Meeting Report

Sex and Gender Differences in ARV-Based Prevention Research

An Affiliated Event at CROI 2013
Acknowledgements

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SEX AND GENDER DIFFERENCES IN ARV-BASED PREVENTION RESEARCH

Introduction

The Promise and Challenges of ARV-Based Prevention

Over the past five years, a number of ecological and clinical studies have demonstrated that HIV antiretroviral (ARV) drugs, initially developed to treat HIV infection, are also effective at reducing risk for HIV transmission. The landmark HIV Prevention Trials Network (HPTN) 052 randomized controlled trial of serodiscordant partners in six countries found that combination antiretroviral therapy (ART) reduced secondary transmission to uninfected partners by 96%1. Trials using ARV-based prevention interventions among HIV-negative populations at increased risk for HIV infection, administered through a variety of delivery mechanisms and drug formulations, have demonstrated widely varying levels of efficacy, ranging from non-efficacy (in the Fem-PrEP and VOICE trials) to 75% efficacy (in the Ugandan Partners PrEP study) [see Table 1: PrEP Clinical Trials]. While further data analysis is providing some answers regarding the potential underlying factors for these discrepancies, many questions remain, including whether the protective benefit will vary among different populations at risk for HIV infection and via different routes of transmission. The ARV-based prevention field has seen both exhilaration and disappointment as various studies report their findings. Of critical importance in the drive to end AIDS is the need for a female-controlled method (or methods) that will be effective at preventing HIV infection among women.

Women represent almost 50% of the global epidemic and more than 60% in the hyperendemic settings of sub-Saharan Africa2. The holy grail of a discrete, highly efficacious, female-controlled HIV prevention method would be of incalculable benefit in reducing vulnerability to HIV infection among women and accelerating progress to end the epidemic. With this backdrop in mind, the International AIDS Society’s Industry Liaison Forum (IAS-ILF) hosted a meeting in conjunction with the 2013 Conference on Retroviruses and Opportunistic Infections (CROI 2013) in Atlanta, USA, to address sex and gender differences in ARV-based prevention research. Advocates, industry representatives, investigators and technical experts from a range of organizations gathered to review scientific data from completed trials, provide updates on current or planned Phase III clinical trials, and review the compounds that show promise in preclinical stages of development.

Over the past several years, the IAS-ILF has hosted multi-stakeholder meetings and satellite sessions that convene experts and advocates working on HIV research related to women and children. In early 2010, following an extensive literature review and consultation process, the IAS-ILF released a Consensus Statement, Asking the Right Questions: Advancing an HIV Research Agenda for Women and Children [see Figure 1: Consensus Statement]. The statement was endorsed by a wide range of organizations, including UN agencies, non-governmental organizations and community organizations, and offered a series of recommendations on research priorities related to women and children. Since then, the IAS-ILF has hosted a number of meetings to follow up on those recommendations, with the CROI 2013 meeting focusing on sex and gender differences in the rapidly evolving field of ARV-based prevention.


CROI Meeting Report 2013

http://www.iasociety.org/ilf.aspx
**Contextualizing TasP and PrEP**

Cate Hankins (Amsterdam Institute for Global Health and Development, The Netherlands) provided a brief overview of studies that evaluated the efficacy of both early treatment for prevention (T4P), also known as treatment as prevention (TasP), and pre-exposure prophylaxis (PrEP) clinical trials. She urged researchers and advocates to consider biomedical interventions within the broader context of women’s lives, underscoring the need for an optimal “combination prevention” approach for TasP and PrEP: a package of interventions designed to address socio-economic, behavioural and biological vulnerability to HIV for women in a variety of settings. She emphasized that the full potential of TasP and PrEP will be realized if delivered in combination with well-established, evidence-informed interventions, such as medical male circumcision, male and female condoms, and early diagnosis and treatment of sexually transmitted infections (STIs) and opportunistic infections [see Box 1: Combination HIV Prevention].

The potential multiplier effect of both ARV-based prophylaxis methods and expanded coverage of ART in reducing HIV incidence could be considerable. A recent prospective cohort study (2004-2011) in KwaZulu-Natal, South Africa, found that the acquisition risk was reduced by 38% in communities with 30-40% ART coverage compared with communities with less than 10% coverage, demonstrating the preventive impact of ART rollout at a population level. With PrEP, of course, key requirements will include ensuring the right intervention is available in the right biological compartment (e.g., in vaginal or rectal mucosa) at the right time to the right population. The delivery approach will also have to address some of the adherence challenges that have contributed to some of the disappointing PrEP results to date, including the VOICE trial results released at CROI 2013 after the IAS-ILF meeting.

