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The syndemic of opioid misuse, overdose, HCV and HIV: Structural-level causes and interventions

David C Perlman[1,2,*] and **Ashly E Jordan**[2,3]

[1]Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, New York, NY 10003 USA

[2]Center for Drug Use and HIV Research, New York, NY 10003 USA

[3]City University New York, Graduate School of Public Health and Health Policy, New York, NY 10016 USA

Abstract

Purpose of review—This article reviews the case for recognizing 1) the epidemics of opioid misuse, overdose, hepatitis C virus, and HIV as a syndemic, and 2) the importance of examining and addressing structural factors in responses to this syndemic. We focus on the current syndemic in the US, but also consider data from other locations to highlight the issues existing and arising in various contexts.

Recent findings—Advances in multi-level theory and statistical methods allow sound ecologic and multi-level analyses of the impact of structural factors on the syndemic. Studies of opioid misuse, overdoses, hepatitis C virus and HIV demonstrate that area-level access to healthcare, medication assisted treatment of opioid use disorders, sterile injection equipment, and overdose prevention with naloxone, as well as factors such as opioid marketing, income inequality, intensity of policing activities, and health care policies, are related to the prevalence of substance misuse, overdoses, infection risk and morbidity. Structural variables can predict area-level vulnerability to the syndemic. The implementation of combined prevention and treatment interventions can control and reverse components of the syndemic.

Summary—Recognizing and monitoring potent structural factors can facilitate the identification of areas at risk of vulnerability to the syndemic. Further, many structural factors are modifiable through intervention and policy to reduce structural vulnerability and create health-enabling environments. Evidence supports the immediate implementation of broader HCV and HIV testing and substance use screening, medication assisted treatment, needle/syringe exchange programs, naloxone programs, increased population-level implementation of HCV treatment, and further

*Corresponding Author David C Perlman, MD, Professor of Medicine, Icahn School of Medicine at Mount Sinai, Chief, Infectious Diseases, Mount Sinai Beth Israel, 350 East 17th St, 19th Floor, New York, NY 10003, (p) 212-844-8549, (f) 212-844-8556, david.perlman@mountsinai.org.

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This article does not contain any studies with human or animal subjects performed by any of the authors.

attention to structural-level factors predicting, and contributing to, area-level vulnerability, such as degrees of opioid marketing, distribution, and prescribing.

Keywords

opioids; structural determinants of health; hepatitis C virus; HIV; overdose; opioid use disorders

Introduction

The United States (US) is in the midst of an epidemic of opioid misuse and its consequences[1-3]. In fact, the opioid epidemic is probably best viewed as a set of inter-related and overlapping epidemics of the misuse of prescription and illicit opioids, fatal and non-fatal overdoses, and HIV and hepatitis C virus (HCV) transmission[1, 4-8]. These inter-related epidemics are occurring in communities and areas already marginalized by a range of structural conditions including poverty, de-industrialization, underemployment and rising inequality[9-15]. These overlapping epidemics and contextual conditions can productively be viewed as a *syndemic*, and recognition of this would strengthen optimal public health and policy responses[13, 16, 17]. Further, optimal responses will require recognition of the multi-level forces contributing to the development and perpetuation of the opioid misuse, overdose, HCV and HIV syndemic[17-21].

There is increasing recognition of the importance of what have variously been called *supraindividual, social*, or *structural* determinants, or *area-* or *place-based* factors, in shaping the epidemiology of health generally, and specifically with respect to the components of this syndemic[11, 17, 19, 20, 22-24]. Area-level access to healthcare, substance use treatment, sterile injection equipment, and overdose prevention (e.g., naloxone), and factors such as income inequality, segregation, degrees of opioid marketing, and mass incarceration and degrees of aggressive policing activities, have all been shown to be related to risk and disease rates and prevalence of drug misuse[23, 25-31]. Conceptual models and increasing data support an important role of structural factors in shaping the opioid misuse, overdoses, HCV, and HIV epidemics, and point toward a central role of structural-level responses to the syndemic[11].

Factors including the previous underdevelopment of relevant theory, methods, and of training for research and health professionals, and variable and incomplete understandings of the importance of structural health influences by health professionals, general public and policymakers, have contributed to the under-attention to modifiable structural factors which are driving this syndemic[11, 13]. Structural factors are often important fundamental causes of health outcomes, and are often modifiable factors whose importance should be studied and used to inform public health monitoring, clinical programs, and policies and funding[18, 23, 28].

We will review: 1) the case for recognizing the epidemics of opioid misuse, overdose, HCV, and HIV as a syndemic (referred to here as "*the syndemic*" or individually as "*component(s) of the syndemic*") and 2) the importance of examining and addressing structural factors in public health and policy responses to this syndemic. We will briefly review advances in multi-level theory and methods, and then review selected recent work examining a range of

structural factors with respect to the components of the syndemic. We will discuss structural factors and interventions that are being, or could be, examined or implemented to: 1) predict components of the syndemic, 2) respond to the syndemic and its components, and 3) prevent future re-emergences these epidemics in the US and elsewhere. We focus on the current syndemic in the US, but also consider data from other locations to highlight the issues existing and arising in various contexts, both because a) trends towards rising inequality in the US resemble those of low- and middle-income settings, and b) the forces shaping the current US syndemic pose analogous risks to non-US settings that require global public health planning.

Theory and methods for examining structural influences

A key assumption of standard multivariate analysis is the independence of the outcome variable from all independent variables. When analyses examine group-level independent variables and a group-level outcome (i.e., ecologic studies) the assumptions of independence are generally met and standard multivariate analysis is appropriate[32]. When analyses take into consideration data at two or more levels (i.e., multi-level studies), the assumption of independence is commonly violated (e.g., individual-level income is not the same construct as the median income in that individual's area, but they are not independent) as observations at one level tend to be clustered at another level (e.g., residents are clustered into neighborhoods). If clustering of data is not accounted for, standard errors may be under- or over-estimated[33]. Earlier approaches to handle clustered data included 'population average models' which account for correlation between levels and distinguish structural from individual health effects. *Multi-level models* are powerful approaches to more fully account for the hierarchical relationships between levels of data[32, 33].

There are a range of multi-level theories to guide research and public health responses[28]. While these theories have some key differences, they share the understanding that forces can operate at multiple levels and that these forces can act in a variety of ways (e.g., as mediators, or primary causes) to impact outcomes[18, 28, 33]. Two major conceptual frameworks that can help focus attention on multi-level factors relevant to these overlapping epidemics are: *ecosocial theory* and *Rhode's social-structural production of substance use related risk*[21, 28].

Ecosocial theory provides a framework recognizing the importance of constructs of scale and macro structural factors in the production of risks and disease. It highlights that structural forces should not be viewed as the more 'distal' end of a linear path beginning with 'proximal' individual-level factors, but must be viewed instead as dialectically interrelated forces[20]. Rhodes provides an elaboration of this framework conceptualizing the risk environment "as the space-whether social or physical- in which a variety of factors interact to increase the chances of drug-related harm" where important components include: movements of populations; area-level deprivation and social capital; legal status of drug use; needle and syringe exchange programs (NSPs) and medication assisted treatment (MAT) for opioid use disorders (OUD); criminal justice activities; and the impact of '*big events*'[21, 34]. A key corollary of the concept of a risk environment is that environments may be modified to become *health-enabling environments*[19].

Pathways through which structural variables may act

Central to understanding the importance of structural factors in the production of disease and risk is understanding the pathways through which they may act[22, 35]. (Table 1). One hypothesized pathway through which structural factors influence outcomes is through impacting *individual-level factors* (e.g., behavior) directly (i.e., the 'theory of social comparison')[22]. According to this construction, real and perceived hierarchical social relations may directly cause individual psychologic or biologic responses (e.g., depression) or may directly influence behavior (e.g., increased risk-tasking)[26, 36]. Another hypothesized pathway is that structural factors may act at the social network level, for example, through reducing degrees of social support or, through exchange of skills to navigate systems (i.e., 'an erosion of social capital')[21, 23, 37, 38]. Structural factors acting at either the individual or social network level may influence or restrict individual behavioral choices.

Structural factors may also influence individual-level outcomes completely independent of individual-level behavior. For example, areas of greater income inequality may receive less government funding which many change environmental factors impacting individual-level health outcomes beyond anything an individual can overcome through changed behavior (Table 1)[22]. A corollary of the fact that structural factors may impact disease rates independent of individual behavior is that some structural forces can only be, or may best be, addressed at the structural-level rather than solely through efforts to change individual behavior.

The syndemic: Opioid misuse, overdose, HCV, and HIV in contexts made vulnerable

A syndemic has been defined as "the aggregation of two or more diseases or other health conditions in a population in which there is some level of deleterious biological or behavior interface that exacerbates the negative health effects of any or all of the diseases involved" [16]. These may involve any combination of infectious or non-communicable conditions, as well as the social and environmental conditions within which the epidemics are embedded and interact[12, 39-41]. Unlike the concept of co-morbidities, syndemic theory considers population-level clusters of health conditions and social problems as occurring and interacting in specific social, temporal, and geographic contexts, which promote the development and inter-relatedness of the conditions[13].

