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Expanding single-venue services to better engage young people who inject drugs: insights from India

Lakshmi Ganapathi[1,2,3*†], Aylur K. Srikrishnan[4†], Allison M. McFall[5], Mihili P. Gunaratne[5], Muniratnam Suresh Kumar[4,6], Gregory M. Lucas[7], Shruti H. Mehta[5] and Sunil S. Solomon[7]

Abstract

Background Over the last decade, India has had an alarming rise in injection of opioids across several cities. Although scale-up of public sector services for people who inject drugs (PWID) in India has occurred over decades, accessibility has been diminished by fragmented services across physical locations. To circumvent this barrier, and in alignment with the World Health Organization's guidelines to provide comprehensive care to key populations, Integrated Care Centers (ICCs) were established across 8 Indian cities as a public–private service delivery model for providing free single-venue services to PWID. ICCs have been very successful in expanding service availability and convenience for PWID generally. However, few studies from low- and middle-income countries (LMIC) have evaluated how well young PWID (defined as those ≤ 29 years of age) engage with single-venue service models like ICCs or specific services provided in such models. Young PWID are an important subpopulation in India, as they bear a disproportionate burden of new HIV infections because of greater risk and evidence of lower receipt of HIV testing and harm reduction services compared to older PWID. In this comment, we offer insights specific to young PWID drawn from multiple quantitative and qualitative studies examining the reach and effectiveness of ICCs, which may provide generalizable insights into limitations of services for young PWID more broadly in India and globally.

Findings Our studies suggest that while ICCs have expanded service availability, particularly in cities with emerging injection drug use epidemics, population-level reach to foster initial engagement among young PWID can be optimized. Additionally, young PWID who do engage with ICCs experience gaps in substance use treatment receipt and retention, and experience barriers to receipt of ICC services that are distinct from those experienced by older PWID. Notably, HIV incidence among ICC clients is concentrated in young PWID. Finally, ICCs were not intended to reach adolescent PWID, and new services are needed for this subpopulation.

Conclusions In addition to co-locating services, iterative optimization of models such as ICCs should incorporate youth-specific differentiated interventions and be accompanied by policy changes that are critical to improving the reach and effectiveness of harm reduction and HIV services among young PWID in India.

Keywords Young people who inject drugs, India, Harm reduction, HIV, Single-venue services, Low-and middle-income countries, Engagement

†Lakshmi Ganapathi and Aylur K. Srikrishnan have contributed equally.

*Correspondence:
Lakshmi Ganapathi
lganapathi@mgh.harvard.edu
Full list of author information is available at the end of the article

Background

Injection drug use in India is primarily driven by the injection of opioids. With 2.1% of the population using opioids (translating to ~23 million), India has among the largest number of people who use opioids in the world [1, 2]. Opioid use (heroin, pharmaceutical opioids, opium and opium variants) is shaped by several geo-political and socio-economic factors [3–5]. Historically, opioid use has been endemic for several decades in the Northeast states given their proximity to the "golden triangle" countries of heroin production in Southeast Asia [6]. More recently, the Northwest states have also become destinations and intermediary routes of heroin trafficking from countries in Central Asia [2]. Additionally, diversion of pharmaceutical opioids within India occurs in the context of a thriving pharmaceutical industry and poor regulation of pharmacies [7]. In the last two decades, this has partly led to rapidly expanding injection drug use epidemics with pharmaceutical opioids contributing to HIV and hepatitis C epidemics in multiple states in the North/Central regions of India [8–11].

Public sector substance use treatment, harm reduction and HIV services for people who inject drugs (PWID) have been scaled up over three decades in India under the auspices of the National AIDS Control Organization [12]. Medications for opioid use disorder (known as "opioid substitution therapy" or OST in India—nomenclature that is retained in this commentary), needle and syringe exchange, condoms, HIV testing and antiretroviral therapy (ART) are provided free of cost [13]. These services are provided by way of a collaborative model between government hospitals (which provide inpatient treatment, outpatient OST medications, HIV testing and ART), and non-governmental organizations (NGO) which provide OST at various community locations, and run "targeted intervention" programs (i.e., programs that provide needle and syringe exchange, condoms, and undertake outreach and follow-up of key populations in India) [12, 14–16]. Most OST centers provide buprenorphine, while buprenorphine-naloxone and methadone are available in select locations [17]. While the government hospital-NGO model has facilitated the scale up of services, limitations include the fragmentation of services between multiple physical locations. Additionally, there continues to be a dearth in the availability of services particularly in cities in the North/Central region with emerging injection drug use epidemics [18, 19].

