

NIDA CTN Protocol 0056

**Testing and Linkage to HIV Care in China:
A Cluster Randomized Trial**

Study 1

Lead Investigator: Zunyou Wu, MD, PhD

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CONTACT INFORMATION

NCAIDS

National Center for AIDS/STD Control and Prevention
Chinese Center for Disease Control and Prevention
155 Changbai Road, Changping District
Beijing 102206, China

Lead Investigator

Zunyou Wu, MD, PhD

Director

Tel: +86-10-5890-0901

Fax: +86-10-5890-0900

Email: wuzy@263.net; wuzunyou@chinaaids.cn

Co-Investigator

Zhengzhu Tang, MD, MS

Director, Guangxi Center for Disease Control
and Prevention, Nanning, Guangxi

Tel: +86-771-2518766

Fax: +86-771-2518768

Email: tangzhzh@163.com

Co-Investigator

Yurong Mao, MD, PhD

Acting Director of Division of Integration
and Evaluation, Beijing

Tel: +86-10-5890-0985

Fax: +86-10-5890-0984

Email: zoemao@gmail.com

Co-Investigator

Yan Zhao, MD, MS

Deputy Director of Division of Treatment
and Care, NCAIDS, Beijing

Tel: +86-10-5890-0927

Fax: +86-10-5890-0929

Email: zhaoyan1973@sina.cn

Co-Investigator

Shicheng Yu, PhD

Senior Epidemiologist and Biostatistician
Division of Health Statistics, NCPHSIS,
Beijing

Tel: +86-10-5890-0420

Fax: +86-10-5890-0450

Email: shicheng_yu@163.com

Co-Investigator

Keming Rou, BSW

Acting Director of Division of Prevention
Intervention, NCAIDS, Beijing

Tel: +86-10-5890-0948

Fax: +86-10-5890-0947

Email: kemingrou@gmail.com

Project Manager

Diane Dai Gu, MPH

CTN 0056 Project Office, Beijing

Tel: +86-10-5890-0919

Fax: +86-10-5890-0920

Email: dianedaigu@gmail.com

Research Assistant

Cynthia Shi

CTN 0056 Project Office, Beijing

Tel: +86-10-5890-0919

Fax: +86-10-5890-0920

Email: cynthiashshi@gmail.com

Research Assistant

Xia Jin, MS

Division of Integration and Evaluation, Beijing

Tel: +86-10-5890-0984

Fax: +86-10-5890-0984

Email: jinxiajiangsu@126.com

Research Assistant

Houlin Tang, MS
Division of Integration and Evaluation,
NCAIDS, Beijing
Tel: +86-10-5890-0627
Fax: +86-10-5890-0627
Email: tanghoulin99@163.com

Research Assistant

Sitong Luo, MS
CTN 0056 Project Office, Beijing
Tel: +86-10-5890-0919
Fax: +86-10-5890-0920
Email: lst_violet@163.com

Co-Investigator

Walter Ling, MD
Professor of Psychiatry and Director
Integrated Substance Abuse Programs
Dept. of Psychiatry & Biobehavioral Sciences
David Geffen School of Medicine at UCLA
1640 S. Sepulveda Blvd., Suite 120
Los Angeles, CA 90025-7535 United States
Tel: +1-310-267-5888
Fax: +1-310-312-0552
Email: wling@mednet.ucla.edu

Albert Hasson, MSW
Tel: +1-310-267-5224
Email: alhasson@ucla.edu

Betty Tai, PhD
Tel: +1-301-443-2397
Email: btai@nida.nih.gov

Lynda Erinoff, PhD
Tel: +1-301-402-1972
Email: lerinoff@nida.nih.gov

Ron Dobbins, MBA
Tel: +1-301-451-9575
Email: rdobbins@nida.nih.gov

Carol Cushing, BBA, RN
Tel: +1-301-443-9815
Email: ccushing@nida.nih.gov

Research Assistant

Xiao'ai Qian
CTN 0056 Project Office, Beijing
Tel: +86-10-5890-0919
Fax: +86-10-5890-0920
Email: 840273693@qq.com

Field Director

Zhiyong Shen, MD
Guangxi Center for Disease Prevention
and Control, Nanning, Guangxi
Tel: +86- 15177198299
Email: shenzhiyong99999@sina.com

UCLA

Co-Investigator

Roger Detels, MD, MS
Professor of Epidemiology
UCLA School of Public Health
10833 Le Conte Ave.
Box 177220, 71-267 CHS
Los Angeles, CA 90095 United States
Tel: +1-310-206-2837
Email: detels@ucla.edu

Larissa Mooney, MD
Tel: +1-310-267-5419
Email: lmooney@mednet.ucla.edu

NIDA

David Liu, MD
Tel: +1-301-443-9802
Email: dliu@nida.nih.gov

Jacques Normand, PhD
Tel: +1-301-402-1919
Email: jnormand@nida.nih.gov

Steve Sparenborg, PhD
Tel: +1-301-496-4844
Email: sparenborgs@nida.nih.gov

Paul Wakim, PhD
Tel: +1-301-402-3057
Email: pwakim@nida.nih.gov

EMMES

Robert Lindblad, MD
Tel: +1-301-251-1161
Email: rlindblad@emmes.com

Colleen Allen, MPH
Tel: +1-301-251-1161 Ext. 252
Email: callen@emmes.com

Paul Van Veldhuisen, PhD
Tel: +1-301-251-1161 Ext. 143
Email: pvanveldheisen@emmes.com

Janet Van Dyke
Tel: +1-301-251-1161 Ext. 272
Email: jvandyke@emmes.com

Neal Oden, PhD
Tel: +1-301-251-1161
Email: noden@emmes.com

Consultants

Mark Hull, MD, MHSc
British Columbia Centre for Excellence in
HIV/AIDS (BC CfE)

Julio Montaner, MD, FRCPC, FCCP
British Columbia Centre for Excellence in
HIV/AIDS (BC CfE)

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1.0 LIST OF ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ACT	Assessment Coordination Team
ART	Antiretroviral Treatment
CAB	Community Advisory Board
CDC	Center for Disease Control and Prevention
COC	Certificate of Confidentiality
CRF	Case Report Form
CRIMS	Comprehensive Response Information Management System
CRT	Cluster Randomized Trial
CTN	Clinical Trials Network
CTP	Community Treatment Program
DEA	Drug Enforcement Administration
DSMB	Data and Safety Monitoring Board
DST	Data and Statistics Team
DU	Drug User
EIA	Enzyme Immunoassay
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability Accountability Act
HIV	Human Immunodeficiency Virus
ICC	Intra-Cluster Correlation
ICH	International Conference of Harmonization
IRB	Institutional Review Board
LDL	Lower Detection Limit
LI	Lead Investigator
MMT	Methadone Maintenance Treatment
NCAIDS	National Center for AIDS/STD Control and Prevention (China)
NIDA	National Institute on Drug Abuse (United States)
P4P	Pay for Performance
PID	Personal Identification Number
PITC	Provider-Initiated Testing and Counseling
POC	Point-of-Care
QA/QC	Quality Assurance/Quality Control
SAE	Serious Adverse Event
SFDA	State Food and Drug Administration (China)
SOC	Standard of Care
STTR	Seek, Test, Treat, and Retain
US	United States
VCT	Voluntary Counseling and Testing
VL	Viral Load
WB	Western Blot

2.0 STUDY SYNOPSIS AND SCHEMA

Study Objectives

This study will evaluate the effects of a comprehensive diagnostic approach to enhance the percentage of participants that receive their HIV testing results and counseling, given they are HIV positive on the initial EIA screening. All enrolled participants will be followed for 12 months with the viral load (VL) measured at that time point in addition to the status of any HIV treatment they have received.

Study Design

The study consists of a cluster randomized trial (CRT) at county hospitals in Guangxi, China to assess the effectiveness of a structural intervention: a new testing algorithm, consisting of rapid point-of-care (POC) HIV and CD4 testing, with viral load (VL) testing in parallel, designed to ensure completeness of diagnostic assessment and accelerate time to ART initiation for patients deemed ART eligible (hereafter called the One4all Test Intervention).

This CRT will be conducted in 12 county general hospitals with an estimated average of 30 participants per hospital, totaling an estimated 360 participants. The unit of randomization is the hospital. Hospitals will be randomized to 1) the One4all Test Intervention, or 2) the control condition, consisting of the current standard of care (SOC). The efficacy of the intervention will be evaluated at 1, 3 and 12-month follow-up assessments, and the differential efficacy for drug users (DUs) and non-drug users will be examined, if an adequate number of DUs is enrolled.

Study Population

The study population will consist of adult participants who screen positive on an initial HIV enzyme immunoassay (EIA) in the 12 study hospitals. Since the study will be conducted in China, the vast majority of participants will be of Chinese or Asian descent. Women will be included and are expected to represent approximately 26% of the study population.

Eligibility Criteria

Site Eligibility Criteria: The location of our study is Guangxi Zhuang Autonomous Region (Guangxi). We will select county-level general hospitals in order to ensure sufficient caseload at each hospital and homogeneity across hospitals. Guangxi counties usually have one general hospital (a limited number of counties have two or more general hospitals); this hospital has been designated as the only setting for delivering ART services in the respective county.

Study hospitals (n=12) will be selected based on the number of reported HIV positive screenings in the first 6 months of the previous year (2012) and on homogeneity in testing procedures between hospitals. Selected hospitals will have reported at least 30 patients who screened positive during the period of January to June 2012. Should more than 12 hospitals be identified, the lowest screen positive hospital will not be considered for participation.

Participant Eligibility Criteria: Inclusion criteria will be 1) age 18 or older, 2) seeking care in study hospitals, 3) local residency or intent to live in study area for at least 90 days, and 4) received HIV positive results on the initial screening test. Any patient who does not meet these inclusion criteria will be excluded from the study. Additionally, patients who are pregnant or who have previously received confirmation of HIV infection in other care settings (e.g. CDC clinic, infectious disease hospital, sub-county-level hospital) are not eligible to participate. Any patient who is a prisoner or detainee at the time of initial screening will be excluded from the study. In the event that a participant is enrolled at a study hospital and subsequently incarcerated, data will be collected via standard of care and abstracted for study purposes.

Treatments

The One4all Test Intervention will employ a new testing algorithm, consisting of rapid Point of Care (POC) HIV screening and CD4 testing, with VL testing in parallel, designed to enhance completeness of diagnostic assessment (primary objective) and accelerate time to ART initiation for treatment-eligible participants (secondary objective). In this intervention, differences from current SOC include immediate POC CD4 testing and results and in-parallel VL testing (results available in 10-14 days) for all participants who screen HIV-positive on two rapid, POC EIA tests. No additional blood sample will be taken for later confirmatory HIV testing via Western blot (WB). CD4 testing will be POC using new PIMA analyzers on-site in all intervention hospitals. POC VL testing cannot be conducted in this study since these assays are not approved by China's State Food and Drug Administration (SFDA). Therefore, VL testing will be conducted at an offsite location (Guangxi CDC laboratory). Blood draw for VL testing will be done for all One4all intervention arm participants following positive screening and will serve as the confirmatory test in the One4all testing algorithm. In SOC the WB is the confirmatory test and the VL is only conducted annually after ART is initiated. Testing completeness for the One4all Test Intervention condition is defined as delivering results and counseling to the participant after: 1) HIV screening and CD4 test, and 2) VL test. Testing completeness for the control condition is defined as delivering results and counseling to the participant after: 1) HIV screening (2-4 EIA), 2) WB confirmatory test, and 3) CD4 test.

Safety Assessment

The intervention in this trial, comparing HIV testing strategies, poses no specific safety risk to the participants. HIV testing will involve several blood draws, up to 4 in SOC, and 1-2 in One4all arms. There will be no increase in the volume of blood drawn or the typical risk associated with blood draws. Standard of care will be compared to a new strategy (One4all) with a goal to improve HIV initiation of treatment in HIV screened positive cases. Risk of loss of confidentiality is a safety concern and will be managed throughout the study utilizing standard protections within the China health care system, and de-identified data will be used whenever possible. The study team extracting data from either the local hospital records or the Chinese national HIV data base (CRIM) system will assign a participant ID number to protect confidentiality of information. Any infringement or loss of confidentiality will be reported to the Chinese Ethics Committee for review and action if required. Throughout the course of the study, any deaths and hospitalizations will be captured through review of the hospital based care information systems and the CRIMS system. All of these events will be made available for ongoing monitoring by the Data and Safety Monitoring Board (DSMB). It is expected that there will be an initial protocol review board (PRB) review and approval of the protocol prior to study implementation. The DSMB (formed by members of the PRB with additional members as needed) will review for data and safety at the study's halfway mark, e.g., 3-6 months from study start and a second review will be conducted as needed.

Outcome Assessments

The primary outcome is increasing the proportion of participants who receive complete HIV test results and counseling, after an initial HIV EIA screen positive. This will be measured by the proportion of HIV-screen positive individuals on the initial screening EIA who have received their test results and counseling within 30 calendar days of the HIV-screen positive result on the initial EIA test. The secondary outcome is the proportion of individuals with $CD4 \leq 350$ cells/mm³ who have initiated ART (i.e., received their first prescription of ART medicines) within 90 days of initial EIA screening, given they are HIV-positive based on the initial EIA screening test. In all cases, follow-up time is counted from the date of initial EIA HIV screen positive result. An additional follow up time point at 12 months will assess HIV treatment status and VL.

