

Executive summary and recommendations
from the UNAIDS/GCWA/ICRW/Tibotec
expert group consultation on 'Making HIV
Trials Work for Women and Adolescent Girls'

10-11 December, 2007
UNAIDS, Geneva, Switzerland



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Executive Summary

Women are rarely included in HIV therapeutic trials in numbers adequate for study power to draw conclusions about them. Adolescents, a priority population for effective HIV prevention tools, are not recruited to biomedical HIV prevention trials, with the result that there will be significant delays in licensing prevention products for adolescents when they are found efficacious in adults. A consultation entitled *Making HIV trials work for women and adolescent girls*, convened in Geneva in December 2007 by the Joint United Nations Programme on HIV/AIDS (UNAIDS), Global Coalition on Women and AIDS (GCWA), International Center for Research on Women (ICRW), and Tibotec, Inc., gathered expert delegates from international organisations, governments, pharmaceutical industry, civil society, academic institutions, and research agencies to discuss the involvement of women and adolescent girls in HIV therapeutic and prevention trials. Historically, clinical trial participation has suffered from inadequate female representation. Women's body composition, hormonal cycle, metabolism, and reactions to drugs are different from those of men. Scientific results from trials involving only men cannot be assumed to apply to women. The gender-related inequalities that place women and adolescent girls at increased risk of acquiring HIV, failing treatment, or dropping out of trials, warrant special measures to overcome barriers and facilitate enrolment and retention of women in biomedical HIV prevention and treatment trials. An action plan containing recommendations for policy and programming, a research agenda, and an advocacy framework details out necessary steps to change research norms to rectify HIV trial practice imbalances.

Introduction

Recent years have been marked by real progress in global responses to the HIV epidemic. Activism created a new norm around the right to access to treatment for people living with HIV worldwide, and 3 million people are now taking antiretroviral medication[1]. UNAIDS and other key actors are redoubling prevention efforts through systematic analysis to determine what works and what can be scaled up. While there have been some setbacks in research on new prevention technologies, such as vaccines and microbicides, investment and attention continue to grow. At the same time, sobering statistics underscore that neither prevention nor treatment is keeping pace with the epidemic. Every day some 6,800 people are newly infected with HIV, and over 5,700 die from AIDS[2]. For every person newly accessing antiretroviral therapy, more than 4 people are becoming newly infected.

The epidemic continues to be devastating for women. More than 15.4 million women over the age of 15 are now living with HIV, comprising half of the total in this age group worldwide; in sub-Saharan Africa, 61% of adults living with HIV are women[2]. HIV prevalence in young women is even more sobering: among people aged 15-24, the ratio of women to men with HIV infection is 3:1[3]. In short, the current global response to the HIV epidemic is clearly not working for women.

While the complex, deeply rooted, and multi-faceted structural inequalities that condition women's risk and constrain their access to prevention and treatment are increasingly recognized, responses rarely address them. There is still no prevention method women can use without partners' involvement and cooperation. Emerging evidence around sex differences in biomarkers, such as CD4 cell count and viral load, and in responses to treatment suggests that the guidelines on treatment initiation and choice of drug regimens may not be optimal for women.

Much of HIV-related biomedical research does not provide answers that are applicable to women, and many 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. When women are included in clinical trials, it is rarely in sufficient numbers to be able to draw statistically significant conclusions about sex differences. Currently,

many HIV trials that do enrol women – such as trials of prevention of mother-to-child-transmission – do not answer questions specific to women’s health because they focus on other outcome measures. There is little HIV research involving adolescent girls despite high HIV incidence in this population group, particularly in generalized epidemics. From this perspective, HIV trials clearly are not “working” for women and adolescent girls.

Objectives of Meeting

“Making HIV Trials Work for Women and Adolescent Girls” was convened: to review past participation of women and adolescent girls in clinical trials; to assess how well HIV trials are collecting, measuring, analysing and presenting data related to health determinants and health outcomes in women or adolescent girls; to identify barriers to including women and adolescents in trials; and develop an action plan to address these concerns.

The meeting was co-sponsored by the Joint United Nations Programme on HIV/AIDS (UNAIDS), the Global Coalition on Women and AIDS (GCWA), the International Center for Research on Women (ICRW), and Tibotec Inc. These co-conveners reflect some of the complexity and diversity of the meeting themes. UNAIDS is the leading international, normative body, that plays a critical role in highlighting neglected issues and developing guidance on addressing many of the complex factors driving the epidemic. ICRW pioneered work on women and AIDS, and played a key role in articulating and focusing attention on stigma and on the structural inequalities that condition women’s risk of HIV. The Global Coalition on Women and AIDS was established in 2004 to respond to the growing concern that existing AIDS strategies did not adequately address women’s needs. It focuses on education for girls; property and inheritance rights; violence against women; preventing HIV in young women and girls; female-controlled prevention; access to treatment; community based care; and leadership. Finally, Tibotec was the first pharmaceutical company to provide a royalty-free license to a product-development partnership in the field of microbicides when it licensed dapivirine (TMC-120) to the International Partnership for Microbicides for development and testing as a vaginal microbicide.

Making HIV trials work for women and adolescent girls requires knowledge of sex differences between men and women, and of biological differences between women and girls. It also requires knowing the implications and consequences of gender and how gender inequalities influence women’s health across their lifetimes. To answer key questions about the health and structural interventions needed to improve health outcomes, women and girls need to first participate in clinical trials and other research. This requires conceptualizing trials to ensure that they address the questions that are most critical for women in order to provide answers that are both useful and actionable. It also requires identifying effective ways to facilitate women’s participation through structuring research recruitment and implementation in ways that encourage women to enrol and remain in trials. Finally, the information that is generated through trials involving women needs to be analysed, synthesized, and disseminated in ways that are clear, actionable, and relevant for science, policy, services, communities, and individuals.

The meeting brought together a diverse and dynamic group of some 50 people (see list at the end of the report): researchers from the biomedical, clinical, and social sciences; research funding agencies; activists; civil society; pharmaceutical executives; policymakers; donors; and representatives from key normative agencies. These constituencies work across the full spectrum encompassing the cellular to the clinical to the structural to the global levels. During two days of presentations, debate, and discussion, participants developed an ambitious set of recommendations and an action plan for changing current norms and making trials work for women and girls.

Meeting Overview

To centre the discussion, the terms 'sex' and 'gender' were defined. Sex refers to the biogenetic differences, such as anatomy and physiology, that distinguish females and males. Gender refers to socially constructed notions of femininity and masculinity that translate into socially defined differences between men and women, including roles, behaviours, customs, relative power and influence, and access to the determinants of health[4].



