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MAJOR ARTICLE

Treatment Switch to Dolutegravir With 2 Nucleoside Reverse-Transcriptase Inhibitors (NRTI) in Comparison to Continuation With Protease Inhibitor/Ritonavir Among Patients With Human Immunodeficiency Virus at Risk for Prior NRTI Resistance: A Cohort Analysis of Real-World Data

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Background. Switching antiretroviral regimens when human immunodeficiency virus (HIV) viremia is controlled for a new regimen is challenging when there is the potential for prior nucleoside reverse-transcriptase inhibitor (NRTI) resistance. The objective was to study virologic outcomes after switching to dolutegravir compared with remaining on a boosted protease inhibitor (protease inhibitor/ritonavir [PI/r]) regimen in people with HIV (PWH) with prior documented virologic failure and/or exposure to mono/dual NRTIs.

Methods. We used the Quebec HIV Cohort including 10 219 PWH whose data were collected at 4 sites in Montreal, Canada. We included all PWH with documented virologic failure or exposure to mono/dual NRTI therapy who were virologically suppressed on a PI/r-based regimen for at least 6 months on or after January 1, 2014 (n = 532). A marginal structural Cox model analysis was used to estimate the effect of the switch to dolutegravir on virologic outcome compared with remaining on PI/r. The outcome was defined as 2 consecutive viral loads (VLs) >50 copies/mL or 1 VL >50 copies/mL if it occurred at the last VL available.

Results. Among 532 eligible participants, 216 (40.6%) had their regimen switched to dolutegravir with 2 NRTIs, whereas 316 (59.4%) remained on the PI/r with 2 NRTIs. The weighted hazard ratio for the effect of dolutegravir switch on virologic failure compared with patients whose regimen remained on PI/r was 0.57 (95% confidence interval, 0.21–1.52).

Conclusions. We did not find evidence of an increased risk for virologic failure after switching to dolutegravir from PI/r among patients with previous virologic failure or prior exposure to mono/dual NRTI.

Keywords. antiretroviral regimen (ART); dolutegravir switch; protease inhibitor/ritonavir (PI/r); previously documented virologic failure and prior exposure to mono/dual NRTI combination antiretroviral therapy.

It remains unknown whether people with human immunodeficiency virus (PWH) who are virologically suppressed on a boosted protease inhibitor (protease inhibitor/ritonavir [PI/r]) regimen but who are at risk for prior nucleoside reverse-transcriptase inhibitors (NRTIs) resistance can be safely switched to dolutegravir. The European AIDS Clinical Society [1] and US Department of Health and Human Services [2] recommend, when contemplating a regimen switch in these situations, to maintain a suppressive regimen or to replace it only if the other 2 NRTIs in the antiretroviral therapy (ART) combination are effective in maintaining virologic suppression [1] or to consult a human immunodeficiency virus (HIV) specialist [2].

Previous studies with the first-generation of integrase strand transfer inhibitors (INSTIs) have shown that the replacement of an ART among patients with previously documented virologic failures, or proven or suspected resistance

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mutations, lead to more virologic failures than the maintenance of the boosted protease inhibitors (PIs) regimen. For example, the SWITCHMRK study showed that replacing a lopinavir/ritonavir regimen with raltegravir led to more virologic failures in a population with prior treatment failures [3]. After these results, switch studies have excluded patients with prior virologic failures or resistance mutations or those who were exposed to suboptimal mono/dual NRTI therapies [4–7].

However, even if these strategies have never been tested, there are indirect indications that the second generation of INSTIs could be an effective therapeutic choice for switch strategies in experienced patients with documented virologic failure or resistance mutation. Unlike raltegravir and elvitegravir, INSTIs such as dolutegravir or bictegravir are recognized to have a high genetic barrier with fewer side effects and lower risk for resistance mutations at failure [8–11]. The efficacy of dolutegravir is well recognized for the replacement of ART among patients without documented virologic failure or resistance mutations [4, 8, 12]. Some studies have also shown that dolutegravir was superior or noninferior to the first generation of INSTIs or to PI/r in experienced and naive patients [13–16]. Moreover, some treatment failure studies have shown the superiority of a dolutegravir-based regimen. The DAWNING study [17] showed the superiority of dolutegravir with 2 NRTIs when comparing dolutegravir to PI/r among patients with current virologic failure to a first-line non-NRTI (NNRTI)-based regimen. The SAILING study [18] showed that given with an optimized background regimen, dolutegravir was superior to raltegravir in experienced patients failing their current regimen. These data support the high genetic barrier to resistance of dolutegravir and its potential role in switching therapy in case of prior presumed or documented resistance.

