

New: a project or initiative that has never been funded, **Expansion:** a project or initiative that has been funded at the President's Budget or Commitment base levels with AIDS funds

NIDA FY17 Priorities

Project Title: Unsolicited Investigator-Initiated Research

Mechanism(s): R01, R21, R34, R03, R13, P30, P50, R24, U01, UG1, P01, Contracts

New or Expansion: Expansion

% of Minority/International: M 35%, I 12%

Areas of Emphasis: 1A, 1B, 1C, 2A, 2B, 2C, 2D, 2E, 2G, 4A, 5A, 5B, 5C, 5D, 6C, 6D, 6E7A, 7B, 8A, 8B, 8C, 9A, 9B

Narrative Justification:

This initiative addresses the following overarching priorities: 1) Reducing the incidence of HIV/AIDS; 2) Develop the next generation of HIV therapies with improved safety and ease of use; 3) Research towards a cure; and Improve our capacity to prevent and treat HIV-associated comorbidities and coinfections. In addition, NIDA's portfolio addresses the cross cutting areas of basic research, health disparities, and training. NIDA supports domestic and international research on HIV/AIDS associated with both injection and non-injection substance use. NIDA's research focuses on vulnerable populations who tend to be underserved and not engaged by health care services. Use of illicit and licit drugs, often in the context of polysubstance abuse continues to be a major factor in driving HIV incidence and in adversely impacting HIV treatment success. NIDA's seeks to prevent HIV acquisition and transmission associated with use of injection paraphernalia and/or high-risk sexual behavior in the context of substance use. In addition, NIDA's research seeks to improve the HIV continuum of care by improving access, linkage to treatment services, adherence, and long-term retention. Another priority is reduction and mitigation of HIV- associated co-infections and co-morbidities associated with HIV/AIDS among substance users.

To improve individual health and reduce HIV transmission to the community, NIDA supports studies of the seek, test, treat, and retain paradigm (STTR), which seeks out hard-to-reach substance using populations, tests them for HIV, links them to treatment and retains them in care. As recently highlighted in the White House's "National HIV/AIDS Strategy for the United States Update to 2020," treatment for substance use disorders is an efficient HIV prevention intervention that has been shown to increase adherence to HAART. Research on substance abuse treatment as a component of HIV prevention including studies combining substance abuse and AIDS treatment to enhance adherence and retention, are significant component of NIDA's HIV/AIDS research. NIDA also supports research on the natural history, epidemiology, etiology and pathogenesis, prevention, and treatment of HIV/AIDS and AIDS-related co-infections (e.g., hepatitis C virus (HCV), other sexually transmitted infections (STIs)) and other comorbid conditions (e.g., Neurologic, cardiovascular). NIDA supports studies of drug-drug interactions between medications used to treat substance abuse and medications used to treat HIV, HCV, and other conditions and studies of long-term consequences

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of HIV and therapy for HIV and coinfections in drug using populations. In order to be better able to explore multiple issues relating to HIV in substance using populations, NIDA has enhanced its portfolio of cohort studies, adding MSM cohorts and continuing IDU cohorts, and facilitating harmonization across cohorts. Another research area supported by NIDA is basic research; this includes the use of animal models (including model development) and in vitro systems to study the role of drugs of abuse in HIV/AIDS etiology and pathogenesis; including a major focus on neuroAIDS and research on eradication of HIV reservoirs in the CNS. Research on genetics (host and viral genetic factors), epigenetics, proteomics, and systems biology are major areas of focus of this program; included in this basic research program are studies that examine the effects of drugs of abuse on HIV reservoirs, HIV latency, and other cure-related topics. Because HIV/AIDS associated with substance abuse knows no national boundaries, NIDA supports international research to reduce the intertwined epidemics of HIV/AIDS and substance use. NIDA also participates in collaborative efforts with other Institutes and Agencies in order to leverage resources and conduct complementary research in areas such as HIV and aging, HIV and the CNS, HIV persistence, HIV and HCV co-infection.

NIDA supports initiatives to enhance dissemination of research findings, develop and distribute state-of-the-art treatment and prevention guiding principles. NIDA disseminates the results of important medical discoveries resulting from NIDA funded research initiatives. The NIDA utilizes multiple media platforms, including TV, radio, Web, portable communication devices, print, and social media, to reach both scientific and lay audiences. NIDA sponsors and supports a myriad of meetings, conferences, and workshops each year that bring together scientific experts to discuss critical scientific issues and develop recommendations, or research agendas.

FY 2017 Plan: This initiative is consistent with all the scientific objectives and emphasis areas in the NIH/OAR FY 2017 Trans-NIH Plan for HIV-Related Research except that there are no studies in Emphasis Area #3 Microbicides. Through the NIDA Clinical Trials Network (CTN), NIDA supports studies that integrate HIV care with therapy for addiction. This broad based initiative supports drug abuse researchers who have an ongoing commitment to reducing HIV acquisition and transmission and to improving the lives of drug users living with HIV. Drug users are frequently marginalized and may have multiple comorbid conditions. They are often viewed as "difficult" populations to study. NIDA investigators accept the challenges of research on drug users and have been successful in conducting studies that advance HIV treatment and prevention.

