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Minireview

Donor Screening for Human T-cell Lymphotrophic Virus 1/2: Changing Paradigms for Changing Testing Capacity

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Organ Procurement and Transplant Network (OPTN) policy currently requires the testing of all potential organ donors for human T-cell lymphotrophic virus (HTLV)-1/2. Most Organ Procurement Organizations (OPO) use the Abbott HTLV-I/HTLV-II Enzyme Immunoassay (EIA). This assay will no longer be manufactured after December 31, 2009; the only commercially available FDA-licensed assay will be the Abbott PRISM HTLV-I/II assay which poses many challenges to OPO use for organ donor screening. As a result, screening donors for HTLV-1/2 in a timely manner pretransplant after December 31, 2009 will be challenging. The true incidence of HTLV-1 in United States (U.S.) organ donors is not well described but appears to be low (∼0.03–0.5%). HTLV-1 is associated with malignancy and neurological disease; HTLV-2 has not been convincingly associated with disease in humans. Donors that are HTLV-1/2 seropositive are infrequently used despite most results being either false positive or resulting from HTLV-2 infection. There is urgent need to encourage the development of assays, instruments and platforms optimized for organ donors that can be used to screen for transmissible disease in donors; these must have appropriate sensitivity and specificity to identify all infections while minimizing organ loss through false positive testing.

Key words: Donor evaluation, donor-to-host transmission, infectious diseases, viral infection

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Introduction

Human T-cell lymphotrophic Virus 1 (HTLV)-1 is a delta retrovirus endemic in the Caribbean, parts of South America, West Africa, Asia and Oceania. In the Caribbean, 2–5% of adults are infected (1). In the United States (U.S.), 0.035–0.046% of blood donors are infected with HTLV-1 or HTLV-2 (2). Breast feeding is the most common form of transmission. Intravenous drug use, sexual intercourse, solid organ transplantation (SOT) and transfusion of cell-containing blood products (14.4–47.3% of recipients) may also result in transmission of infection (3,4).

HTLV-1 is associated with development of acute T-cell leukemia/lymphoma (ATL) in 2–5% of infected individuals and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) in a smaller percentage (4). Other inflammatory disorders have been associated with HTLV-1 and there is no reliably effective treatment. Most individuals have no clinical sequelae of HTLV-1 infection.

HTLV-2 is primarily found in intravenous drug users and sexual contacts of infected persons and is endemic in American Indian populations and in West and Central Africa. Unlike HTLV-1, the link between HTLV-2 and human disease is uncertain, although there have been occasional case reports of neurological disease, inflammatory disorders and leukemia in infected patients (5).

An enzyme-linked immunosorbent assay (EIA) is currently used to screen organ donors for HTLV-1/2. These tests do not distinguish between HTLV-1/2. This test is sensitive but lacks significant specificity and therefore the positive predictive value is low when applied to low seroprevalence populations (6,7). A positive EIA result can be confirmed by a Western blot or specific line immunoassay, although this

is not standard practice for organ donation. In many cases these confirmatory assays distinguish between HTLV-1 and HTLV-2 but none are FDA-licensed or approved for this purpose. Polymerase chain reaction (PCR) tests may also be useful to confirm infection and can distinguish between infection with HTLV-1 and HTLV-2. At present, no FDA-licensed, commercially available nucleic acid test (NAT) with a turnaround time appropriate for donor screening is available.

Currently, OPTN policy requires that all potential solid organ donors are tested for HTLV-1/2 using an FDA-licensed screening test (8). There are presently 3 FDA-licensed tests for this purpose (9): the Abbott HTLV-I/HTLV-II Enzyme Immunoassay (EIA), Abbott PRISM HTLV-I/HTLV-II and the bioMerieux-Vironostika HTLV-I/II Microelisa System. Most OPOs currently use the Abbott HTLV-I/HTLV-II EIA test (10) but this system will no longer be manufactured after December 31, 2009 and the bioMerieux system is no longer commercially available. The Abbott PRISM HTLV I-II assay will be the only commercially available licensed test after December 31, 2009. It is designed to test large numbers of samples in a high-throughput setting and is not optimized to the time constraints associated with organ donation.

