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Methadone Maintenance for HIV Positive and HIV Negative Patients in Kyiv: Acceptability and Treatment Response

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Abstract

Background—With up to 40% of opioid injectors infected with HIV, Ukraine has one of the most concentrated HIV epidemics in the world, mainly due to unsterile injection practices and a historical absence of effective prevention services. Harm reduction programs, including syringe exchange and a small buprenorphine treatment program, were introduced in 2004 and methadone maintenance was allowed in 2007. Despite an initial expansion, by 2009, only 3221 injectors were receiving methadone treatment. A growing body of research on methadone maintenance has found high retention rates with reduction in opioid use and HIV risk behaviors. We report on the acceptability and initial outcome of methadone treatment as a function of HIV status, an issue that has not yet been reported for injectors in Ukraine.

Methods—Longitudinal observational study of a 12-week course of methadone treatment in 25 HIV+ and 25 HIV− opioid addicted individuals recruited from a harm reduction program and the city AIDS Center. Drug use and HIV risk were assessed at baseline and weeks 4, 8, 12 and 20; all patients were offered continued methadone maintenance in the Kyiv city program at the end of 12 weeks.

Conflict of interest
All authors declare that they have no conflict of interests.

Contributors
Anatoiy Viyevskiy provided administrative support for this study. Richard Needle provided input into study design. Irina Trofimchenko helped with data entry.

Results—Fifty-four individuals were asked if they were interested in the study and 50, demographically similar to other samples of opioid addicted Ukrainians, agreed to participate. Two died of non-study related causes; the other 48 completed assessments at weeks 4, 8 and 12, and 47 completed followups at week 20. Significant reductions were seen in use of heroin ($p < .0001$), other opiates/analgesics ($p < 0.0001$), and HIV risk behaviors (drug, sex, total; all $p < 0.0001$). All 48 patients chose to continue methadone after the 12-weeks of study medication ended. Unlike most opioid treatment studies, sexual risk was somewhat higher than injecting risk at study intake.

Conclusions—Methadone maintenance was well accepted by HIV+ and HIV− opioid dependent individuals and has the potential for significant public health impact if made more widely available with sustained access and support.

Keywords

Methadone maintenance; HIV risk; Ukraine; PWID

1. INTRODUCTION

In response to a growing HIV epidemic among injection drug users in the mid-1990's, international experts encouraged Ukraine to develop harm reduction programs. These efforts resulted in the development of non-governmental organizations using outreach workers who focused on not sharing injection equipment among persons living with HIV, startup of a few syringe and needle exchange programs, voluntary HIV testing and counseling programs with educational materials on reducing HIV injection and sex risk, and dissemination of condoms and medicines for treatment of injection-related skin damage (Booth et al., 2008, 2009, Smyrnov et al., 2012). Access to these programs was limited since there were large differences between cities and districts in terms of coverage, and addiction treatment was not part of their focus. By 2011, the number of people who injected drugs (PWID) in Ukraine was estimated at 310,000 with HIV prevalence ranging from 21.5% – 41.8% (Bobrovsky, 2012).

Addiction treatment in Ukraine had traditionally used the Soviet model that was developed for alcoholism but applied to opioids and involves inpatient detoxification and rehabilitation (Golovanevskaya et al., 2012). Serious questions emerged about its effectiveness in view of the HIV epidemic that was mostly due to a combination of injecting drug (mainly opiate) use, unsterile injecting practices, limited access to harm reduction programs, high relapse following hospital discharge, and prohibition of agonist maintenance (Mathers et al., 2008; Wessing et al., 2008; Comprehensive External Evaluation Team of the National AIDS Response in Ukraine, 2009).

As these problems were developing, clinicians and administrators began showing interest in opioid substitution therapy (OST). Methadone maintenance had been highly effective in reducing drug use and injection related risk behaviors and transmission events in other countries and was recommended by the World Health Organization (WHO, 2005) and the U.S. Substance Abuse and Mental Health Services Administration (TIP Series 43, 2005). Although methadone is the most widely studied OST, buprenorphine has also been effective (Johnson et al., 1992; Strain et al., 1996; Ling et al., 1998), and in 2004 it was allowed as the first OST in Ukraine (Bruce et al., 2007) but only for treating HIV positive addicts, due to long-standing opposition to OST for treating addiction http://www.moz.gov.ua/ua/portal/dn_20050413_161.html.

