

# Immune Compromise in HIV-1/HTLV-1 Coinfection With Paradoxical Resolution of CD4 Lymphocytosis During Antiretroviral Therapy

## A Case Report

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**Abstract:** Human immunodeficiency virus type-1 (HIV-1) and human T lymphotropic virus type-1 (HTLV-1) infections have complex effects on adaptive immunity, with specific tropism for, but contrasting effects on, CD4 T lymphocytes: depletion with HIV-1, proliferation with HTLV-1. Impaired T lymphocyte function occurs early in HIV-1 infection but opportunistic infections (OIs) rarely occur in the absence of CD4 lymphopenia. In the unusual case where a HIV-1 infected individual with a high CD4 count presents with recurrent OIs, a clinician is faced with the possibility of a second underlying comorbidity.

We present a case of pseudo-adult T cell leukemia/lymphoma (ATLL) in HIV-1/HTLV-1 coinfection where the individual fulfilled Shimoyama criteria for chronic ATLL and had pulmonary *Mycobacterium kansasii*, despite a high CD4 lymphocyte count. However, there was no evidence of clonal T-cell proliferation by T-cell receptor gene rearrangement studies nor of monoclonal HTLV-1 integration by high-throughput sequencing. Mutually beneficial interplay between HIV-1 and HTLV-1, maintaining high level HIV-1 and HTLV-1 viremia and proliferation of poorly functional CD4 cells despite chronicity of infection is a postulated mechanism.

Despite good microbiological response to antimycobacterial therapy, the patient remained systemically unwell with refractory

anemia. Subsequent initiation of combined antiretroviral therapy led to paradoxical resolution of CD4 T lymphocytosis as well as HIV-1 viral suppression and decreased HTLV-1 proviral load. This is proposed to be the result of attenuation of immune activation post-HIV virological control.

This case illustrates the importance of screening for HTLV-1 in HIV-1 patients with appropriate clinical presentation and epidemiological risk factors and explores mechanisms for the complex interactions on HIV-1/HTLV-1 adaptive immunity.

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**Abbreviations:** AIDS = acquired immunodeficiency syndrome, ATLL = adult T cell leukemia/lymphoma, BAL = bronchoalveolar lavage, cART = combination antiretroviral therapy, CSF = cerebrospinal fluid, DNA = deoxyribonucleic acid, HAM = HTLV-1 associated myelopathy, Hb = hemoglobin, HIV-1 = human immunodeficiency virus type-1, HPLC = high performance liquid chromatography, HTLV-1 = human T lymphotropic virus type-1, NR = normal range, OI = opportunistic infection, PBMCs = peripheral blood mononuclear cells, PVL = proviral load, STLV = simian T-lymphotropic virus, TCR = T cell receptor, UIS = unique integration site, VL = viral load.

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## INTRODUCTION

Human immunodeficiency virus type-1 (HIV-1) is well known to cause opportunistic infection (OI) and this is typically accompanied by declining levels of CD4 T-lymphocytes leading to impaired cell-mediated immunity. In the unusual case where a HIV-1 infected individual with a high CD4 cell count presents with recurrent infections, a clinician is faced with the possibility of a second underlying comorbidity. Coinfection with a second retrovirus, human T lymphotropic virus type-1 (HTLV-1), should also be considered, particularly in individuals of specific ethnic or geographic origins with a prevalence of greater than 1% in the general population. HIV-1 and HTLV-1 infections have complex effects on adaptive immunity, with specific tropism for, but contrasting effects on CD4<sup>+</sup> T-cells.

