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The Globalization of Addiction Research:

Capacity Building Mechanisms and Selected Examples

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Abstract

Over the past decade, the amount and variety of addiction research around the world has increased substantially. Researchers in the United States, Western Europe, United Kingdom, Canada, and Australia have significantly contributed to knowledge about addiction and its treatment. However, the nature and context of substance use disorders (SUDs) and the populations using drugs are far more diverse than is reflected in studies done in Western cultures. To stimulate new research from a diverse set of cultural perspectives, the National Institute on Drug Abuse (NIDA) has promoted the development of addiction research capacity and skills around the world for over 25 years. This review will describe the programs NIDA has developed to sponsor international research and research fellows and will provide some examples of the work NIDA has supported. NIDA fellowships have allowed 496 individuals from 96 countries to be trained in addiction research. The United Arab Emirates and Saudi Arabia have recently developed funding to support addiction research to study SUD problems that impact their societies with NIDA guidance.. Examples from Malaysia, Tanzania, Brazil, Russian Federation, Ukraine, Republic of Georgia, Iceland, China, and Vietnam are used to illustrate research being conducted with NIDA support. Health services research, collaboratively funded by NIH and the Department of State, addresses a range of addiction service development questions in low- and middle-income countries. Findings have expanded the understanding of addiction and its treatment and are enhancing the ability of practitioners and policy makers to address SUDs using data to guide their decision-making.

Keywords: Addiction; International; International training fellowships, National Institute on Drug Abuse; Health services research; Drug-related disorders

Substance use disorders (SUDs) are a worldwide problem that contributes to the spread of HIV, hepatitis C, tuberculosis, criminal behavior, and other medical and psychosocial problems. Across societies, there is great diversity in capabilities to treat SUDs and even greater diversity regarding the capacity to conduct research on SUDs. Globally, demand for treatment exceeds capacity, and the gap is greatest in low- and middle-income countries (LMICs).[1] Only 20% of LMIC residents with mental, neurological, or substance abuse disorders receive treatment, but they constitute 80% of the global population needing treatment.[2]

Societies have typically developed treatment capacity for SUDs in response to the crime associated with SUDs, including drug trafficking, or their medical/psychiatric sequelae, including infectious diseases. After treatment services are initiated, policy makers often want to gain knowledge about the nature and extent of drug use in their society, the populations affected, and the effectiveness of their treatments. As a result, there is expanding interest in the development of addiction research and evaluation capacity. In addition, many young professionals in countries with developing SUD services recognize that training in addiction research can be a pathway for career advancement. This training is also critical to support the large global investment in addressing infectious diseases, such as the human immunodeficiency virus (HIV) and tuberculosis, since injection drug use and addiction are a critical focus in such prevention and treatment programs of LMIC. With this background in mind, our focus in this article is to review the development of research capacity on tobacco, prescription medications, and illicit drugs in developing countries.

Surely, other work to promote international research on substance use-related issues pre-dates and is contemporaneous to the National Institute on Drug Abuse (NIDA) programs described below. Researchers from Maudsley Institute, led by Griffith Edwards, M.D., and

others, led international research and research promotion efforts as early as the 1970s.[3] Research supported by NIAAA, led by Tom Babor, Ph.D., and others has created research and research capacity in the area of alcohol use and misuse.[4] Additionally, research on a variety of SUDs has been funded by the World Health Organization (WHO) and the U.S. Department of State. We have chosen to limit the scope of this paper to a review of the programs of research and research capacity-building efforts on drug use, in order to explore the themes of extant work in this topical area as well as research efforts being built in a variety of societies around the world.

NIDA International Research and Training Program Mechanisms to Promote Drug Abuse Research

Since 1990, NIDA, which is part of the National Institutes of Health, has addressed the need for building addiction research and treatment capacity internationally through research training fellowships and professional development activities.[5] Postdoctoral researchers, midcareer professionals, and senior scientists have received addiction training and conducted mentored research on addiction topics ranging from basic science to epidemiology, prevention, treatment, medical and social consequences, and policy. The impact of NIDA-supported science and these training programs has influenced addiction treatment policies and practices in many parts of the world.[5]

