Review

HTLV-1, ATLL, severe hypercalcaemia and HIV-1 co-infection: an overview

Abdullah Ebrahim Laher¹,², Osman Ebrahim²

¹Abdullah Ebrahim Laher, Department of Emergency Medicine and Department of Critical Care, Faculty of Health Sciences, University of the Witwatersrand, 5 Jubilee Road, Parktown, Johannesburg, 2193, South Africa

²Corresponding author: Abdullah Ebrahim Laher, Department of Emergency Medicine and Department of Critical Care, Faculty of Health Sciences, University of the Witwatersrand, 5 Jubilee Road, Parktown, Johannesburg, 2193, South Africa

Key words: HIV-1, HTLV-1, ATLL, refractory hypercalcaemia, severe hypercalcaemia

Received: 03/07/2017 - Accepted: 30/04/2018 - Published: 28/05/2018

Abstract

HIV and HTLV (Human T-lymphotropic Virus) are the only known retroviruses responsible for causing infection in humans. HTLV-1 and HIV-1 are frequent co-pathogens, however, despite its potential for accelerated progression of HIV disease and the risk of developing adult T-cell lymphoma/leukemia (ATLL), HTLV-1 is seldom considered for investigation in the HIV-1 positive individual. Severe/refractory hypercalcaemia, unresponsive to conventional calcium lowering therapy may complicate up to 70% of cases of ATLL. In addition, HTLV-1 and ATLL have both been associated with a rise in dysfunctional CD4 lymphocytes, thereby conveying a false sense of immune competence in the HIV-1 infected individual.

Pan African Medical Journal. 2018;30:61. doi:10.11604/pamj.2018.30.61.13238

This article is available online at: http://www.panafrican-med-journal.com/content/article/30/61/full/

© Abdullah Ebrahim Laher et al. The Pan African Medical Journal - ISSN 1937-8688. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Introduction

Human T-lymphotropic virus 1 (HTLV-1) was first described in the 1980’s, but in actual fact is an “ancient” pathogen that has infected humans for many centuries [1]. Besides human immunodeficiency virus (HIV), HTLV is the only other retroviruses known to cause disease in humans [2]. HTLV-1 and HIV-1 are frequent co-pathogens [3]. With the current HIV epidemic affecting predominantly sub-Saharan Africa [4], there is renewed interest in this organism. Many clinicians treating patients with HIV-1 are unaware of the possibility of HTLV-1 co-infection and its associated potential for accelerated progression to AIDS as well as the risk of developing adult T-cell lymphoma/leukemia (ATLL) or HTLV-associated myelopathy / tropical spastic paraparesis (HAM/TSP) [5]. In the HIV positive patient presenting with severe/refractory hypercalcaemia, the likelihood of occult ATLL and HTLV-1 co-infection must be considered. The triad presentation of HTLV-1, ATLL and severe/refractory hypercalcaemia has been described in case reports [6-9]. However, the true prevalence of this presentation is unknown, largely due to misdiagnosis and underreporting as HTLV-1 is seldom considered for investigation in HIV infected individuals [10]. Current areas of uncertainty surrounding HTLV-1 co-infection include its impact on the progression of HIV disease and the initiation of antiretroviral therapy in countries where access to these drugs are restricted [3,11]. We (authors) have recently managed and been made aware of a number of HIV-1 infected individuals that had presented with refractory hypercalcaemia secondary to HTLV-1 associated ATLL. In this article, we review aspects of this presentation with the aim of improving awareness of the concurrent presence of HTLV-1 co-infection in the HIV-1 infected individual, especially in sub-Saharan Africa and other high HIV prevalence settings. We also aim to emphasize the potential for accelerated progression of HIV-1 disease, the difficulties in interpreting the CD4 cell count when deciding on the initiation of (antiretroviral therapy) ART or when monitoring HIV-1 disease progression as well as the pathogenesis and basic management of refractory hypercalcaemia in the HIV-1 infected individual with concurrent HTLV-1/ATLL.

