

Section 4. Participant Accrual

4.1 Overview of Section 4

This section provides an overview of requirements and procedures for recruiting, screening, and enrolling participants in the study. Additional procedure-specific detail can be found in the visit checklists in Section 6 as well as in Sections 9 and 10.

4.2 Target Enrollment

A total of 1750 HIV-serodiscordant couples will be enrolled into HPTN 052. Per-site targeted enrollment will be determined by the Protocol Chair and will be based upon the number of sites that are actively enrolling into the study. Sites will be informed of their enrollment target as well as their actual enrollment via reports issued by SCHARP and FHI.

Once enrollment begins, if any site is unable to reach their enrollment goals, their enrollment slots may be reallocated to other sites as deemed appropriate by the Protocol Chair.

4.3 Recruitment Plan

Each site is responsible for establishing a recruitment plan/SOP for this study, and for updating the plan if needed to meet the targeted enrollment goals. At a minimum, the recruitment plan/SOP should contain the following elements:

- Site-specific accrual goals
- Methods for tracking actual accrual versus accrual goals
- Recruitment methods and venues
- Methods for identifying the recruitment source of participants who present to the site for screening
- Methods for timely evaluation of the utility of recruitment methods and venues
- Pre-screening activities (if any)
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements

- QC/QA procedures related to the above (if not specified elsewhere)
- Attached copies of recruitment worksheets, scripts, and other operational tools

4.4 Description of Study Arms

HPTN 052 consists of the following two arms:

Cohort 1: ART upon enrollment plus HIV primary care.

Cohort 2: HIV primary care without initiation of ART until the participant has two consecutive measurements of a CD4+ cell count within or below the range of 200-250 cells/mm³, or develops an AIDS-defining illness.

A total of 875 HIV-serodiscordant couples will be enrolled into each arm of the study (1750 couples total).

4.5 Eligibility Determination

It is the responsibility of the site IoR, and other designated staff, to ensure that only participants who meet the study eligibility criteria are enrolled in the study. As a condition for study activation, study sites must establish an SOP that describes how study staff will fulfill this responsibility. At a minimum this SOP should contain the following elements:

- Eligibility determination procedures, including:
 - During-visit eligibility assessment procedures
 - Post-visit eligibility assessment and confirmation procedures
 - Final confirmation and sign-off procedures prior to enrollment
 - Documentation
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements
- QC/QA procedures related to the above (if not specified elsewhere)

Section 3 (Documentation Requirements) includes a table that sites may use to identify the source documents that will be used to demonstrate participant eligibility.

4.6 Screening and Enrollment

The study screening and enrollment procedures are described in detail in the study protocol and visit checklists (see Section 6).

4.6.1 Screening and Enrollment Timeframe

Enrollment must be completed within 60 days from the time the potential participant signs or marks the screening informed consent form. Note that for the HIV-negative Partner, a negative HIV serology (via HIV EIA antibody test) must be documented **WITHIN 14 days** prior to enrollment. Note that this means that the blood draw, not the test results, must be done within 14 days of enrollment. There are other inclusion/exclusion criteria for the index that have specific time periods, including:

- No documented or suspected acute hepatitis within 30 days prior to enrollment
- No acute therapy for serious illnesses, in the opinion of the site investigator, within 14 days prior to enrollment.
- Radiation or systemic chemotherapy within 45 days prior to enrollment
- Any immunomodulator or other investigational therapy within 30 days prior to enrollment

If all screening procedures are not completed within 60 days of obtaining informed consent for screening, the participant must repeat the entire screening process, including the screening informed consent process. The term “Screening Attempt” is used to describe each time a participant screens for the study. There is no limit to the number of times that a potential participant may be screened for the study.

4.6.2 Assignment of Screening ID Numbers

A screening number must be assigned to all participants who screen for the study. The SDMC (SCHARP) will not assign these numbers; instead, sites should develop their own nomenclature and assign the numbers sequentially. All potential participants who are re-screened should be given the original screening number that was first used; however, it should be documented on the screening and enrollment log that this is another screening attempt (2nd, 3rd, etc. screening attempt).