The specific syndemic we address is that of opioid misuse, overdose, HCV, and HIV. Each health condition has its own epidemiologic trajectory, and each interacts with the others at levels of causes, consequences, and needed responses in context. Prescription opioid misuse has risen sharply since 1990 and overdose deaths have tripled between 1999 and 2015; both are linked temporally with increases in licit opioid marketing, distribution and prescribing, and illicit opioid markets[1, 2, 42, 43]. Further, substance misuse and substance use disorders (SUDs) contribute to significant morbidity and mortality directly and via increases in HCV and HIV transmission[3-5, 42, 44, 45].

The importance of both the degrees of overlap of the components of the syndemic and of area-level variations in populations and structural variables, has been highlighted by the HIV outbreak in Indiana, and by rural, suburban, and urban outbreaks, often in regions of poverty, high underemployment, and often significant deindustrialization[2, 6, 9, 12, 30, 44, 46, 47]. Many of these settings have limited access to MAT and NSPs and are characterized by local policies which do not adequately promote health-enabling environments.[25] As few as one in 10 Americans with SUDs receive any treatment; one-third of those who do not, cite cost or lack of health insurance coverage as the reason[48]. MAT is the most efficacious evidence-based treatment for OUDs, yet approximately 10% of substance use treatment facilities in the US offer it[49, 50]. Programs to prevent overdoses (e.g., naloxone training and distribution) have increasingly been implemented[29, 51]. However, as a function of public policy, there is significant variation in the geographic distribution of both naloxone programs and of the availability and coverage of MAT[52, 53]. Further, gaps in the implementation of MAT constitute a structural barrier that has implications for components of the syndemic; for example, lower county-level access to buprenorphine is associated with greater county-level vulnerability to HCV and HIV epidemics[25].

It may be for HIV that the literature has most extensively addressed the impact of structural factors and for which structural interventions have been implemented[19-21, 40, 54]. (Table 2) Since the beginning of the HIV epidemic, public health responses involved multi-level interventions; *combined prevention* efforts (NSPs, pharmacy-based syringe access, MAT, HIV and HCV testing, antiretroviral treatment (ART), and condom distribution) have reduced HIV transmission among PWID[55]. These data highlight the important contribution of structural factors to the syndemic, and that multi-level interventions can contain and reverse epidemics[17].

Prescription opioid misuse in the US: Marketing as a key structural factor

The opioid epidemic has involved voluminous marketing, distribution, and prescribing in the licit drug market and evolutions in the illicit drug market[2, 56]. Structural forces that drive markets have long histories. In the mid-19th century, the British waged military operations that have come to be called the ‘Opium Wars’, to force China to allow the sale of opium (which Britain grew in its Indian colony for the express purposes of sale to China)[14, 57]. British traders, backed by their government and military, considered opium marketing normal trade; however, China banned opium imports and considered the British to be smuggling and creating an illicit drug market, highlighting ongoing important interrelationships between licit and illicit drug markets[15, 58]. British traders developed flavored opium poppy products, to appeal to young people (including children) and develop a long-term market; China experienced a prolonged and major opioid epidemic[58]. These marketing strategies foreshadowed now well-documented efforts by the American tobacco industry to downplay evidence of nicotine dependence and to develop strategies to attract young users.

The marketing of opioids in the US has a similarly checkered history[14]. As late as 1912, Bayer marketed heroin for use in adults and children as a remedy for coughs and colds. By

1899, it produced one ton of heroin annually, marketed to 23 countries. Heroin's history as a licit and then illicit drug over subsequent decades has been well reviewed[14].

More recently, between the mid-1990s-mid-2000s highly potent oral opioids (with new patents, e.g., oxycodone and fentanyl) were heavily marketed and distributed (which may be considered a 'big event')[42, 43]. Marketing focused both on the putative under-treatment of pain and on claims that new formulations had less addictive potential, claims that were weak at best, and fraudulent at worst[56]. Campaigns included starter coupons which provided 7 – 30 day supplies of free OxyContin®[42]. Area-level characteristics were used to direct opioid marketing and distribution, by focusing on areas with active pain clinics and populations with high rates of injuries and disability-related pain[2, 59]. These marketing efforts led to increases in sales of opioids in unequivocal temporal association with the rise of OUDs and overdoses[42]. Marketing efforts and the laws and policies regulating the marketing of licit opioids are important factors in driving opioid epidemics[56].

HCV: Under-implementation of prevention and treatment

The HCV epidemic historically preceded the HIV epidemic. The combined prevention interventions that have effectively contributed to control of HIV have been less effective in controlling HCV.[45] Reasons include both the under-implementation of NSP and MAT and the higher infectivity of HCV[60]. Further, while the expansion of ART coverage among HIV-infected PWID contributed to reductions in HIV transmission, analogous expansion of HCV treatment remains under-implemented[61, 62].

The excellent efficacy of current HCV treatment raises the possibility that the expansion of treatment may serve as population-level HCV treatment as prevention (TasP) in a manner analogous to the role of ART as HIV TasP. However, modeling studies suggest that HCV TasP alone is likely to have an incomplete impact on HCV transmission; models suggest that concomitant expansion of structural interventions (i.e., NSP, MAT) is necessary. Many insurers have established criteria to limit access to HCV treatment, often putting in place eligibility restrictions greater than those contained in the Food and Drug Administration (FDA) approval of the drugs and that specifically exclude people who use drugs (PWUD) [63-65]. Translating the principle of HCV TasP into effective population-level implementation would require that issues of healthcare access, structural stigma associated with substance use, and medication costs be addressed[62].

Recognition of structural vulnerability and need for structural competency

Structural vulnerability is a construct reflecting the vulnerability of a population or a region, to adverse conditions; it is produced by a convergence of structural factors in geographic locations, embedded in existing social conditions[66]. Improved provider-level '*structural competency*' may facilitate providers' and patients' joint understanding of the importance of accessing concrete services (e.g., social work or patient navigation), and of interventions to increase an individual's ability to manage structural barriers (e.g., increasing self-efficacy) [66]. An analogous need exists for improved structural competency among researchers, public health and policymakers ensuring understanding that structural factors are important

causes and modifiable factors to be studied and included in policy responses to the syndemic. Nonetheless, any individual-level responses to structural forces (while valuable) do not treat the primary cause or remove key mediators; other options exist at the policy-level to more directly address structural barriers.

Predicting vulnerability to the syndemic

A wide range of structural factors may be useful as predictors of syndemic risk and be potentially modifiable at the public health and policy-level[19, 20, 54, 56]. (Tables 2 and 3). A recent analysis found that rising county-level unemployment rates predicted rises in opioid deaths and opioid-related emergency department visits[46]. Van Handel, *et al.* identified a set of area-level indicators associated with acute HCV infection; indicators included overdose rates, licit prescription opioid sales, buprenorphine capacity, and non-Hispanic white ethnicity. Indicators were used to develop a score reflecting area-level vulnerability to HIV or HCV outbreaks; 220 counties in 26 states were identified as being within the 95% percentile of the most vulnerable. This vulnerability index serves as one valuable formulation of the construct of structural vulnerability[67]. Note that five of these six predictors of county-level vulnerability were structural factors that are themselves adverse outcomes (low per capita income and buprenorphine prescribing potential; and high overdose rates, prescription opioid prescribing, and high unemployment). Structural domains not included in this model but that may be relevant to components of the syndemic include housing, criminal justice, economic, and trade[68-76].

Housing and criminal justice

Housing is one factor through which policy, social and economic conditions influence health[69]. Individual-level homelessness is associated with outcomes including overdose, injection and sexual risk, infection transmission, and adverse engagement and retention in both substance use and anti-viral treatments[69]. Neighborhood characteristics, including neighborhood disadvantage, affect the age of initiation of injection drug use (IDU), rates of drug use, and other health outcomes[10, 76-78]. (Table 2) Among PWID in 19 US cities, those living in zip codes with higher levels of gentrification had higher odds of past year homelessness[69].

Another important structural factor impacting this syndemic is criminal justice activity (e.g., incarceration, stop and frisk)[11, 26, 70, 79, 80]. The US has the world's highest incarceration rates; 3.2% of the population is under some form of correctional control[81, 82]. Criminal justice exposures vary among racial and ethnic groups and racial/ethnic minorities make up a disproportionate number of those in the correctional system. The health impacts of criminal justice exposures are incompletely delineated with respect to drug use and components of the syndemic[77, 81, 83], but exposures have been associated with greater individual-level psychological distress, greater HIV risk, and reduced engagement in preventive interventions[36, 84]. PWID reporting prior police stops are less likely to use NSPs consistently, and those who had syringes confiscated are more likely to share syringes[79]. Cooper, *et al.* found that living in areas with better access to sterile syringes

was associated with higher arrest rates, and that adjacent policing activities diminished NSPs' beneficial impact on sterile injection and infection risk[70].

