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Research paper

Adherence to antiretroviral therapy among HIV positive men who inject drugs in Pakistan

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ABSTRACT

Background: People who inject drugs (PWID) living with HIV have poorer adherence to HIV antiretroviral therapy (ART) and elevated mortality compared to other populations. Little is known about factors associated with adherence among PWID in low-and middle-income countries, including in countries where opioid agonist therapy (OAT) is unavailable. We aimed to estimate ART adherence among men who inject drugs (MWID) living with HIV in Pakistan and identify factors independently associated with adherence.

Methods: Nai Zindagi Trust (NZT) provides a range of HIV prevention, testing and treatment services to PWID in Pakistan. This study utilized data from HIV positive MWID who received ART refill/s from public sector ART Centres via NZT's Social Mobilizer Adherence Support Unit between September 2016 and December 2018. Multivariable logistic regression modelled factors independently associated with ART adherence.

Results: Among 5,482 HIV positive MWID registered with NZT who had attended the AAU and were supplied with ART refills between September 2016 and December 2018., 55% were adherent to ART. Independent predictors of adherence were being married (AOR 1.38, 95% CI:1.23–1.55, $p<0.001$) and >5 years of education compared to those with no education (AOR 1.19, 95% CI:1.05–1.35, $p = 0.005$). MWID living on the street at night had lower adjusted odds of ART adherence (AOR 0.75, 95% CI:0.62–0.91, $p = 0.003$).

Conclusions: Findings indicate that MWID living with HIV continue to face barriers to ART adherence in Pakistan. Despite considerable evidence supporting the impact of OAT in increasing ART adherence among PWID, OAT remains illegal and inaccessible in Pakistan. Evidence-based interventions, including OAT, are needed to increase adherence and improve clinical outcomes, health equity and survival among PWID living with HIV in Pakistan.

Introduction

Human immunodeficiency virus (HIV) remains a leading cause of mortality and morbidity worldwide. HIV antiretroviral therapy (ART) suppresses HIV-1RNA plasma viral load, prevents the emergence of resistance, increases survival, and reduces AIDS-related mortality and morbidity (Cohen et al., 2011; Ledergerber et al., 1999; Lima et al., 2007). Optimizing adherence to ART is essential for both individual and population-level outcomes, including prevention of transmission (Cohen et al., 2016; Montaner et al., 2010; Pasternak et al., 2012).

People who inject drugs (PWID) are a key population in the HIV epidemic and response (United Nations Office on Drugs & Crime et al., 2017). Of the estimated 11.3 million PWID globally in 2019, including 3.6 million in South Asia and Southeast Asia, 13% were estimated to be living with HIV (Harm Reduction International, 2020). PWID living with HIV are at higher risk of all-cause mortality than people living with HIV who do not inject drugs (Spiller et al., 2015). In addition to poorer access to ART, studies have consistently shown that PWID have lower adherence and are more likely to experience treatment interruptions and to discontinue treatment than people living with HIV who do not inject drugs (Feelemyer, Des Jarlais, Arasteh, & Uuskula, 2015; Malta, Strathdee, Magnanini, & Bastos, 2008; Wood, Kerr, Tyndall, & Montaner, 2008). Factors associated with sub-optimal ART adherence in PWID include homelessness and a lack of social support, medication-related issues such as regimen, pill burden, dosing frequency and adverse effects, mental health co-morbidities, and the effects of stigma and discrimination (Malta, Magnanini, Strathdee, & Bastos, 2010). Barriers to ART adherence by PWID also include incarceration which has been associated with sub-optimal virological suppression and lower adherence self-efficacy (Krusi, Wood, Montaner, & Kerr, 2010; Palepu et al., 2004; Wood, Kerr, Tyndall, & Montaner, 2008). Hepatitis C virus co-

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infection, common among PWID, can increase side effects and reduce the tolerability of ART regimens (Palepu et al., 2006).