The meeting began with a historical review of women's participation in clinical trials, drawing on the policies and practices of the US National Institutes of Health (NIH) and recent efforts to increase the participation of women in research. Several presentations and discussions focused on what is and is not known about sex differences from a biomedical perspective including how HIV infection manifests *itself*, progresses to AIDS, and responds to treatment. Key interactions between sexual and reproductive health and HIV, including pharmacokinetic and clinical interactions between contraception and antiretroviral treatment, were summarized to identify research priorities. The structural intervention trial *Intervention with Microfinance for AIDS and Gender Equality (IMAGE)* in rural South Africa was examined to draw out considerations in designing such trials and in scaling up complex programmes based on the trial findings to address women and HIV.

Among the issues that echoed throughout the meeting were the importance of designing trials that ask questions relevant to women; enrolling women in trials in sufficient numbers to be able to draw conclusions about sex differences and their implications for HIV management; barriers to the enrolment and retention of women in trials and, conversely, facilitators of their participation; and the urgency of moving forward a gender-sensitive research agenda including sex and gender-based analyses to answer these questions.

Throughout the meeting, discussions returned to the changing context of research, highlighting how several different dimensions of research need to be pushed further to better identify and meet the needs of women and adolescent girls: community participation; access to care; standard of prevention; integrating medical and social science; partnerships among industry, the public sector, and activists; and balancing expectations of research, all of which are reviewed in this report. Consensus recommendations from the meeting for continued work to make HIV trials work for women and adolescent girls may be found at the end of the report.

Background

Historical Evolution of Women's Participation in Clinical Trials: The example of NIH Policies and Practices

Historically, women have been excluded from many clinical trials, not just in the HIV field. Women are seen as more "difficult" and expensive to study: their oestrous cycle is generally viewed as a "methodological complication" that necessitates more participants and control groups; and concern about potentially endangering a foetus has meant that women of childbearing age have been excluded from trials. The evolution of women's participation in clinical trials sponsored by the US National Institutes of Health (NIH), a major sponsor of health research and one of the main funders and leaders in HIV research worldwide, is distinct but it does illustrate some of the trends in health research globally.

In 1977 the US Food and Drug Administration (FDA) issued guidelines restricting research on women of “childbearing potential”. Many of the early large cohort studies sponsored by NIH to examine critical health issues, such as cardiovascular disease, smoking, cholesterol, and other risk factors, enrolled thousands of men but no women; ironically, even the first study of the role of oestrogen in preventing heart disease enrolled only men[5].

While several other large cohort studies did include women, most epidemiological and health research – and almost all clinical trials – primarily or exclusively studied men. However, the results were applied to women who seemed to be regarded as “smaller men” with little consideration for their physiological or biochemical differences. Results from men cannot be simply extrapolated to women. This has been demonstrated, for example, in a sex-specific analysis of randomised controlled trials examining the effects of low-dose aspirin on risk of cardiovascular events. Contrary to the findings in men, aspirin did not reduce women’s risk of either myocardial infarction or haemorrhagic stroke, only of ischemic stroke[6, 7].

In the 1980s, activists from the women’s health movement pressured for changes in policies and practices, arguing that women help fund health research as taxpayers so they deserve to benefit from it. In 1986, NIH policy *urged* the inclusion of women in federally funded research, and the following year it *encouraged* the inclusion of minorities; however, not until 1993 did a revised policy, enacted by public law, explicitly state that women and minorities *must* be included in any clinical studies conducted or supported by the NIH. Nevertheless, many companies and researchers outside of the NIH still hesitate to include pre-menopausal women in research.

At NIH, the Women’s Health Initiative was established in 1991 as a \$625 million, 15 year programme to research the most common causes of death, disability, and poor quality of life in post-menopausal women. The FDA created an Office of Women’s Health to address disparities in drug research and administration policies. “Women’s health” had generally been taken to relate primarily to reproductive health. NIH broadened this definition to include a wider array of health issues that are unique to women, are more prevalent among women, or present differently in women.

In the HIV field, these inequities in research conceptualization and participation have paralleled the understanding and evolution of the disease. Drug development and other research have been shaped by the modes of transmission and have followed affected populations. In the US, the HIV epidemic was initially driven by sexual contact among men who have sex with men, and this was reflected in clinical definitions and in most clinical research including treatment trials. In 1993, some ten years after the first cohort study of men who have sex with men, the NIH-sponsored Women’s Interagency HIV Study was started. With greater recognition of the global epidemic, the International Epidemiologic Databases to Evaluate AIDS (IeDEA) has provided a framework since 2006 to evaluate a range of critical and emerging clinical issues for patients in diverse settings[8]. While women are now included in most large NIH-supported AIDS cohort studies and research networks, men still represent 70–90% of the participants in pivotal trials conducted on investigational compounds by private sector companies[9–13].

Even when women are included in trials, they do not necessarily reap health benefits from them. The main outcome measures may not be specific to women’s health. For example, all of the initial trials which enrolled pregnant women to study the prevention of mother-to-child transmission determined almost nothing that would benefit women directly because the outcome measures all focused on neonatal and infant health. Two trials of GlaxoSmithKline’s HSV-2 vaccine did show significant protection against HSV infection in women who were HSV-1 and HSV-2 seronegative at study entry, but not for men or for women already infected with one virus, and the vaccine was not further developed[14]. Finally, women tend to be underrepresented among trial participants with the result that there is insufficient statistical power to draw conclusions about sex differences. For example, only 6 per cent of the participants in the VaxGen HIV vaccine trial were women[15]. This meant that the trial was not able to draw any statistically significant conclusions about apparent higher

neutralization titres in women trial volunteers.

Reviewing experience with NIH and AIDS research more broadly served to highlight many of the themes and recommendations that surfaced throughout the meeting:

- Conceptualize research both *for and about* women rather than only *about* women
- Ensure that research leads and stays ahead of the epidemic rather than following it.
- Adapt advocacy strategies for a range of agencies and regulatory bodies to mandate women's full participation in clinical trials.
- Identify barriers and facilitating factors related to women participating in trials.
- Look beyond the US and Europe to explore perspectives of other regulatory agencies and policy-making bodies that may have different priorities based on the status and evolution of the epidemic in their settings.
- Mount a sustained, multi-pronged strategy to call attention to and mobilize resources for answering key questions for women. Given that it has taken almost two decades to start *asking* the right questions about women and HIV – and that many have not begun to be *answered* – an “evolutionary strategy” to correct the paucity of trial information specific to women is not appropriate.



Knowledge of Sex Differences in HIV presentation, progression and treatment: What we know and don't know

As with many other areas of health and disease, knowledge of the “natural history” of HIV is based primarily on studies in men. Much of clinical practice, including guidelines for initiating treatment, is applied uniformly to men and women despite the fact that many are based on studies that enrolled only men. A growing body of evidence underscores sex differences in how HIV infection presents, manifests, and progresses to AIDS.

