

Low-level HIV RNA viraemia in the MONET trial: effects of assay variability and inter-current infection

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Introduction

The aim of antiretroviral treatment is sustained HIV RNA suppression below 50 copies/mL.

However, HIV RNA PCR assays have high variability at the lower detection limit. Inter-current infections can lead to transient, low-level viraemia.

This analysis assessed the reasons for elevations in HIV RNA during the MONET trial.

Methods

In the MONET trial, 256 patients with HIV RNA <50 copies/ml for at least 6 months were randomised to 48 weeks of DRV/r 800/100 mg OD, either as monotherapy or with two NRTIs.

Patients were evaluated at screening, baseline and Weeks 4, 12 and then every 12 weeks thereafter. HIV RNA was tested at a central laboratory using the Roche Amplicor Monitor 1.5 assay.

Each sample with HIV RNA between 50-100 copies/mL was re-tested using the same assay.

In the DRV/r monotherapy arm, patients had the option to intensify treatment with nucleoside analogues if the HIV RNA levels was at least 50 copies/mL for two consecutive visits.

In the triple therapy arm, patients could remain on randomised treatment after two consecutive HIV RNA levels above 50 copies/mL.

Results

At baseline there were 22 patients (17%) with Hepatitis C co-infection in the DRV/r monotherapy arm, versus 12 (9%) in the triple therapy arm.

During the trial, there were three patients with acute Hepatitis C infection in the DRV/r mono arm, but none in the triple therapy arm.

Table 1: MONET trial: Baseline characteristics by treatment arm

	DRV/r mono n=127	Triple therapy n=129
Mean age, years	43	44
Gender (% male)	78%	83%
Race (% Caucasian)	92%	90%
IV drug user (%)	16%	9%
Mean weight (kg)	72	75
Mean CD4 count (cells/uL)	571	579
HCV antibody positive	17%	9%
HIV RNA >50 copies/mL at baseline*	7%	3%
Known duration of HIV infection (years)	9.1	7.5
Duration of ARV treatment (years)	7.4	5.9
PI naive at screening (%)	23%	28%
PI treatment at screening (%)	56%	57%
NNRTI treatment at screening (%)	44%	43%

* screening HIV RNA was used for trial entry

Screening versus baseline HIV RNA levels

13/256 patients (5%) had HIV RNA levels above 50 copies/mL at the baseline visit (i.e. before the first dose of randomised treatment was received), despite HIV RNA <50 copies/mL at screening.

Nine of these patients were in the DRV/r monotherapy arm and four in the triple therapy arm (Table 1). 11/13 had HIV RNA <400 copies/mL at baseline. These blips may be caused by either poor adherence or testing error.

Transient HIV RNA elevations – testing error

Of the 38 re-tested samples with HIV RNA 50-100 copies/mL during the trial, 25 (66%) showed HIV RNA levels <50 copies/mL on re-testing at the same central laboratory (Table 2)

Table 2: re-tested HIV RNA if first sample shows results between 50-100 copies/mL

1st Test	Re-test	1st Test	Re-test
100	<50	68	<50
96	<50	67	<50
95	125	65	<50
89	<50	65	<50
87	104	63	<50
82	<50	62	<50
87	104	61	<50
82	<50	57	63
80	94	56	<50
79	56	55	<50
78	154	55	<50
75	<50	54	<50
75	129	53	<50
74	51	52	<50
73	<50	50	<50
73	120	50	80
71	<50	50	<50
69	<50	50	<50

One patient had a transient double HIV RNA elevation (167 and 67 copies/mL) around the Week 4 visit, when tested at the central lab. However the HIV RNA stayed below 50 copies/mL on both visits tested at the investigator site. This patient then had HIV RNA below 50 copies/mL to Week 48, tested at the central laboratory.

Other patients had one local HIV RNA test result <50 copies/mL, taken around the time of a confirmed HIV RNA elevation measured at the central laboratory (Table 3).

Inter-current infections

Table 3 shows details of 18 patients with double elevations in HIV RNA up to Week 48.

Of the 7 patients with these elevations in HIV RNA in the triple therapy arm, two patients had co-infection with Hepatitis C at baseline.

Of the 11 patients with double elevations in HIV RNA in the DRV/r monotherapy arm, five had Hepatitis C co-infection at baseline and three had acute infection with Hepatitis C during the trial.

In both arms, efficacy was lower for patients with Hepatitis C co-infection (Figure 1). There was a significantly lower response rate for patients with Hepatitis C co-infection (p<0.01).