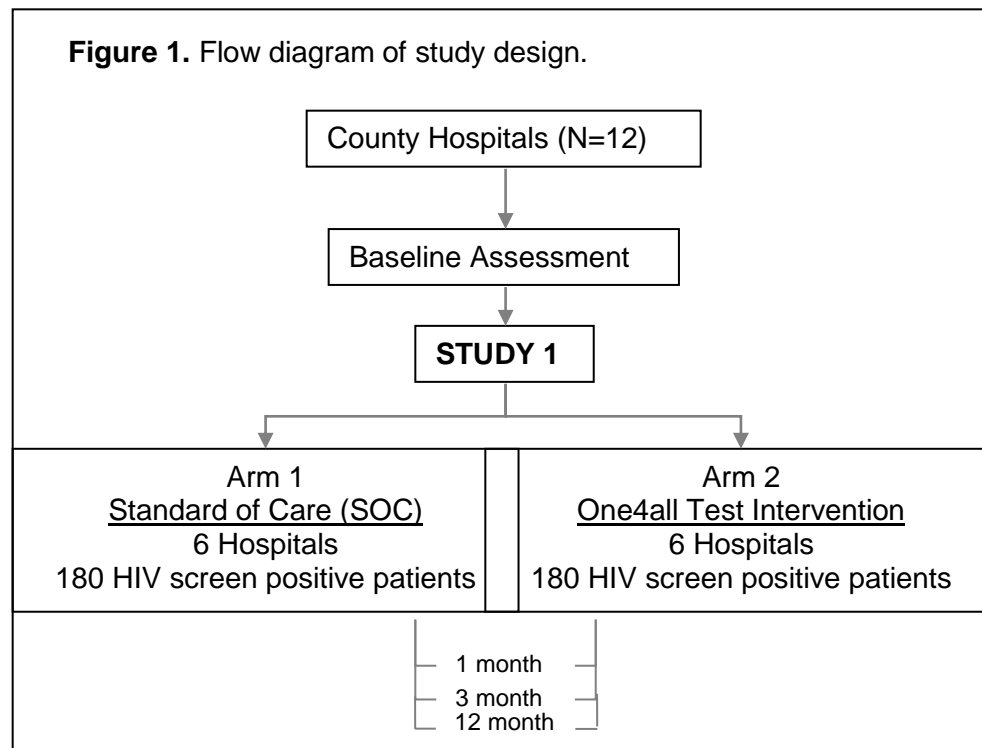
Primary Outcome Analysis

The primary endpoint is the receipt of the testing results and post-testing counseling. Receipt of results and eligibility for counseling after receipt of results, requires three components for each study arm: 1) HIV screening testing (with at least 2 EIA), 2) CD4 testing, and 3) confirmatory testing - WB in the SOC arm and VL results in the One4all arm. Laboratory processing times for VL and WB testing are 10-15 days. The primary endpoint is based on the participant receiving the test results and the post-test counseling.

Regulatory Issues

The trial will be conducted in compliance with the protocol, International Conference of Harmonization (ICH) guidelines for Good Clinical Practice (GCP), and applicable federal and local regulatory requirements.

3.0 STUDY FLOW CHART



4.0 INTRODUCTION

4.1 Background

Global experiences over the past 10 years have confirmed the life-saving benefits of ART for treating HIV-positive patients in developing countries.(1-4) However, in many settings, including China, patients are lost at each step along the continuum of HIV care.(5) In Guangxi, where the study will take place, only 50.4% of those who screen HIV-positive at hospital settings receive confirmatory testing, and only 76.0% of those confirmed to be HIV-positive receive their HIV test results. Furthermore, 31.4% of individuals who are notified of their HIV-positive status fail to receive CD4 testing. Since CD4 levels are used to determine ART eligibility (current requirement in China is $CD4 \leq 350$ cells/mm³ or AIDS diagnosis), it is estimated that nearly 80% of newly-identified, ART-eligible patients in Guangxi are not engaged in ART.(6) These missed opportunities for patient engagement in HIV care ultimately translate into high mortality rates.

Other significant barriers to testing and treatment initiation are fear of HIV/AIDS-related stigma(7-9) and patients' inability to meet out-of-pocket costs despite the free ART program.(10) Particular challenges for DUs, who experience late testing and disproportionately low rates of treatment initiation, include fear of registration and detention, and provider perceptions of DUs as being non-compliant patients.(11) Other barriers reported by providers include reluctance to treat HIV-positive patients,(12) insufficient training, limited resource capacity,(13) and uncertainty about recommended guidelines.(14)

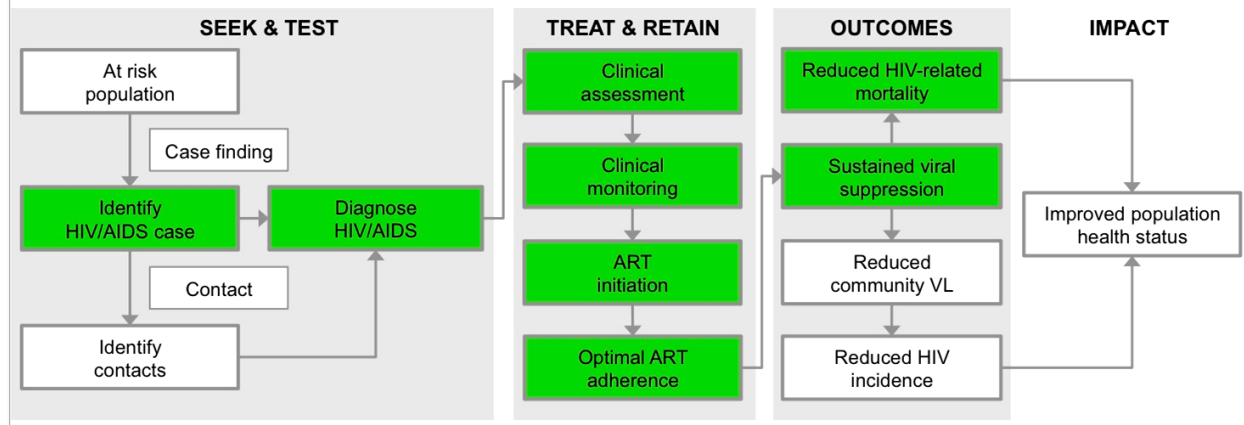
In 2011, Guangxi reported the highest number of AIDS-related deaths among all provinces in China, 22% of the national total.(15) The high rate of patient loss to follow-up along the continuum of HIV care is even more pronounced among DUs. As a result, mortality among DUs is also higher. Recent studies of HIV-positive, injecting DUs who are engaged in ART indicate that mortality rates among this population range from 10.4 to 15.9 per 100 person-years.(4, 16)

The seek test treat and retain (STTR) strategy provides a process framework for engaging HIV-positive, treatment-eligible patients in ART with the ultimate goal of helping patients achieve and sustain viral suppression, thereby extending their lives. This research will address the following question: "Can implementation of One4all improve the percentage of participants that screen positive for HIV to receive their results and counseling and ultimately increase the number of ART eligible participants to initiate ART therapy?" To answer this question, a CRT will be conducted at 12 county hospitals in Guangxi to assess the effectiveness of a structural intervention: the One4all Test Intervention, a new testing algorithm consisting of rapid POC HIV screening and CD4 testing, and in-parallel VL testing designed to enhance completeness of diagnostic assessment and participants receiving their test results and counseling.

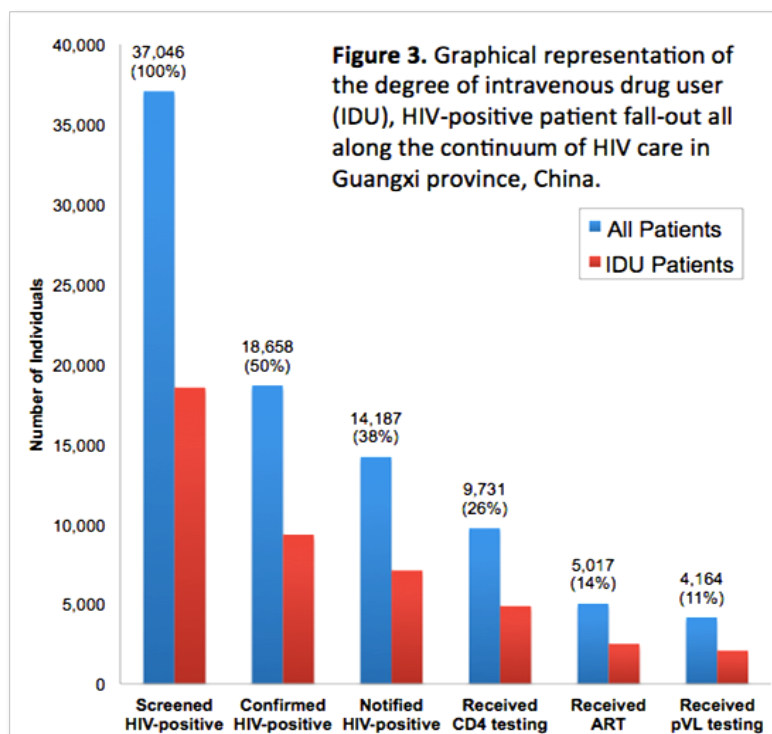
4.1.1 Significance to the Field

Despite the rapid global expansion of ART over the past decade, poor engagement in care for HIV-positive individuals remains a major problem. In order for HIV-positive patients to fully benefit from ART, they need to be aware they are HIV+, be engaged in HIV care, and receive and adhere to their ART regimen.(17) Successful engagement in care is also a precondition for realizing the potential public health benefits of increased ART coverage that may be achieved through the STTR strategy (**Figure 2**). (18) The STTR strategy is intended to increase engagement in HIV care, and to improve hospital-based HIV testing and treatment services in Guangxi, China. This study endeavors to improve the seek, test and treat portion of the strategy.

Figure 2. Seek, Test, Treat and Retain (STTR) holistic approach to the control of HIV/AIDS. Green boxes highlight points of failure along the continuum of HIV care addressed by the interventions contained within the present study.



Many HIV-positive patients are lost early in the continuum of HIV care due to complicated testing practices. Although HIV screening services are now widely available across China, and HIV provider-initiated testing and counseling (PITC) programs are being rolled out in hospitals in areas of high HIV prevalence, many individuals who screen HIV-positive still do not receive confirmatory testing or are not notified of their results, presenting a first major barrier to accessing HIV care. In Guangxi, site of the planned research, only 50.4% of those who screen HIV-positive receive confirmatory testing, and only 76.0% of those confirmed to be HIV-positive receive their HIV test results (**Figure 3**). Approximately 31.4% of individuals who are notified of their HIV-positive status fail to receive CD4 testing. Since CD4 level is used to determine ART eligibility, this represents a second major barrier to accessing HIV care. Because of these barriers to ART access, nearly 80% of newly-identified, ART-eligible patients in Guangxi are not engaged in HIV treatment. Application of the new testing algorithm in the One4all Test Intervention will help patients overcome these barriers to treatment, and findings from the research will have direct policy implications in both developed and developing country settings.



Early loss to follow-up along the continuum of HIV care is reflected in late AIDS diagnosis and high levels of preventable mortality. High patient attrition along the continuum of care prior to ART initiation means that a large proportion of the individuals who screen HIV-positive do not receive adequate care. In Guangxi, over one-third of newly-reported HIV cases have already progressed to AIDS. Late diagnosis is well-known to be associated with reduced survival. In Guangxi, the mean time to death after confirmed diagnosis is 16.3 months (median: 5.2 months), and 79% of those who die of AIDS had never received ART.(6) With less than 1 in 3 treatment-eligible patients in Guangxi receiving ART, AIDS mortality is unacceptably high. In 2011, Guangxi reported 3,852 AIDS-related deaths, the highest number of deaths among all of China's provinces and 22% of the national total.(6) We expect that the interventions will dramatically increase access to HIV care, thereby reducing premature AIDS-related deaths, one of the major goals of China's current 5-Year Action Plan.(19)

Drug users (DUs) face unique challenges at each step along the continuum of HIV care. These challenges include late HIV testing, low ART uptake, ART treatment interruptions, ART failure due to active injecting drug use, and need for clinical management of common comorbidities such as hepatitis C.(20) While DUs in China benefit from more frequent HIV testing, as a function of either engagement in methadone treatment, or incarceration, a high proportion are lost to follow-up immediately after testing (**Figure 3**). Among those who successfully initiate ART, many are subsequently lost to follow-up. Those patients who remain on ART, clinical outcomes are generally poorer among DUs compared to other patient subpopulations and as a result, mortality is higher. In Guangxi, DUs account for 12% of existing and 8% of newly-identified HIV cases. However, a disproportionately high number (562/3852, 14.6%) of AIDS deaths were found among DUs in 2011.(6) The differential impact of the interventions on DUs, compared with other subgroups will be examined in this study.

High-level support from the Chinese government means that study findings will be quickly translated into health policy. This study is closely aligned with the objectives of China's current 5-Year Action Plan.(19) Because of this, the Chinese government will share a significant proportion of the cost burden associated with the research. This high-level support means that the study team is uniquely positioned to generate research findings that will be rapidly translated into national policy in China, which confers unique advantages on the work.

Mandatory disease reporting, initial investigation and follow-up of HIV-positive individuals as it currently exists in China. Once an individual has a confirmed HIV infection (screen HIV positive with a WB confirmation), the doctor who ordered the HIV test files an electronic report in CRIMS, which includes the patient's name, national ID number, locator information, date of birth, gender, education, occupation, marital status, diagnosis, etc. CRIMS covers all reportable diseases, including HIV infection and AIDS.(21) Public health officials at the local county CDC are notified which triggers an initial epidemiological investigation of the newly-reported case. The initial epidemiological investigation results in the collection of additional information including history of HIV testing, date of HIV confirmation, risk factors for HIV infection, number of sexual and drug injecting contacts, etc. A blood specimen for CD4 testing is usually collected during this initial investigation. The original initial investigation record in paper form is stored in a newly-created file located in the local county CDC.

Antiretroviral treatment processes currently in China. Prior to initiating ART, patients with $CD4 \leq 350$ cells/mm³ are required to complete a physical health exam (including tests of liver function, kidney function, etc.), at a cost of approximately 500 RMB (~81 USD). Under the China's New Rural Cooperative Medical Insurance Program (which costs roughly 20 RMB [~3 USD] per year per person), patients will be reimbursed at a rate of 90% for inpatient medical costs and 65% for outpatient medical costs. For the first three months of ART, the patient will be scheduled for monthly follow-up visits. Follow-up visits include symptom review, evaluation of

medication side effects, and ART medication dispensing. After the first three months, the ART follow-up visits will be scheduled for every 3 months.

CD4 count is re-tested 2 times per year and VL is assessed once a year. Both are free to patients at county/city CDCs.

4.2 Study Rationale

The overall goal of this study is to determine whether the implementation of the One4all hospital-based, structural intervention will 1) increase the proportion of HIV-positive individuals who receive complete testing, 2) will increase the proportion of ART initiation among treatment-eligible participants and 3) VL testing at 12 months will assess the impact of the One4All intervention on VL suppression at 12 months. The One4All Test Intervention, which is a new testing algorithm for HIV, CD4, and VL tests will be compared to the SOC by conducting a two-arm CRT. In addition, the differential effectiveness of these interventions on DUs versus non-DUs will be assessed recognizing that there may be too few cases observed in this study to note any differences.

A CRT design was selected for this study primarily because of the nature of the intervention (revised clinical guidelines requiring all providers to change clinical practice), and secondarily because of the logistics of the intervention (randomizing at the hospital level reduces the complexity of the provider-patient interaction). The study sites are in close geographical proximity, but distant enough from one another to minimize the risk of contamination.

