

HPTN 052 Study Monitoring Committee Review
Review Date: 30 September 2005
10:00am – 12:00pm ET

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)
Monica Ruiz, Division of AIDS (DAIDS), National Institutes of Health
Chuck Hicks, Duke University

HPTN 052 Protocol Chairs/Site Representatives:

Mike Cohen, University of North Carolina
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
Suwat Chariyalertsak, Research Institute for Health Sciences, Chiang Mai, Thailand
Beatriz Grinsztejn, Instituto de Pesquisa Clínica Evandro Chagas, Rio de Janeiro, Brazil
Breno Santos, Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil

Observers:

Alain Kouda, DAIDS
David Burns, DAIDS
Lydia Soto-Tores, DAIDS
Ana Martinez, PAB
Estelle Piwowar-Manning, HPTN CL
Sten Vermund, Vanderbilt University
Ben Masse, SCHARP
Ying Chen, SCHARP
Leslie Cottle, SCHARP
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Observers:

Wayne Sheldon, SCHARP
Melissa Kaufman, SCHARP
Drew Edwards, SCHARP
Missie Allen, HPTN CORE, FHI
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Marybeth McCauley, HPTN CORE, FHI
Carolyn Yanavich, HPTN CORE, FHI
Theresa Gamble, HPTN CORE, FHI
Anne Coletti, HPTN CORE, FHI
Jackie Talley, HPTN CORE, FHI

ACTION ITEMS

- M. Cohen will work with the pharmaceutical companies to secure all drugs required for the full study. In particular, he will approach Merck (for efavirenz) and BMS (for atazanavir, ddi, and d4T), and will determine a drug for use during pregnancy (perhaps nelfinavir from Pfizer).
- Additional information will be provided to C. Hicks regarding the responsibilities of the SMC.

SUMMARY OF COMMENTS AND RECOMMENDATIONS:

The following are comments from the Study Monitoring Committee about HPTN 052.

- **There has been diversity in the study activation timeframe for the sites, which has impacted the overall duration of the run-in period.**

- Three sites (located in Lilongwe, Malawi; Pune, India; and Chiang Mai, Thailand) are activated and have completed enrollment for the run-in period (10 couples at each site).
- Two sites (located in Blantyre, Malawi and Rio de Janeiro, Brazil) are activated and enrollment is expected to be complete by December 2005.
- One site (located in Boston, MA) has been activated, but has not yet enrolled any participants (activation was approximately 7 months ago).
- Three sites (located in Chennai, India; Porto Alegre, Brazil; and Harare, Zimbabwe) have not yet been activated; although they are expected to be activated over the next three months and it is plausible that enrollment will be accomplished within the expected 3-month period.
- **The correct population is being identified and enrolled.**
 - All enrolled participants had a CD4+ cell count between 300-500 cells/mm³ during screening; although, there were some values outside of this range at enrollment. The SMC advises that these values be continuously monitored across all sites for both the run-in period and full study.
- **Early visit adherence results are encouraging, with near 100% attendance by both the Index Cases and Partners.**
- **Retention results, although very early and somewhat limited, are favorable.**
 - One couple has been terminated at the site located in Lilongwe, Malawi, despite the site staff's best efforts to prevent the situation.
 - The SMC reiterated the importance of making all reasonable efforts in cases where relationships are terminated to let the Index Case know that their continued participation in the trial is encouraged and welcome.
- **Given the results thus far, the run-in period is successfully demonstrating the feasibility of conducting HPTN 052.**
 - The sites that have been activated and have completed enrollment have clearly demonstrated their ability to enroll the targeted population, conduct the study procedures properly, and, at least preliminarily, retain their participants.
 - If the remaining sites can be activated as scheduled and enroll in a timely fashion without difficulties, implementation of the full HPTN 052 study is viable.
- **Drug acquisition remains the most critical factor in implementation of the full study.**
 - The SMC recognizes the need to provide evidence of the successful implementation of the run-in period in order to approach the pharmaceutical companies who have not yet committed drug for the full study.
 - It would be best to avoid the situation where sites have proven their capacity to conduct the study, but cannot move forward to the full study due to delays in drug availability.

The following are the recommendations from the Study Monitoring Committee for HPTN 052.

