Title: Indonesia Intervention Study to Test & Treat people with Acute HIV infection

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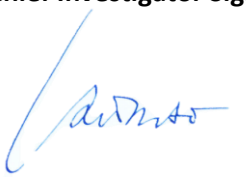

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Conflicts of interest

The investigators declare no potential conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1 LAY SUMMARY

There is an uncontrolled HIV epidemic among key populations at highest risk of HIV infection in Indonesia, including men who have sex with men (MSM), transgender people and sex workers. Innovative, context-specific interventions are urgently needed to break HIV transmission. Multi-component intervention models based on detection of individuals with acute HIV infection (AHI), using symptom and behaviour risk scores and point-of-care HIV viral load diagnostic testing, have been successful in curbing local HIV epidemics in several Western cities, by enabling direct linkage to care and immediate initiation of antiretroviral therapy (ART) as well as enhanced HIV testing of their sexual partners. There is a thus a strong impetus to tailor those successful models to explosive epidemics in low- and middle-income countries (LMIC) such as in Indonesia.

Our research proposal will address one overarching question: can we curb the rapidly growing HIV epidemic among key populations in Indonesia by implementing a person-centered, cost-effective clinical care pathway for the enhanced diagnosis and treatment of AHI?

The INTERACT project will implement an AHI clinical pathway in three sexual health clinics serving high-risk populations in Jakarta and Bali, combined with the implementation of a digital behaviour tool to promote AHI screening among the wider at-risk population. The uptake, yield, feasibility and acceptability of the AHI clinical pathway will be evaluated using qualitative and quantitative analytical methods. Ultimately, mathematical modelling and cost-effectiveness analyses will be used to estimate the population impact of several intervention scenarios if rolled out at scale.

The INTERACT project will strengthen local capacities to adopt implementation science approaches to improve HIV service delivery, reduce new HIV infections, death and health costs, and provide critical evidence to health policy makers in Indonesia, and in other LMIC.

2 SYNOPSIS

Title	**Indonesia Intervention Study to Test & Treat people with Acute HIV infection (INTERACT)**	
Design	Implementation study of screening individuals at risk of HIV acquisition for acute HIV infection (AHI) using HIV-RNA diagnostic testing, as part of a clinical care pathway for the enhanced diagnosis and treatment of AHI, integrated into routine sexual health services	
Population	Clinic attendees who (i) seek HIV testing, or (ii) are newly HIV diagnosed	
Setting	Three sexual health clinics in South Jakarta (Globalindo), Denpasar and Ubud (Bali Peduli)	
Study Period	36 months (start date of data collection December 2022)	
Aim	The aim of this implementation study is to demonstrate the proof-of-concept that context-specific implementation of AHI diagnostic screening, as part of a clinical pathway for same-day diagnosis and treatment of AHI, can optimize current HIV care delivery and strengthen the HIV care cascade, and thereby curb the explosive HIV epidemic in key populations in Jakarta and Bali, Indonesia.	
	Study Objectives	**Outcome Measures**
Primary	To evaluate the effectiveness/yield of an AHI clinical pathway	*AHI screening outcomes*:* • Performance of the Amsterdam screening risk score in diagnosing AHI expressed as sensitivity, specificity and Area Under the Curve (AUC); • Yield of HIV-RNA in diagnosing AHI compared with standard-of-care 4th gen HIV Ag/Ab testing and 3rd gen HIV Ab RDT testing; • Prevalence of reported symptoms and risk behaviour, and their association with AHI; • Number and proportion of participants who are newly diagnosed with AHI (compared to historical records for all HIV diagnoses); ** Outcomes are expressed overall, and, as relevant, stratified by time window until confirmed diagnosis received (same-day, <24 hours, <72 hours, or after 3 days or longer after initial testing).* *HIV care cascade outcomes**:* • Proportion of those HIV diagnosed who start ART (compared to historical records); • Time (days) from confirmed HIV diagnosis to ART initiation (compared to historical records); • HIV-RNA load levels (mean/median and proportion <50 cps/mL) at the time of HIV diagnosis and after 12 and 24 weeks of ART (compared to historical records for all HIV diagnoses); • CD4 T-cell counts (median and categories) at the time of HIV diagnosis and after 12 and 24 weeks of ART; *** Outcomes are expressed overall, and, as relevant, stratified by time window between confirmed diagnosis and ART initiation (<24 hours, <7 days, <30 days, or longer after confirmed HIV diagnosis)*

	To evaluate the uptake/adoption, acceptance and feasibility of enhanced HIV testing and partner screening and notification, as part of the AHI clinical pathway	• Number of AHI risk screens conducted; • Number of individuals who are tested for HIV/STI for the first time ever and at the study clinic; who repeat the HIV/STI test at the study clinic; and the time interval since previous HIV/STI test; • HIV and STI incidence among individuals in follow-up; • Number of HIV-negative individuals who are eligible for PrEP (according to WHO guidelines); • Number of sexual partners of individuals who are newly HIV diagnosed (index clients), who are contacted, tested for HIV, and newly HIV diagnosed; • Barriers and enablers of implementing the AHI clinical pathway from the participant's and provider's perspective;
	To estimate the potential population impact and cost-effectiveness of an AHI clinical pathway on curbing the HIV epidemic in Indonesia	• Projections of HIV infections, hospitalizations, and deaths averted and QALYs gained under different intervention scale-up scenarios, including maintenance of the status quo. • Cost-effectiveness of different intervention scale-up scenarios, expressed as ICER measured as cost-per QALY gained.
Secondary	To improve the implementation of the AHI clinical pathway through a tailored digital behavioural/risk assessment intervention and community outreach	• Uptake of a tailored digital risk reduction intervention amongst MSM at risk in the local area in all clinical sites • Usability of the tool via user-centred interaction design methods including focused user questionnaires and remote usability testing (subjective feedback on the interface by users). • Number of digital engagements and length of digital interaction time spent on the tool, and number of returning digital users. • Number of those engaged enrolling in the INTERACT study.

3 ABBREVIATIONS

Ab	HIV antibody
Ag	HIV antigen
AHI	Acute HIV infection
AUC	Area Under the Curve
ART	Antiretroviral therapy
CHI	Chronic (established) HIV infection
CRF	Case Report Form
COVID-19	Coronavirus disease 2019
CSW	Commercial sex worker
CT	Chlamydia
EHI	Early HIV infection
GCP	Good Clinical Practice
GN	Gonorrhoea
FKUI	Faculty of Medicine Universitas Indonesia (Jakarta)
HCW	Health care worker
HIV	Human immunodeficiency virus
ICF	Informed consent form
IN	Integrase
LMIC	Low and middle-income countries
MOH	Ministry of Health (Kementerian Kesehatan Republik Indonesia)
MSM	Men who have sex with men
MTA	Material Transfer Agreement
NGO	Non-government organisation
OUCRU-ID	Oxford University Clinical Research Unit Indonesia (Jakarta)
OUCRU-VN	Oxford University Clinical Research Unit Vietnam (HCM City)
OXTREC	Oxford Tropical Research Ethics Committee
PI	Principal Investigator
PIC	Participant informed consent
PIS	Participant information sheet
PLWH	Person living with HV
POC	Point-of-care
PR	Protease
PrEP	HIV pre-exposure prophylaxis
QoL	Quality of life
RDT	Rapid Diagnostic Test
REC	Research Ethics Committee
RNA	Ribonucleic acid
RT	Reverse transcriptase
SARS-CoV-2	Severe acute respiratory disease coronavirus 2
SOP	Standard operating procedure
STI	Sexually transmitted infection
TG	Transgender
VL	HIV viral load
WHO	World Health Organisation

4 BACKGROUND AND RATIONALE

4.1 Explosive HIV epidemic in Indonesia

Indonesia is a socio-culturally, economically and geographically diverse, Muslim-majority, lower-middle-income country. It is Southeast Asia's biggest economy with the world's fourth largest population (278 million). However, economic development is uneven, and stark inequalities and major gaps in health indicators persist across regions and communities. Indonesia has one of the fastest growing HIV epidemics in the world, with the fourth largest number of new infections per year, estimated at 46,000 (behind China, India and Russia), and the only country in the Asia-Pacific region where HIV prevalence is increasing, up to ~640,000 people currently living with HIV (PLWH)[1]. Dramatic increases in new HIV infections are being observed among key population groups that are particularly vulnerable to HIV exposure, specifically young urban men who have sex with men (MSM), transgender people, and sex workers and their sexual partners. Data from successive surveys suggest that national HIV prevalence estimates in MSM have risen sharply from 5.2% (2007), 8.5% (2011), to 25.8% (2015) and 17.9% (2018-2019)[2,3], and almost quadrupled among adolescent MSM between 2011 (3.8%) and 2015 (15.6%)[4]. An estimated 32% and 36% of MSM in Jakarta and Bali, respectively, and 34% of transgenders in Jakarta have been estimated to be living with HIV[5]. The most recent national data from 2018-2019 estimated that 17.9% of MSM, 11.9% of transgenders and 2.1% of female sex workers are living with HIV[2]. Given the strong evidence that people with an undetectable viral load cannot transmit HIV (undetectable=untransmissible, U=U), it is crucial that all PLWH are diagnosed as early as possible, and access antiretroviral treatment (ART) immediately to rapidly achieve viral suppression −as stipulated in the UNAIDS 90-90-90 goals[1]. However, to date, Indonesia has significant shortfalls in getting people tested, diagnosed, linked to care and on to suppressive ART: by the end of 2019, of ~640,000 PLWH, only 59% (377,564) knew their HIV status, 20% (127,613) received ART, and 2% (10,216) had suppressed viral load on ART[6,7]

This was further illustrated in the longitudinal HATI study[7] that reported on the HIV care cascade for key populations diagnosed with HIV in Bali, Bandung, Jakarta or Yogyakarta, including MSM (77%), female sex workers (14%), transgenders (3%), people who inject drugs (6%); of those enrolled, 85% were linked to HIV care, 73% started ART; 55% were retained in care; 39% had a viral load test after 6 months; 35% had viral load suppression; overall, 24% who started ART were lost to follow-up.

