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Nucleic Acid Testing (NAT) of Organ Donors: Is the 'Best' Test the Right Test? A Consensus Conference Report

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**The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of UNOS, AATB or AOPO.*

Nucleic acid testing (NAT) for HIV, HBV and HCV shortens the time between infection and detection by available testing. A group of experts was selected to develop recommendations for the use of NAT in the HIV/HBV/HCV screening of potential organ donors. The rapid turnaround times needed for donor testing and the risk of death while awaiting transplantation make organ donor screening different from screening blood-or tissue donors. In donors with no identified risk factors, there is insufficient evidence to recommend routine NAT, as the benefits of NAT may not outweigh the disadvantages of NAT especially when false-positive results can lead to loss of donor organs. For donors with identified behavioral risk factors, NAT should be considered to reduce the risk of transmission and increase organ utilization. Informed consent balancing the risks of donor-derived infection against the risk of remaining on the waiting list should be obtained at the time of candidate listing and again at the time of organ offer. In conclusion, there is insufficient evidence to recommend universal prospective screening of organ donors for HIV, HCV and HBV using current NAT platforms. Further study of viral screening modalities may reduce disease transmission risk without excessive donor loss.

Key words: Donor screening, hepatitis B virus (HBV), hepatitis C virus, HIV, Nucleic acid diagnostics, organ and tissue donation, transplantation

Abbreviations: HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus.

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Introduction and Background

Recent highly publicized transplant-associated infection transmission events have prompted debate and controversy about optimal organ donor screening. In 2007, HIV

Table 1: Estimates of window period length for different testing methods*

Pathogen	Standard serology	Enhanced serology (fourth generation or combined antibody-antigen tests)	Nucleic acid testing
HIV	17–22 days (5–8)	~7–16 days (9,10)	5–6 days (5,6)
HCV	~70 days (5,8,11)	~40–50 days (12–14)	3–5 days (5,11)
HBV	35–44 days (15,16)	Not applicable	20–22 days (8,15)

*Window period = time to detection of infection by a specific testing method. HIV, HCV and HBV NAT data are listed for the most sensitive NAT currently used in blood-donor screening (Gen Probe TMA for HIV and HCV, and Roche Cobas MPX for HBV on individual donation); the window period will be longer if less sensitive NAT is used for donor screening. HIV- and HCV-antibody and HBV surface antigen data are for tests licensed and currently used in blood-donor screening (enzyme immunoassays or chemiluminescent assays). Window period estimates for fourth generation assays are derived from more limited data and show substantial variation with different manufacturer's test kits.

and HCV were transmitted to four organ recipients from a donor with behavioral risks for recently acquired infection (1,2). Serologic testing was negative (on a posttransfusion sample) but subsequent nucleic acid amplification testing (NAT) revealed detectable viremia. This may have been a true window period infection or false-negative serology due to hemodilution. (3) Regardless, opinions on the use of NAT in screening organ donors and appropriate informed consent for potential recipients have circulated in the medical literature and the lay media (2,4). NAT for HIV-1 and HCV is performed for blood-donor screening in the United States and Canada. In tissue donation, NAT is required screening in the United States and recommended in Canada. NAT for HBV is being considered in blood- and tissue-donor settings. No recommendations exist for the use of NAT in screening organ donors.

The 'window period' for a pathogen is the time between infection and detection by a specific testing method. NAT shortens the window period for HIV, HCV and HBV relative to serology and therefore may decrease the risk of transmitting disease from a serologically negative donor (see Table 1) (5–16). Although routine NAT of potential organ donors may seem logical, it has not been rigorously studied. NAT is costly and may be logistically challenging. Most importantly, false-positive results may lead to unnecessary loss of uninfected organs. On the other hand, NAT in donors with identified behavioral risk factors may actually increase organ utilization (17).

