## **CASE REPORT Progressive HIV infection in the presence** of a raised CD4<sup>+</sup> count: HIV/HTLV-1 co-infection

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There are a number of pathophysiological causes for a normal or raised CD4 count in the context of progressive HIV infection. These include various co-infections, previous splenectomy, and lymphoproliferative disorders. Such circumstances can both confound HIV diagnosis and delay initiation of chemoprophylaxis and highly active antiretroviral therapy (HAART). We describe the case of a patient co-infected with HIV and human T-cell lymphotropic virus type 1 (HTLV-1) who, prior to HAART initiation, was found to have progressive immune deficiency associated with a raised CD4 count.

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A 51-year-old married man from Gauteng province, South Africa (SA), originally from the Northern Cape, tested HIV-positive on an enzyme-linked immunosorbent assay (ELISA)

in March 2002 as part of a routine medical examination for insurance purposes. His CD4+

count was 794 cells/µl and his HIV viral load was 19 365 copies/ml. He gave no history of any infectious diseases, but was receiving treatment for hypertension. On examination he was generally healthy, with normal vital signs and all systems proved unremarkable. On account of being asymptomatic with a CD4+ count within normal range, he was neither

initiated on highly active antiretroviral therapy (HAART) nor chemoprophylaxis, and was told to follow-up with his general practitioner for regular immune monitoring (Table 1).

An abnormally high CD4+ count was detected on follow-up in September 2002 prompting T-cell receptor polymerase chain reaction (PCR) studies, which revealed no

Table 1. CD4 <sup>+</sup>	and HIV viral I	oad monitoring	(2002 - 2009)
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Table 1. CD+ and five vital load monitoring (2002 - 2009)				
Date	CD4 <sup>+</sup> count (cells/µl)	CD4 <sup>+</sup> (%)	HIV-1 viral load (copies/ml)	
March 2002	794	15.0	19 365	
September 2002	6 043	15.6	59 900	
March 2003	4 891	13.9	31 400	
September 2003	7 775	17.0	37 200	
November 2003	7 799	21.0	58 300	
June 2004	5 893	15.0	252 000	
April 2006	13 820	23.1	133 281	
September 2008	12 731	23.6	1 226 897	
January 2009	2 875	73.0	494 510	
April 2009	6 939	72.0	1 920	
October 2009	1 973	61.1	Undetectable (<20)	

evidence of a clonal T-cell lymphoproliferative disorder. A bonemarrow biopsy was also performed and showed non-malignant T-cell hyperplasia. No further studies were conducted and expert opinion from HIV clinicians recommended that no antiretroviral therapy (ART) be given at that stage.

In January 2009 the patient was referred to us with a history of weight loss, fatigue and night sweats. On examination, he had increased reflexes affecting the right leg, with weakness in both arms; otherwise, examination was essentially normal. Magnetic resonance imaging of the spine revealed a collapsed vertebra at T9; a biopsy showed a chronic inflammatory process but no granulomata. On account of the history and clinical presentation, spinal tuberculosis (TB) was considered and TB treatment was commenced. Furthermore, despite the high CD4<sup>+</sup> count, it was felt that the patient would benefit from ART on account of being clinically immune-compromised and having a high HIV viral load. He was initiated on a regimen of Truvada (tenofovir/ emtricitabine) and efavirenz (EFV) to which he responded well with a drop in RNA copies/ml of >2 log<sub>10</sub> after three months of treatment and an undetectable HIV viral load six months thereafter. As the CD4<sup>+</sup> count remained above normal limits, repeat bone marrow and flow cytometry studies were carried out, identifying a population of T-lymphocytes with abnormal flow characteristics. T-cell receptor PCR showed the presence of a clonal cell population and bone marrow histology revealed infiltration by tumour cells with scattered atypical uninucleated cells and binucleated Reed-Sternberg cells. Immunophenotypic analysis showed no overt evidence of a B-cell lymphoproliferative disorder. Antibodies to human T-cell lymphotropic virus type 1/2 (HTLV-1/2) were detected by ELISA and the patient was diagnosed with a smouldering type of adult T-cell leukaemia/lymphoma (ATLL) secondary to HTLV-1 infection (HTLV-2 not being associated with this condition). He was treated with four cycles of infusional chemotherapy consisting of etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone (EPOCH), which he tolerated well. Interferon-alpha therapy was subsequently commenced and mantained three times per week. At the time of writing, the patient is clinically well with no neurological deficits, an undetectable HIV viral load and a CD4+ count of 4 430 cells/µl.