In Indonesia, HIV care cascades for testing, diagnosing, linkage to care and suppressive treatment are often fractured, particularly for key populations, due to social, economic and structural factors, including the decentralized health system, lack of government investment, public health services not being tailored to key populations, and −of great concern− increasing stigma and discrimination against lesbian, gay, bisexual and transgender people and PLWH[3,8]. Few organisations provide health services for HIV and other sexually transmitted infections (STI) tailored to key populations, mostly not-for-profit private or non-government organisations (NGOs).

AIDS-related deaths have never fallen in Indonesia and have increased by 60% since 2010 which imparts a cost burden on the existing fragile health system. Increasing AIDS deaths additionally have social and economic impacts on families and communities who suffer these losses. Social and economic deprivation affects key populations at risk of HIV infection disproportionately further increasing their vulnerability to HIV. For example, due to bridging of risk from key populations to lower risk populations observed (partners and babies from members of key populations); increasing AIDS related deaths impact the lives of the communities and families affected by that loss; impact of hospital admissions due to complex, advanced HIV and AIDS and the cost and occupancy burden to the health system.

4.2 Acute HIV infection

Acute HIV infection (AHI) is the phase immediately after infection, characterized by an initial burst of viremia with detectable HIV-RNA and/or p24 viral antigen (Ag), but anti-HIV antibodies (Ab) are still absent. Since acute retroviral syndromes mimic many common febrile illnesses, including infectious

mononucleosis, influenza, malaria, and rickettsial diseases, AHI is rarely considered at an initial patient encounter. The diagnostic challenge in AHI is made more difficult by the fact that routine HIV antibody (Ab) tests will typically remain negative for 1-2 weeks beyond the onset of acute retroviral symptoms, and additional virus-specific diagnostic tests (e.g., HIV p24 antigen [Ag] and HIV-RNA nucleic acid amplification assays) are needed to detect AHI prior to the appearance of antibodies. The rate of sexual transmission has been estimated to be 8-20 times higher during AHI than during established infection[9], and phylogenetic and mathematical models, largely from Europe and the Americas, estimate that AHI accounts for 10-50% of all transmissions, with variations explained by differences in epidemic stage, AHI definitions, risk behaviours and model design[10,11]. Reliable estimates for AHI as a driver of epidemics among Asian key populations are lacking. A cohort study of MSM in Bangkok estimated that AHI detection and immediate ART initiation could reduce onward transmissions by 89%[12].

Biomedical and behavioral intervention in persons with AHI and their social networks are crucial in limiting the spread of HIV. Evidence suggests that identifying and treating persons with AHI has major clinical and public health benefits[10], given that high viral loads and continued high-risk behaviour are major determinants of onward transmission[13]:

Sensitive screening for AHI Availability of (near) point-of-care (POC) 4th generation Ag/Ab (p24) and HIV-RNA tests has enabled prompt AHI diagnosis, shortening the post-transmission detection window from 2-6 weeks (Ab), to 15-20 days (p24 Ag) or even 7-10 days (HIV-RNA). Standard HIV testing in Indonesia generally relies on 3rd generation Ab Rapid Diagnostic Tests (RDT), hence easily missing AHI. 4th generation Ag/Ab assays are simpler and cheaper than HIV-RNA tests, but may have variable sensitivities (28-88% across cohorts[14–16]). A systematic review estimated that the diagnostic yield of AHI screening with HIV-RNA testing targeted to MSM with symptoms and/or sexual risk behaviour was 3.3% (95%CI, 2.2-4.6%) and up to 12.4% if early HIV infections (EHI) are also included[17]. AHI risk/symptom screening scores have been validated largely on retrospective datasets from Western and African MSM communities[17], hence further prospective studies are needed to assess their yield in real-world settings. In the face of limited resources, pooled (group) sample testing, a method that involves testing a group of multiple samples and then re-testing each individual sample separately when the group (pool) tests positive, has been successfully applied to increase testing efficiency and reduce resources required [15,18,19].

Immediate ART initiation for rapid viral suppression Rapid ART initiation before T-cell depletion can occur, shortens time to viral suppression, improves retention in care, and leads to improved long-term clinical outcomes, by preserving the immune system and limiting the viral reservoir[10,20,21]; rapid achievement of U=U can greatly reduce HIV-associated shame/stigma for PLWH.

Enhanced opportunities for behavioural interventions AHI screening allows for enhanced engagement and behavioural interventions with highest-risk individuals and their sexual partners by promoting AHI awareness and testing, partner notification and testing, and identifying individuals[15,22].

4.3 Intervention models targeting HIV transmission

AHI awareness campaigns, an optimally sensitive AHI screening approach and targeted HIV-RNA testing have been shown to contribute to earlier HIV diagnosis[15,22], and enable same-day ART initiation. Combined with contextualised HIV epidemic data, such targeted, people-centred approaches, can improve effectiveness, efficiency and quality of prevention and treatment programmes with greater public health impact within existing resources[23]. These combined prevention and treatment approaches have been effective in containing HIV epidemics in urban MSM communities in, for instance, San Francisco[24], British Columbia[25], London[26] and Amsterdam[27], indicating that multifaceted interventions (including AHI/EHI detection and immediate ART) with city-specific strategies to remove structural barriers for access to services, are potentially most successful to significantly reduce incident HIV infections[28]. Keys to success have been to make services attractive to high-risk groups; encourage more frequent testing; be user

focused and innovative, and tailor services based on up-to-date local epidemiological data and community engagement.

There is thus a strong impetus to tailor successful models to explosive epidemics in low- and middle-income countries (LMIC). Implementation research is needed to assess the effectiveness, acceptability, and feasibility of a person-centered AHI/EHI care pathway among Indonesian MSM and other key populations, coupled with innovative digital outreach approaches, and to estimate their potential individual and population impacts and cost-effectiveness. Furthermore, AHI-focused intervention models also contribute to identifying high-risk, HIV-negative individuals, which enables enhanced preventive interventions, including community education and preparedness of pre-exposure prophylaxis (PrEP). The Indonesian government is implementing pilot PrEP programmes in high-risk populations as of 2022, delivered through community-based non-government organisations (NGOs), with Global Fund support. A 2017 study in Bali found that MSM and transgenders had limited knowledge of PrEP, while willingness to take PrEP was high[29], underscoring the need for community education.

4.4 Study rationale

There is a gap between the promise of scientifically proven health interventions and their successful implementation in the real-world, especially in local contexts in LMIC. Addressing this gap, implementation research involves local engagement with patients, practitioners and policy makers and aims to develop acceptable, feasible, cost-effective, scalable, and transferable solutions to improve the quality and effectiveness of health services, produce generalizable knowledge that can be applied across settings and contexts, thereby taking an interdisciplinary approach, considering influence on individual and organizational behaviours and recognizing the complexity of health systems[30,31].

This implementation study will thus assess the effectiveness/yield, uptake/adoption, acceptance, feasibility, cost-effectiveness, and estimate its potential for impact at scale, of a person-centered AHI clinical pathway to optimize service delivery to Indonesian key populations. Addressing an unmet need of high priority, the principal overarching research question of the INTERACT project is to evaluate whether implementing a patient-centered AHI clinical pathway, coupled with a digital behavioural intervention reaching out to the wider target community, can curb the rapidly growing HIV epidemic among key populations in Jakarta and Bali.

The INTERACT project aims to answer the following key scientific questions:

1. What is the effectiveness/yield of implementing an AHI clinical pathway?
    - Is a risk/symptom screening score an effective method for detecting AHI among MSM and other key populations in Jakarta and Bali? Can the score be locally optimized?
    - Do same-visit delivery of diagnosis and immediate initiation of ART shorten the time to reaching undetectable viral load?
    - What are factors associated with AHI diagnosis and immediate ART failure/success?

2. What is the uptake/adoption, acceptability and feasibility of an AHI clinical pathway?
    - Does the clinical pathway lead to an increased number of individuals and their sexual partners tested for and diagnosed with AHI, and starting immediate ART during AHI, compared to the usual care? What is the uptake, feasibility, acceptability of the clinical pathway?
    - Are AHI patients willing to start ART at the day of diagnosis and adhere to immediate ART? And what are barriers and facilitators to immediate ART start?
    - Can we identify HIV-negative, high-risk populations for enhanced sexual health counselling, and preparation for future PrEP introduction?

3. What is the potential impact of implementing an AHI clinical pathway on curbing the HIV epidemic in Indonesia?

- How many infections and deaths would be averted, and quality-adjusted life-years (QALYs) gained in various intervention scale-up scenarios?
- What are incremental costs or cost savings of those possible scenarios?

4.5 Expected study impacts

With support from The Global Fund, the Indonesian MOH has launched an acceleration plan for models of person-focused HIV care and stakeholder engagement[32]. The INTERACT project is aligned with this priority, addressing inequity and unmet needs in access to HIV care and treatment focusing on individuals at the highest risk of acquiring and transmitting AHI, and is expected to result in a highly efficient and cost-effective approach, thus maximizing test yield at minimal required resources.

The INTERACT project will be implemented through Indonesian research organisations and existing sexual health and HIV services to enable the public service to be more effective, and to ensure the model is feasible, acceptable to and sustainable by the diversity of stakeholders. The evidence-based, context-specific AHI clinical pathway will be scalable to the public sector, leveraged by existing widespread GeneXpert capacity and equitable, multidisciplinary collaborations between health care providers, local and overseas scientists and government and non-government policy stakeholders. Demonstration of effectiveness/yield, acceptability/uptake, and impact will have direct relevance to patients, affected communities, health providers, government, as well as global stakeholders (such as WHO and UNAIDS) to support innovative models to curb the HIV epidemic in Indonesia and elsewhere. Ultimately, this will contribute to the Government of Indonesia's Universal Health Coverage national agenda through better service delivery, reduced HIV incidence, morbidity, mortality and health costs. Dissemination of findings to peer communities and policy makers will be augmented through local government and non-government stakeholders. The research findings will be amplified through high-quality scientific publications.