National surveys have provided some size estimates of young PWID—defined here as those ≤29 years of age. The National Integrated Biobehavioral Surveillance (NIBBS) last conducted between 2014 and 2015—one of the largest national surveys across key populations (i.e., sex workers, men who have sex with men and PWID)—has provided estimates of HIV and related behavioral risk among PWID [20]. Among 19,902 PWID surveyed across 29 states in the NIBBS, at least half were young PWID ≤29 years of age [20]. In a separate contemporaneous cross-sectional survey our group conducted among 14,481 PWID across 15 Indian cities in 2013, the median age was 29 years and 30 years in the Northeast and North/Central cities, respectively (i.e., at least half were young people) [10]. In both the NIBBS and our 2013 cross-sectional survey [10, 20], the low median age of injection initiation at 19 years points to at least half of PWID initiating injection as adolescents. Additionally, a more recent 2018 national household survey has estimated that approximately 1.8% of adolescents (i.e., those between the ages of 10–17 years) use opioids [1].

There is limited age-disaggregated contemporary data on the engagement and retention of young people who use opioids (regardless of route) in harm reduction and HIV services in India. Available data are mainly restricted to those who report injection, although age-disaggregated data on the burden of HIV and Hepatitis C in this population is also sparse. In our 2013 cross-sectional survey, nearly 70% of young PWID had never participated in needle/syringe services programs, while 83% had never received OST [21]. Additionally, approximately 60% had never received HIV testing [21]. These gaps in receipt of harm reduction services among young PWID are particularly significant given data on risk behaviors and HIV incidence in this population. Studies in India note significantly greater needle-sharing and unprotected sex among young PWID compared to older PWID [21–23]. While the NIBBS does not routinely provide age-disaggregated data on HIV burden, in our 2013 cross-sectional survey, annual HIV incidence was highest (~5%) among young PWID in the North/Central cities with emerging opioid injection epidemics [21].

Beginning in 2014, in a public–private partnership with the National AIDS Control Organization (NACO), State AIDS Control Societies and Johns Hopkins University, the NGO Y.R. Gaitonde Centre for AIDS Research and Education established "Integrated Care Centers" (ICCs) across 8 cities in India [24]. ICCs were designed to simultaneously address the relative paucity of services for PWID in cities with rapidly burgeoning injection drug use and HIV and hepatis C epidemics, and barriers to care due to fragmentation of services in existing service delivery models. In line with the World Health Organization's (WHO) consolidated guidelines to provide comprehensive care to members of key populations [25], each ICC was designed to provide single-venue or "one-stop" co-located services free of cost. These services include OST (primarily buprenorphine; one ICC also provides methadone), HIV and hepatitis C testing, ART

and hepatitis C treatment either on-site or by linkage to government hospitals, field-based needle and syringe exchange, condoms, tuberculosis screening, and counseling. The following ICCs are currently in operation: Three in the Northeast cities of Aizawl (Mizoram State), Churachandpur (Manipur State), and Dimapur (Nagaland State) and five in the North/Central cities of Ludhiana and Amritsar (Punjab State), Bilaspur (Chhattisgarh State), Kanpur (Uttar Pradesh State), and New Delhi. Except for the ICCs in the Northeast cities which are located within NGOs, all other ICCs are located within government hospitals or other facilities. PWID client visits and services received, including daily observed OST [17], are captured via a biometric linked ID, providing an accurate mechanism to track service utilization over time. In all states, Indian consent laws dictate that adolescents < 18 years of age require parental consent for OST receipt as well as receipt of HIV and hepatitis C testing, and ART.

