CONSULTATION SUBMISSION - TGA

Therapeutic Goods Order No:XX

Standards for minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapies

australian biotechnologies

HUMAN TISSUE PROCESSING FACILITY, FRENCHS FOREST, NSW

CONSULTATION SUBMISSION - TGA

Therapeutic Goods Order No:XX

Standards for minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapies

Table of Contents

CONSULTATION SUBMISSION - TGA

Therapeutic Goods Order No:XX

Standards for minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapies

1. Definitions

Physical Examination:

The definition as given includes the need for a Physical Examination of Living Donors. Given that these donors are (in the main) patients undergoing total hip arthroplasty the possibility of the examination being completed are minimal at best. Patients are assessed as suitable for surgery by the treating Orthopaedic Surgeon; acceptance into the donor program is dependant on completion of Medical / Social Questionnaire rather than a physical examination.

Recommend:

- Delete the words "living or" from first line of current definition. To now read: *"Physical Examination means a clinical based inspection of a deceased potential donor to determine suitability of the person to be a donor and includes at minimum the relevance of any abrasion/laceration, bruise/haematoma, fracture, tattoo, piercing, scars, skin lesion, surgical incision or other distinguishing external feature that may be indicative of a behaviour, lifestyle or disease."*

2. Schedule 3 Medical & Social History

(2) A "Qualified Interviewer" can collect the required information via a telephone interview – this statement has created a double standard between deceased and living donors. In the decease donor setting it is routine to complete a Medical / Social History Interview over the phone with Next of Kin and medical Officers.

Recommend:

- Delete the words "at a face-to-face interview" from last line of paragraph. To now read: *"human blood and blood components, human tissues or human cells must not be collected from a living donor unless the Medical and Social History interview has been conducted by a qualified interviewer with the donor or guardian/next-of-kin".*

(2) (a) Interviews can, and often do, occur up to 30 days prior to donation; especially when interviews are conducted within hospital pre-admission clinics. Documentation of Medical / Social History within this timeframe doesn't have a deleterious effect on acceptance of the particular donor.

Recommend:

- Change the words "at no more than 7 days prior to donation" from first line of paragraph. To now read: *"The interview must occur as close as possible to, but at no more than 30 days prior to donation, unless(c) or (d) applies, and the history must be documented at that tine".*

- Delete (b)

Table 2: Minimum medical and social criteria required to define a donor's risk of recent exposure to infectious disease:

Recommend (recommended changes in red):

Donor Medical/Social History Criteria	Ineligibility Period	
	Allogeneic	Autologous
Tattoo or body piercing	Agree as written	Agree as written
Acupuncture	Agree as written	Agree as written
Needle stick injury etc	Agree as written	Agree as written
Inmate of a prison	Agree as written	Agree as written
Sex worker, or received money for sex	Agree as written	Agree as written
Male to male sexual relationship	Permanent	Agree as written
Sexual relationship with a person known to have: - Hepatitis C - HIV - Male to male sex	Permanent	Agree as written
Sexual relationship with a person known to be a sex worker	Agree as written	Agree as written
Ever injected any drug for a non-medical reason	Agree as written	Agree as written
A recipient of human derived clotting factors that do not meet the requirements of this order	12 months	Agree as written
A recipient of viable animal cells or tissues	Agree as written	Agree as written
Known to be infected with: - Hepatitis C - HIV - HTLV 1/HTLV 2	Agree as written	Agree as written
Suspected to be infected with: - Hepatitis C - HIV - HTLV 1/HTLV 2	Agree as written	Agree as written
Known, suspected or at risk of being infected with Hepatitis B	Agree as written	Agree as written
Physical evidence of sepsis ..... etc	Agree as written	Agree as written
Active infection of the cells and tissue to be retrieved ..... etc	Agree as written	Agree as written
Active infection of Tuberculosis	Agree as written	Agree as written

Recommendations Cont'd:

Donor Medical/Social History Criteria	Ineligibility Period	
	Allogeneic	Autologous
Typhus	Agree as written	Agree as written
Risk of Prion Disease	Assessment to be made according to type of tissue being donated (low risk with MS Tissue, high risk with neural / limbal tissue)	Agree as written
Recipient of human pituitary derived growth hormone	Agree as written	Agree as written
Recipient of allogeneic organ(s)	Agree as written	Agree as written
Recipient of allogeneic cells or deceased donor tissue allograft that do not meet the requirements of this Order	12 months	Nil
Recipient of live vaccine(s) or Hepatitis B vaccine	Agree as written	Agree as written

3. Schedule 5 Donor Testing & Examination

(1) Each donor of human blood and blood components, human tissues or human cellular therapies must be tested and examined for evidence of infectious diseases in accordance with the relevant and applicable donor groups. Assessment of donor blood samples and the physical examination of the donor are key determinants of donor acceptability or rejection. Donors of human blood and blood components, human tissues and cellular therapies must be evaluated as follows:

(a) Donor testing must include, at minimum serological and NAAT testing for the infectious disease markers as indicated in Table 4 of this Schedule.

The Council of Europe (Guide to Safety and Quality Assurance for Organs, Tissue and Cells [1]) state the following:
"For tissues prepared from surgical residues (an example of a surgical residue is a femoral head retrieved during the course of total hip arthroplasty) HIV 1 & 2 and HCV antibody testing should be undertaken on the donor at least 6 months after the donations before the tissue can be released unless validated antigen testing for HIV (p24Ag) or molecular biology test (eg PCR) for HIV and HCV was negative at donation or unless a validated method for viral inactivation is used.

Recommend:

- Insert the following – *"All tissue donors must be subject to HIV, HCV and HBV NAAT Screening. For tissue grafts prepared from Living Donors initial serological screening must include NAAT testing for HIV, HCV and HBV. Repeat serological screening should be undertaken on the donor at least 1 month (30 days) after the donation before the tissue can be released."*

(c) A physical examination must be conducted by a competent person to ascertain the suitability of a donor to donate cells or tissues and must take place,

i. On the day of blood, cell or tissue collection; or
ii. If not possible for cells and tissue, as close as practicable prior to the time of cell or tissue collection, i.e. generally within 5 days and no more than 7 days; or
iii. For a deceased donor, prior to cell or tissue collection and no later than 24 hours after death.

Musculoskeletal tissue living donors are patients scheduled for elective total hip arthroplasty – they are assessed as suitable for surgery by their treating Orthopaedic Surgeon. Typically, tissue banks don't have physical contact with these donors; the inclusion of a requirement for physical examination will diminish the availability of donor tissue of this type without adding to the safety of the donation..

Recommend:

- Change wording to (1) (c) as follows – *"A physical examination must be conducted on all deceased donors ……."*

(2) Where cells and tissues can be stored for long periods without impairing fitness for use, repeat sampling and serological or NAAT testing of the living donor

(a) For HIV, HBV and HCV must be performed at a minimum of 180 days after collection of the donation sample, to provide assurance that the initial sample was not collected during the window period for infection.
(b) And the donor of a rare cell or tissue type is not available for the repeat 180 day sampling; the initial donor sample must be tested by NAAT for HIV, HCV and HBV.

Nucleic Acid Amplification testing (NAAT) is among the newest technologies available to increase the safety of tissue donor screening. It utilises the ability of the screening laboratory to isolate and detect genetic material from deadly viruses such as Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV).

Previous testing methods involved the detection of antibodies that the body produces in response to an infection. The main problem with this detection method is that the body takes a certain amount of time to produce the antibodies in detectable amounts. This period of time, from the time of infection to the time of production of detectable amounts of antibodies is called the "seroconversion window" or the "window period".

Historically to the "window period" problem; antibody screening had a very high rate of false-positives. To err on the side of safety screening tests for HIV, HCV, HBV and HTLV were designed to detect as many positive blood donors as possible, including those with very low levels of antibodies. Unfortunately some perfectly healthy donors sometimes tested positive for these tests as test kit manufacturers sacrificed test specificity to gain test sensitivity.

The advantage of NAAT is that it is both sensitive and specific.

F. Yao et al has published two papers referencing NAAT screening for Australian tissue donors, the first study discusses the risk of HIV, HBV, HCV and HTLV infection among musculoskeletal tissue donors in Australia. His initial study published in 2007 compared the "window period" when donors were screened by routine serological screening methods versus NAAT screening [2]. Results given were:

Table: 1.1 Seroconversion Window Times Serological V Nat Screening – F. Yao et al

Agent	Window Period Serological Screen (Days)	Window Period NAT (Days)
▪ HIV Ab	22	7
▪ HBsAg	59	20
▪ HCV Ab	70	7
▪ HTLV	51	-

The stated "window period can be further confirmed by reports published by S. Zou et al [3] which gives the "seroconversion window" with NAAT screening in place as:

Table: 1.2 Seroconversion Window Times Serological V Nat Screening – S. Zou et al

Seroconversion Period NAT
▪ 7 Days HIV
▪ 7 Days HCV
▪ 20 Days HBV

The second study by F. Yao et al investigated and compared the risk of viral infection between the living and non-living musculoskeletal tissue donor pool whereby the incidence rates among tissue donors were determined by extrapolating from rates among first-time blood donors [4]. Estimated probability that the living donor was viraemic at the time of donation was detailed as follows:

Table: 1.3 Estimated Incidence of Undetected Viraemia among Surgical Donors – F. Yao et al

Serological Screening	NAT Screening
▪ 1 in 128,000 HIV	▪ 1 in 312,000 HIV
▪ 1 in 238,000 HBV	▪ 1 in 476,000 HBV
▪ 1 in 52,000 HCV	▪ 1 in 455,000 HCV
▪ 1 in 130,000 HTLV	

A poster presented by Ming-Hao Zheng at the 6th Combined Meeting of the Orthopaedic Research Societies (2006) discussed the cost-effectiveness of NAAT for HIV and HCV screening in musculoskeletal tissue donors [4]. While drawing the conclusion that the introduction of NAT testing for musculoskeletal tissue donors is not cost-effective, graphical representation contained in the poster presented again shows the marked reduction in the "window period" for each NAAT screening method.

Since the availability of NAAT screening tissue banks worldwide have modified their Standards and accepted best practices to allow for the dramatic reduction in "window period" timeframes.

