LETTER

Reply to Pomara *et al.* and Valcour *et al.*: Age and the *APOE* ε4/ε4 genotype in HIV-1-associated dementia

It was encouraging to note that Valcour *et al.* (1) report data in their letter that support our findings (2) regarding the detrimental impact of the *APOE* ε4 allele on HIV disease course. Furthermore, because age is a strong risk factor for developing HIV-associated dementia (HAD) (3), we thank Pomara *et al.* (4) for their inquiry into whether the younger age of the patients we studied in the Wilford Hall Medical Center cohort might account for the failure to detect an association between *APOE* genotype and HAD (2).

Our previous reports had provided extensive clinical characteristics of the cohort (e.g., ref. 5). The age at entry into our cohort (Fig. 1*A*, open bars) was a strong predictive factor of time to HAD (Fig. 1*B*). Fifty-four (≈5%) of the 1,126 subjects developed HAD (age at diagnosis is shown in Fig.1*A*, filled bars), a proportion similar to that observed in the United States in the pre-HAART (highly active antiretroviral therapy) era (6). None of these 54 subjects had received HAART, one had the *APOE* ε4/ε4 genotype, and 11 were heterozygous for the *APOE* ε4 allele. The prevalence of *APOE* genotypes did not change with age (Fig. 1*C*). Furthermore, compared to those with a non-ε4/non-ε4 genotype, the relative hazard (RH) for the rate of progression to HAD for patients possessing the *APOE* ε4/ε4 genotype was 0.90 [95% confidence interval (CI) = 0.12–6.57, $P = 0.919$] for subjects >30 years of age and 1.86 (95% CI = 0.25–13.9, $P = 0.546$) for subjects >40 years of age. Finally, when age at recruitment was included as a covariate in multivariate Cox proportional hazards model, an association between the *APOE* ε4/ε4 genotype and rate of progression to HAD was still not detected (RH = 0.96, 95% CI = 0.13–7.01, $P = 0.969$).

Collectively, these findings underscore that, even after accounting for age, there was no association between the *APOE* ε4/ε4 genotype and HAD, and this negative association could not have been due to treatment with HAART as argued previously (7). Therefore, additional studies are warranted to elucidate the relationship between the *ApoE* ε4 allele and HAD susceptibility, especially because, contrary to their expectations, Pomara *et al.* (4) find that this allele is associated with better neurocognitive performance. Moreover, in the same cohort that we used to study the role of *APOE* alleles, homozygosity for the *MCP-1* (*CCL2*) *−2578G* allele was associated with an increased risk of HAD. Hence, it is conceivable that, because HIV is usually acquired at a younger age, host factors that affect initiation of HAD in younger patients (e.g., MCP-1-mediated increased monocyte recruitment to the brain or microglial activation) might be different from those factors that heighten susceptibility to dementia (including HIV-associated dementia) in older HIV-positive subjects. In this respect, the *ApoE* ε4 allele is a determinant of many forms of dementia and cerebrovascular disease, including Alzheimer's disease, which typically occurs in the elderly. Consequently, the risk of dementia from any cause, including HAD, which shares many features with age-associated dementias, might be increased in those older HIV-positive subjects who also possess the *APOE* ε4 allele.

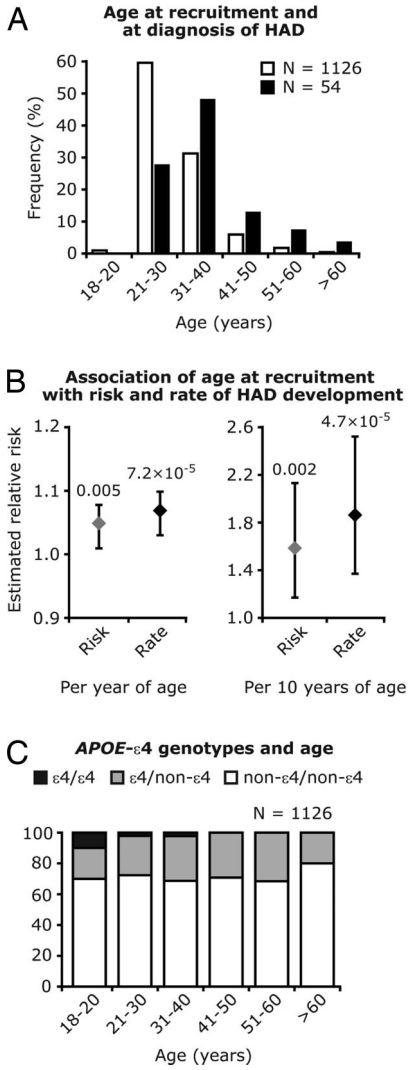

Fig. 1. Age and *APOE* genotypes in the study cohort. (*A*) Distribution of age at time of recruitment (open bars) into the Wilford Hall Medical Center (WHMC) cohort and at the diagnosis of HAD (filled bars). The mean age ± SD at cohort entry was 29.9 ± 7.2 years, and the mean age ± SD at diagnosis of HAD was 36.37 ± 9.42 years. (*B*) Association of age at entry into the cohort with the risk and rate of developing HAD. Age at entry was treated as a continuous variable (*Left*) and as 10 yearly categories (*Right*). The diamonds and error bars represent the point and 95% CI estimates, respectively. Gray color indicates odds ratios estimated from logistic regression analyses for the outcome of ''risk'' of HAD, and black color indicates the relative hazards estimated from the Cox proportional hazards modeling for time to HAD (denoted as ''rate'' on the *x* axis). The numbers above the error bars indicate the significance values from respective regression models. (*C*) Prevalence of *APOE* genotypes based on the age at recruitment into the cohort. *P* for linear trend using χ^2 test for the prevalence of the *APOE* ε4/ε4 genotype was 0.2147. *N*, number of HIV-positive subjects.

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The authors declare no conflict of interest.

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