A meta-analysis has shown that for a given CD4 cell count and disease stage, women have a lower viral load than men[16], but the lower viral load does not translate into a difference in disease progression[17]. On the other hand, women *not* on ART have higher CD4 cell counts than men at seroconversion, at AIDS diagnosis, and at death from AIDS[18]. Therefore, a CD4 cell count threshold for ART initiation that does not take sex into account may result in delays in treatment initiation for some women. HIV programmes need to consider starting women on antiretroviral treatment at a higher CD4 cell count.

Current proposed treatment regimens in low- and middle-income countries are based on a public health approach and practical considerations for what drugs are most affordable and easiest to roll out quickly. While these treatments have prolonged many lives, it is unknown whether certain aspects of these regimens, such as drug choice, dosage, or timing of initiation of treatment, are optimal for the populations (including women) being targeted by treatment programmes. Given that most of them were developed based on research in men in the US and Europe, the implications for other populations such as women, people in Africa and in Asia, and people with non-clade B virus are less well known. It is important to ask whether there is a sex-specific optimal regimen, and to look across drug classes and drug doses to see which are working best for women. Further study is needed to identify the most effective treatment strategies for women through carefully designed and pre-planned research and through monitoring and evaluation of programmes scaling up treatment.

To date, large cohort studies have not demonstrated sex differences in clinical responses to treatment. Women may have equivalent and possibly better responses to antiretroviral treatment, but further research is needed to explore and better understand this phenomenon.

Statistically significant sex differences in pharmacokinetics have been documented for several drugs, but the mechanism and clinical significance of these differences is uncertain. There is substantial evidence that toxicity to antiretroviral treatment is greater in women[19], but it is not clear whether this toxicity is related to hormonal, immunological, pharmacokinetic, or other factors. For example, due to risk of hepatotoxicity, antiretroviral treatment guidelines recommend that women do not initiate treatment with nevirapine if their CD4 cell count is greater than 250 cells per micro litre, while in men this threshold is 400 cells per micro litre[20, 21]. A real concern for women is that stavudine and nevirapine – two drugs for which sex differences in toxicity have been clearly demonstrated -- are the most widely used worldwide. Low body mass index (BMI) may exacerbate this risk of toxicity, a concern in many settings in Africa where women are chronically undernourished. The risk of lactic acidosis is greater in women taking Nucleoside Reverse Transcriptase Inhibitors (NRTI), especially among women who are pregnant and those who have increased body mass index (BMI) or obesity[22, 23]. Differences in the distribution of lipodystrophy with increased breast hypertrophy have also been observed[24–26].

To determine whether sex specific differences exist in toxicity and/or efficacy, adequate numbers of women must be included in trials before drugs are approved and in follow-up post-marketing surveillance and monitoring studies after they are introduced in different settings and populations. It is equally important to analyse and report these data in subset analyses.

Determining the best general approaches to treatment for women of childbearing age and beyond is also important. Many women whose CD4 cell count is above the threshold for antiretroviral treatment will have had one or more rounds of short course antiretroviral treatment for prevention of mother-to-child transmission. It is important to understand the impact these interventions have on long-term outcomes for women. Recent research is encouraging in that resistance to single dose nevirapine as a result of mother-to-child transmission prophylaxis does not affect treatment effectiveness in women who do not start antiretroviral treatment until at least 6 months post-partum. More research is needed to determine the impact of breastfeeding on disease progression in women and to identify appropriate treatment regimens during lactation. Finally, there is an urgent need to identify treatment regimens that can be taken by women with a CD4 cell count greater than 250 cells per micro litre and that are safe in pregnancy. It may be appropriate to establish different thresholds for starting antiretroviral treatment among women, including during pregnancy.

Many of these issues reflect the complex interplay among biological, gender, and structural factors. For example, psychosocial considerations regarding disclosure of HIV status to partners and other family members may strongly influence whether women will adhere to or discontinue treatment. Similarly, women who take antiretroviral therapy without adequate food may experience more side effects, greater toxicity, and compromised efficacy. As more and more people have access to antiretroviral therapy, it is critical to continue research to determine which regimens “work” best for women in different circumstances.

Sexual and Reproductive Health

While “women’s health” cannot be limited to sexual and reproductive health, this remains central to both research and programmes addressing women and HIV. Women’s decisions regarding HIV prevention and care may be influenced by the desire or expectation to bear children, further underscoring the importance of addressing reproductive and sexual health alongside HIV-related prevention and care[27, 28]. No consensus exists on the sexual and reproductive health package that should be provided for HIV-positive or HIV-negative women who participate in trials. Meeting participants reviewed and discussed evidence on fertility choices and pregnancy for HIV-positive women; prevention of mother-to-child transmission; contraception; termination of pregnancy; and prevention of acute HIV infection during pregnancy and lactation.

Fertility, pregnancy, and breastfeeding

Many women with HIV want to become pregnant. Intentions to have a child are increasing as more women receive antiretroviral therapy and experience improvements in health[29]. Although it is sometimes thought that women with HIV cannot become pregnant and deliver a child safely, they have a right to make sexual and reproductive health decisions and to manage their fertility. At present there is little guidance or evidence base to inform counselling and advice to women living with HIV or to serodiscordant couples, regardless of which partner is seropositive, who want to become pregnant. Fertility is lower among HIV-infected women in all but the youngest age groups. In some low resource settings, discordant couples are seeking assisted conception, but there is little to offer them in terms of intervention or guidance. If the male partner has HIV infection, antiretroviral treatment will help increase CD4 counts and decrease viral load. Approaches such as sperm washing are only available in high-income settings.

Most evidence on HIV and pregnancy concerns preventing mother-to-child transmission. It is critically important to identify appropriate treatment regimens for pregnant women and to study the short- and long-term effects of antiretroviral therapy for the woman, foetus, and infant. This may have important implications for what is considered "front line treatment". One approach is to expand and enhance the use of pregnancy registries to further study use of antiretroviral treatment in pregnancy in diverse settings, analysing and reporting the findings. Finally, more research is needed to determine the effects of breastfeeding on disease progression in women and to identify optimal treatment regimens for breastfeeding women.

Contraception

Contraception itself is an important public health intervention and an unmet need for many women, whether or not they are HIV-infected. It can have a direct impact on maternal, infant, and child mortality, and on preventing mother-to-child transmission. Given the high rates of unintended, unwanted pregnancies among women living with HIV, contraception provides a cost-efficient and effective way to prevent mother-to-child transmission. Contraception to prevent unwanted pregnancy may be the "best kept secret" in HIV prevention[30].

At the same time, a range of questions surrounding contraception and HIV remain unanswered. Women who are at risk of HIV need to consider whether a contraceptive may help prevent or enhance HIV acquisition. Women who are already infected with HIV have other considerations. Will a contraceptive method have an effect on infectivity, disease progression, the response to antiretroviral treatment, or the effects of treatment for opportunistic infections?