The Council of Europe gives the choice of donor screening method to the retrieving bank. The following quotation is taken from page 52 of the 3rd Edition of the Council of Europe Guide to safety and quality assurance for organs, tissues and cells (2006) [4]:

> *"3.5 Re-testing of living donors of stored allogeneic material*
> *In living tissue/cord blood donors, re-testing for transmissible diseases after 6 months is mandatory unless the donated tissue underwent a terminal validated inactivation step. If re-testing is not performed, then tests of higher sensitivity (validated NAT) may be performed from the initial sample in line with national guidelines."*

Recommend:

- Add new (2) (b) as follows – *""for living donors initially screened with NAAT technology; repeat screening for HIV, HBV and HCV must be performed at a minimum of 30 days after collection of the donation sample, to provide assurance that the initial sample was not collected during the window period for infection.*

Eg: Proposed Living (Femoral Head) Donor Screening Protocol:

Initial Screen	30 Day Screen
HIV 1&2 Combo (Ab / Ag)	HIV 1&2 Combo (Ab / Ag)
Hepatitis B S Ag / Core Ab	Hepatitis B S Ag / Core Ab
Hepatitis C	Hepatitis C
Syphilis	HTLV 1 & 2
HIV 1 NAT	CMV
HCV NAT	RhD (If required)
HBV NAT	

- Re-number current (2) (b) as (2) (c)

4. References:

1. Council of Europe Publishing. Guide to safety and quality assurance for organs, tissues and cells. 3rd edition: 2006 version. 2006.
2. F. Yao, C. Seed, A. Farrugia, D. Morgan, S. Cordner, D. Wood and M.H. Zeng. The Risk of HIV, HBV, HCV and HTLV Infection among Musculoskeletal Tissue Donors in Australia. American Journal of Transplantation 2007; 7:2723-2726
3. Shimian Zou, Roger Y. Dodd, Susan L. Stramer, D. Michael Strong. Probability of Viraemia with HBV, HCV, HIV and HTLV among Tissue Donors in the United States. The New England Journal of Medicine 2004; 351:751-759
4. Felix Yao, Clive Seed, Albert Farrugia, David Morgan, David Wood and Ming-Hao Zheng. Comparison of the risk of viral infections between the living and nonliving musculoskeletal tissue donors in Australia. Transplant International Journal 2008.

American Journal of Transplantation 2007; 7: 2723–2726
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2007.02012.x

The Risk of HIV, HBV, HCV and HTLV Infection Among Musculoskeletal Tissue Donors in Australia

F. Yao[a,*], C. Seed[a,b], A. Farrugia[c], D. Morgan[d,e], S. Cordner[f], D. Wood[a,g] and M. H. Zheng[a,g]

[a]*Centre for Orthopaedic Research, School of Surgery and Pathology, University of Western Australia, Perth, Australia*
[b]*Australian Red Cross Blood Services, Perth, Australia*
[c]*Therapeutic Goods Administration, Australian Capital Territory, Australia*
[d]*Department of Orthopaedic Surgery, University of Queensland, Brisbane, Australia*
[e]*Queensland Bone Bank, Queensland, Australia*
[f]*Donor Tissue Bank of Victoria, Melbourne, Australia*
[g]*Perth Bone and Tissue Bank, Perth, Australia*
[*]*Corresponding author: Felix Yao, felixcyao@gmail.com*

In Australia, there are no current national estimates of the risks of transmission of human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) or human T-lymphotrophic virus (HTLV) by musculoskeletal tissue transplantation. We determined the prevalence rates of antibodies against HIV (anti-HIV), HCV (anti-HCV) and HTLV (anti-HTLV) and Hepatitis B surface antigen (HBsAg) for 12415 musculoskeletal tissue donors from three major bone tissue banks across Australia for the period 1993–2004. The prevalence (per 100000 persons) was 64.44 for anti-HIV, 407.13 for HBsAg, 534.63 for anti-HCV and 121.88 for anti-HTLV. The estimated probability of viremia at the time of donation was 1 in 128 000, 1 in 189 000, 1 in 55 000 and 1 in 118 000, respectively. With the addition of nucleic acid amplification testing (NAT), the probability of donor viremia would be reduced to 1 in 315 000 for HIV, 1 in 385 000 for HBV and 1 in 500 000 for HCV. The prevalence of HIV, HBV, HCV and HTLV although low, are higher among musculoskeletal tissue donors than among first-time blood donors. The risks associated with musculoskeletal donation will be reduced with NAT, though further cost analysis is required prior to its implementation.

Key words: Biomaterials, bone allotransplantation, orthopedic surgery, virus transmission

Received 19 June 2007, revised 07 August 2007 and accepted for publication 28 August 2007

Introduction

Besides blood, musculoskeletal allografts are the most frequently transplanted human tissue (1). In Australia, the majority are from surgical donors, though some are retrieved from postmortem organ donation patients and deceased donors (1). Current measures to safeguard tissue recipient safety include the evaluation of all potential donors by a medical history questionnaire, donor serological screening, microbiological monitoring of bone grafts and bio-burden reduction with gamma radiation. In addition, assessment of plasma hemodilution was undertaken routinely to ensure the validity of serology test results.

Mandatory serological screening (as defined by the Australian Therapeutic Goods Administration) for musculoskeletal tissue and blood donors includes hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc) and antibodies against hepatitis C virus (anti-HCV), human immunodeficiency virus (anti-HIV) and human T-lymphotrophic virus (anti-HTLV). All of these viruses have been transmitted by bone tissue allo-transplantation predominantly associated with donations collected in the window period, defined as the time between infection and the first detectable viral marker (2–7). The residual risk of hepatitis B virus (HBV), HCV, HIV and HTLV transmission from screened blood has been estimated for a number of countries including Australia (3,4,8,9). Equivalent probability estimates for musculoskeletal allografts would be helpful to:

1. Monitor and benchmark internationally safety standards for musculoskeletal tissue implantation;
2. Evaluate the safety impact and determine cost-benefit of proposed risk reduction measures (e.g. nucleic acid amplification testing [NAT]);
3. Support the patient consent process with evidence-based risk estimates and
4. Contribute to increased confidence in the subsequent use of bone tissue products by medical practitioners and patients.

Methods

Prevalence of viral infections among musculoskeletal tissue donors

Prevalence was defined as the number of donors with confirmed positive tests divided by the total number of donors tested (10). Data on the

Table 1: Prevalence of viral infection among musculoskeletal tissue donors in comparison to first-time blood donors for the period 1993–2004

	Musculoskeletal tissue donors		First-time blood donors	
Year	Number tested	Confirmed positive (prevalence per 100 000 persons)	Number tested	Confirmed positive (prevalence per 100 000 persons)
Anti-HIV				
1993–2004	12 415	8 (64.44)*	664 686	34 (5.12)
HBsAg				
1993–2004	12 281	50 (407.13)*	664 686	904 (135.97)
Anti-HCV				
1993–2004	12 345	66 (534.63)*	664 686	1431 (215.29)
Anti-HTLV				
1993–2004	11 487	14 (121.88)*	664 686	23 (3.46)

The asterisk denotes a statistically significant difference ($p < 0.05$) between musculoskeletal tissue donors and first-time blood donors.

prevalence rates of anti-HIV, HBsAg, anti-HCV and anti-HTLV in musculoskeletal tissue donors were obtained from databases of the Perth Bone and Tissue Bank (PBTB), Queensland Bone Bank (QBB) and Donor Tissue Bank of Victoria (DTBV) for the period 1993–2004. During this period, all three bone banks followed the Code of Good Manufacturing Practice—Human Blood and Tissues (11).

Estimated incidence of viral infections among musculoskeletal tissue donors

For blood donors, incidence was defined as the number of donors who seroconverted per 100 000 person-years at risk among a group who repeatedly donated blood (12). As described by Seed et al. (4), the number of 'person years of observation' was not available necessitating a minor modification to the incidence estimate for donors from the Australian Red Cross Blood Services (ARCBS). Further, the incidence for HBV was multiplied by an ARCBS adjustment factor of 1.88 to compensate for potential underestimation of HBV incidence because of the transient nature of HBsAg (3,4). First-time blood donor incidence rates were derived by multiplying the repeat donor incidence rates by a correction factor of 2.03 (3).

The incidence rate of new infections among musculoskeletal tissue donors was estimated using a method similar to Zou et al. (2) as follows. First, the ratio of the reported prevalence rates in new blood donors and tissue donors was calculated. Second, it was assumed that prevalence differences between populations are proportional to incidence differences. The incidence in tissue donors was then calculated by multiplying the incidence in new blood donors by the prevalence ratio of the two populations. Because of the lack of seroconversions during some 3-year intervals precluding incidence estimation for that period, the incidence estimation in musculoskeletal donors was restricted to the 2002–2004 period.

Estimated probability of viral infections among musculoskeletal tissue donors

The estimated risk of infectivity—the probability of an undetected window period donation occurring within the study period—was determined by the Incidence/Window Period Model (3,4,8,12,13). This estimate of the residual risk of viral transmission is calculated by assessing the rate of new infection in repeat donors (viral incidence), then multiplying this by the probability of such a donor donating while in the undetectable window period. The accuracy of this risk modeling for HIV/HCV NAT has been retrospectively validated, confirming its utility as a component of cost-benefit analyses (4,9,14,15).

Results

Prevalence of viral infections among musculoskeletal tissue donors and first-time blood donors

Measured prevalence rates among 12 415 musculoskeletal tissue donors (10 937 surgical donors, 1478 deceased donors) for the period 1993–2004 are shown in Table 1. This database encompasses approximately 85% of the total number of musculoskeletal tissue donations in Australia within that period (1). The prevalence rate (per 100 000 persons) was 64.44 for anti-HIV, 407.13 for HBsAg, 534.63 for anti-HCV and 121.88 for anti-HTLV.

Estimated incidence of viral infection among musculoskeletal tissue donors

We determined the incidence rates among tissue donors by extrapolating from the rates among first-time blood donors. The estimated incidence rates among musculoskeletal tissue donors was 12.97 per 100 000 person-years for HIV, 4.43 per 100 000 person-years for HBV, 10.04 per 100 000 person-years for HCV and 6.06 per 100 000 person-years for HTLV (Table 2).

Estimated risk of infectivity among musculoskeletal tissue donors

Table 3 shows the estimated probability of a viremic but serologically negative donation and the predicted NAT yield for HIV, HBV and HCV. We calculated this probability by multiplying the estimated incidence in musculoskeletal donors by the estimated window period of each viral marker denoted as a fraction of a year. By virtue of the shorter window periods afforded by NAT, the projected probability of undetected viremia (per 100 000 donors) is reduced from 0.78 to 0.32 for HIV, 0.53 to 0.26 for HBV and 1.82 to 0.20 for HCV.

