Review

JHEP|Reports

Opioid epidemic and liver disease

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Summary

Opioid use in the United States and in many parts of the world has reached epidemic proportions. This has led to excess mortality as well as significant changes in the epidemiology of liver disease. Herein, we review the impact of the opioid epidemic on liver disease, focusing on the multifaceted impact this epidemic has had on liver disease and liver transplantation. In particular, the opioid crisis has led to a significant shift in incident hepatitis C virus infection to younger populations and to women, leading to changes in screening recommendations. Less well characterized are the potential direct and indirect hepatotoxic effects of opioids, as well as the changes in the incidence of hepatitis B virus infection and alcohol abuse that are likely rising in this population as well. Finally, the opioid epidemic has led to a significant rise in the proportion of organ donors who died due to overdose. These donors have led to an overall increase in donor numbers, but also to new considerations about the better use of donors with perceived or actual risk of disease transmission, especially hepatitis C. Clearly, additional efforts are needed to combat the opioid epidemic. Moreover, better understanding of the epidemiology and underlying pathophysiology will help to identify and treat liver disease in this high-risk population.

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Scope of the opioid epidemic

At this time, though the United States (U.S.) is disproportionately suffering the effects of the opioid epidemic compared to other countries, the problem is not limited to its borders. As it remains a growing problem in other nations, the opioid crisis threatens the global population and has a particularly high burden on young adults, therefore resulting in a disproportionately high amount of person-years of life lost.

United States

Between 1999 and 2017, over 700,000 people died from drug overdoses in the U.S. (Fig. 1).[1–3] During this time, nearly 400,000 of these deaths involved either prescription or illicit opioids.[4] In 2017 alone, over 70,200 deaths were attributed to drug overdose, among which about 68% involved an opioid.[1,5] This amounts to an average of 130 deaths per day from an opioid overdose in the U.S.[4]

Historically, the mid-20th century marked the beginning of a predominantly pharmacologic approach to the treatment of pain.[1,6] The initial rise in the prescription rates of opioids and subsequent overdose deaths in the U.S. began in the 1990s and steadily increased through 1999. The use of opioids broadened to include not only acute and cancer-related pain, but chronic non-cancer pain as well. Yearly prescriptions of opioids increased by 2–3 million each year starting in 1990 and continuing through 1995 when long-acting oxycodone (Oxycontin) was approved by the U.S. Food and Drug Administration and marketed as a non-addictive alternative to the opioids available at the time, based on little scientific evidence.[1,7,8] During this time, agencies such as the American Pain Society and the Joint Commission in 2001 stressed the need for increased emphasis on pain identification and treatment, declaring pain the "fifth vital sign.".[1,8–10] The Institute of Medicine and the Agency for Healthcare Research and Quality of the Hospital Consumer of Healthcare Providers and Systems (HCAHPS) then pronounced patient experience and satisfaction as indicators of the quality of medical care, driven by an emphasis on adequate pain control.[1,10,11] In 2005 when hospitals were asked to reveal the results of patient satisfaction surveys or risk monetary and other penalties, opioid prescribing was liberalized to maximize patient experience and the opportunity for institutional financial reward.[1,12] Thus, beginning in 1999, prescription opioid-related deaths have risen concurrently with the increase in opioid prescriptions, which increased from 72.4 to 81.2 prescriptions per 100 people from 2006 to 2010.[5,13–15]

More recently, a new opioid crisis began in 2013, driven in large part by illicitly manufactured fentanyl and other synthetic opioids.[4,8,16–21] This has become more acute as attempts to limit prescription opioids have strengthened. Between

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2010-2015, the drug overdose death rate in the U.S. increased from 12.3 to 16.3 per 100,000.[14] In 2014, a total of 47,055 drug overdose deaths were reported, 28,647 of which involved an opioid.[14] This increased in 2015, when 52,404 people died of a drug overdose, 63.1% (33,091) involving opioids.[14] This amounted to an age-adjusted opioid-involved death rate increase of 15.6%, from 9.0 per 100,000 in 2014 to 10.4 per 100,000 in 2015.[14] Between 2013-2017, the rates of drug overdose death increased in 35 out of 50 states, with synthetic opioids accounting for a significant increase in death rates in 15 out of 20 states.[5,22] While clearly addictive, the use of hydrocodone, oxycodone, or even heroin alone is often not sufficiently potent to cause death. However, when cut with fentanyl, carfentanil, or other analogues,[23–25] the resulting opioid cocktails are 100- to 10,000-fold more potent and are more likely to lead to asphyxiation.[26,27] There is also significant geographic variation in opiate use throughout the U.S. The greatest relative rates of increased death due to opioids between 2016-2017 were in North Carolina (28.6%), Ohio (19.1%) and Maine (18.7%).[5] Deaths involving prescription opioids in 2017 were highest in West Virginia (17.2 per 100,00), Maryland (11.5), and Utah (10.8).[5]

Key points

While the opioid epidemic is disproportionately affecting the United States, it is a growing problem globally.

The opioid epidemic has significant implications for the transmission of viral hepatitis and must be considered in future screening strategies.

A significant portion of individuals with a history of opioid misuse also have a history of alcohol use disorders.

Overdose death liver donors represent an increasingly significant and underused portion of the donor organ pool, particularly considering the non-inferior, if not superior outcomes they can confer.

Changing demographics

In the U.S., the opioid epidemic has been associated with race-, gender- and age-specific differences. Between 1979 and 2015, the rate of opioid deaths for whites increased from 0.44 to 12 per 100,000 individuals, or about 10% per year, while among blacks, this increased from 0.62 to 6.6, or an average increase of 6% per year during the same time period.[6] However, since 2010, the rates of opioid-related overdose increased in both races as synthetic opioid use, which define this period, have affected blacks and whites at similarly high rates.[28,29] From 2016 to 2017, the largest relative change in the rate of opioid-involved overdose deaths was among blacks (25.2%).[5,6]

Men have historically been affected to a greater extent by overdose mortality and opioid use disorder than women, but there are signs that this is also changing. Even though hospitalizations related to opioid use increased for both men and women between 2005 and 2014, the percentage rate increases were greater for women (75%) than for men (55%).[8,30,31] Additionally, women are more likely to be prescribed opioid pain medications, continue to use them chronically, and receive them in higher doses compared to men.[32] From 1999-2010, opioid-related overdose deaths increased 415% for women and 265% for men.[30,33] The rate of drug overdose death among women was greatest among women aged 45-54 years (21.8 per 100,000), and highest between American Indian/Alaska Native (14.5) and non-Hispanic white (12.7)