Consensus Development Process

A consensus conference was held to develop practical recommendations for using NAT in the screening of potential organ donors for HIV, HCV and HBV. Conference participants included authorities from the United States and Canada in organ and tissue donation and transplantation, transplant infectious diseases, blood banking, laboratory medicine and epidemiology. Prior to the conference four working groups were formed to address technical issues in testing for HIV, HCV and HBV; modeling and risk benefit analysis of NAT; candidate informed consent issues and logistical issues with NAT. Each group summarized existing data, performed modeling based on published evidence, and distributed a report to all participants. At the conference, the working group findings were discussed in detail. Participants developed recommendations. Each of these recommendations was then discussed in detail. Votes were taken and a two-thirds majority was required for approval. If this majority was not obtained then the recommendation was discussed and refined further and voted on again until the two-thirds majority was obtained for each recommendation. Where possible, a level of evidence was provided for recommendations (see Supporting Material Appendix S1) (18).

Current NAT Practices

A 2008 survey of the 58 U.S. organ procurement organizations (OPOs) documented that 47% performed NAT on all potential donors (19). Another 28% performed NAT on a subset of donors, usually based on the identification of behaviors thought to increase the risk of infection. OPOs tested for different pathogens using different assays, platforms and confirmatory algorithms with varied turn-around times and testing volumes. Some OPOs noted geographic challenges in NAT accessibility, which makes prospective testing untenable. At the time of the survey some OPOs specifically stated that if prospective NAT were a policy requirement, they would be unable to comply. Tissue donors routinely undergo NAT for HIV-1 and HCV. For organ donors who are also tissue donors, NAT may be performed by or for tissue banks although the time constraints upon such testing are very different from organ donors. In such settings, NAT results may only be available after organs have already been transplanted.

The cost of NAT is variable among OPOs depending on testing volumes, transportation costs and the time of day (or night) NAT is performed. From the OPO survey, the median cost per NAT was US$ 460 (range US$ 60–1200). In addition the median costs for transportation of sample to a laboratory that could perform NAT was US$ 270 (range US$ 25–1000). The turnaround time for NAT also appears to be highly variable. Of 41 OPOs who perform prospective NAT in some or all donors, 18 reported always being able to obtain NAT results within 12 h of drawing the blood sample. Six reported never being able to obtain the results

within 12 h and two reported obtaining results only after 24 h.

Organ Donation versus Blood- and Tissue-Donation

Screening procedures that include NAT for HIV-1 and HCV have reduced the risk of transmitting these viruses after blood- or tissue-donation. In the United States, the estimated residual risk of HIV transmission with blood transfusion is 1 in 1.6 to 2.3 million units (5). Because of the public perception of 'zero-tolerance' for infection transmission with blood transfusion and tissue transplantation, current blood- and tissue-donation screening errs on the side of excluding high-risk donors. Organ donation differs because loss of donated organs increases the morbidity and mortality associated with remaining on the transplant waitlist (20). There is a recognized and accepted risk of disease transmission for certain pathogens (e.g. cytomegalovirus) as well as the considerable risks associated with the transplant procedure itself. Time is critical in organ donation, since delays in organ recovery and prolongation of cold-ischemic time affects organ utilization and posttransplant function (21,22).

The following principles were agreed upon:

- The risk: benefit analysis of NAT in organ transplantation differs from that in blood- and tissue-donation (20,23). Current practices in blood- and tissue-donation cannot be extrapolated to the screening of organ donors (level III).
- Testing recommendations for potential organ donors must reflect the urgency, geography and other logistical issues inherent to organ donation.

Behavioral Risk Assessment of Donors

To assess the potential for recently acquired (window period) infection with HIV, HCV or HBV, behavioral risk factors are assessed by history and physical examination of the donor. For deceased donors, historical information obtained from the next of kin may be limited or inaccurate. The 1994 CDC behavioral criteria for 'high-risk' donors for HIV transmission or a local modification are commonly utilized by U.S. and Canadian OPOs to estimate the risk of HIV, HCV and HBV transmission. The criteria for defining the high-risk donor are shown in Table 2 (24). These guidelines have not been updated to reflect current understanding of infection transmission and may not be accurate for risk factor assessment or appropriate for exclusion of donors. In an independent analysis of the UNOS database of 29 950 organ donors from 2004 to 2008 from which at least one organ was transplanted, HCV seroprevalence was 18.3% in donors meeting the CDC's definition of 'high-risk' and 2.8% in low-risk donors (25). HBV core antibody was positive in 14.6% versus. 4.9%, respectively; HBV surface antigen (HBsAg) was positive in 0.3% and 0.2%. The HIV seroprevalence was 0% in both groups because the only data from donors, where at least one organ was used was collected (25).

