Harm Reduction: A Missing Piece to the Holistic Care of Patients Who Inject Drugs

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**Background.** The rise in injection drug use (IDU) has led to an increase in drug-related infections. Harm reduction is an important strategy for preventing infections among people who inject drugs (PWID). We attempted to evaluate the harm reduction counseling that infectious diseases physicians provide to PWID presenting with infections.

**Methods.** An electronic survey was distributed to physician members of the Emerging Infections Network to inquire about practices used when caring for patients with IDU-related infections.

**Results.** In total, 534 ID physicians responded to the survey. Of those, 375 (70%) reported routinely caring for PWID. Most respondents report screening for human immunodeficiency virus (HIV) and viral hepatitis (98%) and discussing the risk of these infections (87%); 63% prescribe immunization against viral hepatitis, and 45% discuss HIV preexposure prophylaxis (PrEP). However, 55% of respondents (n = 205) reported not counseling patients on safer injection strategies. Common reasons for not counseling included limited time and a desire to emphasize antibiotic therapy/medical issues (62%), lack of training (55%), and believing that it would be better addressed by other services (47%). Among respondents who reported counseling PWID, most recommended abstinence from IDU (72%), handwashing and skin cleansing before injection (62%), and safe disposal of needles/drug equipment used before admission (54%).

**Conclusions.** Almost all ID physicians report screening PWID for HIV and viral hepatitis and discussing the risks of these infections. Despite frequently encountering PWID, fewer than half of ID physicians provide safer injection advice. Opportunities exist to standardize harm reduction education, emphasizing safer injection practices in conjunction with other strategies to prevent infections (eg, HIV PrEP or hepatitis A virus/hepatitis B virus vaccination).

**Keywords.** Harm reduction; patients who inject drugs; substance use disorder.

The United States is in the midst of an injection drug use (IDU) epidemic. Close to 3.7 million people injected drugs in 2018 [1]. Overdose deaths have continued to rise steadily, with an estimated 109,000 people dying of overdose in 2021 [2]. There has been a concurrent increase in infectious complications of IDU, including outbreaks of human immunodeficiency virus (HIV) infection [3–5], viral hepatitis [6–8], and bacterial infections [9]. This confluence of epidemics—referred to by some as the “opioid syndemic”—has increasingly involved nonopioid drugs as well.

Harm reduction has been defined as “a set of practical strategies and ideas aimed at reducing negative consequences associated with drug use.” [10] This broadly includes a wide range of evidence-based interventions built on a philosophy that patients who use drugs should receive evidence-based and risk-mitigating care, regardless of their substance use. The use of sterile injection equipment, appropriate skin preparation, and adequate preparation of drugs can reduce the risk of injection-related infections [11, 12]. Vaccinations, such as those against hepatitis A, hepatitis B, and tetanus, as well as medications to prevent HIV infection (ie, pre-exposure prophylaxis [PrEP]), can also dramatically reduce the risk of infectious complications associated with IDU. Taking active steps to help patients prevent health complications associated with drug use is part of the harm reduction model, which is one of the pillars of holistic care for patients who inject drugs (PWID) [13].

Infectious diseases (ID) physicians are increasingly responsible for treating the infectious complications of IDU, both during acute illness and as part of long-term care (eg, hepatitis C or HIV). However, limited data exist regarding ID physician perceptions and practices when caring for PWID. In a previous Emerging Infections Network (EIN) survey, administered in 2017, fewer than half of respondents felt comfortable assessing patient injection practices and offering counseling on infection prevention [14]. The current study sought to better understand the current harm reduction practices
promoted by ID physicians in order to inform future efforts to improve longitudinal care for PWID.

METHODS

In April 2022, an electronic survey was distributed via e-mail to all adult ID physicians who are members of the EIN [15]. The goal of the survey was to evaluate current standards of care for PWID and determine which harm reduction strategies ID physicians commonly recommend to PWID to reduce future injection-related infections. No incentive was offered for participation. The survey included 10 questions that were developed collaboratively by the authors, with input from addiction specialists, addressing antibiotic practices when caring for PWID, the use of vaccinations to prevent viral infections (eg, hepatitis A, hepatitis B, and tetanus), initiation of PrEP to prevent HIV infection, screening for sexually transmitted infections (STIs), and counseling on safer injection practices.

