

Virologic Outcomes Among People Living With Human Immunodeficiency Virus With High Pretherapy Viral Load Burden Initiating on Common Core Agents

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Background. People living with human immunodeficiency virus (PLWH) initiating antiretroviral therapy (ART) with viral loads (VLs) $\geq 100\,000$ copies/mL are less likely to achieve virologic success, but few studies have characterized real-world treatment outcomes.

Methods. ART-naive PLWH with VLs $\geq 100\,000$ copies/mL initiating dolutegravir (DTG), elvitegravir (EVG), raltegravir (RAL), or darunavir (DRV) between 12 August 2013 and 31 July 2017 were identified from the OPERA database. Virologic failure was defined as (i) 2 consecutive VLs ≥ 200 copies/mL after 36 weeks of ART; (ii) 1 VL ≥ 200 copies/mL with core agent discontinuation after 36 weeks; (iii) 2 consecutive VLs ≥ 200 copies/mL after suppression (≤ 50 copies/mL) before 36 weeks; or (iv) 1 VL ≥ 200 copies/mL with discontinuation after suppression before 36 weeks. Cox modeling estimated the association between regimen and virologic failure.

Results. There were 2038 ART-naive patients with high VL who initiated DTG (36%), EVG (46%), DRV (16%), or RAL (2%). Median follow-up was 18.1 (interquartile range, 12.4–28.9) months. EVG and DTG initiators were similar at baseline, but RAL initiators were older and more likely to be female with low CD4 cell counts while DRV initiators differed notably on factors associated with treatment failure. Virologic failure was experienced by 9.2% DTG, 13.2% EVG, 18.4% RAL, and 18.8% DRV initiators. Compared to DTG, the adjusted hazard ratio (95% confidence interval) was 1.46 (1.05–2.03) for EVG, 2.24 (1.50–3.34) for DRV, and 4.13 (1.85–9.24) for RAL.

Conclusions. ART-naive PLWH with high VLs initiating on DTG were significantly less likely to experience virologic failure compared to EVG, RAL, and DRV initiators.

Keywords. antiretroviral therapy; high viral load; HIV; treatment naive; virologic failure.

Baseline viral load (VL) in antiretroviral therapy (ART)-naive people living with human immunodeficiency virus (PLWH) is an important prognostic and, as such, a key component in the choice of an initial ART regimen [1]. Accordingly, most studies characterize, and adjust for, baseline human immunodeficiency virus (HIV) VL using either continuous or categorical measures. However, few studies stratify results on such measures, and even fewer focus exclusively on populations with a high baseline VL.

The proportion of ART-naive PLWH presenting with a high baseline VL varies based on the study country, time frame, design, and population, with reports ranging from 16% in a subset of HIV-specific clinics in Vietnam in 2013 to 76% among late presenters in midwestern Brazil between 2009 and 2012 [2–11]. Similar variation is observed in US-based studies (19%–44%) [8, 9, 11]. While the majority of studies use a threshold of 100 000 copies/mL to define “high VL,” others have used a higher threshold, $>500\,000$ copies/mL [12–14].

Viral load is relatively stable during asymptomatic infection, fluctuating around a set-point, likely heritable (ie, viral genetic factors may influence the VL set-point), although the magnitude of heritability is still the subject of some debate [15–17]. Other factors that can impact VL set-point include infection with human leukocyte antigen (HLA) class I alleles, HIV-1 subtype, infection with multiple HIV type 1 (HIV-1) subtypes, and individual immune response. A higher VL set-point is positively correlated with infectiousness, with a decreased likelihood of achieving viral suppression on ART, longer times to suppression, and increased risk of viral rebound and disease

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progression [2, 13, 16–20]. Some researchers have suggested that VL set-points have been increasing during the course of the epidemic, either as a result of changes in behavior, changes in the characteristics of individuals at risk for infection, or an adaptive evolution of the virulence of the HIV-1 virus [15, 16, 21, 22].

