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A model to estimate the probability of human immunodeficiency virus and hepatitis C infection despite negative nucleic acid testing among increased-risk organ donors

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Abstract

Background: In 2013, guidelines were released for reducing the risk of viral blood-borne pathogen transmission through organ transplantation. Eleven criteria were described that result in a donor being designated at increased infectious risk. Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) transmission risk from an increased-risk donor (IRD), despite negative nucleic acid testing (NAT), likely varies based on behavior type and timing.

Methods: We developed a Monte Carlo risk model to quantify probability of HIV among IRDs. The model included NAT performance, viral load dynamics, and per-act risk of acquiring HIV by each behavior. The model also quantifies the probability of HCV among IRDs by non-medical intravenous drug use (IVDU).

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AUTHOR CONTRIBUTIONS

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DISCLOSURE

The authors of this article have no conflicts of interest to disclose.

Results: Highest risk is among donors with history of unprotected, receptive anal male-to-male intercourse with partner of unknown HIV status (MSM), followed by sex with an HIV-infected partner, IVDU, and sex with a commercial sex worker.

Conclusion: With NAT screening, the estimated risk of undetected HIV remains small even at 1 day following a risk behavior. The estimated risk for HCV transmission through IVDU is likewise small and decreases quicker with time owing to the faster viral growth dynamics of HCV compared with HIV. These findings may allow for improved organ allocation, utilization, and recipient informed consent.

Keywords

hepatitis C virus; human immunodeficiency virus; increased infectious risk; increased-risk donor; nucleic acid testing

1 | INTRODUCTION

In 1994, the U.S. Public Health Service (PHS) released guidelines for preventing human immunodeficiency virus (HIV) transmission through organ transplantation.[1] These guidelines were updated in 2013 to reflect advances in laboratory HIV screening of organ donors, changes in understanding of risk factors, and further expanded to include hepatitis B and hepatitis C virus (HCV) transmission risks. Specifically, the updated guidelines describe 11 criteria that result in a deceased organ donor being designated as 'increased risk' for viral bloodborne pathogen transmission.[1,2] Three specific criteria were revised, men having sex with another man (MSM), non-medical intravenous drug use (IVDU), and sex in exchange for money (with a commercial sex worker [CSW]), to result in an 'increased-risk' donor (IRD) designation if behaviors occurred within the previous 12 months, rather than 5 years per the 1994 guideline.[1,2] Another criterion, sex with a known HIV-infected partner (serodiscordant sex) in the previous 12 months resulted in an 'increased-risk' designation under both guidelines.[2]

Increased-risk designation results in additional requirements for organ donor screening using nucleic acid testing (NAT), specific recipient informed consent, and enhanced post-transplant surveillance for detection of viral bloodborne pathogen transmission.[2] Use of IRD organs seldom results in transmission of HIV or HCV through solid organ transplantation, although such events have been recognized.[1–9] However, patient and provider apprehension regarding the perceived risks of HIV transmission from accepting organs from IRDs may result in under-utilization of potentially lifesaving organs.[10,11] The apprehension regarding perceived risks of HCV transmission from accepting organs from an IRD because of a history of IVDU also may result in under-utilization of organs.[5,6] The IRD designation results in a dichotomous (yes or no) classification based on whether the behavior occurred within the 12 months preceding organ donation.

In actuality the risk of HIV transmission from IRDs is likely to vary based on the type and timing of the increased-risk behavior.[12] In addition, the risk of HCV transmission from an IRD with a history of IVDU is likely based on the timing of the behavior.[6] In the setting of deceased organ donation, precise timing and type of behavior may be unknown to next-of-

kin providing medical and behavioral risk information on a donor history questionnaire. The risk is further mitigated in the setting of highly sensitive and specific NAT, which has a window period of detection of 5–7 days from time of infection.[12] To improve organ utilization and better inform patients of actual risk of HIV and HCV transmission through use of IRD organs, a more quantitative assessment of risk based on type and timing of increased-risk behavior is required.

We developed a mathematical model to estimate the probability of undetected HIV infection in an IRD based on negative NAT and type of IRD behavior (including MSM, IVDU, serodiscordant sex, and sex with a CSW) from the time of increased-risk behavior relative to organ donation. The same model was used, with different parameters, to estimate the probability of undetected HCV infection in an IRD, specifically with history of IVDU, based on negative NAT and from the time of IVDU relative to organ donation. Estimates have been determined using data and modeling for per-act risk of transmission. This model may be helpful to providers and patients in making informed decisions regarding acceptance of an IRD organ. Implications for organ allocation are discussed.

2 | METHODS

To develop this mathematical model, two separate sets of methods were implemented in a sequential pattern. First, the published literature was reviewed to determine estimates related to the per-act HIV transmission rate for each increased-risk behavior entered in to the model (MSM, IVDU, sex with a CSW, and sex with a serodiscordant sex partner), performance characteristics of laboratory screening assays, and dynamics of acute HIV infection, specifically viral load (VL) growth. The revised PHS guidelines were expanded to include HCV owing to the risk of transmission because of IVDU and hemo-dialysis. Another review was completed to determine the estimated per-act HCV transmission rate of the increased risk behavior of IVDU, performance characteristics of laboratory screening assays, and dynamics of HCV infection, specifically VL growth. Per-act HCV transmission risks for hemodialysis were unavailable and were therefore not included in the analyses. Second, the estimates derived from published data were entered into a Monte Carlo statistical model to determine the probability of undetected HIV or HCV infection in an IRD based on negative NAT and type and timing of the behavior (including MSM, IVDU, serodiscordant sex, and sex with a CSW) in relation to the date of the NAT assay. The per-act IVDU risk of HCV transmission derived from the published data was also entered into a Monte Carlo statistical model to determine the probability of undetected HCV infection based on negative NAT and IVDU and timing of the IVDU behavior.

