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Dolutegravir-based dual maintenance regimens combined with lamivudine/emtricitabine or rilpivirine: risk of virological failure in a real-life setting

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Background: Maintenance ART with dolutegravir-based dual regimens have proved their efficacy among HIV-1-infected subjects in randomized trials. However, real-life data are scarce, with limited populations and follow-up.

Objectives: We assessed virological failure (VF) and resistance-associated mutations (RAMs) on dolutegravir maintenance regimens in combination with rilpivirine or with lamivudine or emtricitabine (xTC) and analysed the factors associated with VF.

Methods: Between 2014 and 2018, all HIV-1-infected adults included in the Dat'AIDS cohort and starting dolutegravir/rilpivirine or dolutegravir/xTC as a maintenance dolutegravir-based dual regimen were selected. VF was defined as two consecutive HIV RNA values >50 copies/mL or a single value >400 copies/mL. We compared cumulative genotypes before initiation of a maintenance dolutegravir-based dual regimen with genotype at VF.

Results: We analysed 1374 subjects (799 on dolutegravir/rilpivirine and 575 on dolutegravir/xTC) with a median follow-up of 20 months (IQR = 11–31) and 19 months (IQR = 11–31), respectively. VF occurred in 3.8% ($n = 30$) of dolutegravir/rilpivirine subjects and 2.6% ($n = 15$) of dolutegravir/xTC subjects. Among subjects receiving dolutegravir/rilpivirine, two genotypes harboured emerging RAMs at VF: E138K on NNRTI ($n = 1$); and E138K+K101E on NNRTI and N155H on INSTI ($n = 1$). Among subjects receiving dolutegravir/xTC, no new RAM was detected. The only predictive factor of VF on dolutegravir/rilpivirine was the history of failure on an NNRTI-based regimen (adjusted HR = 2.97, 95% CI = 1.28–6.93). No factor was associated with VF on dolutegravir/xTC.

Conclusions: In this large real-life cohort, dolutegravir/rilpivirine and dolutegravir/xTC sustained virological suppression and were associated with a low rate of VF and RAM emergence. Careful virological screening is essential before switching to dolutegravir/rilpivirine in virologically suppressed patients with a history of NNRTI therapy.

Introduction

Dual therapies with integrase strand transfer inhibitors (INSTIs) as maintenance therapies in people living with HIV are nowadays recommended in international guidelines, allowing reduction of potential side effects, drug exposition and drug–drug interactions.[1,2] Two dolutegravir-based dual therapies have been evaluated in large controlled randomized trials. SWORD-1 and SWORD-2 trials demonstrated the long-term efficacy of the

dolutegravir/rilpivirine combination, which was non-inferior to continuing the current three-drug regimen up to 100 weeks with a good safety profile.[3,4] The dolutegravir/lamivudine combination has shown a sustained efficacy over 96 weeks in maintenance therapy compared with a standard tenofovir disoproxil/emtricitabine-based triple therapy.[5] Real-life data investigated most often small sample size populations and short follow-up[6–10] with limited virological and genotyping data.[5,11] We aimed to analyse virological failure and resistance-associated mutations (RAMs) during dolutegravir-based dual regimens in combination with rilpivirine or with emtricitabine or lamivudine (xTC) and to identify the factors associated with virological failure from a large French cohort (Dat'AIDS cohort).

Methods

Study design and setting

The Dat'AIDS cohort is a national French multicentre cohort involving 28 French HIV reference centres (clinicaltrials.gov reference NCT02898987). The data collection was approved by the French Data Protection Authority (CNIL number 1357652) and all subjects signed informed consent before being included in the cohort. Patient-related data obtained during medical encounters are recorded prospectively in a structured database. Data quality is ensured by automated checks during data capture, regular controls, annual assessments and *ad hoc* processes before any scientific analysis is performed. We designed an observational cohort study assessing prospectively collected data to evaluate virological failures on a dolutegravir-based maintenance dual regimen (2DR).

