Time to HIV-1 RNA Suppression Below 5 copies/ml During First-Line Protease Inhibitor-Based Antiretroviral Treatment – Any Impact of Residual Viremia on Treatment Success?

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Abstract

When antiretroviral treatment suppresses HIV RNA levels to below 50 copies/ml, traces of viremia may still be detected with more sensitive assays. In the ARTEMIS trial, 689 antiretroviral treatment-naive patients were randomized to tenofovir/emtricitabine plus either darunavir/ritonavir (n = 343) or lopinavir/ritonavir (n = 346). HIV-1 RNA was evaluated using the Roche Amplicor® Ultrasensitive assay: plasma samples with HIV RNA < 50 copies/ml were classified as either "No HIV RNA detected" (< 5 HIV RNA copies/ml, optical density = background) or HIV RNA detected (5-50 copies/ml).
The percentage of patients in each arm with HIV RNA < 5 copies/ml rose progressively from week 2 to week 192. For patients with baseline HIV RNA ≥ 100,000, the percentage with HIV RNA < 5 copies/ml at week 192 was 66% for darunavir/ritonavir and 63% for lopinavir/ritonavir. For patients with baseline HIV RNA < 100,000 copies/ml, the percentage with HIV RNA < 5 copies/ml at week 192 was 79% for darunavir/ritonavir versus 77% for lopinavir/ritonavir. Of the patients on darunavir/ritonavir with HIV RNA < 50 copies/ml, 63% had levels < 5 copies/ml at week 48, versus 80% at week 192. In summary, HIV-1 RNA suppression to < 5 copies/ml is dependent on baseline HIV RNA levels. The HIV RNA levels can remain under quantification limits but still detectable after 2-4 years of antiretroviral treatment. **(AIDS Rev. 2013;15:230-6)**

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Key words

HIV RNA. Protease inhibitor. Darunavir. Lopinavir. Ritonavir. Antiretroviral therapy. Low level viremia.

Introduction

The main measure of successful antiretroviral treatment is HIV RNA suppression below the limits of quantification of polymerase chain reaction (PCR) assays – this is typically < 50 copies/ml, but can vary between assays[1-3]. Below these limits of assay quantification, it is still possible to detect traces of HIV RNA in some patients during long-term antiretroviral treatment using standard PCR assays. These traces of low-level viremia are not normally reported by laboratories to patients or clinicians during routine practice.

More sensitive HIV RNA PCR assays have also been used to measure low-level viremia. In one study of seven years of treatment with stavudine, lamivudine, and lopinavir/ritonavir, 77% of patient samples had detectable HIV RNA levels (> 1 copy/ml) between weeks 60 and 384 of treatment, and all patients had at least one detectable result during this time[4]. In a related analysis, the plasma HIV RNA was found to reach a low but stable level (set point) during long-term treatment, which was correlated with pretherapy HIV RNA levels[5]. Persistent viremia on antiretroviral therapy may be derived from long-lived cells that were infected prior to initiation of therapy[5]. However, phylogenetic analysis of sequential samples shows no evidence for evolution of plasma HIV RNA or PBMC HIV-1 DNA during long-term suppressive antiretroviral therapy[6].

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Table 1. Baseline characteristics and summary efficacy data at week 192

Treatment arm	DRV/r (n = 343)	LPV/r (n = 346)
Baseline demographics		
– Female, n (%)	104 (30.3%)	105 (30.3%)
– Caucasian, n (%)	137 (40.1%)	153 (44.5%)
– Mean age, years (SD)	35.5 (9.2)	35.3 (9.2)
Disease characteristics		
– Mean baseline $\log_{10}$ HIV RNA copies/ml (SD)	4.86 (0.64)	4.84 (0.60)
– Median CD4 cell count, cells/ul (range)	228 (4-750)	218 (2-714)
– HBV or HCV coinfection	43 (12.5%)	48 (13.9%)
Stratification factors, n (%)		
– HIV RNA ≥ 100,000 copies/ml	117 (34.1%)	120 (34.7%)
– CD4 count < 200 cells/ul	114 (41.1%)	148 (42.8%)
HIV RNA <50 copies/ml (ITT TLOVR) at week 192, n/N (%)		
– All patients	236/343 (68.8%)	198/346 (57.2%)
– Baseline HIV RNA < 100,000 copies/ml	157/226 (69.5%)	136/226 (60.2%)
– Baseline HIV RNA ≥ 100,000 copies/ml	79/117 (67.5%)	62/120 (51.7%)

