An Advocate's Guide to Research in Pregnant and Lactating People

AVAC
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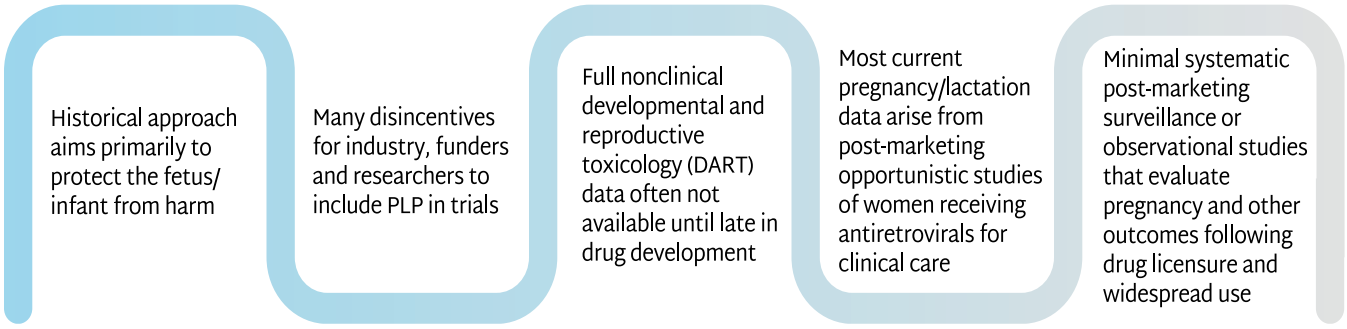
The Need

- Cisgender women are 2-3 times more likely to acquire HIV during pregnancy and 4 times more likely post-partum than otherwise
- Women who acquire HIV during pregnancy have an 18% chance of transmitting HIV to their newborn, and up to a 27% chance if they acquire HIV while breastfeeding
- The exclusion of Pregnant and Lactating People (PLP) from research results in:
  - A lack of data on dosing and maternal and fetal safety
  - Limitations around prescribing potentially beneficial interventions
  - PLP lack the data needed to make informed health and HIV prevention decisions
  - Exclusion from potential direct benefits of research participation
  - Delays and discrepancies in health policies and programs
- HIV prevention options for PLP are limited, and there are major evidence gaps across studies of oral and injectable pre-exposure prophylaxis (PrEP), vaginal rings and gels, monoclonal antibodies and vaccines

PLP include cisgender women, transgender men and those who identify as gender non-binary who are able to get pregnant. For transgender and gender-diverse pregnant people, evidence is glaringly absent—a reflection of the overall failure to conduct meaningful HIV prevention research in gender-diverse populations. Research is needed to better understand the potential population size of those likely to become pregnant, barriers to accessing HIV prevention, interactions between hormones and HIV prevention options and their implications on safety and efficacy.

Aside from recent exceptions, most biomedical HIV research excludes PLP, and those who become pregnant during a trial are stopped from further use of the study drug (see Figure 4 for details pointing to progress). Researchers, ministries of health, funders and regulators often make protectionist decisions regarding inclusion of PLP in trials, that are ultimately disempowering and reinforce their heightened vulnerability to HIV. (Figure 1).

Figure 1: Current Practices Resulting in Delayed Data in PLP (WHO/IMPAACT, 2021)



Lessons from Ebola and COVID-19

During the 2013-2016 Ebola outbreak, pregnant women were at high risk—previous outbreaks showed up to 93% maternal and 100% fetal/neonatal mortality. Clinical trials were the only source of access to potentially life-saving interventions, but pregnant women were excluded from all drug and vaccine trials out of a desire to contain research risk. This exclusion left pregnant women and their children "protected to death".

In the case of the COVID-19 pandemic, pregnant individuals who contracted COVID-19 had higher rates of adverse outcomes, including maternal mortality, preeclampsia and preterm birth. Despite increased risk, PLP remained excluded from most vaccine trials until February 2021—months after vaccines received emergency use authorization and were publicly rolled out. Without definitive guidance, pregnant people and their clinicians were left to weigh the risks of COVID-19 with the unknown safety risks of the vaccines when determining whether to get vaccinated.

