

Human T-lymphotropic virus and transfusion safety: does one size fit all?

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Human T-cell leukemia viruses (HTLV-1 and HTLV-2) are associated with a variety of human diseases, including some severe ones. Transfusion transmission of HTLV through cellular blood components is undeniable. HTLV screening of blood donations became mandatory in different countries to improve the safety of blood supplies. In Japan and Europe, most HTLV-infected donors are HTLV-1 positive, whereas in the United States a higher prevalence of HTLV-2 is reported. Many industrialized countries have also introduced universal leukoreduction of blood components, and pathogen inactivation technologies might be another effective preventive strategy, especially if and when generalized to all blood cellular products. Considering all measures available to minimize HTLV blood transmission, the question is what would be the most suitable and cost-effective strategy to ensure a high level of blood safety regarding these viruses, considering that there is no solution that can be deemed optimal for all countries.

Human T-lymphotropic virus 1 (HTLV-1) and human T-lymphotropic virus 2 (HTLV-2) are retroviruses responsible for persistent human infection but only rarely with severe clinical manifestations.^{1,2} To date, although there has been no conclusive evidence that HTLV-2 is an etiologic agent of any specific disease, it has been associated to several pathologies.³

As soon as they were discovered, it was clear that HTLV-1 and HTLV-2 were transmitted by the transfusion of cellular blood products.⁴ To date, the safety measures are primarily based on donor suitability assessment and leukoreduction of cellular blood components.⁵ Plasma and plasma-derived medicinal products cannot transmit these viruses. The introduction of routine screening of blood donations for HTLV antibodies was motivated in many countries, especially in Europe, by the need to prevent HTLV-positive donations by donors from endemic areas from entering the blood supply.

ABBREVIATIONS: ATL = adult T-cell leukemia; HAM/TSP = HTLV-associated myelopathy/tropical spastic paraparesis; PRT(s) = pathogen reduction technology(-ies); QALY = quality-adjusted life-year; WB = Western blot; WP = window period.

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Pathogen reduction technologies (PRTs) offer a new approach to increasing blood safety by actively or directly targeting possible even emerging pathogens or donor white blood cells (WBCs), but their use is still hampered by the fact that none of the various technologies has so far been applied to whole blood or red blood cells (RBCs).⁶ The aim of this review article is to analyze the role played by HTLVs in transfusion medicine and to assess preventive measures and their cost-effectiveness.

THE VIRUSES: CHARACTERISTICS AND RELATED DISEASES

HTLV-1 and its congener HTLV-2 are retroviruses belonging to the *Deltaretrovirus* genus of the subfamily *Orthoretrovirinae*.⁷ HTLV-1 was the first human retrovirus discovered in 1980 by Poiesz and others;⁸ 2 years later, HTLV-2 infection was documented for the first time.⁹ Seven different HTLV-1 subtypes exist, each endemic to a particular region.^{10,11} HTLV-2 is classified into four molecular subtypes each with a specific geographic association.¹²

HTLV-1 and HTLV-2 show considerable homology in terms of genome structure, replication pattern, and properties of the structural, regulatory, and accessory proteins. Both viruses utilize the glucose transporter type 1 and neuropilin-1 cellular receptors for their entry, although only HTLV-1 is dependent on heparan sulfate proteoglycans.¹³ Still today, little is known about many aspects of HTLV transmission. HTLV-1 mainly affects CD4+ lymphocytes, while HTLV-2 predominantly affects CD8+ lymphocytes albeit dendritic cells also carry proviruses. Although cell-to-cell virus replication is “more efficient than cell-free transmission,” recent insights suggest that the mechanism of transmission differs from the dogma that cell-cell transmission of HTLV-1 only involves interaction between T cells.¹⁴

HTLV-1 and HTLV-2 are very different in terms of clinical impact. The majority of HTLV-1-infected individuals will remain asymptomatic and only a minority of them develop disease. The two most common pathologies are adult T-cell leukemia (ATL) and HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP).¹⁵ Depending on ethnicity and sex, approximately 2% to 3% of infected individuals develop ATL and 0.25% to 4% develop HAM/TSP.³ Other associated pathologies include neurologic diseases,¹⁶ uveitis,¹⁷ chronic inflammatory arthropathy,¹⁸ infective dermatitis,¹⁹ Sjögren's syndrome,²⁰ polymyositis,²¹ bronchopneumopathy,²² and oral manifestations such as aphthous stomatitis, herpes labialis, and nongenital warts.²³ Most infected individuals remain lifelong asymptomatic carriers and in some cases with only cutaneous manifestations, thus confirming the importance of anamnesis and physical examination of blood donors with suspected infection.^{23,24} The mechanisms by which HTLV-1 causes such different clinical pic-

tures are not understood and it is also not known why disease typically occurs decades after initial infection and affects less than 10% of carriers. Since no viral genotype has been associated with any particular disease and there is a large antiviral immune response, the currently accepted hypothesis is that the host immune response is the main determinant of the risk of disease.²⁴