Barrier Methods: Barrier methods, some of which allow for dual protection against pregnancy and HIV, are largely neglected as contraceptives. Condoms are effective when used correctly and consistently, but this has been difficult to achieve either for contraception or HIV prevention. Supply of both male and female condoms falls far short of what is needed. Access to female condoms has been extremely limited. Efforts to develop more user-friendly and affordable products have been slow. A recent trial of the diaphragm and lubricant gel to prevent acquisition of HIV showed no effect, possibly because women in the diaphragm arm were less likely to use condoms. Trial participants overall found the diaphragm acceptable and easy to use, suggesting that it may be a viable contraceptive method for women at risk of HIV exposure.

Hormonal contraceptives: Studies examining the effects of hormonal contraception on HIV acquisition have not found an increased risk in the general population[31, 32]. However, subgroup analyses in two studies suggest that injectable progesterone may be associated with a modest increased risk of HIV acquisition in younger women[31, 33]. The effect is not large and the evidence not conclusive; however, given the pattern of HIV infection and injectable progestin use in young women, it warrants further research.

Some studies suggest that hormonal contraceptive use, especially injectables, may be associated with more rapid disease progression but the results are mixed[34, 35]. Relatively little is known about drug interactions among hormonal contraceptives and antiretroviral drugs, although a recent review has summarized the effects of antiretrovirals on hormonal contraception[36]. Adequately powered studies of clinical outcomes are urgently needed to inform policies and individual decision making. These studies should include women who use various hormonal methods, who are or are not receiving antiretroviral treatment, and who have different CD4 cell counts.

Intrauterine devices (IUD) do not increase risk of HIV acquisition or have an impact on disease progression or treatment efficacy, although the evidence base is weak. Limited data also suggest that IUDs do not increase HIV shedding. Data on the levonogestrel IUD and HIV suggest that it is safe to use[37, 38]. World Health Organization guidelines that caution against IUD use in women at risk of sexually transmitted infections may need to be reconsidered because there is inadequate evidence to support this recommendation for many women living with HIV.

Termination of Pregnancy: Termination of pregnancy in the context of HIV infection has been largely overlooked in research. While both surgical and medical abortion is thought to be safe for HIV-infected women, there is insufficient evidence from low-resource settings and for women with varying CD4 cell counts.

Research priorities: A WHO-convened expert consultation on research on HIV, hormonal contraception, and IUDs prioritized the following topics[39]:

- Design and implement a separate study to examine disease progression for women using hormonal contraception in different scenarios: different hormonal contraceptives; women on and off treatment, and with a range of CD4 cell counts.
- Examine existing data to determine whether concern about injectable progestins and HIV acquisition in younger women merits a new study;
- Examine infectivity through looking at shedding and vaginal immunology among women using different contraceptives and who are on and off treatment; and
- Work with existing cohorts, such as women enrolled in microbicide trials and in programmes such as those supported by the US President's Emergency Plan for AIDS Relief, to review existing data, identify opportunities for new cohort studies, and ensure that adequate data on contraception are being collected.

Several participants underscored the urgency of either making clear recommendations where the evidence-base is sufficient or undertaking essential research that will find answers to these questions. Individual women are facing decisions about contraceptive choice and providers are developing their own contraceptive algorithms in the absence of guidance or evidence to inform their decisions.

Women and Statistical Power: Generating and Using Data to Benefit Women

One of the key points amplified throughout the meeting is that women must participate in research in sufficient numbers to be able to draw statistically significant conclusions about the implications for them of biomarkers, biological responses, and treatments. More simply, the issue is one of "women and power". Enrolling sufficient numbers of women in trials is not necessarily difficult, but it requires conceptualizing, planning, and implementing research in ways that will facilitate their participation. For example, the Gender, Race and Clinical Experience (GRACE) study to evaluate different responses to HIV treatment among women and men has enrolled some 300 women by working through community health service settings, some of which are not traditional research sites[40]. Microbicide trials have been very successful overall in recruiting and retaining women in a range of diverse and sometimes difficult circumstances. [see following section *Facilitating Women and Adolescent Girls' Participation in Trials*]

At the same time, even when data are collected, they are often not made public and may not be part of reporting requirements for regulatory consideration. These so called “fugitive data”, that do not find their way into the published scientific literature, exist in pharmaceutical companies, regulatory bodies, and research agencies. This potentially rich source of information could be accessed and analyzed to make the results public at a relatively low cost.



Finally, data on critically important questions can often be collected outside the context of formal trials. Service delivery programmes provide an opportunity for conducting observational research with large numbers of people in real world settings, but such research may not be a priority for programmes working to provide treatment on a large scale. Monitoring and evaluation and operational research need to be pre-planned, supported, and mandated to ensure that service delivery programmes collect key data. For example, large scale programmes to provide antiretroviral therapy that are supported by domestic governments and by donors such as the Global Fund to Fight AIDS, Tuberculosis and Malaria; the US President’s Emergency Plan for AIDS Relief (PEPFAR); the World Bank; and others should be required to collect and report data disaggregated by sex and collect data on issues that are critical for women such as method of contraception. Registries in diverse service and research settings that report on key outcome variables can draw on a much larger number of participants over longer periods of time than any one trial. For example, registries can look at effects of drugs taken during pregnancy and gather information about viral load set points across diverse geographical settings.

All of these strategies need to be supported and strengthened by creating a new norm around requiring and reporting sex-disaggregated data among regulatory authorities, ethical review committees, host country governments, journal editors and reviewers, research sponsors, and donors. It should simply no longer be acceptable to design studies that will not answer questions in a way that is relevant to women[41]. Strong and sustained advocacy to create a new norm across constituencies is a key recommendation of the meeting.

Facilitating Women’s and Adolescent Girls’ Participation in HIV Prevention Trials

Women can and do participate in trials that enrol only women (i.e. microbicides, prevention of mother-to-child transmission) and in trials that enrol both women and men (i.e. pre-exposure prophylaxis, HIV treatment, vaccine candidates, herpes simplex-2 suppression, index partner treatment). Despite a general perception that it is difficult to enrol women in trials, many research efforts have done so successfully by identifying and responding to women’s circumstances, interests, and constraints. Preparedness studies and community consultation have informed implementation strategies to facilitate women’s enrolment and ongoing participation.