The objective of our study was to analyze virologic outcomes after switching to dolutegravir compared with remaining on a boosted PI (PI/r) regimen in PWH with prior documented virologic failure and/or exposure to mono/dual NRTIs. A weakness of many observational studies is that they ignore the longitudinal nature of exposure and confounding. The aim of our study was also to avoid these pitfalls by applying an established causal inference method to provide strong evidence with "real-world" data.

METHODS

The Quebec HIV Cohort is an observational cohort of PWH followed in 4 centers that specialized in HIV care in Montreal. Sites included 2 community clinics, "Clinique Médicale l'Actuel (CMA)" and "Clinique de Médecine Urbaine du Quartier Latin (CMUQL)", and 2 hospital clinics, "Centre Hospitalier de l'Université de Montréal (CHUM)" and "McGill University Health Center (MUHC)." Patient charts were used to prospectively collect data at every clinical visit that usually takes place every 3 to 6 months. Data collection was done independently in each center. It began in 1985 at CMA, in 1997 at CMUQL, and in 1989 at both CHUM and MUHC. Data were integrated into individual databases using ACCESS and were merged into a central database using encryption while considering visits belonging to the same patient followed across several sites. After the validation step (data completeness and correction), 10 219 PWH were included in the cohort, 5844 of whom were currently being followed in clinics as of August 31, 2017. The following variables were assessed: date of HIV diagnosis, sociodemographic variables (age, sex, centers), and risk factors for HIV acquisition. We also used time-varying variables documented or potentially updated at every patient's visit including ART received, resistance mutations, and biochemical laboratory results (CD4 count, viral load [VL], and testing for antihepatitis C virus antibodies and hepatitis B surface antigen). The mean (standard deviation [SD]) and median (interquartile range) age at entry in the Quebec HIV Cohort were 37.4 years (10.3) and 36.4 years (30.1–43.8), respectively, males constituted 84.1% of the cohort, and patients belonged to different risk groups (men who have sex with men, injection drug users, those who were infected by vertical transmission, and those from endemic countries).

We included all PWH in the cohort who, on January 1, 2014 or later, had documented virologic failure and/or who had been exposed to mono/dual NRTI therapy, and who were virologically supressed on a PI/r-based ART for at least 6 months. The PIs considered in the study included lopinavir, darunavir, or atazanavir. The inclusion of PWH with previously documented virologic failure in the cohort was based on the definition of virologic failure recommended by the Guidelines for adults living with HIV used by health professionals in Quebec [19], which is defined as follows: a documented VL >1000 copies/mL after 16 weeks of therapy, or VL >400 copies/mL after 24 weeks, or 2 consecutive VL >50 copies/mL after 48 weeks or after having reached suppressive viremia (<50 copies/mL), or VL >50 copies/mL at discontinuation treatment. Prior exposure to mono/dual NRTI therapy was defined as any previous exposure to a single NRTI or 2 NRTIs for at least 1 month. The mono-NRTI therapy included zidovudine or didanosine used until 1997. Dual NRTI therapy included the following combinations: lamivudine/zidovudine, lamivudine/stavudine, didanosine/lamivudine, zalcitabine/zidovudine, didanosine/zidovudine, zalcitabine/lamivudine, and didanosine/stavudine that were used between 1996 and 2005.

There were 532 PWH who, on January 1, 2014 or later, had documented virologic failure and/or who had been exposed to mono/dual NRTI therapy based on these definitions, and who were all on a virologically suppressed PI/r-based ART for at

least 6 months. This included 15 new users of PIs who fulfilled these criteria after January 1, 2014.

Patient Consent Statement

This study was approved by the Research Ethics Boards of the Sainte Justine University Hospital Center, MUHC, and CHUM with a waiver of consent.