For postdoctoral researchers, five different programs offer varying levels of training and mentored research experience: the INVEST and INVEST/Clinical Trials Network (CTN) Fellowship Program; the U.S.–Mexico Drug Abuse Prevention Fellowship Program; the NIDA–International AIDS Society (IAS) Drug Use and HIV/AIDS Fellowship Program; and the NIDA-Inserm Fellowship Program. Midcareer professionals from eligible LMIC countries may apply

for the NIDA Hubert H. Humphrey Drug Abuse Research Fellowships, which provide mentoring and professional development activities along with the academic and cultural programs of the Humphrey fellowship programs sponsored by the U.S. Department of State. Three programs serve senior scientists: Distinguished International Scientist Collaboration Awards (DISCA), Distinguished International Scientist Collaboration Awards for U.S. Citizens (USDISCA), and NIDA–IAS Professional Development Fellowships.[6] As part of the training and mentored research activities, fellows in these programs participate in scientific conferences and meet officials at NIDA, the John E. Fogarty International Center at NIH, the Substance Abuse and Mental Health Services Administration (SAMHSA), the Department of State, and the White House Office of National Drug Control Policy.

Impact of NIDA Fellows on International Drug Abuse Research, Policy, and Treatment

By May 2014, there were 496 current and former NIDA International Program fellows from 96 countries. The majority of fellows have returned to their home countries, where their new knowledge and experiences have strengthened evidence-based policy approaches to prevention and treatment of substance use problems. A 2013 assessment conducted by Virginia Commonwealth University (VCU) found that one year after completing their fellowships, 53% of the Humphrey Fellows who attended VCU from 2007 through 2012 had a new job and 71.4% said their fellowship helped them obtain the job and that the new job represented a change in career goals. Since completing their training, nearly half (47%) of the fellows reported having conducted research, more than a third (35.9%) reported continuing collaborations with a U.S. partner, and one-fifth (20%) had enrolled in an academic program.[7] A 2012 VCU assessment of fellows from 2007 through 2011 found that former fellows (37%) managed or administered treatment or prevention programs, 28% worked in clinical settings, 26% worked in policy

development and planning, and 9% conducted research. Former fellows began their research careers quickly. At the 12- and 36-month follow-up, 17% had received a research grant, 38% were collaborating with U.S. colleagues, and 17% were collaborating with other fellows. Fellows also have contributed to the evidence base: 29% reported publishing research results in a peer-reviewed journal, and 60% reported making a presentation at a scientific conference.[8] Three former NIDA International fellows edit journals in Australia, Brazil, and Nigeria, and former fellows have published more than 1,000 articles in peer-reviewed journals.

Former fellows direct governmental, nongovernmental, and academic drug abuse research programs in Albania, Brazil, Burma (Myanmar), China, Colombia, Republic of Georgia, Indonesia, Israel, Kenya, Kosovo, Mexico, Nepal, Peru, Russian Federation, South Africa, Sweden, Tajikistan, Uganda, and Ukraine. Two former fellows currently work for NIDA. Former NIDA fellows shape international drug policies by working for organizations such as WHO, United Nations Office on Drugs and Crime, Joint United Nations Programme on HIV/AIDS, European Monitoring Centre on Drugs and Drug Abuse, and Colombo Plan Drug Advisory Programme in Southeast Asia. In 2014, three former NIDA Humphrey Drug Abuse Research Fellows were nominated to join the International Narcotics Control Board, and a former NIDA INVEST Fellow from Mexico co-chaired the WHO guidelines development committee that drafted recommendations for treating substance abuse in pregnant women.[9] Former fellows also shape drug policies in their own countries and currently hold government positions in Bangladesh, Brazil, India, Indonesia, Iraq, Israel, Mexico, Peru, Tanzania, and Uruguay.

Developments in International Addiction Research Capacity

In addition to promoting and funding the training of international addiction researchers, NIDA has a number of mechanisms for funding research outside the United States. Currently,

NIDA has Program Announcements for International Research Collaboration on Drug Abuse and Addiction Research in the R03, R21, and R01 categories. Other mechanisms include supplements to R01 grants that enhance the parent grant with international data. The grant supplement mechanism has been utilized by NIDA to promote international addiction health services research in the President's Emergency Plan for AIDS Relief (PEPFAR). The use of pharmacotherapies in the treatment of opioid dependence, as well as other substance abuse treatment issues, has been addressed in key populations as a part of HIV prevention efforts. Career and research opportunities provided by these mechanisms have also been realized, as seen by a May 2014 internal NIDA review that found that NIDA International fellows had been the principal investigator or foreign principal investigator for 53 NIH grants in Asia, Eurasia, Latin America, the Russian Federation, former Soviet States, Southeast Asia, and the United States.

