Virological rebound in human immunodeficiency virus-infected patients with or without residual viraemia: results from an extended follow-up

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Abstract

Human immunodeficiency virus (HIV) -infected patients with HIV RNA loads of < 50 copies/mL were followed-up for a median (interquartile range) of 30.8 (11.7–32.9) months to study the effect of residual viraemia (RV) on virological rebound (VR). At baseline, 446 (60.3%) patients had undetectable HIV RNA (group A) and 293 (39.7%) had RV (1–49 HIV RNA copies/mL, group B) by kinetic PCR. VR occurred in 4 (0.9%) patients in group A and in 12 (4.1%) patients in group B (p 0.007). Time to VR was shorter among patients of group B (Log-rank test: p 0.003). However, the proportion of VR was extremely low also among patients with RV.

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The effect of residual viraemia (RV) on virological rebound (VR) in human immunodeficiency virus (HIV) -infected patients on antiretroviral therapy is still debated. We found that the rate of VR in patients with viral loads of <50 HIV RNA copies/mL was very low, and RV was not associated with VR over 1 year of follow up [1]. A limitation of this study was the relatively short follow up and we hypothesized that an effect of RV on virological breakthrough would have been seen only after some years of observation.

More recently, two large studies with a similar rationale and objective have obtained different results [2,3].

The aim of the present analysis was to reconsider the role of RV on VR through an extended follow up of all the patients included in the original study.

Study methods have been reported elsewhere [1]; in brief, at the San Raffaele Scientific Institute HIV RNA was quantified on the basis of the branched DNA Versant HIV-1 RNA 3.0 Assay (bDNA, Siemens Diagnostics, Terrytown, NY, USA; limit of quantification 50 HIV RNA copies/mL) up to February 2009; since March 2009, all patients have been routinely tested using the kinetic PCR molecular system (kPCR, Versant HIV-1 RNA kPCR 1.0; Siemens Diagnostics). The kPCR assay gives three possible outputs: (i) a quantitative result for HIV RNA values of >37 copies/mL; (ii) a semi-quantitative result for HIV RNA values between 1 and 37 copies/mL; (iii) a qualitative result ('undetectable') if no signal can be detected.

Patients were included from the original analysis (and then followed up) if the last four consecutive HIV RNA values were <50 copies/mL, that is: two consecutive HIV RNA values of <50 copies/mL as tested by bDNA, followed by two consecutive HIV RNA values of <50 copies/mL as tested by kPCR.

Two groups of patients were identified on the basis of the first two kPCR results: patients with undetectable HIV RNA confirmed in two consecutive samples (group A) and patients with RV, defined as an HIV RNA load undetectable in one sample and not in the other or two HIV RNA values of between 1 and 49 copies/mL (group B).

The detectability ratio was calculated as the number of HIV RNA measurements of >50 copies/mL divided by the number of HIV RNA values available from the start of antiretroviral therapy to the first kPCR test.

In the current analysis, the RV ratio was defined as the ratio between the number of HIV RNA values of 1–49 copies/mL observed during follow up and the number of viral loads tested during follow up. The RV ratio was stratified according to deciles.

The primary analysis was the time to VR (Kaplan–Meier curves, with comparison of groups A and B by the log-rank test). VR was defined as two consecutive HIV RNA values of >50 copies/mL after baseline. The proportion of VR between group A and B was compared by the chi-square test.

Patients who changed any of the antiretroviral drugs in their regimen during follow up while their HIV RNA load was

<50 copies/mL were censored (and follow up was interrupted) at the time of the switch.

The multivariable analysis was performed using the Cox regression proportional hazard model. The outcome was the occurrence of VR.

All of the statistical tests were two-sided at the 5% level, and were performed using SAS Software (release 9.2; SAS Institute, Cary, NC, USA).

There were 739 eligible patients; at baseline, 446 (60.3%) had undetectable HIV RNA (group A) and 293 (39.7%) had RV (1–49 HIV RNA copies/mL, group B). During a median (interquartile range) follow up of 30.8 (11.7–32.9) months, 122 (27.4%) patients in group A and 81 (27.7%) patients in group B stopped at least one drug of the baseline regimen while their HIV RNA was <50 copies/mL.

Virological rebound occurred in 16/739 (2.17%) patients, 4/446 (0.9%) in group A and 12/293 (4.1%) in group B (p 0.007). Patients with RV at baseline had a higher probability of VR (log-rank test: p 0.003, Fig. 1a).

One hundred and sixty-four (36.8%) patients in group A were able to maintain undetectable HIV RNA throughout the entire follow up, whereas the remaining 282 (63.2%) had at least one episode of RV during follow up. Four (1.4%) patients in group B always had HIV RNA values between 1 and 49 copies/mL, whereas 289 (98.6%) had at least one value of undetectable HIV RNA during follow up.

