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CD4+ cell counts in men with known dates of HIV seroconversion [3] and also with lower HIV RNA loads [3, 5]. This indicates that the CD4+ cell counts and HIV RNA loads are not exogenous to (or independent of) GBV-C infection, but they are likely to be part of the causal pathway by which GBV-C infection influences survival in those infected with HIV; adjustment for these time-varying covariates is therefore inappropriate [6]. Additionally, for those whose GBV-C status changed, the date of change was imputed from only 2 or 3 measurements, typically taken years apart [1]. The uncertainty in the actual date of GBV-C acquisition or clearance, like that of the date of HIV-1 seroconversion, was not accounted for [1].

3. The results of Van der Bij et al.’s study confirm the results of 2 studies in which mortality rates were significantly greater in individuals who lost GBV-C infection than in individuals who were persistently negative for GBV-C infection [3, 4]. Is the increased risk of death due to the loss of GBV-C infection, or does 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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Figure 1. Survival in HIV-infected individuals with CD4+ cell counts ≤50 CD4+ cells/mm3, stratified by GB virus C (GBV-C) infection status. Data represent Kaplan-Meier survival curves for subjects who entered the University of Iowa HIV Clinic with CD4+ cell counts ≤50 cells/mm3. GBV-C RNA testing was performed on the date of CD4+ cell count testing (first visit to the clinic), and mortality in the GBV-C RNA-positive group (11/28; 44%) was significantly lower than that observed in the GBV-C RNA-negative group (38/48; 75%) (2-tailed P = .01). Note that 32% of patients entering the clinic with CD4+ cell counts ≤50 cells/mm3 had GBV-C infection. Adapted and reprinted with permission from [7].

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
study already infected with HIV-1 within subjects entering the Amsterdam Cohort HIV-1 seroconversion and for most of the subjects in subjects without GBV-C infection, that is an intermediate step in the causal pathway between GBV-C infection and HIV-1 disease progression. 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 in subjects with 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 confounding 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 1. Median and time of baseline CD4+ cell counts in 326 HIV-1–positive homosexual men, according to their GB virus C (GBV-C) RNA and envelope protein–2 antibody (E2-Ab) status shortly after HIV-1 seroconversion.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Negative for GBV-C RNA</th>
<th>Positive for GBV-C RNA</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since seroconversion at which the baseline CD4+ cell count was measured</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 68)</td>
<td>(n = 121)</td>
<td>(n = 124)</td>
<td>(n = 13)</td>
</tr>
<tr>
<td>23.9 (12.1–29.0)</td>
<td>21.5 (12.4–28.4)</td>
<td>24.3 (13.6–28.3)</td>
<td>26.6 (16.8–29.0)</td>
</tr>
<tr>
<td>600 (390–780)</td>
<td>595 (457–822)</td>
<td>490 (360–710)</td>
<td>550 (450–730)</td>
</tr>
</tbody>
</table>

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

* 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 Bjorkman 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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