Methods

A comprehensive literature search strategy was conducted using the following electronic databases: cochrane database of systematic reviews, Google Scholar, PubMed, Scopus and Web of Science (June 2017). The following search terms were used; HIV, HTLV, human T-cell lymphotropic virus, ATLL, Adult T-cell leukemia/lymphoma, hypercalcaemia. The citations of literature generated by the search were also reviewed for any additional literature. The search was restricted to all literature relating to the topic that was published in English and after the year 1970. Articles included in the review met the following criteria: i) publications were scientific in nature and included journal articles, conference abstracts as well as book chapters ii) the full text of the publication was available. The search yielded 652 articles as follows: google scholar 353, pubmed 214, scopus 65 and cochrane database of systematic reviews 18. The publications were screened for both duplicates and content. Sixteen other articles were identified from the citations provided by the selected publications. Two hundred and seventy four duplicate entries and another 321 entries were removed as they were not directly related to the topics identified for discussion. The remaining 73 publications had full text available. Fifty seven references were included in the final draft. Details of the above are summarized in Figure 1.

Current status of knowledge

HTLV-1: HTLV-1 was first described in the USA in 1980 [12] and independently again in 1982 in Japan [13,14]. In endemic regions such as Japan, the Carribean, South America and sub-Saharan Africa, the reported prevalence of HTLV-1 amongst the general population is between 0.5% and 20% [10,15]. Like HIV, HTLV-1 is a retrovirus that not only also infects CD4 T-lymphocytes but is similar in structure and route of transmission to the HIV virus [16]. HTLV-1, however, is not as easily transmitted as HIV-1 [17]. HIV-1 and HTLV-1 have also been shown to co-infect the same CD4+ cell [18]. Ninety five percent of individuals infected with HTLV-1 remain asymptomatic. The other 5% manifest with ATLL or HTLV associated myelopathy/tropical spastic paraparesis (HAM/TSP) [19,20]. In the Carribean HTLV-1 is commonly associated with refractory and persistent staphylococcal and streptococcal cutaneous infections [21]. There have also been case reports linking HTLV-1 to the presentation with uveitis, arthritis, sjogrens syndrome and strongyloides stercoralis hyperinfection [22]. In terms of diagnosis, antibodies to HTLV-1 can be detected with a screening ELISA test. A positive result must be confirmed with detection of gene products on Western blot analysis. PCR has a poor sensitivity
for the detection of viral RNA as a detectable plasma viral load is seldom present in most cases [5]. Antiretroviral agents such as lamivudine, zidovudine and raltegravir have not shown clear benefit in patients with HTLV-1 infection [23,24].

ATLL: HTLV-1 has oncogenic potential and is invariable present in almost all cases of ATLL, a neoplasm of mature CD4 T-lymphocytes [25]. Not surprisingly, the prevalence is highest in HTLV-1 endemic regions described above [26]. The median age of diagnosis is in the 6th decade of life in HIV uninfected individuals, but has been shown to be much earlier in HIV co-infected individuals [17]. Several forms of ATLL have been described [27]. More than half of patients present with the acute form which is characterised by organomegally, lymphadenopathy and a leukaemic picture on laboratory analysis. About half of these patients also present with skin lesions and hypercalcaemia which has a tendency to be severe/refractory. In the chronic form, patients present with chronic lymphocytosis that develops over months to years, skin lesions, small volume lymphadenopathy and no hypercalcaemia. The smouldering form is the most benign. Patients are usually asymptomatic or present with skin rashes that is generally responsive to the application of a topical corticosteroid ointment. In the lymphoma form, patients manifest with organomegally, raised LDH, occasional hypercalcaemia but no blood involvement [27,28]. In terms of therapy, the best results are achieved with a combination of zidovudine, alpha interferon and chemotherapy. However the overall prognosis of ATLL is poor [29]. The median survival of the acute and lymphoma forms is less than 1 year, whilst the prognosis with the other subtypes is slightly better [30]. The chemotherapeutic regimen of choice comprising VCAP-AMP-VCEP (VCAP-vincristine, cyclophosphamide, doxorubicin, prednisone; AMP-doxorubicin, ranimustine, prednisone; VCEP-videsine, etoposide, carboplatin, prednisone) has been associated with a trend towards an improved 3 year survival. However, due to significant toxicity, not many patients are able to complete therapy with this regimen and besides, ranimustine and vindesine are not widely available in many countries including South Africa and the USA [31]. The addition mogamulizumab, a humanised anti-CC chemokine receptor 4 antibody has also shown to improve outcomes, but again is not widely available [32].

