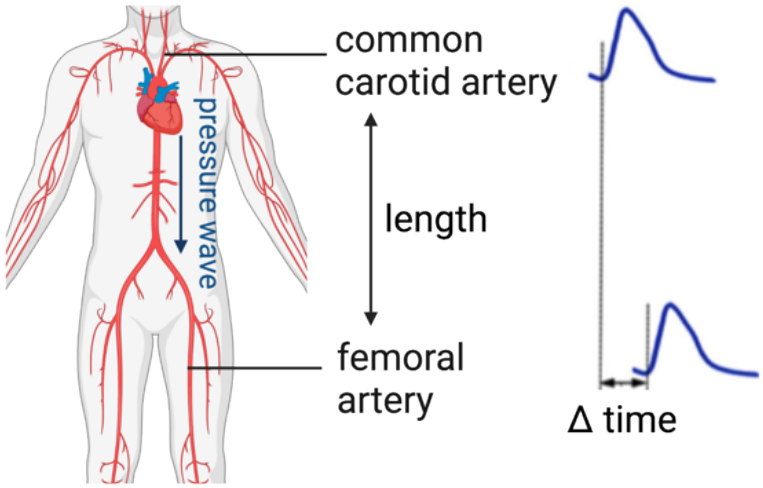
Protocol PH601

Aortic STiffness and ChROnic Comorbidities in Young Adults with Perinatal HIV Infection or Exposure (ASTRO) Standalone Study

A Multi-Center Study of the Pediatric HIV/AIDS Cohort Study (PHACS)



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List of Abbreviations and Definition of Terms

Abbreviation	Definition
ABCD	Adolescent Brain Cognitive Development
ACASI	Audio Computer-Assisted Self-Interview
ACEs	Adverse Childhood Experiences
AES	Advanced Encryption Standard
AFNI	Analysis of Functional Neuro Images
AMP	Adolescent Master Protocol
AMP Up	Adolescent Master Protocol for Participants 18 Years of Age and Older
AMY	Amygdala
ART	Antiretroviral Therapy
ARV	Antiretroviral
ASEBA	Achenbach System of Empirically Based Assessment
ASR	Adult Self-Report
BASC-2	Behavior Assessment System for Children, Second Edition
BMI	Body Mass Index
BRIEF-2	Behavior Rating Inventory of Executive Functioning, Second Edition
BRIEF-A	Behavior Rating Inventory of Executive Functioning, Adult Version
BRS	Brief Resilience Scale
CBCL	Child Behavior Checklist
CDI-2	Children's Depression Inventory 2
CDQ	Client Diagnostic Questionnaire
CEN	Central Executive Network
cfPWV	Carotid-femoral Pulse Wave Velocity
CFR	Code of Federal Regulations
CNS	Central Nervous System
ComBat	Combined Association Test
CRF	Case Report Form
CRP	C- reactive protein
CYRM-R	Child and Youth Resilience Measure-Revised
dACC	Dorsal Anterior Cingulate Cortex
DERS-P	Difficulties in Emotion Regulation Scale – Parent Report
DHHS	Department of Health and Human Services
DICOM	Digital Imaging and Communications in Medicine
dlPFC	Dorsolateral Prefrontal Cortex
DMC	Data Management Center
DMN	Default Mode Network

Abbreviation	Definition
DSMB	Data Safety Monitoring Board
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imaging
DUA	Data Use Agreement
EDC	Electronic Data Capture
EN-back	Emotional N-back
EP	Emotional Processing
ER-40	Penn Emotion Recognition Test
ERQ	Emotion Regulation Questionnaire
ERQ-CA	Emotion Regulation Questionnaire for Children and Adolescents
ESC	Epidemiological and Statistical Methods Core
FA	Fractional Anisotropy
FDA	Food and Drug Administration
FDR	False Discovery Rate
FSF	Frontier Science Foundation
fMRI	functional Magnetic Resonance Imaging
FSL	Functional Magnetic Resonance Imaging of the Brain Software Library
FS-LDDMM	FreeSurfer-initiated Large-Deformation Diffeomorphic Metric Mapping
GAD-7	Generalized Anxiety Disorder-7
GAM	Gambling
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
GHAC	General Health Assessment for Children
HCP	Human Connectome Project
HCP-YA	Human Connectome Project Young Adults
HIPAA	Health Insurance Portability and Accountability Act
HIPP	Hippocampus
HIV	Human Immunodeficiency Virus
HLC IRB	Harvard Longwood Campus IRB
HSPH	Harvard T. H. Chan School of Public Health
HTTPS	Hyper Text Transfer Protocol Secure
HUU	HIV-Unexposed, Uninfected
ICA	Independent Component Analysis
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFO	Inferior Fronto-Occipital Fasciculus

Abbreviation	Definition
INS	Insula
IPAQ	International Physical Activity Questionnaire – Short Form
IRB	Institutional Review Board
LAR	Legally Authorized Representative
LEGACY	Longitudinal Epidemiologic Study to Gain Insight into HIV/AIDS in Children and Youth
LPC	Laboratory Processing Chart
MID	Monetary Incentive Delay
MNPP	Manual of Network Policies and Procedures
MRI	Magnetic Resonance Imaging
MOP	Manual of Procedures
NAFLD	Nonalcoholic Fatty Liver Disease
NB-WM	N-back Working Memory
NCI	The National Cancer Institute
NHLBI	The National Heart Lung and Blood Institute
NIAAA	The National Institute of Dental and Craniofacial Research
NIAID	The National Institute of Allergy and Infectious Diseases
NICHD	The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	The National Institute of Deafness and Other Communication Disorders
NIDCR	The National Institute of Dental and Craniofacial Research
NIH	National Institutes of Health
NIMH	The National Institute of Mental Health
NINDS	The National Institute of Neurological Disorders and Stroke
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NURIPS	Northwestern University Research Image Processing System
OD	Office of the Director, National Institutes of Health
OFC	Orbitofrontal Cortex
OHRP	Office of Human Research Protection
ORARC	Office of Regulatory Affairs and Research Compliance
PASS	Power Analysis & Sample Size
PDS	Pubertal Development Scale
PHACS	Pediatric HIV/AIDS Cohort Study
PHEU	Perinatal HIV Exposure who are Uninfected
PHI	Protected Health Information
PHIV	Perinatally Acquired HIV
PHQ-9	Patient Health Questionnaire-9

Abbreviation	Definition
PI	Principal Investigator
PID	Participant Identification Number; also known as Patid
PIN	Personal Identification Number
PNS	Peripheral Nerve Stimulation
PRIME-MD	Primary Care Evaluation of Mental Disorders
PSQI	Pittsburgh Sleep Quality Inventory
PWV	Pulse Wave Velocity
QA	Quality Assurance
QoL	Quality of Life
QNS	Query and Notification System
RAVLT	Rey-Auditory Verbal Learning Test
RIAS	Reynolds Intellectual Assessment Scales
ROI	Region of Interest
rs	Resting-State
rsFC	Resting-State Functional Connectivity
SCARED	Screen for Child Anxiety Related Disorders
SD	Standard Deviation
SEM	Structural Equation Modeling
SES	Study Enrollment System
SID	Study Identification Number
sIRB	Single Institutional Review Board
SMARTT	Surveillance Monitoring for ART Toxicities
SMR	Standardized Mortality Ratio
SN	Salience Network
SSL	Secure Sockets Layer
SST	Stop Signal Task
STI	Sexually Transmitted Infection
SUD	Substance Use Disorders
T1	T1-weighted Magnetic Resonance Imaging
T2	T2-weighted Magnetic Resonance Imaging
TBSS	Tract Based Spatial Statistics
THAL	Thalamus
TERBO BRAIN	Trajectories of Emotional Regulation and Behavior Outcomes and related Brain Regions And Intrinsic Networks
UPS	Uninterruptible Power Supply
URL	Uniform Resource Locator
U.S.	United States

