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 pictures 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 coworkers[38] 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 Cassar[44] 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 Inuma[45] 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-1[47] 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

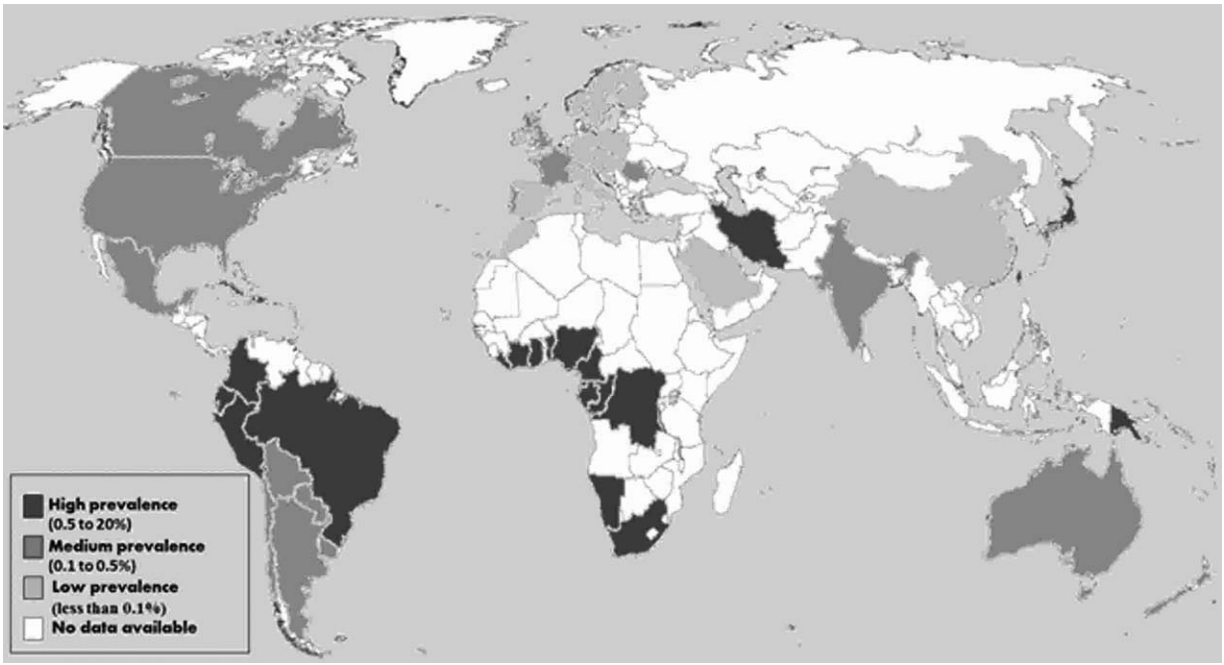

Fig. 1. HLTV-1 prevalence worldwide.[43]

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 coworkers[72] 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 1991[74] 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

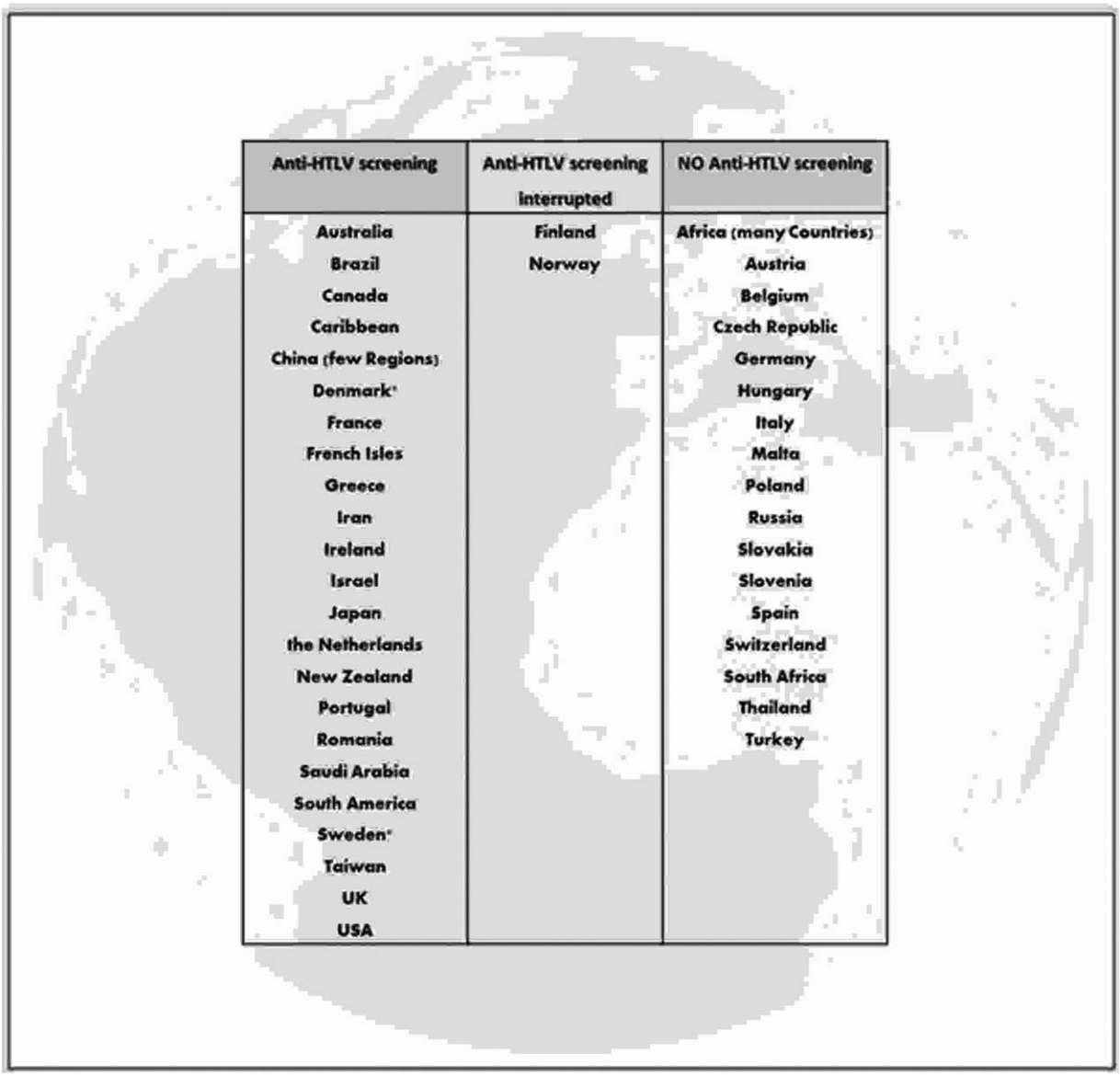

Fig. 2. HTLV-1 and -2 screening in different countries (year 2015).[39,81-86] *Only first-time donors screened.

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 colleagues[87] 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 colleagues[91]

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 Sato[95] 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 granulocytes[98-100] 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 WBCs[98] 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 Recommendations[106]), 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 minimal[39] 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 Zaaijer[71] 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 Pillonel[42] 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 freezing[4] 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 Couroucé and coworkers[116] 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 collaborators[117] 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, Sailly and colleagues[118] 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 colleagues[84] 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 colleagues[120] 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 colleagues[121] 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 infection[71] 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 epidemiology[125] might play a key role.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

REFERENCES

1. NCBI Taxonomy Browser. Human T-lymphotrophic virus [Internet]. Bethesda (MD): National Center for Biotechnology Information; [cited 2015 Feb 10]. Available from: http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi
2. Verdonck K, González E, Van Dooren S, et al. Human T-lymphotropic virus 1: recent knowledge about an ancient infection. Lancet Infect Dis 2007;7:266-81.

3. Murphy EL, Biswas HH. Human T-cell lymphotropic virus types I and II. In: Mandell G, Bennett J, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 7th ed. Philadelphia (PA): Churchill Livingston/Elsevier; 2010.
4. Okochi K, Sato H, Hinuma Y. A retrospective study on transmission of adult T cell leukemia virus by blood transfusion: seroconversion in recipients. Vox Sang 1984;46:245-53.
