CASE REPORT

Control and non-progression of HIV-1 infection in sub-Saharan Africa: A case and review

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Elite and viraemic controllers represent unique subsets of HIV-infected patients who may also be long-term non-progressors (LTNPs). LNTPs constitute an estimated 1 - 15% of the total HIV-positive population in the USA and Europe, but less is known about their epidemiology in sub-Saharan Africa. Though the exact mechanisms for long-term non-progression appear to be numerous and are still under investigation, research on elite controllers may hold the key to new therapeutics and vaccine development. The clinical management of such patients can be challenging, as there are no standard guidelines for treatment, particularly in resource-limited settings. We describe the case of an HIV-infected Botswanan man who is likely an elite or viraemic controller.

S Afr J HIV Med 2012;13(3):152-155. DOI:10.7196/SAJHIVMED.848

In 2005, a 54-year-old Motswana male with no known history of medical problems, travel outside Botswana, or HIV risk exposure to persons beyond Botswana, was diagnosed with HIV (rapid test). He was asymptomatic upon presentation, his baseline CD4 was 989 cells/mm^3 (35%) and baseline HIV viral load was <400 copies/ml (assay limit of detection: 400 copies/ml). In 2006, a subsequent rapid HIV-test was also positive, as was qualitative HIV-PCR, although quantitative viral load remained <400 copies/ml. From diagnosis to date of this report, the patient remained asymptomatic with a robust CD4 cell count (Fig. 1) and undetectable viral load, without antiretroviral therapy (ART).

The patient's wife was diagnosed with HIV in 2003 at the age of 37 years. She was severely immunosuppressed at presentation (CD4 count of 40 cells/mm^3). She was initiated on ART and remained virologically suppressed (unclear baseline viral load). The couple's daughter was diagnosed with HIV in 2005 at the age of 9 years (CD4 count – 254 cells/mm^3; baseline viral load – 144 000 copies/ml). At the time of the report, she was virologically suppressed with robust immune response on ART.

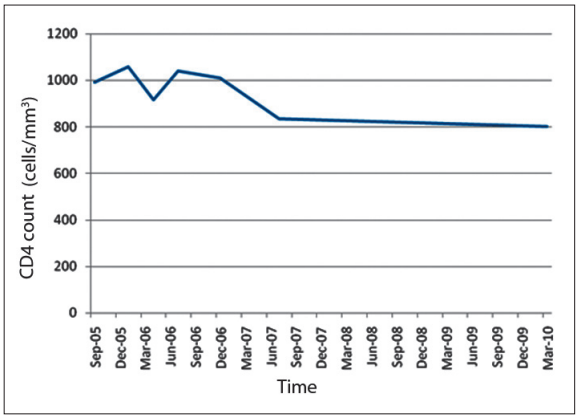

Fig. 1. CD4 cell count of the patient over time.

Discussion

HIV-infected individuals who take longer than 10 years to progress to AIDS have historically been called long-term non-progressors (LTNPs). The study of LTNPs has revealed much about the natural history of HIV infection. Most infected individuals who are not treated with ART advance to AIDS over approximately a decade.[1] Since first investigated

in the late 1990s, it has been shown that not all elite controllers follow the same natural history; some control the virus but eventually progress and others control the virus without progression.[1,2] Whether HIV elite controllers are 'ultra-slow progressors' or totally non-progressive remains to be determined. Little is known about the epidemiology of LTNPs in sub-Saharan Africa (SSA). A Ugandan study found rates of long-term non-progression and elite control among 9% and 1%, of the total HIV-seropositive population, respectively.[3] In the few studies demonstrating the existence thereof in SSA, the cohorts have been very small, the viral and host genetics have not been explored and, in some cases, the cohorts have used significantly different definitions of long-term non-progression.[3-5] Therefore, the mean progression of elite controllers or LTNPs without ART in SSA is largely undefined, especially with regard to HIV subtype C.

Multiple attempts have been made to define and classify HIV disease by clinical progression. The HIV controller consortium has defined 2 groups of HIV-infected patients: elite controllers with viral loads off ART <50 HIV RNA copies/ml for at least 1 year, and viraemic controllers who maintain viral loads of 50 - 2 000 copies/ml without treatment for at least 1 year.[1,6] Casado and colleagues further differentiated groups into elite controllers, 'classic' LNTPs (viraemic controllers v. viraemic non-controllers depending on the viral load), chronic progressors and rapid progressors (who progress to AIDS within 3 years of diagnosis).[7] They defined elite controllers as patients with a positive HIV test, who have viral loads consistently lower than the assay detection level for longer than 10 years.

