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96-week results of a dual therapy with darunavir/ritonavir plus rilpivirine once a day *vs* triple therapy in patients with suppressed viraemia: virological success and non-HIV related morbidity evaluation

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Antiretroviral therapies have been tested with the goal of maintaining virological suppression with a particular attention in limiting drug-related toxicity. With this aim we designed the DUAL study: a randomized, open-label, multicenter, 96 weeks-long pilot exploratory study in virologically suppressed HIV-1+ patients with the aim of evaluating the immunovirological success and the impact on non-HIV related morbidity of switching to a dual therapy with darunavir-ritonavir (DRV/r) and rilpivirine (RPV). We recruited patients who received a PI/r-containing HAART for ≥6 months, HIV-RNA < 50 cp/mL for ≥3 months, eGFR > 60 mL/min/1,73m2, without DRV or RPV RAMs. We randomized patients in arm A: RPV + DRV/r QD or arm B: ongoing triple therapy. The primary endpoint has been defined as the percentage of patients with HIV-RNA < 50 cp/mL at week 48 (ITT). VACS index, Framingham CVD risk (FRS) and urinary RBP (uRBP) were calculated. We used Chi-square or Fisher statistics for categorical variables and Mann-Whitney U for continuous ones. Forty-one patients were enrolled (22 in arm A, 14 in arm B, plus 5 screening failures): 30 patients reached 96 weeks: 100% had HIV-RNA < 50 cp/mL in arm A *versus* 91.7% in arm B. Similar changes were observed in median CD4/mL between baseline and week 96 (+59 *versus* − 31, p: n.s.). Thirty-one in arm A and 23 in arm B adverse events took place, whereas only 1 was serious (arm A: turbinate hypertrophy, unrelated to HAART). Among the 6 discontinuations (3 in A, 3 in B), only 1 was related to adverse event (arm A: G3 depression, insomnia, weakness). VACS index, median FRS and median uRBP values did not vary from baseline to week 96. At 96-weeks all patients switched to a QD 2-drug regimen based on DRV/r + RPV maintained HIV-RNA suppression, but a single patient who showed a virological failure at week 4. CD4 counts increased overtime without significant differences between the two arms. The novel dual regimen was well tolerated with the same amount of discontinuation as the control arm. VACS index, FRS and uRBP did not differ between arms at week 96.

Keywords: HIV-1, Darunavir, Rilpivirine, Dual therapy, Immunovirological success, Safety

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This work has been partially presented at EACS 2017, Milan, Italy – e-poster PE8/1.
This trial has been registered as HLS03/2012 on EUDRACT (2012-005192-14) and Clinicaltrial.gov (NCT01792570).

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Introduction

The clinical approach to HIV infection nowadays is stably based on the combination of three antiretroviral drugs: a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) and a third drug among non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INIs).[1–3] The effectiveness of HAART, meant as a 3-drug regimen (3DR), with the increase in survival and the parallel reduction in mortality, has highlighted the need to reflect on its long-term consequences.[4,5] Side effects of HAART, such as the impact on kidney function of some drugs, like tenofovir (TDF), or the alterations of bone and lipid metabolism, are still the main concern in our patients' management.[6,7]

Therapeutic simplification during HAART is recommended by the international guidelines and represents an effective optimization option in virologically-suppressed patients with relevant comorbidities, pharmacological interaction or adherence issues.[1]

The main therapeutic options are the reduction in the number of regimen components (less drug regimens) and the reduction in the number of doses/administrations and in the daily amount of pills (management simplification). The de-intensification schemes contemplate two-drug combinations (dual therapies), as recommended by the recent EACS guidelines, version 10 (8): these strategies are theoretically able to reduce the NRTIs-related toxicity and the costs of the HAART.

Dual therapies were initially prescribed to HIV patients with the aim of reducing long-term toxicity by reducing or excluding NRTIs from their ongoing therapeutic regimen. More recently, regimens based on the combination of boosted PIs (PIs/r) and lamivudine (3TC) have been studied[9–11] in assuming that 3TC is free from long-term toxicity, or at least has significantly less side effects than other molecules from the same class. Also, DTG + 3TC-based therapies have been tested as an effective and well tolerated simplification strategy.[12] Recent studies in drug-experienced and virologically suppressed patients were performed to support the virological efficacy of DTG + 3TC dual therapy, both in small cohorts and in international clinical trials.[13–15] We acknowledge the fact that there are other 2-drug regimens (2DR) of interest, such as boosted PI + NNRTI[16] and INI + NNRTI,[17] as reported by several guidelines including the recent EACS v.10.[8]

Aim of our study was to evaluate the virological success, cardiovascular risk, renal toxicity and overall frailty, and mid-long term safety within 96 weeks after the switch in HIV-patients with suppressed viraemia of a dual therapy, excluding NRTI, with Darunavir/ritonavir (DRV/r) plus Rilpivirine (RPV) once daily (QD) versus triple NRTI-containing therapy. The main reason for simplification to a boosted PI-based 2DR was NRTI toxicity/tolerability or NRTI resistance.

Methods

Study design

The present study was designed as a multicentric, randomized, open-label, 96-week clinical trial, on HIV-1-infected adults who were virologically suppressed and who were receiving a PIs/r at baseline, from 6 Italian Departments of Infectious Diseases.