Statistical Analysis

A survival analysis was conducted to analyze the risk of virologic failure of patients initially on a virologically suppressed boosted PI (PI/r) regimen where some eventually switched to dolutegravir. The index date or time zero was defined as January 1, 2014 or the earliest subsequent date where the inclusion criteria were met. An exploratory Kaplan-Meier plot with an unadjusted Peto-Prentice test were used to estimate and compare the cumulative incidence of virologic outcome in the group that maintained their original regimen versus the patients who eventually switched (PI/r + 2 NRTIs maintenance versus dolutegravir + 2NRTIs switch). Following the Target Trials approach [20], for the main analysis treatment switch was defined as the first change in regimen from PI/r to dolutegravir, and switched patients were considered exposed to dolutegravir thereafter. The follow-up time was considered from time 0 until a virologic failure occurred or, for censored observations, the last visit for which a VL measurement was available. In the case of therapy interruption outside of the treatment switch of interest, patients were censored on the date of interruption. The outcome of postindex date virologic failure was defined as 2 consecutive VL >50 copies/mL or 1 VL >50 copies/mL if the last VL available was VL >50 copies/mL.

We fit a marginal structural Cox model to estimate the effect of time-dependent exposure to dolutegravir on the hazard of virologic outcome using the approach described by Fewell et al [21, 22]. The database was discretized into 5-month intervals. We applied stabilized inverse probability of treatment and censoring weights (IPW) using logistic regression models for the probability of therapy switch to dolutegravir and for the probability of not being censored at every 5-month time point (t). These models were adjusted for past CD4 counts (continuous) as a time-dependent variable and baseline covariates (measured at time zero), namely, ART duration (continuous), HIV infection duration (continuous), and age (continuous). Missing CD4 values were replaced by the most recent documented CD4 value. A 5% truncation was used for the censoring weights due to large values. To approximate the hazard ratio (HR) for the effect of exposure at time t to dolutegravir with 2 NRTIs on virologic outcome in the marginal structural Cox model, we used our IPW in a pooled logistic regression conditional on switch status at time t [23]. All statistical analyses were performed using STATA version 14 software with the *pscore* package (StataCorp, College Station, TX).

RESULTS

Among 532 eligible participants, 216 (40.6%) had their regimen switched to dolutegravir with 2 NRTIs, whereas 316 (59.4%) remained on their PI/r with 2 NRTIs regimen throughout follow-up. Our definition of previously documented virologic failure included virtually no patient (only 2 per group) with a failure based on a VL 50–100. Most patients continued the same 2 NRTIs when switching to dolutegravir

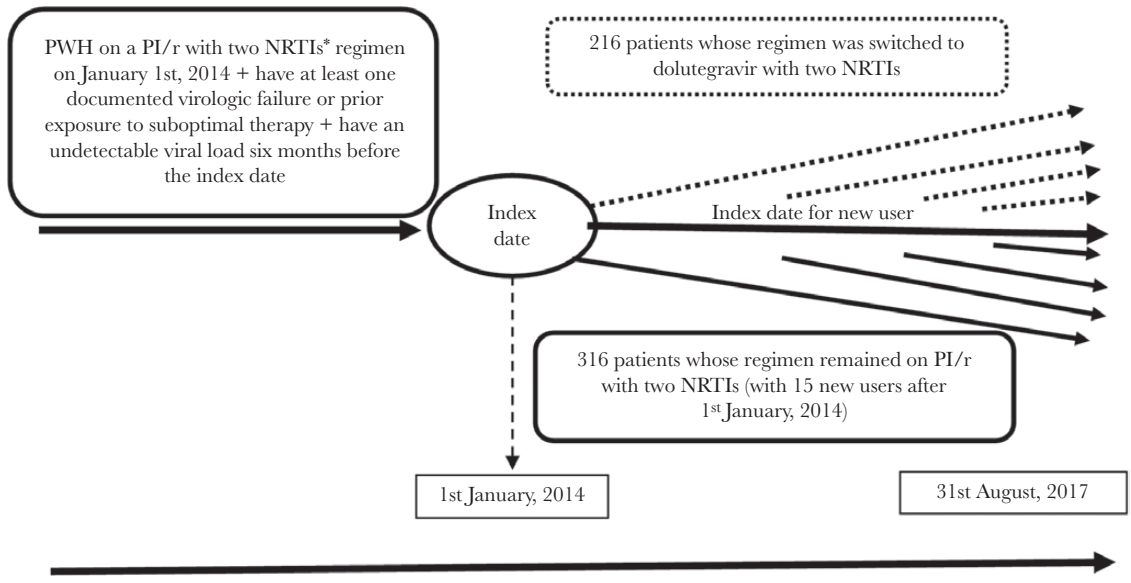


Figure 1. Patients from the Quebec HIV Cohort who were eligible for the study. CI, confidence interval; PHW, people with human immunodeficiency virus; PI/r, protease inhibitor/ritonavir; NRTIs, nucleoside reverse-transcriptase inhibitors. *NRTIs = abacavir + lamivudine or tenofovir disoproxil + emtricitabine or tenofovir disoproxil + lamivudine.