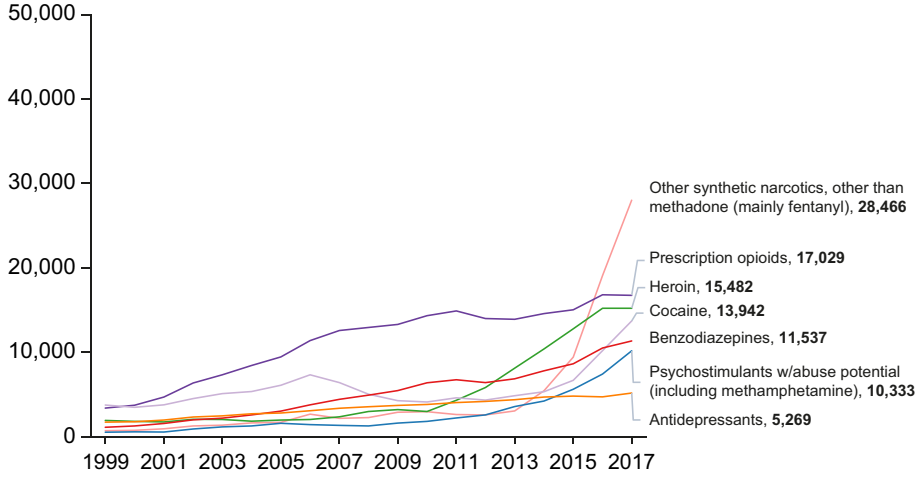

Fig. 1. Drug overdose deaths in the United States from 1999-2017 among all ages and by type of opioid.[2–4,232] Figure reproduced from.[232] Opioid overdose deaths were identified using ICD-10 codes X40-X44, X60-X64, X85, Y10-Y14, and multiple cause codes T40.0, T 40.1, T40.2, T40.3, T40.4, T40.6. Drugs included natural/semisynthetic opioids, methadone, heroin, synthetic opioids other than methadone, cocaine, and psychostimulants with abuse potential. Death rates are age-adjusted, and calculated by using age-specific death rates and applying them to the 2000 U.S. standard population age distribution. For each type of opioid, multiple cause of death code was T40.1 for heroin, T40.2 for natural and semisynthetic opioids, T40.3 for methadone, and T40.4 for synthetic opioids excluding methadone, T40.5 for cocaine, and T43.6 for psychostimulants with abuse potential. Deaths may involve more than one drug and are not mutually exclusive.

women.[30] In particular, opioid use disorder has increased among pregnant women. From 1999 to 2014, the rate of opioid use disorder in the antepartum period increased from 1.5 to 6.5 per 1,000 births, and the incidence of neonatal abstinence syndrome (NAS) increased 400% between 2000 and 2012.[30,34–36]

Finally, children have also been affected by this epidemic. Between 1999 and 2016, there were 8,986 deaths from prescription and illicit opioids among the paediatric and adolescent population.[37] Among these, 7,921 (88.1%) occurred in adolescents aged 15 to 19 years, while 605 (6.7%) occurred in children aged 0 to 4 years of age.[37] During this time, the highest rates of annual mortality increase were among adolescents aged 15 to 19 years, from 0.78 per 100,000 in 1999 to 2.75 in 2016, or a 252.6% increase.[37] Of all total paediatric deaths related to opioid overdose from 1999 to 2016, prescription opioids accounted for 6,561 (73.0%) deaths, and 7,263 (80.8%) were unintentional and occurred outside a medical setting, a trend similarly to that seen in the adult population.[37,38] Among adolescents aged 15 to 19 years, mortality rates related to synthetic opioids increased from 0.04 to 1.21, or an increase of 2,925.0%.[37] Even though the mortality rates due to opioid poisoning among the paediatric population differ from adults, these distinct populations share similar patterns of drug use, underscoring the severity of this epidemic.

Global perspective

In Canada, opioid prescribing rates have risen from over 10,000 daily doses per 1,000,000 people per day from 2001-2003, to over 30,000 between 2012-2014, making it the second highest rate of opioid prescribing in the world.[39–43] In Australia, from 2006 to 2015, total opioid use has increased by 51% when measured by oral morphine equivalents per 1,000 people per day.[39,43–46] In New Zealand, opioid-related overdose deaths rose by 33% from 2001 to 2012, which paralleled a steady increase in the annual number of opioid prescriptions during the same period.[39,47] Europe is also facing the threat of an opioid epidemic. Within the United Kingdom, most opioid prescriptions are written for chronic non-cancer pain. One report described over 2.6 million prescriptions of strong opioids (defined as buprenorphine, diamorphine, dipipanone, fentanyl, hydromorphone, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, or tapentadol) written for around 178,000 patients, 87.8% of which were for chronic non-cancer pain.[48,49] In Germany, between 2000 and 2010, the number of opioid prescriptions rose from 3.31% to 3.53%.[39,43,50] Concerning patterns of opioid misuse and poor prescribing habits have been reported in Norway, Russia, Ukraine, and Central Asia as well.[51–55] It is thus evident that the opioid epidemic is a global issue.

Opioid epidemic and chronic liver disease

Hepatitis C virus

Epidemiology

Undoubtedly, the increase in intravenous drug use (IVDU) as a result of the opioid epidemic has brought with it a rise in hepatitis C virus (HCV) transmission in the U.S. Between 1992 and 2003, the declining rates of acute HCV were reassuring.[56,57] However, this trend has now reversed with HCV incidence rising every year since 2013 (Fig. 2).[58] People who inject drugs (PWID) acquire HCV at a rapid rate, with incidence rates reported to be around 28% in the first year of IVDU.[59] Perhaps even more frightening is the elaborate and communal network of needle sharing among PWIDs, exposing large numbers of people to the risk of infection in a short period of time. This trend has been observed in many other countries as well..[60–63] The multiple steps involved in the preparation and intake of opioid drugs allow for several points of possible transmission among IVDUs despite a denial of needle sharing.[63–67]