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**Box 1: Combination HIV Prevention**

- Evidence-informed, human rights-based and context-specific, tailored to local epidemics and needs
- Fully engages affected communities, promoting human rights and gender equality
- Operates synergistically on multiple levels – individual, family and society
- Invests in decentralized and community responses
- Flexible: adapts to changing epidemic patterns and rapidly deploys innovations
- Combines biomedical, behavioural and structural elements to address immediate risks, underlying vulnerabilities and pathways that link them

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José Gerardo García-Lerma (Centers for Disease Control and Prevention, USA) provided insights using animal models into variability in drug penetration in mucosal tissues (vaginal and rectal) and biological factors that might potentially reduce the efficacy of PrEP. Macaque studies show that although the PK profiles of emtricitabine (FTC) and tenofovir (TFV) are different in the vaginal and rectal mucosa, intermittent PrEP with an FTC/tenofovir disoproxil fumarate (TDF) combination is effective against both routes of infection.

An additional consideration is the strong dose response relationship between depot medroxyprogesterone acetate (DMPA), a hormonal contraceptive, and its impact on thinning of vaginal epithelium, potentially increasing the risk of infection. However, data from a trial where DMPA was co-administered with FTC/TDF did not show a reduction in the prophylactic efficacy of FTC/TDF in macaques. This is particularly important given the wide usage of DMPA in many HIV endemic settings. Preclinical studies may also shed light on the distribution of antiretroviral drugs in rectal tissues after vaginal product application (or vice versa), a term also known as bi-directional dosing. These studies may help understand if the concentrations of drug achieved in the vaginal and rectal compartments are sufficient to prevent infection. Animal model studies with other potential candidates for ARV-based prevention, such as the CCR5 inhibitor maraviroc, are ongoing and a trial of maraviroc alone or in combination with FTC/TDF is currently underway.

### Table 1: PrEP clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRISA 004 South Africa</td>
<td>Women</td>
<td>889</td>
<td>39% [CI=6-60] efficacy, coitally dependent vaginal TFV gel</td>
</tr>
<tr>
<td>iPrEx Brazil, Ecuador, Peru, South Africa, Thailand, USA</td>
<td>Gay men, other MSM, transgender women</td>
<td>2,499</td>
<td>44% [CI=15-63] efficacy, daily oral FTC/TDF</td>
</tr>
<tr>
<td>TDF2 Study Botswana</td>
<td>Men and women</td>
<td>1,200</td>
<td>62% [CI=22-83] efficacy, daily oral FTC/TDF</td>
</tr>
<tr>
<td>Partners PrEP Study Kenya, Uganda</td>
<td>Serodiscordant couples</td>
<td>4,758</td>
<td>67% [CI=44-81] efficacy, daily oral TDF; 75% [CI=55-87] efficacy, daily oral FTC/TDF</td>
</tr>
<tr>
<td>FEM-PrEP Kenya, South Africa, Tanzania</td>
<td>Women</td>
<td>1,950</td>
<td>Futility of daily oral FTC/TDF</td>
</tr>
<tr>
<td>VOICE South Africa, Uganda, Zimbabwe</td>
<td>Women</td>
<td>5,029</td>
<td>Futility of daily oral TDF; Futility of daily vaginal TFV gel; Futility of daily oral FTC/TDF</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study Thailand</td>
<td>Injection drug users</td>
<td>2,400</td>
<td>Daily oral TDF: ongoing; Results expected by June 2013</td>
</tr>
<tr>
<td>FACTS 001 South Africa</td>
<td>Women</td>
<td>2,900</td>
<td>Coitally dependent vaginal TFV gel: enrolling; Results expected in 2015</td>
</tr>
</tbody>
</table>

5. Tenofovir exists as three different forms. The prodrug (tenofovir disoproxil fumarate, TDF) is hydrolysed to tenofovir (TFV) which is then phosphorylated to tenofovir diphosphate (TFV-DP), the active form for which intracellular levels are measured clinically. TDF is administered orally while TFV is administered in topical gels.


