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Advanced HIV Infection in Treatment-Naïve Individuals: Effectiveness and Persistence of Recommended 3-Drug Regimens

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Background. Approximately 20% of newly diagnosed people with HIV (PWH) in the United States have advanced HIV infection, yet the literature on current antiretroviral therapy (ART) options is limited. The discontinuation/modification and effectiveness of common regimens were compared among ART-naïve people with advanced HIV infection (CD4 cell count <200 cells/μL).

Methods. ART-naïve adults with advanced HIV infection initiating bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) or a boosted darunavir (bDRV)-, dolutegravir (DTG)-, or elvitegravir/cobicistat (EVG/c)-based 3-drug regimen between January 1, 2018, and July 31, 2019, in the OPERA cohort were included. The association between regimen and discontinuation or viral suppression (<50 or <200 copies/mL) was assessed using Cox proportional hazards models with inverse probability of treatment weights.

Results. Overall, 961 PWH were included (416 B/F/TAF, 106 bDRV, 271 DTG, 168 EVG/c); 70% achieved a CD4 cell count ≥200 cells/μL over a 16-month median follow-up. All regimens were associated with a statistically higher likelihood of discontinuation than B/F/TAF (bDRV: adjusted hazard ratio [aHR], 2.65; 95% CI, 1.75–4.02; DTG: aHR, 2.42; 95% CI, 1.75–3.35; EVG/c: aHR, 3.52; 95% CI, 2.44–5.07). Compared with B/F/TAF, bDRV initiators were statistically less likely to suppress to <50 copies/mL (aHR, 0.72; 95% CI, 0.52–0.99) and <200 copies/mL (aHR, 0.55; 95% CI, 0.43–0.70); no statistically significant difference was detected with DTG or EVG/c.

Conclusions. Among people with advanced HIV infection, those initiating B/F/TAF were less likely to discontinue/modify their regimen than those on any other regimen, and more likely to achieve viral suppression compared with those on bDRV but not compared with those on other integrase inhibitors.

Keywords. advanced HIV; antiretroviral therapy; cohort; discontinuation; effectiveness; late presenters.

Advancements in antiretroviral therapy (ART) over the past 3 decades [1] have changed HIV infection from a fatal illness to a manageable chronic disease [2]. Despite the advent of effective ART, advanced HIV infection in treatment-naïve people remains a concern. In a consensus definition developed by the European Late Presenter Consensus working group, advanced HIV infection is defined as presenting with a CD4 cell count <200 cells/μL or with an AIDS-defining event (ADE) [3]. Advanced HIV infection has been associated with an increased risk of clinical progression [4], morbidity [5, 6], mortality [5–7], and HIV transmission [6], as well as poor

long-term retention in care [7, 8] and higher health care costs [9–11].

Advanced HIV infection remains a common scenario, even in high-income countries. An analysis of CD4 cell counts at ART initiation across 54 countries from 2002 to 2015 by the International epidemiology Databases to Evaluate AIDS (IeDEA) and the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) showed that the prevalence of ART initiation with a CD4 cell count <200 cells/μL has plateaued around 29% in high-income countries [12]. In the United States, 21% of newly diagnosed individuals in 2015 had stage 3 HIV disease, defined as having either an opportunistic infection, a CD4 cell count <200 cells/μL, and/or a CD4 % <14% [13].

Current guidelines support the immediate initiation of therapy for people with HIV (PWH), irrespective of their disease stage [14], despite risks of immune reconstitution inflammatory syndrome (IRIS), an exaggerated inflammatory reaction that can occur when the immune system begins to recover after ART initiation, causing the flare-up of a previously undiagnosed infection or the worsening of a previously treated infection

[15]. The same treatment options are recommended for initial therapy whether someone has early or advanced HIV infection. However, the use of rilpivirine and of the combination of darunavir/ritonavir (DRV/r) + raltegravir (RAL) is discouraged among those with low pretreatment CD4 cell counts due to their association with higher risks of virologic failure [14].