Table 2: CDC criteria for increased-risk donors*

CDC criteria for increased-risk donors
• Men who have had sex with another man in the preceding 5 years.
• Nonmedical intravenous, intramuscular or subcutaneous injection of drugs in the preceding 5 years.
• Hemophilia or related clotting disorders that have received human-derived clotting factor concentrates.
• Persons who have had sex in the preceding 12 months with any of the above persons or a person known or suspected to have HIV infection.
• Persons who have been exposed in the preceding 12 months to known or suspected HIV-infected blood through percutaneous inoculation or through contact with an open wound, nonintact skin or mucous membranes.
• Inmates of correctional systems.
• Children born to mothers with HIV infection or mothers who meet the behavioral or laboratory exclusionary criteria for adult donors, unless HIV infection can be definitely excluded.
• Persons who cannot be tested for HIV infection because of hemodilution (may cause false-negative tests).
• Persons whose history, physical exam, medical records or autopsy reports reveal other evidence of HIV infection or high-risk behavior, such as a diagnosis of AIDS, unexplained weight loss, night sweats, blue or purple spots on the skin or mucous membranes typical of Kaposi's sarcoma, unexplained lymphadenopathy lasting >1 month, unexplained temperature >100.5 F (38.6 C) for >10 days, unexplained persistent cough and shortness of breath, opportunistic infections, unexplained persistent diarrhea, male-to-male sexual contact, sexually transmitted diseases or needle tracks or other signs of parenteral drug abuse.

*Adapted from Morbid Mortal Wkly Rept/MMWR; 43(RR-8):1994, 1–17

The following recommendations were agreed upon:

- Although current definitions of high-risk behavior have utility (level II-2), additional studies are needed to validate the use of this tool for risk stratification in potential organ donors.
- There was strong consensus that donor behavioral risks associated with a higher risk of HIV infection should be updated to emphasize risk factors for newly acquired (incident) infection. Definitions should be expanded beyond HIV to include HCV and HBV as well as consideration of behaviors (e.g. drug snorting), which are not currently part of the CDC definitions (level II-2) (26). The process of updating these guidelines is currently being undertaken by the CDC.
- A uniform donor infection risk assessment questionnaire should be developed and implemented. This would help provide more homogeneity in donor risk assessment and better facilitate future research in the utility of donor risk assessment.

Table 3: Estimated impact of false-positive HIV NAT results in average risk donors on quality adjusted life years (QALYS) lost or gained*

NAT false-positive rate	False positives per year (n = 7000 average-risk donors)*	False-positive donors per infected donor detected by NAT			Net QALYs loss or gain per one year of organ transplant activity*		
		HIV	HCV	HBV	HIV	HCV	HBV
High: 1/500	14.0	151.2	89.1	136.0	–180	–178	–179
Low: 1/1000	7.0	75.6	44.6	68.0	–89	–87	–88
Ideal: 1/5000	1.4	15.1	8.9	13.6	–16	–15	–16

*Table numbers shown are based on 7000 average-risk deceased donors per year in the United States. The calculations are done separately for HIV, HCV and HBV. False-positive (FP) donors per year is the FP rate multiplied by the number of donors each year. Residual risks for a donor with negative serologic testing for HIV (1/55 000), HCV (1/42 000) and HBV (1/34 000) were calculated assuming NAT testing reduced the window period of infection (22–6 days for HIV; 70–4 days for HCV and 40–20 days for HBV). The annual number of infected donors per year detected by NAT but missed by serology is then 0.09526 for HIV, 0.14667 for HCV and 0.10294 for HBV. The FP donors per infected donor detected by NAT but missed by serology is the FP number (column 2) divided by the annual number of infected donors per year detected by NAT. The potential QALYs gained by NAT testing are calculated by assuming all recipients would have die immediately from infection if transplanted (worse case scenario 22 lost QALYS per infected donor). Potential QALYs lost by NAT testing are calculated by the FP donors each year (assumed to be discarded) multiplied by 13 QALYS per donor (49). The net QALYs are the difference between QALYs gained minus QALYs lost.

