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Implementation opportunities for scaling up methadone maintenance treatment in Kyrgyzstan: Methadone dosage and retention on treatment over two years

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Abstract

Background: Methadone maintenance treatment (MMT) is the most effective and cost-effective strategy to control HIV in Central Asian countries, where the epidemic is concentrated among people who inject drugs (PWID) who use opioids.

Methods: Using data from a prospective observational database of all people initiated on MMT in Kyrgyzstan since 2008, we analyzed a more contemporary subset of data for all persons receiving MMT from January 2017 through June 2021 after the national treatment guidelines were changed. Retention on MMT was assessed at 1, 6, 12, and 24 months and predictive variables included were dosage levels, HIV status, and type of clinical setting using survival analysis. Predictors of treatment dropout were estimated using Cox multivariate regression models.

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Declaration of Competing Interest

The authors report no declarations of interest, except FLA.

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CRediT authorship contribution statement

Roman Ivasiy: Conceptualization, Formal analysis, Writing – original draft. **Lynn M. Madden:** Conceptualization. **Natalia Shumskaya:** Data curation, Methodology. **Samy J. Galvez de Leon:** Data curation, Methodology. **Daniel J. Bromberg:** Conceptualization, Data curation, Methodology. **Ainura Kurmanalieva:** Data curation, Methodology. **Aibek Duishenaliev:** Data curation, Methodology. **Frederick L. Altice:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing.

Results: Among the 940 MMT patients, the proportion receiving low (<40mg), medium (40–85mg), and high (>85mg) dosage levels was 37.9%, 42.2%, and 19.9%, respectively. Increasing MMT dosage level was significantly ($p<0.0001$) correlated with retention at 1 (90%, 98%, 100%), 6 (42%, 63%, 95%), 12 (33%, 55%, 89%), and 24 (16%, 45%, 80%) months, respectively, with no differences between community and correctional settings. Significant predictors of dropout at 12 months included low (aHR=8.0; 95%CL=5.8–11.0) and medium (aHR=3.5; 95%CL=2.5–4.9) methadone dosage level relative to high dose, receiving MMT in three administrative regions relative to the capital Bishkek, and lower in the tuberculosis-specialized clinic in Bishkek. Clients with HIV receive higher average MMT doses (79.5mg vs 63.1mg; $p<0.0001$), but MMT retention did not differ after controlling for dosage in this group.

Conclusions: The proportion of patients receiving optimal dosage was low (19.9%). An implementation strategy that focused on getting a larger proportion of MMT on the optimal dosage to promote retention could potentially improve the quality of existing treatment and promote further scale-up of MMT in Kyrgyzstan.

Keywords

Methadone; Dosage; People who inject drugs (PWID); Opioids; HIV prevention; Implementation science; Treatment retention; Prisons; Kyrgyzstan

1. Introduction

Despite reductions in HIV incidence and mortality worldwide (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2020), both indicators are increasing in Kyrgyzstan and throughout Central Asia, a region that inherited the Soviet Semashko model of care (Sheiman, 2013; Sheiman et al., 2018). This model, as in other post-Soviet countries, includes organizational barriers to services but especially to methadone treatment, which has contributed to an HIV epidemic concentrated in people who inject drugs (PWID). The model stipulates that treatment be limited to licensed governmental specialty care settings and linked to rigid regulatory oversight. PWID are primarily opioid users due to opioid trade routes. HIV is 70-fold higher in PWID relative to the general population (14.3% vs 0.2%) (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2021). Adequate coverage of methadone in settings where the HIV epidemic is concentrated among PWID is the most effective strategy to control HIV (Tan et al., 2020) and also the most cost-effective (Alistar et al., 2011).

Despite maintenance on opioid agonists like methadone being part of the WHO's list of essential medications and evidence-based treatment for opioid use disorder (Degenhardt et al., 2019), coverage in Kyrgyzstan remains low (4.4%) with approximately 850 of 25,000 estimated PWID being on treatment (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2019; Vickerman et al., 2014); buprenorphine is not available. Despite Kyrgyzstan introducing methadone as pilot projects in 2004 to address HIV prevention in PWID, the legacy of Russian influence looms large throughout countries in the former Soviet Union and its continued ban on methadone continues to influence its scale-up among both patients (Bojko et al., 2015; O'Hara et al., 2022; Rozanova et al., 2017) and providers (LaMonaca et al., 2019). Scale-up challenges persist despite methadone

maintenance treatment (MMT) not only improving a number of health and social outcomes (Degenhardt et al., 2019; Wakeman, 2020), but it is especially crucial for the prevention of HIV and HCV in both community (Alistar et al., 2011; Hodder et al., 2021; MacArthur et al., 2012; Platt et al., 2017) and carceral settings (Altice et al., 2016; Stone et al., 2021). Methadone, when scaled up in prisons, not only decreases HIV and HCV transmission in PWID (Altice et al., 2016), but reduces death when continued 12 months after release (Stone et al., 2021; Stone et al., 2018). It is also cost-effective for reintegrating people experiencing incarceration into society and further reduces crime and re-incarceration (Chetty et al., 2017).

With methadone being crucial for HIV prevention efforts, great concern have emerged as daily census steadily decreased from 1200 at its peak in 2017 (Stone and Shirley-Beavan, 2016) to about 850 in 2021, including in both community and carceral settings. This observed decrease has occurred due to high dropout and low enrollment of new patients. A recent mixed methods study of incarcerated persons provides essential insights into why methadone patients may dropout or fail to initiate it despite great need (Liberman et al., 2021). Empiric studies of dropout dynamics, however, have not been assessed, which may provide important insights into better implementation strategies.