4.3 Innovativeness of Approach

Innovative HIV testing algorithm. The process of identifying and assessing HIV-positive patients in hospital settings in Guangxi will be streamlined by adopting the One4all Test Intervention. A recent study found that POC CD4 testing in HIV care departments can help reduce pre-treatment losses to follow-up and close the gap between confirmation of an HIV diagnosis and establishment of treatment eligibility.(22) In a recent trial in South Africa, investigators reported that simultaneous delivery of HIV confirmatory test results and CD4 test results increased rates of enrollment in HIV care within 30 days, and initiation of ART within 90 days.(23) This innovative approach will be further expanded by adding VL testing to the suite of testing services. It is recognized that the VL will take 10-14 days for results and will introduce a delay in obtaining results compared to a completely POC algorithm.

Innovative packaging of interventions aimed at multiple points along the continuum of HIV care. Multiple barriers to engagement in HIV care require a comprehensive approach to changing clinical practice. Findings from this study will provide evidence for implementation of this improved One4all strategy in China and in other resource-limited settings globally.

Innovative path from study findings to policy and practice. The collaboration with the Chinese government offers a number of unique advantages. First, the infrastructure required for a study of this size is already in place in the form of China's national AIDS program. NCAIDS is already intimately involved in the day-to-day operations of the national AIDS program and maintains a robust national HIV/AIDS data system, which will expedite data collection and analysis. Second, because the national AIDS program is led and funded by the Chinese government, costs associated with the research will be shared. The Chinese government will cover costs for testing and treatment services provided under the current SOC. Finally, by conducting this research in partnership with the Chinese government, research findings can be quickly translated into policy and practice. Very few studies can claim this level of potential impact.

4.4 Preliminary Studies

The study team in China has supported multiple interventions within China to advance HIV care, that are in line with the overall aims of this study to enhance the seek, test and treat components of the STTR strategy.

Treatment 2.0 Pilot

A pilot intervention study in Hubei province intended to improve the continuum of HIV care from diagnosis to treatment (in which Drs. Wu and Mao participated) has resulted in a tripling of the proportion of individuals who receive confirmation of their test results among those who screen positive in the 6 month period from October 2011 to March 2012, compared to the prior six months. In addition, the proportions of individuals completing CD4 testing and receiving care each doubled.

From June 1, 2011 to June 30, 2012, the project sites screened 6649 individuals and 338 participants had positive screen results (5.1%). Of the positive–screen individuals, 298 received confirmation testing (88.1%). The number of confirmed, newly diagnosed individuals was 282 (4.2% of screened individuals). The existing national HIV/AIDS data system was used to document these changes, thus demonstrating the feasibility of its use for the study.

Guangxi Pilot Study

In addition to the Treatment 2.0 pilot study, there has been another recent pilot study in Guangxi. The Guangxi pilot study intervention was designed to decrease the time between screening, diagnosis, and treatment initiation with the aim of decreasing HIV/AIDS mortality and increasing treatment coverage. Two pilot sites and two control sites were selected based on similar baseline core assessment indicators. The study population consisted of two cohorts: 1) participants who received an initial HIV infection diagnosis within the study period and 2) participants who have received an HIV infection diagnosis prior to the study start date and did not accept ART. The intervention comprised of implementing a pre-determined timetable for reporting positive HIV screenings, blood draws for further testing, delivery of blood samples to testing sites, and immediate referral to treatment. Main outcomes that will be measured are HIV/AIDS related mortality rates and treatment coverage. Preliminary findings show from June 2012 to April 2013, the testing completeness rates are 35% and 12% in the two control sites, and 32.14% and 60% in the two pilot sites.

Provider Interventions in China

The investigative team has extensive experience in conducting behavioral intervention studies among service providers. In the past seven years, Dr. Wu has collaboratively led two studies (grant R01MH070931 [2003-2006] and grant R01MH081778 [2007-2011]) to address HIV-related stigma among service providers in primary care settings. The findings have been disseminated via 16 papers in peer-reviewed journals and a dozen presentations at national and international conferences.(24-28) These studies demonstrate this team's ability to successfully work within the Chinese healthcare system and their ability to implement intervention programs that target service providers in China.

Cluster/community Intervention Trials in China

Dr. Wu has conducted several HIV/AIDS-related cluster/community intervention trials in China, including trials to reduce the incidence of drug use (grant WAF 112 [96–014]);(29) spread HIV/AIDS knowledge and change attitudes and behaviors through training healthcare professionals (grant WAF143 [97-042]);(30) reduce sexually transmitted diseases among sex workers (grant WAF 195 [99-011]);(31) reduce HIV among injecting DUs (grant WAF 217 [00-009]);(32) and improve home-based HIV care services (grant WAF 303 [03-003]).(33) As the China country PI, Dr. Wu has participated in the NIMH Collaborative HIV/STD Prevention Trial

(grant U10MH61513).(34-42) With support from NIAID (U19 AI51915), Dr. Wu has conducted a community trial to reduce AIDS-related stigma in rural China.(7) With support from Chinese government, Dr. Wu has also conducted community trials to reduce HIV incidence among DUs and HIV-discordant couples (grant 2008ZX10001-016).

Pre-assessment of the Study Sites and Interventions

To assess potential study sites, including the willingness of local hospitals to participate in the study, Dr. Wu and his team have made 3 visits to Guangxi in the past year. Twenty-four doctors and 11 laboratory technicians from county hospitals as well as 39 patients living with HIV were interviewed. In addition, Dr. Mao has collected background information about county hospitals, including the number of patients tested for HIV and the number of reported HIV cases, demonstrating the feasibility of using the existing unified, web-based national HIV/AIDS information system (officially named China's HIV/AIDS Comprehensive Response Information Management System [CRIMS]),(43) to collect data for the study.

5.0 OBJECTIVES

The overall goal is to examine the effectiveness of the One4all intervention to increase the number of HIV screen positive participants who receive their test results and counseling in Guangxi, China.

5.1 One4all Testing Algorithm

5.1.1 Primary Objective

The primary objective is to assess whether the One4all Test Intervention will increase the proportion of individuals who receive the results of their tests and post-test counseling, given they screen HIV positive.

5.1.2 Secondary Objectives

The secondary objective is to assess the effectiveness of the One4all Test Intervention in increasing the proportion of participants who initiate ART within 90 days of their initial HIV screen positive test.

5.1.3 Tertiary Objectives

The tertiary objective is to assess the effectiveness of the One4All test intervention in increasing the proportion of participants who are VL suppressed (≤ 200 copies/mL) at 12 months from their initial HIV screen positive test.

6.0 STUDY DESIGN

6.1 Overview of Study Design

A flow chart describing the overall study design is shown in **Figure 1**. In this two-arm clinical trial, the effectiveness of the One4All Test Intervention will be compared to the current SOC. Prior to study enrollment, eligible hospitals will be randomized and assigned to either the intervention or control arm.

6.2 Duration of Study and Visit Schedule

Recruitment and enrollment at each hospital site will be open for approximately 9 months to have each hospital meet the recruitment target. For each participant, enrollment, screening, baseline assessment including collection of demographic, HIV history and locator information will be collected per local provider practices using the case report form (CRFs). The 12 month visit will also use a CRF to collect VL and HIV treatment status data including medications if on ART therapy. The CRF data will be stored in a web-based database system developed specifically for the study. All confirmed cases will additionally be registered in the national HIV/AIDS reporting system (CRIMS), which will be used for this study and for future HIV care monitoring. Data for the study will be assessed from both the web-based database and the CRIMS databases at 1, 3 and 12-months post-screening.

7.0 STUDY POPULATION

For this study, 30 individuals from each of 12 participating hospitals (total of 360 participants) who screen HIV-positive during the study period will be included in the study. The study population will consist of adult participants who screen HIV-positive on their initial EIA in one of the 12 study hospitals. Since the study will be conducted in China, the vast majority of participants will be of Chinese descent. Women will be included and are expected to represent approximately 26% of the study population.

7.1 Inclusion Criteria

Participating individuals must:

1. Be at least 18 years old.
2. Be an inpatient or outpatient seeking care in study hospitals.
3. Test positive on an initial EIA HIV screen.
4. Have local residency or intent to live in study area for at least 90 days.

7.2 Exclusion Criteria

Individuals will be excluded from study participation if they:

1. Do not meet any one or more of the above inclusion criteria.
2. Test result negative on initial EIA HIV screen.
3. Have previously received confirmation of HIV infection in the study hospital or in any other setting (e.g., CDC clinic, infectious disease hospital, sub-county-level hospital).
4. Are prisoners or detainees at the time of initial screening.
5. Are pregnant women (pregnant women are subject to mandatory testing).

7.3 Participant Recruitment

All patients who screen HIV positive in the 12 selected hospitals will be included as study participants. These patients will be enrolled sequentially at each hospital until 30 eligible patients are enrolled. Information about the study will be provided to each participant in each of the 12 hospitals via a printed handout (**Appendix B**). The participant handout will inform participants that no additional laboratory tests other than HIV care services will be performed and that their data will be analyzed to determine which testing algorithm works the best. Participants will have the option to opt out of having their data collected, but their positive initial EIA will still count towards the denominator.

7.4 Number of Study Sites

For this study, 12 hospitals will be randomly assigned to either the One4all Test Intervention group or the SOC control group. Hospitals will be stratified according to historical hospital-level data on the proportion of HIV positive patients who had completed testing and counseling under standard care.

7.5 Study Site Background

In each county, there is a primary hospital that provides HIV screening and ART therapy. Each county also has a CDC office. The hospitals range in size and volume of HIV testing depending on location. In most cases, the hospitals perform two EIA screening tests followed by a confirmatory Western Blot which is sent out to County CDC. Following Western blot confirmation, participants return to the hospital or the local CDC for another blood draw for CD4 testing, which is performed at the city CDC. The One4all diagnosis algorithm would require two

EIA screening tests followed by the POC CD4 testing and the VL blood draw that would be sent out. These procedures will require training in the One4all hospitals.

Patients in both groups that do not show up for appointments are contacted by the clinical staff at each hospital based on their usual practice and are not contacted by study staff. In this way the intervention is only the testing algorithm and not study-conducted follow-up procedures. Counseling following test results will be done by clinical staff per national guidelines.

7.6 Study Site Characteristics

Hospitals are selected only if they have the following characteristics:

1. Located in Guangxi, China.
2. Level 2A county-level general hospital.
3. Full-service HIV care department, including ART counseling and care.

7.7 Rationale for Site Selection

The location of our study is Guangxi Zhuang Autonomous Region (Guangxi). Guangxi has reported the second highest cumulative number of HIV/AIDS cases in China (75,716, 17% of the national total); the highest number of newly reported HIV/AIDS cases in 2011 (14,250, 19% of the national total); the highest number of newly-reported AIDS cases in 2011 (7,571, 19% of the national total); and the highest number of AIDS-related deaths in 2011 (3,852, 22% of the national total).(6)

Study hospitals will be selected for homogeneity in structural characteristics, past patient caseloads, and testing procedures. All study hospitals are administratively classified as Level 2A county-level general hospitals that have been designated as ART delivery sites. Hospitals in China are classified on a three-tier system (1, 2, or 3, with 3 being the highest level) based on the hospital's size, function, ability to provide specialized care, and role in medical education and research. Level 2 hospitals are usually affiliated with a medium-size county or city, have between 100-500 beds, and are able to provide comprehensive services for the region. The levels are further divided into subgroups (A, B, and C, with A being the highest level) based on the hospital's size, service provision, quality of service, medical technology, and other factors.

Level 2A county-level general hospitals at the county and district levels are the largest health care facilities in China's hospital system, with the highest numbers of inpatients and outpatients. In each county, nearly one-third of the total number of HIV cases are identified and reported from these level 2A county-level general hospital. Guangxi counties usually have one general hospital (a limited number of counties have two or more general hospitals), which have been designated as the only setting for delivering ART services in the respective county. **Note:** The exception is that in Guangxi, all pregnant women receive medical care, including ART if necessary, at specialized maternity care hospitals. Due to this separate system of care, pregnant women are not eligible to seek care at the study hospitals and thus pregnant women are excluded from this study.

The selected study hospitals will have reported at least 25 cases of newly positive HIV screenings in the 6-month period from January 1, 2013 to June 30, 2013. Hospitals will also be selected for a high degree of homogeneity in testing procedures (i.e., the site of blood sample collection and the type of laboratory utilized for CD4 and VL testing). Should more than 12 hospitals meet these criteria, then the hospital(s) with the lowest past number of screen positive patients would not be considered for participation in this study.

8.0 OUTCOME MEASURES

8.1 One4all Testing Algorithm

8.1.1 Primary Outcome Measure

The primary outcome measure is defined as the proportion of participants who achieve testing completeness and receive their test results and post-test counseling within 30 days, given they received a positive HIV result on the initial EIA. Testing completeness is defined as completion of three required components: 1) Initial EIA (3 in One4all and 2-4 in SOC) HIV testing, 2) CD4 testing, and 3) confirmatory testing - WB in the SOC, or confirmatory VL in the One4all arm. Receipt of results with post-test counseling completion rates will be compared at 30 days after initial HIV screen EIA.

8.1.2 Secondary Outcome Measures

To maintain consistency with the definitions provided in the CRIMS database, the secondary outcome measure is the proportion of participants with $CD4 \leq 350$ cells/mm³ who initiate ART within 90 calendar days, defined as starting from the date of initial EIA HIV-positive screening to the date of first receiving ART prescriptions. The denominator is the total number of participants who screened positive on the initial HIV EIA. Participants who are ART-eligible with $CD4 > 350$ are included in the denominator but are not included in the numerator for this secondary outcome. An additional secondary analysis will include use of a broader numerator: all participants who are ART-eligible as decided by a local hospital provider based on national treatment guidelines. (**Appendix A**).

8.1.3 Tertiary Outcome Measures

The tertiary outcome measure is the proportion of participants who are VL suppressed at 12 months. The denominator is the total number of participants who screened positive on the initial HIV EIA. This follow-up time is counted from the date of the initial positive EIA result.

9.0 STUDY PROCEDURES

9.1 Randomization

Hospitals will be used as the unit of randomization. Study hospitals (n=12) will be selected based on the number of newly reported HIV positive screenings in the first 6 months of the 2013 and on homogeneity in testing procedures between hospitals. The selected hospitals will be stratified by testing completeness rates determined by historical rates of testing completeness followed by post test counseling.

9.2 Study Interventions

The intervention is the new One4All Test Intervention. Details of the intervention are described in **Section 12.2**.