Given changing availability of FDA licensed assays for HTLV-1/2, the OPTN/UNOS *Ad Hoc* Disease Transmission Advisory Committee (DTAC) requested the formation of an advisory group (Table 1) to gather information regarding the need for HTLV-1/2 screening and possible alternative screening strategies. The purpose of this paper is to report the findings of this group.

Table 1: Ad Hoc HTLV Donor Screening Advisory Group Membership

Member	Organization
Daniel Kaul, Chair	University of Michigan (TID)
Charlie Alexander	Living Legacy Foundation (OPO)/OPTN/UNOS Vice-President
Scott Brubaker	AATB
Shandie Covington	UNOS
Bradley Eisenbrey	Gift of Life (OPO Lab Director)
Mary D. Ellison	UNOS
David Hull	Organ Availability Committee
Rick Hasz	Gift of Life (OPO)/OPTN/UNOS Operations
Bob Higgins	Rush University (Surgery)/OPTN/UNOS Immediate Past President
Michael Ison	Northwestern University (TID)/OPTN/UNOS DTAC
Andrés Jaramillo	Gift of Hope Organ and Tissue Donor Network (OPO Lab Director)
Lin Johnson McGaw	OPTN/UNOS
Marilyn Levi	University of Colorado (TID)
Michael Marvin	University of Louisville (Surgery)
Mark Mathieson	Abbott
Bob Metzger	OPTN/UNOS Medical Director
Marek Nowicki	NIT Laboratory
Jeff Orlowski	Ctr. for Donation & Transplantation (OPO)/OPTN/UNOS OPO Committee
Carol Pancoska	LABs-Inc., Centennial, CO
Timothy L. Pruett	University of Virginia (Surgery, TID)/OPTN/UNOS DTAC
David Snydman	Tufts Medical Center (TID)
Sarah Taranto	UNOS
Charles Wright	LifeLink (OPO)
James Wynn	Medical College of Georgia/OPTN/UNOS President

OPO = Organ Procurement Organization; TID = transplant infectious diseases; OPTN = Organ Procurement and Transplantation Network; UNOS = United Network for Organ Sharing; DTAC = Ad Hoc Disease Transmission Advisory Committee.
Representatives of HRSA, FDA and CDC were present as observers.

Currently Licensed HTLV-1/2 Screening Tests

Abbott PRISM HTLV-I/II assay

The Abbott PRISM HTLV-I/II assay is a chemiluminescence immunoassay for HTLV-1/2 screening and is part of an automated testing system designed for high throughput labs. In volunteer blood donors, the specificity of the assay was 99.93%. Sensitivity of the assay is estimated to approach 100% (11).

Abbott HTLV-I/II EIA

The Abbott HTLV-I/II EIA is less expensive than the PRISM system and practical for OPO labs. Specificity of the assay is estimated at 99.73% among blood donors and sensitivity is also estimated to approach 100% (12).

bioMerieux–Vironostika HTLV-I/II Microelisa System

The bioMerieux ELISA assay is not commercially available in the United States. The manufacturer estimates a specificity of 99.95% for this test; sensitivity was 100% compared to other licensed and confirmatory tests (13).

Experience with the Use of HTLV-1/2 Positive Organs

Several case reports described likely donor-derived transmission of HTLV-1 after SOT (Table 2); in some of these reports, recipients developed HTLV-1-associated disease (14–17). The most definitive case occurred in Spain; three seronegative recipients of an HTLV-1/2 seropositive donor developed myelopathy within 2 years of transplantation (16). Less definitive reports include a pretransplant seronegative renal recipient without other identifiable risk factors who developed HAM/TSP 4 years after transplantation (14). A documented case of HTLV-1 transmission without evidence of disease at 4 years follow up in a recipient of a living related renal donor (15), and a seronegative renal transplant recipient who developed ATL after transplant; the HTLV-1 status of the donor is not described (17).

