Evaluation of Multiple Interventions to Improve HIV Treatment Outcomes Among People Who Inject Drugs in India: a Randomized Factorial Trial With a Randomized Adaptive Component for Those Experiencing Early Treatment Failure

PWID Opportunities to Improve TrEat and Retain (POINTER)

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2. LIST OF ABBREVIATIONS

AE	Adverse Event
ART	Antiretroviral Therapy
CD4	Cluster of differentiation 4
CFIR	Consolidated Framework for Implementation Research
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FWA	Federalwide Assurance
GEE	Generalized estimating equations
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPTN 074	HIV Prevention Trials Network 074
ICC	Integrated Care Centre
ICF	Informed Consent Form
IDIs	In-depth interviews
INR	India Rupee
IRB	Institutional Review Board
JHM	Johns Hopkins Medicine
JHU	Johns Hopkins University
LMIC	Low- and Middle-Income Countries
MOP	Manual of Procedures
MOU	Memorandum of Understanding
MOUD	Medication for opioid use disorder
MSM	Men who have sex with men
NACO	National AIDS Control Organisation
NGO	Non-governmental organization
NIH	National Institutes of Health
OAT	Opioid Agonist Treatment
ORW	Outreach worker
PWH	People living with HIV
PWID	People who inject drugs
POC	Point of care
RDS	Respondent-driven sampling
RNA	Ribonucleic acid
SACS	State AIDS prevention and control societies
SSP	Syringe Services Program
STI	Sexually Transmitted Infection
TB	Tuberculosis
TDF	Tenofovir
TLD	Tenofovir disoproxil fumarate /lamivudine /dolutegravir
USD	United States Dollar
WHO	World Health Organization
YRGCARE	Y.R. Gaitonde Centre for AIDS Research and Education

3. PROTOCOL SUMMARY

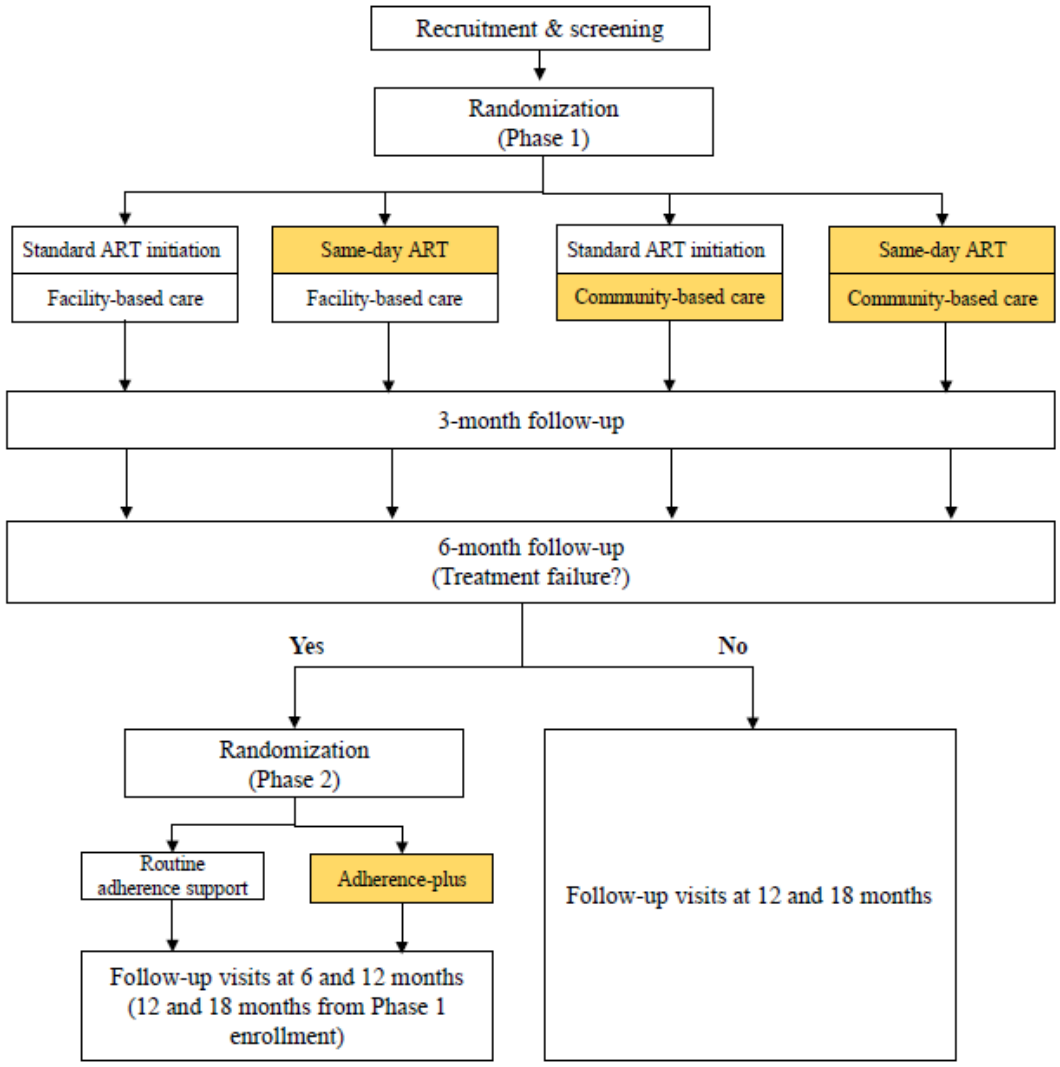
Full Title:	Evaluation of Multiple Interventions to Improve HIV Treatment Outcomes Among People Who Inject Drugs in India: a Randomized Factorial Trial With a Randomized Adaptive Component for Those Experiencing Early Treatment Failure
Short Title:	PWID Opportunities to Improve TrEat and Retain (POINTER)
Sample Size:	800
Study Population:	PWID living with HIV, 18 years or older, who are either ART-naive or defaulted from ART for greater than 60 days, and have HIV RNA of 1,000 c/mL or higher
Participating Sites:	YR Gaitonde Centre for AIDS Research and Education (YRGCARE), Chennai, Tamil Nadu, India
Study Design:	Non-blinded, randomized, factorial trial (phase-1) with a secondary adaptive randomization (phase-2), designed to assess the effectiveness of three interventions (relative to standard care) to increase viral suppression among PWID living with HIV in India
Study Duration:	The study will last 5 years. Research participants will be asked to complete screening plus 5 study visits (baseline, 3, 6, 12, and 18 months)
Study Regimen/ Intervention:	Three interventions will be implemented among participants treated with antiretroviral therapy (ART) for HIV. 1) Same-day ART initiation vs. standard ART initiation 2) Community-based care (integrated HIV and PWID care) vs. facility-based care (centralized government-based HIV care) 3) Adherence-plus: Enhanced adherence support for participants who experience treatment failure at 6 months (vs. routine adherence support)
Primary Objectives:	Phase-1 – To determine whether same-day ART initiation (compared with standard ART initiation) or whether community-based care (compared with facility-based care) increases the proportion of PWID living with HIV with viral suppression at 6 months. Phase-2 – To determine whether adherence-plus, compared with routine adherence support, increases the proportion with viral suppression at 6 months (12 months from beginning Phase I) among participants that

experience treatment failure at the end of phase-1.

Primary Endpoint: Phase-1: Viral suppression at 6 months.
Phase-2: Viral suppression 6 months following the second randomization (12 months from enrollment in phase-1)

Study Schema:

Figure 1. Study design



*Boxes with yellow highlight are the experimental arms

4. INTRODUCTION

People who inject drugs (PWID) are at high risk for HIV infection and experience worse antiretroviral therapy (ART) outcomes than other key populations, particularly in low- and middle-income countries (LMIC). India has the largest number of people who use opioids in the world, and new injection drug epidemics have emerged in the North and Central regions of the country. We will enroll people living with HIV who are 18 years of age or older who report recent injection drug use, are ART-naïve or who have defaulted from ART for greater than 60 days, and have HIV RNA of 1,000 c/mL or higher

In phase-1, we will evaluate two structural interventions to improve treatment outcomes among PWID living with HIV in India. First, same-day ART (initiating ART on the day of HIV diagnosis/confirmation rather than waiting until standard evaluations are completed in an HIV clinic), was found to increase 12-month viral suppression rates in three African studies but has not been evaluated in PWID. The second intervention is community-based care. At present, all publicly financed HIV treatment is provided at centralized government ART centers (facility-based care). In prior work, we found that PWID-centric integrated care centers (ICCs) were effective at engaging the population, increasing HIV testing uptake, and were rated favorably by clients in anonymous surveys. ICCs linked HIV-positive PWID to facility-based care at government clinics, but did not provide on-site ART. However, ICCs can be scaled-up to provide ART on-site (community-based care) and we hypothesize this will improve initiation and retention to ART among PWID. We will use a randomized factorial design to determine the individual and joint effects of same-day ART and community-based care. The primary outcome of the phase-1 trial is viral suppression at 6 months, with longer term follow-up to 18 months.

