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Health Outcomes around Pregnancy and Exposure to HIV/Antiretrovirals (HOPE) study protocol: a prospective observational cohort study of reproductive-aged women living with HIV

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ABSTRACT

Introduction Over 265 000 women are living with HIV in the USA, but limited research has investigated the physical, mental and behavioural health outcomes among women living with HIV of reproductive age. Health status during the reproductive years before, during and after pregnancy affects pregnancy outcomes and long-term health. Understanding health outcomes among women living with HIV of reproductive age is of substantial public health importance, regardless of whether they experience pregnancy. The Health Outcomes around Pregnancy and Exposure to HIV/Antiretrovirals (HOPE) study is a prospective observational cohort study designed to investigate physical and mental health outcomes of young women living with HIV as they age, including HIV disease course, engagement in care, reproductive health and choices and cardiometabolic health. We describe the HOPE study design, and characteristics of the first 437 participants enrolled as of 1 January 2024.

Methods and analysis The HOPE study seeks to enrol and follow 1630 women living with HIV of reproductive age, including those with perinatally-acquired HIV, at 12 clinical sites across 9 US states and Puerto Rico. HOPE studies multilevel dynamic determinants influencing physical, mental and social well-being and behaviours of women living with HIV across the reproductive life course (preconception, pregnancy, post partum, not or never-pregnant), informed by the socioecological model. Key research areas include the clinical course of HIV, relationship of HIV and antiretroviral medications to reproductive health, pregnancy outcomes and comorbidities and the influence of racism and social determinants of health. HOPE began enrolling in April 2022.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Health Outcomes around Pregnancy and Exposure to HIV/Antiretrovirals (HOPE) longitudinal study will enrol and follow a cohort of women of reproductive age living with HIV, including those with perinatally-acquired HIV, from across the USA and Puerto Rico to understand their health and well-being outcomes over time.

⇒ Most follow-up visits are conducted remotely, which encourages enrolment by offering flexibility for completing assessments and improves efficiency by reducing participant and staff burden compared with in-person visits.

⇒ A unique feature of the HOPE study design is recruitment of a subgroup of women living with perinatally-acquired HIV, making HOPE uniquely poised to assess distinct influences of lifelong HIV and antiretroviral exposure on health outcomes compared with individuals acquiring HIV later in life.

⇒ Because HOPE largely recruits participants from clinical sites, results may not be generalisable to women living with HIV who are not engaged in care.

⇒ HOPE does not enrol women who are HIV seronegative; thus, the absence of a comparison group of women without HIV limits the ability to evaluate the contribution of HIV status to risks of health conditions or behaviours of interest.

Ethics and dissemination The HOPE study received approval from the Harvard Longwood Campus Institutional Review Board, the single institutional review board of

record for all HOPE sites. Results will be disseminated through conference presentations, peer-reviewed journals and lay summaries.

INTRODUCTION

Globally, there are 19.7 million women living with HIV, accounting for 54% of adults living with HIV.[1] Each year, over 1 million women living with HIV experience pregnancy, with an increasing proportion receiving antiretroviral therapy in pregnancy, from 49% in 2010 to 82% in 2022.[2] In the USA, over 265 000 women are living with HIV, comprising 22% of adults living with HIV.[3] However, the physical, behavioural and mental health outcomes of young women living with HIV of reproductive age in the USA and individual and social determinants of these outcomes have not been well-studied.

Despite advances in HIV treatment and care, a suboptimal proportion of women living with HIV in the USA engage in HIV care, adhere to antiretrovirals and achieve viral suppression, which are all crucial to promoting health and reducing the risk of HIV transmission.[4] In 2021 about 25% of all US adult women living with HIV were not receiving HIV care, and only 64% were virally suppressed at the time of their most recent clinical visit.[5] Over 60% of postpartum women living with HIV are not virally suppressed 6–24 months after giving birth.[6–10] Women with perinatally-acquired HIV (PHIV) have even lower rates of viral suppression, with 70–85% not virally suppressed at 12 months post partum.[11 12]

Women living with HIV are disproportionately black and/or Latina, reflecting the influence of structural racism in driving disparities in access to prevention and care, antiretroviral medication adherence, mental health, comorbidities and overall well-being.[13 14] 'Weathering' induced by chronic exposure to racism and forms of social and economic disadvantage, has the potential to accelerate ageing and declines in health among minoritised women and is a possible mechanism linking structural racism to adverse health outcomes.[15–17] Structural racism shapes racialised residential segregation, disproportionate exposures to environmental hazards, less access to quality healthcare, discrimination during medical encounters and increased negative experiences with the criminal legal system.[18–21] Yet little is known about the specific effects of structural racism and other associated harmful social policies (eg, living in states with more laws criminalising HIV) on the health of women living with HIV.

Additionally, women experiencing HIV-related stigma may also experience higher levels of social isolation and depression, which could contribute to suboptimal adherence.[22] The intersection of HIV-related stigma and racism, classism, sexism, disability and heterosexism, have been associated with suboptimal HIV care, posing additional threats to positive health outcomes.[23 24] However, few studies to date have examined the impact of racism, and intersectional stigma and discrimination on the health of marginalised women living with HIV of childbearing age, despite the fact that HIV disproportionately impacts women who identify as black and Latina in the USA.

Although there has been extensive research examining the health of older women living with HIV in the USA,[25–27] less is known about the health of women living with HIV currently of reproductive age in the USA. Investigating the complex milieu of biological, social, environmental and structural events influencing the health and well-being of women living with HIV across their reproductive life course, including those who are nulliparous, pregnant, post partum or parous and women who have never been or will not become pregnant is imperative for achieving health equity and informing interventions to optimise long-term health of women living with HIV.