2.1 | Literature search and review methods

Review of the published literature consisted of a multistep process. While the PHS guidelines describe 11 specific increased risk criteria for HIV infection, 9 of the 11 involve four specific behaviors: MSM, IVDU, sex with a CSW, and sex with a serodiscordant partner. These four behaviors were selected for this study because each of them is associated with the highest HIV risk according to the literature.[13–20] The two additional criteria mentioned in the PHS guidelines that are relevant to HIV risk, incarceration and newly

diagnosed sexually transmitted infection, were not included in this study, because per-encounter or per-act HIV transmission risk estimates were not available in the literature. The published literature was reviewed for cohort studies from which the per-act HIV transmission risk could be quantified for the four selected behaviors and the per-act HCV transmission for IVDU could be quantified. Next, the literature was reviewed for studies that contained quantifiable estimates on the performance characteristics of HIV NAT screening assays and HCV NAT screening assay used in organ donation. Finally, studies were included quantifying the dynamics of acute HIV infection and HCV infection with specific estimates on VL growth and development of detectable HIV nucleic acid.

To conduct the literature reviews, English language papers were searched in the PubMed database with no date restrictions. Initially, searches were restricted to U.S.-based studies, but owing to a dearth of studies conducted among some subgroups, papers published using data from non-U.S. based cohorts were included. Studies that quantify the per-act HIV transmission risk for the four selected increased-risk behaviors and the per-act HCV transmission risk for IVDU were identified using the PubMed search terms: HIV, HIV infection, human immunodeficiency virus, AIDS and disease transmission, per-contact, per-act coupled with heterosexual, homosexual, coital, anal, or needle sharing. Another PubMed search was conducted using the following terms: HCV, HCV infection, per-contact, and needle sharing. To identify published papers that quantify performance characteristics of HIV/HCV NAT screening assays and the dynamics of HIV/HCV infection, the following search terms were used: HIV screening, HCV screening, NAT assay, mathematical models (searches were also done of secondary references in the important primary references). Another PubMed search was conducted using the following search terms: VL of HIV, VL of HCV, HIV NAT, and HCV NAT. Papers describing the time course of HIV VL following acute infection were reviewed.

Papers related to the four selected increased risk behaviors were reviewed and studies were selected that estimated the per-act HIV transmission risk for the respective behavior along with associated 95% confidence intervals. Articles were reviewed and selected that estimated the per-act HCV transmission risk for IVDU along with the associated 95% confidence intervals. Articles describing mathematical models that generated transmission risk estimates, especially among populations engaging in increased-risk behaviors, were also selected.

The initial HIV PubMed search to determine published studies describing per-act transmission risk of the four selected increased-risk behaviors resulted in 8264 abstracts. Of these, 16 papers were identified that described randomized trials or observational, cohort-based studies where a per-act HIV transmission risk could be quantified for MSM, IVDU, sex with a CSW, or sex with a serodiscordant partner. These 16 studies included 2 meta-analyses, which provided pooled estimates. Of these 16 studies, 5 were selected for inclusion into the model based on several factors (Table 1[5,13,15,19,21]). The studies chosen had robust design, large cohorts, and long follow-up period. Therefore, the precision of the resulting estimates from these studies was robust and could be used in the model as the most accurate available estimation of per-act transmission risk for each increased-risk behavior. For this model, MSM behavior is defined as unprotected receptive anal intercourse because

this confers the highest HIV transmission risk.[19,20] Specifically, separate estimates were modeled based on ejaculation inside the rectum (MSM1) and risk regardless of ejaculation (MSM2). In the present study, per-act risk of HIV transmission, as described in a Thailand cohort among IVDU, was used.[13,14] Serodiscordant couples are defined as a stable couple in which one partner is HIV positive.[17,18] Table 1 includes the per-act risk estimates for each increased-risk behavior used to develop the model.

The HCV PubMed search to determine the published studies describing the per-act transmission risk for IVDU behavior resulted in 2166 abstracts. Of these, nine were identified that described randomized trials or observational, cohort-based studies where a per-act HCV transmission risk could be quantified for IVDU. The per-act risk used in the model was taken from Boelen et al.[5]

The second PubMed search was conducted to understand the performance characteristics of HIV/HCV NAT screening assays in relation to the dynamics of acute HIV/HCV infection. The specific characteristics of the HIV/HCV NAT screening assays that were of interest were window period, sensitivity, specificity, and limit of detection. The viral dynamics of HIV/HCV were of interest in determining the VL from the day of infection to the day of seroconversion. After reviewing several studies of the performance of HIV/HCV NAT assays and the viral dynamics of HIV/HCV, these two cofactors for our model development were selected based on one mathematical modeling study.[22] This study was selected because it describes the risk of HIV/HCV transmission by NAT window-period blood donations.

2.2 | Statistical methods

Using estimates derived from the literature as described above, risks of undetected HIV and HCV infection among IRDs were computed using Monte Carlo and statistical methods, first for single-act risk performed at a known time point prior to donation, and presuming a negative NAT result in each case. All computations were done on a single high-performance workstation using the Mathematica 8.1 software (Wolfram Research, Champaign, IL, USA). Some peripheral computations and visualizations were performed using JMP version 10 (SAS Institute, Cary, NC, USA).

The single-act risk Monte Carlo computations were performed as follows. Initial viral inoculums for each type of risk act were assumed to have a mean proportional to the per-act risk and to be lognormally distributed with a variance independent of the mean, consistent with Wilson et al. and Pilcher et al. respectively.[23,24] This distribution is also consistent with experiments on primates, as the initial VL cannot be measured directly from experiments in humans.[25] Those viral inoculums were allowed to grow at an exponential rate with a normally distributed rate constant. The mean and standard deviation of the exponential growth rate constants for HIV and HCV are based on Weusten et al.[22] Finally, the threshold for detection by the NAT assays for HIV and HCV were also assumed to be lognormally distributed,[22] with means and variances consistent with the 95% high confidence bounds for the assay.

