

## **HPTN 052**

# **A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples**

### **A Study of the HIV Prevention Trials Network**

#### **Sponsored by:**

Division of AIDS, U.S. National Institute of Allergy and Infectious Diseases

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**Investigator of Record Signature Page**

**HPTN 052**

**A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy Plus  
HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual  
Transmission of HIV-1 In Serodiscordant Couples**

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Sponsored by:

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I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the FDA is notified that the IND is discontinued. Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be submitted to the HPTN Manuscript Review Committee, DAIDS, and the product Co-Sponsors for review prior to submission.

I have read and understand the information in the Investigator's Brochures or Package Inserts, including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

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Name of Investigator of Record

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Signature of Investigator of Record

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Date

## HPTN 052

### **A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy Plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples**

#### **LIST OF ABBREVIATIONS AND ACRONYMS**

3TC	lamivudine
AACTG	Adult AIDS Clinical Trials Group
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AIDSCAP	AIDS Control and Prevention
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the curve
BID	twice daily
BMD	bone mineral density
BV	bacterial vaginosis
CBC	complete blood count
CDC	Center for Disease Control
CL	(HPTN) Central Laboratory
CMC	(HPTN 052) Clinical Management Committee
CNS	central nervous system
CORE	(HPTN) Coordinating and Operations Center
CRF	case report form
CT	Chlamydia trachomatis
d4T	stavudine
DAIDS	Division of AIDS
ddI	didanosine
DEXA	dual-energy x-ray absorptiometry
DSMB	Data Safety Monitoring Board
EC	ethics committee
ELISPOT	enzyme linked immunosorbent spot assay
EFV	efavirenz
EIA	enzyme immunoassay
GC	Neisseria gonorrhea
FDA	(United States) Food and Drug Administration
FHI	Family Health International
HAART	highly active antiretroviral therapy
HBV	hepatitis B
HCV	hepatitis C
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPTN	HIV Prevention Trials Network
HSR	hypersensitivity reaction
IATA	International Air Transport Association

ICH	International Conference on Harmonization
ID	identification
IFA	immunofloresence assay
IDV	indinavir
INH	isoniazid
IRB	institutional review board
ITT	intent-to-treat
LDMS	Laboratory Data Management System
LFT	liver function tests
LPA	lymphoproliferation assay
LPV	lopinavir
MTCT	maternal-to-child-transmission
NBAC	National Bioethics Advisory Committee
NFV	nelfinavir
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NVP	nevirapine
OI	opportunistic infection
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PPD	purified protein derivative (of tuberculin)
PI	protease inhibitor
PRN	as occasion requires
PSRT	Protocol Safety Review Team
PTT	partial thromboplastin time
QD	once daily
RNA	ribonucleic acid
RTV	ritonavir
SAE	serious adverse event
SDMC	(HPTN) Statistical and Data Management Center
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamate pyruvate transaminase
SMC	(HPTN) Study Management Committee
SOP	standard operating procedure
SSP	Study-Specific Procedures
STD	sexually transmitted disease
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TID	three times a day
TV	<i>Trichomonas vaginalis</i>
ULN	upper limit of normal
UNAIDS	The Joint UN Programme on HIV/AIDS
U.S.	United States
USPHS	United States Public Health Service
VCT	voluntary counseling and testing
WHO	World Health Organization
ZDV	zidovudine

## HPTN 052

### A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy Plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples

#### SCHEMA

**Purpose:** The purpose of this study is to determine whether antiretroviral therapy (ART) can prevent the sexual transmission of HIV-1 in HIV-1 serodiscordant couples.

**Design:** The study is a Phase III, two-arm, randomized, controlled, multi-center trial. A run-in period is planned prior to fully enrolling the study.

**Study Population:** HIV serodiscordant couples in which the HIV-infected partner is ART-naïve and has a CD4+ cell count of 300-500 cells/mm<sup>3</sup>.

**Study Size:** Approximately 1750 couples total, with a maximum of 90 couples who will take part in the run-in period.

**Study Arms:** HIV-infected index cases will be assigned at random in a 1:1 ratio to one of two treatment arms:

**Arm 1:** ART upon enrollment plus HIV primary care.

**Arm 2:** HIV primary care without initiation of ART until the participant has two consecutive measurements of a CD4+ cell count < 200 cells/mm<sup>3</sup>, or develops an AIDS-defining illness.

The ART drugs available for the run-in period of the study are Combivir<sup>®</sup> [3TC/ZDV], ATV, EFV, NVP, TDF, 3TC, ddI-EC, and d4T; available for the full study are Combivir<sup>®</sup> [3TC/ZDV], 3TC, NVP, and TDF. Before the full study can be initiated, at a minimum, another nucleoside (such as ddI), and a protease inhibitor (such as ATV or Kaletra<sup>®</sup> [lopinavir/ritonavir]) must be available for the length of the full study. The study team has not yet secured commitments for these types of drugs for the full study. Therefore, HPTN 052 will begin with a run-in period using the ART drugs currently available. While the run-in period is being conducted, it is planned to pursue commitments for the full study. If commitments are not obtained, the full study will not proceed, and the study will end.

**Study Duration:** Approximately 87 months total. Accrual into the run-in period will require 3 months, and all couples will be followed until the last couple enrolled completes their 6-month follow-up visit. Accrual into the full study will require approximately 18 months total, and all couples will be followed until the last couple enrolled completes their 60-month follow-up visit.

#### Study Objectives:

The primary objective of the study is to compare the rates of HIV infection among partners of HIV-infected participants in the two study arms below:

- (1) ART upon enrollment plus HIV primary care.
- (2) HIV primary care without initiation of ART until the participant has two consecutive measurements of a CD4+ cell count  $\leq$  200 cells/mm<sup>3</sup>, or develops an AIDS-defining illness.



The secondary objectives of the study are to:

- Determine the long-term safety of two ART regimen strategies (ART immediately upon enrollment vs. ART when the participant has two consecutive measurements of a CD4<sup>+</sup> cell count  $\leq 200$  cells/mm<sup>3</sup> or develops an AIDS-defining illness) for the treatment of HIV-1 infection.
- Characterize and compare the patterns and rates of antiretroviral drug resistance of two antiretroviral treatment strategies.
- Assess factors associated with adherence and to compare the adherence rate of two antiretroviral treatment strategies.
- Evaluate the usefulness of measures of virologic and immunologic efficacy, and measures to detect antiretroviral drug resistance.
- Determine, characterize, and compare the rates of AIDS-defining illnesses, sexually transmitted diseases, opportunistic infections, and immune reconstitution syndromes, with regard to outcomes and survival as observed in different geographic settings and by treatment strategies.
- Determine and characterize the rates of antiretroviral drug-associated toxicities observed in different geographic settings and by treatment strategies.
- Evaluate the effectiveness of couples HIV counseling and characterize the patterns of sexual behavior in couples in both arms of the study.

#### **Study Sites:**

- Porto Alegre and Rio de Janeiro, Brazil (considered one site)
- Chennai, India
- Pune, India
- Blantyre, Malawi
- Lilongwe, Malawi
- Chiang Mai, Thailand
- Boston, Massachusetts, United States of America
- Harare, Zimbabwe

# **1 INTRODUCTION**

## **1.1 Background**

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 40 million adults and children were living with the human immunodeficiency virus (HIV) or living with acquired immunodeficiency syndrome (AIDS) at the end of 2003, of which 5 million were new infections occurring in 2003 alone.<sup>1</sup> Of the 40 million, 31.6 million are in sub-saharan Africa<sup>1</sup>. Over 95 percent of new infections are acquired in developing countries, and the majority of new infections are transmitted through heterosexual contact. As such, it is clear that prevention of HIV will depend on a multi-pronged strategy that employs all available biological and behavioral prevention interventions.

Several different approaches to HIV prevention are being planned, or studies are on-going. For example, the UNAIDS and AIDS Control and Prevention (AIDSCAP) approach has focused on safer sex counseling, provision of condoms, and sexually transmitted disease (STD) control. This approach to HIV prevention includes an “ABC “ (Abstinence, Be Faithful, Condoms) campaign, which has had considerable success in Uganda<sup>72</sup>. In particular, monogamy and partner number reduction may play a critical role in HIV prevention, a goal that must be emphasized in all HIV prevention strategies, including with concomitant use of ART. A variety of other prevention interventions include vaccines<sup>2</sup>, and topical microbicides<sup>3</sup>, treatment of bacterial vaginosis, the diaphragm, male circumcision, and other antiretroviral therapy studies (e.g. pre-exposure prophylaxis).

This study is designed to determine whether ART can prevent the sexual transmission of HIV. ART is widely available in developed countries, and is now being introduced into many developing countries<sup>4-5</sup>. The separation between HIV treatment and HIV prevention may represent an unfortunate “false dichotomy” for the following reasons:

- HIV treatment affects HIV transmission<sup>6</sup>;
- HIV prevention strategies in the treatment setting have essential value<sup>7</sup>; and
- HIV treatment may become a central prevention strategy in the coming years, as appropriate new agents are developed.

This study addresses these issues by providing HIV treatment, specifically by administering ART drugs according to their U.S. FDA approved use, and then measuring the effect on further sexual transmission of the virus.

## **1.2 Partnership with the Adult AIDS Clinical Trials Group (AACTG)**

The NIAID-sponsored Adult AIDS Clinical Trials Group (AACTG) is developing an HIV treatment study for implementation at each HPTN 052 site, and other additional international sites in the ACTG International Therapeutic Clinical Trials Training and Research Initiative. The AACTG study may be able to serve as an alternative clinical trial

for some index cases that are not eligible for HPTN 052 due to screening with a CD4+ cell count less than 300 cells/mm<sup>3</sup>.

### **1.3 Rationale**

#### **1.3.1 Can Antiretroviral Therapy Reduce the Sexual Transmission of HIV?**

In the absence of therapy, HIV leads to inexorable destruction of critical immune cells (CD4+), opportunistic infections that can be correlated with the magnitude of CD4+ cell loss, and death. ART developed in the late 1980s has been shown to dramatically reduce the morbidity and mortality of HIV infection through sustained reduction in HIV viral replication<sup>8</sup>. However, such therapy does not cure HIV infection, and viral resistance can be expected to develop in most patients on regimens that are not completely suppressive. Therefore, the modification of ART is usually required to maintain viral suppression<sup>9</sup>. Although the use of combination ART has dramatically improved clinical outcomes and decreased mortality, recent evidence suggests that patients who initiate therapy with CD4+ cell counts below 200 cells/mm<sup>3</sup> have a greater risk of disease progression and death when compared to those who initiate treatment with CD4+ cell counts above 200 cells/mm<sup>3</sup><sup>10</sup>. However, some antiviral agents have side effects that limit their long-term application. For this last reason, ART is often withheld until some degree of immunosuppression has developed.

Deductive reasoning strongly suggests that ART might render HIV-infected people less contagious. First, plasma HIV-1 ribonucleic acid (RNA) levels can be correlated with the sexual transmission of HIV. In a study of 415 HIV serodiscordant couples in Uganda, 21.7% of the initially uninfected partners became infected over 30 months of follow-up, translating to a transmission rate of approximately 12 infections per 100 person years<sup>11</sup>. No transmission events occurred in those couples in which the infected partner had a plasma HIV-1 RNA level of less than 1500 copies/mL, and the transmission risk increased as plasma HIV-1 RNA levels increased. In a prospective study of 1067 counseled HIV serodiscordant couples in Zambia, 15% of the initially uninfected partners became infected<sup>12</sup>, yielding a slightly lower transmission rate of 8.5 infections per 100 person years. Again, plasma HIV-1 RNA level was the best predictor for HIV transmission. This bears particular significance for the ongoing AIDS epidemic, as many African people with clade C HIV infection have markedly elevated plasma HIV-1 RNA levels<sup>13</sup>, possibly leading to increased transmissibility. While a recent study in Thailand also demonstrated a similar relationship between plasma HIV-1 RNA levels and sexual transmission, the majority of transmission events were observed at a very low plasma HIV-1 RNA level, suggesting that plasma HIV-1 RNA level is not the only determinant and that efficiency of transmission may vary by clade<sup>14</sup>.

Plasma HIV-1 RNA levels generally correlate positively with the concentration of HIV in genital secretions, rectal mucosa, and saliva, although inflammation can stimulate local replication<sup>15</sup>. ART decreases the concentration of HIV-1 RNA in male<sup>16</sup> and female genital secretions<sup>17</sup>, rectal mucosa,<sup>18</sup> and saliva<sup>19</sup>, thereby reducing the levels of HIV inoculum to which the susceptible partner is exposed. Further, studies of the pharmacology of ART in penetrating male and female genital secretions (*i.e.* semen and vaginal

secretions) indicate that the degree of penetration into genital secretions varies according to physical characteristics of the drug. For example, nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) penetrate the semen to a greater degree than do protease inhibitors (PIs). Also, zidovudine (ZDV) and lamivudine (3TC) achieve greater concentrations in semen than in blood<sup>20</sup>. ART could be particularly effective in prevention of transmission of HIV from men to their sexual partners since the high concentration of drugs may be transferred with the ejaculate<sup>20</sup>. ART selects for resistant viral variants which grow in the presence of ZDV<sup>9,21</sup>, other nucleoside analogues<sup>22</sup>, and protease inhibitors<sup>23</sup>; however, these variants are often less “fit” to replicate *in vitro*. It is unclear to what degree a reduction in “fitness” affects HIV transmissibility.

A single retrospective study demonstrated the expected benefit of ART on HIV transmission. Musicco *et al* observed a 50% reduction in expected transmission events in more than 400 HIV serodiscordant couples when a small number of HIV-infected participants used ZDV<sup>6</sup>. Even greater reductions would be expected with ART designed to maximally suppress plasma HIV-1 RNA and concentrate in genital secretions.

In a model generated by Gray *et al* from the Uganda transmission study, ART would be predicted to reduce incident HIV by 80%<sup>24</sup>. Subsequent models by Blower<sup>25</sup> and Law<sup>26</sup> also have concluded that ART could decrease HIV transmission. However, these models question the overall effectiveness of ART for HIV prevention based on the assumption that increases in high-risk behavior and evolution of viral resistance might offset the benefit of decreased viral burden.

### **1.3.2 Limitations to Antiretroviral Therapy as an Intervention**

While it seems likely that ART might reduce the risk of sexual transmission of HIV, this hypothesis requires definitive proof with special attention to the many criticisms of this method of prevention:

- deductive reasoning allows the conclusion that ART prevents the sexual transmission of HIV; therefore, no further proof of this approach is required;
- conversely, studies in humans demonstrate persistent excretion of HIV DNA (or even positive culture) in the genital secretions of some participants on ART<sup>27</sup>;
- ART could promote risky sexual behavior (disinhibition)<sup>28-29</sup>;
- success of the approach requires a high and often unrealistic degree of patient adherence; development of antiretroviral resistance is inevitable, and could compromise therapy of the partner as well as the community<sup>5</sup>;
- the available regimens are too complex or expensive to be employed to prevent transmission; and

- since HIV transmission may be greatest during primary infection, intervention directed at chronically infected patients will have little public health benefit.

As indicated in Section 1.1, the effects of ART on prevention (both positive and negative) are inevitable whether they are understood or not. Second, the limitations cited are based on assumptions that may not be entirely correct. Third, and perhaps most important, by understanding the benefits and limitations of this approach, we will be able to modify therapy and develop new drugs that might have the desired impact on HIV transmission.

To this end, this study has been designed to determine the ability of ART regimens plus HIV primary care to prevent the sexual transmission of HIV over several years. HIV-infected individuals with CD4+ cell counts of 300 - 500 cells/mm<sup>3</sup> and their HIV-uninfected sexual partners will be enrolled to compare the effects of two treatment strategies: (1) ART upon enrollment plus HIV primary care (primary care defined in Section 1.3.4), and (2) HIV primary care, without the initiation of ART until the participant has two consecutive measurements of a CD4+ cell count  $\leq$  200 cells/mm<sup>3</sup>, or develops an AIDS-defining illness. As further developed below, the current understanding of the costs and benefits of ART allows for ethical comparison of these two treatment strategies among persons with CD4+ cell counts in this range. Since short-term interruption of transmission of HIV could be offset by delayed transmission of resistant variants, assessing rates of HIV transmission over a five year time period will provide data on the long-term effectiveness and public health utility of ART in preventing the sexual transmission of HIV.

### **1.3.3 Other Applications of Antiretroviral Therapy for Prevention**

ART might also be used as pre-exposure (PREP) or Post Exposure (iPEP and nPEP) prophylaxis to prevent HIV acquisition. This subject has recently been reviewed<sup>73</sup>. Three trials to determine the efficacy of PREP are planned. USPH Guidelines regarding PEP for needlestick or occupational exposure to HIV (iPEP) are available<sup>74, 75</sup>, and updated guidelines for nPEP will be released in 2004 (see MMWR 1997, 1998 for current recommendations and concerns<sup>74, 76</sup>). Briefly, experiments with primates suggest that ART provided within 48-72 hours of exposure to HIV and continued for a full 28 days will provide at least partial protection from HIV. However, such use of ART is expensive, and adherence to the regimen is difficult because of toxicity. The benefit of nPEP in humans has not been established. The cost-benefit ratio is very unfavorable because of the limited efficiency of transmission of HIV after any single sexual exposure<sup>74</sup>. Accordingly, while nPEP should be available for special circumstances (eg. after sexual assault), it is not recognized as a credible public health HIV prevention strategy, and would not be recommended for routine usage in HIV discordant couples in a steady relationship.

### 1.3.4 Antiretroviral Therapy Considerations

It seems inevitable that ART will become available on a global basis, regardless of its current cost and infrastructure limitations. Recent World Health Organization (WHO)/UNAIDS Guidance Modules provide guidelines for the use of ART in resource poor settings, and the initiation and changes of regimens proposed in this study are consistent with these guidelines<sup>30</sup>. In addition, the successful introduction of these agents in UNAIDS pilot programs in several developing countries<sup>4-5</sup> are especially relevant and instructive to this study.

This study plans to use U.S. FDA-approved ART drugs that are believed to provide maximal viral suppression in order to treat the index case and potentially minimize transmission of HIV from the index case to the partner. The drugs used in this trial must also address and balance concerns related to ease of use, pill burden, tolerability, toxicity, drug interactions, and penetration into genital compartments.

#### 1.3.4.1 Antiretroviral Drugs

The ART drugs that are available now for use in the run-in period and full study are Combivir<sup>®</sup> [3TC/ZDV], ATV, EFV, NVP, TDF, 3TC, ddI-EC, and d4T. The study team hopes to obtain other drugs for use during the full study.

The following provides background safety and efficacy data for the drugs listed above:

#### **Lamivudine/Zidovudine Combination (Combivir<sup>®</sup> [3TC/ZDV])**

A combination tablet of ZDV 300 mg and 3TC 150 mg is approved for marketing by the United States (U.S.) Food and Drug Administration (FDA) and the European Agency of the Evaluation of Medicinal Products (EMA), at a dosage regimen of one tablet twice daily. The 3TC/ZDV-combination tablet has been shown in a clinical study to be bioequivalent to the two individual antiretroviral drugs<sup>31</sup>.

A randomized, open-label, parallel-group, multicenter study (n = 223) conducted to establish the clinical equivalence of a regimen using the 3TC/ZDV combination tablet given BID plus a PI versus a regimen containing ZDV TID plus 3TC BID plus a PI, has been completed<sup>32</sup>. Prior to entry into this study, each subject must have been receiving a three-drug regimen consisting of ZDV 200 mg TID (or ZDV 300 mg BID) plus 3TC 150 mg BID plus a PI for at least 10 weeks, and have a plasma HIV-1 RNA <10,000 copies/mL and a CD4+ lymphocyte count of >300 cells/mm<sup>3</sup>. At enrollment, subjects were randomized to either continue their current three-drug regimen or switch to 3TC/ZDV BID, while continuing their current PI. Results from this study indicate that the 3TC/ZDV combination tablet given twice daily with a PI is at least as effective as the three-drug regimen of ZDV 200 mg TID plus 3TC 150 mg BID plus a PI in suppressing plasma HIV-1 RNA to <400 copies/mL at 16 weeks (80% and 74% of subjects in the combination tablet and standard groups, respectively). No new or serious adverse events attributed to the 3TC/ZDV-combination tablet were observed. Results from a self-reported adherence questionnaire (Pain Medications Attitude Questionnaire [PMAQ] version 1.0) used in this study indicated that subjects in the combination tablet group

were less likely to miss doses of nucleoside analogue medication at weeks 8 ( $p = 0.007$ ) and 16 ( $p = 0.046$ ).

Refer to the **Combivir<sup>®</sup> [3TC/ZDV]** package insert for more information.

### **Zidovudine (Retrovir<sup>®</sup>, ZDV)**

ZDV is a nucleoside analogue reverse transcriptase inhibitor (NRTI) that has been extensively studied and shown to be active in the treatment of subjects with HIV infection at all stages of disease. In subjects with advanced HIV disease, ZDV reduces the risk of disease progression and death. This latter observation provides a strong rationale for including this drug in combination regimens.

ZDV is generally well tolerated, particularly in persons with CD4+ > 200 cells/mm<sup>3</sup>. The major side effects include headache, fatigue, malaise, nausea, anemia, and neutropenia. Long-term ZDV therapy is associated with myopathy and rare cases of steatosis with hepatic failure and death.

Refer to the **Retrovir<sup>®</sup>** package insert for more information.

### **Lamivudine (Epivir<sup>®</sup>, 3TC)**

3TC is a potent nucleoside that is widely used in the management of HIV-1-infected patients. Although 3TC is an effective NRTI, virus with a resistance mutation at codon 184 rapidly emerges within 2 weeks of monotherapy and is also seen with dual nucleoside regimens.

3TC is one of the best-tolerated nucleoside analogues. Adverse events occur in less than 5% of patients. Toxicities include headache, nausea and vomiting, malaise, fatigue and sleeplessness, anorexia, dizziness, rash, depression, anemia, neutropenia, and hyperamylasemia.

Persons who are co-infected with hepatitis B may experience increased values in liver function tests and exacerbation of hepatitis symptoms when 3TC is stopped. Usually these symptoms are self-limiting; however, death has been reported. The causal relationship to 3TC discontinuation is unknown. Patients should be followed closely for the first several months following 3TC discontinuation.

Refer to the package insert for **Epivir<sup>®</sup>** for more information.

### **Efavirenz (Sustiva<sup>®</sup>/ Stocrin<sup>®</sup>, EFV)**

EFV is a once daily NNRTI that has been shown to be effective in the treatment of HIV disease.<sup>33</sup> The most notable side effects associated with EFV are central nervous system (CNS) symptoms and rash. Fifty-three percent of those receiving EFV reported CNS symptoms. These symptoms included, but were not limited to, dizziness, impaired concentration, somnolence, abnormal dreams, and insomnia. Symptoms usually begin during the first or second day of therapy and generally resolve after the first 2 to 4 weeks

of therapy. Symptoms may also be less noticeable if EFV is taken at bedtime. Potential for additive symptoms may occur if used concomitantly with alcohol or psychoactive drugs. Nervous system symptoms were severe in 2.0% of patients receiving EFV 600 mg QD and in 1.3% of patients receiving control regimens; and, 2.1% of EFV-treated patients discontinued therapy because of nervous system symptoms.

In multi-study comparisons of EFV-treated versus (vs.) controls, severe acute depression (1.6% vs. 0.6%) and suicidal ideation (0.6% vs. 0.3%) were reported. Patients with a history of psychiatric disorders are at greater risk. There has been occasional post marketing reports of delusions and aberrant behavior, predominantly in those with a history of mental illness or substance abuse. Persons who experience psychiatric symptoms should contact their doctor immediately to assess the possibility that the symptoms may be related to EFV.

Among approximately 2200 treated subjects in all studies and expanded access programs, the incidence of Grade 4 rash (e.g., erythema multiforme and Stevens-Johnson syndrome) was 0.14%. The median time to onset of rash in adults was 11 days, and the median duration was 16 days. EFV should be discontinued in persons developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

Other side effects associated with EFV include upset stomach, diarrhea, anorexia, headache, tiredness, pancreatitis, elevated cholesterol (including HDL), elevated triglycerides, and elevated transaminases.

Refer to the EFV (**Stocrin<sup>®</sup>/Sustiva<sup>®</sup>**) package insert and the Investigator Brochure (if not registered in country) for more information.

### **Atazanavir (Reyataz<sup>™</sup>, ATV)**

ATV is one of a new class of azapeptide PIs for HIV that differs from the existing peptidomimetic PIs by its C-2 symmetric chemical structure. ATV has antiviral activity that has been demonstrated in separate studies to be comparable to nelfinavir and EFV.

Phase II and III studies have demonstrated good overall safety and tolerability of ATV. The most frequently seen AEs in the phase II and III studies are infection (46%), nausea (28%), headache (24%), abdominal pain (19%), diarrhea (19%), rash (19%), peripheral neurologic symptoms (15%), vomiting (13%), flu syndrome (12%), increased cough (12%), jaundice (12%), and fever (10%).

The most common abnormality observed in clinical studies of ATV is an isolated increase in unconjugated (or indirect) bilirubin, the mechanism for which has been shown to be inhibition of the enzyme UDP glucuronosyl transferase. For subjects who received the 400-mg dose, elevations in serum levels of unconjugated bilirubin were common. While the median increase above baseline for total bilirubin was only 0.6 mg/dL, approximately 40% of subjects had a total bilirubin >2.5 times the upper limit of normal



(ULN). However, only 5% of subjects had a total bilirubin >5 times the ULN. Up to 10% of subjects demonstrated clinical signs of hyperbilirubinemia (scleral icterus or jaundice). Rates of hyperbilirubinemia as well as absolute levels were higher in subjects with a genetic phenotype similar to that observed for subjects with Gilbert's syndrome

Results from embryo-fetal development and genetic toxicology studies show that ATV is not teratogenic in rats or rabbits and does not present a genotoxic risk to humans. To date, there are no adequate or well-controlled studies in pregnant women.

Refer to the **ATZ (Reyataz™)** package insert and the Investigator Brochure (if not registered in country) for more information.

### **Nevirapine (Viramune® , NVP)**

NVP is an NNRTI with activity against HIV-1. The most frequently reported adverse events related to NVP therapy are rash, fever, nausea, headache, and abnormal liver function tests (LFTs). The safety of NVP has been assessed in more than 2800 patients in clinical trials. The experience from clinical trials and clinical practice has shown that the most serious adverse reactions are clinical hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions (HSRs) characterized by rash, constitutional findings, and organ dysfunction.

#### **Hepatic toxicity**

In clinical trials, the risk of hepatitis is approximately 1%. Increased AST or ALT levels before the start of ART and/or history of hepatitis B or C infection are associated with a greater risk of hepatic adverse events. Cases of hepatitis, severe and life-threatening hepatotoxicity, and fatal fulminant hepatitis have been reported in patients treated with NVP. These events have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, prolonged PTT, or eosinophilia. Symptoms of clinical hepatitis include fatigue, malaise, anorexia, nausea, jaundice, acholic stools, liver tenderness, or hepatomegaly. NVP-related hepatotoxicity can occur in the setting of normal LFTs or in the presence of a possible alternative diagnosis. Hepatic dysfunction may be isolated or associated with signs of hypersensitivity including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, or renal dysfunction.

The risk of hepatotoxicity in women with CD4+ counts >250 cells/mm<sup>3</sup>, including pregnant women receiving chronic treatment for HIV infection, is considerably higher (12 fold) compared to women with CD4 < 250 cells/mm<sup>3</sup> (11% vs. 0.9%). Some of these events have been fatal. Men with higher CD4 counts (>400 cells/mL) also have a higher risk of hepatotoxicity than men with lower CD4 counts (6.3% vs. 2.3%). This subset of patients was identified by analyses of CD4+ cell count at the time of initiation of NVP treatment. The greatest risk of severe and potentially fatal hepatic events (often associated with rash) occurs in the first 6 weeks of NVP treatment. However, the risk continues after this time and patients should be monitored closely for the first 18 weeks

of NVP treatment. In some cases hepatic injury progresses despite discontinuation of treatment.

Intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of NVP treatment to detect potentially life-threatening hepatic events and skin reactions. The greatest risk of severe rash or hepatic events associated with rash occurs in the first 6 weeks of therapy. However, the risk of any hepatic event (with or without rash) continues past this period, and monitoring should continue at frequent intervals. NVP should not be restarted following severe hepatic, skin, or HSR. In addition, the 14-day lead-in period with NVP 200 mg daily dosing must be strictly followed. LFT monitoring is required after initiation of NVP at weeks 2, 4, 6, and then monthly for the first 20 weeks on NVP treatment. All patients developing a rash, at any time during NVP treatment, but particularly during the first 18 weeks, should have liver function tests performed at that time. After the initial 18 week period, frequent clinical and laboratory monitoring should continue throughout NVP treatment.

### Rash

The most common clinical toxicity of NVP is rash (16% of patients on combination regimens in phase II/III controlled studies). Severe and life-threatening skin reactions, including fatal cases, have occurred in subjects treated with NVP. These have included cases of SJS, TEN, and HSR characterized by rash, constitutional findings, and organ dysfunction.

Severe rashes occur most frequently within the first 28 days of treatment; 25% of the patients with severe rashes required hospitalization and one patient required surgical intervention. Approximately 7% of patients discontinue NVP due to rash.

In one trial, concomitant use of prednisone to prevent NVP-associated rash increased the incidence and severity of rash during the first 6 weeks of NVP therapy. The use of prednisone to prevent NVP-associated rash is not recommended. Subjects should be advised to promptly notify their health care provider if they develop any rash or signs and symptoms of a HSR. Subjects who experience rash during the first 2 weeks of treatment should not have the dose of NVP increased until the rash has resolved.

Patients developing signs or symptoms severe skin reactions, or HSRs must discontinue NVP immediately and must not be re-challenged.

### EFV Substitution with NVP

The strategy for substituting NVP for treatment-limiting toxicity related to EFV has not been well studied. Given the known toxicity profiles of the two drugs, it would seem reasonable to try substitution of NVP for treatment-limiting CNS toxicity (e.g., dizziness, somnolence, bad dreams, and confusion) ascribed to EFV. Although the molecular structures of NVP and EFV are not related, substitution for NNRTI class-specific toxicities (e.g., increased AST/ALT, rash) is less supported, although some anecdotal information is available<sup>34</sup>.

Clarke et al. reported eight subjects who experienced NVP-related toxicity and subsequently changed to an EFV-containing regimen. Of these eight, five continued their EFV regimen without recurrence of side effects. Podzamczar et al. reported two subjects who experienced severe HSRs with NVP, then changed to an EFV-containing regimen (with a corticosteroid taper) with good tolerance. Soriano et al. reported findings from their subjects participating in an EFV expanded access program: of eight subjects with a history of NVP-associated rash, only one developed a rash after beginning EFV. Although the temporal sequence was NVP to EFV in each report, the incidence of cross-toxicity between the two drugs is unknown.

Refer to the **Viramune®** package insert, and in the management of rash and hepatic events guidelines available at the Viramune website (<http://www.viramune.com>) for more information.

### **Tenofovir Disoproxil Fumarate (Viread®, TDF)**

TDF (formerly known as PMPA prodrug or GS-4331-05) is used for the treatment of HIV-1 infection in combination with other agents. TDF is an orally bioavailable acyclic nucleotide analogue with activity in vitro against retroviruses, including HIV-1 and HIV-2 and hepadnaviruses. Although TDF is a nucleotide analogue, it has the same mechanism of action and resistance pattern as NRTIs.

### **Safety Profile**

Assessment of AEs is based on two studies (902 and 907) in which 653 treatment-experienced patients received double-blind treatment with TDF 300 mg (n=443) or placebo (n=210) for 24 weeks followed by extended treatment with TDF. The most common AEs in patients receiving TDF with other ARVs in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting, and flatulence. Less than 1% of patients discontinued participation in the clinical studies because of gastrointestinal AEs. Laboratory abnormalities observed in these studies occurred with similar frequency in the TDF and placebo-treated groups.

### **Renal Impairment**

Evidence of renal toxicity was noted in four animal species at exposures (based on AUCs) 2 to 20 times higher than those observed in humans.

In study 903, involving 592 treatment-naïve patients treated for up to 96 weeks, changes in renal function were observed with similar frequency in the TDF-containing arm as compared with the d4T-containing arm. In studies 902 and 907, no patient permanently discontinued the studies for serum creatinine elevation or hypophosphatemia. Serum creatinine elevations and mild hypophosphatemia were infrequent, generally transient, and resolved with continued TDF treatment.

Serious renal adverse events were reported in 0.3% of patients (N = 8870) treated with TDF in the Viread global expanded access program. Renal events reported in clinical

practice include increased serum creatinine, renal insufficiency, renal failure, acute renal failure, proximal tubulopathy, proteinuria, acute tubular necrosis, and Fanconi syndrome.

TDF should be avoided with concurrent or recent use of a nephrotoxic agent. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in renal function and serum phosphorus.

### Hepatitis B Virus (HBV)

Exacerbations of HBV have been reported in patients after discontinuation of TDF. Patients, who are coinfectd with HBV, may have increased values on liver function tests and exacerbation of hepatitis symptoms when TDF is stopped. Usually these symptoms are self-limiting; however, serious complications have been reported. The causal relationship to TDF discontinuation is unknown. Patients coinfectd with hepatitis B (HBV) and HIV should be closely monitored with both clinical and laboratory for several months after stopping TDF treatment.

### Bone Toxicity

GS-01-926. Because TDF administered in toxicology studies to rats, dogs, and monkeys at exposures (areas under the curve [AUCs]) between 6- and 12-fold higher than those achieved in humans caused bone toxicity, study 926 included a number of assessments for bone-related toxicity in pediatric patients. All patients enrolled had baseline lumbar spine densitometry by dual-energy x-ray absorptiometry (DEXA) to measure bone mineral density (BMD). There was a high prevalence of osteopenia in these patients at baseline. Two patients were shown to have confirmed decreases in BMD of >6% at week 24 relative to baseline, with no consistent trends in bone-related laboratory changes or TDF blood levels found.

In study 903 through 48 weeks, decreases from baseline BMD were seen at the lumbar spine and hip in both arms of the study. The proportion of patients who met a protocol-defined value of BMD loss (5% decrease in spine or 7% decrease in hip) was higher in the TDF group than in the d4T group. In addition, there were significant increases in levels of four laboratory parameters of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the TDF group compared with the d4T group, suggesting increased bone turnover. Serum parathyroid hormone levels were also higher in the TDF group. There was one bone fracture reported in the TDF group compared with four in the d4T group; no pathologic fractures were identified over 48 weeks of study treatment. The clinical significance of changes in the BMD and the biochemical markers is unknown, and follow-up is continuing to assess long-term impact.

### Teratogenicity/Developmental Toxicity

Chronic administration of TDF to fetal and immature animals of multiple species at doses higher than used in humans has resulted in bone abnormalities; these effects were dose-, exposure-, age-, and species-specific. Abnormalities ranged from minimal decrease in

bone mineral density and content to severe, pathologic osteomalacia. Evidence of nephrotoxicity has been observed. Studies in rats have demonstrated that TDF is secreted in milk. Subcutaneous administration of TDF to pregnant cynomolgus monkeys resulted in a fetal/maternal concentration of 60%, demonstrating that TDF does cross the placenta (Van Rompay KKA, et al. 1998). There are no data on whether TDF crosses the placenta or is excreted in breast milk in humans. No studies of TDF have been conducted in pregnant women or neonates.

Refer to the **Viread®** package insert and the Investigator Brochure (if not registered in country) for further information.

#### **Didanosine (Videx®, ddI-EC)**

ddI-EC is an enteric-coated (EC) capsule of ddI. The capsule does not require the buffering used in the tablet formulation. The same restrictions on food intake apply to the EC capsules as to the tablets. The most common toxicities associated with ddI are gastrointestinal upset, peripheral neuropathy, and pancreatitis.

#### **TDF - ddI-EC Pharmacokinetic Interaction**

Once daily ddI-EC 400 mg (all individuals  $\geq 60$  kg) given 2 hours before TDF 300 mg with a light meal, resulted in an approximately 46% increase in ddI exposure relative to the administration of ddI-EC alone in the fasted state, as measured by AUC ddI concentration. Coadministration of ddI-EC and TDF 300 mg with a light meal resulted in an approximate 60% increase in ddI exposure relative to the administration of ddI-EC alone in the fasted state. Coadministration of ddI EC capsules had no effect on the AUC of TDF.

Refer to the **Videx-EC®** package insert for further information.

#### **Stavudine (Zerit®, d4T) Immediate Release Formulation**

d4T is an approved nucleoside analogue that has been approved for use in combination with other ARV drugs for the treatment of HIV-infected individuals<sup>77-81</sup>.

The most common toxicity associated with d4T is peripheral neuropathy and, much less commonly, hepatic damage, pancreatitis, and lactic acidosis (which may have an increased risk when it is used with ddI in pregnancy.)

When substitution of d4T for ZDV was permitted in ACTG 320, no difference in outcome was seen with use of either NRTI combination<sup>82</sup>.

Refer to the **Zerit®** package insert for further information.

### **1.3.4.2 Initiation of Antiretroviral Therapy**

Another important issue is the timing of ART initiation. Currently there is considerable scientific debate as to the precise time at which therapy should be initiated. The United

States Public Health Service (USPHS) guidelines for the use of ART in adults recommend that therapy be initiated when CD4+ cell count reaches 350 cells/mm<sup>3</sup> or lower<sup>30</sup>. The UNAIDS guidelines recommend initiation of therapy at a CD4+ cell count of 200 cells/mm<sup>3</sup><sup>35</sup>. The National Institute of Allergy and Infectious Diseases (NIAID) is also supporting a trial designed to compare early versus delayed ART, entitled “A Large Simple Trial Comparing Two Strategies for Management of Antiretroviral Therapy” (SMART study); however, the results from that study will not be available for several years. HPTN 052 will randomly assign participants infected with HIV with CD4+ cell counts of 300 to 500 cells/mm<sup>3</sup> to receive ART and HIV primary care either upon enrollment in the study or when the participant has a CD4+ cell count of 200 cell/mm<sup>3</sup> or experiences an AIDS-defining illness. Given the current state of knowledge, both treatment strategies offer potential benefit to study participants and the withholding of therapy among some participants with a CD4+ cell count above 200 cells/mm<sup>3</sup> will not disserve this group.

#### 1.3.4.3 HIV-1 Drug Resistance

Regardless of use of multi-drug ART cocktails, the mutability of HIV ultimately leads to selection of variants with some degree of resistance, and such variants may permit clinically important viral rebound. Because some resistance mutations also confer cross-resistance to other antiretroviral drugs in the same class, emergence of drug resistance may severely limit a patient’s future treatment options. For these reasons, HIV genotyping is now recommended in the U.S. to help guide ART <http://www.aidsinfo.nih.gov/><sup>30</sup>. However, for all study sites except one in the U.S., the current plan is to perform resistance testing retrospectively, as the resources are not available to perform resistance testing for patient management at many of the sites, nor is it clear that this technology could be used cost-effectively in these settings in the future. Therefore, the patient management algorithm for ART depends on prospective evaluation of HIV viral load and other laboratory markers, clinical evaluation, and adherence behavior.

In addition, interpretation of resistance testing in a population is complex because: 1) not all genotypic resistance is associated with phenotypic resistance; 2) the magnitude of resistance observed in different countries where ART is used is changing rapidly and (in some cases) in unexplained ways 3) resistant variants may on occasion be less fit for transmission or less pathogenic; 4) continued ART in the face of resistance may have a salutary effect; 5) resistant variants cannot be easily detected in the absence of selective pressure, and their re-emergence at a later time is only now being studied; and 6) resistance mutations have been characterized predominantly in subtype B and there is little information about how to interpret resistance mutations in other subtypes.

Considering all these issues, a plan for resistance testing in HPTN 052 has been developed (excluding the one U.S. sites). Samples will be collected from a subset of study subjects receiving ART for retrospective analysis of ART resistance. Three regional laboratories (located in India, South Africa, and Brazil) will perform resistance testing for HPTN 052. Selected samples will be tested at the HPTN Central Laboratory for quality control. Some specialized testing (e.g., fitness or phenotypic resistance testing) may be performed in commercial laboratories. These data will **not** be used for

routine management of patients, but will be conveyed to the investigators as trends. However, all viruses transmitted to partners will be studied for evidence of resistance.

While resistance testing in HPTN 052 is not designed to guide patient management (except at U.S. sites where it is the standard of care), it is expected that the results will offer critical information about inception of resistance in the countries involved, the epidemic spread of resistance, and the durability of resistance in these settings. It is recognized that the use of resistance testing for patient management might be introduced at some point over the course of this 7-year study as infrastructure and technology improves at the study sites. Should this occur, any changes in monitoring and use of data will be brought to the attention of the sponsor, IRBs/ECs and the NIAID Vaccine and Prevention Data and Safety Monitoring Board (DSMB). Finally, it must be emphasized that development of resistance to ART and transmission of resistant HIV variants are an inevitable consequence of the biology of HIV and therapy, and not specific to HPTN 052. HPTN 052 does, however, provide an opportunity to measure these important events prospectively, so as to better inform public health policy.

It is anticipated that a variety of regional factors may influence the effectiveness of ART regimens and the emergence of resistant strains. The effectiveness of treatment programs may be influenced by cultural, behavioral, and logistical factors that vary from one region to another. There are also likely to be regional differences in the prevalence of other infectious diseases (*e.g.* TB, hepatitis) and other clinical illnesses, which could influence immunologic and other factors important in viral containment. Such co-morbidities are also likely to be associated with regional differences in use of other medications, which may in turn influence the activity and pharmacokinetics of antiretroviral drugs. Regional differences in host genetics may also influence response to antiretroviral regimens, and regional differences in HIV-1 strains may not only influence the susceptibility of the virus to antiretroviral drugs, but also the emergence of resistant strains under treatment.

Finally, in developing countries, regimens used for perinatal prophylaxis are likely to include single drug regimens (*e.g.* ZDV monotherapy or single dose NVP), increasing the probability that resistance may result from the use of prophylaxis. Any of these factors could potentially influence outcome and emergence of drug resistance in HPTN 052. Analysis in HPTN 052 will allow a comparison of resistance rates across the study sites for each treatment regimen. Data collected in the trial may also help identify other regional variables that influence resistance rates.