There is an opioid crisis in the USA, with opioid use driven largely by use of prescription opioids.[28] Additionally, cannabis legalisation in many US states for both medical and recreational use may affect substance use trends across the reproductive life course among women living with HIV.[29] Substance use has been linked to food insecurity, suboptimal adherence and challenges in retention in HIV care among older women living with HIV in the USA,[30] however, less is known about alcohol and other substance use and its treatment among younger women living with HIV.

Due to improvements in HIV treatment and medical advances which dramatically reduce the risk of perinatal HIV transmission, more women living with HIV are now choosing to have children.[31–35] In the USA, approximately 3500 women living with HIV give birth annually.[36] Pregnancy rates for women living with HIV are comparable to women without HIV.[31] However, about 80% of pregnancies among women living with HIV in the USA are reported to be unintended, compared with 40–50% in the general population.[12 37–39] This disparity highlights a need to better understand and support the reproductive intentions, concerns about HIV transmission and health of women living with HIV, as well as the environmental, psychosocial, economic and sociopolitical conditions in which they live. Women living with PHIV represent a unique subset of individuals, and there is a dearth of information on the potential impact of lifelong HIV and antiretrovirals on their long-term health and pregnancies.

Understanding individual, biological and social determinants of health of women living with HIV of reproductive age before, during and after pregnancy is of clinical and public health importance both to improve short-term pregnancy outcomes and to mitigate long-term chronic disease risk. Although pregnancy is a time of increased risk for physical and mental health complications, the contribution of pregnancy to long-term health of women living with HIV has not been sufficiently examined. For example, hypertensive disorders of pregnancy are potent signals for elevated risk of long-term cardiovascular (CVD) and metabolic disease[40–43] and antiretroviral medications may influence CVD risk.[44] Additionally, mental health conditions are prevalent among women living with HIV who are parenting,[45] yet the influence of parenting on

the physical and mental health of women living with HIV, and on their ability to engage in their own HIV care and maintain adherence to antiretrovirals, particularly if children have acute or chronic health needs, has not been well-studied. Finally, although neighbourhood deprivation has been linked to viral load, little is known about the relationship of other social and physical environmental factors (eg, air pollution and extreme temperature) to pregnancy and the overall well-being of women living with HIV.[46–48]

To address these scientific gaps, the Health Outcomes around Pregnancy and Exposure to HIV/Antiretrovirals (ARVs) (HOPE) longitudinal study, funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, will enrol and follow a large US-based cohort of women living with HIV of reproductive age, including those with PHIV, to understand their health and well-being outcomes over time. In this paper we present the HOPE study protocol, including the conceptual framework, aims, design, methods and characteristics of the first 437 participants enrolled as of 1 January 2024. Due to its focus on the reproductive life course, HOPE enrols only individuals assigned female sex at birth. For simplicity, the terms 'woman' and 'women' are used throughout this paper. However, the HOPE study population includes cisgender women, transgender men, non-binary individuals and gender-diverse people.

METHODS AND ANALYSIS

HOPE study objectives

The HOPE study has four primary aims: (1) Establish the HOPE cohort to evaluate the health and well-being of women living with HIV of reproductive age using innovative epidemiological study designs and cost-effective methods for enrolment, follow-up and data collection; (2) assess HIV-related outcomes in multiple domains (defined below) and overall health of women living with HIV over their reproductive life course, including reproductive health, coinfections, long-term non-communicable diseases, as well as potential inflammatory and epigenetic processes associated with these outcomes; and psychosocial determinants of health including mental health diagnoses, stigma, racism, inequity, disclosure of HIV and opioid and other substance use/misuse; (3) determine the association of HIV disease-related factors, including timing of acquisition, treatment, disease course and engagement in care, with the overall physical, mental and behavioural health of women living with HIV during their reproductive years; (4) assess the relationship of adverse infant or child health outcomes to the health of women living with HIV.

In addition to four overall study aims, the HOPE study is designed to address aims examining multilevel dynamic determinants of health within specific domains: Mental health, reproductive health, cardiometabolic health, coinfections, HIV outcomes, HIV care continuum, substance use and stigma, racism and social determinants of health. The domain-specific aims and selected hypotheses are summarised in online supplemental table 1. Key exposures include ARV regimens received over the life course, comorbidities and social and structural determinants of health, including HIV-related stigma, poverty, racism and discrimination. Many variables of interest in the HOPE study can be evaluated as exposures and as outcomes, depending on the research question.

Conceptual framework

The HOPE study conceptual framework is informed by the socioecological model, which recognises that factors operating at multiple levels including individual, interpersonal and family, community and institutional and structural/societal, may affect individuals' health and risk of adverse outcomes.[49–51] The HOPE framework also