Time to cross the threshold of detection is given in Equation 1,

$$\theta = v_0 e^{\lambda \Delta t} \quad (1)$$

where θ is the threshold of detection of the NAT assay, v_0 is the initial viral inoculum, λ is the rate of viral growth, and Δt is the time required for viral growth in the bloodstream to exceed the threshold. The equation can be log transformed and inverted into a more convenient form to compute Δt, which is the goal of the Monte Carlo simulation (Equation 2):

$$\Delta t = \left(\mathrm{Ln}(\theta) - \mathrm{Ln}\left(v_0\right)\right)/\lambda \quad (2)$$

For each Monte Carlo run, the variables on the right side of Equation 2 are distributed as described above, and in particular distribution parameters for the initial viral inoculum, v_0, are assumed proportional to the values shown in Table 1.

The resulting simulated values for Δt were recorded for all Monte Carlo runs and fit to a Johnson Su distribution,[26] where the probability density function (pdf) for the distribution is (as a function of time from infection, t):

$$\mathrm{pdf}(t) = \frac{\delta}{\sigma\sqrt{2\pi}} \frac{1}{\sqrt{1 + (t - \xi/\sigma)^2}} e^{-0.5\left(\gamma + \delta \sinh^{-1}(t - \xi/\sigma)\right)^2} \quad (3)$$

where σ, δ, ξ, and γ are estimated parameters of the distribution.

Even for up to 10 000 Monte Carlo samples, the fit to the distribution was very good, and always exceeded the threshold to guarantee the null hypothesis was reasonable (P>.35). This flexible and powerful distribution often arises in cases of some basic transformations of combinations of normal random variables. The cumulative distribution function of the resulting Johnson Su distribution, in turn, was used to compute risk with time. Because risk is computed from a closely fit distribution, and not from the results of the Monte Carlo directly, risk probabilities well below 1 in 10 000 (or however many Monte Carlo runs are used) are justified.[27]

The fit of the Monte Carlo results to the Johnson Su distribution described above made the single-act risk probability calculations very computationally efficient. Because the per-act risk probabilities of transmitted HIV were relatively small (typically <2%, see Table 1), the risk probabilities for multiple risk acts behaved as if the probabilities for each risk act were working independently, so that the probabilities could be summed to a good approximation.

Computations of the risk for HIV exposures that occurred at uncertain times during a specified time interval were computed by numerically integrating (averaging) the risk probabilities over the interval, assuming the risk was uniformly distributed over that interval

(ie, all times were equally likely for the risks to have occurred). Combinations of each type of risk, as shown in Figures 2 and 3, were assumed to occur independently of one another.

3 | RESULTS

Results for a single risk-act of each type at known time of exposure are shown in Figure 1. Of the six curves shown in Figure 1, one applies to HCV infection (in bright red), the rest are for different types of HIV risk. These results are also presented in tabular form for certain time points in Table 2. MSM1 risk for HIV infection was computed with the highest per-act risk defined as ejaculation inside rectum; MSM2 were computed with transmission risk regardless of ejaculation. The highest probability of undetected HIV infection for an individual risk behavior was for MSM1 at 1 day after engaging in the behavior. At 5 days after engaging in the behavior, the risk for MSM1 is 2.22%, which then decreases to 0.03% by 10 days, <0.01% by 14 days, and is negligible at 28 days. At the 6-month and 12-month marks, the probability of undetected HIV infection for MSM1 is effectively 0% with NAT screening. The probability of undetected HIV infection for MSM2 behavior was similar to MSM1 in the setting of NAT screening, although it decreases somewhat more slowly, as explained below. The risk of undetected HIV infection with negative NAT screening is lowest for sex with a CSW. At 1 and 10 days following exposure, the risks are 0.06% and 0.05%, respectively, but drop relatively more slowly compared to higher risk behaviors, for reasons explained below. Similar to the other behaviors studied, the risk rapidly declines after 7–10 days, and is near zero at 28 days. The dynamics are similar for HCV IVDU risk, except are faster than HIV owing to higher viral growth rates for HCV, which are somewhat offset by the higher threshold of detection for the NAT assay.

Confidence intervals and uncertainty bounds are built into the Monte Carlo calculation, which can be seen if the results are presented slightly differently. For example, MSM1 risk carries a 2.85% risk of infection with HIV with 95% confidence, and will be detected by NAT in a mean of 5.91 days and with 95% confidence in 8.48 days. Similarly, IVDU with needle sharing carries a 1.05% risk of HCV infection at the 95% confidence bound, detected by NAT in a mean of 6.55 days and with 95% confidence in 9.07 days. The parameter values for the Johnson Su distribution change slightly between Monte Carlo runs, but these variations can be minimized to negligible with more iterations of the Monte Carlo, as we observed after running 10 000 times.

Note that while the height of each curve is determined by the per-act risk, the rate of decrease of each curve with time is largely determined by the lower number in the confidence interval of the per-act risk. The reason for this is that the lower bound of the confidence interval determines the maximum time it takes for an initial inoculum to cross the threshold of detection of the NAT assay: a lower initial inoculum could lead to a longer period of undetected infection. Therefore for MSM1 behavior, while having the highest per-act risk and initial risk at 0–4 days post exposure, within less than a week has a lower risk of infection than MSM2 behavior, because it would have been detected with NAT screening quicker than MSM2.

Figures 2 and 3 show the risk vs time for two possible risk exposures for HIV (since only one type of risk is modeled for HCV). Figure 2 shows the combined risk when the time since both risk acts is known to within 1 day; Figure 3 shows the combined risk when the timing of each risk act is only known to a given time interval in the past (shown to a maximum of 60 days). While higher than individual acts, the risk of undetected HIV infection with combined risk behaviors is low (<5%). The highest risk of undetected HIV infection with combined risk behaviors is among MSM1 and serodiscordant sex (4.35% risk) behaviors, followed by MSM1 and IVDU (3.77% risk), while the lowest risk is among IVDU and CSW (0.98% risk) at 1–5 days. By 20 days following exposure to any combination of two increased-risk behaviors, the probability of undetected HIV infection with negative NAT is negligible.

The combined risk calculations discussed here assume that the risk acts are temporally independent of one another. This assumption is conservative, as correlated risk acts would result in a higher initial VL and therefore cross the NAT threshold quicker. The absolute risks per-acts are summed (height of the risk surface), but the probabilities of the Johnson Su distribution for each type of risk are integrated over the time interval to distribute the risk uniformly over the entire time interval.