Analysis of drug resistance in HPTN 052 will include an analysis of the HIV-1 subtypes in this region. Major (M) group HIV-1 viruses can be categorized into nine pure subtypes (A, B, C, D, F, G, H, J, K), six circulating recombinant forms, and incidental viral variants<sup>36-37</sup>. Different subtypes predominate in different geographical regions. To date, almost all studies of HIV drug resistance have been performed for subtype B, the most common subtype in the U.S. In contrast, there is remarkably little information on drug resistance in other subtypes. Research on drug resistance in cohorts infected with non-subtype B HIV-1 is becoming increasingly important for two reasons: (1) the

prevalence of non-subtype B is increasing in the U.S. and other regions where antiretroviral drugs are widely used, and (2) the availability and use of antiretroviral drugs is growing throughout the world, where most infections are caused by non-B HIV-1. In HPTN 052, most HIV-1 infections are expected to be caused by non-B subtypes, with different subtype distributions at each site (Table 1).

**Table 1:** Predominant subtypes found in countries with HPTN 052 enrollment sites.

Country	Predominant Subtypes (approx. %)	References
Brazil	B (80%), F (14%), C (3%)	[39]
		[40]
India	C (80-95%), B (2-10%), A (2%)	[41]
		[42]
Malawi	C (>90%)	[43]
Thailand	CRF01_AE (80-95%), B (5-20%)	[44]
		[45]
		[46]
Zimbabwe	C (70%), B (12%), A (12%), D (7%)	[47]
		[48]

Although data are limited, some studies suggest that the natural susceptibility of HIV-1 to antiretroviral drugs may be influenced by subtype<sup>48-49</sup>, and polymorphisms associated with drug resistance are frequently detected in antiretroviral drug naive individuals with non-subtype B infection<sup>50</sup>.

In the Ugandan HIVNET 012 trial, the rate of NVP resistance following single dose NVP prophylaxis was different for women with subtype A vs. D HIV-1<sup>51</sup>. This suggests that the rates of resistance emerging during antiretroviral drug exposure may vary from region to region, depending on which subtypes are prevalent. Recent studies have shown that HIV-1 subtype may influence the pattern of resistance mutations that emerge after exposure to antiretroviral drugs<sup>52-53</sup>. Subtype-specific differences in protease and RT sequences may influence the rate at which a specific mutation emerges<sup>54</sup>, and the type of amino acid selected at a given position under drug pressure<sup>55-56</sup>. Differences in sequences of non-subtype B viruses may also lead to emergence of novel subtype-specific drug resistance mutations at positions not associated with drug resistance in subtype B<sup>57</sup>. HIV-1 subtype may also affect viral fitness, in the presence or absence of drug resistance mutations. Such differences could in turn influence the dynamics of emergence drug resistance following antiretroviral drug exposure.

It is not known whether HIV-1 subtype will influence treatment response in HPTN 052. A retrospective study comparing 50 patients with subtype B and 50 patients with non-B subtypes did not find a difference in virologic responses to highly active antiretroviral therapy (HAART)<sup>58</sup>. However, that study did not compare the response among patients with different non-B subtypes. In another study, 79 drug naive African patients with



different non-B subtypes had a similar response to HAART<sup>59</sup>. However, the number of patients in that study with each subtype was small. Furthermore, in both studies, different antiretroviral regimens were used to treat individual patients; this may have made it difficult to detect a subtype-based difference in response to treatment.

Methods used for HIV-1 genotyping in HPTN 052 will allow determination of the HIV-1 subtype (based on *pol* region sequences). This will allow exploration of the relationship between subtype, treatment response and drug resistance. Samples will also be stored to examine potentially complex relationships between HIV-1 subtype, phenotypic drug susceptibility (in the presence and absence of known drug resistance mutations), viral fitness, and host genetics.

The issue of ART for prophylaxis in pregnancy has been considered for this study and it has been determined that women who have received either single dose NVP or ZDV monotherapy for perinatal prophylaxis are eligible for enrollment. While this study focuses on implementation of ART regimens in developing countries, it is recognized that implementation of effective regimens for prevention of HIV-1 mother-to-child transmission in these countries is also extremely important. Cost and other factors currently limit availability of highly active multi-drug regimens for perinatal prophylaxis in many developing countries. However, less expensive, simpler regimens are being implemented in resource-poor countries throughout the world. It is recognized that resistance to ZDV and NVP can emerge when these drugs are used for perinatal prophylaxis. However, it is not known whether emergence of resistance in this setting will compromise subsequent treatment of HIV- infection with a multi-drug regimen. As described below, resistance is relatively uncommon following short courses of ZDV monotherapy. While NVP resistance is frequently seen after single dose NVP prophylaxis, resistance mutations fade from detection in plasma after delivery. It is not known whether this brief exposure to NVP is sufficient to establish resistant variants (*e.g.* in latent reservoirs or as minor variants in plasma) at sufficient levels to compromise subsequent treatment with an NNRTI-containing regimen. If a sufficient number of women who have received these regimens are enrolled in HPTN 052, it will allow for examination as to whether prior perinatal prophylaxis limits the efficacy of treatment regimens in HPTN 052. Resistance studies in HPTN 052 will also determine the rate of emergence of ZDV and NNRTI resistance following treatment with each of the HPTN 052 regimens. This information will help evaluate the potential impact of the HPTN 052 regimens on the efficacy of ZDV and NVP prophylaxis in future pregnancies. Additional information on emergence of drug resistance following ZDV monotherapy and single dose NVP perinatal prophylaxis is provided below.

### **Drug resistance following ZDV prophylaxis**

ACTG 076 was the first clinical trial to demonstrate a reduction in the rate of HIV-1 mother-to-child transmission with antiretroviral drug prophylaxis<sup>60</sup>. In that trial, women received ZDV or a placebo from 34 weeks of gestation to delivery, in addition to intrapartum ZDV. Some women had also received ZDV prior to pregnancy. Prior experience with longer regimens of ZDV monotherapy for treatment of HIV-1

infection suggested that the rate of resistance would be low in the first few months of drug exposure<sup>61</sup>.

Resistance studies performed on a subset of women in ACTG 076 detected only 1 woman with selection of the K70R mutation at delivery, and none with T215Y/F<sup>62</sup>; however, that study did not analyze other ZDV resistance mutations. Analysis of resistance in women who received ZDV during pregnancy in the Swiss Collaborative HIV and Pregnancy Study<sup>63</sup> and the Women and Infants Transmission Study (WITS)<sup>64</sup> found higher rates of ZDV resistance. Shorter regimens of ZDV monotherapy have also been introduced for use in developing countries. In one study from Cote d'Ivoire, where ZDV was started at 36 weeks in ZDV naive women, no development of ZDV resistance was detected in 20 women analyzed<sup>65</sup>. A number of other studies have examined ZDV following ZDV perinatal prophylaxis. Rates of resistance vary from study to study, and are likely influenced by the duration of ZDV exposure, the assay(s) used for resistance testing, the timing of testing, and other factors.

#### **Drug resistance following NVP prophylaxis**

The HIVNET 012 trial in Uganda demonstrated that a regimen of single dose NVP was superior to a short course of ZDV for prevention of HIV-1 vertical transmission<sup>66</sup>. In HIVNET 012, pregnant women received a single dose of NVP at the onset of labor. NVP resistance mutations were detected in 21 of 111 (19%) of women 6-8 weeks after delivery<sup>51</sup>. Those mutations faded from detection in all evaluable women by 12-24 months. The most common NVP resistance mutation detected was K103N, which is associated with cross-resistance to all NNRTIs. The long-term clinical impact of these mutations are unclear. Emergence of NVP resistance was associated with higher baseline viral loads and lower baseline CD4 cell counts. Furthermore, the rate of NVP resistance was higher in women with subtype D than subtype A, suggesting that resistance rates may vary from one geographical region to another, depending on which subtypes are prevalent<sup>67</sup>. The rate of NVP resistance was also examined in HIVNET 023, where Zimbabwean women received the same single dose NVP regimen as in HIVNET 012. Most women in HIVNET 023 had subtype C infection, and the rate of resistance in those women was similar to that seen in Ugandan women with subtype D<sup>52</sup>.

The SAINT trial, which was conducted in South Africa, compared two maternal doses of nevirapine (the first dose given during labor, the second given 48 hours post-partum) with 7 days of ZDV/3TC. The use of the 2 dose maternal NVP regimen resulted in a 67% selection frequency of resistance mutations, which is three times greater than observed in HIVNET 012 (19%). The predominant NVP mutations found were K103N (62%) and Y181C (45%)<sup>68</sup>.

#### **1.3.4.4 Additional Substudies**

In addition to laboratory evaluations related to the primary and secondary endpoints in this study, it is anticipated that substudies may be proposed during the course of the main study to address a variety of immunologic, pharmacologic, virologic, and other questions related to HIV-1 and HIV-1 transmission.

Sub-study protocols may be developed that optimize the unique scientific opportunities within this study, as well as to facilitate consistency in assay methods utilized by the various related NIAID-sponsored networks. Table 2 outlines the types of samples to be collected and stored during the course of the study, along with a brief list of the types of assays that are likely to be required for sub-studies:

**Table 2:** Sample Storage and Assays for Potential Substudies

Sample	Assay
Plasma	Extended resistance studies ( <i>e.g.</i> analysis of regions other those routinely analyzed that may influence resistance to antiretroviral drugs), extended HIV subtyping, <i>etc.</i> , timing of emergence of resistance, analysis of minority variants, <i>etc.</i>
Serum	Additional serologic studies ( <i>e.g.</i> hepatitis C (HCV), hepatitis B (HBV) serology), neutralizing antibody, chemokine and cytokine assays, seroconversion for other diseases ( <i>e.g.</i> pneumococcus, syphilis, <i>etc.</i> ).
Whole Blood	Genomic characterization ( <i>e.g.</i> human leukocyte antigen (HLA) typing, co-receptor polymorphisms, genetic polymorphisms that may be related to drug transport, hypersusceptibility). Note: special consent will be required for genomic testing of study subjects.
PBMCs	HIV subtyping, T cell immunity ( <i>e.g.</i> ELISPOT, flow cytometry), tetramer assay, lymphoproliferation assay (LPA), microarray analysis for gene expression ( <i>e.g.</i> cytokines, chemokines, <i>etc.</i> ).

### 1.3.5 HIV Primary Care and Counseling Considerations

Currently, many HIV-infected people living in developing countries receive no care for their HIV infection, let alone access to affordable antiretroviral therapy. Based on several studies of morbidity and mortality in developing countries, standardized “HIV primary care” can be expected to benefit both arms of this study. In addition, HIV primary care can be expected to produce a modest reduction in plasma HIV-1 RNA, decrease progression to AIDS, reduce serious opportunistic infections, and reduce or eliminate death.

At non-US sites, the HIV primary care delivered in this study is derived from WHO/UNAIDS guidelines in combination with local standards of care at the study sites, and will include systematic attention to vitamin deficiency, STDs, tuberculosis, endemic infections (*e.g.* enteric parasites and malaria), expected opportunistic pathogens, and other AIDS-related conditions. For the US site, participants will receive care in line with local standards of care provided at the particular study site. All participants will receive prompt and effective symptomatic care as clinically indicated per local guidelines and locally developed study operating procedures (SOPs). The study team believes that it would be unethical to perform this study if such care were not provided.

In addition, an important component of this study is the individual and couples HIV counseling, which will be provided on an on-going basis throughout the entire study in accordance with standard study counseling methods. Participants will be counseled that consistent use of condoms is the only known way to potentially prevent sexual transmission of HIV, and condoms will be provided free of charge to all participants at each study visit. In addition, counseling will emphasize the unknown efficacy of ART in preventing HIV infection.

#### **1.4 Study Implementation Plan**

The ART drugs available for the run-in period of the study are Combivir<sup>®</sup> [3TC/ZDV], ATV, EFV, NVP, TDF, 3TC, ddI-EC, and d4T; available for the full study are Combivir<sup>®</sup> [3TC/ZDV], 3TC, NVP, and TDF. Before the full study can be initiated, at a minimum, another nucleoside (such as ddI), and a protease inhibitor (such as ATV or Kaletra<sup>®</sup> [lopinavir/ritonavir]) must be available for the length of the full study. The study team has not yet secured commitments for these types of drugs for the full study. Therefore, HPTN 052 will begin with a run-in period using the ART drugs currently available. While the run-in period is being conducted, it is planned to pursue commitments for the full study. If commitments are not obtained, the full study will not proceed, and the study will end.

The run-in period will follow the same study design and clinical and laboratory evaluations as the full study (refer to Section 2.0 and 5.0 respectively), but with limited enrollment and follow-up. Accordingly, up to 10 couples per site (number enrolled may vary across sites) will enroll over a 3 month period, and each couple will be followed until the last couple enrolled at the site completes their 6 month follow-up visit. Index cases randomized to receive ART drugs immediately (Arm 1) will receive a starting regimen of Combivir<sup>®</sup> [3TC/ZDV] and EFV or ATV. ATV, EFV, NVP, TDF, 3TC, ddI-EC, and d4T will be available for toxicity management or as drugs for a second-line regimen in the event of virologic failure. During the run-in period, study sites will accept responsibility for providing ART drugs beyond those currently available through the study now to those participants who clinically require them during or after the run-in period is completed, for a period of time deemed appropriate by the individual study sites. For couples enrolling into the run-in period, a separate informed consent that explains the components of the run-in period will be used.

The run-in period will also serve as a means of allowing the study sites an opportunity to optimize local study procedures before the full study proceeds. As such, for each study site participating in the run-in period, a study-conduct review will take place after the last couple enrolled has completed their 6-month follow-up visit. This review will be conducted in part by the HPTN Study Management Committee (HPTN SMC). The review will include evaluation of screening, enrollment, and retention data. It may also involve a general evaluation of other key operational components of the study such as adherence to clinical management and counseling procedures, data management procedures, and laboratory procedures, all in accordance with International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP). Follow-up of the couples enrolled in the run-in period will continue uninterrupted during the time the

run-in period is being evaluated. This provides for continuity of study operations at the study sites should the full study proceed.

## **2 STUDY OBJECTIVES AND STUDY DESIGN**

### **2.1 Primary Objectives**

The primary objective of the study is to compare the rates of HIV infection among partners of HIV-infected participants in the two arms below:

- (1) ART upon enrollment plus HIV primary care.
- (2) HIV primary care, without initiation of ART until the participant has two consecutive measurements of a CD4+ cell count  $\leq 200$  cells/mm<sup>3</sup>, or develops an AIDS-defining illness.

### **2.2 Secondary Objectives**

The secondary objectives of the study are to:

- Determine the long-term safety of two ART regimen strategies (ART immediately upon enrollment vs. ART when the participant has two consecutive measurements of a CD4+ cell count  $\leq 200$  cells/mm<sup>3</sup> or develops an AIDS-defining illness) for the treatment of HIV-1 infection.
- Characterize and compare the patterns and rates of antiretroviral drug resistance of two antiretroviral treatment strategies.
- Assess factors associated with adherence and compare the adherence rate of two antiretroviral treatment strategies.
- Evaluate the usefulness of measures of virologic and immunologic efficacy, and measures to detect antiretroviral drug resistance.
- Determine, characterize, and compare the rates of AIDS-defining illnesses, sexually transmitted diseases, opportunistic infections, and immune reconstitution syndromes, with regard to outcomes and survival as observed in different geographic settings and by treatment strategies.
- Determine and characterize the rates of antiretroviral drug-associated toxicities observed in different geographic settings and by treatment strategies.
- Evaluate the effectiveness of couples HIV counseling and characterize the patterns of sexual behavior in couples in both arms of the study.

The primary objective will be evaluated per the algorithm outlined in Appendix II. AIDS-defining illnesses are defined in Appendix III. The secondary objectives will be

evaluated through clinical procedures, laboratory evaluations, and behavioral assessments outlined in Section 5.0, and Appendix I A and B, Appendix III, Appendix IV, and AACTG's Appendix 60 – Diagnoses Appendix (which can be found in the Study Specific Procedures [SSP] Manual.)

## **2.3 Study Design**

The study is a Phase III, two-arm, multi-site, randomized, controlled trial to determine the effectiveness of two treatment strategies in preventing the sexual transmission of HIV in HIV serodiscordant couples. Only one person infected with HIV and their one HIV negative primary sexual partner, same or opposite sex, will be considered as a serodiscordant couple. The study will be implemented in two parts, a run-in period followed by the full study. Accrual of a maximum of 90 couples into the run-in period will require 3 months, and all couples at each site will be followed until the last couple enrolled completes their 6-month follow-up visit. Accrual of a maximum of 1660 couples into the full study will require approximately 18 months total, and all couples will be followed until the last couple enrolled completes their 60 month follow-up visit. Therefore, the total number of couples in the study is 1750 (3500 people), and the total length of the trial will be up to 87 months.

The HIV Prevention Trials Network (HPTN) sites participating in the run-in period and the full study include sites in Brazil, India, Malawi, Thailand, Zimbabwe, and the United States of America.

Once an HIV serodiscordant couple is determined to be eligible for the run-in period or full study, the index case will be randomized to one of two treatment arms:

**Arm 1:** ART upon enrollment plus HIV primary care.

**Arm 2:** HIV primary care without initiation of ART until the participant has two consecutive measurements of a CD4+ cell count  $\leq 200$  cells/mm<sup>3</sup>, or develops an AIDS-defining illness (defined in Appendix III).

The starting regimen available for the run-in period is Combivir<sup>®</sup> [3TC/ZDV] and EFV or ATV (choice of 3<sup>rd</sup> drug in the “triple combination” is at the discretion of the study clinician during the run-in period). Also available for the run-in period are ATV, EFV, NVP, TDF, 3TC, ddI-EC, and d4T for toxicity management or virologic failure.

The starting regimen for the full study will be determined when additional ART drugs become available, but will include Combivir<sup>®</sup> [3TC/ZDV]. In addition to Combivir<sup>®</sup> [3TC/ZDV], the full study has commitments for NVP, TDF, and 3TC.

Secondary or salvage regimens are not defined by this protocol, and will be determined at the discretion of the study clinicians. However, guidelines for the appropriate use of secondary and salvage regimens will be provided, and documentation of their use will be included in the participant's study chart, and on applicable case report forms (CRFs).

Clinical procedures, behavioral procedures, and laboratory evaluations will be performed for both partners of a couple throughout the course of the study for primary and secondary endpoint determination.

Index cases in both arms will receive care for their HIV; both defined by the protocol and as clinically indicated. This care will consist of screening, prophylaxis, treatment for various disease manifestations, and monitoring of disease progression (refer to Section 5.0 and Appendix I A). Treatment for disease manifestations found during the study will be consistent with host country guidelines, local standards of care, and locally developed standard operating procedures (SOPs).

Partners of index cases will receive treatment for those conditions screened for during their clinical study visits (refer to Section 5.0 and Appendix I B.) Treatment for disease manifestations found during the study will be consistent with host country guidelines, local standards of care, and locally developed SOPs.

### **2.3.1 Criteria For Switching Antiretroviral Therapy Regimen Due to Virologic Failure**

The U.S. site participating in this study will follow U.S. standards of care regarding resistance testing.

For study sites outside of the U.S., index cases will switch ART due to virologic failure based on the following definition that is deemed appropriate for the settings in which this study will take place: virologic failure will be defined as two consecutive plasma HIV RNA measurements greater than 1,000 copies/mL at week 16 or later (in the absence of recent systemic illness, vaccination, or obvious non-adherence to study medications) and will prompt a switch to a secondary regimen.

Index cases in whom failure to respond is believed to be due to non-adherence, systemic illness, vaccination, or other circumstances determined by the study clinicians, will be evaluated and will not be required to switch therapy. The starting regimen should continue and the index case will be re-evaluated for plasma HIV-1 RNA monthly unless the study clinician advises that therapy should be changed. If plasma HIV-1 RNA is still greater than 1,000 copies/mL eight or more weeks after virologic failure, adherence will be re-evaluated and a switch to a secondary regimen may be undertaken. An appropriate secondary regimen will be determined at the discretion of the study clinicians.

Index cases who have a confirmed virologic failure while on a secondary regimen may require salvage therapy (a third regimen). However, they may remain on the secondary regimen if it is determined that a further switch would not be in the best interest of the participant. This decision will be at the discretion of the study clinicians. In addition, while antiretroviral resistance testing will not be used as part of clinical management in HPTN 052, sites that have the capability to perform resistance testing in real time may do so in order to guide the choice of antiretroviral drugs **ONLY** in instances of confirmed virologic failure to a secondary regimen.

### **2.3.2 Index Case and Partner Follow-Up Visit Schedule**

The follow-up visit schedule for index cases and their partners enrolled in both the run-in period and full study will be the same. It should be noted that clinical procedures and laboratory evaluations might be performed at any study visit, scheduled or unscheduled, if clinically indicated. Such procedures and evaluations will be recorded in the participant's study chart, and on applicable case report forms (CRFs).

All enrolled study participants will complete monthly follow-up visits throughout their participation in the study. These regular visits should be conducted every 30 days, and couples should return for the visit together. Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, visits may be completed within a one-week window around the target date (i.e., +/- 7 days from the target date).

For participants who do not complete scheduled visits within the allowable window, the visit will be considered "missed" and relevant case report forms will be completed to document the missed visit.

Refer to the SSP Manual for more information related to study visit scheduling.

All on-study procedures and evaluations for index cases and partners are outlined in Sections 5.0, and Appendix I A and B.

#### **2.3.2.1 Index Case Follow-up**

As stated in Section 2.3.2, index cases will be required to report for monthly follow-up visits for the entire study. For those on ART, these visits will consist of obtaining a monthly allotment of ART drugs, completing clinical procedures and laboratory evaluations, completing adherence assessments, participating in adherence counseling, completing sexual history assessments monthly for the first 3 months and then quarterly thereafter, and participating in couples HIV counseling with their partner. For those not on ART, visits will include completing clinical procedures and laboratory evaluations, completing sexual history assessments monthly for the first 3 months and then quarterly thereafter, and participating in couples HIV counseling with their partner. For both arms of the study, most clinical procedures and laboratory evaluations will occur at screening, enrollment and during the quarterly visits. However, once an index case is placed on their initial ART regimen, it is recommended that a closer safety assessment be performed two weeks after. Assessments should include hematology, liver function, and blood chemistry assessments, as well as a directed history and physical exam. In cases where the index case stops ART, they and their respective partner should continue to be followed monthly and complete the required study assessments per the protocol (except the adherence assessment).

#### **2.3.2.2 Partner Follow-up**

As stated in Section 2.3.2, all partners are required to report for monthly visits with the index case to complete a sexual history assessment (monthly for the first 3 months and then quarterly thereafter), participate in couples HIV counseling, and adherence



counseling (only while partner is on ART). Clinical procedures and laboratory evaluations will take place during screening, enrollment, quarterly, and yearly visits.

#### **2.3.2.3 STD Management**

Both index cases and their partners will be screened for STDs (chlamydia, gonorrhea, syphilis, BV, TV, candida, and genital ulcer disease) at enrollment and at the yearly visit. Moreover, if the partner seroconverts, both the index case and partner will be examined for genital ulcer disease. In addition to these protocol-dictated procedures, clinicians will diagnose and treat STDs at any time during the study if clinically indicated. Whenever a genital ulcer is found during examination, a swab will be taken and sent to the HPTN CL for etiology determination.

#### **2.3.3 Rules of Participation for Both Index Case and Partner**

The following rules for participation will apply throughout the course of the run-in period and full study for the index case and the partner.

##### **2.3.3.1 Both Partners of a Discordant Couple:**

Only one person infected with HIV and their HIV-negative primary sexual partner will be considered a serodiscordant couple. Additional sexual partners of either the index case or their partner will not be eligible to enroll while the initial couple is being followed, and will not be considered in the analysis.

##### **2.3.3.2 Index Case**

In cases where the partner is lost to follow-up, withdraws from the study permanently, the relationship with the index case has permanently ended (based on self-report), has become infected with HIV, or dies, the index case should continue to be followed for assessment of secondary endpoints per the protocol.

A new partner of the index case will be eligible to enroll provided that this new couple meets the definition of a serodiscordant couple and the partner meets the eligibility criteria (see Section 3.1). The index case and partner would then be followed per the protocol.

If the index case does not have a new partner, he or she should still be followed for assessment of secondary endpoints per the protocol.

##### **2.3.3.3 Partner**

In cases where the index case is lost to follow-up or withdraws from the study permanently, but the partner reports that the couple still meets the study definition of a serodiscordant couple and are still involved in a sexual relationship (per the inclusion criteria), the partner should continue to be followed per their study visit schedule for assessment of the primary endpoint.

In cases where the index case dies (based on partner report, or verification if available, *e.g.* death certificate or notice) or the partnership has permanently ended (based on self-report), the partner's participation in the study will end.

In cases where the partner becomes infected with HIV, the partner's participation in the study will end. (Refer to Section 8.3 regarding a partner becoming infected with HIV during the course of the trial).

It is difficult to predict at this time the full range of scenarios that might affect the participation of couples in this study. The SSP Manual will be updated to include any scenarios that may occur throughout the course of the study that are not included above.

### **3 STUDY POPULATION AND SCREENING, RECRUITMENT, AND ENROLLMENT PROCEDURES**

#### **3.1 Inclusion Criteria**

Couples are defined as sexual partners, same or opposite sex, who are married, have been living together, or consider each other a primary partner. They must have been together for a minimum of three months, and at the time of study enrollment expect to maintain their relationship for the duration of the study.

Additional sexual partners of either the index case or their partner will not be eligible to enroll while the initial couple enrolled is being followed. Each partner of an HIV serodiscordant couple must meet the criteria presented below to be eligible for inclusion in this study.

##### **3.1.1 Index Case**

- Positive HIV serology obtained within 60 days (NOTE: during screening, a 2nd confirmatory blood draw is not necessary for positive HIV serology.)
- Has a sexual partner (as defined above) who is not infected with HIV (documented by negative HIV serology), and who is willing to participate in the study.
- Plans to maintain a sexual relationship with the person who is enrolled in the study with them.
- Reports having sex (vaginal or anal) with partner at least 3 times in the last 3 months.

THE FOLLOWING INCLUSION CRITERIA MARKED WITH AN ARROW WILL APPLY ONLY DURING THE RUN-IN PERIOD:

- For female participants of reproductive potential, a negative serum or urine pregnancy test performed within 48 hours before initiating study treatment.

NOTE: “Reproductive potential” is defined as girls who have reached menarche or women who have not been post-menopausal for at least 24 consecutive months (i.e., who have had menses within the preceding 24 months) or have not undergone surgical sterilization (e.g., hysterectomy, bilateral oophorectomy, or salpingotomy).

- Female participants who are participating in sexual activity that could lead to pregnancy (BUT not receiving EFV) must use at least one reliable method of contraception while receiving the protocol-specified drugs and for 6 weeks after stopping the medications.
  - Female participants who are participating in sexual activity that could lead to pregnancy and are receiving EFV must agree to use two reliable methods of contraception: a barrier method of contraception (condoms or cervical cap) together with another reliable form of contraception (condoms, with a spermicidal agent; a diaphragm or cervical cap with spermicide; an IUD; or hormonal-based contraception) while receiving the protocol-specified drugs and for 6 weeks after stopping the drugs. Another ART drug may be substituted for EFV if participants are not able, or willing, to use two concurrent forms of contraception, or they will be excluded (if another ART drug is not available).
  - Female participants who are without reproductive potential, as defined above, or whose male partner(s) have undergone successful vasectomy with documented azoospermia or have documented azoospermia for any other reason, are eligible without requiring the use of contraception. Participant-reported history is acceptable documentation of menopause, hysterectomy, bilateral oophorectomy, or tubal ligation.
- For full study only, if pregnant or breastfeeding at enrollment, willing to be randomized to either arm of the study. (THIS DOES NOT PERTAIN TO THE RUN-IN PHASE OF THE STUDY.)

The following conditions must be met for laboratory parameters within 60 days prior to enrollment:

- CD4+ cell count of 300-500 cells/mm<sup>3</sup>
- Hemoglobin > 7.0 g/dL
- Platelet count ≥ 50,000/μL.

- AST (SGOT), ALT (SGPT), and alkaline phosphatase < 5 x ULN
- Total bilirubin < 2.5 x ULN

### **3.1.2 Partner**

- Negative HIV serology within 14 days prior to enrollment.
- Has a sexual partner infected with HIV who is willing to participate in the study.
- Plans to maintain a sexual relationship with the person who is enrolled in the study with them.
- Reports having sex (vaginal or anal) with partner at least 3 times in the last 3 months.

### **3.1.3 Both Index Case and Partner**

- Men and women age  $\geq 18$  years.
- Willing to disclose HIV test results to partner.
- Not intending to relocate out of the area for the duration of study participation and does not have a job or other obligations that may require long absences from the area.

## **3.2 Exclusion Criteria**

### **3.2.1 Index Case**

- Current or previous use of any ART drugs (exceptions will be outlined in the SSP Manual. For example, previous short-term use of ART for prevention of perinatal transmission will be waived as an exclusion).
- Hemoglobin < 7.0 g/dL
- In cases where the participants' starting regimen contains ATV or NVP, documented or suspected acute hepatitis within 30 days prior to enrollment, irrespective of AST (SGOT) and ALT (SGPT) values.
- Current or previous AIDS-defining illness (as defined in Appendix III). (Note: active TB, as defined by the AACTG Appendix 60 - Diagnoses Appendix, is an exclusion, as well as currently being on intensive phase of TB treatment, but previously treated cases of pulmonary TB may be waived at the discretion of the study clinician. Specific guidelines for TB treatment at each site will be included in the SSP Manual.)

- Pregnancy (run-in period only). NOTE: Breastfeeding is allowed at enrollment; however, during the run-in period, women may not be on a regimen containing study-provided ATV the entire time they are breastfeeding.

### 3.2.2 Both Index Case and Partner

- Reports a history of injection drug use within the last five years.
- Receipt of an experimental HIV vaccine.
- Any condition that, in the opinion of the study staff, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.
- Incarceration in a correctional facility, prison, or jail; and involuntary incarceration in a medical facility for psychiatric or physical (e.g. infectious disease) illness.

### 3.3 Screening and Enrollment Procedures

Identification of HIV serodiscordant couples will vary across sites and within an individual site (e.g. couples already identified as HIV serodiscordant and referred to the site by a local voluntary counseling and testing (VCT) center, referral of HIV-infected individuals from local STD/HIV clinics or other research protocols, or referral of HIV-uninfected individuals to the study site). Thus, it will be the responsibility of the site to determine the best screening methods for their locale, and will likely be dictated on a case-by-case basis.

The protocol will not define an algorithm for HIV screening for study eligibility. Study sites will be responsible for developing a local SOP for this study component; however, the HPTN Central Laboratory should approve the screening algorithm employed. In addition, previous HIV screening with positive test results will be accepted as eligibility for this study only if:

- the testing occurred within the dictated timeframe for this study (within 60 days)
- the testing was performed during a time that the site had HPTN Central Laboratory certificate of accreditation
- the testing has appropriate documentation (*i.e.* documentation is consistent with what would otherwise be required for research purposes such as test date, test results, and identification of the testing laboratory)

Anyone with a prior HIV negative test result must be re-tested for screening for this study.

### **3.3.1 Screening Procedures**

Both individuals of a couple must provide independent written informed consent for screening, be assigned a screening identification (ID) number, undergo an interviewer-administered eligibility checklist, provide demographic and locator information, undergo individual HIV counseling and testing, and participate in HIV couples counseling. Potential index cases must also have samples collected for the laboratory inclusion criteria (CD4+ cell count measurement, hematology, and liver and renal function testing.) If the potential index case is female, urine pregnancy testing must be performed. Potential index cases must also undergo a directed history and physical exam to rule out any AIDS-defining illnesses.

Regardless of the number of screening visits required, enrollment must be completed within 60 days from the time of the first screening tests and exams. These procedures are outlined in Section 5.0, and Appendix I A and B.

### **3.3.2 Enrollment Procedures**

Each partner will be asked to provide independent written informed consent to take part in the study. If both partners agree to take part, the couple will be assigned at random to a study treatment arm and on-study procedures will be completed as described in Section 5.0, and Appendix I A and B.

### **3.4 Co-Enrollment Guidelines**

Due to the complex nature of this study, participation in other clinical trials will be strongly discouraged; however, if participants choose to participate in another study, decisions about their continued participation will be made by the study staff on a case-by-case basis depending on the nature of the other study.

## **4 STUDY TREATMENT CONSIDERATIONS**

The run-in period will employ a starting regimen of Combivir<sup>®</sup> [3TC/ZDV] and EFV or ATV. Also available for the run-in period are ATV, EFV, NVP, TDF, 3TC, ddI-EC, and d4T for toxicity management or virologic failure.

The full study starting regimen will be determined when additional ART drugs become available, but will include Combivir<sup>®</sup> [3TC/ZDV].

Sites will also provide care for HIV, which will consist of systematic attention to vitamin deficiency, STDs, tuberculosis, endemic infections (*e.g.* enteric parasites and malaria), expected opportunistic pathogens, and other AIDS-related conditions. Treatment for disease manifestations found during the study will be consistent with host country guidelines, local standards of care, and locally developed SOPs.

Individual and couples counseling will be provided to participants in accordance with standard study counseling methods. Participants will be counseled that consistent use of condoms is the only known way to prevent sexual transmission of HIV, and condoms will be provided free of charge to all participants at each study visit. In addition, counseling will emphasize the unknown efficacy of ART in preventing HIV infection.

#### **4.1 Supply and Accountability**

##### **4.1.1 Antiretroviral Drugs**

The ART study drugs currently available for the run-in period of the study are 3TC/ZDV, EFV, ATV, NVP, TDF, 3TC, ddI-EC, and d4T. The ART study drugs currently available for the full study are 3TC/ZDV, 3TC, NVP, and TDF. Study drugs will be provided by the study to participants while they are on study, and are being provided by, or purchased from:

- 3TC/ZDV, 3TC: GlaxoSmithKline
- EFV: Merck & Co., Inc.
- ATV, ddI-EC, d4T: Bristol-Myers Squibb, Inc.
- NVP: Boehringer-Ingelheim Pharmaceuticals, Inc.
- TDF: Gilead Sciences, Inc.

Any other ART drugs used during the run-in period will be provided by non-study prescription.

The ART study drugs provided through this study, with the exception of EFV, will be distributed to the study sites by the NIAID Clinical Research Products Management Center (CRPMC), and possibly through regional distribution facilities outside of the U.S. (as approved by the Division of AIDS). The provision of EFV will be managed by Family Health International (FHI) who will facilitate the purchasing of EFV locally (refer to SSP Manual for additional details). The study site pharmacist can obtain the ART study drugs available through the CRPMC by following the instructions provided in the latest version of the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trial Networks*, and instructions in the SSP Manual. The study site pharmacist is required to maintain records of all ART study drugs received and subsequently dispensed to study participants. All unused study drugs are to be held until the study is completed, terminated, or otherwise instructed by the sponsor. Specific instructions will be provided for the final disposition of the study products.

##### **4.1.2 HIV Primary Care Agents**

Each site will be responsible for purchasing and maintaining their own supply of non-study drugs (HIV primary care medications). All medications will be dispensed to participants in the amount required to prevent or treat its indication, and according to

other applicable local practice standards (*e.g.* directly observed daily therapy for TB treatment.)

#### **4.2 Regimens and Administration**

Table 3 outlines specifications related to the ART study drugs used for this protocol. All medications will be administered orally.



**Table 3: Antiretroviral Therapies**

Medication	Class	Formulation	Daily Dose	Frequency	Storage
<b>Combivir<sup>®</sup></b> 3TC/ZDV	NRTI	150 mg/300 mg tablet	300 mg/600 mg	150 mg/300 mg BID with or without food	2° - 30° C 36° - 86° F
<b>Lamivudine</b> 3TC Epivir <sup>®</sup>	NRTI	300 mg tablets	300 mg	150 mg BID with or without food	25°C 77° F Excursions permitted between 15-30° C (59-86° F)
<b>Zidovudine</b> ZDV Retrovir <sup>®</sup>	NRTI	300 mg tablets	600 mg	300 mg BID with or without food	15° - 25° C 59-77°F protect from light
<b>Efavirenz</b> EFV Sustiva <sup>®</sup> or Stocrin <sup>®</sup>	NNRTI	600 mg tablet	600 mg	600 mg QD, bedtime recommended, take on an empty stomach (1 hour before or 2 hours after a meal)	25°C 77° F Excursions permitted between 15-30° C (59-86° F)
<b>Atazanavir</b> ATV Reyataz <sup>™</sup>	PI	150 mg and 200 mg capsules	400 mg 300 mg with 100mg ritonavir	400mg (two 200 mg capsules) QD with food, or 300 mg (two 150 mg capsules with 100 mg ritonavir QD with food.	25°C (77°F). Excursions permitted between 15°-30°C (59°- 86°F)
<b>Nevirapine</b> NVP Viramune <sup>®</sup>	NNRTI	200 mg tablet	200 mg (initial for 14 days) then 400 mg	200 mg QD for first 2 weeks (lead-in), 200 mg BID or 400 QD thereafter, with or without food.	25°C 77° F Excursions permitted between 15-30° C (59-86° F)
<b>Didanosine</b> ddI-EC Videx <sup>®</sup>	NRTI	125 mg, 200 mg, 250 mg, and 400 mg capsules	400 mg, weight ≥60 kg 250 mg, weight <60 kg	1 PO QD at least 1 hour before or 2 hours after a meal.	15°-30°C 59°-86°F
<b>Stavudine</b> d4T Zerit <sup>®</sup>	NRTI	15 mg, 20 mg, 30 mg, and 40 mg capsules	40 mg, weight > 60 kg 30 mg, weight ≤ 60 kg	1 PO BID with or without food	15°-30°C 59°-86°F
<b>Tenofovir Disoproxil</b> Fumarate TDF <sup>1</sup> Viread <sup>®</sup>	NRTI (nucleotide)	300-mg tablet	300-mg	300 mg QD with food	room temperature 15° - 30° C 59° - 86° F

1: Note for TDF - tablets should be stored and dispensed in the original container. Each bottle contains a silica gel desiccant canister to protect the product from humidity and should remain in the original container.

## 4.3 Concomitant Medications

### 4.3.1 Required Medications

No concomitant medications are required. Medications recommended for prophylaxis or treatment of AIDS-defining or other conditions will be outlined in site-specific local SOPs and the SSP manual, and will be based on prevalence of the conditions in the host country (*e.g.* some study sites are not located in a malarious region).

### 4.3.2 Prohibited Medications

Table 4 lists medications that CANNOT be used in combination with efavirenz, nevirapine, or protease inhibitors.

**Table 4:** Prohibited Concomitant Medications with Efavirenz, Nevirapine, ddI-EC, and Protease Inhibitors

Medication Class	Medication
Antihistaminics	Astemizole (Hismanal <sup>®</sup> )
	Terfenadine (Seldane <sup>®</sup> )
GI Motility	Cisapride (Propulsid <sup>™</sup> )
Alternative/complementary	St. John's wort ( <i>Hypericum perforatum</i> )
Sedative/hypnotics	Midazolam* (Versed <sup>®</sup> )
	Triazolam (Halcion <sup>®</sup> )
Other	Dihydroergotamine
	Ergonovine
	Ergotamine
	Methylergonovine
	Allupurinol (for ddI)

\*Midazolam can be used with caution as a single dose, when given in a monitored situation for procedural sedation.

### 4.3.3 Precautionary Medications

Package inserts of antiretroviral and concomitant agents should be referred to whenever a concomitant medication is initiated or dose changed to avoid drug interaction adverse events.

Some of the precautionary medications include, but are not limited to, those listed in Table 5. Use of these agents while on study may require additional monitoring of drug levels or for adverse events.

**Table 5:** Prohibited Concomitant Agents with ATV, and other Protease Inhibitors

Agent Class	Prohibited with ATV, and other PI's
Antiarrhythmics	Amiodarone (Cordarone™)
	Lidocaine (Xylocaine®)
	Quinidine (Quinaglute®, Quinidex®)
	Flecainide
	Propafenone
Anti-infective	Rifampin (Rifadin™, Rimactane™)
Antineoplastic agent	Irinotecan (Camptosar®) (prohibited with ATV only)
Calcium channel blockers	Bepridil (Vasacor®)
HMG CoA reductase inhibitors	Lovastatin (Mevacor®)
	Simvastatin (Zocor®)
H2 blockers (prohibited with ATV only)	cimetidine (Tagamet®),
	ranitidine (Zantac®).
Neuroleptic	Pimozide (Orap®)
Protease inhibitors	Indinavir (Crixivan®) [prohibited with ATV only]
Proton pump inhibitors (prohibited with ATV only)	Rabeprazole (Aciphex®)
	Esomeprazole (Nexium®)
	Omeprazole (Prilosec®)
	Lansoprazole (Prevacid®)
	Pantoprazole (Protonix®)
Other agents	Warfarin (Coumadin®)
	Antacids and other buffered products (prohibited with ATV only)

**NOTE:** Information on drugs without trade names, those that either have many marketed forms, or are not available in the U.S. is available at:  
[http://www.hiv-druginteractions.org/drug/pdf/pi\\_col.pdf](http://www.hiv-druginteractions.org/drug/pdf/pi_col.pdf) and  
[http://www.ucsf.edu/hivcntr/pharmacy/Drug\\_Intxn\\_Web.htm](http://www.ucsf.edu/hivcntr/pharmacy/Drug_Intxn_Web.htm).

The following outlines additional drug-specific related precautions:

- Concurrent Use of ddI-EC plus d4T

The concurrent use of ddI-EC and d4T is not recommended. They may be used together if no other alternatives exist. ddI plus d4T should not be used in pregnant women.

- Oral Contraceptives

Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives are coadministered with either NVP or RTV and other PIs, since the effectiveness of estrogen-based contraceptives is unknown. Contraceptive drug levels may be increased as with ATV. The long term effects of these increased levels are unknown. The effectiveness of estrogen-based contraceptives when coadministered with EFV-containing regimens is unknown.

- Sildenafil (Viagra®) and other Phosphodiesterase Type 5 (PDE5) Inhibitors and NNRTI's and PI's

EFV and NVP are inducers of this pathway. Data defining any interaction with sildenafil are insufficient to determine a clinical significance.

Particular caution should be used when prescribing these agents (sildenafil, [Viagra®], tadalafil (Cialis®), vardenafil (Levitra®), and similar agents) to participants receiving concurrent PI agents or RTV-boosted PIs. Coadministration of RTV with a PDE5 inhibitor is expected to increase their concentrations substantially, which may cause hypotension, syncope, visual changes, and prolonged erection. When coadministered with any PI, the initial dose of sildenafil should be reduced to 25 mg, repeated no more frequently than every 48 hours. Vardenafil should not exceed a maximum single dose of 2.5 mg in 72 hours. Tadalafil should not exceed a maximum single dose of 10 mg in 72 hours.

- Methadone

The dose of methadone may need to be increased in regimens containing EFV or NVP. Participants on NVP or EFV-containing regimens should be closely monitored for symptoms of opiate withdrawal.