HTLV-2 has been linked to several cases of HAM/TSP and to increased overall neurologic disability.²⁵⁻²⁷ Recent data suggest that HTLV-1 and HTLV-2 carry similar risks in terms of resulting in non-HAM neurologic illness. HTLV-2 may have an impact on platelet (PLT) count and be responsible for infection with pneumonia, bronchitis, arthritis, asthma, and dermatitis.^{28,29}

THE DIAGNOSIS: TESTS AND ALGORITHMS

The serologic diagnosis of the infection is based on an enzyme immunoassay (EIA), which usually requires a confirmation with immunoblot assays, namely, Western blot (WB) or line immunoassays. The first screening tests for the detection of HTLV-1 and -2 antibodies, introduced in the mid-1980s, used HTLV-1 whole viral lysate as the only antigen and had a poor HTLV-2 detection capacity.³⁰ The new generations of assays recently released are based on recombinant and/or synthetic peptide antigens alone or in combination with viral lysate, include HTLV-2-specific antigens and, therefore, have an improved sensitivity for HTLV-2 antibody-positive specimens.³⁰

Although these serologic screening assays generally have a higher specificity than the earlier tests, they cannot be accurate enough to distinguish one virus infection from the other as some antibodies recognize both HTLV-1 and HTLV-2 antigens. In addition, they have a low positive predictive value, especially in low-risk populations such as blood donors. Therefore, all repeatedly reactive specimens must be further tested to confirm the presence of HTLV-1- and/or HTLV-2-specific antibodies.

WB is most frequently used for this purpose and commonly exploits HTLV-1 viral lysate, to which recombinant envelope type-specific antigens can be added to improve sensitivity and specificity for serologic confirmation of HTLV-1 and HTLV-2 infections.³⁰ Confirmatory testing excludes HTLV infection in a high percentage of blood donors who initially tested positive to EIA.³¹ The sample will be considered seronegative if no reactivity to viral antigens is observed with WB, indeterminate if there is specific reactivity for HTLV antigens without fulfilling the criterion for seropositivity, and seropositive if reactivity to all antigens defined by the manufacturer as a positive pattern is found.³²

Usually, indeterminate WB profiles do not represent true HTLV infection but, in high-risk populations or endemic areas, where they can range from 0.02% to 50%,³³

they may reveal a seroconversion.³⁰ The causes of indeterminate WB tests as well as their clinical meaning are still not clear.³³ The high proportion of indeterminate results is a challenge worldwide and a serious problem for blood banks because, depending on the reactivity profile, WB may not be able to detect HTLV-1 or HTLV-2 infections.³⁴ Molecular tests have been particularly useful for: 1) discrimination between infection from Type 1 or Type 2 virus; 2) definition of dual infection (HTLV-1 and HTLV-2); 3) definition of virus subtypes; 4) diagnosis in subjects with suspected seroconversion; 6) resolution of cases with seroindeterminate results;³⁴ and 6) investigation of neonatal transmission, since the serologic tests in infants can detect maternal antibodies.³⁵

They are also used to quantify the level of HTLV infectivity, or proviral load, which is an important risk marker for the development of diseases associated with HTLV-1. Indeed, the proviral load of HTLV-1 in peripheral blood is higher compared to infection by other retroviruses, and although the numbers vary greatly between infected individuals, the average proviral load in healthy carriers is significantly lower than that of symptomatic patients.^{32,34,36}

Real-time polymerase chain reaction (PCR) has been preferentially employed over conventional PCR because of its much higher sensitivity and specificity and low contamination risk. It is also easy to use, gives rapid results, and has proved to be a valid substitute for confirmatory serologic tests. As HTLV does not have large quantities of circulating viral RNA, plasma and serum are not suitable for molecular diagnosis. Considering the HTLV tropism for lymphocytes, whole blood is the biologic sample of choice for the molecular diagnosis of infection.

TRANSMISSION ROUTES

HTLV-1 and HTLV-2 have similar transmission patterns. Data on the length of the HTLV serologic window period (WP) are determined by the sensitivity of the antibody assay utilized and are reported in the 1992 study by Manns and colleagues,³⁷ which yielded a median 51-day WP but was calculated with early-generation assays. Although in the past 23 years there has been significant improvement in assay sensitivity (third-generation assay) and the WP is likely much shorter, to the knowledge of the authors there are no recent data on this important topic. Interestingly, a 5-day noninfectious WP was deducted from the above-mentioned 51-day WP in the 2009 study by Davison and coworkers³⁸ who, in the calculation to estimate the risk of HTLV potentially infectious donations entering the UK blood supply, used a 46-day WP. There are no reports of infected individuals who had viral clearance.