Data on the efficacy of common regimens to treat advanced HIV are limited. Most trials have had <20% of participants with CD4 cell counts <200 cells/μL, and these trials were not powered to detect differences in this subpopulation [16–24]. Only 1 trial was restricted to participants with CD4 cell counts <200 cells/μL (DRV/r vs RAL, in combination with abacavir/lamivudine [ABC/3TC]) [25], and in 2 trials, at least a third of participants had CD4 cell counts <200 cells/μL (dolutegravir [DTG] vs efavirenz, in combination with tenofovir disoproxil fumarate [TDF] + 3TC; DRV/r vs lopinavir/r, in combination with emtricitabine [FTC]/TDF) [26, 27]. Moreover, recent observational studies conducted in Europe have been focused on class associations rather than specific regimens [28, 29]. This study aimed to compare regimen discontinuation, virologic effectiveness, and immunologic response with common first-line 3-drug regimens (3DRs) in ART-naïve PWH initiating ART with CD4 cell counts <200 cells/μL in a real-world setting in the United States.

METHODS

Study Population

The study population for this observational clinical cohort analysis was derived from the Observational Pharmaco-Epidemiology Research and Analysis (OPERA) cohort. The OPERA cohort is a database of prospectively collected electronic health record (EHR) data from 84 clinics across 18 US states/territories. At the time of this study, it included >118 000 PWH. The PWH included in this study were ART-naïve, at least 18 years of age, and had advanced HIV infection, defined as a CD4 cell count <200 cells/μL at the time of ART initiation between January 1, 2018, and July 31, 2019. Of those, only PWH initiating a 3DR consisting of either bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF), boosted DRV (bDRV) + 2 nucleoside reverse transcriptase inhibitors (NRTIs), DTG + 2 NRTIs, or elvitegravir/cobicistat (EVG/c) + 2 NRTIs with an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m² were included. PWH were considered ART-naïve if their last viral load before ART initiation was ≥1000 copies/mL and if there was no evidence in the EHR of a prior ART exposure.

Baseline was defined as the date of ART initiation, and follow-up ended at any change in the third agent (ie, stop, add, or substitute third agent), 12 months after last clinical contact (ie, telephone contact, visit, lab test, or consultation), death, or study end (ie, July 31, 2020), whichever censoring event came first. Analyses of virologic or immunologic outcomes were further restricted to PWH with at least 1 follow-up viral load or CD4 cell count.

Measurements

Regimen discontinuation was defined as either a modification of the third agent (ie, stop, add, or substitute third agent) or a gap of >45 days without any ART prescriptions. Reasons for regimen discontinuation were derived from the provider's notes in the EHR, supplemented with a review of laboratory results, diagnoses, and the regimen prescribed. More specifically, unfavorable events were defined as those noted in the chart, as a diagnosis of a new mental health, liver, renal, or bone comorbidity within 21 days before discontinuation of the regimen, or a lab abnormality. Lab abnormalities consisted of alanine transaminase, aspartate transaminase, alkaline phosphatase or bilirubin >3X ULN, or an eGFR <45 mL/min/1.73 m² at the last reading within 21 days before discontinuation. Simplification was defined as noted in the chart or as a reduction in total pill count for bDRV- and DTG-based regimens only; B/F/TAF- or EVG/c-based regimens could not be simplified because they are only available as single-tablet formulations. Pregnancy was defined as any diagnosis indicative of pregnancy within 3 months of discontinuation. Drug holiday was defined as a gap in ART of >45 days. Other possible reasons for regimen discontinuation were identified through notes in the chart: access issues (eg, cost, formulary, or availability issues), nonadherence, patient or provider choice, or any other reason noted. Reasons for discontinuation were not mutually exclusive.

Viral suppression was defined using both a more stringent threshold (ie, first viral load <50 copies/mL) and a more lenient threshold (ie, first viral load <200 copies/mL). IRIS was documented by the provider in the EHR and captured through both text and diagnosis code searches. A nurse reviews all new diagnosis titles on a regular basis to determine if they are consistent with IRIS. Immune recovery was defined as achieving a CD4 cell count ≥200 cells/μL; the first CD4 cell count over the threshold was considered. CD4:CD8 ratio normalization was defined as the first CD4:CD8 ratio ≥1.

