Identifying Heavily Treatment-Experienced Patients in the OPERA Cohort

Ricky Hsu[1,2], Cassidy Henegar[3], Jennifer Fusco[4], Vani Vannappagari[3], Cyril Llamoso[5], Philip Lackey[6], Gerald Pierone[7], and Gregory Fusco[4]

[1]AIDS Healthcare Foundation, New York, NY; [2]NYU Langone Health Center, New York, NY; [3]ViiV Healthcare, Research Triangle Park, NC; [4]Epividian, Inc., Durham, NC; [5]ViiV Healthcare, Branford, CT; [6]Carolinas Healthcare System, Charlotte, NC; [7]Whole Family Health Center, Fort Pierce, FL

Contact Information:
Jennifer Fusco
4505 Emperor Blvd, Suite 220, Durham, NC 27703
P: 224-632-1863 Email: jennifer.fusco@epividian.com

OPERA® The Longitudinal Cohort

BACKGROUND

- Ineffective ART combinations, patient non-compliance to treatment regimens, and drug intolerance can lead to decreased efficacy of multiple classes of ART
- Heavily treatment-experienced patients (HTE) can be challenging to treat effectively and often require highly-tailored ART regimens
- Investigation of the prevalence and characteristics of HTE patients is needed to support and guide development of new therapies for this unique and under-served population

OBJECTIVE:

To assess the prevalence and describe the baseline demographics and clinical characteristics of HTE patients in a real-world setting

METHODS

Study Population & Statistical Analyses

- Observational clinical cohort study utilizing prospectively collected electronic medical record (EMR) data from the OPERA® Observational Database, following patients at 79 locations across 15 US states
- Inclusion criteria: HIV-1 positive patients ≥18 years of age and active in care (defined as a ≥1 clinic visit or telephone contact in the previous 12 months) on 31 Dec 2016
- HTE was defined using three definitions of interest (Table 1)

Table 1. Proposed Definitions of HTE Patients Using Real World Data in the Absence of Resistance Testing

DEFINITION	LABEL	DESCRIPTION
1	4th line	Currently on 4th line of ART (line defined as any switch in core agent, any non-NRTI ARV medication)
2	≥3 Core Classes	Exposed to ≥3 core agent classes (NNRTI, PI, INSTI, etc.) prior to current regimen
3	Regimen indicative of HTE	Current regimen includes either (i) dolutegravir (DTG), twice daily, (ii) darunavir (DRV), twice daily, (iii) etravirine (ETR) + DTG, (iv) integrase strand transfer inhibitor (INSTI) + protease inhibitor (PI), (v) maraviroc (MVC), or (vi) enfuvirtide (ENF)

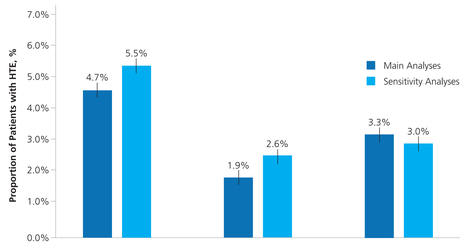
- Point prevalence estimates with 95% confidence intervals were calculated as the number of patients meeting the criteria for HTE out of all adult patients active in care as of 31 Dec 2016
- Patient demographic and clinical characteristics were described for each definition
- A sensitivity analysis was performed restricting the population to patients who initiated ART in OPERA or who were experienced and had historical data on ART use (excluding patients with missing ART history); to evaluate the impact of missing data on our conclusions

RESULTS

Patients Meeting HTE Definitions

- At the time of analysis, there were 80,626 HIV-infected patients in the OPERA database, nearly all of whom were infected with HIV-1 exclusively (n=80,546; 99.9%)
- A total of 41,939 adult patients were identified as active in care on 31 Dec 2016
- Main analysis: Prevalence was greater with Definition 1 [4.7% (95% CI: 4.5, 4.9)] than Definition 2 [1.9% (95% CI: 1.7, 2.0)] or Definition 3 [3.3% (95% CI: 3.2, 3.5)] [Figure 1]
- Sensitivity analysis: In analyses excluding patients with missing ART histories (n=20,583), prevalence for each definition was similar to the original estimates [Def 1: 5.5% (95% CI: 5.2, 5.8), Def 2: 2.6% (95% CI: 2.3, 2.8), and Def 3: 3.0% (95% CI: 2.8, 3.2)] [Figure 1]

Figure 1. Prevalence[1] of HTE among OPERA HIV Patients in Care[2] on 31 Dec 2016

