eterious effect that the loss of GBV-C infection without the accompanying development of GBV-C envelope protein–2 antibodies has on survival, which was observed by others [4, 6]. This again confirms that persistent GBV-C infection is beneficial.

Van der Bij et al. are to be commended for examining the effect that GBV-C acquisition has after HIV-1 seroconversion; previous studies have not included enough patients who had acquired the infection after seroconversion to allow for evaluation of this issue. Again, however, Van der Bij et al. show in table 3 that there is a statistically significant beneficial effect of GBV-C acquisition on the HR of first CD4+ cell count <200 cells/μL (HR, 0.34, 0.33, and 0.52), AIDS (HR, 0.56, 0.74, and 0.79), and death (HR, 0.35, 0.53, and 0.44) in models 1, 2, and 3, respectively, and progression from AIDS to death in model 1 (HR, 0.56).

In summary, contrary to Van der Bij et al.’s interpretation, the ACS does show that persistent GBV-C infection has a beneficial effect on HIV-1 disease progression—in accordance with the results of other studies—when the effect is not adjusted for causal variables associated with GBV-C infection, which is statistically invalid [2]. The results of Van der Bij et al.’s study also confirm previous findings regarding the deleterious effect that the loss of GBV-C infection has, and it is the first study to show that GBV-C acquisition has a statistically significant benefit after HIV-1 seroconversion has occurred.

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References

GB Virus C Infection and Survival in the Amsterdam Cohort Study

To the Editor—Research on the interaction between GB virus C (GBV-C) infection and HIV infection stems from 2 conflicting hypotheses. One is that GBV-C infection is causally related to the prolonged survival observed in many studies of HIV-positive individuals. The other is that GBV-C infection is present in HIV-positive individuals with preserved CD4+ cell counts because these T cells are necessary to support GBV-C replication, and thus, GBV-C infection is simply a marker of CD4+ cell preservation in individuals with HIV infection. Van der Bij et al. examined the relationship between GBV-C coinfection and survival in the HIV-1–infected subjects in the Amsterdam Cohort Study (ACS) [1] and concluded: “GBV-C infection does not seem to protect against either CD4+ cell loss or HIV-1 disease progression” (p. 684). We believe that these conclusions are not justified, for the following reasons.

1. To study the association between GBV-C infection and HIV-1 disease progression, it is important to accurately know the duration of HIV-1 infection. No HIV-1 seroconversion window was available for 62% of the ACS participants, although seroconversion was imputed on the basis of the first available CD4+ cell count [2]. The imputation method used to estimate the date of HIV-1 infection in the ACS participants assumed a homogeneous population with similar changes in CD4+ cell counts after HIV-1 seroconversion. In fact, according to table 1 in Van der Bij et al.’s study [1], ACS participants with GBV-C infection at the time their first available serum sample was tested had ~100 fewer CD4+ cells/μL than did those without GBV-C infection (P = .03). This raises the distinct possibility of heterogeneity in the duration of HIV-1 infection or in disease progression between those with and without GBV-C infection. The uncertainty in the date of HIV-1 seroconversion calls into question any conclusions concerning the effect of GBV-C infection on HIV-1 disease progression, and the imbalance in the CD4+ cell counts raises the possibility of bias [1]. Previous work in populations with documented dates of HIV seroconversion found a trend toward an association between early GBV-C infection and prolonged survival [3, 4].

2. Van der Bij et al. concluded that persistent GBV-C infection is not associated with a beneficial effect, because, when controlling for the time-updated CD4+ cell count, HIV-1 RNA load, and GBV-C status in a Cox proportional hazards model using time-varying covariates, the significantly prolonged survival observed in subjects with persistent GBV-C infection in models 1, 2, and 3 in table 3 was no longer statistically significant in model 4 [1]. This outcome is consistent with the hypothesis that GBV-C infection influences HIV-1 disease progression via preservation of CD4+ cells and/or control of HIV-1 viremia. Persistent GBV-C infection has previously been shown to be associated with slower rates of decline in

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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].

**Figure 1.** Survival in HIV-infected individuals with CD4+ cell counts ≤50 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 (11/25; 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].

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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