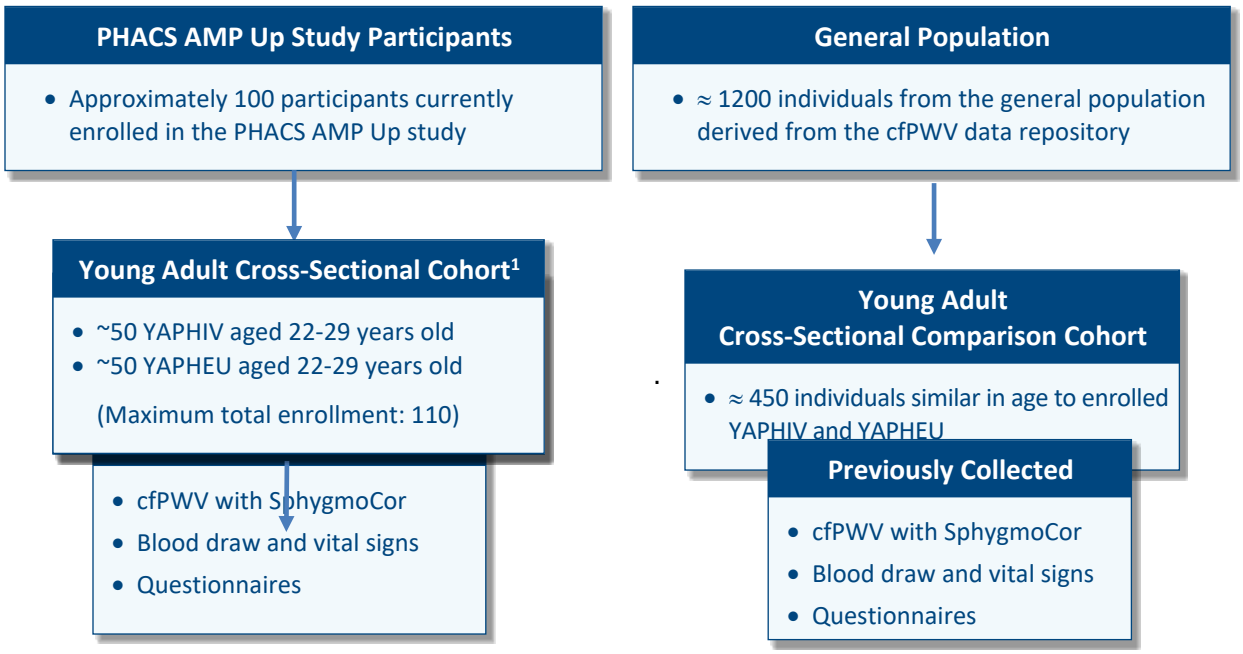
Abbreviation	Definition
vlPFC	Ventrolateral Prefrontal Cortex
vmPFC	Ventromedial Prefrontal Cortex
vs.	versus
vSTR	Ventral Striatum
WAIS-IV	Wechsler Adult Intelligence Scale, Fourth Edition
WIHS	Women's Interagency HIV Study
WISC-IV	Wechsler Intelligence Scale for Children, Fourth Edition
XNAT	Extensible Neuroimaging Archive Toolkit
YAHUU	Young Adults who are HIV-Unexposed, Uninfected
YAPHEU	Young Adults with Perinatal HIV Exposure who are Uninfected
YAPHIV	Young Adults with Perinatally Acquired HIV
YPHIV	Youth with Perinatally Acquired HIV
YHUU	Youth who are HIV-Unexposed, Uninfected

ASTRO Standalone Study Synopsis

Study Description	The ASTRO Standalone Study is a cross-sectional study to investigate aortic stiffness and its contribution to end-organ damage in young adults with perinatal HIV infection (YAPHIV) and young adults with perinatal HIV exposure without infection (YAPHEU) (22-29 years old). Aortic stiffness will be compared between study groups as well as to similar-age individuals from the general population. Lastly, the relationship of aortic integrity with metabolic, immune, and neurocognitive parameters within PHIV and PHEU groups will be delineated. Data from the ASTRO Standalone Study will be pooled with data from the ASTRO Nested Substudy within the PHACS TERBO BRAIN study for analysis.
Study Aims	• **Aim 1:** To investigate the impact of in utero HIV exposure and perinatal HIV infection on aortic stiffness in young adults. • **Aim 2:** To evaluate the role of aortic stiffness in the pathogenesis of neurocognitive dysfunction in individuals with PHIV and PHEU.
Study Population	enrolled ,YAPHEU and YAPHIV aged 22-29 years who are current participants in AMP Up and who have agreed to be re-contacted about future studies will consent to participate and complete a single visit.
Study Sample Size	The ASTRO Standalone Study (PH601) and the ASTRO Nested Substudy of the TERBO Brain study (PH600) together aim to enroll a target of approximately 50 YAPHEU and 50 YAPHIV. The ratio of YAPHIV to YAPHEU may range from 1:1 up to 3:1 with a maximum total enrollment of 110 individuals..
Study Assessments and Data Collection Measures:	• Carotid-femoral pulse wave velocity (cfPWV) • Vital signs and anthropometrics: weight, height, blood pressure, and mid-waist and hip circumferences • Interviewer-administered questionnaires: education of primary caregiver, and physical activity • Online survey: adverse childhood experiences (ACEs); questions on education, work, and social habits • Fasting blood: metabolic and immune serologic markers and eicosanoid profiling; CD4 count and HIV viral load (for YAPHIV, if not available within the last 3 months).. • Neurocognitive testing (NIH Toolbox) in AMP Up • The ASTRO Standalone Study will leverage existing data that has already been collected in AMP Up, such as diagnoses, medications, CD4 count and HIV viral load (for YAPHIV, if within the last 3 months), and neurocognitive testing. • Clinical data since the last AMP Up visit will be abstracted from the medical record such as diagnoses, medications (e.g., ART), and CD4 T cell count and HIV viral load (for YAPHIV, if within the last 3 months)
Study Duration	The ASTRO Standalone Study is expected to be open for accrual until the target sample sizes in the combined ASTRO Standalone Study and ASTRO Nested Substudy are achieved.
Participant On-Study Duration	Participants in the ASTRO Standalone Study will complete a single study visit.

Study Monitoring	• The ASTRO Protocol Team will review implementation of the ASTRO Standalone Study being conducted at clinical sites during regularly (i.e. at least once per month) scheduled protocol team meetings. The protocol team will review Data Monitoring and other administrative reports. • Monitoring of any adverse impact of the study will rely on the PHACS Protocol Query and Notification System (QNS), which is a real-time, web-based interactive reporting system. Sites will also record and enter in the study database all untoward effects associated with study participation, which will be reviewed by the Protocol Team.

ASTRO Standalone Study Schema



[1]Enrollment estimates reflect pooled enrollment of the ASTRO Standalone Study (PH601) and the ASTRO Nested Substudy within TERBO BRAIN (PH600).

2. ASTRO Standalone Study Introduction

Individuals who are living with PHIV and PHEU have been found to have increased adiposity [132, 133], insulin resistance [134, 135], dyslipidemia [136, 137], and inflammation [138-140], likely due to the interplay of chronic infection, antiretroviral therapy (ART), and effects on fetal programming. In the general population, increased aortic stiffness is an early consequence of metabolic dysfunction and immune activation that results in excess transmission of pulsatile pressure to the microvasculature with resultant end-organ damage [141]. As a low-resistance organ, the brain is particularly vulnerable to pressure and pulsatility induced by increased arterial stiffness [142], which in turn has been linked to neurocognitive impairment [143, 144]. Nonetheless, whether aortic stiffness is increased or contributes uniquely to the pathogenesis of multi-systemic comorbidities in individuals with PHIV and PHEU remains a critical gap in knowledge. This standalone study will investigate aortic stiffness and its contribution to end-organ damage in young adults born to mothers with HIV. The central hypothesis of this study is that the abnormal metabolic and pro-inflammatory milieu in individuals with PHIV and PHEU will promote aortic stiffness, which in turn will predispose to altered neurocognitive function as a key indicator of end-organ damage. To test this hypothesis, carotid-femoral pulse wave velocity (cfPWV) will be ascertained among participants as a low-cost and reproducible index of aortic stiffness. First, differences in aortic stiffness between those living with PHIV and PHEU, as well as similar-age individuals from the general population, will be investigated. Furthermore, associations of metabolic and inflammatory parameters with aortic stiffness will be assessed in people with PHIV and PHEU to uncover novel mechanisms of aortic dysfunction. Second, the role of aortic stiffness in the pathogenesis of altered neurocognitive function in those with PHIV and PHEU will be delineated by assessing relationships of cfPWV with neurocognitive outcomes measured in AMP Up. This study could uncover increased aortic stiffness as an as-yet unrecognized sequela of perinatal HIV infection and in utero HIV exposure that may serve as a harbinger for adverse health outcomes. Moreover, this pilot study will inform the development of targeted interventions to attenuate aortic stiffness as an early and modifiable risk factor in these populations.

2.1 Background and Significance

Multiple studies of individuals with PHIV have shown a high prevalence of metabolic and inflammatory comorbidities including insulin resistance [134, 145, 146], hypertriglyceridemia [136], altered fat distribution [132], and increased immune activation [138, 140]. Individuals with PHEU similarly manifest metabolic and immune perturbations, including higher rates of obesity [133], hypertension [147], and inflammation [148], as well as lower insulin sensitivity [134, 135], compared to HIV-unexposed, uninfected (HUU) individuals. ART, persistent viral infection, and effects of an altered intrauterine milieu on fetal programming have been posited to contribute to the pathogenesis of these findings. In the general population, metabolic and inflammatory abnormalities predispose to increased aortic stiffness as a key mechanism of end-organ damage [141]. Nonetheless, despite the high prevalence of metabolic dysfunction and immune activation in the PHIV and PHEU populations, the integrity of the large arterial system and its contribution to multi-systemic disease remains a critical gap in knowledge.

