

ORIGINAL ARTICLE

Real-world use and effectiveness of fostemsavir in a US clinical setting: Insights from Trio Health HIV Research Network

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Abstract

Objective: To describe real-world patterns of use, virologic and immunologic outcomes and treatment persistence among people with HIV (PWH) initiating fostemsavir (FTR) in a diverse US cohort.

Design: Retrospective cohort study of adults receiving FTR in clinical practice, stratified by baseline viral suppression status.

Methods: Adults with ≥ 1 FTR prescription between July 2020 and August 2023 were included and followed for 12 months. Individuals with trial participation were excluded. Outcomes included virologic suppression (< 50 and < 200 copies/mL), confirmed virologic failure, viral blips, CD4 changes and immunologic recovery among those with baseline CD4 < 350 cells/mm³. Persistence and adherence were assessed using dispensing data and proportion of days covered.

Results: Seventy-seven PWH were included (60% viremic, 40% suppressed). Multidrug resistance was observed in a subset (31%). At 12 months, most individuals remained on FTR, with high adherence among the subset with available dispensing data. Among viremic initiators, a minority achieved viral suppression, though reductions in viral load were observed. Among suppressed initiators, most maintained suppression. CD4 counts increased in both subgroups, with greater gains among those suppressed at initiation. Modifications to optimized background therapy were infrequent.

Conclusions: In this real-world, diverse cohort, FTR was well tolerated, with high persistence and, in the dispensing-data subset, high adherence. It effectively maintained viral suppression among suppressed individuals and provided immunologic benefits across subgroups, including viremic initiators.

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These findings support FTR as a valuable treatment option for heavily treatment-experienced PWH.

KEYWORDS

antiretroviral therapy, drug resistance, HIV, treatment experienced, viremia, virologically suppressed

INTRODUCTION

HIV treatment has improved over the past decade, with increasingly high proportions of people with HIV (PWH) achieving and maintaining viral suppression on modern antiretroviral therapy (ART). Despite these advances, a subset of PWH struggles with viremia or treatment failure on ART regimens, underscoring the ongoing need for novel therapeutic options. The causes of treatment failure are multifactorial, including poor adherence, prior resistance, drug–drug interactions, adverse events and toxicities.

Novel therapeutic targets to supplement existing ARTs are needed to ensure viral suppression among those with limited treatment options. Ideally, these new agents must have unique targets and excellent tolerability profiles with a reduced likelihood of drug–drug interactions. Fostemsavir (FTR) is a unique HIV-1 attachment inhibitor that binds to the surface of the HIV-1 virus at the glycoprotein (gp) 120 binding site and inhibits binding to the CD4 T-cell site. It is the prodrug of temsavir and was approved in July 2020 by the Federal Drug Administration (FDA) for use in highly treatment-experienced (HTE) adults with multidrug-resistant (MDR) HIV-1 infection who are on a currently failing regimen due to intolerance, safety concerns or drug resistance. The medication was approved for twice-daily use combined with antiretrovirals (ARVs) selected based on both susceptibility via resistance testing and clinical congruence. Virological efficacy, safety and tolerability of FTR were demonstrated through 240 weeks in the phase III BRIGHT clinical trial.

The BRIGHT study was the foundation for the FDA approval of FTR, reporting outcomes at 48, 96 and 240 weeks. Outcomes were reported for a total of 371 individuals from 23 countries, enrolled in either a randomized cohort ($n = 272$) or non-randomized cohort ($n = 99$). Participants in the randomized cohort had one or two fully active ART classes available, while those in the non-randomized cohort had no fully active ART classes available. In the randomized group, individuals were randomized 3:1 to receive blinded FTR 600 mg or blinded placebo twice daily with their current failing regimen from days 1 to 8. After 8 days, participants in the randomized group received open-label FTR 600 mg twice daily in combination with an OBT chosen by the

managing investigator. Participants in the non-randomized group received open-label FTR 600 mg twice daily in combination with OBT throughout the study.