In India, ICCs have been highly successful in providing services to more than 23,000 new PWID clients since they were established, testing nearly 20,000 of these new clients for HIV at least once. However, given the enormous need for co-located comprehensive services, the initial design of ICCs was not tailored to any specific sub-population of PWID, including young PWID, but rather premised on integration of services as a mechanism to engage PWID more broadly. A major strength of ICCs is that they have integrated, systematic, high quality data collection embedded in service delivery which provides a unique opportunity to understand engagement in services in an age-disaggregated manner. A series of analyses we have conducted examining various aspects of service delivery at ICCs, including the reach and effectiveness of this model, have illuminated key insights specific to young PWID, which we summarize in this comment. A summary of the previous published analyses that inform this comment is provided in Table 1. The goal of this commentary is not to highlight challenges within ICCs alone but rather to provide more generalizable insights that may be relevant to service delivery to young PWID more broadly across India and globally. In general, there are few studies in low- and middle-income country (LMIC) settings that interrogate how well young PWID in particular engage with single-venue service delivery, and with specific services provided via such models. Yet, the global incidence of HIV is concentrated in young people, including young PWID [26], and substance use harms disproportionately impact young people [27, 28]. Engaging young people in health services is therefore a key programmatic goal of national and international agencies. As the WHO-endorsed single-venue service delivery model for PWID is established and expanded in LMIC settings, including India, the insights provided here can inform program delivery and additional interventions tailored to young people.

Key insights

ICCs can be optimized to achieve population-level reach among young PWID

In 2017, we completed a cluster-randomized trial [24]—including six ICCs that were intervention sites in comparison to six other sites (without ICCs) providing usual care—to evaluate the effectiveness of the ICC service delivery model on increasing HIV testing as well as changes in risk behaviors, HIV care continuum outcomes, and HIV incidence among adult PWID and men who have sex with men. These outcomes were evaluated at the individual and population levels. In 2 years, ICCs provided testing to 10,757 unduplicated PWID clients (5407 who were young PWID) [24]. At an individual level, PWID who had visited an ICC had significantly higher rates of recent HIV testing, and lower rates of injection-related and sexual risk behaviors and were more likely to be aware of their status and to be taking ART (among HIV-positive individuals) compared to PWID who had not visited an ICC. However, at a population level, there was a nonsignificant increase in HIV testing in the PWID populations at the sites where ICCs were established compared with usual care sites.

While several factors likely contributed to these findings, most prominently the limited number of ICC sites, another potential contributing factor may have been that young PWID (among whom risk and HIV incidence is concentrated) were not sufficiently engaging with the ICC model [29]. In a post-hoc analysis, we found that the median age of PWID who sought services at ICCs was between 26 and 35 years, and this was higher than the median age of PWID in the ICC cities according to responding-driven sampling surveys [29]. This observation is consistent with other large "HIV test and treat" trials in other LMIC, which similarly did not translate to reduction in population HIV incidence, in part due to the limited reach of services among young people in these trials [30].

As the goal of the National AIDS Control Program in India is for service delivery to translate into population-level outcomes, these findings underscore the need for several additional strategies. First, obtaining accurate size estimates of PWID populations, including young PWID subpopulations, when establishing single-venue services can inform scale up of services in a manner that impacts both reach as well as effectiveness. Additionally, augmented approaches are needed to find and link young PWID to single-venue services such as ICCs.

Table 1 Summary of studies that provide insights on engagement of young people who inject drugs with Integrated Care Centers in India

Study	Citation	Total number of PWID	Number of young PWID (18–29 years)	Number of adolescent PWID (10–17 years)	Type of analysis	Primary/subgroup analysis specific to young PWID (18–29 years)
Integrated HIV testing, prevention, and treatment intervention for key populations in India: a cluster-randomised trial	*Lancet HIV*. 2019;6(5):e283–e296	10,757	5407	None	Primary analysis of Integrated Care Center longitudinal visit data from all PWID clients	No
		11,745	5854	None	Primary analysis of cross-sectional data collected using respondent-driven sampling	
Buprenorphine treatment receipt characteristics and retention among people who inject drugs at Integrated Care Centers in India	*Drug Alcohol Depend*. 2023;246:109839	1312	786	4 (excluded from analysis)	Primary analysis of Integrated Care Center longitudinal visit data from all PWID clients	No
Poor Engagement in Substance Use Treatment and HIV services among Young People who inject Drugs in India	*International Society of Addiction Medicine Global Congress*. November 19–21, 2021	–	786	4 (excluded from analysis)	Sub-group analysis of Integrated Care Center longitudinal visit data from young PWID	Yes
Young and invisible: a qualitative study of service engagement by people who inject drugs in India	BMJ Open. 2021;11(9):e047350	43	33	None	Qualitative analysis of primary data from young PWID	Yes*

* Perspectives of 10 PWID > 29 years not excluded given focus group format

Young PWID experience unique barriers that shape substance use treatment receipt and retention at ICCs