Table 2: Estimated incidence of viral infection among musculoskeletal tissue donors in Australia

	Total donors				
Year	Total number	Prevalence ratio *Musculoskeletal: first-time blood donors*	Incidence rate in *first-time blood donors per 100000 person-years*	Estimated incidence rate in musculoskeletal donors	Number of cases expected among musculoskeletal donors
Anti-HIV					
2002–2004	5258	13.12	0.30	3.94	0.21
1993–2004	12416	12.59	1.03	12.97	1.61
HBsAg					
2002–2004	5198	2.71	1.13	3.06	0.16
1993–2004	12281	2.99	1.48	4.43	0.54
Anti-HCV					
2002–2004	5212	5.12	2.40	12.29	0.64
1993–2004	12345	2.48	4.04	10.04	1.24
Anti-HTLV					
2002–2004	4903	16.09	0.30	4.83	0.24
1993–2004	11487	36.22	0.17	6.06	0.70

Discussion

This is the first Australian study of viral prevalence, incidence and residual risk in musculoskeletal tissue donors, combining data from three bone tissue banks for the period 1993–2004. The majority were surgical bone donors (88.10%), though some tissues were retrieved from post-mortem organ donation patients and deceased donors. Benchmarking with anti-HIV, HBsAg, anti-HCV and anti-HTLV prevalence data from Australian blood donors confirms that while prevalence rates in musculoskeletal allografts are low, they are comparably higher than blood donor rates ($p < 0.05$).

By applying the Incidence/Window Period model to our incidence estimates for musculoskeletal donors, we calculated the probability of a donor being viremic but serologically negative at the time of donation to 1 in 128 000 for HIV infection (upper limit 1 in 74 000), 1 in 188 000 for HBV infection (upper limit 1 in 167 000), 1 in 55 000 for HCV infection (upper limit 39 000) and 1 in 118 000 for HTLV infection (upper limit 1 in 83 000). These figures indicate that the risk of viral infection from musculoskeletal tissue transplantation in Australia is low. However, the common perception among clinicians that the risks associated with the transmission of viral infections from a musculoskeletal tissue donor is equivalent to that of a first-time blood donor is inaccurate.

In this study implementing NAT to screen individual tissue donors is estimated to reduce the residual risk of transmission of HIV from 1 in 128 000 to 1 in 315 000, HBV from 1 in 188 000 to 1 in 385 000 and HCV from 1 in 55 000 to 1 in 500000. However, this risk reduction comes at a cost. NAT is more complex, time consuming and expensive than most serological testing. Some costs may be offset by the discontinuation of less effective serological tests and spread over the total number of products sourced from one donor. Despite demonstrating its ability to interdict HCV sero-negative organ and tissue donors and

Table 3: Estimated probability of undetected viral infections in musculoskeletal tissue donors in Australia

				Nucleic-acid amplification testing	
Viral marker	Window period *days (95% CI)*	Estimated incidence *per 100000 person-years*	Estimated probability *per 100000 donors (95% CI)*	Window period *days*	Projected probability *per 100 000 donors*
Anti-HIV					
2002–2004		3.94	0.24 (0.06–0.41)		0.10 (0.08–0.11)
1993–2004	22 (6–38)[16]	12.97	0.78 (0.21–1.35)	9 (7.8–10.2)[15]	0.32 (0.28–0.36)
HBsAg					
2002–2004		3.06	0.37 (0.31–0.42)		0.18
1993–2004	43.6 (37.4–49.7)[17]	4.43	0.53 (0.45–0.60)	21.8[17]	0.26
Anti-HCV					
2002–2004		12.29	2.22 (1.28–3.16)		0.26 (0.21–0.29)
1993–2004	66 (38–94)[13,18]	10.04	1.82 (1.05–2.59)	7.4 (6.1–8.7)[16]	0.20 (0.17–0.24)
Anti-HTLV					
2002–2004		4.83	0.67 (0.48–0.95)	–	–
1993–2004	51 (38–72)[19]	6.06	0.85 (0.60–1.20)	–	–

advocating its implementation in a French study (20), the cost-effectiveness of nucleic acid testing may not compare favorably with that of other health preventative measures such as the application of more stringent donor exclusion criteria or better reporting methods such as the formation of a central database. This is certainly the experience with HIV and HCV NAT donor screening in the United States where its cost effectiveness has been assessed as poor (14).

Prospective studies are now no longer feasible in developed countries like Australia with a very low residual risk of viral infection. The results of this study are highly dependent on the validity of the assumptions inherent in the mathematical risk model (3,4,8,12,13) and the accuracy of the data used. Musculoskeletal donors are usually only able to donate once during their lifetime, therefore incidence was extrapolated from rates obtained in first-time blood donors. However, the accuracy of the Incidence/Window Period model in predicting the NAT yield for HIV and HCV in US and Australian blood donations has been validated by retrospective analysis, and risk modeling is now the most practical method of estimating the residual risk of viral transmission in developed countries (4,21). It is also important to emphasize that our conclusions were based on predominantly surgical musculoskeletal tissue donors in Australia, which represent a low prevalence setting, and may not be generalized to other regions.

We conclude that the existing measures used to evaluate musculoskeletal tissue donors are effective with the probability of collecting a graft from a donor with viremia being small, but not negligible. Evidence from countries having already implemented NAT for tissue donor screening as well as the 'residual risk' modeling applied here indicate that the probability could be further reduced by addition of NAT. Whether or not this is appropriate is dependent on a formal cost-benefit analysis yet to be undertaken.

Acknowledgments

We would like to acknowledge Kellie Hamilton, Lyn Ireland and Vicky Winship from the DTBV, Morris Benkovich and Ron Simard from the QBB, Joyleen Winter and Anne Cowie from the PBTB and Susan Parker and Philip Kiely from the ARCBS for helping with data collection and procurement. We also thank Haider Mansan for statistical assistance in data analysis and interpretation. This research was supported by a grant from the Sir Charles Gairdner Hospital Research Foundation awarded to Professor Ming-Hao Zheng and Dr. Felix Yao.

References

1. Transplantation Society of Australia and New Zealand. Bank Activities (2002–2204). Available from: http://www.atbf.org.au, accessed August 2005.
2. Zou S, Dodd RY, Stramer SL, Strong DM. Probability of viremia with HBV, HCV, HIV, and HTLV among tissue donors in the United States. N Engl J Med 2004; 351: 751–759.
3. 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: 592–598.
4. Seed CR, Cheng A, Ismay SL et al. Assessing the accuracy of three viral risk models in predicting the outcome of implementing HIV and HCV NAT donor screening in Australia and the implications for future HBV NAT. Transfusion 2002; 42: 1365–1372.
5. 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: 975–979.
6. Petersen LR, Satten GA, Dodd R et al. Duration of time from onset of human immunodeficiency virus type 1 infectiousness to development of detectable antibody. The HIV Seroconversion Study Group. Transfusion 1994; 34: 283–289.
7. Tugwell B, Patel P, Williams I. Transmission of hepatitis C virus to several organ and tissue recipients from an antibody-negative donor. Ann Intern Med 2005; 143: 648–654.
8. Glynn SA, Kleinman SH, Wright DJ, Busch MP. International application of the incidence rate/window period model. Transfusion 2002; 42: 966–972.
9. Coste J, Reesink HW, Engelfriet CP et al. Implementation of donor screening for infectious agents transmitted by blood by nucleic acid technology: Update to 2003. Vox Sang 2005; 88: 289–303.
10. Gales G, Dow BC. Comparison of prevalence rates of microbiological markers Betweenbone/tissue donations and new blood donors in Scotland. Vox Sang 2006; 91: 28–33.
11. Australian Therapeutic Goods Administration. Code of Good Manufacturing Practice - Human Blood and Tissues. Australian Therapeutic Goods Administration, Wooden ACT Australia 2000.
12. Kleinman S, Busch MP, Korelitz JJ, Schreiber GB. The incidence/window period model and its use to assess the risk of transfusion-transmitted human immunodeficiency virus and hepatitis C virus infection. Transfus Med Rev 1997; 11: 155–172.
13. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. N Engl J Med 1996; 334: 1685–1690.
14. Jackson BR, Busch MP, Stramer SL, AuBuchon JP. The cost-effectiveness of NAT for HIV, HCV, and HBV in whole-blood donations. Transfusion 2003; 43: 721–729.
15. Busch MP, Glynn SA, Stramer SL et al. A new strategy for estimating risks of transfusion-transmitted viral infections based on rates of detection of recently infected donors. Transfusion 2005; 45: 254–264.
16. Busch MP, Lee LL, Satten GA et al. Time course of detection of viral and serologic markers preceding human immunodeficiency virus type 1 seroconversion: Implications for screening of blood and tissue donors. Transfusion 1995; 35: 91–97.
17. Kleinman SH, Busch MP. Assessing the impact of HBV NAT on window period reduction and residual risk. J Clin Virol 2006; 36(Suppl 1) S23–S29.
18. Pillonel J, Saura C, Courouce AM. Prevalence of HIV, HTLV, and hepatitis B and C viruses in blood donors in France, 1992–1996. Transfus Clin Biol 1998; 5: 305–312.
19. 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: 886–891.
20. Challine D, Pellegrin B, Bouvier-Alias M, Rigot P, Laperche L, Pawlotsky JM. HIV and hepatitis C virus RNA in seronegative organ and tissue donors. Lancet 2004; 364: 1611–1612.
21. Kleinman S, Stramer S, Mimms L et al. Comparison of preliminary observed yield of HCV and HIV minipool (MP) nucleic acid testing (NAT) with predictions from the Incidence/Window Period (INC/WP) Model. Transfusion 2000; 40: S6–S30.

2.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

◄ Previous Volume 351:751-759 August 19, 2004 Number 8 Next ►

Probability of Viremia with HBV, HCV, HIV, and HTLV among Tissue Donors in the United States

Shimian Zou, Ph.D., Roger Y. Dodd, Ph.D., Susan L. Stramer, Ph.D., D. Michael Strong, Ph.D., for the Tissue Safety Study Group

ABSTRACT

Background Tissue-banking organizations in the United States have introduced various review and testing procedures to reduce the risk of the transmission of viral infections from tissue grafts. We estimated the current probability of undetected viremia with hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and human T-lymphotropic virus (HTLV) among tissue donors.