DRV/r: darunavir/ritonavir; LPV/r: lopinavir/ritonavir: SD: standard deviation; ITT: intent to treat; TLOVR: time to loss of virological response; HBV: hepatitis B virus; HCV: hepatitis C virus.

Recent studies have suggested that patients may have higher rates of virological failure if their HIV RNA levels during treatment are below limits of quantification of standard PCR assays but still detectable, compared with patients who have no traces of HIV RNA detectable during antiretroviral treatment[7-11]. However, not all studies have reached the same conclusion[12,13]. Two randomized trials of patients with low-level viremia on standard triple combination antiretroviral treatment showed that intensification with the integrase inhibitor raltegravir did not reduce the HIV RNA levels further[14,15].

In the ARTEMIS trial, 689 antiretroviral treatment-naive patients were randomized to tenofovir/emtricitabine plus either darunavir/ritonavir (DRV/r) or lopinavir/ritonavir (LPV/r)[16,17]. HIV RNA was evaluated using the Roche Amplicor® Ultrasensitive assay and the trial was continued for four years (192 weeks). The aim of this analysis was to assess the dynamics of HIV RNA suppression to below the quantification limit of the assay (< 50 copies/ml) and then below the detection limit (< 5 copies/ml). In addition, we aimed to assess whether the dynamics of HIV RNA suppression depended on the treatment received and/or baseline HIV RNA levels.

HIV RNA measurement in the ARTEMIS trial

The design and methods of the ARTEMIS trial have been described elsewhere[16,17]. Briefly, in this randomized, open-label trial, 689 antiretroviral treatment-naive patients were randomized 1:1 to receive tenofovir/emtricitabine plus either DRV/r 800/100 mg once daily or LPV/r at a total daily dose of 800/200 mg (either once daily or twice daily). The randomization was stratified by baseline HIV RNA (< or ≥ 100,000 copies/ml) and CD4 cell count (< or ≥ 200 cells/ul). The primary efficacy analysis was conducted at week 48, but the trial was continued to week 192. There were patient visits at baseline, weeks 2, 4, 8, 12, 16, and 24, and then every 12 weeks to week 192.

During the trial, HIV RNA tests were performed at a central laboratory using the Roche Amplicor® Ultrasensitive method[1]. For samples with HIV RNA below the quantification limit of 50 copies/ml, the Roche Amplicor® assay produces two different results. Either traces of HIV RNA can be detected, which are below the 50 copy limit, or no HIV RNA is detected (the optical density from the sample is the same as from the negative control).

For visits from baseline to week 192, HIV RNA test results for each patient were classified as either > 400 copies/ml, 50-399 copies/ml, "HIV RNA detected" (5-49 copies/ml), or "no HIV RNA detected" (< 5 HIV RNA copies/ml, optical density = background). HIV RNA suppression rates were compared between the treatment arms using different cut-off levels of HIV RNA suppression.

The percentage of patients with HIV RNA at these levels was analyzed over time by treatment arm and by