By 48 weeks, virologic suppression occurred in 54% of individuals in the randomized cohort and in 38% of those in the non-randomized cohort; the mean increase in CD4+ T-cell count was 139 cells/mm³ and 64 cells/mm³, respectively [1]. At 96 weeks, sustained virologic responses and continued immunologic improvements were reported [2]. Week 240 efficacy and safety reports provided long-term data showing durable virologic responses of 45% in the randomized cohort and 22% in the non-randomized cohort, and continued increases in CD4+ counts: mean change from baseline in CD4 + T-cell count was 296 cells/mm³ (randomized) and 240 cells/mm³ (non-randomized) [3]. There were few discontinuations, and the drug was well tolerated. Additionally, FTR demonstrated minimal cross-resistance, favourable drug–drug interactions and retained sensitivity to its co-receptor [4].

Current real-world evidence of FTR utilization is limited. The objective of our study was to describe real-world patterns of use as well as immunologic and virologic responses in individuals starting FTR.

METHODS

This study was conducted using the Trio Health HIV Research Network, which includes electronic health records (EHR) data from 70 000 PWH receiving care from 14 sites across the United States. This robust dataset includes prescription and dispensing records, laboratory results including genotypic HIV resistance testing and encounter and procedure data. To enhance the dataset, Labcorp shared de-identified, tokenized HIV resistance testing data from sites participating in the Trio Health HIV Research Network. Trio Health integrated the resistance data with individual clinical histories, creating a comprehensive registry to enable the assessment of outcomes based on resistance profiles and treatment experiences. This study was granted Institutional Review Board (IRB) oversight exemption through 45 CFR 46.104(d) (4) by Advarra Central IRB (Advarra, 6100 Merriweather Drive, Suite 600, Columbia, Maryland, USA).

Adult PWH receiving at least 1 prescription for FTR from July 2020 to August 2023 were included and followed for 12 months from the date of their first FTR prescription (index date). Those with clinical trial participation during the study period, or prior evidence of participation in clinical trials for FTR, were excluded from the analysis. Individuals were followed from the index date until FTR discontinuation, loss to follow-up, death or study end (August 2024). Analyses were stratified by virologic suppression status at baseline (closest HIV RNA viral load within less than 12 months prior to FTR initiation).

HIV ARV resistance was analysed using available HIV genotype data at two time points: any point prior to FTR initiation (baseline) and after the date of virologic failure. HIV mutation data was interpreted using the Stanford HIV Drug Resistance Database to determine the impact of identified resistance-associated mutations (RAMs) [5]. ARV class resistance was defined as intermediate or high resistance to at least 1 ARV within the class. Multidrug resistance (MDR) was defined as resistance to at least one drug in three separate ARV classes.

FTR should be administered with optimized background therapy (OBT), an ART regimen tailored to each individual's needs for treatment. OBTs were summarized by ARV class and individual ARVs prescribed, and regimen switch at start (new regimen with FTR vs. adding FTR to prior ART).

Discontinuation of FTR was defined as a >90-day gap in prescription coverage or change to ART regimen without FTR. Changes to OBT during follow-up on FTR were described as observed. Individuals were censored as lost to follow-up at last available visit if no further encounters were observed for 6 months or more. Adherence was measured using dispensing data, rather than prescription data. Past studies have demonstrated correlations between dispensing data and adherence in PWH [6]. We utilized proportion of days covered (PDC) as our adherence metric to reflect the percentage of dosages that were taken as a function of dispensing data and rates of refills.

Virologic outcomes included proportion of virologically suppressed (VL <50 copies/mL and VL <200 copies/mL) via snapshot analysis at 6 months and 12 months from index. Snapshot analysis used viral load nearest to 6-month and 12-month time points (within 90–269 and 270–450 days from index, respectively). Additional virologic outcomes included confirmed virologic failure, defined as two consecutive viral loads ≥ 200 copies/mL or 1 viral load ≥ 200 copies/mL with discontinuation of FTR within 4 months. Viral blips were defined as isolated VL between 50 and 500 copies/mL with suppression at subsequent viral load measurement. Proportion of PWH achieving suppression, time to virologic suppression and

virologic non-response (VNR: VL ≥ 50 copies/mL at more than 6 months from index) were analysed among those viremic at start. Proportion of PWH with viral failure, blips and time to viral failure and blips were analysed among those suppressed at start and among viremic initiators who suppressed during follow-up.

