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REDUCING RATES OF PREVENTABLE HIV/AIDS-ASSOCIATED MORTALITY AMONG PEOPLE LIVING WITH HIV WHO INJECT DRUGS

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Abstract

Purpose of review—The modern antiretroviral therapy (ART) era has seen substantial reductions in mortality among people living with HIV. However, HIV-positive people who inject drugs (PWIDs) continue to experience high rates of suboptimal HIV-related outcomes. We review recent findings regarding factors contributing to premature and preventable mortality among HIV-positive PWID, and describe the promise of interventions to improve survival in this group.

Recent findings—The current leading causes of death among HIV-positive PWID are HIV/AIDS-related causes, overdose, and liver-related causes, including infection with hepatitis C virus. Elevated mortality levels in this population are driven by social–structural barriers to ART access and adherence, particularly criminalization and stigmatization of drug use. In contexts where opioid substitution therapy and ART adherence support programs are widely accessible, evidence highlights comparable levels of survival among HIV-positive PWID and people living with HIV who do not inject drugs.

Summary—The life-saving benefits of ART can be realized among HIV-positive PWID when it is paired with strategies that address barriers to evidence-based medical care. Joint administration of ART and opioid substitution therapy, as well as repeal of punitive laws that criminalize drug users, are urgently needed to reduce HIV and injection-related mortality among PWID.

Keywords

antiretroviral therapy; HIV; injection drug use; mortality; survival

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

The widespread rollout of combination antiretro- viral therapy (ART) has markedly altered the natural history of HIV infection. Improved tolerability, safety, and efficacy of therapies, in addition to scale-up of strategies to promote access and adherence to ART, have led to dramatic declines in all-cause mortality of people living with HIV (PLHIV) across a variety of settings and among diverse populations [1**,2,3**,4].

Unfortunately, the gains made in the modern ART era have not fully extended to all PLHIV, including many of the estimated 1.7 million HIV- positive people who inject drugs (PWIDs) worldwide [5]. Despite advances in availability and tolerability of treatment, mortality remains high among HIV- positive PWID when compared with other key populations of PLHIV, in low-, middle-, and high-income settings [6–9,10*,11,12,13*,14,15,16*,17–23]. For example, across the 16 European and North American cohorts in the Antiretroviral Therapy Cohort Collaboration, which comprise 32 703 HIV-positive adults who started ART between 2000 and 2009, all- cause mortality among people with a history of injection drug use (IDU) was more than twice that of individuals with no history of IDU [10*]. Such stark inequities are especially troubling in the context of healthcare settings with well established ART delivery systems, programming, and supports for individuals who experience barriers to treatment adherence.

As the estimates of lower life expectancy among PWID are frequently grounded in individual-level analyses, most research cites IDU as a risk factor for premature mortality because of higher levels of various health and social harms (e.g., higher prevalence of comorbidities [24*] and injection-related illnesses, greater socioeconomic disadvantage [25*], inferior contact with the healthcare system [9,11,26]). However, the influence of sociostructural factors on mortality of PWID in the era of modern ART remains relatively under-researched. We review recent research that identifies factors contributing to premature and preventable mortality of HIV- positive PWID, drawing attention to the dearth of research on the social, systemic, and structural barriers that drive these inequities, and describe the promise of interventions to remove such obstacles and improve survival in this group.

HIV/AIDS-RELATED MORTALITY IN THE MODERN TREATMENT ERA

Given high levels of adherence, ART suppresses HIV to undetectable levels in plasma, restoring immune function and preventing progression to death [27], as well as secondarily preventing HIV transmission [28]. Accordingly, the expansion of ART has led to important shifts in the causes of death in comparison with deaths preceding the widespread availability of ART. Recent data from The Joint United Nations Programme on HIV/AIDS described a 19% decline in AIDS-related deaths from 2011 to 2014, and a 35% decline from 2005 to 2014 [1**]. Among HIV-positive PWID however, the leading cause of death remains HIV/AIDS-related causes [2,3**,7,29,30,31*,32–34,35*,36**,37], reflecting suboptimal levels of ART access, and adherence in this population.