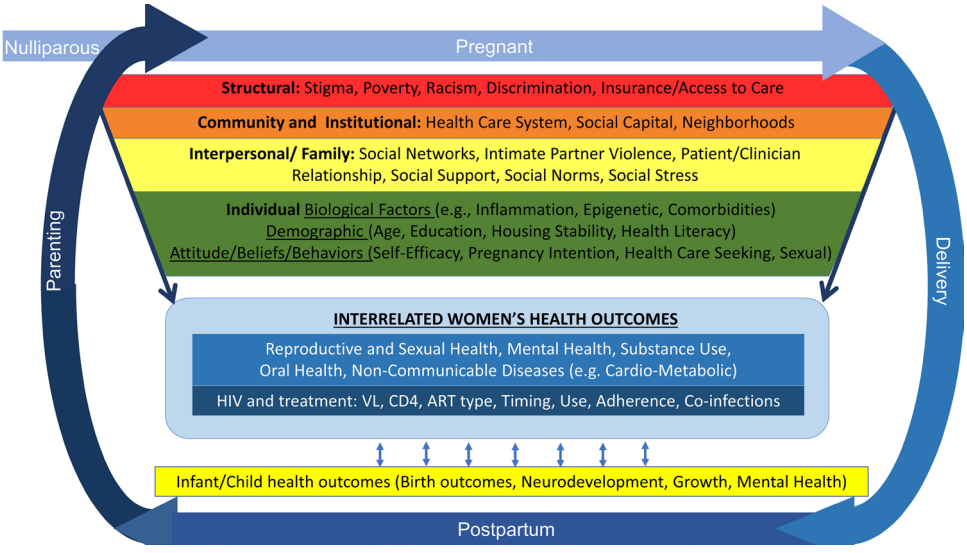

Figure 1 Health Outcomes around Pregnancy and Exposure to HIV/Antiretrovirals conceptual model. ART, antiretroviral therapy; VL, viral load.

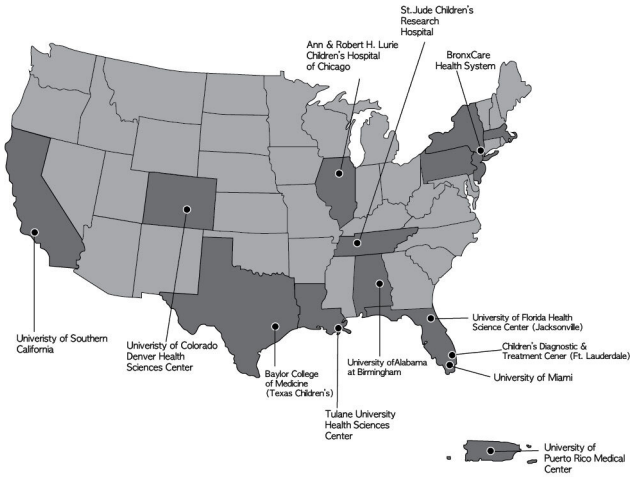

Figure 2 Geographical locations of HOPE study sites across the USA and Puerto Rico. States in darker shade are locations of Pediatric HIV/AIDS Cohort Study sites. HOPE, Health Outcomes around Pregnancy and Exposure to HIV/Antiretrovirals.

incorporates a life course perspective and Developmental Origins of Health and Disease framework, which acknowledge that biological and social factors across generations, at early stages of development and across the reproductive life span, are critical determinants of reproductive health, which in turn, influence later chronic health conditions[52–55] (figure 1). Changes in exposure to these factors, in HIV disease, as well as pregnancy and postpartum events, may affect health. Infections other than HIV, the mode of HIV acquisition and timing of HIV diagnosis, type and timing of ARV treatment and adherence can influence engagement in care, HIV outcomes and overall health of women living with HIV.[56 57] The needs and health of children in turn may affect women's health. This cyclical and dynamic relationship, occurring in the context of structural factors including HIV-related stigma, violence, racism, inequity and poverty as well as trauma and depression may negatively influence HIV outcomes through direct or indirect pathways, including toxic stress, potentiating health outcome disparities among women living with HIV.[50 58–63] Conversely, resilience resources including individual, family and interpersonal resources, social support and availability and access to community resources may mitigate potential adverse effects on health and well-being and support positive outcomes.[64–68]

Leveraging the Pediatric HIV/AIDS Cohort Study infrastructure

The HOPE study is designed to address questions regarding the long-term health of women living with HIV of reproductive age during young adulthood, pregnancy and parenting (for those who have given birth to or are raising children as foster parents or through guardianship or adoption). HOPE is affiliated with the Pediatric HIV/AIDS Cohort Study (PHACS) network, a national multisite research network conducting longitudinal studies of long-term effects of HIV and ARV exposure on infants, children, adolescents and young adults with PHIV and those living with perinatal HIV exposure who are not living with HIV. The PHACS Surveillance Monitoring for ART Toxicities (SMARTT) study is an ongoing observational cohort study established in 2007 that follows children with perinatal HIV exposure who are not living with HIV from birth along with their biological mothers (women living with HIV) or other caregivers, to evaluate the safety of fetal exposure to ARVs.[69 70] The PHACS Adolescent Master Protocols for Participants 18 Years of Age and Older (AMP Up Series) follow young adults living with PHIV and a comparison cohort of individuals with perinatal HIV exposure.[71] Individuals in SMARTT and the AMP Up Series who meet HOPE eligibility criteria may co-enrol in HOPE, thus enriching the data collection for these individuals. The unique HOPE research platform fosters opportunities for multidisciplinary and cross-cutting research to inform public health policy for optimising the health of women living with HIV.

Patient and public involvement

The HOPE protocol, research focus and data collection instruments were designed in partnership with women living with HIV from the PHACS Community Advisory Board (CAB) and/or members of the PHACS Health Education and Community Core Community Task Force. A core principle of the HOPE study is to support research that reflects the perspectives and priorities of people living with HIV. Once all sites were open to accrual, we engaged HOPE participants to join a HOPE-specific CAB established to ensure representation of participants' priorities in HOPE, drive the creation of health education materials and promote insights and opportunities to support participant retention. HOPE participants also serve on the PHACS Community Task Force, using the PHACS Health Education and Community Core infrastructure to work as paid consultants providing input and ensuring representation of HOPE participant priorities in all protocol activities. In collaboration with the HOPE protocol team, HOPE CAB members conduct reviews of research proposals using HOPE data, providing extensive written feedback. They also advise and assist with the development of resources supporting recruitment, retention and study conduct, coauthor publications and support the dissemination of study findings, aiming to use results to inform policy changes that promote health equity for women living with HIV. They have informed the creation of a video describing geocoding for participants and illustrated instructions to assist participants with vaginal and anal swab self-collection.

