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# Donor-derived hepatitis C in the era of increasing intravenous drug use: A report of the Disease Transmission Advisory Committee

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## Abstract

The opioid epidemic has resulted in a potential increase in donors in the testing window period for hepatitis C virus (HCV). We analyzed HCV reports to the Disease Transmission Advisory Committee (DTAC) between 2008 and 2016 to estimate the risk of HCV transmission. In 15 of 95 (16%) reports, at least one recipient developed proven/probable donor-derived HCV resulting in 32 infected recipients. Seven transmissions occurred during the nucleic acid testing (NAT) window period; four occurred during serological window period. The other four transmission occurred due to human error (3) and false-negative serology (1). All seronegative-exposed liver and lung recipients contracted HCV; 18/21 (86%) kidney and 3/4 (75%) heart recipients developed HCV. Four transmitting donors died of intravenous drug overdose, three in 2016 and one in 2012. Among donors with a history of intravenous drug use (IVDU), drug intoxication as a mechanism of death, or increased risk status, and negative screening HCV testing, the risk of transmission to a recipient was about 1 in 1000. The overall risk of transmitting HCV from NAT-negative donors with IVDU is low and consistent with modeling data. This information may be helpful to clinicians counseling potential recipients offered these organs.

## 1 | INTRODUCTION

The ongoing opioid epidemic has resulted in an increase in the number of deaths due to overdose with drugs of abuse. Between 2002 and 2013, the rate of heroin-related overdose almost quadrupled, leading to a significant increase in donors classified as U.S. Public Health Service (PHS) increased risk of recent infection with HIV, hepatitis C, or hepatitis B.[1,2] Donors with very recent intravenous drug use (IVDU) might have bloodborne infections not detected by serologic and nucleic acid testing (NAT) (ie, be in the window period) required of all PHS increased risk donors (IRD).

The Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) Disease Transmission Advisory Committee (DTAC) receives reports of all potential donor disease transmission events with the goal of collecting information that can be used to improve OPTN/UNOS policy and educate the transplant community to promote patient safety related to disease transmission from donors to recipients. The purpose of this study is to analyze potential donor-derived hepatitis C virus (HCV) reported to the OPTN and to estimate the risk of transmission of HCV from donors with various risk factors for recent acquisition of HCV.

## 2 | MATERIALS AND METHODS

All reports of potential donor-derived transmission events (PDDTEs) received and reviewed by the DTAC from January 2008 to December 2016 were searched for HCV. The determination of whether or not donor-derived infection occurred was based on previously published standard DTAC criteria.[3-5] Each organ recipient was classified

as having proven, probable, possible, unlikely, or excluded donor-derived HCV. For all proven and probable instances of a donor transmitting HCV to at least one recipient, the following information was collected: demographics, number of recipients exposed and number of organs infected, results of donor HCV serological testing and (if done) NAT testing, donor PHS increased risk designation, and time from admission to performance of NAT (if done).

In addition to donor screening test results, further test results including NAT testing performed at tissue banks (typically done after the organ transplants were completed) as well as testing done by the CDC as part of the case investigation was collected. Using this information, each proven or probable donor transmission event was classified as one of the following:

1. Serological window period
   a. Donor screening serology nonreactive
   b. NAT performed on donor specimen at tissue bank or as part of transmission investigation resulted reactive
2. NAT window period
   a. Donor screening serology nonreactive
   b. Donor screening NAT nonreactive
3. Human error
   a. Positive HCV screening test on either blood vessels or donor was not properly communicated leading to HCV transmission
4. False negative serology
   a. Initial donor serologic testing was negative, NAT screening was not performed, but repeat serology as part of investigation was positive

Donors from recipients with proven or probable donor-derived HCV were reviewed to determine if donor death was a result of active injectable drug use. This information was obtained by specifically reviewing donor information collected by the Organ Procurement Organization as it is not a specific searchable OPTN data field.

