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GBV-C infection clear because HIV-1 disease progression lowers the CD4+ cell count? Van der Bij et al. conclude the latter and suggest that the presence of GBV-C is a marker for the CD4+ cell count and is not beneficial. However, previous studies have found that GBV-C infection is associated with prolonged survival in subjects with very low CD4+ cell counts (figure 1) [7] and in subjects classified as having AIDS when first tested for GBV-C [4, 7]. To date, published data do not fully explain the mortality associated with the loss of GBV-C infection; however, no study has fully accounted for the timing of GBV-C clearance and HIV-1 disease progression, and further work is needed to understand the relationship between them.

Several in vitro studies have identified mechanisms by which GBV-C may alter HIV-1 disease progression. GBV-C exerts an inhibitory effect on HIV replication in vitro [7–9], and GBV-C infection and exposure of cells to the GBV-C envelope glycoprotein E2 results in induction of anti-HIV chemokines and down-regulation of the HIV coreceptor CCR5 [8–10]. These mechanistic data provide biological plausibility to support the hypothesis that GBV-C infection is causally related to the improvement in survival observed in HIV-infected populations [3, 5, 7].

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References


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Reply to George and to Stapleton et al.

To the Editor—We recently demonstrated that loss of GB virus C (GBV-C) RNA was associated with HIV-1 disease progression [1], confirming the results of other recent studies [2, 3]. Williams et al. [3] also observed an association between persistence of GBV-C RNA and slower HIV disease progression, relative to individuals who lack GBV-C RNA. We did not observe this in our study.

In the letters by George [4] and Stapleton et al. [5] written in response to our study, concerns are raised about the imputation method used to determine the date of HIV-1 seroconversion. We fully agree that a date of HIV-1 seroconversion cannot be determined on the basis of the CD4+ cell count at entry if the cofactor of
interest is correlated with the CD4+ cell count. This is considered to be a problem of the marker-based approach [6]. Therefore, the imputed date of HIV-1 seroconversion was derived from a cohort-based estimate of the date of HIV-1 seroconversion and was not based on the CD4+ cell count [7]. Geskus [7] showed that, for the Amsterdam Cohort Study, a conditional mean imputation based on the cohort HIV-1 seroincidence curve gives unbiased results and that the uncertainty in the date of seroconversion hardly changes P values and confidence intervals (CIs). Moreover, in our study, similar results were obtained when the analysis was restricted to seroconverters (n = 123) [1]. For instance, the unadjusted hazard ratio (HR) for death in men who lost GBV-C RNA, compared with men who had no evidence of GBV-C infection, was 3.00 (95% CI, 1.60–5.61) in seroconverters and was 3.26 (95% CI, 2.31–4.59) in the total group. The HR decreased toward 1 when adjusted for time-updated CD4+ cell count in seroconverters (HR, 0.66 [95% CI, 0.28–1.51] and in the total group (HR, 1.21 [95% CI, 0.84–1.76]) [1].

We do agree with Stapleton et al. that the date of change in GBV-C status was imputed with a large degree of uncertainty. Therefore, we assessed the robustness of our findings by varying the time of GBV-C RNA loss. George raises concerns about the completeness of our data. However, CD4+ cell counts were available for all seroconverters at 12–18 months after HIV-1 seroconversion and for most of the subjects entering the Amsterdam Cohort Study already infected with HIV-1 within 2 years after HIV-1 seroconversion, which is only 6 months after the maximum time at which Williams et al. measured baseline CD4+ cell counts [3]. During follow-up, CD4+ cell counts were measured every 3 months. Information on yearly HIV-1 load was available for almost all subjects already infected with HIV-1. In addition, information on HIV-1 load at baseline was available for almost all subjects already infected with HIV-1. If the HIV-1 load was unavailable, it was obtained from a random-effects model for the joint development of CD4+ cell count and HIV-1 load, which is a reliable method to estimate viral load [8].

George and Stapleton et al. also comment that, in our study, the CD4+ cell counts at baseline in subjects with GBV-C infection were significantly lower than those in subjects without GBV-C infection and raise concerns about whether subjects positive for GBV-C RNA and subjects negative for GBV-C RNA were matched for the duration of HIV-1 infection. However, in our cohort, subjects positive for GBV-C RNA and subjects negative for GBV-C RNA were homogeneous in their duration of HIV-1 infection at the time the baseline CD4+ cell count was obtained (table 1). In addition, in the seroconverters, CD4+ cell counts at baseline were also significantly lower in subjects positive for GBV-C RNA than in those negative for GBV-C RNA (P = .033).

George interpreted a significant benefit of GBV-C acquisition on HIV-1 disease progression from our data. However, in table 3 in our study, 95% confidence intervals (CIs) for each category of GBV-C status—and not overall P values for GBV-C status—should be used to evaluate the significance of GBV-C acquisition. Because 1 was always within the 95% CI of the hazard ratio, the data in our study do not support a significant effect of GBV-C acquisition on HIV-1 disease progression. Similarly, in model 1 of table 3, the data do not show a significant benefit of GBV-C RNA persistence on progression from AIDS to death (HR, 0.66 [95% CI, 0.40–1.11]). Indeed, we did observe that GBV-C RNA persistence was associated with a decreased risk of death in models 1, 2, and 3 of table 3 (not on the basis of P < .0001, which, again, is the overall P value) but not with any of the other end points. However, the beneficial effect of GBV-C RNA persistence on progression to death disappeared when adjusted for time-updated CD4+ cell counts during follow-up—which George and Stapleton et al. considered to be invalid. However, this is exactly what confusing is about. Indeed, it is invalid to control for a variable that is an intermediate step in the causal pathway between exposure and disease if exposure is the variable of interest [9], but we adjusted for time-updated CD4+ cell counts and HIV-1 load to explore possible causal pathways. Because the effect of GBV-C RNA persistence and loss largely disappeared when adjusted for time-updated CD4+ cell counts, our study gives a possible explanation for the effects found: either the CD4+ cell count is an intermediate step in the causal pathway between GBV-C infection and HIV-1 disease progression or the effect of GBV-C infection can be explained by changes in CD4+ cell counts during follow-up, suggesting that

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Negative for GBV-C RNA</th>
<th>Positive for GBV-C RNA</th>
<th>P a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since seroconversion at which baseline CD4+ cell count was measured</td>
<td>23.9 (12.1–29.0) 21.5 (12.4–28.4)</td>
<td>24.3 (13.6–28.3) 26.6 (16.8–29.0)</td>
<td>.11</td>
</tr>
<tr>
<td>Baseline CD4+ cell count, cells/μL</td>
<td>600 (390–780) 595 (457–822)</td>
<td>490 (360–710) 550 (450–730)</td>
<td>.03</td>
</tr>
</tbody>
</table>

NOTE. Data are median (interquartile range), unless otherwise indicated.

a Kruskal-Wallis test.
GBV-C infection is associated with high CD4+ cell counts. The latter hypothesis seems biologically more plausible, because GBV-C can replicate in CD4+ cells [10]. The loss of CD4+ cells during the course of HIV-1 infection, therefore, implies a loss of target cells for GBV-C.

In conclusion and in agreement with the results of a study by Bjørkmann et al. [2], our study provides evidence to support the hypothesis that GBV-C RNA loss is a consequence of—and not a cause of—CD4+ cell loss. We fully agree with Stapleton et al., however, that further studies, with frequent measurement of GBV-C load in each individual, are required to fully understand the relationship between GBV-C infection and HIV-1 disease progression.

**References**


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