- Rifampicins and Rifabutin

Rifampicin decreases EFV and NVP serum levels, however, the clinical significance of this effect is unknown. It is recommended that EFV dose not be adjusted when EFV is coadministered with rifampicin (i.e., EFV 600 mg daily should be used). It is recommended that rifampicin not be used concomitantly with NVP-containing regimens.

Rifabutin (Mycobutin®) dose should be increased when coadministered with EFV. See EFV package insert for dosing recommendations. Data assessing dose adjustments of rifampicin or rifabutin when coadministered with NVP are insufficient.

Rifampicin may decrease ATV levels. Subjects who are taking ATV and require rifampicin for the treatment of active TB must either replace rifampicin with rifabutin or replace ATV with EFV during TB treatment. Subjects who receive rifabutin for the treatment of TB may remain on ATV.

NOTE: Whenever ATV and rifabutin are used concurrently, a single trough blood sample will be collected prior to the ATV dose on day 14 after initiation of rifabutin.

Rifabutin should be reduced when coadministered with PIs. See package inserts of individual PIs for dosing recommendations. If RTV is used to boost PIs, rifabutin should be reduced to 150 mg two or three times per week and close monitoring for rifabutin-associated AEs is advised.

- Tenofovir

TDF has been shown to increase the serum concentrations of ddI, even when the drugs are given 2 hours apart or with a meal. Subjects taking TDF and ddI concomitantly should be monitored closely for ddI-associated adverse events, such as pancreatitis and neuropathy. In addition, when TDF and ddI are coadministered, ddI doses should be adjusted as follows: reduce 400 mg QD to 250 mg QD for subjects who weigh  $\geq 60$  kg; and reduce 250 mg QD to 200 mg QD day for subjects who weigh  $< 60$  kg.

Coadministration of TDF and LPR/rtv increases both the AUC and C<sub>min</sub> of TDF. This could result in an increase in TDF-associated toxicities (including renal disorders) and subjects receiving these drugs should be monitored closely.

Coadministration of agents with either a nephrotoxic potential (for example, amphotericin B, aminoglycosides, cidofovir, acyclovir, ganciclovir) or agents that are renally excreted with TDF may increase serum drug concentrations of TDF and/or increase the concentrations of the other renally excreted agents. Additional monitoring may be indicated if subjects are placed on these agents while on TDF.

- Atazanavir

Coadministration of ATV with clarithromycin increases clarithromycin levels, which could result in QTc prolongation. Dose reduction of clarithromycin by 50% should be considered.

When taken with TDF, ATV plasma levels may be decreased and result in reduced virologic efficacy. When coadministered with TDF, ATV 300 mg with ritonavir (RTV) 100 mg and TDF 300 mg should be given all as a single daily dose with food. ATV should not be coadministered with TDF or RTV. It is required that a drug combination other than TDF + ATV be used if ritonavir-boosted ATV is not available.

Coadministration of ATV with diltiazem resulted in a 2-fold increase in the steady-state concentration of diltiazem. A 50% dose reduction in diltiazem may be necessary. Other hepatically metabolized calcium channel blockers (e.g., nifedipine, felodipine) may also have increased serum concentrations when co-administered with ATV.

When taken with TDF, ATV plasma levels may be decreased and result in reduced virologic efficacy. It is required that a drug combination other than TDF + ATV be used if ritonavir-boosted ATV is not available. Low-dose ritonavir must be used whenever ATV is given with TDF.

All buffered products and drugs that reduce gastric acid may reduce the plasma concentrations of ATV, including but not limited to antacids (Maalox®, Mylanta®). Subjects may take ATV one hour before or two hours after antacids, or buffered solutions.

The risk of myopathy, including rhabdomyolysis may be increased when PIs are used in combination with HMG-CoA reductase inhibitors that are metabolized by the CYP3A4 pathway (e.g., atorvastatin). Caution should be used when taking these agents, and when possible, alternative agents should be considered.

#### **4.4 Adherence Counseling and Assessment**

Adherence counseling will be provided to study participants who are on ART study drugs at each study visit. This counseling will be provided in accordance to local SOPs developed using standardized materials developed by the protocol team and external experts. These materials will address topics such as the complexity of the regimen, regimen, potential side-effects, the length of the regimen, and the need to continue treatment despite symptomatic improvement. As a result, guidelines for adherence counseling will help to ensure that participants understand their own regimen, understand the importance of adherence to their health, and can strategize with their clinicians about barriers and facilitators to adherence.

Assessment of adherence will involve both self-report and at least one additional objective indicator of adherence. Measures may include asking individuals to recall the number of pills they took for varying time periods, including “yesterday,” “the day before,” and the “past four days.” Additionally, it asks participants how they typically take their pills, using a Likert-type scale with anchor points ranging from “all of the time,” to “sometimes” to “never.” A similar assessment may be used.

An example of an objective adherence assessment that may be employed is using pill counts. If adopted, a typical visit would involve counting the number of pills (per medication) that are left when the next month’s supply of medications is dispensed. The number remaining would be subtracted from the number given to determine how many pills were actually taken. Percent adherence would then be calculated by dividing the number of pills prescribed (per medication) by the number of pills taken.

Additional or alternative objective adherence assessments may be implemented during the course of the study.

Strategies and methods for optimizing adherence will be provided to sites for adoption into site-specific SOPs.

## **4.5 Toxicity Management**

Toxicity management related to the use of ART in the developing world setting will rely on both laboratory markers, clinical symptoms and study clinician judgment since alternatives to study-provided medications may be very limited and baseline levels of certain laboratory parameters (*e.g.* hemoglobin) may be different than in the developed world setting. Since toxicity management needs to be more directly relevant to the setting of this particular study, and considering the objectives of this study, a guiding principle for all study clinicians (U.S. and in-country) will be to reduce the risks of antiretroviral to index cases on treatment regimens to the greatest extent possible.

Toxicities will be graded using the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences, located on at <http://rcc.tech-res-intl.com>, and also included in the SSP Manual.

This section provides guidelines for management of toxicities related to ART study drugs only, and may include specifications for ART drugs not outlined in this protocol, or not provided through the study. Study site clinicians will be encouraged to discuss toxicity management-related questions and concerns with the HPTN 052 Clinical Management Committee (CMC), which consists of designated protocol team members such as co-chairs and investigators, protocol statistician, DAIDS Medical Officer and Pharmacist, SCHARP Protocol Operations Coordinator, HPTN CORE Clinical Trial Managers, and other protocol team members deemed necessary by the HPTN 052 CMC.

In general, when one study drug is held for resolution of toxicity, all study drugs in a particular regimen should be held concurrently.

It is recommended that NRTIs be continued for 7 days past NNRTI (*e.g.* EFV, NVP) discontinuation unless they are suspected in a given toxicity. Or if available, a PI may be substituted during the 7 days that the NNRTI has been discontinued.

3TC has activity against HBV. TDF also may have activity against HBV. Permanent discontinuation of 3TC or TDF may result in re-activation of HBV.

ddI-EC and d4T should not be coadministered.

### **4.5.1 Grade 1 or 2**

Index cases who develop a Grade 1 or 2 adverse event or toxicity may continue study drugs without alteration of the dosage except as stated in Section 4.5.5 (Guidelines for Specific Management of Laboratory Abnormalities and Clinical Syndromes). Index cases experiencing Grade 1 or 2 toxicities will be managed at the discretion of the study clinicians.

### **4.5.2 Grade 3**

If there is compelling evidence that the adverse event has NOT been caused by the ART drug(s), dosing may continue. Participants who develop a Grade 3 adverse event or toxicity, except as stated in Section 4.5.5, should have one or more of their ART study

drugs withheld, at the study clinicians discretion. The participant should be reevaluated weekly to the extent possible, until the adverse event returns to Grade <2, at which time the study drugs may be reintroduced at the discretion of the study clinician.

#### **4.5.3 Grade 4**

Participants who develop a symptomatic Grade 4 adverse event or toxicity not specifically addressed below will have all ART study drug(s) withheld until resolution of the adverse event to a Grade  $\leq 2$ . Under certain circumstances the ART study drug thought most likely to be related to the adverse event may be resumed at the discretion of the study clinicians. Alternative medications should be considered.

Index cases with Grade 4 asymptomatic laboratory abnormalities, not specifically addressed below, may continue ART drug therapy if the study clinician has compelling evidence that the toxicity is NOT related to the ART study drug(s).

Asymptomatic elevations of triglycerides or creatine kinase (CPK) do not require that study medications be withheld.

Every attempt should be made to continue to follow participants who discontinue ART drug therapy due to a Grade 3 or 4 adverse events until resolution of the adverse event can be documented.

#### **4.5.4 Antiretroviral Therapy Dosage Reductions**

Recommended dosage reductions are presented in Table 6 and include a range of ART drugs that may or may not be used during the course of the study, but are included for guidance.



**Table 6: ART Dosage Reduction Table**

DRUG	INITIAL DOSE	DAILY DOSE	REDUCED DOSE	DAILY REDUCED DOSE
EFV	600 mg QHS	600 mg	None	None
ATV	400 mg QD	400 mg	None	None
3TC	150 mg BID	300 mg	None	None
3TC	300 mg QD	300 mg	None	None
ddI EC <sup>1</sup>	400 mg QD	400 mg	250 mg QD	250 mg
ddI EC <sup>2</sup>	250 mg QD	250 mg	125 mg QD	125 mg
TDF	300 mg QD	300 mg	None	None
d4T <sup>1</sup>	40 mg BID	80 mg	20 mg BID	40 mg
d4T <sup>2</sup>	30 mg BID	60 mg	15 mg BID	30 mg
NVP	200 mg QD x 14 d, then 200 mg BID	200 mg x 14 d, then 400 mg	None	None
NFV <sup>3</sup>	1250 mg BID	2500 mg	500-750 mg BID	1000-1500 mg
LPV/RTV	133.3 mg lopinavir/33.3 mg ritonavir 3 capsules BID	800 mg/200 mg	None	None

<sup>1</sup>For subjects weighing  $\geq 60$  kg.

<sup>2</sup>For subjects weighing  $< 60$  kg.

<sup>3</sup>Dose reduction of NFV is not standard of practice, but it may be necessary in the case of limited treatment options. First dividing dose to 750 mg TID may improve tolerance.

## 4.5.5 Guidelines for the Specific Management of Laboratory Abnormalities and Clinical Syndromes

### 4.5.5.1 Rash

#### Rash Management for Participant NOT on NVP:

For Grade 1 or 2 rash study treatment should continue without interruption. Participants with a Grade 1 or 2 rash may be treated symptomatically with permitted antipyretic, antihistamine, and/or nonsteroidal anti-inflammatory medications, but should be monitored closely by the study clinicians.

For Grade 3 rash, all study medications should be held, unless the rash is determined to be unrelated to study medications. Study medications may be restarted if clinically indicated when resolution to Grade  $\leq 2$ .

For Grade 4 rashes all study medications should be permanently discontinued.

#### Rash management (for participants on Nevirapine):

Liver function tests should be performed promptly and participants evaluated for signs and symptoms related to clinical hepatitis and hypersensitivity reactions. If LFT's are increased, that is elevated above the baseline level, NVP must be permanently discontinued regardless of the grade of the rash or grade change in LFT's.

If participants have constitutional symptoms (fever, not felt to be due to other intercurrent illnesses, blistering rash, oral mucosal lesions, facial edema, myalgias/arthralgias) and rash of any grade, NVP must be permanently discontinued.

If participants have signs or symptoms of clinical hepatitis (which may include N/V, anorexia, jaundice, acholic stools, hepatomegaly, hepatic tenderness, fever, fatigue, arthralgia) and rash, NVP should be permanently discontinued.

For participants on NVP who develop a Grade 1 or 2 rash but with no constitutional symptoms, no increase above baseline of the LFT's, and no evidence of clinical hepatitis, NVP may be continued with close follow-up at the discretion of the study clinicians.

For participants on NVP who develop a Grade 3 or 4 rash, but with no constitutional symptoms, no increase above the baseline of the LFTs, and no evidence of clinical hepatitis, NVP should be discontinued.

Participants who have mild to moderate urticaria, without constitutional symptoms, without increases above baseline of the LFTs, or without evidence of clinical hepatitis, NVP may be continued with close follow-up at the discretion of the study clinicians. If participants have an urticarial rash and NVP is discontinued for whatever reason, NVP should not be restarted.

#### **4.5.5.2 Lipase Elevations and Pancreatitis**

Pancreatitis will be reported as a clinical finding (*i.e.*, symptomatic pancreatitis). The primary enzyme abnormality that will be used for making diagnoses is the lipase level. When obtained, lipase determinations will be recorded in the CRF. A triglyceride level should be drawn with the lipase.

Lipase will be obtained for participants if development of clinical symptoms suggests pancreatitis. If a baseline measurement is needed, it will be performed from stored samples. (Pancreatic amylase also is acceptable).

For symptomatic (gastrointestinal symptoms, particularly abdominal pain) participants with elevations in lipase:

- Grade <1: Search for other causes of symptoms. If none are found and symptoms persist, repeat lipase within 2 weeks. If repeat is elevated then participant should stop ddI-EC.
- Grade 1 or 2: Participants should be contacted as soon as the results are available, and instructed to return for clinical assessment and a repeat lipase level as soon as possible; within one to two days is optimal. If lipase remains elevated, but is

Grade  $<3$  and symptoms persist, then participants should either be considered to have clinical pancreatitis or continue to be followed at frequent intervals, depending on the best available clinical judgment. CT scan of the abdomen, if available, may be helpful in determining whether clinical pancreatitis is present.

- Grade  $\geq 3$ : Exclude other possible diagnoses (*e.g.*, renal insufficiency causing false elevations in lipase). If none is found, diagnose as clinical pancreatitis.

For a diagnosis of pancreatitis (clinical), all study medications should be held.

After complete resolution of the episode in a setting in which other concomitant illness might have reasonably contributed to the development of pancreatitis, rechallenge with study medications may be performed in consultation with the HPTN 052 CMC. If the study regimen included ddI, substitute with TDF. If the study regimen included d4T, substitute with ZDV and then the subject can be rechallenged with the new regimen.

Upon rechallenge, lipase determinations should be performed at approximately monthly intervals. Any elevation of lipase of Grade  $\geq 2$  or any recurrence of symptoms during this period will lead to a re-evaluation and permanent discontinuation of the suspected study drugs.

#### 4.5.5.3 CK Elevation

CK measures will not be performed routinely as part of the protocol. CK will be measured only if participants develop clinical symptoms consistent with a diagnosis of myopathy. If a baseline measurement is needed, it will be performed from stored samples.

For persistent CK elevations  $>3000$  mg/dL (about 20 x ULN) in symptomatic participants, CK should be redrawn after participants abstain from exercise for 24 hours before treatment modifications are made. If CK is still  $>3000$  mg/dL, ZDV should be discontinued and replaced with d4T, if appropriate.

#### 4.5.5.4 AST and ALT Elevation

Nearly all the antiretrovirals and INH (isoniazid) can cause alterations in liver functions tests. Further, concomitant illness may also alter these laboratory parameters. Therefore, changes in AST or ALT should be evaluated within the clinical context of the abnormalities. Initiation of ART and INH has been staggered to facilitate the interpretation of liver function tests. Because INH and the NNRTIs have been associated with serious, life-threatening hepatitis, evaluation of LFTs in the setting of these drugs will be highlighted separately.

General Considerations: For asymptomatic elevation in AST or ALT = 5-10  $\times$  ULN (Grade  $\leq 3$ ), medications may be continued at the discretion of the study clinicians. Careful assessments should be done to rule out the use of alcohol, non-study medication-related drug toxicity, the lactic acidosis syndrome, and viral hepatitis as the cause of the transaminase elevation. If the AST/ALT elevation is considered most likely to be due to

concomitant illness or medication, standard management, including discontinuation of the likely causative agent, should be undertaken.

For asymptomatic elevation  $5-10 \times \text{ULN}$  (Grade 3) believed secondary to study medications, all agents should be held until levels are Grade  $\leq 2$ , at which time therapy may be reintroduced with the substitution of NFV for EFV or NVP, if applicable. For asymptomatic or symptomatic elevation of AST or ALT  $>10 \times \text{ULN}$  (Grade 4), all medications should be discontinued and held until levels are Grade  $\leq 2$ , at which time therapy may be reintroduced with the substitution of a PI for EFV or NVP. All medications may be restarted if the laboratory abnormalities were thought secondary to a concomitant illness. If the subject was receiving an NNRTI (EFV or NVP), either of these medications should be considered the most likely cause of the elevations. The medications should be substituted and the NRTI medications can be resumed. If elevations  $>10 \times \text{ULN}$  (Grade 4) recur in the absence of an NNRTI drug, all current ART and INH (if subject is receiving INH) should be discontinued. Alternative ART and TB prophylactic regimens may be considered, at the discretion of the study investigator.

INH Prophylaxis: Participants will not start INH if AST/ALT are  $>3 \times \text{ULN}$ . At 1 month following initiation of INH, if AST/ALT  $> 3$  times the baseline value, INH will be discontinued. In the event of AST or ALT  $>5 \times \text{ULN}$  (Grade  $\geq 3$ ), at any point thereafter INH should be discontinued.

NNRTI: The major hepatic toxicities related to NNRTI occur within the first 8 weeks of therapy. Therefore, any substitution with NVP will require monthly AST/ALT monitoring for the first 3 months of therapy and abnormalities during this time period should be considered likely secondary to NVP.

Clinical (Symptomatic) Hepatitis with NVP or EFV: Participants taking EFV or NVP should be monitored for the development of signs and symptoms of hepatitis, which include fatigue, malaise, anorexia, nausea, acholic stools, bilirubinuria, jaundice, liver tenderness, or hepatomegaly, with or without initially abnormal serum transaminase levels. Anyone with these signs and symptoms must seek medical attention immediately and have LFTs performed. If the study clinician determines that the participant has clinical hepatitis with or without LFT abnormality or regardless of the degree of LFT abnormality, and NVP cannot be excluded as the cause, NVP should be permanently discontinued and not restarted after recovery. For asymptomatic elevation in AST (SGOT) or ALT (SGPT)  $>5 \times \text{ULN}$  (Grade  $\geq 3$ ), NVP should be discontinued.

Hepatitis B or C Coinfection: At enrollment, hepatitis B surface antigen (HBsAg), will be obtained. Results will be made available to study clinicians. The purpose of this procedure is to facilitate management of hepatitis B coinfecting participants in the event 3TC or TDF need to be discontinued, which would potentially worsen hepatitis B disease. Hepatitis C serologies will not be performed prospectively. Hepatitis B or C seropositivity is not an inclusion or exclusion criterion nor a criteria for enrollment into specific study arms.

#### **4.5.5.5 Anemia/Neutropenia/Thrombocytopenia**

Participants who develop Grade 1 or Grade 2 (hemoglobin  $\geq 7.0$  but  $\leq 7.9$  g/dL), anemia, which is considered treatment limiting in the opinion of the study clinician, may have d4T substituted for ZDV.

For Grade 3 anemia, neutropenia, or thrombocytopenia believed secondary to ZDV, d4T, or another appropriate nucleoside analogue (TDF, ddI) may be substituted for ZDV. Alternatively, ZDV may be held until the toxicity event returns to Grade  $\leq 2$ , at which time ZDV may be resumed at a reduced dose. If the same Grade 3 adverse event recurs on a reduced dose of ZDV, then ZDV should be replaced with d4T or another appropriate nucleoside analogue (TDF, ddI). The study clinician in conjunction with the study team may choose to continue ZDV at a reduced dose in the setting of Grade 3 anemia if the risks of discontinuing the ZDV outweigh the benefits and a switch to an alternative NRTI (preferably d4T) is not feasible.

Participants with Grade 4 anemia, neutropenia, or thrombocytopenia attributed to ZDV will have treatment interrupted until the adverse event has returned to Grade  $\leq 2$ . Once the toxicity has returned to Grade  $\leq 3$ , all ART should be restarted, with d4T or another appropriate nucleoside analogue substituted for ZDV (TDF, ddI), or if necessary, ZDV administered at a reduced dose of 200 mg BID.

Recurrent Grade 4 anemia, neutropenia, or thrombocytopenia will result in discontinuation of ZDV and substitution of d4T or an equivalent NRTI or NtRTI.

#### **4.5.5.6 CNS Symptoms (for Participants on EFV)**

Participants should be informed that EFV might cause dizziness, impaired concentration, and/or drowsiness. Participants should be informed that these symptoms are likely to improve with continued therapy. Dosing at bedtime improves the tolerability of these symptoms and is recommended during the first weeks of therapy and in participants who continue to experience these symptoms. Those receiving EFV should be alerted to the potential for additive CNS effects when EFV is used concomitantly with alcohol or psychoactive drugs.

In the event that a participant experiences treatment-limiting CNS symptoms as described above that are likely attributable to EFV, EFV should be discontinued and may be replaced with another drug like NVP.

#### **4.5.5.7 Peripheral Neuropathy (for Participants on ddI and d4T)**

Participants experiencing Grade 1 symptoms may continue their study medications at their present dosage. Symptomatic treatment may be provided at the discretion of the site investigator.

Participants experiencing Grade 2 symptoms will be managed per study clinician discretion, which may include dose reduction (See Table 6, Dosage Reductions), or temporary cessation of d4T or ddI, or symptom management.

If Grade 2 toxicity resolves to Grade  $\leq 1$  within 28 days after a dose reduction in d4T, then d4T may be continued at the reduced dose or increased back to the initial dose at the discretion of the study clinician.

For Grade  $\geq 3$ , participants who experience symptoms consistent with peripheral neuropathy that is unrelieved with non-narcotic analgesics (Grade  $\geq 3$ ) must have d4T and/or ddI permanently discontinued, and another NRTI should be substituted. Symptomatic treatment may be provided at the discretion of the study clinician.

#### **4.5.5.8 Nausea (with or without vomiting)**

Although common, nausea following initiation of therapy with antiretroviral medications usually subsides or resolves during the first few weeks of treatment.

Steps in the management of nausea include taking the medication with food (with the exception of ddI) and administration of antiemetics. In the event of intractable nausea for participants receiving ZDV, after pancreatitis, lactic acidosis, etc. have been ruled-out, substituting another NRTI for ddI or ZDV is permitted.

#### **4.5.5.9 Lactic Acidosis**

The following definition will be used in this study:

##### **Symptomatic Hyperlactatemia**

New, otherwise unexplained, and persistent ( $\geq 2$  weeks) occurrence of one or more of the following symptoms:

- Nausea and vomiting
- Abdominal pain or gastric discomfort
- Abdominal distention
- Increased LFTs
- Unexplained fatigue
- Dyspnea

AND

Lactate level (if available)  $> 2 \times$  ULN confirmed by repeat lactate level analysis. In the absence of lactate levels, serum bicarbonate levels and anion gap should be assessed. The presence of depressed bicarbonate levels or an increased anion gap would suggest the possibility of lactic acidosis.

**NOTE:** All lactates  $> 2 \times$  ULN should be repeated as soon as possible, generally within 1 week. If the second result confirms hyperlactatemia ( $> 2 \times$  ULN), participants should immediately discontinue their current study regimen. Substitution of TDF for ZDV or d4T should be considered once symptoms resolve and lactate levels return to  $< 2 \times$  ULN.

See the SSP Manual for background, lactate collection and storage guidelines.

#### **4.5.5.10 Diarrhea**

Diarrhea is a common side effect of infection and medication toxicity. If no infectious cause of diarrhea is found and onset is temporally related to new medication, symptomatic management with antidiarrheal agents is appropriate.

#### **4.5.5.11 Hypophosphatemia (for Participants on TDF)**

For Grades 1 and 2 hypophosphatemia, the phosphate should be repeated preferably within 2 weeks and TDF may be continued without other signs of renal tubular acidosis, at the discretion of the study clinician. For Grades 3 and 4 hypophosphatemia, the phosphate should be repeated preferably within 1 week. Supplemental phosphate or foods high in phosphates should be given and other causes of low phosphate should be investigated. Persistent hypophosphatemia (Grade 3 or 4) should lead to permanent discontinuation of TDF.

#### **4.5.5.12 Hyperbilirubineia (for participants on ATV)**

Participants taking ATV may experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase. This hyperbilirubinemia is reversible upon discontinuation of ATV. Hepatic transaminase elevations that occur with hyperbilirubinemia should be evaluated for alternative etiologies. No long-term safety data are available for participants experiencing persistent elevations in total bilirubin  $\geq 5 \times \text{ULN}$ . ATV discontinuation may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for the subject. Dose reduction of ATV is not permitted.

#### **4.5.5.13 Cardiac Management (for participants on ATV)**

Obtain EKG (if available) for participants who have symptoms potentially related to heart block (e.g., unexplained dizziness, syncope, palpitations or dyspnea).

#### **4.5.5.14 Renal Insufficiency**

Dose modifications are recommended for TDF, ddI-EC, d4T, and 3TC in subjects with reduced creatinine clearance (see the most recent package inserts).

TDF should be held for a confirmed creatinine clearance  $< 50 \text{ ml/min}$  until an underlying etiology for the renal insufficiency is determined. If the cause of renal insufficiency is from TDF, no other etiology is determined or the renal insufficiency improves with holding TDF, permanently stop TDF.

#### 4.5.6 Drug Substitutions

In the event of treatment-limiting toxicity, the following substitutions are allowed at any time:

**Table 7. Drug Substitutions**

Initial Drug	Substitution Drug	Other Indication /Comment
ZDV	d4T	For Grade 2 anemia (hemoglobin $\geq 7.0$ but $\leq 7.9$ g/dL) at Step 1 study entry, or at any regimen switch. d4T and ZDV should never be used together.
d4T	ZDV	None
EFV	NVP	Conversely, use EFV for NVP. There are little data available about the risks/benefits of changing from EFV to NVP for EFV-related AEs. NVP should be started at a dose of 200 mg daily for the first 14 days, followed by 200 mg BID; and will require LFT monitoring at weeks 2, 4, 6 and 8, after initiation of NVP, then monthly through the 20 <sup>th</sup> week of NVP treatment.
EFV, NVP	ATV	Use when neither EFV nor NVP can be used.
ATV	EFV	If EFV is contraindicated, NVP may be used.
TDF	ddI-EC	Use if subjects experience dose-limiting toxicity to TDF (e.g., confirmed calculated creatinine clearance $<50$ mL/min).
ddI-EC	TDF	Use for dose-limiting toxicity with ddI-EC (e.g., pancreatitis) TDF will not be used in the ATV arm unless ATV is boosted with low-dose ritonavir.

#### 4.5.7 Management of ART and Pregnancy, Contraception, and Breastfeeding

While ART during pregnancy will be provided to participants on both arms of the study, prenatal care for women who become pregnant, postpartum testing, or care to infants born to women will not be provided through this study. All women who become pregnant will be referred to local care facilities for the appropriate prenatal and postpartum care.

Monitoring for toxicity related to ART will continue during and after pregnancy. Refer to section 5.0 for additional procedures related to ART and pregnancy.



#### **4.5.7.1 Pregnant Women on a Regimen Containing EFV**

Women who are taking EFV and become pregnant will immediately stop EFV and substitute a different ART drug for the full course of pregnancy. The study clinicians will determine which ART drug should be substituted for EFV, and whether the woman should return to EFV following pregnancy. In particular for pregnant women with CD4+ counts  $>250$  cells/mm<sup>3</sup>, an ART drug other than NVP should be considered.

#### **4.5.7.2 Pregnant Women on a Regimen Containing ddI and d4T**

ddI will be replaced with 3TC, and d4T will be replaced with ZDV. Women in this case may return to their secondary regimen following pregnancy at the discretion of the study clinician.

#### **4.5.7.3 Pregnant Women on a TDF or ATV-Containing Regimen**

Data on the safety of TDF and ATV in pregnancy are limited; data on the appropriate dose of ATV for use in pregnancy has not yet been determined. During the run-in period, if a woman becomes pregnant while on a regimen containing ATV, ATV will be stopped and she will be placed on an appropriate substitute.

#### **4.5.7.4 Pregnant Women on a Regimen Containing Two ART Drugs with Hepatic Toxicity Potential**

Women who become pregnant on study should be monitored closely for liver toxicities when they are taking two hepatotoxic ARV drugs (e.g., d4T, NVP) concurrently.

#### **4.5.7.5 Contraception and a Regimen Containing NVP, NFV or LPV/RTV**

Interactions of study drugs with oral contraceptives: the effectiveness of estrogen-based contraceptives when co-administered with NVP, NFV, or LPV/RTV is unknown; NVP, NFV, and LPV/RTV decrease plasma levels of ethinyl estradiol; therefore, estrogen-based oral contraceptives are not reliable for women receiving LPV/RTV or NVP.

#### **4.5.7.6 Women Who Breastfeed**

During the run-in period, women who are breastfeeding must not take ATV. Other changes in ART for women who are breastfeeding while enrolled in HPTN 052 will be at the study clinician's discretion, and per package insert guidelines.

WHO guidelines for breastfeeding and replacement feeding will be made available in the SSP Manual, and sites will be encouraged to tailor these guidelines for local use as appropriate.

#### **4.5.8 Management of ART and Immune Reconstitution Inflammatory Syndromes**

Inflammatory syndromes have been reported to occur shortly after the initiation of potent combination ART. When these syndromes are suspected the following management plan is suggested. Consultation with the HPTN 052 CMC is recommended.

- Continue antiretroviral treatment.
- Confirm diagnosis of opportunistic infection (OI).
- Continue or initiate specific therapy for the infection.
- Evaluate the participant clinically to exclude a new infectious process if the subject was already receiving therapy for the OI.
- Initiate anti-inflammatory agents, initially non-steroidals or, if needed corticosteroids, at the discretion of the study clinician in consultation with the HPTN 052 CMC.

#### **4.5.9 Management of ART When OIs Occur**

When OIs are associated with inflammatory signs or symptoms and accompanied by an increase in the CD4+ T lymphocyte count and a drop in HIV-1 RNA level.

- These events may not represent clinical failure and should not initially be considered clinical endpoints.
- These events should be captured as clinical events without virologic and immunologic failure and managed as outlined above (*i.e.*, continue study treatment while treating the OI.)

When OIs occur despite complete virologic suppression and/or immunologic improvement (but without an inflammatory component):

- Confirm and document the clinical event.
- Initiate treatment for the OI.
- Altering of the ART regimen will be at the discretion of the study clinician.

When OIs occur in the setting of virologic and/or immunologic failure

- These events will be considered as primary study endpoints.
- Initiate specific therapy for the clinical event.
- Switch ART regimen if criterion for virologic failure is met (refer to Section 2.3.1)

#### **4.5.10 Management of ATV When Treating Tuberculosis**

Participants who are taking ATV and require rifampicin for the treatment of active TB should either replace rifampicin with rifabutin or replace ATV with EFV, during the period of rifampicin treatment. Participants should wait approximately 2 weeks after

stopping rifampicin before resuming ATV. Participants who receive rifabutin for the treatment of TB may remain on ATV. Refer to the ATV package insert.

## **5 STUDY PROCEDURES, CLINICAL PROCEDURES, AND LABORATORY EVALUATIONS**

An overview of the study visit and procedures schedule for both partners is presented in Appendix I A and B. Presented below is additional detail on visit-specific, and general study procedures. The procedures listed below and in Appendix I A and B must be performed at the visit indicated. It is important to note, however, that clinical examinations and laboratory evaluations can be performed at any time the study clinician thinks it is warranted (during a scheduled or unscheduled visit); such instances will be documented in the participants' study records and on applicable CRFs.

The definition of all study visits will be included in the SSP Manual, e.g. monthly visits may equal 4 weeks, quarterly visits may equal 12 weeks, and so on.

### **5.1 Screening Visits**

It is the responsibility of the local site to determine the best approach to screening. For each participant, independent written informed consent for screening will be obtained before screening procedures are initiated. For each couple, the screening process will proceed in a step-wise manner until either all screening procedures are completed or one of the partners is found to be ineligible. Enrollment must occur within 60 days from the time of the first screening tests and exams. See Section 3.3 for important screening information.

#### **5.1.1 Screening**

##### **5.1.1.1 Administrative, Behavioral, and Regulatory Procedures Both Index Case and Partner**

- Screening informed consent
- Demographic information
- Eligibility checklist
- Locator information
- HIV pre-test, risk-reduction, and post-test counseling
- Couples HIV counseling

##### **5.1.1.2 Clinical Procedures – Index case**

- Urine collection (women only)

- Blood collection
- Directed history and physical exam to ascertain/rule out AIDS-defining illnesses

#### **5.1.1.3 Laboratory Evaluations – Index Case**

- Urine pregnancy test (women only)
- HIV EIA antibody test/Western blot/IFA
- CBC (including hemoglobin and platelets)
- Blood chemistry (defined as sodium, potassium, chloride, phosphate, bicarbonate, creatinine, and albumin)
- LFTs (defined as AST [SGOT], ALT [SGPT], alkaline phosphatase, and total bilirubin)
- CD4+ cell count
- Sample storage:
  - plasma
  - serum

#### **5.1.1.4 Clinical Procedures – Partner**

- Blood collection

#### **5.1.1.5 Laboratory Evaluations – Partner**

- HIV EIA antibody test/Western blot/IFA

### **5.2 Enrollment**

Note: Screening and treatment for malaria, and parasitic diseases will be performed only at sites located in endemic areas, and is denoted throughout the sections below with the term “site specific”.

#### **5.2.1 Administrative, Behavioral, and Regulatory Procedures – Both Index and Partner**

- Study informed consent
- Locator information
- Randomization
- Sexual history assessment

- Couples HIV counseling

### **5.2.2 Clinical Procedures – Index Case**

- Urine collection
- Fecal collection (site specific)
- Semen collection
- Blood collection
- Complete medical history, concomitant medications, and physical exam including signs and symptoms, height, weight, vital signs (temperature, blood pressure and pulse) and directed evaluation for HIV and/or AIDS related conditions
- Chest x-ray (U.S. site only: obtain PPD first. If > 5mm induration then chest x-ray is obtained. Refer to local SOP for instructions regarding treatment.)
- Genital exam (swab if genital ulcer is observed for multiplex PCR)
- Pelvic exam (women only) including cervical swab
- Provide treatment (as clinically indicated)
- Provide study medications (ART and/or HIV primary care, if applicable)
- Adherence counseling (only while on study medication)

### **5.2.3 Laboratory Evaluations – Index Case**

- Urine pregnancy test (women only)
- Urine PCR for chlamydia trachomatis (CT) and Neisseria gonorrhea (GC) for men, vaginal swab for PCR for GC and CT for women
- Urine smear for parasites (site specific)
- Fecal smear for parasitic diseases (site specific)
- Cervical/seminal HIV-1 RNA PCR
- Wet mount for TV, BV, candida
- Multiplex PCR (if genital ulcer is observed)
- CBC
- Blood chemistry

- Other blood chemistries prn
- LFTs
- CD4+ cell count
- Blood plasma HIV-1 RNA PCR
- Hepatitis B serology
- Syphilis serology
- HIV genotyping (when instructed by HPTN Central Lab)
- Malaria thick/thin smears (site specific)
- Samples for storage:
  - plasma, to include a separate sample for HIV genotyping
  - serum
  - whole blood (subset)
  - PBMCs (subset)
  - genital secretions

#### **5.2.4 Clinical Procedures – Partner**

- Urine collection
- Blood collection
- Complete medical history and physical exam including signs and symptoms, height, weight, vital signs (temperature, blood pressure and pulse)
- Genital exam (swab if genital ulcer is observed)
- Pelvic exam (women only) with cervical swab
- Provide treatment (as clinically indicated)
- Adherence counseling (only while index case is on study medication)

#### **5.2.5 Laboratory Evaluations – Partner**

- Urine PCR for chlamydia and gonorrhea for men, and vaginal swab for PCR for GC and CT in women

- Wet mount for TV, BV, candida
- Multiplex PCR (if genital ulcer is observed)
- Syphilis serology
- Samples for storage:
  - plasma
  - serum
  - whole blood (subset)
  - PBMCs (subset)

### **5.3 On-Study Follow-up**

#### **5.3.1 Week Two**

##### **5.3.1.1 Administrative, Behavioral, and Regulatory Procedures – Both Index and Partner**

- Locator information
- Couples HIV counseling
- Adherence assessment (index case only, while on study medications)

##### **5.3.1.2 Clinical Procedures – Index Case**

- Blood collection
- Directed history, concomitant medications, and physical exam to assess signs and symptoms, and ascertain any HIV/AIDS related conditions
- Provide treatment (as clinically indicated)
- Provide study medications (ART and/or HIV primary care, if applicable)
- Adherence counseling (only while on study medication)

##### **5.3.1.3 Laboratory Evaluations – Index Case**

- CBC
- Blood chemistry
- Optional blood chemistries prn

- LFTs
- Multiplex PCR (if genital ulcer is observed)

#### **5.3.1.4 Clinical Procedures – Partner**

- Provide treatment (as clinically indicated)
- Adherence counseling (only if index case is on study medications)

#### **5.3.1.5 Laboratory Evaluations – Partner**

- Multiplex PCR (if genital ulcer is observed)

### **5.3.2 Monthly Visits (months other than quarterly or yearly visit months)**

Monthly study visits are required for all couples regardless of treatment arm.

#### **5.3.2.1 Administrative, Behavioral, and Regulatory Procedures – Both Index and Partner**

- Locator information
- Sexual history assessment (Month 1 and 2)
- Couples HIV counseling
- Adherence assessment (index case only, while on study medications)

#### **5.3.2.2 Clinical Procedures – Index Case**

- Urine collection (women only)
- Blood collection (first two months after initiation of ART only)
- Directed history, concomitant medications, and physical exam to assess signs and symptoms, and ascertain any HIV/AIDS related conditions
- Provide treatment (as clinically indicated)
- Provide study medications (ART and/or HIV primary care, if applicable)
- Adherence counseling (only while on study medication)

#### **5.3.2.3 Laboratory Evaluations – Index Case**

- Urine pregnancy test (women only)
- CBC



- Blood chemistry
- Optional blood chemistries prn
- LFTs
- Multiplex PCR (if genital ulcer is observed)

Note: CBC, blood chemistry, LFTs will be measured at two consecutive monthly study visits immediately following initiation of ART only.

#### **5.3.2.4 Clinical Procedures – Partner**

- Provide treatment as clinically indicated
- Adherence counseling (while index case is on study medications)

#### **5.3.2.5 Laboratory Evaluations – Partner**

- Multiplex PCR (if genital ulcer is observed)

### **5.3.3 Quarterly Visits**

#### **5.3.3.1 Administrative, Behavioral, and Regulatory Procedures – Both Index and Partner**

- Locator information
- Sexual history assessment
- HIV pre-test, risk reduction, and post-test counseling (partner only)
- Couples HIV counseling
- Adherence assessment (index case only, while on study medications)

#### **5.3.3.2 Clinical Procedures – Index Case**

- Urine collection (women only, for pregnancy testing)
- Blood collection
- Directed history, concomitant medications, and physical exam
- Provide treatment (as clinically indicated)
- Provide study medications (ART and/or HIV primary care, if applicable)
- Adherence counseling (only while index case is on study medication)

#### **5.3.3.3 Laboratory Evaluations – Index Case**

- Urine pregnancy test (female only)
- CBC
- Blood chemistry
- Optional blood chemistries prn
- LFTs
- CD4+ cell count
- Blood plasma HIV-1 RNA PCR
- Multiplex PCR (if genital ulcer is observed)
- Samples for storage:
  - plasma
  - serum
  - PBMCs (subset only)

#### **5.3.3.4 Clinical Procedures – Partner**

- Blood collection
- Directed history and physical exam
- Adherence counseling (only if index case is on study medications)
- Provide treatment (as clinically indicated)

#### **5.3.3.5 Laboratory Evaluations - Partner**

- HIV EIA test/Western blot/IFA
- Multiplex PCR (if genital ulcer is observed)
- Samples for storage:
  - plasma
  - PBMC's (subset only)

#### **5.3.4 Yearly Visits**

##### **5.3.4.1 Administrative, Behavioral, and Regulatory Procedures – Both Index and Partner**

- Locator information
- Sexual history assessment
- HIV pre-test, risk reduction, and post-test counseling (partner only)
- Couples HIV counseling
- Adherence assessment (index case only, while on study medications)

##### **5.3.4.2 Clinical Procedures – Index Case**

- Urine collection
- Fecal collection (site specific)
- Semen collection
- Blood collection
- Directed history, concomitant medications, and physical exam to assess signs and symptoms, and ascertain any HIV/AIDS related conditions
- Genital exam (swab if genital ulcer is observed for multiplex PCR)
- Pelvic exam (women only) with cervical swab
- US site only: Obtain PPD. If > 5mm induration, obtain chest x-ray. (Refer to local SOP for instructions regarding treatment).
- Provide treatment (as clinically indicated)
- Provide study medications (ART and/or HIV primary care, if applicable)
- Adherence counseling (only while on study medication)

##### **5.3.4.3 Laboratory Evaluations – Index Case**

- Urine pregnancy test (women only)
- Urine PCR for chlamydia and gonorrhea for men, and vaginal swab for PCR for GC and CT for women
- Urine smear for parasitic protozoa (site specific)

- Fecal smear for parasitic diseases (site specific)
- Cervical/semenal HIV-1 RNA PCR
- Wet mount for TV, BV, candida
- Multiplex PCR if genital ulcer is observed
- CBC
- Blood chemistry
- Optional blood chemistries prn
- LFTs
- CD4+ cell count
- Blood plasma HIV-1 RNA PCR
- Syphilis serology
- Malaria thick/thin smears (site specific)
- Samples for storage:
  - plasma
  - serum
  - PBMCs (subset only)
  - genital secretions

#### **5.3.4.4 Clinical Procedures – Partner**

- Urine collection
- Blood collection
- Directed history and physical exam
- Genital exam (swab if genital ulcer is observed)
- Pelvic exam (women only) with cervical swab
- Provide treatment (as clinically indicated)
- Adherence counseling (only while index case is on study medication)

#### **5.3.4.5 Laboratory Evaluations – Partner**

- Urine PCR for chlamydia and gonorrhea for men, and vaginal swab for PCR for GC and CT
- Wet mount for TV, BV, candida
- Multiplex PCR if genital ulcer is observed
- HIV EIA antibody test/Western blot/IFA
- Syphilis serology
- Samples for storage:
  - plasma
  - serum
  - PBMCs (subset only)

#### **5.3.5 Procedures For Off Study Regimen/On Study**

“Off study regimen” will be defined as permanently stopping all study treatment prior to study completion. In these situations, participants should be encouraged to continue in the study to receive their on-study evaluations through the completion of the study to the extent possible for secondary endpoint evaluations as defined in Table 12.

#### **5.3.6 Procedures for Both Index Case and Partner if Partner Becomes HIV Infected**

In the event that a partner seroconverts at any time during the course of the study, the following procedures and evaluations should be performed, unless they are already being performed as part of a regularly scheduled study visit.