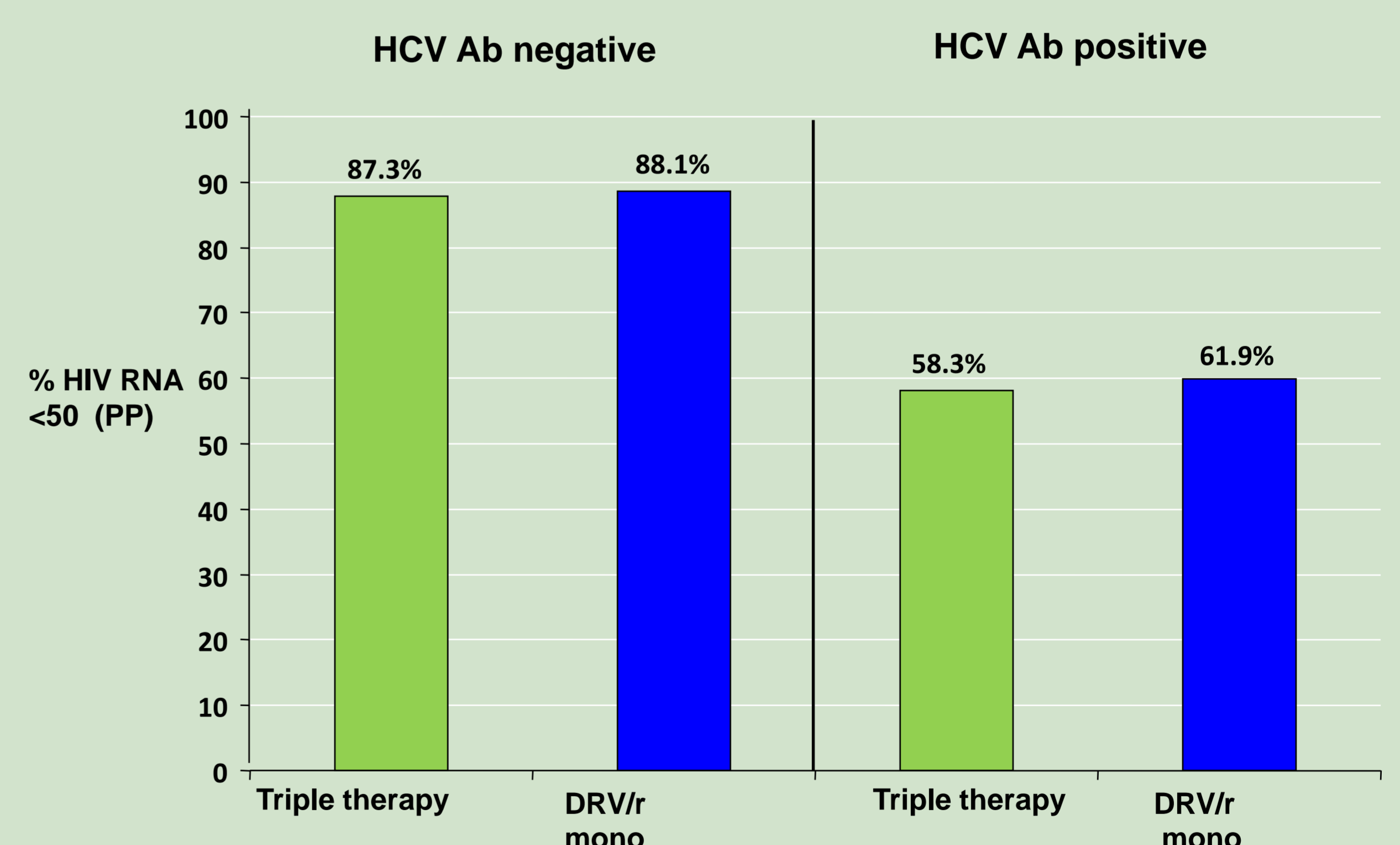
Of the 34 patients with Hepatitis C co-infection, 31 (91%) were also IV Drug users. IV drug users had significantly worse adherence during the trial, and were more likely to have HIV RNA >50 copies/mL at the baseline visit.

Table 3: Details of patients with confirmed elevations in HIV RNA up to Week 48

Patient	HCV	HIV RNA levels at least 50 copies/mL	Changed ARVs	Last HIV RNA (Week)
Triple therapy (DRV/r + 2NRTI) arm				
1	HCV+	294, 116 (wk 48)	No change	<50 (Week 84)
2	HCV+	54000, 3400 (wk 36)	No change	<50 (Week 84)
3	No	78, 50 (wk 12)	No change	<50 (Week 84)
4	No	164, 67 (wk 4)	No change	<50 (Week 60)
5	No	989, 59 (wk 12)	No change	<50 (Week 84)
6	No	746, 2230 (wk 48)	No change	<50 (Week 72)
7	No	128, 548 (wk 48)	No change	<50 (Week 84)
DRV/r monotherapy arm				
8	No	140, 133 (wk 24)	No change	147 (Week 84)
9	No	59, 214 (wk 24)	ZDV/3TC/NVP	<50 (Week 108)
10	Acute HCV	132, 139 (wk 24)	LPV/r mono	<50 (Week 72)
11	HCV+	539, 862 (wk 12)	TDF/FTC/EFV	<50 (Week 84)
12	HCV+	67, 810 (wk 48)	No change	980* (Week 72)
13	HCV+	40500, 628 (wk 48)	No change	<50 (Week 96)
14	No	158, 140 (wk 12)	ABC/3TC/DRV/r	<50 (Week 84)
15	Acute HCV	51, 80 (wk 36)	No change	100 (Week 80)
16	Acute HCV	106, 268 (wk 24)	TDF/FTC/DRV/r	<50 (Week 84)
17	HCV+	722, 157 (wk 24)	TDF/FTC/DRV/r	<50 (Week 84)
18	HCV+	779, 267 (wk 24)	ABC/3TC/DRV/r	<50 (Week 96)

* Treatment interruption

Figure 1: HIV RNA <50 copies/mL (Per Protocol, switch=failure) by baseline Hepatitis C antibody status



Conclusions

There were more patients with Hepatitis C co-infection at baseline in the DRV/r monotherapy arm (17%) than the triple therapy arm (9%). Infection with Hepatitis C was highly correlated with HIV RNA viraemia in the MONET trial (p<0.01), but elevations were mainly low-level (<200 copies/mL) and transient. Of the 34 patients with Hepatitis C co-infection, 91% were also IV Drug users.

Of the 18 patients with confirmed HIV RNA elevations during the MONET trial, most had HIV RNA <50 copies/mL at their last visit, with no change in treatment. In the DRV/r monotherapy arm, patients who intensified with 2 NRTIs, or switched back to their pre-baseline HAART, showed re-suppression of HIV RNA <50 copies/mL. Virological failure should not be based on isolated HIV RNA results in the range of 50-200 copies/mL.