9.3 Enrollment Procedures

Information on testing procedures and study data collection will be provided to each individual who presents for HIV screening via the Participant Handout (**Appendix B**) prior to HIV screening. Receipt of the handout will be documented. Participants with questions about the study may have their questions answered by designated local providers, CDC or NCAIDS staff. The 12 hospitals in the study will use one of two testing algorithms, with 6 hospitals randomly assigned to each algorithm. Each hospital will only offer HIV testing according to its assigned algorithm. Patients who screen positive on the initial EIA HIV screen will be enrolled in the study. Local hospital data will be protected per local hospital practices. Study data will be extracted and assigned an ID so that the data are de-identified; the participant's name will be scrubbed.

9.4 Baseline Assessment

Initial baseline assessment and information will be obtained by the local CDC study team from the local county hospital. The baseline assessment is conducted shortly after the participant receives a positive screening and identified as an eligible study participant. The baseline assessment study includes information on the participant's age, gender, marital status, ethnicity, educational attainment, occupation, likely route of transmission, basic sex and drug use risk behaviors, and clinical symptoms consistent with data collected for the CRIMS data base. Further details regarding baseline assessment are provided in **Section 11.2**. There will be collection of study specific data on study CRFs by local hospital providers.

9.5 Follow-Up Visits

All follow-up visits will occur according to standard of care procedures in both arms. Off-site laboratory test results are reported to study hospitals within 10-15 days after the blood sample collection. When laboratory test results are available, participants will be contacted by the local care providers using local SOC procedures and asked to return to the hospital to receive results and post-testing counseling. Locating screen positive participants will also be performed by local care providers and not the study staff.

If CD4 test results determine that the participant is eligible for ART and the participant is confirmed HIV positive based on positive EIAs and a positive WB in SOC or positive EIAs result and the VL in the One4all group, (**Appendix A**), the participant will be asked to visit the hospital to complete ART initiation counseling, physical examinations, medical insurance forms, and other laboratory tests. ART treatment will be per SOC in terms of the drug regimens and the visit schedules.

The dates of the participant visits to the study hospital and visit purposes will be documented. Location strategies, including obtaining detailed locator information from participants at intake,

will be obtained through SOC methods. Locator information consists of the participant name, national ID number, phone number, and current residential address. Follow-up for all cases will occur per SOC, and follow-up efforts will be the same between the two study groups. To schedule a follow-up visit, the primary method of contacting participants is by phone. In rare cases, if the participant is not reachable by phone, the provider may attempt to contact the participant at the provided residential address. All follow-up attempts, by phone or in-person, will be documented for the study in the local hospital records.

Details of measures and assessments are further described in **Section 11.2**.

9.6 12 Month Assessment

At 12 months all study subjects will be re-contacted to obtain additional information regarding their HIV status and to obtain a blood sample for VL. Subjects will be consented for this assessment. A 2 month window is acceptable to obtain the VL specimen for testing. For those subjects that are not on ART therapy, this visit will be used for counseling to encourage testing completion or initiation of ART therapy as appropriate.

9.7 Study Discontinuation

While not anticipated, the sponsor may decide to discontinue the study for any reason. Reasons for the sponsor terminating the study may include, but are not limited to, lack of funding or support, DSMB or Ethics committee early termination based on review of the study data. All participants would continue to receive standard of care testing and treatment should the study end early.

9.8 Participant Reimbursement

As all visits are SOC, there will be no study-related reimbursement for any visit. After the initial screening for HIV, the laboratory tests and counseling will be provided per usual SOC.

9.9 Dispensing of Study-Related Medication

This study has no medication component and no medicine will be specified in this protocol. All medication will be prescribed through standard of care practices for the treatment of HIV infection.

10.0 TRAINING PROCEDURES

10.1 Training Timeline

Training will take place in two separate sessions. One session will be targeted at intervention group hospital providers and CDC staff, and one session will be targeted at control group hospital providers and CDC staff. The intervention group session will take 2 full days, and the control session will take one day in a centralized location prior to the start of the study. Refresher training will be provided as needed, in particular for those hospitals where a longer time has elapsed between the date training was received and the start of the study.

10.2 Selection of Expert Trainers

The Assessment Coordination Team (ACT) is composed of the Lead Investigator, Co-Investigators, research staff, and consultants from NCAIDS, UCLA, NIDA, NIDA CTN Pacific Region Node, and NIDA CTN Data and Statistics Center (EMMES). The role of the ACT is to provide overall supervision and to concentrate on the progress of the study, adherence to the protocol, and the provision of technical expertise to ensure successful study implementation. As needed, the ACT will also seek out additional consultants in designing and implementing the training. If necessary, NIDA staff and/or designees will participate in the training of the trainers at a central location in China.

10.3 Training of Providers

Training will be provided for both healthcare providers and public health officials working at hospitals and local CDCs. Providers at hospitals and public health officials at the respective county CDCs will be trained on the study design, study activities, and documentation procedures using the study CRFs. Specific training will be given for obtaining consent for the 12 month follow-up visit. Separate sessions will be held for HIV care department staff and laboratory staff.

The study design and study CRFs will be described in detail, focusing on the timeline of events, the importance of adhering to study protocols, and the importance of prompt and accurate documentation and case reporting. Materials covered in the training sessions will include the national AIDS policy, characteristics of the local HIV epidemic, ethics, pathogenesis of HIV, diagnosis of HIV, determination of clinical eligibility for ART, patient barriers to ART access, and an overview of the clinical management of HIV/AIDS. Training on human subjects protection and subject confidentiality will also be provided at this time.

The laboratory staff associated with One4all intervention group sites will be trained on use of the PIMA POC CD4 analyzers.

10.4 Training of Independent Assessors

CAB Training. A Community Advisory Board (CAB) will be established to assist with study activities and implementation. The CAB will be comprised of key stakeholders from local CDCs, provincial health departments, county health bureaus, service providers, and people living with HIV/AIDS. The CAB will meet prior to initial enrollment to provide advice to investigators about recruitment, training, intervention sustainability, and confidentiality issues. A second CAB meeting will be held 3 months into the study to review recruitment rates and problems encountered. The CAB will also help to interpret the assessment findings, ensuring that key values and beliefs are identified and factored into the analysis. The CAB will be trained on the national AIDS policy, characteristics of the local HIV epidemic, ethics, pathogenesis of HIV, diagnosis of HIV, determination of clinical eligibility for ART, patient barriers to ART access, an overview of clinical management of HIV/AIDS, the importance of adhering to study protocols, and data related issues.

10.5 Study Fidelity (Evaluation of Study Integrity)

A centralized Data and Statistics Team (DST) will be formed, composed of Dr. Yurong Mao, Dr. Shicheng Yu, Dr. Houlin Tang, and Diane Gu of NCAIDS and epidemiologists from the county CDCs related to the 12 participating study hospitals. The DST will be responsible for the validation of data from the patient care information systems, NCAIDS-based study database, and CRIMS, ensuring data integrity and security, and training the participating hospital and CDC staff on applicable data management procedures.

The Assessment Coordination Team (ACT) comprised of investigators and statisticians from NCAIDS, NIDA, and EMMES, will monitor the study integrity. An in-person meeting will be held prior to initial enrollment, and conference calls will be conducted every month during the study with additional calls as needed. The enrollment data will be reviewed by the ACT at every ACT meeting to monitor study progress. A quarterly report will be sent to each Study Steering Committee member and epidemiologists in the hospitals assigned to the intervention arms.

11.0 STUDY ASSESSMENTS

Data collected for the study will be documented and stored in two online data systems, CRIMS (after confirmed HIV positive) and a web-based database system for study-specific data.

11.1 Study Timetable

This study will need 14 months for site preparation, 9 months for enrollment and conduct, and 12 additional months for follow-up. Primary endpoint data analysis and report preparation will take about 9 months. A detailed timeline for this 2 1/2-year study is shown in **Figure 5**.

Figure 5. Study Timeline

	Year	Year One												Year Two												Year Three											
	Month	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
IRB preparation and submission																																					
Staff training & site preparation																																					
Intervention implementation																																					
1-month follow-up (for testing)																																					
3-month follow-up (for ART)																																					
12-month follow-up (for VL suppression)																																					
Data analysis and reporting																																					
	Month	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
	Year	Year One												Year Two												Year Three											

11.2 Measures and Assessments

11.2.1 Initial Assessments

Data from the initial assessments will be first recorded using the case report forms (CRFs) in addition to standard patient record keeping. Study data will be uploaded daily to the centralized NCAIDS-based study database. Data from the initial assessments include:

SOC Baseline Assessments and Procedures:

Personal and demographic information

Participants will provide the following information: full name, national ID number, date of birth, gender, ethnic group, educational level, marital status, occupation, date of HIV screening, and HIV screening results as part of their baseline information obtained at the local hospital. The participant's receipt of the Participant Handout will also be documented.

Locator information

Participants will supply standard of care locator information, which will be used by the local health care providers to contact them to remind them of follow-up visits and to locate participants who cannot be contacted. Participants will be required to provide their names, present addresses, and telephone numbers.

Counseling

It is standard practice that all individuals receiving HIV screening tests will receive post-test counseling (See Appendix D for details).

Study-Specific Supplementary Initial Assessment:

HIV Risk Behaviors. Participants will be briefly asked about past sexual risk behaviors (i.e., condom use), drug use behaviors (i.e., injecting drug use), and likely route of HIV transmission consistent with data collected for the CRIMS national data base.

11.2.2 Follow-up Assessments

Utilizing the hospital-based patient care information systems and CRIMS database, providers will use study-specific CRFs to report participant locator efforts, follow-up visit dates, test results, dates of all test result notifications and all post-test counseling sessions, ART eligibility, and hospitalizations.

Participants who are confirmed HIV-positive (through WB or VL testing) will then have records created in CRIMS, and those data will be available for analysis. The CRIMS forms and assessments are SOC. Basic information collected for CRIMS includes full name, national ID number, date of birth, gender, ethnic group, educational level, marital status, occupation, and date of HIV testing/screening. The CRIMS forms also include detailed information in the following areas:

Medical History

Participants will provide the following information as per routine medical care at the local hospital: history of HIV testing and results, current syphilis, tuberculosis, and hepatitis status, history of former plasma donation, history of blood/blood product transfusion, history of occupational exposure, history of surgeries, suspicious symptoms of tuberculosis, and AIDS-related clinical symptoms.

Sexual Risk Behaviors

Questions will include total number of sex partners in prior 3 months; total number of vaginal sex partners and anal sex partners; total number of unprotected vaginal and anal sex partners; status of HIV infection of the spouses.

Drug Use and Injection Risk Behaviors

Questions will include frequency and amount of use, including heroin, and methamphetamine; frequency and types of drugs injected, and sharing of drugs, needles, and other paraphernalia. We will ask about overdoses and any drug-related hospitalizations.

Confirmatory Testing, CD4 Testing, ART, and Deaths

CRIMS information includes the participant's dates and results of WB, ART, and VL tests. If the participant has initiated ART, his/her date of ART initiation, the ART regimen, and follow-up visits will be recorded in CRIMS. If the patient has died, the date of death will be recorded on CRIMS forms and study CRFs.

11.2.3 Clinical Assessments

All clinical assessments are provided through standard of care treatment.

11.2.4 Laboratory Tests

HIV Screening

Control Arm. All hospitals will use their SOC testing systems. This typically includes the Wantai Screening HIV (1+2) Ag&Ab EIA (Beijing Wantai Manufacturer of Infectious Diseases Diagnostics, China) and is followed by two different EIAs that may vary between sites. The SOC typically performs 2-4 EIAs. These data will be recorded to document the SOC practice at each control hospital.

Intervention Arm. All hospitals will use three HIV screening tests. The first HIV screening uses the Wantai Screening HIV (1+2) Ag&Ab EIA (Beijing Wantai Manufacturer of Infectious Diseases Diagnostics, China) for qualitative determination of antigens or antibodies to HIV type 1 and/or type 2 in serum or plasma. This method is also known as a 4th generation EIA for HIV detection, with 100% sensitivity and 99.8% specificity. Plasma or serum samples giving absorbance less than the cut-off value ($S/CO < 1$) are diagnosed as negative. Plasma or serum samples giving an absorbance equal to or greater than the cut-off value ($S/CO \geq 1$) are considered initially reactive. Participants receiving a positive result will be included in the study, while participants receiving negative and borderline results will be excluded from the study.

The second screening test is the Determine HIV-1/2[®] rapid test (Abbott Laboratories, USA), which detects HIV-reactive IgG and IgM in whole blood, serum, or plasma, with 100% sensitivity and 99.97% specificity. In this assay, the whole blood, serum, or plasma sample is added to the sample pad on the test strip. If a red line appears at the window, the sample is considered positive; if not, the sample is considered negative.

The third screening test is the InTec HIV rapid test (Xiameng InTec Products, Inc., China), which detects HIV-reactive IgG and IgM in whole blood, serum, or plasma, with 100% sensitivity and >99.8% specificity. The second and third rapid tests are performed simultaneously only after an initial positive first test. Participants receiving two positive results, or one positive and one negative result from the second and third rapid tests will have their blood drawn the second time for CD4 and VL testing.

HIV Confirmatory Tests

Control arm. A blood sample will be collected from the participant at the study hospital and sent to the local city CDC for WB confirmatory testing. Blood sample collection may occur immediately following the HIV screening or on a subsequent visit. Confirmatory testing usually takes 10-15 days; participants are usually discharged from the study hospital during this period and contacted later with the results.

Intervention arm. The VL test (below) will be used as the confirmatory test for HIV status.

CD4 T-cell Count

Control arm. Upon receipt of the HIV confirmatory results from the city CDC, participants will be asked to return to the study hospital for a blood draw for CD4 testing, often together with an initial epidemiological investigation. Blood specimens are sent to the city CDC for CD4 testing using plasma samples, which usually takes 10-15 days. Participants will be contacted and asked to return to the study hospital to receive the CD4 testing results and, if eligible, ART counseling.

Intervention arm. Blood samples for CD4 testing (and viral load) are collected at the study hospital immediately following receipt of positive HIV screening results. Numeration of CD4+ T-lymphocytes will be performed in the study hospital lab using a PIMA POC CD4 analyzer (Alere Healthcare, USA) using venous whole blood samples. POC CD4 testing results are available in less than 30 minutes.

Plasma HIV RNA VL Testing

Control arm. VL testing is performed only after ART initiation, about a year later. Blood samples for VL testing are collected at the study hospital.

Intervention arm. Blood samples for VL testing are collected at the study hospital (at the same time the CD4 sample is collected) immediately following receipt of positive HIV screening results and at the same time as the blood draw for CD4 testing (see above).

Both arms. VL testing is performed at the province CDC using plasma samples, which takes 10-15 days. Participants will be contacted and asked to return to the study hospital to receive the VL testing results and, if eligible, ART counseling.

