

**HPTN 052 Study Monitoring Committee Review**  
**Review Date: 26 May 2006**  
**10:00am – 12:00pm ET**

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**Participating SMC Reviewers:**

Tom Fleming, SMC Chair, University of Washington  
Jim Hughes, SMC Co-Chair, University of Washington  
Ward Cates, HPTN CORE, Family Health International (FHI)  
Mary Fanning, Division of AIDS (DAIDS), National Institutes of Health  
Chuck Hicks, Duke University

**HPTN 052 Protocol Chairs/Site Representatives:**

Mike Cohen, University of North Carolina  
David Celentano, Johns Hopkins University/RIHES, Baltimore MD  
Sheela Godbole, National AIDS Research Institute, Pune, India  
Mina Hosseinipour, UNC Project, Lilongwe, Malawi  
Kenneth Mayer, Fenway Community Health, Boston, MA, U.S.A.  
Taha Taha, Johns Hopkins/Malawi College of Medicine Project, Blantyre, Malawi  
James Hakim, University of Zimbabwe Clinical Research Center, Harare, Zimbabwe  
Breno Santos, Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil

**Observers:**

David Burns, DAIDS	Lei Wang, SCHARP
Estelle Piwowar-Manning, HPTN CL	Missie Allen, HPTN CORE, FHI
Drew Edwards, SCHARP	Nirupama Sista, HPTN CORE, FHI
Ben Masse, SCHARP	Marybeth McCauley, HPTN CORE, FHI
Ying Chen, SCHARP	Carolyn Yanavich, HPTN CORE, FHI
Geetha Beauchamp, SCHARP	Theresa Gamble, HPTN CORE, FHI
	Jackie Talley, HPTN CORE, FHI

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**SUMMARY OF COMMENTS AND RECOMMENDATIONS:**

**The following are comments and recommendations from the Study Monitoring Committee:**

- **The PIs and team members have achieved significant success in the run-in period of HPTN 052.**
- **All international sites have completed enrollment.**
  - It was noted that some sites (*e.g.* Blantyre and Porto Alegre) took longer than the intended 3 months for full accrual and that other sites achieved enrollment targets in much less than 3 months. Some of this diversity in accrual may be reflective of a site's ability to pre-screen couples for enrollment. Sites are encouraged to continue to identify couples as appropriate in preparation for the full study.
- **Fenway Community Health Center (located in Boston, MA, USA) has had difficulty fully enrolling into the run-in period primarily due to the unwillingness of potential participants to be randomized to immediate or delayed treatment (lack of equipoise).**

- The SMC strongly encourages the site to continue with all reasonable efforts to fully enroll participants into the run-in period.
- The SMC encourages the team to seek clarification from DAIDS regarding whether the site will be allowed to initiate its enrollment into the full study at the time the international sites begin.
- **It is important to enroll a population with the intended risk level so that the study will be adequately powered to meet its primary objectives.**
  - Early data reflect that, at some sites, the Index Case and Partners are somewhat older than anticipated and, in some cases, the couples are reporting less sexual activity and higher condom use than expected.
  - It appears that sites are identifying cohorts that will achieve the targeted levels of risk over the full duration of the trial.
- **The data show some discrepancies between screening and enrollment CD4+ cell count values for some Index Cases, with all meeting the eligibility criteria of 300-500 cells/mm<sup>3</sup> at screening, followed by a higher or lower value at enrollment.**
  - Two to three of the sites are more heterogeneous in their enrollment CD4+ cell count values than others, which may be due to cofactors such as malaria.
  - CD4 cell counts can be highly variable, and this kind of fluctuation is not necessarily reflective of a true difference in values.
  - The SMC encourages the team to continue monitoring this issue so that proper accommodations can be made, if necessary, to ensure that there is an adequate time difference between ART initiation in the two groups.
- **The retention rates are as expected at this early point in the study, with some sites experiencing a 100% retention rate.**
  - It is important for the sites to achieve the protocol target of 2-4% lost-to-follow-up on an annual basis.
  - There is some early indication that the targeted level of retention might not be achieved for individual clinic visits; however, in most of cases, the couples are facing temporary difficulties that have been subsequently resolved. The site-specific teams expect to recover the participants at future visits.
  - The SMC reiterates the importance of high levels of retention of both the Index Cases and the Partners.
- **The most recent data indicates a very high adherence to study drug (ART).**
- **The team has achieved significant successes since the time of the last meeting in the area of drug procurement.**

- It appears now that Efavirenz will be available and that, while Kaletra is still being pursued, all drugs required for the full study will be available.
- **The team intends to initiate the full study by late summer 2006.**
- **Two sites (Blantyre and Harare) have experienced on-going laboratory-related issues; however, efforts are underway at both sites to implement corrective action measures in order to resolve the issues.**

**General Commentary on the Report:**

The run-in period is well underway and approaching completion. All sites have been activated and all international sites have completed enrollment. Fenway Community Health Center (located in Boston, MA, USA) has enrolled one couple and, thus, has not completed enrollment to date. The study was to have 86 couples enrolled into the run-in period across all sites; however, total enrollment to date is 81 couples.

**Table 2:** This table provides the number of participants enrolled per site as well as the number of person-years follow-up at each site. Enrollment at Blantyre and Porto Alegre took considerably longer than the intended 3 months.

**Table 4a:** This table shows the age of both Index Cases and Partners. Some sites are enrolling participants that are considerably older than anticipated. The SMC was reminded that the sample size is small at this point and that once enrollment numbers increase, the demographics may be more in line with expectations.

