# Adolescent Master Protocol for Participants 18 Years of Age and Older (AMP Up)
# PH300

**Version 2.3**
**January 31, 2023**

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

*Sponsored by:*
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

*With Co-funding from:*
Office of the Director, National Institutes of Health (OD)
The National Institute of Dental and Craniofacial Research (NIDCR)
The National Institute of Allergy and Infectious Diseases (NIAID)
The National Institute of Neurological Disorders and Stroke (NINDS)
The National Institute of Deafness and Other Communication Disorders (NIDCD)
The National Heart Lung and Blood Institute (NHLBI)
The National Institute of Mental Health (NIMH)
The National Institute on Drug Abuse (NIDA
The National Cancer Institute (NCI)
The National Institute on Alcohol Abuse and Alcoholism (NIAAA)

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**TABLE OF CONTENTS**

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ACASI | Audio Computer Assisted Survey Instrument |
| ACEs | Adverse Childhood Events |
| ACTG | AIDS Clinical Trials Group |
| ADHD | Attention Deficit Hyperactivity Disorder |
| AMP | Adolescent Master Protocol |
| AMP Up | Adolescent Master Protocol for Participants 18 Years of Age and Older |
| ART | Antiretroviral Therapy |
| ARV | Antiretroviral |
| ASCUS | Atypical Squamous Cells of Undetermined Significance |
| BMI | Body Mass Index |
| cART | Combination Antiretroviral Therapy |
| CDC | Centers for Disease Control and Prevention |
| CDQ | Client Diagnostic Questionnaire |
| CELF | Clinical Evaluation of Language Fundamentals |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CIN | Consent Identification Number |
| CMV | Cytomegalovirus |
| CLIA | Clinical Laboratory Improvement Amendments |
| CPT | Cell Preparation Tube |
| CRF | Case Report Form |
| *C. trachomatis* | *Chlamydia trachomatis* |
| CVD | Cardiovascular Disease |
| DAG | Directed Acyclic Graph |
| dbGaP | Database of Genotypes and Phenotypes |
| DHHS | Department of Health and Human Services |
| DMFS | Decayed, Missing, and Filled Surfaces |
| DMC | Data Management Center |
| DNA | Deoxyribonucleic Acid |
| DRC | Data Resources Core |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders-IV |
| EBV | Epstein-Barr virus |
| EDTA | Ethylenediaminetetraacetic Acid |
| FDA | Food and Drug Administration |
| FGF | Fibroblast Growth Factor |
| GAD-7 | Generalized Anxiety Disorder 7-Item Scale |
| GCP | Good Clinical Practice |
| GDS | Genomic Data Sharing |
| GED | General Educational Development |
| GEE | Generalized Estimating Equation |
| GINA | Genetic Information Nondiscrimination Act |
| GWAS | Genome-Wide Association Studies |
| GYN | Gynecological |
| HDL | High-Density Lipoprotein |
| HECC | Health Education and Community Core |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |

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| HLA | Human Leukocyte Antigen |
| HLC | Harvard Longwood Campus |
| HOMA-IR | Homeostatic Model Assessment of Insulin Resistance |
| HOPE | Health Outcomes around Pregnancy and Exposure to HIV/ARVs |
| HPV | Human Papillomavirus |
| HSIL | High-Grade Squamous Intraepithelial Lesions |
| HSPH | Harvard T. H. Chan School of Public Health |
| HSV | Herpes Simplex Virus |
| HTTPS | Hypertext Transfer Protocol Secure |
| IATA | International Air Transport Association |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IL-12 | Interleukin-12 |
| IMPAACT | International Maternal Pediatric Adolescent AIDS Clinical Trials Network |
| INSTI | Integrase Inhibitor |
| IRB | Institutional Review Board |
| LAR | Legally Authorized Representative |
| LDL | Low-Density Lipoprotein |
| LDMS | Laboratory Data Management System |
| LEGACY | Longitudinal Epidemiologic Study to Gain Insight into HIV/AIDS in Children and Youth |
| LOESS | Locally Estimated Scatterplot Smoothing |
| LPC | Laboratory Processing Chart |
| LSIL | Low-Grade Squamous Intraepithelial Lesions |
| MNPP | Manual of Network Policies and Procedures |
| MSM | Men who have Sex with Men |
| NaF/K oxalate | Sodium Fluoride/Potassium Oxalate |
| *N. gonorrhoeae* | *Neisseria gonorrhoeae* |
| NCI | The National Cancer Institute |
| NHLBI | The National Heart Lung and Blood Institute |
| NIAAA | The National Institute on Alcohol Abuse and Alcoholism |
| NIAID | The National Institute of Allergy and Infectious Diseases |
| NICHD | The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development |
| NIDA | The 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 | The National Institutes of Health |
| NIMH | The National Institute of Mental Health |
| NINDS | The National Institute of Neurological Disorders and Stroke |
| NNRTI | Non-Nucleoside Reverse Transcriptase Inhibitor |
| NRTI | Nucleoside Reverse Transcriptase Inhibitor |
| NtRTI | Nucleotide Reverse Transcriptase Inhibitor |
| OAR | The National Institutes of Health Office of AIDS Research |
| OD | The National Institutes of Health Office of the Director |
| OHD | Hydroxy-Vitamin D |
| OHRP | Office of Human Research Protection |
| OR | Odds Ratio |
| ORARC | Office of Regulatory Affairs and Research Compliance |

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| OSHA | Occupational Safety and Health Administration |
| PACTG | Pediatric AIDS Clinical Trial Group |
| Pap | Papanicolaou Test |
| PBMCs | Peripheral Blood Mononuclear Cells |
| PDAY | Pathobiological Determinants of Atherosclerosis in Youth |
| PHACS | Pediatric HIV/AIDS Cohort Study |
| PHEU | Living with Perinatal HIV Exposure without Perinatally Acquired HIV |
| PHQ-9 | Patient Health Questionnaire-9 |
| PHI | Protected Health Information |
| PHIV | Perinatally Acquired HIV |
| PI | Protease Inhibitor |
| PID | Participant Identification Number |
| PIN | Personal Identification Number |
| PMOC | PHACS Management Oversight Committee |
| PTA | Pure Tone Average |
| PrEP | Pre-Exposure Prophylaxis |
| PRIME-MD | Primary Care Evaluation of Mental Disorders |
| PTSD | Post-Traumatic Stress Disorder |
| QNS | Query and Notification System |
| QoL | Quality of Life |
| REACH | Reaching for Excellence in Adolescent Care and Health |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| SES | Study Enrollment System |
| SID | Study Identification Number |
| sIRB | Single Institutional Review Board |
| SMARTT | Surveillance Monitoring for ART Toxicities |
| SNR | Signal-to-Noise Ratio |
| SSL | Secure Sockets Layer |
| STI | Sexually Transmitted Infection |
| TasP | Treatment as Prevention |
| *T. vaginalis* | *Trichomonas vaginalis* |
| "U = U" | "Undetectable equals Untransmittable" |
| vs. | Versus |
| WIN | Words-in-Noise |
| WITS | Women and Infants Transmission Study |
| WLHIV | Women Living with HIV |
| WLPHEU | Women Living with Perinatal HIV Exposure without Perinatally Acquired HIV |
| WLPHIV | Women Living with Perinatally Acquired HIV |
| YAPHEU | Young Adults Living with Perinatal HIV Exposure without Perinatally Acquired HIV |
| YAPHIV | Young Adults with Perinatally Acquired HIV |
| YPHEU | Youth Living with Perinatal HIV Exposure without Perinatally Acquired HIV |
| YPHIV | Youth with Perinatally Acquired HIV |

**LIST OF APPROVED STUDIES MEETING THE ELIGIBILITY REQUIREMENT FOR ENROLLMENT INTO AMP UP (PH300) PRIOR TO JANUARY 30, 2017**

- PHACS AMP
- PACTG 219C *(Opened to AMP Up enrollment in September 2015)*
- IMPAACT 1074 *(Opened to AMP Up enrollment in September 2015)*
- PHACS SMARTT – Youth living with perinatal HIV exposure without perinatally acquired HIV (YPHEU) and mothers with perinatally acquired HIV (PHIV) *(Opened to AMP Up enrollment in August 2016)*

Additional studies as approved by the AMP Up Protocol Team

This list will be updated and maintained on the PHACS website at https://phacsstudy.org.

As of January 30, 2017, enrollment in the "AMP Up young adult PHIV (YAPHIV)" cohort was opened to all eligible individuals not previously or currently enrolled in one of the approved studies.

Under the protocol version 2.0, enrollment in the "AMP Up young adults living with perinatal HIV exposure without perinatally acquired HIV (YAPHEU)" cohort is open to all eligible individuals at all AMP Up sites; previous enrollment in PHACS SMARTT or AMP is encouraged but not required.

## STUDY ABSTRACT

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| **Design:** | This is a prospective cohort study designed to define the impact of human immunodeficiency virus (HIV) infection and antiretroviral therapy (ART) on young adults with perinatally acquired HIV (YAPHIV) as they transition into adulthood. A group of young adults living with perinatal HIV exposure without perinatally acquired HIV (YAPHEU) from a similar sociodemographic background and age distribution will be enrolled for comparison. |
| **Population:** | YAPHIV and YAPHEU who are at or beyond their 18th birthday will be recruited at participating PHACS sites. |
| **Sample Size:** | • YAPHIV Cohort: Approximately 650 participants<br>• YAPHEU Cohort: Approximately 200 participants |
| **Primary Objectives:** | • To identify infectious and non-infectious complications of HIV disease and toxicities resulting from long-term ART, including disease progression, immune dysfunction, viral resistance, end-organ disease, and mortality.<br>• To define the impact of HIV infection and ART on the long-term clinical outcomes in YAPHIV, including:<br>o Metabolic abnormalities and risk factors for cardiovascular disease (CVD), including derangements in glucose and lipid metabolism, blood pressure, and body composition.<br>o STIs (*Chlamydia (C.) trachomatis, Neisseria (N.) gonorrhoeae, Trichomonas (T.) vaginalis*, syphilis, human papillomaviruses (HPV), genital and anal warts, and herpes simplex virus (HSV)) among males and females, and cervical HPV-associated pre-cancers and cancers and other vaginal microbiota, and pelvic inflammatory disease among females.<br>o Reproductive health, fertility, and pregnancy outcomes including perinatal transmission of HIV.<br>• To define the impact of perinatal HIV infection, its concomitant risk factors, and ART on long-term neurocognitive and behavioral health outcomes, including:<br>o Mental health (both psychiatric disorders and emotional/behavioral functioning) and neurocognitive functioning.<br>o Health care behaviors, including adherence to ART, participation in health care services, and transition to adult clinical care.<br>o Risk behaviors, including sexual behavior and substance use (alcohol, tobacco, vaping, and licit and illicit drugs).<br>o Hearing and language impairments.<br>o Independent living skills, vocational and education achievement, life satisfaction, resilience, and health-related quality of life (QoL) |
| **Domain-Specific Aims:** | **<u>Infectious and Non-Infectious Complications of HIV and Its Treatment</u>** |

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| | • To evaluate the long-term immunologic and virologic course of YAPHIV, including immune competence and activation, disease progression, viral resistance, and the response to changes in therapy.<br>• To identify cofactors which impact the short- and long-term course of HIV disease, including incident co-infections and host genetics.<br>• To evaluate the incidence and course of HIV end-organ disease (i.e., renal, hepatic, cardiac, pulmonary, and peripheral and central nervous system) and HIV-associated malignancies and mortality of YAPHIV, and to describe the relationship of these outcomes with HIV virologic status, ART, immune impairment, and chronic immune activation.<br>• To contribute to HIV remission/cure studies by understanding the viral dynamics and compartmentalization of perinatally acquired HIV (PHIV) in the context of novel HIV therapeutics, age at ART initiation, long-term viral suppression, immunologic control, and the presence and size of the viral reservoir.<br>• To evaluate access to testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), access to and acceptance of testing, treatment, and prevention strategies for other important infections among YAPHIV and YAPHEU.<br>• To assess vaccine acceptance among YAPHIV and YAPHEU, including receipt and intent to receive a SARS-CoV-2 vaccine and explore reasons for acceptance or hesitancy<br>• To define the oral health of YAPHIV and YAPHEU and to identify risk factors associated with declining oral health.<br>• Among YAPHIV, to determine risk behaviors for HIV transmission and their understanding of Undetectable equals Untransmittable (U = U) as an approach to the prevention of HIV transmission.<br>• Among YAPHEU, to determine their level of knowledge about and use of pre-exposure prophylaxis (PrEP) and their rates of HIV acquisition.<br>**Metabolic Complications**<br>• To evaluate longitudinal changes in parameters of cardiometabolic risk by HIV status (YAPHIV versus [vs.] YAPHEU), including body weight and composition, lipid levels, insulin sensitivity, blood pressure, and modified pathobiological determinants of atherosclerosis in youth (PDAY) scores (a predictor of atherosclerosis).<br>• Among YAPHIV, to evaluate the association of ART switches with changes in body weight and composition, lipid levels, insulin sensitivity, and blood pressure.<br>• To evaluate food insecurity and diet in YAPHIV and YAPHEU and their associations with body composition and metabolic outcomes. Among YAPHIV, to evaluate the associations of food security with adherence to ART and whether the association is mediated through engagement in clinical care. |

**Cardiopulmonary Complications**

- To evaluate the distribution of PDAY scores for YAPHIV and YAPHEU and compare the distributions by HIV status, and to assess the association of PDAY scores and cardiac biomarkers with neurocognitive function as reflected by NIH Toolbox measures.
- To determine the association between pulmonary function and left and right ventricular structure and function.
- To determine the prevalence of marijuana and nicotine vaping in YAPHIV and YAPHEU and evaluate associations of vaping with presence of asthma, pulmonary disease, and hospitalization by PHIV status.

**Sexually Transmitted Infections**

- To evaluate access to testing and treatment for genital STIs and bacterial vaginosis, and the incidence of and risk factors for acquiring STIs (e.g., *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, syphilis, HPV, HSV) and microbiome dysbiosis including clinical bacterial vaginosis among YAPHIV and YAPHEU, and acquisition of HIV among YAPHEU.
- To evaluate the incidence of and risk factors for pelvic inflammatory disease among females.
- To evaluate the occurrence of high-grade squamous intraepithelial lesions (HSIL), external genital warts, and persistent cervical, oral, and anal high-risk HPV, and the factors associated with persistent anogenital or oral high-risk HPV, including the vaginal microbiome.

**Reproductive Health**

Among women living with PHIV (WLPHIV) and women living with PHEU (WLPHEU):

- To describe the use of pregnancy prevention methods and their associations with pregnancy and STI outcomes.
- To determine incidence of and factors associated with pregnancy intention.
- To examine pregnancy outcomes and factors associated with these outcomes.
- To identify rates of menstrual irregularities and risk factors for menstrual irregularity, including stress, hormonal disturbances, HIV-related health, and ART use.
- To determine the incidence of perinatal transmission of HIV.

Among WLPHIV, in comparison to women living with non-perinatally acquired HIV from the Health Outcomes around Pregnancy and Exposure to HIV/ARVs (HOPE) study:

- To evaluate individual, mental health, and interpersonal factors associated with unintended pregnancy, contraceptive discontinuation or non-use, discordant family planning behaviors and desires, and incident STIs.

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| | • To compare factors associated with unintended pregnancy, contraceptive discontinuation or non-use, discordant family planning behaviors and desires, and incident STIs by mode of HIV acquisition (PHIV vs. non-PHIV).<br><br>**Neurocognitive Functioning and Mental Health**<br><br>• Among YAPHIV and YAPHEU, to describe the trajectories of cognitive functioning and mental health in young adulthood and examine factors associated with these trajectories.<br><br>• To identify the trajectories of co-occurring risks in cognitive, mental health, and behavioral health (sexual behaviors and drug and alcohol use) in young adulthood.<br><br>• To identify factors associated with trajectories of co-occurring risks in cognitive, mental, and behavioral health in young adulthood, including PHIV status, and individual, interpersonal and systemic influences experienced during childhood and adolescence including adverse childhood experiences (e.g., exposure to violence, neglect, etc.), and young adulthood experiences (e.g., racism, low levels of social support, etc.)<br><br>• To define the impact of the SARS-CoV-2 pandemic and its associated mitigation strategies on the mental health of participants affected by HIV.<br><br>**Health Care Behaviors and Transition to Adult Health Care**<br><br>• To describe factors associated with adherence to ART and health care and changes in adherence over time.<br><br>• Among YAPHIV, to estimate the associations between cognitive, mental health, and behavioral health (sexual, drug, and alcohol) risk trajectories during adolescence and ART adherence and viral suppression in young adulthood.<br><br>• To describe the transition from pediatric or adolescent to adult clinical care and to identify the individual, social, and health care system barriers and facilitators of adherence, access to and retention in adult health care, and clinical outcomes after transition (including sustained viral suppression).<br><br>**Risk and Protective Behaviors**<br><br>• To examine the prevalence, changes over time, and factors associated with sexual behaviors (including vaginal, oral, and anal intercourse, condom use, and multiple sexual partners), disclosure of HIV status, and knowledge of partner's HIV status.<br><br>• To examine the prevalence, changes over time, consequences of, and factors associated with use of licit (alcohol, tobacco) and illicit substances.<br><br>• To compare the prevalence and factors associated with sexual and substance use behaviors between YAPHIV and YAPHEU.<br><br>**Transition to Adult Functioning and QoL** |

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| | • To examine whether successful transition to adult functioning varies by HIV infection status.<br>• To examine life satisfaction, resilience, health-related QoL, sleep, friendship, and successful adult functioning (including educational attainment, employment, and independent living) of YAPHIV and YAPHEU, and to identify childhood, adolescent and young adult factors associated with these outcomes.<br>• To determine the association between trajectories of co-occurring mental health and behavioral risks with attainment of adult milestones, including employment and ongoing education.<br>**Hearing and Language**<br>• To assess changes in language acquisition from childhood to young adulthood in YAPHIV and YAPHEU and, among YAPHIV, the association of these changes with HIV disease severity and antiretroviral (ARV) exposure.<br>• To determine how language abilities and hearing in adolescence predict employment status, educational status, reading abilities and life satisfaction in young adulthood.<br>• To evaluate hearing sensitivity of YAPHIV and YAPHEU, and to evaluate the associations of ARV exposure and HIV disease severity with these outcomes. |
| **Evaluations:** | • Study visits at Entry and every 3 years starting at Year 3 (e.g., Years 3, 6, 9, 12…) will include clinical assessments (height, weight, other body measurements, blood pressure, male circumcision status [at entry only]), neurocognitive functioning, mental health assessments, language and hearing assessments, physical activity, real-time laboratory testing, and collection of specimens for central testing and the PHACS Repository.<br>*These visits are intended to be conducted in-person. If circumstances preclude an in-person visit, the visit can be conducted remotely, e.g., clinical assessment data will be collected through chart abstraction (when available), surveys and questionnaires may be completed via telephone (with Protocol Team approval), and research Aptima sexually transmitted infection (STI) test specimens may be self-collected and shipped to the clinical site.*<br>• Annual chart abstraction will include interval medical diagnoses, ART history (participants with HIV only) and other medications, immunizations, social history, reproductive history, height, weight, blood pressure, and results of laboratory testing conducted for clinical care.<br>• Annual web-based survey will collect information on socio-demographics, general health and health care-related, mental health, social determinants of health, reproductive health, sexual behaviors, substance use, and ARV medication adherence (participants with HIV only). |

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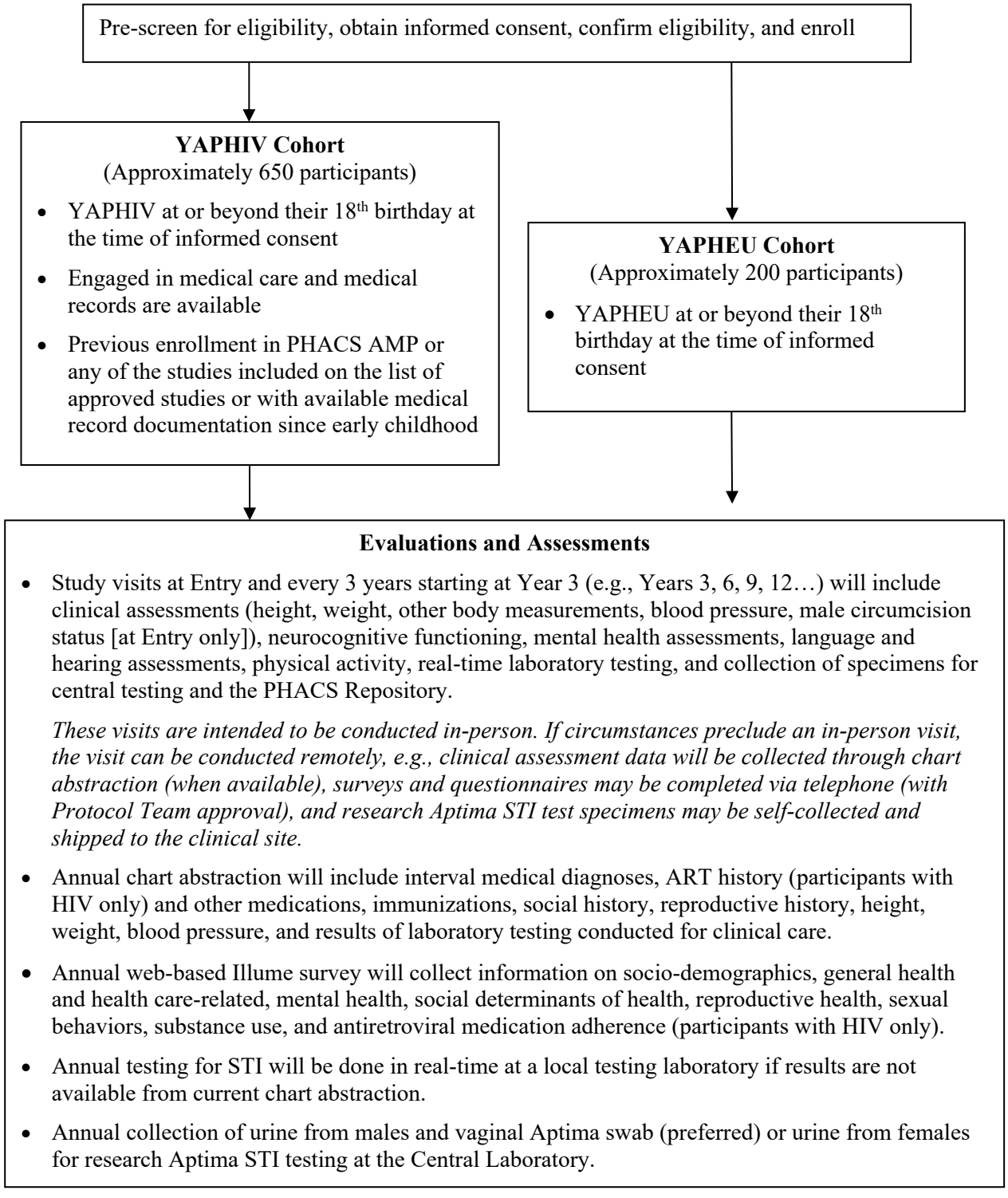
| | • Testing for STIs will be done annually in real-time at a local testing laboratory if results are not available from current chart abstraction. In addition, urine from males and vaginal swab (preferred) or urine from females will be collected annually for research Aptima STI testing. HIV testing will be offered to YAPHEU at the Years 3 and 9 in-person study visits. |
| **Monitoring:** | Routine team monitoring of any adverse impact of the study will rely on the PHACS Protocol Query and Notification System (QNS), 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. |

**STUDY SCHEMA**



# 1.0 INTRODUCTION

## 1.1 Scientific Background

Improvements in the treatment of infants, children, and young adults with HIV have been remarkable, ensuring that most previously infected American infants and children have survived through adolescence and are entering adulthood. It is estimated that in 2016 there were approximately 12,000 young persons with perinatally acquired HIV (PHIV) in the U.S. of whom 85% were adolescents and young adults (Centers for Disease Control and Prevention, 2018). In addition, the number of adolescents and young adults with PHIV worldwide is growing substantially in both resource-poor settings and settings with increasing levels of health care. Thus, there is a global cohort of adolescents and young adults with PHIV who have been living with HIV infection since birth and are now aging into young adulthood. However, the lifelong impact of HIV infection and its treatment on their overall health is unknown.

In the Pediatric HIV/AIDS Cohort Study (PHACS) Adolescent Master Protocol (AMP), 451 youth with PHIV (YPHIV) and 227 youth living with perinatal HIV exposure without perinatally acquired HIV (PHEU) aged 7 to < 16 years were enrolled from 2007-2009. These participants are all now over the age of 18. The majority of the young adults (294 young adults with PHIV (YAPHIV) and 124 young adults with PHEU (YAPHEU)), have now enrolled in the PHACS Adolescent Master Protocol for Participants 18 Years of Age and Older (AMP Up) for continued follow-up. The AMP Up protocol is also enrolling other YAPHIV not previously followed in AMP (See list of approved studies meeting the eligibility requirement for enrollment into AMP Up on page 15).

The AMP Up protocol will investigate the long-term outcomes of PHIV and its treatment, knowledge that can be used to help design treatment protocols and intervention strategies that will increase survival and minimize harmful effects. The protocol provides a dynamic framework and resource in which to investigate current and future questions regarding the medical and behavioral consequences of HIV and its therapy, genetic associations, disease processes and causation, interventions, and quality of life (QoL) among YAPHIV. Domains to be investigated include complications of HIV infection, adjustment to adulthood, metabolic risk factors for cardiovascular disease (CVD), neurocognitive functioning and mental health, hearing and language, behavioral function including health care behaviors, substance use, sexual behaviors, sexually transmitted infections (STIs), sexual and perinatal secondary transmission of HIV, and reproductive choices and outcomes. Additionally, the advent of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic along with its resulting mitigation strategies must be examined for the potentially far-reaching consequences on health care and on the physical and mental health of these young adults.

The study is designed as a prospective cohort study to define the impact of HIV infection and antiretroviral therapy (ART) on YAPHIV. A group of YAPHEU previously enrolled in PHACS AMP and Surveillance Monitoring for ART Toxicities (SMARTT) and from a similar sociodemographic background and age distribution are being enrolled as a comparison group.

### 1.1.1 Impact of HIV Infection on Young Adults

The advances in treatment to prevent maternal HIV transmission to neonates have been groundbreaking. As a result, the number of newborns and children with PHIV in the U.S. is now small. Subsequent improvements in the treatment of infants and children with HIV have been equally remarkable, ensuring that most children with PHIV in the U.S. have survived and are entering young adulthood.