Active substance use, especially severe or high intensity drug use, has also been associated with poor adherence (Malta et al., 2008). While stimulant, particularly methamphetamine, use is associated with worse HIV outcomes and current methamphetamine use is a strong predictor of ART non-adherence (Hinkin et al., 2007; Moore et al., 2012), several studies have shown that opioid agonist therapy (OAT) can increase adherence among PWID (Dutta, Wirtz, Baral, Beyrer, & Cleghorn, 2012; Malta et al., 2008). An early review of 41 studies concluded that ART adherence among drug users living with HIV can be similar to that observed in other people living with HIV when treatment includes management of comorbidities, psychosocial support, and drug treatment, particularly OAT (Malta et al., 2008). A Canadian study of 1852 PWID living with HIV found that OAT substantially increased the odds of adherence to ART (Nosyk et al., 2015). A recent systematic review found that OAT was associated with a 69% increase in initiation of ART, a 54% increase in ART coverage, a 45% increase in viral suppression and a 2-fold increase in adherence (Low et al., 2016).

Of the estimated 190,000 people living with HIV in Pakistan in 2019, the majority (79%) are unaware of their HIV status and only 23,000 (12%) were receiving ART (UNAIDS, 2020). HIV prevalence among PWID is estimated at 38% (Harm Reduction International, 2020), with injection drug use accounting for the majority of new HIV infections (Bergenstrom et al., 2015). Given that ART coverage among PWID was 16% in 2019 (UNAIDS, 2020), optimizing ART coverage in this population is essential to controlling the epidemic in Pakistan. Moreover, little is known about factors associated with ART adherence among PWID in low-and middle-income countries. The only systematic review included 15 studies conducted in Brazil, China, Estonia, India, Indonesia, Russia, and Vietnam between 1996 and 2012 containing a total of 21,258 participants, only 60 of which were identified as current PWID (Feelemyer et al., 2015). Results indicated adherence ranged from 33% to 97% with a mean weighted adherence of 72%. Adherence was associated with different methods of measuring adherence and higher levels of adherence were observed in studies conducted in Eastern Europe and East Asia.

In Pakistan, a cross-sectional study of 375 PWID attending an outpatient HIV clinic at a Karachi hospital in 2015 reported that only 17% were adherent, with non-adherence higher in patients who were single and did not have children, however 343 (91%) also had an alcohol use disorder (Bakht, Nisar, & Nawab, 2018). Another published report from Pakistan consisted of a descriptive study of 162 men (81 PWID, 81 non-PWID) followed from 2008 to 2012 which found that 59% of PWID were lost to follow up and only 20% were adherent, compared to 2% and 90%, respectively, in the non-PWID group (Daud, Qazi, & Bashir, 2014). Historically, Pakistan's national guidelines required that PWID complete two weeks of drug detoxification prior to ART initiation (Nai Zindagi Trust, 2016). Concerns among clinicians about the potential emergence of treatment resistant HIV strains continue to be reported as one of the main reasons for insisting upon detoxification prior to commencing PWID on ART. A problem with this "no initiation without rehabilitation" approach to treating PWID in this setting is the limited availability and accessibility of evidence-based drug treatment (Nai Zindagi Trust, 2016:3).

The role of detoxification as a barrier to ART initiation for PWID was a key consideration during the development of Pakistan's HIV Concept Note for the Global Fund in 2015. While a pilot OAT program was originally budgeted into the first iteration of Round 9, this was subsequently removed because of strong political opposition. In response to this situation the Nai Zindagi Trust (NZT), the civil society Principal Recipient for the Global Fund grant in Pakistan, implemented a residential rehabilitation facility for PWID living with HIV to comply with the requirement by ART treatment centres that PWID undergo a minimum of 2 weeks inpatient detoxification prior to ART initiation. The ART Adherence Unit (AAU) combines eight weeks of opioid detoxification with HIV treatment adherence support. A 2016 evaluation examining clients with 7 to 19 months of treatment history found a statistically significant impact on ART adherence with 77% of clients who completed AAU treatment adherent compared to 51% among clients who did not attend AAU (Nai Zindagi Trust, 2016). The most commonly cited reasons for non-adherence were side effects (47%) and relapse to drug use (37%). Overall, 87% of adherent clients reported receiving some kind of adherence support, including being accompanied to clinics by NZT Social Mobilisers (66%), having medicines brought from clinics by Social Mobilisers (21%), receiving motivational support from family members (67%) and Social Mobilisers (64%), and receiving medical (55%) and transportation support (43%).