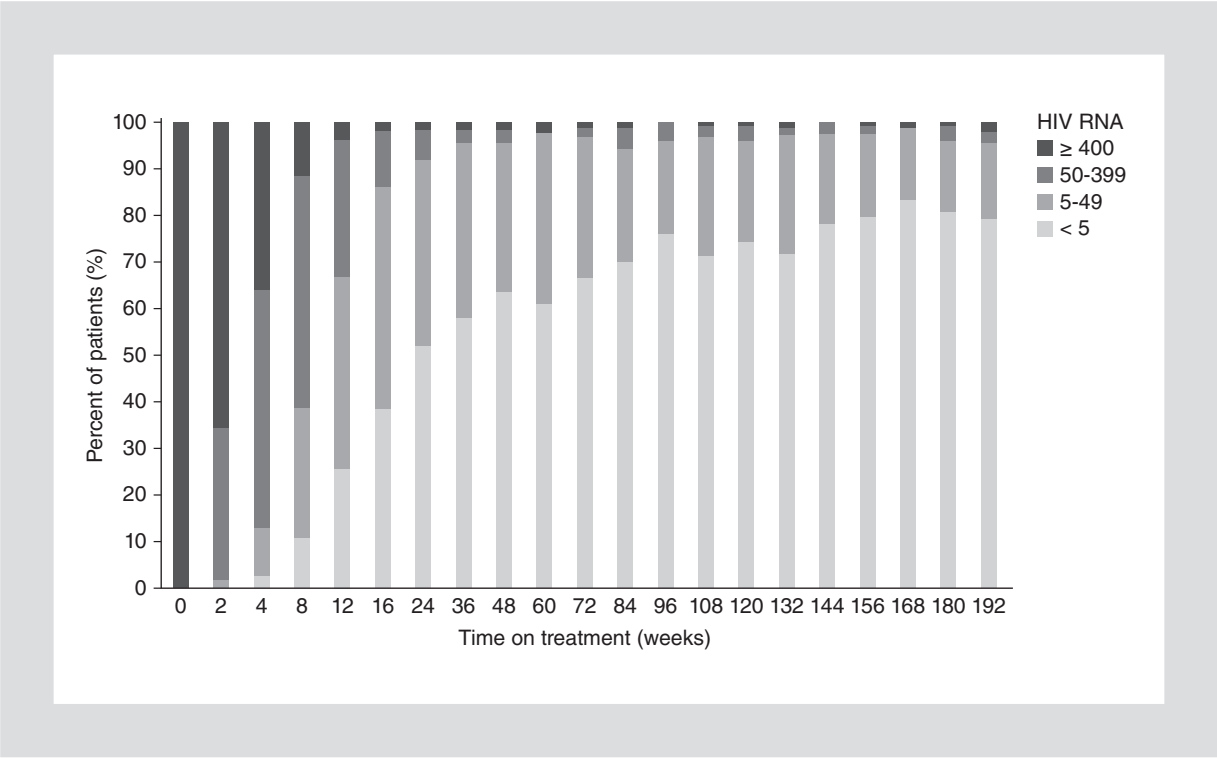

Figure 1. *HIV RNA versus time on darunavir/ritonavir plus tenofovir/emtricitabine. Baseline HIV RNA < 100,000 copies/ml.*

baseline HIV RNA level, according to the original stratification (< vs. ≥ 100,000 copies/ml). The HIV RNA levels at week 96 were compared with week 192 to assess durability of responses at different HIV RNA levels. In addition, the HIV RNA levels at week 180 were compared with week 192 to assess longitudinal variability.

We used the Intent to Treat (ITT) Observed Failure analysis for the main treatment comparisons. This analysis excluded patients who discontinued from the trial for adverse events or other reasons, with HIV RNA levels < 50 copies/ml. We repeated the tests for the full ITT population, including all discontinuations as a sensitivity analysis. Chi-square tests were used to analyze differences in HIV RNA suppression rates between subgroups.

Baseline characteristics

Baseline characteristics and summary efficacy results at week 192 are shown in table 1. The median baseline HIV RNA was 4.86 $\log_{10}$ copies/ml in the DRV/r arm and 4.84 $\log_{10}$ copies/ml in the LPV/r arm. Overall, 34.4% of patients had HIV RNA ≥ 100,000 copies/ml at baseline. At week 192, the percentage of patients with HIV RNA < 50 copies/ml (ITT TLOVR analysis) was 68.8% in the DRV/r arm and 57.2% in the LPV/r arm (p = 0.002 for superiority). This difference in efficacy between the treatment arms was consistent in sensitivity analyses, excluding protocol violators or early discontinuations[17].