Area-level economic factors and the syndemic

Economic inequality has increased in many countries[9]. Data demonstrate potent relationships between area-level economic factors and a variety of health outcomes[22, 73, 85, 86]. As an example, after the dissolution of the Soviet Union, gross domestic product (GDP) fell and unemployment rose, and austerity policies (which mandated social service and health expenditure cuts) were required of several new Eastern European countries by international lenders; (Table 1) this led to increases in IDU, HIV, HCV, sexually transmitted infections, and tuberculosis[78, 85, 86].

With respect to HIV, there are significant relationships between 1) rising national income inequality and declining GDP growth rates, and increases in HIV diagnoses among PWID in Europe; and 2) between increased income inequality and higher HIV-related mortality[61, 73]. A study of the European Economic Area found that decreases in the GDP, and two additional measures of income inequality, were associated with increases in the odds of an HIV outbreak[34]. (Table 2).

Novel structural variables have been examined in diverse settings that may be useful if applied to examinations of this syndemic. The US has experienced increased rates of foreclosures linked to the recession of 2008; surges in foreclosures are relevant '*big events*' [68]. Having undergone foreclosure oneself is associated with worse health outcomes, including not having filled prescriptions because of cost and depression[35, 87]. Living in an area with greater foreclosures is associated with increased individual-level rates of depression[68]. (Table 1) Recognizing that income inequality and race/ethnicity-based housing segregation may have a combined impact on populations, investigators have developed a measure termed the *Index of Concentration at the Extremes* (ICE) which examines both income inequality and segregation at area-levels[88]. It has been shown to be potently associated with several adverse health outcomes including infant mortality and hypertension[88]. There are no data examining the relationship between either foreclosures or the ICE and components of the sydnemic, but their sociologic plausibility suggest these may be important factors to be studied and addressed[19].

Links between unemployment and public health outcomes, such as components of the syndemic, may occur through several of the mechanisms. One pathway is the link between employment and health insurance. A large proportion of the US population is insured through employer-provided plans; unemployment, temporary or part-time employment, and even full-time employment in certain sectors, may leave individuals without health insurance. Lack of health insurance is associated with increased overall mortality[89]. Specific to this syndemic, lack of health insurance serves as a barrier to engagement in MAT and HCV treatment and to delayed HIV diagnosis and treatment[65, 90-92]. (Table 2).

Interconnections between national and international policy and the syndemic

One of the major successes in the global response to the HIV epidemic has been the expansion of ART. Critical to this expansion were policy changes, driven by social activism, facilitating access to generic medications. One threat to further ART expansion, and a potential threat to the expansion of MAT and HCV treatment, are elements of existing and proposed multi-national 'trade deals' which could extend patents and restrict area-level access to generic medications[74, 93].

These factors are not unrelated to the current US syndemic. Medicare Part D regulations include a prohibition against Medicare negotiating for lower than retail pricing, creating barriers in the form of co-payments by patients. Medicaid coverage for HCV treatment and MAT is highly variable by State, and remains constrained by patent-driven medication costs[94, 95].

Structural factors are addressable through intervention and policy

There are a range of structural variables that are associated with, and maybe causal of, the components of the syndemic and impact the effectiveness of public health responses[7, 23]. Monitoring these factors can facilitate the identification of vulnerable areas and predict epidemiologic trends, and many are modifiable through public health interventions and policy changes[25, 46]. (Table 3) One form of structural intervention to improve the healthcare of PWUD is to recognize the multiplicity of co-existing risks and morbidities in the syndemic and to implement systems of integrated care rather than disease-specific vertical care models[39].

Enhanced structural competency may assist providers in recognizing structural barriers and coordinating responses to these. Expanding health insurance coverage is vital[23, 89]. Further, implementation of single payer or national health services, as has been done in other resourced countries, would solve many of these issues, not only removing lack of insurance as a 'barrier', but directly addressing what should be viewed as an epidemic of the absence of health insurance; this would contribute substantially to disentangling one critical structural aspect of the current syndemic[89].

As discussed, marketing can contribute to and cause opioid epidemics[56]. Recognizing this would suggest a need for tighter regulation by the FDA, and suggest the potential utility of public health monitoring of opioid marketing and distribution to predict upsurges in licit and illicit opioid use[8, 10]. A corollary of recognizing the contribution of marketing to the creation of opioid epidemics is that provider and pharmacist education will need to overcome marketing pressures, something more likely to be effectively accomplished through regulation of marketing than through an exclusive reliance on provider and pharmacist education and monitoring. Similar logic suggests a need for stronger regulations deterring potential conflicts in guidelines development.

Increasing restrictions on opioid marketing, distribution, and prescribing may contribute to primary prevention of opioid misuse, but for those already misusing opioids, it is critical that restrictions be accompanied by parallel increases in access to MAT, to avoid transitions to use of heroin, fentanyl, and IDU. There is substantial variability in the evidence-base for, and effectiveness of, OUD treatment interventions, with substantially more evidence for MAT than non-MAT treatments; therefore, expansion of OUD treatment should emphasize use of MAT[49, 50]. Further, experience with HIV epidemics and modeling suggest that combination prevention will also need to include expanded access to NSPs and naloxone training and distribution.

Communicating the importance of structural factors to policymakers

Unfortunately, while structural factors may be modifiable through public health intervention, the need to do so comes at a time when funding has languished; both public health and public healthcare funding streams remain at risk. There are unique dissemination issues with respect to information on structural determinants of health; qualitative studies have identified that policy makers (e.g., government officials) are commonly aware of these issues and of disparities among populations and regions[96]. However, they perceive them to be “complex issues,” or frankly political issues, and policies that approach structural determinants often end up only offering individual-level solutions[96-98]. (Table 3). Available data clearly demonstrate area-level structural vulnerability. Use of a continuum model depicting engagement in substance use screening, prevention and treatment could provide compelling depictions of addressable gaps in implementation[99, 100].

Global implications

Similar constellations of individual and structural factors fuel analogous syndemics in other countries.[43, 56] The global spread of IDU has been influenced by ‘globalization of both the licit and illicit drug industries’ and the diffusion of peoples and technologies[41]. It would appear that this holds equally true for the syndemic, influenced by structural factors including economic inequality, unemployment, housing characteristics, trade agreements and marketing. In fact, opioid manufacturers are currently eager to expand sales into Latin America, the Middle East, and Africa, and sales of prescription opioids are currently booming in China[101, 102]. As was done in the US, companies are employing many of the same marketing strategies including sponsoring seminars urging prescribers to overcome ‘opiophobia’, again claiming rates of potential addiction are very low, and broadly promoting patented opioids rather than non-opioids or generic opioids for pain[43, 102]. With respect to this potential for the syndemic to grow internationally, former US Surgeon Vivak Murthy said “I would urge them to be very cautious of the marketing of these medications”[102].

Conclusions

The US is in the midst of a syndemic of opioid misuse, overdose, HCV and HIV. Recent data further demonstrate the links between these epidemics: significant national increases in the incidence of active HCV are strongly associated with increases in admissions for OUDs

attributed to prescription opioids and heroin injection[103]. Structural factors contribute potently to creating the context that render individuals and areas vulnerable to the syndemic. Further recent data support the findings of Van Handel, *et al.* in demonstrating that structural factors, including per capita income, rates of opioid prescribing and others, are predictive of HIV and HCV transmission[25, 104]. Recognizing these factors can facilitate the prediction and identification of areas at risk. Many of these structural factors are potentially modifiable through intervention and policy, with the potential to reduce structural vulnerability and create health enabling environments. Federal and state policy and funding needs to explicitly support MAT and HCV treatment as well as ART, and to address other relevant structural factors such as marketing, economic and housing disparities, and criminal justice activity. Greater attention to issues of structural vulnerability by providers, public health officials, and likely most critically policy makers, is essential to formulating and implementing effective societal responses to the syndemic.

