Adolescent Master Protocol for Participants 18 Years of Age and Older - Lite (AMP Up Lite)
PH400

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

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LIST OF ABBREVIATIONS

ACTG	AIDS Clinical Trial Group
ADHD	Attention Deficit Hyperactivity Disorder
AES	Advanced Encryption Standard
AIDS	Acquired Immunodeficiency Syndrome
AMP	Adolescent Master Protocol
AMP Up	Adolescent Master Protocol for Participants 18 Years of Age and Older
ART	Antiretroviral Therapy
ARV	Antiretroviral
BMI	Body Mass Index
CBC	Complete Blood Count
CD4	Cluster of Differentiation 4
CDC	Centers for Disease Control and Prevention
CES-D 10	Center for Epidemiologic Studies Short Depression Scale
CFR	Code of Federal Regulations
CI	Confidence Interval
CMV	Cytomegalovirus
CRF	Case Report Form
C. trachomatis	*Chlamydia trachomatis*
DAIDS	Division of Acquired Immunodeficiency Syndrome
dbGaP	Database of Genotypes and Phenotypes
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic Acid
DOC	Data and Operations Center
DMC	Data Management Center
DSMB	Data Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
EBV	Epstein-Barr virus
EC	Executive Committee
FDA	Food and Drug Administration
FSTRF	Frontier Science and Technology Research Foundation
GCP	Good Clinical Practice
GDS	Genomic Data Sharing
GEE	Generalized Estimating Equation
GWAS	Genome-Wide Association Studies
HAART	Highly Active Antiretroviral Therapy
HDL	High Density Lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSIL	High-grade Squamous Intraepithelial Lesions
HSPH	Harvard T.H. Chan School of Public Health
HSV	Herpes Simplex Virus
HTTPS	Hyper Text Transfer Protocol Secure
IATA	International Air Transport Association
ICH	International Conference on Harmonization
IL-12	High Interleukin-12
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network

IRB	Institutional Review Board
IUD	Intrauterine Device
LAC	Long Acting Contraceptives
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
LPC	Laboratory Processing Chart
LSIL	Low-grade Squamous Intraepithelial Lesions
MHP	Mental Health Problem
MI	Myocardial Infarction
MOGO	Manual of General Operations
MOU	Memorandum of Understanding
MRI	Magnetic Resonance Imaging
mtDNA	Mitochondrial Deoxyribonucleic Acid
N. gonorrhoeae	*Neisseria gonorrhoeae*
NDI	National Death Index
NICHD	The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIH	National Institutes of Health
NRTI	Nucleoside Reverse Transcriptase Inhibitor
OAR	Office of AIDS Research
OHRP	Office of Human Research Protection
OR	Odds Ratio
OSHA	Occupational Safety and Health Administration
PASS	Power Analysis and Sample Size
Pap	Papanicolaou
PBMCs	Peripheral Blood Mononuclear Cells
PHACS	Pediatric HIV/AIDS Cohort Study
PHEU	Perinatally HIV-Exposed, -Uninfected
PHI	Protected Health Information
PHIV+	Perinatally HIV-infected
PI	Principal Investigator
PID	Patient Identification Number
PIN	Personal Identification Number
PrEP	Pre-Exposure Prophylaxis
PTSD	Post-Traumatic Stress Disorder
QNS	Query and Notification System
REACH	Reaching for Excellence in Adolescent Care and Health
RNA	Ribonucleic Acid
SD	Standard Deviation
SES	Subject Enrollment System
SF-20	Short Form Health Survey
SID	Study Identification Number
SMARTT	Surveillance Monitoring for ART Toxicities
SSL	Secure Sockets Layer
STI	Sexually Transmitted Infection
T. vaginalis	*Trichomonas vaginalis*
ZDV	Zidovudine

UPS	Uninterruptible Power Supply
URL	Uniform Resource Locator
U.S.	United States
WITS	Women and Infants Transmission Study

STUDY ABSTRACT

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 perinatal HIV infection as they transition into adulthood.
Population:	Young adults with perinatal HIV infection at or beyond their 18th birthday.
Sample Size:	Approximately 500 perinatally HIV-infected (PHIV+) young adults will be enrolled in the study.
Study Duration:	At least six years after the last participant is enrolled.
Evaluations:	The following will be completed at the Entry time point: --Clinical assessments: height, weight, and blood pressure measurements. --Interviewer-administered medical history questionnaire: targeted medical and medications history, and family medical history. --Web-based Illume survey: demographics, health care access and utilization, transition to adult HIV care, depression (Center for Epidemiologic Studies Short Depression Scale (CES-D 10)), health-related quality of life (Short Form Health Survey (SF-20)), social support, relationships, self-efficacy, HIV-related stigma, reproductive history, sexual behavior, substance use, ART adherence, fracture history, and self-reported hearing issues. --Chart abstraction: 1) medical diagnoses, ART medications, immunizations, Cluster of Differentiation 4 (CD4), viral load, HIV resistance testing, complete blood count (CBC) profile, chemistry panel, lipid profile, glucose, pregnancy and pregnancy outcomes, results of sexually transmitted infection (STI) testing, and abnormal cytology and histology in the 12 months prior to Entry, 2) nadir CD4 and lifetime history of acquired immunodeficiency syndrome (AIDS)-defining illness and Centers for Disease Control and Prevention (CDC) classification, and 3) mental health diagnoses including mood, anxiety, post-traumatic stress disorder (PTSD), psychosis, and attention deficit hyperactivity disorder (ADHD) in the 12 months prior to Entry. --Collection of specimens for the Pediatric HIV/AIDS Cohort Study (PHACS) Repository: serum, plasma, and peripheral blood mononuclear cells (PBMCs). If an in-person visit cannot be completed at Entry, then height, weight, and blood pressure measurements will be collected through chart abstraction, and the interviewer-administered medical history questionnaire will be completed via telephone. After the Entry time point, chart abstraction and the web-based Illume survey will be completed annually and will include the following: --Web-based Illume survey: demographics, height and weight, health care access and utilization, transition to adult HIV care, depression (CES-D 10), health-related quality of life (SF-20), social support, relationships, self-efficacy, HIV-

	related stigma, reproductive history, sexual behavior, substance use, ART adherence, interval fractures, and self-reported hearing issues. --Chart abstraction: height and weight, blood pressure, interval medical diagnoses including AIDS-defining illness, CDC classification, ART medications, immunizations, CD4, viral load, HIV resistance testing, CBC profile, chemistry panel, lipid profile, glucose, pregnancy and pregnancy outcomes, results of STI testing, abnormal cytology and histology, and mental health diagnoses including mood, anxiety, PTSD, psychosis, and ADHD. At Year 5 only: --Collection of specimens for the PHACS Repository: serum, plasma, and PBMCs.
Primary Objectives:	1. To identify infectious and non-infectious complications of HIV disease and toxicities resulting from long-term ART, including disease progression, immune suppression, viral resistance, end-organ disease, and mortality. 2. To define the impact of HIV infection and ART on the long-term clinical outcomes of young adults with perinatal HIV, including: • Risk factors for cardiovascular disease. • STIs (*Chlamydia (C.) trachomatis, Neisseria (N.) gonorrhoeae, Trichomonas (T.) vaginalis*, syphilis, human papillomavirus (HPV), genital warts, and herpes simplex virus (HSV)) among men and women, and HPV-associated pre-cancers and cancers. • Reproductive health, fertility, and pregnancy outcomes, including mother-to-child transmission of HIV. • Hearing impairments. 3. To define the impact of perinatal HIV infection and ART on long-term mental and behavioral health outcomes, including: • Mental health diagnoses, including depression, mood, anxiety, PTSD, psychosis, and ADHD. • 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, and licit and illicit drugs). • Independent living skills and vocational and education achievement necessary for successful transition to adult functioning and health-related quality of life.
Domain-Specific Aims:	Infectious and Non-Infectious Complications of HIV and Its Treatment • To define the long-term immunologic and virologic course of young adults with perinatal HIV infection, including disease progression, viral resistance, and the response to changes in therapy.

	• To identify cofactors that impact the course of HIV disease, including co-infections and host genetic markers. • To define the course of end-organ disease (i.e., renal, hepatic, cardiac, pulmonary, and peripheral and central nervous system) and HIV-associated malignancies and mortality among young adults with perinatal HIV infection, and to describe the relationship of these outcomes with HIV virologic status, ART, and immune status. <u>Metabolic Complications</u> • To estimate the prevalence, incidence, and risk factors for dyslipidemia, hypertension, obesity, and overall cardiometabolic risk and their relationship to HIV disease status and specific ART regimens over time. <u>Sexually Transmitted Infections</u> • To evaluate access to testing and treatment for genital STIs, and the incidence of and risk factors for acquiring STIs (e.g., *Chlamydia (C.) trachomatis, Neisseria (N.) gonorrhoeae, Trichomonas (T.) vaginalis*, syphilis, HPV, and HSV) among PHIV+ young adults. • To estimate the incidence of and risk factors for pelvic inflammatory disease among PHIV+ young women. • To examine the rate of cervical and anogenital high-grade squamous intraepithelial lesions (HSIL) in PHIV+. <u>Reproductive Health</u> • To describe the use of pregnancy prevention methods in PHIV+ young adults. • To estimate incidence and predictors of intended and unintended pregnancies. • To determine pregnancy outcomes and their predictors. • To identify HIV- and ART-associated and other risk factors for menstrual irregularity among PHIV+ young women. • To determine the incidence of and risk factors for mother-to-child transmission of HIV among PHIV+ young women. <u>Mental Health</u> • To examine the impact of mental health problems (MHPs) on health outcomes, including medication and medical care adherence, sexual behavior, and substance use. <u>Health Care Behaviors and Transition to Adult Health Care</u> • To describe predictors of adherence to ART and health care and changes in adherence over time. • To describe the transition into adult health care and to determine the individual and institutional factors that predict a successful transition to

	adult health care, as indicated by retention in adult health care and viral load suppression post-transition. • To evaluate whether individual factors, including age at transition, ability to manage health care, and participant involvement in transition decisions, and institutional factors (such as setup of adult clinic [family clinic, adult only, etc.], presence of social worker at an adult clinic) are associated with retention in adult health care and viral load suppression post-transition. <u>Risk Behaviors</u> • To examine the prevalence, changes over time, and predictors of sexual behaviors, including vaginal, oral, and anal intercourse, condom use, multiple sexual partners, and disclosure of HIV status and knowledge of partner's HIV status. • To examine the prevalence and predictors of use of licit (alcohol, tobacco) and illicit substances. <u>Transition to Adult Functioning and Health-Related Quality of Life</u> • To identify factors associated with successful transition to adult functioning (defined by educational attainment, employment, and independent living), health-related quality of life, and social support, relationships, and self-efficacy. <u>Hearing</u> • To explore the frequency of hearing problems and their impact on educational and employment attainment.
Monitoring:	Routine team monitoring of any adverse impact of the study will rely on the PHACS Protocol Query & Notification System (QNS), which is a real-time, web-based interactive reporting system. Sites will also record and enter in the study database, all untoward effects associated with study participation, which will be reviewed by the protocol team.

STUDY SCHEMA

(Target N = 500)

- Young adults with perinatal HIV infection at or beyond their 18th birthday at the time of informed consent with no upper age limit;
- Willing to provide access to any existing medical records; and
- Willing to participate and provide legal informed consent.

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Obtain informed consent, confirm eligibility, and enroll.

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Evaluations and Assessments at the Entry Time Point

- Clinical assessments: height, weight, and blood pressure measurements;
- Interviewer-administered medical history questionnaire: targeted medical and medications history, and family medical history;
- Web-based Illume survey: demographics, health care access and utilization, transition to adult HIV care, depression, health-related quality of life, social support, relationships, self-efficacy, HIV-related stigma, reproductive history, sexual behavior, substance use, ART adherence, fracture history and self-reported hearing issues;
- Chart abstraction: 1) medical diagnoses, ART medications, immunizations, CD4, viral load, HIV resistance testing, CBC profile, chemistry panel, lipid profile, glucose, pregnancy and pregnancy outcomes, results of STI testing, and abnormal cytology and histology in the 12 months prior to Entry, 2) nadir CD4 and lifetime history of AIDS-defining illness and CDC classification, and 3) mental health diagnoses including mood, anxiety, PTSD, psychosis, and ADHD in the 12 months prior to Entry; and
- Collection of repository specimens: serum, plasma, and PBMCs.

If an in-person visit cannot be completed at Entry, then height, weight, and blood pressure measurements will be collected through chart abstraction and the interviewer-administered medical history questionnaire will be completed via telephone.

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Annual Follow-Up Evaluations and Assessments

- Web-based Illume survey: demographics, height and weight, health care access and utilization, transition to adult HIV care, depression, health-related quality of life, social support, relationships, self-efficacy, HIV-related stigma, reproductive history, sexual behavior, substance use, ART adherence, interval fractures, and self-reported hearing issues;
- Chart abstraction: height and weight, blood pressure, interval medical diagnoses including AIDS-defining illness, CDC classification, ART medications, immunizations, CD4, viral load, HIV resistance testing, CBC profile, chemistry panel, lipid profile, glucose, pregnancy and pregnancy outcomes, results of STI testing, abnormal cytology and histology, and mental health diagnoses including mood, anxiety, PTSD, psychosis, and ADHD; and
- At Year 5 only: collection of repository specimens: serum, plasma, and PBMCs.

1.0 INTRODUCTION

1.1 Scientific Background

Improvements in the treatment of human immunodeficiency virus (HIV)-infected infants, children, and young adults have been remarkable, ensuring that most previously infected American infants and children have survived through adolescence and are approaching adulthood. It is estimated that there are approximately 10,000 perinatally HIV-infected (PHIV+) adolescents and young adults currently in the United States (U.S.) with 7,000 over 13 years of age; nearly 20% of these are over 18 years of age (Centers for Disease Control and Prevention (CDC), 2012). In addition, the number of PHIV+ adolescents and young adults worldwide is growing substantially in both resource-poor settings and settings with increasing levels of health care. There is a global cohort of PHIV+ adolescents and young adults who have been living with HIV infection since birth and who are aging into young adulthood. In the Pediatric HIV/Acquired Immunodeficiency Syndrome (AIDS) Cohort Study Adolescent Master Protocol (PHACS AMP), 451 PHIV+ young adult aged 7 - <16 years were enrolled from 2007-2009 with 72 remaining on study and 212 having enrolled in Adolescent Master Protocol for Participants 18 Years of Age and Older (AMP Up). In addition, 188 participants in other cohort studies (International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1074, 219/219C, and the Surveillance Monitoring for ART Toxicities (SMARTT) study) have enrolled into AMP Up (as of March 2017). Little is definitively known about the impact of HIV infection and its treatment on the long-term survival and outcomes among these young adults.

This study is designed as a prospective cohort study to define the impact of HIV infection and antiretroviral therapy (ART) on young adults with perinatal HIV infection as they age into adulthood. It will investigate the long-term outcomes of perinatal HIV infection and its treatment. This knowledge 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 conduct focused sub-studies addressing the medical and behavioral consequences of HIV and its therapy, genetic associations, disease processes and causation, interventions, and quality of life among PHIV+ young adults. Potential domains for future studies include complications of HIV infection, adjustment to adulthood, metabolic risk factors for cardiovascular disease, neurocognitive functioning and mental health, hearing, 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.

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 new PHIV+ children in the U.S. is now small. Subsequent improvements in the treatment of HIV-infected infants and children have been equally remarkable, ensuring that most infected American children have survived and are approaching adolescence. It is estimated that there are about 10,000 PHIV+ children and adolescents currently living with HIV in the U.S., with 76% of them 13 years of age and over (CDC, 2012). In addition, the number of HIV-infected adolescents worldwide is growing substantially in both resource-poor countries and in countries with increasing levels of health care.

PHIV+ children face unique challenges as they reach older childhood and adolescence. The advent of antiretroviral (ARV) treatment has only recently made surviving childhood a possibility for PHIV+ young adults, and AMP has 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 has been strongly correlated with lower viral loads and higher Cluster of Differentiation 4 (CD4) cell counts, even among children with a previous AIDS-defining condition (Van Dyke et al., 2011). However, PHIV+ young adults in AMP are also at increased risk for stunted growth, altered body composition, lipid abnormalities, and insulin resistance resulting from HIV and ARV drugs (Jacobson et al., 2011). These outcomes, along with elevated biomarkers of vascular dysfunction, may place PHIV+ young adults at higher risk for complications such as cardiovascular disease and metabolic abnormalities (Miller et al., 2010). Compared to perinatally HIV-exposed, -uninfected (PHEU) young adults, PHIV+ young adults appear to be at increased risk for other conditions, including atopic dermatitis and asthma (Siberry et al., 2012), and low bone mineral density (DiMeglio et al., 2013). Previous studies have found that PHIV+ young adults are also at risk for impaired cognitive and adaptive functioning. While HIV infection alone does not appear to increase the risk for cognitive impairment for youth in AMP, PHIV+ young adults who had an AIDS-defining illness in childhood may have an increased risk for specific and severe cognitive impairments (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, PHIV+ and PHEU young adults 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, but also for ability to adhere to medication regimens.

Medication adherence is a critical issue in understanding the long-term health status of PHIV+ young adults. More than one-fifth of young adults 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 young adults in AMP have been associated with higher viral loads (Usitalo et al., 2010). Further study is needed to understand the dynamics of variability in responses to ARV treatment interruption.