The most important routes of HTLV-1 transmission are mother to child (mainly through breastfeeding), sexual intercourse, and transfusion of blood products containing infected lymphocytes,³⁷ which is the most efficient mode

of HTLV-1 transmission.³⁹ Many reports have also documented its transmission through kidney, liver, marrow, and lung transplant.⁴⁰ The efficiency of the mother-to-child transmission is estimated to be 20% and has been correlated with individual variables such as HTLV-1 proviral load, the concordance of HLA Class I type between mother and child, and the duration of breastfeeding.⁴¹ The higher the exposure and proviral load, the higher the risk of sexual transmission of both HTLV-1 and HTLV-2. HTLV-2 shares some of these transmission routes but intravenous (IV) drug use is its main mode of transmission.⁴²

EPIDEMIOLOGY

Prevalence in the general population

According to HTLV-1 prevalence, the world regions are defined endemic (0.5 to 20%), at medium prevalence (0.1 to 0.5%), or not endemic (less than 0.1%; Fig. 1).⁴³ However, at the moment, the global epidemiology of HTLVs is still not clear. Prevalence data available are not accurate due to several reasons such as: 1) the lack of data from some parts of the world (Fig. 1); 2) prevalence overestimation related to the low specificity of the early serologic screening tests; 3) selective testing of population groups (e.g., blood donors, pregnant women, and hospitalized patients); and 4) an exceedingly heterogeneous distribution of the infection in some countries.⁴²

In 2012, Gessain and Cassar⁴⁴ reported that worldwide there are 5 to 10 million HTLV-1 carriers, a lower estimate in comparison to the previous one of 10 to 20 million. HTLV-1 is not a ubiquitous virus but is present throughout the world with clusters of high endemicity often close to areas where the virus is almost nonexistent. In these foci, the HTLV-1 seroprevalence in adults is estimated to be at least 1% to 2% but, in some specific clusters, it can reach 20% to 40% in persons older than 50 years.⁴⁴ Furthermore, there is a higher prevalence in women.

Most epidemiologic data are based on serologic studies rather than on molecular tests. In 1986, Ishida and Inuma⁴⁵ clearly demonstrated that Japan was a high endemic area for HTLV-1. Interestingly, from the beginning, in Japan the geographic distribution of HTLV-1 carriers has been irregular and the greatest prevalence is observed in southwestern Japan (Kyushu island and the Okinawa archipelago).⁴⁶ Almost contemporarily, US researchers showed that the Caribbean and surrounding regions were also endemic for HTLV-1⁴⁷ and ATL patients were reported in the Caribbean community living in the United Kingdom.⁴⁸

Other endemic zones are some areas of Colombia and French Guyana in South America, some parts of Sub-Saharan Africa and the Middle East (Mashad region in