11.3 Safety Assessments

The intervention in this trial, comparing HIV testing strategies, poses no specific safety risk to the participants. HIV testing will involve several blood draws, up to 4 in SOC, and 1-3 in One4all arms. There will be no increase in the volume of blood drawn or the typical risk associated with blood draws. Standard of care will be compared to a new strategy (One4all) with a goal to improve HIV initiation of treatment in HIV screened positive cases. Risk of loss of confidentiality is a safety concern and will be managed throughout the study utilizing standard protections within the China health care system, and de-identified data will be used whenever possible. The study team extracting data from either the local hospital records or the CRIM system will assign a participant ID number to protect confidentiality of information. Any infringement or loss of confidentiality will be reported to the Chinese Ethics Committee for review and action if required. Throughout the course of the study, any deaths and hospitalizations will be captured through review of the hospital based care information systems and the CRIMS system. All of these events will be made available for ongoing monitoring by the Data and Safety Monitoring Board (DSMB). It is expected that there will be an initial review and approval of the protocol prior to study implementation. The DSMB will review for data and safety at the study halfway mark, e.g., 3-6 months from study start and a second review will be conducted as needed.

11.4 Projected Assessment Summary

Table 1 – Project Summary Assessments

Procedure	Baseline		Follow-up 1		Follow-up 2	Follow-up 3	
	SOC	One4all	SOC	One4all	SOC One4all	SOC	One4all
Eligibility Assessments							
Inclusion/Exclusion Criteria	X	X					
Initial Assessments							
Demographic Information	X	X					
Locator Information	X	X	X	X	X X	X	X
Medical History	X	X					
Sexual Risk Behaviors	X	X					
Drug Use Risk Behaviors	X	X					
Physical Examination	X	X	X	X	X X	X	X
Review of Clinical Symptoms	X	X	X	X	X X	X	X
Medications						X	X
Laboratory Assessments							
HIV Screening Tests							
Blood Draw	X	X					
- Screening Results	X	X					
WB Confirmatory Test							
Blood Draw	X						
- WB results + counseling			X*				
CD4 count Blood Draw		X	X*				
- CD4 results + counseling		X			X*	X*	X*
VL Test Blood Draw^		X				X	X
- VL results + counseling				X*			
ART counseling + initiation					X* X*	X*	X*

* These tests will occur at any time point after baseline assessment and likely before the scheduled time points above.^ Under SOC, VL testing is conducted after ART initiation.

12.0 CONDITIONS

12.1 Both Conditions

HIV Screening and Study Enrollment

Medical and health care institutions within Guangxi are required to provide free HIV testing service to all patients through the Voluntary Counseling and Testing Program or the New Rural Cooperative Health Insurance.

In most cases, a patient for whom an HIV test has been ordered will first be screened using the Wantai screening test. Blood samples that produce a reactive result are immediately re-screened using Wantai and a rapid test. Patients are asked to wait in the study hospital for their results. Patients with samples yielding reactive results in the first screening test are enrolled in the study and will proceed with further testing procedures according to the hospital assignment.

Patients with samples yielding a negative result are diagnosed as negative. The patient will be notified and provided post-test counseling.

Per SOC, the patient will be provided post-test counseling and asked to return to the hospital in 3 months to be re-screened. At the re-screening, a reactive result will be eligible for the study.

Patients that receive screening tests but leave prior to learning the results will count towards the denominator if they have a positive test. They will be contacted to return for further testing through SOC or One4all, depending upon the hospital assignment, to continue with their evaluation of their HIV status.

At the time of being notified of test results, patients will receive post-test counseling. If the patient is eligible for the study, he/she will be informed of the study through the Participant Handout and enrolled through the hospital-based patient care system. Counseling occurs at 5 points: post-screening test, post-WB test, post-CD4 test, post-VL test, and pre-ART initiation. Key components of each counseling stage are summarized in **Appendix C**. Participants who are eligible for treatment (**Appendix A**) will be given counseling on treatment and will immediately start preparation for ART. Participants who are not eligible for treatment are given counseling about HIV infection, disease progression, national AIDS policies, follow-up requirements, etc. If a participant has sexual partners or drug use partners, he/she will be encouraged to bring them to the HIV care department to have an HIV test.

12.2 Control Condition

The control condition is the current standard of care (SOC) utilized within the county hospitals in Guangxi, China (**Figures 6-7**). This SOC has some variability between counties but in general follows the national policies. The usual process is described below. After the initial positive screening on EIA and subsequent repeat screening, participants will receive post-screening test counseling. Participants will then be tested by WB either at the same visit or a subsequent visit. The WB is sent offsite; it generally takes 10 to 15 days to obtain the results.

After WB test results are reported to the hospital, the health care provider will contact the participant by phone. The participant will be asked to return to the hospital for results and post-WB test counseling. At this visit, a blood sample will be collected for CD4 testing, and an initial epidemiological investigation will be carried out, using the CRIMs forms. CD4 laboratory testing is performed at the city CDC, which also usually takes 10 to 15 days.

Once CD4 test results are available, participants must be located again to inform them of their results and ART eligibility and to provide post-CD4 test counseling (designated as the study endpoint post-test counseling) (**Appendix C**). Those who are eligible for ART as determined by the local hospital provider (**Appendix A**) are encouraged to seek HIV care at the study hospitals

via China's National Free ART program. Following CD4 measurement, participants will be referred to the HIV care department to begin preparation and pre-ART initiation counseling. Participants are only offered annual VL testing at the city CDC after ART initiation.

Figure 6. Standard of care (SOC) for HIV testing and linkage to HIV care in China. Critical path from initial HIV screening to HIV treatment highlighted by blue arrows.

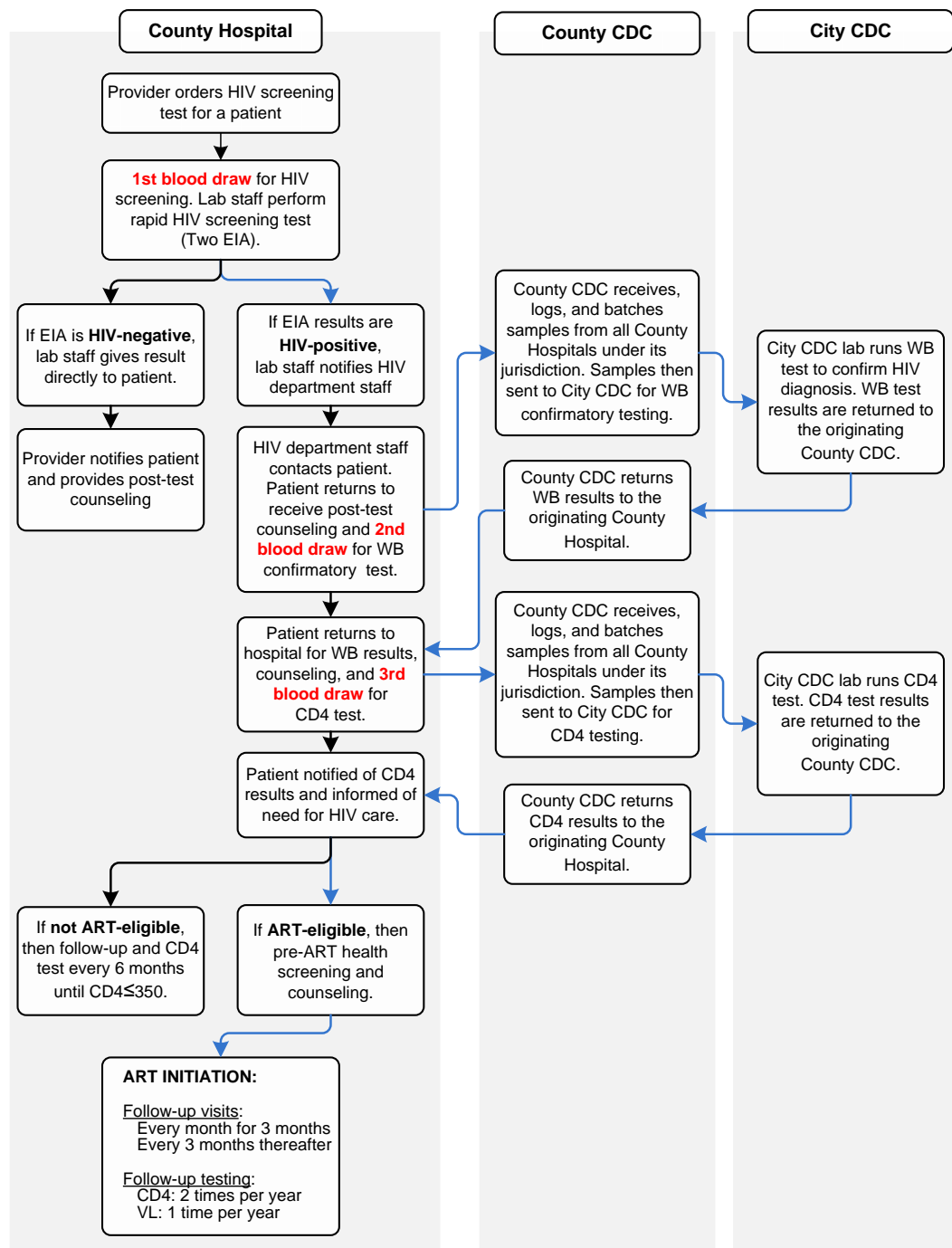
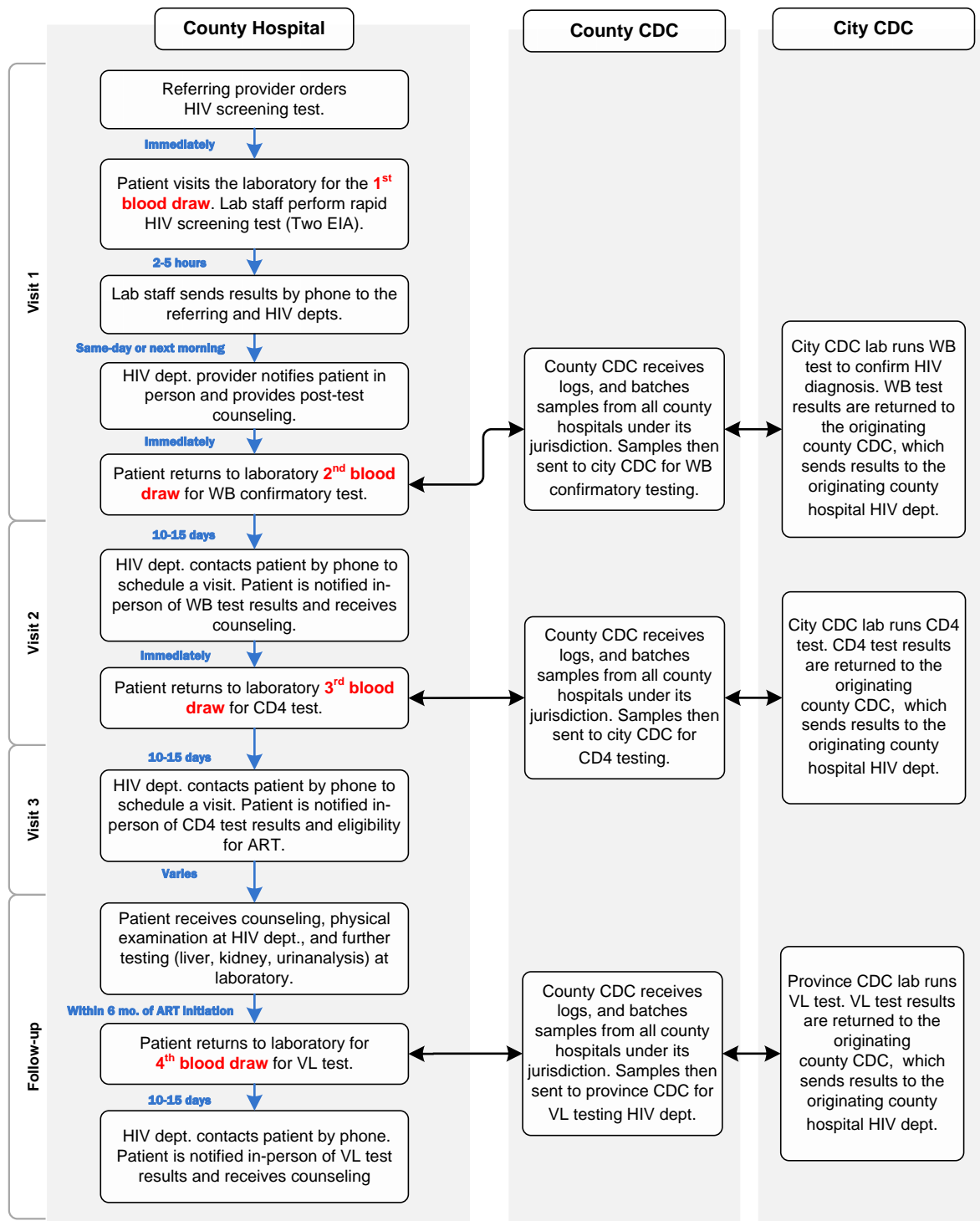
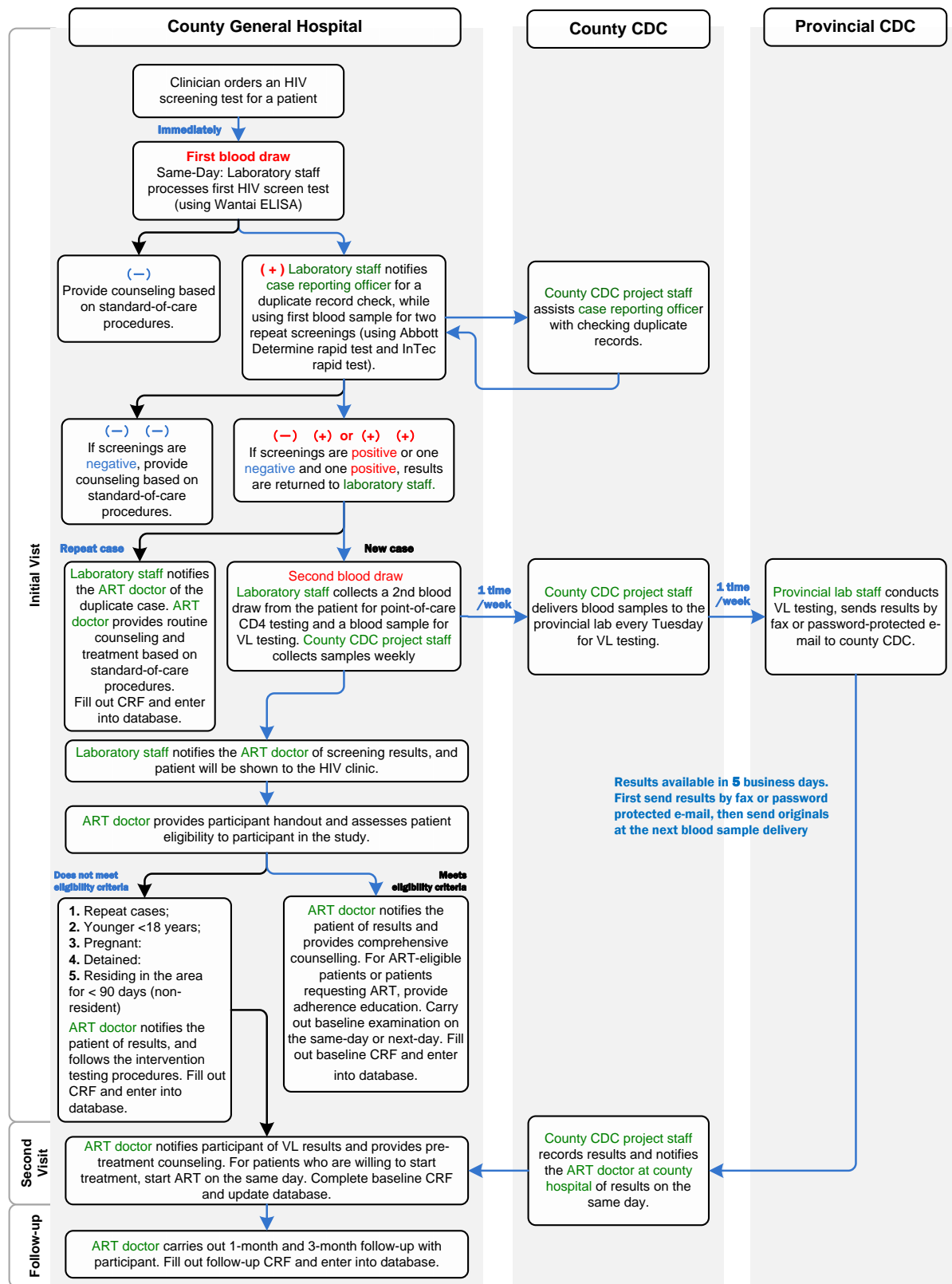