Methods Rates of prevalence of hepatitis B surface antigen (HBsAg) and antibodies against HIV (anti-HIV), HCV (anti-HCV), and HTLV (anti-HTLV) were determined among 11,391 donors to five tissue banks in the United States. The data were compared with those of first-time blood donors in order to generate estimated incidence rates among tissue donors. The probability of viremia undetected by screening at the time of tissue donation was estimated on the basis of the incidence estimates and the window periods for these infections.

Results The prevalence of confirmed positive tests among tissue donors was 0.093 percent for anti-HIV, 0.229 percent for HBsAg, 1.091 percent for anti-HCV, and 0.068 percent for anti-HTLV. The incidence rates were estimated to be 30.118, 18.325, 12.380, and 5.586 per 100,000 person-years, respectively. The estimated probability of viremia at the time of donation was 1 in 55,000, 1 in 34,000, 1 in 42,000, and 1 in 128,000, respectively.

Conclusions The prevalence rates of HBV, HCV, HIV, and HTLV infections are lower among tissue donors than in the general population. However, the estimated probability of undetected viremia at the time of tissue donation is higher among tissue donors than among first-time blood donors. The addition of nucleic acid–amplification testing to the screening of tissue donors should reduce the risk of these infections among recipients of donated tissues.

Hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and human T-lymphotropic virus (HTLV) have all been transmitted by tissue transplantation.[1,2,3] These viruses have also been transmitted by blood transfusion, almost always as a result of the collection of blood during the so-called viremic window period, before infection can be detected by laboratory testing.[4,5,6,7] The probability of collecting blood during this window period has been extensively evaluated.[8,9,10,11] However, similar estimates have not been made for tissue donors, even though such estimates would be helpful in evaluating the efficiency of current and future measures designed to ensure the safety of tissue transplantation.

Tissue banks in the United States obtain, process, and distribute a variety of tissues, including heart valves, venous tissue, bone, bone-derived products (such as powders used for dental work), and connective tissue. The vast majority of these tissues come from cadavers, and all are essentially avascular and can be stored for long periods. Although tissue donors may also provide organs for transplantation, the converse is not necessarily true. The infectivity of different tissues varies, in part as a reflection of their anatomical origin and nature, but also as a result of processing after collection. For example, a highly processed bone powder would be much less likely to transmit a viral infection than would a fresh-frozen bone segment. Currently, the measures used to assess tissue donors include a retrospective review of the donor's medical history and testing of cadaveric blood samples for hepatitis B surface antigen (HBsAg) and antibodies against HIV (anti-HIV), HCV (anti-HCV), and HTLV (anti-HTLV).

Methods

The Study

We estimated the probability of viremia at the time of tissue donation by using the incidence–window-period model developed to estimate the residual risk of viremia among blood donors.[4,5,6,8] In order to do this, we estimated the incidence rates of HIV, HBV, HCV, and HTLV infection on the basis of measured prevalence rates among tissue donors and available data from other sources. Information on the duration of the window periods of viremia, before seroconversion, for these infections was obtained from the peer-reviewed literature.[8,11]

Determination of Prevalence Rates among Tissue Donors

Data on the prevalence of anti-HIV, HBsAg, anti-HCV, and anti-HTLV in tissue donors were obtained from existing databases of the Northwest Tissue Center (for 2001 through 2002), the American Red Cross Tissue Services (for 2000 through 2002), the Musculoskeletal Transplant Foundation (for 2002), the Community Blood Center/Community Tissue Services (for 2001), and LifeNet (for 2002). The data did not include any donor identifiers. During the periods covered, all five centers followed the review and testing standards of the American Association of Tissue Banks.[12] Four of the centers reported confirmed positive results; one reported only the results of the screening tests. For donors at this center, we estimated the rates of confirmed positive results by subtracting the number of false positive results (determined on the basis of specificity analyses of data from the other sites) from the number of reactive screening results. Pooled data were used to determine age- and sex-specific prevalence rates for the markers; prevalence was defined as the number of donors with confirmed positive tests divided by the total number of donors tested.

Estimation of Incidence Rates among Tissue Donors

The incidence rate of new infections among tissue donors was estimated by applying age- and sex-specific incidence rates for first-time blood donors to the tissue-donor population. Prevalence and incidence rates among voluntary donors and donors of directed whole blood were obtained from a research database of blood donors to the American Red Cross Blood Services.[11] Incidence was defined as the number of donors who seroconverted per 100,000 person-years among a group who repeatedly donated blood. Dodd et al.[11] and Janssen et al.[13] reported incidence ratios among first-time donors as compared with those who made repeated donations of 2.42 for HCV infection and 2.43 for HIV infection. No such data were available for HBV and HTLV infections. On the basis of the ratios for HIV and HCV, a ratio of 2.5 was assumed for HBV and HTLV. The ratios were applied to the incidence rates among persons who donate blood repeatedly to estimate incidence rates for first-time blood donations. These incidence rates were adjusted to reflect the difference in prevalence rates between blood and tissue donors by multiplying by the ratios of prevalence rates in the two groups. Prevalence and incidence rates for corresponding groups in the general population were also obtained through a search for published epidemiologic data[14,15,16] and unpublished data from the Centers for Disease Control and Prevention (CDC) (Alter M: personal communication) and were used in a similar manner to derive alternative estimates of incidence rates among tissue donors.

Estimation of the Probability of Viremia

We estimated the risk of infectivity — the probability that any tissue donor was in the viremic window period with an infection that was undetected by means of serologic screening methods at the time of donation — by the method developed by Petersen et al.,[4] Busch et al.,[5] Lackritz et al.,[6] and Schreiber et al.[8] The estimated probability is obtained from the product of the incidence rate and the length of the window period for each infection.

Unless otherwise specified, frequencies were compared with the use of the chi-square test; all reported P values are two-sided. Possible ranges of the estimated risks of infectivity resulting from the collection of tissues during the window periods for these infections were determined by means of Monte Carlo simulation with the use of Crystal Ball software.[17] Basically, possible variations in the prevalence rates among tissue donors and first-time blood donors according to sex and age, incidence rates among those who repeatedly donated blood according to sex and age, overall prevalence and incidence estimates and their assumed sex- and age-based distributions in the general population, incidence ratios for first-time donors as compared with those who repeatedly donated blood, and window periods were incorporated into the incidence- and risk-determination models to derive the 2.5 and 97.5 percentiles of the risk estimates. For prevalence and incidence rates, 95 percent confidence intervals were incorporated into all models except for those for the prevalence of HIV and for the incidence of the three markers in the general population; these models used a 50 percent variation owing to the lack of data on confidence intervals. A variation of 50 percent was also applied to the incidence ratios for HIV, HBV, HCV, and HTLV infections between first-time donors as compared with those who repeatedly donated on the basis of the variations in the incidence rates for HIV[13] and HCV.[11] All the ratios were assumed to follow triangular distributions. The window periods were assumed to follow triangular distributions with different degrees of variation, as reported by Schreiber et al.[8]

Results

Prevalence of Viral Infections among Tissue Donors

Results obtained from 2000 through 2002 from a total of 11,391 tissue donors are shown in Table 1. The data include the numbers of tissue donors with results that were confirmed to be positive and, when necessary, the estimated numbers of confirmed positive results, as explained above. The rate of confirmed positive results (prevalence rate) was 0.093 percent for anti-HIV (95 percent confidence

interval, 0.036 to 0.150), 0.229 percent for HBsAg (95 percent confidence interval, 0.139 to 0.319), 1.091 percent for anti-HCV (95 percent confidence interval, 0.896 to 1.286), and 0.068 percent for anti-HTLV (95 percent confidence interval, 0.019 to 0.117). The prevalence rate of anti-HCV was higher among male donors than female donors, whereas the reverse was true for anti-HIV and anti-HTLV.

View this table: [in this window] [in a new window] **Table 1.** Prevalence of Infectious-Disease Markers among Tissue Donors, According to Age and Sex.

To check the estimated frequency of confirmed positive results among the unconfirmed reactive results from a single center, we used a recombinant immunoblot assay (RIBA 3.0 SIA test, Chiron) to test 50 serum samples obtained post mortem that were initially reactive for anti-HCV. Thirty-six (72 percent) were positive, seven (14 percent) were indeterminate, and seven (14 percent) were negative. Similarly, we used Western blotting (HIV Western Blot Kit, Cambridge Biotech) to test nine serum samples that were initially reactive for HIV. Seven were negative, and two were indeterminate. Among tissue donors from other tissue centers, 74 percent of samples that were reactive to anti-HCV on initial screening were confirmed to be positive (81 of 110) and 11 percent of samples that were reactive to anti-HIV on initial screening were confirmed to be positive (2 of 19). The differences between these values and values found by evaluation testing were not significant (x^2=0.006, P=0.98 for anti-HCV and P=1.00 for anti-HIV by Fisher's exact test), indicating that the approach used to extrapolate the rates of confirmed positive results was appropriate.

Prevalence and Incidence of Viral Infections among Blood Donors

Table 2 shows the prevalence rates of confirmed positive results for anti-HIV, HBsAg, anti-HCV, and anti-HTLV among first-time blood donors, stratified according to sex and age. Incidence rates of new infections were obtained for those who repeatedly donated blood in the period from 2000 through 2001, according to sex and age group, as previously published.[11] For HBsAg, the incidence was adjusted as described by Schreiber et al.[8] and Korelitz et al.[18] This adjustment involves multiplying the incidence rate by a correction factor (2.38) to compensate for the transient expression of HBsAg in acute infections.

View this table: [in this window] [in a new window] **Table 2.** Prevalence of Infectious-Disease Markers among First-Time Donors of Whole Blood in 2001, According to Age and Sex.

Prevalence and Incidence of Viral Infections in the General Population

According to U.S. data from the CDC[16] (and from the AIDS [Acquired Immunodeficiency Syndrome] Public Information Data Set at www.cdc.gov/hiv/software/apids.htm), the current prevalence of HIV infection (excluding AIDS) is approximately 0.20 percent. The incidence of HIV infection is estimated to be 40,000 cases per year, with approximately 70 percent of cases in males and 30 percent in females; the age distribution of incident HIV infections is not available. The age distribution of patients with AIDS — 18.30 percent of whom are less than 30 years of age, 70.85 percent 30 to 49 years of age, and 10.85 percent 50 years of age or older — was assumed for HIV infections.