4.6.3 Randomization and Assignment of Participant ID Numbers (PTID)

At all study sites, HIV infected Index Cases will be randomly assigned in equal numbers to one of two study arms: ART upon enrollment plus HIV primary care or HIV primary care without initiation of ART until the participant has two consecutive measures of a CD4+ cell count within or below the range of 200-250 cells/mm³, or develops an AIDS-defining illness. The SDMC (SCHARP) will generate and maintain the study randomization scheme and associated materials including HPTN 052 Randomization Assignment Envelopes, HPTN 052 Assignment Letters (Figures 4-1 and 4-2) and HPTN 052 Envelope Tracking Records (Figure 4-3).

HPTN 052 Randomization Assignment Envelopes will be shipped from the SDMC (SCHARP) to each study clinic. These envelopes will be shipped prior to beginning the study. The envelopes will be stored in the clinic and assigned in sequential order to participants who have been confirmed as eligible and willing to take part in the study.

The numbered envelopes will contain an Assignment Letter indicating assignment of either immediate or delayed therapy, an index PTID, a linked Partner PTID and nine extra Partner PTIDs.

Envelopes must be assigned in sequential order, and only one envelope may be assigned to each Index Case. Once an envelope is assigned to an Index Case, it may not be reassigned to any other participants.

Envelope assignment to eligible participants will be documented on the HPTN 052 Envelope Tracking Record that will accompany the initial envelope shipment to each site. The act of opening the HPTN 052 Randomization Assignment Envelope is considered the effective act of randomization and enrollment in the study. Once an envelope is assigned and opened, the couple is considered enrolled in the study. The randomization envelope itself, as well as its contents, should be kept as part of the Index Case's source documentation.

For each couple, random assignment will take place after both the index and Partner have been confirmed eligible and willing to take part in the study, as documented by both members of the couple signing or marking an informed consent for enrollment. The randomization procedures listed below will then be performed.

1. Obtain the next sequential HPTN 052 Randomization Assignment Envelope and inspect it to verify that the correct envelope has been obtained and that there is no evidence that the envelope has previously been opened or otherwise tampered with.
2. Open the envelope, remove the assignment letter, and confirm the envelope number printed on the letter matches the number printed on the outside of the envelope. If the envelope does not contain a letter or if any information pre-

printed on the letter appears to be incorrect, contact the SDMC (SCHARP) Protocol Manager immediately. Do not proceed with this randomization or the randomization for any other participant until instructed to do so by the SDMC (SCHARP).

3. Initial, date, and sign the assignment letter and document the assignment in the HPTN 052 Envelope Tracking Record by recording the Index Case name, date of birth, date assigned, time assigned and authorized clinic staff initials in the row corresponding to the assigned envelope number and PTID. File the assignment letter and randomization envelope in the index study chart.
4. Inform the couple of the Index Case assignment and follow appropriate procedures for the visit.

The PTID format is shown below:

027—001—01—1
(site number) (index number) (Partner number) (check digit)

Figure 4-1: Assignment Form, Arm 1

HPTN 052

Assignment Form

Instructions: All entries must be made in dark ink. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

Site Name: [Pre-print] _____ Site Number: [Pre-print] _____

Clinic Name: [Pre-print] _____ Clinic Randomization Envelope #: [Pre-print] _____

Index ID: [Pre-print] _____ Partner ID: [Pre-print] _____

Assignment: Arm 1 (Immediate Therapy)																						
<p>Clinic Staff Name: _____ <small>Please Print</small></p> <p>Clinic Staff Signature: _____</p>	<p>Date Randomized</p> <table style="width: 100%; text-align: center;"> <tr> <td style="border: 1px solid black; width: 20px; height: 20px;"> </td> <td style="border: 1px solid black; width: 20px; height: 20px;"> </td> <td style="border: 1px solid black; width: 20px; height: 20px;"> </td> <td style="border: 1px solid black; width: 20px; height: 20px;"> </td> <td style="border: 1px solid black; width: 20px; height: 20px;"> </td> <td style="border: 1px solid black; width: 20px; height: 20px;"> </td> </tr> <tr> <td><i>dd</i></td> <td></td> <td><i>MMM</i></td> <td></td> <td><i>yy</i></td> <td></td> </tr> </table> <p>Randomization Time</p> <table style="width: 100%; text-align: center;"> <tr> <td><i>hr</i></td> <td><i>min</i></td> <td></td> </tr> <tr> <td style="border: 1px solid black; width: 20px; height: 20px;"> </td> <td style="border: 1px solid black; width: 20px; height: 20px;"> </td> <td style="border: 1px solid black; width: 20px; height: 20px;"> </td> </tr> <tr> <td colspan="2"></td> <td><i>24-hr clock</i></td> </tr> </table>							<i>dd</i>		<i>MMM</i>		<i>yy</i>		<i>hr</i>	<i>min</i>							<i>24-hr clock</i>
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<i>hr</i>	<i>min</i>																					
		<i>24-hr clock</i>																				