The United States has not been alone in this area, as Australia, Canada, United Kingdom, Iceland, Israel, and the European Union have also supported international research. A bibliometric study of articles published between 1998 and 2004 in two international research journals – *Drug and Alcohol Dependence* and *Addiction* – identified 443 unique funding sources from 39 nations. The five most frequently acknowledged funders supported 60% of the research: NIDA, 40.9%; NIAAA, 11.6%; NIH, 3.8%; SAMHSA, 2.1%; and U.S. Department of Veterans Affairs, 1.7%.[10] Recently several new countries have initiated funding for addiction research. Examples from the United Arab Emirates and Saudi Arabia illustrate new addiction funding initiatives.

Addiction Research Initiative at the National Rehabilitation Center of Abu Dhabi

In the United Arab Emirates (UAE), the National Rehabilitation Center (NRC) of Abu Dhabi initiated funding for a program of addiction research to address the epidemiological,

prevention, treatment, and policy needs of the Emirates. A former NIDA senior researcher has joined the NRC to lead the research effort and the NRC has signed MOUs with NIDA and UCLA for input on the research agenda. Research projects are underway to assess the nature and extent of drug use in the UAE, to test the effectiveness of SBIRT training for primary care, and to identify genetic markers that predispose individuals of Middle Eastern descent to substance use disorders. A plan of research and a corresponding budget to expand addiction research in UAE is currently under development.

Substance Abuse Research Center (SARC) at Jazan University, Saudi Arabia

In 2011, the government of the Kingdom of Saudi Arabia granted Jazan University a 3-year award to establish a university-based organization to coordinate and fund SUD research throughout the Kingdom of Saudi Arabia. This 3-year award was made with the intention to: (1) develop a set of research priorities to address major SUD problems in the Kingdom; (2) establish a research funding infrastructure at Jazan University to support a systematic peer review of research proposals and a competitive award process; (3) create a grants management capacity to oversee the quality assurance of research awards and ensure appropriate fund management; (4) promote greater attention to addiction research at Jazan University; and (5) develop an intramural addiction research capability at Jazan University initially focusing on issues in Southern Saudi Arabia. Representatives of NIDA and NIDA-funded researchers have been active in developing the agenda for research and advising on the grant application and grant review process.

During the first three years of operation, the resulting Substance Abuse Research Center (SARC) established as its priorities research on: khat (a major concern in the Jazan region, Yemen, and East Africa); Captagon (a tablet form of methamphetamine/caffeine that is the most

widely used illicit drug in Saudi Arabia); and smoking tobacco cigarettes and "shisha," a form of tobacco smoked in water pipes. Initial studies funded by SARC included an assessment of the extent of khat use in Southern Saudi Arabia[11-13] and reasons for stopping khat use.[14] Other projects were funded and completed on the dental consequences of khat use[15] and the neuropsychological functioning of chronic khat users.[16] Work from the first 3 years of funding of SARC has generated 13 peer-reviewed publications, with a number of others in press or under review. In 2013, the first annual conference on addiction research (with an emphasis on khat) was held in Jazan and included Saudi and international researchers. Plans are underway to increase funding for SARC and expand the research portfolio to include intervention and basic research as part of a broader portfolio of addiction research topics.

Building Global Addiction Research Capacity: Selected Examples

During the early years of NIDA's international efforts, much of the work was done in Australia, United Kingdom, Canada, and Western Europe; in recent years much of NIDA's sponsored research has been focused on regions where drug use plays an important role in the spread of HIV. This focus is particularly important for collaborations with PEPFAR in which health services research exploring how evidence-based treatments have been implemented has broadened the evidence base on substance abuse treatment in LMICs as part of their HIV prevention care and treatment programs. These novel treatment algorithms involve stepped care, task shifting of health care provider duties, service integration of substance abuse treatment into HIV care, as well as the inclusion of substance abuse treatment in closed penal settings. These activities have greatly expanded the scope of substance abuse treatment research globally and expanded the use of evidence-based treatment paradigms.