While medications for opioid use disorder (MOUD) may not be considered part of the spectrum of harm reduction by some groups, the authors believe that offering low-barrier access to MOUD falls in line with the harm reduction–based principle of meeting patients where they are, and they therefore included questions regarding MOUD as part of the survey. The survey can be viewed in Supplement 1. Respondents who reported treating patients with IDU were included for further analysis. Respondents were not required to answer all questions. The online survey remained open for 4 weeks. Two weekly reminders were sent to increase response rates. We collected standard participant demographics and report descriptive statistics from the survey. No patient information was used in this study, which was thus exempt from the need for patient consent.

Analysis of the survey was performed using IBM SPSS Statistics for Windows software, version 28 (IBM). Categorical variables were compared using $\chi^2$ tests, and differences were considered significant at $P < .05$.

RESULTS

Demographics

The survey was distributed to all members of the EIN. For the purposes of response rate, we included 1449 EIN physician members with an adult ID practice who have previously responded to an EIN survey, of whom 37% (534 of 1449) responded. Baseline characteristics of survey respondents are reported in Table 1. Participants were drawn from across the United States and were employed in a range of practice settings, including academic, community, and government hospitals. Years of ID practice since fellowship varied among respondents (Table 1). Of those who responded, 70% (359 of 534) reported routinely caring for PWID. Within this subgroup of respondents, 70% (263 of 359) reported caring for PWID at least multiple times per month.

### Table 1. Baseline Characteristics of Respondents

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Respondents, No. (%)</th>
</tr>
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<tbody>
<tr>
<td><strong>Geographic region</strong></td>
<td></td>
</tr>
<tr>
<td>South Atlantic</td>
<td>100 (19)</td>
</tr>
<tr>
<td>Pacific</td>
<td>92 (17)</td>
</tr>
<tr>
<td>Mid Atlantic</td>
<td>76 (14)</td>
</tr>
<tr>
<td>East North Central</td>
<td>71 (13)</td>
</tr>
<tr>
<td>West North Central</td>
<td>62 (12)</td>
</tr>
<tr>
<td>New England</td>
<td>44 (8)</td>
</tr>
<tr>
<td>West South Central</td>
<td>33 (6)</td>
</tr>
<tr>
<td>Mountain</td>
<td>32 (6)</td>
</tr>
<tr>
<td>East South Central</td>
<td>18 (3)</td>
</tr>
<tr>
<td>Canada/Puerto Rico</td>
<td>6 (1)</td>
</tr>
<tr>
<td><strong>Length of practice, y</strong></td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>193 (36)</td>
</tr>
<tr>
<td>15–24</td>
<td>101 (19)</td>
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<tr>
<td>5–14</td>
<td>164 (31)</td>
</tr>
<tr>
<td>&lt;5</td>
<td>76 (14)</td>
</tr>
<tr>
<td><strong>Primary hospital type</strong></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>202 (38)</td>
</tr>
<tr>
<td>Community</td>
<td>138 (26)</td>
</tr>
<tr>
<td>Nonuniversity teaching hospital</td>
<td>126 (24)</td>
</tr>
<tr>
<td>VA/Department of Justice</td>
<td>35 (7)</td>
</tr>
<tr>
<td>City or county hospital</td>
<td>29 (5)</td>
</tr>
<tr>
<td>Outpatient only</td>
<td>4 (1)</td>
</tr>
<tr>
<td><strong>How often ID physicians care for PWID</strong></td>
<td></td>
</tr>
<tr>
<td>Do not routinely care for PWID</td>
<td>159 (30)</td>
</tr>
<tr>
<td>Multiple times a week</td>
<td>111 (21)</td>
</tr>
<tr>
<td>Multiple times a month</td>
<td>162 (30)</td>
</tr>
<tr>
<td>Once per month</td>
<td>59 (11)</td>
</tr>
<tr>
<td>Less than monthly</td>
<td>42 (8)</td>
</tr>
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</table>

Abbreviations: ID, infectious diseases; PWID, people who inject drugs; VA, Veterans Administration.