Additional Partner IDs:

[Pre-print]
 [Pre-print]
 [Pre-print]
 [Pre-print]
 [Pre-print]
 [Pre-print]
 [Pre-print]
 [Pre-print]
 [Pre-print]

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Figure 4-2: Assignment Form, Arm 2

HPTN 052

Assignment Form

Instructions: All entries must be made in dark ink. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

Site Name: [Pre-print] _____ Site Number: [Pre-print] _____

Clinic Name: [Pre-print] _____ Clinic Randomization Envelope #: [Pre-print] _____

Index ID: [Pre-print] _____ Partner ID: [Pre-print] _____

Assignment: Arm 2 (Delayed Therapy)	
Clinic Staff Name: _____ <small>Please Print</small>	Date Randomized <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; display: flex; align-items: center; justify-content: center;"> </div> <div style="border: 1px solid black; width: 20px; height: 20px; display: flex; align-items: center; justify-content: center;"> </div> <div style="border: 1px solid black; width: 20px; height: 20px; display: flex; align-items: center; justify-content: center;"> </div> </div> <div style="display: flex; justify-content: space-around; margin-top: 5px;"> <i>dd</i> <i>MMM</i> <i>yy</i> </div>
Clinic Staff Signature: _____	Randomization Time <div style="display: flex; justify-content: space-around; align-items: center;"> <i>hr</i> <i>min</i> </div> <div style="display: flex; justify-content: space-around; align-items: center; margin-top: 5px;"> <div style="border: 1px solid black; width: 20px; height: 20px; display: flex; align-items: center; justify-content: center;"> </div> : <div style="border: 1px solid black; width: 20px; height: 20px; display: flex; align-items: center; justify-content: center;"> </div> <i>24-hr clock</i> </div>

Additional Partner IDs:

[Pre-print]
 [Pre-print]
 [Pre-print]
 [Pre-print]
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 [Pre-print]
 [Pre-print]
 [Pre-print]

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accrual process. In addition, the SDMC (SCHARP) will report to the team the number of participants enrolled monthly based on data received and entered into the DataFax study database.

As the study accrual period comes to an end at each site, care must be taken to manage the recruitment, screening, and enrollment process in order not to exceed the protocol-specified sample size (see Section 4.2). Particularly in the last 2-4 weeks of accrual, enrollment must be monitored closely, and potential participants must be informed that although they may screen for the study, they may not be enrolled if the target sample size is reached before they are able to complete the screening and enrollment process. This may be difficult to explain to potential participants — especially those who are very interested in taking part in the study — therefore all sites are advised to work with their local community advisory board (CAB) members to develop strategies to address this issue.

4.6.6 Screening Scenarios

Presented below are several examples of screening scenarios that may occur during HPTN 052.

4.6.6.1 A participant meets all index eligibility requirements on May 1. The participant's Partner meets all eligibility requirements on May 3. The couple returns to the clinic together on May 20, to complete the enrollment visit. What tests need to be performed before the enrollment visit can begin?

The protocol dictates that Partner HIV eligibility testing must be conducted within 14 days of enrollment. Because the Partner was tested 17 days ago, he/she must be re-tested to confirm negative HIV status. In addition, all other inclusion/exclusion criteria should be reviewed to ensure that no other criteria have been violated since the beginning of May.

If the Partner's HIV EIA test is negative, continue with enrollment visit procedures.

If Partner test results are indeterminate, perform a Western Blot using the same blood sample. Schedule the next appointment for receipt of results, within 14 days. Encourage the couple to attend the next visit together. Explain that the next visit can be the enrollment visit based on results of confirmatory test and whether both individuals are present.