HTLV-1 and HIV-1 co-infection: Sub-Saharan Africa, with more than two-thirds of global HIV cases, boasts the highest prevalence of HIV in the world. South Africa, having more people with HIV than any other country in the world, has an estimated 18.9% HIV prevalence amongst individuals 15 years of age and older [4]. The co-prevalence of HTLV-1 and HIV-1 has been reported as 4-23% in asymptomatic HIV infected persons and 5-28% in individuals with AIDS [10,33-35]. In a study conducted in 1993 in Northern KwaZulu-Natal (KZN) that comprised 1018 subjects, the HTLV-1 seroprevalence was reported as 2.6%, whilst the HIV-1 seroprevalence was 3.5%. The relative risk of co-infection with HIV-1 and HTLV-1 was noted as 1.16 (95% CI 1.08-1.24) [36]. Another South African study that included asymptomatic urban and rural black subjects from the Free State region, reported a HTLV-1 seroprevalence of 1.6%. Six percent of HIV seropositive patients in this study were also co-infected with HTLV-1 [37]. More recently and of concern, 24% of HIV-positive sera tested positive for the presence of HTLV-1/2 IgG antibodies in a study that included 170 HIV-positive plasma specimens from the Limpopo province of South Africa [33]. HTLV-1 may also induce HIV-1 viral replication. Whilst it is uncertain whether HTLV-1 is associated with a shortened survival [38,39], studies have suggested an accelerated progression of HIV disease and worsened outcomes after infection with opportunistic organisms in co-infected individuals [11,40]. Persons co-infected with both HIV and HTLV-1 have a 2.5 fold higher risk of contracting tuberculosis, especially in countries with a high prevalence of tuberculosis, such as sub-Saharan Africa and Brazil. These patients also have a higher associated morbidity and mortality risk [41,42].

Interpretation of the CD4 cell count in individuals with HTLV-1/ATLL and HIV-1 co-infection: The CD4 cell count must be interpreted with caution in the HIV-1 positive individual with concurrent ATLL and or HTLV-1 co-infection. Both HTLV-1 and ATLL have been associated with a rise in CD4 cells. Whilst reactive polyclonal proliferation of infected CD4 cells accounts for the rise in HTLV-1 infection, clonal expansion of CD4 lymphocytes may additionally contribute to the relative rise in individuals with concurrent ATLL [1,27,43]. A Mozambican study demonstrated that HTLV-1 co-infected individuals were 7 times more likely to present with a CD4 cell counts > 500 cells/µl [44]. In another study that comprised 184 HIV infected individuals from Nigeria, the mean CD4 cell count was noted as 742 cells/µl in HTLV-1-positive subjects compared to 380 cells/µl in HTLV-1-negative subjects [10]. HIV and HTLV-1 both independently induce a functional modification of CD4 and other T cell populations [45,46] that is characterized by an increase in naïve cells and a higher level of cell activation when compared to uninfected persons [11]. Progress of immunosuppression in individuals with ATLL/HTLV-1 co-infection is evidenced by an increasing HIV-1 viral loads and clinical progression...
of AIDS despite a stable or rising CD4 cell count [47]. Therefore, in
the HIV infected individual with ATLL and or HTLV-1 co-infection,
the absolute CD4 cell count may mask the degree of
immunosuppression. These individuals may actually present a more
advanced stage of HIV disease and are at increased risk of acquiring
opportunistic infections and presenting with other immune
suppression related clinical manifestations despite similar CD4 cell
counts as HIV positive individuals without ATLL/HTLV-1 co-infection
[3,48,49]. Although South Africa has recently adopted the World
Health Organization (WHO) recommendation with regards the
initiation of ART in all individuals living with HIV, irrespective of the
CD4 cell count or the degree of immune suppression [50,51], the
falsely raised CD4 cell count in individuals with concurrent
ATLL/HTLV-1 co-infection may have implications with regards to the
initiation of antiretroviral therapy in other resource limited-settings
such as sub-Saharan Africa which bears the brunt of the global HIV
burden [3,4]. Hence CD4+ counts in HIV-1/HTLV-1 co-infected
individuals is considered an unreliable marker of immunologic
competence and the need to initiate ART. Similarly quantitative
HTLV-1 proviral load (PVL) has also been reported to correlates
poorly with disease severity and the need to initiate ART's [41].