2. Methods

2.1. Setting

Kyrgyzstan is a low-income country in Central Asia with an uncontrolled HIV epidemic, which is concentrated among PWID and their sexual partners. Kyrgyzstan introduced the first methadone program in Central Asia in 2002 as a four-year pilot project, followed by community expansion in 2006 and in carceral settings in 2008. Despite methadone coverage in Kyrgyzstan being the highest in Central Asia (LaMonaca et al., 2019), the methadone census is currently decreasing. During the study period, opioids are the primary drug injected. Recent data from prisons, however, suggest increasing levels of diphenhydramine injection among those on MMT and since the COVID-19 pandemic, opioid access has decreased with new introduction of stimulants in the community (Meyer et al., 2020). Methadone census increased from 729 in 2008 to 1200 in 2017 (Subata et al., 2016); it has since declined due to increasing dropout and a sluggish enrollment of new patients (Michels et al., 2021). All methadone treatment is funded by international donors, and as of 2021, 24 sites provide methadone, including six prisons, two pre-trial detention centers, and one penal colony. Patients may initiate methadone in both community and carceral settings and can transition between them. For those on methadone in the community and who become incarcerated, there may be a lapse in treatment if they are admitted to a pre-trial detention center that does not have methadone. As many newly incarcerated persons initiate injection of opioids in prison (Azbel et al., 2018), patients may also initiate MMT for the first time there. Methadone is now available in the city administrative regions of Bishkek and Osh and 4 of 7 administrative regions (oblasts).

The Kyrgyzstan National Healthcare system is based on the Semashko model relies primarily on specialized care in secondary and tertiary clinics (Sheiman, 2013; Sheiman et al., 2018). The model restricts diagnosis of opioid use disorder (OUD) and treatment

to addiction treatment specialists (i.e., narcologists), but according to the Joint United Nations Programme on HIV/AIDS (UNAIDS), there are only 198 narcologists in the country (0.3 per 10,000 population), which is guided by rigid clinical protocols (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2019) that restrict new physicians from gaining expertise in prescribing methadone. The clinical protocol for prescribing MMT is a legislative order that defines a patient's eligibility for methadone and provides conservative treatment algorithms, including recommended dosage during induction and maintenance. The protocol recommends but does not require psychosocial counseling, which is not available in all settings and is highly variable in its delivery. The clinical protocol was revised by a national group of experts and approved by the Ministry of Health on May 29, 2015, which recommends treatment dosages that target 60mg or more and do not allow for take-home dosing.

2.2. Study design

The Republic Narcology Center prospectively maintains a structured database of all patients ever prescribed opioid agonist treatment (OAT) since 2008. This database, however, was revised on January 1, 2017, after training and implementation of the national clinical protocol and excluded individuals who had dropped out of treatment before that date. The prospective dataset includes a unique identifier for every patient who received at least one dose of methadone, including demographic data, OAT treatment setting, date of the first enrollment, date of transfer to another site, dropout date, HIV status, ART regimen prescribed, whether patients received take-home dosing and duration of drug injection. The dataset was constructed to be congruent with one used in Ukraine and allows for the creation of a prospective cohort, including individuals with multiple treatment episodes (Farnum et al., 2021). Methadone dose for each treatment episode is based on the last dose prescribed, and dose changes are not recorded. All patients entered in the database are those newly enrolled after January 1, 2017, through June 15, 2021, to reflect the new clinical protocol and newly established database.

2.3. Data analysis

For analytical purposes, only patients who were enrolled in treatment after January 1, 2017, were included in the final analysis to minimize misclassification bias (Supplementary Table 1). Study participants have single or multiple treatment episodes. In accordance with national guidelines, treatment dropout was defined if the patient missed ten or more consecutive days of treatment. For the study period, there were 940 unique patients in the cohort who comprised 1,200 treatment episodes; 17.3% were treated more than once. Patients with multiple treatment episodes ranged from 1 to 6 methadone-intake sequences. Data were censored on June 15, 2021, the date of data extraction from the national registry. As Kyrgyzstan provides OAT in penitentiary facilities, incarceration did not result in treatment cessation for 99.8% of the study sample. Data were not right-censored at the time of transfer to prison. Records of 64 patients were censored due to death; the cause and date of death is not recorded.

The primary outcome was the time-to-treatment discontinuation at one, six, twelve, and twenty-four months. For the 17.3% of the study sample with multiple treatment episodes,

only the last episode was included because only the last methadone dose was included in the database. The methadone dosage was not categorized based on the Kyrgyz national guidelines but rather on WHO classification: high (recommended >85mg), medium (40 – 85 mg), and low (< 40 mg) as analyzed elsewhere (Farnum et al., 2021) to provide insights into implementation opportunities. Variables defining age at the time of admission, year of MMT treatment initiation, sex, and duration of drug injection were tested for the potential confounding. Since age and duration of injection (both in years) were not normally distributed and not collinear with each other, the lower quartiles of 35 and 5 years were used as cutoffs, respectively, to dichotomize those variables.

