BUPRENORPHINE AND PRIMARY HIV CARE

REPORT OF A FORUM FOR COLLABORATIVE HIV RESEARCH WORKSHOP
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FORUM FOR COLLABORATIVE HIV RESEARCH

DEPARTMENT OF PREVENTION AND COMMUNITY HEALTH
THE GEORGE WASHINGTON UNIVERSITY
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This report summarizes the discussions held at the "Integration of Buprenorphine in the Primary HIV Care Setting" workshop held on June 3-4, 2004 in Washington, D.C.

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[*] http://www.hivforum.org/about/sponsors.htm

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EXECUTIVE SUMMARY

Opioid dependence and HIV both represent serious public health threats to the US. The Drug Addiction Treatment Act (DATA) of 2000 allowing prescription of Schedule III-V drug dependence treatment medications in office-based practices together with the approval of buprenorphine and buprenorphine/naloxone (2002) provided promising new directions for the treatment of opioid addiction and particularly, for improved care of patients with HIV-infection *and* opioid dependence. The integration of buprenorphine into HIV primary care has not been as rapid or extensive as expected.

The Forum for Collaborative HIV Research convened experts in HIV medicine and/or opioid dependence treatment from academia, community and private practices, patient community, US government agencies and industry to review issues associated with the integration of buprenorphine into HIV primary care, identify barriers to this integration and develop recommendations for increased uptake of this new opioid treatment modality into HIV primary care settings.
The goals for the workshop were:

- To review the current state of knowledge and gaps in knowledge
- To identify barriers to the integration of buprenorphine into HIV primary care, at the patient, clinic and systemic level
- To review and discuss policy and financing issues
- To review and discuss evaluation of program impacts
- To recommend strategies for the integration of buprenorphine into HIV primary care, with special emphasis for the Ryan White CARE Act-funded programs.

According to the Office of National Drug Control Policy, 810,000 persons were opioid dependent in 1999, with only 225,000 receiving treatment in 2004. Injecting drug use (IDU) is the second most prevalent risk behavior associated with HIV transmission:

an estimated 25% of the approximately 40,000 new infections each year are due to injection drug use. The effect on the HIV epidemic extends to the sexual partners and children born to injecting drug users and their partners.

Injection drug use fuels the HIV epidemic directly and indirectly, and negatively impacts on HIV treatment outcomes. HIV-positive drug users experience higher morbidity and mortality than non-using HIV-positive individuals on antiretroviral treatment. Contributing factors are HIV and non-HIV related illnesses, decreased access to and utilization of health care and decreased prescription of and adherence to antiretroviral treatments. Stigma plays a major role in both diseases. The majority of the HIV and hepatitis C (HCV) co-infected individuals are injecting drug users. A public health policy promoting integrated treatment for HIV+ individuals with opioid dependence is an essential strategy to curb the epidemic, given the role of intravenous drug use in the spread of HIV and its association with suboptimal access to care.

Treatment of opioid dependence leads to fewer HIV infections and results in other significant public health benefits. Treatment of opioid addiction is based on pharmacological interventions combined with psychosocial approaches; long-term maintenance treatment coupled with intensive counseling has proven to be the most effective strategy. Treatment has been demonstrated to decrease heroin use, mortality for overdose and spread of blood-borne pathogens such as HIV and HCV. In addition, crime rates are decreased and integration into society is improved. Pharmacological treatment includes methadone and buprenorphine

Buprenorphine, a partial agonist, has less potential than methadone for overdose and a wider safety margin. Co-formulation with the antagonist naloxone prevents intravenous injection abuse. Currently, a maximum of 30 concurrent patients may be treated per group practice. Long-term maintenance treatment in combination with intensive counseling and therapy is significantly more effective than the

shorter supervised withdrawal treatment combined with counseling and therapy in retaining patients in treatment and drug-free as well as decreasing mortality.

Early knowledge of HIV status and counseling for prevention are essential for curbing the spread of disease. Intravenous drug users are more likely to be tested late and receive care late. Although antiretroviral treatment has significantly reduced HIV associated morbidity and mortality, this benefit has been less evident in injection drug using populations. HIV treatment requires considerable expertise and the complexity of quality treatment is compounded in patients with substance dependence and the accompanying associated co-morbidities such hepatitis C infection and mental health disorders. Barriers to treatment of opioid addiction by HIV providers include lack of expertise, bias, intolerance, lack of patient-physician trust and lack of resources.

A number of knowledge gaps were identified and these need to be addressed through research programs. Buprenorphine needs to be investigated in diverse patient populations, including women, minorities, youth and adolescents. The safety of buprenorphine during pregnancy and breast-feeding needs to be established. More knowledge on drug interactions, including interactions with drugs for treatment of co-infections and co-morbidities needs to be gained.

The models for integrated care include standard on-site dependence specialist treatment, enhanced on-site dependence specialist treatment, and induction-stabilization within the substance abuse setting and subsequent transfer to the HIV care system for maintenance treatment of the dependence. Currently existing programs include community health centers, hospital based settings and mobile health care units. These models illustrate that integrated care of HIV-infected injecting drug users is feasible in these settings.

Integrated care requires patient centered approaches that emphasize adherence and reducing HIV transmission behaviors. Applying the lessons learned from the HIV advocacy model is important. Cultural competency of clinicians is a key factor in establishing communication. Patient centered approaches include models of treatment "agreements" which include patient-oriented and physician-oriented goals. Care teams require adequate support to deliver high-quality, evidence-based substance abuse treatment in HIV clinics. Multi-level education complemented by hands-on experience, is a key component for providing effective tools and changing negative attitudes. The involvement of professional societies and the AIDS Education and Treatment Centers should be recruited for education and training support. Addiction can be "medicalized" like other chronic diseases and ways to apply the principles of the chronic disease model should be explored.

Programs requirements for integrated care include flexible access to core and support services -- including case management – that are responsive to the changing needs of the patient. Integrated programs will include support for induction of treatment, access to outside consultants, training on substance abuse and cultural issues, and, consistent with the chronic care model, include support for patient activation and linkages to community resources. Program evaluation is an integral need, and should include number of HIV physicians qualified to prescribe buprenorphine, number of physicians actively prescribing buprenorphine, number of patients on buprenorphine, and the ability to report the number of current clients with substance abuse problems. Outcome measures for effective, integrated treatment programs include the initiation of antiretroviral treatment in a healthier status, decreased intermittent care and increased treatment retention, improved adherence to treatment, decreased development of antiretroviral resistance, improved cost-effectiveness to individuals and community, improved general health status, improved mental health status and improved quality of life.

Financing of buprenorphine treatment involves navigation of several funding streams, including Medicaid, Ryan White Care Act, Substance Abuse Block Grants and Mental Health Services Block Grants. This results in a challenging and complex system from which to operate. For example, substance abuse may be covered as a medical service but not as a rehabilitation service by Medicaid programs. Buprenorphine is covered by some ADAP programs, but not others. In the context of flat federal funding for ADAP programs, rationing of care has become a reality for many organizations. The Veterans Administration provides a unique model, in that all eligible patients qualify for comprehensive physical and behavioral health service and the VA is exempt from the 30 patient limit per group practice.

Supportive policy changes include eliminating the 30-patient limit, changing Medicaid coverage and reimbursement levels, increasing ADAP coverage for buprenorphine and promotion of integrated treatment within the CARE Act programs. Mechanisms whereby this can be achieved through quality measures and quality management should be explored. In addition, the manner in which funding is made available at the local level needs to be streamlined. Studies demonstrating cost-effectiveness are crucial and they should include outcomes such as improved adherence to both treatments, improved treatment outcomes such as less hospitalization and less co-morbidities, and improved quality of life.

In summary, effective integration of buprenorphine and HIV care requires bridging the two "cultures" and medical fields, developing supportive policies and addressing the research gaps. The recommendations are summarized below.

SUMMARY RECOMMENDATIONS

TRAINING CLINICIANS & CLINICAL TEAMS	
Medical Schools	• More comprehensive incorporation of substance abuse training into medical school curriculum and residency programs • Specific training and information packets on medical components of integrated treatment, such as brief interventions, urine toxicology testing, drug interactions, dosing, etc
Post- Medical School	• Integrate training into the programs of professional societies such as IDSA, HIVMA, AAHIVM, Nursing Societies, and others
Clinical Teams	• Develop training aimed at improving attitudes and biases vis-à-vis substance dependence • Develop training to break down barriers due to "cultural differences" of the two medical fields • Use currently available models of effective integration in training programs • Develop training for substance abuse clinical teams in recognizing signs and symptoms of HIV infection, and referral mechanisms for HIV treatment • Develop training for effective communication and interviewing strategies • Develop special training initiatives for application in the correctional institution setting • Develop mechanisms for mentoring and ongoing support of clinical team members
Training Patients	• Use patient centered approaches emphasizing adherence and reducing HIV transmission behaviors

	• Train patients to raise drug dependence issues with their providers • Establish effective use of advocacy, using HIV advocacy as a model
PROGRAMS & SERVICES RECOMMENDATIONS	• Integrate treatment of opioid dependence and HIV infection into chronic disease models, including information systems, patient activation, community resources, provider teams and disease-specific specialist as well as treatment for mental health disorders and other co-morbidities such as hepatitis C co-infection • Provide support systems, including case management • Integrate counseling (group or individual, as needed) into buprenorphine/HIV treatment programs • Consider models for integrating depression into primary care • Incorporate social marketing strategies to increase number of clients seeking integrated care • Develop treatment agreements with patient-centered and clinician-centered goals • Develop strategies for delivery of substance abuse services with a range of intensity, from daily medication dispensing for unstable patients to medication-only programs for patients in stable recovery • Explore mechanisms to exploit to replicate the VA model of integrated HIV/substance abuse treatment in other settings • Establish and integrate program evaluation and treatment outcome criteria • Establish a mechanism for rapid transfer of knowledge from research into programs
POLICY & FINANCING RECOMMENDATIONS	• Negotiate new patient number limits for group practices (or remove 30-patient limit) • Assure that substance abuse treatment with buprenorphine is considered a core service in the reauthorization of the CARE