Access to Subspecialty Addiction Medicine Care and MOUD

Only 223 of 373 respondents (60%) reported having access to outpatient addiction medicine services, including access to MOUD, with an even smaller number having access to inpatient addiction medicine consultation (200 of 373 [54%]). Multiple respondents included additional comments in their surveys regarding the need for addiction medicine services when caring for PWID. One respondent commented that it is “difficult, if not impossible in the absence of addiction services to get very far,” while another responded, “we need better resources for treatment of the primary problem.” This was a common theme repeated in many of the comments.

Fewer than half of ID physicians reported linking patients to a prescriber for MOUD as part of standard care for injection-related infections (166 of 374 [44%]). Overall, most ID physicians surveyed (254 of 359 [68%]) reported not having an X-waiver (a specialized Drug Enforcement Administration designation that was required to prescribe buprenorphine for
opioid use disorder [OUD]) and being uninterested in obtaining an X-waiver in the future (of note, this survey was administered before federal removal of the X-waiver requirement to prescribe buprenorphine for OUD). Among those who reported having an X-waiver, even fewer (15 of 45 [33.3%, or 4% of the total sample]) reported actively prescribing buprenorphine to patients. A small number of respondents (n = 20 [5%]) answered through free text that they had other groups that prescribed for them, were not allowed to prescribe buprenorphine by their practice, had an expired X-waiver, or did not know what an X-waiver was. As one respondent commented, “Management of OUD is critical in caring for our patients. At the most fundamental level, I am interested in providing this service. However, there are many practical barriers, including education for me as a prescriber and health system support/protocols/guidelines.” Very few ID physicians reported prescribing naloxone to PWID (78 of 374 [21%]), for reversal of opioid overdose, despite the lack of regulatory barriers to offering this life-saving medication (Figure 1).

Screening and Immunization Practices
When asked to consider what practice patterns form their standard care and counseling for PWID, ID physicians almost universally reported screening for HIV (98%) but were less likely to offer screening for other STIs, such as syphilis or gonorrhea (63%). Fewer than half reported discussing PrEP for HIV and linking to a provider if interested (45%). Similarly, screening for viral hepatitis was widely reported by ID physicians (98%); however, fewer physicians reported discussing the risks of viral infections (HIV, hepatitis B virus [HBV], or hepatitis C virus [HCV] infection) related to IDU (87%), and only 63% reported offering immunizations for hepatitis A and B to seronegative patients. Immunizations for tetanus were also uncommon, with only 36% of ID physician respondents routinely including this as part of standard care for PWID (Figure 1).

Physician Views on Harm Reduction Education
We queried survey participants regarding their perspectives on harm reduction philosophies and counseling practices. ID physicians largely reported positive attitudes toward harm reduction strategies. When asked to rate their agreement with specific statements, only a minority believed that recommending needle exchanges and/or safe injection practices enabled drug use (9.7%), while most either disagreed (28.7%) or strongly disagreed (51.7%) with that sentiment. However, when asked to describe their routine clinical practices, only 170 of 375 (45%) reported routinely incorporating harm reduction education on safer injection strategies into patient care. Among the 198 physicians who reported not providing counseling on safer injection strategies, the most common reason was that they had limited time with patients and wished to emphasize antibiotic therapy or other medical issues (122 of 198 [62%]), followed closely by physicians reporting that they did not feel educated or have appropriate training on safer injection strategies (108 of 198 [55%]) and/or that they believed that counseling on safer injection strategies was better addressed by other services (93 of 198 [47%]). Only a minority of
physicians reported concerns that counseling would be interpreted as promoting drug use or would increase a patient’s drug use (13 of 198 [7%]). This question allowed for multiple reasons to be selected, and totals add up to >100%.