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References

1. Centers for Disease Control and Prevention. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. MMWR. 2016; 65:1445–52. [PubMed: 28033313]
2. Quinones, S. Dreamland: The true tale of America’s opiate epidemic. 1. New York, New York: Bloomsbury Press; 2015.
3. Degenhardt L, Charlson F, Mathers B, Hall WD, Flaxman AD, Johns N, et al. The global epidemiology and burden of opioid dependence: results from the global burden of disease 2010 study. Addiction. 2014; 109:1320–33. [PubMed: 24661272]
4. Valdiserri R, Khalsa J, Dan C, Holmberg S, Zibbell J, Holtzman D, et al. Confronting the Emerging Epidemic of HCV Infection Among Young Injection Drug Users. Am J Public Health. 2014; 104:816–21. [PubMed: 24625174]
5. Centers for Disease Control and Prevention. Increases in hepatitis C virus infection related to injection drug use among persons aged </=30 years - Kentucky, Tennessee, Virginia, and West Virginia, 2006-2012. MMWR. 2015; 64:453–8. [PubMed: 25950251]
6. Centers for Disease Control and Prevention. Community Outbreak of HIV Infection Linked to Injection Drug Use of Oxymorphone--Indiana, 2015. MMWR. 2015; 64:443–4. [PubMed: 25928470]
7. Unick GJ, Rosenblum D, Mars S, Ciccarone D. Intertwined epidemics: national demographic trends in hospitalizations for heroin- and opioid-related overdoses, 1993-2009. PLoS One. 2013; 8:e54496. [PubMed: 23405084]
8. Dowell D, Zhang K, Noonan RK, Hockenberry JM. Mandatory Provider Review And Pain Clinic Laws Reduce The Amounts Of Opioids Prescribed And Overdose Death Rates. Health Aff. 2016; 35:1876–83.
9. McLean K. “There’s nothing here”: Deindustrialization as risk environment for overdose. Int J Drug Policy. 2016; 29:19–26. [PubMed: 26868674]
10. Storr CL, Chen CY, Anthony JC. “Unequal opportunity”: neighbourhood disadvantage and the chance to buy illegal drugs. J Epidemiol Comm Health. 2004; 58:231–7.
11. Friedman SR, Tempalski B, Brady JE, West BS, Pouget ER, Williams LD, et al. Income inequality, drug-related arrests, and the health of people who inject drugs: Reflections on seventeen years of research. Int J Drug Policy. 2016; 32:11–6. [PubMed: 27198555]

12. Mizuno Y, Purcell DW, Knowlton AR, Wilkinson JD, Gourevitch MN, Knight KR. Syndemic vulnerability, sexual and injection risk behaviors, and HIV continuum of care outcomes in HIV-positive injection drug users. AIDS Behav. 2015; 19:684–93. [PubMed: 25249392]
13. Singer M, Clair S. Syndemics and public health: reconceptualizing disease in bio-social context. Med Anthropol Q. 2003; 17:423–41. [PubMed: 14716917]
14. Courtwright, DT., Courtwright, DT. Forces of habit: Drugs and the making of the modern world. 1. Cambridge, MA: Harvard University Press; 2009.
15. Singer, M. Drugging the poor: Legal and illegal drugs and social inequality. 1. Long Grove, IL: Waveland Press; 2008.
16. Singer M, Bulled N, Ostrach B, Mendenhall E. Syndemics and the biosocial conception of health. Lancet. 2017; 389:941–50. [PubMed: 28271845]
17. Dean HD, Fenton KA. Addressing social determinants of health in the prevention and control of HIV/AIDS, viral hepatitis, sexually transmitted infections, and tuberculosis. Public Health Rep. 2010; 125(Suppl 4):1–5.
18. Link BG, Phelan J. Social conditions as fundamental causes of disease. J Health Soc Behav. 1995; (Spec No):80–94. [PubMed: 7560851]
19. Auerbach JD, Parkhurst JO, Caceres CF. Addressing social drivers of HIV/AIDS for the long-term response: conceptual and methodological considerations. Global Public Health. 2011; 6(Suppl 3):S293–309. [PubMed: 21745027]
20. Friedman SR, Rossi D. Dialectical theory and the study of HIV/AIDS and other epidemics. Dialect Anthropol. 2011; 35:403–27. [PubMed: 23894218]
21. Rhodes T, Singer M, Bourgois P, Friedman SR, Strathdee SA. The social structural production of HIV risk among injecting drug users. Soc Sci Med. 2005; 61:1026–44. [PubMed: 15955404]
22. Kawachi I, Kennedy BP. Income inequality and health: pathways and mechanisms. Health Serv Res. 1999; 34:215–27. [PubMed: 10199670]
23. Braveman P, Egerter S, Williams DR. The social determinants of health: coming of age. Ann Rev Public Health. 2011; 32:381–98. [PubMed: 21091195]
24. Ford JA, Sacra SA, Yohros A. Neighborhood characteristics and prescription drug misuse among adolescents: The importance of social disorganization and social capital. Int J Drug Policy. 2017; 46:47–53. [PubMed: 28609748]
25. Van Handel MM, Rose CE, Hallisey EJ, Kolling JL, Zibbell JE, Lewis B, et al. County-Level Vulnerability Assessment for Rapid Dissemination of HIV or HCV Infections Among Persons Who Inject Drugs, United States. J Acquir Immune Defic Syndr. 2016; 73:323–31. [PubMed: 27763996]
26. Sewell AA, Jefferson KA. Collateral Damage: The Health Effects of Invasive Police Encounters in New York City. J Urban Health. 2016; 93(Suppl 1):42–67. [PubMed: 26780583]
27. Cooper H, Des Jarlais D, Ross Z, Tempalski B, Bossak BH, Friedman SR. Spatial access to sterile syringes and the odds of injecting with an unsterile syringe among injectors: a longitudinal multilevel study. J Urban Health. 2012; 89:678–96. [PubMed: 22585448]
28. Krieger, N. Epidemiology and the people's health: theory and context. 1. New York, New York: Oxford University Press; 2011.
29. Siegler, A. Effect of the New York City overdose prevention program on unintentional heroin-related overdose death, 2000 - 2012. City University of New York, Graduate Center; 2016.
30. Zoorob MJ, Salemi JL. Bowling alone, dying together: The role of social capital in mitigating the drug overdose epidemic in the United States. Drug Alcohol Depend. 2017; 173:1–9. [PubMed: 28182980]
31. Monnet E, Ramee C, Minello A, Jooste V, Carel D, Di Martino V. Socioeconomic context, distance to primary care and detection of hepatitis C: a French population-based study. Soc Sci Med. 2008; 66:1046–56. [PubMed: 18164525]
32. Diez-Roux AV. Multilevel analysis in public health research. Ann Rev Public Health. 2000; 21:171–92. [PubMed: 10884951]
33. Snijders, TAB., Bosker, RJ. Multilevel Analysis: An introduction to basic and advanced multilevel modeling. 2. Sage Publishing; 2012.

34. Nikolopoulos GK, Sypsa V, Bonovas S, Paraskevis D, Malliori-Minerva M, Hatzakis A, et al. Big Events in Greece and HIV Infection Among People Who Inject Drugs. Subst Use Misuse. 2015; 50:825–38. [PubMed: 25723309]
35. McLaughlin KA, Nandi A, Keyes KM, Uddin M, Aiello AE, Galea S, et al. Home foreclosure and risk of psychiatric morbidity during the recent financial crisis. Psychol Med. 2012; 42:1441–8. [PubMed: 22099861]
36. Sewell AA, Jefferson KA, Lee H. Living under surveillance: Gender, psychological distress, and stop-question-and-frisk policing in New York City. Soc Sci Med. 2016; 159:1–13. [PubMed: 27155224]
37. Sundquist J, Johansson SE, Yang M, Sundquist K. Low linking social capital as a predictor of coronary heart disease in Sweden: a cohort study of 2.8 million people. Soc Sci Med. 2006; 62:954–63. [PubMed: 16081195]
38. Holtgrave DR, Crosby RA. Social capital, poverty, and income inequality as predictors of gonorrhoea, syphilis, chlamydia and AIDS case rates in the United States. Sex Transm Infect. 2003; 79:62–4. [PubMed: 12576618]
39. Belani H, Chorba T, Fletcher F, Hennessey K, Kroeger K, Lansky A, et al. Integrated prevention services for HIV infection, viral hepatitis, sexually transmitted diseases, and tuberculosis for persons who use drugs illicitly: summary guidance from CDC and the US Department of Health and Human Services: US Department of Health and Human Services. Recommendations and Reports from the Centers for Disease Control and Prevention. 2012; 61(RR05):1–40.
40. Wilson PA, Nanin J, Amesty S, Wallace S, Cherenack EM, Fullilove R. Using syndemic theory to understand vulnerability to HIV infection among Black and Latino men in New York City. J Urban Health. 2014; 91:983–98. [PubMed: 25155096]
41. Bulled N, Singer M. Syringe-mediated syndemics. AIDS Behav. 2011; 15:1539–45. [PubMed: 19885727]
42. Van Zee A. The promotion and marketing of oxycontin: commercial triumph, public health tragedy. Am J Public Health. 2009; 99:221–7. [PubMed: 18799767]
43. Helmerhorst GT, Teunis T, Janssen SJ, Ring D. An epidemic of the use, misuse and overdose of opioids and deaths due to overdose, in the United States and Canada: is Europe next? Bone Joint J. 2017; 99-b:856–64. [PubMed: 28663389]
44. Peters PJ, Pontones P, Hoover KW, Patel MR, Galang RR, Shields J, et al. HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014-2015. N Engl J Med. 2016; 375:229–39. [PubMed: 27468059]
45. Jordan AE, Des Jarlais DC, Arasteh K, McKnight C, Nash D, Perlman DC. Incidence and prevalence of hepatitis c virus infection among persons who inject drugs in New York City: 2006-2013. Drug Alcohol Depend. 2015
46. Hollingsworth, A., Ruhm, CJ., Simon, K. Working Paper No 23192. National Bureau of Economic Research; 2017. Macroeconomic conditions and opioid abuse. Accessed from: http://www.nber.org/papers/w23192
47. Wright ER, Kooreman HE, Greene MS, Chambers RA, Banerjee A, Wilson J. The iatrogenic epidemic of prescription drug abuse: county-level determinants of opioid availability and abuse. Drug Alcohol Depend. 2014; 138:209–15. [PubMed: 24679840]
48. Substance Abuse and Mental Health Services Administration. Results from the 2015 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: Series H-48, Series H-48, HHS Publication No. (SMA) 14-4863
49. The White House. The President's Commission on Combating Drug Addiction and the Opioid Crisis. Accessed from: https://www.whitehouse.gov/sites/whitehouse…/Final_Report_Draft_11-1-2017.pdf
50. Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. Health Technol Assess. 2007; 11:1–171.
51. Centers for Disease Control and Prevention. Community-based opioid overdose prevention programs providing naloxone - United States, 2010. MMWR. 2012; 61:101–5. [PubMed: 22337174]

52. Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. J Addict Med. 2014; 8:153–63. [PubMed: 24874759]
53. Hansen HB, Siegel CE, Case BG, Bertollo DN, DiRocco D, Galanter M. Variation in use of buprenorphine and methadone treatment by racial, ethnic, and income characteristics of residential social areas in New York City. J Behav Health Serv Res. 2013; 40:367–77. [PubMed: 23702611]
54. Blankenship KM, Friedman SR, Dworkin S, Mantell JE. Structural interventions: concepts, challenges and opportunities for research. J Urban Health. 2006; 83:59–72. [PubMed: 16736355]
55. Des Jarlais DC, Arasteh K, McKnight C, Feelemyer J, Campbell AN, Tross S, et al. Consistent Estimates of Very Low HIV Incidence Among People Who Inject Drugs: New York City, 2005-2014. Am J Public Health. 2016; 106:503–8. [PubMed: 26794160]
56. Becker WC, Fiellin DA. Limited evidence, faulty reasoning, and potential for a global opioid crisis. BMJ. 2017; 358:j3115. [PubMed: 28679499]
57. Marx, K., Wheen, F., Ledbetter, J. Dispatches for the New York Tribune: Selected Journalism of Karl Marx. 1. London, England: Penguin Classics; 2007.
58. Merwin, S. Drugging a nation: The story of China and the opium curse. New York, New York: Fleming H Revell Company; 1908.
59. Slavova S, Costich JF, Bunn TL, Luu H, Singleton M, Hargrove SL, et al. Heroin and fentanyl overdoses in Kentucky: Epidemiology and surveillance. Int J Drug Policy. 2017; 46:120–9. [PubMed: 28735777]
60. Perlman DC, Des Jarlais DC, Feelemyer J. Can HIV and Hepatitis C Virus Infection be Eliminated Among Persons Who Inject Drugs? J Addict Dis. 2015; 34:198–205. [PubMed: 26075647]
61. Friedman SR, West BS, Pouget ER, Hall HI, Cantrell J, Tempalski B, et al. Metropolitan social environments and pre-HAART/HAART era changes in mortality rates (per 10,000 adult residents) among injection drug users living with AIDS. PLoS One. 2013; 8:e57201. [PubMed: 23437341]
62. Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, Vickerman P. Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. Clin Infect Dis. 2013; 57:S39–S45. [PubMed: 23884064]
63. Canary LA, Klevens RM, Holmberg SD. Limited Access to New Hepatitis C Virus Treatment Under State Medicaid Programs. Ann Intern Med. 2015; 613(3):226–8.
64. Do A, Mittal Y, Liapakis A, Cohen E, Chau H, Bertuccio C, et al. Drug Authorization for Sofosbuvir/Ledipasvir (Harvoni) for Chronic HCV Infection in a Real-World Cohort: A New Barrier in the HCV Care Cascade. PLoS One. 2015; 10:e0135645. [PubMed: 26312999]
65. Kuniholm MH, Leach T, Lunievicz J, Olivo N, Anastos K, Vazquez Y, et al. Hepatitis C Direct Acting Antiviral Therapies in a New York City HIV/AIDS Special Needs Plan: Uptake and Barriers. AIDS Patient Care STDs. 2015; 29:643–5. [PubMed: 26669792]
66. Metzl JM, Hansen H. Structural competency: theorizing a new medical engagement with stigma and inequality. Soc Sci Med. 2014; 103:126–33. [PubMed: 24507917]
67. McNeil R, Kerr T, Anderson S, Maher L, Keewatin C, Milloy M, et al. Negotiating structural vulnerability following regulatory changes to a provincial methadone program in Vancouver, Canada: A qualitative study. Soc Sci Med. 2015; 133:168–76. [PubMed: 25875323]
68. Cagney KA, Browning CR, Iveniuk J, English N. The onset of depression during the great recession: foreclosure and older adult mental health. Am J Public Health. 2014; 104:498–505. [PubMed: 24446830]
69. Linton SL, Cooper HL, Kelley ME, Karnes CC, Ross Z, Wolfe ME, et al. Cross-sectional association between ZIP code-level gentrification and homelessness among a large community-based sample of people who inject drugs in 19 US cities. BMJ Open. 2017; 7:e013823.
70. Cooper HL, Des Jarlais DC, Tempalski B, Bossak BH, Ross Z, Friedman SR. Drug-related arrest rates and spatial access to syringe exchange programs in New York City health districts: combined effects on the risk of injection-related infections among injectors. Health Place. 2012; 18:218–28. [PubMed: 22047790]

71. Nandi A, Galea S, Ahern J, Bucciarelli A, Vlahov D, Tardiff K. What explains the association between neighborhood-level income inequality and the risk of fatal overdose in New York City? Soc Sci Med. 2006; 63:662–74. [PubMed: 16597478]
72. Paraskevis D, Nikolopoulos G, Fotiou A, Tsiara C, Paraskeva D, Sypsa V, et al. Economic recession and emergence of an HIV-1 outbreak among drug injectors in Athens metropolitan area: a longitudinal study. PLoS One. 2013; 8:e78941. [PubMed: 24265730]
73. Nikolopoulos GK, Fotiou A, Kanavou E, Richardson C, Detsis M, Pharris A, et al. National income inequality and declining GDP growth rates are associated with increases in HIV diagnoses among people who inject drugs in Europe: a panel data analysis. PLoS One. 2015; 10:e0122367. [PubMed: 25875598]
74. Linh NN, Huong NT, Thuy HT. Evolving trade policy and the Trans-Pacific Partnership Agreement: does it threaten Vietnam's access to medicine and its progress towards scaling up HIV prevention, treatment and care? Global Public Health. 2015; 10(Supppl 1):S149–60. [PubMed: 25469870]
75. Bassols MN, Vall Castello J. Effects of the great recession on drugs consumption in Spain. Econ Hum Biol. 2016; 22:103–16. [PubMed: 27039369]
76. Zierler S, Krieger N, Tang Y, Coady W, Siegfried E, DeMaria A, et al. Economic deprivation and AIDS incidence in Massachusetts. Am J Public Health. 2000; 90:1064–73. [PubMed: 10897184]
77. Cooper HL, Linton S, Kelley ME, Ross Z, Wolfe ME, Chen YT, et al. Risk Environments, Race/Ethnicity, and HIV Status in a Large Sample of People Who Inject Drugs in the United States. PLoS One. 2016; 11:e0150410. [PubMed: 26974165]
78. Uuskula A, McMahon JM, Raag M, Silm S, Ruutel K, Talu A, et al. Emergent properties of HIV risk among injection drug users in Tallinn, Estonia: synthesis of individual and neighbourhood-level factors. Sex Transm Infect. 2010; 86(Suppl 3):iii79–84. [PubMed: 21098060]
79. Beletsky L, Heller D, Jenness SM, Neaigus A, Gelpi-Acosta C, Hagan H. Syringe access, syringe sharing, and police encounters among people who inject drugs in New York City: a community-level perspective. Int J Drug Policy. 2014; 25:105–11. [PubMed: 23916801]
80. Dauria EF, Elifson K, Arriola KJ, Wingood G, Cooper HL. Male Incarceration Rates and Rates of Sexually Transmitted Infections: Results From a Longitudinal Analysis in a Southeastern US City. Sex Transm Dis. 2015; 42:324–8. [PubMed: 25970309]
81. Drucker, E. A Plague of Prisons: The Epidemiology of Mass Incarceration in America. Reprint Edition. New York, New York: New Press; 2011.
82. Human Rights Watch. World Report, United States Events of 2015. 2015. Accessed from: https://www.hrw.org/world-report/2015/country-chapters/united-states#91bb48
83. Geller A, Fagan J, Tyler T, Link BG. Aggressive policing and the mental health of young urban men. Am J Public Health. 2014; 104:2321–7. [PubMed: 25322310]
84. Milloy M, Kerr T, Buxton J, Rhodes T, Guillemi S, Hogg R, et al. Dose-response effect of incarceration events on nonadherence to HIV antiretroviral therapy among injection drug users. J Infect Dis. 2011; 203:1215–21. [PubMed: 21459814]
85. Murray M, King G. The effects of international monetary fund loans on health outcomes. PLoS Med. 2008; 5:e162. [PubMed: 18651790]
86. Ruckert A, Labonté R. The financial crisis and global health: the International Monetary Fund's (IMF) policy response. Health Promot Int. 2012; 28(3):357–66. [PubMed: 22504946]
87. Pollack CE, Lynch J. Health status of people undergoing foreclosure in the Philadelphia region. Am J Public Health. 2009; 99:1833–9. [PubMed: 19696373]
88. Krieger N, Waterman PD, Spasojevic J, Li W, Maduro G, Van Wye G. Public Health Monitoring of Privilege and Deprivation With the Index of Concentration at the Extremes. Am J Public Health. 2016; 106:256–63. [PubMed: 26691119]
89. Woolhandler S, Himmelstein DU. The Relationship of Health Insurance and Mortality: Is Lack of Insurance Deadly? Ann Intern Med. 2017; 167:424–31. [PubMed: 28655034]
90. Ransome Y, Galea S, Pabayo R, Kawachi I, Braunstein S, Nash D. Social Capital is Associated With Late HIV Diagnosis: An Ecological Analysis. J Acquir Immune Defic Syndr. 2016; 73:213–21. [PubMed: 27632146]