**Table 6a & b:** The decrease in risk behaviors was noted in the run-in cohort, based on the decreased numbers of non-primary partners and increased use of condom use. These factors may not be optimal for a study looking for transmission. It was noted that numbers are small at this time and that as the full study proceeds, it will be important to enroll a population with the intended risk level so that the study will be adequately powered to meet its primary objectives.

**Table 7:** The SMC asked and was informed that HSV serology is not being measured in this study.

**Table 9:** This table reports the screening and enrollment CD4+ cell count values. CD4+ cell counts between 300-500 cells/mm<sup>3</sup> are required for screening, and the sites are adhering to this requirement. Two or three of the sites in particular are more heterogeneous in their enrollment CD4+ cell count values than others, which may be due to cofactors such as malaria. It was noted that CD4+ cell count values can be highly variable, even over short periods of time, and this kind of fluctuation is not necessarily reflective of a true difference in values. It was suggested that CD4+ percent might be added to this table in order to help analyze the importance of the variable CD4+ cell count values. Of note is the issue of whether the time of initiation algorithm needs to be refined in the delay arm of the study based on variability in the baseline CD4+ cell count values.

**Table 10:** The SMC noted that these data look very encouraging regarding HIV counseling attendance.

**Table 11:** The SMC asked whether this table indicated if a visit was missed. SCHARP representatives clarified that the table only reflects participants who attended their appropriate visits.

**Table 13:** At the time of the last SMC review, one couple had already been terminated at the Lilongwe site. There is now a second couple in Thailand that has permanently separated. In this case the Index Case will stay in the study, but the Partner will be terminated.

**Table 14a & b:** These tables indicate that Index Cases were retained at a very high level out to 6 months. A few sites have reported retention issues with a small number of their couples. Retention is targeted at 2-4% LFU per year and sites are reminded of the importance of retaining both Index Cases and Partners.

### **General Issues:**

Predictors of incidence and retention will be followed closely by the SMC over time.

Regarding the fact that the site in Blantyre, Malawi took longer to complete enrollment than other sites, it should be noted that some of the other sites had a pre-screened cohort that they had been following and were able to enroll from quickly once activated. It may be that the situation in Blantyre will be more reflective of enrollment for the full study. It is anticipated that V. 3.0 of the protocol will be available in July, 2006 and sites can begin obtaining IRB site approval and then perhaps start enrolling in August, 2006. With this in mind, sites should take time now to identify couples who may become potential participants in the full study.

Merck has indicated that efavirenz will be provided to the study and Kaletra is being pursued from Abbott. If Kaletra is obtained, all the drugs that are required for the full study will be available.

Two sites (Blantyre and Harare) have experienced on-going laboratory-related issues; however, efforts are underway at both sites to implement corrective action measures in order to resolve the issues.

### **Input from the Sites:**

**Fenway Community Health Center, Boston, MA, U.S.A. (update given by K. Mayer):** K. Mayer reported that Fenway continues efforts to screen and enroll into the run-in period of the study. The team is considering expanding to Miriam Hospital in order to attempt to identify couples in Providence. There is a question of whether Fenway will move into screening for the full study prior to enrolling their targeted number of participants for the run-in period.

**YRG CARE, Chennai, India (update given by K. Mayer):** K. Mayer indicated that the study is progressing well at YRG CARE. The site team has a list of pre-identified couples ready to be screened and enrolled into the full study.

**RIHES, Chiang Mai, Thailand (update given by D. Celetano):** D. Celetano reported that extensive pre-screening and community orientation activities have continued and as a result, there are a number of couples lined-up for enrollment into the full study.

**University of Zimbabwe Clinical Research Center, Harare, Zimbabwe (update given by J. Hakim):** J. Hakim reported that pre-screening efforts are continuing at the Harare site. It was noted that in Harare, the couples that have been enrolled are in their upper 40s (age), report to have less sexual activity and increased condom use than expected. J. Hakim indicated that the team will look at the situation as a group and attempt to develop some strategies to ensure that participants that are enrolled will exhibit the behaviors that are necessary to achieve the end-points of the trial. The Zimbabwe site has been having difficulty with critical value reporting. The site is working on updating their SOPs and representatives from the Central Lab are working with the site to resolve the issues. Considerable time has been invested in management of the Zimbabwe lab as well.

**UNC Project, Lilongwe, Malawi (update given by M. Hosseinipour):** M. Hosseinipour reported that the variability of CD4+ cell count values at Lilongwe may in part be due to the presence of malaria. Regarding retention of the couple in question at this site, M. Hosseinipour reported that during times that the couple is having marital difficulties, one member of the couple may leave the home for a period of time, but the team makes the effort to bring them back in for their required visits and provides extensive counseling. The lapse in retention is not permanent, but rather sporadic, given marital issues that occasionally arise.

**Johns Hopkins/Malawi College of Medicine Project, Blantyre, Malawi (update given by T. Taha):** T. Taha reported that the variability in CD4+ cell count values has been observed for several years and may be due to concurrent infections and other underlying factors such as nutrition. The Blantyre site is still working on getting their RNA panels completed for validation so that they can stop sending their samples to Lilongwe. The site is working on updating their SOPs and representatives from the Central Lab are working with the site to resolve lab-related the issues. It was reported that there have been changes in lab management at the Blantyre site and it is anticipated that these changes will have a positive impact on lab operations and results.

**NARI, Pune, India (update given by S. Godbole):** S. Godbole reported that the site continues with recruitment strategies and pre-screening activities in order to get started on the full study as soon as possible.

**Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil (update given by B. Santos):** B. Santos reported that the study is progressing smoothly. The site has recently completed enrollment into the run-in period, and they have a number of pre-screened couples waiting to be screened and enrolled into the full study. The CAB is publicizing the study throughout the city.