The transition into adolescence and adulthood presents additional challenges for PHIV+ and PHEU young adults. Although findings suggest that young adults in AMP are similar to nationally representative samples in terms of substance use (Alperen, et al., 2013) and sexual initiation (Tassiopoulos et al., 2013), HIV adds a layer of complexity to these issues that can make poor medication adherence, non-disclosure of HIV status to sexual partners, and risky sexual behaviors difficult for PHIV+ young adults and their caregivers to navigate. For many HIV-affected young adults, a myriad of physical, psychosocial, family, and environmental stressors increase the risk of mental health problems (MHPs) and of initiating substance use and risky 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., 2013; Kacanek, et al., 2016). Rates of MHPs (such as attention problems, anxiety, and depression) among AMP young adults are higher than national averages for U.S. young adults, but are consistent with other studies of young adults with chronic illness (including PHIV+ and PHEU young adults). For PHIV+ young adults, MHPs 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 MHPs among PHEU young adults compared to PHIV+ young adults (Mellins et al., 2011).

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 highly active antiretroviral therapy (HAART) (Gona et al., 2006; Nachman et al., 2009; Purswani et al., 2012; Patel et al., 2009; Patel 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. 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. However, at their most recent study visit, 35% of HIV-infected AMP Up participants had a detectable viral load and it will be important 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. PHIV+ young adults are unique, having HIV exposure beginning 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 unclear how specific ARV drugs may affect PHIV+ young adults concerning long-term risk for organ system toxicities. For example, risk for nephrotoxicity due to tenofovir disoproxil fumarate exposure may differ for PHIV+ young adults compared to healthy HIV-infected adults due to their prolonged exposure to HIV or diverse history of ARV drug exposure (Fernandez-Fernandez et al., 2011). A recent study reported a potential duration effect of tenofovir disoproxil fumarate on proteinuria among PHIV+ adolescents, therefore, continued follow up is necessary to assess future risk of clinical disease (Purswani et al., 2012).

The uniqueness of the PHIV+ young adult 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 PHIV+ young adults are common (Siberry et al., 2011). As a result, they are more likely to have resistant virus than the overall HIV population in the U.S. (Van Dyke, et al., 2016). There is a need therefore to estimate the risks and benefits of alternative treatment strategies particularly after treatment failure. Accumulating a longitudinal history of viral load and CD4 cell counts may also help with identifying young adults for future cure strategies.

Host genetic variants are increasingly being identified which influence the course of HIV infection and its response to therapy. Examples include polymorphisms on chromosome 22 which predispose African Americans to HIV-associated nephropathy (Wyatt, Meliambro, & Klotman, 2012; Purswani, et al., 2016) and CYP2B6 genetic polymorphisms associated with differences in efavirenz concentrations (Elens et al., 2010). PHACS has established a repository of amplified genomic deoxyribonucleic acid (DNA) in order to address genetic determinants of host response. Similarly, co-infections such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV) may affect the pathogenesis of HIV disease (Leruez-Ville et al., 2012; Lichtner et al., 2012).

PHIV+ adolescents and young adults who are now aging into adulthood were born in the pre-HAART era and may have received many of their childhood vaccines prior to HAART initiation. Previous studies have demonstrated that they may lack protective immunity to vaccine-preventable diseases such as measles, mumps, rubella and varicella, which have informed vaccination guidelines for PHIV+ children and adolescents worldwide (Siberry, et al., 2015).

1.1.3 Metabolic Complications in PHIV+ Young Adults

Since the advent of ART, patients with HIV have longer life expectancies, but chronic conditions such as metabolic and cardiovascular disease are becoming more prevalent in this population (Fitch & Grinspoon, 2011). HAART 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, Samaras, Chisholm, & Cooper, 1998; Grinspoon & Carr, 2005). Following exposure to ART, there are increases in total, low density lipoprotein (LDL), and high density lipoprotein (HDL) cholesterol in both adults and children.

The physiologic effect of the metabolic syndrome places patients at risk for cardiovascular disorders. In fact, in adults with HAART-related fat redistribution, several studies have suggested an increase in the risk of myocardial infarction (MI) relating to the level of viral control (increased inflammation) or to ART exposures (including protease inhibitors and certain nucleoside reverse transcriptase inhibitors (NRTIs)) (Friis-Moller et al., 2003; Mary-Krause, Cotte, Simon, Partisani, & Costagliola, 2003; Palella, Jr. & Phair, 2011). However, there is controversy whether the metabolic syndrome in HIV-infected patients is exclusively related to ART exposure or HIV; 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 an older age and longer duration of HAART (Arpadi et al., 2009; Geffner et al., 2011; Jacobson et al., 2011; Miller et al., 2008; Miller et al., 2012; Sanchez Torres et al., 2005). The onset of puberty has been proposed as another factor that is associated with these changes (Moscicki, Ellenberg, Murphy, & Jiahong, 2006).

1.1.4 Sexually Transmitted Infections in HIV-Infected Young Adults

Rates of chlamydia, gonorrhea, herpes simplex virus (HSV), human papillomavirus (HPV) and *Trichomonas (T.) vaginalis* all peak in men and women under the age of 25 years (CDC, 2016). The risks associated with chlamydia, gonorrhea and *T. vaginalis* in HIV-infected persons are likely similar to those of uninfected persons and include unprotected intercourse, high risk sex such as anal sex, substance use during sex, and having sex with high risk partners (Setse et al., 2011). One study of pregnant HIV-infected women found that low CD4 cell counts increased the risk of chlamydia, syphilis and *T. vaginalis* (Landes et al., 2007). Unfortunately, the consequences associated with these infections may be of greater importance in HIV-infected persons since increased genital shedding of HIV has been shown to occur with these infections, raising the risk of transmission to other partners (Kalichman, Pellowski, & Turner, 2011). In addition, it remains unknown whether rates of infertility are higher in HIV-infected women due to these infections (Kushnir & Lewis, 2011; Badell & Lindsay, 2012). Little is known regarding risk for these STIs among PHIV+ young adults.

Among the STIs confronting sexually active adolescents and young adults, HPV has the greatest known sequelae in HIV-infected persons. 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, Frederiksen, Munk & Iftner, 2010). Unfortunately, HIV and other immunocompromised situations (i.e., organ transplants) are associated with not only increased persistence (Moscicki, Ellenberg, Farhat, & Xu, 2004) but also a 2-200 fold higher risk of developing one of these cancers (Denny et al., 2012). 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 (Hellberg & Stendahl, 2005). 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, Wahlroos, Syrianen, Johansson, & Syrianen, 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 expected since HPV persistence has been linked to disordered cell mediated immune responses (Kadish et al., 2002; Scott, Nakagawa, & Moscicki, 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 HIV-infected females (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 HIV-infected than uninfected (21.5% vs. 4.8% incidence by end of follow-up). This finding was even more dramatic for HIV-infected adolescents with baseline or early low-grade squamous intraepithelial lesions (LSIL) where 31% progressed to HSIL. In the final multivariable 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 HIV-infected women (Munoz et al., 1993).

The data regarding ART and HPV control is complicated. It appears that control of HIV replication and improved CD4 cell counts resulting from ART may lower the risk of developing HSIL. However, once HSIL develops, ART does not appear to influence its natural history strongly (Schuman et al., 2003; Ahdieh-Grant et al., 2004). A study by 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. Unfortunately, little is known about the natural history of HPV in adolescents and young adults with perinatal HIV infection, limiting our ability to care for this group adequately. This is particularly important since a recent study (Farhat, Ma, Puga, & Moscicki, 2012) found that prevalence of genital HPV was more common in non-sexually active PHIV+ girls compared to non-sexually active HIV-uninfected girls. This might not be too surprising since exposure to HPV occurs at birth in many infants and continues throughout infancy (Rintala et al., 2005). However, persistence of any one HPV type is rare in non-immunocompromised infants. HIV-infected children may be at particular risk since mothers are more likely to shed HPV at birth and during infancy. In turn, these children may be more predisposed to persistence when exposed to HPV.

The REACH study included adolescents with behaviorally acquired HIV who had been HIV-infected for a relatively short period. Most were not receiving ART. One of the only studies of reproductive health in PHIV+ adolescents 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, 2013). 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 HPV to be studied in the context of long-term perinatal HIV infection and ART.

HPV has recently been recognized as an important pathogen in oropharyngeal (Gillison et al., 2012). As with other HPV-associated cancers, oropharyngeal cancers are also higher in HIV-infected persons than in uninfected persons (Gillison, 2009). Data suggest that oral HPV infections are more common and more likely to persist in HIV-infected persons explaining the increased risk (Beachler et al., 2012). Oral sex behaviors are also associated with oral cancer risks (Upile et al., 2012).

1.1.5 Reproductive Health

Pregnancy and Contraception

As young PHIV+ women and men reach adulthood, sexual activity and pregnancy will become more common. Desire for pregnancy among HIV-infected women in the U.S., especially young women, varies, with some reporting a desire to have children after learning of their HIV infection (Craft, 2007). Decisions about keeping or terminating a pregnancy, whether initially wanted or unwanted, are particularly complex for HIV-infected women. Job security, goals, family support, relationship history, desire to have a child with a particular partner, the partner's desire for pregnancy, abuse, health status, substance use, cognition, and access to reproductive health services including abortion 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, Mosher, & Daniels, 2012). Use of and adherence to effective contraceptive methods affects efficacy since long acting contraceptives (LAC) such as medroxyprogesterone and intrauterine devices (IUD) have been shown to be superior to daily methods (i.e., oral contraceptives) (Winner et al., 2012). Adherence plays a significant role since the LAC requires less attention to adherence. 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., IUD) or irreversible. There is virtually little to no information regarding PHIV+ young adults' contraceptive choices 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 known of PHIV+ young men's reproductive health choices and desires for children.

In the few studies of pregnancy rates and outcomes in PHIV+ young women in the U.S. (Levine, Aaron, & Foster, 2006; Brogly et al., 2007; Williams, Keane-Tarchichi, Bettica, Dieudonne, & Bardeguez, 2009; Agwu, Jang, Korthuis, Araneta, & Gebo, 2011; Koenig et al., 2007), many young women reported that their pregnancy was unplanned (Koenig et al., 2007), and the 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 are critical in anticipation of a wanted pregnancy, during pregnancy, and postpartum. Adherence issues may affect decisions about carrying a pregnancy to term, as well as contraceptive choices, the acceptability of various contraceptive methods, and may be associated with complications of pregnancies. 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 are incorporated into these different health care settings.

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 HIV-infected women are more likely to have amenorrheic episodes (Chirgwin, Feldman, Muneyyirci-Delale, Landesman, & Minkoff, 1996; Cejtin et al., 2006). The mechanisms remain elusive. A few studies have shown there is no association between being HIV infected and amenorrhea after adjusting for age, body mass index (BMI) and substance use (Ellerbrock et al., 1996; Harlow et al., 2000). However, in more recent studies, HIV-infected women were found to be three times more likely to have prolonged amenorrhea than HIV-negative controls 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. (2004) found pregnancy rates of 7.4 per 100 person-years in HIV-infected women compared to age comparative rates of 15.2 in HIV-uninfected women ($p < 0.001$). Among the HIV-infected, 36% ended in live birth, 2% still birth, 36% elective abortion, 24% miscarriage, and 5% ectopic pregnancies. These outcomes were no different from HIV-uninfected women. Overall, women with HIV 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.

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

Zidovudine (ZDV) and other NRTIs 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 ZDV-treated pregnant primates, ZDV 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 (Pavili et al., 2010; Lopez et al., 2008). Oocytes with low levels of mitochondrial deoxyribonucleic acid (mtDNA) 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. HAART 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 HIV-infected men. Tuberculosis, also more common in HIV-infected persons, is associated with uterine disease and infertility.

Fertility data in PHIV+ women 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, Townsend, Peckham, Newell, & Tookey, 2007). A recent study in New York found higher risk of small for gestational age outcomes in children of PHIV+ women vs. women infected later in life (Jao et al., 2012). There are some data to suggest that preterm delivery is increased with protease inhibitor regimens as well as substance use and advanced HIV disease (Badell & Lindsay, 2012). Preterm delivery is associated with significant neonatal morbidity and mortality.

1.1.6 Mental Health

MHPs among PHIV+ children and adolescents, including attention deficit hyperactivity disorder (ADHD), anxiety, and depression, were identified prior to and during the HAART era (Brouwers et al., 1995; Brown,

Lourie, & Pao, 2000; Mellins et al., 2003; Mellins et al., 2009b; Papola, Alvarez, & Cohen, 1994; Sharko, 2006). Prevalence and types of problems varied due to assessment and sampling methodologies, but rates of MHPs in both PHIV+ and HIV-affected young adults were higher than expected (Bauman, Camacho, Silver, Hudis, & Draimin, 2002; Mellins et al., 2003; Mellins et al., 2009b).

There is increasing evidence that long-term survivors with PHIV are at high risk for new or persisting MHPs given genetic, biomedical, familial, and environmental risk factors (Havens & Mellins, 2008; Donenberg & Pao, 2005; Gadow et al., 2012; Mellins et al., 2012; Nachman et al., 2012). Recent longitudinal investigations of PHIV+ young adults documented high rates of Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) diagnosed psychiatric disorders among PHIV+ young adults and HIV-affected young adults, including anxiety, depression and behavioral disorders, such as ADHD (Chernoff et al., 2009; Gadow et al., 2010; Gadow et al., 2012; Kapetanovic et al., 2011; Mellins et al., 2009b; Mellins et al., 2012; Wood et al., 2009). Rates of disorder over time are high, with large numbers of young adults in both PHIV+ and HIV-affected groups 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 MHPs among PHIV+ and HIV-affected young adults (Malee et al., 2011a; Malee et al., 2011b; Nozyce et al., 2006) and high rates of specific disorders, such as depression, among PHIV+ young adults (Elkington et al., 2011).

The etiology of MHPs among PHIV+ 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 young adults 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 HIV-infected young adults, secondary to suboptimal ARV treatment or intermittent nonadherence (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 young adults at risk for MHPs during late adolescence and young adulthood. Significant and subtle neurocognitive deficits are observed in some PHIV+ young adults (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 MHPs, as observed among adults with advanced HIV disease.

Older adolescents and young adults coping with HIV since birth share stressors experienced by young adults with other chronic illnesses, including ongoing medical treatment, hospitalizations, and exposure to pain (Gortmaker et al., 1990; Hysing et al., 2007). They also face a host of unique issues related to the psychosocial impact of HIV, a highly stigmatized and transmittable illness. Young adults with perinatal HIV infection 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; Steele, Nelson, & Cole, 2007), all of which have been associated with increased rates of MHPs during childhood and adolescence (Achenbach, Howell, Quay, & Conners, 1991; Bradley & Corwyn, 2002; McCarty & McMahone, 2003). Furthermore, many PHIV+ young adults have grown up in single parent households or have experienced multiple caretaking transitions due to parental illness or death (Havens & Mellins, 2008; Rotheram-Borus et al., 2002).

Parental psychiatric and substance abuse disorders are additional risk factors for MHPs in many PHIV+ young adults. Psychiatric disorders, such as depression, disproportionately affect women and are common among women with HIV/AIDS (Kapetanovic et al., 2011; Morrison et al., 2002; Rotheram-Borus, Lightfoot, & Shen, 1999), and particularly HIV-infected mothers (Mellins et al., 2008; Malee et al., 2013). As a result, HIV-affected young adults 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, Versage, & Gladstone, 1998; Cummings & Davies, 1994; Cummings, Keller, & Davies, 2005; Leve, Kim, & Pears, 2005; Pilowsky et al., 2006; Reef et al., 2009). These outcomes 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 PHIV+ young adults. Caregiver-young adult relationships, caregiver support, caregiver limit setting, and parent-child communication and involvement have been associated with young adults' mental health (Elkington et al., 2011; 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 disadvantaged neighborhoods, are critical predictors of mental health (Kang et al., 2011) and may be experienced at higher rates as young adults 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 (Elliot-DeSorbo et al., 2009) and may be protective.

In summary, young adults with HIV infection are at risk for MHPs and behavioral health problems (Mellins et al., 2009a; Mellins et al., 2011; 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 PHIV+ young adults emerge into young adulthood in increasing numbers.

1.1.7 Health Care Behaviors and Transition to Adult Health Care

As young adults with perinatally-acquired HIV infection enter adulthood, maintaining adherence to ARV medications and transitioning from pediatric to adult HIV medical care systems are substantial challenges (Hazra, Siberry, & Mofenson, 2010; Dowshen & D'Angelo, 2011; MacDonnel, 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 (Paterson et al., 2000; Bangsberg et al., 2001; Van Dyke et al., 2002). In addition, adherence to ARV medications is a critical component of preventing mother-to-child as well as sexual transmission of HIV. Adherence is more frequently suboptimal at older ages among young adults living with HIV disease (Williams et al., 2006; Mellins, Brackis-Cott, Dolezal, & Abrams, 2004). By late adolescence, many young adults 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 PHIV+ adolescents enter young adulthood, their ability to access providers of reproductive health care services and contraceptives that can meet the unique needs of PHIV+ young women and men will also be important. In order to develop effective interventions to help PHIV+ young adults 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 who are PHIV+ are not well understood. HIV disease severity and regimen-related factors, including side effects, complexity, and duration on treatment are associated with suboptimal adherence in studies of behaviorally infected and perinatally infected children and young adults. PHIV+ young adults may experience treatment fatigue and lapses in adherence during their lifetimes because of their long histories

of ARV use, taking ARVs since childhood. These contribute to the high rates of ARV resistance in this population. As a result, many PHIV+ young adults 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, Kekwaletswe, Hosek, Martinez, & Rodriguez, 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 PHIV+ woman or man 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, Wilson, Durako, Muenz, & Belzer, 2001; Murphy et al., 2005; Williams et al., 2006), conduct disorder (Walkup, Akincigil, Bilder, Rosato, & Crystal, 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 non-adherence in studies of HIV-infected adults, the role of violence and trauma in HIV+ adults is not known.