Participants were randomized 1:1 to switch to RPV 25 mg QD plus DRV/r 800/100 mg QD (Arm A), or to continue their current 3-drug NRTI-containing ART (Arm B). We initially planned to randomly assign 60 patients to each of the two arms. Hypothesizing a percentage of 10% lost to follow-up, the total number of patients to be randomized was 132. The randomization was performed in blocks and stratified basing on serological status for HCV (positive or negative) and immunological status (CD4 $<$ 200 cell/μL, CD4 = 200–500 cell/μL, CD4 $>$ 500 cell/μL. This study was designed as a pilot exploratory study, so there was not a formal calculation of the study sample and consequently of its statistical power. The sample size of 132 subjects was set based on feasibility reasons and estimated number of eligible patients.

After the signature of the informed consent, a visit was performed including clinical evaluation, vital signs measurement, laboratory analyses (haematology, lymphocyte subpopulations, blood chemistry, urinalysis, HIV-RNA) and an ECG record (for Q-T interval measurement). Follow-up visits were performed at weeks: 4 (including ECG control), 12, 24, 36, 48, 60, 72, and 96 (with laboratory analyses and clinical evaluation). Adverse events (AE) and serious adverse events (SAE) were collected and graded according to the Division of AIDS (DAIDS, NIAID, NIH) method.[18]

Study population

All the enrolled patients were at least 18 years-old, HIV-1 infected adults under HAART for at least 12 months, under PI-containing HAART for at least 6 months, with HIV-RNA $<$50 cp/mL for at least 3 months, without viral blips, with an eGFR $>$60 mL/min/m^2.

Exclusion criteria were: a genotypic test documenting any mutation associated to RPV or DRV, according to 2011 IAS-USA list (RT: K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, M230I/L; protease: V11I, V32I, L33F, I47V, I50V, I54M/L, T74P, L76V, I84V, L89V) (RAM), Child-Pugh grade C or grade 3-4 abnormalities of transaminases, acute cardiovascular event occurring in the last

6 months, AIDS-defining event during the last 6 months, current drug abuse, HBsAg positivity, pregnancy or breastfeeding.

Virological success and safety analyses

The study's primary endpoint was HIV-RNA < 50 cp/mL at week 48 (96) according to Intention to Treat approach. Secondary endpoints were: for immunology, comparison of the variation in CD4 count (absolute and percentage) vs BL in the two arms; for safety, comparison of the variation of VACS index (a score validated in the US Veterans Aging cohort and used as HIV and non-HIV related morbidity and hospitalization risk indicator in HIV-positive patients),[19] Coronary Heart Disease risk (by Framingham score), urinary retinol-binding protein (RBP: as marker of proximal kidney tubulopathy), lipid panel (total cholesterol, HDL, LDL, triglycerides) and glycemia. Safety analyses were performed also as Per Protocol. We also examined plasma DRV and RPV trough concentrations (C trough) in patients who presented a virological failure.

Randomization strategy and statistical methods

The stratified randomization method was selected to assign the subjects into 2 arms in our trial. This method was used to achieve balance among groups in terms of subjects' baseline characteristics (covariates). In our trial, the specific covariates which we identified were the anti-HCV antibodies (positive or negative) and the level of CD4 lymphocytes (<200 cell/μL, 200-500 cell/μL, and >500 cell/μL). The distribution provided a block of 6 subjects for each possibility, divided in the 2 study arms. The combination of these 6 stratification possibilities and the scarce enrolment by clinical centers determined the unbalance between the 2 arms.

Results were shown in descriptive analyses as count and percentages for categorical variables, and 25-50-75 percentiles for continuous ones. In statistical analyses we compared Arm A and B for differences at each time-point and versus baseline according to χ^2, Fisher's exact, McNemar tests, and according to t-test, if assumptions of normality were respected, non-parametric Mann-Whitney U test otherwise.

When analysing endpoints of virological success, the Intention-To-Treat approach was adopted. In the ITT analyses on virological suppression, single missing values at each timepoint were interpolated from all the previous observations and the one following for each patient. In case of two or more consecutive missing values, data were imputed according to LOCF technique. For safety endpoints, Per-Protocol analyses were also performed.

The level of statistical significance for any test, two-tailed, was set at $\alpha = .05$.

All statistical analyses were performed using the software package SPSS (IBM Corp; Version 24.0 Armonk, NY).

Ethics statement

The central ethical approval, as communicated to the Italian Ministry of Health, was provided by the Comitato Etico per la Sperimentazione clinica (IRB) at 'Luigi Sacco' Hospital, Milan, Italy. All the ethics committees/institutional review boards of the participating centres approved this study, and each participant provided informed consent. Our trial has been registered as HLS03/2012 on EUDRACT (2012-005192-14) and ClinicalTrials.gov (NCT01792570).

Results

Forty-two patients from 6 Italian Centres (DIBIC Luigi Sacco, Milan; Policlinico San Matteo, Pavia; Policlinico Universitario of Bari; ASST Valle Olona, Ospedale di Circolo, Busto Arsizio; Policlinico Universitario of Turin; First Division of Infectious Diseases of Luigi Sacco Hospital, Milan) were screened. Five screening failures occurred. The reasons for the 5 screening failures were the following: two patients had genotypic mutations that were not admitted, one patient was not virogically suppressed for at least 3 months, one patient was pregnant and one patient did not respect the eGFR criterion.