Univariate analysis was used to compare demographic, clinical, and demand characteristics across the groups categorized methadone dosage levels (low, medium, high). Chi-square and ANOVA methods were applied to test the significance of these associations. Kaplan-Meier survival analysis was used to estimate and compare OAT retention probabilities across methadone-dosage-defined groups. Multivariate Cox regression model was used to compute adjusted hazard ratios of covariates expressed as the time to MMT dropout. Multivariable Cox regression incorporated time-to-event covariates such as methadone dosage (low, medium, high), previous experience of OAT, type of site, HIV status, and region. Since people released from prison are at increased risk of treatment discontinuation (Bachireddy et al., 2022; Chandra et al., 2019), the estimates were controlled for the additional variable reflecting loss-to-follow-up after release. Hazard ratios were adjusted for the year of enrollment to minimize temporal change biases in treatment, political and secular trends. Model selection was performed using backward elimination with Bonferroni correction, where only significant covariates ($p < 0.05$) were retained in the final model. Patients enrolled in the program within the observation period and who remained on treatment by its end were right-censored. The analysis was performed in SAS 9.4 statistical software package (SAS Institute, Cary, NC).

3. Results

Participant characteristics are presented in Table 1, stratified by methadone dosage levels. Of the 940 unique patients, nearly all (94.7%) were male, mostly in their early 40s (mean=42.1 years); <1% are 25 years or younger. On average patients, participants had injected opioids for 11.9 years. The proportions receiving high, medium, and low dosages are 37.9%, 42.2%, and 19.9%, respectively. Most patients are in the city of Bishkek (36.8%) or its surrounding region (Chuy Oblast, 34.0%), the most populous areas with the highest numbers of OAT sites. The cities of Bishkek and Osh have the highest proportion of patients receiving high methadone dosage levels, 20.5%, and 25.6%, respectively. HIV prevalence in OAT patients is 21.1%; 120 (12.7 %) patients were not tested and have unknown status. OAT was prescribed most often (38.3%) in carceral (both prisons and pre-trial detention centers) settings, followed by general hospitals with onsite OAT clinics (31.9%). Additional treatment was provided in specialty narcology, AIDS Centers and TB Centers, the latter two were only available in Bishkek (15.3%, 8.7%, and 5.7%, respectively). Though the Bishkek TB center accounted for the lowest proportion of patients (Table 1), they had the largest proportion of patients receiving a high methadone dosage (33%).

Kaplan-Meier curves show treatment retention over 24 months (Fig. 1A), stratified by dosage level. Retention on methadone was significantly higher over 24 months with increasing methadone dosage levels. For high, medium and low dosages, retention was 95%, 63%, and 42% at 6 months, 89%, 55%, and 33% at 12 months and 80%, 45%, and 16% at 24 months, respectively. Even at one and three months, retention was significantly higher for the high dosages compared to medium and low dosages (100% vs 98%, and 90% and 98% vs 75%, 49%, respectively (Fig. 1B). The retention data are similarly presented for community and carceral settings in Figs. 2A and B, respectively. Retention in community rather than carceral settings, however, was higher for high (90% vs. 69%) and medium (48% vs. 40%) dosages, but not for low (14 vs. 20%) dosages. When using a different metric, mean methadone dose, there was no significant differences between community and carceral settings (66.1mg vs. 61.5mg; p=0.15). The differences do not persist when controlling for dosage level and risk for treatment discontinuation after the release from incarceration and previous OAT experience (Table 2). Patients with HIV and on MMT have, on average, significantly higher mean methadone dosages (79.5mg vs. 63.1mg; $p < 0.001$). After controlling for methadone dosage level, however, HIV status does not influence OAT dropout (i.e., retention) (Table 2).

The independent predictors of dropout from MMT at one, six, twelve, and twenty-four months are presented in Table 2. For each time point, dosage category contributed most to dropout. For example, at 12 months, relative to receiving a high (recommended) dosage, receiving a low methadone dose portended an 8.0-fold (95%CL=5.8–11.0) increased adjusted hazard of dropout, which decreased to 3.5-fold (95%CL=2.5–4.9) for those prescribed medium dosages. There were, however, higher rates of dropout in some regions relative to Bishkek, the place with the longest experience with MMT. The type of clinical setting where methadone was prescribed was also predicted dropout. Relative to a general hospital-based clinic, dropout was significantly lower in specialty addiction treatment settings (Narcology clinics) and Bishkek's TB clinic. HIV status, however, did not contribute to treatment dropout after controlling for all other factors, nor did sex, age, and duration of drug injection.

4. Discussion

Findings from this study provide important insights to guide future MMT implementation in a setting where census has continually decreased since 2017, mostly related to drop-out. Here, supporting MMT patients to achieve the highest category of methadone dosage was the single most important factor associated with retention – a dosage level that markedly exceeds the existing national guidelines. Findings here are similar to those in Ukraine (Farnum et al., 2021) using a similar dataset and an analogous analytical strategy, but in a context where patient census was increasing. The relationship between dosing and retention was echoed in a smaller data set with more complete data from Ukraine (Dumchev et al., 2017). Findings from Ukraine resulted in a change in the national guidelines to support higher dosing levels, which is urgently needed in Kyrgyzstan. Though higher doses for retention are generally supported in meta-analyses, these older analyses restrict data for higher dosages of ≥60mg daily, similar to treatment guidelines in Kyrgyzstan (Bao et al., 2009). Several clinical trials and observational studies suggest higher retention when on

higher methadone dosages (Donny et al., 2005; Strain et al., 1999; Wickersham et al., 2013), yet these findings have not yet found their way into treatment guidelines. Though international guidelines suggest that flexible dosing be used, better guidance around dosage is needed. Moreover, average methadone dose has become a commonly use quality metric for MMT programs (Kumar, 2012), though findings from this study and confirmed with data from Ukraine (Dumchev et al., 2017; Farnum et al., 2021) potentially calls for an additional quality treatment indicator to be the proportion of methadone patients in a treatment program as being on >85mg per day.