For viral hepatitis, the CDC estimates that 78,000 HBV infections and 25,000 HCV infections occurred in 2001 (from the Division of Viral Hepatitis, at www.cdc.gov). The age distribution of incident HBV infections for 2000 — 37.09 percent younger than 30 years of age, 46.80 percent 30 to 49 years of age, and 16.11 percent 50 years of age or older — was assumed for cases of HBV. The age distribution for incident HCV infections for 2001 was 29 percent younger than 30 years of age, 64 percent 30 to 49 years of age, and 7 percent 50 years of age or older, and the male:female ratio was 1.7:1 (Alter M: personal communication).

No current prevalence data are available for HBV or HCV. On the basis of testing of serum samples from persons who participated in the Third National Health and Nutrition Examination Survey from 1988 through 1994, McQuillan et al.[15] reported a prevalence rate of HBsAg of 0.42 percent, and Alter et al.[14] reported a prevalence of anti-HCV of 1.8 percent. Furthermore, the study by McQuillan et al.[15] showed a male:female ratio of 1.4:1 with respect to the prevalence of total HBV infections. These data are assumed to represent the current status and were used in this assessment. No data are available on HTLV infection in the general population.

Estimated Incidence Rates among Tissue Donors

By extrapolating from the rates among first-time blood donors, we estimated that the incidence rates among tissue donors were 30.118 per 100,000 person-years for HIV, 18.325 per 100,000 person-years for HBsAg, 12.380 per 100,000 person-years for HCV, and 5.586 per 100,000 person-years for HTLV (Table 3). The prevalence ratios for tissue donors relative to those in the general population were 0.46 for HIV, 0.54 for HBsAg, and 0.61 for HCV; the corresponding estimated incidence rates per 100,000 person-years for tissue donors were 7.099, 15.100, and 4.910, respectively (Table 4). The estimates derived from the blood-donor approach were higher than those derived from the general-population approach. Prevalence and incidence data from blood donors are less likely to be underestimates, owing to the systematic testing of each donation.

View this table: [in this window] [in a new window] **Table 3.** Estimated Incidence of HIV, HBsAg, HCV, and HTLV among Tissue Donors.

View this table: [in this window] [in a new window] **Table 4.** Estimated Probability of Viremia Undetected by Testing Methods at the Time of Tissue Donation, According to the Blood-Donor Approach and the General-Population Approach.

Estimated Risk of Infectivity among Tissue Donors

Table 4 shows the estimated probability of viremia at the time of tissue donation that was undetected on screening with the use of current serologic methods, as well as the projected effect of nucleic acid–amplification testing of individual samples on the window periods of infection and the projected probabilities. The estimates of incidence rates that were derived from the blood-donor approach were used for the projection.

Discussion

Our prevalence results were based on data from five tissue banks across the United States. A survey of tissue banks accredited by the American Association of Tissue Banks, conducted in June 2000 for calendar year 1999, showed rates of reactivity on screening of 0.35 percent for HIV (66 of 19,091 donations), 0.94 percent for HBsAg (179 of 19,090 donations), 1.49 percent for HCV (285 of 19,130 donations), and 0.53 percent for HTLV (101 of 19,072 donations).[20] Our results — 0.34 percent, 0.71 percent, 1.51 percent, and 0.60 percent, respectively — are close to those of the survey. Such consistency suggests that our data are representative of the tissue-donor population in the United States.

The measured prevalence rates among tissue donors fall between those found among first-time blood donors and those attributed to the general population. This is not surprising, since tissue donors, although more representative of the general population than are blood donors, are carefully selected on the basis of medical history, physical examination, and interviews with the next of kin. Such a process, however, is not as effective as the face-to-face interview that is conducted with blood donors.[21]

By imputing rates from first-time blood donors and, separately, from the general population, we used an indirect approach to assign incidence rates to tissue-donor populations. For our primary estimates, we adjusted these rates to reflect the different prevalence rates among the tissue donors and the populations used for comparison. We used the resulting incidence rates with estimated window periods to estimate the probability of viremia at the time of tissue donation that would have gone undetected on screening with the use of current serologic tests.

Our data are based on information from 11,391 tissue donors. Donations from approximately 20,000 tissue donors are processed annually in the United States, generating roughly 1 million separate products. According to our estimates, the probability that a donor is viremic at the time of donation is 1 in 55,000 in the case of HIV infection, 1 in 34,000 in the case of HBV infection, 1 in 42,000 in the case of HCV infection, and 1 in 128,000 in the case of HTLV infection. We suggest that the respective upper bounds of these figures would be 1 in 22,000, 1 in 19,000, 1 in 17,000, and 1 in 41,000; in other words, 1 or fewer donors would be viremic per year. These figures clearly indicate that the risk of infectivity is low, and in fact, most transplanted products are treated to reduce or eliminate the risk of infectivity. However, since tissues from a single donor may be used in an average of 50 patients, a single donor has the potential to infect an unknown, although probably small, number of recipients.[2]

The implementation of nucleic acid–amplification testing of "minipools" (pools of 16 to 24 blood donations) has markedly reduced the residual risk of viremia and transfusion-transmitted infection; the reduction in risk is directly proportional to the decrease in the length of the window period achieved by the use of this approach, by 5 days for HIV and by 60 days for HCV.[11,22] Studies have shown that nucleic acid–amplification testing of individual donations would reduce the window period to 7 days for HIV and HCV and to 20 days for HBV.[19,23] If individual testing were to be used for tissue donors, the probability of donor viremia would be reduced to 1 in 173,000 for HIV, 1 in 421,000 for HCV, and 1 in 100,000 for HBV. Assuming that it would cost approximately $150 ($50 per virus on the basis of current charges) to test each donor for the three viruses, the overall cost of eliminating one potentially infectious donor would be $4.0 million in the case of HIV infection, $2.3 million in the case of HCV infection, and $2.6 million in the case of HBV infection. Presumably, that cost would be spread over 1 million or more tissue products each year. Currently, efforts are under way to implement nucleic acid–amplification testing of cadaveric samples.

Overall, we believe that current measures used to evaluate tissue donors are effective and that the probability of collecting products from a viremic donor is low, but not negligible. On the basis of the model used for donated blood, this probability could be further reduced by the addition of nucleic acid–amplification testing at an approximate cost of less than $5 per product.

Dr. Dodd reports having received consulting or lecture fees from Roche and Chiron; Dr. Strong consulting and lecture fees from Roche Molecular Systems and holding equity in Human BioSystems; and Dr. Stramer consulting fees from Chiron and Gen-Probe.

We are indebted to Ed Notari and Fahti Musavi from the Jerome H. Holland Laboratory of the American Red Cross for help with processing and analysis of the data, and to Duke Kasprisin for valuable advice and comments.

Source Information

From the American Red Cross, Rockville, Md. (S.Z., R.Y.D.), and Gaithersburg, Md. (S.L.S.); and the Puget Sound Blood Center/Northwest Tissue Center, Seattle (D.M.S.).

Address reprint requests to Dr. Zou at the Transmissible Diseases Department, American Red Cross, 15601 Crabbs Branch Way, Rockville, MD 20855, or at zous@usa.redcross.org.

References

1. Joyce MJ, Greenwald AS, Rigney R, et al. Report on musculoskeletal allograft tissue safety. Presented at the American Academy of Orthopaedic Surgeons 71st Annual Meeting, San Francisco, March 10--14, 2004.
2. Hepatitis C virus transmission from an antibody-negative organ and tissue donor -- United States, 2000-2002. MMWR Morb Mortal Wkly Rep 2003;52:273-4, 276. [Medline]
3. Eastlund T, Strong DM. Infectious disease transmission through tissue transplantation. In: Phillips GO, ed. Advances in tissue banking. Vol. 7. Singapore: World Scientific, 2004:51-131.
4. Petersen LR, Satten GA, Dodd RY, et al. Duration of time from onset of human immunodeficiency virus type 1 infectiousness to development of detectable antibody. Transfusion 1994;34:283-289. [CrossRef][Web of Science][Medline]
5. Busch MP, Lee LL, Satten GA, et al. Time course of detection of viral and serologic markers preceding human immunodeficiency virus type 1 seroconversion: implications for screening of blood and tissue donors. Transfusion 1995;35:91-97. [CrossRef][Web of Science][Medline]
6. Lackritz EM, Satten GA, Aberle-Grasse J, et al. Estimated risk of transmission of the human immunodeficiency virus by screened blood in the United States. N Engl J Med 1995;333:1721-1725. [Free Full Text]
7. Dodd RY. Current viral risks of blood and blood products. Ann Med 2000;32:469-474. [Web of Science][Medline]
8. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections: The Retrovirus Epidemiology Donor Study. N Engl J Med 1996;334:1685-1690. [Free Full Text]
9. Dodd RY, Stramer SL, Aberle-Grasse J, Notari E IV. Risk of hepatitis and retroviral infections among blood donors and introduction of nucleic acid testing (NAT). Dev Biol Stand 2000;102:19-27.
10. Glynn SA, Kleinman SH, Schreiber GB, et al. Trends in incidence and prevalence of major transfusion-transmissible viral infections in US blood donors, 1991 to 1996: The Retrovirus Epidemiology Donor Study (REDS). JAMA 2000;284:229-253. [Free Full Text]
11. Dodd RY, Notari EP IV, 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;42:975-979. [CrossRef][Web of Science][Medline]
12. American Association of Tissue Banks. Standards for tissue banking. 10th ed. McLean, Va.: American Association of Tissue Banks, 2002.
13. Janssen RS, Satten GA, Stramer SL, et al. New testing strategy to detect early HIV-1 infection for use in incidence estimates and for clinical and prevention purposes. JAMA 1998;280:42-48. [Erratum, JAMA 1999;281:1893.] [Free Full Text]
14. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999;341:556-562. [Free Full Text]
15. McQuillan GM, Coleman PJ, Kruszon-Moran D, Moyer LA, Lambert SB, Margolis HS. Prevalence of hepatitis B virus infection in the United States: the National Health and Nutrition Examination Surveys, 1976 through 1994. Am J Public Health 1999;89:14-18. [Free Full Text]
16. Karon JM, Fleming PL, Steketee RW, De Cock KM. HIV in the United States at the turn of the century: an epidemic in transition. Am J Public Health 2001;91:1060-1068. [Abstract]
17. Crystal Ball software 2000.2 user manual. Denver: Decisioneering, 2000.
18. Korelitz JJ, Busch MP, Kleinman SH, et al. A method for estimating hepatitis B virus incidence rates in volunteer blood donors: National Heart, Lung, and Blood Retrovirus Epidemiology Donor Study. Transfusion 1997;37:634-640. [CrossRef][Web of Science][Medline]
19. Jackson BR, Busch MP, Stramer SL, AuBuchon JP. The cost-effectiveness of NAT for HIV, HCV, and HBV in whole-blood donations. Transfusion 2003;43:721-729. [CrossRef][Web of Science][Medline]
20. 2002 Annual registration survey of accredited tissue banks. McLean, Va.: American Association of Tissue Banks, 2002.
21. Scardino MK, Hwang SJ, Hanna CL, Danneffel-Mandelkorn MB, Wilhelmus KR. The postmortem sociomedical interview: uncertainty in confirming infectious disease risks of young tattooed donors. Cornea 2002;21:798-802. [Medline]
22. Stramer SL, Caglioti S, Strong DM. NAT of United States and Canadian blood supply. Transfusion 2000;40:1165-1168. [Erratum, Transfusion 2001;41:1079.] [CrossRef][Web of Science][Medline]
23. Busch MP. Should HBV NAT replace HBsAg and/or anti-HBc screening of blood donors? Transfus Clin Biol 2004;11:26-32. [Medline]