5. Seghatchian J. Universal leucodepletion: an overview of some unresolved issues and the highlights of lesson learned. Transfus Apher Sci 2003;29:119-21.
6. Picker SM. Current methods for the reduction of blood-borne pathogens: a comprehensive literature review. Blood Transfus 2013;11:343-8.
7. Bangham CR, Cook LB, Melamed A. HTLV-1 clonality in adult T-cell leukaemia and non-malignant HTLV-1 infection. Semin Cancer Biol 2014;26:89-98.
8. Poiesz BJ, Ruscetti FW, Gazdar AF, et al. 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;77:7415-9.
9. Kalyanaraman VS, Sarngadharan MG, Robert-Guroff M, et al. A new subtype of human T-cell leukemia virus (HTLV-II) associated with a T-cell variant of hairy cell leukemia. Science 1982;218:571-3.
10. Pessôa R, Watanabe JT, Nukui Y, et al. Molecular characterization of human T-cell lymphotropic virus type 1 full and partial genomes by Illumina massively parallel sequencing technology. PLoS One 2014;9:e93374.
11. Wolfe ND, Heneine W, Carr JK, et al. Emergence of unique primate T-lymphotropic viruses among central African bushmeat hunters. Proc Natl Acad Sci U S A 2005;102:7994-9.
12. Ishak R, Vallinoto AC, Azevedo VN, et al. Molecular evidence for infection by HTLV-2 among individuals with negative serological screening tests for HTLV antibodies. Epidemiol Infect 2007;135:604-9.
13. Jones KS, Fugo K, Petrow-Sadowski C, et al. Human T-cell leukemia virus type 1 (HTLV-1) and HTLV-2 use different receptor complexes to enter T cells. J Virol 2006;80:8291-302.
14. Pique C, Jones KS. Pathways of cell-cell transmission of HTLV-1. Front Microbiol 2012;3:378.
15. Araujo A, Hall WW. Human T-lymphotropic virus type II and neurological disease. Ann Neurol 2004;56:10-9.
16. McKendall RR. Neurologic disease due to HTLV-1 infection. Handb Clin Neurol 2014;123:507-30.
17. Buggage RR. Ocular manifestations of human T-cell lymphotropic virus type 1 infection. Curr Opin Ophthalmol 2003;14:420-5.
18. Nishioka K, Maruyama I, Sato K, et al. Chronic inflammatory arthropathy associated with HTLV-I. Lancet 1989;1:441.
19. Okajima R, Oliveira AC, Smid J, et al. High prevalence of skin disorders among HTLV-1 infected individuals independent of clinical status. PLoS Negl Trop Dis 2013;7:e2546.
20. Nakamura H. [Cell death of salivary gland epithelial cells and involvement of HTLV-I in Sjögren's syndrome]. Nihon Rinsho Meneki Gakkai Kaishi 2014;37:117-24. Japanese.
21. Caldwell CJ, Barrett WY, Breuer J, et al. HTLV-1 polymyositis. Neuromuscul Disord 1996;6:151-4.
22. Seki M, Higashiyama Y, Kadota J, et al. Elevated levels of soluble adhesion molecules in sera and BAL fluid of individuals infected with human T-cell lymphotropic virus type 1. Chest 2000;118:1754-61.
23. Yazdanpanah MJ, Maleki M, Joneidi N, et al. Cutaneous manifestations in HTLV-I positive blood donors. Iran J Basic Med Sci 2013;16:273-7.
24. Cook LB, Elemans M, Rowan AG, et al. HTLV-1: persistence and pathogenesis. Virology 2013;435:131-40.
25. Dooneief G, Marlink R, Bell K, et al. Neurologic consequences of HTLV-II infection in injection-drug users. Neurology 1996;46:1556-60.
26. Orland JR, Engstrom J, Fridey J, et al. Prevalence and clinical features of HTLV neurologic disease in the HTLV outcomes study. Neurology 2003;61:1588-94.
27. Biswas HH, Engstrom JW, Kaidarova Z, et al. Neurologic abnormalities in HTLV-I-and HTLV-II-infected individuals without overt myelopathy. Neurology 2009;73:781-9.