	Act • Incorporate buprenorphine treatment into quality management for HRSA programs • Consider mechanisms for merging funding streams at the local level • Investigate mechanisms to achieve fuller Medicaid funding and incorporation into ADAP programs
MONITORING & EVALUATION	• Incorporate program evaluation and monitoring into programs at local, state and federal levels • Implement monitoring of program and treatment outcomes
RESEARCH GAPS	• Assess the cost-effectiveness of integrated treatment compared to non-integrated treatment • Investigate the impact of buprenorphine on transmission of HIV in diverse HIV+ injecting drug using populations and reducing seroconversion in HIV- injecting drug users • Establish the safety of buprenorphine in pregnancy and during breast-feeding • Investigate the impact of buprenorphine on improving access to care, adherence to treatment and improved treatment outcomes, including quality of life • Investigate the use of buprenorphine in women, minorities, youth and adolescents • Carry out drug interaction studies, including drugs for treatment of co-infections and co-morbidities such as hepatitis C and tuberculosis • Assess the appropriateness of buprenorphine or methadone for individual patients • Investigate the feasibility and appropriateness of sequencing methadone and buprenorphine treatments

INTRODUCTION

The Drug Addiction Treatment Act (DATA) of 2000 was passed by Congress to allow prescription of Schedule III-V drug dependence treatment medications in office-based practices. In October 2002, the Food and Drug Administration (FDA) approved buprenorphine and buprenorphine/naloxone, a partial opiate agonist ideally suited for office-based prescription, for treatment of opioid addiction. These two events opened up a promising new direction through which to address some of the major barriers to opioid addiction treatment. The potential for improved care of patients with HIV-infection *and* opioid dependence presented by these developments led to the expectation that buprenorphine would be integrated rapidly into the HIV primary care setting. Experience has not confirmed this, however: the uptake of buprenorphine into HIV primary care practices and clinics in the US has been minimal and sporadic. The opportunities for effectively addressing both epidemics should provide inspiration to face the unique challenges inherent in bridging the two medical fields.

The Forum for Collaborative HIV Research convened experts in HIV medicine and/or opioid dependence treatment to review the issues associated with the integration of buprenorphine into HIV primary care, identify barriers to this integration and develop recommendations for increased uptake of this new opioid treatment modality into HIV primary care settings. This intersectoral and interdisciplinary workshop included participants from academia, community and private practices, patient community, US government agencies[†] and industry.

The goals for the workshop were:

- To review the current state of knowledge and gaps in knowledge

[†] Centers for Disease Control; Health Resources and Services Administration; National Institutes of Health; Substance Abuse and Mental Health Services Administration.

- To identify barriers to the integration of buprenorphine into HIV primary care, at the patient, clinic and systemic level
- To review and discuss policy and financing issues
- To review and discuss evaluation of program impacts
- To recommend strategies for the integration of buprenorphine into HIV primary care, with special emphasis for the Ryan White CARE Act-funded programs.

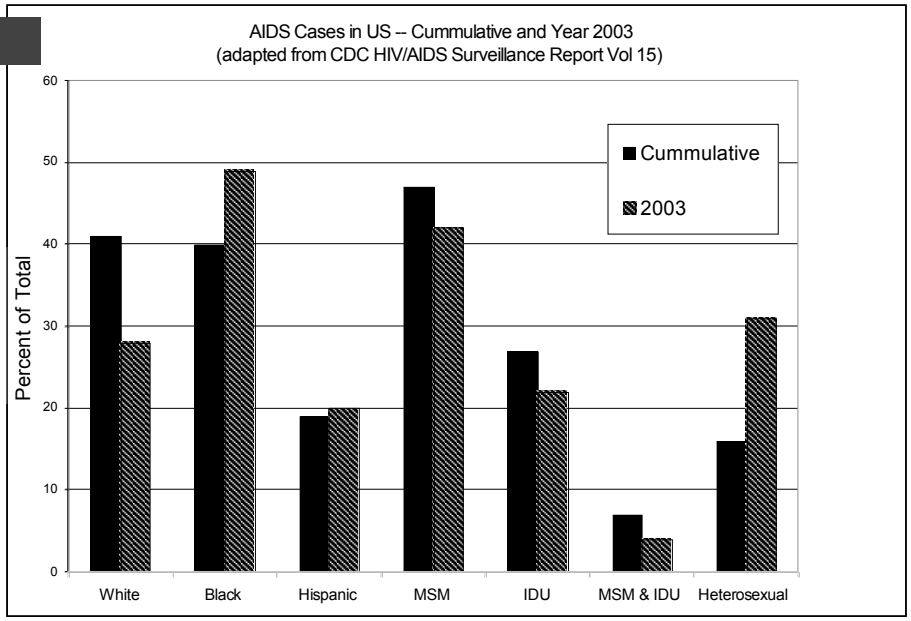
This report summarizes the proceedings of this workshop. It is based on the presentations, break-out group discussion and open discussion during the workshop. The workshop's agenda is provided in Appendix C of this report. The presentations may be viewed at www.hivforum.org/projects/Buprenorphine.htm .

THE TWO EPIDEMICS: AN OVERVIEW

Opioid dependence and HIV infection are two epidemics currently affecting an alarming number of individuals living in the United States. According to the Office of National Drug Control Policy, 810,000 persons were opioid dependent in 1999, with only 225,000 receiving treatment in 2004. The Substance Abuse and Mental Health Agency (SAMHSA) National Survey on Drug Use and Health [1] reported that in 1996, 2.4 million Americans reported using heroin at least once. The non-medical use of prescription opioids increased from 628,000 to 2.4 million in the period of 1990 to 2001, with a further increase to 4.4 million in 2002. Emergency department visits for heroin increased 47%, and emergency department visits for non-medical use of prescription pain relievers increased 117% during 1992-2001 (SAMHSA Drug Abuse Warning Network).

Injecting drug use (IDU) is the second most prevalent risk behavior associated with HIV transmissions, based on cumulative AIDS cases [2]. Approximately 40,000 individuals are infected each year, and nearly 25% of these are estimated to be due to injection drug use [3]. The Centers for Disease Control and Prevention (CDC) estimates that approximately 850,000-950,000 individuals are currently infected with HIV. An estimated 929,885 AIDS cases accumulated since the beginning of the epidemic through 2003, with 676,569 (73%) of cases in 25 - 44 year-olds. Although the majority of cumulative AIDS cases occurred in non-Hispanic Whites (40%), in 2003, the major burden of AIDS diagnoses was born by the non-Hispanic Black population. Forty-nine percent of the 2003 AIDS diagnoses were in non-Hispanic Blacks, compared with 28% in non-Hispanic Whites and 20% in Hispanics [2]. Of the total number of AIDS cases diagnosed in 2003, 42% were ascribed to infection through male-to-male sexual contact (MSM), 22% to injecting drug use and 4% to male-to-male contact with injecting drug use.

Figure 1



The interaction between the two epidemics is especially relevant to the African American community. HIV has been the leading cause of death among 25-44 year old black men since 1991, whereas among white men, HIV-infection dropped to the fifth leading cause of death since 1997 [4]. Among black women 25-44 years old, HIV infection was the leading cause of death from 1993 through 1996, and the second leading cause of death in 2000, compared to eighth leading cause of death for white women [4]. Blacks constituted 56.9% of HIV and AIDS cases among injecting drug users, based on data from the 32 States that have used confidential name-based reporting of HIV and AIDS cases for the last 4 years [5].

The impact of injecting drug use on the HIV epidemic extends beyond those involved directly in injecting behavior, to heterosexual partners of injection drug users and children whose mothers are injection drug users or sex partners of injection drug users. Fifty-six percent of AIDS cases associated with injection drug use in this broader sense were Black, 22% White and 21% Hispanic. Female injection drug users comprised 22% of the estimated AIDS cases associated with injection drug use; 17% were heterosexual sex partners of injection drug users [2].

In some jurisdictions, injection drug use is the primary exposure factor for seroconversion. This is true, for example, among Hispanics born in Puerto Rico and diagnosed with AIDS in the USA. In this population, 45% of AIDS cases were attributed to injection drug use and 34% to heterosexual transmission [6].

In addition to its contribution to HIV transmission, drug use complicates HIV disease management and treatment [7]. HIV-positive drug users experience higher morbidity and mortality, compared to age-matched HIV-positive individuals that are not drug users [8,9]. Contributing factors are HIV and non-HIV related illnesses [8], decreased access to and utilization of health care [10,11] and decreased prescription of [12,13,14,15] and adherence to [16,17] antiretroviral treatments. A history of injecting drug use characterizes the majority of the HIV and Hepatitis C (HCV) co-infected individuals; co-infection combined with substance dependence complicates treatment for all three conditions [18,19].

Thus the epidemics of opioid addiction and HIV infection intersect at several levels: injection drug use fuels the HIV epidemic directly and indirectly, and negatively impacts on HIV treatment outcomes. The demographic overlaps among the two epidemics contribute to the syndemic nature of the two diseases. Both are characterized by stigma and have a high proportion of patients with mental health issues (see below).