If the Partner is not eligible based on HIV results, stop screening procedures and document the reason for the couple's ineligibility in the screening log.

4.6.6.2 A couple is being screened to participate in the study and you discover one of the pair has shingles. Are they still eligible to participate in the study?

Yes, shingles is not an AIDS-defining illness, and is, therefore, not an exclusion criterion. Continue screening procedures.

4.6.6.3 A couple shows up for the screening visit and both people test HIV positive. Do you continue the screening process?

You may inquire if there is another Partner (perhaps a man with more than one wife) that is HIV negative. If not, stop screening procedures and document the reason for ineligibility in the screening log.

4.6.6.4 The following lab results come back for a potential Index Case:

- **CD4 = 450 cells/mm³**
- **Hemoglobin = 5.5 g/dL**
- **Platelet count = 65,000// μ L**
- **AST = 30 U/L**
- **ALT = 25 U/L**
- **Alkaline phosphatase = 125 U/L**
- **Total bilirubin = 1.5 mg/dL**
- **Creatinine clearance = 80 mL/min**
- **Absolute neutrophil count = 1000 mm³**

Is this candidate eligible for HPTN 052? If so, explain why. If not, what options do you have for rescreening?

Yes, the potential candidate has a CD4 measurement that falls between 350 and 550 cells/mm³, meeting the corresponding inclusions criterion. The candidate's values for AST, ALT, alkaline phosphatase, and total bilirubin all fall within the normal ranges and, thus, meet the protocol criteria. The platelet count, creatinine clearance, and absolute neutrophil count also match the index inclusion criterion that requires values $\geq 50,000/\mu\text{L}$, ≥ 60 mL/min, and ≥ 750 mm³, respectively. However, this person is anemic and the cause should be determined and treated. Retesting after 1-2 months is allowed and encouraged.

Normal ranges:

AST: 5 - 40 U/L

ALT: 10 – 60 U/L

Total bilirubin: 0.2 – 1.3 mg/dL

The normal range for alkaline phosphatase varies by age and gender; however, 125 falls within the normal ranges of adults (>18) of both genders.

4.6.7 Enrollment Scenarios

4.6.7.1 A female index participant pregnancy results are positive when tested during the enrollment visit, prior to randomization. What do you do?

This participant's enrollment into the HPTN 052 study should be delayed until the second trimester of her pregnancy, since according to the U.S. standard of care, pregnant women with high CD4 levels, between 350 and 550 cells/mm³, should not begin ART during their first trimester of pregnancy, due to risks that it may pose.

4.6.7.2 A female index participant randomized to the immediate arm becomes pregnant after enrollment. How should you manage her ART?

This participant's ART regimen should be switched to a regimen that is appropriate for pregnancy if she is not on one already.

4.6.7.3 A female index participant randomized to the delay arm becomes pregnant during the study. What do you do?

You must start this participant on ART at the beginning of her second trimester.

4.6.7.4 A couple meets all eligibility criteria for the study. When randomized to the delayed ART arm, the index decides he does not want to continue in the study. What do you do?

Encourage the Index Case to continue study participation, pointing out the benefits of the delayed arm such as frequent medical care, couples counseling, compensation and, if and when necessary, ART. If he still refuses, complete an Index Termination form.

4.6.7.5 A couple returns for the enrollment visit and upon questioning, you realize the Partner had received an experimental HIV vaccine several years ago, but had forgotten to report it during the screening visit. Is the couple still eligible to participate? Is either the Partner or index eligible to participate alone?

No, receipt of an experimental HIV vaccine is an exclusion criterion for both the index and Partner. As well, having a Partner is an inclusion criterion for the index. Therefore, neither person is eligible to participate in the study. However, you may inquire if there is another Partner (perhaps a male with more than one wife) that is HIV negative.

If the couple has not been randomized, explain they are ineligible to participate in the study. Stop the enrollment visit and document the reason for ineligibility in the screening log.

If the couple has been randomized, they are enrolled in the study. Notify the Clinical Management Committee (CMC) of the protocol violation. The CMC will decide whether the couple can remain in the study.

