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NOTES FROM THE FIELD

Double Jeopardy: Methamphetamine Use and HIV as Risk Factors for COVID-19

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Among men who have sex with men (MSM), the co-occurrence of methamphetamine (meth) use and HIV could create a double jeopardy for coronavirus disease 2019 (COVID-19). Co-occurring meth and HIV could amplify biological and behavioral risk for infection with the novel coronavirus (SARS-CoV-2), presenting unique challenges to halting community-level transmission. This confluence of bio-behavioral risk factors related to meth and HIV may also synergistically enhance vulnerability to COVID-19 progression. Below we provide an overview of important areas for further research regarding the potential implications of the intertwining epidemics of meth use and HIV for the COVID-19 pandemic in MSM.

The use of meth and other stimulants has consistently been identified as a potent driver of the HIV/AIDS epidemic in MSM [1–3]. Despite successful deployment of public health interventions that specifically targeted meth in MSM [4–6], there is a resurgent epidemic of meth use in the United States [7]. Beginning in 2011, recent meth use doubled (from 4 to 9%) among MSM in New York City [8], and comparable increases in meth use were observed among MSM in San Diego [9]. This trend is corroborated by concomitant increases in meth use in other urban areas such that national rates are meeting or exceeding 2005 peaks [10]. There is also increasing recognition that stimulant use is prevalent in ethnic minority MSM where HIV incidence is the highest [11]. For example, recent findings from our team indicate that one-in-five young Black MSM in Texas reported stimulant use in the past 2 months [12]. There is an urgent need to deploy comprehensive, multi-level interventions targeting the intersection of stimulant use and HIV among MSM [1, 13].

The resurgence of meth use in MSM threatens to compromise biomedical approaches to HIV/AIDS prevention, such as treatment as prevention (TasP), and fuel the COVID-19 pandemic. The prevalence of stimulant use is twofold greater among MSM living with HIV [14], and stimulant use undermines the clinical and public health benefits of TasP. Our team and others have demonstrated that people living with HIV who use stimulants experience profound difficulties with navigating the HIV care continuum, including poorer anti-retroviral therapy (ART) adherence and persistence, that lead to slower rates of viral suppression [15–18] and faster mortality [19, 20]. Even in the era of universal ART, stimulant users in a clinical cohort comprised mostly of MSM receiving HIV care at Zuckerberg San Francisco General Hospital reached viral suppression more slowly [15]. It is plausible that the COVID-19 pandemic will present new barriers to engagement along the HIV care continuum, which could disproportionally affect people who use stimulants. This could include difficulties with obtaining timely laboratory results or refilling ART medications. The difficulties that people who use stimulants experience with achieving and maintaining viral suppression could enhance biological vulnerability to SARS-CoV-2 infection as well as lead to faster COVID-19 progression.

HIV is already damaging the immune system even when people are virally suppressed, a phenomenon referred to as residual immune dysregulation [21], which meth use amplifies to create a double jeopardy for COVID-19.

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There is increasing evidence from our team and others that meth use can induce gut-immune dysregulation, even among those with treated HIV infection [22–26]. In our prior bio-behavioral research conducted with MSM with treated HIV infection who use meth, those who provided a urine sample that was reactive for stimulants (i.e., meth or cocaine) displayed differential expression of genes and 2-directional perturbation of pathways relevant to systemic immune activation and inflammation [25]. These perturbations in gene expression relevant to immune dysregulation among those providing a urine sample that was reactive for stimulants were paralleled by elevations in plasma tumor necrosis factor-alpha (TNF-α), an important marker of systemic inflammation. We also observed concomitant elevations in soluble CD14 (sCD14), a clinically relevant plasma marker of monocyte activation [27], in those providing a urine sample that was reactive for stimulants. This partially reflects stimulation of monocytes with lipopolysaccharide leaking from the gastrointestinal tract [26]. The clinical relevance of these findings is supported by the fact that markers of systemic immune activation and inflammation are implicated in multiple, chronic medical conditions such as cardiovascular disease in people living with HIV, which have been identified as key risk factors for COVID-19 progression [28, 29].