91. Ransome Y, Kawachi I, Dean LT. Neighborhood Social Capital in Relation to Late HIV Diagnosis, Linkage to HIV Care, and HIV Care Engagement. AIDS Behav. 2017; 21:891–904. [PubMed: 27752875]
92. Ransome Y, Terzian A, Addison D, Braunstein S, Myers J, Abraham B, et al. Expanded HIV testing coverage is associated with decreases in late HIV diagnoses. AIDS. 2015; 29:1369–78. [PubMed: 26091296]
93. Baker BK. Trans-Pacific Partnership Provisions in Intellectual Property, Transparency, and Investment Chapters Threaten Access to Medicines in the US and Elsewhere. PLoS Med. 2016; 13:e1001970. [PubMed: 26954325]
94. Perlman DC, Jordan AE, Uuskula A, Huong DT, Masson CL, Schackman BR, et al. An international perspective on using opioid substitution treatment to improve hepatitis C prevention and care for people who inject drugs: Structural barriers and public health potential. Int J Drug Policy. 2015
95. Ford N, Wiktor S, Kaplan K, Andrieux-Meyer I, Hill A, Radhakrishnan P, et al. Ten priorities for expanding access to HCV treatment for people who inject drugs in low-and middle-income countries. Int J Drug Policy. 2015; 26:1088–93. [PubMed: 26074094]
96. Baum FE, Laris P, Fisher M, Newman L, Macdougall C. “Never mind the logic, give me the numbers”: former Australian health ministers’ perspectives on the social determinants of health. Soc Sci Med. 2013; 87:138–46. [PubMed: 23631789]
97. Embrett MG, Randall GE. Social determinants of health and health equity policy research: exploring the use, misuse, and nonuse of policy analysis theory. Soc Sci Med. 2014; 108:147–55. [PubMed: 24641879]
98. Carey G, Crammond B. Action on the social determinants of health: views from inside the policy process. Soc Sci Med. 2015; 128:134–41. [PubMed: 25616195]
99. Perlman DC, Jordan AE. Considerations for the Development of a Substance-Related Care and Prevention Continuum Model. Front Public Health. 2017; 5:180. [PubMed: 28770195]
100. Perlman DC, Jordan AE, Nash D. Conceptualizing Care Continua: Lessons from HIV, Hepatitis C Virus, Tuberculosis and Implications for the Development of Improved Care and Prevention Continua. Front Public Health. 2017; 4:296. [PubMed: 28119910]
101. China’s Oxycontin boom is a gold mine for this drugmaker. Bloomberg News [newspaper on the Internet]. Dec 18. 2016 Accessed from: https://www.bloomberg.com/news/articles/2016-12-18/china-s-oxycontin-boom-is-a-goldmine-for-this-drugmaker2016
102. Ryan, HGL., Glover, S. OxyContin goes global—“We’re only just getting started”. Los Angeles Times [newspaper on the Internet]. Dec 16. 2016 Accessed from from: http://www.latimes.com/projects/la-me-oxycontin-part3/
103. Zibbell JE, Asher AK, Patel RC, et al. Increases in Acute Hepatitis C Virus Infection Related to a Growing Opioid Epidemic and Associated Injection Drug Use, United States, 2004 to 2014. Am J Public Health. 2018; 108(2):175–181. [PubMed: 29267061]
104. Rickles M, Rebeiro PF, Sizemore L, Juarez P, Mutter M, Wester C, McPheeters M. Tennessee’s In-State Vulnerability Assessment for a ‘Rapid Dissemination of HIV or HCV Infection’ Event Utilizing Data about the Opioid Epidemic. Clin Infect Dis. 2017; Epub ahead of print. doi: 10.1093/cid/cix1079

Table 1

Pathways through which structural variables may act and how mechanisms affect risk

Pathway of influence	Mechanism	Structural factor's impact on individual choice	Example
Act through impact on individual behavior	Structural factors[2] impact individual- level[1] conditions to either cause psychologic or biologic responses		The conditions of neighborhoods with a higher social vulnerability index[3] score, or other measures of neighborhood disadvantage or neighborhood physical decay, may act by contributing to an individual's depression or fatalism, or through this, to an increased individual likelihood of risky drug use or non-use of preventive interventions (e.g., regardless of access to needle syringe exchange programs (NSP)).
		Acts through the individual with no significant constraint on choice	Opt-out hepatitis C virus (HCV) antibody testing in methadone maintenance treatment programs has resulted in very high HCV testing rates.
		Acts through the individual resulting in constrained choice	An individual has access to a NSP but because of adjacent police activity may be disincentivized to use the NSP because the probability of being stopped or frisked overcomes their motivation to use the NSP.
Act at level of social network	These structural factors impact social interactions among those in social networks[4]	Acts through influence on individual choice	Supraindividual factors[4] impact social interactions (e.g., degrees of social support or mistrust) among those in social networks. Someone may have fewer people in their social network who practice preventive behaviors (e.g., carrying extra sterile syringes) or who reinforce protective norms by encouraging peers to use their own cookers and cottons as well as to syringes. Social support may increase individual willingness to be tested for HIV or HCV, to accept anti-viral therapy for HIV or HCV, and to accept medication assisted treatment (MAT) for opioid use disorders.
Act independent individual behavior or social network	These factors may shape disease patterns beyond anything that an individual can overcome by changed behaviors	Acts independent of individual choice	Areas of greater income inequality may experience lower social and health spending and these may change numerous environmental service and policy factors beyond anything an individual can readily overcome by changed behavior. A person who injects drugs (PWID) may have the knowledge, motivation, and self-efficacy to engage in sterile injection drug use or to engage in MAT however, if the individual lives in an area where as matter of law, policy, or funding (i.e., place-based[5] factors) there are no NSPs or MAT, the structural environment thwarts and overcomes their attempts to do so. That is, a PWID with any specified level of knowledge of prevention interventions and the motivation and self-efficacy to implement them, may inject in an area of a specified HCV prevalence in which sterile syringes are readily available through legal prevention programs. In contrast, there may be a PWID with the exact same level of information, motivation, and self-efficacy who injects in an area of the same HCV prevalence with no sources of sterile syringes are available as a matter of law, policy and program. An estimated per-event probability of HCV transmission from an infected to an uninfected PWID of 0.5% results in very different transmission dynamics if that risk event occurs in a region of 0% HCV prevalence or a region of 60% HCV prevalence. In each case, factors external to the individual and independent of individual behavior, impact transmission risk.

[1]The term *structural* relates to constructs measured above the individual or social network level, and includes factors such as policies or laws, economic measures, as well as other factors that vary as a function of area.

[2]The term *individual-level* refers to characteristics measured at the level of the individual (e.g., genetic, socio-demographic, experiential).

[3]The Social Vulnerability Index was designed initially for use in disaster management and is a composite measure of 15 variables at the census-tract level.

[4]The term *supraindividual* refers to all constructs measured above the level of the individual; this includes *social network factors* which refers to interactions between an individual and specific (known or unknown) other individuals.

[5]The terms *place-based* or *area-level* refers to a subset of structural variables, commonly constructed with data derived for specific geographic units (e.g., zip codes).