Shortly after Ukraine approved buprenorphine the WHO conducted a study of OST in seven developing and emerging countries (China, Indonesia, Thailand, Iran, Lithuania, Poland,

Ukraine) to see if the results were similar to those found elsewhere. This study included 726 patients that were recruited between late 2003 and mid-2005 and evaluated within two weeks of when they began treatment, and again at 3 and 6-months using past month as the reference point. Methadone was the focus in all countries except Ukraine where buprenorphine was the only medication available at the time. Findings showed significant reductions in opioid use and HIV injecting risk in all countries with most also showing reductions in criminal behavior and improved physical and mental health (Dvoryak, 2008; Lawrinson et al., 2008.)

After a series of advocacy efforts Ukraine approved methadone in 2007 and there was a rapid scale up between 2008 when 941 patients were receiving OST (114 methadone; 827 buprenorphine), to June, 2009 when 4,052 patients were receiving it (3,221 methadone; 831 buprenorphine). The number of OST programs increased from 12 to 87 (http://www.ukraids.gov.ua/attachments/article/544/STM%2001.01.13.xls,2013) and clinicians began enrolling patients that were HIV negative as well as those that were HIV positive, however, expansion of methadone treatment slowed following a change in government from one oriented toward the European Union to one leaning toward Russia (S. Dvoryak, personal communication, 2013). A 6-month followup of 140 patients that started methadone treatment in 8 Ukrainian cities before this change showed 85% retention and significant reductions in opioid use and HIV risk (Schaub et al, 2009), however this report did not present data on outcomes as a function of HIV status though 60% of the patients were HIV-positive.

Given the high prevalence of HIV in PWID in Ukraine, it is important to understand the acceptability and efficacy of methadone treatment among injectors that are already infected relative to those who are not infected, and to explore methadone treatment's impact on access and retention in ARV treatment. Here we present some of the first data on these issues.

2. METHODS

2.1 Study participants and design

Participants were 25 HIV positive and 25 HIV negative opioid addicted individuals seeking outpatient treatment in Kyiv. Inclusion criteria were: primary diagnosis of opioid dependence with physiological features present for at least a year; 18 years of age or over; stable address in Kyiv and not planning to move; home or cellular telephone number where they can be reached; and willingness and ability to give informed consent, participate in daily observed dosing, and complete assessments. Exclusion criteria were: clinically significant cognitive impairment that would compromise the ability to give informed consent; schizophrenia, paranoid, bipolar, or seizure disorder; advanced neurological, cardiovascular, renal, hepatic or other medical disorders that would impair or make hazardous their ability to participate; active tuberculosis; currently dependent on alcohol, benzodiazepines or other sedative drugs; impending incarceration; planning to move from the Kyiv area during the next 6 months; and concurrent participation in another treatment study.

2.2 Study site and procedures

The study was done at the Kyiv City AIDS Center and its adjacent OST program. These facilities are part of a larger medical complex that is located on the outskirts of Kyiv and accessible by public transportation. Members of the research team (GW, RB, SD, NC) assisted by a translator, trained Kyiv staff on study procedures during a 5-day site visit prior to enrolling the first patient. Upon completion of training, Kyiv staff used a three step process to enroll subjects: 1) provision of detailed information about the study to persons

applying for treatment who appeared to meet study criteria along with an opportunity to ask and receive answers to questions. If interested, subjects were asked to review, discuss and sign the screening consent form; 2) completion of a medical history and physical examination including pretest counseling and HIV/hepatitis B/C testing for those of unknown status along with behavioral assessments; and, 3) HIV/hepatitis B/C post-test counseling, confirm study eligibility, sign consent to participate and enroll.

