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Virologic failure among people living with HIV initiating dolutegravir-based versus other recommended regimens in real-world clinical care settings

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Abstract

Background: Guidelines for initial antiretroviral treatment (ART) regimens have evolved, with integrase strand transfer inhibitors (INSTI) increasingly prominent. Research on virologic failure (VF) with INSTI therapy is predominantly from clinical trials not care settings, especially for recently approved medications including dolutegravir. We compared outcomes among people living with HIV (PLWH) who initiated recommended regimens in clinical care across the United States.

Setting: We examined two groups of PLWH at eight clinics who initiated ART regimens (August 1, 2013–March 31, 2017): those ART treatment-naive at initiation, and those treatment-experienced.

Methods: The outcome in this longitudinal cohort study was VF, defined as a viral load of ≥400 copies/mL ≥6 months after ART initiation. We examined the proportion of individuals who remained on, switched, or discontinued the regimen. Associations between regimens and outcomes were examined with adjusted Cox proportional hazards models.

Results: Among 5177 PLWH, a lower proportion experienced VF on dolutegravir- versus other INSTI- or darunavir-based regimens for previously treatment-naive (7% vs. 12% vs. 28%) and treatment-experienced PLWH (6% vs. 10% vs. 21%). In adjusted analyses, hazard ratios (HRs) were similar across regimens for the combined outcome of regimen discontinuation or treatment switch. The HR for VF comparing dolutegravir- to darunavir-based regimens was 0.30 (95%CI: 0.2–0.6) among previously treatment-naive PLWH and was 0.60 (95%CI:0.4–0.8) among treatment-experienced PLWH.

Conclusions: The proportion of previously treatment-naïve PLWH remaining on recommended ART regimens did not differ by regimen. The likelihood of VF was lower with dolutegravir- than darunavir-based regimens for previously treatment-naïve and treatment-experienced PLWH.

Keywords

viral failure; viremia; dolutegravir; viral load; viral suppression; darunavir; integrase strand transfer inhibitors; antiretroviral therapy; virologic failure

INTRODUCTION

Treatment guidelines for initial antiretroviral treatment (ART) regimens for people living with HIV (PLWH) have evolved, with integrase strand transfer inhibitors (INSTI) increasingly prominent.[1] In contrast, darunavir-based regimens (a protease inhibitor) are being deemphasized, although still remain first-line treatment in specific populations (e.g., those whose resistance testing is not yet available).[1] Much of the outcomes data, such as virologic failure with INSTI, are from trials[2–8] rather than more generalizable care. In particular, less is known about virologic failure for the more recently approved INSTI dolutegravir in care settings. However, there is interest in INSTI, particularly dolutegravir, because they may have superior tolerability, reduced pill burden, and improved outcomes.[3,4,6,9–14] It has been proposed that dolutegravir can result in viral suppression, even potentially with preexisting INSTI mutations.[15,16] This is likely due, in part, to favorable pharmacodynamic profiles, even in comparison with other INSTI.[17] Therefore, we conducted this longitudinal cohort study to compare regimen switching and virologic failure rates among PLWH who initiated recommended regimens in clinical care.

METHODS

Data source

The CFAR Network of Integrated Clinical Systems (CNICS) is a dynamic cohort of >32,000 PLWH attending clinical care at eight sites. The CNICS data repository integrates comprehensive clinical data including laboratory test results, ART use, diagnoses, demographic data, and historical information, including prior ART.[18] Institutional review boards at each site approved CNICS protocols.

Study participants

We examined two groups of PLWH who initiated one of the recommended ART regimens between 8/½013–3/3½017: PLWH known to be ART treatment-naive at initiation and those with prior ART exposure. Follow-up was censored at death, regimen change, or loss to follow-up (LTFU).

Regimen

We compared dolutegravir versus other recommended INSTI- versus darunavir-based regimens included in contemporary guidelines for initiating ART. We were interested in three regimen categories.

- Dolutegravir-based: dolutegravir/abacavir/lamivudine OR dolutegravir/tenofovir/emtricitabine

- Other recommended INSTI-based: raltegravir/tenofovir/emtricitabine OR elvitegravir/cobicistat/tenofovir/emtricitabine
- Darunavir/ritonavir/tenofovir/emtricitabine

We did not distinguish between lamivudine and emtricitabine or between tenofovir formulations (most of which were tenofovir disoproxil fumerate: TDF) (see Supplemental Digital Content Table 1 for distribution of regimens).

