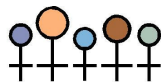


Women and HIV Think Tank

AUGUST 21-24, 2003

DEER VALLEY, UTAH

CONVENED BY

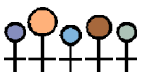


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PREFACE

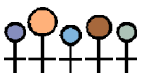
The Women and HIV Think Tank was the first of its kind convened by The Well Project, a newly formed organization dedicated to reducing the total human cost of the AIDS pandemic through a unique focus on women. The Think Tank was held Thursday, August 21 to Sunday, August 24, 2003 in Deer Valley, Utah and brought together a diverse, multi-disciplinary group of participants experienced in a broad range of issues related to the management of HIV in women. The Think Tank was designed to identify the gaps and controversies in research on women and HIV, develop research questions, and consolidate Pharma Advisory Board meetings without excluding industry from interaction and feedback. The Well Project pledged to broadly disseminate this Think Tank Meeting Summary Report, actively seek interest in the list of research questions, and develop additional educational materials based on the findings of the first Women and HIV Think Tank meeting.



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DETAILED MEETING SUMMARY

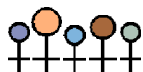
INTRODUCTION

The management of HIV disease in women is a complex and challenging task. Although women are being infected and diagnosed with HIV at an alarming rate in many regions of the United States (and certainly worldwide), the participation of women with HIV in clinical research has not been sufficient to clearly elucidate the sex-based similarities and differences in the clinical management of HIV disease. In addition, the availability of an extensive arsenal of drugs, longer survival, co-morbidities, and aging are all playing confounding roles in this already complex landscape.

The Women and HIV Think Tank was designed to address the gaps and controversies in research on women and HIV disease (see Appendix C for the Meeting Agenda). This goal was intentionally broad allowing the participants to determine what the needs are rather than imposing a specific focus on the group. The invitees and participants represented a diverse body of expertise ranging from microbiology to epidemiology and basic research to clinical management. All of the participants impact research (from funding to implementation) or manage women with HIV in a clinical setting, with a significant percentage doing both. Each participant was provided with a background document, *Not Just A Complication, But A Basic Variation, a comprehensive literature review on women and HIV*, written by David Gilden for The Well Project (see Appendix D).

The Think Tank panel was charged with the following meeting objectives:

1. Examine the current state of research related to women and HIV and identify key gaps and controversies.
2. Review, discuss, and provide feedback to three pharmaceutical partners on existing data, planned and ongoing research, and key initiatives focusing on women and HIV.
3. Develop a list of research questions in response to the identified gaps and controversies.
4. Identify next steps to facilitate future development of research questions into viable research projects.
5. Provide feedback on education needs and preferred learning tools for physicians about the management of HIV disease in women.



GAPS AND CONTROVERSIES

In addition, a few issues were identified over the course of the meeting that generated action items beyond the stated meeting objectives. These action items are described in context and listed in the left margin of this meeting summary.

Seven of the participants were asked to prepare an informal 15-minute presentation on the gaps and controversies in one of four assigned areas: Treatment, Complications and Co-morbidities, Reproductive Health and Fertility, and Behavioral Issues.

These presentations gave the Think Tank panel an opportunity to hear perspectives from their colleagues and to begin thinking broadly about the issues from a variety of viewpoints. The presentations also served as a starting point for the following days of conversation. Recognizing that there are many issues that could fall under these sections, the presenters were asked specifically to highlight issues which represent the key deficits in our understanding.