Many of the issues related to women’s enrolment in trials derive from gender inequality. Trials generally enrol individuals, but in many circumstances women’s position in the household and community – and their lack of autonomy -- mean that decision-making about participating in a trial is not an individual one. While trials need to respect women’s autonomy, women may wish to – or need to -- consult with or get permission from husbands or partners, family members, friends, or others. Lack of autonomy can also impede a woman’s ability to manage her time or travel independently. Her multiple roles can lead to time constraints and logistical barriers, all of which can make it difficult to keep frequent appointments. Women tend to undervalue their own health, and can be more willing to participate in trials (like prevention of mother-to-child transmis-

sion) that benefit their children rather than themselves. In many trials, pregnancy or desired pregnancy is an exclusion criterion and either the woman or her partner may be uncertain about this or may not wish to use contraception. The experimental nature of many trial interventions can raise concerns about future fertility and possible birth defects. Finally, trials and services related to HIV can be stigmatised and associated with marginalised populations, and women may in particular fear being stigmatised as sex workers.

Despite these barriers, participating in clinical trials can benefit women. It offers an important opportunity for women to access free, high quality health care, new treatment, information, counselling, and other services. Many trial sites have worked to meet women's practical needs through, for example, locating the research site in a setting that is safe and convenient, providing transportation or funds to cover this expense, scheduling flexible clinic times that are convenient for women, and establishing child care or play spaces near the research site so that women can bring their children if they need to. Trials can also provide women with a safe and supportive environment, and many women cite less tangible issues such as a sense of purpose and belonging to a group as being benefits of participating in trials. Participation can provide women with an ongoing sense of community and support; several powerful AIDS activist groups have emerged out of trials.

Several presentations during the meeting cited common barriers and strategies for facilitating women's participation in different settings and for different types of trials; many of these echo long-standing knowledge about facilitating women's access to health services more broadly. Disseminating and publicizing this information and highlighting strategies and successes can help to challenge some of the myths around women's participation in trials. A range of different trial communities, research networks, and institutions can benefit from sharing strategies and undertaking joint preparedness work.

Facilitating Adolescent Girls' Participation in Trials

HIV prevention research needs to focus on the populations most at risk of HIV exposure. It follows that it is a clear priority to develop new answers, technologies, and strategies for adolescents to prevent HIV acquisition. Adolescent girls' high risk of exposure to HIV, coupled with differing physiology, social constraints, motivations, and resources all mean that they need to be included in trials of new prevention technologies. For these, regulators generally will only consider data and demographics of trial participants for product licensure. This means that there is an urgent need to obtain safety data in adolescents followed by bridging studies to ensure that licensing of future products can proceed for adults and adolescents in tandem to avoid delaying access for adolescents.

Including adolescents in trials can present particular challenges[42-46]. Definitions of adolescence may be imprecise, non-existent, or varied, even within a particular country or community. For example, the International Committee on Harmonization defines adolescents as "those of age 12 to 16 or 18" while different government agencies within the US define adolescents variously as: "ages 12-15 years up to 16 years" (FDA); included with children as "individuals under the age of 21" (NIH Policy and Guidelines on inclusion of children); or "the period of life from puberty to maturity" (USA National Center for Health Statistics). Even within these age groups, adolescents may have differing degrees of autonomy based on their marital status, whether they are parents, or whether they live independently.

Even with a clear definition of adolescence, in many settings the laws, policies, and practices that may influence the participation of adolescents in trials are non-existent or ill-defined. For example, in some settings participating in trials may require parental or guardian consent, with the adolescent's assent, while in other settings adolescents over a certain age (such as 16 or 18 years) can consent on their own. Requiring parental consent can create challenges for confidentiality, particularly with respect to treatment for sexually transmitted infections and other conditions, as well as for accurate reporting of sensitive issues such as sexual behaviour. Establishing who are legal guardians for adolescent participants can also be a challenge. Stigma that labels participants in HIV trials as being sexually active, HIV-infected or "promiscuous" may be especially concerning

for adolescents and parents, and trials that provide contraception may be even more sensitive in some communities. Recruitment strategies and trial practices need to be sensitive to this and work to minimize stigma. Adolescents' differing and sometimes fluid perceptions of causality, risk, and responsibility will likely require age-appropriate and –sensitive information provision, informed consent, and tailored counselling strategies. Similarly, follow-up may be particularly challenging with adolescent trial participants, and their participation may be influenced by external factors such as the school calendar.

While hesitation among some communities and policymakers may exist, in reality, ethical review committees and regulators in many settings recognize the terrible burden of HIV disease among young women, and would like to find ways to facilitate adolescents' participation in trials and ensure that paediatric trial results are disaggregated by age. It is therefore important that researchers not make assumptions about what is or is not possible. Meeting participants underscored the importance of finding practical solutions to facilitate adolescents' participation in trials. Developing an evidence base and disseminating this information are first steps. Noting that this is a particularly complex issue, and one that concerns many actors in the HIV field and beyond, they deemed work on adolescents an urgent priority and recommended that an expert group be tasked with reviewing and synthesizing information and experience as the basis for prioritizing further work and strategies. While there are many challenges to including adolescents in trials, researchers, policymakers, regulatory agencies, and communities simply must find practical solutions to these challenges.

Structural Determinants of Vulnerability to HIV Exposure

Many people and institutions working in the field of women and AIDS recognize the importance of underlying structural factors, but approaches to HIV prevention continue to be primarily technical and health sector driven. The dynamics among structural factors such as poverty and economic inequality, gender inequality, and mobility and migration are complex, overlapping, and mutually reinforcing. While structural factors are acknowledged, it is unusual to look at them in a systematic manner and even less common to work to address them through specific actions. This complexity has made it difficult to generate evidence that such approaches can have a direct impact on reducing HIV risk.

The Intervention with Microfinance for AIDS and Gender Equality or IMAGE Project in rural South Africa worked to test the efficacy of a structural intervention -- microfinance with gender and HIV training – on a range of outcomes related to HIV prevention and gender-based violence[47, 48]. The project used “gold standard” research methods, applying a cluster randomized controlled trial design comparing intervention and matched control groups in a multi-level evaluation strategy following some 5,000 people for 2-3 years. The intervention led to improvements in food security and household assets; improvements in several indicators of women's empowerment; a 25% increase in levels of condom use; and a 55% reduction in past year experience of intimate partner violence – all of which are known to be associated with HIV acquisition risk. The study did not find a direct impact on HIV acquisition itself, possibly due to the relatively short timeframe of the study.

The experience highlights a number of key issues for programmes and trials addressing structural determinants. Perhaps the most compelling lesson is that it is possible to change seemingly entrenched gender and social norms such as gender-based violence, even within a relatively limited period of several years. HIV interventions can work to meet basic needs through building on existing programmes outside the health sector. Partnering with organizations expert in key programme areas -- in this case a strong, existing microfinance organization – is important to overall programme effectiveness and credibility but building such partnerships and devising strategies for integrating diverse programme components takes time. Finally, addressing an overall “risk environment” rather than a specific “risk group” may mean that there are a number of indirect target – and beneficiary – groups.