Outcomes

The primary outcome was virologic failure, defined as a viral load of ≥400 copies/mL ≥6 months after regimen initiation. We selected this cut-off, given the increased mortality associated with viremia at levels as low as 400 copies/mL.[19] We repeated analyses using ≥200 copies/mL to define virologic failure.[1] In addition, we examined the proportion who remained on, switched, or discontinued regimens. We defined switching in two ways: (1) any change to any regimen component whether or not it resulted in a regimen outside the initial regimen category and (2) any change to the anchor medication resulting in a regimen not part of the initial regimen category (as in previously published studies[20]). For example, changing from dolutegravir/tenofovir/emtricitabine to dolutegravir/abacavir/lamivudine would be a switch with the first definition but not the second.

Statistical analyses

We used chi-square tests for categorical variables and *t*-tests for continuous variables to assess differences in demographic and clinical characteristics by regimen category. To examine virologic failure and treatment switching during follow-up, we used Cox proportional hazards models, adjusting for age, sex, race/ethnicity, hepatitis B, hepatitis C, tuberculosis, HIV transmission risk factor, CD4 count at treatment initiation, HIV viral load, days from baseline HIV viral load until ART initiation, and site. Due to insufficient numbers, tuberculosis and hepatitis B were dropped from smaller analyses (previously treatment-naïve PLWH). Among previously treatment-experienced individuals, we also adjusted for prior INSTI use. Sensitivity analyses varied LTFU censoring definitions from 0 to 12 months after last activity and included or excluded inverse probability censoring weights based on the same variables in the main models.[21]

RESULTS

We observed 1280 treatment-naive and 3897 previously treatment-experienced PLWH from CNICS sites across the United States who initiated recommended regimens. Table 1 shows demographic and clinical characteristics by regimen and prior treatment experience. Patients who initiated a dolutegravir-based regimen were, on average, slightly older, and more likely female among previously treatment-naive but not treatment-experienced individuals, and more likely to have hepatitis C among treatment-experienced individuals (Table 1). In addition, among those who were treatment-experienced, mean CD4 count at initiation was lower, and the percentage with a viral load ≥100,000 was higher among those on darunavir (Table 1).

Treatment-naive at regimen initiation

Among treatment-naive PLWH at regimen initiation, the percentage who started and remained on dolutegravir-based regimens was similar to those on other INSTI- or darunavir-based regimens (74–79%) (Table 2). The percentage who switched regimens (all changes) was also similar among those on dolutegravir- versus other INSTI- or darunavir-based regimens (15%, 12%, 16%, respectively). However, of dolutegravir users who switched regimens, 32% changed to another dolutegravir-based recommended regimen [Triumeq: dolutegravir/abacavir/lamivudine]. The proportion who experienced virologic failure differed across regimens; it was lower for those who initiated dolutegravir- versus other INSTI- or darunavir-based regimens (7%, 12%, 28%, respectively) (Table 2).

Treatment-experienced at regimen initiation

The percentage of treatment-experienced individuals who remained on their regimens was highest for dolutegravir- (74%) and lowest for darunavir-based regimens (59%) (Table 2). The percentage who switched regimens was lower among those on dolutegravir- versus other INSTI- or darunavir-based regimens (15%, 19%, 22%, respectively). Furthermore, 18% of those who were treatment-experienced and switched regimens from a dolutegravir-based regimen changed to another recommended dolutegravir-based regimen. A lower proportion experienced virologic failure among those on dolutegravir- versus other INSTI- or darunavir-based regimens (6%, 10%, 21%, respectively).

Adjusted analyses: regimen discontinuation or treatment switch

For the combined outcome of regimen discontinuation or treatment switch, defined as changing any component of a regimen, the adjusted hazard ratios (aHRs) for previously treatment-naive PLWH were higher for dolutegravir- versus other INSTI-based regimens (1.42; 95% confidence interval [CI]:1.1–1.8) but not versus darunavir-based regimens (1.23; 95%CI:0.7–2.2). Among treatment-experienced PLWH, the aHR was not different for dolutegravir-based versus other INSTI-based (0.91; 95%CI:0.8–1.04) or darunavir-based (1.12; 95%CI:0.9–1.4) regimens. When the switching definition excluded changes to the same anchor within the same regimen category, the aHR for dolutegravir was lower than for other INSTI-based regimens (0.84; 95%CI:0.7–0.96) for treatment-experienced, but not treatment-naive PLWH (1.07; 95%CI:0.8–1.4); other regimen category comparisons were not significant.