Study population and eligibility criteria

HOPE is a prospective observational cohort study enrolling women living with HIV who are 18–39 years of age at 12 clinical sites across 9 US states and Puerto Rico (figure 2). Individuals eligible to participate in HOPE are (1) woman, based on biological sex assignment at birth; (2) living with HIV as documented in their medical record; (3) 18 to <40 years of age if pregnant or parous

and 18–30 years of age if nulliparous and non-pregnant; (4) at least 13 weeks of gestation at time of enrolment if pregnant; (5) willing to provide access to medical records and provide legal consent/assent and able to complete study assessments in English or Spanish. Individuals who are currently incarcerated and individuals concurrently enrolled in studies not approved by the HOPE protocol team are ineligible for HOPE.

Recruitment and retention

The study began enrolling participants in April 2022 with a goal of enrolling 1630 participants over 4 years from the following four groups:

- Nulliparous, non-pregnant participants 18–30 years of age (N~370).
- Participants who are pregnant or recently gave birth (≤3 days) and are 18 to <40 years of age (N~430).
- Postpartum (>3 days up to 12 months after delivery), non-pregnant participants 18 to <40 years of age (N~260).
- Parous, non-pregnant (>12 months after delivery) participants 18 to <40 years of age (N~570).

The study aims to recruit a population that includes at least 15% women living with PHIV in all of the above categories. The HOPE team is in the process of modifying the HOPE protocol eligibility criteria to accelerate accrual. This includes increasing the maximum eligible age to 45 years of age, removing the minimum weeks of gestation in pregnancy and expanding eligibility to women whose preferred language for completing assessments is Haitian Creole.

In addition to co-enrolling eligible PHACS participants, each site enrols qualifying participants who are not part of the PHACS network through outreach to local CABs and to clinicians who provide care to women living with HIV. Recruitment strategies were informed by CAB members and site staff. Women living with HIV consenting to participate in the study will complete follow-up visits through 31 August 2025 (6 months prior to the funding period end date), or longer if the study receives renewed funding.

Multiple methods to retain participants in HOPE are informed by site staff, the HOPE CAB and HOPE members of the PHACS Community Task Force. Capitalising on existing patient-provider relationships, sites partner with clinical providers and local and national CABs throughout the course of this study to support participants for continued HOPE study retention. Study staff maintain contact with HOPE participants at least every 6 months to maintain rapport, inquire if they had become pregnant or experienced any other significant changes and to support study retention.

Schedule of evaluations

The HOPE study has two schedules of evaluations, one for participants who are pregnant or have recently given birth and another for participants who are not pregnant (online supplemental figure 1). Entry visits are in-person and annual follow-up visits are remote. The entry visit for participants who are pregnant can occur either during pregnancy or in the peripartum period. Participants who enrol while pregnant have follow-up visits at delivery, 6 weeks postpartum, 1-year postpartum and annual remote visits thereafter. Participants who are not pregnant have one in-person entry visit followed by annual remote visits. Annual visits are conducted remotely, and include completion of an online survey by the participant and medical chart abstraction by site staff. Participants who are not pregnant at enrolment but who subsequently experience pregnancy are invited to modify their frequency of evaluations from annually to the pregnancy schedule described above, followed by annual remote visits thereafter.

Data collection and measures

The data collection at each HOPE visit is summarised in table 1. Data collection at the entry visit consists of collection of residential addresses for geocoding, clinical assessments, an interviewer-administered medical and psychosocial history questionnaire, a self-completed online survey and collection of specimens for the HOPE Biorepository. Trained research staff complete medical record abstraction concurrently with each visit.

Geocoding

To examine structural racism and other area-based social, environmental and structural determinants of health (eg, historical redlining, air quality, green space and proximity to high-quality clinics/hospitals), HOPE employs geocoding. Participants who consent to provide their residential addresses for geocoding provide all addresses where they resided for the 2-year period prior to the entry visit and the address where they resided longest between ages 14–18 years. Site staff record the addresses and use ArcGIS Pro V.3.0 software[72] to transform each address into a Federal Information Processing System code for the census tract corresponding to each location.

Clinical assessments

Height, weight, waist and hip circumference and blood pressure measurements are collected.

Interviewer-administered questionnaires

A questionnaire collects medical history including medications, diagnoses and family medical history. Participants complete assessments of pregnancy and reproductive history, health literacy measured using the Newest Vital Sign[73] and social history (eg, food security via the Six-Item Short Form of the US Household Food Security Scale[74] and housing security). In addition, interviewers screen participants for symptoms of depression via the Patient Health Questionnaire-9,[75] anxiety symptoms via the Generalised Anxiety Disorder-7 Scale[76] and Post-Traumatic Stress Disorder (PTSD) via the Primary Care PTSD screen for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[77]

Table 1 Health Outcomes around Pregnancy and Exposure to HIV/Antiretrovirals data collection