When harm reduction counseling on safer injection strategies was provided, ID physicians varied substantially in the types of counseling routinely incorporated into their clinical practice. The most common recommendations included complete abstinence from IDU (n = 146 [72%]), handwashing and soap/water to clean injection sites (n = 127 [62%]), disposal of needles and drug equipment that were used before infection/admission (n = 110 [54%]), avoiding injecting into areas of skin breakdown (n = 108 [43%]), cleaning reused needles with alcohol and bleach (n = 99 [49%]), and using alcohol swabs before injecting (n = 61 [30%]). Of note, respondents were able to select multiple responses from each category (reasons for no counseling; counseling provided) regardless of whether they reported counseling patients routinely.

Using \( \chi^2 \) analysis, we evaluated demographic factors for correlation to the provision of harm reduction counseling. Size of hospital, practice setting, and the region of practice was not correlated with providing harm reduction counseling. However, the number of years an ID physician had been in practice was inversely correlated with providing harm reduction counseling (\( P < .001 \)), with recent graduates being more likely to provide harm reduction counseling (Figure 2).

**Free-Text Responses**

There were 104 free-text responses offered in response to the survey question, “Do you have any comments about providing medical care for PWID?” Of these responses, we found several predominant concerns, including limitations in resources, difficulty in accessing medications for treatment of addiction, and concern of medicolegal ramifications when offering best practice care. There seems to be strong interest in the use of long-acting lipoglycopeptides as treatment in this population, which is stymied by a lack of evidence and guidance. Although several respondents felt that they did not have the expertise or experience to provide addiction care, many suggested that the ID community should take the lead in coordinating these efforts. All free-text responses can be reviewed online (https://www.int-med.uiowa.edu/Research/EIN/PWID2022_comments.pdf). Selected quotes are displayed in Box 1.

**DISCUSSION**

Our findings offer an important national sample of the current harm reduction, screening and vaccination practices of ID physicians caring for PWID. We found that most ID physicians generally supported evidence-based harm reduction principles, including recommending needle exchanges and prescription of naloxone. ID physicians also reported routinely screening for HIV and viral hepatitis among PWID. However, fewer reported offering preventive vaccinations, and fewer than half reported offering or linking to HIV PrEP. ID providers were relatively divided on personally providing guidance on safer injection strategies—which may be an important practice to prevent future bacterial infections.

The opioid synderm has challenged the existing healthcare infrastructure. Traditional care pathways, such as patients presenting to the hospital for acute illnesses and then following up in primary care settings for vaccination and health counseling, may not be effective. PWID are frequently uninsured or underinsured and lack access to stable housing, and they may struggle navigating outpatient follow-up appointments [16, 17]. To directly address these barriers to care, the Centers for Disease Control and Prevention has suggested that nontraditional healthcare settings, including acute hospitalization or other community health settings, provide PWID service bundles that include key aspects of preventive care and treatment services. Recommended services include MOUD, targeted preventive healthcare (vaccinations for hepatitis A and B and HIV PrEP), and testing and treatment for infectious diseases [18, 19]. While not yet widely implemented, strategies using hospital admission for complications of IDU as an opportunity to provide preventive/primary care may be crucial for reaching this population. However, as our survey reveals, there remain substantial questions about the ownership of these responsibilities, ranging from the timing and location of immunizations (ie, inpatient vs outpatient settings), to when screening for other infections, such as HIV, HBV, and HCV, should occur, and
Box 1. Selected Quotes From Free-Text Responses

“I would love to see more joint ID fellowship/addiction medicine fellowships and I would like to see treatment of SUD become a core competency for all ID fellows.”

“I have no objections to counseling or providing services to assure safe injecting practices. However, institutionally and locally support services are minimal and personally it is not where I am going to invest my time, although I would definitely support development and availability of these services.”

“Management of OUD is critical in caring for our patients. At the most fundamental level, I am interested in providing this service. However, there are many practical barriers, including education for me as a prescriber and health system support/protocol/guidelines. Given the number of patients who primarily need ID care (which is often limited outside of large urban areas), I would really like to partner with PCPs, psychiatrists, etc. who have this expertise and co-manage patients with OUD.”