In phase-2, we will evaluate a psychosocial/navigation intervention (adherence-plus) among participants who experience treatment failure during the first trial phase, defined as HIV RNA ≥1,000 c/mL at the 6-month visit. These participants will be randomly assigned (in a second randomization) to adherence-plus or routine adherence support. The primary outcome of phase-2 will be viral suppression 6 months following the second randomization (12 months from enrollment in phase-1).

4.1 Background Information

4.1.1 Injection drug use is a substantial and expanding problem in India

Located between the “Golden Triangle” and the “Golden Crescent”, the leading producers of opium globally, India has a large number of opioid users. By one estimate, there are 167,882 current opioid users in the state of Punjab alone.[1] In the northeast region of India, which borders Myanmar, injection drug use has been endemic since the 1970s and has always been the major driver of the HIV epidemic in this region. However, in recent years, there has been an epidemic of injection drug use in the north (bordering Pakistan) and central regions of India that has attracted news and political coverage.[2-4] In a community survey of adolescents and young adult men in a rural district of Punjab, 21% report past-year heroin use, with two-thirds of those reporting injection.[5] In 2017 we conducted systematic respondent-driven sampling (RDS) surveys of PWID in 12 Indian cities (~1000 per city). We found an average HIV prevalence of 20% and an average HIV incidence of 4.57 per 100 person-years.[6] These data highlight a growing epidemic of injection drug use in India with high HIV prevalence and incidence.

4.1.2 Poor treatment outcomes persist for PWID living with HIV

HIV care continuum outcomes are worse in PWID than in other key populations,[7,8] and this disparity appears to be larger in LMICs.[9-12] In a recent survey of 2,906 PWID living with HIV in 15 Indian cities, we found that only 41% were aware of their HIV-positive status, 31% were linked to ART, and 15% had a suppressed viral load.[13] There is no "quick-fix" to this challenge. This is illustrated by the fact that in three well-conducted clinical trials aimed at improving HIV treatment outcomes among PWID, no study arm achieved viral suppression above 50%.[14-16] Moreover, we presented data comparing progress along the HIV care continuum among men who have sex with men (MSM) and PWID in India between 2013 and 2017. We found that, over this 4-year period, MSM increased use of ART by 33 percentage points (95% CI: 15, 52) more than PWID did over the same period. Similarly, viral suppression rates increased 15 percentage points (95% CI: 0, 31) more among MSM than PWID over the observation period (CROI 2020). These data support the need to identify tiered approaches to improve treatment outcomes among PWID in India.

4.2 Rationale

4.2.1 Rationale for factorial randomized controlled trial in phase-1

We aim to simultaneously evaluate two potentially feasible and scalable interventions to improve treatment and retention outcomes among PWH who inject drugs. Under the assumption of no effect modification between the outcomes, a factorial design offers the potential to efficiently evaluate the main effects of more than one intervention.[17] We will assess interventions at different levels: policy (same-day ART) and structural (community-based care).

4.2.2 Rationale for adaptive, second randomization in phase-2

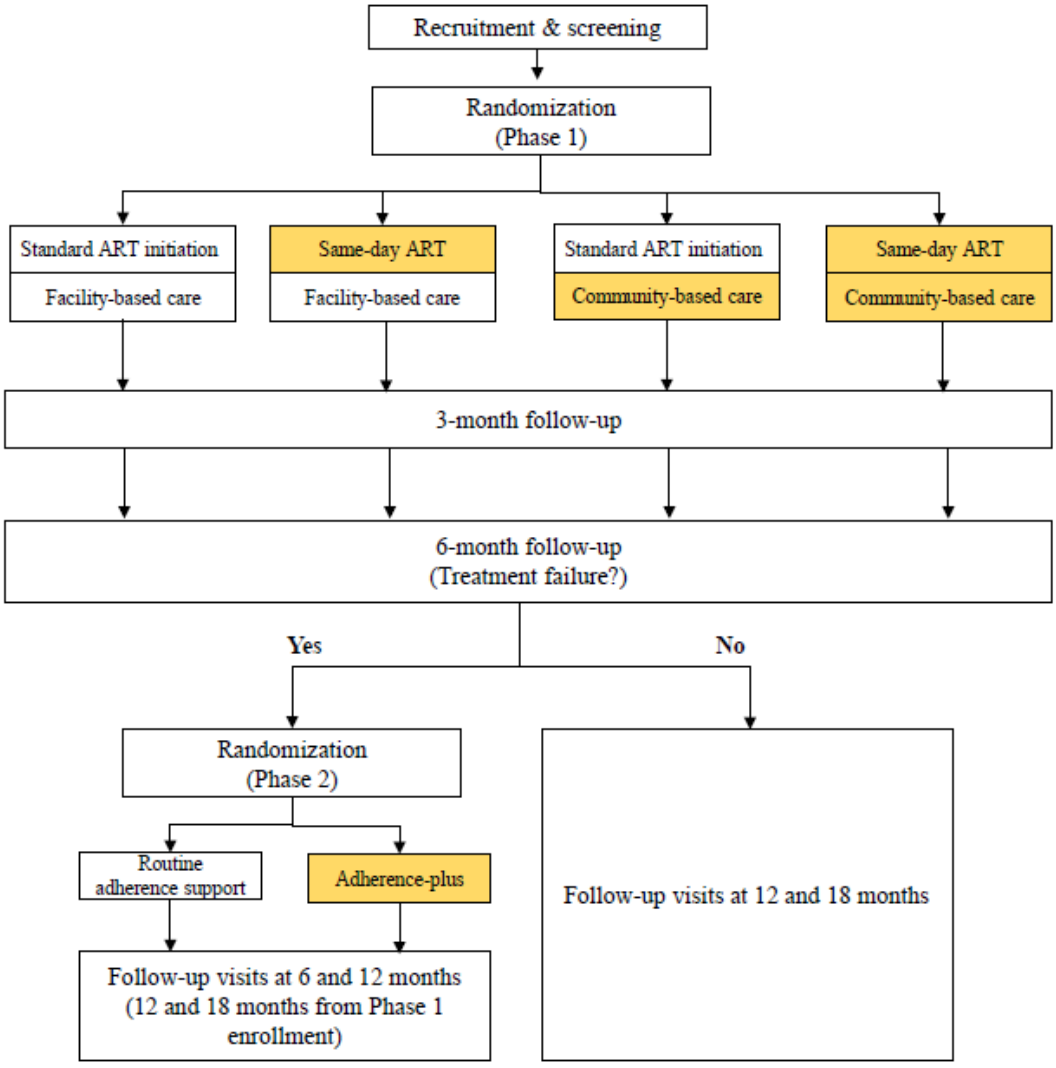
In phase-2, our objective is to use an adaptive trial design[18,19] to evaluate the effectiveness of the adherence-plus intervention among participants who experience treatment failure at 6 months of phase-1. Adherence-plus is a psychosocial/navigation intervention that addresses patient-level barriers and builds on prior work[14-16] and theories, including social cognitive and maintenance theories.[20,21] While the effectiveness of behavioral interventions for HIV treatment adherence have been mixed,[14-16,22,23] the HIV Prevention Trials Network (HPTN) 074 study demonstrated the effectiveness of a psychosocial/systems navigation intervention on HIV viral suppression and mortality among PWID living with HIV.[16] By virtue of our study design, we are asking a different question than was addressed in HPTN 074, where the intervention was evaluated up front. In the current trial, we are asking whether more selective use of the intervention, specifically only in those experiencing treatment failure in the short-term, can improve subsequent treatment outcomes compared with routine adherence support. This question is relevant because adherence-plus is relatively resource intensive with dedicated staff who must be trained and supervised. If the intervention is successful when tailored only to those experiencing difficulties, it may be more feasible to implement.

5. STUDY DESIGN

This is a non-blinded, randomized, factorial trial (phase-1) with a secondary adaptive randomization (phase-2), designed to assess the effectiveness of three interventions (relative to standard care) to increase viral suppression among PWID living with HIV in India.

In phase-1 of the trial, we will evaluate the individual and joint effectiveness of 2 interventions: i) same-day ART and ii) community-based care (orange boxes, **Figure 1**). Each intervention will be compared against standard of care in India, standard ART initiation and government facility-based HIV care, respectively. Following recruitment and screening, participants will be randomized in 1:1:1:1 ratio to 1 of 4 arms, in which they may receive neither intervention (double control), one intervention or the other, or both interventions. Participants experiencing virologic failure at the 6-month visit will undergo a second randomization to either adherence-plus or routine adherence support. Follow-up visits will be at 3, 6, 12, and 18 months.