Adolescents with PHIV and those living with perinatal HIV exposure without perinatally acquired HIV (PHEU) face unique challenges as they enter young adulthood. The advent of ART has made survival beyond childhood significantly more likely for YPHIV, and AMP made significant advances in understanding the long-term physical, mental, and behavioral impact of HIV infection and its treatment on the maturation process in these children. Improvements in treatment options for HIV have made earlier and more comprehensive treatment of perinatal HIV infection possible. In AMP, this was strongly correlated with lower viral loads and higher CD4 cell counts, even among children with a previous AIDS-defining condition (Van Dyke et al., 2011). However, older adolescents with PHIV and YAPHIV are at increased risk of suboptimal adherence, viremia (Kacanek et al., 2019), immunosuppression, Centers for Disease Control and Prevention (CDC) Class B and C events, and mortality compared to younger YPHIV (Neilan et al., 2017). They are also at higher risk of viremia compared to adolescents and young adults in the Ryan White Care Program, most of whom were not PHIV (Patel et al., 2019a). YPHIV in AMP were also at increased risk for stunted growth, altered body composition, lipid abnormalities, and insulin resistance resulting from HIV and antiretroviral (ARV) drugs (Jacobson et al., 2011a). In a longitudinal analysis of YPHIV, higher body mass index (BMI) and higher waist circumference were also associated with an increased risk of developing insulin resistance (Geffner et al., 2018). These outcomes, along with elevated biomarkers of vascular dysfunction, may place YPHIV at higher risk for complications such as CVD and metabolic abnormalities (Miller et al., 2010). Compared to YPHEU, YPHIV appear to be at increased risk for other conditions, including atopic dermatitis and asthma (Siberry et al., 2012), irreversible airflow obstruction (Shearer et al., 2017), and low bone mineral density (DiMeglio et al., 2013). Previous studies have found that YPHIV are also at risk for impaired or delayed cognitive and adaptive functioning. While HIV infection alone does not appear to increase the risk for cognitive impairment for youth in AMP, YPHIV who had previously had an AIDS-defining illness do appear to have an increased risk for specific and severe cognitive impairments compared to YPHIV with no AIDS-defining illness and YPHEU (Smith et al., 2012). Early ARV treatment to prevent early AIDS-defining illnesses may be critical for maintaining long-term cognitive functioning (Smith et al., 2012). Additionally, YPHIV and YPHEU in AMP experience language impairment at rates nearly three times those found in previous studies (Rice et al., 2012), which has implications not only for academic performance and vocational attainment, but also for mental health, social functioning, and ability to adhere to medication regimens.

Medication adherence is a critical issue in understanding the long-term health status of YPHIV. More than one-fifth of youth in AMP have experienced an interruption in ARV treatment of at least three months, which was likely to lead to a decline in CD4 percentage and CD4 cell counts (Siberry et al., 2011). Additionally, self-reports of low medication adherence from youth in AMP have been associated with higher viral loads (Usitalo et al., 2010). Lower executive and adaptive functioning and higher exposure to violence are also associated with poorer adherence (Kacanek et al., 2016). Lower levels of adherence were also found when YPHIV held primary responsibility for their medication management (Garvie et al., 2017). Further study of AMP youth as they transition into adulthood is needed to understand not only the dynamics of variability in responses to ARV treatment interruption, particularly with the new integrase inhibitors (INSTIs), but also the safety of potential interruption of treatment during childhood for infants and children who are prescribed combination ART (cART) (Siberry et al., 2011).

The transition into adolescence and adulthood presents additional challenges for YPHIV and YPHEU. Although findings suggest that youth in AMP are similar to nationally representative samples in terms of substance use (Alperen et al., 2014) and sexual initiation (Tassiopoulos et al., 2013), HIV adds a layer of complexity to these issues that can make poor medication adherence, nondisclosure of HIV status to sexual partners, and sexual behaviors difficult for YPHIV and their caregivers to navigate. For many youth with HIV, myriad physical, psychosocial, family, and environmental stressors increase the risk of mental health problems and of initiating substance use and sexual behaviors. This, in turn, can then

exacerbate these same stressors and lead to further risky behaviors, poor medication adherence, and worsened symptoms of HIV (Alperen et al., 2014; Kacanek et al., 2016). Rates of mental health problems (such as attention problems, anxiety, and depression) among AMP youth are higher than national averages for U.S. youth, but are consistent with other studies of youth with chronic illness (including YPHIV and YPHEU) (Smith et al., 2019). For YPHIV, mental health problems may affect adherence to medications, sense of isolation, willingness to disclose HIV status in a healthy way, and overall physical health. However, contrary to earlier studies, findings in AMP suggest higher rates of mental health problems among YPHEU compared to YPHIV (Malee et al., 2011c; Mellins et al., 2011). Considering the growing number of children with PHEU born in the U.S. and around the world as prenatal ARV treatment becomes more widespread and rates of perinatal transmission drop, this is a concerning finding and warrants further study to better understand the causes and potential interventions that might address this challenge (Malee et al., 2011c).

### 1.1.2 Infectious and Non-Infectious Complications of HIV and Its Treatment

Many HIV-associated complications such as opportunistic infections, nephropathy, encephalopathy, and cardiomyopathy have decreased in incidence with the advent of cART (Gona et al., 2006; Nachman et al., 2009; Patel et al., 2009; Patel et al., 2012; Purswani et al., 2012). Concern is now focused on long-term complications resulting from past and ongoing HIV viremia, immune dysfunction, chronic immune activation, ARV drugs, viral resistance, and interactions between these exposures and host genetics. Complications associated with these exposures include immunosuppression and disease progression, immune activation, and ARV drug toxicity including mitochondrial dysfunction. The goal of ART is to suppress viral replication. It will therefore be important to continue to determine the course of their infection, including their response to new therapies.

ARV drugs have been highly efficacious in suppressing viral replication, but long-term toxicities and management of therapy continue to raise concern. YAPHIV are unique, having HIV exposure prior to birth and initiation of multiple and sequential ARV drugs early in life and throughout the growth process (Van Dyke et al., 2011). It is therefore unclear how specific ARV drugs may affect YAPHIV with regards to long-term risk for organ system toxicities. For example, risk for nephrotoxicity due to tenofovir disoproxil fumarate exposure may differ for YAPHIV compared to healthy adults with HIV due to prolonged exposure to HIV or diverse history of ARV drug exposure (Fernandez-Fernandez et al., 2011). An AMP study reported a potential duration effect of tenofovir disoproxil fumarate on proteinuria among adolescents with PHIV so continued follow-up is necessary to assess future risk of clinical disease (Purswani et al., 2012).

The uniqueness of the YAPHIV population is also apparent when trying to determine optimal treatment strategies to maintain viral suppression and immune-competence through their transition into adulthood (Wong et al., 2012). Medication fatigue has been noted among older adolescents in this population (Saitoh et al., 2008) and treatment interruptions among YPHIV are common (Siberry et al., 2011). There is a need therefore to estimate the risks and benefits of alternative treatment strategies, particularly after treatment failure, and identify predictors and consequences of ARV drug resistance. Accumulating a longitudinal history of viral load and CD4 cell counts may also help with identifying young adults for future cure strategies. Longitudinal viral load data were used in a recent study to identify a cohort of AMP participants with long-term virologic suppression in which to assess decay of HIV reservoirs. This study suggested that early effective, long-term ART initiated from infancy leads to decay of HIV-1-infected cells to exceedingly low concentrations desired for HIV-1 remission strategies (Uprety et al., 2017). This same cohort was also utilized to assess the value of quantitative HIV antibody levels as biomarkers of HIV reservoir size (McManus et al., 2020). As this cohort of children has now aged into young adulthood,

they may be a suitable population in which to assess therapeutic strategies aimed at achieving a functional cure for this population.

Host genetic variants which influence the course of HIV infection and its response to therapy are increasingly being identified. An example includes CYP2B6 genetic polymorphisms associated with differences in efavirenz concentrations (Elens et al., 2010). PHACS has established a repository of amplified genomic DNA in order to address genetic determinants of host response. It was used to show that genetically determined ancestry provides a more robust assessment of continental ancestry than self-reported race/ethnicity in children with HIV or PHEU (Spector et al., 2016). Co-infections such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV) may also impact the pathogenesis of HIV disease (Leruez-Ville et al., 2012; Lichtner et al., 2012).

Adolescents and young adults with PHIV now aging into adulthood were born in the mono- and dual-ARV era and may have received many of their childhood vaccines prior to cART initiation. It has been shown that they lack protective immunity to vaccine-preventable diseases such as measles, mumps, rubella and varicella in young adulthood (Pensieroso et al., 2009; Purswani et al., 2016; Siberry et al., 2012; Sutcliffe & Moss, 2010). Response to vaccines administered in later childhood may also differ among YPHIV. For example, human papillomavirus (HPV) vaccine response was lower for all serotypes in YPHIV compared to PHEU youth (Moscicki et al., 2019a). Protection against abnormal cytology was also diminished in sexually active females with PHIV in this study. Seroprevalence studies of YAPHIV would help assess their risk for preventable and potentially serious infections as well as inform vaccination guidelines for children and adolescents with PHIV world-wide.

Little is known about the oral health and associated oral microbiome of YPHIV, as well as the impact of poor oral health on supporting bone structure, systemic immune activation, neurocognition, and HIV-disease progression. Oral biomarkers of inflammation have been associated with clinical indicators of periodontal inflammation and systemic immune activation among YPHIV which may put them at higher risk for developing significant periodontal disease, associated with tooth loss and HIV progression (Moscicki et al., 2019b). A recent study also suggested that integrase strand transfer inhibitors may be associated with untreated active caries among YPHIV (Shiboski et al., 2018) and another study found the microbiomes of YPHIV seemed to have fewer "health"-associated taxa such as Corynebacterium species suggesting that HIV infection, or its treatment, may contribute to oral dysbiosis (Starr et al., 2018). A longitudinal assessment of oral health is necessary to understand the consequences of these findings as well as longer term effects of ART.

### 1.1.3 Metabolic Complications in YAPHIV

Since the advent of cART, persons living with HIV have longer life expectancies, but chronic conditions such as metabolic and cardiovascular complications, are becoming more prevalent in this population (Fitch & Grinspoon, 2011). ART causes a metabolic syndrome well-characterized in adults as unfavorable body composition (reduction in subcutaneous and increase in visceral fat), insulin resistance and abnormal glucose metabolism, and dyslipidemia (Carr et al., 1998; Grinspoon & Carr, 2005). These components of the metabolic syndrome place individuals at risk for cardiovascular disorders. In fact, in adults with ART-related fat redistribution, several studies have suggested an increase in the risk of myocardial infarction relating to the level of viral control (increased inflammation) or to ART exposures (including protease inhibitors [PIs] and certain nucleoside reverse transcriptase inhibitors [NRTIs]) (Friis-Moller et al., 2003; Mary-Krause et al., 2003; Palella & Phair, 2011). However, there is controversy whether the metabolic syndrome in individuals with HIV is exclusively related to HIV or its treatment; other causes may include underlying family risk factors, or a combination of traditional risk factors, disease burden, or ART exposures. Studies in children show similar although not identical findings,

including abnormal body composition, insulin resistance, and dyslipidemia, with increased risk at older age and with longer duration of ART (Arpadi et al., 2009; Geffner et al., 2011; Jacobson et al., 2011a; Miller et al., 2012; Miller et al., 2008b; Sanchez Torres et al., 2005; Tassiopoulos et al., 2008). The onset of puberty has been proposed as another factor that is associated with these changes (Moscicki et al., 2006).

Early studies in children showed that PI therapy improved weight, weight-for-height, and mid-arm muscle circumference of children with HIV, independent of the concurrent decrease in viral load and improved CD4 cell counts (Miller et al., 2001). The immediate treatment effects were most apparent with an improvement in weight and mid-arm muscle circumference and there was a trend toward increased height and lean body mass. In addition to the positive improvement in growth and lean body mass, ART is also associated with abnormalities in fat distribution in children though some studies report similar lean mass in children with and without HIV (Aldrovandi et al., 2009). Arpadi et al. (2009) observed similar total fat, trunk fat, and percent total fat between children with and without HIV, but lower leg and higher arm fat in children with HIV. Jacobson et al. showed there were decreased limb/trunk fat ratios in children with HIV when compared with children with PHEU (Jacobson et al., 2011a). These findings suggest that both peripheral lipoatrophy, as well as central obesity, occur in these children. Further studies have shown that a majority of children develop fat redistribution within three years of initiating a PI-containing regimen, and that these changes progress over time (Vigano et al., 2003). Other studies have identified metabolic abnormalities induced by other specific classes of drugs. Stavudine use has been associated with lipoatrophy (Arpadi et al., 2001) potentially by altering mitochondrial number and function (Arpadi et al., 2001).

Following exposure to ART, there are increases in total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol in both adults and children. Evaluating metabolic changes in children as they start or change ART can be helpful to determine specific effects of ART because children have fewer confounding psychosocial factors (such as smoking, alcohol, obesity) that can independently impact metabolic outcomes. Children newly exposed to ART experienced a rapid rise in LDL cholesterol over the first 6 months that continued through 12 months (Sztam et al., 2011). Ten percent of a cohort of 449 children in the United Kingdom had LDL-cholesterol levels over the 95$^{th}$ percentile for age and PIs caused greater rises in total cholesterol than non-nucleoside reverse transcriptase inhibitors (NNRTIs). The authors concluded dietary and exercise interventions, and a change in ART, may help address these metabolic abnormalities (Jao et al., 2018; Rhoads et al., 2011). In children with incident hypercholesterolemia, Jacobson et al. (Jacobson et al., 2011b) found that a switch in ARV regimen was associated with cholesterol levels that returned to normal. There was limited power to detect effects of switching to specific ARVs; however, higher viral load at baseline was associated with normalization of cholesterol. According to the Department of Health and Human Services' (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents, switching from one PI to another PI or to bictegravir, dolutegravir, raltegravir, doravirine, or rilpivirine regimens may reduce dyslipidemia (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2019).

Insulin resistance is of particular concern in children and adolescents with HIV, with all adolescents naturally experiencing a relative insulin resistance in puberty. Geffner et al. (2011) found a 15.2% prevalence of insulin resistance in children in AMP that was associated with higher body mass index (BMI), higher nadir CD4 count and amprenavir treatment. In another study by Geffner et al., the prevalence of insulin resistance did not differ between children with PHIV and children with PHEU (Geffner et al., 2018). Some studies report no difference in fasting insulin and glucose levels in children treated with PIs compared to children treated with other drugs (Lainka et al., 2002). However, insulin levels become elevated across both groups after initiating cART. Bitnun et al. (Bitnun et al., 2003) surveyed several pediatric HIV cohorts and found insulin resistance with full metabolic syndrome

increasingly prevalent. These symptoms slowly increased in severity with increasing age. Verkauskiene et al. (Verkauskiene et al., 2006) found significantly higher fasting insulin levels in children with HIV with some aspect of lipodystrophy than those without.

The etiology of insulin resistance is multifactorial and has been linked with both PI and NRTI/nucleotide reverse transcriptase inhibitor (NtRTI) use singly and in combination. Exact mechanisms have not been well-defined. A study by Beregszaszi et al. (Beregszaszi et al., 2003) demonstrated that insulin resistance occurs at the level of the adipose tissue and that children with lipodystrophy have more pronounced insulin resistance than those without, suggesting that metabolic changes occur as a result of the central adiposity. A possible mechanism by which ART causes insulin resistance is by direct inhibition of the transport function of the Glut4 glucose transporter, which is responsible for insulin-stimulated glucose uptake into muscle and fat (Murata et al., 2000). Another potential cause of insulin resistance is mitochondrial dysfunction. Although there are limited data in adults (Grinspoon, 2006; Shikuma et al., 2005), there are striking similarities with rare mitochondrial disorders, such as multiple symmetrical lipomatosis, a condition which is phenotypically very similar to ART-associated lipodystrophy (Brinkman et al., 1999). The mitochondrial deoxyribonucleic acid (DNA) mutations in multiple symmetrical lipomatosis lead to impaired function of cytochrome c oxidase and a subsequent decrease in fat turnover. Among children with PHIV, Takemoto et al. found that mitochondrial respiration markers were lower, on average, in those with insulin resistance compared to those without (Takemoto et al., 2017). Insulin resistance was also associated with lower nadir CD4 count and higher peak viral load (Gojanovich et al., 2020).

Low bone mineral density has been observed in children with PHIV children compared to children with PHEU. Children with PHIV had lower bone mineral density Z-scores than children with PHEU, but these differences were attenuated after height and/or weight adjustment (DiMeglio et al., 2013). In both children with PHIV and children with PHEU, lower BMD was observed in those with low 25-hydroxy-vitamin D (OHD) concentrations (Jacobson et al., 2017). Fracture rates were similar between children with PHIV and children with PHEU 6 years and older, but slightly higher in children with PHIV than children with PHEU among children < 6 years of age (Jacobson et al., 2020).

Most previous studies of growth, puberty, and body composition in children with HIV have either been conducted in small numbers of participants, in mixed cohorts of vertically- and horizontally-acquired disease, or analyzed in a cross-sectional as opposed to a longitudinal manner. In addition, a well-matched comparison cohort is often lacking and a mechanistic component is usually not included. The power of the current protocol is that it allows for the continuation of this longitudinal study of a large, homogeneous population of YAPHIV who have had prior sequential and comprehensive cardiometabolic evaluations both prepubertally and through puberty. The inclusion of YAPHEU as a comparison group helps to differentiate contemporary trends from HIV and ART effects. Through this protocol, the relationships between disease status (e.g., immune deficiency) and ART with body composition and other cardiometabolic risk factors, in the absence of many of the confounders of deleterious lifestyle habits (years of obesity, tobacco use, chronic alcoholism, other drug use, etc.) that plague adult HIV studies, can be determined. The results could lead to alterations of existing viral-specific therapeutic protocols and earlier initiation of adjunctive therapies to treat cardiometabolic risk.

### 1.1.4 Cardiopulmonary Complications

Cardiopulmonary diseases are observed in YPHIV despite treatment with cART (Bonnet et al., 2004; Shearer & Corry, 2012; Shearer et al., 2017). Emerging data indicate that HIV may be an independent risk factor for chronic lung diseases, including obstructive lung diseases, such as asthma, bronchiectasis, and obliterative bronchiolitis as well as restrictive lung diseases (Attia et al., 2018; Attia et al., 2017;

Desai et al., 2018; Ferrand et al., 2012). ART-induced immune reconstitution is related to the development of asthma, particularly with certain human leukocyte antigen (HLA)-A and HLA-C antigens expressed on antigen presenting cells (Foster et al., 2010; Foster et al., 2008). These HLA antigens bind to stimulatory and inhibitory killer-cell immunoglobulin-like receptors on natural killer cells, representing a possible role of natural killer cell control in the development of asthma (Mahapatra et al., 2019). Nonetheless, in a contemporary study, YPHIV demonstrated decreased airflow reversibility, which is atypical of asthma and may suggest an early stage of chronic obstructive pulmonary disease (Shearer et al., 2017). In a substudy, higher CD8 and lower CD4/CD8 were associated with lower lung function among YPHIV, even in the setting of preserved or reconstituted CD4 (Attia et al., 2020). Additionally, in light of the increasing prevalence of nicotine and marijuana vaping by adolescents and young adults, it is essential to explore the potential role of vaping on asthma and other chronic lung diseases in both YAPHIV and YAPHEU (Bradford et al., 2020; Hedman et al., 2018).

The effects of ARVs, HIV and HIV-related inflammation and immune dysfunction on the cardiovascular and pulmonary systems of children and youth with PHIV remain poorly understood. It has been shown that cART is protective of cardiomyopathy (Fisher et al., 2016; Lipshultz et al., 2013). In AMP, YPHIV receiving a regimen containing a PI had significantly better cardiac function than those on other regimens (Williams et al., 2018). However, the highly energy-dependent heart is vulnerable to mitochondrial toxicity (Sherr, 2014), which may be a consequence of HIV infection and/or ARVs. Individual ARV medications were associated with impaired cardiac structure and function (Williams et al., 2018). For instance, zidovudine was associated with higher wall stress, and zidovudine and nevirapine were each associated with larger heart size. Long-term cardiac effects of HIV and ARV exposures could also include dilated cardiomyopathy, as seen with other cardiotoxic exposures, and premature atherosclerosis leading to adverse cardiac remodeling. In addition, compared to children with PHEU, those with PHIV had modestly but significantly elevated serum levels of specific biomarkers of inflammation and myocardial injury, including high-sensitivity cardiac troponin-T (Wilkinson et al., 2018). Higher biomarker levels were associated with lower left ventricular mass and shifts in left ventricular structure on echocardiogram. Importantly, cardiac and pulmonary inflammation may share common pathways. If pulmonary inflammation is associated with concurrent myocardial inflammation, increased pulmonary artery pressure and pulmonary vascular resistance, both left ventricular diastolic dysfunction and increased right ventricular end-diastolic pressures might be expected along with lung function impairment. It is critical to examine pathophysiologic mechanisms that may simultaneously drive disorders of the interconnected cardiac and pulmonary systems, especially given the near-normal lifespans these children and youth may attain.

The risk for premature CVD may be increased among youth and young adults with PHIV aging into adulthood (Miller et al., 2008a). CVD risk scores have become a standard approach for better understanding long-term CVD risk in adults, and some scoring systems have been developed for younger adults or adolescents (Strong et al., 1997; Wilson et al., 1998). A modified score developed from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, which estimates the probability of persons between 15 and 34 developing advanced atherosclerotic lesions in the coronary arteries or abdominal aorta, was previously calculated (McMahan et al., 2005; Strong et al., 1997). The modified PDAY risk score was calculated in a subgroup of the AMP YPHIV when they were 15 to 19 years old, 48% had a coronary artery risk score ≥ 1 and 24% had an abdominal aorta risk score ≥ 1, suggesting increased CVD risk (Patel et al., 2014). The ability of cardiac and biomarker data collected to predict the probability of CVD is also of key interest in understanding the future long-term risk of perinatal HIV infection and exposure. These will be measured on a subset of AMP Up participants through the externally-funded PHACS Cardiac Toxicity Substudy, which has been conducting follow-up echocardiograms and measuring cardiac and inflammatory biomarkers, markers of mitochondrial function, and arterial stiffness in 200 AMP Up young adults with previous PHACS echocardiograms.

In the general population of older adults with and without HIV infection, traditional cardiovascular risk factors have been linked to lower cognitive performance (Fabbiani et al., 2013; McCutchan et al., 2012; Yu et al., 2019). It is unclear whether these observed associations will also be seen at younger ages among those with PHIV. Previous studies have demonstrated persistent inflammation and immune activation among YAPHIV, which may underlie both metabolic and cognitive problems. Earlier identification of links between CVD risk factors and poor neurocognition may provide a window for intervention not available in older adult populations.

CVD may also be linked to deficits in bone mineral metabolism. Low 25-OHD and elevated parathyroid hormone were associated with lower mean left ventricular mass Z-scores and elevated parathyroid hormone was associated with higher mean fractional shortening Z-scores (Margossian et al., 2019). For both YPHIV and YPHEU, 25-OHD, parathyroid hormone, and fibroblast growth factor (FGF)-23 were associated with structural and functional cardiac parameters, supporting links between bone mineral metabolism and cardiac status.

### 1.1.5 Sexually Transmitted Infections in Young Adults with HIV

Rates of chlamydia, gonorrhea, herpes simplex virus (HSV), HPV, and *Trichomonas (T.) vaginalis* all peak in men and women under the age of 25 years. The risks associated with chlamydia, gonorrhea and *T. vaginalis* in persons with HIV are likely similar to those of persons without HIV and include condomless sex, substance use during sex, and having sex with high-risk partners (Setse et al., 2011). One study of pregnant women living with HIV (WLHIV) found that low CD4 count increased risk of chlamydia, syphilis and *T. vaginalis* (Landes et al., 2007). Unfortunately, the consequences associated with these infections may be of greater importance in persons with HIV since increased genital shedding of HIV has been shown to occur with these infections, raising the risk of transmission to other partners (Kalichman et al., 2011). In addition, it remains unknown whether rates of infertility are higher in WLHIV due to these infections (Badell & Lindsay, 2012; Kushnir & Lewis, 2011).

Among the STIs faced by sexually active adolescents and young adults, HPV has the greatest known sequelae in persons with HIV. HPV is a well-established cause of significant morbidity and is necessary for the development of invasive genital cancers including cervical, vulvar, vaginal, penile, and anal cancers, as well as oral cancer. Although HPV infections peak in young adults (Moscicki et al., 2001), the majority of infections in non-immunocompromised persons are transient with clearance occurring within two years in the majority of individuals (Moscicki et al., 1998; Moscicki et al., 2004b). Persistence in these few individuals is what places them at risk for cancer development (Kjaer et al., 2010). Unfortunately, HIV and other immunocompromised situations (i.e., organ transplants) are associated with not only increased persistence (Moscicki et al., 2004a) but also a 2-200 fold higher risk of developing one of these cancers (Denny et al., 2012). This increased risk remains true even with the advent of cART (Grabar et al., 2019; Robbins et al., 2015; Shiels et al., 2018). Smoking cigarettes, prolonged hormonal contraceptive use (> 6 years), and history of *Chlamydia (C.) trachomatis* have been implicated as important co-factors in cervical cancer development (Roura et al., 2014; Roura et al., 2016; Zhu et al., 2016). Nicotine and its metabolites can be detected directly from cervical mucus. Hence smoking may have direct carcinogenic effects or may alter immunologic responses in cervical mucus. Estrogen and progesterone have also been associated with abnormal cell proliferation in *in vitro* studies (Modiano et al., 1991; Ruutu et al., 2006). The role for chlamydia is less obvious but may be associated with high-risk behavior. Its biologic effect may be due to inflammatory changes that create a vulnerable environment for cancer development. The association between HIV and HPV persistence is not unexpected since HPV persistence has been linked to disordered cell mediated immune responses (Kadish et al., 2002; Scott et al., 2001). A study of adolescents and young women from the Reaching for Excellence in Adolescent

Care and Health (REACH) cohort showed that persistence of cervical HPV and the development of high-grade squamous intraepithelial lesions (HSIL) were extremely common in WLHIV (Moscicki et al., 2004a). Approximately 45% of the adolescent females with HIV demonstrated HPV persistence, particularly with HPV type 16, the most common type seen in invasive cancers. This persistence paralleled progression of HPV infection to significant precancerous lesions. In this same cohort, the incidence of HSIL was higher for those with HIV than those without HIV (21.5% vs. 4.8% incidence by end of follow-up). This finding was even more dramatic for adolescents with HIV with baseline or early low-grade squamous intraepithelial lesions (LSIL) where 31% progressed to HSIL. In the final multivariate analysis, hormonal contraceptive use, high interleukin-12 (IL-12) concentrations of the cervical mucus, and persistent LSIL prior to HSIL were significantly associated with the development of HSIL. These factors were found to be independent of CD4 cell counts. The high IL-12 concentrations in cervical mucus associated with HSIL may be suggestive of a local immune dysregulation to HPV caused in part by HIV infection. The role of hormonal contraception deserves further investigation given the proposed relationship between hormonal contraceptive use and cervical cancer and the need for adequate but safe birth control in WLHIV.

The data regarding ART and HPV control are complicated. It appears that control of HIV replication and improved CD4 cell counts resulting from ART may lower the risk of developing HSIL. A recent study demonstrated high rates of high-risk types of HPV infection (over 40%) despite good viral control (Thorsteinsson et al., 2019). Once HSIL develops, ART does not appear to strongly influence its natural history (Ahdieh-Grant et al., 2004; Schuman et al., 2003). A recent study by Minkoff et al. (Minkoff et al., 2010) found a reduction in prevalence and incidence of high-risk HPV infection and a more rapid clearance of squamous intraepithelial lesions than during the pre-cART era. Unfortunately, little is known about the natural history of HPV in adolescents and YAPHIV, limiting our ability to adequately care for this group.

