Reply to Itaya et al

To the Editor—We are grateful for the opportunity to respond to the correspondence of Itaya et al [1] on the role of the apolipoprotein B messenger RNA (mRNA) editing enzyme, catalytic polypeptide-like 3B (APOBEC3B) gene deletion in human immunodeficiency virus (HIV) acquisition and clinical outcome in Asians. Previously we reported that the homozygous deletion of the entire APOBEC3B gene might be a risk factor for HIV infection and disease progression in European Americans [2]. Because of the low allele frequency of the deletion in African and European populations, the power of our study was limited by the small number of individuals carrying two copies of APOBEC3B deletions. However, the consistency of the statistically significant associations of the APOBEC3B homozygous deletion (del/del) genotype with unfavorable outcomes for HIV infection and disease progression were supportive of a role for APOBEC3B—the only member of the APOBEC3 family that is both resistant to degradation by HIV Vif and that has anti-HIV activity in vitro [2]. Although our results require replication to rule out false positive associations, we do not believe the study by Itaya et al [1] offers convincing evidence to either support or refute the role of the APOBEC3B gene deletion in HIV infection or disease progression.

To test for susceptibility to HIV-1 infection, the Itaya et al study [1] compared healthy donor control subjects to a group of HIV-1-infected individuals [1]. We argue that such a design is inappropriate. First, the control subjects were not exposed to HIV-1; if they had been exposed, then the overall chance of infection for these individuals would have been very high and not becoming infected would have been the rarer condition. In our study [2], we observed the absence of the APOBEC3B del/del genotype among subjects in the HIV-1 exposed, uninfected control group; this group is not considered by Itaya et al [1]. Second, the group of Japanese HIV-1-positive case patients represents individuals with hemophilia who were infected in the early 1980s with HIV-1 and who were enrolled in the study in 1995 [3]. The most susceptible group (ie, those hypothesized to carry the APOBEC3B del/del genotype) would be more likely to succumb to AIDS before enrollment—contributing to frailty bias in this group. The use of a full range of HIV progressors would provide a more accurate determination of the genotype distribution in the group of HIV-1-infected case patients. A test of the infection hypothesis that uses a group of case patients among whom APOBEC3B del/del carriers may be underrepresented and a group of control subjects who are not exposed to HIV-1 infection is unlikely to detect meaningful differences in APOBEC3B genotypes.

Selection of the appropriate control group is an important issue in the design of epidemiological studies to detect host genetic factors in infectious diseases and is worthy of careful consideration. For those pathogens that are highly prevalent or ubiquitous in the population (eg, hepatitis B virus among Asians), the use of a population control group may be justified; but in the case of HIV-1 infection, prevalence rates in the general population are generally quite low, and a more appropriate control group is one comprising individuals who have been exposed to HIV-1 but are uninfected. Certainly, a control group from the general population nearly always leads to a loss of power if the prevalence of exposure is low.

A similar situation, due to frailty bias, occurs in the assessment of the association between the APOBEC3B del/del genotype and disease progression. The group of Japanese HIV-1-positive case patients represents a group of individuals who survived for at least 10 years prior to study enrollment; individuals who progressed to AIDS and death prior to the 1995 enrollment date would be missing. No information was provided about the group of Indian HIV-1-infected individuals. In addition, the duration of infection was not accounted for in this study. Viral loads and CD4+ T cell counts in HIV-1-infected individuals vary greatly, depending on the length of time since infection and the clinical stage of HIV-1 disease. The authors do not state how the viral loads and CD4+ T cell counts were determined (eg, at baseline, at set point, or averaged across all time points). Comparison of the viral loads and CD4+ T cell counts of individuals who represent different durations of infection would undermine the power to detect differences in APOBEC3B genotypes associated with progression.

Although early reports indicated that APOBEC3B is not expressed in lymphoid cells targeted by HIV [4, 5], more recent studies have shown APOBEC3B mRNA expression in activated CD4+ T cells and lymphoid cells [6–8], although at expression levels that are 50% lower than those of either APOBEC3F or APOBEC3G [8]. It was further found that human APOBEC3B mRNA levels were higher in HIV-negative individuals and in slow progressors than in patients with AIDS, and that these levels were positively correlated with CD4+ T cell count and negatively correlated with HIV-1 viral load.
and disease progression among HIV-1-infected persons [8].

In summary, appropriately designed and well-powered studies in different populations are required to assess the effect of the APOBEC3B deletion on HIV-1 infection or disease progression.

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References


Potential conflicts of interest: none reported.

Financial support: Intramural Research Program, Center for Cancer Research, National Cancer Institute (grants HHSN261200800001E and N02-CP-55504); National Institute on Drug Abuse (grants R01-DA04334 and R01-12586).

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The Journal of Infectious Diseases 2010;202(5):816–818 © 2010 by the Infectious Diseases Society of America. All rights reserved. 0022-1899/2010/20205-0022$15.00 DOI: 10.1086/655228