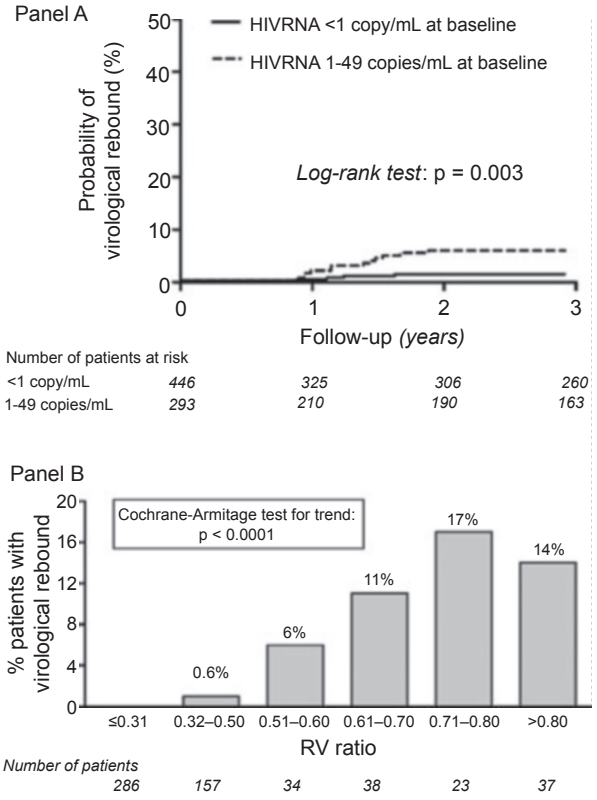

FIG. 1. (a) Time to virological rebound according to study groups. (b) virological rebound according to the residual viraemia ratio during follow up, among 579 patients with at least one episode of residual viraemia during follow up. RV: residual viraemia; pts: patients.

All VRs occurred among patients who had at least one episode of RV during follow up, but none of the four patients who always had RV during follow up showed VR. Almost all VRs were observed in patients with an RV ratio of >0.5 during follow up (Fig. 1b).

In the 16 patients who showed VR, the median (interquartile range) VL at VR was 165 (73–1141) copies/mL. Resistance testing at VR was available in 4/16: a wild-type virus was detected in one case and drug-resistance mutations were found in the remaining three. Nine out of 16 had changed treatment after VR, whereas seven were able to attain <50 copies HIV RNA/mL without changing treatment. All the 16 patients who showed VR were beyond the first-line regimen.

The results of the multivariable analysis are illustrated in Table 1.

Consistently with more recent studies [2,3], this extended follow up showed that RV favours VR; in particular, RV confers roughly a four-fold risk of VR and the risk of VR increases with increasing episodes of RV during follow up. Nevertheless, and in contrast with another study [2], the VR rate remained extremely low, even among patients with RV. These findings prompt the question as to whether treatment should be changed in the presence of RV.

At present, no clinical trial supports a change in the current antiretroviral regimen in a patient with <50 HIV RNA copies/

TABLE 1. Risk of virological rebound from fitting a multivariate Cox proportional hazard model

Characteristic	HR	95% CI	p-value
Gender (male versus female)	0.343	0.086–1.361	0.128
Age (<50 years versus ≥50 years)	2.862	0.589–13.898	0.192
IVDU versus UKN/other	1.861	0.318–10.872	0.491
Heterosexual versus UKN/other	1.676	0.293–9.584	0.562
MSM versus UKN/other	4.630	0.751–28.535	0.099
HIV stage C3 (no versus yes)	3.769	0.770–18.459	0.102
Years of ARV (per 5 years longer)	1.262	0.748–2.128	0.383
Duration of last ARV regimen (per year longer)	0.994	0.674–1.466	0.974
Detectability ratio up to BL	23.693	1.647–340.771	0.020
Nadir $CD4^+$ cell count (≤200 versus >200 cells/μL)	3.745	1.013–13.841	0.048
BL $CD4^+$ (per 100 cells/μL higher)	1.028	0.845–1.251	0.781
RV (group B) versus 'undetectable' (group A) at BL	3.862	1.137–13.116	0.030
NRTI-based versus PI/r-based regimen at BL	1.356	0.143–12.894	0.791
NNRTI-based versus PI/r-based regimen at BL	0.633	0.115–3.488	0.600
Unboosted-PI versus PI/r-based regimen at BL	1.441	0.401–5.180	0.576

ARV, antiretroviral therapy; BL, baseline; HIV, human immunodeficiency virus; HR, hazard ratio; IVDU, intravenous drug user; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI/r, boosted protease inhibitors; RV, residual viraemia; UKN, unknown.

mL and, in general, in a patients with RV the risks of new untoward effects with a different regimen are likely to be higher than the risk of VR, at least based upon data from patients starting their first antiretroviral regimen [4,5]. Furthermore, it would be very difficult in a patient with VLs alternating between RV and maximal viral suppression to identify 'the right moment' to change treatment. It would also be extremely difficult to decide whether the change should involve a single drug in the regimen or the entire regimen with no available data to support the decision.

Treatment intensification with a fourth drug is not supported by available data [6–8].

As the detectability ratio is an index of exposure to viral replication, it is not surprising that its highest impact is on the risk of VR. The fact that the risk of VR due to previous exposure to HIV replication was higher than that due to presence of RV adds further support to the hypothesis that patients with RV do not have relevant ongoing replication in most cases.

Many clinical trials and cohort data have shown that a low nadir $CD4^+$ cell count is associated with a worse virological response and so it not surprising that it is also associated with a higher risk of VR [9–12].

In conclusion, RV favoured VR through almost 3 years of follow up; however, the rate of this event remained extremely low, even among patients with RV. The frequency of episodes of RV had significant effect on VR.

Authorship/Contributions

Nicola Gianotti conceived the study, collected the data and wrote the first draft of the manuscript; Laura Galli performed the statistical analyses and wrote the first draft of the manuscript; Stefania Salpietro collected and managed the data; Massimo Cernuschi, Simona Bossolasco, Vincenzo Spagnuolo, Myriam Maillard and Adriano Lazzarin collected the data and contributed to the writing of the manuscript; Filippo Canducci and Massimo Clementi performed the laboratory tests and contributed to the writing of the manuscript; Antonella Castagna conceived the study, collected the data and contributed to the writing of the manuscript.

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Transparency Declaration

The authors declare no conflicts of interest.

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