##### **5.3.6.1 Clinical Procedures – Index Case**

- Semen collection
- Blood collection
- Pelvic exam (women only) including cervical swab for HIV-1 RNA PCR
- Provide treatment (as clinically indicated. This refers to study-provided non-ART treatment. See Section 8.3 for more information.)

##### **5.3.6.2 Laboratory Procedures – Index Case**

- Cervical/seminal HIV-1 RNA PCR

- Multiplex PCR if genital ulcer is observed
- Blood plasma HIV-1 RNA PCR
- HIV genotyping
- Samples for storage:
  - Plasma, to include a separate sample for HIV genotyping
  - PBMCs (subset)
  - genital secretions

#### **5.3.6.3 Clinical Procedures – Partner**

- Semen collection
- Blood collection
- Directed history, concomitant medications, and physical exam to assess signs and symptoms, and ascertain any HIV/AIDS related conditions
- Genital exam (swab if ulcer is observed)
- Pelvic exam (women only) with cervical swab for HIV-1 RNA PCR
- Provide treatment (as clinically indicated)

#### **5.3.6.4 Laboratory Evaluations - Partner**

- Cervical/semenal HIV-1 RNA PCR
- Multiplex PCR if genital ulcer is observed
- CBC
- Blood chemistry
- Optional blood chemistries prn
- LFTs
- CD4+ cell count
- Blood plasma HIV-1 RNA PCR
- HIV genotyping

- Samples for storage:
  - plasma, to include a separate sample for HIV genotyping
  - serum
  - PBMCs (subset)
  - genital secretions

### **5.3.7 Procedures for Confirmed Virologic Failure**

The following clinical procedures and laboratory evaluations should be performed, unless they are already being performed as part of a regularly scheduled study visit.

#### **5.3.7.1 Administrative, Behavioral, and Regulatory Procedures – Index Case**

- Adherence assessment

#### **5.3.7.2 Clinical Procedures – Index Case**

- Blood collection
- Adherence counseling
- Provide treatment (as clinically indicated)

#### **5.3.7.3 Laboratory Evaluations – Index Case**

- Blood plasma HIV-1 RNA
- HIV genotyping (when instructed by HPTN Central Lab)
- Sample collection for storage:
  - plasma, to include a separate sample for HIV genotyping

#### **5.3.7.4 Clinical Procedures – Partner**

- Adherence counseling
- Provide treatment (as clinically indicated)

### **5.3.8 Interim Visit (Ad Hoc)**

Interim visits may be conducted at participant request, or study clinician request, at any time during the study. Interim visits include any unscheduled visit taking place within a fixed amount of time from the previous visit, or before the next scheduled visit. Clinical reasons may include follow-up care for particular infections, or follow-up care for responses to particular treatments. Study staff will also instruct the index case to report to

the study clinic at any time for any symptoms possibly related to HIV or their study medications. Partners will be instructed to report to the study clinic at any time for symptoms suggesting acute HIV infection.

All visits will be documented in participants' study records and on applicable CRFs.

#### **5.4 Procedures to be Followed in the Event of Pregnancy or Breastfeeding**

In addition to what is outlined below, refer to Section 4.5.7.

##### **5.4.1 Procedures For Pregnancy or Breastfeeding at Enrollment**

In the run-in period, pregnant women are not eligible for enrollment. In the full study, pregnancy or breastfeeding women are eligible for enrollment, and must agree to be randomized. Breastfeeding or pregnant women on Arm 1 (immediate ART arm) should be prescribed ART drugs that are known to be safe during pregnancy or breastfeeding. (e.g. EFV, and the combination of ddI and d4T together should not be prescribed to these women.). During the run-in period, women who are breast-feeding should not receive study-provided ATV as part of their regimen.

##### **5.4.2 Procedures For Female Index Case on ART Who Becomes Pregnant During Study**

A pregnancy informed consent must be obtained. If the pregnant index case is already on a regimen containing EFV, EFV will be discontinued immediately and replaced with another NNRTI or PI during the remainder of the pregnancy, chosen at the discretion of the study clinician. However, during the run-in period pregnant women must not receive a regimen containing study-provided ATV. At the time the site becomes aware a participant is pregnant, study-provided ATV must be stopped and an appropriate drug given as substitution. In addition, during the run-in period women not already on ART who become pregnant should not be given study-provided ATV at any time during their pregnancy. If during the run-in period the site has access to ATV outside of the study, it may be provided per study clinician discretion and/or package insert guidelines. It should be noted that ddI-EC and d4T must not be coadministered during pregnancy.

##### **5.4.3 Procedures for Breastfeeding Women on ART**

Changes in ART for women who are breastfeeding will be at the study clinician's discretion. EFV is an evaluable drug for use in HIV-exposed infants and HIV-infected children. For this reason, breastfeeding women receiving EFV will be allowed to continue study drugs while breastfeeding. If a woman is breastfeeding during the run-in period, she must not be provided a regimen containing study-provided ATV.

##### **5.4.4 Procedures for Women Not on ART Who Become Pregnant**

Pregnant index cases not on ART (Arm 2) will be followed per study procedures, and placed on a triple regimen of ART regardless of CD4 + cell count at approximately the beginning of the 2<sup>nd</sup> trimester of pregnancy (e.g. 12-14 weeks of pregnancy), and for 4-6 weeks following birth. The ART will be provided through the study. The choice of regimen for such women should be documented in the study participant's chart and on



any applicable CRF's. The choice of the regimen must NOT include study-provided ATV, unless the site has access to it outside of the study. It should be noted that ddI-EC and d4T should not be coadministered.

Certain follow-up procedures during pregnancy may be modified in consultation with the CMC, as the study clinician may deem certain procedures as not appropriate in the pregnant woman at the time of the study visit. For example, after 24 weeks of pregnancy, blood collection may be limited. Study site clinicians should also refer to package inserts (on file at the sites) regarding the specific ART drug of concern for use during pregnancy.

## **5.5 Participant Retention**

Once a couple enrolls in this study, the study site will make every reasonable effort to retain them for the entire length of follow-up in order to minimize possible bias associated with loss-to-follow up. Optimally, participant retention procedures will be established at each site such that loss rates do not exceed the incidence rate of the primary study outcome. The study site staff is responsible for developing and implementing local SOPs to target this goal. Components of such procedures may include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process, and re-emphasis at each study visit.
- Thorough explanation of the importance of both treatment arms to the overall success of the study.
- Collection of detailed locator information at the study Screening Visit, and active review and update of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other locator venues.
- Use of appropriate and timely visit reminder mechanisms.
- Immediate and multifaceted follow-up on missed visits.
- Mobilization of trained outreach workers or “tracers” to complete in-person contact with participants at their homes or other community locations.
- Regular communication with the study community at large to increase awareness about HIV/AIDS and explain the purpose of HIV prevention research and the importance of completing research study visits.

## **5.6 Participant Withdrawal**

Participants may voluntarily withdraw from the study for any reason at any time. The site Investigator may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the Protocol Chair, SDMC Protocol Statistician, and CORE Protocol Specialist. Participants also may be withdrawn if the study sponsor, government or

regulatory authorities, or site IRBs/ECs terminate the study prior to its planned end date.

Participants will be withdrawn from the study if they become incarcerated in a correctional facility, prison, or jail, or if they are involuntary incarcerated into a medical facility for psychiatric or physical illness (e.g. infectious diseases).

Every reasonable effort will be made to complete a final evaluation of participants who terminate from the study prior to their final study visit. Study staff will record the reason(s) for all withdrawals from the study in participants' study records and any applicable CRFs.

## **6 EXPEDITED ADVERSE EVENT REPORTING**

This study will follow standard reporting requirements (Grade 4 and higher) throughout the study period and will follow the Manual for Expedited Reporting of Adverse Events to DAIDS and the Division of AIDS Table for Grading Adult and Pediatric Adverse Experiences. This document is included in Appendix VI and in the SSP Manual. The SSP Manual also will provide more detailed instructions regarding expedited reporting.

This level of reporting is required for an index case once they initiate ART study drugs, and will continue during the entire study follow-up period. Infants born to mothers enrolled in this study also will follow standard reporting requirements up to 18 months of age. The study agents for the purposes of expedited reporting of adverse events are: Atazanavir (ATV), Combivir (3TC/ZDV), Didanosine (ddI-EC), Efavirenz (EFV), Lamivudine (3TC), Nevirapine (NVP), Stavudine (d4T), Tenofovir (TDF), and Zidovudine (ZDV).

These adverse events must be documented on the Division of AIDS Expedited Adverse Event (EAE) Form found in the SSP Manual and submitted to the DAIDS Safety Office as described in the reporting guidelines. The Division of AIDS Table for Grading Adult and Pediatric Adverse Experiences must be used for determining and reporting the severity of adverse events, and can be found in the SSP Manual.

In addition to submitting EAE information to the DAIDS Safety Office, the site investigator is required to submit AE information as required by local regulatory or other local authorities.

For index cases, Grade 3 and higher AEs will be collected on standard case report forms (CRF's) for entry into the study database. AEs will not be collected for partners.

HIV/AIDS related conditions found in Appendix IV of this protocol, will not be captured as adverse events, but will be collected on standard CRF's for entry into the study database.

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience, except for possible

life-threatening events, for which they will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek medical care where the study clinician is based. With appropriate permission of the participant, whenever possible records from all non-study medical providers related to AEs will be obtained and required data elements will be recorded on study case report forms. All participants reporting an AE will be followed clinically, until the AE resolves, returns to baseline, or stabilizes.

Information on Grade 3 and higher AE's will be included in reports to the U.S. FDA, and other government and regulatory authorities as applicable. Site staff will report information regarding AE's to their IRB/EC in accordance with all applicable regulations and local IRB/EC requirements.

## **7 STATISTICAL CONSIDERATIONS**

### **7.1 Review of Study Design**

This is a multi-site, two-arm, randomized, controlled trial comparing two treatment strategies over 5 to 7.25 years of follow up (for an average of 5.82 years) for the prevention of HIV transmission in HIV serodiscordant couples.

Since short-term interruption of transmission of HIV could be offset by delayed transmission of resistant variants, evaluation of HIV transmission over 5 to 7.25 years will provide data on the longer-term effectiveness and public health utility of antiretroviral therapy. A 5 to 7.25 years follow-up will provide data on the relative utility of the strategies of immediate versus delayed antiretroviral therapy. Therefore, it is expected that the reduction in HIV rates after 5 to 7.25 years of follow-up will be smaller than observed during the first 18 months of follow-up because many participants will stop therapy, fail therapy, or develop resistant HIV variants (at least based on experience in the United States).

A run-in period of up to 9 months in duration will precede full enrollment in the trial. A total of up to 90 couples, in which the index case has a CD4+ cell count of 300-500 cells/mm<sup>3</sup>, will be recruited over a 3 month period during this run-in period, enrolled, and assigned at random in equal proportions to the two treatment strategies. If the run-in period is successfully completed and the necessary ART drugs are obtained to continue enrollment, a total of up to 1660 serodiscordant couples will be recruited in 12 to 18 months. These couples will be followed for a minimum of 5 years. Therefore, the total trial duration is up to 7.25 years (87 months). All participants, regardless of entrance date, will be followed until the end of study, which is 7.25 years after enrollment in the run-in period begins.

Couples enrolled during the run-in period will have an expected median follow-up of 7.125 years while couples enrolled during the full study will have an expected median follow-up of 5.75 years. Thus, a total of 1750 participants will be recruited with an overall expected median follow-up of 5.82 years .

## **7.2 Study Endpoints**

### **7.2.1 Primary Endpoints**

Corresponding to the primary objective of the study, incident HIV infections occurring in the partners of randomized HIV-infected index cases will be assessed as the primary endpoint for the study. Only acquisition from the index partner will be included in the primary analysis, therefore, each endpoint will need to be confirmed (by genotyping) such that the viral envelope sequence in the index case matches that of the partner. A complementary analysis will consider acquisition from index partners and non-index partners. Therefore, all transmission events will be included in this analysis. The effectiveness obtained via this latter analysis will provide a measure of the overall public health effect of ART in the prevention of HIV transmission.

### **7.2.2 Secondary Endpoints**

Corresponding to the secondary objectives specified in Section 2.2, Table 8 outlines the secondary endpoints and how they will be measured:

**Table 8: Secondary Endpoints**

<b>SECONDARY ENDPOINT</b>	<b>MEASURED AS:</b>
Survival of index cases	<ul style="list-style-type: none"> <li>• Time from enrollment to death (all causes)</li> </ul>
Immunologic response of index case	<ul style="list-style-type: none"> <li>• CD4+ cell count over time</li> <li>• Time from enrollment to immunologic failure. (Immunologic failure is defined as two consecutive measurements of CD4+ cell count &lt; 200 cells/mm<sup>3</sup>, or develops an AIDS-defining illness).</li> <li>• Time from initiation of ART to immunologic failure.</li> <li>• Time from initiation of secondary regimen to immunologic failure.</li> </ul>
Virologic response of index case	<ul style="list-style-type: none"> <li>• Blood plasma HIV-1 RNA level over time.</li> <li>• Seminal plasma HIV-1 RNA levels over time in males.</li> <li>• Cervico vaginal HIV-1 RNA levels over time in females.</li> <li>• Time from initiation of the starting regimen to confirmed virologic failure.</li> <li>• Time from initiation of secondary regimen to confirmed virologic failure.</li> </ul>
Initiation of secondary regimen	<ul style="list-style-type: none"> <li>• Time to initiation of secondary regimen (any reason).</li> </ul>
Safety and toxicity of treatment	<ul style="list-style-type: none"> <li>• Time from enrollment to time of first development and any subsequent occurrence of Grade 3 or 4 ART-related toxicities</li> <li>• Time from enrollment to time to first serious AIDS related events (Grade 4 and higher)</li> <li>• Time from enrollment to time to first serious cardiovascular or other metabolic events (Grade 4 and higher)</li> <li>• Time from enrollment to time to first Grade 4 and higher events (any event)</li> </ul>
HIV drug resistant virus	<ul style="list-style-type: none"> <li>• Prevalence of drug resistant HIV virus</li> <li>• Proportion of infected partners acquiring a drug resistant HIV virus.</li> </ul>
Incidence of STDs in index case and partners	<ul style="list-style-type: none"> <li>• Time from enrollment to the time of first development and subsequent development of STDs</li> </ul>
Adherence in index case	<ul style="list-style-type: none"> <li>• Adherence to all treatment over time.</li> <li>• Adherence to treatment over time following initiation of antiretroviral therapy starting regimen.</li> <li>• Adherence to treatment over time following initiation of an antiretroviral therapy secondary treatment regimen.</li> </ul>
Sexual behavior of index cases on ART, and their partners	<ul style="list-style-type: none"> <li>• Sexual behavior over time following initiation of starting regimen.</li> <li>• Sexual behavior over time following initiation of a secondary regimen.</li> </ul>

### 7.3 Accrual, Follow -up, and Sample Size

In order to achieve sufficient statistical power, a total of 1750 serodiscordant couples in which the index case has a CD4+ cell count of 300-500 cells/mm<sup>3</sup> will be enrolled in this study over a period of 27 months. As mentioned in Section 7.1, up to 90 couples (6-10 couples for each of the 9 sites) will be enrolled in the first 3 months during the run-in phase of the trial. A total of 1660 couples will be enrolled from month 9 to 27 after the completion of the run-in phase. All couples will be followed until the end of the trial at 7.25 years (87 months).

For the purpose of simplifying the sample size and power calculations, it is assumed that 1750 couples will be recruited and enrolled over 18 months and that the total trial duration is 6.5 years (78 months). This yields a median follow-up of 5.75 years instead of 5.82

years, if the run-in phase is taken into account. This has negligible effect on the sample size and power calculations.

The rationale for the sample size determination revolves on three key assumptions: (1) risk of HIV transmission within a couple will decline over time, (2) effectiveness of ART may decrease over time, and (3) the time of delay before the initiation of ART in Arm 2 will impact transmission. Given these three assumptions, expected differences in cumulative HIV rates at the end of the trial between Arm 1 and Arm 2 can be computed and used to establish the sample size. Tables 9, 10, 11, and 12 describe the assumptions used for (1), (2), and (3), respectively. The power calculations for the trial, under several scenarios, are given in Table 14.

The sample size was determined in two steps:

- Step 1: Expected differences in cumulative HIV rates at the end of the trial are computed under the assumption that participants in Arm 2 do not initiate antiretroviral therapy at any point in time during follow-up. Under this assumption, the expected differences in rates are between 5.5% and 8.3%. These differences translate into an average effectiveness (favoring Arm 1) between 35% and 52% (see Table 11). A sample size of 1750 couples would provide 90% power to detect an average effectiveness  $\geq 37\%$  (see Table 12).
- Step 2 : Using the assumption on the delay time before initiation of antiretroviral therapy in Arm 2 (see Table 13), the average effectiveness (and power) computed in Step 1 are re-computed in order to account for the delayed initiation of antiretroviral therapy in Arm 2. Of course, initiation of antiretroviral therapy in Arm 2 will lower the expected effectiveness computed in Step 1. The decrease in the expected effectiveness can be seen in Table 11, they range from 17% to 46% under different scenarios. A sample of 1750 couples provides high and moderate statistical power to detect expected effectiveness under most of the scenarios (see Table 14).

The five (5) assumptions used in the two above steps are described in more details below.

- **Assumption 1:** Table 9 provides the cumulative one year HIV incidence rates (rates of acquisition) among the partners of index cases who received HIV primary care plus no treatment only (*e.g.*, no initiation of antiretroviral therapy at any point in time):

**Table 9:** Cumulative 1-year HIV Incidence Rates Among Partners of Index Cases Receiving HIV Primary Care

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Cumulative 1-year HIV incidence rates	5%	5%	3%	3%	1%	1%	1%

This yields a cumulative HIV rate at the end of the trial of 16.6%.

- **Assumption 2:** Table 10 outlines the expected effectiveness for Arm 1 (immediate initiation of antiretroviral therapy) compared to HIV primary care only over time under two scenarios of decreasing effectiveness over time:

**Table 10:** Expected Effectiveness of Arm 1 Compared to HIV Primary Care Alone

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
(1) High effectiveness early with rapid decrease to 20%	80%	60%	40%	20%	20%	20%	20%
(2) Medium effectiveness early with decrease to 10%	50%	40%	30%	20%	10%	10%	10%

Each of the above two scenarios (combined with assumption 1) yields a different expected cumulative HIV incidence rate among partners of index cases in Arm 1.

Table 11 outlines the expected cumulative HIV incidence rates at the end of the trial for Arm 1 under the two above scenarios for the expected effectiveness over time. The average effectiveness is computed by subtracting the following quotient from 1: the expected incidence rate in Arm 1 divided by the expected rate among partners of index cases who receive HIV primary care only .

**Table 11:** Expected Cumulative HIV Incidence Rates at the end of the trial for Arm 1

Scenario	Cumulative HIV Rates at end of trial	Average Effectiveness
HIV primary care alone	16.6%	---
(1) High effectiveness early with rapid decrease to 20%	8.3%	52%
(2) Medium effectiveness early with decrease to 10%	11.1%	35%

- **Assumption 3:** Table 12 provides the total sample size required for different power and effectiveness assuming the HIV rate of assumption 1 (*i.e.* cumulative HIV rate of 16.6% at the end of the trial).

**Table 12:** Total Sample Size Required for a Total Trial Duration of 6.5 Years Trial with 1.5 years accrual, cumulative HIV rate of 16.6% at the end of the trial and 5% per Year Loss to Follow-up.

Effectiveness	Number of Required Study Couples	
	80% Power	90% Power
50%	640	860
45%	820	1100
40%	1070	1440
35%	1450	1940
25%	3020	4050

A total sample size of 1750 provides 87% power to detect an effectiveness of 35% as in the case of scenario (2) in Table 11. Given the above assumptions, a 35% effectiveness translates into an approximately 5.5% absolute difference in the cumulative HIV rates (from 16.6% to 11.1%). Under scenario (1), 1750 couples provides >99% power to detect a 52% effectiveness, which translates into an approximately 8.3% absolute difference in the cumulative HIV rates (from 16.6% to 8.3%).

- **Assumption 4:** The expected effectiveness obtained in Table 12 has been obtained by comparing the effectiveness of immediate antiretroviral therapy to HIV primary care alone (with no initiation of antiretroviral therapy at any point in time). Participants in the delayed arm in this trial will receive antiretroviral therapy if their CD4+ cell count drops below 200 cells/mm<sup>3</sup> during follow-up and/or because of AIDS-defining illness. Therefore, it is expected that the initiation of antiretroviral therapy during follow-up for participants in Arm 2 will decrease the overall risk of acquisition in Arm 2 described in assumption 1.

In order to assess the impact on HIV rates of the initiation of antiretroviral therapy for some participants in Arm 2, further assumptions on the number of participants initiating antiretroviral therapy during follow-up must be made.

Assuming uniform distribution of CD4+ cell count in the study population ( $300 \leq \text{CD4} \leq 500$ ), a rate of CD4 cell loss of 60 cells per year, and 10% annual incidence of AIDS-defining illnesses (independent of CD4+ cell counts), Table 13 represents the expected proportion of participants on Arm 2 who will initiate antiretroviral therapy over follow-up:



**Table 13:** Expected Cumulative Percentage of Index Cases in Arm 2 Initiating ART because of CD4+ Cell Count < 200 cells/mm<sup>3</sup> or an AIDS-defining Illness

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Percentage of participants in Arm 2 initiating ART	10%	27%	56%	80%	100%	100%	100%

Based on Table 13 and on uniformly distributed starting time for ART within year intervals, the average delay time before initiating antiretroviral therapy for participants in Arm 2 is approximately 2.8 years. More than three quarters (78%) of all the participants will be on antiretroviral therapy after three (3) years of follow-up (100% and 56% of participants in arm 1 and 2, respectively).

- Assumption 5:** In order to compute expected HIV incidence rates for partners of index cases in Arm 2, a further assumption needs to be made on the rates of HIV acquisition for the partners of those initiating antiretroviral therapy during follow-up (the participants from assumption 4). A risk reduction from 25% to 50% is anticipated for these participants. This assumption combined with assumptions 1 and 4 will yield an expected HIV cumulative rate for the participants of Arm 2. For instance, the expected cumulative HIV rate for HIV primary care alone drops from 16.6% to 14.9% if initiation of antiretroviral therapy during follow-up for participants of Arm 2 is taking into account with a 25% reduction in the rates for those participants (14.2% and 13.2% expected cumulative HIV rate for 35% and 50% reduction in rates, respectively).

In addition, the above assumes the risk of acquisition to be homogenous. That is, the risk of acquisition for partners of those with CD4+ cell count dropping below 200 cells/mm<sup>3</sup> and/or developing AIDS-defining illnesses is similar to the one for partners of those with CD4+ cell count above 200 cells/mm<sup>3</sup> with no AIDS-defining illnesses. This is a reasonable assumption because, if the risks were quite different, the overall risk of acquisition would greatly increase over time. In the absence of ART, the number of infected partners with CD4+ cell count dropping below 200 cells/mm<sup>3</sup> and/or experiencing AIDS-defining illnesses is increasing rapidly over time, which would greatly increase the overall rates over time. This increase would contradict assumption 1 which is based on observed data from the literature.

Table 14 represents the power under different scenarios for a total sample size of 1750 participants, a total trial duration of 6.5 years, an accrual period of 1.5 years, and 5% per year loss to follow-up per arm.

**Table 14:** Power and Effectiveness of the Trial Under Scenarios (1) and (2)

Scenario	Expected Cumulative HIV Rate at the End of Trial for Arm 1	Percentage of Rate Reduction for Index Cases in Arm 2 Initiating ART	Expected Cumulative HIV Rates at the End of Trial for Arm 2	Power	Effectiveness
(1) High effectiveness early with rapid decrease to 20%	8.3%	25%	14.9%	98%	46%
		35%	14.2%	95%	43%
		50%	13.2%	87%	39%
(2) Medium effectiveness early with decrease to 10%	11.1%	25%	14.9%	61%	27%
		35%	14.2%	46%	24%
		50%	13.2%	25%	17%

Under Scenario (1), power is greater than 87% to detect effectiveness  $\geq 39\%$ , which translates to a  $\geq 4.9\%$  absolute difference between the cumulative rate (13.2% versus 8.3% for scenario (1)). This power is achieved with an upper limit of a 50% reduction of risk of acquisition for partners of index case who initiate antiretroviral therapy in Arm 2 during follow-up.

Under Scenario (2), a total sample size of 1750 couples provides 61% power to detect a 3.8% absolute decrease in the cumulative HIV incidence rate (14.9% versus 11.1%). If the decrease in risk of acquisition for partners of those on arm 2 who initiate antiretroviral therapy is more than 25%, the trial will be greatly underpowered under this scenario. However in this case, the absolute difference in the cumulative HIV rate will be less than 3.1%, which would not be of clinical importance.

Assumptions on the cumulative one year HIV incidence rates of acquisition (*e.g.*, assumption 1) were made conservatively. Power calculations performed in Table 18 were re-computed using higher HIV rates. Higher HIV rates will increase the power. For instance if the year 1 to year 7 HIV rates are 7%, 7%, 5%, 5%, 2%, 2%, and 2% the power under Scenario 1 are all above 90%. For Scenario 2, moderate power (*i.e.* 50% < power < 75%) is achieved if the decrease in risk of acquisition for partners of those on arm 2 who initiate antiretroviral therapy is 25% or 35%.

#### 7.4 Randomization

Eligible couples will be randomized in a 1:1 ratio to either the Arm 1 group or the Arm 2 group. Randomization will be stratified by site using permuted block randomization such that approximately equal numbers of couples are assigned to each treatment group within each site. Instructions for how randomization will be conducted at the sites will be provided in the SSP Manual.

## 7.5 Blinding

This is an unblinded study. Participants are not blinded since the aim of the trial is to estimate and to compare the long-term effectiveness of the two treatment strategies. Treatment effects on behaviors, for instance, are part of the intervention that need to be included in the assessment of effectiveness. Furthermore, an unblinded design will allow for the proper clinical management of index cases.

## 7.6 Data Analysis

### 7.6.1 Primary Analyses

The primary analysis will be performed on an intent-to-treat basis. The primary analysis will be based on incident HIV infections in the partners as defined in section 7.2.1. More specifically, follow-up of partners will be censored for the following situations:

- If the index case dies, the partner's follow-up will be censored at the time of death of the index partner.
- If the sexual relationship between the partner and the index case ends, the partner's follow-up will be censored at the time when the relationship ended.
- Follow-up of new partner will be included (see description of analysis below) if the index case forms a relationship with a new partner after his/her previous relationship has ended and/or the previous partner died, and this new partnership meets all the inclusion criteria. The period of time between partnership, if any, will be excluded from the risk set in the analyses.
- If the transmission of the virus to the partner is proven to be **not** from the index case (by HIV genotyping), the partner's follow-up will be censored at the time of HIV infection (and will not be counted as a primary endpoint).
- If the partner is lost to follow-up, the partner's follow-up will be censored at the time of his/her last visit.

For each treatment arm, the distribution of time to HIV infection will be described using Kaplan-Meier curves. Treatment differences will be evaluated using the Andersen Gill Proportional hazard model with robust variance estimates. A two-sided stratified test at a 5% level of significance with strata defined by the participant sites will be used. The Andersen Gill model allows the censoring scheme described above, in particular, the exclusion from the risk set of time period between partnerships.

The Andersen Gill model is equivalent to the Cox model if there are no breakups among all the couples. If the initiation of treatment affects the partnership duration, the analyses could be confounded by the effect of this informative censoring. Given the countries of the participant sites and the inclusion and exclusion criteria, we are expecting that only a small proportion of partnership will end during follow-up. Nevertheless, the possible effect of

informative censoring induced by the above censoring scheme will be investigated by adapting the methods of Robins and Scharfstein<sup>69-70</sup>.

Given that the effectiveness is expected to decrease over time, the proportional hazards assumption will be evaluated formally using a test similar to the one described in Grambsch and Therneau. If the effectiveness is found to be varying over time, methods similar to the one described in Gilbert *et al* will be used to describe the effectiveness curve over time along with simultaneous confidence bands. This analysis should provide evidence if the short-term effectiveness differs substantially from the long-term-effectiveness, that is, treatment difference that favors one arm early in follow-up but that is reversed with more follow-up.

The effect of baseline characteristics (*e.g.*, plasma HIV-1 RNA baseline level, CD4 count, age, gender, *etc*) will be explored using the Andersen Gill proportional hazards model. In addition, the effect of potential prospective confounders (*e.g.*, adherence, HIV risk behaviors) will be explored (see next section for more details).

Using a similar approach as the one described above, a complementary analysis will be performed where all the transmission endpoints will be included in the analysis. For this analysis, unlike the previous analysis where HIV infections proven to be **not** from the index partner (by HIV genotyping) were censored, all HIV infections will be counted as primary endpoints. The effectiveness obtained via this latter analysis will provide some measure of the overall public health effect of ART in the prevention of HIV transmission. Although the assessment of the overall public health effect of ART would need to include all transmissions including transmissions from the index cases outside the partnership and all the secondary transmissions, these cannot be assessed within the design of the trial.

### 7.6.2 Secondary Analyses

Many secondary analyses will be performed using the secondary endpoints described in Table 12. Time to event data will be analyzed according to the Kaplan-Meier method where treatment strategy differences will be tested using the stratified log-rank test while secondary endpoints involving repeated assessment over time (*e.g.*, adherence and sexual behavior) will be compared at selected time points. At each of the selected time points, comparison of the two treatment arms will be made using Fisher exact test or Wilcoxon rank-sum test as appropriate. More generally, GEE (Generalized Estimating Equation)<sup>72</sup> methods and robust variance estimates will be used to evaluate treatment effect and trends over time. These analyses will be used to compare between the two arms outcomes related to mortality, disease progression, morbidity, safety, toxicity, and transmission of HIV drug resistant virus. See the complete list of secondary endpoints in Table 9. As for the primary analysis, the proportionality of the hazards over time will be evaluated using similar methods as describe in Section 7.6.1.

In addition, within each treatment arm, many exploratory analyses will be performed in order to identify predictors of plasma viral load, drug resistance, CD4 cell count, toxicity, opportunistic disease, clinical responses and outcomes.

Given that the trial is unblinded, an important secondary analysis will focus on adherence to study treatment strategy and sexual behavior. Self-reported adherence and sexual behavior will be measured monthly and quarterly, respectively. The main self-reported sexual behavior outcome that will be used in the analyses is the proportion of sexual acts, vaginal and anal, unprotected by condom.

For adherence, this data structure will permit the estimation of:

1. Adherence rates
2. The testing of differences in adherence between the two treatment strategies
3. The testing of trends over time in adherence rates and
4. The examination of the relationship between adherence and HIV infection.

Descriptive statistics will be used to estimate (1) at selected time points. Since the analysis will involve repeated observations, GEE methods and robust variance estimates, will be used to evaluate statistical significance and compute confidence intervals for (2) and (3). The Andersen Gill proportional hazards model with robust variance estimates will be used for (4) with HIV infection as the endpoint. Similar analyses as described above will be performed for the sexual behavior outcome. The relationship between adherence, sexual behavior and risk of incident HIV infection will also be examined. For this analysis, an Andersen Gill proportional hazards model with HIV infection as the endpoint and treatment arm, time-dependent adherence and sexual behaviors as covariates will be fit to the data.

## **7.7 Study Monitoring Plan**

Both treatment strategies are expected to differentially affect the immunologic and virologic responses throughout follow-up. It is expected that initially the HIV-1 RNA levels will be lower in the ART 'immediate' arm compared to the 'delayed' arm. Early in the trial, this should result in a reduced rate of HIV acquisition in the 'immediate' arm compared to the 'delayed' arm. Later in follow-up, these differences may diminish or even be reversed. Therefore, we are expecting short-term differences in effectiveness with a possible reversal in effectiveness in the longer term.

Thus, the study data monitoring plan must balance the need to protect trial participants, while enabling the trial to address its primary objective regarding the evaluation of the relative long-term effectiveness of two intervention strategies ('immediate' versus 'delayed').

The HPTN Study Monitoring Committee (SMC) and the Division of AIDS Data and Safety Monitoring Board (DSMB) will monitor the study. The SMC and DSMB will review the study data at least once per year. For each review, two reports will be produced: the open and closed report. The open report will include, at a minimum, data on recruitment, baseline characteristics, eligibility violations, adherence to study regimens, subject retention, and follow-up information. Most of the information in the open report will be pooled by treatment arm. The closed report will include, at a minimum, all the

information presented in the open report by treatment arm. In addition at each formal interim analysis review, analyses of efficacy and safety endpoints by treatment arm will be included. Typically, the SMC review of the open report will take place one to two weeks prior to the DSMB review.

The SMC review minutes of the open report will be sent to the DSMB along with the closed report. The closed report will only be reviewed by the DSMB. The open report will/may be used during the open session of the DSMB meeting. The study database will be closed no later than 8 weeks prior to the date of the DSMB meeting. The HPTN Statistical Data Management Center (SDMC) and the study statistician will prepare both reports.

Review of the safety and operational characteristics of the study will take place during each DSMB meeting (see Section 7.7.2). Based on these reviews, the DSMB could recommend early termination (or modification) if there is clear evidence of benefit or harm and/or if the quality of the study is judged as unacceptable. Continuation of the study will be recommended if the balance of benefit to harm remains adequate and if the study quality is acceptable.

#### **7.7.1 Monitoring Quality of Study Conduct Operational Characteristics and Implementation**

The study may be terminated or modified for poor recruitment, adherence, and/or retention. The following guidelines and measures will be used for stopping or modifying the study early. These guidelines are not intended to be kept as strict rules.

- Recruitment: The study sites are expected to enroll into the full study over the course of up to an 18 month period. Stopping or modifying the study may be considered if the study team fails to recruit 500 couples in the first 15 months, 1200 couples by the end of 21 months, and 1750 within 27 months after all sites have been opened for enrollment.
- Retention and losses to follow-up: Based on the expected incidence of HIV transmission, the target retention rate for the study is 98% per year (*i.e.* 2% lost to follow-up per year). At this rate, about 11% of couples will be lost to follow-up at the end of follow-up. Stopping or modifying the study may be considered if the study team fails to retain more than 96% of couples per year (*i.e.* 4% lost to follow-up per year). At a rate of 96% per year, about 1 in 5 couples will be lost to follow-up at the end of follow-up.

Differential (by study arm) “loss to follow-up” and site specific “loss to follow-up” data should be reviewed carefully since participants might choose to leave the study if treatment appears to fail and/or if other treatments become available. This type of informative censoring could seriously bias the study primary analysis.

This retention guideline may be modified if the baseline incidence is determined to be much lower/higher than predicted.

- Delay time: The primary objective of the study cannot be addressed if the time before initiation of ART in the “delayed” arm is too small. Based on various assumptions outlined in Section 7.3, it is expected that ART will be initiated 2 to 3 years (median 2.8 years) after enrollment of participants in the “delayed” ART arm of the trial.

Stopping or modifying the study may be considered if the median delay time is less than 1 year. For a median delay of 6 and 12 months (under scenario (1)), the expected differences between the two arms in the cumulative HIV incidence rates are in the range of [0.3%-4.3%] and [1.4%-4.9%], respectively, compared to a range of [4.9%-6.6%] for a median delay time of 2.8 years.

This delay time guideline should be evaluated in light of the safety and efficacy endpoint data collected since the expected differences in HIV transmission rely heavily on assumptions about the effectiveness of ART over time.

- Adherence: Given that the rationale for the study is based on the suppression of viral load, the primary objective of the study may not be addressed if viral suppression is not achieved in those initiating ART. However, given the ability of ART to concentrate in the genital tract, it is possible that HIV transmission will be prevented even if suppression of viral burden is less than optimal. Regardless of these possibilities, the overall benefits of ART depend on adherence to the regimens prescribed. Therefore, direct and indirect measures of adherence will be reviewed: (1) adherence to the study medication (*e.g.*, pill counts, self-report), (2) measurement of viral load assessed by blood plasma HIV-1 RNA levels, and (3) for index cases in the “delayed” arm, the difference between the time of ART initiation and the time CD4+ cell count drops below 200 cells/mm<sup>3</sup> and/or the occurrence of an AIDS-defining illness. The latter is assessing if index cases in the “delayed” arm are initiating ART when they should have according to the protocol, that is, when CD4+ cell count drops below 200 cells/mm<sup>3</sup> and/or the occurrence of an AIDS-defining illness.

The difference in viral load between the two arms at a given time point will depend on the CD4+ cell count decline rate, the incidence of AIDS-defining illnesses, and the rate of treatment failures. In the first 3 years of follow-up it is expected that the difference in viral load will be substantial, therefore for (2), stopping or modifying the study should be considered if there is less than a 3-fold difference in viral load between the two arms (favoring the immediate arm) within the first 3 years of follow-up (*i.e.* less than 0.5 difference in log<sub>10</sub> viral load).

For (3), the adherence to the treatment strategy in the ‘delayed’ arm, stopping or modifying the study should be considered if the median time (absolute) difference between the ART initiation time and the time the CD4+ cell count drops below 200 cells/mm<sup>3</sup> and/or the occurrence of an AIDS-defining illness is more than 4 weeks.

### 7.7.2 Monitoring of Efficacy and Safety Endpoints

A total of five formal interim analyses are planned. After the first couple is enrolled in the study, two safety only analyses will be reviewed at 6 and 12 months. In addition, three safety and efficacy analyses will be reviewed at 2, 3.5, and 5 years after the first couple is enrolled in the study. The final analysis will take place at the expected end of the study (*i.e.* 6.75 years after the first couple is enrolled in the study).

Acquisition of HIV will be the only efficacy endpoint to be reviewed while four safety endpoints will be reviewed:

- Acquisition of drug resistant HIV virus\*\*
- Serious AIDS related events (Grade 4 and higher)
- Serious cardiovascular and other metabolic events (Grade 4 and higher)
- Any Grade 4 and higher events

For example, it is possible that, in the short-term, the “immediate” arm may have a lower rate of HIV acquisition and of AIDS related AEs while possibly having a higher rate of cardiovascular and metabolic AEs than the “delayed” arm.

\*\* ART resistance can be expected to arise in participants (index cases) receiving therapy. Virologic assays to measure resistance are difficult to obtain and interpret. Accordingly, during the course of the trial the DSMB will be provided information about virologic failure and ART adherence in all index cases. In addition, we recognize that HIV-infected participants receiving ART through enrollment in the “immediate arm” could transmit resistant HIV variants to their sexual partners. However, the clinical consequences of acquisition of such HIV variants are currently not well understood because such resistance may not be sustained in the new host, genotypic resistance markers may not confer clinically relevant resistance, and the resistant variants transmitted may be less pathogenic. In addition, we will not be able to prove prospectively that the virus causing a new infection was actually acquired from the relevant sexual partner. Furthermore, participants with newly acquired HIV in this study will be unlikely to receive ART therapy themselves during the course of the study. We will, however, review all clinical and virologic information available about newly acquired HIV with the DSMB.

The DSMB may recommend early termination of the study or modification when there is clear evidence of benefit or harm or may recommend continuation of the study if the balance between benefit and harm remains adequate. Therefore, the DSMB may recommend stopping or modifying the study early in the following situations:

Clear evidence of serious safety problems including:

- An excess in frequency of serious AIDS related events (Grade 4 and higher) among the “delayed” arm participants compared to the immediate arm participants.



- An excess in frequency of serious cardiovascular and other metabolic events (Grade 4 and higher) among the “immediate” arm participants compared to the “delayed” arm participants.
- An excess in frequency of serious any serious adverse events (Grade 4 and higher) in one of the arm.
- Excess transmission of drug resistant HIV variants in the “immediate” arm AND clear-cut evidence that such resistance will compromise the immediate and future health and clinical care of the study participants.

Clear evidence of benefit:

- A statistically significant difference in the rate of HIV acquisition between the two arms appropriately adjusted for the sequential analysis.

Interim and final analyses will be adjusted to maintain an overall 5% type I error rate. Adjustments will be based on Lan and DeMet's implementation of the O'Brien-Fleming grouped sequential stopping boundary with time measured on the cumulative number of primary endpoints. This implementation permits early stopping only for very strong positive or negative effects and maintains nearly all the nominal power for the final analysis.

## **8 HUMAN SUBJECTS CONSIDERATIONS**

### **8.1 Ethical Review**

Studies such as this one raise issues unique to research in resource-limited settings. The protocol team has considered many of these issues, with special attention to the “World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants” Report, and the recent National Bioethics Advisory Committee (NBAC) Report. In addition, this protocol, any subsequent modifications to the protocol, and all initial site-specific informed consent forms will be reviewed and approved by the HPTN Protocol Review Committee and DAIDS Prevention Science Review Committee with respect to scientific content and compliance with research and human subjects regulations.

The protocol, site-specific informed consent forms, participant education and recruitment materials, and other requested documents — and any subsequent modifications — will also be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site.

Subsequent to initial review and approval, the responsible local Institutional Review Boards/Ethical Committees (IRBs/ECs) will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs/ECs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who

completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others.

## **8.2 Informed Consent**

Written informed consent will be obtained from each study participant (or a mark for those who are illiterate, which will be witnessed by a third party). Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendix IV, that describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations.

The study site is also responsible for translating the template forms into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

Participants will be provided with a copy of their informed consent forms if they are willing to receive them.

## **8.3 Access to HIV-Related Care**

This study will enroll men and women who are infected with HIV and their uninfected partners. At all study sites, HIV testing and counseling and couples HIV counseling will be provided. Condoms will be provided to participants throughout the duration of their participation.

Index cases will either begin on ART immediately upon enrollment (Arm 1) or when two consecutive measurements of their CD4+ cell counts becomes  $\leq 200$  cells/mm<sup>3</sup>, or they develop an AIDS-defining illness (Arm 2). Index cases will remain on therapy as long as clinically possible during their participation in the study. Index cases on both arms will be provided free HIV clinical care and other primary care during the course of the study to include screening and treatment for a variety of disease manifestations. This clinical care will be provided to index cases under the best clinical judgment of the study clinicians.

HIV-infected individuals identified through screening for all parts of the study who do not meet eligibility criteria, or who do not wish to enroll in the study, will be referred to local HIV care services, or other agencies that provide care or access to treatment. They will also be referred for possible enrollment into other available HIV treatment clinical trials.

For partners who become infected with HIV during the course of all parts of the study, the site will make every effort possible to provide HIV-related care to those individuals as resources will allow. They will also be referred to local HIV care services, NGO's, or other agencies that provide care or access to treatment. They will also be referred for possible enrollment into other available HIV treatment clinical trials.