Statistical Analyses

Baseline demographic and clinical characteristics were described using medians with interquartile ranges (IQRs) for continuous variables and frequencies with proportions for categorical variables. For all outcomes, unadjusted incidence rates were estimated with univariate Poisson regression. Unadjusted cumulative probability of immune recovery was estimated over time with Kaplan-Meier methods.

The association between regimen and either discontinuation or viral suppression was assessed using Cox proportional hazards models with a robust variance estimator. Stabilized inverse probability of treatment weights (sIPTWs) were employed to control for confounding in marginal structural models.

Propensity scores for the probability of receiving each regimen were obtained from multinomial logistic regression including baseline age, CD4 cell count, viral load, and index year, all measured continuously and modeled using a quadratic term, as well as sex, Black race, and hepatitis B coinfection.

RESULTS

Study Population

The study population included a total of 961 PWH, including 416 (43%) on B/F/TAF, 106 (11%) on a bDRV-based 3DR, 271 (28%) on a DTG-based 3DR, and 168 (18%) on an EVG/c-based 3DR. Most bDRV-based regimens were single- or multiple-tablet regimens with FTC/TAF (92%). DTG-based regimens were evenly divided between a single-tablet regimen with abacavir/lamivudine (52%) and a multiple-tablet regimen with FTC/TAF (46%); 2% were multiple-tablet regimens with FTC/TDF. B/F/TAF- and EVG/c-based regimens were always formulated as a single-tablet regimen; only 52% of DTG-based regimens and 25% of bDRV-based regimens were single-tablet regimens (Table 1).

Key baseline characteristics were generally well balanced across groups, although some notable differences were observed (Table 1). Compared with other regimens, PWH on EVG/c were most likely to be Black, those on B/F/TAF- or EVG/c-based regimens were most likely to have a very low CD4 cell count (ie, ≤50 cells/μL), those on bDRV and DTG were most likely to have a very high viral load (ie, ≥100 000 copies/mL), and those on bDRV and EVG/c were most likely to have hepatitis B virus coinfection.

Regimen Discontinuation

The maximum follow-up time was 31 months, with a median follow-up (IQR) of 17 (13–21) months on B/F/TAF, 14 (11–20) months on bDRV, 17 (12–23) months on DTG, and 14 (8–23) months on EVG/c. The unadjusted incidence rate of regimen discontinuation (ie, stop, add, or substitute third agent, or >45-day gap in ART) was significantly lower with B/F/TAF (11.2 per 100 person-years; 95% CI, 8.8–14.3), compared with bDRV (32.0; 95% CI, 23.4–43.8), DTG (28.6; 95% CI, 23.5–34.5), and EVG/c (40.7; 95% CI, 32.9–50.4).

Out of 64 B/F/TAF discontinuers, no reason for discontinuation could be identified among 56%; a treatment-related reason (ie, unsuppressed at discontinuation or unfavorable event) was identified among 14%; the remaining 30% discontinued for other reasons (drug holiday, provider choice). Out of 39 PWH who discontinued bDRV, 23% had no identifiable reason for discontinuation, 41% had a treatment-related reason, and 36% had another reason identified (simplification, drug holiday, patient/provider choice). Out of 105 DTG discontinuers, 41% had no identifiable reason, 24% had a treatment-related reason, and 35% had another reason for discontinuation (simplification, access issues, drug holiday, provider choice). Finally, out of 85 PWH who discontinued EVG/c, 42% discontinued without any identifiable reason; a treatment-related reason was identified in 35%, and another reason was identified in 22% (drug holiday, provider choice).

Reasons for discontinuation were not mutually exclusive, although multiple reasons per individual were uncommon. The most common reasons for discontinuation identified were provider choice (B/F/TAF: 28%; bDRV: 54%; DTG: 36%; EVG/c: 31%) and absence of viral suppression, defined as last viral load ≥200 copies/mL within 30 days before discontinuation (B/F/TAF: 6%; bDRV: 33%; DTG: 17%; EVG/c: 26%). A pregnancy was recorded for 3 discontinuations only. Among bDRV and DTG discontinuers, a majority discontinued a multiple-tablet regimen (80% and 53%, respectively); regimen simplification was observed in 44% of bDRV discontinuations and 25% of DTG discontinuation. While most bDRV- and EVG/c-based regimens discontinued included a backbone of FTC/TAF (85% and 86%, respectively), most DTG-based regimens discontinued included either FTC/TAF (48%) or ABC/3TC (48%).

