Efficacy of a nucleoside-sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naive HIV-1-infected patients (ACTG A5262)

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Abstract

Objective—To explore darunavir/ritonavir (DRV/r) plus raltegravir (RAL) combination therapy in antiretroviral-naive patients.

Design—Phase IIb, single-arm, open-label, multicenter study.

Methods—One hundred and twelve antiretroviral-naive, HIV-1-infected patients received DRV/r 800/100 mg once daily and RAL 400 mg twice daily. Primary endpoint was virologic failure by week 24. Virologic failure was defined as confirmed viral load of 1000 copies/ml or more at week 12, or an increase of more than $0.5 \log_{10}$ copies/ml in viral load from week 4 to 12, or a confirmed viral load of more than 50 copies/ml at or after week 24. Protease and integrase genes were sequenced in patients experiencing virologic failure.

Results—Virologic failure rate was 16% [95% confidence interval (CI) 10–24] by week 24 and 26% (95% CI 19–36) by week 48 in an intent-to-treat analysis. Viral load at virologic failure was 51–200 copies/ml in 17/28 failures. Adjusting for age and sex, virologic failure was associated

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with baseline viral load of more than 100 000 copies/ml [hazard ratio 3.76, 95% CI (1.52–9.31), *P* =0.004] and lower CD4 cell count [0.77 per 100 cells/µl increase (95% CI 0.61–0.98), *P*=0.037]. When trough RAL concentrations were included as a time-varying covariate in the analysis, virologic failure remained associated with baseline viral load more than 100 000 copies/ml [hazard ratio =4.67 (95% CI 1.93–11.25), *P*<0.001], whereas RAL level below detection limit in plasma at one or more previous visits was associated with increased hazard [hazard ratio =3.42 (95% CI 1.41–8.26), *P*=0.006]. All five participants with integrase mutations during virologic failure had baseline viral load more than 100 000 copies/ml.

Conclusion—DRV/r plus RAL was effective and well tolerated in most patients, but virologic failure and integrase resistance were common, particularly in patients with baseline viral load more than 100 000 copies/ml.

Keywords

antiretroviral therapy; darunavir; nucleoside sparing; raltegravir

Introduction

Reverse transcriptase inhibitor (RTI) sparing antiretroviral regimens are needed given potential toxicities of some nucleos(t)ide RTIs (NRTIs) [1] and the frequency of transmitted NRTI and nonnucleoside RTI (NNRTI) resistance [2]. Two fully active antiretroviral drugs may be sufficient to suppress HIV-1 replication in treatment-naive patients [3]. Darunavir (DRV) is a potent and well tolerated protease inhibitor with no observed resistance during virologic failure when combined with two NRTIs in treatment-naive patients [4]. Raltegravir (RAL), an integrase inhibitor, is potent and well tolerated for initial therapy in combination with two NRTIs, but RAL resistance emerges in approximately one-third of patients with virologic failure [5]. AIDS Clinical Trials Group (ACTG) Study A5262 was designed to explore a two-drug, RTI-sparing regimen of DRV/ritonavir (DRV/r) plus RAL for initial antiretroviral therapy.

Methods

Study participants

A5262 participants were treatment-naive, HIV-1-infected adults (18 years old) with plasma HIV-1 RNA concentration (viral load) at least 5000 copies/ml. Exclusion criteria included active hepatitis B, renal failure requiring dialysis and protocol-specified abnormal laboratory values. Patients with more than one DRV resistance-associated mutation (RAM) (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, I84V, and L89V), L76V alone, or known major integrase RAM (N155H, Q148H/R/K, Y143C/R, and G140S) were also excluded. Ethics review committees at each research site approved the study. Each participant provided a written informed consent.

Study design and interventions

Study participants received open-label DRV 800 mg (two 400 mg tablets) and ritonavir 100 mg (one capsule) daily plus RAL 400 mg (one tablet) twice daily. The site investigator was permitted to construct a new regimen if a patient experienced virologic failure or treatment-limiting adverse effects.