The climbing incidence of acute HCV infection in the U.S. began around 2004.[62] Overall, the annual incidence rate of acute HCV infection between 2004 and 2014 grew 133% from 0.3 per 100,000 to 0.7 per 100,000, respectively.[62] This was most notable in states such as Kansas, Maine, Wisconsin, Ohio, Massachusetts, and New Jersey, where acute HCV infection rose 1,000% or more from 2004-2014, and an additional 9 states where an increase of 500% was reported during the same period.[68–71] These rates of newly acquired HCV in recent years parallel increasing hospital admissions for opioid injection and its complications, mirroring the geographic and demographic distribution of the opioid epidemic. The most significant increases of acute HCV infection were among young adults aged 18 to 39 years, with one study reporting an increase of over 300% between 2004 and 2014.[62] Several studies have reported similar results among young PWID, particularly those living in non-urban areas, signalling that this population may be at increased risk.[62,71–75] Between 2006 and 2012, there was a reported 13% increase in HCV incidence per year among non-urban counties in the U.S., compared to a 5% increase in incidence per year among urban areas.[72] Among these reported cases, both men and women were significantly affected, and were mostly non-Hispanic white, or Hispanic.[68–70,72,76] IVDU was reported in a significant proportion of these cases during this time, with over 75% of people admitting to IDU every year between 2011 and 2014.[71]

HCV screening

HCV screening recommendations in the U.S. were recently updated to include one-time screening for patients born between 1945-1965 (baby boomers). However, there have been longstanding

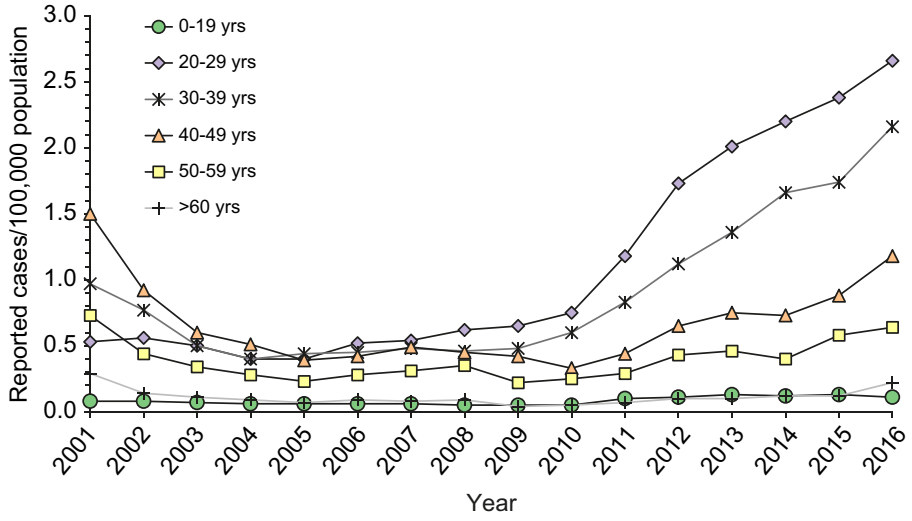

Fig. 2. Incidence of acute hepatitis C infection by age group – United States, 2001-2016.[58] Figure reproduced from[58]

recommendations for risk factor-based screening, with any history of IVDU being the strongest risk factor for transmission.[77,78] It is estimated that between 60%–90% of injection drug users may be infected with HCV.[79–86] Linking HCV screening and treatment to patients participating in methadone maintenance treatment programmes is cost effective, and targets those at high risk of acute HCV infection within the context of the opioid epidemic.[87–90] However, a robust effort is still needed to encourage on-site screening in this setting rather than referral-based screening. In 2005, a reported 53% of opioid treatment programmes offered on-site HCV testing, compared with only 34% in 2011.[87] In addition, for patients not in opioid treatment programmes, the major limitation to risk factor-based screening is the high likelihood of misinformation or denial from the patient at the time of a clinical encounter and risk factor assessment.[91–98] As a result of this and the changing epidemiology of HCV in the U.S., with an ever-increasing numbers of young patients, some have advocated for universal screening among adults, not limited only to those in the baby boomer birth cohort.[99–101]

Another population in which screening recommendations are evolving is pregnant women. There has been a striking rise in the incidence of acute HCV among women of childbearing age, and corresponding data about the prevalence of HCV positivity among antepartum women in certain regions (Fig. 3).[102–106] The overall prevalence of HCV among pregnant women is reportedly 1.0%–2.5% in the U.S., and up to 8.0% in certain populations globally.[107–109] The risk of HCV transmission to the child is around 6%, and 15% in HIV-coinfected mothers, increasing the risk of foetal growth complications.[107,110–112] An 89% increase in HCV infection at the time of delivery, from 1.8 to 3.4 per 1,000 live births, was reported during 2009-2014 in states where HCV is recorded on birth certificates.[105] More recently, in 2015 an estimated 14,417 (0.38%) of 3,823,723 live births were delivered by HCV-infected mothers.[106] The highest percentage of infection was in West Virginia (2.78%), and the lowest in Hawaii (0.07%).[106] A majority of HCV-infected mothers, compared with their non-HCV counterparts, were between 20–29 years of age (60.7% *vs.* 50.9%), white non-Hispanic (80.2% *vs.* 52.8%), and living in rural areas (26.0% *vs.* 14.0%).[106] In Tennessee, where the rate of HCV infection was 10.1 per 1,000 live births in 2014, further analysis revealed that there was a 3-fold greater risk of HCV infection at the time of delivery among women living in rural areas, a 4.5-fold increased risk among women who used tobacco during pregnancy, and a striking 17-fold higher risk among women with HBV coinfection.[105] Taken together, this represents a harrowing threat to maternal-foetal health. Among 189 HCV-positive patients identified in Appalachia between 2014 and 2015, only 136 (72.0%) admitted to a history of IVDU.[113] Risk-based screening alone would have missed 28.0% of these infections.[113] Several other studies have reported similar results, arguing that risk-based screening for HCV in pregnancy is ineffective, and that providers should be encouraged to screen pregnant women universally for HCV at the start of pregnancy.[114–117] Screening of pregnant women has now been recommended in professional society guidance documents, though not yet endorsed by federal agencies in the U.S.[118]

Treatment of HCV in IVDU

The use of direct-acting antivirals (DAAs) for the treatment of HCV among PWID is equally effective as in those who do not inject opioids, but continuing challenges remain regarding the reluctance of providers to start treatment and concerns about adherence to treatment regimens and the risk of reinfection. Several DAA regimens have been studied in clinical trials in the PWID population, with high rates of sustained virologic response (SVR)

