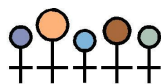


Women and HIV Think Tank

AUGUST 21-24, 2003

DEER VALLEY, UTAH

CONVENED BY



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Funding for this meeting provided through unrestricted educational grants from:
Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer-Agouron

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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APPENDICES

- a. About The Well Project
- b. Think Tank Roster
- c. Meeting Agenda
- d. Not Just a Complication, But a basic Variation (Think Tank Backgrounder)
- e. Complete List of Research Questions
 - 1. Top 10 Research Questions by Priority with Hypothesis
 - 2. Ranked by Category
 - 3. Ranked by Priority

APPENDIX A. ABOUT THE WELL PROJECT

The Well Project is a 501c3 Non-profit organization committed to reducing the total human cost of the HIV/AIDS pandemic through a unique and comprehensive focus on women.

Founded in 2001 by Dawn Averitt Bridge, The Well Project spent two years researching, designing, and building the most comprehensive and current web-based resource available for women with HIV disease and those who provide care for them. The web portal, www.thewellproject.org, which launched in September 2003, provides the latest information on living with and managing HIV disease for HIV positive women, health care providers, and advocates. The information on the The Well Project website is multi-layered and designed to facilitate communication between patients, support service providers, and clinicians by providing complex information in an accessible, conversational style. Women, now the fastest growing population of new HIV infections in the U.S. and worldwide, can log-on to www.thewellproject.org and help educate themselves and others on the challenges and solutions facing women living with HIV today.

The Well Project has identified three key areas where our expertise will have the greatest possible impact on the HIV/AIDS pandemic:

- Treatment and Care — Through the web portal, The Well Project will continue to provide accurate and timely information about the latest treatment and care available for all women living with HIV and AIDS. By focusing on the whole woman, The Well Project provides a wide range of information and tools necessary to help women, and the people who care for them, manage HIV more successfully.
- Thought and Action Leadership — The Well Project will utilize an extensive network of multidisciplinary stakeholders — comprised of clinicians, researchers, allied-health professionals, and HIV positive women — to convene meetings, generate consensus, develop and implement action plans in order to advance the state of research, treatment, education and awareness of HIV disease in women.
- Advocacy, Education and Awareness - The Well Project will work diligently to generate better public awareness and understanding of HIV and AIDS, which in time will lead to the destigmatization of HIV and AIDS in the US and abroad. The Well Project will also work to increase funding domestically and internationally to effectively address the HIV/AIDS crisis and to stem the tide of new infections and preventable deaths in both women and children.



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APPENDIX B. THINK TANK ROSTER

Women and HIV Think Tank 2003 List of Invitees and Participants
(• indicates individuals who attended the meeting)

Aberg, Judith MD
Washington University, St. Louis

Anastos, Kathryn MD •
Montefiore Medical Center, Albert Einstein College of Medicine

Anderson, Jean MD
Johns Hopkins HIV Women's Health Program

Arnsten, Julia MD, MPH
Montefiore Medical Center, Albert Einstein College of Medicine

Auerbach, Judith PhD •
American Foundation for AIDS Research

Averitt, Dawn •
The Well Project

Bardequez, Arlene MD, MPH •
New Jersey Medical School

Beckerman, Karen MD
University of Southern California

Brown, Gina MD •
Cicatelli Associates

Cargill, Victoria MD, MSCE
National Institutes of Health Office of AIDS Research



Clark, Rebecca MD, PhD
Louisiana State University Medical Center

Cohen, Mardge MD
Cook County Hospital

Cohn, Susan MD
University of Rochester Medical Center

Creagh, Terri PhD •
Clinical and Epidemiologic Research

Currier, Judith MD •
University of California Los Angeles Care Center

Denison, Rebecca •
WORLD

Dumestre, Jeanne NP •
Louisiana State University Health Sciences Center

Feinberg, Judith MD
University of Cincinnati

Futterman, Donna MD
Montefiore Medical Center, Albert Einstein College of Medicine

