March 26, 2025

Anne Eder, M.D., Ph.D., Director
Office of Blood Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Eder,

AABB (Association for the Advancement of Blood & Biotherapies), America's Blood Centers (ABC), and the American Red Cross (ARC) are submitting this joint letter to request an evidence-based reconsideration of current testing recommendations for human T-lymphotropic virus types I and II (HTLV-I/II). We respectfully request that you consider updating the testing requirement to one-time donor testing for antibodies to HTLV-I/II coupled with effective leukoreduction in donations of Whole Blood and blood components intended for transfusion. This letter was developed through the expertise of AABB's Transfusion Transmitted Diseases Committee.

Consistent with CBER's ongoing evidence-based updates, we believe the HTLV-I/II antibody testing requirement at each donation of Whole Blood and blood components intended for transfusion should be revised based on: (1) the declining prevalence of HTLV-I/II infection in US blood donors; (2) the low incidence observed among US repeat blood donors; (3) the low likelihood of infection and disease in individuals receiving HTLV-I/II antibody-reactive Whole Blood and blood components, (4) the efficacy of leukoreduction in reducing the infectivity of HTLV-I/II antibody-reactive donations, and (5) the use of effective pathogen reduction technology (PRT) for some platelets.

We request the agency consider the following information supporting alteration of the current HTLV testing requirement.

Background

HTLV types I and II are retroviruses transmitted from mother to child at birth and/or via breast milk, sexually (with more efficient transmission from male to female), and through intravenous drug use and other blood exposure. HTLV-I/II may also be transmitted via transfusion of cellular blood components but has not been demonstrated to be transmitted by plasma.

HTLV is a strict intraleukocytic agent. Therefore, leukoreduction is highly efficient at preventing transmission from cellular blood components containing residual lymphocytes. In addition to donor antibody testing, transfusion transmission mitigation strategies also include use of PRT for platelet components. Lastly, transmission is markedly reduced or eliminated following refrigerated storage for approximately 10 days.

Studies conducted before the widespread use of leukoreduction demonstrate a 9-63% seroconversion rate in recipients of HTLV-I/II–positive non-leukoreduced cellular blood components, in part, dependent upon storage duration. HTLV-I is associated with two disease states, adult T-cell leukemia/lymphoma (ATLL), and HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP). However, only 2-5% of infected individuals develop ATLL, usually after a lengthy latency starting in infancy. Infection among adults may result in HAM/TSP, but the lifetime risk of developing disease is also low, 0.25-3.8%, in infected individuals. In contrast, HTLV-II has not been definitively associated with any specific disease state. Even with non-universal transmission and low rates of the development of clinical disease, because HTLV is a retrovirus that can be transfusion transmitted, and with the development and licensure of antibody screening tests, the US implemented universal blood donation screening in 1989. Consistent with the evolution of testing policies for other screened agents, and consistent with policy changes outside of the US, we believe that it is time for the US to review the policy of ongoing universal testing.

American Red Cross US study

A study of the results of US blood donation HTLV-I/II antibody testing by the American Red Cross was published in 2023. A total of 75,687,426 donations from 18,420,249 donors were tested between 2008 and 2021. During this period, 1,550 donations were confirmed positive for antibodies to HTLV, for an overall rate of 2.05 per 100,000 (pht) donations. Of these, 1,438 (92.7%) were from 13,926,422 first-time donors for a rate of 10.32 pht. Identified cases in these donors fell from 298 (12.3 pht) in 2008-2009 to 134 (9.5 pht) in 2020-2021. Among donations from repeat donors over this 14-year period, there were 112 (0.18 pht) test-positive donations from 57 incident donors (within 2-year incidence monitoring periods). Among repeat donors, the incidence of new infections fell from 0.30 pht person-years in 2008/2009 to 0.25 pht person-years in 2020-2021. The residual risk (the likelihood of collecting a unit during the published 51-day window period) was 1 per 3.22 million donations from repeat donors. However, recognizing that leukoreduction essentially eliminates infectivity in cellular components, risk would be reduced to only those components in which leukoreduction failed (<0.30%; range 0.08-0.28%), yielding a residual risk for donations from repeat donors of 1 in 1.74 billion for the entire study period and 1 in 3.32 billion for the latest 2-year period.

Supportive Experience Outside the US

Several high-income countries that have implemented universal or near universal leukoreduction have moved forward with first-time donor selective testing in lieu of universal testing without any observed impact on blood safety. The table below reflects first-time donor prevalence compared to repeat donor reactivity in these countries and the timing of their switch from

universal to one-time only donor testing. Following introduction of effective leukoreduction, several countries have abandoned testing altogether based upon low disease prevalence seen during universal testing (Norway [2007] and Finland [2008]), while others (e.g., Germany) never enacted a testing a requirement, based upon low HTLV-I/II seroprevalence in their blood donors.