Reports from cases that were not classified as proven or probable were reviewed to determine the reason for filing the report. Categories included false-positive antibody (defined by negative on retest at CDC), false-positive NAT, infection not donor-derived, and other/unknown.

While OPTN data fields do not categorize donors as having active intravenous drug at time of death, fields do include "drug intoxication as a mechanism of death" although this field is not limited to drug intoxication due to injected drugs of abuse but includes other mechanisms of death unrelated to risk of HCV transmission such as acetaminophen overdose. In addition, the OPTN collects "history of intravenous drug use" but use may have occurred at any time in the donor's life. OPTN data were used to determine the number of donors from 2008 to 2016 who were positive for either/both "drug intoxication as a mechanism of death" or "history of intravenous drug use." Further OPTN data were reviewed to determine which donors that transmitted HCV to at least one recipient were positive for either of these data fields. We could then calculate the risk of donor-derived HCV for various risk factors using as a denominator characteristics recorded for all donors that would be available to clinicians offering organs to potential recipients. These denominators included all donors during the study period with "drug intoxication as a mechanism of death" and "history of intravenous drug, either of those characteristics or both of those characteristics. Numerators were donors with those same characteristics with proven or probable transmission of hepatitis C to at least one recipient. The same analysis was conducted using all donors nationally classified as increased risk donors during the study period.

DTAC reviews information under confidential medical peer review, and information was summarized to prevent recognition of an individual case or institution.

## 3 | RESULTS

Between January 2008 and December 2016, 2053 total PDDTE reports were reviewed by the DTAC. Of these reports, 95 involved HCV (Table 1). For 15 of these reports, at least one recipient developed proven or probable donor-derived HCV infection (Figure 1). Among the 36 HCV seronegative recipients of an organ from these donors, 32 (89%) acquired donor-derived HCV infection. All susceptible lung and liver recipients developed donor-derived HCV infection. Donor-derived HCV infection occurred in 18/21(86%) of susceptible kidneys and 3/4 (75%) of susceptible heart recipients.

In 80 reports, no recipient developed proven or probable donor-derived HCV. Nineteen of these reports were generated due to a false-positive serology, 15 due to a false-positive NAT, and 21 were a result of infection in the recipient which after analysis was determined not to be donor-derived. In 25 cases, reports were made for other reasons or due to a positive test in a recipient that was not likely donor-derived but information was insufficient to determine whether the test was a false-positive or true-positive. In most cases, this was due to an HCV-seropositive NAT-negative recipient, often reported years after transplant.

Eleven of the fifteen (73%) cases with proven or probable HCV transmission were due to window period infection (seven NAT window period and 4 serological window period) (Figure 1). Among donors who had screening NAT performed preprocurement, the time from hospital admission to blood sample drawn for NAT ranged from 13 to 96 hours. All four donors in the serological window period had a positive NAT test performed or resulted postprocurement (most commonly done as part of screening for tissue donation). In three of the other four cases, pretransplant HCV testing was not properly noted or communicated and organs were unintentionally transplanted into seronegative recipients. In one case, a screening serology resulted negative, but subsequent postprocurement serological and NAT testing of stored donor specimens performed at the CDC demonstrated this to be a false-negative test.

In all seven cases of NAT window period transmission, the donor was classified as a PHS IRD. Two of four serological window period donors were IRD. Reasons for increased risk status among these nine IRDs included IVDU (5), prison (2), sexual exposure (1), and lack of medical history (1). The 11 window period donors were further reviewed to