	Pregnant or recently delivered at enrolment				Not pregnant at enrolment	
	Enrolment					
	Pregnancy	Delivery	6 weeks post partum	1-year post partum and annually	Enrolment	Annual follow-up
	In person	In person	In person	Remote	In person	Remote
Residential address information/location for geocoding purposes	X	(X)			X	
Contact and check-in between visits	X	X	X	X	X	X
Change in pregnancy status	X		X	X		X
Clinical assessments (collected in-person)						
Height	X	(X)	X		X	
Weight	X	X	X	X	X	X
Waist and hip circumference			X	X	X	
Blood pressure	X	X	X	X	X	X
Interview						
Family and personal medical history	X	(X)			X	
Reproductive history	X	(X)			X	
Depression*	X	(X)	X		X	
Anxiety†	X	(X)	X		X	
PTSD‡	X	(X)			X	
Health literacy§	X	(X)			X	
Social history	X	(X)			X	
Online survey (detail provided in table 2)	X	X	X	X	X	X
Medical chart abstraction						
Weight	X	X	X	X	X	X
Blood pressure	X	X	X	X		X
HIV RNA level, lymphocytes and subsets	X	X	X	X	X	X
ART medications	X	X	X	X	X	X
Non-ART medications	X	X	X	X	X	X
HIV, primary care, OB, gynaecologic, mental healthcare engagement	X	X	X	X	X	X
Immunisations	X	X	X	X	X	X
Medical and mental health diagnoses and hospitalisation	X	X	X	X	X	X
Laboratory test results	X	X	X	X	X	X
Pregnancy and pregnancy outcomes	X	X		X	X	X
Cervical and anal dysplasia screening	X	X	X	X	X	X
STI testing and results	X	X		X	X	X
Sample collection/ repository						

Continued

Table 1 Continued

	Pregnant or recently delivered at enrolment				Not pregnant at enrolment	
	Enrolment					
	Pregnancy	Delivery	6 weeks post partum	1-year post partum and annually	Enrolment	Annual follow-up
	In person	In person	In person	Remote	In person	Remote
Serum, plasma (EDTA and heparin) and non-viable PBMCs	X	X			X	
Rectal swab for microbiome	X	(X)			X	
Vaginal swab for microbiome	X	(X)			X	
Vaginal swab for metabolomics	X	(X)			X	
Vaginal swab for STI testing	X	X			X	
Oral swab	X	X			X	
Saliva	X	X			X	
Hair	X	X			X	

Brackets () indicate that the assessment takes place at the delivery visit only if the delivery visit is an enrolment visit.
*Depressive symptoms assessed via interview using the Patient Health Questionnaire-9.[75]
†Anxiety symptoms assessed via interview using the Generalised Anxiety Disorder-7.[76]
‡Post-traumatic stress disorder assessed via interview using the Primary Care Post-Traumatic Stress Disorder Screen for DSM-5.[77]
§Health literacy assessed via interview using the Newest Vital Sign.[73]
ART, antiretroviral therapy; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; OB, obstetrical; PBMC, peripheral blood mononuclear cells; STI, sexually transmitted infection.

Specimen collection

Site staff collect bio-specimens from HOPE participants at the in-person entry visit. Specimens include serum, plasma, non-viable peripheral blood mononuclear cells, anal, oral and vaginal swabs, hair specimens and saliva. Participants who enrol while pregnant provide bio-specimens again at the delivery visit. All HOPE bio-specimens are stored in a bio-repository, allowing for future investigations of biological processes and conditions (eg, testing for sexually transmitted infections, inflammation, epigenetics, the microbiome and biological markers of stress).

Medical record abstraction

For participants who are nulliparous or enrolling more than 1 year after giving birth and not pregnant at enrolment, site staff abstract data from participant medical records for the period starting 12 months prior to the visit. For participants who are pregnant or recently gave birth or within the 1-year postpartum period, site staff abstract medical record data for the period beginning 6 months prior to conception of the most recent pregnancy. Health conditions abstracted from participants' medical records include HIV history, general and obstetrical/gynaecological history, mental health history, medical diagnoses and care engagement details. HIV history includes ARV medications, CD4 count including nadir CD4 count and HIV viral load. General history includes non-ARV medications, immunisations, weight, blood pressure and results of selected laboratory tests (eg, lipids, blood urea nitrogen, white blood cell count). Obstetrical/gynaecological history includes gravidity, parity, pregnancy outcomes, results of STI testing, as well as normal and abnormal cervical cancer screening results and associated histology. Mental health diagnoses include depression, anxiety, PTSD, psychosis and substance use disorders. Medical diagnoses include, but are not limited to, diabetes (including gestational diabetes), hypertension (including hypertensive disorders of pregnancy), obesity, dyslipidaemia and anaemia. Care engagement details include HIV, primary care, obstetrics/gynaecologic and mental healthcare engagement.

Online survey

The online survey collects information on sociodemographic characteristics, physical and mental health, behaviours (eg, substance use) and social determinants of health, described in table 2,[78–94] and assesses feasibility/acceptability of a wearable actigraphy device for collection of participant sleep and physical activity data. An online survey audio component reads the questions aloud to support the engagement of participants with limited literacy.

Data analysis and sample size considerations

Data analysis

The HOPE study is designed to evaluate the health of women living with HIV over their reproductive lifespan.