Country	Selective Testing Implemented	Ab+ FT Donations (pht)	Ab+ Repeat Donations (pht)	Time Frame	Risk of Transmission FTD Testing	Risk of Transmission 100% Testing	Reference
Australia (FTDs)	2018	2.98	0.02	2004 -2014	1 per 21.6 million	1 per 1.7 billion	4
UK (FTDs & non-LR donations)	2017	5.2	0.08	2004 -2014	1 per 19 million	1 per 1.7 billion	5
Continental France (FTDs)	2017	3.9 (pht donors)	0.04 (pht donor-years)	2012 (FTDs) 2010-2012	Not determined per donation		6
Netherlands (FTDs)	2013	3.66 (pht donors)	0.12 (pht donors)	2001 -2010			7

Two other high-income countries have completed complex modeling supporting change and are contemplating a switch to one-time only testing. Canadian Blood Services reported a Monte Carlo simulation model to estimate the risk of a potentially infectious unit being released following (1) testing all donations, (2) testing only first-time donations, and (3) without any testing. For each scenario, 10 billion donations were simulated assuming 2 annual donations per donor for 13 years, published proviral copies per leukocyte and presumed infectious dose, and product leukocyte counts from their QC datasets. With universal testing, the residual risk of releasing an infectious unit was 1 in 1.2 billion units; for first-time donor-only testing, the risk would be 1 in 7.1 million; and with no testing, 1 in 1.0 million. The risk of transmission would be substantially lower based on longer component storage time, with units transfused after 10 days of storage unlikely to transmit HTLV.

The Irish Blood Transfusion Service (IBTS) also used a modeling approach to evaluate the risk of transfusion transmission with universal testing of all donations versus testing only first-time donations. Factoring HTLV prevalence and conservative leukoreduction failure cell counts, they estimated residual risk at 1 per 6,271,052 donations with first-time donor-only testing versus 1 per 63,905,984 with universal testing. IBTS is currently considering replacing universal testing with one-time only testing.

Summary

US data are consistent with those from other high-income countries in which HTLV risk modeled from testing only first-time donors coupled with effective leukoreduction resulted in associated policy change or strong consideration of this change. We therefore believe that in the US, testing only first-time donors coupled with effective leukoreduction would provide similarly acceptable levels of safety.

Weighing the established evidence demonstrating the unlikely transmission of HTLV from repeat donors, we respectfully request the alteration of HTLV-I/II testing to one-time testing for donors of Whole Blood and blood components intended for transfusion in the US. We believe

that the elimination of universal HTLV-I/II antibody testing is a first step in an ongoing dialogue of how to streamline the qualification of blood donations that maintains safety while eliminating unnecessary testing.

Member Statements

AABB (Association for the Advancement of Blood & Biotherapies) is an international, not-for-profit organization representing individuals and institutions involved in the fields of transfusion medicine and biotherapies. The Association works collaboratively to advance the field through the development and delivery of standards, accreditation and education programs. AABB is dedicated to its mission of improving lives by making transfusion medicine and biotherapies safe, available and effective worldwide.

Founded in 1962, America's Blood Centers is North America's largest network of community-based, independent blood programs. The network operates more than 600 blood donor centers providing over half of the US, and a quarter of the Canadian blood supply. These blood centers serve more than 150 million people and provide blood products and services to more than 3,500 hospitals and healthcare facilities across North America. America's Blood Centers' US members are licensed and regulated by the US Food and Drug Administration. Canadian members are regulated by Health Canada.

The American Red Cross shelters, feeds and provides emotional support to victims of disasters; supplies about 40 percent of the nation's blood; teaches skills that save lives; provides international humanitarian aid; and supports military members and their families. The Red Cross is a not-for-profit organization that depends on volunteers and the generosity of the American public to perform its mission. About 5.6 million units of Whole Blood are collected from roughly 3.3 million Red Cross volunteer donors, separated into 8 million transfusable blood products and supplied to approximately 2,700 hospitals and transfusion centers across the country for patients in need.

Thank you for the opportunity to offer this letter.

Sincerely,

[*signatures on file*]

Sharon Carayiannis	Kate Fry	J. Chris Hrouda
Vice President, Science & Practice	Chief Executive Officer	President, Biomedical Services
AABB	America’s Blood Centers	American Red Cross

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