TAG
Treatment Action Group

Treatment Action Group Public Comment on NIDA Strategic Plan for Research at the Intersection of HIV/AIDS and Substance Use, Misuse, and Addiction

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1 Treatment Action Group (TAG) thanks the National Institute on Drug Abuse (NIDA) for the opportunity to comment on its Strategic Plan for advancing science at the intersection of HIV/AIDS and substance use.

2 TAG is an independent, activist, and community-based research and policy think tank fighting for better treatment and prevention, a vaccine, and cure for HIV, tuberculosis (TB), and hepatitis C virus (HCV). We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions to end the HIV, TB, and HCV epidemics.

3 **We encourage the NIDA Strategic Plan to recognize the importance of research into preventing and treating TB in the context of HIV, HCV, and drug use**. Incorporating TB into the Strategic Plan would reinforce several of the high priority research areas identified at the two NIDA-hosted scientific workshops. In particular, the aims to "reduce comorbidities and complications related to substance use disorders (SUD) and HIV/AIDS" and to "enhance patient centered approaches to HIV and SUD treatment."

4 Drug use is associated with a higher prevalence of TB infection and incidence of TB disease, and HIV-associated immunosuppression is one of the most important drivers of high TB incidence among people who use drugs (PWUD).[1] In turn, people with HIV who use drugs are at a higher risk of TB infection progressing to active TB disease, and may also experience a higher risk of TB transmission owing to a combination of biomedical and structural factors.[2] These factors range from an impaired cell-mediated immune response (owing to either the effects of opiates or HIV) to the crowded, poorly ventilated settings in which drug use is common (e.g., prisons, drug treatment programs, homeless shelters).

5 While the close linkages between HIV, TB, and drug use are well recognized, challenges in the clinical care and management of these three conditions remain in need of solutions. In particular**, we call NIDA's attention to the need for additional research on managing the complex drug-drug interactions arising from concomitant treatment of drug use, HIV, and TB**. Drugs used to treat opioid addition, HIV, and TB share metabolic pathways (e.g., the cytochrome P450 system). The induction of hepatic enzymes by rifampicin is well known to reduce exposures to both opioid substitution therapies (OST) and key antiretroviral agents (ARVs) in clinically significant ways. Even where these rifamycin-related pharmacokinetic/pharmacodynamic (PK/PD) effects are well characterized, as with methadone, there is a need to fill research gaps that have emerged in the wake of changes to the treatment of TB infection and disease in recent years.

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[1] Deiss R, Rodwell T, Garfein R. Tuberculosis and illicit drug use: review and update. Clin Infect Dis. 2009;48(1):72–82. doi: 10.1086/594126.

[2] Friedland G. Infectious disease co-morbidities adversely affecting substance users with HIV: hepatitis C and tuberculosis. J Acquir Immune Defic Syndr. 2010;55(1):S37–42. doi: 10.1097/QA1.0b013e3181f9c0b6.

6 **Of high priority is additional research into drug-drug interactions between methadone and buprenorphine and new, short-course regimens to treat TB infection based on TB drug rifapentine**. The 3HP regimen (12 once-weekly doses of isoniazid and rifapentine) and the 1HP regimen (one month of daily isoniazid-rifapentine) have not yet been studied in the presence of OST. Without such research, it may be difficult for clinicians to extrapolate from knowledge of how treating active TB disease with rifampicin affects OST exposures to predict effects when rifapentine-based TB preventive therapy is given with OST.

7 In addition, **drug-drug interactions between OST, ARVs and second-line TB drugs for the treatment of drug-resistant TB remain poorly defined**. For example, research is needed into whether newer TB drugs bedaquiline and delamanid interact with methadone and buprenorphine. Bedaquiline, delamanid, and methadone all prolong the QTc interval, but whether this effect is additive or even clinically meaningful is not known. **In addition to defining drug-drug interactions, it is important to study the safety of TB medications in PWUD being treated for HIV and HCV.** For example, TB drugs such as isoniazid pose a risk of hepatotoxicity and may therefore be difficult for PWUD with HCV to tolerate.

8 Research into TB, HIV, HCV, and OST drug-drug interactions will likely require dedicated PK/PD studies. In addition, **we urge NIDA to explore whether TB-related questions can be answered using data from biological, phenotypic, and clinical data in NIDA's Collaborating Consortium of Cohorts**. Incorporating TB questions into these cohorts may offer a sustainable way to collect data that would have a significant impact on improving clinical guidelines for addressing TB in the context of HIV, HCV, and drug use.

9 **In addition to supporting work to better define drug-drug interactions between TB, HIV, HCV, and OST medications, we urge NIDA to support research into models of care that can safely and successful treat TB infection and TB disease in PWUD with HIV**. TB should be incorporated into work NIDA supports under the research aim to "increase understanding of stigma and structural determinants of health and their role in effectively preventing and treating HIV/AIDS and SUDs." There is also a need to study optimal models of care and timing of co-treatment of HCV and HIV in patients with drug-resistant TB. The long duration of drug-resistant TB treatment (which can last up to 18–24 months depending on the regimen used) may make normal guidance to complete TB treatment before starting HCV treatment ill advisable for some patients.

10 We thank NIDA for the opportunity to provide this feedback and ask that you please contact Mike Frick, TAG TB Project Co-director, with any further correspondence (mike.frick@treatmentactiongroup.org).

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