OPIOID ADDICTION AND ITS TREATMENT

Opioid addiction is a chronic, relapsing medical disorder, associated with increased prevalence of co-morbid infectious diseases such as HIV and HCV. The underlying etiology encompasses multifactorial genetic components, post-exposure biologic changes and behavioral factors. Thus treatment strategies need to include both neurobiological and behavioral approaches. *Stigma, both social and medical, is a significant barrier to care and treatment of substance abuse [20]. Stigma is also highly associated with HIV infection [21].*

Text Box 1

Opioid Dependence & Stigma: A Historical Perspective

Prior to the 20th century, opioid dependence was far less stigmatized and considered to be a problem of "more sensitive" individuals. In contrast, in the early 20th century, opioid dependence has been linked with criminality or character deficits, and the term "addict" has a pejorative meaning. The Harrison Narcotic Drug Act of 1914 and the Webb vs. United States, precedent decisions that served to warn physicians with the message "Treat an addict, and go to jail", have left a legacy. Many physicians continue to be reluctant to treat patients with opioid dependence and even to treat pain in non-dependent patients. In 1964, the World Health Organization recommended that the term "addiction" be replaced with "drug dependence" but the terminology remains confusing as dependence may also occur when opioids are taken as prescribed.

Profound neurobiologic changes accompany the transition from opioid use to abuse to dependence. Addictive substances elicit their effect via neurologic reward pathways, resulting in release of dopamine and stimulation of the nucleus accumbens. The accompanying experiences are euphoria and reward. Drug-induced behavioral changes reflect alterations in normal brain function, and can impact an individual's mood, feeling, thinking and perception. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) classifies opioid dependence as follows (3 or more of the following within one year):

- Tolerance

- Withdrawal
- Larger amounts/longer period than intended
- Inability to/persistent desire to cut down or control
- Increased amount of time spent in activities necessary to obtain opioids
- Social, occupational and recreational activities given up or reduced
- Opioid use is continued despite adverse consequences

Text Box 2

Why are opioids addicting?

Opioids bind to the μ receptor, which has a high affinity for enkephalins, beta endorphins and opioids. Binding of the μ receptor results in increases of cyclic adenosine monophosphate (AMP) levels, leading to increased expression of protein kinase C. This, in turn, is responsible for the regulation of numerous cellular processes including activation of intracellular pathways associated with craving. The mesolimbic dopamine system, which arises in the ventral tegmental area (VTA) of the brain, is activated and is an important neural substrate for opioid reinforcement and dependence. Chronic exposure to opioids is known to produce biochemical adaptations in this brain region, leading to structural changes in VTA dopamine neurons.

Psychiatric co-morbidities are common among opioid abusers. In one study, 47% of opioid addicted individuals seeking methadone treatment presented with a psychiatric co-morbidity, antisocial personality disorder and major depression being the two most common diagnoses [22]. *Depression is also quite common among HIV-infected patients, and is often undiagnosed or untreated. When left untreated, depression is associated with illicit drug use, poor adherence and increased costs [23].*

TREATMENT OF OPIOID ADDICTION

Treatment of opioid addiction has transitioned from a primarily psychosocial based approach to a medical based treatment. Medically supervised withdrawal treatment

("detoxification") covers the transition from the state of physical dependence to an opioid-free state, and consists of an induction phase and a dose-reduction phase. Maintenance treatment starts with an induction phase, and continues with stabilization and maintenance. Current standard of care for treatment of opioid dependence is based on pharmacologic treatment coupled to psychotherapy, and is based on long-term, ongoing strategies rather than simply getting through the stages of acute withdrawal [24,25]. Opioid addiction can be an all-encompassing occupation and patients may need to make significant lifestyle changes and find new ways of coping with stresses.

There is a large body of evidence that long-term maintenance treatment is more effective than supervised withdrawal treatment in increasing adherence to treatment, lessen illicit drug use, and reducing mortality [25,26, 27, 28]. Low retention rates in treatment programs based on psychosocial interventions without parallel pharmacological interventions severely restrict the effectiveness of non-pharmacologic treatment. However, counseling remains an important component of treatment [29]. Pharmacologic treatment (methadone, buprenorphine) plus enhanced counseling resulted in higher treatment retention rates and negative urine toxicology results compared to pharmacologic treatment with standard counseling or no counseling at all [30,31].

The rationale of pharmacologic intervention is to prevent withdrawal, relieve cravings for opioids and block or attenuate the euphoric effects of exogenous opioids.

Text Box 3

Methadone Treatment

Historically, much of our knowledge of the effects of the effects of treating opioid dependence in the context of HIV infection comes from methadone studies. Methadone has been extensively researched; it is safe and cost effective. When taken under medical supervision, long-term administration does not cause adverse effects or impair cognitive function. At approximately $13 per day, the cost is certainly much

less than the cost per day of incarceration and/or the cost of treating HIV and associated infections and hospitalizations.

Methadone takes about 30 minutes to be distributed in the blood, therapeutic benefits last 24-36 hours and there is no associated euphoria when dosed appropriately. The patient is still dependent on the opioid, but is not controlled by compulsive urges as seen in heroin dependence. Withdrawal from methadone is a slow process, and patients can be adequately maintained for years. Yet, approximately only 15-20% of the estimated 810,000 heroin users in the United States receive methadone maintenance treatment [32,33, 34,35].

The field of substitution therapy has gained most of its knowledge from experience with methadone treatment. Despite the effectiveness of methadone treatment (summarized above and see below: Benefits of Treating Opioid Addiction), opioid dependence treatment rates have been relatively low (see Text Box 3). Federal rules restrict the use and availability of methadone to strictly regulated environments in which medication is taken under clinical observation. Provisions for self-administer methadone outside the clinic are severely restricted. These requirements of methadone treatment programs are associated with stigma and are not optimal for facilitating reintegration into normal life. Regulations also restrict the type of patients (chronic vs. recent dependence) eligible for treatment. Furthermore, many physicians who practice in primary care settings have limited knowledge and experience in treating substance abuse disorders [36]. Traditionally, medical schools and residency training programs have not emphasized the importance of intervention models for substance abuse treatment [37].

BENEFITS OF TREATING OPIOID ADDICTION

Effective treatment of opioid addiction results in an improved quality of life for the patient. Treatment of opioid addiction has the potential to enhance health, decrease behavior that places individuals at risk for infectious diseases and improves integration into society.

Treating opioid dependence leads to fewer HIV infections. In a study published by Metzger and colleagues, 3.5% of 152 individuals receiving methadone treatment seroconverted during the 18 month follow-up, compared with 22% of 103 injection opioid users not receiving treatment [38]. The benefits of treatment of opioid dependence have been confirmed in numerous studies. Methadone has provided effective treatment and shown to decrease heroin use, mortality for overdose and spread of blood-borne pathogens such as HIV and HCV [39,40,41,42]. HIV incidence and prevalence rates are significantly lower among injecting drug users on treatment compared to individuals not on treatment in their communities at times of rapid HIV transmission [43,44,45]. The positive impacts of methadone treatment on HIV seroconversion are associated with longer duration of treatment [46,47,48]. A study comparing the 180-day psychosocially enriched detoxification to methadone maintenance found that maintenance led to lower rates of heroin use and of HIV infection risk behaviors [31]. Crime rates among opioid users decline when they are maintained on methadone [33,41,49,50]. These benefits amply demonstrate the cost-effectiveness of opioid dependence treatment [51,52].

Nevertheless, the challenges encountered in treatment of substance abuse are many. Relapse is common and use of other drugs may also complicate treatment. This may be frustrating to clinicians, and patients may perceive that they are being morally judged or viewed as indolent, both of which may compromise the doctor-patient relationship thus hindering future treatment progress. The temptation to discontinue treatment upon relapse can also contribute to poor outcomes [53].

DRUG ADDICTION TREATMENT ACT 2000

The Drug Addiction Treatment Act 2000 (DATA) allows qualifying office-based physicians to use approved schedule III-V narcotic medications, like buprenorphine and buprenorphine/naloxone [54]. The signing of this Act into law was one of three

federal initiatives for the care of opioid-dependent patients. The other two initiatives are: exemptions for office-based opioid agonist treatment and the transfer of the administrative responsibility for the use of narcotic drugs in maintenance and detoxicfication treatment from the Food and Drug Administration (FDA) to SAMHSA [54]. These three initiatives pave the way for the integration of substance use disorders within standard medical practice. Effective treatment may now be provided by qualified physicians and it is expected that this will provide treatment opportunities to patients who previously did not seek treatment [54]. These new opportunities come at a time of increasing heroin use and high rates of HIV and HCV transmission among injection drug users.

DATA specifies the prescription of FDA approved medications for maintenance and detoxification treatment of opioid dependence. Buprenorphine and the buprenorphine-naloxone combination were the first medications to be approved for this purpose. Potential barriers to the implementation of the new federal initiatives include physician and patient acceptance, lack of reimbursement mechanisms, office logistic considerations, inappropriate prescribing, medication diversion, and appropriate strategies for patient confidentiality [54]. The 30 concurrent patient limit currently in place is a potential disincentive for program participation. It may also encourage short-term treatment modalities, which are not as effective as longer maintenance treatment periods (see above).

Text Box 4

DATA Requirements

The mechanisms for qualification for physicians licensed under state law are: 1) certification by a subspecialty board in addiction medicine, 2) participation in approved training in the treatment and management of opioid-dependent patients (8 hour minimum), 3) service as an investigator in a clinical trial leading to drug approval, and 4) training or experience deemed appropriate by the state medical licensing board or the Secretary of the Department of Health and Human Services. Physicians must notify the Secretary of Health and Human Services of their intention

to provide this treatment. The physician must be able to refer patients to counseling and ancillary services. Currently, there is a 30 patient per practice limit in place.

BUPRENORPHINE: OFFICE-BASED OPIOID DEPENDENCE TREATMENT

Buprenorphine, a partial opioid agonist, was approved by the FDA in 2002 for use in supervised withdrawal and maintenance treatment of opioid dependence. Buprenorphine is a good alternative to methadone in specific circumstances, although it will not replace methadone for many opioid dependent people. Buprenorphine requires a prescription, and is classified as a Schedule III medication. Like any pharmacological treatment for drug dependence, the therapeutic benefit of buprenorphine may be enhanced when there is a counseling component made available to patients receiving treatment. As for methadone, long-term treatment, compared to short-term supervised withdrawal treatment, is significantly more effective in retaining individuals in treatment programs and remaining drug-use free.