Methadone was administered daily under observation since Ukrainian regulations do not permit take-homes; program staff can deliver methadone to patients in other facilities (hospitals, at home) in cases of acute trauma or serious illness. Dosing and clinical guidelines were similar to the U.S. and to guidelines adopted by a special order from the Ministry of Health http://www.moz.gov.ua/ua/portal/dn_20081110_645.html. Patients and staff were counseled about the delayed onset and long half-life of methadone since they had been using buprenorphine and were used to providing more rapid dose increases than can be safely done with methadone. Stabilization was achieved when medical staff judged that the patient had no signs or symptoms of sedation or withdrawal during the 24-hour dosing period and usually occurred in the first two weeks on an average dose of 60 mg. Doses were then gradually increased to 120 mg/day over the next 6–8 weeks though some patients with HIV required 140–160 mg/day due to apparent increased metabolism from interactions with antiretroviral medication, particularly efavirenz. Doses were withheld for patients that were significantly intoxicated by alcohol or sedatives (difficulty walking, slurred speech, sedated) due to safety concerns, and they were asked to return in several hours or the next day for a medical evaluation to determine if their impairment had resolved such that it was safe to continue dosing. Patients were offered transfer to the city methadone program or a dose taper over 3–4 weeks at the end of the 12-week dosing period.

All patients received a brochure “About Methadone: a Manual for Clients” (Catania, 2000) along with weekly group and individual counseling by addiction psychiatrists (“narcologists”) or psychologists that had several years experience treating opioid addicted patients. NC and GW, working in collaboration with a translator and SG, provided an overview of drug counseling using the individual counseling manual by Mercer and Woody that was used in the NIDA Cocaine Collaborative Treatment study (Crits-Christoph et al., 1999; manual available on the NIDA web site) and modified for opioid addiction and translated into Russian (Mercer and Woody, 2001). Almost all Ukrainians are fluent in Russian due to historical ties, and the instruments from Russian studies (Krupitsky et al., 2012) were used with no apparent difficulty. Counseling sessions were not tape-recorded or subject to the kinds of adherence assessments typically used in psychotherapy studies as the main focus was pharmacotherapy. Patients were paid the equivalent of $8 in Ukrainian currency for the time spent completing measures at 4, 8, 12 and 20 weeks, and $1 for completing brief weekly reports of drug use, craving and adverse events. No reimbursement was provided at baseline in order to discourage subjects who wanted only to earn $8 and then drop out.

2.3 Measures

The revised version of the Addiction Severity Index (ASI; McLellan et al, 1992); Time Line Follow-Back (TLFB; Sobel and Sobel, 1992); and Risk Assessment Battery (RAB; Metzger et al., 2001) were administered at baseline and at weeks 4, 8, 12 and 20. The ASI obtains basic demographic information and assesses lifetime and past 30-day drug and alcohol use. The TLFB obtained information about past 30-day drug and alcohol use. The RAB assessed past 30-day injecting and sexual HIV risk behaviors using 38 closed end items that cover issues of recent substance use, including frequency, needle sharing and cleaning, frequency and type of sexual activity, and condom use. Scores from the RAB have discriminated between cocaine and opioid abusers, as well as those who seroconverted, from those who

remained seronegative (Metzger et al., 1993, 2001). Composite drug, sex, and total risk scores were calculated by adding responses to selected items. The drug risk score ranges from 0–22 and is comprised of eight items: drug injection, sharing needles, number of people shared needles with, frequency of visits to a shooting gallery, sharing rinse water, sharing cookers, sharing cotton, and sharing syringes to backload. Sex risk score ranges from 0–18 and is comprised of nine items: number of partners, frequency of sex for drugs and vice versa, frequency of sex for money and vice versa, and frequency of condom use. The total score is the sum of the drug and sex risk scores. Higher scores indicate greater frequency of occurrence of that behavior and imply greater risk.

Urine drug testing was planned to be done weekly at random and follow-ups using OnTrac kits that test for opioids, amphetamines, benzodiazepines, and THC, however administrative delays in transferring funds to purchase test kits resulted in fewer tests being done than originally planned.

The number and duration of individual and group therapy sessions was noted using clinic records and the number of self-help groups attended since the last visit was recorded weekly and at each evaluation point. Patients were asked about adverse events weekly or since the last visit, and events were categorized as Adverse Events (AE) or Serious Adverse Events (SAE) using standard FDA criteria. Weekly assessments had a window of +/− two days; monthly assessments had a window of +/− one week; and the 20-week assessment had a window of +/− 3 weeks.