“There are innumerable upstream structural determinants of health pressing down on this population that optimally would be addressed as part of their overall care if we are approaching their care as a medical system trying to pursue optimized individual and population health.”

“There are not enough ID providers in my area to manage the patient volume for strictly infectious disease diagnoses. Subsequently I am absolutely unwilling to try to overextend myself even further to try to address prescription of opioid replacement therapy, although we DESPERATELY need more help and resources dedicated to this end.”

Abbreviations: ID, infectious diseases; OUD, opioid use disorder; PCPs, primary care physicians; SUD, substance use disorder.

which consultation services should provide harm reduction counseling and MOUD.

It is noteworthy that while ID physicians have been strong proponents of vaccinations, many did not report routinely incorporating immunizations for hepatitis A, hepatitis B, or tetanus into their routine clinical care for PWID. Offering and administering vaccines in the United States has historically been considered an outpatient practice. However, current outbreaks of hepatitis A occurring across the United States suggest that these views may need to be revisited [20]. There is now increasing evidence that many outbreaks may occur via percutaneous routes [8, 20], with hepatitis A surviving on needles and syringes for up to 10 weeks [21]. Increasing vaccination among hospitalized PWID, who are an at-risk group for hepatitis A infection and may not present to outpatient clinic appointments, may help attenuate future outbreaks.

Another preventable viral illness closely linked to IDU is HIV infection. The use of injection opioids has been linked to multiple HIV outbreaks in the United States [22]. Despite being an efficacious [23] and cost-effective treatment for the prevention of HIV infection [24], PrEP for HIV remains underused in this population [25]. This is likely related to a lack of perceived HIV risk, as well as lack of knowledge of, and interest in, PrEP among PWID [26]. Interestingly, however, engagement with PrEP may create opportunities to offer other forms of preventive care [27], effectively linking PWID into a primary care system that was previously not accessible.

Screening for bacterial STIs in admitted PWID may be another missed opportunity [28]. PWID are at an increased risk for STIs, likely related to reduced use of prophylaxis, reduced opportunities for screening, and transactional sexual encounters. One analysis suggested that almost 17% of asymptomatic PWID screened for STIs, as part of a care bundle, were positive for STIs [29]. Rates of syphilis, particularly, have been increasing in many regions of the United States, with an epidemiologic link to those who use drugs [30].

Addiction medicine specialists are increasingly being recognized as critical leaders in providing care for PWID. However, many medical centers lack access to subspecialty-trained addiction medicine physicians. Recognizing these limitations, there has been a growing call for ID physicians to fill this gap for patients with infectious complications of IDU [31]. One way ID physicians can fill this gap is by prescribing MOUD to PWID with infectious complications of injection opioid use. MOUD, including buprenorphine, are safe, evidence based, and effective in decreasing the all-cause mortality rate and IDU-related risk behaviors associated with HIV transmission [32, 33]. Previous X-waiver requirements created barriers to prescribing buprenorphine, though this requirement was recently discontinued by the Drug Enforcement Administration [34]. However, it is unclear how many ID physicians will want to add buprenorphine prescribing to their ever-growing list of medical competencies.

X-waiver uptake has historically been low among ID physicians [35]. Adding addiction management to traditional ID care likely presents an opportunity cost to the ID physician, who may feel pulled away from other critical work. This sentiment was expressed in some of the free-text comments collected in this survey. Interestingly, years since fellowship graduation was inversely correlated with X-waiver attainment [35], which mirrors our data around counseling. Thus, knowledge gaps related to clinical training, or generational differences in perceived role of the consultant, might represent additional barriers to both prescribing MOUD and counseling on harm reduction. Continuing medical education targeting in-practice ID clinicians may improve comfort in these topics and reduce some of these obstacles.