Table 2 Health Outcomes around Pregnancy and Exposure to HIV/Antiretrovirals online survey data collection

	Not pregnant at enrolment		Pregnant or recently delivered at enrolment			
Survey domains	**Entry**	**Annually**	**Pregnancy/ delivery (entry)**	**Delivery (follow-up)**	**6 weeks postpartum**	**1-year post partum and annually**
Background						
Race and ethnicity	X		X			
Gender and sexual identity	X	X	X			X
Education, employment, income	(SH-I)	X	(SH-I)	X	X	X
Housing security/living situation^^^	(SH-I)	X	(SH-I)	X	X	X
Food Security*	(SH-I)	X	(SH-I)			X
Health and healthcare						
HIV care engagement, access and medical insurance	X	X	X	X	X	X
Self-efficacy re: HIV care management	X	X	x		X	X
Trust in healthcare system† and providers‡		biannual (Y1, Y3, …)				biannual (Y1, Y3, …)
Medication adherence§	X	X	X	X	X	X
Life events						
Self-rated health and pain	X	X	X		X	X
Quality of life¶		X			X	X
Physical activity	X	X	X		X	X
Sleep quality** and shift work	X	X	X		X	X
Perceived stress††	X	X	X		X	X
Life events checklist	X	X	X	X	X	X
Adverse childhood experiences	X		X			
Intimate partner violence (sexual, physical, emotional)	X	X	X		X	X
Neighbourhood safety‡‡	X	X	X		X	X
Everyday discrimination, experiences of discrimination and reactions to race§§, ¶¶	X	biannual (Y2, Y4, …)	X		X (healthcare setting version)	biannual (Y2, Y4, …)
Internalised HIV stigma***	X	biannual (Y2, Y4,)	X			biannual (Y2, Y4, …)
Disclosure	X	X	X			X
PLHIV Resilience Scale†††	X	biannual (Y2, Y4, …)	X			biannual (Y2, Y4,…)
Brief Resilience Scale‡‡‡		X				X
Social integration§§§	X		X			
Social support¶¶¶	X	X	X			X
Sexual behaviour						
Number of sexual partners	X	X	X		X	X
HIV risk reduction strategies (eg, condoms, PrEP, U=U)	X	X	X		X	X
Perception of PrEP and U=U effectiveness	X	biannual (Y2, Y4 …)	X			biannual (Y2, Y4, …)
Female Sexual Function Index (three questions)	X		X			
Sexual Relationship Power Scale****		X				X
Reproductive Health						

Continued

Table 2 Continued

Survey domains	Not pregnant at enrolment		Pregnant or recently delivered at enrolment			
	Entry	Annually	Pregnancy/ delivery (entry)	Delivery (follow-up)	6 weeks postpartum	1-year post partum and annually
Pregnancy status and intention (current)	X	X	X		X	X
Contraceptive use and discontinuation reasons	X	X	X		X	X
STI testing	X	X	X			X
Pap smear	X	X	X			X
Influenza vaccination	X	X	X	X		X
HPV vaccination	X		X			
Pregnancy history (intention, outcome)	X	X	X		X	X
Postpartum care engagement	X	X	X			X
Breastfeeding intentions and practices	X	X	X	X	X	X
Children parented/parenting (relation, health conditions)	X		X			
Substance use and mental health						
Substance use and abuse††††	X	X	X		X	X
Cannabis use	X	X	X		X	X
SAMISS alcohol questions‡‡‡‡	X	X	X		X	X
Depression symptoms§§§§	(^)	X	(^)		(^^)	X
Anxiety symptoms¶¶¶¶	(^)	X	(^)		(^^)	X
Post-traumatic stress disorder symptoms*****	(^)		(^)			
Wearables for actigraphy						
Feasibility and acceptability	X		X			

^Asked separately at entry via interview.
^^Asked separately at follow-up via interview.
^^^Accountable Health Communities Health-Related Social Needs Screening Tool.
*Six-Item Food Security Scale.[74]
†Health Care System Distrust Scale.[78]
‡Healthcare Relationship Trust Scale.[79]
§Three question adherence measure.[80]
¶Medical Outcomes Study SF-20.[81]
**Brief Pittsburgh Sleep Quality Index.[82]
††Perceived Stress Scale-4.[83]
‡‡Neighborhood safety.[84]
§§Everyday Discrimination Scale.[85]
¶¶Experiences of Discrimination.[86]
***Internalised HIV Stigma Scale.[87]
†††People Living with HIV Resilience Scale.[88]
‡‡‡Brief Resilience Scale.[89]
§§§Berkman Social Network Index.[90]
¶¶¶Medical Outcomes Study Social Support Survey.[91]
****Sexual Relationship Power Scale.[92]
††††Alcohol Smoking and Substance Involvement Screening Test.[93]
‡‡‡‡SAMISS alcohol questions.[94]
§§§§Patient Health Questionnaire-9.[75]
¶¶¶¶Generalised Anxiety Disorder-7.[76]
*****Primary Care Post-Traumatic Stress Disorder Screen for DSM-5.[77]
DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; HPV, human papillomavirus; PLHIV, people living with HIV; PrEP, pre-exposure prophylaxis; SAMISS, Substance Use and Mental Illness Symptoms Screener; SF-20, 20-Item Short-Form Survey; SH-I, asked in social history interview at entry; STI, sexually transmitted infection; U=U, undetectable=untransmittable.

Table 3 Characteristics at entry of participants enrolled in the Health Outcomes around Pregnancy and Exposure to HIV/Antiretrovirals Cohort by enrolment group, 2022–2023

