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Reducing Infection Transmission in Solid Organ Transplantation Through Donor Nucleic Acid Testing: A Cost-Effectiveness Analysis

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For solid organ transplant (SOT) donors, nucleic acid-amplification testing (NAT) may reduce human immunodeficiency virus (HIV) and hepatitis C virus (HCV) transmission over antibody (Ab) testing given its shorter detection window period. We compared SOT donor NAT + Ab versus Ab alone using decision models to estimate incremental cost-effectiveness ratios (ICERs; cost per quality-adjusted life year [QALY] gained) from the societal perspective across a range of HIV/HCV prevalence values and NAT costs. The cost per QALY gained was calculated for two scenarios: (1) favorable: low cost ($150/donor)/high prevalence (HIV: 1.5%; HCV: 18.2%) and (2) unfavorable: high cost ($500/donor)/low prevalence (HIV: 0.1%; HCV: 1.5%). In the favorable scenario, adding NAT screening cost $161 013 per QALY gained for HIV was less costly) for HCV, and cost $86 653 per QALY gained for HIV/HCV combined. For the unfavorable scenario, the costs were $15 568 484, $221 006 and $10 077 599 per QALY gained, respectively. Universal HCV NAT + Ab for donors appears cost-effective to reduce infection transmission from SOT donors, while HIV NAT + Ab is not, except where HIV NAT is ≤$150/donor and prevalence is ≥1.5%. Our analyses provide important data to facilitate the decision to implement HIV and HCV NAT for deceased SOT donors and shape national policy regarding how to reduce infection transmission in SOT.

Key words: Cost-effectiveness analysis, graft, organ transplantation, surgery

Abbreviations: AB, antibody; CDC, Centers for Disease Control and Prevention; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; NAT, nucleic acid-amplification testing; OPO, organ procurement organization; OPTN, Organ Procurement and Transplantation Network; QALY, quality-adjusted life year; SOT, solid organ transplantation.

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Introduction

Donor-derived infection transmission in solid organ transplantation (SOT) remains a critical patient safety and public health concern. Between 2005 and 2007, the Organ Procurement Transplantation Network (OPTN) Patient Safety System received nine reports of donor-derived hepatitis C virus (HCV) infections from five donors and seven reports of donor-derived human immunodeficiency virus (HIV) infections from three donors (1). Eight of these donor-derived infections resulted in confirmed infections in the SOT recipients; two resulted in death (1).

Guidelines for infection screening of organ donors—established in 1994—recommend *serologic* testing for HIV and HCV (2). But an alternative method of HIV and HCV screening exists—nucleic-acid amplification testing (NAT)—which significantly shortens the window period during which infection cannot be detected through serologies alone (3–6). Given this advantage, NAT has already been incorporated routinely into screening of blood donors. Recently, the Centers for Disease Control and Prevention (CDC) issued guidelines proposing the incorporation of HIV and HCV NAT into screening algorithms for deceased SOT donors; specifically, the guidelines recommended HCV NAT for all deceased donors and HIV NAT for those at increased risk for HIV infection transmission (7). However, HIV and HCV NAT take longer to run and are more expensive than serologic testing, particularly when performed on the urgent, single-sample basis necessary for expeditious organ placement. Furthermore, the prevalence of HIV and HCV in the United States varies widely by organ procurement organization (OPO), potentially reducing the benefit of SOT donor NAT in low-prevalence areas (8).

Therefore, to facilitate the decision to implement SOT donor NAT by individual OPOs, we aimed in this study to determine specific thresholds of HIV and HCV prevalence and NAT costs using cost-effectiveness analysis.

Methods

The model

Two models were created (1) for HIV and (2) for HCV. The basic model is shown in Figure 1. Potential donors were tested by either antibody (Ab) alone or Ab + NAT. Donors who tested positive by Ab (regardless of NAT result) or by NAT alone were assumed to have a 0% probability of infection transmission (i.e. the donor organs were discarded). Organs of donors with true infection that tested falsely negative by Ab or NAT and were subsequently utilized were assumed to have a higher risk of transmission of active infection compared with transmission in nontransplant settings given the presence of high-dosed immunosuppression posttransplant. The final model outcome was the incremental cost-effectiveness ratio (ICER). This was calculated from the following equation:

$$\text{ICER} = \frac{[\text{Costs of Ab test} - \text{Costs of Ab test and NAT}]}{[\text{Effect of Ab test} - \text{Effect of Ab test and NAT}]}$$

where

- The costs of each strategy included the costs of testing and the lifetime costs of HIV or HCV therapy to newly infected recipients.
- The effect on health status of each strategy was measured in terms of added quality-adjusted life years (QALY) due to infections averted.

