FINANCIAL INCENTIVES TO INCREASE PEDIATRIC HIV TESTING (FIT STUDY)

Study Sponsors: UW Center for AIDS Research (CFAR) International AIDS Society, Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Grant

Draft or Version Number: 4.0

February 18, 2018

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ANC	Antenatal Care
ART	Combination Antiretroviral Therapy
CATCH	Counseling and Testing for Children with HIV
CCC	Comprehensive Care Clinic
CFAR	Center for AIDS Research
ELISA	Enzyme-Linked Immunosorbent Assay
ERC	Ethics and Research Committee
FI	Financial incentives
FIT	Financial Incentives to Increase Pediatric HIV Testing
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
KES	Kenya Shilling
KNH	Kenyatta National Hospital
KPS	Kenya Paediatric Studies
ODK	Open Data Kit
OVC	Orphaned and Vulnerable Children
PCR	Polymerase Chain Reaction
PMTCT	Prevention of Mother-to-Child Transmission
RCT	Randomized Clinical Trial
TBD	To be determined
UON	University of Nairobi
VCT	Voluntary Counseling and Testing for HIV

EXECUTIVE SUMMARY

Title: Financial Incentives to Increase Pediatric HIV testing (FIT)

Objective: The study will have 2 phases: The pilot phase and the trial phase.

PILOT

The aim of the pilot phase is to evaluate the feasibility, acceptability and costs of a financial incentive intervention to motivate pediatric HIV testing in Western Kenya. The study will evaluate 3 cash incentive values and determine percent uptake of testing. A post-test questionnaire will explore parental satisfaction, mechanisms of incentive effectiveness and the impact of testing on emotional health and pediatric healthcare utilization.

TRIAL

This pilot will provide key data for the efficient launch of the trial phase. The trial will test 4 levels of financial incentives and compare to an un-incentivized control group and determine uptake and cost-effectiveness of pediatric HIV testing in Western Kenya.

Aims:

PILOT

1. To pilot 3 levels of FI to motivate pediatric HIV testing, parents/caregivers with children of unknown HIV status attending an HIV treatment program will receive a financial incentive of 500, 1000, or 1500KES. Incentives will be collected when parents/caregivers bring children for pediatric HIV testing, and the proportion completing HIV testing within will be compared between groups.
2. To evaluate: a) satisfaction with incentives, b) motivational impact/mechanism, c) emotional impact of finding out child's HIV status d) impact of finding out child's HIV status on care-seeking behavior for the child.
3. Secondary aims: To develop and pilot study protocols, questionnaires, data systems, and expertise for the conduct of the future RCT. To collect program cost data.

TRIAL

1. To determine whether offering small financial incentives increases uptake of pediatric HIV testing among HIV-infected parents.

2. To evaluate the cost-effectiveness of financially incentivizing pediatric HIV testing in Kenya

Methods

PILOT

Aim 1: parents/caregivers with children of unknown HIV status attending HIV treatment programs will receive a financial incentive of 500, 1000, or 1500KES. Incentives will be collected when parents/caregivers bring children for pediatric HIV testing, and the proportion completing HIV testing will be compared between groups.

Aim 2: Post-test questionnaire to assess acceptability.

Secondary aims: Collect program cost data.

TRIAL

Aim 1: Parents/caregivers with children of unknown HIV status attending an HIV treatment program will be randomized to receive a financial incentive of 0 125, 250, 500, or 1000KES. Incentives will be collected when parents/caregivers bring children for pediatric HIV testing, and the proportion completing HIV testing will be compared between groups.

Population

HIV-infected parents/caregivers and their children of unknown HIV status.

Sites:

Kisumu East County Hospital, Homabay County Referral Hospital, Siaya County Referral Hospital, Additional sites in Western Kenya (TBD)

Study Duration:

24 months

Outcomes

PILOT

Aim 1: Percent completing HIV testing overall and within each incentive stratum.

Aim 2: Post-test questionnaire:

a) Parent satisfaction with financial incentive

b) Motivational mechanism

c) Emotional impact of finding out child's HIV status

d) Impact of finding out child's HIV status on care-seeking behavior for the child

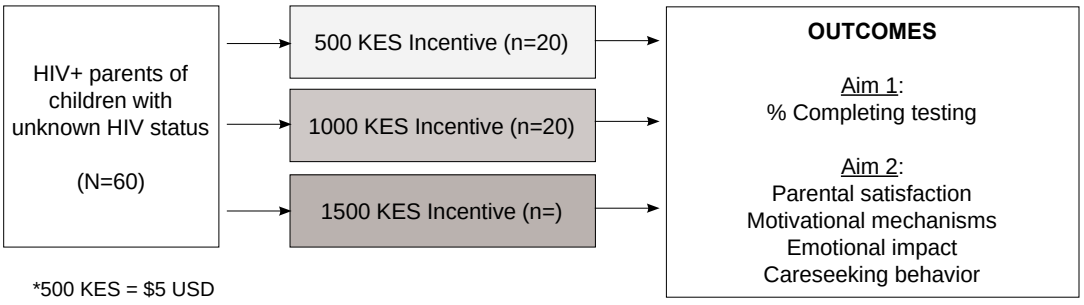
TRIAL

Aim 1: Percent completing HIV testing and time to testing overall and within each incentive stratum.

Aim 2: Incremental cost effectiveness ration (ICER) per child tested, positive child identified, positive child identified and linked to care, DALY averted comparing no incentive to 4 levels of incentives.

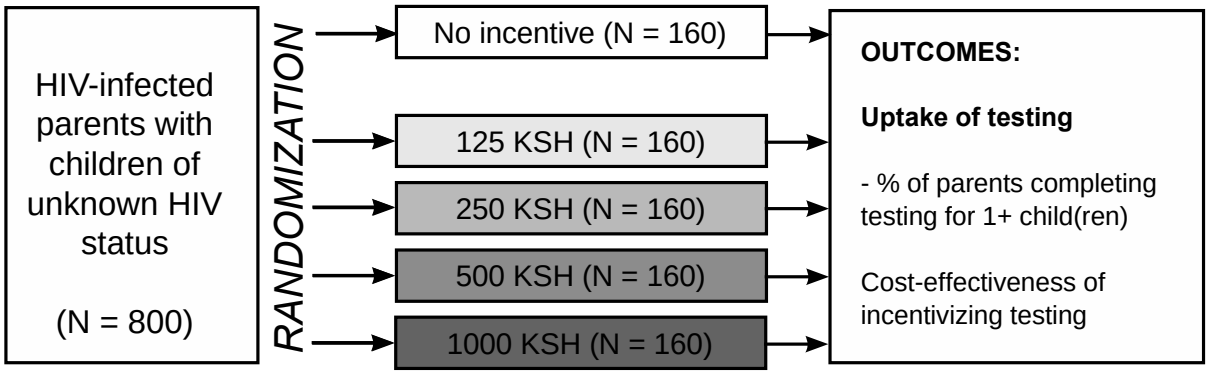
Figure 1. Schematic of Study Design:

