A call for randomized controlled trials of antiretroviral therapy for HIV-2 infection in West Africa

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HIV-2 is endemic in West Africa, but, unlike HIV-1, has had limited spread to other locales [1]. HIV-1 has emerged in West Africa more recently and because HIV-1 and HIV-2 cocirculate in this region, some individuals become dually infected with both viruses [2,3]. Compared with HIV-1 infection, HIV-2 infection is characterized by a much longer asymptomatic stage, lower plasma viral loads, slower decline in CD4 cell count, decreased mortality rate due to AIDS, lower rates of mother-to-child transmission, genital tract shedding, and sexual transmission [1,4–12]. Nonetheless, a significant proportion of HIV-2-infected individuals eventually progress to AIDS [6,13–15]. The clinical consequences of dual infection with both HIV-1 and HIV-2 need to be more fully understood, but current data suggest the majority of such patients also eventually progress to AIDS [2,16–20].

Antiretroviral therapy (ART) is becoming increasingly available in West Africa where up to 1–2 million people are infected with HIV-2 [21]. As ART 'scale-up' programs proliferate in West Africa, significant numbers of HIV-2 and dually infected individuals will have access to and will be treated with antiretrovirals developed against HIV-1 [22–25]. However, HIV-2 is intrinsically resistant to the nonnucleoside reverse transcriptase inhibitors (NNRTIs) and T-20 (enfurvirtide), and reports suggest that HIV-2 may be partially resistant to some protease inhibitors (e.g., amprenavir, atazanavir, and nelfinavir) and have a low genetic barrier to nucleoside reverse transcriptase inhibitor (NRTIs) resistance [26–39]. In addition, at least one recent report from Burkina Faso suggested the NRTI mutations M184V and Q151M may rarely be found in antiretroviral-naive individuals [40]. The presence of HIV-2 in dually infected patients complicates treatment, requiring drugs that are active against both HIV-1 and HIV-2.

Several observational cohort studies in developed countries have shown variable but generally poor outcomes of ART for HIV-2 infection [15,41–49], with similar results reported from the few small cohort studies from resource-limited settings in Senegal, The Gambia, and Ivory Coast, West Africa [24,25,50].

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Recently, there have been efforts in Europe to develop an international consortium [ACHIeV$_2$e (A Collaboration on HIV-2 Infection)] of HIV-2 cohorts to better study HIV-2 infection and standardize its management, including HIV-2 viral load testing and treatment [51]. These efforts should ultimately lead to better care of HIV-2 infected individuals in the developed world and West Africa.

To date, there has not been a single randomized clinical trial of ART for HIV-2 infection. This is despite a gap of more than 20 years since the discovery of HIV-2 [52] and the advent of zidovudine, more than 10 years since the landmark studies showed the benefit of HAART for HIV-1 [53–55], and currently six different classes of antiretroviral drugs available for HIV-1 (NRTI, NNRTI, protease inhibitors, fusion inhibitors, CCR5 coreceptor blockers, and integrase inhibitors) of which four show in-vitro and/or in-vivo activity against HIV-2 [37,38,56–58]. The WHO currently recommends two NRTIs and a protease inhibitor boosted by ritonavir as the first-line therapy of HIV-2-infected patients [59]; they make no explicit recommendations for dually infected patients or for second-line HIV-2 (or dual) infection regimens and little such data is available. In resource-limited West Africa, biological monitoring (CD4 cell counts) is limited and HIV-2 viral load and genotypic or phenotypic resistance testing are not commercially available, standardized or routinely obtainable; thus regimen failure is often assessed on clinical criteria and the data suggest that CD4 cell count recovery with ART in HIV-2 infection is often poor [48,49]. Consequently, an assessment of the relative efficacy of potential first-line and salvage regimens including the newer generation of protease inhibitors, integrase inhibitors, and CCR5 coreceptor blockers among HIV-2 (and dually) infected patients is needed. A key issue in West Africa, where HIV and tuberculosis are common, is to find the ART regimens for HIV-2 that can be given with concurrent treatment for tuberculosis, given interactions between protease inhibitors and rifampicin [59]. Finally, albeit rare, proven regimens to prevent mother-to-child transmission of HIV-2 (or dual infection) are needed [60].

We believe the 1–2 million people and communities in West Africa most affected by HIV-2 (and dual infection) deserve the same evidence-based medicine and efforts that those with HIV-1 have justly demanded [61]. Rigorous, well designed, randomized controlled trials that demonstrate which antiretroviral regimens are effective in treating HIV-2-infected people are urgently needed to guide patients and the clinicians who care for them. The outcome of such trials will also be beneficial in treating patients dually infected with HIV-1 and HIV-2, although, ultimately, trials of ART in dually patients are also needed. However, the apparent decline of HIV-2 in some West African locales [3,61,62] highlights the importance of involving multiple West African countries to establish large multicenter collaborative studies and trials. We believe the best place to carry out such trials is in West Africa, the locale where HIV-2 is endemic and effective treatment is most likely to serve the local population. We, therefore, call on the wider AIDS community to support efforts for evidenced-based treatment of HIV-2 infection.

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