Table 1. Baseline Characteristics of Patients (n = 532) With Prior Virologic Failure or Exposure to Mono/Dual NRTI Therapy According to ART Exposure Group

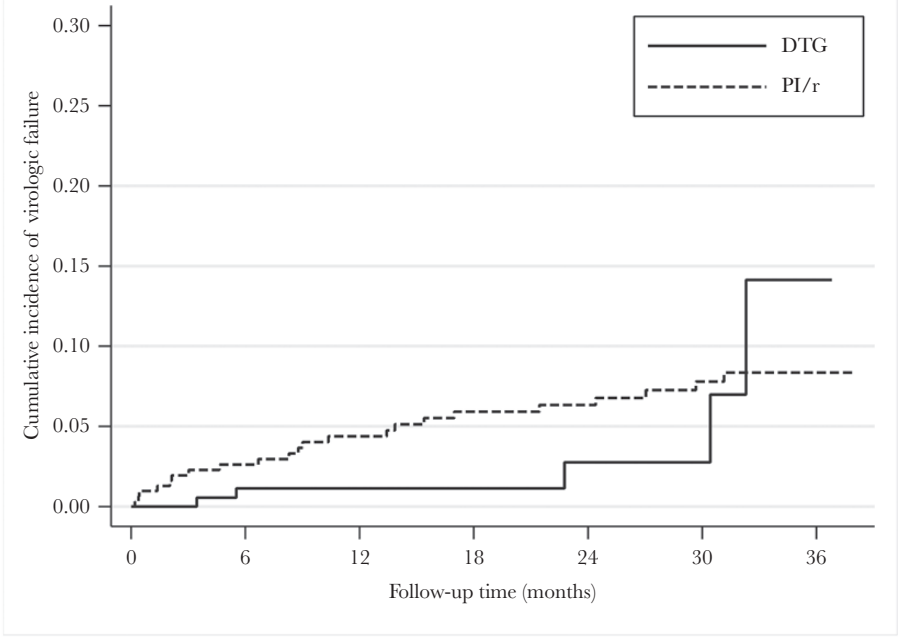
Patient Characteristics Measured at Baseline (Index Date)		PWH Whose Regimen Was Switched to Dolutegravir With 2 NRTIs (n = 216)	PWH Whose Regimen Remained on PI/r With 2 NRTIs (n = 316)
Age in years	Mean (SD)	50.8 (9.5)	52.6 (8.6)
	Median (IQR)	51.2 (44.9–56.9)	52.4 (47.5–57.8)
Sex, N (%)	Male	190 (87.9%)	272 (86.1%)
	Female	26 (12.1%)	44 (13.9%)
Risk factor for HIV acquisition, N (%)	MSM	153 (70.8%)	222 (70.2%)
	Bisexual	7 (3.2%)	10 (3.2%)
	Heterosexual	46 (21.3%)	59 (18.7%)
	From endemic	20 (9.3%)	33 (10.4%)
	Vertical transmission	2 (0.9%)	1 (0.3%)
Backbones, N (%)	Abacavir/lamivudine	159 (73.6%)	124 (39.2%)
	Tenofovir disoproxil/ emtricitabine	57 (26.4%)	186 (58.9%)
	Tenofovir disoproxil/ lamivudine	0 (0%)	6 (1.9%)
CD4 count (cells/mm^3)	Mean (SD)	675.9 (287.9)	618.9 (288.9)
	Median (IQR)	621.5 (480.0–851.0)	590.0 (430.0–748.0)
HIV Infection duration (in year)	Mean (SD)	15.3 (6.1)	16.8 (4.9)
	Median (IQR)	15.9 (11.0–19.0)	17.5 (15.5–19.3)
ART duration (in years)	Mean (SD)	13.6 (5.0)	16.8 (4.9)
	Median (IQR)	15.2 (9.9–17.0)	17.5 (15.5–19.3)
Mutations 184V/I, N (%)	Yes	25 (32.5%)	59 (48.4%)
	No	52 (67.5%)	63 (51.6%)
	Not tested	139	194
Other NRTI mutations[a]	Yes	29 (37.7%)	57 (46.7%)
	No	48 (62.3%)	65 (53.3%)
	Not tested	139	194
Previously documented virologic failure	Yes	204 (94.4%)	152 (48.1%)
	No	12 (5.6%)	164 (51.9%)
Previous exposure to mono/ dual NRTI therapy[b]	Yes	64 (29.6%)	217 (68.7%)
	No	152 (70.4%)	99 (31.3%)
Hepatitis B history, N (%)	Positive for HBsAg	8 (3.7%)	39 (12.3%)
Hepatitis C history, N (%)	Positive for anti-HCV	28 (12.9%)	46 (14.6%)