PILOT



*500 KES = $5 USD

TRIAL



*500KES=$5 USD

1 KEY ROLES AND CONTACT INFORMATION

Project Directors

Irene Njuguna, MBChB, MSc
Study Physician
University of Nairobi/University of Washington
njugunairene06@yahoo.com

Jennifer Slyker, PhD, MSc
Assistant Professor, Global Health
University of Washington
jslyker@uw.edu

Dalton Wamalwa MBChB, MMed, MPH
Senior Lecturer, Paediatrics & Child Health
University of Nairobi / Kenyatta National Hospital
Email: dalton@africaonline.co.ke

Co-Investigators

Grace John-Stewart, PhD, MPH, MD
Professor, Medicine, Epidemiology, Pediatrics, Global Health
University of Washington
gjohn@uw.edu

Joseph Babigumira, PhD, MS, MBChB
Assistant Professor, Global Health, Pharmacy
University of Washington
babijo@uw.edu

Elizabeth Maleche-Obimbo, MBChB, MMed, MPH
Chair and Professor, Paediatrics & Child Health
University of Nairobi / Kenyatta National Hospital
eobimbo@hcc.or.ke

Anjuli Wagner, MPH, PhDc
Pre-doctoral Fellow, Epidemiology
University of Washington
anjuliw@uw.edu

Institutions

University of Washington
4333 Brooklyn Avenue NE
Box 359472
Seattle WA 98195 USA

University of Nairobi / Kenyatta National Hospital
Off Ngong Road
PO Box 19676
Nairobi, Kenya 00202

Funding agencies

PILOT: University of Washington Center for AIDS Research (CFAR) International Pilot Award (Principal Investigator, J Slyker)

TRIAL: International AIDS Society, Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Grant (Principal Investigator, I Njuguna)

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Despite encouraging parents to test older children for HIV, most of the world's 3.2 million HIV-infected children are diagnosed only when hospitalized or severely ill, after which they have extremely high mortality. Although early initiation of HIV treatment in children decreases mortality substantially[1], children lag adults in HIV treatment, ART-eligible children a third less likely to be on treatment compared to adults [2]. Although infants are systematically tested in prevention of mother-to-child HIV transmission (PMTCT) programs, there are no effective systems to systematically test *older* children until they are ill. ***We recently found that systematically asking HIV-infected parents to test their children increased testing 4-fold, however, 86% of parents still did not complete testing.*** New approaches are needed to motivate parents to test their HIV-exposed children.

Financial incentives (FI) have been used to motivate desirable health behavior changes, including immunization[3], school attendance[4], medication adherence[5], smoking cessation in pregnancy[6], and tuberculosis screening[7, 8]. In the setting of HIV, FI have been used to motivate HIV testing [9-13], prevention [14] and ART adherence [5, 15]. The effectiveness of FI is hypothesized to depend upon our prioritization of immediate over long-term economic and health benefits [16]). Poverty alleviation also may overcome real financial and logistical barriers such as transport, time off work and food insecurity. In a randomized trial (RCT) of FI for schoolgirls and their families in Malawi, FI were associated with a >60% reduction in HIV and ~80% reduction in HSV-2 prevalence at 18 months[14]; incentives were used to pay school fees, and thus eliminated the need for girls to engage in transactional sex with older men.

We are aware of no studies to date that have examined FI for pediatric HIV testing. FI for pediatric HIV testing has many unique aspects. Unlike adults, children are unable to present themselves for care. There is urgency as undiagnosed HIV infection is often fatal; diagnosis is essential for monitoring of HIV infection and initiation of ART and prophylaxis for opportunistic infections. Once an undiagnosed child becomes sick, their HIV status will ultimately be revealed during hospitalization, a situation likely to present more stress for the parent than undergoing testing in a supportive outpatient setting when the child is well. Unlike FI for HIV prevention or adherence, where programs must be ongoing, pediatric HIV testing only need occur only once for children who are no longer HIV-exposed. Finally, parents may assume incorrectly that their child is infected; in Nairobi, ~90% of untested HIV-exposed children <12 tested negative (*CATCH preliminary data*). Learning a child's negative status may provide enormous relief for the parent and improve family relationships. Parents who assume their child is positive may avoid accessing pediatric healthcare services for minor illnesses, for fear of an HIV test.

2.2 Rationale

Testing HIV-exposed children in an outpatient setting prior to symptomatic illness potentially has widespread benefits for both infected and uninfected children, as well as their families. We hypothesize that offering a simple cash financial incentive (FI) will significantly increase pediatric HIV testing.

3 OBJECTIVES

3.1 General Objective

The study will evaluate the feasibility, acceptability, effectiveness and cost-effectiveness of a financial incentive intervention to motivate pediatric HIV testing in parents receiving HIV treatment services in Western Kenya.

Specific Aims:

PILOT

Aim 1: To pilot 3 levels of financial incentives to motivate pediatric HIV testing, parents/caregivers with children of unknown HIV status attending an HIV treatment program will receive a financial incentive of 500 KES (approximately $5), 1000 KES ($10), or 1500 KES ($15). Incentives will be collected when parents/caregivers come for pediatric HIV testing, and the proportion completing HIV testing will be compared between groups.

Aim 2: Among parents completing pediatric HIV testing, to evaluate: a) satisfaction with incentives, b) motivational impact/mechanism, c) emotional impact of finding out child's HIV status d) impact of finding out child's HIV status on care-seeking behavior for the child.

Secondary aims: To collect program cost data.

TRIAL

AIM 1: To determine whether offering small financial incentives increases uptake of pediatric HIV testing among HIV-infected parents. We will compare the proportion of children tested and time to testing between parents randomized to no incentive versus 4 different levels of financial incentive.

AIM 2: To evaluate the cost-effectiveness of financially incentivizing pediatric HIV testing in Kenya.

Aim 2a: To determine the most cost-effective incentive value for the population under study. We will use cost-effectiveness analysis to determine the incremental cost effectiveness ratio (ICER) comparing standard targeted pediatric HIV testing to three levels of incentivized targeted pediatric HIV testing.