Sex and Gender in Clinical Trials of PrEP and TasP

Patrick Ndase (University of Washington, USA) reviewed data from PrEP studies conducted to date, noting the conflicting efficacy data from trials over the past three years [see Table 1: PrEP clinical trials]. Data analysis of several trials of PrEP indicated a strong correlation between high levels of adherence and the protective efficacy of the intervention, as well as significant discrepancies between self-reported measures of adherence and actual plasma concentrations of drug. Patrick noted the higher levels of adherence among individuals receiving ARVs for treatment, suggesting distinct (and more compelling) motives for adherence that may be less immediate or pressing for those who are HIV negative. A recent Soweto, South Africa, study, for example, suggested that even among treatment-eligible HIV-positive individuals, willingness to start ART was closely tied to whether they felt well or not (irrespective of CD4+ cell count)9.

Patrick raised the possibility that PrEP efficacy for men and women may be comparable, but that adherence among women may be more fragile due to factors related to gender inequality. A number of questions regarding gender-based differences arise from social, economic and cultural contexts faced by women. Intriguingly, in a sub-group analysis of women in the Partners PrEP trial, higher levels of efficacy were reported among women taking TDF (71% efficacy; 37-87% CI) than on the combination compound of TDF/FTC (56% efficacy; 27-84% CI). Also worth noting are data from a sub-group analysis of individuals in the iPrEx and Partners PrEP trials; for those with high levels of drug concentration in blood plasma, the protective benefit was dramatically higher in trial participants with detectable tenofovir (92% and 90% protection in the two studies, respectively) [see Figure 2: Plasma tenofovir levels and HIV protection]. Again, this underscores the role that adherence plays in determining the extent of protective benefit of ARV-based prevention methods.

Patrick concluded his presentation by noting that the data suggest that ARV-based oral prophylaxis may result in comparable preventive benefits for both women and men, but that women may encounter more difficulty with adherence, for a variety of reasons. He pointed to the need for behavioural and other social science research to address questions, including:

- How to best implement prevention trials among women (particularly younger women)
- How women perceive these trials (particularly regarding motivation for trial participation)
- How to best devote efforts to women’s HIV prevention needs
- Whether or not young women will use PrEP if offered.

In discussion, colloquium participants noted that gender differences also play out in men who present significantly later in disease progression than women and have poorer levels of ART coverage (a more than 10% worldwide gap in the 2012 UNAIDS Global Report on AIDS). Participants noted that the need to develop strategies to get men diagnosed and into care earlier also has implications for women’s HIV vulnerability, given men’s higher viral load and probability of transmission to female sexual partners in later stages of disease progression. Finally, participants noted that unwillingness to start ART earlier in the disease course may present additional barriers to reducing secondary transmission. The rollout and high uptake of Option B+ (providing lifelong ART to HIV-positive pregnant women, irrespective of CD4+ cell count) may provide only a partial picture of overall willingness to start ART early, given incentives for both maternal and infant health9.

Figure 2: Plasma tenofovir levels and HIV protection

<table>
<thead>
<tr>
<th>% with tenofovir detected</th>
<th>HIV protection: detection vs. no detection of tenofovir</th>
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<tbody>
<tr>
<td></td>
<td>Seroconverters</td>
</tr>
<tr>
<td>iPrEx10</td>
<td>9%</td>
</tr>
<tr>
<td>Partners PrEP FTC/TDF arm11</td>
<td>25%</td>
</tr>
</tbody>
</table>

The Importance of Gender on Acceptability, Impact of Risk Behaviour or Compensation for TasP and PrEP

Kate MacQueen (FHI 360, USA) provided a much-needed social science perspective to the discussion, highlighting the need for a systematic examination of gender norms and inequalities that have implications for determining the most effective approaches for delivering ARV-based prevention interventions. Studies have suggested variances between self-reported risk perception and actual risk among women, with social constructs regarding “faithfulness” among couples not necessarily equating with sexual exclusivity. She also noted the evidence of “seasons of risk”, i.e. periods of time, such as adolescence, post-separation/divorce or motherhood, when women may be particularly vulnerable to HIV infection. A community consultation of microbicide acceptability undertaken by FHI 360 in four regions of Kenya found that different populations of women had different motivations for using prevention methods. She summarized the reasons for a female-controlled prevention method like PrEP:

- Acute infection of partners
- Refusal of partners to learn/divulge their HIV status
- Delayed treatment of infected partners
- Poor adherence to treatment by infected partners
- Unknowns regarding how to balance early treatment for prevention with optimal treatment for health.

Kate emphasized the need to undertake meaningful consultations with populations vulnerable to HIV infection (and other STIs) in order to establish baseline information on the most appropriate prevention methods and service delivery approaches for sub-populations of women and their partners. She also noted the need for social sciences research on ethical considerations in biomedical prevention trials, which has been a controversial issue in past PrEP trials. Also highlighted was the need for data from clinical trials to be disaggregated by sex and for gender considerations regarding the relative preventive benefits for women and men in early treatment for prevention trials (TasP) and PrEP trials to be incorporated in the overall analysis of trial results.