Abbreviations: ART, antiretroviral therapy; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range (25%–75%); MSM, men who have sex with men; NRTI, nucleoside reverse-transcriptase inhibitor; PI/r, protease inhibitor/ritonavir; PWH, people with HIV; SD, standard deviation.

[a]Others NRTIs mutations in mutation sites: M41, K65, D67, T69, K70, L74, Y115, Q151, L210, and T215.

[b]Monotherapy or dual therapy with 1 or 2 NRTIs for at least 1 month before baseline.

with 17.6% (38 of 216) who also have had a switch to 2 new NRTIs. Figure 1 shows the details regarding the selection of PWH in the study. Table 1 shows the characteristics of patients at index date according to exposure status; mean age (SD) was 50.8 years (9.5) and 52.6 years (8.6) for patients whose regimen was switched to dolutegravir and for those who remained on PI/r, respectively. The NRTI backbones used with dolutegravir in the switch group were abacavir/lamivudine (73.6%) or tenofovir disoproxil/emtricitabine (26.4%). In the PI/r maintenance group, 39.2% used abacavir/lamivudine, 58.9% used tenofovir disoproxil/emtricitabine, and 1.9% used tenofovir disoproxil/lamivudine, and the PI used was lopinavir in 26.6% (84 of 316), darunavir in 39.6% (125 of 316), and atazanavir in 33.8% (107 of 316). There were 199 PWH tested for mutations before time 0, from which 84 cases documented M184 V/I mutations. Among the subjects tested in the dolutegravir switch group, 32.5% (25 of 77) had the M184 V/I mutation, whereas 48.4% (59 of 122) of those tested in the PI/r maintenance group had that mutation. Among the 25 PWH with M184V whose regimen was switched to dolutegravir, 60% (15 of 25) included the backbone abacavir/lamivudine and 40% (10 of 25) included tenofovir disoproxil fumarate/emtricitabine. There was no virologic failure in this subpopulation. Among the subjects tested for genotyping before time 0, other NRTIs resistance mutations (in mutation sites: M41, K65, D67, T69, K70, L74, Y115, Q151, L210, and T215) have been found in 37.7% (29 of 77) patients of the dolutegravir switch group and in 46.7%



	0	6 months	12 months	18 months	24 months	30 months	36 months
Exposed: PWH whose regimen was switched to dolutegravir +2 NRTIs during follow-up							
Number at risk	205	167	136	103	50	24	4
Failure		2	0	0	1	0	2
Cumulative incidence (%) (95% CI)		1.1 (0.28–4.4)	1.1 (0.28–4.4)	1.1 (0.28–4.4)	2.7 (0.8–9.6)	2.7 (0.8–9.6)	14.1 (4.5–39.7)
Unexposed: PWH whose regimen remained on PI/r + 2 NRTIs throughout follow-up							
Number at risk	314	287	261	232	213	170	122
Failure		8	5	4	1	3	1
Cumulative incidence (%) (95% CI)		2.6 (1.3–5.2)	4.4 (2.6–7.4)	5.9 (3.7–9.4)	6.4 (4.0–9.9)	7.8 (5.1–11.8)	8.3 (5.5–12.5)

Figure 2. Cumulative incidence of postindex virologic failure for people with human immunodeficiency virus (PWH) whose regimen was maintained on protease inhibitor/ritonavir (PI/r) relative to those whose regimen was switched to dolutegravir (DTG). Peto-Prentice $P = .15$. CI, confidence interval; NRTIs, nucleoside reverse-transcriptase inhibitors.

(57 of 122) of the PI/r group. One PI mutation was documented in a patient who switched to dolutegravir compared with 0 patients in the PI/r group, whereas INSTI resistance mutations (all mutation site E138) were documented among 4 patients in the dolutegravir group compared with 5 in the PI/r group.

