OPEN

Patient Self-Reported Adherence to Ritonavir-Boosted Darunavir Combined With Either Raltegravir or Tenofovir Disoproxil Fumarate/Emtricitabine in the NEAT001/ANRS143 Trial

Adriana Ammassari, MD, Wolfgang Stöhr, PhD,† Andrea Antinori, MD,* Jean-Michel Molina, PhD,‡ Christine Schwimmer, PhD,§ Pere Domingo, MD,‖ Anders Thalme, MD, PhD,¶ Massimo Di Pietro, MD,# Cedrick Wallet, MSc,§ Anton Pozniak, MD,** Laura Richert, PhD,§ and François Raffi, MD, PhD,†† the NEAT001/ANRS143 Trial Study Group*

Background: The NEAT001/ANRS143 trial demonstrated non-inferiority of ritonavir-boosted darunavir combined with either raltegravir (RAL + DRV/r) or tenofovir disoproxil fumarate/emtricitabine (TDF/FTC + DRV/r) in HIV-positive, antiretroviral-naive adults. In post hoc analyses, however, RAL + DRV/r showed inferiority in patients with baseline $CD4^+$ <200/mm^3 and HIV-1 RNA ≥100,000 copies per milliliter. This preplanned ancillary study was conducted to assess whether differences in adherence might explain efficacy results.

Setting: Phase III, open-label, randomized, multicenter study in 15 European countries (ClinicalTrials.gov, NCT01066962).

Methods: Seven hundred seventy-four participants self-reported adherence (modified AIDS Clinical Trials Group questionnaire) over 96 weeks [383 RAL + DRV/r (twice daily; 5 pills/day), 391 TDF/FTC + DRV/r (once daily; 4 pills/day)]. Primary endpoint was ≥95% versus <95% adherence to prescribed doses recorded (1) over the last 4 days or (2) on the visual analogue scale over the last 30 days.

Results: Characteristics, except age, were similar between arms; 9% had $CD4^+$ <200 cells/mm^3 and HIV-1 RNA ≥100,000 copies per milliliter. Adherence ≥95% in the last 4 days (P = 0.029) or at the visual analogue scale (P = 0.0072) was higher with TDF/FTC + DRV/r than with RAL + DRV/r. Adherence ≥95% over the last 4 days was associated with lower probability of virological failure (P = 0.015). Adherence in patients with baseline $CD4^+$ <200 cells/mm^3 and HIV-1 RNA ≥100,000 copies per milliliter was similar to the rest of the population, and not significantly associated with efficacy measures, with no significant differences between arms.

Conclusion: Adherence was high and slightly better in the TDF/FTC + DRV/r than in the RAL + DRV/r arm. No convincing evidence was found that higher failure rate in the RAL + DRV/r arm in the subgroup with worse baseline viroimmunological status is caused by adherence differences.

Key Words: adherence, HIV, antiretrovirals, NtRTI-sparing regimen, raltegravir, darunavir/ritonavir

(*J Acquir Immune Defic Syndr* 2018;79:481–490)

Received for publication January 2, 2018; accepted July 9, 2018.

From the *HIV/AIDS Unit, INMI "L. Spallanzani" IRCCS, Rome, Italy; †Medical Research Council Clinical Trials Unit at UCL, London, United Kingdom; ‡Infectious Diseases Department, Hôpital Saint-Louis, University of Paris Diderot, INSERM U941, Paris, France; §Bordeaux Population Health Research Center, University of Bordeaux, INSERM, UMR 1219, Bordeaux, France; ‖Infectious Diseases Unit, Hospital de la Santa Creu I Sant Paul, Barcelona, Spain; ¶Department of Infectious Diseases, Karolinska University Hospital, Stockolm, Sweden; #Infectious Diseases Unit, S. Maria Annunziata Hospital, Florence, Italy; **Chelsea and Westminster NHS Trust St Stephens Centre, London, United Kingdom; and ††Infectious and Tropical Diseases Department, INSERM CIC 1413, CHU, Nantes, France.

NEAT is a project funded to the Instituto Superiore di Sanità–Rome, by the European Union under the Sixth Framework Programme, project number LSHP-CT-2006-037570. The trial was also supported by Gilead Sciences, Janssen Pharmaceuticals, and Merck Laboratories, and The French National Institute for Health and Medical Research–France Recherche Nord&Sud Sida-HIV Hépatites (Inserm-ANRS) is the sponsor and a funder of the trial.

Presented at the 16th European AIDS Conference (EACS); October 25–27, 2017; Milan, Italy.

A. Ammassari received speaker's fees from AbbVie, BMS, Gilead, Janssen Cilag, Merck, and ViiV and participated in advisory boards for Janssen and Merck. A. Antinori received grants from AbbVie, BMS, Gilead, Merck, ViiV, and Janssen Cilag. A.T. received speaker's fees from Gilead and participated in advisory boards for Gilead, Janssen, and ViiV. F.R. received speaker's fees from AbbVie, BMS, Gilead, Janssen Cilag, Merck, and ViiV. C.S., C.W., and L.R. are involved in the EU-IMI-2–funded EBOVAC2 project assessing Ebola candidate vaccines from Johnson and Johnson and Bavarian Nordic, and in the PREVAC project (funded by NIH and Inserm) assessing Ebola candidate vaccines from Merck, Johnson and Johnson, and Bavarian Nordic. The remaining authors had no conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

Correspondence to: Adriana Ammassari, MD, HIV/AIDS Unit, INMI "L. Spallanzani" IRCCS, 00149 Rome, Italy (e-mail: adriana.ammassari@inmi.it).

INTRODUCTION

Treatment of HIV infection relies on combination antiretroviral therapy (ART), which is highly effective in

achieving control of HIV replication, in recovering immune deficiency and thus in allowing for improved life expectancy.[1] Nevertheless, effectiveness of ART may be hampered by suboptimal adherence to medication intake.[2] Many factors, which may be related to the patient, the circumstances and the treatment, may impede drug intake exactly as prescribed. It has been widely demonstrated that a negative impact on medication adherence is mainly driven by 2 factors: complexity of the regimen, determined by repeated daily dosing and number of pills, and treatment side effects.[3,4] In an era with more convenient antiretroviral (ARV) regimens, patients' perceived side effects and treatment convenience or satisfaction are becoming the most important factors for sustained adherence.[5]