ATLL associated hypercalcaemia: The pathogenesis of
hypercalcaemia in patients with ATLL has been associated with
elevated serum macrophage colony-stimulating factor (M-CSF)
levels, over expression of receptor activator of nuclear factor kappa
B ligand (RANKL), ATLL infiltration into the bone marrow and
perhaps parathyroid hormone-related peptide (PTH-rP) secretion
[52]. In contrast, to patients with non-Hodgkin’s lymphoma where
the incidence of hypercalcaemia on presentation is < 3% [53],
severe and refractory hypercalcaemia has been shown to complicate
ATLL in approximately 70% of cases and is one of the chief causes
of early mortality [54]. Therefore the possibility of occult ATLL and
HTLV-1 co-infection must be considered as part of the differential
diagnosis in the HIV positive patient presenting with
hypercalcaemia. Basic calcium lowering therapy such as the
administration of high volume intravenous fluids, loop-diuretics,
corticosteroids and intravenous bisphosphonate is frequently
inadequate in sufficiently lowering calcium levels. Literature on the
application of haemodialysis in the management of refractory
hypercalcaemia is surprisingly scarce with no available consensus
guidelines. Case reports and case series have reported success with
haemodialysis using a low calcium concentrate dialysate (1-1.5
mmol/L) [55,56]. Recently denosumab, a fully humanised
monoclonal antibody has been associated with success in 2 cases of
bisphosphonate refractory hypercalcaemia [57].

Conclusion

In conclusion, more studies are required to determine the
prevalence of HTLV-1 and its impact on CD4 lymphocyte counts
(both absolute and relative), HIV viral load and AIDS progression in
co-infected individuals in sub-Saharan Africa and other regions with
a high HIV burden. The clinician managing the HIV positive patient
presenting with hypercalcaemia must consider the possibility of
occult ATLL and HTLV-1 co-infection.

What is known about this topic

- The co-prevalence of HTLV-1 and HIV-1 has been
  reported as 4-23% in asymptomatic HIV infected persons
  and 5-28% in individuals with AIDS;
- The CD4 cell count must be interpreted with caution in
  the HIV-1 positive individual with concurrent ATLL and or
  HTLV-1 co-infection as both HTLV-1 and ATLL have been
  associated with a rise in CD4 cells;
- Severe and refractory hypercalcaemia has been shown to
  complicate approximately 70% of cases of ATLL and is
  one of the chief causes of early mortality.

What this study adds

- Many clinicians treating patients with HIV-1 are unaware
  of the possibility of HTLV-1 co-infection and its associated
  potential for accelerated progression to AIDS as well as
  the risk of developing adult T-cell lymphoma/leukemia
  (ATLL);
- The possibility of occult ATLL and HTLV-1 co-infection
  must be considered as part of the differential diagnosis in
  the HIV positive patient presenting with hypercalcaemia.

