OPINION

THE FIGHT AGAINST KAPOSI'S SARCOMA IN AIDS – LESSONS FROM BRAZIL

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This article presents a brief review on 'epidemic' Kaposi's sarcoma (KS), an AIDS-defining illness, and laboratory data obtained by a group of researchers from São Paulo, Brazil, concerning the aetiological agent of KS (human herpesvirus 8, HHV-8). Brazil earned international acclaim in the fight against AIDS, providing universal free access to antiretroviral treatment for all patients and promoting education programmes for blocking virus transmission/acquisition. Drawing on her experience, the author suggests the use of highly active antiretroviral therapy (HAART) to combat AIDS and KS in countries where both diseases are epidemic. The lessons learned by Brazil, a developing country, and the techniques used there might help sub-Saharan countries to fight HIV and KS/AIDS, decreasing morbidity and mortality in these geographical regions.

Since the begining of HIV pandemic 25 years ago, Kaposi's sarcoma (KS) has been detected in AIDS patients, and it is considered an AIDS-defining illness.[1,2] The first report on disseminated KS in younger homosexual men from the USA contrasted with the three forms of KS previously described in elderly persons from Mediterranean countries, in children and adults from the sub-Saharan countries, and in post-transplant patients receiving corticosteroid and immunossupressive therapies.[3] KS in AIDS patients assumed a more aggressive pattern, disseminating into the viscera and being associated with a greater likehood of death.

KS in AIDS or 'epidemic' KS has been detected worldwide and is related to mode of HIV transmission: high frequencies of KS have been observed among homosexual men and low frequencies among haemophiliacs, suggesting that a sexually transmitted agent could account for the tumour.[4-6] In fact, in 1994 a novel human herpesvirus provisionally called Kaposi's sarcoma-associated herpesvirus (KSHV) and more recently named human herpesvirus 8 (HHV-8) was detected in KS lesions from AIDS patients.[7] The same herpesvirus was subsequently detected in all forms of KS, classic, endemic, and iatrogenic.[3]

Interestingly, after the introduction of HAART, a reduction in the number of KS/AIDS cases was observed in the Western world.[8] *In vitro* and *in vivo* studies supported the benefit of antiretroviral therapy in controlling HHV-8 growth and disease development and progression.[9-12] The tat protein of HIV was implicated in enhancing the entry of HHV-8 into endothelial cells, and/or in increasing HHV-8 viral load by reactivation of HHV-8 from a latent state.[12,13] Antiretroviral therapy could therefore have a synergistic effect on KS/AIDS, allowing immune reconstitution and the clearance of HIV and consequently of HHV-8.

In 1994, antiretroviral treatment in AIDS patients was started in Brazil, first with transcriptase inhibitors, and from 1996 also with protease inhibitors. Since then, a decrease in the number of KS/AIDS cases has been detected by the Brazilian Ministry of Health. In São Paulo, Brazil, a seroepidemiological study conducted by our group in HIV/AIDS patients receiving antiretroviral therapy revealed 17% HHV-8-seropositive cases, and a 5-year follow-up showed that only 2% of these patients developed KS.[14] This result contrasts with the 20% prevalence of KS in AIDS patients detected in the same region before the HAART era. Taking these data into account, we advocated the use of antiretroviral therapy in developing countries where KS is endemic, such as in sub-Saharan Africa, in order to fight both HIV and HHV-8 infections and diseases.[15]

Since then we have been trying to detect HHV-8 infection in several populations from Brazil, searching for at-risk individuals, the HHV-8 subtypes, and the routes of virus transmission/acquisition. By means of in-house serological assays we were able to detect HHV-8-endemic populations among Amerindians from Amazonia,[16] homosexual/ bisexual men and promiscuous women,[14,17-19] and HIV-infected children.[20]

Using DNA sequencing of HHV-8 ORF K1 we were able to detect the three most common HHV-8 subtypes described around the world (A, B and C) in HIV/AIDS patients from São Paulo, south-east Brazil, and subtype B in a similar population from Salvador (north-east Brazil).[21-23] These data may reflect the ethnic background of the individuals who live in these regions; São Paulo received European and Asiatic immigrants during its colonisation and has a mixed race/colour population, while Salvador was colonised by black individuals from Africa during the African slave trade, so black/mullatto is the predominant population.

Furthermore, among Indians from the Amazon region (northern Brazil) we detected HHV-8 subtype E, which is phylogenically related to subtype D (Australasia) and subtype Hok (North of Japan), along with HHV-8 subtype A.[23] We

speculated that there could have been prehistoric migration of HHV-8-infected native populations from Asia through North America, reaching the North region of Brazil, resulting in the maintenance of HHV-8 subtype E in isolated populations from Brazil, but this hypothesis needs to be confirmed by phylogenetic analysis of several isolates.

Of interest was our finding of an alternative method for HHV-8 subtyping that utilises a restriction fragment length polymorphism analysis of ORF K1 (VR1) instead of sequencing assay.[21,22] This technique is able to rapidly subtype HHV-8, and it could be used in developing countries because of its low cost.

We still do not know whether there is a correlation between HHV-8 subtype and virus pathogenicity, but we are attempting to correlate HHV-8 subtype and tumour aggressiveness.

On the other hand, it seems evident that the routes of virus transmission differ between endemic and epidemic HHV-8 regions; sexual virus transmission could account for KS infection in adults from endemic and epidemic areas, and horizontal transmission for infection in children and infants from endemic areas.[3]

Using nested PCR for detecting several DNA segments of HHV-8, we confirmed HHV-8 shedding in blood, saliva, and urine from HIV/AIDS patients with and without KS, and suggested virus transmission/acquisition by these body fluids.[24] In addition, we recently found HHV-8 shedding in urine and suggested virus transmission in populations living in poor socioeconomic and sanitary conditions,[25] as previously demonstrated in a study conducted among Ugandan families with limited access to water and consequently poor hygiene.[26] Several sanitary practices that prevent contact with saliva and urine could therefore be employed in developing countries to avoid virus transmission/acquisition.

Brazil and Africa share several sociodemographic characteristics and sanitary conditions: South America and Africa are both large continents, their populations are educationally and socioeconomically diverse, rural and urban areas in both have very different populations and sanitary conditions, and both experience a large number of tropical and infectious diseases. In spite of this, Brazil has earned international acclaim in the fight against AIDS by a series of programmes including prevention and free access to antiretroviral treatment for all patients.[27,28] The lessons learned in Brazil, our experiences and the data we have gathered could therefore help developing countries to fight and control HIV/AIDS, especially in Africa where KS is endemic.

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