

Research News

Potential viability of HIV medications for HIV prevention in high-risk populations, but not for standard use

New approaches to HIV prevention are urgently needed to stem the estimated 2.7 million new HIV infections that occur worldwide each year. One promising approach being explored is pre-exposure prophylaxis (PrEP)—the use of HIV treatment medications to protect uninfected individuals from HIV infection. Recent studies have shown that a combination of two antiretroviral drugs, Tenofovir and Emtricitabine (TDF/FTC), may hold promise—especially in high-risk populations. To assess the viability of TDF/FTC in reducing HIV transmission, NIDA-funded researchers adapted a computer simulation of HIV acquisition, detection, and care to predict the long-term impact of PrEP among men who have sex with men (MSM) in the United States. The simulation took into account different variables such as age, HIV incidence, assumed success rate, and cost of treatment. When assuming PrEP treatment prevented 50% of new HIV infections (an estimate based on current research), researchers found that for males aged 34 years old,



ALSO IN THIS ISSUE

- p1** Potential viability of HIV medications for HIV prevention in high-risk populations, but not for standard use
- p2** Understanding more about the needs and expectations of patients seeking outpatient substance abuse treatment
Individuals with substance addiction, bipolar disorder share overlapping genetic profile
- p3** Low dose naltrexone + methadone during detox eases withdrawal symptoms, reduces cravings
Predicting risk and resilience in children of opiate-dependent parents
- p4** Key receptors, brain areas in nicotine withdrawal identified
Drug prevention programs during adolescence may have long-term benefits against risky sexual behavior
- p5** Consistent behavioral outcomes and neural activity shown in real and hypothetical discounting

PrEP substantially reduced HIV transmission from 44% to 25%, however life expectancy increased only 0.8% from 39.9 to 40.7 years of age and the lifetime cost of TDF/FTC treatment increased substantially from \$81K per person to \$233K per person—thus the costs did not outweigh the benefits given existing circumstances. The practicality of PrEP was more favorable, however, when simulations were performed targeting a younger, riskier population and assumptions about efficacy and cost were improved. For example, if PrEP efficacy was increased to 90%, lifetime infection risk fell from 44% to 6%, survival increased from 39 to 42.5 years and lifetime treatment costs were reduced. If effective, PrEP could play an important role in slowing the spread of HIV around the world, however, its future impact on the HIV epidemic will ultimately be determined by medication price reductions and/or increases in efficacy as well as how effectively strategies are used in combination to provide the greatest protection to those at risk.

Paltiel AD, Freedberg KA, Scott CA, Schackman BR, Losina E, Wang B, Seage GR III, Sloan CE, Sax PE, Walensky RP. HIV Pre-exposure Prophylaxis (PrEP) in the United States: Impact on Lifetime Infection Risk, Clinical Outcomes, and Cost-effectiveness. *Clin Infect Dis*. 2009 Mar 15;48(6):806-15.

Understanding more about the needs and expectations of patients seeking outpatient substance abuse treatment

For many, addiction is a chronic condition that persists and increases in severity over many years before individuals seek help. While research has shown that longer stays in addiction treatment programs are associated with improved recovery, attrition rates from substance abuse treatment programs are often high, limiting program effectiveness. Recently, NIDA researchers interviewed 135 individuals participating in outpatient treatment programs to identify factors that may keep them in treatment, and found that participants' reasons for not staying engaged in treatment fell into two categories: program-level factors (e.g., dissatisfaction with the program, unmet social services needs, dissatisfaction with counselors, and lack of flexibility in scheduling) and individual-level factors (e.g., low problem recognition and continued substance use). Two-thirds of the participants who left treatment reported that nothing

more would have kept them engaged in services, while for the remaining third, addressing unmet social service needs (54.2%) was most frequently cited as something that could have been done differently to retain them. The findings emphasize the need to understand and address needs and expectations of patients undergoing treatment for substance abuse starting at intake to maximize treatment retention and the likelihood of positive outcomes. Additionally, while the program's priority was to promote complete abstinence, patients often had priorities other than abstinence, such as finding a job (28.3%), education (24.1%), or getting a child back (18.7%). The authors note that this may indicate "abstinence... as a means to an end rather than an end in itself."

Laudet, AB, Stanick, V, Sands B. What could the program have done differently? A qualitative examination of reasons for leaving outpatient treatment. *J Subst Abuse Treat.* 2009; Sept; 37(2): 182-190.