Figure 2 shows the crude cumulative incidence of patients whose regimen was switched to dolutegravir and those whose regimen was maintained on PI/r. A total of 28 postindex virologic failures occurred in the cohort (5 in the dolutegravir switch group and 23 in the PI/r maintenance group). The crude cumulative incidence of virologic failure at 2 years was 1.1%

Table 2. Marginal Structural Cox Model Estimates for the Effect of Treatment Regimen on Postindex Virologic Failure (n = 532)

Exposure	Person-Years	Number of Virologic Failure	Crude HR (95% CI)	IPTW×IPCW-Weighted Marginal Structural Model HR (95% CI)
Exposure to PI/r with 2 NRTIs	723.56	23	1 (reference)	1 (reference)
Exposure to dolutegravir with 2 NRTIs	291.54	5	0.54 (0.23–1.24)	0.57 (0.21–1.52)

Abbreviations: CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weights; IPTW, inverse probability of treatment weights; NRTIs, nucleoside reverse-transcriptase inhibitors; PI/r, protease inhibitor/ritonavir.

(95% confidence interval [CI], 0.2–4.4) for patients whose regimen was switched to dolutegravir and 6.3% (95% CI, 4.0–9.8) for those who remained on PI/r (Peto-Prentice test $P = .15$). Virologic failure outcome was defined using the last available VL >50 copies/mL for 80% (4 of 5) and 30.4% (7 of 23) of the patients who switch to dolutegravir and those who remain on PI/r, respectively. Among patients who switch to dolutegravir (n = 216) and among those who remained on PI/r (n = 316), 20 and 86 were censored because of treatment discontinuation, respectively. Table 2 presents the HR estimated following the IPW marginal structural model. The point estimate suggests that dolutegravir switch is associated with a better outcome, but the wide CIs for the HR do not allows us to conclude that a difference exists (weighted HR, 0.57; 95% CI, 0.21–1.52). If we restricted the analysis to only patients with documented M184 mutation (n = 84, total follow-up time of 152.9 person-years), the crude cumulative incidence of virologic failure at 24 months for patients whose regimen was switched to dolutegravir and for those whose regimen remained on PI/r were 0% (0–0) and 4.3% (1.7%–16.3%), respectively (P value/log-rank test = .42) (data not shown).

DISCUSSION

There is only indirect evidence that a 2-NRTI + PI/r virologically suppressed regimen could be replaced by a 2-NRTI + dolutegravir regimen, and these switches are not openly recommended for patients with previously documented virologic failure or prior exposure to suboptimal mono/dual NRTI [1, 2]. Our study, undertaken among patients with previously documented virologic failure or prior exposure to suboptimal therapy, brings new support to this strategy. In addition, it suggests that virologic outcomes may be better after dolutegravir switch compared with PI/r maintenance.

