

Non-inferior efficacy shown across different efficacy endpoints in the MONET trial of darunavir/ritonavir (DRV/r) monotherapy.

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Introduction

In previous trials of PI monotherapy, the conclusions on efficacy have often depended on the analysis conducted: in particular HIV RNA <50 versus <400 copies/mL endpoints, and whether re-intensification with NRTIs was classified as success or failure.

Methods

In the MONET trial, 256 patients with HIV RNA <50 copies/ml on current HAART (57% with PI, 43% with NNRTI), and no history of virological failure, were randomised to 48 weeks of DRV/r 800/100 mg OD, either as monotherapy (monotherapy arm) or with two NRTIs (triple therapy arm).

After a confirmed HIV RNA level above 50 copies/mL patients could re-intensify with new antiretrovirals. The primary efficacy endpoint was HIV RNA <50 copies/mL at Week 48 for the Per Protocol population, using the TLOVR algorithm, with re-intensification of treatment classified as failure. Several sensitivity analyses were conducted.

Results

In the primary efficacy analysis, HIV RNA suppression rates at Week 48 were 86.2% in the monotherapy arm and 87.8% in the triple therapy arm, proving non-inferiority (delta = -1.6%, 95% ci = -10.1 to +6.8%). Of the 30 patients with protocol defined treatment failure, 18 had confirmed HIV RNA blips, of which 13 were in the range of 50-200 HIV RNA copies/mL; an additional 12 patients switched or discontinued randomised treatment.

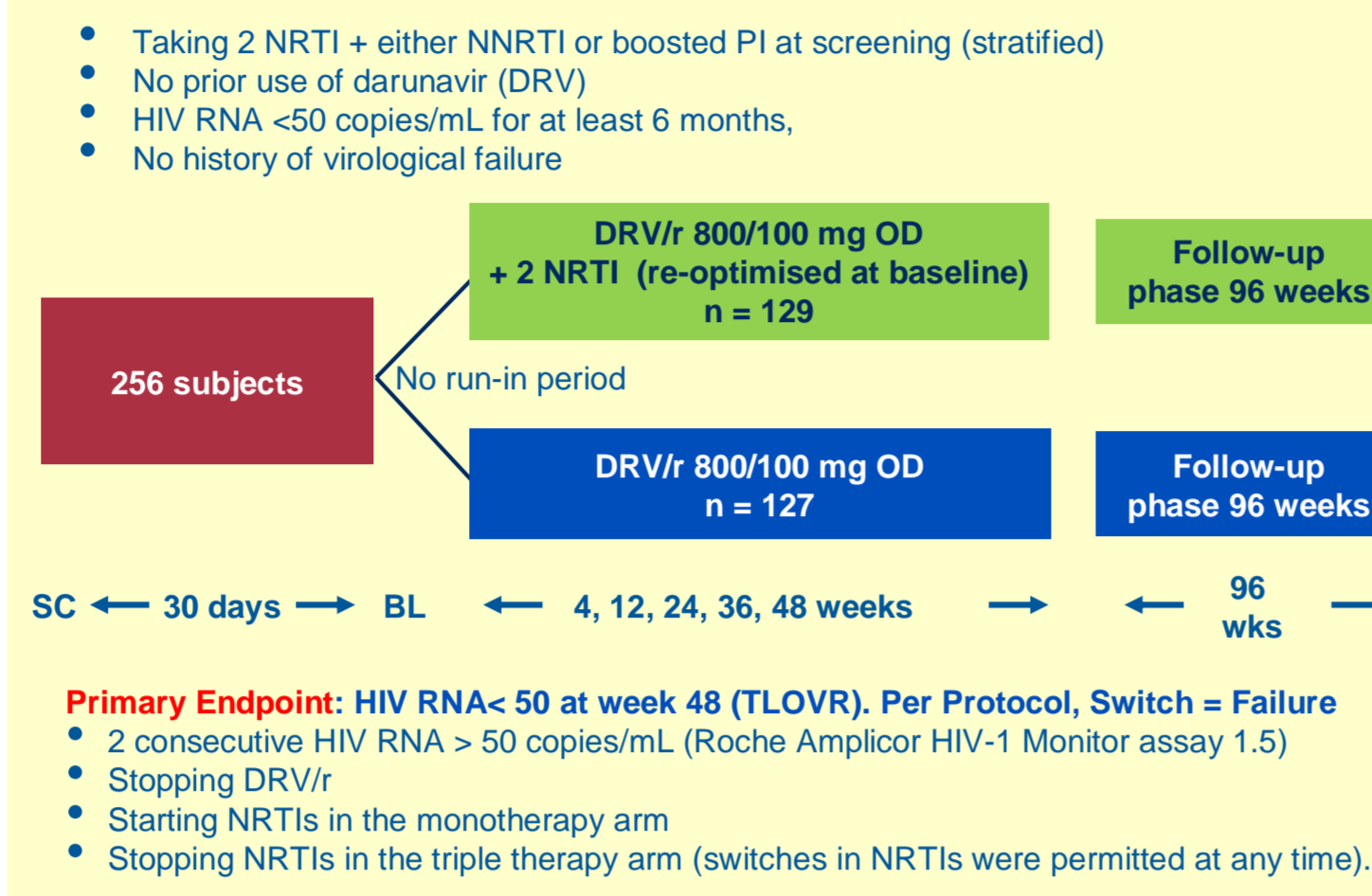
In the sensitivity analyses, the response rates for the monotherapy and triple therapy arms (delta, 95% ci) were: (i) ITT analysis, 84.3% versus 85.3% (-1.0%, -9.9% to +8.9%) (ii) 200 copy endpoint, 91.9% versus 88.6% (-3.3%, -10.7% to +4.2%); (iii) Switch included analysis: 93.5% versus 93.1% (-1.6%, -8.9% to 5.5%). (iv) Virological endpoints only, 90.6% versus 92.3% (-3.2%, -9.5% to +3.1%).