Low levels of ART coverage among PWID populations is a concern in both low and high-income settings worldwide, with only an estimated one in 10 HIV-positive PWID on ART

[1**]. A review of care and treatment targets for HIV-positive PWID in six countries that account for half of the global PWID population demonstrated staggering short- falls in ART access among this population. The review noted increasing ART coverage in Malaysia, China, Ukraine, and Vietnam; however, policies governing care and treatment of HIVpositive PWID in the United States and Russia have not shifted. For example, Russia's most recent update demonstrates approximately 1% of all HIV-positive PWID were accessing ART in 2010. The deficiencies in ART coverage across these countries were driven largely by macrolevel barriers, such as funding gaps and policies, deterring effective HIV prevention, and treatment for PWID [38]. Additionally, criminalization of drug use in these and other settings [39] continues to clash with public health policies aimed at improving access to HIV prevention and treatment coverage.

Moreover, many studies describe suboptimal ART adherence among PWID [40] despite wide- spread evidence that PWID are able to achieve the same levels of adherence as PLHIV who do not inject drugs [41], suggesting that both social and policy- level barriers to optimal ART adherence among this group persist. For example, research has shown that physicians often defer ART initiation for some PWID because of concerns of a so-called unstable lifestyle and competing priorities that could lead to noncompliance, and potentially the emergence and transmission of drug-resistant HIV [38]. Such concerns have subsequently contributed to lower levels of access to treatment among HIV-positive PWID [42], thus contributing to higher mortality rates in this group.

Additionally, PWID systemically experience disproportionate levels of homelessness [9,25*, 29], untreated mental health comorbidities [37], polysubstance use [32] (including alcohol use [33]), and lower levels of healthcare engagement [9], all of which shape access and adherence to ART, as well as progression to AIDS and death. Additionally, incarceration [1**,43] and personal violence [3**,7,10*] remain persistent issues among HIV-positive PWID, with research demonstrating increased rates of suicides [7,44] being independently associated with a history of IDU (adjusted hazard ratio: 3.95; confidence interval: 1.99 – 7.86) [44]. Studies conducted in settings without universal healthcare may not be able to distinguish the effect of the aforementioned factors independent of the influence of financial need. However, Joseph and colleagues [45] demonstrated that even in a setting with free access to HIV care, becoming non-adherent was associated with periods of homelessness, active IDU, and incarceration. In the same setting, Zivanovic and colleagues [25*] found that after adjusting for confounders such as HIV infection and drug use patterns, housing instability was independently associated with all-cause mortality in a cohort of PWID. This research highlights the need to consider contextual factors in the design of HIV care and treatment to PWID beyond treatment access, extending to the provision of basic subsistence needs, including supportive housing.

Additionally, studies undertaken in healthcare settings with programs that address barriers to ART access and adherence through low-threshold approaches such as maximally assisted therapy and directly administered ART programs provide an opportunity to observe the impact of treatment on survival of PWID. A study of PLHIV on treatment in British Columbia, Canada, where ART treatment and care are provided free of charge, highlighted that cumulative non-accidental mortality rate was not statistically different between

individuals with a history of injection compared with non-injectors [46]. These results were echoed in a study from Melbourne, Australia, where PWID on HIV treatment were no more likely to experience AIDS or death than non-injectors [47]. More recently, Hayashi and colleagues [3**] reported rates and predictors of death among HIVpositive PWID in the context of a province-wide treatment as prevention (TasP) initiative aimed at improving access and adherence to ART in British Columbia. The 18-year cohort study of com- munity recruited HIV-positive PWID showed slow declines in HIV-related death in the late 1990s to early 2000s with high overall levels of mortality among PWID. Significant reductions in HIV-related mortality rates were observed among PWID from 2010 onward, coinciding with TasP-based efforts to scale-up treatment in this population [3**]. Such studies add to the growing consensus that where care is taken to address ART access and adherence barriers faced by HIV-positive PWID, this population can experience the same outcomes as non-injecting PLHIV, including improved life expectancy.

DRUG-RELATED FATALITIES

A review examining non-AIDS mortality among HIV-positive and HIV-negative PWID across 42 cohort studies in 18 countries, found that HIV- positive PWID experience greater levels of mortality from non-AIDS-related causes than their HIV- negative counterparts. The authors suggest the need for further research to understand if this finding is driven by HIV-positive PWID's poorer physical health, increased social disadvantage, or greater likelihood of engaging in higher risk behaviors that may contribute to fatal outcomes, namely, drug overdose [24*]. Indeed, overdose and accidental poisoning have been highlighted in recent scholar- ship as a leading cause of death for HIV-positive PWID [3**,7,11,31*,32–34,35*, 36**]. In a prospective multicenter study of HIV and HCV co-infected patients across six Canadian provinces, 18% of the cohort died because of drug overdose during the study period [11].

