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Residual viraemia does not influence 1 year virological rebound in HIV-infected patients with HIV RNA persistently below 50 copies/mL—authors’ response

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Sir,

We thank Iannotti et al.1 for their comments on our work,2 because they give us the opportunity to further discuss a topic with relevant implications for HIV-infected patients. Our main finding was that residual viremia was not associated with 1 year virological rebound; Iannotti et al.1 argue that the hypothesis of a statistically different proportion of virological failure between subjects who attain less than 1 copy and those with residual viremia was not detected because of a low statistical power. This argument is based on power calculations retrospectively performed on the results of our study. However, the retrospective evaluation of the statistical power they performed is highly debated and the fallacies associated with its use can lead to misleading suggestions.3–8

The importance of doing a power analysis before beginning a study (prospective power analysis) is universally accepted. Unfortunately, at the time of conception of our study, no data were available that could help us in formulating a statistical hypothesis (i.e. based on an ‘a priori’ effect size). In their paper, Maggiolo et al.9 do not give any reference for the data used in the power calculation, nor in the introduction or in the methods. We agree that statistical non-significance needs to be taken with caution, as it is not conclusive as to whether the true effect did not exist or whether the sampling error was too large to detect such an effect. Nevertheless, as Kline10 clearly outlined, a warning about statistical significance is also needed: in fact, if the sample size is increased enough, any result will be statistically significant, thus supporting the hypothesis that the effect exists.

It follows that when considering a big ‘a priori’ effect, minimal statistical power (80%) can be easily reached even with small sample sizes, whereas when considering a very low proportion of virological failure (such as we observed), >4060 subjects would be required to have 80% power to demonstrate that a significant effect of residual viremia on the 1 year virological outcome exists. We cannot say which is the ‘true’ proportion of virological failure, but we are sure that the evidence of a different result (obtained by analysing the data of their larger cohort) may not be considered and suggested as evidence that our finding is not true.

The risk and frequency of virological rebound because of residual viremia need to be defined accurately, as they have at least two clinically relevant implications: the definition of the cut-off for antiretroviral efficacy, and the decision on how and when to change a regimen able to maintain viral load at <50 copies HIV RNA/mL, but not <1 copy HIV RNA/mL. Comparing the results of studies with different methodological characteristics may lead to misleading conclusions. The unexpected high frequencies of virological rebound (>30% over 1 year), reported by both Maggiolo et al.9 and Doyle et al.,11 are far from our daily clinical practice and may be related to different patient selection criteria, duration of viral suppression before inclusion in the analysis, cut-offs used to define residual viremia, primary endpoints and, probably even more important, the decision to maintain or not in the primary analysis patients who changed treatment only for toxicity (while HIV RNA was <50 copies/mL, i.e. not for a true virological rebound).

Finally, we believe that the major limit of our study, rather than the potency, is the relatively short follow-up of the patients. For this reason, we are still following-up our patients to verify if over 3 years, with a foreseeable higher rate of virological rebound, residual viraemia results are still unrelated to virological failure. We are going to reach a median follow-up of 3 years in the coming months: we will then repeat the analyses and present the updated results.

Transparency declarations
None to declare.

References
1 Iannotti N, Masini G, Bernardini C et al. Comment on: Residual viremia does not influence 1 year virological rebound in HIV-infected patients...
with HIV RNA persistently below 50 copies/mL. *J Antimicrob Chemother* 2012; 67: 2540–42.