All the sensitivity analysis showed non-inferiority for DRV/r monotherapy versus triple therapy.

Conclusions

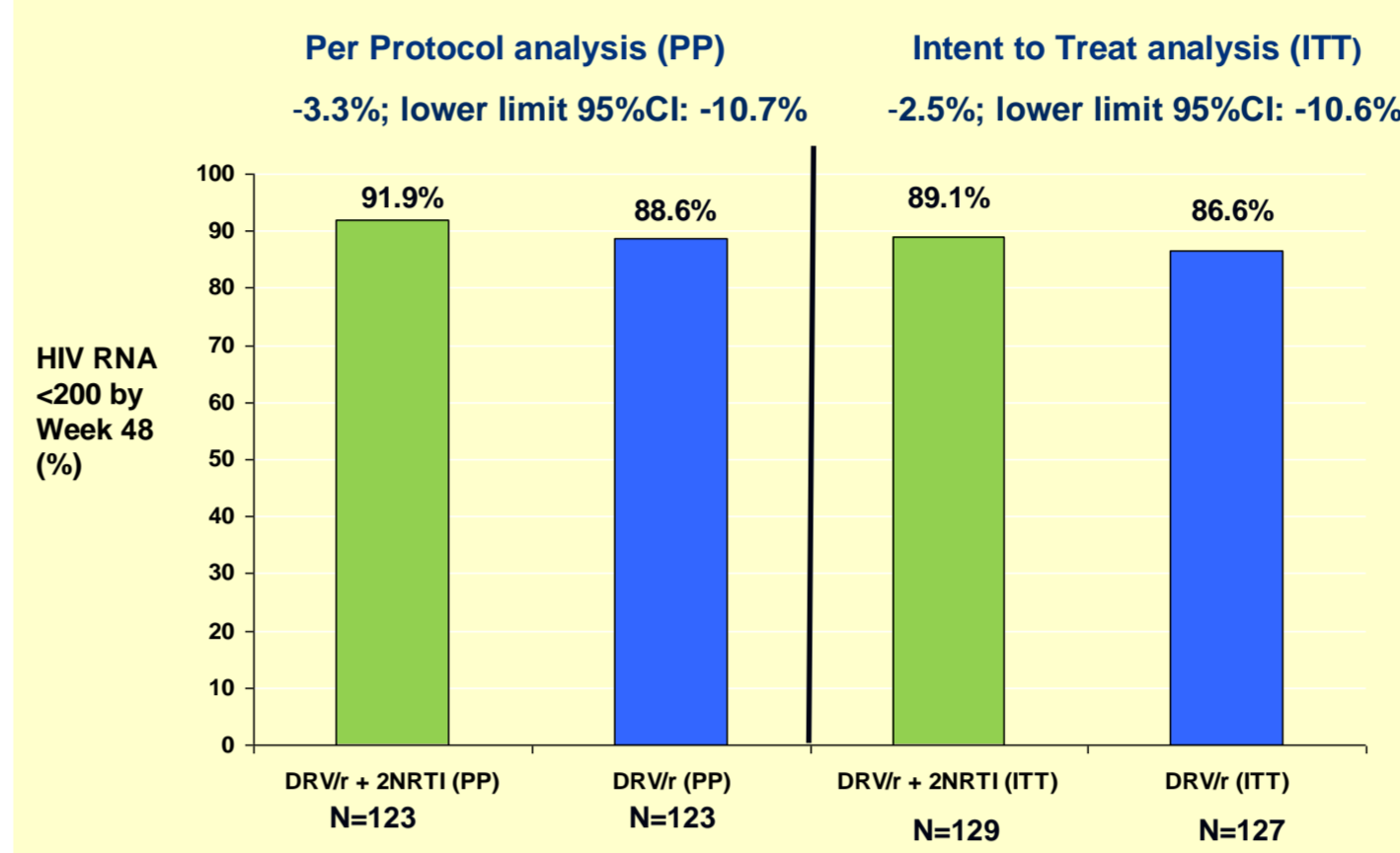
In the MONET trial of darunavir/r monotherapy, non-inferior efficacy was shown across a wide range of efficacy analyses.

MONET - Trial Design



MONET:

HIV RNA <200 copies/mL at Week 48, TLOVR, S=F



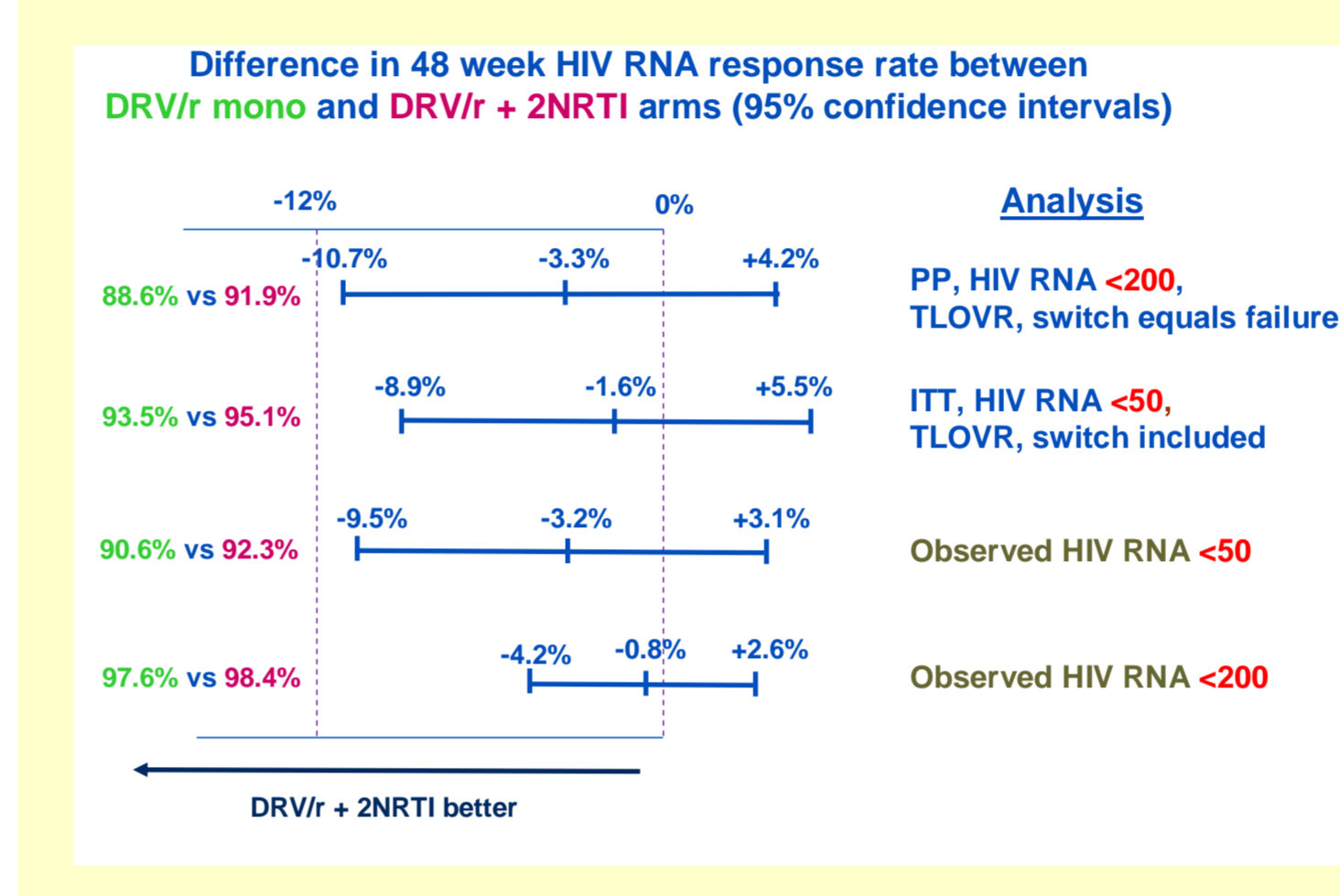
MONET: Outcome of discontinuations in DRV/r + 2 NRTI arm (9 patients)

Patient number	Reason for d/c	Change in ARVs	HIV RNA at Week 48
8	Withdraw consent	TDF/FTC/NVP	<50 (local)
9	Withdraw consent	ZDV/3TC/NVP	<50 (local)
10	Pregnancy	ZDV/3TC/NVP	<50 (local)
11	Investigator decision	ZDV/3TC/NVP	<50 (local)
12	Private reasons	TDF/FTC/3TC	<50 (local)
13	Pregnancy	ZDV/3TC/LPV/r	<50 (local)
14	History of VF	TDF/FTC/DRV/r	<50 (local)
15	RNA >50 at SCR+ BL	TDF/FTC/DRV/r	No data
16	Switched to DRV/r	DRV/r	<50

MONET: Study Design and Objectives

- Primary objective:** to show non-inferior efficacy for DRV/r monotherapy (800/100 mg OD dose) versus standard HAART (DRV/r + 2 NRTI).
- Study power:** 80% to show non-inferiority for DRV/r vs DRV/r + 2 NRTIs, with a sample size of 125 patients per arm (delta = -12%).
- Primary Analysis:**
 - Per protocol (PP):** excluded patients with major protocol violations such as a history of virological failure, or patients randomised incorrectly (n = 10). Time to loss of virological response (TLOVR)
- Secondary Analyses:**
 - Observed:** only virological endpoints.
 - Intent To Treat (ITT) – all randomised patients**
 - Switch = Failure (S = F)
 - Switch Included (S = F)
- All patients were followed up to Week 48