Table 2

Selected studies examining the role of structural variables on syndemic and related outcomes

Topic	Report	Study year(s)	Study design: Ecologic or multi-level	Location	Geographic level of structural variable	Dependent variable(s)	Independent variable(s) (structural variable(s))	Findings
Substance use								
	Bassols, et al., 2016 [75]	2005 - 2011	Multi- level	Spain	Province	Rates of illicit drug use	Unemployment rates	Ten percent increases in unemployment were signficantly associated with increases in marijuana use (3%) and cocaine use (1.2%).
	Cooper, et al., 2012 [70]	1995 - 2006	Multi- level	New York, New York, USA	NYC health districts	Drug injection with an unsterile needle	1) Drug-related arrest rates and 2) access to needle/syringe exchange program (NSPs)	Districts with better access to NSPs had higher arrest rates, and arrest rates undermined the protective relationship between access to NSPs and rates of sterile injection.
	Ford, et al., 2017 [24]	2000	Ecologic	USA	Aggregates of census-blocks	Prescription opioid misuse in the last 12 months	Measures reflecting social disorganization, social capital, and social participation	All three measures of neighborhood characteristics were significantly related with prescription opioid misuse: social disorganisation (aOR (adjusted Odds Ratio): 1.04, 95% CI: 1.01 - 1.06), social capital (aOR: 0.92, 95% CI: 0.87 - 0.97), and social participation (aOR: 1.05, 95% CI: 1.01 - 1.10).
	Hansen, et al., 2013 [53]	2000 - 2007	Ecologic	New York, New York, USA	Zip code	Buprenorphine and methadone treatment rates	1) Percent of population below two times the poverty level and 2) the percent of the population who were Black or non-Hispanic White	Buprenorphine treatment rates were significantly negatively associated with the percent of residents in poverty, Black, and non-Hispanic White (all $p < 0.01$). Methadone treatment rates were positively correlated with the same factors ($p < 0.01$).
	Storr, et al., 2004 [10]	1998	Multi- level	USA	Neighborhood[2]	Opportunity to purchase illegal drugs	Neighborhood disadvantage (composite of 11 items)	Residents in the most disadvantaged neighborhoods were more likely to have an opportunity to obtain drugs (aOR 2.2, 95% CI: 1.7 - 2.7, $p < 0.001$) as compared with residents in the lowest quartile of neighborhood disadvantage.
	Sundquist, et al., 2016 [37]	2003 - 2010	Ecologic	Sweden	Neighborhood[1]	First episode of substance misuse	1) Linking social capital (i.e., proportion of people in a geographically defined neighborhood who voted in local government elections) and 2) neighborhood deprivation (a composite measure)	Low linking social capital was significantly associated with higher rates of substance misuse among men (aOR: 2.11, 95% CI: 2.02 - 2.21). Among men living in high deprivation neighborhoods, the odds of substance misuse

Topic	Report	Study year(s)	Study design: Ecologic or multi-level	Location	Geographic level of structural variable	Dependent variable(s)	Independent variable(s) (structural variable(s))	Findings
								increased from 1.20 to 1.71 when the level of linking social capital decreased.
	Wright, et al., 2014 [47]	2011	Ecologic	Indiana, USA	County	Availability of prescription opioids and rate of opioid use disorders as measured by entry into opioid use disorder (OUD) treatment programs	Access to healthcare examined as county density of primary care providers, dentists, nurse practioners, physician assistants, and pharmacists	The per capita rate of dentists, and of pharmacists, were significantly associated with the number of opioid prescriptions (p: 0.009 and 0.036, respectively). Higher unemployment and higher numbers of opioid prescriptions were significantly associated with rates of OUD treatment initiation (p: 0.01 and 0.021, respectively).
Overdose								
	Dowell, et al., 2016 [8]	2006 - 2013	Ecologic	USA	State	1) Rate of fatal overdose deaths (per 100,000 residents) and 2) prescribing rates	1) Laws and regulations requiring providers to follow opioid prescribing guidelines (mandated prescription drug monitoring program (PDMP) review) and 2) pain clinic laws	States that mandated both PDMP and pain clinic laws were associated with reduced prescribing rates (80 morphine milligram equivalents per State resident) and fewer fatal overdoses (-1.1 per 100,000 residents) compared with those States that only mandated PDMPs but did not implement pain clinic laws.
	Hollingsworth, et al., 2017 [46]	1999 - 2014	Ecologic	USA	State and County	Opioid overdose deaths and opioid overdose emergency department (ED) visits per 100,000 residents, respectively.	Unemployment rate	County unemployment rate increases of 1% were associated with increased opioid overdose death rates of 0.019 per 100,000 and with opioid overdose ED visit rates of 0.95 per 100,000. These associations were also significant at a State-level.
	Nandi, et al., 2006 [71]	1996	Ecologic	New York, New York, USA	Zip code	Overdose deaths	1) Income inequality measured by a) the Gini coefficient and b) the percent of total income earned by the lowest earning 70% of households and 2) level of environmental disorder (i.e., unclean sidewalks); quality of the built environment (i.e., % dilapidated buildling); and police activity.	Compared to the midpoint of the lowest Gini decile, the relative odds of overdose death was 1.63 (95% CI: 1.06 - 2.52) in neighborhoods in 95th percentile of the Gini distribution (with analogous findings also for the percent of total income earned by the lowest earning 70% of households). Thirty-six percent of the association was a direct effect of Gini on overdose rates and 64% was mediated by environmental disorder, policy activity, and the quality of the built environment.
	Siegler, 2016 [29]	2000 - 2012	Ecologic	New York, New York, USA	Neighborhoods[4]	Unintentional heroin-related and opioid analgesic- related overdose deaths	Implementation of the NYC overdose prevention program	Neighborhoods with overdose prevention programs had greater decreases in overdose mortality rates, comparing to neighborhoods

Topic	Report	Study year(s)	Study design: Ecologic or multi-level	Location	Geographic level of structural variable	Dependent variable(s)	Independent variable(s) (structural variable(s))	Findings
								without overdose prevention programs (- 3.1 compared with -0.8 per 100,000 population).
	Zoorob, et al., 2017 [30]	1999 - 2014	Ecologic	USA	County	Overdose death rate per 100,000 residents, categorized as low, moderate, or high mortality	1) Social capital (i.e., density of civic associations and non-profit organizations, percentage of adults who voted in presidential elections, response rate to the census, number of tax- exempt non-profit organizations, median household income, and poverty) and 2) proportion of Medicare Part D prescriptions that were for opioids	Counties in the highest quintile of social capital were significantly more likely to have low overdose mortality (aOR: 0.13, 95% CI: 0.11 - 0.15). Counties in which a higher proportion of Medicare Part D prescriptions were for opioids had substantially increased odds of high overdose mortality (>=8% vs. <3%, OR: 65.8, 95% CI: 46.5 - 93.1).
HCV								
	Monnet, et al., 2008 [31]	1994 - 2001	Ecologic	France	City	HCV case detection rates	Distance from individual's residence to primary healthcare	The distance to primary healthcare had a significant influence on HCV case detection rates (adjusting for age and sex), with a detection rate ratio of 0.89 (95% CI: 0.84 - 0.96) indicating an 11% decrease in rate when the distance increased by 1 km.
	Paraskevis, et al., 2013 [72]	2011	Ecologic	Athens, Greece	City	Incident cases of HCV	Annual change in gross domestic product (GDP)	Significant negative association between annual change in GDP and incident HCV cases among new people who inject drugs (beta: -3.33, p: 0.001).
	Van Handel, et al., 2016 [25]	2012 - 2013	Ecologic	USA	County	Acute incident cases of HCV	1) Buprenorphine prescribing capacity; 2) per capita income; 3) overdose death rate; 4) prescription opioid sales; 5) proportion non- Hispanic White; and 6) unemployment rate	All 6 independent structural variables were significantly associated with incidence of acute HCV (all $p < 0.0001$).
HIV/AIDS								
	Holtgrave, et al., 2003 [38]	1999	Ecologic	USA	State	AIDS case rates per 100,000 population	1) Poverty defined as the % of State population living in poverty and 2) income inequality measured as the ratio of mean income for the top earning one-fifth of families to the bottom one-fifth.	Social capital and income inequality were significantly correlated with AIDS case rates. The more social capital, the lower the AIDS case rate; the more income inequality, the higher the AIDS case rate. (all $p < 0.01$).