A key finding here is that dosing matters early in treatment, as early as one month, similar to findings from Ukraine (Farnum et al., 2021). Strategies that escalate dosages rapidly and safely at the time of induction may therefore promote early clinical improvement. Kyrgyzstan's clinical guidelines call for an initial dose of 30mg followed by a dose escalation of 5mg to 10mg every seven days (Ministry of Health of Kyrgyz Republic, 2015), which is likely too slow to effectively engage patients and reduce early dropout. As MMT induction processes in most settings involve daily observation where symptoms of opioid excess can be monitored, a more rapid dose escalation protocol should be considered. Trade-offs between standard dose escalation to optimize dose must balance efficacy (i.e., significantly lower dropout) with safety (i.e., concerns about overdose).

To our knowledge, this is the first report of similar retention outcomes for MMT patients treated in both community and carceral settings, which was accomplished through the integrated database that includes treatment irrespective of site. A recent study of methadone treatment in carceral settings in, however, found a remarkably low linkage to treatment post-release, but for those who were released on methadone, higher dosage was correlated with linkage to and retention on treatment (Bachireddy et al., 2022); increased dosage was similarly associated with higher retention in treatment after release in Malaysia (Wickersham et al., 2013). These findings are especially important given the social hierarchy within Kyrgyz prisons, that lowers the social status of those who enroll on methadone and limit access to prison community resources (Azbel et al., 2022). Prospective trials in the U.S. show low linkage to MMT after release, especially for those not started on methadone while still incarcerate (Kinlock et al., 2009). In the U.S., where the volatile opioid epidemic claimed over 100,000 lives in 2021 alone, one surveillance study showed unequal coverage of OAT in prison, mostly due to funding restrictions and little attention to transitional care (Scott et al., 2021). Modeling studies that incorporate seamless OAT treatment in carceral and community settings are likely to have the greatest impact on mortality (Degenhardt et al., 2019) and other post-release outcomes (Stone et al., 2021 2018). A recent modeling study that included Central Asia of decriminalizing drug use for personal use or possession would markedly reduce HIV transmission and be cost saving (Ward et al., 2022). Such an approach in Kyrgyzstan where sentencing guidelines for drug use are harsh and persons spending considerable time (>3 years) incarcerated could be an alternative strategy.

With most (80.1%) patients receiving less than optimal methadone dosages that are predictive of higher dropout, flexible dosing practices might first focus on patients attaining an adequate dosage of 90 mg and then increasing dosages for those with the increased clinical need. Important in these findings is the observation that achieving higher methadone

dosages during the first treatment experience increases the likelihood that the patient will return for treatment after an initial interruption (Zhang et al., 2015), a finding that occurred for nearly one-fifth of methadone patients in Kyrgyzstan. This finding may represent treatment satisfaction with the first treatment episode. One potential impediment to helping patients achieve optimal dosing, however, is the indirect influence from Russia that bans methadone and persistent negative attitudes toward MMT in Central Asia among healthcare providers likely still undermines program scale-up (Subata et al., 2016), resulting in physician-influenced practices of maintaining lower dosages or restricting treatment duration.

Findings from this study could inform revisions of the current national methadone guidance, which now recommends achieving dosages of 60mg (Ministry of Health of Kyrgyz Republic, 2015). Until such guidelines are changed, the Network for the Improvement of Addiction Treatment (NIATx) could be deployed as an evidence-based process improvement strategy for introducing, testing, and modifying current practices to reduce dropout (Hoffman et al., 2008; McCarty et al., 2007). Findings from NIATx could in turn, prompt changes in treatment guidelines as occurred in Ukraine (Farnum et al., 2021). NIATx is a customer-focused, quality-driven collaborative learning model designed to work with leaders and providers in behavioral health care settings to scale-up OAT. It can be used to reduce waiting times, promote entry, and reduce dropout, in this case by optimizing dosage using several process improvement tools that help understand both patient and clinic-level barriers, fix key problems using rapid-cycle change projects to incrementally introduce changes until the desired outcome (e.g., higher retention, higher census, improved health-related quality of life, etc.) is attained (Gustafson and Hundt, 1995; McCarty et al., 2007). Until OAT guidelines are revised in Kyrgyzstan, NIATx could help clinicians optimize treatment outcomes. Reciprocally, findings from the NIATx treatment improvement process could promote national guideline changes, creating a learning-implementing cycle of process improvement for methadone treatment in the country.