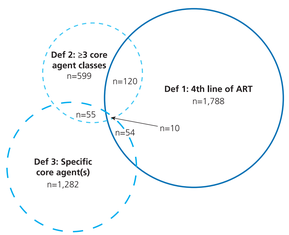


[1]Dark blue bars represent main results (n=41,939); light blue bars represent results from sensitivity analyses (n=20,583) restricted to patients initiating ART in OPERA or with historical data on ART. Error bars represent 95% confidence intervals for prevalence estimates
[2]In care defined as a ≥1 clinic visit or telephone contact in the previous 12 months

- Overlap of patients captured as HTE by definitions 1, 2, and 3 was minimal.
- A total of 3,908 (9.3%) OPERA patients were captured by at least one definition for HTE; 239 (0.6%) patients were included in more than one definition and 10 (0.02%) patients met the criteria for all three definitions [Figure 2]

Figure 2. Overlap of HTE Patients Identified by Definitions 1, 2, and 3

3,908 (9.3%) individual patients met at least one definition of HTE
1,972 met definition 1
784 met definition 2
1,401 met definition 3



Patient Characteristics at Baseline [Table 2]

- The patients defined by these definitions were similar in age and sex but differed by race, ethnicity, route of infection, and region of care
- History of AIDS-defining illness and time since ART initiation were greatest for the patients in Definition 2 with far more initiating therapy more than 10 years ago and experiencing AIDS
- Patients in Definition 3 had far less time since ART initiation, suggesting more rapid progression or missing ART history due to falling out of care or changing care providers
- Half of all patients started HTE regimen virologically suppressed or without a viral load test being done; suggesting their provider is switching due to reasons other than suspected failure

Table 2. Baseline[1] Demographic and Clinical Characteristics of Various HTE Definitions

	Definition 1: On 4th line of ART[2] N=1,972	Definition 2: ≥3 core agent classes[3] N=784	Definition 3: Regimens indicative of HTE[4] N=1,401
Demographics			
Age, median years (IQR)[5]	48.9 (41.8, 55.1)	50.9 (44.8, 57.2)	48.3 (39.5, 54.5)
Female, n (%)	351 (17.8%)	139 (17.7%)	258 (18.4%)
African American, n (%)	666 (33.8%)	256 (32.7%)	655 (46.8%)
Hispanic, n (%)	578 (29.3%)	259 (33.0%)	298 (21.3%)
MSM[6], n (%)	1015 (51.5%)	468 (59.7%)	574 (41.0%)
Region, n (%)			
Northeast	215 (10.9%)	17 (2.2%)	167 (11.9%)
South	781 (39.6%)	295 (37.6%)	782 (55.8%)
Midwest	12 (0.6%)	2 (0.3%)	34 (2.4%)
West	964 (48.9%)	470 (59.9%)	418 (29.8%)
Clinical Characteristics			
History of AIDS-defining Illness[7], n (%)	552 (28.0%)	380 (48.5%)	308 (22.0%)
VACS Score (median, IQR)[8]	18.0 (10.0, 28.0)	22.0 (12.0, 35.0)	22.0 (12.0, 34.0)
History of syphilis	719 (36.5%)	281 (35.8%)	381 (27.2%)
Median months (IQR) from ART initiation	88.0 (52.8, 136.0)	141.6 (89.9, 206.1)	31.7 (9.8, 70.5)
Year of ART initiation, n (%)			
<2000	162 (8.2%)	205 (26.1%)	64 (4.6%)
2000-2006	433 (22.0%)	244 (31.1%)	127 (9.1%)
2007-2011	777 (39.4%)	243 (31.0%)	226 (16.1%)
2012-2016	600 (30.4%)	92 (11.7%)	984 (70.2%)
Viral Load at start of current regimen[9] n, (%)			
<50 copies/mL	1130 (57.3%)	360 (45.9%)	434 (31.0%)
≥50 to <200 copies/mL	170 (8.6%)	94 (12.0%)	102 (7.3%)
≥200 to <1,000 copies/mL	91 (4.6%)	38 (4.8%)	98 (7.0%)
≥1,000 to <10,000 copies/mL	104 (5.3%)	64 (8.2%)	112 (8.0%)
≥10,000 to <100,000 copies/mL	161 (8.2%)	119 (15.2%)	212 (15.1%)
≥100,000 copies/mL	70 (3.5%)	60 (7.7%)	135 (9.6%)
Missing	246 (12.5%)	49 (6.3%)	308 (22.0%)