MONET trial: sensitivity analyses



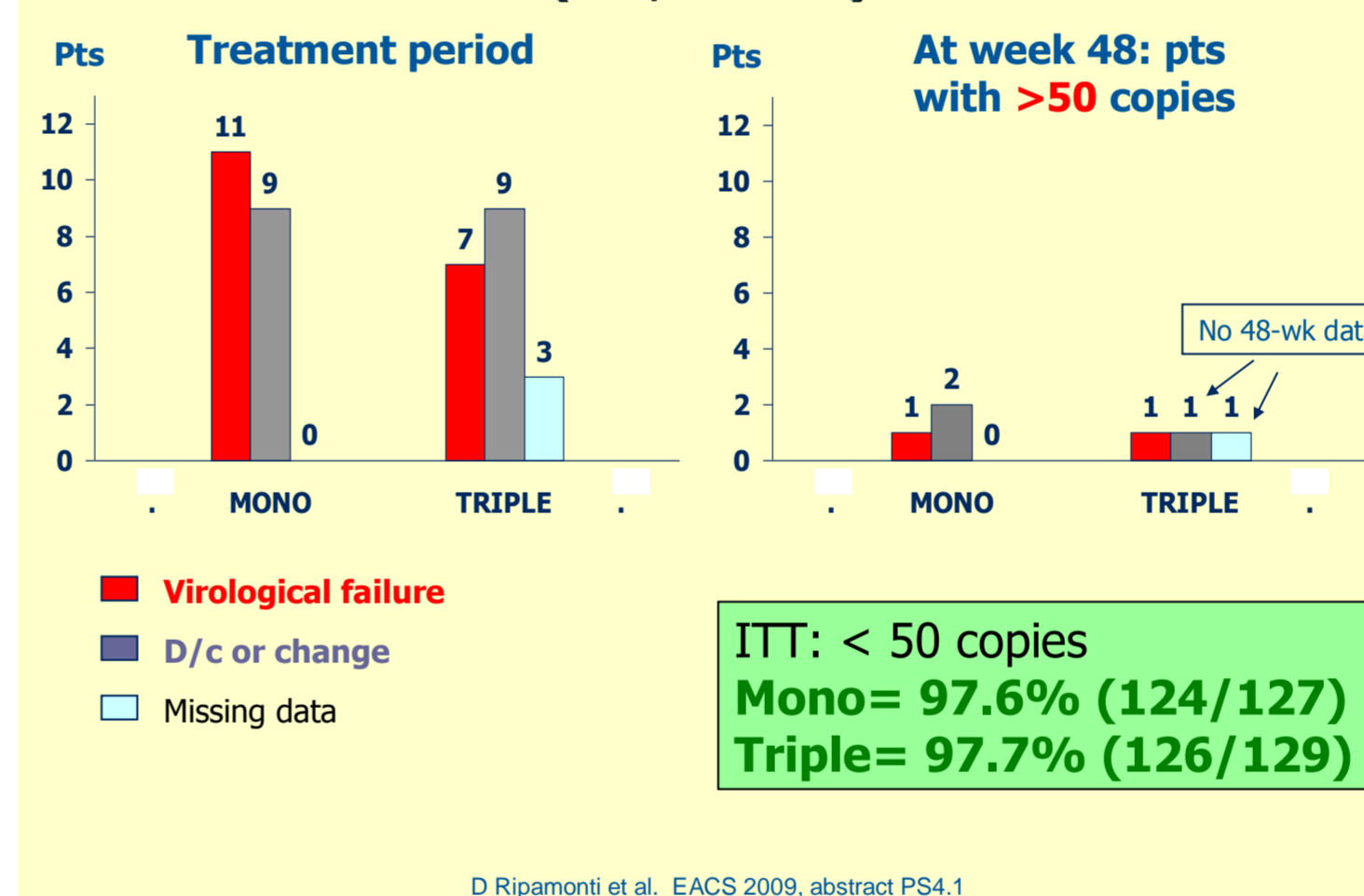
MONET: Outcome of discontinuations in DRV/r mono arm (9 patients)