Figure 7. Detailed standard of care (SOC) procedures for HIV testing and linkage to HIV care in China. Patient pathway and timeframe is highlighted in blue.



12.3 Intervention Condition

Figure 8. New streamlined process for HIV testing and linkage to HIV care. Critical path to treatment highlighted by blue arrows.

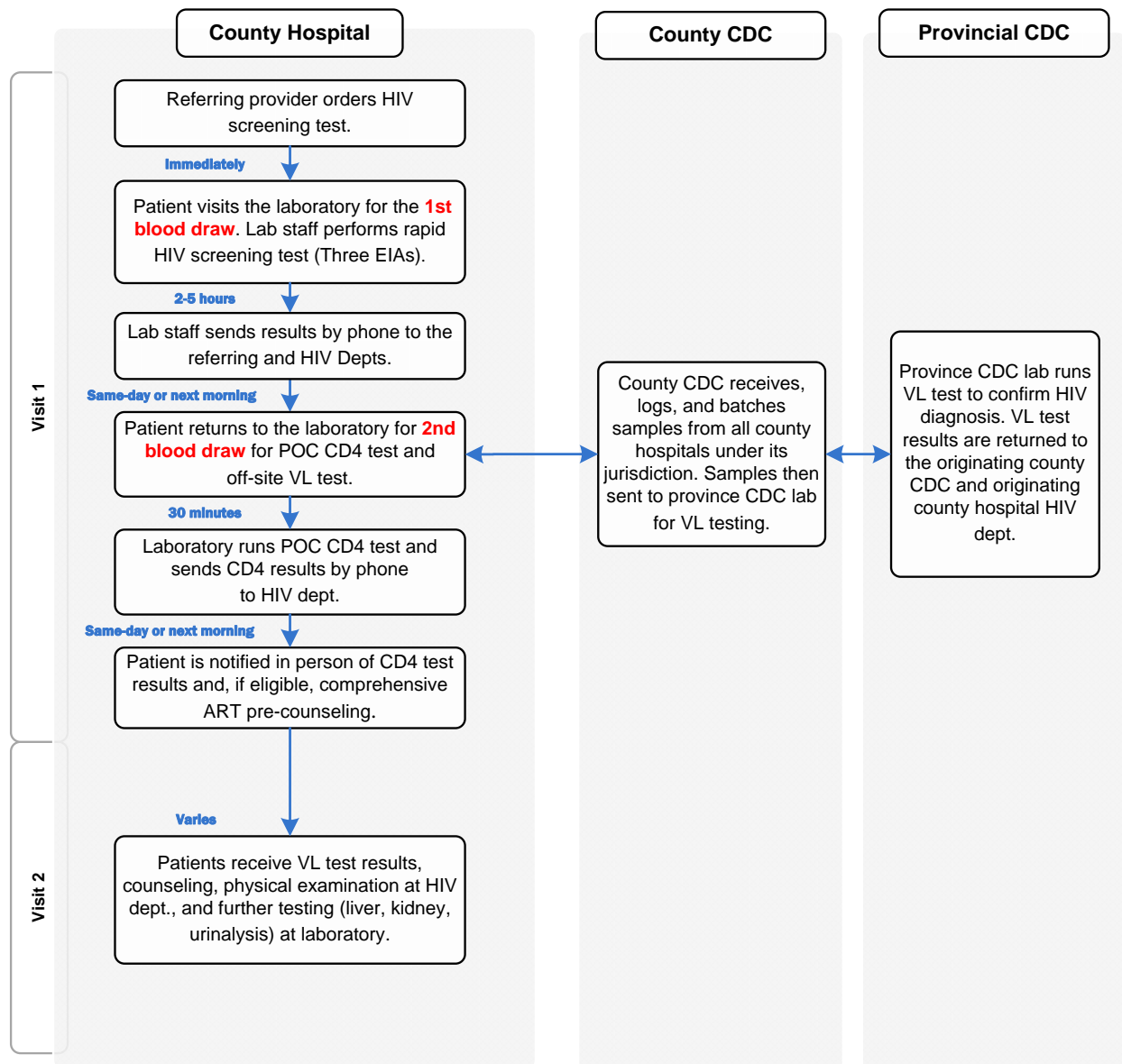


New One4all Testing Algorithm (Figures 8-9).

Participants with HIV-positive screening results on EIA will immediately have their blood drawn for CD4 and VL tests. Two venous blood samples (4mL, and 10mL) will be collected—one for immediate numeration of CD4⁺ T-lymphocytes in the same hospital lab using a PIMA POC CD4 analyzer (Alere Healthcare, USA) and the other for later VL testing at the province CDC, which takes 10-15 days. Participants will be notified in-person of their CD4 results on the same day and provided post-CD4 test counseling (**Appendix C**). Counseling in the One4all intervention has been modified from the national SOC guidelines due to the different order of tests and the shortened time period between screening and CD4 testing. The participant will be provided with a tentative assessment of ART eligibility based on CD4 results and other factors. Those who are eligible for ART (**Appendix A**) are encouraged to seek HIV care at the study hospitals via China's National Free ART program. If indicated, the participant may begin preparation for ART initiation by completing a physical exam, other laboratory tests (liver, kidney, urinalysis), and medical insurance paperwork. ART initiation will not occur until the VL test is returned, which confirms HIV infection.

The VL serves as the confirmatory test for the One4all group and success for this group will be obtaining the results of the three EIAs, the POC CD4, the viral load, and the post-VL test counseling. Once the VL test results are available, the hospital will contact the participant by phone and ask him/her to return to the hospital for their results and post-VL test counseling (designated as the study endpoint post-test counseling). ART eligibility will be re-assessed based on the VL results. No confirmatory testing via WB will be conducted unless HIV status is not resolvable, a situation which is expected to be a rare occurrence. (44-47)

Figure 9. Detailed Study 1 Intervention procedures for HIV testing and linkage to HIV care in China. Patient pathway and timeframe is highlighted in blue.



13.0 STATISTICAL ANALYSIS

13.1 General Design

13.1.1 Study Hypotheses

Hypothesis 1a

The new testing algorithm will increase the proportion of individuals who have completed all tests to confirm HIV diagnosis and received counseling within 30 days of screening HIV-positive, given they have screened HIV-positive on the initial EIA, from 23% to at least 50% (primary outcome).

Hypothesis 1b

The new testing algorithm will increase the proportion of individuals with a CD4 ≤ 350 cells/mm³ who initiate ART within 90 days of screening, given that they have screened HIV positive on the initial EIA (secondary outcome).

Hypothesis 1c

The effectiveness of the new testing algorithm will yield no significant differences for DUs at 1-month follow-up on testing completeness and at 3-month follow-up on ART treatment initiation, compared to non-DUs.

Hypothesis 2

The new testing algorithm will increase the proportion of individuals with a VL ≤ 200 copies/mL at 12 months, given that they have screened HIV positive on the initial EIA (tertiary outcome).

13.1.2 Primary and Secondary Outcomes (Endpoints)

Primary Outcome (Hypothesis 1a)

The primary outcome of this study is the receipt of post-test results and counseling following testing completeness. The numerator is the number of HIV-positive participants who have received post-test results and counseling within 30 days of initial screening blood draw. The denominator is the number of participants who screened positive on the initial HIV EIA in the study arm (control or intervention).

Testing completeness is defined as completion of all three required components: 1) rapid, POC HIV testing, 2) CD4 testing, and 3) confirmatory testing by WB in the SOC or confirmatory testing by VL in the One4all.

The primary endpoint variable (receipt of all post-test results and counseling) will be defined as a binary variable. If an HIV-positive individual has completed and received results on the three required testing components (as defined above) and received post-test counseling within 30 days from his/her HIV screening, it is defined as a complete case, and the variable is defined equal to one. If any test, all three test results, or post-testing counseling are missing, we will define the case as an incomplete case, and the variable is defined equal to zero. Only individuals who have screened positive on the initial EIA will be analyzed. A secondary analysis of the primary endpoint will compare between the two treatment groups time from EIA screening to testing completeness among those who screened HIV-positive on the initial EIA but not restricting to the 30 days period, with those not completing testing censored at the endpoint of the study.

Secondary Outcome (Hypothesis 1b)

A secondary outcome is the proportion of treatment-eligible participants with $CD4 \leq 350$ cells/mm³ who have initiated ART within 90 days of an initial positive HIV screening. We will define the secondary endpoint variable for Hypothesis 1b as a binary variable. If a participant with $CD4 \leq 350$ cells/mm³ initiates ART within 90 days of a positive screening, the variable is defined equal to one. Otherwise, the variable is defined equal to zero. All participants who screened HIV-positive on the initial EIA at screening will be included in the analysis.

Secondary Outcome (Hypothesis 1c)

Study participants will be classified as drug users or non-drug users based on the baseline assessment. A variable will be included in the statistical model for the primary and secondary outcomes to estimate the association between drug user status and receipt of post-test results and counseling following testing completeness and the initiation of ART therapy, respectively.

Tertiary Outcome (Hypothesis 2)

A tertiary outcome is the proportion of participants who have viral suppression based on the 12-month viral load test, where viral suppression is defined as viral load ≤ 200 copies/mL. We will define the tertiary endpoint variable as a binary variable. If a participant with $VL \leq 200$ copies/mL at 12 months after initial screening, the variable is defined equal to one. Otherwise, the variable is defined equal to zero. All participants who screened HIV-positive on the initial EIA at screening will be included in the analysis.

13.1.3 Factors for Stratification and Covariate Adjustment

The study design is a cluster randomized clinical trial. Ideally, the randomization should ensure that the distribution of characteristics across the intervention and control groups is the same at baseline, thus not requiring adjustment of covariates for data analysis. However, in practice, randomization cannot guarantee complete balance between the intervention and control groups, especially since the randomization unit for this study is the hospital. A single stratified randomization creating two strata will be used to allocate hospitals to either the intervention group or the control group. Stratification will be based on historical rates of receipt of post-test results and counseling following testing completeness and will be included in the primary outcome statistical model. The correlation of participants within each hospital will also be adjusted. Other factors for covariate adjustment will be considered, such as participant-level variables including age at baseline, ethnicity, gender, primary drug use (injection drug use versus non-injection drug use, opiate versus non-opiate), and socioeconomic status and hospital-level characteristics such as number of hospital beds. Details on the process by which covariates will be considered in the statistical models are detailed in the study's Statistical Analysis Plan.

We use baseline completeness rates as a variable to stratify the 12 hospitals under SOC. Medical record review at the 12 hospitals was performed to serve as the basis for determining the stratification. Cases that were newly screened HIV positive between January 1, 2013 and June 30, 2013 from each of the 12 hospitals were assessed for completion of HIV confirmation and counseling within 30 days of initial HIV screening. The completeness rates of the 12 hospitals were ranked to establish the strata. Furthermore, the baseline completeness rate will be treated as the second level predictor variable in our multi-level (mixed) logistic regression analysis.

13.2 Rationale for Sample Size and Statistical Power

We have selected a sample size of 180 HIV-positive participants (including approximately 10% DUs) in the control arm and 180 (including approximately 10% DUs) in the intervention arm, across 12 clusters (n=30 individuals in each cluster). This sample will achieve 93% power

based on a one-sided test ($\alpha=0.05$) to detect a difference between the group proportions of 0.28, where under the alternative hypothesis the intervention group proportion is assumed to be 0.50 and the control group proportion is assumed to be 0.22. This calculation assumes an intra-cluster correlation (ICC) within hospitals of 0.082 based on preliminary data. To assess the sensitivity of these calculations based on the 12 clusters and 30 patients per cluster, we examined in the table below effect sizes of 0.28, 0.33, and 0.38 and ICC estimates of 0.072, 0.082, and 0.092, assuming a one-side test at $\alpha=0.05$ and the SOC success rate of 0.22.

		Intra-cluster correlation (ICC)		
		0.072	0.082	0.092
Success rate in One4All	0.50 ($\delta=0.28$)	95.2%	93.6%	92.0%
	0.55 ($\delta=0.33$)	98.8%	98.2%	97.5%
	0.60 ($\delta=0.38$)	99.8%	99.7%	99.5%

Power calculations were also performed for the secondary outcome of initiating ART within 90 days and having a CD4 count ≤ 350 , among all the HIV-screened positive study participants. Data from preliminary data in Guangxi showed that 14% of HIV screened positive patients had CD4 counts ≤ 350 and initiated ART within 90 days. We will have 93% power to detect an increase to 40% in the intervention group of initiating ART with CD4 ≤ 350 within 90 days. For these calculations, we used an ICC of 0.082 and a one-sided test at $\alpha=0.05$. All power calculations were performed by the PASS (Version 8) software.