Immunologic outcomes included absolute and percent change in CD4 count at 6 and 12 months from index, and proportion of population with baseline CD4 <350 cells/mm³ achieving immunologic recovery, defined as increase of 50 cells/mm³ per 6 months on FTR or achieving CD4 ≥ 350 cells/mm³. Snapshot analysis reported CD4 outcomes nearest to 6- and 12-month time points (within 90–269 and 270–450 days from index, respectively).

Data analyses were conducted using R statistical software (version 4.3).

RESULTS

Study population

During the study period, 77 PWH qualified for inclusion in the analysis (5 were excluded due to absence of the baseline viral load). At FTR initiation, 46 (60%) were viremic, and 31 (40%) were suppressed.

Compared to those suppressed at initiation, viremic initiators were younger (46% vs. 10% under 50 years old), with increased proportions of female gender (26% vs. 10%), Black race (54% vs. 23%) and Medicare/Medicaid insured individuals (37% vs. 16%) (Table 1).

The majority of both cohorts had experienced at least 1 AIDS defining event (58% viremic vs. 70% suppressed), with nadir CD4 <200 cells/mm³ the most common AIDS-defining event (96% of cases). Over half had baseline CD4 <350 cells/mm³ (65% viremic vs. 55% suppressed). Both subgroups had a high prevalence of comorbidities (Table 1).

HIV Genotyping prior to FTR was available in 63% of viremic and 39% of suppressed. Most had resistance to at least 1 ARV class (76% viremic vs. 67% suppressed), and MDR was observed in 31% of viremic and 17% of suppressed initiators with genotype results, corresponding to 20% and 6% of all individuals, respectively. Resistance to INSTIs was the least frequently observed and present only in those viremic at initiation (7%).

Most PWH had prior treatment experience with at least 1 INSTI (93% both viremic and suppressed), with 80% viremic and 74% suppressed having an INSTI in their regimen prior to FTR. (Table 2). Only 3/37 (8%) of viremic and 2/23 (13%) changed their INSTI agent when adding FTR. (Table 2).

TABLE 1 Characteristics of the study population.

N (%) or median (IQR)	Viremic (VL ≥50 copies/mL), N = 46	Suppressed (VL <50 copies/mL), N = 31
Age <50 years at FTR start	22 (48%)	3 (10%)
Gender		
Male	32 (70%)	28 (90%)
Female	12 (26%)	3 (10%)
Other	2 (4%)	0 (0%)
Race		
White	18 (39%)	19 (61%)
Black/African American	25 (54%)	7 (23%)
Other	3 (7%)	5 (16%)
Years since diagnosis	7 (3, 8)	5 (1, 9)
Viral load (log10 copies/mL)	3.3 (2.2, 4.5)	N/A
Absolute CD4 (cells/mm ³)	156 (27, 452)	260 (189, 486)
Absolute CD4 <350 cells/mm ³	28/45 (62%)	14/27 (52%)
Nadir CD4 (cells/mm ³)	43 (20260)	166 (49355)
Comorbidities		
Cardiovascular disease	14 (30%)	18 (58%)
Neuropsychiatric disorder	16 (35%)	15 (48%)
Diabetes type 2	6 (13%)	9 (29%)
Liver disease (mild or severe)	5 (11%)	6 (19%)
Chronic kidney disease	9 (20%)	5 (16%)
Hepatitis B	3 (7%)	1 (3%)
Hepatitis C	2 (4%)	2 (7%)
Cumulative prior ARV exposure*		
PI	33/41 (81%)	18/27 (67%)
NRTI	38/41 (93%)	26/27 (96%)
NNRTI	22/41 (54%)	14/27 (52%)
INSTI	38/41 (93%)	25/27 (93%)
Prior regimen by ARV class*		
INSTI + 2 NRTI	12/41 (29%)	8/27 (30%)
INSTI + PI + 2 NRTI	5/41 (12%)	4/27 (15%)
PI + 2 NRTI	3/41 (7%)	4/27 (15%)
Available HIV genotype prior to initiation	29 (63%)	12 (39%)
INSTI resistance	2/29 (7%)	0/12 (0%)
PI resistance	7/29 (24%)	4/12 (33%)
NNRTI resistance	19/29 (66%)	5/12 (42%)

(Continues)

TABLE 1 (Continued)

N (%) or median (IQR)	Viremic (VL ≥50 copies/mL), N = 46	Suppressed (VL <50 copies/mL), N = 31
NRTI resistance	20/29 (69%)	5/12 (42%)
No resistance	7/29 (24%)	4/12 (33%)
1 Class resistance	5/29 (17%)	4/12 (33%)
2 Class resistance	8/29 (28%)	2/12 (17%)
3 Class resistance (MDR)	9/29 (31%)	2/12 (17%)

*Denominator restricted to individuals with prior treatment history documented in Trio EHR.