Changes in HIV RNA over time

Figures 1 to 4 show the percentage of patients with HIV RNA in the categories of < 5, 5-49, 50-399, and at or above 400 copies/ml for all patient visits from baseline to week 192. The results are shown for the two treatment arms and for the strata of baseline HIV RNA < 100,000 and ≥ 100,000 copies/ml. Table 2 shows summary data at weeks 48 and 192. During the trial, there was a progressive reduction in HIV RNA through the categories of 50-400, 5-50, and then < 5 copies/ml. The percentage of patients with HIV RNA < 5 copies/ml rose from baseline to week 96, and then showed a plateau until week 192. In the first eight weeks of treatment, the majority of patients with HIV RNA < 50 copies/ml still had traces of HIV RNA detectable. However, by week 192 most patients with HIV RNA <50 copies/ml had no traces of HIV RNA detected (Figs. 1 to 4).

In both treatment arms, patients with baseline HIV RNA < 100,000 copies/ml were more likely to have HIV RNA < 5 copies/ml at week 48 and week 192 (Table 2). For example, in the LPV/r arm, the percentage of patients with HIV RNA < 5 copies/ml at week 48

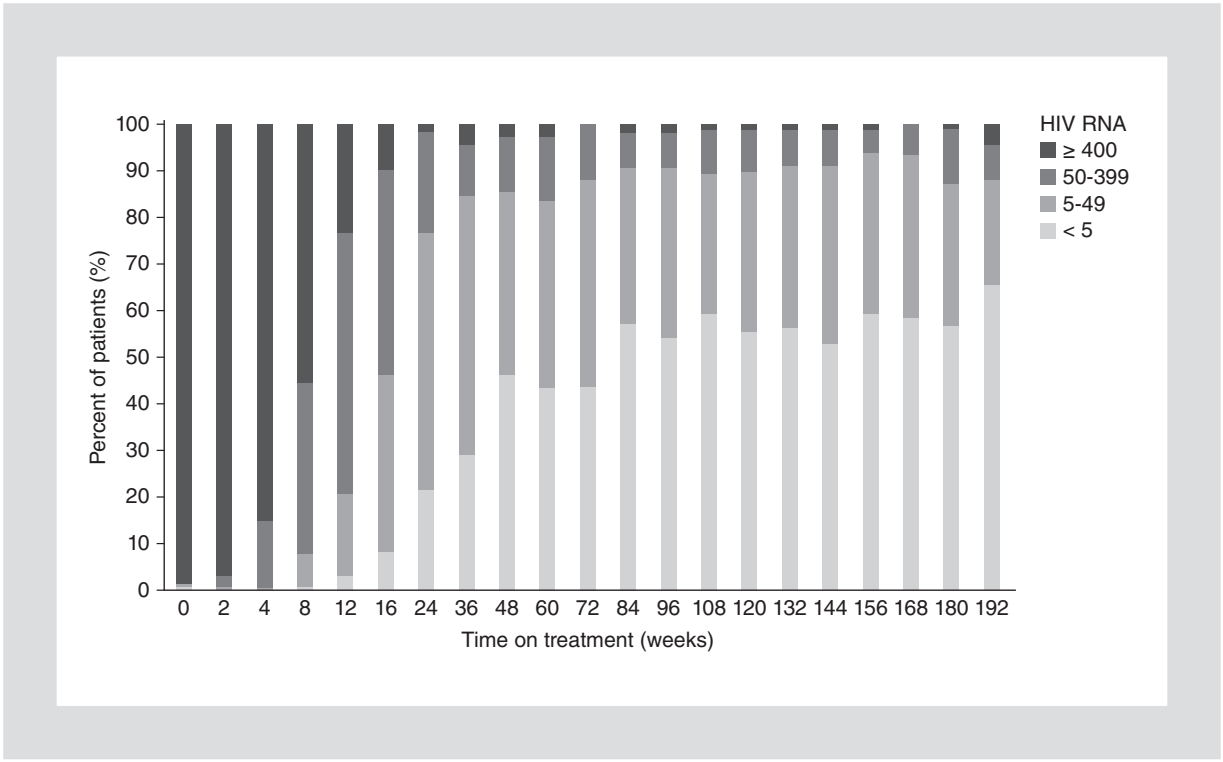

Figure 2. *HIV RNA versus time on darunavir/ritonavir plus tenofovir/emtricitabine. Baseline HIV RNA ≥ 100,000 copies/ml.*

was 128/195 (66%) for patients with HIV RNA < 100,000 copies/ml at baseline, versus 39/112 (35%) for those with baseline HIV RNA ≥ 100,000 copies/ml (p = 0.0001). A similar trend was seen in the DRV/r arm, but this did not reach statistical significance (p = 0.07).