The study Principal Investigator will work closely with the individual study sites to identify funding sources for HIV related care (e.g. access to, or provision of, ART and ART-related care) for enrolled index cases after the discontinuation of the study's financial support by the National Institutes of Health (NIH). Individual study sites will

provide to the NIH a written plan for provision of ART or HIV-related care. The plans will focus on those index cases in whom ART and HIV-related care would be considered required according to local standards of care and accepted guidelines (e.g. WHO/UNAIDS, USPHS for U.S. sites).

#### **8.4 Incentives**

With IRB/EC approval, participants can be compensated for their time and effort in this study. Site-specific reimbursement amounts will be specified in the study informed consent forms.

#### **8.5 Confidentiality**

All study-related information will be stored securely at the study site. All participant information will be stored securely in areas with access limited to study staff. To maintain participant confidentiality a coded number will identify all study specific laboratory specimens, reports, study data collection, process, and administrative forms. All study records that contain names or other personal identifiers will be stored separately from other study records. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate area with limited access. A participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the NIAID and/or its contractors; pharmaceutical companies; representatives of the HPTN CORE, SDMC, and/or CL; the U.S. FDA, other government and regulatory authorities, and/or the site IRB/EC.

#### **8.6 Communicable Disease Reporting Requirements**

Study staff will comply with all applicable local requirements to report communicable diseases identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

#### **8.7 Study Discontinuation**

The study may be discontinued at any time by NIAID, the HPTN, pharmaceutical companies, the U.S. FDA, in-country government or regulatory authorities, and/or the study site IRB/EC.

### **9 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT**

#### **9.1 Local Laboratory Specimens**

The following types of specimens will be collected for testing at the local laboratory:

- Blood for HIV-1 EIA, Western blot, IFA, HIV-1 RNA PCR, syphilis serology, CD4+ cell count, CBC, blood chemistry, LFTs, Hepatitis B serology, malaria thick/thin smears, and plasma, serum, whole blood, and PBMC storage;
- Urine for pregnancy testing, gonorrhea and chlamydia PCR, and parasitic protozoa smear;
- Vaginal wet mount for TV, BV, and candida;
- Genital secretions for storage;
- Fecal smears for parasitic diseases

Each study site will adhere to standards of GCP, and local standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens to the local lab. Specimen collection, testing, and storage at the local lab will be documented using the HPTN Laboratory Data Management System (LDMS).

HPTN guidelines require that the HPTN Central Lab (CL) certify each local laboratory for all protocol-specified assays, and that each local laboratory must maintain proficiency as certified by the HPTN CL throughout the duration of the study.

## **9.2 Central Laboratory Specimens**

As described in Section 5.0, the following types of specimens will be collected for storage and testing at the HPTN CL:

- Plasma for HIV genotyping (See “Note” below)
- Cervical swab for HIV-1 RNA;
- Semen for HIV-1 RNA; and
- Genital ulcer swab for multiplex PCR.

Each study site will adhere to standards of GCP, the SSP Manual, and local SOPs for proper collection, processing, labeling, and transport of specimens for the CL.

Note: Three regional laboratories will test plasma for HIV genotyping. If a regional laboratory is unable to perform this test, these samples will be sent to the HPTN CL. Procedures for shipment of specimens to the appropriate laboratory will be outlined in the SSP Manual.

## **9.3 Quality Control and Quality Assurance Procedures**

The HPTN CL has established a proficiency-testing program at each study site. CL staff also will conduct periodic visits to each site to assess the implementation of onsite laboratory quality control procedures, including proper maintenance of laboratory testing equipment and the use of appropriate reagents. CL staff will follow-up directly with

site staff to resolve any quality control or quality assurance problems identified through proficiency testing or on-site assessments.

On a quarterly basis throughout the study, the HPTN CL will select a random sample of stored specimens to test for quality assurance (QA) purposes.

The CL will inform site staff of the samples selected for quality assurance testing, and site staff will ship the selected specimens to the CL. All specimens will be shipped in accordance with the SSP Manual and IATA specimen shipping regulations. All shipments will be documented using the HPTN LDMS.

#### **9.4 Specimen Storage and Possible Future Research Testing**

Study site staff will store all collected specimens in this study until all quality assurance testing at the HPTN Central Lab has been completed. In addition, a separate consent will be administered asking for permission for specimens to be stored after the end of the study for possible future testing. The specimens of participants who do not consent to long-term storage and additional testing will be destroyed at the end of the study.

#### **9.5 Biohazard Containment**

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the U.S. Centers for Disease Control and Prevention (CDC). All infectious specimens will be transported in accordance with U.S. regulations.

### **10 ADMINISTRATIVE PROCEDURES**

#### **10.1 Study Activation**

Following ethical review and approval, study sites will submit required administrative documentation — as listed in the SSP Manual — to the HPTN CORE. CORE staff will work with study site staff and complete DAIDS protocol registration in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual. Included in this step will be CORE and DAIDS review of each site-specific study informed consent form.

Pending successful protocol registration and submission of all required documents, CORE staff will “activate” the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site.

#### **10.2 Study Coordination**

Study implementation will be directed by this protocol as well as the SSP Manual. The SSP Manual – which will contain reference copies of the DAIDS SOPs for Source

Documentation and Essential Documents, as well as the Manual for Expedited Reporting of Adverse Events to DAIDS and the DAIDS Table for Grading Adult and Pediatric Adverse Experiences– will outline procedures for conducting study visits; data and forms processing; AE assessment, management and reporting; dispensing study medications and documenting drug accountability; and other study operations. The SSP will be submitted to the sponsor prior to implementation of the study and will be made available to the IRBs/ECs, the U.S. FDA, and other in-country regulatory authorities upon request.

The study team and HPTN SDMC will develop study case report forms. Data will be transferred to the HPTN SDMC, where the data will be entered and cleaned. Quality control reports and queries will be routinely sent back to sites for verification and resolution.

Close cooperation between the study Investigator, NIAID Medical Officer, HPTN Clinical Research Manager, Biostatistician, Data Managers, and other study team members will be necessary in order to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. The study team will monitor rates of accrual, adherence, follow-up, and AE incidence closely. Representatives of the HPTN CORE and SDMC will also evaluate these rates on a regular basis.

### **10.3 Study Monitoring**

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to:

- verify compliance with human subjects and other research regulations and guidelines;
- assess adherence to the study protocol and local SOPs; and
- confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN CORE, SDMC, CL, NIAID, pharmaceutical companies if applicable, and U.S. and in-country government and regulatory authorities. A site visit log will be maintained at the study site to document all visits.

### **10.4 Protocol Compliance**

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and NIAID Medical Officer. All protocol amendments must be submitted to and approved by the relevant

IRB(s)/EC(s) and the DAIDS Regulatory Compliance Center (RCC) prior to implementing the amendment.

#### **10.5 Investigator's Records**

The Investigator will maintain and store in a secure manner complete, accurate, and current study records throughout the study. In accordance with U.S. regulations, for each of the products tested, the Investigator will retain all study records for at least two years following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the FDA is notified that the IND is discontinued. Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

#### **10.6 Use of Information and Publications**

Publication of the results of this study will be governed by DAIDS and HPTN policies. Any presentation, abstract, or manuscript will be submitted by the Investigator to the HPTN Manuscript Review Committee, DAIDS, and pharmaceutical companies for review prior to submission.

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## **Appendices**

## Appendix I. A. Schedule Of Procedures And Evaluations – Index Case

	Screening	Enrollment	Week 2	Monthly (other than quarterly/yearly)	Quarterly	Yearly	Partner Seroconverts	Confirmed Virologic Failure
<b>Administrative, Behavioral and Regulatory Procedures</b>								
Informed consent (screening or study informed consent form)	X	X						
Demographic information	X							
Eligibility checklist	X							
Locator information	X	X	X	X	X	X		
Randomization		X						
Sexual history assessment		X		X <sup>5</sup>	X	X		
HIV pre-test, risk reduction, and post-test counseling	X							
Couples HIV counseling	X	X	X	X	X	X		
Adherence assessment			X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>		X <sup>4</sup>
<b>Clinical Procedures</b>								
Urine collection	X <sup>1</sup>	X		X <sup>1</sup>	X <sup>1</sup>	X		
Fecal collection		[X]				[X]		
Semen collection		X				X	X	
Blood collection	X	X	X	X <sup>3</sup>	X	X	X	X
Complete medical history, con meds, physical exam		X						
Directed history, con meds, physical exam	X		X	X	X	X		
Chest x-ray (see Footnote #6)		X						
Genital exam (swab if ulcer is observed)		X				X		
Pelvic exam (women only, including swab)		X				X	X	
Provide treatment		[X]	[X]	[X]	[X]	[X]	[X]	[X]
Provide study medications (ART and/or primary HIV medications)		X	X	X	X	X		
Adherence counseling		X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>		X <sup>4</sup>
<b>Laboratory Evaluations</b>								
Urine pregnancy test (women only)	X	X		X	X	X		
Urine PCR for GC and CT (men only)		X				X		
Urine smear (O&P)		[X]				[X]		
Fecal smear (O&P)		[X]				[X]		
Cervical/semenal HIV-1 RNA		X				X	X	
Wet mount for TV, BV, candida		X				X		
Multiplex PCR (if genital ulcer observed) (see Footnote #7)		[X]	[X]	[X]	[X]	[X]	[X]	
PCR for GC and CT (vaginal swab)		X				X		
HIV EIA/Western blot/IFA	X							
CBC	X	X	X	X <sup>3</sup>	X	X		
Blood chemistry	X	X	X	X <sup>3</sup>	X	X		
LFTs	X	X	X	X <sup>3</sup>	X	X		
CD4+ cell count	X	X			X	X		
Blood plasma HIV-1 RNA		X			X	X	X	X
Hepatitis B serology		X						
Syphilis serology		X				X		
HIV genotyping (see Footnote # 2)		X					X	X
Malaria thick/thin smear		[X]				[X]		
<b>Sample Storage</b>								
Plasma	X	X <sup>2</sup>			X	X	X <sup>2</sup>	X <sup>2</sup>
Serum	X	X			X	X		
Whole Blood (see Footnote #2)		X						
PBMC's (see Footnote #2)		X			X	X	X	
Genital Secretions		X				X	X	

BV, bacterial vaginosis; CBC, complete blood count; IFA immunofluorescence assay; LFT ( liver function tests); O&P (ova and parasites); PBMC (peripheral blood mononuclear cells); TV (*Trichomonas vaginalis*). [ ] = If clinically indicated, or site specific

1 = Women only

2 = Refer to SSP for specific instructions.

3 = Perform at the first two months following initiation of antiretroviral therapy. When starting NVP, perform LFTs at week 2, 4, 6, then monthly for first 20 weeks.

4 = Administer/perform only if index case is on study medication.

5 = Perform at Study Month 1 and 2 only

6 = U.S. sites only: obtain PPD first. If > 5mm induration then chest x-ray is obtained.

7 = A swab should be taken for multiplex PCR at any time an ulcer is observed upon examination for shipment to the HPTN CL.



## Appendix I. B. Schedule Of Procedures And Evaluations – Partner

	Screening	Enrollment	Week 2	Monthly (other than quarterly/yearly)	Quarterly	Yearly	Partner Seroconverts	Confirmed Virologic Failure
<b>Administrative, Behavioral and Regulatory Procedures</b>								
Informed consent (screening or study informed consent form)	X	X						
Demographic information	X							
Eligibility checklist	X							
Locator information	X	X	X	X	X	X		
Randomization		X						
Sexual history assessment		X		X <sup>3</sup>	X	X		
HIV pre-test, risk reduction, and post-test counseling	X	X			X	X		
Couples HIV counseling	X	X	X	X	X	X		
<b>Clinical Procedures</b>								
Urine collection		X				X		
Semen collection							X	
Blood collection	X	X			X	X	X	
Complete medical history and physical exam		X						
Directed history and physical exam					X	X	X	
Genital exam (swab if ulcer is observed)		X				X	X	
Pelvic exam (women only, including swab)		X				X	X	
Provide treatment		[X]	[X]	[X]	[X]	[X]	[X]	[X]
Adherence counseling		X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>		X
<b>Laboratory Evaluations</b>								
Urine PCR for GC and CT (men only)		X				X		
Cervical/semenal HIV-1 RNA							X	
Wet mount for TV, BV, candida		X				X		
PCR for GC and CT (vaginal swab)		X				X		
Multiplex PCR (if genital ulcer observed) (see Footnote # 4)		[X]	[X]	[X]	[X]	[X]	[X]	
HIV EIA/Western blot/IFA	X				X	X		
CBC							X	
Blood chemistry							X	
LFTs							X	
CD4+ cell count							X	
Blood plasma HIV-1 RNA							X	
Syphilis serology		X				X		
HIV genotyping (see Footnote # 2)							X	
<b>Sample Storage</b>								
Plasma		X			X	X	X <sup>2</sup>	
Serum		X				X	X	
Whole Blood (see Footnote #2)		X						
PBMC's (see Footnote #2)		X			X	X	X	
Genital Secretions							X	

1 = Perform only if index case is on ART.

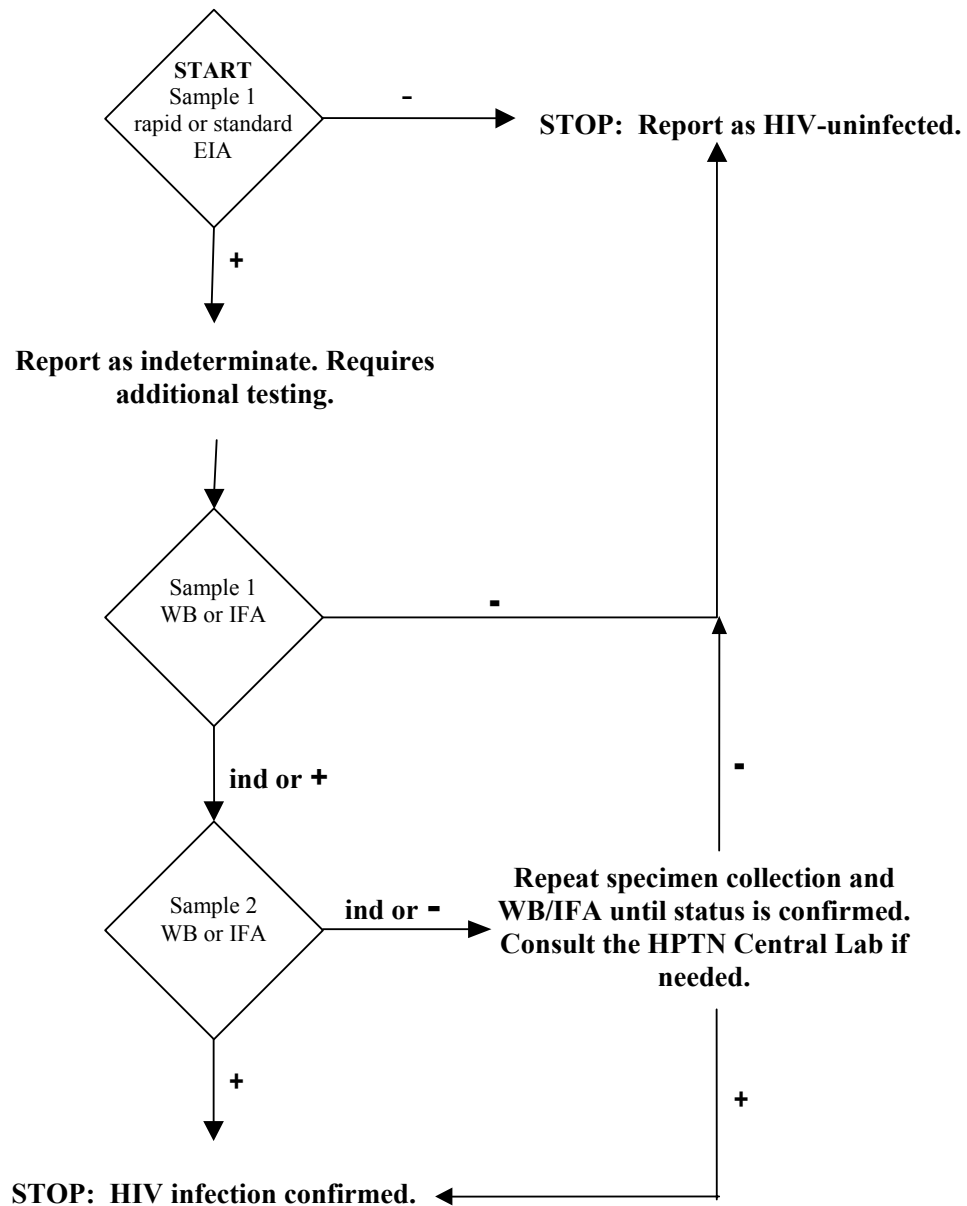
2 = Refer to SSP for specific instructions.

3 = Perform at Study Month 1 and 2 only

4= A swab should be taken for multiplex PCR at any time an ulcer is observed upon examination for shipment to the HPTN CL.

## Appendix II. HIV Antibody Testing Algorithm for Endpoint Ascertainment at Follow-up

(Partner Only)



### **Appendix III. WHO, CDC, and In-Country Derived AIDS Case Definition For Exclusion Criteria and Initiation of ART while on Arm 2**

The following list will be used for purposes of excluding a person from the study, and for participants on Arm 2 of the study as criteria for initiation of ART despite CD4 + cell count.

For purposes of the study, a person will be considered to have AIDS if they meet these case definitions for AIDS. The list below also includes some specific conditions per the definition of AIDS in Brazil and Thailand, and is noted accordingly.

#### **Current WHO Case Definition for AIDS<sup>1</sup>**

AIDS defined as at least 2 of the following major signs in combination with at least 1 of the minor signs listed below, and if these signs are not known to be due to a condition unrelated to HIV:

##### **Major signs:**

- weight loss  $\geq 10\%$  of body weight
- chronic diarrhea
- prolonged fever for more than 1 month (intermittent or constant)

##### **Minor signs:**

- persistent cough for more than 1 month (patients with TB would be considered a major sign)
- generalized pruritic dermatitis
- history of herpes zoster
- oropharyngeal candidiasis
- chronic progressive or disseminated herpes simplex infection
- generalized lymphadenopathy

#### **Current CDC Case Definition of AIDS<sup>2</sup> plus Country-specific Diseases for Brazil and Thailand**

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Chagas' disease (Rio de Janeiro and Porto Alegre, Brazil only)
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal ( $> 1$  month's duration)
- Cytomegalovirus disease, invasive
- Cytomegalovirus retinitis
- Encephalopathy, HIV-related

- Herpes simplex: chronic ulcer(s) (> 1 month's duration), bronchitis, pneumonitis, or esophagitis
  - Histoplasmosis, disseminated or extrapulmonary
  - Isosporiasis, chronic intestinal (> 1 month's duration)
  - Kaposi's sarcoma (progression to visceral disease)
  - Leshmaniaiasis (Rio de Janeiro, Brazil only)
  - Lymphoma, Burkitt's (or equivalent term)
  - Lymphoma, immunoblastic (or equivalent term)
  - Lymphoma, primary, of brain
  - *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
  - *Mycobacterium tuberculosis*, any site (pulmonary<sup>1</sup> or extrapulmonary)
  - *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
  - Nocardiosis, pulmonary, brain or disseminated
  - Paracoccidiomycosis (Porto Alegre, Brazil only)
  - Penicilliosis marneffi, disseminated (Thailand only)
  - Pneumonia, recurrent
  - *Pneumocystis carinii* pneumonia (new or recurrent diagnosis)
  - Progressive multifocal leukoencephalopathy
  - *Salmonella* septicemia, recurrent
  - Toxoplasmosis of brain
  - Wasting syndrome due to HIV
1. WHO Case Definitions for AIDS Surveillance in Adults and Adolescents. Weekly Epidemiological Record, No. 37, 16 September 1994, pp. 273-275.
  2. 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults. MMWR, Recommendations and Reports, December 18, 1992/41(RR-17)

**Appendix IV: HIV/AIDS Related or Defining Conditions for Inclusion into the Study  
Database (NOT for capture as an Adverse Event)**

**PARASITIC INFECTIONS**

Chagas's Disease  
Cryptosporidiosis, > 1 month duration  
Cyclospora  
Isosporiasis  
Leishmaniasis  
Microsporidiosis  
Pneumocystis Carinii Pneumonia (PCP)  
Extra-Pulmonary Pneumocystosis  
Toxoplasmic Encephalitis  
Non-CNS Toxoplasmosis

**FUNGAL INFECTIONS**

Disseminated Blastomycosis  
Esophageal Candidiasis  
Candidiasis of bronchi/trachea/lungs when obtained by tissue specimen (not from micro culture of surface specimen)  
Disseminated Coccidioidomycosis  
Disseminated Cryptococcosis  
Paracoccidioidomycosis  
Disseminated Histoplasmosis  
Penicilliosis Marneffeii, Disseminated

**BACTERIAL/MYCOBACTERIAL INFECTIONS**

Bacterial Gastroenteritis/Diarrhea, persistent, > 1 month duration  
Mycobacterium Avium Complex (MAC)  
Mycobacterial Infection, Other Non-Tuberculous, Non-MAC  
Bacterial Pneumonia, recurrent, more than once a year  
Salmonella Sepsis  
Pulmonary Tuberculosis  
Extra Pulmonary Tuberculosis

## **VIRAL INFECTIONS**

CMV Colitis

CMV Encephalitis

CMV Esophagitis

CMV Gastroenteritis

CMV Pneumonitis

CMV Proctitis

CMV Retinitis

Other CMV Syndromes

HSV Esophagitis

HSV Pneumonitis

Progressive Multifocal Leukoencephalopathy (PML)

Cutaneous Varicella Zoster (VZV, Shingles, Herpes Zoster) Varicella Zoster (VZV, Herpes Zoster) with Visceral Dissemination

## **NEOPLASTIC DISEASES**

Invasive Cervical Carcinoma

Kaposi Sarcoma (KS) Mucocutaneous and Visceral

Primary CNS Lymphoma (PCL)

Systemic Non-Hodgkin Lymphoma (NHL)

## **NEUROLOGICAL DISORDERS**

HIV-Associated Dementia

## **OTHER DISEASES**

Malignancy

Wasting Syndrome

## **Appendix V. Informed Consent Form Templates:**

Index Case and Partner Screening: Run-In Period and Full Study

Index Case Enrollment: Run-In Period and Full Study

Partner Enrollment: Run-In Period and Full Study

Index Case and Partner Screening: Full Study

Index Case Enrollment: Full Study

Partner Enrollment: Full Study

Specimen Storage

Index Case Pregnancy

## **SAMPLE INFORMED CONSENT FORM**

**DIVISION OF AIDS, NIAID, NIH**

**HPTN 052**

**A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples**

**Version [X.X]**

### **INDEX CASE AND PARTNER SCREENING: RUN-IN PERIOD AND FULL STUDY**

**PRINCIPAL INVESTIGATOR:** [insert name]

**PHONE:** [insert number]

#### **INTRODUCTION:**

You are being asked to volunteer for screening tests to find out if you are eligible for the investigational research study named above. This study is sponsored by the United States National Institutes of Health. The person in charge of the study at this site is [insert name of principal investigator].

This is a study for couples in which one person is infected with HIV and the other person is not. HIV is the virus that causes AIDS. The study will be conducted in two parts. In the first part, about 90 couples will participate (up to 10 couples at your clinic) for up to about one year. In the second part, about 1660 more couples will participate for at least 5 years. The 90 couples from the first part of the study will also participate in the second part. About 1750 couples will participate in the whole study, which includes both parts (about 245 couples total at your clinic). The couples participating in this study will come from Asia, Africa, South America, and North America. The first part of the study will help to find out if the study can be conducted at your clinic. If it cannot, the second part of the study will not happen.

Before you decide whether or not to take part in the screening tests for this research study, you need to know the purpose of the screening tests, the possible risks and benefits of being screened, and what will be expected of you during the tests. This consent form provides that information. The study staff will discuss the information with you. They will answer any questions you may have. After the screening tests have been fully explained to you, you can decide whether or not you want to participate. If you understand the tests and agree to participate, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy of this form to keep.

Please note that:

- Your participation in the screening tests is entirely voluntary.



- You may decide not to take part or to withdraw from the screening tests at any time without losing the benefits of your standard health care.
- You are only being asked to take part in the screening tests at this time. Even if you agree to have the screening tests, you do not have to join the research study.

## **DESCRIPTION OF THE STUDY:**

The main purpose of the study is to find out whether treating people infected with HIV with anti-HIV drugs will prevent them from passing the virus to their partner through sex. Another purpose is to determine when the best time is to start taking anti-HIV drugs in order to prevent passing the virus to a partner through sex. Also, even though these drugs are used in other places in the world, we will study more about how safe they are to take, especially over a long period of time. The drugs being used in the study are approved by the United States Food and Drug Administration (U.S.FDA) for the treatment of HIV, but not approved for the prevention of HIV. Therefore, we do not know if what we are doing in this study will work and so it is called an investigational study.

During the study, everyone with HIV will receive health care, which may include medications to treat infections or other conditions that we find. Some people will also receive anti-HIV drugs to treat their HIV infection, and will start taking these drugs as soon as they join the study. Others may start to take the anti-HIV drugs later in the study, after their T-cell count [*or whatever term is commonly used locally*] is lower or if they become sick. The T-cell count is a blood test that we use to measure the amount of damage that HIV has done to your body. Regardless of which group you are in, you will be started on anti-HIV drugs *before your* T-cell count gets to a point that would make you very sick.

There are two parts to the research study: the run-in period, and the full study. The main purpose of the first part of the research study is to find out whether the full study can be done at your clinic. At the end of the first part, a decision will be made whether the full study can be done. The first part of the study will be the same as the second part; including how often you return to the clinic and when you receive treatment and/or anti-HIV drugs.

## **PURPOSE OF THE SCREENING TESTS:**

The purpose of the screening tests is to find out if you are eligible for the research study described above. Some people may not be able to join the research study because of information found during the screening tests.

The screening tests for the study include interview questions and at least one blood test. You may also have another blood test, a physical exam, and a pregnancy test (if you are female) during these visits. If you agree to be screened for the study you will have at least two visits over the course of several weeks, and each visit will last approximately one or two hours.

You will be told the results of all of your screening tests as soon as they are available.

After the screening tests, you will find out if you are eligible for the research study. If you are eligible, the study staff will fully explain the research study to you and answer any questions you have. After the

research study has been fully explained to you and if you decide to participate, you will be asked to sign another consent form.

## **PROCEDURES:**

If you agree to have the screening tests, you may be asked to come back to the clinic several times over the next few weeks.

During these visits:

- We will ask you where you live and how to find you.
- We will ask you questions about you (like your age), your sexual activities, and your sexual partners.
- We will talk with both you and your partner about HIV and we will provide you information about how to prevent the spread of HIV.
- We will draw some of your blood (no more than 5 mL each time, which is about 1 teaspoon [*change to local equivalent, if appropriate*]). This blood will be tested to see if you are infected with HIV. We may test you more than once for HIV. Before we draw your blood, we will talk with you about the HIV test, what it may mean to know your HIV status, and whether you are prepared to receive your HIV test result. Sometimes an HIV test is not clearly positive or negative. If this happens, we will test your blood again until we know the result for sure. We will tell you if your HIV test is positive or negative. [*If the site is using an HIV rapid test for screening, this bullet point should be changed to reflect the procedure.*]

### **If you do not have HIV:**

If your blood test shows that you do not have HIV, you may be eligible to participate in the study. We will ask you other questions related to your sexual practices, and whether or not you are willing to talk to your partner about your sexual activities together with a counselor. Your partner must be willing to participate in the study. We may need to test you again to see that you still do not have HIV.

### **If you have HIV:**

If your blood test shows that you do have HIV, we will continue with the following activities:

- We will examine your body to see if you are sick.
- We will draw additional blood (no more than 30 mL, which is about 6 teaspoons [*change to local equivalent, if appropriate*]). This blood will be tested to see how much damage HIV has done to your body's ability to fight off infections (your immune system). This blood will also be tested to find out if your kidneys, liver, and blood are healthy. We may store some of this blood for possible future HIV-related testing.
- If you are a woman, we will ask for a urine sample. This sample will be tested to find out if you are pregnant.

If the results of your screening tests show that you have HIV, but that the virus has not done too much damage to your body, you may be eligible to participate in the study. In order to participate in the study, you must have a long-term sexual partner who does not have HIV. We will ask you other questions related to your sexual practices, and whether or not you are willing to talk to your partner about your sexual activities together with a counselor. Your partner must be willing to participate in the study.

### **RISKS and/or DISCOMFORTS:**

If you participate in the screening, there are a few risks or discomforts you should know about.

You may feel discomfort, dizzy, or even faint when your blood is drawn. Redness, pain, swelling, bruising, or an infection may occur where the needle goes into your arm.

You may become embarrassed, worried, or anxious when discussing your sexual practices, talking about HIV or sex with your partner, or discussing or waiting for your test results. Learning that you have HIV may make you worried or anxious. It is also possible that participation in this screening process may cause disagreements between you and your partner. A trained counselor will help you deal with any feelings or questions you may have.

We will make every effort to protect your privacy and confidentiality while you are being screened for this study. Your visits here will take place in private. However, it is possible that others may learn of your participation here, and think you or your partner has HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You could also have problems being accepted by your family or community.

### **POTENTIAL BENEFITS:**

You may get no direct benefit from the screening tests. However, you will receive counseling about HIV and information on your HIV status. You and your partner will receive information about how to prevent the spread of HIV and you will get free condoms. If you are infected with HIV, but not eligible to be in the study, you will be told where you can receive health care, counseling, and other services, as well as information about other research studies.

### **REASONS WHY YOU MAY BE WITHDRAWN FROM THE SCREENING TESTS WITHOUT YOUR CONSENT:**

You may be removed from the screening tests without your consent for the following reasons:

- The study is stopped or cancelled.
- Undergoing the screening tests would be harmful to you.
- You are not able to attend the screening visits or complete the screening tests.
- Your partner is not willing or able to attend screening visits or complete the screening tests.
- You are not willing to find out your HIV test result.

- You are not willing to tell your partner your HIV test result or have HIV counseling with him or her.

## **COSTS AND COMPENSATION:**

There is no cost to you for the screening tests. At the end of each visit, you will be given *[insert amount of money or incentive package to compensate participant for food, travel expenses, lost work time, etc.]*

## **CONFIDENTIALITY:**

Efforts will be made to keep your screening records and test results confidential to the extent permitted by law. However, we cannot guarantee confidentiality. You will be identified by a code (a number), and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study. However, your records may be reviewed, under guidelines of the United States Federal Privacy Act [*U.S. sites only*], by the United States Food and Drug Administration (FDA); the sponsor of the study (United States National Institutes of Health [NIH]), the *[insert name of site]* Institutional Review Board (IRB)/Ethics Committee (EC), study staff, study monitors, the companies that make the drugs used in this study, and *[insert applicable local authorities]*.

If you are infected with HIV, some of the blood collected for these screening tests may be stored for tests done later. These samples will be stored in containers that do not have your name on them but that use a code to protect your privacy. These tests are to help learn more about HIV and anti-HIV drug treatment.

If during the course of these screening tests, we find out that you have *[insert all applicable reportable diseases (e.g., HIV)]*, we must report it to *[insert the name(s) of the local health authorities]*. Although we must report that we have treated someone with *[insert all applicable reportable diseases]*, your name will not be reported to the agency. *[Amend this paragraph to reflect the local requirements. If there are no local requirements to report communicable diseases, delete this paragraph.]*

*[For U.S. sites only:]* In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the U.S. Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. Even with the Certificate of Confidentiality, however, if the study staff learn of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

## **RESEARCH-RELATED INJURY:**

*[Site-specific: insert institutional policy]* It is unlikely that you will be injured as a result of having the screening tests. If you are injured, the *[institution]* will give you immediate necessary treatment for your injuries. You *[will/will not]* have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of

compensation for such injuries either through this institution or the U.S. National Institutes of Health (NIH). You do not give up any legal rights by signing this consent form.

**PROBLEMS or QUESTIONS:**

For questions about this study or a research-related injury, contact:

- *[insert name of the investigator or other study staff]*
- *[insert telephone number and physical address of above]*

For questions about your rights as a research subject, contact:

- *[insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*
- *[insert telephone number and physical address of above]*

**SIGNATURE PAGE: SCREENING: RUN-IN PERIOD AND FULL STUDY**

**HPTN 052: A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV  
Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In  
Serodiscordant Couples, Version [X.X]**

If you have read this informed consent, or have had it read and explained to you, and understand the information, and you voluntarily agree to undergo the screening tests for this research study, please sign your name or make your mark below.

\_\_\_\_\_  
Participant Name (print)

\_\_\_\_\_  
Participant Signature and Date

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (print)

\_\_\_\_\_  
Study Staff Signature and Date

\_\_\_\_\_  
Witness Name (print)  
(As appropriate)

\_\_\_\_\_  
Witness Signature and Date

## **SAMPLE INFORMED CONSENT FORM**

**DIVISION OF AIDS, NIAID, NIH**

**HPTN 052**

**A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples**

**Version [X.X]**

### **INDEX CASE ENROLLMENT: RUN-IN PERIOD AND FULL STUDY**

**PRINCIPAL INVESTIGATOR:**     *[insert name]*

**PHONE:**                             *[insert number]*

#### **INTRODUCTION:**

You are being asked to volunteer for the investigational research study named above. This study is sponsored by the U.S. National Institutes of Health. The person in charge of the study at this site is *[insert name of principal investigator]*.

This is a study for couples in which one person is infected with HIV and the other person is not. HIV is the virus that causes AIDS. The study will be conducted in two parts. In the first part, about 90 couples will participate (up to 10 couples at your clinic) for up to about one year. In the second part, about 1660 more couples will participate for at least 5 years. The 90 couples from the first part of the study will also participate in the second part. About 1750 couples will participate in the whole study, which includes both parts (about 245 couples total at your clinic). The couples participating in this study will come from Asia, Africa, South America, and North America. The first part of the study will help to find out if the study can be conducted at your clinic. If it cannot, the second part of the study will not happen.

Before you decide whether or not to take part in this research study, you need to know the purpose, the possible risks and benefits to you, and what will be expected of you during the study. This consent form provides that information. The study staff will discuss the information with you. They will answer any questions you may have. After the study has been fully explained to you, you can decide whether or not you want to participate. Once you understand this study, and if you agree to take part, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy of this form to keep.

Please note that:

- Your participation in this study is entirely voluntary.

- You may decide not to take part or to withdraw from this study at any time without losing the benefits of your or your partner's standard health care.

## **PURPOSE OF THE STUDY:**

The main purpose of the study is to find out whether treating people infected with HIV with anti-HIV drugs will prevent them from passing the virus to their partner through sex. Another purpose is to determine when the best time is to start taking anti-HIV drugs in order to prevent passing the virus to a partner through sex. Also, even though these drugs are used in other places in the world, we will study more about how safe they are to take, especially over a long period of time. The drugs being used in the study are approved by the United States Food and Drug Administration (U.S.FDA) for the treatment of HIV, but not approved for the prevention of HIV. Therefore, we do not know if what we are doing in this study will work and so it is called an investigational study.

During the study, everyone with HIV will receive health care, which may include medications to treat infections or other conditions that we find. Some people will also receive anti-HIV drugs to treat their HIV infection, and will start taking these drugs as soon as they join the study. Others may start to take the anti-HIV drugs later in the study, after their T-cell count [*or whatever term is commonly used locally*] is lower or if they become sick. The T-cell count is a blood test that we use to measure the amount of damage that HIV has done to your body. Regardless of which group you are in, you will be started on anti-HIV drugs *before your* T-cell count gets to a point that would make you very sick.

There are two parts to the research study: the run-in period, and the full study. The main purpose of the first part of the research study is to find out whether the full study can be done at your clinic. At the end of the first part, a decision will be made whether the full study can be done. The first part of the study will be the same as the second part; including how often you return to the clinic and when you receive treatment and/or anti-HIV drugs.

## **Study Groups**

If you decide to take part in the study, you and your partner will be placed in 1 of 2 groups. Your group will be chosen "by lot" [*or other equivalent local term*]. You have an equal chance of being placed in each group, but you cannot choose your group. Both groups are very important to this study. Couples in both groups will have the same study visits. During the study, one group will start anti-HIV drugs as soon as they join the study. Others may start the anti-HIV drugs later in the study, if their T-cell count [*or whatever term is commonly used locally*] is lower or if they become sick.

## **PROCEDURES:**

If you agree to join this study, you will be asked to come back to the clinic with your partner on a regular basis. We will also tell you the results of any tests we do in this study as soon as they become available. If we find any infections or other conditions during your physical examination or from your laboratory tests, you will receive free treatment for the conditions to the extent possible.

The procedures conducted at each visit are the same for both parts of the study. During the first part of the study, you will come to the clinic for the enrollment visit and at least 5 monthly follow-up



visits. If you start anti-HIV drugs during the first part, you will return to the clinic two weeks after starting the drugs.

### **First Study Visit (Enrollment):**

During your first study visit, the study will be explained to you. You will have time to ask questions and discuss any concerns you may have with the study staff. This visit may last up to 4 hours.

We will ask you for detailed information about where you live and how we can find you. This information will be very important because we may need to contact you to give you new information or we may need to find you if you miss an appointment. If you miss an appointment during the study, we will try to reach you through the contact information you provide. If we talk to people on this list, we will not tell them why we are trying to reach you. If you are not willing to give us this information, you should not agree to be in this study.

We will ask you to answer a few questions about your health, how you have been feeling, and about your sexual activities. You will then have a complete physical examination. During the exam, we will measure your temperature, blood pressure, height, and weight, and we will take an x-ray of your chest. *[NOTE: US site only – state that participant will receive PPD first, and if > 5mm induration then chest x-ray is obtained.]* In addition, we will examine your penis if you are a man, or we will look in your vagina if you are a woman. If you are a woman, we will collect fluid from your vagina with a swab to find out if there is HIV in your vagina or if you have any infections. Some of this sample will be stored for future HIV-related testing. If you are a man, we will ask you to give a semen sample by masturbation so we can see if there is HIV in the semen. Some of this semen will be stored for future HIV-related testing. If sores are found on your penis or in your vagina, a swab sample will be taken to find out what has caused it.

We will draw a blood sample (no more than 45 mL, which is about 9 teaspoons *[can be changed to local equivalent]*). This blood will be tested to see how much HIV is in your blood, and how much damage HIV has done to your body's ability to fight off infections. We will also check your blood for malaria *[site-specific: sites located in endemic regions include malaria testing]*, hepatitis B, and syphilis, and make sure your kidneys, liver, and blood are healthy. Some blood may be stored for future HIV-related testing. We will ask you to give a urine sample to test for sexually transmitted diseases and parasites *[site-specific: sites located in endemic regions include parasitic protozoa testing]*. If you are a woman, we will also check your urine to see if you are pregnant. Pregnant women are not allowed to enroll in the first part of the study (the run-in period), but will be allowed to enroll in the second part.

*[Instruction to site personnel: Insert the following language ONLY if enteric parasites are endemic for your region: We will ask you to give a stool sample so we can test it for parasites.]*

At this visit, you and your partner will find out which group you are in. The groups are:

- Group 1: Health care for your HIV plus getting anti-HIV drugs immediately
- Group 2: Health care for your HIV plus anti-HIV drugs after your T-cell count is a low number or after you become sick

If you are assigned to Group 1, you will be given enough anti-HIV pills to last you until your next visit to the clinic. The study staff will tell you exactly how and when to take them. It is very important that you take this medication every day in the way that the study staff tells you to. If you are not willing to take medication every day, you should not agree to be in this study.

During the course of the study, you may get many different kinds of drugs as part of caring for your HIV infection. The study staff will tell you how and when to take these drugs. You must take these drugs as directed by the study staff.

You and your partner will be told how to prevent the spread of HIV infection. We will give you condoms and advise you or your partner to wear a condom every time you have sex. You cannot count on anti-HIV drugs to prevent you from passing HIV to your partner, so you should avoid all activities where you could pass your HIV infection, even if you are taking the anti-HIV drugs.

### **Two Week Study Visit:**

After you start taking anti-HIV drugs, you will be asked to return to the clinic two weeks later. This visit will last about an hour. At this visit:

- We will ask you to bring back any study pills that you did not take if you are in the group taking anti-HIV drugs. We will count any left over study pills you may have and give you enough new pills to last until your next visit. We will ask you questions and talk with you about taking your study pills.
- We will confirm where you live and how to find you.
- You will have a physical exam. If we find that you are sick, we will treat your symptoms.
- We will counsel you and your partner about using condoms during sex and give you condoms. Even if you come to the clinic alone, we will still talk to you about how to prevent the spread of HIV.
- We will draw blood (no more than 10 mL, which is about 2 teaspoons [*can be changed to local equivalent*]) to check the health of your kidneys, liver, and blood.

### **Monthly Study Visits:**

You will come back to the clinic every month during the entire study. These visits will last about an hour. At each monthly visit:

- If you are taking anti-HIV drugs, we will ask you to bring back any study pills that you did not take. We will count any left over study pills you may have and give you enough new pills to last until your next visit. We will ask you questions and talk with you about taking your study pills.
- If you are a woman, we will take urine to test for pregnancy.
- We will confirm where you live and how to find you.

- If you are sick, we will treat your symptoms.
- We will counsel you and your partner about using condoms during sex and give you condoms. Even if you come to the clinic alone, we will still talk to you about how to prevent the spread of HIV.

At the first two monthly visits of the study, we will ask you questions about your sexual activities.

At the first two monthly visits after you start taking anti-HIV drugs:

- We will draw blood (no more than 10 mL, which is about 2 teaspoons [*can be changed to local equivalent*]) to check the health of your kidneys, liver, and blood.
- We will ask you questions about your health and examine your body to see if you are sick.

### **Quarterly Study Visits (Every Three Months):**

In addition to the regular monthly procedures, at every 3-month visit:

- We will ask you questions about your health and sexual activities.
- You will have a physical exam.
- We will draw blood (no more than 30 mL, which is about 6 teaspoons [*can be changed to local equivalent*])). This blood will be tested to see how much HIV is in your blood, how much damage HIV has done to your body's ability to fight off infections, and the health of your kidneys, liver, and blood. Some of this blood may be stored for future HIV-related testing.

The visit every 3 months will last about 1 and 1/2 hours.

### **Yearly Visits:**

Once a year we will include a few more procedures that will make your visit last longer (about 2 hours):

- We will examine your penis if you are a man, and we will look in your vagina if you are a woman. During the exam for women, we will collect fluid from your vagina with a swab to test how much HIV you may have in your vagina and to find out if you have other infections. Some of this sample may be stored for future HIV-related testing. We will ask the men to give a semen sample by masturbation so we can see how much HIV infection is in the semen. Some of this semen may be stored for future HIV-related testing. If any sores are found on your penis or in your vagina, a swab sample will be taken to determine what has caused it.
- We will ask you to give a urine sample to test for sexually transmitted diseases (gonorrhea and chlamydia) and parasites [*site-specific: sites located in endemic regions include parasitic protozoa testing*].