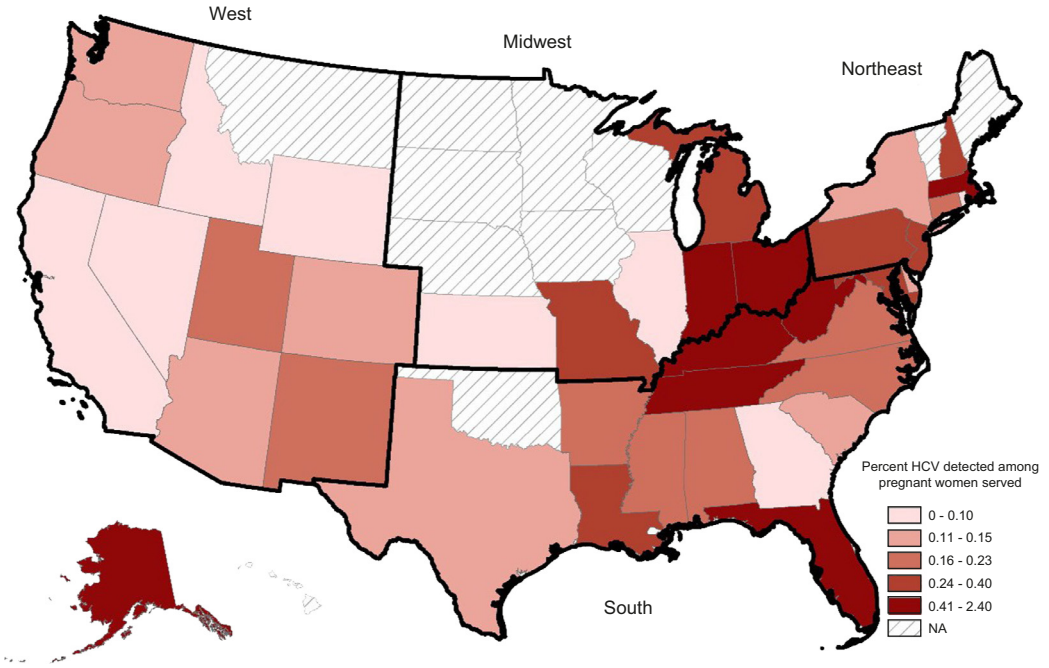

Fig. 3. Hepatitis C infection among pregnant women at time of delivery – United States, 2015.[105,106] Figure reproduced with permission from.[106] Data were obtained from National Center for Health Statistics. Maternal HCV infection was indicated from infant birth certificates at the time of delivery. Urbanicity was established using data from 2013 NCHS Urban Rural Classification Scheme for Counties.

equal to non-drug users.[119–126] Equally encouraging are the studies reporting similar rates of treatment completion and SVR of 80%–90% and >90%, respectively, regardless of whether or not patients are receiving opioid substitution therapy at the time of treatment, even among patients with recent injection drug use in the past 6 months.[127–129]

Reinfection remains a concern among IVDUs after the completion of treatment and must be overcome to keep rates of acute HCV infection low, as the opioid epidemic continues to permeate. However, existing data is encouraging. Estimated rates of reinfection after treatment range from 0.0 to 5.3 per 100 person-years.[130–134] In a systematic review and meta-analysis of active IVDUs, the pooled risk of HCV reinfection among 14 studies of PWID and prisoners was 10% over an average of 2.8 years of follow-up, compared to 1% among "low-risk" individuals.[135] However, the rate of reinfection among truly low-risk individuals is likely even lower than this. A 2018 study reported a reinfection rate of 3.11 per 100 person-years among PWID, with higher rates of reinfection among those born after 1975 (10.2 per 100 person-years), with HIV coinfection (5.67 per 100 person-years), and with disordered alcohol use (4.55 per 100 person-years).[136] Additionally, the cumulative risk of reinfection at 52 weeks post-SVR was 2.8%, 1.2%, and 0.2% overall among recent, former, and non-PWID, respectively.[136] Distinguishing reinfection from persistent infection or relapse makes it difficult to quantify true reinfection rates, particularly if testing is performed in the context of undulating low-level viraemia which can be mistaken for clearance.[135,137,138] The most effective approach to prevent reinfection in PWID may be largely educational, focusing on risk reduction, in combination with opioid substitution therapy and clean needle programmes.

Increasing access to DAA therapy for PWID remains a challenge, and may prevent efforts to expand treatment within this population. Several modelling studies have shown that increased penetrance of treatment into these high-risk communities will have a dramatic effect on the pool of HCV in the population.[139–145] However, reimbursement for DAA therapy continues to be limited for patients with high-risk behaviour, regardless of their degree of liver disease at the time of diagnosis.[146] Expanding access to appropriate DAA therapy for PWID will rely on efforts to promote universal coverage for these medications, in combination with lowering drug prices. This will be dependent upon concerted effort by providers, patients, and governmental organizations to improve diagnosis, linkage to care, and treatment completion.

Hepatitis B virus

Injection drug use is also a significant risk factor for hepatitis B virus (HBV) infection, and efforts to decrease transmission rates should focus on vaccination of individuals with this behaviour. Similar to HCV, the incidence of acute HBV infection in the U.S. has increased in recent years concurrently with the widespread opioid epidemic, though to a lesser extent. Overall, the incidence

of acute HBV infection in the U.S. rose from 2,895 cases in 2012 to a peak of 3,370 cases in 2015, and a slight decrease to 3,218 in 2016.[58] Between 2006 and 2013, a total of 3,305 cases of acute HBV infection were identified in Tennessee, West Virginia, and Kentucky, with the incidence between 2009 and 2013 alone rising 114%.[147] Additionally, mirroring the demographic characteristics of those most heavily affected by the opioid epidemic, the number of whites aged 30 to 39 years old diagnosed with acute HBV grew significantly between 2010 and 2013.[147,148] Geographically, 1,344 of 3,185 (42%) cases reported living in non-urban areas.[147] Similar results have been observed in other countries. Among several European countries, the estimated prevalence of HBV surface antigen positivity ranges from 0.5%–6.3% in PWID.[149,150] In the UK, where a reported 22% of PWID are thought to be affected by HBV, and in Demark, sudden outbreaks of HBV have been linked to IVDU.[151,152] A recent study of PWID in Germany reported a prevalence of HBV that was 5-fold higher than in the general population.[150] In Australia, between 28% and 59% of PWID are thought to be exposed to HBV.[153]