**TABLE 1** Hepatitis C Reports to Disease Transmission Advisory Committee (DTAC), 2008-2016

| Year | Reported cases | Proven/Probable hepatitis C transmission | No proven/probable hepatitis C transmission | Donor with drug intoxication as mechanism of death | Donor with history of intravenous drug use (IVDU) | Infected recipients/ exposed recipients[a] |
|---|---|---|---|---|---|---|
| 2008 | 8 | 1 | 7 | 1 | 0 | 3/3 |
| 2009 | 10 | 2 | 8 | 1 | 1 | 2/2 |
| 2010 | 7 | 1 | 6 | 0 | 0 | 1/1 |
| 2011 | 11 | 3 | 8 | 2 | 1 | 4/4 |
| 2012 | 11 | 1 | 10 | 3 | 3 | 2/2 |
| 2013 | 11 | 0 | 11 | 2 | 1 | 0/0 |
| 2014 | 14 | 2 | 12 | 1 | 2 | 6/8 |
| 2015 | 6 | 1 | 5 | 0 | 0 | 3/3 |
| 2016 | 17 | 4 | 13 | 4 | 4 | 11/13 |
| Total | 95 | 15 | 80 | 14 | 12 | 32/36 |

[a]Excluded exposed recipients hepatitis C antibody-positive pretransplant.

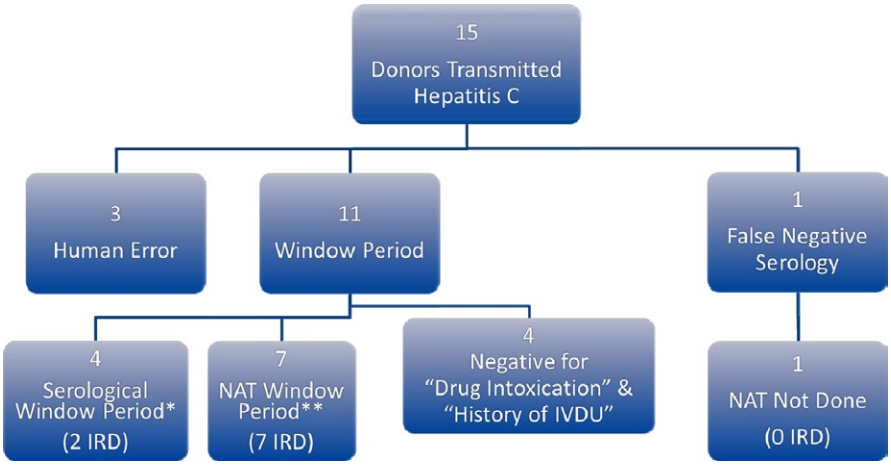



**FIGURE 1** Characteristics of 15 donors that transmitted hepatitis C to at least one recipient

see whether they qualified for the OPTN data fields "history of IVDU" and "drug intoxication" as mechanism of death; four of these donors were negative for both categories. A separate review of the charts of 15 donors who transmitted HCV to at least one recipient was conducted to determine how many died of active IVDU. Four of these 15 donors died of active IVDU, one in 2012 and three in 2016 (Figure 2).

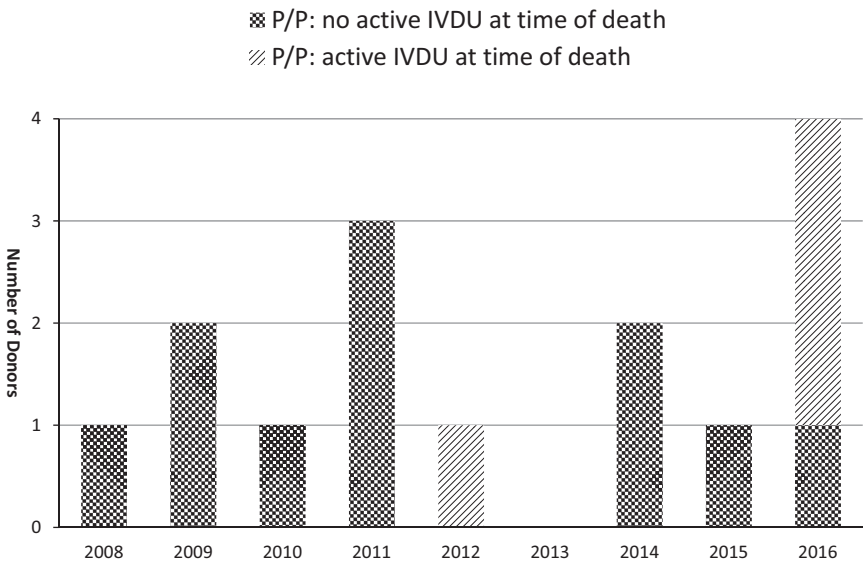
From January 2008 to December 2016, organs from 5294 organs from donors with a history of IVDU, 5156 donors with drug intoxication as a mechanism of death, and 11 143 donors characterized as increased risk were procured. These data were used to estimate the risk of HCV transmission from donors in these risk groups. Table 2 describes the risk of donor-derived HCV originating from donors with these risk factors.

