Editorial Commentary

Transfusion transmitted HTLV-1 and incidence of HTLV-1 in South African blood donors

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HTLV-1 occurs world-wide but is more prevalent in some areas including southern Japan, the Caribbean region, parts of South America, Sub-Saharan Africa and the Middle East, Australia and Melanesia (1-3). The reason for this unusual geographical distribution is not known. An interesting aspect of this virus is that only a few nucleotide substitutions are observed among virus strains of HTLV-1. This variability of nucleotides is specific to the geographical origin of the patients. HTLV-1 was originally acquired by humans through interspecies transmission from STLV-1 (simian T-cell leukaemia virus type 1) infected monkeys in Africa, Europe and Asia (1).

HTLV-1 infection can lead to two serious diseases: a malignant T CD4+ cell lymphoproliferation, of very poor prognosis, known as adult T-cell leukaemia/lymphoma (ATLL) and a severe chronic neuro-myelopathy named tropical spastic paraparesis or HTLV-1-associated myelopathy (TSP or HAM) (4). HTLV was the first retrovirus shown to cause malignancy in humans (4). Other diseases are associated to HTLV-1 infection in some high endemic areas, such as uveitis in Japan, infective dermatitis in Jamaica, Brazil and Africa. Of individuals who are true positive and carriers there is about 1% to 5% chance of developing ATL during a 70-year lifespan. Another 2% may develop TSP after 5 to 10 years (5).

The world and regional estimation of HTLV-l prevalence are reasonably well known but some large regions/areas have not been investigated for HTLV-1 infection. This is true of some highly populated regions of Asia and in North and East Africa. Most data on the prevalence of HTLV-1 is based on the study of blood donors, pregnant women and hospitalized patients (1). There are not many population-based studies to estimate HTLV-1 prevalence in large areas, or at a country level. Interestingly, HTLV-1 distribution is not homogeneous and instead may be present, as small foci or clusters with a high prevalence near areas with low endemicity (1). This has been reported in southern Japan and some areas of South America and Central Africa. The most extensive summary of HTLV-1 prevalence in the general population of different countries or areas can be found in the Appendix of the technical report by European Centre for Disease Prevention and Control (1). HTLV-1 infected persons were most numerous in Japan the African continent and South America (1). Twenty-six years ago, de Thé and Bomford (6) estimated the total number of HTLV-1 carriers to be 10–20 million people world-wide. Later Gessain and Cassar (7) estimated that there are at least 5–10 million HTLV-1 infected individuals. But these results were based on individuals originating from known endemic areas with reliable epidemiological data, representing a base population of approximately 1.5 billion. Correct estimates in other highly populated regions, such as China, India, North West Africa and East Africa are not available but the current number of HTLV-1 carriers is probably much higher than reported by Gessain and Cassar (7).

In localized high endemic areas, virus prevalence may be 1–2% but can be as high as 40% in people >50 years of age (1) yet might be nearly absent in nearby areas. Vermeulen *et al.* (8) report a virus prevalence ranging from 1% to as high as 9% in several sub-Saharan Africa countries

but advise caution in comparing these rates because of different testing methodologies or uncertainty about the nature of confirmatory studies. Ngoma *et al.* (3) summarized 25 published reports of HTLV in sub-Saharan Africa blood donors. The rates of occurrence ranged from 0% to 5.0% with an overall rate of 0.68% for HTLV-1 and 1.11% for HTLV-1, -2. The heterogeneity of results seemed more related to the size of the study rather than other factors. The carrier rate varies in different populations and increases with age although data is limited about many different populations. It is interesting that there appears to be some difference in the prevalence of HTLV-1 versus HTLV-2.

This virus can be transmitted by blood transfusion, sexual contact, IV drug abuse or from an infected mother to her child (9-12). Most individuals who become infected are asymptomatic and many or most may not be aware of their infection. Severe complications occur in only a small percent of those who become infected. This also means that there may be infected individuals who harbor the virus but are unaware and could donate blood. After transfusion of cellular blood products containing anti-HTLV approximately 60% of the recipients develop anti-HTLV indicating transmission of infection (9-11,13).

Because of the high likelihood of transmission from an infected donor there is considerable interest in the prevalence on HTLV in blood donors. Screening blood donors is done mostly in areas of high prevalence. The WHO reports that 37 countries test all blood donors for HTLV-1, -2 and seven others do selective testing of first-time donors or those not previously tested (14). The distribution of those countries is Africa 1, Americas 23, E Mediterranean 5, Europe 11, W Pacific 4. The incidence of HTLV in blood donors is very low in the US. Screening of donors for HTLV was initiated in the US in 1988 (15) but is no longer done there.