Finally, Figure 4 shows the risk of HCV infection for IVDU as a function of exposure window, when the timing of the exposure within the window is uncertain (similar to Figure 3 for HIV, but with only one type of risk modeled).

4 | DISCUSSION

We developed a mathematical model to estimate the probability of undetected HIV or HCV infection in an IRD despite negative NAT screening results. Risk varied, depending on type and timing of increased-risk behavior. The model was based on parameters previously defined related to the following: (i) the per-act transmission risk, (ii) VL dynamics of acute HIV or HCV infection, and (iii) performance characteristics of NAT assays. With a single risk behavior, the risk of HIV infection among IRDs with negative NAT is highest within 5 days of engaging in the behavior, significantly decreased at 14 days following exposure, and continues to decline until 2 months, beyond which it is negligible. The highest risk is among donors with history of MSM behavior, followed by sex with a known HIV-infected partner of the opposite gender (serodiscordant sex), IVDU, and sex with a CSW respectively. However, the risk including among MSM, even at 1 day after the behavior, is small (<3%) if the donor is screened by NAT. Even with multiple behaviors being conducted by a donor near the time of testing and organ recovery, the estimated risk of undetected HIV infection remains small (<5% for MSM and serodiscordant sex behaviors combined). Risk of infection by HCV for those with IVDU who share equipment is similarly small, with even faster viral dynamics than HIV, so that risk of undetected infection by NAT is even smaller with time. These estimates provide more information to enhance recipient informed consent and could lead to increased utilization of organs from IRDs.

According to the Organ Procurement and Transplant Network, 122 642 people are awaiting organ transplantation in the United States with only approximately 30 000 transplant

surgeries occurring annually. Despite this shortage in available organs, along with studies that have demonstrated acceptable outcomes with transplantation of IRD organs, under-utilization of these organs has been reported.[11,12,28,29] This under-utilization has been attributed to patient apprehension and provider reluctance owing to the perceived risk of viral bloodborne pathogen transmission.[11] The findings of the present study suggest that that the actual risk of HIV and HCV transmission is likely to be far lower than the perceived risk, particularly given the superior performance and low limit of detection of NAT assays used for screening organ donors, although this perception needs to be objectively measured. The decision to accept or reject an organ must be made after an individualized risk/benefit assessment by the patient and respective clinical team. However, the findings of this study can serve as a guide for informed consent discussions between potential recipients and transplant clinicians to more quantitatively convey risk estimates.

The present analysis suggests that, although the risk of HIV is low in the setting of NAT, MSM behavior conveys the highest risk for undetected acute HIV infection. This observation is consistent with previous epidemiologic findings that suggest a high HIV incidence among MSM in the United States.[20,30] Furthermore, MSM constitute the largest proportion of new HIV infections in the U.S.[31] In the U.S., the HIV prevalence among MSM has been reported to be substantially higher than among those with IVDU.[20,32] The findings of this study are consistent with observations among other populations in the U.S. in that, at 1 and 5 days after exposure, the undetected HIV risk among MSM was approximately twice the risk among donors with IVDU.

The findings of this study are subject to the following limitations. First, the per-act transmissions rates of HIV for each increased-risk behavior were derived from some cohorts, specifically for serodiscordant sex, IVDU, and sex with a CSW, that were based in non-U.S. settings. In some cases, these countries have different predominant HIV sub-types, prevalence, and incidence than the U.S. The impact on model findings are unknown, but could over-estimate the HIV transmission risk, specifically related to sex with a CSW. The per-act transmission rate for HCV was derived only from an IVDU cohort. There may be other risks for acquiring HCV; for example, hemodialysis and other healthcare-associated acquisition of infection. Specifically, per-act HCV transmission risks for hemodialysis were unavailable and therefore not included in the analyses, and this risk is assumed minor compared with that associated with IVDU.

Second, this model estimates the probability of undetected HIV and HCV infection with discrete increased-risk acts occurring either at a known time or during a known time interval. In actuality, the exact timing or even time interval of an increased-risk behavior may be unknown to the next of kin who completes the medical and behavioral risk questionnaire prior to organ procurement. Although the impact on the subsequent HIV and HCV risk estimates has not been quantified, the risk will not exceed the per-act risk at day 1 after NAT.

Third, the revised PHS guidelines recommend either HIV NAT or screening with a combined p24 antigen and HIV antibody assay for IRDs. We did not develop HIV risk estimates based on p24 antigen detection, as most organ procurement organizations in the U.S. currently use NAT for HIV screening. However, the risk could be higher in the setting

of only p24 antigen and HIV antibody assay screening, owing to the longer window-period of detection in comparison with NAT. Finally, this model did not include estimates for presumably lower risk exposures within each increased-risk category, as reliable estimates were not available in published literature. These lower risk exposures could include MSM behavior within long-term monogamous partnerships, which confers lower HIV transmission risk than the MSM estimates used for the present study.

The model quantifies a more precise estimate of the risk of undetected HIV and HCV infections among IRDs who have negative pre-donation NAT screening. The use of the model could lead to improvements in organ allocation and utilization, given that in many cases the computed risks are relatively small, compared with clinician and patient perception.

Abbreviations:

CSW	commercial sex worker
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IRD	increased-risk donor
IVDU	intravenous drug use
MSM	men having unprotected receptive anal intercourse with men
MSM1	MSM with ejaculation inside rectum
MSM2	MSM regardless of ejaculation
NAT	nucleic acid testing
PHS	U.S. Public Health Service
VL	viral load

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Guidelines for preventing transmission of human immunodeficiency virus through transplantation of human tissue and organs. MMWR Morbid Mortal Weekly Rep. 1994;43(RR-8):1–17.
2. Seem DL, Lee I, Umscheid CA, Kuehnert MJ. PHS guideline for reducing human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission through organ transplantation. Public Health Rep. 2013;128:247–343. [PubMed: 23814319]
3. CDC. Human immunodeficiency virus infection transmitted from an organ donor screened for HIV antibody–North Carolina. MMWR Morbid Mortal Weekly Rep. 1987;36:306–308.
4. CDC. HIV transmitted from a living organ donor–New York City, 2009. MMWR Morbid Mortal Weekly Rep. 2011;60:297–301.
5. Boelen L, Teutsch S, Wilson DP, et al., on behalf of the HITS investigators. Per-event probability of hepatitis C infection during sharing of injecting equipment. PLoS One. 2014;9:1–8.