An estimated 10 to 20 million people worldwide are infected with HTLV-1 with prevalence exceeding 1% in southern Japan, central Africa, and the Caribbean.<sup>1</sup> HTLV-1 infection is associated with asymptomatic carriage in more than 90% of infections. HTLV-1 associated myelopathy (HAM) occurs in 0.3% to 3% of carriers and the life-time risk of adult T cell leukemia/lymphoma (ATLL) is 1% to 5%.<sup>2</sup> HTLV-1 is also associated with a range of inflammatory diseases: HAM,

uveitis, pneumonitis, lymphocytic arthritis, and bronchiectasis. HTLV-1 infection is also associated with a range of infections implying selective immune impairment, most notably disseminated strongyloides infection, Norwegian scabies, infective dermatitis, bladder, and kidney infections.<sup>1,2</sup>

Rhew *et al*'s<sup>3</sup> review of the literature showed that being a carrier for HTLV-1 was a risk factor for OI, particularly following the development of ATLL. There have been conflicting reports of the prevalence of HTLV-1 and *Mycobacterium tuberculosis* (MTB) coinfection in case-control studies carried out in geographical areas with high HTLV-1 prevalence.<sup>4-7</sup>

A patient with HIV-1/HTLV-1 coinfection presenting with an acquired immunodeficiency syndrome (AIDS) defining diagnosis of *Mycobacterium kansasii* and pseudo-adult T-cell leukemia/lymphoma (ATLL) is presented. The mechanism of potentiated immune activation driving proliferation is postulated. Informed consent was obtained from the patient before all investigations and before publication of this case report.

### CASE

The patient, a 47-year-old West Indian man was diagnosed with HIV-1 infection in the United Kingdom in 2002. He was heterosexual, had no history of injecting drug use and had a 20 pack year smoking history. He originally presented with recurrent cutaneous fungal infections, bacterial tonsillitis, varicella zoster infection, and oral candida. At diagnosis, his CD4 lymphocyte count was 757 cells/mm<sup>3</sup> (normal range [NR] 300–1400) and HIV-1 viral load (VL) was 26,905 copies/ml.

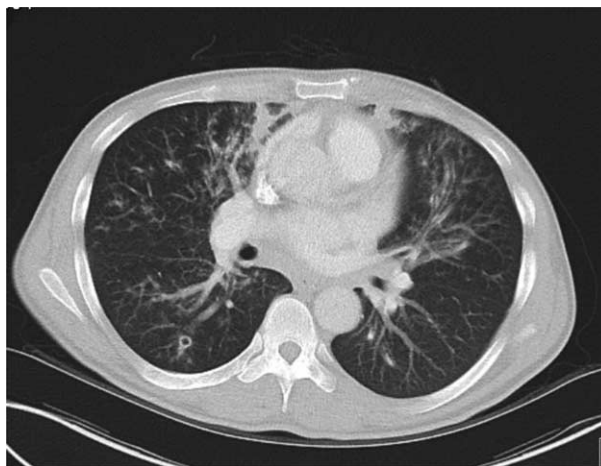
He remained clinically stable without antiretroviral therapy until 2010 when he presented with symptomatic anemia, night sweats, and a productive cough unresponsive to courses of antibiotics in the community. He also complained of erectile dysfunction and obstructive urinary tract symptoms. He had notable xeroderma, oral candida, obstructive airway chest wall movements, a peak expiratory flow rate of 300 L/minute (predicted 580 L/minute), coarse widespread crepitations on auscultation and palpable hepatosplenomegaly. He had normal tone and power, brisk lower limb reflexes with down-going plantar responses, conserved sensation, and normal anal tone.