Scenarios

In this model, we considered scenarios over a range of HIV and HCV prevalence values and costs of NAT per donor. The favorable scenario assumes a high prevalence of infection in organs (and thus a great chance of averted infection transmission) and low implementation cost. The unfavorable scenario assumes a low prevalence of infection and high implementation costs. The range of values of HIV and HCV prevalence was based on a survey of 17 representative US OPOs conducted by Ellingson et al. (9). Given the very high ICER associated with even the highest prevalence of HIV infection reported (1%) and the very low ICER associated with even the lowest prevalence of HCV infection (3.5%) reported in this paper, we included an additional upper bound of 1.5% for HIV and a lower bound of 1.5% for HCV to assess the ICER for a wide range of these critical assumptions. As NAT for organ donation requires processing on an urgent, single-sample basis at specialized transplant laboratories that is much costlier than standard NAT used for clinical purposes, we obtained a range of NAT costs based on personal communication with three US laboratories that provide NAT services to OPOs. All costs were reported in US$ and adjusted to 2012 US$ using the Consumer Price Index factors available from the US Bureau of Labor Statistics (stats.bls.gov/cpi/). Scenarios that yielded cost *savings* per QALY gained were considered ''dominant.''

Model inputs

Model inputs were obtained from a comprehensive search of the published literature. The assumptions used in the model are shown in Table 1. In order to obtain the QALYs gained from each infection averted, we first estimated baseline patient survival for primary liver or kidney transplant (as these are