6. Pouget ER, Hagan H, Des Jarlais DC. Meta-analysis of hepatitis C seroconversion in relation to shared syringes and drug preparation equipment. Addiction. 2012;107:1057–1065. [PubMed: 22168373]
7. Hahn JA, Page-Shafer K, Lum PJ, et al. Hepatitis C virus serocon-version among young injection drug users: Relationships and risks. J Infect Dis. 2002;186:1558–1564. [PubMed: 12447730]
8. Hagan H, Pouget ER, Williams IT, et al. Attribution of hepatitis C virus seroconversion risk in young injection drug users in 5 cities. J Infect Dis. 2010;201:378–385. [PubMed: 20053137]
9. Hagan H, Thiede H, Des Jarlais DC. Hepatitis C virus infection among injection drug users. Epidemiology. 2004;15:543–549. [PubMed: 15308953]
10. Ison MG, Stosor V. Transplantation of high-risk donor organs: A survey of US solid organ transplant center practices as reported by transplant infectious diseases physicians. Clin Transplant. 2009;23:866–873. [PubMed: 19473202]
11. Ros RL, Kucirka LM, Govindan P, Sarathy H, Montgomery RA, Segev DL. Patient attitudes toward CDC high infectious risk donor kidney transplantation: Inferences from focus groups. Clin Transplant. 2012;26:247–253. [PubMed: 21554396]
12. Sahulee R, Lytrivi ID, Savla JJ, Rossano JW. Centers for Disease Control “high-risk” donor status does not significantly affect recipient outcome after heart transplantation in children. J Heart Lung Transplant. 2014;33:1173–1177. [PubMed: 25037771]
13. Hudgens MG, Longini IM, Jr, Vanichseni S, et al. Subtype-specific transmission probabilities for human immunodeficiency virus type 1 among injecting drug users in Bangkok. Thailand. 2002;155:159–168.
14. Kaplan EH, Heimer R. A model-based estimate of HIV infectivity via needle sharing. J Acq Immun Defic Synd. 1992;5:1116–1118.
15. Kimani J, Kaul R, Nagelkerke NJ, et al. Reduced rates of HIV acquisition during unprotected sex by Kenyan female sex workers predating population declines in HIV prevalence. AIDS. 2008;22:131–137. [PubMed: 18090401]
16. Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: A systematic review. AIDS. 2014;28:1509–1519. [PubMed: 24809629]
17. Wawer MJ, Gray RH, Sewankambo NK, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis. 2005;191:1403–1409. [PubMed: 15809897]
18. Hughes JP, Baeten JM, Lingappa JR, et al. Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples. J Infect Dis. 2012;205:358–365. [PubMed: 22241800]
19. Jin F, Jansson J, Law M, et al. Per-contact probability of HIV transmission in homosexual men in Sydney in the era of HAART. AIDS. 2010;24:907–913. [PubMed: 20139750]
20. Xu F, Sternberg MR, Markowitz LE. Men who have sex with men in the United States: Demographic and behavioral characteristics and prevalence of HIV and HSV-2 infection: Results from National Health and Nutrition Examination Survey 2001–2006. Sex Transm Dis. 2010;37:399–405. [PubMed: 20473245]
21. Vittinghoff E, Douglas J, Judson F, McKirnan D, MacQueen K, Buchbinder SP. Per-contact risk of human immunodeficiency virus transmission between male sexual partners. Am J Epidemiol. 1999;150:306–311. [PubMed: 10430236]
22. Weusten JJ, van Drimmelen HA, Lelie PN. Mathematic modeling of the risk of HBV, HCV, and HIV transmission by window-phase donations not detected by NAT. Transfusion. 2002;42:537–548. [PubMed: 12084161]
23. Wilson DP, Law MG, Grulich AE, Cooper DA, Kaldor JM. Relation between HIV viral load and infectiousness: A model-based analysis. Lancet. 2008;372:314–320. [PubMed: 18657710]
24. Pilcher CD, Tien HC, Eron JJ, Jr, et al. Brief but efficient: Acute HIV infection and the sexual transmission of HIV. J Infect Dis. 2004;189:1785–1792. [PubMed: 15122514]
25. Parker RA, Regan MM, Reimann KA. Variability of viral load in plasma of rhesus monkeys inoculated with simian immunodeficiency virus or simian-human immunodeficiency virus: Implications for using nonhuman primate AIDS models to test vaccines and therapeutics. J Virol. 2001;75:11234–11238. [PubMed: 11602764]
26. Johnson NL. Systems of frequency curves generated by methods of translation. Biometrika. 1949;36(Pt 1–2):149–176. [PubMed: 18132090]

27. Querec TD, Gurbaxani BM, Unger ER. Randomization modeling to ascertain clustering patterns of human papillomavirus types detected in cervicovaginal samples in the United States. PLoS One. 2013;8:e82761. [PubMed: 24367553]

28. Kucirka LM, Namuyinga R, Hanrahan C, Montgomery RA, Segev DL. Provider utilization of high-risk donor organs and nucleic acid testing: Results of two national surveys. Am J Transplant. 2009;9: 1197–1204. [PubMed: 19422344]

29. Reese PP, Feldman HI, Asch DA, et al. Transplantation of kidneys from donors at increased risk for blood-borne viral infection: Recipient outcomes and patterns of organ use. Am J Transplant. 2009;9: 2338–2345. [PubMed: 19702645]

30. CDC. Prevalence and awareness of HIV infection among men who have sex with men–21 cities, United States, 2008. MMWR Morbid Mortal Weekly Rep. 2010;59:1201–1207.

