Heavily Treatment-Experienced Patients with HIV

Summary

- Heavily treatment-experienced (HTE) patients with HIV are a subset of the overall HIV population who possess limited remaining antiretroviral therapy (ART) options due to resistance, intolerance, and potential interactions with concomitant medications.[1]
- Due to advances in ART, multidrug resistance has been declining.[2-6]
- The prevalence of HTE, assessed by observational cohorts using varying definitions, ranged from 1.9% to 10.4%.[1,7-9]
- The goal of treatment is to establish virologic suppression.[10] When designing a regimen for patients with virologic failure, at least 2 (but preferably 3) fully active antiretrovirals (ARVs) should be included.
- Evidence of viral evolution and resistance mutations, a loss of future treatment options, and disease progression are some of the consequences of HTE patients failing current therapy.[10]

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OVERVIEW OF HTE PATIENTS

Steady improvement in ART for the treatment of HIV has dramatically reduced the rates of morbidity and mortality and has transformed HIV into a manageable chronic condition for most patients who remain adherent to therapy.[2,10] Though undiagnosed infections and a failure to link/retain patients in care have kept rates of maximal viral suppression low (51% in U.S. in 2016), regimens currently recommended for initial therapy have a high likelihood of achieving and maintaining virologic suppression below the limits of detection.[10] Despite the success of modern ART, treatment failure still occurs, and those with persistent viral loads ≥ 200 copies/mL (and particularly when ≥ 500 copies/mL) may develop drug-resistance mutations to one or more components of their regimen.

HTE patients have been described as a subset of persons with HIV (PWH) who possess limited remaining ART options due to resistance, intolerance, and potential interactions with concomitant medications, though no definition has been standardized.[1] The HTE population is complex given the many possible contributors to virologic failure and loss of treatment options.[10] Potential causes of virologic failure in the HTE population can include the following:

- Patient-related factors: adherence challenges, poor access to care, adverse drug effects, pill burden, cost, psychosocial factors.
- HIV-related factors: higher pre-treatment viral load, transmitted or acquired drug-resistance, prior treatment failure, innate resistance.
- ART-related factors: Suboptimal virologic potency or pharmacokinetics, low genetic barrier to resistance, prior exposure to suboptimal regimens, drug-drug interactions.

EPIDEMIOLOGY OF HTE PATIENTS

Prevalence of Multidrug Resistance

Several studies have evaluated resistance trends among HIV patients and their results generally indicate the prevalence of multidrug resistance to be declining over the last two decades.[2-6]

A recent study that utilized a large US laboratory database found that dual- and triple-class antiretroviral (ARV) drug resistance declined over a 12-year period from 2006-2017.[2] This trend was marked by sharp declines in nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) resistance between 2006 and 2012 and declining non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance from 2012 to 2017. The prevalence of resistance to only a single class increased over the same 12-year period. Likewise, another US database study found decreased prevalence of 3-class resistance and increased prevalence of 1-class resistance between 2003 and 2012.[3] The downward trend for 3-class resistance was consistent since 2007, suggesting a correlation to greater susceptibility to PI and NRTI classes.

A retrospective study in Europe found ≥ 1 resistance mutation in 71% of individuals in 2008 (compared to 81% in 1997).[5] Resistance to 3 classes peaked to 4.5% in 2005 and decreased thereafter. The proportion of cases exhausting available treatment options decreased from 32% in 2000 to 1% in 2008. A systematic literature review (primarily US and Western European articles) found a modest decrease in the prevalence of 3-class resistance (NRTI+NNRTI+PI), with the lowest rates from 8.3% in 2009 to 6.7% in 2014.[11] The prevalence of 4-class resistance (NRTI+NNRTI+PI+INSTI) since 2009 was about 2%, with lower rates occurring in more recent years.

A recent analysis from a large US database also observed decreasing prevalence of multi-class resistance, including for resistance to 4 classes.[6]

Factors that are likely contributing to the overall decline in multidrug resistance include the availability of new or novel agents with a high barrier to resistance, improved ARV tolerability, once daily, fixed-dose combination regimens that promote adherence, improved ART sequencing, and earlier genotype testing.[2,11] Increased rates of virologic suppression have also confounded estimates of resistance, as standard HIV genotype requires levels ≥ 500 copies/mL and the utility of obtaining archived resistance data through proviral DNA genotyping is not yet established.[12]

Prevalence of HTE Population

The population of HTE patients has evolved in the modern ART era with the introduction of more potent treatment options, though prevalence data is still limited.[7] The following observational cohorts have estimated the prevalence of the HTE population using a variety of definitions.