Procedures and assessments

Study participants had screening, preentry, and entry visits (day 0). Subsequent evaluations occurred at weeks 1, 4, 12, 24, 36, 48, and 52. At entry and weeks 4, 12, 24, 36, and 48, viral load, hematology, liver function tests, and blood chemistries were analyzed. Viral load was

also determined at week 1 in all participants and at week 52 in participants with suspected virologic failure at week 48. CD4$^+$ and CD8$^+$ T-cell counts were determined at entry and weeks 12, 24, 36, and 48. Fasting lipid levels were measured at entry and weeks 24 and 48. Adherence was assessed at weeks 1, 4, 12, 24, and 48 by self-report (number of missed doses over a 4-day recall) [6]. Plasma samples for trough concentrations (C_{trough}) of RAL and DRV were stored at each visit that had an adherence assessment. Participants with suspected virologic failure were asked to return for a failure confirmation visit within 7–35 days of collecting the initial failure sample. At the failure confirmation visit, adherence was assessed and samples collected for viral load, protease and integrase genotype, T-cell counts, and C_{trough}.

Viral load was measured centrally using the Abbott RealTime HIV-1 Test on the m2000 system (Abbott RT/m2000 assay) (Abbott Molecular Inc., Des Plaines, Illinois, USA). Population sequencing of the integrase and protease genes was performed during virologic failure. Genotypic mutations according to the 2009 International AIDS Society (IAS) USA [7] plus G140S for integrase were considered. DRV and RAL plasma concentrations were determined using internally and externally validated mass spectrometry (RAL) and ultra-performance liquid chromatography (DRV) methods. All interday and intraday variability was less than 10%; the lower limits of detection for RAL and DRV were 10 and 50 ng/ml, respectively.

An independent Study Monitoring Committee reviewed study conduct, safety and efficacy approximately 24 weeks after enrollment of the 40th participant. To assess the impact of assay variation on viral load determinations, stored plasma samples from the first 10 patients with low-level viremia (viral load 51–200 copies/ml) during virologic failure were retested posthoc using the Roche Amplicor HIV-1 Monitor Test, version 1.5 (Roche Diagnostic Systems, Branchburg, New Jersey, USA).

Outcome measures

The primary endpoint was virologic failure prior to or at week 24. Virologic failure was defined as confirmed viral load 1000 copies/ml or more at week 12, or an increase of more than 0.5 $\log_{10}$ copies/ml in viral load from week 4 to 12 (including rebound to >50 copies/ml from week 4 to 12 for patients with week 4 value 50 copies/ml), or confirmed viral load more than 50 copies/ml at or after week 24. Secondary outcome measures included virologic failure through week 48, viral load less than 50 or less than 200 copies/ml at weeks 24 and 48, incidence of adverse events that was at least grade 3 (severe) or any grade if it led to permanent drug discontinuation, changes in fasting lipid concentrations, protease or integrase inhibitor resistance during virologic failure, adherence to study treatment, C_{trough} of RAL and DRV, and changes in CD4$^+$ T-cell counts (CD4 cell count).

Statistical analysis

For the primary analysis, the cumulative proportion of participants experiencing virologic failure at or before week 24 and corresponding two-sided 95% confidence interval (CI) were estimated using the Kaplan–Meier method and Greenwood's formula [8]. The primary efficacy analysis used the intent-to-treat (ITT) approach, including all treated patients regardless of study treatment modification and censoring follow-up if a participant was lost to follow-up or died without previously meeting the definition of virologic failure. Enrolled participants who never started the study treatment were excluded. Log-rank test and Cox proportional hazards regression were used to assess predictors of virologic failure.

Acceptable virologic failure rate was estimated using week 24 virologic failure rates observed in large phase III trials of current preferred regimens: efavirenz plus two-NRTI

arm of ACTG A5142 (22%) [3]; efavirenz plus two-NRTI arm of ACTG A5095 (17%) [9]; and tenofovir/emtricitabine (TDF/FTC) plus RAL (10–15%) [10]. It was prespecified that RAL plus DRV/r would be considered satisfactory if the upper bound of the CI for cumulative virologic failure at week 24 was less than 35%. With a sample size of 100 evaluable participants, the study was estimated to have 91% probability that the upper bound of the two-sided 95% CI for the virologic failure rate would be less than 35% if the underlying true failure rate was 20%. The planned sample size was increased by 10% to 111 participants to account for loss to follow-up.

Proportions of participants with viral load less than 200 and less than 50 copies/ml at weeks 24 and 48 were estimated using ITT (missing/off study without virologic failure ignored) and modified ITT (missing/off treatment considered failure) approaches.