It has been suggested that ID consultation, during a hospital admission for complications of drug use, is an opportune time to offer a bundled harm reduction program that screens PWID for IDU-associated infections, provides vaccinations, offers harm reduction counseling, and initiates treatment with MOUD [36]. However, the pragmatic deployment of this type of program without additional resources may be logistically complicated. Counseling and preventive services are generally poorly reimbursed, which may reduce the motivation for ID physicians to take the time to provide these services. Indeed, one common barrier ID physicians reported in the survey was that they are currently too busy to provide additional counseling. In addition, some hospitals do not carry outpatient vaccines on their formularies, and though screening for STIs and offering PrEP are something that ID physicians can easily perform, it does add additional time and complexity to the encounter.
Furthermore, this model may not work in community hospitals without regular ID support.

Perhaps one evidenced-based way for ID physicians to improve care for PWID is through the formation of multidisciplinary care teams. Creating standard pathways of care for PWID admitted with complications of drug use allows patients to benefit from integrated, interprofessional care aimed at serving their holistic needs. The composition of this team will likely vary based on local resources. ID physicians with stronger local resources may be able to link patients to local opioid treatment programs or addiction medicine providers or internists who regularly prescribe MOUD. However, areas with less robust resources may need to seek creative solutions to gaps in care, such as telehealth [37] or the creation of localized treatment algorithms or electronic medical record bundles. Other allied health professionals, such as peer recovery specialists, nurse educators, and pharmacists, may also be able to provide counseling, education, and vaccinations. Integrated care teams have been successful in both inpatient and outpatient settings and provide a model for hospitals looking to improve the care of PWID [38–40].

Substantial resources will be needed to effectively implement low-barrier and nontraditional models of care for PWID. One recent modeling analysis suggested that the average primary care physician would incur approximately $13,000 in excess costs (both direct and indirect) over a 5-year period if they were to incorporate harm reduction into their practice. Notably, this was associated with a 33% decrease in mortality rate and decreased costs of hospitalization [41]. Given the required investment, we believe that mechanisms to compensate this work are needed both to encourage the development of such programs and promote their sustainability. It is likely that payors and/or health systems will need to create alternative funding models to incentivize this care, which is frequently uncompensated. The realization that IDU-related hospitalizations represent a significant financial loss for the healthcare system should be motivation for investment in this space [42].

ID clinicians play an important role in the healthcare system, interacting with patients who often do not have the benefit of continuity of care. Despite the above limitations, there is an important opportunity for ID clinicians to improve the care of PWID. With the removal of barriers to prescribing buprenorphine, clinicians in many disciplines can feel empowered to prescribe this medication. Naloxone, which for many can be lifesaving, was recently approved by the Food and Drug Administration to be over the counter and in most of the United States is available for purchase without a prescription, which means it could easily be incorporated into routine recommendations and counseling for PWID. Vaccinations and screening easily fall within the realm of the ID clinician. Creating replicable note templates, order sets, or resource documents can, with upfront time investment, lead to dramatically improved outcomes and enable clinicians to provide more holistic care.

Our study has several notable limitations. First, EIN is a convenience sample of physicians and overrepresents academic medical centers and larger hospitals; thus, our results may be less generalizable to other ID physicians at smaller community hospitals. Second, we relied on self-reports, which are subject to recall bias. It is likely that our findings may be an overestimate of real-world screening and counseling that is provided by ID physicians. It is possible that some ID physicians may have reported screening for HIV, HBV, HCV, and STIs and comprehensive counseling on safer injection strategies because they believed this was the “correct response” on the survey, whereas in daily clinical practice these quality measures may often be missed in the time pressures of busy clinical practices.

In the setting of the escalating overdose crisis, ID physicians endorsed evidence-based harm reduction strategies, such as syringe exchange, naloxone, and counseling on safer injection strategies. Furthermore, ID providers self-reported doing an excellent job of screening PWID for viral hepatitis and HIV. However, gaps exist in providing preventive care for PWID, such as vaccinations and harm reduction counseling. How these gaps in care should be addressed on a national level remains unclear. A tailored approach based on local resources will likely be necessary. We suggest that ID physicians work with hospitals to develop multidisciplinary teams based on local resources to ensure that PWID receive adequate screening for ID, obtain access to medication treatment, if interested, and undergo counseling to reduce their risk of future infections and hospitalizations.

**Supplementary Data**

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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**References**