Salient laboratory findings were: erythrocyte sedimentation rate of 126 mm/hour (NR 0–10 mm/hour), hemoglobin (Hb) 7 g/dl (NR 12.5–17.0), mean cell volume 76.8 fl (NR 83.0–101.0), ferritin 410 µg/L (NR 20–300), high performance liquid chromatography (HPLC) showed HbC 67.8%; HbA2 4.6% (NR 2.0–3.3%); HbF 5.6% (NR 0–1%). Blood film showed anisopoikilocytosis, mature lymphocytosis with 14% atypical lymphocytes and no flower cells. Serum B12: 360 ng/L (NR 160–800), red cell folate: 145.6 ng/ml (NR 126–480), iron: 23 µmol/L (NR 9–29), Total iron binding capacity: 31 µmol/L (NR 49–78), transferrin saturation: 74 (NR 20–45%), pretransfusion reticulocyte count was  $48.9 \times 10^9$  (NR  $28.1-86.1 \times 10^9$ ), reticulocyte %: 1.6 (0.52–1.84%). A vasculitic screen was negative for anticyclic citrullinated peptide, antineutrophil cytoplasmic antibody, antinuclear antibody, and antiglomerular basement antibody. Serology revealed no evidence of previous or current hepatitis B or C virus infection. There was no evidence of hematological malignancy, Epstein-Barr virus, parvovirus or human herpes virus-8 infection on bone marrow examination. Upper and lower gastrointestinal endoscopy revealed only chronic gastritis. Serum albumin was 24 g/L (NR 22–47) and liver transaminases and bone

biochemical profile were unremarkable. Urinalysis revealed microscopic hematuria and proteinuria with a urine protein:creatinine ratio of 146 (normal range <20). His estimated glomerular filtration rate was 79 ml/minute/1.73 m<sup>2</sup> (NR >59 ml/minute/1.73 m<sup>2</sup>) and computerized tomography of kidneys, ureters and bladder, flexible cystoscopy, renal, and prostate ultrasound were unremarkable. Computerized tomography of the thorax revealed bilateral upper lobe bronchiectasis along with several ill-defined nodules, some with cavitation, and foci of consolidation in both the upper lobes, significant right middle lobe consolidation and associated volume loss (Figure 1). Bronchoalveolar lavage (BAL) washings revealed an acute inflammatory response with no malignant cells. *M. kansasii* grew from BAL and sputum culture. HIV-1 VL at this time was  $4.62 \times 10^6$  copies/ml, absolute lymphocyte count 8000 cells/mm<sup>3</sup> (NR 1100–3600) and CD4<sup>+</sup> count 2239 cells/mm<sup>3</sup>.

Despite sputum culture conversion within 6 months of antimycobacterial therapy (rifampicin, isoniazid, ethambutol), he remained symptomatic with weight loss, productive cough, and refractory anemia requiring multiple transfusions. HIV-1 VL was now  $7.44 \times 10^6$  copies/ml, CD4<sup>+</sup> count 2477 cells/mm<sup>3</sup>. At this point HTLV-1 infection was considered and anti-HTLV-1 antibodies were detected with Western blot confirmation. HTLV-1 proviral load (PVL) was 42.9 deoxyribonucleic acid (DNA) copies/100 peripheral blood mononuclear cells (PBMCs).<sup>8</sup> Ninety-two percent of CD4<sup>+</sup> lymphocytes expressed CD25 (NR 15.7–34.9) with no evidence of clonal T cell receptor (TCR) gene rearrangement.

Combination antiretroviral therapy (cART) was commenced in August 2011 with emtricitabine, etravirine, and darunavir/ritonavir (a tenofovir sparing regimen was selected in light of his renal function). Within 3 months, he showed clinical and radiological improvement. The CD4<sup>+</sup> count decreased to 1495/mm<sup>3</sup> HTLV-1 PVL to 20.4% and HIV VL to 5098 copies/ml. Cerebrospinal fluid (CSF) obtained 4 months postinitiation of cART revealed 538 copies/ml CSF (paired plasma HIV VL 932 copies/ml) and CSF HTLV-1 PVL of 41.8 % CSF white cells (paired PBMC PVL 28.2 %). After nine months on cART, HIV VL was undetectable in plasma, with decreases in HTLV-1 PVL to 10.7% PBMCs and CD25



**FIGURE 1.** CT thorax at the time of diagnosis of *M. kansasii* showing consolidation and bronchiectasis in upper lobes bilaterally.

expression on CD4<sup>+</sup> cells to 87%. Table 1 summarizes total lymphocyte, CD4 lymphocyte count, HIV-1 and HTLV-1 VL before and in response to cART.