28. Bartman MT, Kaidarova Z, Hirschkorn D, et al. Long-term increases in lymphocytes and platelets in human T-lymphotropic virus type II infection. Blood 2008;112:3995-4002.
29. Poiesz BJ, Poiesz MJ, Choi D. The human T-cell lymphoma/leukemia viruses. Cancer Invest 2003;21:253-77.
30. Thorstensson R, Albert J, Andersson S. Strategies for diagnosis of HTLV-I and -II. Transfusion 2002;42:780-91.
31. Tomazini Pinto M, Strazza Rodrigues E, Maistro Malta T, et al. HTLV-1/2 seroprevalence and coinfection rate in Brazilian first-time blood donors: an 11-year follow-up. Rev Inst Med Trop Sao Paulo 2012;54:123-30.
32. Costa EA, Magri MC, Caterino-de-Araujo A. The best algorithm to confirm the diagnosis of HTLV-1 and HTLV-2 in at-risk individuals from São Paulo, Brazil. J Virol Methods 2011;173:280-6.
33. Waters A, Oliveira AL, Coughlan S, et al. Multiplex real-time PCR for the detection and quantitation of HTLV-1 and HTLV-2 proviral load: addressing the issue of indeterminate HTLV results. J Clin Virol 2011;52:38-44.
34. Andrade RG, Ribeiro MA, Namen-Lopes MS, et al. Evaluation of the use of real-time PCR for human T cell lymphotropic virus 1 and 2 as a confirmatory test in screening for blood donors. Rev Soc Bras Med Trop 2010;43:111-5.
35. Ribeiro MA, Proietti FA, Martins ML, et al. Geographic distribution of human T-lymphotropic virus types 1 and 2 among mothers of newborns tested during neonatal screening, Minas Gerais, Brazil. Rev Panam Salud Publica 2010;27:330-7.
36. Barbeau B, Hiscott J, Bazarbachi A, et al. Conference highlights of the 16th international conference on human retrovirology: HTLV and related retroviruses, 26-30 June 2013, Montreal, Canada. Retrovirology 2014;11:19.

37. Manns A, Wilks RJ, Murphy EL, et al. A prospective study of transmission by transfusion of HTLV-I and risk factors associated with seroconversion. Int J Cancer 1992;51:886-91.
38. Davison KL, Dow B, Barbara JA, et al. The introduction of anti-HTLV testing of blood donations and the risk of transfusion-transmitted HTLV, UK: 2002-2006. Transfus Med 2009;19:24-34.
39. Gonçalves DU, Proietti FA, Ribas JG, et al. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. Clin Microbiol Rev 2010;23:577–89.
40. European Centre for Disease Prevention and Control. Risk assessment of HTLV-I/II transmission by tissue/cell transplantation. Part 2: Risks by tissue type, impact of processing and effectiveness of prevention measures. Stockholm: ECDC; 2012.
41. Li HC, Biggar RJ, Miley WJ, et al. Provirus load in breast milk and risk of mother-to-child transmission of human T-lymphotropic virus type I. J Infect Dis 2004;190:1275-8.
42. Laperche S, Pillonel J. [Relevance of safety measures to avoid HTLV transmission by transfusion in 2014]. Transfus Clin Biol 2014;21:167-72. French.
43. Martins ML, Andrade RG, Nédir BH, et al. Human T-lymphotropic viruses (HTLV). In: Kochhar PK, editor. Blood transfusion in clinical practice. Rijeka (Croatia): InTech; 2012. Available from: http://cdn.intechopen.com/pdfs-wm/32730.pdf
44. Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. Front Microbiol 2012;3:388.
45. Ishida T, Hinuma Y. The origin of Japanese HTLV-I. Nature 1986;322:504.
46. Tajima K. Ethnic distribution of HTLV-1-associated diseases. Clin Virol 1992;20:366-73.
47. Caribbean Epidemiology Center. Public health implications of HTLV-1 in the Caribbean. Wkly Epidemiol Rec 1990;65: 63-5.
48. Catovsky D, Greaves MF, Rose M, et al. Adult T-cell lymphoma-leukaemia in blacks from the West Indies. Lancet 1982;1:639-43.
