Title
Impact of transient viremia and treatment interruptions on clinical progression

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Introduction
In many patients who achieve sustained suppression of HIV RNA to levels <50 cp/ml on combination antiretroviral therapy (cART), transient periods of low-level viremia are observed. The impact of these often short-lasting episodes of viremia on disease progression appears to be limited. In this analysis, we investigated the impact of both low-level and high-level viremia as well as treatment interruptions on disease progression and immunologic response.

Methods
From the ATHENA national observational cohort, 2546 previously therapy-naïve patients were selected who had RNA plasma levels <50 cp/ml at baseline, i.e. 24 weeks after starting cART. After baseline, episodes of viremia started when RNA rose above 50 cp/ml and ended when RNA returned to <50 cp/ml, which marked the start of a (new) period of suppression. Periods of viremia were subdivided into low-level (median RNA 50-1000 cp/ml) and high-level (>1000). In addition, periods of treatment interruptions were considered.
The association between periods of viremia and interruptions and endpoints – death, AIDS/death, or immunologic response (CD4 cell count increase ≥100 cells/mm^3 from baseline) – was studied using discrete time hazard models, adjusting for age, gender, transmission risk, region of origin, and CD4 counts at 24 weeks. Periods of viremia and interruptions were included as time-updated variables, either as the cumulative fraction of follow-up time spent in each type of period (cumulative model) or as indicator variable of the most recent period, distinguishing short (<3 months) or long (≥3 months) periods of viremia (immediate effect model). Generalising estimating equations were used to account for correlation between observations within one patient.

Results
During 18,870 person-years of follow-up, 49 patients died, 69 patients developed a new AIDS event, and 1728 had a CD4 cell increase ≥100 cells/mm^3. For the cumulative models, treatment interruptions were associated with higher risk of death (hazard ratio (HR) 1.25; 95% confidence interval (CI) 1.05-1.49 per 10% increase in fraction of time) and death/AIDS (HR 1.28; 95% CI 1.17-1.40), and a reduced probability of CD4 increase (0.78; 0.73-0.84) compared to episodes of suppression. Analogously, periods of high-level viremia were associated with a worse clinical outcome (death: 1.18, 0.92-1.52; AIDS/death: 1.26, 1.12-1.43; CD4 increase: 0.89, 0.84-0.95), whereas no significant association between periods of low-level viremia and outcome was observed.

Due to the limited number of events, the immediate effect models could not be estimated for the endpoints death and AIDS/death. The effect of interruptions and both short and long-lasting high-level viremia in the immediate effect model on CD4 increase were similar as in the cumulative models. Short-lasting periods of low-level viremia were associated with a better immunologic response (1.49, 1.16-1.91; p=0.002), whereas for long-lasting low-level viremia no difference was observed compared to periods with suppressed viral load (0.97, 0.77-1.21; p=0.8).

Conclusions

Treatment interruptions and high-level viremia are strongly associated with progression to death and AIDS, and with a smaller probability of CD4 restoration. Our finding that short-lasting low-level viremia is associated with a better immunologic response is in accordance with results of studies of short-lasting structured therapy interruptions.