4.7 Informed Consent

Informed consent is a process by which an individual voluntarily expresses his/her willingness to participate in research, after having been informed of all aspects of the research that are relevant to his/her decision. Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process, with four key considerations — information exchange, comprehension, voluntariness, and documentation — each of which is described below. See Section 4.8 of the ICH GCP guideline and the informed consent section of the *DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-CL-04.00)* for detailed guidance on the informed consent process and documentation requirements.

For this study, informed consent is first obtained for screening procedures only. Then, for participants found to be eligible, informed consent is obtained for enrollment. For both screening and enrollment, informed consent must be obtained prior to undertaking screening and enrollment procedures, respectively. For enrolled participants, informed consent should be considered as an ongoing process that continues throughout the study follow-up period.

If an Index Case becomes pregnant during the study, she must sign the Index Case Pregnancy informed consent form in order to continue in the study.

Potential participants will be asked to provide informed consent for storage of blood and genital secretion specimens for possible future research testing. Potential participants who choose not to have their specimens stored for future testing will still be eligible to enroll in the study.

U.S. regulations specify the elements of informed consent that must be conveyed to research participants through the informed consent process (45 CFR 46 and 21 CFR 50). It is the responsibility of the IoR, and his/her delegated staff, to deliver all required information to potential research participants.

Based on the technical and regulatory reviews that are completed as part of the HPTN protocol development and study activation processes, there is adequate assurance that once the HPTN CORE has “activated” a site for study implementation, the site-specific informed consent form specifies all information required by the regulations. However, responsibility for informed consent does not end with preparation of an adequate informed consent form. It also is the responsibility of the IoR and designated study staff to perform the activities described in sections 4.7.1 through 4.7.5.

4.7.1 Deliver All Required Information In A Manner That Is Understandable To Potential Participants

If the participant is literate, give him/her a copy of the informed consent form to read during the screening and enrollment visits. Also provide the participant with other (IRB/EC-approved) informational materials developed to complement the informed consent form, if any. If the participant is not literate, the materials may be read to him/her verbatim or summarized. After the participant has read the written material (or had it read to him/her), verbally review the information provided. A checklist or the informed consent form itself may serve as a useful guide for this. For example, you may note the main points described in each paragraph of the informed consent form, and ask if the participant has questions or concerns about each point. Listen carefully to the questions or concerns expressed by the participant, and discuss these thoroughly. Take as much time as needed to address each question and concern.

If the participant is illiterate, **an impartial witness must be present during the entire informed consent discussion**. The witness will be asked to sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant. The ICH GCP guideline identifies an “impartial” witness as a person who is independent of the study, who cannot be unfairly influenced by people involved with the study. Each site must specify its procedures for obtaining informed consent from illiterate persons in its SOP for obtaining informed consent. The SOP should define who may serve as an impartial witness to the informed consent process. It is recommended that each site seek IRB/EC review and approval of these procedures.

4.7.2 Assure That Informed Consent Is Obtained In A Setting Free Of Coercion And Undue Influence.

During the informed consent discussion, take care to not overstate the possible benefits of the study, nor to understate the risks. Also emphasize to the participant that the availability of medical care and other services routinely obtained from the clinic or hospital will not be affected by her decision whether or not to take part in the study. Encourage the participant to take as much time as he/she needs — and to talk about his/her potential participation with others, if he/she chooses — before making a decision.

If the participant is illiterate, and therefore a witness is present during the entire informed consent discussion, care should be taken to minimize the perception of coercion due to the presence of the witness. For example, the purpose of having the witness present should be clearly explained to the participant, with emphasis on the fact that the witness is there as a protection for the participant, not as an agent of the study per se.

4.7.3 Confirm That the Participant Comprehends the Information

The participant must not be asked to agree to take part in the screening/study, or to sign or make her mark on the informed consent form, until he/she fully understands the screening process/study. Study staff are responsible for implementing procedures to ensure that each participant understands the screening process and the study prior to signing/marketing the screening and enrollment informed consent forms, respectively, and undertaking any screening or study procedures.