All HIV-1-infected, ART-experienced and virologically suppressed adults who switched to dolutegravir/rilpivirine or dolutegravir/xTC as maintenance therapy between 1 January 2014 and 2 September 2018 were included. The dual regimen was considered as maintenance if the last plasma HIV RNA value (assessed <6 months before the dual regimen initiation) was ≤50 copies/mL and if ART was ongoing at the time of dual regimen initiation. The exclusion criteria were: (i) absence of plasma HIV RNA in the prior 6 months before the start of the dual regimen; (ii) absence of plasma HIV RNA between the initiation and discontinuation of the dual regimen (or censoring at the end of the study period) not permitting outcome assessment; (iii) duration of dual therapy <7 days; and (iv) a previous history of dual therapy, whatever the drugs. For subjects with multiple episodes of dolutegravir-based dual therapy during the inclusion period, only the first episode was considered for analysis.

Outcomes

The primary outcome was virological failure during the dual regimen, defined as two consecutive plasma HIV RNA values >50 copies/mL or a single value >400 copies/mL. The secondary outcomes were: (i) the frequency and reasons for dual regimen discontinuation; (ii) the identification of new RAMs at virological failure; and (iii) the factors associated with virological failure.

Data collection and study variables

Demographic data, HIV and antiretroviral history, the reasons for current and previous ART line discontinuation, history of HIV plasma viral load, history of CD4 cell counts and genotypic resistance data were extracted from the database. Duration of viral suppression was defined as the period before the 2DR during which plasma HIV RNA persisted ≤50 copies/mL.

History of virological failure was defined as the discontinuation of the ART regimen prior to the 2DR having 'virological failure' as the reason reported by the clinician. This variable was stratified according to the class of antiretroviral contained in the regimen concerned (NRTI, NNRTI, INSTI). The initiation of the first ART was dichotomized in the analysis of the results according to whether it occurred before or after the arrival of HAART in 1996. Regarding resistance analysis, all the genotypes available prior to the initiation of the 2DR were cumulated and compared with the genotypes available at virological failure. The genotypes could be determined using RNA or proviral DNA and were analysed according to the French ANRS algorithm of resistance.[12] Regarding virological failure, the detection of the event could be followed or not by discontinuation of the 2DR. All causes of dolutegravir-based 2DR discontinuation reported by the physician were collected.

Statistical analysis

A subgroup analysis was performed according to the second agent associated with dolutegravir, i.e. rilpivirine or xTC. First, a descriptive analysis was performed considering baseline patient characteristics and primary and secondary outcomes. Continuous variables are summarized as medians and IQRs. Categorical variables are summarized as frequencies and percentages. Second, a univariate and multivariate Cox proportional hazards regression model was built to determine factors associated with virological failure, estimating HRs and 95% CIs. Subjects were right-censored at the date of the last follow-up visit. Age, CDC stage C, CD4 cell count nadir, plasma HIV RNA zenith, duration of undetectable HIV RNA before initiation of the 2DR, history of virological failure leading to discontinuation of NRTIs, NNRTIs or INSTIs and first ART started ≤1996 were considered as explicative variables. Variables associated with *P* values <15% in the bivariate analysis were entered into the multivariable model. A two-sided *P* value of <5% was considered to indicate statistical significance for all analyses. Statistical analyses were performed using R software (version 3.6.1).

Results

Among the 1691 adults living with HIV who started dolutegravir/rilpivirine or dolutegravir/xTC maintenance therapy in the Dat'AIDS cohort, 133 (7.9%) were excluded because no plasma viral load was available in the 6 months prior to the initiation of the 2DR, 155 (9.1%) were excluded because no plasma viral load was available while receiving the 2DR and 29 (1.7%) were excluded because the duration of the 2DR was <7 days. Finally, a total of 1374 subjects were included and analysed: 799 (58.2%) subjects in the dolutegravir/rilpivirine group and 575 (41.8%) subjects in the dolutegravir/xTC group (Figure 1).

Baseline characteristics

The patient baseline characteristics are described in Table 1. In the dolutegravir/rilpivirine group, 69.1% (*n* = 552/799) were male, the median age was 54.5 years, 28.9% (*n* = 231/799) were CDC stage C and 50.2% (*n* = 401/799) had a nadir CD4 cell count ≤200 cells/mm^3. The duration of viral suppression was >12 months in 93.7% (*n* = 741/799) of cases with a median of 90 months (IQR = 45.6–136.8). History of virological failure was reported in 43.8% of cases (*n* = 350/799) and in 41.7% of cases (*n* = 333/799) under an NRTI regimen.