Buprenorphine in Clinical Trials

The importance of long term treatment was demonstrated in a randomized, placebo controlled study reported by Kakko and colleagues [25] in patients who were not eligible for methadone treatment. Patients were randomized to receive a short term (6 day) course of buprenorphine (supervised withdrawal treatment followed by placebo) or a long-term (12 month) course of active treatment, and both groups received intensive psychosocial treatment consisting of relapse prevention group therapy, weekly counseling sessions and thrice weekly urine screens. Retention in treatment – the primary outcome – was significantly better in the maintenance treatment arm, with a risk ration of 58.7 [95% CI 7.4 – 467.4; p=0.0001]. All patients in the placebo arm discontinued the treatment program before 2 months, with 75% dropping out by 2 weeks, whereas 16 out of 20 patients in the maintenance arm remained in treatment for 12 months. Urine analysis showed drug

use in all patients in the placebo arm prior to discontinuation. Maintenance treatment was associated with significant improvements in the area of drug use, crime, and occupation. The 1 year mortality rate in the control group was 20%, compared to 0% for the active treatment arm.

Text Box 5

Buprenorphine: Key Facts

Buprenorphine hydrochloride is a derivative of the morphine alkaloid thebaine. The synthetic opioid binds to the μ opiate receptor, with partial agonist effects. Its low intrinsic activity on the μ receptor produces a "ceiling" effect. Thus, higher doses of buprenorphine do not increase its agonist activity but rather, extend its duration of action. The clinically relevant result is that it can be dispensed on less than once-daily basis. Preliminary reports suggest little effects of buprenorphine on the breastfeeding infant but as there is little data the risks and benefits should be carefully considered [55]. Compared to methadone, buprenorphine has a greater margin of safety from death by respiratory depression and overdose is uncommon. Buprenorphine, like methadone, is extensively metabolized by the cytochrome oxidase enzyme system. Buprenorphine may be combined with naloxone, a short-acting antagonist in an attempt to minimize diversion. If taken sublingually as prescribed, the patient absorbs the buprenorphine but not the naloxone. However, if the pill is crushed and injected, on opioid dependent person would experience a primary naloxone effect which results in immediate and uncomfortable precipitated withdrawal. Naloxone binds strongly to the μ receptor, thus blocking all opioids without providing the opiate effect. The buprenorphine/naloxone combination, available in a 4:1 ratio as a sublingual tablet is effective in daily or thrice weekly dosing.

Other studies have investigated the efficacy of buprenorphine, with or without naloxone, in treating opioid addiction. [56,57, 58].

Johnson and colleagues compared buprenorphine, levomethadyl acetate and two doses of methadone in a 17 week randomized study of 220 patients. Buprenorphine was similarly effective in reducing the use of illicit opioids as levomethadyl acetate and high-dose methadone [56]. In a larger study, 326 opioid dependent individuals were randomized to receive buprenorphine plus naloxone, buprenorphine alone, or

placebo [58]. The primary outcomes of this 4-week study were the percentage of opioid-negative urine samples and the subjects' self-reported craving for opioids. An additional 461 patients participated in an open label study of buprenorphine and naloxone. Buprenorphine, alone and in combination proved to be significantly more efficacious than placebo for both endpoints. Eighteen and twenty-one percent of urine samples from the treatment groups, compared with 6% of urine samples from the placebo group, were negative for opioids ($p<0.0001$) and the patients in the active arms reported significantly less craving ($p<0.0001$). The treatment appeared to be well tolerated and safe [58].

In a report describing the field experience provided by buprenorphine/naloxone studies performed within the National Institutes of Drug Abuse (NIDA, NIH) Clinical Trials Network further confirmed the safety and efficacy of this treatment modality. The majority of the 234 patients (68%) completed the detoxification program, with an excellent toxicity profile. Interestingly, all providers, including those with minimal experience in the provision of opioid based pharmacotherapy, were able to integrate buprenorphine-naxolone into their existing addiction treatment practices [59].

Buprenorphine in the clinical setting

Assessing patients' readiness to change their drug-using behaviors is the first step in a treatment program [60]. Maintenance buprenorphine treatment consists of three phases: induction, stabilization and maintenance. During the induction phase, patients begin the switch from the opioid to buprenorphine; the minimum dose of buprenorphine necessary for discontinuing or markedly reducing opioid use without withdrawal symptoms and craving for the drug of abuse is established. The initial induction doses should be administered under observation. Dosage adjustments may be necessary during stabilization; frequent contact between patient and physician increases the likelihood of compliance during this phase. The maintenance period may be indefinite. While a few patients may benefit from a

short course of maintenance treatment, many patients will require many years or a lifetime of treatment. SAMHSA has published clinical guidelines for buprenorphine use [61].

Text Box 6

Physician Clinical Support System (PCSS) for office-based treatment of opioid dependence

The American Society of Addiction Medicine, in consortium with other specialty medicine societies has announced a Physician Clinical Support System (funded through SAMHA) to assist physicians in the appropriate use of buprenorphine. A national network of 45-50 trained physician mentors with expertise in buprenorphine treatment will be supported by 8-10 national experts in the use of buprenorphine as well as a medical director. The PCSS expects to provide support services to 1350-2250 primary care physicians, pain specialists, psychiatrists and other non-addiction medical practitioners. An estimated 40,500-67,500 patients will benefit from this program.

OPIOID ADDICTION IN THE SETTING OF HIV/AIDS

Both opioid dependence and HIV represent serious public health threats to the US. Infection with HIV requires the transmission of viral particles from one individual to another and needle-sharing provides an optimal pathway for this transmission. The clinical course of the disease is noted by a primary infection, asymptomatic stage, early symptomatic stage and an advanced immunodeficiency stage with opportunistic complications. A patient is said to have AIDS once he or she develops one of a set of AIDS-defining illnesses, or the CD4 cell count drops below 200 cells/ul. Viremia is highest during the primary infection stage; this is the time when HIV+ individuals are most infectious [62,63,64]. Knowledge of HIV status early on, coupled with counseling for prevention are considered essential elements for curbing the spread of disease. Intravenous drug users are more likely to be tested late and receive care late [10,11,12,13,14,15].

Care and treatment of HIV infected individuals requires expertise at many levels. Treatment requires addressing biomedical as well as social components of the disease. Social aspects of the disease are attended to by addressing stigma, housing, family issues and providing education to reduce risk factors for transmission. Biomedical components of HIV/AIDS and opportunistic infections are addressed by treating the underlying HIV infection and opportunistic pathogens. Additional co-morbidities are addressed by treating substance dependence and mental health disorders.

Certainly, antiretroviral treatment has dramatically reduced the morbidity and mortality associated with HIV/AIDS [9,65,66] although injecting drug users, as a group, have not benefited to the same extent as age and sex-matched counterparts [8,9]. However, treatment is complex, requiring knowledge of the various antiretrovirals (more than 20 drugs in four different drug classes) and their use in combination. Treatment is frequently associated with drug toxicity, and HIV drug

resistance is a common problem. Thus, a high level of commitment and adherence is asked of the patient and the clinical team for optimal treatment management. Treatment of HIV+ infected individuals with opioid dependence presents additional challenges to many HIV practitioners. The barriers to treatment include lack of expertise with respect to addiction medicine, bias and intolerance within the clinical team, lack of trust between patient and clinician, lack of resources for opioid addiction treatment, etc. Integrating HIV care into drug dependence treatment centers is even more difficult. Traditionally, the two fields of medicine simply have not "mixed".

POINTS OF INTERSECTION

HIV and substance abuse are not isolated problems, but influence the progression of each other and are often intertwined with mental illness [67]. Thus, treatment of substance abuse will provide many benefits in terms of HIV disease. First, treatment of substance dependence improves access to HIV and general health care. Secondly, treating opioid dependence has the potential to reduce the transmission of HIV and viral hepatitis as well as bacterial infections. Thirdly, it decreases the need for hospitalization. Lastly, it improves poverty, employment and social integration.

HIV Transmission

Intravenous drug use is the second most prevalent risk behavior associated with HIV transmission. Needle-sharing is a primary route of HIV transmission from HIV-positive injecting drug users to HIV-negative injecting drug users. However, transmission through sexual intercourse is also an important mechanism for transmission, not only within but also beyond the drug-using community. In addition, transmission from mother-to-child may occur. In one study, 90 percent of drug users reported being sexually active, and 20% of the participating men reported having more than five regular sexual partners. Condom use ranged from

35-39%. A more recent study reported 54% of injection drug users with more than one partner were not using condoms [68,69]. In a study of illicit-drug-using men reported by the CDC [70], those who reported having sex without a condom were more likely than those who used condoms to report multiple sex partners, trading sex for money or drugs and failure to disclose HIV serostatus.

Decreased Access to Treatment

Bogart reported the reduced willingness to prescribe antiretroviral medications to intravenous drug users, African-Americans and Hispanics, based on a sample of treating physicians [71]. Medicaid data from New Jersey identified injection drug users, African American race and receiving no case management as correlates of later initiation of therapy [72]. Unfortunately, injection drug use is also a correlate of discontinuation of antiretroviral treatment [73] and HIV treatment responses have been shown to be less optimal than in other HIV infection risk groups in some cohort studies [17]. In contrast, in France, where buprenorphine has been available since 1996, buprenorphine was shown to be associated with increased adherence to antiretroviral treatment [56,77].

Hepatitis C

Approximately 16% of the HIV-infected population living in the US is estimated to be co-infected with HCV, the majority having a history of injection drug use [18,19]. HCV co-infection, with a prevalence of 65-90% in HIV-infected injection drug users is another complicating factor for treatment. Although studies of the impact of HCV on HIV progression have not yielded conclusive results, it is clear that HIV infection contributes to faster progression of end-stage liver disease among HCV infected patients. Treatment for HCV is complex, requiring a combination of pegylated interferon and ribavirin. Furthermore, there are drug-drug interactions among drugs used for HIV and HCV treatments. Treatment toxicities include depression, which may lead to relapse in drug use. Despite these obstacles, the integration of HCV treatment in HIV clinics is being actively studied and

buprenorphine may play an important role in relapse prevention for this population [74].