There was consensus that the term 'high-risk' donor may be misleading, as organ transplantation is associated with much more common, recognized infection risks and significantly greater risks of allograft failure, waiting list mortality and surgical and posttransplant mortality (that are likely greater than the risk of unintentional HIV, HCV or HBV transmission). The terms 'average risk' (for donors with no identified risk factors for infection with HIV, HCV or HBV) and 'increased risk' (in donors with identified risk factors for these infections) are preferred.

Table 4: Advantages and disadvantages of nucleic acid testing (NAT)

Advantages
- Reduction in inadvertent transmission of HIV, HCV and HBV due to improved detection of window period infections.
- Increased organ utilization from increased-risk donors. Use of NAT for average-risk donors does not appear to improve organ utilization.
- Enhanced public perception of the safety of organ transplantation.

Disadvantages
- Loss of donors and organs due to false-positive NAT results. This is especially true in average-risk donors, in whom the predictive value of a positive screen is low. The loss of organs and subsequent wait-list mortality outweighs the benefit of reduced disease transmission with NAT for average-risk donors.
- There are logistical issues with prospective NAT due to the need for urgent testing, after-hours testing, single sample testing and/or testing at facilities that may be geographically distant from the donor and recipient transplant centers. These issues may increase the turnaround time for laboratory testing.
- Increased turnaround time may lead to organ loss as a result of withdrawal of consent for donation or from donor instability and cardiac death. For organs that have been procured, delays in testing may increase cold-ischemic time, adversely affecting utilization and outcomes (21,22).
- With current testing platforms and a requirement for STAT testing, the cost of NAT is significant and greater for the organ-donor population than the cost of batched testing in the blood- or tissue-donor populations.

NAT Risk: Benefit Analysis

Improvements in the assessment of disease transmission using NAT must be weighed against the risk of discarding organs from donors with false-positive results (see Tables 3 and 4). Although reliable data on infection rates in potential organ donors are lacking, incidence rates are likely higher than those reported in potential blood donors due to the demographics of the donor population and an inability to obtain a medical and behavioral risk assessment history from the deceased donor (5,27). The yield of NAT in average-risk donors can be estimated from tissue donor modeling and the limited data available on NAT for potential organ donors. This is valid because many organ donors are also tissue donors, specifically in the subset of organ donors where no behavioral risk factors are identified. The yield in increased-risk donors can be estimated from published data on incident infections in specific behavioral risk groups. Tissue donors are excluded if any behavioral risk factors are identified (28,29). In a study of 11 391 deceased tissue donors from five U.S. tissue banks, the estimated NAT yield was 1 in 55 000 for HIV, 1 in 42,000 for HCV and 1 in 34 000 for HBV (27).

There may be other settings where NAT may have clinical utility. For example in donors who are hepatitis B core antibody positive, NAT for HBV may help guide posttransplant management of recipients (30). NAT in patients who are HCV-antibody positive has been proposed as a method of stratifying risk of transmission but further study is needed. (31)

Estimating NAT Yield in Increased-Risk Donors

Data on NAT screening of increased-risk organ donors are not available. Using published incidence data on various behavioral risks, incidence window-period (I-WP) modeling was used to calculate the likelihood of a missed window period HIV, HCV or HBV infection utilizing standard serology alone versus serology plus NAT (see Figure 1) (32–46). The I-WP model predicts that NAT reduces the residual risk of infection to a greater extent in increased-risk donors than for average-risk donors and when added to a screening test with a relatively long versus a short window period (e.g. HCV vs. HIV serology). Figure 1 shows the estimated residual risk with serology versus NAT for specific incidence groups based on incidence data from several studies. For example, in intravenous drug users (IVDUs) the residual risk of HIV with serology ranges from 0.48 to 2.11 window period infections per 1000 persons. This is decrease to 0.15–0.67 using NAT. Similarly for HCV, the residual risk for IVDUs is 14.2–65.2 window period infections per 1000 persons with serology and decreases to 1.4–6.5 with NAT.