49. Carneiro-Proietti AB, Anna Bárbara F, Catalan-Soares BC, et al. HTLV in the Americas: challenges and perspectives. Rev Panam Salud Pública 2006;19:44-53.
50. Fujiyoshi T, Li HC, Lou H, et al. Characteristic distribution of HTLV type I and HTLV type II carriers among native ethnic groups in South America. AIDS Res Hum Retroviruses 1999;15:1235-9.
51. Nur YA, Groen J, Elmi AM, et al. Prevalence of serum antibodies against blood borne and sexually transmitted agents in selected groups in Somalia. Epidemiol Infect 2000;124: 137-41.
52. Mojaat N, Kaabi H, Hmida S, et al. Seroprevalence of HTLV-I/II antibodies in blood donors and different groups at risk in Tunisia. J Acquir Immune Defic Syndr 1999;22:314-5.
53. Hamza T, Moftah M. Detection of human T cell lymphotrophic virus type I infection among Egyptian blood donors. Vox Sang 2010;99:316.
54. Larsen O, Andersson S, da Silva Z, et al. Prevalence of HTLV-1 infection and associated risk determinants in an urban population in Guinea-Bissau, West Africa. J Acquir Immune Defic Syndr 2000;25:157-63.
55. Gastaldello R, Fazzola P, Caeiro L, et al. [Absence of HTLV-I/II virus circulation in blood donors from the provinces of Santa Fe and Santiago del Estero]. Rev Argent Microbiol 2002;34:107-9. Spanish.
56. Daisley H, Charles W, Landeau P, et al. Screening for HTLV-1 in healthy blood donors in Trinidad and Tobago, West Indies. Trop Med Parasitol 1991;42:404-6.
57. Pouliquen JF, Hardy L, Lavergne A, et al. High seroprevalence of human T-cell lymphotropic virus type 1 in blood donors in Guyana and molecular and phylogenetic analysis of new strains in the Guyana shelf (Guyana, Suriname, and French Guiana). J Clin Microbiol 2004;42:2020-6.
58. Whyte GS. Is screening of Australian blood donors for HTLV-I necessary? Med J Aust 1997;166:478-81.
59. Polizzotto MN, Wood EM, Ingham H, et al. Reducing the risk of transfusion-transmissible viral infection through blood donor selection: the Australian experience 2000 through 2006. Transfusion 2008;48:55-63.
60. Singh R, Thomas R. A comparative evaluation of prevalence of HTLV-1 antibodies in blood donors in Delhi India by PAT and LIA method. J Commun Dis 2003;35:263-5.
61. Tanggo Y, Gultom SP, Simanjuntak T, et al. Human T-lymphotropic virus I in Indonesia. Very low seroprevalence in the Jakarta area: antibodies in healthy blood donors and in various non hematological diseases. Intervirology 2000;43:77-9.
62. Mortezaie Z, Bouzari M, Roghanian R. Evaluating the frequency of HTLV-I/II infection among blood donors, major thalassemic patients and individuals infected with hepatitis B and C viruses in Isfahan, Iran. IJBC 2012;1:169-75.
63. Naman R, Klayme S, Naboulsi M, et al. HTLV-I and HTLV-II infections in volunteer blood donors and high-risk groups in Lebanon. J Infect 2002;45:29-31.
64. Batsuuri J, Dashnyam B, Maidar J, et al. Absence of human T-lymphotropic retrovirus type-1 (HTLV-1) in different populations of Mongolia. Scand J Infect Dis 1993;25:398-9.
65. Kawashti MI, Hindawi SI, Damanhouri GA, et al. Serological screening of human T cell lymphotropic virus I and II (HTLV I/II) in blood banks by immunoblotting and enzyme-immuno assays: to demand or to defeat? Egypt J Immunol 2005;12:137-42.
66. Sertöz R, Turhan A, Bozkurt H, et al. Investigation of anti-HTLV I/II seroprevalence in healthy blood donors in Izmir region, Turkey. Turkish. Mikrobiyol Bui 2010;44:579-84.
67. Chaudhari CN, Shah T, Misra RN. Prevalence of human T cell leukaemia virus amongst blood donors. MJAFI 2009; 65:38-40.