As the largest and most distensible blood vessel in the body, the aorta buffers the systemic circulation from the high pulsatile pressures generated by the heart. In particular, the elastic nature of this vessel allows it to expand to accommodate blood that enters the arterial system during systole and to recoil to expel blood to the peripheral tissues during diastole, thereby maintaining

steady non-pulsatile blood flow within small blood vessels throughout the cardiac cycle [149, 150]. Increased aortic stiffness augments the transmission of pulsatile pressure from the heart to peripheral tissues, which in turn has deleterious impacts on multiple organs including the heart, kidney, and brain [149]. High arterial stiffness has been implicated in coronary ischemia [151, 152], heart failure [153, 154], and arrhythmia [155, 156]. Longitudinal studies have further shown a bidirectional causal link between aortic stiffness and hypertension [157, 158]. Given the role of aortic dysfunction in the pathogenesis of chronic comorbidities, identifying high aortic stiffness would expose a critical vulnerability in the long-term health of the PHIV and PHEU populations.

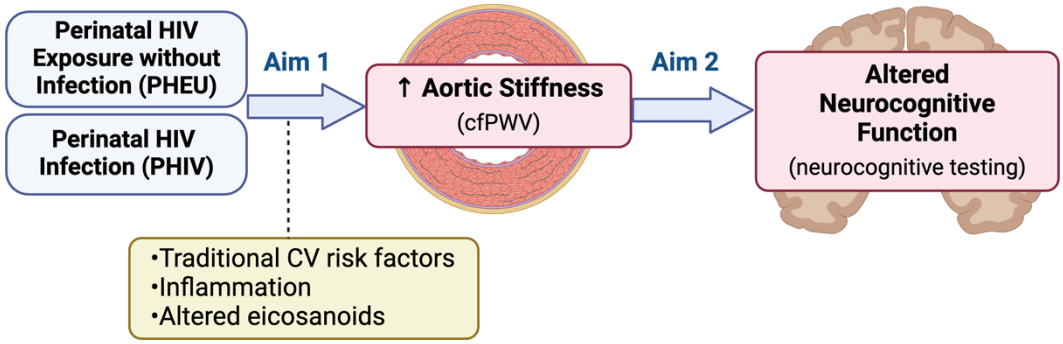
Various pathologic stimuli may result in abnormal stiffening of the aortic wall, resulting in impaired cushioning [141]. Among the general population, aortic dysfunction has been linked to traditional cardiovascular risk factors including obesity, insulin resistance, hypertension, and dyslipidemia [141]. The Bogalusa Heart Study found that young adults with a greater number of features of metabolic syndrome at baseline had steeper rises in aortic stiffness over time [159]. Conversely, attenuation of metabolic dysfunction such as with weight loss, exercise, antagonism of the renin-angiotensin-aldosterone system, statins, or omega-3 fatty acid supplementation was found to restore normal aortic elasticity [160]. In addition to traditional cardiovascular risk factors, systemic inflammation also has been recognized as a key risk factor for arterial dysfunction [141]. In particular, individuals with autoimmune conditions including rheumatoid arthritis and inflammatory bowel disease were found to have elevated aortic stiffness [161, 162], which declined following immunomodulatory therapy [163]. Additionally, inflammatory markers such as C-reactive protein (CRP) have been shown to positively predict higher aortic stiffness in healthy individuals [164], including in our own data in young adults. Based on the high burden of metabolic and immune abnormalities in those with PHIV and PHEU, there are strong imperatives to evaluate the integrity of the arterial system in these populations. By delineating relationships of metabolic and immune indices with aortic function, this study may inform the rational design of tailored interventions to restore aortic integrity in these groups, to be explored in future work.

The brain is a densely vascularized organ that requires high blood flow to meet its metabolic requirements. Increased aortic stiffness results in excess transmission of pulsatile pressure to its microvasculature, which in turn predisposes to altered tissue structure and function [149]. White matter hyperintensities are a late complication of increased aortic stiffness, which are preceded by microstructural changes to neuronal tract fibers that can be detected using advanced magnetic resonance imaging (MRI) techniques [165, 166]. Gray matter atrophy has also been observed among individuals with increased arterial stiffness, including in brain regions such as the thalamus and cortex [166, 167]. Underlying these structural changes, higher aortic stiffness has been correlated with impaired autoregulation of cerebral blood flow both at rest and during activity, as measured by functional MRI (fMRI) [168]. In addition to these radiographic abnormalities, aortic stiffness has been linked to decline in neurocognitive performance, particularly in the domains of executive function, memory, and global cognition [142-144]. Given our hypothesis that individuals living with PHIV and PHEU may be prone to heightened aortic stiffness, there is a pressing need to examine the contribution of aortic stiffness to altered brain structure and function in these patient populations.

Building upon the protocol team's expertise in endocrinology, cardiology, infectious diseases, epidemiology, neuroimaging, and neurodevelopment, the integrity of the large arterial system in those with PHIV and PHEU vs. similar-age individuals from the general population will be evaluated for the first time, along with its role in the pathogenesis of chronic comorbidities (Figure 2). The central hypothesis is that metabolic and inflammatory abnormalities in the PHIV and PHEU

populations will lead to increased aortic stiffness, which in turn will predispose to altered neurocognitive function as key indicators of end-organ damage. This hypothesis is supported by findings in the general population juxtaposed with evidence of an extensive burden of metabolic and inflammatory derangements in people with PHIV and PHEU. Based on this work, aortic stiffness may come to be used as a simple tool to identify individuals with PHIV and PHEU who are at high risk for adverse health outcomes and who thus require intensive monitoring. Findings from this study may guide the development of interventions to target aortic stiffness as an early and modifiable risk factor on the path to end-organ damage.

Figure 2. ASTRO Standalone Study Conceptual Framework of Specific Aims



2.2 Rationale

In the general population, aortic stiffness is an early sequela of metabolic dysfunction and immune activation that predisposes to multi-systemic morbidity including cardiac, renal, and neurologic disease [142-144, 149]. While those living with PHIV and PHEU have a high prevalence of traditional cardiovascular disease risk factors [133, 145, 147, 170] and immune abnormalities [138, 140, 148], the integrity of the large arterial system in these individuals has not been previously well evaluated in comparison to individuals from the general population. Nonetheless, we have previously shown that youth with PHIV in South Africa have endothelial dysfunction of the microvasculature [171, 172]. Furthermore, in a prior PHACS analysis, children with PHIV were found to have higher circulating biomarkers of endothelial dysfunction vs. controls in association with greater abdominal adiposity and HIV infection severity [173]. As endothelial dysfunction is intimately tied to abnormalities in aortic stiffness [149, 174], these data stress the urgency to further delineate the vascular phenotype among those with PHIV and PHEU within PHACS. Consistent with the mission of PHACS to improve the lives of people with PHIV and PHEU, the findings from this study may illuminate carotid-femoral pulse wave velocity (cfPWV, a measure of aortic stiffness) as a simple and noninvasive tool to identify individuals who are at high risk of chronic comorbidities and thus require intensive long-term monitoring. Moreover, this pilot study will inform the development of targeted interventions to attenuate aortic stiffness as an early and modifiable risk factor in these populations, which can be further explored in future work.

3 Aims and Hypotheses

The ASTRO Standalone Study will investigate aortic stiffness and its contribution to end-organ damage among young adults (22-29 years old) born to mothers with HIV.

3.1 Aim 1

To investigate the impact of in utero HIV exposure and perinatal HIV infection on aortic stiffness in young adults.

Hypotheses:

1a: Young adults with perinatal HIV infection (YAPHIV) will have the highest aortic stiffness, followed by young adults with perinatal HIV exposure without infection (YAPHEU), followed by similar-age individuals from the general population.

1b: In YAPHIV and YAPHEU, alterations in traditional cardiovascular risk factors, immune markers, and pro-inflammatory eicosanoids will be associated with higher aortic stiffness.

3.2 Aim 2

To evaluate the role of aortic stiffness in the pathogenesis of neurocognitive dysfunction in individuals with PHIV and PHEU.

Hypotheses:

Among YAPHIV and YAPHEU, higher aortic stiffness will be associated with worse neurocognitive outcomes, particularly in global cognition, executive function, and memory.

4. Study Design

The ASTRO Standalone Study is a cross-sectional study that will evaluate differences in aortic stiffness among young adults (22-29 years old) in YAPHIV and YAPHEU, and similar-age individuals from the general population (n ≈ 450). Participants in the ASTRO standalone study will be pooled for analysis with participants in the ASTRO Nested Substudy of the TERBO BRAIN study (PH600) for a total of approximately 50 YAPHIV and 50 YAPHEU. Participants from AMP Up who consent to enroll in the ASTRO Standalone Study will undergo several brief procedures at a single time point. Furthermore, their data collected in AMP Up will be incorporated into study analyses to address novel research questions, which in turn will maximize the insights to be gained from existing efforts in PHACS.