Late presentation of PLWH for care, either due to late diagnosis or delayed ART initiation in PLWH who were previously diagnosed, has also been associated with higher VL burden, in part because its late presentation is defined based on low CD4 cell counts, which are frequently inversely correlated with VL [23]. Globally, a large percentage of PLWH still present late and experience a delay in initiating treatment, in countries of varying income levels [6, 24–27], despite its association with higher levels of morbidity, mortality, and HIV transmission [2, 13, 16–20, 28]. Nonetheless, not all late presenters have a high VL burden, nor are all PLWH with high pretherapy VL late presenters.

To date, few real-world studies have examined the efficacy of first-line ART in PLWH who present with a high VL [3, 12]. In a recent meta-analysis, authors concluded that the probability of viral suppression among ART-naive PLWH with high baseline VL was higher among those initiating a dolutegravir (DTG)-containing regimen (vs non-DTG), but the study was based solely on data from clinical trials with observation limited to 48 weeks [29]. Accordingly, we assessed the effectiveness of 4 commonly used core agents (DTG, elvitegravir [EVG], raltegravir [RAL], and darunavir [DRV]) on the risk of virologic failure in ART-naive patients initiating therapy with a high VL burden ($\geq 100\,000$ copies/mL).

METHODS

Study Design and Population

This observational analysis of a US clinical cohort utilized prospectively captured electronic health record data obtained from the Observational Pharmaco-Epidemiology Research and Analysis (OPERA) database to both describe the demographic and clinical characteristics of ART-naive PLWH, initiating ART with 1 of 4 commonly prescribed core agents for ART and a high, pretherapy, VL ($>100\,000$ copies/mL) as well as to assess virologic outcomes among patients initiating on those core agents. The OPERA database includes data from 85 clinics across 54 cities in the United States. The $\geq 90\,000$ PLWH in the OPERA database through 2018 represented approximately 7% of the HIV patients diagnosed and linked to care in the US (Supplementary Figure 1).

The OPERA database, refreshed from each clinic's individual electronic health record daily, complies with all Health Insurance Portability and Accountability Act of 1996 (HIPAA) and Health Information Technology for Economic and Clinical Health (HITECH) requirements, which expand upon the

ethical principles detailed in the 1964 Declaration of Helsinki. The OPERA database receives annual institutional review board (IRB) approval by Advarra IRB including a waiver of informed consent and authorization for use of protected health information. Proprietary algorithms are used to sort, classify, and aggregate the data pulled from each system. The process includes automated classification of clinical terms with review by trained medical staff. The patient health data gathered, classified, and aggregated include medical and social history, visit dates, vital signs, laboratory orders and results, medications, problems and diagnoses, and procedures.

Patients were included in the study sample if they met all of the following criteria: (i) had a diagnosis of HIV-1 as evidence of a positive HIV-1 Western blot, enzyme-linked immunosorbent assay (ELISA), or VL test; (ii) initiated ART for the first time with a DTG-, EVG-, RAL-, or DRV-based treatment regimen between 12 August 2013 and 31 July 2017; and (iii) had a baseline VL $\geq 100\,000$ copies/mL. Patients with a diagnosis of HIV type 2 (HIV-2) (a positive HIV-1/HIV-2 Multispot, HIV-2-specific ELISA or Western blot, or detectable HIV-2 VL test) were excluded from the study. Figure 1 details sample selection. Observation began upon initiation of first regimen containing the core agent of interest (index) and continued until the first of the following censoring events: (i) discontinuation of the core agent (DTG, EVG, RAL, DRV); (ii) cessation of continuous clinical activity; (iii) death; or (iv) study end (31 July 2018). Patients failing to meet the continuous clinical activity requirement were censored 12 months after their last contact.

Study Endpoints

Time to virologic failure was the primary study endpoint. Virologic failure was defined as either failure to achieve virologic suppression or failure to maintain suppression once achieved. Failure to achieve virologic suppression was defined as either (i) 2 consecutive HIV RNA VL levels ≥ 200 copies/mL after 36 weeks or (ii) 1 HIV RNA VL levels ≥ 200 copies/mL after 36 weeks followed by core agent discontinuation. Failure to maintain suppression once achieved was defined as either (i) 2 consecutive HIV RNA VL levels ≥ 200 copies/mL after suppression to <50 copies/mL prior to 36 weeks or (ii) 1 HIV RNA VL levels ≥ 200 copies/mL after suppression to 50 copies/mL prior to 36 weeks followed by core agent discontinuation.