31. Hall HI, An Q, Tang T, et al. Prevalence of diagnosed and undiagnosed HIV infection-United States, 2008–2012. MMWR Morbid Mortal Weekly Rep. 2015;64:657–662.

32. Lansky A, Finlayson T, Johnson C, et al. Estimating the number of persons who inject drugs in the United States by meta-analysis to calculate national rates of HIV and hepatitis C virus infections. PLoS One. 2014;9:e97596. [PubMed: 24840662]

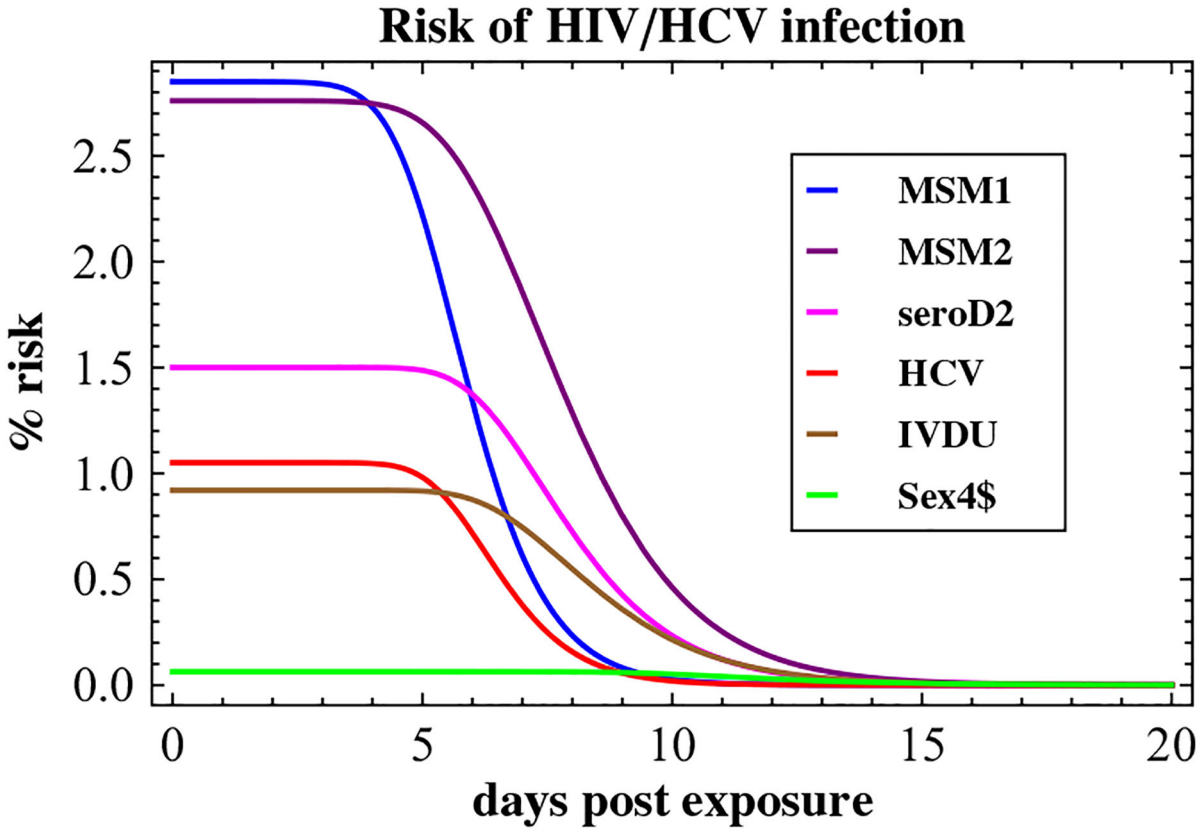

FIGURE 1.

The figure shows risk of human immunodeficiency virus (HIV) or hepatitis C virus (HCV) being present despite negative nucleic acid testing vs time for different types of risk behavior, out to 20 days. MSM1 behavior is shown in blue, MSM2 in purple, sex with a serodiscordant partner (SeroD2) in magenta, HCV infection due to intravenous drug use (IVDU) in bright red, HIV infection due to IVDU in brown, and commercial sex work (Sex4$) in bright green. The high-risk act in each case is assumed to have occurred at day 0. MSM1, men having unprotected receptive intercourse with men with ejaculation inside the rectum; MSM2, men having unprotected intercourse with men regardless of ejaculation; serodiscordant, sex with a known HIV-infected partner