Treatment

Veronica Miller, Kathryn Anastos

- lack of networks to identify and follow women in early primary/acute infection
- resistance data on women
- impact of hormones
- little information on genital tract immunology
- pharmacogenetics role in managing HIV disease in women
- individual management tools and techniques
- pharmacokinetics (in relation to both race and sex)

Complications and Co-morbidities

Judith Currier, Tonia Poteat

Metabolic complications

- increased lactic acidosis and hepatic steatosis in women
- lower triglycerides, clinical relevance
- difference in osteoporosis (treatment for HIV+ vs. HIV- women)
- lipotrophy

HCV

- risk of disease progression and response to therapy
- sexual transmission of HCV
- impact of coinfection

Mental health

Street drugs

- impact on HIV
- drug interactions



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Reproductive Health and Fertility

Gina Brown, Rebecca Denison

- impact of intermittent treatment on Mother-to-Child-Transmission (STI style)
- breastfeeding and antiretroviral use
- menopause

Behavioral Issues

Judith Auerbach

- the lack of both qualitative and quantitative research in general and, more specifically, the critical relationship between the qualitative and quantitative findings when treating women

Group discussion/brainstorm

The individual presentations were thought-provoking and addressed a range of issues for the Think Tank to consider. The participants then engaged in group discussion and brainstorming to continue to flesh out the gaps and controversies in research on women and HIV. Below is the complete list of the gaps and controversies as cited during the brainstorming session:

- long term non progression in women
- lack of normative values for women
- estrogen receptors
- individual drugs impact on each metabolic parameter
- incarcerated women
- breastfeeding impact on women's health (possible increased risk of death)
- alternative medicine impact
- female to female transmission
- role of spirituality
- most effective and safe contraception for HIV+ women
- best treatments for depression in HIV+ women
- adolescent girls issues
- PK effect in unique situations (ie: pregnancy)
- treatment strategies for both vaginal and anal HPV
- breast cancer/HIV relationship and impact
- cardiovascular/sudden death
- issues for perinatally infected adolescents emerging into adulthood
- medical ethics
- meaning of HIV infection in women's lives
- guidelines on assistive reproductive technology
- impact of HIV on women's fertility
- autoimmunity and acquisition of HIV disease
- disclosure of HIV positive status to infected children/adolescents
- actual risk of infection from female to male

PARTNER SESSIONS

Action Item #1:

The Well Project will follow up with each of the presenting partners on actions they have taken in regards to the issues discussed in their closed session. The Well Project will provide this update at the next Think Tank gathering.

DEVELOPMENT AND PRIORITIZATION OF RESEARCH QUESTIONS

The meeting was convened with the support of four pharmaceutical partners. Each partner was given the opportunity to address the Think Tank in a 2-hour closed session in order to discuss their research and education initiatives designed to enhance knowledge on the management of HIV disease in women. Three partners chose to have closed sessions. Each of these varied dramatically due to the area of focus of the partner, the partner representatives and presenters, and the candor with which the Think Tank was addressed. Each of the partners who participated in a closed session will receive a separate closed session report for their internal use.

The Think Tank participants had mixed feelings about the partner sessions. Generally, the group felt like it was good to hear from each company what HIV-specific and women-specific programs have been implemented in the past and what programs are planned for the future. The participants also felt like it was very valuable to have the pharmaceutical company representatives listen to the broader discussion about needs, research questions, and issues impacting women with HIV. However, due to the marketing focus of some presentations, the group felt their scientific knowledge and expertise was underutilized. The Think Tank also wanted to know how follow up would occur so that the important feedback to these pharmaceutical companies would not be lost.

Upon completion of the partner sessions, the Think Tank panel had completed the review of the background literature document, heard colleagues speak to the gaps and controversies, brainstormed and discussed additional gaps and controversies, and interacted with three pharmaceutical partners on various levels to review their research and educational efforts in regard to women with HIV disease. This provided the panel a broad landscape to begin to discuss how to prioritize needs and to develop ranked research questions based on that prioritization.

In order to prioritize criteria, the Think Tank posed several objective questions. After much discussion, the group decided that *relevance* and *utility* were the guiding criteria moving forward.



RESEARCH QUESTIONS

Action Item #2:

The Well Project will investigate the potential for a dynamic compendium or database of past, present, and planned research initiatives on women and HIV and report back to the Think Tank on these findings.