While ICCs offer an array of services, our prior studies have indicated that OST receipt is a primary reason for attendance among PWID [24]. As optimal treatment of opioid use disorders is foundational to health outcomes and overall well-being of PWID, we have scrutinized the opioid use treatment cascade to identify gaps in receipt of medications at ICCs [31]. A recent analysis using pre-pandemic 2018 data on buprenorphine initiation and retention at ICCs, stratified by region, has indicated that the median age at treatment initiation among PWID at Northeast ICCs and North/Central ICCs is 29 years and 27 years, respectively [31]. This suggests that among all PWID who newly initiate buprenorphine at ICCs, at least half are young PWID. In sub-group analysis of 786 young PWID who newly initiated buprenorphine at ICCs, we found 6-month retention to be comparable to global reports and prior studies in India, with 43% of PWID in Northeast ICCs and 66% in North/Central ICCs being retained in treatment [32]. However, our analysis also revealed significant treatment attrition beyond 6 months, as well as substantial gaps in treatment adherence. As daily observed buprenorphine receipt is the national policy in India, daily visits are a measure of treatment adherence. Utilizing daily visit data by way of biometric ID tracking, we found that only 38% of young PWID in the Northeast ICCs and 52% of young PWID in the North/Central ICCs received buprenorphine at a frequency of more than twice a week on average over the first 6 months [32]. Preliminary analysis examining OST engagement and other ICC service utilization among young PWID has suggested that those who are under-engaged in substance use treatment are also less likely to utilize other services such as receipt of regular HIV testing [32]. Formal analysis is underway to explore service utilization disparities at ICCs.

Qualitative exploration of the diverse barriers PWID experience for OST initiation, regular receipt of medications and retention in treatment has offered a greater understanding of the opioid use treatment gaps at ICCs [33]. Importantly, it has also shed light on barriers that are unique to young PWID. For example, some structural barriers, including the need for daily attendance to receive buprenorphine, challenges with travel, and ICC hours of operation that are incompatible with work and school schedules, are experienced by PWID across all age groups. Similarly, psychosocial facilitators, such as family support, enable substance use treatment engagement for all PWID. At the same time, young PWID experience challenges that are distinct from older PWID. These include developmental and psychosocial vulnerabilities such as lower risk perception and consequently a diminished perception of the need for services (particularly in the early stages of injection drug use), greater need for adult support, and greater susceptibility to social pressures and stigma [33]. These findings support the development and implementation of differentiated interventions that identify vulnerabilities and better match supports to facilitate substance use treatment engagement (and broadly uptake of other services) among young PWID at ICCs. ICC data suggests that the although the majority (~80%) of young PWID do not have HIV at initial registration, HIV incidence in this group is not only high but also significantly higher than older PWID [34] (Fig. 1). While improving substance use treatment engagement is important for all PWID, positively shaping this engagement early via differentiated and individualized care approaches is an even more urgent HIV preventive strategy for young PWID.

Health services designed for adolescents (defined as those between ages 10–17 years in our setting) who inject drugs are limited

ICCs and many other public sector outpatient services for PWID across India only have a mandate to address the needs of adults (defined as those ≥18 years of age in our setting), who comprise most PWID. In the absence of easily accessible outpatient services like ICCs, adolescents often have to access care for opioid use disorder at tertiary hospitals or selected public sector inpatient facilities [35, 36]. In general, adolescents face several structural barriers to receiving services for injection drug use. These barriers include the need to disclose substance use to parents or other caregivers in order to receive services (due to parental consent laws), fear of loss of confidentiality, the need to access services in settings perceived to be overly "medicalized", and the stigma of being seen with older PWID at sites where adults also receive care [33]. As such, despite national data [10, 20] suggesting that a substantial proportion of PWID in India initiate injection as adolescents, among PWID, adolescents remain one of the most underserved groups. Additionally, ongoing injection is a criterion for receipt of OST at ICCs and public sector OST centers. This precludes the provision of OST for people with non-injection opioid use disorders at these venues (who are generally referred to other programs, including programs run under the auspices of the Ministry of Social Justice and Empowerment). Studies in India indicate that most adolescents who initiate injection have used opioids via other non-injection routes and experience opioid use disorders much earlier in the injection continuum (i.e., prior to injection initiation) [33, 37–39]. Negative experiences at "detoxification only" inpatient programs, the paucity of outpatient services, including provision of medications for adolescents