Evidence-based harm reduction may mitigate risk of death among HIV-positive PWID by reducing fatal overdose, as well as facilitating adherence to life-saving ART [48]. Studies undertaken in Vancouver, Canada, between 1996 and 2011 report a marked decline in rates of all-cause mortality among PWID [3**,29]. For example, Lappalainen and colleagues [29] found that rates of accidental death, inclusive of overdose, fell from 12.79 deaths per 1000 person-years from 1996 to 1999 to 8.56 deaths per 1000 person-years in 2008 – 2011. The shift is credited to significant investments in harm reduction approaches in this setting, including North America's first legal supervised injection site. Researchers have also hypothesized that positive interactions between clients and staff at harm reduction facilities and shifts in type of drug use might partially explain the declines in drug overdose during the study period [29].

Additionally, several studies have demonstrated the efficacy of pharmacological interventions, such as provision of opioid substitution therapy (OST) [24*,36**], including methadone maintenance therapy [37]. Notably, in a systematic review examining non-AIDS mortality among PWID, non-AIDS crude mortality rates were more than three times greater during periods without OST than during periods with OST, although the authors caution that data on OST coverage are limited [24*]. Nosyk and colleagues showed a significant

reduction in risk of death associated with both ART and OST, although the greatest reduction in risk of death was observed when both OST and ART were used together. This study provided compelling evidence of the benefit of combined ART and OST services to protect against HIV-related and drug-related death and death from other causes [36**]. However, the World Drug Report shows that only 79 of 192 countries providing data offered OST [5]. Such evidence highlights the sociostructural factors – including punitive laws, severe human rights abuse, inadequate prevention services, and stigma associated with IDU – impeding access to harm reduction worldwide [1**]. It is important to note that even in settings with access to OST, barriers to initiate OST (e.g., rigid intake criteria and lengthy waitlists) and maintain treatment (e.g., no individualization of treatment and no patient choice on medication and dose) [49] remain, which impacts ART adherence for HIV-positive PWID [48]. In light of the evidence of the efficacy of OST reducing drug-related fatalities, and facilitating access to life-saving ART, these impediments urgently need to be addressed.

ADDRESSING HEPATITIS C VIRUS- RELATED MORTALITY

Research has underscored the impact of liver-related diseases [2,11,30,31*,50], including hepatitis C virus (HCV) [7,34,51], on premature mortality among HIV-positive PWID, with HIV – HCV co-infected individuals having a significantly increased risk of death [11]. A 15-year prospective cohort study investigating predictors of liver-related death in a cohort of PWID in Vancouver showed that HIV seropositivity was independently and positively associated with liver-related mortality [31*]. Notably, individuals who were HIV – HCV co-infected had a 2.53 (95% confidence interval 1.18 – 5.46) times hazard of liverrelated death compared with individuals who were HCV mono-infected. These findings add to the wealth of studies [52] calling for expansion of HCV testing and treatment, specifically among HIV-positive PWID [31*].

In light of the new direct-acting antivirals for HCV treatment, which have the potential to reduce incidence of liver-related disease, the research reviewed here, in addition to lessons leveraged from the early history of ART, may prove pivotal in addressing HCV-related mortality among PWID. First, the various barriers to adherence described above are modifiable because of the development of evidence-based interventions. When these barriers are addressed, PWID – presumed to be ‘hard to reach’ – are able to achieve similar outcomes to people who do not inject drugs. Second, where possible, service integration (e.g., HCV and ART treatment with addictions treatment) facilitates treatment success. Third, addressing stigma in all of its manifestations (e.g., in healthcare settings and in public policy) is critical as individuals who are marginalized are far less likely to access care and treatment.

Although various lessons learned from HIV treatment interventions may be suitable to mitigate HCV-related mortality, possible HCV reinfection often adds to provider concerns around prescribing HCV treatment to PWID; particularly, patients who are likely to continue injecting drugs after clearing HCV. Research on the likelihood of reinfection for PWID is inconclusive, with some studies suggesting reinfection is low among PWID [53], whereas others reporting high reinfection rates among patients who continue to inject during and

following HCV treatment [54]. Taken together, this research suggests that in addition to provision of harm reduction programming and OST, there is an urgent need to apply a TasP approach to HCV treatment (i.e., scale-up of prevention and treatment services) to reduce HCV-related mortality among PWID.

