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Hepatitis B virus and human T-cell lymphotropic virus type 1 co-infection in the Northern Territory, Australia

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SUMMARY

Objective: To establish the relationship between hepatitis B virus (HBV) and human T-cell lymphotropic virus type 1 (HTLV-1) serological markers in the Northern Territory, Australia.
Methods: A retrospective serological study of patients presenting to public healthcare facilities in the Northern Territory between 2008 and 2015 was performed in order to determine the presence and relationships of serological markers of HBV and HTLV-1.
Results: Seven hundred and forty individual patients were found to be serologically positive for HTLV-1 in the Northern Territory over the 8-year period. Hepatitis B results were available for 521 of these patients. Hepatitis B surface antigen (HBsAg) positivity was demonstrated in 15.9% (83/521) of this cohort, which was significantly different to the HTLV-1-negative group (3.7%, 125/3354) ($p < 0.001$). Excluding individuals with isolated hepatitis B surface antibody (anti-HBs), those in the HTLV-1-positive group had a higher HBV exposure history (67.5%, 352/521) when compared to HTLV-1-negative individuals (37.8%, 1259/3354) ($p < 0.001$). HTLV-1-positive individuals had a lower prevalence of HBV combined anti-HBs and hepatitis B core antibody (anti-HBc) positive markers compared to those who were HTLV-1-negative (56.3% (198/352) versus 73.8% (937/1269), respectively; $p < 0.001$).
Conclusions: A significantly higher prevalence rate of HBV was found in HTLV-1-positive individuals from the Northern Territory. When considering the higher exposure to HBV in HTLV-1-positive individuals, the clearance of HBV appears lower than in those individuals testing HTLV-1-negative. A lower prevalence of clearance in HTVL-1-positive individuals than in HTLV-1-negative individuals, as signified by formation of HBVcAb and HBVsAb in HTVL-1 positive individual's may equate to higher prevalence of ongoing coinfection.

Introduction

Human T-cell lymphotropic virus type 1 (HTLV-1), a human onco-retrovirus that preferentially infects CD4+ cells, is known to be endemic among Indigenous Australians living in Central Australia.[1] The Northern Territory of Australia, geographically comprising a sparsely populated region of 1.5 million square kilometres, has a population of 244 900 people. Approximately one third of this population identifies as Indigenous.[2] The prevalence rate of HTLV-1 varies geographically from 13.9% in the central districts to 0.4% in the more northern aspects of the territory.[3] Indigenous Australians in the Northern Territory have a high prevalence of chronic hepatitis B (CHB) (0.8% to 13.3%), although the prevalence rate varies with age and vaccination status.[4–9] Vaccinated groups in the Northern Territory have a CHB prevalence at 0.8%, which increases to 14.2% in individuals born in the pre-vaccination era (prior to 1988).[5] Despite a high prevalence of markers for both viruses, the rate of hepatitis B virus (HBV) and HTLV-1 co-infection for the entire Northern Territory is not clear.

The Northern Territory has distinct features when compared to other HTLV-1 and HBV endemic communities. Recent work has shown unique genotypes of HBV in the Northern Territory.[10] The unique HBV sub-genotype C4 has molecular markers associated

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with increased progression to cirrhosis and hepatocellular carcinoma (HCC).[10] The Australo-Melanesian HTLV-1c subtype, while not unique to the Northern Territory, has been linked with bronchiectasis, strongyloidiasis, HTLV-associated myelopathy (HAM), acute T-cell leukaemia/lymphoma (ATLL), and blood stream infection (BSI).[1,11] Given the relatively high rates of both infections, it is not unexpected that co-infection will also be present.

A prior review of hospitalized patients in Central Australia found that 19.2% of individuals with HTLV-1 were positive for hepatitis B surface antigen (HBsAg).[1] Globally, regions endemic for HTLV-1/2 that have reported estimated co-infection prevalence include Japan,[12] Brazil,[13,14] Argentina,[15] and northern Iran[16,17] (summarized in Table 1).