This project lays the foundation for further health system research on and implementation of optimized HIV care models in Indonesia, sharing knowledge, learning and collaboratively managing context-specific challenges, as well as further operational research on HIV transmission and prevention, scalability of the model, and novel diagnostic, prevention and treatment strategies. If shown to be feasible and effective in Indonesia, the INTERACT project will demonstrate the proof-of-concept that AHI intervention models can indeed be translated to diverse settings with high HIV incidences and integrated in health systems, after context-specific adjustments. Although different key populations will require tailor-made approaches, a focus on improving AHI detection and treatment has the potential to curb transmission among many high-risk populations across settings. The project will build on the successful long-standing partnerships between the University of Oxford, C&W Trust and Indonesian universities, NGOs and government stakeholders, and their leading position in driving improvements in education, research and health care in Indonesia.

5 AIMS, OBJECTIVES AND OUTCOME MEASURES

5.1 Aim

The aim of this implementation study is to demonstrate the proof-of-concept that context-specific implementation of AHI diagnostic screening, as part of a clinical pathway for same-day diagnosis and treatment of AHI, can optimize current HIV care delivery and strengthen the HIV care cascade, and thereby curb the explosive HIV epidemic in key populations in Jakarta and Bali, Indonesia.

5.2 Objectives and outcome measures

	Study Objectives	Outcome Measures
Primary	To evaluate the effectiveness/yield of an AHI clinical pathway	*AHI screening outcomes*:* • Performance of the Amsterdam screening risk score in diagnosing AHI expressed as sensitivity, specificity and Area Under the Curve (AUC); • Yield of HIV-RNA in diagnosing AHI compared with standard-of-care 4th gen HIV Ag/Ab testing and 3rd gen HIV Ab RDT testing; • Prevalence of reported symptoms and risk behaviour, and their association with AHI; • Number and proportion of participants who are newly diagnosed with AHI (compared to historical records for all HIV diagnoses); ** Outcomes are expressed overall, and, as relevant, stratified by time window until confirmed diagnosis received (same-day, <24 hours, <72 hours, or 3 days or longer after initial testing).* *HIV care cascade outcomes**:* • Proportion of those HIV diagnosed who start ART (compared to historical records); • Time (days) from confirmed HIV diagnosis to ART initiation (compared to historical records); • HIV-RNA load levels (mean/median and proportion <50 cps/mL) at the time of HIV diagnosis and after 12 and 24 weeks of ART (compared to historical records for all HIV diagnoses); • CD4 T-cell counts (median and categories) at the time of HIV diagnosis and after 12 and 24 weeks of ART; *** Outcomes are expressed overall, and, as relevant, stratified by time window between confirmed diagnosis and ART initiation (<24 hours, <7 days, <30 days, or longer after confirmed HIV diagnosis)*
	To evaluate the uptake/adoption, acceptance and feasibility of enhanced HIV testing and partner screening and notification, as part of the AHI clinical pathway	• Number of AHI risk screens conducted; • Number of individuals who are tested for HIV/STI for the first time ever and at the study clinic; who repeat the HIV/STI test at the study clinic; and the time interval since previous HIV/STI test; • HIV and STI incidence among individuals in follow-up; • Number of HIV-negative individuals who are eligible for PrEP (according to WHO guidelines); • Number of sexual partners of individuals who are newly HIV diagnosed (index clients), who are contacted, tested for HIV, and newly HIV diagnosed; • Barriers and enablers of implementing the AHI clinical pathway from the participant's and provider's perspective;

	To estimate the potential population impact and cost-effectiveness of an AHI clinical pathway on curbing the HIV epidemic in Indonesia	• Projections of HIV infections, hospitalizations, and deaths averted and QALYs gained under different intervention scale-up scenarios, including maintenance of the status quo. • Cost-effectiveness of different intervention scale-up scenarios, expressed as ICER measured as cost-per QALY gained.
Secondary	To improve the implementation of the AHI clinical pathway through a tailored digital behavioural/risk assessment intervention and community outreach	• Uptake of a tailored digital risk reduction intervention amongst MSM at risk in the local area in all clinical sites • Usability of the tool via user-centred interaction design methods including focused user questionnaires and remote usability testing (subjective feedback on the interface by users). • Number of digital engagements and length of digital interaction time spent on the tool, and number of returning digital users. • Number of those engaged enrolling in the INTERACT study
Exploratory	To estimate the prevalence of transmitted HIV drug resistance in newly HIV diagnosed individuals and to understand HIV transmission dynamics in Indonesia	• Proportions of participants with any, reverse-transcriptase (RT), protease (PR) and integrase (IN) resistance, and specific drug resistance mutations • HIV transmission networks within and between different risk groups and geographic regions, mixing and source attribution, based on phylogenetic inference

6 STUDY METHODOLOGY

6.1 Study design

INTERACT is an implementation study of screening individuals at risk of HIV acquisition for acute HIV infection (AHI) using HIV-RNA diagnostic testing, as part of a clinical care pathway for the enhanced diagnosis and treatment of AHI, integrated into routine sexual health services, in compliance with current MOH guidelines. The INTERACT project aims to **optimize current HIV care delivery**, following current WHO recommendations for HIV prevention, diagnosis and immediate ART[35].

INTERACT activities comprise:
- Implementing an optimally sensitive AHI screening approach through a client self-completed risk assessment ("Risk Checker"), coupled with HIV-RNA diagnostic testing (sequential to and additional to current local standard-of-care HIV Ag/Ab based testing).
- Strengthening HIV care cascades by same-day delivery of HIV-RNA test results, immediate offer of ART in newly HIV diagnosed persons, and monitoring HIV-RNA at 3 and 6 months after ART initiation to ensure response and adherence to treatment;
- Implementing an evidence-based digital behavioural intervention tool, tailored to the wider target population at high risk of HIV, through media platforms, to promote uptake/adoption of HIV prevention, testing and the AHI clinical pathway.

Clinic attendees at risk of HIV acquisition who have come to the clinic for HIV testing will thus receive additional AHI diagnostic screening (sequential to and additional to local standard-of-care HIV Ag/Ab based

testing), and are encouraged to return to the clinic for regular (three-monthly or earlier when they experience AHI or STI symptoms) HIV/STI screening visits, in accordance with current clinic procedures. Clinic attendees who are diagnosed with HIV will be followed after ART initiation, in accordance with current clinic procedures. Routinely collected data from the participants' medical records at each clinic visit will be extracted, after being de-identified, to the study database.

Several inter-related *quantitative* outcome measures will be measured, related to the effectiveness/yield, uptake/adoption, acceptability, feasibility and potential impact of the AHI clinical pathway. A *qualitative* implementation evaluation, based on semi-structured interviews with clinic and study staff, will help identify barriers and enablers associated with implementing the AHI clinical pathway. The study data will be used to perform a *cost-effectiveness analysis* and *predict the impact* of scalable intervention scenarios on the Indonesian HIV epidemic.

A subset of study participants who are newly diagnosed with HIV during the course of the project will be invited to participate, with written informed consent, in a "Virologic Sub-Study" to investigate transmitted antiretroviral drug resistance and HIV transmission networks in Bali and Jakarta (target 500 participants) based on HIV-1 genotypic testing.

Study procedures are summarized in the study schedule (**Appendix 2**).

6.2 Research setting and population

The INTERACT project will be implemented at three high-volume sexual health clinics providing person-centered free or low-cost, open-access HIV and STI testing, sexual health advice and support and HIV diagnosis and care to at-risk key populations, integrated in general care centres. About 70-80% of clients identify as MSM, with smaller fractions of transgenders (TG), commercial sex workers (CSW) and other risk groups, and on average ~40% of clients return for repeat HIV testing.

Yayasan Bali Peduli (www.balipeduli.org), operates clinics in Denpasar and Ubud, since 2011. Yayasan Kasih Globalindo (www.yayasankasihglobalindo.org), opened in January 2018 in South Jakarta. All sites offer on-site point of care (POC) rapid HIV testing (3rd generation HIV Ab and 4th generation HIV Ag/Ab), usually on a whole blood sample, in accordance with MOH guidelines. Rapid STI diagnosis and treatment of early syphilis (RPR/TPPA) and rectal/throat/urine chlamydia and gonorrhea infections (Cepheid GeneXpert) are available, although currently offered for symptomatic screening and not for routine screening (due to resource limitations). HIV viral load (HIV-RNA) monitoring is offered at the 6-month follow up visit for PLWH on ART and annually thereafter. Routine hepatitis B screening (HbsAg) is offered where appropriate. Hepatitis C screening (HCV IgG) is offered following risk assessment (particularly history of intravenous drug use). All sites have an operational GeneXpert system and trained laboratory staff.

Currently Globalindo and Bali Peduli sites combined perform an estimated 8,000 HIV tests per year. HIV prevalence among all new attendees is estimated to be 5-10%. Recent numbers of HIV tests and diagnosis are summarized in **Table 1**.