There is considerable center-to-center variation in the utilization of increased-risk donors, a factor that is difficult to quantify in models. Evidence suggests that performing NAT in these donors improves organ utilization due to the perception by transplant physicians and surgeons of reduced risk of disease transmission (17,25). In a surveys of U.S. transplant centers an association between NAT performance and higher provider utilization of increased-risk donors was observed (17). Both HIV- and HCV-NAT performance were associated with significantly higher odds of being high-utilizers (HIV odds ratio 1.58, HCV 2.69, $p < 0.005$) (17). Therefore, NAT utilization in increased-risk donors may expand the donor pool in addition to reducing the risk of viral transmission.

False-Positive NAT and Risk: Benefit Analysis

The false-positive rate of NAT assays in potential organ donors is unknown. Estimates from tissue- and blood-donor NAT screening studies are that 0.1–0.85% of tests may be initially-reactive false positives (47–49). Supplemental testing is available for some assays to validate positive results thereby substantially lowering false-positive rates (49). An example of such an algorithm for the Procleix HIV/HCV assay is as follows: if an initial combined NAT is positive (e.g. combined HCV- and HIV-NAT). Then two separate discriminatory NAT assays are performed, one for HIV and one for HCV. If the discriminatory assays are negative, then the initial assay is repeated. If this is negative, the final result can be reported as negative. However, turnaround times required for deceased organ donation may preclude performance of these types of confirmatory tests in many labs (49). Occasionally, despite duplicate and triplicate testing, it may be difficult to distinguish a false-positive result from viral loads near the detection threshold, since stochastic sampling may result in discordant results with repeated testing (50). In organ donor screening, several factors in addition to the specificity of the assay will affect the false-positive rate. These include testing volume, training, competency and experience of the laboratory personnel performing the assay. Time constraints limit batch testing and testing performed after usual hours may lead to significant logistic and performance challenges.

A risk: benefit modeling analysis of false-positive NAT rates for HIV, HCV and HBV, using assumptions based on published literature, was performed for average-risk donors. Each donor was assumed to provide an average of 2.6 organs, resulting in a gain of 13 quality-adjusted life years for recipients (51). As a very conservative estimate, viral transmission was assumed to result in 100% immediate mortality. A risk: benefit analysis for HIV-, HCV- and HBV-NAT in average-risk donors is shown in Table 3. Even assuming low-false positive rates (e.g. 0.1%), NAT implementation for average risk donors is expected to result in a net loss of organs and a reduction in quality-adjusted life years for recipients. The modeling suggests that in average-risk donors, a true NAT positive window period (seronegative infection) would be picked up once every 10.8 years for HIV, once every 9.7 years for HBV and once every 6.36 years for HCV.

NAT Recommendations for Deceased Organ Donors

Based on a risk: benefit analysis and current published data, the following are recommended:

- There is insufficient evidence to recommend routine NAT for HIV, HCV and HBV as the standard of care for screening all potential organ donors (level III).
- NAT testing of donors with no identified behavioral risk factors (average-risk donors) is not likely to identify true-positive infections with sufficient frequency to offset the false-positive rate of the currently available tests. The benefits of NAT in this setting may not outweigh the potential disadvantages of NAT (see Tables 3 and 4). Therefore NAT testing of average-risk donors is not routinely necessary at this time (level II-2).
- For increased-risk donors, NAT should be considered to reduce the risk of disease transmission and potentially increase organ utilization (level II-2).
- For increased-risk donors, the highest yield NAT is for HCV infection, due to the substantial reduction in window period relative to serology (level II-1) and significant differences in the prevalence of HCV for increased- versus average-risk donors (level II-2).