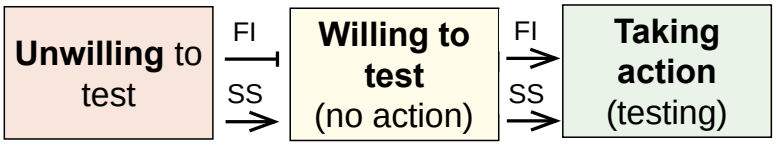
AIM 2b: To model the cost-utility of small FI in diverse areas and populations with varying underlying infection prevalence. We will conduct a cost-utility analysis to compare the cost per disability adjusted life year (DALY) averted between standard targeted pediatric HIV testing and three levels of incentivized targeted pediatric HIV testing in areas with varying underlying infection prevalence, age, PMTCT coverage, uptake of testing, health care costs, transport costs, and patient wages.

4 METHODS

4.1 Study Design

Conceptual framework: Our conceptual framework is shown in Figure 2. FI may motivate parents who are **willing** to test but face logistical or financial barriers, to take **action to** test. **Unwilling** parents, who face extreme fear or real dangers from revealing their HIV status may not be motivated by FI to take **action to test**. Social services (SS)—including enhanced counseling and peer support groups—may help parents move from **unwilling** to **willing**. We hypothesize that the proposed FI intervention will primarily move willing parents from "Willing to test" to "Taking action".

Figure 2: Conceptual framework



Study design*:

PILOT

This pilot will be a 3-arm (1:1:1 allocation of 500, 1000, and 1500 KES incentives), un-blinded randomized interventional study involving 60 HIV-infected mothers receiving HIV care at the Kisumu East County Hospital. The primary outcome will be **% completing child HIV testing**. Because incentive programs may have opposite effects in women and men, we will limit this small pilot to mothers only, while the larger trial will include both women and men and powered to enable sex-stratified analyses.

TRIAL

The trial will be a randomized controlled trial (RCT) with 5 arms (1:1:1:1:1 allocation) no incentive, 125 KES, 250 KES, 500 KES and 1000 KES). We will randomize 800 parents with children of unknown status at HIV treatment clinics in Western Kenya (Figure 1). The primary outcome will be **% of parents completing child HIV testing and time to testing**. Because incentive effects may vary by sex, we will conduct secondary sex-stratified analyses.

**The values of the FI for the pilot were estimated from the CATCH study to approximate: direct costs (the median cost of transport for a parent and 2 children, plus food/beverage for a day spent at the clinic) (500KES), direct costs plus one day's wages (1000 KES), and direct costs plus two days wages (1500 KES).*

The values of the FI for the trial were adjusted after preliminary pilot study results showed very high uptake of testing (>70%) and no differences in testing uptake in the 3 arms. Because of the small sample size in the pilot but very high testing uptake compared to CATCH, lower incentive level (125, 250 KES) was included and the 1500 arm dropped.

4.2 Sites

The pilot will be conducted at several sites (to be determined) in Western Kenya, which may include: Kisumu East County Hospital, Homabay County Referral Hospital, Siaya County Referral hospital and other satellite HIV clinics in Western Kenya.

4.3 Population

Justification for involvement of children: Infants and children have a rapid HIV disease progression, and in the absence of diagnosis and treatment, are at a high risk for death. Earlier diagnosis and treatment improves not just survival, but decreases morbidity and improves growth and cognitive development. In our recent CATCH study, we approached parents receiving HIV care at the KNH CCC and offered to test their children of unknown status either in the clinic or in the home. We found that approximately 8% of children <13 years old with unknown HIV status were infected with HIV. This high prevalence is reflective of the parents who opted for testing after counseling alone; for parents refusing to test their children the prevalence of HIV infection is unknown.

4.3.1 Inclusion Criteria

- **Parent/caregiver receiving HIV care**
- **Parent/caregiver* has one or more children <13 years old**
- **Child is HIV exposed (parent/caregiver report or clinic confirmation)**
- **Caregiver reports child's HIV status is unknown**

For the purposes of this study, both biologic parents and *caregivers of orphaned or abandoned children will be eligible for enrollment and pediatric testing. The reason for including non-biologic caregivers is that orphans and other vulnerable children (OVC) often have a high risk for HIV infection, given that their parents may have died from HIV infection.

4.3.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- At enrollment, parents/caregivers will be asked about the safety of themselves and their family members using a standardized assessment tool; individuals experiencing or at risk of abuse will not be enrolled, but will instead be referred for counseling through the existing mechanisms available at their clinic using SOPs developed and tested during the CATCH study.

4.3.3 Recruitment, Enrollment and Randomization

Pre-trial sensitization: We will conduct pre-trial sensitization activities to inform the Community Advisory Board and clinic staff about the study, and to gather insights into the appropriateness of our proposed incentive size and format. Additionally, we will utilize pre-trial discussions to determine appropriate measures for incentivizing families with >1 child, and how to logistically and sustainably operationalize cash disbursements.

Randomization: Randomization will occur at recruitment in order to minimize bias associated with the drop-off between referred/enrolled participants. Individuals will be provided with a

scratch-card, which when scratched will reveal their financial incentive (FI) value. Scratch-cards will be valid for a 2-month period, with individual exemptions to accommodate school holidays. We will **not enroll** at randomization, but will collect minimal data needed to link scratch cards from origin to testing. Data collected at randomization will include eligibility checklist, parent age and sex, number and ages and sexes of children and telephone contact number. The scratch-card will contain a QR code, readable by smartphone [encoding scratch-card serial number and value, date activated & date of expiration]. ***Scratch-cards will ultimately be linked between randomization and test by ticket code and telephone number.*** Comparing the phone number given at the two visits will enable us to tell if the original randomization scratch-card has changed hands, without collecting patient names. Parents who do not consent to providing a phone contact will still be offered study and enrollment if they present later for pediatric HIV testing.

Recruitment and randomization

HIV-infected adults attending the CCC will be approached by a study peer counselor. The peer counselor will take oral consent, assess eligibility and randomize those who are eligible. The peer counselor will assess interest in scheduling for the testing visit; and if interested, participant will give oral consent during which they will provide the study with their phone number. A post-recruitment script to inform the caregiver of the risks of depression and stress associated with disclosure and availability of disclosure services will be read to the participant.

Enrollment and HIV testing visit

Participants will be enrolled in the study when they present for pediatric HIV testing. At the enrollment and testing visit the study staff (nurse counselor) will assess the individual risk of interpersonal violence. Participants will be given further information on the study and will give consent for enrollment and HIV testing for the children. Data on socio-demographics, PMTCT history, child medical history and costs data will be collected.