Figure 1. Study design



*Boxes with yellow highlight are the experimental arms

6. STUDY POPULATION

The target population is PWH who inject drugs, are 18 years or older, and ART-naïve or have been off ART for a prolonged period.

6.1 Study Context and Selection of Study Cities

This study will be conducted in the context of PWID-focused epidemiological and implementation research in the study cities since 2013. This background work was funded by research grants from the US National Institutes of Health, Elton John AIDS Foundation and support from the National AIDS Control Organization (NACO), India.

Table 1. Survey data from PWID recruited by RDS in in 2017

Characteristic	Kanpur	New Delhi
Surveyed, n	999	999
Estimated PWID population size, n	18,537	10,448
Female, n	1	3
Age, median (IQR)	35 (28, 43)	32 (27, 38)
Injected in prior 6 months, %	94	98
Shared prior 6 months, %	33	44
HIV prevalence, %	21	38
HIV RNA >500 c/mL,%	91	95
HIV incidence, %	11.1	18.5

Our prior work includes robust epidemiologic assessments of PWID populations in 15 Indian cities. We found substantial city-to-city variability in HIV prevalence/incidence and in the care continuum among PWID living with HIV.[13,24] These background data allow us to select cities for the trial where injection drug use is on the rise,[2] HIV burden is high, and care continuum outcomes are poor. **Table 1** shows 2017 data from PWID in the proposed study cities. Percentages are weighted for respondent-driven sampling (RDS). The estimated PWID population sizes are based on a biometrically-based capture-recapture method.[25] HIV incidence was estimated using a validated multi-assay algorithm.[26]

6.2 Inclusion/Exclusion Criteria

6.2.1 Participant Inclusion Criteria

<u>Randomized factorial trial (phase-1)</u>
Inclusion criteria:

1. 18 years of age or older
2. Reports injection drug use in prior 24 months
3. Documented HIV positive status
4. Antiretroviral therapy status (a or b)
   a. Antiretroviral therapy naïve
      OR

b. Antiretroviral experienced, defaulted from care, and has not taken antiretroviral therapy in >60 days

5. HIV RNA ≥1,000 c/mL
6. If previously linked to HIV care, able and willing to provide government ART book for documentation of care received

Randomized adaptive trial (phase-2)
Inclusion criteria:

1. Enrolled in phase-1 trial
2. Experiences treatment failure (HIV RNA ≥1,000 c/mL) at 6 months

6.2.2 Participant Exclusion Criteria

Randomized factorial trial (phase-1)
Exclusion criteria:

1. Pregnant (if female)
2. Breastfeeding (if female)
3. Does not speak English, Hindi, or local language
4. Plans to migrate in next 12 months
5. Not competent to participate in the study or provide written informed consent

Randomized adaptive trial (phase-2)
Exclusion criteria:

Not applicable

6.3 Recruitment Process

Our research team has nearly 15 years of experience working with PWID in the target cities, which will facilitate study recruitment. We will meet with PWID groups, NGOs, State AIDS Control Societies, and other stakeholders to disseminate information about the trial to potential participants. Additionally, we will be in the process of completing respondent-driven sampling (RDS) surveys in the target cities. These are the third serial surveys in the target surveys. From prior surveys we learned that RDS surveys are effective in identifying PWID living with HIV who are either unaware of their status or have not engaged in HIV treatment. Finally, word-of-mouth referrals are an important component of recruitment efforts.

6.4 Participant Retention

Retention to follow-up is a challenge among PWID, and loss-to-follow-up is particularly challenging in New Delhi. Standard retention measures will be used to ensure that participants adhere to their study visits.

Detailed locator/contact information will be collected/updated in the electronic database at the time of enrollment, including information on mobile phone number, alternate phone numbers, home address, hangout locations (injection venues), and addresses and phone numbers of two to three contacts. Each client will be asked whether study staff may contact these individuals regarding appointment reminders.

For study visits, site coordinators will generate weekly reports to identify clients who are due for study visits over the next two weeks.

Once a visit is missed, outreach workers will make at least three attempts to contact participants using different approaches and different times of the day. The first attempt will be via their mobile phone (if provided). Additional attempts will include a visit to their home and/or other designated locations and/or contacts and hang out locations as needed. Outreach staff will continue to contact participants for up to one month after the missed study visit.

All tracking attempts (including the results of each attempt) will be recorded in the database.

Instances of migration (permanent or transient) will be documented.

Mortality rates are high in this population (PWID living with HIV) in India. Reports of participants' deaths will be investigated by outreach workers. Information on death and cause (via verbal autopsy) will be recorded where possible. Deaths will be considered verified if one of the following applies: i) hospital records or death certificate, ii) confirmation of death by a family member, or iii) confirmation of death from an eyewitness (usually another PWID). Reports of migration and incarceration will be noted, but we will continue to track these individuals.

7. INTERVENTIONS

7.1 Policy Intervention: Standard ART Initiation vs. Same-Day ART

Clinical trials conducted in Africa (2 clinic-based and 1 field-based) have found rapid (same-day) ART initiation to be associated with significant increases in 12-month viral suppression compared with standard ART initiation.[27-30] Subsequently, same-day ART initiation has been implemented in several African settings.[31,32] The same-day ART strategy is low cost and has the potential to integrate well with outreach methods to identify unlinked (unaware of status or out of care) PWID living with HIV. However, same-day ART has never been evaluated outside of Africa or among PWID.

In the standard ART initiation arm, participants will receive counseling and a referral card (either to facility-based or community-based care, according to randomization). A standard ART initiation protocol[33] will be used in both facility-based and community-based settings, namely a baseline visit (history, physical, and laboratory assessments) and typically one follow-up visit in 7-14 days with ART counseling and initiation. Universal treatment (irrespective of CD4 count) is standard care across India.

In the same-day ART initiation arm, participants will receive the same counseling and referrals as the standard ART initiation arm, but in addition, staff will provide focused ART counseling and an informational pamphlet. The study clinician will conduct a health assessment to screen for any conditions that might affect management/selection of antiretroviral medication, specifically history of kidney disease, tuberculosis treatment/symptoms, or history of adverse reactions to antiretroviral drugs. We will use a modified SLATE II pre-ART screening approach.[34] Participants who have a positive screen will not be started on ART until medical evaluation is completed. Women will be tested for pregnancy and screened for breastfeeding at enrollment. Pregnancy and breastfeeding are exclusion criteria for the trial because specialist treatment and monitoring is required to ensure proper care of both the woman and child. Women who are pregnant or breastfeeding will be linked to a government ART center immediately for specialist care per national guidelines. After counseling, review of medical

history, and a physical exam, participants will be given a 30-day supply of ART and follow-up instructions (either at a government ART clinic [facility-based care] or to the community-based care site, per randomization). We will dispense the same antiretroviral medications and formulations for same-day ART initiation as are used in the government ART centers for first-line treatment. Currently, the regimen of dolutegravir-based therapy (combined with TDF and lamivudine) is the national standard in India, consistent with the World Health Organization (WHO) 2018 guidelines for first-line ART.

7.2 Structural Intervention: Facility-Based Care vs. Community-Based Care

7.2.1 Overview of history with integrated care centers

In a recently completed cluster-randomized trial, we developed and evaluated PWID-focused integrated care centers (ICCs) that co-located HIV testing, counseling, and linkage to care with key PWID risk-reduction services (MOUD and SSP). These centers were not equipped to provide ART directly as the National AIDS Control Organisation (NACO) in India has historically followed a strictly centralized model for providing free ART in the public sector. However, NACO is explicitly exploring decentralized/differentiated care models for HIV, given its assessment that current ART facilities are "overloaded and understaffed."[35] Our ongoing experience with ICCs, suggests they can be scaled to provide and monitor first-line ART for PWID. We hypothesize that greater accessibility in a PWID-focused setting care will lead to higher linkage and retention to ART in the community-based vs. the facility-based model. This is supported by favorable ICC client satisfaction data.[6]

7.2.2 Assisted linkage to care in the two study arms

After randomization, in both arms, an outreach worker will be offered to support each participant. Outreach workers will have the goal of linking participants to care, defined as being assigned a medical ID number. Outreach workers will accompany participants to their assigned treatment sites and assist them in getting a verified HIV-positive test result (if needed). The goal of providing linkage assistance in both arms is to prevent minor administrative barriers from interfering with linkage in either arm. Outreach workers will assist with linkage for a maximum of 15 days.