Statistical Analysis

Patient characteristics were summarized using medians and interquartile range (IQR) for continuous data and percentages for categorical data. Statistical comparisons between DTG and each comparator were performed using Pearson χ^2 or Fisher exact tests for categorical variables and Wilcoxon rank-sum test for continuous variables. Mortality risk was assessed using the Veterans Aging Cohort Study (VACS) Index, which is a composite index used to estimate a 5-year risk of all-cause mortality

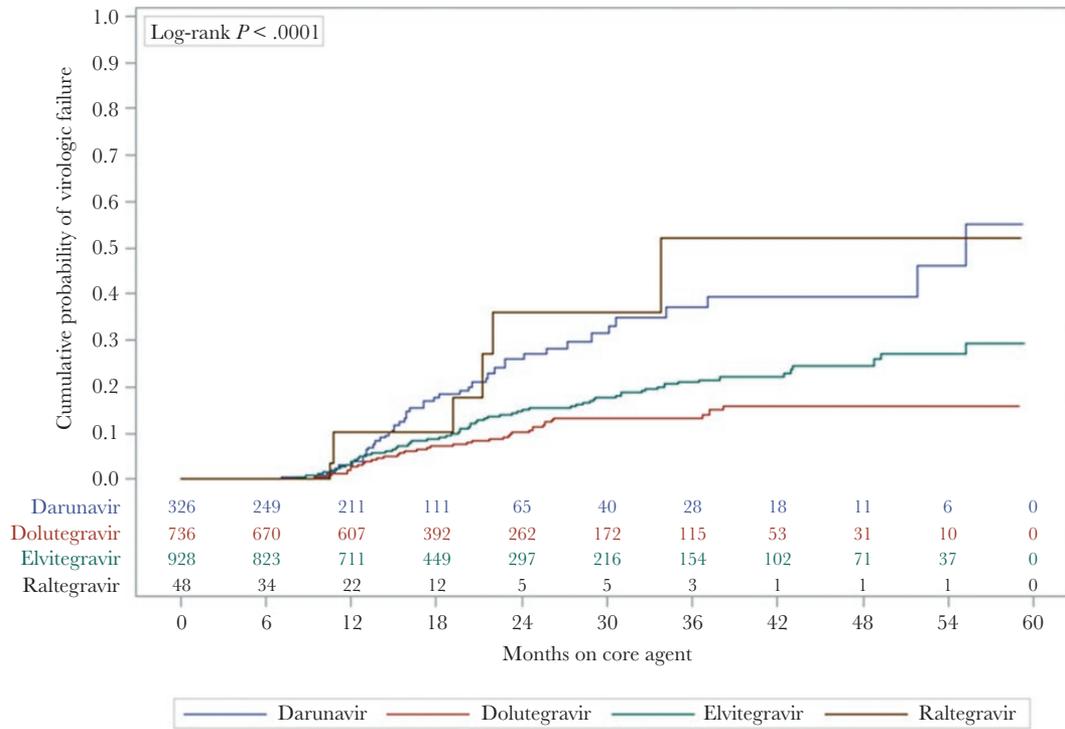


Figure 1. Unadjusted Cumulative Probability of Virologic Failure over Time on Core Agent.

[30]. The VACS Index is calculated based on age, CD4 cell count, HIV VL, hemoglobin, FIB-4 index, estimated glomerular filtration rate, and hepatitis C virus coinfection. A higher VACS score is associated with a higher risk of mortality.

