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Highlights from the HTLV-1 symposium at the 2017 Australasian HIV and AIDS Conference held jointly with the 2017 Australasian Sexual Health Conference, November 2017, Canberra, Australia

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Abstract

We are pleased to report on the inaugural HTLV-1 symposium at the 2017 Australasian HIV and AIDS Conference joint with 2017 Australasian Sexual Health Conference in Canberra, Australia. Our understanding of HTLV-1 epidemiology, pathogenesis, laboratory diagnostics and treatment options for HTLV-1 diseases has advanced tremendously over the last 40 years. However, the awareness of healthcare providers and the general population about HTLV-1, and the effective promotion and implementation of HTLV-1 transmission-prevention strategies, lag behind current knowledge. Here we present a summary of the symposium, plenary and poster presentations on HTLV-1.

Keywords: HTLV-1, HTLV-1-associated myelopathy/tropical spastic paraparesis, HAM/TSP, ATL, adult T cell leukaemia/lymphoma, human T leukaemic virus type 1, bronchiectasis, bronchiolitis, mortality, Australia, sexual transmission, treatment, service provision, patient feedback, serology

Introduction

In November, the 2017 Australasian HIV and AIDS Conference held jointly with the 2017 Australasian Sexual Health Conference in Canberra, Australia, hosted an inaugural HTLV-1 symposium. Discovered in 1978 by Bob Gallo [1], human T leukaemic virus type 1 (HTLV-1) is a sexually transmitted [2] and blood-borne [3] retrovirus, endemic in many regions of the world [4]. Currently, four subtypes of HTLV have been described (HTLV-1, 2, 3 and 4) [5], and an estimated 10 million people are infected with this virus worldwide [4]. Of people infected with HTLV-1, 8–10% suffer from diseases caused by HTLV-1; these may be inflammatory conditions [6] such as HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [7] or an aggressive type of haematological T cell malignancy named adult T cell leukaemia/lymphoma (ATL) [8]. HTLV-1 can be transmitted through body fluids that carry infected T lymphocytes, for example through condomless sex, breast-feeding [9], used needles [10], blood transfusions [11] and organ donation [12]. It is therefore a preventable infection. In addition, due to its sexual transmission, HTLV-1 co-infections with HIV-1 [13] and syphilis [2] have been commonly described.

Raising the awareness of HTLV-1 amongst HIV and sexual health scientists and clinicians was a timely response to a large-scale field research project in central Australia, conducted by Lloyd Einsiedel's team, reporting an HTLV-1 prevalence of up to 45% in adults in some Indigenous communities and its association with inflammatory lung disease and an increased mortality [14].

Here we provide the highlights of the HTLV-1 presentations at the conference.

Conference report

The HTLV-1 symposium opening address was given by the Australian HTLV patient representative, Mr Shane Schinke, who had recently been diagnosed with rapidly progressing HAM/TSP. He is a 59-year-old white man, who had been fit and healthy up to 3 years previously, when he noticed intermittent involuntary muscle movements in both legs as well as sexual dysfunction. The symptoms were of slow onset and the patient related them to work-related stress. In 2016, he developed urinary incontinence and constipation, he lost the ability to run or walk long distances unaided, and suffered considerable weight loss. By February 2017 he needed to use a wheelchair. It took several weeks and two hospital admissions until HTLV-1 infection and HAM/TSP were diagnosed. The patient was commenced on high doses of intravenous methylprednisolone once daily for 3 days, followed by daily oral prednisolone. The treatment improved his symptoms rapidly. Mr Schinke reported how relieved he was to receive a diagnosis, but also how difficult it was for him to obtain detailed information about his condition. By sharing his story, Mr Schinke gave testimony on how devastating diseases caused by HTLV-1 are. By making the effort to attend this conference he wished to raise the awareness of health policy-makers and care providers about the scarcity of accessible information and support for people affected by HTLV-1 in Australia. In addition, Mr Schinke highlighted the importance of advancing HTLV-1 vaccine development as the most important solution to eradicate HTLV-1.

In a poster presentation, entitled 'Connecting patients with experts: www.HTLVaware.com', **Fabiola Martin** reported on the web traffic of the HTLV patient website, www.HTLVaware.com, the patient blog, the Facebook page and the @HTLVaware Twitter account. HTLVaware was set up in 2013 to provide free, online, patient-friendly and accurate HTLV healthcare information. From 2013 to 2017, 25,444 people used the website. The majority of people accessed the website from the United States (50%), followed by the United Kingdom (11%), Russia (10%), India (4%), Brazil (4%), Canada (3%), China (3%), Italy (2%) and Germany (2%); for the remaining 11% the access location was unknown. Since 2013, 6508 Twitter followers have been accumulated, and 1661 Tweets have been sent. Forty-three user enquires were analysed: 18 were from HTLV-negative persons, 16 were from people infected with HTLV-1, one HTLV-2, three HAM/TSP and one ATL. Sixteen patients needed to be referred to a specialist in their respective country, 20 enquired about exposure risk, seven needed additional

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educational information and all needed information and reassurance. For one HTLV-1-positive pregnant woman, specialist care was not available in her country. Four users became patient representatives in their countries; three were connected with the UK patient representative. Patients from countries outside the UK reported that clear referral pathways for HTLV-positive people were scarce and partner notification support absent. Those people with indeterminate HTLV serology found the results particularly confusing and stressful. This social media platform has received 100% positive patient feedback for providing patient-friendly information and rapid access to specialist care and peer support where available.

