

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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**A Study of the HIV Prevention Trials Network
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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.

Name of Investigator of Record

Signature of Investigator of Record

Date

LIST OF ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
ACTG	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
CHAVI	NIH Center for HIV/AIDS Vaccine Immunology
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 gonorrhoea
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	immunofluorescence assay
IDV	indinavir

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

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 SCHEMA

Title: 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

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. This trial consists of a run-in period, which has been completed, and a full study.

Study Population: HIV serodiscordant couples in which the HIV-infected partner is ART-naive and has a CD4+ cell count of 350-550 cells/mm³.

Study Size: Approximately 1750 couples total

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 within or below the range of 200-250 cells/mm³, or develops an AIDS-defining illness.

The ART drugs provided through the study include Combivir[®] [3TC/zidovudine(ZDV)], efavirenz [EFV], atazanavir [ATV], nevirapine [NVP], tenofovir [TDF], lamivudine [3TC], didanosine [ddI-EC], stavudine [d4T], Kaletra[®]/Aluvia[®] [lopinavir(LPV)/ritonavir (r)], and Truvada[®] [emtricitabine (FTC)/tenofovir (TDF)].

Study Duration: The duration of the full study will be approximately 78 months total. Accrual into the 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 within or below the range of 200-250 cells/mm³, or develops an AIDS-defining illness.

HPTN 052 SCHEMA (continued)

The secondary objectives of the study are to:

- Determine the long-term safety of two antiretroviral treatment strategies (*i.e.*, immediate upon enrollment vs. ART initiation when the participant has two consecutive measurements of a CD4+ cell count within or below the range of 200-250 cells/mm³, or develops an AIDS-defining illness).
- 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 antiretroviral 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.
- Characterize and compare Quality-of-Life (QOL) indicators in different geographic settings and by antiretroviral treatment strategies.

Study Sites:

- Porto Alegre, Brazil
- Rio de Janeiro, Brazil
- 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 38.6 million adults and children were living with the human immunodeficiency virus (HIV) or living with acquired immunodeficiency syndrome (AIDS) at the end of 2005, of which 4.1 million were new infections occurring in 2005 alone¹. Of the 38.6 million, 24.5 million are in sub-saharan Africa, and heterosexual intercourse is the main route of transmission¹.

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 Uganda². 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 vaccines³, and topical microbicides⁴, 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^{5,6}. The separation between HIV treatment and HIV prevention may represent an unfortunate “false dichotomy” for the following reasons:

- HIV treatment affects HIV transmission⁷;
- HIV prevention strategies in the treatment setting have essential value⁸; 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 Rationale

1.2.1 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 replication⁹. 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 suppression¹⁰.

The decision of when to start antiviral therapy is the subject of great debate, and subject to fairly frequent revision. Patients who initiate therapy with CD4+ cell counts below 200 cells/mm³ have a greater risk of disease progression and death when compared to those who initiate treatment with CD4+ cell counts above 200 cells/mm³.¹¹ More recently evidence suggests that waiting for CD4+ cell count to fall below 200 cells/mm³ may put patients at increased risk for infection, leading to changes in WHO recommendations relevant to this study. The obvious benefits of antiviral therapy must be weighed against a global shortage of antiviral agents and treatment infrastructure (leading to de facto rationing), cost, short and long-term side effects, and severe challenges with adherence.

Deductive reasoning strongly suggests that ART might render HIV-infected people less contagious¹². 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 years¹³. 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 infected¹⁴, 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 levels¹⁵, 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 clade¹⁶.

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 replication¹⁷. ART decreases the concentration of HIV-1 RNA in male¹⁸ and female genital secretions¹⁹, rectal mucosa²⁰, and saliva²¹, 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 blood²². 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 ejaculate²². ART selects for resistant viral variants which grow in the presence of

ZDV^{10;23}, other nucleoside analogues²⁴, and protease inhibitors²⁵; however, these variants are often less “fit” to replicate *in vitro*. It is unclear to what degree a reduction in “fitness” affects HIV transmissibility.

Two retrospective clinical studies 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 ZDV⁷. Castilla *et al* examined HIV transmission in discordant couples before and after the availability of ART and noted substantial reduction in HIV transmission events²⁶. Of four population based studies²⁷⁻²⁹ of HIV incidence before and after the availability of ART, two reported substantial reduction in the number of anticipated HIV cases.

Mathematical models have been used to predict the ability of HIV treatment to reduce HIV incidence and prevalence. In a model generated by Gray *et al* from the Uganda transmission study data, ART would be predicted to reduce incident HIV by 80%³⁰. Subsequent models by Blower³¹ and Law³² also have concluded that ART could decrease HIV transmission. More recently, Baggely argued that ART could not reduce HIV prevalence³³. All models are limited by their assumptions about the degree and duration of effect(s) of ART, the development and transmission of resistant variants, and changes in risk taking behavior. Models with optimistic assumptions show the greatest benefits. It should be emphasized that the current trial can be expected to generate empirical data that will allow revision of these models, and allow more accurate predictions. Furthermore, the application of ART for prevention is not static. The results of this study will direct development of therapy designed to better suppress HIV transmission.

1.2.2 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 ART³⁴;
- ART could promote risky sexual behavior (disinhibition)^{35;36};
- 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 community⁶;
- 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 350 - 550 cells/mm³ 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 within or below the range of 200-250 cells/mm³, 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.

1.2.3 Other Applications of Antiretroviral Therapy for Prevention

ART might also be used as pre-exposure (PREP), occupational, or non-occupational Post Exposure (iPEP and nPEP) prophylaxis to prevent HIV acquisition¹², and this subject has been reviewed¹². USPH Guidelines regarding PEP for needlestick or occupational exposure to HIV (iPEP)^{37;38}, and nPEP³⁹ have been developed. Given that discordant couples may on occasion encounter circumstances that could warrant application of nPEP, this topic must be discussed in greater detail.

Briefly, experiments with primates suggest that ART provided within 72 hours of exposure to HIV and continued for a full 28 days can provide at least partial protection from HIV. However, such use of ART in this fashion is expensive, and adherence to the regimen is difficult because of toxicity. Most importantly, the benefit of nPEP in humans has not been established. The cost-benefit ratio of this approach is very unfavorable because of the limited efficiency of transmission of HIV after any single sexual exposure³⁷.

Accordingly, while nPEP should be available for special circumstances (*e.g.* after sexual assault), it is not recognized as a viable public health HIV prevention strategy, and would not be recommended for routine usage in HIV discordant couples in a steady relationship. These issues are discussed in greater detail by Cohen *et al*¹². The USPH Guidelines for nPEP are available to the study Investigators, should they find themselves in situations

where such an intervention is deemed necessary. It is not anticipated that nPEP will affect the results of this trial.

1.2.4 Antiretroviral Therapy Considerations

ART will become available on a global basis, regardless of its current cost and infrastructure limitations. World Health Organization (WHO)/UNAIDS Guidance Modules provide for the use of ART in the resource poor settings selected for this study. The strategies and regimens used in this study are consistent with the most recent revision in WHO guidelines⁴⁰.

This study uses 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.

1.2.4.1 Antiretroviral Drugs

The ART drugs provided through the study include Combivir[®] [3TC/ZDV], ATV, EFV, NVP, TDF, 3TC, ddI-EC, d4T, Kaletra[®]/Aluvia[®] [LPV/r], and Truvada[®] [FTC/TDF], and this section provides background safety and efficacy data only for these drugs. Other drugs not provided through the study may be available for use at some sites. In such cases, these drugs may be used only if approved by the HPTN 052 Clinical Management Committee (CMC), and in accordance with the respective package insert.

Lamivudine/Zidovudine Combination (Combivir[®], 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 BID. The 3TC/ZDV-combination tablet has been shown in a clinical study to be bioequivalent to the two individual antiretroviral drugs³¹. The efficacy of 3TC/ZDV was established in a randomized, open-label, parallel-group, multicenter study (n =223) that compared a regimen using the 3TC/ZDV combination tablet given BID plus a PI versus a regimen containing ZDV TID plus 3TC BID plus a PI³².

Persons who are co-infected with hepatitis B (HBV) may experience increased levels 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. Participants should be followed closely with both clinical and laboratory follow-up for the first several months following Combivir[®] discontinuation, as it contains 3TC.

Additional information regarding 3TC/ZDV is available in the most recent Combivir[®] package insert.

Zidovudine (Retrovir[®], ZDV)

ZDV is generally well tolerated, particularly in persons with CD4+ > 200 cells/mm³. 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.

Additional information regarding ZDV is available in the most recent Retrovir[®] package insert.

Drug Resistance Following ZDV Prophylaxis of Mother-to-Child Transmission (MTCT)

A number of studies have examined use of ZDV following ZDV perinatal prophylaxis. Rates of resistance vary from study to study (Eastman et al. 1998; Ekpini et al. 2002; Kully et al. 1999; Welles et al. 2000) and are likely influenced by the duration of ZDV exposure, the assay(s) used for resistance testing, the timing of testing, and other factors.

Lamivudine (Epivir[®], 3TC)

3TC is a potent nucleoside analogue (NRTI) 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 NRTIs. 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 (HBV) may experience increased levels 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. Participants should be followed closely with both clinical and laboratory follow-up for the first several months following 3TC discontinuation.

Additional information regarding 3TC is available in the most recent Epivir[®] package insert.

Efavirenz (Sustiva[®]/Stocrin[®], EFV)

EFV is a once daily NNRTI that has been shown to be effective in the treatment of HIV disease⁴¹. 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. Participants 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. Participants 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.

Teratogenicity/Developmental Toxicity

The U.S. FDA use-in- pregnancy category for EFV has been changed from Category C (Risk of Fetal Harm Cannot Be Ruled Out) to Category D (Positive Evidence of Fetal Risk). This change is a result of four retrospective reports of neural tube defects in infants born to women with first trimester exposure to EFV, including three cases of meningomyelocele and one of Dandy Walker syndrome. As EFV may cause fetal harm when administered during the first trimester to a pregnant woman, pregnancy should be avoided in women receiving EFV. Women should be instructed not to breast-feed while taking EFV. If a woman becomes pregnant while taking EFV during the first trimester of pregnancy, she should be apprised of the potential harm to the fetus.

Additional information regarding EFV is available in the most recent Stocrin[®]/Sustiva[®] package insert.

Atazanavir (Reyataz[®], ATV)

ATV is one of a new class of azapeptide PIs for HIV-1 that differs from the existing peptidomimetic PIs by its C-2 symmetric chemical structure. ATV has antiviral activity that has been demonstrated in several 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 individuals 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 individuals had a total bilirubin >2.5 times the upper limit of normal (ULN). However, only 5% of individuals had a total bilirubin >5 times the ULN. Up to 10% of individuals demonstrated clinical signs of hyperbilirubinemia (scleral icterus or jaundice). Rates of hyperbilirubinemia as well as absolute levels were higher in individuals with a genetic phenotype similar to that observed for individuals 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.

Additional information regarding ATV is available in the most recent Reyataz[®] package insert.

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 experience from clinical trials and clinical practice has shown that the most serious adverse reactions are clinical hepatitis/hepatic failure, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and hypersensitivity reactions (HSRs) characterized by rash, constitutional findings, and organ dysfunction.

Hepatic toxicity

In controlled clinical trials, symptomatic hepatic events, regardless of severity, occurred in 4% (range 0% to 11.0%) of participants who received NVP and 1.2% of participants in control groups. Increased AST or ALT levels before the start of ARV treatment and/or history of HBV or hepatitis C virus (HCV) infection are associated with greater risk of hepatic AEs. Severe, life-threatening, and in some cases fatal hepatotoxicity (including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure) has been reported in patients treated with NVP. In some cases, participants presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, prolonged PTT, or eosinophilia. Physicians and participants should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness, or hepatomegaly. The diagnosis of hepatotoxicity should be considered in this setting, even if liver function tests are initially normal or alternative diagnoses are possible. 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/mm³, including pregnant women receiving chronic treatment for HIV infection, is considerably higher (12 fold) compared with women with CD4+ counts ≤ 250 cells/mm³ (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. 1.2%). This subset of patients was identified by analyses of CD4+ cell count at the time of NVP treatment initiation. 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 participants 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. 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. LFTs are required at weeks 2, 4, 6, and 8, after each time NVP is initiated, then monthly through the 20th week of 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 individuals 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. Participants should be advised to promptly notify their health care provider if they develop any rash or signs and symptoms of a HSR. Participants who experience rash during the first 2 weeks of treatment should not have the dose of NVP increased until the rash has resolved.

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

Drug Resistance Following Single-Dose NVP Prophylaxis

In HIVNET 012, pregnant women received a single dose of NVP at the onset of labor. NVP resistance mutations were detected in 70 of 279 (25%) women 6-8 weeks after delivery⁴². The frequency of NVP resistance after single dose NVP varies by HIV-1 subtype, and is particularly high among women with subtype C⁴³. Furthermore, recent studies show that population-sequencing-based genotyping assays tend to underestimate the risk of NVP resistance, compared with more sensitive resistance assays⁴⁴. In HIVNET 012, HIV variants with NVP resistance mutations faded from detection by 12-24 months after delivery using a population-sequencing-based assay⁴⁵. However, more recent studies using a more sensitive resistance assay show that K103N-containing HIV-1 variants persist above baseline levels for a year or more after single dose NVP in some women⁴⁶. Among participants who failed prior treatment with an NNRTI, selection of minority variants with NNRTI resistance mutations may compromise subsequent treatment with an EFV-containing regimen^{47;48}. In the setting of single dose NVP prophylaxis, prior exposure of women to SD NVP may lower their virologic response to a subsequent NNRTI-containing treatment regimen⁴⁹. Further studies are needed to evaluate the clinical impact of NVP resistance after single dose NVP prophylaxis.

EFV Substitution with NVP

The strategy of 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 available⁵⁰⁻⁵².

Clarke et al. reported on eight individuals who experienced NVP-related rash 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 that two individuals who experienced severe HSRs with NVP changed to an EFV-containing regimen (with a corticosteroid taper) with good tolerance. Soriano et al. reported findings from an EFV expanded access program: of eight individuals 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.