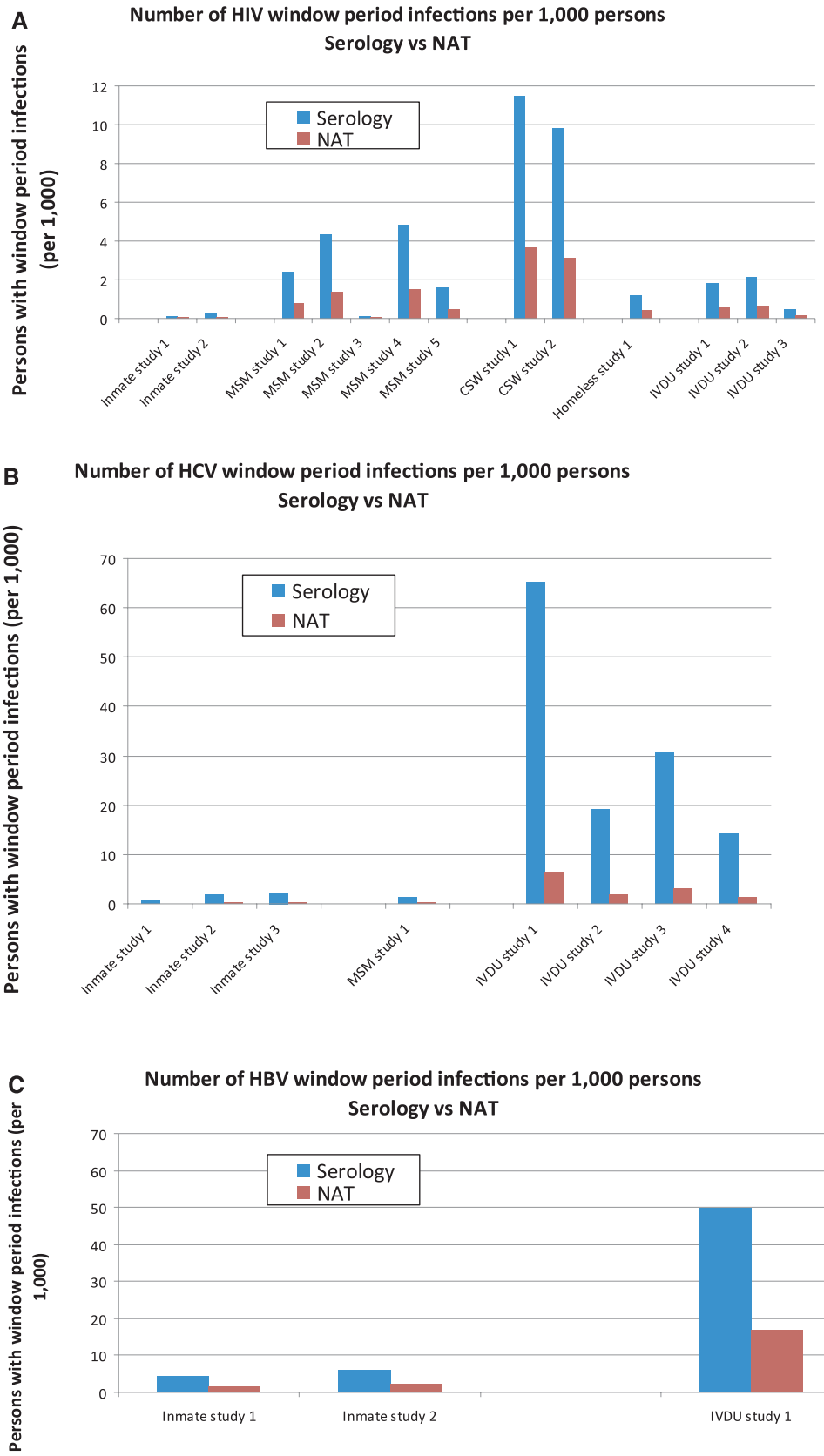

Figure 1: (A) Estimated NAT yield for HIV in various risk categories based on incidence data from selected studies. (B) Estimated NAT yield for HCV in various risk categories based on incidence data from selected studies. (C) Estimated NAT yield for HBV in various risk categories based on incidence data from selected studies *MSM = men who have sex with men; Inmate = prison inmates; IVDU = intravenous drug users; CSW = commercial sex-trade workers. Bars for each graph show the number of window period infections per 1000 persons using either serology (blue) or NAT (red) calculated from the HIV, HCV or HBV infection incidence in a type of donor population as published in literature references 32–46 and the HIV, HCV and HBV screening test window periods shown in Table 1. Modeling estimates assume high-risk behavior is carried out right to the time of consideration for organ donation.