Kaplan-Meier methods were used to generate unadjusted cumulative virologic failure probabilities. Incidence rates of virologic failure were estimated using Poisson regression, with a univariate model for unadjusted rates and a multivariate model for adjusted rates. A multivariate Cox proportional hazards model was used to assess the association between core agent initiated and time to virologic failure. The proportional hazards assumptions (constant ratio of hazards independent of time) was evaluated by the addition of an interaction term between treatment group (ie, regimen) and time. Baseline covariates included in the multivariate model included the following: baseline age, sex, race, CD4 cell count, HIV RNA VL, history of AIDS, VACS score, drug abuse, history of syphilis infection, calendar year of ART initiation, route of infection, and type of health coverage. Hazard ratios and 95% confidence intervals (CIs) were reported.

RESULTS

Among the 94 145 PLWH in OPERA who were HIV-1 infected, 16 259 (17%) were treatment naive, age 13 or older, and initiated 1 of the core regimens of interest during the population selection window. Among these, 6233 (38%) were prescribed regimens containing 3 antiretrovirals, met laboratory

requirements, and had continuous clinical activity. Thirty-three percent of these PLWH ($n = 2038$) initiated with a high baseline VL ($\geq 100\,000$ copies/mL) (Supplementary Figure 2). The majority of study eligible PLWH initiated with DTG ($n = 736$ [36%]) or EVG ($n = 928$ [46%]); fewer PLWH initiated with DRV ($n = 326$ [16%]) or RAL ($n = 48$ [2%]).

In terms of ART formulation, most (89%) of the DTG initiators were prescribed either a single-tablet regimen (DTG/abacavir/lamivudine, $n = 502$) or DTG plus emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) ($n = 154$). All EVG initiators were prescribed a single-tablet regimen, either EVG/cobicistat (c)/FTC/TDF ($n = 558$) or EVG/c/FTC/tenofovir alafenamide (TAF) ($n = 360$). Eighty-eight percent of DRV initiators were prescribed DRV/ritonavir plus FTC/TDF ($n = 173$), DRV/c plus FTC/TAF ($n = 56$), or DRV/c plus FTC/TDF ($n = 55$). Two-thirds of RAL initiators initiated with RAL plus FTC/TDF.

Table 1 summarizes select demographic and clinical characteristics by core agent initiated. Overall, differences in baseline characteristics were more notable when comparing DTG to DRV or RAL. Compared to DTG users, RAL users were older, more likely to be female, with low CD4 cell counts and high VACS scores. PLWH initiating DRV also differed notably in comparison to DTG users. DRV initiators were older, more likely to be African American, and more likely to have Medicare as the primary payer. DRV initiators also had higher baseline VLs, higher VACS scores, and lower baseline CD4 cell

Table 1. Population Baseline Demographic and Clinical Characteristics

Characteristic	DTG	EVG	DTG vs EVG	RAL	DTG vs RAL	DRV	DTG vs DRV
	(n = 736)	(n = 928)	PValue	(n = 48)	PValue	(n = 326)	PValue
Age, y, median (IQR)	32.8 (25.7–43.2)	32.0 (25.9–43.7)	NS	40.3 (28.7–47.8)	.0206	36.9 (28.7–45.4)	.0014
Female sex	90 (12.2)	99 (10.7)	NS	15 (31.3)	.0015	46 (14.1)	NS
African American race	311 (42.3)	418 (45.0)	NS	21 (43.8)	NS	164 (50.3)	.0149
Hispanic ethnicity	189 (25.7)	253 (27.3)	NS	9 (18.8)	NS	9 (18.8)	NS
Government-assisted healthcare ^a	441 (59.9)	487 (52.5)	.0105	29 (60.4)	NS	206 (63.2)	NS
AIDS diagnosis	196 (26.6)	239 (25.8)	NS	15 (31.3)	NS	131 (40.2)	<.0001
MSM	349 (47.4)	411 (44.3)	NS	12 (25.0)	.0025	146 (44.8)	NS
Baseline VL, log ₁₀ , median (IQR)	5.3 (5.1–5.6)	5.3 (5.1–5.7)	NS	5.5 (5.2–5.7)	NS	5.4 (5.2–5.8)	<.0001
Baseline VL ≥500 000 copies/mL	147 (20.0)	208 (22.4)	NS	13 (27.1)	NS	96 (29.4)	.0007
Baseline CD4 count ≤200 cells/μL	294 (39.9)	399 (43.0)	NS	30 (62.5)	.0021	205 (62.9)	<.0001
VACS score, median (IQR)	30 (20–53)	30 (20–53)	NS	46 (30–65)	.0018	49 (30–65)	<.0001
History of drug abuse	79 (10.7)	97 (10.5)	NS	2 (4.2)	NS	39 (12.0)	NS
History of syphilis	208 (28.3)	267 (28.8)	NS	11 (22.9)	NS	112 (34.4)	.0459
Southern United States	448 (60.9)	628 (67.7)	.0039	33 (68.8)	NS	33 (68.8)	.0396