Also, in clinical trials, adherence to study medications is essential for reaching study outcomes and may influence trial results. ARVs are highly efficacious in suppressing HIV but associated with low adherence rates and may eventually lead to low virologic efficacy and selection of drug resistance compromising future treatment options. The NEAT001/ANRS143 study was a phase 3, open-label, noninferiority, randomized, multicenter clinical trial comparing the efficacy and safety of the nucleotide reverse-transcriptase inhibitor (NtRTI)-sparing regimen of ritonavir-boosted darunavir (DRV/r) plus raltegravir (RAL) with the standard triple drug regimen of DRV/r plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for first-line combination ART in HIV adults naive to ARVs.[6] Notably, the 2 study arms were different in respect to number of daily dosages and pills with a higher complexity burden in the RAL + DRV/r than in the TDF/FTC + DRV/r arm. The final results, obtained in 805 patients with a median of 123 weeks of follow-up, showed noninferiority of the NtRTI-sparing regimen compared with the standard treatment. In prespecified subgroup analysis, this finding was confirmed for patients with $CD4^+$ cells >200 cells/mm^3, whereas in patients with <200 cells/mm^3, the RAL + DRV/r arm was inferior to the standard triple regimen. A nonsignificant difference toward more failures in the NtRTI-sparing treatment group was also observed in patients with baseline HIV-1 RNA of 100,000 copies per milliliter or more. A post hoc analysis indicated that the inferiority of the NtRTI-sparing regimen was restricted to patients with baseline $CD4^+$ cell count <200/mm^3 and HIV-1 RNA ≥100,000 copies per milliliter. It may be possible that in this patient subgroup, composed of more difficult-to-treat patients with advanced HIV disease, nonadherence behaviors may have played a relevant role.

The preplanned ancillary study on patient self-reported adherence to ARVs was conducted to compare levels and time trends of different adherence measures by treatment arms, to evaluate association of adherence with virological failure, and particularly to assess whether differences in adherence to RAL + DRV/r or TDF/FTC + DRV/r might explain subgroup efficacy results in the NEAT001/ANRS143 trial.

METHODS

Study Design and Participants

The NEAT001/ANRS143 trial was a phase III, open-label, randomized trial performed in 15 European countries. The full study design and procedures are described elsewhere.[6] Eight hundred five ARV-naive adults were randomized in a 1:1 ratio to receive either 2 pills of darunavir 400 mg and ritonavir 100 mg once daily combined with 1 pill of raltegravir 400 mg twice daily (5-pill twice-daily regimen) or 1 pill of tenofovir/emtricitabine 245/200 mg fixed-dose combination once daily (4-pill once-daily regimen). In agreement with the principles of the Helsinki declaration, the Ethics Committee of each participating center approved the study protocol, and all study patients gave written informed consent. The study was registered with ClinicalTrials.gov, number NCT01066962.

Adherence Assessment and Procedures

Adherence assessment was based on patient-reported measures, and participants were asked to complete a modified version of the AIDS Clinical Trials Group questionnaire.[7] This was considered useful based on literature showing that best estimate of adherence should be based on a combination of several measures.[8] The following questions were asked: Please report the number of doses of your anti-HIV medications you have eventually missed over the last 4 days (for each drug, number of doses missed "yesterday"; "2 days ago"; "3 days ago"; and "4 days ago"); How closely did you follow your timing-specific schedule? (more than 2 hours deviation over the last week; response options: "never," "some of the time"; "about half of the time"; "most of the time"; and "all of the time"); Did you interrupt your anti-HIV medications in the absence of provider input (response options: "no"; "yes") and in case of affirmative answer number of days with missed medications (response options: "1 day"; "2 days," "3–4 days"; "5–6 days"; and "≥7 days"); What was the adherence to your anti-HIV medications over the last 30 days? (response options on a visual analogue scale [VAS] from 0 [not taken any dose of the anti-HIV medication] to 100% [taken every single dose]). On average, participants needed 5 minutes to fill the questionnaire. Patients were asked to complete the adherence questionnaire at 5 study visits after the start of study medications: week (W) 04, W12, W24, W48, and W96. The questionnaires were centralized in sealed anonymous envelopes, so that site staff remained unaware of the patient's replies. Blood samples were obtained concomitantly. CD4 cell counts and viral loads in plasma were measured at local laboratories with commercially available viral load assays, with no change in the kits throughout the trial.[6]

Adherence Endpoints Outcomes

The percentage of prescribed ARVs taken during the previous 4 days was calculated as: (1 − [number of self-reported missed doses/number of doses prescribed])*100. Of note, the number of doses (tablets) prescribed in 4 days was different in the 2 treatment arms: 16 in the TDF/FTC + DRV/r arm and 20 in the RAL + DRV/r arm. For both number of doses taken/prescribed and the VAS, the primary endpoint was predefined as ≥95% versus <95% adherence. Furthermore, predefined adherence categories were <80%, ≥80–95%, ≥95–99%, and 100%. As secondary endpoints, "no timing deviation" was defined as reporting to follow the

timing-specific schedule "all of the time" versus all other categories together. We also analyzed timing deviations as ordered variable but did not find any differences and so we did not report the results. Unplanned treatment interruptions since the last visit were analyzed as "yes" (ie, any interruptions) versus "no," and as ordered categories.

Statistical Analyses

The 2 arms of the trial were compared as randomized according to and based on available data. As secondary analysis, participants were analyzed per-protocol with censoring when any component of the initial randomized trial treatment was stopped. The primary endpoint was compared between the 2 randomization arms across all study visits using generalized estimating equation (GEE) models. Secondary endpoints were the variation of adherence at different time points of follow-up and determination of the level of adherence required for successful virological suppression among the 2 treatment arms. Possible determinants of adherence across study visits were analyzed using GEE models, including time on ART, sex, age, mode of HIV infection (homosexual/bisexual men versus other route of transmission), ethnicity (white versus nonwhite), country, baseline $CD4^+$ cell count, and baseline HIV-1 RNA. The association between adherence measures and time to virological failure was evaluated by using Cox regression with time-updated adherence in univariable and multivariable models (using the same factors as described above). Confirmed virological failure was defined as change of any component of the initial randomized regimen before week 32 because of documented insufficient virological response (defined as reductions of less than 1 $\log_{10}$ copies per milliliter in HIV-1 RNA by week 18 or HIV-1 RNA 400 copies per milliliter or higher at week 24); failure to achieve virological response by week 32 (defined as HIV-1 RNA concentrations of 50 copies per milliliter or higher); and HIV-1 RNA concentrations of 50 copies per milliliter or higher at any time after week 32. All virological components of the primary endpoint had to be confirmed by a second measurement.[6]

In post hoc analyses, we also looked at the association of adherence with the primary endpoint of the NEAT001/ANRS143 trial, which was time to virological or clinical failure.[6] Patients with failure before the first adherence assessment were excluded in these analyses. Because in NEAT001/ANRS143 higher failure rates in the RAL + DRV/r arm were seen in those with $CD4^+$ cells <200 cells/mm^3 and HIV-1 RNA $\geq$100,000 copies per milliliter at baseline, we examined whether adherence was lower in this subgroup or whether, in this subgroup, the association with HIV-1 RNA suppression/virological failure differed between the randomization arms. Statistical analyses were performed using Stata Statistical Software Release 14 (StataCorp, College Station, TX).