An exhaustive review of NIDA's international portfolio is beyond the scope of this review. What follows are examples that illustrate the diversity of the NIDA-sponsored addiction research recently conducted or currently underway.

Malaysia

In mid-2005, the Malaysian government was faced with rapidly escalating epidemics of drug use and drug-related HIV, increasing drug-related crime, and relapse rates of 70% to 90%. A NIDA-supported bi-national research team documented the injection drug use and needle-sharing risk behaviors associated with the increasing prevalence of HIV, hepatitis, and tuberculosis,[17] and the government developed guidelines for agonist treatment that NIDA-supported researchers helped shape.[18] Subsequent trials demonstrated the efficacy of buprenorphine (BUP) to treat heroin-dependent injection drug users (IDUs)[19] and showed improved outcomes with the addition of behavioral drug and HIV risk reduction counseling.[20] More recent research has demonstrated the cost-effectiveness of BUP treatment for heroin dependence and compared the cost of treating heroin addiction with buprenorphine in Malaysia and 32 other countries.[21]

As a result of this research and its resulting policy changes, by 2013 about 10,000 patients had enrolled in BUP maintenance administered by 380 specially trained general medical practitioners and more than 27,750 patients have been enrolled at 333 government-run methadone maintenance programs.[22] With this national scale-up of treatment for opioid dependence, the evolving community-based treatment system in Malaysia is conducting research to determine the role to be played by NGO advocacy organizations and the importance of establishing community connections with local law enforcement, political leaders, and related officials, whose implicit and explicit approval is needed to locate and operate local treatment and related addiction support services. In addition, ongoing studies are conducting cognitive,

neuropsychological, and epidemiological assessments of individuals who abuse amphetamine-type stimulants (ATS) and heroin, and testing the efficacy of ATS treatment medications administered in conjunction with BUP maintenance therapy. NIDA-supported researchers have built an effective partnership that developed substance abuse treatment training programs for primary care providers, needle exchange programs, and scientific publications and presentations. Their work helped improve the availability of HIV treatment for injection drug users and was instrumental in shifting Malaysian policy from incarceration of drug users to medical treatment.

Sub-Saharan Africa

In July 2010, the government of Tanzania announced that in an effort to control the country's IDU-related HIV epidemic, it would change long-standing drug policies and launch the first medication-assisted treatment (MAT) program for drug users in sub-Saharan Africa. In 2002, the NIDA International Program issued an administrative supplement to test peer-delivered HIV risk reduction programs in Tanzania, and researchers from the University of Texas at Houston (UT-Houston) and Muhimbili University of Health and Allied Sciences (MUHAS) received additional NIDA support that documented the emerging HIV epidemic among IDUs in Tanzania.[23-27] Among their findings were one of the first reports to identify HIV transmission via shared injection works among an African IDU population[28] and the first report of a novel practice—called "flashblood"—among female IDU sex workers in Dar es Salaam, in which they draw back a syringe full of blood immediately after injecting heroin and give that blood to a friend who injects it.[29,30]

Recognizing that high-risk practices related to drug use, particularly injection drug use, contribute to HIV transmission, the Tanzanian government sought support from PEPFAR to implement evidence-based interventions to prevent HIV among drug users.[31] A former NIDA

Hubert H. Humphrey Drug Abuse Research Fellow worked with colleagues from Tanzania AIDS Prevention Program (TAPP), PEPFAR, and the U.S. Centers for Disease Control and Prevention to help draft five documents based, in part, on evidence from the UT-Houston–MUHAS research team. The documents include policy guidelines, an outreach service guide for HIV prevention among drug users, healthcare facility standards for MAT programs, clinical guidelines, and a substance abuse screening and brief intervention protocol for primary care settings. Research conducted by this team found appropriate methadone dosing in this newly established clinic and that retention in methadone maintenance treatment for opioid dependence at MUHAS was comparable to other methadone treatment programs in North America, Europe and Asia.[32] Older and female clients were less likely to prematurely discontinue treatment, whereas those who reported a history of sexual abuse were more likely to leave care and treatment. Such data point to the importance of addressing gender-related issues and male norms as part of substance-base treatment. Other research is evaluating the effectiveness of policy changes regarding the treatment of opioid dependence and is now identifying ways to improve treatment access and nationally scale-up methadone treatment in Tanzania at public health facilities[33] as well as making the case for adopting MAT throughout Africa.[34] PEPFAR is supporting the initiation of methadone treatment for opioid dependence in Kenya as well as Ghana, with research addressing access to methadone treatment for female sex workers in Kenya and the utilization of civil society organizations to enhance access to the HIV care continuum and methadone treatment.