Lloyd Einsiedel reported on HTLV-1c as a major cause of morbidity and mortality in Indigenous Australians in central Australia. Approximately half of all Indigenous adults residing in these remote communities live with HTLV-1c [14]. Internationally observed HTLV-1 diseases such as ATL, HAM/TSP [15], infective dermatitis [16] and uveitis [17], as well as sepsis due to *Strongyloides stercoralis* and HTLV-1 co-infection [18], have also been reported in these communities. However, the most commonly observed HTLV-1 diseases are chronic inflammatory respiratory diseases, including bronchiolitis and bronchiectasis, and invasive bacterial infections causing sepsis [19,20]. This region has the highest reported prevalence of adult bronchiectasis, and bloodstream infection incidence rates, worldwide. In recent studies, bronchiolitis has been identified as a precursor to bronchiectasis. The risk and severity of bronchiectasis are strongly associated with the HTLV-1 proviral load (pVL), which also predicts risk of invasive bacterial infection. The association between HTLV-1 pVL and these life-threatening conditions is consistent with recent findings of Einsiedel *et al.* that a high HTLV-1 pVL is associated with an increased risk of death (in preparation for publication). High rates of HTLV-1 infection and HTLV-1 diseases contribute substantially to the burden of ill-health and early mortality among Indigenous Australians living in central Australia.

Damian Purcell presented new data on genomics and pathogenesis of HTLV-1c prevalent in central Australian Indigenous communities [21]. In contrast to other regions of the world, ATL and HAM/TSP are less commonly observed; instead, bronchiolitis and bronchiectasis prevalence is significantly higher in these communities. In order to identify biological evidence for these epidemiological differences, blood samples were obtained from HTLV-1c-positive patients following ethics approval and patient consent in their first language. HTLV-1c infects predominantly CD4+, CD8+ and $\gamma\delta$ T cells, and to a lesser extent B cells, monocytes and dendritic cells. The HTLV-1c genome was sequenced from 30 patient samples and the structure of HTLV-1c spliced mRNA examined. The involvement of HTLV-1c-infected T cells in clinical pathogenesis was assessed in longitudinal analysis of 84 HTLV-1-positive individuals, using a digital droplet PCR (ddPCR) assay capable of quantifying the HTLV-1c proviral load (pVL) in total peripheral blood mononuclear cells and in T cells. The T cell receptor V-beta locus (TCRβ) gene repertoire of HTLV-1c-infected cells from 22 patients was examined to test for antigen-driven T cell clonal expansion. Comparison of cosmopolitan (A) and Austral-Melanesian (C) HTLV-1 clades showed greater than 90% homology across the entire genome. However, the HBZ and p12 coding regions exhibited considerable differences at both the nucleotide (12% and 18%, respectively) and amino acid levels (18% and 25%, respectively), and lacked spliced mRNA and an initiation codon for p12 ORF. These features may contribute to the observed low rates of T cell leukaemia, which depends on HBZ for tumorigenesis. Indigenous Australians exhibited a wide pVL/T cell ranging from 8×10^2, 5×10^6 copies/10^6 T cells and suggested an expansion in myeloid cells. High pVL strongly associated with chronic inflammatory conditions of the lung, especially bronchiectasis. Further studies are needed to examine the functions of HTLV-1c regulatory and accessory genes and to develop vaccines and antiviral drug treatments to combat HTLV-1c transmission.