3. RESULTS

3.1 Participant characteristics

Fifty-four individuals were approached for the study and 50 were consented and enrolled: 25 HIV positive and 25 HIV negative. Among those that declined, two said they did not want to be part of an experiment; the other two did not want to spend time with counselors in the therapy sessions that were part of the study.

Table 1 presents the baseline characteristics of participants and comparisons between the groups. Most opiate use involved home-brewed preparations made from poppy straw or raw opium (e.g. “other opiates/analgesics”) since heroin is more expensive and less available in Ukraine than in Western Europe or the U.S (Booth et al., 2003; 2004; Abdala et al. 2006). Except for cannabis use in the past 30 days, drug and alcohol use, and RAB drug and sex risk scores, tended to be higher in HIV+ individuals though no group differences were significant.

3.2 Retention

Two patients died – one from a myocardial infarction and one from pneumonia related to HIV. The remaining 48 patients completed followups at weeks 4, 8, and 12 and 47 completed the 20-week follow-up. None of these 48 patients were interested in a dose taper and non-agonist treatment at the end of the study dosing period, and all continued on methadone at the Kyiv city program.

3.3 Analyses

Self-reported drug use in the past 30 days was modeled as count data and a negative binomial distribution was specified using the PROC GENMOD procedure. Risk behavior scores were treated as continuous variables and their log values were modeled as repeated measures ANOVA using PROC MIXED. HIV risk behaviors (drug risk, sex risk, total risk) and the number of days using alcohol, heroin, other opiates/analgesics, sedatives/hypnotics/

tranquilizers and cannabis were compared across time (baseline and 4, 8, 12, and 20 week follow-up), and between groups.

3.4 Outcomes

As seen in Table 2, there were no significant between group or interaction effects for any type of drug use in the last 30 days and highly significant time effects for heroin ($p<.0001$) and other opiates/analgesics use ($p<0.0001$), and HIV risk behavior of any kind (drug, sex or total) showed a significant time effect (all $p<0.0001$) with no significant differences between groups or interaction effects. Among those who were HIV positive, 6 were receiving antiretroviral treatment at their baseline assessment and 13 were receiving it at the final assessment point.

Administrative difficulties delayed transfer of funds to purchase the urine drug test kits and at baseline, only 4 participants completed the urine-drug screen; 34 completed it at 4 weeks, 38 at 8 weeks, 42 at 12 weeks, and 38 at 20-weeks. We analyzed the percent agreement between urine-drug test results and self reported drug use from the ASI for amphetamines, benzodiazepines, cannabinoids and opioids and found correlations ranging between 82 and 100%.

4. DISCUSSION

In spite of a large amount of data and experience since methadone maintenance was introduced in 1964, it continues to arouse controversy, even in the US. This controversy is particularly strong in Ukraine, the Russian Federation, and Central Asian Republics where implementation of opioid agonist treatment has faced huge barriers while at the same time HIV is being spread through opioid injecting (Das, 2010). For example, data from the Ukrainian Ministry of Health (2008) have shown that 97% of all registered drug addicts are opioid PWID and that approximately 75% of persons with HIV are opioid IDUs (Balakireva et al., 2003; Berleva et al., 2010).

The introduction of buprenorphine in 2004 provided the first opportunity to study the impact of opioid maintenance treatment, and three years later the President of Ukraine signed special Decree # 1208/2007 entitled “Additional Measures to Fight HIV-Epidemic in Ukraine” http://zakon1.rada.gov.ua/laws/show/1208/2007. One paragraph of this decree stated that Ukraine must meet the obligations of the Global Fund to Fight AIDS, Malaria and Tuberculosis (GFAMT). A clear requirement was that Ukraine provides methadone treatment to help control the HIV-epidemic and in June 2007 customs officials allowed importation of methadone for opioid addiction and treatment expanded but then slowed, as discussed above.

Though clinicians are typically interested in treating the disorder that brings the patient to treatment, and perhaps due to the long-standing ambivalence about OST within Ukrainian society, professionals were encouraged to emphasize that its main purpose was to prevent HIV-transmission and increase access to ART. The data presented here show that this goal can be realized but also that, as in other countries, methadone maintenance treats the addiction and that patients welcome it since 50 out of the 54 individuals that were approached agreed to participate, drug use was very low once maintenance treatment began, and all but the two patients who died during the 12-week study medication phase continued it. It should be noted that these data were obtained in conditions where patients had to visit the clinic every day and patients also experienced harassment and discrimination by local police (Mimiaga et al., 2010).