Alternatively, dosing adequacy can be used to supplement actual target dosages, which is a supplemental flexible dosing strategy that is distinct from absolute dosage (Trujols et al., 2010). When combined with actual dosing recommendations, it improves treatment outcomes and satisfaction more than dosing guidance alone (Reimer et al., 2014; Walcher et al., 2016). Dosing adequacy addresses ways to alleviate withdrawal symptoms, eliminate ongoing illicit opioid use, and markedly reduce craving while avoiding signs of opioid excess. Such strategies are patient-centered and can optimize treatment outcomes like retention by minimizing or removing the often-paternalistic management strategies used by physicians caring for patients with OUD. Dosing adequacy can be measured using the Opioid Dosage Adequacy Scale (ODAS), which helps patients participate in the treatment decision-making process (Gardini et al., 2010; Gonzalez-Saiz et al., 2018). Using standardized instruments like the ODAS and reducing underdosing which can be influenced by patients themselves if they prefer to keep the dose low due to concerns about methadone safety or to allow them to continue experiencing euphoria through ongoing drug use (Bojko et al., 2015). The validated ODAS is guided by shared decision-making and has emerged as an individualized strategy that aligns provider expertise and patient expectations in order to promote retention and post-interruption treatment, which could prove helpful for clinicians

in Kyrgyzstan (Elwyn et al., 2012, 2016; Reimer et al., 2014; Walcher et al., 2016; Zhang et al., 2015).

Similar to findings elsewhere (Dumchev et al., 2017; Farnum et al., 2021), the type and location of sites contributed to dropout. Relative to Bishkek, where the first methadone programs started, the city of Osh and Chuy regions have higher dropout rates even after controlling for dosage. One explanation might be that Bishkek has the longest experience treating patients with methadone, and the clinic staff developed better skills, acquired more resources like counseling and support, or learned to make treatment more accessible to patients. Additionally, the type of facility where treatment is provided contributed to dropout. Relative to receiving methadone at general hospital-based clinics, treatment in addiction specialty clinics and the TB clinic in Bishkek had lower dropout. While this study could not disentangle the reason, contextual factors that reduce demands on patients (e.g., geographical proximity, take-home dosing, hours of operation, etc) or provide enhanced quality services (e.g., supportive services, staff with better clinical skills) may have contributed to better outcomes.

Insights from studies conducted elsewhere, specifically in Ukraine, found differences in treatment outcomes based on location or setting. For example, OAT patients treated in TB clinics had lower retention (Farnum et al., 2021), potentially due to well-known drug-drug pharmacokinetics interactions between methadone and rifampin resulting in pharmacodynamic underdosing (Altice et al., 2010); therefore, the finding of decreased dropout at the TB center in Bishkek is intriguing, especially after controlling for all other factors like dosing. Consequently, it is not surprising that the TB center had significantly higher mean methadone dosing and a larger proportion of patients on 90mg or more because of pharmacokinetic drug interactions between methadone and rifampicin (Altice et al., 2010), yet retention persisted even after controlling for these factors. One likely explanation for this increased retention at this site is the funding for supportive services to address OUD, HIV, and TB – the other sites did not receive support for TB and given the high prevalence of TB in Kyrgyzstan and support for controlling HIV among PWH, additional supports may have contributed to better outcomes.

Of interest are the outcomes for PWH on methadone. Most PWH receive support for both methadone and HIV, and it appears as though personnel recognized known pharmacokinetic drug interactions between methadone and ART, resulting in significantly higher methadone dosing for PWH (Altice et al., 2010). These findings support the need to optimize methadone dose in patients concomitantly on efavirenz-based ART regimens. Recently, however, efavirenz has been replaced by dolutegravir in most ART regimens. Importantly, given that these patients are treated primarily at AIDS Centers, dropout did not differ for PWH when controlling for dosage, irrespective of whether in carceral or community settings. As the country transitions patients from efavirenz-based to dolutegravir-based ART regimens, it is anticipated that higher methadone dosage levels for PWH will be less substantial.

While the study provides crucial country-specific insights for HIV prevention and treatment in Kyrgyzstan, there are several limitations. First, temporal trends from January 1, 2017,

through June 15, 2021, including during the global COVID-19 pandemic, may influence outcomes. This concern is partially mitigated by controlling by year in the analyses. Additionally, the introduction of selection bias may have occurred by limiting only new patients enrolled after January 2017, a period that reflects the introduction of new national guidelines. Such an approach may have excluded more stable patients who were adequately treated with methadone before the observation period. The national registry lacks the ability to assess changes in methadone dose over time, including early in treatment, as only the last dose is recorded. Consequently, changes in dosage or the rate of change cannot be ascertained or included as a dependent variable. The methadone dose at the time of dropout, however, was recorded as the last dose recorded during the last treatment episode. Twenty percent of our sample had more than one treatment episode. Selecting the most recent episode may result in estimates closer to the null hypothesis and underestimating the association between the methadone dose and treatment retention as re-admission is a predictor of higher methadone retention (Zhang et al., 2018); however, our findings remained robust in our sensitivity analyses using first treatment episode. Last, several unmeasured patients' personal and programmatic characteristics such as supportive counseling, social support, having psychiatric comorbidities, polysubstance use, peer network characteristics, and distance to methadone site were not controlled during the analysis.

5. Conclusions

Data from Kyrgyzstan confirm that only one fifth of patients who received methadone after the initiation of the national guidelines and revision of the national database received an optimal methadone dose. Implementation strategies that target consistent and timely dosing and patient-side clarifying of the sufficient dosing utility are urgently needed to abrogate the current dropout from methadone. Such implementation strategies should target induction with standardized dose escalation practices during the first 30 days, along with focusing on dosing adequacy for more stabilized patients. Such strategies would benefit from their inclusion in more updated national methadone treatment guidelines.