With the advent of next generation sequencing for microbiome analysis, there has been much interest in the vaginal microbiome and its role in HPV progression. Microbiome dysbiosis (often defined clinically as bacterial vaginosis) is linked to HPV acquisition, HSIL and cervical cancer (Brusselaers et al., 2019; Kyrgiou et al., 2017; Norenhag et al., 2020; Usyk et al., 2020). Mechanisms thought to be associated with HPV progression include chronic inflammation associated with this dysbiosis. Women living with HIV appear to have altered vaginal microbiomes placing them at increased risk for progression to cervical cancer (Siqueira et al., 2019).

The REACH study included adolescents with situationally acquired HIV who had been living with HIV for a relatively short period of time. Most were not receiving ART. One of the only studies of reproductive health in adolescents with PHIV showed that the greatest morbidity was abnormal cytology (Brogly et al., 2007). Whether these abnormalities followed or preceded the onset of sexual intercourse is not known. The current guidelines recommend annual cervical cancer screening in young adults with HIV and for screening to begin within one year after onset of sexual activity (Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents, 2019). A recent study showed that less than half of sexually active adolescents with HIV underwent cervical cancer screening (Setse et al., 2011). This study allows for HPV to be studied in the context of long-term perinatal HIV infection and ART.

HPV has been recognized as an important pathogen in oropharyngeal cancers (Mahal et al., 2019). As with other HPV-associated cancers, oropharyngeal cancers are also higher in persons with HIV than in persons without HIV (Wilkin, 2018). Data suggest that oral HPV infections are more common and more likely to persist in persons with HIV explaining the increased risk (Beachler et al., 2012). Oral sex behaviors are also associated with oral cancer risks (Shah et al., 2017).

### 1.1.6 Reproductive Health

Pregnancy and Contraception

As young people with PHIV reach adulthood, sexual activity and pregnancy will become more common. Desire for pregnancy among WLHIV in the U.S., especially young women, varies, with some reporting a desire to have children after learning of their HIV infection (Cohn et al., 2018; Craft et al., 2007; Haddad et al., 2016; Jones et al., 2016). Decisions about keeping or terminating a pregnancy, whether initially wanted or unwanted, are particularly complex for WLHIV. Job security, goals, family support, relationship history, desire to have a child with a particular partner, and the partner's desire for pregnancy will all affect an individual's decisions related to pregnancy. Additionally, the individual's exposure to abuse, their health status, levels of substance use, and their cognition and access to reproductive health services including abortion will all affect the decision whether to initiate a pregnancy or keep an unplanned pregnancy. In addition, the current number of children, or outcomes of a past pregnancy may play a critical role. Most young women in the U.S. seek birth control since pregnancy is often deferred into mid to late 20's (Jones et al., 2012). Use of and adherence to effective contraceptive methods affects efficacy since long-acting reversible contraceptives such as intrauterine devices and implants have been shown to be superior to daily methods (i.e., oral contraceptives) (Winner et al., 2012). Adherence plays a significant role since the long-acting reversible contraceptives require less attention to adherence, although these methods require ready access to healthcare providers trained in insertion. On the other hand, choices to obtain these methods are complex since many young women do not adopt long-acting methods because they perceive them as invasive (i.e., intrauterine devices) or irreversible. There is virtually no to little information regarding contraceptive choices in YAPHIV and the factors that lead to these choices, as well as decisions, in the case of unplanned pregnancies, about whether to terminate a pregnancy or carry it to term. Little is also known of the reproductive health choices and desires for having children in young men with PHIV.

In the few studies of pregnancy rates and outcomes in young women living with PHIV (WLPHIV) in the U.S. (Agwu et al., 2011; Brogly et al., 2007; Koenig et al., 2007; Levine et al., 2006; Patel et al., 2020; Williams et al., 2009), many young women reported that their pregnancy was unplanned (Koenig et al., 2007; Patel et al., 2020) and prevalence of STIs was common (Brogly et al., 2007; Williams et al., 2009) . Both factors raise the question of the risk of HIV transmission to sexual partners and children.

Issues of ARV treatment compliance in anticipation of a wanted pregnancy, during pregnancy, and postpartum are critical. In addition, adherence issues may affect decisions about carrying a pregnancy to term, as well as contraceptive choices, the acceptability of various contraceptive methods, and may also be associated with complications of pregnancies. A recent study found that WLPHIV had a lower CD4 count and higher viral load than women with situationally acquired HIV (Byrne et al., 2017). Prospective studies that characterize these factors are essential (Badell & Lindsay, 2012). The transition from pediatric to adolescent and adult health care is one element of future research that has to be considered, including how clinical and mental health, as well as treatment adherence and discussions of sexual behavior, are incorporated into these different health care settings.

For young reproductive aged women, family planning is a major concern. Currently, pregnancy rates among WLHIV are comparable to that of the general population. There is evidence for earlier ovarian insufficiency and menopause among WLHIV which could lead to infertility. WLHIV who seek to delay pregnancy may encounter barriers to contraceptive use with resulting unintended pregnancy. While studies have demonstrated lower rates of effective contraception use among WLHIV, the availability of highly effective long-acting reversible contraceptive options may reverse this trend. WLHIV may experience contraception coercion, stigmatization from providers in cases of partner nondisclosure or

condom non-use, and barriers to care that reduce their confidence in the healthcare system. Furthermore, the benefits of viral suppression and the "Undetectable equals Untransmittable (U = U)" initiative are underappreciated by women. It is therefore critical to understand sexual risk behaviors among young WLHIV given the expanding epidemic of STIs in the U.S.

Menstrual Irregularities and Fertility

Amenorrhea and oligomenorrhea are well known factors associated with infertility. HIV infection also may introduce factors associated with infertility either directly (i.e., factors associated with the induction of menstrual irregularities) or indirectly (i.e., behaviorally through substance use, depression, etc.). The effect of exposure to HIV and ART during embryonic gonadal development or pubertal development remains unknown, but may likely affect fertility potential because of the potential mitochondrial damage or other enzymatic influences. In addition, HIV is associated with wasting syndromes similar to anorexia nervosa where menstrual irregularities are common.

Several studies have shown that WLHIV are more likely to have amenorrheic episodes (Cejtin et al., 2006; Chirgwin et al., 1996; King et al., 2019; Valiaveettil et al., 2019). The mechanisms remain elusive. Although a few studies have shown no association with amenorrhea after adjusting for age, BMI and substance use (Ellerbrock et al., 1996; Harlow et al., 2000), in more recent studies, WLHIV were three times more likely to have prolonged amenorrhea than women who are HIV uninfected without hormonal evidence of ovarian failure (Cejtin et al., 2006).

Menstrual irregularities are sensitive but not specific indicators of infertility issues. A report by Massad et al. (Massad et al., 2004) found pregnancy rates of 7.4 per 100 person-years in WLHIV compared to age comparative rates of 15.2 in HIV-uninfected women ($p < 0.001$). Among WLHIV, 36% ended in live birth, 2% stillbirth, 36% induced abortion, 24% spontaneous abortion, and 5% ectopic pregnancies. These outcomes were no different than for HIV-uninfected women. Overall, WLHIV were less likely to become pregnant but outcomes of pregnancy did not appear different. Since these studies were in women who acquired HIV through sexual transmission, infertility may also be associated with other concomitant STIs known to be associated with tubal blockage and infertility. A study from South Africa found similar higher rates of infertility in WLHIV than women who are uninfected (Marston et al., 2017).

The study by Massad and colleagues (Massad et al., 2004) also found that spontaneous abortions were less likely to occur during the cART era compared to before cART. However, data from the United Kingdom and Ireland showed no change in spontaneous abortion rates from 1990 through 2006 despite the initiation of cART. The follow-up of pregnancy rates and outcomes in WLPHIV is essential.

Zidovudine and other NTRIs can damage mitochondria *in vivo* and *in vitro*. This can result in injury to tissues with high energy requirements such as the heart, skeletal muscle, liver, kidney, and brain. In a study of zidovudine-treated pregnant primates, zidovudine was found to be incorporated into fetal mitochondrial DNA from skeletal muscle, liver, kidney, and placenta (Gerschenson et al., 2004). Mitochondrial depletion has been noted in the sperm and oocytes of individuals exposed to NRTIs (Lopez et al., 2008; Pavili et al., 2010). Oocytes with low levels of mitochondrial DNA are associated with infertility (Kushnir & Lewis, 2011). Thus, infertility is a potential outcome of children exposed to ARVs *in utero*.

Infertility in women may also be associated with endocrinopathies. cART is associated with hyperandrogenemia, lipodystrophy and insulin resistance, a phenotype similar to polycystic ovarian syndrome which is known to be associated with infertility. Comorbidities associated with HIV can also influence fertility. CMV, salmonella, toxoplasmosis, mycoplasma, and other pathogens have been

associated with orchitis and epididymitis in men living with HIV. Tuberculosis, also more common in persons living with HIV, is associated with uterine disease and infertility.

Fertility data in WLPHIV are sparse. However, there is evidence to suggest that preterm birth is higher than expected with rates of preterm delivery reported up to 44% (Thorne et al., 2007). A study in New York found higher risk of small for gestational age outcomes in children of WLPHIV vs. children of women acquiring HIV later in life (Jao et al., 2012); however, no differences in preterm birth or low birthweight were observed among infants of WLPHIV vs. women acquiring HIV later in life (Jao et al., 2017). There are some data to suggest that preterm delivery is increased with PI regimens as well as substance use and advanced HIV disease as reviewed by Badell and Lindsay (Badell & Lindsay, 2012). Preterm delivery is associated with significant neonatal morbidity and mortality. A recent retrospective study of case series in the United Kingdom found that fertility rates in WLPHIV were similar to the general population (Teh et al., 2019).

### 1.1.7 Neurocognitive Functioning and Mental Health

Neurocognitive Functioning

Neurocognitive impairments have been well described in infants and children with PHIV (Crowell et al., 2014), as well as in adolescents and adults with situationally acquired HIV infection (Nichols et al., 2013). However, reports describing long-term neurocognitive outcomes in adolescents and young adults with PHIV, a growing population worldwide, are only now emerging. These adolescents and young adults with PHIV have survived early exposure to HIV and delayed or suboptimal HIV therapy during early critical periods of neurodevelopment. In addition, they have experienced nearly three decades of continued exposure to HIV, potentially toxic ARVs, and variable penetrance of the blood-brain barrier by ART which may allow a reservoir of latent HIV to persist in the brain, potentially increasing risk for cognitive deficits, even with peripheral viral suppression (Hermetet-Lindsay et al., 2017; Spudich, 2016). The risks associated with long-term HIV infection are often amplified by concomitant exposure to unique psychosocial and environmental stressors often present among families affected by HIV. Understanding the current and emerging neurocognitive consequences of these early and long-term exposures in YAPHIV is critical in providing adequate support for educational, vocational, health behavior, mental health and other QoL outcomes.

Although existing literature varies in the methodology, characteristics of participants, and definition of variables, there is agreement that overall, adolescents with PHIV are at greater risk for poor neurocognitive outcomes compared to normative populations (Blanchette et al., 2002; Paramesparan et al., 2010; Puthanakit et al., 2013; Ruel et al., 2012; Smith et al., 2012; Wood et al., 2009). However, comparisons of mean performance typically showed small differences (Blanchette et al., 2002; Hoare et al., 2012; Smith et al., 2012), and some smaller studies found no significant differences compared to YPHEU or the normative sample (Bagenda et al., 2006; Koekkoek et al., 2008). Differences between studies may be at least partly related to variability in controlling disease severity within groups with PHIV. Early and severe disease progression in YPHIV, despite reconstituted immune and virologic status, has consistently been found to predict later poor neurocognitive outcome in adolescents (Shanbhag et al., 2005; Smith et al., 2012; Wood et al., 2009). Despite recovery from previous episodes of high plasma viral load, low CD4 cell counts, and an AIDS defining illness, particularly early encephalopathy, there is persistent neurocognitive impairment even during adolescence (Garvie et al., 2014; Smith et al., 2012; Wood et al., 2009), suggesting that the central nervous system may not make a comparable recovery. Atypical brain network integrity has been observed among those who remain immunologically stable during childhood as well as those with more significant HIV-related disease, including encephalopathy (Herting et al., 2015; Uban et al., 2015). For example, a neuroimaging study in YPHIV revealed

significant associations between abnormal deformities of caudate and thalamus shape with higher peak viral load, elevated past HIV disease severity, and worse cognitive functioning (Lewis-de Los Angeles et al., 2016; Lewis-de Los Angeles et al., 2017).

U.S. and international studies investigating more specific and subtle areas of adolescent neurocognitive impairment suggest HIV-related vulnerability in several domains, including executive functioning, processing speed, prospective memory, attention and visual-spatial processing (Garvie et al., 2017; Harris et al., 2018; Kerr et al., 2019; Koekkoek et al., 2008; Malee et al., 2017; Nachman et al., 2012; Nichols et al., 2016; Patel et al., 2019b; Ruel et al., 2012; Smith et al., 2012). Visual-spatial memory and integration was significantly impaired in several groups of younger adolescents compared to PHEU and normative groups (Hoare et al., 2012; Koekkoek et al., 2008; Puthanakit et al., 2013). This pattern differs somewhat from that seen in adults, who show deficits in executive functions, episodic memory, attention and psychomotor skills, with relative sparing of basic language and visuoconstruction functions (Dawes et al., 2008; Heaton et al., 2010; Reger et al., 2002; Wood et al., 2009). While a recent investigation revealed generally low-average to average functioning across multiple memory and executive functioning tasks, increased risk was observed among youth with histories of severe HIV disease; they achieved lower, clinically relevant scores on multiple memory and executive functioning tasks during two years of follow-up, with higher rates of impairment than observed in the general population (Malee et al., 2017). The well-described impact of HIV-related neurocognitive deficits, particularly in executive functioning and working memory, on functional outcomes such as adherence, risk behaviors, educational achievement, employment, driving, and activities of daily living in adolescents and adults (Garvie et al., 2017; Gorman et al., 2009; Heaton et al., 2004; Sirois et al., 2016) raises concerns that similar or greater risks will be observed among YPHIV as they enter adulthood.

Cognitive functioning significantly contributes to a young adult's ability to complete educational goals, attain and maintain employment, develop meaningful relationships, make sound health behavior decisions including adherence to medications (Garvie et al., 2017), and navigate expectations of daily functioning. As PHACS continues to follow adolescents into adulthood, it is critical to understand the long-term neurocognitive trajectory of young adults with lifelong exposure to HIV, ARVs, and concomitant family and psychosocial risk and protective factors to better understand factors associated with emerging or ongoing neurocognitive risk, stability, or recovery among YAPHIV (Robbins et al., 2020).

Mental Health

Mental health problems among children and adolescents with PHIV, including attention deficit hyperactivity disorder (ADHD), anxiety, and depression, were identified prior to and during the cART era (Brouwers et al., 1995; Brown et al., 2000; Mellins et al., 2009a; Mellins et al., 2003; Papola et al., 1994; Scharko, 2006). Prevalence and types of problems varied due to assessment and sampling methodologies, but rates of mental health problems in both YPHIV and YPHEU were higher than expected (Bauman, 2002; Mellins et al., 2009a; Mellins & Malee, 2013; Mellins et al., 2003).

There is evidence that long-term survivors with PHIV are often at risk for new or persisting mental health problems given genetic, biomedical, familial, and environmental risk factors (Donenberg & Pao, 2005; Gadow et al., 2012; Havens & Mellins, 2008; Mellins et al., 2012; Nachman et al., 2012). Recent longitudinal investigations of YPHIV documented high rates of Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV diagnosed psychiatric disorders among YPHIV as well as among YPHEU, including anxiety, depression and behavioral disorders, such as ADHD (Chernoff et al., 2009; Gadow et al., 2012; Gadow et al., 2010; Kapetanovic et al., 2011; Mellins et al., 2009a; Mellins et al., 2012; Smith et al., 2019; Wood et al., 2009). Rates of disorder over time are often high, with large numbers of youth in both groups with PHIV and PHEU meeting criteria for a disorder at either baseline or follow-up. Multiple

studies of emotional and behavioral problems, as measured by symptom checklists, also identify higher than average rates of mental health problems among YPHIV and YPHEU (Malee et al., 2011a; Malee et al., 2011b; Malee et al., 2011c; Nozyce et al., 2006; Smith et al., 2019) and high rates of specific disorders, such as depression, among YPHIV (Elkington et al., 2011).

The etiology of mental health problems among YPHIV is multifactorial. Exposure to maternal immune dysregulation and ARV medications, infections (e.g., sexually transmitted diseases; CMV) and/or teratogens (e.g., alcohol and illicit drugs) was likely for some youth during the prenatal period and may have neurobehavioral effects (Van den Bergh et al., 2005). Throughout development, neurotoxicity associated with HIV infection and aberrant immune activation remains possible for youth with HIV, secondary to suboptimal ARV treatment or intermittent nonadherence (Kapetanovic et al., 2014; Kapetanovic et al., 2010; Mekmullica et al., 2009). Importantly, HIV may affect subcortical white matter and frontostriatal systems (Sharer, 2005) involved in the regulation of emotion and behavior, further placing youth at risk for mental health problems during late adolescence and young adulthood. Significant and subtle neurocognitive deficits are observed in some YPHIV (Smith et al., 2012; Wood et al., 2009), likely affecting their school achievement, relationships, and functional autonomy (Paramesparan et al., 2010); and increasing the likelihood of mental health problems, as observed among adults with advanced HIV disease. Of interest, a recent analysis using machine learning methodology identified novel risk factors for suboptimal neurocognitive outcomes in a cohort of YPHIV, including numerous multi-level interactions between mental health and biological indices (Paul et al., 2020), highlighting the critical relationship between mental health and neurocognition in those affected by HIV.

Older adolescents and young adults coping with HIV since birth share histories of early childhood stressful events associated with HIV, including difficult and sometimes disruptive medical treatment, hospitalizations, and exposure to pain (Gortmaker et al., 1990; Hysing et al., 2007). They also face a host of unique challenges related to the psychosocial impact of HIV, a highly stigmatized and transmittable illness. YPHIV often live in impoverished, limited-resource communities affected by violence, substance abuse, and neighborhood disintegration (Costello et al., 2003; Donenberg & Pao, 2005; Havens & Mellins, 2008; Kang et al., 2011; Steele et al., 2007) all of which have been associated with increased rates of mental health problems during childhood and adolescence (Achenbach et al., 1991; Bradley & Corwyn, 2002; McCarty et al., 2003), including YPHIV (Kang et al., 2011; Mutumba et al., 2016). Furthermore, many YPHIV have grown up in single parent households or have experienced multiple caregiving transitions due to parental illness or death (Havens & Mellins, 2008; Rotheram-Borus et al., 2002). These and other adverse experiences during early childhood have been associated with poor mental and physical health in adulthood (Merrick et al., 2019).

Parental psychiatric and substance abuse disorders are additional risk factors for mental health problems in many YPHIV and YAPHIV. Psychiatric disorders, such as depression, disproportionately affect women and are not uncommon among WLHIV (Kapetanovic et al., 2011; Morrison et al., 2002; Rotheram-Borus, 1999), and particularly mothers living with HIV (Malee et al., 2013; Mellins et al., 2008). As a result, youth affected by PHIV are at increased genetic and environmental risk for negative psychological outcomes, including emotional and behavioral problems, poor school and social adaptation, elevated rates of internalizing behaviors, and specific risk for depression (Beardslee et al., 1998; Cummings & Davies, 1994; Cummings et al., 2005; Leve et al., 2005; Pilowsky et al., 2006; Reef et al., 2009), which may become more prevalent or severe during late adolescence and young adulthood.

Other aspects of the caregiving environment, such as family processes, are of potential importance in the psychological adjustment of youth and young adults with PHIV and PHEU as they age. Caregiver-youth relationships, caregiver support, caregiver limit-setting, and parent-child communication and involvement have been associated with youth mental health (Elkington et al., 2011; Hermetet-Lindsay et al., 2017;

Malee et al., 2011a; Murphy et al., 2009; Nichols et al., 2012) and may be problematic among families affected by HIV, even as youth age into young adulthood. Increasing evidence suggests that social and contextual influences, including exposure to stressful life events and under-resourced neighborhoods, are critical predictors of mental health (Kang et al., 2011) and may be experienced at higher rates as youth seek more autonomy and independence from caregivers and family. Increased peer, parent, and teacher social support, on the other hand, have been associated to varying degrees with less anxiety and depression, fewer withdrawal symptoms, and fewer behavioral problems among those with HIV infection (Elliott-DeSorbo et al., 2009) and may be protective.

Despite substantial evidence of mental health risk among those affected by HIV, evidence of resilience in emotional-behavioral functioning has also been observed among some YHIV. In a study of children in Thailand and Cambodia, emotional and behavioral functioning remained within the normal range throughout longitudinal follow-up, with limited differences observed among those YPHIV, YPHEU, and HIV-unexposed and -uninfected peers (Malee et al., 2019). Even among YAPHIV, with significant histories of adversity and ongoing challenges of managing a chronic illness independently, two-thirds had a low prevalence of psychiatric disorders from adolescence to young adulthood. Yet for those with consistent or escalating trajectories of psychiatric disorders, increased likelihood of viremia was identified, highlighting the importance of ongoing surveillance of mental health and appropriate treatment for those in need (Nguyen et al., 2020).

In summary, youth and young adults with HIV are at risk for mental health problems and behavioral health problems (Mellins et al., 2009b; Mellins & Malee, 2013; Mellins et al., 2011; Smith & Wilkins, 2015; Tassiopoulos et al., 2013) during transitions through adolescence and young adulthood, given their exposure to multiple biomedical, family and psychosocial factors known to influence mental health. Given that mental health functioning is among the most significant predictors of both health and behavioral outcomes, it is critical to understand its prevalence and correlates as YPHIV emerge into young adulthood in increasing numbers.

### 1.1.8 Health Care Behaviors and Transition to Adult Health Care

As YPHIV enter adulthood, maintaining adherence to ARV medications and transitioning from pediatric to adult HIV medical care systems are substantial challenges (Dowshen & D'Angelo, 2011; Hazra et al., 2010; MacDonell et al., 2013). Optimal adherence to ART is essential to achieving viral suppression and to survival, as well as to preventing the emergence and transmission of resistant strains of HIV infection (Bangsberg et al., 2001; Paterson et al., 2000; Van Dyke et al., 2002). In addition, adherence to ARVs is a critical component of preventing mother to child transmission as well as sexual transmission of HIV. Adherence is more frequently suboptimal at older ages among young adults with HIV (Mellins et al., 2004; Williams et al., 2006). By middle adolescence, many youth are expected to assume responsibility for taking their ARV medications. In addition, as they transition out of pediatric HIV care, they may face barriers to accessing and negotiating new and complex systems of adult care to manage their HIV disease, which could in turn lead to gaps in ARV medication access that undermine their health and ability to adhere to ARV medications (Andiman, 2011). As YPHIV enter young adulthood their ability to access providers of reproductive health care services and contraceptives that can meet the unique needs of young women and men with PHIV will also be important. In order to develop effective interventions to help YAPHIV navigate this transition it is critical to understand the extent and determinants of adherence to ART and successful entry and retention in care for their HIV disease as well as for reproductive health, diagnosis and treatment of sexually transmitted diseases and other psychosocial conditions.

The determinants of medication adherence during the transition to young adulthood in young women and men with PHIV are not well understood. In one recent longitudinal study of adolescents and young adults

in AMP, the factors associated with suboptimal adherence and unsuppressed viral load varied at different stages of development. For example, in middle adolescence, multiple social and structural factors, including indirect exposure to violence, stigma, and stressful life events, were associated with nonadherence. Perceived side effects of ARVs were associated with suboptimal adherence in young adulthood and at most ages (Kacanek et al., 2019). HIV disease severity and regimen-related factors, including side effects, complexity, and duration on treatment are associated with suboptimal adherence in studies of children and youth with behavioral infection and those with PHIV. Because YAPHIV have long histories of ARV use, taking ARVs since childhood, they may experience treatment fatigue and lapses in adherence during their lifetimes, which contribute to high rates of ARV resistance in this population. As a result, many YAPHIV must use "salvage" ARV regimens that are more complex and more difficult to tolerate, which in turn can pose challenges to maintaining adherence (Hazra et al., 2010). On the other hand, some studies have found that young adults with fewer disease symptoms or those who feel well were more likely to be non-adherent. Disclosure issues, including fear of the consequences of revealing their HIV status to peers, sexual partners and co-workers may lead to nonadherence (Rao et al., 2007). Sexual and other social relationships may also affect ART adherence during this transitional period. For example, entering a new sexual relationship may lead to improved adherence if the woman or man with PHIV is aware of and motivated to prevent transmission to an uninfected partner, or if the couple (or individual) hopes to have children in the near future. Conversely, desires to hide HIV disease from a new sexual partner because of fears of rejection, stigma, or violence may lead to poor adherence. Substance use, a diagnosis of depression or anxiety (Murphy et al., 2005; Murphy et al., 2001; Williams et al., 2006), conduct disorder (Walkup et al., 2009) and the occurrence of recent stressful life events (Malee et al., 2009; Williams et al., 2006) have been associated with nonadherence in studies of children and adolescents; these conditions are likely to increase in young adulthood. Although experiences of trauma have been associated with nonadherence in studies of adults with HIV, and exposure to violence has been associated with nonadherence and unsuppressed viral load in adolescents and young adults with PHIV (Cluver et al., 2018; Kacanek et al., 2019; Kidman & Violari, 2018) the role of violence and trauma in adults with PHIV is not fully understood.

The growing population of adolescents with HIV worldwide who are transitioning to adult health care is of special concern (Fair et al., 2010; Gilliam et al., 2011; Straub & Tanner, 2018; Wiener et al., 2011). The transition can be difficult due to the increased responsibility placed on the young adults for their own self-care, at an age where adherence to both ARV medications and medical appointments is critical for their continued HIV viral suppression and overall health (Fair et al., 2010). In a recent AMP Up analysis, the ability to self-manage health care and high perceived emotional social support were both associated with better retention in care after transition (Tassiopoulos et al., 2020). There has been a call for coordinated communication between pediatric and adult care clinics and clinicians to enhance successful transition, and a policy statement has recently been published by the American Academy of Pediatrics to provide guidance to clinics in developing a formal transition plan (American Academy of Pediatrics Committee On Pediatric AIDS, 2013). Despite these recommendations, programs vary widely across the U.S. and there is relatively little data regarding effectiveness of transition programs, particularly in YPHIV (Andiman, 2011; Dowshen & D'Angelo, 2011; Peter et al., 2009; Vijayan et al., 2009; Wiener et al., 2011). Youth transitioning to adult clinics have reported the environment to be "cold and unfamiliar," and felt more sensitive towards the visibility and potential stigma of HIV (Remien & Mellins, 2007; Vaudre et al., 2012; Wiener et al., 2011). In a qualitative study of youth who transitioned to adult care, immune function reflected by CD4 count tended to decline and one-third were unable to identify psychological support services. Some of the major barriers towards successful transition included a lack of continuity of care, lack of assistance with logistical aspects such as insurance and transportation to appointments, difficulties in identifying an adult provider, and coordinated communication with the primary caregiver (Wiener et al., 2011).