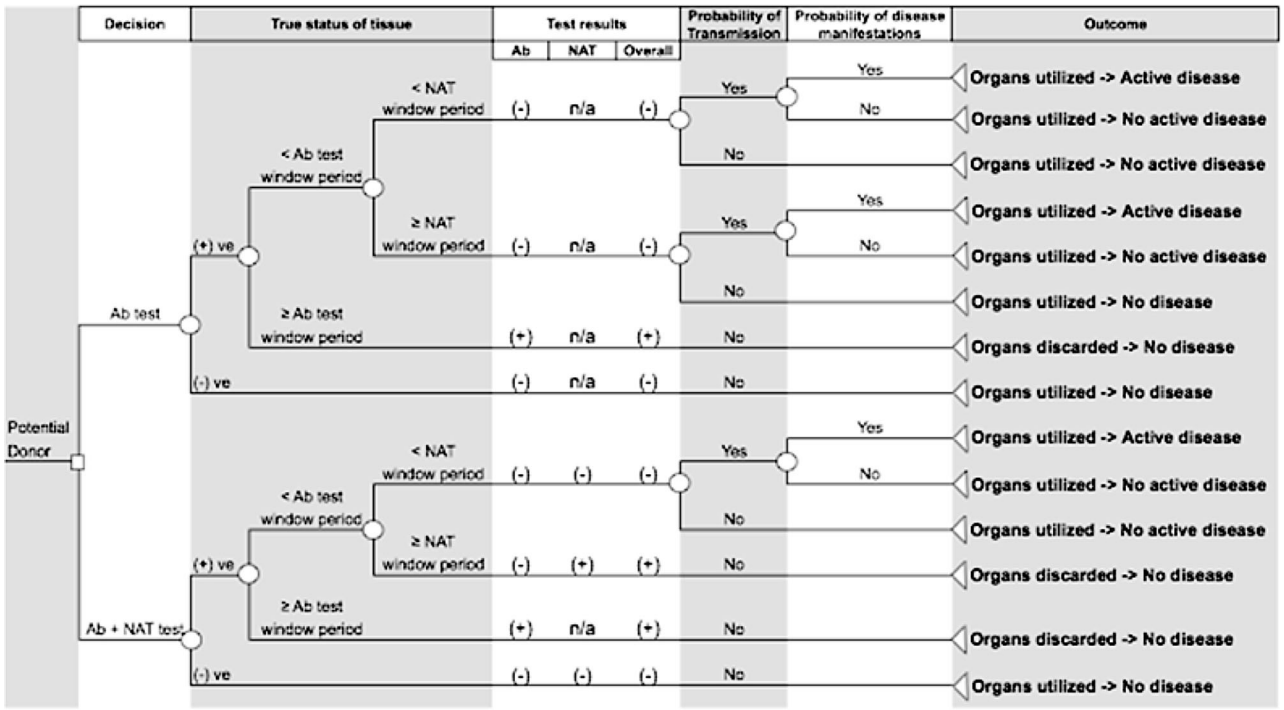

Figure 1: Schematic of the decision-analysis model for Ab testing alone versus Ab + NAT of potential solid organ donors. Ab, antibody; NAT, nucleic acid testing.

Table 1: Assumptions used in the model

	Inputs	Value	Refs.
HIV and HCV	Number of transplants per donor	3.6 (range 1.9–5.3)	Malinoski et al. (19)
	Utility for 1 posttransplant year	0.08 (range 0.72–0.89)	Kontodimopoulos et al. (10) and Åberg et al. (11)
HIV	Window period during which Ab cannot be detected	3 weeks	Humar et al. (29)
	Window period during which NAT cannot be detected	1 week	Humar et al. (29)
	Probability of infection during NAT window-period	33%	Humar et al. (29)
	NAT specificity	99.95% (range 99.90–99.97%)	Food and Drug Administration (30–32)
	Risk of transmission (approximated from risk from a blood transfusion from an infected donor)	95% (range 90–99%)	Donegan et al. (33) and Berglund et al. (34)
	Probability of symptomatic disease posttransplant	0.90 (0.85–0.95)	Landin et al. (35) and Norman et al. (36)
	Utility of 1 year	0.74 (range 0.07–0.93)	Tengs and Lin (37)
	QALYs gained per infection averted	2.15 (range 1.0–5.0)	Kauf et al. (15)
	Lifetime cost of infection	$319 910 (range $240 904–$398 916)	Owusu-Edusei et al. (38)
HCV	Window period during which Ab cannot be detected	10 weeks	Humar et al. (29)
	Window period during which NAT cannot be detected	1 week	Humar et al. (29)
	Probability of infection during NAT window period	10%	Humar et al. (29)
	NAT specificity	99.95% (range 99.90–99.97%)	Food and Drug Administration (31,39)
	Risk of transmission (assumed to be higher than in nontransplant population)	95% (range 90–99%)	CDC (40)
	Probability of symptomatic disease posttransplant	0.95 (range 0.90–0.99)	Everhart et al. (41) and Neumann et al. (42)
	Utility of 1 year	0.725 (range 0.6–0.8)	Chong et al. (17)
	QALYs gained per infection averted	2.34 (range 1.0–5.0)	Chong et al. (17) and Sherman et al. (18)
	Lifetime cost of infection	$ 65 884 (range $47 762–$74 727)	Razavi et al. (43)

Ab, antibody; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NAT, nucleic acid-amplification testing; QALYs, quality-adjusted life years.

the two most common types of transplant) at 12.5 years (based on OPTN data as of July 20, 2012) and multiplied this by 0.8, the utility of a posttransplant year (10,11). For HIV infection, we accounted for a 7–30% decrease in patient survival (mean 18.5% $\times$ 12.5 years = 2.3 years) depending upon whether the patient was mono- or co-infected with HCV (12–14). We then multiplied posttransplant utility by 0.74, a low estimate of the utility with HIV infection in the era of highly active anti-retroviral therapy (15), starting at Year 6 and extending through the end of life. This approach accentuates the benefit of avoiding HIV. This resulted in a difference of QALYs between an HIV-infected and a non-HIV-infected transplant recipient of 2.15. For HCV, we accounted for a 10–25% decrease in patient survival (mean 17.5% $\times$ 12.5 years = 2.2 years) for recipients infected with chronic HCV compared with non-HCV recipients (14,16). We multiplied posttransplant utility by 0.725 (17,18) starting at Year 5 through the end of life. This resulted in a difference of QALYs between an HCV-infected and a non-HCV-infected transplant recipient of 2.34. For both analyses, we discounted all future QALYs by 3% per year, the standard rate.