Adherence was classified as perfect (zero reported missed doses) or imperfect (any missed doses of DRV/r or RAL, failure to answer the 4-day recall question, or missed the study visit). Pharmacokinetic analyses included geometric mean of trough concentrations [$C_{trough(avg)}$] obtained within a defined window (within 9–15 and 20–28 h after the last dose for RAL and DRV, respectively). Only C_{trough} up to and including the time of virologic failure confirmation visit was included for participants with virologic failure. C_{trough} below the assay detection limits was replaced with half of the corresponding lower limit of quantification. Sensitivity analysis examined $C_{trough(avg)}$ using all available C_{trough} values. Adverse events were graded according to the severity scale of the Division of AIDS, National Institutes of Health [11]. Safety analyses used as-treated approach, including all patients who initiated study treatment and censoring follow-up at treatment discontinuation.

Baseline viral load level and CD4 cell count were calculated as the geometric and arithmetic means, respectively, of preentry and entry evaluations. Changes in continuous measures from baseline were assessed by Wilcoxon signed rank test. Comparisons between participants with and without virologic failure used Wilcoxon rank sum test for continuous measures, Fisher's exact test for binary measures and Cochran–Armitage test for ordered categorical measures.

All *P* values and CIs presented were two-sided and nominal, unadjusted for interim analysis and multiple comparisons. Analyses were done using SAS, version 9.2 (SAS Institute, Cary, North Carolina, USA), StatXact 8 PROCs (Cytel, Cambridge, Massachusetts, USA), and Splus, version 6 (Insightful, Seattle, Washington, USA).

Results

Study participants

A total of 113 patients were enrolled at 22 sites in the USA. One participant did not initiate study drugs and was taken off study. Of 112 participants who initiated DRV/r plus RAL with a median age of 36 years, 88% were men and 44% were white non-Hispanic. Median CD4 cell count and viral load were 271 cells/μl and 4.87 $\log_{10}$ copies/ml, respectively (Table 1). Forty-nine (44%) participants had baseline viral load more than 100 000 copies/ml including six (5%) with levels higher than 750 000 copies/ml. Pretreatment antiretroviral drug resistance was detected in 21 (19%) participants: nine with (8%) NNRTI, eight (7%) with NRTI, two (2%) with protease inhibitor, one (1%) with NRTI plus NNRTI, and one (1%) with NRTI plus NNRTI and protease inhibitor mutations. No participant had a DRV RAM. Ninety-seven (87%) participants completed 52 weeks follow-up. Fifteen (13%) participants discontinued participation due to inability to get to clinic (seven), inability of study staff to reach participant (four), withdrawal of consent (two), unwillingness to adhere to study requirements (one), and death (one).

Efficacy

Seventeen participants (16%, 95% CI 10–24) experienced virologic failure by week 24: 11 failed to suppress viral load (one with >1000 copies/ml at week 12; 10 with > 50 copies/ml at week 24) and six due to viral rebound. Eleven participants experienced virologic failure (due to viral load rebound to > 50 copies/ml) after week 24. Thus, virologic failure occurred in 28 participants by week 48 (Table 2); virologic failure rate by week 48 was 26% (95% CI 19–36). Three participants with virologic failure subsequently attained viral load less than 50 copies/ml without changing therapy. In ITT analysis, viral load was less than 50 copies/ml in 79% (95% CI 70–86) of participants at week 24 and in 71% (95% CI 61–79) at week 48; using modified ITT analysis, viral load was less than 50 copies/ml in 74% (95% CI 66–82) of participants at week 24 and in 61% (95% CI 52–70) at week 48 (Fig. 1). Viral load less than 200 copies/ml was achieved in 93% (95% CI 87–97) at week 24 and 86% (95% CI 78–92) at week 48 in ITT analysis and in 88% (95% CI 81–94) and 73% (95% CI 65–81) at week 24 and 48 in the modified ITT analysis.

Participants with virologic failure had higher baseline viral load (median 5.22 vs. 4.70 $\log_{10}$ copies/ml, P=0.002) and lower baseline CD4 cell count (192 vs. 322 cells/μl, P=0.007) compared with those who did not experience virologic failure (Table 1). Of the 28 participants with virologic failure, 21 had baseline viral load more than 100 000 copies/ml and these patients had more rapid time to virologic failure (P<0.001) (Fig. 2). Multivariable model for time to virologic failure, adjusting for age and sex, demonstrated that virologic failure was associated with baseline viral load more than 100 000 copies/ml (hazard ratio =3.76, 95% CI 1.52–9.31, P=0.004) and lower CD4 cell count (hazard ratio =0.77, 95% CI 0.61–0.98 per 100 cells/μl increase, P=0.037). Seventeen (15%) participants were classified as having imperfect adherence. No association was detected between virologic failure and adherence, age, sex, intravenous drug use, race/ethnicity, or presence of any mutation at baseline (all P>0.10).