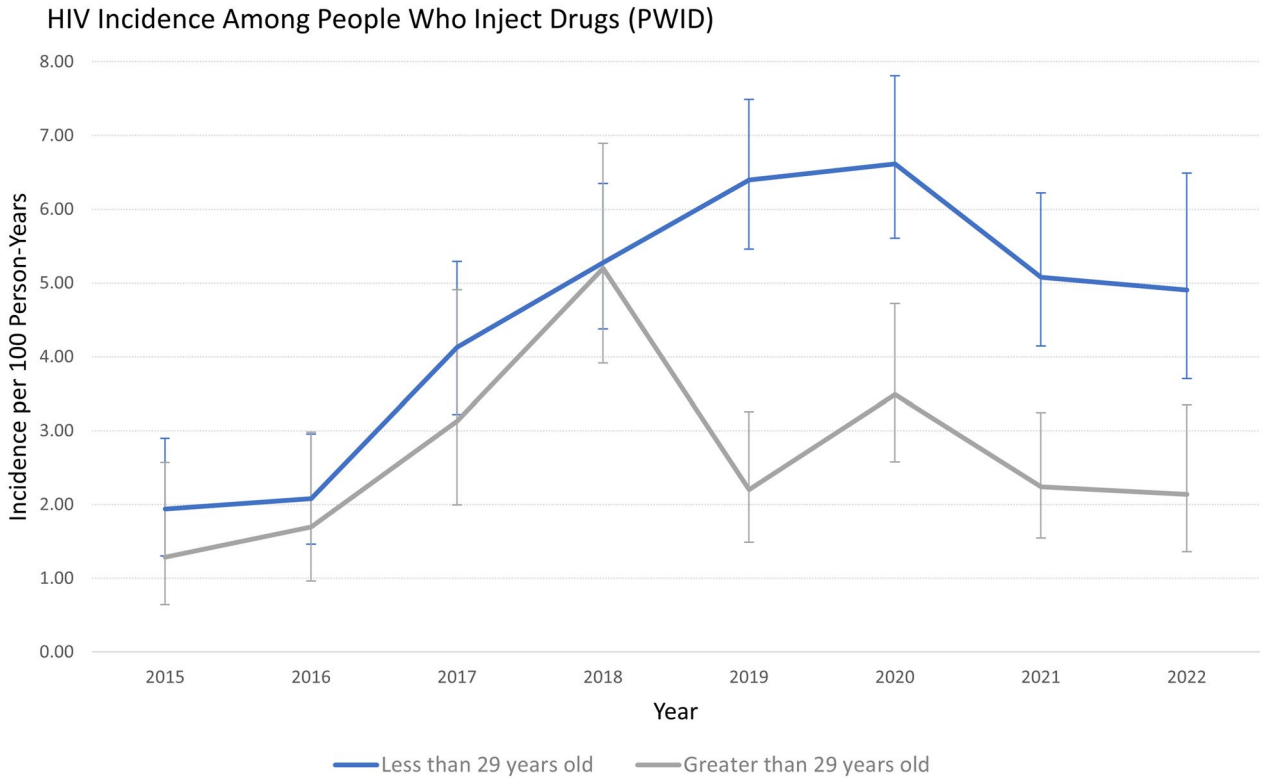

Fig. 1 Annual HIV incidence among people who inject drugs (PWID) at Integrated Care Centers is higher among young PWID compared to older PWID. Similar to methods in McFall et al. [34], client HIV testing data (N = 7779 across 8 ICCs) were included in the analysis if they had ≥ 2 tests at the ICC and were not positive on the first test. Person-time was accrued between HIV test dates with an exception for those with a positive result, for whom the seroconversion date was estimated as the midpoint between the last negative and first positive test and person-time was calculated accordingly. Annual HIV incidence rates per 100 person-years and corresponding 95% confidence intervals were calculated using Stata 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC)

with non-injection opioid use disorders at easily accessible venues like ICCs, have also emerged as key barriers and gaps in the provision of services to adolescents [33].

Future directions

Taken together, these key insights highlight areas in need of further inquiry in India and other similar settings.