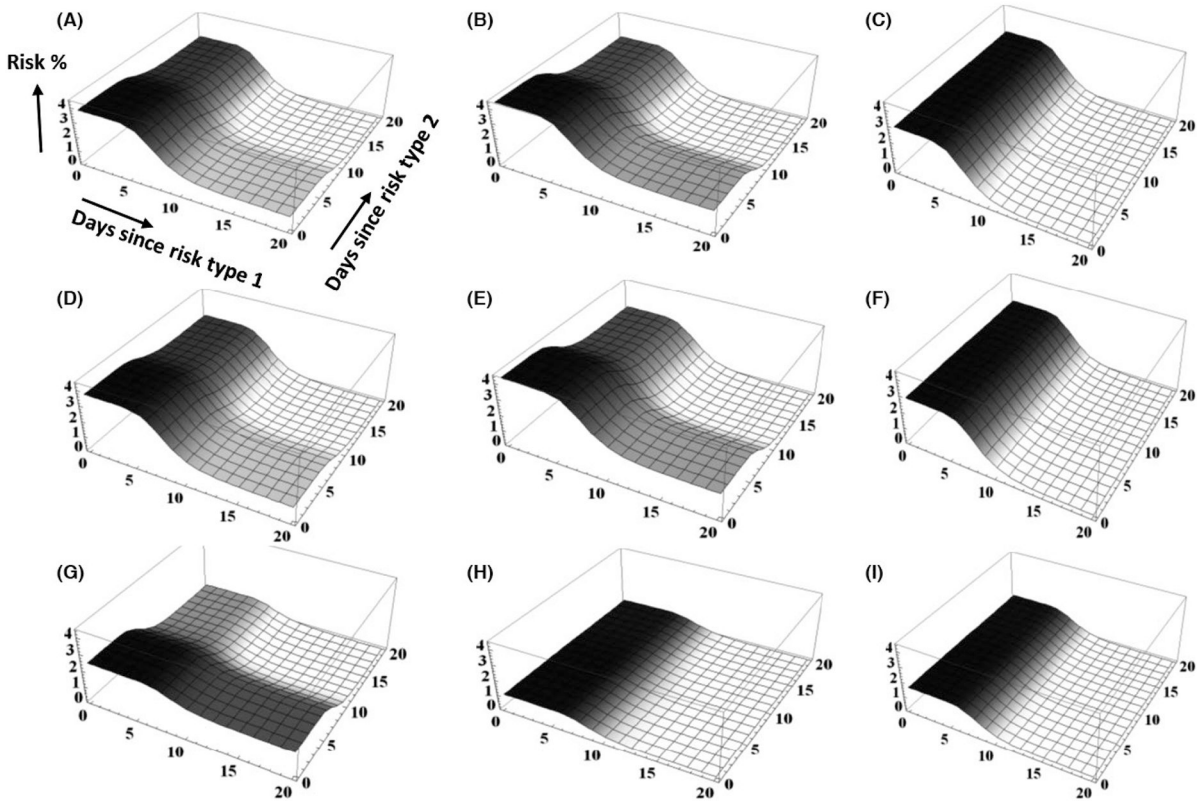

FIGURE 2.

Surface plots show risk of human immunodeficiency virus (HIV) infection given negative nucleic acid testing as a function of days after two different risk behaviors. The plot z-axis shows risk in percentage points, the *x*-axis shows days since risk behavior type 1, and the y axis shows days since risk behavior type 2, out to 20 days at which the risks for both types become negligible (see Figure 1). A, Men having unprotected receptive anal intercourse with men (MSM1) behavior (*x*-axis) and intravenous drug use (IVDU) (*y*-axis), B, MSM1 and serodiscordant sex (sex with a known HIV-infected partner), C, MSM1 and sex with commercial sex worker (CSW), D, Men having sex with men regardless of ejaculation (MSM2) behavior and IVDU, E, MSM2 and serodiscordant sex, F, MSM2 and CSW, G, IVDU and serodiscordant sex, H, IVDU and CSW, and I, serodiscordant sex and CSW

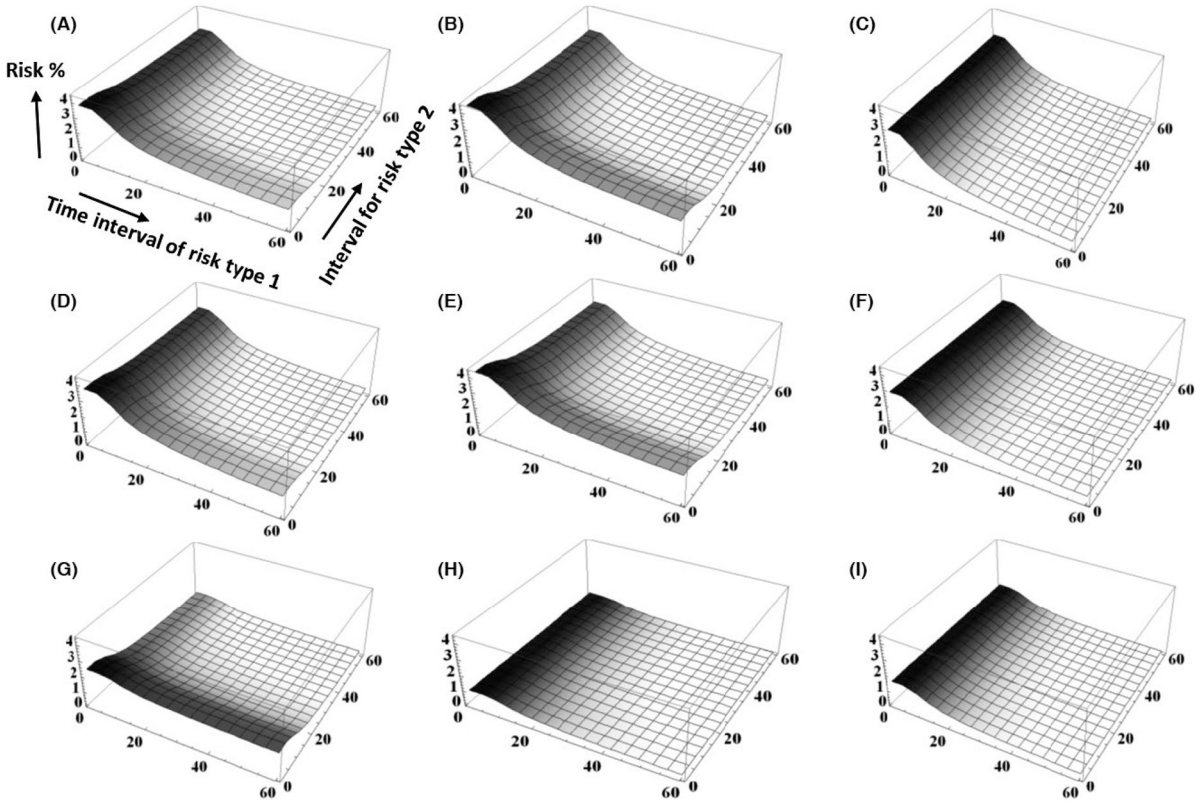

FIGURE 3.