The highest prevalence of co-infection (outside of the earlier Australian study) was reported from Japan in a study of 7761 individuals from two endemic islands who were screened in 1986. Of these 7761 individuals, 1609 were found to be HTLV-1-positive. Of those who were HTLV-1-positive, 4.7% (76/1609) had an HBV/HTVL-1 co-infection. This was in the setting of CHB prevalence of between 2.5% and 5.5%.[12,17,18] Attempting to define HBV immune clearance in this cohort (hepatitis B surface antibody (anti-HBs) positivity in the setting of HTLV-1 prior to vaccination), the prevalence rates were found to be similar in HTLV-1-positive and negative individuals: 16.2% versus 16.6%, respectively, in males and 22.4% versus 22.2%, respectively, in females (age-adjusted).[12]

Wider population screening has also taken place in South America. In a retrospective study of blood transfusion databases included 1,038,489 donors screened. Analysis was restricted to 301,470 who donated for the first time. Within this donor cohort, 296 persons were positive for HTLV-1/2, with 24 (8.4%) of them concurrently displaying hepatitis B core antibody (anti-HBc) positivity. One individual was HBsAg-positive.[13] More recent work from the same research group found seven co-infected individuals

in 88 330 first-time donors over a 3-year period (2011–2014).[13] Further data from Brazil have been obtained from an antenatal study. An observational review of 54 784 women screened prior to delivery found 118 individuals infected with HTLV-1, 4.2% of whom were co-infected with HBV.[19] There has also been focused screening of high-risk populations in north-eastern Iran. An intravenous drug using cohort admitted to hospital was reviewed prospectively, and one co-infection was found in 109 HTLV-1-positive subjects. This was in the setting of an endemic community CHB prevalence of between 1.4% and 2.5%.[17]

For most of these studies, the implications and potential interactions of the HBV/HTLV-1 co-infections remain unclear. Recent work has suggested an immunomodulatory role for HTLV, and HTLV-1 infection in the setting of hepatitis C virus (HCV) may predispose to the development of HCC.[20,21]

The aim of the present study was to examine the prevalence rates of HBV/HTLV-1 co-infection in the Australian setting, which may have therapeutic implications.

Methods

A review of the serological presence of HTLV and HBV co-infection in patients in the Northern Territory over an 8-year period (2008–2015) was performed. This was a retrospective analysis of pathology results ordered by public hospital clinical staff.

Serological assays for HBV were performed as per the manufacturer's instructions (Abbott Architect HBV; Abbott Laboratories, Chicago, IL, USA). The screening HTLV assay used in 2008 was Serodia particle agglutination (Fujirebio Inc., Tokyo, Japan) and in 2009–2015 was the Abbott Architect HTLV-1/2 chemiluminescent EIA (Abbott Laboratories, Chicago, IL, USA). Reactive and indeterminate serology results were sent to the National Serological Reference Laboratory (Melbourne, Victoria) for review by Western blot (WB). A positive result on the WB requires

Table 1
Major studies on HTLV-1/2 and HBV co-infection.

Author	Study year(s)	Population	Location	Number screened	HTLV-1/2 Ab-positive prevalence %	HTLV-1/2 Ab-positive	CHB endemic prevalence %	HBsAg-positive	Anti-HBc-positive	Anti-HBs/anti-HBc positive	Co-infected (HBsAg/HTLV-1/2 Ab)
Moura et al.[34]	2007–12	Pregnant females	Brazil	54 783	Brazil 0.08–1.35%	118	0.3–0.8%	226	–	–	5
Pinto et al.[19]	2011–14	First time blood donors	Brazil	88 330	Brazil 0.08–1.35%	65	Sao Paulo 0.29%[35]	–	7/65	–	7
Einsiedel et al.[1]	2005–10	Hospitalized patients	Australia	1614	Northern Territory 0.4–13.9%	507	Northern Territory 0.8–14.2%[5]	65	201/337	–	65
Chenari et al.[22]	2011–13	HTLV-positive individuals	Iran	109	Khorasan Razavi 1.6–7%	109	1.4–2.5%[33]	0	34/109	16	1 × (HBV viral load positive)
Pinto et al.[10]	2000–10	First time blood donors	Brazil	301 470	Ribeirão Preto 0.02–1.35%	297	Sao Paulo 0.29%[35]	1	24/297	–	1
Berini et al.[32]	2007	IVDU/MSM/TB/FSW	Argentina	2055	Buenos Aires 0.03–0.08%	49	–	17/49 with either HBsAg or anti-HBc	–	–	–
Alavi et al.[16]	2001–03	Hospitalized HIV-positive IVDU	Iran	104	Nationally 0.02%	17	Iran 0.7%	46	–	–	9
Tachibana et al.[21]	1985–86	General population	Japan								
			Goto Island	2084	24%	500	2.5%	52	–	–	13
			Tsushima Island	5677	20%	1109	5.6%	306			63