- For increased-risk donors, NAT for HIV and HBV will also reduce the risk of inadvertent transmission due to window period reduction, but the yield of NAT testing is lower than for HCV due to shorter discordant periods between serologic and nucleic acid testing positivity (level II-2).
- Because neither serology nor NAT eliminate the risk of inadvertent transmission, appropriate informed consent should be obtained from candidates (level II-3).
- For donors where information about behavioral risk factors is inadequate, NAT may be performed as for increased-risk donors.

NAT Recommendations for Living Donors

Behavioral risk information obtained from potential living donors is generally more accurate than that for deceased donors, and there are opportunities for intervention and retesting prior to proceeding with transplantation. The following are recommended for living donors:

- For average-risk living donors, routine NAT for HIV, HCV and HBV is not mandatory (level III).
- For increased-risk living donors, consideration should be given for delaying the transplant to allow for repeat serological testing after the window period of infection. NAT may be considered near the time of organ donation (level III).
- When delay of transplantation from an increased-risk living donor is not possible, NAT should be considered (level III).

Testing Recommendations for Recipients

The following are recommended for organ transplant recipients:

- All transplant recipients receiving organs from increased-risk donors should be tested for HIV, HCV and HBV at periodic intervals posttransplant (e.g., 1 month, 3 months, 6 months and 1 year after transplant) (level III). This is recommended regardless of whether prospective NAT was performed for the donor. Posttransplant screening for HIV and HCV should include NAT since seroconversion may be delayed or absent in the setting of immunosuppression (1). Posttransplant screening for HBV should include HBsAg and anti-HBc testing. The additional benefit of NAT for HBV in this setting is not clear.
- For recipients of average-risk donor organs, further study is needed to determine whether additional testing posttransplant is warranted.
- Results of posttransplant testing should be collected and centrally reported.

Recommendations for Laboratories Performing NAT

Because many of the current impediments to NAT are technical and logistic issues, the following are recommended:

- Standards should be established for testing laboratories. This may include considerations regarding minimum testing volumes required for competency maintenance, participation in proficiency testing and minimum staff training requirements.
- When possible, dedicated samples should be collected for NAT assays. Samples obtained prior to transfusion are preferred for all testing. Standardized approaches to specimen labeling and transport should be developed, implemented and audited to optimize NAT yield.
- Laboratories should develop and implement standardized algorithms for real-time discrimination of initially reactive NAT results.

It is recognized that in many settings, real-time discrimination of true- positive NAT versus false-positive NAT results will not be possible. Often, only a single positive result may be available or, if the test is repeated, discordant results can occur. Transplant programs should be informed about these organs to determine whether or not there are appropriate candidates who have agreed to accept such organs. If a positive NAT is discovered after the organs have been transplanted appropriate notification of the transplant programs and identification of recipients is mandatory. The donor sample should undergo further discriminatory testing to determine the likelihood of a false-positive result or confirm a true positive NAT. All recipients should be notified and monitored for possible disease transmission. Depending on the NAT result, testing in the recipient may include serology and NAT for HCV and HIV and Hepatitis B surface antigen testing. In some instances prophylactic or preemptive therapy may be considered in recipients in consultation with an infectious diseases and/or viral hepatitis expert.

Organ Candidate Informed Consent

Current UNOS policy requires informing organ candidates of identified-donor risk factors that may increase the risk of HIV transmission (52). The following additional recommendations were made:

- Information on the potential for donor-derived infection should be conveyed to every transplant candidate in general terms at the time of listing and more specifically when a potential donor (average risk or increased risk) is identified (see Table 5).
- Evidence suggests that formal policies detailing informed consent for increased-risk organs result in higher donor utilization (53).

