Support for Women's Inclusion in HIV-Related Clinical Research

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Abstract

The opportunity to participate in and benefit from scientific advances derived from research is a human right that is not equitably afforded to all populations. Women are unfairly subjected to social and contextual factors that have historically limited their participation in HIV-related clinical research despite the disproportionate impact of HIV among this group. These factors include intrusive and unreasonable contraception requirements, a hyper-focus on pregnancy potential and unknown harms to the developing fetus, nonscientific sex biases, and a lack of women-centered recruitment strategies. Collectively, such practices will limit the generalizability of key research findings among populations of women and continue to harm the health of all women disproportionately affected by HIV. This policy statement recommends that APHA call on federal actors to continue to fund and support the strategic goals of federal research offices that aim to increase women's participation in HIV-related clinical research. Also, it calls on federal, private, and other funders, participants, advocates, governmental agencies, and all other entities to support data analyses by sex/gender to determine whether there are sex/gender differences in response to medical treatments under study, develop a workforce inclusive of women living with and affected by HIV, and use evidence-based practices to support informed decision making among women as participants and potential beneficiaries of advances in scientific research.

Relationship to Existing APHA Policy Statements

- APHA Policy Statement 20162: Strengthening the National HIV/AIDS Strategy to Achieve an HIV/AIDS-Free Generation
- APHA Policy Statement 201413: Strengthening the National HIV AIDS Strategy to Achieve an HIV AIDS-Free Generation
- APHA Policy Statement 20171: Supporting Research and Evidence-Based Public Health Practice in State and Local Health Agencies

- APHA Policy Statement 20189: Achieving Health Equity in the United States
- APHA Policy Statement 200410: Proposed Resolution Condemning Actions Against LGBT and HIV Related Research and Service Delivery
- APHA Policy Statement 202111: Sexual and Gender Minority Demographic Data: Inclusion in Medical Records, National Surveys, and Public Health Research

Problem Statement

The Universal Declaration of Human Rights (1948) and the International Covenant on Economic, Social and Cultural Rights (1996) afford the right to the benefits of scientific progress to all people.[1] Unfortunately, not all populations are afforded equal access to benefits from scientific research owing to their limited participation in clinical trials. According to the National Institutes of Health (NIH) Revitalization Act of 1993, women (and members of racial/ethnic minority groups) must be included as participants in NIH-funded clinical research, defined as (1) patient-oriented research (research conducted with human participants or on material of human origin, such as tissues and specimens, in which an investigator directly interacts with human participants), (2) epidemiological and behavioral studies, and (3) outcome and health service research.[2] The statute prohibits cost as an acceptable rationale for exclusion. Furthermore, the act stipulates that "[w]omen of childbearing potential should not be routinely excluded from participation in clinical research."[3]

Despite directives for ethical and equitable inclusion and fair participant selection in clinical research from federal entities, women's health advocates, and other frameworks,[3–5] cisgender women (hereafter referred to as women) have historically been and continue to be consistently and systematically underrepresented in HIV-related clinical research[6,7] even though they represent 53% of all people living with HIV globally and 19% domestically.[8,9] Black women in the United States are grossly disproportionately affected by HIV, accounting for 54% of incident diagnoses.[10]

Women's participation in HIV-related clinical research varies depending on the type of research being conducted (e.g., HIV treatment, HIV cure, HIV vaccines). A 2016 systematic review conducted by Curno et al. demonstrated that women represented only 19.2% of participants involved in antiretroviral therapy (ART) studies, 38.1% of those participating in HIV vaccine

studies, and a paltry 11.1% of those taking part in HIV cure studies.[11] Several social and structural factors have affected women's ability to meaningfully participate in HIV-related clinical research, including (1) intrusive and unreasonable contraception requirements, (2) ability to become pregnant and potential harm to the developing fetus, (3) sex biases, and (4) women-centered recruitment strategies.

As part of participation in HIV-related clinical research studies, women are subjected to intrusive and unreasonable contraception requirements to prevent pregnancy during the study period. Stipulations include the use of two forms of reliable contraception or barrier methods to prevent pregnancy.[12] This assumes that (1) participants have seamless access to sexual and reproductive health services and affordable contraceptive methods, (2) participants cannot make a personal decision to control their ability to become pregnant, and (3) pregnancy prevention is a reasonable exclusion criterion for participation in an HIV clinical trial. Although a common caveat for inclusion in HIV clinical research, safe and reliable contraception is rarely provided free of cost to study participants to address pregnancy prevention. This requirement presents additional barriers and creates undue harm for women. Participants' ability to become pregnant is frequently a barrier to participation in HIV-related clinical research. Informed consent language often directs participants to "inform their doctor immediately" if they become pregnant during the study, as if pregnancy is the primary potential adverse event or ethical concern to investigators.[12]