One approach to assessing comprehension is to use a “quiz” (either oral or written) or other assessment tool that participants must complete prior to signing/marketing the informed consent form. Another approach is to use open-ended questions to ascertain participant understanding during the informed consent discussion. It is possible to incorporate a scoring system into these assessment tools and to re-review the contents of the informed consent until the potential participant can answer a certain percentage of the questions correctly. Three types of informed consent assessment tools, two using specific and the other using open-ended questions, are included at the end of this section. For sites that choose to adopt tools such as those included at the end of this section, detailed instructions for their use must be specified in the site SOP for obtaining informed consent.

Regardless of the method used to assess comprehension, if the assessment results indicate misunderstanding of certain aspects of the study, review those aspects again until the participant fully understands them. If after all possible efforts are exhausted, the participant is not able to demonstrate adequate understanding of the study, do not ask him/her to sign/mark the informed consent form or screen for/enroll in the study. Similarly, if the participant has concerns about possible adverse impacts on him/her if he/she were to take part in the study, or indicates that he/she may have difficulty adhering to the study requirements, do not ask him/her to sign the informed consent form to screen for or enroll in the study.

Sample Informed Consent Assessment Tool for Enrollment in HPTN 052

Question	Answers	√	Comments
1. Please describe your understanding of the purpose of this study.	study is treating people infected with HIV with anti-HIV drugs to prevent them from passing the virus to their Partner through sex		
	testing to see if anti-HIV drugs are safe		
	testing to learn the best time to start treating people infected with HIV with anti-HIV drugs in order to prevent the spread of HIV		
2. What do you understand that you are being asked to do in this study?	have pelvic/genital exams, blood draws, give semen/vaginal fluid samples, give urine samples (if applicable), take study medication (Index Case)		
	have HIV tests, pelvic/genital exams, blood draws, urine samples (if applicable) (Partner)		
	come for follow-up visits for 5 years with their Partner		
	participate in couples counseling		
3. What do you understand about possible risks that might happen as a result of being in the study?	there may be side effects to the study medication (Index Case)		
	possibility the drugs may stop working (resistance)		
	possibility of social harms		
4. What will happen to you if you decide not to join the study?	free to make own decision about joining		
	there will be no effect on access to care		
5. Please tell me about the different groups of couples in the study.	one group will receive ART immediately, the other will receive ART when the Index Case gets sick or has two consecutive measurements of a CD4+ cell count within or below the range of 200-250 cells/mm ³ .		
	no one knows in advance which group a couple will be assigned to		
6. How will the information about you be protected?	information kept under lock and key		
	only certain people (those working on the study or the U.S. government) have access		
7. What are the benefits to you of participating in this study?	Access to ART, primary HIV/AIDS care, couples counseling, reimbursement, general clinical care, potentially prevent the spread of HIV to Partner (<i>should mention at least one</i>)		
8. What should you do if you have any questions about what is happening in this study?	knows contact information		
9. Is there anything else you'd like to ask or talk about?			
<p>Outcome: _____</p> <p>Proceed to enrollment _____</p> <p>Declined to consent _____</p> <p>Rescheduled for another consent visit _____</p> <p>Unable to consent _____</p> <p style="text-align: center;">Notes:</p>			

Sample Informed Consent Assessment Tool for Enrollment in HPTN 052

No.	Question	True	False
1	This study is part of the regular medical care offered here at [clinic name].	<input type="checkbox"/>	<input checked="" type="checkbox"/>
2	One purpose of this study is to find out if drugs to treat HIV can reduce the risk of transmission.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
3	Each person in this study will be in the study for two years	<input type="checkbox"/>	<input checked="" type="checkbox"/>
4	Study participants will have study visits every month.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
5	Study participants who are HIV-negative will have HIV tests every three months.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
6	Study participants will undergo a pelvic and/or genital exam once a year.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
7	If you join this study, you must stay in the study for as long as the study nurse says.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
8	If you join this study, you will automatically get to participate in other research studies done here in the future.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
9	If you join this study you or your Partner will receive anti-HIV drugs immediately.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
10	Participants' study records will be available to everyone at the [clinic name].	<input type="checkbox"/>	<input checked="" type="checkbox"/>
11	Anti-HIV drugs can make you or your Partner feel sick.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
12	If you decide not to join this study, you can still come to the [clinic name] for medical care.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
13	Study participants can get condoms and HIV counseling from the study staff at any time.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
14	Study participants can return for their study visits without their Partner.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
15	If the study staff determines that you have any medical problems, they will treat you or refer you to available sources of medical care for those problems.	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Sample Open-Ended Discussion Questions for Assessing Comprehension of HPTN 052