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Project Title: Promoting Retention in HIV Care

Mechanism(s): R01, R21, R34

New or Expansion: Expansion

% of Minority/International: M 60%, I 10%

Areas of Emphasis: 5B, 5C, 5D

Narrative Justification:

This initiative addresses the following overarching priorities: 1) Reducing the incidence of HIV/AIDS; and 2) Develop the next generation of HIV therapies with improved safety and ease of use. The cascade (or continuum) of HIV care proposed by Gardner et al. has had a major impact on understanding the HIV epidemic in the U.S. Although the initial use of the continuum focused on the clinical implications for morbidity and mortality, it has been adopted as a major prevention tool and is used by the National AIDS Prevention Strategy to measure progress in preventing HIV transmission. In order for Treatment as Prevention to be effective in eliminating AIDS, increased attention has been focused on HIV testing in order to reduce the number of HIV+ unaware of their infection. The CDC has estimated that about 60% of transmissions are due to those who are diagnosed but not retained in care (Skarbinski et al. JAMA Int. Med. 175, 588-97, 2015). Generally, those who know that they are HIV+ reduce their risk behavior although the category of those diagnosed but not in care still exhibits significant risk behavior. In addition, identification of new infections enables individuals to engage in HIV care and potentially achieve viral suppression. But in many ways, increasing testing is low hanging fruit. Technologies enable individuals to learn their HIV status within minutes and testing can be performed in a variety of settings. After HIV diagnosis, the next stage in the cascade is linkage to care. Linkage to care is critical, and there are studies underway on linkage to care, including several funded under two Seek, Test, Treat, and Retain (STTR) RFAs.

Long term retention in care has not been well explored. Recently published studies have highlighted how relatively few HIV+ are retained in care (Fleishman et al. JAIDS 60, 249-59, 2012; Hall et al. JAIDS 60, 77-82, 2012). In both studies blacks, younger patients, IDU had worse retention. Fleishman et al. using data from the multi-site HIV Research Network from 2001 to 2009 found that only 21% of all patients established HIV care, met retention criteria in every year, and were not lost to follow-up. Hall et al. analyzed CDC data from people living with HIV (PLWH) in 13 areas in the U.S. in 2009. Less than half of PLWH had laboratory evidence of ongoing clinical care and only two thirds established care within one year after diagnosis. A community based study of IDU indicated that lapses in care were associated with issues related to health care access but that failure to maintain suppressed viral load was associated with social and behavioral factors including alcohol and crack cocaine use (Westergaard et al., 2013). Physicians have hesitated to place IDU on ART even after their CD4 counts had declined as low as 200 (Westergaard et al. 2012). It will be important to determine whether denial of ART to substance abusers, (IDU and those who use non-injection drugs such as

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crack cocaine and methamphetamine) after HIV diagnosis is a factor influencing retention in care. Initiating ART was found to be the strongest correlate of retention in care in a multi-site study of retention in care of patients within one year of their initial care visit (Tedaldi et al., 2014).

Until there is a cure for HIV, PLWH will have to be retained in care throughout their life. Retention in care frequently involves multiple cycles of an individual cycling in and out of care. The concept of "churn," the analysis of the pattern of aggregate measures of retention patterns over time at a population level, may be useful in identifying intervention targets for a particular group. It is important to understand the complex interaction of factors that influence retention in care--these range from individual patient factors such as gender, age, psychiatric or medical comorbidity, SES, through network factors such as social and sexual networks, and system level factors such as access to health care, reimbursement. It may be necessary to tailor the retention intervention to the particular population—an intervention targeted for those who have been in and out of care multiple times may have additional components than one for those newly diagnosed and entering treatment for the first time. A number of strategies have been employed to increase retention in care such as use of peer navigators, case management, incentives, use of technology such as cell phone reminders, but many issues remain in implementing these strategies individually and in combination. For example, while peer navigation has been adopted in many studies, there is no agreement on the elements that should be included in peer navigation. In Africa, there are interventions involving the family and/or the community in maintaining PLWH in care, but there has been little research on adapting such strategies in the U.S. It is important to understand the patient and system level factors that contribute to poor retention. Retention in care is also a broader health care issue for all chronic diseases, and it is possible that strategies employed for other conditions can be adapted to HIV. Re-engagement in care of patients who have dropped out of care is related issue which has also received little attention. Given that substance users may experience HIV treatment interruptions because of life events that they are more likely to encounter such as incarceration, loss of stable housing, it is important that studies be directed toward locating and re-engaging those who have dropped out of treatment.

FY 2017 Plan: This initiative is consistent with the NIH/OAR FY 2017 Trans-NIH Plan for HIV-Related Research for Behavioral and Social Science (Objectives: B, C, and D) targeting entry and retention and re-engagement in care. NIDA has supported Treatment as Prevention (TasP) since 2008. Dr. Julio Montaner's DP1 award proposed that, at a population level, transmission in IDUs could be reduced by aggressively reaching out to IDU (Seek) getting them tested for HIV (Test), getting them onto ARV treatment (Treat), and retaining them in Treatment (Retain). This initiative supports the White House Continuum of Care Initiative by addressing long term retention in care of drug using populations. Many studies have indicated that drug users are less likely to be retained in care. Substance using populations are more likely to experience HIV treatment interruptions because of life events that they are more likely to encounter such as incarceration, loss of stable housing, etc. so there is a need for interventions tailored to substance using populations. NIDA has a number of outstanding researchers, (including a core of infectious disease specialists) who are devoting their research to addressing the complexities of retaining substance users in care and achieving sustained reductions in viral load.