Appendix

The Tissue Safety Study Group consists of the following: M. Moogk, Northwest Tissue Center; H. Korent, C. Nettles, S. Williams, and S. Haight, American Red Cross Tissue Services; D. Gocke, R. Maas, and J. Yeager, Musculoskeletal Transplant Foundation; J. Woll and R. Hinely, Community Blood Center/Community Tissue Services; and R. Hurwitz, S. Bottenfield, L. Weiss, and P. Flotten, LifeNet.

Related Letters:

HIV-1 and HCV Infections among Antibody-Negative Blood Donors

THIS ARTICLE
Abstract
PDF

Begovac J., Mihaljevic I., Perrin L., Laperche S., Pillonel J., Herve P., Prince A. M., Kainer M. A., Jarvis W. R., Stramer S. L., Dodd R. Y., Busch M. P., Goodman J. L.
Extract | Full Text | PDF
N Engl J Med 2004; 351:2232-2235, Nov 18, 2004. **Correspondence**

This article has been cited by other articles:

- Fishman, J. A., McCullough, L. B., Halpern, S. D., Shaked, A., Caplan, A. L. (2008). Informing Candidates for Transplantation about Donor Risk Factors. *NEJM* 359: 1182-1183 [Full Text]
- Halpern, S. D., Shaked, A., Hasz, R. D., Caplan, A. L. (2008). Informing Candidates for Solid-Organ Transplantation about Donor Risk Factors. *NEJM* 358: 2832-2837 [Full Text]
- Yao, F., Seed, C., Wood, D., Zheng, M.-H. (2008). Prevalence and Incidence of Viral Infections among Musculoskeletal Tissue Donors and First-Time Blood Donors. *ANN INTERN MED* 148: 792-794 [Full Text]
- Martin-Davila, P., Fortun, J., Lopez-Velez, R., Norman, F., Montes de Oca, M., Zamarron, P., Gonzalez, M. I., Moreno, A., Pumarola, T., Garrido, G., Candela, A., Moreno, S. (2008). Transmission of Tropical and Geographically Restricted Infections during Solid-Organ Transplantation. *Clin. Microbiol. Rev.* 21: 60-96 [Abstract] [Full Text]
- McAllister, D. R., Joyce, M. J., Mann, B. J., Vangsness, C. T. Jr (2007). Allograft Update: The Current Status of Tissue Regulation, Procurement, Processing, and Sterilization. *Am J Sports Med* 35: 2148-2158 [Abstract] [Full Text]
- Schwab, I. R., Johnson, N. T., Harkin, D. G. (2006). Inherent Risks Associated With Manufacture of Bioengineered Ocular Surface Tissue. *Arch Ophthalmol* 124: 1734-1740 [Abstract] [Full Text]
- Tugwell, B. D., Patel, P. R., Williams, I. T., Hedberg, K., Chai, F., Nainan, O. V., Thomas, A. R., Woll, J. E., Bell, B. P., Cieslak, P. R. (2005). Transmission of Hepatitis C Virus to Several Organ and Tissue Recipients from an Antibody-Negative Donor. *ANN INTERN MED* 143: 648-654 [Abstract] [Full Text]
- Padeh, Y. C., Rubinstein, A., Shliozberg, J. (2005). Common Variable Immunodeficiency and Testing for HIV-1. *NEJM* 353: 1074-1075 [Full Text]
- Kotton, C. N., Fishman, J. A. (2005). Viral Infection in the Renal Transplant Recipient. *J. Am. Soc. Nephrol.* 16: 1758-1774 [Abstract] [Full Text]
- Begovac, J., Mihaljevic, I., Perrin, L., Laperche, S., Pillonel, J., Herve, P., Prince, A. M., Kainer, M. A., Jarvis, W. R., Stramer, S. L., Dodd, R. Y., Busch, M. P., Goodman, J. L. (2004). HIV-1 and HCV Infections among Antibody-Negative Blood Donors. *NEJM* 351: 2232-2235 [Full Text]
- (2004). New Level of HIV Testing for Blood and Tissue Donors. *AIDS Clin Care* 2004: 7-7 [Full Text]
- (2004). Banked Blood and Tissue: Safer but Still Not Perfect. *Journal Watch Cardiology* 2004: 5-5 [Full Text]
- (2004). Viral Infections from Blood Transfusions and Tissue Grafts: Reducing the Risk. *JWatch Infect. Diseases* 2004: 3-3 [Full Text]
- (2004). Banked Blood and Tissue: Safer but Still Not Perfect. *JWatch General* 2004: 4-4 [Full Text]
- Goodman, J. L. (2004). The Safety and Availability of Blood and Tissues -- Progress and Challenges. *NEJM* 351: 819-822 [Full Text]

Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Comparison of the risk of viral infection between the living and nonliving musculoskeletal tissue donors in Australia

Felix Yao,[1] Clive Seed,[1,2] Albert Farrugia,[3] David Morgan,[4,5] David Wood[1,6] and Ming-Hao Zheng[1,6]

1 Centre for Orthopaedic Research, School of Surgery and Pathology, University of Western Australia, Perth, WA, Australia
2 Australian Red Cross Blood Services, Perth, WA, Australia
3 Therapeutic Goods Administration, Canberra, ACT, Australia
4 Department of Orthopaedic Surgery, University of Queensland, Brisbane, Qld, Australia
5 Queensland Bone Bank, Brisbane, QLD, Australia
6 Perth Bone and Tissue Bank, Perth, WA, Australia

Keywords
bone transplantation, musculoskeletal tissue, viral transmission.

Correspondence
Dr Felix Yao, Centre for Orthopaedic Research, University of Western Australia, M508 2nd Floor M Block, QEII Medical Centre, Nedlands, WA 6009, Australia. Tel.: +61 8 9346 4050; fax: +61 8 9346 3210; e-mail: felixcyao@gmail.com

Received: 2 January 2008
Revision requested: 18 January 2008
Accepted: 7 May 2008

doi:10.1111/j.1432-2277.2008.00703.x

Summary

Screening of musculoskeletal tissue donors with nucleic acid testing (NAT) for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) has been implemented in the United States and other developed nations. However, in contrast to the donor demographics in the United States, the majority of Australian musculoskeletal tissue donations are primarily from living surgical donors. The objective of our study was to determine and compare the risk of viral infection associated with musculoskeletal tissue donation from living and nonliving donors in Australia. We studied serum samples from 12 415 consecutive musculoskeletal tissue donors between 1993 and 2004. This included 10 937 surgical donations, and 1478 donations obtained from postmortem organ donation patients and cadaveric donors. Current mandatory retesting of surgical donors 6 months postdonation reduces the risk of viral infection by approximately 95% by eliminating almost all donors in the window period. The addition of nucleic acid amplification testing for nonliving donors would similarly reduce the window period, and consequently the residual risk by approximately 50% for hepatitis B virus, 55% for HIV, and 90% for HCV. NAT, using appropriately validated assays for nonliving donors, would reduce the residual risk to levels comparable to that in living donors (where the 95% reduction for quarantining pending the 180-day re-test is included).

Introduction

Musculoskeletal tissue is only second to the blood as the most frequently transplanted human tissue and there continues to be an enormous demand for these allografts throughout the world. Currently in Australia, the majority of musculoskeletal tissue donations are from living surgical donors, predominantly consisting of retrieved femoral heads postprimary hip arthroplasty. However, to fulfil the increasing demand for tissues, there is a trend to begin the use of materials obtained from postmortem organ donation patients and cadaveric donors.

Transplantation of tissue from a living or deceased donor exposes the recipient to viral transmission. Measures to safeguard tissue recipient's safety include a review of the donor's medical history, microbiological monitoring, bio-burden reduction, plasma haemodilution, and donor serological screening for hepatitis B surface antigen (HBsAg), and antibodies against human immunodeficiency virus (anti-HIV), hepatitis C virus (anti-HCV), and human T-cell lymphotropic virus (anti-HTLV). However, the donor-selection procedures for nonliving donors are more challenging – the medical history questionnaire has to be completed by the next-of-kin, and the

confirmatory serological testing undertaken routinely for living donors 6 months postretrieval cannot be performed in the case of nonliving donors. This article describes the prevalence and estimated incidence of HIV, hepatitis B virus (HBV), HCV, and HTLV in living donors compared with rates obtained during the same period from nonliving donors in Australia, to ascertain whether there is a greater risk of viral infection associated with tissues obtained from nonliving donors.

Methods

We studied serum samples from 12 415 consecutive musculoskeletal tissue donors from three large tissue banks in Australia between 1993 and 2004. This included 10 937 surgical donations (living donations), and 1478 donations obtained from postmortem organ donation patients and cadaveric donors (nonliving donations). Informed oral consent to tissue donation and blood sampling for virological testing was obtained from either the next-of-kin or donor who had fulfilled the medical exclusion criteria and behavioural risk assessment. Mandatory serological testing for HIV, HBV, HCV, and HTLV were performed for all specimens obtained at the time of donation, and surgical donors were required to return for a follow-up test 6 months post-tissue donation to rule out seroconversion. Allografts from these donors were not utilized until the 6-month postretrieval serology testing returned a negative result.