Sensitivity analyses

The following sensitivity analyses were performed varying the (1) number of organs utilized per donor, (2) lifetime costs of infection, (3) QALYs gained per infection averted, (4) utility for 1 posttransplant year, (5) utility for infection infection, (6) risk of infection transmission and (7) probability of symptomatic disease given infection transmission using the ranges reported in Table 1. We also performed a separate analysis in which we incorporated the lost value of transplantation due to a false-positive NAT—first, for the base case NAT specificity of 99.95%, then varying the NAT specificity over a clinically relevant range.

Results

Table 2 shows the ICERs over a range of NAT costs and HIV or HCV prevalence values. For HIV, the ICER ranged from $161 013 for the favorable scenario (low cost and high prevalence) to $15 568 484 for the unfavorable scenario (high cost and low prevalence). For HCV, the ICER ranged from dominant (i.e. more effective and less costly) for the favorable scenario to $221 006 for the unfavorable scenario. The ICER for combined HIV/HCV NAT for each donor ranged from $86 653 for the favorable scenario to $10 077 599 for the unfavorable scenario. Scenario

Table 2: Incremental cost-effectiveness ratios (ICERs) over a range of HIV/HCV NAT costs and population prevalence values

Cost of NAT, $ (for each test)	HIV		HCV		HIV/HCV combined
	Prevalence (%)	ICER[1] ($)	Prevalence (%)	ICER[1] ($)	ICER[2] ($)
150	1.5[3]	161 013	18.2[3]	Dominant	86 653
	1.0	318 344	12.9	Dominant	188 727
	0.5	790 336	5.6	Dominant	497 589
	0.21	2 093 933	3.5	3290	1 337 023
	0.10	4 566 272	1.5	46 631	2 943 124
300	1.5	470 989	18.2	Dominant	287 814
	1.0	785 650	12.9	Dominant	491 963
	0.5	1 729 634	5.6	10 301	1 109 687
	0.21	4 336 828	3.5	34 680	2 788 553
	0.10	9 281 506	1.5	121 363	6 000 756
500	1.5	884 289	18.2	Dominant	556 029
	1.0	1 408 725	12.9	Dominant	896 277
	0.5	2 982 031	5.6	35 901	1 925 817
	0.21	7 327 354	3.5	76 534	4 723 927
	0.10[3]	15 568 484	1.5[3]	221 006	10 077 599

''Dominant'' = resulted in improved outcomes at reduced costs. HCV, hepatitis C virus; HIV, human immunodeficiency virus; NAT, nucleic acid-amplification testing.
[1]The ICER is the ratio of the (difference in costs)/(difference in quality-adjusted life years) with the implementation of NAT plus antibody testing versus antibody testing alone of solid organ transplant donors.
[2]The range of ICERs for the combined HIV/HCV NAT is reported for testing at 2× the cost quoted in Column 1 (i.e. $300, $600 and $1000).
[3]The ''favorable'' scenario is low costs and high prevalence. The ''unfavorable'' scenario is high costs and low prevalence. All other scenarios are intermediate.

definitions are presented in the Methods section above and in Table 2.

We then performed multiple sensitivity analyses, shown in Figure 2, based on the ranges of inputs reported in Table 1. For individual NAT for HIV and HCV, we also performed a sensitivity analysis that incorporated the value of transplantation due to a false-positive NAT—first, using the base case NAT specificity and then varying it across a range of NAT specificity values. We assumed that the value to society of one donor is $1 086 000 (19) based on a willingness-to-pay analysis that determined that the typical donor generates 13 QALYs (valued at $100 000 each = $1.3 million) at an added medical cost of $214 000 ($1.3 million − $214 000 = $1 086 000) (20). We did not perform this sensitivity analysis for the scenario of a false-positive combined HIV and HCV NAT, as we considered this to be a highly improbable event.