Gooze, Lisa
Santa Clara Valley Medical Center

Greenblatt, Ruth MD
University of California San Francisco

Hitti, Jane MD
University of Washington

Lee, Sharon MD •
Southwest Boulevard Family Health Care Services

Lindsey, Michael MD
Grady Health System

McComsey, Grace MD
Case Western Reserve University

Mildvan, Donna MD
Beth Israel Medical Center

Miller, Veronica PhD •
Forum for Collaborative HIV Research

Mitchell-Samon, LeVonne MD •
University of Florida

Mudersspach, Laila MD
University of Southern California

Neumann, Meg MD
University of California San Francisco

Nielsen, Karin MD •
University of California Los Angeles

Norman, Nancy MD, MPH
Fenway Community Health

Palmore, Melody MD
Grady Health System and Emory University

Pavia, Andrew MD •
University of Utah

Poteat, Tonia MMSc, PA-C •
Grady Health System

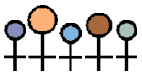
Saint-Cyr, Marie
Iris House

Schoenbaum, Ellie MD
Montefiore Medical Center, Albert Einstein College of Medicine

Smith, Kimberly MD, MPH
Rush-Presbyterian-St. Luke's Medical Center

Squires, Kathleen MD
University of Southern California

Stone, Valerie MD, MPH
Massachusetts General Hospital



Sweet, Donna MD
University of Kansas School of Medicine

Trauscht VanHorne, Jennifer MD •
University of Utah

Tuomala, Ruth MD
Brigham and Women's Hospital

Veronese, Fulvia, PhD •
National Institutes of Health

Young, Mary MD
Georgetown University

Zorilla, Carmen MD
University of Puerto Rico School of Medicine

Women and HIV Think Tank 2003 List of Pharmaceutical Representatives

Susan Conner
Kay Mitzel
Agouron-Pfizer

Christopher Dezii
Donne Newbury
Bristol-Myers Squibb

Keri Oberg
Boehringer Ingelheim

David Frey
Christina Hill-Zabala
Karen Moldt
Kim Williams
GlaxoSmithKline



APPENDIX C. MEETING AGENDA

WOMEN AND HIV THINK TANK

Thursday, August 21 – Sunday, August 24 2003

Stein Erikson Lodge, Deer Valley, Utah

Thursday, August 21, 2003

Noon – 6:00 Optional pre-meeting activities (hike, swim, spa, massage, etc)

7:00 – 9:00 Welcome Reception and Dinner (also optional)

Friday, August 22, 2003

7:30 – 8:30 Breakfast

8:30 – 9:30 Welcome and Framing of the Meeting

Introductions and Meeting Objectives

9:30 – 10:00 Women and HIV – Review of the Backgrounder

A comprehensive review of the literature on gender and HIV to lay the groundwork for the rest of the meeting.

10:00 – 10:15 Break

10:15 – 11:45 Gaps and Controversies

A series of presentations outlining the gaps and controversies in research on women and HIV related to one of the following topic areas:

- Treatment
- Complications and Co-morbidities
- Reproductive health/fertility
- Behavioral Issues

11:45 – 12:30 Discussion

12:30 – 1:30 Lunch

1:30 – 3:30 First Partner Segment: Pfizer-Agouron

3:30 – 4:00 Break (Snack)

4:00 – 6:00 Second Partner Segment: GlaxoSmithKline

7:00 Dinner Function

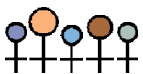


Saturday, August 23, 2003

7:30 – 8:30	Breakfast
8:30 – 9:00	Welcome Back/Plan for the Day
9:00 – 11:00	Third Partner Segment: Bristol Myers Squibb
11:00 – 12:30	Partner Session Implications (Closed Session)
12:30 – 1:30	Lunch
1:30 – 2:15	Group Interaction – Prisoners' Dilemma Exercise
2:15 – 2:45	Target Gaps and Controversies
2:45 – 3:00	Burning Research Questions
3:00 – 4:00	Small Groups – Development of Research Questions
4:00 – 4:15	Break (Snack)
4:15 – 5:15	Large Group – Discussion of Research Questions
5:15 – 6:00	Criteria Discussion
7:30	Dinner Function