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Project Title: Health Disparities and HIV Prevention and Treatment

Mechanism(s): R01, R21, R03, R34, U01

New or Expansion: Expansion

% of Minority/International: M 85%

Areas of Emphasis: 1A, 1B, 1C, 5A, 5B, 5C, 5D

Narrative Justification:

This initiative addresses the following overarching priorities: 1) Reducing the incidence of HIV/AIDS; and 2) Develop the next generation of HIV therapies with improved safety and ease of use. As the US AIDS epidemic has evolved; ethnic/racial minorities, particularly African-Americans and Latinos bear an increasingly disproportionate share of new HIV infections and people living with HIV. At every step of the HIV cascade of care, minorities are less engaged than the general population. Blacks/African Americans tend to be diagnosed later than Caucasians. Sexual networking patterns and concurrent STI may be significant contributors to the dissemination of HIV among Black/African Americans, particularly within defined geographic areas (e.g., South). HIV risk may be greater in Black/African-American communities because of sexual mixing patterns that involve a greater proportion of same-race partners and more partnerships that cross socio-economic lines. While new infections have remained relatively stable, there has been an increased incidence of HIV among men who have sex with men (MSM), which is being driven by increases in young MSM who are members of ethnic/racial minority groups, particularly young, Black MSM. NIDA has had a an ongoing program addressing vulnerable populations in the U.S., but it is now placing increased emphasis on research on Black/African American women (BAAW) and young Black/African-American men who have sex with men (YBAAMSM).

Black/African American men represented 11% of the male population in the U.S. in 2010, but 42% of HIV infection diagnoses. Black/African-American men who have sex with men account for disproportionate numbers of new cases, particularly among younger men. This is the one population segment where the numbers of new cases has continuously grown in recent years. Knowledge of HIV status is less common among Black/African American MSM than among their Caucasian counterparts, and despite comparable rates of ever receiving HIV testing, the frequency of testing is lower. Incidence appears much greater among YBAAMSM under 25 and most of the HIV+ men in this age group are not aware of their HIV status.

There is a continuing need for new and novel interventions, that can be combined with efficacious interventions (e.g., pre-exposure prophylaxis, post-exposure prophylaxis) to better address the

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heighten risk of transmission and acquisition among substance abusing minority MSM. Substance use, particularly stimulant abuse, has been a barrier to adherence to HIV medications. Studies are needed in MSM to determine whether substance use interferes with the effective use of medication-based pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). High risk MSM who also engage in injection risk behavior may be important targets for PrEP because PrEP has also been shown to be efficacious in preventing injection related HIV transmission as well as sexual transmission. This priority supports the development of comprehensive, multidisciplinary approaches that focus on the interdependent nature of sexual and substance use risk, as well as effects of substance use on adherence to antiretroviral treatment (ART) for HIV treatment and for prevention (including PrEP).

FY 2017 Plan: This initiative is consistent with the NIH/OAR FY 2017 Trans-NIH Plan for HIV-Related Research for Natural History and Epidemiology (Objective A) by characterizing risk factors in vulnerable populations, (Objective B) by evaluating factors influencing uptake and adherence to all steps of the testing and treatment process, and (Objective C) by ensuring that domestic epidemiological studies accurately represents populations at risk for HIV/AIDS. This initiative also supports Behavioral and Social Science (Objectives: A, B, C, and D) in developing, evaluating, and advancing prevention interventions (at both the individual and community level); conducting basic and behavioral research on factors influencing HIV risk behaviors and on the consequences of HIV disease; conducting treatment, health, and social services research for people infected and affected by HIV; quantitative and qualitative research to enhance HIV prevention and care. By focusing on prevention in vulnerable populations in the U.S., this priority area seeks to reduce HIV health disparities, a major goal of the National HIV/AIDS Strategy. Because drug users, particularly minorities, have high rates of incarceration, NIDA has had an ongoing research program in criminal justice populations that seeks to enable criminal justice populations to achieve sustained treatment for substance abuse and HIV. In addition, NIDA researchers have been in the forefront of research on networks, which is particularly applicable to research on minority populations.

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Project Title: Screening, Prevention, and Treatment of Comorbidities and Coinfections in Substance Users

Mechanism(s): R01, R21, R34

New or Expansion: Expansion

% of Minority/International: M 35%, I 10%

Areas of Emphasis: 2 D, 2 E, 6 C, 6 D

Narrative Justification:

This initiative addresses the following overarching priorities: Improve our capacity to prevent and treat HIV-associated comorbidities and coinfections.