Other important social and structural factors that may lead to suboptimal adherence to ARVs and care during this transition include poverty, inadequate insurance coverage, employment instability, housing instability, lack of access to supportive social networks (Andiman, 2011; Dowshen & D'Angelo, 2011), the type and organization of services in the adult clinic (family services, adult-only, etc.), and mistrust of the health care system or experiences of discrimination in health care settings (Bogart et al., 2021; Cunningham et al., 2007). Adverse childhood experiences are also associated with poor mental and physical health in adulthood (Merrick et al., 2019) and may impact medication adherence and the ability to successfully transition to the responsibilities of adult clinical care. The U.S. DHHS' recommendations for promoting a successful transition from HIV pediatric/adolescent to adult care highlight provider-related factors, including strong communication between adolescent and adult clinics, counseling YAPHIV regarding management of health insurance, entitlements, appropriate use of a primary care provider and appointments; addressing stigma and disclosure issues; and incorporating a family planning component into health care (Dowshen & D'Angelo, 2011).

Although caregiver characteristics are important determinants of adherence in children and adolescents, little is known about the role of caregiver characteristics in young adults' adherence to ARVs; the role of the caregiver in the administration of ARV medications will attenuate for most young adults, however for other young adults who are living with their families, or who have severe disease or who face cognitive or psychological disorders accompanying HIV disease, caregiver factors may continue to play an important role. Family factors found to be associated with adherence include having an adult other than the biological parent as the primary caregiver (Katko et al., 2001; Williams et al., 2006), parent-child communication (Mellins et al., 2004), and using a buddy system to remember to take ART medications (Williams et al., 2006). For children and adolescents, caregiver-related factors are found to be associated with nonadherence including caregiver psychiatric distress or general stress (Marhefka et al., 2006; Mellins et al., 2004), caregiver drug and alcohol use (Naar-King et al., 2006), and lower caregiver education level (Williams et al., 2006).

Understanding the individual, disease-related, and social factors contributing to adherence and health care behaviors is critical to supporting YAPHIV as they transition into adulthood. Continuing to follow youth into adulthood provides the opportunity to evaluate the impact of these factors on adherence and health care behaviors in order to appropriately intervene during this critical period.

### 1.1.9 Risk Behaviors (Sexual Behaviors, Substance Use, Disclosure to Sexual Partners)

Adolescents and young adults with PHIV face the same decisions and challenges as those faced by youth who are not living with HIV during the transition into adulthood; however, these decisions may be further complicated by living with HIV long-term, psychological distress, tapered family networks resulting from HIV-related loss, and poverty. Decisions about the initiation of sexual activity, negotiation of condom use, communication about and disclosure of HIV status to sexual partners, as well as whether, when, and with whom to have children are impacted by these realities. In addition, substance use affects job stability and establishment of meaningful relationships.

Studies of adolescents with PHIV show high prevalence of sexual behaviors and substance use which are similar to their uninfected peers. Over half of 16-18 year olds in AMP have reported vaginal or anal sex; as the cohort enters young adulthood this prevalence will likely increase. Inconsistent condom use was common among sexually active youth in AMP as it is among other cohorts of YPHIV and uninfected youth in the U.S. Unfortunately, many AMP young adults reported that they did not disclose their HIV status to their sexual partners (Koenig et al., 2007; Tassiopoulos et al., 2013).

Although individuals on ART who maintain an undetectable viral load cannot transmit HIV to sexual partners (Eisinger et al., 2019) and despite a global campaign to disseminate this information, knowledge of this "U = U" campaign and of the concept of treatment as prevention (TasP) remains low or inconsistent among some groups living with or affected by HIV, including men who have sex with men (MSM) (Siegel & Meunier, 2019) as well as providers who treat people living with HIV (Lippman et al., 2020). Knowledge of the protective role of pre-exposure prophylaxis (PrEP) is higher than that of TasP among young MSM, although it is lower among those without HIV than those with HIV. Knowledge and accurate understanding of TasP is higher among MSM without HIV who themselves use PrEP (Meanley et al., 2019; Rendina et al., 2020). There has been no research to date on uptake of "U = U" messaging and knowledge of TasP among YAPHIV, or about knowledge of PrEP among YAPHEU. AMP Up provides the opportunity to assess this knowledge, to measure use of PrEP among YAPHEU as well as by the partners of YAPHIV.

The prevalence of substance use in AMP, particularly alcohol and marijuana, is also high (Alperen et al., 2014; Nichols et al., 2021), and it is expected that the prevalence of both licit and illicit substance use will increase as this cohort enters young adulthood and as legalization of marijuana use increases across the U.S.

The young adults in AMP Up provides an opportunity to observe how young adults who grew up with HIV infection navigate the transition to young adulthood. Their involvement in sexual and substance use risk behaviors will influence other important outcomes including acquisition of STIs, pregnancy, disease progression, job stability, and relationships as well as potential transmission of HIV to sexual partners and children. Understanding the factors that influence these behaviors will therefore help in the development of interventions that can help them make or sustain healthier decisions.

### 1.1.10 Transition to Adult Functioning and QoL

Success in transitioning to adult health care may also be related to other aspects of successful adult functioning. For example, completion of high school and entry into further educational programs, vocational training, or employment, as well as living independently are measures of adult functioning which may be influenced by social support and interdisciplinary health care. Such models of coordinated medical and psychosocial support from a single provider are more common among pediatric settings than in adult care (Battles & Wiener, 2002). Adherence to ARV medications is a clear challenge among youth transitioning to adult care, and loss of health insurance may be a major contributor towards inability to maintain consistent adherence (Dowshen & D'Angelo, 2011). In addition, while sexual behavior is of critical importance given HIV transmission risk, potentially with drug-resistant virus (Tassiopoulos et al., 2013), formation of close personal adult relationships is another measure of successful adult functioning and QoL. High rates of cognitive, language (Abrams et al., 2018; Rice et al., 2012; Smith et al., 2012) and mental health problems among YPHIV (Malee et al., 2011a; Mellins et al., 2011), including anxiety, depression, ADHD, and substance use may pose barriers towards successful development of close personal relationships with friends and partners. These factors may also significantly impact a young adult's health-related QoL as well as their mental and emotional well-being and their self-efficacy. This study plans to evaluate successful transitioning to adult functioning including educational attainment, employment and independent living, and important QoL outcomes including health-related QoL, mental health, self-efficacy, friendship, and life satisfaction. This study will also evaluate factors associated with successful transition to adult functioning and QoL, including racism, stigma, resilience, and adverse childhood experiences.

### 1.1.11 Hearing and Language

There is a higher rate of sensorineural hearing loss in children and adolescents with PHIV and PHEU when compared to uninfected, unexposed children of comparable age (Torre et al., 2012). Because this type of hearing loss (although it may be a mild degree of hearing loss) is permanent, it can impact language/pragmatic and academic skills as these children transition into adulthood. By implementing a measure of hearing from the NIH Toolbox (Words-in-Noise [WIN] test), an efficient assessment of hearing can be obtained. This measure of hearing will benefit PHACS in two ways. First, results from the repeated WIN tests can be used to investigate any change in hearing over time. And secondly, the inclusion of the WIN measure will complement the language, social, and cognitive batteries conducted among AMP Up participants.

There is an elevated risk for language impairment, relative to the general population, in children with PHIV and children with PHEU aged 7 to 16 years (Rice et al., 2012); the two groups show equivalent levels of risk. There was a higher proportion of children with language impairments plus nonverbal cognitive impairments (24%) than children with language impairments only and no nonverbal cognitive impairments (11%). For children without exposure to HIV, longitudinal studies document that young children with language impairment are not likely to "outgrow" the impairment; relatively low levels of language ability are likely to persist into young adulthood (Conti-Ramsden et al., 2012; Johnson et al., 1999; Tomblin et al., 2003). The persistence of language impairment was also observed in the AMP cohorts with two assessments conducted 18 months apart (Redmond et al., 2016). Language competency is crucial for navigating the transition between adolescence and adulthood. For children with language impairments without exposure to HIV, studies document that they are at risk for limited academic achievement, social adjustment challenges at the sub-clinical level as well as increased risk for clinical levels of social adjustment problems, and limited friendship networks, all of which lead to economic consequences for adult life (Conti-Ramsden & Botting, 2004; Redmond, 2011; Ruben, 2000). They are also at risk for having children with language impairments (Rice et al., 2009). Language outcomes in the 18-25 age range are not currently documented for YAPHIV and YAPHEU. What is especially needed is information about outcomes in this age range of young adults with documented levels of low or adequate language performance in childhood. Further, given the associations of language impairment with other developmental challenges in school-age and adolescent children, any assessments of social, vocational, and educational outcomes of YAPHIV and YAPHEU in the 18-25 year range would benefit from detailed assessments of language to serve as a covariate in causal analyses. Participants in AMP received the Clinical Evaluation of Language Fundamentals-4 (CELF-4) (Semel et al., 2003) at two times of measurement. CELF is a strong language assessment that measures grammar as well as vocabulary, with validated population norms and relevant research reports; a third time of measurement on CELF is preferred to a new measure such as the Cognitive test in the NIH Toolbox, which tests vocabulary only. A third CELF assessment is being conducted in AMP Up for those participants who had historic CELF-4 assessments up through age 21 years and 11 months to provide data that can be interpreted longitudinally and will be sensitive to age-related gains or decrements associated with treatment or disease severity indicators. It complements the single time measurement on the vocabulary assessment of the NIH Toolbox.

## 1.2 Rationale

The advent of potent ART has resulted in the survival into adolescence and young adulthood of a substantial proportion of infants and children with PHIV. In parallel, the number of new infants with PHIV in the U.S. has decreased dramatically since 1993 with the development of effective means to prevent perinatal transmission of HIV. Thus, the largest group of children with PHIV in the U.S. consists of older adolescents and young adults. Some of these youth represent long-term slow-progressors, while

the majority includes those who benefited from potent combination ART. The impact of HIV infection and its treatment on the growth and development of children who have been living with HIV infection since birth was the focus of PHACS AMP. AMP addressed outcomes including growth and pubertal development, neurocognitive development and mental health, bone health, fat distribution, metabolic abnormalities, and hepatic, renal, and cardiovascular function including risk factors for CVD. Between 2007 and 2012, 451 PHIV+ children and 227 PHEU children between 7 and 15 years of age enrolled in AMP. In October 2012, the median duration of follow-up of the participants with PHIV and PHEU was 4.2 and 3.6 years, respectively, with 17% of PHIV and 12% of PHEU lost to follow-up. Of concern, the highest rates of loss-to-follow-up are seen among the oldest participants - those 17 and 18 years of age.

PHACS AMP Up was created to continue to follow AMP participants, as well as other YAPHIV, as they age into adulthood in order to identify longer-term outcomes of HIV in those with PHIV and its treatment, including changes in previously recognized abnormalities (Tassiopoulos et al., 2016). The protocol offers a simplified approach to data collection in order to maximize retention of participants, incorporating chart abstraction and phone and internet contact while requiring less frequent in-person study visits. In-person visits may be conducted remotely if circumstances preclude the participant from going into the clinical site in-person. Areas of emphasis include: HIV disease progression; risk factors for CVD; bone fractures and end-organ disease; neurocognitive functioning and mental health; sexual health, STIs, and reproductive outcomes; sexual and substance use risk behaviors; secondary transmission of HIV (including the transmission of resistant virus); and the transition to adult living and adult health care.

The knowledge gained from this study will form the basis for interventions to improve the QoL of YPHIV and YAPHIV. Unfortunately, while the number of perinatal infections in the U.S. has decreased significantly, worldwide the number of infants, children, adolescents, and young adults with PHIV is growing substantially in both resource-poor countries and in countries with increasing levels of health care. Thus, the information gained from this study will benefit YPHIV and YAPHIV worldwide.

## 2.0 OBJECTIVES AND HYPOTHESES

### 2.1 Primary Objectives

1. To identify infectious and non-infectious complications of HIV disease and toxicities resulting from long-term ART, including disease progression, immune dysfunction, viral resistance, end-organ disease, and mortality.

2. To define the impact of HIV infection and ART on the long-term clinical outcomes in YAPHIV, including:

    - Metabolic abnormalities and risk factors for CVD, including derangements in glucose and lipid metabolism, blood pressure, and body composition.
    - STIs (*C. trachomatis, Neisseria (N.) gonorrhoeae, T. vaginalis*, syphilis, HPV, genital and anal warts, and HSV) among males and females, and cervical HPV-associated pre-cancers and cancers and other vaginal microbiota, and pelvic inflammatory disease among females.
    - Reproductive health, fertility, and pregnancy outcomes including perinatal transmission of HIV.

3. To define the impact of perinatal HIV infection, its concomitant risk factors, and ART on long-term neurocognitive and behavioral health outcomes, including:

- Mental health (both psychiatric disorders and emotional/behavioral functioning) and neurocognitive functioning.
- Health care behaviors, including adherence to ART, participation in health care services, and transition to adult clinical care.
- Risk behaviors, including sexual behavior and substance use (alcohol, tobacco, vaping, and licit and illicit drugs).
- Hearing and language impairments.
- Independent living skills, vocational and educational achievement, life satisfaction, resilience, and health-related QoL.

## 2.2 Domain-Specific Aims and Hypotheses

### 2.2.1 Infectious and Non-Infectious Complications of HIV and Its Treatment

Specific Aims:

- To evaluate the long-term immunologic and virologic course of YAPHIV, including immune competence and activation, disease progression, viral resistance, and the response to changes in therapy.
- To identify cofactors which impact the short- and long-term course of HIV disease, including incident co-infections and host genetics.
- To evaluate the incidence and course of HIV end-organ disease (i.e., renal, hepatic, cardiac, pulmonary, and peripheral and central nervous system) and HIV-associated malignancies and mortality of YAPHIV, and to describe the relationship of these outcomes with HIV virologic status, ART, immune impairment, and chronic immune activation.
- To contribute to HIV remission/cure studies by understanding the viral dynamics and compartmentalization of PHIV in the context of novel HIV therapeutics, age at ART initiation, long-term viral suppression, immunologic control, and the presence and size of the viral reservoir.
- To evaluate access to testing for SARS-CoV-2, access to and acceptance of prevention strategies for SARS-CoV-2, and acceptance of testing, treatment, and prevention strategies for other important infections among YAPHIV and YAPHEU.
- To assess vaccine acceptance among YAPHIV and YAHEU including receipt and intent to receive a SARS-CoV-2 vaccine and explore reasons for acceptance or hesitancy.
- To define the oral health of YAPHIV and YAPHEU and to identify risk factors associated with declining oral health.
- Among YAPHIV, to determine risk behaviors for HIV transmission and their understanding of "U = U" as an approach to the prevention of HIV transmission.
- Among YAPHEU, to determine their level of knowledge about and use of PrEP and their rates of HIV acquisition.

Hypotheses:

- Participants without viral suppression will experience disease progression, increasing viral resistance, and increasing immune impairment. These changes will be increasingly difficult to reverse with advances in ART.
- Immune suppression early in life (or later in life with loss of virologic control) results in an impaired immune response to immunizations and infections, resulting in long-term susceptibility to infection. Immunization once immune reconstitution is achieved will be necessary for most vaccines.
- Congenital and acquired CMV infection results in HIV disease progression and potentiates end-organ disease.
- Specific host genetic polymorphisms and epigenetic changes are associated with HIV disease progression, response to ART, response to co-infections, and specific end-organ disease.
- Chronic immune activation, lack of viral suppression, decreased CD4 counts, and ARV exposures will be independently associated with HIV disease progression and end-organ diseases.
- YAPHIV who are virally suppressed will have a higher incidence of end-organ disease than YAPHEU, related to immune activation.
- The viral dynamics, reservoir size, and compartmentalization of PHIV and the host response to the infection will be different than that of young adults without PHIV.
- Incident infections, including SARS-CoV-2, STIs, CMV, toxoplasmosis, and EBV, and the resulting immune activation, will lead to HIV disease progression and potentiate end-organ disease.
- Vaccine hesitancy will be less common among YAPHIV than YAPHEU.
- YAPHIV when compared to YAPHEU will be at increased risk of periodontal disease, resulting in local and systemic immune activation and alterations in the oral microbiome, which in turn will hasten the decline in oral health.
- Bone loss in YAPHIV will be associated with ARVs and immune activation.
- Both knowledge and use of PrEP by YAPHEU will be low; HIV infection will be uncommon.
- Use of PrEP will increase over time, but use of PrEP and its rate of change over time will vary by sex.

### 2.2.2 Metabolic Complications

Specific Aim:

- To evaluate longitudinal changes in parameters of cardiometabolic risk by HIV status (YAPHIV vs. YAPHEU), including body weight and composition, lipid levels, insulin sensitivity, blood pressure, and modified PDAY scores (a predictor of atherosclerosis).
- Among YAPHIV, to evaluate the association of ART switches with changes in body weight and composition, lipid levels, insulin sensitivity, and blood pressure.
- To evaluate food security and diet in YAPHIV and YAPHEU and their associations with body composition and metabolic outcomes. Among YAPHIV, to evaluate the association of food

security with adherence to ART and whether the association is mediated through engagement in clinical care.

Hypotheses:

- YAPHIV will manifest parameters of increased cardiometabolic risk, with unfavorable trajectories compared to YAPHEU.
- Switching to newer-line ART will result in improvement in some but not all parameters of cardiometabolic risk.
- YAPHIV will have greater food insecurity than YAPHEU, and YAPHIV with food insecurity will be more likely to be obese, have poorer metabolic outcomes, and be less likely to engage in clinical care.
- YAPHIV with food insecurity will have poorer adherence to ART medications that is mediated through engagement in care.

### 2.2.3 Cardiopulmonary Complications

Specific Aims:

- To evaluate the distribution of PDAY scores for YAPHIV and YAPHEU and compare the distributions by HIV status, and to assess the association of PDAY scores and cardiac biomarkers with neurocognitive function as reflected by NIH Toolbox measures.
- To determine the association between pulmonary function and left and right ventricular structure and function.
- To determine the prevalence of marijuana and nicotine vaping in YAPHIV and YAPHEU and evaluate associations of vaping with presence of asthma, pulmonary disease, and hospitalization by PHIV status.

Hypotheses:

- YAPHIV will have increased modified PDAY scores as compared to YAPHEU, which will be inversely associated with neurocognitive function. Both past and recent cardiac and inflammatory biomarkers will be inversely associated with neurocognitive function.
- Pulmonary obstructive and/or restrictive disease will be associated with left and right ventricular diastolic dysfunction, global cardiac strain, increased pulmonary artery pressure, and pulmonary vascular resistance.
- Prevalence of vaping will be similar among YAPHIV and YAPHEU, yet the presence of asthma, pulmonary disease, and hospitalization will be more pronounced among YAPHIV.

### 2.2.4 Sexually Transmitted Infections

Specific Aims:

- To evaluate access to testing and treatment for genital STIs and bacterial vaginosis, and the incidence of and risk factors for acquiring STIs (e.g., *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, syphilis, HPV, HSV) and microbiome dysbiosis including clinical bacterial vaginosis among YAPHIV and YAPHEU, and acquisition of HIV among YAPHEU.
- To evaluate the incidence of and risk factors for pelvic inflammatory disease among females.

- To evaluate the occurrence of HSIL, external genital warts, and persistent cervical, oral, and anal high-risk HPV, and the factors associated with persistent anogenital or oral high-risk HPV, including the vaginal microbiome.

Hypotheses:

- YAPHIV will have similar frequencies and risks as YAPHEU for acquiring STI infections such as *C. trachomatis*, *N. gonorrhoeae*, and *T. vaginalis*. On the other hand, infections such as HPV, bacterial vaginosis and HSV will be found more frequently in YAPHIV and will be associated with lower CD4 cell counts.
- The risk of pelvic inflammatory disease will be higher in female YAPHIV since there is evidence that the vaginal dysbiosis that has been linked to pelvic inflammatory disease will be more common in female YAPHIV.
- Genital high-risk HPV persistence and its associated risk of HSIL will be higher in WLPHIV than for women without HIV and WLPHEU. Risk factors for high-risk types of HPV persistence and development of HSIL will include vaginal dysbiosis and its associated inflammatory states, low CD4 cell counts, smoking, and substance use. Similar risk factors will be associated with external genital warts. Women who received HPV vaccination before the onset of sexual debut will be at lower risk of HSIL and external genital warts.

### 2.2.5 Reproductive Health

Specific Aims:

Among WLPHIV and WLPHEU:

- To describe the use of pregnancy prevention methods and their association with pregnancy and STI outcomes.
- To determine incidence of and factors associated with pregnancy intention.
- To examine pregnancy outcomes and factors associated with these outcomes.
- To identify rates of menstrual irregularities and risk factors for menstrual irregularity, including stress, hormonal disturbances, HIV-related health, and ART use.
- To determine the incidence of perinatal transmission of HIV.

Among WLPHIV, in comparison to women living with non-perinatally acquired HIV from the Health Outcomes around Pregnancy and Exposure to HIV/ARVs (HOPE) study:

- To evaluate individual, mental health, and interpersonal factors associated with unintended pregnancy, contraceptive discontinuation or non-use, discordant family planning behaviors and desires, and incident STIs.
- To compare factors associated with unintended pregnancy, contraceptive discontinuation or non-use, discordant family planning behaviors and desires, and incident STIs by mode of HIV acquisition (PHIV vs. non-PHIV).

Hypotheses:

- The majority of WLPHIV who use pregnancy prevention will choose long-acting contraceptives. These methods will be superior to combined oral contraceptive pill in preventing pregnancies; however, they will be linked to lack of condom use and higher STI rates.
- Predictors of pregnancy intention will be similar for WLPHIV and WLPHEU and will include older age and perceived close relationship to partner.
- Young WLPHIV who are not on contraceptives will be more likely than young WLPHEU to have anovulatory cycles (defined as having cycles < 21 and > 35 days). Irregular cycles will be affected by stress, depression, BMI, and substance use, and for WLPHIV, CD4 cell count and ART adherence.
- Young WLPHIV will have fewer pregnancies than WLPHEU after adjusting for BMI, STI history, and substance use. Vaginal dysbiosis will be associated with fewer pregnancies.
- Young pregnant WLPHIV will have higher spontaneous abortion rates than WLPHEU after adjusting for substance use. Vaginal dysbiosis will play a role in this increased rate of spontaneous abortion.
- The rate of perinatal transmission of HIV will be low.
- Pregnant and postpartum WLHIV who are virologically suppressed will have greater knowledge of the health benefits of breastfeeding than those who are unsuppressed. This association will be stronger for women without PHIV than for WLPHIV. WLHIV with viral suppression will have a greater likelihood of breastfeeding than women with detectable virus.
- More severe HIV disease, mode of HIV acquisition (PHIV vs. non-PHIV), depression, low social support, and poor engagement in HIV care will be associated with unintended pregnancy, contraceptive discontinuation or non-use, discordant family planning behaviors and desires, and incident STIs.
- Factors associated with unintended pregnancy, contraceptive discontinuation or non-use, discordant family planning behaviors and desires, and incident STIs will differ by mode of HIV acquisition (PHIV vs. non-PHIV).

### 2.2.6 Neurocognitive Functioning and Mental Health

Specific Aims:

- Among YAPHIV and YAPHEU, to describe the trajectories of cognitive functioning and mental health in young adulthood and examine factors associated with these trajectories.
- To identify the trajectories of co-occurring risks in cognitive, mental health, and behavioral health (sexual behaviors and drug and alcohol use) in young adulthood.
- To identify factors associated with trajectories of co-occurring risks in cognitive, mental, and behavioral health in young adulthood, including PHIV status, and individual, interpersonal, systemic and structural influences experienced during childhood and adolescence, including adverse childhood experiences (e.g., exposure to violence, neglect, etc.) and young adulthood experiences (e.g., racism, low levels of social support, etc.).
- To define the impact of the SARS-CoV-2 pandemic and its associated mitigation strategies on the mental health of participants affected by HIV.

Hypotheses:

- YAPHIV will demonstrate lower cognitive abilities than YAPHEU and young adults without PHIV exposure when compared to national norms for young adults.
- Unique trajectories of cognitive, mental health, and behavioral risk in adulthood will be associated with youth, family, and community influences experienced during childhood and adolescence.
- YAPHIV with advanced disease will demonstrate cognitive vulnerabilities in executive functioning, processing speed, and working memory compared to healthier YAPHIV and YAPHEU.
- YAPHIV will exhibit higher rates of mental health problems relative to the normative population, but these rates will be similar to YAPHEU.
- Among YAPHIV, prevalence and severity of mental health problems will be higher among those with prior and/or current evidence of nonadherence and immune dysfunction (low CD4 cell count, detectable HIV RNA viral load) during adolescence and young adulthood.
- Participants will report SARS-CoV-2 pandemic-related stress, with effects more pronounced among those with a history of psychiatric or substance use. Participants who report closely following pandemic-related mitigation strategies will be more likely to report depressive symptoms and negative emotions than participants not closely following these strategies.

### 2.2.7 Health Care Behaviors and Transition to Adult Health Care

Specific Aims:

- To describe factors associated with adherence to ART and health care and changes in adherence over time.
- Among YAPHIV, to estimate the associations between cognitive, mental health, and behavioral health (sexual, drug, and alcohol) risk trajectories during adolescence and ART adherence and viral suppression in young adulthood.
- To describe the transition from pediatric or adolescent to adult clinical care and to identify the individual, social, and health care system barriers and facilitators of adherence, access to and retention in adult health care, and clinical outcomes after transition (including sustained viral suppression).

Hypotheses:

- Longer duration on ARV treatment will be associated with higher rates of nonadherence as a result of treatment fatigue.
- Young adults with inadequate insurance and young adults in locations lacking a pediatric to adult care transition program will evidence lower rates of adherence to care and ART.
- HIV-related stigma, medical mistrust, and experiences of discrimination in the health care setting will be associated with higher rates of nonadherence and lower rates of retention in adult health care.
- Social factors including poverty, exposure to partner and community violence and stressful life events will be associated with nonadherence to treatment and care.

- YAPHIV with a higher prevalence and co-occurrence of cognitive, mental health and behavioral health risks over time in adolescence will be less likely to report successful ART adherence and be virally suppressed during adulthood.
- Stressful life events, inadequate social support and psychosocial resources (e.g., housing, health insurance), lack of site- or patient-specific transition plan, and inadequate insurance will be associated with less successful transition to adult health care.
- Neurocognitive deficits, mental health problems, history of nonadherence, and substance use will be associated with difficulties with transition to adult health care.
- Adult health care will be associated with lower rates of retention in health care and worse clinical outcomes (lower CD4 count, higher viral load) than pediatric clinical care, but rates of retention in adult care will increase in later adulthood.
- Factors associated with a less successful transition will include mental health problems, inadequate social support, lack of advanced transition planning, and medical mistrust or experiences of discrimination in the health care setting.

### 2.2.8 Risk and Protective Behaviors

Specific Aims:

- To examine the prevalence, changes over time, and factors associated with sexual behaviors (including vaginal, oral, and anal intercourse, condom use, and multiple sexual partners), disclosure of HIV status, and knowledge of partner's HIV status.
- To examine the prevalence, changes over time, and factors associated with use of licit (alcohol, tobacco) and illicit substances.
- To compare the prevalence and factors associated with sexual and substance-use behaviors between YAPHIV and YAPHEU.

Hypotheses:

- The majority of YAPHIV will be sexually active and prevalence of vaginal and anal intercourse will be similar to that of both YAPHEU and unexposed, uninfected adults of the same age.
- Rates of inconsistent condom use will be high, similar to that of uninfected young adults. The rate of consistent condom use will increase with increasing age.
- For YAPHIV, condom use will be influenced by participant's viral load, partner type, knowledge of partner's HIV status, pregnancy intention, sexual coercion, and whether a discussion of condom use preceded intercourse, and whether substance use preceded intercourse.
- Disclosure of HIV status to sexual partners will be incomplete and will be influenced by condom use, partner type, and viral suppression, as well as stigma, self-efficacy and perceived social support.
- Use of both licit and illicit substances will increase as the population ages and will be associated with mental health status, lack of social support, unstable housing and exposure to violence. In turn, substance use will influence the prevalence of condomless sexual intercourse and other sexual behaviors including lack of disclosure to sexual partners.