The growing population of adolescents with HIV who are transitioning to adult health care is of special concern (Gilliam et al., 2011; Wiener, Kohrt, Battles, & Pao, 2011; Fair, Sullivan, & Gatto, 2010; Pavia, 2006). 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 to medical appointments is critical for their continued HIV viral suppression and overall health (Fair et al., 2010). 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 PHIV+ young adults (Dowshen & D'Angelo, 2011; Wiener et al., 2011; Peter, Forke, Ginsburg, & Schwarz, 2009; Andiman, 2011; Vijayan, Benin, Wagner, Romano, & Andiman, 2009). Young adults 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 (Vaudre, Sylvain, Delmas, Dollfus, & Leverger, 2012; Wiener et al., 2011; Remien & Mellins, 2007). In a qualitative study of young adults who transitioned to adult care, immune function reflected by CD4 cell 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 ARV medications and care during this transition include poverty, inadequate insurance coverage, employment instability, housing instability and lack of access to supportive social networks (Andiman, 2011; Dowshen & D'Angelo, 2011), as well as the set-up of the adult clinic (family services, adult-only, etc.). The U.S. Department of Health and Human Services (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 PHIV+ young adults 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).

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

1.1.8 Risk Behaviors (Sexual Behaviors, Substance Use, Disclosure to Sexual Partners)

PHIV+ adolescents face the same decisions and challenges as those faced by non-infected adolescents during the transition into young adulthood; however, these decisions may be further complicated by their lifelong infection with HIV, 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 PHIV+ adolescents show high prevalence of risky 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 and as the cohort enters young adulthood this prevalence will increase. Inconsistent condom use is common among sexually active young adults in AMP as it is among other cohorts of PHIV+ and uninfected young adults in the U.S. Unfortunately, many AMP young adults reported that they did not disclose their HIV status to their sexual partners (Tassiopoulos et al., 2013; Koenig, Espinoza, Hodge, & Ruffo, 2007). The prevalence of substance use in AMP, particularly alcohol and marijuana, is also high (Alperen et al., 2013). The prevalence of both licit and illicit substance use will likely increase as individuals enter young adulthood.

The young adults in AMP Up and AMP Up Lite provide the first 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.

1.1.9 Transition to Adult Functioning and Health-Related Quality of Life

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 young adults 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 quality of life. High rates of cognitive, language (Rice et al., 2012; Smith et al., 2012) and mental health problems among PHIV+ youth (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 be barriers during young adulthood and significantly impact a young adult's health-related quality of life as well as their mental and emotional well-

being and their self-efficacy. Successful transitioning to adult functioning will be evaluated, including educational attainment, employment and independent living, and important quality of life outcomes including health-related quality of life, mental health, self-efficacy, and presence of close personal relationships. Factors associated with successful transition to adult functioning and health-related quality of life will also be evaluated.

1.1.10 Hearing

There is a higher rate of hearing loss in children and adolescents who are 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.

1.2 Rationale

The advent of potent ART has resulted in the survival of a substantial proportion of PHIV+ infants and children into adolescence and young adulthood. In parallel, the number of newly HIV-infected infants in the U.S. has decreased dramatically since 1993 with the development of effective means to prevent mother-to-child transmission of HIV. Thus, the largest group of children with perinatal HIV infection in the U.S. consists of adolescents and young adults. Some of these young adults represent long-term slow-progressors, while the majority is those who have 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 is the focus of PHACS AMP and AMP Up (Tassiopoulos, et al., 2016). AMP and AMP Up address 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 cardiovascular disease. Between 2007 and 2012, 451 PHIV+ children between 7 and 15 years of age enrolled in AMP. As of March 2017, their median duration of follow-up was 6.5 years, with 72 remaining on study and 212 having enrolled in AMP Up. In addition, 188 participants previously in other cohort studies (IMPAACT P1074, 219/219c, and SMARTT) have enrolled into AMP Up.

The goal of AMP Up Lite is to enroll additional PHIV+ young adults who have not participated in the AMP and AMP Up studies and to follow them in order to identify longer-term outcomes of HIV in those with perinatally-acquired infection and its treatment. This protocol offers a simplified approach to data collection in order to maximize retention of participants, incorporating chart abstraction and web-based data collection. The only in-person visit is at the Entry time point. At Year 5, participants will return for the repository specimen collection. Participants who cannot complete an in-person Entry visit and/or return for the Year 5 repository specimen collection can still participate in the study. Areas of emphasis include HIV disease progression; bone fractures and end-organ disease; 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 quality of life of young adults with perinatal HIV. 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 perinatal HIV 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 PHIV+ young adults 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 suppression, viral resistance, end-organ disease, and mortality.

2. To define the impact of HIV infection and ART on the long-term clinical outcomes of young adults with perinatal HIV, including:

   - Risk factors for cardiovascular disease.
   - STIs (*Chlamydia (C.) trachomatis, Neisseria (N.) gonorrhoeae, Trichomonas (T.) vaginalis*, syphilis, HPV, genital warts, and HSV) among men and women, and HPV-associated pre-cancers and cancers.
   - Reproductive health, fertility, and pregnancy outcomes, including mother-to-child transmission of HIV.
   - Hearing impairments.

3. To define the impact of perinatal HIV infection and ART on long-term mental and behavioral health outcomes, including:

   - Mental health diagnoses, including depression, mood, anxiety, PTSD, psychosis, and ADHD.
   - 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, and licit and illicit drugs).
   - Independent living skills and vocational and educational achievement necessary for successful transition to adult functioning and health-related quality of life.

2.2 Domain-Specific Aims and Hypotheses

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

Specific Aims:

- To define the long-term immunologic and virologic course of young adults with perinatal HIV infection, including disease progression, viral resistance, and the response to changes in therapy.
- To identify cofactors that impact the course of HIV disease, including co-infections and host genetic markers.
- To define the course of end-organ disease (i.e., renal, hepatic, cardiac, pulmonary, and peripheral and central nervous system) and HIV-associated malignancies and mortality among young adults with perinatal HIV infection, and to describe the relationship of these outcomes with HIV virologic status, ART, and immune status.

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 results in an impaired immune response to immunizations and infections, resulting in long-term susceptibility to infection. Re-immunization once immune reconstitution is achieved will be necessary for most childhood vaccines.
- CMV infection contributes to HIV disease progression and potentiates end-organ disease.
- Host genetic polymorphisms and epigenetic changes are associated with HIV disease progression, response to ART, and specific end-organ disease.
- Chronic inflammation and immune activation are associated with HIV disease progression and specific end-organ disease.
- Participants without viral suppression will have a higher incidence of end-organ disease progression related to both HIV infection and ART therapy compared to those with suppression.
- PHIV+ participants with viral suppression will have an increased incidence of end-organ disease due to persistent immune activation relative to the general population related.

2.2.2 Metabolic Complications

Specific Aim:

- To estimate the prevalence, incidence, and risk factors for dyslipidemia, hypertension, obesity, and overall cardiometabolic risk and their relationship to HIV disease status and specific ART regimens over time.

Hypotheses:

- Specific ART regimens, ART classes, HIV viral burden, and immune activation will have differential effects on individual cardiometabolic outcomes over time.

2.2.3 Sexually Transmitted Infections

Specific Aims:

- To evaluate access to testing and treatment for genital STIs, and the incidence of and risk factors for acquiring STIs (e.g., *C. trachomatis, N. gonorrhoeae, T. vaginalis*, syphilis, HPV, and HSV) among PHIV+ young adults.
- To estimate the incidence of and risk factors for pelvic inflammatory disease among PHIV+ young women.
- To examine the rate of cervical and anogenital HSIL in PHIV+.

Hypotheses:

- HPV and HSV will be found more frequently in PHIV+ young adults with lower CD4 cell counts.
- Young adults with HIV will have a high rate of oral high-risk HPV persistence. Risks for oral high-risk HPV persistence will include lower CD4 cell counts.

- PHIV+ young women will have high rates of abnormal cervical cytology.

2.2.4 Reproductive Health

Specific Aims:

- To describe the use of pregnancy prevention methods in PHIV+ young adults.
- To estimate incidence and predictors of intended and unintended pregnancies.
- To determine pregnancy outcomes and their predictors.
- To identify HIV- and ART-associated and other risk factors for menstrual irregularity among PHIV+ young women.
- To determine the incidence of and risk factors for mother-to-child transmission of HIV among PHIV+ young women.

Hypotheses:

- The majority of PHIV+ young women who use pregnancy prevention will choose long acting contraceptives. These methods will be superior to combined oral contraceptive pill in preventing pregnancies.
- Predictors of pregnancy intention will include younger age, lack of social support, substance use history, and depression.
- Among PHIV+ young adults, the frequency of successful intended pregnancies will be associated with those with high CD4 cell count, lower viral loads, and higher perceived social support.
- PHIV+ young women will have evidence of anovulatory cycles, defined as having cycles < 21 and > 35 days after adjusting for type of hormonal contraceptive use (long acting vs. other), BMI, and substance use.
- Irregular cycles will be affected in PHIV+ young women by stress/depression, BMI, CD4 cell count, type of hormonal contraception (long acting vs. other), and substance use.
- The rate of maternal-to-child transmission of HIV will be low, and will be influenced by viral load, maternal adherence to ART, and engagement in medical care.

2.2.5 Mental Health

Specific Aims:

- To examine the impact of MHPs on health outcomes, including medication and medical care adherence, sexual behavior, and substance use.

Hypotheses:

- Prevalence and severity of MHPs will be higher among PHIV+ young adults with HIV-associated disease characteristics, including history of AIDS-defining illness and evidence of immune dysfunction (low CD4 cell count, detectable HIV ribonucleic acid (RNA) viral load, presence of drug resistant viral mutations).

- Factors such as social support, self-efficacy, and close personal relationships will be associated with mental health outcomes and attainment of transition milestones (educational attainment, employment).
- Presence of MHPs will be associated with other behavioral health risks including substance use/abuse, sexual behaviors (unprotected sex, unplanned parenthood, non-disclosure of HIV status), and non-adherence.

2.2.6 Health Care Behaviors and Transition to Adult Health Care

Specific Aims:

- To describe predictors of adherence to ART and health care and changes in adherence over time.
- To describe the transition into adult heath care and to determine the individual and institutional factors that predict a successful transition to adult health care, as indicated by retention in adult health care and viral load suppression post-transition.
- To evaluate whether individual factors, including age at transition, ability to manage health care, and participant involvement in transition decisions, and institutional factors (such as setup of adult clinic [family clinic, adult only, etc.], presence of social worker at adult clinic) are associated with retention in adult health care and viral load suppression post-transition.

Hypotheses:

- Young adults with inadequate insurance and those lacking a pediatric to adult care transition plan will evidence lower rates of adherence to care and ART following transition.
- The presence of supportive, personal relationships will be associated with higher rates of adherence following transition.
- Inadequate social support and psychosocial resources (housing, health insurance) will be associated with difficulties in transitioning to adult health care.
- HIV-related stigma will be associated with higher rates of nonadherence and lower rates of engagement in adult health care.
- MHPs, history of non-adherence, and substance abuse will be associated with difficulties with transition to adult health care.
- Lack of a site- or patient-specific plan to transition to adult health care will be associated with lower rates of engagement in adult health care and worse clinical outcomes (lower CD4 cell count, higher viral load).
- Presence of a social worker at the adult health care clinic will be associated with greater retention in adult health care and better clinical outcomes (higher CD4 cell count, lower viral load).

2.2.7 Risk Behaviors

Specific Aims:

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

Hypotheses:

- The majority of PHIV+ young adults will be sexually active and prevalence of vaginal and anal intercourse will be similar to that of uninfected young 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 and may be lower with the use of pre-exposure prophylaxis (PrEP).
- Condom use will be influenced by participant's viral load, partner type, knowledge of partner's HIV status, pregnancy intention, sexual coercion, and by whether a discussion of condom use preceded intercourse, and whether substance use preceded intercourse.
- Disclosure of HIV status to sexual partners will be incomplete, influenced by condom use, partner type, viral suppression, as well as 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 and lack of social support. In turn, substance use will influence the prevalence of unprotected sexual intercourse and other risky sexual behaviors, including lack of disclosure to sexual partners.

2.2.8 Transition to Adult Functioning and Health-Related Quality of Life

Specific Aims:

- To identify factors associated with successful transition to adult functioning (defined by educational attainment, employment, and independent living), health-related quality of life, and social support, relationships, and self-efficacy.

Hypotheses:

- MHPs, history of non-adherence, as well as inadequate social support, will be associated with difficulties in transitioning to adult functioning and with poorer health-related quality of life.

2.2.9 Hearing

Specific Aims:

- To explore the frequency of hearing problems and their impact on educational and employment attainment.

Hypotheses:

- Participants with hearing impairments will have lower educational attainment.
- Hearing impairments will be strong predictors of socio/emotional, education, and employment outcomes.

3.0 STUDY DESIGN

This study will establish a cohort of up to 500 PHIV+ young adults. Recruitment and enrollment will close once the desired number of participants is enrolled.

Participants will be evaluated prospectively according to an established schedule of evaluations, conducted both in-person and online (see Appendix I). The study will prospectively document infectious and non-infectious complications of HIV and ART annually by chart abstraction. 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 sub-studies designed to address specific scientific questions.

3.1 Study Population

Participants in this study will be young adults with perinatal HIV infection at or beyond their 18th birthday.

3.2 Sample Size

Approximately 500 PHIV+ young adults will be enrolled in the study.

3.3 Study Duration

The length of participation for each individual study participant is at least six years. The expected duration of the entire study is at least six years after the last participant is enrolled.

3.4 Biological Specimens

Biological specimens will be collected for the PHACS Repository at Entry and Year 5 and will include serum, plasma, and peripheral blood mononuclear cells (PBMCs).

4.0 SELECTION AND ENROLLMENT OF STUDY PARTICIPANTS

4.1 Inclusion Criteria

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

- Perinatal HIV infection as documented in the medical record.
- At or beyond their 18th birthday at the time of informed consent with no upper age limit.
- Willingness to provide access to existing medical records.
- Willingness to participate and provide legal consent.

4.2 Exclusion Criteria

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

- Prisoner status.

4.3 Study Registration Procedures

Prior to implementation of the study, sites must have the study protocol and consent form approved by their local institutional review board (IRB). In addition, sites must receive protocol registration approval from the Regulatory Affairs Office at 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. The procedures for registration are outlined in the PHACS Manual of General Operations (MOGO). The MOGO chapter pertaining to protocol registration can be found on the PHACS website.

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 for the study. Potential participants will be identified and referred to the clinical research team for potential enrollment. A research staff member will provide an overview of the study and gauge the potential participant's interest in participating.

4.5 Informed Consent

Once it is determined, that a participant may qualify for the protocol, informed consent will be obtained before any study-related medical abstraction or evaluation is performed (see Appendices VI and VII). 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 will be conducted at the clinical site prior to study enrollment. Remote (online) consent may be available at select study sites for participants who cannot go in person to the clinical site. When necessary, re-consenting may occur via a web-based informed consent form when there are protocol amendments requiring re-consent or when the participant is no longer affiliated with the local clinical site (see next paragraph). The PHACS Leadership will work with the clinical sites to ensure that the web-based informed consent completed by each site's participants is developed in accordance with sites' local IRB requirements and has been approved by their IRB. If web-based informed consent should occur, clinical site staff will be available for phone consultation to address questions or concerns. Participants will also be offered the option of coming to the clinic to re-consent in person. Clinical site staff will monitor whether the mental capacity of a participant changes throughout the course of the study. Each site employs psychology staff that can advise when a participant's competence to give continuing consent is in question, and sites will contact their local IRB for guidance.

When a participant is unable (due to, for example, participant moves or site closure) or unwilling to continue to be followed by their clinic site after Entry, they may continue to be followed by the PHACS Data and Operations Center (DOC) at the Harvard T.H. Chan School of Public Health (HSPH). This may be accomplished by either web- or telephone-based consenting. For participants followed at HSPH, HSPH staff will be available for telephone consultation when online informed consent is conducted.

The online consent form may include verification of comprehension and require participants to acknowledge that they have read and agree to the consent form by checking a box following each section of the consent. Verification of identification during the consent process will be confirmed using a personal identification number (PIN) provided to the participant by the clinical site at the Entry time point. 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 Subject Enrollment System (SES) at Frontier Science and Technology Research Foundation (FSTRF), 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 patient identification number (PID). Participants recruited from IMPAACT or AIDS Clinical Trial Group (ACTG) will retain their IMPAACT or ACTG PID. A new PID will be assigned to participants who were not enrolled in any of these studies. For all participants, once confirmed eligible and enrolled, the SES will generate a study identification number (SID). In AMP Up Lite the SID will serve as the participant's protocol-specific PIN.

4.7 Co-Enrollment Guidelines

Enrollment of AMP Up Lite participants in other studies (with or without similar goals/data collection as AMP Up Lite) is at the discretion of the clinical site Principal Investigator (PI). However, he or she 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. Enrollment into AMP Up Lite of participants who are already enrolled in other studies of PHIV+ youth and young adults with similar goals and data collection as AMP Up Lite is at the discretion of the protocol co-chairs. Sites should query for permission to enroll these individuals into AMP Up Lite.

Children born to HIV-infected female participants are encouraged to be enrolled in the PHACS SMARTT Dynamic Cohort.

5.0 CLINICAL AND WEB-BASED 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 Appendix I for a tabulated summary of the evaluations described below and their schedule for completion.