- *[Instruction to site personnel: Insert the following language ONLY if enteric parasites are endemic for your region. You will be asked to give a stool sample so we can test it for parasites.]*
- We will check your blood for malaria [*site-specific: sites located in endemic regions include malaria testing*] and syphilis.

### **Additional Study Visits:**

If you become sick during the study, you may be asked to return to the clinic more frequently than every month. We will let you know if this is necessary and help you schedule any additional visits.

### **IF YOUR PARTNER BECOMES INFECTED WITH HIV WHILE PARTICIPATING IN THIS STUDY:**

If your partner becomes infected with HIV while participating in this study, the following procedures will take place and your partner's participation in the study will end.

We will draw blood (no more than 30 mL, which is about 6 teaspoons [change to local equivalent]). Some of this sample will be used to measure the HIV in your blood, and to check to see if the infection in your blood is the same as the infection in your partner's blood. The rest of the blood will be stored for future HIV-related testing.

If you are a woman, we will look in your vagina and collect fluid with a swab to test how much HIV you may have in your vagina. Some of this sample may be stored for future HIV-related testing. If you are a man, we will ask you to give a semen sample by masturbation so we can see how much HIV is in your semen. Some of this semen may be stored for future HIV-related testing. If any sores are found on your penis or in your vagina, a swab sample will be taken to determine what has caused it.

Even if your partner is no longer a part of the study, you will still be a part of the study and will return to the clinic on a regular basis.

### **RISKS and/or DISCOMFORTS:**

#### **Anti-HIV Drugs:**

There are many drugs available to treat HIV and AIDS. The study doctors will determine the best combination of these drugs to treat you. It is possible that the study pills will make you feel sick or will affect your blood tests, in which case the study doctor may either switch you to different drugs or stop them all together. It is very important for you to return to the clinic whenever you feel sick. Feeling sick may be due to the pills or it may be due to a sickness caused by your HIV infection. Either way, we want to see you when you feel sick so we can take care of you.

All anti-HIV drugs can cause side effects, which can be more serious or severe with long-term use. Some of these side effects are mild and may go away after you have taken the drugs for a few weeks. Examples of these types of side effects include upset stomach, vomiting, headache, and

changes in your mood, sleep, or concentration. Other side effects are severe and may require treatment or hospitalization. Examples of these types of side effects include rash, liver problems, severe depression or psychosis, and pancreas problems. Rarely, some people taking HIV medications can develop a condition called “lactic acidosis.” Some symptoms that might be caused by lactic acidosis include: unexplained weight loss, stomach upset, nausea, vomiting, fatigue, weakness, and shortness of breath. Lactic acidosis, along with an enlarged and fatty liver, may result in problems such as liver failure. In some cases, this condition results in death. The liver problems and death have been seen more in women on these drugs.

The anti-HIV pills may stop working against HIV. If that happens, we will try to give you different drugs that will work. We may have to draw your blood (no more than 30 mL, which is about 6 teaspoons [*can be changed to local equivalent*]) to figure out how well your drugs are working against the virus. Some of this blood may be stored for future HIV-related testing.

At the end of this consent form, there is information that describes the side effects for anti-HIV drugs that you may receive during this study. When the study doctor gives you the study pills, he or she will review the possible side effects with you. Throughout the study, these side effects will be reviewed with you. If the study doctor gives you an anti-HIV drug that is not listed in this information, he or she will make sure that you understand the side effects of the drug. If you have questions concerning study drug side effects, please ask the study staff.

After you begin taking the anti-HIV drugs, do not stop taking any of them unless you discuss it with the study doctor. Suddenly stopping your treatment can cause an increase in the amount of HIV in your blood, and the virus can become resistant, which means that the drugs will no longer work.

There is a risk of serious and life-threatening side effects when some non-study medications are taken with study drugs. For your safety, you must tell the study doctor about any medications you are taking before you start the study and before taking any non-study medications while you are on the study.

*[Place information here regarding what the current recommendation is at your local site for initiation of antiretroviral therapy. If neviraprine is not recommended as first line therapy for treatment-naïve individuals, please state it here].*

#### **Risks Associated with Early versus Delayed Treatment with Anti-HIV Drugs:**

During this study, you may receive anti-HIV drugs as soon as you start the study, or later, if your body becomes weak or you become sick. There are risks associated with both ways the anti-HIV drugs are given in the study.

If you get the drugs immediately, when you are feeling healthy, the drugs may make you feel sick. Also, by taking the drugs right away and staying on them, you may experience side effects that last a long time. These side effects can be very serious. Also, when you take anti-HIV drugs there is always a risk that the drugs will stop working to fight the virus. The longer you take the drugs, the greater the chance is that the drugs may stop working. If this happens, your HIV infection may develop into AIDS.

It is possible that taking anti-HIV drugs right away when you are healthy may help your body stay strong. If you receive the drugs only when you become sick, you may be too sick for the drugs to fully help your immune system in fighting the infection. The damage done to your immune system by the virus may be permanent, even when you are treated with the anti-HIV drugs. Also, by waiting to take the anti-HIV drugs, you may be more likely to pass the HIV to your partner through sex.

### **Primary Care Drugs:**

There may be side effects to the other drugs given to you to treat other infections. If the study doctor gives you these drugs, he or she will explain the possible side effects that you may experience.

### **Pregnancy and Breastfeeding:**

If you are not pregnant but are on a drug combination that includes a drug called efavirenz, or EFV for short, you and your partner must use two methods of birth control. One method must be from number 2 or 3 below. You must continue to use both methods until 6 weeks after stopping EFV. (If you are a woman and are unable to use two methods, your doctor will talk with you about taking a drug called nevirapine, or NVP for short, rather than EFV.)

If you are not taking EFV, you must use one method of birth control that you discuss with the study staff. You may choose from any of the birth control methods listed below:

1. Birth control drugs that prevent pregnancy given by pills, shots, the “patch”, or placed on or under the skin (some birth control drugs will not work if you are taking certain anti-HIV drugs, your doctor will tell you if this is a problem for you) ;
2. Male or female condoms with or without a cream or gel that kills sperm
3. Diaphragm or cervical cap with a cream or gel that kills sperm
4. Intrauterine device (IUD)

If you become pregnant, you must notify the study doctor immediately. You will be asked to sign another consent form stating that you understand that you are pregnant and either taking anti-HIV drugs or you may become sick during pregnancy and the doctor may want you to start taking anti-HIV drugs. The consent form will explain to you the risks associated with pregnancy and anti-HIV drugs because some of the anti-HIV drugs are unsafe for unborn babies. Women will be tested for pregnancy at every study visit except for the two-week visit after starting anti-HIV drugs. Even if you are assigned to Group 2 and have not received study pills, we will make sure that you and your baby get anti-HIV drugs to reduce the chance of giving HIV to your baby.

A mother who is infected with HIV may infect her baby through breast milk. It is unknown whether the study drugs pass through the breast milk and cause harm to your infant. It is also unknown whether the study drugs reduce the chances that HIV can pass to your baby through your breast milk.

**Other Risks Associated with HIV transmission:**

There are other risks involved with HIV transmission that you should know about. These risks are additional reasons why you and your partner must always wear a condom when having any kind of sex:

- If the HIV in your body is at a high level (called “viral load”) it may make it easier to pass HIV to your partner.
- If you or your partner has an ulcer on your penis or vagina, it may make it easier to pass HIV to your partner.
- If you and your partner practice unprotected oral sex, it may make it easier to pass HIV infection to your partner.
- Not being circumcised may make it easier to get HIV.

**Other Risks:**

You may feel discomfort, dizzy, or even faint when your blood is drawn. Redness, pain, swelling, bruising, or an infection may occur where the needle goes into your arm.

You may feel discomfort during the examination of your vagina or penis, especially if you have a sore.

You may be exposed to low levels of radiation by getting a chest x-ray.

You may become embarrassed, worried, or anxious when discussing your sexual practices, ways to protect your partner against HIV, or discussing or waiting for your test results during the study. Knowing that you have HIV or other infections passed through sex may make you worried or anxious. A trained counselor will help you deal with any feeling or questions you have.

We make every effort to protect your privacy and confidentiality while you are in the study. Your visits here will take place in private. However, it is possible that others may learn of your participation here, and think you or your partner has HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You could also have problems being accepted by your family or community.

**POTENTIAL BENEFITS:**

There may be no direct benefit to you from this study. However, you will receive the anti-HIV drugs either at the beginning of the study, or if your T-cell count has fallen. The anti-HIV drugs are not a cure for HIV infection or AIDS, but we know that they can make people infected with HIV feel better, not get as sick, and live longer. You will also get other treatments for your HIV if you need them.

You will also get physical exams, urine tests, and blood tests that will help us evaluate your overall health and will allow us to treat you for problems we might find. We will also check to see if you have any other infections passed during sex. We will tell you the results of any tests we do as soon as they become available. During the study, you will receive information related to your health. You will be able to talk to counselors about your health and feelings. You and your partner

will get counseling to talk about ways to avoid spreading HIV. You will also receive free condoms throughout the entire course of the study. In addition, knowledge gained from this study may help others infected with HIV in the future.

Although participation in this study may help you to prevent giving your partner HIV, no guarantee can be made.

## **ACCESS TO CARE AFTER THE STUDY ENDS**

Whenever the study ends, you (*will/will not*) have on-going access to anti-HIV drugs to treat your infection if you need them. (*This section will need to be tailored for each site. State if ART is available for free or at cost, and include the length of time that participants will have access to these drugs after the run-in period (if the study ends) and after the full study. If ART is not clinically indicated, state if monitoring of status would be available, e.g. CD4+ testing, etc, and also state if other primary care would be offered. If the site does know if ART or other care will be available or not, it should state that.*)

## **NEW FINDINGS:**

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them.

## **REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT:**

You may be removed from the study without your consent for the following reasons:

- The study is stopped or cancelled.
- Staying in the study would be harmful to you.
- You are not able to attend study visits or complete the study procedures.
- Your partner is not able to attend study visits or complete the study procedures.

## **PREMATURE DISCONTINUATION OF STUDY TREATMENT:**

You may decide to stop taking your anti-HIV drugs during the study. If you decide to do this, the study doctors will discuss with you the risks to your health. We would also like for you to continue to come to the study clinic with your partner just like you did when you were taking your anti-HIV drugs. You will undergo many of the same procedures that you did when you taking your anti-HIV drugs and your study doctor will discuss this with you.



## **ALTERNATIVES TO PARTICIPATION:**

If you choose not to take part in this study, it will have no effect on your regular health care at this clinic.

This clinic *[can or cannot – site specific]* provide you with drugs to prevent or treat infections related to HIV. However, the clinic *[can or cannot]* provide anti-HIV drugs. In order to receive anti-HIV drugs, you would have to buy the drugs from a private doctor or local pharmacy. *[This paragraph should be changed to be site-specific, indicating what kind of HIV-care can be normally provided by the clinic to the HIV-infected individual.]*

Even if you choose to participate in this study, it is not known whether taking anti-HIV drugs can prevent you from giving HIV to your partner.

## **COSTS AND COMPENSATION:**

There will be no cost to you for study-related visits, study pills, physical examinations, laboratory tests or other procedures. At the end of each visit, you will be given *[insert amount of money or incentive package to compensate participant for food, travel expenses, lost work time, etc. Additional incentives may be given for particular procedures, such as semen collection, stool collection, or pelvic exams.]*

## **CONFIDENTIALITY:**

Efforts will be made to keep your study records and test results confidential to the extent permitted by law. However, we cannot guarantee absolute confidentiality. You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study. However, your records may be reviewed, under guidelines of the United States Federal Privacy Act *[U.S. sites only]*, by the United States Food and Drug Administration (FDA); the sponsor of the study (United States National Institutes of Health [NIH]), the *[insert name of site]* Institutional Review Board (IRB)/Ethics Committee (EC) study monitors, the companies that make the drugs used in this study, and *[insert applicable local authorities]*.

During the study, some of your samples (blood, semen, or vaginal fluid) may be stored for tests done later. These samples will be stored in containers that do not have your name on them but rather a code to protect your privacy. These tests are to help learn more about HIV and anti-HIV drug treatment.

If during the course of the study, we find out that you have *[insert all applicable reportable diseases (e.g., HIV, gonorrhea, chlamydia, syphilis)]*, we must report it to *[insert the name(s) of the local health authorities]*. Although we must report that we have treated someone with *[insert all applicable reportable diseases]*, your name will not be reported to the agency. *[Amend this paragraph to reflect the local requirements. If there are no local requirements to report communicable diseases, delete this paragraph.]*

*[For the U.S. site only:]* In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the U.S. Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give

for study purposes. Even with the Certificate of Confidentiality, however, if the study staff learn of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

#### **RESEARCH-RELATED INJURY:**

The study staff will monitor your health closely while you are in this study. You will have a study visit every month. If you have any health problems between visits, please contact the study staff. If you have a medical emergency that requires immediate care, *[insert site-specific instructions]*.

*[Sites to specify institutional policy:]* If you are injured as a result of being in this study, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries either through this institution or the U.S. National Institutes of Health (NIH). You do not give up any legal rights by signing this consent form

#### **PROBLEMS or QUESTIONS:**

For questions about this study or a research-related injury, contact:

- *[site insert name of the investigator or other study staff]*
- *[site insert telephone number and physical address of above]*

For questions about your rights as a research subject, contact:

- *[site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*
- *[site insert telephone number and physical address of above]*

Anti-HIV Drug	Side Effects
Combivir® [3TC/ ZDV]	Same side effects as listed for 3TC and ZDV.
Lamivudine [3TC]	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Feeling of vague overall discomfort</li> <li>• Lack of energy, tiredness</li> <li>• Dizziness</li> <li>• Depression</li> <li>• Stomach ache, upset stomach, throwing up, loose or watery stools</li> <li>• Have trouble falling asleep or cannot sleep at all</li> <li>• Skin rash</li> <li>• Not hungry, eating less than usual</li> <li>• Numbness, tingling, and pain in the hands or feet</li> <li>• Decrease in the number of white blood cells that help fight infection</li> <li>• An increase in a substance in the blood (a type of pancreatic enzyme) that could mean a problem with the pancreas</li> <li>• Increased liver function tests, which could mean liver damage. The signs of liver damage that you may notice are: upset stomach, throwing up, stomach pain, yellow skin or eyes, dark urine, and pale stool. Severe liver damage can cause death. For patients with HIV and hepatitis B, liver damage can get worse when the drug is stopped, possibly leading to death. Liver damage is more commonly found in women.</li> <li>• Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, and shortness of breath. Lactic acidosis can cause death.</li> </ul>
Zidovudine [ZDV]	<ul style="list-style-type: none"> <li>• Decrease in the number of white blood cells that help fight infection</li> <li>• Decrease in the number of red blood cells (anemia), which may cause weakness, dizziness, and tiredness</li> <li>• Muscle aches, weakness, and wasting</li> <li>• Headache</li> <li>• Upset stomach, throwing up, heartburn</li> <li>• Not hungry, eating less than usual</li> <li>• Feeling of vague overall discomfort</li> <li>• Lack of energy, tiredness</li> </ul>

Anti-HIV Drug	Side Effects
Zidovudine [ZDV] (continued)	<ul style="list-style-type: none"> <li>• Have trouble falling asleep or cannot sleep at all</li> <li>• Liver damage. The signs of liver damage that you may notice are: tiredness, not feeling hungry, upset stomach, throwing up, stomach pain, yellow skin or eyes, dark urine, and pale stool. Severe liver damage can cause death. Liver damage is more commonly found in women.</li> <li>• Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, and shortness of breath. Lactic acidosis can cause death.</li> </ul>
Efavirenz [EFV]	<ul style="list-style-type: none"> <li>• Problems of the nervous system, mental health, and/or sleep – like dizziness, feeling disconnected, sleeping too much, difficulty sleeping or falling asleep, vivid dreams, seeing visions when you are awake, confusion, difficulty concentrating, feeling nervous or having extra energy, an exaggerated feeling of well-being. For most people, these problems disappear after a few days or weeks.</li> <li>• Although it is much less common, some people may experience severe mental problems such as severe depression, thinking about or attempting suicide, acting aggressively, having strange, unreal thoughts, or thinking that people are trying to hurt you.</li> <li>• Skin rash</li> <li>• Upset stomach, loose or watery stools</li> <li>• Headache</li> <li>• Increases in the fat and cholesterol found in your blood, which can cause cardiovascular disease</li> <li>• Increased liver function tests, which could mean liver damage. The signs of liver damage that you may notice are: tiredness, not feeling hungry, upset stomach, throwing up, stomach pain, yellow skin or eyes, dark urine, and pale stool. Severe liver damage can cause death.</li> <li>• An increase in a substance in the blood (a type of pancreatic enzyme) that could mean a problem with the pancreas</li> <li>• Trouble seeing</li> <li>• Fever</li> <li>• Abnormal or unusual distribution of body fat</li> <li>• Birth defects have been observed when giving this drug to pregnant monkeys. Therefore, you <u>should not</u> become pregnant while taking efavirenz. If you are not pregnant and choose to take EFV, you must agree to use two forms of birth control.</li> <li>• A false-positive urine test for marijuana</li> </ul>

Anti-HIV Drug	Side Effects
Atazanavir [ATZ]	<ul style="list-style-type: none"> <li>• Abnormal body fat distribution, which may result in an increase in fat in your waist, stomach, breasts, or on the back of your neck, or a decrease in fat in your face, legs, or arms.</li> <li>• Increases in the fat and cholesterol found in your blood, which can cause cardiovascular disease.</li> <li>• In increase in blood sugar or the development or worsening of diabetes.</li> <li>• Possibility of increased bleeding.</li> <li>• Increased bilirubin, which may be associated with yellowing of the eyes</li> <li>• Upset stomach, throwing up, stomach pain, or loose or watery stools</li> <li>• Increase in liver function tests.</li> <li>• Headache</li> <li>• Skin rash, which may be itchy</li> <li>• Numbness, pain, or tingling in the arms and legs</li> <li>• Have trouble falling asleep or cannot sleep at all</li> <li>• Flu-like symptoms, such as fever, joint and muscle pain, tiredness</li> <li>• Increased cough</li> <li>• In pregnant women: lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, and shortness of breath. Lactic acidosis can cause death.</li> <li>• The electric current in your heart may slow down.</li> </ul>
Nevirapine [NVP]	<ul style="list-style-type: none"> <li>• Skin rash, which in some cases may become severe. Rash is more common in women. Rash is more likely to occur if nevirapine is not taken properly during the first 14 days of treatment.</li> <li>• Hypersensitivity reaction (“allergic reaction”). The symptoms that you may notice are: skin rash, fever, tiredness, joint pain, muscle pain and weakness, blisters, sores in your mouth, swelling of the face, red or sore eyes, feeling of vague overall discomfort.</li> <li>• Liver damage. The signs of liver damage that you may notice are: tiredness, not feeling hungry, upset stomach, throwing up, stomach pain, yellow skin or eyes, dark urine, and pale stool. Severe liver damage can cause death. Patients with higher CD4 cell counts, hepatitis B or C, or with abnormal liver function tests are at greater risk for liver damage. Both pregnant and non-pregnant women with CD4 cell counts greater than 250 are at an even higher risk for developing liver damage.</li> <li>• If you stop taking nevirapine because of severe skin rash, a hypersensitivity reaction, or liver damage, you should never take it again.</li> <li>• Abnormal body fat distribution, which may result in an increase in fat in your waist, stomach, breasts, or on the back of your neck, or a decrease in fat in your face, legs, or arms.</li> <li>• Fever</li> <li>• Headache</li> <li>• Upset stomach</li> </ul>

Anti-HIV Drug	Side Effects
Didanosine [ddI]	<ul style="list-style-type: none"> <li>• Changes to your eyes that may make it hard to see.</li> <li>• Upset stomach, throwing up, or loose or watery stools</li> <li>• Numbness, pain, or tingling in the arms and legs, especially if you are taking both ddI and d4T.</li> <li>• Headache</li> <li>• Increase in uric acid in your blood</li> <li>• Damage to the pancreas or abnormal pancreatic function tests: The signs of pancreas damage that you may notice are stomach pain, upset stomach, throwing up, and lack of appetite. Severe pancreas damage may cause death. Pancreatic damage is more commonly found in people who are taking both ddI and d4T.</li> <li>• Liver damage or abnormal liver function tests. The signs of liver damage that you may notice are: tiredness, not feeling hungry, upset stomach, throwing up, stomach pain, yellow skin or eyes, dark urine, and pale stool. Severe liver damage can cause death. Liver failure is more commonly found in people, especially pregnant women, who are taking both ddI and d4T.</li> <li>• Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, and shortness of breath. Lactic acidosis can cause death.</li> </ul>
Stavudine [d4T]	<ul style="list-style-type: none"> <li>• Rash</li> <li>• Upset stomach, throwing up, stomach pain, or loose or watery stools</li> <li>• Muscle aches and pains</li> <li>• Rarely, severe muscle weakness may occur that can lead to paralysis and the inability to breathe. This may be associated with the elevation of lactic acid in the blood.</li> <li>• Numbness, pain, or tingling in the arms and legs, especially if you are taking both ddI and d4T.</li> <li>• Damage to the pancreas or abnormal pancreatic function tests: The signs of pancreas damage that you may notice are stomach pain, upset stomach, throwing up, and lack of appetite. Severe pancreas damage may cause death. Pancreatic damage is more commonly found in people who are taking both ddI and d4T.</li> <li>• Liver damage or abnormal liver function tests. The signs of liver damage that you may notice are: tiredness, not feeling hungry, upset stomach, throwing up, stomach pain, yellow skin or eyes, dark urine, and pale stool. Severe liver damage can cause death. Liver failure is more commonly found in people, especially pregnant women, who are taking both ddI and d4T.</li> <li>• Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, and shortness of breath. Lactic acidosis can cause death.</li> </ul>

Anti-HIV Drug	Side Effects
Tenofovir [TDF]	<ul style="list-style-type: none"> <li>• Stomach ache, loose or watery stools, upset stomach, throwing up, passing gas</li> <li>• Dizziness</li> <li>• Lack of energy</li> <li>• Shortness of breath</li> <li>• Skin rash</li> <li>• Low phosphate, a chemical in the blood</li> <li>• Possible changes in bone growth and strength</li> <li>• Allergic reaction. The symptoms that you may notice are: skin rash, fever, upset stomach, throwing up, loose or watery stools, stomach ache, joint or muscle pain, shortness of breath, or general feeling of illness.</li> <li>• Damage to the pancreas, an organ in your abdomen. The signs of pancreas damage that you may notice are stomach pain, upset stomach, throwing up, and lack of appetite.</li> <li>• Kidney damage or failure</li> <li>• Liver damage. The signs of liver damage that you may notice are: tiredness, not feeling hungry, upset stomach, throwing up, stomach pain, yellow skin or eyes, dark urine, and pale stool. Severe liver damage can cause death. Liver damage is more commonly found in women. If you are infected with both HIV and hepatitis B, you are more likely to have liver damage, which may worsen if you stop taking tenofovir.</li> <li>• Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, and shortness of breath. Lactic acidosis can cause death.</li> <li>• Abnormal body fat distribution, which may result in an increase in fat in your waist, stomach, breasts, or on the back of your neck, or a decrease in fat in your face, legs, or arms.</li> <li>• There is only a small amount of information on tenofovir in pregnant women; therefore, tenofovir should only be used during pregnancy if clearly needed.</li> </ul>

**SIGNATURE PAGE: INDEX CASE ENROLLMENT: RUN-IN PERIOD AND FULL STUDY**

**HPTN 052: A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV  
Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In  
Serodiscordant Couples, Version [X.X]**

If you have read the informed consent, or have had it read and explained to you, and understand the information, and you voluntarily agree to join the run-in period and full study, please sign your name or make your mark below.

\_\_\_\_\_  
Participant Name (print)

\_\_\_\_\_  
Participant Signature and Date

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (print)

\_\_\_\_\_  
Study Staff Signature and Date

\_\_\_\_\_  
Witness Name (print)  
(As appropriate)

\_\_\_\_\_  
Witness Signature and Date



## **SAMPLE INFORMED CONSENT FORM**

**DIVISION OF AIDS, NIAID, NIH**

**HPTN 052**

**A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples**

**Version [X.X]**

### **PARTNER ENROLLMENT: RUN-IN PERIOD AND FULL STUDY**

**PRINCIPAL INVESTIGATOR:** [insert name]

**PHONE:** [insert number]

#### **INTRODUCTION:**

You are being asked to volunteer for the investigational research study named above. This study is sponsored by the U.S. National Institutes of Health. The person in charge of the study at this site is [insert name of principal investigator].

This is a study for couples in which one person is infected with HIV and the other person is not. HIV is the virus that causes AIDS. The study will be conducted in two parts. In the first part, about 90 couples will participate (up to 10 couples at your clinic) for up to about one year. In the second part, about 1660 more couples will participate for at least 5 years. The 90 couples from the first part of the study will also participate in the second part. About 1750 couples will participate in the whole study, which includes both parts (about 245 couples total at your clinic). The couples participating in this study will come from Asia, Africa, South America, and North America. The first part of the study will help to find out if the study can be conducted at your clinic. If it cannot, the second part of the study will not happen.

Before you decide whether or not to take part in this research study, you need to know the purpose, the possible risks and benefits to you, and what will be expected of you during the study. This consent form provides that information. The study staff will discuss the information with you. They will answer any questions you may have. After the study has been fully explained to you, you can decide whether or not you want to participate. Once you understand this study, and if you agree to take part, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy of this form to keep.

Please note that:

- Your participation in this study is entirely voluntary.

- You may decide not to take part or to withdraw from this study at any time without losing the benefits of your or your partner's standard health care.

## **PURPOSE OF THE STUDY:**

The main purpose of the study is to find out whether treating people infected with HIV with anti-HIV drugs will prevent them from passing the virus to their partner through sex. Another purpose is to determine when the best time is to start taking anti-HIV drugs in order to prevent passing the virus to a partner through sex. Also, even though these drugs are used in other places in the world, we will study more about how safe they are to take, especially over a long period of time. The drugs being used in the study are approved by the United States Food and Drug Administration (U.S.FDA) for the treatment of HIV, but not approved for the prevention of HIV. Therefore, we do not know if what we are doing in this study will work and so it is called an investigational study.

During the study, everyone with HIV will receive health care, which may include medications to treat infections or other conditions that we find. Some people will also receive anti-HIV drugs to treat their HIV infection, and will start taking these drugs as soon as they join the study. Others may start to take the anti-HIV drugs later in the study, after their T-cell count [*or whatever term is commonly used locally*] is lower or if they become sick. The T-cell count is a blood test that we use to measure the amount of damage that HIV has done to your body. Regardless of which group you are in, your partner will be started on anti-HIV drugs *before his/her* T-cell count gets to a point that would make him/her very sick.

There are two parts to the research study: the run-in period, and the full study. The main purpose of the first part of the research study is to find out whether the full study can be done at your clinic. At the end of the first part, a decision will be made whether the full study can be done. The first part of the study will be the same as the second part; including how often you return to the clinic and when you get tested for HIV infection.

## **Study Groups**

If you decide to take part in the study, you and your partner will be placed in 1 of 2 groups. Your group will be chosen "by lot" [*or other equivalent local term*]. You have an equal chance of being placed in each group, but you cannot choose your group. Both groups are very important to this study. Couples in both groups will have the same study visits. During the study, one group will start anti-HIV drugs as soon as they join the study. Others will start the anti-HIV drugs later in the study, after their T-cell count [*insert local term*] is lower or if they become sick.

## **PROCEDURES:**

If you agree to join this study, you will be asked to come back to the clinic with your partner on a regular basis. You will be told the results of any tests you undergo as soon as they become available, and will be treated if you are sick to the extent possible.

During this study, your blood will be tested for HIV at least every 3 months. You must receive your HIV test result to be in this research study. Every time you are tested, the study staff will talk to you about your HIV test results. Sometimes HIV test results are not clearly positive or negative. If this

happens, we will test your blood again until we know the result for sure. If at any point during the study the test shows that you have HIV, your participation in the study will end.

The procedures conducted at each visit are the same for both parts of the study. During the first part, you will come to the clinic for the enrollment visit and at least 5 monthly follow-up visits. Whenever your partner starts anti-HIV drugs, you will return to the clinic two weeks later with your partner.

### **First Study Visit (Enrollment):**

During your first study visit, which may last up to 4 hours, the study will be explained to you. You will have time to ask questions and discuss any concerns you may have with the study staff.

We will ask you for detailed information about where you live and how we can find you. This information will be very important because we may need to contact you to give you new information or we may need to find you if you miss an appointment. If you miss an appointment during the study, we will try to reach you through the contact information you provide. If we talk to people on this list, we will not tell them why we are trying to reach you. If you are not willing to give us this information you should not agree to be in this study.

We will ask you to answer a few questions about yourself, how you have been feeling, and about your sexual activities. You will then have a complete physical examination. During the exam, we will measure your temperature, heart rate, blood pressure, height, and weight. In addition, we will examine your penis if you are a man, or we will look in your vagina if you are a woman. If you are a woman, we will collect fluid from your vagina with a swab to test for infections. If any sores are found on your penis or in your vagina, a swab sample will be taken to find out what has caused it.

We will draw a blood sample (no more than 25mL, which is about 5 teaspoons [*change to local equivalent, if appropriate*])). This blood will be tested to see if you have a sexually transmitted disease called syphilis. Some blood may be stored for future HIV-related testing. We will also ask you to give a urine sample to test for other sexually transmitted diseases.

At this visit, you and your partner will be told what group you are in. The groups are:

- Group 1: Your partner will get health care for his or her HIV and immediately get anti-HIV drugs.
- Group 2: Your partner will get health care for his or her HIV and will get anti-HIV drugs after his or her T-cell count falls to a low level or he or she becomes sick.

If you and your partner are in Group 1, your partner will be given anti-HIV drugs. You will be told how to help your partner take these pills correctly.

You and your partner will be told how to prevent the spread of HIV. We will supply you with condoms and advise you or your partner to use a condom every time you have sex. You cannot count on the anti-HIV drugs to prevent your partner from passing HIV to you. You should avoid all activities where HIV could pass to you, even if your partner is taking the anti-HIV drugs.

**Two Week Study Visit:**

After your partner starts taking anti-HIV drugs, you will be asked to return to the clinic two weeks later. This visit will last about an hour. At this visit:

- We will confirm where you live and how to find you.
- If you are sick, we will treat your symptoms.
- We will counsel you and your partner about using condoms during sex and give you condoms. Even if you come to the clinic alone, we will still talk to you about ways to protect yourself from getting HIV.
- If your partner is taking anti-HIV drugs, we will talk to you about how you can help your partner continue to take the study pills.

**Monthly Study Visits:**

You will come back to the clinic every month during the study for a study visit. Most of these visits will last about an hour.

At each visit:

- We will confirm where you live and how to find you.
- If you are sick, we will treat your symptoms.
- We will counsel you and your partner about using condoms during sex and give you condoms. Even if you come to the clinic alone, we will still talk to you about ways to protect yourself from getting HIV.
- If your partner is taking anti-HIV drugs, we will talk to you about how you can help your partner continue to take the study pills.

At the first two monthly visits, we will ask you questions about your sexual activities.

**Quarterly Study Visits (Every Three Months):**

In addition to the regular monthly procedures, at every 3-month visit:

- We will ask you questions about your sexual activities.
- You will get a physical exam.

- We will draw blood (no more than 15 mL, which is about 3 teaspoons [*change to local equivalent, if appropriate*]). This blood will be tested to see if you have HIV. Before you have this blood drawn, we will talk with you about the HIV test and what it may mean to know your HIV status. Some blood may be stored for future HIV-related testing.

The visit every 3 months will last about 1 and ½ hours.

#### **Yearly Visits:**

Once a year, we will include a few additional procedures that will make your visit last longer (about 2 hours):

- We will examine your penis if you are a man, and we will look in your vagina if you are a woman. During the exam for women, we will collect fluid from your vagina with a swab to find out if you have any infections. If any sores are found on your penis or in your vagina, a swab sample will be taken to determine what has caused it.
- Another 5ml of your blood, which is about 1 teaspoon [*change to local equivalent if appropriate*] will be drawn to test your blood for syphilis.
- We will also ask you to give a urine sample to test for other sexually transmitted diseases.

#### **Additional Study Visits:**

There may be additional times when you will be asked to return to the clinic with your partner. For example, if the anti-HIV drugs stop working for your partner and he or she is given new ones, you will be asked to return to talk about the new drugs and ways that you can help your partner take them correctly.

#### **IF YOU BECOME INFECTED WITH HIV WHILE PARTICIPATING IN THIS STUDY:**

If you become infected with HIV while participating in this study, the following procedures will take place and your participation in the study will end:

- We will draw blood (no more than 40 mL, which is about 8 teaspoons [*change to local equivalent, if appropriate*]). This blood will be tested to see how much HIV is in your blood, how much damage the virus has done to your body's ability to fight off infections, to determine the health of your kidneys, liver, and blood, and to see if the infection in your blood is the same as the infection in your partner's blood. Some of this blood may be stored for future HIV-related testing.
- We will examine your penis if you are a man, and we will look in your vagina if you are a woman. During the exam for women, a swab sample will be taken to test how much HIV you may have in your vagina. Some of this sample may be stored for future HIV-related testing. We will ask the men to give a semen sample by masturbation so we can see how much HIV is in the semen. Some of this semen

may be stored for future HIV-related testing. If any sores are found on your penis or in your vagina, a swab sample will be taken to determine what has caused it.

- We will examine your body to see if you are sick. If you are sick, we will treat your symptoms.

The study staff will refer you to places where you can receive health care for your HIV infection. If there are other research studies that you can join, the study staff will tell you about them.

### **RISKS and/or DISCOMFORTS:**

You may feel discomfort, dizzy, or even faint when your blood is drawn. Redness, pain, swelling, bruising, or an infection may occur where the needle goes into your arm.

You may feel discomfort during the examination of your vagina or penis, especially if you have a sore.

You may become embarrassed, worried, or anxious when discussing your sexual practices, ways to protect yourself against HIV, or discussing or waiting for your test results during the study. Learning that you have HIV or other infections passed through sex may make you worried or anxious. A trained counselor will help you deal with any feeling or questions you have.

If the anti-HIV drugs stop working to fight the infection in your partner and then you become infected with HIV, the anti-HIV drugs may not be able to fight your infection when you need them.

We will make every effort to protect your privacy and confidentiality while you are in the study. Your visits here will take place in private. However, it is possible that others may learn of your participation here, and think you or your partner has HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You could also have problems being accepted by your family or community.

### **Other Risks Associated with HIV transmission:**

There are other risks involved with HIV transmission that you should know about. These risks are additional reasons why you and your partner must always wear a condom when having any kind of sex:

- If the HIV in your partner's body is at a high level (called "viral load") it may make it easier to pass HIV to you.
- If you or your partner has an ulcer on your penis or vagina, it may make it easier to pass HIV to you.
- If you and your partner practice unprotected oral sex, it may make it easier to pass HIV infection to you.
- Not being circumcised may make it easier to get HIV.

**POTENTIAL BENEFITS:**

There may be no direct benefit to you from this study. However, you will get physical exams and urine tests, and you will be tested for HIV on a regular basis. We will also check to see if you have any infections that passed during sex. If these exams or tests show that you have a health problem, we will treat you. This treatment, which may include medication, may help you feel better.

During the study, you will receive information related to your health. You will be able to talk to counselors about your health and feelings. You and your partner will get counseling to talk about ways to prevent spreading HIV. You will also receive free condoms throughout the entire course of the study.

If you take part in this study, your partner may receive anti-HIV drugs to treat his or her HIV infection. These drugs are not a cure for HIV infection or AIDS, but anti-HIV drugs may help HIV-infected people feel better and live longer. Your partner will also receive other care, which will include other drugs to prevent or treat HIV-related symptoms and other illnesses. These medications may help your partner feel better.

Because your partner will be treated for HIV, your chance of getting HIV from your partner may be reduced, but no guarantee can be made. In addition, knowledge gained from this study may help others infected with HIV in the future.

**NEW FINDINGS:**

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them.

**REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT:**

You may be removed from the study without your consent for the following reasons:

- The study is stopped or cancelled.
- Staying in the study would be harmful to you.
- You are not able to attend study visits or complete the study procedures.
- Your partner is not able to attend study visits or complete the study procedures.
- You are unwilling to be tested for HIV on a regular basis.

**ALTERNATIVES TO PARTICIPATION:**

If you choose not to take part in this study, it will have no effect on your regular health care at this clinic.

This clinic can provide your partner with drugs to prevent or treat infections related to HIV. However, the clinic will not be able to provide anti-HIV drugs. To receive that treatment your partner would have to buy the drugs from a private doctor or local pharmacy. *[This paragraph should be changed to be site-specific, indicating what kind of HIV-care can be normally provided by the clinic to the HIV-infected individual.]*

Even if you choose to participate in this study, it is not known whether giving anti-HIV drugs to your partner can prevent the spread of HIV to you. The only known way to prevent the sexual spread of HIV infection is to use condoms properly every time you have sex.

#### **COSTS AND COMPENSATION:**

There will be no cost to you for study-related visits, physical examinations, laboratory tests or other procedures. At the end of each visit, you will be given *[insert amount of money or incentive package to compensate participant for food, travel expenses, lost work time, etc. Additional incentives may be given for particular procedures, such as semen collection or pelvic exams.]*

#### **CONFIDENTIALITY:**

Efforts will be made to keep your study records and test results confidential to the extent permitted by law. However, we cannot guarantee absolute confidentiality. You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study. However, your records may be reviewed, under guidelines of the United States Federal Privacy Act *[U.S. sites only]*; the United States Food and Drug Administration (FDA); the sponsor of the study (United States National Institutes of Health [NIH]), the *[insert name of site]* Institutional Review Board (IRB)/Ethics Committee (EC), study staff, study monitors, the companies that make the drugs used in this study, and *(insert applicable local authorities)*.

During the study, some of your samples (blood, semen, or vaginal fluid) may be stored for tests done later. These samples will be stored in containers that do not have your name on them but rather a code to protect your privacy. These tests are to help learn more about HIV and anti-HIV drug treatment.

If during the course of the study, we find out that you have *[insert all applicable reportable diseases (e.g., HIV, gonorrhea, chlamydia, syphilis)]*, we must report it to *[insert the name(s) of the local health authorities]*. Although we must report that we have treated someone with *[insert all applicable reportable diseases]*, your name will not be reported to the agency. *[Amend this paragraph to reflect the local requirements. If there are no local requirements to report communicable diseases, delete this paragraph.]*

*[For U.S. sites only:]* In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the U.S. Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. Even with the Certificate of Confidentiality, however, if the study staff learn of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.



**RESEARCH-RELATED INJURY:**

[The study staff will monitor your health closely while you are in this study. You will have a study visit every month. If you have any health problems between visits, please contact the study staff. If you have a medical emergency that requires immediate care, [insert site-specific instructions].

[*Site-specific: insert institutional policy:*] If you are injured as a result of being in this study, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries either through this institution or the U.S. National Institutes of Health. You do not give up any legal rights by signing this consent form.

**PROBLEMS or QUESTIONS:**

For questions about this study or a research-related injury, contact:

- [site insert name of the investigator or other study staff]
- [site insert telephone number and physical address of above]

For questions about your rights as a research subject, contact:

- [site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]
- [site insert telephone number and physical address of above]

**SIGNATURE PAGE: PARTNER ENROLLMENT: RUN-IN PERIOD AND FULL STUDY**

**HPTN 052: A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV  
Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In  
Serodiscordant Couples, Version [X.X]**

If you have read the informed consent, or have had it read and explained to you, and understand the information, and you voluntarily agree to join the run-in period and full study, please sign your name or make your mark below.

\_\_\_\_\_  
Participant Name (print)

\_\_\_\_\_  
Participant Signature and Date

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (print)

\_\_\_\_\_  
Study Staff Signature and Date

\_\_\_\_\_  
Witness Name (print)  
(As appropriate)

\_\_\_\_\_  
Witness Signature and Date

## **SAMPLE INFORMED CONSENT FORM**

### **DIVISION OF AIDS, NIAID, NIH**

#### **HPTN 052**

#### **A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples**

**Version [X.X]**

#### **INDEX CASE AND PARTNER SCREENING: FULL STUDY**

**PRINCIPAL INVESTIGATOR:** [insert name]

**PHONE:** [insert number]

#### **INTRODUCTION**

You are being asked to volunteer for screening tests to find out if you are eligible for the research study named above. This study is sponsored by the United States National Institutes of Health. The person in charge of the study at this site is [insert name of principal investigator].

This is a study for couples in which one person is infected with HIV and the other person is not. HIV is the virus that causes AIDS. About 1750 couples will participate in the full study (about 245 couples at your clinic). The couples participating in this study will come from Asia, Africa, South America, and North America. Each couple will be in the study for at least 5 years.

Before you decide whether or not to take part in the screening tests for this research study, you need to know the purpose of the screening tests, the possible risks and benefits of being screened, and what will be expected of you during the tests. This consent form provides that information. The study staff will discuss the information with you. They will answer any questions you may have. After the screening tests have been fully explained to you, you can decide whether or not you want to participate. If you understand the tests and agree to participate, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy of this form to keep.

Please note that:

- Your participation in the screening tests is entirely voluntary.
- You may decide not to take part or to withdraw from the screening tests at any time without losing the benefits of your standard health care.
- You are only being asked to take part in the screening tests at this time. Even if you agree to have the screening tests, you do not have to join the research study.

## **DESCRIPTION OF THE STUDY:**

The main purpose of the study is to find out whether treating people infected with HIV with anti-HIV drugs will prevent them from passing the virus to their partner through sex. Another purpose is to determine when the best time is to start taking anti-HIV drugs in order to prevent passing the virus to a partner through sex. Also, even though these drugs are used in other places in the world, we will study more about how safe they are to take, especially over a long period of time. The drugs being used in the study are approved by the United States Food and Drug Administration (U.S.FDA) for the treatment of HIV, but not approved for the prevention of HIV. Therefore, we do not know if what we are doing in this study will work and so it is called an investigational study.

During the study, everyone with HIV will receive health care, which may include medications to treat infections or other conditions that we find. Some people will also receive anti-HIV drugs to treat their HIV infection, and will start taking these drugs as soon as they join the study. Others may start to take the anti-HIV drugs later in the study, after their T-cell count *[or whatever term is commonly used locally]* is lower or if they become sick. The T-cell count is a blood test that we use to measure the amount of damage that HIV has done to your body. Regardless of which group you are in, if you have HIV we will start you on anti-HIV drugs *before your* T-cell count gets to a point that would make you very sick.