Comorbidities:

Consistent with the NIH HIV/AIDS research priorities, the proposed NIDA's priority supports research on co-morbidity associated with HIV among substance abusing populations in domestic and international settings. This research will include the study of physiological/biochemical systems, including, but not limited to: (a) cardiovascular, renal, hepatic, endocrine, neurologic consequences of drugs of abuse and HIV, respiratory/pulmonary consequences of smokable drugs and HIV, excess mortality among HIV treated drug users, and prematurely aging in HIV infected substance abusers; (b) development of integrated medical/therapeutic interventions for drug abuse, and HIV associated diseases; (c) studies of pharmacokinetic/pharmacodynamics drug-drug interactions between drugs of abuse, medications for drug addiction and other co-morbid conditions, and current or potential new HIV/AIDS antiretroviral and HCV antiviral medications.

Cohort studies have demonstrated that drugs of abuse such as cocaine accelerate HIV disease progression and enhance comorbidities, e.g., cardiovascular, metabolic disorders, and neurologic effects. NIDA has an ongoing portfolio of research understanding the mechanisms of HIV neuropathogenesis and the effects of drugs of abuse on CNS disease progression. These studies range from in vitro studies to human cohort studies assessing neurologic disorders and dysfunction. While the era of cART has greatly reduced HIV associated dementia, the prevalence of HIV associated neurocognitive disease has increased as the numbers of PLWH increase. A better understanding of neuroAIDS in drug using populations may lead to more effective therapies.

Coinfections:

The predominant co-infection need among substance abusers is Hepatitis C and HIV co-infection. Although, NIDA does support other HIV co-infections including TB and STIs. Acquisition and

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transmission of hepatitis C (HCV) virus is linked to drug abusing populations in at least 3 distinct ways. First, the primary route of HCV acquisition and transmission is through the use of non-sterile syringes and injection paraphernalia (e.g., rinse water, cotton, cookers). In the US, HCV prevalence in older adults ("baby boomer" age group) is often linked to past injection drug use (IDU). Additionally there are racial and ethnic disparities in viral hepatitis that are not well studied; African Americans are twice as likely to be HCV infected compared to the general U.S. population. Second, HCV incidence is increasing among young white adults (15 to 30 years of age) living in rural and suburban areas who are transitioning from prescription opiate abuse to opioid injection. Third, high risk sexual behavior (often associated with drug abuse) has been linked with HCV transmission among men who have sex with men (MSM). HCV infection is six to eight fold more likely in HIV infected MSM than in those who are HIV negative.

In the U.S., deaths from hepatitis C (HCV) now exceed those due to HIV. HCV progression is enhanced by HIV co-infection, and liver disease caused by HCV infection has emerged as a major threat to the survival of co-infected HCV/HIV individuals. Most people living with HCV are unaware of their infection. Rapid HCV point-of-care antibody testing has improved HCV screening, but those screening positive for the presence of HCV antibodies require follow-up testing for the presence of HCV RNA to distinguish between antibody positive individuals who have cleared the virus and those who are actively infected (having detectable HCV RNA). Improvement in HCV treatment has given new impetus to identifying those who are HCV infected so they might be treated. Treatment regimens are now more effective at producing sustained virologic response (SVR), better tolerated, and require a shorter course of therapy to cure HCV infection than prior regimens. It has been suggested that a Treatment as Prevention (TasP) or seek, test, and treat strategy, analogous to that for HIV, may ultimately lead to the eradication of HCV disease. There are various challenges to adopting TasP for HCV/HIV coinfection that will need to be studied if this strategy is to be successful at a broad population level. While new therapies have greatly improved the likelihood of attaining HCV SVR, reinfection is possible, and it will be important to develop screening and monitoring approaches that account for reinfection and can ascertain reinfection rates in at-risk groups. To this end, studies are needed to improve HCV/HIV coinfection testing through encouraging use of rapid HCV/HIV point-of-care testing among populations at increased risk such as criminal justice populations. Models of care that integrate HCV/HIV treatment with primary care, substance abuse treatment and other services must be explored. As new therapeutic agents become available, it is important to test for interactions with HIV antiretroviral drugs, medications used to treat substance abuse, and abused substances. Because of the critical role that drug abuse plays in HCV/HIV disease, NIDA is conducting research aimed at breaking down barriers to accessing HCV/HIV coinfection screening, treatment, and prevention services.

FY 2017 Plan: This priority supports studies under Etiology and Pathogenesis, 2 D Pathogenesis of Opportunistic Infections and Coinfections and 2 E Pathogenesis of Metabolic and Body Composition Change. This initiative is consistent with emphasis areas 6C and 6D Therapeutics, Prevent and Treat Coinfections, in the NIH/OAR FY 2017 Trans-NIH Plan for HIV-Related Research as it pertains to managing consequences of HIV infection and its treatment and to prevention and treatment of HIV

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and HCV coinfection in drug using populations. The availability of HCV rapid testing and new treatment regimens make this a timely initiative.

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Project Title: Implementation Science Research

Mechanism(s): R01, P01

New or Expansion: Expansion

% of Minority/International: M 35%, I 25%

Areas of Emphasis: 1A, 1B, 1C, 5A, 5B, 5C, 5D

Narrative Justification:

This initiative addresses the following overarching priorities: Develop the next generation of HIV therapies with improved safety and ease of use. Efficacious interventions developed to prevent or treat HIV/AIDS in a particular setting often yield disappointing results on scale-up in diverse settings. Another issue is how to choose between competing interventions. Implementation science research is the multidisciplinary field that addresses such issues. Implementation science research seeks to understand the etiology of gaps between expected results and observed outcomes. Implementation science studies the effectiveness and cost-effectiveness of interventions; its goal is the integration of research findings and evidence-based interventions into healthcare policy and practice and, hence, to improve the quality and effectiveness of prevention, treatment, health services and care.