Individuals with substance addiction, bipolar disorder share overlapping genetic profiles

Addiction and bipolar disorder are commonly co-occurring disorders, with up to 60% of individuals with bipolar disorder experiencing some form of substance abuse in their lifetime. While it is known that genetic factors contribute substantially to the likelihood of developing either illness, new studies suggest shared genetic roots for both disorders. Researchers, partly funded by NIDA, analyzed data from five different genome-wide association studies (GWAS), which

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compared DNA from individuals diagnosed with either bipolar disorder or substance abuse disorder. GWAS scan an individual's entire genome to identify SNPs (i.e., single-nucleotide polymorphisms) or slight changes in a gene's sequence that may be associated with a particular disease. In this analysis, researchers found remarkable convergence in at least three of the studies, identifying 69 common "bipolar disorder vulnerability" genes, 23 of which also contained clustered SNPs associated with substance abuse vulnerability. These findings provide evidence of a common genetic architecture between



substance abuse and bipolar disorder, suggesting that variants in “addiction/bipolar” genes can potentially influence the brain in ways that increase a person’s vulnerability to both conditions. The results of this study “promise to enhance understanding of features that are common to human addictions and bipolar disorder in ways that could facilitate efforts to personalize prevention and treatment strategies for these debilitating diseases,” conclude the authors.

Johnson C, Drgon T, McMahon FJ, Uhl GR. Convergent genome wide association results for bipolar disorder and substance dependence. *Am J Med Genet B Neuropsychiatr Genet.* 2009 Mar 5;150B(2):182-90.

Low dose naltrexone + methadone during detox eases withdrawal symptoms, reduces cravings

Opioid dependence is a major public health problem, especially when considering the high rates of prescription opioid abuse. Medical detoxification is often a necessary step to reduce withdrawal symptoms and maximize treatment retention and success for individuals entering long-term opioid treatment. Recent studies have found that very low dose naltrexone (VLNTX) is associated with attenuated withdrawal intensity during detoxification. NIDA-funded researchers recently conducted the first multi-site randomized clinical study to evaluate the safety and efficacy of VLNTX + methadone to reduce withdrawal symptoms during inpatient opioid detoxification. 174 opioid-dependent patients were randomized to receive either VLNTX or placebo along with tapering doses of methadone daily for 6 days. VLNTX+ methadone treated individuals reported less severe withdrawal symptoms—including reduced anxiety and insomnia—and reduced cravings for opioids compared to placebo. While VLNTX did not increase retention rates, results provide evidence that VLNTX is safe and effective in reducing withdrawal severity and treatment discomfort in opioid-dependent people undergoing methadone detoxification. The authors suggest that treatment combinations of methadone and buprenorphine should be tested as potential adjuncts to VLNTX treatment.

Mannelli P, Patkar AA, Peindl K, Gorelick DA, Wu L, Gottheil E. Very low dose naltrexone addition in opioid detoxification: A randomized, controlled trial. *Addict Biol.* 2009 Apr;14(2):204-13.

Predicting risk and resilience in children of opiate-dependent parents

Children of drug abusers are at high risk for a wide-range of negative outcomes, including developmental and cognitive disabilities and substance abuse disorders. A recent NIDA-funded clinical trial described the adversities experienced by children of opiate-dependent individuals in methadone treatment and the ability of some of these children to overcome these adversities (i.e., functional resilience), in an effort to predict the factors which contribute to resiliency. Between 1993 and 1994, 130 families participated in the Focus on Families (FOF) project (a family-focused intervention); in 2005 and 2006, researchers re-interviewed the children in adulthood and found that 70% of them had experienced two or more childhood adversities (e.g., physical or sexual abuse, family substance abuse, mental illness or incarceration, etc), while 20% experienced four or more. Of the now young-adult sample, only 24% (whether enrolled in the intervention or not) met all established criteria for functional resilience, which included being actively employed or enrolled in school, having no history of substance abuse or dependence, and having no adult criminal charges in the prior 5 years. Researchers attempted to uncover which factors might predict functional resilience and found that females were almost four times more likely to exhibit functional resilience in young adulthood than males, and individuals who demonstrated behaviors associated with internalizing problems (e.g., anxiety or depression) and externalizing problems (e.g., bullying, lying, having temper tantrums) were less likely to demonstrate functional resilience. Contrary to evidence in other samples, race/ethnicity and the number of adverse experiences in childhood were not reliable predictors of resilience in this study. Authors conclude that while participation in the FOF program didn’t have a significant effect on resiliency in this sample, early intervention to prevent and reduce childhood internalizing and externalizing problems holds the most promise of supporting functional resilience later in life.

Skinner, ML, Haggerty, KP, Fleming, CB, Catalano, RF. Predicting Functional Resilience Among Young-Adult Children of Opiate-Dependent Parents. *J Adolesc Health.* 2009 Mar;44(3):283-90.