At the week 192 visit, the patients with baseline HIV RNA < 100,000 copies/ml were also more likely to have HIV RNA levels < 5 copies/ml. For example, in the LPV/r arm the percentage with HIV RNA < 5 copies/ml was 116/150 (77%) for those with baseline HIV RNA < 100,000 copies/ml, versus 50/79 (63%) for those with baseline HIV RNA ≥ 100,000 copies/ml (p = 0.04).

Among patients with HIV RNA < 50 copies/ml, the percentage with HIV RNA < 5 copies/ml also correlated with time on treatment. At week 48 across the two treatment arms, there were 557 patients with HIV RNA < 50 copies/ml, of whom 344 (62%) had HIV RNA < 5 copies/ml. At the week 192 visit, there were 443 patients with HIV RNA < 50 copies/ml, of whom 354 (80%) had HIV RNA < 5 copies/ml.

Between weeks 96 and 192, there was no overall change in the percentage of patients with HIV RNA levels < 5 copies/ml. We analyzed the variation in HIV RNA levels for individual patients during this time, using paired data from the combined treatment groups. Overall, there were 330 patients with HIV RNA levels < 5 copies/ml at week 96, of whom 266 (81%) maintained HIV RNA < 5 copies/ml at week 192. Of the 123 patients with HIV RNA of 5-49 copies/ml at week 96, 36 (29%) maintained HIV RNA levels in this range at week 192; 76 patients (62%) had HIV RNA levels < 5 copies/ml at week 192. The number of patients with HIV RNA elevations > 400 copies/ml at week 192 was 8/330 (2%) for those with HIV RNA < 5 copies/ml at week 96, versus 3/123 (2%) for those with HIV RNA of 5-49 copies/ml at week 48.

However, there were also longitudinal variations in HIV RNA levels between consecutive study visits. We analyzed data from the combined data from the two treatment arms for the week 180 and week 192 visit. During this 12-week interval there were patients with HIV RNA levels switching between the < 5 and 5-49 copies/ml categories. Of the 343 patients with HIV RNA < 5 copies/ml at week 180, 44 (13%) had HIV RNA 5-49 copies/ml at the next visit, while 5 (1.5%) had HIV RNA in the range of 50-399 copies/ml. Conversely, of 97 patients with HIV RNA in the range of 5-49 copies/ml at week 180, 57 (59%) had HIV RNA levels < 5 copies/ml at the next visit.

Conclusions

In the ARTEMIS trial of first-line treatment with two nucleoside analogues and boosted protease inhibitors, there