### 2.2.9 Transition to Adult Functioning and QoL

Specific Aims:

- To examine whether successful transition to adult functioning varies by HIV infection status.
- To examine life satisfaction, resilience, health-related QoL, sleep, friendship, and successful adult functioning (including educational attainment, employment, and independent living) of YAPHIV and YAPHEU, and to identify childhood, adolescent and young adult factors associated with these outcomes.
- To determine the association between trajectories of co-occurring mental health and behavioral risks with attainment of adult milestones, including employment and ongoing education.

Hypotheses:

- Neurocognitive deficits, mental health problems, history of nonadherence, adverse childhood experiences, as well as inadequate social support and low levels of resilience, will be associated with difficulties in transitioning to adulthood and with poorer health-related QoL.
- YAPHIV will have lower rates of successful transitioning to adult functioning, and poorer health-related QoL, and will report less life satisfaction, than will YAPHEU.
- Greater life satisfaction, social support, self-efficacy and perceived friendships will be associated with higher health-related QoL, while adverse childhood experiences will be associated with poor QoL; these associations will be more pronounced among YAPHIV.
- Poorer sleep quality will be associated with lower health-related QoL and life satisfaction.
- Young adults with co-occurring and ongoing risks in cognition (working memory, processing speed, and executive functioning), mental health, and risk behaviors will be at increased risk for incomplete attainment of educational and vocational milestones.
- YAPHIV will have lower levels of friendship than YAPHEU.

### 2.2.10 Hearing and Language

Specific Aims:

- To assess changes in language acquisition from childhood to young adulthood in YAPHIV and YAPHEU and, among YAPHIV, the association of these changes with HIV disease severity and ARV exposure.
- To determine how language abilities and hearing in adolescence predict employment status, educational status, reading abilities and life satisfaction in young adulthood.
- To evaluate hearing sensitivity of YAPHIV and YAPHEU, and to evaluate the associations of ARV exposure and HIV disease severity with these outcomes.

Hypotheses:

- Language impairments will be stable over time in both YAPHIV and YAPHEU.
- Among YAPHIV, ARV effects will differ by ARV type, age, and specific language outcomes.
- Young adults with language or hearing impairment will be at increased risk of negative social, academic, and employment outcomes.

- Compared to YAPHEU, YAPHIV will have poorer hearing and language outcomes, which are associated with HIV disease status and ARV exposure.

## 3.0 STUDY DESIGN

This study will establish a cohort of approximately 650 YAPHIV. A comparison cohort of approximately 200 YAPHEU will also be included. They will come from a similar sociodemographic background with a similar age distribution to that of YAPHIV, and will have been exposed to ART *in utero*. The YAPHEU comparison cohort will be important in evaluating whether observed abnormalities are related to PHIV and/or ART, since the groups should be well matched for other risk factors for behavioral, developmental, and health issues.

Participants will be evaluated prospectively according to an established schedule of evaluations, both in-person and web-based (see Appendices I and II). The study will prospectively document infectious and non-infectious complications of HIV and ART at each study visit. Events will be classified by diagnosis rather than by signs and symptoms, using standardized definitions. Some events will be further evaluated in future, separate, focused substudies designed to address specific scientific questions.

### 3.1 Study Population

Participants in this study will be YAPHIV and YAPHEU at or beyond their 18$^{th}$ birthday who were born to mothers living with HIV during their pregnancy. Eligible participants will be recruited from PHACS sites and will include those with a well-documented history of their major medical events history, and for participants with HIV only, HIV infection status, viral load and CD4 cell count history, and ART since early childhood.

### 3.2 Sample Size

- YAPHIV Cohort: Approximately 650 participants
- YAPHEU Cohort: Approximately 200 participants

### 3.3 Biological Specimens

Biological specimens to be collected include plasma, serum, viable peripheral blood mononuclear cells (PBMCs), urine, throat wash/gargle, unstimulated saliva, and vaginal swabs. Laboratory studies will be performed as indicated in Appendix III. Biological specimens will be collected according to visit schedule in Appendices I and II.

## 4.0 SELECTION AND ENROLLMENT OF STUDY PARTICIPANTS

All former AMP participants are eligible for enrollment in the YAPHEU and YAPHIV cohorts. Enrollment in the YAPHIV cohort is also open to all eligible individuals including those not previously enrolled in one of the approved studies (see page 15). Under protocol version 2.0, YAPHEU at all participating sites are also eligible to enroll; previous enrollment in PHACS SMARTT or AMP is not required but enrollment of these individuals is encouraged.

Prior to enrollment of individuals not previously enrolled in one of the approved studies, a request for approval that includes the following information must be submitted to the Protocol Team via the Query and Notification System (QNS): individual's current age and age range(s) for which individual's medical records (including records from other facilities) are available. An approval notification must be received from the Protocol Team before the individual can be enrolled.

## 4.1 YAPHIV Cohort

### 4.1.1 Inclusion Criteria

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

- Has perinatal HIV infection as documented in the medical record.
- Is at or beyond their 18th birthday at the time of informed consent.
- Is willing to provide access to existing medical records.
- At least one of the following is true:
  - Previously enrolled in any of the studies included on the list of approved studies (see list of approved studies meeting the eligibility requirement for enrollment into AMP Up on page 15), or
  - Available medical record documentation* since early childhood, if possible, but no later than 12 years of age. Medical records must also be available starting no later than 2 years after HIV diagnosis and include:
    - ART exposure history,
    - Opportunistic infection prophylaxis exposure history,
    - Viral load and CD4 cell count history, and
    - Major medical events history.

  *Medical record documentation should consist of all existing records from when the participant entered care with no gaps in existing records of more than 12 months.
- Is willing to participate and provide legal written consent.

### 4.1.2 Exclusion Criteria

To be considered eligible for enrollment, an individual must not:

- Have HIV acquired by other than maternal-child transmission (e.g., blood products, sexual contact, and IV drug use) as documented in the medical record.

## 4.2 YAPHEU Cohort

### 4.2.1 Inclusion Criteria

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

- Is living with perinatal HIV exposure and without perinatally acquired HIV.

- Is at or beyond their 18th birthday at the time of informed consent.
- Is willing to provide access to existing medical records.
- Is willing to participate and provide legal written consent.

### 4.2.2 Exclusion Criteria

To be considered eligible for enrollment, an individual must not:

- Have confirmed perinatal HIV infection as documented in the medical record.

## 4.3 Protocol Registration

Prior to implementation of this study, the Harvard Longwood Campus (HLC) Institutional Review Board (IRB), the single IRB (sIRB) of record for this study, will approve the study protocol, including informed consent forms (ICFs) 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 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 at https://phacsstudy.org.

## 4.4 Participant Recruitment

Potential participants will be identified by the study personnel at the participating sites. Clinical staff members such as case managers and healthcare providers at clinical sites will be made aware of the eligibility criteria of the study. Potential participants will be identified and referred to the clinical research team for potential enrollment. A research staff member will approach potential participants to provide an overview of the study, gauge the potential participant's interest in participating, and determine their eligibility. Clinical research teams will be encouraged to approach all eligible former AMP and SMARTT participants and other eligible YAPHIV and YAPHEU regarding participation in this study. The major criterion for approval is the completeness of documentation of ART exposure history, viral load and CD4 cell count, and major medical events.

Young adults formerly enrolled in pediatric protocols will be approached for willingness to enroll in adult protocols once they reach the age of majority. This is a common practice at our clinical sites.

A common reason reported on pediatric studies for discontinuation is that the caregiver is unable to commit the time required for study visits. These families typically continue to receive clinical care at the clinical site and maintain relationships with study staff. Participants often welcome the opportunity to enroll in research studies once they have reached the age of majority and can consent on their own behalf.

Enrollment will remain open until the required number of participants is enrolled or until enrollment is closed by the Protocol Team in order to allow adequate duration of follow-up of participants.

## 4.5 Informed Consent

Once it is determined that a participant may qualify for the protocol and is interested in participating, written informed consent or legal guardian permission and participant assent will be obtained. Study details including the information to be collected and the evaluations and assessments involved will be discussed with potential participants who show interest in the study and all questions will be answered.

The initial informed consent procedure is intended to be conducted at the clinical site prior to the Entry (Year 0) visit. If circumstances preclude an in-person Entry (Year 0) visit, informed consent may be conducted remotely along with the remote Entry visit. Remote consenting (initial and re-consent) will be conducted using the web-based ICF or via telephone. PHACS Leadership will work with the clinical sites to ensure that the web-based ICF used at each participating site has been approved by the HLC IRB as well as their local IRB, when indicated. If remote consenting should occur, clinical site staff will be available for phone consultation to address questions or concerns.

Clinical site staff will monitor whether the mental capacity of a participant changes throughout the course of the study (see Section 8.2). Each site employs psychology staff that can advise when a participant's competence to give continuing consent is in question, and they will contact the HLC IRB or local IRB for guidance, as needed.

When a participant is unable or unwilling to continue to be followed in-person at the clinical site after the Entry visit, they will be encouraged to transfer to another AMP Up site or to continue to be followed remotely by the originating site, if transfer to a new site is not possible. If neither of these options are possible, the participant may be consented to continue study participation through the PHACS Data Resources Core (DRC) at the Harvard T. H. Chan School of Public Health (HSPH). The informed consent process at HSPH will occur remotely either by using the web-based ICF or via telephone. HSPH staff will be available for telephone consultation when web-based informed consent is conducted.

The web-based ICF will include verification of comprehension and require participants to acknowledge that they have read and agree to the ICF by checking a box following each section of the consent. Verification of identification during the consent process will be confirmed through the use of a consent identification number (CIN) provided to the participant by the clinical site prior to study enrollment. Security questions may be employed for further verification.

## 4.6 Enrollment Procedures

When a participant is eligible for the 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 who were previously enrolled in PHACS will continue to use their PHACS participant identification number (PID). Participants recruited from International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) or AIDS Clinical Trials Group (ACTG) will retain their IMPAACT or ACTG PID. The SES will generate a study identification number/personal identification number (SID/PIN) specific to the AMP Up study for participants who are confirmed eligible and enrolled. In AMP Up, the SID will serve as the participant's PIN that will be used as the participant identifier in web-based assessments.

At initial consent or re-consent (for participants previously enrolled in protocol version 1.0), participants will be asked to consent to provide their address information for the purpose of future geocoding. The address information will be stored at the clinical site and will not be part of the AMP Up database.

### 4.7 Co-Enrollment Guidelines

Enrollment of AMP Up participants in other studies (with or without similar goals/data collection as AMP Up) is at the discretion of clinical site principal investigators. However, they must take into account any issues that enrollment in the additional study may require, and which may compromise the site's ability to fulfill the requirements of PHACS.

Children born to female YAPHIV AMP Up participants are encouraged to be enrolled along with their mothers in the SMARTT dynamic cohort.

Participants who indicate they would like to be contacted for studies opening in the future will provide their contact information to the clinical site. Each site will maintain this information and, in the event a participant changes their mind and no longer wishes to be contacted, the clinical site will track these requests and update their documentation accordingly.

## 5.0 CLINICAL AND LABORATORY EVALUATIONS

The following clinical and laboratory evaluations will be performed on each participant, after signed informed consent is obtained, as part of participation in this study. See Appendices I and II for a tabulated summary of the evaluations described below and their schedule of completion.

The study visits at Entry (Year 0) and every 3 years starting at Year 3 (e.g., Years 3, 6, 9, 12…) are intended to be conducted in-person. If circumstances preclude an in-person visit, the visit can be conducted remotely, e.g., clinical assessment data will be collected through chart abstraction (when available), surveys and questionnaires may be completed via telephone (with Protocol Team approval), and specimens may be self-collected and shipped to the clinical site. Any remaining assessments that cannot be completed (e.g., NIH Toolbox, body measurements, Block Physical Activity Screener, blood draw for repository specimens) will be considered missed. However, missed assessments may be completed at the next annual visit, with Protocol Team approval (see Section 8.1).

### 5.1 Entry Visit (Year 0) Evaluations

For participants previously enrolled in other studies such as WITS, IMPAACT 219/219c, 1025, and 1074, and the CDC LEGACY study and other PHACS studies who agreed to share their data from these other studies with AMP Up, the Protocol Team will abstract relevant information on medications, viral load and CD4 cell count, and major medical events from the study database of these other studies; clinical site staff will abstract any remaining data from the medical record.

Entry (Year 0) visit evaluations for all participants will include chart abstraction, clinical assessments, real-time laboratory testing, collection of specimens for central testing and the PHACS Repository, hearing, language (for a subset of participant only; see Section 9.4), cognitive and mental health assessments, the Block Physical Activity Screener, and a web-based survey (see Section 9.1 and Appendices I and II). The web-based survey can be conducted either at the clinic during the in-person visit or remotely. The entire Entry visit is expected to take up to 4 hours to complete.

### 5.2 In-Person Evaluations

As with the Entry (Year 0) visit evaluations, evaluations every 3 years starting at Year 3 (e.g., Years 3, 6, 9, 12…) will include chart abstraction, clinical assessments, real-time laboratory testing, collection of specimens for central testing and the PHACS Repository, cognitive, hearing, and mental health assessments, the Block Physical Activity Screener, and the web-based survey. The web-based survey can be conducted either in-person or remotely. Each of the in-person follow-up visits is expected to take up to 3 hours to complete.

### 5.3 Web-Based Surveys, Specimen Collection, and Chart Abstraction

During years without in-person visits (e.g., Years 1, 2, 4, 5, 7, 8, 10, 11, 13, 14…) study assessments will consist of web-based surveys, self-collection of specimens for STI testing (real-time and research Aptima testing), and chart abstraction. Web-based surveys and specimen collection can be completed outside of the clinical site. However, participants will have the option to complete them at the clinical site if they prefer. Chart abstraction will be completed annually in the clinic by clinical site staff.

### 5.4 Additional Web-based Surveys

From time to time, technological developments, events impacting public health, or geopolitical events may be expected to impact the health and wellbeing of YAPHIV and YAPHEU. If such events occur, additional surveys may be developed to address these issues. These surveys would first be submitted to the HLC IRB as a protocol modification. Once approved by the HLC IRB, these surveys would be administered to participants. These additional surveys may be administered by clinical site staff as interviews or as web-based surveys (completed in clinic or sent by the site to participants as survey links) or sent as survey links by the PHACS DMC at Frontier Science (if the participant gave their permission for the DMC to receive and retain their contact information from the site).

## 6.0 DATA AND SPECIMEN COLLECTION AND SITE MONITORING

### 6.1 Data Records

For medical record reviews and other non-web-based data collection, case report forms (CRF)/data entry screens will be provided for each participant. Participants must not be identified by name on any CRFs, web-based assessments, laboratory specimens, clinical evaluation results, and laboratory results that are part of the research records. Participants are to be identified by the PID and SID/PIN numbers assigned by PHACS. Study research records with PID and SID/PIN must be stored separately from source documents that include personal identifiers.

Web-based data collection will utilize multiple sources. The majority of the annual web-based data collection (“web-based surveys”) as well as collection of participant contact information (see Section 8.3) will be conducted via the commercial software tool Illume that was designed by DatStat, Inc. specifically for creating web-based data collection instruments. The Illume software tool uses secure hypertext transfer protocol secure (HTTPS) connections that adhere to the Food and Drug Administration (FDA) guidelines for secure electronic data capture. (See Appendix IV for a detailed description of DatStat measures for data security and user confidentiality for web-based surveys). The collected data will be stored on DatStat's server and transferred to the PHACS central database at Frontier Science. Respondent data are protected by state-of-the-art security controls including firewalls and encryption. Access to the

server will be highly restrictive and limited to a small number of project staff who have been authorized by PHACS Leadership to have access.

The web-based Block Physical Activity Screener will be used to collect physical activity data at the in-person visits (Entry and every 3 years). Hosted by NutritionQuest, their Data-on-Demand web-based survey system uses the standard Secure Sockets Layer (SSL) encryption protocol to ensure that data are transmitted securely. The database itself is password protected, and passwords are changed regularly. Data are retained until indicated by project investigators. The servers hosting all NutritionQuest web-based services are dedicated (not shared) and are located in rooms with 24-hour security. Every effort is made to keep identifying information secure and confidential.

Neurocognitive data will be collected at the in-person visits (Entry and every 3 years) using the NIH Toolbox instruments available through the NIH Toolbox iPad App. All data submitted are encrypted and stored on a secure server. Security measures designed to protect against the loss, misuse, or alteration of data are also in place at the physical facilities where servers are housed at Northwestern University in Chicago, IL, and the National Institutes of Health (NIH).

The PHACS DMC will use HTTPS to securely download all data collected via the web from all of the sources outlined above to the PHACS central database. In addition, the policies and procedures governing the collection, storage and transfer of all data collected via the web will be reviewed annually by the PHACS Leadership, or immediately in the event that any breaches are discovered or reported.

### 6.2 Data Collection

For CRFs/data entry screens used at the clinical site, instructions on recording study data on the CRFs and the entry of data into the computerized database will be provided by the PHACS DMC. The DMC will provide training, as needed, for clinical site staff on the use of the web-based survey and on how to access the Block Physical Activity instrument. NIH Toolbox training will be conducted through a self-directed web-based training and supplemented by a central web-based or individual training session depending on site training needs.

At the Entry visit, clinical site staff will access the web-based survey via links provided to them by the DMC. The Block Physical Activity Screener and the NIH Toolbox will be accessed through the website and the iPad application, respectively, hosted by the institutions maintaining the respective surveys. Clinical site staff will introduce participants to each survey and explain the process of completing them. Participants will then complete the surveys. The web-based survey may be completed remotely if the participant cannot go to the clinic to complete it.

Most of the questions in the AMP Up web-based survey are incorporated into a single primary survey, while other questions may be administered separately as short, stand-alone surveys. Only one stand-alone survey will be administered each year. Participants will receive a link to the longer, primary survey and - if applicable - a separate link to the stand-alone survey. The participant can choose to complete both the primary and the stand-alone survey at the same time, or they can complete the stand-alone survey at a later time. If the stand-alone survey is completed at a later time, participants will receive the link either from the clinical site or from the PHACS DMC at Frontier Science (the latter only if participants gave their permission for the DMC to receive their information).

When participants complete the follow-up web-based survey outside the clinic, they can link to the web-based survey either through the links provided to them by the clinical site staff or Frontier Science or

through the AMP Up participant website (see Section 8.5). Participants will log in to the website using a unique, participant-specific username and passcode to access the link to the survey they need to complete.

### 6.3 Data Quality Assurance

Clinical site monitoring for protocol and regulatory compliance will be conducted by Westat at each participating PHACS site.

The clinical site principal investigator will make study documents (e.g., ICFs, CRFs, electronic medical records) and pertinent hospital or clinic records readily available for inspection by the local IRB, HLC IRB, the NIH, the Office of Human Research Protection (OHRP), and the site monitors acting on behalf of the NIH to confirm the study data and regulatory compliance.

Note: Participating sites are responsible for specifying these individuals and the PHACS investigators as recipients of private health information in the individual's authorization required under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule.

### 6.4 Testing of Specimens in Real-Time

YAPHEU will have an HIV test performed in real-time at a local clinical lab at the Years 3 and 9 in-person study visits.

For participants with neither *N. gonorrhoeae* nor *C. trachomatis* testing results available in the medical records during the 12 months prior to the visit, urine for males and vaginal swab (preferred, or urine if swab is declined) for females will be self-collected as per local clinical lab requirements for real-time STI testing at the local clinical lab. At the Entry and every 3 years starting at Year 3(e.g., Years 3, 6, 9, 12,…), the sample will be self-collected at the clinic and at other time points self-collected either at the clinic, a commercial lab, or at home.

### 6.5 Specimens for Central Testing

Specimens for fasting glucose and insulin, fasting lipids and renal and cardiac biomarkers will be held locally at the site and subsequently shipped in batches to the PHACS Repository for temporary storage prior to testing at the Central Laboratory. Specimens for research Aptima STI testing (urine for males and vaginal swab [preferred, or urine if swab is declined] for females) to be done centrally will be handled similarly.

### 6.6 Repository Specimens

This study will store fasting serum and plasma (ethylenediaminetetraacetic acid (EDTA) and heparin), frozen viable PBMCs, throat wash/gargle, unstimulated saliva, urine and vaginal swabs (females) as repository specimens for future, currently undetermined research testing. This storage will be at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Repository and will be governed by the PHACS Repository Policy (See PHACS MNPP). For participants co-enrolled in another PHACS study or the HOPE study, repository specimens collected in this study may be shared with those studies in order to avoid collection of duplicate repository specimens.

### 6.7 Cataloguing of Specimens

All specimens collected at the clinical site and self-collected specimens returned to the site by participants will be catalogued using the Laboratory Data Management System (LDMS) developed and supported by Frontier Science.

The clinical site will create a spreadsheet to document all self-collection kits provided to participants for at-home collection and track whether STI testing results from real-time testing were subsequently received. If a self-collected specimen is not submitted to the clinical site within one month from the date the participant completes the web-based survey portion of the visit, clinical site staff will follow-up with participants regarding the status of the self-collected specimens. Repeated follow-up will ensue if appropriate.

Results from real-time STI testing will be reported on CRFs and entered in the study database. Results from research Aptima STI testing will be reported to the DMC through the Data Submission System by the Central Laboratory. Clinicians will share results from real-time STI testing with their participants. Positive results from the research Aptima STI testing done at the Central Laboratory will be returned to clinicians to share with their participants, but since testing is batched, these results will be delayed and returned weeks to months after collection.

## 7.0 STUDY MANAGEMENT

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) Guidelines, and the applicable regulatory requirement(s).

### 7.1 Protocol Query Management

For the integrity of the study and the welfare of the participants, it is important for the site staff and research participants to have access to the research team. Site staff will send all queries for this protocol to the AMP Up Protocol Team using the QNS accessible via the PHACS website at (https://phacsstudy.org). It is expected that queries will be responded to within 48 hours of receipt by the AMP Up Protocol Co-Chairs or designee. Queries and replies will automatically be archived by the PHACS webmaster. Those queries deemed relevant to all sites will be posted on the PHACS website, 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.

### 7.2 Data Management

This study follows PHACS standards and recommended guidelines for data management. Instructions concerning the recording of study data on CRFs will be provided by the PHACS DMC. Data will be entered into electronic CRFs using an electronic data capture system. Each site is responsible for entering the data in a timely fashion according to standards set by the PHACS Network. The electronic data capture 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 will take place. Data will be checked for completeness, accuracy, and consistency. Data errors found during

the automatic processing and loading of the data will be communicated to clinical sites via reports. Additional data checks will be performed by the study data manager and communicated to the site.

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.

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 databases.

### 7.3 Rolling Implementation and New Protocol Versions

As this study will be implemented across multiple clinical sites, 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 Team 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. Sites should not enroll or follow participants under the new protocol version prior to the effective implementation date.

### 7.4 Collaboration with Outside Studies

It will be useful for the AMP Up protocol to collaborate with outside investigators and other cohort studies to increase the sample size or make available unique methodologies. Collaborations will be approved by the PHACS Leadership Group and a Data Use Agreement will be executed defining the extent and nature of the data sharing. The Data Use Agreement will include an understanding of the control of the use of the data, publication rights, and authorship rights and will address the human participant confidentiality issues.

## 8.0 PARTICIPANT MANAGEMENT

### 8.1 Study Visit Management

All study visits are to be conducted according to the Schedule of Evaluations in Appendices I and II. The target visit date for all follow-up visits, including the in-person study visits (e.g., Years 3, 6, 9, 12…) is the anniversary of the Entry (Year 0) visit. All visits must be conducted within six months prior to or after the target visit date (visit window). All visit assessments should be conducted as closely together as possible, preferably all on the same day or no more than six weeks apart.

The annual web-based survey may be completed in more than one sitting but must be completed in its entirety within four weeks after its initiation and by the end of the visit window, regardless of when it was initiated. An exception to this requirement will be made if some of the survey questions are administered separately from the primary survey, as a short, stand-alone survey. In this situation, the stand-alone survey may be completed within three months of receipt.

If the participant is unable to have a visit conducted within the visit window, or unable to complete all visit assessments within the required timeframe, the clinical site must query the Protocol Team for guidance through the QNS. Many of the assessments of the in-person visits, which only take place every 3 years, can only be done in person (e.g., NIH Toolbox, body measurements, Block Physical Activity Screener, blood draw for repository specimens). Therefore, if all or part of an in-person visit is not completed within the required timeframe, the missed assessment(s) may be completed at the next annual visit with permission from the Protocol Team if the participant is able and willing to go to the clinic. The participant's file and the appropriate CRF should be updated.

If a participant in the YAPHEU cohort is documented to have acquired HIV infection, the participant will be asked to agree to remain on study and be followed according to the schedule of evaluations for the YAPHIV cohort.

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.

### 8.2 Enrollment and Participation of Individuals with Cognitive Impairment

Individuals with cognitive impairment meeting study eligibility criteria will not be excluded from enrollment. Enrollment of individuals with cognitive impairment is justified given that the cause of the cognitive impairment may be related to the exposure being studied and not enrolling these individuals would introduce bias into the study. AMP Up is an observational study and any potential risks or negative impacts on the well-being of these individuals are minimal. Given these conditions, enrollment of individuals with cognitive impairment is in line with DHHS and FDA regulations.

Participants with cognitive impairment will consent on their own behalf if legally able. For individuals with cognitive impairment who have a legally authorized representative (LAR), legal guardian permission and participant assent will be obtained. Clinical sites should consult with the HLC IRB and their local IRB for guidance when needed. Caregivers of participants with cognitive impairment will answer questions as proxies on behalf of participants and will therefore not be consented and enrolled as study participants themselves.

The web-based survey may be administered as an interview to participants with cognitive impairment by clinic staff, though in these instances participants will not complete reproductive health, sexual activity, or substance use questions. Surveys will be adapted for interviewer administration on-site at the clinic or by telephone. For participants whose impairments prevent them from responding to survey questions, the participant's primary caregiver will complete survey questions on demographics, health and health care, diet, and medication adherence. In the case of distress resulting from completing the web-based survey, clinical site staff will be available to consult by telephone or on-site. As with participants without cognitive impairment, participants with cognitive impairment will have the option of completing the web-

based survey at the clinic during years without in-person visits (e.g., 1, 2, 4, 5, 7, 8, 10, 11, 13, 14… if they prefer.

Participants with cognitive impairment will take part in assessments conducted at the in-person visits at Entry and every 3 years starting at Year 3 (e.g., Years 3, 6, 9, 12…), which take place in the clinic and will allow clinic staff to closely monitor their participation. Specific assessments of concern may be withheld if deemed necessary by the clinical site principal investigator. Participants will be taken off-study if they appear to be unduly distressed as a result of protocol activities.

### 8.3 Participant Retention

Participant retention is challenging and maintaining retention is a high priority. Retention and participation in study visits will be monitored carefully.

Clinical sites will establish a plan for tracking participants. This includes collecting initial participant contact information at Entry (Year 0) and updating information between study visits, and during study visits both in clinic and occurring remotely. At the Entry (Year 0) visit, initial participant contact information will be entered into a web-based contact information tracking form by the site using the Illume software tool. At each follow-up visit and between study visits, participants will be asked to review their initial contact information and will be able to assist the sites with reviewing and keeping their contact information current. Site staff will also have view-only access to participant contact information. See Appendix IV for a description of DatStat data security and user confidentiality.