	Enrolment group				
	Nulliparous (N=87)	Pregnant or recently delivered (N=59)	Post partum and non-pregnant (N=80)	Parous and non-pregnant (N=211)	Total (N=437)
Age (in years)					
≤25	74 (85%)	16 (27%)	24 (30%)	17 (8%)	131 (30%)
26 to 30	13 (15%)	20 (34%)	20 (25%)	50 (24%)	103 (24%)
31 to 35	0 (0%)	15 (25%)	20 (25%)	78 (37%)	113 (26%)
36 to <40	0 (0%)	8 (14%)	16 (20%)	66 (31%)	90 (21%)
Site region					
Northeast	10 (11%)	5 (8%)	7 (9%)	43 (20%)	65 (15%)
Midwest	7 (8%)	10 (17%)	7 (9%)	22 (10%)	46 (11%)
South	54 (62%)	22 (37%)	45 (56%)	85 (40%)	206 (47%)
West	15 (17%)	18 (31%)	20 (25%)	47 (22%)	100 (23%)
Puerto Rico	1 (1%)	4 (7%)	1 (1%)	14 (7%)	20 (5%)
Race					
White	17 (20%)	13 (23%)	18 (26%)	53 (27%)	101 (25%)
Black or African American	67 (78%)	41 (73%)	50 (71%)	139 (70%)	297 (72%)
Asian	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
American Indian	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
More than one race	1 (1%)	2 (4%)	2 (3%)	5 (3%)	10 (2%)
Unknown	1	3	10	13	27
Ethnicity					
Hispanic or Latina	13 (15%)	15 (25%)	25 (32%)	69 (33%)	122 (28%)
Not Hispanic or Latina	74 (85%)	44 (75%)	54 (68%)	142 (67%)	314 (72%)
Unknown	0	0	1	0	1
Gender identity					
Female	67 (97%)	50 (100%)	61 (100%)	162 (100%)	340 (99%)
Male	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Non-binary	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Unknown*	18	9	19	49	95
Current living situation					
Steady place to live	65 (90%)	35 (73%)	50 (85%)	145 (86%)	295 (85%)
Place to live today but worried about losing it	4 (6%)	6 (13%)	6 (10%)	15 (9%)	31 (9%)
Do not have a steady place to live	1 (1%)	7 (15%)	3 (5%)	4 (2%)	15 (4%)
Rather not answer	2 (3%)	0 (0%)	0 (0%)	4 (2%)	6 (2%)
Unknown*	15	11	21	43	90
Food security status†					
High or marginal food security (0–1)	53 (78%)	38 (86%)	37 (65%)	104 (65%)	232 (71%)
Low food security (2–4)	7 (10%)	3 (7%)	11 (19%)	29 (18%)	50 (15%)
Very low food security (5–6)	8 (12%)	3 (7%)	9 (16%)	27 (17%)	47 (14%)
Unknown*	19	15	23	51	108
Mode of HIV acquisition					
PHIV	58 (76%)	11 (21%)	11 (19%)	43 (25%)	123 (34%)
Non-PHIV	18 (24%)	42 (79%)	48 (81%)	126 (75%)	234 (66%)

Continued

Table 3 Continued

	Enrolment group				
	Nulliparous (N=87)	Pregnant or recently delivered (N=59)	Post partum and non-pregnant (N=80)	Parous and non-pregnant (N=211)	Total (N=437)
Unknown*	11	6	21	42	80
Age first learning of HIV diagnosis, in years					
Median (IQR)	12 (8–16)	21.8 (17.1–25.6)	22.0 (17.8–25.3)	20.0 (15.8–23.9)	19.20 (13.0–23.5)
HIV viral load (copies/mL)					
≤50	37 (71%)	15 (83%)	45 (83%)	71 (75%)	168 (77%)
>50 to ≤400	5 (10%)	2 (11%)	4 (7%)	6 (6%)	17 (8%)
>400 to ≤1000	0 (0%)	0 (0%)	1 (2%)	2 (2%)	3 (1%)
>1000	10 (19%)	1 (6%)	4 (7%)	16 (17%)	31 (14%)
Unknown‡	35	41	26	116	218
CD4 count (cells/mm^3)					
0 to 250	3 (6%)	4 (15%)	1 (2%)	10 (11%)	18 (8%)
251 to 500	8 (15%)	9 (35%)	12 (25%)	13 (14%)	42 (19%)
501 to 750	17 (32%)	2 (8%)	18 (38%)	21 (23%)	58 (26%)
751 to 1000	12 (23%)	6 (23%)	8 (17%)	29 (31%)	55 (25%)
>1000	13 (25%)	5 (19%)	9 (19%)	20 (22%)	47 (21%)
Unknown‡	34	33	32	118	217
Depressive symptoms§					
Minimal (0–4)	35 (48%)	30 (56%)	31 (51%)	100 (60%)	196 (55%)
Mild (5–9)	25 (34%)	16 (30%)	18 (30%)	42 (25%)	101 (29%)
Moderate (10–14)	10 (14%)	5 (9%)	5 (8%)	18 (11%)	38 (11%)
Moderately severe (15–19)	3 (4%)	3 (6%)	4 (7%)	3 (2%)	13 (4%)
Severe (20–27)	0 (0%)	0 (0%)	3 (5%)	3 (2%)	6 (2%)
Unknown*	14	5	19	45	83
Anxiety symptoms¶					
Minimal (0–4)	36 (49%)	31 (57%)	34 (55%)	98 (59%)	199 (56%)
Mild (5–9)	24 (33%)	15 (28%)	17 (27%)	42 (25%)	98 (28%)
Moderate (10–14)	10 (14%)	6 (11%)	6 (10%)	19 (11%)	41 (12%)
Severe (15–21)	3 (4%)	2 (4%)	5 (8%)	8 (5%)	18 (5%)
Unknown*	14	5	18	44	81

Data as of 1 January 2024.
*Unknown data reflect time lag between data collection and becoming available in the database (longer time lag for chart abstracted data), assessment not yet completed or no measurement at or prior to study entry visit.
†Six-Item Food Security Scale.[62]
‡Unknown viral load or CD4 data reflect time lag between data collection and becoming available in the database or no measurement at or prior to study entry visit. The viral load and CD4 data are from the most recent measurement at or prior to study entry visit.
§Depressive symptoms assessed via interview using the Patient Health Questionnaire-9 (Kroenke, 2001).
¶Anxiety symptoms assessed via interview using the Generalised Anxiety Disorder-7 (Spitzer, 2006).[76]
PHIV, perinatally-acquired HIV infection.