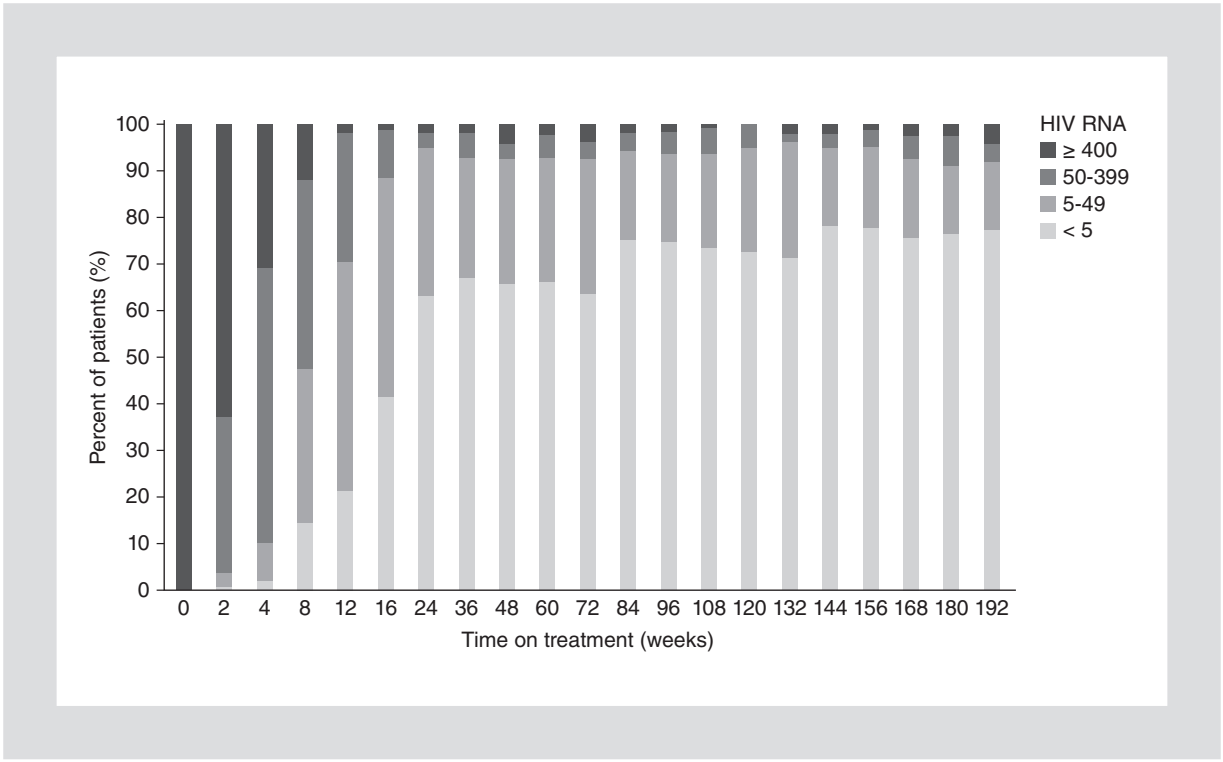

Figure 3. *HIV RNA versus time on lopinavir/ritonavir plus tenofovir/emtricitabine. Baseline HIV RNA < 100,000 copies/ml.*

were progressive reductions in HIV RNA over 192 weeks of treatment, first to 5-50 copies/ml and then < 5 copies/ml. Patients with baseline HIV RNA < 100,000 copies/ml were more likely to show HIV RNA < 5 copies/ml by week 192. Overall, 20% of patients with HIV RNA < 50 copies/ml at week 192 had traces of HIV RNA detected, in the range of 5-50 copies/ml. Between weeks 96 and 192, there was no overall change in the percentage of patients with HIV RNA levels < 5 copies/ml.

These results are consistent with a previous study, which showed a correlation between baseline HIV RNA levels and the "set-point" lowest level of HIV RNA measured during long-term treatment[5]. In the ARTEMIS trial, 80% of patients with HIV RNA levels < 50 copies/ml at week 192 also had HIV RNA < 5 copies/ml. This percentage is similar to the baseline data from the MONET trial, in which a similar analysis was conducted. The MONET trial recruited patients with long-term HIV RNA suppression (median 6.9 years on HAART and no history of virological failure) on nonnucleoside reverse transcriptase inhibitor- or protease inhibitor-based therapy; overall, 88% of patients with HIV RNA < 50 copies/ml at the baseline visit also had HIV RNA levels < 5 copies/ml[18]. In the MONOI trial[10], which had a similar design and baseline characteristics to MONET, but a median of 8.3 years of prior HAART, 46% of patients had HIV RNA levels < 1 copy/ml using a dedicated ultrasensitive HIV RNA assay. In another retrospective cohort study of 739 patients who had a median 11 years of HIV RNA suppression on HAART, 60% had HIV RNA < 1 copy/ml, using the Versant kinetic PCR molecular system[12].