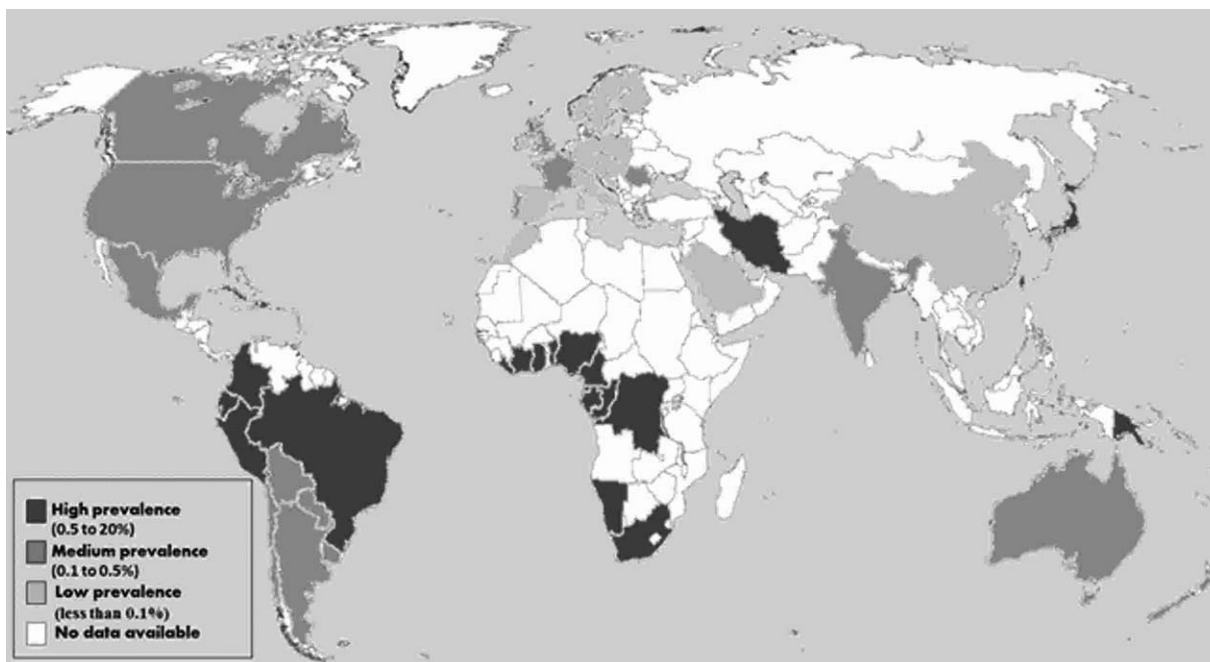


Fig. 1. HTLV-1 prevalence worldwide.⁴³

Iran), and rare isolated clusters in Austral-Melanesia.⁴⁴ In Europe, only Romania seems an HTLV-1–endemic region.⁴⁴ Although the reason for this “ethnic distribution” is not well understood, it is probably related to a “founder effect” and a subsequent persistently high viral transmission rate in some populations.⁴²

HTLV-2 is endemic in some African populations and in Amerindian tribes from North, Central, and South America, especially from Brazil, where some tribes show a prevalence of 33%.⁴⁹ It shares similar epidemiologic features with HTLV-1: 1) the presence of population clusters with high prevalence, 2) a higher prevalence in women, 3) an increased prevalence rate with age, and 4) the same routes of transmission. HTLV-2 is also present among IV drug users, mainly in the United States and in Europe.⁴³ Interestingly, in Amerindians the seroprevalence of HTLV-1 and HTLV-2 ranges from 0.8% to 6.8% and from 1.4% to 57.9%, respectively.⁵⁰

Prevalence in blood donors

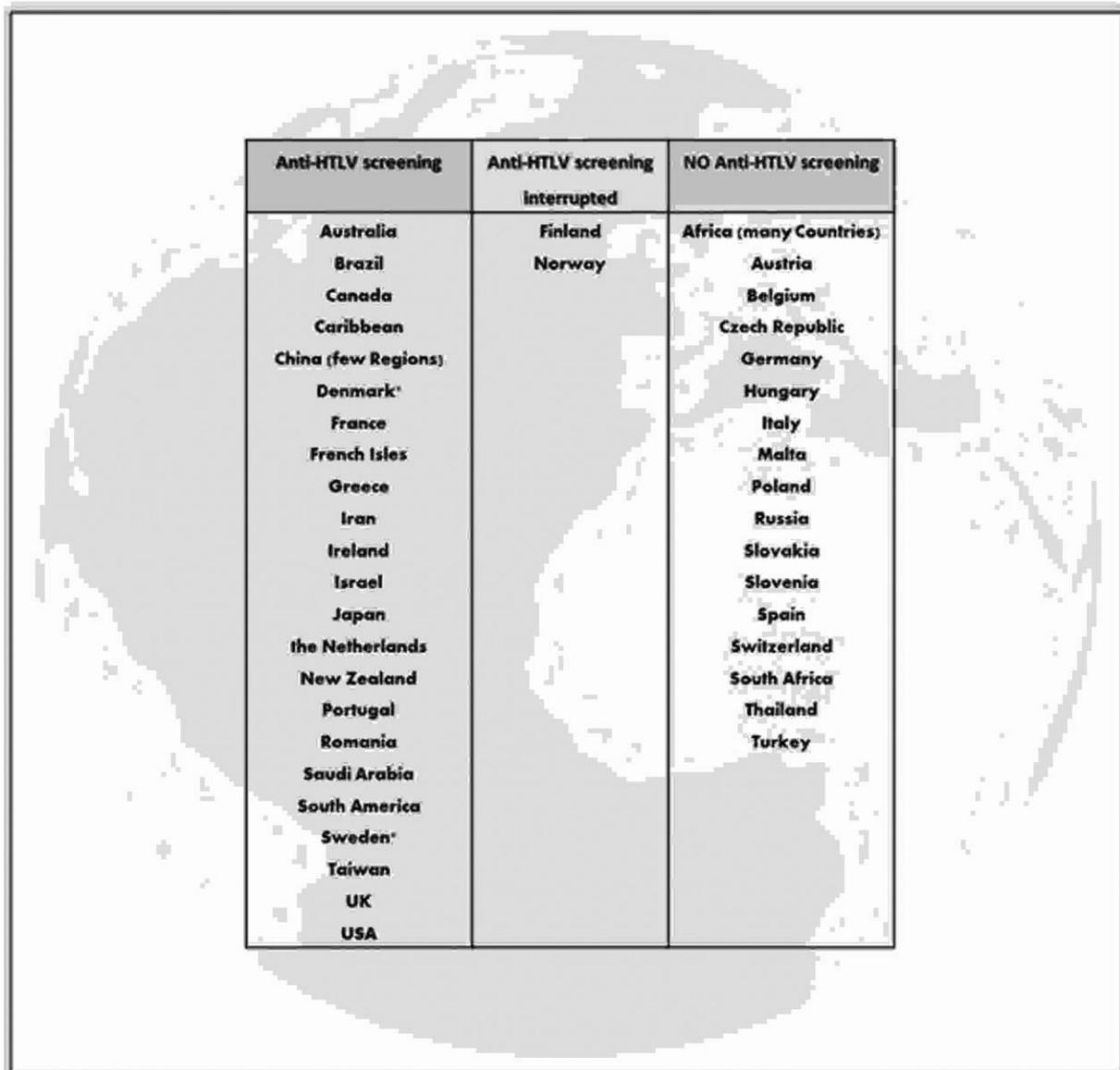
The HTLV (mainly HTLV-1) prevalence in blood donor populations ranges from 0% to approximately 5% to 6% in some areas such as the Seychelles, some islands of South Japan, and African countries.⁴⁴ There are different seroprevalence rates for each continent. They range from 0%^{51–53} to 3.6%⁵⁴ in Africa and from 0%⁵⁵ to 1.5%⁵⁶ in the Americas (with a peak of 2% in some Caribbean islands).⁵⁷ In Australia, the prevalence ranges from 0.001%⁵⁸ to 0.3%⁵⁹ and in Asia from 0%^{60–66} to 1.9%,⁶⁷ while in Europe it ranges from 0%^{68–70} to 2.12%.⁷¹ This last figure, reported in the Netherlands in 1993, decreased to 0.41% in the