Twenty-three patients were randomised to arm A (simplification to dual antiretroviral therapy), among them 1 patient immediately after randomization withdrawn the informed consent, thus he has not taken investigational drugs and has not been included in the analysis. Fourteen patients were randomized to arm B (continuing their triple antiretroviral therapy). Therefore, the analysis population included 36 patients. The previous backbone regimens were as follow: 20 subjects received TDF/FTC (12 in arm A and 8 in arm B) and 17 subjects received ABC/3TC (11 in arm A and 6 in arm B).

Demographic characteristics at baseline in the two arms

Our study population did not show significant differences between the two arms at baseline (Table 1). Indeed, the two groups had homogeneous characteristics regarding (arm A vs Arm B), *e.g.*: CD4 nadir (187 *vs* 222 cell/mmc), median values of CD4 at enrollment (745 *vs* 670 cell/mmc), VACS index (21 *vs* 22 points) and median basal values of urinary retinol-binding protein (RBP) (4.9 *vs* 11.4).

Table 1 Demographic characteristics at baseline in the two arms

		Arm		
		A (22 pts)	B (14 pts)	*p*
Sex	F % (#)	22.7% (5)	28.6% (4)	ns
	M % (#)	77.3% (17)	71.4% (10)	
Age	Median (IQR)	44.8 (40.9-49.2)	50.6 (42.0-587.3)	ns
CD4 Nadir #	Median (IQR)	187 (30-310)	222 (91-350)	ns
Risk factor	IDU % (#)	22.7% (5)	21.4% (3)	ns
	Sexual % (#)	68.2% (15)	71.4% (10)	
	Other % (#)	9.1% (2)	7.1% (1)	
HIV+ (yrs)	Median (IQR)	7.00 (5.00-16.00)	10.50 (3.00-17.00)	ns
ART (yrs)	Median (IQR)	6.50 (2.51-12.24)	5.03 (3.04-7.90)	ns
BL - CD4	Median (IQR)	745 (598-1265)	670 (549-823)	ns
BL - VACS	Median (IQR)	21 (12-30)	22 (9-38)	ns
BL - uRBP		4.9	11.4	ns

Notes: CD4 median values, with interquartile range (IQR) 25 and 75, IDU: intravenous drug user, Arm A: 2DR, Arm B: continued 3DR; VACS: Veteran Aging Cohort Study, uRBP: urinary Retinol-binding protein, ns: not significative.

Immunovirological response in the two arms

We analysed the percentage of patients with HIV-RNA <50 copies/mL at different timepoints (Figure 1A). HIV-RNA measurements were unavailable for two patients in arm A since W12 and W48, and for one patient in arm B since W36, due to withdrawal from the study. These missing data were imputed according to LOCF. For nine patients (2 in arm A and 7 in arm B) having a single missing observation during the 96 weeks of follow-up, data were always imputed as <50 copies/mL, since the viral load was undetectable in all the previous observations and the one following. Six HIV-RNA blips were observed in one patient in arm A and five in Arm B.

At screening, 95.5% *vs* 100% of patients presented with HIV-RNA <50 copies/mL in arm A and in arm B, respectively; at baseline and week 4, 90.9% *vs* 100%; at week 12, 90.9% *vs* 92.9%; at week 24, 90.9% *vs* 92.9%; at week 48, 90.9% *vs* 85.7%; and at week 96, 90.9% *vs* 91.7%. No statistical difference was inferred in the comparison between arms at any timepoint nor versus baseline. These findings were confirmed even in a "worst scenario" analysis, that is when setting to ≥50 copies/mL each LOCF observation.

We did not find statistically significant differences between the two groups when comparing median, with IQR, values of CD4 lymphocytes at established timepoints (week 4, 12, 24, 48 and 96) and vs BL between the two arms (Figure 1B). Median values of CD4 were constantly above 500 cell/mmc (at baseline 745 *vs* 670 cell/mmc in arm A and in arm B respectively; at week 4, 663 *vs* 608 cell/mmc; at week 12, 651 *vs* 615 cell/mmc; at week 24, 771 *vs* 667 cell/mmc; at week 48, 767 *vs* 606 cell/mmc; at week 96, 822 *vs* 712 cell/mmc).

Effects on toxicity (VACS index, Framingham risk score, urinary retinol-binding protein)

One of the main aims of our study was the evaluation of the therapeutic simplification to DRV/r + RPV impact on toxicity, investigated in terms of cardiovascular risk, renal toxicity and all cause and cause specific mortality. Thus, we evaluated: our patients' cardiovascular risk at 10 years according to Framingham score, VACS index, and finally we dosed the urinary RBP.

We did not find statistically significant differences in Framingham risk score median values neither at baseline or in the evolution at week 48 or 96 in the two arms (at baseline, 10 *vs* 11 in arm A and in arm B, respectively *p* 0.829; at week 48, 9.41 *vs* 9.1 in arm A and in arm B *p* 0.359; at week 96, 10.5 *vs* 7.25 in arm A and in arm B *p* 0.724).

Median values of VACS index, yet homogeneous in the two arms at baseline (21 *vs* 22 in arm A and in arm B, respectively), did not significantly change in the evolution from baseline to week 12 (24 *vs* 32 in arm A and in arm B, *p* 0.583) and week 48 (29 *vs* 30 in arm A and in arm B, p 0.999). At week 96, arm A compared to arm B (12 *vs* 27 in arm A and in arm B, p 0.377) showed a trend towards improvement.