Implementation science research recognizes that the environment, economics, culture, gender, behavior, and social circumstances are all factors that may complicate adapting interventions from one setting or population to another. Because drug abuse is stigmatized and often dealt with punitively rather than from a public health perspective, implementation science research may be particularly useful in identifying barriers and testing possible solutions for HIV/AIDS interventions in drug using populations. The ultimate goal of implementation research is to determine how best to provide a comprehensive, integrated mix of high quality, sustainable, cost-effective interventions to reduce HIV risk behavior and infections.

Implementation gaps in the U.S. and internationally that this initiative addresses include but are not limited to:

Combination, integrated prevention--While advances in HIV prevention and treatment make it now possible to look forward to a generation without AIDS, understanding how to evaluate local epidemiologic data and then develop programs to meet local needs for combination, integrated prevention is critical. There is no one size fits all; prevention must be tailored to local conditions and resources. Epidemiologic data are needed to guide prevention efforts, but reliance on national or state-wide data may not capture local conditions and/or may not be available in many resource poor settings. Focusing on gathering local data from high risk groups may provide sentinel data to focus prevention efforts. In addition, it is important to assess the local social, economic, and policy environments in which risk behavior occurs and which will affect the choice of interventions. Evaluation of resources available for HIV prevention and modeling different scenarios can help to determine the most cost-effective approach for a given setting. The constituents of comprehensive prevention and the integration of these components will also vary. Combination prevention has been

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defined by UNAIDS as, "The strategic, simultaneous use of different classes of prevention activities (biomedical, behavioral, social/structural) that operate on multiple levels (individual, relationship, community, societal), to respond to the specific needs of particular audiences and modes of HIV transmission, and to make efficient use of resources through prioritizing, partnership, and engagement of affected communities." To further enhance this prevention approach, this initiative calls for integrating as well as combining interventions. Integration would be more than co-localization of services—it would aim to use the same team to deliver a variety of interventions. For example, ART and drug abuse treatment and treatment for co-infections and risk reduction counseling could be provided by the same staff that provides linkages to housing and other assistance.

To date, several promising integrated behavioral and biomedical treatments and approaches have shown positive outcomes in decreasing the rate of new HIV infections, promoting greater adherence to HIV treatment and overall medical management, improving engagement and retention in HIV care, and reducing substance abuse. However, there remains a large gap regarding translation from research models into combination approaches that are effective in "real world" settings, such as front-line community based organizations, substance abuse treatment venues and other direct providers of clinical care. Maximizing adherence in the broadest sense is key to effective implementation. Specifically, this initiative seeks to explore mechanisms to successfully transfer and sustain efficacious integrated combination preventive and treatment interventions (e.g., targeting use of and adherence to ART, screening and risk reduction, engagement and long-term retention in HIV care, and overall medical management for co-morbid conditions, such as substance use, mental health impairments, Hepatitis C, TB) for at-risk and HIV+ populations in real-world practice settings. This may include investigating the optimal settings and approaches for intervention delivery (primary care, urgent care and/or specialized care settings, home) as well as a structured analysis of local community resources to understand the capacity needed to deliver the optimal "dose" of required treatment. In short, it is critical to understand how evidence-based interventions are transported into and maintain their potency in real-world community-based practice settings (e.g., ERs, primary care, criminal justice settings, drug treatment etc.).

New methodologies are needed to evaluate the effectiveness of combination prevention. Randomized controlled trials using incidence as an endpoint have to be very large and limited to settings with high incidence. Even with limited HIV prevention efforts to date, these settings are becoming rare. Therefore, alternative study and evaluation designs are needed.

ART as HIV prevention-Improving the continuum of care by focusing on local level data. Identifying infected substance users earlier in the course of their infection and, engaging and retaining them in care to achieve viral suppression. Initiating care earlier in the course of HIV infection, fostering long-term retention in care, and pursuing re-engagement in care for those who drop out are crucial to maximizing prevention opportunities, preserving the efficacy of first-line ART, and improving individual and population health outcomes. Examples of research topics include: 1) Testing of models to optimize coverage of care services; 2) Comparing models of service provision and adherence/retention support; 3) Delineating key issues that result in suboptimal clinical outcomes; 4) Identifying appropriate portals for HIV testing; and 5) Identifying social and structural barriers as

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well as individual-level barriers to improve ART initiation and retention. The continuum of care varies by population (age, gender, type of drug use, etc.) and geographic region (as granular as neighborhood differences within a city); it is important to tailor programs to specific drug using populations within local communities.