On the other hand, among the dolutegravir/xTC group, 488 (84.9%) received dolutegravir/lamivudine and 87 (15.1%) received dolutegravir/emtricitabine. Furthermore, in the dolutegravir/xTC group, 69.9% (*n* = 402/575) were male, the median age was 52.5 years (IQR = 44.8–60.8), 19% (*n* = 109/575) were CDC stage C and 30.8% (*n* = 177/575) had a nadir CD4 cell count ≤200 cells/mm^3. The duration of viral suppression was >12 months in 92.8% (*n* = 533/575) of cases with a median of 74.4 months (IQR = 40.8–

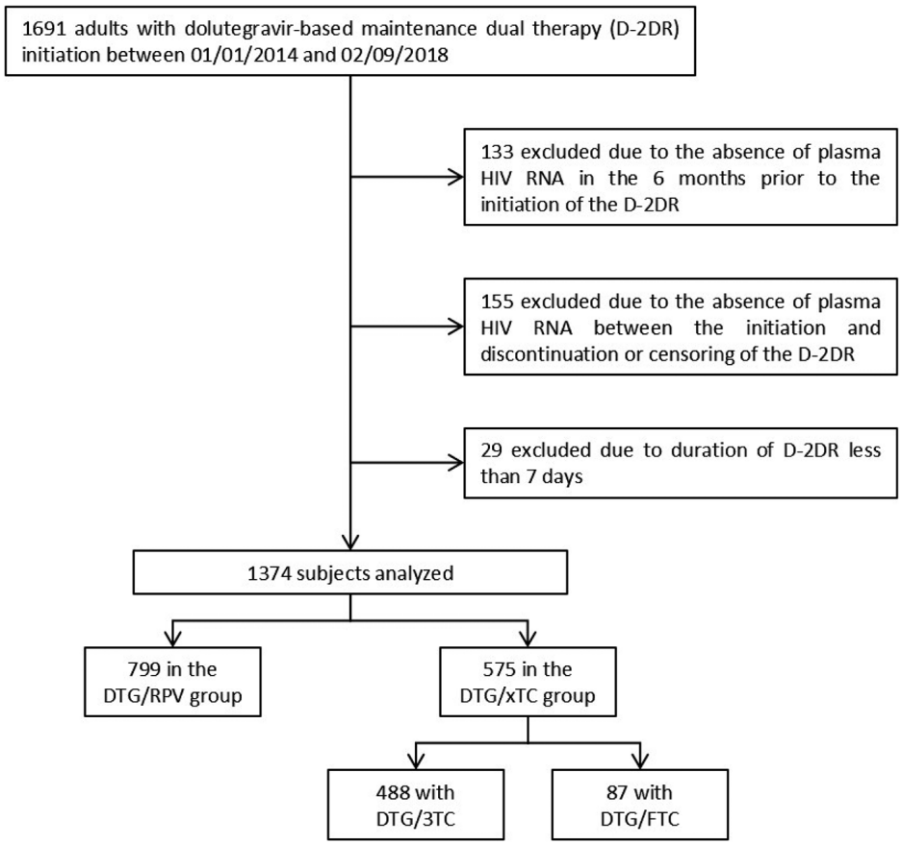

Figure 1. Flow chart. xTC, emtricitabine or lamivudine; 3TC, lamivudine; FTC, emtricitabine; RPV, rilpivirine; DTG, dolutegravir.

124.8). History of virological failure was reported in 19.8% of cases ($n = 114/575$) and in 18.8% of cases ($n = 108/575$) under an NRTI regimen.