We dosed the urinary RBP our cohort (Figure 2); at baseline, we didn't find statistically significant differences in median values between the two arms. Evaluating the evolution at week 12, 48 and 96, statistically significant differences did not emerge (at week 96, the comparison between arms showed *p* 0.894).

Discontinuations and adverse events

Overall, we registered 51 non serious adverse events in our cohort, occurred in 19 patients (Table 2). Specifically, 31 non serious adverse events occurred in 13 patients in arm A and 20 non serious adverse events in 6 patients in arm B. Analysing them in detail, 24 adverse events were related to pre-existing diseases, whereas 23 to diseases occurred during the study participation (fracture of the left homerus, hidradenitis, epigastric pain, tickly cough, sore throat, acute otitis,

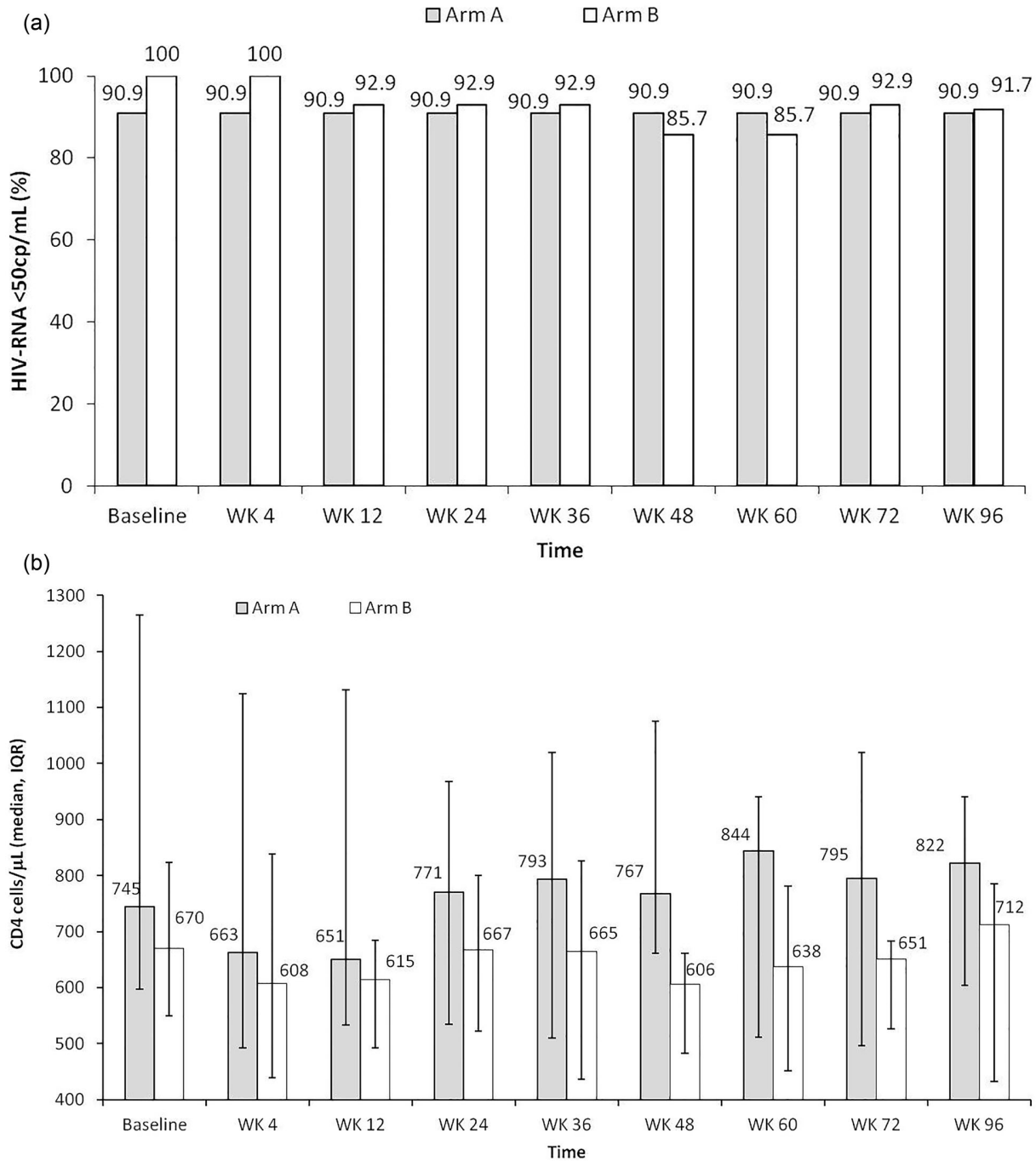

Figure 1 A. Percentage of subjects with HIV-RNA <50 copies/mL from baseline to week 96 of the study. Notes. Arm A: 2DR; Arm B: continued 3DR; WK: week; cp: copies
B. CD4/μL median values, with IQR 25 and 75 from baseline to week 96 of the study. Notes. Arm A: 2DR; Arm B: continued 3DR; WK: week

hypertension, hyperglycemia, hemorrohoids, constipation, hypercholesterolemia, hepatic steatosis, supraclavicular pain, headache, rhinitis, right knee pain, breast fibroadenoma); more adverse events occurred in the same patients and the attending clinician related them to the current investigational therapy, that was interrupted, as we will discuss later. Among the adverse events occurred during the study, only in 2 cases a possible relation to the therapy was supposed by the clinician: in both cases the event was low grade hypercholesterolemia and occurred in arm A.

