Comment on: Residual viraemia does not influence 1 year virological rebound in HIV-infected patients with HIV RNA persistently below 50 copies/mL

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Keywords: low-level viraemia, HAART failure, cohort, test power

Sir,

The main goal of highly active antiretroviral therapy is to reduce the viral load to undetectable values and maintain it as such for as long as possible. By convention, a plasma HIV RNA value of 50 copies/mL represents the threshold of undetectability with a recognized clinical importance.

The use of third-generation assays has revealed that HIV RNA may still be measured in many treated patients below this cut-off [low-level viraemia (LLV)].

The source of LLV is still unknown; it could reflect ongoing replication in ‘sanctuary sites’ with the emergence of drug-resistant virus or it could result from the release of HIV from long-lived latently infected cells. Probably, the two mechanisms coexist, which makes the clinical significance of LLV a highly debated and regularly updated topic; LLV could turn out to be a marker which makes the clinical significance of LLV a highly debated and regularly updated topic; LLV could turn out to be a marker of therapeutic efficacy and/or clinical outcome.

The recent paper by Gianotti et al.1 analysed if the presence of LLV could predict virological failure (two consecutive viral loads >50 copies/mL). The study was based on 739 HIV-infected patients with steady viraemia <50 copies/mL, who were followed for 1 year. The authors observed very low rates of virological failure either in the 446 patients (60.4%) who had a viral load <1 copy/mL (0.9%) or in the 293 patients (39.6%) with LLV (2%) (log-rank test $P=0.231$) and concluded that LLV assessed by real-time PCR was not associated with virological rebound during 1 year of follow-up. A similar conclusion was drawn by Charpentier et al.,2 who investigated virological outcome during the year following the detection of LLV (above or below 20 copies/mL) in 656 adult patients. In that study the failure rate was 4% in the 618 patients with all viral loads <20 copies/mL and 8% in the 38 patients with at least two viral loads between 20 and 50 copies/mL.

In our opinion, the conclusion reached by the two research groups must be taken with caution. We believe it could be deeply influenced by the very low failure rates they observed, which lowered the potency of their trials to 18% in the case of the French experience and to a modestly higher 25% in the Italian cohort.

Negative results with such a relative statistical power should be at least regarded as inconclusive, especially when larger studies offer completely different results.

Recently, a cohort analysis (1247 HIV-infected patients) by Doyle et al.3 showed a virological failure rate over 1 year (two consecutive tests >50 copies/mL) of 34.2% in patients with viral loads of 40–49 copies/mL, of 11.3% in patients with viral loads <40 copies/mL (detectable but not quantified) and of 4.0% in patients with undetectable HIV RNA; rebound rates >400 copies/mL were 13.0%, 3.8% and 1.2%, respectively. All the differences were statistically significant and LLV was regarded as highly predictive of virological failure.

Our group5 recently confirmed these results in a cohort of 1214 suppressed patients, monitored prospectively every 4 months for 1 year. In patients with steady HIV RNA <3 copies/mL, the risk of failure (>50 copies/mL) was 1.2%; those with variable HIV RNA levels showed a risk of 1.9% that increased to 34.2% for patients with steady HIV RNA levels between 3 and 50 copies/mL ($P<0.0001$). When a 200 copies/mL threshold was used to define failure, the corresponding values were 1.2%, 1.9% and 17.8% ($P<0.0001$), respectively.

In our opinion these data are only apparently discordant. Because of the low statistical power, the study by Gianotti et al.1 cannot exclude an effect of LLV on virological failure and can only observe that the failure risk (2%) was more than doubled in patients with detectable viraemia compared with those with an HIV RNA below detection (0.9%), therefore supporting, although not to a significant statistical extent, the results of larger studies.

Transparency declarations
None to declare.

References


J Antimicrob Chemother 2012
doi:10.1093/jac/dks259
Advance Access publication 3 July 2012

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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Keywords: HIV, antiretroviral therapy, viral load

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 viraemia 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 viraemia 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 viraemia 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 viraemia 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.11 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 viraemia, 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 viraemia does not influence 1 year virological rebound in HIV-infected patients