Beyond the Evidence Base: Rights and Justice for Women

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International AIDS Society
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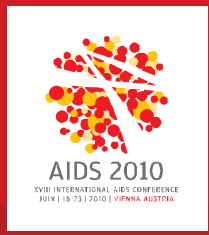
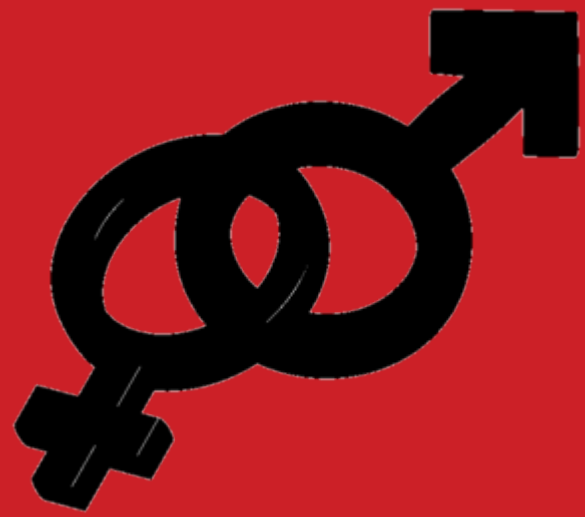
AIDS2010 Vienna



- Why women are underrepresented in clinical trials?

A brief history of medical research

- What do we know and do not know about sex differences in HIV research?



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History of clinical research

- Medical Research 1930s and 1940s
- Tuskegee Syphilis Study 1960s

Ethical concerns in medical research

History of clinical research

- Medical Research 1930s and 1940s
- Tuskegee Syphilis Study 1960s
- Thalidomide Birth defects 1950s

Major damages can be done to infants of women exposed to drugs during pregnancy

History of clinical research

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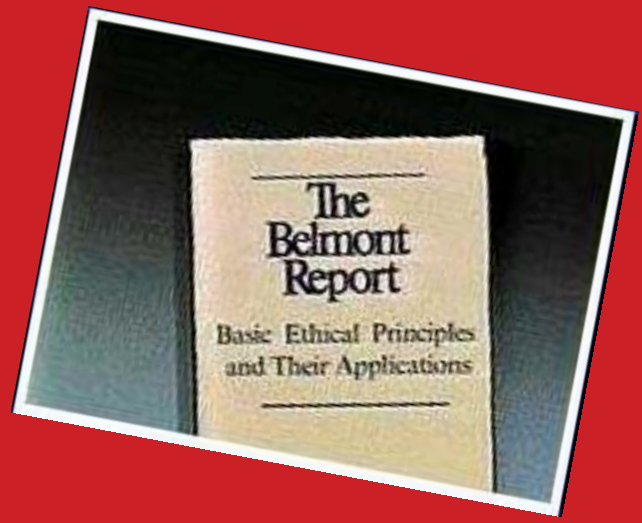
- Tuskegee Syphilis Study 1960s
- Thalidomide Birth defects 1950s
- Belmont Report 1970s

Justice: if women are going to "reap the benefits of the research," they have the right and the responsibility to participate in the research



History of clinical research

- Medical Research 1930s and 1940s
- Tuskegee Syphilis Study 1960s
- Thalidomide Birth defects 1950s
- Belmont Report 1970s
- FDA guidelines 1977

"premenopausal women capable of becoming pregnant to be excluded from early drug trials"