Per the most recent Viramune[®] package insert it is recommended that NVP be dosed BID. Additional information regarding NVP is available in the most recent Viramune[®] package insert.

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 the area under the curve [AUC]) 2 to 20 times higher than those observed in humans.

In study 903, involving 600 treatment-naïve patients treated for up to 144 weeks, changes in renal function (serum creatinine elevation, hypophosphatemia, glycosuria, proteinuria) were observed with similar frequency in the TDF-containing arm as compared with the d4T-containing arm. No patients were discontinued from the study for renal adverse events.

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, Fanconi syndrome, and nephrogenic diabetes insipidus.

TDF should be avoided with concurrent or recent use of a nephrotoxic agent. Participants 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. Participants, who are coinfecting 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. Participants coinfecting with

hepatitis B (HBV) and HIV should be closely monitored with both clinical and laboratory follow-up 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 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 144 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 were five bone fractures reported in the TDF group compared with eleven 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 rhesus macaque monkeys resulted in a fetal/maternal concentration of 60%, demonstrating that TDF does cross the placenta⁵³. 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.

Additional information regarding TDF is available in the most recent Viread[®] package insert or the Investigator Brochure (if not registered in country).

Emtricitabine and Tenofovir Disoproxil Fumarate Fixed Dose Combination (FDC) Tablet (Truvada[®], FTC/TDF)

Gilead Sciences has developed Truvada[®], a new product containing FTC 200 mg and TDF 300 mg in an FDC tablet formulation. A New Drug Application (NDA) for the FDC was filed with the U.S. FDA on March 12, 2004, and was approved on August 2, 2004.

Study GS-US-104-172 was a phase I, 28-day, randomized, four-way crossover, pharmacokinetic (PK) study in healthy volunteers designed to evaluate the bioequivalence of the FTC/TDF combination tablet compared with the FTC capsule and TDF tablet administered concurrently and also the effect of food (high-fat meal and light meal) on pharmacokinetics⁵⁴. The results demonstrated bioequivalence between the FTC/TDF combination tablet and the FTC capsule and TDF tablet formulations when administered separately. Administration of the FTC/TDF combination tablet with either a high-fat meal or light meal increased TDF exposure by approximately 30% compared with fasted-state administration. Clinical experience with TDF indicates that the effect of food on TDF exposure is not of clinical relevance. FTC and TDF, either administered as an FDC tablet (containing FTC 200-mg/TDF 300-mg) or coadministered as FTC 200 mg capsule and TDF 300-mg tablet administered separately, were well tolerated.

Several studies have assessed the safety and efficacy of FTC with TDF, albeit none using FDC. Study M02-418 was a phase III, randomized, open-label, multicenter study designed to compare lopinavir (LPV) 800 mg/ritonavir (RTV) 200 mg QD vs. LPV 400 mg/RTV 100 mg BID with the background regimen of FTC 200 mg QD and TDF 300 mg QD in ARV-naïve patients with HIV-1 RNA >1000 copies/mL⁵⁵⁻⁵⁷. A total of 190 patients between the ages of 19-75 years were enrolled; 115 to the QD arm and 75 to the BID arm. At week 48, based on the intention to treat (ITT) (NC=F) analysis, 70% of participants in the QD regimen demonstrated HIV-1 RNA <50 copies/mL compared with 64% of those in the BID group (95% CI: -7%; 20%). Gastrointestinal AEs were the most common cause for discontinuation. Overall, the most common AEs (>3%) reported were diarrhea, nausea, and vomiting, with diarrhea being reported significantly higher in the QD group (16% vs. 5%; p=0.04). The most common Grade 3/4 laboratory abnormalities (> 3%) reported were increased ALT (>5 x upper limit of normal [ULN]), AST (> 5 x ULN), triglyceride (>750 mg/dL), and amylase (>2 x ULN) levels; no significant differences between the two groups were observed⁵⁷.

Study 934 is a phase III, randomized, open-label, noninferiority, multicenter study designed to compare a regimen of TDF 300 mg + FTC 200 mg + EFV QD with a regimen of ZDV 300 mg/3TC 150 mg BID (as FD Combivir[®]) + EFV QD in antiretroviral-naïve, HIV-1-infected participants⁵⁸. The 48-week data demonstrated that using the time to loss of virologic response as the primary analysis (where missing, switch, or early termination is counted as a failure), the proportion of participants with plasma HIV-1 RNA levels < 400 copies/mL in an ITT population (n=487) was 84% in the TDF + FTC group compared with 73% in the ZDV/3TC group (p=0.002). The proportion of participants with plasma HIV-1 RNA levels < 50 copies/mL was 80% in the TDF+FTC group versus 70% in the ZDV/3TC group (p=0.020). Significant

differences were also seen between the TDF+FTC and the ZDV/3TC groups in the proportion of participants with increases in CD4+ cell counts (190 and 150 cells/mm³, respectively; p=0.002). Safety analysis, based on 511 participants who received any study medication, showed that discontinuation due to AEs occurred more frequently in the ZDV/3TC group (9%) than in the TDF + FTC group (4%) (p=0.02). The most common AE resulting in discontinuation related to study drug for the ZDV/3TC group was anemia (14/254) and NNRTI-associated rash (2/257) for the TDF+FTC group. Renal safety was similar in the two groups, and no participant discontinued study medication because of renal events. A significantly (p<0.001) greater percentage of participants in the TDF+FTC arm had a lower mean increase from baseline in fasting total cholesterol levels (21 mg/dL) compared with participants in the ZDV/3TC arm (35 mg/dL). At week 48, total limb fat was significantly less in a subset of participants receiving ZDV/3TC (mean of 6.9 kg or 15.2 pounds; n=49) compared with a subset of participants receiving TDF+FTC (mean 8.9 kg or 19.6 pounds; n=51; p=0.03). All participants with confirmed >400 copies/mL of HIV-1 RNA at week 48 or early discontinuation were analyzed for genotypic resistance. Genotype data were limited to 23 participants on ZDV/3TC and 12 participants on TDF+FTC and showed mostly M184V/I (3% in ZDV/3TC participants vs. 1% in TDF + FTC participants) and/or EFV-resistance mutations (7% in ZDV/3TC vs. 4% in TDF + FTC participants), with no participants developing the K65R mutation.

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

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including FTC, TDF, and other ARVs.

FTC/TDF is designated as FDA use-in-pregnancy Category B. More information concerning FTC/TDF coformulation, is available in the most recent Truvada[®] package insert.

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. No one with a history of pancreatitis should be given ddI-EC.

TDF - ddI-EC Pharmacokinetic Interaction

Once daily ddI-EC 400 mg (all individuals ≥ 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.

The recommended dosing is ddI EC 250 mg (if ≥ 60 kg), or 200 mg (if < 60 kg), with TDF 300 mg, administered as a single daily dose with or without food.

Additional information regarding ddI is available in the most recent Videx-EC[®] package insert.

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-1-infected individuals⁵⁹⁻⁶³.

The most common toxicity associated with d4T is peripheral neuropathy and, much less commonly, hepatic damage, pancreatitis, and lactic acidosis (for which women 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 combination⁶⁴.

Additional information regarding d4T is available in the most recent Zerit[®] package insert.

Lopinavir/Ritonavir (Kaletra[®]/Aluvia[®], LPV/r)

Lopinavir is a potent inhibitor of HIV-1 protease. When co-formulated with LPV, ritonavir inhibits the CYP3A-mediated metabolism of LPV, thereby providing increase plasma levels of LPV. Lopinavir/ritonavir (LPV/r) has been evaluated and approved by the FDA for use in combination with other ART agents for the treatment of HIV-1 infection.

The most common AEs associated with LPV/r therapy were diarrhea and nausea, which were generally of mild to moderate severity. Rates of discontinuation of randomized therapy due to AEs were 5.8% in LPV/r-treated and 4.9% in NFV-treated patients. Pancreatitis has been reported in patients receiving LPV/r, although a causal relationship has not been established. The most common laboratory abnormalities in patients receiving LPV/r were elevations in triglycerides and cholesterol, which may be marked, and less commonly elevations in AST and ALT.

LPV/r has not been studied in African populations nor in other areas in which non-clade B HIV subtypes predominate. The safety and pharmacokinetics of LPV/r in pregnancy have not been established. There has been no evidence of teratogenicity with administration of LPV/r to pregnant rats or rabbits.

LPV/r Pharmacokinetics During Pregnancy

LPV/r pharmacokinetics during pregnancy is currently under study in PACTG 1026s. Fourteen of 17 pregnant American women studied to date have failed to meet the PK target for the study of a LPV AUC above the 10th percentile that is seen in non-pregnant adults, suggesting that during pregnancy LPV concentrations may be low with administration of the standard dose of 400 mg of LPV and 100 mg of RTV BID. Three of 8 women with available postpartum data also had LPV AUC less than the 10th percentile⁶⁵. However, trough concentrations in 15 of 17 pregnant women and 7 of 8 postpartum women were above 1000 ng/mL (Stek, personal communication), which is likely adequate to treat wild-type virus.

It is not known how long any pregnancy-related changes in LPV/r PK might persist following delivery. In addition, women in resource-limited settings will likely have smaller body size and impaired nutritional status compared with HIV-infected women in the United States. While the physiologic changes associated with pregnancy may lead to lower LPV/r concentrations, the anticipated smaller size of women participating in this study may result in increased LPV concentrations. The standard adult dosing regimen for LPV/r will be used in this protocol. The unpublished data regarding trough LPV concentrations from PACTG 1026s suggest that the standard dose should be sufficient for suppression of wild-type HIV replication.

Additional information about LPV/r can be found in the most recent Kaletra[®]/Aluvia[®] package insert.

1.2.4.2 Initiation of Antiretroviral Therapy

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 falls to 350 cells/mm³. However, these guidelines are generally not appropriate for resource limited settings where ART remain in short supply, and treatment infrastructure is limited. In addition, the benefits of earlier initiation of therapy have not been demonstrated.

HIV-infected participants with CD4+ cell counts between 350 and 550 cells/mm³ will be randomized to receive ART and HIV primary care either i) upon enrollment in the study, or ii) when the study participant has two consecutive measurements of a CD4+ cell count within or below the range of 200-250 cells/mm³, or iii) has developed an AIDS-defining illness.

Current WHO guidelines⁴⁰ suggest that ART should be considered in asymptomatic patients who have a CD4+ cell count between 200 and 350 cells/mm³ and they emphasize that it is best to initiate ART **before** CD4+ cell count falls below 200 cells/mm³. It is the

intent of this protocol to be consistent with current WHO guidelines and initiate ART in the delay arm (described in “ii” above) between 200-250 cells/mm³. In cases where CD4+ cell count goes below 200 cells/mm³ without first having a measurement between 200-250 cells/mm³, ART will be initiated appropriately.

1.2.4.3 HIV-1 Drug Resistance

Regardless of the 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 (www.aidsinfo.nih.gov)⁶⁶. For this study, local genotyping results may be utilized for patient management if they are available in real time.

However, 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.

In addition, a plan for resistance testing in HPTN 052 for research purposes has been developed. 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.

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^{67,68}. 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% (30% in southern and south-eastern Brazil)]	[69] [70] [71]
India	C (90-95%), B (1-3%), A (2 - 5%)	[72] [73] [74]
Malawi	C (>90%)	[75]
Thailand	CRF01_AE (80-95%), B (5-20%)	[76] [77] [78]
Zimbabwe	C (70%), B (12%), A (12%), D (7%)	[79] [80]

Although data are limited, some studies suggest that the natural susceptibility of HIV-1 to antiretroviral drugs may be influenced by subtype^{80,81}, and polymorphisms associated with drug resistance are frequently detected in antiretroviral drug naive individuals with non-subtype B infection⁸².

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-1⁸³. 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^{84;85}. Subtype-specific differences in protease and RT sequences may influence the rate at which a specific mutation emerges⁶⁹, and the type of amino acid selected at a given position under drug pressure^{84;86}. 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 B⁸⁷. 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)⁸⁸. 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 HAART⁸⁹. 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-1 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 prophylaxis⁹⁰. 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 exposure⁹¹.

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/F⁹²; 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 Study⁹³ and the Women and Infants Transmission Study (WITS)⁹⁴ 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 analyzed⁹⁵. 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 transmission⁹⁶. 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 delivery⁸³. 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

prevalent⁴⁵. 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 D⁹⁷.

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%)⁹⁸.

1.2.4.4 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.

Ancillary or substudies may be developed that optimize the unique scientific opportunities within this study, as well as to facilitate consistency in assay methods utilized by other networks, including the NIH Center for HIVAIDS Vaccine Immunology (CHAVI), which has great need for the specimens to be generated through HPTN 052. Table 2 outlines the types of samples that will 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	Potential Assays (both CHAVI and non-CHAVI)
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> , measuring cytokine levels using ELISPOT or Luminex assays
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, comparisons using matrices of optimized peptide epitopes), tetramer assay, lymphoproliferation assay (LPA), microarray analysis for gene expression (<i>e.g.</i> cytokines, chemokines, <i>etc.</i>), intracellular cytokine staining.

1.2.5 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 accordance 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).

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.

1.3 Study Implementation Plan

The original design of this study included a run-in period during which each site enrolled a limited number of participants (between 5 and 10 couples at each site, with up to a maximum of 90 couples total) and followed them for a minimum of 6 months. The primary purpose of the run-in period was to demonstrate that study implementation was feasible, and to identify any operational issues prior to executing the full study. The 82 couples enrolled during the run-in period are included in the full study cohort (1750 couples) and will be followed from the time they were enrolled into the run-in period until the last couple enrolled into the full study completes their 60-month follow-up visit. A detailed description of the run-in period can be found in Version 1.0 and 2.0 of the protocol (available at www.hptn.org/research_studies/hptn052.asp). The results of the run-in are available upon request to the HPTN 052 Protocol Chair.