5.1 Entry Time Point (Year 0) Evaluations

Entry time point evaluations for all participants will include clinical assessments, an interviewer-administered medical history questionnaire, the web-based Illume survey, chart abstraction, and collection of specimens for the PHACS Repository.

- Clinical assessments will include height, weight, and blood pressure measurements. If an in-person visit cannot be completed at Entry, then height, weight, and blood pressure measurements will be collected through chart abstraction.
- An interviewer-administered medical history questionnaire will be completed to collect targeted medical and medications history, and family medical history. This questionnaire may be completed via telephone for subjects who cannot complete an in-person visit at Entry.
- The web-based Illume survey will collect information on demographics, health care access and utilization, transition to adult HIV care, depression (CES-D 10), health-related quality of life (SF-20), social support, relationships, self-efficacy, HIV-related stigma, reproductive history, sexual behavior, substance use, ART adherence, fracture history, and self-reported hearing issues.
- Chart abstraction will include: 1) medical diagnoses, ART medications, immunizations, CD4, viral load, HIV resistance testing, complete blood count (CBC) profile, chemistry panel, lipid profile, glucose, pregnancy and pregnancy outcomes, results of STI testing and abnormal cytology and histology in the 12 months prior to Entry, 2) nadir CD4 and lifetime history of AIDS-defining illness and CDC classification, and 3) mental health diagnoses including mood, anxiety, PTSD, psychosis, and ADHD in the 12 months prior to Entry.

- Blood (serum, plasma, and PBMCs) will be collected for storage in the PHACS Repository.

5.2 Annual Chart Abstraction and Web-Based Illume Survey Evaluations

After the Entry time point, chart abstraction and the web-based Illume survey will be completed annually.

- The web-based Illume survey will be completed remotely outside of the clinic and will include questions on demographics, height and weight, health care access and utilization, transition to adult HIV care, depression (CES-D 10), health-related quality of life (SF-20), social support, relationships, self-efficacy, HIV-related stigma, reproductive history, sexual behavior, substance use, ART adherence, interval fractures, and self-reported hearing issues.
- Chart abstraction will include height and weight, blood pressure, interval medical diagnoses including AIDS-defining illness, CDC classification, , ART medications, immunizations, CD4, viral load, HIV resistance testing, CBC profile, chemistry panel, lipid profile, glucose, pregnancy and pregnancy outcomes, results of STI testing, abnormal cytology and histology, and mental health diagnoses including mood, anxiety, PTSD, psychosis, and ADHD.
- At Year 5 only: blood (serum, plasma, and PBMCs) will be collected for storage in the PHACS Repository.

6.0 DATA AND SPECIMEN COLLECTION AND SITE MONITORING

6.1 Data Records

For medical record abstractions 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, laboratory specimens, clinical evaluation results, and laboratory results that are part of the research records. Participants are to be identified by the PID and PIN numbers assigned by PHACS. Study research records with PID and PIN must be stored separately from source documents that include personal identifiers.

6.1.1 Commercial Healthcare Information Coordinator

A commercial healthcare information coordinator may be used to help locate medical records prior to study entry and for interval diagnoses during the study when the clinic site does not have the participant's medical record. For each participant, an account will be set up with the company to collect medical records from all the participant's providers and store them on the company's private platform to be accessed by PHACS. Medical records will include office visit notes, hospitalization records, surgery records, test results such as labs, X-rays, and magnetic resonance imagings (MRIs), current and past medications, allergies, and any other medical conditions. Medical records will be stored as scanned documents and specific information such as medications, medical conditions, and visit information are entered in organized fields so that they can be easily accessed. The commercial healthcare information coordinator will operate in compliance with all current Health Insurance Portability and Accountability Act (HIPAA) regulations.

6.1.2 Web-Based Illume Surveys

Web-based surveys will be administered using Illume, a commercial software tool that was designed by DatStat, Inc. specifically for creating web-based data collection instruments. The web-based surveys can be completed on any device on which the internet can be accessed, including a smartphone. Skip patterns

will be programmed into the survey, and questions can be skipped by participants if they choose. Questions will not be accompanied by sound. See Appendix III for completion tips for the web-based Illume survey.

Web-based survey data collected using the Illume program will be transferred using Hyper Text Transfer Protocol Secure (HTTPS) connections that adhere to the Food and Drug Administration (FDA) guidelines for secure electronic data capture. The collected data will be stored on DatStat's server and transferred to the PHACS central database at FSTRF. 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. See Appendix IV for details on web-based data security and user confidentiality.

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 or by direct data entry from source documents into the computerized database will be provided by the PHACS DMC. The PHACS DMC will also conduct training of clinical site staff on the use of the Illume web-based survey.

At the Entry time point, clinical site staff will access the web-based Illume survey via links provided to them. Clinical site staff will introduce participants to the survey and explain the process of completing the web-based survey. Participants will then complete the survey in the clinic. For participants who cannot go in person to the clinical site, site staff will send the link to the web-based Illume survey to the participant and guide them via telephone on how to access and complete the survey.

When participants complete follow-up web-based survey remotely outside the clinic, they can connect to the web-based survey through either links provided by the clinical site staff or a study-specific participant website. Participants will log in to the website, where links to the survey they need to complete will be posted, using a unique participant-specific username and passcode.

6.3 Data Quality Assurance

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

The clinical site PI will make study documents (e.g., consent forms, CRFs, electronic medical records) and pertinent hospital or clinic records readily available for inspection by the local IRB, the National Institutes of Health (NIH), the Office of Human Research Protection (OHRP), and the site monitors acting on behalf of the NIH, to confirm study data and regulatory compliance. For additional details pertaining to protocol-specified source documentation and record retention requirements, sites should refer to 1) the Requirements for Source Documentation in Division of AIDS (DAIDS) Funded and/or Sponsored Clinical Trials (available at https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf); 2) the list of PHACS AMP, AMP Up, AMP Up Lite, and SMARTT Case Report Forms Approved as Source Documents; and 3) the PHACS Policy on Long-Term Maintenance of Case Report Forms (CRFs), Study Instruments, Regulatory Documents, and Medical Records.

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 HIPAA Privacy Rule.

6.4 Repository Specimens

This study will store serum, plasma, and PBMCs as repository specimens for future, currently undetermined research testing (See Appendix II). 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 Appendix V). Refer to the AMP Up Lite Laboratory Processing Chart (LPC) for details on collection and processing.

6.5 Cataloguing of Specimens

All specimens collected at clinical sites will be catalogued using the Laboratory Data Management System (LDMS) developed and supported by FSTRF.

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 rapid access to the research team. Site staff will send all queries for this protocol to the PHACS PH400 Protocol Team using the Protocol Query and Notification System (QNS) accessible via the internal PHACS website. It is expected that the PH400 Protocol Chair or designee will respond to queries within 48 working hours of receipt. Queries and replies will be automatically archived by the PHACS webmaster. Those queries deemed relevant to all sites will be posted on the PHACS website, where they will be available to all sites for future reference, as well as emailed weekly to all PHACS staff. The categories of queries 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

It is the responsibility of the PHACS DMC to ensure the quality of computerized data for each PHACS study. This role extends from protocol development to generation of the final study databases.

This study follows PHACS standards and recommended guidelines for data management. The PHACS DMC will provide instructions concerning the recording of study data on CRFs or direct data entry. Each site is responsible for keying the data in a timely fashion according to standards set by the PHACS Network. Data will be entered locally into a computer-based data management program (eData). The eData System will have built-in basic error checking capability so that minor errors can be resolved at the site. The data will then be exported to the PHACS central database where additional data checking will take place and data errors will be communicated to the site via various reports.

The LDMS will be used to manage and track specimens collected in the PHACS Network.

7.3 Collaboration with Outside Studies

It will be useful for the AMP Up Lite 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 Executive Committee (EC) and a memorandum of understanding (MOU) executed defining the extent and nature of data sharing. The MOU will include an understanding of the control of the use of the data, publication rights, authorship rights, as well as address participant confidentiality issues.

8.0 PARTICIPANT MANAGEMENT

8.1 Data Collection Time Point Management

All data collections are to be conducted according to the Schedule of Evaluations in Appendix I. The target date for the follow-up data collection time points will be the anniversary of the Entry data collection date. It should occur at least six months after the last data collection time point. Completion of web-based surveys and medical record abstractions should be conducted as close to the target data collection time point as possible. The web-based Illume survey should be initiated within a six-month window: three months prior to or up to three months after the target data collection time point; the full schedule of Illume survey questionnaires/modules required for the time point should be completed within three months of initiation of the first survey module.

8.2 Enrollment of Cognitively Impaired Participants

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

Clinical sites will evaluate cognitive impairment through multiple means. In many cases, the clinical sites will have extensive experience with and knowledge of the skills and capabilities of the participant including thorough neuropsychological testing through their previous participation on other studies. All clinical sites have psychologists on staff who can conduct further assessments when appropriate.

The web-based Illume surveys do not need to be completed by the participant if the clinical site PI determines that the participant is incapable of completing the surveys. Clinic staff has the option of administering the web-based surveys to cognitively impaired participants by either telephone interview or in person at the clinic if determined to be appropriate, although in these instances, participants will not complete the reproductive health, sexual activity, or substance use modules. Surveys will be adapted for interviewer administration with cognitively impaired participants. For participants who are too cognitively impaired to respond to survey questions, the participant's primary caregiver will complete web-based surveys on demographics, health care access and utilization, circumcision status (for male participants), transition to adult HIV care, ART adherence, fractures, and hearing issues. In this circumstance, the primary caregiver will also complete at Entry the interviewer-administered medical history questionnaire.

Cognitively impaired participants will be taken off-study if it is determined that they are unduly distressed as a result of protocol activities. In the case of distress resulting from completion of web-based assessments, clinical site staff will be available to consult by telephone. Site staff may also bring cognitively impaired

participants to the clinic to complete the web-based surveys and monitor for signs of distress if determined to be appropriate.

Cognitively impaired participants will consent on their own behalf if legally able. For individuals with a legally authorized representative (LAR), LAR permission and participant assent will be obtained. Clinical sites will consult with their IRBs for guidance when needed. Caregivers of cognitively impaired participants will answer questions as proxies on behalf of participants and will therefore not be consented and enrolled as study participants themselves.

8.3 Participant Retention

Participant retention will be a challenge and maintaining retention is a high priority. Retention and completion of data collection time points will be monitored carefully. The target retention rate, excluding unavoidable causes of loss (e.g., moving out of the area and death), for participants is 96% per year. This target will be re-evaluated periodically.

Clinical sites will be provided with monthly reports listing PIDs for whom study assessments are due. Clinical site staff are responsible for contacting participants to inform them of impending data collection time points. If expected web-based surveys are not completed within the protocol-defined window, clinical sites will follow up with participants to encourage completion of these assessments.

For those participants who move out of the area to a location that has a PHACS site, the originating site personnel will make every effort to encourage transfer of the participant to the site at the new location. If it is not possible to transfer the participant to another clinical site, the participant may be consented to continue taking part in the study through the HSPH. In these instances, the informed consent process will be handled 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. Clinical site staff may also handle the signing of the medical record release allowing HSPH staff to request medical records when allowed by the local IRB and agreeable to the participant. Participants followed by HSPH would complete web-based surveys, and HSPH staff would be responsible for obtaining medical records, conducting the medical record abstractions, and tracking participants.

8.4 Participant Website

Participants will have access to the PHACS Participant website, which is used by participants in AMP Up and the SMARTT Young Adult Cohort. The identity of participants is verified by the use of a participant-specific username and passcode. In addition to allowing participants to link to the follow-up web-based surveys, the website serves as a portal for health education materials. Furthermore, summary study results may be disseminated to participants through the website. The PHACS leadership collaborates with local clinical site staff to ensure that participants are not given access to materials that require local IRB review before the review has been conducted.

8.5 Discontinuing Study Participation

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

- The participant withdraws permission.

- The participant fails to comply with the study requirements so as to cause harm to himself or herself or seriously interfere with the validity of the study results and the clinical site PI believes that compliance is unlikely to improve.
- The clinical site PI determines that further participation would be detrimental to the participant's health or well-being.
- The study is stopped by a governmental agency, including the NIH or DHHS.
- The clinical site is terminated for significant participant safety concerns, study integrity, poor performance issues, or lack of funding. (**Note:** If a clinical site closes, participants may be transferred to another site or followed by HSPH as described in Section 8.3).

8.6 Participant Compensation

Compensation will be provided for completion of the evaluations at Entry and at each annual follow-up.

8.7 Death of a Participant

Sites will obtain a copy of the autopsy report or death certificate and medical records on any participant who dies while a participant in this study. A final chart abstraction should be performed covering the period between the last data collection time point up to and including the date of death. Permission to obtain these records will be obtained from the participant at the time of study enrollment. If a participant is known to have died but no cause of death is available or if a participant has been lost to follow-up, a National Death Index (NDI) search will be instituted (also see Section 12.1).

8.8 Incidental Findings

Incidental findings in this observational cohort study will be rare. The clinical site PI will be responsible for monitoring for incidental findings and handling them according to their respective institution's policies. Incidental findings of medical importance will be shared with the participant.

8.9 Test- and Evaluation-Specific Management of Medical and ART History

8.9.1 Medical and ART History

Targeted medical and medications history, and family medical history will be captured through the interviewer-administered medical history questionnaire. If an in-person visit cannot be completed at Entry, then the questionnaire will be completed via telephone. Results of any HIV resistance testing performed (genotype, phenotype, and viral co-receptor tropism testing) will be transmitted to the PHACS DMC for data entry.

In cases where the specific assessment described in the protocol cannot be employed, an instrument evaluating comparable outcomes may be substituted.

8.9.2 Web-Based Illume Surveys

The web-based Illume survey consists of a series of web-based questionnaires. Each questionnaire focuses on a specific topic and begins with an introduction explaining the purpose of the questionnaire. Most questionnaires will be structured to allow for completion on any device that a participant might use to access

the internet, including a smartphone. Participants can skip any question they choose not to answer. Questions will not be accompanied by sound. Appropriate skip patterns will be programmed into the questionnaire. At the end of the survey, the participant must click "submit" in order to transmit their responses.

The web-based Illume survey will be available in Spanish. If the participant is monolingual Spanish speaking or bilingual but prefers Spanish, the Spanish language version of the survey 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 survey should be used.

8.9.3 Blood Pressure

Systolic and diastolic blood pressure will be performed two times at the in-person visit at Entry using an appropriately sized blood pressure cuff. If either the systolic or the diastolic values differ by more than 5 mm Hg, a third reading should be obtained.

Blood pressure will be measured as part of clinical assessments if an in-person visit is completed at Entry. If an in-person visit cannot be completed at Entry, the data will be collected through chart abstraction. After Entry, blood pressure will be collected through chart abstraction.

8.9.4 Height and Weight

Height and weight will be measured as part of the clinical assessments if an in-person visit is completed at Entry. If an in-person visit cannot be completed at Entry, the data will be collected through chart abstraction. After Entry, height and weight will be collected though chart abstraction and self-reported through the web-based survey.

8.9.5 Repository Specimens

Site personnel will be responsible for ensuring that the specimens for the PHACS Repository are appropriately processed for storage. See Appendix II of this protocol for more detailed specifications on repository specimen collection and refer to the AMP Up Lite LPC for instructions on sample collection and processing.

Collection of repository specimens may occur at the study clinic site, a commercial lab, or at the provider's office.

8.9.6 STI Testing and Reproductive Health

Data will be collected from web-based surveys and medical charts for history of STIs (*N. gonorrhoeae, C. trachomatis, and T. vaginalis*) as well as for HSV, abnormal cytology and histology, genital warts and pelvic inflammatory disease. Web-based surveys will also obtain history of testing, treatment and prevention for STIs and history of Papanicolaou (Pap) smears, as well as frequency of lower abdominal discomfort and genital infection symptoms such as vaginal discharge and urethral irritation.

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 Lite annually.

9.0 DRUG-ASSOCIATED ADVERSE EVENT REPORTING

This study is not a therapeutic study and no medications are prescribed as part of this study. Young adults enrolled in this study may develop common conditions requiring treatment during the course of the study period. PHACS AMP Up Lite personnel will assist the participants in receiving appropriate care. The participants may also experience adverse events associated with HIV infection, ART exposure, or other medications. Clinical site PIs will be encouraged to use the FDA's MedWatch system to report any events possibly associated with medications clinically prescribed for the participant. The Protocol Team does not anticipate any adverse events associated with involvement in the study.

10.0 STUDY IMPACT AND SAFETY MONITORING

The Protocol Team, NIH program officials, and local IRBs will monitor participant-associated or community-associated untoward events. Monitoring will consider the impact of the study on the welfare of three groups of people:

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

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

All clinical sites have psychologists, social workers, and other staff qualified to address situations if a participant becomes distressed.

10.1 Grading of Impact

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

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

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

10.2 Reporting Requirements

All moderate and major impact events involving study participants or staff are to be reported to the Protocol Team through the QNS and by the site reporting the event to their local IRB. Any community event is to be similarly reported.

Examples of moderate and major impact events for study participants include:

- Disruptive or violent behavior during the scheduled study session.
- Information regarding personal harm which is disclosed (e.g., current suicidal or homicidal ideation, physical or sexual abuse, depression).
- Feelings of anxiety, depression, suicidal ideation etc. at the end of completing the web-based Illume survey).
- Visible distress or injury resulting from the research encounter.

Examples of moderate and major impact events for study staff include:

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

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

Examples of events for the community include:

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

10.2.1 State Mandated Reporting Requirements

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

10.3 Monitoring Plan

The PHACS Leadership will hold regular conference calls to review site progress. These calls will occur at least every other month. More frequent calls or ad hoc calls may occur at the discretion of the Protocol Chair if a problem is identified that needs to be addressed immediately.