4.1 Study Population

YAPHEU and YAPHIV aged 22-29 years who are current participants in AMP Up and who have agreed to be re-contacted about future studies will consent to participate and complete a one-time evaluation.

4.2 Study Sample Size

The ASTRO Standalone Study (PH601) and the ASTRO Nested Substudy of the TERBO BRAIN study (PH600) will together enroll approximately 50 YAPHEU and 50 YA PHIV. The ratio between YAPHIV and YAPHEU may range from 1:1 up to 3:1 with maximum total enrollment of 110 participants.

4.3 Study Comparison Populations

Young adult participants will be compared to ~450 similar-age individuals from the general population. General population comparison groups will be derived from the repository of cfPWV data that has been previously curated by Dr. Elaine Urbina.

4.4 Study Duration

The ASTRO Standalone Study is expected to be open for accrual until the target sample sizes in the combined ASTRO Standalone Study (PH601) and ASTRO Nested Substudy of the TERBO BRAIN study (PH600) are achieved.

4.5 Participant On-Study Duration

Participants who consent to participate in this standalone study will undergo several brief procedures at a single time point.

4.6 Relationship with the ASTRO Nested Substudy

As a substudy of PHACS TERBO BRAIN the ASTRO Nested Substudy (PH601) engages youth and young adults enrolled in TERBO BRAIN to complete additional study procedures, specifically measurement of pulse wave velocity, fasting blood draw, and questionnaires. The ASTRO Standalone Study (PH601) has been initiated to augment recruitment of young adults to achieve our sample size goals (approximately 50 per YAPHIV and YAPHEU groups) for a pooled analysis.

Participants in the ASTRO Standalone Study will undergo the same study procedures as the ASTRO Nested Substudy with a few modifications as specified in Section 7 and Appendix I.

5. Selection and Enrollment of ASTRO Standalone Study Participants

5.1 Inclusion Criteria

To be considered eligible for enrollment, an individual must meet all the criteria listed below:

- PHEU or PHIV as documented in the medical record;
- Between 22 and 29 years of age at time of informed consent/assent, inclusive;
- Current participant in the PHACS AMP Up study;
- English or Spanish speaking;
- Completed a neurocognitive assessment (NIH Toolbox) in AMP Up within the past 2 years;
- Willing to provide access to existing medical records; and
- Willing to participate and provide legal consent, and assent if required.

5.2 Exclusion Criteria

To be considered eligible for enrollment, an individual must not meet any of the criteria listed below:

- Living with non-perinatally acquired HIV;
- Active untreated psychotic disorders that would interfere with participation in study procedures as determined by the clinical site PI or designee;
- Self-reported traumatic brain injury that resulted in loss of consciousness for 30 minutes or longer anytime in the past;
- Motor, sensory, cognitive, or other impairments that preclude participation in study assessments as determined by the clinical site PI or designee;
- Participants who think they are or may be pregnant
- Active substance use of a severity to interfere with participation in study procedures based on the judgement of the clinical site PI or designee;
- Currently incarcerated or pending incarceration; or
- Current or prior participation in the ASTRO Nested Substudy.

5.3 Protocol Registration

Prior to implementation of this study, the Harvard Longwood Campus Institutional Review Board (HLC IRB), the single IRB (sIRB) of record for this study, will approve the study protocol, including template informed consent and assent forms. Subsequently, the local IRBs at participating sites will cede review of this study to the HLC IRB through the execution of a reliance agreement. All site-specific participant-facing materials including informed consent form (ICF) addendums (to incorporate local IRB requirements), fact sheets, and recruitment materials must then be reviewed and approved by the HLC IRB. Finally, sites must receive protocol registration approval from Westat. Confirmation of protocol registration must occur before any participant is enrolled in the protocol. Original approved regulatory documents must be maintained at the site. This study will follow the PHACS procedures for protocol registration which are outlined in the PHACS Manual of Network Policies and Procedures (MNPP). The MNPP chapter pertaining to protocol registration can also be found on the PHACS website (https://my.phacsstudy.org).

5.4 Participant Recruitment

Site research staff will pre-screen all YAPHEU and YAPHIV who are current participants in AMP Up and have agreed to be re-contacted about future studies.. For participants found to be potentially eligible, site staff will approach the participant, or caregiver and participant, if the potential participant lacks the capacity to consent, to provide an overview of the study and gauge their interest in participating in the study.

The clinical site team will follow their standard practices and local institutional guidelines for reviewing patient records to pre-screen participants for eligibility. Site staff should consult with the Protocol Team via the Protocol Query and Notification System (QNS) if they have any concerns regarding a participant's eligibility for the study. Site staff will not perform any study assessment or collect any data for the study until after informed consent/assent has been obtained.

The ASTRO Standalone Study will be open for accrual until this study and the ASTRO Nested Substudy of the TERBO BRAIN study together achieve their combined targeted sample sizes.

5.5 Informed Consent

Once the participant is pre-screened eligible for the ASTRO Standalone Study, informed consent will be obtained from the participant or the participant's legally authorized representative (LAR) with assent from the participant, as applicable, prior to enrollment and before conducting any study assessments. The informed consent process may occur in-person using paper ICF/assent form or occur remotely through web-based electronic ICF/assent. Study details, including risks and benefits, the information to be collected and assessments to be completed will be discussed with the potential participant and/or their LAR, and all questions will be answered. A copy of the signed ICF and assent form, if applicable, will be provided to the participant and/or their LAR.

If remote consenting using web-based electronic ICF should occur, research staff will be available for phone consultation to address any questions or concerns the participant and/or their LAR may have. The web-based electronic ICF will include verification of comprehension and require participants or their LARs to acknowledge that they have read and agree to the consent form by checking a box following each section of the consent. Verification of identification during the consent process will be confirmed using a consent ID number provided to the participant or their LAR by the clinical site at the time of consent. Security questions may be employed for further verification.

5.6 Enrollment Procedures

When a participant is eligible for the ASTRO Standalone Study and informed consent has been obtained, the site will use the Study Enrollment System (SES) at Frontier Science, the Data Management Center (DMC) for PHACS, to enter participant and eligibility information. Participants will continue to use the PHACS participant identification number (PID) they were assigned from their participation in the AMP Up study. Once confirmed eligible and enrolled, the SES will generate a study identification number (SID). The SID will also serve as the participant's protocol-specific Personal Identification Number (PIN) that will be used as the participant identifier in ASTRO Standalone Study online assessments.

6.7 Co-Enrollment Guidelines

Enrollment of ASTRO Standalone Study participants in other studies (with or without similar goals/data collection as ASTRO) is at the discretion of the clinical site PI and the ASTRO Protocol Chair. The clinical site PI must take into account any issues that enrollment in the additional study may require and which may compromise the participant's ability to fulfill the requirements of the ASTRO Standalone Study.

Enrollment of participants who are already enrolled in other studies of young adults with PHIV and PHEU into the ASTRO Standalone Study is at the discretion of the Protocol Chair.

Sites must query the Protocol Team through the QNS for permission to co-enroll participants.

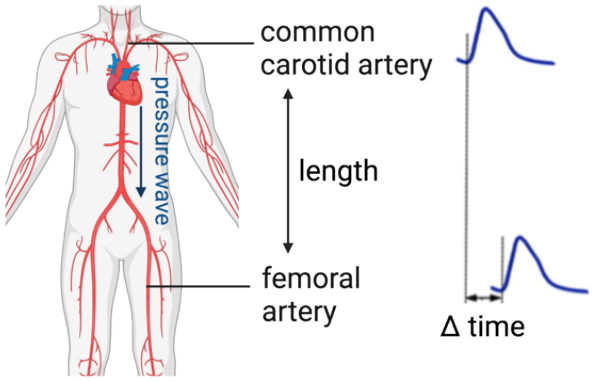
7. Study Procedures and Assessments

Participants who consent to participate in the ASTRO Standalone Study will complete the procedures described below during a single study visit. The study entry procedures, recruitment, and informed consent procedures are described in Sections 7 and 8, as well as the ASTRO Standalone MOP. All study procedures are to be conducted according to the Schedule of Evaluations (SOE) in Appendix II. According to Human Subjects Protection guidelines, a participant may voluntarily decline any specific protocol assessment or specimen collection and any such missed assessments will not be considered a protocol deviation. We will operate under this practice, and thus, voluntary participant refusals of any research activities do not require HLC IRB notification. The site should document the participant's decline of a specific protocol assessment or specimen collection in the participant's study record and/or on the appropriate CRF.

7.1 Carotid-Femoral Pulse Wave Velocity

SphygmoCor technology will be used to ascertain cfPWV as the gold standard measure of aortic wall stiffness. The cfPWV describes the speed at which a pressure wave propagates down the aorta with higher values indicating a stiffer vessel. Pressure waveforms at the common carotid and femoral arteries will be assessed transcutaneously in the supine position by trained site personnel. The length between the two body surface sites and the time delay between the waveforms will be used to derive cfPWV (Figure 3). The SphygmoCor device can be used following basic training and yields highly reproducible results. Dr. Urbina will oversee the acquisition of cfPWV on study participants across all participating sites.