At HTLV-1 diagnosis, HTLV-1 unique integration site (UIS) analysis by Illumina high-throughput sequencing<sup>9</sup> revealed a polyclonal distribution in which the largest clone contributed 1.77% of the total HTLV-1 PVL. One year later, HTLV-1 PVL 19%, the polyclonal distribution was similar and the same clone remained largest, contributing 0.96% of the total HTLV-1 PVL (Figure 2).

At HTLV-1 diagnosis, the majority of CD4<sup>+</sup> T cells, as determined by flow cytometry, were effector memory cells (T<sub>EM</sub>, CD45RA<sup>-</sup>CCR7<sup>-</sup> 94.9%). The CD4 T<sub>EM</sub> cells had CCR4<sup>+</sup>CD25<sup>+</sup>CD127<sup>low</sup>FOXP3<sup>-</sup> immunophenotype. One year later, there was reduction in both absolute and relative frequency of CD4 T<sub>EM</sub> cells but no change in immunophenotype.

He remains well 4 years later.

**DISCUSSION**

This case caused diagnostic uncertainty since the absolute lymphocyte count, HTLV-1 serology and % atypical lymphocytes fulfilled Shimoyama criteria<sup>10</sup> for the diagnosis of chronic ATLL. However, there was no evidence of clonal T-cell proliferation by TCR gene rearrangement studies nor of monoclonal HTLV-1 integration by high-throughput sequencing.

HTLV-1 infection results in increased T lymphocyte proliferation, which is usually balanced by a higher rate of infected cell death due to immune surveillance.<sup>2</sup> Total lymphocyte, CD4 and CD8 T lymphocyte subsets are usually within the normal range in HTLV-1 mono-infection. Unlike HIV-1 infection in which viremia is maintained by infectious spread, HTLV-1 PVL, in chronic infection is thought to be substantially maintained by proliferation of infected cells and HTLV-1 integration site analysis reveals multiple clonal expansions of CD4 T lymphocytes.<sup>9</sup> The very high HIV-1 viremia, despite the chronicity of infection, may reflect the abnormally high CD4 cell count due to HTLV-1 infection, similar to that seen in

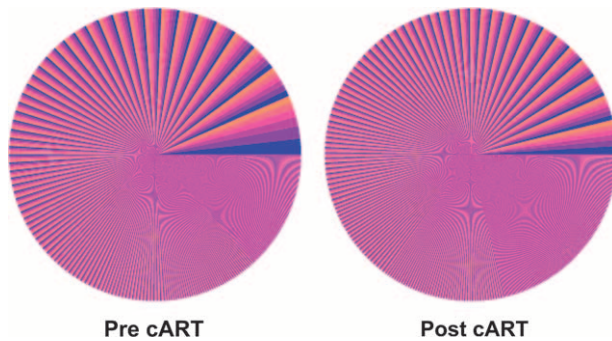
infants and young children. This patient had lymphocytosis predominantly due to an increased frequency of activated CD4<sup>+</sup>CCR4<sup>+</sup>T<sub>EM</sub> cells. A high proportion of HTLV-1 infected cells express CCR4. It has been suggested that active HIV infection increases CCR4<sup>+</sup> T-cells via secretion of the CCR4 ligands TARC and MDC by activated monocyte/macrophages.<sup>11</sup> This would result in the proliferation of HTLV-1-infected CCR4<sup>+</sup> T cells. We postulate that the coinfection with the 2 viruses led to overproduction of poorly functional lymphocytes whilst providing an environment for high levels of HIV virion production. It is possible that CD4<sup>+</sup>T-lymphocytes were coinfecting with the 2 viruses, but we have not been able to demonstrate this.

