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Withdrawing Inactive NRTIs in Subjects with Suppressed Viremia. A Randomized Trial.

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Background

Extensively pretreated subjects with virological failure may receive salvage regimens containing NRTIs with only residual or no activity. Once virological suppression is achieved, the contribution of these NRTIs to the antiretroviral treatment (ART) remains elusive. Withdrawing NRTIs with intermediate to complete genotypic resistance when viral load (VL) is suppressed <50 c/mL could have non-inferior efficacy to their maintenance, with lower potential toxicity and costs.

Methods

Multicenter, randomized, prospective, open study. Subjects with ≥1 prior VF, VL<50 c/mL for ≥ 6 months thereafter, any CD4 count, without hepatitis B, receiving a regimen with ≥2 active drugs (one of them an active boosted protease inhibitor [PI]), and ≥1 NRTI without complete activity (assessed using the Spanish RIS Resistance Score), were randomly allocated to stop NRTIs without complete activity (one or both NRTIs, Exp arm) or to maintain the treatment unchanged (Ctrol arm). No drug changes were allowed during last 6 months or at screening. Main endpoint: VL<50 c/mL at 48 weeks (Snapshot analysis), non-inferiority margin at -12. *EudraCT: 2012-000198-21.*

Results

92 subjects were screened and 90 randomized (Exp. n=45, Ctrol. n=45) (Figure 1). There were no significant differences in baseline characteristics among groups (Table 1). The mean age was 50 (±7) years old, 80% were male, 37% had a CDC stage C3, 40% had chronic hepatitis C, and the mean CD4⁺ count at randomization was 542 (±273) cells. Subjects had been a mean of 16,2 (±4,1) years on ART, and had received a mean of 10,4 (±5,3) lines of ART, 3,9 (±1,6) PIs, and had a median of 3 (1-4) prior virological failures.

The baseline regimen contained 4 drugs in 46 (51%) subjects, and 3 in 37 (41%). 74 subjects (82%) harbored the mutation M184V/I, and the median number of thymidine-associated mutations was 3 (2-4; T215X and D67X the most frequent). 32 (71%) subjects removed 1 NRTI and 13 (29%) 2 NRTIs (Table 2). Overall, 22/45 (49%) subjects discontinued tenofovir.

In the primary study endpoint (Table 3), 41/45 (91.1%, Exp Arm) and 44/45 (97.8%, Ctrol Arm) had a VL<50 c/mL at 48 weeks (treatment difference -6.7%; 95%CI: -17.4, 4.1). In an exploratory analysis allowing NRTI reintroduction, rates of VL <50 c/mL at 48 weeks were 95.6% (Exp Arm) and 97.8% (Ctrol Arm) (treatment difference -2.2% 95%CI: -7.2, 2.7).

CD4+ cell counts remained stable in both arms, without significant differences between groups.

The rates of discontinuation at 48 weeks were low in both arms (2% and 2%, respectively).

One subject developed a late virological failure (confirmed VL>200 c/mL, Exp Arm) at the week 48 visit. The genotypic resistance tests showed mutations in the reverse transcriptase (M41L, L210W, T251Y, Y188L, G190A) and protease (L33F, M46L, I84V, L90M) that were all present before randomisation. The integrase genotyping showed N155H and T97A. The patient failed with a regimen that included raltegravir in the study. Previously she had received regimens including raltegravir during 5 years but all HIV-RNA samples during those years showed values <50 c/mL. Therefore, it cannot be excluded that the integrase resistance was selected during the present failure.

There were 10 grade 3/4 adverse events, 5 in each arm (none related to study drugs). There was one death (lung cancer, Exp Arm), unrelated to treatment allocation or the baseline antiretroviral treatment.

Table 1. Baseline demographics and disease characteristics.

