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In the TORO, RESIST and POWER trials, the HIV-RNA < 50 copy endpoint showed the strongest durability over time, whereas HIV-RNA reductions of more than 1 log₁₀ or below 400 copies/ml were less sustained during 48 weeks of treatment. Clinical trials of new antiretroviral drugs in highly experienced patients also show high rates of HIV-RNA suppression below 50 copies/ml. HIV-RNA suppression below 50 copies/ml should now become the standard efficacy endpoint across trials of both naive and experienced patients.

Plasma HIV RNA is now used as the primary efficacy endpoint in most randomized clinical trials, with the CD4 cell count a key secondary efficacy parameter.^[1] The latest International AIDS Society USA adult HIV treatment guidelines recommend plasma HIV-RNA levels of less than 50 copies/ml as the virological target for all patients.^[2] For clinical trials of first-line HAART, the most common primary efficacy analysis is the proportion of patients with HIV RNA under 50 copies/ml. For clinical trials in treatment-experienced patients, numerous endpoints involving HIV-RNA levels have been used: HIV RNA less than 50 copies/ml (DUET trials of darunavir boosted with ritonavir and TMC125); HIV RNA less than 400 copies/ml (TITAN trial of darunavir/ritonavir), BENCHMRK trials of the integrase MK-0518,^[3,4] HIV-RNA reduction greater than 1 log₁₀ copy/ml (TORO trials of enfuvirtide,^[5-7] RESIST trials of tipranavir/ritonavir,^[8] POWER trials of darunavir/ritonavir^[9]); and a continuous log₁₀ reduction in HIV RNA from baseline (MOTIVATE trials of maraviroc,^[10,11] BMS-045 trial of atazanavir/ritonavir,^[12] the Gilead 907 trial of tenofovir^[13] and the CONTEXT trial of fosamprenavir/ritonavir.^[14]

Given the availability of new treatments with activity against drug-resistant HIV, the efficacy of HAART is improving for highly treatment-experienced patients, enabling increasing proportions to reach undetectable plasma HIV-RNA levels. Three controlled sets of trials of antiretroviral agents in treatment-experienced patients, POWER 1 and 2, RESIST 1 and 2 and TORO 1 and 2, were analysed using different HIV-RNA endpoints, to assess their relative durability over time. In all the trials, highly treatment-experienced patients received study medication plus an individually optimized background regimen (OBR) of other antiretroviral agents.

The POWER 1 and 2 trials compared four doses of darunavir/ritonavir with investigator-selected control protease inhibitors (PI). All patients also received an OBR of at least two nucleoside reverse transcriptase inhibitors (NRTI) with or without enfuvirtide. Only data from the 131 patients receiving the licensed dose of darunavir/ritonavir, 600/100 mg twice a day, were included in this analysis. The RESIST 1 and 2 trials compared the efficacy of tipranavir/ritonavir 500/200 mg twice a day (*n* = 746) with that of control PI. Patients also received an OBR of NRTI and non-nucleoside reverse transcriptase inhibitors (NNRTI) with or without enfuvirtide. The TORO 1 and 2 trials compared the virological outcomes of patients who received 90 mg enfuvirtide subcutaneously plus an OBR of three to five antiretroviral drugs including NRTI, NNRTI and PI (*n* = 661) compared with a control arm of the OBR without enfuvirtide.

For the three pairs of trials, the proportions of patients in the experimental treatment arms reaching the endpoints of HIV-RNA reduction greater than 1 log₁₀ copy/ml, HIV RNA less than 400 copies/ml or HIV RNA less than 50 copies/ml were assessed over time using published intent-to-treat, time to loss of virological failure analyses.

The maximum response for the HIV-RNA reduction greater than 1 log₁₀ copy/ml endpoint was observed after 4 weeks of treatment ([Table 1](#)), with a gradual reduction in response from weeks 24 to 48. For the HIV RNA less than 400 copies/ml endpoint, the maximum response was observed at week 16, with subsequent gradual reductions in response at weeks 24 and 48. For the HIV RNA less than 50 copies/ml endpoint, the HIV RNA less than 50 copy responses remained stable between weeks 24 and 48. This trend is also seen from the time-course of the different endpoints over 48 weeks for the POWER 1 and 2 trials, shown in Figure 1.