Amplifying this example will require building a body of evidence around structural interventions, including

careful consideration of how best to approach research in this area. The randomized controlled trial design lent a great deal of credibility to the IMAGE programme and its findings, but it may not be the best way to measure key outcomes or to really understand such a complex and multifaceted programme. The strengths of using randomized controlled trials for structural interventions need to be balanced against the challenges: enrolling a large number of clusters; anticipating all relevant outcome measures; balancing flexibility in the approaches with the need for a rigorous study design; and explaining to communities acting as control populations why experimental programmes are being “withheld”. Ongoing efforts need to consider how to maintain the strength of the study design without losing the ability to detect real effects. Given the complexity and limited opportunity for conducting trials of structural interventions, it is also important to build research around “natural experiments” where structural interventions are ongoing in a community or being created in response to policy changes.

The ultimate aim of generating evidence that structural interventions “work” is to benefit more women and communities through wider scale implementation of effective programmes. Mainstreaming and scaling up these approaches will require commitment, resources, and experimentation on the part of many different actors. For example, if structural interventions work they could be incorporated into National AIDS Plans and other policy platforms to garner cross-sectoral collaboration. Organizations and political entities at international, national, and local levels will need to champion and fund this approach, while technical expertise will be needed to lead programme implementation and analysis. This will demand new types of partnerships across sectors and disciplines. The current structures of funding agencies, research approaches, and implementing organizations are generally not well-suited to this kind of collaboration.

In the lively discussion about the relation of such structural approaches to clinical trials, several participants argued that clinical trials should more effectively recognize and address the complex structural issues around women’s lives by including structural interventions for trial participants. However, others cautioned that such efforts are well beyond the capacity of biomedical researchers who conduct clinical trials and most clinical trials in low-resource settings are already so large and complex that they can be difficult to complete. While it may be possible to partner with a local organization to address livelihood concerns, for example, this could be unwieldy. In addition, while some may see it as an opportunity to provide additional support to women, others may perceive it as coercive through providing “undue inducement” for women to enrol in a clinical trial.

Meeting participants strongly endorsed the importance of structural interventions to address HIV and identified structural intervention randomized controlled trials, and other research designs, as priorities for women and girls. There was a great deal of interest in developing this area, with a small group established to pursue it further.

The Changing Research Context

HIV research has created a number of new norms and expectations about how to “do” research, and several of these were discussed during the meeting. Many research efforts involve a wide range of stakeholders – participants, communities, activists, health professionals, policymakers and many others – in developing, advising, and implementing research, as well as disseminating results. UNAIDS and the AIDS Vaccine Advocacy Coalition (AVAC) published in 2007 *Good participatory practice guidelines for biomedical HIV prevention trials* to guide these efforts[49]. Prompted in part by controversies surrounding the Tenofovir pre-exposure prophylaxis trials, activists also pushed for new norms around access to care and standard of prevention in prevention trials. Many of these perspectives are now reflected in the UNAIDS/WHO 2007 *Ethical considerations in biomedical HIV prevention trials* which promotes this new norm especially with respect to ensuring that trial participants who become HIV-infected during the trial will have access to care, including to internationally recognised antiretroviral treatment regimens when needed[42]. Recognizing the complex interplay of social, economic, political, sexual, and biological factors that influence the epidemic, a number of HIV researchers from diverse backgrounds have continued to work to integrate social science and biomedical approaches. Finally, the epidemic has generated new partnerships among industry, the public sector, and activists to prioritize and ac-

celerate critical research, and provide access to life prolonging medicines. The following section summarizes some of the ways that changing dimensions of research need to work to serve the interests of women and girls in several key areas: community participation; access to care; standard of prevention; integrating social science; and new partnerships among industry, public sector, and activists.

Community Participation

While many HIV research efforts have set new standards for transparency and community consultation, these processes have tended to engage mainly activists and community-based organizations working specifically on HIV. To make trials work for women and girls, HIV prevention and treatment researchers and research sponsors need to actively and consciously reach out to and include organizations and individuals with an explicit gender perspective that work on women's rights, economic empowerment, and sexual and reproductive health. Participatory and community involvement in trials can also help articulate and protect the interests of trial communities and participants, and it is critical to ensure that women are included in these processes. Research questions need to be defined in consultation with women, providers, and policymakers to identify those of highest priority; trials need to answer questions in ways that are relevant to women – for women, not just about them; and research findings need to be translated into actionable plans.

Access to care and standard of prevention

Evolving notions around access to care provide a useful example of how including women and a gendered approach can influence trial design to better benefit women and reflect their priorities and needs. Access to antiretroviral treatment for people who become HIV-infected during trials is a particular concern for women in settings where they may be disadvantaged in access to treatment. A gendered perspective would highlight the importance of services to be provided during trials such as on-site contraceptive services, pregnancy care for trial participants, access to safe abortion when needed and desired, provision of cervical screening and care for cervical dysplasia, and counselling by care providers trained to handle issues such as gender-based violence. Meeting participants called for greater emphasis on ensuring consistency in standard of care across trials, and expanding the concept of “access to care and standards for prevention” beyond HIV treatment to include standards for sexual and reproductive health and a basic health package.

Integrating Social Science

Many trials are already integrating social science methods to understand and address the complex needs and motivations of women, and barriers to and facilitators of women's participation in trials. Preparedness studies use social science approaches, often qualitative methods, to identify and address barriers and facilitating factors. Prevention trials have also used social science out of necessity to develop tools for maximizing adherence to product use and study procedures and to improve accurate reporting of sensitive information, including sexual behaviours. This information is critical to interpreting the trial results, as well as to understanding the more subtle motivations and considerations around trial participation, product use, sexual behaviours, adherence, and so forth.

Social science methods should also be integrated more consistently into treatment trials and treatment programmes. In many countries of southern Africa women are disproportionately more represented among those on treatment in comparison with the proportion of people living with HIV in need of treatment who are women. This may be because their HIV and health status is identified in antenatal and other health services. However, women may be more likely to drop out of treatment programmes due to responsibilities for housework and child care, among other constraints. It is important to understand the considerations and factors that contribute to women accessing and staying on treatment. Social science approaches can contribute critically in many areas to make trials work for women and girls, particularly in ensuring that trials are designed and data are collected in a manner that results can be translated and applied to women's real lives.

Partnerships among industry, public sector and activists

Given that 70-90% of trial participants in pharmaceutical trials are men [9-13], the research community, including pharmaceutical companies, needs to do a much better job at including women in clinical trials and then collecting, analysing, and making public relevant data concerning women. Most registration studies for new drugs are only powered to look at biomarker endpoints and are not powered to look at sex differences in outcomes. The meeting noted that representation of women in most pivotal registration trials is completely inadequate. Pharmaceutical companies as well as research funding agencies need to commit and be held accountable for including women in trials in sufficient numbers. All research partners can work to find innovative and creative ways to meet this challenge and to monitor progress. Industry is also a major repository of “fugitive data” on women, data that have been collected but not analyzed separately as part of submissions for licensure that have not become public. Such data could be made available for analysis and applied to programmatic and policy decisions. With these approaches, industry can help champion new approaches for making HIV trials work for women and adolescent girls.