Surface plots show risk of HIV infection given a negative nucleic acid test as a function of time interval uncertainty for two different risk behaviors. The plot z-axis shows risk in percentage points, the *x*-axis shows the size of the unknown time interval (in days) for risk behavior type 1, and the y axis shows the unknown time interval for risk behavior type 2, out to 60 days. Thus, a value of 10 on the *x*-axis indicates that risk behavior 1 happened sometime in the last 10 days. A, MSM1 behavior (*x*-axis) and intravenous drug use (IVDU) (*y*-axis), B, MSM1 and serodiscordant sex (sex with a known HIV-infected partner), C, MSM1 and sex with commercial sex worker (CSW), D, MSM2 behavior and IVDU, E, MSM2 and serodiscordant sex, F, MSM2 and CSW, G, IVDU and serodiscordant sex, H, IVDU and CSW, and I, serodiscordant sex and CSW. MSM1, men having unprotected receptive anal intercourse with men with ejaculation inside the rectum; MSM2, men having sex with men regardless of ejaculation

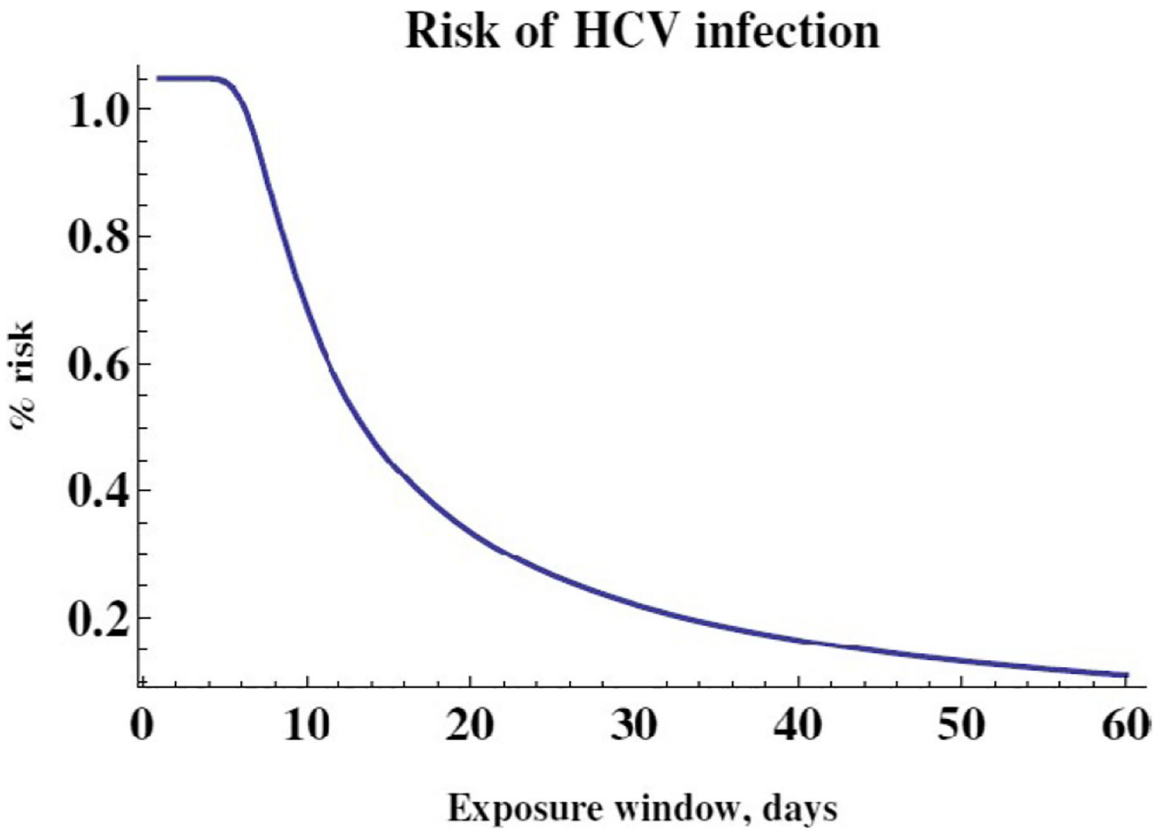

FIGURE 4.

The figure shows the risk of hepatitis C virus (HCV) infection despite a negative nucleic acid test vs an exposure window duration, where the timing of the exposure in the window is unknown. The HCV risk is from intravenous drug use with needle and equipment sharing

TABLE 1

Per-act risk of viral acquisition by exposure route

Exposure route	Risk per 10 000 exposures	95% CI	Author Reference (country, year)
Per-act of acquiring human immunodeficiency virus by exposure route			
Needle sharing IVDU	63	41–92	Hudgens et al.[13] (Thailand, 2002)
Serodiscordant couples	82	39–150	Wawer et al.[17] (Uganda, 2005)
Commercial sex	6.3	5.55–7.05	Kimani et al.[15] (Kenya, 2008)
Receptive anal intercourse			
With ejaculation inside rectum	143	48–285	Jin et al.[19](Austriala, 2010)
With withdrawal prior to ejaculation	65	15–153	Jin et al.[19](Austriala, 2010)
Regardless of ejaculation	82	24–276	Vittinghoff et al.[21] (CA, CO, IL USA, 1998)
Per-act risk of acquiring hepatitis C virus by exposure route			
Needle sharing IVDU	57	32–105	Bolene et al.[5] (Australia, 2014)

CI, confidence interval; IVDU, intravenous drug use; serodiscordant, sex with a known HIV-infected partner.

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TABLE 2

Risks as a function of time since exposure for each risk type

	Days since exposure (%)						
Risk behavior	**1**	**5**	**10**	**28**	**91**	**182**	**365**
HCV IVDU	1.05	0.98	0.02	1.05×10^{-9}	0	0	0
HIVIVDU	0.92	0.92	0.21	5.13×10^{-6}	9.19×10^{-16}	0	0
MSM1	2.85	2.22	0.03	2.79×10^{-9}	0	0	0
MSM2	2.76	2.66	0.46	4.72×10^{-6}	0	0	0
Sex with CSW	0.06	0.06	0.05	3.56×10^{-5}	1.26×10^{-11}	1.68×10^{-16}	0
Serodiscordant couple	1.50	1.49	0.23	3.02×10^{-6}	6.66×10^{-16}	0	0

HCV, hepatitis C virus; IVDU, intravenous drug use; HIV, human immunodeficiency virus; MSM1, men having unprotected receptive anal intercourse with men with ejaculation inside the rectum; MSM2, men having sex with men regardless of ejaculation; CSW, commercial sex worker; serodiscordant, sex with a known HIV-infected partner.