Hsu et al[8]

This was an analysis of data from the OPERA Observational Database that utilized prospective electronic medical data at 79 locations across 15 US states. HTE was defined using 3 proposed definitions and assessed on December 31, 2016.

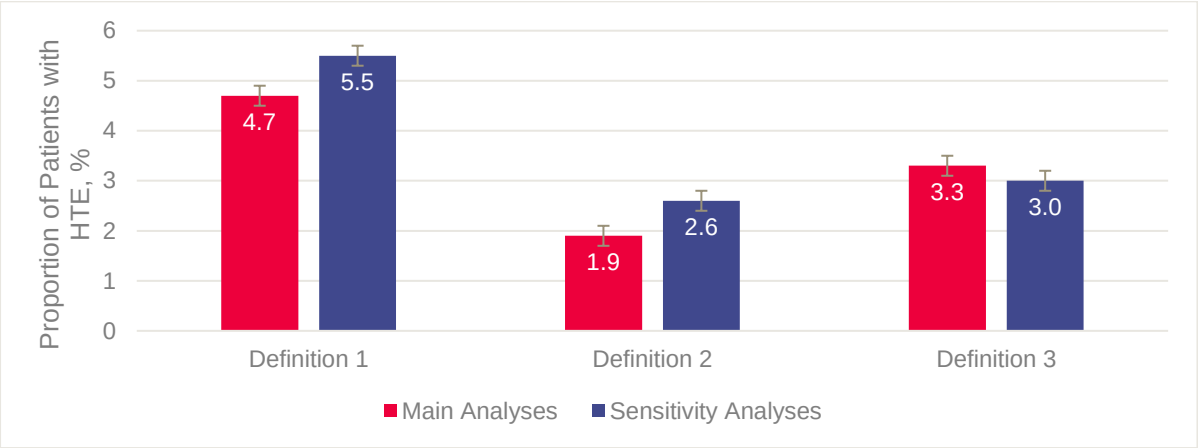
Table 1. Proposed Definitions of HTE and Number of OPERA Patients Who Met Definition

Definition Label	Description	Met Definition (N = 41,939)
1: 4th Line	Currently on 4th line of ART (any switch in core agent or non-NRTI)	1972
2: ≥ 3 Core classes	Exposed to ≥ 3 core agent classes (NNRTI, PI, INSTI) prior to current regimen	784
3: Regimen Indicative of HTE	Current regimen includes either DTG twice daily, DRV twice daily, ETR + DTG, INSTI + PI, MVC, or ENF	1401

ART = antiretroviral therapy; DRV = darunavir; DTG = dolutegravir; ENF = enfuvirtide; ETR = etravirine; HTE = heavily treatment-experienced; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

Prevalence was the greatest with Definition 1 at 4.7% (95% CI 4.5 – 4.9) and overlap of patients captured by all 3 definitions was minimal (n = 10). A total of 3908 (9.3%) were captured by at least one definition. History of AIDS-defining illness and time since ART initiation were greatest for Definition 2. The markedly less time since ART initiation for Definition 3 suggested more rapid progression or missing ART history. Half of all patients started an HTE regimen virologically suppressed or without a viral load test performed, suggesting a switch in regimen other than suspected failure.

Figure 1. Prevalence of HTE among OPERA HIV Patients in Care, December 2016



Sensitivity analysis: Excluded patients with missing ART histories (n = 20,583).

The authors concluded that Definition 1 appeared too narrow in focus and expanding to 4th line or later was too inclusive, resulting in a prevalence of > 11%. Unlike Definition 1, Definition 2 captures patients at different points on their treatment history, with patients most frequently on their 10th line of therapy or greater. Combining Definition 2 and 3 (5.1% prevalence) may be the best definition for HTE as patients with and without extensive histories would be captured. Given that regimen changes for virologically suppressed patients is now typical practice, an HTE definition that incorporates virologic failure should be evaluated.

Henegar et al[1]

Using a composite definition from real-world claims data in the US (129,208 patients included in analysis), HTE patients were estimated to represent approximately 6% of the overall HIV population.

Table 2. Prevalence of HTE among Claims Data According to Definition

Definition	Prevalence (95% CI)	n
1. Regimen indicative of HTE[a]	3.7% (3.6%–3.8%)	4757
2. Multiple Treatment Switches (A, B, or C)	8.5% (8.3%–8.6%)	10,964
2A. ≥ 4 different core agents	8.3% (8.1%–8.4%)	10,684
2B. ≥ 10 different ART agents	0.9% (0.9%–1.0%)	1184
2C. ≥ 4 different core agent classes	3.0% (2.9%–3.1%)	3877
3. Treatment switches following resistance tests[b]	6.0% (5.8%–6.1%)	7703

[a] Took any of following on 12/31/2017: dolutegravir twice daily, darunavir twice daily, enfuvirtide, etravirine + maraviroc, ≥ 2 core agents + any other ARV; [b] Resistance test followed by core agent switch within 90 days, at least twice prior to 12/31/2017.
ART= antiretroviral therapy; ARV = antiretroviral; HTE = heavily treatment experienced.