The biggest challenge in containing the spread of HBV among PWID lies in encouraging those who are at risk to participate in vaccine regimens that involve multiple doses. Those who do not complete the full vaccination schedule remain at risk of HBV infection due to incomplete immunity, which remains a significant obstacle in this at risk population. Several strategies to improve vaccine participation and completion have been studied, including contingency management, vaccination programmes in prisons, on-site vaccination during education sessions, as well as newly approved 2 dose shortened vaccination schedules which can be accomplished in 1 month. In particular, the use of monetary incentives to encourage patients to return to clinics to complete the vaccination series has been shown to be cost effective and a worthwhile use of healthcare resources to control transmission.[154–157] One study of contingency management in the UK reported a vaccination completion percentage between 40%–50% for those who were offered monetary incentives, versus 9% for those who received the standard vaccination regimen without additional benefits.[151] For programmes such as this to be successful, further studies investigating the use of incentives to improve rates of vaccination participation and completion should be undertaken, as this offers an encouraging road towards lower rates of acute HBV among people affected by the opioid epidemic.

Public health response

Public health efforts to eradicate HCV and HBV are underway in the U.S. and throughout the world. In a 2016 report, the World Health Organization (WHO) set a goal committed to ending the threat of hepatitis B and C viral hepatitis by 2030. The specific WHO targets include a 90% reduction in new chronic cases and a 65% reduction in mortality, through: i) 3-dose HBV vaccine for infants, ii) prevention of vertical transmission of HBV, iii) blood and injection safety, iv) harm reduction in the form of sterile syringe/needle kits for injection drug users, and v) diagnosis and treatment of prevalent HBV and HCV.[158] The financial requirement for such an effort is estimated at $11.9 billion for middle- and low-income countries, driven by testing and treatment for HBV and HCV.[158] This Global Health Sector Strategy would prevent approximately 7.1 million deaths worldwide between 2015 and 2030.[158] A total of 194 countries committed to this strategy, and as of February 2019, 124 countries have developed or are developing disease action plans.[159] According to the WHO and Center for Disease Analysis, 5 million people with HCV were treated with DAAs at the end of 2017.[159,160] In developing countries, which account for 62% of all HCV cases, the price of pangenotypic DAAs has fallen to $89 under the United Nations Development Program, reducing financial barriers to treatment.[160] Regarding HBV, the percentage of infected children under 5 years of age declined from 1.3% in 2015 to 0.8% in 2017.[160] Treatment for HBV reached approximately 4.5 million people at the end of 2016.[160]

However, challenges remain in order to expedite progress towards these elimination goals. Sustained focus on harm reduction for PWID, accounting for 23% of new infections, is one obstacle.[160] By the end of 2017, only one-tenth of the goal to distribute safe syringe needle sets to every PWID had been met.[159,160] Financial resources remain an ongoing challenge, with only 58% of countries allocating funding to support the growth of hepatitis elimination programmes.[159,160]

In the U.S., the National Viral Hepatitis Action Plan for 2017-2020 has been developed as a collaboration across federal agencies.[161] In addition, several individual states have hepatitis elimination initiatives. In March 2018, New York State became the first jurisdiction to embark on an evidence-based strategy to eliminate HCV, promoting the establishment of the Hepatitis C Elimination Task Force to guide state lawmakers, advocates, and community members working with vulnerable populations who are disproportionately at risk.[162–165] This has led to increased funding for HCV programmes, Medicaid reimbursement for harm reduction services, expansion of syringe exchange centres, removing barriers to care limited by insurance, and the development of multimedia platforms to raise awareness of HCV.[163,164] In San Francisco, “End Hep C SF” put forth a similar agenda to end HCV as a public health threat, and dissolve HCV-related health inequities by

supporting those in the community affected by the virus.[166]

Alcohol-related liver disease

An estimated one-third of individuals with a history of opioid misuse or addiction are thought to have alcohol use disorder, representing a significant comorbidity that can be easily overlooked and difficult to treat in this population.[167,168] Few large-scale studies describe the prevalence of alcohol-related liver disease and alcohol use disorder in the context of the opioid epidemic, although there is a trend towards decreased alcohol ingestion while patients are maintained in opioid treatment programmes. One study of the outcomes of biweekly educational interventions over the course of 3 weeks, in an urban setting among PWIDs newly diagnosed with HCV, found varied patterns in alcohol consumption after the first year of follow-up, with many participants returning to previous habits.[169] However, no significant difference was observed among people who received counselling specifically on liver health versus standard follow-up educational material. In 2013, a study of PWID in rural Appalachia reported a decrease in alcohol consumption at 6 months, although no difference was observed when stratified by HCV seropositivity or post-diagnosis counseling.[170] The results of this study conflict with others, some of which have reported a decrease in alcohol consumption only in the short-term (3 months), with a return to baseline drinking status at 6 months and 1 year.[170,171] Concurrent use of marijuana, drinking to intoxication in the past 30 days prior to HCV diagnosis, and antisocial personality disorder have all been reported to be linked to increased alcohol intake among PWID with acute HCV infection.[170] Although few studies have been performed assessing the extent of alcohol ingestion as is relates to the opioid epidemic, given the modifiable nature of this behaviour, there is significant potential for decreasing the well-known adverse effects of increased alcohol consumption on liver disease, particularly among the rising rates of acute HCV associated with the worsening opioid use crisis.

Direct and indirect effects of opioids that may promote liver injury

While the majority of liver-related diseases in PWID are related to HBV and HCV infection, as well as alcohol, opioids may also directly contribute to or exacerbate liver disease. Many opioids including fentanyl, oxycodone, methadone and tramadol are metabolized in the liver via the P450 system.[172]Others such morphine, oxymorphone, and hydromorphone undergo glucuronidation via UGT2B7 in the liver.[172] These metabolic pathways, as well as lipid oxidation and mitochondrial oxidative injury,[173,174] may contribute to or worsen liver injury. δ-opioid receptors, known to contribute significantly to cellular development and found in abundance within liver tissue, have been shown to affect the initiation and progression of liver diseases.[175] Histopathologic examination of hepatocytes retrieved from rat models of chronic opioid use have depicted sinusoidal dilatation, perivenular (zone 3) ballooning degeneration extending to the midzonal region (zone 2), perivenular necrosis, haemorrhage, and focal microvesicular steatosis.[176] Similar studies have exhibited increases in cell death following the administration of morphine to rat hepatocytes.[177] In humans, elevation in biochemical markers, particularly alanine aminotransferase, lactate dehydrogenase, and lipid peroxides among chronic heroin users has been reported, and may suggest direct hepatotoxic effects perpetuated by these drug metabolites.[178]

Indirect mechanisms of liver injury are also postulated. Severe constipation due to opioid administration may lead to increased intestinal permeability and bacterial translocation.[179,180] Opioid use has also been associated with derangement of cholesterol and bile acid metabolism, though the exact mechanism by which this occurs remains largely unknown.[181–186] However, the direct and non-direct effects of opioids on liver disease remain an area in need of additional research and may be difficult to isolate from other opiate-related liver diseases, such as viral hepatitis.