> ***Parents with multiple children requiring testing****:* In families where testing is needed for more than one child, we will offer the opportunity to test all children of unknown status in the household. However in order to minimize the risk of testing unexposed children, we will only reimburse the scratch-card FI value for the first tested child. However, we will reimburse the cost of transport for additional children who require testing.

Parents will retain their scratch-card and present it at the HIV testing visit. If the scratch-card is lost, we will use the telephone number to retrieve the FI value information.

Child HIV testing will be completed by study staff. Following completion of child HIV testing, parents will receive the equivalent of the value indicated on the scratch-card. We anticipate using M-Pesa money transfers to reimburse clients; this is done via a cellphone. This process will provide a more secure audit trail and poses less risk to the study staff than cash reimbursement from the clinic.

Following HIV testing, parents/caregivers will be asked to complete a post-test questionnaire to evaluate a) satisfaction with incentives, b) motivational impact/mechanism, c) emotional impact of finding out child's HIV status d) impact of finding out child's status on care-seeking behavior, e) costs associated with the HIV testing visit (transport, food, time off work, etc).

Transport reimbursement

All participants, including participants randomized to receive no FI will be provided with transport reimbursement following the completion of their child's test. In order that this does not act as incentive, participants will not be told about this until after they have completed testing.

Detailed list of enrollment and testing procedures
Listed below are HIV testing procedures for this study.

a) Written informed consent for enrollment and HIV testing
b) Pre-HIV-1 test counseling
c) Collect child assent for blood draw *(optional parent choice)*
d) Conduct child HIV-1 testing
e) Provide the child's HIV-1 test results to the parent/caregiver and provide post-test counseling (with assisted disclosure to the child, where desired). For children under 18 months who require DNA PCR test, a separate visit to provide results will be planned once results are available
f) Reimburse parent/caregiver with the value of their FI scratch-card
g) Referral of child to HIV-1 care clinic of the parent/caregiver's choice, provide parent with written test results, if desired.*
h) Complete study Post-Test Questionnaire

*To optimize follow-up counseling for parents/caregivers, we will request permission to provide the child's test result to the CCC where the adult is enrolled, so that it can be recorded in their medical record. This will enable clinic staff to appropriately tailor counseling at future visits and to coordinate care between parent and child. For example, if the child tests HIV negative and is no longer HIV-exposed, the parent will not be asked again to test their child; if exposure is ongoing the parent will be prompted to re-test, as appropriate. If the child tests positive, parents will receive further counseling and information, which may include reminders to follow-up with child enrollment in the Youth CCC program, and counseling regarding pediatric care, treatment, and disclosure.

Assessment of linkage to care:
All HIV positive children will be followed up to assess linkage to care. We will contact parents/caregivers at 1, 3, 6, 9 and 12 months post diagnosis. Study staff will make very attempt to ensure HIV positive children link to care. Caregivers who have not linked to care will be referred for additional psychosocial support as needed.

End of study follow-up:

HIV-negative children: At completion of HIV test visit
HIV-positive children: At confirmation of linkage to care *or* at 12 month post-test call

Reminders and tracing for missed testing visits:
Once a child/caregiver pair is randomized in the study, the study staff will make a reasonable effort to test the child for HIV. Participants who are randomized and do not present at clinic will be called using the telephone number obtained at randomization.

Participant withdrawal
Participants may voluntarily withdraw from the study for any reason at any time. The site investigator may also withdraw participants from the study in order to protect their safety.

Alternatives to participation
Parents who wish to test their children but do not wish to participate in the study will be referred to the VCT.

4.3.4 Laboratory procedures

All specimen transport, processing, testing and results reporting will be conducted in compliance with standards of good clinical and laboratory practice. The study site will establish standard operating procedures, including specimen chain of custody and quality assurance and quality control procedures, for all protocol-specified laboratory tests prior to study initiation. As the transmission of HIV can occur through contact with contaminated needles, blood and blood products, appropriate precautions will be employed by all personnel in the drawing of blood, handling and shipping of blood samples during this study, as currently recommended by the United States Centers for Disease Control and Prevention.

Study site staff will collect blood to test for HIV but samples will **NOT** be stored for future use.

Rapid HIV-1 antibody test: Children (aged >18 months and not breast-feeding) who are recruited to the study will be given a rapid HIV-1 test. This assay is a commercial ELISA kit to test for HIV-1 antibodies in blood that gives results within half an hour of specimen collection and can be administered in the home or in clinic.

HIV-1 DNA PCR Assay: For children who are <18 months or have breast fed in the last 6 weeks, a few drops of blood will be collected on a filter paper for HIV-1 diagnosis, and subjected to a HIV-1 DNA PCR assay at the designated local laboratory. If results from this assay are indeterminate, the child's blood sample will be sent to a local laboratory for HIV-1 RNA testing.

4.4 Sample Size and Framework

PILOT:

A total of 60 parent/caregivers will be offered 3 levels of financial incentives (1:1:1). This pilot study will be used to compare the proportion of parents testing their children for HIV in the setting of three financial incentives, but this study is not powered to determine efficacy.

Outcome Measures

Aim 1: Enrollment and testing uptake

- % completing pediatric HIV testing, overall and within different incentive strata

Aim 2: Post-test questionnaire

- Parent satisfaction with financial incentive
- Motivational mechanism
- Emotional impact of finding out child's HIV status
- Impact of finding out child's HIV status on care-seeking behavior for the child

TRIAL:

Sample size: Given 160 adults in each of 5 randomization arms, we will have >80% power to detect a minimum of 10-20% difference between each of the arms (Table 1), a substantial improvement in testing rates. Assumptions for the un-incentivized group are based on data from CATCH. We will have sufficient power to detect differences over a range of uptake scenarios (Table 1).

Table 1: Power calculations

N=160

No incentive	Power	125 KES	Power	250 KES	Power	500 KES	Power	1000 KES
0.13	>0.99	0.40	0.95	0.60	0.98	0.80	0.71	0.90
0.13	0.96	0.30	0.96	0.50	0.96	0.70	0.90	0.85
0.13	0.84	0.26	0.82	0.40	0.95	0.60	0.82	0.75
0.13	0.39	0.20	0.54	0.30	0.96	0.50	0.78	0.65

4.5 Data Collection

Enrollment and testing visit: A brief enrollment questionnaire will assess characteristics of participants, including: previous PMTCT history, time since parental diagnosis, parent on ART, caregiver relationship to child, previous child illnesses and costs information.