## Discussion

HTLV-1 was the first retrovirus to be identified in humans and is structurally related to other viruses within the retroviridae family, such

as HIV-1 and HIV-2, sharing similar routes of transmission. Since its discovery in 1979 three additional human deltaretroviruses (HTLV-2, HTLV-3 and HTLV-4) have been found, but only HTLV-1 and HTLV-2 have so far been associated with human disease. Antibodies to HTLV-1 were first identified in SA in 1984 and the first report of isolation of the virus was published in 1988.<sup>[1,2]</sup> Subsequently, a number of seroprevalence studies have been conducted in SA, where HTLV-1 has been found to be endemic in areas of Mpumalanga, the Eastern Cape, Free State and KwaZulu-Natal (KZN).<sup>[3,4]</sup> However, there are no recent representative data regarding prevalence in the general SA population or specific patient subgroups.<sup>[5]</sup>

Like other human retroviruses, HTLV-1 causes a lifelong infection of T-lymphocytes, in particular CD4+ cells. However, unlike HIV, the immunological hallmark of HTLV-1-infected individuals is a sustained proliferation of T-cells driven by the HTLV-1-encoded Tax protein.<sup>[6]</sup> The subsequent transactivation of cellular genes by the Taxencoded region can result in malignant transformation, although this is rare.<sup>[7]</sup> In the majority of cases, cytotoxic T-cells effectively control the virus by lysis of infected lymphocytes, which in turn results in the release of inflammatory cytokines that can be pathogenic.<sup>[6]</sup> On account of these various pathophysiological mechanisms, HTLV-1 is associated with a diverse range of pathology, including malignant disease, inflammatory syndromes and infective complications.<sup>[6]</sup> A number of these conditions have been described in SA, including ATLL, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/ TSP) and infectious dermatitis.<sup>[8-10]</sup> Although the life-time risk for HTLV-1-associated diseases in general is considered close to 10%, an indication of a long history of viral-human co-evolution,<sup>[6]</sup> this may be an under-representation when the interaction between HTLV-1 and other infective agents is considered. TB has been found to occur more frequently in patients infected with HTLV-1 and is also thought to be associated with a worse prognosis.<sup>[6]</sup> HTLV-1 has been shown to up-regulate hepatitis C viral replication and is implicated as a co-factor in the development of hepatocellular carcinoma. Furthermore, two studies have demonstrated an increased rate of cervical carcinoma in HTLV-1-infected patients.<sup>[7]</sup> Whether HIV-1 co-infection with HTLV-1 is associated with a faster progression to AIDS remains a contentious issue, although a number of studies have suggested as much.<sup>[11]</sup> What is, however, less controversial and perhaps of greater relevance is the effect of HTLV-1 on T-lymphocytes, and in particular, its association with CD4<sup>+</sup> lymphocytosis in HIV-1 co-infected patients.<sup>[12,13]</sup>