7.2.3 Facility-based care arm

Study staff will refer participants assigned to facility-based care to government ART centers, which are managed and supplied by NACO. Clients with a documented HIV positive status can walk-in to any government ART facility and register for care. At the registration visit, a history and a physical exam (including screening for TB/STIs) are conducted by a physician, and a blood sample is drawn for baseline laboratories (CD4 cell count, chemistry panel, hemogram, hepatitis B surface antigen). Patients are typically asked to return to clinic in 1-2 weeks to review laboratory results, receive additional counseling, and (usually) initiate first-line ART. Following ART initiation, patients return to clinic in 2 weeks, followed by monthly ART refill visits thereafter. Longer ART dispensations (2- or 3-months) may be used for stable patients and these longer dispensations were used extensively during the COVID-19 pandemic.

7.2.4 Community-based care arm

Study staff will refer participants assigned to community-based care to an integrated care center (ICC). In each city we will scale-up an existing ICC to enable independent ART management. We established the ICC model for PWID in 2013 and have maintained them in multiple cities with funding/support from NIH (research), NACO (HIV testing supplies, staffing and medication for opioid use disorder (MOUD), SSP supplies, etc.) and the Elton John AIDS Foundation (charity). ICCs routinely provide HIV and HCV testing, counseling services (substance abuse, depression, adherence to HIV care, etc.), STI and TB screening and referrals, MOUD (mostly buprenorphine), and clean needles/syringes provided by outreach workers. Currently ICCs are staffed by i) a site coordinator (record keeping, staff oversight), ii) a counselor, iii) a nurse (additional nurses are provided by the government solely for MOUD management), iv) a phlebotomist, and v) outreach workers. To scale-up ICCs for ART management we will hire a part-time physician with ART experience/training in each ICC. We will establish a supply chain for ART with the assistance of government ART centers. ART will be stored with buprenorphine and STI treatment packs in secure double-locked storage facilities. The scaled-up ICCs will provide HIV care that is consistent with Indian guidelines and treatment provided in the government sector.[33] ICCs will use the same HIV and routine adherence counseling materials , HIV record-keeping forms, and clinical and laboratory monitoring protocols. ICCs will stock first-line antiretroviral therapy and first-line alternate therapy. Currently, the single-pill regimen that is universally used as first-line treatment in LMICs is dolutegravir /tenofovir disoproxil fumarate /lamivudine. In the government sector standard laboratory monitoring includes kidney and liver function tests, a hemogram, CD4 testing, and viral load testing every 6 to 12 months, depending on patient stability.

The community-based clinics will follow standard Indian practices for prevention of HIV-associated conditions. Participants will initiate daily cotrimoxazole preventive therapy (CPT) for prevention of Pneumocystis jirovecii and bacterial infections. Participants will be eligible for CPT, in conjunction with ART, if they have WHO stage 3 or 4 disease, or have a CD4 cell count <350 cells/mm^3 at presentation. CPT may be discontinued when participants are clinically well and have two consecutive CD4 cell count >350 cells/mm^3 (separated by at least 6 months). Isoniazid preventive therapy (IPT) is used in people living with HIV to reduce the risk of TB. Daily IPT is generally started 3 months after ART initiation if a chest X-ray is clear and the participant does not have 4S symptoms. IPT is given for 6 months and then discontinued. Clinic physicians will refer participants with serious symptoms to government hospitals for emergency-level care. If government practice changes during the trial period, community-based care will revise treatment protocols to match standard care. Community-based care clinics will refer participants who meet criteria for second-line (generally protease inhibitor-based regimens) to government ART centers. We anticipate the such situations will be relatively rare because of the durability of dolutegravir-based treatment.[36] Participants randomized to the community-based care arm will be free to seek HIV care in the government or private sector.

7.3 Adaptive component (phase-2): routine adherence support vs. adherence-plus for those experiencing early treatment failure

In phase-2, participants who experience treatment failure (HIV RNA ≥1000 c/mL) at 6 months will undergo randomization to either routine adherence support (provided at their assigned site) or to the adherence-plus intervention (provided at the research site). Routine adherence support includes administering standardized adherence counseling at the clinic. The adherence-plus intervention includes two components: 1) navigation and 2) psychosocial support and counseling. These components may be provided by a single individual, but we anticipate that peer outreach workers will focus on tracking/outreach while trained counselors will provide the

psychosocial/navigation component. The objectives of adherence-plus are to educate, provide psychosocial support, and build skills needed for treatment independence. Counselors will seek to achieve these goals through a motivational interviewing (MI) (or strengths-based case management)[14,16] framework, in which participants are guided to identify internal motivations and strengths and apply them to HIV and substance use treatment. Counselors will have sufficient education and aptitude to learn MI methods and core information about HIV and its treatment, acquire a detailed knowledge of local PWID resources, and to accurately document services provided.

7.3.1 Protocol and components of adherence-plus

Adherence-plus will be a tailored intervention that will last a maximum of 6 months. Under the guidance of Prof. Carl Latkin, who led the development, piloting, and operationalization of the HPTN 074 psychosocial/navigation intervention,[16] we will assemble counselor training curricula and detailed scripts for content sessions. Counselors/navigators will conduct individual sessions with participants that cover topics relevant to PWID living with HIV (**Table 2**). The content for these sessions will be revised and further developed in a manual of procedures (MOP). At the end of the session the counselor will provide the participant with a mutually agreed upon action plan. We anticipate that sessions will be 30-45 minutes in duration, and sessions may be repeated. Field activity will be strongly emphasized in the intervention. The navigator function is to provide material support to remove barriers to care (e.g., assistance with transportation).

Facilitators will be used when participants attend scheduled counseling sessions. Potential facilitators include: clean syringes, bleach packets, condoms, bus passes to attend clinics, mobile phone minutes, food supplements, and outreach worker (ORW) support attending medical or substance use appointments. We anticipate making adherence-plus flexible, so that attention may be reduced for people making progress and intensified for those continuing to have difficulties.

Table 2 Likely session components of adherence-plus intervention

Number / Session title	Description
1) Introduction to adherence-plus	Needs assessment (depression, substance abuse, sustenance needs, etc.); Social / geospatial assessment (social support network, where does s/he spend time); Client goals
2) HIV treatment – basics	Basics of HIV (not curable, highly treatable); HIV treatment – adherence, side-effect management, lifelong treatment; Meaning of CD4 and viral load
3) Drug and alcohol use	Inventory of drug and alcohol use, and resulting social harms; Motivation to change assessment; Treatment options; Successful HIV treatment with active substance abuse
4) Dyad counseling with supporter	Identify treatment supporter for dyad counseling; Risk reduction strategies; Strategies to support index in HIV treatment and OAT (if appropriate)
5) Injection- and sex-related risk reduction	Clean needles – SSP resources; Drug splitting strategies to minimize risk; Overdose; Safe sex; Discussing HIV status with sex partner; sex partner HIV testing; Role of effective HIV treatment in reducing transmission risk
6) Opioid agonist treatment	Experience with OAT or preconceptions about OAT; Stabilization; Chronic disease model of opioid use disorder
7) HIV treatment for the long run	Re-engaging in care after a lapse; Treatment continues even when you feel well; Strategies for remaining engaged; Side-effect management

7.3.2 Training, supervision, and fidelity monitoring

Navigators will complete a curriculum modeled after HPTN 074.[16] Training will include MI strategy, role-playing, and didactic instruction on HIV and substance use. It is anticipated that navigators will manage a patient load of no more than 15 at one time. Navigators will liaise with both government ART clinics (facility-based care) and ICCs (community-based care), according to participants' treatment assignments. Experienced counselors from YRGCARE will supervise the work of navigator /outreach worker teams and meet with them as a group monthly to discuss cases, challenges, and strategies. The supervisor will sit-in on a subset of counseling sessions and use a check-list to score the session. The supervisor will review the checklist with the counselor for quality control and fidelity.

8. STUDY PROCEDURES/EVALUATIONS

8.1 Schedule of Procedures/Evaluations

The schedule of follow-up visits and associated data collection is listed in **Table 3**. We will develop an electronic interviewer-administered survey that will capture information on demographics, risk assessment and adherence assessment. We will use standardized surveys that we have used among PWID in India since 2004. To maximize retention, we will capture and update detailed locator information at all study visits for tracking. At the enrollment visit, we will capture biometric data (either an iris scan and/or a fingerprint scan) to verify the identity of the participant. No biometric images will be stored – the images will be converted into unique hexadecimal codes, and these codes will be stored. At all subsequent visits, the biometric verification will be performed prior to initiation of visit procedures. We have used biometric tracking among PWID in India since 2013 and it is highly acceptable to participants.