Table 2: Selected Reports of the Outcome of Transplant with HTLV-1/2 Seropositive Donors or Recipients

Study	Design	Recipient characteristics	Follow up or time to disease	Development of HTLV disease	Comment
Marvin et al. (21) United States	Retrospective review of OPTN database prior to August 2007 (liver only)	81 adult liver recipients	0–7.7 years 1.21 years (average) 0.62 years (median)	No patients developed HTLV associated disease	Short follow-up Donor infection not confirmed
Unpublished* United States	Retrospective review of OPTN database 1999–2008	162 recipients liver (101) kidney (44) heart (8) panc (2) kid-panc (3) lung (4)		10 with post-transplant malignancy (none HTLV associated)	Not able to assess for neurological disease Donor infection not confirmed
Shames et al. (7) United States	Retrospective review OPTN database 1988–2000	22 recipients	11.9 months (median)	No HTLV associated disease	Short follow-up Donor infection not confirmed
Toro et al. (16) Spain	Case report or 3 recipients from one HTLV-1nfected donor	3 recipients (one donor) 1 liver, 2 kidney	18 months 24 months 24 months	All 3 recipients developed HTLV associated myelopathy	Confirms potential for rapid progression to disease after donor-derived infection
Nakatsuji et al. (14) Japan	Case report of possible transmission from one donor	1 kidney recipient	48 months	One recipient developed HTLV associated myleopathy	Donor not tested for HTLV but no other recipient risk factors noted
Nakamura et al. (28) Japan	Case series	10 kidney recipients (4 donor negative recipient positive)	11–17 years	No HTLV associated disease	Included six cases R+ also without disease with similar follow up
Remesar et al. (15)	Case report of transmission without disease	1 kidney recipient	4 years	Seroconversion but not disease at 4 years	Single case
Tanabe et al. (20) Japan	Case series	16 HTLV-1 positive kidney recipients	7–13 years (range)	No cases of ATL	High HTLV-1 incidence area in Japan
Kawano et al. (18) Japan	Case series	8 HTLV-1 carriers receiving living donor liver transplants	6 months 9 months 25 months	3/8 recipients developed ATL	High HTLV- I incidence area in Japan
Nakamura et al. (19) Japan	Case series	15 kidney recipients (8 recipient positive)	1–9 years (range)	No HTLV-1 associated disease	Series included some D+R−
Hoshida et al. (17) Japan	Case series of PTLD patients after renal transplant	5 kidney recipients with ATL (of 24 PTLD cases)	48 months (median) (all patients in series)	5 cases of ATL (unknown how many patients were HTLV positive and did not develop disease)	One patient was seronegative for HTLV-1 at time of transplant

*This represents data pulled by the OPTN at the request of the *ad hoc* Disease Transmission Advisory Committee to assess the donor utilization and outcomes of transplant of recipients of HTLV+ organ donors.

Table 3: Number of donors and organs recovered and transplanted for HTLV-1/2 screen-positive donors: United States, 1999–2008

Year of transplant	Donors N	Organ						Total N
		Heart N	Kidney N	Kidney pancreas N	Liver N	Lung N	Pancreas N	
1999	3	0	0	0	2	0	0	2
2000	5	1	0	0	2	1	0	4
2001	3	0	2	0	1	0	0	3
2002	8	4	2	0	7	0	0	13
2003	5	0	4	0	4	0	0	8
2004	9	0	2	0	5	0	0	7
2005	23	1	8	1	19	1	0	30
2006	35	2	16	2	31	1	2	54
2007	27	0	5	0	19	0	0	24
2008	16	0	5	0	11	1	0	17
Total	134	8	44	3	101	4	2	162

A few case series from Japan describe the rapid development of HTLV–1 associated disease in recipients that were seropositive prior to transplant (17,18); others describe no cases of HAM/TSP or ATL in seropositive recipients with extended follow-up (19,20).