HTLV, human T-cell lymphotropic virus; HBV, hepatitis B virus; Ab, antibody; CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; IVDU, intravenous drug user; MSM, men who have sex with men; TB, tuberculosis; FSW, female sex workers.
aUpdated and adapted from Chenari et al.[22]

reactivity to both recombinant envelope proteins (Rgp21 and Rgp46-I) and/or envelope gp46 and reactivity to at least three other virus-specific proteins of the gag and pol series. WB results were subsequently interpreted as per the World Health Organization (WHO) criteria.[3] The patients' results were extracted from the centralized pathology database for hospitals across the Northern Territory. HTLV antibody, HBsAg, anti-HBc, and anti-HBs results were collected. Demographic data including age and sex were also recorded. HTLV-2 antibodies have not been found in patients in the Northern Territory, therefore the results discussed are specific for patients with HTLV-1.

There was no correlation with clinical parameters, nor was an analysis of the indication for the tests performed. As data were extracted from a public hospital pathology system, serological testing was restricted to assays ordered for routine clinical care. In the Northern Territory, hepatitis B testing is often performed as part of screening processes, such as antenatal screening, or at sexual health visits. HTLV testing tends to be mostly clinically driven, except in patients with end-stage renal disease where routine testing is part of haemodialysis workup, for pre-transplant screening, or for blood-borne virus exposure protocols.[22]

Data were analysed in Stata version 14 (StataCorp, College Station, TX, USA) using the median, interquartile range (IQR), and standard deviation (SD) for significant parameters. Proportions were calculated using the denominator of the parameter in question. The Chi-square test was used for the calculation of p-values. The Mann–Whitney test was used for non-parametric variables.

Ethical approval was obtained from the Human Research Ethics Committee of the Menzies School of Health Research (Ref. 2016-2654) and from the Central Australia Human Research Ethics Committee (Ref. 16-429).

Results

Between 2008 and 2015, 4857 individuals were tested for HTLV (Abbott Architect HTLV-1/2 chemiluminescent EIA), of whom 774 were positive. Confirmatory WB testing resulted in 623 positives and 151 indeterminate results. These indeterminate WB results represented 117 further positives when WHO criteria were employed for interpretation.[3,23] This resulted in a total of 740 unique HTLV-1 cases. The median age of these subjects was 48 years (IQR 40–59 years). Although the screening assay tested for both HTLV-1 and -2, no cases of HTLV-2 were detected. There were 4117 patients who tested negative for HTLV-1; the median age of these subjects was 41 years (IQR 28–54 years), which was significantly different to the median age of those who were HTLV-1-positive ($p < 0.001$).

Throughout the Northern Territory, 42 891 assays were performed for hepatitis B serology between the years 2008 and 2015, corresponding to 34 706 individual patients when duplicate results were removed. This was performed by keeping the first HBsAg-positive test, and any instance of a previous positive for anti-HBc or anti-HBs in the period. During the 8-year period, there were 1319 individuals who tested positive for HBsAg and 19 761 who tested positive for anti-HBs.

Of those who were HTLV-1-positive, 70.4% (521/740) had HBV serology performed during the study period (Table 2). This compared to 81.4% (3354/4117) of those who were HTLV-1 serologically negative ($p < 0.001$).

HBsAg was present in 15.9% (83/521) of those patients who were HTLV-1-positive, compared to 3.7% (125/3354) of those who were negative for HTLV-1 ($p < 0.001$).

In the HTLV-1-positive group, 19.8% (103/521) showed the presence of isolated anti-HBs without any other serological marker (Figure 1). This compared to 34.3% (1151/3354) in the HTLV-1-negative group who had isolated anti-HBs positivity ($p < 0.001$) (Figure 2).

In the HTLV-1-positive group, 38.7% (198/521) had both anti-HBc and anti-HBs detected concurrently. This was significantly different to the HTLV-1-negative group, in which anti-HBc and anti-HBs were detected concurrently in 28.3% of cases (937/3354) ($p < 0.001$).