Sunday, August 24, 2003

7:30 – 8:30	Breakfast
8:30 – 10:30	Protocol Concepts
10:30 – 10:45	Break
10:45 – 12:15	Discussion/Next Steps/Action Items
12:15 – 12:30	Closing
12:30	Lunch (box lunch)



APPENDIX E. COMPLETE LIST OF RESEARCH QUESTIONS

1. TOP 10 RESEARCH QUESTIONS BY PRIORITY WITH HYPOTHESIS

RESEARCH QUESTION	DOTS	HYPOTHESIS
What are the effects of cyclic changes on antiretroviral therapy and vice versa; what are the pharmacokinetics/interactions of HRT, commonly used oral contraceptives, 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?	43	Hormonal variation in women impacts antiretroviral efficacy
What are the drug-drug interactions with exogenous and endogenous hormones and other drugs taken by HIV + women	18	Hormonal variation in women impacts antiretroviral efficacy
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?	18	The efficacy of drug therapy varies with sex and race
Microbicide research; vaginal washes (big pharma?)	18	Female-controlled methods of STD prevention and contraception may significantly impact the lives of both HIV- and HIV+ women
What is the natural history of Hepatitis-C in women with HIV?	17	The natural history of Hepatitis-C in women with HIV may be different than in men or in HIV-negative women.



RESEARCH QUESTION	DOTS	HYPOTHESIS
What are the safe ways to become pregnant if a woman has an HIV + partner; how safe is sperm washing?	15	Safe and effective conception technologies for sero-discordant and sero-positive couples will reduce risk of horizontal and vertical transmission
Do hormonal levels (menstrual cycles, hormonal contraception, HRT, pregnancy) affect viral load or CD4; 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, T4 and drugs	15	Hormonal variation in women impacts antiretroviral efficacy
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?	14	The biology of ARV in women may be different and therefore may impact efficacy, toxicity, dosage and QOL
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)?	14	The emergence of resistance may negatively impact long-term maternal health and effectiveness of subsequent treatment
Metabolic Question – what are the treatment implications; what is effective...what are the predictors...lipo-atrophy	14	Sex differences in metabolic complications... treatment...



APPENDIX E. COMPLETE LIST OF RESEARCH QUESTIONS

2. Research Questions by Category

TREATMENT

DOT RANKING

What are the effects of cyclic changes on antiretroviral therapy and vice versa; what are the pharmacokinetics/interactions of HRT, commonly used oral contraceptives, 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?	43
What are the drug-drug interactions with exogenous and endogenous hormones and other drugs taken by HIV + women?	18
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?	18
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?	14
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)?	14
Should drug dosages be different for women and for people of different sizes?	13
Are once/day regimens effective and preferable for adolescents with HIV infection; What are the treatment issues, including adherence, for adolescents; what strategies and treatments are best for adolescents?	8
When is the optimal time to start HAART in women – by CD4 count, viral load; is there a difference by race, with lower viral load in African-Americans; is a CD4 count threshold alone adequate?	7

TREATMENT (continued)	DOT RANKING
How do the most commonly used herbal products (Echinacea, milk thistle, St. John's Wort) effect the immune system and interact with antiretroviral agents?	7
What are the effects of ART and HIV+ women's sexuality, including desire, sense of identity as a sexual person, sexual function and sexual satisfaction?	6
Hormone replacement – to whom; what are the criteria; what should we use; what are the potential risks?	4
How do drugs of abuse interact with antiretroviral agents?	4
How do non-progressors control infection; how can this information help us identify effective, less toxic treatments for non-progressives?	2
What interactions can help improve women's adherence to ART?	2
What happens after a woman stops drugs postpartum (for women using drugs for preventing transmission)?	0