Brazil

In Brazil, cocaine use is the most significant public health problem posed by illicit drug use.[35,36] Researchers from the University of Pennsylvania, together with Brazilian colleagues from the Center for Drug and Alcohol Research at the Federal University of Rio Grande do Sul,

Brazil, received funding from the NIH Fogarty Center (FIRCA) to initiate a research program to investigate the connection between cocaine use and HIV transmission. Findings from this FIRCA grant suggested that cocaine use was a factor in the spread of HIV in Brazil.[37] A subsequent larger project involving researchers from the University of Delaware confirmed the cocaine use-HIV link[38,39] and demonstrated the research capabilities of the Brazilian research team. Consequently, in 2012, the Brazilian government established the Collaborating Center on Drug and Alcohol in Porto Alegre as a new center to develop treatments for crack cocaine.

Russian Federation

The spread of injection drug use and HIV have been well documented in Russia.[40,41] Russian addiction treatment programs focus almost entirely on inpatient detoxification and rehabilitation since Russian law prohibits methadone and other opioid agonist treatments. However, naltrexone is approved in Russia, and the widespread use of inpatient detoxification makes it easy to initiate the medication during inpatient treatment. Following a NIDA/Pavlov State Medical University meeting in St. Petersburg in 1998, researchers from the University of Pennsylvania (Penn), Pavlov State Medical University, and the Leningrad Narcology Center developed a plan to study the efficacy of naltrexone for opioid (heroin) relapse prevention. Subsequently, with support from NIDA, a series of randomized 6-month trials of naltrexone were conducted. All were prospective, placebo-controlled, 6-month trials with follow-ups at 12 months and approved by the Pavlov and University of Pennsylvania IRBs. The primary outcome was remaining in treatment without relapsing. Secondary outcomes included ASI domains, HIV risk, psychiatric symptoms, and quality of life. A brief summary of their results follows:

- A trial involving 52 patients showed that oral naltrexone was superior to placebo in preventing relapse. Results were that 12% of placebo patients remained in treatment and had not relapsed by Month 6, as compared to 44% of patients on oral naltrexone.[42]
- A study involving 280 patients evaluated the addition of an SSRI to oral naltrexone and found that it did not significantly improve outcomes over naltrexone alone, but the superiority of naltrexone to placebo was replicated.[43]
- Findings from these studies provided the background for a study that led to the U.S. Food and Drug Administration (FDA) approval of extended-release naltrexone (Vivitrol®) for preventing relapse to opioid addiction.[44] The study, a randomized, placebo-controlled trial of extended release naltrexone funded by Alkermes, Inc., demonstrated the efficacy of extended-release naltrexone in reducing relapse to heroin use. As a result, extended-release naltrexone is now an approved medication in the United States for individuals that do not have access to agonist maintenance treatment or are not interested in it.
- At about the same time that the Alkermes study was underway, the Penn-Pavlov team was conducting a NIDA-funded study in which 306 participants were randomized to three groups (102/group) using: (1) a naltrexone implant that blocks opioid for 2–3 months (Prodetoxon®; http://www.prodetoxon.ru) + oral naltrexone placebo; (2) 50 mg oral naltrexone + placebo implant; or (3) double placebo. Results were that 58% of the implant patients remained in treatment for 6 months without relapsing as compared to 16% of the oral naltrexone patients and 12% of the double placebo group. No serious adverse events were observed in association with naltrexone treatment.[45]
- A current study is comparing oral naltrexone with Prodetoxon® for improving outcomes among HIV-positive, opioid-addicted patients. This 48-week trial has randomized 200 detoxified opioid-addicted individuals starting their first episode of antiretroviral treatment (ART) to: (1) Prodetoxon® + oral naltrexone placebo, or (2) oral naltrexone +

placebo Prodetoxon®. The primary outcome is viral load to <400 copies; the hypothesis is that Prodetoxon® patients will show better outcomes due to less relapse and better adherence to antiretroviral medication. Study results should be available in early 2015.