Opioid epidemic and liver transplant

Impact on the organ donor pool

There remains a profound global discrepancy between the supply and demand of donor organs. There are currently over 100,000 patients awaiting transplant for all organ types in the U.S., and in 2018 only 10,721 deceased donors.[187] In 2000, drug overdose deaths represented less than 6% of donors in all 50 states.[188] However, organ donors with overdose-related deaths have rapidly increased in the setting of the opioid epidemic. Between 2003 and 2014, the relative increase in overdose as the cause of death among organ donors reached 350%.[189] From 2000 to 2016, the median number of transplants from overdose-death donors increased from 2 to 10 across 274 transplant centres nationwide.[188] In 2016, the percentage of deceased donors who died of drug overdose was at minimum 10% in 29 states, but reached above 20% (in Maryland and New York) or even 30% (Massachusetts and New Hampshire) in some states (Fig. 4).[188,189] While all Organ Procurement and Transplantation Networks (OPTN) regions have seen increases in donor organs from drug overdose, the states with the highest growth including New Jersey, Pennsylvania, Delaware, Maryland, West Virginia, Michigan, Indiana, Ohio, and Washington DC, mirroring the high rates of drug overdose deaths attributable to the opioid epidemic in those areas of the U.S. (Fig. 5).[188] Overdose-death donors tend to be white

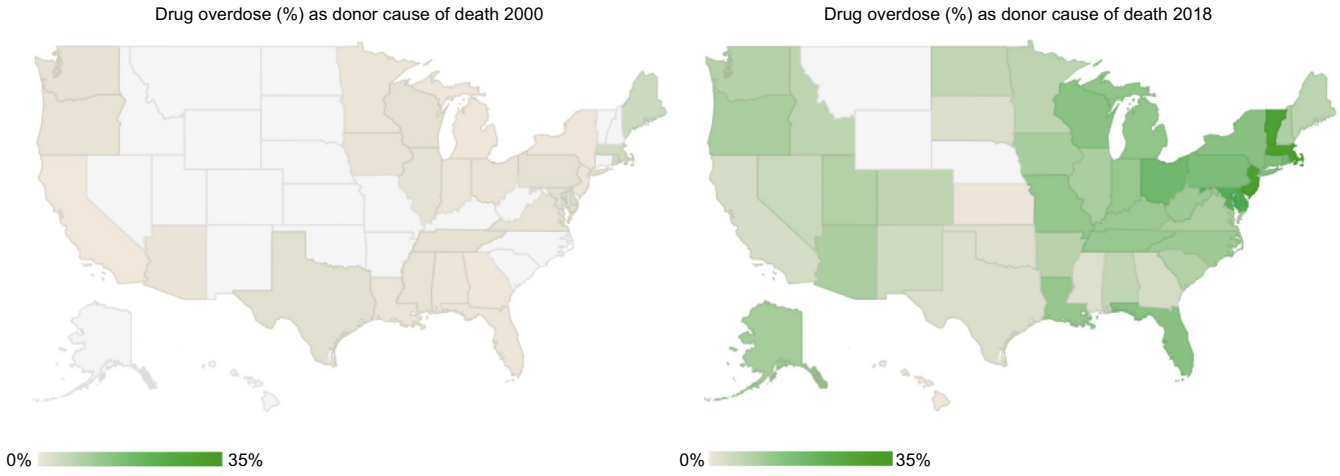

Fig. 4. Percentage of overdose-death donors in state-wide donor pool, 2000 and 2018.[187] Donor mechanism of death was categorized as overdose (drug intoxication) using the cause of death from the OPTN database of donors.

(86.3%), and younger (median age 31) when compared to donors who died due to cardiovascular disease (median age 47) or cerebrovascular accident (median age 52).[189] Moreover, the fraction of decreased donors <40 years of age who died of drug overdose rose from 3.6% in 2003 to 11.7% in 2014.[189] Taken together, these donor trends overlay those seen among the citizens disproportionately affected by the current opioid epidemic.

In total, 3,533 transplants from overdose donors were performed in 2016 (1,804 kidney, 1,013 liver, 454 heart, 262 lung) compared to only 149 in 2000.[188] The largest percentage increase in donors from overdose-related deaths was seen in liver transplant. Between 2003 and 2014, 40% of the overall increase in deceased donor liver transplants were a result of drug overdose deaths (Fig. 6).[189]

In addition to increased numbers, patients who receive organs from overdose-death donors maintain non-inferior and, in some cases, superior outcomes to other donor types. The clinical and demographic characteristics of these drug overdose donors have some favourable aspects with regards to donor quality, as they have fewer medical comorbidities compared to donors from other causes of death, and therefore afford similar or better outcomes compared to others. Among liver transplant recipients who received overdose death organs, patient survival rates from 2000 to 2017 were 76.8%, compared to 76.4% for trauma-death donors, and 71.9% for medical-death donors.[188] Similar rates of 5-year survival between overdose-, trauma-, and medical-related deceased donors have been reported in heart, lung, and kidney recipients as well.[190–192] After adjustment, survival differences among patients who received grafts from overdose-death donors were highest in lung transplant recipients (+3.9%) and lowest in kidney