REPRODUCTIVE HEALTH

	DOT RANKING
What are the safe ways to become pregnant if a woman has an HIV + partner; how safe is sperm washing?	15
Is EFV superior or equivalent to NVP in prevention of late postnatal transmission; can EFV be used in this setting?	9
What is the best way to prevent transmission during breastfeeding?	9
Biology and immunology of the reproductive tract of HIV+ and HIV- women and girls	8
What is the optimal way to dose each drug in pregnancy?	8
What is the impact of breastfeeding on the overall health of HIV+ women	4
What are the risks and benefits of different contraceptive methods for HIV+ women; what are the drug interactions, genital viral shedding, infections (patch, IUD, cap and tubal block)	4
What are the optimal regimens for women who want to get pregnant?	4

REPRODUCTIVE HEALTH (continued)	DOT RANKING
What happens when there are different drug interactions or background NRTI's	3
What is the pharmacokinetics of most recently developed antiretroviral therapy in breast milk, pregnant women and neo-natals?	3
Define HIV impact on fertility and pregnancy success	3
How do we increase access to assisted reproductive technology for women with HIV?	3
Assessing osteoporosis and osteopenia in ARV therapy in HIV- exposed infants	2
What are AER of use of emergency contraception in protease inhibitor and non-protease inhibitor regimens; is emergency contraception (with and without condoms) a viable option for birth control for women on HAART?	2
What is the impact of prior intermittent treatment for mother to child transmission on subsequent pregnancy risk?	2
How does the CD4 and viral load at the time of contraception affect the outcome of pregnancy for mother and baby; is there a cutoff for each parameter where pregnancy is not advised?	2
What determines the HIV+ woman's likelihood of accepting ART in pregnancy?	1
What determines an HIV+ mom's likelihood of continuing ART after delivery?	1
How to prevent development of NVP resistance in women in developing countries; should we provide NVP to infants only shortly after delivery?	0
What is the optimal treatment for pregnant women at risk of toxo/CMV pregnancy for her and transmission for the infant?	0
Compartmentalization of each individual drug and combination	0
Look at impact of fertility drugs on drug levels and on HIV- hormone manipulation for ovulation and uterine lining?	0
Can short-course triple drug regimens prevent emergence of NNRTI resistance in pregnancy?	0



COMORBIDITY

DOT RANKING

What is the natural history of Hepatitis-C in women with HIV?	17
What is the optimal approach to screening and treatment of depression in women with HIV; what is the most effective treatment for depression; does treatment impact HIV disease progression; what is the psychiatric impact of treatment; is HAART associated with increased depressive symptoms in women?	13
Why are HIV positive people dying suddenly with no warning?	11
Why is drug-induced liver injury and hepatic death more prevalent in women?	8
Is diabetes a complication of HIV infection, or is it only related to specific antiretroviral agents?	8
What makes accessing mental health care acceptable to people of color; what are the best mental health and substance abuse treatment approaches for people of color?	6
HCV/HIV/diabetes	4
How do drugs of abuse affect women with HIV immune function and viral dynamics in vitro and in vivo?	3
Prevalence and consequences of non-alcoholic hepatic steatosis in HIV	3
Does HIV cause autoimmune disease in women; does autoimmune disease influence natural history and susceptibility?	3
Hepatitis-C – is C-section always indicated?	3
What are the drug interactions between various antiretrovirals and crack, alcohol...	2
How do you treat high-grade anal lesions?	2
What is the best way to treat/manage cervical dysplasia; what is the best intervention for cervical high grade SIL?	2
Prevention strategies and implementation of screening strategies for cervical cancer in HIV infected women in developing countries	1
Are we seeing increased cancer risks among HIV+ women – breast cancer, non-genital cancers, ovarian cancer...	0

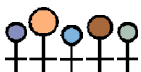
COMORBIDITY (continued)	DOT RANKING
What are the impacts of co-infections on treatment outcomes and progression to disease in women	0