The current study aimed to a) estimate adherence to ART among men who inject drugs (MWID) who attended the AAU, initiated ART and were provided with adherence support via NZT's Social Mobilizer Adherence Support Unit and b) identify factors independently associated with adherence in this population.

Methods

NZT provides a range of HIV prevention, testing and treatment services to people who inject drugs (PWID) in Pakistan, covering 30 Districts in all four provinces. This study included all HIV positive MWID who attended the AAU, initiated ART and received a minimum of one ART refill from public sector ART Centres through the Social Mobilizer Adherence Support Unit during the study period. Data collection of the date and quantity of ART refill supplies commenced in September 2016, and the time-period for this study ceased in December 2018. These data were used to assess adherence to ART. ART was defined as adherent when the number of ART refills supplied covered the number of days on ART. Respondents were considered non-adherent if they did not have sufficient refills to cover 100% of days on ART or if ART was discontinued. MWID who attended the AAU and commenced ART before September 2016 were eligible for inclusion in the study if a refill was supplied between September 2016 and December 2018. A range of demographic characteristics and behavioural data were collected from NZT clients at the time of first attendance and an anonymous unique identifier (registration code) was allocated. NZT subsequently recorded details of each occasion of service provided to registered individuals using the unique identifier. For this study, demographic characteristics and behavioural data were obtained from the NZT client registration records and merged with the NZT ART dataset using the unique identifier. The NZT Institutional Review Board granted ethical approval for this study.

Statistical analysis

The primary outcome for this study was adherence to ART. The Chi-square test was used to analyze categorical variables. Univariable and multivariable logistic regression were used to model associations between demographic characteristics (geographic location, age, education, main income source and marital status) and behavioural data (type of drug injected and living on the street at night). Odds ratios (OR), adjusted odds ratios (AOR) and 95% confidence intervals (95% CI) were used to assess significance. Factors hypothesized to be associated with ART adherence were assessed, including age (Arnsten et al., 2007), marital status (Bakht et al., 2018), years of education (Arnsten et al., 2007), source of income (Feelemyer et al., 2015), type of drug/s injected (Wood et al., 2008) and housing status (Malta et al., 2008). All variables associated with the outcome at $P<0.10$ in bivariate analyses were considered for multiple logistic regression modeling. The final model was derived using stepwise backward approach, with factors sequentially eliminated according to the result of a likelihood ratio test. All analyses were conducted using STATA software version 14.2 (Stata Corporation, College Station, TX, USA).

Table 1
Demographic characteristics and drugs injected among men who inject drugs who initiated ART.

Variable	Total $N = 5482$	ART non-adherent $N = 2474$ (45)	ART adherent $N = 3008$ (55)
Age initiated ART (quartiles,%)			
≤27 years	1417 (26)	682 (48)	735 (52)
28–31 years	1618 (30)	753 (47)	865 (53)
32–36 years	1183 (22)	505 (43)	678 (57)
≥37 years	1264 (23)	534 (42)	730 (58)
Marital status (%)*			
Unmarried (reference)	2480 (45)	1189 (48)	1291 (52)
Married	2181 (40)	865 (40)	1316 (60)
Separated/divorced	821 (15)	420 (51)	401 (49)
Education, years (%)*			
None (reference)	2585 (47)	1216 (47)	1369 (53)
1–5 years	1119 (20)	499 (45)	620 (55)
>5 years	1778 (32)	759 (43)	1019 (57)
Source of income (%)*			
Daily wages (reference)	3011 (55)	1338 (44)	1673 (56)
Begging, selling sex/drugs	288 (5)	147 (51)	141 (49)
Family/friends	653 (12)	299 (46)	353 (54)
Business/self employed	1254 (23)	560 (45)	694 (55)
None	277 (5)	130 (47)	147 (53)
Drugs injected (%)*			
Heroin	4246 (77)	1907 (45)	2339 (55)
Other opioids	574 (10)	258 (45)	316 (55)
Other drugs	470 (9)	219 (47)	251 (53)
Not reported	192 (4)	90 (47)	102 (53)
Live on the street at night (%)*			
No (reference)	4992 (91)	2216 (44)	2776 (56)
Yes	471 (9)	253 (54)	218 (46)

* At baseline registration; ART: Anti-retroviral therapy.

