lenacapavir

Lenacapavir (LEN) will prove to be the first HIV capsid inhibitor by inhibiting the p24 protein, thereby hindering both viral assembly and disassembly as well as preventing the transport of viral proteins and RNA across nuclear pores. LEN is supported thus far by two phase II/III clinical trials: CALIBRATE in treatment-naive patients and CAPELLA in HTE patients. In the randomized cohort of CAPELLA in which 36 patients received an optimized background regimen plus either oral or subcutaneous LEN, 81% achieved a viral load of less than 50 copies/mL at week 26 in a snapshot analysis.[44] Data from CAPELLA (including an additional non-randomized cohort) are ongoing.

Conclusion

The treatment and management of HTE patients can be challenging to even the most experienced providers and no single example will exactly resemble another. Providers must have a detailed understanding of the underlying processes that caused previous treatment failures, diagnostics to define the amount of resistance present, the resistance mechanisms and ARV pharmacology (including investigational drugs). Unless a practitioner is extremely comfortable with the management of HTE patients, it is not recommended to approach any problem alone, as multiple different solutions may equal similar results. In the case where practitioners may not have any additional local resources, external assistance can be obtained through the national clinician consultation centre ('HIV warmline') operated by the University of California San Francisco.[45] Additionally, despite the challenges that HTE patients present, medication development programmes using unique mechanisms of action remain strong and will aid in the greater goal of all patients with HIV able to achieve an undetectable viral load.

Key practice points

- Heavily treatment-experienced (HTE) patients with HIV are described as having two or less antiretroviral classes available for use with limited fully active agents within each class.
- Amongst HTE patients who are failing their regimen, barriers to adherence, pharmacokinetic barriers and drug interactions need to be addressed.

- When constructing a new regimen for an HTE patient, all genotypic, phenotypic and tropism testing must be reviewed as all resistance is cumulative, even if archived.
- One active medication should not be added to a failing regimen. Ideally, a regimen should incorporate at least two fully active medications.
- New and novel classes under development (attachment/post-attachment inhibitor, capsid inhibitor, nucleoside reverse transcriptase translocation inhibitor) can be used to construct a complete regimen for HTE patients.

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