Page 1 of 2

1. If you wanted to tell a friend or family member about this study, how would you describe it to them?

- Study objectives/purpose
- Study population
- Overall study design: duration, visit and procedures schedule, clinic- and community-based visit locations

2. How do you think it would affect your day-to-day life to be in this study?

- Study duration: 5 year
- Study visit schedule
- Study visit duration: 1-4 hours
- Taking or helping my Partner take ART every day
- Perceived risks and benefits of study participation
- Potential social harms
- No costs to participants

3. What do you think you will get out of being in this study?

- HIV/STD education, counseling, and testing
- Condoms
- Physical exams and lab tests, for my Partner or me
- STD treatment
- Access to ART for my Partner or myself
- Personal satisfaction

4. Do you think being in this study could help you or your Partner avoid becoming infected with HIV?

- HIV education, counseling, and testing provided
- Condoms provided
- ART treatment provided

5. Are there things about being in this study that you would be worried about?

- Embarrassment/worry/anxiety when answering interview questions about sexual activities
- Embarrassment/worry/anxiety when discussing HIV/AIDS and risk behaviors
- Worry/anxiety while waiting for or after receiving test results
- The side effects of ART
- Social harms

Sample Open-Ended Discussion Questions for Assessing Comprehension of HPTN 052

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6. **What kind of clinical procedures will you undergo in this study?**
- Blood collection
 - Urine collection
 - Semen/vaginal secretion collection
 - Physical examination
 - Genital/pelvic examination
7. **What happens to participants who become pregnant during the study?**
- Can remain in the study as originally scheduled if willing to sign consent
 - ART regimen may be changed
8. **What might the study staff do if you miss a study visit?**
- Mail, phone, other contacts to re-schedule the visit
 - Work through locator contacts to reach the participant
9. **What are some reasons why the study staff might end your participation in the study?**
- The study is stopped or cancelled
 - The staff feels it would be harmful for the participant to stay in the study
 - The HIV-negative Partner becomes infected with HIV
 - The participant is unable to attend study visits or complete study procedures
10. **What will the study staff do to protect your privacy and confidentiality during the study?**
- Conduct visits in private
 - Keep information about study participation and all study records confidential
 - Maintain privacy and confidentiality when conducting locator activities
 - However some “outsiders” will review records
11. **What would you do if you joined the study and then you didn't feel comfortable about the way you were treated in the study?**
- Role of IRB/EC and human subjects contact person
 - Voluntary participation — can leave the study at any time
 - Voluntary participation — can continue to receive other services at the study clinic

4.7.4 Document the Process

U.S. regulations require that informed consent be documented by "the use of a written informed consent form approved by the IRB/EC and signed and dated by the subject or the subject's legally authorized representative at the time of consent."

To fulfill this requirement, complete all signature and date blocks on the informed consent form per local IRB/EC requirements. Per the *DAIDS Policy for Requirements for Source Documentation in DIADS Funded and/or Sponsored Clinical Trials (DWD-POL-CL-04.00)*, participants must sign the informed consent form using their complete last name (not just an initial); the SOP also recommends, but does not require, that the participant's complete first name (not just an initial) be used as well. It is essential that the date documented on the form either precedes or coincides with the (first) study screening date. In addition, enter a note in the participant chart documenting that informed consent was obtained prior to the initiation of any study procedures. Finally, regulations require that participants be offered a signed copy of the informed consent forms. If a participant opts not to receive a copy, document this in a chart note.

If the participant is illiterate, the impartial witness present during the informed consent discussion must sign and date the informed consent form to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant. In addition, the participant printed name, signature, and signature date blocks on the informed consent form should be completed as follows:

- The study staff member who completed the informed consent process with the participant should enter the participant's name below the "participant's printed name" block, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.
- The participant should make his/her mark (thumbprint or "X") in the "participant's signature" block.
- If possible, the participant should write the date in the "participant signature date" block. If the participant is unable to do this, the study staff member who completed the informed consent process with the participant should enter the date below the "participant signature date" together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.