Retrospective reviews of the OPTN database have assessed the outcome of elective transplantation of HTLV-1/2 seropositive organs (7,21) (Table 2). To update these results, the OPTN database was queried for this group and identified 162 recipients of 134 donors testing positive for HTLV-1/2 from 1999 to 2008 (Table 3); 10 developed post-transplant malignancies but these were skin cancers (except for one case of recurrent liver cancer) and no cases of ATL or post-transplant lymphoproliferative disease were reported. Thirty-three donors were used from 1999 to 2004; and 101 donors from 2005 to 2008. These studies are limited as the database does not report if confirmatory testing was done, so the proportion of organs from confirmed HTLV-1-infected donors is not known for these patients. This would likely underestimate the risk associated with donor-derived transmission from a true positive HTLV-1 donor. Further, the results of testing recipients to determine if HTLV-1/2 transmission occurred are not available and neurological sequelae is not recorded in the database.

Prevalence of HTLV-1/2 in Organ Donors

While HTLV-1/2 donor antibody testing is required and performed by all OPOs on all prospective donors, only data on donors whose organs are procured are collected in the OPTN database. Some European countries have surveyed all potential organ donors; in France 0.047–0.067% were found to be HTLV-1/2-positive (22). A similar survey was conducted in Spain; over one-thousand potential organ donors were tested and none was positive for HTLV-1 and one was positive for HTLV-2 (23).

Based on higher rates of immigration from high prevalence countries, HTLV-1/2 rates would be expected to be higher in the United States than in Europe. In one study of 1,408 potential donors, 1.6% were positive on repeated EIA testing with only one patient (0.07%) confirmed positive for HTLV-1 (6). Similar low rates of HTLV-1 infection among screen positive donors in Wisconsin was reported (7).

In order to better determine the prevalence of HTLV-1/2 among potential organ donors, we surveyed the results of several OPOs (those participating in the Ad Hoc HTLV Donor Screening Advisory Group) regarding their rates of positive HTLV-1/2 (Table 4). Overall 1.04% of donors

Table 4: HTLV-1/2 seroprevalance among potential organ donors

OPO/Lab UNOS REGION	Time period	Donors screened	SCRN (−)	SCRN (+)	% SCRN (+)	CONF DONE	CONF (+)	CONF (−)	CONF IND	CONF HTLV-1	CONF HTLV-2	% CONF HTLV-1/2	% CONF HTLV-1 (+)
3	2002–2009	1658	1644	11	0.66%	ND	ND	ND	ND	ND	ND	ND	ND
3	7/1/92–3/19/09	4169	4150	19	0.46%	18	5	10	3	ND	ND	0.12%	ND
11	1995–2008	130	129	1	0.77%	ND	ND	ND	ND	ND	ND	ND	ND
5	2006–2008	3490	3459	31	0.89%	30	22	1	7	1	20	0.63%	0.03%*
9	1/1/04–3/24/09	349	346	3	0.86%	ND	ND	ND	ND	ND	ND	ND	ND
10	1/1/06–12/31/08	1273	1267	17	1.32%	ND	ND	ND	ND	ND	ND	ND	ND
7	05/01/99– 3/01/09	3363	3295	68	2.02%	60	29	19	12	ND	ND	0.86%	ND
TOTAL		14 432		150	1.04%	108	56	30	22	1	20	0.51%	0.03%

IND = Indeterminate.
Screening done using Abbott HTLV I/II EIA or Abbott PRISM HTLV I/II EIA.
*Confirmation done using the Genelabs HTLV 2.4 Western blot.

screened positive for HTLV-1/2; in the three labs in which a confirmatory assay was performed 0.5% of donors were confirmed positive for HTLV-1/2 (in these labs, most but not all positives were confirmed). Only one lab attempted to distinguish HTLV-1 from HTLV-2 (using Genelabs HTLV 2.4 Western blot), and documented a HTLV-1 positive rate of 0.03%. While the overall rate of HTLV-1 infection in the donor population is likely very low, it should be noted that local areas of higher prevalence, likely based on immigration patterns from high incidence countries, have been described (24,25).

Similar findings have been documented in studies of the Abbott HTLV-I/II EIA assay among volunteer blood donors and patients with other medical conditions. Among 15,215 volunteer blood donors, 51 (0.35%) were repeatedly reactive for HTLV-1/2; only 10 (0.07%) of these were positive on confirmatory testing and 4 (0.03%) had HTLV-1 (12). In patients with medical conditions unrelated to HTLV-1/2, higher rates of positive screens are obtained 26/639 (4%); only 3 (0.47%) were confirmed to be HTLV-1 (12). Thus, in both our limited data in potential organ donors, volunteer blood donors and patients with other medical conditions, most screen positive patients do not have HTLV-1 infection.