68. de Stasio G, Canavaggio M, Rizzi L, et al. Screening for anti-human T-lymphotropic virus antibody in blood donors and polytransfused patients in Apulia (Italy). Vox Sang 1990;59: 167-71.

69. Kozireva S, Nemceva G, Danilane I, et al. Prevalence of blood-borne viral infections (cytomegalovirus, human herpesvirus-6, human herpesvirus-7, human herpesvirus-8, human T-cell lymphotropic virus-I/II, human retrovirus-5) among blood donors in Latvia. Ann Hematol 2001;80:669-73.
70. Jovanovič P, Levičnik-Stezinar S. Prevalence of anti-HTLV-I/II in Slovenian blood donors and the impact on blood screening. Zdrav Vestn 2008;77:I-193-7.
71. Prinsze FJ, Zaaijer HL. The outcome of donor screening for human T-cell lymphotropic virus infection in the Netherlands. Vox Sang 2012;102:198-203.
72. Zaaijer HL, Cuypers HT, Dudok de Wit C, et al. Results of 1-year screening of donors in the Netherlands for human T-lymphotropic virus (HTLV) type I: significance of Western blot patterns for confirmation of HTLV infection. Transfusion 1994;34:877-80.
73. O'Brien SF, Goldman M, Scalia V, et al. The epidemiology of human T-cell lymphotropic virus types I and II in Canadian blood donors. Transfus Med 2013;23:358-66.
74. Vasquez P, Sanchez G, Volante C, et al. Human T-lymphotropic virus type I: new risk for Chilean population. Blood 1991;78:850-1.
75. Chandiá L, Sotomayor C, Ordenes S, et al. Seroprevalence of human T-cell lymphotropic virus type 1 and 2 in blood donors from the regional hospital of Valdivia, Chile. Med Microbiol Immunol 2010;199:341-4.
76. Lima GM, Eustáquio JM, Martins RA, et al. [Decline in the prevalence of HTLV-1/2 among blood donors at the regional blood center of the city of Uberaba, state of Minas Gerais, from 1995 to 2008]. Portuguese. Rev Soc Bras Med Trop 2010;43:421-4.
77. Carneiro-Proietti AB, Sabino EC, Leão S, et al. Human T-lymphotropic virus type 1 and type 2 seroprevalence, incidence, and residual transfusion risk among blood donors in Brazil during 2007-2009. AIDS Res Hum Retroviruses 2012;28:1265-72.
78. Dodd RY, Notari EP, Stramer SL. Current prevalence and incidence of infectious disease markers and estimated window-period risk in the American Red Cross blood donor population. Transfusion 2002;42:975-9.
79. Stramer SL, Notari EP, Zou S, et al. Human T-lymphotropic virus antibody screening of blood donors: rates of false-positive results and evaluation of a potential donor reentry algorithm. Transfusion 2011;51:692-701.
80. Transfusion-transmissible infections in Australia: 2014 Surveillance Report. Sydney: The Kirby Institute, The University of New South Wales and Australian Red Cross Blood Service; 2014.
81. Inaba S, Sato H, Okochi KK, et al. Prevention of transmission of human T-lymphotropic virus type 1 (HTLV-1) through transfusion, by donor screening with antibody to the virus. One-year experience. Transfusion 1989;29:7-11.
82. Centers for Disease Control (CDC). Human T-lymphotropic virus type I screening in volunteer blood donors--United States, 1989. MMWR Morb Mortal Wkly Rep 1990;39:921-24.
83. O'Brien SF, Yi QL, Fan W, et al. Current incidence and estimated residual risk of transfusion-transmitted infections in donations made to Canadian Blood Services. Transfusion 2007;47:316-25.
84. Tynell E, Andersson S, Lithander E, et al. Screening for human T-cell leukaemia/lymphoma virus among blood donors in Sweden: cost effectiveness analysis. BMJ 1998;316:1417-22.
85. Davidson F, Lycett C, Jarvis LM, et al. Detection of HTLV-I and II in Scottish blood donor samples and archive donations. Vox Sang 2006;91:231-36.