Substance abuse treatment (both medication-assisted treatment (MAT) and behavioral therapy) as HIV prevention is unavailable or of limited availability in many settings. In the U.S., MAT is limited or unavailable in criminal justice settings. In the U.S. physician adoption of buprenorphine/naloxone has been relatively slow due to regulatory, financial, and attitudinal barriers. Yet, because buprenorphine/naloxone can be prescribed by physicians and dispensed at community pharmacies as opposed to methadone, which usually requires daily visits to a specialized clinic, there are advantages in terms of patient acceptability. In addition, because a specialized dispensing clinic is not required, it may be easier to integrate buprenorphine/naloxone treatment with HIV care in infectious disease clinics or primary care. Internationally, there are many countries with large numbers of IDUs and high HIV prevalence that have little or no substance abuse treatment. Implementation science research is needed on how best to expand substance abuse treatment for a given setting. The use of substance abuse treatment as a stand-alone intervention with referrals to care for HIV and for other conditions compared with integration of substance abuse treatment, ART, and treatment for comorbid conditions is another major area for study by implementation scientists. It will be important to determine which programs are most effective in expanding substance abuse treatment coverage and the relationship between substance abuse treatment coverage and reductions in risk behavior. In addition, studies should evaluate whether substance abuse treatment leads to increased adherence to ART, retention in care, viral suppression, and improved HIV treatment success including quality of life indicators. For example, a study from British Columbia, which has universal health, demonstrated that opioid substitution therapy (office-based methadone) enhanced ART adherence (AIDS:29:965-73, 2015).

Long-lasting opioid pharmacotherapy with depot naltrexone—Intramuscular injection of extended release naltrexone can be used as a once a month treatment. In countries that do not allow opioid substitution therapy (OST), the use of agonists to treat opioid addiction, this medication assisted therapy offers an alternative. Similarly, long acting treatment with opioid antagonists may be more readily adopted in criminal justice settings. This therapy may also be beneficial in situations where adherence is an issue, health care staff are limited, or patients have to travel long distances to reach caregivers. Implementation research studies are needed on long-lasting opioid antagonists. It will be important to determine whether patients remain in treatment and to what extent they reduce their HIV risk behavior and/or engage and are retained in HIV care including durable adherence to ART.

FY 2017 Plan: This initiative is consistent with the FY17 Trans-NIH Plan for HIV-Related Research Natural History and Epidemiology (Objectives A, B, and C) by supporting studies on the uptake and adherence to frequent HIV testing and linkage to and retention in care, studies on the cost-effectiveness of preventive interventions, determinants of HIV acquisition among vulnerable populations, research on substance abuse treatment modalities as HIV prevention interventions,

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evaluating the impact of substance abuse treatment on the effectiveness and, and consequences of ART, and encouraging more HIV prevention research in at-risk marginalized and vulnerable populations. It supports Behavioral and Social Sciences (Objectives A, B, C, D) by supporting research substance use and sexual transmission, designing and testing interventions for vulnerable populations, studying risk and protective behaviors associated with HIV transmission and progression in specific social and cultural contexts, studying barriers to health care utilization, refining techniques for measuring social networks and for collection of reliable information on sexual and drug-use risk behaviors. This initiative supports research on the feasibility, effectiveness, and sustainability required for scale-up and implementation of interventions for communities at risk in the U.S. and internationally, and includes collaborative efforts with networks such as ACTG and HPTN.

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Project Title: Transformative Research

Mechanism(s): DP1, R01, DP2

New or Expansion: Expansion

% of Minority/International: M 10%, I 5%

Areas of Emphasis: 1A, 2A, 2B, 2C, 2G, 4A, 5A, 5D, 6A, 9A, 9B

Narrative Justification:

This initiative addresses the following overarching priorities: 1) Reducing the incidence of HIV/AIDS; 2) Develop the next generation of HIV therapies with improved safety and ease of use; 3) Research towards a cure; and Improve our capacity to prevent and treat HIV-associated comorbidities and coinfections. NIDA Director's Avant-Garde Award Program for HIV/AIDS Research: In FY08, NIDA introduced the Avant-Garde award to encourage cutting edge, high-risk, high payoff HIV/AIDS research that has the potential to open new avenues of research and/or have broad public health impact by leading to new breakthroughs in HIV/AIDS prevention and treatment interventions for substance users. It uses the DP1 mechanism; the same mechanism as the NIH Director's Pioneer award. This ongoing program selects 2-3 awardees each year. Several Avant-Garde awardees are conducting studies that are highly relevant to efforts towards a cure by focusing on strategies that may lead to new therapies to control or eliminate HIV. Among the funded projects are: studies of HIV reservoirs and latency, systems biology of immune reconstitution, proteomics of virus-host interactions, HIV transmission between cells, development of a mouse model containing human genes that regulate replication, pathogenesis, and immunity, public health approaches to prevention that combine behavioral/social science data with phylogenetic information to intervene in network transmission, and new therapeutic approaches suited to treat infections in populations with limited access to health care. Treatment as prevention in injection drug users was one of the projects funded in 2008, and several significant papers have resulted from this award, and the work is continuing under an Advancing Exceptional Research on HIV/AIDS award. In 2013 NIDA developed the Advancing Exceptional Research on HIV/AIDS award that utilizes an R01 mechanism and complements the Avant-Garde DP1. It supports research by individual and multiple principal investigators and is an ideal mechanism to support continuation of the research begun under the DP1 award or new, innovative projects. In 2015, NIDA initiated the Avenir Award Program for research on Substance Abuse and HIV/AIDS, which uses the DP2 mechanism to support highly creative, early stage investigators (ESI).