RESULTS

Between August 2010 and September 2011, 805 treatment-naive adults were enrolled into the NEAT001/ANRS143 trial and randomized to RAL + DRV/r (n = 401) or TDF/FTC + DRV/r (n = 404). Of these, 10 withdrew before the first adherence assessment at week 4. Additional 21 participants (13 in the RAL-DRV/r arm and 8 in the TDF/FTC + DRV/r arm) did not provide any adherence data after W0 and were excluded from the adherence analyses (characteristics of these patients were similar to the whole study population; data not shown). Of the remaining 774 participants, 310 (40%), 227 (29%), 96 (12%), 76 (10%), and 65 (8%) had 5, 4, 3, 2, and 1 adherence assessments, with no differences between the treatment arms. Baseline characteristics of the 774 participants retained in analysis were broadly similar between the 2 treatment groups (383 RAL + DRV/r and 391 TDF/FTC + DRV/r), except for a small difference in age. 72/774 (9%) patients had $CD4^+$ cells <200 cells/mm^3 and HIV-1 RNA $\geq$100,000 copies per milliliter, with no differences in the 2 treatment arms (Table 1). During follow-up, 55 (7%) patients discontinued any component of their randomized regimen for any reason for more than 30 days between randomization and their last adherence assessment (RAL + DRV/r: n = 33; TDF/FTC + DRV/r: n = 22). The proportion of patients who had discontinued was similar in the 2 treatment arms with overall percentages of $<$0.5%, 1%, 2%, 4%, and 8% at W04, W12, W24, W48, and W96, respectively.

Medication Adherence Overall and by Treatment Arm

Adherence by treatment arm as assessed by the different adherence measurements is shown in Figure 1 and a summary over all visits in Table 2.

Number of Doses Taken Over the Last 4 Days

Across all visits, the percentage of participants who have taken $\geq$95% of their medications was higher in the TDF/FTC + DRV/r arm and ranged from 91% to 93% compared with 87% to 91% in the RAL + DRV/r arm [odds ratio (OR) 1.43; 95% confidence interval (CI): 1.04 to 1.97; P = 0.029]. Results were similar when analyzing drugs taken in the 4 ordered categories $<$80%, $\geq$80–95%, $\geq$95–99%, and 100% (OR 1.71; 95% CI: 1.14 to 2.58; P = 0.0096). Overall adherence and the difference between the arms did not change over time (no significant statistical interaction between arm and time). When looking at individual drugs, we found no difference between the arms in adherence to DRV or ritonavir. Although in the TDF/FTC + DRV/r arm, there was no difference in adherence to DRV, ritonavir, and TDF/FTC, in the RAL + DRV/r arm, adherence to RAL was slightly lower than to DRV or ritonavir (proportion of patients with $\geq$95% of medication taken across all visits was 88% for RAL versus 91% for DRV/r; $P < 0.001$).

Adherence on the Visual Analogue Scale

The proportion of patients with $\geq$95% of prescribed medication taken over the last 30 days ranged from 90% to 92% without difference between the arms (P = 0.66). However, patients in the TDF/FTC + DRV/r arm had significantly better adherence across all visits when compared with the RAL + DRV/r arm (OR 1.55; 95% CI: 1.13 to 2.13;

TABLE 1. Baseline Characteristics of the Study Population Shown by Randomization Arm

Factor	RAL + DRV/r n = 383	TDF/FTC + DRV/r n = 391	Overall n = 774	*P*
Sex, male, n (%)	339 (89)	345 (88)	684 (88)	0.61
Age, yr, n (IQR)	37 (31–45)	39 (31–46)	38 (31–46)	0.035
Ethnicity, n (%)				0.60
Nonwhite	50 (13)	44 (11)	94 (12)	
White	315 (82)	324 (83)	639 (83)	
Other	18 (5)	23 (6)	41 (5)	
Mode of HIV infection, n (%)				0.68
Homosexual/ bisexual	258 (67)	270 (69)	528 (68)	
Heterosexual	90 (23)	92 (69)	182 (23)	
Other/unknown	35 (9)	29 (7)	64 (8)	
$CD4^+$ nadir, cells/ mm^3, n (IQR)	320 (240–376)	309 (249–370)	311 (244–373)	0.35
$CD4^+$, cells/mm^3, n (IQR)	336 (261–394)	328 (248–406)	333 (257–400)	0.29
HIV-1 RNA, $\log_{10}$ copies per milliliter, n (IQR)	4.8 (4.3–5.2)	4.7 (4.3–5.1)	4.8 (4.3–5.1)	0.43
$CD4^+$ (cells/mm^3) and HIV-1 RNA ($\log_{10}$ copies per milliliter) categories, n (%)				0.37
CD4 + ≥200, HIV-1 RNA < 100,000	222 (58)	246 (63)	468 (60)	
CD4 + <200, HIV-1 RNA < 100,000	23 (6)	21 (5)	44 (6)	
CD4 + ≥200, HIV-1 RNA ≥ 100,000	104 (27)	86 (22)	190 (25)	
CD4 + <200, HIV-1 RNA ≥ 100,000	34 (9)	38 (10)	72 (9)	
Country, n (%)				1.0
France	109 (28)	115 (29)	224 (29)	
Italy	57 (15)	55 (14)	112 (14)	
Germany	47 (12)	50 (13)	97 (13)	
United Kingdom	46 (12)	50 (13)	96 (12)	
Spain	37 (10)	37 (9)	74 (10)	
Belgium	26 (7)	26 (7)	52 (7)	
Other country	61 (16)	58 (15)	119 (15)	

P value is from comparisons between RAL + DRV/r and TDF/FTC + DRV/r arms using *t* test (continuous variables) or χ^2 test (categorical variables).
IQR, interquartile range.

$P = 0.0072$). Adherence in both arms was decreasing over time ($P < 0.0001$): 100% adherence at weeks 04, 24, and 96 was reported in 88%, 77%, and 71% in TDF/FTC + DRV/r, and in 76%, 71%, and 67% in RAL + DRV/r.

Of note, concordance for the adherence category of ≥95% between adherence in the last 4 days and VAS across all visits was 88%, with no difference between the randomization arms.

Following the Timing-Specific Schedule Over the Last Week

The proportion of patients with no timing deviation of more than 2 hours ranged from 45% to 50%, with a trend for better adherence in the TDF/FTC + DRV/r compared with the RAL + DRV/r arm (OR 1.26; 95% CI: 0.99 to 1.62; $P = 0.06$), and no significant change over time ($P = 0.45$). Across all visits, 16% patients reported to have never followed the timing schedule, 13% some of the time, 2% half of the time, and 21% most of the time ($P = 0.53$ for comparison of arms).

Unplanned Treatment Interruptions After the Last Visit

Across all visits, no treatment interruption was reported in 92% with no statistically significant difference between the arms ($P = 0.30$); on 5%, 1%, 1%, <0.1%, and 0.6% of visits, treatment interruptions of 1 day, 2 days, 3–4 days, 5–6 days, or ≥7 days were reported. Of note, treatment interruptions were more frequently reported with longer follow-up ($P = 0.008$) and were 6%, 9%, and 11% at weeks 04, 24, and 96 across both arms.