In discussion, participants noted the need for HIV prevention trials to make concerted efforts to enrol younger women, who are particularly vulnerable to HIV infection, and to ensure that the broader cultural, social and economic context of women are addressed in the planning, enrolment and post-hoc data analysis of trials evaluating biomedical prevention interventions.
TasP and/or ARV-based Prevention: How Many Eggs in Which Basket?

Colloquium participants engaged in a lively debate regarding the extent to which the ARV-based prevention field should focus on accelerating ART rollout (thereby reaping both the treatment and prevention benefits of increased ART coverage) or whether research efforts and investment in ARV-based prevention interventions for HIV-negative women, such as ARV-based topical gels, vaginal rings and oral prophylaxis, should be redoubled. Debaters were assigned a position (either “pro” or “con”) for the sake of the debate, which might have been different from their own personal opinion.

**Pro**

Those arguing that the focus should be on TasP noted the high levels of preventive protection afforded by ART in reducing HIV transmission at both an individual and population level, referencing the dramatic results of HPTN 052. The focus, this argument goes, should be on how to better reach key populations with HIV diagnostic, care and treatment services and thereby maximize the proven preventive benefits of ART. Study findings to date have suggested that early ART is more efficacious than ARV-based PrEP interventions. Bob Grant noted the robust clinical evidence on when to initiate ART to maximize both its treatment and preventive benefits, contrasting this with the more limited knowledge regarding how and when to use PrEP. Bob Grant and Anna Zakowicz argued that the HIV research field needed to be pragmatic about the inevitable issue of resources: in a context of limited (and increasingly constrained) research funding and resources for health, the priority should be on scaling up ART to treatment-eligible people and on redoubling efforts to encourage earlier diagnosis and uptake in care, treatment and support as the most effective strategy to reduce HIV acquisition among women. Some participants suggested that the focus should be on prioritizing the scale up of ART to key populations and then shift to expanding the resource-intensive task of biomedical, behavioural and social science research investments required to identify the most efficacious and effective approaches to ARV-based interventions for women.

A recent modelling study on their combined and relative merits found that concurrent delivery of TasP and PrEP could make a substantial and cost-effective impact on the epidemic; providing PrEP to the uninfected partner could be at least as cost-effective as initiating ART earlier in the infected partner. This would be the case if the annual cost of PrEP is less than 40% of the annual cost of ART and PrEP is more than 70% effective. To date, however, only one PrEP study has demonstrated an efficacy range that reaches 70% (the Partners PrEP trial in Uganda). It is thus unlikely that concurrent delivery of TasP and PrEP would be more effective than scale up of TasP.

**Con**

Linda Gail-Bekker and Dázon Dixon Diallo challenged the “false bifurcation” of treatment and prevention, emphasizing the need to focus on testing and linkage to care regardless of HIV diagnosis. This argument conceptualized TasP and ARV-based prevention as a “double-helix” of the treatment and prevention cascade, and emphasized the ongoing and urgent need to develop multiple female-controlled prevention interventions. They advocated investing in research required to develop and deliver as many prevention intervention options as possible into the hands of women (including both HIV-negative and undiagnosed women). The “con” side also raised questions about the disproportionate focus on ART which, while important, is unlikely to be sufficient in providing the level of self-agency needed for HIV-negative women to protect themselves and not depend on their male sexual partners being on effective ART.

This argument also challenged the notion that we have definitive evidence regarding the effectiveness of TasP in contexts outside of carefully monitored clinical trials. Linda Gail-Bekker presented
data from a recent community-based survey that indicated that, among those on ART, 58% had a viral load of more than 1,500 copies/mL; 43% had a viral load of more than 10,000 copies/mL. Given the correlation between high viral load and increased transmissibility, the data suggest that being on ART is not necessarily going to provide the much-vaunted benefits demonstrated in randomized controlled trials.

Discussion

Participants agreed that the conflicting data among clinical trials evaluating ARV-based interventions among women underscore the need for studies designed to better understand the social, behavioural and biological variables that affect the efficacy and effectiveness of biomedical interventions. The need to better market the benefits of treatment on secondary transmission was also raised, with participants noting that the HIV response had been effective in communicating the benefits of ARV prophylaxis and ART in preventing vertical transmission to pregnant women. However, unlinked transmissions occur and were clearly documented in HPTN 052. Participants in the discussion noted the on-going need to carefully analyse such data in order to determine the individual and social determinants of HIV risk.