- **Commitments for all study drugs required for the full study should be obtained as soon as possible.**
- **If at the end of 2005, one or two sites have not yet been activated or are not able to achieve their enrollment goals, but all other sites are in good standing, it would appear to be appropriate for the protocol team to move forward with implementation of the full study.**

- **If there is the constraint that 90 couples must be enrolled during the run-in period, the SMC encourages the protocol team to obtain authorization for sites that have successfully implemented the run-in period to enroll additional couples. Alternatively, the protocol team could consider obtaining authorization for moving forward with full study implementation with less than 90 couples enrolled during the run-in period.**

GENERAL COMMENTARY

The SMC thanked and congratulated the teams that have put together the very informative and well-organized report for review by the SMC. Thanks and congratulations from the SMC were also expressed to the investigators and colleagues from DAIDS, FHI, and SCHARP on what has been an enormous accomplishment in getting this run-in period underway where there are already some significant and impressive successes at a number of the sites.

Key Observations:

Table 1. Number of Couples Randomized per Month, by Site: According to Table 1, five sites are activated. The three Rio de Janeiro clinics have been activated since the generation of the Table 1; however, the clinic in Porto Alegre, Brazil remains un-activated. As of the date of the report, the sites located in Pune, India; Lilongwe, Malawi; and Chiang Mai, Thailand had completed enrollment (10 couples) and the site located in Blantyre, Malawi had enrolled one couple. A fifth site, located in Boston, Massachusetts, has been open for the longest period of time (7 months), but has yet to enroll their first couple.

Table 3a and b. Demographics: The overall median age of enrolled participants is 31.

Table 5. Behavioral Characteristics at Enrollment, by Site: By reviewing the data collected about the number of sex partners reported in the past 3 months, it appears that the Index Cases and their Partners are predominately in monogamous relationships. The exceptions to this are the Index Case in Pune, India who reported two partners and the Partner in Lilongwe, Malawi who reported four partners.

Table 8. CD4 and HIV RNA at Enrollment, by Site: Per protocol design, all of the enrolled participants should have CD4+ cell counts in the range of 300-500 cells/mm³ during their screening assessment, which is the case. At the enrollment visit, about two-thirds of the participants remain within this range, with the others fairly evenly split above (18%) and below (16%) the range. The site located in Lilongwe, Malawi had the most variability in their enrollment CD4+ cell count and the majority (6 out of 11) of the out-of-range or missing values at this visit. It was noted that the small number of enrollees might have some impact on the variability of the CD4+ cell counts.

Tables 9a, 9b, 10a, 10b, 11a and 11b. HIV Counseling Attendance and Visit Adherence: Both Index Cases and Partners are achieving high levels of HIV counseling attendance and visit adherence during follow-up. Although couples are encouraged to return for their follow-up visits together, they may return as individuals, which explains the discrepancies in visit adherence between Index Cases and Partners at Months 2 and 3 (e.g., 15 Index Cases and 13 Partners completed their visits at Month 2). The overall evidence for adherence is very favorable.

Tables 12a and 12b. Reasons for Termination: One couple has been terminated at the site located in Lilongwe, Malawi. When the couple's relationship ended, the Index Case moved to another town and chose to withdraw from the study despite all the reasonable efforts made by the staff to retain the participant.

Tables 13a and 13b. Retention: Data out to Month 4 indicate that retention through the first 3 months has been excellent for all Index Cases. There are two Index Case no-shows at Month 4 at the site located in Lilongwe, Malawi. Retention for the Partners is not as high as the Index Cases with missed visits at Months 2, 3, and 4, all of which occurred at the site located in Lilongwe, Malawi. This issue could become problematic if it continues as the study moves forward.

Input from the Protocol Chair, site representatives and FHI representatives focusing on:

- The likelihood that sites that have not yet been activated will achieve activation in the near future (sites located in Porto Alegre, Brazil; Chennai, India; and Harare, Zimbabwe).
- Whether or not it will be possible to initiate the full study at sites that have achieved their targeted enrollment and are successfully conducting the study, even if one or two sites are not meeting these goals.
- If 90 couples are required to complete the run-in period, whether sites that have completed their targeted enrollment of 10 couples can enroll additional couples.
- Drug availability for the full study.

