

HPTN 052 Protocol-Specific Training

Protocol Overview

Differences Between V2.0 and V3.0



Overall Changes

- ◆ **All information relevant only to the run-in period has been removed.**

Primary Study Objectives

V2.0

- ◆ HIV primary care without initiation of ART until the participant has two consecutive measurements of a CD4+ cell count < 200 cells/mm³, or develops an AIDS-defining illness.

V3.0

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

Secondary Study Objectives

V2.0

- ◆ Determine the long-term safety of two ART regimen strategies (ART immediately upon enrollment vs. ART when the participant has two consecutive measurements of a CD4+ cell count < 200 cells/mm³ or develops an AIDS-defining illness) for the treatment of HIV-1 infection.

V3.0

- ◆ 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 between 200-250 cells/mm³, or develops an AIDS-defining illness).

Secondary Study Objectives

- ◆ A secondary objective to characterize and compare **quality-of-life (QOL)** indicators in different geographic settings and by antiretroviral treatment strategies **was added.**

Study Design

- ◆ **The overall study design remains the same**
- ◆ **Brazil** is now comprised of **two sites** (Rio de Janeiro and Porto Alegre)

Inclusion Criteria

Index Case

- ◆ An **algorithm** required to determine **HIV positive serology** has been added
- ◆ All inclusion criteria related to **pregnancy, breastfeeding, and required contraception** have been removed.
- ◆ Potential participants may be **pregnant** (not allowed in pilot)
- ◆ If a woman is in her **first trimester** during screening the **HPTN 052 CMC must be consulted** prior to enrollment.

Inclusion Criteria

Index Case (continued)

- ◆ CD4 **350-550 cells/mm³** (previously 300-500)
- ◆ Hemoglobin \geq **7.5 g/dL** (previously 7.0)
- ◆ **Creatinine clearance \geq 60 mL/min (new)**
- ◆ **Absolute neutrophil count \geq 750 mm³
or 0.750 x 10⁹/L (new)**

Inclusion Criteria

Partner

- ◆ An **algorithm** required to determine **HIV negative serology** has been added

Exclusion Criteria

Index Case

- ◆ **Pregnancy** has been removed as an exclusion criteria
- ◆ Criteria related to **hemoglobin and absolute neutrophil count removed** (part of inclusion only)
- ◆ **Documented or suspected acute hepatitis** within 30 days prior to enrollment, irrespective of AST (SGOT) and ALT (SGPT) values. (previously only for those who would receive ATV or NVP)

Exclusion Criteria

Index Case (continued)

- ◆ **Acute therapy** for serious medical illnesses with **14 days prior to enrollment** has been added.
- ◆ **Radiation therapy or systemic chemotherapy** within **45 days prior to enrollment** has been added.
- ◆ **Any immunomodulator or other investigational therapy** within **30 days prior to enrollment** has been added.

Exclusion Criteria

Index Case (continued)

- ◆ **Active drug or alcohol use** or dependence that would **interfere with study participation** has been added.
- ◆ **Vomiting or inability to swallow medications** due to an active, pre-existing condition that prevents adequate swallowing and absorption of study medication has been added.

Exclusion Criteria

Index Case (continued)

- ◆ **Need for a prohibited medication** as defined in the protocol has been added.
- ◆ **Allergy or sensitivity to any study drugs or their formulation** has been added.

Exclusion Criteria

Both Index Case and Partner

V2.0

- ◆ Receipt of an experimental HIV vaccine.

V3.0

- ◆ Previous and/or current participation in an HIV vaccine study.

Study Treatment Regimen

The ART drugs available for the study include

- ◆ Combivir® (**revised info**)
[3TC/zidovudine(ZDV)]
- ◆ efavirenz [EFV] (**revised info**)
- ◆ atazanavir [ATV]
- ◆ nevirapine [NVP] (**revised info**)
- ◆ tenofovir [TDF] (**revised info**)
- ◆ lamivudine [3TC] (**revised info**)
- ◆ didanosine [ddl-EC] (**revised info**)
- ◆ stavudine [d4T]
- ◆ Kaletra (**new**)
[lopinavir(LPV)/ritonavir (r)]
- ◆ Truvada (**new**)
[(TDF)/emtricitabine (FTC)]

Study Treatment Regimen

- ◆ 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.**
- ◆ **Resistance testing**, where locally available, **may be used** to guide ART selection for individual participants.
- ◆ 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.

Study Treatment Regimen

- ◆ **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.**
- ◆ The **precautionary medication and toxicity management** sections have been **revised** to align with ACTG A5175.

Study Treatment Regimen

- ◆ **Carefully review all the ART-related sections** as there have been revisions throughout.
- ◆ Most changes are **additional background information or rewriting for clarity or consistency.**

Study Treatment Regimen

- ◆ NVP
 - 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 (**the measurement at week 8 is new**).
- ◆ Truvada
 - Dosing and toxicity information has been added.
- ◆ Kaletra
 - Dosing and toxicity information has been added.

Study Treatment Regimen

- ◆ The section on **adherence counseling and assessment was revised** to indicate the tools being used to measure adherence.
- ◆ A subsection on the **management of HBV-HIV co-infection** has been added.

Initiating ART in the Delay Arm

- ◆ 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**.
- ◆ 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**.

Initiating ART in the Delay Arm

- ◆ 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.

Initiating ART in the Delay Arm

- ◆ 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.