Discussion

We utilized cost-effectiveness analysis to estimate the costs per QALY gained of universal HIV and HCV NAT compared with HIV and HCV Ab testing alone of potential organ donors across a range of HIV and HCV prevalence values and NAT costs. Assuming an ''acceptable'' cost-effectiveness ratio threshold of <$150 000 (21), we found that universal HIV NAT of all donors is *not* cost-effective. Only in the lowest cost ($150 per test)/highest prevalence (1.5%) scenario did the ICER ($161 000) approach this threshold. In contrast, given the higher prevalence of HCV and longer window period between NAT versus serologic testing for HCV compared with HIV (9,22), universal HCV NAT is cost-*effective* at nearly all HCV NAT costs and HCV prevalence values, with the exception of the highest cost ($500 per test)/lowest prevalence (1.5%) scenario, in which the ICER was $221 000. In fact, in many scenarios, HCV NAT dominated (i.e. resulted in improved outcomes and reduced costs) over HCV Ab testing alone. Given the high ICERs associated with HIV NAT relative to HIV Ab testing alone, it is not surprising that combined HIV/HCV NAT for all donors was cost-*ineffective* compared with HIV/HCV Ab testing alone except for the lowest cost ($150 per test) and the highest prevalence (1.5% for HIV, 18.2% for HCV) scenario.

We acknowledge that the implications of our analyses depend upon what society is willing to pay to reduce infection transmission from SOT. In this specific scenario, does the customary $100 000–$150 000 threshold—which was originally based on the inflation-adjusted cost of caring for a dialysis patient for 1 year (21,23)—apply? There is no doubt that there are harms to the organ transplantation community beyond immediate recipient infection that must be considered, such as unfavorable publicity toward individual transplant programs and OPOs or candidate unwillingness to accept organs from donors at increased risk for infection transmission. One might consider an analogous scenario to be NAT screening of blood donors, a practice that has been in place in the United States since 1999 (www.cdc.gov/bloodsafety/basics.html). Several studies have shown that this practice is cost-*ineffective* at conventional thresholds (i.e. $150 000)—ranging from