Adherence by Treatment Arm and Viroimmunological Parameters

When comparing medication adherence between patients with different baseline $CD4^+$ cell count (<200 versus ≥200 cells/mm^3) or baseline HIV-1 RNA (<100,000 versus ≥100,000 copies per milliliter), there were no significant differences in any of the adherence measures, neither overall nor differential in the 2 study arms (no statistically significant interaction with treatment arms; results not shown). There were also no differences when comparing participants with $CD4^+$ <200 cells/mm^3 and HIV-1 RNA ≥100,000 copies per milliliter with the rest of the study population (Table 2).

Among participants with at least 1 adherence measurement, virological suppression at HIV-1 RNA <50 copies per milliliter was achieved at W04 in 26% of cases (12% in the TDF/FTC + DRV/r arm; 40% in the RAL + DRV/r arm), and at W12 in 63% of cases (48% in the TDF/FTC + DRV/r arm; 78% in the RAL + DRV/r arm). Thereafter, the proportion of patients with HIV RNA <50 copies per milliliter was similar in the 2 arms with overall percentages of 84%, 86%, 91%, 92%, 93%, and 91% at weeks 24, 32, 48, 64, 80, and 96, respectively. The associations between adherence and HIV-1 RNA <50 copies per milliliter at the time of assessment are summarized in Table 1, Supplemental Digital Content http://links.lww.com/QAI/B212.

Association of Adherence Measures With Virological Failure and Primary Endpoint

The analysis of adherence measures and virological failure according to the virological component of the main

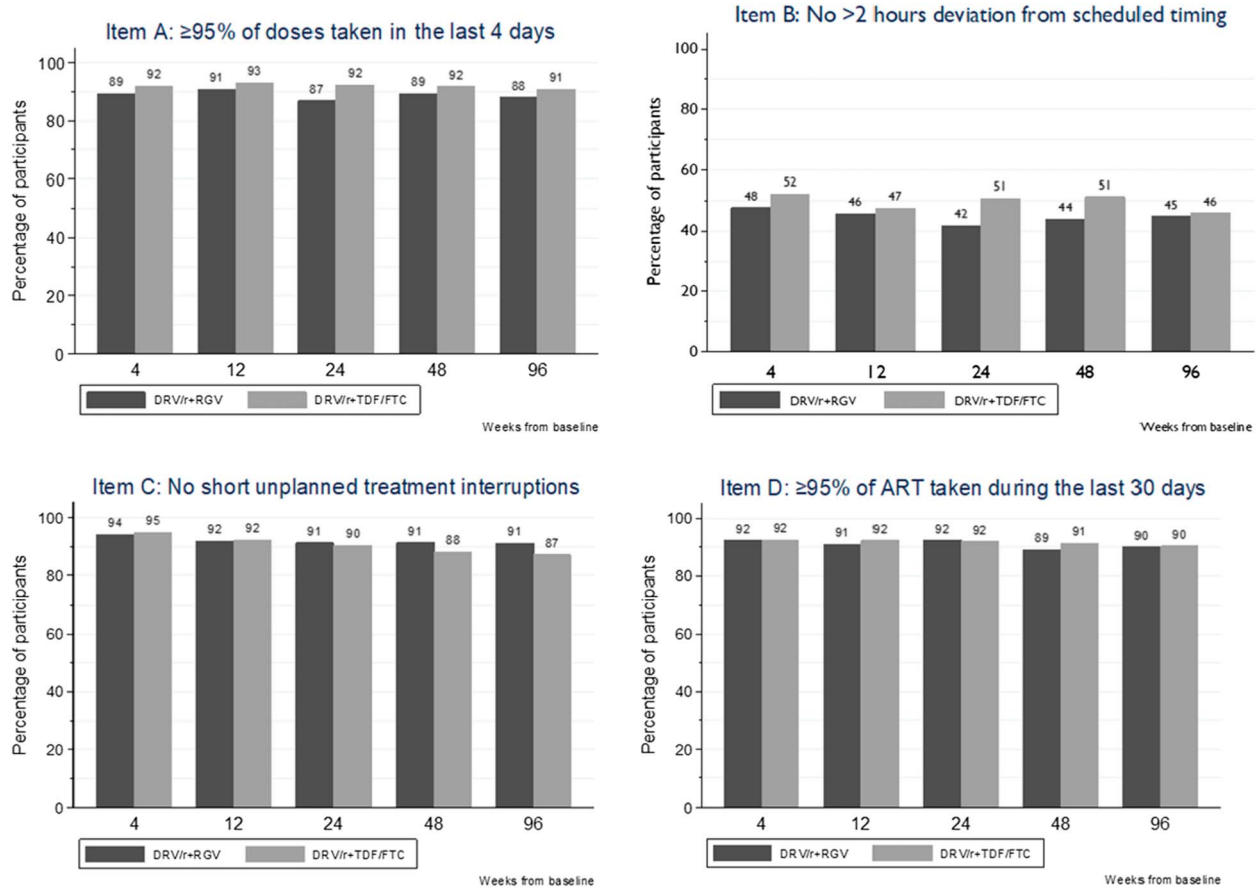

FIGURE 1. Adherence by treatment arms as assessed by different adherence measurements.

trial's primary endpoint definition included 770 patients with 111 virological failures (Table 3). We found that patients with ≥95% of doses taken in the last 4 days had a lower risk of virological failure (univariable hazard ratio [HR] 0.54; 95% CI: 0.33 to 0.89; $P = 0.015$), with no difference between the 2 arms (P value of the interaction term 0.19). Unplanned treatment interruptions (any versus none; the same for time of interruption in ordered categories, results not shown), never >2 hours timing deviations, or ≥95% adherence during the last 30 days on the VAS were not associated with virological failures. For all adherence measures, multivariable analyses gave similar results, as did analyses censoring patients after switch from their allocated regimen (results not shown).

In addition to virological failure, we analyzed the relationship between adherence measures and the primary endpoint of the NEAT001/ANRS143 trial including also clinical failures (122 failures, of which 104 were virological failures), and found similar associations.

We then repeated the analyses for the subgroup with baseline $CD4^+$ <200 cells/mm^3 and HIV-1 RNA ≥100,000 copies per milliliter, where higher failure rates had been seen in the RAL + DRV/r arm compared with the TDF/FTC + DRV/r arm. No significant associations of adherence with virological failure or the primary endpoint were observed. In the RAL + DRV/r arm, for this specific group of patients, the HR was <1 and lower for all 4 adherence measures compared with all patients in the RAL + DRV/r arm and with participants in the TDF/FTC + DRV/r arm suggesting that in this subgroup, good adherence might be more relevant than in the TDF/FTC + DRV/r arm; however, P values were not significant.