FY17 Plan: This initiative attracts extremely creative scientists who wish to pursue high-risk, high pay-off research that has the potential to transform treatment and/or prevention for drug users. It includes basic and therapeutic research focused on elimination of viral reservoirs leading toward a

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cure. This initiative supports emphasis areas Etiology and Pathogenesis 2A, 2B, 2C and Therapeutics 6A. It also supports potentially transformative Behavioral and Social Sciences interventions 5A, Natural History and Epidemiology 1A, 4A and 4B Vaccines, and 9A Cure.

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Project Title: Training, Infrastructure, and Capacity Building

Mechanism(s): R25, F 31, F32, T32, R03, D43

New or Expansion: Expansion

% of Minority/International: M 20%, I 7%

Areas of Emphasis: 7A, 7B

Narrative Justification:

This initiative addresses the following overarching priorities: Cross cutting area of training.

Humphrey Fellowship Program: The Humphrey program is a partnership with the U.S. Department of State to support a unique training program for midcareer drug abuse professionals; some of NIDA's Humphrey fellows have an interest in HIV/AIDS. In addition, NIDA participates in the national Humphrey Fellowship seminar and has organized sessions focusing on HIV/AIDS and invited participation of fellows from Emory Humphrey Program, which has an HIV/AIDS concentration. Through contacts with NIDA staff, further interactions between foreign HIV/AIDS researchers and U.S. investigators have been facilitated.

A-START: To facilitate the entry of newly independent and early career investigators into the area of AIDS research, NIDA has developed the AIDS-Science Track Award for Research Transition (A-START) mechanism. This program supports feasibility studies using the R03 mechanism and providing up to \$100,000 direct costs for two years to facilitate the entry of new investigators into drug abuse and HIV/AIDS research.

Research Training: This program supports research efforts through institutional training research grants (T32), pre-doctoral (F31), post-doctoral (F32) mechanisms, as well as through collaborations with FIC. The NIDA Research Education Program for Clinical Researchers and Clinicians (R25) also supports careers as clinical researchers, clinicians/service providers, or optimally, a combination of the two and includes HIV/AIDS as a topic of interest. To increase the numbers of underrepresented minorities in research careers in drug abuse research, including HIV/AIDS, NIDA supports a program of diversity supplements at the pre-doctoral, post-doctoral, and investigator level to train minority investigators in HIV/AIDS research. In addition NIDA co-funds the FIC international HIV training grant program (D43). The purpose of all of these programs is to help ensure that a diverse and highly trained workforce is available to assume leadership roles related to the Nation's biomedical and behavioral research agenda in the areas of substance abuse and HIV/AIDS.

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FY 2017 Plan: This initiative is consistent with the NIH/OAR FY 2017 Trans-NIH Plan for HIV-Related Research for Training, Infrastructure, and Capacity Building (Objectives A and B) by supporting predoctoral, postdoctoral, and advanced research training across a broad range of AIDS-related disciplines. It is also consistent with the goal of establishing and maintaining the appropriate infrastructure needed to conduct HIV research domestically and internationally.

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Project Title: Research Towards a Cure: Role of substances of abuse in the pathogenesis of HIV and effects on HIV latency, reservoirs, and persistence

Mechanism(s): R03, R21, R01, R33, P01

New or Expansion: Expansion

% of Minority/International: M 20%, I 7%

Areas of Emphasis: 2B, 2C, 2E, 2G, 6C, 6E, 9A, 9B

Narrative Justification:

This initiative addresses the following overarching priorities: Research towards a cure. Numerous in vivo and ex vivo studies have demonstrated diverse effects of drugs of abuse on cells of the immune system and on immune function. Studies in animal models have also shown effects of drugs of abuse on HIV pathogenesis. It is also important to determine how cycles of drug abuse and drug withdrawal affect HIV pathogenesis, latency, reservoir size and persistence. NIDA has an ongoing portfolio of research directed at understanding the mechanisms of HIV neuropathogenesis and the effects of drugs of abuse on HIV in the CNS. In addition, understanding the mechanisms underlying CNS HIV infection is important to understanding the brain as a potential reservoir of HIV infection. CNS is a major focus of NIDA's research as are studies on the effects of drugs of abuse (including nicotine and alcohol and drug combinations) on reservoirs throughout the body, e.g., gut and lung.

CNS reservoirs may serve as a barrier to cure strategies, in part, because many therapeutic drugs do not penetrate the blood brain barrier. Drugs of abuse are known to exacerbate the role of HIV in the CNS for example; the deleterious synergistic effects of methamphetamine and HIV on CNS structure and function are well established. Drugs of abuse have been shown to increase HIV transcription in cells of the CNS. Amphetamine induces HIV transcription in human CNS microglial cells, and cocaine enhances HIV transcription in primary human macrophages in culture. In addition, drugs of abuse have been shown to exert epigenetic effects in the CNS. These interactions may have implications for the establishment of latency within cells in the CNS, for reactivation, and for maintenance of HIV reservoirs within cells of the CNS. HIV enters the brain early in infection and replicates and evolves within the CNS. In the CNS, HIV may actively, persistently, or latently infect perivascular and meningeal macrophages, microglia, and astrocytes. HIV is not uniformly distributed throughout the brain, highest viral loads are found in basal ganglia where drugs of abuse act through dopaminergic transmission. To understand the brain as an HIV reservoir, it will be important to establish which cell types harbor replication competent virus and to quantify this in different brain regions.