History of clinical research

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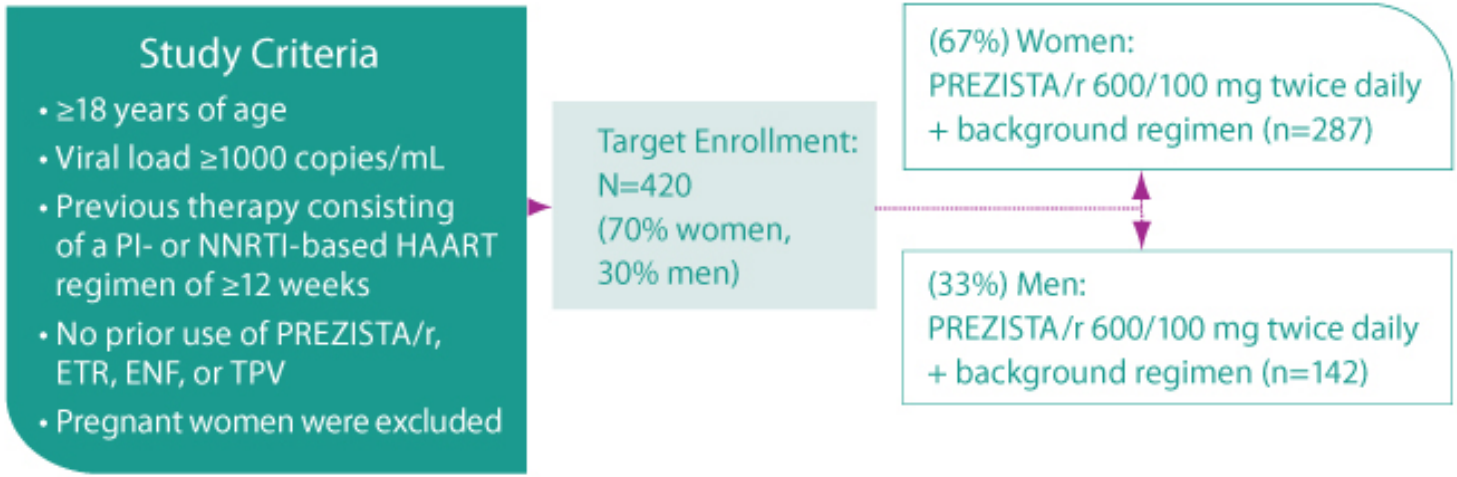
- Thalidomide Birth defects 1950s
- Belmont Report 1970s
- FDA guidelines 1977
- NIH Revitalization Act 1990s

"…research funded by NIH include women as subject in all clinical trials, and that studies are large enough to be able to identify, if any, differences between men and women."

Are women underrepresented in clinical trials? and why?

- Ethical Concerns: Protecting woman's potential fetus
- Physiological differences: increased variability
- Cost: larger study population
- Complexity: recruitment and retention of women

GRACE: Gender, Race and Clinical Experience



tibotec THERAPEUTICS

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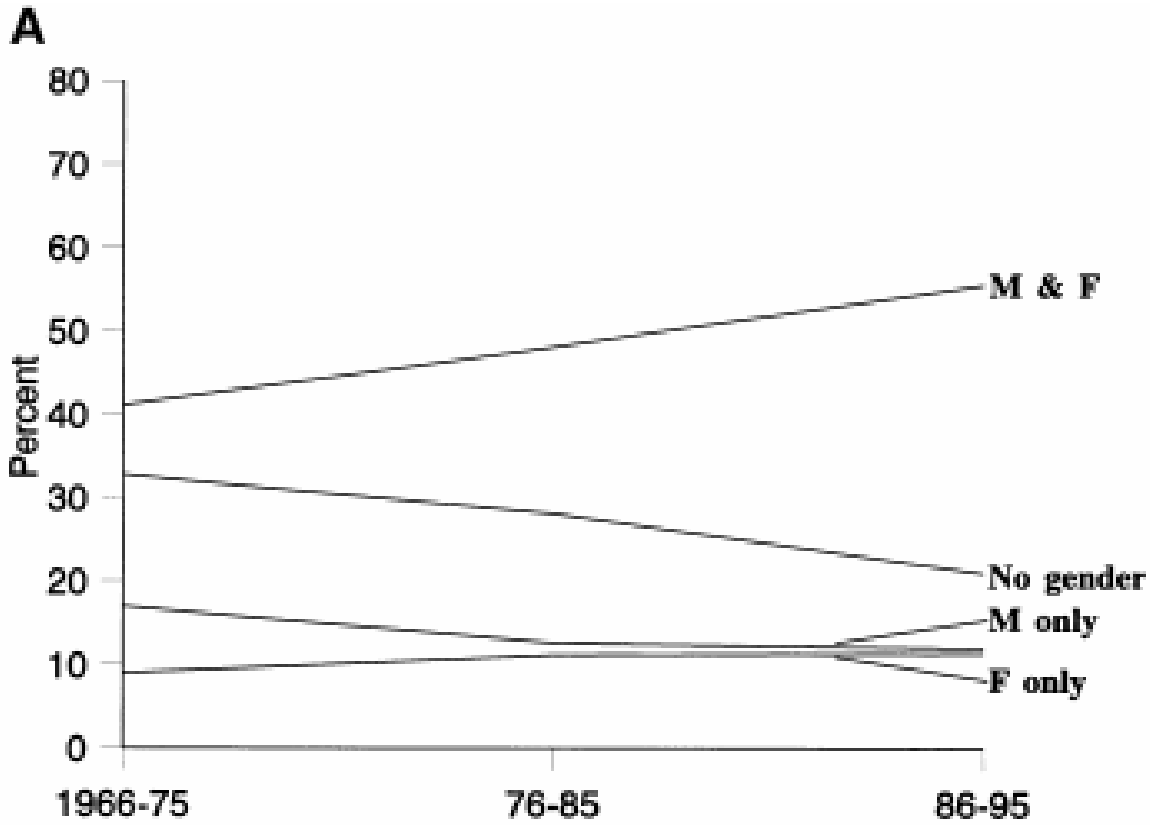
Gender Representation in Trials