Factors Associated With Adherence

Multivariable analyses confirmed the associations described above between specific adherence measures and randomization arm and time on study (Table 4). In addition, older age was significantly associated with better medication adherence (except time deviation). We also found that nonwhites had significantly worse adherence than whites across various measures (except treatment interruptions), and that adherence significantly differed between countries. We did not find an association of any of the adherence measures with either sex, or baseline $CD4^+$ cell count, or baseline HIV-1 RNA.

DISCUSSION

Adherence to ART, the key determinant of virological response is a very complex parameter because it reflects human behavior and as such varies from 1 patient to another

TABLE 2. Adherence Summary

	100% of Doses Taken		No Timing Deviation		No Treatment Interruption		100% on the VAS		≥95% of Doses Taken		≥95% on the VAS	
	RAL + DRV/r	TDF/FTC + DRV/r	RAL + DRV/r	TDF/FTC + DRV/r	RAL + DRV/r	TDF/FTC + DRV/r	RAL + DRV/r	TDF/FTC + DRV/r	RAL + DRV/r	TDF/FTC + DRV/r	RAL + DRV/r	TDF/FTC + DRV/r
Adherence over all visits*												
Always	266 (70%)	304 (78%)	58 (15%)	76 (19%)	296 (77%)	283 (72%)	157 (41%)	187 (48%)	277 (72%)	304 (78%)	298 (78%)	296 (76%)
Sometimes	108 (28%)	78 (20%)	216 (56%)	227 (58%)	78 (20%)	100 (26%)	191 (50%)	175 (45%)	99 (26%)	78 (20%)	73 (19%)	85 (22%)
Never	9 (2%)	9 (2%)	109 (28%)	88 (23%)	9 (2%)	8 (2%)	35 (9%)	29 (7%)	7 (2%)	9 (2%)	12 (3%)	10 (3%)
Total no. of visits with this level of adherence	1265 (87%)	1392 (92%)	645 (45%)	747 (50%)	1323 (92%)	1363 (91%)	1003 (70%)	1163 (78%)	1288 (89%)	1392 (92%)	1308 (91%)	1373 (92%)
Adherence by baseline $CD4^+$ cells and HIV-1 RNA†												
$CD4^+ \geq 200/mm^3$ or HIV-1 RNA $<100{,}000$	171/1335 (87%)	111/1365 (92%)	729/1325 (45%)	689/1358 (49%)	105/1327 (92%)	131/1358 (90%)	412/1324 (69%)	306/1352 (77%)	150/1335 (89%)	111/11,365 (92%)	118/1324 (91%)	113/1352 (92%)
$CD4^+ < 200/mm^3$ and HIV-1 RNA $\geq 100{,}000$	13/114 (89%)	11/149 (93%)	64/113 (43%)	70/148 (53%)	11/112 (90%)	12/148 (92%)	23/114 (79%)	30/147 (79%)	11/114 (90%)	11/149 (93%)	12/114 (89%)	13/147 (91%)
Interaction test of baseline strata with arm	$P = 0.96$		$P = 0.55$		$P = 0.41$		$P = 0.37$		$P = 0.91$		$P = 0.86$	

*Always = at 100% of assessed visits; never = at 0% of assessed visits; sometimes = >0% and <100% of assessed visits.
†Average across all visits.

and can change over time. In the NEAT001/ANRS143 study, ART-naive subjects on average self-reported high levels of adherence to study drugs in both treatment arms. More in depth analysis of adherence behaviors showed for the TDF/FTC + DRV/r group compared with the RAL + DRV/r group significantly higher adherence rates at all time points in 3 of 4 adherence measures (number of doses taken over the last 4 days, 30 days of adherence on the VAS, and deviation from timing-specific schedule). The only adherence measure significantly associated with time to virological failure or the primary endpoint of the NEAT001/ANRS143 trial including also clinical failures was <95% adherence at short-term patient recall (ie, "doses taken in the last 4 days"), with no difference between the 2-arm subgroups based on viroimmunological baseline status; we did not see significant differences in any of the adherence measures, neither overall nor differential in the 2 study arms.

The threshold of >95% adherence to prescribed doses and tablets was established as a requirement for achieving virological suppression with first-generation unboosted protease inhibitors, a class with short half-live, low genetic barrier to resistance development, and limited forgiveness.[9] Further studies showed that adherence and virological suppression improved with simplified regimens and lower pill burden, although in a meta-analysis of 19 studies published through March 2013, patients on once-daily regimens did not achieve virological suppression more frequently than patients on twice-daily regimens.[10] Impact of adherence behavior might also depend on the drug class considered. With ritonavir-boosted protease inhibitors, average adherence was a better determinant of virological success than was the duration or frequency of treatment interruption, whereas for non-nucleoside reverse-transcriptase inhibitors, consecutive missed doses were associated with the highest risk of virological failure.[11–13] RAL is a well-tolerated and effective drug that demonstrated durable virological suppression in first-line ART through 240 weeks of therapy.[14] However, because of its twice-daily formulation, RAL may be highly susceptible to various nonadherence behaviors, such as selective morning or evening dose skipping, short treatment interruptions, and suboptimal levels of adherence. These patterns are common in clinical practice.[15] In a prospective study assessing the patterns of adherence to RAL-based regimens, longer treatment interruption and average adherence were both independently associated with virological failure.[16] Of note, TDF/FTC is considered as the most forgiving N(t)RTI combination because of the very prolonged intracellular half-lives of the 2 drugs.[17]

Our study seems to confirm the importance of high adherence levels (ie, >95%) on likelihood of virological success. Keeping in mind that self-reported adherence may overestimate real drug intake attributing virological failure to differences in efficacy between treatment arms and leading to incorrect study conclusions, the only adherence measure associated with virological failure was self-reporting <95% of doses taken/prescribed in the past 4 days, with no difference between treatment arms. These results, suggesting that adherence in the past 4 days had a greater impact on

TABLE 3. Adherence and Time to Virological Failure or Primary Endpoint: (1) Overall and (2) in the Subgroup Baseline CD4 Cells <200/mmc and HIV-1 RNA ≥100,000 Copies per Milliliter