Seventeen participants with virologic failure (61%) had viral load of 51–200 copies/ml at the first viral load determination during virologic failure, four (14%) had 201–1000 copies/ml and seven (25%) had more than 1000 copies/ml. Viral load levels in the first 10 patients with low-level viremia during virologic failure were similar when determined using the Roche HIV Monitor v1.5 and Abbott RT/m2000 assays. Baseline CD4 cell count, viral load, resistance, adherence, and detection of mutations at the time of virologic failure were not significantly different between participants who failed with viral load higher than 200 vs. 51–200 copies/ml (all P 0.40). Participants with virologic failure as a result of failure to suppress viremia vs. viral rebounders were similar with respect to baseline characteristics (age, sex, race/ethnicity, intravenous drug use, CD4 cell count, and viral load) and RAL and DRV trough concentrations/detectability, adherence (all P>0.10).

HIV-1 drug resistance

Integrase resistance testing was successful in 25 of the 28 virologic failures. All five participants with evidence of integrase RAMs [N155H (one), N155H/N (two), Q148Q/R, and N155H/N (one), Q148K/Q and N155H/N (one)] had baseline viral load more than 100 000 copies/ml. None of these patients had documented treatment interruption. No new protease inhibitor RAMs were detected in the 23 participants with successful protease sequencing following virologic failure.

Pharmacokinetics

Considering the defined trough period, median (quartile 1–quartile 3) $C_{\text{trough(avg)}}$ was 1218 (789–1809) ng/ml for DRV and 117 (52–250) ng/ml for RAL (Supplementary Table 1, http://links.lww.com/QAD/A177). DRV and RAL $C_{\text{trough(avg)}}$ values within the defined

trough period were not significantly different for patients with and without virologic failure, perfect vs. imperfect adherence, viral load more than 200 vs. 51–200 copies/ml at the time of virologic failure, and presence or absence of resistance mutations at virologic failure (all $P>0.10$). Similar results were obtained in sensitivity analyses that included all available DRV and RAL C_{trough} except for DRV $C_{trough(avg)}$, which was lower in those with virologic failure (1042 vs. 1649 ng/ml, $P=0.017$). For RAL, at least one C_{trough} below detection limits (BDLs) occurred in 10/27 (37%) participants with virologic failure compared with seven of 76 (9%) nonvirologic failure participants ($P=0.002$); for DRV, five of 21 (24%) virologic failure participants had BDL levels compared to two of 62 (3%) nonvirologic failure participants ($P=0.01$) (Table 3). When adjusted for DRV or RAL C_{trough} [either continuous or categorical variable (BDL or not)] as a time-varying covariate with one-study-visit lag (at the visit immediately before or at all previous visits) in Cox PH models, baseline viral load more than 100 000 copies/ml remained significantly associated with hazard of virologic failure ($P<0.05$). More specifically, when RAL C_{trough} was evaluated as a categorical variable, having RAL C_{trough} BDL within the defined trough period at the visit immediately before was associated with increased hazard of virologic failure (hazard ratio =5.25, 95% CI 1.41–19.58, $P=0.014$] and the hazard ratio was 5.05 (95% CI 1.64–15.56) ($P=0.005$) for baseline viral load; the hazard ratio for having RAL C_{trough} BDL at one or more previous visits was 3.42 (95% CI 1.41–8.26) ($P=0.006$) and 4.67 (95% CI 1.93–11.25) ($P<0.001$) for baseline viral load. Marginally significant association was found between virologic failure and a DRV C_{trough} BDL within the defined trough window at the visit immediately before (hazard ratio =4.28, 95% CI 0.92–20.04, $P=0.065$; baseline viral load hazard ratio =3.75, 95% CI 1.13–12.41, $P=0.030$). The association became significant when all DRV C_{trough} were included (hazard ratio = 3.89, 95% CI 1.32–11.49, $P=0.014$; baseline viral load hazard ratio =4.34, 95% CI 1.73–10.86, $P=0.002$).