There are three main limitations of this analysis. Firstly, the Roche Amplicor® Ultrasensitive assay[1] used in the ARTEMIS trial was the standard assay for testing of HIV RNA in pivotal clinical trials. However, this assay is no longer in routine use, and these results would need to be repeated using commercially available assays. Previous cross-validation studies have shown differences between the Roche Amplicor®, Roche TAQMAN® and Abbott RealTime® HIV RNA PCR assays, especially around the lower limits of quantification[19-21]. The comparison of HIV RNA levels at weeks 180 and 192 in the present study shows that many patients could switch between the < 5 and 5-49 copy levels between visits. The results using the Roche Amplicor® may therefore be more useful to show trends at the population level; in addition, in 181 plasma samples with residual viremia (all with HIV RNA < 50 copies/ml), a recent comparison among three commercially available assays confirms that more than 50% of results cannot be reproduced on the three aliquots, suggesting that more accurate HIV RNA PCR assays may be required for routine patient monitoring of low-level viremia[22].

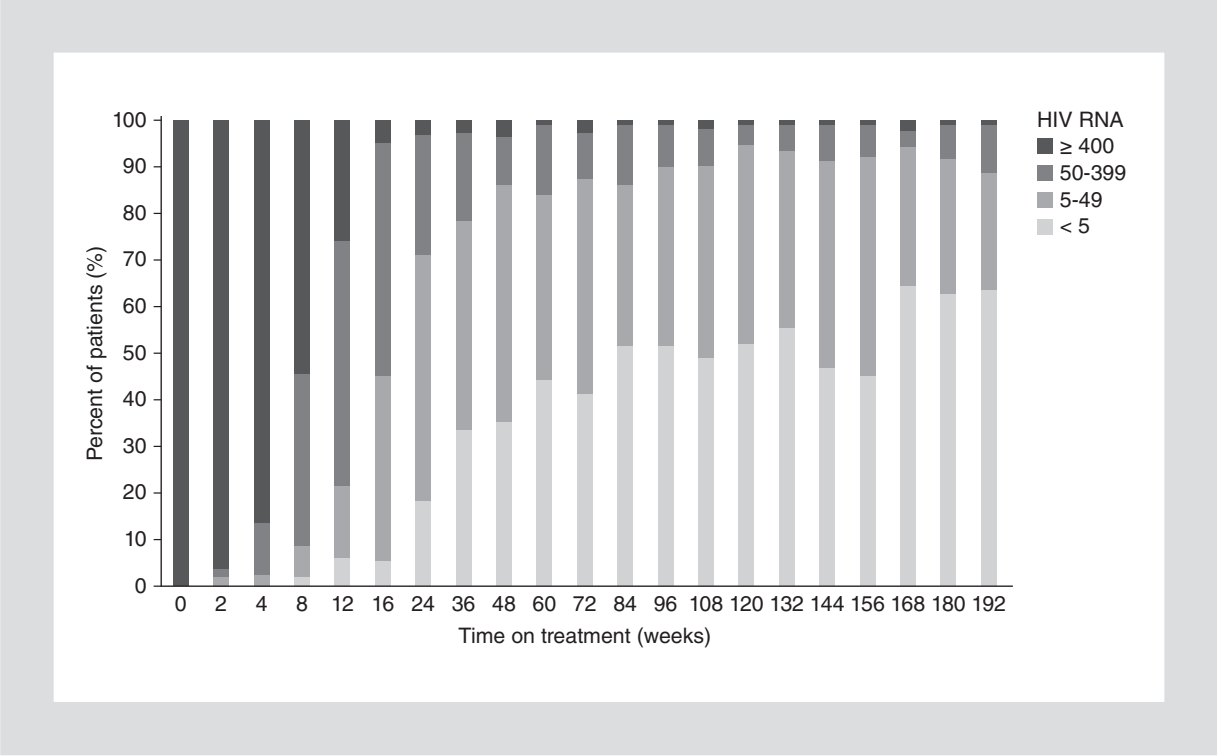

Figure 4. *HIV RNA versus time on lopinavir/ritonavir plus tenofovir/emtricitabine. Baseline HIV RNA ≥ 100,000 copies/ml.*

Secondly, although this was a prospective randomized trial, 245 of the 689 patients (36%) had missing HIV RNA data at week 192, typically because they had discontinued from the trial by this time. This level of attrition over four years of treatment is normal for a phase III trial of first-line treatment. However there is the potential for survivor effects in the analyses presented.