Initiating ART in the Delay Arm

- ◆ 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**.
- ◆ **Viral load testing** will be done at the **next monthly visit following ART initiation** for both Arm 1 and 2

Criteria for Switching ART Due to Virologic Failure

- ◆ If possible, the **two plasma HIV RNA measurements** should be done **within a month of each other**.
- ◆ **Resistance testing**, where locally available, **may be used** to guide ART selection for the secondary regimen.
- ◆ 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.

Study Procedures, Clinical Procedures, And Laboratory Evaluations

Screening Visit: Index and Partner

- ◆ **Demographic information** is no longer being collected.
- ◆ Use of the **eligibility checklist** is no longer a protocol requirement.
- ◆ **Post-test counseling should be administered when the test results are available**, which may be at the current or following visit (previously not explicit)

Study Procedures, Clinical Procedures, And Laboratory Evaluations

Screening Visit: Index

- ◆ Testing for **hepatitis B** has been added.
- ◆ **Plasma and serum samples** are no longer being collected for long-term storage.

Study Procedures, Clinical Procedures, And Laboratory Evaluations

Enrollment Visit: Index and Partner

- ◆ **Demographic information** is being collected
- ◆ **PBMCs** will be collected on **all participants**, not just a subset.

Study Procedures, Clinical Procedures, And Laboratory Evaluations

Enrollment Visit: Index

- ◆ A **quality-of-life assessment** is being performed for Index cases.
- ◆ **Stool and urine samples** are no longer being collected for parasitic disease testing.
- ◆ **Malaria testing** is no longer being done.
- ◆ **Hepatitis B** testing is no longer being done.

Study Procedures, Clinical Procedures, And Laboratory Evaluations

Additional Assessments/Procedures

- ◆ Information was added reminding study staff that **additional assessments/procedures** may be required based on the **ART-related sections** of the protocol

Study Procedures, Clinical Procedures, And Laboratory Evaluations

Week Two Visit: Index and Partner

- ◆ 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.

Study Procedures, Clinical Procedures, And Laboratory Evaluations

Monthly Visit: Index and Partner

- ◆ The **sexual history assessment** is **no longer done** at Month 1 and 2

Study Procedures, Clinical Procedures, And Laboratory Evaluations

Monthly Visit: Index

- ◆ A note was added to remind staff **not to collect a blood sample** unless the visit is one of the **first two monthly visits** following ART initiation.
- ◆ **Viral load testing** was added one month after ART initiation.

Study Procedures, Clinical Procedures, And Laboratory Evaluations

Quarterly Visit: Index and Partner

- ◆ **PBMCs** will be collected on **all participants**, not just a subset.

Study Procedures, Clinical Procedures, And Laboratory Evaluations

Quarterly Visit: Index

- ◆ A **quality-of-life assessment** is being performed for Index cases.

Study Procedures, Clinical Procedures, And Laboratory Evaluations

Annual Visit: Index and Partner

- ◆ **PBMCs** will be collected on **all participants**, not just a subset.

Study Procedures, Clinical Procedures, And Laboratory Evaluations

Annual Visit: Index

- ◆ A **quality-of-life assessment** is being performed for Index Cases.
- ◆ **Stool and urine samples** are no longer being collected for parasitic disease testing.
- ◆ **Malaria testing** is no longer being done.
- ◆ **TB testing** (PPD/chest x-ray) is no longer a requirement for the U.S. site.

Study Procedures, Clinical Procedures, And Laboratory Evaluations

Seroconversion: Index and Partner

- ◆ **PBMCs** will be collected on **all participants**, not just a subset.

Study Procedures, Clinical Procedures, And Laboratory Evaluations

- ◆ Criteria for **permanent treatment discontinuation** (off treatment/on study) were added:
 - 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.

Pregnancy and Breastfeeding

- ◆ **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 ddl 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.**

Pregnancy and Breastfeeding

- ◆ 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.

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.

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.

AE and EAE Reporting

- ◆ The **current versions** of the DAIDS EAE manual and grading table are referred to in the text.
 - **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**
 - **Manual for Expedited Reporting of Adverse Events to DAIDS (dated 6 May 2004)**

AE and EAE Reporting

- ◆ Clarifies that, 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 an SAE and can be associated with study participation or procedures, it will be reported as an EAE.
- ◆ **Table 8** was added as a reference guide for reporting AEs and EAEs.

Human Subjects Considerations

- ◆ Information about **certain aspects of ethical review was removed** as these details are contained in the **HPTN MOP**.
- ◆ The requirement that **all study records containing names** or other personal identifiers **be stored separately** from other study records **has been removed**.

Confidentiality

- ◆ The following information was removed from the protocol: **All study records that contain names or other personal identifiers will be stored separately from other study records.**
- ◆ The following information was added to the protocol: 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...

Laboratory Specimens and Biohazard Containment

- ◆ **Malaria testing and the collection of stool and urine samples** for the diagnosis of parasitic diseases have been removed.
- ◆ The requirement of compliance with **IATA shipping regulations** has been added.

Administrative Procedures

- ◆ The information stating that the **DAIDS SOPs, EAE manual, and toxicity grading table** can be found in the SSP has been removed as it is inaccurate.
- ◆ Detailed information about the **coordination between the protocol team members** has been removed.

Appendix IA and IB

- ◆ The **Schedules of Procedures and Evaluations** for both the Index case and the Partner were revised to reflect the changes made to the protocol.

Appendix III

- ◆ Appendix III and IV from Version 2.0 were combined and revised to create **one list of AIDS-defining illnesses** to be used for eligibility determination and as part of the criteria to initiate ART in the delay arm.

HPTN 052 V3.0

Questions?