FTR was prescribed as an addition to a prior regimen without other changes in 46% of the viremic subgroup and 70% of the suppressed subgroup. OBTs included at least 1 INSTI component (80% viremic and 77% suppressed), with DTG the most commonly prescribed agent (57% viremic vs. 42% suppressed), followed by BIC (17% viremic vs. 29% suppressed) and PIs (20% viremic vs. 22% suppressed). Bictegravir (BIC/FTC/TAF) was used as a single STR, whereas dolutegravir was used in several different regimen combinations (Table 2).

Persistence on FTR and OBT

High persistence on FTR was observed during follow-up, with the majority remaining on FTR through 12 months (67% viremic and 68% suppressed). Discontinuation was more frequent (23% suppressed vs. 11% viremic) and occurred sooner after initiation (median 5.4 months vs. 8.0 months) in those suppressed at initiation. Those viremic at initiation were more frequently lost to follow-up (22% viremic vs. 10% suppressed). Trio EHRs do not include mortality data; therefore, lost to follow-up may include individuals who died (Figure 1). Modifications to OBT were infrequent, with 2 (4%) of viremic individuals and 3 (10%) of suppressed receiving modifications to OBT through 12 months.

Adherence on FTR and OBT

Among the subset of individuals with dispensing data (26 viremic and 16 suppressed), adherence to FTR through 12 months was high in both subgroups, with median PDC of 90% (IQR: 66%, 100%) for viremic initiators and 100% (IQR: 82%, 100%) for suppressed initiators. Half of viremic initiators were highly adherent (PDC >95%; $n = 13$, 50%)

TABLE 2 FTR regimen characteristics.

	Viremic (VL ≥50 copies/ mL), N = 46	Suppressed (VL <50 copies/ mL), N = 31
Has prior therapy documented in EHR	N = 41	N = 27
FTR as addition to prior therapy	19 (46%)	19 (70%)
FTR addition and therapy change	27 (54%)	12 (30%)
Has INSTI in prior regimen	37 (80%)	23 (74%)
Bictegravir	8 (17%)	9 (29%)
Dolutegravir	11 (24%)	10 (32%)
Other INSTI	5 (11%)	4 (13%)
Changes INSTI agent with FTR addition	3/37 (8%)	2/23 (13%)
Removed INSTI with FTR addition	5/37 (13%)	0/23 (0%)
Has INSTI in OBT	36 (80%)	23 (77%)
Bictegravir	8 (17%)	9 (29%)
INSTI +2 NRTI	7 (88%)	8 (89%)
Dolutegravir	26 (57%)	13 (42%)
INSTI + PI +2 NRTI	4 (15%)	4 (31%)
INSTI + NNRTI	7 (27%)	1 (8%)
INSTI +2 NRTIs	4 (15%)	0 (0%)
INSTI + PI	4 (15%)	0 (0%)
Other	7 (27%)	8 (61%)
Other INSTI	3 (6%)	2 (6%)
PI without INSTI	9 (20%)	7 (23%)
PI +2 NRTI	5 (56%)	4 (57%)

while a majority of suppressed initiators were highly adherent to FTR ($n = 11$, 69%). Adherence to OBT was similarly high, with the median of 88% (IQR: 71%, 99%) for the viremic subgroup and 94% (IQR: 77%, 100%) for the suppressed.