Of those who were HTLV-1-positive, 67.5% (352/521) had anti-HBc and/or the presence of HBsAg. Positivity with the same combination of serological results in the HTLV-1-negative group showed a significant difference (37.8% (1269/3354); $p < 0.001$) (Figure 2).

When comparing those with combined anti-HBs and anti-HBc positive in the HTLV-1 group to a denominator of those with positive serological results other than isolated anti-HBs, the results were 56.3% (198/352) for HTLV-1-positive subjects and 73.8% (937/1269) for HTLV-1-negative subjects, respectively ($p < 0.001$). These results were compared to published data (Table 1).

Discussion

The patterns of HBV serological markers in HTLV-1-positive individuals in the Northern Territory were described in this retrospective serological study.

It is evident from this analysis that there was a higher prevalence of HBsAg and anti-HBc seropositivity in HTLV-1-positive individuals when compared to HTLV-1-negative individuals. These serological markers reflect differences in previous exposure to HBV. Such a difference in HBV exposure is not unexpected given that both viruses are transmitted vertically and horizontally. It is postulated but not proven that the major route of

Table 2
HBV and HTLV-1 co-infection in the Northern Territory.

Descriptor/assay	HTLV-1-positive (%)	HTLV-1-negative (%)	p-Value	Total (%)
Patients tested	740	4117		4857
Patients with HBV serology	521	3354		3875
Total HBsAg-positive	83 (15.9)	125 (3.7)	<0.001	208 (5.4)
HBsAg/anti-HBc-positive	75 (14.4)	113 (3.4)	<0.001	188 (4.8)
Total anti-HBc-positive	344 (66)	1257 (37.5)	<0.001	1601 (41.3)
Isolated anti-HBc	60 (11.5)[a]	153 (4.7)[b]	<0.001	213 (5.9)
Anti-HBs/anti-HBc-positive	198 (38.7)	937 (28.3)	<0.001	1035 (26.7)
Total anti-HBs-positive	306 (60.6)	2104 (66.9)	0.16	2410 (62.2)
Isolated anti-HBs	103 (19.8)	1151 (34.3)	<0.001	1254 (32.4)

HBV, hepatitis B virus; HTLV-1, human T-cell lymphotropic virus type 1; HBsAg, hepatitis B surface antigen; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody.
[a] Eleven anti-HBc-positive, HBsAg-negative, and anti-HBs result missing (HTLV-1-positive).
[b] Fifty-four anti-HBc-positive, HBsAg-negative, and anti-HBs result missing (HTLV-1-negative).
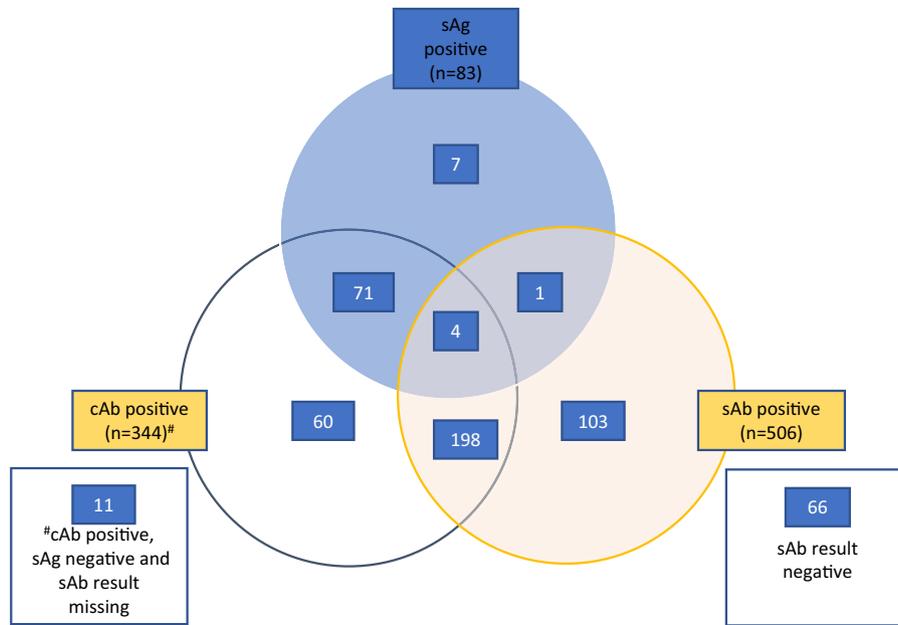
Figure 1. HBV status of HTLV-1-positive subjects (*n* = 521).