Pain & Depression

Pain syndromes are frequent in HIV, presenting with multiple etiologies, including headache, peripheral neuropathies, rheumatologic diseases and myopathies. The role of buprenorphine in these patients has not yet been examined. Depression represents another intersection point between the HIV and opioid dependence epidemics. Twenty-two to forty-six percent of patients in clinical care settings have reported depression, and it is untreated in a significant proportion of patients [23]. Untreated depression is associated with illicit drug use, poor adherence and increased costs. Could models for integrating treatment for depression in primary care settings assist with the development of buprenorphine treatment models?

INTEGRATION ISSUES

Issues related to integration of opioid addiction treatment into HIV primary care include:

- Who should prescribe opioid addiction treatment? Drug dependence specialists, HIV treating physicians or both?
- Should the induction process occur within or outside an HIV clinical setting?
- Which HIV-infected patients should be considered for buprenorphine treatment?
- Should the medical doctors, nurses or social workers or drug counselors provide psychosocial services?
- How often should the patient receive counseling? Who decides?
- When should the patients be discontinued from buprenorphine?

Potential conflicts exist for integration of services and care. The "cultures" of substance abuse treatment and HIV care are vastly different and difficulties exist in bridging these. Conflict between patient and physicians are another source of problems for effective integration. Clinicians' disappointment in patients and patients' mistrust of clinicians play a major role. Different goals for patients and clinicians may exist but are rarely acknowledged. Finally, there may be conflict between providers, such as primary HIV clinician and counselor, or primary HIV clinician and substance abuse expert, again rarely acknowledged but with the potential to impede progress in integrating care and services.

Potential Drug Interactions

Patients being treated for opioid dependence and HIV infection face potential drug interactions. Buprenorphine is metabolized by the cytochrome P450 3A4 enzyme, thus raising concerns for potential drug-drug interactions with non-nucleoside reverse transcriptase inhibitors and protease inhibitors. To date, limited data exist on interactions between buprenorphine and antiretroviral drugs. Specifically, zidovudine [75] and efavirenz [76] have both been examined. Buprenorphine levels were not obtained in the zidovudine study, but no subjects experienced withdrawal. In the efavirenz study, buprenorphine levels did decrease, but again, no subjects experienced withdrawal.

Other medications potentially affected include cytochrome P450 3A4 inhibitors, such as fluconazole and macrolide antibiotics; inducers such as phenobarbital, carbemazepine, phenytoin and rifampicin and sedatives such as benzodiazepines. Drug interactions have not been examined in controlled studies. However, studies report the expected CD4 cell increases and viral load decreases in patients on antiretroviral treatment plus buprenorphine [77,78]. More studies investigating drug interactions relevant for HIV treatment are urgently needed.

POLICY FOR INTEGRATED TREATMENT

A public health policy promoting integrated treatment for HIV+ individuals with opioid dependence is an essential strategy to curb the HIV epidemic, given the role of intravenous drug use in the spread of HIV and its association with suboptimal access to care. Furthermore, a policy acknowledging the need to treat both diseases promotes patient wellbeing, reduces stigma and promotes the delivery of comprehensive, ethical medical care.

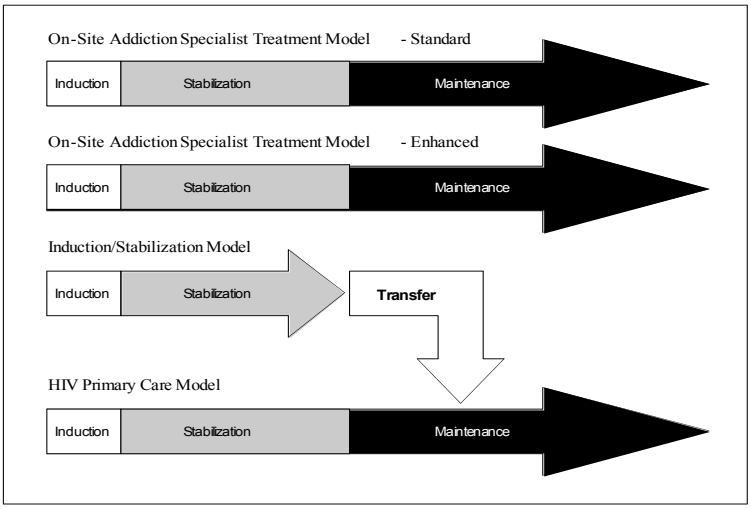
MODELS OF INTEGRATION

Possible approaches to integrating buprenorphine into HIV clinical care settings include:

- Standard on-site dependence specialist treatment model
- Enhanced on-site dependence specialist treatment model
- Induction-stabilization model within substance abuse setting with transfer to HIV care system for dependence treatment maintenance

Figure 2

Possible Approaches to Integrating Buprenorphine into HIV Clinical Care Settings



Few effective programs for integrated HIV and substance abuse care exist at the current time. The models that are currently available include community health centers, hospital based settings and mobile units.

LESSONS LEARNED: COMMUNITY HEALTH CENTER MODEL

Text Box 7

Chase Brexton Community Health Center, Baltimore

Chase Brexton Health Services, Inc. is a non-profit, community-based organization providing medical, psychological and social services on a non-discriminatory basis, with an emphasis on HIV/AIDS care. Services include medical care, dental care, mental health services, nutritional assessments and counseling, drug dependence counseling, anonymous HIV counseling & testing, case management and outreach services, health promotion and disease prevention, in-house pharmacy, pediatric care, primary medical care, sexually transmitted diseases clinic, and women's health services (www.chasebrexton.org).

Of the 5,000 patients served by Chase Brexton (see box), about 1000 are HIV positive. The patient population is diverse, including men who have sex with men and intravenous drug users. The decision to start a buprenorphine program was based heavily on the needs of the HIV positive patient population. Realizing the impediment that active drug use is to being fully engaged in and realizing the full benefit from medical treatment for HIV/AIDS, the center shifted to a more proactive mode in integrating substance abuse treatment needs assessment for all clients with HIV. This necessitated not only increasing the number of counselors, but the implementation of new strategies. The new strategies included the design of an Intensive Outpatient Program (IOP), preparing for the integration of buprenorphine treatment on-site, as well as a satellite methadone program. The IOP was developed in response to client's need to be treated for their substance abuse in an explicitly HIV aware and gay affirming setting, something that was not possible in an off-site substance abuse treatment program. The integration of buprenorphine treatment was seen as an opportunity to bring substance abuse medicine and HIV care together, focusing on comprehensive, collaborative, integrative medical care. Having the IOP center operational and running prior to the start of buprenorphine treatment was considered essential.

Barriers: Initially, clinicians as well as the drug dependence community greeted the plans for the IOP and integrated treatment programs with considerable resistance. Staff members feared the additional influx of "addicts", seen as potential detractors to non-addicted patients. Clinicians, including physicians and nurse practitioners, did not see themselves as "drug dependence specialists". Many negative attitudes were inherited from real or perceived experiences from methadone programs. Counselors regarded buprenorphine treatment as a crutch, not a real recovery. Generally, staff felt overburdened and overwhelmed, and the fact that "something new" was to be learned was not welcomed.

Overcoming barriers: The resistance and fears were overcome by education and open dialogue. Physician training for providing buprenorphine proved to be very effective in allaying fears regarding treatment of HIV patients with opioid dependency. Moreover, clinicians saw the potential benefit of an effective dependency treatment for their HIV treatment program. Having seen and experienced the damage to HIV treatment created by untreated dependency and the frustration of ineffective substance abuse treatment, the opportunity for actively engaging in the resolution of this problem was welcomed. Counselors and the drug dependence community came to understand buprenorphine treatment as a transition to drug-free life, easier to come off from than methadone. Understanding and realizing the usefulness of buprenorphine for patients who did not make it on methadone due to the stigma of methadone clinics and the restrictive structure of the methadone setting, also contributed to the eventual acceptance by the clinic staff. Overall, the center was able to see how an integrated approach to treating substance dependence confirmed the values and mission of the clinic.

From theory to practice: Chase Brexton physicians begun prescribing buprenorphine in November 2004 and as of January 2005, a total of 9 patients have started on buprenorphine treatment, with 7 still actively on treatment. In preparation for initiating treatment, an interdisciplinary group had developed

written procedures prior to the first patient entering the treatment program. The group had predicted that these procedures would need to be revised once the treatment program started; this prediction turned out to be correct, with each new patient presenting the need for new decisions or clarification. Maintaining a forum for staff to communicate on these issues was essential to finding solutions. The group viewed the need to rewrite procedures as strength, rather than a weakness, in that they were able to use their experience to refine procedures. The circle of communication was increased over time to include addiction counselors, physicians, nurses, pharmacists, case managers and front desk staff.

How did resistance to and acceptance of an integrated buprenorphine change over time? The intensive efforts to prepare staff (see above) resulted in reduced resistance by the time the first prescription was written. However, indirect signs of resistance continued to be seen, such as emphasizing financing and scheduling problems (legitimate though they were) and using "buprenorphine" as an explanation for other problems in the clinic. However, most staff members view the unanticipated challenges as problems to solve; resistance and skepticism have dwindled even further as more patients enter the program and are seen to be doing well in their use of buprenorphine to treat their addiction as well as support their HIV therapy. Buprenorphine has become "just another treatment" offered to meet the needs of the patient, and for many staff members, acceptance has changed to enthusiasm.

Remaining questions: Questions that have arisen and for which answers are being sought include:

- How structured and intense does the counseling program need to be? Is flexibility an option?
- What is the effectiveness rate for people already on methadone that are switching to buprenorphine?