## **PURPOSE OF THE SCREENING TESTS:**

The purpose of the screening tests is to find out if you are eligible for the research study described above. Some people may not be able to join the research study because of information found during the screening tests.

The screening tests for the study include interview questions and at least one blood test. You may also have an additional blood test, a physical exam, and a pregnancy test (if you are female). If you agree to be screened for the study you will have at least two visits over the course of several weeks, and each visit will last approximately one or two hours.

You will be told the results of all of your screening tests as soon as they are available.

After the screening tests, you will find out if you are eligible for the research study. If you are eligible, the study staff will fully explain the research study to you and answer any questions you have. After the research study has been fully explained to you and if you decide to participate, you will be asked to sign another consent form.

## **PROCEDURES:**

If you agree to have the screening tests, you may be asked to come back to the clinic several times over the next few weeks.

During these visits:

- We will ask you where you live and how to find you.

- We will ask you questions about you (like your age), your sexual activities, and your sexual partners.
- We will talk with both you and your partner about HIV and we will provide you with information about how to prevent the spread of HIV.
- We will draw some of your blood (no more than 5 mL, which is about 1 teaspoon [*change to local equivalent, if appropriate*]). This blood will be tested to see if you are infected with HIV. Before you have this blood drawn, we will talk with you about the HIV test, what it may mean to know your HIV status, and whether you are prepared to receive your HIV test result. Sometimes an HIV test is not clearly positive or negative. If this happens, we will test your blood again until we know the result for sure. We will tell you if your HIV test is positive or negative. [*If the site is using an HIV rapid test for screening, this bullet point should be changed to reflect the procedure.*]

**If you do not have HIV:**

If your blood test shows that you do not have HIV, you may be eligible to participate in the study. We will ask you other questions related to your sexual practices, and whether or not you are willing to talk to your partner about your sexual activities together with a counselor. Your partner must be willing to participate in the study. We may need to test you again to see that you still do not have HIV.

**If you have HIV:**

If your blood test shows that you do have HIV, we will continue with the following activities:

- We will examine your body to see if you are sick.
- We will draw additional blood (no more than 30 mL, which is about 6 teaspoons [*change to local equivalent, if appropriate*]). This blood will be tested to see how much damage HIV has done to your body's ability to fight off infections. This blood will also be tested to find out if your kidneys, liver, and blood are healthy. We may store some of this blood for possible future HIV-related testing.
- If you are a woman, we will ask for a urine sample. This sample will be tested to find out if you are pregnant.

If the results of your screening tests show that you have HIV, but that the virus has not done too much damage to your body, you may be eligible to participate in the study. In order to participate in the study, you must have a long-term sexual partner who does not have HIV. You must be willing to tell this partner that you have HIV and to talk about your sexual activities together with a counselor. Your partner must be willing to participate in the study.

**RISKS and/or DISCOMFORTS:**

If you participate in this screening, there are a few risks or discomforts you should know about.

You may feel discomfort, dizzy, or even faint when your blood is drawn. Redness, pain, swelling, bruising, or an infection may occur where the needle goes into your arm.

You may become embarrassed, worried, or anxious when discussing your sexual practices, talking about HIV or sex with your partner, or discussing or waiting for your test results. Learning that you have HIV may make you worried or anxious. It is also possible that participation in this screening process may cause disagreements between you and your partner. A trained counselor will help you deal with any feelings or questions you may have.

We will make every effort to protect your privacy and confidentiality while you are being screened. Your visits here will take place in private. However, it is possible that others may learn of your participation here, and think you or your partner has HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You could also have problems being accepted by your family or community.

### **POTENTIAL BENEFITS:**

You may get no direct benefit from the screening tests. However, you will receive counseling about HIV and information on your HIV status. You and your partner will receive information about how to prevent the spread of HIV and you will get free condoms. If you are infected with HIV, but not eligible for the study, you will be told where you can receive health care, counseling, and other services, as well as information about other research studies.

### **REASONS WHY YOU MAY BE WITHDRAWN FROM THE SCREENING TESTS WITHOUT YOUR CONSENT:**

You may be removed from the screening tests without your consent for the following reasons:

- The study is stopped or cancelled.
- Undergoing the screening tests would be harmful to you.
- You are not able to attend the screening visits or complete the screening tests.
- Your partner is not willing or able to attend screening visits or complete the screening tests.
- You are not willing to find out your HIV test result.
- You are not willing to tell your partner your HIV test result or have HIV counseling with him or her.

### **COSTS AND COMPENSATION:**

There is no cost to you for the screening tests. At the end of each visit, you will be given *[insert amount of money or incentive package to compensate participant for food, travel expenses, lost work time, etc.]*

### **CONFIDENTIALITY:**

Efforts will be made to keep your screening records and test results confidential to the extent permitted by law. However, we cannot guarantee absolute confidentiality. You will be identified by a code, and personal information from your records will not be released without your written

permission. You will not be personally identified in any publication about this study. However, your records may be reviewed, under guidelines of the United States Federal Privacy Act [*U.S. sites only*], by the United States Food and Drug Administration (FDA); the sponsor of the study (United States National Institutes of Health [NIH]), the [*insert name of site*] Institutional Review Board (IRB)/Ethics Committee (EC), study staff, study monitors, the companies that make the drugs used in this study, and [*insert applicable local authorities*].

If you are infected with HIV, some of the blood collected for these screening tests may be stored for tests done later. These samples will be stored in containers that do not have your name on them but that use a code to protect your privacy. These tests are to help learn more about HIV and anti-HIV drug treatment.

If during the course of these screening tests, we find out that you have [*insert all applicable reportable diseases (e.g., HIV)*], we must report it to [*insert the name(s) of the local health authorities*]. Although we must report that we have treated someone with [*insert all applicable reportable diseases*], your name will not be reported to the agency. [*Amend this paragraph to reflect the local requirements. If there are no local requirements to report communicable diseases, delete this paragraph.*]

[*For U.S. sites only:*] In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the U.S. Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. Even with the Certificate of Confidentiality, however, if the study staff learn of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

#### **RESEARCH-RELATED INJURY:**

[*Site-specific: insert institutional policy*] It is unlikely that you will be injured as a result of having the screening tests. If you are injured, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries either through this institution or the U.S. National Institutes of Health. You do not give up any legal rights by signing this consent form.

**PROBLEMS or QUESTIONS:**

For questions about this study or a research-related injury, contact:

- *[insert name of the investigator or other study staff]*
- *[insert telephone number and physical address of above]*

For questions about your rights as a research subject, contact:

- *[insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*
- *[insert telephone number and physical address of above]*



**SIGNATURE PAGE: SCREENING: FULL STUDY**

**HPTN 052: A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV  
Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In  
Serodiscordant Couples, Version [X.X]**

If you have read this informed consent, or have had it read and explained to you, and understand the information, and you voluntarily agree to undergo the screening tests for the study, please sign your name or make your mark below.

\_\_\_\_\_  
Participant Name (print)

\_\_\_\_\_  
Participant Signature and Date

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (print)

\_\_\_\_\_  
Study Staff Signature and Date

\_\_\_\_\_  
Witness Name (print)  
(As appropriate)

\_\_\_\_\_  
Witness Signature and Date

## **SAMPLE INFORMED CONSENT FORM**

**DIVISION OF AIDS, NIAID, NIH**

**HPTN 052**

**A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples**

**Version [X.X]**

### **INDEX CASE ENROLLMENT: FULL STUDY**

**PRINCIPAL INVESTIGATOR:** [insert name]

**PHONE:** [insert number]

#### **INTRODUCTION:**

You are being asked to volunteer for the investigational research study named above. This study is sponsored by the U.S. National Institutes of Health. The person in charge of the study at this site is [insert name of principal investigator].

This study includes couples in which one person is infected with HIV and the other person is not. HIV is the virus that causes AIDS. About 1750 couples will participate in the full study (about 245 couples at your clinic). The couples participating in this study will come from Asia, African, South America, and North America. Each couple will be in the study for at least 5 years.

Before you decide whether or not to take part in this research study, you need to know the purpose, the possible risks and benefits to you, and what will be expected of you during the study. This consent form provides that information. The study staff will discuss the information with you. They will answer any questions you may have. After the study has been fully explained to you, you can decide whether or not you want to participate. Once you understand this study, and if you agree to take part, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy of this form to keep.

Please note that:

- Your participation in this study is entirely voluntary.
- You may decide not to take part or to withdraw from this study at any time without losing the benefits of your or your partner's standard health care.

## **PURPOSE OF THE STUDY:**

The main purpose of the study is to find out whether treating people infected with HIV with anti-HIV drugs will prevent them from passing the virus to their partner through sex. Another purpose is to determine when the best time is to start taking anti-HIV drugs in order to prevent passing the virus to a partner through sex. Also, even though these drugs are used in other places in the world, we will study more about how safe they are to take, especially over a long period of time. The drugs being used in the study are approved by the United States Food and Drug Administration (U.S.FDA) for the treatment of HIV, but not approved for the prevention of HIV. Therefore, we do not know if what we are doing in this study will work and so it is called an investigational study.

During the study, everyone with HIV will receive health care which may include medications to treat infections or other conditions that we find. Some people will also receive anti-HIV drugs to treat their HIV infection, and will start taking these drugs as soon as they join the study. Others may start to take the anti-HIV drugs later in the study, after their T-cell count *[or whatever term is commonly used locally]* is lower or if they become sick. The T-cell count is a blood test that we use to measure the amount of damage that HIV has done to your body. Regardless of which group you are in, you will be started on anti-HIV drugs *before your* T-cell count gets to a point that would make you very sick.

## **Study Groups**

If you decide to take part in the study, you and your partner will be placed in 1 of 2 groups. Your group will be chosen “by lot” *[or other equivalent local term]*. You have an equal chance of being placed in each group, but you cannot choose your group. Both groups are very important to this study. Couples in both groups will have the same study visits. During the study, one group will start anti-HIV drugs as soon as they join the study. Others may start the anti-HIV drugs later in the study, if their T-cell count *[or whatever term is commonly used locally]* is lower or if they become sick.

## **PROCEDURES:**

If you agree to join this study, you will be asked to come back to the clinic with your partner on a regular basis.

We will also tell you the results of any tests we do in this study as soon as they become available. If we find any infections or other conditions during your physical examination or from your laboratory tests, you will receive free treatment for the conditions to the extent possible.

## **First Study Visit (Enrollment):**

During your first study visit, the study will be explained to you. You will have time to ask questions and discuss any concerns you may have with the study staff. This visit may last up to 4 hours.

We will ask you for detailed information about where you live and how we can find you. This information will be very important because we may need to contact you to give you new information or we may need to find you if you miss an appointment. If you miss an appointment during the

study, we will try to reach you through the contact information you provide. If we talk to people on this list, we will not tell them why we are trying to reach you. If you are not willing to give us this information you should not agree to be in this study.

We will ask you to answer a few questions about your health, how you have been feeling, and about your sexual activities. You will then have a complete physical examination. During the exam, we will measure your temperature, blood pressure, height, and weight, and we will take an x-ray of your chest. [NOTE: US site only – state that participant will receive PPD first, and if > 5mm induration then chest x-ray is obtained.] In addition, we will examine your penis if you are a man, or we will look in your vagina if you are a woman. If you are a woman, we will collect fluid from your vagina with a swab to find out if there is HIV in your vagina or if you have any infections. Some of this sample will be stored for future HIV-related testing. If you are a man, we will ask you to give a semen sample by masturbation so we can see if there is HIV in the semen. Some of this semen will be stored for future HIV-related testing. If sores are found on your penis or in your vagina, a swab sample will be taken to find out what has caused it.

We will draw a blood sample (no more than 45 mL, which is about 9 teaspoons [*can be changed to local equivalent*]). This blood will be tested to see how much HIV is in your blood, and how much damage HIV has done to your body's ability to fight off infections. We will also check your blood for malaria [*site-specific: sites located in endemic regions include malaria testing*], hepatitis B, and syphilis, and make sure your kidneys, liver, and blood are healthy. Some blood may be stored for future HIV-related testing. We will ask you to give a urine sample to test for sexually transmitted diseases (gonorrhea and chlamydia) and parasites [*site-specific: sites located in endemic regions include parasitic protozoa testing*]. If you are a woman, we will also check your urine to see if you are pregnant.

[Instruction to site personnel: Insert the following language ONLY if enteric parasites are endemic for your region: We will ask you to give a stool sample so we can test it for parasites.]

At this visit, you and your partner will find out which group you are in. The groups are:

- Group 1: Health care for your HIV plus getting anti-HIV drugs immediately
- Group 2: Health care for your HIV plus anti-HIV drugs after your T-cell count falls or after you become sick

If you are assigned to Group 1, you will be given enough pills to last you until your next visit to the clinic. The study staff will tell you exactly how and when to take them. It is very important that you take this medication every day in the way that the study staff tells you to. If you are not willing to take medication every day, you should not agree to be in this study.

During the course of the study, you may get several different kinds of drugs as part of helping to treat your HIV infection. Some of the drugs will be given to you to help you stay healthy. Others will be given to you if you get sick. The study staff will inform you of how and when to take these drugs. You must take these drugs as directed by the study staff.

You and your partner will be told how to prevent the spread of HIV. We will supply you with condoms and advise you or your partner to wear a condom every time you have sex. You cannot count on anti-HIV

drugs to prevent you from passing HIV to your partner, so you should avoid all activities where you could pass your HIV infection, even if you are taking the anti-HIV drugs.

### **Two Week Study Visit:**

After you start taking anti-HIV drugs, you will be asked to return to the clinic two weeks later. This visit will last about an hour. At this visit:

- We will ask you to bring back any study pills that you did not take. We will count any left over study pills you may have and give you enough new pills to last until your next visit. We will ask you questions and talk with you about taking your study pills.
- We will confirm where you live and how to find you.
- You will have a physical exam. If we find that you are sick, we will treat your symptoms.
- We will counsel you and your partner about using condoms during sex and give you condoms. Even if you come to the clinic alone, we will still talk to you about ways to prevent spreading HIV.
- We will draw blood (no more than 10 mL, which is about 2 teaspoons [*can be changed to local equivalent*]) to check the health of your kidneys, liver, and blood.

### **Monthly Study Visits:**

You will come back to the clinic every month during the entire study. These visits will last about an hour. At each monthly visit:

- If you are taking anti-HIV drugs, we will ask you to bring back any study pills that you did not take. We will count any left over study pills you may have and give you enough new pills to last until your next visit. We will ask you questions and talk with you about taking your study pills.
- If you are a woman, we will take urine to test for pregnancy.
- We will confirm where you live and how to find you.
- If you are sick, we will treat your symptoms.
- We will counsel you and your partner about using condoms during sex and give you condoms. Even if you come to the clinic alone, we will still talk to you about ways to prevent spreading HIV.

At the first two monthly visits of the study, we will ask you questions about your sexual activities.

At the first two monthly visits after you start taking anti-HIV drugs:

- We will draw blood (no more than 10 mL, which is about 2 teaspoons [*can be changed to local equivalent*]) to check the health of your kidneys, liver, and blood.
- We will ask you questions about your health and examine your body to see if you are sick.

#### **Quarterly Study Visits (Every Three Months):**

In addition to the regular monthly procedures, at every 3-month visit:

- We will ask you questions about your health and sexual activities.
- You will have a physical exam.
- We will draw blood (no more than 30 mL, which is about 6 teaspoons [*can be changed to local equivalent*]). This blood will be tested to see how much HIV is in your blood, how much damage HIV has done to your body's ability to fight off infections, and the health of your kidneys, liver, and blood. Some of this blood may be stored for future HIV-related testing.

The visit every 3 months will last about 1 and ½ hours.

#### **Yearly Visits:**

Once a year, we will include a few additional procedures that will make your visit last longer (about 2 hours):

- We will examine your penis if you are a man, and we will look in your vagina if you are a woman. During the exam for women, we will collect fluid from your vagina with a swab to test how much HIV you may have in your vagina and to find out if you have other infections. Some of this sample may be stored for future HIV-related testing. We will ask the men to give a semen sample by masturbation so we can see how much HIV is in the semen. Some of this semen may be stored for future HIV-related testing. If any sores are found on your penis or in your vagina, a swab sample will be taken to determine what has caused it.
- We will ask you to give a urine sample to test for sexually transmitted diseases (gonorrhea and chlamydia) and parasites [*site-specific: sites located in endemic regions include parasitic protozoa testing*].
- [*Instruction to site personnel: Insert the following language ONLY if enteric parasites are endemic for your region.* You will be asked to give a stool sample so we can test it for parasites.]
- We will check your blood for malaria [*site-specific: sites located in endemic regions include malaria testing*] and syphilis.

#### **Additional Study Visits:**

If you become sick during the study, you may be asked to return to the clinic more often than every month. We will let you know if this is necessary and help you schedule any additional visits.

## **IF YOUR PARTNER BECOMES INFECTED WITH HIV WHILE PARTICIPATING IN THIS STUDY:**

If your partner becomes infected with HIV while participating in this study, the following procedures will take place and your partner's participation in the study will end.

We will draw blood (no more than 30 mL, which is about 6 teaspoons [*change to local equivalent*]). Some of this sample will be used to measure the HIV in your blood, and to check to see if the infection in your blood is the same as the infection in your partner's blood. The rest of the blood will be stored for future HIV-related testing.

If you are a woman, we will look in your vagina and collect fluid with a swab to test how much HIV you may have in your vagina. Some of this sample may be stored for future HIV-related testing. If you are a man, we will ask you to give a semen sample by masturbation so we can see how much HIV is in the semen. Some of this semen may be stored for future HIV-related testing. If any sores are found on your penis or in your vagina, a swab sample will be taken to determine what has caused it.

Even if your partner is no longer a part of the study, you will still be a part of the study and will return to the clinic on a regular basis.

## **RISKS and/or DISCOMFORTS:**

### **Anti-HIV Drugs:**

There are many drugs available to treat HIV and AIDS. The study doctor will determine the best combination of these drugs to treat you. It is possible that the study pills will make you feel sick or will affect your blood tests, in which case the study doctor may either switch you to different drugs, or stop them all together. It is very important for you to return to the clinic whenever you feel sick. Feeling sick may be due to the pills or it may be due to a sickness caused by your HIV infection. Either way, we want to see you when you feel sick so we can take care of you.

All anti-HIV drugs can cause side effects, which can be more serious or severe with long-term use. Some of these side effects are mild and may go away after you have taken the drugs for a few weeks. Examples of these types of side effects include upset stomach, vomiting, headache, and changes in your mood, sleep, or concentration. Other side effects are severe and may require treatment or hospitalization. Examples of these types of side effects include rash, liver problems, severe depression or psychosis, and pancreas problems. Rarely, some people taking HIV medications can develop a condition called "lactic acidosis." Some symptoms that might be caused by lactic acidosis include: unexplained weight loss, stomach upset, nausea, vomiting, fatigue, weakness, and shortness of breath. Lactic acidosis, along with an enlarged and fatty liver, may result in problems such as liver failure. In some cases, the condition results in death. The liver problems and death have been seen more in women on these drug regimens.

The anti-HIV pills may stop working against HIV. If that happens, we will try to give you different drugs that will work. We may have to draw your blood (no more than 30 mL, which is about 6 teaspoons [*can be changed to local equivalent*]) to figure out how well your drugs are working against the virus. Some of this blood may be stored for future HIV-related testing.

At the end of this consent form, there is a table that describes the side effects for anti-HIV drugs that you may receive during this study. When the study doctor gives you the study pills, he or she will tell you the possible side effects with you. Throughout the study, these side effects will be told to you, particularly if you receive a new anti-HIV drug. If the study doctor gives you an anti-HIV drug that is not listed in the table, he or she will make sure that you understand the side effects of the drug. If you have questions concerning study drug side effects, please ask the study staff.

After you begin taking the anti-HIV drugs, do not stop taking any of them unless you discuss it with the study doctor. Suddenly stopping your treatment can cause an increase in the amount of HIV in your blood, and the virus can become resistant, which means that the drugs will no longer work.

There is a risk of serious and life-threatening side effects when non-study medications are taken with study drugs. For your safety, you must tell the study doctor about all medications you are taking before you start the study and before taking any non-study medications while you are on the study.

*[Place information here regarding what the current recommendation is at your local site for initiation of antiretroviral therapy. If neviraprine is not recommended as first line therapy for treatment-naïve individuals, please state it here]*

#### **Risks Associated with Early versus Delayed Treatment with Anti-HIV Drugs:**

During this study, you may receive anti-HIV drugs as soon as you start the study, or later, if your body weakens or you become sick. There are risks associated with both ways the anti-HIV drugs are given in the study.

If you get the drugs immediately, when you are feeling healthy, the drugs may make you feel sick. Also, by taking the drugs right away and staying on them, you may experience side effects that last a long time. These side effects can be very serious. Also, when you take anti-HIV drugs there is a risk that the drugs will stop working to fight the virus. The longer you take the drugs, the greater the chance is that the drugs may stop working. If this happens, your HIV infection may develop into AIDS.

It is possible that taking anti-HIV drugs sooner may help your body stay strong. If you receive the drugs only when you become sick, you may be too sick for the drugs to help your body in fighting the infection. The damage done to your immune system by the virus may be permanent, even when you are treated with the anti-HIV drugs. Also, by waiting to take the anti-HIV drugs, you may be more likely to spread HIV to your partner.



**Primary Care Drugs:**

There may be side effects to the medications given to you to treat other infections. If the study doctor gives you these drugs, he or she will explain the possible side effects that you may experience.

**Pregnancy and Breastfeeding:**

If you are not pregnant but are on a drug combination that includes a drug called efavirenz, or EFV for short, you and your partner must use two methods of birth control. One method must be from number 2 or 3 below. You must continue to use both methods until 6 weeks after stopping EFV. (If you are a woman and are unable to use two methods, your doctor will talk with you about taking a drug called nevirapine, or NVP for short, rather than EFV.)

If you are not taking EFV, you must use one method of birth control that you discuss with the study staff. You may choose from any of the birth control methods listed below:

1. Birth control drugs that prevent pregnancy given by pills, shots, the “patch”, or placed on or under the skin (some birth control drugs will not work if you are taking certain anti-HIV drugs, your doctor will tell you if this is a problem for you);
2. Male or female condoms with or without a cream or gel that kills sperm
3. Diaphragm or cervical cap with a cream or gel that kills sperm
4. Intrauterine device (IUD)

If you become pregnant, you must notify the study doctor immediately. You will be asked to sign another consent form stating that you understand that you are pregnant and either taking anti-HIV drugs or you may become sick during pregnancy and the doctor may want you to start taking anti-HIV drugs. The consent form will explain to you the risks associated with pregnancy and anti-HIV drugs because some of the anti-HIV drugs are unsafe for unborn babies. Women will be tested for pregnancy at every study visit except for the two-week visit after starting anti-HIV drugs. Even if you are assigned to Group 2 and have not received study pills, we will make sure that you and your baby get anti-HIV drugs to reduce the chance of giving HIV to your baby.

A mother who is infected with HIV may infect her baby through breast milk. It is unknown whether the study drugs pass through the breast milk and cause harm to your infant. It is also unknown whether the study drugs reduce the chances that HIV can pass to your baby through your breast milk.

**Other Risks Associated with HIV transmission:**

There are other risks involved with HIV transmission that you should know about. These risks are additional reasons why you and your partner must always wear a condom when having any kind of sex:

- If the HIV in your body is at a high level (called “viral load”) it may make it easier to pass HIV to your partner.

- If you or your partner has an ulcer on your penis or vagina, it may make it easier to pass HIV to your partner.
- If you and your partner practice unprotected oral sex, it may make it easier to pass HIV infection to your partner.
- Not being circumcised may make it easier to get HIV.

### **Other Risks:**

You may feel discomfort, dizzy, or even faint when your blood is drawn. Redness, pain, swelling, bruising, or an infection may occur where the needle goes into your arm.

You may feel discomfort during the examination of your vagina or penis, especially if you have a sore.

You may be exposed to low levels of radiation by getting a chest x-ray.

You may become embarrassed, worried, or anxious when discussing your sexual practices, ways to protect your partner against HIV, or discussing or waiting for your test results during the study. Knowing that you have HIV or other infections passed through sex may make you worried or anxious. A trained counselor will help you deal with any feeling or questions you have.

We make every effort to protect your privacy and confidentiality while you are in the study. Your visits here will take place in private. However, it is possible that others may learn of your participation here, and think you or your partner has HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You could also have problems being accepted by your family or community.

### **POTENTIAL BENEFITS:**

There may be no direct benefit to you from this study. However, you will receive the anti-HIV drugs either at the beginning of the study, or when your T-cell count has fallen or you become very sick. The anti-HIV drugs are not a cure for HIV infection or AIDS, but we know that they can make people infected with HIV feel better, not get as sick, and live longer.

You will also get physical exams, urine tests, and blood tests that will help us evaluate your overall health and will allow us to treat you for problems we might find. We will also check to see if you have any other infections passed during sex. During the study, you will receive information related to your health. You will be able to talk to counselors about your health and feelings. You and your partner will get counseling to talk about how to prevent the spread of HIV. You will also receive free condoms throughout the entire course of the study. In addition, knowledge gained from this study may help others infected with HIV in the future.

Although participation in this study may also prevent you from spreading the HIV virus to your partner, no guarantee can be made.

## **ACCESS TO CARE AFTER THE STUDY ENDS:**

After this study ends, you (*will/will not*) have on-going access to care for your HIV infection. (*This section will need to be tailored for each site. State if ART is available for free or at cost, and include the length of time that participants will have access to these drugs. If ART is not clinically indicated, state if monitoring of status would be available, e.g. CD4 testing, etc, and also state if other primary care would be offered. If the site does know if ART or other care will be available or not, it should state that.*)

## **NEW FINDINGS:**

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them.

## **REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT:**

You may be removed from the study without your consent for the following reasons:

- The study is stopped or cancelled.
- Staying in the study would be harmful to you.
- You are not able to attend study visits or complete the study procedures.
- Your partner is not able to attend study visits or complete the study procedures.

## **PREMATURE DISCONTINUATION OF STUDY TREATMENT:**

You may decide to stop taking your anti-HIV drugs. If you decide to do this, the doctors will discuss with you the risks to your health. We would also like for you to continue to come to the study clinic with your partner just like you did when you were taking your anti-HIV drugs. You will undergo many of the same procedures that you did when you taking your anti-HIV drugs and your doctor will discuss this with you.

## **ALTERNATIVES TO PARTICIPATION:**

If you choose not to take part in this study, it will have no effect on your regular health care at this clinic.

This clinic can provide you with drugs to prevent or treat infections related to HIV. However, the clinic will not be able to provide anti-HIV drugs. To receive that treatment you would have to buy the drugs from a private doctor or local pharmacy. [*This paragraph should be changed to be site-specific, indicating what kind of HIV-care can be normally provided by the clinic to the HIV-infected individual.*]

Even if you choose to participate in this study, it is not known whether taking anti-HIV drugs can prevent you from giving HIV to your partner.

## **COSTS AND COMPENSATION:**

There will be no cost to you for study-related visits, study pills, physical examinations, laboratory tests or other procedures. At the end of each visit, you will be given *[insert amount of money or incentive package to compensate participant for food, travel expenses, lost work time, etc. Additional incentives may be given for particular procedures, such as semen collection, stool collection, or pelvic exams.]*

## **CONFIDENTIALITY:**

Efforts will be made to keep your study records and test results confidential to the extent permitted by law. However, we cannot guarantee absolute confidentiality. You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study. However, your records may be reviewed, under guidelines of the United States Federal Privacy Act *[U.S. sites only]*, by the United States Food and Drug Administration (FDA); the sponsor of the study (United States National Institutes of Health [NIH]), the *[insert name of site]* Institutional Review Board (IRB)/Ethics Committee (EC), study staff, study monitors, the companies that make the drugs used in this study, and *[insert applicable local authorities]*.

During the study, some of your samples (blood, semen, or vaginal fluid) may be stored for tests done later. These samples will be stored in containers that do not have your name on them but rather a code to protect your privacy. These tests are to help learn more about HIV and anti-HIV drug treatment.

If during the course of the study, we find out that you have *[insert all applicable reportable diseases (e.g., HIV, gonorrhea, chlamydia, syphilis)]*, we must report it to *[insert the name(s) of the local health authorities]*. Although we must report that we have treated someone with *[insert all applicable reportable diseases]*, your name will not be reported to the agency. *[Amend this paragraph to reflect the local requirements. If there are no local requirements to report communicable diseases, delete this paragraph.]*

*[For U.S. sites only:]* In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the U.S. Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. Even with the Certificate of Confidentiality, however, if the study staff learn of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

## **RESEARCH-RELATED INJURY:**

The study staff will monitor your health closely while you are in this study. You will have a study visit every month. If you have any health problems between visits, please contact the study staff. If you have a medical emergency that requires immediate care, *[insert site-specific instructions]*.

*[Sites to specify institutional policy:]* If you are injured as a result of being in this study, the *[institution]* will give you immediate necessary treatment for your injuries. You *[will/will not]* have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries either through this institution

or the U.S. National Institutes of Health. You do not give up any legal rights by signing this consent form.

**PROBLEMS or QUESTIONS:**

For questions about this study or a research-related injury, contact:

- *[site insert name of the investigator or other study staff]*
- *[site insert telephone number and physical address of above]*

For questions about your rights as a research subject, contact:

- *[site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*
- *[site insert telephone number and physical address of above]*

Anti-HIV Drug	Side Effects
Combivir® [3TC/ ZDV]	Same side effects as listed for 3TC and ZDV.
Lamivudine [3TC]	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Feeling of vague overall discomfort</li> <li>• Lack of energy, tiredness</li> <li>• Dizziness</li> <li>• Depression</li> <li>• Stomach ache, upset stomach, throwing up, loose or watery stools</li> <li>• Have trouble falling asleep or cannot sleep at all</li> <li>• Skin rash</li> <li>• Not hungry, eating less than usual</li> <li>• Numbness, tingling, and pain in the hands or feet</li> <li>• Decrease in the number of white blood cells that help fight infection</li> <li>• An increase in a substance in the blood (a type of pancreatic enzyme) that could mean a problem with the pancreas</li> <li>• Increased liver function tests, which could mean liver damage. The signs of liver damage that you may notice are: upset stomach, throwing up, stomach pain, yellow skin or eyes, dark urine, and pale stool. Severe liver damage can cause death. For patients with HIV and hepatitis B, liver damage can get worse when the drug is stopped, possibly leading to death. Liver damage is more commonly found in women.</li> <li>• Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, and shortness of breath. Lactic acidosis can cause death.</li> </ul>
Zidovudine [ZDV]	<ul style="list-style-type: none"> <li>• Decrease in the number of white blood cells that help fight infection</li> <li>• Decrease in the number of red blood cells (anemia), which may cause weakness, dizziness, and tiredness</li> <li>• Muscle aches, weakness, and wasting</li> <li>• Headache</li> <li>• Upset stomach, throwing up, heartburn</li> <li>• Not hungry, eating less than usual</li> <li>• Feeling of vague overall discomfort</li> <li>• Lack of energy, tiredness</li> </ul>

Anti-HIV Drug	Side Effects
Zidovudine [ZDV] (continued)	<ul style="list-style-type: none"> <li>• Have trouble falling asleep or cannot sleep at all</li> <li>• Liver damage. The signs of liver damage that you may notice are: tiredness, not feeling hungry, upset stomach, throwing up, stomach pain, yellow skin or eyes, dark urine, and pale stool. Severe liver damage can cause death. Liver damage is more commonly found in women.</li> <li>• Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, and shortness of breath. Lactic acidosis can cause death.</li> </ul>
Efavirenz [EFV]	<ul style="list-style-type: none"> <li>• Problems of the nervous system, mental health, and/or sleep – like dizziness, feeling disconnected, sleeping too much, difficulty sleeping or falling asleep, vivid dreams, seeing visions when you are awake, confusion, difficulty concentrating, feeling nervous or having extra energy, an exaggerated feeling of well-being. For most people, these problems disappear after a few days or weeks.</li> <li>• Although it is much less common, some people may experience severe mental problems such as severe depression, thinking about or attempting suicide, acting aggressively, having strange, unreal thoughts, or thinking that people are trying to hurt you.</li> <li>• Skin rash</li> <li>• Upset stomach, loose or watery stools</li> <li>• Headache</li> <li>• Increases in the fat and cholesterol found in your blood, which can cause cardiovascular disease</li> <li>• Increased liver function tests, which could mean liver damage. The signs of liver damage that you may notice are: tiredness, not feeling hungry, upset stomach, throwing up, stomach pain, yellow skin or eyes, dark urine, and pale stool. Severe liver damage can cause death.</li> <li>• An increase in a substance in the blood (a type of pancreatic enzyme) that could mean a problem with the pancreas</li> <li>• Trouble seeing</li> <li>• Fever</li> <li>• Abnormal or unusual distribution of body fat</li> <li>• Birth defects have been observed when giving this drug to pregnant monkeys. Therefore, you <u>should not</u> become pregnant while taking efavirenz. If you are not pregnant and choose to take EFV, you must agree to use two forms of birth control.</li> <li>• A false-positive urine test for marijuana</li> </ul>

Anti-HIV Drug	Side Effects
Atazanavir [ATZ]	<ul style="list-style-type: none"> <li>• Abnormal body fat distribution, which may result in an increase in fat in your waist, stomach, breasts, or on the back of your neck, or a decrease in fat in your face, legs, or arms.</li> <li>• Increases in the fat and cholesterol found in your blood, which can cause cardiovascular disease.</li> <li>• In increase in blood sugar or the development or worsening of diabetes.</li> <li>• Possibility of increased bleeding.</li> <li>• Increased bilirubin, which may be associated with yellowing of the eyes</li> <li>• Upset stomach, throwing up, stomach pain, or loose or watery stools</li> <li>• Increase in liver function tests.</li> <li>• Headache</li> <li>• Skin rash, which may be itchy</li> <li>• Numbness, pain, or tingling in the arms and legs</li> <li>• Have trouble falling asleep or cannot sleep at all</li> <li>• Flu-like symptoms, such as fever, joint and muscle pain, tiredness</li> <li>• Increased cough</li> <li>• In pregnant women: lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, and shortness of breath. Lactic acidosis can cause death.</li> <li>• The electric current in your heart may slow down.</li> </ul>
Nevirapine [NVP]	<ul style="list-style-type: none"> <li>• Skin rash, which in some cases may become severe. Rash is more common in women. Rash is more likely to occur if nevirapine is not taken properly during the first 14 days of treatment.</li> <li>• Hypersensitivity reaction (“allergic reaction”). The symptoms that you may notice are: skin rash, fever, tiredness, joint pain, muscle pain and weakness, blisters, sores in your mouth, swelling of the face, red or sore eyes, feeling of vague overall discomfort.</li> <li>• Liver damage. The signs of liver damage that you may notice are: tiredness, not feeling hungry, upset stomach, throwing up, stomach pain, yellow skin or eyes, dark urine, and pale stool. Severe liver damage can cause death. Patients with higher CD4 cell counts, hepatitis B or C, or with abnormal liver function tests are at greater risk for liver damage. Both pregnant and non-pregnant women with CD4 cell counts greater than 250 are at an even higher risk for developing liver damage.</li> <li>• If you stop taking nevirapine because of severe skin rash, a hypersensitivity reaction, or liver damage, you should never take it again.</li> <li>• Abnormal body fat distribution, which may result in an increase in fat in your waist, stomach, breasts, or on the back of your neck, or a decrease in fat in your face, legs, or arms.</li> <li>• Fever</li> <li>• Headache</li> <li>• Upset stomach</li> </ul>



Anti-HIV Drug	Side Effects
Didanosine [ddI]	<ul style="list-style-type: none"> <li>• Changes to your eyes that may make it hard to see.</li> <li>• Upset stomach, throwing up, or loose or watery stools</li> <li>• Numbness, pain, or tingling in the arms and legs, especially if you are taking both ddI and d4T.</li> <li>• Headache</li> <li>• Increase in uric acid in your blood</li> <li>• Damage to the pancreas or abnormal pancreatic function tests: The signs of pancreas damage that you may notice are stomach pain, upset stomach, throwing up, and lack of appetite. Severe pancreas damage may cause death. Pancreatic damage is more commonly found in people who are taking both ddI and d4T.</li> <li>• Liver damage or abnormal liver function tests. The signs of liver damage that you may notice are: tiredness, not feeling hungry, upset stomach, throwing up, stomach pain, yellow skin or eyes, dark urine, and pale stool. Severe liver damage can cause death. Liver failure is more commonly found in people, especially pregnant women, who are taking both ddI and d4T.</li> <li>• Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, and shortness of breath. Lactic acidosis can cause death.</li> </ul>
Stavudine [d4T]	<ul style="list-style-type: none"> <li>• Rash</li> <li>• Upset stomach, throwing up, stomach pain, or loose or watery stools</li> <li>• Muscle aches and pains</li> <li>• Rarely, severe muscle weakness may occur that can lead to paralysis and the inability to breathe. This may be associated with the elevation of lactic acid in the blood.</li> <li>• Numbness, pain, or tingling in the arms and legs, especially if you are taking both ddI and d4T.</li> <li>• Damage to the pancreas or abnormal pancreatic function tests: The signs of pancreas damage that you may notice are stomach pain, upset stomach, throwing up, and lack of appetite. Severe pancreas damage may cause death. Pancreatic damage is more commonly found in people who are taking both ddI and d4T.</li> <li>• Liver damage or abnormal liver function tests. The signs of liver damage that you may notice are: tiredness, not feeling hungry, upset stomach, throwing up, stomach pain, yellow skin or eyes, dark urine, and pale stool. Severe liver damage can cause death. Liver failure is more commonly found in people, especially pregnant women, who are taking both ddI and d4T.</li> <li>• Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, and shortness of breath. Lactic acidosis can cause death.</li> </ul>

Anti-HIV Drug	Side Effects
Tenofovir [TDF]	<ul style="list-style-type: none"> <li>• Stomach ache, loose or watery stools, upset stomach, throwing up, passing gas</li> <li>• Dizziness</li> <li>• Lack of energy</li> <li>• Shortness of breath</li> <li>• Skin rash</li> <li>• Low phosphate, a chemical in the blood</li> <li>• Possible changes in bone growth and strength</li> <li>• Allergic reaction. The symptoms that you may notice are: skin rash, fever, upset stomach, throwing up, loose or watery stools, stomach ache, joint or muscle pain, shortness of breath, or general feeling of illness.</li> <li>• Damage to the pancreas, an organ in your abdomen. The signs of pancreas damage that you may notice are stomach pain, upset stomach, throwing up, and lack of appetite.</li> <li>• Kidney damage or failure</li> <li>• Liver damage. The signs of liver damage that you may notice are: tiredness, not feeling hungry, upset stomach, throwing up, stomach pain, yellow skin or eyes, dark urine, and pale stool. Severe liver damage can cause death. Liver damage is more commonly found in women. If you are infected with both HIV and hepatitis B, you are more likely to have liver damage, which may worsen if you stop taking tenofovir.</li> <li>• Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, and shortness of breath. Lactic acidosis can cause death.</li> <li>• Abnormal body fat distribution, which may result in an increase in fat in your waist, stomach, breasts, or on the back of your neck, or a decrease in fat in your face, legs, or arms.</li> <li>• There is only a small amount of information on tenofovir in pregnant women; therefore, tenofovir should only be used during pregnancy if clearly needed.</li> </ul>

**SIGNATURE PAGE: INDEX CASE ENROLLMENT: FULL STUDY**

**HPTN 052: A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV  
Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In  
Serodiscordant Couples, Version [X.X]**

If you have read the informed consent, or have had it read and explained to you, and understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below.

\_\_\_\_\_  
Participant Name (print)

\_\_\_\_\_  
Participant Signature and Date

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (print)

\_\_\_\_\_  
Study Staff Signature and Date

\_\_\_\_\_  
Witness Name (print)  
(As appropriate)

\_\_\_\_\_  
Witness Signature and Date

## **SAMPLE INFORMED CONSENT FORM**

**DIVISION OF AIDS, NIAID, NIH**

**HPTN 052**

**A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples**

**Version [X.X]**

### **PARTNER ENROLLMENT: FULL STUDY**

**PRINCIPAL INVESTIGATOR:**      *[insert name]*

**PHONE:**                              *[insert number]*

#### **INTRODUCTION:**

You are being asked to volunteer for the investigational research study named above. This study is sponsored by the U.S. National Institutes of Health. The person in charge of the study at this site is *[insert name of principal investigator]*.

This is a study for couples in which one person is infected with HIV and the other person is not. HIV is the virus that causes AIDS. About 1750 couples will participate in the full study (about 245 couples at your clinic). The couples participating in this study will come from Asia, Africa, South America, and North America. Each couple will be in the study for at least 5 years.

Before you decide whether or not to take part in this research study, you need to know the purpose, the possible risks and benefits to you, and what will be expected of you during the study. This consent form provides that information. The study staff will discuss the information with you. They will answer any questions you may have. After the study has been fully explained to you, you can decide whether or not you want to participate. Once you understand this study, and if you agree to take part, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy of this form to keep.

Please note that:

- Your participation in this study is entirely voluntary.
- You may decide not to take part or to withdraw from this study at any time without losing the benefits of your or your partner's standard health care.

## **PURPOSE OF THE STUDY:**

The main purpose of the study is to find out whether treating people infected with HIV with anti-HIV drugs will prevent them from passing the virus to their partner through sex. Another purpose is to determine when the best time is to start taking anti-HIV drugs in order to prevent passing the virus to a partner through sex. Also, even though these drugs are used in other places in the world, we will study more about how safe they are to take, especially over a long period of time. The drugs being used in the study are approved by the United States Food and Drug Administration (U.S.FDA) for the treatment of HIV, but not approved for the prevention of HIV. Therefore, we do not know if what we are doing in this study will work and so it is called an investigational study.

During the study, everyone with HIV will receive health care, which may include medications to treat infections or other conditions that we find. Some people will also receive anti-HIV drugs to treat their HIV infection, and will start taking these drugs as soon as they join the study. Others may start to take the anti-HIV drugs later in the study, after his/her T-cell count *[or whatever term is commonly used locally]* is lower or if he/she becomes sick. The T-cell count is a blood test that we use to measure the amount of damage that HIV has done to your body. Regardless of which group you are in, your partner will be started on anti-HIV drugs *before* his/her T-cell count gets to a point that would make him/her very sick.

## **Study Groups**

If you decide to take part in the study, you and your partner will be placed in 1 of 2 groups. Your group will be chosen “by lot” *[or other equivalent local term]*. You have an equal chance of being placed in each group, but you cannot choose your group. Both groups are very important to this study. Couples in both groups will have the same study visits. During the study, one group will start anti-HIV drugs as soon as they join the study. Others will start the anti-HIV drugs later in the study, after their T-cell count *[or whatever term is commonly used locally]* is lower or if they become sick.