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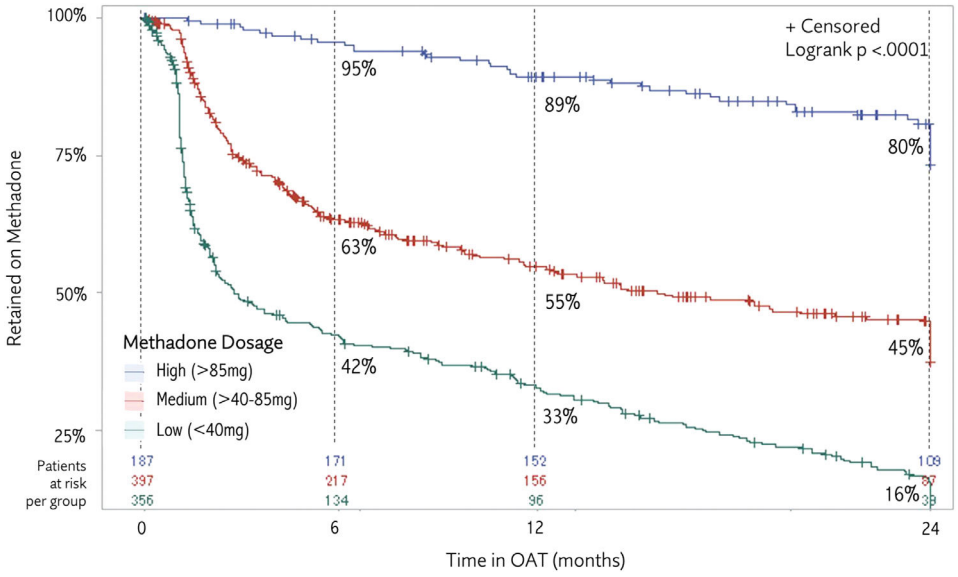

Fig. 1A.

Retention on methadone for all patients over 24 months, stratified by dosage, $N = 940$.

OAT: opioid agonist treatment.

Note: Color should be used for Fig. 1A in print and online.

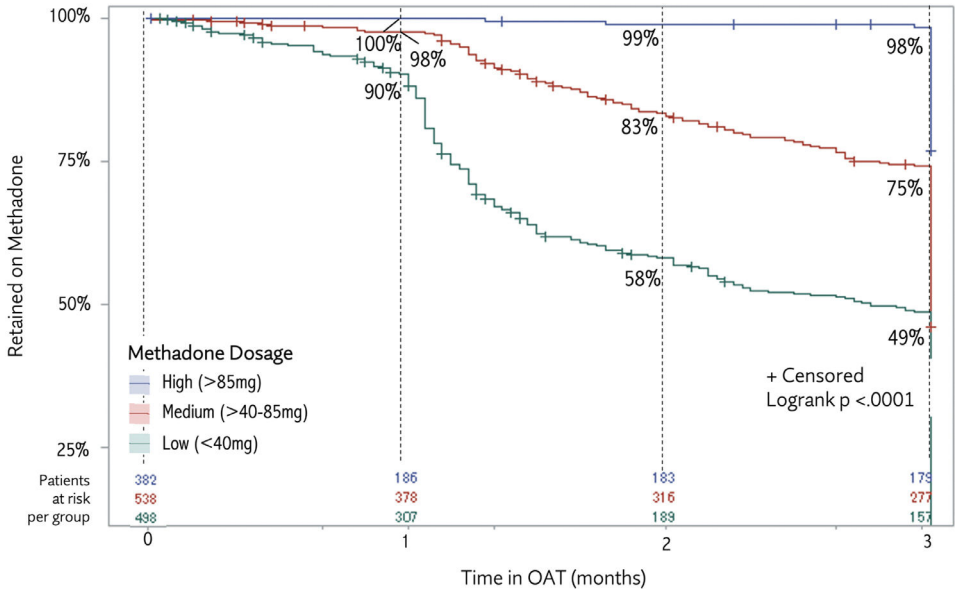

Fig. 1B.

Retention on methadone for all patients over 3 months, stratified by dosage ($N = 940$). OAT: opioid agonist treatment.

Note: Color should be used for Fig. 1B in print and online.

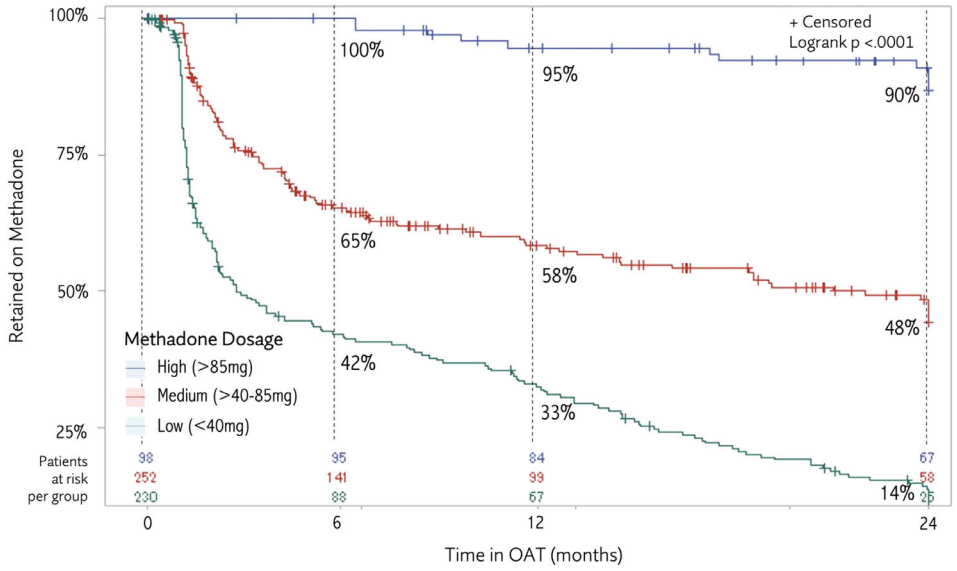

Fig. 2A.