Virologic effectiveness

Among 39 (85%) viremic initiators with follow-up viral loads, 14 (36%) achieved VL <50 copies/mL during follow-up. Of these, 2 (14%) had CVF during follow-up after suppression (both occurred <3 months following suppression). VNR was observed in 11 (28%); the remaining 14 (35%) did not suppress during follow-up but did

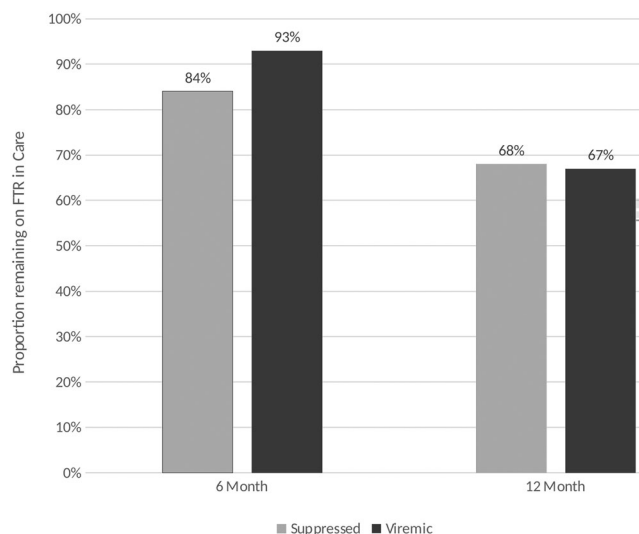


FIGURE 1 Persistence on fostemsavir at 6 and 12 months of follow-up. Bars show the proportion of individuals remaining on FTR and in care at each time point, by viral suppression status at FTR initiation.

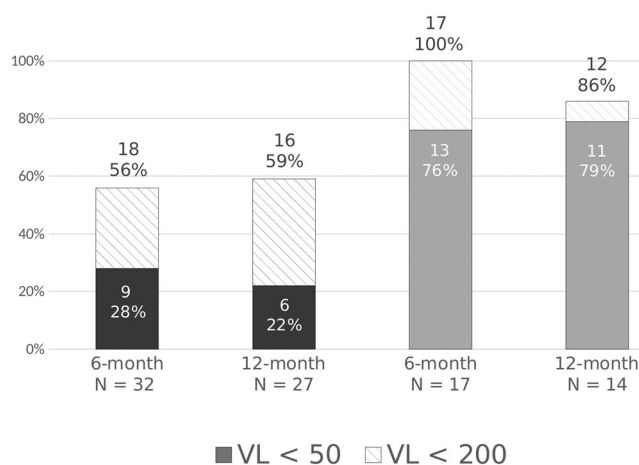


FIGURE 2 Virologic outcomes at 6 and 12 months by suppression status at FTR initiation. Stacked bars show the proportion with VL <50 copies/mL and the additional proportion with VL <200 copies/mL; the value above each bar is the total with VL <200 copies/mL. Denominators are individuals with an evaluable viral load in each analysis window.

not meet VNR criteria due to insufficient viral loads after 6 months on FTR. Via snapshot analysis, at 6 months, 56% had VL <200 copies/mL and 28% had VL <50 copies/mL, while at 12 months, 59% had VL <200 copies/mL and 22% had VL <50 copies/mL (Figure 2). Viremic initiators who did not suppress tended to have lower baseline CD4 and higher baseline viral load, and more often added FTR to an existing regimen; multidrug resistance was similar. Given the few events, these comparisons are descriptive.