In the adjusted analysis, B/F/TAF remained statistically significantly associated with a lower likelihood of regimen

Table 1. Baseline Demographic and Clinical Characteristics

	B/F/TAF n = 416	bDRV n = 106	DTG n = 271	EVG/c n = 168
Age, median (IQR), y	36 (29–46)	35 (27–46)	36 (28–45)	37 (28–47)
Female, No. (%)	85 (20)	19 (18)	46 (17)	34 (20)
Black race, No. (%)	257 (62)	67 (63)	170 (63)	116 (69)
CD4 cell count, median (IQR), cells/μL	87 (33–155)	94 (30–151)	93 (38–153)	91 (26–145)
CD4 ≤50 cells/μL, No. (%)	151 (36)	35 (33)	82 (30)	64 (38)
Log$_{10}$ viral load, median (IQR), copies/mL	5.3 (4.8–5.7)	5.4 (4.8–5.7)	5.3 (4.7–5.7)	5.2 (4.8–5.7)
Viral load ≥100 000 copies/mL, No. (%)	257 (62)	72 (68)	178 (66)	100 (60)
Hepatitis B coinfection, No. (%)	19 (5)	10 (9)	19 (7)	19 (11)
Single-tablet regimen, No. (%)	416 (100)	26 (25)	140 (52)	168 (100)
eGFR ≥90 mL/min/1.73 m^2, No. (%)	363 (87)	84 (79)	231 (85)	135 (80)

Abbreviations: B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; bDRV, boosted darunavir; DTG, dolutegravir; EVG/c, elvitegravir/cobicistat; IQR, interquartile range.

discontinuation compared with other regimens. In fact, compared with B/F/TAF, the likelihood of regimen discontinuation was 2.65 times higher with bDRV-based regimens (95% CI, 1.75–4.02), 2.42 times higher with DTG-based regimens (95% CI, 1.75–3.35), and 3.52 times higher with EVG/c-based regimens (95% CI, 2.44–5.07) (Figure 1).

Viral Suppression

In a subset of the population with follow-up viral loads (n = 771), 356 PWH initiated B/F/TAF, 77 initiated a bDRV-based regimen, 220 initiated a DTG-based regimen, and 118 initiated an EVG/c-based regimen. Unadjusted incidence rates of suppression at <50 copies/mL were of 100.7 per 100 person-years (95% CI, 89.0–114.0) with B/F/TAF, 70.9 (95% CI, 52.2–96.2) with bDRV-based regimens, 95.4 (95% CI, 81.1–112.2) with DTG-based regimens, and 85.5 (95% CI, 67.3–108.6) with EVG/c-based regimens. Using a cutoff of <200 copies/mL, the unadjusted incidence rate was 237.4 per 100 person-years (95% CI, 212.6–265.0) with B/F/TAF, 123.5 (95% CI, 94.3–161.7) with bDRV-based regimens, 200.9 (95% CI, 173.8–232.4) with DTG-based regimens, and 182.4 (95% CI, 148.2–224.5) with EVG/c-based regimens.

In adjusted analyses, B/F/TAF appeared to be associated with a higher likelihood of virologic suppression compared with bDRV-based regimens (Figure 2). Indeed, people with advanced HIV infection on a bDRV-based regimen were statistically significantly less likely to achieve virologic suppression compared with those on B/F/TAF when defined as the first viral load <50 copies/mL (adjusted hazard ratio [aHR], 0.72; 95% CI, 0.52–0.99) or as the first viral load <200 copies/mL (aHR, 0.55; 95% CI, 0.43–0.70). No statistically significant difference was observed in the likelihood of achieving virologic suppression at <50 or <200 copies/mL between B/F/TAF and other integrase strand transfer inhibitor (INSTI)–based regimens (Figure 2).