86. Laperche S, Worms B, Pillonel J, et al. Blood safety strategies for human T-cell lymphotropic virus in Europe. Vox Sang 2009;96:104-10.
87. Kataoka R, Takehara N, Iwahara Y, et al. Transmission of HTLV-I by blood transfusion and its prevention by passive immunization in rabbits. Blood 1990;76:1657-61.
88. Seto A, Kawanishi M, Matsuda S, et al. Adult T cell leukemia-like disease experimentally induced in rabbits. Jpn J Cancer Res 1988;79:335-41.
89. Ogawa K, Matsuda S, Seto A. Induction of leukemic infiltration by allogeneic transfer of HTLV-I-transformed T cells in rabbits. Leuk Res 1989;13:399-406.
90. Zhao TM, Robinson MA, Sawasdikosol S, et al. Variation in HTLV-I sequences from rabbit cell lines with diverse in vivo effects. Virology 1993;195:271-4.
91. Kannian P, Yin H, Doueiri R, et al. Distinct transformation tropism exhibited by human T lymphotropic virus type 1 (HTLV-1) and HTLV-2 is the result of postinfection T cell clonal expansion. J Virol 2012;86:3757-66.
92. Nakamura H, Tanaka Y, Komuro-Tsujimoto A, et al. Experimental inoculation of monkeys with autologous lymphoid cell lines immortalized by and producing human T-cell leukemia virus type-I. Int J Cancer 1986;38:867-75.
93. Kazanji M, Moreau JP, Mahieux R, et al. HTLV-I infection in squirrel monkeys (Saïmiri sciureus) using autologous, homologous, or heterologous HTLV-I-transformed cell lines. Virology 1997;231:258-66.
94. McGinn TM, Tao B, Cartner S, et al. Association of primate T-cell lymphotropic virus infection of pig-tailed macaques with high mortality. Virology 2002;304:364-78.
95. Okochi K, Sato H. Transmission of adult T-cell leukemia virus (HTLV-I) through blood transfusion and its prevention. AIDS Res 1986;2 Suppl 1:S157-61.
96. DePalma L, Luban NL. Transmission of human T-lymphotrophic virus type I infection to a neonatal infant by transfusion of washed and irradiated red cells. Transfusion 1993;33:582-4.
97. Césaire R, Kérob-Bauchet B, Bourdonné O, et al. Evaluation of HTLV-I removal by filtration of blood cell components in a routine setting. Transfusion 2004;44:42-8.
98. Roback JD, Bray RA, Hillyer CD. Longitudinal monitoring of WBC subsets in packed RBC units after filtration: implications for transfusion transmission of infections. Transfusion 2000;40:500-6.

99. Rider JR, Want EJ, Winter MA, et al. Differential leucocyte subpopulation analysis of leucodepleted red cell products. Transfus Med 2000;10:49-58.
100. Pennington J, Garner SF, Sutherland J, et al. Residual subset population analysis in WBC-reduced blood components using real-time PCR quantitation of specific mRNA. Transfusion 2001;41:1591-600.
101. Guber SE, Neumüller J, Schwartz DW, et al. Removal of T and B lymphocytes by in-line filtration: evaluation of the efficiency of a polyester filter type (Pall WBF-2) by flow cytometric counting. Vox Sang 2002;83:234-8.
102. Hewitt PE, Davison K, Howell DR, et al. Human T-lymphotropic virus lookback in NHS blood and transplant (England) reveals the efficacy of leukoreduction. Transfusion 2013;53:2168-75.
103. Sobata R, Matsumoto C, Uchida S, et al. Estimation of the infectious viral load required for transfusion-transmitted human T-lymphotropic virus type 1 infection (TT-HTLV-1) and of the effectiveness of leukocyte reduction in preventing TT-HTLV-1. Vox Sang 2015;109:122-8.
104. Leukocyte reduction. AABB Association Bulletin #99-7. Bethesda: American Association of Blood Banks; 1999 Aug 2.
105. Food and Drug Administration (FDA) recommendations for licensure requirements for leukocyte-reduced blood products. Silver Spring (MD): CBER, U.S. Food and Drug Administration; 1996 May 29.