Post-test interviews: The child's HIV test result will be recorded following the test. Following the HIV test, parents will complete a short interview to assess a) satisfaction with FI, b) motivational impact/mechanism of FI, c) impact of finding out child's HIV status on caregiver/family emotional health, and d) impact of finding out child's HIV status on care-seeking behavior for the child. Costs: We will collect program cost and medical care resource utilization data to enable estimation of direct medical costs, direct non-medical costs and indirect costs. Direct medical costs include HIV test kits, medications, other lab tests, and personnel. Direct non-medical costs include incentive and transportation costs. Indirect costs include wages lost due to time off of work. Data from local sources and literature will be used to estimate unit costs for resource-use estimates and complement data collected in the study.

5 ANALYSIS PLAN

PILOT Summary

Aim 1:

This pilot will compare the proportion of parents testing their children for HIV in the setting of three financial incentives. Table 3 describes the key variables that will be collected to enable comparisons between arms. Specifically, we will compare the proportion of enrolled parents completing testing in arms i (500 KES), ii (1000 KES), and iii (1500 KES): X_i/N_i vs X_{ii}/N_{ii} vs X_{iii}/N_{iii}. With this small sample size, we will not have statistical power to compare arms; however, we expect to observe a dose-response curve of increasing uptake with increasing FI, known as a *demand curve*. We will use this demand curve to identify incentive levels after which there are diminishing returns—that is, uptake begins to plateau with increasing levels of FI. If a plateau is observed, we will evaluate program costs and the proportion tested to determine the optimal value for the FI for the RCT. If the proportion testing is similar among the three FIs, we will utilize the lowest value to minimize costs.

Table 2. Key data collected during the pilot.	
S	Total clients screened
N	Number of eligible clients given scratch-card
E	Number of clients enrolled into cohort study
X	Number completing pediatric testing
Y	Number not completing pediatric testing
Notes. Arm i=500KES, arm ii=1000KES, arm iii=1500KES	

Aim 2:

The post-test questionnaire will be used to reassess the level and format of financial incentives employed in the study as we design the RCT. If incentives are felt to be "too big to turn down," we will reassess their suitability in the RCT. Answers regarding the format, motivational impact/mechanism of the FI, the emotional impact of testing and potential effect on health-seeking behavior for the child will be used to refine protocols, improve counseling, and inform how best to include additional downstream outcomes (% children enrolled in HIV care programs, retention, % on ART) for the larger trial.

TRIAL Summary:

Aim 1: We will compare the proportion of parents testing and time to testing between groups randomized to no incentive versus incentive, and between the 5 arms (Figure 3), using a series of chi-squared tests. If randomization fails to balance potential confounders, we will compare the proportion of parents testing between arms using relative risk regression, adjusting for unbalanced confounders and time to testing using a stratified Cox proportional hazards regression model, adjusting for confounders. (Table 4).

Aim 2: We will plot a dose-response curve of testing proportion over increasing FI (*demand curve*, Figure 3). Demand curves will identify FI levels after which there are diminishing returns (uptake plateaus). We will conduct a cost-effectiveness analysis (Aim 2a) and a cost-utility

analysis (Aim 2b) comparing un-incentivized to three levels of FI. This will enable estimation of an incremental cost-effectiveness ratio (ICER) per:

Aim 2a: a) child tested, b) HIV-infected child identified, c) child linked to care

Aim 2b: a) disability adjusted life years (DALYs) averted

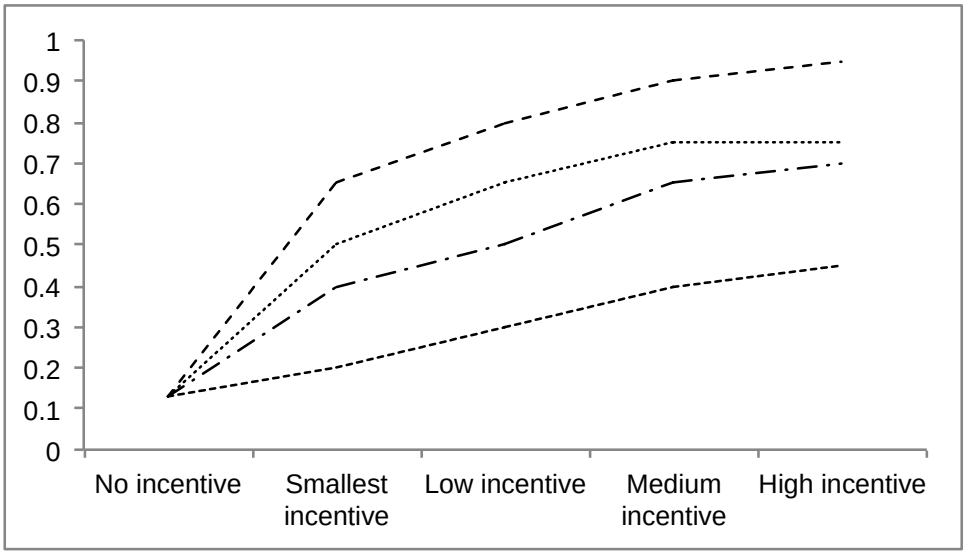


Figure 3: Example demand curves: *We will plot a dose-response curve (demand curve) of proportion of adults who test their children with each increasing level of financial incentive. Demand curves will identify FI levels after which there are diminishing returns (uptake plateaus). These tools will be accompanied by a cost-effectiveness analysis to quantitatively identify levels after which increased incentives do not result in sustained cost-effectiveness.*

We will model cost-effectiveness and cost-utility use decision trees (accompanied by Markov models for Aim 2b), and a lifetime horizon. We will perform these analyses from the perspective of the Kenyan government and from a societal perspective[24]. We will conduct a series of one way and probabilistic sensitivity analyses. For aim 2b, sensitivity analyses will be used to estimate the differences in cost-utility by region in Kenya, informed by region-specific parameters for underlying infection prevalence, age, PMTCT coverage, uptake of testing, health care costs, transport costs, and patient wages (Table 4).

Table 4: Data analysis: **TRIAL**

	Aim 1	Aim 2a	Aim 2b
Data	Proportion of parents completing testing in no, low, medium, and high incentives arms	Direct medical costs: HIV test kits, medications, other lab tests, and personnel salaries Direct non-medical costs: incentive and transportation Indirect costs: wages lost due to time off of work. Data from local sources and literature will be used to estimate unit costs for resource-use estimates and complement data collected in the study. Outcomes: Numbers of children testing, testing positive, and linked to care will be measured directly during the study period. Disability adjusted life years averted (DALYs) will be estimated based on existing literature describing survival and disease progression in HIV-infected treated and untreated pediatric cohorts.	