Discontinuation

Dolutegravir-based 2DR discontinuation is detailed in Table 2. The median follow-up from dual regimen initiation was 20 months (IQR = 11–31) for dolutegravir/rilpivirine and 19 months (IQR = 11–31) for dolutegravir/xTC. At the time of analysis, 79.7% ($n = 629$) of dolutegravir/rilpivirine subjects and 81.9% ($n = 471$) of dolutegravir/xTC subjects were still undergoing dual therapy. Among those who discontinued treatment, median times to discontinuation were 9.6 months (IQR = 4.2–19) and 9.6 months (IQR = 3.6–18.7) for the dolutegravir/rilpivirine group and the dolutegravir/xTC group, respectively. Adverse events leading to discontinuation occurred in 80 (10%) and 47 (8.2%) subjects in the dolutegravir/rilpivirine group and the dolutegravir/xTC group, respectively. The main adverse events leading to 2DR discontinuation were CNS symptoms [$n = 31$ (3.9%) and $n = 19$ (3.3%), respectively] and gastrointestinal symptoms [$n = 7$ (0.9%) and $n = 8$ (1.4%), respectively] for the dolutegravir/rilpivirine group and the dolutegravir/xTC group.

Virological failure

Dolutegravir-based 2DR virological failure is detailed in Table 2. Virological failure was detected in 3.8% ($n = 30$) of dolutegravir/rilpivirine subjects and 2.6% ($n = 15$) of dolutegravir/xTC subjects, with a median delay to virological failure of 232 days (IQR = 100–507) and 301 days (IQR = 188–427.5), respectively. Among them, virological failure led to ART discontinuation in 17 out of 30 subjects (57%) in the dolutegravir/rilpivirine group and in 6 out of 15 subjects (40%) in the dolutegravir/xTC group. Virological failure leading to discontinuation was therefore 2.1% in the dolutegravir/rilpivirine group and 1% in the dolutegravir/xTC group. Among the 30 subjects with dolutegravir/rilpivirine failure, 33% ($n = 9$) had a history of an NNRTI-based regimen failure and 13.3% ($n = 4$) had a duration of viral suppression prior to dolutegravir/rilpivirine of $\leq$12 months. Whereas, among the 15 subjects with dolutegravir/xTC failure, 33.3% ($n = 5$) had a history of an NRTI-based regimen failure and 1 subject had a duration of viral suppression prior to dolutegravir/xTC of $\leq$12 months.

Emergence of RAMs at virological failure

Genotypes at virological failure with NRTI-, NNRTI- or INSTI-associated resistance mutations are detailed in Table 3.

Among the 30 subjects with dolutegravir/rilpivirine virological failure, the genotype was missing or not amplified for 13 of them at virological failure. Among the 17 available genotypes at virological failure, 2 harboured NNRTI RAMs previously detected for historical genotypes (E138A; E138A, L100I), whereas 2 harboured new RAMs. New RAMs included in one case mutation E138K and in the other case mutations E138K, K101E and N155H. For the latter subject, failure was confirmed

Table 1. Baseline characteristics of HIV-1-infected subjects who initiated dolutegravir-based maintenance dual therapy

Variable	Dolutegravir/rilpivirine, *N* = 799	Dolutegravir/xTC, *N* = 575
Age (years), median (IQR)	54.5 (48.7–62.4)	52.5 (44.8–60.8)
Age (years), *n* (%)		
≤50	236 (29.5)	238 (41.4)
>50	563 (70.5)	337 (58.6)
Gender, *n* (%)		
male	552 (69.1)	402 (69.9)
female	247 (30.9)	173 (30.1)
CDC stage C, *n* (%)		
no	568 (71.1)	466 (81.0)
yes	231 (28.9)	109 (19.0)
Exposure, *n* (%)		
other/unknown	504 (63.1)	334 (58.1)
MSM	295 (36.9)	241 (41.9)
Nadir CD4 cell count (cells/mm^3), median (IQR)	199 (90–315)	288 (169–415)
Nadir CD4 cell count (cells/mm^3), *n* (%)		
>200	386 (48.3)	391 (68.0)
≤200	401 (50.2)	177 (30.8)
Zenith plasma HIV RNA (log_{10} copies/mL), median (IQR)	4.99 (4.33–5.49)	4.88 (4.16–5.40)
Zenith plasma HIV RNA (log_{10} copies/mL), *n* (%)		
≤5	411 (51.4)	327 (56.9)
>5	388 (48.6)	248 (43.1)
Duration of viral suppression (months), (IQR)	90 (45.6–136.8)	74.4 (40.8–124.8)
Duration of viral suppression (months), *n* (%)		
≤12	50 (6.3)	41 (7.2)
>12	741 (93.7)	533 (92.8)
Previous ART lines, *n* (%)		
≤5	330 (41.3)	359 (62.4)
>5	469 (58.7)	216 (37.6)
Previous virological failure, *n* (%)		
regardless of the regimen	350 (43.8)	114 (19.8)
under NRTI regimen	333 (41.7)	108 (18.8)
under NNRTI regimen	90 (11.3)	38 (6.6)
under INSTI regimen	38 (4.8)	10 (1.7)
Start of first ART regimen, *n* (%)		
>1996	597 (74.7)	503 (87.5)
≤1996	202 (25.3)	72 (12.5)