Retention on methadone for all patients in community settings over 24 months, stratified by dosage (N=580).

OAT: opioid agonist treatment.

Note: Color should be used for Fig. 2A in print and online.

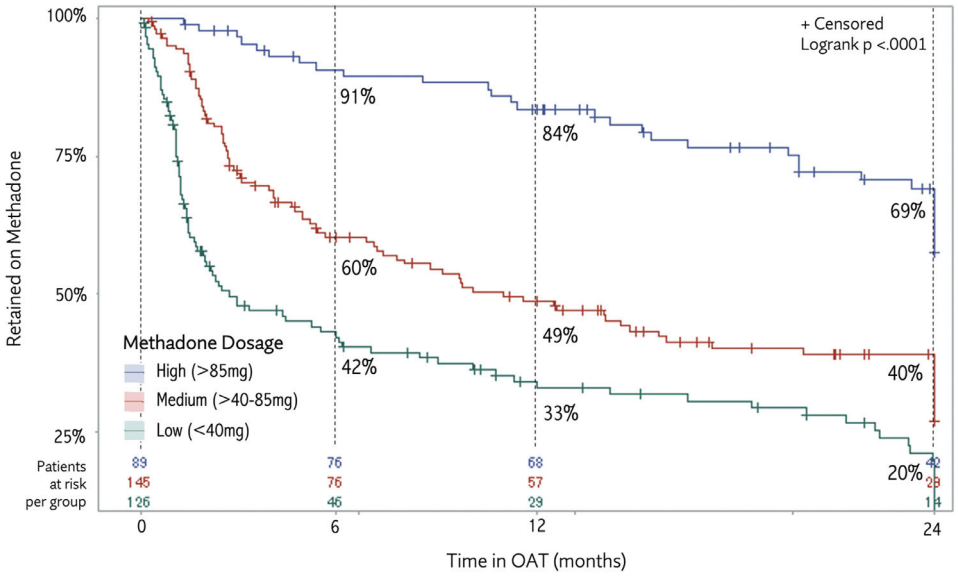

Fig. 2B.

Retention on methadone for all patients in carceral settings over 24 months, stratified by dosage (N=360).

OAT: opioid agonist treatment.

Note: Color should be used for Fig. 2B in print and online.

Table 1

Characteristics of patients receiving methadone maintenance treatment, stratified by dosage levels, $N = 940$.

Characteristic	Overall N=940	Low (≤40 mg) N=356 (37.9%)	Medium (41–85 mg) N=397 (42.2%)	High (>85 mg) N=187 (19.9%)	p-value
Age at enrollment, years					0.002
≤35	242 (25.7%)	98 (40.5%)	81 (33.5%)	63 (26.0%)	
>35	698 (74.3%)	258 (36.7%)	316 (42.4%)	124 (17.9%)	
Sex					0.06
Male	890 (94.7%)	330 (37.1%)	378 (42.4%)	182 (20.5%)	
Female	50 (5.3%)	26 (52.0%)	19 (38.0%)	5 (10.0%)	
Administrative Region					<0.0001
City of Bishkek	346 (36.8%)	144 (41.6%)	131 (37.9%)	71 (20.5%)	
City of Osh	142 (15.1%)	71 (50.0%)	54 (38.0%)	17 (12.0%)	
Chuy Region	320 (34.0%)	92 (28.8%)	146 (45.6%)	82 (25.6%)	
Osh Region	97 (10.4%)	28 (28.8%)	57 (58.8%)	12 (12.4%)	
Batken Region	5 (0.5%)	4 (80.0%)	1 (20.0%)	0	
Jalal-Abad Region	30 (3.2%)	17 (56.7%)	8 (26.7%)	5 (16.6%)	
HIV Status					<0.0001
Positive	197 (21.1%)	60 (30.5%)	76 (38.6%)	61 (31.0%)	
Negative	623 (66.2%)	208 (33.4%)	291 (46.7%)	124 (19.9%)	
Unknown	120 (12.7%)	88 (73.3%)	30 (25.0%)	2 (1.7%)	
Years of injecting drugs					0.005
≤5	255 (27.1%)	118 (46.4%)	95 (37.3%)	42 (16.5%)	0.005
>5	685 (72.9%)	238 (34.7%)	302 (44.1%)	145 (21.2%)	
Site where methadone is prescribed					<0.0001
AIDS Center	82 (8.7%)	45 (54.9%)	25 (30.5%)	12 (14.6%)	
Narcology Center	144 (15.3%)	68 (47.3%)	64 (44.4%)	12 (8.3%)	
General Hospital	300 (31.9%)	99 (33.0%)	145 (48.3%)	56 (18.7%)	
TB Center	54 (5.7%)	18 (33.3%)	18 (33.3%)	18 (33.3%)	
Penitentiary	360 (38.4%)	126 (35.0%)	145 (40.3%)	89 (24.7%)	

Table 2

Cox regression model of factors associated with lower retention (dropout) on opioid agonist therapy, N=940.