- Are the financing issues resolvable over the long term? (85% of patients referred to the IOP are uninsured)
- How soon is the 30 patient-limit going to be a problem?

LESSONS LEARNED: PRIMARY HEALTH CARE MODEL

Text Box 8

Clinical Addiction Research and Education Unit, Boston University Medical Center

The Boston Medical Center is a large, academic inner-city facility, with three practices offering substance abuse treatment: General Medicine, Family Medicine and Health Care for the Homeless. The General Medicine Practice includes six trained physicians, and between three and five physicians in the other practices.

The Boston Medical Center is an interdisciplinary clinic model for integrating opioid dependence into primary care. It is based on and dependent on, a nurse case manager, funded through outside funding. The model includes counseling and other support services. Patients are referred through emergency rooms, urgent care sites and primary care facilities. The center provides medical withdrawal as well as maintenance treatment. Treatment of homeless patients is coordinated with shelter systems. Youth and adolescents present special challenges, requiring a higher level of support. Counseling and drug dependence support services are mandatory for all enrolled patients. Financing the care has not been an overwhelming problem since the hospital setting, with its infrastructure and resources, is able to absorb the costs. The Boston Medical Center program has begun to work with community health centers.

Positive experiences: Buprenorphine treatment has provided considerable stability to patients entering in unstable social conditions. For example, patients have been housed, been able to move back in with their families and able to take antiretroviral treatment. Through working with the Public Health Commission, sufficient resources are available for counseling (including one-on-one) and other services.

Having all medical care needs -- including HCV and HIV care -- on site, is considered crucial to the success of the program, as are dedicated support staff and effective communication within the facility.

Emergency cards are a key ingredient to the program. These cards ensure that emergency room staff knows what treatment they are on and how to treat them appropriately.

The Center works with consents and contracts between patients and providers, but treatment plans are individualized and tailored to patient's needs. In the case of youth and adolescents, extensive involvement with parents to monitor dosing and take responsibility for medications appears to be very successful.

Issues: Patients who have attained greater stability through buprenorphine treatment may experience psychiatric comorbidities that were previously masked by their drug use. The Center refers these patients for psychiatric treatment.

In summary, the Boston Medical Center program demonstrates that buprenorphine treatment is feasible in the primary care setting, involving physician input comparable to that required for the treatment of other chronic diseases. Offering buprenorphine treatment will allow treating individuals earlier in their abuse history and attract individuals with untreated medical and psychiatric problems into primary health care.

LESSONS LEARNED: MOBILE HEALTH UNIT FOR TRIPLY DIAGNOSED PATIENTS

Text Box 9

Mobile Health Unit for Triply Diagnosed Patients – New Haven

The Community Health Care Van is a mobile health unit funded by the Ryan White CARE Act and was developed to reach patient populations that are difficult to treat within established settings, such as hospitals, clinics or private offices. Clients

include homeless individuals, people who will not often seek treatment within established structures, and/or patients who have trouble maintaining the schedule and motivation necessary to continually attend treatment sessions. A 36-foot long truck moves from neighborhood to neighborhood offering free primary health care to anybody who wants it. While the primary purpose of the project is to reach HIV-positive substance abusers, the fact that anybody can utilize the services being offered, regardless of HIV or substance abuse status, decreases the stigma that can often accompany treatment for both of these diseases and encourages greater use of the van's services.

Currently, the van serves four primary New Haven communities that have been determined to have high rates of opioid use and/or sex workers. The mobile task team is able to spend time getting to know the neighborhood and the people within the neighborhood, thereby building trust in what they are doing with prospective clients. By spending time simply building relationships and a reputation within each neighborhood, the mobile task team actually makes it easier for people to take advantage of the services being offered.

Decreasing the stigma that surrounds treatment is a significant step, but the strongest advantage of this model is in how it can get people who are still using opioids into treatment. Within a hospital or clinic setting, both induction and maintenance are heavily dependent on a patient's ability to initiate and maintain treatment within a structured system – often based on scheduled appearances during which the patient is examined and medicated. For active drug users, these schedules are often forgotten or even avoided as a result of their drug dependence. The mobile treatment team, in effect, keeps the schedule for these patients by offering treatment within each neighborhood on a designated schedule. Instead of relying on memory, this approach creates a system in which people are comfortable seeking treatment, and then ensures that the treatment is easily attainable when needed. This leads to an increase in both induction and adherence among a patient community that is otherwise often left without continuous treatment for either their drug dependence or HIV infection. The mobile van works in tandem with a needle exchange program, providing an opportunity for interaction and cross-referral.

Innovative model for integrating HIV care: The mobile health unit is an innovative and unique way to provide treatment to triply diagnosed patients: those with substance dependence, HIV and mental illness. A mobile van (see box) provides

neighborhood based care for all the medical needs. Clients do not need to be HIV positive to participate in the program. However, the program takes advantage of the "on-site" approach to provide a modified version of directly-observed therapy to those requiring antiretroviral treatment, as well as any additional medication for mental health issues or other comorbidities. A case manager is available on the van; the patients can meet with the case manager confidentially to discuss their treatment needs. The success of this program – especially when combined with buprenorphine treatment – is illustrated by individual case histories of patients with triple diagnoses - active heroin users - who were able to access treatment for both HIV and heroin use in a linked fashion -- all services provided on the van. The mobile health unit model is also useful for care and treatment of patients released from correctional facilities in need of relapse prevention and continuous, high-quality HIV-care. Another patient population that benefits from this program is patients who are "suddenly" ready to be treated. The need to be able to offer substance abuse treatment when patients are ready to start cannot be overemphasized. The mobile unit offers the opportunity to initiate treatment immediately, whereas it is not possible to enter a methadone clinic immediately.

In summary, the mobile health unit provides an example of successful integration of treatment for three difficult diagnoses: substance abuse, mental health, and HIV, often including HCV. Linking the treatment for all three conditions is the only way to assure successful treatment of any one of these conditions.

PERSPECTIVES ON INTEGRATION

For integration to be effective, it needs to be viewed from the patient-centered, the care team, and the systems and programs perspective.

PATIENT PERSPECTIVE

Patient centered approaches include the acceptance of changing treatment paradigms, emphasizing adherence and reducing HIV transmission behaviors. An emphasis on a primary care model will result in continuous, comprehensive, integrated and compassionate approaches. Cultural competency of treating clinicians is a must. Access to treatment can be increased by appropriate social marketing, immediate assessment and induction in the clinical care setting and ensuring adequate number of treating physicians. Advocacy within the HIV community has had substantial impact on HIV treatment; such advocacy has not yet developed within the substance dependent community. *Learning from the positive lessons of the role of advocacy in HIV, including patient empowerment, may be useful in the context of dually diagnosed individuals.*

Communication between clinicians and clients needs to be established, and should be based on trust. Models of treatment "agreements", with mutually agreed upon patient-oriented goals and physician-oriented goals were recommended. Training for both patients and clinicians is paramount and organization of services. Support services and supervision of doses allowing adjustment to individual patient needs were identified as being significant to the success of programs. Patients need a clear understanding of buprenorphine treatment, and physicians need training on interviewing techniques, how to take a patient-centered approach. Antiretroviral treatment readiness skills could be used as a model for assessing buprenorphine readiness. Stigma is still associated with people who are opioid dependent and terminology plays a significant role. Terms like "addicts", "detox", "dirty urines",

"bad users", "good users" and "unmotivated" should be avoided and replaced with "patients", "supervised opioid withdrawal", "opioid positive urines", "injectors", "non-injectors" and "not-ready yet".

CLINICAL TEAM PERSPECTIVE

Care teams also require support in order to deliver high-quality, evidence-based substance abuse treatment in HIV clinics. Education is a key component for increasing knowledge base, providing effective tools for care and changing negative attitudes on the part of clinical team members [79]. Clinic settings vary widely, and the differences in setting need to be considered for program design. Large, multi-disciplinary, urban clinics may be more likely to have ready access to dedicated substance dependence experts. Standardization and protocols will be important to contribute to the maintenance of consistent high-quality delivery of care. In this setting, the 30-patient limit per group practice may be a particularly serious disincentive. At the other end of the spectrum, small, rural general medical practices may afford limited experts. Cross-training of staff will be required, physician coverage more of an issue and the reimbursement structure more difficult to work out.

All members of a care team need to be recognized, including physicians, nurse practitioners, physician assistants, nurses, counselors, social workers, case managers, pharmacists, administrators, medical assistants and clerical staff. Education includes clinical practice guidelines, conferences, case management discussion forums, videos, and longitudinal learning, such as continuous medical education. A large component of education should address attitudes towards individuals with substance dependence, emphasizing the motivational model. General knowledge (or lack thereof) will affect clinical team member's attitude to drug dependence problems. As the models of integrated treatment (see above) demonstrated, hands-on experience and training will go a long way to remove the

barriers set up by negative attitudes and fear of engaging in treatment of doubly diagnosed patients. "Addiction" can be "medicalized", similar to the diabetes treatment model, or depression treatment model. Patients need to be encouraged to raise drug dependence issues with their providers though providers must be aware that patients may be reluctant to do so. Dependence in illicit opioids is illegal and patients may be concerned about issues such as parole, housing and child custody in disclosing drug use.

Education on substance abuse treatment for clinicians needs to start at the nursing and medical school level and be integrated into residency programs. Many opportunities are provided by the professional societies, such as the Infectious Diseases Society of America, the HIV Medical Association, the American Academy of HIV Medicine, the American Association of Addiction Medicine, the nursing societies, such as the Association of Nurses in AIDS Care, to incorporate training on specific topics in post-graduate and continuing medical education programs. Not least, the AIDS Education and Training Centers (AETCs) provide an ideal mechanism for training according to a multidisciplinary chronic care model, including integrated buprenorphine treatment. Special initiatives for training of clinicians working in correctional settings and for medical providers in rural areas can and should be sponsored by the professional societies and the AETCs.