period 2001 to 2010;⁷¹ moreover, in 1994, Zaaijer and coworkers⁷² showed a reduction of the seroprevalence rate from 0.13% to 0.002% after WB confirmatory testing. Furthermore, in Europe and Japan, most HTLV-infected donors are HTLV-1 positive, whereas in the United States a higher prevalence of HTLV-2 positivity is reported.^{36,43} Interestingly, a reduction of HTLV seroprevalence was reported in some regions of the Americas: it decreased from 0.0093% in 1990 to 0.0011% in 2010 in Canada,⁷³ from 0.73% in 1991⁷⁴ to 0.24% in 2010 in Chile,⁷⁵ and from 0.6% in 1995 to 2000 to 0.1% in 2002 to 2008 in the Minas Gerais Region (Brazil).⁷⁶

Regarding HTLV incidence (per 100,000 donors/year), it is closely connected with the local rate of prevalence in this selected population and often estimated by mathematical models. From 2007 to 2009, in Brazil, it was 3.59 per 100,000;⁷⁷ from 2010 to 2012, in France, it was 0.4 per 100,000;⁴² from 1995 to 2001 and from 2008 to 2009, in the United States, it was 0.239 and 0.304 per 100,000, respectively.^{78,79} Interestingly, from 2005 to 2013, in Australia, only one case of HTLV positivity among previously negative repeat donors was reported.⁸⁰

PREVENTIVE MEASURES

The prevention of transfusion transmission of HTLVs can be performed through testing blood donors. An anti-HTLV-1 screening program of donated blood was introduced in Japan in 1986.⁸¹ In 1988, the Centers for Disease Control and Prevention recommended anti-HTLV-1 screening in the United States.⁸² In Canada, the



Anti-HTLV screening	Anti-HTLV screening interrupted	NO Anti-HTLV screening
Australia	Finland	Africa (many Countries)
Brazil	Norway	Austria
Canada		Belgium
Caribbean		Czech Republic
China (few Regions)		Germany
Denmark*		Hungary
France		Italy
French Isles		Malta
Greece		Poland
Iran		Russia
Ireland		Slovakia
Israel		Slovenia
Japan		Spain
the Netherlands		Switzerland
New Zealand		South Africa
Portugal		Thailand
Romania		Turkey
Saudi Arabia		
South America		
Sweden*		
Taiwan		
UK		
USA		

Fig. 2. HTLV-1 and -2 screening in different countries (year 2015).^{39,81-86} *Only first-time donors screened.