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 within or below the range of 200-250 cells/mm³, 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 antiretroviral treatment strategies (*i.e.*, immediate upon enrollment vs. ART initiation when the participant has two consecutive measurements of a CD4+ cell count within or below the range of 200-250 cells/mm³, or develops an AIDS-defining illness).
- 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 antiretroviral 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.
- Characterize and compare Quality-of-Life (QOL) indicators in different geographic settings and by antiretroviral treatment strategies.

The primary objective will be evaluated per the algorithm outlined in Appendix II. For the purposes of this study, 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, and Appendix III.

2.3 Study Design

The study is a Phase III, two-arm, multi-site, randomized, controlled trial to determine the effectiveness of two antiretroviral treatment strategies in preventing the sexual transmission of HIV in HIV serodiscordant couples. This trial consists of a run-in period, which has been completed, and a full study. 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. At entry, all HIV-infected participants will have a CD4+ cell count between 350 and 550 cells/mm³. Accrual for 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. The total number of couples in the study is 1750 (this total includes the couples enrolled during the run-in period), and the total length of the full study will be approximately 78 months.

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

Once an HIV serodiscordant couple is determined to be eligible for the 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 within or below the range of 200-250 cells/mm³, or develops an AIDS-defining illness (defined in Appendix III).

The ART drugs provided through the study include Combivir[®] [3TC/zidovudine(ZDV)], efavirenz [EFV], atazanavir [ATV], nevirapine [NVP], tenofovir [TDF], lamivudine [3TC], didanosine [ddI-EC], stavudine [d4T], Kaletra[®]/Aluvia[®] [lopinavir(LPV)/ritonavir (r)], and Truvada[®] [emtricitabine (FTC)/tenofovir (TDF)]. It is recommended that Combivir[®] and EFV or ATV be used as the primary regimen; however, study clinicians may use other study-provided ART after obtaining permission from the HPTN 052 CMC. Secondary and salvage regimens are not defined by the protocol and may contain any viable combination of three or more of the HPTN 052-provided study drugs at the discretion of the site investigator. Non-study-provided ART (including generic agents that are or become approved or tentatively approved by the U.S. FDA) may also be used in secondary and salvage regimens if approved by the HPTN 052 CMC. If non-study ART is used during the study, it must be provided by non-study prescription.

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 Initiating ART in the Delay Arm (Arm 2)

As indicated in the primary objective, ART will be initiated in Index cases in Arm 2 (the delay arm) when they have two consecutive measurements of CD4+ cell count within or below the range of 200-250 cells/mm³ or they develop an AIDS-defining illness. In accordance with current WHO guidelines, it is the intent of the protocol to initiate ART in Arm 2 (the delay arm) **before** CD4+ cell count falls below 200 cells/mm³. Once an Index case in the delay arm has a CD4+ cell count measurement between 200 and 250 cells/mm³, the next CD4+ cell count measurement should be done within 6 weeks.

Once two consecutive CD4+ cell count measurements between 200 and 250 cells/mm³ have been obtained, the following should be considered prior to ART initiation:

- Is there any indication that the CD4+ cell count measurement is incorrect (*e.g.* normal diurnal variation, lab equipment malfunction). If there are any doubts, the test should be repeated.
- Is there any indication that the CD4+ cell count has been temporarily suppressed due to a transient medical condition (*e.g.*, malaria). If so, treat the underlying condition and re-test.

In the situation where an Index case in the delay arm has a CD4+ cell count below 200 cells/mm³, but there has been no previous measurement between 200 and 250 cells/mm³, a second, confirmatory, CD4+ cell count measurement should be performed as soon as possible. If the subsequent CD4+ cell count measurement is < 250 cells/mm³, ART should be initiated unless there is an indication that the measurements are incorrect or there is a transient medical condition.

Study clinicians are encouraged to consult the HPTN 052 CMC for guidance in making the decision to initiate ART for participants in the delay arm. If the decision is made to delay ART despite two consecutive CD4+ cell counts < 250 cells/mm³, the reasons for the delay should be thoroughly documented in the source documentation.

2.3.2 Criteria For Switching Antiretroviral Therapy Regimen Due to Virologic Failure

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. If possible, the two plasma HIV RNA measurements should be done within a month of each other. Resistance testing, where available, may be used to guide selection of the 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 not be required to switch therapy. The starting regimen should continue and the plasma HIV-1 RNA evaluated 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, a switch to a secondary regimen is mandatory, unless a longer delay in making this switch is approved by the HPTN 052 CMC.

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. Resistance testing, where available, may be used to guide selection of a third regimen.

2.3.3 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 defined visit window. The SSP defines the visit window associated with each visit type (2-week visit, monthly visit, etc.).

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.

2.3.3.1 Index Case Follow-up

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 (on a quarterly basis), 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 (on a quarterly basis), and participating in couples HIV counseling with their partner. For both arms of the study, most clinical procedures and laboratory evaluations will occur during the quarterly and yearly visits. However, once an index case is placed on their initial ART regimen, it is required that a closer safety assessment be performed two weeks after. Assessments should include hematology, liver function, and blood chemistry assessments, as well as a targeted 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).

2.3.3.2 Partner Follow-up

Partners are required to report for monthly visits to complete a sexual history assessment (on a quarterly basis), participate in couples HIV counseling, and adherence counseling (only while partner is on ART). Partners are also required to attend the visit that takes place two weeks after ART initiation. Clinical procedures and laboratory evaluations will take place during quarterly and yearly visits.

2.3.3.3 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 when clinically indicated. Whenever a genital ulcer is found during examination, a swab will be taken and sent to the HPTN CL for etiology determination.

2.3.4 Rules of Participation for Both Index Case and Partner

The following rules for participation will apply throughout the course of the study for the index case and the partner.

2.3.4.1 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.

2.3.4.2 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.

2.3.4.3 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.

Whether individual HBV/HIV coinfecting persons are enrolled into HPTN 052 will be left to the discretion of the site investigator.

3.1.1 Index Case

- Positive HIV serology obtained within 60 days prior to enrollment

Note: Confirmation of the initial positive or discordant test results (the initial test may be the results from two rapid tests) must use a test that is different than the one used for the initial assessment. Initially reactive rapid tests should be confirmed by Western blot or a plasma HIV-1 RNA. An initial ELISA result must be confirmed with another method such as Western blot or plasma HIV-1 RNA, but not by a repeat ELISA test.

- 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.
- If pregnant or breastfeeding during screening or at the time of enrollment, willing to be randomized to either arm of the study.

Note: If a woman is in her first trimester during screening, the HPTN 052 CMC **must** be consulted prior to her enrollment.

- The following conditions must be met for laboratory parameters within 60 days prior to enrollment:
 - CD4+ cell count of 350-550 cells/mm³
 - Hemoglobin \geq 7.5 g/dL (see Section 4.5.5.5 for information on anemia)
 - Platelet count \geq 50,000/ μ L.
 - AST (SGOT), ALT (SGPT), and alkaline phosphatase \leq 5 x ULN
 - Total bilirubin \leq 2.5 x ULN
 - Calculated creatinine clearance \geq 60 mL/min (use the Cockcroft and Gault method to calculate)
 - Absolute neutrophil count \geq 750 mm³ or 0.750 x 10⁹/L (see Section 4.5.5.5 for information on neutropenia)

3.1.2 Partner

- Negative HIV serology within 14 days prior to enrollment.

Note: If the initial test is two negative rapid tests, the participant will be considered HIV-negative and no further testing is required. If the initial test is a non-reactive EIA, the participant will be considered HIV-negative and no further testing is required.

- 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 ≥ 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 AIDS-defining illness (as defined in Appendix III). (Note: active TB, as defined by the ACTG 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.)
- 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).
- Documented or suspected acute hepatitis within 30 days prior to enrollment, irrespective of AST (SGOT) and ALT (SGPT) values.
- Acute therapy for serious medical illnesses, in the opinion of the site investigator, within 14 days prior to enrollment. Candidates with chronic, acute, or recurrent infections that are serious, in the opinion of the site investigator, who must

continue with chronic (maintenance) therapy (*e.g.*, TB), must have completed at least 14 days of therapy prior to study entry and be clinically stable.

- Radiation therapy or systemic chemotherapy within 45 days prior to enrollment.

NOTE: Anticipated need for systemic chemotherapy while on study is not permitted.

- Any immunomodulator or other investigational therapy within 30 days prior to enrollment.
- Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.
- Vomiting or inability to swallow medications due to an active, pre-existing condition that prevents adequate swallowing and absorption of study medication.
- Need for a prohibited medication listed in Section 4.3.2.
- Allergy/sensitivity to any study drugs or their formulations.

3.2.2 Both Index Case and Partner

- Reports a history of injection drug use within the last five years.
- Previous and/or current participant in an HIV vaccine study.
- 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 each participating 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)

3.3.1 Screening Procedures

Both members of a couple must provide independent written informed consent for screening, be assigned a screening identification (ID) number, provide 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 targeted 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 participating site Investigator of Record on a case-by-case basis depending on the requirements of the other study.

4 STUDY TREATMENT CONSIDERATIONS

The ART drugs provided for use in this study include Combivir[®] [3TC/zidovudine (ZDV)], efavirenz [EFV], atazanavir [ATV], nevirapine [NVP], tenofovir [TDF], lamivudine [3TC], didanosine [ddI-EC], stavudine [d4T], Kaletra[®]/Aluvia[®] [lopinavir(LPV)/ritonavir (r)], and Truvada[®] [emtricitabine (FTC)/tenofovir (TDF)]. It is

recommended that Combivir[®] and EFV or ATV be used as the primary regimen; however, study clinicians may use other study-provided ART after obtaining permission from the HPTN 052 CMC. Secondary and salvage regimens are not defined by the protocol and may contain any viable combination of three or more of the HPTN 052-provided study drugs at the discretion of the site investigator. Non-study-provided ART (including generic agents that are or become approved or tentatively approved by the U.S. FDA) may also be used in secondary and salvage regimens if approved by the HPTN 052 CMC. If non-study ART is used during the study, it must be provided by non-study prescription.

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 drugs available for the study include Combivir[®] [3TC/zidovudine(ZDV)], efavirenz [EFV], atazanavir [ATV], nevirapine [NVP], tenofovir [TDF], lamivudine [3TC], didanosine [ddI-EC], stavudine [d4T], Kaletra[®]/Aluvia[®] [lopinavir(LPV)/ritonavir (r)], and Truvada[®] [emtricitabine (FTC)/tenofovir (TDF)]. Study drugs will be provided by the study to participants while they are on study. These drugs are being provided by or obtained from:

- 3TC/ZDV, 3TC: GlaxoSmithKline
- EFV (for all non-U.S. sites): Merck & Co., Inc.
- ATV, ddI-EC, d4T, EFV (for U.S. site): Bristol-Myers Squibb, Inc.
- NVP: Boehringer-Ingelheim Pharmaceuticals, Inc.
- TDF, FTC/TDF: Gilead Sciences, Inc.
- LPV/r: Abbott

ART that is not provided by the study (including generic agents that are or become approved or tentatively approved by the U.S. FDA) may be used for study participants if

approved by the HPTN 052 CMC. If non-study-provided ART is used during the study, it must be provided by non-study prescription.

The ART study drugs provided through this study 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 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. The site pharmacist will receive instructions from the DAIDS Pharmaceutical Affairs Branch regarding the final disposition of unused 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 provided by the study only. All medications will be administered orally.

Table 3: Antiretroviral Therapies

Medication	Class	Formulation	Daily Dose	Frequency	Storage	Notes
Lamivudine/ Zidovudine 3TC/ZDV Combivir®	NRTI	150 mg/300 mg tablets	300 mg/600 mg	1 PO BID with or without food	2° - 30°C 36° - 86°F	None
Lamivudine 3TC Epivir®	NRTI	300 mg tablets	300 mg	1 PO QD with or without food	25°C 77°F Excursions permitted between 15-30°C (59-86°F)	None
Efavirenz EFV Sustiva® or Stocrin®	NNRTI	600 mg tablets	600 mg	1 PO QHS without food	25°C 77°F Excursions permitted between 15-30°C (59-86°F)	Participants should be informed that if they experience CNS symptoms they should avoid potentially hazardous tasks such as driving or operating machinery; and they should be informed that CNS 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 for participants who continue to experience CNS symptoms. Those receiving EFV should be alerted to the potential for additive CNS effects when EFV is used concomitantly with alcohol or psychoactive drugs.
Atazanavir ATV Reyataz®	PI	150 mg and 200 mg capsules	400 mg alone OR 300 mg if boosted with ritonavir	2 PO QD with light meal or snack	25°C (77°F). Excursions permitted between 15°-30°C (59°-86°F)	ddI-EC should be taken on an empty stomach 1 hour before or 2 hours after ATV is taken with food. If ATV and TDF are used together, ATV should be boosted with RTV.

Medication	Class	Formulation	Daily Dose	Frequency	Storage	Notes
Nevirapine NVP Viramune®	NNRTI	200 mg tablets	200 mg for 14 days, then 400 mg	1 PO QD for first 14 days (lead-in), then 1 PO BID thereafter with or without food.	25°C 77°F Excursions permitted between 15-30°C (59-86°F)	Whenever NVP is initiated (even if as a substitution for EFV), it should be started with the lead-in of 200 mg PO QD for 14 days; then 200 mg PO BID. If the person tolerates NVP for ≥ 3 months, the dose may be changed to 400 mg PO QD. It is recommended that the QD dose be taken at bedtime, although this is not required. Health care providers must review signs and symptoms of NVP-related hypersensitivity and hepatitis with the participant prior to dispensing NVP. Participants should contact their site physician if they develop rash or signs and symptoms of hypersensitivity or hepatitis. If rash occurs during lead-in, do not increase dose until the rash has resolved. After reaching full dose, if NVP dosing is interrupted for >7 days NVP should be started with the lead-in of 200 mg PO QD for 14 days; then 200 mg PO BID. If the person tolerates NVP for ≥3 months, the dose may be changed to 400 mg QD.
Didanosine ddI-EC Videx®	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	Should be taken on an empty stomach, <i>i.e.</i> , at least 1 hour before or 2 hours after a meal. ddI-EC should be taken on an empty stomach 1 hour before or 2 hours after ATV is taken with food. If given with TDF reduce dose of ddI-EC
Stavudine d4T Zerit®	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	None

Medication	Class	Formulation	Daily Dose	Frequency	Storage	Notes
Tenofovir Disoproxil Fumarate TDF Viread®	NRTI (nucleotide)	300 mg tablets	300 mg	1 PO QD with or without food	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 this should remain in the container. TDF should be stored at 25°C (77°F). Excursions permitted between 15°-30°C (59°-86°F).	None
Emtricitabine/ Tenofovir Disoproxil Fumarate FTC/TDF Truvada®	NNRTI/ NRTI (nucleotide)	200 mg/300 mg tablets	200 mg/300 mg	1 PO QD with or without food	Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F). Keep container tightly closed. Dispense only in original container.	None
Lopinavir / Ritonavir* LPV/r Kaletra® or Aluvia®	PI	200 mg/50 mg tablets	800 mg/200 mg	2 PO BID with or without food	20°-25°C 68°-77°F Excursions permitted between 15-30°C (59-86°F)	None

*The information provided is for Kaletra®/Aluvia® tablets. As some sites may be provided with Kaletra® soft gel capsules, investigators should refer to the Kaletra® soft gel capsule package insert for information.