	Adherence and Time to Virological failure*			Adherence and Time to Primary Endpoint†		
Adherence Measure	RAL + DRV/r	TDF/FTC + DRV/r	Overall	RAL + DRV/r	TDF/FTC + DRV/r	Overall
Doses taken in the last 4 days: ≥95% versus <95%						
Overall	0.75 (0.37–1.52), $P = 0.423$	0.38 (0.19–0.77), $P = 0.007$	0.54 (0.33–0.89), $P = 0.015$, $P_{int} = 0.19$	0.64 (0.34–1.23), $P = 0.185$	0.46 (0.23–0.90), $P = 0.024$	0.55 (0.34–0.87), $P = 0.012$, $P_{int} = 0.47$
CD4 < 200 and RNA > 100,000	0.46 (0.11–2.03), $P = 0.307$	0.62 (0.08–4.86), $P = 0.645$	0.50 (0.15–1.65), $P = 0.245$, $P_{int} = 0.82$	0.42 (0.12–1.45), $P = 0.170$	0.70 (0.09–5.45), $P = 0.731$	0.47 (0.16–1.35), $P = 0.162$, $P_{int} = 0.59$
No time deviation versus deviation						
Overall	0.89 (0.53–1.50), $P = 0.669$	1.43 (0.82–2.50), $P = 0.209$	1.10 (0.75–1.60), $P = 0.624$, $P_{int} = 0.22$	0.75 (0.45–1.26), $P = 0.283$	1.35 (0.80–2.28), $P = 0.257$	0.99 (0.69–1.42), $P = 0.955$, $P_{int} = 0.12$
CD4 < 200 and RNA > 100,000	0.74 (0.29–1.92), $P = 0.536$	2.76 (0.71–10.70), $P = 0.143$	1.17 (0.56–2.46), $P = 0.676$, $P_{int} = 0.12$	0.56 (0.23–1.40), $P = 0.216$	2.14 (0.63–7.32), $P = 0.226$	0.90 (0.45–1.81), $P = 0.771$, $P_{int} = 0.091$
No interruption versus interruption						
Overall	1.05 (0.42–2.62), $P = 0.915$	2.22 (0.69–7.12), $P = 0.182$	1.50 (0.73–3.09), $P = 0.267$, $P_{int} = 0.33$	0.79 (0.36–1.74), $P = 0.564$	1.48 (0.59–3.70), $P = 0.404$	1.08 (0.59–1.96), $P = 0.804$, $P_{int} = 0.31$
CD4 < 200 and RNA > 100,000	1.28 (0.17–9.67), $P = 0.809$	0.97 (0.12–7.79), $P = 0.980$	1.17 (0.28–4.95), $P = 0.832$, $P_{int} = 0.89$	0.53 (0.15–1.81), $P = 0.310$	1.17 (0.15–9.22), $P = 0.884$	0.67 (0.23–1.93), $P = 0.460$, $P_{int} = 0.49$
VAS: ≥95% versus <95%						
Overall	0.65 (0.32–1.32), $P = 0.236$	1.03 (0.41–2.60), $P = 0.949$	0.78 (0.45–1.37), $P = 0.391$, $P_{int} = 0.44$	0.55 (0.29–1.06), $P = 0.073$	0.98 (0.42–2.28), $P = 0.962$	0.70 (0.42–1.17), $P = 0.175$, $P_{int} = 0.30$
CD4 < 200 and RNA > 100,000	0.83 (0.19–3.64), $P = 0.810$	0.82 (0.10–6.54), $P = 0.853$	0.86 (0.26–2.85), $P = 0.805$, $P_{int} = 0.96$	0.45 (0.15–1.34), $P = 0.150$	0.98 (0.12–7.70), $P = 0.984$	0.57 (0.22–1.48), $P = 0.247$, $P_{int} = 0.48$

*Analysis included 770 patients with 111 virological failures based on a separate Cox model for each adherence measure. P_{int}: P value for the interaction adherence level × arm.
†Analysis included 763 patients with 122 failures based on a separate Cox model for each adherence measure. P_{int}: P value for interaction randomization arm × adherence.

virological failure than treatment interruption, can probably be explained by the fact that treatment interruptions ≥5 days were seen in less than 0.7% of visits. Indeed, over a 30-day period, missing 1 dose on 7 consecutive days (clustered missed doses) will not have the same impact as missing 7 doses on single independent days (interspaced missed doses).[18] Of interest, in our study, unplanned treatment interruptions were very infrequent, increased with prolonged follow-up, but with no differences between treatment arms. This could reflect treatment fatigue or some interfering social/personal events independent of ARV regimen. In our study, given the short plasma half-life of RAL, even short-term RAL interruptions could have led to ineffective intracellular concentrations in some patients, even with high levels of average adherence.

In the subgroup of patients with baseline $CD4^+$ <200/mmc and HIV-1 RNA >100.000 copies per milliliter, there were no significant associations of adherence with virological failure or the primary endpoint, and no significant difference between the arms. In the RAL + DRV/r arm, we noted a decreased hazard ratio in this specific patient group for all 4 adherence measures compared with all patients in this arm, and to participants in the TDF/FTC + DRV/r arm suggesting that in this subgroup, good adherence might be more relevant than in the TDF/FTC + DRV/r arm; however, P values were not significant. Based on this result, the higher rate of virological failure in the subgroup of patients with baseline $CD4^+$ <200/mm^3 and HIV-1 RNA >100,000 copies per milliliter found at the explanatory post hoc analysis was not explained by differences in adherence. However, it should be considered that numbers were small in this subgroup, and the trial was not specifically powered to conduct subgroup analyses to this regard. In fact, it is possible that, rather than an absence of effect, the sample size was not large enough to detect a significant association between adherence levels and inferiority of RAL + DRV/r in respect to TDF/FTC + DRV/r in patients with worse viroimmunological status (ie, CD4 cells <200/mm^3 or CD4 cells <200/mm^3 and HIV RNA >100,000 copies per milliliter).

The best way to measure adherence, from a clinically relevant standpoint, is still debated.[19,20] Patient self-reported measures of ARV adherence can greatly vary in terms of item content, format, or period investigated.[21] Nevertheless, the method is frequently used because of utilization ease, low costs, nonintrusiveness, and wide applicability. Overestimation of real adherence rates due to desirability bias may be of concern for the validity of self-reported adherence measure but applies in a randomized clinical trial to both treatment arms equally. An analysis of 1247 HIV-positive subjects participating in multicenter medication adherence-promotion

TABLE 4. Determinants of Adherence in Multivariable Analyses (GEE Models)