Clinical sites staff will generate reports listing PIDs of participants for whom study assessments are due using utilities on the Frontier Science Portal. Clinical site staff are responsible for contacting participants to inform them of impending study visits. If an expected web-based survey is not completed and/or self-collected specimens are not submitted within the visit window, clinical sites should follow up with participants to encourage completion of these assessments.

For those participants who move out of the area to a location near another AMP Up site, the originating site personnel will make every effort to encourage transfer of the participant to the new AMP Up site or to continue following the participant remotely, if transfer to a new site is not possible. If it is not possible to transfer the participant to another clinical site or to continue being followed remotely at the originating site, the participant may be consented to continue taking part in the study through the PHACS DRC at the HSPH. Participants can only consent for continued participation through the DRC at the HSPH if they have enrolled at a clinical site. After the transfer, the informed consent process will be handled by HSPH staff as described in Section 4.5. Participants will be asked to complete a web-based medical record release or will have the option of receiving a hard copy of the release through the mail. Staff at the originating clinical site may also handle the signing of the medical record release allowing HSPH staff to request medical records when allowed by the HLC IRB and local IRB and agreeable to the participant. Participants followed by the DRC at the HSPH will complete the web-based survey, and HSPH staff will be responsible for obtaining medical records, conducting the medical record review, and tracking participants. No laboratory assessments will be conducted for these participants.

### 8.4 Participant Contact Information

As part of the informed consent process, permission will be requested from participants to allow study staff at the PHACS DMC at Frontier Science to receive their electronic contact information (e.g., email

address or phone number for text messaging) from the clinical site in order to allow the DMC to send participants links to stand-alone surveys for completion.

Separate permission will be requested from participants to allow the DMC to receive their electronic contact information from the clinical site in order to allow the DMC to send participants links to additional web-based surveys for completion.

In addition, permission will be obtained from participants at the time of the informed consent process to periodically touch base with them for updated contact information after their participant in AMP Up ends, so that they can be notified of important study findings and/or be contacted regarding their interest in participating in future evaluations or studies.

## 8.5 Participant Website

A private website portal has been developed for participants of this study. The website is maintained by the PHACS Health Education and Community Core (HECC). The identity of participants will be verified by the use of a participant-specific username and passcode. In addition to allowing participants to link to the web-based survey at follow-up visits, the website will serve as a portal for health education materials. Furthermore, summary study results may be disseminated to participants through the website. PHACS will collaborate with the HLC IRB and local clinical site staff to ensure that participants are not given access to materials that require IRB review before they have been reviewed and approved as required.

## 8.6 Discontinuing Study Participation

The rate and reason for discontinuing follow-up will be monitored by the Protocol Team. Participants will be discontinued from the study if any of the following occurs:

- The participant withdraws consent;
- The participant fails to comply with the study requirements so as to cause harm to himself/herself or seriously interfere with the validity of the study results and the clinical site principal investigator believes that compliance is unlikely to improve;
- The clinical site principal investigator 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; or
- The clinical site is terminated for significant participant safety concerns, study integrity, poor performance issues, or lack of funding. (Note: If a clinical site closes, participants may be transferred to another site or followed by the HSPH as described in Section 8.3.).

## 8.7 Participant Compensation

Participants will receive compensation valued at $100 for completion of the annual web-based surveys as approved by the HLC IRB. If some of the questions are split out into a separate stand-alone survey, participants will receive compensation valued at $75 for the primary survey and a $25 gift code for the stand-alone survey. In addition, participants will be compensated for each in-person study visit with the amount as indicated in an informed consent addendum to be approved by the HLC IRB. Sites will be encouraged to provide compensation commensurate with the time and effort required by the protocol and as per IRB guidelines.

### 8.8 Incidental Findings

Incidental findings in this observational cohort study will be rare. The principal investigator at each clinical site will be responsible for monitoring incidental findings and handling them according to their respective institution's policies. Incidental findings of medical importance will be shared with the participant, the Protocol Team, and the HLC IRB.

## 9.0 EVALUATION-SPECIFIC MANAGEMENT

### 9.1 Web-Based Surveys

The web-based survey consists of a series of web-based questionnaires. Each questionnaire is focused on a specific topic and begins with an introduction explaining the purpose of the questions. The questionnaires are structured to allow for completion on any device that a participant might use to access the internet, including a cell phone. Questions are not accompanied by sound. Appropriate skip patterns are programmed into the survey, and questions can be skipped by participants if they choose. The web-based survey is available in English and Spanish. Most of the questions are incorporated into a single primary survey, while other questions may be administered separately as a short, stand-alone survey.

**The web-based survey includes the following assessments (all or a subset of which will be administered each year):**

- Socio-demographics (e.g., education, housing, employment, gender identity);
- General health and health care-related questions (e.g., health care and utilization, disability and health, transition to adult health care, health-related behaviors and attitudes, sleep, diet);
- Mental health: including depression, anxiety and PTSD screens, resilience;
- Social determinants of health (e.g., food security, zip code, HIV-related stigma, experiences of discrimination, and recent and early life stressful events);
- Reproductive health (e.g., contraceptive use and attitudes, pregnancy circumstances and intention, sexually transmitted infections);
- Sexual behaviors (e.g., condom use, disclosure of HIV status, PrEP use, sexual orientation);
- Substance use; and
- ARV medication adherence.

The web-based surveys will include information on how and where participants can obtain assistance should they have feelings of anxiety, depression, suicidal ideation, etc. after completing the survey.

### 9.2 Physical Activity Screener

Data on physical activity will be obtained using the web-based version of the Block Physical Activity Screener for adults from NutritionQuest. Physical activity will be assessed in-person at Entry and every 3 years starting at Year 3 (e.g.,Years 3, 6, 9, 12, …).

### 9.3 Neurocognitive Functioning and Mental Health

The NIH Toolbox Cognition Battery and Emotion domain (self-efficacy, perceived social support (emotional and instrumental), friendship, and life satisfaction only) will be administered in-person at Entry and every 3 years starting at Year 3 (e.g., Year 3, 6, 9, 12, …).

The NIH Toolbox was developed for longitudinal epidemiologic studies and prevention or intervention trials to assess cognition, sensation, motor, and emotion domains via streamlined computer-based measures. The NIH Toolbox uses Item Response Theory and Computer Adaptive Testing to provide a brief, low burden assessment with reliability and validity comparable to psychometrically sound, longer assessments. The NIH Toolbox was normed on 4859 participants (aged 3 to 85 years) representative of the U.S. population based on gender, race/ethnicity, and socioeconomic status (2010 census data). The cognitive portion of the NIH Toolbox will be proctored by centrally trained PHACS staff and does not require administration by a psychologist. The subdomains of the Cognitive portion of the NIH Toolbox include: attention, episodic memory, working memory, language, executive function, and processing speed; all these measures are either deemed important in the monitoring of HIV-related neurocognitive functioning in adults or areas of potential risk for individuals with PHIV. Scores yielded include individual measure scores as well as a Cognitive Function Composite Score, Fluid Cognition Composite Score, and Crystallized Cognition Composite Score. Measures of the Emotion domain that will be administered include self-efficacy, perceived social support (emotional and instrumental), friendship, and life satisfaction. The Emotion domain does not need to be proctored.

The Client Diagnostic Questionnaire (CDQ) will be conducted in-person every 3 years starting at Year 3 (e.g., Years 3, 6, 9, 12, …). The CDQ is a psychiatric screening tool designed and validated for populations affected by HIV (Aidala et al., 2004). The CDQ is a structured interview used to identify current symptoms of psychiatric disorder(s), including depression, anxiety, PTSD, and psychosis, as well as alcoholic and nonalcoholic substance abuse. The CDQ will be administered by a trained psychologist. Training will be conducted for the psychologist. The CDQ was used in AMP for caregivers only, and the same procedure for monitoring consistency in administration used in AMP will be used in AMP Up.

The Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder 7-Item Scale (GAD-7) will be administered as an interview at Entry. After Entry, the PHQ-9 and the GAD-7 will be administered through the web-based survey. The PHQ is a self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) diagnostic instrument for common mental disorders. The PHQ-9 is the depression module of the PHQ, and scores each of the 9 DSM-IV criteria as “0” (not at all) to “3” (nearly every day). PHQ-9 scores of 5, 10, 15, and 20 represented mild, moderate, moderately severe, and severe depression, respectively. The PHQ-9 is considered a reliable and valid screening of depression severity. The GAD-7 is a brief, psychometrically sound screener that identifies presence and severity of generalized anxiety disorder symptoms in adults (Spitzer et al., 2006). The Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) is a 5-item screen designed to identify individuals with probable PTSD (Prins et al., 2016).

All neurocognitive and mental health measures are only available in English and Spanish and can only be administered to English-speaking or Spanish-speaking participants. If the participant is monolingual Spanish speaking or bilingual but prefers Spanish, the Spanish language version of the instrument should be used. If the participant is bilingual but expresses no language preference (i.e., they feel equally competent in English and Spanish), the English version of the instrument should be used. The psychologist/examiner who administers the Spanish version of a measure must be fluent in Spanish. If the examiner is not fluent in Spanish, they may not use a Spanish-speaking translator to administer the measure. However, Spanish-speaking staff, such as a Spanish-speaking research assistant or study nurse,

can administer specific questionnaires or interviews that do not require administration by the psychologist.

### 9.4 Language and Hearing Assessments

The CELF-4 is a standardized test to be administered to those participants previously enrolled in AMP and who have completed at least one previous CELF-4 while in AMP. Only those participants in AMP who had at least one CELF completed in AMP will be administered the CELF-4 in AMP Up. The CELF-4 should be administered at the Entry visit for those participants who will be 22 years or older by the time of their Year 3 visit. All others will have the CELF-4 administered at the Year 3 visit. Clinical site staff can obtain a list of PIDs for participants that meet the criteria for CELF administration from the AMP Up CELF-4 Visit Calculator located on the Frontier Science PHACS Portal. The CELF-4 will be administered by centrally trained PHACS staff and does not require administration by a psychologist. Subtests include Recalling Sentences, Formulated Sentences, Word Classes-Receptive, Word Classes-Expressive, and Word Definitions. The assessment incorporates culturally appropriate contexts and visual stimuli. Updated norms are based on a diverse standardization sample of 2,650 participants that reflect the updated 2000 U.S. Census, including children with identified conditions and diagnosed language disorders (Semel et al., 2003). The Core Language and Expressive Language composite scores will be analyzed.

Participants will be screened at the Entry, Year 3, 6, 9, and 12 visits for hearing problems using the WIN hearing test from the NIH Toolbox. WIN measures a person's ability to recognize single words presented amid varying levels of background noise to assess how much difficulty a person might have hearing in a noisy environment. A recorded voice instructs the participant to listen to and then repeat words. The task becomes increasingly difficult as the background noise gets louder. See Section 9.3 for more information about the NIH Toolbox.

### 9.5 Blood Pressure

Systolic and diastolic blood pressure will be performed and recorded two times at each in-person visit using an appropriately-sized cuff. If the results differ by more than 5 mm Hg, a third reading should be obtained and all readings recorded.

### 9.6 Blood Tests

Refer to the schedule of evaluations in Appendices I and II for laboratory tests to be performed as part of this study.

The type of tube/anticoagulant for specific tests is critically important and testing specifications can be found in the AMP Up Laboratory Processing Chart (LPC).

See Section 9.8 and Appendix III for specimen collection specifications for repository specimens.

### 9.7 Fasting

Fasting is required for some specimens, 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.

### 9.8 Central Testing and Repository Specimens

Site personnel will be responsible for ensuring that the specimens for testing at the Central Laboratory and for storage in the PHACS Repository are appropriately collected and processed for storage.

- In the case of fasting serum and fasting plasma specimens, the serum and plasma must be separated within 24 hours of the draw. Blood for viable PBMCs/plasma should be collected and processed as soon as possible.
- For female participants, a vaginal swab will be self-collected by the participant for research Aptima STI testing at the Central Laboratory and two additional swabs will be collected for long-term storage at the PHACS Repository.
- About 20 ml of clean-catch urine will be collected after the first void of the day and processed and stored at the local lab until shipping to the PHACS Repository. The urine will be split into one 10-ml aliquot and two 5-ml aliquots for research Aptima STI testing, renal biomarker testing, and storage in the PHACS Repository, respectively.
- Unstimulated saliva (about 3 ml) will be collected using a sterile container and stored at the local lab until shipping to the PHACS Repository.
- About 10 ml but no less than 5 ml of throat wash/gargle will be collected, processed, and stored at the local lab until shipping to the PHACS Repository.

Shipping of repository specimens will occur on a regularly scheduled basis. See Appendix III of this protocol and the AMP Up LPC for detailed repository specimen collection and processing specifications.

### 9.9 STI Testing and Reproductive Health

Real-time screening for STIs (*N. gonorrhoeae*, *C. trachomatis*, *and T. vaginalis*) will be done annually for participants with neither *N. gonorrhoeae* nor *C. trachomatis* testing results available in the medical records from the 12 months prior to the visit. Results for both tests must be available in the record in order for the site to forego real-time STI testing. Self-collected urine for males and a self-collected vaginal swab for females will be tested for *N. gonorrhoeae*, *C. trachomatis*, and *T. vaginalis* at a local clinical lab and results made available to the site. It is preferred that testing be done on a vaginal swab for females because the swab is more sensitive than urine for the detection for cervical *N. gonorrhoeae*, *C. trachomatis*. However, if a female participant does not agree to vaginal swabs, urine should be collected. Participants will be instructed at the Entry visit by clinical site staff on the correct technique for specimen self-collection. The vaginal swab will be collected blindly and should not be inserted beyond the cervical os. When collection is required during years without in-person visits (e.g., Years 1, 2, 4, 5, 7, 8, 10, 11, 13, 14…), sites will provide participants with collection kits, instructions for collection and return of the sample to the clinical site, and a contact number in case of questions. The collection kit used will be determined by the testing requirements of the local laboratory. Collection kits will be provided discreetly, with no study name or description included on the packaging in order to protect the participant's confidentiality. If self-collection takes place at home, the specimen will be delivered or mailed by the participant to the clinical site, with the mode of delivery based on the requirements of the assay used by

the local laboratory. Most labs "test" for *T. vaginalis* in female participants by microscopic examination of a wet mount of vaginal secretions. Diagnosis of trichomoniasis in male participants is generally performed only when symptomatic by microscopic examination of urine. If the lab does not perform a specific test for *T. vaginalis*, wet mounts of vaginal secretions or urine are adequate. If real-time testing for *T. vaginalis* is not available or cannot be done for a participant, it should be considered missed and the reason it was not done should be documented in the participant's research record.

Research Aptima STI research testing will also be conducted annually. Urine for males and a vaginal swab (preferred), or urine if swab is declined for females, will be self-collected by the participant at the clinic or at home and delivered to the clinical site. Similar to the real-time testing described above, it is preferred that testing be done on a vaginal swab for females. However, if a female participant does not consent to vaginal swabs, urine should be collected. The clinical site will then ship the samples to the PHACS Repository, where they will subsequently be forwarded in batches to the Central Laboratory for research Aptima STI testing for *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis*, and HPV (on vaginal swabs only). Clinical sites will be provided with the collection kits and shipping materials so the samples can be collected appropriately and delivered to the clinical site if the sample is self-collected at home. The Central Laboratory may not be a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, so these results are for research purposes only. As stipulated in the consent, sites will be informed of positive results so that the participant can have repeat testing performed in a CLIA-certified or similarly approved clinical laboratory.

When the results of screening tests or examinations are ascertained through medical record review (urine, swab, genital visual exam, speculum aided exam, or blood), a copy of cervical cytology/histology and/or STI testing results will be obtained. If the participant has an abnormal cytology and is referred to colposcopy, a record of the histology results will also be obtained. It is expected that the diagnoses of atypical squamous cells of undetermined significance (ASCUS), LSIL, or HSIL will be made according to the Bethesda system for cervical cytological diagnosis by a laboratory at the location institution that is accredited by the Colleges of American Pathology.

The type of STI test (swab, urine, blood) and the date and result of the test (positive or negative) obtained from medical charts will be recorded. The results of clinical examinations done as part of routine care will be abstracted for AMP Up annually.

Participants in the YAPHEU cohort will be offered HIV testing at the Years 3 and 9 visits.

## 10.0 ADVERSE EVENT REPORTING

This study is not a therapeutic study and no medications are being prescribed as part of this study. Participants enrolled in this study may develop common conditions requiring treatment during the course of the study period. Study personnel will assist the participants in receiving appropriate care as appropriate to their roles at their sites. The participants may also experience adverse events associated with HIV infection, ART exposure, or other medications. Clinical site principal investigators are encouraged to use the FDA's MedWatch system to report any events possibly associated with medications clinically prescribed for the participant. No adverse events associated with involvement in the study are anticipated.

## 11.0 STUDY IMPACT AND SAFETY MONITORING

Monitoring the full impact of research studies includes evaluating the impact of the study on the welfare of three groups of people:

- Research participants;
- Research staff; and
- 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 examination of study procedures, as necessary, to address concerns about participant management, recruitment, enrollment, adequacy of training, and/or 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 staff qualified to address situations if a participant becomes distressed. In addition, PHACS has developed standard operating procedures for sites to follow in these circumstances (available on the PHACS website at https://my.phacsstudy.org).

### 11.1 Reporting Requirements

All more than minimal 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 clinical site through the QNS. Reportable events could involve study participants and/or staff members.

Examples of more than minimal 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 or uncovered during interview or sessions (e.g., current suicidal or homicidal ideation, physical or sexual abuse, depression);
- Significant visible distress or injury resulting from the research encounter (e.g., responding to questions/surveys about exposure to violence, abuse, etc. may provoke emotional responses/distress and may require involvement of clinical staff to provide support/guidance to the participant); and
- Breach of confidentiality.

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 site to ensure that the site's local IRB is notified of the event, as required.

Note: The distinguishing feature of more than minimal impact events is the need for enlisting additional support outside the research staff and the research encounter. The web-based surveys will include information on how and where participants can obtain assistance should they have feelings of anxiety, depression, suicidal ideation, etc. after completing the survey.

### 11.1.1 State Mandated Reporting Requirements

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

## 11.2 Monitoring Plan

NICHD has determined that a formal Data and Safety Monitoring Board will not be established; the NIH PHACS Management Oversight Committee (PMOC) will act as the oversight body for the study. The PMOC is comprised of program officials from NICHD, each co-funding NIH institute, and the NIH Office of AIDS Research (OAR).

# 12.0 ANALYTIC CONSIDERATIONS

The AMP study design initially included a PHIV cohort of 451 participants and a comparison cohort of 227 PHEU participants. Over the course of the AMP study, some youth were lost to follow-up, died, moved, or were otherwise unable to be continued in follow-up. Thus, the target sample size for the current AMP Up protocol has been expanded to targets of 650 YAPHIV and 200 YAPHEU enrolled at age 18 or older. The YAPHEU comparison cohort is expected to consist mostly of young adults exposed to ARVs *in utero*, but young adults unexposed to ARVs will not be excluded, just as they are not excluded from the YAPHIV group. Ideally, the comparison cohort will come from the same population as the YAPHIV group for comparability on many non-HIV measures that also influence outcomes of interest. Prenatal ART exposures in both groups will exhibit a time-confounding effect because of changes in clinical practice which cannot be controlled.

Evaluation of several stated study hypotheses will involve comparison of the distributions of outcomes between YAPHIV and YAPHEU. These comparisons will allow us to assess whether the outcomes are different between YAPHIV and YAPHEU. For some hypotheses, for example growth, neurocognitive measures, and HPV prevalence, the YAPHEU cohort will provide a comparison group from a similar socioeconomic background and home environment. However, there is little ability to separate out the effects of HIV infection from postnatal ART exposure due to the study design. It should be noted that many of our primary hypotheses for evaluating the impact of ART regimens on outcomes in this study will be evaluated by comparing assessments across subgroups of YAPHIV; these analyses will not include the YAPHEU cohort.

Since all participants previously enrolled in AMP Up from AMP are expected (when available) to have previous data collected from Women and Infants Transmission Study (WITS), Pediatric AIDS Clinical Trial Group (PACTG) 219C or a comparable cohort providing detailed ART exposure information, most of the statistical analyses described below will use the existing historical data from these studies in evaluating the hypotheses of this study. New AMP Up young adults who enroll but were not previously in AMP will have information on ART exposure abstracted from past data or completed by sites as necessary.

## 12.1 Power and Sample Size Consideration

In the context of this study, many targeted outcomes, some continuous (e.g., BMI, and height and weight z-scores) and some binary (insulin sensitivity, and neurodevelopmental impairment) will be measured.

For relatively rare events, the calculations for binary outcomes can serve as good approximations for survival outcomes, and for more common outcomes they often serve as an upper bound (i.e., a survival analysis would have greater power than comparison of proportions of events at a fixed time). All of the following calculations were conducted using PASS 15.0.4 (NCSS, 2017).

### 12.1.1 Comparisons between YAPHIV and YAPHEU

For continuous outcomes, the sample size of 650 YAPHIV vs. 200 YAPHEU provides 80% power to detect a difference in means of 0.227 standard deviations based on a 2-sample t-test (assuming normality holds), and 0.240 based on a non-parametric Wilcoxon rank sum test (for skewed outcomes) at alpha = 0.05. For example, if the full-scale IQ scores of YAPHIV is compared with YAPHEU and a standard deviation of 15 points is assumed, a difference of 3.40 points or more in the mean IQs could be detected. Assuming loss to follow-up and/or incomplete/missing assessments of 4% per year for infected and 6% per year for uninfected participants at two years after enrollment into AMP Up is completed, then an adjusted sample size of 415 YAPHIV vs. 101 YAPHEU provides 80% power to detect a difference of 0.311 standard deviations, or 4.67 points in mean IQ scores. Once adjusted for potential confounders, some power will typically be lost so the minimum detectable difference will usually increase.

For binary outcomes, the table below shows the minimum difference that can be detected in proportions in terms of the Odds Ratio (OR) based on comparing YAPHIV vs. YAPHEU, at 80% power with a 0.05 significance level. For this type of outcome, the detectable differences depend on the underlying rate of the event in the comparison cohort. For simplicity here, it is assumed that the event rate is higher in the YAPHIV cohort than the YAPHEU cohort.

**Table 12.1. Minimum detectable ORs between YAPHIV and YAPHEU at 80% power and a 0.05 significance level for various event rates in the comparison cohort**

| Sample Size for YAPHIV Cohort | Sample Size for YAPHEU Cohort | Event rate in YAPHEU Cohort | Minimum Detectable OR | Detectable Rate in YAPHIV Cohort |
|---|---|---|---|---|
| 650 | 200 | 4% | 2.92 | 10.8% |
| | | 5% | 2.64 | 12.2% |
| | | 10% | 2.05 | 18.6% |
| | | 20% | 1.73 | 30.2% |
| | | 30% | 1.63 | 41.0% |
| | | | | |
| 415 | 101 | 4% | 4.36 | 15.4% |
| | | 5% | 3.79 | 16.6% |
| | | 10% | 2.68 | 22.9% |
| | | 20% | 2.13 | 34.7% |
| | | 30% | 1.95 | 45.5% |

### 12.1.2 Comparisons within YAPHIV

For the second type of comparison, subgroups of the YAPHIV will be examined. For example, comparisons can be made between those YAPHIV who initiated ART before age 5 vs. those who initiated ART at a later age. The table below summarizes the detectable differences in means relative to the standard deviation that can be detected assuming 650 YAPHIV or 415 participants (under an assumption of 4% loss per year) when two subgroups of the YAPHIV are being compared.

**Table 12.2. Detectable differences in means (relative to SD) between subgroups of YAPHIV**

| Comparison Between Group 1 and Group 2, with indicated percentage in each group | | Detectable Differences in Means (Relative to SD) | |
|---|---|---|---|
| Group 1 | Group 2 | N = 650 | N = 415 |
| 50% | 50% | 0.220 | 0.276 |
| 40% | 60% | 0.224 | 0.281 |
| 30% | 70% | 0.240 | 0.301 |
| 20% | 80% | 0.275 | 0.345 |
| 10% | 90% | 0.366 | 0.462 |

Similarly, proportions with events between two subgroups of YAPHIV could be compared; for example, defined by prior receipt of cART with PI vs. cART without PI, or use of a specific ARV drug vs. unexposed to that drug. The following table provides the minimum detectable differences in terms of ORs.

**Table 12.3. Detectable differences in ORs based on logistic regression models comparing two subgroups of YAPHIV with N = 650 participants or N = 415**

| Percent in Each group | | Event Rate in Group 2 | OR for Given Sample Size | |
|---|---|---|---|---|
| Group 1 | Group 2 | | N = 650 | N = 415 |
| 50% | 50% | 4% | 2.59 | 3.20 |
| | | 5% | 2.38 | 2.89 |
| | | 10% | 1.93 | 2.25 |
| | | 20% | 1.68 | 1.90 |
| | | 40% | 1.56 | 1.75 |
| | | | | |
| 40% | 60% | 4% | 2.73 | 3.43 |
| | | 5% | 2.49 | 3.07 |
| | | 10% | 1.99 | 2.33 |
| | | 20% | 1.71 | 1.94 |
| | | 40% | 1.58 | 1.77 |
| | | | | |
| 30% | 70% | 4% | 3.02 | 3.92 |
| | | 5% | 2.73 | 3.45 |
| | | 10% | 2.11 | 2.53 |
| | | 20% | 1.78 | 2.05 |
| | | 40% | 1.63 | 1.84 |
| | | | | |
| 20% | 80% | 4% | 3.69 | 5.06 |
| | | 5% | 3.25 | 4.33 |
| | | 10% | 2.39 | 2.96 |
| | | 20% | 1.95 | 2.30 |
| | | 40% | 1.75 | 2.02 |

In evaluating both continuous outcomes and binary outcomes, greater power will be attained in longitudinal analyses of repeated measures over time.

### 12.1.3 Evaluating Interactions between HIV Status and Other Factors

Much scientific interest may be directed at whether relationships between specific measures and AMP Up outcomes differ between YAPHIV and YAPHEU. While the sample size for this study provides high power for detecting differences between YAPHIV and YAPHEU with respect to continuous outcomes and more common binary outcomes, the study will have only limited power to address potential interactions between HIV status and other outcomes. For example, if the interest is to evaluate whether the relationship between low vitamin D levels and height z-score differed between YAPHIV and YAPHEU, there would be relatively low power and such analyses would be primarily descriptive. Power calculations for detecting multiplicative interaction effects based on several combinations of underlying assumptions and magnitudes of interaction effects are shown below, determined via simulation with 5000 datasets simulated, each with the sample size indicated. These simulation studies present best case scenarios in that the outcomes are assumed to be continuous and normally distributed. The table below suggests that power could be adequate for detecting interactions if the sample size of young adults is achieved and the interaction effect is twice as large as either of the main effects. It is likely that power for binary outcomes would be substantially lower.