14.6% of individuals met at least one candidate definition of HTE, and comorbidities and concomitant medications were common for all definitions. Nearly all patients included in Definition 2 had experienced ≥ 4 separate core agents. The authors concluded that Definitions 2A and 2B includes too many virologically suppressed patients, and Definition C overestimates true switches due to resistance. Minimal overlap suggests use of a composite definition that considers both current and past treatment, and Definition 1 and Definition 2C are most likely to correctly classify a patient as HTE, though some patients may be missed.

Pelchen-Matthews et al[9]

Prevalence of HTE in the EuroSIDA study (a European cohort that has followed > 22,000 HIV-1 patients) was estimated between 2010 and 2016. A composite definition for HTE included everyone with genotypic resistance results available and was known to have resistance to NRTIs, NNRTIs and PIs, or else those who fulfilled criteria of at least 2 of 3 specific definitions related to class availability or specific agents used. Of 15,570 eligible individuals, 10.4% were HTE and overall prevalence increased

by 0.5% per year. Compared to those not HTE, a larger proportion of HTE patients had CD4+ T-cell counts ≤ 200 cells/μL. HTE individuals were at a higher risk of developing AIDS and non-AIDS events, which was mostly explained by their older age, greater pre-existing comorbidities, and lower CD4 counts.

Bajema et al[7]

Trends in HTE prevalence among ART experienced PWH were examined from 2000 to 2017 in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), a US cohort of > 27,133 PWH. Genotypic resistance predictors were then determined. HTE was defined as ≤ 2 available classes, each with ≤ 2 active drugs for NRTIs, NNRTIs, or PIs, or ≤ 1 active drug for integrase strand-transfer inhibitors (INSTIs). Prevalence of HTE was 5.2%–7.5% from 2000–2006, after which it declined significantly to 1.8% in 2007 with the addition of the INSTI class. Prevalence remained < 1% after 2012. Lower baseline CD4 nadir and higher baseline viral load were significantly associated with a risk of becoming HTE. Neither switching due to virologic failure nor the number of ARVs received accurately identified HTE patients. HTE PWH were resistant to 3 times the number of ARVs compared to PWH who were not HTE.

TREATMENT APPROACH FOR HTE PATIENTS

According to the DHHS Guidelines, assessing and managing a patient who is experiencing treatment failure (including for HTE patients) is complex and expert advice should be sought.[10] Evaluating treatment failure should include assessments of adherence, drug-drug interactions, tolerability, viral load, CD4+ T-cell count, ART history, and resistance test results. Resistance testing should occur while the patient is taking the failing regimen or within 4 weeks of discontinuation to ensure comprehensive detection of mutations.

The treatment approach for HTE patients has more recently shifted from the sole management of virologic failure towards greater focus on the optimization of ART to improve tolerability and avoid drug-drug interactions.[13] Upon reaching virologic suppression, the identification of non-AIDS complications and comorbidities that may require modification to ART regimens are also important criteria. Still, the primary goal of treatment for ART-experienced patients with drug resistance and virologic failure is to establish virologic suppression below the limits of detection.[10] When designing a new ART regimen for patients with virologic failure, at least 2 (but preferably 3) fully active ARVs should be included, based upon prior treatment history, resistance testing, and mechanisms of action. If maximal virologic suppression is not possible, regimens should be designed to minimize toxicity, preserve CD4 counts, and delay clinical progression. Cohort studies have found that even modest reductions in HIV RNA levels can translate into meaningful clinical benefits, although with a risk of further resistance.[14,15]

See the full Management of the Treatment-Experienced Patient section from the DHHS Guidelines.[10]

IMPACT OF HTE PATIENTS FAILING CURRENT THERAPY

Persistent HIV RNA levels ≥ 200 copies/mL can be associated with evidence of viral evolution and a loss of treatment options due to accumulation of drug-resistance mutations.[10] Likewise, disease progression can occur when patients are unable to become virologically suppressed. CD4 count decline is a well-documented predictor of disease progression, with CD4 < 200 cells/μL increasing the risk for opportunistic infections. Higher healthcare expenditures are also linked to lower CD4 counts.[16,17] HTE patients may also be on regimens in which maximal suppression is not being reached, and recent data indicates both high-level viremia (viral loads 200–1000 copies/mL) and low-level viremia (50–199 copies/mL) to be associated with an increased risk of virologic failure.[18]

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