Immune Recovery

Out of 765 people with advanced HIV infection with follow-up CD4 cell counts, 355 initiated B/F/TAF, 76 initiated a bDRV-based regimen, 218 initiated a DTG-based regimen, and 116 initiated an EVG/c-based regimen. The 12-month cumulative probability of achieving a CD4 cell count ≥200 cells/μL was 67% (95% CI, 62%–72%) with B/F/TAF, 63% (95% CI, 51%–74%) with bDRV-based regimens, 68% (95% CI, 61%–74%) with DTG-based regimens, and 60% (95% CI, 51%–69%) with EVG/c-based regimens (Figure 3). Overall, 70% achieved a CD4 cell count ≥200 cells/μL over up to 31 months of follow-up, and no statistically significant difference was detected across groups in unadjusted assessments of immune recovery. The unadjusted incidence rate of a first CD4 cell count ≥200 cells/μL was of 120.0 per 100 person-years (95% CI, 106.3–135.4) with B/F/TAF, 115.6 (95% CI, 87.1–153.4) with bDRV-based regimens, 109.3 (95% CI, 93.3–128.2) with DTG-based regimens, and 92.1 (95% CI, 73.5–115.5) with EVG/c-based regimens. In a population restricted to 545 PWH with at least 1 CD4:CD8 ratio during follow-up, only 4% achieved normalization of the ratio overall (ie, CD4:CD8 >1). Of note, a diagnosis of IRIS in the EHR was rare during follow-up, with only 7 cases recorded overall (3/416 with B/F/TAF-, 1/106 with bDRV-, 2/271 with DTG-, and 1/168 with EVG/c-based regimens).

DISCUSSION

In this OPERA study, among 961 ART-naïve people with advanced HIV infection in the United States, those initiating B/F/TAF were less likely to discontinue their regimen compared with PWH initiating other 3DRs in adjusted analyses. Moreover, those initiating a bDRV-based 3DR were 28% less likely to achieve viral suppression at <50 copies/mL and 44% less likely to achieve viral suppression at <200 copies/mL compared with
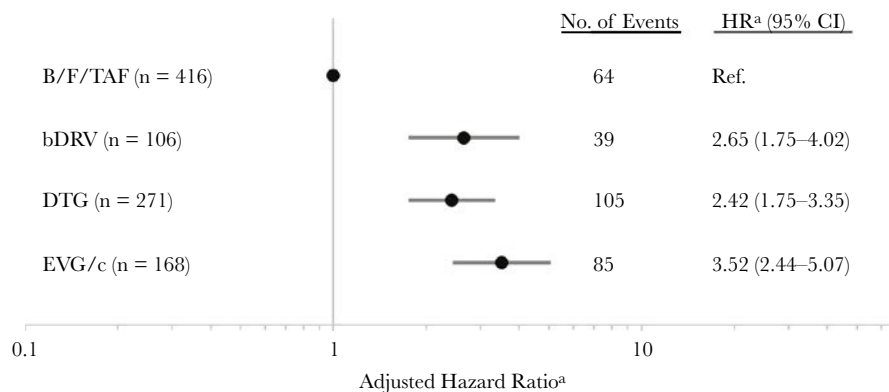