- Another study initiated in 2013 is being done at the National Research Center in Addiction in Moscow and is recruiting 130 HIV-negative, consenting, detoxified opioid-addicted patients and randomizing them to 48 weeks of Vivitrol®, or 24 weeks of Vivitrol® followed by 24 weeks of Vivitrol® placebo.[46] All patients are offered biweekly drug counseling with follow-ups at Weeks 60 and 72. The aim is to see if a 12-month course of naltrexone treatment reduces remission after treatment ends.
- Other studies have documented the association between injecting heroin use and HIV infection in the Russian Federation;[41] documented the potential of naltrexone for preventing overdose death;[47] shown that the opioid blockade from naltrexone can be overcome by using massive doses of heroin;[48] replicated U.S. studies showing high levels of psychiatric symptoms and HIV risk among opioid-addicted individuals and that effective treatment reduces both problems;[40,41] and described naltrexone use in Russia.[48-50]

These studies have provided Russian investigators experience in conducting prospective randomized trials using NIH standards and technologies and point to the importance of integrating treatment for substance use disorders, primary care, and HIV. As a consequence, an academic course on integrated treatment has been approved by the Ministry of Health for use in postgraduate training programs throughout the Russian Federation.

Other research has supported the collaboration between non-governmental organizations with several government institutions of the Russian Federation to develop and implement model programs to provide access to health services for opioid dependent individuals, including those living with HIV.[51] In an initial research effort, partnership agreements provided the basis for a

continuum-of-care model that identified a recommended package of HIV prevention services for injecting drug users to be used by treatment programs that cannot access methadone treatment. Other collaborations developed and implemented a model program of retention and continuity of care for patients with opioid dependence and HIV infection. The model utilized the narcology treatment and rehabilitation centers managed by the Narcology Detoxification Service, State AIDS Centers, Non Government Organization (NGO), as well as NGO outreach programs and the community. The model program was developed and implemented as a pilot demonstration project to provide essential health services to injection drug users and retain them in care. The interventions developed and implemented comprised HIV testing and counseling, peer support groups as recovery communities, narcological follow-up phone monitoring, women's narcological services, and short messaging services for injection drug users.[52] These services and interventions promoted the integration and utilization of health services to form an evidence-based health service delivery model providing essential services to people who inject drugs and people living with HIV/AIDS in a substance use disorder care setting.

Ukraine

Injection heroin use and HIV are recognized public health problems in Ukraine. Buprenorphine was introduced in 2004, followed by approval of methadone in 2007. A team from the University of Pennsylvania and Kiev was awarded a NIDA R21 to assess the usefulness of methadone to engage 25 HIV-positive and 25 HIV-negative IDUs in treatment and reduce their drug use and HIV risk behaviors. Treatment was offered for 12 weeks, with results showing excellent compliance with very little drug use during treatment and with almost all patients electing to continue methadone in the Kiev City program after the medication phase ended.[53] In the course of this study, a NIDA supplement funded a pilot study of "Life Steps," an

HIV medication adherence intervention developed by Safren and colleagues,[54,55] with an additional 25 patients. Focus groups were conducted in Kiev to determine modifications needed to make Life Steps applicable to Ukrainian culture, and Kiev research staff was trained in the modified intervention. Research in Ukraine is addressing improving engagement in substance abuse treatment, particularly methadone treatment, as well as adherence to medication treatment regimens for people living with HIV and who inject drugs.

Republic of Georgia

Two researchers from the Republic of Georgia (a Humphrey fellow and a NIDA CTN fellow) spent part, or all of their fellowships at the Penn/VA Addiction Treatment and Research Center. Buprenorphine injecting was a significant problem in the Republic of Georgia and the Penn/Georgia team was awarded a R21 to study the efficacy of buprenorphine/naloxone versus methadone for opioid-addicted patients in Tbilisi. Patients were randomized (40/group) to daily methadone or daily buprenorphine/naloxonefor 12 weeks. Results showed very little drug use during treatment with both medications. After study medication ended, drug use remained low for patients who continued in treatment in the methadone or buprenorphine/naloxone programs in Tbilisi, but increased use was found for those that did not continue treatment.[56,57]

Iceland

Amphetamine use is a significant problem in Iceland.[58] A study in Sweden reported that naltrexone might be useful for treating amphetamine dependence.[59] To extend the Swedish finding, a NIDA-funded study led by researchers at Penn and the SAA-National Center of Addiction Medicine and Vogur Hospital in Reykjavik[58] was conducted in which 100 amphetamine-dependent participants were randomized to a 6-month course of extended-release naltrexone or placebo, each with drug counseling. The primary outcome was proportion of amphetamine-negative urine tests during weeks

1–24 of outpatient treatment. Results showed marked improvements, with very little drug use among the approximately 50% of patients who remained in treatment. However, there was no evidence of medication effect. These findings were presented at the 2013 College on Problems of Drug Dependence and a paper describing them is being prepared.