Table 1: Clinic data from 2019 to mid 2022

	2019	**2020**	**2021**	**2022**
Globalindo (South Jakarta)				
N HIV tests	5171	5180	6053	1255 (first 3 mo)
N HIV diagnosis	552	617	534	88 (first 3 mo)
Positivity %	9.4%	8.4%	11.3%	7.0%
Bali Peduli (Denpasar)				
N HIV tests	1646	1.266	1.791	1.128 (first 6 mo)

N HIV diagnosis	135	63	56	25
Positivity %	8.2%	5.0%	3.1%	2.2%
Bali Peduli (Ubud)				
N HIV tests	836	531	689	307 (first 6 mo)
N HIV diagnosis	41	16	51	13
Positivity %	4.9%	3.0%	7.4%	4.2%

6.3 Study screening and eligibility assessment

The central guiding principle for project implementation is that INTERACT study procedures will be integrated into the routine client services, and comply with MOH guidelines. All routine services and clinical assessments will be done by the clinic staff, who will receive additional training on study procedures in accordance with study-specific SOPs. The HIV testing algorithm in INTERACT is shown in **Figure 2.**

Upon entry into the clinic, all clinic attendees who attend the clinic for HIV testing (both first-time and repeat testers) will be informed about the ongoing INTERACT project through a Patient Information Sheet (PIS) (**Appendix 3**, refer to section 6.6).

Consecutive clinical attendees are then invited to, confidentially, answer AHI screening eligibility questions and provide their digital consent (**FORM 1, Appendix 4**) using a mobile device (tablet) provided by the clinic.

If all above study eligibility questions and digital consent are answered YES, the clinic attendee will proceed to AHI screening procedures (next section). For clinic attendees who are not eligible, or wish to opt out of study participation for any reason, the reason for exclusion/refusal will be recorded. A study screening log will be maintained for this purpose. All clinic attendees will receive sexual health services as usual, according to standard clinic procedures.

6.4 Visit procedures for first and return visits for AHI screen clients

At each clinic visit, the clinic attendee will be asked to fill the AHI "Risk Checker" (**FORM 2, Appendix 5**), modified from the Amsterdam AHI risk score[36], using a mobile device (tablet) provided by the clinic.

The first eight items represent validated risk factors of AHI (according to the Amsterdam AHI risk score [36]), and presence of one or more risk factors will classify the client as "high-risk".

After completion, the client-provided responses will be confidentially reviewed and verified between the client and a clinic nurse/counsellor in a private consultation room, combined with routine pre-test counselling.

At each clinic visit, clinic staff will extract the following routine demographic and clinical data from the clinic attendee's medical records into the study's Electronic Data Capture (EDC):
- Clinic visit date;
- Basic demographic data (age, gender, place of residence);
- Details of present health, including any signs and symptoms;
- Medical history including comorbidities, co-infections, allergies, medication use and pregnancy;
- HIV risk group;
- Recent HIV risk behavior;
- Recent PEP and PrEP use;
- HIV and STI testing history during past year;
- Routine lab testing results (including standard HIV test, STIs, blood counts, biochemistry, co-infections);

At each clinic visit, clinic staff will:

- Perform an additional study-related HIV-RNA Qualitative test, on a routinely collected remnant blood sample, according to the AHI testing algorithm (**Figure 1**). Refer to the laboratory testing plan below.
- Ask about health-related quality of life (EQ-5D-5L, 5-item questionnaire);

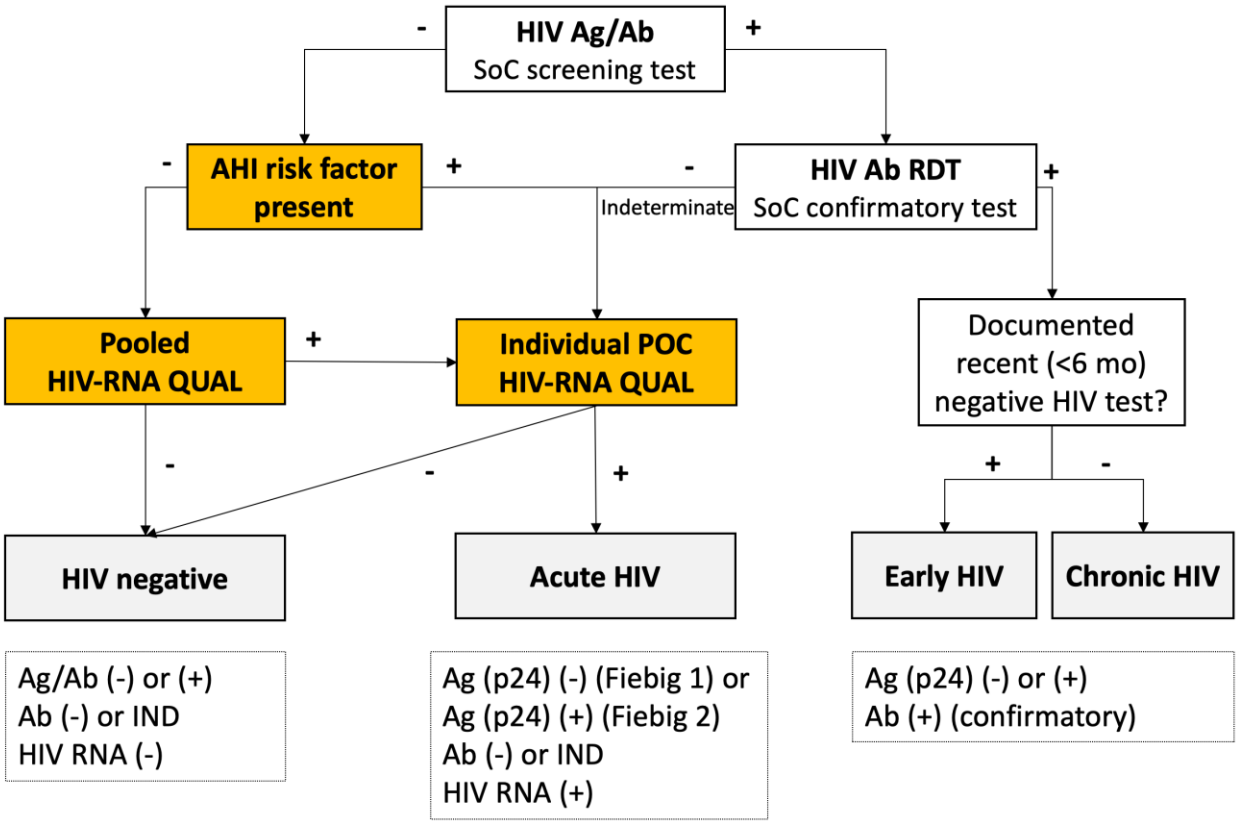

Figure 1: AHI testing algorithm in the INTERACT project**.**

The white boxes represent the standard-of-care HIV testing algorithm in the clinic. The orange boxes represent the add-on AHI screen procedures. The grey boxes represent the final HIV diagnostic classification.

Client attendees who test HIV-negative will be invited to regular subsequent HIV/STI screening visits (e.g. every 3 months), or earlier if they experience any STI or AHI symptoms, in accordance with existing clinic procedures (**Figure 2**).

Each clinic attendee will be given a card with her/his study identification number. To maximize the return rate, with consent of the clinic attendee, the clinic will record home address and telephone number of the client and their relatives/carers (these data will not be recorded in the electronic study database). Phone messages will be sent as reminders for subsequent visits. Follow-up information about health status may be obtained from the participant, relative or caregiver.

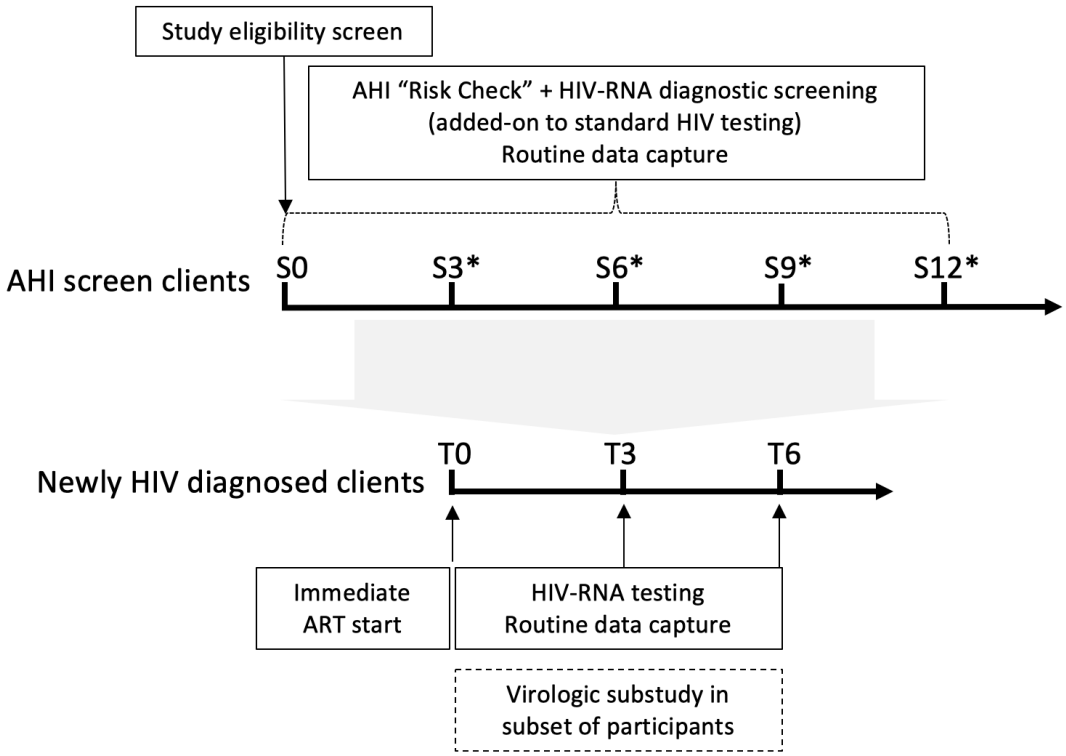

Figure 2: Client visits captured in the INTERACT project

** HIV screening visits are represented as an example only; clients are invited to return to the clinic for regular HIV/STI testing (e.g. 3-monthly: S3, S6, S9, S12), whilst client-initiated testing may occur at any timepoint in between (e.g if they experience STI or AHI symptoms: Sx).*

6.5 Visit procedures for follow-up visits for newly HIV diagnosed clients

Clinic attendees who are newly HIV diagnosed (including AHI) will receive standard follow-up visits according to existing clinic procedures. Additional unscheduled visits may occur in case of any social or medical problem, in accordance with current clinic procedures (**Figure 2**).