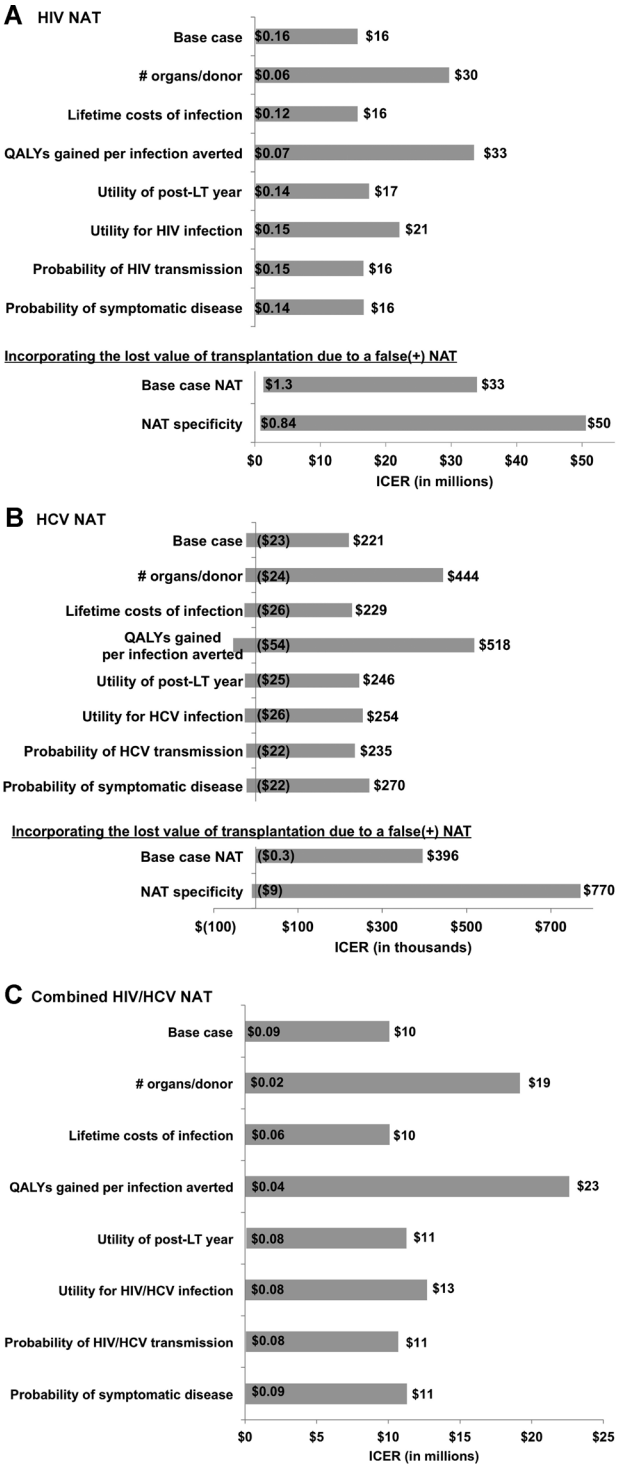

Figure 2: Results of one-way sensitivity analyses of input variables for the cost-effectiveness model for (A) HIV NAT, (B) HCV NAT and (C) combined HIV/HCV NAT. In this analysis, the base case is the range of results given that we varied two inputs for each infection: (1) NAT costs and (2) prevalence values for each infection, as detailed in Table 2. The lower bound of each bar represents the ICER for the lowest cost/highest prevalence scenario and the most favorable value for the indicated input; the upper bound represents the ICER for the highest cost/lowest prevalence scenario and the least favorable value for that input. (Note: The ICERs in (A) and (C) are reported in $millions; the ICERs in (B) are reported in $thousands.) HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; NAT, nucleic acid-amplification testing.

Table 3: CDC guidelines for behavioral and nonbehavioral donor characteristics associated with HIV or HCV infection (2)

Behavior/history criteria
1. Men who have had sex with another man in the preceding 5 years.
2. Persons who report nonmedical intravenous, intramuscular or subcutaneous injection of drugs in the preceding 5 years.
3. Persons with hemophilia or related clotting disorders who have received human-derived clotting factor concentrates.
4. Men and women who have engaged in sex in exchange for money or drugs in the preceding 5 years.
5. Persons who have had sex in the preceding 12 months with any person described in Items 1–4 above or with a person known or suspected to have HIV infection.
6. 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 membrane.
7. Inmates of correctional systems. (This exclusion is to address issues such as difficulties with informed consent and increased prevalence of HIV in this population.)
Laboratory and other medical criteria
1. Persons who cannot be tested for HIV infection because of refusal, inadequate blood samples (e.g. hemodilution that could result in false-negative tests) or any other reasons.
2. Persons with a repeatedly reactive screening assay for HIV-1 or HIV-2 antibody regardless of the results of supplemental assays.
3. Persons whose history, physical examination, medical records or autopsy reports reveal other evidence of HIV infection or increased 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 greater than 1 month, unexplained temperature greater than 100.5 F (38.6°C) for greater than 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.

CDC, Centers for Disease Control and Prevention; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

$1.5 million to $11.2 million per QALY gained (24–26)—but is well accepted as a necessary step to protect the public from unintended infection transmission. That being said, should society be expected to bear costs to reduce these harms as high as $10 million per QALY gained? $1 million? $500 000? We must, as a community, determine a reasonable threshold that balances patient safety with NAT feasibility, NAT costs and likelihood of infection transmission.

An additional controversy that our analyses raise is whether our model should be applied to decision making for testing of donors at increased risk for HIV or HCV infection (Table 3) (2). We specifically included the high prevalence values of HIV (0.5% for increased risk, 1% for missing risk) and HCV (18.2% for increased risk, 12.9% for missing risk) infection among increased risk donors in our analyses, which were obtained from a report from Ellingson et al., which estimated these prevalence values based on data available from 17 OPOs from 2004 to 2008 (9). We acknowledge that there is likely selection bias with respect to which donors are tested that might lead to a significant underestimation of the incidence of HIV and HCV infections occurring during the window period in certain increased risk populations (27,28). In addition, there is substantial variation in the risk of window-period infections by donor infection risk category (e.g. intravenous drug user, commercial sex worker, multiple sexual partners, etc.) (22,27). A more thorough analysis specific to increased risk donors is needed for decision making regarding NAT testing in this group. However, we believe that, in general, it is highly unlikely that an OPO would decide *not* to perform NAT among donors at increased risk for HIV and HCV infection. At the very least, however, our analyses should inform national policy regarding the costs of performing universal NAT for these donors, perhaps as a benchmark to determine an acceptable cost-effectiveness threshold for universal NAT among low or average risk donors.