Meth use could also contribute local immune dysregulation as well as alter the expression of angiotensin-converting enzyme 2 (ACE-2) receptors, a key site for SARS-CoV-2 binding in the lungs and small intestine [30]. Smoking is a prevalent mode of administration for meth and crack-cocaine that could enhance local immune dysregulation in the lungs and modify the expression of ACE-2 receptors to increase vulnerability to SARS-CoV-2 infection and COVID-19 progression. There are also three plausible biological pathways for meth-associated exacerbation of microbial translocation (i.e., the leaky gut) that could serve as a primary driver of systemic immune dysregulation, particularly among those living with HIV. First, the meth decreases parasympathetic tone [31], which could increase intestinal permeability. Second, meth directly damages gut barrier integrity in self-administering HIV-1 transgenic rats [32]. Third, meth-associated indoleamine 2,3-dioxygenase upregulation in treated HIV infection damages gut barrier integrity [33]. These meth-induced alterations to the gastrointestinal tract may be partially responsible for systemic immune dysregulation in people living with HIV who use meth and further research is needed to determine if meth use alters ACE-2 receptor expression in the small intestine [30]. Taken together, pulmonary immune dysregulation, gut-immune dysregulation, and enhanced ACE-2 receptor expression are biologically plausible pathways whereby co-occurring meth use and HIV could heighten vulnerability to SARS-CoV-2 infection and COVD-19 progression.

In early March of 2020, epidemiologic experts warned that as much as 70% of the population could become infected with SARS-CoV-2 without broad implementation of social distancing such as restrictions on interactions in large groups [34]. Recent forecasting models and data strongly suggest that the number of COVID-19 cases will grow exponentially in countries that do not achieve high rates of adherence to social distancing guidelines [35]. Because meth use has been consistently linked to sexual risk taking behaviors among MSM [1], it is likely that people who use meth will experience greater difficulties with adhering to COVID-19 social distancing guidelines. Men will continue to seek out partners for substance use and sex, which will potentiate COVID-19 clusters among MSM and present a key challenge to halting community-level transmission. In fact, there are reports of meth-fueled sex parties among MSM during the COVID-19 lockdown in Spain [36] and COVID-19 clusters from a recent Miami circuit party [37]. Further research is needed to examine meth use and other behavioral correlates of adherence to social distancing guidelines. This represents a critical first step to informing targeted deployment of limited public health resources to "flatten the curve" of the COVID-19 pandemic.

It is also clear that the COVID-19 pandemic represents a chronic, uncontrollable stressor that could exacerbate psychiatric disorders and increase risk for SARS-CoV-2 infection. Those living with stimulant use disorders could experience new barriers to accessing and remaining engaged in substance use disorder treatment programs as well as 12-step self-help groups, increasing risk for relapse [38]. Furthermore, the stress and social isolation individuals experience during social distancing could serve as a potent trigger for alcohol and other substance use. There is a clear need for scalable, mHealth interventions to address the psychiatric burden of the COVID-19 pandemic. We have previously demonstrated the efficacy of a positive affect intervention for improving psychological adjustment and achieving durable reductions in viral load for people living with HIV [39], including MSM living with HIV who use methamphetamine [40, 41]. We have also demonstrated that it is feasible and acceptable to deliver this positive affect intervention to various populations in a self-guided, online format [42–45]. Furthermore, there is other evidence to support the potential benefits of text messaging for reducing condomless sex [46] and mHealth applications for improving ART adherence in MSM who use meth [47]. Further clinical research is needed to characterize the psychiatric consequences of the COVID-19 pandemic and test novel mHealth approaches to improve adherence to social distancing guidelines in MSM who use meth and other stimulants.

The COVID-19 pandemic is rapidly evolving, leaving more questions than answers regarding how best to mitigate its devastating effects. At this stage, there clearly is

an urgent need for research to examine the implications of co-occurring meth use and HIV for SARS-CoV-2 acquisition as well as COVID-19 progression. Identifying the bio-behavioral mechanisms that could account for the potential double jeopardy experienced by those living with co-occurring meth use and HIV will inform efforts to halt community-level SARS-CoV-2 transmission and reduce risk for COVID-19 progression. It is also clear that the COVID-19 pandemic presents unique challenges to engagement along the HIV care continuum as well as engagement in substance use disorder treatment that warrant further study. Finally, the COVID-19 pandemic underscores the urgent need for mHealth approaches to reach high priority populations to "flatten the curve" of the COVID-19 pandemic. Efforts to stem the tide of the COVID-19 pandemic will require a sustained, coordinated response that integrates behavioral and biomedical approaches much like we have witnessed in over three decades of the HIV/AIDS epidemic.

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