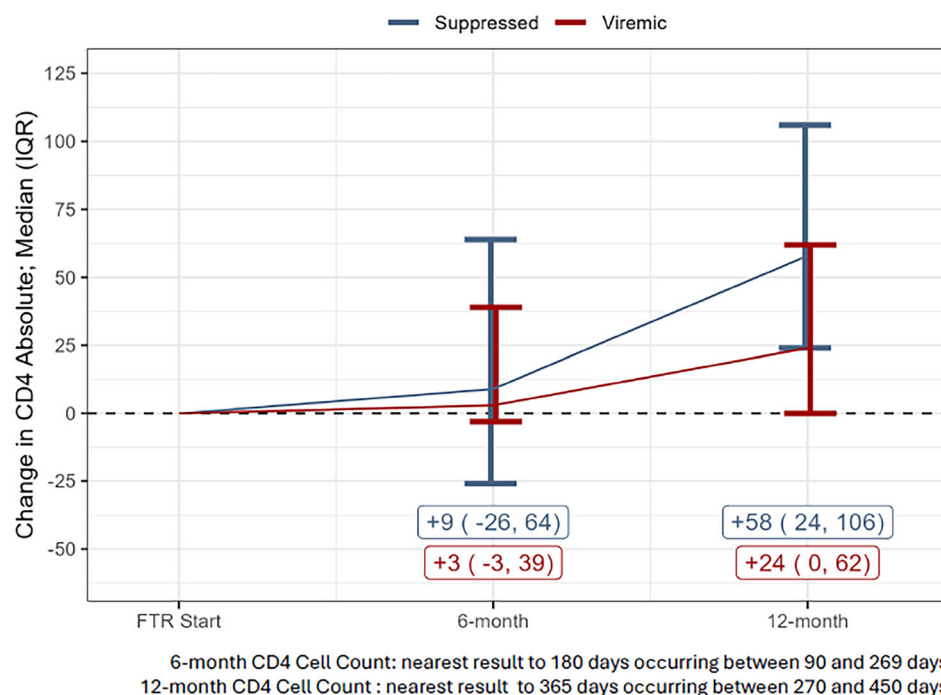


FIGURE 3 Change in absolute CD4 count from FTR initiation at 6 and 12 months, by suppression status at initiation. Points show the median change and error bars the interquartile range.

Among 26 (83%) suppressed initiators with follow-up viral loads, 20 (77%) maintained VL <50 copies/mL through the end of follow-up, while 3 (12%) had CVF (median 65 days from index) and 3 (12%) experienced virologic blips (median 98 days from index). Via snapshot analysis, at 6 months, 100% had VL <200 copies/mL and 76% had VL <50 copies/mL, while at 12 months, 86% had VL <200 copies/mL and 79% had VL <50 copies/mL (Figure 2).

Of the five cases of CVF, one suppressed initiator had HIV genotype performed at viral failure, demonstrating multidrug resistance (PI, NRTI and NNRTI classes). No HIV genotype information prior to index was available to assess emergent treatment resistance.

Immunologic outcomes

Increases in CD4 counts were observed during follow-up in both subgroups. At 6-months, a limited increase was observed: Viremic +3 cells/mm³ (IQR: -3, 39) and Suppressed +9 cells/mm³ (IQR: -26, 64), with a noticeable increase at 12 months that was smaller in the viremic subgroup: +24 cells/mm³ (IQR: 0, 62) vs. +58 cells/mm³ (IQR: 24, 106). Relative median CD4 increases were +11% and +16% at 12 months and +8% and +3% at 6 months (viremic and suppressed, respectively) (Figure 3).

Among 30 viremic and 17 suppressed initiators with CD4 <350 cells/mm³ at baseline, 30% of viremic and 29%

of suppressed met the definition for immune recovery during follow-up. Recovery occurred at a median of 231 days (IQR: 99, 326) for the viremic subgroup and 93 days (IQR: 77, 111) for the suppressed subgroup.

DISCUSSION

The use of new antiretroviral agents with unique mechanisms of action is an integral component of improvements in HIV therapeutics. Those with virologic failure and genotypic resistance need unique agents to achieve viral suppression. This study provides valuable real-world insights into the use of FTR in a cohort of 77 treatment-experienced individuals with HIV. At the time of FTR initiation, 60% were viremic and 40% suppressed. Significant differences in demographic and clinical baseline characteristics were found between individuals who were viremic at FTR initiation vs. suppressed. A high prevalence of ARV resistance was observed among individuals with available resistance test results, with most PWH having resistance to at least one ARV class (76% viremic vs. 67% suppressed). Multidrug resistance was present (31% viremic vs. 17% suppressed among those with available results). Integrase resistance was less common and only seen in viremic initiators (7%). Viremic initiators frequently started FTR with a completely new optimized background therapy, whereas suppressed initiators often added FTR to existing regimens.

High persistence on FTR was observed, with over two-thirds of both viremic and suppressed initiators remaining on therapy through 12 months. Discontinuation occurred more frequently and sooner in the suppressed group, while lost to follow-up was more common among viremic individuals, potentially including unobserved deaths. Adherence to both FTR and OBT was high, with median PDC of 90% for viremic and 100% for suppressed initiators for FTR, and similarly high rates for OBT.