Finally, but not least important, are mentoring and on-going support. Many university medical centers offer telephone accessible experts in a variety of clinical areas. The possibility of integrating buprenorphine mentoring into such existing systems need to be explored. Of interest is the Physician Clinical Support System for office-based treatment of opioid dependence described in Text Box 6.

SYSTEMS & PROGRAMS PERSPECTIVE

A discussion of integration of buprenorphine into HIV care will involve discussion of the structure of services, of how to pay for buprenorphine and related services, and outcomes and performances measures.

The integration of buprenorphine into HIV care should occur in the setting of the "chronic disease model" [80], with flexible access to core services, depending on client characteristics and provider resources. The overall program should be patient-centered and provide access to support services, including case management. The scope of services needs to be responsive to the changing needs of the client. Communication structures need to be established (and fostered) among the various providers. Cross-training of staff will help eliminate duplication.

The program models include that of a solo practitioner, an academic health center, or a specialized HIV clinic. Core services available on-site, for any of these three models, include a physician with a federal X DEA number to monitor both HIV and buprenorphine treatments needs, and medical services for HIV and substance abuse. Substance abuse counseling by a physician or other provider is another required component. This will provide, at a minimum, brief intervention, motivational enhancement, and adherence services. Other services, either on-site or available by referral, that are required include a pharmacy to provide HIV medications and buprenorphine as well as group and/or individual counseling. Mental health services, housing services and family support are additional elements essential to successful programs. Integrated programs will include induction of treatment support, access to outside consultants, training on substance abuse, cultural issues and buprenorphine for staff, as well as urine analysis. Consistent with the chronic disease model, integrated programs will include support for patient activation and linkages to community resources as well as information systems to support clinicians and patients [80].

Financing buprenorphine treatment involves navigation of several funding streams, including Medicaid, Ryan White CARE Act, Substance Abuse Block Grants and Mental Health Services Block Grants (see below). Guidance on how to accomplish this effectively is needed. For solo practitioners not eligible for these funding streams, payment from public and private insurers needs to be in place. For many solo practitioners, payment issues represent an insurmountable barrier to providing buprenorphine treatment.

A re-evaluation of the necessity of the 30 patient restriction and research into alternative mechanisms to control buprenorphine is necessary[‡].

Program evaluation is integral to any effective program. Data on number of people with HIV needing substance abuse treatment is limited, making evaluation difficult. Additionally, some clinics do not have data analysis capacity. Process measures which should be considered for evaluation include:

- Number of HIV physicians qualified to prescribe buprenorphine
- Number of HIV physicians actively prescribing buprenorphine
- Number of patients on buprenorphine
- Ability to report the number of current clients with substance abuse problems

Outcome measures for effective, integrated treatment programs include:

- Initiation of antiretroviral treatment in a healthier status
- Decreased intermittent care and increased treatment retention
- Improved adherence to treatment
- Decreased development of antiretroviral resistance
- Cost effectiveness to individuals and community

[‡] The US Senate passed a bill to remove this limit in June 2004. This legislation is currently stalled in the House.

- Improved general health status
- Improved mental health status
- Improved quality of life

Text Box 8

Integrated Buprenorphine & HIV Care Evaluation & Support Center

The HIV/AIDS Bureau of the Human Resources and Services Administration funded an initiative for programs that integrate HIV primary care and buprenorphine treatment through its Special Projects of National Significance (SPNS) branch in September 2004. Ten SPNS sites around the country were funded to develop and evaluate integration programs. For more information see www.bhives.org.

The hallmarks of the US healthcare financing and insurance system are lack of universality, complexity and lack of consistency in scope of coverage and in eligibility within sectors and across sectors. Despite the number of dollars spent, the system is not optimally effective. A population based safety net does exist, primarily in the form of community health centers. In this context, the unprecedented step of creating a disease specific safety net program, the Ryan White CARE Act, provides unique opportunities.

HIV care in the United States is dependent in large part on public system funding. Approximately 22% of individuals with HIV are already on Medicaid at the time of their diagnosis; overall, 33% have private insurance. Only 18% of injection drug users are on private insurance and 27.5% are on Medicaid [[81]]. According to the HIV Cost and Services Utilization Study (HCSUS), an estimated 44% of patients with HIV *who are in care* are on Medicaid, 6% on Medicare, and 20% are uninsured. This compares to the total US population, of which 13% are on Medicaid, 12% on Medicare and 15% are uninsured. Although many public funding streams exist, navigating these effectively has proven to be a challenge. This is not made easier when attempting to integrate buprenorphine into HIV primary care settings.

What are the public funding provisions for substance abuse and HIV treatment? The largest amount of HIV specific money is provided by Medicaid. Medicare does not fund prescription drugs and provides at the most, limited substance abuse treatment. Medicaid, on the other hand, mandates that all FDA approved drugs be available, although significant restrictions can be imposed, limiting their use. Substance abuse treatment, as a rehabilitation service is optional, whereas substance abuse treatment as a medical service is not optional. This means that while methadone clinics and related centers of this nature are often covered, the

supporting services that enable full rehabilitation – e.g. counseling, mental health services – may not be.

Even though Medicaid is by far the largest payer of publicly-funded HIV care in the US, there are many limits on eligibility and coverage, which vary from state to state and hamper the provision of optimal care. Many are familiar with the "catch-22" of eligibility that exists in most states: a person with HIV must be poor and disabled in order to become eligible for Medicaid because of his/her HIV condition. In order to access the very treatments that can prevent disability, one must first become disabled. Of equal importance, with reforms passed in the mid-1990s, the federal government no longer considers drug addiction to be a qualifying disability for Medicaid. Thus, to the degree that individuals receive substance abuse treatment through Medicaid, it is because they have become eligible for the program through another pathway.

The Ryan White CARE Act fills in the gaps in Medicaid eligibility and benefit. The CARE Act covers substance abuse treatment, but only as the payer of last resort. ADAP programs may offer buprenorphine, depending on local choices. A limited number of jurisdictions currently cover buprenorphine in their ADAP programs.

Despite its formation as a safety net, the availability of treatment through the CARE Act is limited by financial constraints that are very similar to those seen in Medicaid. Many states have decreased their contribution levels to their respective ADAPs during the same time that federal funding of the CARE Act has been flat. As a result, many organizations that rely on this money to provide HIV and substance abuse services are facing grant cuts and, consequently, are forced to stretch their budgets further by rationing care. These constraints are combined with an increasing demand for CARE Act services realized though a combination of continuing infections coupled with fewer deaths as well as less disability among treated patients, thereby reducing the number that can be transferred to Medicaid

and maximizing the cost to the CARE Act. Increasing drug prices and the need to treat the co-morbidities that come with new HIV and opioid-dependence cases put further pressure on already limited budgets.

SAMHSA also provides a funding stream to states that can be used for both HIV and substance abuse treatment. SAMHSA manages two block grants, a mental health block grant totaling $434 million and a substance abuse block grant totaling $1.8 million. The substance abuse block grant includes a mandatory set-asides for HIV early intervention. The HIV-related funding is relatively minor when compared to Medicaid and the Ryan White CARE Act, however, and has only totaled approximately $60 million a year for each of the last two years. The inability for most states to account for where and how this money is spent also makes it a less viable option on which to rely in formulating policy.

The Veterans Administration (VA) is the largest single provider of HIV care in the country serving approximately 20,000 people living with HIV at an estimated cost of $390 million per year. The VA is a unique situation, however, as the people who are eligible for treatment in the VA system qualify for comprehensive physical and behavioral health services for both HIV and related co-morbidities. The VA also covers buprenorphine and is exempt from the 30 patient limit that is placed on other agencies and clinics[82]. The Center for Substance Abuse Treatment (CSAT) has designated that, within the VA, the limit of 30 patients applies only to individual physicians, with no limit for group practices. This unique set of factors would make it a desirable referral for eligible patients and future updates on the efficiency of integration of buprenorphine into HIV primary care within the VA will be of interest. The fact that these special conditions were set up for practitioners within the VA raises the question whether this could also be done for other public programs, such as Ryan White CARE Act funded clinics serving more than 30 patients.

One of the most fundamental aspects of integration will be the rationalization of multiple funding streams through which buprenorphine, HIV, and supporting service and treatments are funded. According to a recent Institute of Medicine Report (IOM) [83], the first step in making government funding more responsive to the needs of the more general HIV-positive community is to create a federally funded entitlement, earmarked for HIV, to cover those that make less than 2.5 times the federal poverty level. This entitlement should cover substance abuse treatment and mental health services as well as all currently provided services for HIV treatment. In adopting this type of entitlement, the government would move closer to developing a system in which the overlapping needs of HIV and substance abuse treatment are able to be simultaneously managed to the benefit of both patient populations.

While it is unlikely that Congress will adopt the IOM's recommendations, the ongoing discussion surrounding the reauthorization of the CARE Act provides another opportunity to define, at a national level, core services to include comprehensive substance abuse treatment for HIV infected individuals. Other structural innovations include the possibility of merging funding streams at the local level.

Policy changes that would support integrated buprenorphine treatment include changing the 30 patient limit, changing Medicaid coverage and reimbursement levels, increasing ADAP coverage for buprenorphine and promotion of integrated treatment within the CARE Act programs. For example, would it be possible to require primary care sites receiving CARE Act funds to have physicians qualified to prescribe buprenorphine? HRSA cannot require anything other than what is included in statute. However, the agency can create program expectations, which would have an impact on how the programs are implemented. One way to approach this would be within the context of quality measures and quality management. Quality management processes were developed to reduce health disparities for

intravenous drug users. Thus, recognizing the quality of care benefits resulting from integrated buprenorphine programs would serve to prioritize this within the HRSA system.