Competing interests

The authors declare no competing interest.
**Authors’ contributions**

Abdullah Ebrahim Laher was the guarantor of the manuscript and responsible for drafting, writing, review and incorporating co-author feedback, revision and final approval of the submission. Osman Ebrahim contributed to the writing, review, revision of the article for important intellectual content and approval of the manuscript. All the authors have read and agreed to the final manuscript.

**Figure**

**Figure 1**: Flow diagram for literature search

**References**

1. Verdonck K, González E, Van Dooren S, Vandamme A-M, Vanham G, Gotuzzo E. Human T-lymphotropic virus 1: recent knowledge about an ancient infection. Lancet Infect Dis. 2007 Apr; 7(4): 266-81. PubMed | Google Scholar

2. Shindo N, Alcantara LCJ, Van Dooren S, Salemi M, Costa MCR, Kashima S et al. Human Retroviruses (HIV and HTLV) in Brazilian Indians: seroepidemiological study and molecular epidemiology of HTLV Type 2 isolates. AIDS Res Hum Retroviruses. 2002 Jan 5; 18(1): 71-7. PubMed | Google Scholar

3. Ticona E, Huaman MA, Yanque O, Zunt JR. HIV and HTLV-1 coinfection: the need to initiate antiretroviral therapy. J Int Assoc Provid AIDS Care. 2013 Nov-Dec; 12(6): 373-4. PubMed | Google Scholar

4. UNAIDS. Accessed 2017 Jun 21.

5. Nicolas D, Ambrosioni J, Paredes R, Marcos M’mgeles, Manzardo C, Moreno A et al. Infection with human retroviruses other than HIV-1: HIV-2, HTLV-1, HTLV-2, HTLV-3 and HTLV-4. Expert Rev Anti Infect Ther. 2015 Aug 3; 13(8): 947-63. PubMed | Google Scholar

6. Shahnaz S, Reich D, Arévalo-Valencia D, Kucinska S, Tulczynska J, Fleischman J. HTLV-1-associated adult T cell leukemia lymphoma presenting as granulomatous pneumocystis jiroveci pneumonia (PJP) and hypercalcemia. J Gen Intern Med. 2007 Mar; 22(3): 420-3. PubMed | Google Scholar

7. Lyell V, Khatamzas E, Allain T. Severe hypercalcaemia and lymphoma in an HTLV-1 positive Jamaican woman: a case report. J Med Case Rep. 2007 Jul 25; 1: 56. PubMed | Google Scholar

8. Edwards OMB, Edwards SJE, Bhumbra RP, Chowdhury TA. Severe refractory hypercalcaemia in HTLV-1 infection. J R Soc Med. 2003 Mar; 96(3): 126-7. PubMed | Google Scholar

9. Naik S, Kodali S, Agheli A, Dumiao T, Singh V, Plummer K et al. HTLV-1 Adult T cell leukemia-lymphoma presenting with refractory hypercalcemia, cranial neuropathy and diagnosis by flow cytometry and cytogenetic findings. Blood. 2015; 110: 3864. Google Scholar

10. Nasir IA, Ahmad AE, Emeribe AU, Shehu MS, Medugu JT, Babayo A. Molecular detection and clinical implications of HTLV-1 infections among antiretroviral therapy-naïve HIV-1-infected Individuals in Abuja. Nigeria Virology (Auckl). 2015 Jan; 6: 17-23. PubMed | Google Scholar

11. Gudo ES, Bhatt NB, Bila DR, Abreu CM, Tanuri A, Savino W et al. Co-infection by human immunodeficiency virus type 1 (HIV-1) subtype C and human T cell leukemia virus type 1 (HTLV-1): does immune activation lead to a faster progression to AIDS. BMC Infect Dis. 2009 Jan; 9: 211. PubMed | Google Scholar

12. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci U S A. 1980 Dec; 77(12): 7415-9. PubMed | Google Scholar

