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On the issue of treating HIV in people with syndemic mental-health and substance-use disorders

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SUMMARY:

People with HIV and comorbid substance use problems may be among those who benefit most from long-acting HIV antiretroviral treatment, but they are routinely excluded from Phase 3 clinical trials. Their inclusion would permit an examination of the clinical value of long-acting therapies for people with adherence problems and an exploration of syndemic interactions between HIV, mental health conditions, and substance use problems, which compound into a major challenge in the efforts to end the HIV epidemic.

Syndemic theory is a useful biopsychosocial framework to understand the higher prevalence of mental health conditions and substance use problems among people with HIV (PWH). The theory entails that it is fundamental to examine the synergy of coexisting epidemics to explain the confluence of factors leading to vulnerabilities and the emergence of disease. Based on observations that social factors strongly influence vulnerability to infection, and that infections interact (e.g., HIV and hepatitis C virus co-infection) at the biological level to accelerate disease progression, the syndemic theory argues that the development and accumulation of psychosocial health problems would further interact to exert a synergistically negative impact on health¹ and infection outcomes. Although studies have demonstrated that greater accumulation of psychosocial conditions such as depression,

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Author Contributions

DJG – conceptual development, discussions, and manuscript writing; JM – clinical data analytic input and discussions; VDW – basic science input, discussions and manuscript revision; JI – discussions; RE – discussions and manuscript revision; IG – conceptualization, discussions, and manuscript revision; SL – discussions; MCGM – conceptualization, conceptual development, discussions, coordination, and manuscript writing; MC – conceptualization and coordination.

Competing interest's statement

The authors declare no conflicts of interest.

violence victimization, hazardous alcohol use, and/or drug use is additively associated with higher rates of HIV transmission and worse health outcomes among PWH¹, evidence from these same individual-level data supporting synergistic interactions between psychosocial conditions is limited². However, studies have not routinely explored how interactions with or between biological factors affect health outcomes, or how intervention treatments, including antiretroviral treatment (ART) in the context of HIV, might modify these relationships. Syndemically, HIV, mental health conditions, and substance use problems highlight the merging of three epidemics into one of the most significant social and health crises of modern times, we need to understand how these conditions and their treatment interact at the biological level to affect health outcomes.

The known interactions of HIV and psychosocial health conditions remind us of the unique challenge mental health and substance use problems pose to HIV prevention and care. For example, methamphetamine use is associated with behaviors (e.g., injection use, unprotected sex with multiple partners) that increase the likelihood of exposure to HIV. At the biological level, methamphetamine exposure increases susceptibility to HIV transmission and disease progression through mechanisms that facilitate HIV viral entry, promote resistance mutations, compromise immune defenses, have the potential to create persistent low-level viral replication despite ART, contributing to the severity of a spectrum of HIV-associated neurocognitive disorders (HAND)³⁻⁵. Mental health conditions and substance use problems, such as depression and methamphetamine use, have also been associated with inflammation and immune-metabolic and blood-brain barrier disruptions that contribute to end-organ injury in the central nervous system (CNS) leading to neurocognitive impairment⁶.

Failure to address these syndemic conditions is problematic from a clinical and a public health perspective. PWH and mental health and substance use problems face challenges in maintaining viral suppression, mostly due to difficulties in adhering to antiretroviral treatment (ART)⁷. This increases individual morbidity and mortality and interferes with the considerable public investment in treatment as prevention. HIV treatment prevents HIV transmission through viral suppression. HIV is not transmissible from PWH who have an undetectable HIV viral load, an important public health message referred to as Undetectable=Untransmissible or U=U. Available long-acting ART (Table 1) presents a treatment option that enhances ART adherence by eliminating the need for daily oral therapy. In the absence of effective cures or vaccines, long-acting oral, injectable, implantable, intravenous, and/or combination treatment strategies, including pre-exposure prophylaxis, hold great promise in leveraging treatment as prevention to reduce HIV incidence. Although adherence to daily oral therapy is worse among PWH who use drugs⁸, data on adherence to long-acting ART among PWH and substance use do not exist in part due to the exclusion from clinical trials of PWH with any “mental condition (including substance use disorder) which, in the opinion of the Investigator, may interfere with the subject’s ability to comply with the dosing schedule and/or protocol evaluations”. A similar gap exists in understanding the effects of methamphetamine and other illicit drugs on long-acting ART, including efficacy, drug-drug interactions, downstream health consequences including CNS integrity and neurobehavioral functioning (e.g., cognition, mental health), sex, gender, and other biological and social factors⁹.

Long-acting ART is not without its logistical challenges (Table 1), but PWH and SUD and mental disorders may benefit most from long-acting treatments to improve rates of viral suppression and decrease HIV transmission¹⁰. Therefore, it is imperative that long-acting ART be tested among PWH and mental and substance use disorders by including them in Phase 3 clinical trials, as well as effectiveness-implementation hybrid design studies conducted in diverse HIV care settings. Concurrently, studies ought to explore biological and social factors and their interactions that might affect long-acting ART efficacy and its impact on health outcomes, including reducing mental health problems and preventing progression of neuropsychiatric comorbidities (e.g., by reductions in systemic and neuro-inflammation). These data can inform the development and delivery of long-acting ART approaches to enhance durable viral suppression and improve CNS health among PWH and mental and substance use disorders to reduce morbidity and mortality in this population and end the HIV epidemic.

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Table 1.

Current long-acting injectable antiretroviral therapy

Drug regimen	cabotegravir + rilpivirine
Brand name	Cabenuva
Current Indication	Treatment of HIV in people 12 years and older who weigh at least 77 pounds. Treatment of HIV in those who are virologically suppressed (HIV-1 RNA < 50 copies/ml) on a stable antiretroviral regimen with no history of treatment failure and no known or suspected resistance to either cabotegravir or rilpivirine.
Oral lead-in	Optional
Dosing	600 mg/3 mL cabotegravir and 900 mg/3 mL rilpivirine at baseline, 1 month, then every 2 months
Administration	Two intramuscular injections at separate gluteal sites during same visit
Logistical challenges	Clinic-administered. Can be given +/- 7 days of when due. Missed doses require immediate bridging with oral therapy due to risk of developing resistance. Requires 45 min at room temperature before administering injection.

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