Thirdly, the ARTEMIS trial only evaluated protease inhibitor-based treatments – darunavir/ritonavir and lopinavir/ritonavir. Despite the low-level viremia observed in this trial, no patients developed treatment-emergent resistance to protease inhibitors. There were four patients in the DRV/r arm and seven in the LPV/r arm who developed the M184V mutation, which confers resistance to lamivudine or emtricitabine. Two recent studies have shown that low-level viremia is more common for patients taking protease inhibitor-based treatment, compared with nonnucleoside-based treatment[23,24]. A third study has shown that low-level viremia is less common among patients treated with nevirapine compared with efavirenz[25]. Even so, two large studies have shown a higher risk of treatment-emergent drug resistance for first-line treatment with nonnucleosides compared with protease inhibitors[26,27]. This disconnect between low-level viremia and the risk of drug resistance may be caused by different genetic barriers to resistance between the drug classes: some drugs may be able to withstand low-level viremia without a significant risk of resistance. The analyses of the ARTEMIS trial should be repeated for similar trials of nonnucleosides and integrase inhibitors to determine whether the same correlations are seen.

Several recently reported studies have shown an association between low-level viremia and a higher risk of rebounds in HIV RNA above 400 copies/ml[7,8,10,11]. These studies have been conducted using the Roche TAQMAN® assay[8], the Abbott RealTime® assay[7] and dedicated ultrasensitive HIV RNA PCR assays[10,11]. So far, these studies have not investigated the effects of low-level viremia on treatment-emergent drug resistance. They have also not assessed whether low-level viremia has different clinical consequences for different antiretroviral drug classes.

The clinical management of patients with low-level viremia is unclear. Low-level HIV RNA showed substantial variability between visits in the ARTEMIS trial – patients could have HIV RNA levels < 5 copies/ml at one visit and then 5-49 copies/ml at the next, or vice versa. When patients with low-level viremia were intensified with raltegravir in two randomized trials, there was no virological benefit[14,15]. A recently reported cohort study showed no association between low-level viremia and the risk of non-AIDS-related diseases for

Table 2. HIV RNA levels at week 48 and week 192, by treatment arm and baseline viral load

Treatment arm	DRV/r		LPV/r	
Baseline HIV RNA	**< 100 K**	**≥ 100 K**	**< 100 K**	**≥ 100 K**
Patients with HIV RNA data at week 48	n = 196	n = 110	n = 195	n = 112
– < 5 copies/ml	125 (64%)	52 (47%)	128 (66%)	39 (35%)
– 5-49 copies/ml	62 (32%)	42 (38%)	52 (27%)	57 (51%)
– 50-399 copies/ml	6 (3%)	13 (12%)	7 (4%)	12 (11%)
– ≥ 400 copies/ml	3 (1.5%)	3 (3%)	8 (4%)	4 (4%)
Patients with missing data	30	7	31	8
Patients with HIV RNA data at week 192	n = 160	n = 93	n = 150	n = 79
– < 5 copies/ml	127 (79%)	61 (66%)	116 (77%)	50 (63%)
– 5-49 copies/ml	26 (16%)	21 (23%)	22 (15%)	20 (25%)
– 50-399 copies/ml	4 (2.5%)	7 (8%)	6 (4%)	8 (10%)
– ≥ 400 copies/ml	3 (2%)	4 (4%)	6 (4%)	1 (1%)
Patients with missing data	66	24	76	41

DRV/r: darunavir/ritonavir; LPV/r: lopinavir/ritonavir.

patients on suppressive therapy[28]. There needs to be more detailed analysis of long-term clinical trials and cohort studies, by treatment class, to assess the implications of low-level viremia for drug resistance, changes in CD4 count, and clinical disease progression.

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