Results

Sample characteristics

A total of 5482 HIV positive MWID registered with NZT had attended the AAU and were supplied with ART refills between September 2016 and December 2018. The sample comprised MWID from 29 cities, from all four Provinces (Balochistan, Khyber Pakhtunkhwa, Punjab, and Sindh). The median age at ART initiation was 31 years (interquartile range 26–36 years). Among MWID who initiated ART, 45% were unmarried, 40% were married and 15% were divorced or separated, while the majority had little or no education ($n = 3704$, 68%) and worked for daily wages ($n = 3011$, 55%). Although most MWID reported injection of more than one drug at first NZT registration, three quarters ($n = 4246$, 77%) reported heroin injection and a further 10% ($n = 574$) reported injection of other opioids. A minority of MWID who received ART were living on the streets at night at the time of NZT registration ($n = 471$, 9%).

Correlates of adherence to ART

Among the $n = 5482$ HIV positive MWID who had initiated ART, just over half ($n = 3008$, 55%) were assessed as adherent (Table 1). In univariable analysis (Table 2), there were no associations with adherence to ART and source of income or drug injected at baseline registration. Independent predictors of ART adherence were being married at NZT registration (AOR 1.38, 95% CI 1.23–1.55, $p<0.001$) and completion of more than five years of education compared to those with no education (AOR 1.19, 95% CI 1.05–1.35, $p = 0.005$). MWID who reported living on the street at night at the time of NZT registration had lower adjusted odds of ART adherence (AOR 0.75, 95% CI 0.62–0.91, $p = 0.003$).

Discussion

Findings indicate that just over just over half (55%) of 5482 HIV positive MWID in Pakistan registered with NZT who initiated ART during this study were assessed as adherent. While this is higher than the estimates of 17% (Bakht et al., 2018) and 20% (Daud et al., 2014) from earlier studies, it is lower than the mean weighted estimate of 72% derived from a recent review of adherence among PWID in low and middle income settings (Feelemyer et al., 2015). Our finding of 55% adherence sits between estimates derived from studies in high-income settings which report adherence in PWID, including in the United States (26.7%) (Fu et al., 2012), France (65.5%) (Moatti et al., 2000) and Canada (76.9%) (Palepu et al., 2003). However, our estimate is lower than the 77% adherence observed in an earlier study of NZT clients who completed AAU treatment (Nai Zindagi Trust, 2016). Given the absence of OAT and the requirement for PWID to undergo detoxification prior to ART initiation in this setting, the AAU is likely to optimize adherence as the only program that simultaneously addresses both opioid dependence and HIV treatment support (Nai Zindagi Trust, 2016).

Participants with more than five years of education were 1.16 times more likely than those with no education to be adherent. Education has been associated with adherence to ART in previous studies. A US study of PWID found that PWID with more than a high school education had increased odds of adherence compared to PWID who had not completed high school (Arnsten et al., 2007). Studies in Taiwan (Yen et al., 2014), India (Shah et al., 2007) and Columbia (Gonzalez, Mimiaga, Israel, Andres Bedoya, & Safren, 2013) have also reported associations between illiteracy and low levels of education and ART non-adherence in PWID. And in Pakistan Bakht et al. (2018)), were unable to examine this association because most of their patients were illiterate.

In our study, MWID who were married were 1.4 times more likely to be adherent to ART. Social support has previously been identified as an important enabling factor for PWID living with HIV (Knowlton et al., 2006) and for people living with HIV in developing countries in Asia (Wasti et al., 2012). An earlier study in Karachi also found that non-adherence was higher in HIV positive MWID who were single and that PWID who were married and who had children were more likely to be adherent to ART (Bakht et al., 2018).

Table 2
Univariable and multivariable logistic regression of factors associated with ART adherence (n = 5482).