In summary, the results of this study indicate that methadone was well accepted and highly effective in reducing opioid use and HIV risk behaviors among persons with and without HIV infection, and suggest that a significant expansion of methadone maintenance could be very helpful in reducing opioid use and HIV spread in Ukraine. These findings are particularly important in view of the data showing that OST facilitates entry into ART (Uhlman et al., 2010), that continuing OST facilitates adherence and response to ART (Roux et al., 2009), and that antiretroviral therapy can suppress virus and reduce transmission (Quinn et al., 2000; Montaner et al., 2010; Cohen et al., 2011). For example, a review of determinants of HIV infection among injection drug users estimated that between 2010 and 2015, the incidence of HIV could be reduced by 41% in Odessa by a 60% reduction in the unmet need of programs for opioid substitution treatment, needle exchanges, and antiretroviral therapy (Strathdee et al., 2010). While treatment as prevention has not yet been directly tested among injectors, it is clear that opioid addicted injectors need both substance use and ARV treatment. The data reported here suggests that this is both feasible and acceptable in Ukraine.

Study findings are limited by the small sample size, the self-selection of participants, limited duration of methadone treatment, restrictive conditions under which treatment was provided, and self-reported nature of some outcome data. Items used to construct drug and sex risk scores from the RAB may not perfectly map to Ukraine (shooting galleries, for example), but most probably do (sharing rinse water, frequency of sex partners, etc), and the characteristics of study participants are similar to those reported among opiate injectors enrolled in other larger projects in Ukraine (Taran et al., 2011; Schaub et al., 2009). Also, the high rate of acceptability of methadone and retention in treatment is consistent with studies in other settings and suggests that the results reported here are representative of opioid addicted individuals in Ukraine.

It is important to note that the patients in this study were treated in a program that is only 50 yards away from the Kiev City AIDS-clinic and part of a single medical complex. Methadone and buprenorphine patients in the Ukraine, as reviewed above, were all being treated in specialized narcology centers where the focus is on behavior change, as is common throughout Former Soviet States. Data from this study were collected at a site where staff were oriented toward risk reduction and where treatment for addiction, HIV, and other medical and psychiatric problems were available in close proximity, all operational details that have been identified as having significant public health benefits (Altice et al. 2011, 2010). Though such integrated treatment, and expansion of other harm reduction approaches may be more distant goals, these findings provide strong evidence of the likely reductions in drug use, HIV risk, and other public health benefits that can be achieved by resuming the expansion of methadone and buprenorphine treatment in Ukraine that began in 2004, but has slowed down or even been prohibited in the last several years.

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Table 1

Baseline (WEEK 0) characteristics

Mean (standard deviation)	Total (n=50)	HIV negative (n=25)	HIV positive (n=25)	P value
Age	32.6 (5.2)	32.8 (6.0)	32.4 (4.3)	0.8159
Gender % (n)				
Male	80 (40)	84 (21)	76 (19)	0.4795
Female	20 (10)	16 (4)	24 (6)	
Marital Status % (n)				
Married	50 (25)	56 (14)	44 (11)	0.7087
Other	50 (25)	44 (11)	56 (14)	
Employment Status % (n)				
Full time	30 (15)	40 (10)	20 (5)	0.2525
Part time	28 (14)	24 (6)	32 (8)	
Unemployed	34 (17)	28 (7)	40 (10)	
Other	8 (4)	8 (2)	8 (2)	
Alcohol use (30 days)	4.9 (8.1)	4.8 (7.8)	5.0 (8.6)	0.9318
Heroin use (30 days)	4.4 (9.3)	3.8 (7.9)	4.9 (10.6)	0.6975
Other opiates/Analgesics (30 days)	20.7 (12.4)	17.7 (13.1)	23.7 (11.2)	0.0835
Sedatives/Hypnotics/Tranquilizers (30 days)	9.4 (13.4)	8.7 (13.2)	10.0 (13.9)	0.7323
Cannabis (30 days)	4.5 (6.8)	6.9 (8.1)	3.0 (4.7)	0.1172
Alcohol use (Years)	2.6 (4.5)	3.7 (5.7)	1.5 (2.6)	0.0838
Heroin use (Years)	2.3 (3.1)	2.8 (4.0)	1.8 (1.7)	0.2965
Other opiates/Analgesics (Years)	9.8 (6.3)	9.5 (7.3)	10.1 (5.2)	0.7566
Sedatives/Hypnotics/Tranquilizers (Years)	2.9 (4.3)	2.3 (4.3)	3.4 (4.2)	0.3773
Cannabis (Years)	6.5 (5.6)	7.1 (5.8)	6.0 (5.4)	0.5001