Only one serious adverse event occurred (hospitalization for surgery for turbinate hypertrophy) in arm A.

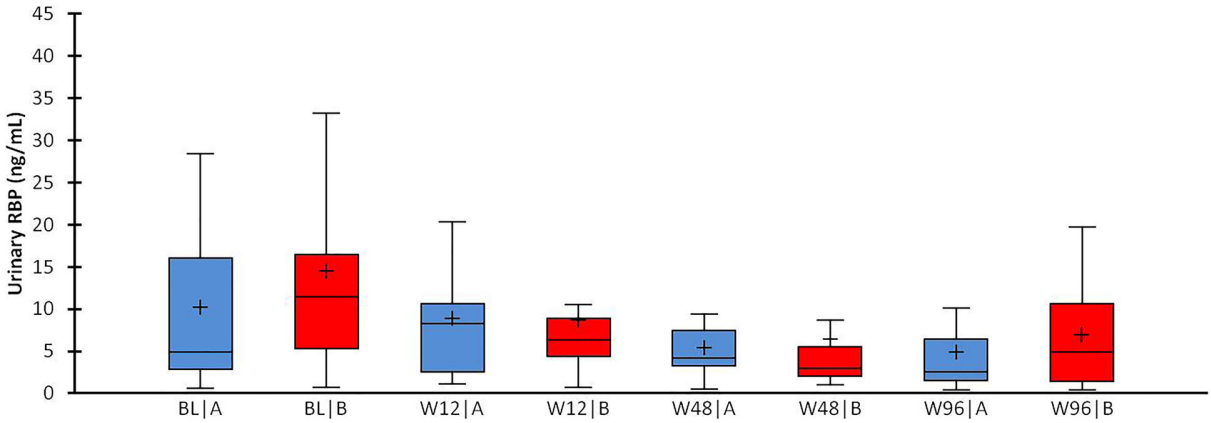

Figure 2 Retinol binding protein (RBP) profile in arm A and arm B form baseline (BL) to week (W) 96. Notes: Arm A: 2DR; Arm B: continued 3DR; marked "+" is the mean, marked line is the median, sides of the rectangle are the 25% and 75% IQR with their whiskers

Table 2 Adverse events in the 2 study arms

	Total	Arm A	Arm B
# events	51	31	20
# patients	19	13	6

Notes: Arm A: 2DR, Arm B: continued 3DR.

Neither pregnancies nor new HIV-related events occurred in our cohort.

After analysing the study discontinuations, we found that 3 occurred in arm A and 3 in arm B. In arm A: one patient was a virological failure without taking the experimental drug combination (this patient will be described in a short while) at week 8, one patient experienced a non-serious adverse event and the attending physician decided to discontinue the treatment at week 48 and one patient was a virological failure at week 24. In arm B: one patient was discontinued by the physician after the onset of non-serious adverse events at week 60, one patient was discontinued by the physician after the onset of non-serious adverse events at week 84 and one patient discontinued the study without giving any explanation at week 36.

In arm A, 1 discontinuation occurred because of viral rise (955 cp/mL) detected at baseline, thus before therapeutic simplification. At week 4, HIV-RNA was found positive again (14,082 cp/mL), thus identifying a virological failure (defined by the protocol as two consecutive values of HIV-RNA >50 cp/mL or a single value > 1,000 cp/mL). At week 4, DRV and RPV plasmatic concentrations were evaluated, showing drug concentrations in therapeutic ranges. A genotypic resistance test was performed, documenting the presence of 35 D, 63 P, 93 L in the protease region and no mutations in the reverse transcriptase region. The described mutations had already been detected by a genotypic test performed in 2011.

Discussion

Our data show a persistence of virological suppression in all patients who were randomised to the experimental arm, based on a dual therapy with DRV/r plus RPV QD. We observed one virological failure in one patient randomised to arm A, but this patient had reported positive HIV-RNA (955 cp/mL) at baseline, thus before the change to the study treatment occurred. The virological failure was defined with week 4 blood test (HIV-RNA 14,082 cp/mL), when the resistance test was performed. It did not detect new RAMs compared to the previous tests. At the interview with his clinician, the patient reported poor adherence to the antiretroviral treatment in that period.

From week 12, every patient randomised to arm A mantained HIV-RNA below 50 cp/mL, without viral blips, so this simplification strategy during 96 weeks showed an excellent virological outcome like the Probe study at 48 weeks[20] and the RIDAR observational study.[21]

Regarding tolerability, VACS index and Framingham risk score at week 48 and 96 did not differ between the two arms. Retinol binding-protein values, yet homogeneous at baseline in the two groups, did not vary statistically significantly at weeks 48 and 96 between control arm and simplification arm.

In our study, the same number of discontinuations (n. 3) occurred in the two arms; among them, only one was related to antiretroviral treatment: in arm A one patient complained occurrence of fatigue, insomnia and malaise, that the physician related to HAART. Thus, it was decided to interrupt the study treatment and resume the initial regimen. In our study, pregnancies and HIV-related events did not occur.