Determination of prevalence, estimated incidence, and estimated probability of viral infections among musculoskeletal tissue donors

Prevalence was defined as the number of donors with confirmed positive tests divided by the total number of donors tested [1]. Age- and gender-specific prevalence rates of anti-HIV, HBsAg, anti-HCV, and anti-HTLV in musculoskeletal tissue donors were obtained from databases of the Perth Bone and Tissue Bank (PBTB), Queensland Bone Bank (QBB), and Donor Tissue Bank of Victoria (DTBV) for the period 1993 through 2004. During this period, all three bone banks complied with the Code of Good Manufacturing Practice – Human Blood and Tissues [2]. First-time blood donor rates were obtained from the corresponding Australian Red Cross Blood Services (ARCBS) sites. Statistical comparisons were performed using Fisher's exact test or Pearson chi-squared test as appropriate. A P-value <0.05 indicated that a difference was significant. The 95% confidence interval (CI) for prevalence rates were obtained by the Fleiss quadratic method, which is adapted when proportions are close to zero.

The incidence rate of new infections among musculoskeletal tissue donors was estimated using a previously published method [3] as follows. First, the ratio of the reported prevalence rates in new blood donors and tissue donors was calculated. Second, it was assumed that prevalence differences between populations are proportional to incidence differences. The incidence in tissue donors was then calculated by multiplying the incidence in new blood donors by the prevalence ratio of the two populations.

The estimated risk of infectivity – the probability of an undetected window period (WP) donation occurring within the study period – was determined by the Incidence/Window Period Model [4–8]. This estimate of the residual risk of viral transmission is calculated by assessing the rate of new infection in repeat donors (viral incidence), then multiplying this by the probability of such a donor donating while being in the undetectable WP. The accuracy of this risk modelling for blood donor HIV/HCV nucleic acid testing (NAT) has been retrospectively validated, confirming its utility as a component of cost–benefit analyses [5,9–11].

Results

In total, we obtained results from 12 415 musculoskeletal tissue donors between 1993 and 2004, including 10 937 surgical donors (88.10%) and 1478 donations obtained from postmortem or cadaveric donors (11.90%). This database encompasses approximately 85% of the total number of musculoskeletal tissue donations in Australia within that period [12]. On average, there were 918 living donors (range: 380–2212) and 123 nonliving donors (range: 63–261) screened per year, and 45.58% of all donors were female.

Prevalence of viral infections among living and nonliving donors

Age- and gender-matched prevalence rates among 10 937 surgical musculoskeletal tissue donors for the period 1993–2004 are shown in Table 1. Surgical donors were mostly in the older age group as donors tend to be patients undergoing joint replacement procedures. Approximately 95% of living donors were 50 years of age or older (median age 65 years [inter-quartile range (IQR): 59–73 years)] and 49.14% were female. The prevalence rate (per 100 000 persons) amongst surgical donors was 64.00 (95% CI, 25.75–131.48) for anti-HIV, 342.34 (95% CI, 241.04–471.21) for HBsAg, 570.48 (95% CI, 437.61–730.92) for anti-HCV, and 111.82 (95% CI, 58.09–195.26) for anti-HTLV.

The prevalence rates of confirmed positive results for viral infection among deceased donors, stratified accord-

Table 1. Prevalence of viral markers among living musculoskeletal donors, according to age and gender (1993–2004).

	Male donors (prevalence per 100 000 persons)		Female donors (prevalence per 100 000 persons)		All donors (prevalence per 100 000 persons)	
	Number tested	Confirmed positive	Number tested	Confirmed positive	Number tested	Confirmed positive
Anti-HIV						
<30	35	0 (0.00)	31	0 (0.00)	66	0 (0.00)
30–49	305	0 (0.00)	218	0 (0.00)	523	0 (0.00)
≥50	5223	4 (76.58)	5125	3 (58.54)	10 348	7 (67.65)
Total	5563	4 (71.90)	5374	3 (55.82)	10 937	7 (64.00)
HBsAg						
<30	29	0 (0.00)	31	0 (0.00)	60	0 (0.00)
30–49	297	3 (1010.10)	211	0 (0.00)	508	3 (590.55)
≥50	5166	16 (309.72)	5074	18 (354.75)	10 240	34 (332.03)
Total	5492	19 (345.96)	5316	18 (338.60)	10 808	37 (342.34)
Anti-HCV						
<30	30	0 (0.00)	31	0 (0.00)	61	0 (0.00)
30–49	298	3 (1006.71)	214	3 (1401.87)	512	6 (1171.88)
≥50	5203	31 (595.81)	5092	25 (490.97)	10 295	56 (543.95)
Total	5531	34 (614.72)	5337	28 (524.64)	10 868	62 (570.48)
Anti-HTLV						
<30	31	0 (0.00)	33	0 (0.00)	64	0 (0.00)
30–49	301	0 (0.00)	210	0 (0.00)	511	0 (0.00)
≥50	5128	6 (117.01)	5029	6 (119.31)	10 157	12 (118.15)
Total	5460	6 (109.89)	5272	6 (113.81)	10 732	12 (111.82)

Table 2. Prevalence of viral markers among nonliving musculoskeletal donors, according to age and gender (1993–2004).

	Male donors (prevalence per 100 000 persons)		Female donors (prevalence per 100 000 persons)		All donors (prevalence per 100 000 persons)	
	Number tested	Confirmed positive	Number tested	Confirmed positive	Number tested	Confirmed positive
Anti-HIV						
<30	261	0 (0.00)	56	0 (0.00)	317	0 (0.00)
30–49	449	1 (222.72)	111	0 (0.00)	560	1 (178.57)
≥50	483	0 (0.00)	118	0 (0.00)	601	0 (0.00)
Total	1193	1 (83.82)	285	0 (0.00)	1478	1 (67.66)
HBsAg						
<30	261	3 (1149.43)	55	0 (0.00)	316	3 (949.37)
30–49	449	8 (1781.74)	109	0 (0.00)	558	8 (1433.69)
≥50	483	2 (414.08)	116	0 (0.00)	599	2 (333.89)
Total	1193	13 (1089.69)	280	0 (0.00)	1473	13 (882.55)
Anti-HCV						
<30	261	0 (0.00)	55	1 (1818.18)	316	1 (316.46)
30–49	449	0 (0.00)	111	1 (900.90)	560	1 (178.57)
≥50	483	2 (414.08)	118	0 (0.00)	601	2 (332.78)
Total	1193	2 (167.64)	284	2 (704.23)	1477	4 (270.82)
Anti-HTLV						
<30	154	0 (0.00)	36	0 (0.00)	190	0 (0.00)
30–49	228	1 (438.60)	75	0 (0.00)	303	1 (330.03)
≥50	244	1 (409.84)	18	0 (0.00)	262	1 (381.68)
Total	626	2 (319.49)	129	0 (0.00)	755	2 (264.90)

ing to age and gender, are shown in Table 2. In contrast to surgical donors, 21.45% of nonliving donors were less than 30 years of age, 37.89% 30–49 years of age, and 40.66% 50 years of age or older [median age 46 years (IQR: 39–53 years)]. In addition, only 19.28% of deceased donors were female. Excluding anti-HCV, the prevalence

Table 3. Estimated incidence and probability of undetected viral infections among living and nonliving musculoskeletal tissue donors in Australia.

		Estimated incidence rate* per 100 000 person-years	Estimated probability† (antibody) per 100 000 donors (95% CI)	Estimated probability (NAT)
Living donors	Anti-HIV	12.88	0.78 (0.21–1.34)	0.32 (0.28–0.36)
	HBsAg	3.53	0.42 (0.36–0.48)	0.21
	Anti-HCV	10.71	1.94 (1.12–2.76)	0.22 (0.18–0.26)
	Anti-HTLV	5.49	0.77 (0.54–1.08)	–
Nonliving donors	Anti-HIV	13.61	0.82 (0.22–1.42)	0.34 (0.29–0.38)
	HBsAg	9.61	1.15 (0.98–1.31)	0.57
	Anti-HCV	5.08	0.92 (0.53–1.31)	0.10 (0.08–0.12)
	Anti-HTLV	13.02	1.82 (1.28–2.57)	–

*Estimated incidence in tissue donors (per 100 000 person years) = {(prevalence in tissue donors)/(prevalence in first-time blood donors)} × incidence in first-time blood donors [3,19].

Tissue donor prevalence rates were retrieved from databases of the Perth Bone and Tissue Bank, Queensland Bone Bank, and Donor Tissue Bank of Victoria. First-time blood donor prevalence rates were retrieved from databases of the corresponding Australian Red Cross Blood Services (ARCBS) sites.

Incidence in first-time blood donors (per 100 000 person-years) = (number of seroconverters × 100 000 × 2.03)/(number of repeat donors × 0.42) [4,5].

First-time blood donor incidence rates were derived by multiplying the repeat donor incidence rates by a correction factor of 2.03, and the number of person-years of observation which is equivalent to 0.42, as calculated by the standard incidence method in a published study of Australian blood donors [4,5].

Further, the incidence of HBV was multiplied by the ARCBS adjustment factor of 1.88 to compensate for the potential underestimation of HBV incidence because of the transient nature of hepatitis B surface antigen.

†Estimated probability of viremia = (window period/365 days) × incidence rate; 95% CIs were calculated from the 95% CIs of the window periods (WP).

Antibody WP: 22 (95% CI, 6–38) for anti-HIV [13], 43.6 (95% CI, 37.4–49.7) for HBsAg [14], 66 (95% CI, 38–94) for anti-HCV [7,15], 51 (95% CI, 36–72) for anti-HTLV [16].

NAT WP: 9 (95% CI, 7.8–10.2) for anti-HIV [11], 21.8 for HBsAg [14], 7.4 (95% CI, 6.1–8.7) for anti-HCV [11].

of viral infection was higher for deceased donors than surgical donors. The rate of confirmed positive results (prevalence rate per 100 000 persons) for nonliving donors was 67.66 (95% CI, 1.85–376.06) for anti-HIV, 882.55 (95% CI, 471.01–1504.53) for HBsAg, 270.82 (95% CI, 73.79–691.96) for anti-HCV, and 264.90 (95% CI, 32.34–953.91) for anti-HTLV. However these differences only reached statistical significance for HBV infection (882.55 vs. 342.34, $\chi 2 = 9.29$, $P = 0.002$).