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: DRV, darunavir; DTG, dolutegravir; EVG, elvitegravir; IQR, interquartile range; MSM, men who have sex with men; NS, not significant; VACS, Veterans Aging Cohort Study; VL, viral load.

^aIncludes Medicare, Medicaid, Ryan White HIV/AIDS Program, and AIDS Drug Assistance Program.

counts. Conversely, there were few differences between those who initiated an EVG- or DTG -based regimen.

Overall, median follow-up was 18.1 (IQR, 12.4–28.9) months, ranging from a low of 12.0 (IQR, 3.0–17.8) months in RAL initiators to a high of 20.2 (IQR, 13.8–30.3) months in DTG initiators. Core agent discontinuation occurred more frequently ($P < .001$) among RAL (79.2%), DRV (54.6%), and EVG (41.1%) initiators than among those initiating with DTG (32.5%). The most common reason for discontinuation identified was virologic failure, though no reason could be identified in 39.4% of discontinuations (Table 2). Between 54% and 79% of those with at least 1 VL achieved suppression (VL <50 copies/mL) over follow-up (Supplementary Table 1). DTG initiators were significantly more likely ($P < .001$) to achieve virologic suppression during the initial regimen (85.7%) than were EVG (82.1%), RAL (63.1%), or DRV (60.8%) initiators. Most

virologic failures observed were due to a failure to suppress; loss of suppression rarely occurred over follow-up (Supplementary Table 1). Between 9.2% (DTG) and 18.8% (DRV) of PLWH experienced virologic failure, occurring at an unadjusted rate that ranged from a low of 46.4 (95% CI, 36.2–59.5) per 1000 person-years in DTG initiators to a high of 132.1 (95% CI, 63.0–277.2) per 1000 person-years in RAL initiators. After statistical adjustments, all incidence rates were slightly attenuated, though the relationship between groups remained unchanged (Table 3). Figure 1 depicts the unadjusted cumulative probability of virologic failure over time on core agent.

Compared to DTG, the adjusted hazard ratio for virologic failure was 1.46 (95% CI, 1.05–2.03) for EVG, 2.24 (95% CI, 1.50–3.34) for DRV, and 4.13 (95% CI, 1.85–9.24) for RAL. Being African American, having a baseline CD4 count ≤200 cells/μL, having a history of syphilis, and having a government-based

Table 2. Core Agent Discontinuation

Discontinuation	DTG	EVG	DTG vs EVG	RAL	DTG vs RAL	DRV	DTG vs DRV
	(n = 736)	(n = 928)	PValue	(n = 48)	PValue	(n = 326)	PValue
Core agent discontinued, No. (%)	239 (32.5)	381 (41.1)	.0003	38 (79.2)	<.0001	178 (54.6)	<.0001
Reasons for discontinuation ^a , No. (%)							
Virologic failure	61 (25.5)	124 (32.5)	NS	13 (34.2)	NS	67 (37.6)	.0080
Simplification	35 (14.6)	≤5	<.0001	11 (28.9)	.0278	73 (41.0)	<.0001
Laboratory abnormality	≤5	6 (1.6)	NS	≤5	NS	≤5	NS
Adverse diagnosis/side effects	43 (18.0)	56 (14.7)	NS	12 (31.6)	NS	24 (13.5)	NS
Drug holiday (≥45 d without ART)	41 (17.2)	51 (13.4)	NS	≤5	NS	14 (7.9)	.0054
Other	14 (5.9)	32 (8.4)	NS	≤5	NS	20 (11.2)	.0690
None	96 (40.2)	173 (45.4)	NS	12 (31.6)	NS	48 (27.0)	.0050

Abbreviations: ART, antiretroviral therapy; DRV, darunavir; DTG, dolutegravir; EVG, elvitegravir; NS, not significant.