The therapeutical simplification from a standard 3-drug regimen to DRV/r plus RPV QD in our study

proved to be safe and effective in HIV-infected patients in virological suppression, within a 96-weeks interval, which can be considered a sufficient observation time for switch trials. Moreover, our simplification strategy was based on a 2-drug regimen, *i.e.* less drug burden, which potentially averted tolerability events.[22]

The major limit of our study is the poor numerousness of our sample, which limits its extrapolation. In fact, the number of enrolled patients was below what we expected when this study was designed. As possible explanations, we identified some limitative factors: such as the need to examine previous genotypic resistance tests to ensure the absence of resistance mutations to the study drugs among the inclusion criteria and the poor motivation of satellite centres participating to our study. This trial was concluded when simplification regimens appeared to be more oriented to integrase inhibitor and, notably, this is the difficulty that nowadays every investigator finds when conducting independent studies.[23] The initial history of 2-drug regimens started to show beneficial effects from PI/r + 3TC regimens, such as Atlas, Salt, and Dual trials,[9–11] which may have a higher burden of drug interactions due to PIs/r, then moved to INI-including regimens. So it is very likely that this last strategy polarized investigators attention. Nevertheless, we have to consider that INI-containing regimens, in particular dolutegravir, had some tolerability issues.[24,25]

In our trial, the randomisation per blocks properly identified subjects in the two study arms, including them in the first available ''slot'' according to two predefined parameters: serogical status for HCV and lymphocytes CD4 number/μL). We did not manage to complete the predefined number of enrolments, thus the subjects disposition in the two study arms resulted numerically unbalanced towards the experimental arm versus the control arm. After acknowledging this intrinsic unbalance, we still observe that viro-immunological success was preserved in Arm A. We observed only one virological failure in arm A - a subject who would not be enrolled in the trial from the beginning – and no immunological failure; in arm A 86.3% of subjects continued the 2-drug regimen for 2 years with the maintenance of the good clinical initial conditions, whereas 11/14 (78.5%) kept the on-going treatment in arm B. In parallel, our per-protocol analysis did evidence any difference in regards to safety among the 2 arms.

We can conclude that, although our small numbers can lead to a limited generalizability of our results, we used stringent enrollment criteria and in our study the dual regimen based on rtv-boosted darunavir plus rilpivirine was a reliable simplification option in not immune-compromised HIV-infected patients.

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Conflicts of interest

RM received consulting fees or honoraria, fees for participation in review activities such as data monitoring boards and support for travel to meetings from Gilead Sciences, Bristol-Myers Squibb, Merck Sharp and Dohme, ViiV. PM received grants and travel support from AbbVie, Gilead Sciences, Janssen, ViiV Healthcare. SB received grants and travel support from AbbVie, Gilead Sciences, Janssen, ViiV Healthcare, Merck Sharp and Dohme. SR received research grants to his Institution from ViiV Healthcare, Gilead Sciences and Janssen, outside the submitted work; he was also a paid consultant for ViiV Healthcare, Gilead Sciences, Merck Sharp and Dohme, Bristol-Myers Squibb, Janssen and Mylan.

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Notes on contributors

Valentina Di Cristo received her medical degree from the Catholic University of Sacred Heart of Rome in 2010 and completed her specialization in Tropical Medicine at the University of Milan in 2017. While she completed her residency in Tropical Medicine she practiced the intrahospital and outpatient management of acute and chronic infectious diseases (viral hepatitis, tuberculosis, viral, bacterial, mycotic and parasitic infections in the immunocompetent and immunocompromised host). Particularly, for more than two years she was involved independently in the outpatient management of patients with HIV, HBV and HCV infections. Furthermore, she was responsible of recruiting, enrolling and managing HIV-infected patients within phase III and IV clinical trials. Since July 1, 2019 she works as Medical Doctor in an Outpatient Clinic of ATS (Agency of Health Protection) in Milan, where she is involved in the prevention, diagnosis and treatment of sexually transmitted infections.

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Renato Maserati got his Medical Degree in July 1979 and then on, worked at the Infectious Disease Department of the University Hospital (Policlinico San Matteo) in Pavia, Italy during his entire professional life. He holds two Specialization Board Certifications, (Infectious Diseases and Gastroenterology). He was involved both as caring physician and as clinical researcher in the HIV/AIDS epidemics at the very first appearance in Italy. As Head of HIV/AIDS Clinic now coordinates the care of @2000 HIV+ patients. He co-authored >200 papers on different aspects of this pathology.

Marco Annovazzi Lodi got his Medical Degree in March 2012 and then he were trained at the Infectious Disease Department of the University Hospital (Policlinico San Matteo) in Pavia, Italy. He holds one Specialization Board Certification (Infectious Diseases). His researches are focused on uncommon infections of the immunocompromised host, especially HIV/AIDS subjects.

Giuseppe Bruno: Degree in Medicine and Surgery obtained at the University of Bari, on July 15, 2010 with 110/110, magna cum laude; Diploma of Specialist in Infectious Diseases obtained at the University of Bari, on June 30, 2016 with 70/70 magna cum laude. Professional appointments: Admission to the Board of Physicians obtained at the University of Bari, year 2011; Physician in Charge at the Division of Internal Medicine, at Public Hospital, Argenta (Ferrara), from July 2017 until May 2018; Physician in Charge at the Division of Infectious Diseases, at San Giuseppe Moscati Hospital, Taranto, from May 2018, until now; Consultant Infectious Disease Specialist at: San Giuseppe Moscati Hospital, Taranto, from May 2018, until now. Since 2011, Dr. Bruno has been engaged in diagnostic, clinical, laboratory, and therapeutic research in the field of Infectious Diseases, focusing on HIV infection and AIDS, immunodeficiencies, opportunistic infections, viral hepatitis, and taking part in numerous international trials and national research projects. He is author of 21 publications in the field of HIV infection.