Immunological outcomes

The median CD4 cell count increase from baseline was 142 (80–196) cells/μl at week 24 and 200 (114–318) cells/μl at week 48 (all $P<0.001$) and were similar at week 24 in patients with baseline viral load less than or equal to or more than 100 000 copies/ml ($P>0.1$). At week 48, the median increase was 233 cells/μl in patients with baseline viral load higher than 100 000 copies/ml vs. 180 cells/μl in those with viral load 100 000 copies/ml or less ($P=0.044$).

Safety and tolerability

Twenty-one participants (19%) reported at least one grade 3 (severe) or higher clinical or laboratory adverse events, five of which were classified as possibly related to study treatment: dyslipidemia (three), diabetes mellitus (one), and elevated aspartate transaminase/alanine transaminase (one). No events were considered probably or definitely related to study treatment. One participant permanently discontinued study treatment due to grade 2 (moderate) maculopapular rash and abdominal pain. Death occurred in one patient at week 9 from cryptosporidiosis.

Median increases in fasting high-density lipoprotein (HDL), low-density lipoprotein, total cholesterol, and triglycerides from baseline to week 48 were 9, 17, 30, and 23 mg/dl, respectively ($P<0.001$, except triglycerides $P=0.006$). Fasting total cholesterol: HDL ratio did not change significantly from baseline (0.40 at weeks 24 and 48).

Discussion

In HIV-1-infected treatment-naive participants enrolled in A5262, an RTI-free, two-drug regimen comprising DRV/r plus RAL met the protocol definition of acceptable virologic

efficacy (at week 24), but only 71 and 61% of participants had viral load less than 50 copies/ml (86 and 73% <200 copies/ml) at week 48 in ITT and modified ITT analyses, respectively. Baseline viral load more than 100 000 copies/ml was associated with an increased risk of virologic failure. Baseline CD4 cell count per 100-cell increase was associated with reduced risk of virologic failure. In multivariable models fitted with DRV or RAL C_{trough} BDL, baseline viral load more than 100 000 copies/ml remained strongly associated with increased risk of virologic failure. Having RAL C_{trough} BDL at the visit immediately before or at one or more previous visits was also associated with an increased hazard of failure.

Potential explanations for our findings were explored. Self-reported adherence (4-day recall) was not significantly different between those with and without virologic failure, or between those with baseline viral load less than or equal to or more than 100 000 copies/ml. However, having one or more DRV and RAL plasma concentrations below detection limits was significantly more common in those with virologic failure, possibly related to unreported suboptimal adherence. Other investigators have demonstrated discordance between self-reported adherence and objectively measured adherence [12]. Adverse effects of therapy are unlikely to have been the major determinant of adherence or virologic efficacy as RAL and DRV were well tolerated. An alternative hypothesis is that asymmetrical dosing of DRV/r (once daily) and RAL (twice daily) predisposed to suboptimal adherence and virologic failure, but such association has not emerged as a concern with RAL twice daily plus TDF/FTC, a similarly asymmetrically dosed regimen [13]. It was suggested recently that RAL–DRV interactions may lower plasma concentrations of DRV [14], but DRV C_{trough} observed in this study (Supplementary Table 1, http://links.lww.com/QAD/A177) are within the range reported in an intensive pharmacokinetic study of DRV 800/100 mg daily [15]. Finally, because over half of the patients who experienced virologic failure had low-level viremia (51–200 copies/ml) at the time of failure, we considered virologic failure artifacts due to assay variability [16]. This possibility was excluded because viral load determinations during low-level viremia were similar with the Abbott m2000 and the Roche Amplicor Ultrasensitive Assays in the first 10 participants with low-level virologic failure.

An association between efficacy and baseline viral load has been demonstrated with other antiretroviral regimens. In some but not all studies of two NRTIs plus a third preferred agent, smaller proportions of patients with baseline viral load more than 100 000 copies/ml achieved HIV RNA less than 50 copies/ml at 48 weeks [5,13,17–21], but these differences tend to be small, are in part related to tolerability and associated with low CD4 cell count [16], and may not be synonymous with subsequent virologic failure [22]. In our RTI-sparing study in which we specifically examined virologic failure, as opposed to a combined endpoint, the differences in virologic outcomes between the high and low viral load strata were striking and the results were consistent or even more evident in multivariable analyses that included baseline CD4 cell count or assessments of drug concentrations. A pilot study evaluating twice-daily atazanavir (ATV) plus RAL was prematurely terminated at week 24 due in part to adverse events and frequent RAL resistance in those with virologic failure [23]. A larger randomized study, however, found no significant difference in viral load less than 40 copies/ml at week 48 in patients treated with RAL plus lopinavir/ritonavir (LPV/r) compared with TDF/FTC plus LPV/r [24]. The mean baseline viral load in the latter study was 4.25 $\log_{10}$ copies/ml, which is lower than the 4.9 $\log_{10}$ copies/ml in the twice-daily RAL plus ATV study and 4.83 $\log_{10}$ copies/ml in our study. Our study is also the first to report virologic outcomes by baseline viral load less than or equal to or more than 100 000 copies/ml separately from nonvirologic treatment discontinuations, further limiting cross-study comparisons. The mechanisms underlying the poorer virologic outcomes in some patients with high baseline viral load, as observed in this study, are uncertain. One possibility is that high baseline viral load may be associated with more extensive reservoir