Patient number	Reason for d/c	Change in ARVs	HIV RNA at Week 48
12	History of VF	ABC/3TC/ATV/r	<50 (local)
13	Adverse Events	TDF/FTC/EFV	<50 (local)
14	Investigator decision	TDF/FTC/LPV/r	<50 (local)
15	Adverse Events	ABC/3TC/NVP	<50 (local)
16	Adverse Events	ABC/3TC/ATV/r	<50 (local)
17	Withdraw Consent	ZDV/3TC/EFV	<50 (local)
18	History of VF	DRV/r	<50 (local)
19	AE: Jaundice	No ARV's	>75,000
20	In prison	DRV/r	<50 (local)

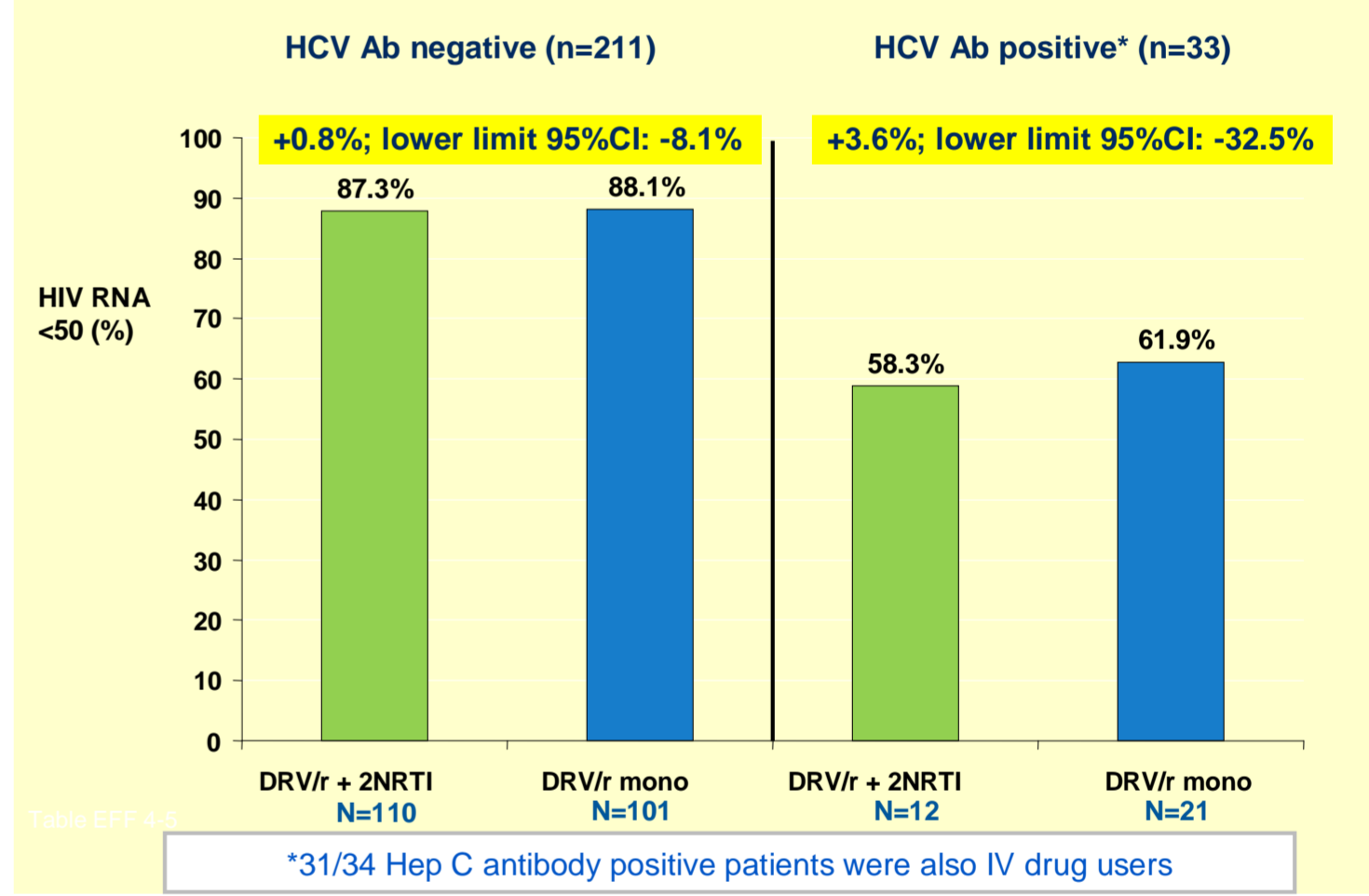
MONET: Statistical issues

- How many of the primary endpoints were **true virological failures**?
- How many failures were HIV RNA >200 copies/mL versus low-level blips?