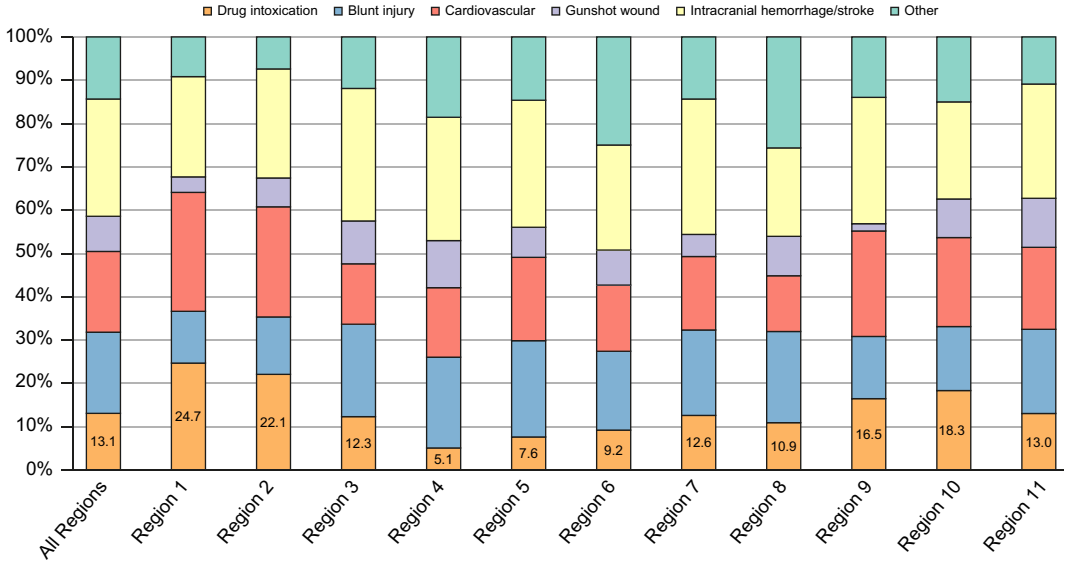

Fig. 5. Regional variation in percentage of drug-overdose death donors in 2018.[187]

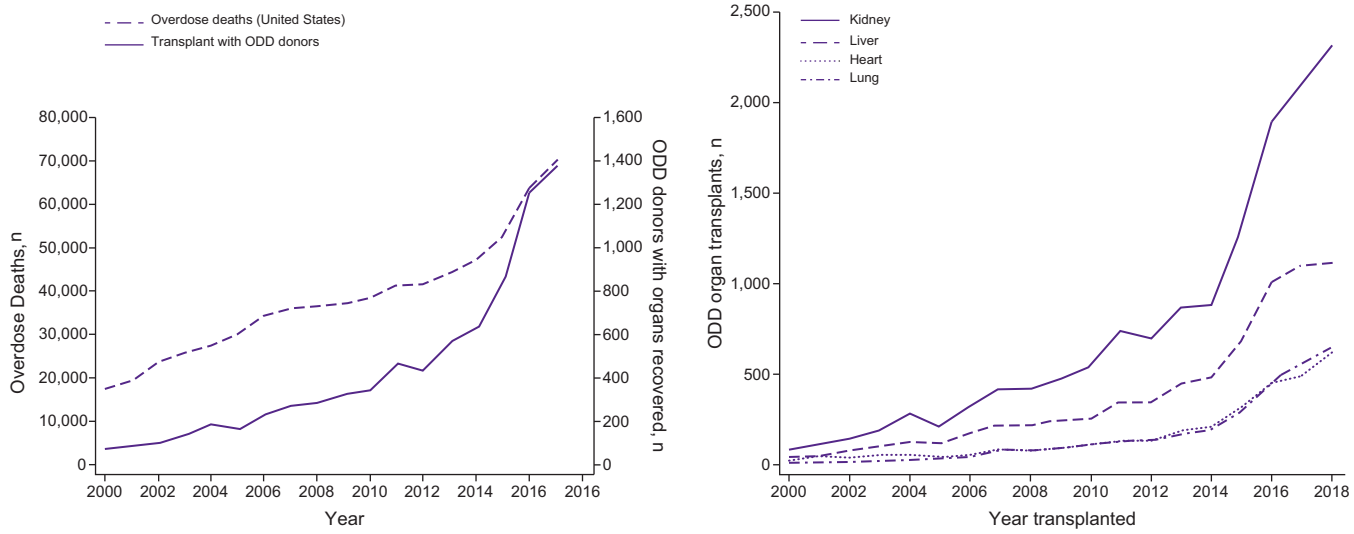

Fig. 6. Overdose deaths and overdose death donors with organs recovered and transplants performed using ODD organs by organ type, 2000-2018.[187] ODD, overdose-death donors.

recipients (-3.1%), compared with trauma-death donors, which were traditionally considered to be the highest quality donors.[188] Compared with medical-death donors, standardized 5-year survival differences ranged from 2.1% higher in kidney recipients, to 5.2% higher in lung transplant recipients.[188] Since trauma-death donors are likely to offer optimal grafts, observations that overdose-death donors achieve 5-year survival rates that are equal to or even higher than trauma-death donors indicate a potential opportunity to safely increase the donor pool.

Underutilization of overdose-death donor organs and risk of infection

Transmission

Despite the increase in donors available due to overdose deaths, these organs remain underutilized. Between 2000 and 2017, one study identified a total of 2,306 donor organs in the U.S. (1,665 kidney, 501 liver, 117 heart, 23 lung) obtained from overdose-death donors that were discarded.[188] The percentage of discarded organs from drug overdose-death donors (14.1% kidney, 8.8% liver, 1.0% heart, 8.1% lung) was higher across all organs when compared with trauma-death donors (8.8% kidney, 6.8% liver, 0.6% heart, 5.9% lung) despite evidence that survival outcomes from these different types of donors are at minimum, equivalent.[188] This remained true for liver grafts even after adjusting for HCV and increased-infectious risk status. The driving force behind the continuous discard of overdose-death donor organs is mostly due to a fear of increased infection risk, as well as the increased prevalence of HCV infection seen in these organs.[193,194]

However, the currently used nucleic acid testing (NAT) to detect viral infections is very sensitive, and the risk of HCV, HBV, or HIV transmission in NAT-negative donors is exceedingly low. Thus many have advocated for the use of all of these organs, since the alternative of remaining on the waitlist likely portends worse outcomes.[195] Waitlisted patients have a greater chance of survival if they agree to accept increased risk donor organs compared to those who remain on the waitlist, and the risk of death outweighs the risk of possible infection transmission.[195–197] The prevalence of HCV-positive overdose-death donors, originally defined by the United Network for Organ Sharing as HCV antibody seropositivity, but only recently by HCV-viraemia, has risen in recent years and remains higher than that of trauma-death and medical-death donors.[190,191] Since 2000, the prevalence of HCV among overdose-death donors increased significantly from 7.8% to 24.2% in 2016 and 30.0% in 2017, while remaining relatively unchanged for trauma-death donors and medical-death donors.[190]