4.3 Concomitant Medications

4.3.1 Required Medications

No concomitant medications are required.

4.3.2 Prohibited Medications

Table 4a lists medications that CANNOT be used in combination with efavirenz, nevirapine, or atazanavir. Table 4b lists additional medications that CANNOT be used in combination with atazanavir.

Table 4a: Prohibited Concomitant Medications with Efavirenz, Nevirapine, and Atazanavir

Agent Class	<u>Prohibited with EFV, NVP, ATV</u>
Antihistaminics	Astemizole (Hismanal®)
	Terfenadine (Seldane®)
GI Motility	Cisapride (Propulsid™)
Psychiatric Medications	St. John's Wort (Hypericum perforatum)
Sedatives/Hypnotics	Midazolam (Versed®) (Can be used with caution as a single dose, when given in a monitored situation for procedural sedation.)
	Triazolam (Halcion®)
Other	Dihydroergotamine
	Ergonovine
	Ergotamine
	Methylergonovine

Table 4b: Additional Prohibited Concomitant Medications with Atazanavir

Agent Class	Prohibited with ATV
Antiarrhythmics	Amiodarone (Cordarone®)
	Lidocaine (Xylocaine®)
	Quinidine (Quinaglute®, Quinidex®)
Anticonvulsants	Phenobarbital
	Phenytoin (Dilantin®)
	Carbamazepine (Tegretol®)
Anti-infective	Rifampin (Rifadin®, Rimactane®)
Antineoplastic agent	Irinotecan (Camptosar®)
Calcium channel blockers	Bepridil (Vascor®)
All H2 blockers	Cimetidine (Tagamet®)
	Ranitidine (Zantac®)
	Nizatidine (Axid®)
	Famotidine (Pepcid®)
HMG CoA reductase inhibitors	Lovastatin (Mevacor®)
	Simvastatin (Zocor®)
Neuroleptic	Pimozide (Orap®)
Protease inhibitors	Indinavir (Crixivan®)
Proton pump inhibitors	Rabeprazole (Aciphex®)
	Esomeprazole (Nexium®)
	Omeprazole (Prilosec®)
	Lansoprazole (Prevacid®)
	*Pantoprazole (Protonix®)
Triptan	Eletriptan (Relpax®)
Other Agents	Warfarin (Coumadin®)

* Wait 2-3 days after stopping Protonix before starting ATV

4.3.3 Precautionary Medications

To avoid drug interactions and AEs, refer to the most recent package inserts of ARV and concomitant agents whenever a concomitant medication is initiated or dose is changed.

Use of the agents listed below may require additional monitoring of drug levels or AEs. These PRECAUTIONARY MEDICATIONS include, but may not be limited to those listed in Table 5.

Table 5. Precautionary Agents

Agent Class	Precautionary Concomitant Medications
Anticonvulsants	Carbamazepine (Tegretol®)
	Phenobarbital
	Phenytoin (Dilantin®)
Anti-infectives	Artenoil
	Atovaquone (Mepron)
	Atovaquone/proguanil (Malarone®)
	Caspofungin (Cancidas®)
	Clarithromycin (Biaxin®)
	Dapsone
	Fluconazole (Diflucan®)
	Systemic itraconazole (Sporonox®)
	Proguanil (Malarone®)
Alternative/Complementary	Milk thistle (Silymarin, Silybum, Marianum)
Hormonal Agents	Glucocorticoids
Hypoglycemics	Pioglitazone (Actos®)
Sedatives/Hypnotics	All benzodiazepines
	Alprazolam (Xanax®)
	Diazepam (Valium®)
	Estazolam (ProSom®)
	Flurazepam (Dalmane®)
	Oxazepam (Serax®)
	Temazepam (Restoril®)
	Buspirone (BuSpar®)
	Trazodone (Desyrel)
Sedatives/Hypnotics (cont.)	Zaleplon (Sonata®)
	Zolpidem (Ambien®)
Triptan	Eletriptan (Relpax®)
Other Agents	Theophylline
	Warfarin (Coumadin®)
	Fluticasone (Flonase)
	Antacids

NOTE: Information on drugs without trade names, with many marketed forms, or those not available in the U.S. may be found at:

www.hiv-druginteractions.org/drug/pdf/pi_col.pdf

Other links may be found at:

www.ucsf.edu/hivcntr/Clinical_Resources/Pharmacy/PDFs/Drug_Interaction_2005.pdf

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, but they may be used together if no other alternatives exist. ddI plus d4T should not be used in pregnant women.

- EFV-, NVP-, and ATV-Related Precautions

- Oral Contraceptives

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

- Sildenafil (Viagra®) and Other Agents Used to Treat Erectile Dysfunction-Related Precautions

Sildenafil and other Phosphodiesterase Type 5 (PDE5) Inhibitors are metabolized by the CYP 3A4 pathway. 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 PIs or RTV-boosted PIs. Coadministration of RTV with a PDE5 inhibitor is expected to substantially increase their concentrations, which may cause hypotension, syncope, visual changes, and prolonged erection. When coadministered with PIs, the initial dose of sildenafil should be reduced to 25 mg, and 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.

- EFV- and NVP-Related Precautions

- 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.

- Anticonvulsants

Because anticonvulsants may reduce levels of both EFV and NVP, they should be used with caution when co-administered with these drugs.

- Rifampicin- and Rifabutin-Related Precautions

Rifampicin decreases EFV and NVP serum levels, however, the clinical significance of this effect is unknown. It is recommended that the 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 the most recent 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. Participants (either entering or on study), who take ATV and require rifampicin for the treatment of active TB, must either replace rifampicin with rifabutin or replace ATV with EFV during TB treatment. Once rifampicin treatment is completed, the participant should be switched back to ATV. Participants who receive rifabutin for the treatment of TB may remain on ATV.

See the most recent package inserts of individual PIs for rifabutin 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.

- ATV-Related Precautions

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

Caution should be used when ATV is coadministered with drugs known to increase the PR interval (e.g., diltiazem, atenolol)

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®). Buffered products and antacids may be used with ATV, but dosing must be separated in time from the ATV dose. Participants may take ATV 2 hours before or 1 hour after antacids or buffered solutions.

The risk of myopathy, including rhabdomyolysis, may be increased when ATV or other 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.

Wait 2-3 days after stopping Protonix before starting ATV.

- TDF-Related Precautions

TDF has been shown to increase the serum concentrations of ddI, even when the drugs are dosed 2 hours apart or with a meal. Participants taking TDF and ddI concomitantly should be monitored closely for ddI-associated AEs, 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 participants who weigh ≥ 60 kg; or reduce 250 mg QD to 200 mg QD for participants who weigh < 60 kg.

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

The use of TDF + ddI together with an NNRTI is associated with early virologic failure in treatment-naive patients. This combination should only be used if suitable alternative NRTI combinations are not available.

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 and will be conducted using a checklist developed by the protocol team and external experts. Topics such as the complexity of the regimen, potential side-effects, and the need to continue treatment despite symptomatic improvement will be covered during the adherence counseling sessions.

Adherence will be assessed by analyzing data collected via an adherence questionnaire and a pill count case report form. This questionnaire and pill count case report form will be administered to all index cases who are on ART study drugs at every follow-up visit.

4.5 Toxicity Management

Toxicity management related to the use of ART in the developing world setting will rely on 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 Table for Grading the Severity of Adult and Pediatric Adverse Experiences, Version 1.0, December 2004 (or current version) located at <http://rcc.tech-res-intl.com>. Every attempt should be made to continue to follow participants who discontinue study treatment because of a Grade 3 or 4 AE until resolution of the AE can be documented.

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 for both study-provided and non-study-provided ART with the HPTN 052 CMC, which consists of designated protocol team members such as co-chairs and investigators, protocol statistician, DAIDS Medical Officer and Pharmacist, HPTN SDMC Protocol Managers, 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 unless otherwise specified.

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 and then also stopped when the NRTIs are discontinued at the discretion of the site investigator.

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

4.5.1 Grades 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 AE has NOT been caused by the study drug(s), dosing may continue. Except as stated in section 4.5.5, participants who develop a Grade 3 AE or toxicity thought secondary to study medications or of unknown etiology may have all of their ARV study drugs withheld, at the site investigator's discretion. Dose reductions are not permitted.

Investigators are encouraged to discuss toxicity management with the HPTN 052 CMC. The participant should be re-evaluated weekly, if possible, until the AE returns to Grade ≤ 2 , at which time the study drugs may be reintroduced at the discretion of the site investigator.

4.5.3 Grade 4

Index cases 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 ≤ 2 . Under certain circumstances the ART study drug thought most likely to be related to the AE may be resumed at the discretion of the study clinicians after discussion with the HPTN 052 CMC. Alternative study-provided and non-study-provided ART should be considered.

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

4.5.4 Antiretroviral Therapy Dosage Reductions

Recommended dosage reductions are presented in Table 6 for antiretroviral toxicity management.

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
ddI EC ¹	400 mg QD	400 mg	250 mg QD	250 mg
ddI EC ²	250 mg QD	250 mg	125 mg QD	125 mg
NVP	200 mg QD x 14 days, then 200 mg BID ³	200 mg x 14 days, then 400 mg	None	None
3TC	300 mg QD	300 mg	None	None
FTC	200 mg QD	200 mg	None ⁴	None ⁴
TDF	300 mg QD	300 mg	None ⁴	None ⁴
d4T ¹	40 mg q12h	80 mg	20 mg q12h	40 mg
d4T ²	30 mg q12h	60 mg	15 mg q12h	30 mg
FTC/TDF (Truvada [®])	200 mg/300 mg QD	200 mg/300 mg	None ⁴	None ⁴
LPV/r (Kaletra [®] /Aluvia [®])	400 mg/100 mg BID	800 mg/200 mg	None	None

¹ For participants weighing ≥60 kg.

² For participants weighing <60 kg.

³ If 200 mg BID is tolerated for ≥ 3 months, the dose may be changed to 400 mg QD.

⁴ In the case of renal impairment, drug exposure may be decreased by increasing the dosing interval. Please consult the HPTN 052 CMC for guidance in such situations

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 ≤ 2 .

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

Rash management for Participants on NVP:

Liver function tests should be performed promptly and participants evaluated for signs and symptoms related to clinical hepatitis and hypersensitivity reactions. If LFTs are increased 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 not thought to be due to other intercurrent illness (fever, 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 nausea and/or vomiting, 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 used for making diagnoses is the lipase level. 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 is also acceptable.

Obtain baseline (entry) lipase/triglycerides at any initiation of ddI-EC or at any time ddI-EC is substituted for another drug.

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

- Grade 1: Search for other causes of symptoms. If none is found and symptoms persist, repeat lipase within 2 weeks. IF REPEAT IS ELEVATED THEN PARTICIPANT SHOULD STOP ddI-EC.
- Grade ≥ 2 : Follow participants and repeat lipase as soon as possible. If lipase is persistently elevated and accompanied by symptoms, then participants should be considered to have clinical pancreatitis. CT scan of the abdomen, if available, may also be helpful in determining whether clinical pancreatitis is present. 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 or d4T, these medications should be permanently discontinued. ddI-EC should be substituted with TDF.

Upon rechallenge, lipase determinations should be performed monthly. Any elevation of lipase of Grade ≥ 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, (before treatment modifications are made) CK should be redrawn after

participants abstain from exercise for 24 hours. If CK is still >3000 mg/dL, ZDV should be discontinued and replaced with d4T or another NRTI, if appropriate.

4.5.5.4 AST and ALT Elevation

Nearly all the antiretrovirals, INH (isoniazid) and concomitant illnesses can cause alterations in liver functions tests. Therefore, changes in AST or ALT should be evaluated within the clinical context of the participant. 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 is discussed separately.

General Considerations: For asymptomatic elevation in AST or ALT of $5-10 \times$ ULN (Grade 3), medications other than NNRTIs and INH may be continued at the discretion of the site investigator. Careful assessments should be done to rule out alcohol use, 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 $5-10 \times$ ULN (Grade 3) believed secondary to study medications, all agents must be held until levels are Grade ≤ 2 , at which time therapy may be reintroduced with the substitution of ATV for EFV or NVP, if applicable.

For asymptomatic or symptomatic elevation of AST or ALT $>10 \times$ ULN (Grade 4), all medications should be discontinued and held until levels are Grade ≤ 2 , at which time therapy may be reintroduced with the substitution of ATV for EFV or NVP, if applicable. All medications may be restarted if the laboratory abnormalities were thought secondary to a concomitant illness. If the participant 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 $>10 \times$ ULN (Grade 4) recur in the absence of an NNRTI drug, all current ART and INH (if participant is receiving INH) must be discontinued. Alternative ART treatment and TB prophylactic regimens may be considered, at the discretion of the site investigator.

INH Prophylaxis: Participants will not start INH if AST/ALT are $>3 \times$ 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 $>5 \times$ ULN (Grade ≥ 3), at any point thereafter INH should be discontinued.