## 4 | DISCUSSION

Among potential donors with risk factors for window period infection with HCV but negative screening tests, donor-derived infection remains rare. Donors with either drug intoxication as a mechanism of death or a history of IVDU had an approximately 1 in 1000 risk of transmitting HCV to at least one recipient. This risk is similar to that calculated using modeling techniques.[6,7] A recent CDC publication estimated a risk of HCV donor infection of about 1% for NAT-negative donors with IVDU in the 5 days prior to procurement.[6] A meta-analysis of studies describing incidence rates of HCV in various high-risk populations calculated risk of NAT window period transmission of 3.24 per 1000 donors with a history of IVDU.[7] It is not surprising that this estimate is slightly higher than this report as most studies reviewed in the meta-analysis included recent (past 1-2 months) drug use rather than a history of ever using intravenous drugs. Further, the category of drug intoxication as a mechanism of death includes deaths unrelated to the risk of window period HCV infection (eg, suicide due to acetaminophen overdose).

All HCV-exposed pretransplant seronegative liver recipients did develop HCV infection, but 3/21 (14%) exposed kidney recipients and 1/4 (25%) exposed heart recipients did not develop HCV infection. This may be due to the presence of HCV in the liver but not in the blood early in infection.

The circumstance of greatest concern to clinicians for NAT window period infection with HCV is the donor who died from active IVDU. Clinicians are commonly faced with this situation given the




p/p= proven or probable

IVDU= active intravenous drug use at time of death

**FIGURE 2** Donors that transmitted hepatitis C with and without active intravenous drug use as a mechanism of death. p/p, proven or probable; IVDU, active intravenous drug use at time of death

**TABLE 2** Risk of proven or probable donor transmission of hepatitis C by risk factor 2008-2016

| | Increased risk donors | History of IVDU | Drug intoxication | IVDU and/or drug intoxication | IVDU and drug intoxication |
|---|---|---|---|---|---|
| Proven or probable donors/Total donors | 9/11 143 (0.08%) | 5/5294 (0.09%) | 6/5156 (0.12%) | 7/8040 (0.08%) | 3/2410 (0.12%) |

IVDU, intravenous drug use.

almost 10-fold increase in donors with a history of IVDU or drug intoxication as a mechanism of death from 2008 to 2016. Further, the number of PHS IRD has increased substantially.[8]

To provide optimal informed consent to patients offered these organs, clinicians need data on the risk of NAT window period HCV transmission, particularly from donors who die of active intravenous drug use. The data in this study provide some information on the risk associated with donors with active IVDU—needle in the arm donors—at the time of procurement. First, an increased number of NAT window period transmissions was observed in 2016 with three infected donors compared to only one during the preceding 8 years among donors with active IVDU at the time of hospitalization (as determined by reviewing individual donor charts). These numbers are small and may not reflect a trend, but as more donors with active IVDU at the time of death are used, it would be expected that an increase in window period HCV transmissions would occur. Second, while OPTN data do not specifically separate IVDU as the mechanism of death (as compared with other forms of drug intoxication), donors that meet both criteria may reflect a population more likely to have died from overdose with intravenous drugs. From 2008 to 2016, 2410 donors met the criteria of both a history of IVDU and drug intoxication. Among these donors, 3 transmitted HCV to at least one recipient suggesting a risk of about 1/1000.