13.2.1 Projected Number of Sites

Twelve county hospitals will be randomly selected and assigned to either the One4all Test Intervention group or the SOC control group.

13.2.2 Projected Number of Participants per Site

The target enrollment for each hospital will be 30 HIV-positive participants.

13.3 Statistical Methods for Primary and Secondary Outcomes

13.3.1 Primary Outcome

Primary Analysis for Hypothesis 1a

Hierarchical regression models (e.g., mixed-effect models or random-effect models (48, 49)) will be used to compare the proportion of HIV-positive individuals who received a complete suite of test services, results and post-test counseling within 30 days between individuals assigned to the One4all Test Intervention arm (i.e., individuals who receive a new testing algorithm, consisting of HIV, CD4, and VL tests) and individuals receiving SOC in the control arm. Specifically, proportions will be compared using logistic regression with hospital-level random effects to account for potential ICC within hospitals. Models that do not account for ICC will underestimate standard errors. Testing completeness rates will be compared at 30 days after being screened HIV-positive in the hospital. In addition to the inclusion of a covariate for the intervention arm (1=intervention, 0=SOC), random effect logistic regression models will control for the stratification factor and potential confounding variables, including age, gender, transmission mode, drug use, and other characteristics that are found to differ at baseline.

Secondary Analyses for Hypothesis 1a

A secondary analysis of primary endpoint will also be performed: comparison between the time from initial EIA positive screen to completion of testing between the two treatment groups, not

restricted to the 30 days period. Participants who did not complete testing will be censored at the endpoint of the study. Kaplan-Maier will be used to compare time differences by days from the positive HIV screening to the receipt of post-test counseling (can extend beyond the 30 day cut point period) between the intervention and control groups. An extended Cox model accounting for the effects of clustering will be used to calculate the intervention effect by hazard ratios while controlling for other covariates. Further, testing completeness will be compared between the two treatment groups at additional thresholds of 45, 60, and 90 days, analyzing these endpoints in a similar fashion to the primary analysis.

13.3.2 Secondary Outcomes

Analysis for Hypothesis 1b

The number of participants who have a CD4 count ≤ 350 cells/mm³ and are newly-enrolled in ART within 90 calendar days (i.e., from the date of screening HIV-positive to the date of first receiving ART prescription), will be defined as the numerator for both the One4all Test Intervention and the SOC control groups, separately. The denominator will be defined the number of participants who had a HIV-positive initial EIA screening. Similar to analysis for Hypothesis 1a, random-effect logistic regression will be used to compare the proportion of participants newly enrolled in ART between the two groups.

Secondary Analysis for Hypothesis 1b

The same as the secondary analysis for hypothesis 1a, the outcome variable will not be treated as a binary outcome variable (enrolled in ART within 90 days=1, not enrolled in ART=0) for the secondary data analysis. The time between the initial HIV positive screen by EIA to initiation of ART will be treated as continuous variable (in term of days). HIV-positive participants based on initial screening who did not initiate ART will be censored at the endpoint of the study. Kaplan-Maier and extended Cox model will be used for the data analysis.

Additional Secondary Analysis for Hypothesis 1b

The primary analysis for Hypothesis 1b will be re-calculated with all participants deemed eligible for ART per local hospital provider decision, and would include all participants from the primary Hypothesis 1b analysis (with CD4 ≤ 350) with the additional participants with CD4 > 350 who were recommended for ART by their local providers based on criteria other than CD4. This includes index partners of serodiscordant couples, participants with active tuberculosis, participants with active Hepatitis B, and other conditions summarized in Appendix A. Local providers' decisions on participant ART eligibility will be recorded on study CRFs. Clinical decisions on ART eligibility – particularly for reasons other than CD4 levels - are results of complex decision-making processes and may vary from provider-to-provider. Note that the focus of this analysis is on the proportion of participants deemed eligible for ART who did initiate ART within the 90 days specified timeframe, and not on the decision-making by the local providers.

Analysis for Hypothesis 1c

The analyses described above (for Hypotheses 1a and 1b) will be repeated by including a predictor variable in the statistical model that is defined by classifying study participants as drug users or non-drug users based on the baseline assessment. This analysis will estimate the association between drug use status at baseline and testing completeness at 1-month follow-up and ART initiation at 3-month follow-up between the One4all Test Intervention and the SOC control groups.

Analysis for Hypothesis 2

The number of participants who have a VL ≤ 200 copies/mL at 12 months will be defined as the numerator for both the One4all Test Intervention and the SOC control groups, separately. The

denominator will be defined as the number of participants who had a HIV-positive initial EIA screening. Similar to analysis for Hypothesis 1a, random-effect logistic regression will be used to compare the proportion of participants virally suppressed between the two groups. Additional descriptive analyses will be performed related to this tertiary outcome, including describing the ART therapy regimen and the adherence to the regimen.

13.4 Significance Testing

A 5% level one-tailed test will be used for the analysis of the primary endpoint and secondary endpoints.

13.5 Interim Analysis for Sample Size Re-estimation

We plan to conduct a sample size re-estimation when 35-40% of the participants have reached the primary endpoint. The goal of the analysis will be to estimate the intra-class correlation (ICC), as misspecification of the ICC in the original sample size calculations will impact study power. The analysis will be performed without estimating the treatment effect. If the results of the analysis suggest a modification to the sample size, the modifications will first be to the number of participants within a cluster (i.e., hospital) before consideration for modifying the number of clusters. The timing of the sample size re-estimation will be impacted by the rate of participant recruitment and when the hospitals initiate study enrollment. If these factors suggest an analysis may not yield useful results (e.g., half the hospitals have complete outcomes and the remaining hospitals do not have any outcomes), a sample size re-estimation may not be performed. Decisions related to performing the sample size re-estimations, and any suggested modifications to the sample size, will be made after careful review by study leadership, NIDA, and the DSMB.

13.6 Missing Data and Dropouts

The outcome is the completeness of the endpoints (i.e., receipt of post-test counseling following providing results of testing to the participant and ART initiation). Dropouts and missing data indicate that the endpoints were not successfully reached. There will be no special treatment for missing values.

13.7 Demographic and Baseline Characteristics

Baseline demographic and clinical characteristics will be summarized for each arm. Distribution, frequency, and percentage will be checked for discrete variables. Distribution, mean, median, and range will also be checked for continuous variables. The balance of the intervention and control group will be checked by statistical tests such as a Chi-squared test, Fisher's exact test, or Wilcoxon test.

13.8 Safety Analysis

Rates of hospitalizations and rates of mortality will be compared between the intervention arms as an assessment of safety. Loss of confidentiality and what was done to remedy the loss will also be tracked and reported. In addition, rates of incarceration and detention that are reported through the course of follow up will also be tracked.

14.0 CONCOMITANT THERAPY

14.1 General Considerations for Participants Receiving ART

HIV-positive participants can have comorbidities with HIV-related diseases, including malignancies, hepatitis B and C, and non-AIDS related diseases, including diabetes mellitus, heart disease, and hypertension. Clinicians should be careful to monitor for drug-drug interactions and to adjust ART and opportunistic infection medications if needed. Women taking ART drugs that have significant pharmacokinetic interactions with oral contraceptives should use an additional or alternative contraceptive method.

For IDUs receiving methadone maintenance treatment, concurring ART may diminish the effectiveness of either or both therapies by causing opioid withdrawal or overdose, increased methadone toxicity, and/or decreased ART efficacy. Providers should prescribe and monitor appropriate dosages of methadone.

Deferral of ART may be considered when presentations of other medical conditions could complicate the treatment of HIV infection. An example is a previously scheduled surgery.

14.2 Medications Prohibited Before/During the Trial

Clinical data regarding on drug-drug interactions between ART and traditional Chinese medicines is insufficient. Participants are requested to avoid traditional medicines while receiving ART.

14.3 Medications Allowed During the Trial

14.3.1 Ancillary Medications

Any medication without known drug-drug interactions with ART may be used to treat concurrent conditions. Providers must review the safety, efficacy, and pharmacokinetic data provided by the manufacturing pharmaceutical company prior to prescription.

14.3.2 Rescue Medications

If participants present with any life-threatening conditions such as development of an allergic reaction or aggravation of concurrent disease, providers may decide to stop ART. Any appropriate rescue medications may be used.

15.0 REGULATORY COMPLIANCE AND SAFETY

15.1 Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, supporting documents, and any advertising for participant recruitment from the Chinese Ethics Committee in order to participate in the study. Prior to study initiation, the protocol will be reviewed by NIDA's Protocol Review Board/DSMB, and approved by the UCLA IRB and China CDC IRB. Any amendments to the protocol or study materials must be approved before they are implemented. Annual progress reports will be submitted to the IRBs, according to its usual procedures.

In the event of conflicting Chinese and US regulatory requirements, Chinese law will take precedence.

15.2 Regulatory Files

The regulatory files should contain all required documents, study-specific documents, and important communications and will be maintained throughout the study.

15.3 Informed Consent

This study introduces no new testing procedures or treatment interventions. There is no increased risk with HIV testing, with the use of HIV test methods already in current practice. A Participant Handout describing the study, HIV testing and data collection procedures will be provided to all participants, and its receipt will be documented. (Appendix B) The participant may discuss any concerns with the local care provider who will be knowledgeable about the study or can discuss with the local CDC study team. Participants may opt out regarding having their data used for the study, but the positive EIA result will count in the denominator. We expect this to be very rare.

The outcome of this study is the completeness of the endpoints (i.e., receipt of post-test counseling following providing results of testing to the participant and ART initiation). Therefore it is necessary to use all of the data collected on all enrolled participants. Informed Consent administered after HIV screening could result in refusal to participate by some patients, and allowing for withdrawal of study consent could result in the loss of some study data, which would compromise the validity of study results.

Thus, the usual process of obtaining individual Informed Consent on all study participants will not be implemented in this study. Study information will be provided, and opportunities for participants to ask questions will be provided.

Prior communications and a preliminary review by the Chinese Ethics Committee Chair regarding this approach have been favorable. A similar request submitted to the UCLA IRB is also favorable to this approach.

Finally, this protocol will be submitted for approval by NIDA's Protocol Review Board/DSMB, UCLA IRB and the NCAIDS Ethics Committee. Once approved, the waiver from individual Informed Consent procedures for this study is implied.

Gathering additional information and VL testing at the 12 month follow-up time point poses a protocol specified time point and evaluation. Because this procedure is different than standard of care, an oral consent will be obtained to both draw a VL at 12 months and to ensure that data can be obtained and analyzed as part of this study. As follow up does occur as a standard of care for those that are HIV positive and either ART eligible or not ART eligible, and laboratory

assessments are performed as part of this follow up, the one year time point and the collection of data do not create either undue burden or undue risk to the participant. This contact will also provide an opportunity to re-engage into testing/treatment those participants who did not follow through with treatment, if and when they are successfully re-contacted by study staff.

15.4 Confidentiality

By signing the protocol signature page, the investigator affirms that study information will be maintained in confidence and such information will be divulged to the IRB, or similar expert committee; affiliated institution; NIDA; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

15.5 Investigator Assurances

Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the Chinese Ethics Committee provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the principal investigator at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

15.6 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will have an up-to-date signed financial disclosure form on file.

15.7 Inclusion of Women and Minorities

A diverse group of study sites will be involved so that these sites can attract a diverse study population. Since the study will be carried out in China, the vast majority of study participants will be Asian or Chinese. The study will track the number of participants who belong to a Chinese minority ethnic group (e.g. Zhuang, Hui, Manchu, Uyghur, Miao). In Guangxi, 32% of the population is of Zhuang ethnicity, the largest minority ethnicity in China. Based on the preliminary assessment in Guangxi, we estimate about 26% of study participants will be women.

15.8 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, and regulatory files) are to be maintained by the investigator in a secure location for a minimum of 3 years after the study is completed and closed. These records are also to be maintained in compliance with the Chinese Ethics Committee, and national requirements, whichever is longest. The sponsor and lead investigator must be notified in writing and acknowledgment must be received by the site prior to the destruction or relocation of research records.

15.9 Monitoring

On-site monitoring will occur at regularly scheduled times by local, provincial, and national study staff. The site PI will conduct monthly monitoring. Guangxi CDC study staff will conduct monitoring every other month. National CDC study staff will conduct quarterly monitoring.

15.10 Reporting to NIDA

The site principal investigator agrees to submit accurate, complete, legible and timely reports to the lead investigator, as required. These include, but are not limited to, reports of any changes

that significantly affect the conduct or outcome of the trial or increase risk to study participants. At the completion of the trial, the study Lead Investigator will provide a final report to NIDA.

15.11 Study Documentation

Study documentation includes all case report forms, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Committee correspondence. Study documentation includes electronic and paper versions.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

15.12 Safety Monitoring

15.12.1 Data and Safety Monitoring Board (DSMB)

This study will utilize the CTN DSMB to oversee ongoing trial progress. The purpose of this board is to determine whether risks emerge during the conduct of the trial that make continuation unethical. This process is intended to assure the IRBs/Ethics Committee, the sponsor, and investigators that participants are provided with an accurate and ongoing risk evaluation when participating in NIDA CTN research trials. Safety monitoring begins with the initial review of the protocol during the study development process. It is anticipated that the DSMB will meet first within 3-6 months of study start for data and safety monitoring. If there is adequate data for a meaningful interim analysis to re-estimate the sample size, the review of the interim analysis will be performed concurrently. If not, the interim analysis can be carried out at a separate time. The need for additional DSMB meetings over the study duration will be at the discretion of the DSMB.

15.12.2 Unanticipated Problems Reporting and Management

Any “Unanticipated” Problems defined by the Chinese Ethics Committee associated with this study including breaches of confidentiality will be reported to the Lead Investigator, the Chinese Ethics Committee overseeing this research, and the NIDA DSMB.

15.12.3 Safety Monitoring

The intervention in this trial, comparing HIV testing strategies, poses no specific safety risk to the participants. HIV testing will involve several blood draws, up to 4 in SOC, and 3 in One4all arms. There will be no increase in the volume of blood drawn or the typical risk associated with blood draws. Standard of care will be compared to a new strategy (One4all) with a goal to improve HIV initiation of treatment in HIV screened positive cases. Risk of loss of confidentiality is a safety concern and will be managed throughout the study utilizing standard protections within the China health care system, and de-identified data will be used whenever possible. The study team extracting data from either the local hospital records or the CRIM system will assign a participant ID number to protect confidentiality of information. Any infringement or loss of confidentiality will be reported to the Chinese Ethics Committee for review and action if required. Throughout the course of the study, any deaths and hospitalizations will be captured through review of the hospital based care information systems and the CRIMS system. All of these events will be made available for ongoing monitoring by the Data and Safety Monitoring Board (DSMB). It is expected that there will be an initial review and approval of the protocol prior to study implementation. The DSMB will initially review for data and safety monitoring within 3-6 months of study start. Additional reviews will be at the discretion of the DSMB.