Table 3. Schedule of monitoring events in factorial (phase 1), adaptive (phase 2) trial

	Screening	Enrollment	3 m	6 m	12 m	18 m
Oral screening consent	X					
Rapid HIV test (if needed)	X					
Pregnancy test (if female)	X					
Biometric duplicate check	X					
Biometric registration	X					
Screener questionnaire	X					
Biometric verification		X	X	X	X	X
Locator information		X	X	X	X	
Written informed consent		X				
Phase 1 randomization		X				
Study questionnaire		X	X	X	X	X
Demographics		X				
Drug & alcohol use		X	X	X	X	X
Risk behaviors		X	X	X	X	X
Depression PHQ-9		X	X	X	X	X
Quality of life		X	X	X	X	X
Harm reduction services		X	X	X	X	X
Social support		X	X	X	X	X
Stigma		X	X	X	X	X
Hepatitis B and C		X	X	X	X	X
Healthcare utilization		X	X	X	X	X
HIV care continuum		X	X	X	X	X
Adverse effects		X	X	X	X	X
Adherence		X	X	X	X	X
Self-efficacy		X	X	X	X	X
Phase 2 randomization			X			
HIV RNA	X		X	X	X	X
CD4 cell count	X					
Urine drug test	X		X	X	X	X
Blood storage		X	X	X	X	X
Interventions close out						X

9. SAFETY MONITORING

Safety monitoring is described in greater detail in the Data Safety and Monitoring Plan (DSMP). This trial also has a Data Safety Monitoring Board (DSMB), summarized in the DSMB Charter.

9.1 Trial management

This study will be coordinated by the YR Gaitonde Centre for AIDS Research and Education (YRGCARE) in Chennai, Tamil Nadu, India, with oversight from investigators at the Johns Hopkins Bloomberg School of Public Health and the Johns Hopkins School of Medicine. YRGCARE will oversee all day-to-day aspects of the trial including participant recruitment, data collection, laboratory testing, biological sample storage, and data management. YRGCARE was established in 1993 with joint missions in HIV service and research. Over the years, YRGCARE has also developed a broad research portfolio including clinical trials, cohort and cross-sectional studies related to the epidemiology, prevention and management of HIV disease.

Of relevance to the current proposal, YRGCARE has a proven track record of promoting change through public-private partnerships and has substantial prior experience with large randomized

trials. YRGCARE is a site for numerous multisite trials and is a clinical research site for AIDS Clinical Trials Group (ACTG). The proposed trial will be conducted in two cities in which we have documented large HIV epidemics among PWID and poor treatment outcomes:

- New Delhi, National Capitol Territory
- Kanpur, Uttar Pradesh

Study activities will take place at three locations in each city: a research site (for recruitment, screening, and data collection at study visits), a PWID-focused community-based care center (i.e., the ICC), and one or more government ART centers.

9.2 Data management

9.2.1 Recruitment and screening

Potential participants joining POINTER will come from several sources. It is expected that the majority of participants will be referred to POINTER via their participation in a respondent driven sampling (RDS) survey that is taking place in each site at the same time. Other potential participants will be referred from the local ICC, MOUD clinics, other NGOs, enrolled peers, local injecting venues/hotspots, and other sources.

Our group has previously shown that RDS surveys are an effective method to identify more difficult-to-reach populations and to identify PWID living with HIV who are unaware of their status or unlinked to care.

All participants screened for eligibility into POINTER will undergo the following procedures:

- COVID-19 pre-screen (if not completed already on same day)
- Oral consent
- Biometric registration
- Screening questionnaire
- Complete an HIV point of care (POC) rapid test (if needed to confirm HIV positive status),
- A POC HIV RNA test (GeneXpert) among persons with confirmed HIV positive status.
- Collect biometric data (fingerprint or iris scan) to prevent duplicate enrollment and for clinical trial tracking. The software converts images into 1024-digit alphanumeric codes that are encrypted with proprietary software into a unique identifier. The biometric scanning systems protect participant confidentiality because the images are not saved in the system and codes cannot be used to reconstruct fingerprint images.

9.2.2 Data collection for enrolled participants

Trial participants will be followed for up to 18 months and will be asked to complete a total of 5 study visits, including the entry visit. Table 1 shows the planned monitoring schedule.

The following data will be collected and stored:

- Written informed consent documents
- Survey modules
    - Demographics
    - Substance use (including alcohol)

    - Harm reduction service use
    - Drug-related and sexual risk behavior
    - Depressive symptoms
    - Social support
    - Stigma
    - Quality of life
    - Self-efficacy
    - Hepatitis C and B testing and medication
    - Healthcare utilization
    - HIV care continuum outcomes via verified medical record abstraction and self-report (e.g., experience with HIV testing, HIV care and HIV treatment)
- HIV test results
- HIV RNA test results (GeneXpert)
- Detailed contact and locator information
- CD4 count (in local laboratory)
- HIV resistance testing

9.2.3 Data entry methods

Data from the clinical trial cohort will be collected using tablets on which we will program an electronic data collection application. The survey will be downloaded onto the tablets with participant data routinely pushed to a secure web cloud server. The interviewer will read out the questions and enter the appropriate answers into the tablet in a private area. Logic checks and field restrictions will be built into the survey to maximize accuracy/integrity of data collected as there will be no paper copies of the survey. All interviewers will be adequately trained on the use of the tablets for capturing data prior to coming into contact with study participants.

The database management system will provide a confidential and secure database with accurate records. Data files will be maintained in two computer systems and routine backups conducted to protect against data loss. Laboratory data from the YRG CARE laboratory will be merged into the study database on a regular basis by study ID. The lab has a network server (HP E2000) and a backup tape device (SUREDAT) for storage of data. Data confidentiality will be maintained by storing signed consent forms in double-locked filing cabinets on-site at the research site and electronic data forms with personal identifiers will be available on the tablet for local research site staff but all identifiers will be removed before export to JHU. Data will be imported into Stata and R where further editing and checks will be performed prior to data analyses.

10. CLINICAL MANAGEMENT

10.1 Clinical Management of Adverse Events

The objective of community-based care is to provide first-line ART in a setting that welcomes PWID and provides other relevant services for them. Based on prior experience with this population we anticipate high rates of AEs and SAEs. The medical team will manage common health issues such as bandaging skin wounds, providing symptomatic treatment for diarrhea and upper respiratory tract infections, and evaluating fevers. Participants with confirmed or suspected TB will be referred to one of many TB diagnosis, treatment, and support resources,

managed by National TB Elimination Program (NTEP). Participants needing urgent care will be referred and accompanied to the nearest public sector hospital.

10.2 Pregnancy

Pregnant women are excluded from joining this study as they require specialized HIV management. Women who become pregnant while already enrolled in the study, will be referred to specialized government clinics for HIV treatment. In such cases, women may continue to be followed in the trial if they wish.

10.3 Treatment Failure

Treatment failure is defined in this protocol as HIV RNA ≥1000 c/mL. Participants experiencing treatment failure at the 6-month visit will be enrolled in the adaptive trial, where they will be assigned to adherence-plus or routine adherence support. In cases where clinically significant drug resistance is suspected (i.e., virologic failure in persons with convincing evidence of high adherence), we will refer participants to centers where they can be evaluated for second-line treatment.

11. ANALYTICAL CONSIDERATIONS

11.1 Design Overview

For phase-1, our design is a 2x2 individual randomized factorial design to evaluate two interventions: 1) same-day ART vs. standard ART initiation; and 2) community-based care vs. facility-based care. Phase-2 is adaptive and includes participants experiencing treatment failure at 6 months in phase-1, who will be randomized a second time to adherence-plus vs. routine adherence support.

The primary outcome for both phase-1 and 2 of this trial is viral suppression. For phase-1, viral suppression will be assessed at 6 months and for phase-2, viral suppression will be assessed at 12 months (i.e., 6 months after the second randomization). Please see the ***statistical analysis plan (SAP)***, a separate document, for detailed analytic approach.

11.2 Hypotheses

11.2.1 Phase-1: Factorial trial

Among PWID living with HIV who are ART-naïve or who have been off ART for a prolonged period, and have an HIV RNA ≥1,000 c/mL, same-day ART and community-based care will increase the proportion with viral suppression at 6 months, compared with standard ART initiation and facility-based care.

11.2.2 Phase-2: Adaptive trial

Use of enhanced navigation and psychosocial support (adherence-plus) for participants who experience treatment failure at 6 months will increase the proportion with viral suppression at 12

months (i.e., 6 months after the second randomization), compared with routine adherence support.

11.3 Study Objectives

11.3.1 Primary Objectives

11.3.1.1 Phase-1 – To determine the effects of same-day ART (compared with standard ART initiation) and community-based care (compared with facility-based care) on viral suppression at 6 months following phase-1 randomization, among PWID living with HIV.

11.3.1.2 Phase-2 – To determine the effect of adherence-plus (compared with routine adherence support) on viral suppression at 6 months following phase-2 randomization (corresponding to 12 months after phase-1 randomization), among PWID living with HIV who experience early virologic failure.