Variable	Unadjusted		Adjusted	
	OR (95% CI)	p-value	AOR (95% CI)	p-value
Age initiated ART (quartiles,%)				
≤27 years	–			
28–31 years	1.07 (0.92–1.23)	0.381	ǂ	
32–36 years	1.25 (1.07–1.46)	0.006		
≥37 years	1.27 (1.09–1.48)	0.002		
Marital status (%)*				
Unmarried (reference)	–		–	
Married	1.40 (1.25–1.57)	<0.001	1.38 (1.23–1.55)	<0.001
Separated/divorced	0.88 (0.75–1.03)	0.110	0.88 (0.75–1.03)	0.116
Education, years (%)*				
None (reference)	–		–	
1–5 years	1.10 (0.96–1.27)	0.170	1.11 (0.96–1.28)	0.160
>5 years	1.19 (1.06–1.35)	0.005	1.19 (1.05–1.35)	0.005
Source of income (%)*				
Daily wages (reference)	–			
Begging, selling sex/drugs	1.10 (0.86–1.42)	0.424	ǂ	
Family/friends	0.85 (0.61–1.18)	0.329		
Business/self employed	1.04 (0.79–1.38)	0.764		
None	1.10 (0.84–1.42)	0.491		
Drugs injected (%)*				
Heroin	–			
Other opioids	1.00 (0.83–1.19)	0.987	ǂ	
Other drugs	0.93 (0.77–1.13)	0.487		
Not reported	0.92(0.69–1.23)	0.593		
Live on the street at night (%)*				
No (reference)	–		–	
Yes	0.69 (0.57–0.83)	<0.001	0.75 (0.62–0.91)	0.003

* At baseline registration ART: Anti-retroviral therapy.
ǂ Excluded from final model.

Homelessness and housing instability are independently associated with both HIV, and HCV infection and homeless PWID are more likely to engage in injection risk behavior (Arum et al., 2018). Stable housing is also associated with improved health (Hickman et al., 2007), including more frequent and timely utilization of health and social services by PWID (Nickasch & Marnocha, 2009). In the current study, living on the street at night was also associated with reduced adherence, with MWID who lived on the street at night having 25% lower odds of adherence (AOR 0.75, 95% CI 0.62–0.91, p = 0.004). This is consistent with previous studies which documented independent associations between homelessness and unstable housing and increased risk of non-adherence in this population (Palepu, Milloy, Kerr, Zhang, & Wood, 2011). Being without a home inhibits the establishment of daily routines, limits privacy and the storage of medications, and restricts access to health services (Bazzi et al., 2019; Joseph et al., 2015; Milloy et al., 2012). More generally, social instability including homelessness, unemployment, and a history of incarceration have been associated with suboptimal adherence among PWID, highlighting the role of social support in establishing and maintaining ART adherence in this population (Malta et al., 2008).

A systematic review by Chaiyachati et al. (2014) found strong evidence to support five interventions - cognitive behavioural therapy, education, treatment supporters, directly observed therapy, and active reminder devices – to improve ART adherence in the general population of people living with HIV (Chaiyachati et al., 2014). A recent review by Kanters et al. (2017) based on 85 trials with 16,271 participants found that short message service interventions were superior to standard care in improving ART adherence both globally and in low and middle-income countries (Kanters et al., 2017).

For PWID living with HIV however, OAT is the single most important facilitator of ART initiation and adherence. An early review of 38 studies found higher adherence among people who use drugs receiving OAT than those who were not (Malta et al., 2010). A recent review identified 12 studies which found that substance use treatment, especially OAT, supported ART adherence in this population (Bazzi et al., 2019) and a meta-analysis found that OAT was associated with a 69% increase in recruitment to ART, a 54% increase in ART coverage, and a two-fold increase in adherence among PWID (Low et al., 2016). OAT has been identified as a core component of the comprehensive package of HIV services recommended by the United Nations Programme on HIV/AIDS, the United Nations Office on Drugs and Crime and the World Health Organization, and methadone and buprenorphine are now included in the WHO's list of Essential Medicines.