16.0 DATA MANAGEMENT AND PROCEDURES

16.1 Design and Development

A centralized Data and Statistics Team (DST) will be formed, composed of Drs. Shicheng Yu, Yurong Mao, and Houlin Tang, and Diane Gu of NCAIDS and epidemiologists from the county CDCs related to each of the 12 participating study hospitals. The DST will be responsible for the validation of the web-based study database, and CRIMS, ensuring data integrity and security, and training the participating hospital and CDC staff on applicable data management procedures.

Data from this study are generated from one new study database system and one existing database. Using the case report forms (CRFs), we will collect baseline assessment information, including participant demographic information, laboratory screening results and dates, and tracking of test result notification dates and post-test counseling dates. The CRF data will then be stored in a newly designed web-based database for the study, which will serve as a centralized location for electronic storage of all study-related data. Study-related data from each hospital system will be retrieved weekly and uploaded to the web-based study database.

The existing database, CRIMS,(43) is a nationwide ongoing epidemiological database for confirmed HIV cases. CRIMS contains a unique code number for each county hospital nationwide, including all participating study hospitals. CRIMS stores information on HIV confirmatory testing, initial investigations of newly-diagnosed HIV cases, follow-up visits for each individual HIV/AIDS case, CD4 test, ART regimen, VL test, etc. Therefore, CRIMS can generate the following measures that can be used to construct study outcomes: the number of confirmed HIV cases; the number of participants who have received a CD4 test, their CD4 result, and the CD4 test date; the number of participants who have received VL test and the VL test date; and the number of participants who have initiated ART, the start date, and the ART regimen used. The CRIMS system will be used to supplement the web-based study database with any additional patient information that needs to be captured for study purposes.

The DST will be responsible for weekly retrieval of data from each study hospital. Drs. Shicheng Yu and Yurong Mao will be responsible for retrieving data from the web-based study database and CRIMS. Data retrieved from these two data systems will be uploaded weekly and merged into one dataset. Personal identification will be removed from the merged dataset to create the study dataset for data analysis on a weekly basis. The DST will be responsible for a weekly transfer of the study dataset to the Assessment Coordination Team (ACT), comprised of investigators and statisticians from NCAIDS, NIDA, and EMMES.

16.2 Site Responsibilities

The data management responsibilities of each study hospitals will be to routinely collect and report the data into the hospital information systems and CRIMS, and maintaining all original forms in locked file cabinets at a secure local county CDC office. At the end of the study, the study-specific paper CRFs will be transferred from the local county CDC offices to the central NCAIDS for storage.

16.3 DST, ACT, and DSMB Responsibilities

The DST epidemiologists from the AIDS divisions of the 12 county CDCs will be responsible for weekly retrieval of data from each of study hospital. Drs. Shicheng Yu and Yurong Mao will be responsible for retrieving data from CRIMS. The DST will: 1) develop a data management plan and will conduct data management activities which include, but are not limited to, method for ensuring participant confidentiality in the database; 2) provide instructions for the collection of all data required by the study; 3) provide data dictionaries for each database that will

comprehensively define each data element; and 4) conduct ongoing data validation and cleaning activities on study data from all participants through database lock; and 5) prepare de-identified study datasets for transfer to the ACT.

The ACT investigators and statisticians from NCAIDS, NIDA, and EMMES will review enrollment data, conduct ongoing data editing and checks on data integrity for baseline, follow-up, and final assessments. The ACT will meet in-person prior to initial enrollment and participate in monthly conference calls with additional calls as needed.

The NIDA DSMB will review and approve the study protocol and research plan. The DSMB will review data for participant safety, study conduct and progress, and make recommendations concerning the continuation, modification, or termination of the trial. Special DSMB meetings can be scheduled, as needed, to discuss and resolve issues.

The DSMB will also have a role in reviewing potential policy changes over the course of the study. Any changes to HIV testing policies in Guangxi during the study period, and the proposed response to those policy changes, will be reported to the DSMB.

16.4 Data Acquisition and Entry

Completed forms and electronic data will be entered into the hospital information system and CRIMS in accordance with instructions for the hospital information system and the national CRIMS guidelines. The latter were established by NCAIDS in 2008 and updated in 2011. Data for the study will be acquired weekly from the two above data systems and uploaded to the NCAIDS-based study database. Access to the databases is restricted to authorized individuals.

16.5 Data Editing

If incomplete or inaccurate data are found in the data systems, a data clarification request will be generated and distributed to the related study hospital for a response by the DST. The Lead Investigator and the DST will monitor progress in responding to queries. Sites should resolve data inconsistencies and errors and enter all corrections and changes into the hospital information system or CRIMS. Data status reports will be issued on a regular basis to assist the sites.

16.6 Data Transfer/Lock

Data will be transmitted by the DST to the NIDA data and statistical center as requested by NIDA. The DST will conduct final data quality assurance checks and "lock" the study database from further modification. The final analysis dataset will be returned to NIDA and the Lead Investigator, as requested, for storage and archive.

16.7 Data Training

The Data Management team will be required to attend initial and biannual refresher training on data management. They will routinely review the data retrieved from the hospital system and downloaded from CRIMS for completeness and to check that values are appropriate (e.g., dates are reasonable). The training includes provisions for training on data retrieving, data editing, data merging, assessments, and computerized systems.

16.8 Data QA/QC

Two-level data validations will be conducted. First, at the hospital level, all written documentation in hospitals will be double entered into the electronic databases. Second, at the NCAIDS level, data will be checked for completeness and logistical consistency (e.g., reported date for confirmatory testing is later than the reported date for initial screening test). Queries to resolve and follow-up on data inconsistencies will be the responsibility of the DST study staff.

17.0 PUBLICATIONS AND OTHER RIGHTS

In order to share the results with the international research community and public at large, manuscripts describing the key findings will be drafted for publication in peer-reviewed journals, both Chinese and English. The planning, preparation, and submission of manuscripts will be drafted according to the policies of the Publications Committee of the CTN. Results from this study will be written as letters, short reports, original research articles, and press releases. The research findings will also be disseminated to provincial and national AIDS control staff for use in policy and planning.

18.0 SIGNATURES

SPONSOR'S REPRESENTATIVE

Typed Name	Signature	Date
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_____	_____	_____
CCTN Designee		

INVESTIGATOR(S)

- I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the sponsor except when necessary to protect the safety, rights, or welfare of Participants.
- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
- I agree to report to the sponsor adverse experiences that occur in the course of the investigation, and to provide annual reports and a final report in accordance with 45 CFR 46.
- I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with 45 CFR 46.
- I will ensure that an IRB that complies with the requirements of 45 CFR 46 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human Participants or others.
- Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human Participants.
- I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.
- I agree to comply with all the applicable federal, state and local regulations regarding the obligations of clinical investigators as required by DHHS, the state and the IRB.

Typed Name	Signature	Date
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_____	_____	_____
Lead Investigator		

_____	_____	_____
Co-Investigator		

_____	_____	_____
Co-Investigator		

_____	_____	_____
Co-Investigator		

_____	_____	_____
Co-Investigator		

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20.0 APPENDIX A - ANTIRETROVIRAL TREATMENT CRITERIA

Eligibility Criteria for China's National Free ART Program for HIV-Positive Individuals

Clinical Criteria	CD4 Level	Recommendation
Acute syndromes	Any level	Recommended to treat
WHO Stage III/IV	Any level	Treat
Any WHO stage	$\leq 350/\text{mm}^3$	Treat
Any WHO stage	$350 - 500/\text{mm}^3$	Treat if any one of the below requirements apply: <ol style="list-style-type: none"> 1. higher viral load (e.g. >100000 copies/ml); 2. rapidly declining CD4 (e.g. decreases greater than $100/\text{mm}^3$ per year); 3. age greater than 65 years old
Any WHO stage	Any level	Treat if any one of the below requirements apply: <ol style="list-style-type: none"> 1. active Hepatitis B 2. HIV-associated nephropathy 3. active tuberculosis 4. pregnancy 5. HIV-positive partner of a serodiscordant couple

21.0 APPENDIX B - PARTICIPANT HANDOUT

HIV Testing Procedures

This notice is to inform you that this hospital is participating in a study to test HIV testing procedures.

What do I have to do?

HIV testing requires that we will take a small sample of your blood, which will feel like a sharp pin prick, and we will ask you some questions regarding your sexual behaviors and history of drug use, which may make you feel a little uncomfortable.

Your test results and responses to our questions will be kept confidential. This information will be sent to the local China Center for Disease Control, so we can continue to monitor HIV across Guangxi Zhuang Autonomous Region. If you become incarcerated, your progress will continue to be monitored and that information will be kept confidential.

How many people will participate?

A total of 12 hospitals and 360 people in the Guangxi Zhuang Autonomous Region will take part in this study. When completed, we will be able to determine the testing procedure that takes the least amount of time for patients to receive test results, and treatment if necessary.

The use of your information for this study is voluntary. If you have any questions regarding the study please contact the principal investigators: Dr. Zhengzhu Tang (Guangxi CDC) at 771-2518766 or Dr. Zunyou Wu (NCAIDS) at 010-5890-0919 during office hours (09:00-17:00).

Thank you for your participation.

22.0 就诊者告知艾滋病检测流程就诊者告知

艾滋病检测流程就诊者告知

本须知是告诉您这家医院正在参加一个测试艾滋病检测流程的调研。

您需要做哪些事情？

做这个艾滋病检测，我们需要抽一点您的血，会有一些刺痛感，同时我们会问您一些与您的性行为 and 吸毒史有关的问题，这可能会让您稍微感到不安，但请放心，我们一定会对您的检测结果和回答保密。这些信息将会安全保密地被送到当地疾病预防控制中心，从而使我们对广西壮族自治区的艾滋病情况进行持续的监测。如果您被羁押，我们会持续检测您的治疗情况，并保密所有信息。

有多少人会参加调研？

在广西的 12 家医院中的 360 人将会参加这项调研。当这项调研完成后，我们会根据结果确定一个最优化的检测流程，让病人在最短的时间内获得艾滋病的检测结果、在必要情况下参加抗病毒治疗。

您的信息在这项调研中的使用是完全自愿的，如果有任何疑问，请在工作时间（09:00–17:00）联系本调研的主要负责人：唐振柱博士（广西疾病预防控制中心） 0771-2518766 或吴尊友博士（国家性病艾滋病中心） 010-5890-0919。

感谢您的参与！

23.0 APPENDIX C - KEY COUNSELING COMPONENTS

SOC Control Group:

1. Post-screening test counseling
 - a. Basic HIV knowledge
 - b. Positive screening result notification
 - c. Explanation of the next laboratory tests (WB, CD4)
 - d. Emotional and psychological support
 - e. Explanation of national HIV policy ("Four Freed and One Care")
2. Post-WB test counseling
 - a. WB result notification and explanation
 - b. Emotional and psychological support
 - c. Importance of disclosing HIV status to a spouse/partner and encouraging the spouse/partner to accept HIV testing
 - d. Explanation of national HIV policy ("Four Freed and One Care")
 - e. Information related to ART and treatment initiation
3. Post-CD4 test counseling
 - a. CD4 result notification
 - b. Explanation of CD4 result and relationship to ART eligibility criteria
 - c. Explanation of national HIV policy ("Four Freed and One Care")
 - d. Information related to ART and treatment initiation

Intervention Group:

1. Post-screening test counseling
 - a. Basic HIV knowledge
 - b. Positive screening result notification
 - c. Explanation of the next laboratory tests (WB, CD4)
 - d. Emotional and psychological support
 - e. Explanation of national HIV policy ("Four Freed and One Care")
2. Post-CD4 test counseling
 - a. CD4 result notification
 - b. Explanation of CD4 result and relationship to ART eligibility criteria
 - c. Emotional and psychological support
 - d. Explanation of national HIV policy ("Four Freed and One Care")
 - e. Information related to ART and treatment initiation
 - f. Introduce VL and the importance of VL testing
3. Post-VL test counseling
 - a. VL result notification and interpretation
 - b. Emotional and psychological support
 - c. Importance of disclosing HIV status to a spouse/partner and encouraging the spouse/partner to accept HIV testing
 - d. Explanation of national HIV policy ("Four Freed and One Care")

- e. Information related to ART and treatment initiation

Both Groups:

- 4. ART initiation counseling
 - a. Benefits of early treatment
 - b. Explanation of the National Free ART Program
 - c. Treatment compliance education to prevent ART resistance
 - d. For SOC Control group only: Introduce VL and the importance of VL testing

24.0 APPENDIX D - 2013 NATIONAL HIV TESTING AND COUNSELING GUIDELINES (EXCERPTS)

2013 National HIV Testing and Counseling Guidelines: Post-Screening Counseling

- a)** Inform and explain the HIV screening positive results, and provide help to patient to understand and respond to the result.

If the HIV screening result is negative, the post-test counseling session for the patient should include:

- *Provide interpretation of the test result and further testing recommendations due to the window period or pre-exposure.*
- *Provide recommendation for regular HIV testing (every 6 months or 1 year) if the patient engages in high risk behaviors (e.g. commercial sex work, MSM, IDU or has multiple sexual partners, etc.)*
- *Provide recommendation for regular HIV testing if the patient is a partner/spouse of an HIV positive individual.*
- *Provide recommendations for prevention measures (e.g. discuss concerns related to activities or situations that might increase the transmission of HIV, discuss needs for further education and access to harm reduction supplies.)*

If the HIV screening result is positive, the post-test counseling session for the patient should include:

- *Provide interpretation of the positive test result, and place emphasis on the necessity for a confirmatory test.*
 - *After establishing that the patient is fully aware of the meaning of a positive screening, discuss and confirm a time for the confirmatory test.*
- b)** Document the demographic and contact information for future follow-up.
- c)** Provide information about CD4 testing and referral services for ART.
- d)** Illustrate the rights and obligations for HIV infected people and introduce HIV related national policies.
- e)** Provide emotional and psychological support as needed.
- f)** Recommend result notification and HIV testing to spouse or sexual partner.
- g)** Provide HIV prevention services, including basic information of HIV/AIDS transmission, prevention and treatment, clean needles, condom use and risk behaviors change.
- h)** Provide information and referral services about opportunistic infections, sexually transmitted diseases, diagnosis and treatment of tuberculosis, reproductive health, family planning and the prevention of mother to child transmission.