There were scenarios that we did not account for in our analyses but are worthy of discussion. One consideration that would result in a more favorable ICER for HIV and/or HCV NAT is the scenario in which a donor tested positive by serology but negative by NAT. This would suggest either a false-positive Ab test (for either HIV or HCV) or spontaneous clearance of HCV, which might, theoretically, facilitate utilization of organs from that donor. However, given that any infection transmission in this scenario—no matter how small the risk—would be detrimental to a transplant program and perceived as a highly undesirable result to the recipient, we believe that this scenario is unlikely to result in a significant increase in organ utilization. A second scenario that we did not account for in our analyses is the cost of delay in organ utilization from lack of availability of NAT in some donation service areas at certain times of the day. Time is of the essence in organ donation; unnecessary delays can result in not only loss of precious donor organs but also wait-list mortality in candidates for whom hours make all the difference.

As with any cost-effectiveness analysis, there are limitations to our model. Data on the costs of HIV and HCV infection after transplant were lacking, so they had to be estimated using the costs reported in nontransplant populations. While this allowed us to capture the costs of HIV or HCV infection *in excess of* routine posttransplant care, we acknowledge that the course of HIV and HCV infection in the face of immunosuppression may be more aggressive and, therefore, more costly. Incorporating these costs would increase the already very high ICER associated

with HIV NAT and potentially make HCV NAT a cost-*ineffective* option. Similarly, as QALYs gained per HIV or HCV infection averted after liver transplant were not available in the published literature, we based the years of life lost from acute HIV and HCV infection after transplant on comparisons of median survival between HIV- versus non-HIV-infected recipients and HCV- versus non-HCV-infected recipients. A sensitivity analysis varying this value within clinically reasonable ranges did not change the qualitative interpretation of the analyses. In other words, HIV NAT was generally cost-ineffective even at higher QALYs gained per infection averted and HCV remained dominant (i.e. more effective and less costly) or cost-effective at lower values. Last, for the primary analysis, we assumed that all organs from donors who tested positive for HIV or HCV were discarded, when in reality, some organs from HCV-infected donors are utilized in HCV-positive recipients (and in very rare cases, in HCV-negative recipients). The recent passage of the HIV Organ Policy Equity Act, legislation that allows the transplantation of organs from HIV-positive donors to HIV-positive recipients, will also result in increased utilization of donors that tested positive by NAT (28). However, incorporation of these factors into our primary model would not have changed the ICER per QALY gained, as no previously *uninfected* recipients would receive organs from HIV- or HCV-positive donors through transplantation. Indeed, being able to use HCV-infected organs for suitable donors lessens the further downside of screening for an already dominant (i.e. more effective and less costly) or cost-effective strategy.

Despite these limitations, our analyses provide important data to the organ transplant community. As of a 2008 survey, only half of OPOs routinely use HIV and HCV NAT to test all potential organ donors, a quarter use it only for donors at increased risk for recent HIV/HCV infection and a quarter never use NAT at all (8). Our analyses can be used to facilitate the decision to implement deceased donor NAT by individual OPOs and help shape policy on a national level regarding how to reduce infection transmission through SOT. Future cost-effectiveness analyses are needed to estimate the costs of unintended infection to the transplant community as a whole—beyond that to the individual patient—to determine whether this changes the risk–benefit ratio in a cost-effectiveness analysis from the societal perspective. Although we can all agree that recipient patient safety should be our top priority, in the current environment of escalating healthcare costs and in settings where infection transmission is highly unlikely, we must take greater efforts to balance the concern for patient safety with the costs that society can—and should—bear.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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