Adjusted analyses: virologic failure

The aHR for virologic failure did not differ between dolutegravir-based versus other INSTI-based regimens, but it was lower for dolutegravir-based versus darunavir-based regimens among previously treatment-naive (0.30; 95%CI:0.2–0.6) and treatment-experienced (0.60; 95%CI:0.4–0.8) individuals (Supplemental Table 2). In the adjusted models, demographic and clinical characteristics had little association with virologic failure in previously treatment-naive individuals, however factors such as younger age, Black race, prior INSTI use, and lower CD4 count were associated with virologic failure in some treatment experienced comparisons (e.g. Supplemental Table 3 shows full model results for dolutegravir vs. darunavir models for previously treatment-naïve vs. experienced PLWH).

We conducted sensitivity analyses defining virologic failure as ≥200 copies/mL and results were similar (Supplemental Table 2). In sensitivity analyses examining virologic failure with varying censoring definitions, the aHR was consistently significantly lower for dolutegravir- versus darunavir-based regimens. In contrast, the aHR for virologic failure for dolutegravir- versus other INSTI-based regimens varied (0.7–1.2) depending on censoring definitions for LTFU with both significant and non-significant associations. Results from sensitivity analyses with inverse probability weighting for censoring were similar to results from models without inverse probability weighting (data not shown).

DISCUSSION

This study found that the proportion of PLWH in clinical care in the U.S. who remained on recommended ART regimens did not differ by regimen during follow-up for previously treatment-naive individuals. However, among treatment-naive and treatment-experienced individuals, those initiating dolutegravir-based regimens were more likely when changing regimens to remain on the same anchor (dolutegravir), suggesting regimen simplification rather than dolutegravir intolerance, which was in contrast to switches from other regimens. In unadjusted analyses, we found differences in the proportion who experienced virologic failure by regimen: a lower proportion on dolutegravir-based regimens experienced virologic failure compared with those on other INSTI- or darunavir-based regimens. In adjusted analyses, PLWH initiating dolutegravir-based regimens were less likely to experience virologic failure than those starting darunavir-based regimens, regardless of previous treatment status.

These findings build on trials of ART-naive and treatment-experienced PLWH that suggested dolutegravir may be superior to other recommended anchors,[2,5] but not consistently.[3] For example, the SAILING trial of treatment-experienced PLWH with ART resistance found a larger proportion randomized to dolutegravir versus raltegravir had viral suppression at week 48.[2] In the FLAMINGO trial of ART-naive individuals, viral suppression rates were 68% versus 80% in the darunavir versus dolutegravir arms at 96 weeks.[4,5] In contrast, SPRING-2 found no significant difference in the percentages of treatment-naive PLWH with viral suppression who received dolutegravir (88%) versus raltegravir (85%) at 48 weeks.[3] A systematic review concluded that darunavir-based regimens were inferior to dolutegravir- and raltegravir-based regimens at 96 weeks.[22] Similarly, a meta-analysis found small but significant superiority of dolutegravir- versus raltegravir- or elvitegravir-based regimens.[23] While trial results do not always generalize well to the diverse populations of PLWH in clinical care, they have suggested potential benefits of dolutegravir over other recommended regimen options.

This study builds on clinical care studies that compared dolutegravir-based regimens with others. However, several of these studies included small numbers on dolutegravir[24–29] or were single-center design, limiting generalizability[24,26–29]; or they lacked comparison arms, [24,28,29] limiting conclusions. One study compared PLWH on dolutegravir who had preexisting nucleoside reverse transcriptase inhibitor mutations to those on one of several protease inhibitors and found similarly low virologic failure rates.[25] However, with only 122 individuals in each of the two groups (including a mixture of protease inhibitors as well as a

mix of some suppressed at initiation and some not), conclusions are limited. One of the largest studies to date included 739 treatment-naive and 352 treatment-experienced individuals receiving care at the Hospital Clinic of Barcelona and suggested that discontinuations might be lower among elvitigrivir users, although questions were raised regarding whether this difference was due to elvitigrivir-based regimens always being available in a single pill, with changes in other regimens potentially due to regimen simplification.[20]