First, the premise of single-venue service delivery models such as ICCs is that integrating services facilitates engagement by minimizing barriers for PWID. Several studies evaluating integrated service delivery models for PWID in both high income and LMIC countries provide evidence for improved health outcomes broadly among PWID who have access to such models [40–44]. Indeed, ICCs have been successful in expanding access to comprehensive health services for PWID broadly in Indian cities. However, given data on persistent age-related disparities in outcomes, such as the disproportionate burden of HIV incidence among young PWID, additional exploration is needed on the types of youth-tailored differentiated interventions and integrated care approaches that can be nested within co-located service delivery models. In ICCs, as young PWID experience various barriers to engagement and retention in services, multi-pronged interventions must address the unique vulnerabilities and needs of the young PWID. For example, family-centered psychosocial interventions have been found to be effective in reducing substance use and improving engagement in substance use treatment and other health services among young people who use substances, as they strengthen protective factors by improving family functioning and addressing the developmental need for adult support [45–47]. However, many of these interventions have primarily been developed, studied, and implemented in high income countries. In order to be feasibly implemented in high client volume, low resource contexts, incorporating such interventions into routine service delivery by lay counselors, for example, could be one way to offer differentiated care for young PWID at ICCs in LMIC.

Second, service delivery models such as ICCs by and large have relied on existing physical "brick and mortar"

facilities, with several ICCs located within government hospitals. While young PWID do engage with facility-based services and this facilitates access and referrals to other higher-level services, adolescent PWID in particular may perceive facility-based services as overly "medicalized" and primarily for "older people" and therefore less appealing. If the intent is to engage young PWID, including adolescents, then physical venues designed solely for adolescents and young adults may circumvent some barriers, including the stigma associated with receiving services at venues where older people who use and inject drugs also receive services. Youth-friendly physical venues have demonstrated success in facilitating engagement and improving HIV and substance use care continuum outcomes across a variety of settings, including in LMIC [48–50]. Youth-dedicated models of care for young PWID, including programs developed and housed in tertiary healthcare centers and that address health broadly by integrating primary care with substance use and HIV services, may be particularly effective [51]. Community-based models developed for, by, and with youth have also demonstrated success, particularly in engaging street-involved and other hard to reach young PWID [52]. Notably, by offering services and interventions that address structural and social determinants of health, these community-based programs leverage "non-health" entry points (e.g., ameliorating food and housing insecurity, facilitating education and employment re-entry) to engage young PWID in an array of health services [52]. Such models may be particularly attractive and less threatening to young PWID, as they do not solely rest on a "medical model" and address foundational needs that play a significant role in shaping health outcomes. While some of these principles have also been applied under India's National Adolescent Health Programme [53], wherein adolescent-friendly clinics that are designed to offer confidential health services have been established, evaluation of these clinics has in general showed poor attendance by adolescents [54, 55]. Additionally, little is known about whether and how well young PWID engage with these clinics, as key services such as OST and HIV testing and treatment are not provided within these clinics and can only be accessed through referrals to government-designated OST and HIV counseling and testing centers and ART programs. Stand-alone models of care for substance-using adolescents that both address broader social structural determinants of health and provide evidence-based substance use treatment (including medications for opioid use disorders) to those who are opioid-dependent but are yet to initiate injection offer opportunities for early intervention, and potentially prevention of injection initiation. Providing newer modalities including long-acting HIV pre-exposure prophylaxis and long-acting ART to young PWID in tandem with substance use treatment and harm reduction services (in stand-alone models or within existing services) also hold significant potential for HIV prevention and transmission reduction in this population.

Third, given the limitations of facility-based services in achieving reach among young PWID, decentralization of these services away from physical venues needs to be a key implementation consideration. We need a greater understanding of the social spatial networks of young PWID in India, with the goal of bringing services to where young people naturally gather. Mobile services (e.g., through the use of outreach vans), for example, have expanded the reach of harm reduction services and access to substance use treatment among PWID in underserved settings in high income countries [56–59]. The substance use treatment gap is particularly exacerbated in rural regions of both high income and LMIC settings [60–63]. Specific to India, there is a dearth of government OST centers, including in rural regions and cities with rising opioid injection [64]. While existing targeted intervention programs do provide some decentralized services such as field-based distribution of clean needles, mapping hotspots where young PWID congregate and delivering an array of integrated mobile services could be one strategy to address access gaps as well as reach the most vulnerable young PWID who are less likely to engage with facility-based services. Some early models of mobile methadone dispensing vans in urban cities in India have led to a greater number of PWID accessing these services, as well as improved retention in substance use treatment [65]. Mobile health interventions that leverage mobile phones and virtual online platforms have also demonstrated ability to reach and increase uptake of HIV services among other hard to reach populations in India (such as men who have sex with men and transgender individuals) [66]. Mobile phone, including smart phone ownership, has increased considerably in India [67]. Recent studies indicate interest among PWID to receive mobile phone-based support for substance use treatment and other services [68]. Additional research is needed on how best to tailor mobile health interventions to young PWID.