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 ≥ 3), NVP should be discontinued.

HBV Coinfection: At screening, hepatitis B surface antigen (HBsAg) will be obtained to facilitate management of HBV coinfecting participants in the event 3TC (alone or as a component of Combivir[®]), FTC (alone or as a component of Truvada[®]) or TDF (alone or as a component of Truvada[®]) need to be discontinued, which would potentially worsen HBV disease. Any participant who tested negative for HBsAg at screening must be retested prior to discontinuation of 3TC, FTC, TDF, Combivir[®], or Truvada[®] to facilitate management of HBV coinfection unless the participant has completed HBV immunization.

4.5.5.5 Anemia/Neutropenia/Thrombocytopenia

Clinicians should be alert to clinical signs of anemia, neutropenia, and thrombocytopenia and participants should receive education or counseling about the associated symptoms. Participants who develop anemia, neutropenia, and/or thrombocytopenia on study should be evaluated for causes of anemia and/or neutropenia, such as concurrent bacterial, mycobacterial or fungal infection, malaria, helminthiasis malignancy and/or malnutrition. Transfusion should be considered if clinically appropriate.

Participants who develop Grade 1 anemia and/or neutropenia during treatment with ZDV, which is considered treatment-limiting in the opinion of the site investigator, may have the ZDV substituted with d4T.

Participants who develop Grade 2 anemia and/or neutropenia during treatment with ZDV should have a substitution of d4T for ZDV.

For Grade 3 anemia, neutropenia, or thrombocytopenia believed secondary to ZDV, d4T should be substituted for ZDV. A hematology panel should be rechecked within 4 weeks after treatment modification.

Participants with Grade 4 anemia, neutropenia or thrombocytopenia attributed to ZDV will have treatment interrupted until the AE has returned to Grade ≤ 2 . Once the toxicity has returned to Grade ≤ 2 , all ART should be restarted, with d4T substituted for ZDV. Alternatively, at the discretion of the site investigator, d4T or an equivalent NRTI may be substituted for ZDV without interruption of study treatment. A hematology panel should be rechecked within 4 weeks after treatment modification.

Recurrent Grade 4 anemia, neutropenia, or thrombocytopenia will result in discontinuation of ZDV and substitution of d4T or an equivalent NRTI. A hematology panel should be rechecked within 4 weeks after treatment modification.

Additionally, if Grade 2 to 4 anemia and/or neutropenia do not respond to the interruption/discontinuation of ZDV, then other causes should be sought. Invasion of the

bone marrow by mycobacterial infection, lymphoma, or sepsis should be considered and excluded.

NOTE: The use of d4T is recommended as a substitution drug for management of ZDV-related anemia, neutropenia, or thrombocytopenia. However, TDF may be used instead of d4T at the discretion of the site investigator.

4.5.5.6 CNS Symptoms (for Participants on EFV)

There have been reports of delusions and inappropriate behavior, predominantly in individuals with a history of mental illness or substance abuse. Severe acute depression has also been infrequently reported in both EFV-treated and control-treated individuals. Discontinuation of EFV may be required and substitution of NVP, or another suitable drug, implemented.

In the event that a study participant experiences treatment-limiting CNS AEs attributable to EFV, EFV should be discontinued and may be replaced with NVP or another suitable drug.

4.5.5.7 Peripheral Neuropathy

Grade 1: Study medications may be continued at their present dosage. Symptomatic treatment may be provided at the discretion of the site investigator.

Grade 2: Participants experiencing Grade 2 symptoms will be managed per site investigator discretion, which may include dose reduction, or temporary cessation of d4T or ddI, or symptom management.

If Grade 2 toxicity resolves to Grade 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 site investigator.

Grade 3: Participants who experience symptoms consistent with peripheral neuropathy that is unrelieved with non-narcotic analgesics (Grade 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 site investigator.

4.5.5.8 Nausea (with or without vomiting)

Isolated nausea following initiation of ARV drugs 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 (≥ 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 Grades 1 and 2 hypophosphatemia, phosphate should be repeated as soon as possible (within 2 weeks is optimal), and TDF may be continued without other signs of renal tubular acidosis at the discretion of the site investigator.

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. If Grade 3 or 4 hypophosphatemia persists discontinue TDF permanently.

4.5.5.12 Hyperbilirubinea (for participants on ATV)

Participants taking ATV may experience asymptomatic elevations in indirect (unconjugated) bilirubin. 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 ≥ 5 X ULN. ATV discontinuation may be considered if jaundice or scleral icterus associated with bilirubin elevations presents cosmetic concerns for the participant. Dose reduction of ATV is not permitted. ATV-related, asymptomatic hyperbilirubinemia (Grade 4 total bilirubin) or jaundice without LFT elevation (Grade ≤ 1 AST, ALT, and alkaline phosphatase) does not require expedited adverse event (EAE) reporting.

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 participants with reduced creatinine clearance (see the most recent package inserts). TDF should be held for a confirmed calculated creatinine clearance < 50 ml/min until an underlying etiology for the renal insufficiency is determined. If no other etiology is determined or the renal insufficiency improves with holding TDF, permanently stop TDF.

Baseline serum creatinine will be the mean of the screening and enrollment values for participants on Arm 1. Since participants on Arm 2 may initiate ART any time during the study, a repeat serum creatinine should be performed prior to initiation, and will be considered the baseline value.

If at any time serum creatinine is increased > 1.5 -fold above baseline (as defined above), the serum creatinine should be repeated as soon as possible (preferably within 1 week). Participants with confirmed serum creatinine increases > 1.5 -fold above baseline should undergo an evaluation for potential causes of decreased renal function. Participants with confirmed increased serum creatinine > 1.5 -fold above baseline should have serum creatinine monitored more frequently, at the discretion of the site investigator, until serum creatinine either stabilizes or decreases to ≤ 1.5 -fold above baseline. Drug dosing adjustments should be done based on the calculated creatinine clearance.

4.5.6 Drug Substitutions

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

Table 7. Drug Substitutions

Initial Drug	Substitution Drug	Other Indication / Comment
ZDV	d4T	<p>For anemia at study entry, at any regimen switch, or toxicity management.</p> <p>The protocol recommends d4T as a substitution drug for ZDV; however, TDF may be used instead of d4T for any reason stated in these sections, at the discretion of the site investigator.</p> <p>d4T and ZDV should never be used together.</p>
d4T	ZDV	None
EFV	NVP	<p>NVP may be substituted for EFV.</p> <p>There are little data available about the risks/benefits of changing from EFV to NVP for EFV-related AEs.</p> <p>NVP will require LFT monitoring at weeks 2, 4, 6 and 8, after initiation of NVP, then monthly through the 20th week of NVP treatment.</p> <p>If NVP is substituted for EFV, dose NVP 200 mg PO QD for the first 14 days. Thereafter, dose NVP 200 mg PO BID. If NVP is tolerated for ≥ 3 months, the dose may be changed to 400 mg QD.</p> <p>ATV may be substituted for EFV if there is toxicity or contraindication to both EFV and NVP.</p>
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	<p>Use if participants experience dose-limiting toxicity to TDF (<i>e.g.</i>, confirmed calculated creatinine clearance < 50 mL/min).</p> <p>d4T may be substituted for TDF if there is toxicity or contraindication to both TDF and ddI.</p>
ddI-EC	TDF	<p>Use for dose-limiting toxicity with ddI-EC (<i>e.g.</i>, pancreatitis).</p> <p>d4T may be substituted for ddI if there is toxicity or contraindication to ddI or TDF.</p> <p>TDF will not be used in the ATV arm unless ATV is boosted with low-dose ritonavir.</p>

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.

After a pregnancy informed consent is obtained, 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/mm³, an ART drug other than NVP should be considered.

4.5.7.2 Pregnant Women on a Regimen Containing ddI and d4T

The use of ddI-EC plus d4T is not allowed for pregnant women. ddI-EC will be replaced with 3TC, and/or d4T will be replaced with ZDV. Women may return to their secondary regimen following pregnancy at the discretion of the site investigator.

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. Therefore, women who become pregnant while taking TDF or ATV will be informed of the lack of safety data in humans taking these drugs during pregnancy. ATV may not be included in the regimen of any study participant who is pregnant. If other ARV drugs are available and appropriate (e.g., ZDV), women may be counseled to change therapy to an appropriate substitute.

4.5.7.4 Pregnant Women on a Regimen Containing Two ART Drugs with Hepatotoxic Toxicity Potential

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

4.5.7.5 Women Who Breastfeed

Women who are breastfeeding must not take ATV.

Changes in ART treatment for women who are breast-feeding will be at the discretion of the site investigator. EFV is used in HIV-exposed infants and HIV-infected children. Data on the use of TDF and other ART agents during breast-feeding are limited. Breast-

feeding participants receiving study drugs will be allowed to continue their use while breast-feeding at the discretion of the site investigator. Breast-feeding is permitted where formula feeding is not a viable option per WHO guidelines.

4.5.8 Management of ART and Immune Reconstitution Inflammatory Syndromes

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.

When OIs are associated with inflammatory signs or symptoms and accompanied by an increase in the CD4+ T lymphocyte counts and a drop in plasma HIV-1 RNA levels, 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 in the setting of virologic and/or immunologic failure:

- These events will be considered as secondary study endpoints.
- Initiate specific therapy for the clinical event.
- Switch ARV regimen if criterion for virologic failure is met.

4.5.9 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 most recent ATV package insert.

4.6 Treatment of Hepatitis B Virus Infection

The World Health Organization (WHO) issued revised guidelines for the use of ART for HIV infection in adults and adolescents in resource-limited settings in August 2006 (see

[www.who.int/hiv/pub/guidelines/WHO Adult ART Guidelines.pdf](http://www.who.int/hiv/pub/guidelines/WHO_Adult_ART_Guidelines.pdf)). The WHO guidelines recommend that two antiretroviral agents active against HBV be used when antiretroviral therapy is commenced in persons co-infected with HIV-1 and HBV because of the potential for development of drug-resistant HBV when a single agent is used.

The WHO guidelines are relevant to HPTN 052 because participants who are potentially HIV-1 and HBV coinfecting may receive ART regimens in which some drugs are active against HBV (3TC, FTC, and/or TDF). Because participation in HPTN 052 may provide a benefit to HBV coinfecting persons, HBV co-infected persons are not excluded from participation in the study. The following special considerations will be made for participants with HIV/HBV coinfection:

- Hepatitis B surface antigen tests will be performed at screening and results of the test will be provided to participants undergoing screening irrespective of whether they enter the study. Site investigators will discuss with all HIV/HBV coinfecting persons the test results and what options, if any, exist for HBV treatment outside of HPTN 052 at their sites.
- Information about the implications of chronic HBV infection and the potential effects of the study-assigned antiretroviral regimens on HBV will be included in the sample informed consent document. Participants who are infected with HBV will be encouraged to discuss with their care providers whether study participation is in their best interest.
- Whether individual HBV/HIV coinfecting persons are enrolled in HPTN 052 will be left to the discretion of site investigators.
- HBV/HIV coinfecting persons who choose to participate in HPTN 052 and who receive only one study-provided, active anti-HBV agent may receive entecavir, as provided outside of the study, for the treatment of HBV infection, at the discretion of the site investigator and with the approval of the HPTN 052 CMC. Locally-available treatments for HBV may be used to treat HBV/HIV coinfecting participants after receiving approval from the HPTN 052 CMC.

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.

For the purposes of calculating visit dates for this study, one week is defined as 7 days and one month is defined as 30 days.

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
- Locator information
- HIV pre-test, risk-reduction, and post-test counseling (note that post-test counseling should be administered when the test results are available, which may be at the current or following visit)
- Couples HIV counseling

5.1.1.2 Clinical Procedures – Index case

- Urine collection (women only)
- Blood collection
- Targeted 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

- Hepatitis B serology

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

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

- Study informed consent
- Locator information
- Demographic information
- Randomization
- Sexual history assessment
- Couples HIV counseling
- Adherence counseling (only when index case on ART)

5.2.2 Administrative, Behavioral, and Regulatory Procedures – Index Case

- Quality-of-Life assessment

5.2.3 Clinical Procedures – Index Case

- Urine collection
- Semen collection
- Blood collection
- Complete medical history, concomitant medications, and physical exam including signs and symptoms, and a 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)

5.2.4 Laboratory Evaluations – Index Case

- Urine pregnancy test (women only)
- Urine PCR for chlamydia trachomatis (CT) and Neisseria gonorrhoea (GC) for men, vaginal swab for PCR for GC and CT for women
- Cervical/seminal 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
- Samples for storage:
 - plasma, to include a separate sample for HIV genotyping (see SSP for further instructions)
 - serum
 - whole blood
 - PBMCs
 - genital secretions

5.2.5 Clinical Procedures – Partner

- Urine collection (men only)
- Blood collection
- Complete medical history and physical exam including signs and symptoms
- Genital exam (swab if genital ulcer is observed)
- Pelvic exam (women only) with cervical swab
- Provide treatment (as clinically indicated)

5.2.6 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
 - PBMCs

5.3 On-Study Follow-up

There are a few procedures that are required outside of the normally scheduled follow-up visits. As an example, LFTs must be monitored at weeks 2, 4, 6, and 8 each time NVP is initiated, then monthly through the 20th week of NVP treatment. Refer to the ART-related sections of the protocol for these exceptions.

5.3.1 Week Two

The Week Two Visit should be conducted two weeks after the index case initiates ART. For participants in Arm 1, the Week Two visit will occur two weeks after they enroll into the study. For participants in Arm 2, this visit will take place two weeks after the index case begins ART, which may occur at any regularly scheduled visit throughout the study.

If a participant begins ART due to pregnancy, they, too, must be seen for the Week Two Follow-up Visit.