11.3.2 Secondary Objectives

11.3.2.1 Phase-1 – To determine the effects of same-day ART and community-based care on viral suppression among PWID living with HIV at 3, 12, and 18 months, relative to their control conditions.

11.3.2.2 Phase-2 – To determine the effect of adherence-plus (compared with routine adherence support) on viral suppression at 12 months following phase-2 randomization (18 months following phase-1 randomization), among PWID living with HIV who experience early virologic failure.

11.3.2.3 Phase-1&2 – To determine the effects of same-day ART, community-based care, and adherence-plus on all-cause mortality among PWID living with HIV, relative to their control conditions.

11.3.2.4 Phase-1&2 – To determine the effects of same-day ART, community-based care, and adherence-plus on linkage to ART at the clinics at 3 and 6 months among PWID living with HIV, relative to their control conditions.

11.3.2.5 Phase-1&2 – To determine the effects of same-day ART, community-based care, and adherence-plus on self-reported ART adherence among PWID living with HIV, relative to their control conditions.

11.3.2.6 Phase-1&2 – To determine the effects of same-day ART, community-based care, and adherence-plus on ART adherence measured by medication possession ratio among PWID living with HIV, relative to their control conditions.

11.3.3 Exploratory Objectives

11.3.3.1 Phase-1&2 - To determine the effects of same-day ART, community-based care, and adherence-plus on quality of life (QOL) among PWID living with HIV, relative to their control conditions.

11.3.3.2 Phase-1&2 - To determine the effects of same-day ART, community-based care, and adherence-plus on use of medication for opioid use disorder (MOUD) among PWID living with HIV, relative to their control conditions.

11.3.3.3 Phase-1&2 - To determine the effects of same-day ART, community-based care, and adherence-plus on HIV- and drug use-related stigma among PWID living with HIV, relative to their control conditions.

11.3.3.4 Phase-1&2 - To determine the effects of same-day ART, community-based care, and adherence-plus on depression symptoms among PWID living with HIV, relative to their control conditions.

11.3.3.5 Phase-1&2 - To determine the effects of same-day ART, community-based care, and adherence-plus on HIV treatment self-efficacy among PWID living with HIV, relative to their control conditions.

11.3.3.6 Phase-1 - To determine the effects of same-day ART and community-based care on the development of new antiretroviral drug resistance among PWID living with HIV, relative to their control conditions.

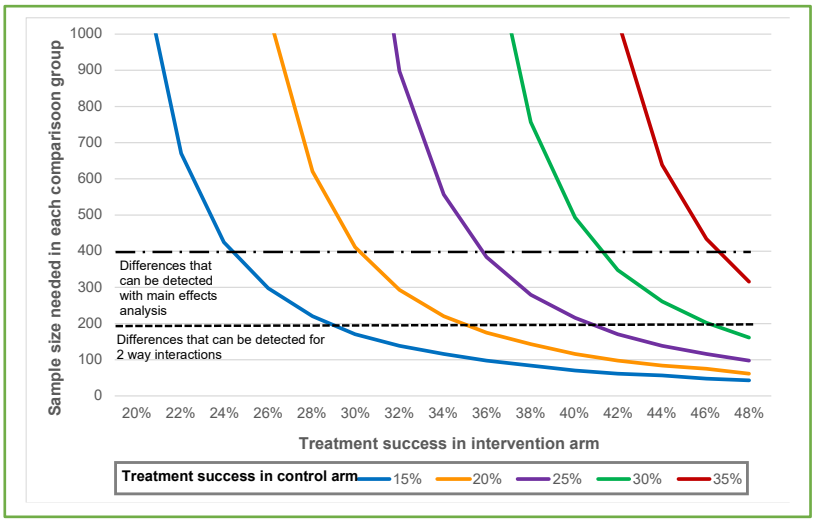
11.4 Outcome measures

Table 4. Study outcome measures		
Title	**Description**	**Time Frame**
Primary Outcomes		
1) Percentage of participants with viral load suppression (HIV RNA <1000 c/mL) at 6 months after phase-1 randomization	HIV RNA levels in blood measured with GeneXpert 2 module, Xpert HIV-1 Viral Load XC Cartridge (Cepheid AB, Sweden). Lower limit of quantification 40 copies/mL	Measured at 6 months following phase-1 randomization
2) Percentage of participants with viral load suppression (HIV RNA <1000 c/mL) at 6 months after phase-2 randomization	HIV RNA levels in blood measured with GeneXpert 2 module, Xpert HIV-1 Viral Load XC Cartridge (Cepheid AB, Sweden). Lower limit of quantification 40 copies/mL	Measured at 6 months following phase-2 randomization (corresponding to 12 months after phase-1 randomization)
Secondary Outcomes		
1) Percentage of participants randomized in phase-1 with viral suppression (HIV RNA <1000 c/mL) at non-primary time points (i.e., 3, 12, and 18 months).	HIV RNA levels in blood measured with GeneXpert 2 module, Xpert HIV-1 Viral Load XC Cartridge (Cepheid AB, Sweden). Lower limit of quantification 40 copies/mL	Measured at 3, 12, and 18 months following phase-1 randomization
2) Percentage of participants randomized in phase-2 with viral suppression (HIV RNA <1000 c/mL) at non-primary time point (18 months).	HIV RNA levels in blood measured with GeneXpert 2 module, Xpert HIV-1 Viral Load XC Cartridge (Cepheid AB, Sweden). Lower limit of quantification 40 copies/mL	Measured at 12 months following phase-2 randomization (corresponding to 18 months after phase-1 randomization)
3) All-cause mortality rate	Research staff and outreach workers collected reports on participant deaths. Verified deaths required one of the following: i) hospital records or death certificate, ii) confirmation of death from a family member, or iii) confirmation of death from an eyewitness (usually another PWID). Rate will be presented as events per unit observation time.	Measured up to outer window of 18-month visit (21 months)
4) Percentage of participants who link to ART at a clinic by 3- or 6-months following randomization	Linkage to ART will be defined as collecting one or more ART prescriptions from a clinic by 3 months and 6 months, captured by medical record abstraction or, in the absence of medical record data, participant self-report of ART collection from a clinic.	Measured at 3 months and 6 months following phase-1 randomization and 6 months following phase-2 randomization (corresponding to 12 months after phase-1 randomization)
5) Percentage of participants adherent to ART measured by self-report	Participants will be classified as adherent if they report taking ART in the prior 30 days and report adherence of 80% or higher using a visual analog scale (range: 0% to 100%), with higher numbers indicating higher adherence	Measured at 6 months following phase-1 randomization and 6 months following phase-2 randomization (corresponding to 12 months after phase-1 randomization)

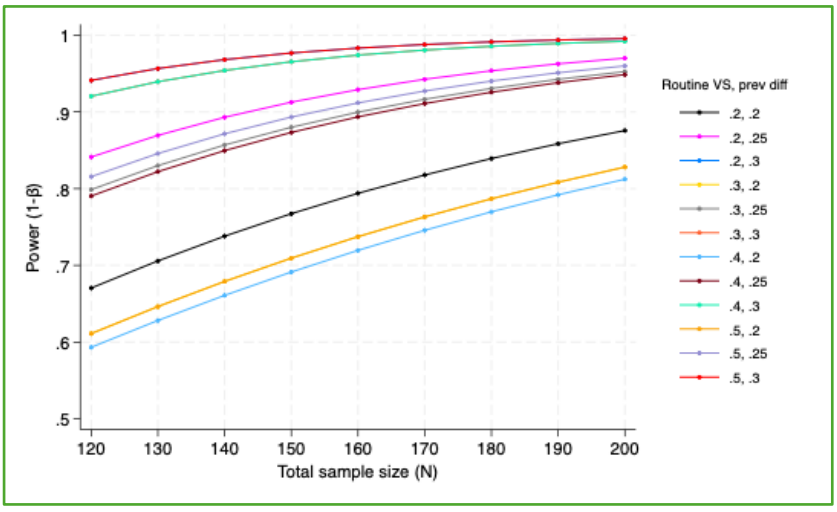
6) Percentage of participants adherent to ART measured by medication possession ratio (MPR)	ART fill data will be abstracted from medical records. In phase-1, participants will be classified as adherent if they have at least one ART refill by 3 months (91 days) and have an MPR of 80% or higher in the period between the first ART fill in the clinic and 6 months (182 days). In phase-2, participants will be classified as adherent if they have at least one ART refill by 3 months (91 days) following the second randomization (or prior to the second randomization) and have an MPR of 80% or higher in the period between the first ART refill (or the second randomization if the first ART refill was prior to the second randomization) and 6 months (182 days following the second randomization).	Measured at 6 months following phase-1 randomization and 6 months following phase-2 randomization (corresponding to 12 months after phase-1 randomization)
Exploratory outcomes		
1) Quality of life (QOL) score	QOL will be measured with a modified EuroQol EQ-5D-3L questionnaire with a visual analogue scale. Higher scores on both the EQ-5D-3L (range 0 to 1) and visual analog scale (range 0 to 100) indicate higher QOL	Measured at 3, 6, 12, and 18 months after phase-1 randomization
2) Percentage of participants who use of medication for opioid use disorder (MOUD)	Use of MOUD is captured by self-reported in the research visit questionnaire. Participants are asked whether they received MOUD in the prior 6 months and, if they did so, they are asked about frequency of MOUD visits.	Measured at 3, 6, 12, and 18 months after phase-1 randomization
3) Stigma score	We will measure both HIV-related and drug use-related stigma as separate constructs using a survey (https://doi.org/10.1016/j.drugpo.2021.103354). Each construct is evaluated by three sub-scales: 1) anticipated healthcare stigma, 2) enacted healthcare stigma, and 3) internalized stigma. All stigma subscales will be queried using Likert scales that range from 0 to 3, with higher scores indicating more stigma. For anticipated and enacted stigma, participants will be classified as experiencing stigma if the Likert scale is >0 for any one item (i.e., analyzed as a dichotomous outcome). For the internalized stigma subscale, scores will be converted to a continuous mean outcome from 0 to 3.0, with higher scores indicating more stigma.	Measured at 3, 6, 12, and 18 months after phase-1 randomization
4) Percentage of participants with at least moderate depression symptoms	Depression will be measured with the PHQ-9 questionnaire. The scoring range is 0 to 27, with higher values indicating more depression symptoms. Participants will be categorized as having at least moderate depression symptoms if the score is ≥ 10.	Measured at 3, 6, 12, and 18 months after phase-1 randomization
5) HIV treatment self-efficacy	HIV treatment self-efficacy will be measured with a modified HIV Treatment Adherence Self-Efficacy Scale. Items will be averaged to calculate a self-efficacy score, ranging from 0 to 100, with higher scores indicating higher self-efficacy.	Measured at 3, 6, 12, and 18 months after phase-1 randomization