^aNot mutually exclusive; percentage of those with core agent discontinuation.

Table 3. Virologic Failure Rates Among Those With at Least 1 Viral Load Test Result During Follow-up

Drug	No. of Persons with At Least 1 VL	No. of Virologic Failures ^a	% of Virologic Failures	Person-Years	Unadjusted IR	Unadjusted IR per 1000 PY (95% CI)	Adjusted ^b IR per 1000 PY (95% CI)
DTG	676	62	9.2%	1336.55	0.04639	46.4 (36.2–59.5)	42.9 (32.9–56.0)
EVG	840	111	13.2%	1654.46	0.06709	67.1 (55.7–80.8)	60.8 (49.2–75.1)
RAL	38	7	18.4%	52.97	0.13213	132.1 (63.0–277.2)	125.8 (59.0–268.3)
DRV	276	52	18.8%	445.73	0.11666	116.7 (88.9–153.1)	86.3 (63.0–118.2)

Abbreviations: CI, confidence interval; DRV, darunavir; DTG, dolutegravir; EVG, elvitegravir; IR, incidence rate; PY, person-years.

^aVirologic failure defined as (i) 2 viral loads (VLs) ≥ 200 copies/mL after 36 weeks, (ii) 1 VL ≥ 200 copies/mL after 36 weeks plus discontinuation (DC), (iii) 2 VLs ≥ 200 copies/mL after suppression prior to 36 weeks, or (iv) VL ≥ 200 copies/mL after suppression prior to 36 weeks plus DC.

^bAdjusted for baseline age, sex, race, CD4 cell count, human immunodeficiency virus RNA VL, history of AIDS, Veterans Aging Cohort Study score, drug abuse, history of syphilis infection, calendar year of antiretroviral therapy initiation, route of infection, and type of health coverage.

payer (AIDS Drug Assistance Program, Ryan White HIV/AIDS Program, Medicaid, or Medicare) at baseline were also associated with a statistically significant ($P < .05$) increased hazard of virologic failure. Being identified as a man who has sex with men was associated with a statistically significant reduced hazard of virologic failure (Figure 2).

DISCUSSION

While baseline VL is a core component in the multivariable assessment of virologic efficacy, few real-world studies have focused specifically on the subset of patients who present with a high VL. The current study assessed the effectiveness of 4 commonly used core agents (DRV, DTG, EVG, RAL) on rates of virologic failure in ART-naïve patients who initiated therapy with a high VL burden in a real-world setting. Study findings were 2-fold: (i) there were notable differences in baseline demographic and clinical characteristics across the 4 treatment groups, and (ii) ART-naïve patients with high VLs initiating on DTG were significantly less likely to experience virologic failure as compared to EVG, RAL, and DRV initiators even after adjusting for differences in baseline characteristics.

Our findings are similar to those reported by Cruciani and Parisi [29] in a meta-analysis that used data from 7 randomized controlled trials to compare rates of virologic suppression and failure in ART-naïve patients initiating DTG-containing regimens vs non-DTG-containing regimens. The authors noted that while the likelihood of achieving viral suppression (<50 copies/mL) at 48 weeks overall was higher in the DTG-based (vs non-DTG-based) regimens, the average benefit was particularly evident in those with high baseline VL (risk difference, 0.10 [95% CI, .05–.15]; $P < .0001$). Similarly, Snedecor et al [31] conducted a subgroup analysis in PLWH with baseline VL $>100\,000$ copies/mL or CD4 count ≤ 200 cells/ μ L as part of a larger network meta-analysis comparing the efficacy and safety of DTG with other recommended or commonly used core antiretroviral agents. In total, 18 studies were used in the subgroup analysis. Data from 3 of these studies evaluated efavirenz vs rilpivirine, despite rilpivirine being indicated only for patients with a VL $\leq 100\,000$ copies/mL. The authors

concluded that the odds of achieving viral suppression (<50 copies/mL) by week 48 with DTG were superior or similar to other core agents.