INSTI, integrase strand transfer inhibitor; xTC, lamivudine or emtricitabine.
Continuous variables are summarized as medians and IQRs. Categorical variables are summarized as frequencies and percentages.

after two plasma HIV RNA values >50 copies/mL (142 and 189 copies/mL respectively) and the 2DR was continued for 18 months until discontinuation (viral load at discontinuation of 787 copies/mL) (Table 3).

Among the 15 subjects with dolutegravir/xTC virological failure, the genotype was available and amplified for 6 of them. Among these six genotypes at virological failure, no new RAM was detected and one genotype harboured M184V, already detected for historical genotypes.

Factors associated with virological failure

Regarding the dolutegravir/rilpivirine group, age ≤50 years (HR = 2.27, 95% CI = 1.1–4.76), history of virological failure of an NNRTI-including regimen (HR = 3.37, 95% CI = 1.54–7.39) and history of virological failure of an INSTI-including regimen (HR = 2.95, 95% CI = 1.02–8.56) were associated with a higher risk of virological failure in univariate analysis, while only history of virological failure on an NNRTI-including regimen (adjusted HR = 2.97, 95% CI = 1.28–6.93) remained significant in multivariate analysis (Table 4). Regarding the dolutegravir/xTC group, no factors were associated with a higher risk of virological failure in univariate or multivariate analysis (Table 5).

Discussion

In this large longitudinal cohort conducted in a real-life setting, the two dolutegravir-based maintenance dual therapies (dolutegravir/

Table 2. Description of dolutegravir-based maintenance dual therapy discontinuation and virological failures

Variable	Dolutegravir/ rilpivirine, *N* = 799	Dolutegravir/xTC, *N* = 575
Virological failure, *n* (%)	30 (3.8)	15 (2.6)
one plasma HIV RNA value >400 copies/mL, *n* (%)	18 (2.3)	12 (2.1)
followed by discontinuation of dolutegravir-based maintenance dual therapy	8 (1.0)	5 (0.8)
two consecutive plasma HIV RNA values >50 copies/mL, *n* (%)	12 (1.5)	3 (0.5)
followed by discontinuation of dolutegravir-based maintenance dual therapy	9 (1.1)	1 (0.2)
time between two consecutive plasma HIV RNA values >50 copies/mL (days), median (IQR)	31 (18–54)	35 (21–74)
Dual therapy discontinuation, *n* (%)	170 (21.3)	104 (18.1)
time to discontinuation (months), median (IQR)	9.6 (4.2–19)	9.6 (3.6–18.7)
virological failure leading to discontinuation, *n* (%)	17 (2.1)	6 (1)
adverse event, *n* (%)	80 (10)	47 (8.2)
CNS symptom, *n* (%)	31 (3.9)	19 (3.3)
gastrointestinal disturbance, *n* (%)	7 (0.9)	8 (1.4)
cutaneous event, *n* (%)	5 (0.6)	2 (0.3)
arthralgia, *n* (%)	3 (0.4)	3 (0.5)
renal impairment, *n* (%)	3 (0.4)	2 (0.3)
dyslipidaemia, *n* (%)	1 (0.1)	0 (0)
other adverse event, *n* (%)	30 (3.8)	13 (2.3)
miscellaneous, *n* (%)	73 (9.1)	51 (8.9)
death, *n* (%)	12 (1.5)	9 (1.6)
drug–drug interaction, *n* (%)	7 (0.9)	2 (0.3)
other, *n* (%)	54 (6.8)	40 (7)

xTC, lamivudine or emtricitabine.