Mean (standard deviation)	Total (n=50)	HIV negative (n=25)	HIV positive (n=25)	P value
RAB drug score	3.6 (3.3)	3.3 (3.2)	3.9 (3.5)	0.5267
RAB sex score	4.1 (1.9)	3.9 (2.2)	4.3 (1.6)	0.5175
RAB total score	7.7 (4.2)	7.2 (3.9)	8.2 (4.4)	0.4224
In the past six months, have you shared needles or works? % (n)				
No/I have not shot up in the past six months	88 (44)	92 (23)	84 (21)	0.3841
Yes	12 (6)	8 (2)	16 (4)	
With how many different people did you share needles in the past six months? % (n)				
0/I have not shot up in the past six months	86 (43)	88 (22)	84 (21)	0.3290
1 other person	10 (5)	12 (3)	8 (2)	
2 or 3 different people	4 (2)	0 (0)	8 (2)	
In the past six months, how often have you shared rinse-water? % (n)				
Never/I have not shot up in the past 6 months	100 (50)	100 (25)	100 (25)	
In the past six months, how often have you shared a cooker? % (n)				
Never or I have not shot up in the past 6 months	88 (44)	88 (22)	88 (22)	0.7165
A few times or less	6 (3)	8 (2)	4 (1)	
Once or more each week	6 (3)	4 (1)	8 (2)	
In the past six months, how often have you divided or shared drugs with others by using one syringe (yours or someone else's) to squirt or load the drugs into the other syringe(s) (backloading, for example) ? % (n)				
Never or I have not shot up in the past 6 months	78 (39)	88 (22)	68 (17)	0.1550
A few times or less	1 (1)	4 (1)	0 (0)	
A few times each month	10 (5)	4 (1)	16 (4)	
Once or more each week	10 (5)	4 (1)	16 (4)	

Table 2

HIV Risk behavior

	HIV negative					HIV positive					P values		
	0W	**4W**	**8W**	**12W**	**20W**	**0W**	**4W**	**8W**	**12W**	**20W**	**HIV**	**Time (visit)**	**HIV*time**
Drug use behavior [a]													
Mean number of days Alcohol use	4.8	2.1	2.7	2.5	2.6	5.0	0.79	0.33	1.0	1.7	0.4445	0.3394	0.6284
Mean number of days Heroin use	3.8	0.04	0	0	0	4.9	0.04	0	0	0	0.6836	**<.0001**	0.8692
Mean number of days Other opiates/Analgesics	17.7	0.13	0.29	0.17	0.08	23.7	0.13	0.29	0.13	0.78	0.9319	**<.0001**	0.1080
Mean number of days Sedatives/Hypnotics/Tranquilizers	8.7	0.13	0.25	0.20	0.08	10.0	0	0.04	0	0.22	0.9179	0.1057	0.8012
Mean number of days Cannabis	6.9	1.3	1.25	1.13	1.3	3.0	0.63	0	0.08	1.1	0.1451	0.4277	0.7927
Risk behavior [b]													
Mean RAB drug score	3.3	0.91	0.33	0.17	0.08	3.9	0.83	0.13	0.17	0.74	0.4324	**<.0001**	0.4516
Mean RAB sex score	3.9	2.9	3.3	2.9	2.8	4.3	3.3	3.3	3.3	3.0	0.5657	**<.0001**	0.7969
Mean RAB total score	7.2	3.8	3.6	3.1	2.9	8.2	4.1	3.4	3.5	3.8	0.5028	**<.0001**	0.7304

[a] Negative binomial models

[b] Mixed models (log of dependent variable)