In general, lymphocytosis can be classified as belonging to one of two groups: either a reactive polyclonal proliferation, which can be caused by a variety of infective agents, hypersensitivity reactions, autoimmune conditions and splenectomy, or a clonal expansion as a result of a lymphoproliferative disorder. In the context of HIV co-infection, lymphocytosis has been described during early seroconversion associated with CMV, as well as in HIV/HTLV-1 co-infection where CD4+ lymphocytosis can be caused by both a reactive or clonal expansion. Consequently, patients with untreated HIV-1 who are co-infected with HTLV-1 show a dissociation between immunological and virological markers. That is to say, HIV-1/HTLV-1 co-infected patients have been found to progress to AIDS with a high HIV viral load, but in the presence of a normal or higher than normal CD4<sup>+</sup> count (both absolute and percentage).<sup>[12]</sup> A recent study in Mozambique demonstrated that co-infected pre-HAART adult patients were seven times more likely to have CD4+ counts >500 cells/µl (median 525 cells/µl) than HIV mono-infected patients.[13] However, as these CD4<sup>+</sup> cells are likely to be functionally altered, associated with a loss of naive cells and a higher activation pattern, CD4+ lymphocyte counts in HIV-1/ HTLV-1 co-infected patients cannot be considered to be a reliable marker of immunological competence.[12] Furthermore, CD4<sup>+</sup> counts can be dramatically raised on account of ATLL (i.e. clonal expansion), which occurs in ≤5% of HTLV-1 infections.<sup>[6]</sup> As most cases of ATLL develop in individuals infected early in life through breastfeeding,[6] it is probable that our patient was already infected with HTLV-1 when he first presented in 2002 with a CD4+ count of 794 cells/µl. Whether initiation of HAART at this juncture would have prevented the development of ATLL cannot be determined. However, it is thought that zidovudine (AZT) may protect HTLV-1-infected peripheral blood mononuclear cells from immortalisation on account of its genotoxic/mutagenic properties.[14]

The last sizeable HTLV-1 seroprevalence study in SA was conducted in northern KZN in 1993; a prevalence of 2.6% was found among the general population.<sup>[4]</sup> In the same study an HIV-1 prevalence of 3.5% was noted. As the risk factors for HTLV-1 and HIV are shared, an epidemiological association between these two retroviruses is to be expected. In 1996, HTLV-1 was found in 2% of asymptomatic urban black people in the Free State, but in 6% of HIV-seropositive patients from the same region.<sup>[3]</sup> More recently, and alarmingly, in a small retrospective study of 170 HIV-positive plasma specimens collected between 2007 and 2008 from Limpopo, 24% of specimens tested positive for HTLV-1/2 antibodies by ELISA.[15] Unfortunately, further testing to confirm the diagnosis or differentiate between HTLV-1 and HTLV-2 infection was not performed. Nevertheless, these findings highlight the evident gap in current knowledge and the need for clinicians to be aware of retroviruses other than just HIV.

## Conclusion

A CD4<sup>+</sup> lymphocyte count cannot always be considered to be a reliable marker of immunological competence in HIV-infected people, especially in patients co-infected with HTLV-1. Normal or raised CD4+ counts in such persons can be on account of reactive or clonal expansion of T-lymphocytes and can confound HIV diagnosis and delay initiation of chemoprophylaxis and HAART. As we lack up-to-date epidemiological data but know that certain areas in SA are endemic for HTLV-1, we suggest maintaining a high index of suspicion of HTLV-1 infection in all HIV-positive adult patients in Southern Africa. In particular, HIVpositive persons who are clinically immunecompromised and have a raised CD4+ count should be tested for HTLV-1, as well as patients who present with clinical features in keeping with ATLL, HAM/TSP or infective dermatitis. As locally available serological tests are unable to differentiate HTLV-1 and -2, a PCR or western blot analysis may be required subsequent to a positive HTLV-1/2 ELISA test to confirm the diagnosis and distinguish between HTLV-1 and -2. Furthermore, the decision to initiate HAART in co-infected patients is better determined by clinical stage and HIV viral load than CD4<sup>+</sup> count.

More research is needed to understand the epidemiology of HTLV-1 infection in Southern Africa; not only with regard to co-infections such as HIV-1/ HTLV-1 and TB/ HTLV-1, but

also in terms of the wider public health impact, including implications for PMTCT practices and safety of the blood supply.

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