Curtis L. Meinert, PhD, Adele Kaplan Gilpin, JD, PhD, Aynur Ünalp, MD, PhD, and Christopher Dawson
Center for Clinical Trials, The Johns Hopkins University, School of Hygiene and Public Health, Baltimore, Maryland



Controlled Clinical Trials 21:462–475 (2000)

Women's Participation in Clinical Trials and Gender-Related Labeling: Review of New Molecular Entities Approved 1995-1999

Evelyn, B., Toigo, T., Banks, D., Pohl, D., Gray, K., Robins, B., Ernat, J.
June, 2001, *Office of Special Health Issues, Office of International and Constituent Relations, Office of the Commissioner, U.S. Food and Drug Administration*

Summary

Context: There continues to be a perception that women are under-represented in clinical trials of new drugs. Few data are available from formal evaluations of approved new drug applications. This study reviews women's participation in clinical trials and gender-related labeling for new molecular entities approved during a five-year period by the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER).

Objectives: The objectives of the study were to assess to what extent women participated in clinical trials, to describe what FDA medical officers concluded about gender differences in sponsors' evaluations, and to determine to what extent sponsors described gender-related information in the approved product labeling.

Design: This was a retrospective review of clinical trial protocols and labeling for 185 new molecular entities approved by CDER between January 1, 1995, and December 31, 1999. Enrollment data were derived from medical officers' reviews and tabulated according to gender. The approved product labeling was searched for statements related to product use in humans. All data were compiled and analyzed using Microsoft Access.

Main Outcome Measures: This study quantifies women's participation as described by enrollment data in clinical trials by year, phase of study, and product type as defined by the CDER division responsible for the product review. Additionally, the study categorizes labeling based on the inclusion of gender-specific information.

Results: Overall, women appear to participate in the clinical trials at nearly the same rate as men even when gender-specific products are excluded. Some differences in participation are seen when year-to-year or division-to-division comparisons are made. Labeling for two-thirds of the products contained some statement about gender, although only 22% described actual gender effects. Four labels described more than one gender effect. Ninety percent (90%) of the effects discussed in the labeling were pharmacokinetic, 12% were safety, and 5% were efficacy. No product recommended a change in dosage for women.

Conclusions: Women are participating in clinical trials of new drugs in approximate proportion to their representation in the population. The majority of product labeling contains references to gender evaluation. Most of the gender effects were pharmacokinetic. Few products demonstrated safety or efficacy effects, and none recommended changes in dosage based on gender effects.

Reporting?

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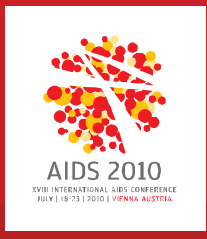
Gender Analysis in Abstracts

Inclusion of gender breakdown of data is strongly encouraged, and should be provided as well as a comprehensive gender analysis in the results section whenever possible. If applicable, your abstract should include the number and percentage of men, women and transgender who participated in your research or project, and disaggregation of results by gender. If your research or project was specific to one gender, please state.



Reporting?

JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

About *Journal of the International AIDS Society*

Analysis of differences by race and gender

Submitting authors are strongly encouraged to include data disaggregated by sex (and, whenever possible, by race) and provide a comprehensive analysis of gender and racial differences.