Table 3. Description of genotypes at virological failure with NRTI-, NNRTI- or INSTI-associated resistance mutations

					Resistance mutations			
					historical genotype		genotype at VF	
n	Second regimen	Time to VF	History of VF	Plasma HIV RNA at VF (copies/mL)	NRTI or NNRTI	INSTI	NRTI or NNRTI	INSTI
1	rilpivirine	W75	NNRTI	68, 133	K103H/N/S/T	none	K103H/N/S/T	none
2	rilpivirine	W6	no	531	none	none	E138K	none
3	rilpivirine	W32	no	142, 189[a]	none	none	K101E, E138K	N155H
4	rilpivirine	W86	no	474	not available	none	E138A	none
5	rilpivirine	W34	no	52 310	E138K	none	E138A, L100I	L74I[c]
6	rilpivirine	W5	no	109, 109	K103H/N/S/T	none	K103H/N/S/T	none
7	xTC	W29	NRTI	66, 59[b]	M184V	none	M184V	none

INSTI, integrase strand transfer inhibitor; VF, virological failure; xTC, lamivudine or emtricitabine.
[a]Plasma HIV RNA at discontinuation of dolutegravir-based maintenance dual therapy was 787 copies/mL.
[b]All plasma HIV RNA values following virological failure were ≤50 copies/mL.
[c]L74I alone does not confer genotypic resistance to dolutegravir.

rilpivirine and dolutegravir/xTC) proved to be safe and effective treatments in this population of middle-aged subjects with a long history of HIV infection and sustained viral suppression. After a median follow-up of around 20 months, the rate of detection of virological failure was low, at 3.8% in the dolutegravir/rilpivirine group and 2.8% in the dolutegravir/xTC group, and lead to treatment discontinuation in only 2.1% and 1% of patients on dolutegravir/rilpivirine and dolutegravir/xTC, respectively. Regarding dolutegravir/xTC, this rate seems similar to the rate reported both in randomized controlled trials with one case of failure out of 44 subjects after 24 weeks of treatment in the ASPIRE trial[13] and one failure out of 344 subjects after 48 weeks of treatment in the TANGO trial[5] and in real-life setting studies.[10,11,14] Regarding dolutegravir/rilpivirine, the rate is similar both in SWORD-1 and SWORD-2 at 3% at 100 and 148 weeks of follow-up[4,15] and in observational studies.[6,8,10,16]

Table 4. Factors associated with dolutegravir-based maintenance dual therapy virological failures on dolutegravir/rilpivirine

	No virological failure, $N = 769$	Virological failure, $N = 30$	Univariate analysis		Multivariate analysis	
			crude HR	P	adjusted HR	P
Age (years), *n* (%)						
≤50	547 (71.1)	16 (53.3)	2.27 (1.1–4.76)	0.03	2.13 (0.98–5.26)	0.06
Gender, *n* (%)						
female	233 (30.3)	14 (46.7)	2.02 (0.99–4.14)	0.06	1.84 (0.77–4.45)	0.17
CDC stage, *n* (%)						
C	223 (29.0)	8 (26.7)	0.9 (0.4–2.03)	0.80		
Exposure, *n* (%)						
MSM	288 (37.5)	7 (23.3)	0.52 (0.22–1.21)	0.13	0.74 (0.26–2.1)	0.57
Nadir CD4 cell count (cells/mm^3), *n* (%)						
≤200	386 (50.2)	15 (50.0)	0.98 (0.48–2)	0.95		
Zenith plasma HIV RNA ($\log_{10}$ copies/mL), *n* (%)						
>5	368 (47.9)	20 (66.7)	2.01 (0.94–4.3)	0.07	1.88 (0.87–4.1)	0.11
Duration of viral suppression (months), *n* (%)						
≤12	46 (6.0)	4 (13.3)	2.41 (0.84–6.93)	0.10	2.35 (0.81–6.81)	0.12
Previous virological failure, *n* (%)						
regardless of the regimen	333 (43.3)	17 (56.7)	1.64 (0.79–3.4)	0.18		
under NRTI regimen	318 (41.4)	15 (50.0)	1.39 (0.67–2.85)	0.38		
under NNRTI regimen	81 (10.5)	9 (30.0)	3.37 (1.54–7.39)	0.002	2.97 (1.28–6.93)	0.02
under INSTI regimen	34 (4.4)	4 (13.3)	2.95 (1.02–8.56)	0.04	1.66 (0.47–5.80)	0.42
Start of first ART regimen, *n* (%)						
≤1996	196 (25.5)	6 (20.0)	0.7 (0.28–1.72)	0.44		