Since 2015, HCV NAT testing has been required of all potential organ donors. Licensed donor screening NAT tests have a window period (3-5 days compared to 70 days for serological assay.).[9] Nonetheless, given that HCV may be intermittently detectable by NAT prior to the "ramp up phase" of rapid viral load increase, nonreactive NAT assays could occur later than the generally reported NAT window period.[10,11] In the current study, the median time between admission to the hospital and obtaining the specimen for NAT was 41 hours with a range of 13-96 hours. Thus, nonreactive NAT testing outside of the reported window period was not found. Modeling data suggest that the risk of a negative NAT test in a recently infected donor decays considerably after 5 days from exposure to HCV.[6] Thus, ideally, NAT would be obtained as late in the process as possible, but practical considerations limit the feasibility of performing NAT testing later in the evaluation period as results are most useful if available at the time of organ offer.

In 2013, PHS guidelines were revised to better identify potential donors at higher risk of window period infection with HIV, HCV, or hepatitis B.[12] Based on cases described in this report, PHS increased criteria did identify all NAT window period transmissions, including 4 NAT window period donors classified as PHS increased risk based on criteria other than IVDU. It is worth noting, however, that the vast majority of NAT-negative IRD are not in the window period and cannot transmit HCV virus.

This study has a number of limitations. The DTAC reporting system for PDDTE is mandatory but passive, and donor-derived infections may have occurred that were not reported. This would result in our numbers underestimating the risk of window period transmission. Further adherence to policy requirements for follow-up testing of recipients of IRD organs has not been universally followed, possibly resulting in undiagnosed cases of transmission.[13] As donor-derived infection with HCV is a relatively high profile event compared to other more routine or difficult to diagnose donor-derived infections, the number of unreported transmissions would be expected to be low. The use of screening NAT testing for all donors has only been required since 2015, although use was fairly common prior to that time. Universal NAT would be expected to prevent some transmission in later years that might diminish any temporal trend and result in an overestimation of the overall risk of HCV transmission during the study period. Changes in required testing combined with the opioid epidemic itself and local outbreaks of HCV among the IVDU population might alter the local risk of HCV transmission from a donor with a history of intravenous drug use and/or drug intoxication as a mechanism of death. Further limitations include the overall small number of donor-derived infections that occurred making it difficult to determine whether a trend of increased window period infections was occurring in 2016 or whether the increase was an anomaly. It should also be noted that cases from a previous investigation of three clusters of probable donor-derived hepatitis C are included in this paper.[14] Finally, we did not have information on the precise time of the injection leading to fatal overdose, and substituted time from hospital admission to obtaining NAT. This would have the effect of underestimating the true window period associated with NAT testing.

As the number of organ offers received from potential donors with recent active IVDU continues to increase, categorically declining to use these organs due to fear of window period HCV infection will significantly limit the number of donors available for recipients listed at a particular center. In order to counsel potential recipients, clinicians need more information to help them communicate to potential recipients the risk of window period HCV infection and subsequent risk of recipient infection. Based on reports to OPTN/UNOS, this study demonstrates a risk of about 1/1000 among donors with a history of IVDU, drug intoxication as a mechanism, or a combination of those behaviors. Based on previous modeling studies and the reporting limitations discussed above, the true risk of window period HCV infection is likely <1%. This low risk should be considered in the context of highly effective hepatitis C treatments that can be administered after transplantation. While more cases of donor-derived HCV from window period active IVDU donors were observed in 2016 compared to previous years, the absolute risk appears to be low. A multicenter collaborative study conducted among centers that use significant numbers of active IVDU donors with careful recipient follow-up would provide further data regarding the true risk associated with these donors. Given the mismatch between organ availability and need, it is critical that information is available to allow this growing proportion of potential organ donors to be optimally but safely used.

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## CONFLICT OF INTERESTS

The authors have no relevant conflict of interests.

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