Analysis technique	Chi-squared tests. If confounders not balanced by randomization, relative risk regression controlling for confounders	Cost-effectiveness analysis in terms of cost per additional a) child tested, b) positive child identified, c) child linked to care; decision tree, univariate & probabilistic sensitivity analyses	Cost-utility analysis in terms of cost per DALY averted; decision trees & Markov models, univariate and probabilistic sensitivity analyses
Power	Given 160 adults in each of 5 randomization arms, we will have >80% power to detect a minimum of 10-20% difference between each of the arms *(Table 1)*	N/A	

6 ETHICS/PROTECTION OF HUMAN SUBJECTS

Institutional Review Board:

This is a collaborative research proposal that will involve field and laboratory procedures in Nairobi, Kenya and data analyses in Nairobi and Seattle, Washington. The study will be reviewed by the Institutional Review Board (IRB) at the University of Washington and the Kenyatta National Hospital/University of Nairobi (KNH/UON) Ethics and Research Committee (ERC). The study will not recruit subjects prior to approval from both the University of Washington IRB and the KNH/UON ERC.

6.1 Potential Risks and Benefits

Although PMTCT services are widely implemented and have wide coverage for infants, there are currently no routinely available systematic approaches to diagnosing older children with HIV infection prior to symptomatic illness. Early HIV diagnosis reduces morbidity and mortality and improves growth and development. This study has potential to inform novel strategies to increase HIV testing rates for HIV-exposed children.

6.1.1 Potential Risks

Parent/caregiver: Parents may feel stress and discomfort at the prospect of testing their children for HIV infection, and in completing the test. Despite our attempt to make the financial incentive non-coercive in its value, some parents may find this value too big to turn down. Finding out the child's HIV test result is positive may cause stress and depression. Although we will do our best to preserve the parent's/caregiver's privacy with regard to their own HIV status, and that of children testing positive, there is a risk for inadvertent disclosure of parental or child HIV status to the child being tested.

Children: The HIV test itself involves a blood draw which children may find this frightening, stressful, and mildly painful. They may experience confusion at the conduct of the test if they are not told by the parent/caregiver why they are being tested.
There is potential risk of stress and depression in children related to learning their caregiver's HIV status if caregivers disclose either before or after child HIV testing.

Confidentiality: There is a non-negligible risk of loss of confidentiality of HIV status or other medical information. All key personnel have been trained in the Protection of Human Subjects and HIPAA. The Kisumu Clinical Trials field team has many years experience managing HIV-infected children in the setting of clinical trials, and will take every precaution to protect participants' and their children's confidentiality. Study staff will take strict measures to maintain confidentiality for participants. All data will be kept in password-protected databases, in a locked study office, accessible only to study personnel. Study identifiers will be linked to coded data; clinical staff will have access to patient identifiers, but the analysts will receive only coded data. Links between patient identifiers and study codes will be kept for a period of 5 years after the end of the study, at which time the link between patient IDs and codes will be destroyed.

Alternatives to study participation: Adults who wish to have their children tested for HIV or but do not wish to participate in the study will be referred to VCT for HIV counseling and testing.

Potential SAEs and how these will be handled:

Anticipated SAE from this study could include: parent/caregiver psychological trauma from a positive HIV test result, injury to the caregiver/parent/child from interpersonal violence from a partner, or injury to the child from the blood draw for the HIV test.

Risk for these factors will be assessed at the enrollment/HIV testing visit, and additionally during follow-up communications to assess linkage-to-care. If SAEs are uncovered, these will be reported to the study personnel, who will report these to the IRB and ERC.

After recruitment caregivers who are randomized will be informed of the risk of depression and stress in children related to HIV disclosure and will be informed that there are services available in the clinic to support this process. They will also be informed that disclosure of caregiver HIV status to the child is not necessary for enrollment. (Post-randomization recruitment script)

6.1.2 Potential Benefits

Parents/caregivers of children testing negative: Based on data from our earlier study at this site, we anticipate approximately 90% of children will test HIV negative. For parents with children testing negative, receiving these test results will provide enormous psychological relief. Parents who had previously been reluctant to bring the child for other medical care (for fear of the child being tested for HIV) may be more willing to bring the child for treatment following the test. This may lead to better healthcare for the child.

Parents of children testing positive: Receipt of a positive test result may be a relief to some parents, compared with the stress of "not knowing". Upon receiving a positive result, parents will be linked to treatment services for their children. These services are free, and include treatment monitoring, prophylaxis for opportunistic infections, antiretroviral therapy, and psychosocial services will help HIV-infected children to live longer healthier lives. Parents who had previously been reluctant to bring the child for other medical care (for fear of the child being tested for HIV) may be more willing to bring the child for treatment following the test. This may lead to improved healthcare for the child.

Child: Identifying the child's HIV status will enable parent/caregivers to make better-informed decisions regarding their treatment and care. Children with undiagnosed HIV infection are at a very high risk of death, and starting antiretroviral therapy (ART) as soon as possible is lifesaving. Starting ART also reduces the risk of other associated infections, growth and developmental impairment. Knowing the child's status also enable parents and healthcare providers to appropriately tailor psychosocial and behavioral messages to children as they enter adolescence.

Societal: The results of this this study may benefit society broadly by providing ***a new tool to encourage pediatric HIV testing***. If acceptable, feasible, and cost-effective this approach could be implemented at other sites to increase HIV testing rates children.

The societal **costs** of having a large population of children with unidentified HIV infection include impaired cognitive development, poor school performance, reduced earning potential in adulthood, and high medical costs for those surviving childhood. ***Early HIV diagnosis thus improves long-term survival and reduces long-term economic costs.***

Additionally, adolescents becoming sexually active have the potential to pass on HIV infection if undiagnosed. Treatment initiation greatly reduces the risk of onward HIV transmission, so ***increasing the number of children on treatment has the potential to further reduce downstream infection in their future sexual partners.***

6.2 Informed Consent Process

Adults:
A short oral consent will be obtained from caregivers prior to randomization. Oral consent will be collected to obtain phone numbers. Written, informed consent will then be obtained from all study participants for enrollment and child testing. Prior to enrollment, participants will have the proposed study explained to them, will have their questions answered, and will be asked to provide written consent for their participation. Interviews will be conducted in private by trained

personnel, and data collected will be kept confidential and access restricted to study staff. Consent forms will be available in the subject's preferred language of English or Kiswahili or Dholuo.