COMPLICATIONS	DOT RANKING
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Do differences by sex and race in drug transport and metabolism alter the likelihood of specific adverse effects of medications – lipo-atrophy, lipo-hypertrophy, lipids, insulin resistance, rash, etc.	13
Can lipo-atrophy be prevented by the use of antiretroviral regimens not associated (...) mitochondrial toxicity	13
What treatments are effective for metabolic complications (e.g. statins vs. diet, exercise for lipids); can a low-carbohydrate diet reduce lipid and fat distribution problems; are there renal changes?	12
For the metabolic complications, what is the influence of HIV and of HIV treatment (specific drugs) and age, sex, race; effects of individual drugs on metabolic changes	11
Are women with HIV infection at increased risk of cardiovascular disease; can this risk be reduced?	10
What are predictors of lactic acidosis?	9
Are lipo-atrophy and lipo-dystrophy related to dose, sex or ethnicity? (ask pharmaceutical companies to combine their data sets)	7
Meta-analysis of CVD and HIV (with or without ART) – to get to guidelines; (combine large cohort data sets)	3
Is RBV contraindicated in someone who has had nucleoside associated lactic acidosis from HAART	0

PREVENTION	DOT RANKING
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Microbicide research; vaginal washes (big pharma?)	18
What are the barriers to participation in HIV vaccine trials for women at risk for HIV?	13

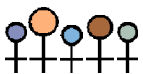


PREVENTION (continued)	DOT RANKING
How do we insure adequate screening for HIV in women?	12
Prevention of acquisition of HIV disease in prepubescent girls; behavioral interventions and vaccine trials; what is the most effective way to reach adolescents with HIV prevention messages that are likely to be translated into behavior change?	11
What motivates men to be sexually responsible?	8
What is the risk of HIV infection and transmission during menopause?	8
What are the best venues for imparting prevention information strategies to HIV positive women (i.e. within clinical care, in other community institutions)?	6
Efficacy of post-exposure prophylaxis for women after rape or sex with HIV+ partner (what to use and for how long)	4
Should acyclovir be given prophylactically to all women with HSV?	4
How risky is oral (mouth/vagina) sex man-woman or woman-woman	3
Define culture-specific risks for HIV (i.e. cultural practices in specific communities)	3
What are the most compelling reasons that HIV+ women have for adopting or not adopting HIV prevention strategies?	1
What are the most effective transmission prevention methods for women who have sex with women?	0

OTHER	DOT RANKING
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Do hormonal levels (menstrual cycles, hormonal contraception, HRT, pregnancy) affect viral load or CD4; 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, T4 and drugs	15
How can we enroll more women in the acute infection network; acute and primary infection in women – how to identify women and what is the pathogenesis?	13
How do we ensure that clinical studies are powered to perform analysis by sex?	13
Where sex differences are observed (e.g. in clinical outcomes, natural history, response to treatment), why do they exist?	9

OTHER (continued)	DOT RANKING
How can the traditional women's health organization be convinced to become more involved in advocacy around women and HIV?	9
Develop valid measure of gender that can be integrated in HIV research	8
What is the most efficient and effective method to get research results to people who provide care for women with HIV?	4
What are the 'normative' values for people of color (CD4, WBC, PMNS) and how does that affect acquisition of HIV and the natural history of HIV and or HCV; combine HIV- groups in cohort studies that include an HIV- group; create a single data base for examining normative values for women (by ethnicity and co-morbidities)	2
What are the changes in non-progressors women vs. men; is there a difference in non-progressors (men vs. women);	1
What is the prevalence of anal intercourse among women HIV+ and HIV-?	1
How can HIV be de-stigmatized for women	0
Are guidelines actually followed by HIV treaters?	0



APPENDIX E. COMPLETE LIST OF RESEARCH QUESTIONS

3. Complete list of research questions by ranked priority

RESEARCH QUESTIONS	DOT RANKING
What are the effects of cyclic changes on antiretroviral therapy and vice versa; what are the pharmacokinetics/interactions of HRT, commonly used oral contraceptives, 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?	43
What are the drug-drug interactions with exogenous and endogenous hormones and other drugs taken by HIV+ women	18
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?	18
Microbicide research; vaginal washes (big pharma?)	18
What is the natural history of Hepatitis-C in women with HIV?	17
What are the safe ways to become pregnant if an HIV+ woman has an HIV+ partner; how safe is sperm washing?	15
Do hormonal levels (menstrual cycles, hormonal contraception, HRT, pregnancy) affect viral load or CD4; 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, T4 and drugs	15
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?	14