Features unique to Botswana and Southern Africa

In resource-limited settings, the differentiation of elite controllers from viraemic controllers may be complicated. Though modern assays can detect viraemia >50 copies/ml, older assays – widely used in Botswana's national HIV programme – have a minimum detection level of 400 copies/ml. Even though 95% of all HIV patients do eventually show signs of progression, without highly specialised testing for protective and progressive factors, it is difficult to practically categorise and predict disease progression.[8] Viral suppression is correlated with certain practical clinical outcomes, including partner and mother-to-child transmissibility, and AIDS-free survival.[9]

In Botswana's national ART programme, where patients qualify for ART at a CD4 count <350 cells/mm^3, baseline viral loads are not performed, without which the practitioner cannot differentiate between an LTNP, who has a higher probability of progression of AIDS, and an elite controller. There are case reports of elite controllers progressing after super-infection with 2 different HIV subtypes,[10,11] heightening the importance of secondary prevention strategies in counselling patients.

Some limitations of our case merit further discussion. The lack of subtype analysis is notable; this was neither available nor cost-effective for the patient, given the constraints of Botswana's HIV programme, and the lack of value that this would add to clinical management under current national HIV guidelines. The patient's viral load was repeated at 3-monthly intervals and remained <400 copies/ml. However, viral loads were performed with the Standard Roche Amplicor HIV-1 Monitor test, which is not designed to detect non-M-group HIV (such as group O) or HIV-2.[12,13]

Though HIV-2 and group O HIV-1 could not be ruled out, the patient was presumed to have HIV-1 subtype C. HIV epigenetics of southern Africa, and Botswana in particular, show that the majority of HIV-infected patients are infected with HIV-1 subtype C.[12-14] A 2005 study found a 98.6% prevalence of HIV-1 subtype C among randomly selected samples of HIV-infected patients from 22 health districts in Botswana.[15] Cases of subtype A, B, F1, G, U and CH recombinant have been confirmed in South Africa,[13] while isolated cases of group O have been noted in Zambia.[12] Regional prevalence of HIV-2 is very low in southern Africa, with most cases reported in Angola and Mozambique.[12] The prevalence of HIV-2 is highest in West Africa, with HIV-1 group O being more prevalent in west and central Africa, particularly Cameroon, Guinea and Gabon.[12] While the possibility that our patient acquired HIV from a different source cannot be excluded, the patient denied travel outside of Botswana or to any of the aforementioned regions, as well as sexual relations with commercial sex workers and intravenous drug use. The HIV status of the wife and child also served to support the patient's diagnosis of HIV-1 subtype C; the child was perinatally infected and all members were presumed to have the same strain of HIV. The child had a detectable baseline viral load and both the wife and child experienced immune decline to AIDS, necessitating highly active ART (HAART). This case is particularly interesting because little is known about the rate of the clinical progression of subtype C, compared with other subtypes. Moreover, the epigenetics of subtype C in southern Africa may not be conducive to LTNPs. One study of HIV-1 subtype C in Botswana showed a potentially higher median viral load for extended periods of time.[14] Prior to that in a Senegalese study, HIV-1-infected patients with subtype C, D or G were at higher risk of developing AIDS than their subtype A counterparts.[16]

This case of a likely elite or viraemic controller LTNP in Botswana illuminates gaps in our knowledge of the molecular mechanisms and clinical management of such patients. Most research on elite controllers and LTNPs has been confined to the basic sciences to elucidate the immune mechanisms involved, in hope of providing the basis for new therapeutics and vaccine development.[17-30] Complex host factors appear to be implicated in the control of HIV viral replication as well as viral dynamics.

Our case highlights the importance of the host immune response. The patient's daughter was unable to halt HIV progression and the wife had progressive immune decline, despite questionable viral suppression at baseline. Both were presumed to be infected with the same strain of HIV-1 as our patient.

Important knowledge gaps

Elite controllers are an area of ongoing research and discovery. Numerous viral factors have been posited as the aetiology of elite control. Some studies have confirmed infection with an attenuated replication-incompetent HIV virus in some patients.[8] In particular, mutations in specific HIV genes such as *nef*, *rev*, *tat*, *vif*, *vpr* and *vpu* have been implicated.[18,19,31] However, the majority of elite controllers have been found to be infected with replication-competent HIV,[7,32,33] leaving the interaction with complex host immune mechanisms as the predominant explanation for the existence of most elite controllers. The transmission of HIV from a patient with AIDS to an elite controller has been described[34] as well as a case of continued viral suppression in the face of super-infection with a pathogenic HIV-1 strain.[35] However, the exact viral factors and associated roles in the development of elite controllers is still unknown.