NICHD has determined that a formal Data and Safety Monitoring Board will not be established; NICHD will use the NIH PHACS Steering Committee as an oversight body for the study. The NIH PHACS Steering Committee consists of program officials from NICHD, each co-funding NIH Institute, and the NIH Office of AIDS Research (OAR).

11.0 ANALYTIC CONSIDERATIONS

11.1 Power and Sample Size Consideration

The target sample size for the AMP Up Lite protocol is 500 participants. In the context of this study, many targeted outcomes, some continuous (e.g., BMI, and height and weight z-scores) and some binary (hypertension, pregnancy) 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 Power Analysis and Sample Size (PASS) 11 software (Hintze, 2011).

The table below summarizes the detectable differences in means relative to the standard deviation (SD) that can be detected assuming 500 PHIV+ participants or 440 participants (under an assumption of 4% loss per year) when two subgroups of the PHIV+ participants are being compared.

Table 11.1. Detectable differences in means (relative to SD) between subgroups of PHIV+ young adults

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 = 500	N = 440
50%	50%	0.25	0.27
40%	60%	0.26	0.27
30%	70%	0.27	0.29
20%	80%	0.32	0.34
10%	90%	0.42	0.45

We may wish to compare proportions with events between two subgroups; for example, defined by prior receipt of HAART with protease inhibitor vs. HAART without protease inhibitor, or use of a specific ARV drug vs. unexposed to that drug. The following table provides the minimum detectable differences in terms of odds ratios (ORs).

Table 11.2. Detectable differences in ORs based on logistic regression models comparing two subgroups of HIV-infected participants with N = 500 participants or N = 440

Percent in Each group		Event Rate in Group 2	OR for Given Sample Size	
Group 1	Group 2		N = 500	N = 440
50%	50%	4%	2.81	2.98
		5%	2.581	2.73
		10%	2.08	2.17
		20%	1.79	1.85
		40%	1.66	1.71
40%	60%	4%	2.82	2.98
		5%	2.59	2.73
		10%	2.10	2.19
		20%	1.80	1.87
		40%	1.67	1.73
30%	70%	4%	2.93	3.10
		5%	2.70	2.85
		10%	2.17	2.27
		20%	1.87	1.94
		40%	1.73	1.80
20%	80%	4%	3.24	3.44

Percent in Each group		Event Rate in Group 2	OR for Given Sample Size	
		5%	2.97	3.14
		10%	2.47	2.48
		20%	2.02	2.10
		40%	1.87	1.95
10%	90%	4%	4.14	4.43
		5%	3.76	4.02
		10%	2.93	3.11
		20%	2.46	2.59
		40%	2.31	2.44

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

In certain situations, we will be interested in comparing specific outcomes between PHIV+ young adults in AMP Up Lite with those of PHEU young adults. For these comparisons (discussed in more detail below), we will use the data collected for PHEU young adults enrolled in AMP Up.

Data from PHIV+ young adults in the AMP Up cohort will also potentially be incorporated into these analyses, increasing our power to see more modest effects than those summarized in the above tables.

11.2 Domain-Specific Statistical and Analytic Considerations

11.2.1 Infectious and Non-Infectious Complications of HIV and Its Treatment

Incidence of HIV disease progression and end-organ disease will be estimated under a Poisson distribution based on person-years of follow-up at risk. Factors associated with incidence of disease progression and end-organ disease will be identified using Cox-proportional hazards models. Factors associated with changes in CD4 cell count and viral load over time will be identified using generalized estimating equation (GEE) or mixed effects models. Factors of interest for these outcomes include virologic suppression, immune impairment, immune activation, changes in 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 defining what constitutes a switch in ART regimen (i.e., what ARV drug changes constitute an ART switch). Viral resistance will be calculated using the Stanford HIV Resistance Database which contains drug susceptibility data for selected mutations (Shafer, 2006; Liu and Shafer, 2006; HIVdb, 2017; https://hivdb.stanford.edu). The presence of co-infections such as CMV and EBV will be assessed by testing repository samples obtained prior to the events of interest. Host genetic polymorphisms of interest will be identified using the established PHACS repository of amplified genomic DNA. Whole genome sequencing will be done for all participants. Effect modification between host genetic polymorphisms and ART will be assessed as appropriate and feasible based on power issues noted above, and based on a priori hypotheses.

11.2.2 Metabolic Complications

We are interested in estimating the prevalence and incidence of insulin resistance, dyslipidemia, hypertension, 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.

Dyslipidemia, hypertension, and obesity as binary outcomes

Prevalence: Dyslipidemia, hypertension, and obesity will be considered as binary variables. Dyslipidemia and hypertension diagnoses will be abstracted from medical charts. BMI will be calculated from height and weight as ascertained from chart abstraction and through the Illume survey. BMI above 30 kg/m^2 will be classified as obese.

We will estimate the prevalence of each binary metabolic outcome at each AMP Up Lite evaluation time point among PHIV+ participants and compare them to PHEU participants enrolled in AMP Up. Prevalence will be calculated as the number of participants with the specific outcome at that time point, divided by the total number of participants who are tested and have a measure for each outcome at that time point. We will also calculate the 95% confidence intervals (CIs) for each prevalence estimate.

We will evaluate the association of each metabolic outcome with specific ART regimens (particularly protease inhibitors and NRTIs, which have been implicated in various metabolic disorders) in PHIV+ participants by comparing the prevalence across ART regimens using chi-square tests. We will also estimate the association between each exposure and the prevalence of each metabolic risk factor using logistic regression. These will be adjusted for confounders, which may include race, gender, age, CD4 cell count, and viral load.

Incidence: We will estimate the incidence rate of all the binary metabolic outcomes in PHIV+ young adults. 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 participants initially free of the risk factor at baseline (or first measurement). The 95% confidence limits (95% CI) for these incidence rates will be calculated using the Poisson distribution.

We will estimate the association between specific ART regimens and HIV disease severity (as measured by viral load) and incidence of the above outcomes. 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. These analyses will be adjusted for confounding. For outcomes that are observed to occur less frequently, Poisson regression models may be used to compare incidence rates.

Lipid levels, BMI, and cardiometabolic risk measures as continuous outcomes

Lipid levels (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), and BMI will be considered as continuous outcomes. These measures will be normalized for age and sex.

For cross-sectional data, we will compare outcomes in PHIV+ participants versus PHEU participants from AMP Up using linear regression. Potential confounders that may be included in the models of lipids are BMI, sex, race, and tobacco use. We will investigate the association of each class and type of ART for each outcome. To examine the effect of exposures that vary over time, we will use mixed effects models, which will account for the correlations between these repeated measures. The change over time in BMI will be compared by HIV status.

11.2.3 Sexually Transmitted Infections

Incidence of STIs, LSIL, and HSIL, as well as the rate of regression of LSIL to normal cytology, will be estimated under a Poisson distribution based on participant-years of follow-up. Only participants with a

first Pap smear indicative of normal 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 estimate accurately the rate of regression, descriptive case data will be reported.

The incidence of each outcome will be compared between PHIV+ participants and the PHEU comparison group from AMP Up. Factors associated with incidence of each outcome will be identified using Cox proportion hazards models and will adjust for important potential confounders including: contraceptive use, number of sexual partners, and smoking (for LSIL and HSIL), and additionally, for analyses restricted to PHIV+ participants, CD4 cell count, HIV viral load, ART use, and CDC disease classification.

11.2.4 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, abortion, miscarriage), the incidence of maternal-to-child HIV transmission; and the prevalence of menstrual irregularity.

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 PHIV+ participants and the PHEU comparison group from AMP Up using chi-square tests as crude analyses. Logistic regression models will be used 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, 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.

11.2.5 Mental Health

The analysis of mental health outcomes will focus on estimating prevalence at study entry and over follow-up. We will also evaluate the changes over time in these outcomes. For the prevalence analyses, 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 based on follow-up data will be calculated under a Poisson distribution based on participant-years of follow-up. Mental health outcomes including depression, anxiety, PTSD, psychosis, and ADHD will be evaluated as binary measures.

The prevalence of MHPs will be compared between the PHIV+ young adults and the PHEU young adults in AMP Up using chi-square tests for crude analyses and using logistic regression models for each separate outcome as a function of HIV status, adjusting for important demographic and psychosocial factors (such as age, race/ethnicity, sex, socioeconomic factors, and social support).

Logistic regression models will be used to evaluate the associations between mental health outcomes and HIV-associated disease characteristics as well as other behavioral factors such as risky sexual practices, substance use, and non-adherence.

Associations between MHPs and educational and vocational attainment will be evaluated using linear and logistic regression models.

Factors associated with changes in mental health outcomes over time will be identified using GEE models.

11.2.6 Health Care Behaviors and Transition to Adult Health Care

To address the specific aims and hypotheses regarding adherence and health care, we will calculate 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 study entry and over follow-up among PHIV+ young adults who provide information on ARV use, and calculate 95% CIs. We will use logistic regression methods to identify and evaluate factors associated with non-adherence to ART and non-adherence 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 and social support.

11.2.7 Risk Behaviors

The analysis of risk behaviors will focus on estimating the prevalence at study entry and over follow-up of vaginal and anal sexual intercourse, oral sex, unprotected vaginal or anal intercourse, multiple sexual partners, licit and illicit drug use, tobacco and alcohol use. We will also evaluate the frequency of disclosure of HIV status to sexual partners, and of serosorting (asking about partner's HIV status). 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 risk behaviors, including risky sexual behavior and licit and illicit substance use, will be compared between the PHIV+ participants and the PHEU comparison group from AMP Up using chi-square tests as crude analyses. Logistic regression models will be used for each separate outcome as a function of HIV status controlling for important demographic, clinical, and social factors (socioeconomic factors, partner characteristics, 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 unprotected 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.

11.2.8 Transition to Adult Functioning and Health-Related Quality of Life

We will estimate the prevalence of successful transition to adult functioning (including educational attainment, employment, independent living) and health-related quality of life [SF-20], mental health [depression, anxiety, PTSD, psychosis, and ADHD], self-efficacy, and presence of close personal relationships [questions taken from NIH Toolbox emotion domain (Gershon, et al., 2013)]) at the entry time point and at each follow-up time point. Prevalence of milestones associated with successful adult function (including employment, educational attainment [e.g., high school diploma or GED, enrollment in college or certificate program], independent living) will be calculated as the number of participants with each specific outcome at each time point, divided by the total number of participants who have a measure for each outcome at that time point. 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 mental health outcomes will be estimated and 95% CIs will be calculated for each prevalence estimate. The median (interquartile range) and mean (SD) scores for health-related quality of life (SF-20), self-efficacy, and presence of close personal relationships will be calculated.

Successful transition to adult functioning and health-related quality of life will be compared by perinatal HIV status and other factors using chi-square tests and Wilcoxon rank sum test as appropriate. Factors associated with successful transition to adult function and with health-related quality of life will be further examined with univariable and multivariable logistic and linear regression models.

11.2.9 Hearing

Hearing will be assessed by self-reported hearing loss difficulties or diagnoses associated with hearing difficulties.

12.0 HUMAN SUBJECTS

This study will be conducted in compliance with the protocol, International Conference on Harmonization (ICH) GCP guidelines, and 45 Code of Federal Regulations (CFR) §46.

12.1 Participant Confidentiality

All participants enrolled in the PHACS Network are assigned unique PHACS PID and PIN numbers as described in Section 4.6. The PID and 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 secured area in locked files.

An information sheet was developed for participants to assist them in protecting their confidentiality while completing web-based Illume survey at a location other than the clinical site (see Appendix III). See Appendix IV for the confidentiality and security measures suggested for participants and in place for Illume survey data.

All research staff persons at the clinical sites are required to sign non-disclosure forms pledging to hold research information in confidence. All off-site PHACS investigators and collaborators are required to sign data use agreements pledging 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.

Cause of death is critical information in this study. For participants who are known dead but for whom the cause of death is unavailable, AMP Up Lite will conduct an NDI search. The NDI is a government service using national vital record databases. Since the CFR apply to living participants only, consent for this procedure will not be required. If the location or vital status of a lost participant cannot be ascertained, AMP Up Lite also intends to conduct an NDI search. As these participants are not known to be dead, all requirements of the CFR apply and the need for this search is anticipated and explained in the AMP Up Lite consent (permission) process. Several layers of confidential assurances govern application to the NDI and all information provided to the NDI is destroyed once the search is completed. NDI searches do require personally identifying information (first and last name, sex, city of birth, and date of birth will be used in AMP Up Lite). To preserve the coded nature of the AMP Up Lite database to which identifying information of study participants is not readily ascertainable, the DOC will subcontract with Westat, an administratively and institutionally distinct entity, to interact with the AMP Up Lite research staff at the PHACS clinical sites and the central NDI staff to accomplish the NDI searches. Westat will receive information from the NDI if a match is successful. This information will be confidentially provided to designated Westat staff who will enter the data in the AMP Up Lite database. Westat staff will also provide the PID of participants known to be dead through the NDI search to clinical site staff so that they can cease their attempts to reach these participants. Personally identifying information will not be released by the sites without written permission of the participant or his or her legal guardian, except as necessary for monitoring by Westat or the NICHD or as consented and authorized for NDI searches.

12.2 Certificate of Confidentiality

To further protect the privacy of the study participants, PHACS has obtained a Certificate of Confidentiality from the U.S. DHHS. With this Certificate in place, the PHACS investigators cannot be forced to turn over identifying information about a study participant in any Federal, State, or local criminal, administrative, legislative, or other proceedings. This Certificate does not prevent a study participant from volunteering to turn over their research information nor does it prevent investigators from providing research-related information to others when requested by the study participant or when required by law such as in cases of suspected or actual harm to or by the study participant.

The clinical site PI will make study documents (e.g., consent forms, 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.

12.3 Risks and Benefits

12.3.1 Risks Associated with Participation in This Study

Participation in this study poses no more harms or discomforts to research participants than they may experience in normal daily life or during routine medical tests.

The evaluations that are involved in this study require venipuncture, clinical assessment, and answering questions about mental health, sexual behavior, substance use, and ART adherence. 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.
- The information that participants provide through 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 ART adherence and mental health.

- Despite the multiple measures taken to protect participant confidentiality, online communications may be at risk for hacking, intrusions, and other violations.

Another potential risk for participants is inadvertent disclosure of their 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 the web-based Illume survey. Participants will be encouraged to complete their web-based survey in a private location on a device that is not publicly shared. Clinical sites will make space available for participants to complete surveys when a participant does not have access to a private space or device. See Appendix III 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.

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. Identified data could potentially be used to discriminate against or stigmatize participants, their families, or groups.

12.3.2 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 his or her legal guardian chooses, the information obtained in this study can be made available to their health care providers and it may inform their primary health care. Participants and legal guardians will be encouraged to make this information available to providers in order to maximize the potential for benefits.

12.3.3 Sexual Behavior and Health

Information on sexual activity and substance use reported by participants in the confidential web-based Illume survey will not be disclosed to the PHACS clinical site staff or to the clinicians responsible for their health care. If a participant is unable to complete the web-based survey independently due to technical challenges, the web-based survey may be completed at the clinical site, where a research staff member may assist with this process as needed. In these cases, clinical site staff will make every effort to maintain participant confidentiality.

12.4 Institutional Review Board Review and Informed Consent

This protocol, the informed consent documents, and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for the oversight of the study. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. 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. If completed online, participants will receive a copy of their informed consent.

In accordance with 45 CFR §46.116, a legal informed consent will be obtained from the participant or his or her 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.

12.5 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 evaluations as long as they are considered prisoners.

12.6 45 CFR §160 and 164 Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule" pursuant to HIPAA)

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

12.6.1 Database

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

- PHACS DMC and PHACS site monitors.
- PHACS investigators and their collaborators.
- Participant's primary care provider if so desired by the participant.
- NIH.
- Westat, for the purpose of an NDI search, to be referred to as "national health department database search" to prevent dismay from the use of "death."
- Technical support staff at the institutions hosting the web-based assessments for the sole purpose of providing technical assistance.

12.6.2 PHACS Repository Policies

It is not expected that 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 can be found in Appendix V. Consent for collection of repository specimens is included within the sample study consent/assent forms (see Appendices VI and VII). Participants may participate in the study without agreeing to the collection and storage of repository specimens.

12.7 Study Discontinuation

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

13.0 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). Any presentation, abstract, or manuscript will be made available for review by the study sponsor prior to submission.

Participant summaries of findings will be developed and provided directly to the clinical sites to allow for submission for IRB review prior to distribution to participants.

14.0 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.