of infected cells and prolonged viral decay time to levels below 50 copies/ml. However, only one of the 28 virologic failures in the current study had viral dynamics that may be explained solely by this specific hypothesis. Another possibility is that high baseline viral load may predispose to greater diversity of HIV-1 quasispecies and an increased opportunity to select drug-resistant mutants. Q148R minority variants were detected at very low levels (median 0.46%) in 86% of treatment-naive patients in one study [25]. The effect of pretherapy RAL-resistant minority variants on virologic outcome in treatment-experienced patients has not been clearly demonstrated [25,26] and to our knowledge has not yet been reported in treatment-naive patients.

Baseline viral load more than 100 000 copies/ml appears to increase the risk of RAL resistance in patients receiving DRV/r plus RAL. All the patients with evidence of RAL resistance mutations at virologic failure (20% of those genotyped) had baseline viral load more than 100 000 copies/ml. None of these patients had documented treatment interruption, and no significant difference in RAL C_{trough} was observed between those with or without RAL resistance. Viral load at the time of integrase genotyping in the five participants ranged from 62 to 685 copies/ml. Notably, a participant who achieved HIV RNA less than 50 copies/ml at week 12 and had no subsequent documentation of viral load level more than 100 copies/ml experienced virologic failure at week 48 with detection of Q148K/Q and N155H/N. Thus, like NNRTI and NRTI resistance mutations [27], RAL resistance mutations may be present during low-level viremia [28], an important observation as recent guidelines state that viral load more than 200 copies/ml can be considered the threshold for virologic failure in clinical practice [1]. Protease inhibitor resistance was not detected in any participant experiencing virologic failure, consistent with evidence that boosted protease inhibitor resistance seldom develops early in virologic failure [29].

Interpretation of this study should take into account its single-arm design as a randomized trial could have reduced the potential impact of patient characteristics and other variables. Also, patients were not screened for pretreatment RAL resistance, but primary mutations that confer resistance to RAL are uncommon in RAL-naive patients [30]. Despite these limitations, the results of A5262 raise important issues that should be examined carefully in future clinical trials evaluating DRV/r plus RAL and perhaps in all RTI-sparing two-drug regimen trials. We urge caution in patients with baseline viral load more than 100 000 copies/ml and emphasize a need to further elucidate the implications of low-level viremia in patients receiving the regimen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix

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Fig. 1.
Proportion of participants with HIV-1 RNA level less than 50 and less than 200 copies/ml.

(a) Overall

(b) By baseline HIV-1 RNA

Logrank test: $P = 0.0002$

HIV-1 RNA ≤ 100000 copies/ml
HIV-1 RNA > 100000 copies/ml

Week

Week

n withVF: 0 0 3 14 5 6
n at risk: 112 111 110 105 89 81

HIV-1 RNA ≤ 100000 copies/ml
n withVF: 0 0 1 4 1 1
n at risk: 68 63 62 59 54 50
HIV-1 RNA > 100000 copies/ml
n withVF: 0 0 2 10 4 5
n at risk: 49 48 48 46 35 31

Fig. 2.
Kaplan–Meier plots of time to virologic failure (VF) using intent-to-treat approach.

Table 1

Baseline characteristics of participants who initiated darunavir/r plus raltegravir ($n = 112$) by virologic failure status.