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

- Locator information
- Couples HIV counseling
- Adherence assessment (index case only)
- Adherence counseling

5.3.1.2 Clinical Procedures – Index Case

- Blood collection
- Targeted 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)

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)

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
- Couples HIV counseling
- Adherence assessment (index case only, only when index case on ART)
- Adherence counseling (only when index case on ART)

5.3.2.2 Clinical Procedures – Index Case

- Urine collection (women only, refer to the SSP for exceptions)
- Blood collection (first two months after initiation of ART only, **DO NOT** collect this sample at any other monthly follow-up visit unless clinically indicated)
- Targeted 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)

5.3.2.3 Laboratory Evaluations – Index Case

- Urine pregnancy test (women only, refer to the SSP for exceptions)
- CBC
- Blood chemistry
- Optional blood chemistries prn
- LFTs
- Blood plasma HIV-1 RNA PCR one month following ART initiation (also refer to Section 5.3.7).
- 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

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, only when index case on ART)
- Adherence counseling (only when index case on ART)

5.3.3.2 Administrative, Behavioral, and Regulatory Procedures – Index Case

- Quality-of-Life assessment

5.3.3.3 Clinical Procedures – Index Case

- Urine collection (women only, refer to the SSP for exceptions)
- Blood collection
- Targeted history, concomitant medications, and physical exam
- Provide treatment (as clinically indicated)
- Provide study medications (ART and/or HIV primary care, if applicable)

5.3.3.4 Laboratory Evaluations – Index Case

- Urine pregnancy test (women only, refer to the SSP for exceptions)
- CBC
- Blood chemistry
- Optional blood chemistries pm
- LFTs

- CD4+ cell count
- Blood plasma HIV-1 RNA PCR
- Multiplex PCR (if genital ulcer is observed)
- Samples for storage:
 - plasma
 - serum
 - PBMCs

5.3.3.5 Clinical Procedures – Partner

- Blood collection
- Targeted history and physical exam
- Provide treatment (as clinically indicated)

5.3.3.6 Laboratory Evaluations - Partner

- HIV EIA test/Western blot/IFA
- Multiplex PCR (if genital ulcer is observed)
- Samples for storage:
 - plasma
 - PBMCs

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, only when index case on ART)
- Adherence counseling (only when index case on ART)

5.3.4.2 Administrative, Behavioral, and Regulatory Procedures – Index Case

- Quality-of-Life assessment

5.3.4.3 Clinical Procedures – Index Case

- Urine collection
- Semen collection
- Blood collection
- Targeted 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
- Provide treatment (as clinically indicated)
- Provide study medications (ART and/or HIV primary care, if applicable)

5.3.4.4 Laboratory Evaluations – Index Case

- Urine pregnancy test (women only, refer to the SSP for exceptions)
- Urine PCR for chlamydia and gonorrhea for men, and vaginal swab for PCR for GC and CT for women
- Cervical/seminal 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
- Samples for storage:
 - plasma
 - serum
 - PBMCs
 - genital secretions

5.3.4.5 Clinical Procedures – Partner

- Urine collection (men only)
- Blood collection
- Targeted history and physical exam
- Genital exam (swab if genital ulcer is observed)
- Pelvic exam (women only) with cervical swab
- Provide treatment (as clinically indicated)

5.3.4.6 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

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 9.

The criteria for permanent treatment discontinuation (off treatment/on study) include:

- Drug-related toxicity.
- Requirement for prohibited concomitant medications.
- Participant repeatedly noncompliant with study medications as prescribed.
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity management of the protocol.
- Request of the primary care provider if s/he thinks the study treatment is no longer in the best interest of the participant.

5.3.6 Procedures for Both Index Case and Partner if Partner Becomes HIV Infected (Partner Seroconversion Visit)

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)

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

- Samples for storage:
 - Plasma, to include a separate sample for HIV genotyping (see SSP for further instructions)
 - PBMCs
 - 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, see Section 8.3 for more information)

5.3.6.4 Laboratory Evaluations - Partner

- Cervical/seminal HIV-1 RNA PCR
- Multiplex PCR if genital ulcer is observed
- CBC
- Blood chemistry
- Optional blood chemistries pmn
- LFTs
- CD4+ cell count
- Blood plasma HIV-1 RNA PCR
- Samples for storage:
 - plasma, to include a separate sample for HIV genotyping (see SSP for further instructions)
 - serum

- PBMCs
- genital secretions

5.3.7 Procedures for ART Initiation Visit

This section applies to participants on Arm 2 who initiate ART during the course of the study. (Procedures for ART initiation for participants on Arm 1 are included under the Enrollment Visit – Section 5.2).

The initiation of ART may only begin at a regularly scheduled study visit, *i.e.* not at an interim visit. 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 Clinical Procedures – Index Case

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

5.3.7.2 Laboratory Evaluations – Index Case

- CBC
- Blood chemistry
- LFTs
- Blood plasma HIV-1 RNA PCR

5.3.7.3 Clinical Procedures – Partner

- Adherence counseling

5.3.8 Procedures for Confirmed Virologic Failure

The following clinical procedures and laboratory evaluations should be performed once virologic failure has been confirmed, and should include the elements listed below unless they are already being performed as part of a regularly scheduled study visit.

5.3.8.1 Administrative, Behavioral, and Regulatory Procedures – Index Case

- Adherence assessment
- Adherence counseling

5.3.8.2 Clinical Procedures – Index Case

- Blood collection
- Provide treatment (as clinically indicated)

5.3.8.3 Laboratory Evaluations – Index Case

- Blood plasma HIV-1 RNA (Results from the viral load testing that was performed for confirmation of virologic failure may be used as the value reported for this visit.)
- Sample collection for storage:
 - plasma, to include a separate sample for HIV genotyping (see SSP for further instructions)

5.3.8.4 Clinical Procedures – Partner

- Adherence counseling
- Provide treatment (as clinically indicated)

5.3.9 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.

Sites or study participants are encouraged to prospectively register pregnancies that occur on study to The Antiretroviral Pregnancy Registry by fax at +44-1628-789-666 (for

non-U.S. sites) or 1-800-800-1052 from within the U.S. More information is available at: www.apregistry.com.

5.4.1 Procedures For Pregnancy or Breastfeeding at Enrollment

Pregnant or breastfeeding women are eligible for enrollment; however, they must agree to be randomized to either treatment arm and must be willing to sign the pregnancy informed consent form. 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). ATV may not be included in the regimen of any study participant who is pregnant or breastfeeding.

If a women is in her first trimester during screening, the HPTN 052 CMC **must** be consulted prior to enrollment.

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

A pregnancy informed consent must be obtained at the time that pregnancy is confirmed. 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. It should be noted that ddI-EC and d4T must not be coadministered during pregnancy. ATV may not be included in the regimen of any study participant who is pregnant.

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. Women receiving EFV will be allowed to continue study drugs while breastfeeding. ATV may not be included in the regimen of any study participant who is breastfeeding.

5.4.4 Procedures for Women Not on ART Who Become Pregnant

If an index case not on ART (Arm 2) becomes pregnant, she must sign a pregnancy informed consent form in order to continue her participation in the study. Once consent is obtained, she will be followed per the schedule of procedures and evaluations and will be placed on a triple regimen of ART appropriate for use during pregnancy regardless of CD4+ cell count at approximately the beginning of the 2nd 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 CRFs. It should be noted that ddI-EC and d4T must not be coadministered. ATV may not be included in the regimen of any study participant who is pregnant.

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 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 Procedures for Women of Reproductive Potential

Investigators of Record are responsible for the appropriate management of ART and contraception. For example, women of reproductive potential who are on a regimen containing EFV, should be given appropriate contraception. If a given women is unwilling to use contraception, her ART regimen should be modified appropriately.

5.6 Procedures for nPEP

nPEP is not promoted for use in this study; however, there may be circumstances under which nPEP is necessary. The SSP Manual will provide guidelines for the use of nPEP in such cases.

5.7 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.

5.8 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 ADVERSE EVENT (AE) AND EXPEDITED ADVERSE EVENT (EAE) REPORTING

This study will follow standard level 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 the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (or most current version). The Manual for Expedited Reporting of Adverse Events to DAIDS (dated 6 May 2004 or most current version) can be found at <http://rcc.tech-res-intl.com/eae.htm>. The SSP Manual also will provide more detailed instructions regarding expedited reporting.

This level of standard reporting is required for all index cases once they initiate ART 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), Kaletra[®]/Aluvia[®] (LPV/r), and Truvada[®] (FTC/TDF)].

In general, EAEs will not be reported for index cases not on ART or for partners; however, if an event occurs that fits the regulatory definition of a serious adverse event (SAE) and can be associated with study participation or procedures, it will be reported as an EAE.

EAEs must be documented on the Division of AIDS Expedited Adverse Event (EAE) Form and submitted to the DAIDS Safety Office as described in the reporting guidelines. The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, December 2004 must be used for determining and reporting the severity of

adverse events. The EAE reporting form and DAIDS grading table are both available on the RCC website at <http://rcc.tech-res-intl.com/>.

In addition to submitting EAE information to the DAIDS Safety Office, the site investigator may be required to submit AE and EAE information to local regulatory agencies or other local authorities.

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

HIV/AIDS related conditions will not be captured as adverse events, but will be collected on standard CRFs for entry into the study database.

Table 8 provides a reference guide for reporting AEs and EAEs in this study.

Table 8: Reference Guide for Reporting AEs and EAEs

Type of Adverse Event	All Index Cases (on AND not on ART)	Partner	Index Case on ART	Index Case NOT on ART	Partner
	Report on CRF		Report as EAE		
Results in death	Yes, report on AE log	No	Yes, regardless of relationship to ART	No	No
Congenital anomaly, birth defect, or fetal loss	Yes, report on pregnancy outcome form	No	Yes, regardless of relationship to ART	No	No
Results in persistent or significant disabilities or incapacities	Yes, report on AE log	No	Yes, regardless of relationship to ART	No	No
Requires/prolongs hospitalization or requires intervention to prevent significant/permanent disability or death	Yes, report on AE log	No	Report as EAE if relationship to ART is definitely, probably, possibly, or probably not related	No	No
Is life-threatening (includes all Grade 4 AEs)	Yes, report on AE log	No	Report as EAE if relationship to ART is definitely, probably, possibly, or probably not related	No	No
Other Grade 3 AEs	Yes, report on AE log	No	No	No	No
Is considered a <u>serious AE that is not related to study product</u> , but could be associated with study participation or procedures	Yes, report on AE log	No	Yes	Yes	Yes
Other Grade 1 and 2 AEs	No	No	No	No	No

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 experiencing 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 for the prevention of HIV transmission in HIV-serodiscordant couples.

This trial consists of a run-in period, which has been completed, and a full study. Approximately 1750 HIV-serodiscordant couples will be enrolled into the trial (run-in period plus full study). During the run-in period, 82 couples were enrolled into the study, assigned at random in equal proportions to the two treatment strategies, and followed for a minimum of 6 months. The run-in period couples were enrolled under Version 2.0 of the protocol, and, as such, the index case had a CD4+ cell count between 300-500 cells/mm³. Follow-up of the run-in period couples will continue on a monthly basis until the last couple enrolled into the full study has completed follow-up.

Approximately 1668 additional HIV-serodiscordant couples will be recruited over the 18 month accrual period of the full study, each of whom will be followed for a minimum of 60 months (5 years). The total duration of the full study is expected to be approximately 6.5 years (78 months), which is a combination of the accrual period (18 months) and the follow-up period (60 months).

Since short-term interruption of transmission of HIV could be offset by delayed transmission of resistant variants, evaluation of HIV transmission over 5 to 6.5 years will provide data on the longer-term effectiveness and public health utility of antiretroviral therapy. A 5 to 6.5 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 6.5 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).

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 9 outlines the secondary endpoints and how they will be measured:

Table 9: Secondary Endpoints

SECONDARY ENDPOINT	MEASURED AS:
Survival of index cases	<ul style="list-style-type: none"> Time from enrollment to death (all causes)
Immunologic response of index case	<ul style="list-style-type: none"> CD4+ cell count over time Time from enrollment to immunologic failure. (Immunologic failure is defined as two consecutive measurements of CD4+ cell count within or below the range of 200-250 cells/mm³, or develops an AIDS-defining illness). Time from initiation of ART to immunologic failure. Time from initiation of secondary regimen to immunologic failure.
Virologic response of index case	<ul style="list-style-type: none"> Blood plasma HIV-1 RNA level over time. Seminal plasma HIV-1 RNA levels over time in males. Cervico vaginal HIV-1 RNA levels over time in females. Time from initiation of the starting regimen to confirmed virologic failure. Time from initiation of secondary regimen to confirmed virologic failure.
Initiation of secondary regimen	<ul style="list-style-type: none"> Time to initiation of secondary regimen (any reason).
Safety and toxicity of treatment	<ul style="list-style-type: none"> Time from enrollment to time of first development and any subsequent occurrence of Grade 3 or 4 ART-related toxicities Time from enrollment to time of first serious AIDS-related events (Grade 4 and higher) Time from enrollment to time of first serious cardiovascular or other metabolic events (Grade 4 and higher) Time from enrollment to time of first Grade 4 and higher events (any event)
HIV drug resistant virus	<ul style="list-style-type: none"> Prevalence of drug resistant HIV virus Proportion of infected partners acquiring a drug resistant HIV virus.
Incidence of STDs in index case and partners	<ul style="list-style-type: none"> Time from enrollment to the time of first development and subsequent development of STDs
Adherence in index case	<ul style="list-style-type: none"> Adherence to all treatment over time. Adherence to treatment over time following initiation of antiretroviral therapy starting regimen. Adherence to treatment over time following initiation of an antiretroviral therapy secondary treatment regimen.

SECONDARY ENDPOINT	MEASURED AS:
Sexual behavior of index cases on ART, and their partners	<ul style="list-style-type: none"> • Sexual behavior over time following initiation of starting regimen. • Sexual behavior over time following initiation of a secondary regimen.
Quality-of-Life indicators of index case	<ul style="list-style-type: none"> • Quality-of-Life indicators over time following initiation of starting regimen • Quality-of-Life indicators over time following initiation of a secondary regimen

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 350-550 cells/mm³ (300-500 cells/mm³ for the run-in couples) will be enrolled in this study. As mentioned in Section 7.1, 82 couples were enrolled during the run-in period. A total of 1668 couples will be enrolled over an 18 month accrual period for the full study. All couples will be followed until the last couple enrolled into the study has been followed for 5 years.