Proposed host immune mechanisms are numerous and have been reviewed elsewhere.[6,8,31-33] Briefly, roles for both adaptive and innate immune mechanisms have been elucidated.[31] HLA class alleles have been implicated: one study showed the expression of allele HLA B*57 in half of their elite controller cohort;[6] however, other studies did not detect this in the majority of their cohort.[9,29]

Natural killer responses and high HIV-specific CD4 and CD8 activation may also be involved.[32,33] Studies evaluating the presence and titres of anti-HIV antibodies have yielded conflicting data, but may have uncovered a potential mechanism in some elite controllers.[21,26,27,32] With continued basic science research, perhaps a greater understanding of the interactions between host and viral factors will become clearer.

Approach to management

As elite controllers appear to comprise less than 1% of the total population of HIV-infected individuals,[31] there is a paucity of data on the mortality, natural progression and optimal management of these individuals.[1] Historically, studies have enrolled a relatively small number of elite controllers, lacked the further differentiation and unified definitions of LTNP and/or elite controllers, evaluated data from subsets from larger studies, and focused on immune mechanisms instead of clinical progression.[1,8,9,36]

Though the majority of elite controllers maintain high and stable CD4 cell counts for longer than 10 years with low rates of clinical progression,[37,38] a minority of patients eventually require treatment as a result of a loss of viral control or progressive immune decline despite continued viral suppression.[1,11] The exact mechanisms, though unknown, may involve low levels of viral replication or factors independent to viral load, such as immune and T-cell activation and pro-inflammatory markers.[1,37,39] In a trial of HIV-1 seroconverters with spontaneous viral suppression, 6.7% of patients progressed to an AIDS-defining illness with 3 patients developing progressive disease in the face of continued viral suppression.[38,40] However, given that the dynamics and clinical progression of elite controllers may differ from other LTNPs (such as viraemic controllers), the lack of differentiation of these groups limits the utility of many older studies.[1,36] Though a system based on clinically distinct classifications is advocated by Graber *et al.*, Casado and colleagues support clinical definitions based on viral and host factors.[7,36] Though there is no standard consensus, more recent studies have capitalised on our evolving knowledge of the different classifications of LTNPs. Okulicz and colleagues have recently shown a decreased risk of AIDS-defining illnesses,[1] stable CD4 and longer duration of CD4>350 cells/mm^3 in elite controllers than in viraemic controllers.[1] There is also conflicting evidence regarding the rate of recovery after the initiation of antiretroviral therapy (ART) in LTNPs. Okulicz *et al.* showed that the LTNP elite controllers appear to reconstitute T-cells more slowly than other patients, while McKinnon and colleagues found that only CD4 nadir, and not elite controller status, was associated with slower rates of immune reconstitution.[1,5,41]

The clinical management of elite controllers is not discussed in the World Health Organization (WHO) HIV/AIDS guidelines, but is briefly touched upon in the United States Department of Health and Human Services (DHHS) and International AIDS Society (IAS) guidelines. The DHHS guidelines mention LTNPs with high viral loads and elite controllers with immune or clinical failure and state that: 'although therapy may be theoretically beneficial for patients in either group, clinical data supporting therapy for non-progressors and elite controllers are lacking.'[42] The IAS HIV guidelines state that ART should be considered for patients with CD4<500 cells/mm^3, 'unless the patient is an elite controller or has stable CD4 with low level viraemia.'[43] Though most expert consultants commence ART in elite controllers based on the same criteria as for HIV progressors, optimal management is unknown. There has been some suggestion that elite controllers may benefit from ART, in decreasing immune activation, which appears to play a central role in immune decline over time[40] and in non-AIDS complications such as cardiovascular and neurological disease.

Conclusion

This case of an elite or viraemic controller illustrates the limitations of national health guidelines, such as those in Botswana, which do not specifically address treatment strategies for elite controllers and/or LTNPs. The case also emphasises how further classification of LTNP types may guide strategies in the future, particularly in the developing world where assays are generally not as sensitive. The omission of LNTP subsets, such as elite or viraemic controllers, from the national guidelines of most African countries is not surprising given that they comprise a very small minority of patients, and emphasis has historically been on preventing and treating opportunistic infections and AIDS. Further research should be devoted to assessing the prevalence, natural history, morbidity and mortality of elite controllers and LTNPs in sub-Saharan African, to create consensus on rational and optimal management.

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