Central Asian Republics

Injection drug use has been described as the main driver of the regional HIV epidemic in the Central Asian Republics. NIDA-funded research has recently provided data that expands the driver to sexual transmission through female sex workers who inject drugs.[60] The odds of HIV infection are up to 20 times higher among female sex workers who inject drugs, characterizing a key population for increased risk of HIV acquisition and HIV transmission. Other research is addressing the effectiveness of providing different modes of needle and syringe service programs to injection drug users in Kyrgyzstan as well as the development and implementation of co-located methadone treatment with HIV treatment and/or treatment for tuberculosis.

China

Everything in China happens on a large scale. The HIV problem in China is in great degree being driven by injection drug use. Consequently, a massive network of methadone maintenance treatment (MMT) programs has been developed to address the needs of 340,000 patients in the first 8 years of its implementation.[61] Over the past decade, NIH researchers, including NIDA researchers, have been very active in China addressing a broad range of health issues.

China has made significant strides in the implementation of MMT nationwide, but high rates of continued use and drop-out among MMT patients remain problematic. The wide proliferation of cell phones in China provides opportunities to collect ecological momentary assessment (EMA) data with drug users on their coping responses in the natural environment and

social context. UCLA researchers in collaboration with investigators in China have been conducting NIDA-funded research developing and examining a smartphone-based intervention that uses cognitive behavioral therapy and self-management principles to reduce relapse and improve treatment retention among Chinese patients in methadone maintenance. Other studies are testing evidence-based interventions (e.g., contingency management, case management) to address substance abuse and HIV problems in China.[62,63]

A former NIDA INVEST fellow who trained at UCLA returned to China when she finished her INVEST fellowship training, obtained an NIH R01, and is now conducting a study addressing HIV/HCV issues in China. Current studies report that the HCV-positive rate ranges from 50% to 80% among MMT patients,[64,65] and many patients are unaware of their HCV status. Recently, a 12-week HCV educational intervention trial was conducted in four MMT clinics. Compared with the control group, HIV and HCV knowledge improved in the intervention group, and their depression (Beck Depression Inventory) and anxiety (Beck Anxiety Inventory) scores decreased at the 12-week follow-up. Patients in the intervention group were significantly more likely to express motivation to use these HIV/HCV screening and treatment services. Service providers improved their HIV and HCV knowledge, self-efficacy, and service provision in their routine work compared to baseline.[67]

The Guangxi Autonomous Region in the south of China is among the hardest hit provinces in all of China in terms of AIDS-related deaths. In 2011, 22% of the national total of AIDS-related deaths occurred in Guangxi. Overly burdensome HIV testing practices are a potential stumbling block and deterrent to individuals identified as high-risk and referred for testing by their medical provider. In an effort to engage individuals who screen positive for HIV, researchers from NIDA, the Chinese National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, and UCLA are evaluating a “seek, test and retain, point-of-

care" strategy in 12 hospitals throughout the province. A testing algorithm, called "One4All," was designed to engage patients by shortening the time between screening, CD4 testing, assessment of antiretroviral therapy (ART) eligibility, and receipt of ART.

Led by a Chinese researcher, Chinese policy makers, and UCLA investigators, and funded by a supplement to the UCLA Clinical Trials Network grant, this cluster-randomized trial will evaluate the effects of a comprehensive diagnostic approach to enhance the percentage of participants that receive their HIV-test results, counseling, and, if eligible, ART, in 12 county hospitals in the Guangxi Zhuang Autonomous Region in southern China. Six county hospitals will be randomized to standard care, while the other six county hospitals will be randomized to the new One4All testing algorithm. A total of 360 patients will participate in this trial. Recruitment began in March 2014 and is expected to run through August 2014. This study will provide important data on effective and efficient methods of providing HIV testing.