6) Percentage of participants who acquire drug resistance mutations (DRMs) at 12 months	New antiretroviral drug resistance will be defined as the detection of one or more reverse transcriptase or integrase gene DRMs at follow-up that was not present at baseline, among participants with HIV RNA ≥1000 c/mL at the 12-month visit. DRMs will be interpreted using the online Stanford HIV Database (https://hivdb.stanford.edu)	Measured at baseline and 12 months after phase-1 randomization

11.5 Sample Size Considerations



For phase, 1, sample size calculations were done for the primary hypothesis of improved viral suppression at 6 months for each intervention, assuming no interaction between interventions (i.e., powered for intervention main effects) using an intention to treat approach. Thus, the effective sample size for each of the two comparisons is equivalent to the overall sample. For example, to assess the efficacy of same-day ART, we would compare outcomes in the 2 arms with same-day ART to those in the 2 arms without same-day ART. Assuming a two-sided α=0.05 and a range of viral suppression in the standard ART initiation arm of 15-35%, which is consistent with what we have observed in this population previously, we calculated sample sizes needed for a range of effect sizes (5-30%). The figure reflects the sample size needed per comparator group (e.g., 2 groups for main effects) assuming equal distribution across arms. We chose a total sample of 800 (or 200 per 4 intervention arms; 400 per the 2 comparison groups) because we will have 90% power to detect viral suppression rates of 10-12 percentage points or larger for the main effects of same-day ART and community-based care.



For phase-2, sample size calculations were done for the primary hypothesis of improved viral suppression at 6 months following phase-2 randomization (corresponding to 12 months after phase-1 randomization) for the adherence-plus intervention compared to routine adherence support. Assuming a two-sided α=0.05 and a range of viral suppression (VS) in the routine adherence support arm of 20-50%, we

calculated power for a range of sample sizes – given the sample size is out of our control due to the adaptive design – and effect sizes (i.e., prevalence differences). Sample sizes ranged from 120 to 200, representing 15%-25% of the 800 enrolled trial participants. The figure reflects the total sample size needed assuming equal distribution across the two arms (i.e., 1:1 randomization). With a total sample size of 125 or more, we will have at least 80% power to detect a prevalence difference of at least 25%.

11.6 Enrollment/Stratification/Randomization/Blinding Procedures

Participants enrolling in phase-1 will be randomized to one of four arms (1:1:1:1) according to the factorial design. In phase-2, participants meeting the definition of treatment failure at the 6-month visit will be randomized (1:1) (a second time) to routine adherence support or adherence-plus. In both phases, randomization allocation lists will be stratified by site and lists will be blocked – block sizes of 4, 8, and 12 for phase-1 and sizes 2, 4, and 6 for phase-2.

Randomization lists will be generated at the US data management/analysis site using statistical software. Then, site-specific randomization allocations lists will be programmed into the study's electronic data collection application, which will automatically select the next allocation for each eligible and enrolled participant and display this for study staff on the tablet. Study site staff will not have access to the randomization allocation list; rather, they will only see the allocation for the participant currently being randomized. As an additional check on randomization, site staff will contact the study coordinator (who will keep a partial allocation list) to check that the most recent allocation matches the list.

11.7 Participant Enrollment and Follow-up

We anticipate enrolling 800 (approximately 400 per site) people over a period of 20-24 months with an average of 15-20 participants per site per month. Enrolled participants will complete the baseline survey and be randomized. Participants will be followed at 3, 6, 12, and 18 months.

12. DATA HANDLING AND RECORDKEEPING

12.1 Data Management Responsibilities

Our team will follow previously established data protocols that we used in prior projects. We will develop an electronic data collection application for the collection of individual participant data at study sites. Site interviewers will record responses to survey questions directly into the tablet. The survey will be downloaded onto the tablets with participant data routinely pushed to a secure web cloud server. Researchers at Johns Hopkins, led by Allison McFall, PhD, will have full access to data on the web cloud server from all recruitment sites via a secure password protected web-portal. Study analyses will be conducted by research members at the Bloomberg School of Public Health.

12.2 Quality Control and Quality Assurance

12.2.1. Procedures to ensure the validity and integrity of the data

All field staff, interviewers, phlebotomists and clinicians who will come into contact with study participants will be required to complete research ethics and good clinical practice (GCP) training.

Lab technicians/phlebotomists at YRG CARE have undergone training on research ethics and good clinical laboratory practices (GCLP). The YRG CARE Infectious Disease Lab is certified by the *College of American Pathologists, United Kingdom National External Quality Assurance Scheme, and the Virologic Quality Assessment Program, US* and by the *AIDS Clinical Trials Group and Abbott Laboratories Inc, US* to perform HIV-1 genotypic resistance testing. GCLP are monitored by Johns Hopkins, Family Health International, and PPD.

Additional details can be found in the Data Safety and Monitoring Plan.

12.2.2. Procedures to guarantee the accuracy and completeness of the data

Our primary mode of data collection will be through the electronic data collection application. Additional details can be found in the Data Safety and Monitoring Plan.

13. HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Board/Ethics Committee

As in past studies, we are using JHM templates for the study protocol, informed consent form (ICF), and waiver of written consent (oral consent scripts). Once these documents are reviewed, approved, and stamped by the JHM IRB, we will submit them to the YRGCARE IRB. Following this approval (including the occasional need to go back to JHM IRB with a change required by YRGCARE), we will send ICF and other critical documents for translation to Hindi and other languages (other than English) that will be needed. Finally, the translated versions and certificates of translation will be submitted back to both IRBs. All sites will use the same consent forms.

Y.R. Gaitonde Med, Educational & Rsch Foundation IRB #1 (IRB00001423) has reviewed and approved an early version of this proposal. They will review all subsequent amendments once approved by JHM IRB.

13.2 Vulnerable Participants

13.2.1 Pregnant women and fetuses

Pregnant women are excluded from joining this study as they require specialized HIV management. Women who become pregnant while already enrolled in the study, will be referred to specialized government clinics for HIV treatment. In such cases, women may continue to be followed in the trial if they wish.

13.2.2 Prisoners

It is possible that persons who are enrolled may become prisoners during the course of the study. This means that they may become prisoners while they are taking HIV treatment. We do

not have formal agreements in place to provide medication while participants are in prison. However, we will work with the prisons in each of the cities to establish agreements where possible. The goal will be to support study participants to continue their treatment while in prison by either delivering treatment through peers, family members and other prison staff. However, we will not conduct any research activities while study participants are in prison.

13.2.3 Illiterate participants

Some of our research participants will be illiterate. As required by the JHM and YRGCARE IRB, all informed consent documents will be read verbatim and participants who cannot sign will be asked to provide a thumb print.

