About 2 years ago, in a past issue of *Clinical Infectious Diseases*, Geretti et al. [1] reported the virologic and immunologic response to highly active antiretroviral therapy (HAART) in drug-naïve human immunodeficiency virus type 1 (HIV-1) infected patients comparing subtype B (n = 1150) versus non-B (n = 566) in the United Kingdom. Response (<50 copies/mL of plasma of HIV RNA at 1 year) in non-B subtypes (also known as non-B clades) was about 90% and similar, if not better, than for B subtypes at least for the most common subtypes (C, A, CRF_AF, and D). It was a retrospective cohort study. Despite the relatively high sample size adjustment for other confounding factors like ethnicity, it was difficult because the majority (86%) of persons infected with B subtype were whites as opposed to black Africans for the vast majority of non-B subtypes. One of the recommendations of Kosakovsky et al. [2] in an accompanying editorial comment was to “evaluate the impact of host characteristics of the infected population on antiretroviral therapy efficacy and viral subtype.” In this issue of the journal, Scherrer et al. [3] addressed this point using patients included in the Swiss HIV cohort study by restricting the analysis exclusively to Caucasians who received HAART from 1996 to 2009 with or without previous exposure to suboptimal therapies (mono- or bitherapies with nucleoside analogs exclusively). They claimed a significantly better response among non-B subtypes driven by the improved outcome in subtypes A and CRF02_AG and, at least in part, in the subgroups exposed to unboosted protease inhibitors in the early era of HAART. The study [3] has some limitations. Like several studies in non-B subtypes, it is a retrospective unplanned cohort analysis, the subtypes were derived exclusively from the sequence analysis of the reverse transcriptase (RT) and protease (PR) genes, the definition of virological response was relatively unique for this particular study, not all patients had virological determinations at all evaluated time points, and many patients received some drugs (unboosted protease inhibitors) or combinations (zidovudine plus lamivudine; Combivir®) almost no longer in use for new patients in developed countries. The response to HAART of non-B subtypes have already been measured in several additional retrospective cohort studies from Europe [4, 5] and Canada [6] in adults and also in children [7]. Moreover, several recent pivotal registrational studies for new drugs like raltegravir [8], or ritonavir-boosted atazanavir [9] or darunavir [10], comparing with older drugs like efavirenz or ritonavir-boosted lopinavir have addressed the issue of response to HAART in non-B subtypes. All these large studies were randomized and multicenter, including centers from many countries where non-B subtypes are highly prevalent; as a consequence, from 10% to 50% of recruited patients were infected by non-B subtypes. The overall conclusion can be that response rate to combinations, including drugs like efavirenz, ritonavir-boosted lopinavir, atazanavir, or darunavir, or to raltegravir, had been almost identical when B subtypes were compared with non-B subtypes.

Why has the issue of response to HAART among non-B subtypes or even in HIV-2-infected patients become more important? The HIV pandemic (with a total of 33.3 million people living with HIV, 2.6 million people newly infected, and 1.8 million AIDS deaths in 2009) is in fact a conglomerate of several or many overlapping parallel epidemics. At least 3 independent transmission events from nonhuman primates to humans were the origin of the 3 HIV-1 groups—M (major), O (outliers), and N (new or nonmajor nonoutliers)—and have most likely occurred in the first half of the 20th century [11]. One additional transmission event might have been responsible for the HIV-2 infections. Nine subtypes have then been identified within the M group (A1-4, B, C, D, F1-2, G, H, J, and K), plus 43 circulating recombinant forms (CRFs) defined as the detection of at least 3 strains without epidemiological linkage, plus many unique recombinant forms (URFs) when less than 3 unlinked
strains were detected. The URFs may represent up to 10% of the infections in some settings [2]. The overall genetic divergence between clades is about 25%–30%, and up to 10% in the more conserved regions like the RT and PR genes. The explanation may be the lack of proofreading of the HIV RT, the recombination capability in dually infected patients, and the need of the virus to escape from the immune system pressure [11]. The subtype B is the most prevalent in America, Western Europe, and Australia, but when corrected for the estimated number of infected people in these regions, subtype B accounts for no more than 10%–12% of the global HIV epidemic. Globally, the most prevalent subtype is C followed by the CRFs and A [12–14]. Yet, all antiretrovirals in use have been discovered, tested, and largely developed for the treatment of people infected with subtype B. It is true that, since very recently, the vast majority of antiretroviral-treated patients (mostly in developed parts of the world) were infected with subtype B. However, with the recent and very rapid scale-up of antiretroviral therapy, up to 5.2 million people in low- and middle-income countries receive HAART, and patients infected with the B subtype are no longer the largest treated group. Moreover, in western countries like the United States, France, United Kingdom, or Spain, the prevalence of non-B subtypes in recently infected patients range from 5% to 50%, and is increasing [15–17].

Not surprisingly, the genetic diversity among clades may explain differences in transmission rates, natural history, rate of CD4+ decline and recovery in response to HAART, the range of sensitivity of wild-type strains or the pathways to escape from the pressure on nonfully suppressive HAART regimens [11]. In fact, these differences have been documented not only between B and non-B subtypes but also within non-B subtypes. Transmissibility may be lower for clade D (although disease progression may be faster) and higher for clade C [18]. Thai people infected with CRF_AE (former known as subtype E) have higher plasma viral load and higher transmissibility rate [19]. The calculated genetic barrier for first major resistance mutation to nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) are similar for B and for non-B subtypes [20], but the frequent polymorphisms present in wild-type strains of untreated individuals may translate into some phenotypic sensitivity differences [21]. Strains of the O group, likewise the HIV-2, are intrinsically resistant to NNRTIs, and not all non-B subtypes of the M group are equally sensitive to them [22]. No major differences among non-B subtypes have been detected for entry inhibitors like maraviroc or enfuvirtide, but HIV-2 is intrinsically resistant to enfuvirtide [11]. D and C subtypes select resistance mutations more frequently than subtype A after a single dose of nevirapine, and the K65R mutation are more easily selected in subtype C, both in vitro and in vivo [23]. The escape pathway for NNRTI resistance for subtype C may be through the V106M mutation rarely seen in B subtype [24]. Finally, genotypic drug resistance interpretation algorithms display high levels of discordance when applied to non-B subtypes [25]. Finally, all major guidelines for antiretroviral therapy (ART) [26–29] provide precise recommendations for performing resistance testing before starting ART because, despite remaining stable, the prevalence of primary resistance ranges between 5% and 15% in Europe and the United States. The increase in the prevalence of non-B subtypes, even in Western countries, may have important future implications. At present, guidelines mention the problem but do not provide specific recommendations, as guidelines do for other viruses like hepatitis C [30].

Notes

Potential conflicts of interest. J. M. G. has received honoraria for lectures and advisory boards, and research grants from Boehringer Ingelheim, Bristol-Myers Squibb, Abbott, Gilead, Merck Sharp & Dohme Corp., Tibotec, Janssen, Virco, and Tobita. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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