	Doses Taken in the Last 4 days	Doses Taken in the Last 4 days	Time Deviation	Interruption	VAS	VAS
		<80%				<80%,
		80%–94.9%				80%–94.9%
		95%–99.9%				95%–99.9%
	≥95% Versus <95%	100%	No Versus Yes	No Versus Yes	≥95% Versus <95%	100%
Sex						
Male	Ref	Ref	Ref	Ref	Ref	Ref
Female	0.87 (0.52–1.48)	0.71 (0.37–1.34)	0.84 (0.57–1.23)	0.79 (0.44–1.42)	1.72 (0.89–3.31)	1.06 (0.58–1.94)
	$P = 0.618$	$P = 0.288$	$P = 0.366$	$P = 0.434$	$P = 0.108$	$P = 0.840$
Age (per 5 yrs)	1.15 (1.06–1.25)	1.15 (1.04–1.27)	1.03 (0.98–1.09)	1.14 (1.04–1.25)	1.21 (1.09–1.33)	1.14 (1.05–1.23)
	$P = 0.001$	$P = 0.006$	$P = 0.197$	$P = 0.004$	$P < 0.001$	$P = 0.002$
Ethnicity						
White	Ref	Ref	Ref	Ref	Ref	Ref
Nonwhite	0.66 (0.44–1.00)	0.70 (0.42–1.17)	0.64 (0.48–0.86)	0.90 (0.57–1.43)	0.35 (0.22–0.55)	0.52 (0.33–0.84)
	$P = 0.048$	$P = 0.176$	$P = 0.003$	$P = 0.668$	$P < 0.001$	$P = 0.007$
Mode of HIV infection						
Homosexual/bisexual	Ref	Ref	Ref	Ref	Ref	Ref
Other	0.71 (0.48–1.06)	0.68 (0.42–1.11)	1.17 (0.88–1.54)	1.00 (0.64–1.57)	0.64 (0.41–0.99)	0.82 (0.53–1.26)
	$P = 0.098$	$P = 0.125$	$P = 0.275$	$P = 0.997$	$P = 0.043$	$P = 0.370$
Baseline CD4+: (Per 100 cells/mmc)	0.91 (0.80–1.04)	0.89 (0.75–1.05)	0.96 (0.89–1.05)	0.90 (0.79–1.03)	0.93 (0.80–1.08)	0.87 (0.76–1.00)
	$P = 0.156$	$P = 0.159$	$P = 0.383$	$P = 0.134$	$P = 0.344$	$P = 0.051$
Baseline HIV-1 RNA (per $\log_{10}$ copies per milliliter)	1.01 (0.78–1.32)	0.99 (0.72–1.37)	1.05 (0.89–1.25)	0.99 (0.75–1.30)	0.95 (0.69–1.30)	1.14 (0.88–1.48)
	$P = 0.924$	$P = 0.952$	$P = 0.536$	$P = 0.923$	$P = 0.748$	$P = 0.320$
Country						
France	Ref	Ref	Ref	Ref	Ref	Ref
Belgium	0.75 (0.44–1.26)	0.62 (0.32–1.18)	1.03 (0.70–1.53)	0.87 (0.47–1.62)	0.62 (0.34–1.14)	0.67 (0.35–1.28)
Germany	2.62 (1.43–4.80)	3.64 (1.80–7.37)	1.61 (1.15–2.27)	2.04 (1.13–3.68)	2.45 (1.20–5.04)	1.19 (0.73–1.94)
Spain	0.98 (0.60–1.60)	0.97 (0.51–1.85)	0.75 (0.51–1.12)	0.64 (0.37–1.11)	0.72 (0.38–1.37)	0.62 (0.35–1.13)
United Kingdom	2.82 (1.26–6.30)	3.72 (1.46–9.51)	1.28 (0.89–1.83)	0.84 (0.49–1.45)	1.07 (0.57–2.00)	0.93 (0.52–1.63)
Italy	2.24 (1.19–4.21)	2.67 (1.31–5.45)	1.49 (1.08–2.07)	1.73 (0.97–3.08)	0.89 (0.52–1.55)	0.71 (0.43–1.18)
Other	0.98 (0.61–1.56)	1.04 (0.58–1.86)	1.15 (0.83–1.59)	1.20 (0.70–2.08)	1.14 (0.64–2.03)	0.98 (0.60–1.61)
	$P = 0.0004$	$P < 0.001$	$P = 0.0052$	$P = 0.0140$	$P = 0.0371$	$P = 0.3028$
Study arm						
RAL + DRV/r	Ref	Ref	Ref	Ref	Ref	Ref
TDF/FTC + DRV/r	1.32 (0.97–1.81)	1.55 (1.05–2.29)	1.19 (0.97–1.45)	0.78 (0.57–1.08)	0.99 (0.69–1.40)	1.44 (1.06–1.97)
	$P = 0.081$	$P = 0.027$	$P = 0.094$	$P = 0.140$	$P = 0.934$	$P = 0.020$
Study week						
04	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
12	1.21 (0.84–1.73)	1.23 (0.80–1.88)	0.87 (0.72–1.06)	0.67 (0.44–1.00)	0.89 (0.62–1.28)	0.58 (0.42–0.81)
24	0.90 (0.63–1.29)	0.85 (0.56–1.30)	0.87 (0.70–1.07)	0.57 (0.37–0.89)	0.96 (0.65–1.42)	0.55 (0.40–0.77)
48	0.96 (0.66–1.41)	0.93 (0.59–1.45)	0.89 (0.72–1.10)	0.49 (0.33–0.75)	0.73 (0.50–1.06)	0.37 (0.27–0.52)
96	0.87 (0.60–1.26)	0.82 (0.52–1.27)	0.81 (0.65–1.00)	0.45 (0.30–0.69)	0.73 (0.49–1.09)	0.37 (0.26–0.52)
	$P = 0.4913$	$P = 0.4063$	$P = 0.3899$	$P = 0.0033$	$P = 0.3444$	$P < 0.001$

trials showed that self-report overestimated actual medication ingestion by an average of 26% points compared with electronic drug monitoring.[22] Furthermore, the patient's recall of medication intake in answering diverse adherence questions may reflect not only drug ingestion but also other aspects, such as patient's perception and/or satisfaction to treatment. In fact in our study, the rather low concordance observed between categories of self-reported number of doses taken in the last 4 days and 30-day adherence at the VAS (88%) is likely to be due to these aspects. Medication event monitoring system, the gold standard in some studies, can by itself represent an interventional bias and could be associated to poor adherence to the device that measures the adherence behavior.[23] Evaluation of differences between adherence measures remains an interesting aspect to investigate, and methods for cocalibration of different instruments are needed.[24] The fact that adherence worsened over time in our results is consistent with previously reported data.[25]

Our results show that nonwhite ethnicity was associated with lower adherence and rate of virological failure or primary endpoint occurrence. Lower adherence in nonwhite patients cared for in Australian centers has been associated with social and cultural issues, independently of regimen composition.[26] Complying to a twice-daily regimen might be

more problematic in patients faced with poverty, poor housing, and eating insecurity. Older age was associated with better adherence, independently of regimen allocated, and whatever the measure of adherence. Many studies have documented younger age as a relevant factor associated to lower adherence, emphasizing the need for targeted counseling on adherence barriers in this population.[27–29]

With regards to study limitations, the most important issue as mentioned above is that, besides missing adherence data, the study was not specifically powered to conduct subgroup analyses. Therefore, it is not possible to determine whether our findings substantiate the hypothesis of efficacy difference between TDF/FTC + DRV/r and RAL + DRV/r in ART-naive subjects with worse baseline viroimmunological status or whether they are due to insufficient power for subgroup analyses. Furthermore, disparities in clinical management across centers may have impacted adherence behaviors, and we cannot exclude the fact that some nonadherence behaviors may have been missed because of the infrequent collection of self-administered questionnaires. Finally, measurement of adherence by patient self-report can overestimate medication intake, but more objective measures such as plasma drug concentrations or medication event monitoring system have other disadvantages, such as "white coat adherence" close before clinic visit or intrusiveness in the patient's daily life. On the contrary, one of the main strengths of the study is the evaluation of adherence to ARVs within a randomized clinical trial comparing of TDF/FTC + DRV/r versus RAL + DRV/r in a large patient population that was followed up for a considerable period. Second, as the study protocol did not include adherence interventions, the results provide valuable information about adherence dynamics in ARV-naive HIV-infected persons and its relation to virological outcome.