At each follow-up visit, clinic staff will extract the following routine clinical data from the clinic attendee's medical records into the study's Electronic Data Capture (EDC):
- Visit date;
- Details of present health, including any signs and symptoms;
- Recent medical history and comorbidities, co-infections, allergies, medication use and pregnancy;
- Recent HIV risk behaviour;
- Recent HIV and STI testing history;
- Partner contact tracing;
- Recent routine lab testing results (including blood counts, biochemistry, CD4+ T-cell count, HIV viral load, co-infections);
- Recent ART details (regimen, start/stop dates, drug substitution/switch, side effects)

At follow-up visits before ART start and at 3 and 6 months after ART start, clinic staff will:
- Perform an additional study-related HIV-RNA Quantitative test, on a routinely collected blood sample;
- Ask about health-related quality of life (EQ-5D-5L, 5-item questionnaire);
- Obtain an extra blood sample in "Virologic sub-study" participants only (after written consent).

6.6 Informed consent approach in core protocol

6.6.1 Digital consent for the "AHI clinical pathway"

The INTERACT project aims to optimize current HIV care delivery and strengthen HIV care cascades, in line with current WHO recommendations for HIV prevention, diagnosis and immediate ART[35]. To avoid introducing any additional obstacles to the HIV/STI screening of hard-to-reach risk groups who are at high risk of acquiring HIV, the research ethics committee will be requested to waive the need for a formal written individual informed study consent for the AHI diagnostic screening, and instead, allow that the clinic attendees, provide digital consent as part of the study eligibility screening process ("Have you read the Participant Information Sheet?" and "Do you agree to the anonymised use of your medical record and your blood sample, for the purpose of this acute HIV screening study?") (**Appendix 3 and 4**). This approach is deemed justified for the following reasons:

- The INTERACT core protocol is a minimal risk activity, consisting of implementation of accepted quality improvement tools to optimize HIV diagnosis, and collection and use of limited clinical data that is expected to be collected as part of standard of care;
- The INTERACT core protocol aims to avoid introducing any additional obstacles (i.e. formal written informed study consent procedure) to the HIV/STI screening of hard-to-reach risk groups who are at high risk of acquiring HIV;
- In the INTERACT core protocol, no samples will be collected other than those taken for routine clinical diagnostic purposes (standard-of-care), and no extra samples will be collected compared to routine care;
- In the INTERACT core protocol, only indirectly identifying information will be collected (patient's clinic ID and date of birth) in order to link screening, clinical and laboratory data held in the site laboratory. The data will be de-identified (pseudonymised) prior to data entry into the study database;
- In the INTERACT core protocol, all clinic attendees will be given an information sheet (PIS) with details about the study (**Appendix 3**). The PIS will inform clinic attendees regarding the purpose and procedures of the study, what it will involve for the participant, and any risks involved in taking part as well as how to get more information. It will be clearly stated that clinic attendees have the right to refuse participation at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. It will also be stated how to withdraw. Any clinic attendee who requests not to be included in the AHI screening study will be recorded accordingly in the screening logbook and will be diagnosed and treated according to standard clinical care. Clinic staff will be readily available to provide further information and answer any questions. For those unable to read the PIS, it will be read to them by clinic staff.

6.6.2 Additional maturity assessment for adolescents

Adolescents in Indonesia are at a particularly high risk of acquiring HIV [4], whilst they may be reluctant to come for HIV testing and disclose this to their parents/legal guardian. This reality makes it challenging to obtain parental consent for participation in INTERACT. To ensure that this important risk group can be included in the AHI screening study, INTERACT will include an assessment of the capability/maturity of individuals aged 16 or 17 years (age 15 and below are excluded), adapted from the Fraser guidelines[37]. The Fraser guidelines were originally developed in the UK in 1985 to help healthcare professionals who work with children to balance the need to listen to children's wishes with the responsibility to keep them safe, applied specifically to advice and treatment about contraception and sexual health. Therefore, a clinic counsellor/doctor will first explain the INTERACT study using the Participant Information Sheet, and then assess if the young person is capable to consent to study participation, based on the following criteria [37] (**Appendix 4**):

1) The young person is 16 or 17 years of age;

2) It is in the young person's best interest to receive access to HIV prevention and testing services, with or without their parents'/carers' consent;
3) The young person cannot be persuaded to inform their parents/carers, or allow the practitioner to do so, that he/she is giving permission to participate in this screening study;
4) The young person understands the purpose of the study, what is required from participants, the risk and benefits of participating; and is able to make an informed, independent decision about his/her study participation;

6.7 Discontinuation/withdrawal of participants from study

There are no criteria for stopping or discontinuing this study, as this is not an experimental study. All participants will be informed about their right to withdraw from the study at any time without having to provide a reason for withdrawal nor having to fear negative consequences. Data, samples and results collected prior to study withdrawal will be used for analysis, unless the participant withdraws consent altogether, in which case these will be destroyed. There is no participant replacement procedure.

6.8 Definition of end of study

The end of study will be the date of the last follow-up visit of the last enrolled participant.

6.9 Laboratory procedures in core protocol

6.9.1 Sample collection

The additional HIV-RNA diagnostic screening in the core protocol will be done on the remnant blood sample already taken for the standard-of-care HIV testing, according to clinic procedures. A trained phlebotomist/nurse will perform the blood drawing in accordance with the clinic SOP. We will use approximately 1 mL of remnant EDTA plasma to perform the HIV-RNA test.

6.9.2 Sample processing

Study samples will be labelled with the study code along with patient ID and date and time of collection. Date and time of collection and receipt will be recorded and samples are processed immediately, as per study SOP. The specimen details will be entered immediately into a study database upon receipt. Specimens in EDTA tube will be centrifuged at room temperature to separate the plasma. The plasma will be stored at -4ºC in the site laboratory until use (usually on the same day, in exceptional cases the next day).

6.9.3 Laboratory assays and plan for testing

The current standard-of-care HIV testing algorithm at the clinics (compliant with MOH guidelines) includes a fourth generation HIV Ag/Ab screening test (i.e. Alere Determine HIV1/2 Ag/Ab Combo, or equivalent) on a whole blood sample. Ag/Ab-reactive specimens undergo confirmatory testing with a third-generation HIV Ab RDT (i.e. Bioline HIV1/2, or equivalent) on a whole blood sample (**Figure 1**).

The study protocol will apply sequential, additional HIV-RNA diagnostic screening to all specimens that are HIV Ag and Ab negative or indeterminate, using a study-specific SOP (**Figure 1**). Briefly:

- All specimens are identified by testing number only and the laboratory staff will be blinded to clinical information other than the AHI risk being high or low ("Risk Checker").

- HIV Ag/Ab-negative participants who are at high-risk of AHI (based on presence of one or more risk factors in the "Risk Checker") receive an individual, point-of-care HIV-RNA diagnostic test (Xpert HIV-

1 Qual); only if an individual specimen is HIV-RNA-positive, confirmatory testing is done with Xpert HIV-1 Qual (final result reported on the same day, or in exceptional cases <24h).

- All other participants who are not at high-risk of AHI (based on absence of any risk factor in the "Risk Checker") will be screened for HIV-RNA using a pooled (group) sampling approach (Xpert HIV-1 Qual). No further testing will be carried out on any pooled samples that are HIV-RNA-negative; only if a pool is HIV-RNA-positive, resolution/deconvolution testing will be done on the constituent individual samples using Xpert HIV-1 Qual (final results reported <72h).

- Using this approach, confirmatory RT-PCR is being performed on all HIV-RNA-positive specimens before they are reported as being HIV positive.

Considering the high test specificity of the Xpert HIV-RNA Qual assay (>99%), laboratory operator workload, the current practice of daily PCR runs, number of daily HIV tests, and a preference to avoid freeze-thaw cycles, a simple two-stage manual pooling scheme, modified from a protocol described by Quinn et al., is deemed most feasible to achieve an optimal combination of diagnostic accuracy, rapid diagnosis (turnaround time) and test efficiency[15,18,19]. Currently, no local data are available to reliably inform the expected AHI incidence in the study population. Based on the global literature among MSM populations[17], we assumed a probability of an individual sample testing HIV-RNA positive 0.2% (95%CI 0.1-0.3). Given a test specificity and sensitivity of >99%, Saraniti et al. [38] estimated the optimally efficient pool size for a two-stage testing approach to be between 49 and 100 specimens at a prevalence between 0.1% and 0.3%. To avoid any operating errors in the site laboratories, we will start off with a manageable pool size of maximum 10 specimens. An initial lab evaluation will be performed to adjust and optimise the pooling scheme as needed. The pooled testing procedure will be trained to site laboratory staff and further described in detail in a study-specific SOP, with close monitoring and oversight provided by the OUCRU-ID laboratory experts.

Xpert HIV-1 Qual assay (AHI diagnosis)

The Xpert HIV-1 Qual assay (Cepheid), performed on the GeneXpert Instrument Systems, is a qualitative in vitro diagnostic test designed to detect HIV-1 total nucleic acids on the automated GeneXpert Systems using human whole blood or dried blood spot specimens from individuals suspected of HIV-1 infection and is validated for specimens across Group M (subtypes A, B, C, D, F, G, H, J, K, CRF01_AE, CRF02_AG, and CRF03_AB), Group N, and Group O. The assay has a linear range of 1,000 to 10,000,000 copies/ml.
The limit of detection (LOD) in whole blood is 278 copies/mL (WHO reference standard). Equivalent performance has been shown for whole blood and plasma specimens. The assay combines automated and integrated sample preparation, nucleic acid extraction and amplification, and detection of the target sequence using real-time reverse transcription PCR (RT-PCR) technology. It includes an internal control and is performed in single-use disposable cartridges thereby minimizing cross-contamination between samples. The HIV-1 Qual assay's intended use is to detect early HIV-1 infection (before antibody detection) such as for Early Infant Diagnosis or AHI.