13. Yoshida M, Miyoshi I, Hinuma Y. Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. Proc Natl Acad Sci U S A. 1982 Mar; 79(6): 2031-5. PubMed | Google Scholar
14. Gonçalves DU, Proietti FA, Ribas JGR, Araújo MG, Pinheiro SR, Guedes AC et al. Epidemiology, treatment and prevention of human T-cell leukemia virus type 1-associated diseases. Clin Microbiol Rev. 2010 Jul; 23(3): 577-89. PubMed | Google Scholar

15. Gessain A, Cassar O. Epidemiological Aspects and World Distribution of HTLV-1 Infection. Front Microbiol. 2012; 3: 388. PubMed | Google Scholar

16. Mazanderani AH, Ebrahim O. Progressive HIV infection in the presence of a raised CD4+ count: HIV/HTLV-1 co-infection. South African J HIV Med. 2013; 14(2): 92-4. Google Scholar

17. Pierik LT, Murphy EL. The clinical significance of HTLV-I and HTLV-II infection in the AIDS epidemic. AIDS Clin Rev. 1991 Jan; 39-57. PubMed | Google Scholar

18. De Rossi A, Saggioro D, Calabrò ML, Cenzato R, Chieco-Bianchi L. Reciprocal activation of human T-lymphotropic viruses in HTLV-I-transformed cells superinfected with HIV-1. J Acquir Immune Defic Syndr. 1991 Jan; 4(4): 380-5. PubMed | Google Scholar

19. Osame M, Usuku K, Izumo S, Ijichi N, Amitani H, Igata A et al. HTLV-I associated myelopathy, a new clinical entity. Lancet (London, England). 1986 May 3; 1(8488): 1031-2. PubMed | Google Scholar

20. Gessain A, Barin F, Vernant JC, Gout O, Maurs L, Calender A et al. Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. Lancet (London, England). 1985 Aug 24; 2(8452): 407-10. PubMed | Google Scholar

21. LaGrenade L, Hanchard B, Fletcher V, Cranston B, Blattner W. Infective dermatitis of Jamaican children: a marker for HTLV-I infection. Lancet (London, England). 1990 Dec 1; 336(8727): 1345-7. PubMed | Google Scholar

22. Ijichi S, Matsuda T, Maruyama I, Izumihara T, Kojima K, Nimura T et al. Arthritis in a human T lymphotropic virus type I (HTLV-I) carrier. Ann Rheum Dis. 1990 Sep; 49(9): 718-21. PubMed | Google Scholar

23. Taylor GP, Goon P, Furukawa Y, Green H, Barfield A, Mosley A et al. Zidovudine plus lamivudine in human T-lymphotropic virus type-I-associated myelopathy: a randomised trial. Retrovirology. 2006 Sep 19; 3: 63. PubMed | Google Scholar

24. Trevino A, Parra P, Bar-Magen T, Garrido C, de Mendoza C, Soriano V. Antiviral effect of raltegravir on HTLV-1 carriers. J Antimicrob Chemother. 2012 Jan 1; 67(1): 218-21. PubMed | Google Scholar

25. Kikuchi M, Jaffes E, Ralfkiaer E. World Health Organization Classification of Tumours. Tumours of Haemopoietic and lymphoid tissues. Jaffes E, Harris N, Stein H, Vardiman J, editors. Lyon: IARC press; 2001. pg. 200-203.

26. Matutes E, Catovsky D. Adult T cell leukaemia lymphoma. 3rd ed Oxford: blackwell scientific publications; 1998. 416-433.

27. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma: a report from the lymphoma study group (1984-87). Br J Haematol. 1991 Nov; 79(3): 428-37. PubMed | Google Scholar

28. Aouba A, Lambotte O, Vasiliu V, Divine M, Valensi F, Varet B et al. Hemophagocytic syndrome as a presenting sign of transformation of smoldering to acute adult T-cell leukemia/lymphoma: efficacy of anti-retroviral and interferon therapy. Am J Hematol. 2004 Jun; 76(2): 187-9. PubMed | Google Scholar

29. Gill PS, Harrington W, Kaplan MH, Ribeiro RC, Bennett JM, Liebman HA et al. Treatment of adult T-cell leukemia-lymphoma with a combination of interferon alfa and zidovudine. N Engl J Med. 1995 Jun 29; 332(26): 1744-8. PubMed | Google Scholar