[1]Baseline characteristics evaluated on 31 Dec 2016
[2]Definition 1: On 4th line of ART; a change in core agent = a change in line of therapy
[3]Definition 2: ≥3 core agent classes; started and discontinued core agents from at least three separate ART classes including PI, NNRTI, INSTI, AI, or FI
[4]Definition 3: Regimens indicative of HTE; DTG twice daily, DRV twice daily, ETR + DTG, INSTI + PI, MVC, or ENF
[5]IQR=Interquartile range
[6]MSM=Men who have sex with men
[7]AIDS-defining illness at or prior to 31 Dec 2016
[8]VACS Mortality Index = A score to estimate risk of 5-year all-cause mortality; by summing pre-assigned points for age, HIV disease, and general indicators of organ system injury including hemoglobin, platelets, transaminases, creatinine, and viral hepatitis C infection. A higher score is associated with a higher risk of mortality
[9]Viral load measured at start date of regimen taken as of 31 Dec 2016; viral load measured within 120 days of regimen start

Follow-Up of HTE Regimens by Definition [Table 3]

- Despite considerable ART exposure, a substantial number of HTE patients were able to remain on their regimen for at least 20 months and achieve or remain virologically suppressed

Table 3. Durability and Response to Regimens by Various HTE Definitions

	Definition 1: On 4th line of ART[1] N=1,972	Definition 2: ≥3 core agent classes[2] N=784	Definition 3: Regimens indicative of HTE[3] N=1,401
Regimen Durability			
Duration, median months (IQR)	20.2 (12.0, 35.0)	19.0 (11.0, 30.8)	21.3 (12.3, 42.1)
Still on regimen at study end[4]	1476 (74.8%)	521 (66.5%)	1000 (71.45)
Discontinued regimen	441 (22.4%)	241 (30.7%)	322 (23.0%)
Lost to follow-up	47 (2.4%)	16 (2.0%)	75 (5.3%)
Died	8 (0.4%)	6 (0.8%)	4 (0.3%)
Virologic Suppression			
Ever suppressed (VL<50 cpm) on regimen	1483 (75.2)	506 (64.5)	912 (65.1)

[1]Definition 1: On 4th line of ART; a change in core agent = a change in line of therapy
[2]Definition 2: ≥3 core agent classes; started and discontinued core agents from at least three separate ART classes including PI, NNRTI, INSTI, AI, or FI
[3]Definition 3: ART regimen of interest; patients taking any of the following: DTG twice daily, DRV twice daily, ETR + DTG, INSTI + PI, MVC, or ENF
[4]Study end = 31 Aug 2017

DISCUSSION

- Definition 1 (4th line of ART only) appeared too narrow in focus as many patients initiated this regimen suppressed. Expanding this definition to 4th line or later, was too inclusive resulting in a prevalence >11%; capturing many patients still relatively early in their treatment experience with several treatment options remaining.
- Definition 2 requires that a patient has started and discontinued core agents from 3 or more classes. Unlike definition 1, definition 2 captures patients at variable places in their treatment histories; it may take more than four line-changes before the patient has experienced exposure to 3 or more core ART classes. Patients identified by Definition 2 were most frequently on their 10th line of therapy or greater.
- Definition 3 is based on the current regimen only being indicative of HTE. While EHR data allows for evaluation of treatment history to a greater extent than some other data sources, patient reported medication history may not be accurate or complete prior to prospective follow up.
- Definition 2 and 3 together may be the best definition for HTE (5.1% prevalence) as the combination captures both patients with extensive histories and those lacking complete ART histories.
- As more patients who are virologically suppressed change regimens for a variety of reasons beyond intolerance such as convenience, cost, or drug interactions; it may be important to evaluate a definition of HTE incorporating virologic failure. This is an area for future research.
- This analysis provides a first look at this complex patient population and a beginning for describing appropriate criteria, in the absence of resistance data, for identifying HTE patients in observational settings.

KEY FINDINGS

Three proposed definitions for identifying HTE patients in an observational database resulted in a prevalence of 1.9-4.7% among patients who were active in care. Minimal overlap of patients identified as HTE by these criteria suggests multiple definitions may be required to fully capture this complex and varied population who are in need of new therapeutic approaches.

ACKNOWLEDGMENTS

This research would not be possible without the generosity of the OPERA HIV caregivers and their patients. Additionally, we are grateful for the following individuals: Robin Beckerman (SAS programming), Jeff Briney (QA), Ted Ising (Database Arch & Mgmt), Bernie Stooks (Database Mgmt), Judy Johnson (Med Terminology Classification), Rodney Mood (Site Support & Data Analyst)

SPONSORSHIP

This research was funded by ViiV Healthcare

ViiV Healthcare

Epividian®