Reply to Manfredi

To the Editor—We read with interest the comments of Manfredi. The aim of our study was to determine the seroprevalence of cytomegalovirus (CMV) antibodies among human immunodeficiency virus (HIV)–positive subjects in the ICONA cohort and to define the impact of CMV serostatus on the risk of AIDS and severe non-AIDS events/death. Although we agree that our analysis has several limitations, mentioned in the discussion section of the article [1], we believe that we have contributed useful new data to the debate about whether CMV infection might be associated with the risk of clinical progression in HIV-infected individuals.

CMV is a herpes virus characterized by persistence in a latent state, resulting in lifelong infection [2]. Chronic CMV infection is diagnosed on the basis of detection of persistently positive CMV

immunoglobulin G (IgG) antibodies, which can be detected in immunodeficient individuals and elderly individuals, except those with common variable immunodeficiency [3]. There is incontrovertible evidence that CMV infection has an important role in human immunity [4]. As shown by many studies, there is a significant correlation between the increase in $CD57^+$ and $CD28^-$ T cells and CMV IgG antibody positivity [5–7]. These cells, characterized by short telomeres, loss of CD28 expression, and/or gain of CD57 expression, play a significant role in various conditions associated with chronic immune activation, such as cancer and autoimmune diseases [8, 9]. Because of these findings, CMV serostatus (and not, for example, T-cell–specific CMV response or level of CMV viremia) was included in the immune risk phenotype markers panel, a cluster of immune markers predictive of increased mortality in elderly individuals. For these reasons, we believe that it is appropriate to use CMV serostatus as a marker of CMV chronic infection, assessed by a standard test for anti-CMV IgG used in clinical practice.

Manfredi also pointed out that a limitation of our study is the cumulated time elapsed from the CMV-positive serologic test until the occurrence of end-point events. Our analysis was, indeed, performed using the data from a large cohort of HIV-positive, disease-free Italian subjects monitored for almost 6 years, on average (interquartile range, 2–10 years), until they developed AIDS or a severe non–AIDS-defining event/death. It is also true that a single measurement of CMV antibodies was used in the analysis, which, in most cases, was performed at enrollment (baseline) and that, therefore, potential new incident CMV infections occurring after baseline were ignored. However, previous observations showed that the CMV seroconversion rate over time is low [10], so current exposure might have been potentially misclassified only for a minority of our population. Moreover, although it is true that clinical progression can be determined by many events over follow-up, it was originally hypothesized that would take several years for chronic CMV infection to influence the analyzed clinical outcomes. Indeed, CMV serostatus was evaluated at baseline with the aim of assessing whether it was a predictor of the risk of clinical progression independently of other classical factors (eg, nadir $CD4^+$ T-cell count, Centers for Disease Control and Prevention HIV disease stage, and age). To reduce bias due to these potential confounding factors, in particular for the risk of cardiovascular and cerebrovascular disease, we conducted a multivariable analysis. Moreover, we also explored the potential confounding role of smoking status. In contrast, the interpretation of the association between CMV serostatus, fitted as a time-dependent covariate, and the risk of progression is not free of caveats and potentially requires sophisticated modeling able to correctly control for potential time-dependent confounding factors affected by CMV seroconversion, which was beyond the scope of our analysis.

Finally, Manfredi was surprised by the absence of an association between positive anti-CMV serostatus and AIDS events/death. Most people included in the analysis achieved viral suppression during antiretroviral therapy (ART) and showed a good recovery in the $CD4^+$ T-cell count. CMV reactivation with clinical manifestations are typical of severe immunodeficiency, which is uncommon among ART recipients. In fact, the natural history of CMV infection has changed in terms of viral replication and reactivation as a result of suppression of HIV replication and improved patient immunity.

In conclusion, we think that our analysis contributes to existing knowledge regarding the role of CMV in HIV disease progression. Indeed, it is the first large cohort study in which CMV/HIV-coinfected individuals were compared to HIV-monoinfected individuals in terms of their risk of future morbidity and mortality. The analysis provided strong evidence that coinfected persons are at higher risk for severe non–AIDS-related events/death than those with HIV monoinfection. Additional studies are needed to investigate the possible mechanisms through which CMV might increase this risk and whether CMV coinfection should be considered for inclusion in scores for the prediction of severe non–AIDS-related events.

Notes

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