Fourth, adolescence represents a developmental stage where in general there is greater sensitivity to peers [69]. Prior studies in India, consistent with global literature, indicate that peers significantly influence injection initiation, continued substance use, and receipt of harm reduction services among young PWID [33, 38, 70]. Peer-delivered interventions that leverage strengths of social networks have been utilized to find and link PWID to services and support recovery in many settings [71–75]. Specific to ICCs, social network strategies such as

respondent driven sampling methods have been successful in finding and linking PWID to ICCs in our studies [76–78]. Peer educators and navigators are also embedded within ICCs. Developing and implementing youth-tailored peer-delivered interventions, and optimizing respondent driven sampling methods for adolescent PWID are strategies that hold potential to find and link young PWID, including adolescents.

Finally, service delivery models for PWID—be they single-venue models such as ICCs, or other models—cannot achieve reach or sustained engagement among young PWID in India without a paradigm change in approaches to the design of services, as well as changes in national policies that significantly impact the receipt of services among adolescents specifically. We propose the following crucial shifts: first, the perspectives of young PWID in general are under-represented in the design and implementation of services. Inclusion of young PWID, including adolescents, in national technical advisory groups is one way to ameliorate this gap. Second, a pathway for adolescent PWID to not only receive services but also participate in research cannot be forged without liberalization of consent laws—specifically, lowering age of consent or eliminating parental consent requirements for adolescents to receive HIV and harm reduction services, as has been done in countries in sub-Saharan Africa, Southeast Asia and other LMIC [79–84]. Such a pathway is needed to better delineate the needs and elevate the voices of adolescents to inform the design of services and early interventions. Third, the entry point to substance use treatment often begins with initial engagement with other services (e.g., HIV testing). Significantly lowering the thresholds for this initial engagement among adolescent PWID by lowering age of consent or eliminating parental consent requirements, also facilitates trust and the establishment of longer-term care, which in turn offers opportunities for the eventual inclusion of family members in care.

Conclusions

In the context of burgeoning opioid injection and overlapping HIV and hepatitis C epidemics in multiple cities across India, ICCs have had considerable success in greatly expanding service availability and convenience for PWID in India. However, analyses of ICC data reveal that young PWID bear a disproportionate impact of these simultaneous epidemics, while also experiencing unique barriers in accessing services. These challenges revealed by the ICC data provide key insights that likely apply to other care models for PWID in India and globally. Given these challenges, there is an urgent need to not only iteratively optimize service delivery models like ICCs, but also to develop new service delivery models to better engage young PWID, especially adolescents. These investments should be of high priority as they have the potential to yield lasting benefits across the life-course of PWID in India and other similar settings.

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LG and AKS conceived the study with support from AMM, MPG, MSK, GML, SHM, and SSS; AMM and MPG analyzed the data included in this study. LG drafted the manuscript. MPG prepared Fig. 1. AKS, AMM, MPG, MSK, GML, SHM, and SSS provided key edits to the manuscript.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

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Not applicable.

Consent for publication
Not applicable.

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Author details
[1]Division of Pediatric Global Health, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA. [2]Division of Pediatric Infectious Diseases, Massachusetts General Hospital for Children, 55 Fruit Street, Boston, MA 02114, USA. [3]Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA. [4]Y.R. Gaitonde Centre for AIDS Research and Education, No. 34, East Street, Kilpauk Garden Colony, Chennai, Tamil Nadu 600010, India. [5]Department of Epidemiology, The Johns Hopkins Bloomberg School of Public Health, 733 N Broadway, Baltimore, MD 21205, USA. [6]Psymed Hospital, 49 Harrington Road, Chetpet, Chennai, Tamil Nadu 600031, India. [7]Division of Infectious Diseases, The Johns Hopkins University School of Medicine, 733 N Broadway, Baltimore, MD 21205, USA.

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