Public-private partnerships have worked to broaden the goals of drug development to meet public health needs, and a number of companies are working with product development partnerships through donating intellectual property for products that can then be developed further with public and philanthropic investment. For example, the International Partnership for Microbicides has agreements with Pfizer, Tibotec, Merck, and Bristol-Myers Squibb to develop antiretroviral compounds as vaginal microbicides. In order to accelerate and expand efforts to meet the needs of women and girls, this kind of collaboration should shift even further. Resources of the pharmaceutical industry should be integrated even more into the process of developing public goods through, for example, sharing best practices such as efficient conduct of clinical trials and private-sector approaches to deciding which products are advanced into large scale clinical trials. While collaboration among industry, the public sector, civil society, and activists has been substantial, these efforts need to be stepped up and expanded.

Balancing expectations of research

Research provides a real opportunity to bring new resources – information, technology, money, and expertise – into a community. However, research processes cannot be expected to meet all of a community’s needs – or even all of the needs of trial participants. Growing expectations that researchers will work closely with communities to provide state-of-the-art health care and address other multiple needs may not be realistic. They may make research so unwieldy that it is impossible to do. Although community mechanisms can hold researchers accountable, they also need to direct their attention to the responsibilities of governments, civil society, local service providers, employers, families, and funders.

Recommendations

Recommendations addressing the research, advocacy, policy, and programmatic spheres emerged throughout the meeting. There was a high degree of consensus about the urgency and importance of strategies for moving forward. These recommendations are grouped under the following themes:

Establish a new norm around women and trials

- Establish a “new norm” that all research on critical health and drug interventions must include a scientifically meaningful number of women.
- Make the case for the increased participation of women in research by articulating the gaps in knowledge and the consequences for women.
- Raise awareness about the under representation of women in research and the consequent implications for their health among key constituencies, such as women’s groups, HIV programmes, sexual

and reproductive health groups, HIV activists, regulatory and ethical review agencies, research sponsors, and researchers.

- Make investigation of sex differences part of clinical research conceptualization, implementation, and reporting.
- Build further mechanisms of accountability within regulatory frameworks and other standard setting bodies to require trials to gather, analyze, and report sex-disaggregated data. These mechanisms may include: research agency guidelines for calls for proposals; standards used by Institutional Review Boards (IRBs); pre-registration with international trial registries; Good Clinical Practice (International Committee on Harmonisation); review criteria for scientific publications; and Consolidated Standards of Reporting Trials (CONSORT) guidelines. This effort should involve science, policy, and advocacy groups.
- Explore how ethical guidelines for HIV treatment trials can be used to support these arguments or can be modified to address gender in the same way as do the existing UNAIDS/WHO ethical guidelines for biomedical HIV prevention trials.
- Actively sensitize and/or conduct training on the gaps in knowledge and research in women's health for key constituencies such as journal editors, institutional review boards, researchers, donors, and so forth.
- Create a sense of possibility and urgency that things can and must change.



Women and power

- Promote the design of trials for women that specifically address women and answer questions about women.
- Ensure that women are adequately represented in all HIV-related trials that may have an impact on them – basic science, prevention, treatment, and structural trials.
- Ensure that women are enrolled and retained in sufficient numbers to allow for adequate power to draw conclusions based on subgroup analyses.
- In trials where women subjects are enrolled (i.e. in prevention of mother-to-child transmission), encourage trial outcomes that will be specific to women's health and relevant to their vulnerability and social status.
- Develop a “score card” approach to track HIV trials over time and establish an evidence base on the degree to which trials collect, analyze, and report on sex-disaggregated data.
- Develop a strategy to identify and analyse “fugitive data” from research on women and HIV conducted by industry, public programmes, and other entities.
- Establish and fund registries to allow for sharing data across ongoing research, prevention, and treatment programmes. One clear priority is to evaluate the need for a registry for pregnancy and antiretroviral treatment beyond the current international, pharmaceutical-based registry on adverse effects of antiretroviral drugs in pregnancy.

Reconceptualise how research is conducted

- Re-conceptualise the way that research questions are developed. Ask national policymakers or provider communities to identify those HIV research questions that are most pressing, so that research addresses what is most urgent and relevant for women along with what is most interesting from a scientific perspective. Explore whether and how research priorities in general, and those for women specifically, can be included as part of national AIDS plans.
- Build community literacy and understanding of research to stimulate local community activism for research relevant to women, and build partnerships, support, and clear understanding for community based trials.
- Involve women's groups and gender experts in conceptualizing and setting HIV research agendas and

ensure that they are included in community preparation and consultation of processes.

- Integrate biomedical and social science approaches so that trials can draw operational and actionable conclusions that reflect women's health and lives.
- Identify and promote the most effective evidence-based HIV treatment strategies for women through carefully designed research and through analysis of programmes scaling up treatment.
- Focus more funding for and attention to trials and studies that evaluate potential structural interventions in order to build the evidence base, particularly addressing HIV among women and adolescent girls in the hyper-endemic of southern Africa.
- Develop standard of care guidelines for a reproductive health package and basic health package for trial participants. This would include general guidelines that could be modified at the national or community level that would outline a process for determining who should be involved in defining and delivering such a package, such as governmental, non-governmental, or other service delivery groups working with the researchers.
- Ensure that research findings are shared broadly and translated more effectively for use by policymakers, providers, and individuals. Re-examine existing studies on key issues and draw out lessons and implications for policy.

Develop concrete strategies and actions for including adolescents in trials

- Review and document laws and policies as they pertain to adolescent participation in research trials. Examine how their rationale and/or criteria influence whether adolescents can be included in trials and how trials that include adolescents can be developed.
- Identify, analyze, and draw lessons from trials and bridging studies that have included adolescents, such as those of the Carraguard microbicide and the Merck and GlaxoSmithKline human papillomavirus vaccines.
- Develop key advocacy messages regarding the importance of HIV research that answers questions about and benefits adolescents, in light of high HIV incidence in this age group in many generalized epidemics.
- Convene a working group/panel that involves adolescents to examine issues that pertain to them, develop strategies, and ensure momentum in pushing forward research in this population group.