Two other real-world studies from OPERA and PRESTIGIO cohorts provide context for observed results. OPERA is a US community-based cohort that conducted a study with similar inclusion criteria, though our analysis included more recent data (2020–2022 OPERA vs. 2020–2023 Trio). The OPERA cohort reported data on 182 individuals initiating FTR between July 2020 and September 2022: 64% were viremic at FTR initiation, and 36% were virally suppressed (viral load [VL] <50 copies/mL), roughly half with low CD4 counts <350 cells/mm³ in each group [7]. Most individuals who were already virologically suppressed at baseline maintained suppression on FTR. Nearly half of the viremic/high CD4 group and a third of the viremic/low CD4 group achieved viral suppression at either 6 or 12 months.

In this real-world study, virologic suppression was lower in viremic initiators at 12 months (22%) compared to BRIGHTHE's mostly viremic at baseline randomized cohort at 48 weeks (62% randomized <40 copies/mL, and 84% <200 copies/mL) [1], despite lower baseline CD4 counts and higher ARV resistance in BRIGHTHE's population, based on their inclusion criteria. However, virologic effectiveness at 6 months was similar to real-world data from the OPERA cohort for viremic initiators (40% vs. 37%), though suppression at 12 months was less observed (22%) compared to OPERA (40%) or PRESTIGIO (67%) cohorts [7, 8]. PRESTIGIO had three arms for resistance: FTR, Ibalizumab and Lenacapavir. OPERA also identified differences in suppression by baseline CD4 count, with baseline CD4 count <350 cells/mm³ associated with lower suppression at 6 months (31% vs. 48%) and 12 months (33% vs. 52%). Further research into demographic or clinical characteristics associated with virologic non-response is warranted. The lower 12-month suppression relative to BRIGHTHE likely reflects real-world differences in adherence, follow-up and OBT selection rather than any single factor; a formal multivariable analysis is precluded by the small number of non-response events.

Those initiating FTR while suppressed mostly maintained virologic suppression at 6 months (76%) and 12 months (79%), consistent with results from the OPERA cohort (85% and 80%, respectively), the only other real-world cohort to analyze FTR use in PWH suppressed at initiation.

The immunologic benefits seen initially in BRIGHTHE including persistent elevations in CD4 count and improvements in CD4/CD8 ratios through 240 weeks were surprising in light of these participants' advanced disease. The largest increases were seen in those with the greatest extent of immunosuppression, and even in those who did not achieve viral suppression [3]. While increases to CD4 counts at 12 months in our study (median + 24 cells/mm³ viremic and + 58 cells/mm³ suppressed) were lower than observed in BRIGHTHE (+139 cells/mm³ in randomized and + 64 cells/mm³ in non-randomized), our cohort included individuals with higher baseline CD4 counts (median 156 cells/mm³ viremic and 260 cells/mm³ suppressed) compared to BRIGHTHE's study population (median 99 cells/mm³). As BRIGHTHE reported comparable CD4 gains across baseline strata, the smaller increases here are more likely to reflect shorter follow-up than higher baseline CD4. Compared to other real-world studies, similar increases in CD4 count were observed in OPERA (median + 66 cells/mm³ suppressed with baseline CD4 <350 cells/mm³) and PRESTIGIO cohorts (+97 cells/mm³ at last CD4), though PRESTIGIO CD4 count increase only included those who remained on FTR at the end of follow-up.

The success of modern ART has produced fewer cases of MDR HIV in harder-to-treat PWH. The prevalence of PWH with resistance to three or more core ART classes in a Spanish chart review study conducted at five centres was approximately 0.5% among 14 955 screened PWH [9]. Lombardi et al. reported similar results: a declining percentage of resistance and multidrug resistance in Antiviral Response Cohort Analysis, a nationwide Italian cohort. The study found 9% of the cohort had multidrug resistance defined as resistance to 3 or more ARV classes [10]. McClung et al. reported on rates of transmitted drug resistance in the US between 2014 and 2018, with 18.9% of 50 747 people with drug resistance: an increase from previously reported 14.6% in 2006–2014 [11]. In our study, multidrug resistance was found in 20% of individuals viremic at FTR start and 6% of the suppressed, although genotype results were available only in a subset of individuals (63% viremic and 39% suppressed).