30. Hermine O, Bouscary D, Gessain A, Turlure P, Leblond V, Franck N et al. Brief report: treatment of adult T-cell leukemia-lymphoma with zidovudine and interferon alfa. N Engl J Med. 1995 Jun 29; 332(26): 1749-51. PubMed | Google Scholar
31. Tsukasaki K, Utsunomiya A, Fukuda H, Shibata T, Fukushima T, Takatsuka Y et al. VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan clinical oncology group study JCOG9801. J Clin Oncol. 2007 Dec 1; 25(34): 5458-64. PubMed | Google Scholar

32. Ishida T, Jo T, Takemoto S, Suzushima H, Uozumi K, Yamamoto K et al. Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukaemia-lymphoma: a randomized phase II study. Br J Haematol. 2015 Jun; 169(5): 672-82. PubMed | Google Scholar

33. Bessong PO, Mathomu LM. Seroprevalence of HTLV1/2, HSV1/2 and Toxoplasma gondii among chronic HIV-1 infected individuals in rural northeastern South Africa. African J Microbiol Res. 2010; 4(23): 2587-91. Google Scholar

34. Cortes E, Detels R, Aboulaifia D, Li XL, Moudgil T, Alam M et al. HIV-1, HIV-2 and HTLV-I infection in high-risk groups in Brazil. N Engl J Med. 1989 Apr 13; 320(15): 953-8. PubMed | Google Scholar

35. Hattori T, Koito A, Takatsuki K, Ikematsu S, Matsuda J, Mori H et al. Frequent infection with human T-lymphotropic virus type I in patients with AIDS but not in carriers of human immunodeficiency virus type 1. J Acquir Immune Defic Syndr. 1989 Jan; 2(3): 272-6. PubMed | Google Scholar

36. Bhigjee AI, Vinsen C, Windsor IM, Gouws E, Bill PL, Tait D. Prevalence and transmission of HTLV-I infection in Natal/KwaZulu. S Afr Med J. 1993 Sep; 83(9): 665-7. PubMed | Google Scholar

37. van der Ryst E, Joubert G, Smith MS, Terblanche M, Mollentze F, Pretorius AM. HTLV-I infection in the Free State region of South Africa: a sero-epidemiologic study. Cent Afr J Med. 1996 Mar; 42(3): 65-8. PubMed | Google Scholar

38. Casoli C, Pilotti E, Bertazzoni U. Molecular and cellular interactions of HIV-1/HTLV coinfection and impact on AIDS progression. AIDS Rev. 2007 Jul-Sep; 9(3): 140-9. PubMed | Google Scholar

39. Cleghorn FR, Blattner WA. Does human T-cell lymphotropic virus type I and human immunodeficiency virus type 1 coinfection accelerate acquired immunodeficiency syndrome? The jury is still out. Arch Intern Med. 1992 Jul; 152(7): 1372-3. PubMed | Google Scholar

40. Brites C, Pedroso C, Netto E, Harrington W, Galvão-Castro B, Couto-Fernandez J et al. Co-Infection by HTLV-I/II is Associated With Increased Viral Load in PBMC of HIV-1 Infected Patients in Bahia, Brazil. Braz J Infect Dis. 1998 Apr; 2(2): 70-7. PubMed | Google Scholar

41. Demontis MA, Hillburn S, Taylor GP. Human T cell lymphotropic virus type I viral load variability and long-term trends in asymptomatic carriers and in patients with human T cell lymphotropic virus type 1-related diseases. AIDS Res Hum Retroviruses. 2013 Feb; 29(2): 359-64. PubMed | Google Scholar

42. Pedral-Sampaio D, Martins Netto E, Pedroso C, Brites C, Duarte M, Harrington W. Co-infection of tuberculosis and HIV/HTLV retroviruses: frequency and prognosis among patients admitted in a Brazilian hospital. Braz J Infect Dis. 1997 Mar; 1(1): 31-5. PubMed | Google Scholar