Loss of Organs Associated with Current HTLV-1/2 Screening Strategy

Previous papers have commented on the loss of usable organs resulting from the high false positive rate with currently available screening tests (7,21). There are approximately 8000 potential deceased donors reported to the OPTN database each year for which at least one organ is procured. Using this information along with the studies and data presented here, it is estimated that there are 83 potential donors that screen positive for HTLV-1/2; of these only 2–22 (that is between 3% and 27% based on the one lab differentiating between HTLV-1 and HTLV-2) are likely actually infected with HTLV-1; and only 16 screened positive donors were used during 2008. As a result, between 45 and 65 donors are not used annually although they are uninfected with HTLV-1. Further, during 2008 the average number of organs transplanted per HTLV-1/2- negative donor was 3; for HTLV-1/2 screen positive donors it was only 1.1. If one estimates three organs per donor from the 45–65 donors (135–195 organs) plus the extra two organs from the 16 that were used (32 organs), there is a loss of 167–227 organs annually using existing technology.

Alternatives to Current Testing Strategy

After December 31, 2009, the Abbott HTLV-I/II EIA used in most OPOs will no longer be available. Alternative solutions to the current OPTN/UNOS requirement for screening include the Abbott PRISM HTLV-I/HTLV-II assay, an assay using RUO reagents, or forgoing pretransplant screening for HTLV-1/2.

Table 5: Costs associated with two HTLV-1/2 screening assays

	MP diagnostics HTLV-1/II ELISA 4.0*	Abbott PRISM HTLV-1/II
Methodology	Enzyme-linked immunoassay	Chemiluminescence immunoassay
FDA licensed	No	Yes
Turn around time	90 minutes	60 minutes
Cost of instrumentation	$12,000	$850,000
Cost of test kit	$380	$14,637
Yearly cost of assay	$47,500	$912,000
Estimated cost of test per donor	$65	$1500+

*This assay is not FDA licensed and available for research use only in the United States.

Abbott PRISM HTLV-I/HTLV-II assay

The Abbott PRISM HTLV-I/ II assay is FDA licensed for HTLV-1/2 screening and will continue to be supported by Abbott. This testing system, however, is designed to test large numbers of samples (up to 160 samples an hour) in a high throughput setting, and both technical and cost barriers will impact the availability and usefulness of this assay when used for single donor testing. OPO lab directors expressed a number of concerns. The system requires investing in expensive equipment and reagents that may be wasted when used as OPOs currently test donors. A significant investment is also necessary to train laboratory technicians to ensure proficiency and quality assurance. One large donor testing laboratory analyzed the costs associated with the Abbott PRISM HTLV-I/II assay compared to the MP Diagnostics HTLV-I/II ELISA 4.0, an RUO assay (Table 5). The cost per assay is estimated to be >20-fold higher with the PRISM system (26). Further, many OPOs outsource in labs in which in they have no control and in such situations, availability of Abbott PRISM HTLV I/II testing on a stat, afterhours basis is unlikely. OPO directors were concerned that mandating the use of the Abbott PRISM HTLV I/II system could result in delaying organ offers and recovery up to 36 h as samples are sent to large labs to be batched with nondonor samples.

RUO tests

The group was aware of three manufacturers that produce RUO serological reagents for HTLV-1/2 testing that are inexpensive, rapid and have protocols amendable to being done in OPO laboratories. Currently, a number of testing laboratories are evaluating these tests side by side with the FDA-licensed screening assays. In some of these evaluations, RUO assays that use recombinant antigens rather than the viral lysate used in the FDA licensed assays appear to have lower false positive rates (27). RUO assays lack a national standard (i.e. FDA licensure) making them less appropriate as part of a national testing strategy. Even if adequately performing and evaluated RUO tests were available, under FDA regulation

(these assays would be classified as Class III, subject to either licensing or approval requirements), manufacturers of RUO tests cannot knowingly provide these tests to labs if the results will be reported and used for clinical purposes. Additionally, RUO assays are subject to market forces and can be discontinued by the manufacturer without notice. Because of these regulatory requirements and the uncertain performance characteristics of the assays, RUO tests will not likely be a viable option.