The authors should include the number and percentage of men, women and, if appropriate, transgender who participated in the research study. Anatomical and physiological differences between men and women (height, weight, body fat-to-muscle ratios, cell counts, hormonal cycles, etc.), as well social and cultural variables (socio-economic, education, access to care, etc.), should be taken into consideration in the presentation of data and/or analysis of the results. If statistically significant differences are found - between men and women or between different racial or cultural groups - in the effects of the studied intervention, the implications, if any, for clinical and/or public health should be adequately discussed.

If the research study was specific to one sex/gender, the reasons for this should be clearly stated.

- Why women are underrepresented in clinical trials?
- What are the HIV research gaps related to needs of women?

Does sex matter in clinical research?

Autoimmune disease
e.g. Multiple Sclerosis, Rheumatoid Arthritis

Cancer Risk
e.g. lung cancer

Cardiovascular Diseases
e.g. Stroke, Heart Attack

Treatment Response:
e.g. Antidepressants

XY vs XX

Reproductive organs

Hormones

Size

Etc.

RACE

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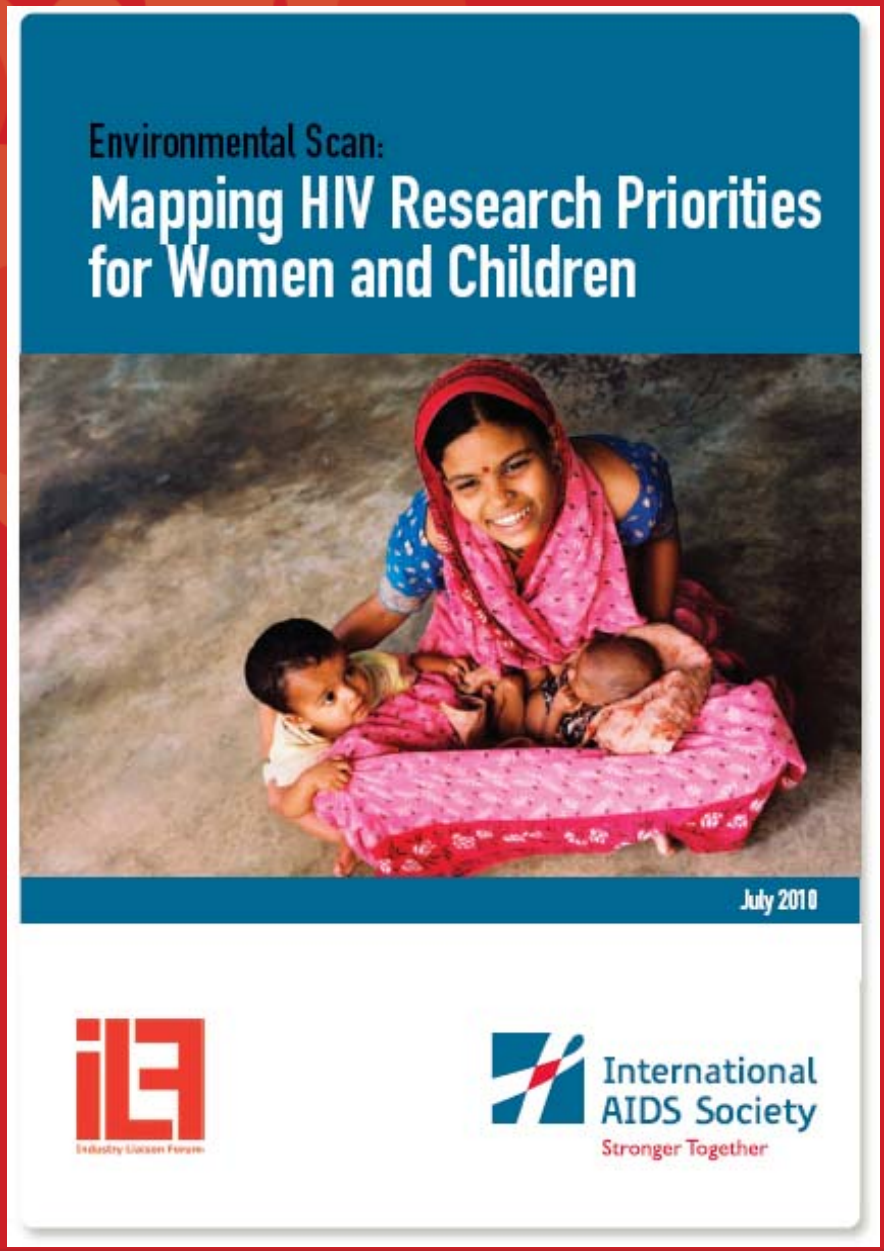
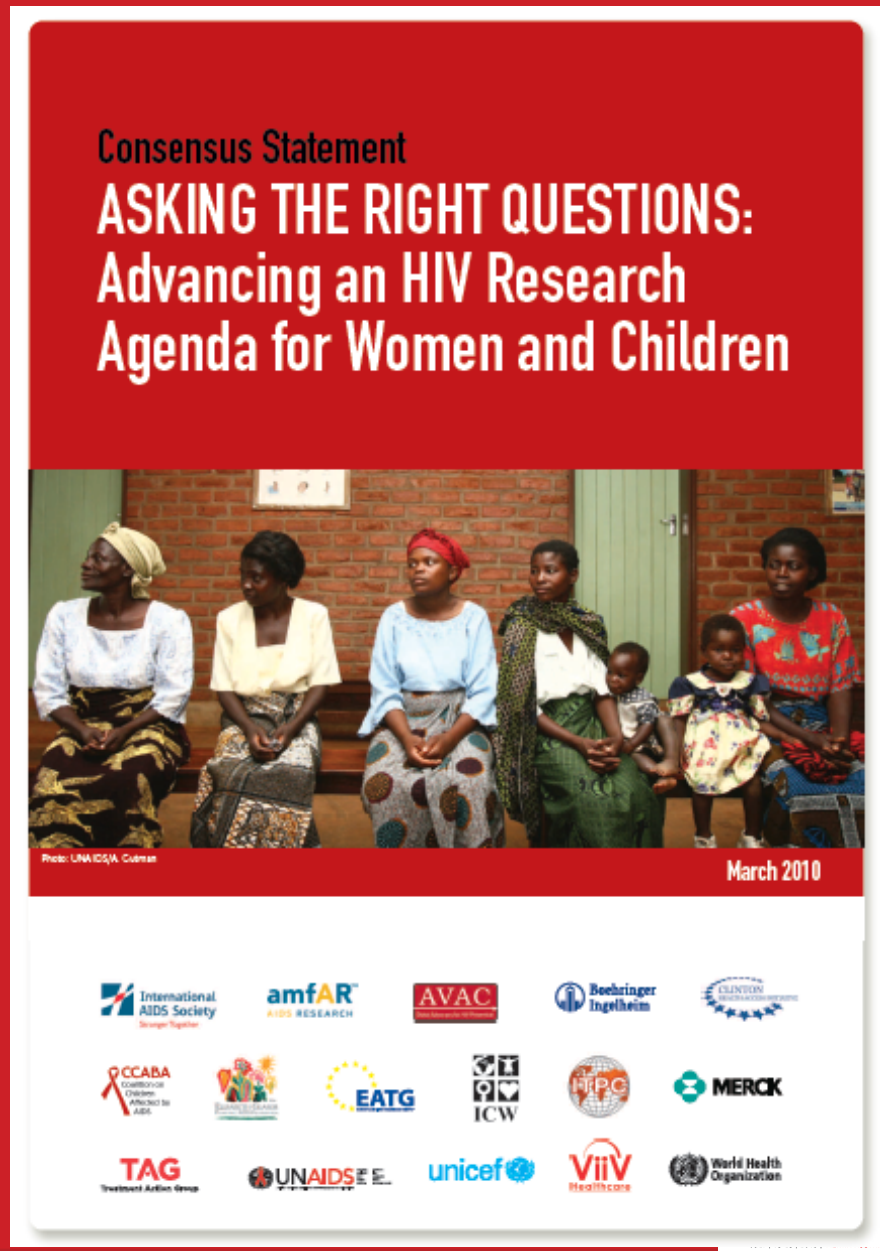
Table 5. Frequency of Gender Differences by Product Type

Division and Drug Product	Differences Found in Label	
	Number	Percent
110 Cardio-Renal	6/22	27%
120 Neuropharmacology	9/21	43%
150 Oncology	4/18	22%
160 Medical Imaging	1/11	9%
170 Anesthetic	0/6	0%
180 Gastrointestinal/Coagulation	0/11	0%
510 Metabolic/Endocrine	7/25	28%
520 Anti-Infectives	2/12	17%
530 Antivirals	3/17	18%
540 Dermatologic/Dental	0/8	0%
550 Analgesics	2/13	15%
570 Pulmonary/Allergy	0/7	0%
580 Reproductive/Urologic	0/6	0%
590 Special Pathogens	7/8	88%