RESEARCH QUESTIONS (continued)	DOT RANKING
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)?	14
Should drug dosages be different for women and for people of different sizes?	13
What is the optimal approach to screening and treatment of depression in women with HIV; what is the most effective treatment for depression; does treatment impact HIV disease progression; what is the psychiatric impact of treatment; is HAART associated with increased depressive symptoms in women?	13
Do differences by sex and race in drug transport and metabolism alter the likelihood of specific adverse effects of medications ñ lipo-atrophy, lipo-hypertrophy, lipids, insulin resistance, rash, etc.	13
Can lipo-atrophy be prevented by the use of antiretroviral regimens not associated (...) mitochondrial toxicity	13
What are the barriers to participation in HIV vaccine trials for women at risk for HIV?	13
How can we enroll more women in the acute infection network; acute and primary infection in women ñ how to identify women and what is the pathogenesis?	13
How do we ensure that clinical studies are powered to perform analysis by sex?	13
What treatments are effective for metabolic complications (e.g. statins vs. diet, exercise for lipids); can a low-carbohydrate diet reduce lipid and fat distribution problems; are there renal changes?	12
How do we insure adequate screening for HIV in women?	12
Why are HIV positive people dying suddenly with no warning?	11
For the metabolic complications, what is the influence of HIV and of HIV treatment (specific drugs) and age, sex, race; effects of individual drugs on metabolic changes	11
Prevention of acquisition of HIV disease in prepubescent girls; behavioral interventions and vaccine trials; what is the most effective way to reach adolescents with HIV prevention messages that are likely to be translated into behavior change?	11

RESEARCH QUESTIONS (continued)	DOT RANKING
Are women with HIV infection at increased risk of cardiovascular disease; can this risk be reduced?	10
Is EFV superior or equivalent to NVP in prevention of late postnatal transmission; can EFV be used in this setting?	9
What is the best way to prevent transmission during breastfeeding?	9
What are predictors of lactic acidosis?	9
Where sex differences are observed (e.g. in clinical outcomes, natural history, response to treatment), why do they exist?	9
How can the traditional women's health organization be convinced to become more involved in advocacy around women and HIV?	9
Are once/day regimens effective and preferable for adolescents with HIV infection; What are the treatment issues, including adherence, for adolescents; what strategies and treatments are best for adolescents?	8
Biology and immunology of the reproductive tract of HIV+ and HIV- women and girls	8
What is the optimal way to dose each drug in pregnancy?	8
Why is drug-induced liver injury and hepatic death more prevalent in women?	8
Is diabetes a complication of HIV infection, or is it only related to specific antiretroviral agents?	8
What motivates men to be sexually responsible?	8
What is the risk of HIV infection and transmission during menopause?	8
Develop valid measure of gender that can be integrated in HIV research	8
When is the optimal time to start HAART in women ñ by CD4 count, viral load; is there a difference by race, with lower viral load in African-Americans; is a CD4 count threshold alone adequate?	7
How do the most commonly used herbal products (Echinacea, milk thistle, St. John's Wort) effect the immune system and interact with antiretroviral agents?"	7

RESEARCH QUESTIONS (continued)	DOT RANKING
Are lipo-atrophy and lipo-distrophy related to dose, sex or ethnicity? (ask pharmaceutical companies to combine their data sets)	7
What are the effects of ART and HIV+ women's sexuality, including desire, sense of identity as a sexual person, sexual function and sexual satisfaction?	6
What makes accessing mental health care acceptable to people of color; what are the best mental health and substance abuse treatment approaches for people of color?	6
What are the best venues for imparting prevention information strategies to HIV positive women (i.e. within clinical care, in other community institutions)?	6
Hormone replacement \bar{n} to whom; what are the criteria; what should we use; what are the potential risks?	4
How do drugs of abuse interact with antiretroviral agents?	4
What is the impact of breastfeeding on the overall health of HIV+ women	4
What are the risks and benefits of different contraceptive methods for HIV+ women; what are the drug interactions genital viral shedding, infections (patch, IUD, cap and tubal block)	4
What are the optimal regimens for women who want to get pregnant?	4
HCV/HIV/diabetes	4
Efficacy of post-exposure prophylaxis for women after rape or sex with HIV+ partner (what to use and for how long)	4
Should acyclovir be given prophylactically to all women with HSV?	4
What is the most efficient and effective method to get research results to people who provide care for women with HIV?	4
What happens when there are different drug interactions or background NRTI's	3
What is the pharmacokinetics of most recently developed antiretroviral therapy in breast milk, pregnant women and neo-natals?	3
Define HIV impact on fertility and pregnancy success	3