Vietnam

During the late 1990s and the early 2000s, epidemiological data indicated that geographical areas in Vietnam had very high rates of HIV infection among injection drug users.[68] Because injection heroin use is the major driver of Vietnam's HIV epidemic, the Vietnam Ministry of Health has prioritized expansion of opioid agonist treatment as a major health priority to reduce the spread of HIV. Since 2008, a network of methadone clinics has been established with over 20,000 patients receiving methadone as of 2014. The connection between HIV and IDUs in Vietnam, in addition to inducing interest by the Government of Vietnam to address this public health problem with policies and practices using empirical evidence, has provided a situation where NIDA researchers can make significant contributions. In 2012, the Director of NIDA, Dr. Nora Volkow, visited several universities in Vietnam and has helped Vietnamese health leaders

identify priority research areas. There are a number of NIDA researchers currently working in Vietnam and this work is likely to expand. Below are brief summaries of several of these projects.

- MMT is a highly effective treatment, but in Vietnam (and many other places) it is delivered from specially licensed clinics with census limits, and the clinics are generally only located in large cities. As a result, access to methadone treatment is seriously limited. Buprenorphine/naloxone is a partial agonist approved in many countries for the treatment of opiate addiction and its use has the potential to expand access to treatment. Vietnam offers a unique opportunity to test the efficacy of integrating buprenorphine/naloxone treatment for heroin users who are newly entering HIV care.

  Two NIDA-funded projects are currently comparing buprenorphine/naloxone and methadone for the treatment of opiate dependence. In Ho Chi Minh City, researchers from Philadelphia, Bourdeax, France and Ho Chi Minh City are in the second year of a randomized clinical trial to compare the relative effectiveness of buprenorphine/naloxone and methadone. In the Northern Vietnam, a research team from Oregon Health and Science University (OHSU) and Hanoi Medical University has received a NIDA R01 grant to conduct a multisite, randomized trial of HIV clinic-based buprenorphine/naloxone (BUP/NX) versus referral to methadone (MMT)for treatment of opioid dependence in HIV-infected patients. All subjects will receive clinic-based counseling and HIV care. Self-reported drug use, urine drug screens, and measures of HIV care engagement and outcomes will be assessed through 12 months of follow-up. Annual qualitative interviews with HIV clinic providers, administrators, and patients will document formative implementation strategies, challenges, and best practices to inform national scale-up of clinic-based BUP/NX. The proposed work is the first large-scale

randomized trial of HIV clinic-based BUP/NX versus referral for MMT in an international HIV clinic setting. Lessons learned will directly inform government policies for implementing BUP/NX in Vietnam and in outpatient healthcare settings in other LMIC.

- At present in Vietnam, the HIV outpatient testing, treatment, and counseling clinics are completely independent of the newly developing network of methadone treatment programs and other SUD treatment services. There is a widely held perception that many of the patients in HIV care may have unrecognized and unaddressed SUDs that may be resulting in suboptimal HIV care. For this reason, a team from UCLA, the University of Minnesota, OHSU, and Hanoi Medical University have received a NIDA supplement to a U.S.-based R01 grant to evaluate the usefulness of a screening, brief intervention, and referral to treatment (SBIRT) procedure in HIV care settings in Vietnam. The project is designed to screen patients who receive HIV services, to conduct brief interventions on those with moderate SUDs, and to refer those addicted to alcohol/drugs to local SUD treatment programs, including methadone programs. The results of the pilot project will be used to guide the development of an R01 proposal to fully evaluate the value of SBIRT in HIV care.

Conclusions

During the past decade there has been a substantial proliferation of addiction research and funding for addiction research globally. Training programs sponsored by NIDA and research grants in international settings have been important contributors to the promotion of addiction research and the development of necessary skills and expertise among providers, especially addiction treatment for preventing the spread of HIV. NIDA researchers have played an important role in encouraging, mentoring, and collaborating with their international colleagues.

The many new international researchers and research teams are building research capacity and adding to the knowledge about addiction in cultures where addiction has not been previously studied. This information will be invaluable in the development of effective prevention, care, and treatment services that meet the needs of policy makers, public health leaders, and most important, patients with substance-related and addiction disorders around the world.

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