Caribbean, and the French Islands, blood screening for HTLV-1 started in 1989.⁸³ In the 1990s screening started in France, Brazil, Australia, Denmark, Portugal, and Greece.³⁹ In 1995, Sweden decided to screen only the first blood donation for anti-HTLV-1 due to the almost nonexistent local transmission of the virus.⁸⁴ In 2002, the United Kingdom decided to test minipools (mixture of plasma from blood donors) using an EIA.⁸⁵ Finland and Norway interrupted HTLV screening in 2007 and 2008, namely, 7 and 13 years after its introduction, respectively.⁸⁶ The current situation of HTLV screening in different countries is reported in Fig. 2.

The results of hemovigilance and lookback studies have provided evidence correlating the transmission of

HTLV with cellular blood component transfusion. The factors critical to the efficiency of transmission include the number of contaminating WBCs. The HTLV proviral load and/or the number of infected lymphocytes required to cause infection and disease in recipients were addressed by several studies carried out in animal models. In 1990, the study by Kataoka and colleagues⁸⁷ carried out in a rabbit model of HTLV-1 showed that 0.01 mL of HTLV-1-infected blood containing 1.7×10^4 infected lymphocytes was able to transmit the infection. Other studies were aimed at setting up a rabbit model of clinical HTLV-1 disease and showed that reproducing an "ATL-like disease" required a minimum of 1×10^8 cells by intraperitoneal or IV injection.⁸⁸⁻⁹⁰ In addition, Kannian and colleagues⁹¹



Fig. 3. Current use of universal leukoreduction.

recently showed that, in rabbits, HTLV-2 has a lower infection and replication efficiency in comparison to HTLV-1. Experimental HTLV-1 infection, without disease development, in nonhuman primates was demonstrated in several monkey species inoculated with autologous (1×10^8)^{92,93} or homologous (1×10^7)⁹³ infected cells. More recently, development of clinical disease was reported in pig-tailed macaques after inoculation with 5×10^6 to 10×10^6 mangabey cells infected with an HTLV-1 molecular clone.⁹⁴

As far as HTLV-1 transmission in transfusion recipients is concerned, the early study by Okochi and Sato⁹⁵ pointed out that more than 10^7 lymphocytes were necessary for HTLV-1 infection through blood transfusion. A 1993 lookback study reported the transmission of HTLV-1 infection to a neonatal infant by transfusion of RBCs containing an estimated number of 8×10^7 contaminating WBCs.⁹⁶

A 2004 evaluation of HTLV-1 removal by filtration of blood components focused on provirus associated with mononuclear cell (MNC) fraction and showed a reduction of HTLV-1 (4.9 to 5.8 log) higher than that of WBCs.⁹⁷ This is consistent with the observation that commercially available filters remove more MNCs than granulocytes⁹⁸⁻¹⁰⁰ and efficiently retain T cells.¹⁰¹ The number of HTLV-1 copies detected in the MNC fraction was lower than 5×10^2 copies per filtered blood component.⁹⁷ These data are consistent with the findings that, in filtered blood components, lymphocytes are 2% to 7% of residual WBCs⁹⁸ and T cells range from 1.68×10^2 to 4.09×10^4 .¹⁰¹ Evidence of the protective effect of leukoreduction was also produced by the UK lookback study published in 2013, which

showed at least 93% reduction in the odds of transfusion-transmitted HTLV in comparison to nonleukoreduced blood components.¹⁰² Finally, a recent estimation of the infectious viral load required for HTLV-1 transfusion transmission and of the effectiveness of leukoreduction in preventing transfusion-related infectivity claimed that the transfer of more than 9×10^4 cells containing the HTLV-1 provirus is required to establish transfusion-transmitted HTLV-1 infection and leukoreduction “decreases the number of HTLV-1-infected leucocytes below this level in most blood components contaminated with HTLV-1.”¹⁰³

Therefore, besides the legal requirements regarding the highest amount of residual WBCs tolerated in blood components (namely, fewer than 5×10^6 per unit as required by the AABB,¹⁰⁴ the US Food and Drug Administration,¹⁰⁵ and EU Recommendations¹⁰⁶), a really efficacious leukoreduction of blood components is theoretically able to prevent HTLV transfusion transmission, although this has not been proven in humans. The current use of universal leukoreduction in different countries is reported in Fig. 3.¹⁰⁷

PRTs can be exploited for PLT concentrates and the irradiation of cellular blood components is an additional tool to reduce the number of WBCs and the consequent risk of seroconversion in immunosuppressed recipients.^{6,108}