15.0 REFERENCE LIST

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APPENDIX I: SCHEDULE OF EVALUATIONS

	ENTRY [1]	YR 1	YR 2	YR 3	YR 4	YR 5	YR 6	Data Collection Method
Sign consent	X							In clinic or remotely (online)
Height and weight	X	X	X	X	X	X	X	At Entry: self-report (Illume survey) and measure in clinic if in-person visit conducted; otherwise through chart abstraction; At all other time points: self-report (Illume survey) and chart abstraction
Blood pressure	X	X	X	X	X	X	X	At Entry: measure in clinic if in-person visit conducted; otherwise through chart abstraction; At all other time points: through chart abstraction
Targeted medical and medications history, and family medical history	X							Interviewer-administered medical history questionnaire; complete in clinic or via telephone
Demographics	X	X	X	X	X	X	X	Self-report (Illume survey)
Health care access and utilization and transition to adult HIV care	X	X	X	X	X	X	X	Self-report (Illume survey)
Depression (CES-D 10)	X	X	X	X	X	X	X	Self-report (Illume survey)
Health-related quality of life (SF-20), social support, relationships, self-efficacy, and HIV-related stigma [2]	X	X	X	X	X	X	X	Self-report (Illume survey)
Sexual behavior	X	X	X	X	X	X	X	Self-report (Illume survey)
Substance use [3]	X	X	X	X	X	X	X	Self-report (Illume survey)
ART adherence	X	X	X	X	X	X	X	Self-report (Illume survey)
Medical diagnoses including AIDS-defining illness, CDC classification, ART medications, immunizations, CD4, viral load, and HIV resistance testing [4], [5]	X	X	X	X	X	X	X	Annual chart abstraction
Nadir CD4	X							Chart abstraction

	ENTRY [1]	YR 1	YR 2	YR 3	YR 4	YR 5	YR 6	Data Collection Method
CBC profile, chemistry panel, lipid profile, and glucose [6]	X	X	X	X	X	X	X	Annual chart abstraction
Mental health diagnoses (including mood, anxiety, PTSD, psychosis, and ADHD) [7]	X	X	X	X	X	X	X	Annual chart abstraction
Fractures and hearing issues [7]	X	X	X	X	X	X	X	Chart abstraction and self-report (Illume survey)
Reproductive history [7], [8]	X	X	X	X	X	X	X	Chart abstraction and self-report (Illume survey)
Repository								
Serum and plasma (EDTA and heparin), and PBMCs	X					X		In clinic at provider's office, or at a commercial laboratory

** The window for completion of the Illume survey and chart abstraction is within three months prior through six months after the target data collection time point.

[1] Enrollment is allowed without an in-person visit. If an in-person visit cannot be completed at Entry, height, weight, and blood pressure measurements will be collected through chart abstraction, and the interviewer-administered medical history questionnaire will be completed via telephone.

[2] Social support, relationships, and self-efficacy questions are all obtained with permission from the NIH Toolbox Emotion domain.

[3] Alcohol, tobacco, over-the-counter medications and prescription drugs taken for purposes of intoxication, and illicit substances.

[4] At Entry, record all medical diagnoses, ART medications, CD4, viral load, HIV resistance testing, and immunizations in the 12 months prior to Entry. At all subsequent time points, record all interval medical diagnoses, ART medications, CD4, viral load, HIV resistance testing, and immunizations since the last chart abstraction.

[5] At Entry, record lifetime history of AIDS-defining illness and CDC classification. At all subsequent time points, record interval AIDS-defining illness and change in CDC classification.

[6] At Entry, record the most recent results for each six-month period in the 12 months prior to Entry. At all subsequent time points, record the most recent results for each six-month period since the last chart abstraction. Include CBC, chemistries (BUN, creatinine, lipase, AST, ALT, and CPK), lipids (total cholesterol, LDL, HDL, and triglycerides), and glucose.

[7] For chart abstraction at Entry, record all mental health diagnoses, fractures, hearing issues, and reproductive history in the 12 months prior to Entry. At all subsequent time points, record all interval mental health diagnoses, fractures, hearing issues and reproductive history since the last chart abstraction.

[8] Illume survey includes pregnancy and pregnancy outcomes, occurrence/treatment/prevention of STIs, contraception use, menstrual irregularity, and PAP smears. Chart abstraction includes pregnancy and pregnancy outcomes, results of STI testing, and abnormal cytology and histology.

APPENDIX II: ROUTINE SAMPLE COLLECTION SPECIFICATIONS FOR REPOSITORY SPECIMENS

Specimen	Volume of draw	Anticoagulant (tube color) or container
Serum	6-7 ml	Serum separator or red top tube
Plasma (EDTA)	6-7 ml	EDTA (lavender top)
Plasma (heparin)	6-7 ml	Heparin (green top)
PBMCs	8 ml	CPT tube [1]

Note: Serum and plasma repository specimens must be frozen in 0.5 ml aliquots.

[1] Or an EDTA tube (lavender top) if PBMCs are to be separated using ficoll-hypaque as an alternative to the CPT tube. See Repository Specimens in Section 8.9.5.

APPENDIX III: WEB-BASED ILLUME SURVEY COMPLETION TIPS

Tips to Protect your Privacy When Filling Out the Online Illume Survey

We understand that your privacy is very important to you, and it is very important to us as well. We want to make sure it is protected while you are filling out our surveys. Here are some tips for how to do that.

Where to complete your survey:

- If possible, fill out your survey on a personal computer or device.
- Take extra precautions if you use a shared computer in a public place like school, work, or the library. Shared computers may not give you much privacy because so many other people also use them.
- Before you start the surveys, make sure you are answering the questions in a space where you feel comfortable. Some people might feel uncomfortable if they take a web-based survey while surrounded by people in a public place.
- Remember that you are always welcome to go to the study clinic to complete your web-based survey.

Privacy tips for shared computers:

- Do not leave the computer while the survey is open on the screen.
- If you are logged in to the study website, make sure to log out and close the browser before you leave the computer.
- If possible, clear the cache on the browser you used. This will help prevent the browser from storing your information.
- Turn on the "privacy" feature on the web browser. This will stop the browser from saving a record of your visit to the study website. All of the main browsers like Internet Explorer, Safari, Google Chrome, and Firefox have a privacy feature.

Privacy tips for personal computers:

- Create a password to protect your personal computer, even if you are the only person using it. This will prevent anybody else from being able to log in and see your information.
- Use firewalls for your hardware and software. Firewalls can prevent others from getting access to your computer through the internet. One effective free software firewall is available from Zone Alarm. Firewalls are also included in many virus protection programs. One example is AVG, which also offers a free version. Both of these programs are easy to find and download from the internet.
- Make sure you are using the most recent versions of operating systems. For example, "Windows" and "Mac OS" are examples of operating systems.
- Make sure you are using the most recent versions of web browsers and software. For example, "Internet Explorer" is a web browser, and "Microsoft Word" is software.
- Make sure to update your operating system, browsers, and software regularly.

APPENDIX IV: DATSTAT WEB-BASED SURVEY DATA SECURITY AND USER CONFIDENTIALITY

DatStat hosts the Illume surveys. They maintain 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 (DSMB) standards for the protection of research participants and electronic records. DatStat's technology platform including servers, database, and web presences 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 (UPS) 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 AddTrust that provide for advanced encryption over the wire. As each user moves through the survey form, his or her responses are encrypted while in-transit between the browser and DatStat's server using secure sockets layer (SSL) and 128 or 256-bit Public Key Encryption.

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 Advanced Encryption Standard (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 personal identification number (PIN) to gain access to the on-line survey. Where appropriate, survey participants may receive an email with the survey PIN embedded in the survey uniform resource locator (URL), which is encrypted by SSL. It is ONLY the 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.

APPENDIX V: PEDIATRIC HIV/AIDS COHORT STUDY (PHACS) HUMAN SUBJECTS POLICIES AND PROCEDURES: REPOSITORY

Adopted 18 July 2006
Status: In effect

The Pediatric HIV/AIDS Cohort Study (PHACS) is a clinical research network funded through a cooperative agreement with the National Institute of Child Health and Human Development (NICHD). PHACS subcontracts a network of clinical sites and maintains the capacity to conduct epidemiologic research in support of the PHACS objectives. As a part of many of the PHACS protocols, biological specimens will be collected and stored for future study. Specimens collected under this policy will be stored in an institutionally distinct facility under contract to NICHD. Two types of specimens may be in the repository: 1) temporary short-term holding of specimens that will be used for a protocol-specified test (e.g., temporary storage of participant specimens collected in a protocol where batched testing of specimens will be conducted for a specific assay when a particular volume is attained, such as endocrinology assays); and 2) long-term storage of specimens for testing that is not specified in the protocol. Testing of temporary short-term holding specimens is approved by the IRB at the collecting institution as part of the initial reviewed study and is not addressed in this policy. This policy addresses the management of specimens collected for long-term storage and unspecified future testing.

1.0 Regulatory and Background Information

In recent years, there has been growing concern over the use of stored specimens from individuals for a wide array of purposes without the individual's knowledge or consent. The U.S. Office for Human Research Protections (OHRP), in the Department of Health and Human Services (DHHS) issued guidance in 1997[1] and in 2004[2]. The National Bioethics Advisory Commission published its deliberations on the issue in 1999[3] and the Office of Extramural Research, NIH, issued its guidance in 2005[4].

These documents provide guidance for institutionally-distinct central repositories that hold potentially identifiable, coded specimens collected from living individuals and stored for future unspecified research.

An appropriately-constituted IRB may deem such specimens as not involving human subjects research if, in reviewing the policy and procedures governing the repository, the IRB determines that all the following criteria have been met:

- Specimens are coded and can be linked to identifiable living individuals by the staff at the collecting institution but no staff from the collecting institution is participating in the proposed future research; and
- Specimens are provided to the recipient investigator with the code that can link them to identifiable living individuals but the recipient investigator and the holder of the key to the code enter into an agreement preventing the release of the key under any circumstances

2.0 Features of the PHACS Repository

2.1 Compliance with OHRP Guidance

The PHACS Repository Policy is established to comply with OHRP guidance and DHHS regulations, "Protection of Human Subjects," at 45 CFR § 46. Under this policy, any specimen collected for storage through a NICHD-supported study must be collected after obtaining informed consent and/or assent. In

addition, the NICHD has obtained a Certificate of Confidentiality to give further privacy protection to information at PHACS sites. The PHACS-funded investigators will release only coded specimens to the repository, will secure identifying linking information in confidence at the site, and will sign non-disclosure forms to that effect (Attachment A). The Repository will not possess participant identifiers or the means of obtaining such identifiers. Investigators proposing to conduct future studies on repository specimens will be unable to obtain the participants' names to contact them directly and will sign a specimen use agreement to that effect. These procedures, taken together, and in combination with storage at an institutionally-distinct facility (the NICHD Repository), effectively change the status of the specimens from constituting human subjects to not involving human subjects under 45 CFR § 46.101(4) and 102(f) (2).

If the future proposed study to use repository specimens involves an investigator who is based at a collecting institution, the extra protections of this policy are breached and the status of the specimens revert back to human subjects research requiring IRB review. Another situation requiring collecting institution IRB review would be if a study is proposed to use repository specimens that would require contact with the donating participants. In this situation, the contact of participants will be through the research staff at the clinical sites of the collecting institutions (clinical sites) after review and approval of the new project by that site's IRB. It is the IRB of the collecting institution that must decide if these participants may be identified and contacted.

2.2 Health Insurance Portability and Accountability Act (HIPAA)

Because specific protected health information (PHI) will not be needed to create and operate the PHACS Repository, the Privacy Rule under HIPAA will not apply to the creation of the PHACS Repository. See 45 CFR § 164.501. However, specimens for the repository will be collected within clinical studies that do collect PHI and the volunteers for these research studies will be asked for consent to comply with 45 CFR § 46.116 and authorization to comply with 45 CFR § 164.514.

When presented with a proposed study for the future use of repository specimens that requires linkage to data in the study database, the PHACS data center will provide to the proposing investigators only a limited data set that honors the minimum necessary rule, in compliance with 45 CFR § 164.514(e) (2). The investigators will be required to sign a data use agreement, in compliance with 45 CFR § 164.514(e) (4). Employing the combination of a limited data set and a data use agreement eliminates the HIPAA requirement for individual authorization of the PHI use in future studies.

2.3 IRB Approval of this Policy

The Institutional Review Board of the National Institute of Child Health and Human Development has reviewed and approved this policy and the procedures delineated herein.

3.0 Definitions

Collecting Institutions: These are the clinical sites participating in PHACS at which study participants will be recruited and from whom legal informed consent will be obtained for enrollment into the PHACS studies and for collection and storage of specimens.

Storage Institution: NICHD constitutes the storage institution in that NICHD has contracted with a commercial entity to receive, process, track, and store specimens in a repository, and these specimens have been obtained from eligible participants who would have provided legal informed consent for enrollment into the PHACS studies and for collection and storage of specimens.

Recipient Institution: This is the home institution of the proposing investigator who is requesting use of repository specimens. This institution may or may not also be a Collecting Institution. If the recipient institution is also a collecting institution, the stored specimens from participants recruited at that institution revert to human subjects status since the identity of the donating participant is maintained at that site and is now "readily ascertainable" under 45 CFR § 46.102(f) (2). Under this condition, the study would have to be submitted to the recipient/collecting institution IRB. If, on the other hand, the proposing investigator and the recipient institution are not also part of the specimen collection process, the protection "firewall" remains intact and the IRB of the recipient institution may deem the investigator as "not engaged in human subjects research" (see OHRP Guidance on Engagement in Research).

Repository Policy Adherence and Non-Disclosure Agreement (Attachment A): A document to be signed by all research staff at collection institutions binding these individuals to adhere to the Repository Policy and to not disclose identifying information either anyone, including recipients of repository specimens, unless required by law or as authorized by the participant, other than the clinical research team members (and then only on a "need to know" basis).

Repository Policy Adherence and Specified Data and Specimen Use Agreement (Attachment B): A document to be signed by the research investigator team at the recipient institution that binds these investigators to adhere to the Repository Policy, to use the data and specimens for the specified purposes in the approved protocol, to seek new pre-approval for any other use, to destroy or return leftover specimens at study end, and to report any violations of these stipulations to their own IRB, the PHACS Executive Committee (EC), and the NICHD.

4.0 Responsibilities of the Collecting Institution

Prior to participant enrollment and collection of specimens for any PHACS protocol, the Collecting Institution's Principal Investigators are required to submit the protocol and consent documents specifying the collection and storage of specimens to their IRB for review and approval.

Specimens will be collected by the Collecting Institution and stored, as per protocol, at the Collecting Institution until transferred to the PHACS Repository on a periodic basis determined by PHACS Scientific Leadership Group. Collected specimens will be labeled with a unique identification code number for the participant (PID). The only information linking the participant's identity to the PID will be kept in a secure area with restricted access by the Principal Investigator at the Collecting Institution. Investigators and research staff with access to this linked information must sign a non-disclosure agreement (See Attachment A). In addition, PHACS Repository Staff will not seek or receive any information from the Collecting Institution that will lead to the identification of the participants from whom the specimens were collected.

Collecting Institution IRBs will only review proposals for the use of repository specimens if:

- An investigator from a Collecting Institution who is a member of the study team requests permission to analyze repository specimens in his/her laboratory (thus becoming a Recipient Institution). In this instance, the investigator would have access to the identifying link between participants and specimens, as well as the new information generated by this study about these participants.
- The research proposal requires the contact of donating participants for additional information or biologic specimens.

If the Collecting Institution's IRB has reviewed the proposal for use of repository specimens, the Principal Investigator at the Collecting Institution will forward the IRB's determination to the following individuals:

- The Principal Investigator and Project Director of the PHACS Coordinating Center and through them to;
- The proposing investigator at the Recipient Institution.

5.0 Responsibilities under this Policy

Note: Under the terms of the awards to the institutions conducting PHACS, the PHACS Scientific Leadership Group will retain custody and have primary rights to the data (including biologic specimens) collected under these awards, subject to government rights of access consistent with current HHS, PHS, and NIH policies. (PHACS structural organization can be found in Figure 1. A schema of the oversight of the PHACS repository activities can be found in Figure 2.)

5.1 Responsibilities of the PHACS Scientific Leadership Group

The PHACS Scientific Leadership Group will review and approve the scientific merit and priority of all proposals to access specimens for future studies from the PHACS Repository and recommend approval of projects of sound scientific merit and high priority to the PHACS EC.

5.2 Responsibilities of the PHACS Coordinating Center

The PHACS Coordinating Center will collate the necessary information for PHACS EC action including:

- Proposal (Concept Sheet proposal approved by the Leadership Group); and
- A signed Data and Specimen Use Agreement (Attachment B) from the potential recipient

5.3 Responsibilities of the PHACS Executive Committee

The PHACS EC will provide oversight in the operation of the PHACS Repository. Specifically, the EC will:

- Review and approve, as necessary, research proposals to access specimens stored in the PHACS Repository, the signed Repository Policy Adherence and Specified Data Use Agreement from the proposing investigator at the Recipient Institution, and the specific clinical protocol for which the samples were collected (the PHACS protocol will describe sample collection and storage procedures and includes the protocol informed consent forms).
    - The EC will judge whether the research is within the scope of the original consent specific to the genetic or non-genetic provisions of the original study consent document. If the proposed research is judged to be within the scope of the original consent, the EC may allow the research to proceed contingent upon NICHD approval.
    - If the EC judges the research to be of a sensitive nature that could impact the overall community from which the participants were recruited, the EC will seek the review of an ethicist to determine what additional safeguards or protections may be required to allow the research to proceed.
- Transmit the decision to the following:
    - The Principal Investigator at the Recipient Institution proposing the new research.

5.4. Responsibilities of the Storage Institution

The NICHD constitutes the Storage Institution. Responsibilities include the following:

- Notify the Repository of approval for release of repository specimens following review, and Collection and Recipient Institution IRBs, as necessary.

5.5 Responsibilities of the Recipient Institution

The Recipient Institution is the home institution of the proposing investigator requesting use of specimens from the PHACS Repository. Once a proposal is approved by the PHACS EC and NICHD, the proposing investigator must:

- Submit a proposal for use of specimens from the PHACS Repository to the Recipient Institution's IRB. If the proposing investigator is not affiliated with a Collecting Institution, the proposing investigator should discuss the proposal with the Recipient Institution IRB for a ruling on the institution's engagement in research as defined by OHRP and comply with the review requirements of the Recipient Institution's IRB. Under OHRP Guidance on Engagement in Research, investigators who are not at collecting institutions may be considered as not engaged in research if receiving specimens under circumstances like those operating under this policy. If the proposing investigator is affiliated with a Collecting Institution, a full review by the Collecting/Recipient Institution IRB may be required.
- Submit the necessary specimen specifications to NICHD (Maternal and Pediatric Infectious Disease Branch (MPIDB)), the Storage Institution and interact with the PHACS Data and Operations Center to identify the limited dataset honoring the minimum necessary rule under HIPAA.
- Fulfill all stipulated activities and sign the PHACS Repository Policy Adherence and Specified Data and Specimen Use Agreement for Collaborating Investigators (Attachment B) for filing at the PHACS Coordinating Center. A copy must be submitted to the NICHD.