Paolo Maggi is a specialist in Infectious Diseases, Microbiology and Pharmacology; associate professor in Infectious Diseases, Director of the Unit of Infectious Diseases, Caserta Hospital. He is author or co-author of over 350 peer reviewed papers, mainly on the topic of non-communicable diseases in HIV.

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Paola Vitiello got her medical degree at the University of Milan in 2007 and received her Specialization in Infectious Diseases at the same University in 2012. During her studies she focused her research activities on virology. In particular, she was interested both in laboratory and clinical aspects of HIV treatment. In 2010, She attended a fellowship in UK where she worked on HIV low level viremia detection. From 2012 to 2018 she worked at Busto Arsizio Hospital, Italy as Infectious Diseases physician and she is actually working at the University Hospital San Gerardo in Monza. She is mainly involved in the management of HIV infected patients with a special interest in the field of nutrition in HIV infection.

Clara Abeli obtained her medical degree at Milan University (Università degli Studi di Milano) in 1995, where she completed her Fellowship in Infectious Diseases in 2000. She has been working as an Infectious Diseases Specialist at ASST Valle Olona in Busto Arsizio since April 2001. Dr. Abeli has a wide experience as Sub-Investigator in Phase III and IV Clinical Trials according to GCP (Therapeutic Areas: HIV, HCV).

Stefano Bonora is Associate Professor of Infectious Diseases and Chief of HIV Outpatient Service at the University of Turin. He is also the medical responsible of the Laboratory of Clinical Pharmacology and Pharmacogenetics of Antiretrovirals of the University of Torino. He collaborated in numerous studies of HIV treatment as an expert of clinical pharmacology of antiretrovirals.

Micol Ferrara graduated in Medicine at University of Pisa with a final mark of 110/110 cum laude. She has been a Resident in Infectious Diseases at University of Torino where she graduated in August 2018 with a final mark of 70/70 cum laude and recommendation for publication. During these years, as Resident and now as a Scholar, she worked mainly at Outpatient HIV Clinic of Amedeo di Savoia Hospital and her

major area of interest was based on Clinical HIV and Antiretroviral Pharmacokinetics. She has presented several abstracts at Italian and European Conferences and co-authored 7 papers, and other 2 in submission. Since last year, she is working as Teaching Assistant at University of Torino at Nursing Degree and Obstetric Degree. She has been collaborating with different colleagues of other Italian Universities in Multicenter Studies and Clinical Trials. In 2017, she spent several months at University of San Diego, California, USA to improve her skills in HIV Research and since then she has been collaborating on different projects.

Maria Vittoria Cossu received her medical degree from the University of Milan in 2008 and completed her specialization in pharmacology at the same University in 2014. While she completed her residency in pharmacology her main fields of research have been the study of the impact of nitric oxide in the pathophysiology of muscle degenerative disorders and the pharmacology of HIV drugs. She worked in the implementation of a Phase I Unit in the Luigi Sacco to conduct study on healthy volunteers. Currently, since July 1, 2014 she works as Medical Assistant in the Outpatient Unit of the 1st Division of the infectious Diseases. She is involved in the conduction international clinical trials, which are ongoing at her site, related to HIV, HCV, NASH and antibiotic therapeutic areas.

Maria Letizia Oreni graduated in computer science from the University of Milan in 2009. Since 2011, she carries out collaboration activities with the Department of Biomedical and Clinical Sciences "L. Sacco" for data analysis in studies on HIV patients.

Elisa Colella obtained her medical degree at University of Milan in 2009, and got her Specialization degree in Tropical Medicine in 2016 at the same University. During her studies she focused her research activities on HIV virology, especially on antiretroviral drugs, both in their laboratory and clinical setting. From 2016, she works as Infectious Diseases physician at San Gerardo Hospital, in Monza, where she at first focused her studies on immune-activation and lymphoproliferative disorders in HIV patients, and then she focused also on viral hepatitis, that are still her current prevalent field of study.

Stefano Rusconi is an Associate Professor in infectious diseases at the DIBIC Luigi Sacco, University of Milan, Italy, since February 1, 2015, where he is the quality assurance referent since January 2019. After his M.D. in 1988, he got post-graduate specialties in allergy & clinical immunology and infectious diseases. He is on staff at Luigi Sacco hospital in Milan since February 1994. His research interests are: (i) experimental models of antiretroviral therapy and viral mutants in vitro; (ii) genotypic and phenotypic analysis of resistance to antiretroviral drugs; (iii) design and conduct of clinical trials with antiretroviral drugs. He holds post-graduate certifications in design and conduct of clinical trials and in advanced bioethics and has been the scientific secretary at Milan Area 1 Inter-hospital IRB from July 1999 to January 2017. He is the Association of American Medical Colleges (AAMC) Visiting Student Learning Opportunities™ (VSLO™) representative at the University of Milan. He has been elected as EACS regional representative in 2012–2016. Academic Years 2010/11-ongoing: teaching Infectious Diseases to Medical School students; 2012/13-ongoing: teaching Infectious Diseases to Prevention Health Sciences students, both at Università degli Studi di Milano, Italy. Since 2012: member of HIV/AIDS ITALIAN EXPERT PANEL for Italian Guidelines. Referee: HIVERA for European Research Projects on HIV/AIDS, International AIDS Conference, World AIDS Conference, Italian Ministry of University and Scientific Research.