RESEARCH QUESTIONS (continued)	DOT RANKING
How do we increase access to assisted reproductive technology for women with HIV?	3
How do drugs of abuse affect women with HIV immune function and viral dynamics in vitro and in vivo?	3
Prevalence and consequences of non-alcoholic hepatic steatosis in HIV	3
Does HIV cause autoimmune disease in women; does autoimmune disease influence natural history and susceptibility?	3
Hepatitis-C – is C-section always indicated?	3
Meta-analysis of CVD and HIV (with or without ART) – to get to guidelines; (combine large cohort data sets)	3
How risky is oral (mouth/vagina) sex man-woman or woman-woman	3
Define culture-specific risks for HIV (i.e. cultural practices in specific communities)	3
How do non-progressors control infection; how can this information help us identify effective, less toxic treatments for non-progressives?	2
What interactions can help improve women's adherence to ART?	2
Assessing osteoporosis and osteopenia in ARV therapy in HIV-exposed infants	2
What are AER of use of emergency contraception in protease inhibitor and non-protease inhibitor regimens; is emergency contraception (with and without condoms) a viable option for birth control for women on HAART?	2
What is the impact of prior intermittent treatment for mother to child transmission on subsequent pregnancy risk?	2
How does the CD4 and viral load at the time of contraception affect the outcome of pregnancy for mother and baby; is there a cutoff for each parameter where pregnancy is not advised?	2
What are the drug interactions between various antiretrovirals and crack, alcohol...	2
How do you treat high-grade anal lesions?	2

RESEARCH QUESTIONS (continued)	DOT RANKING
What is the best way to treat/manage cervical dysplasia; what is the best intervention for cervical high grade SIL?	2
What are the 'normative' values for people of color (CD4, WBC, PMNS) and how does that affect acquisition of HIV and the natural history of HIV and or HCV; combine HIV- groups in cohort studies that include an HIV- group; create a single data base for examining normative values for women (by ethnicity and co-morbidities)	2
What determines the HIV woman's likelihood of accepting ART in pregnancy?	1
What determines an HIV+ mom's likelihood of continuing ART after delivery?	1
Prevention strategies and implementation of screening strategies for cervical cancer in HIV infected women in developing countries	1
What are the most compelling reasons that HIV+ women have for adopting or not adopting HIV prevention strategies?	1
What are the changes in non-progressors women vs. men; is there a difference in non-progressors (men vs. women);	1
What is the prevalence of anal intercourse among women HIV+ and HIV-?	1
What happens after a woman stops drugs postpartum (for women using drugs for preventing transmission)?	0
How to prevent development of NVP resistance in women in developing countries; should we provide NVP to infants only shortly after delivery?	0
What is the optimal treatment for pregnant women at risk of toxo/CMV pregnancy for her and transmission for the infant?	0
Compartmentalization of each individual drug and combination	0
Look at impact of fertility drugs on drug levels and on HIV ñ hormone manipulation for ovulation and uterine lining?	0
Can short-course triple drug regimens prevent emergence of NNRTI resistance in pregnancy?	0
Are we seeing increased cancer risks among HIV + women – breast cancer, non-genital cancers, ovarian cancer...	0

RESEARCH QUESTIONS (continued)	DOT RANKING
What are the impacts of co-infections on treatment outcomes and progression to disease in women	0
Is RBV contraindicated in someone who has had nucleoside associated lactic acidosis from HAART	0
What are the most effective transmission prevention methods for women who have sex with women?	0
How can HIV be de-stigmatized for women	0
Are guidelines actually followed by HIV treaters?	0