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. Although this median follow-up time period does not reflect the follow-up of run-in period couples prior to the start of the full study, their contribution to follow-up prior to the full study has a negligible effect on the overall median follow-up of the study. Furthermore, the CD4+ cell count inclusion criteria as well as the rules for initiation of ART in the delayed arm have been changed since the initiation of the run-in study. For the purpose of simplifying sample size and power calculations, it is assumed that all 1750 couples have the same CD4+ cell count inclusion criteria and rules for initiation of ART in the delayed arm. Again, 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 10, 11-13, and 14 describe the assumptions used for (1), (2), and (3), respectively. The power calculations for the trial, under several scenarios, are given in Table 15.

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 12). A sample size of 1750 couples would provide 90% power to detect an average effectiveness $\geq 37\%$ (see Table 13).

- Step 2 : Using the assumption on the delay time before initiation of antiretroviral therapy in Arm 2 (see Table 14), 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 15, 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 15).

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

- **Assumption 1:** Table 10 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 10: 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 11 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 11: 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 12 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 12: 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 13 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 13: 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 12. 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 13 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 250 cells/mm³ 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 ($350 \leq \text{CD4} \leq 550$) 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 14 represents the expected proportion of participants on Arm 2 who will initiate antiretroviral therapy over follow-up:

Table 14: Expected Cumulative Percentage of Index Cases in Arm 2 Initiating ART because of CD4+ Cell Count < 250 cells/mm³ 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 14 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 taken 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 250 cells/mm³ and/or developing AIDS-defining illnesses is similar to the one for partners of those with CD4+ cell count above 250 cells/mm³ 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 250 cells/mm³ 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 15 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 15: 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 15 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. $50\% < \text{power} < 75\%$) 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 partnerships 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^{99,100}.

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 9. Time-to-event secondary endpoints 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)⁷² 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. A complete set of secondary endpoints to be analyzed is listed 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, and Quality-of-Life indicators.

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, retention, and/or low HIV acquisition rate. 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. Given the completion of the run-in period, for 1668 couples to be recruited in the full study, the study targets to recruit at the rates of 60 couples/month for the first 6 months and 110 couples/month for the rest of 12 months. It is important to note that the full study will be implemented

in a staggered fashion across the participating sites due to the varying regulatory approval systems in place within each host country, and will result in a range of several months from the time the first and last site obtain approval to begin. These differences in starting time will be taken into account in the recruitment rate calculation. Stopping or modifying the study may be considered if the study team fails to recruit at less than 75% of the targeted rates.

- 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 250 cells/mm³ 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 250 cells/mm³ 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 log₁₀ 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 250 cells/mm³ and/or the occurrence of an AIDS-defining illness is more than 4 weeks.

- HIV acquisition rate: Pooled (across arms) rate of HIV acquisition will be monitored. Stopping or modifying the study may be considered if the pooled rate of HIV acquisition is smaller than expected.

7.7.2 Monitoring of Efficacy and Safety Endpoints

A total of four formal interim analyses are planned. After the first couple is enrolled in the study, two safety only analyses will be reviewed at approximately 6 and 12 months. In addition, three safety and efficacy analyses will be reviewed at approximately 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, futility, 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 any serious adverse events (Grade 4 and higher) in one of the arms.
- 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.

Clear evidence of futility:

- Futility defined to be results sufficiently unfavorable to rule out that the rate of HIV acquisition in the immediate arm is smaller than the rate of HIV acquisition

in the delayed arm. Therefore, a lack of 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

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), when they have two consecutive measurements of a CD4+ cell count within or below the range of 200-250 cells/mm³ (Arm 2), or when 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. When appropriate, participants will 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 Investigator of Record at each site will work 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 after the study ends. 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 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 to authorized medical care providers and 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, and plasma, serum, whole blood, and PBMC storage;
- Urine for pregnancy testing, gonorrhea and chlamydia PCR;
- Vaginal wet mount for TV, BV, and candida;
- Genital secretions for storage;

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

Note: Several 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. HPTN CL staff will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control procedures, including proper maintenance of laboratory testing equipment and the use of appropriate reagents. HPTN 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 HPTN CL will inform site staff of the samples selected for quality assurance testing, and site staff will ship the selected specimens to the HPTN 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) and the World Health Organization (WHO). All diagnostic specimens will be transported in accordance with IATA regulations. In

addition, individual carrier guidelines (e.g. World Courier) will be referred for specific instructions. The SSP Manual will specify further instructions regarding shipping.

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 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 Manual 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.

The protocol 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 ¹	Monthly (other than quarterly/yearly)	Quarterly	Yearly	Partner Serconverts	Confirmed Virologic Failure
Administrative, Behavioral and Regulatory Procedures								
Informed consent (screening or study informed consent form)	X	X						
Demographic information		X						
Locator information	X	X	X	X	X	X		
Randomization		X						
Sexual history assessment		X			X	X		
HIV pre-test, risk reduction, and post-test ² counseling	X							
Couples HIV counseling	X	X	X	X	X	X		
Adherence assessment			X	X ³	X ³	X ³		X
Adherence counseling		X ³	X	X ³	X ³	X ³		X
Quality-of-Life assessment		X			X	X		
Clinical Procedures								
Urine collection	X ⁴	X		X ⁴	X ⁴	X		
Semen collection		X				X	X	
Blood collection	X	X	X	X ⁵	X	X	X	X
Complete medical history, con meds, physical exam		X						
Targeted 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		
Laboratory Evaluations – Local Laboratory								
Urine pregnancy test (women only, see SSP for exceptions)	X	X		X	X	X		
Urine PCR for GC and CT (men only)		X				X		
Wet mount for TV, BV, candida		X				X		
PCR for GC and CT (vaginal swab)		X				X		
HIV EIA/Western blot/IFA	X							
CBC	X	X	X	X ⁵	X	X		
Blood chemistry	X	X	X	X ⁵	X	X		
LFTs	X	X	X	X ⁵	X	X		
CD4+ cell count	X	X			X ¹⁰	X ¹⁰		
Blood plasma HIV-1 RNA		X		X ⁹	X	X	X	X
Hepatitis B serology	X							
Syphilis serology		X				X		
Laboratory Evaluations – Regional Laboratory or HPTN CL								
Cervical/seminal HIV-1 RNA		X				X	X	
Multiplex PCR (if genital ulcer observed) (see Footnote #7)		[X]	[X]	[X]	[X]	[X]	[X]	
HIV genotyping (see Footnote # 8)		X					X	X
Sample Storage								
Plasma		X ⁸			X	X	X ⁸	X ⁸
Serum		X			X	X		
Whole Blood (see Footnote #8)		X						
PBMC's (see Footnote #8)		X			X	X	X	
Genital Secretions		X				X	X	

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

1 = Two-week visit should be conducted once the index case initiates ART. 6 = US site only: obtain PPD first. If > 5mm induration, obtain chest x-ray.

2 = Post-test counseling may be conducted at this visit, or the subsequent visit, depending on when test results are available. 7 = A swab should be taken for multplex PCR at any time an ulcer is observed upon examination for shipment to the HPTN CL.

3 = Administer/perform only if index case is on study medication. 8 = Refer to SSP for specific instructions.

4 = Women only

9 = For Arm 1, in addition to quarterly testing, perform at first monthly visit. For Arm 2, in addition to quarterly testing, perform one month following initiation of ART.

5 = Perform at the first two months following initiation of antiretroviral therapy. When starting NVP, perform LFTs at week 2, 4, 6, 8 and then monthly for first 20 weeks.

10 = Confirmatory testing is required if CD4+ < 250 cells/mm³ (see protocol section 2.3.1).

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

	Screening	Enrollment	Week 2 ¹	Monthly (other than quarterly/yearly)	Quarterly	Yearly	Partner Serocoverts	Confirmed Virologic Failure
Administrative, Behavioral and Regulatory Procedures								
Informed consent (screening or study informed consent form)	X	X						
Demographic information		X						
Locator information	X	X	X	X	X	X		
Randomization		X						
Sexual history assessment		X			X	X		
HIV pre-test, risk reduction, and post-test ² counseling	X				X	X		
Couples HIV counseling	X	X	X	X	X	X		
Adherence counseling		X ³	X	X ³	X ³	X ³		X
Clinical Procedures								
Urine collection (men only)		X				X		
Semen collection							X	
Blood collection	X	X			X	X	X	
Complete medical history and physical exam		X						
Targeted 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]
Laboratory Evaluations- Local Laboratory								
Urine PCR for GC and CT (men only)		X				X		
Wet mount for TV, BV, candida		X				X		
PCR for GC and CT (vaginal swab)		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		
Laboratory Evaluations- Regional Lab or HPTN CL								
Cervical/seminal HIV-1 RNA							X	
Multiplex PCR (if genital ulcer observed) (see Footnote # 4)		[X]	[X]	[X]	[X]	[X]	[X]	
HIV genotyping (see Footnote # 5)							X	
Sample Storage								
Plasma		X			X	X	X ⁵	
Serum		X				X	X	
Whole Blood (see Footnote #5)		X						
PBMC's (see Footnote #5)		X			X	X	X	
Genital Secretions							X	

1 = The two-week visit should be conducted once the index case initiates ART.

3 = Perform only if index case is on ART

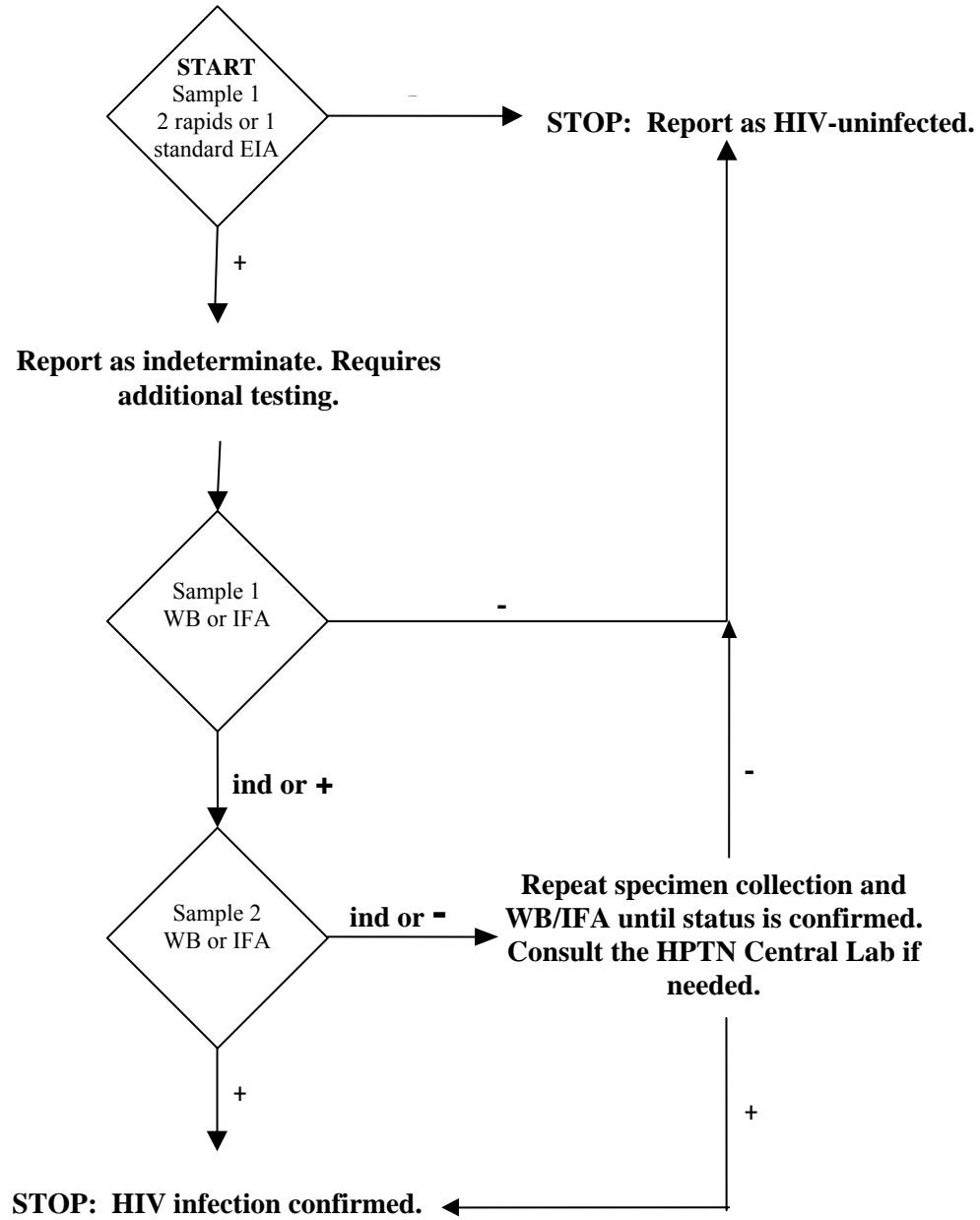
5 = Refer to SSP for specific instructions

2 = Post-test counseling may be conducted at this visit, or the subsequent visit, depending on when test results are available

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. List of AIDS-Defining Illnesses for HPTN 052

For purposes of the study, a person will be considered to have AIDS if they have a condition listed below. This 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 regardless of CD4+ cell count.