Elimination of the requirement for pretransplant HTLV-1/2 donor screening

Given the very low prevalence of HTLV-1 in the donor population, wastage of organs with the currently available serological assays, and favorable short-term follow up of recipients of HTLV-1/2 screen positive organs in the United States, the Committee opined that elimination of pretransplant HTLV-1/2 screening was a reasonable option.

Some members of the group were concerned that the level of data on outcomes of HTLV-1 positive organs was limited and that additional information should be collected to inform future policy. As one potential option before outright discontinuing HTLV-1/2 testing, a period of retrospective testing to obtain more robust prospective data (as opposed to the retrospective data collected for this paper) on the true incidence and clinical sequelae of HTLV-1 in donors and recipients should be considered. After a fixed period of time, this retrospective testing and its outcomes should be reviewed to determine if this strategy should be continued. The Committee recommends that, if this strategy is implemented, samples can be batched and sent for testing using a FDA-licensed assay, such as the Abbott PRISM HTLV-I/II, which is currently available through blood centers and reference labs throughout the country. If this policy is to be implemented, public comment should be obtained. There are significant logistic hurdles that would need to be addressed with retrospective testing: (1) collecting and storing the appropriate samples to do both the primary and confirmatory testing for all donors, (2) developing a consensus on how to inform recipients and how best to test and monitor recipients post-transplant, and (3) developing an infrastructure to efficiently collect data on all of these issues to inform future policy.

Since all existing screening tests do not distinguish between HTLV-1 and HTLV-2 and have a high false-positive rate in a low seroprevalence population, it will be essential to perform confirmatory testing on all screen positive retrospectively tested samples. The two most commonly used confirmatory tests are the Genelabs HTLV 2.4 (Western blot) and the Innogenetics HTLV-I/II Line Immunoassay. Both tests can be used for confirmation of a positive screening assay and, in some cases, virus typing (HTLV-1 vs. HTLV-2). Neither test is FDA-licensed, and cannot be used for direct clinical purposes. These tests could, however, be used as part of a protocol to determine the prevalence of HTLV-1 and HTLV-2 in the donor population. Likewise, molecular diagnostic tools, such as NAT, could be used to determine the presence of HTLV-I in the cells of screen-positive donors, confirming the infection. While no FDA-licensed test is available, if patients are to be informed post-transplant of positive donor results and confirmatory testing is not required, the result will be unnecessary follow-up and anxiety for patients who have not been exposed to HTLV-1. Other challenges with retrospective testing include the stress and potential legal ramifications associated with disclosing the retrospective results to the recipients and a lack of data to determine what type of follow-up is appropriate for these individuals. As a result, even if viral replication is recognized, it is unclear what could be done and if an intervention is even warranted as there is no proven therapy for HTLV-1.

Future Directions

There are a wide range of infectious agents that cause clinically significant disease when transmitted from donors to recipients, including HTLV-1. Unfortunately, decisions on which agents to screen for and development of optimal assays have not been made using robust data nor have they been supported by appropriate research funding. Based on the current data, the current HTLV-1/2 testing platforms lead to far greater loss of organs than disease prevention. As such, interim discontinuation of the requirement for HTLV-1 testing is appropriate when considering a societal perspective. Optimally, research needs to be conducted to understand the true incidence of HTLV-1 in the U.S. donor population and the natural history of transmitted HTLV-1 infection in the recipient population. Research and development of novel screening tests that detects only HTLV-1 are desperately needed; these assays would need to be developed with organ transplantation in mind such that they could be applied on a stat basis, and result in the fewest possible false positive results. Companies should be encouraged to seek FDA-licensure for these assays. Given the limited market for these assays, stimulus for companies to invest in these assays is also needed.

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