The Recipient Institution's IRB will transmit the decision to the proposing investigator, who will forward the decision to the Principal Investigator and Project Director of the PHACS Coordinating Center who will inform the Principal Investigator for the original protocol through which the specimens were collected, the PHACS EC, and the NICHD.

6.0 Procedure for Accessing Specimens in PHACS Repository

Prior to accessing specimens stored in the PHACS Repository, the following procedure must be followed:

- The proposing investigator must submit to the PHACS Coordinating Center for distribution to the PHACS Scientific Leadership Group a Concept Sheet proposal and, if required, previously reviewed and approved by the groups designated in the relevant network's study development and review;
- Once the Concept Sheet proposal is approved by PHACS Scientific Leadership Group and subsequently the PHACS EC, the proposing investigator will sign and forward to PHACS Coordinating Center and the NICHD (MPIDB) the Repository Policy Adherence and Specified Data Use Agreement;

- Once the proposal is approved, NICHD (MPIDB) will instruct the Repository to transfer specimens; and
- No specimens will be released until all agreements are signed and, if required, recipient institution IRB approval is documented.

REFERENCES

1. Office for Protection from Research Risks, *Issues to Consider in the Research Use of Stored Data or Tissues.* November 7, 1997. Retrieved from http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm
2. Office for Human Research Protection, *Guidance on Research Involving Coded Private Information or Biological Specimens.* August 10, 2004. Retrieved from http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf
3. National Bioethics Advisory Commission, *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance Volume I. Report and Recommendations of the National Bioethics Advisory Commission*, August 1999. Rockville, Maryland.
4. *Research involving private information or biological specimens.* Retrieved from http://grants.nih.gov/grants/policy/hs/PrivateInfoOrBioSpecimensDecisionChart.pdf

Figure 1. Structural Organization of the Pediatric HIV/AIDS Cohort Study (PHACS)

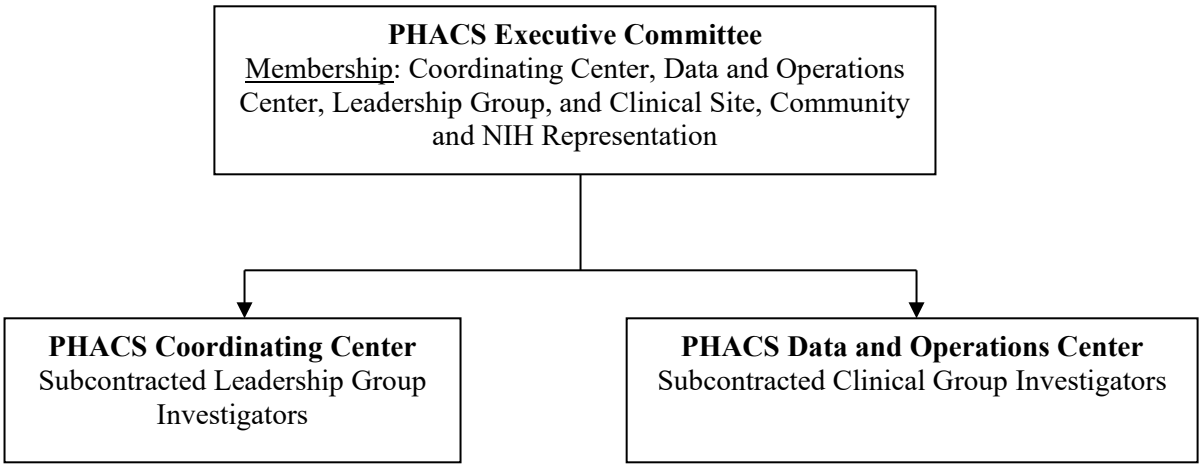
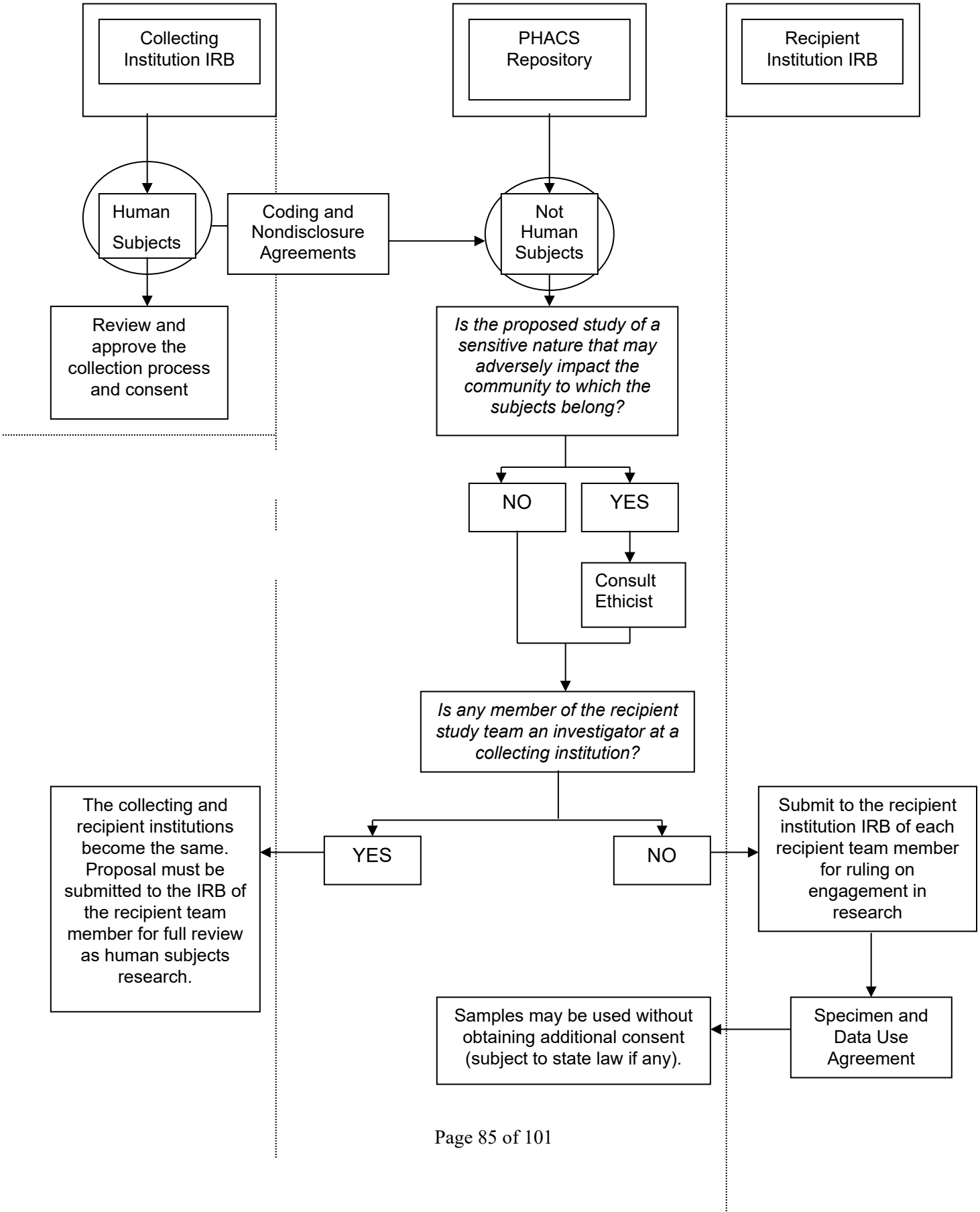


Figure 2. Oversight of the PHACS Repository Activities



Attachment A

PHACS Non-Disclosure and Repository Policy Agreement for Research Staff at Collecting Institutions

This agreement is to be signed by every member of the research team at Collecting Institutions. Each original is to be kept with administrative documents on site and one copy of each signed document is to be submitted to the Regulatory Associate at Westat before enrolling subjects.

1. I will disclose no identifying information about study subjects to anyone other than research team members and then only on a "need-to know" basis, for (1) subject safety, (2) monitoring of the protocol, (3) as required by law, or (4) as authorized by the subject.

2. I will make every effort to keep subjects' records confidential.

3. I pledge to be particularly vigilant about safeguarding this information from collaborating investigators who may have an interest in obtaining specimens from the PHACS Repository.

4. I will adhere to the document entitled "PHACS Human Subjects Policies and Procedures: Repository".

_____	_____
Staff Name	Principal Investigator Name
_____	_____
Signature	Signature
_____	_____
Date	Date

Attachment B

PHACS Repository Policy Adherence and Specified Data Use Agreement for Collaborating Investigators at Recipient Institutions

This agreement establishes the terms under which the research material will be disclosed to and used by the research team proposing to utilize specimens stored at the PHACS Repository, and others who may have access to these specimens. Every laboratory-based member of the proposing research team and others who may have access to PHACS Repository specimens must sign it. Research material may not be disclosed to or used by individuals who have not signed this agreement. A copy of the signed agreement will be kept with administrative documents at the laboratory site and one copy is to be submitted to the Regulatory Associate at Westat.

Recipient acknowledges that the conditions for use of this research material are governed by the NICHD in accordance with U.S. Department of Health and Human Services regulations at 45 CFR § 46.

Recipient agrees to comply fully with all such conditions and to report promptly to the NICHD through the Project Director at the PHACS Coordinating Center any proposed changes in the research project and any unanticipated problems involving risks to subjects or others. Recipient remains subject to applicable State and local laws or regulations and institutional policies that provide additional protections for the human subjects.

This research material may only be used in accordance with the conditions stipulated by the PHACS Leadership Group and outlined in the approved proposal/sub-study. Specimen material not used or in excess of that required may not be used for any other purpose or shared with or given to a third party. Such material is to be returned to the PHACS Repository or destroyed as previously agreed. Data are provided for the analysis stipulated in the proposal/sub-study and may not be used for any other purpose or shared in any fashion with a third party. Any additional use of this material or these data require prior review and approval by the PHACS Scientific Leadership Group, and, where appropriate, by the Recipient Institution IRB, which must be convened under the applicable U.S. Office of Human Research Protections-approved Federal Wide Assurance. If the recipient becomes aware of any use of this research material not provided for by this data use agreement, it must be reported to the PHACS EC, NICHD, and the local IRB.

The recipient agrees to refrain from seeking the identities of any donors of the specimens directly or indirectly from the sites at the collecting institutions, and agrees to refrain from contacting these donors should their identity become known.

_____	_____
Staff Name	Principal Investigator Name
_____	_____
Signature	Signature
_____	_____
Date	Date

APPENDIX VI: SAMPLE INFORMED CONSENT FORM FOR PARTICIPATION IN THE STUDY

NOTE FROM OFFICE OF HUMAN RESEARCH PROTECTION (OHRP) TO SITES ENROLLING PARTICIPANTS IN THIS STUDY:

Please note that this sample language does not preempt or replace local IRB review and approval. Investigators are required to provide the local IRB with a copy of this sample language intended for local use. Local IRBs are required to weigh the unique risks, constraints, and population considerations as a condition of any approval. Any deletion or substantive change of information concerning risks or alternative treatment must be justified by the investigator, approved by the local IRB, and noted in the IRB minutes. Justification and IRB approval of such changes must be forwarded to the Harvard T.H. Chan School of Public Health site registration desk for any NICHD-sponsored trial, or as may be otherwise specified. Sponsor-approved changes in a protocol must be approved by the local IRB before use unless intended for the elimination of apparent immediate hazard. New information shall be shared with existing participants at next encounter, with all new participants prior to involvement, or as the local IRB may otherwise additionally require.

TITLE OF STUDY: ADOLESCENT MASTER PROTOCOL FOR PARTICIPANTS 18 YEARS OF AGE AND OLDER – LITE (AMP UP LITE)

PRINCIPAL INVESTIGATOR: _____

PHONE: _____

If you are a legally authorized representative (LAR) of a potential participant in this study, in the rest of the document, "you" refers to "the participant you are representing."

We are asking you to be in the AMP Up Lite research study.

This study will help us better understand how HIV and HIV medications affect people living with HIV since birth. We want to learn more about what happens to young adults with HIV as they grow and develop into adulthood. You are being asked to join the study because you are at least 18 years old and your medical record shows you have had HIV since birth.

This consent form gives you information about the study, which we will discuss with you. Once you understand the study, if you want to take part you will be asked to sign this consent form. You will be given a copy to keep. It is important that you know the following:

- It is your choice whether or not you take part in this study.
- If you do not want to take part, it will not change any health care or benefits that you may receive.

Why is this study being done?

Approximately 10,000 young adults in the United States have been living with HIV since birth. Most have been taking HIV medications for most of their lives. Previous studies have helped us learn about the effects of HIV and its treatment on younger children and teens. But we know that many young adults with HIV face certain challenges. Some may struggle with their health, well-being, and development (such as how they do in school and at work and get along with others). We do not know enough about how and when young adults living with HIV make certain life decisions. These include decisions about continued education, work, family, sexual behavior, and substance use. This study will help us understand these decisions better. We can use the information we learn to find ways to improve their health and quality of life.

What is involved in this study?

In this study, we will collect information about you and your health, and take some measurements (height, weight, and blood pressure) and blood samples for laboratory tests. The study is set up to be flexible for you. Here are the different parts of the study:

Entry Evaluations:

If you complete the Entry evaluations at the clinic, here are some things we will do. The visit may take up to 3 hours.

- Check your height, weight, and blood pressure.
- Have you complete a questionnaire with clinic staff that asks about your medical and medications history, and family medical history.
- Have you do an online survey. The survey takes about 30-45 minutes to complete and asks about:
  - your education, income, work, and housing;
  - how well you can access health care and how you use it;
  - whether you've moved to an adult HIV care clinic/doctor and how the process went;
  - how you are feeling (for example, if you're sad or anxious);
  - your relationships with family and friends;
  - your sexual activity and choices around birth control;
  - whether you have had any sexually transmitted infections;
  - your choices around alcohol and substance use;
  - for women; if you had pregnancies or irregular periods;
  - for men; if you have been circumcised;
  - the kinds of HIV medications you have taken and how well you are able to take them; and
  - whether you have had any broken bones or hearing problems.
- Record information from your medical records and your physical exams about any medical or mental health conditions you have, immunizations, HIV-related and other test results, and HIV medicines you are taking.

- Collect blood (about two tablespoons) to be stored for testing in the future. This is explained in more detail later in this form.

If you are unable to come to the clinic for the Entry evaluations, we will take your height, weight, and blood pressure from your medical record and do the questionnaire by telephone. You can complete the online survey from your home or from anywhere you can securely connect to the internet.

(ONLY INCLUDE FOR PARTICIPANTS ENROLLING AT PHACS SITES.)

Yearly Follow-Up:

After Entry, once per year we will review your medical records for information about your health. We will record the same type of information we recorded at Entry. The follow-up online survey will be the same as the one you complete at Entry.

You do not have to come to the clinic for the yearly follow-up. At Year 5, we will collect blood (about two tablespoons) in the clinic or at another location to be stored for testing in the future.

(ONLY INCLUDE FOR PARTICIPANTS ENROLLING AT NICHD-WESTAT SITES.)

Yearly Follow-Up:

After Entry, your follow-up will be coordinated by researchers at the Harvard T. H. Chan School of Public Health (HSPH). A researcher from HSPH will contact you at the Year 1 follow-up to get your consent to continue being in the study. This may be done via telephone or online. If you agree to continue being in the study, once per year, researchers at HSPH will review your medical records for information about your health. They will record the same type of information that was recorded at Entry. The follow-up online survey will be the same as the one you completed at Entry.

You do not have to go into a clinic for the yearly follow-up. At Year 5, the researchers will let you know where to go to have your blood (about two tablespoons) collected to be stored for testing in the future.

How will my samples be stored? What kinds of tests could be done with them?

The blood collected from you as part of this study will be stored in the PHACS repository for future laboratory tests. A repository is a laboratory with freezers for samples like blood, tissue cells, and body fluids that are taken during a study. Your name will not be on these samples. The samples will have the same code that is on all of your other information in the AMP Up Lite Study. The people at the repository will not know your name.

You do not have to agree to store your samples in the PHACS repository in order to be in this study. You will not lose any benefits to which you are entitled if you decide against storing samples. You will be asked at the end of this consent form if you will let us store your samples for future testing. If you give permission, your samples may be used for future research without anyone contacting you again for permission.

Researchers can learn a lot from a study. Over time, the tests they use may get better, or new tests are developed. More can be learned with these new tests. Researchers may also think of new, important

questions to answer that were not known at the start of the study. Your rights and privacy will be protected in any of these new studies.

You will not receive the results of research done with your samples. This is because research can take a long time and must use samples from many people before results are known. In addition, when studies are first done, it is not always clear how to use the information to change the health care that people receive. None of these study results is likely to affect your care right now. They may be helpful to people like you in the future. Your samples can last in the freezer for many years. There is no time limit to when studies could be done in the future.

Some research may lead to new discoveries, such as new medicines or tests. You will not receive any money or other type of payment from the discovery and sale of these new medicines or tests.

If you change your mind and do not want your stored samples to be used, you should tell the research staff. They will then tell the repository and the samples will be destroyed.