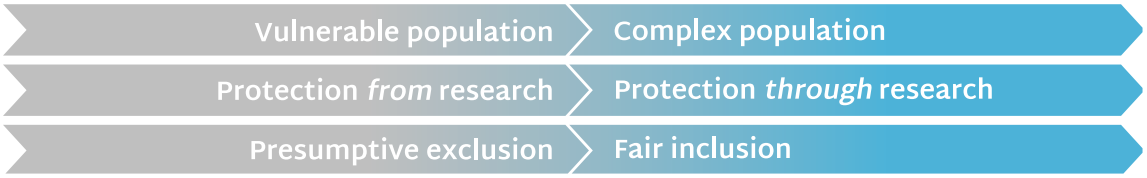
Reframing through a Reproductive Justice Lens

There is a need to reframe the importance of the inclusion of PLP in clinical trials as a reproductive justice issue. **Reproductive justice** is the human right to maintain personal bodily autonomy, have children, not have children and parent children in safe and healthy communities. Developed by a Black women's collective in 1994, reproductive justice elevates and centers the needs, voices, lived experiences and leadership of African and other Black and Brown women, transgender and gender-diverse people and youth. Under this framework, pregnant individuals have the human right to maintain personal bodily autonomy, which includes responsible, ethical involvement in clinical trials and access to life-saving prevention.

Paradigm Shifts & Progress

Since 2017, a number of initiatives have been established to address the exclusion of PLP in research. One such initiative, the Pregnancy and HIV/AIDS Seeking Equitable Study (PHASES), identified three critical paradigm shifts needed to move towards an ethical framework for the inclusion of this population (Figure 2). The shifts are: considering pregnant women as a complex population rather than a vulnerable population; protecting pregnant women through research rather than from research; and promoting fair inclusion in clinical drug trials, rather than presumptive exclusion from them. This re-framing facilitates responsible inclusion of PLP in research as the default rather than the exception.

Figure 2: Ethical Shifts in the Framing of Research in PLP (Phases, 2020)



More recently, the World Health Organization (WHO), the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and the International AIDS Society (IAS) released a Call to Action that includes a new framework for accelerating inclusion in clinical trials. A primary goal of the framework is to have pharmacokinetic (PK) and preliminary safety data on all new HIV agents in pregnancy available at the time of drug approval. The call to action also outlines the roles of various stakeholders in supporting greater inclusion.

Informed by such consensus recommendations, **AVAC, as part of the Coalition to Accelerate & Support Prevention Research (CASPR) and PHASES held a multi-disciplinary think tank and civil society convening in 2022 to identify priority actions and develop an action plan for moving them forward**. The action plan outlines four priority goals for advancing responsible research in PLP: with specific objectives and action steps for each. The goals speak to framing the need for inclusion through:

- a rights-based reproductive justice lens
- early, sustained and meaningful stakeholder engagement
- harmonized regulatory frameworks
- supportive ethics review processes.

Figure 3 contains details on these and other key initiatives, namely Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT), the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) and PRomoting Equity for Pregnant Adolescents in REsearch (PREPARE). Together, these initiatives call for and document a global consensus for more inclusion of these populations in HIV research.

Figure 3: Select Initiatives to advance inclusion of PLP

Initiative	Purpose	Key Goals/Priorities
The UNAIDS/WHO Global HIV Strategic Information Working Group 2015: Guidelines for Conducting HIV Surveillance Among Pregnant Women Attending Antenatal Clinics Based on Routine Programme Data	Shape global guidance and technical notes related to HIV surveillance and prevention efforts	Ensure that HIV surveillance systems adapt to changing dynamics, including the needs of PLP
Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies PREVENT 2017: Pregnant Women and the Zika Virus Vaccine Research Agenda: Ethics Guidance on Priorities, Inclusion, and Evidence Generation 2021: Pregnant Women & Vaccines Against Emerging Epidemic Threats: Ethics Guidance for Preparedness, Research, and Response	Provide ethics guidance at the intersection of pregnancy, vaccines and emerging and re-emerging epidemic threats (Global)	■ Pregnant women are not unjustifiably excluded from participating in vaccine studies ■ Pregnant women and their offspring benefit from advances in vaccine technologies ■ Pregnant women have access to safe and effective vaccines to protect them and their offspring
Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) 2018: PRGLAC Report, Recommendations and Implementation Plan	Advise the US Secretary of Health and Human Services (HHS) regarding gaps in knowledge and research on safe and effective therapies for pregnant and lactating women (US)	Alter "protective" cultural assumptions that have significantly limited scientific knowledge of therapeutic product safety, effectiveness and dosing for pregnant and lactating women