## **PROCEDURES:**

If you agree to join this study, you will be asked to come back to the clinic with your partner on a regular basis. You will be told the results of any tests you undergo during the study and be treated if you are sick to the extent possible.

During this study, your blood will be tested for HIV at least every 3 months. You must receive your HIV test result to be in this research study. Every time you are tested, the study staff will talk to you about your HIV test results. Sometimes HIV test results are not clearly positive or negative. If this happens, we will test your blood again until we know the result for sure. If at any point during the study the test shows that you have HIV, your participation in the study will end.

## **First Study Visit (Enrollment):**

During your first study visit, which may last up to 4 hours, the study will be explained to you. You will have time to ask questions and discuss any concerns you may have with the study staff.

We will ask you for detailed information about where you live and how we can find you. This information will be very important because we may need to contact you to give you new information or we may need to find you if you miss an appointment. If you miss an appointment during the study, we will try to reach you through the contact information you provide. If we talk to people on this list, we will not tell them why we are trying to reach you. If you are not willing to give us this information you should not agree to be in this study.

We will ask you to answer a few questions about yourself, how you have been feeling, and about your sexual activities. You will then have a complete physical examination. During the exam, we will measure your temperature, heart rate, blood pressure, height, and weight. In addition, we will examine your penis if you are a man, or we will look in your vagina if you are a woman. If you are a woman, we will collect fluid from your vagina with a swab to test for infections. If any sores are found on your penis or in your vagina, a swab sample will be taken to find out what has caused it.

We will draw a blood sample (no more than 25mL, which is about 5 teaspoons [*change to local equivalent, if appropriate*]). This blood will be tested to see if you have a sexually transmitted disease called syphilis. Some blood may be stored for future HIV-related testing. We will also ask you to give a urine sample to test for other sexually transmitted diseases (gonorrhea and chlamydia). If we find any infections during your physical examination or from your laboratory tests, you will receive treatment for these conditions.

At this visit, you and your partner will be told which group you are in. The groups are:

- Group 1: Your partner will get health care for his or her HIV and immediately get anti-HIV drugs.
- Group 2: Your partner will get health care for his or her HIV and will get anti-HIV drugs after his or her T-cell count falls to a certain level or he or she becomes sick.

If you and your partner are in Group 1, your partner will be given anti-HIV drugs. You will be told how to help your partner take these pills correctly.

You and your partner will be told how to prevent the sexual spread of HIV from your partner to you. We will supply you with condoms and advise you or your partner to use a condom every time you have sex. You cannot count on anti-HIV drugs to prevent you from passing HIV to your partner, so you should avoid all activities where you could pass your HIV infection, even if you are taking the anti-HIV drugs.

### **Two Week Study Visit:**

After your partner starts taking anti-HIV drugs, you will be asked to return to the clinic two weeks later. This visit will last about an hour. At this visit:

- We will confirm where you live and how to find you.
- If you are sick, we will treat your symptoms.

- We will counsel you and your partner about using condoms during sex and give you condoms. Even if you come to the clinic alone, we will still talk to you about ways to protect yourself from getting HIV.
- If your partner is taking anti-HIV drugs, we will talk to you about how you can help your partner continue to take the study pills.

### **Monthly Study Visits:**

You will come back to the clinic every month during the study for a study visit. Most of these visits will last about an hour.

At each visit:

- We will confirm where you live and how to find you.
- If you are sick, we will treat your symptoms.
- We will counsel you and your partner about using condoms during sex and give you condoms. Even if you come to the clinic alone, we will still talk to you about ways to protect yourself from getting HIV.
- If your partner is taking anti-HIV drugs, we will talk to you about how you can help your partner continue to take the study pills.

At the first two monthly visits, we will ask you questions about your sexual activities.

### **Quarterly Study Visits (Every Three Months):**

In addition to the regular monthly procedures, at every 3-month visit:

- We will ask you questions about your sexual activities.
- You will get a physical exam.
- We will draw blood (no more than 15 mL, which is about 3 teaspoons [*change to local equivalent, if appropriate*]). This blood will be tested to see if you have HIV. Before you have this blood drawn, we will talk with you about the HIV test and what it may mean to know your HIV status. Some blood may be stored for future HIV-related testing.

The visit every 3 months will last about 1 and ½ hours.

### **Yearly Visits:**

Once a year, we will include a few additional procedures that will make your visit last longer (about 2 hours):

- We will examine your penis if you are a man, and we will look in your vagina if you are a woman. During the exam for women, we will collect fluid from your vagina with a swab to find out if you have any infections. If any sores are found on your penis or in your vagina, a swab sample will be taken to see what has caused it.
- Another 5ml of your blood, which is about 1 teaspoon [*change to local equivalent if appropriate*], will be drawn to test it for syphilis.
- We will also ask you to give a urine sample to test for other sexually transmitted diseases (gonorrhea and chlamydia).

#### **Additional Study Visits:**

There may be more times when you will be asked to return to the clinic with your partner. For example, if the anti-HIV drugs stop working for your partner and he or she is given new drugs, you will be asked to return to talk about the new drugs and ways that you can help your partner take them correctly.

#### **IF YOU BECOME INFECTED WITH HIV WHILE PARTICIPATING IN THIS STUDY:**

If you become infected with HIV while participating in this study, the following procedures will take place and your participation in the study will end.

- We will draw blood (no more than 40 mL, which is about 8 teaspoons [*change to local equivalent, if appropriate*]). This blood will be tested to see how much HIV is in your blood, how much damage the virus has done to your body's ability to fight off infections, to see the health of your kidneys, liver, and blood, and to see if the infection in your blood is the same as the infection in your partner's blood. Some of this blood may be stored for future HIV-related testing.
- We will examine your penis if you are a man, and we will look in your vagina if you are a woman. During the exam for women, a swab sample will be taken to test how much HIV you may have in your vagina. Some of this sample may be stored for future HIV-related testing. We will ask the men to give a semen sample by masturbation so we can see how much HIV is in the semen. Some of this semen may be stored for future HIV-related testing. If any sores are found on your penis or in your vagina, a swab sample will be taken to determine what has caused it.
- We will examine your body to see if you are sick. If you are sick, we will treat your symptoms.

The study staff will refer you to places where you can receive health care for your HIV infection. If there are other research studies that you can join, the study staff will tell you about them.



**RISKS and/or DISCOMFORTS:**

You may feel discomfort, dizzy, or even faint when your blood is drawn. Redness, pain, swelling, bruising, or an infection may occur where the needle goes into your arm.

You may feel discomfort during the examination of your vagina or penis, especially if you have a sore.

You may become embarrassed, worried, or anxious when discussing your sexual practices, ways to protect yourself against HIV, or discussing or waiting for your test results during the study. Learning that you have HIV or other infections passed through sex may make you worried or anxious. A trained counselor will help you deal with any feeling or questions you have.

If the anti-HIV drugs stop working to fight the infection in your partner and then you become infected with HIV, the anti-HIV drugs may not be able to fight your infection when you need them.

We will make every effort to protect your privacy and confidentiality while you are in the study. Your visits here will take place in private. However, it is possible that others may learn of your participation here, and think you or your partner has HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You could also have problems being accepted by your family or community.

**Other Risks Associated with HIV transmission:**

There are other risks involved with HIV transmission that you should know about. These risks are additional reasons why you and your partner must always wear a condom when having any kind of sex:

- If the HIV in your partner's body is at a high level (called "viral load") it may make it easier to pass HIV to you.
- If you or your partner has an ulcer on your penis or vagina, it may make it easier to pass HIV to you.
- If you and your partner practice unprotected oral sex, it may make it easier to pass HIV infection to you.
- Not being circumcised may make it easier to get HIV.

**POTENTIAL BENEFITS:**

There may be no direct benefit to you from this study. However, you will get physical exams and urine tests, and you will be tested for HIV on a regular basis. We will also check to see if you have any infections passed during sex. If these exams or tests show that you have a health problem, we will treat you. This treatment, which may include medication, may help you feel better.

During the study, you will get information related to your health. You will be able to talk to counselors about your health and feelings. You and your partner will get counseling to talk about safe sex practices. You will also get free condoms throughout the entire study.

If you take part in this study, your partner may get anti-HIV drugs to treat his or her HIV infection. These drugs are not a cure for HIV infection or AIDS, but anti-HIV drugs can help HIV-infected people feel better and live longer. Your partner will also get health care, which will include drugs to prevent or treat HIV-related symptoms and other illnesses. These medications may help your partner feel better.

Because your partner will be treated for HIV, your chance of getting HIV from your partner through sex may be reduced, but no guarantee can be made. In addition, knowledge gained from this study may help others infected with HIV in the future.

#### **NEW FINDINGS:**

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them.

#### **REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT:**

You may be removed from the study without your consent for the following reasons:

- The study is stopped or cancelled.
- Staying in the study would be harmful to you.
- You are not able to attend study visits or complete the study procedures.
- Your partner is not able to attend study visits or complete the study procedures.
- You are unwilling to be tested for HIV on a regular basis.

#### **ALTERNATIVES TO PARTICIPATION:**

If you choose not to take part in this study, it will have no effect on your regular health care at this clinic.

This clinic can provide your partner with drugs to prevent or treat infections related to HIV. However, the clinic will not be able to provide anti-HIV drugs. To receive that treatment your partner would have to buy the drugs from a private doctor or local pharmacy. *[This paragraph should be changed to be site-specific, indicating what kind of HIV-care can be normally provided by the clinic to the HIV-infected individual.]*

Even if you choose to participate in this study, it is not known whether giving anti-HIV drugs to your partner can prevent the spread of HIV to you. The only known way to prevent the sexual spread of HIV infection is to use condoms properly every time you have sex.

#### **COSTS AND COMPENSATION:**

There will be no cost to you for study-related visits, physical examinations, laboratory tests or other procedures. At the end of each visit, you will be given [*insert amount of money or incentive package to compensate participant for food, travel expenses, lost work time, etc. Additional incentives may be given for particular procedures, such as semen collection or pelvic exams.*]

#### **CONFIDENTIALITY:**

Efforts will be made to keep your study records and test results confidential to the extent permitted by law. However, we cannot guarantee absolute confidentiality. You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study. However, your records may be reviewed, under guidelines of the United States Federal Privacy Act [*U.S. sites only*], by the United States Food and Drug Administration (FDA); the sponsor of the study (United States National Institutes of Health [NIH]), the [*insert name of site*] Institutional Review Board (IRB)/Ethics Committee (EC), study staff, study monitors, the companies that make the drugs used in this study, and (*insert applicable local authorities*).

During the study, some of your samples (blood, semen, or vaginal fluid) may be stored for tests done later. These samples will be stored in containers that do not have your name on them but rather a code to protect your privacy. These tests are to help learn more about HIV and anti-HIV drug treatment.

If during the course of the study, we find out that you have [*insert all applicable reportable diseases (e.g., HIV, gonorrhea, chlamydia, syphilis)*], we must report it to [*insert the name(s) of the local health authorities*]. Although we must report that we have treated someone with [*insert all applicable reportable diseases*], your name will not be reported to the agency. [*Amend this paragraph to reflect the local requirements. If there are no local requirements to report communicable diseases, delete this paragraph.*]

[*For U.S. sites only:*] In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the U.S. Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. Even with the Certificate of Confidentiality, however, if the study staff learn of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

#### **RESEARCH-RELATED INJURY:**

The study staff will monitor your health closely while you are in this study. You will have a study visit every month. If you have any health problems between visits, please contact the study staff. If you have a medical emergency that requires immediate care, [*insert site-specific instructions*].

[Sites to specify institutional policy:] If you are injured as a result of being in this study, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries either through this institution or the U.S. National Institutes of Health. You do not give up any legal rights by signing this consent form.

**PROBLEMS or QUESTIONS:**

For questions about this study or a research-related injury, contact:

- *[site insert name of the investigator or other study staff]*
- *[site insert telephone number and physical address of above]*

For questions about your rights as a research subject, contact:

- *[site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*
- *[site insert telephone number and physical address of above]*

**SIGNATURE PAGE: PARTNER ENROLLMENT: FULL STUDY**

**HPTN 052: A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV  
Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In  
Serodiscordant Couples, Version [X.X]**

If you have read the informed consent, or have had it read and explained to you, and understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below.

\_\_\_\_\_  
Participant Name (print)

\_\_\_\_\_  
Participant Signature and Date

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (print)

\_\_\_\_\_  
Study Staff Signature and Date

\_\_\_\_\_  
Witness Name (print)  
(As appropriate)

\_\_\_\_\_  
Witness Signature and Date

## **SAMPLE INFORMED CONSENT FORM**

**DIVISION OF AIDS, NIAID, NIH**

**HPTN 052**

**A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples**

**Version [X.X]**

### **SPECIMEN STORAGE**

**PRINCIPAL INVESTIGATOR:**     *[insert name]*

**PHONE:**                             *[insert number]*

#### **INTRODUCTION:**

You have decided to take part in the investigational research study named above, sponsored by the United States National Institutes of Health. While you are in this study, blood and semen (if you are a man) or vaginal fluid (if you are a woman) will be collected from you. These samples may be useful for future research. You are being asked to agree to the storage of these samples. This consent form gives you information about the collection, storage, and use of these samples. The study staff will talk to you about this information. Please ask if you have any questions. You will be asked to sign or make your mark on this form to indicate whether you agree to have your samples stored and tested. You will be offered a copy of this form to keep.

#### **YOUR PARTICIPATION IS VOLUNTARY:**

Allowing your samples to be stored is completely voluntary. You may decide not to have any samples stored other than what is needed to complete this study and still be in this research study or any future study.

Even if you decide now that your samples can be stored for future research, you may change your mind at any time. If this happens, you must tell the study staff that you have changed your mind. If you decide not to have your samples stored or used for future research, they will be destroyed at the end of the study.

#### **PURPOSE:**

The specific research to be done on your samples is not known at this time. Your samples will only be used to look for HIV infection or other infections, damage caused by infection, or how your body reacts to the infection. For example, the tests may look at cells, proteins, and other chemicals in your body. Tests may also examine your genes (DNA), since they might affect your response to HIV in important ways.

For example, your genes may make you more or less susceptible to becoming infected, your responses to infection or to treatment stronger or weaker, or make HIV progress faster or slower. No other kinds of genetic test will be done by anyone on your stored specimens without first explaining the test to you and obtaining your permission.

The study researchers do not plan to contact you or your regular doctor with any results from tests done on your stored samples. This is because research tests are often done using experimental procedures, so the results may not help for making decisions on managing your health. In the rare case that a specific test result gives important information about your health, the researchers will tell the study staff and the study staff will try to contact you. If you wish to be contacted with this type of test result, you must give the study staff any change to your contact information. If you have a regular doctor and you want the study staff to tell this doctor your test results, you must give the study staff your doctor's contact information.

Your samples will not be sold or used directly to produce commercial products.

Research studies using your samples will be reviewed by the United States National Institutes of Health and a special committee at the researcher's institution (an Institutional Review Board).

#### **PROCEDURES:**

Each time your blood is drawn, up to 18 mL (which is about 3.5 teaspoons [*change to local equivalent, if appropriate*]) of the sample may be stored. For each sample of semen or vaginal fluid given, part of the sample will be tested immediately and the rest will be stored.

Your blood will be stored safely and securely in a storage facility. Only the people who work at the facility and approved researchers will have access to your samples. The people who work at the facility will not have any information that identifies you. The approved researchers may be given information about you such as your age and sex, but they will not be given your name or any other information that identifies you.

There is no time limit on how long your samples will be stored.

#### **RISKS and/or DISCOMFORTS:**

There are few risks related to storing your samples. When tests are done on the stored samples there is a small but possible risk to your privacy. It is possible that if others found out information about you that is learned from tests (such as information about your genes) it could cause you problems with your family (having a family member learn about a disease that may be passed on in families or learning who is the true parent of a child) or problems getting a job or insurance.

#### **POTENTIAL BENEFITS:**

There are no direct benefits to you from having your samples stored. You and others could benefit in the future from research done on your blood.

## **CONFIDENTIALITY:**

To keep your information private, your samples will be labeled with a code that can only be traced back to your study clinic. Your name, where you live, and other personal information will be protected by the study clinic. When researchers are given your stored samples, they will not be given your personal information. The results of future tests will not be included in your health records. Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Efforts will be made to keep your study records and test results confidential to the extent permitted by law. However, we cannot guarantee absolute confidentiality. You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study. However, your records may be reviewed, under guidelines of the United States Federal Privacy Act [*U.S. sites only*], by the United States Food and Drug Administration (FDA); the sponsor of the study (United States National Institutes of Health [NIH]), the [*insert name of site*] Institutional Review Board (IRB)/Ethics Committee (EC), study staff, study monitors, the companies that make the drugs used in this study, and (*insert applicable local authorities*).

[*For U.S. sites only:*] In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the U.S. Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. Even with the Certificate of Confidentiality, however, if the study staff learn of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

## **PROBLEMS OR QUESTIONS:**

For questions about the storage of your samples, contact:

- [*site insert name of the investigator or other study staff*]
- [*site insert telephone number and physical address of above*]

For questions about your rights related to the storage of your samples for research, contact:

- [*site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site*]
- [*site insert telephone number and physical address of above*]



## SIGNATURE PAGE: SPECIMEN STORAGE

### **HPTN 052: A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples, Version [X.X]**

## CONSENT FOR SPECIMEN STORAGE

Please carefully read the statements below (or have them read to you) and think about your choice. No matter what you decide it will not affect whether you can be in the research study, or your routine health care.

\_\_\_\_\_ I agree to have samples of my blood, semen (if I am a man), and vaginal fluid (if I am a woman) stored and used for future testing related to HIV infection (including genetic testing).

\_\_\_\_\_ I agree to have samples of my blood, semen (if I am a man), and vaginal fluid (if I am a woman) stored and used for future testing related to HIV infection. However, I do not agree to have genetic testing performed on my samples.

\_\_\_\_\_ I do not agree to have samples of my blood, semen (if I am a man), and vaginal fluid (if I am a woman) stored and used for future testing related to HIV infection.

\_\_\_\_\_  
Participant Name (print)

\_\_\_\_\_  
Participant Signature and Date

\_\_\_\_\_  
Study Staff Conducting

\_\_\_\_\_  
Study Staff Signature and Date

\_\_\_\_\_  
Consent Discussion (print)

\_\_\_\_\_  
Witness Name (print)

\_\_\_\_\_  
Witness Signature and Date

(As appropriate)

## **SAMPLE INFORMED CONSENT FORM**

### **DIVISION OF AIDS, NIAID, NIH**

#### **HPTN 052**

#### **A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples**

**Version [X.X]**

#### **INDEX CASE PREGNANCY**

**PRINCIPAL INVESTIGATOR:**     *[insert name]*

**PHONE:**                             *[insert number]*

#### **INTRODUCTION:**

Because you are now pregnant, you are being asked if you want to continue taking part in the investigational research study named above, sponsored by the United States National Institutes of Health. This consent form gives more information about how this research study may affect your pregnancy and your baby. The study staff will talk with you about this information. You may also talk with your own doctor about what is best for you and your baby and if you should remain on study medicines, choose other anti-HIV drugs, or start anti-HIV drugs. If you agree to stay in this study, you will be asked to sign this consent form. You will be offered a copy of this form to keep.

You are free to ask questions of the research staff at any time.

Please note that:

- Your participation in this study is entirely voluntary.
- You may decide not to take part or to withdraw from the study at any time without losing the benefits of your or your partner's standard health care.

#### **ADDITIONAL INFORMATION FOR PREGNANT PARTICIPANTS**

If you decide to remain in the study, the requirements for your participation will not change, but some of the procedures that you were undergoing while you were not pregnant may change. For example, the doctor may decide to take less blood from you while you are pregnant. If you are already receiving anti-HIV drugs, you will continue to do so unless your doctor thinks you may need to stop during your pregnancy; however, the doctor may need to change some of the drugs you are taking to ones that are safer during pregnancy. If you have not yet started anti-HIV drugs, they will be available to you.

It is not known if the drug or drug combinations in this study harm unborn babies. Tests in pregnant animals do show some risk for some anti-HIV drugs. If you are currently taking anti-HIV drugs, the study doctor will explain the particular risks of these drugs to you.

This study will not provide care related to your pregnancy, the delivery of your baby, or the care of your baby after birth. You must arrange for your care and your baby's care outside of this study.

If you are not taking anti-HIV drugs, the study doctor will provide you with drugs to help prevent you from passing your HIV infection to your baby.

The study staff will talk with you about care for your baby once he or she is born.

## **RISKS ASSOCIATED WITH STUDY PARTICIPATION WHILE PREGNANT**

Now that you are pregnant, there are some possible risks you should know. These possible risks to you and your baby are in addition to the risks that are described in the study consent you already signed.

### **Risks to You if You Begin or Are On Anti-HIV Drugs:**

- Different side effects or more severe side effects may occur in pregnant women taking anti-HIV drugs. This may make it more difficult for you to take your study drugs. Not taking anti-HIV drugs as directed may cause the drugs not to work on the HIV in your blood.
- The amount of anti-HIV drug in your blood may change during pregnancy. If the amount of anti-HIV drug in your blood decreases, the drugs may not work well or may stop working completely.
- Some risks of pregnancy may be made worse by anti-HIV drugs and may result in death.

### **Risks to Your Baby if You Begin or Are On Anti-HIV Drugs:**

- It is not known if some anti-HIV drugs may cause you to have a baby that is born early or dead.
- It is not known if some anti-HIV drugs may cause your baby to be sick or have birth defects. Not all birth defects are seen at birth. Some birth defects are seen later as the baby grows.
- It is possible for you to give HIV to your baby. The study doctor will talk to you about using one or more anti-HIV drugs to decrease the risk of passing HIV to your baby.

## **Breastfeeding**

After delivery, if you decide to breastfeed your baby you may continue taking anti-HIV drugs. Doctors know that HIV can pass through breast milk and taking anti-HIV drugs has not been proven to decrease the chance of passing HIV through your breast milk to your baby.

**POTENTIAL BENEFITS:**

If you continue to take part in this study, there may be a benefit to you and your baby, but no guarantee can be made. It is also possible that you and your baby will receive no benefit from continuing in this study. Information learned from this study may help others who have HIV.

Taking anti-HIV drugs may prevent passing HIV infection to your baby.

**NEW FINDINGS:**

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study while you are pregnant or breastfeeding.

**REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT:**

You may be removed from the study without your consent for the following reasons:

- The study is stopped or cancelled.
- Staying in the study would be harmful to you.
- You are not able to attend study visits or complete the study procedures.
- Your partner is not able to attend study visits or complete the study procedures.

**ALTERNATIVES TO PARTICIPATION:**

Instead of staying on the study medicines you have the choice of:

- treatment with medicines available to you [*Instruction to site personnel: insert standard-of-care for prevention of MTCT*]
- treatment with experimental drugs being studied for use during pregnancy, if available at your clinic and if you qualify
- no treatment

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

**COSTS AND COMPENSATION:**

In addition to any costs that are described in the study consent you already signed; this study will not cover any cost related to your pregnancy, delivery of your baby or care of your baby after birth. [*Instruction*

*to site personnel: change this paragraph to reflect what is normally provided to pregnant women and their babies at your site and any costs involved.]*

#### **CONFIDENTIALITY:**

Efforts will be made to keep your study records and test results confidential to the extent permitted by law. However, we cannot guarantee absolute confidentiality. You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study. However, your records may be reviewed, under guidelines of the United States Federal Privacy Act [*U.S. sites only*], by the United States Food and Drug Administration (FDA); the sponsor of the study (United States National Institutes of Health [NIH]), the [*insert name of site*] Institutional Review Board (IRB)/Ethics Committee (EC), study staff, study monitors, the companies that make the drugs used in this study, and (*insert applicable local authorities*).

During the study, some of your samples (blood, semen, or vaginal fluid) may be stored for tests done later. These samples will be stored in containers that do not have your name on them but rather a code to protect your privacy. These tests are to help learn more about HIV and anti-HIV drug treatment.

If during the course of the study, we find out that you have [*insert all applicable reportable diseases (e.g., HIV, gonorrhea, chlamydia, syphilis)*], we must report it to [*insert the name(s) of the local health authorities*]. Although we must report that we have treated someone with [*insert all applicable reportable diseases*], your name will not be reported to the agency. [*Amend this paragraph to reflect the local requirements. If there are no local requirements to report communicable diseases, delete this paragraph.*]

[*For U.S. sites only:*] In addition to the efforts made by the study staff to keep your personal information confidential, a Certificate of Confidentiality has been obtained from the U.S. Federal Government for this study. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. Even with the Certificate of Confidentiality, however, if the study staff learn of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

#### **RESEARCH-RELATED INJURY:**

The study staff will monitor your health closely while you are in this study. You will have a study visit every month. If you have any health problems between visits, please contact the study staff. If you have a medical emergency that requires immediate care, [*insert site-specific instructions*].

[*Sites to specify institutional policy:*] If you or your baby are injured as a result of being in this study, the [*institution*] will give you both immediate necessary treatment for your injuries. You [*will/will not*] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries either through this institution or the U.S. National Institutes of Health. You do not give up any legal rights by signing this consent form.

**PROBLEMS or QUESTIONS:**

For questions about this study or a research-related injury, contact:

- *[site insert name of the investigator or other study staff]*
- *[site insert telephone number and physical address of above]*

For questions about your rights as a research subject, contact:

- *[site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*
- *[site insert telephone number and physical address of above]*

**SIGNATURE PAGE: INDEX CASE PREGNANCY**

**HPTN 052: A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV  
Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In  
Serodiscordant Couples, Version [X.X]**

**CONSENT FOR INDEX CASE PREGNANCY**

If you have read this informed consent or have had it read and explained to you, you understand the information, and you voluntarily agree to continue participating in the run-in period and the full study, please sign your name or make your mark below.

\_\_\_\_\_  
Participant Name (print)

\_\_\_\_\_  
Participant Signature and Date

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (print)

\_\_\_\_\_  
Study Staff Signature and Date

\_\_\_\_\_  
Witness Name (print)  
(As appropriate)

\_\_\_\_\_  
Witness Signature and Date

## **Appendix VI: Manual for Expedited Reporting of Adverse Events to DAIDS**



# **Manual for Expedited Reporting of Adverse Events to DAIDS**

**Final**  
**May 6, 2004**

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## **1.0 PURPOSE OF MANUAL**

### **1.1 Purpose**

The purpose of this Manual is to describe the criteria and method for expedited reporting of certain serious and other reportable adverse events to the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), through the DAIDS Safety Office.

### **1.2 Scope**

This Manual applies only to those clinical studies/trials requiring expedited reporting of adverse events to the DAIDS Safety Office as stated in the protocol.

This Manual applies to all study agents specified in the protocol as requiring expedited reporting to DAIDS. Although not covered under this Manual, note that DAIDS may require MedWatch reporting (using e.g., Form FDA 3500A or CIOMS I Form) to the Food and Drug Administration (FDA) and/or DAIDS for some studies. MedWatch reporting may only be applied to studies/trials of US FDA-approved study agents. Any requirements for MedWatch reporting will be identified in the study/trial protocol.

### **1.3 Introduction**

For adverse events requiring expedited reporting to DAIDS, sites must follow the general reporting requirements and procedures described in this Manual. In order to fully define the expedited adverse event reporting requirements that apply to an individual study/trial, the protocol will specify:

- One of three Levels of Adverse Event Reporting (Section 3.1) and any other adverse events to be reported on an expedited basis (Section 3.2).
- The duration of the protocol-defined expedited reporting period.
- The name or category of each study agent (US FDA-approved or investigational) that requires expedited reporting of adverse events to DAIDS. This may include study agents in addition to those provided by the study/trial.

## **2.0 DESCRIBING AN ADVERSE EVENT BY SERIOUSNESS, SEVERITY, RELATIONSHIP TO STUDY AGENT, AND EXPECTEDNESS**

The criteria for expedited reporting of adverse events to the DAIDS Safety Office include the seriousness of the outcome of the event, the severity (intensity) of the event, its relationship to study agent, and (only for the Targeted Level) expectedness, i.e., whether the adverse event is expected or unexpected.

### **2.1 Seriousness**

The first consideration for expedited reporting of adverse events to DAIDS is the seriousness of the outcome of the event. The April 1996 International Conference on Harmonisation (ICH) guidance, “Good Clinical Practice: Consolidated Guidance,” (ICH E6) defined a serious adverse event (SAE) as “any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.”

“Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above” may also be considered to be serious. (October 1994 ICH guidance (E2A), “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.”)

### **2.2 Severity (Intensity)**

The second consideration for expedited reporting of adverse events to DAIDS is the severity (intensity) of the event. In order to maintain consistency among studies/trials and sites, DAIDS has developed a list of common clinical and laboratory adverse events and defined grade 1 – 5 severity parameters to generate the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences (also known as “the toxicity tables”). These tables are located on the DAIDS Safety Office website at <http://rcc.tech-res-intl.com>.

Unless stated otherwise in the protocol, study staff is required to use the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences to determine the intensity of adverse events in order to establish consistency in adverse event reporting to DAIDS. Specific protocols may include additional or modified criteria for grading adverse events that are not included in the current versions of the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences.

## 2.3 Seriousness vs. Severity (Intensity) of Adverse Events and Reporting Criteria

For expedited reporting to DAIDS, the term “severity” (or “intensity”) is described as the grade for a specific event, i.e., mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). This is *not* the same as “serious,” which is based on subject/event *outcome or action* criteria usually associated with events that pose a threat to a subject’s life or functioning (ICH E2A).

## 2.4 Relationship to Study Agent

The third consideration for expedited reporting of adverse events to DAIDS is the judgment of causal association (relationship) between an adverse event and the study agent. The protocol must specify by name or category each study agent (either approved or investigational) that requires expedited reporting of adverse events to DAIDS. The study physician makes the site’s final assessment of the causal association based upon the temporal relationship to administration of the study agent(s), the pharmacology of the study agent(s), and his/her clinical judgment.

The terms used in DAIDS studies/trials to assess relationship of an event to study agent are:

- **Definitely Related.** The adverse event and administration of study agent are related in time, and a direct association can be demonstrated.
- **Probably Related.** The adverse event and administration of study agent are reasonably related in time, and the adverse event is more likely explained by study agent than other causes.
- **Possibly Related.** The adverse event and administration of study agent are reasonably related in time, and the adverse event can be explained equally well by causes other than study agent.
- **Probably Not Related.** A potential relationship between study agent and the adverse event could exist (i.e., the possibility cannot be excluded), but the adverse event is most likely explained by causes other than the study agent.
- **Not Related.** The adverse event is clearly explained by another cause not related to the study agent.
- **Pending.** Pending may be used as a temporary relationship assessment only for death and only if data necessary to determine relationship to study agent are being collected. The site is required to submit a final assessment within 3 business days after reporting the death. If no final assessment is made within 3 business days after the date of submission, the event will be assessed as possibly related to study agent. Any additional information received at a later time, including an autopsy report, should be submitted as a Follow-up Report.

A **suspected adverse drug reaction (SADR)** is an adverse event that could potentially have a causal relationship to the study agent (definitely, probably, possibly, probably not related, or for deaths, pending).

## **2.5 Expectedness (Expected vs. Unexpected)**

Expected refers to the perspective of events previously observed, *not* on the basis of what might be anticipated from the pharmacological properties of the study agent. (ICH E2A)

Unexpected refers to events whose nature or severity (intensity) is not consistent with those included in the package insert/summary of study agents that have been approved by the US FDA or in the Investigator's Brochure. (ICH E2A)

### **3.0 ADVERSE EVENTS REQUIRING EXPEDITED REPORTING AND THE STUDY/TRIAL REPORTING PERIOD**

#### **3.1 Levels of Adverse Event Reporting**

The protocol will specify one of three Levels of Adverse Event Reporting. The Level of Adverse Event Reporting chosen for expedited reporting is based primarily upon the degree of risk that may be associated with the study agent.

##### **3.1.1 Standard Level**

Report all adverse events following any exposure to study agent that:

- Result in death **regardless** of relationship to study agent.
- Are congenital anomalies, birth defects, or fetal losses **regardless** of relationship to study agent.
- Result in persistent or significant disabilities or incapacities **regardless** of relationship to study agent.
- Are a **suspected adverse drug reaction**, i.e., definitely, probably, possibly, and probably not related, to a study agent that requires or prolongs existing hospitalization, or requires intervention to prevent significant/permanent disability or death.
- Are life-threatening (including all Grade 4 adverse events) **suspected adverse drug reactions**, i.e., definitely, probably, possibly, and probably not related to a study agent.

##### **3.1.2 Intensive Level**

In addition to all adverse events reported for the Standard Level, also report all Grade 3 suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent. (The Intensive Level includes reporting Grades 3 and 4 SADRs.)

### 3.1.3 Targeted Level

Use of the Targeted Level of reporting is limited to non-IND studies/trials of US FDA- approved agents and doses for approved indications and populations. Report **only** the following adverse events:

- All events that result in death **regardless of relationship** to study agent.
- All congenital anomalies, birth defects, or fetal losses **regardless of relationship** to study agent.
- All persistent or significant disability or incapacity **regardless of relationship** to study agent.
- **Unexpected\* suspected adverse drug reactions**, i.e., definitely, probably, possibly, and probably not related to a study agent, that require or prolong existing hospitalization, or require intervention to prevent death or significant/permanent disability.
- **Unexpected\* life-threatening clinical suspected adverse drug reactions**, i.e., definitely, probably, possibly, and probably not related to a study agent. **DO NOT report** Grade 4 laboratory values that are not associated with a life-threatening clinical event.

\*Unexpected events are events whose nature or severity is not consistent with the package insert/summary of product characteristics for a US FDA-approved study agent.

### 3.2 Additional Protocol-Required Expedited Reporting Requirements

In addition to specifying one of the reporting levels above, a protocol may require other adverse events to be reported on an expedited basis. In this case, the protocol will explicitly state the additional adverse events to be reported to DAIDS. For example, in rare instances a protocol may specify use of the Intensive Level and also require Grades 1 and 2 SADRs to be reported, or a protocol may require reporting of a specific type of adverse event regardless of grade.

### 3.3 Additional Adverse Events That Should Be Reported for Any Study/Trial Requiring Expedited Reporting to DAIDS

In addition to the reporting requirements described above, sites should report any of the following adverse events on an expedited basis:



- Suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent, that **do not meet the protocol-required reporting criteria**, but the Investigator believes are of sufficient concern to be reported on an expedited basis to DAIDS. This includes adverse events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent a serious adverse event. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm or blood dyscrasias or convulsions that do not result in hospitalization.
- Unexpected, serious suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent, that occur at any time **after the protocol-defined expedited reporting period** if the study staff become aware of its occurrence. These events include deaths, permanent disabilities, congenital anomalies, hospitalizations, and life-threatening clinical events. (Do not report Grade 4 laboratory values unless associated with a life-threatening clinical event.)
- Serious adverse events that are not related to a study agent, but could be associated with **study participation or procedure** (e.g., pulmonary embolism secondary to an intravenous catheter placed for study agent administration).

### 3.4 Protocol-Defined Expedited Adverse Event Reporting Period

The protocol-specified reporting level continues throughout the study/trial period (from enrollment of a subject through the end of study follow-up visits for that subject). The protocol may also require the same level of adverse event reporting to be continued beyond the end of study follow-up for each subject, and if so, the protocol must specify the duration of this additional reporting period.

#### **4.0 METHOD AND TIMEFRAME FOR EXPEDITED REPORTING OF INDIVIDUAL ADVERSE EVENTS**

All information requested on the DAIDS Expedited Adverse Event Reporting Form must be provided and the form submitted to the DAIDS Safety Office. This form can be found at the web site for the DAIDS Safety Office. Contact information for the DAIDS Safety Office is provided in Appendix B.

The timeframe for expedited reporting of individual adverse events begins when the site recognizes that an event fulfills the criteria outlined in this Manual for expedited reporting to DAIDS. Sites must submit adverse events requiring expedited reporting to the DAIDS Safety Office as soon as possible, **but no later than 3 business days**, after the site's recognition that the event fulfills the criteria for expedited reporting.

## **5.0 ADDITIONAL EXPEDITED REPORTING REQUIREMENTS**

### **5.1 Follow-up Reporting of Adverse Events**

#### **5.1.1 Submitting Follow-Up Information on Adverse Events**

For the circumstances listed below, the site is required to submit follow-up information when it becomes available on a new Expedited Adverse Event Form as a Follow-up Report.

- Requests by DAIDS for additional information.
- A change in the relationship between the adverse event and study agent by the study physician.
- Additional significant information that becomes available for a previously reported adverse event. This is particularly important for new information addressing cause of death if the initial assignment was “pending.”
- Results of rechallenge with the study agent(s), if performed.

#### **5.1.2 Outcome of Adverse Events**

The site **must** follow each reported adverse event and record eventual outcomes in the source documentation. However, report of the outcome of a reported adverse event to the DAIDS Safety Office is not required unless specifically requested by DAIDS.

### **5.2 Reporting Recurrent Adverse Events**

For events that have been previously reported to the DAIDS Safety Office, if the event has fully resolved and then re-occurs to a level requiring expedited reporting, the adverse event must be reported as a New Report to the DAIDS Safety Office.

### **5.3 Reporting Change in Severity of Adverse Events**

Any ongoing event that increases in severity to a higher grade than previously reported must be reported again as a New Report on a new DAIDS Expedited Adverse Event Reporting Form.

Ongoing events that improve, but are not resolved, and then increase in severity to the same or lower severity grade than previously reported do not have to be reported again to the DAIDS Safety Office. Resolution is the normalization or return to baseline (i.e., prior to study agent exposure) of laboratory values, signs, or symptoms related to the event.

#### **5.4 Study Physician Assessment and Signature**

A study physician listed on the Form FDA 1572 for IND studies or the DAIDS Investigator of Record Agreement (IoR) for non-IND studies must review and verify the data on the DAIDS Expedited Adverse Event Reporting Form for accuracy and completeness. This physician also makes the site's final assessment of the relationship between the study agent and the adverse event. This physician must sign the completed DAIDS Expedited Adverse Event Reporting Form. If necessary to meet timely reporting requirements, sites can submit an expedited adverse event report without a completed signature page. However, the completed signature page, and necessary corrections or additions, must be submitted within the next 3 business days.

## 6.0 APPENDICES

### 6.1 Appendix A: Definition of Terms

**Adverse Event (AE):** An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH E6) (Synonym: Adverse Experience)

**DAIDS Safety Office:** The Office to which adverse events requiring expedited reporting are submitted. (DAIDS)

**Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences (Toxicity Tables):** Lists of common terms and severity (intensity) parameters used to describe adverse events occurring in DAIDS-sponsored clinical studies/trials. (DAIDS)

**IND:** An investigational new drug application. (21 CFR 312.3)

**Investigator's Brochure:** A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects. (ICH E6)

**Non-IND Study/Trial:** A study/trial for which there is no IND filed with the US FDA.

**Package Insert:** The approved package circular in marketed drug packaging containing the drug description, clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence, dosage and administration, how drug is supplied, "clinical studies," and "references." (21 CFR 201.57)

**Serious Adverse Event (SAE):** Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. This includes important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. (ICH E6 and E2A)

**Study Agent:** Drugs, biological products, or combination of drugs and biological products (approved or investigational) defined in the protocol as requiring expedited reporting to DAIDS. (DAIDS)

**Study Physician:** A physician listed on the Form FDA 1572 for IND studies or on the DAIDS Investigator of Record Agreement (IOR) for non-IND studies. (DAIDS)

**Suspected Adverse Drug Reaction (SADR):** An adverse event that could potentially have a causal relationship to a study agent (definitely, probably, possibly, probably not related or for deaths, pending). (DAIDS)

**Toxicity:** An adverse event that has an attribution of possibly, probably, or definitely related to a study agent. (DAIDS) NOTE: This term should not be used for expedited reporting of adverse events to DAIDS.

**Unexpected Event:** An adverse event, the nature or severity (intensity) of which is not consistent with the applicable product information (Investigator's Brochure, package insert, or summary of product characteristics for a US FDA-approved study agent. (DAIDS)

## 6.2 Appendix B: Contact Information for DAIDS Safety Office

All completed DAIDS Expedited Adverse Event Forms are submitted to the DAIDS Safety Office.

For questions or other communication, please note the following:

Website:	<a href="http://rcc.tech-res-intl.com">http://rcc.tech-res-intl.com</a>
Office Phone*:	1-800-537-9979 (US only) or +1-301-897-1709
Office Fax*:	1-800-275-7619 (US only) or +1-301-897-1710
Office Email:	<a href="mailto:SAE@tech-res.com">SAE@tech-res.com</a>
Office Hours:	Monday through Friday, 8:30 AM to 5:00 PM (US Eastern Time)
Mailing Address:	DAIDS Safety Office 6500 Rock Spring Drive Suite 650 Bethesda, MD 20817

\*Office phone and fax are accessible 24 hours per day.

### 6.3 Appendix C: Summary Chart for Expedited Reporting of Adverse Events to DAIDS for Protocol-Specified Study Agents

	Standard Level	Intensive Level	Targeted Level
<b>Deaths</b>	All Events	All Events	All Events
<b>Congenital anomalies, birth defects, fetal losses</b>	All Events	All Events	All Events
<b>Disabilities/Incapacities</b>	All Events	All Events	All Events
<b>Hospitalization<sup>1</sup></b>	All Suspected Adverse Drug Reactions <sup>2</sup>	All Suspected Adverse Drug Reactions <sup>2</sup>	Unexpected Suspected Adverse Drug Reactions <sup>2,3</sup>
<b>Other events</b>	All Grade 4 Suspected Adverse Drug Reactions <sup>2</sup>	All Grades 3 and 4 Suspected Adverse Drug Reactions <sup>2</sup>	Unexpected Life-Threatening Clinical Suspected Adverse Drug Reactions <sup>2,3</sup>

<sup>1</sup>This category includes hospitalization, prolongation of hospitalization or requirement of intervention to prevent permanent disabilities or death.

<sup>2</sup>Suspected adverse drug reactions are adverse events that are assessed as definitely, probably, possibly, probably not related to a study agent (or for deaths, pending).

<sup>3</sup>Unexpected events are adverse events, of a nature or severity (intensity) that is not consistent with the applicable product information (package insert/summary of product characteristics) for a US FDA-approved study agent.

#### Timeframe for Expedited Reporting of Individual Adverse Events:

Adverse events requiring expedited reporting are to be reported to the DAIDS Safety Office **no later than 3 business days** after the site's recognition that the event fulfills the criteria for expedited reporting.

#### Protocol-Defined Expedited Adverse Event Reporting Period

The protocol-specified reporting level continues throughout the study/trial period (from enrollment of a subject through the end of study follow-up visits for that subject). The protocol may also require the same level of adverse event reporting to be continued beyond the end of study follow-up for each subject.