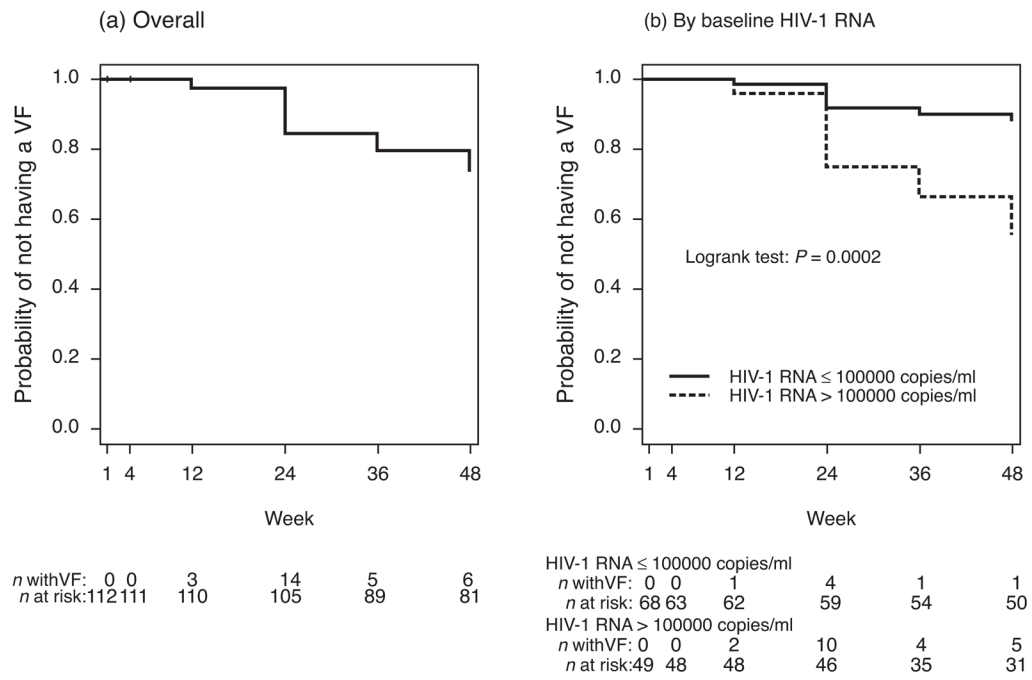| Characteristic	Total	With VF	Without VF	P
		VF status		
Age (in years)				
N	112	28	84	0.835[*]
Mean (SD)	37 (11)	37 (13)	37 (11)	
Median (Q1–Q3)	36 (27–45)	35 (26–44)	36 (28–45)	
18–29	33 (29%)	9 (32%)	24 (29%)	0.760[***]
30–39	38 (34%)	7 (25%)	31 (37%)	
40–49	25 (22%)	7 (25%)	18 (21%)	
50–59	12 (11%)	4 (14%)	8 (10%)	
60	4 (4%)	1 (4%)	3 (4%)	
Sex				
Male	98 (88%)	25 (89%)	73 (87%)	1.000[**]
Female	14 (13%)	3 (11%)	11 (13%)	
Race/ethnicity				
White non-Hispanic	49 (44%)	10 (36%)	39 (46%)	0.618[**]
Black non-Hispanic	45 (40%)	14 (50%)	31 (37%)	
Hispanic (regardless of race)	16 (14%)	4 (14%)	12 (14%)	
Asian, Pacific Islander	2 (2%)	0 (0%)	2 (2%)	
IV drug history				
Never	102 (91%)	26 (93%)	76 (90%)	0.194[**]
Currently	1 (1%)	1 (4%)	0 (0%)	
Previously	9 (8%)	1 (4%)	8 (10%)	
Baseline CD4 (cells/µl)				
Mean (SD)	284 (199)	199 (167)	312 (202)	0.007[*]
Median (Q1–Q3)	271 (107–419)	192 (51–310)	322 (147–442)	
<200	40 (36%)	15 (54%)	25 (30%)	0.018[***]
200 to <350	32 (29%)	8 (29%)	24 (29%)	
350 to <500	26 (23%)	3 (11%)	23 (27%)	
500	14 (13%)	2 (7%)	12 (14%)	
Baseline HIV-1 RNA ($\log_{10}$ copies/ml)				
Mean (SD)	4.83 (0.60)	5.14 (0.61)	4.73 (0.57)	0.002[*]
Median (Q1–Q3)	4.87 (4.33–5.31)	5.22 (4.85–5.60)	4.70 (4.31–5.16)	
Baseline HIV-1 RNA (copies/ml)				
5000	3 (3%)	1 (4%)	2 (2%)	0.006[***]
5001 to 10 000	5 (4%)	1 (4%)	4 (5%)	
10 001 to 100 000	55 (49%)	5 (18%)	50 (60%)	
100 001 to 750 000	43 (38%)	18 (64%)	25 (30%)	

Characteristic	Total	VF status		P
		With VF	**Without VF**	
>750 000	6 (5%)	3 (11%)	3 (4%)	

IV, intravenous; VF, virologic failure.