Figure 3 cfPWV = Length/Δ Time



7.2 Vital Signs and Anthropometrics

Weight, height, and blood pressure will be assessed in light clothing using standard techniques. Mid-waist and hip circumferences will also be measured in triplicate by trained study staff.

7.3 Interviewer-Administered Questionnaires

Caregiver education and physical activity (International Physical Activity Questionnaire [IPAQ] - Short Form) will be collected via interviewer-administered questionnaires. Responses may be provided by the study participant and/or the participant's legally authorized representative if required [217, 228].

- The primary caregiver education questionnaire is comprised of a single question regarding the highest educational degree held by the participant's primary caregiver while growing up.

- The International Physical Activity Questionnaire – Short Form (IPAQ) is a 7-item questionnaire that assesses the types of physical activity that the participant was engaged in within the past 7 days.

7.4 Online Survey

The ACEs-Revised Questionnaire for Adults will be used for all participants. This questionnaire is available through the ACEs Aware project and asks whether the participant experienced each of 10 adverse circumstances (e.g., neglect, abuse, loss of caregiver) during their first 18 years that can have long-term impacts on health, opportunity, and well-being. The ACEs-Revised Questionnaire for Adults will be administered through the online survey tool. Participants also may be asked questions through online surveys pertaining to their education, work, and social habits.

7.5 Fasting Blood Draw

Fasting blood will be drawn, processed at individual study sites, stored, and shipped to the PHACS Repository per the ASTRO Standalone Study Laboratory Processing Chart (LPC). Approximately 30 mL of blood will be drawn in total for both pre-specified assays (~15 mL) and future studies (~15 mL) as described below.

7.5.1 Metabolic and Immune Serologic Markers

Fasting blood will be drawn for plasma glucose and serum insulin and lipids. Glucose and insulin will be used to calculate HOMA-IR as a measure of insulin resistance [229]. Serum high-sensitivity CRP [230, 231], plasma soluble CD163 (sCD163) [232, 233], and soluble CD14 (sCD14) [234, 235], also will be measured as key immune markers that have been shown to be elevated in both cardiovascular disease and HIV infection. CD4 T cell count and HIV viral load in YAPHIV participants will be ascertained from AMP Up as measures of HIV infection severity. HIV viral load and CD4 T cell count also will be drawn if not available within the past 3 months from AMP Up or routine clinical care.

7.5.2 Eicosanoid Profiling

Fasting blood will be drawn for eicosanoid profiling. Eicosanoid profiling (>100 eicosanoids) will be performed on fasting plasma samples using semi-targeted metabolomics techniques in the Einstein Stable Isotopes and Metabolomics Core under the direction of Irwin Kurland, MD, PhD. Samples will be processed, stored locally, and shipped to the PHACS Repository as specified in the ASTRO Standalone Study LPC. Eicosanoids are a complex network of bioactive lipids that play critical roles in biologic processes including metabolism, inflammation, and endothelial function [236]. In collaboration with Dr. Kurland, we have previously shown a distinct eicosanoid signature in infants with PHEU vs. controls in association with metabolic and immune parameters [148]. In the general population, plasma eicosanoids have been shown to strongly correlate with blood pressure [237], which is mechanistically linked to arterial stiffness [141]. Furthermore, supplementation of omega-3 polyunsaturated fatty acids (key eicosanoid precursors) has been found to attenuate arterial stiffness in several small studies [160], possibly due to a favorable shift in the eicosanoid profile [238]. In this study, relationships of eicosanoids with aortic stiffness among the PHIV and PHEU populations will be investigated. Evidence of novel associations between eicosanoids and aortic stiffness may implicate omega-3 fatty acid supplementation as a potential intervention to attenuate aortic stiffness in these groups, to be explored in future studies.

7.5.3 Specimens for Future Studies

Fasting blood will be drawn and processed for serum and EDTA plasma for storage in the PHACS Repository for yet to-be-determined future studies. Samples will be processed, stored locally, and shipped to the PHACS Repository as specified in the ASTRO Standalone Study LPC. Permission to store specimens in the PHACS Repository for future studies will be obtained from participants as part of the ASTRO Standalone Study consent process. Participants who do not agree to the storage of their specimens in the PHACS Repository for future studies may still participate in ASTRO.

8. Schedule of Evaluations and Procedures

The ASTRO Standalone Study will consist of a single study visit. Study procedures and assessments are expected to take approximately one hour.

The visit should preferably occur anytime from when the consent/assent are signed until 6 months following consent. However, the visit may occur outside the 6-month window if needed, to accommodate scheduling constraints. An extended window does not impact data/specimen fidelity but is meant to minimize disruption to and burden on participants; however, the site must **first** seek approval from the ASTRO Standalone Study Protocol Chair to conduct the study visit later than the designated 6-month window via the QNS. If the Protocol Chair approves an extended window, the site will file the QNS documentation of the approval in the participant's record. A note to file will not be required in this case.

Data abstraction from the participant's medical record must be completed within 3 months following the study visit.

The evaluations outlined below (Section 8.2) will be performed with each participant, after signed informed consent is obtained, as part of their participation in this study. See Appendix II for tabulated summaries of the ASTRO Standalone Study procedures and evaluations described below and their schedule for completion.

Refer to the ASTRO Standalone Study MOP for additional detailed information on the evaluations and administration procedures.

8.1 Scheduling Considerations

The visit should be completed after an overnight fast for ≥8 hours (except water and medications). Refer to Section 8.3 if participant did not fast for at least 8 hours.

The visit should be performed in the participant's usual state of health. If a participant has an active acute infection (e.g., upper respiratory infection, urinary tract infection) with ongoing symptoms or use of short-course anti-microbial agents including antibiotics, study procedures should be rescheduled to when after the infection has resolved

8.2 Clinical Evaluations

- cfPWV
- Vital signs (height, weight, and blood pressure)
- Anthropometrics (mid-waist and hip circumferences)
- Fasting blood draw (metabolic, immune, and eicosanoid biomarkers; CD4 count and HIV viral load for YAPHIV if not available within 3 months prior to study participation)
- Interview and online survey assessments

8.3 Blood Draw

Refer to the ASTRO Standalone Study schedule of evaluations in Appendix II for laboratory tests that will be performed as part of the study. The type of tube/anticoagulant for specific tests is critically important and testing specifications can be found in the ASTRO Standalone Study LPC.

Fasting is required for the ASTRO Standalone Study blood draw, unless determined to be unfeasible due to a valid medical condition by the local clinical investigator. The minimum duration of fasting is 8 hours. Water and medications are allowed during fasting.

If a participant did not fast for at least 8 hours, it is advised to not proceed with the blood draw. Other procedures can be performed, but the blood draw should be rescheduled for a different day. If a participant cannot return on a different day, a query should be sent to the protocol team via the QNS for guidance.

8.4 Interview and Online Survey Assessments

- Interviewer-administered questionnaires: education of primary caregiver, and International Physical Activity Questionnaire (IPAQ) – Short Form
- Online survey: adverse childhood experiences (ACEs); questions on education, work, and social habits

8.5 Existing Data To Be Utilized

- cfPWV data from the general population (from Dr. Urbina)
- Neurocognitive testing (NIH Toolbox) in AMP Up
- Additional data collected in AMP Up, including diagnoses, medications (e.g., ART), and CD4 T cell count and HIV viral load (for YAPHIV, if within the last 3 months)

8.6 Medical Record Abstraction

Clinical data since the last AMP Up visit will be abstracted from the medical record such as diagnoses, medications (e.g., ART), and CD4 T cell count and HIV viral load (for YAPHIV, if within the last 3 months)

9. Data Collection and Monitoring

9.1 Participant Identification

Participants must not be identified by name on any case report forms (CRFs), online surveys, or blood specimens that are part of their research record. Participants are to be identified only by the PID and SID/PIN numbers assigned by the ASTRO Standalone Study. Study research records with PID and SID/PIN numbers must be stored separately from source documents that include personal identifiers.

9.2 Pulse Wave Velocity Data Management and Quality Assurance (QA)

On the first study visit of each month, site staff will transfer pulse wave velocity data to the Frontier Science Portal using a secure File Exchange Utility. Pulse wave velocity data can be additionally transferred to Drs. Lindsay Fourman and Elaine Urbina via secure email on a more frequent basis as requested. Data will be reviewed by Drs. Fourman and/or Urbina to ensure that quality control standards are met. Drs. Fourman and/or Urbina will communicate with the sites as necessary should additional action be required.

9.3 Online Survey

The online survey will be administered using a secure cloud-based software tool, that is specifically used for creating online surveys. The online survey can be completed on any device on which the internet can be accessed, including a smartphone. The online survey data will be transferred using Hyper Text Transfer Protocol Secure (HTTPS) connections that adhere to the Food and Drug Administration (FDA) guidelines for secure electronic data capture. The collected data will be stored on a secure cloud server and transferred to the PHACS central database at Frontier Science. Access to the server will be highly restrictive and limited to a small number of technical and project staff members who have been authorized by PHACS Leadership to have access. The DMC will provide information to clinical sites on how to access the online survey for participants.