	Control Arm (n=45)	Experiment. Arm (n=45)
Age, years (mean, SD)	49,2 (6.4)	52 (7.3)
Gender, male (n,%)	31 (69%)	41 (91)
Previous lines of ART, number (mean, SD)	10.4 (5.2)	10.5 (5.6)
Number of PIs received (mean, SD)	3,7 (1.5)	4 (1.7)
CDC Stage		
A3	6 (13%)	10 (22)
B3	1 (2%)	5 (11)
C1, C2	3 (7%)	2 (4)
C3	15 (33%)	18 (40)
Hep C Co-infection	18 (40)	18 (40)
Time with HIV Infection, y (mean, SD)	20.4 (8.2)	19.4 (4.8)
Time on ART, y (mean, SD)	15.9 (3.5)	16.6 (4.6)
Baseline CD4⁺ cell count (mean, SD)	535 (242)	549 (304)
Median number of ARV drugs in the regimen*		
3 drugs	19 (42)	18 (40)
4 drugs	24 (53)	22 (49)
5 drugs	2 (4)	5 (11)
Protease inhibitor in the regimen (n)		
Darunavir/r	33	32
Atazanavir/r	4	8
Lopinavir/r	5	2
Other	3	3
Risk factor for HIV (n, %)		
IVDU	18 (40)	16 (36)
MSM	10 (22)	11 (24)
Heterosexual	15 (33)	16 (36)
Haemophilia	1 (2)	1 (2)
Unknown	1 (2)	1 (2)
Patients with previous DRMs to NRTIs (n, %)		
M184V/I	35 (77.8)	39 (86.6)
L74I/V	8 (18)	8 (18)
K65R	-	4 (9)
A62V	2 (4)	2 (4)
T69D/G/N	4 (8.9)	13 (28.9)
V75A/I	5 (11.1)	4 (9)
Q151M	2 (4)	2 (4)
Y115F	2 (4)	1 (2)
Thymidine-associated mutations		
M41L	17 (38)	26 (57.8)
D67E/G/N	20 (44.4)	26 (57.8)
K70R	13 (29)	13 (29)
L210W	16 (36)	22 (48.9)
T215F/Y	21 (46.7)	30 (56.7)
T215C/D/E/I/S/V	3 (6.7)	3 (6.7)
K219E/N/Q/R/T/W	13 (28.9)	16 (35.6)

* Number of antiretrovirals in the regimen at randomization; ART: antiretroviral treatment; IVDU: intravenous drug use; MSM: men having sex with men; DRM: drug-resistance mutations; NRTIs: nucleos/tide reverse transcriptase inhibitors.

Table 2. NRTIs removed in the experimental arm (n=45).

Removed 1 NRTI (32/45, 71,1%)		Removed 2 NRTIs (13/45, 28,9%)	
Tenofovir	12	Tenofovir + Emtricitabine	9
Emtricitabine	9	Abacavir + Lamivudine	3
Lamivudine	8	Abacavir + Tenofovir	1
Abacavir	2		
Didanosine	1		

Figure 1. Trial profile with 48-week subject disposition.

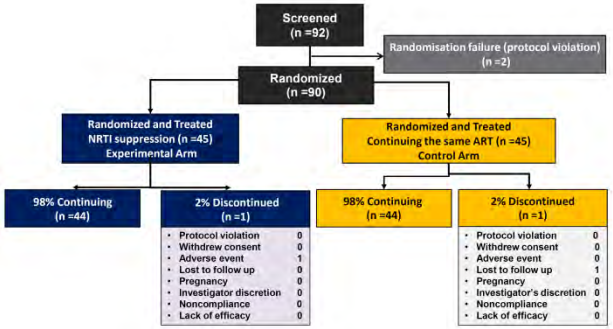


Table 3. Virological outcome at 48 weeks.

	Experimental N=45	Control N=45
Virologic Success at Week 48		
HIV-1 RNA < 50 copies/mL	41 (91.1%)	44 (97.8%)
Virologic Failure (VF) at Week 48		
HIV-1 RNA ≥ 50 copies/mL	1 (2.2%)	0
Discontinued study drug due to lack of efficacy	2 (4.4%)	0
Discontinued study drug due to other reasons and last available HIV-1 RNA ≥ 50 copies/mL	0	0
No Virologic Data in Week 48 Window		
Discontinued study drug due to AE	1 (2.2%)	0
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL	0	1 (2.2%)
Missing data during window but on study drug	0	0

Conclusions

In heavily treated patients receiving a successful salvage regimen with at least 2 active drugs (one a boosted PI), the withdrawal of NRTIs without complete activity was safe and associated with high rates of continued virological suppression at 48 weeks.

Non-inferiority was not met in the main endpoint. However, the strategy met non-inferiority in a NRTI-reintroduction allowed analysis.

Removing NRTIs without complete activity in this scenario could save potential long term toxicities, reduce the number of drugs received, and constitute a cost-saving strategy.

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Study Investigators

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