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Reply to Karch et al

To the Editor—We appreciate the interest by Karch et al [1] in our study of raltegravir intensification in treated human immunodeficiency virus (HIV)–infected patients [2]. Our study showed that intensification resulted in a rapid and transient increase in the level of 2–long terminal repeat (2-LTR) circles in a proportion of treated HIV-infected subjects, suggesting that low-level viral replication persists in some individuals even after long-term antiretroviral therapy. Intensification also reduced the level of D-dimer, a coagulation biomarker that has been shown to be predictive of morbidity and mortality among treated HIV-infected individuals [3].

We performed a randomized, double-blind, placebo-controlled trial as described [2], making it the first such study to show that intensification led to an increase in the level of 2-LTR circles and a decrease in D-dimer. Our findings were consistent with those of a previous open-label, randomized study of raltegravir intensification, which showed that intensification led to an increase in the level of 2-LTR circles [4].

Karch et al [1] correctly noted a lack of clarity in our clinicaltrials.gov entry; we have edited it to clarify the study structure. We performed 2 independent, randomized, double-blind, placebo-controlled intensification studies (one in “immunologic nonresponders” [n = 30] [5] and the other in “immunologic responders” [n = 31] [2]). All subjects from both studies were offered coenrollment into a cardiovascular study before randomization to evaluate whether raltegravir intensification led to an improvement in endothelial function; the cardiovascular outcomes from both intensification studies have been published elsewhere [6].

The impact of raltegravir intensification on the dynamics of 2-LTR circles has been controversial. Other intensification studies that measured 2-LTR circles at later time points have failed to show changes in 2-LTR circles, perhaps because they were measured too late after intensification was initiated (at 4 weeks [7] and 12 weeks [8] after intensification). Given the discrepant results of these previous studies [4, 7, 8], our second intensification study in immunologic responders was specifically designed to obtain samples from very early time points (weeks 1 and 2) [2]; our first intensification study in immunologic nonresponders had already begun enrollment, so 2-LTR data were not collected or analyzed for that study [5]. The 2-LTR data in our recent article [2] were, therefore, obtained only from our second intensification study in immunologic responders and hence do not represent a “nonspecified subgroup.”

Our most recently published raltegravir intensification study was an independent, randomized, double-blind, placebo-controlled study, with enrollees required to meet inclusion and exclusion criteria, as described before randomization [2]. Thus, any real or perceived imbalances between the raltegravir and placebo groups at baseline were due to random chance. The primary virologic endpoint of the study was an increase in 2-LTR circles at week 1 or 2. This end point was determined a priori (ie, during study design and before any patient enrollment occurred), and specimens were, accordingly and specifically, obtained at early time points (weeks 0, 1, 2, and 8) for measurement of potential changes in 2-LTR circles. All study samples (including those for 2-LTR analysis) were collected and analyzed, and all statistical analyses were completed, before the study code was unlocked. We analyzed all of the 2-LTR data, as shown in our table and figures [2], without imputing values for missing data. Power is widely acknowledged to be irrelevant for interpreting completed studies; the estimates and confidence intervals given in our article permit much more direct and reliable interpretation of our study results than any reasoning involving power calculations [9–11]. The findings of our randomized, double-blind, placebo-controlled study suggest that low-level viral replication may persist in the setting of otherwise effective antiretroviral therapy and may be a modifiable factor in future cure and treatment strategies.

Notes

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Immunity Status Against Influenza A Subtype H7N9 and Other Avian Influenza Viruses in a High-Risk Group and the General Population in India

To the Editor—The article by Boni et al reported higher levels of antibodies against avian influenza A virus subtype H7N9 than against influenza A virus subtype H5N1 in Vietnam [1]. The antibodies against influenza A(H9N2) were highest in the study population [1]. As of May 2013, 131 confirmed cases with 32 deaths in humans with influenza A(H7N9) have been reported from China [2]. The epidemiologic and virologic studies have suggested that poultry exposure may be an important risk factor for influenza A(H7N9) infection in humans [3].

India reported outbreaks of highly pathogenic avian influenza (HPAI) A(H5N1) infection among poultry and wild birds but had no reports of human influenza A(H5N1) infections [4, 5]. The isolation of low-pathogenic avian influenza A(H9N2) from poultry and the sero-prevalence of influenza A(H9N2) in poultry workers have been reported from India [6, 7]. However, there are no reports of isolation of influenza A(H7N9) from birds or humans from India.

There are few reports of serologic studies of influenza A(H7N9) among high-risk groups in China and Vietnam. In India, no such studies have been conducted to trace influenza A(H7N9) infections. We conducted an exploratory study to evaluate the immunity status against influenza A(H7N9), A(H5N1), and A(H9N2) in the following groups: (1) a high-risk group of poultry workers involved in cleaning and disinfection activities during outbreaks of HPAI A(H5N1) infection among wild birds and (2) the general population in India.

A total of 466 serum samples from poultry workers that were available in the repository and 162 serum samples from the general population (the nonrisk group) in Pune were used in this study. The serum samples were from poultry workers in Pune Maharashtra state (n=338) and Jamshedpur (n=128). The samples from poultry workers in Pune were collected between January and November 2010, and samples from those in Jamshedpur were collected during March 2012. Subjects in the nonrisk group were sampled during 2009. The ratio of males to females was 1.84 to 6.44. All participants were aged 15–75 years. The study was approved by the ethics committee at the National Institute of Virology (Pune), and written informed consent was obtained from all study subjects.

A hemagglutination-inhibition (HI) assay and microneutralization (MN) assays were performed for detection of antibodies [8, 9]. The MN assay was not performed for influenza A(H7N9). The viruses used were A/Chicken/Italy/1067/1999(H7N7) (OIE/FAO, Legnaro, Italy), A/Chicken/India/NIV33487/06-RG-2008(H5N1) clade 2.2, A/crow/India/NIV1117307/2012(H5N1) clade 2.3.2.1, A/Hubei/1/2010/H5N1-RG30 clade 2.3.2.1 (kindly provided by Dr Ruben Donis, Centers for Disease Control and Prevention, Atlanta, GA), A/chicken/Pune/099321/2009(H9N2). The full-length hemagglutinin gene nucleotide sequence of the A/Chicken/Italy/1067/1999(H7N1) virus antigen (accession no. GU052938GI:269826292) showed 94% nucleotide homology with the recently isolated A/Shanghai/466T/2013 (H7N9) virus strain (accession no. KF006369.1GI:491874192) from China. The reference antibodies supplied by the World Health Organization (WHO)