Ethically, there may be a reasonable safety concern for participants who become pregnant and their developing fetuses given the uncertainty of calculable risks during participation in a research study.[13] Current research practices explicitly exclude pregnancy as a criterion for research participation and do not fully support bodily autonomy and informed decision making around participation.[12,14] These practices contravene basic ethical principles and guidelines for research involving human participants[15] such as those outlined in the Belmont Report, which include (1) respect for individuals as autonomous agents with free will to make informed decisions; (2) beneficence, ethical treatment of people, and protection from harm; and (3) justice, fairness of distribution, and prevention of injustice.[16]

A consequence of excluding pregnancy in research is limited data on drug safety and efficacy in pregnancy, and the pharmacological effects of therapeutic agents on developing fetuses may be unknown. Therefore, it should not be assumed that pregnancy prevention is a reasonable exclusion criterion for participation in an HIV clinical trial. For example, clinical studies have demonstrated the safety and efficacy of bictegravir (BIC) as an antiretroviral medication option among females living with HIV who are not pregnant.[17] However, according to the Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States, there are no safety or efficacy data on BIC use during pregnancy.[18] Those who become pregnant while taking BIC would have to consider switching their HIV medication regimen, and providers would be responsible for managing unknown side effect profiles during pregnancy.

Excluding women from clinical research only widens gaps in understanding around HIV-related sex/gender differences in pharmacodynamics and therapeutic effects of experimental agents. Sex-biased, nonrepresentative research studies that include only males have limited generalizability to populations of people living with HIV and do not equitably advance the compendium of HIV scientific knowledge among women.[19] Research including women has highlighted sex-linked differences in vaccine responses, HIV pathogenesis, responses to HIV treatments, and HIV reservoir size and dynamics.[20] For example, a study conducted by Scully et al. demonstrated sex-based differences in HIV reservoir activity among a cohort of age-matched adults living with HIV and outlined implications for efforts aimed at HIV curative therapies.[21]

HIV clinical studies do not uniformly employ women-centered, evidence-based retention strategies that increase women's participation in HIV-related clinical research. Women-centered strategies include provision of transportation (e.g., rideshares for medical appointments), stipends for transportation (e.g., bus, train, and rail passes), substantive meals, and stipends for child-care services.[22,23] In a review conducted by Mendez et al., the authors described a higher rate of attrition in studies that did not include multiple retention strategies.[22]

Evidence-Based Strategies to Address the Problem

There is a global and ethical resurgence in efforts to meaningfully include women in HIV-related clinical research. Several policies and guidelines have provided a roadmap for researchers, funders, and other entities to ensure meaningful inclusion of women in HIV-related research and support for sex/gender analyses. While some of those strategies are applicable to research broadly, they have significant relevance to HIV-related clinical research. Examples of strategies are provided below.

- Include women living with HIV in research activities at all stages of development and implementation as early as possible to increase the availability of scientific knowledge among women with HIV over the life span, including during pregnancy[23]: The Greater Involvement of People Living with HIV and Meaningful Inclusion of People Living with HIV/AIDS principles describe the potential of people living with HIV to be meaningful involved in HIV response efforts at all levels and in all sectors of civil society.[24] Also, the 2016 Diverse Women in Clinical Trials Initiative, co-supported by the Office of Women's Health and the NIH Office of Research in Women's Health, raises awareness about the importance of participation among diverse groups of women in clinical research and shares best practices in clinical research design, recruitment, and population analyses.[25]
- Require sex and gender reporting of data from HIV-related clinical research to highlight gaps in scientific knowledge among populations of women who are disproportionately affected by HIV: As of 1998, the Food and Drug Administration (FDA) required that all investigational new drug applications provide data related to participation in clinical trials and that data be presented in annual reports by sex, age, and race.[25]
- Routinize best practices in research settings that have supported women's participation in HIV-related clinical research: Research should center women's lived experiences and address issues such as compensation for transportation, child care, substantive meals, and extended site hours of operation.[4,22]

Opposing Arguments/Evidence

Nexus of vulnerability: Pregnant women and unborn fetuses have been historically categorized as "vulnerable populations" in research.[26] Because an unborn fetus is unable to provide assent to participate in HIV-related clinical research and potential risks for fetal harm are not well

categorized for experimental therapies, pregnant participants, including those who become pregnant while participating in research, should be excluded for safety reasons.

The bodily autonomy of women living with HIV, regardless of pregnancy status, should be supported and their decision to participate in an HIV-related clinical research trial fully respected. Given the need for safe and effective medications for use during pregnancy, research must meaningfully include pregnant women. The Office of Human Research Protections of the U.S. Department of Health and Human Services (DHHS) describes several conditions in which pregnant women and fetuses can participate in research:

> "(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
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> (b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
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> (c) Any risk is the least possible for achieving the objectives of the research;
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> (d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;
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> (e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(j) Individuals engaged in the research will have no part in determining the viability of a neonate."[27]

Pregnancy-related considerations—Teratogenicity: Some researchers and entities would offer that experimental medications can cause abnormal fetal development, and as a result pregnancy is a justifiable exclusion criterion for participation in developmental drug studies.