A direct comparison between our results and those presented in both of these meta-analyses is hindered by differences in study designs and outcome construction. While virologic failure in the current study was a composite of failure to achieve virologic suppression by 36 weeks and loss of virologic suppression after having achieved it in the first 36 weeks of treatment, these measures were evaluated separately in both meta-analyses using a 48-week time point. Moreover, in the clinical trial setting, protocol-defined virologic failure required 2 consecutive HIV-1 RNA values ≥ 50 copies/mL whereas our study definition allowed for real-world practice in which clinicians usually do not discontinue therapy until the VL test result is >200 copies/mL to rule out blips. Accordingly, virologic failure as defined in the studies included in the meta-analyses occurred rarely in either the DTG or comparator groups, constraining the authors' ability to draw conclusions with a high degree of certainty.

PLWH who present for initial treatment with VLs $\geq 100\,000$ copies/mL are often difficult to treat because of their likelihood of presenting with advanced disease, the social determinants of health that frequently exist among late presenters, and/or the virulence associated with their infection [32–34]. Late presentation is associated with a higher frequency of opportunistic infections, increased morbidity and mortality, worse immune reconstitution, and greater comorbidity [6, 24–27, 33–39]. Studies have also suggested that total costs in PLWH are significantly higher among late presenters and those presenting with high VL [40–42]. The first strategy of the Ending the HIV Epidemic is to diagnose all people with HIV as early as possible and is essential in helping to achieve the aggressive goal of reducing new infections by 90% by the year 2030 [43, 44].

This current study used real-world data from electronic health records, including comprehensive laboratory data, in a large, national cohort of PLWH to evaluate virologic outcomes in ART-naïve individuals initiating with a high VL. Our study is not without limitations, and results should be interpreted with these in mind. While the OPERA cohort can provide detailed information on a large subset of the HIV-infected population