If, despite the high CD4 cell count, HIV-1 was contributing to high CD4 lymphocyte turnover, treatment of HIV-1 with cART might be expected to further increase the CD4 cell count, unmasking the true degree of HTLV-1 related CD4 T lymphocyte proliferation. Data from Beilke *et al*<sup>12</sup> suggest that where individuals with HIV/HTLV-1 coinfection have high HTLV-1 VL, cART has limited efficacy in controlling HTLV-1 viremia. However, in this subject cART, which was HIV-1 specific, was associated with normalization of CD4<sup>+</sup> counts and a significant decrease in the proportion of PBMCs infected with HTLV-1. Whilst zidovudine with lamivudine has not impacted on HTLV-1 VL in patients with HAM,<sup>13</sup> zidovudine in combination with interferon-α2a has improved the outcome in ATLL.<sup>14</sup> Raltegravir has been shown to prevent HTLV-1 infection in vitro.<sup>15</sup> In baboons infected with simian (S) TLV-1, treatment with sodium valproate, combined with zidovudine, resulted in significant, sustained reduction in STLV-1 VL.<sup>16</sup> Raltegravir may be a suitable alternative, since the role of ART combined with histone deacetylase inhibition is to prevent an initial increase in HTLV-1 viral replication associated with increased HTLV-1 transcription. The anti-HTLV-1 efficacy of zidovudine, raltegravir, and histone deacetylase inhibitors requires further clinical evaluation and may only impact on continuing infectious spread.<sup>13-16</sup> The normalization of the CD4<sup>+</sup> cell count, with a paradoxical decrease in CD4<sup>+</sup> count during HIV-specific cART, suggested proliferation of HTLV-1-

**TABLE 1.** Total Lymphocyte, CD4 Lymphocyte Count, Human Immunodeficiency Virus-1 and Human T-Lymphotropic Virus Type-1 Viral Load Before and in Response to Combination Antiretroviral Therapy

Time Point	June 2003	November 2010	August 2011	November 2011	April 2012
Stage of clinical management	Time of diagnosis of HIV-1	Pre-commencement of <i>M. kansasii</i> treatment	Month 6 of <i>M. kansasii</i> treatment/pre-commencement of cART	3 months after commencement of cART	9 months after commencement of cART
Total lymphocyte count (cells/mm <sup>3</sup> ) (NR 1100–3600)	6197	8000	5900	4600	2600
CD4 lymphocyte count (cells/mm <sup>3</sup> ) (NR 300–1400)	757	2239	2477	1495	939
HIV-1 viral load (copies/ml)	26,905	4.62 × 10 <sup>6</sup>	7.44 × 10 <sup>6</sup>	5098	<40
HTLV-1 proviral load (DNA copies/100 PBMC)	Unknown	Unknown	42.9	20.4	10.7

cART = combination antiretroviral therapy; DNA = deoxyribonucleic acid; HIV-1 = human immunodeficiency virus-1; HTLV-1 = human T lymphotropic virus type-1; PBMC = peripheral blood mononuclear cells.



**FIGURE 2.** Relative abundance of integration sites. Each pie chart depicts the clonal abundance of unique integration sites using linker-mediated polymerase chain reaction (PCR) followed by high throughput sequencing. Each slice of the pie chart represents the relative abundance of an individual clone within that sample. Precombined antiretroviral therapy (cART), the relative abundance of the largest clone (blue) represents 1.77% of the PVL (76.3/10,000 peripheral blood mononuclear cells (PBMC)) and following 1 year of cART reduces to 0.96% of PVL (18.3/10,000 PBMC).

infected CD4 T-cells driven by HIV-related immune activation; this interpretation was supported by the observation of polyclonal HTLV-1 integration at both time points.

In conclusion, we present a case of pseudo-ATLL in a HIV-1 infected individual whose high CD4 counts were deceptive as he was significantly immunosuppressed. His high CD4 count and ethnic origin prompted screening for HTLV-1 coinfection. Paradoxically, there was a significant improvement of CD4 lymphocytosis and HTLV-1 VL post commencement of HIV-1 specific cART. We postulate that mutually beneficial interplay between HIV-1 and HTLV-1 maintained high loads of each virus, and proliferation of poorly functional CD4<sup>+</sup> cells despite chronic infection. We suggest that the likely mechanism was immune activation of T-cells, which was attenuated by HIV-1 virological control with cART.

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