Topic	Report	Study year(s)	Study design: Ecologic or multi-level	Location	Geographic level of structural variable	Dependent variable(s)	Independent variable(s) (structural variable(s))	Findings
	Nikolopoulos, et al., 2015 [73]	2003 - 2012	Ecologic	European Economic Area (EEA)	Country	Probability of an HIV outbreak among PWID (odds of an HIV outbreak within 1, 2 and 3 years of the current observation period)	1) GDP per capita and 2) the ratio of total income received by the 20% of the population with the highest income to that received by the 20% of the population with the lowest income (Eurostat S80/S20 ratio)	The estimated odds ratio (ORs) for an HIV outbreak associated with a 1% yearly increase in GDP were 0.78 (95% CI: 0.62 - 0.98), 0.66 (95% CI: 0.49 to 0.88) and 0.81 (95% CI: 0.65 - 1.02) for 1, 2, and 3 years from the observation period, respectively. Estimated ORs for an HIV outbreak associatedwith the per unit increase in the S80/S20 ratio (higher inequality) ranged from 3.07 (95% CI: 1.10 - 8.57) for 2 years from observation period to 3.82 (95% CI: 1.09 - 13.40) for year 3.
	Paraskevis, et al., 2013 [72]	2011	Ecologic	Athens, Greece	City	Annual HIV prevalence	Annual change in GDP	Significant negative association between annual change in GDP and HIV prevalence (rate ratio (RR): 0.95, 95% CI: 0.92 - 0.97, p < 0.001).
	Ransome, et al., 2016 [90]	2005 - 2006	Ecologic	New York, New York, USA	Zip code	Late HIV diagnosis rates (i.e., CD4 count test result of 200 cells/ml or less at diagnosis or an AIDS defining illness within 12 months of the date of HIV diagnosis)	Social capital examined as 1) civic participation, 2) political participation, 3) social cohesion, and 4) informal social control	Higher levels of informal social control were signficantly associated with lower relative odds of late HIV diagnosis among men (RR: 0.67, 95% CI: 0.48 - 0.93). Moderate social cohesion was associated with late HIV diagnosis among women (RR: 0.71, 95% CI: 0.55 - 0.92). Low to high political participation and social cohesion were significantly associated (p < 0.0001) with decreasing in late HIV diagnosis rates.
	Ransome, et al., 2017 [91]	2004 -2011	Ecologic	Philadelphia, Pennsylvania, USA	Census-block	1) Late HIV diagnosis, 2) linked to HIV and 3) engaged in HIV care	Social capital (social cohesion, social participation, collective engagement)	Social participation was the only significant social capital indicator scross all three HIV outcomes. For late HIV diagnosis, all three were associated: beta: 1.37, standard error (SE): 0.32; linked to HIV care, beta: 1.13, SE: 0.20, engaged in HIV care, beta: -1.16, SE: 0.30 (all p < 0.0001).
	Ransome, et al., 2015 [92]	2003 - 2010	Ecologic	New York, New York, USA	Zip code	Incident HIV	HIV testing coverage	Within zip codes, each 10% absolute increase in recent HIV testing coverage was associated with a 2.5 per 100 000 absolute decrease in the late HIV diagnosis rate.
	Uuskula, et al., 2010 [78]	2000 - 2007	Multi- level	Tallinn, Estonia	Neighborhood[3]	Individual-level incident HIV	Unemployment rate and residential instability (10% change in residential address between 1989 and 2000).	Each 10% increase in neighborhood-level unemployment was associated with an increased odds of being HIV positive (aOR 5.95, 95% CI: 2.5 - 14.3). Each 10% increase in residential turnover was

Topic	Report	Study year(s)	Study design: Ecologic or multi-level	Location	Geographic level of structural variable	Dependent variable(s)	Independent variable(s) (structural variable(s))	Findings
								associated with an increased odds of being HIV positive (aOR 1.90, 95% CI: 1.09 - 3.30).
	Zierler, et al., 2000 [76]	1988 - 1994	Ecologic	Massachusetts, USA	Census-block	Incident cases of AIDS	Economic deprivation (a composite variable)	The cumulative incidence of AIDS in the total population was nearly 7 times higher among persons in block-groups where 40% or more of the population was below the poverty line (362 per 100,000 residents) than among persons in block-groups where less than 2% of the population was below poverty (53 per 100,000 residents).
Other relevant outcomes								
	Cagney, et al., 2014 [68]	2005 - 2011	Multi-level	USA	Zip code	Depressive symptoms	Three stages of foreclosure process: 1) notice of default; 2) auction; and 3) transition to real-estate	Neighborhood-level foreclosure increases were associated with increases in the rate of depression among adults. Notices of default OR 1.75 (95% CI: 1.14 - 2.67), auction OR 1.45 (95% CI: 0.96 - 2.19), and transition to real estate OR 1.62 (95%CI: 1.06 - 2.47).
	Dauria, et al., 2015 [80]	2005 - 2010	Multi-level	Atlanta, Georgia, USA	Census tract	Incidence of sexually transmitted infections (STIs)	Incarceration rates among males	Higher baseline male incarceration rates were associated with higher rates of newly diagnosed STIs.

[1] Small area market statistics (SAMS)—small administrative areas in Sweden whose average population is 2000 in Stockholm and 1000 in the rest of Sweden were used to define neighborhoods

[2] Neighborhoods were defined area segments approximating groups of housing units that closely equate to each other)

[3] Neighborhoods were ‘habitats’ as categorized in the 2000 Estonian census.

[4] Aggregates of census-tract data

Table 3

Selected possible responses to modifiable structural factors to address the syndemic and its components

Categories [informed by Auerbach, et al. [19]] and examples	
Policy and legal change	
Substance misuse and overdoses	• Expanded funding to implement broad substance use screening.
	• Expanded funding to implement interventions to improve linkages from substance use screening to medication assisted treatment (MAT) and to promote retention in care.
	• Enforce parity of medical and mental health care (and opioid use disorder (OUD) treatment, which of necessity spans the two) and carefully balance confidentially protections for those with OUDs so as to not adversely affect access and engagement in care.
	• Increase access to MAT by Affordable Care Act and other regulatory mandates for insurance to fully cover OUD treatment.
	• Funding to expand implementation of OUD treatment in specialty and primary care office-based settings.
	• Policies and regulations to ensure that all OUD treatment facilities offer and provide MAT for opioid use disorders.
	• Ensure quality of MAT programs (e.g., providing adequate doses).
	• Remove barriers to MAT for opioid use disorders in adolescents.
	• Funding to implement and ensure adequate access to MAT in correctional settings.
	• Funding for training and expanded implementation of naloxone to a wider range including emergency professionals, police, and personal contacts in all geographic areas.
	• Stricter Food and Drug Administration (FDA) review of all opioids.
	• More rigorous and proactive FDA review of opioid marketing materials and strategies.
	• Establish judicious limits for the marketing of all opioids, informed by sound evidence-based practices.
	• Policies and legislation to ban the use of free-starter coupons for opioids.
	• Build evidence base examining the use of monitoring opioid marketing and distribution data as a public health tool to predict upsurges in licit and illicit opioid misuse, OUDs, and overdoses.
	• Regulation of the marketing of OUD treatment (including through social media and search engines) to ensure its basis in evidence.
	• Funding to support the expanded implementation and nationwide coordination of Prescription Drug Monitoring Programs and prescribing guidelines.
	• Implement pain clinic laws and regulate pain clinics.
HCV and HIV	• Policy changes and funding to expand access to needle/syringe exchange programs (NSPs) in all areas.
	• Expanded access to risk factor-based hepatitis C virus (HCV) and HIV testing
	• Expanded funding for and implementation of interventions to improve linkages from HCV and HIV testing to care and to promote retention in care.
	• Funding to ensure adequate access to HCV treatment and to ensure full insurance coverage of HCV treatment (to allow population-level treatment as prevention), eliminating barriers (such as prior approvals and co-pays) to treatment by insurance plans, regulation of medication pricing, and elimination of Medicare Part D restrictions on regulating prices.
	• Funding to implement and ensure adequate access to HCV treatment in correctional settings.
Pan-Syndemic	• Funding to further develop and implement use of care continuum models for substance use and HCV, as well as for HIV, to monitor program, regional, and national progress, as well as to clearly convey gaps in implementation to lay audiences and policy makers.
	• Regulation and enforcement of policies to promote the greater avoidance of potential conflicts of interest in guideline development (e.g., pain, opioid prescribing, MAT, HCV testing and treatment).

Environmental enablers

- Increase access to MAT in geographic distributions which minimize gaps or disparities.
- Funding to expand implementation of integrated prevention and treatment services which simultaneously address the components of syndemic and their contexts.
- Expand the evidence base for use of safe injection facilities.

Shifting harmful norms

- Create health-enabling environments through accessible destigmatized access to NSPs minimizing deincentivizing adjacent policing activities.
- Decrease structural stigmatization of MAT which serves as a barrier to its broader implementation.
- Funding to expand efforts to destigmatize opioid use, OUDs and NSPs.

Promoting social and political change

- Shift emphasis from criminal justice to public health approaches to opioid misuse.
- Develop and implement strategies to coordinate criminal justice activities so as to minimize adverse impacts on prevention interventions such as NSP and MAT.

Economic interventions

- Funding to reduce area-level structural vulnerability by addressing regional economic inequality, poverty, underemployment, and under-insurance through policy.
- Federal funding to expand the geographic distribution and capacity of NSPs, and to allow for pharmacy sales of syringes in all jurisdictions.

Structural competency

- Education of health professionals in structural competency, training in evidence-based pain management and office-based MAT.
- Expansion of training and use of naloxone to wider range including emergency professionals, police, as well as families, friends and contacts.
- Funding to enhance training of researchers and public health officials in theory, methods, and the importance of monitoring and addressing structural factors.
- Efforts to expand the understanding among policymakers of the importance of monitoring and addressing key modifiable structural factors as central components of the policy responses to the syndemic.