INDUSTRY LIAISON FORUM

Linking Experts in HIV Research

Sex and gender differences in ARV-based HIV prevention research

Catherine Hankins[1,2,*], Shirin Heidari[3], Sandra Lehrman[4], Joep Lange[1]

1. Amsterdam Institute for Global Health and Development, Department of Global Health, Academic Medical Centre, University of Amsterdam, 2. London School of Hygiene and Tropical Medicine, 3. International AIDS Society, 4. Scientific Affairs, HIV, Merck & Co, Inc, * Corresponding author: c.hankins@aighd.org

Sex Biological and physiological characteristics that define men and women

Gender Economic, social, political and cultural attributes, constraints and opportunities associated with being a woman or a man

Issues

What is the optimal combination prevention approach for early treatment as prevention or pre-exposure prophylaxis (PrEP) in women?

Are the HIV prevention benefits of antiretroviral (ARV) drugs as evident in women as they are in men and, if not, why not?

What questions concerning the gender and sex aspects of ARV-based prevention are outstanding?

Methods

The Industry Liaison Forum (ILF) of the International AIDS Society (IAS) convened an affiliated event at the 20th Conference on Retroviruses and Opportunistic Infections (CROI) in Atlanta, US, in March 2013 to address the topic of sex and gender differences in antiretroviral (ARV)-based HIV prevention research.

[Agenda and presentations are available at: http://www.iasociety.org/ilf.aspx]

Data were reviewed from trials of early treatment for prevention (before national eligibility criteria are reached) and pre-exposure prophylaxis, as well as from a study of the impact of antiretroviral treatment (ART) scale up on individual risk of HIV acquisition. *In vitro* and pre-clinical evidence of potential sex-based differences and similarities in ARV-based prevention were considered, along with differences between men and women in trial endpoints: seroconversion, safety and tolerability, adverse event profiles, drug resistance and adherence. Social science perspectives included the importance of gender with respect to acceptability and the impact of risk behaviour and risk compensation on ARV-based prevention. Potential areas of collaboration are between pre-clinical, clinical and social science disciplines. Promising ARV-based prevention products in the pipeline were reviewed. A formal lively debate addressed the subject: *it resolved that with respect to antiretroviral-based prevention of sexual transmission, treatment is enough for women.*

Results

An optimal “combination prevention” approach for ARV-based interventions should consider the broader context of women’s lives, including their socioeconomic and behavioural vulnerability to HIV, as well as biological aspects, in order to address immediate risks, underlying vulnerabilities and the pathways that link them.

Macaque studies reveal higher levels of ARV drug penetration in rectal tissues compared with vaginal tissues, suggesting one reason that clinical trials of oral tenofovir (TDF)-based interventions have demonstrated greater efficacy in men who have sex with men (MSM) than in heterosexual women. Even when conditions simulating perfect adherence are met, drug penetration and protection thresholds vary, depending on the compound, dosage, site (e.g., vaginal or rectal mucosa) and other factors.

Conflicting clinical trial efficacy data and significant gaps between self-reported measures of adherence and actual plasma concentrations are observed among both men and women.

Disconnects between self-reported risk perception and actual risk among women appear to be reflected in poor adherence to ARV-based prevention. Evidence suggests that there are “seasons of risk” or periods of time, such as adolescence, post-separation/divorce, motherhood or menopause, when women may be particularly vulnerable to HIV infection.

The pipeline includes delivery systems and active ingredients designed to ensure sufficient concentrations of ARV-drugs within biological compartments exposed to HIV: dapivirine ring, tenofovir (TFV)-based vaginal rings (with or without hormonal contraception), and quick-dissolve TFV/emtricitabine (FTC) tablets and films. Novel candidates include:

- Tenofovir alafenamide fumarate (TAF)
- Elvitegravir, a capsid inhibitor
- Maraviroc (possibly in combination with rilpivirine)
- An ethylene-vinyl-acetate (EVA) copolymer ring for contraception and ARV delivery
- A gp120 binder in pre-clinical analysis.

Key conclusions

- **Data disaggregation and analysis by sex and gender are needed to more fully understand the relative benefits for women and men of ARV-based HIV prevention.**
- **Conflicting data among clinical trials evaluating ARV-based prevention for women underscore the need for studies to further explore the social, behavioural and biological variables that affect efficacy and effectiveness.**
- **Knowledge of the nature, extent and significance of sex and gender differences in ARV-based prevention is essential to inform future policy and programming.**

References

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Competing interests

The Industry Liaison Forum (ILF) is an initiative of the International AIDS Society (IAS) with a mission to accelerate scientifically promising, ethical HIV research in resource-limited countries, with a particular focus on the role and responsibilities of industry as sponsors and supporters of research. The authors declare that they have no competing interests.

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Consensus Statement

ASKING THE RIGHT QUESTIONS: Advancing an HIV Research Agenda for Women and Children

Recommendation 3:
Research data should be disaggregated by sex to ensure opportunities for gender-based analysis using a variety of indicators, such as retention in ART programmes, morbidity and mortality, loss to follow up, and pharmacokinetic (PK) and pharmacodynamic (PD) parameters.

Combination prevention context for antiretroviral-based 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.