	1 month			6 months			12 months			24 months		
	aHR	**95% CI**	**p-val.**	**aHR**	**95% CI**	**p-val.**	**aHR**	**95% CI**	**p-val.**	**aHR**	**95% CI**	**p-val.**
Methadone dosing category	* Controlled for year of enrollment, previous OAT experience, post-release dropout risk											
High	Ref.			Ref.			Ref.			Ref.		
Medium	**2.6**	**1.8–3.6**	**< .0001**	**3.3**	**2.4–4.6**	**<. 0001**	**3.5**	**2.5–4.9**	**<. 0001**	**3.7**	**2.7–5.2**	**<. 0001**
Low	**4.6**	**3.3–6.3**	**< .0001**	**7.4**	**5.3–10.2**	**<. 0001**	**8.0**	**5.8–11.0**	**<. 0001**	**8.9**	**6.4–12.3**	**<. 0001**
Sex	* Controlled for year of enrollment, methadone dose and post-release dropout risk											
Male	Ref.			Ref.			Ref.			Ref.		
Female	1.1	0.7–1.5	0.695	1.0	0.7–1.6	0.828	1.1	0.7–1.5	0.783	1.1	0.7–1.5	0.762
Age, years	* Controlled for year of the first enrollment, previous OAT experience, methadone dose and post-release dropout risk											
≤35	Ref.			Ref.			Ref.			Ref.		
>35	1.0	0.8–1.3	0.684	1.1	0.9–1.3	0.408	1.1	0.9–1.3	0.358	1.1	0.9–1.4	0.268
Administrative Region	* Controlled for year of enrollment, methadone dose and post-release dropout risk											
City of Bishkek	Ref.			Ref.			Ref.			Ref.		
City of Osh	**1.3**	**1.0–1.7**	**0.030**	**2.1**	**1.6–2.6**	**<. 0001**	**2.0**	**1.6–2.6**	**<. 0001**	**1.9**	**1.5–2.5**	**<. 0001**
Chuy Region	1.2	0.9–1.4	0.167	**1.3**	**1.0–1.6**	**0.026**	**1.2**	**1.0–1.5**	**0.004**	**1.2**	**0.9–1.5**	**0.124**
Osh Region	1.2	0.9–1.7	0.565	**1.4**	**1.0–1.9**	**0.035**	1.3	0.9–1.8	0.056	1.3	0.9–1.7	0.113
Batken Region	1.3	0.4–4.0	0.691	2.3	0.7–7.3	0.149	1.9	0.6–6.2	0.244	2.6	0.8–8.1	0.111
Jalal-Abad Region	1.1	0.7–1.7	0.610	**1.7**	**1.1–2.6**	**0.029**	**1.7**	**1.1–2.6**	**0.023**	**1.6**	**1.1–2.5**	**0.048**
Years of Injecting drugs	* Controlled for year of enrollment, previous OAT experience, methadone dose and post-release dropout risk											
≤5	Ref.			Ref.			Ref.			Ref.		
>5	1.0	0.6–1.5	0.866	1.0	0.7–1.6	0.894	1.0	0.7–1.6	0.891	1.0	0.6–1.6	0.994
HIV Status	* Controlled for year of enrollment, previous OAT experience, methadone dose and post-release dropout risk											

	1 month			6 months			12 months			24 months		
	aHR	**95% CI**	**p-val.**	**aHR**	**95% CI**	**p-val.**	**aHR**	**95% CI**	**p-val.**	**aHR**	**95% CI**	**p-val.**
Negative	Ref.			Ref.			Ref.			Ref.		
Positive	1.0	0.6–1.7	0.949	0.9	0.7–1.1	0.266	0.9	0.7–1.1	0.322	0.9	0.7–1.1	0.306
Incarceration Status	* Controlled for year of enrollment, previous OAT experience, methadone dose and post-release dropout risk											
Community Patients	Ref.			Ref.			Ref.			Ref.		
Penitentiary Patients	1.0	0.8–1.2	0.759	0.9	0.7–1.1	0.523	0.9	0.8–1.1	0.370	0.9	0.7–1.1	0.374
Site where methadone was prescribed	* Controlled for year of enrollment, methadone dose, previous OAT experience, and post-release dropout risk											
General Hospital	Ref.			Ref.			Ref.			Ref.		
Narcology Center	0.8	0.6–1.1	0.286	**0.6**	**0.4–0.9**	**0.005**	**0.6**	**0.4–0.9**	**0.004**	**0.6**	**0.4–0.9**	**0.009**
AIDS Center	0.9	0.7–1.3	0.944	0.7	0.5–1.0	0.091	0.8	0.6–1.1	0.174	0.8	0.6–1.1	0.284
TB Center	0.8	0.5–1.3	0.420	**0.6**	**0.4–0.9**	**0.034**	**0.5**	**0.3–0.9**	**0.025**	0.6	0.4–1.0	0.059
Penitentiary	1.0	0.7–1.3	0.997	0.8	0.6–1.0	0.091	0.8	0.6–1.0	0.118	0.8	0.6–1.1	0.141