Detailed statistical analysis plans will be developed for each specific HOPE study question. However, in general, for binary outcomes of interest, such as preterm birth, diagnoses of hypertension or depression, unsuppressed viral load, suboptimal retention in HIV care or substance use, the prevalence or the risk of such outcomes between different exposure groups will be compared using standard modelling techniques such as log-binomial regression, both unadjusted and adjusted for potential confounders. For continuous outcomes, such as body mass index or blood pressure, we will use general linear regression or generalised estimating equation (GEE) models, as appropriate, with and without adjustment for potential confounders. Examples of key 'exposure' groups include reproductive life stage and PHIV status.

Based on the longitudinal follow-up in the HOPE study, we will assess associations between exposures which may change over time and incidence rates of various

conditions of interest, such as depression or hypertension, using Poisson regression models. We will evaluate key outcomes over time (eg, viral suppression, depression, hypertension, blood pressure, sleep quality), and changes in these outcomes. For binary conditions, we will use log-binomial models using GEEs for repeated measures and time-varying exposures or covariates. For continuous outcomes such as weight, $\log_{10}$ RNA or sleep duration, we will first visually inspect the trajectories by exposure group or risk factors using locally estimated scatterplot smoothing plots then use GEE or mixed effect models as appropriate to fit regression models as a function of age or elapsed follow-up time, spanning the reproductive life stages reflected by the HOPE protocol, adjusting for other risk factors or potential confounders. Finite mixture modelling techniques such as group-based trajectory modelling[95] or growth mixture modelling[96] will also be applied to identify subgroups with distinct patterns of trajectories.

To manage and account for data missingness, we will describe the reasons for missed study visits (eg, missed a visit due to hospitalisation, incarceration) and compare the characteristics of participants with missing versus non-missing data. Assumptions needed to obtain valid statistical inferences in the presence of missing data will be thoroughly investigated. When appropriate, for example, for accounting for missingness due to incomplete visit follow-up, factors associated with the propensity of missingness will be identified and included in analyses using missing data methods, such as multiple imputation and inverse probability weighting, to address potential selection bias.

Sample size

Some HOPE study aims and hypotheses will apply to all participants in the HOPE study, while others will be specific to a subgroup. For binary outcomes in cross-sectional comparisons, our target sample size of 1630 will provide 80% power at a 0.05 significance level to detect relative risks (RR) ranging from 1.17 to 2.5 depending on the underlying prevalence of the outcome of interest in the reference exposure group and the sample size distribution between the two exposure groups (online supplemental table 2). For continuous outcomes (eg, HIV stigma), the effect size is expressed as a difference in means between the exposure groups relative to a common SD. Online supplemental table 3 summarises the minimum detectable differences between two exposure groups based on a two-sample t-test at 80% power and alpha=0.05. For example, with a sample size of 1600 including 40% reporting food insecurity,[97] the minimum detectable difference in mean stigma scores between food secure and food insecure participants is 0.14 SD. The power for longitudinal analyses will increase due to multiple measures for each participant and the corresponding minimal detectable RR or difference in mean will decrease.

BASELINE CHARACTERISTICS OF THE FIRST HOPE ENROLLEES

Characteristics of the first 437 participants enrolled into HOPE as of 1 January 2024 are summarised in table 3.

ETHICS AND DISSEMINATION

The Harvard Longwood Campus Institutional Review Board, the single Institutional Review Board of record for all sites in the HOPE study, reviewed and approved the HOPE protocol and all study-specific materials prior to initiating participant enrolment. All participants provided written informed consent. Study results will be presented at local, national and international conferences, published in peer-reviewed journals and disseminated through lay summaries. Results from HOPE aim to significantly advance our understanding of the multilevel determinants of the health of young women living with HIV, inform clinical guidelines and shape supportive interventions and policies that address the needs and priorities of women living with HIV and their families.

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Contributors DK wrote the manuscript, was integrally involved in the conception and design of the protocol, co-directed its implementation and oversaw the analysis. KMP and PLW were integrally involved in the conception and design of the protocol and data collection instruments, co-directed protocol implementation and provided critical input on the organisation and content of the manuscript. LMY and EGC were integrally involved in the conception and design of the protocol and data collection instruments, co-directed protocol implementation, were involved in the acquisition of data and provided critical input on the organisation and content of the manuscript. JJ and SS were integrally involved in the conception and design of the protocol and data collection instruments, were involved in the acquisition of data and provided critical input on the organisation and content of the manuscript. LBH, KMM and A-BM were integrally involved in the conception and design of the protocol, were involved in the development of the data collection instruments and provided important revisions to the manuscript. T-JY is the protocol statistician, was integrally involved in the conception and design of the protocol, the development of the data collection instruments and provided important revisions to the manuscript. JL was involved in the development of the protocol and data collection instruments, conducted the analysis for the manuscript and provided important revisions to the manuscript. MD was involved in the development of the protocol and data collection instruments, was involved in the acquisition of data and provided important revisions to the manuscript. L-GR was involved in the development of the data collection instruments, was involved in the acquisition of data and provided important revisions to the manuscript. CAB, KS and RAS were involved in the development of the protocol and data collection instruments, provided important revisions to the manuscript, led the formation of the HOPE CAB and facilitate partnership between the research team and the HOPE CAB and Task Force members. EAB, AD, AF, LH, DLJ, AK, TJ-T, KP and LS were involved in the development of the protocol and data collection instruments, and provided important revisions to the manuscript. JG and TW were integrally involved in the design and implementation of the protocol, and reviewed and provided important revisions to the manuscript.

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