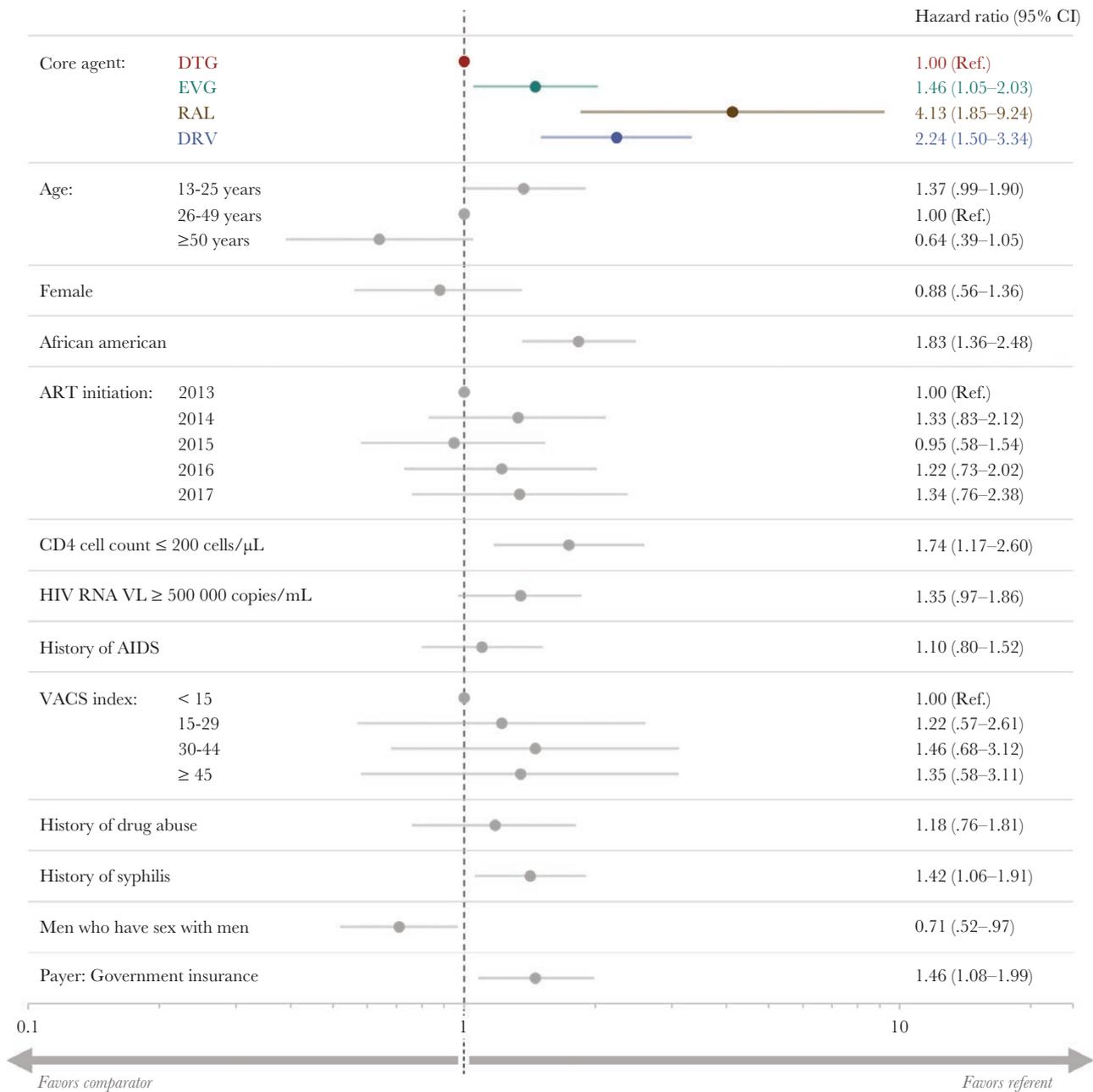


Figure 2. Cox proportional hazards model results, relative hazard of virologic failure (logarithmic scale). Abbreviations: ART, antiretroviral therapy; CI, confidence interval; DRV, darunavir; DTG, dolutegravir; EVG, elvitegravir; HIV, human immunodeficiency virus; RAL, raltegravir; VACS, Veterans Aging Cohort Study; VL, viral load.

in the United States, the potential for information bias remains as OPERA clinical data are collected at point-of-care and are subject to the record-keeping practices of each healthcare provider. In addition, this analysis may be limited by residual confounding as the small number of RAL initiators, and their complex medical presentation, may have constrained our ability to account for observed channeling bias in multivariable modelling. Reasons for discontinuation of a regimen were not documented for most patients, hindering our ability to understand why providers changed regimens in the absence of virologic failure. Finally, the latest Department of Health and Human

Services–recommended agent, bicitegravir, and new formulations of RAL and DRV were not included in this study as their approval occurred after the close of study eligibility.

CONCLUSIONS

A sizeable proportion of ART-naïve patients continue to present with high VLs, with notable differences in demographic and clinical characteristics across treatment groups. ART-naïve patients with high VLs initiating DTG were significantly less likely to experience virologic failure compared to EVG, RAL,

and DRV initiators, even after adjusting for differences in baseline characteristics. New antiretroviral medications should be studied in this subset of patients to help caregivers identify the best therapies for high-quality care in this challenging population.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. A. M. M., J. S. F., K. L. S., L. B., and G. P. F. had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. A. M. M., K. L. S., J. S. F., M. B. W., J. L. P., A. O., L. B., P. C. L., and G. P. F. were involved in the conception and design of this study. A. M. M., J. S. F., M. B. W., P. C. L., and G. P. F. contributed to the acquisition of data. K. L. S. and L. B. performed all analyses. A. M. M., K. L. S., J. S. F., M. B. W., L. B., P. C. L., and G. P. F. contributed to the interpretation of results. K. L. S. drafted the manuscript. All authors critically reviewed and approved the manuscript and participated sufficiently in the work to take public responsibility for its content.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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