- What was the **outcome** of treatment failures, if people were then followed up to the end of the trial?
- Imbalance** in baseline characteristics – how to control for this?

MONET: Patient outcomes in mono and triple Rx (ITT, 48 wks)



MONET: Effects of Hepatitis C co-infection on response HIV RNA <50 copies/mL (PP, Switch = failure)



MONET: Baseline Characteristics (ITT)

	DRV/r + 2NRTI (n=129)	DRV/r (n=127)
Age, years (median, range)	43 (24-72)	43 (25-67)
Male (%)	83%	78%
Caucasian (%)	90%	92%
Disease characteristics		
CD4 count (median, cells/uL)	579	571
CD4 <350 cells/uL (%)	12%	14%
Duration of prior ARVs, years (mean, sd)	6.4 (4.0)	7.4 (4.2)
Use of PI at screening (%)	57%	56%
Use of NNRTI at screening (%)	43%	44%
On their first NRTI combination	48%	35%
PI naive	28%	23%
Hep B Surface Antigen, positive, n (%)	2 (1.6%)	1 (0.8%)
Hep C Antibody, positive, n (%)	12 (9.4%)	22 (17.3%)

MONET: Outcome of "double blips" in HIV RNA DRV/r + 2NRTI arm (7 patients)

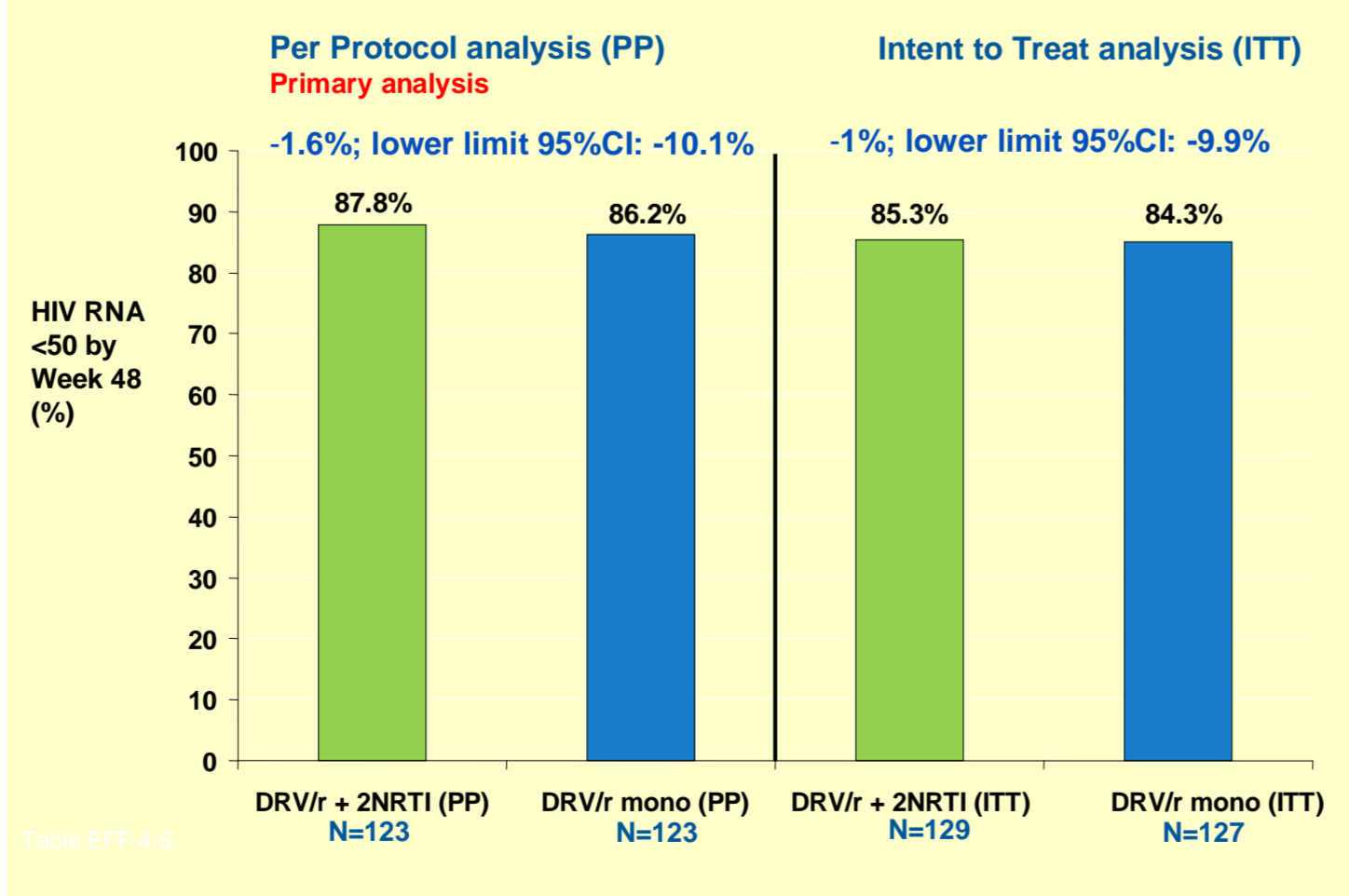
Patient number	Highest HIV RNA on trial	Change in ARVs	HIV RNA at Week 48
1	294 and 116	No	<50
2	54000 and 3400	No - stopped drug	<50
3	78 and 50	No	<50
4	164 and 67	No	<50
5	989 and 59	No	<50
6	746 and 2230	No	2230
7	128 and 548	No	<50