In conclusion, in this randomized study comparing 2 strategies of first-line ART, average adherence assessed by patient self-report was high in both arms, but slightly and significantly better for TDF/FTC + DRV/r compared with RAL + DRV/r. Only adherence <95% in the last 4 days was associated to a higher risk of virological failure, with no differences between the 2 arms. Adherence levels were not different in baseline $CD4^+$ and HIV RNA strata across arms, and there was no convincing evidence that higher failure rate in the RAL + DRV/r arm in the subgroup of patients with baseline $CD4^+$ <200/mmc and HIV-1 RNA >100,000 copies per milliliter found at the explanatory post hoc analysis of the NEAT001/ANRS143 trial was caused by adherence differences.

ACKNOWLEDGMENTS

The authors thank the NEAT001/ANRS143 study participants and their partners, families, and caregivers for participation in the study. They also thank the staff from all the centers participating in the trial.

REFERENCES

1. Antiretroviral Therapy Cohort Collaboration. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *Lancet HIV.* 2017;4:e349–e356.
2. Genberg BL1, Wilson IB, Bangsberg DR, et al; MACH14 Investigators. Patterns of antiretroviral therapy adherence and impact on HIV RNA among patients in North America. *AIDS.* 2012;26:1415–1423.
3. Saberi P1, Neilands TB, Vittinghoff E, et al. Barriers to antiretroviral therapy adherence and plasma HIV RNA suppression among AIDS clinical trials group study participants. *AIDS Patient Care STDS.* 2015; 29:111–116.
4. Duran S, Spire B, Raffi F, et al; the APROCO Cohort Study Group. Self-reported symptoms after initiation of a protease inhibitor in HIV-infected patients and their impact on adherence to HAART. *HIV Clin Trials.* 2001;2:38–45.
5. Al-Dakkak I, Patel S, McCann E, et al. The impact of specific HIV treatment-related adverse events on adherence to antiretroviral therapy: a systematic review and meta-analysis. *AIDS Care.* 2013;25:400–414.
6. Raffi F, Babiker AG, Richert L, et al; NEAT001/ANRS143 Study Group. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRSed non-inferiority trial. *Lancet.* 2014; 384:1942–1951.
7. Reynolds NR, Sun J, Nagaraja HN, et al. Optimizing measurement of selfreported adherence with the ACTG Adherence Questionnaire: a cross-protocol analysis. *J Acquir Immune Defic Syndr.* 2007;46:402–409.
8. Liu H, Golin CE, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med.* 2001; 134:968–977.
9. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000;133:21–30.
10. Nachega JB, Parienti JJ, Uthman OA, et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: a meta-analysis of randomized controlled trials. *Clin Infect Dis.* 2014;58:1297–1307.
11. Nelson M, Girard PM, Demasi R, et al. Suboptimal adherence to darunavir/ritonavir has minimal effect on efficacy compared wit lopinavir/ritonavir in treatment-naive, HIV-infected patients: 96 week ARTEMIS data. *J Antimicrob Chemother.* 2010;65:1505–1509.
12. Parienti JJ, Ragland K, Lucht F, et al. Average adherence to boosted protease inhibitor therapy, rather than the pattern of missed doses, as a predictor of HIV RNA replication. *Clin Infect Dis.* 2010;50:1192–1197.
13. Parienti JJ, Das-Douglas M, Massari V, et al. Not all missed doses are the same: sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels. *PLoS One.* 2008;3:e2783.
14. Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. *J Acquir Immune Defic Syndr.* 2013;63:77–85.
15. Ortego C, Huedo-Medina TB, Llorca J, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. *AIDS Behav.* 2011;15: 1381–1396.
16. Gras G, Schneider MP, Cavassini M, et al. Patterns of adherence to raltegravir-based regimens and the risk of virological failure among HIV-infected patients: the RALTECAPS cohort study. *J Acquir Immune Defic Syndr.* 2012;61:265–269.
17. Stevens RC, Blum MR, Rousseau FS, et al. Intracellular pharmacology of emtricitabine and tenofovir. *Clin Infect Dis.* 2004;39:877–878.
18. Parienti JJ, Paterson DL. Number of missed doses: why 1 x 7 doses does not make 7 x 1? *AIDS.* 2012;26:1437–1440.
19. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care.* 2000;12:255–266.
20. Marcellin F, Spire B, Carrieri MP, et al. Assessing adherence to antiretroviral therapy in randomized HIV clinical trials: a review of currently used methods. *Expert Rev Anti Infect Ther.* 2013;11:239–250.
21. Pearson CR, Pantalone DW, Merrill JO, et al. Self-report measures of antiretroviral therapy adherence: a review with recommendations for HIV research and clinical management. *AIDS Behav.* 2006;10:227–245.
22. Simoni JM, Huh D, Wang Y, et al. The validity of self-reported medication adherence as an outcome in clinical trials of adherence-promotion interventions: findings from the MACH14 study. *AIDS Behav.* 2014;18:2285–2290.

23. Genberg BL, Wilson IB, Bangsberg DR, et al. Patterns of adherence to antiretroviral therapy and impact on HIV-RNA among patients from the MACH14 study. *AIDS.* 2012;26:1415–1423.
24. Nance RM, Delaney JA, Golin CE, et al. Co-calibration of two self-reported measures of adherence to antiretroviral therapy. *AIDS Care.* 2017;29:464–468.
25. Heterogeneity among studies in rates of decline of antiretroviral therapy adherence over time: results from the multisite adherence collaboration on HIV 14 study. *J Acquir Immune Defic Syndr.* 2013;64:448–454.
26. Siefried KJ, Mao L, Kerr S, et al; PAART Study Investigators. Socioeconomic factors explain suboptimal adherence to antiretroviral therapy among HIV-infected Australian adults with viral suppression. *PLoS One.* 2017;12:e0174613.
27. Protopopescu C, Raffi F, Roux P, et al; ANRS CO8 APROCO-COPILOTE Study Group. Factors associated with non-adherence to long-term highly active antiretroviral therapy: a 10 year follow-up analysis with correction for the bias induced by missing data. *J Antimicrob Chemother.* 2009;64:599–606.
28. Shubber Z, Mills EJ, Nachega JB, et al. Patient-reported barriers to adherence to antiretroviral therapy: a systematic review and meta-analysis. *PLoS Med.* 2016;13:e1002183.
29. Sheppard DP, Weber E, Casaletto KB, et al; HIV Neurobehavioral Research Program (HNRP) Group. Pill burden influences the association between time-based prospective memory and antiretroviral therapy adherence in younger but not older HIV-infected adults. *J Assoc Nurses AIDS Care.* 2016;27:595–607.