106. The guide to the preparation, use and quality assurance of blood components. 17th ed. Strasbourg: EDQM Council of Europe; 2013.
107. Lieberman L, Devine DV, Reesink HW, et al. Prevention of transfusion-transmitted cytomegalovirus (CMV) infection: standards of care. Vox Sang 2014;107:276-311.
108. Valerius NH, Johansen KS, Nielsen OS, et al. Effect of in vitro x-irradiation on lymphocyte and granulocyte function. Scand J Hematol 1981;27:9-18.
109. O'Brien SF, Zou S, Laperche S, et al. Surveillance of transfusion-transmissible infections: comparison of systems in five developed countries. Transfus Med Rev 2012; 26:38-57.
110. Seed CR, Kiely P, Keller AJ. Residual risk of transfusion transmitted human immunodeficiency virus, hepatitis B virus, hepatitis C virus and human T lymphotrophic virus. Intern Med J 2005;35:592-98.
111. Calman KC. Cancer: science and society and the communication of risk. BMJ 1996;313:799-802.
112. Sullivan MT, Williams AE, Fang CT, et al. Transmission of human T-lymphotropic virus types I and II by blood transfusion: a retrospective study of recipients of blood components (1983 through 1988): The American Red Cross HTLV-I/II Collaborative Study Group. Arch Intern Med 1991;151: 2043-48.
113. Donegan E, Lee H, Operskalski EA, et al. Transfusion transmission of retroviruses: human T-lymphotropic virus types I and II compared with human immunodeficiency virus type 1. Transfusion 1994;34:478-83.
114. Rezvan H, Motallebi Z, Jalili MA, et al. Safety of blood and plasma derivatives: pathogen reducing technologies. MJIRI 2006;20:86-92.
115. Chorba TL, Jason JM, Ramsey RB, et al. HTLV-I antibody status in hemophilia patients treated with factor concentrates prepared from US plasma sources and in hemophilia patients with AIDS. Thomb Haemost 1985;53: 180-82.
116. Couroucé AM, Pillonel J, Lemaire JM, et al. Seroepidemiology of HTLV-I/II in universal screening of blood donations in France. AIDS 1993;7:841-7.
117. Brennan M, Runganga J, Barbara JA, et al. Prevalence of antibodies to human T cell leukaemia/lymphoma virus in blood donors in North London. BMJ 1993;307:1235-39.
118. Sailly JC, Lebrun T, Coudeville L. [Cost-effective approach to the screening of HIV, HBV, HCV, HTLV in blood donors in France]. French. Rev Epidemiol Sante Publique 1997;45: 131-41.
119. van Hulst M, de Wolf JT, Staginnus U, et al. Pharmaco-economics of blood transfusion safety: review of the available evidence. Vox Sang 2002;83:146-55.
120. Stigum H, Magnus P, Samdal HH, et al. Human T-cell lymphotropic virus testing of blood donors in Norway: a cost-effect model. Int J Epidemiol 2000;29:1076-84.
121. Borkent-Raven BA, Janssen MP, van der Poel CL, et al. Cost-effectiveness of additional blood screening tests in the Netherlands. Transfusion 2012;52:478-88.
122. Custer B, Hoch JS. Cost-effectiveness analysis: what it really means for transfusion medicine decision making. Transfus Med Rev 2009;23:1-12.
123. Custer B, Agapova M, Martinez RH. The cost-effectiveness of pathogen reduction technology as assessed using a multiple risk reduction model. Transfusion 2010;50:2461-73.
124. Katz LM; AABB Transfusion Transmitted Diseases Committee. Joint Statement Before BPAC on HTLV Confirmatory Test Developed by MP Biomedicals: MP Diagnostics HTLV Blot 2.4. Statement Presented Before the Food and Drug Administration's Blood Products Advisory Committee MP Biomedicals' Biologic License Application for the MP Diagnostics HTLV Blot 2.4, a Western Blot Intended for Use as a Confirmatory Test for Blood Donors. Bethesda: American Association of Blood Banks; 2013.
125. Tayou CT, Kouao MD, Touré H, et al. Transfusion safety in francophone African countries: an analysis of strategies for the medical selection of blood donors. Transfusion 2012;52: 134-43.