The resistance patterns to FTR have not been well described [12]. FTR is a prodrug, and the active agent temsavir binds to gp-120 on the HIV virion and prevents HIV binding to the CD4 cell. Schapiro reported on four positions in gp120 that determine the viral susceptibility to the drug. There are few polymorphic forms, and the varying regions of the gp-120 that contribute to the binding pocket are complex. These resistance-associated polymorphisms (RAPs) are modified by changes in the binding pocket, resulting in multiple amino acids

influencing susceptibility. Additionally, *in vitro* measurement of susceptibility of clinical isolates to FTR does not always reflect the heterogeneity of multiple viral species. Determining susceptibility is difficult, with no reliable genotypic pattern that predicts susceptibility or failure. Additionally, although phenotypic resistance assays exist, clinical outcome data correlating phenotypic susceptibility with specific substitutions and treatment response do not. Therefore, the use of resistance testing without reliable genotypes that predict diminished responses is of limited clinical value.

Our study examined clinical outcomes at US sites that reflected the demographics of the HIV epidemic in the United States. The diversity of the demographics of our population is drawn from predominantly Federally Qualified Health Centers and represents real-world needs of this population for novel treatments to improve health outcomes. One of the limitations of our study is the lack of dispensing data for the entire study cohort, making it difficult to assess true drug performance since a history of prior treatment failures has been linked to worse adherence. The dispensing subset may be unrepresentative, potentially overestimating adherence. Because mortality is not captured, some loss to follow-up, especially among viremic initiators, may reflect unobserved deaths, an informative censoring that could overestimate 12-month effectiveness. Secondly, without a phenotypic cut off for susceptibility to FTR, it is difficult to predict who will benefit from the medication or detect resistance patterns in viremic individuals on FTR. The persistence of immunologic improvements was hard to replicate in our study compared to the 240-week follow-up in the BRIGHT clinical trial, possibly due to shorter follow-up. Immunologic improvements seen in both suppressed and viremic initiators, coupled with the mechanism of action of blocking CD4 attachment by new virions, provide a future area for research for longer-term real-world studies. The management of 'immunologic non-responders' is challenging. In their description of HTE PWH in Italy, investigators from ICONA point out the persistent risk of increased morbidity and mortality and the need to explore evolving therapies such as FTR that can be focused on improvements in CD4 counts without viral suppression [13].

The potential to combine FTR with agents with unique targets may increase integration of FTR into care for heavily treatment-experienced individuals and should be the secondary area of future research. The successes of modern ART are significant, but do not diminish the need for ART medications with unique targets. FTR, an attachment inhibitor, provides such a unique option. The virologic effectiveness in FTR demonstrated in numerous

studies, coupled with immunologic improvements in CD4 counts, makes it an important adjunctive therapy.

CONCLUSION

In this real-world setting, FTR demonstrated its utility in sustaining viral suppression when initiated in virologically suppressed individuals. While those initiating FTR with viremia experienced reductions in viral load during follow-up, rates of full suppression were low. Importantly, persistent benefits of CD4+ T-cell expansion were observed in both subgroups and were greater in those with baseline viral suppression.

AUTHOR CONTRIBUTIONS

Richard Elion was the major contributor in writing the manuscript. Isobel McEwen and Andrew Frick analysed and interpreted data and summarized study results and methods. Cassidy Henegar, Leigh Ragone, Vani Vannappagari, Moti Ramgopal, Steven Santiago, Karam Mounzer, Gregory Huhn, and Charles Walworth provided critical revisions and interpretation of the data. Richard Elion served as the principal investigator of the study. All authors read and approved the final manuscript.

FUNDING INFORMATION

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CONFLICT OF INTEREST STATEMENT

Isobel McEwen, Andrew Frick and Richard Elion are employees of Trio Health. Cassidy Henegar, Leigh Ragone and Vani Vannappagari are employees of Viiv Healthcare. Moti Ramgopal is a consultant for Viiv Healthcare, Gilead Sciences and Merck and received research funding from these companies. Steven Santiago serves on the Medical Advisory Board for Gilead and is a Speaker for Gilead. Karam Mounzer has received research grants from Viiv, Merck and Gilead Sciences. He is on the advisory board for EpiVidian. Gregory Huhn advises for Merck, Gilead Sciences, Viiv and Eli Lilly and received grant support from Gilead Sciences and Viiv. Charles Walworth is an employee of Labcorp.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Trio Health, but restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. Data are, however, available from the corresponding author upon reasonable request and with the permission of Trio Health and Gilead Sciences.

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