Action Item #3:

The Well Project will seek support for a survey to be circulated to researchers, government and non-government funded clinical trials groups, and research funding organizations to collect information about the existing data or planned research questions derived by the Think Tank Panel and make it broadly available.



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Drawing upon their own expertise and the previous discussions on gaps and controversies, the group then began brainstorming research questions. Almost 90 questions were collected and then organized into the following categories:

- Treatment
- Reproductive Health
- Co-morbidity
- Complications
- Prevention
- Other

The development of a list of research questions evoked significant discussion about the lack of any single organized system for accessing information about what research has been done or is being done. The Think Tank expressed frustration repeatedly about an environment where it is virtually impossible to avoid duplicating efforts or even to know the breadth of work available to build upon. The need for a research compendium that minimally captures funded research (especially pertaining to women), either ongoing or completed, with contact information for the principal investigator and a listing of any presentations or publications of data, was discussed in depth. (*Action item #2*)

As an immediate need, it was determined that the list of research questions should be circulated to determine where information already exists and whether or not there is research planned or in process to address any of these questions. (*Action item #3*)

After brainstorming an exhaustive list of research questions, each participant was given 35 colored dots and asked to place the dots next to the research question(s) he/she felt were of the highest immediate priority. Participants could choose to place all the dots next to one question or divide the total number of dots among several questions. The goal of this exercise was to prioritize, in a timely manner, the many research questions developed by the Think Tank. We have provided the full list of research questions in the appendices of this document and would encourage anyone interested in the findings to review the list in its entirety. The "dot ranking" as we have called it indicates the total number of dots attributed to each question by the individuals within the panel. We recognize that the prioritization exercise has its methodological flaws, yet feel confident highlighting the following top nine research questions/issues brought to the forefront as a result of this exercise.

1. What are the effects of cyclic changes on antiretroviral therapy and vice versa; what are the pharmacokinetics/interactions of HRT, commonly used oral contraceptives, and emergency contraceptives with all HAART medications; what is the influence of hormone status on PK of individual drugs; PK variation of medications in pregnancy, in menopause and in peripuberty; what are the ART and contraceptive interactions?

2. What are the drug-drug interactions with exogenous and endogenous hormones and other drugs taken by HIV+ women?
3. Do differences in sex and race in drug treatment and metabolism alter clinical efficacy of drug regimens; how do differences in sex and race affect pharmacokinetics and drug absorption?
4. How can we facilitate and influence research on microbicides, vaginal washes, and woman-controlled methods of prevention? What is the role of the pharmaceutical industry?
5. What is the natural history of Hepatitis-C in women with HIV?
6. What are the safe ways to become pregnant if a woman has a HIV+ partner; how safe is sperm washing?
7. Do hormonal levels (menstrual cycles, hormonal contraception, HRT, pregnancy) affect viral load or CD4 values; are CD4 and viral load values affected by the menstrual cycle, and in what way; what are the effects of cyclic hormone changes on viral load, CD4 cells and HIV- related drugs?
8. Among the currently approved agents, what is the optimal initial antiretroviral regimen for women; what is the efficacy; what is the toxicity; what are the quality of life implications?
9. What is the impact of intermittent treatment for reducing perinatal transmission on long-term maternal health and on the effectiveness of subsequent treatment (1 drug; 2 drugs; HAART)?

This research question list has significant crossover and duplication. We recognize that some of the questions are actually comprised of multiple questions and therefore more accurately represent research areas which need to be addressed. Therefore we have identified seven key topic areas that were ranked with highest importance by the Think Tank. These seven key topic areas are:

- the impact of exogenous and endogenous hormones on treatment
- potential sex and race-based differences in response to therapy, toxicity, and disease progression
- the natural history of Hepatitis C in HIV+ women
- the potential difference in biology of antiretroviral treatment in women and the impact on efficacy, toxicity, dosage and quality of life and how this impacts initial regimen, adherence, virologic response, and emergence of virologic resistance
- the need for female-controlled methods of STD prevention and contraception
- safe and efficacious methods (assisted reproductive technologies) for HIV+ or sero-discordant couples to become pregnant
- the need for treatment regimens and strategies for long term maternal health that prevent the emergence of resistance while reducing the risk of mother-to-child transmission

(For a full list of research questions by rank priority, category, and with related hypotheses, please see Appendix E.)