- Bacterial pneumonia, recurrent (2 or more episodes within 12 months)
- Candidiasis of bronchi, trachea, lungs, or esophagus
- Cervical cancer, invasive
- Chagas disease
- Cryptococcosis, extrapulmonary infection
- Cryptosporidiosis, Isosporiasis, Microsporidiosis, or Cyclospora gastroenteritis with diarrhea greater than 1 month's duration
- Cytomegalovirus disease other than liver, spleen, or nodes (includes retinitis)
- Dementia or encephalopathy, HIV-associated
- Endemic mycosis (*e.g.*, Histoplasmosis, Coccidiomycosis, Blastomycosis, Paracoccidiomycosis, and Penicilliosis), disseminated
- Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- HIV wasting syndrome
- Kaposi's sarcoma
- Lymphoma, primary CNS or non-Hodgkin's
- Mycobacterium tuberculosis, extrapulmonary infection
- Mycobacterium, other than *M. tuberculosis*, or unidentified species, disseminated
- Paracoccidiomycosis
- Pneumocystis jiroveci pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (non-typhoid) septicemia, recurrent
- Toxoplasma encephalitis; other disseminated toxoplasmosis
- Visceral Leishmaniasis

Appendix IV – Sample Informed Consent Forms

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 3.0

INDEX CASE AND PARTNER SCREENING

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. About 1750 couples will participate in the full study [insert site-specific enrollment number only if required by local IRB/EC guidelines, which is up to 250 per site). 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 [*for 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 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. We may test you more than once for 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 you have hepatitis B and if your kidneys, liver, and blood are healthy.
- 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

except to health care providers when needed. Any publication of this study will not use your name or identify you personally. 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 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 help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This Certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

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

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 3.0

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 3.0

INDEX CASE ENROLLMENT

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 [insert site-specific enrollment number only if required by local IRB/EC guidelines, which is up to 250 per site). 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 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 tell you the results of any tests we do during the study. 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.

A few of your samples will be sent out of your country for testing because it is not possible to do the tests at your clinic. These samples include semen (if you are a man), fluid from your vagina (if you are a woman), a small amount of blood (to do a special test on the HIV virus), and swab samples (if you have a genital sore). *[Sites should modify this paragraph to accurately reflect what is being done at their clinic. For example, a site may serve as a regional testing facility for HIV genotyping, therefore, those samples will not be sent out of the country. The other samples referred to in this paragraph are the ones being sent to the HPTN CL for testing (see section 9.2 of the protocol).]*

If you are infected with both the hepatitis B virus (HBV) and HIV, you should know that some of the anti-HIV study drugs (3TC, TDF, and Truvada [which is a combination of FTC and TDF]) are also used to treat HBV. Recent World Health Organization (WHO) treatment guidelines recommend using two anti-HIV/HBV drugs together to treat HBV. Your study doctor will try to provide you with at least two drugs that can treat both HIV and HBV while you are in the study. If you are infected with HBV, you should talk to your doctor about whether you should participate in this study and if you should take other medications for HBV that are not provided by this study.

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 yourself (like your age), your health, how you have been feeling, your day-to-day activities, 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 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). If you are a woman, we will also check your urine to see if you are pregnant.

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. If you are in group 1, this visit will take place about two weeks from today. If you are in group 2, this visit will be two weeks after you start taking anti-HIV drugs in the future if you need them. 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.
- We will ask you questions about your health and may examine your body to see if you are sick.
- 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 after you start taking anti-HIV drugs:

- First month: we will draw blood (no more than 15 mL, which is about 3 teaspoons [*can be changed to local equivalent*]) to check how much HIV is in your blood, and the health of your kidneys, liver, and blood.
- Second month: we will draw blood (no more than 10 mL, which is about 2 teaspoons [*can be changed to local equivalent*]) to the health of your kidneys, liver, and blood.

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, how you have been feeling, your day-to-day activities, and your sexual activities.
- 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, in addition to the regular quarterly procedures, 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.
- If you are a man, we will ask you to give a urine sample to test for sexually transmitted diseases (gonorrhea and chlamydia).

- We will check your blood for 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 anti-HIV drugs stop working, you will be asked to give additional blood (no more than 30 mL, which is about 6 teaspoons [*can be changed to local equivalent*]) to test the amount of HIV in your blood and to see how the HIV virus may have changed. Some of this blood may be stored for future HIV-related testing.

Additional Study Procedures That May Happen at Any Study Visit:

As explained at the beginning of this consent form, if you are in group 2 you may need to start taking the anti-HIV drugs at some time while you are on the study. Before you take the drugs for the first time we will draw a blood sample (no more than 15mL, which is about 3 teaspoons [*can be changed to local equivalent*]) if it is not already as part of the regularly scheduled visit procedures. This blood will be tested to see how much HIV is in your blood, and to make sure your kidneys, liver, and blood are healthy.

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 your 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 may 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.

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 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 already taking anti-HIV drugs, or that you will take anti-HIV drugs during your pregnancy to help prevent your baby from getting HIV. 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 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. We will tell you the results of any tests or other information related to your health during the study. 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/cannot*] provide you with drugs to prevent or treat infections related to HIV. However, the clinic [*will/will not*] be able to provide anti-HIV drugs. To receive that treatment you [*would/ would not*] 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 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 except to health care providers when needed. Any publication of this study will not use your name or identify you personally. 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 help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This Certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

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"> • Headache • Feeling of vague overall discomfort • Lack of energy, tiredness • Dizziness • Depression • Stomach ache, upset stomach, throwing up, loose or watery stools • Have trouble falling asleep or cannot sleep at all • Skin rash • Not hungry, eating less than usual • Numbness, tingling, and pain in the hands or feet • Decrease in the number of white blood cells that help fight infection • An increase in a substance in the blood (a type of pancreatic enzyme) that could mean a problem with the pancreas. • 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. • 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.
Zidovudine [ZDV]	<ul style="list-style-type: none"> • Decrease in the number of white blood cells that help fight infection • Decrease in the number of red blood cells (anemia), which may cause weakness, dizziness, and tiredness • Muscle aches, weakness, and wasting • Headache • Upset stomach, throwing up, heartburn • Not hungry, eating less than usual • Feeling of vague overall discomfort • Lack of energy, tiredness • Have trouble falling asleep or cannot sleep at all

Anti-HIV Drug	Side Effects
Zidovudine [ZDV] (continued)	<ul style="list-style-type: none"> • 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. • 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.
Efavirenz [EFV]	<ul style="list-style-type: none"> • 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. • 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. • Skin rash • Upset stomach, loose or watery stools • Headache • Increases in the fat and cholesterol found in your blood, which can cause cardiovascular disease. • 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. • An increase in a substance in the blood (a type of pancreatic enzyme) that could mean a problem with the pancreas. • Trouble seeing • Fever • 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. This side effect may occur when efavirenz is used in combination with other HIV drugs. • The use of this drug during pregnancy and especially early pregnancy should be avoided. Efavirenz may cause fetal harm when taken during the first three months of pregnancy. Serious birth defects, including those of the central nervous system, have been seen in the offspring of animals and women on efavirenz. • A false-positive urine test for marijuana
Atazanavir [ATZ]	<ul style="list-style-type: none"> • 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. • Increases in the fat and cholesterol found in your blood, which can cause cardiovascular disease. • An increase in blood sugar or the development or worsening of diabetes • Possibility of increased bleeding

Anti-HIV Drug	Side Effects
Atazanavir [ATZ] (continued)	<ul style="list-style-type: none"> • Increased bilirubin, which may be associated with yellowing of the eyes or skin. • Upset stomach, throwing up, stomach pain, or loose or watery stools • Increase in liver function tests • Headache • Skin rash, which may be red or itchy • Numbness, pain, or tingling in the arms and legs • Have trouble sleeping • Flu-like symptoms, such as fever, joint and muscle pain, tiredness • Increased cough • A change in the way your heart beats (heart rhythm change). Symptoms you may experience if this occurs include dizziness and light headedness.
Nevirapine [NVP]	<ul style="list-style-type: none"> • Skin rash, which in some cases may become severe and, rarely, may cause death. 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. • Hypersensitivity reaction (“allergic reaction”). The symptoms that you may notice are: skin rash, fever, tiredness, joint pain, muscle pain, flu-like feeling, liver tenderness, blisters, sores in your mouth, swelling of the face, red or sore eyes, feeling of vague overall discomfort. You may also have kidney problems, changes in white blood cell levels, or abnormal liver function tests. • Liver damage. The signs of liver damage that you may notice are: tiredness, not feeling hungry, upset stomach, liver tenderness, flu-like feeling, yellow skin or eyes, dark urine, and pale stool. You may also have abnormal liver function tests. 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. • If you stop taking nevirapine because of severe skin rash, a hypersensitivity reaction, or liver damage, you should never take it again. • 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. This side effect may occur when nevirapine is used in combination with other HIV drugs. • Tiredness • Fever • Headache • Upset stomach • Muscle pain

Anti-HIV Drug	Side Effects
Didanosine [ddI]	<ul style="list-style-type: none"> • Changes to your eyes that may make it hard to see • Upset stomach, throwing up, or loose or watery stools • Numbness, tingling, and pain in your hands or feet • Headache • Increase in uric acid in your blood • 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. This side effect may occur when ddI is used in combination with other HIV drugs. • 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. • 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. • Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, cramps, muscle pain, dizziness, and shortness of breath. Lactic acidosis can cause death.
Stavudine [d4T]	<ul style="list-style-type: none"> • Rash • Upset stomach, throwing up, stomach pain, or loose or watery stools • 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. • Numbness, tingling, and pain in your hands or feet • 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. This side effect may occur when d4T is used in combination with other HIV drugs. • 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. • 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. • Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, cramps, muscle pain, dizziness, and shortness of breath. Lactic acidosis can cause death.

Anti-HIV Drug	Side Effects
Tenofovir [TDF]	<ul style="list-style-type: none"> • Stomach ache, loose or watery stools, upset stomach, throwing up, passing gas • Dizziness • Lack of energy • Shortness of breath • Skin rash • Low phosphate, a chemical in the blood • Changes in bone growth and strength were seen in study animals given tenofovir. Bone thinning has been seen in adults and children taking tenofovir. • 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. • 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. • Kidney damage or failure • 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. • Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, cramps, muscle pain, dizziness, and shortness of breath. Lactic acidosis can cause death. • 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. This side effect may occur when tenofovir is used in combination with other HIV drugs. • There is only a small amount of information on tenofovir in pregnant women; therefore, tenofovir should only be used during pregnancy if clearly needed. • If you are infected with both Hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if tenofovir is stopped.
Truvada® [FTC/TDF]	<ul style="list-style-type: none"> • Stomach ache, loose or watery stools, upset stomach, throwing up, passing gas • Dizziness • Headache • Inability to sleep, unusual dreams • Lack of energy or tiredness • Shortness of breath

Anti-HIV Drug	Side Effects
Truvada® [FTC/TDF] (continued)	<ul style="list-style-type: none"> • Skin rash (may be itchy) • Skin darkening of the palms and/or soles • Increased cough • Runny nose • Low phosphate, a chemical in the blood • An increase in fat in your blood • An increase in creatinine phosphokinase (a substance in your blood), which could mean muscle damage • Changes in bone growth and strength were seen in study animals given tenofovir. Bone thinning has been seen in adults and children taking tenofovir. • 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. • 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. You may have an increase in pancreatic enzyme (a substance in your blood). • Kidney damage or failure • 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. • Lactic acidosis. The signs of lactic acidosis that you may notice are: unexplained weight loss, stomach ache, upset stomach, throwing up, tiredness, weakness, cramps, muscle pain, dizziness, and shortness of breath. Lactic acidosis can cause death. • 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. This side effect may occur when Truvada is used in combination with other HIV drugs. • There is only a small amount of information on tenofovir in pregnant women; therefore, tenofovir should only be used during pregnancy if clearly needed. • If you are infected with both Hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if tenofovir is stopped.
Kaletra®/Aluvia® [LPV/r]	<ul style="list-style-type: none"> • 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. • Large increases in the fat and cholesterol found in your blood, which can cause cardiovascular disease. • An increase in blood sugar or the development or worsening of diabetes. • Possibility of increased bleeding

Anti-HIV Drug	Side Effects
Kaletra [®] /Aluvia [®] [LPV/r] (continued)	<ul style="list-style-type: none"> • 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. You may have abnormal pancreatic enzymes (a substance in your blood). • Abnormal stools, including loose or watery stools, upset stomach, and stomach pain • 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. • Feeling weak and tired • Headache

SIGNATURE PAGE: INDEX CASE ENROLLMENT

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 3.0

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 3.0

PARTNER ENROLLMENT

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 o 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 [insert site-specific enrollment number only if required by local IRB/EC guidelines, which is up to 250 per site). 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 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 on a regular basis. We will tell you the results of any tests we do during the study. 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.

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. If you are a man, 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 your partner from passing HIV to you, so you should avoid all activities where your partner could pass HIV infection 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. If you and your partner are in group 1, this visit will take place about two weeks from today. If you are in group 2, this visit will be two weeks after your partner starts taking anti-HIV drugs in the future. 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.

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, and we will ask you questions about your health.
- 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, in addition to the regular quarterly procedures, 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.
- If you are a man, 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. We will tell you the results of any tests or other information related to your health during the study. If these exams or tests show that you have a health problem, we will treat you to the extent possible. 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/cannot*] provide your partner with drugs to prevent or treat infections related to HIV. However, the clinic [*will/will not*] be able to provide anti-HIV drugs. To receive that treatment your partner [*would/would not*] 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 except to health care providers when needed. Any publication of this study will not use your name or identify you personally. 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 help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This Certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

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

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 3.0

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 3.0

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 very 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 at this site. [*Sites should modify the previous sentence to identify where long-term samples are being stored.*] 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. Your samples may be shipped to approved researchers who work outside of your country.

There is no time limit on how long your samples will be stored. [*Sites should add language here if local regulations put a restriction on the length of time samples may 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. Any publication of this study will not use your name or identify you personally. 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 help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This Certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

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 3.0

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 3.0

INDEX CASE PREGNANCY

(This consent should be used for women who are pregnant prior to enrollment or who become pregnant during the study.)

PRINCIPAL INVESTIGATOR: *[insert name]*

PHONE: *[insert number]*

INTRODUCTION:

Because you are pregnant, you are being asked if you want to begin or 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 start anti-HIV drugs, choose other anti-HIV drugs, or remain on study medicines. If you agree to begin or remain 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 begin or 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, you will begin taking ART during your pregnancy to help prevent you from passing your HIV infection to your baby.

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.

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

Since 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 or will sign to enroll in the study.

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 begin or 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 enrollment consent you already signed or will sign; 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 except to health care providers when needed. Any publication of this study will not use your name or identify you personally. 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 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 help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This Certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

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 3.0

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 begin or continue participating in 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