Initiative	Purpose	Key Goals/Priorities
PHASES PREGNANCY + HIV/AIDS SEEKING EQUITABLE STUDY 2020: Ending the Evidence Gap for Pregnant Women Around HIV & Co-Infections: A Call to Action	Provide concrete and immediately actionable recommendations for advancing timely, needed, responsible research with pregnant women on new and existing preventives and treatments for HIV and its co-infections (Global)	■ Equitable protection of pregnant and breastfeeding women ■ Increased access to first line therapeutics for pregnant and breastfeeding women ■ Respect the health of the woman
 2021: Research for Informed Choices: Accelerating the Study of New Drugs for HIV in Pregnant and Breastfeeding Women: A Call to Action	Gain consensus on the optimal timing and design of studies of new agents for treating and preventing HIV and related conditions in pregnant women, identify strategies to accelerate the study of new agents during pregnancy and formulate a strategic action plan for promoting the inclusion of pregnant women in research of new HIV agents (Global)	■ Early and sustained community engagement ■ Completion of Developmental and Reproductive Toxicity (DART) studies earlier during drug development ■ Offer option to women who become pregnant in pre-licensure trials to stay on study drug (if no indicators of negative safety signals) ■ Conduct pregnancy pharmacokinetic (PK) and preliminary safety earlier ■ Investigate adverse pregnancy and birth outcomes through dedicated pregnancy safety studies ■ Expand active surveillance of drug safety in pregnancy
Promoting Equity for Pregnant Adolescents in REsearch (PREPARE) PREPARE PRomoting Equity for Pregnant Adolescents in REsearch 2022-2025: https://www.adolescentpregnancyethics.org/	Develop empirically informed guidance for conducting ethically responsible HIV and co-infections research with adolescents who are pregnant (Global)	Develop an adolescence-specific framework delineating when and under what circumstances pregnant adolescents can and should be included in HIV and co-infections research (forthcoming)
The WHO HIV, Hepatitis and STIs Pregnancy and Breastfeeding Therapeutics Working Group 2024: Antiretrovirals in Pregnancy Research Toolkit	Provide an inventory of materials to enable inclusion and collection of data on pregnant and breastfeeding women within clinical studies and other research settings (Global)	Support inclusion of pregnant and breastfeeding women in antiretroviral research by providing: ■ Supporting documentation on the rationale for and ethics of inclusion ■ A repository of materials to enable and support inclusion ■ Guidance on standardized measurements and definitions relating to pregnancy and breastfeeding exposures and outcomes

PLP in Ongoing HIV Prevention Trials

Despite increasing support in recent years, PLP are often left out of HIV prevention research or considered as an "afterthought" when designing studies. Figure 4 outlines the PLP inclusion status of recent large-scale HIV prevention trials.

Figure 4: HIV Prevention Research Pipeline for PLP

Efficacy Trial	Inclusion Criteria	Ongoing Research	Prevention Evidence
Vaginal Ring			
Dapivirine Ring (Monthly)	DELIVER	DELIVER and B-PROTECTED: **safety, drug levels** and **adherence** (but not efficacy) in pregnant and breastfeeding women	No known safety risks in pregnancy. Low drug levels in breastmilk
	B-PROTECTED		
Oral PrEP			
F/TAF (Daily pill)	PURPOSE 1	Women who became pregnant could reconsent to **sub-study in PLW and their infants**	There were 219 pregnancies in the F/TAF group. Pregnancy outcomes were similar to those expected and four HIV new infections were observed. More research is needed to understand F/TAF use during lactation and breastfeeding.
MK-8527 (Monthly pill)		Phase II study not enrolling pregnant or lactating individuals.	No evidence
Long-Acting Injectable			
Cabotegravir (Every two months)	HPTN 084	HPTN 084 OLE: **pregnancy incidence, safety and infant outcomes, CAB concentration** in pregnant women	There were 351 incident pregnancies in the OLE. Injectable Cabotegravir use before and during pregnancy was found to be safe for pregnant women and their babies and zero new infections occurred in pregnant women receiving Cabotegravir. Initial data indicate no dose changes are required for pregnant cisgender women, but additional analyses are needed. More research is needed to understand the safety and efficacy of Cabotegravir use during lactation and breastfeeding.
Lenacapavir (Every six months)	PURPOSE	Women who became pregnant could reconsent to **sub-study in PLW and their infants**	There were 193 pregnancies in the lenacapavir group. Pregnancy outcomes were similar to those expected and zero new HIV infections were observed. More research is needed to understand lenacapavir use during lactation and breastfeeding.
	PURPOSE 2	TG men and GNC people who become pregnant can reconsent to **sub-study in PLP and their infants**	Data forthcoming
Preventive HIV Vaccine			
Antibody		No ongoing vaccine or antibody efficacy trials	Meta-analysis of Phase 1 & 2a vaccine studies showed no signal of increased risk for pregnancy or birth (based on 193 pregnancies)

PLP included at enrollment

PLP excluded at enrollment

What can advocates do?