9.4 Data Collection – CRFs

For medical record abstraction and other non-web-based data collection, CRFs will be made available on the PHACS DMC web portal. Whenever possible, sites are encouraged to complete CRFs electronically, including those that are used as source documents, through direct data entry (DDE) into the PHACS central database. The DMC at Frontier Science will provide research staff with instructions about entering study data on electronic CRFs.

9.5 Data QA

Investigators receiving federal funding must adhere to the Code of Federal Regulations (CFR) to protect research participants and produce reliable study information. Clinical sites participating in the ASTRO Standalone Study, sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), will be required to have an internal QA plan that will be employed to identify problems and correct errors in research study records. Clinical sites are responsible for following ASTRO Standalone Study data QA procedures.

Additional pulse wave velocity data quality assurance procedures are performed by site research staff and the neuroimaging team (see Section 11.3).

9.6 Clinical Site Monitoring

Monitoring of any adverse impact of the study will rely on the PHACS Protocol Query and Notification System (QNS), which is a real-time, web-based interactive reporting system. Sites will also record and enter in the study database all untoward effects associated with study participation, which will be reviewed by the Protocol Team.

10. Study Management

The ASTRO Standalone Study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) Guidelines, and the applicable regulatory requirement(s).

10.1 Protocol Query Management

For the integrity of the study and the welfare of the participants, it is important for the research staff and research participants to have rapid access to the protocol team. Site research staff will send all queries to the protocol team using the QNS accessible via the internal PHACS website. It is expected that the Protocol Chair or designee will respond to queries within 48 working hours of receipt. Queries and replies will be automatically archived by the PHACS webmaster. Those queries deemed relevant to all sites will be posted on the PHACS website as Frequently Asked Questions (FAQs), where they will be available to all sites for future reference, as well as emailed weekly to all PHACS staff. Examples of query categories include protocol violations or adverse participant, staff, or community experiences related to the protocol, study management issues requiring clarification, and participant management issues that fall outside the protocol parameters.

10.2 Data Management

It is the responsibility of the PHACS DMC to ensure the completeness, quality, and integrity of clinical and laboratory data for each PHACS study. This role extends from protocol development to generation of the final study database. Data for the ASTRO Standalone Study will be entered into the central PHACS database.

This study follows PHACS standards and recommended guidelines for data management. The PHACS DMC will provide site research staff with instructions concerning the collection and recording of study data. The data will be entered into an electronic CRF using an electronic data capture (EDC) system. Each site is responsible for keying the data in a timely fashion according to standards set by the PHACS Network. The EDC system has built-in basic error checking capability so that minor errors can be resolved at the site. The data entered will then be exported to the PHACS central database where additional data checking and processing will take place. Data errors found during the automatic processing and loading of data will be communicated to the site via daily update reports. The study data manager will perform additional data checks, and any errors found during this process will be communicated via an interactive query mechanism integrated within the EDC system.

The LDMS will be used to label, manage, and track specimens collected in the PHACS Network. The LDMS has built-in basic error checking capability so that minor errors can be resolved at the lab before data is transmitted to the PHACS central database.

Additional pulse wave velocity data management is performed by the protocol team (see Section 11.2).

10.3 Rolling Implementation and New Protocol Versions

The ASTRO Standalone Study will be implemented across multiple clinical sites, initial implementation of the study will occur on a rolling basis as each site becomes ready. Furthermore, deployment of surveys, study assessment tools, and other study-related activities may occur on a

rolling basis depending on their availability and readiness. It is acknowledged that rolling implementation is no fault of the sites.

The introduction of a new protocol version may result in a period of delay between HLC IRB approval and functional roll-out of the new protocol version to sites in order to allow time for operational changes to be made. In addition, data collection instruments may need to be modified as a result of the approved new protocol and may not be available immediately upon receipt of HLC IRB approval. The Protocol Teams will ensure that all infrastructure-based operational components required for initiating implementation of the new protocol version (including the enrollment system's eligibility checklist and the new data collection instruments) have been aligned with the updated protocol version and are completed. The date this is done is the effective implementation date, which will be specified with the protocol amendment. Sites should not enroll or follow participants under the new protocol version prior to the effective implementation date.

11. Participant Management

11.1 Data Collection Management

All assessments and data collections are to be conducted according to the Schedule of Evaluations in Appendix II. Medical record abstraction for current diagnoses and medications should include all data since the participant's last AMP Up visit, and must be completed within 3 months after completion of the ASTRO Standalone Study visit.

For YAPHIV, current HIV disease data (HIV viral load and CD4 T cell count and percent) from within the 3 months prior to the visit should be collected from the participant's AMP Up study record or clinical record. If not available, sites will perform the tests as part of the ASTRO Standalone Study. According to Human Subjects Protection guidelines, a participant may voluntarily decline any specific protocol assessment or specimen collection during a study visit, and any such missed assessments will not be considered a protocol deviation. Thus, voluntary participant refusal of any research activities does not require HLC IRB notification. The site should document the participant's decline of a specific protocol assessment or specimen collection in the participant's file and on the appropriate CRF.

11.2 Enrollment of Participants with Cognitive Impairment

Potential participants with cognitive impairment who meet study eligibility criteria will not be excluded from enrollment. Enrollment of participants with cognitive impairment is justified given that the cause of the cognitive impairment may be related to the exposures being studied and not enrolling these individuals may introduce bias into the study. The ASTRO Standalone Study is an observational study; therefore, any potential risks or negative impacts on the well-being of these individuals are minimal. Given these conditions, enrollment of participants with cognitive impairment is in line with the U.S. Department of Health and Human Services (DHHS) and FDA regulations.

However, potential participants with significant cognitive impairments that would render them unable to complete study assessments (as determined by the clinical site PI or designee) should not be enrolled in the studies. Site staff should consult with the Protocol Team through the QNS if they have any concerns regarding a participant's eligibility for a study.

Participants with cognitive impairment will consent on their own behalf if legally able. For individuals with a LAR, LAR permission and participant assent will be obtained. Participating sites will consult with the HLC IRB, or site IRBs if indicated, for guidance when needed. Caregivers of participants with cognitive impairment may answer questions as proxies on behalf of participants but will not be consented and enrolled as study participants themselves.

11.3 Discontinuing Study Participation

Participants will be discontinued from the ASTRO Standalone Study if any of the following occurs:

- The participant withdraws permission;
- The participant fails to comply with the study requirements so as to cause harm to self or seriously interfere with the validity of the study results and the clinical site PI believes that compliance is unlikely to improve;

- The clinical site PI determines that further participation would be detrimental to the participant's health or well-being;
- The study is stopped by a governmental agency, including the NIH or DHHS;
- The clinical site is terminated for significant participant safety concerns, study integrity, poor performance issues, or lack of funding; or
- The HLC IRB decides to withdraw approval for the study due to participant safety concerns.

11.4 Participant Compensation

As approved by the HLC IRB, participants enrolled in the ASTRO Standalone Study will receive $65 for their time and effort in the completion of study procedures and assessments.

12. Adverse Event (AE) Reporting

The ASTRO Standalone Study is not a therapeutic study and no medications are prescribed or given as part of this study. Young adults enrolled in this study may develop common conditions requiring treatment during the course of the study period. Site study personnel will assist the participants in receiving appropriate care as appropriate to their roles at their site. YAPHIV participants may also experience AEs associated with HIV infection, ART exposure, or other medications. Clinical site PIs are encouraged to use the FDA's MedWatch system to report any events possibly associated with medications clinically prescribed for the participant.

13. Study Impact and Safety Monitoring

The Protocol Teams will monitor participant-, staff-, and community-associated untoward events. Monitoring will consider the impact of the study on the welfare of three groups of people:

- Research participants.
- Site research staff.
- The community in which the research is being conducted.

Reporting of participant or staff-associated negative study impact events to the Protocol Team will result in the re-examination of study procedures and allow changes as necessary to address concerns about participant management, recruitment, enrollment, adequacy of training, and/or the need to modify procedures. Community-associated untoward event reporting will facilitate understanding of the impact of the study on the community and will provide the opportunity to address community-level concerns and to intervene in a timely manner to correct misinformation or perceptions of practices that may cause community concern.

All clinical sites have psychologists, social workers, or other clinical staff qualified to address situations if a participant becomes distressed. In addition, PHACS has developed the PHACS Emergency Procedures for sites to follow in these circumstances (available on the PHACS website at https://my.phacsstudy.org within the PHACS Manual of Network Policies and Procedures).

13.1 Grading of Impact

The grading system for events involving study participants or staff will be as follows:

- Minimal Impact: managed at the time of event with no consequences.
- Moderate Impact: managed by referral for supplemental care/counseling.
- Major Impact: needed immediate professional intervention with or without hospitalization.