13.3 Informed Consent

13.3.1 Informed consent process

Potentially eligible participants will complete an oral consent script prior to screening, which includes biometric registration, a questionnaire, and a blood draw. Participants who are eligible after screening and wish to join the study will be asked to provide written informed consent.

To obtain consent, participants will meet with a research staff member in a private area to discuss the research. Any study staff member who obtains informed consent from study participants will have completed requisite human subjects training. The research staff will present a brief overview of the study and what is being requested of the participant. If participants continue to express interest, the research staff will present the study in detail in conjunction with the informed consent script or document. Participants will be encouraged to ask questions during the consent process. Following this discussion, subjects will be asked comprehension questions to gauge the degree to which they have understood the study procedures. Participants will then be asked to provide a signature or thumbprint (if illiterate).

Consent documents will be approved by JHU and YRGCARE IRBs. The rights and welfare of the participants will be protected by emphasizing to them that the availability of medical care will not be affected if they decline to participate in this study. In particular, receipt of non-research related services at ICCs is not conditioned upon participation in any aspect of the study.

13.3.2 Documentation of informed consent

Participants who provide written consent will be given a copy of the consent. In addition, a signed copy of the consent will be maintained in locked cabinets at each of the study sites.

13.4 Risks

13.4.1 PWID participants in randomized trial

Potential risks to clinical trial participants include loss of confidentiality, minor discomfort from blood draw, embarrassment responding to questions about drug or sexual behaviors, and anxiety from HIV testing. The likelihood of these risks is moderate, and the potential seriousness is minor. Of the 3 interventions being evaluated in the trial, one is policy level (timing of ART initiation), another is structural (site of HIV care) and one is psychosocial (patient counseling and navigation). The medical risks of these interventions are commensurate with

standard treatment of HIV infection. Of note, prior work by our group has documented high all-cause mortality rates among PWID living with HIV in these Indian cities. All trial participants will receive HIV treatment and monitoring consistent with HIV treatment guidelines in India.

13.5 Social Impact Events

Legal and social risks are possible because study participants are PWID who engage in illegal activities. However, we will take multiple precautions to protect against breaches of confidentiality. Identifying information will only be accessible to study site staff. Interviewers will be trained to not discuss the participants in the study. Results will be reported in aggregate form only. Interview and laboratory data will be stored and managed on a secure web cloud server. These data will be password-protected and available only to a defined group of data managers and analysts who are working on the trial.

13.6 Benefits

This study has the potential to provide benefits to study subjects if one or more of the interventions improves treatment outcomes compared with standard care. Additionally, results of HIV viral load testing from baseline and from the 6-month time point will be given to all trial participants.

This study will contribute to knowledge about the effectiveness of three interventions designed to improve HIV treatment outcomes among PWID in India.

13.7 Compensation

US dollar (USD) values based on exchange rate of India Rupee (INR) 72 per USD 1.

13.7.1 PWID participants in randomized trial

Screening/baseline visit (1 or 2 days)
Participants who begin screening but are found ineligible after the oral screening questionnaire (and do not provide blood and urine samples) will be paid 200 INR (2.78 USD). Participants who complete the oral and laboratory screening procedures (requiring a blood sample) will be paid 300 INR (4.17 USD), irrespective of eligibility or decision to participate. Participants will be reimbursed a total of 500 INR (6.94 USD) if they complete screening processes, are determined to be eligible, complete the baseline questionnaire, and are enrolled into the study (300 INR for screening and 200 INR for additional baseline activities).

Follow-up visits
Participants will be paid 500 INR (6.94 USD) for each of the four study follow-up visits they complete (3 months, 6 months, 12 months, and 18 months).

Consequently, PWID participants in the randomized trial can earn a total of 2,500 INR (34.72 USD) for screening, completing the baseline procedures and attending all follow-up visits.

13.8 Participant Privacy and Confidentiality

Loss of confidentiality, particularly regarding stigmatizing information or illegal behavior, is a potential risk to all participants. To minimize this risk among participants in the randomized trial,

we will keep informed consent documents in a locked file cabinet in a locked room, separate from other study data. Interviewers will be trained to not discuss the participants in the study. In electronic databases, identifying information will only be accessible to study site staff, and we will use unique study identification numbers in the other working data files. Electronic data will be transferred to a secure web cloud sever from study sites at 2-3 times per day via secure, encrypted transmission. Blood draws will be conducted by trained phlebotomists. We will conduct point-of-care pregnancy tests and screen for breastfeeding in all women assessed for trial eligibility.

Safeguards will also be taken to ensure that subjects' confidentiality is maintained. These measures include: 1) unique study numbers in databases and on specimens; 2) restricting access to identifiers to only study site staff with the need to use the information for tracking and other study procedures; 3) restricting access to locked files and password protected databases to essential study personnel. All data will be reported in aggregate form only without personal identifiers. In the case of an adverse event, policies and procedures are in place to work with the subject and to keep the study's governing bodies informed.

13.9 Certificates of Confidentiality

Certificates of confidentiality are not recognized by the Indian Government.

13.10 Critical Event Reporting

The Indian research coordinators (Drs. Jiban Baishya and Ashwini Kedar) will report unanticipated problems and study deviations to the local IRB (YRGCARE IRB). Such events will also be communicated with the US investigators and Dr. Lucas (JHU PI) will report to the JHM IRB. Dr. Lucas will report unanticipated problems or study deviations that involve risks to participants or others promptly to the JHM IRB in accordance with Organization Policy. Minor problems and protocol deviations (which pose no risk to subjects or others) will be reported in annual protocol continuing review.

13.11 New Findings

If any study-relevant new findings are reported during the course of the study that may impact the willingness of participants to continue on study and/or willingness to join the study, the new findings will be discussed with study staff and the consent form will be revised and submitted to the relevant IRBs. Participants will be reconsented via a consent form that includes discussion of the new findings.

13.12 Study Discontinuation

The study may be discontinued at any time by the IRB, DSMB, or NIDA as part of their duties to ensure that research participants are protected.

When the study ends or if a participant's participation in the study ends prematurely, participants that were assigned to community-based care at the integrated care centers will either continue to receive care there (if a source of support can be identified) or they will be transferred to facility-based care at a government ART center (current standard of care). The adherence-plus intervention is limited to 6 months; participants will return to routine adherence support after the intervention concludes.

13.13 Ancillary Protection

As is required by the Government of India, if a person is injured as a result of being in the study s/he will be given immediate treatment of injuries as per YRGCARE's standard of care. The entire cost of health care and compensation due to study related injury or death will be covered by YRGCARE through "Clinical Trials Insurance."

1. In the case of an injury occurring to the clinical trial participant, he or she shall be given free medical management as long as required.

2. In case the injury occurring to the trial participant is related to the clinical trial, such participant shall also be entitled for financial compensation as per order of the Licensing Authority (The Drug Controller General of India) and the financial compensation will be over and above any expenses incurred on the medical management of the participant.

3. In the case of clinical trial related death of the participant, his/her nominee(s) would be entitled for financial compensation, as per the order of the Licensing Authority and the financial compensation will be over and above any expenses incurred on the medical management of the participant.

4. Financial compensation shall be paid by the Clinical Trial Insurance (New India Assurance Co. Ltd) if the death is due to the reasons specified under the Rule 122 DAB of the "Drugs and Cosmetics Rules, 1945" and as per the Order from the "Central Drugs Standard Control Organization."

14. ADMINSTRATIVE PROCEDURES

14.1 Protocol Registration

This protocol is registered in ClinicalTrials.gov, ID: NCT05165810.

14.2 Study Implementation

14.2.1 Coordinating Center

This clinical trial will be conducted exclusively at sites in India, through a longstanding collaboration between researchers at Johns Hopkins University, in Baltimore, MD, USA and the YR Gaitonde Centre for AIDS Research and Education (YRGCARE) in Chennai, Tamil Nadu, India. JHU will serve as the coordinating center for this study, consistent with previous trials. YRGCARE has facilities in multiple cities to support research and service delivery for key populations. YRGCARE hires staff at each site and directly oversees activities at each site.

14.2.2 Contact information

The US-based MPIs for this trial (Drs. Lucas and Mehta) have direct contact information for supervisors and site-level YRGCARE personnel.

14.2.3 Federalwide assurance (FWA)

Each site has an active FWA: FWA00000672. This FWA provides assurance and oversight for components in the candidate cites of New Delhi and Kanpur.

14.2.4 Protocol version and amendments

The most recent version of the protocol and any amendments will be available to all study personnel on a shared cloud drive. The senior Indian research coordinator (Dr. Jiban Jyoti Baishya) and the Indian Co-PI (Mr. AK Srikrishnan) will be responsible for assuring that recruitment sites are using the most up-to-date protocol and ICF.

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