Estimated incidence and estimated risk of infectivity among living and nonliving donors

Table 3 compares the estimated incidence rates and the predicted NAT yield for HIV, HBV, HCV, and HTLV between living and nonliving donors. We determined the incidence rates among tissue donors by extrapolating from the rates among first-time blood donors. The incidence of HBV was adjusted by a correction factor to compensate for potential underestimation because of the transient nature of HBsAg [4,5]. We estimated the incidence rates among surgical donors were 12.88 per 100 000 person-years for HIV, 3.53 per 100 000 person-years for HBV, 10.71 per 100 000 person-years for HCV, and 5.49 per 100 000 person-years for HTLV. Besides anti-HCV, the estimates derived for nonliving donors were higher than those derived for living donors, though none of these differences reached statistical significance. The incidence rates for nonliving donors were estimated to be 13.61, 9.61, 5.08, and 13.02 per 100 000 person-years respectively.

The estimated probability that a living donor was viraemic at the time of donation was 1 in 128 000 for HIV, 1 in 238 000 for HBV, 1 in 52 000 for HCV, and 1 in 130 000 for HTLV. With the addition of NAT, this would be reduced to 1 in 312 000 for HIV, 1 in 476 000 for HBV, and 1 in 455 000 for HCV. Similarly, if individual NAT testing were to be used for nonliving tissue donors, the probability of donor viraemia would be reduced to 1 in 294 000 for HIV, 1 in 174 000 for HBV, and 1 in 1 000 000 for HCV.

Discussion

Given its increasing popularity, it is important for medical professionals and the general population to be aware of the risks of transfusion-transmitted diseases associated with musculoskeletal tissue transplantation and the limits of the screening tests used. By way of testimony to the relative safety of the existing Australian system, not a

single case of viral infection on account of musculoskeletal tissue transplantation is known to have occurred in Australia since 1993. This finding is consistent with the residual risk estimates derived here, given the number of donors screened to date (12 415) and the highest estimate (HCV in living donors) of 1 in 52 000 would not as yet predict the occurrence of a breakthrough infection.

With the exception of HCV, prevalence rates of viral infection were higher among deceased donors than surgical donors. Estimated incidence rates were also higher among nonliving donors, with the difference between the incidence rates for HBV and HTLV close to reaching statistical significance (3.53 vs. 9.61 for HBsAg, $\chi 2 = 3.27$, $P = 0.071$; and 5.49 vs. 13.02 for anti-HTLV, $\chi 2 = 3.56$, $P = 0.059$). The underlying causes of these differences could be related to the changes in the risks of these pathogens in the general population, changes in factors that occur around the time of donation, and by the risk factors that are present in early life (age-period-cohort effect). For example young adults in the 1960s and 1970s may have experimented with intravenous drugs and become infected with HCV, and these people would have entered into the 50 years and older age-group during the late 1990s and early 2000. Similar findings were observed in a recent study by Zou *et al.* [17], which showed significant downward trend in the prevalence of all major blood-borne infections among first-time blood donors in the United States with the exception of anti-HCV amongst male 50–59 years of age.

In the context of the recipient risk, it is important to note that the risk estimates we derive for living donor allografts are conservative because they do not consider the risk reduction contributed by the requirement to re-test the donor 6 months after donation. Although it is difficult to accurately determine the quantitative impact of this intervention perhaps it is best considered in the context of the estimated WP for each virus. The upper 95% CI for the duration of the WP is 38 days for anti-HIV, 94 days for anti-HCV, 49.7 days for HBsAg and 72 days for anti-HTLV [7,13–16]. Assuming the worst case scenario where infection occurred on the day of retrieval and the donor was re-tested 180 days postsurgery, then the probability that the donor's infection remains undetectable on both occasions is reduced by more than 95% for all viral markers, as the upper 95% CI for the WP is <180 days.

Despite the low residual risk of viral infection, it is imperative that new interventions with the potential to further reduce the risk are carefully considered as they become available. NAT for HIV and HCV RNA is an example, which has already been widely implemented for screening blood donors as well as for tissue allografts in the United States, where the majority are sourced from nonliving donors [19]. NAT reduces the WP (and consequently the residual risk) by 55% for HIV (WP reduced from 22 to 9 days) and approaching 90% for HCV (WP reduced from 66 to 7.4 days) [11,14]. More recently some countries have also implemented NAT for HBV DNA, which when performed on single blood donations can reduce the WP by approximately 50%. For living donors where retesting already eliminates the majority of the WP infections, NAT may only be clinically significant to prevent HCV transmission from a seronegative HCV RNA-positive donor. A recent French study of NAT in tissue donors showed that serosilent infection may have contributed to 0.2% of confirmed positive HCV infections [18]. In the context of nonliving donors, NAT is certainly a more attractive option given its ability to markedly reduce the WP and consequently the residual risk.

Another benefit in favour of the use of NAT instead of the 180-day retesting for living donors would be the opportunity of increasing the supply of tissue available on account of the inclusion of some donations which would have been deferred from the failure of surgical patients to return for serological retesting. Currently the rate of patients who fail to return for retesting and have completed all other medical exclusion criteria is 10–12% approximately [12]. In a setting where surgical bone is the most significant component of the tissue banking program, and the annual demand appears to be growing faster than the Australian supply, this last reserve may be considered as a viable potential tissue source.

Evidence from countries which have implemented NAT has shown it to be cost-ineffective. However, NAT for HIV and HCV is now mandatory for both tissue and blood products in most developed nations. The results from this study show that the risk of viral infection among living and nonliving musculoskeletal tissue donors in Australia is low, though the differential risk profile between the two donor groups is problematic. One potential solution to address the imbalance is consideration of NAT using appropriately validated assays for nonliving donors which would reduce the residual risk to levels comparable to that in living donors (where the 95% reduction for quarantining pending the 180-day re-test is included).

Authorship

FY: designed and performed study, wrote paper. CS: performed study, contributed to study data and writing of paper. AF: contributed to design of study. DM: contributed to design of study and data. DW: designed study. M-HZ: designed study, contributed to study data and writing of paper.

Funding sources

This research was supported by a grant from the Sir Charles Gairdner Hospital Research Foundation awarded to Professor Ming-Hao Zheng and Dr Felix Yao.

Acknowledgements

We would like to acknowledge Kellie Hamilton, Lyn Ireland, and Vicky Winship from the Donor Tissue Bank of Victoria, Morris Benkovich and Ron Simard from the Queensland Bone Bank, and Joyleen Winter and Anne Cowie from the Perth Bone and Tissue Bank. We also thank Dr Yi Qian for statistical assistance in data analysis and interpretation. This research was supported by a grant from the Sir Charles Gairdner Hospital Research Foundation awarded to Professor Ming-Hao Zheng and Dr Felix Yao.

References

1. Galea G, Dow BC. Comparison of prevalence rates of microbiological markers between bone/tissue donations and new blood donors in Scotland. *Vox Sang* 2006; **91**: 28.
2. Australian Therapeutic Goods Administration. *Code of Good Manufacturing Practice – Human Blood and Tissues*. Wooden ACT, Australia: Australian Therapeutic Goods Administration, 2000.
3. Yao F, Seed C, Farrugia A, *et al*. The risk of HIV, HBV, HCV, and HTLV infection among musculoskeletal tissue donors in Australia. *Am J Transplant* 2007; **7**: 2723.
4. 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.
5. Seed CR, Cheng A, Ismay SL, *et al*. Assessing the accuracy of three viral risk models in predicting the outcome of implementing HIV and HCV NAT donor screening in Australia and the implications for future HBV NAT. *Transfusion* 2002; **42**: 1365.
6. Glynn SA, Kleinman SH, Wright DJ, Busch MP. International application of the incidence rate/window period model. *Transfusion* 2002; **42**: 966.
7. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. *N Engl J Med* 1996; **334**: 1685.
8. Kleinman S, Busch MP, Koreltiz JJ, Schreiber GB. The incidence/window period model and its use to assess the risk of transfusion-transmitted human immunodeficiency virus and hepatitis C virus infection. *Transfus Med Rev* 1997; **11**: 155.
9. Coste J, Reesink HW, Engelfriet CP, *et al*. Implementation of donor screening for infectious agents transmitted by blood by nucleic acid technology: update to 2003. *Vox Sang* 2005; **88**: 289.
10. Jackson BR, Busch MP, Stramer SL, AuBuchon JP. The cost-effectiveness of NAT for HIV, HCV, and HBV in whole-blood donations. *Transfusion* 2003; **46**: 721.
11. Busch MP, Glynn SA, Stramer SL, *et al*. A new strategy for estimating risks of transfusion-transmitted viral infections based on rates of detection of recently infected donors. *Transfusion* 2005; **45**: 254.
12. Transplantation Society of Australia and New Zealand. *Bank Activities* (2002–2004) Available at: http://www.atbf.org.au (last accessed on June 2007).
13. Busch MP, Lee LL, Satten GA, *et al*. Time course of detection of viral and serologic markers preceding human immunodeficiency virus type 1 seroconversion: implications for screening of blood and tissue donors. *Transfusion* 1995; **35**: 91.
14. Kleinman SH, Busch MP. Assessing the impact of HBV NAT on window period reduction and residual risk. *J Clin Virol* 2006; **36**: S23.
15. Pillonel J, Saura C, Courouce AM. Prevalence of HIV, HTLV and hepatitis B and C viruses in blood donors in France 1992–1996. *Transfus Clin Biol* 1998; **5**: 305.
16. Manns A, Wilks RJ, Murphy EL, *et al*. A prospective study of transmission by transfusion of HTLV-1 and risk factors associated with seroconversion. *Int J Cancer* 1992; **51**: 886.
17. Zou S, Notari IVEP, Stramer SL, Wahab F, Musavi F, Dodd RY. Patterns of age- and sex-specific prevalence of major blood-borne infections in the United States blood donors, 1995 to 2002: American Red Cross blood donor study. *Transfusion* 2004; **44**: 1640.
18. Challine D, Pellegrin B, Bouvier-Alias M, Rigot P, Laperche L, Pawlotsky JM. HIV and hepatitis C virus RNA in seronegative organ and tissue donors. *Lancet* 2004; **364**: 1611.
19. Zou S, Dodd RY, Stramer SL, Strong DM. Probability of viremia with HBV, HCV, HIV, and HTLV among tissue donors in the United States. *N Engl J Med* 2004; **351**: 751.