*
Exact Wilcoxon test.

**
Fisher's exact test.

***
Cochran–Armitage Test.

Table 2

Description of participants who experienced virologic failure on darunavir/ritonavir plus raltegravir.

Initial VF HIV-1 RNA	ID number	Age	Sex	Baseline HIV-1 RNA (copies/ml)	Baseline CD4 cell count (cells/μl)	Baseline mutation(s)	Week of initial VF	Initial VF HIV-1 RNA (copies/ml)	Confirmed HIV-1 RNA (copies/ml)	Integrase mutation(s) detected at or after VF
200 copies/ml	1	52	Male	230 627	28		12	173	259	Q148Q/R, N155H/N
	2	25	Male	28 879	262		23	161	142	Amplification failure
	3	48	Male	194 888	47		23	160	258	WT
	4	42	Male	50 309	327	D67G, K219Q, T69ins	24	81	88	WT
	5	27	Male	514 062	208	K103N	24	93	101	WT
	6	32	Male	19 115	240		24	79	26 849	WT
	7	58	Male	17 593	455		24	53	71	WT
	8	43	Male	419 417	202		24	190	158	WT
	9	57	Male	147 076	113	M41L	24	59	89	N155H/N
	10	26	Male	143 422	74		24	108	73	WT
	11	21	Male	215 391	334		35	189	830	WT
	12	31	Male	378 540	185		36	53	88	Amplification failure
	13	40	Male	100 866	280		36	157	250	WT
	14	42	Male	140 031	36		48	134	1 664	WT
	15	38	Male	184 212	86		49	62	89	Q148K/Q, N155H/N
	16	23	Male	137 659	415		50	65		WT
	17	63	Female	851 765	198		50	66	89	Amplification failure
>200 copies/ml	18	25	Female	313 848	60		13	80 073	72 137	WT
	19	32	Male	4682	564		13	3 141		WT
	20	44	Female	825 792	98		22	584 879	2 147	WT
	21	59	Male	911 043	46		24	3 893	685	N155H
	22	35	Male	630 065	9		24	243	113	WT
	23	34	Male	246 270	18		24	231	188	N155H/N
	24	34	Male	429 729	20	T69D, K103N	24	465	411	WT
	25	44	Male	133 415	55		36	178 867	3 485	WT
	26	19	Male	8576	575		36	8 466	73	WT
	27	24	Male	124 901	355		43	649		WT

Initial VF HIV-1 RNA	ID number	Age	Sex	Baseline HIV-1 RNA (copies/ml)	Baseline CD4 cell count (cells/µl)	Baseline mutation(s)	Week of initial VF	Initial VF HIV-1 RNA (copies/ml)	Confirmed HIV-1 RNA (copies/ml)	Integrase mutation(s) detected at or after VF
	28	21	Male	29 677	293		46	1 364		WT

VF, virologic failure; WT, wild type.

Table 3

Trough concentration (categorical) by virologic failure status.[a]

Drug	VF status		Total	P[b]
	With VF	**Without VF**	**Total**	
RAL (within true trough time)				
All above detection	17 (63%)	69 (91%)	86 (83%)	0.002
With 1 concentration BDL	10 (37%)	7 (9%)	17 (17%)	
Missing	1	8	9	
RAL (all available)				
All above detection	15 (54%)	70 (83%)	85 (76%)	0.004
With 1 concentration BDL	13 (46%)	14 (17%)	27 (24%)	
DRV (within true trough time)				
All above detection	16 (76%)	60 (97%)	76 (92%)	0.010
With 1 concentration BDL	5 (24%)	2 (3%)	7 (8%)	
Missing	7	22	29	
DRV (all available)				
All above detection	19 (68%)	77 (92%)	96 (86%)	0.004
With 1 concentration BDL	9 (32%)	7 (8%)	16 (14%)	

BDL, below detection limit; DRV, darunavir; RAL, raltegravir; VF, virologic failure.

[b]Fisher's exact test.

[a]For VF patients, only those concentrations on or before VF confirmation were considered.