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References

1 Linee Guida 2017 sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostica-clinica delle persone con infezione da HIV-1. 2017. http://www.salute.gov.it/imgs/C_17_pubblicazioni_2696_allegato.pdf
2 European AIDS clinical society. Guidelines: clinical management of treatment of HIV infected adults in Europe, 2018. http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf
3 BHIVA (British HIV Association). Treatment of HIV-1-positive adults with antiretroviral therapy guidelines. https://www.bhiva.org/guidelines
4 Nix LM, Tien PC. Metabolic syndrome, diabetes, and cardiovascular risk in HIV. *Curr HIV/AIDS Rep.* 2014;11(3):271–278.
5 Vecchi V, Maggi P, Rizzo M, Montalto G. The metabolic syndrome and HIV infection. *Cpd.* 2014;20(31):4975–5003.
6 Tsoukas C. Immunosenescence and aging in HIV. *Curr Opin HIV AIDS.* 2014;9(4):398–404. Jul
7 Horberg M, Tang B, Towner W, et al. Impact of tenofovir on renal function in HIV-infected, antiretroviral-naïve patients. *J Aquir Immune Defic Syndr.* 2010;53(1):62–69.
8 EACS. Guidelines Version 10.0. November 2019.
9 Fabbiani M, Gagliardini R, Ciccarelli N, et al. Atazanavir/ritonavir with lamivudine as maintenance therapy in virologically suppressed HIV-infected patients: 96 week outcomes of a randomized trial. *J Antimicrob Chemother.* 2018;73(7):1955–1964.
10 Perez-Molina JA, Rubio R, Rivero A, et al. Dual treatment with atazanavir-ritonavir plus lamivudine versus triple treatment with atazanavir-ritonavir plus two nucleos(t)ides in virologically stable patients with HIV-1 (SALT): 48 week results from a randomised, open-label, non-inferiority trial. *Lancet Infect Dis.* 2015 Jul;15(7):775–784.
11 Pulido F, Ribera E, Lagarde M, et al. Dual therapy with darunavir and ritonavir plus lamivudine vs triple therapy with darunavir and ritonavir plus tenofovir disoproxil fumarate and emtricitabine

or abacavir and lamivudine for maintenance of Human Immunodeficiency Virus Type 1 viral suppression: randomized, open-label, noninferiority DUAL-GESIDA 8014-RIS-EST45 trial. *Clin Infect Dis.* 2017;65(12):2112–2118.
12 Daar ES. Novel approaches to HIV therapy. *F1000Res.* 2017;6: 759.
13 Maggiolo F, Gulminetti R, Pagnucco L, et al. Lamivudine/dolutegravir dual therapy in HIV-infected, virologically suppressed patients. *BMC Infect Dis.* 2017;17(1):215.
14 Joly V, Burdet C, Landman R, et al. Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL). *J Antimicrob Chemother.* 2019;74(3):739–745.
15 van Wyk J, Ajana F, Bisshop F, et al. Efficacy and safety of switching to dolutegravir/lamivudine fixed-dose two-drug regimen versus continuing a tenofovir alafenamide-based three- or four-drug regimen for maintenance of virologic suppression in adults with HIV-1: Phase 3, randomized, non-inferiority TANGO Study. *Clin Infect Dis.* 2020;ciz1243.
16 Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med.* 2008;358(20):2095–2106.
17 Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet* 2018;391(10123):839–849.
18 https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. Accessed July 07, 2019.
19 Justice AC, Modur S, Tate JP, et al. Predictive accuracy of the Veterans Aging Cohort Study (VACS) Index for mortality with HIV infection: a North American Cross Cohort analysis. *J Aquir Immune Defic Syndr.* 2013 Feb;62(2):149–163.
20 Maggiolo F, Di Filippo E, Valenti D, Serna Ortega PA, Callegaro A. NRTI Sparing therapy in virologically controlled HIV-1 infected subjects: results of a controlled, randomized trial (Probe). *J Acquir Immune Defic Syndr.* 2016;72(1):46–51.
21 Pasquau J, de Jesus SE, Arazo P, et al. Effectiveness and safety of dual therapy with rilpivirine and boosted darunavir in treatment-experienced patients with advanced HIV infection: a preliminary 24 week analysis (RIDAR study). *BMC Infect Dis.* 2019;19(1):207.
22 de Miguel Buckley R, Montejano R, Stella-Ascariz N, Arribas JR. New strategies of ARV: the road to simplification. *Curr HIV/AIDS Rep.* 2018;15(1):11–19.
23 Mussini C, Roncaglia E, Borghi V, et al. A prospective randomized trial on abacavir/lamivudine plus darunavir/ritonavir or raltegravir in HIV-positive drug-naïve patients with CD4 < 200 cells/uL (the PRADAR study). *PLoS One.* 2019;14(9):e0222650.
24 Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. *HIV Med.* 2017;18(1):56–63.
25 Cattaneo D, Rizzardini G, Gervasoni C. Intolerance of dolutegravir-containing combination antiretroviral therapy: not just a pharmacokinetic drug interaction. *AIDS* 2017;31(6):867–868.