FUTURE DIRECTIONS

Understanding the factors that contribute to higher levels of mortality among HIVpositive PWID is instrumental to both the design of targeted interventions that address modifiable barriers to treatment success and to treatment parity with non-injecting PLHIV. This review suggests that recent research on mortality among HIV-positive PWID has not focused on the underlying social– structural drivers of these harms, although these factors have been well characterized in previous research [55]. For example, it is well established that HIV-positive Indigenous PWID are disproportionately impacted by HIV in a variety of settings [56,57]. However, with the exception of one study that observed significant improvements in Indigenous HIV-positive PWID's HIV treatment and care [58], issues impacting survival in Indigenous communities were not extensively addressed in recent research.

Having identified a need for a social–structural approach to understanding survival of PWID in the modern ART era, we designed a conceptual model adapted from Rhodes' seminal 'risk environment' framework. Rhodes [59] conceptualizes the physical and social spaces in which a multitude of factors exogenous to the individual interact to produce or reduce drug-related harm. He calls for a recognition of the interplay between factors that operate within and across physical, social, economic, and policy environments at the macro, meso, and microlevels [60]. Our proposed framework (Fig. 1) situates the observed elevated levels of mortality among HIV-positive PWID within the various contexts that shape health outcomes, and aims to explain the pervasive inequities that underpin these outcomes. As such, this framework provides a more critical perspective of the broader structural determinants shaping access to ART, harm reduction programming, and basic necessities for individuals to safeguard health and quality of life. Reporting elevated levels of mortality among HIV-positive PWID compared with non-injecting PLHIV without addressing the social – structural factors that shape health outcomes will fail to uncover the root of these inequities. Future research must include improved methods of measuring and reporting the impact of social – structural barriers to treatment, as well as interventions that address basic material needs and rights (e.g., housing support, employment initiatives, nutrition programs, and social sup- port). Moreover, we must continue to examine cause of death, which accurately characterizes the failures of health, social, and legal systems, thus resisting the tendency to downgrade blame to the individual.

CONCLUSION

The potential for ART to have far-reaching benefits on the longevity and health for PWID is within our rasp. However, if treatment barriers are left unchecked as ART expansion continues, disparities between HIV-positive PWID and PLHIV who do not inject will be exacerbated, undermining the advances made in the modern ART era. Now is not the time to consider health inequities and treatment barriers as insurmountable, but to document and

scale-up evidence-based treatment modalities that are effective in facilitating access and adherence to ART.

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KEY POINTS

- Elevated mortality levels among HIV-positive PWID are driven by social–structural barriers to ART access and adherence.
- Recent research suggests that ART expansion, paired with evidence-based harm reduction approaches, is associated with markedly improved life expectancy among HIV-positive PWID.
- In order for the advances of the modern ART era to benefit HIV-positive PWID, efforts to mitigate social– structural barriers to treatment and harm reduction programming must be expanded, particularly strategies to address criminalization and stigmatization of drug use.

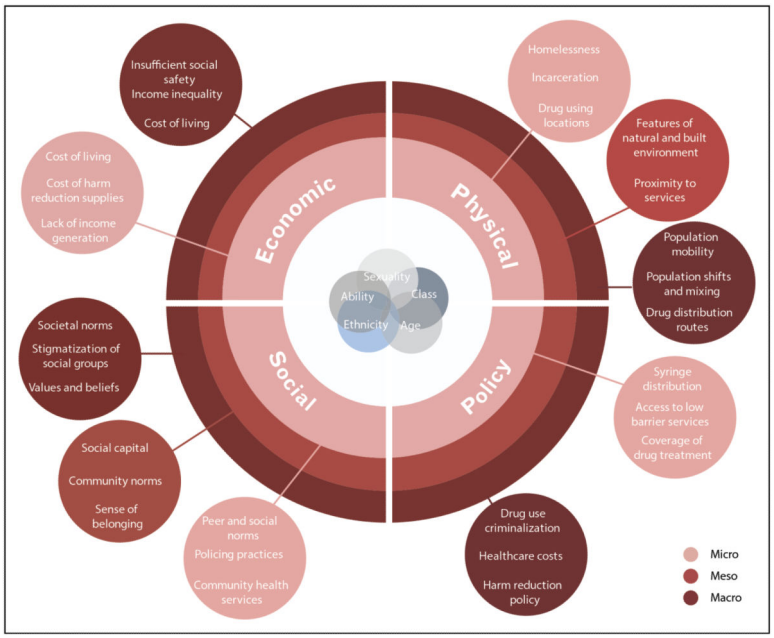

FIGURE 1.
Sociostructural factors impacting survival of HIV-positive people who inject drugs.