Community events will not be graded but will be addressed as they occur.

13.2 Reporting Requirements

All moderate and major impact events involving study participants or staff are to be reported to the Protocol Team through the QNS by the clinical site. Any event that is deemed to have negatively impacted a participant to a more than minimal extent and is related to the study activity must also be reported to the PHACS Regulatory and Compliance Manager by the study site through the QNS. Reportable events could involve study participants and/or staff members.

Examples of moderate and major impact events for study participants that could be related to the study activity include:

- Disruptive or violent behavior during the scheduled study visit session.
- Information regarding personal harm which is disclosed (e.g., current suicidal or homicidal ideation, physical or sexual abuse, active suicidal/homicidal intent, plan, and/or means).

- Significant visible distress or injury resulting from the research encounter (e.g., emotional response/distress as a result of responding to questions about violence, abuse, etc.).
- Breach of confidentiality.

Examples of moderate and major impact events for research staff that could be related to the study activity include:

- Inadequate preparation for management of research-related events.
- Visible distress or injury resulting from the research encounter.

Note: The distinguishing feature of moderate and major impact events is the need for enlisting additional support outside the research staff and the research encounter. The online surveys will include information on how and where participants can obtain assistance should they have feelings of anxiety, or other mental health concerns after completing the survey.

Examples of events for the community include:

- Any adverse community feedback received by the institution or the research team concerning the study.
- The study being portrayed adversely in any community forum or in the media.

The PHACS Regulatory and Compliance Manager will be responsible for reporting such events to the HLC IRB. The PHACS Regulatory and Compliance Manager will also work with the sites to ensure that the site's local IRB is notified of the event as required.

13.2.1 State Mandated Reporting Requirements

Laws governing the reporting of certain communicable diseases and illegal behaviors to authorities vary from state to state. Clinical sites are responsible for adhering to the reporting laws in their respective states. Clinical sites will consult with the HLC IRB and their local IRBs for guidance when needed.

13.3 Study Monitoring Plan

The ASTRO Standalone Study Protocol Team will hold regular conference calls to review study progress. These calls will occur at least monthly. More frequent calls or ad hoc calls may occur at the discretion of study's Protocol Chairs and Co-Chairs if a problem is identified that needs to be addressed immediately.

14. Statistical/Analytic Considerations

14.1 Sample Size

14.1.1 Study Sample

Data from the ASTRO Standalone Study (PH601) will be pooled with data from the ASTRO Nested Substudy of the TERBO BRAIN study (PH600) for analysis. The ASTRO Standalone Study and the ASTRO Nested Substudy will together enroll approximately 50 YAPHEU and 50 YAPHIV. The ratio between YAPHIV and YAPHEU will range from 1:1 up to 3:1 with maximum total enrollment of 110 individuals.

14.1.2 Comparison Participants

Similar-age individuals from the general population (n ≈ 450) from the repository of cfPWV data that had been previously curated by Dr. Urbina will be used as comparison groups.

14.2 Statistical Analyses

Analyses described below are for pooled data from the ASTRO Standalone Study and the ASTRO Nested Substudy.

14.2.1 Aim 1: To investigate the impact of in utero HIV exposure and perinatal HIV infection on aortic stiffness in young adults

In Aim 1, differences in cfPWV between groups will be assessed, and relationships of cfPWV with metabolic and inflammatory parameters within each group will be examined. YAPHIV (n ≈ 50), YAPHEU (n ≈ 50), and young adults from the general population (n ≈ 450) will be compared.

To minimize differences between groups, the general population sample will be standardized to the combined group of YAPHIV and YAPHEU on key covariates using probability weighting [289]. A propensity score for each participant will be obtained using a logistic regression model with study group (combined YAPHIV and YAPHEU, general population) treated as the outcome and rounded age, sex, race, and BMI treated as predictors. All YAPHEU and YAPHIV will be given a weight of 1, whereas the weight for each individual in the general population will be defined as (propensity score)/(1 - propensity score). A sensitivity analysis in which the general population sample is standardized to YAPHIV or YAPHEU individually and compared to each group in separate analyses will also be performed.

For analyses, variables that are not normally distributed and right-skewed will be log-transformed to approximate a normal distribution. **Hypothesis 1a**: The distribution of sociodemographic and clinical variables (including cfPWV) will be described across study groups using the mean (standard deviation, SD) and frequency, as appropriate, before and after weighting. To compare cfPWV between groups, unadjusted and adjusted linear regression models with weighting will be fit using generalized estimating equations (GEE) to obtain the robust variance estimator. The average difference (95% confidence interval, CI) will be reported for each pair of groups. The basic adjusted model will include age, sex, race, and potential confounders (e.g., primary caregiver education [290-292], adverse childhood experiences [293-295], and physical activity [296-298]). Analyses stratified by sex and obesity will also be performed to evaluate qualitatively whether differences in cfPWV between groups differ by strata, acknowledging that these analyses will have limited power.

Hypothesis 1b: Within YAPHIV and YAPHEU, the relationship of cfPWV with each metabolic and immune parameter (i.e., blood pressure, anthropometrics, serologic markers, and eicosanoids) will be plotted and categorizing the parameter will be considered if there is a deviation from a linear relationship. Unadjusted and adjusted linear regression models using GEE will be fitted to determine the association of each parameter with cfPWV. For analyses involving eicosanoids, a graphical lasso approach will be employed to estimate group-specific eicosanoid networks that are associated with cfPWV, as previously done [299]. Networks will be plotted using the R package igraph in which eicosanoids associated with cfPWV are represented as nodes and correlations between eicosanoids (conditional on all other analytes) are indicated by lines between nodes [300]. As an alternate approach, elastic net regression will also be considered in predictive modeling of all metabolic and immune parameters including eicosanoids.

Power calculations. Assuming a mean (SD) of 4.8 m/sec (0.97) in YAPHIV from preliminary data, there is 80% power to detect a difference of at least 0.55 m/sec of cfPWV between YAPHEU and YAPHIV ($\alpha = 0.05$, two-sided) and greater power in comparisons to individuals in the general population. For correlations within groups, there is 80% power to detect a correlation between cfPWV and each factor of interest of at least $r = 0.38$ within YAPHIV and YAPHEU ($\alpha = 0.05$) . The minimum detectable correlation will be slightly higher when adjusted for confounders.

Expected Outcomes. In young adults, it is expected that aortic stiffness will be highest among YAPHIV, followed by YAPHEU, followed by individuals in the general population. It is also hypothesized that markers of metabolic and immune dysfunction (including eicosanoids) will directly relate to aortic stiffness within YAPHIV and YAPHEU.

14.2.2 Aim 2: To evaluate the role of aortic stiffness in the pathogenesis of neurocognitive dysfunction in individuals with PHIV and PHEU.

In Aim 2, relationships of aortic stiffness with neurocognitive measures within YAPHIV and YAPHEU will be interrogated. Each group will be analyzed separately. Descriptive summaries will be prepared using the same approach described in Aim 1. Unadjusted and adjusted linear regression models will be fitted using GEE to assess associations between cfPWV and each neurocognitive parameter. A basic model will adjust for age, sex, race, and potential confounders (as listed in Aim 1). Analyses will be stratified by sex, obesity, and CRP to determine if key relationships differ by strata, acknowledging that these analyses will have limited power.

Power calculations. There is 80% power to detect a correlation of at least $r = 0.38$ within YAPHEU and YAPHIV unadjusted and a slightly higher correlation when adjusted ($\alpha = 0.05$).

Expected Outcomes. In YAPHIV and YAPHEU, cfPWV also will inversely relate to neurocognitive outcomes (e.g., Executive Function, Episodic/Working Memory, Fluid Cognition; NIH Toolbox).

15. Human Subjects

The ASTRO Standalone Study will be conducted in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP guidelines, and 45 CFR §46.

15.1 Participant Confidentiality

All participants enrolled in the PHACS Network are assigned unique PHACS PID and SID (PIN) numbers as described in Section 7.6. All participants co-enrolled in a PHACS study will use the same PHACS PID number assigned for their first PHACS study. The PID and SID (PIN) numbers will be used for identification purposes on all laboratory specimens, evaluation forms, and reports retained in the research records and generated in the PHACS central database, as well as for online assessments such as the online survey. A list linking the participant names with the PID and SID (PIN) numbers will be stored at the clinical site under double locks, separate from all other research records. All research records will be stored in a secured area in locked files.

All PHACS investigators and research staff persons at the clinical sites are required to sign non-disclosure forms pledging to hold research information in confidence. All collaborators seeking PHACS data are required to sign DUAs as described in Section 12.4.

Research staff will work with participants and/or their legal guardians to record contact information, which may also include the names and contact information of people (friends, family, or others) who may always know the whereabouts of participants. Establishing this list is a voluntary exercise and, if used in the event contact is lost with a participant, only a previously agreed to level of information will be disclosed. When contact is re-established with participants who were lost, willingness to continue study participation will be first ascertained.