Moreover, Public Health Service (PHS) defined "increased risk" status is more common among overdose-death donors than trauma-or medical-death donors (56.4%, 14.3%, 8.8%, respectively).[190,198] The 2013 PHS guidelines recommend designating potential donors with "unknown" medical or behavioural history as "increased risk," which may account for the larger fraction specified as such.[198] However, negative donor NAT testing reduces the risk of transmission of HCV and HIV to negligible levels, with estimates of the risk of infection transmission during the window period around <1 in 1,000 for HCV and <1 in 10,000 for HIV.[199–202] The risk of a window-period infection for HCV, HBV, and HIV is incredibly low if testing

is performed more than 3 weeks after a potential exposure, and despite varying high-risk behaviour, remains below 1%.[203,204] More specifically, the estimated risk of window period infection among IV drug users, considered to be the highest risk, who are HCV and HIV NAT negative, is 0.3% and <0.1%, respectively.[203,204] Undetected events of HIV and HCV infection amount to 2.7 and 10.5 cases, respectively, per 100,000 person-years following transplant for patients who receive "increased risk" organs.[189,205]

HCV-viraemic donors

Largely due to the opioid epidemic in the U.S., there has been an increase in donors overall, and an increase in otherwise high donor quality and young HCV-viraemic donors in particular (Fig. 7).[206] Coupled with the availability and efficacy of anti-HCV therapy, there has been an increase in the utilization of HCV-viraemic donors, even for HCV-negative transplant recipients. This was recently addressed at a consensus conference that sought to formally distinguish "HCV-positive" and "HCV-viraemic" donors, and to advocate for a robust consenting process for recipients of these organs, given the unknowns about the safety of this approach.[206]

Among HCV-infected liver transplant recipients who receive HCV-positive grafts, survival has been shown to be no different than for HCV-negative patients.[191] Even with long-term follow-up years after transplant, both graft and recipient survival are equivalent to their non-HCV counterparts,[188,191] especially when younger donors are used.[207] The relative outcomes have been mixed in other organ types. While a portion of the data on kidney transplant recipients with chronic HCV who have received HCV-positive grafts have shown equivalent survival, a majority have shown poorer outcomes.[192,208] Moreover, survival of both heart and lung transplant recipients with chronic HCV in whom HCV positive donors were used has uniformly been worse,[209–212] though this is often in the setting of urgent transplantation and all of these studies were prior to the availability of effective anti-HCV therapy.

The currently available pangenotypic DAAs have been shown to be curative in over 95% of patients infected with HCV in a variety of settings, including those with renal impairment, advanced cirrhosis, patients awaiting transplant, and perhaps most significantly, in the post-transplant period.[213–224] As a result, several small studies have now reported on the use of HCV-viraemic donors in HCV-negative recipients. While no long-term results are available, limited short-term data from liver, kidney, heart and lung transplant recipients have been published. The initial small clinical trials were in kidney transplant recipients who were treated with elbasvir-grazoprevir for 12 weeks and reported 100% SVR and excellent kidney function at 1-year post-transplant.[225–227] For these trials, donor genotyping was required because the baseline regimen supplied was not pangenotypic. There are small series of heart transplant recipients with excellent treatment results as well.[228,229] While overall these experiences have been encouraging, the first treatment failures were reported in 2 lung transplant recipients of HCV-viraemic donors, 1 who experienced a clinically apparent hepatitis with relapse and 1 with biopsy-proven fibrosing cholestatic hepatitis.[230] This highlights the ongoing need for significant patient education and a comprehensive informed consent process when considering HCV-viraemic organs. However, careful use of these organs is likely to shorten waiting times and decrease waitlist mortality in carefully selected patients.[231]

Conclusions

The current landscape of the opioid epidemic in the U.S. is bleak, as prescriptions for opioids remain at levels 4-fold higher than in 1999, at

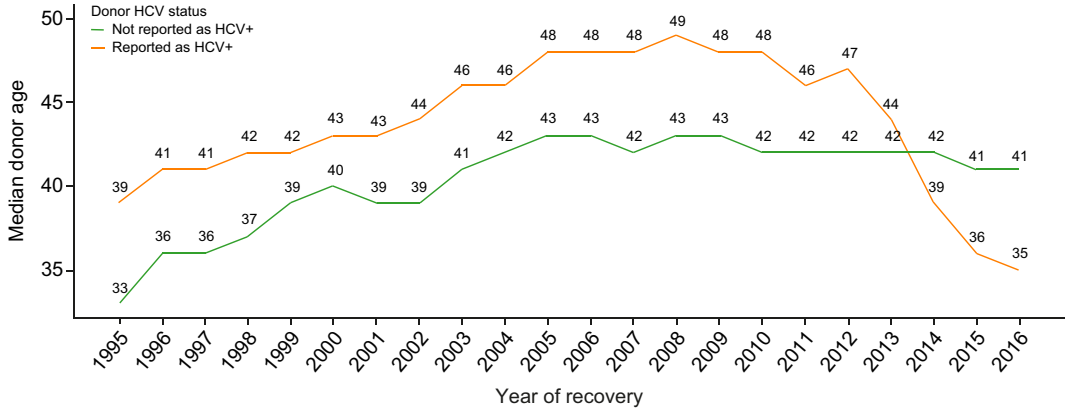

Fig. 7. Median deceased donor age by HCV serostatus, from 2012-2016.[206] Figure reproduced with permission from.[206]

the beginning of this crisis.[21] This epidemic is not limited to the U.S. but now impacts many regions of the world. The impact of pervasive opioid use on human health is vast, but liver disease is of particular concern. The rising incidence of HCV in the U.S., especially among young people, will require changes in screening and linkage to care in order to effectively manage and eliminate this epidemic. Additional efforts are required to understand the contribution of HBV infection and alcohol in this population, as well as the pathophysiological mechanisms that drive liver disease development in these patients. Transplantation has also been significantly impacted by the epidemic with increased numbers of overdose donors and thus increased use of donors that risk disease transmission. It is clear that more must be done to better understand and combat this epidemic in the U.S. and other parts of the world.

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Authors' contributions
Elizabeth C. Verna: Acquisition of data, Drafting of manuscript, Critical revision, including final approval for publication. Aaron Schluger: Acquisition of data, Drafting of manuscript, Critical revision, including final approval for publication. Robert S. Brown Jr.: Acquisition of data, Drafting of manuscript, Critical revision, including final approval for publication.

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