TRANSFUSION RISK

Blood transfusion is still a risk factor for HTLV-1 infection for recipients in most African as well as other developing countries that lack appropriate public health policies and national blood systems. On the other hand, the residual

risk of transfusion-transmitted HTLV-1 in low-prevalence countries is really minimal³⁹ and, therefore, the risk of collecting an infected donation that can be undetected by screening tests is now estimated through mathematical models. These models assume that the aforementioned risk is almost completely due to donors in the acute infection WP and, therefore, is primarily dependent on the HTLV incidence rate and the duration of the assay-dependent WP.¹⁰⁹

The estimated residual risk for HTLV-1 and -2 transmission by blood transfusion is five per million donations in Brazil (2007-2009),⁷⁷ one per 3 million donations in the United States (2000-2001),⁷⁸ one per 7.6 million donations in Canada (2007-2010),⁷³ lower than one per million donations in Australia (2000/2003),¹¹⁰ and one per 20 million donations in France (2010-2012, excluding overseas territories).⁴² Interestingly, the last estimate does not consider the leukoreduction process, an extremely efficient preventive measure for this intracellular pathogen. It is important to underline that, when contextualizing transfusion risks, estimates below the threshold of one in 1 million are generally considered negligible.¹¹¹

In 2012, in the Netherlands, Prinsze and Zaaijer⁷¹ estimated that, without HTLV screening, on average 1.4 infected new donors and 0.5 infected regular donors per year would donate blood, causing 0.8 to 0.007 cases of HTLV disease per year. In 2014, in France, Laperche and Pillonel⁴² claimed that if (in metropolitan France) the antibody screening were abandoned, 104 transfusions of HTLV-positive blood products per year would occur. According to the authors' figures this would result in harmful consequences for one to two transfusion recipients per year without leukoreduction and for one recipient every 192 years in the event of 10% failure of filtration procedures.

However, the probability of HTLV transmission is also inversely proportional to the shelf life of (cellular) blood components, which lose their contaminant power during storage due to the decreasing viability of WBCs.⁴² The highest risk is associated with the transfusion of RBCs. The transmission rate of HTLVs ranges from 13% to 28% if RBCs with a shelf life of 14 days are transfused and increases to 25% to 75% when HTLV infected cellular blood products of less than 6 days are used.^{112,113}

There is no evidence that fresh-frozen plasma and plasma-derived medicinal products transmit HTLV-1 and -2, presumably because of the death of HTLV-infected lymphocytes due to plasma freezing⁴ and fractionation and for the fact that HTLVs are highly susceptible to inactivation by the many methods currently used in plasma fractionation.¹¹⁴ Isolated reports of HTLV-1-positive persons with hemophilia can be found, but in most cases negative results are obtained when HTLV-1 antibodies are assayed in this group of patients.¹¹⁵

COST-EFFECTIVENESS AND APPLICABILITY OF SCREENING TESTS

Several cost-effectiveness analyses of HTLV blood donor screening have been carried out. These studies took into account variables such as the prevalence and incidence of infection in the population, the risks of transmission, the mortality and morbidity of infected patients, and the expected survival rate of recipients of infected blood components.

According to the early study by Courouc e and coworkers¹¹⁶ in 1993, the cost per case of avoided contamination in a 6-month period was 1.36 million French francs. In the same year, in the United Kingdom, Brennan and collaborators¹¹⁷ estimated that the minimum cost of preventing a single transmission event was £30,000 while the cost of preventing one case of HTLV-related disease acquired through transfusion was £1.3 million.

In 1997, Saily and colleagues¹¹⁸ estimated the cost-effectiveness ratios of HTLV screening tests performed in France using two efficiency measures: cost per prevented seroconversion or positive blood donation detected (6,137,346 francs) and cost per case of prevented leukemia (34-307 million francs).

In 1998, in Sweden Tynell and colleagues⁸⁴ showed that the cost of preventing one HTLV transmission was \$440,000 when only new donors were screened. HTLV screening was estimated to prevent one death every 200 years at a minimum cost of \$36 million. They took into account only the screening costs and did not perform sensitivity analysis and discounting.¹¹⁹

In 2000, the study by Stigum and colleagues¹²⁰ showed that when the HTLV prevalence among donors is one per 100,000, the estimated cost of testing all new blood donors for HTLV is US\$9.2 million per life saved or US\$420,000 per quality-adjusted life-year (QALY) gained by the intervention. When the prevalence among donors is 10 per 100,000, the intervention will cost US\$0.9 million per life saved or US\$41,000 per QALY gained.