Interpretation of HIV test results and estimated numbers

Following the standard clinic HIV testing algorithm and the sequential, additional HIV-RNA diagnostic screening, participants will be classified as follows:

Table 2: HIV case definitions

	HIV RNA	HIV Ag (p24)	HIV Ab	Previous test result	Estimated N in this study
HIV-negative	-	+/-	-/IND		6300-6700
AHI	+	- (Fiebig 1) or + (Fiebig 2)*	-/IND		100-150

EHI	+	+	+	AND documented negative HIV test <6 months prior	80-100
CHI	+	+/-	+	AND last negative test >6 months prior OR no previous test result available	700-800

Xpert HIV-1 Viral Load Quant assay (ART monitoring)
The Xpert HIV-1 VL assay (Cepheid) is a quantitative in vitro reverse transcriptase polymerase chain reaction (RT-PCR) assay for the detection and quantification of Human Immunodeficiency Virus type 1 (HIV-1) RNA in human plasma from HIV-1 infected individuals on the automated GeneXpert Instrument Systems. The assay can quantify HIV-1 RNA over the range of 40 to 10,000,000 copies/mL. The Xpert HIV-1 VL assay is validated for quantification of RNA from HIV-1 Group M (subtypes A, B, C, D, F, G, H, J, K, CRF01_AE, CRF02_AG, and CRF03_AB), Group N, and Group O. The Xpert HIV-1 VL assay is intended for use in conjunction with clinical presentation and other laboratory markers for disease prognosis and for use as an aid in assessing viral response to antiretroviral treatment as measured by changes in plasma HIV-1 RNA levels. The assay combines automated and integrated sample preparation, nucleic acid extraction and amplification, and detection of the target sequence using real-time reverse transcription PCR (RT-PCR) technology. It includes an internal control and is performed in single-use disposable cartridges thereby minimizing cross-contamination between samples.

6.9.4 Laboratory quality assurance
All laboratory procedures are performed according to SOPs and with high quality standards by experienced laboratory teams at Globalindo and Bali Peduli, with technical assistance provided by lab experts from OUCRU-ID. A quality management system will be implemented, including SOP for each study procedure performed, internal and external quality control procedures, site supervision and monitoring visits, and a data monitoring plan.

6.10 Implementation evaluation of the AHI clinical pathway

6.10.1 Conceptual framework

This project design and evaluation will be guided by the Consolidated Framework for Implementation Research (CFIR)[31,33]. The CFIR offers an efficient path to systematic knowledge building about barriers and facilitators of implementing multi-component interventions, and thus contributes to defining tailored implementation strategies within learning healthcare systems. The CFIR comprises five domains (intervention characteristics, outer setting, inner setting, characteristics of the individuals involved, and the process of implementation) [33], and can be used to help guide formative evaluations of interventions in context about what works where, prior, during and after implementation. In implementation research, three types of interrelated outcomes can be evaluated[34]: 1) implementation outcomes (e.g. feasibility, fidelity, acceptability, uptake and costs); 2) service outcomes (e.g. effectiveness, efficiency, patient-centeredness and timeliness); 3) client outcomes (e.g. client satisfaction; function; symptomology, improvement in performance of the service provider).

6.10.2 Evaluation procedures
We will conduct an implementation evaluation of the INTERACT intervention to assess barriers and enablers, focusing on the most relevant domains of the CFIR framework[33], i.e. intervention characteristics, inner setting, characteristics of the individuals involved, and the process of implementation. We will conduct 15-20 structured interviews across the 3 study sites, early in the third year of the project. The site implementation leaders and the INTERACT study coordinator will be invited via e-mail to participate in an in-person or online video (MS Teams) interview. After these interviews will be completed, additional staff members involved with the AHI clinical pathway will be interviewed. Interviews will be audio-recorded, and transcribed verbatim. Participants will be asked to provide oral consent at the beginning of the interview audio-recording. The CFIR Interview Guide Tool will be used to build a customized interview

guide based on the relevant CFIR domains that are most relevant to the INTERACT project (https://cfirguide.org/guide/app) (**Appendix 6**). The CFIR provides the structure for the initial codebook to guide qualitative data coding using a descriptive content coding approach, using NVivo software.

7 COMMUNITY ENGAGEMENT

7.1 Stakeholder engagement

The INTERACT project is seeking strong community and policy stakeholder support, including from the Directorate of Communicable Disease Prevention and Control, Ministry of Health (MOH); Joint UN Programme for HIV/AIDS (UNAIDS) Indonesia office; Spiritia, the nationally leading organization for advocacy and community peer support to key populations; and Bali provincial government. At project initiation and completion, we will organize meetings to consult with academic and the abovementioned non-academic stakeholders, specifically the MOH HIV/AIDS and STI Working Group and Expert Panel, to formulate optimal strategies for implementation of the proposed intervention, community engagement, maximizing impact and dissemination plans. A community advisory group will be established for regular consultation and feedback throughout the project.

7.2 Digital behavioural and risk assessment tool

Structural and social barriers impede access to sexual health services for hard-to-reach groups in Jakarta and Bali[39]. We will therefore employ a digital behavioural tool to reach key populations, particularly MSM, to increase motivation to access testing and treatment services, and mobilise them to self-identify AHI symptoms. Our approach combines extensive hands-on and research experience with intervention models targeting HIV transmission in relevant settings in London, Amsterdam, Kenya and Indonesia, with in-depth knowledge and understanding of the Indonesian health system, key populations and stakeholders. The digital tool will be based on the premise and functionality of the 56 Dean Street PRIME intervention (http://prime.dean.st/) and will build on innovative methods implemented through the UTAMA social study in Bali (https://www.utamaindonesia.org). The Utama digital HIV risk reduction tool has been developed and highly tailored to the MSM population through direct target population engagement via a social science study[40,41]. For INTERACT, we will develop interactive digital tools to tailor key health messaging through social media and short films, the content of which is informed by target populations in Jakarta and Bali. Additional features will include tailored health promotion short videos and narratives from the community, message alerts to new content, for example, themed content on HIV testing, AHI and its symptoms, U=U, HIV and STI risk reduction, ART and PrEP)[17]. Digital outreach will use targeted social media and popular gay men's wellbeing apps, using QR codes and text messaged links via codes that users can delete whenever they want. Where feasible, complementary physical outreach by health workers or peer educators will be employed to locate harder-to-reach groups who are less likely to engage in HIV services, who are not on social media, or who do not self-identify within a key population.

8 ANCILLARY STUDIES

8.1 Virological Substudy

8.1.1 Background and study rationale

Little contemporary data exist on the levels and patterns of the transmission of drug-resistant HIV-1 variants in Indonesia. This information is critical to inform policy on optimal, empiric ART regimens used in the public health approach. This study offers a unique opportunity to measure prevalence of transmitted HIV drug resistance in key populations during acute or early HIV infection. Additionally, there is a lack of information on the mixing of local HIV-1 epidemics within and between key populations in Indonesia. In addition, little is known about HIV-1 transmission between different geographic areas in Indonesia. Phylodynamic analysis has been widely used to determine HIV-1 networks, reconstruct virus historical spatial dissemination, as well as assessing rates of virus flow between populations with varying HIV-1

prevalence. However, due to the scarcity of HIV-1 sequences from key populations in Indonesia, phylogeographic assessment of HIV-1 transmission rates between populations and locations are rare.

We propose a combined analysis of HIV-1 phylogenetic and epidemiological data from the INTERACT project to reconstruct HIV-1 networks and to empirically quantify rates of HIV-1 flow between risk groups and geographic regions to identify and determine the contribution of HIV-1 'hotspots' in sustaining HIV-1 transmission in Indonesia. The information from this sub-study can be useful for designing targeted public health interventions, optimizing ART regimens, and strengthening HIV control and can also help understand if the INTERACT intervention will only impact on the actual risk groups involved or could have wider impacts among other risk groups.

8.1.2 Enrolment and consent procedures

Participant enrolment A subset of the INTERACT study participants who are newly diagnosed with HIV during the study enrolment period will be invited to have an additional blood sample taken, outside of standard-of-care, for HIV-1 genotyping and to store the remaining blood sample for the purpose of evaluating the host immune response to AHI, including immunogenetic testing of host DNA. The study sample will comprise all consenting participants who are newly diagnosed with AHI or EHI (estimated N=250), plus a random subset of those newly diagnosed with CHI (N=250) during the study enrolment period (total target N=500).

Written informed consent procedure Individual written informed consent will be obtained to participate in the "Virologic Sub-Study" (**Appendix 7**). Participants who are invited for participation will be given an information sheet (PIS) with details about the Virologic Sub-study. The PIS will inform participants regarding the purpose and procedures of the sub-study, what it will involve for the participant, and any risks involved in taking part as well as how to get more information about the project. It will be clearly stated that participants have the right to refuse participation at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. It will also be stated how to withdraw. Any patient who requests not to be included in the sub-study will be recorded accordingly in the screening logbook and will be diagnosed and treated according to standard clinical care. The study participant (or guardian/representative) must sign and date the latest approved version of the Informed Consent form before any study-specific activities are undertaken. Adolescents aged 16 or 17 years that take part in INTERACT, may also take part in the sub-study, if they provide their written individual assent. The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent will be suitably qualified and authorised by the Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

8.1.3 Laboratory procedures

Sample collection For participants in the "Virologic substudy", an additional blood sample will be drawn at 3 timepoints during clinic visits that are part of routine HIV care follow-up, i.e. before ART start and at 3 and 6 months after ART start:

- 4 mL blood into an EDTA blood collection tube (for HIV-1 sequencing and remnant plasma storage);
- 4 mL blood into a serum (clotted) collection tube (for serum storage);
- 12 mL blood into an EDTA blood collection tube (for PBMC and remnant plasma storage) (Jakarta participants only);

Thus, the total amount of blood taken is 8 mL x 3 time points (total 24 mL) for Bali participants and 20 mL x 3 time points (total 60 mL) for Jakarta participants.