Children: Children aged 7 years old and above will be asked to provide written assent for blood draw, for parents who agree to the assent procedures. Children will not be told the purpose of the test unless the parent desires this and communicates this to study staff at the enrollment counseling visit.

Mature Minors: Adolescents less than 18 years who have their own children will be eligible to give consent and will not be excluded from the study.

6.3 Participant Confidentiality

Study staff will take strict measures to maintain confidentiality for participants. All study staff have been trained in data protection and privacy. All data will be kept in password-protected databases, in a locked study office, accessible only to study personnel. Study identifiers will be linked to coded data; clinical staff will have access to patient identifiers, but the analysts will receive only coded data. Links between patient identifiers and study codes will be kept for a period of 5 years after the end of the study, at which time the link between patient IDs and codes will be destroyed.

7 DATA HANDLING AND RECORD KEEPING

7.1 Data Management

Data collection: Data collection instruments will be developed by the protocol team. Our team plans to use mobile phones and tablets in lieu of paper forms to collect data for this study. Electronic data collection will improve data accuracy by eliminating the extra step of entering data from paper data collection forms into an electronic database. The program used to collect and store the data is entitled Open Data Kit (ODK).

In comparison to paper data collection, electronic data collection is potentially more secure. All data are password protected from the moment of data collection. Data are stored on the password-protected phone/tablet until they are uploaded to the study's secure electronic database, at which point they are automatically deleted from the phones and no longer accessible. Data are transmitted and stored using a high level of encryption – an "HTTPS" website utilizing SSL/TLS (secure socket layer/ transport layer security) – which is comparable to the security used by groups such as Google for data protection. This level of security is present for all mediums of data transmittal (e.g. 3G or wireless internet connection). There still exists a small possibility that the electronic database could be compromised, but this risk is comparable to more traditional data management systems that include paper forms entered into an electronic database.

Data management: A dedicated data manager will be responsible for the management and monitoring of study data. The data team will communicate frequently with the Seattle-based team for reporting, data cleaning, study monitoring, and interim analyses. Weekly enrollment and testing reports will be generated to track study progress and ensure quality data collection.

7.1.1 Data Safety and Monitoring Plan (DSMP)

Given the very low risk of adverse effects for participants posed by this study, we will use a Data Safety Monitoring Plan (DSMP) to ensure that any unforeseen negative impact of study participation on linkage to care are identified and addressed. At the midpoint of the intervention phase, the PI will determine if there is any evidence of a negative impact associated with the intervention by looking at rates of early linkage to care. If we find any evidence of harm during the intervention phase, the investigators will assess the evidence and consider halting the study and providing supplemental counseling to encourage engagement in care.

7.2 Types of Data

Questionnaires

HIV test results

Program cost data

7.3 Study Records Retention

The link between study identifiers and patient IDs will be kept under lock and key. The link between patient identifiers and study ID codes will be retained for 5 years following completion of the study, in order to maintain integrity of the data. After this time, links to identifiable data will be destroyed.

8 PUBLICATION/DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

9 LITERATURE REFERENCES

1. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA*, et al.* Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med* 2008,**359**:2233-2244.
2. UNAIDS. The Gap Report. In; 2014.
3. Weaver T, Metrebian N, Hellier J, Pilling S, Charles V, Little N*, et al.* Use of contingency management incentives to improve completion of hepatitis B vaccination in people undergoing treatment for heroin dependence: a cluster randomised trial. *Lancet* 2014,**384**:153-163.
4. Rivera JA, Sotres-Alvarez D, Habicht JP, Shamah T, Villalpando S. Impact of the Mexican program for education, health, and nutrition (Progresa) on rates of growth and anemia in infants and young children: a randomized effectiveness study. *JAMA* 2004,**291**:2563-2570.
5. Javanbakht M, Prosser P, Grimes T, Weinstein M, Farthing C. Efficacy of an individualized adherence support program with contingent reinforcement among nonadherent HIV-positive patients: results from a randomized trial. *Journal of the International Association of Physicians in AIDS Care* 2006,**5**:143-150.
6. Donatelle RJ, Prows SL, Champeau D, Hudson D. Randomised controlled trial using social support and financial incentives for high risk pregnant smokers: significant other supporter (SOS) program. *Tobacco control* 2000,**9 Suppl 3**:III67-69.
7. Malotte CK, Hollingshead JR, Rhodes F. Monetary versus nonmonetary incentives for TB skin test reading among drug users. *American journal of preventive medicine* 1999,**16**:182-188.
8. Malotte CK, Rhodes F, Mais KE. Tuberculosis screening and compliance with return for skin test reading among active drug users. *American journal of public health* 1998,**88**:792-796.
9. McCoy SI, Shiu K, Martz TE, Smith CD, Mattox L, Gluth DR*, et al.* Improving the efficiency of HIV testing with peer recruitment, financial incentives, and the involvement of persons living with HIV infection. *Journal of acquired immune deficiency syndromes* 2013,**63**:e56-63.
10. Thornton RL. The Demand for, and Impact of, Learning HIV Status. *The American economic review* 2008,**98**:1829-1863.
11. Haukoos JS, Witt MD, Coil CJ, Lewis RJ. The effect of financial incentives on adherence with outpatient human immunodeficiency virus testing referrals from the emergency department. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine* 2005,**12**:617-621.
12. Lee R, Cui RR, Muessig KE, Thirumurthy H, Tucker JD. Incentivizing HIV/STI testing: a systematic review of the literature. *AIDS Behav* 2014,**18**:905-912.
13. Nglazi MD, van Schaik N, Kranzer K, Lawn SD, Wood R, Bekker LG. An incentivized HIV counseling and testing program targeting hard-to-reach unemployed men in Cape Town, South Africa. *J Acquir Immune Defic Syndr* 2012,**59**:e28-34.
14. Baird SJ, Garfein RS, McIntosh CT, Ozler B. Effect of a cash transfer programme for schooling on prevalence of HIV and herpes simplex type 2 in Malawi: a cluster randomised trial. *Lancet* 2012,**379**:1320-1329.
15. Rigsby MO, Rosen MI, Beauvais JE, Cramer JA, Rainey PM, O'Malley SS*, et al.* Cue-dose training with monetary reinforcement: pilot study of an antiretroviral adherence intervention. *Journal of general internal medicine* 2000,**15**:841-847.
16. Operario D, Kuo C, Sosa-Rubi SG, Galarraga O. Conditional economic incentives for reducing HIV risk behaviors: integration of psychology and behavioral economics. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association* 2013,**32**:932-940.