Recently Vermeulen *et al.* (8) have reported a case of transfusion transmission of HTLV. The recipient developed lower limb weakness several months following transfusion and was found to be positive for HTLV-1 in both blood and CSF. The clinical situation was thus tropical spastic paresis or HAM. Look back revealed a blood donor who was found to be HTLV-1 positive. The agent in the blood donor and the recipient was identical based on phylogenetic analysis. While this analysis confirmed the identity between donor and recipient the strain had several nucleic acid sequences that were different from those previously found in South Africa. Thus, the phylogenetic evidence established that these two strains were identical in donor and recipient but do not belong to frequent and widespread strains found throughout South Africa.

The investigators set out to determine the prevalence of HTLV-1/2 in South African blood donors. They placed an over emphasis on testing black and mixed-race donors because those are the groups in which they expected to find a higher prevalence of HTLV-1/2. They also obtained samples from Asian and Caucasian donors and reported testing 46,752 blood donors in South Africa (8). Samples were collected only once from each donor so there was no overlap which makes the data more consistent.

Because they emphasized black and mixed-race donors, the number of samples from these racial groups was different from the racial mix of the blood donors. Thus, the results can only apply directly to the black and mixed-race population. This does not give us direct data of the incidence of HTLV-1/2 in all of the South African donor population although the authors did some calculations to extrapolate the results to the entire donor population.

A total of 46,752 donors were tested of which 73% were black 13% mixed-race 12% white and 2% Asian. Unfortunately, they do not give the racial mix of blood donors, so we do not know the difference between donor population and the donors sampled. Of those samples 133 or 0.28% were initially reactive and a 111 of those were repeat reactive and 57 or 0.12% were confirmed positive. There was a statistically significant difference in positive rates according to age group, gender and race but not the zone or area of the country and also not to new or repeat donor status. The highest prevalence was in black donors at 0.16% with very low rates in other race groups. This was statistically significant with black donors having 20 times the odds of being positive compared to Caucasian donors.

In extrapolating to the total blood supply for South Africa, there was a prevalence rate of 0.062% which would result in 509 potentially infectious units annually.

Previous studies had shown a 6–10 decreased prevalence of HTLV-1 in donors compared with the general population (8). Using this to project the difference between blood donors and the general population, the data from blood donors suggest that there is a prevalence of HTLV-1 of about 1% in the adult black population of South Africa. The issue of rates in the black population is of particular interest to South African National Blood Service (SANBS) because of their efforts over the years to increase blood collections from black donors. Thus, those efforts can be expected to increase the overall prevalence of HTLV in the in the blood supply of SANBS.

The authors projection of 509 prevalence of HTLV-1 positive units in the national blood supply should project many more cases of transfusion transmission than have been observed. This might suggest that this estimate is unreasonably high. If the projection of 60% for asymptomatic infection from an HTLV positive unit of blood is accurate there should be quite a few cases of HTLV infection that are not being identified.

The authors suggest that the apparently lower-than-expected rate of the transfusion transmitted HTLV could be due to: (I) lack of awareness of HTLV infection among the healthcare providers; (II) poor hemovigilance; (III) the assumed 50% mortality after transfusion; (IV) asymptomatic phase in most patients but especially prolonged phase before disease occurs; (V) prolonged blood storage time might possibly decrease infectivity.

Because a relatively large number of infectious units was projected, the question of screening donors for HTLV becomes pertinent and important. However, after detailed analysis using a risk-based decision-making framework and considering the available financial resources and health economics (16) SANBS has not implemented screening for HTLV.

The strength of this study is the large number of samples and weaknesses include limited risk factor information, relatively small number of positive samples, oversampling of black and mixed-race donors and limited ability to extrapolate to the general population (8). Some of the information becomes a little bit complicated to interpret because of the investigators decision to overly sample black donors. While this makes sense that they believed that is where they would find the highest rate of positivity, it limits their ability to project the number and rate of positive donors on a national scale and thus to project the magnitude of potential transmission of HTLV. This increases the difficulty in decision-making as to whether to implement routine testing. It is also striking that given the likely rate of positive donors, only one case of transfusion transmitted infection has been identified and the authors speculate on the reasons for this. This is a helpful well-done study.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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