INSTI, integrase strand transfer inhibitor.
A univariate and multivariate Cox proportional hazards regression model was used to determine factors associated with virological failure, estimating HRs and 95% CIs.

Both dolutegravir-based dual therapies showed a high retention rate of about 80%. This rate is slightly lower than the rate reported in SWORD-1 and SWORD-2 at 89% (100 weeks) and at 84% (148 weeks)[4,15] and in TANGO at 86% at 96 weeks.[17] The rates of adverse events leading to discontinuation of treatment, 8.2% (dolutegravir/xTC) and 10% (dolutegravir/rilpivirine), were similar to previously published data with 5% in TANGO (week 96) and 8% in SWORD-1 and SWORD-2 (week 148).[15,17] Neuropsychological symptoms were the most frequent cause of discontinuation for adverse events, consistent with these studies.[15,17] These results underline the overall good tolerability of dolutegravir, possibly even better than in dolutegravir-based triple therapy as shown in the SWORD-1 and SWORD-2 studies.[3–5,15]

In this study, no emerging mutation was found in subjects who failed during dolutegravir/xTC and the emergence of resistance mutations occurred in only two patients on dolutegravir/rilpivirine. This finding is in agreement with previous observational studies[9,18,19] and randomized trials, such as TANGO and SWORD-1 and SWORD-2 studies.[4,5,15] This very low rate of emergence of new RAMs is related to the high genetic barrier to resistance previously reported for dolutegravir.[20] These conclusions must remain cautious in view of the number of genotypes that cannot be interpreted in our study.

Our study does not allow the evaluation of the impact of archived resistance mutation M184V on the risk of virological failure because historical genotype accumulations of virologically successful subjects were not available at the time of analysis. However, 18.8% of subjects in the dolutegravir/xTC group had a history of virological failure on an NRTI-including regimen, potentially including xTC, and could have potentially archived an M184V mutation. This variable was not found to be associated with virological failure. This could be explained by the sustained duration of viral suppression before a dual regimen (>6 years) before the switch and the sustained clearance of the M184V mutation in the DNA as recently suggested.[21] These data are consistent with several observational studies with a smaller sample size and shorter follow-up[18,22,23] and those presented recently showing no additional risk of virological failure with dolutegravir/lamivudine when the last detection of M184V was at least 5 years before the introduction of this dual therapy.[24]

While in the dolutegravir/xTC group no factor was associated with the risk of virological failure, history of failure on an NNRTI regimen was associated with a higher risk of virological failure in the dolutegravir/rilpivirine group. Among the 17 patients with genotypic data, resistance mutations emerged both on rilpivirine (K101E+E138K) and dolutegravir (N115H) in 1 patient with a long duration of 16 months between the onset of confirmed virological failure and genotyping assessment due to a transitory loss of follow-up and a suboptimal adherence. Introduction of maintenance dual therapy with dolutegravir/rilpivirine should be done with caution and a careful review of previous ART and associated failures.