17. Kohler H-P, Thornton RL. Conditional Cash Transfers and HIV/AIDS Prevention: Unconditionally Promising? *World Bank Economic Review* 2011.

APPENDICES

The following documents are included as appendices:

- Appendix A: Study Timeline
- Appendix B: Study Flow Chart
- Appendix C: List of Data Collection Instruments

APPENDIX A: Study Timeline

Pre-Award Activities:

- Protocol development
- Regulatory approvals (human subjects, foreign clearance)
- Questionnaire development
- First CAB meeting to introduce the study

Award Activities:

YEAR 1

1st Quarter (Site prep):

- Finalize SOPs, staff training, site preparation
- Development of data systems & database

2nd Quarter (Data collection) ***PILOT***

- Recruitment (estimated 2-3 weeks)
- Follow-up and HIV testing visits (estimated 2-3 months)
- Cost data collection

3rd Quarter (Analysis):

- Pilot data analysis
- Begin Recruitment/Enrollment for ***TRIAL***

4th Quarter (Presentation and Stakeholder feedback):

- **TRIAL** Enrollment
- Manuscript submission for PILOT
- Stakeholder feedback (CAB and staff CCC meetings)

YEAR 2

Quarter 1 and 2

Enrollment and follow-up

Follow-up and testing visits

Quarter 3

Complete testing visits

Quarter 4 (Presentation and Stakeholder feedback):

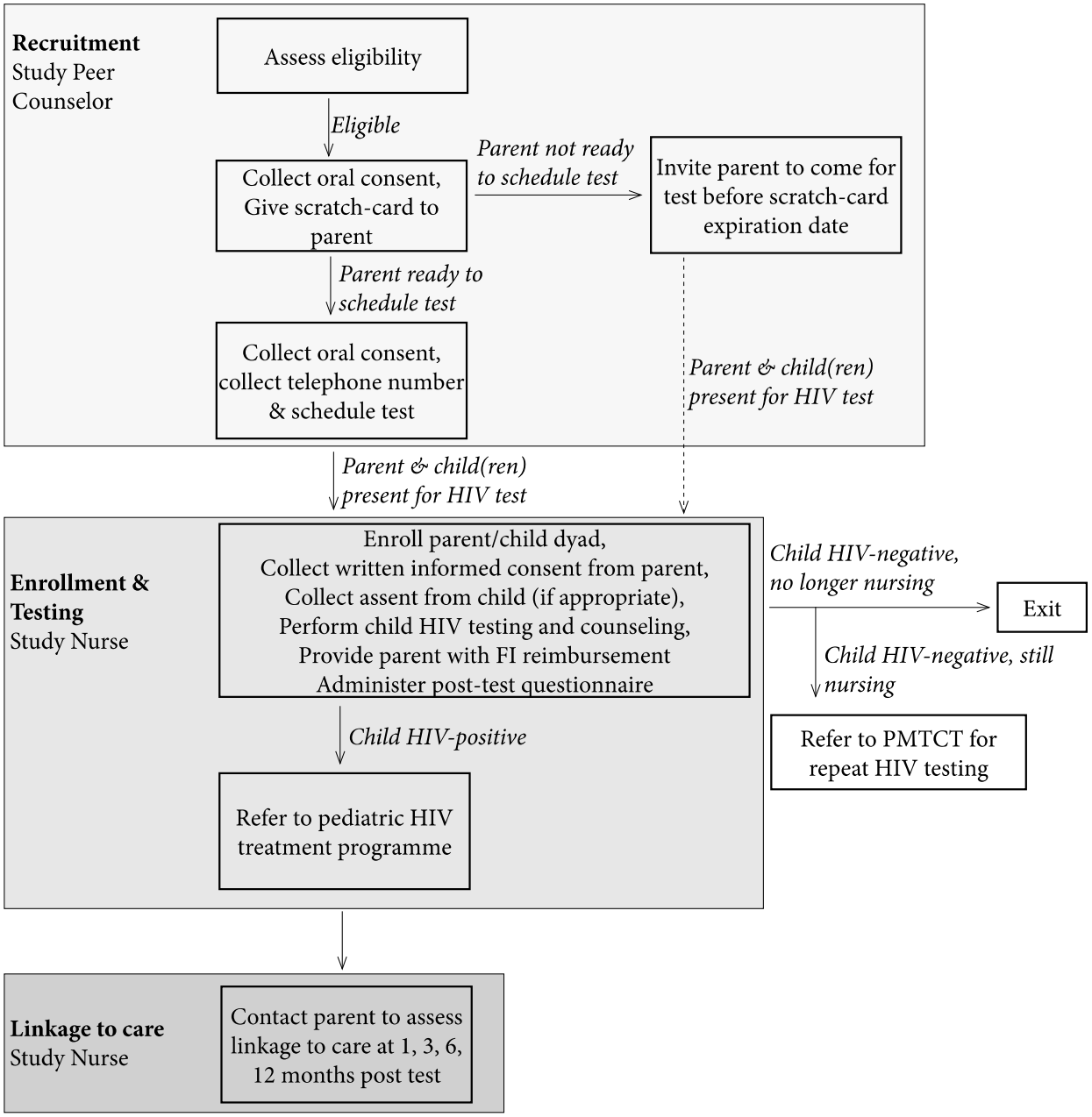
- Data analysis for larger trial
- Manuscript submission
- Stakeholder feedback (CAB and staff CCC meetings

Post-Award Activities:

- CFAR progress and closeout report
- CIPHER closeout report

APPENDIX B: Study Flow Chart

STUDY FLOW DIAGRAM



APPENDIX C: List of Data Collection Instruments

Form Name	Purpose	Responsible Party	Format and Security	Status
Recruitment Log	Collection of basic parent/caregiver information and eligibility, record randomization allocation	Study Peer Counselor	ODK	Draft
Enrollment & Testing Questionnaire	Collection of detailed parent/caregiver information, record of testing visit & result, documentation of FI reimbursement, documentation of referral for HIV+ children	Study Nurse Counselor	ODK	Draft
Post-test Questionnaire	Assess acceptability of FI, collect cost data	Study Nurse Counselor	ODK	Draft
PCR test results	Record and provide parent with HIV PCR result for children <18 months	Study Nurse Counselor	ODK	Draft
Locator form	Detailed tracing information including alternative phone number and physical address (*Needed for the linkage information later on for HIV positive children because people change phone numbers)*	Study Nurse Counselor	Paper based record	Draft