15.2 Certificate of Confidentiality

As an NIH-funded project using identifiable, sensitive information, the ASTRO Standalone Study is automatically covered by a Certificate of Confidentiality issued from the DHHS. With this Certificate in place, the ASTRO researchers cannot be forced to turn over identifying information about a study participant in any Federal, State, or local criminal, administrative, legislative, or other proceedings. This Certificate does not prevent a study participant from volunteering to turn over their research information nor does it prevent investigators from providing research-related information to others when requested by the study participant or when required by law such as in cases of suspected or actual harm to or by the study participant.

The clinical site PI will make study documents (e.g., ICFs, CRFs) and pertinent records available for inspection by the local IRB, the HLC IRB, the PHACS site monitors, the NIH, the OHRP, or the sponsor's designee for confirmation of the study data as needed.

15.3 Risks and Benefits

15.3.1 Risks Associated with Participation

Participation in this study poses no more harms or discomforts to research participants than they may experience in normal daily life or during routine medical tests. Possible risks resulting from this study include the following:

- Measurement of aortic stiffness with SphygmoCor may cause mild discomfort or anxiety as it is an unfamiliar procedure. The procedure will be explained to put the participant at ease.
- Venipuncture to collect blood specimens may cause local discomfort, bleeding, or bruising; rarely a small clot or infection can occur at the blood draw site.
- Fasting is required for 8 hours prior to blood draw and should present little risk. Some participants may feel hunger, irritability, and lightheadedness as a result of fasting.
- There are no risks associated with vital signs or anthropometric evaluation.
- The evaluations that are involved in this study require answering questions about stressful or traumatic events and lifestyle behaviors. Some of the questions may make participants feel distressed or uncomfortable, and they may decline to respond. As the members of the research team have specific and extensive training in dealing with risks of this kind, no additional difficulties are expected beyond those experienced in a typical clinical practice. The PHACS Emergency Protocol provide specific guidance to site staff to address atypical and/or worrisome emotional responses that may occur during a study visit. The online survey tool is designed to reduce the discomfort that some participants may experience in self-reporting some behaviors and increase the likelihood of accurate responses. Despite the multiple measures taken to protect participant confidentiality, web-based communications may be at risk for hacking, intrusions, and other violations.
- While multiple safeguards are in place to protect participant privacy and confidentiality, a participant's health information may be inadvertently disclosed. Research staff members are required to complete human subjects research training and will be trained on protecting participant/caregiver confidentiality in the ASTRO Standalone Study.

15.3.2 Benefits Associated with Participation

While there is no guarantee of direct benefits to the individuals who participate in the ASTRO Standalone Study, benefiting from participating is possible. Participants may learn health information and contribute to scientific understanding.

15.4 Institutional Review Board Review and Informed Consent

All participating sites will rely on the HLC IRB as their sIRB of record.

Prior to initiation of study implementation, participating site IRBs will sign Reliance Agreements detailing the roles and responsibilities of the HLC IRB in relation to participating sites. The HLC IRB and the PHACS Regulatory and Compliance Manager will retain copies of all Reliance Agreements

and communications and facilitate the process of obtaining HLC IRB approval for this protocol, ICFs and assent forms, and any other participant-facing documents (e.g., fact sheets, recruitment materials, assessment surveys/interviews, etc.). All site-specific study materials (e.g., informed consent addendums, recruitment materials, etc.) will also require review and approval by the HLC IRB prior to study initiation. The HLC IRB Reliance Agreement Specialist and the PHACS Regulatory and Compliance Manager will maintain consistent and regular communications to ensure that participating sites are in compliance with the requirements of the HLC IRB.

This protocol, the informed consent documents, and any subsequent modifications will be reviewed and approved by the HLC IRB. The ICFs will describe the purpose of this study, the procedures to be followed, and the risks and benefits of participation. In accordance with 45 CFR §46.116, a legal informed consent will be obtained from the participant or their legal guardian, or person with power of attorney for participants who cannot consent for themselves. The participant's assent must also be obtained if they are able to understand the nature, significance, and risks of the study.

15.5 Participation of Individuals who are Incarcerated

The PHACS and NIH have concluded that this protocol does **NOT** meet Federal requirements governing participation of individuals who are incarcerated in human subjects research and should not be considered by HLC IRB for the recruitment of individuals who are incarcerated. Participants who become incarcerated after enrollment may not be seen for research evaluations as long as they are incarcerated.

15.6 45 CFR §160 and 164 Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule" pursuant to HIPAA)

Each site is responsible for adherence to their individual institution's HIPAA policies and procedures.

15.6.1 Database

Specific protected health information will be needed to create the ASTRO Standalone Study databases. Institutional Privacy Boards (or IRBs serving as such) are requested to add the following persons to the disclosure element of the HIPAA authorization form (45 CFR §164.514):

- PHACS DMC;
- PHACS investigators and their collaborators;
- Participant'sguardian or LAR, if so desired by the participant;
- The NIH; and
- Technical support staff at the institutions hosting the online assessments for the sole purpose of providing technical assistance.

15.7 Study Discontinuation

The study may be discontinued at any time by the NIH

16. Publication of Research Findings

Publication of the results of this study will be governed by PHACS policies as outlined in the PHACS Publication Policy (available on the PHACS website).

Participant summaries of findings will be developed, approved by the HLC IRB, and provided directly to the clinical sites to distribute to participants.

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Appendices

Appendix I
Comparison of the ASTRO Standalone Study (PH601) with the ASTRO Nested Substudy of the TERBO BRAIN Study (PH600)

The procedures in the ASTRO Standalone Study are the same as those in the ASTRO Nested Substudy with the following distinctions:

TERBO BRAIN/ASTRO Nested Substudy PH600	**ASTRO Standalone Study PH601**
Online surveys including Adverse Childhood Experience Questionnaire for Adults are assessed in the TERBO BRAIN parent study	Online surveys including Adverse Childhood Experience Questionnaire for Adults are assessed as part of the ASTRO Standalone Study
Neurocognitive testing (NIH Toolbox) is assessed in the TERBO Brain parent study	Neurocognitive testing data (NIH Toolbox) within 2 years will be ascertained in AMP Up
Medical history is ascertained from clinical records and AMP Up as part of the TERBO Brain parent study	Medical history is ascertained from clinical records and AMP Up as part of the ASTRO Standalone Study
Blood draw for CD4 count and HIV viral load is obtained if not available within 3 months as part of the TERBO Brain parent study (YAPHIV only)	CD4 count and HIV viral load will be incorporated into the existing blood draw for the ASTRO Standalone Study if not available within 3 months (YAPHIV only)

Appendix II
Schedule of Study Evaluations

Participants will complete all assessments outlined in the table below. Participants should be fasting for 8 hours (except water and medications) prior to blood draw.

Task/Assessment	Entry	Comments
Identify and pre-screen for eligibility, obtain informed consent/assent, confirm eligibility, enroll through the Study Enrollment System	X	
Study Procedures		
Carotid-femoral pulse wave velocity (cfPWV)	X	Using SphygmoCor device
Vital signs and anthropometrics		
– Blood pressure	X	
– Weight	X	
– Height	X	
– Mid-waist circumference	X	
– Hip circumference	X	
Laboratories		Fasting for 8 hours except water and meds
– Plasma[1]	X	
– Serum[1]	X	
– Repository specimens[2]	X	To be stored in the PHACS Repository for yet-to-be-determined future studies
Interviewer-administered questionnaires		Participant or legally authorized representative may respond
– Caregiver education	X	
– IPAQ short-form	X	
Online Survey		Participant or legally authorized representative may respond
– Adverse Childhood Experience Questionnaire for Adults	X	
– Questions about education, work, and social habits	X	
Existing Data from Dr. Urbina		
– cfPWV data from general population controls	X	
Existing Data from AMP Up *Data to be obtained for analysis from the DMC at Frontier Science. No chart abstraction/data entry required at the clinical sites'*		
Diagnoses, medications, and neurocognitive testing.	X	
For YAPHIV, CD4 T cell count and HIV viral load	X	If within past 3 months [3]
Neurocognitive testing (NIH Toolbox)	X	

Task/Assessment	Entry	Comments
Medical Record Abstraction		
Clinical data from the medical record, such as diagnoses and medications	X	Since last AMP Up visit
– For YAPHIV, CD4CD4 T cell count and HIV viral load	X	Within 3 months[3]

[1] Approximately 16 mL of fasting blood will be drawn. Plasma for glucose, sCD163, sCD14, and eicosanoids. Serum for insulin and lipids. See ASTRO Standalone study LPC for specimen processing details.

[2] Approximately 14 mL of fasting blood will be drawn, processed per the ASTRO Standalone study LPC and stored in the PHACS Repository for yet to-be-determined future studies.

[3] HIV viral load and CD4 T cell count will be drawn if not available in AMP Up or clinically within 3 months.