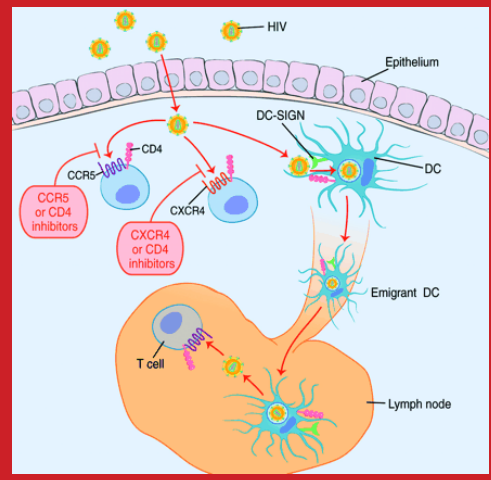
Of the 41 products for which labeling described gender effects, 90% (37/41) were pharmacokinetic, 12% (5/41) were safety, and 5% (2/41) were efficacy. These represent 20%, 3%, and 1% of the total product labels reviewed. Four product labels described more than one effect related to gender. No products required a change in the dosage based on gender differences.

www.iasociety.org/ilf.aspx





Sex differences in response to HIV and ARVs



Women have:

- Higher HIV transmission risk
- Lower Viral Load early on
- Higher CD4 T cells
- Faster disease progression given same VL
- Lower CCR5 density on CD4 cells *(HIV RNA in plasma strongly associated with CCR5 density)*
- Higher CD8 T cell activation

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ART pharmacokinetic

Pharmacokinetics: where does the drug go, how long it takes, how does it change within the body and when does it leave the body

HIV Drug	In women
Nevirapine	Hepatotoxicity >250 CD4
Efavirenz	Higher Plasma level More Neurotoxicity
Indinavir	Lower clearance (?)
Saquinavir	Higher maximum and minimum plasma concentration

Hormones, HIV and women??

Hormonal contraception and HIV:

- Increased infection risk?
- Faster disease progression (in treatment naïve) ?
- Abnormal menstrual cycles, possibly including early menopause for HIV+ women? (CD4, HAART ?)
- Some HIV drugs can cause decreased levels of hormones
- Estrogen can cause decreased levels of some HIV drugs

Limited knowledge about women's hormonal fluctuations (puberty, pregnancy, menopause) or use of hormones and HIV, and interaction with HIV treatment

CLINICAL: TREATMENT FOR WOMEN

- Disaggregate clinical cohorts and clinical trial **data by sex, ethnicity and race**
- How reproductive health and **hormonal changes** affect treatment outcome?
- **Impact of endogenous and exogenous hormonal changes** on ART and treatment outcomes for women?
- What **additional studies** are required to assess if **sex-based PK/PD differences** are clinically relevant?
- Ensure **greater representation of women** in ARV **PK/PD** studies.

Making Clinical Trials Work for Women and Girls

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JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
UNHCR UNICEF WFP UNDP UNFPA UNODC ILO UNESCO WHO WORLD BANK

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Women and HIV trials

- AIDS policies and briefs
- Drivers of the epidemic
- Gender
- Greater Involvement of People Living with HIV/AIDS (GIPA)
- HIV care and support
- HIV prevention
- HIV testing and counselling
- HIV treatment
- Human rights
- Impact of AIDS
- Key populations

Decades after AIDS first became a global health threat, it has become clear that analysis of data by sex is a crucial consideration in trials exploring new ways to stop the spread of HIV and treat HIV-related disease.

Yet, until relatively recently, women were under-represented as participants in trials for all types of clinical interventions, including trials for HIV vaccines. Most HIV trials are not designed with women in mind. Women are considered "difficult" to study and enrol in trials given the complexities of their biology and their lives.

Resources:

Related information:

- Women and girls
- Science and research

Partners:

- Global Coalition on Women and AIDS

Feature stories:

- Meeting ethical concerns over HIV trials (*3 December 2007)*
- The role of women in HIV trials *(5*

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Raising awareness and advocate

- Funding agencies
- Regulators
- Researchers
- Editors
- Publishers

Thank you!