The *DAIDS Policy for Requirements for Source Documentation in DIADS Funded and/or Sponsored Clinical Trials (DWD-POL-CL-04.00)* provides detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the *DAIDS Policy* must be met. In order to

also meet some of the suggestions listed in the DAIDS Policy, site staff may consider the use of an informed consent “coversheet” similar to the example included in this section.

Sample Informed Consent Coversheet for HPTN 052

Participant name:	
Date of informed consent discussion:	
Time of informed consent discussion:	
Name of study staff person completing informed consent discussion (and this coversheet):	
Can the participant read?	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ If no, an impartial witness should be present during the entire informed consent discussion. Refer to informed consent SOP for specific instructions.
In what language was informed consent obtained?	<input type="checkbox"/> [<i>insert local language</i>] (written) <input type="checkbox"/> English (written)
Did the participant accept a copy of the informed consent form?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Notes/Comments (not documented elsewhere):	

4.7.5 Continue the Informed Consent Process Throughout the Study

The previous sections describe aspects of obtaining informed consent from study participants prior to initiating their involvement in the study. Given the ongoing nature of informed consent, key elements of informed consent should also be reviewed at study follow-up visits. At these visits, study staff should review key elements of informed consent with the participant, focusing on the remainder of their study participation. For example, at study month 11, the discussion might focus on the fact that the next visit will be a yearly visit and will involve more clinical procedures than the routine monthly visits.

4.7.6 ICF Requirements for Protocol Amendments

According to DAIDS policy (Protocol Registration Policy and Procedure Manual), the site's IRB/EC are ultimately responsible for determining whether study participants need to be re-consented for a protocol amendment. If there are significant changes between protocol versions which result in changes to the informed consent forms, the protocol team recommends that the participants already enrolled in the study be re-consented to the revised/approved informed consents.

4.7.7 Informed Consent SOP

As a condition for study activation, each study site must establish an SOP for obtaining informed consent from potential study participants. This SOP should reflect all of the information provided in this section and minimally should contain the following elements:

- The minimum legal age to provide independent informed consent in the study site locale
- Procedures for ascertaining participant identity and age
- Procedures for ascertaining participant literacy
- Procedures for providing all information required for informed consent to the participant
- Procedures for ascertaining participant comprehension of the required information
- Procedures to ensure that informed consent is obtained in a setting free of coercion and undue influence
- Procedures for documenting the informed consent process

- Considerations and requirements for illiterate participants, including specification of who may serve as an impartial witness to the informed consent process
- Storage locations for blank informed consent forms
- Storage locations for completed informed consent forms
- Procedures for implementing a change in the version of the informed consent form used
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements
- QC/QA procedures related to the above (if not specified elsewhere)
- Attached copies and instructions for use of all forms, worksheets, or checklists to be used during the informed consent process

For ease of reference, a summary of key instructions from the above sections related to obtaining informed consent from illiterate persons is presented in the box below.

Key Points to Consider when Obtaining Informed Consent from Illiterate Persons

- Each site must specify procedures for obtaining and documenting informed consent from illiterate persons in its SOP for obtaining informed consent. These procedures must be consistent with the *DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-CL-04.00)* and must be followed each time informed consent is obtained. It is recommended that each site seek IRB/EC review and approval of these procedures.
- An impartial witness must be present during the entire informed consent discussion with an illiterate participant. The witness must sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the participant, and that informed consent was freely given by the participant.
- The site SOP for obtaining informed consent should define who may serve as the witness to the informed consent process.
- Take care to minimize the perception of coercion due to the presence of the witness.
- The study staff member who completed the informed consent process with the participant should enter the participant's name below the "participant's printed name" block, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry.
- The participant should make her mark (thumbprint or "X") in the "participant's signature" block.
- If possible, the participant should write the date in the "participant signature date" block. If the participant is unable to do this, the study staff member who completed the informed consent process with the participant should enter the date below the "participant signature date" together with a signed and dated note directly on the ICF document documenting the name of the person who made the entry and the date of the entry.
- Refer to Section 4.8 of the ICH GCP guideline and the informed consent section of the *DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-CL-04.00)* for additional information.