As an example, between 1957 and 1962, thalidomide was prescribed to treat morning sickness in global populations of pregnant women. Thalidomide exposure was eventually linked to a number of severe birth defects through case reports involving more than 10,000 children. Babies were born with limb defects/damaged limbs, extra digits on their hands and feet, shoulder and hip joint damage, poor vision/eye defects, ear damage, facial defects (e.g., enlarged nevus or hemangioma), vertebral column defects (e.g., irregular vertebral spacing, fusion of vertebra, progressive kyphosis), internal organ damage, and nerve and central nervous system damage (e.g., facial palsies, autism, epilepsy).[28] These circumstances provide support for the additional ethical considerations and protections for developing fetuses later defined in the 1977 document General Considerations for the Clinical Evaluation of Drugs, which effectively excluded women of childbearing potential from participation in phase I and early phase II clinical trials.[29]

Although thalidomide was prescribed to treat nausea in pregnancy, it was not originally approved for such use. This exemplifies the need to further examine the pharmacokinetic properties of agents in pregnancy. In the absence of data from preclinical studies and phase II and III trials, these scientific gaps will only proliferate.

In another example, results from the Tsepamo study of birth outcomes among women in Botswana taking the ART medication dolutegravir (DTG) during conception or at birth showed a potential higher risk of neural tube defects.[30,31] Subsequently, global health agencies including the World Health Organization, the FDA, and the DHHS adult and pediatric guidelines panels recommended against the use of DTG during pregnancy out of concern for adverse fetal development.[32]

Subsequent data from in vitro and animal models revealed that higher doses of folate could overcome any effects of DTG on neural tube defects, and further analyses demonstrated that the difference in the prevalence of neural tube defects among women taking DTG regimens relative to those not taking DTG-containing regimens was no longer statistically significant.[32]

Difficulty in reaching and engaging women in HIV-related clinical research: Women have historically been classified by researchers as "hard-to-reach,"[33] often needing additional costly supportive services such as childcare and alternative appointment times to accommodate working schedules that may not be supported by already thinly stretched grant funds.

Categorizing women as difficult to reach is stigmatizing and inaccurate. Use of such terminology to describe women's participation in clinical research could negatively affect their participation. Studies have demonstrated that women are in fact not difficult to reach but require unique and different recruitment and engagement strategies than those that have been historically successful for men. Successful recruitment strategies for women include dedicated women's outreach workers,[34] culturally reflective staff,[35] involvement of community consultants, additional monetary funds for participants, site-specific enrollment plans, and supportive child care and transportation.[22,36]

Action Steps

APHA recommends several actions to address the barriers to the meaningful and equitable participation of women in HIV-related clinical research identified in this policy statement.

APHA calls on:

1. Congress and the NIH to permanently fund the Office of Research on Women's Health (charged with ensuring women's inclusion in NIH-funded research) and the Sexual and Gender Minority Research Office (charged with ensuring that sexual and gender minority populations are included in NIH-funded research).
2. The Office of Research on Women's Health to continue its development efforts and goals to (a) advance rigorous research that is relevant to the health of women with a focus on health equity and diversity; (b) develop methods and leverage data sources to consider sex and gender influences that enhance research for the health of women; (c) enhance dissemination and implementation of evidence to improve the health of women; (d) promote training and careers to develop a well-trained, diverse, and robust workforce to advance science for the health of women; and (e) improve evaluation of research that is relevant to the health of women.
3. The FDA's Office of Women's Health to continue its advocacy for the participation of women in clinical trials, support for scientific sex difference research within and outside the FDA, and provision of sex differences training and other resources for health professionals.
4. The NIH to support HIV clinical trials that include only women (e.g., the AIDS Clinical Trials Group 5366 study[37]).
5. The NIH to promote and create resources to assist researchers with their efforts to engage, recruit, and retain women in clinical research (e.g., the NIH Inclusion Outreach Toolkit).

Also, APHA calls on federal, private, and other funders, participants, advocates, governmental agencies, and all other entities proximally affiliated with HIV-related research to support research best practices such as the following:

1. Increasing women's participation in HIV-related clinical research at all phases.
2. Prioritizing adequate participation of women in clinical trials most likely to involve disease therapies.
3. Mandating analyses of scientific data by sex/gender to determine whether there are sex/gender differences in response to a medical treatment being studied.
4. Implementing enrollment stopping rules to limit the unnecessary overrepresentation of a specific population in HIV research studies.

5. Providing risk and benefit information to women as potential research participants in support of bodily autonomy and the right to decide whether or not they want to participate in a clinical research study.
6. Providing no-cost, easily accessible contraception options to those who wish to access them as part of participation in HIV clinical research.
7. Increasing research and analyses among key subpopulations of women such as transgender women, racial/ethnic minority women (e.g., Black, indigenous, Latinx), and women older than 50 and younger than 30 years.

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