Advocates have a critical role to play in advancing HIV prevention research in PLP. From consultation with a wide range of HIV and women's health advocates in the AVAC/PHASES Think Tank and the WHO/IMPAACT/IAS Call to Action, several key actions emerged. These include:

Asking key questions throughout all stages of research and surveillance

- For clinical and implementation research protocols and ongoing clinical studies:
  - Have Developmental and Reproductive Toxicity (DART) studies been completed. Has dosing in non-pregnant women been established? If not, what is the plan to ensure these studies are completed and by when? If yes to both, are contraception requirements in place for trial participants? Why?
  - If contraceptive requirements are indicated, do they incorporate evidence-based contraceptive counseling and do women have access to other sexual and reproductive health services through the site? If not, why?
  - If contraceptive requirements are not indicated, are trial sites still offering access to evidence-based contraceptive counseling and other sexual and reproductive health services? If not, why?
  - Are cisgender women and gender-diverse pregnant people included in the study? If not, why?
  - Are lactating people included in the study? If not, why?
  - Will study data be disaggregated for different populations?
  - Will those who become pregnant during the study be given the option to continue in the study? Will specific data on key outcomes be collected in these individuals?
  - What is the stakeholder engagement plan? Does the plan detail early and sustained engagement that aligns with the Good Participatory Practice (GPP) Guidelines?
  - Do these plans include engagement of participants' communities and especially influencers (i.e., families, partners, community leaders)?
  - Were PLP and advocates consulted during the research review process? If not, why?
- For implementation research and rollout:
  - Are PLP included or excluded in the eligibility criteria? If excluded, why?
  - What data are still needed on access, feasibility and acceptability for PLP for the specific interventions? How is this data being collected?
  - Do implementation studies link to an existing pregnancy registry to follow long-term outcomes?
  - For approved products with inadequate data in PLP, what is the plan for gathering data?
  - Were PLP and advocates consulted during the research review process? If not, why?
  - What are there plans for results dissemination to PLP, antenatal/postnatal care providers, and community stakeholders?

Taking the lead in building community literacy, peer education and advocacy

- Identify, develop and disseminate resources and tools to build other advocates' knowledge about the need for inclusion of PLP in HIV prevention research
- Help normalize research in PLP by engaging a broad range of community stakeholders, especially PLP and people of reproductive potential, their partners and family members, community leaders and physicians
- Engage pregnant people, adolescents and transgender and gender-diverse individuals and their communities to co-develop advocacy messages that give voice to their lived experiences and ensure research agendas are reflective of their needs
- Seek out other advocates and stakeholders addressing maternal health and reproductive justice issues to identify opportunities for collaboration and amplify efforts to address intersecting issues including racial and gender-based disparities as well as other diseases (e.g., malaria, cancer, TB) that differentially impact these populations

Advocating for and supporting regulatory and ethics processes that protect PLP through research

- Identify and coordinate with key stakeholders to encourage national governments to bolster the ability of drug regulatory agencies to incentivize and/or require the generation of data specific to PLP for approval of new therapeutics
- Encourage the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), African Medicines Regulatory Harmonisation (AMRH) and other drug regulatory harmonization organizations to develop guidelines for the responsible inclusion of PLP in pre-licensure drug development trials
- Support ongoing efforts by WHO to advance harmonization of regulatory frameworks, promoting inclusive involvement of national and regional regulatory bodies in areas with high HIV burden. Harmonization would accelerate PLP-specific data as early as possible in product development and facilitate timely public availability of data
- Develop and disseminate tools and resources to support investigators and research ethics committees/institutional review boards to consider responsible inclusion of PLP in the ethics review process

Please send suggestions and comments to avac@avac.org

About AVAC

AVAC is an international non-profit organization that leverages its independent voice and global partnerships to accelerate ethical development and equitable delivery of effective HIV prevention options, as part of a comprehensive and integrated pathway to global health equity. Follow AVAC on Twitter @HIVpxresearch and find more at www.avac.org.