Figure 1. Adjusted[a] association between regimen and regimen discontinuation. [a]Estimated with a Cox proportional hazards model with stabilized inverse probability of treatment weights, controlling for baseline sex, Black race, hepatitis B, index year, age, CD4 cell count, and viral load. Abbreviations: B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; bDRV, boosted darunavir; DTG, dolutegravir; EVG/c, elvitegravir/cobicistat; HR, hazard ratio.
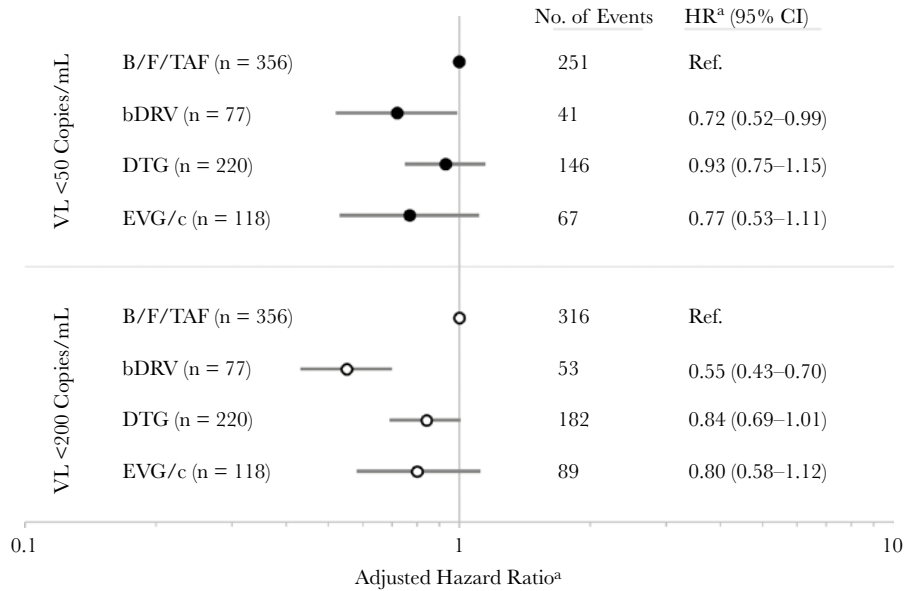
		No. of Events	HR[a] (95% CI)
VL <50 Copies/mL	B/F/TAF (n = 356)	251	Ref.
	bDRV (n = 77)	41	0.72 (0.52–0.99)
	DTG (n = 220)	146	0.93 (0.75–1.15)
	EVG/c (n = 118)	67	0.77 (0.53–1.11)
VL <200 Copies/mL	B/F/TAF (n = 356)	316	Ref.
	bDRV (n = 77)	53	0.55 (0.43–0.70)
	DTG (n = 220)	182	0.84 (0.69–1.01)
	EVG/c (n = 118)	89	0.80 (0.58–1.12)

Figure 2. Adjusted[a] association between regimen and viral suppression. [a]Estimated with a Cox proportional hazards model with stabilized inverse probability of treatment weights, controlling for baseline sex, Black race, hepatitis B, index year, age, CD4 cell count, and viral load. Abbreviations: B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; bDRV, boosted darunavir; DTG, dolutegravir; EVG/c, elvitegravir/cobicistat; HR, hazard ratio; VL, viral load.

those initiating B/F/TAF. However, no statistical difference was observed between B/F/TAF and other INSTI-based regimens, regardless of the definition of suppression used. Of note, the majority of people with advanced HIV achieved a CD4 cell count ≥200 cells/µL during follow-up, without any statistically significant difference detected between groups.

IRIS is of particular concern among people with advanced HIV infection because rapid viral load declines and rapid immune recovery have been identified as risk factors for IRIS [30–32]. Moreover, some studies have shown an association between

INSTI initiation and a higher risk of IRIS among those with advanced infection [33, 34]. However, in OPERA, despite rapid viral suppression, diagnoses of IRIS were rare during follow-up and did not differ notably between groups.

The literature on treatment options for people with advanced HIV infection in the modern ART era is sparse, leaving providers with little guidance on how to select the best regimen. In Germany and Spain, 35% of providers surveyed reported that regimen simplicity was the most important factor when choosing a regimen for people presenting with advanced HIV
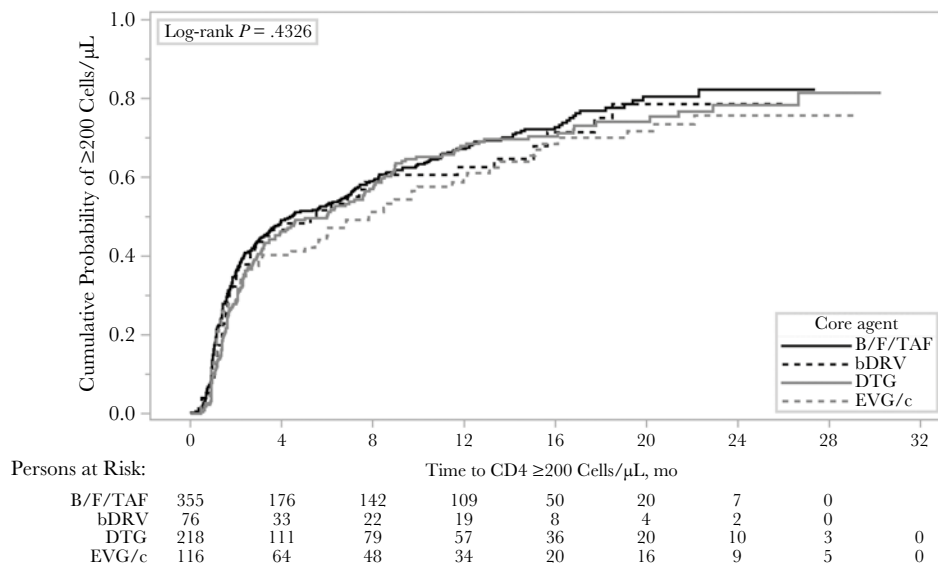