Previous studies (4 randomized controlled trials [RCTs] and 1 observational study) have clearly shown the virologic efficacy of dolutegravir in both naive and experienced patients [14, 15, 24–26]. Dolutegravir may also offer some advantages including a high genetic barrier and a reduced risk of lipid disorders [4, 27]. Integrase strand transfer inhibitors are also recognized to not alter the size of virus reservoirs or immune activation [28]. However, there is uncertainty regarding the safety of dolutegravir switch among PWH who have previously documented virologic failure, prior exposure to suboptimal therapy, or presence of resistance mutations. Some studies (RCTs, meta-analyzes, and observational studies) have clearly shown the superiority of dolutegravir over other first-generation INSTIs [29–32]. Some studies have also shown the superiority or noninferiority of dolutegravir compared with PI/r regimen in patients without documented virologic failure or resistance mutations. For example, the NEAT022 study [4], an RCT, showed no statistically significant difference between patients whose regimen was switched to dolutegravir and those who remained on PI/r: 92.2% of switched patients (n = 205) and 87.0% of maintained patients (n = 210) had a VL <50 copies/mL at 96 weeks of follow-up for a mean difference of 5.2% (95% CI, −0.6 to 11). This study concluded that dolutegravir was noninferior but excluded patients with documented prior virologic failure or resistance mutations. In the context of the treatment of a current virologic failure, DAWNING [17], an RCT among patients failing a first-line NNRTI-based regimen, showed a superiority of dolutegravir with 2 NRTIs compared with PI/r with 2 NRTIs after 48 weeks of follow-up with an adjusted mean difference of 13.8% (95% CI, 7.3–20.3). Chen et al [33], in an observational study of patients on a virologically suppressed regimen, did not show a difference in the virologic outcome (VL >50 copies/mL) at 48 weeks between PWH whose regimen was switched to dolutegravir (1.1%) compared with those who remained PI/r (3.8%), for a mean difference of −2.7% (95% CI, −5.5 to 0.5). In this study, 44.4% and 19.5% of patients had previous documented virologic failures in the group on dolutegravir and on PI/r, respectively. It is interesting to note that 97.1% (34 of 35) and 96.2% (25 of 26) of switched and unswitched patients with documented M184 mutations had a VL <50 copies/mL at 48 weeks, respectively. These results were corroborated by the study by Sörstedt et al [34] who compared patients with previous NRTI mutations (122 whose regimen was switched to dolutegravir and 122 whose regimen was maintained on PI/r) and found that the proportions of virologic success were 96.7% and 97.5%, respectively, after a median of follow-up of 78 weeks. In this study, M184 V/I and NRTI mutations were the most common mutations and were documented in 36.5% and 27.7% of patients in the dolutegravir and PI/r groups, respectively. It is interesting to note that there was an absence of new NRTI and INSTI mutations in patients who switched on dolutegravir. The study 4030 [35] also showed the virologic efficacy of dolutegravir in patients with pre-existing NRTI resistance. In this study, at 48 weeks, 89.4% (42 of 47) and 94.1% (32 of 34) had a VL <50 copies/mL for patients with M184V/I on bictegravir and dolutegravir, respectively. Finally, the prospective cohort study of 5 European cohorts studying patients on abacavir/lamivudine/dolutegravir did not conclude a difference in virologic outcomes between the groups of patients with M184 mutation [36]. In this study with a median follow-up of 289 days, the virologic failure incidence in patients with and without M184V/I mutation was not statistically significant different (29.8 per 1000 person-years [95% CI, 11.2–79.4] vs 13.6 [95% CI, 8.4–21.8], respectively). Our study, undertaken among patients with previously documented virologic failure and/or prior exposure to mono/dual NRTI combination ART, did not demonstrate a difference in the virologic outcomes of patients whose regimen was switched to dolutegravir in comparison with those whose regimen was maintained on PI/r.

Our study also has significant methodological strengths despite certain weaknesses including the potential for unmeasured confounding bias, inherent to all observational design. We used marginal structural models to control for time-dependent confounding by CD4 count that also has the potential to be influenced by prior exposures and other variables. Marginal structural models allow us to define causal effects between the time-dependent exposure and the outcome, although estimation depends on several factors including the above-mentioned, no-unmeasured-confounders assumption and a well defined exposure (comparison of treatment options after a virologic failure or after switch). The analysis was based on an established causal inference method conceived to provide strong evidence using observational and real-world data. Valid causal inference relies on underlying assumptions that include positivity, consistency, noninterference, and absence of unmeasured confounders [37]. Positivity was empirically validated by verifying the size of the weights. Compliance with the consistency criterion is credible because we followed the Target Trials approach [20], and the observed exposure corresponds to an intervention that we could hypothetically assign. Compliance with the noninterference criterion is also credible because it does not seem plausible that the exposure of one person affects the counterfactual result of another. The absence of unmeasured confounding factors cannot be guaranteed, although subject matter knowledge leads us to believe that the likely confounding variables have been measured and considered in the model. Our study also has a high potential for generalizability with a nonnegligible sample size of patients followed across 4 sites with appreciable follow-up time. However, it is important to mention that a very small number of virologic failure occurred during follow-up, which limits the power of the study for the comparison of treatment groups. It would also have been interesting to have genotyping data from patients who experienced virologic failures after time 0, but this was not done systematically in our observational study.

CONCLUSIONS

Our study adds to the body of evidence suggesting that switching to dolutegravir is likely a safe option for patients controlled on PI/r who have prior resistance, although larger studies are still needed to have more precise estimates of virologic failure among such patients. Dolutegravir, recognized as offering some advantages including a high genetic mutation barrier, reduced risk of lipid disorders, and no impact on the virus size reservoirs or immune activation [4, 27, 28], may offer a safe and desirable option for ART replacement for patients on a PI/r regimen with antecedent of virologic failure or prior exposure to mono/dual NRTI.

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