Fabiola Martin reported on the UK-based National Centre for Human Retrovirology (NCHR), which provides patient-centred care through a hub-and-spoke model. The UK is not an HTLV-endemic country; however, 1 in 183 Afro-Caribbean blood donors [22] and an estimated 28,000 people in the UK are HTLV-1 seropositive [4]. HTLV sero-diagnostics were introduced in the UK in 1987, followed by the introduction of UK HTLV blood donation testing in 2002. In order to provide HTLV patient care and advance HTLV research, the NCHR (www.HTLV1.eu) was established in 2004. HTLV-positive donors are referred directly to NCHR by national blood donor services. All Public Health England reports confirming HTLV infection recommend direct referrals and patient self-referrals, and contact-tracing, including family testing, is advocated. From 1987 to 2016, a total of 2024 HTLV-seropositive persons were diagnosed. Prior to 1993 about 38 HTLV-positive people were diagnosed per annum. However, there has been a steady upward trend in HTLV-1 incidence: from 1993 to 2001, 54 new diagnoses per annum, and from 2008 to 2016, 88 new diagnoses per annum [23]. Fifty per cent of people diagnosed are followed up at NCHR. The London clinic serves as a clinical hub and provides specialised diagnostic services to three regional HTLV satellite clinics established (Birmingham, Manchester and York) to improve access and disseminate knowledge, with regular joint clinics at all sites. Services are multidisciplinary, reflecting the broad spectrum of diseases caused by HTLV-1. Patients are predominantly female (64%) with a median age at diagnosis of 52 years. Most are diagnosed with HTLV-1 and the majority are of black Caribbean origin (60%), followed by white ethnicity (19%). In 2016, 320 HTLV-infected patients attended the services; 28% had HTLV-1 inflammatory diseases, predominantly HAM/TSP, and in addition 12% suffered from ATL. Significant sub-groups are patients diagnosed with end-stage renal disease, HIV/HTLV co-infection, uveitis or polymyositis. Newer indications for testing and referral are cord blood storage and *in vitro* fertilisation. HTLV-specific diagnostics include molecular tests to detect, type and quantify HTLV infections, and immune phenotyping of T cells for activation markers in patients at risk of HAM/TSP, and prognostic markers of ATL. The NCHR facilitates HTLV-1 clinical trials and training for clinicians and scientists. The hub-and-spoke model of centralised care in the UK has allowed highly specialised services to be developed and delivered nationally. It also provides HTLV-positive patients rapid access to research participation, including clinical trials.

The mostly wrongly rehearsed HTLV mantra is that 'Nothing can be done for patients, because there is no treatment or cure for diseases caused by HTLV-1.'

However, **Graham Taylor** presented an overview on the world distribution of HTLV [4,24], and emphasised that 80% of HTLV-1 transmission is due to condomless sex, providing a detailed overview on well-established treatment interventions for HTLV -1 diseases.

While there is a paucity of randomised controlled studies on HAM/TSP, a review of the literature reveals several key observations: therapies that target the HTLV-1 life cycle have had no impact on HTLV-1 pVL or clinical outcomes. In order to achieve significant clinical improvement, anti-inflammatory therapy needs to be commenced close to disease onset to restore function, and needs to be prescribed long-term. The most commonly prescribed anti-inflammatory drugs are corticosteroids [25], which are then

switched to cyclosporine A [26], azathioprine [27] or methotrexate [24]. Novel therapies, such as intermittent low-dose infusions of the anti-CCR4 monoclonal antibody mogamulizumab [28], which selectively depletes HTLV-1-infected cells, has been shown to improve neurological deficit. Correct differential diagnosis of ATL from other T cell malignancies, as well as correct subtyping of ATL itself, is essential to select appropriate therapy. First-line treatment of choice for leukaemic presentations of ATL, including acute leukaemia, is high-dose zidovudine plus interferon-alpha [29–31]. Lymphomatous presentations are treated with standard chemotherapy but allografting [32] (not autografting) is the treatment with curative potential. Anti-CCR4 monoclonal therapy may replace zidovudine/interferon-alpha, especially for chronic ATL. HIV-1/HTLV-1-co-infected patients are at higher risk of HAM/TSP than mono-infected, possibly due to the persistence of high levels of T cell activation and associated inflammation, despite suppressive HIV-1 therapies. For these patients, immunosuppressive therapy is used for HAM/SP, as it is for HTLV-1 mono-infection. ATL also occurs in co-infected patients. In the UK, all HTLV-1 carriers from prevalent areas are screened for latent *S. stercoralis* infection, and if tested positive, treated with ivermectin prophylactically to avoid the potential complication of *S. stercoralis* hyperinfection syndrome due to immune dysfunction caused by HTLV-1.

Conclusions

HTLV-1 is a preventable sexually transmittable infection that poses a high morbidity and mortality risk, especially to Indigenous communities in central Australia. With early diagnosis, rapid access to disease-modifying drugs can be facilitated. However, lack of awareness prevents timely diagnosis. In addition, with the implementation of effective transmission strategies, the prevalence of this virus could be significantly reduced. While international research towards effective prevention, therapeutics and vaccine development is ongoing, education of health professionals and high-risk populations, and easy access to HTLV-1 antibody testing in affected regions remain a key priority. In the words of Mr Schinke: 'We need to acknowledge that HTLV-1 poses a significant public health risk and needs to be taken seriously.'

Highlighting HTLV-1 at the 2017 Australasian HIV and AIDS Conference raised the profile of this highly pathogenic and preventable oncovirus in the national consciousness, hopefully encouraging the development of an Australasian HTLV-1 public health strategy.

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Conflicts of interest

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