In 2012, the results of 10 years of Dutch experience showed that the cost of HTLV universal screening was €996,000 per year, while it was estimated at €54,000 per year if testing were limited to new donors.⁷¹ In the same year, the poor cost-effectiveness of HTLV-1 and -2 antibody testing for all donations was confirmed by Borkent-Raven and colleagues¹²¹ who showed that this strategy incurs high costs per QALY gained.⁴ In fact, the incremental cost-effectiveness ratio for anti-HTLV-1 and -2 testing is €45.2 million per QALY if all donations are tested, €2.23 million per QALY if only new donors are screened, and €27 million per QALY if only blood components for pediatric patients are tested.

The different costs reported in the aforementioned studies are probably due to several factors: 1) wide ranges of possible available tests, 2) different donor prevalence

rates, 3) different duration of transfusion recipient follow-up, 4) utilization of nonhomogeneous databases, and 5) differences in health care settings. Moreover, in areas with low prevalence, the cost-benefit of performing systematic blood donor screening for HTLV is really questionable also because many healthy donors with HTLV false positivity are unable to donate. In these areas, two factors play a key role in determining the high cost-effectiveness ratio for HTLV screening: 1) the low rate of morbidity and/or mortality after HTLV transfusion-transmitted infection⁷¹ and 2) the length of incubation time.

Interestingly, the threshold for cost-effectiveness is chosen rather arbitrarily.⁷¹ In the United States, US\$50,000 to US\$100,000 per QALY is accepted, while this figure is £30,000, €20,000, and \$4100 in the United Kingdom, in the Netherlands,⁷¹ and in developing countries,¹²² respectively.

CONCLUSIONS

Although not all infected cellular blood products are able to cause a disease in transfusion recipients,⁴² the impact of HTLV-related pathologies can be serious and the prognosis may be poor in terms of both survival and quality of life. In addition, the financial costs for health systems may be considerable. Therefore, the evaluation of prevalence and incidence in the general population and in blood donors, in countries where HTLV-1 is endemic, and the constant monitoring of HTLV-1 infection in nonendemic countries are of paramount importance to understand the virus burden on human health and to guide the decision process on preventive strategies.

Leukoreduction and freezing have proved to be effective in preventing HTLV transmission,⁹⁷ and PRTs for labile blood products might be an additional step toward the safety of recipients but, at the moment, their use is not generalized to all cellular blood products.¹²³

Many countries have implemented systematic and permanent universal screening of blood donors. However, the HTLV antibody screening (probably maintained in some countries under the precautionary principle, to take into account political, regulatory, and public perception issues, despite the high cost-effectiveness ratio) should be adapted to the particular needs of differing local populations as one size does not fit all.

Since 1988, more than 200,000 HTLV false-positive donors tested with licensed HTLV assays but without any evidence of infection have been deferred and none of these has been eligible for reentry, thus impacting on blood product self-sufficiency.¹²⁴ In developed nonendemic countries (Fig. 1) that started the universal control of donated blood (Fig. 2) and universal leukoreduction (Fig. 3), the current very low observed incidence and prevalence among blood donors (reflecting a very low estimated risk of an HTLV-1–positive donation entering the blood supply)

and the change in either the epidemiology of HTLV or the length of the serologic WP should prompt further review of the transmission risk and a possible change of the prevention strategy.⁸⁴ In these countries the systematic screening of all donations should be questioned (and possibly interrupted if already in use) after accurate evaluation of the residual HTLV transfusion risk, while the leukoreduction of cellular blood products should be maintained. However, withdrawal of HTLV testing should be preceded by the introduction of a permanent and strict control of leukoreduction efficacy to detect failures that could seriously impact on the safety of blood products. An additional and probably cost-effective tool to reduce the risk of HTLV transmission may be the implementation of the screening of selected donor populations (e.g., first-time donors or donors from endemic regions).¹¹⁶

The implementation of universal leukoreduction may be an effective prevention strategy also in industrialized nonendemic countries (Fig. 1) where blood donations are not screened for HTLV (Fig. 2). In developing nonendemic countries (Fig. 1), selective recruitment and/or screening could be exploited as strategies to prevent HTLV transfusion transmission. On the other hand, the suppression of anti-HTLV screening in developed endemic countries (Fig. 1) is not recommended; testing should be combined with leukoreduction until the efficiency of the latter procedure in preventing HTLV transmission is unequivocally proven.

In developing countries where HTLV is endemic (Fig. 1) and the residual risk of transfusion-transmitted infection is greater, unfortunately, the costs of universal testing and leukoreduction can be prohibitive and the limited financial resources are often earmarked for the prevention of other transfusion-transmitted infectious diseases. In these countries, due to the higher virus circulation and, therefore, higher seroconversion rates in repeat blood donors, other strategies such as improving blood donor selection process, counseling blood donor candidates about HTLV infection and its risk factors to limit the spread of the virus, and developing questionnaires validated and adapted to the local epidemiology¹²⁵ might play a key role.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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