Participants agreed that no single product or intervention is likely going to provide a definitive answer to preventing HIV transmission among women in widely varying geographical, social, economic and cultural contexts. Participants also agreed that adherence interventions will be key to the success of either PrEP or TasP, with some participants warning that “treating ourselves out of the epidemic” is unlikely to be a successful long-term strategy. They offered the example of those working on eradicating tuberculosis (TB) in resource-limited settings, which has seen significant setbacks and challenges in relying too heavily on treatment as an approach to eliminating TB.

In a vote following the debate, the overwhelming majority of participants supported the need to invest in both TasP and PrEP strategies. The issue, one participant noted, is about the fiscal priorities of decision makers, suggesting the HIV field needs to redouble its efforts to make the business case for biomedical prevention research investments as a cost-effective public health strategy.
Products in the Pipeline: Industry Update

A number of pharmaceutical companies have ARV-based products in pre-clinical and clinical stages of development and are working with governments, non-governmental organizations and other stakeholders to develop a new generation of prevention products.

Jim Rooney (Gilead Sciences, USA) provided a brief overview of compounds that Gilead is working on. Among topical products are TFV-based vaginal rings (with or without hormonal contraception) and quick-dissolve TFV/FTC tablets and films. The challenge is to ensure the delivery of the active ingredients in sufficient concentrations to the biological compartments where they are needed in order to prevent STIs, such as herpes simplex virus, as well as HIV. Tenofovir alafenamide fumarate (TAF, GS-7340), another prodrug of TFV, may have the potential to deliver higher intracellular concentrations of drug with fewer side effects; Gilead is exploring it as either an oral or topical formulation. Other compounds in development include elvitegravir, a capsid inhibitor, and maraviroc (Pfizer) possibly in combination with rilpivirine (Janssen). There is also a gp120 binder in preclinical stages of development that may be promising as a prevention product. Jim noted that Gilead is working with a number of partners, including the National Institute of Allergy and Infectious Diseases, the US Centers for Disease Control and Prevention and the French Agence nationale de recherches pour le sida on Phase III and Phase IV (post-marketing studies) of its compounds.

Sandra Lehrman (Merck, USA) noted that her company has a project currently in development to use the ethylene vinyl acetate copolymer ring for contraception as a method for also delivering ARVs. Long-acting modalities, such as vaginal rings and injectables, could play an important role in addressing adherence issues.

An interesting question was raised regarding whether a drug developed exclusively as a prevention intervention would be a viable business model for industry. Industry representatives noted that this question was yet to be definitively answered, and part of the answer will depend on the regulatory pathways to approval. Regulatory agencies, such as the US Federal Drug Administration, are demanding larger data sets and more detailed data on adverse events. Also, there are clear differences in risk tolerance for a treatment compound aimed at HIV-positive populations compared with prevention interventions aimed at (comparatively) healthy HIV-negative populations. At this point, it is not clear what the best regulatory approach is going to be, leaving industry in some uncertainty with respect to making strategic investments on a separate HIV prevention pipeline.

Conclusion

Sandra Lehrman, Chair of the colloquium, thanked presenters, participants and debaters for their contributions to the meeting, noting the important strides being made in our understanding of both the promise and challenges of developing and delivering female-controlled ARV-based prevention interventions. She acknowledged the need to redouble efforts aimed at better elaborating and integrating the “double-helix” of treatment and prevention required to deliver on the promising results of research to date.

An appropriate concluding statement for the meeting was provided by Bob Grant, who observed that enormous resources can be marshalled for public safety efforts if policymakers see the potential impact in improving public health. He challenged the idea that resources are inevitably declining, and encouraged the HIV field to reframe the discussion about the short- and long-term impact of investments in prevention research. The need to build on the knowledge gathered from clinical evidence to date to develop more efficacious and effective prevention methods for women has never been greater.
IAS-ILF Mission

The mission of the Industry Liaison Forum is to accelerate scientifically promising, ethical HIV research in resource-limited countries, with a particular focus on the role and responsibilities of industry, namely pharmaceutical and diagnostic companies, as sponsors and supporters of research.

The IAS-ILF fulfills its mission by: identifying research gaps; promoting targeted research; identifying challenges and best practices; analyzing available data and evidence; disseminating information; consulting and convening stakeholders; providing industry expertise; and supporting capacity building for research and health delivery.