Sample processing, storage and shipping Study samples will be labelled with the study code along with patient ID and date and time of collection. The extra samples collected in the "Virologic Sub-study" will be transferred to the OUCRU-ID laboratory in central Jakarta (from Globalindo) or Bali Peduli laboratory in Denpasar (from Bali Peduli) at 4-8°C within 8 hours after collection. Date and time of collection and receipt will be recorded and samples are processed immediately, as per study SOP. The specimen details will be entered immediately into a study database upon receipt. Specimens in clotted blood tube will be centrifuged at room temperature to remove the clotted-blood and collect the sera. Specimens in EDTA tube will be centrifuged at room temperature to separate the plasma. The plasma will be cryopreserved in -80ºC (or if not available on-site temporarily at -20°C for a maximum of 4 weeks). For Jakarta samples, peripheral blood mononuclear cells (PBMCs) will be separated from EDTA whole blood using density gradient centrifugation as per study SOP, and cryopreserved in liquid nitrogen for later use at OUCRU-ID, central Jakarta. Aliquots of serum, plasma and PBMCs will be archived at a secured -80°C freezer at OUCRU-ID, central Jakarta, for later use.

Planned laboratory testing The Investigators are in the process of securing the funding and resources to perform standard HIV-1 sequencing, using either Sanger or next-generation sequencing (whichever locally feasible) of at a minimum HIV-1 reverse transcriptase, protease and integrase gene regions, based on accepted lab protocols. The genotypic lab testing will be conducted in the Virology Department of the Faculty of Medicine Universitas Indonesia, which is a WHO-accredited laboratory for HIV-1 genotyping.

8.1.4 Sample storage for future ethically approved research in "Virologic Sub-study"

The feasibility and range of any additional tests on stored samples will depend on available funding and emerging scientific insights, and **will only be proposed as part of future research after additional EC approval has been obtained through a protocol amendment**, which will include a detailed research plan. To investigate the evolution of the HIV-1 reservoir and host immune response during AHI, plasma markers (including cytokines and microRNAs) and PBMCs are planned to be further evaluated for components of B-cells and T-cells. Immunogenetic testing may be performed, restricted to understanding the host response to infection, such as HLA typing and Toll-like receptor analysis. We will further consider the possibility of applying novel assays for public health benefit in AHI diagnosis or prognosis, driven by advances in diagnostic technologies, and may include HIV recency assays, antibody assays, biomarker detection such as cytokine multiplex assays and proteomics, RNA sequencing and further assays of immune cell phenotype and function. If specific laboratory capacity is not available in-country, sample export to an overseas research laboratory may be considered, only after formal approval of a Material Transfer Agreement through the designated MOH committee.

9 DATA MANAGEMENT

9.1 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, ethics committee and any host institution for monitoring and/or audit of the study to ensure compliance with regulations.

9.2 Data Handling and Record Keeping

All clinic attendees and attendances will be allocated a unique clinic identification number. All data including coded data on HIV risk behaviour, STI diagnoses, HIV status and recreational drug usage will be entered by designated clinic staff into an encrypted study-specific Electronic Data capture (EDC) developed by OUCRU-ID. To enable smooth and efficient data-entry and validation, patient data will be entered into the EDC, with an error reading step, prior to daily uploading onto the secured OUCRU-ID server hosted in Indonesia. To maintain confidentiality, the study EDC will be fully de-identified, and will not include any subject names or other personal identifying information. The only demographic data collected on clinic

attendances will be year of birth or age, gender and area of residence. Personally identifiable information (name, mobile, phone number and/or email address) and identification numbers will not be entered in the EDC, will be kept on site only and physically separate and secure. The EDC will be password protected and encrypted. Data will be stored on secure password protected, encrypted laptop or desktop computers at the study clinic that can only be accessed by designated study trained staff. All code for the individual-based model (IBM) will be made fully open source, along with the sets of parameters used to run each of the simulations, on a long-lived public repositories (e.g. Github). At the beginning of each run, the GSL (GNU scientific library) random number generator seed will be recorded enabling individual simulations to be reproduced. All code and relevant data (including simulation runs) will be stored in the medium-term on a secure local server at the Big Data Institute, Oxford, and in the long term on encrypted hard drives.

9.3 Data retention

Data will be retained for at least 5 years on secured servers in Indonesia after end of study. Standardized protocols and SOPs will be followed for quality control/quality assurance of clinical evaluations, biological sample procurement and preparation, and all laboratory procedures.

9.4 Quality control and assurance procedures

The project will be conducted in accordance with relevant regulations and standard operating procedures. Pre-surveillance site visits will ensure that laboratory diagnostics meet baseline international standards. Clinical quality assurance will comprise clinic staff training on the study protocol and SOPS prior to the start of the study. The local investigator shall be responsible for the conduct of the study at their site, using a standard internal quality control procedure. Data in the study database will be regularly reviewed by the Study Coordinator, or delegate, for completeness and accuracy. The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

10 SAFETY CONSIDERATIONS

The implementation study comprises enhanced diagnostic AHI screening, and is largely observational in nature otherwise, with collection of routine data from clinic attendees. There are no invasive procedures, except for blood draws routinely done as part of clinical care. For participating clinic attendees, risks are essentially no greater than they are for routine health care at the clinic. For this reason, there will be no adverse event reporting.

11 STATISTICS AND ANALYSIS

11.1 Sample size estimation

Data on AHI incidence, risk profiles or clinical syndromes are not available in Indonesia and scarce in LMIC, although our clinic data review at Globalindo and Bali Peduli suggested an expected high uptake of AHI suspected clients. Due to COVID-19 mobility restrictions, April-June 2020 saw a drop in clinic attendance, with a subsequent recovery of clinic operations at Globalindo to 100% and a protracted 30-50% drop at Bali Peduli, expected to show further recovery in 2023.

Based on recent client and test data (numbers and positivity %) at the three study sites (**Table 1**), the estimated number of clients who undergo an HIV test in a 12-month period will be 7,500, of whom ~88% (6,600) HIV Ab-negative. We estimate that the proportion of clinic attendees with a high risk of AHI is ~50% (personal communication with sites) and that the estimated diagnostic AHI yield of risk/symptom targeted, individual RNA testing is 3.3% (95%CI 2.2-4.6) (based on synthesis of the current literature[17]). With these assumptions, we estimate that the proposed AHI screening score and testing algorithm will require 3,300 individual RNA tests to identify 109 new AHI cases in a 12-months period (with 95% confidence of finding between 73 and 152 new AHI diagnoses), yielding an absolute precision of ±1.7%, given alpha 5%. The

complete AHI testing algorithm is estimated to additionally identify 7 persons with AHI through pooled RNA testing (assumed yield 0.2%, 95%CI 0.1-0.3, for universal testing[17]); 86 persons with EHI, and 770 persons with CHI in the same period.

11.2 Effectiveness metrics of the AHI pathway

AHI screening outcomes Descriptive statistics will be used to summarise baseline socio-demographic, behavioural and clinical characteristics, and descriptive outcome measures will be expressed as absolute number and proportions for discrete outcomes and median (IQR) or mean (SD) for continuous outcomes. The performance of the Amsterdam AHI screening score will be prospectively evaluated with respect to diagnostic AHI yield, sensitivity, specificity, positive and negative predictive values, and area under the receiver operator curve (AUC), overall and stratified by key population. To optimise the Amsterdam screening score and adjust the score to the local context, we will assess the association between these socio-demographic, behavioural and clinical characteristics and AHI in the clinic attendees with multivariable logistic regression modelling. Generalised estimating equations with an exchangeable covariance matrix and robust standard errors will be used to adjust for multiple observations per participants. Each predictor associated with AHI in univariable logistic regression at $p<0.20$ will be included in the multivariable model. Variables with $p>0.05$ in the multivariable model will then be dropped by a backward selection approach. We will test for interaction between each of the variables included in the final multivariable model. The variables in the final multivariable model will be used to create an optimised screening score. Regression coefficients rounded to the nearest decimal will be summed to calculate an individual's screening score at each visit. Performance of the optimised screening score in predicting AHI/EHI in our cohort will be examined by calculating sensitivity, specificity and the AUC. We will adjust for optimism using 100 bootstrap draws. AUCs of the Amsterdam score and the locally optimised screening score will be compared using the DeLong method. The best cutoff (i.e. the cutoff at which sensitivity and 1 – specificity are highest) of the optimised screening score will be defined by using the Youden index. If the locally optimised score performs significantly better than the Amsterdam score, the locally optimised score will be validated externally in independent AHI cohorts from Amsterdam and Kenya.

HIV care cascade outcomes To evaluate HIV care cascade outcomes, three groups will be compared: participants who received same-visit delivery of diagnosis (POC HIV-RNA testing), participants who received <72h delivery of diagnosis (pooled HIV-RNA testing), and participants who received their confirmed diagnosed 3 days or longer after initial testing. Additionally, three groups will be compared to assess the impact of early ART initiation on HIV care cascade outcomes (ART initiation within 24 hours, within 7 days, or after 7 days after confirmed HIV diagnosis). HIV care cascade outcomes include time between diagnosis, ART initiation and subsequent viral suppression and will be assessed with Kaplan-Meier estimates. and the groups will be compared by using the log-rank test. Proportions of participants who have achieved viral suppression at 12 and 24 weeks on ART of the three groups will be compared using the Kruskal-Wallis rank test. To assess whether the clinical AHI diagnosis and treatment path leads to an increased number of individuals diagnosed with AHI, starting immediate ART, and achieving faster viral suppression, a historical comparison will be made. These outcomes will be extracted from aggregated routine clinic data in the period 2017-2022 from the 3 study sites, since during this period universal ART has been offered to all routine care clients, regardless of CD4 count at HIV diagnosis. HIV care cascade outcomes of participants included in the study will be compared to outcomes of routine care clients by using the chi squared test or log-rank test as appropriate.