Despite this evidence, Pakistan remains the only country in Asia with a high prevalence of opioid use and dependence that does not provide OAT. Barriers to effective implementation in this setting include a lack of political will, the need for legislative change, social and structural discrimination against PWID, and concerns about costs (Bergenstrom et al., 2015). While under the National Drug Abuse Control Master Plan 2010–2014 Pakistan aims to be drug free by 2020 (Government of Pakistan & Ministry of Narcotics Control/Narcotics Task Force, 2010), the nation continues to experience strident opposition to OAT (Yaqub, 2013). In 2013 the Ministry of Health joined with the WHO-UNODC Joint Programme on Drug Dependence Treatment and Care to auspice a pilot of buprenorphine treatment. Of 80 patients enrolled in the pilot, 73% remained in treatment a year later, demonstrating "a significant reduction in heroin use and injecting among patients receiving treatment as well as significant improvements in health and quality of life" (Bergenstrom et al., 2015:5). Notwithstanding this promising evidence of local efficacy, OAT remains illegal in Pakistan with the absence of an enabling policy environment precluding the implementation of OAT in Pakistan in 2009, despite earmarked funding from the Global Fund (Bergenstrom et al., 2015).

A major strength of our study is the large, national sample of MWID living with HIV who have initiated ART, however there are also limita-

tions. Firstly, ART adherence was based on service delivery data from the NZT Social Mobilizer Adherence Support Unit and does not capture MWID living with HIV who attended ART centres directly or MWID living with HIV who were not registered with NZT. As such, our sample may not be representative of the broader population of MWID living with HIV in Pakistan. Secondly, ART adherence was based on refill supply and measures of administration of doses, viral load or viral suppression were not available. The dichotomous measure of ART adherence used in this study does not accommodate variation in the non-adherent group or the detection of non-administered doses in the group assessed as adherent. Thirdly, data collection on the date and quantity of ART refills only commenced in September 2016 and adherence among those who commenced ART before this time was unable to be assessed. Lastly, socioeconomic (marital status, source of income and housing) and behavioural (drugs injected) data were collected at baseline registration at NZT and may have changed over time.

Conclusions

Our findings indicate that PWID living with HIV in Pakistan continue to face barriers to ART adherence with just over half (55%) assessed as adherent. In our study, education, marital status and housing were independently associated with being adherent. While significant ART-associated survival gains have been observed (Ferreros, Lumbreras, Hurtado, Perez-Hoyos, & Hernandez-Aguado, 2008; Lima et al., 2007; Wood et al., 2008), a range of barriers to ART access and adherence contribute to sub-optimal clinical outcomes in PWID living with HIV. Despite growing evidence to support the impact of interventions to address barriers to access and adherence in this population, uptake remains poor and global coverage patchy (Milloy, Montaner, & Wood, 2012; Wolfe, Carrieri, & Shepard, 2010).

However, it is clear is that both access and adherence to ART among PWID is improved by flexible, comprehensive and well-integrated HIV, harm reduction, and drug treatment. Delivery models include services such as on-site pharmacists, HIV specialist nurses, drop-in clinics, case management and reducing the geographic distance between home and HIV services (Kushel et al., 2006; Sorensen et al., 1998) and, crucially, the provision of OAT (Palepu et al., 2006). In Pakistan, while the National AIDS Control Programme Pakistan AIDS Strategy has acknowledged the role of OAT in HIV prevention and treatment (Bergenstrom et al., 2015), this key intervention remains illegal and inaccessible. In addition to the benefits of evidence-based treatment for opioid dependence, OAT has the potential to optimize adherence to ART among PWID and by suppressing viral load, to prevent secondary transmission of HIV. This may be particularly important in settings such as Pakistan where a high burden of HIV infection among female spouses of MWID has been observed (Malik et al., 2019). Our results support the need for evidence-based interventions, including OAT, to be introduced and brought to scale to improve clinical outcomes, health equity and survival for PWID living with HIV in Pakistan.

Ethics statement

The Nai Zindagi Trust Institutional Review Board granted ethical approval for this study.

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Declarations of Interest

None of the authors have any conflict of interest to declare.

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