Key receptors, brain areas in nicotine withdrawal identified

Nicotine withdrawal is a major reason why smokers have trouble quitting. While it is well-known that nicotine exerts its rewarding effects by attaching to nicotine receptors in the brain, the mechanisms underlying nicotine withdrawal remain poorly understood. To gain a better understanding of these mechanisms, researchers funded by NIDA studied nicotine withdrawal in normal mice, as well as mice lacking the alpha-2 and alpha-5 nicotinic receptor subunits. In the experiments, all mice were chronically provided with nicotine, and then injected with mecamylamine—a drug that blocks nicotine receptors—to precipitate withdrawal. Researchers found that mice lacking the alpha-2 and alpha-5 nicotine subunits showed a decrease in typical withdrawal symptoms, including shaking and repetitive grooming or scratching.

nicotine exerts its rewarding effects by attaching to nicotine receptors in the brain

In a separate experiment, blockade of nicotinic activity, via direct injections of mecamylamine into the medial habenula and interpeduncular nuclear brain regions (but not to the cortex, hippocampus or ventral tegmental area), of normal mice precipitated signs of nicotine withdrawal. These results suggest that the medial habenula and the interpeduncular nucleus and alpha-2 and alpha-5 nicotinic receptor subunits are key mediators of withdrawal. The authors conclude that these brain regions and receptor subtypes are potentially relevant targets for the development of new medications and smoking cessation therapies.

Salas R, Sturm R, Boulter J, De Biasi M. Nicotinic receptors in the habenulo-interpeduncular system are necessary for nicotine withdrawal in mice. *J Neurosci*. 2009 Mar 11;29(10):3014-8.

Drug prevention programs during adolescence may have long-term benefits against risky sexual behavior

Early onset of substance abuse among adolescents is associated with later risky sexual behavior, an important risk factor for HIV, other sexually transmitted diseases and unplanned pregnancy. Researchers funded by NIDA examined whether participation in Project ALERT, a drug prevention program for middle school-aged youth, can have long-term effects on risky sexual behavior among young adults. More than 1,900 high school and middle school-aged youth from 55 schools were assigned to either take part in the core program (receiving 11 prevention lessons in grade 7 and 3 in grade 8), the expanded program (receiving 5 lessons in grades 9 and 10 in addition to the middle school lessons) or the control group (exposed to other non-ALERT prevention curricula already in place at their school). At age 21 (5-7 years after the intervention), all participants were asked questions about their past sexual history. Compared to the control group, Project ALERT participants were significantly less likely as young adults to engage in sex with multiple partners (43.5% vs. 49.7%) and to have unprotected sex because of using alcohol or other drugs (27.2% vs. 31.6%). There was no significant difference between the groups in terms of condom use consistency. In addition, there was no difference in the program's effect based on gender or program length (middle school only vs. middle/high school). These results suggest that drug prevention programs are an effective means of positively influencing certain risky sexual behaviors, even several years after program participation. Authors conclude that while Project ALERT can have long-term effects on risky sexual behavior, the lack of significant effects for inconsistent condom use may reflect greater difficulty of curbing behavior that requires negotiation with a partner and will need to be further examined in future studies.

Ellickson PL, McCaffrey DF, Klein DJ. Long-Term Effects of Drug Prevention on Risky Sexual Behavior Among Young Adults. *J Adol Health*. 2009; 45: 111-17.

Consistent behavioral outcomes and neural activity shown in real and hypothetical discounting

Impulsive decision making is closely linked with drug abuse, both as a contributor and a consequence. Individuals who abuse drugs often choose more immediate and short-term rewards (e.g., the euphoria from the use of drugs) over a variety of delayed larger

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rewards (e.g., improved family relationships). Researchers funded by NIDA recently used a procedure called delay discounting—giving greater value to rewards that are received sooner rather than later—to examine how delayed versus immediate real and hypothetical monetary rewards can influence decision-making behavior and brain activity. Thirty individuals with no underlying drug dependence or other psychological diagnoses underwent fMRI brain imaging scans after completing one of three

discounting conditions where they were asked about their preferences for receiving either real or hypothetical monetary gains or hypothetical monetary losses that would either occur immediately or following a delay (e.g., \$99 now or \$100 in a week). Overall, researchers found that delayed money was no less valuable than money received immediately and real money gained was no more valuable to study participants than money hypothetically lost. Furthermore, while fMRI data showed significant activation in limbic (associated with reward) and executive functioning (associated decision-making) regions of the brain during the discounting challenges in general, there was no difference in activity based on condition. Thus findings indicate that real and hypothetical outcomes produce both comparable behavioral and brain correlates. Authors conclude that the study of hypothetical outcomes can be consistent with real outcomes and that the study of delayed discounting under these conditions should provide valuable insight into the nature of individual decision-making—functional or dysfunctional—in the real world.

Bickel WK, Pitcock JA, Yi R, Angtuaco EJ. Congruence of BOLD response across intertemporal choice conditions: fictive and real money gains and losses. *J Neurosci*. 2009 Jul 8;29(27):8839-46.

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