FY 2017 Plan: This initiative is consistent with the NIH/OAR FY 2017 Trans-NIH Plan for HIV-Related Research 2 Etiology and Pathogenesis (Objectives B, C, E, and G) by supporting studies to understand the effects of drugs of abuse on pathogenesis in various organ systems, with particular attention to the CNS, and on the viral and host mechanisms involved in infection, pathogenesis, and

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persistence. NIDA research also supports Emphasis Area 6 Therapeutics (Objectives C and E) through research on how best to treat substance users, including those with neurological disease. NIDA research is also consistent with Emphasis Area 9 Research Toward a Cure (Objectives A and B).

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Project Title: Seek, Test, Treat and Retain for Rural Communities with Drug Abuse Epidemics

Mechanism(s): R34, R21, R01, P01

New or Expansion: New

% of Minority/International:

Areas of Emphasis: 5A, 5C, 5D

Narative Justification:

This initiative addresses the following overarching priorities: 1) Reducing the incidence of HIV/AIDS; and 2) Develop the next generation of HIV therapies with improved safety and ease of use. Treatment as Prevention (TasP), or "Seek, Test, Treat, and Retain" model of care involves reaching out to high-risk, hard-to-reach groups who have not been recently tested for HIV (seek), engaging them in HIV testing (test), initiating, monitoring, and maintaining antiretroviral therapy (ART) for those testing HIV+ positive (treat) and retaining patients in HIV and other relevant care (retain). Seek, Test, Treat, and Retain is a paradigm that has shown efficacy in reducing HIV transmission at a population level among various key populations. Limited and inconsistent focus has been placed on the Seek, Test, Treat, and Retain paradigm among rural opioid abusers.

In the U.S., there has been an increase in new, young initiates to injection drug use IDU that is fueled by the burgeoning prescription opiate epidemic and a concomitant rise in heroin use. New initiates to injection are at high risk for HIV. TasP has been widely endorsed following the demonstration that reducing viral load through early immediate treatment of those with HIV effectively prevents morbidity and mortality, and additionally prevents HIV transmission. However, frequently there are barriers to IDU accessing HIV services and in particular ARV therapy especially in rural setting. Even if they access ARV therapy, IDUs frequently face obstacles in maintaining adherence to treatment and achieving sustained viral suppression. Young people are less likely to engage in HIV care and more likely to drop out of care and therefore, have extremely low rates of viral suppression. Thus, the IDU population remains a potential reservoir of HIV. The goal is to reduce HIV incidence among rural drug using populations through optimization of seeking out high-risk, hard-to-reach substance abusers, offering them HIV testing and access to HIV treatment, and providing the necessary support to help retain them within effective treatment programs.

Given the lack of health care infrastructure, it is important to adapt effective preventive and treatment strategies as well as develop new innovative interventions. Unique barriers and facilitators to implementing STTR in rural communities may exist at multiple levels and thus, research should investigate individual, community, social, economic and legal/policy level factors. Examples of novel strategies may include the use of mobile vans, distribution of HIV self-testing kits, use of telemedicine, and mobile technology. Research is needed on how best to address the evolving epidemic among IDUs in rural communities and to improve our prevention and treatment knowledge

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base and associated interventional approaches including how best to integrate treatment for substance abuse, HIV, and comorbid conditions, as well as developing new strategies to improve retention of IDUs in care and engage young IDU to the care continuum. It is critically important for practical, replicable, cost-effective and sustainable solutions to these challenges be found and implemented.

FY 2017 Plan: This initiative is consistent with the NIH/OAR FY 2017 Trans-NIH Plan for HIV-Related Research for Behavioral and Social Science (Objectives: B, C, and D).

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Project Title: Trans-NIH HIV Collaborations

Mechanism(s): UM1, U19, U01, D43, P30

Co-Funding (ICs): HD, AI, MH, NIA, FIC, NIAAA, NINDS, NIMHD

New or Expansion: Expansion

% of Minority/International: M 20%, I 7%

Narative justification:

This initiative addresses the following overarching priorities: 1) Reducing the incidence of HIV/AIDS; 2) Develop the next generation of HIV therapies with improved safety and ease of use; 3) Research towards a cure; and Improve our capacity to prevent and treat HIV-associated comorbidities and coinfections. In order to leverage HIV resources and promote the integration of substance use related bio-behavioral research into high-priority NIH HIV initiatives, NIDA co-funds multiple trans-NIH IC programs. These include the MACS, WIHS and PHACS cohorts, the ATN, HPTN, and ACTG clinical trials networks, the IeDEA network, the CFAR program, the Martin Delaney Collaboratory for HIV Cure, and the FIC international HIV training grant program.

Areas of Emphasis: 1A, 1B, 1C, 2A, 2B, 2C, 2G, 5A, 5C, 5D, 6B, 6C, 6D, 6E, 7A, 7B, 9A, 9B