Figure 3. Cumulative probability of achieving a CD4 cell count ≥200 cells/µL. Abbreviations: B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; bDRV, boosted darunavir; DTG, dolutegravir; EVG/c, elvitegravir/cobicistat.

infection, followed by the presence of comorbidities (27%) and the provider's experience with specific antiretrovirals (21%) [35]. Such preferences may in part explain the regimen discontinuations observed in OPERA, as 25% and 44% of discontinuations resulted in regimen simplification among DTG and bDRV users, respectively; 35% of overall discontinuations were justified as the provider's choice. In addition, only 10% of PWH experienced an unfavorable effect of treatment such as a lab abnormality or a new diagnosis before discontinuation, with no notable difference between groups, suggesting that observed differences in discontinuation were not driven by safety concerns. However, despite the best efforts to understand why discontinuations occurred, no reason could be determined in 43% of cases overall. Contrary to this OPERA study, where specific regimens were compared and lower adjusted hazards of discontinuation were seen with B/F/TAF than with other regimens, other published studies only compared discontinuation across classes of antiretrovirals among people with advanced HIV. In a European analysis of 218 newly diagnosed PWH with CD4 cell counts <200 cells/μL and/or an ADE, no statistically significant difference in regimen discontinuation was observed between INSTI- and protease inhibitor (PI)–based regimens by 12 or 48 weeks of ART [28]. However, changes in NRTI backbone were included in the definition of regimen discontinuation and represented the most important reason for discontinuation overall [28]. In Italy, of 272 people with advanced HIV infection, 67% discontinued their first-line regimen, mainly for regimen simplification including switching from TDF to TAF [36]. However, the association between regimen and discontinuation observed in OPERA among people with advanced HIV mirrors findings of other US studies among ART-naïve PWH initiating ART regardless of baseline CD4 cell counts. Indeed, compared with B/F/TAF, statistically significant increases in the likelihood of discontinuation were observed with DTG-based regimens (HRs ranging from 1.58 to 6.20), EVG/c-based regimens (HRs ranging from 1.49 to 2.58), and bDRV-based regimens (HR, 3.56); reasons for discontinuation were not reported [37, 38]. However, in a multicenter cohort study in Italy, no statistically significant difference in the rate of all-cause discontinuations was observed, although discontinuations due to treatment-related adverse events (all grade 1 or 2) were more likely with DTG/ABC/3TC than B/F/TAF (relative risk, 2.32; 95% CI, 11.11–5.16) [39]. With a similar efficacy and safety profile as DTG-based 3DR [40, 41], it could be surmised that B/F/TAF was less likely to be discontinued due in part to its novelty. Indeed, a survey of Australian medical practitioners revealed that DTG/ABC/3TC and B/F/TAF were the preferred regimens for ART initiation due to their high barrier to resistance, and over two-thirds selected B/F/TAF as the anticipated preferred regimen for PLW eventually switching ART in the next 3 to 6 months [42]. The advantages of a single-tablet regimen for adherence and simplification also cannot be ignored [35, 43].