11.3 Modelling the effect of the AHI pathway on HIV epidemic control in Indonesia

Mathematical modelling is a key tool for long-term predictions and policy planning. We will use mathematical and economic modelling to inform policy as to what extent the intervention could contribute to HIV epidemic control in Indonesia. We will involve experienced modellers to extend the PopART

individual-based model (IBM), a computationally efficient, open-source IBM originally designed for the HPTN 071/PopART trial in Zambia and South Africa[42,43]. The project will deliver an adapted IBM suitable for settings where transmission predominates along MSM, transgender people and sex workers, appropriate for Indonesia. PLWH are classified as treated or untreated, and in disease stages. Input parameters assumptions will be based on the study data (e.g. test uptake, HIV positivity fraction, AHI algorithm yield and incidence, care cascade indicators, time to viral suppression), and other publicly available epidemiological and clinical data sources. Where parameters cannot be estimated, a calibration process will be used based on adaptive Monte Carlo Approximation Bayesian Computation. Epidemic projections will be made based on different intervention scenarios.

11.4 Estimating cost-effectiveness of the AHI pathway

The AHI screening intervention will be compared with no intervention in terms of cost and the outcomes measures for assessing the cost-effectiveness. The cost of the intervention will be estimated as the total cost of providing the intervention less cost-of-treatment prevented by it. The intervention cost will be calculated by quantifying and valuing the required resources (e.g. staff, equipment, supplies) using market price. The health facility cost of managing HIV patients will be collected from the clinics. The outcome of the intervention will be measured using quality-adjusted life year (QALY), obtained by multiplying the quality-of-life weight of each health state's (e.g. healthy, diagnosed, treated, death) by the duration spent in that health state and then summing over all of the health states. For this purpose, a random sample of participants (N=100) will be asked to self-complete the 5-item EuroQol-5 Dimension (EQ-5D-5L) questionnaire on health-related quality of life. The incremental cost-effectiveness ratio (ICER) will be estimated using an economic modelling approach. The theory of dominance will be applied to choose a cost-effective strategy. Finally, probabilistic sensitivity analyses will be performed accounting for the uncertainty of model parameters to quantify the level of confidence in the cost-effectiveness of the intervention.

12 STUDY MANAGEMENT

12.1 Time planning

The project duration is foreseen for 36 months, with a start date of 1 December 2022.

	Year 1				**Year 2**				**Year 3**			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Stakeholder meetings	x											x
Protocol approval and permissions	x	x										
Develop electronic data capture	x	x										
Enrolment and AHI screening			x	x	x	x						
Follow-up of newly HIV diagnosed clients			x	x	x	x	x	x				
Development of digital behavioural tool	x	x	x	x								
Implementation of digital behavioural tool			x	x	x	x	x	x	x	x		
Data analysis (Obj 1+2)							x	x	x	x		
CFIR evaluation (Obj 3)									x	x		
Math modelling study (Obj 3)							x	x	x	x	x	x
Cost-effectiveness study (Obj 3)									x	x	x	x
Reporting & Dissemination								x				x

12.2 Study Management

The execution of this study will be a joint effort between Yayasan Globalindo and Bali Peduli, Universitas Atma Jaya, Udayana University, Universitas Indonesia and Oxford University Clinical Research Unit Indonesia (OUCRU-ID). The team of investigators share overall responsibility for managing the study, with the PI having final responsibility. The study will be overseen by a Project Management Group that includes the PI, Co-PIs, Co-Investigators, and study coordinator.

13 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The implementation study will be conducted in accordance with relevant regulations and standard operating procedures. Pre-study site assessments will ensure that clinic and site laboratories meet baseline standards. Clinic staff will be trained in the protocol and relevant study procedures prior to the start of the project. Study support staff will work closely with clinic staff to achieve the project goals while ensuring smooth continuation of services. Data quality will be assured by training, validation steps built into data capture, and central monitoring. The local investigator shall be responsible for the conduct of the study at their site, using a standard internal quality control procedure.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Declaration of Helsinki and Good Clinical Practice

The Investigators will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki, relevant national regulations and Good Clinical Practice.

14.2 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to the Atma Jaya University Research Ethics Committee (REC) and Oxford Tropical Research Ethics Committee (OXTREC) for written approval. The Investigators will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents. Additional government permisson will also be obtained as appropriate. An MTA to allow for possible sample export will be requested through the MOH.

14.3 Reporting

The PI shall submit once a year throughout the study, or on request, a final report will be submitted to the same parties.

14.4 Discontinuation/withdrawal of participants from study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening);
- Significant protocol deviation;
- Significant non-compliance with study requirements;
- Withdrawal of consent.

For participants who withdraw from the study, data, samples and results collected prior to study withdrawal will be used for analysis, unless the participant withdraws consent altogether, in which case these will be destroyed. Withdrawn participants will not be replaced. The reason for withdrawal by researcher (and by participant, if this information is volunteered) will be recorded in a study file.

14.5 Participant confidentiality

The study staff will ensure that the participants' anonymity is maintained in all electronic study documents. Personal information (such as address and telephone) necessary for study follow-up will not be entered into the electronic study database, and will only be kept at the study site. Data stored for analysis will not bear the names of patients or staff and neither patients, staff nor clinics will be named in any published reports. Every participant record will be given a unique, not identifiable study number on all study documents and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. All data will be stored in password-protected computer files. The study will comply with the Data Protection Act, which requires data to be de-identified as soon as it is practical to do so.

14.6 Data ownership

Data ownership will be shared between the members of the INTERACT Research Consortium. The Investigators of Universitas Atma Jaya and OUCRU-ID are guardian of the data within the database and stored samples. The Investigators will jointly analyse the data and generate reports. Access to the study bio-archive intended for future appproved research will follow a formal process of application to the team of Investigators, in order to coordinate and prioritize sample usage for highest public health relevance.

14.7 Expenses and Benefits

Participants will not occur any study-related expenses and will not be paid for their participation. Clinic staff will receive additional training and support on good research practices and quality HIV/STI services, that are considered standard of care in many other settings. This may assist in the appropriate screening/management of HIV/STI, and improve the overall quality of care provided, which may or may not be beneficial to individual participants.

14.8 Risks

This is an implementation study that involves minimal risks to study participants: HIV-RNA testing for diagnostic screening is a well-established and widely used diagnostic method in many other settings (e.g. Early Infant Diagnosis). There are no invasive procedures, except for blood draw, which is associated with the discomfort of having a needle stick, with minor pain and occasional temporary bruising at the site. Potential for loss of confidentiality will be mitigated as described above.

15 FINANCE AND INSURANCE

15.1 Funding

The project has received funding from the Applied Global Health Research Board at the Medical Research Council (MRC)-Research and Innovation (UKRI), UK.

15.2 Insurance

This research will be appropriately covered through the University of Oxford's legal liability insurances.

16 PUBLICATION POLICY

Several summary manuscripts, reporting the results of the implementation study, will be prepared by the core investigator team. Investigators from all institutions will be involved in producing and reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorships will be determined following guidelines developed by the International Committee of Medical Journal Editors, and other contributors will be acknowledged. Publications will be reviewed and approved

by all investigators and their institutions prior to release. Any manuscript derived from this study will be published under Open Access policy.

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18 APPENDIX 1: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
0	1.0			NA (Initial version)

19 APPENDIX 2: STUDY SCHEDULE

	AHI screen clients *Subsequent screen visits[1]*						**Newly HIV diagnosed clients** *ART followup visits[2]*			
	S0	**S3**	**S6**	**S9**	**S12**	**Sx[1]**	**T0**	**T3**	**T6**	**Tx[2]**
Study eligibility screening and digital consent	x									
Maturity assessment (for adolescents only)	x									
AHI "Risk Checker"	x	x	x	x	x	x				
HIV-RNA diagnostic testing on remnant blood sample (QUAL)	x	x	x	x	x	x				
EuroQol-5 Dimension (EQ-5D-5L) questionnaire (random subset N=100)	x	x	x	x	x	x	x	x	x	
In newly HIV diagnosed clients, HIV-RNA monitoring (QUANT)							x	x	x	
De-identification and extraction of routine data from participants' medical records into electronic study database	x	x	x	x	x	x	x	x	x	x
"Virologic Sub-study" participants only:										
- Written informed consent	x						x			
- Additional blood sample collection							x	x	x	

1. HIV screening visits: clients are invited to return to the clinic for regular HIV/STI testing (e.g. 3-monthly: S3, S6, S9, S12), whilst client-initiated testing may occur at any timepoint in between (e.g if they experience STI or AHI symptoms: Sx). Maximum duration of individual participant followup in the screening cohort is 12 months (but may be shorter if participant is enrolled in the course of the project)
2. Unscheduled visit, e.g. for medical or social reasons (Tx).

20 APPENDIX 3: PATIENT INFORMATION SHEET – CORE STUDY

21 APPENDIX 4: STUDY ELIGIBILITY SCREENING AND CONSENT – CORE STUDY (FORM 1)

22 APPENDIX 5: AHI RISK CHECKER – CORE STUDY (FORM 2)

23 APPENDIX 6: CFIR INTERVIEW GUIDE

24 APPENDIX 7: PATIENT INFORMATION SHEET & INFORMED CONSENT FORM _CFIR Interview

25 APPENDIX 8: PATIENT INFORMATION SHEET & INFORMED CONSENT FORM – VIROLOGIC SUB-STUDY