We found a higher switching rate for all regimens, including dolutegravir (e.g., 12%−16% among previously treatment-naive individuals), than might be expected given the low rates (e.g. 3%−11%) of discontinuing or switching due to toxicities in clinical trials.[2,7] However, observed rates are more consistent with the limited data available from care settings.[30] Previous studies questioned whether neuropsychological side-effects associated with dolutegravir could have led to increased discontinuation and whether this was more common among abacavir users.[30] It was hypothesized that this is due to both drugs being metabolized by the same enzyme (UDP-glucuronosyl-transferase). However, others have disputed this by evaluating plasma trough dolutegravir levels among abacavir users and nonusers.[31] Questions regarding whether integrase inhibitors may be associated with weight gain have also been raised.[32] We do not capture complete reasons for stopping or switching regimens; however, we did not see differences in rates among dolutegravir users with (23%) or without (27%) abacavir. We found similar switching rates among previously treatment-naive PLWH on dolutegravir and other INSTI until we excluded switching within category. All changes from one dolutegravir regimen to another were switches to Triumeq (dolutegravir/abacavir/lamivudine) suggesting simplification given the change to a single pill-per-day regimen. This is consistent with a prior Australian study that noted that switching to dolutegravir/abacavir/lamivudine was most often regimen simplification.[33]

Despite limiting analyses to 2013 or after, when all regimens of interest were available, LTFU for initiators of older regimens was higher (darunavir) than it was for dolutegravir initiators, in part because dolutegravir was often started more recently. We censored follow-up at last activity date for primary analyses to prevent bias due to inclusion of person-time during which an event could not occur, in order to provide the most unbiased estimates possible for laboratory outcomes.[34] We followed the guidance of Lesko et al. who demonstrated that the potential bias if this is not done can be substantial as well as unpredictable in magnitude and direction.[34] Sensitivity analyses with different LTFU definitions revealed some variations in results, highlighting the importance of this decision, particularly for analyses focused on newer regimens such as those containing dolutegravir.

This study has several strengths and limitations. It was limited to PLWH who initiated regimens starting 8/2013 and after to ensure all regimens of interest were available. While this enhances comparability across regimens, it decreases follow-up time. Furthermore, channeling bias always remains a concern. We lacked sufficient numbers to distinguish those on TDF (majority of individuals with tenofovir in their regimen) vs. those on the more recently approved tenofovir alafenamide (TAF). The diverse population is a strength, as clinical trials do not necessarily represent populations of PLWH,[35] but CNICS may not generalize to all PLWH in less-resourced U.S. settings or other regions of the world. The

data used for this study came from routine care. There were variable lengths of time between follow-up visits and clinical tests. Therefore, the timing of virologic failure could be misclassified, for example, if a patient's viral load increased but the patient was not seen right away in the clinic and tested. However, it is unlikely that this would occur differentially by regimen.

CONCLUSIONS

This study demonstrated that the proportion who remained on recommended dolutegravir-based regimens was similar to those on INSTI- and darunavir-based regimens for previously treatment-naive PLWH. While switching regimens was common in all categories, dolutegravir users were more often "switched" to another dolutegravir-based regimen with fewer pills, presumably for regimen simplification. PLWH on dolutegravir-based regimens, whether previously treatment-naive or treatment-experienced, were less likely to experience virologic failure than those on darunavir-based regimens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Demographic and clinical characteristics at initiation of regimen by regimen type for people living with HIV who were previously treatment-naive and those who were treatment-experienced