In the only trial restricted to 46 PWH with CD4 cell counts <200 cells/μL, viral suppression at <200 copies/mL was achieved by 77% in the RAL + ABC/3TC arm and 67% in in the DRV/r + ABC/3TC group, the difference being non–statistically significant [25]. While point estimates may suggest favorable virologic outcomes with B/F/TAF compared with DTG- or EVG/c-based regimens, these differences were not statistically significant in this OPERA study. Moreover, in trials comparing B/F/TAF- and DTG-based regimens, 89%–93% achieved suppression at <50 copies/mL, with no difference between groups, although only 11% of participants had a CD4 cell count <200 cells/μL [17, 18]. In addition, viral suppression does not appear to differ between INSTI and PI initiators in observational studies. In 5 European HIV treatment centers in Germany, Spain, and England, no difference in the frequency of suppression at <50 copies/mL was detected between PWH with a CD4 cell count <200 cells/μL and/or an AIDS-defining condition on an INSTI (86%) and those on a PI (81%) after 48 weeks of treatment [28]. Similarly, in the Cohort of the Spanish HIV/AIDS Research Network (CoRIS) between 2010 and 2018, no difference in viral suppression to <50 copies/mL was observed between PWH with CD4 cell counts <350 cells/μL on an INSTI or a PI (adjusted odds ratio [OR], 1.03; 95% CI, 0.75–1.43), although a higher likelihood of viral suppression was observed with NNRTIs compared with INSTIs (adjusted OR, 1.36; 95% CI, 1.00–1.85) [29].

This study has several strengths. The OPERA cohort is a large, diverse cohort representative of the HIV population in care in the United States. At the time of this study, it included EHR data from >118 000 PWH in care in clinics from 65 cities across the United States, ranging from small rural practices to large metropolitan health care centers, which represents ~10% of PWH in the United States. This large database of routine clinical care data allowed the investigation of real-world prescription practices and related health outcomes in a large study population of up to 961 people initiating HIV therapy with advanced HIV infection in recent years. Moreover, a thorough review of lab results, diagnoses, and provider notes was conducted to better understand why regimens were discontinued. Cox proportional hazards model were selected to conduct time-to-event analyses, in recognition of the importance of both the number of events and the speed at which they occur. Finally, inverse probability weighting was employed to ensure the balance of important covariates across groups and to control for confounding in the analyses of discontinuation and viral suppression.

This study has some limitations. Despite the best efforts to characterize reasons for discontinuation, none could be inferred in almost half. This issue is not unique to OPERA, as no reason was documented for close to a third of discontinuations reported in a study of treatment outcomes among people with advanced HIV from 5 European clinics [28]. Another shortcoming is the narrow window of eligibility due to B/F/TAF being

approved in February 2018. This resulted in a smaller sample size for the older drug DRV, as well as short follow-up time for all regimens. Expanding the eligibility window or extending follow-up time may provide more power to detect statistically significant differences between groups. Person-time was censored at changes in the third agent only. B/F/TAF is the only regimen in the study available exclusively as 1 unique fixed-dose combination; a change in any agent therefore automatically results in a change in regimen. In contrast, all the other third agents of interest are available in >1 formulation and/or as a single agent. It is therefore possible to change the backbone while remaining on bDRV, DTG, or EVG/c. Therefore, although regimen simplification is an important reason for switching regimens, adjusted analyses could not be controlled for single-tablet regimen use without violating the positivity assumption. It is possible that some PWH with a viral load ≥1000 copies/mL could have been misclassified as ART-naïve if they had received ART in the past at a different clinic and did not report prior use to their OPERA-participating provider. However, history notes were reviewed to determine if prior ART use was ever reported, thus mitigating the potential magnitude of such misclassification. Also, slightly fewer viral loads were measured during the follow-up period with bDRV-based regimens compared with other regimens, thus reducing the opportunities to observe viral suppression. Moreover, no statistical adjustment was performed for analyses of immune recovery. Finally, the last 5 months of study follow-up occurred during the COVID pandemic, potentially resulting in less patient contact. However, any effect of COVID on HIV care is not expected to have differed among groups.

In conclusion, among people initiating ART with advanced HIV infection, those on B/F/TAF were less likely to discontinue their regimen compared with those on other 3DRs. They also had a higher likelihood of achieving virologic suppression at both <50 copies/mL and <200 copies/mL compared with those on bDRV-based 3DRs but did not differ from those on DTG- or EVG/c-based 3DRs in adjusted analyses. Thus, it appears that B/F/TAF and other INSTI-based regimens are excellent options for initial therapy in people presenting with advanced HIV infection.

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