CONCLUSIONS/ NEXT STEPS

The Think Tank clearly acknowledged the possibility that work has been done and is ongoing in some of the areas, indicated by the list of research questions, but the general state of understanding for both researchers intimately involved in this work, and for clinicians managing patients, is inadequate. The need for a research compendium was again discussed so that specific research on these topics which has been completed or is currently underway would not be lost to the larger research community.

The participants completed the task of identifying research questions with two small group breakouts discussing potential hypotheses or refining areas of focus within each of these topic areas. While this exercise was a useful tool for discussion among participants, the outcome was the realization that this was a level of specificity that this group could not complete in the short time available. In fact, the Think Tank was in agreement that it was more appropriate to disseminate the research questions to interested individuals or groups who could develop protocols to address the gaps identified therein.

The first Women and HIV Think Tank successfully achieved the meeting objectives and allowed room for the experience diverse group to elucidate needs and concerns beyond the confines of the stated agenda. The participants were given a difficult task in a condensed timeframe and managed to bring many important issues to light. Although the participation of women in clinical research has improved over the past five years, there is still a great deal to be learned to enable women living with HIV disease and their clinicians to successfully manage long-term HIV disease in the context of the whole woman.

Clearly, a list of almost 90 research questions indicates that our knowledge is deficient. The need to understand the complex role and relationship of exogenous and endogenous hormones with the virus, the immune system, the drugs, and the female body is paramount to establishing a foundation on which our knowledge base of HIV disease in women must be built. The multiple challenges of research related to the impact of hormones has been noted and discussed exhaustively, but a viable alternative solution has not been found. The impact of exogenous and endogenous hormones on treatment was given almost three times the importance of the next question on the list and is represented in several different variations throughout the list of research questions. The remaining questions/topic areas are very important, yet, the foundational nature of this issue creates a much needed hierarchy of the research agenda. The Think Tank body strongly supports the development of innovative models of research, including recruitment and retention techniques, in order to move beyond this impasse.



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The meeting concluded with a short discussion about educational needs of physicians in the field. The Think Tank felt strongly about integrating basic HIV information into the annual conferences, publications/journals, and meeting agendas of primary care physicians, general practitioners, family practice physicians, and OB/GYN's as a critical starting place. The panel brainstormed professional organizations and meetings where The Well Project could work to have a valuable presence. In addition, the need to enhance and expand the knowledge base of the natural history and management of women with HIV disease for those who identify as HIV Specialists can not be overlooked. To this end, several participants volunteered to draft a Letter to the Editor addressing the gaps and controversies in research on women with HIV disease for submission to top journals.

The challenges of recruiting and maintaining enrollment of women in clinical research led the Think Tank participants to recommend the assembly of a working group to focus specifically on clinical trials reform. The Well Project will seek support for this initiative in 2004.

Universally, the Think Tank participants voiced the need to reconvene the Think Tank within one year to continue to move the research agenda forward. The Well Project welcomes discussion of the issues and concerns addressed in this document. Please send all correspondence via e-mail to contact@thewellproject.org.

TIMELINE FOR NEXT STEPS

March 2004

Disseminate Think Tank Meeting Summary Report

April 2004

Follow-up Conference Call with Think Tank Participants

1. Share updates on activities since meeting
2. Discuss known outcomes or deliverables since meeting
3. Identify Working Group participants and first conference call/meeting time
4. Provide informal update of Partner activities (formal update to happen at next Think Tank)
5. Determine Think Tank II (or Action Panel) focus

Fall 2004

Convene Women and HIV Action Panel: *Moving The Research Agenda Forward*



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