Table 5. Factors associated with dolutegravir-based maintenance dual therapy virological failures on dolutegravir/xTC

	No virological failure, $N = 560$	Virological failure, $N = 15$	Univariate analysis		Multivariate analysis	
			crude HR	*P*	adjusted HR	*P*
Age (years), *n* (%)						
≤50	329 (58.8)	8 (53.3)	1.15 (0.41–3.13)	0.79		
Gender, *n* (%)						
female	166 (29.6)	7 (46.7)	2.12 (0.77–5.84)	0.15		
CDC stage, *n* (%)						
C	106 (18.9)	3 (20.0)	1.13 (0.32–4.01)	0.85		
Exposure, *n* (%)						
MSM	237 (42.3)	4 (26.7)	0.49 (0.15–1.52)	0.22		
Nadir CD4 cell count (cells/mm^3), *n* (%)						
≤200	170 (30.4)	7 (46.7)	2.22 (0.8–6.14)	0.13	1.98 (0.70–5.6)	0.20
Zenith plasma HIV RNA (log_{10} copies/mL), *n* (%)						
>5	240 (42.9)	8 (53.3)	1.46 (0.53–4.03)	0.46		
Duration of viral suppression (months), *n* (%)						
≤12	40 (7.1)	1 (6.7)	1.42 (0.19–10.97)	0.73		
Previous virological failure, *n* (%)						
regardless of the regimen	109 (19.5)	5 (33.3)	2.11 (0.72–6.19)	0.17		
under NRTI regimen	103 (18.4)	5 (33.3)	2.26 (0.77–6.61)	0.14	1.94 (0.65–5.82)	0.24
under NNRTI regimen	36 (6.4)	2 (13.3)	2.39 (0.54–10.58)	0.25		
under INSTI regimen	10 (1.8)	0 (0.0)	–	–		
Start of first ART regimen, *n* (%)						
≤1996	70 (12.5)	2 (13.3)	1.14 (0.26–5.05)	0.87		

INSTI, integrase strand transfer inhibitor; xTC, lamivudine or emtricitabine.
A univariate and multivariate Cox proportional hazards regression model was used to determine factors associated with virological failure, estimating HRs and 95% CIs.

These two dolutegravir-based dual therapies have several advantages over other dual therapies mentioned in the literature. Among them, boosted PI/lamivudine regimens present a greater risk of drug interactions and metabolic complications.[25,26] Furthermore, dolutegravir/rilpivirine and dolutegravir/lamivudine are both available in single tablet regimens, which enhances compliance and quality of life, although only Juluca® (dolutegravir/rilpivirine) and not Dovato® (dolutegravir/lamivudine) was marketed in France at the time of the study. Of all simplification strategies evaluated to date, the dolutegravir/lamivudine combination could be the most readily accessible for patients in low- and middle-income countries; both dolutegravir and lamivudine are available and prequalified by regulatory authorities in generic formulations. However, the main limitation of these dual therapies is the contraindication in subjects with chronic hepatitis B infection. Furthermore, evaluation of a new dual therapy strategy, such as doravirine/raltegravir or doravirine/dolutegravir, is needed in case of adverse events under dolutegravir or RAMs with NRTI.

Our study has some limitations. The first one is that it is a retrospective uncontrolled study with potential biases. However, data were obtained from prospective follow-up of patients seen at centres using the same electronic medical records. Furthermore, despite a heterogeneous population, real-life data provide complementary data to randomized trials that suffer from a strict selection of subjects, a presumed high adherence and restriction on virological mutations or resistance at inclusion. Second, all laboratory tests were performed as part of routine clinical care at the discretion of the healthcare provider, leading to non-standardized biological monitoring. Third, both RNA and DNA genotypes were collected for the analysis of the emergence of RAMs. Finally, our results might have slightly underestimated the proportion of patients with virological failure as individuals who were lost to follow-up might have experienced this outcome without being accounted for. The strength of this study is the large sample size with a long follow-up, which allows us to present results with high statistical power and the ability to provide clinical, virological and genotypic data.

In conclusion, these cohort results are very reassuring regarding the efficacy and safety of dolutegravir/rilpivirine and dolutegravir/xTC following the results of randomized trials. However, the initiation of dual maintenance therapy with dolutegravir/rilpivirine requires careful virological screening in patients with a history of NNRTI treatment. No emergence of M184V resistance mutations was detected following virological failure on dolutegravir/xTC in patients with prolonged virological suppression. Prolonged follow-up is necessary to ensure the continued efficacy and safety of this strategy.

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