There are two kinds of research that can be done with these repository samples: general and special studies.

- For **general** studies, researchers use samples to better understand how diseases including HIV affect young adults. They want to see whether having HIV and taking HIV medications can cause diseases and other problems. They also want to find out how to treat or prevent problems with HIV. Sometimes the samples can be used to learn about new problems that people with HIV have. These problems could be things like liver disease, diabetes, heart disease, and infections. These general studies would **not** include genetic testing (looking at your DNA or genes).

- For **special** studies, researchers will look at some of the same things as general studies. The difference is that researchers will also look at your genetic makeup (DNA or genes). A person's genetic makeup can either protect them or put them at greater risk for some conditions and can affect traits such as blood pressure or weight. The special studies may look at your entire DNA to look for changes in genes. These tests can help us better understand how HIV and HIV medications affect young adults.

(ONLY INCLUDE THE FOLLOWING STATEMENT FOR PARTICIPANTS THAT WERE FORMERLY IN OTHER HIV STUDIES.)

AMP Up Lite plans to use stored samples from other HIV studies, including other PHACS studies. If you had samples stored while you were in another HIV study, we will ask your permission to test them also.

Who will take part in this study?

Other clinics besides this one are also enrolling participants. Across all sites, we will enroll 500 young adults who have had HIV infection since birth. About (*site insert number*) participants will take part at (*insert site name*).

How long will I be in the study?

You will be in this study for at least 6 years after you first join. The study is planned to last until at least 6 years after the last participant is enrolled.

(ONLY INCLUDE FOR PARTICIPANTS ENROLLING AT PHACS SITES.)

What if I cannot or do not want to continue to be followed at my study clinic?

We will try to find another study clinic for you. Otherwise, you may continue taking part in the study through the Harvard T.H. Chan School of Public Health (HSPH). This is where the researchers running this study are located. You will continue to do the online surveys, and they will continue to check your medical chart every year.

What are the risks of the study?

During the blood collection, you might feel pain, or you might bleed or bruise where the needle enters the skin. Some people might faint.

You may feel uncomfortable or upset when asked about your thoughts and feelings, use of alcohol and drugs, and sexual behavior. At the end of the online survey, there is information on how and where you can get help if you need it.

We have taken many steps to protect your information. However, there is always a small chance that the information you submit online may not always be secure. This means that someone who does not know about your HIV status may find out about it. To lessen this risk, the study staff will share with you tips to protect your privacy while filling out the online surveys.

If you agree to the use of your samples for special studies that look at your genetic makeup, there is a risk that researchers who see your DNA testing information may figure out which information is yours. This is because your body's genetic make-up is unique to you. Therefore, even without your name, they could figure out your identity from this information if they have access to your genetic information from another source other than this study and compare them. This risk is small but may increase in the future as technologies advance and as more researchers study your genetic information.

If your genetic information becomes linked to your name, the U.S. federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect you. This law says that providers of health insurance and most employers cannot deny services based on your genetic information. However, GINA does not protect against discrimination by sellers of life, disability, or long-term care insurance.

What are the benefits of the study?

It is possible that taking part will not benefit you directly. The information we learn will help to develop new treatments or programs for others with HIV.

There will be some evaluations that might help you consider if you are leading your life as you would like. This information may reassure you. It might also help you decide whether to seek additional help or services.

What will I be told about what is learned in the study?

We may learn things during the study that could make you change your mind about staying in it. If this happens, we will let you know as soon as possible. We will also tell you how to learn more about these things.

Can I leave the study? What are the alternatives?

You can leave the study at any time. Your participation is voluntary. Doing so will not change any health care or benefits you may receive. Your choice will not affect your participation in other studies you may be eligible for now or in the future. If you decide to leave the study, your health information that was collected may be used as needed for this study or follow-up activities related to this study.

Could I be asked to leave the study before it ends even if I do not want to leave?

You could be asked to leave the study for the following reasons:

- If the person in charge of the study at your clinic determines that your health or well-being could be harmed if you keep participating;
- If the study is stopped by the agencies overseeing this study (the ***Eunice Kennedy Shriver*** National Institute of Child Health and Human Development (NICHD) and the National Institutes of Health (NIH); or
- If the study is stopped for other administrative reasons.

If you are removed from the study, the research staff will explain why you were removed. They will also explain your options to you.

You may decide to take yourself out of the study early. If you do, the information we already collected from you may still be used as planned for this study. It may also be used for follow-up activities related to the study.

Will being in this study cost anything?

You will not have to pay for anything that is done for the study. Medical care you get outside the study will be paid through the usual means, such as insurance.

Will I be paid for taking part in this study?

You will receive a gift card valued at (*insert standardized amount per the protocol team*) for completing the Entry evaluations including the online survey. You will receive the same gift card amount at each yearly follow-up. The gift card will be available immediately or shortly after completing the surveys.

Who will know that I am in this study? Who will see my information?

All of your records, including lab tests, will be confidential. The information we get from you, including through the online surveys, will be stored with a unique code number. The link between the code number and your name is secured at the clinic. Only a few research staff members can see it. When we publish papers or present results from this study to other researchers, only information at a group level will be given. We will never use your name or other information that could identify you.

In the online surveys, we will ask about things that some people may find sensitive. The online surveys are hosted by a company that takes many steps to protect your information. Survey responses are encrypted (coded) when sent from your computer to their servers. The servers are locked in a room. Only a few people approved by the study team can access the information on the servers.

At the follow-up time points, you will access the online survey through a website for study participants. The website requires a user name and password to get in. Only study participants will get a user name and password. Others will not be able to log in to the website.

To help with future research, your information may be included in public use databases. These include databases with general information and ones that are specific to genetic information. All direct identifiers will be removed from your information before they are shared. Your information cannot be removed from a database once it is added. Other researchers can request permission to use the information in the database for their own studies. Requests must be approved by an ethics board before any data is shared. You will be asked at the end of this consent form for your permission to share your information. If you give permission, your information may be used for future research without anyone contacting you again for permission.

We have a paper from the government saying we do not have to share information about people in this study if asked by state, federal, or civil courts. We will make every effort to keep your information confidential. However, we are required to report certain things to the authorities if we have good reason to suspect them. The appropriate authority depends on the situation but it might be the hospital, social services, health authorities, or the police. The things we need to report are:

(THE FOLLOWING LIST SHOULD BE UPDATED BY THE STUDY SITE ACCORDING TO THEIR STATE REPORTING REQUIREMENTS.)

- Suspected or known sexual or physical abuse of a minor.
- A significant risk you will harm yourself or others.

There are a few people who are not research staff at this clinic who may look at study records to make sure the study is running properly. These people may see your name. They may be from the clinic's Institutional Review Board (IRB), the National Institutes of Health (NIH), the Office of Human Research Protection (OHRP), or Westat (a research group helping to run this study).

If is important for us to know what happens to study participants. If we learn that you have died, a copy of the autopsy report or death certificate and medical records will be obtained. If study staff lose contact with you, they will confidentially give your name, sex, and date and city of birth to Westat. Westat will do a computer match with health department records to see if you are still alive. When the computer match is finished, they will destroy any documentation they received.

A description of this study will be available on http://clinicaltrials.gov. This website will not include information that can identify you.

(ONLY INCLUDE FOR PARTICIPANTS THAT WERE FORMERLY IN OTHER PHACS STUDIES.)

What will happen to information that was collected during my participation in other PHACS studies?

If you were previously enrolled in a PHACS study (AMP and/or SMARTT), all of your information from that study will be made available for use by the researchers of this study. This includes information from other studies that you may have been in such as IMPAACT studies, Women and Infants Transmission Study (WITS), and the Centers for Disease Control and Prevention (CDC) Longitudinal Epidemiologic Study to Gain Insight into HIV/AIDS in Children and Youth (LEGACY) study that you previously agreed to share with PHACS.

What happens if I get hurt from being in the study?

If you are hurt in this study, the (*insert the name of the clinic*) will give you the treatment you need right away. The cost of this treatment will be charged to your insurance company or you. This study will not pay for any treatments. Your clinic will then tell you where you can get more treatment if needed. No payment will be made to you by either the research clinic or the agency sponsoring this research. You do not give up your legal rights by signing this form.

Who can I call for more information about this study?

If you have questions about the study or an injury or problem you think was caused by the study, you can call (*name of investigator*) at (*telephone number*).

Who can I call for more information about my rights as someone in this research study?

There is a group of doctors, researchers, and community members who make sure that research is done carefully and that research participants are treated fairly and safely. If you have questions about your rights in this study, you can call a representative of this group. The person who can answer your questions is (*name and title of IRB member*) at (*telephone number*).

FUTURE RESEARCH WITH STORED SAMPLES

- Stored samples will be used for future **general** studies to better understand how HIV affects young adults and whether having HIV and taking HIV medications can cause diseases and other problems.

  Please check your choice below.

  I agree to have samples collected from me during the AMP Up Lite study and stored for future general tests.

  ☐ **Yes, I agree**

  ☐ **No, I refuse**

- Stored samples will be used for future **special** studies that include DNA testing and may look at your entire DNA. These tests will help to find ways to treat or prevent HIV or problems that young adults with HIV might have. Tests can also be done to look for changes in genes, which can help us better understand how HIV affects young adults.

  Please check your choice below.

  I agree to have samples collected from me during the AMP Up Lite study and stored for future special studies (your genetic makeup (DNA or genes)).

  ☐ **Yes, I agree**

  ☐ **No, I refuse**

SHARING OF GENERAL (NON-GENETIC) INFORMATION WITH OTHER RESEARCHERS AND IN PUBLIC USE DATABASES

- May we share your general (non-genetic) information with other researchers, and in public use databases, for future projects on HIV and other topics?

  ☐ **Yes, I agree**

  ☐ **No, I refuse**

(INCLUDE THIS SECTION ONLY FOR PARTICIPANTS WHO AGREED TO HAVE THEIR STORED SAMPLES USED FOR FUTURE SPECIAL STUDIES.)

SHARING OF DNA INFORMATION WITH OTHER RESEARCHERS AND IN PUBLIC USE DATABASES

- May we share your genetic (DNA testing) information with other researchers, and in public use databases, for future projects on HIV and other topics?

  ☐ **Yes, I agree**

  ☐ **No, I refuse**

STATEMENT OF CONSENT

I have read this document or it was read to me. I have been encouraged to ask questions. The researcher or their representative has answered all my questions, and I am satisfied with the answers. I agree to be in this research study. I allow my protected health information to be used and given out as described in this consent form.

SIGNATURES FOR THE STUDY
(This is only a suggested Signature format. Sites may use their own signature page.)

If you read the informed consent (or have had it explained to you) and understand the information, and you voluntarily agree to participate in this study, please sign your name.

Participant Name (print) [If Legally Authorized Representative (LAR) is signing]

Participant/LAR Name (print)	**Participant/LAR Signature**	**Date**
Witness Name (print) (*if required)	**Witness Signature**	**Date**
Study Staff Member Conducting IC Process (print)	**Study Staff Member Conducting IC Process Signature**	**Date**

(INCLUDE THE NEXT SIGNATURE SECTION ONLY FOR PARTICIPANTS FORMERLY ENROLLED IN OTHER HIV STUDIES.)

SIGNATURES TO USE SAMPLES COLLECTED FROM YOU DURING YOUR PARTICIPATION IN OTHER HIV STUDIES

If you read the informed consent (or had it explained to you) and agree that information and samples already collected from you when you were in other HIV studies can be used for this study, please sign your name below.

I give permission for samples collected from me during my participation in other HIV studies to help this study.

☐ **Yes, I agree**

☐ **No, I refuse**

If you checked "Yes, I agree," enter the names of other HIV studies in which you have taken part:

Participant Name (print) [If LAR is signing]

Participant/ LAR Name (print)	**Participant/LAR Signature**	**Date**
Witness Name (print)	**Witness Signature**	**Date**
Study Staff Member Conducting IC Process (print)	**Study Staff Member Conducting IC Process Signature**	**Date**

Note: This consent form with the original signatures MUST be retained on file by the Principal Investigator. A copy must be given to the participant. A copy should be placed in the participant's medical record, if applicable.

APPENDIX VII: SAMPLE ASSENT FORM FOR STUDY PARTICIPATION: ASSENT FOR PARTICIPANTS WITH LEGALLY AUTHORIZED REPRESENTATIVES

Note: No critical elements are specified in the Code of Federal Regulations for assent forms and local IRBs have broad discretion. This is a suggested sample format for young adults who cannot consent themselves to be enrolled in this study.

TITLE OF STUDY: ADOLESCENT MASTER PROTOCOL FOR PARTICIPANTS 18 YEARS OF AGE AND OLDER - LITE (AMP UP LITE)

PRINCIPAL INVESTIGATOR: _____

PHONE: _____

JOINING THE AMP UP LITE STUDY

We are asking you to be in the AMP Up Lite study.

This is a study to learn more about what happens to young adults with HIV as they grow and develop into adulthood. You are being asked to join the study because you are at least 18 years old and your medical record shows you have had HIV since birth. To help you decide if you want to join the study, we are going to tell you about the study and answer any questions you have.

What is this study about?

We know that many young adults with HIV face certain challenges. Some may struggle with how they do in school and at work and get along with others. We do not know enough about how these young people make decisions about continued education, work, family, sexual behavior, and substance use. This study will help us understand these decisions better. We can use the information we learn to find ways to improve their health and quality of life.

Do I have to be in this study?

No, you can choose not to be in this study.

If you choose to be in the study, we will ask you to sign this form. Signing this form shows that you understand what we told you about the study and that you agree to be in the study.

Even if you say you will be in the study, you can change your mind later. But if you decide to be in the study, you have to be serious about it.

If you decide to stop, being in the study before it is over, your health information that has already been collected may be used or released for this study or any follow-up activities related to the study. If you are removed from the study, the research staff will explain why you were removed. If you are removed or decide to stop being in the study, they will also explain the options available to you.

What is involved in this study?

Entry Evaluations:

If you complete the Entry evaluations at the clinic. Here are some things we will do. The visit may take up to 3 hours.

- Check your height and weight, and take your blood pressure.
- Have you complete a questionnaire that asks about your medical and medications history, and family medical history.
- Have you do an online survey. The survey takes about 20 to 30 minutes to complete and asks about:
  - your education, income, work, and housing;
  - how well you can access health care and how you use it;
  - whether you've moved to an adult HIV care clinic/doctor and how the process went;
  - the kinds of HIV medications you have taken and how well you are able to take them;
  - for men, if you have been circumcised; and
  - whether you have had any broken bones or hearing problems.
- Record information from your medical records and your physical exams about any medical or mental conditions you have, immunizations, HIV-related and other test results, and HIV medicines you are taking.
- Collect blood (about two tablespoons) to be stored for testing in the future.

If you are unable to come to the clinic for the Entry evaluations, we will take your height, weight, and blood pressure from your medical records and do the questionnaire by telephone. You can complete the online survey from your home or from anywhere you can securely connect to the internet.

Yearly Follow-Up:

After Entry, once per year we will review your medical records for information about your health. We will record the same type of information we recorded at Entry. The follow-up online survey will be the same as the one you complete at Entry.

You do not have to come to the clinic for the yearly follow-up. At Year 5, we will collect blood (about two tablespoons) in the clinic or at another location to be stored for testing in the future.

Who will take part in this study?

About 500 young adults will take part in this study.

How long will I be in the study?

You will be in this study for at least 6 years after you first join. The study is planned to last until at least 6 years after the last participant is enrolled.

What are the risks of this study?

We'll draw some blood from your arm with a needle. You might feel a little pain, or you might bleed or bruise where the needle enters the skin. Some people might faint.

You may feel uncomfortable or upset when asked about your thoughts and feelings or other questions. At the end of the online survey, there is information on how and where you can get help if you need it.

We have taken many steps to protect your information. However, there is always a small chance that the information you submit online may not always be secure. This means that someone who does not know about your HIV status may find out about it. To lessen this risk, the study staff will share with you tips to protect your privacy while filling out the online surveys.

What are the benefits of this study?

You may not get anything yourself by being in the study. The information we learn will help to develop new treatments or programs for others with HIV.

Being in this study is up to you and your parent or legal guardian. Both of you have to say "yes."

What will I be told about what is learned in the study?

We may learn things during the study that could make you change your mind about staying in it. If this happens, we will let you know as soon as possible. We will also tell you how to learn more about these things.

Can I leave the study? What are the alternatives?

You can leave the study at any time. It is your choice whether or not you want to continue taking part in this study.

Who will know that I am in this study? Who will see my information?

All of your records, including lab tests, will be kept private. Only a few research staff members can see your information. When we share results from this study with other researchers, only information at a group level will be given. We will never use your name or other information that could identify you.

STATEMENT OF CONSENT

Information about this study has been given to you. You had a chance to ask questions about the study. We told you that it is your decision whether to be in the study. You can be in the research only if you want to be **and** your parent or legal guardian gives permission. You can decide not to be in the research, or change your mind without changing your care at this hospital/clinic or changing the way people who work for the hospital/clinic treat you. If, at this time, you voluntarily agree to be in this study, please sign your name below.

SIGNATURES FOR THE STUDY
(This is only a suggested Signature format. Sites may use their own signature page.)

I understand what being in this study means and I got answers for all the questions I had.
I agree to be in this AMP Up Lite study.

Participant Name (print)	**Participant Signature**	**Date**
Witness Name (print)	**Witness Signature**	**Date**
Study Staff Member Conducting IC Discussion (print)	**Study Staff Member Signature**	**Date**

Note: This consent form with the original signatures MUST be retained on file by the Principal Investigator. A copy must be given to the participant. A copy should be placed in the participant's medical record, if applicable.