In addition to changes in the amount and type of funding, the manner in which funding is made available at local levels needs to be streamlined. To enable local governments and clinics to maximize the benefit derived from these various funding outlets, policies are needed that combine parallel funding streams and enable their use without additional bureaucratic hindrance stemming from overlapping administrative accountability. Funneling all applicable funds into one or a few funding streams would enable state and local agencies and service providers to focus on providing necessary services.

Studies demonstrating cost effectiveness are crucial for the overall success of integrating substance abuse and HIV treatment programs. Cost-effectiveness studies should include issues such as improved adherence to both treatments, improved treatment outcomes (less hospitalization, less co-morbidities) and improved quality of life.

SUMMING UP & NEW DIRECTIONS

Over the last 20 years, the HIV community has witnessed extraordinary progress in the development of treatments that suppress HIV replication and slow or even reverse disease progression. The substance abuse community, on the other hand, has had few such milestones. Nevertheless, the recent addition of buprenorphine to the modest armamentarium available for substance abuse treatment represents an opportunity to significantly improve the prospects of substance dependent individuals.

As impressive as the HIV treatments are, their effect will be irrelevant to those that do not access treatment. Furthermore, the benefits of HIV treatment will be diminished for those who access treatment inconsistently and/or too late. Unfortunately, this scenario is true for a large segment of the HIV-infected population in the US – the actively substance dependent HIV-infected individuals. The availability of two manageable pharmacological treatments – one for HIV and one for substance abuse – makes the goal of bringing significant improvement to the two epidemics a realistic one. Treatment of both diseases will provide benefits that extend well beyond the individual patient, and *integrated* treatment stands to synergize the effectiveness even more.

The work to be done can be divided into three major areas:

- Bridging the two "cultures"
- Developing supportive policies
- Addressing research gaps

These areas are not mutually exclusive, but rather, inter-related. However, it is useful to structure the discussion around these three focal points. The major action items listed in this and previous sections are summarized in the Summary Recommendations Table, Executive Summary.

BRIDGING THE TWO CULTURES

Bridging the two cultures involves education, training and gaining experience, as well as development of programs that allow integration of services. Bridging will also benefit by looking at what one community can teach the other – learning from the positive experience and advancements.

Education, Training & Experience

Knowledge and expertise are strongly associated with better quality of care, better health outcomes and more cost-effective care. This has been amply demonstrated for HIV/AIDS and many other chronic conditions [84]. Strategies for building knowledge and expertise were outlined in the section Perspectives on Integration/ Clinical Team Perspective. The problems of bias, intolerance and lack of trust may be addressed in part by education and training; ultimately, first-hand experience of the benefits to patients and society will be a more compelling force. Models such as the Chase Brexton Community Health Center (see Text Box 7 and subsequent text) aptly illustrate the role of experience in addition to training in acceptance and engagement in the program by all clinical team members. Models such as this one and the others presented in the section Models of Integration offer the opportunity to look for and document outcomes such as reduction in stigma and attitudinal barriers to providing integrated care through the building of knowledge and expertise. Training programs should incorporate mechanisms to capture outcome measures – such as improved health outcomes for patients and improved cost-efficiency of treatment.

As these successful models evolve, they can be used for development of teaching, training and support strategies for less experienced providers. The recently announced Physician Clinical Support System (see Text Box 6) illustrates how knowledge and expertise regarding buprenorphine treatment can be transferred to a

large circle of providers. Perhaps such a program could be set up specifically for HIV providers wishing to integrate buprenorphine treatment in their programs. A trained cadre of leaders with expertise in both camps involved in training additional providers would be a good point of departure. Recognition of an integrated perspective of the two cultures is also needed within the published literature.

Education for and with patients

The HIV/AIDS community has benefited from a multitude of programs launched from a community and advocacy perspective, including programs for patients providing basic and highly specific information, training in research methods and opportunities to join advisory boards and committees, such as clinical guidelines and research planning bodies. This community and advocacy "voice" needs to be extended to the community of patients affected by HIV/AIDS and substance dependence. Patient education programs which focus on patient-centered approaches (see section Perspectives on Integration/Patient Perspectives) emphasizing adherence to treatment and reducing HIV transmission behaviors need to be developed. Patients also need training in voicing drug dependence issues with their providers. Patients can help educate providers on what communication models work to build trust.

Development of Programs & Services

Successful models of integration need to be developed and extended beyond the few currently available (see section Models of Integration). The chronic disease model (which includes information systems, patient activation, community resources, provider teams and disease specific specialists) applies to both HIV/AIDS and substance dependence. How this model might facilitate integration is as yet largely unexplored and needs to be investigated. Integration should focus not only specifically on HIV/AIDS care and opioid addiction, but include substance abuse in a broader sense, Hepatitis C and mental health diseases as well.

Program specific and treatment specific outcomes were outlined in the section Perspectives on Integration/Systems & Programs Perspective. The *Integrated Buprenorphine & HIV Care Evaluation & Support Center* funded by HRSA through its Special Programs of National Significance branch since the time of the workshop (see Text Box 8) is a significant step towards the development of useful models of integration. It is expected that many of the questions listed in the section Opioid Addiction in the Setting of HIV/AIDS/Integration Issues will be answered through experience gained at these centers.

Management of quality care and cost-effectiveness are central principles in the building of any health care program. Demonstration of how these can be improved through the HRSA program and other smaller pilot programs, perhaps integrated into ADAP programs, will help the development of better policies. Linking treatment of opioid addiction to reduced transmission expands the sphere of interest to the prevention field. Some jurisdictions have combined HRSA and CDC planning groups. How these can be used to effectively integrate treatment and prevention programs as well as research models is another area of opportunity waiting to be explored.

DEVELOPING SUPPORTIVE POLICIES

The over-arching policy issues are creating an environment that encourages buprenorphine integration and addressing the scarcity of funds, as described in the section Financing Issues: Navigating across Agencies – Maximizing Resources. Mechanisms to demonstrate realistic financing models need to be developed and these need to include cost-effectiveness assessments. Cost-effectiveness needs to be demonstrated at the prevention of HIV infection as well as the treatment outcome level. Consideration of more comprehensive coverage for all medications and services associated with integrated care of people with HIV and substance abuse need to be discussed in the context of the opportunities that the reauthorization of

the Ryan White CARE Act, the goal to reduce health disparities (see the section The Two Epidemics: An Overview and Figure 1) and the current attention on quality care, provide. Attention should extend beyond simply financing buprenorphine alone, but include comprehensive substance abuse treatments. The benefits of involving the state alcohol and drug abuse directors in these discussions should be explored.

ADDRESSING RESEARCH GAPS

Sound and comprehensive research is the key to providing information for program and policy development. Research gaps have been identified throughout this and previous section (see Summary Recommendations Table). In addition, research should include systematic studies of the effectiveness of buprenorphine in reducing HIV transmission in diverse HIV-positive populations, as well as decreasing seroconversion in HIV-negative drug injectors. The effectiveness of buprenorphine in improving access to HIV care, adherence to HIV treatments and improving treatment outcomes, such as reducing viral load, increasing CD4 cell count, and prolonging life as well as improving quality of life needs to be systematically documented for patients in all socio-demographic categories. Similarly, the impact of successful HIV treatment on the retention in buprenorphine programs and injecting drug use and needle sharing events should be investigated. All of these should be coupled to cost-effectiveness studies.

A mechanism for efficient transfer of the knowledge gained through research into program development needs to be in place. Coordination and communication between the various research programs, such as the Clinical Trials Network within the NIH National Institute of Drug Abuse (NIDA) and the HRSA Special Programs of National Significance focusing on integrated buprenorphine and HIV care (see Text Box 8) will aid in translating the knowledge gained into programmatic value. Another example would be coordination and communication between the NIDA

sponsored and the HIV clinical research networks, such as the Adult AIDS Clinical Trials Group. Ongoing or planned collaboration between SAMHSA and NIDA on cost-effectiveness and standards-of-care exist, and knowledge gained from these need to be integrated into developing programs.

Although this workshop focused on domestic programs, issues relating to the integration of substance dependence treatment into HIV programs are highly relevant to the to the US international HIV/AIDS programs. As for the domestic scene, training, research and policy programs need to be developed in order to obtain higher level of effectiveness of US sponsored treatment and prevention programs. These will need to be region and culture specific.

A final question is: are there new medications for substance dependence on the horizon? How will the buprenorphine experience aid in the development of new drugs? Or will the challenge of difficult financing prove too discouraging for the pharmaceutical sector involved in research and development?

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APPENDIX C: WORKSHOP AGENDA

	Speaker/Panelists	Moderator
Welcome and Introductions **HRSA Perspective**	Veronica Miller Laura Cheever	
SESSION I		Lynn Sullivan
Plenary Presentation 1 Buprenorphine 101: Basic Background and Framework **Plenary Presentation 2** Buprenorphine Issues as they relate to HIV **Open Discussion**	David Fiellin Frederick Altice All	
SESSION II		Lois Eldred
Poster Session **Panel Discussion** Experiences of Buprenorphine Use – the Good, Bad, and Hopeful	Colleen LaBelle, Dennis McCarty, Lynn Sullivan, Susan Whitley Douglas Bruce, James Finch, David Haltiwanger, Colleen LaBelle	
SESSION III		
Charge to Breakout Groups Systems & Programs Support for Care Teams Patient-Centered Approaches	Veronica Miller	 Jeff Levi David Fiellin Rick Altice
SESSION IV		Veronica Miller
Breakout Group Reports **Open Discussion**	Alice Gelghorn, David Haltiwanger, Gregory Lucas	

	Speaker/Panelists	Moderator
SESSION V		Sharon Stancliff
Plenary Presentation 3 Financing Issues Across Agencies	Jeff Levi	
Panel Discussion	Lawrence Brown, Laura Cheever, Jerry Flanzer, Steve Kpnis, Robert Lubran, Dennis McCarty, Joseph Merrill	
SESSION VI		Veronica Miller & Jeff Levi
Final Discussion Round	All	

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