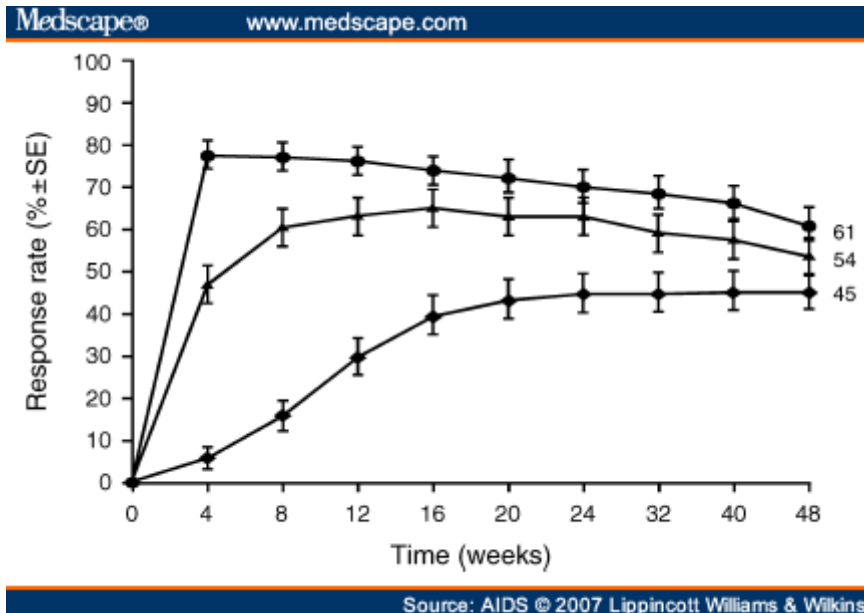


Figure 1.

Darunavir boosted with ritonavir 600/100 mg twice a day: POWER 1 and 2 HIV-RNA responses (time to loss of virological response). ■-■ HIV-RNA reduction $\geq 1 \log_{10}$ copies/ml; ▲-▲ HIV RNA < 400 copies/ml; ◆-◆ HIV RNA < 50 copies/ml. SE, Standard error.

The TORO, POWER and RESIST trials were all designed with a primary endpoint of a greater than 1 log reduction in HIV RNA. The responses in the control arms showed that HIV-RNA suppression below 50 copies/ml was not a realistic goal for the standard of care treatment when these trials were initiated. Given the development of new antiretroviral agents since the start of the new millennium, however, long-term HIV-RNA suppression below 50 copies/ml should be an achievable target for control arms of new clinical trials in highly experienced patients. Combinations of new antiretroviral drugs with a low potential for cross-resistance, such as enfuvirtide, integrase inhibitors, CCR5 antagonists, darunavir, and tipranavir, are likely to lead to full suppression of HIV RNA in the majority of patients with resistance to NRTI, NNRTI and PI. For example, 24-week data from the phase III trials of the integrase inhibitor MK-0518, in which combinations of new antiretroviral drugs were used, showed 61-62% of patients with HIV-RNA levels of less than 50 copies/ml at week 24 in the MK-0518 arm.^[3,4] Phase III trials of the CCR5 antagonist maraviroc have also shown strong antiviral efficacy at week 24.^[10,11] Consequently, the current design of clinical trials for experienced patients, in which an experimental drug is added to optimized background therapy, may soon only be feasible in the most highly experienced patients. For clinical trials of first-line HAART reported in US product labels, most treatment discontinuations have been either for adverse events or patient preference, with only 28% of endpoints being virological failure in intent-to-treat analysis.^[15] The same situation may start to emerge in trials of experienced patients. If the novel antiretroviral agents can be successfully combined, outcomes from most clinical trials in experienced patients may begin to be influenced more by differences in safety and tolerability than by virological potency.

There is a predicted clinical benefit for patients achieving endpoints of at least a 1 log reduction in HIV RNA. In the PLATO cohort of patients with triple class experience, those with HIV-RNA levels sustained below 10 000 copies/ml showed stable or rising CD4 cell counts over time.^[16] Full suppression of HIV RNA below 50 copies/ml leads to progressive reductions in the risk of subsequent virological failure,^[17] and patients with detectable HIV RNA on HAART gradually accumulate resistance to the drug classes being taken.^[18] If HIV-RNA suppression below 50 copies/ml can be achieved by a significant percentage of highly treatment-experienced patients who receive combinations of the newly developed antiretroviral agents, it is appropriate to switch to this endpoint in new clinical trials. Using a standardized HIV-RNA endpoint across clinical trials would make clinical trial results easier to interpret. Full virological suppression should now be a viable treatment goal across the spectrum of antiretroviral treatment experience.

Table 1. Baseline Disease Characteristics and HIV-RNA Endpoints in POWER, RESIST and TORO Trials

Trial	POWER 1 & 2 OBR + DRV/r n = 131	RESIST 1 & 2 OBR + TPV/r n = 746	TORO 1 & 2 OBR + ENF n = 661
Median age (years)	43	43	41
Men (%)	89%	84%	90%
Caucasian (%)	81%	77%	89%
Mean HIV RNA (log ₁₀ copies/ml)	4.61	4.73	5.2
Median CD4 cell count (cells/ μ l)	153	155	88
CDC stage C (%)	36%	57%	79%
1 Log reduction			
Week of peak response	4	4	4
24 week response	70%	42%	47%
48 week response	61%	34%	37%
HIV RNA < 400 copies/ml			
Week of peak response	16	16	16
24 week response	63%	34%	33%
48 week response	54%	30%	30%
HIV RNA < 50 copies/ml			
Week of peak response	40	32	48
24 week response	45%	24%	16%
48 week response	45%	23%	18%

CDC, Centers for Disease Control and Prevention; DRV/r, darunavir boosted with ritonavir; ENF, enfuvirtide; OBR, optimized background regimen; TPV/r, tipranavir boosted with ritonavir.

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