	Treatment-Naive Patients (N = 1280)				Treatment-Experienced Patients (N = 3897)			
Characteristic	**Dolutegravir-based[a] (N=426)**	**Other INSTI-based[b] (N=773)**	**Darunavir-based (N=81)**	***P* value across regimens**	**Dolutegravir-based (N=2054)**	**Other INSTI-based (N=1486)**	**Darunavir-based (N=357)**	***P* value across regimens**
Age, Mean (SD), years	38 (13)	35 (11)	36 (9)	<0.001	48 (11)	44 (11)	43 (10)	<0.001
Sex, N (%)								
Male	349 (82)	679 (88)	79 (98)	<0.001	1605 (78)	1157 (78)	270 (76)	0.6
Female	77 (18)	94 (12)	2 (2)		449 (22)	329 (22)	87 (24)	
Race/ethnicity, N (%)								
White	160 (38)	273 (35)	28 (35)	0.2	931 (45)	577 (39)	104 (29)	<0.001
Black	191 (45)	373 (48)	31 (38)		839 (41)	689 (46)	211 (59)	
Hispanic	39 (9)	69 (9)	14 (17)		212 (10)	158 (11)	30 (8)	
Other	36 (8)	58 (8)	8 (10)		72 (4)	62 (4)	12 (3)	
HIV transmission risk factor, N (%)								
MSM	239 (56)	508 (66)	53 (65)	0.03	1054 (51)	813 (55)	157 (44)	<0.001
Injection drug user	43 (10)	56 (7)	10 (12)		362 (18)	178 (12)	70 (20)	
Heterosexual	119 (28)	171 (22)	15 (19)		582 (28)	448 (30)	121 (34)	
Other/unknown	25 (6)	38 (5)	3 (4)		56 (3)	47 (3)	9 (3)	
Hepatitis B, N (%)								
Yes	11 (3)	26 (3)	2 (2)	0.7	95 (5)	73 (5)	28 (8)	0.04
No	415 (97)	747 (97)	79 (98)		1959 (95)	1413 (95)	329 (92)	
Hepatitis C, N (%)								
Yes	42 (10)	49 (6)	13 (16)	0.003	427 (21)	190 (13)	66 (18)	<0.001
No	384 (90)	724 (94)	68 (84)		1627 (79)	1296 (87)	291 (82)	
Time in care before starting regimen, mean (SD), years	1.0 (2.8)	0.6 (1.9)	0.8 (2.1)	0.02	7.7 (5.7)	5.9 (5.4)	6.1 (5.4)	<0.001
CD4 at regimen initiation, mean (SD), cells/mm^3	370 (256)	397 (278)	388 (262)	0.2	593 (347)	557 (325)	428 (298)	<0.001

Characteristic	Treatment-Naive Patients (N = 1280)				Treatment-Experienced Patients (N = 3897)			
	Dolutegravir-based[a] (N=426)	Other INSTI-based[b] (N=773)	Darunavir-based (N=81)	*P* value across regimens	Dolutegravir-based (N=2054)	Other INSTI-based (N=1486)	Darunavir-based (N=357)	*P* value across regimens
HIV RNA level at ART initiation, copies/mL, N (%)								
<100,000	391 (68)	524 (68)	55 (68)	1.0	1956 (95)	1375 (93)	316 (89)	<0.001
≥100,000	135 (32)	249 (32)	26 (32)		98 (5)	111 (7)	41 (11)	

INSTI = integrase strand transfer inhibitor; MSM = men who have sex with men; SD = standard deviation.

[a]This includes dolutegravir/abacavir/emtricitabine and dolutegravir/tenofovir/emtricitabine

[b]This includes elvitegravir/cobicistat/tenofovir/emtricitabine and raltegravir/tenofovir/emtricitabine

Table 2.

Outcomes by regimen type for people living with HIV who were previously treatment-naive and those who were treatment-experienced

	Treatment-Naive Patients (N = 1280)				Treatment-Experienced Patients (N = 3897)			
Characteristic	**Dolutegravir-based[a] (N=426)**	**Other INSTI-based[b] (N=773)**	**Darunavir-based (N=81)**	***P* value across regimens**	**Dolutegravir-based (N=2054)**	**Other INSTI-based (N=1486)**	**Darunavir-based (N=357)**	***P* value across regimens**
Duration of follow-up, mean (SD), days	342 (283)	494 (353)	564 (422)	<0.001	367 (286)	430 (336)	436 (341)	<0.001
Remained on regimen, N (%)	316 (74)	601 (78)	64 (79)	0.3	1526 (74)	1018 (69)	212 (59)	<0.001
Experienced virologic failure, (≥400 copies/mL) N (%)	28 (7)	93 (12)	23 (28)	<0.001	115 (6)	152 (10)	75 (21)	<0.001
Died, N (%)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	
Discontinued regimen, N (%)	44 (10)	79 (10)	4 (5)	0.3	226 (11)	192 (13)	66 (18)	<0.001
Switched regimen (all changes), N (%)	66 (15)	93 (12)	13 (16)	0.2	302 (15)	276 (19)	79 (22)	<0.001
Switched from regimen (but remained in category), N (%)	21 (32)	1 (1)	0 (0)	<0.001	55 (18)	15 (5)	0 (0)	<0.001
Switched regimen (switch resulted in new category), N (%)	45 (68)	92 (99)	13 (100)	<0.001	247 (82)	261 (95)	79 (100)	<0.001

INSTI = integrase strand transfer inhibitor; SD = standard deviation.

[a] This includes dolutegravir/abacavir/emtricitabine and dolutegravir/tenofovir/emtricitabine

[b] This includes elvitegravir/cobicistat/tenofovir/emtricitabine and raltegravir/tenofovir/emtricitabine