43. Zane L, Sibon D, Mortreux F, Wattel E. Clonal expansion of HTLV-I infected cells depends on the CD4 versus CD8 phenotype. Front Biosci (Landmark Ed. 2009 Jan 1; 14: 3935-41. PubMed | Google Scholar

44. Bhatt NB, Gudo ES, Semá C, Bila D, Di Mattei P, Augusto O et al. Loss of correlation between HIV viral load and CD4+ T-cell counts in HIV/HTLV-I co-infection in treatment naive Mozambican patients. Int J STD AIDS. 2009 Dec; 20(12): 863-8. PubMed | Google Scholar

45. Ginaldi L, De Martinis M, D'Ostilio A, Di Gennaro A, Marini L, Profeta V et al. Activated naive and memory CD4+ and CD8+ subsets in different stages of HIV infection. Pathobiology. 1997 Jan; 65(2): 91-9. PubMed | Google Scholar

46. Mukae H, Kohno S, Morikawa N, Kadota J, Matsukura S, Hara K. Increase in T-cells bearing CD25 in bronchoalveolar lavage fluid from HAM/TSP patients and HTLV-I carriers. Microbiol Immunol. 1994 Jan; 38(1): 55-62. PubMed | Google Scholar
47. Beilke MA, Theall KP, O’Brien M, Clayton JL, Benjamin SM, Winsor EL et al. Clinical outcomes and disease progression among patients coinfected with HIV and human T lymphotropic virus types 1 and 2. Clin Infect Dis. 2004 Jul 15; 39(2): 256-63. PubMed | Google Scholar

48. Regis C, Oliveira A, Brites C. Onset of opportunistic infections in patients co-infected by HTLV-1 and HIV-1, with high CD4+ cells count. Braz J Infect Dis. 2009 Aug; 13(4): 311-3. PubMed | Google Scholar

49. Brites C, Sampalo J, Oliveira A. HIV/human T-cell lymphotropic virus coinfection revisited: impact on AIDS progression. AIDS Rev. 2009 Jan-Mar; 11(1): 8-16. PubMed | Google Scholar

50. World Health Organisation. Guidelines on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. 2015. Google Scholar

51. Cullinan K. ARVs now for anyone with HIV-Motsoaledi. Johannesburg; 2016. Health24, HIV/AIDS. Accessed 2017 May 24.

52. Nosaka K, Miyamoto T, Sakai T, Mitsuya H, Suda T, Matsuoka M. Mechanism of hypercalcemia in adult T-cell leukemia: overexpression of receptor activator of nuclear factor kappaB ligand on adult T-cell leukemia cells. Blood. 2002 Jan 15; 99(2): 634-40. PubMed | Google Scholar

53. Canellos GP. Hypercalcemia in malignant lymphoma and leukemia. Ann N Y Acad Sci. 1974; 230: 240-6. PubMed | Google Scholar

54. Hagler KT, Lynch JW. Paraneoplastic manifestations of lymphoma. Clin Lymphoma. 2004 Jun; 5(1): 29-36. PubMed | Google Scholar

55. Loh HH, Mohd Noor N. The use of hemodialysis in refractory hypercalcemia secondary to parathyroid carcinoma. Case reports Crit care. 2014 Jan; 2014: 140906. PubMed | Google Scholar

56. Camus C, Charasse C, Jouannic-Montier I, Seguin P, Tulzo YL, Bouget J et al. Calcium free hemodialysis: experience in the treatment of 33 patients with severe hypercalcemia. Intensive Care Med. 1996 Feb; 22(2): 116-21. PubMed | Google Scholar

57. Adhikaree J, Newby Y, Sundar S. Denosumab should be the treatment of choice for biphosphonate refractory hypercalcaemia of malignancy. BMJ Case Rep. 2014 Jan; 2014. Google Scholar
Figure 1: Flow diagram for literature search