YRG CARE, Chennai, India (update given by K. Mayer and T. Gamble): It is anticipated that activation will occur within the next two weeks, once the study drugs arrive at the site. The activation delay has been caused by difficulties in obtaining the proper permission to ship the drugs to a non-governmental organization in India. This issue has been resolved and the initial drug shipments will be sent to the site through the U.S. Consulate in Chennai, India. The site has a large database of HIV-serodiscordant couples that they have seen in their clinic and it is expected that the site can draw from this pool and complete enrollment by December 2005.

Fenway Community Health Center, Boston, MA, U.S.A. (update given by K. Mayer): Although the site team was able to identify close to 100 potential participants in the general patient population of Fenway Community Health Center, 30 of whom were in a serodiscordant relationship, and went on to screen 7 of these couples; they have not been able to enroll any participants into the study. Several of the potential couples had CD4+ cell counts outside of the required range; however, the primary reason that no one agreed to enrollment is that they were not willing to be randomized to the immediate and delayed ART treatment arms of the study. The site is doubling its efforts of outreach by working with AIDS service organizations throughout New England. The site is also hosting a dinner this coming Wednesday evening to give local providers the scientific context of the study and discuss recruiting approaches in other clinics.

University of Zimbabwe Clinical Research Center, Harare, Zimbabwe (update given by J. Hakim and M. McCauley): Training for the protocol is scheduled in the next two weeks. It is anticipated that the site will begin screening in December 2005 and complete enrollment in February or March 2006. Despite past problems, Dr. Hakim indicated that things are coming together relatively well and he believes that once the training is complete, the site will be able to get online quickly. The site has identified about 110 HIV-serodiscordant couples who are waiting to be screened.

Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil (update given by B. Santos and C. Yanavich): The issues related to drug importation have been resolved and protocol-specific training is likely to occur the second week of November. It is anticipated that enrollment will begin in December 2005 or early January 2006 and will be completed by March or April 2006. The site has already pre-screened a number of couples who may be eligible to screen for the study at the end of the year.

Instituto de Pesquisa Clínica Evandro Chagas, Hospital Geral de Nova Iguaçu, and Hospital dos Servidores do Estado, Rio de Janeiro, Brazil (update given by B. Grinsztejn): The site has begun screening and feels that they will be able to enroll their allotted 15 couples by the end of 2005.

UNC Project, Lilongwe, Malawi (update given by M. Hosseinipour): As the site has already completed enrollment, they would be happy to enroll more couples into the run-in period. The site team is working hard to retain the couples in the run-in period and is pleased with the manner in which the couples are adhering to the study requirements.

NARI, Pune, India (update given by T. Gamble): The site is fully enrolled and follow-up is progressing well.

Johns Hopkins/Malawi College of Medicine Project, Blantyre, Malawi (update given by T. Taha): To date, the site has enrolled 3 couples and has 3 more potential candidate couples who may be enrolled next week. The site expects to be fully enrolled by the end of 2005.

RIHES, Chiang Mai, Thailand (update given by S. Chariyalertsak): The site has completed enrollment and participant visit adherence and retention is good.

Total enrollment for the run-in period: B. Masse indicated that the purpose of the run-in period is to demonstrate the feasibility of conducting the study at each individual site; therefore, it is not necessary to enroll all 90 couples before proceeding to the full study.

Number of sites required for the full study: In general, it is felt that the full study could proceed without 1 or possibly 2 of the sites; however, if more than 2 sites are unable to enroll or conduct the run-in period successfully, advancement to the full study is not advisable with the current capacity of the remaining sites.

Drug availability: The Protocol Chair indicated that, insofar as drug availability is concerned, if the pilot goes well and NIH indicates their willingness to support the study, then it is his responsibility to obtain all the drugs necessary to begin the full study. The Protocol Chair indicated that he would use data from the run-in period and support from NIH to request drug for the full study. The SMC emphasized the need for the protocol team to obtain commitments for drug for the full study as soon as possible, so as not to cause any unnecessary delays in implementation of the full study. The committee discussed the importance of re-approaching Merck for efavirenz and obtaining commitment for atazanavir, ddI, and d4T from BMS for the full study, as well as identifying a drug for use during pregnancy. If it is not possible to obtain efavirenz, the protocol team should investigate alternative drug regimens for the study.