HBV transmission in the Northern Territory Indigenous population is vertical; however the contribution of early horizontal transmission has not been explored extensively. There are numerous publications supporting acquisition early in life as the major route of transmission prior to the implementation of universal vaccination.[24–26] It is currently not known at what stage of life HTLV-1 is acquired in the Northern Territory. Recent work in one smaller endemic community found relatively few children with the virus, raising the possibility that HTLV-1 may be acquired later in life via horizontal mechanisms.[27]

A significant difference was also seen in isolated anti-HBs status between HTLV-1-positive and negative individuals: 19.8% (103/521) versus 34.3% (1151/3354), respectively (*p* < 0.001). With newborn vaccination of high-risk groups starting in 1988 in the

Northern Territory, these values may represent patients born in the pre-vaccination era.[5] Without linkage to the vaccination history of each patient, it is not possible to describe why a significant difference exists, but this may relate to the statistically significant difference in age groups (*p* < 0.001).

HBV exposure (excluding isolated anti-HBs) was significantly higher in those who were HTLV-1-positive (67.6%) than in those who were HTLV-1-negative (37.8%) (*p* < 0.001). Furthermore, the degree of clearance (as signified by the presence of anti-HBs and coexistence of anti-HBc) was less in the HTLV-1-positive individuals when taking into consideration this higher exposure history to HBV. There were 198 HTLV-1-positive individuals who had serological status consistent with clearance of HBV. When considering those for whom HBV exposure was found, 56.3%
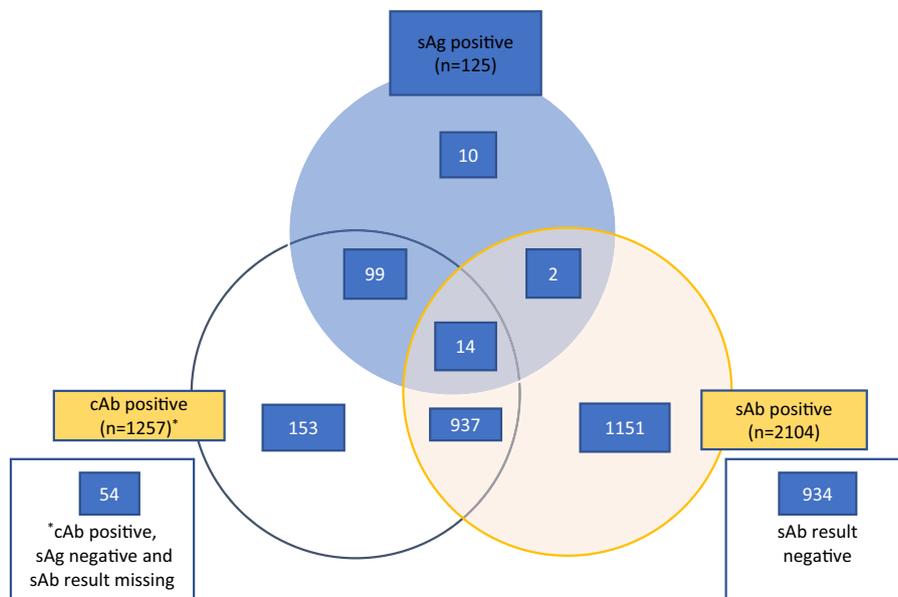

Figure 2. HBV status of HTLV-1-negative subjects (*n* = 3354).

(198/352) had developed serological profiles consistent with clearance. In comparing this to the HTLV-1-negative cohort, 37.8% (1269/3354) had previous exposure to HBV and 27.9% (937/3354) had serology consistent with clearance.[28] This means that 73.8% (937/1269) formed anti-HBs and anti-HBc after HBV exposure. When comparing the difference between HTLV-1-positive and HTLV-1-negative groups and the formation of serological markers consistent with HBV clearance, there was a statically significant difference at 56.3% and 73.8%, respectively ($p < 0.001$). This result shows that the formation of anti-HBs and anti-HBc did not occur as frequently in the HTLV-1-positive individuals despite a higher exposure to HBV.