MONET: Drug resistance

Genotypic results	DRV/r + 2NRTI N= 129	DRV/r mono N= 127
Patients with at least 1 successful genotype	14	24
No primary PI, DRV or NRTI mutations	13/14 (92.9%)	23/24 (95.8%)
M184V	1	0
Primary IAS-USA PI mutations	1	1
DRV mutations	0	1

1 patient per arm had any evidence of genotypic resistance
No patients had phenotypic resistance to DRV

MONET: Primary Efficacy Analysis HIV RNA <50 copies/mL at Week 48, TLOVR, S = F



MONET: Outcome of "double blips" in HIV RNA DRV/r mono arm (11 patients)

Patient number	Highest HIV RNA	Change in ARVs	HIV RNA at Week 48
1	140 and 133	No change (sinusitis)	<50
2	59 and 214	ZDV/3TC/NVP	<50
3	132 and 139	LPV/r mono	<50
4	539 and 862	TDF/FTC/EFV	<50
5	158 and 140	ABC/3TC/DRV/r	<50
6	40500 and 628	No change (stopped drug)	<50
7	51 and 80	No change (Hep C)	<50
8	106 and 268	TDF/FTC/DRV/r	<50
9	722 and 157	TDF/FTC/DRV/r	<50
10	779 and 267	ABC/3TC/DRV/r	<50
11	67 and 810	DRV/r (stopped drug)	810

Conclusions

- In the MONET trial, darunavir/ritonavir monotherapy showed consistently **non-inferior efficacy** versus triple antiretroviral drug treatment at Week 48.
- Most elevations in HIV RNA were low level (**50-200 copies/mL**), and patients were re-suppressed <50 copies/mL at last visit, either on the original randomised treatment or with intensified treatment.
- The efficacy results were sustained in several **sensitivity analyses**: looking only at virological endpoints, stratified by baseline Hepatitis C co-infection, looking at HIV RNA elevations above 400 copies/mL.