Table 5: Recommendations for candidate informed consent (all level III)

Informed consent at the time of listing
• Discuss that all transplantation carries risks, including donor-transmitted infection. Not performing the transplant often carries a higher risk of death than risk attributable to donor-transmitted infection.
• Discuss the risks of transmission from donor to recipient of pathogens such as HIV, HCV and HBV, as well as other pathogens (e.g., bacteria, viruses).
• Discuss the limitations of testing (e.g., there are not screening tests for every transmissible pathogen) and the risks of both false-positive and false-negative test results.
• Transmission of infections should be placed in the broader context of risk, including risks associated with the use of organs from donors after cardiac death and extended-criteria donors, and the risk of transmission of undiagnosed malignancy.
• Stress that it is impossible to know everything about an individual donor, and risk assessment histories reflect only the knowledge of the person providing the history.
• Infection risks should be explained in terms that relate to everyday occurrences so as to make their magnitude more understandable to the potential recipient.
Informed consent at the time of an organ offer
A second discussion should occur at the time of the organ offer, as follows:
• Sufficient information should be provided regarding specific donor history and testing to enable the potential recipient to understand the risk.
• Every effort should be made to protect donor identity.
• The specific donor behavior(s) identified as posing a risk of disease transmission should be disclosed. For example, 'the donor has a history of intravenous drug use, and there may be a higher risk of transmitting an infection'.
• The specific type of testing that has been performed should be explained.
• Emphasize that the transplant team has assessed the risk of the donor in the context of the risk of not performing the transplant.

- Although documentation of this process is essential, institutional requirements vary as to the format of documentation in the medical record. There should be uniform guidelines available to all transplant programs outlining consent standards.

Limitations

There are several limitations to the analysis and recommendations provided here. First and perhaps most importantly, it is difficult to accurately quantify the rate of true positives and false positive with NAT in both average- and increased-risk organ donors. This is due to lack of prospective data comparing third generation serologic assays with NAT in organ donor populations. Second, the performance of NAT assays may vary widely not just based on intrinsic properties of the assays but due to their application in the 'real-world' where variability in expertise and difficulties in performing assays in the middle of the night are real considerations. Finally, many of the recommendations presented here are based on opinion and best data available to the consensus group. It was generally agreed that new technologies should not be widely adopted without specific studies that analyze the utility and cost-effectiveness in the organ donor population.

Future studies

Further studies are critical to assess the utility and feasibility of NAT in organ donors. These should include studies in large groups of donors, both increased risk and average risk, where NAT assays are evaluated and compared to third generation serology assays to determine the true NAT yield in this setting (i.e. how many seronegative/NAT positive donors are identified). Confirmatory testing algorithms and appropriate follow-up of any recipients are needed in such studies to clarify the true incidence of false-positive and/or false-negative results. These studies should ideally also include a careful cost-analysis to help determine the overall cost-effectiveness of NAT implementation. Additional data that should be accrued include the value of the behavioral risk assessment tool and how it relates to serology and NAT results. In addition to NAT, other assays should be properly evaluated in organ donor populations. These include fourth generation serologic assays for HIV and HCV (these are combined antibody/antigen assays) as well as new hepatitis B surface antigen assays. These assays have the potential to further reduce the window period compared to standard serology (see Table 1) and may be more adaptable to implementation for organ donor testing. Finally, data from NAT studies in one country or geographic region may not be applicable to other countries or regions, particularly where the prevalence of infection and behavioral risks are widely different than in North America, and therefore would require further evaluation.

Other recommendations are as follows:

- Currently there is no reporting requirement for unutilized donors. Serology and NAT results for potential donors (including the numbers screened, initially reactive, repeatedly reactive and confirmed positive) should be reported and linked with anonymous behavioral risk assessment data.
- Current donor-licensed assays are designed for high volume, high throughput screening (e.g. 96–5000 tests per kit) and are not optimal for single-sample organ donor testing. Incentives should be developed to encourage assay manufacturers to develop and license NAT assays, which are specifically validated and formatted for use in organ donor screening.
- The OPTN/UNOS electronic database should allow entry of NAT results for donors.

Summary

Screening of organ donors for HIV, HBV and HCV infection is critical to reduce the risk of inadvertent disease transmission. Although new diagnostic tests such as NAT offer

improved sensitivity, their routine use in organ donors may result in loss of transplantable organs due to false-positive results. Best practice should be guided by weighing the benefits and risks of NAT in the overall context of donor testing, organ utilization, and prevention of wait-list morbidity and mortality. Interventions to reduce the risk of HIV, HCV and HBV transmission should be examined and prioritized within the broader context of the infectious and noninfectious risks of solid organ transplantation.

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Supporting Information

The following supporting information is available for this article online:

Appendix S1: Quality of evidence on which recommendations are based

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