Without a clinical correlation or analysis of vaccination status, it was not possible to determine any interaction between HBV and HTLV-1. The immune modulating effects of HTLV-1 are thought to be involved in a higher prevalence of bronchiectasis, Strongyloides infection, BSI, and dermatitis and to play a role in worsening HCV outcomes.[1,20,27,29] The lower formation of anti-HBs and anti-HBc in the HTLV-1-positive group supports the theory that persistent HBV infection exists in the setting of HTLV-1 positivity. Further there may be a decreased incidence of HBV clearance in this group if there is an inability to achieve an anti-HBs and anti-HBc positive status.

Alternatively, it is possible that early perinatal infection with HBV, associated with ongoing CHB infection, is a risk factor for HTLV-1 acquisition later in life. This implies that HBV vaccination may be a tool for the prevention of HTLV-1. Evidence for this hypothesis is sparse; however knowledge of the complex interactions between both viruses (HBV and HTLV-1) and intracellular autophagy pathways is an evolving area.[30–32] It has been reported that the HBV X protein induces autophagy and has a repressive effect on lysosomal function, the combination of which favours viral replication and/or envelopment.[32] Similarly it is reported that HTLV-1 also influences lysosomal function through the modulation of autophagy pathways to enhance its own replication.[31] It is therefore conceivable that the effects of chronic infection with HBV on autophagy could potentially facilitate an environment conducive to the establishment of a chronic HTLV-1 infection. Either of these processes between the two viruses would have implications for the management of HBV in the setting of endemically high HTLV-1.

While there have been efforts to determine co-infection status internationally, there is little evidence in any of the studies to date that HTLV-1 impacts the clearance of HBV (Table 1). This may be because endemic HTLV-positive communities have not documented a prevalence of HBV/HTLV-1 seropositivity as high as that described here.

Given this high prevalence of co-infection not seen previously outside of Australia, it is important to discuss the distinctive features of both HBV and HTLV-1 in the Northern Territory. The Australo-Melanesian subtype 1c is a divergent strain of HTLV-1 unique to Australia, Papua New Guinea, the Solomon Islands, and Vanuatu.[33] Although not unique to this genotype, it has been described as being linked to bronchiectasis, BSI, ATLL, HAM and Strongyloides infection. In a previous study of hospitalized patients in Central Australia, a multivariable model was unable to define an association between HBV infection and HTLV-1, yet the proportions of co-infection were significantly greater in the HTLV-1 group.[1]

Unique to the Northern Territory is the predominance of HBV-infected individuals carrying the HBV C4 sub-genotype. This recently discovered sub-genotype may have a higher potential for progressive liver disease and is a different serotype to that used in vaccination programmes.[8,10] While the clinical correlation between these two unusual virus strains remains to be elucidated, it is possible that the interaction between the viruses may be exacerbated by these differences.

Limitations to this data collection study include the inability to determine the indication for testing, absence of information on vaccination history, and variability of HTLV-1 positivity throughout the Northern Territory. A small number of patients did not have all three serological markers tested. In the HTLV-1-positive group, 11 patients had isolated anti-HBc and were HBsAg-negative, but had no anti-HBs result. In the HTLV-1-negative group, there were 54 with anti-HBc positivity who were HBsAg-negative and for whom there was no anti-HBs result. This does not materially change the results found.

Restricting the data collection to a single Northern Territory pathology provider means that a small proportion of HTLV-1 results may have been missed. There are currently three pathology providers in the Northern Territory; however the majority of testing for the active clinical indications is performed through the provider in this study.[22] With this noted, the HBsAg prevalence of 3.6% in the HTLV-1-negative cohort is similar to the incidence now found more broadly in Northern Territory Australians (personal communication, J. Davies).[5]

A unique HTLV-1-positive population with a higher incidence of HBV exposure than in those who are HTLV-1-negative is described herein. Furthermore, these individuals also have a much higher prevalence of HBsAg positivity when compared to those testing negative for HTLV-1. The lower prevalence of combined anti-HBs with anti-HBc in the HTLV-1-positive individuals does raise the possibility that an interaction with HTLV-1 may be occurring, causing lower rates of clearance. Further investigations into this and the plausible immune interaction between the two viruses are necessary and may have therapeutic implications.

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Ethical approval

This study was approved by the Human Research Ethics Committee of the Menzies School of Health Research (Ref. 2016-2654) and the Central Australia Human Research Ethics Committee (Ref. 16-429).

Conflict of interest

We have no conflict of interest.

Acknowledgements

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