**Table 12.4. Power for Detecting Interactions between a Specific Factor (such as low vitamin D) and HIV Status on a Hypothetical Continuous Outcome (such as height Z-score)**

| Sample Sizes (PHIV and PHEU) | Pr (low vitamin D in PHEU) | OR for low vitamin D in PHIV vs. PHEU | Main effect of low vitamin D on height (shift in z-score) | Main effect of HIV status on height (shift in z-score) | Interaction effect of both low vitamin D and PHIV on height (shift in z-score after main effects) | Empirical Power |
|---|---|---|---|---|---|---|
| 650, 200 | 0.30 | 1.5 (p = 0.39) | 0.25 | 0.25 | 0.25 | 29.6% |
| | | | | | 0.40 | 63.4% |
| | | | | | 0.50 | 82.6% |
| 415, 101 | 0.30 | 1.5 (p = 0.39) | 0.25 | 0.25 | 0.25 | 18.4% |
| | | | | | 0.40 | 38.3% |
| | | | | | 0.50 | 55.1% |

## 12.2 Domain-Specific Statistical and Analytic Considerations

### 12.2.1 Infectious and Non-Infectious Complications of HIV and Its Treatment

Immunologic and virologic trajectories among YAPHIV will be described with locally estimated scatterplot smoothing (LOESS) plots over time (i.e., age) or explored with group-based trajectory models. Factors associated with CD4 and viral load trajectories will be identified using repeated measures generalized estimating equation (GEE) models, mixed effects models, or multinomial regression models as appropriate. Factors of interest for these outcomes include immune activation, changes in ART, cumulative exposure to specific ART, viral resistance, co-infections, and host genetic polymorphisms. Analyses of samples from the PHACS Repository will be required to measure markers of immune activation. Changes in ART will be assessed by first defining what constitutes a switch in ART regimen (i.e., what ARV drug changes constitute an ART switch). Cumulative duration of a specific ART will be

calculated by summing the time intervals exposed. Viral resistance will be calculated using the Stanford HIV Reverse Transcriptase and Protease Sequence Database which contains drug susceptibility data for selected mutations (Liu & Shafer, 2006; Shafer, 2006). The presence of co-infections such as CMV and EBV will be assessed by testing samples from the PHACS Repository prior to the events of interest. Past infection with SARS-CoV-2 will be ascertained from clinical chart review or measurement of antibodies from stored samples. Host genetic polymorphisms of interest will be identified using the established PHACS repository of amplified genomic DNA. Effect modification between host genetic polymorphisms and ART will be assessed as appropriate and feasible based on power issues noted above, based on a priori hypotheses.

Access to testing for SARS-CoV-2, access to and acceptance of prevention strategies for SARS-CoV-2, and acceptance of testing, treatment, and prevention strategies for other important infections will be assessed through participant report on web-based survey. Factors specifically associated with SARS-CoV-2 vaccine hesitancy and uptake among participants with PHIV and PHEU will include sociodemographic and socioeconomic characteristics, prior receipt of vaccines (influenza, HPV, MMR, etc.), participation in interventional clinical trials, reported trust in health care, knowledge/misinformation regarding SARS-CoV-2 infection, and HIV disease status including cumulative CD4 and viral load (for participants with HIV only).

Incidence of end-organ disease will be estimated under a Poisson distribution based on person-years of follow-up at risk. Factors associated with incidence of end-organ disease will be identified using Cox-proportional hazards models and will include HIV virologic status, ART, immune impairment, and chronic immune activation. The PHACS Repository will be the primary longitudinal resource to contribute to HIV remission/cure studies aimed to understand the viral dynamics and compartmentalization perinatal HIV infection.

Oral health will be examined by dental disease, periodontal diseases, and mucosal diseases. Dental disease is measured by the number of decayed, filled, and missing tooth surfaces due to dental caries (decayed, missing, and filled surfaces (DMFS)). The distribution of DMFS is right skewed and tends to have higher proportion of zeros than in a Poisson or negative binomial distribution, therefore the zero-inflated counterparts will be applied to model the prevalence. Progression in dental disease will be studied using the difference in DMFS scores. Periodontal diseases are measured by different parameters examined on multiple tooth sites, such as bleeding on probing (Yes/No) or clinical attachment loss (in millimeter); the latter is a measure of bone loss. Well-defined worsening (Yes/No) of a given parameter will be analyzed using GEE models with a logistic link function, considering the multi-layer clustering of site within tooth and tooth within participant. Mucosal diseases were very rare in our participants at the baseline visit. Cumulative incidence of a particular mucosal disease from baseline to the follow-up visit will be calculated and the relative risk between YAPHIV and YAPHEU can be estimated using a Poisson regression model. In addition to HIV infection status, inflammation level and oral microbiome signature at baseline are the exposures of interest for specific aims regarding periodontal diseases. Access to oral health care, hygienic behavior and diet are factors associated with all oral health outcomes and could be potential confounders in the association between HIV infection status and oral health.

### 12.2.2 Metabolic Complications

For metabolic complications, the interest is in estimating the prevalence and incidence of insulin sensitivity, dyslipidemia, hypertension, fat redistribution, obesity, and cardiometabolic risk (McMahan et al., 2005) as well as evaluating the association of HIV disease status and specific ART regimens with these outcomes. PHACS does not have longitudinal measures of lipids and homeostatic model assessment of insulin resistance (HOMA-IR) in AMP Up YAPHEU. Thus, incidence of insulin sensitivity,

dyslipidemia, and cardiometabolic risk will not be determined in this group. Additionally, the trajectories of blood pressure, and body composition over time between YAPHIV and YAPHEU and HOMA-IR and lipids will be compared, by ART regimens among YAPHIV.

Insulin sensitivity, dyslipidemia, hypertension, and obesity as binary outcomes

Prevalence: Insulin sensitivity, impaired fasting glucose (American Diabetes Association, 2020), and dyslipidemia (considering each of fasting total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides separately), hypertension (Flynn et al., 2017), and obesity will be considered as binary variables. HOMA-IR values will be calculated from fasting insulin and glucose and categorized by insulin resistance (Matthews et al., 1985). BMI above 30 $kg/m^2$ will be classified as obese.

For specific metabolic risk factors that can be calculated in YAPHEU (e.g., obesity, hypertension), the prevalence of each binary metabolic risk factor at each AMP Up visit among YAPHIV and compare them to YAPHEU will be estimated. Prevalence will be calculated as the number of participants with the specific outcome at that visit, divided by the total number of participants who are tested and have a measure for each outcome at that visit. The 95% confidence intervals (CIs) for each prevalence estimate will be calculated.

The association of each metabolic outcome with specific ART regimens (particularly INSTIs, PIs, and NRTIs, which have been implicated in various metabolic disorders) in YAPHIV will be evaluated by comparing the prevalence across ART regimens using chi-square tests. The association between each exposure and the prevalence of each metabolic risk factor will also be estimated using log binomial regression. These will be adjusted for confounders based on the literature and through construction of directed acyclic graphs (DAGs). These may include race, sex assigned at birth, gender identity, age, CD4 cell count, viral load, physical activity, diet, and BMI (except for body composition outcomes).

Incidence: The incidence rate of all the binary metabolic outcomes in YAPHIV incidence of hypertension and obesity in YAPHEU will be estimated. The incidence rate will be calculated by dividing the number of participants with new onset of each metabolic risk factor by the total person-time contributed by children initially free of the risk factor at baseline (or first measurement). The 95% CI for these incidence rates will be calculated using the Poisson distribution.

Among participants who are YAPHIV, the association between specific ART regimens and HIV disease severity (as measured by viral load) and incidence of the above metabolic risk factors will be estimated. The association of BMI and body composition at baseline with all outcomes (except obesity) in the YAPHIV and with hypertension in YAPHEU will be evaluated. The incidence of each outcome (with the possible exception of hypertension) is expected to be fairly common, so Cox proportional hazards models for the time to development of each risk factor will be used to estimate hazard ratios and their associated 95% CIs, adjusting for other risk factors for the outcome, by HIV status or by ART regimen (in the YAPHIV). These analyses will be adjusted for confounding. For metabolic risk factors that are observed to occur less frequently, Poisson regression models may be used to compare incidence rates.

Systolic and diastolic blood pressure, lipid levels, body composition, and cardiometabolic risk measures as continuous outcomes

Systolic and diastolic blood pressure, lipid levels (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), HOMA-IR, and cardiometabolic risk (as measured by PDAY scores) will be considered as continuous outcomes. The body composition measures (waist, mid-upper arm and hip

circumferences, and triceps, biceps, suprailiac, and subscapular skinfolds), and sum of skinfolds will be considered only as continuous outcomes. BMI will be evaluated as a binary or continuous variable.

For cross-sectional data, outcomes in YAPHIV and YAPHEU will be compared using generalized estimating equations for a continuous outcome with the robust variance estimator. Potential confounders that may be included in the models of blood pressure and lipids are BMI, sex, race, physical activity, tobacco use, and diet. Models of body composition may include all of these, but not BMI. Models of cardiometabolic risk (PDAY scores) will include age and sex. The association of each class and type of ART for each outcome in models restricted to YAPHIV will be investigated.

To examine the effect of exposures that vary over time, such as ART regimens (in YAPHIV) or body composition, mixed effects models will be used, which will account for the correlations between these repeated measures. The change over time in waist and mid-upper arm circumferences, waist-to-height ratio, triceps, biceps, suprailiac, and subscapular skinfolds, and BMI will be compared by HIV status.

To examine trajectories of the continuous outcomes between YAPHIV and YAPHEU or within YAPHIV by HIV-associated exposures such ART regimens or CD4 count, mixed effect models will be fit, adjusting for potential confounders.

The food security score will be calculated and YAPHIV and YAPHEU will be categorized into levels of food security. The association of sociodemographic factors and dietary factors with food security level will be examined using chi-square or Wilcoxon tests. In longitudinal analysis, the effect of low food security on change in BMI, lipid concentration and HOMA-IR and on adherence to ART will be evaluated. Mediation analysis will be used to examine whether an association of food security with adherence is mediated through engagement in clinical care.

### 12.2.3 Cardiopulmonary Complications

Current modified PDAY scores for AMP Up participants will be calculated using measured values of HDL cholesterol, non-HDL cholesterol, smoking status, blood pressure, obesity status (BMI > 30 kg/m$^2$), and hyperglycemia status (defined as fasting plasma glucose ≥ 126 mg/dl, or a diagnosis of diabetes or report of diabetes medication). Both the coronary artery score and the abdominal aorta score will be calculated as described previously to reflect risk of atherosclerotic lesions in the coronary artery and abdominal aorta, respectively. The “modified” PDAY scores incorporate only those risk factors which are considered modifiable (e.g., exclude sex, age, and race), although the non-modifiable factors may also be strong predictors of CVD risk. All AMP Up participants with available measurements of these risk factors will be included (e.g., not restricted to the PHACS Cardiac Toxicity Substudy participants). The distribution of modified PDAY risk scores will be compared by HIV status using a Wilcoxon rank sum test. Depending on observed distributions of coronary artery and abdominal aorta scores, the outcomes may be dichotomized as higher vs. lower scores, and then compared as estimated probabilities of higher score using logistic regression models adjusted for age. The association of PDAY scores with neurocognitive function measures from the NIH Toolbox will be evaluated using GEE approaches to improve robustness, with the risk scores as the predictors and the neurocognitive outcomes as the response. If sufficient numbers of AMP Up participants have repeated measurements of cholesterol, other risk factors, and neurocognitive assessments, linear mixed models will be fit for the repeated neurocognitive outcomes as a function of current and past PDAY scores. Because not all AMP Up participants may have cholesterol and other risk factors, as well as neurocognitive measures available, inverse probability weighting approaches will be employed to account for potential selection bias. The association of cardiac and inflammatory biomarkers with neurocognitive function will be restricted to those in the Cardiac Toxicity Substudy who have these measurements obtained during AMP Up (target

120 YAPHIV, 80 YAPHEU); GEE models will be used to evaluate the associations with neurocognitive outcomes from the NIH Toolbox overall and by HIV status, adjusting for age, sex, and other potential confounders.

### 12.2.4 Sexually Transmitted Infections

Incidence of STIs, vaginal microbiota, LSIL, and HSIL, as well as the rate of regression of LSIL to normal cervical cytology, will be estimated under a Poisson distribution based on participant-years of follow-up. Only female participants with a first Pap smear indicative of normal cervical cytology and at least one subsequent Pap smear examination will be included when calculating incidence rates of LSIL and HSIL. If there are too few participants with incident LSIL or HSIL to accurately estimate the rate of regression, descriptive case data will be reported.

The incidence of each outcome will be compared between the YAPHIV and the YAPHEU comparison group using Poisson regression models. Factors associated with incidence of each outcome will be identified using Cox proportion hazards models and will adjust for important potential confounders including: CD4 count or %, viral load, ART use, CDC disease classification, contraceptive use, number of sexual partners, and smoking (for LSIL and HSIL).

### 12.2.5 Reproductive Health

The analysis of reproductive health outcomes will focus on estimating the prevalence and incidence of pregnancies (intended and unintended); pregnancy outcomes (live birth, induced abortion, spontaneous abortion, fetal death); the prevalence and incidence of menstrual irregularities; and the incidence of perinatal HIV transmission.

We will calculate prevalence estimates based on those with the specific outcome of interest divided by those with measurements for that outcome, along with 95% CIs. Incidence estimates will be calculated under a Poisson distribution based on participant-years of follow-up.

The prevalence of each outcome will be compared between the YAPHIV and the YAPHEU comparison group using chi-square tests as crude analyses and using logistic regression models for each separate outcome as a function of HIV status controlling for important demographic, and clinical and social factors (including but not limited to socioeconomic factors, partner characteristics, viral load, adherence, depression, and other behaviors).

Factors associated with prevalence of each outcome will be identified using logistic regression models. Factors associated with the incidence of each outcome will be identified using Cox-proportional hazards models. Factors associated with changes in reproductive health measures over time will be identified using GEE models, or mixed effect models when possible, to account for correlation between assessments on the same participant.

### 12.2.6 Neurocognitive Functioning and Mental Health

The analysis of cognitive and mental health outcomes will focus on the trajectories of cognitive functioning and mental health, and the trajectories of co-occurring risks in cognitive, mental health and behavioral health. Cognitive outcomes (executive functioning, processing speed, episodic and working memory, attention, etc.) will be evaluated both as continuous and binary measures. Mental health outcomes (depression, PTSD, and anxiety) and behavioral health outcomes will be evaluated as binary measures. Group-based trajectory and multi-trajectory models will be used to identify trajectories of

single and co-occurring outcomes. Factors to be evaluated for their association with single and co-occurring trajectories will include PHIV status, individual, interpersonal, systemic and structural influences experienced during childhood and adolescence, including adverse childhood experiences (e.g., exposure to violence, neglect, etc.) and young adulthood experiences (e.g., racism, low levels of social support, etc.), as well as historical [from AMP] information on caregiver cognition, education, etc.).

### 12.2.7 Health Care Behaviors and Transition to Adult Health Care

To address the specific aims and hypotheses regarding adherence and health care, the proportion with suboptimal ART adherence (e.g., last missed taking their ARV medication in the past seven days), and the proportion with a gap in ARV use, at entry and follow-up among YAPHIV who provide information on ARV use will be calculated with 95% CIs. Logistic regression methods will be used to identify and evaluate factors associated with nonadherence to ART and nonadherence to health care. For analyses of changes in adherence over time GEEs will be used. Factors associated with transition to adult health care and clinical outcomes (including changes in CD4 cell count and viral load) will be identified using logistic and linear regression models. Factors of interest for these outcomes include a site- or participant-specific transition plan, social support, psychosocial resources, stressful life events, and neurocognitive functioning. The trajectories of cognitive, mental health and behavioral health during adolescence among AMP Up participants previously followed in AMP with group-based trajectory models will be described.

### 12.2.8 Risk and Protective Behaviors

The analysis of behaviors will focus on estimating the prevalence at study entry and over follow-up of vaginal and anal sexual intercourse, condomless vaginal or anal intercourse, multiple sexual partners, substance use, recreational and medical marijuana use, and tobacco and alcohol use. The frequency of disclosure of HIV status to sexual partners, and of serosorting (asking about partner's HIV status) will also be evaluated. Prevalence estimates based on those with the specific outcome of interest divided by those with measurements for that outcome along with 95% CIs will be calculated. Incidence estimates will be calculated under a Poisson distribution based on participant-years of follow-up.

The prevalence of behaviors will be compared between the YAPHIV and the YAPHEU comparison group using chi-square tests as crude analyses and using logistic regression models for each separate outcome as a function of HIV status controlling for important demographic, clinical, and social factors (socioeconomic factors, partner characteristics, viral load, adherence, and perceived social support).

Factors associated with prevalence of risk factors will be identified using logistic regression models. Factors associated with the incidence of risk behaviors including condomless vaginal or anal intercourse and substance use will be identified using Cox-proportional hazards models. Factors associated with changes in risk behaviors over time will be identified using GEE models.

### 12.2.9 Transition to Adult Functioning and QoL

We will estimate the prevalence of successful transition to adult functioning (including educational attainment, employment, and independent living), health-related QoL [SF-20], HIV-related stigma, mental health [CDQ, PHQ-9, and GAD-7], PTSD [Primary Care PTSD Screen for DMS-V], self-efficacy, life satisfaction, and friendship [from NIH Toolbox emotion domain] at each follow-up visit. Prevalence of milestones associated with successful adult function (including employment, educational attainment [e.g., high school diploma or general educational development (GED), enrollment in college or certificate program], independent living) will be calculated as the number of participants with each specific outcome at each visit, divided by the total number of participants who have a measure for each outcome at that

visit. The number and proportion of young adults who have met most or all of these milestones by specific ages will be estimated. The proportion of participants with psychiatric disorders and with depression (PHQ-9), anxiety (GAD-7), and PTSD will also be estimated. The 95% CIs for each prevalence estimate will be calculated. The median (interquartile range) and mean (standard deviation) scores for health-related QoL (SF-20), HIV-related stigma, self-efficacy, life satisfaction, and friendship will be calculated.

We will compare successful transition to adult functioning and QoL by perinatal HIV status and other factors using chi-square tests and Wilcoxon rank sum tests as appropriate. Factors associated with successful transition to adult function and with QoL will be further examined with univariable and multivariable logistic and linear regression models.

### 12.2.10 Hearing and Language

Hearing Assessments

Hearing will be assessed by WIN assessment from the NIH Toolbox. The WIN outcome will be presented as the lowest signal-to-noise ratio (SNR) where at least 50% of words are correctly identified. The SNR from WIN will be summarized at the in-person visits by HIV status and compared to the normative population. The mean or median WIN SNR will also be compared between the PHIV and YAPHEU cohort using a Wilcoxon rank sum test. The association of HIV infection with WIN SNR will be further examined, both unadjusted and adjusted for possible confounders such as age, gender, aural history, upper respiratory issues, and/or recent exposure to loud noise, using generalized linear models. The changes in SNR over visits and a comparison of the changes between YAPHIV and YAPHEU cohorts will be summarized by descriptive statistics and explored by GEE models if appropriate. When sufficient literature support is available, SNR may be categorized to describe the severity of hearing loss.

WIN SNR will be used as a predictor for impairment in educational attainment and language, psychosocial, and cognitive functions. Depending on the data type of the variable of interest, logistic regression or multinomial regression models for categorical outcomes, and linear models or generalized linear models for continuous outcomes will be utilized to explore the effect of a hearing problem on language, psychosocial, education and cognitive outcomes separately. Effect modification by HIV status will be evaluated by including an interaction term between HIV status and WIN SNR. Successful transition to adult care will be a particular outcome of interest.

Another hearing assessment, the Hearing Threshold Test, may become available later during the conduct of this study. When and if it does, pure-tone thresholds will also be collected and analyzed. Hearing loss can be defined using the pure tone thresholds in various ways. First, pure-tone thresholds across the frequencies measured in the Hearing Threshold Test will be analyzed as continuous data. Second, three calculations of pure-tone average (PTA) will be completed. A low-frequency PTA will be the average of thresholds at 500, 1000, and 2000 Hz; a high-frequency PTA will be the average of thresholds at 4000, 6000, and 8000 Hz; and a clinical PTA will be the average of 500, 1000, 2000, and 4000 Hz will be determined. The clinical PTA will allow for these data to be compared to hearing data in the earlier AMP protocol. A participant with a PTA greater than 20 dB will be defined as having a hearing loss. The pure-tone thresholds of each frequency will then be summarized and compared by HIV status and to the normative population. Association between PTA and WIN SNR will be explored by Pearson or Spearman's rank correlation, and WIN SNR will also be summarized by hearing loss status. The prevalence of hearing loss by each definition will be estimated at each time point. The odds ratio for hearing loss between cohorts will be estimated adjusting for possible confounders. Any changes in hearing loss status over time will also be explored. Hearing loss defined using the clinical PTA will also

be used as a predictor for impairment in educational attainment and language, psychosocial, and cognitive functions.

Language Development

Language development will be assessed on the CELF-4. This test is normed through age 21 years and 11 months, generating standard scores benchmarked to age. The CELF-4 will be administered to participants through 21 years of age (See Section 9.4 for administration details).

Language impairment will be defined as one standard deviation or more below the reference mean, and severe language impairment as two standard deviations below the reference mean. Relevant aggregated scores may be developed for grammar (Recalling Sentences and Formulated Sentences) and vocabulary (Word Classes – Receptive, Word Classes – Expressive and Word Definitions) separately. The prevalence of language impairment will be estimated by HIV infection status, and compared between YAPHIV and YAPHEU, and to the normative population (16% by definition). Individual variation in language development in the full available age range, 5-30 years, is validly measured by raw score performance on the Recalling Sentences and Formulated Sentences subtests administered throughout this age range; in addition, Word Classes Receptive and Word Classes Expressive for ages 9-30, and Word Definitions for the full age range. Summative raw scores per subtest are also available. In addition, item level data needed for these five subtests for the development of trait-level scores will be collected for investigation of changes over time.

Using the CELF-4 test results, risk for language impairment relative to age expectations as a binary outcome will be examined, and predictors of language impairment will be examined using logistic regression models comparing YAPHIV to YAPHEU, adjusting for potential confounders. Within YAPHIV, linear regression models will be fit to evaluate associations of grammar and semantic outcomes with HIV disease severity, and ARV regimens. In addition, multiple logistic regression will be applied to study the association between language impairment and viral load, CD4 count, and CDC class. For the subset with previous assessments in AMP study, the effect of cART on change in language impairment will be investigated by numbers of regimens, type, and duration of cART. Specific ARV drugs for which associations with language outcomes have been previously observed, such as atazanavir, will be studied.

For AMP Up participants with previous language assessments using the CELF-4 at younger ages, availability of a second or third CELF-4 language assessment will allow us to examine consistency of performance relative to age expectations over multiple measurement; evaluate predictors of incident language impairment or resolution of prior language impairment, and evaluate predictors of age-normed language scores over time. Approximately 345 participants with PHIV and 193 participants with PHEU from the AMP study had at least one CELF-4 assessment between the age of 7 to 16 years, and around 80% of these participants had two previous CELF-4 assessments in AMP. Approximately 280 of these participants enrolled into AMP Up are monolingual and younger than 22 years old by the Year 3 visit. The change of CELF scores by HIV status will be studied, adjusting for age, time from the previous assessment(s) in AMP, and other confounders. GEE or mixed effect models will be used to account for the correlation in outcomes measured over time on the same participant. When feasible, growth curve models will also be fitted to explore the pattern of changes over time. Dependent variables are determined by psychometric properties of the CELF-4. For ages 5-21 years, the Expressive Language Total Standard Score is comparable, as are the subtests Recalling Sentences and Formulated Sentences; in addition, for 9-21 years, the subtests Word Classes- Receptive, Word Classes - Expressive and Word Definitions are valid for comparison of the last two times of measurement.

Association between language impairment and hearing and cognitive impairments will be measured using logistic regression models to obtain odds ratios, adjusting for possible confounders. Logistic, multinomial, or generalized linear regression models will be applied to study language impairment as a predictor for socio/emotional, education and employment outcomes separately, adjusting for hearing and cognitive impairments and other possible confounders.

## 13.0 HUMAN SUBJECTS

This study will be conducted in compliance with the protocol, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP guidelines, and 45 CFR § 46.

### 13.1 Participant Confidentiality

All participants enrolled in the PHACS Network are assigned unique PHACS PID and SID/PIN numbers as described in Section 4.6. 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 web-based surveys. A list linking the participant names with the PID number will be stored at the clinical site under double locks, separate from all other research records. All research records will be stored in a secure area in locked files.

An information sheet has been developed for participants to assist them in protecting their confidentiality while completing the web-based survey at a location other than the clinical site. See AMP Up Operations Portfolio for suggested confidentiality and security measures for participants and established for the web-based survey data.

All study staff members at the clinical sites are required to sign nondisclosure forms agreeing to hold research information in confidence. All AMP Up investigators and collaborators are required to sign confidentiality agreements agreeing not to seek the identity of study participants.

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.

### 13.2 Certificate of Confidentiality

As an NIH-funded project using identifiable, sensitive information, AMP Up is automatically covered by a Certificate of Confidentiality issued from the U.S. DHHS. With this Certificate in place, AMP Up 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 researchers 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 principal investigator will make study documents (e.g., ICFs, CRFs) and pertinent records available for inspection by the local IRB, the PHACS site monitors, the NIH, the OHRP, or the sponsor's designee for confirmation of the study data.

## 13.3 Risks and Benefits

### 13.3.1 Risks Associated with Participation in This Study

Participation in this study poses no more harm or discomfort to research participants than they may experience in normal daily life or during routine medical or psychological examinations or tests.

The measurements that are involved in this study require: venipuncture, clinical assessment, neurodevelopmental testing, interviews, surveys, anthropometric evaluation, and a fasting period (not to exceed 8 hours) for laboratory studies. Possible risks resulting from the study include:

- 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.
- Distress resulting from knowing about the result of a clinical or laboratory assessment. All STI lab results will be kept confidential at the clinical site unless the participant gives written permission to share them. Depending on state reporting requirements, clinical sites may be required to report positive results of STI lab results to public health authorities.
- Anthropometric evaluation is obtained through the external grasping of skin and underlying adipose tissue with calipers; it can cause some temporary discomfort and redness at the point of contact.
- Fasting periods will not exceed 8 hours and should present little risk. Some participants may feel hunger, irritability, and lightheadedness as a result of fasting.
- Disclosure of confidential information obtained through behavioral testing, interviews, or surveys. The information that the young adults provide during interviews or web-based surveys will not be shared with medical providers without their permission unless there is serious risk of self-harm or harm to others as specified in the consent and local ethics committee requirement. This includes information about reproductive health, substance use, and mental health.
- Despite the multiple measures taken to protect participant confidentiality (see Section 13.1), web-based communications may be at risk for hacking, intrusions, and other violations.

### 13.3.2 Benefits Associated with Participation in This Study

While there is no guarantee of direct benefit to the individuals who participate in this study, benefiting from participating is possible. If the participant or their legal guardian chooses, the information obtained in this study can be made available to their health care providers and may inform their primary health care. Results of clinical and laboratory evaluations might identify medical conditions that require intervention. Participants and their legal guardian will be encouraged to make this information available to providers in order to maximize the potential for benefits.

### 13.3.3 Procedures, Risks, and Benefits for Young Adults with HIV

The potential risks for YAPHIV and YAPHEU who become infected with HIV include inadvertent disclosure of the young adult's HIV status to someone who does not yet know about the infection. Research staff members will provide guidance to participants to help them to maintain their

confidentiality, including while completing web-based surveys. Participants will be encouraged to complete their web-based surveys in a private location on a device that is not publicly shared. Clinical sites will make space available for participants to complete the surveys when a participant does not have access to a private space or device. See Appendix IV for additional information that sites can provide to participants to help prevent inadvertent disclosure of HIV status due to someone accessing the web-based surveys or study website.