Continue biomedical research on key questions relevant to women and HIV

- Continue to explore why viral load set point appears to be less likely to predict progression of HIV disease in women. One approach would be to create a database to identify and follow women seroconverters from a wide range of existing prevention trials and cohorts. These could include, for example, participants in trials of microbicides, vaccines, pre-exposure prophylaxis, and HSV-2 suppression. In addition, literature reviews of existing evidence on outstanding questions on viral load set points should be regularly updated.
- Design research that includes women of reproductive age and pregnant women much earlier in the product development process to answer questions about whether new drugs and prevention tools are safe and effective for use during pregnancy. This is very important in HIV prevention trials where high pregnancy rates and requirements that pregnant women stop using test products are inhibiting the ability of Phase III trials to answer questions about overall product effectiveness. In reality, if such products are found efficacious and made accessible, they will be used during pregnancy regardless of

labelling.

- Develop standards for appropriate cervical screening and care, including acetic acid visualisation for HIV-positive women, for trials in high HIV prevalence settings.
- Examine the efficacy of human papillomavirus (HPV) vaccines in HIV-positive populations to inform public sector roll-out of these vaccines in Africa.
- Update guidelines for conception for discordant couples and HIV-positive women to include practical, feasible strategies for low resource settings. Convene an expert meeting to set a comprehensive and concrete research agenda (UNAIDS, UNFPA, WHO).
- Explore linking sexual and reproductive health care with HIV care and antiretroviral treatment programmes, for example, linking antenatal, post-partum, and on-going HIV care.
- Identify structural approaches to increasing and sustaining women's access and adherence to antiretroviral treatment.

Looking Ahead

The excellent presentations, dynamic discussions, and compelling evidence of the clear need for further research to guide policy and practice made for a results-oriented meeting. Meeting participants created a six point action plan and designated several working groups to follow up on many of the action plan recommendations. Progress, activities, and plans are being reported at a satellite symposium sponsored by meeting convenors at the XVII International AIDS Conference in Mexico City in August 2008. Participants from all sectors left the meeting as advocates for finding real solutions to make HIV trials work better for women and adolescent girls.

List of participants

Meeting Co-Chairs:

Catherine Hankins, Joint United Nations Programme on HIV/AIDS (UNAIDS); Geneva, Switzerland

Kristan Schoultz, Global Coalition on Women and AIDS (GCWA); Geneva, Switzerland

Geeta Rao Gupta, International Center for Research on Women (ICRW); Washington, USA

Ben Plumley, Tibotec; Mechelen, Belgium

Meeting Participants:

Kawango Agot, University of Nairobi; Nairobi, Kenya

Kim Ashburn, ICRW; Washington, USA

Roberta Black, National Institutes of Health; Bethesda, USA

Kate Bourne, International Women's Health Coalition; New York, USA

Ward Cates, Family Health International; Durham, USA

Nomita Chandhiok, India Council for Medical Research; New Delhi, India

Wairimu Chege, Kenya Medical Research Institute; Nairobi, Kenya

Lynn Collins, United Nations Population Fund (UNFPA); New York, USA

Kathleen Cravero, United Nations Development Programme (UNDP); New York, USA

Suzanne Crowe, Macfarlane Burnet Centre for Medical Research; Melbourne, Australia

Judith Currier, University of California; Los Angeles, USA

Marie-Pierre de Bethune, Tibotec; Mechelen, Belgium

Isabelle de Zoysa, World Health Organization (WHO); Geneva, Switzerland

Nina Ferencic, United Nations Children's Fund (UNICEF); Geneva, Switzerland

Jane Ferguson, WHO; Geneva, Switzerland

Anna Forbes, Global Campaign for Microbicides; Washington, USA

Claudia Garcia Moreno, WHO; Geneva, Switzerland

Beatriz Grinsztejn, Oswaldo Cruz Foundation; Rio de Janeiro, Brasil

Sofia Gruskin, Harvard School of Public Health; Boston, USA

Bryna Harwood, University of Illinois; Chicago, USA

Rebecca Hoppy, Rabin Strategic Partners; New York, USA

Karyn Kaplan, Thai AIDS Treatment Action Group; Bangkok, Thailand

Quarraisha Abdool Karim, CAPRISA; Durban, South Africa

Julia Kim, University of Witwatersrand; Johannesburg, South Africa

Nicolai Lohse, UNAIDS; Geneva, Switzerland

Ruslan Malyuta, UNICEF; Geneva, Switzerland

Karen Manson, Tibotec; Mechelen, Belgium
Elizabeth Mataka, Zambia National AIDS Network; Lusaka, Zambia
Luciana Maxim, International Partnership for Microbicides; Silver Spring, USA
Elizabeth McGrory, independent consultant; Nyack, USA
Pema McGuinness, Rabin Strategic Partners; New York, USA
Julie McHugh, Johnson and Johnson; Yardley, USA
Lydia Mungherera, The AIDS Support Organization (TASO); Kampala, Uganda
Heidi Nass, International Community of Women Living with HIV/AIDS; Madison, USA
Ruth Nduati, Network of AIDS Researchers in East and Southern Africa; Nairobi, Kenya
Bach-Yen Nguyen, Merck Research Laboratories; North Wales, USA
Judy Polsky, UNAIDS; Geneva, Switzerland
Steve Rabin, Rabin Strategic Partners; New York, USA
Gita Ramjee, Medical Research Council; Durban, South Africa
Helen Rees, University of Witwatersrand; Johannesburg, South Africa
Sarah Russell, UNAIDS; Geneva, Switzerland
Shana Ward Ryzowy, Global Business Coalition on HIV/AIDS, TB and Malaria; New York, USA
Sagri Singh, International AIDS Vaccine Initiative; New York, USA
Sharon Walmsley, University of Toronto; Toronto, Canada
Jane Yeo, GlaxoSmithKline; Greenford, United Kingdom

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The Joint United Nations Programme on HIV/AIDS (UNAIDS) brings together ten UN agencies in a common effort to fight the epidemic: the Office of the United Nations High Commissioner for Refugees (UNHCR), the United Nations Children's Fund (UNICEF), the World Food Programme (WFP), the United Nations Development Programme (UNDP), the United Nations Population Fund (UNFPA), the United Nations Office on Drugs and Crime (UNODC), the International Labour Organization (ILO), the United Nations Educational, Scientific and Cultural Organization (UNESCO), the World Health Organization (WHO), and the World Bank.

UNAIDS, as a cosponsored programme, unites the responses to the epidemic of its ten cosponsoring organizations and supplements these efforts with special initiatives. Its purpose is to lead and assist an expansion of the international response to AIDS on all fronts. UNAIDS works with a broad range of partners – governmental and nongovernmental, business, scientific and lay – to share knowledge, skills and best practices across boundaries.



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UNHCR
UNICEF
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WHO
WORLD BANK

UNAIDS
20 AVENUE APPIA
CH-1211 GENEVA 27
SWITZERLAND

Tel: (+41) 22 791 36 66
Fax: (+41) 22 791 48 35
e-mail: distribution@unaids.org

www.unaids.org

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