PHACS Repository specimens may be used in genome-wide association studies (GWAS) that includes sequencing of participant's entire DNA. Per the NIH Genomic Data Sharing (GDS) Policy to facilitate the sharing of large-scale genomic data generated from NIH-funded research, participants' DNA testing information may be deposited in NIH designated data repositories such as the NIH Database of Genotypes and Phenotypes (dbGaP). Data will be stored without a participant's name or other direct identifiers. However, each participant's genetic information is unique and it may be possible to identify a participant based only upon his or her genomic data. Even if access to data is controlled and data security standards are met, confidentiality cannot be guaranteed.

### 13.4 IRB 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 sites 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.). 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 he or she is able to understand the nature, significance, and risks of the study. A copy of the consent/assent form will be given to the participant (and copy of consent to the legal guardian, as applicable) for informed consents conducted in person. Web-based ICF and assent forms will be formatted to allow for printing so that the participant can retain a copy. Participants or legal guardians also will have the option of requesting that a copy of the signed ICF/assent form be mailed or sent via secure email to them.

### 13.5 Prisoner Participation

The PHACS and NIH have concluded that this protocol does NOT meet Federal requirements governing prisoner participation in human subjects research and should NOT be considered by local IRBs for the recruitment of prisoners. Participants who become prisoners after enrollment may not be seen for research visits as long as they are considered prisoners.

### 13.6 45 CFR §160 and 164 Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule" pursuant to the Health Insurance Portability and Accountability Act-HIPAA)

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

#### 13.6.1 PHACS Repository Policies

It is not expected that Protected Health Information (PHI) will be needed to create and operate the PHACS Repository. In addition, since biologic specimens, in and of themselves, do not constitute PHI under 45 CFR §164.501, the Privacy Rule will not apply to the creation of the PHACS Repository. It will be sufficient to seek informed consent from individuals, as required by 45 CFR §46.116, to have their specimens included in the PHACS Repository. The PHACS Repository Policy and samples of the ICFs for the PHACS Repository can be found in the PHACS MNPP. Participants may participate in AMP Up without agreeing to storage of their specimens in the PHACS Repository.

### 13.7 Study Discontinuation

The study may be discontinued at any time by the NIH.

## 14.0 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 at https://phacsstudy.org).

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

## 15.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC. These procedures can be found at www.cdc.gov.

PHACS specimens will be transported in accordance with Federal and local laws, and in compliance with Occupational Safety and Health Administration (OSHA) blood-borne pathogens standards. This policy includes the samples being transported by ground to the local laboratory. Compliance will be achieved by education of personnel involved with packaging and transporting specimens.

All infectious specimens must be shipped as Diagnostic Specimens according to current International Air Transport Association (IATA) Shipping Guidelines for Infectious Substances Class/Div. 6.2. Refer to individual carrier guidelines (e.g., FedEx, Airborne Express) for specific instructions.

## APPENDIX I: SCHEDULE OF EVALUATIONS FOR THE YAPHIV COHORT

The target visit date for follow-up visits, including the in-person study visits (e.g., Years 3, 6, 9, 12…) is the anniversary of the Entry (Year 0) visit. All visits must be conducted within six months prior to or after the target visit date (visit window). All visit assessments should be conducted as closely together as possible, preferably all on the same day or no more than six weeks apart. The annual web-based survey may be completed in more than one sitting but must be completed in its entirety within four weeks after its initiation and by the end of the visit window, regardless of when it was initiated. An exception to this requirement will be made if some of the survey questions are administered separately from the primary survey, as a short, stand-alone, web-based survey. In this situation, the stand-alone survey may be completed within three months of receipt.

| | Year | | | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Entry (Year 0)[1]** | **1** | **2** | **3[1]** | **4** | **5** | **6[1]** | **7** | **8** | **In-person visits (9, 12…)[1]** | **Years without in-person visits (10, 11, 13, 14…)** | |
| **In-Person[1]** | | | | | | | | | | | | |
| Sign consent | | | | | | | | | | | | New enrollees will sign initial consent at Entry. Current enrollees will re-consent at next study visit. |
| Address information/ location for geocoding purposes | X | | | X | | | X | | | X | | |
| Height, weight, blood pressure, body measurements, and male circumcision status | X | | | X | | | X | | | X | | --Body measurements include triceps, biceps, suprailiac, and subscapular skinfolds, and mid-upper arm and waist circumferences.<br>--Circumcision status at Entry only |
| Physical activity | X | | | X | | | X | | | X | | Web-based Block Physical Activity Screener |
| Neurocognitive functioning | X | | | X | | | X | | | X | | Cognitive domain of NIH Toolbox (30 min) |
| Mental health interviews | X | | | X | | | X | | | X | | --At Entry, PHQ-9 and GAD-7 via interview (5 min each)<br>--After Entry, PHQ-9 and GAD-7 via web-based survey (5 min each) |

| | Entry (Year 0)[1] | Year | | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3[1] | 4 | 5 | 6[1] | 7 | 8 | In-person visits (9, 12…)[1] | Years without in-person visits (10, 11, 13, 14…) | |
| | | | | | | | | | | | | --CDQ (except at Entry visit; 15 min)<br>--Emotion domain of NIH Toolbox (self-efficacy, perceived social support [emotional and instrumental], friendship, and life satisfaction) (13 min) |
| Language assessments[2] | X | | | X | | | | | | | | CELF (20 min) |
| Hearing assessments | X | | | X | | | X | | | X | | Words-in-Noise (WIN) test of NIH Toolbox (5 min) |
| Annual Web-Based Survey[3] | The following categories of questions will be included in the annual surveys: socio-demographics, general health and health care-related, mental health, social determinants of health, reproductive health, sexual behaviors, substance use, and ARV medication adherence. | | | | | | | | | | | To be completed on any device with access to the internet, including a cell phone. Most questions are part of a single primary survey, but some may be administered separately as a short, stand-alone survey. |
| Additional Web-based Surveys | In addition to the evaluations specified in the protocol, completion of occasional brief voluntary web-based or interview-administered surveys by participants may be requested to address specific time-sensitive or important issues as they arise. The content of these additional surveys will fall under the aims of the protocol and be covered by the informed consent, with notification of the HLC IRB as required. | | | | | | | | | | | |
| **Chart Abstraction[4]** | | | | | | | | | | | | |
| Interval diagnoses, ART and other medications[5], and family history | X | X | X | X | X | X | X | X | X | X | X | |
| Results of lab tests conducted for clinical care[6] | X | X | X | X | X | X | X | X | X | X | X | |

| | Entry (Year 0)[1] | Year | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3[1] | 4 | 5 | 6[1] | 7 | 8 | In-person visits (9, 12…)[1] | Years without in-person visits (10, 11, 13, 14…) | |
| Height, weight, and blood pressure | X | X | X | X | X | X | X | X | X | X | X | |
| **Laboratory: Real-Time Testing** | | | | | | | | | | | | |
| STI testing[7] | X | X | X | X | X | X | X | X | X | X | X | --Self-collect in clinic at Entry and the in-person follow-up visits (e.g., Years 3, 6, 9, 12…)<br>--Self-collect at home and deliver/mail to clinic at all other years<br>--Do not perform if results are available for both *N. gonorrhoeae* and *C. trachomatis* within the past 12 months<br>--Males: urine<br>--Females: vaginal swab #1 or urine if swab is declined |
| **Laboratory: Central Testing[8]** | | | | | | | | | | | | |
| Urine for renal biomarkers | X | | | X | | | X | | | X | | Collect in clinic |
| Serum for cardiac biomarkers | X | | | X | | | X | | | X | | Collect in clinic |
| Fasting serum lipids | X | | | X | | | X | | | X | | Collect in clinic |
| Fasting plasma glucose and serum insulin | X | | | X | | | X | | | X | | Collect in clinic |
| Research Aptima STI testing[9] | X | X | X | X | X | X | X | X | X | X | X | --Self-collect in clinic at Entry and the in-person follow-up visits (e.g., Years 3, 6, 9, 12…)<br>--Self-collect at home and deliver/mail to clinic at all other years<br>--Males: urine<br>Females: vaginal swab #2 or urine if swab declined |
| **Repository** | | | | | | | | | | | | |

| | Entry (Year 0)[1] | Year | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3[1] | 4 | 5 | 6[1] | 7 | 8 | In-person visits (9, 12…)[1] | Years without in-person visits (10, 11, 13, 14…) | |
| Fasting serum and plasma (both EDTA and heparin) | X | | | X | | | X | | | X | | Collect in clinic |
| Viable PBMCs | X | | | X | | | X | | | X | | Collect in clinic |
| Throat wash/gargle | X | | | X | | | X | | | X | | Collect in clinic |
| Unstimulated saliva | X | | | X | | | X | | | X | | Collect in clinic |
| Urine | X | | | X | | | X | | | X | | Collect in clinic |
| Vaginal swabs #3 and #4 (females) | X | | | X | | | X | | | X | | Self-collect in clinic |

[1] Study visits at Entry and every 3 years starting at Year 3 (e.g., Years 3, 6, 9, 12…) are intended to be conducted in-person at the clinic. If circumstances preclude an in-person visit, the visit can be conducted remotely, e.g., clinical assessment data will be collected through chart abstraction (when available), web-based surveys and questionnaires may be completed via telephone (with Protocol Team approval), and specimens may be self-collected and shipped to the clinical site. Any remaining assessments (e.g., NIH Toolbox, body measurements, blood draw for repository specimens) not completed may be completed at the next annual visit with Protocol Team approval (see Protocol Section 8.1).

[2] Administer the CELF-4 to assess language only to those participants who were in AMP who completed at least one CELF in AMP. Administer only once at Entry or Year 3. Administer at Entry for participants who will be 22 years or older at Year 3. Administer at Year 3 for all others.

[3] The web-based survey will be completed annually and can be completed in the clinic or remotely depending on the participant's preference. Modified versions with selected assessments/questions will be administered as an interview by clinic staff for participants with cognitive impairments or will be completed by the participant's primary caregiver for participants unable to respond to survey questions.

[4] Chart abstraction is to be completed annually. Chart abstraction should be performed during the same window as other study visit assessments.

[5] All medical diagnoses, immunizations, and medications (except short duration [less than two weeks] over-the-counter medications) should be recorded.

[6] Results to be abstracted from routine clinical testing from medical record. Record the most recent for each six-month period since the last abstraction for the following tests: CBC, Chemistries (BUN, creatinine, lipase, AST, ALT, and CPK), lipids, and urinalysis. Record all results since the last abstraction for the following tests: lymphocyte subsets (CD3, CD4, and CD8), HIV RNA viral load, HIV resistance testing, and results of testing for STIs.

[7] Real-time STI testing at local clinical lab: *N. gonorrhoeae*, *C. trachomatis*, and *T. vaginalis* on urine for males and vaginal swab #1 (preferred) or urine for females. The Protocol Team realizes that most labs "test" for *T. vaginalis* in female participants by microscopic examination of a wet mount of vaginal secretions. Diagnosis of trichomoniasis in male participants is generally performed only when symptomatic by microscopic examination of urine. If the lab

does not perform a specific test for *T. vaginalis*, wet mounts of vaginal secretions or urine are adequate. If real-time testing for *T. vaginalis* is not available or cannot be done for a participant, it should be considered missed and the reason it was not done should be documented in the participant's research record.

[8] Specimens will be held temporarily in the PHACS Repository for later central testing. These are not considered repository specimens and should be collected for all participants including those who did not agree to the storage of their specimens in the PHACS Repository.

[9] Urine for males and vaginal swab #2 or urine if swab is declined for females: collected by the participants and shipped to or dropped off at the clinical site; the clinical site will ship the samples to the PHACS Repository where they are subsequently forwarded in batches to the Central Laboratory for research testing for *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis*, and HPV (on vaginal swabs only).

## APPENDIX II: SCHEDULE OF EVALUATIONS FOR THE YAPHEU COHORT

The target visit date for follow-up visits, including the in—person study visits (e.g., Years 3, 6, 9, 12…) is the anniversary of the Entry (Year 0) visit. All visits must be conducted within six months prior to or after the target visit date (visit window). All visit assessments should be conducted as closely together as possible, preferably all on the same day or no more than six weeks apart. The annual web-based survey may be completed in more than one sitting but must be completed in its entirety within four weeks after its initiation and by the end of the visit window, regardless of when it was initiated. An exception to this requirement will be made if some of the survey questions are administered separately from the primary survey, as short, stand-alone, web-based survey. In this situation, the stand-alone survey may be completed within three months of receipt.

| | Entry (Year 0)[1] | Year | | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3[1] | 4 | 5 | 6[1] | 7 | 8 | In-person visits (9, 12…)[1] | Years without in-person visits (10, 11, 13, 14…) | |
| **In-Person[1]** | | | | | | | | | | | | |
| Sign consent | | | | | | | | | | | | New enrollees will sign initial consent at Entry. Current enrollees will re-consent at next study visit. |
| Address information/ location for geocoding purposes | X | | | X | | | X | | | X | | |
| Height, weight, blood pressure, body measurements, and male circumcision status | X | | | X | | | X | | | X | | --Body measurements include triceps, biceps, suprailiac, and subscapular skinfolds, and mid-upper arm and waist circumferences<br>--Circumcision status at Entry only |
| Physical activity | X | | | X | | | X | | | X | | Web-based Block Physical Activity Screener |
| Neurocognitive functioning | X | | | X | | | X | | | X | | Cognitive domain of NIH Toolbox (30 min) |
| Mental health interviews | X | | | X | | | X | | | X | | --At Entry, PHQ-9 and GAD-7 via interview (5 min each)<br>--After Entry, PHQ-9 and GAD-7 via web-based survey (5 min each) |

| | Entry (Year 0)[1] | Year | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3[1] | 4 | 5 | 6[1] | 7 | 8 | In-person visits (9, 12…)[1] | Years without in-person visits (10, 11, 13, 14…) | |
| | | | | | | | | | | | | --CDQ (except at Entry visit; 15 min)<br>--Emotion domain of NIH Toolbox (self-efficacy, perceived social support [emotional and instrumental], friendship, and life satisfaction) (13 min) |
| Language assessments[2] | X | | | X | | | | | | | | CELF (20 min) |
| Hearing assessments | X | | | X | | | X | | | X | | Words-in-Noise (WIN) test of NIH Toolbox (5 min) |
| Annual Web-Based Survey[3] | The following categories of questions will be included in the annual surveys: socio-demographics, general health and health care-related, mental health, social determinants of health, reproductive health, sexual behaviors, and substance use. | | | | | | | | | | | To be completed on any device with access to the internet, including a cell phone. Most questions are part of a single primary survey, but some may be administered separately as a short, stand-alone survey. |
| Additional Web-based Surveys | In addition to the evaluations specified in the protocol, completion of occasional brief voluntary web-based or interview-administered surveys by participants may be requested to address specific time-sensitive or important issues as they arise. The content of these additional surveys will fall under the aims of the protocol and be covered by the informed consent, with notification of the HLC IRB as required. | | | | | | | | | | | |
| **Chart Abstraction[4]** | | | | | | | | | | | | |
| Interval diagnoses, medications[5], and family history | X | X | X | X | X | X | X | X | X | X | X | |
| Results of lab tests conducted for clinical care[6] | X | X | X | X | X | X | X | X | X | X | X | |
| Height, weight, and blood pressure | X | X | X | X | X | X | X | X | X | X | X | |

| | Entry (Year 0)[1] | Year | | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3[1] | 4 | 5 | 6[1] | 7 | 8 | In-person visits (9, 12…)[1] | Years without in-person visits (10, 11, 13, 14…) | |
| **Laboratory: Real-Time Testing** | | | | | | | | | | | | |
| STI testing[7] | X | X | X | X | X | X | X | X | X | X | X | --Self-collect in clinic at Entry and the in-person follow-up visits (e.g., Years 3, 6, 9, 12…)<br>--Self-collect at home and deliver/mail to clinic at all other years<br>--Do not perform if results are available for both *N. gonorrhoeae* and *C. trachomatis* within the past 12 months<br>--Males: urine<br>--Females: vaginal swab #1 or urine if swab is declined |
| HIV test[8] | | | | X | | | | | | X | | Also abstract results for any test conducted after the Entry visit |
| **Laboratory: Central Testing[9]** | | | | | | | | | | | | |
| Urine for renal biomarkers | X | | | X | | | X | | | X | | Collect in clinic |
| Serum for cardiac biomarkers | X | | | X | | | X | | | X | | Collect in clinic |
| Fasting serum lipids | X | | | X | | | X | | | X | | Collect in clinic |
| Fasting plasma glucose and serum insulin | X | | | X | | | X | | | X | | Collect in clinic |
| Research Aptima STI testing[10] | X | X | X | X | X | X | X | X | X | X | X | --Self-collect in clinic at Entry and the in-person follow-up visits (e.g., Years 3, 6, 9, 12…)<br>--Self-collect at home and deliver/mail to clinic at all other years<br>--Males: urine<br>Females: vaginal swab #2 or urine if swab declined |
| **Repository** | | | | | | | | | | | | |

| | Entry (Year 0)[1] | Year | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3[1] | 4 | 5 | 6[1] | 7 | 8 | In-person visits (9, 12…)[1] | Years without in-person visits (10, 11, 13, 14…) | |
| Fasting serum and plasma (both EDTA and heparin) | X | | | X | | | X | | | X | | Collect in clinic |
| Viable PBMCs | X | | | X | | | X | | | X | | Collect in clinic |
| Throat wash/gargle | X | | | X | | | X | | | X | | Collect in clinic |
| Unstimulated saliva | X | | | X | | | X | | | X | | Collect in clinic |
| Urine | X | | | X | | | X | | | X | | Collect in clinic |
| Vaginal swabs #3 and #4 (females) | X | | | X | | | X | | | X | | Self-collect in clinic |

[1] Study visits at Entry and every 3 years starting at Year 3 (e.g., Years 3, 6, 9, 12…) are intended to be conducted in-person at the clinic. If circumstances preclude an in-person visit, the visit can be conducted remotely, e.g., clinical assessment data will be collected through chart abstraction (when available), web-based surveys and questionnaires may be completed via telephone (with Protocol Team approval), and specimens may be self-collected and shipped to the clinical site. Any remaining assessments (e.g., NIH Toolbox, body measurements, blood draw for repository specimens) not completed may be completed at the next annual visit with Protocol Team approval (see Protocol Section 8.1).

[2] Administer the CELF-4 to assess language only to those participants who were in AMP who completed at least one CELF in AMP. Administer only once at Entry or Year 3. Administer at Entry for participants who will be 22 years or older at Year 3. Administer at Year 3 for all others.

[3] The web-based survey will be completed annually and can be completed in the clinic or remotely depending on the participant's preference. Modified versions with selected assessments/questions will be administered as an interview by clinic staff for participants with cognitive impairments or will be completed by the participant's primary caregiver for participants unable to respond to survey questions.

[4] Chart abstraction is to be completed annually. At Entry, chart abstraction should be completed only for the 12 months prior to Entry. Chart abstraction should be performed during the same window as other study visit assessments.

[5] All medical diagnoses, immunizations, and medications (except short duration [less than two weeks] over-the-counter medications) should be recorded.

[6] Results to be abstracted from routine clinical testing from medical record. Record the most recent for each six-month period since the last abstraction for the following tests: CBC, Chemistries (BUN, creatinine, lipase, AST, ALT, and CPK), lipids, and urinalysis. Record all results since the last abstraction for STI tests.

[7] Real-time STI testing at local clinical lab: *N. gonorrhoeae*, *C. trachomatis*, and *T. vaginalis* on urine for males and vaginal swab #1 (preferred) or urine for females. The Protocol Team realizes that most labs "test" for *T. vaginalis* in female participants by microscopic examination of a wet mount of vaginal secretions. Diagnosis of trichomoniasis in male participants is generally performed only when symptomatic by microscopic examination of urine. If the lab

does not perform a specific test for *T. vaginalis*, wet mounts of vaginal secretions or urine are adequate. If real-time testing for *T. vaginalis* is not available or cannot be done for a participant, it should be considered missed and the reason it was not done should be documented in the participant's research record.

[8] YAPHEU participants who become HIV-infected will be re-consented to remain on the study and be followed per the schedule of evaluations for the YAPHIV cohort (see Appendix I).

[9] Specimens will be held temporarily in the PHACS Repository for later central testing. These are not considered repository specimens and should be collected for all participants including those who did not agree to the storage of their specimens in the PHACS Repository.

[10] Urine for males and vaginal swab #2 or urine if swab is declined for females: collected by the participants and shipped to or dropped off at the clinical site; the clinical site will ship the samples to the PHACS Repository where they are subsequently forwarded in batches to the Central Laboratory for research testing for *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis*, and HPV (on vaginal swabs only).

## APPENDIX III: SUGGESTED SAMPLE COLLECTION SPECIFICATION FOR SPECIMENS FOR CENTRAL TESTING AND FOR REPOSITORY STORAGE

For laboratory tests performed in the local clinical laboratory, use the specifications (including tube color) provided by the respective lab.

| Specimen | Minimum volume of draw[3] | Anticoagulant (tube color) or container |
|---|---|---|
| **Specimens for Central Testing (to be shipped to the PHACS Repository for temporary storage)** | | |
| Fasting serum for insulin and cardiac biomarkers | 6-7 ml | Serum separator or red top tube |
| Fasting NaF/K oxalate plasma for glucose testing | 4 ml | NaF/K oxalate (grey top) |
| Fasting serum for lipids | 6-7 ml | Serum separator or red top tube |
| Urine for renal biomarkers[1] | 5 ml | Sterile container |
| Urine[1] for males and vaginal swab #2 (or urine[1] if swab is declined for females) for research Aptima STI testing at the Central Laboratory | 10 ml of urine or 1 vaginal swab | Hologic (formerly GenProbe) Aptima collection kits with Aptima media |
| **Repository Specimens (to be shipped to the PHACS Repository for long-term storage)** | | |
| Fasting serum | 6-7 ml | Serum separator or red top tube |
| Viable PBMCs/plasma[2] | 8 ml | CPT tube |
| Fasting plasma (EDTA)[2] | 6-7 ml | EDTA (lavender top) |
| Fasting plasma (heparin) | 6-7 ml | Heparin (green top) |
| Saliva | 3.0 ml | Sterile container; separate into three 1-ml aliquots and freeze |
| Throat wash/gargle | 10 ml | 50 ml wide-mouth sterile tube |
| Urine[1] | 5 ml | Sterile container |
| Vaginal swabs #3 and #4 (females) | 2 flocked swabs | -Swab #3 1 in 1 cc of normal saline in a 2 cc cryovial<br>-Swab #4 in a sterile dry 2 cc cryovial |

Note: Serum and plasma repository specimens must be frozen in 0.5-ml aliquots. Refer to the AMP Up LPC for further specimen collection, processing and shipping information.

[1] Total urine collection of 20 ml to be split into one 10-ml aliquot and two 5-ml aliquots for STI testing (vaginal swab preferred for females), renal biomarker testing, and storage in the PHACS Repository, respectively.

[2] An EDTA tube (lavender top) if PBMCs are to be separated using Ficoll-Hypaque may be collected as an alternative to the CPT tube. If EDTA tube is used, the plasma may be saved and no additional EDTA tube is needed for the fasting EDTA plasma.

[3] Volumes can be adjusted depending on availability of collection tubes. The maximum total volume of blood for central testing must not exceed 30 ml per visit. The maximum total volume of blood for the PHACS Repository must not exceed 45 ml per visit.

## APPENDIX IV: DATSTAT ILLUME SURVEY DATA SECURITY AND USER CONFIDENTIALITY

DatStat maintains extremely stringent levels of encryption and data storage. Security is a critical issue and DatStat is specifically designed to meet and exceed industry standards for Internet security as well as Institutional Review Board (IRB) and Data Safety and Monitoring Board standards for the protection of research participants and electronic records. DatStat's technology platform including servers, database, and web presences that employ multiple forms of security features to protect data and the participants involved in data collection efforts.

### Data Storage

All DatStat servers used for data collection are highly fault tolerant and are equipped with redundant, hot pluggable power supplies, redundant network interfaces, and RAID 1/5 hot pluggable disk storage. All primary servers are plugged into a monitored uninterruptible power supply offering a minimum of 30 minutes of battery power in the event of a power outage. At least one additional server is available at all times to handle the off chance of a major server crash.

### Data Transmission

DatStat secure servers are registered with site certificates provided by VeriSign Internet Trust Services that provides for advanced encryption over the wire. As users move through the data entry forms, the responses are encrypted while in transit between the browser and DatStat's server using Secure Sockets Layer (SSL) and 40, 56, or 128 bit Public Key Encryption. The matter of 40 bit, vs. 56 bit, vs. 128 bit encryption via SSL is dependent on the browser and the server. Very old browsers were incapable of supporting 128 bit encryption (Pre Netscape 3.0) and instead only supported 40 bit encryption. Also, browsers sold outside the United States are only allowed, by law, to support up to 56 bit encryption. Version and international issues also apply to servers. The DatStat server software was obtained in the United States and supports 128 bit encryption whenever possible. It is possible that 40 or 56 bit encryption will be in use if the browser hitting the DatStat secure server is only capable of supporting 40 bit encryption. Although not as strong as 128 bit encryption, 40 and 56 bit encryption offers more than sufficient security for data entry purposes and has been in use during the past several years for 920 N 34 electronic commerce (e.g., exchange of credit card information online).

### Server Protection

DatStat servers are stored in a locked, well ventilated room in locked server cabinet/racks. The server room is in a building with 24/7 alarm security. Any building compromise will sound the alarm and generate a call to the building supervisor and police, who will subsequently notify DatStat personnel of the intrusion. Protection of servers from remote attacks is accomplished with a dedicated hardware Watchguard firewall with auditing enabled at the recommended settings. Watchguard LiveSecurity keeps information technology staff advised of all known security alerts. The firewall ensures that all traffic is closely monitored and suspicious packets blocked from access to the production systems. Security patches are applied to DatStat servers on a timely and ongoing basis. Logs are created by the web servers to increase accountability and are essential in investigating incidents after the fact. The following are logged: failed and successful logins, attempts to access files/directories without authority, successful and failed attempts to access sensitive data.

**Data Backup**

DatStat SQL Server database backups are conducted by DatStat on a daily basis. Backups are encrypted and streamed over on a private network to a secure offsite location. Backups are encrypted using 256 bit AES encryption.

**Data Access**

Physical access to servers and data backup is restricted to a minimal number of information technology professionals. Such access is provided only with strong passwords that regularly expire to minimize the chance that inadvertently and unknowingly distributed passwords could cause inappropriate data access. Access to data stored on the server is available only to designated Illume users who log in with specified usernames and passwords. Users are logged out after a period of time. A listing of the named users with a description of their access privileges is available within the application.

**Participant Confidentiality**

To ensure an even greater level of security and confidentiality, participants are required to enter a Study Identification Number/Personal Identification Number (SID/PIN) to gain access to the data entry forms. Where appropriate, survey participants may receive an email with the survey SID/PIN embedded in the survey URL, which is encrypted by SSL. It is ONLY the SID/PIN that is stored with the collected survey data, thus ensuring that under no means may the collected survey data reveal a participant's identity. When email invitations are utilized, the email address of the participant is used solely to send the email and is not stored with the collected survey data.

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