Pediatric HIV/AIDS Cohort Study (PHACS)
Adolescent Master Protocol (AMP)
Protocol PH 200

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LIST OF ABBREVIATIONS

ASCUS	Atypical Squamous Cells of Undetermined Significance
BMD	Bone Mineral Density
BMI	Body Mass Index
CV	Cardiovascular
DXA	Dual-energy X-ray Absorptiometry
DOC	Data Operating Center
DMC	Data Management Center
DMS	Data Management System
EC	Executive Committee
GCP	Good Clinical Practice
HPV	Human Papillomavirus
HSIL	High-Grade Squamous Intraepithelial Lesions
LSIL	Low-Grade Squamous Intraepithelial Lesions
LV	Left Ventricular
MDC	**Mitochondrial Determinants Component**
MI	Myocardial Infarction
MOU	Memorandum of Understanding
ND	Neurodevelopment
NDI	National Death Index
OAE	Otoacoustic emissions
OR	Odds Ratio
OXPHOS	**Oxidative Phosphorylation**
STI	Sexually transmitted infection

LIST OF APPROVED STUDIES MEETING THE ELIGIBILITY REQUIREMENT FOR ENROLLMENT INTO AMP (SEE SECTIONS 4.1.1 AND 4.1.2)

PROTOCOL 185

PACTG 076

PACTG 219C

PACTG 316

PACTG 326

PACTG 353

PACTG 394

PACTG 1022

PACTG 1025

PACTG 1038

PACTG 1039

PACTS HOPE (UNINFECTED COHORT ONLY)

WITS

This list will be updated and maintained on the PHACS website.

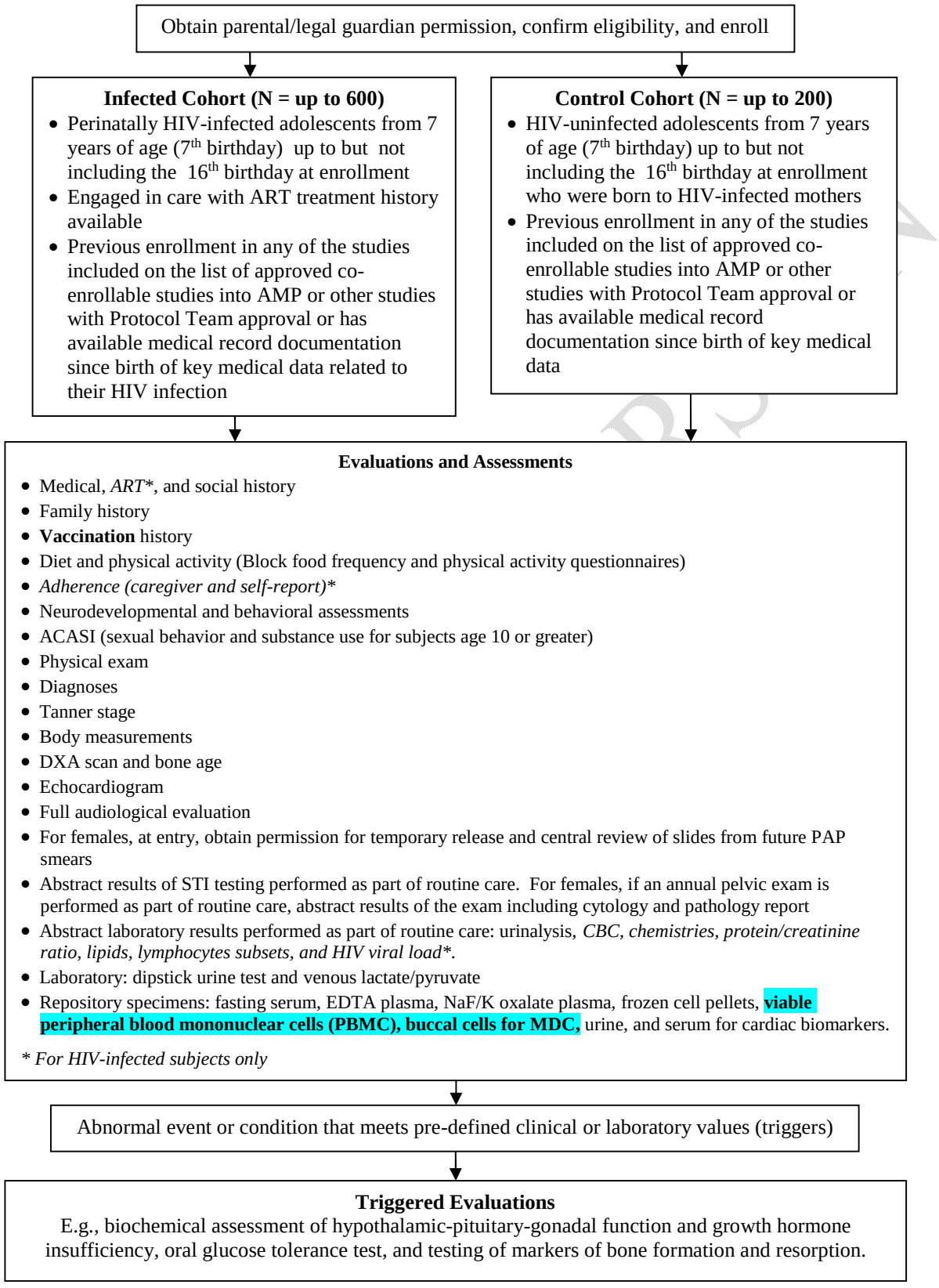
STUDY ABSTRACT

Design:	This is a prospective cohort study designed to define the impact of HIV infection and antiretroviral therapy on pre-adolescents and adolescents with perinatal HIV infection. A group of HIV-uninfected children with perinatal exposure to HIV from a similar sociodemographic background and age distribution will be enrolled for comparison. Domains to be investigated include growth and sexual maturation, metabolic risk factors for cardiovascular disease, cardiac function, bone health, neurologic, neurodevelopment, language, hearing and behavioral function, and sexually transmitted infections (STI).
Population:	HIV-infected and -uninfected children from 7 years of age (7th birthday) up to but not including the 16th birthday born to HIV-infected mothers. Participants will be children previously enrolled in any of the studies included on the list of approved studies for co-enrollment into AMP noted above, or another study with Protocol Team approval or has medical record documentation since birth of key medical data related to their HIV infection.
Sample Size:	• Infected Cohort: 451 perinatally HIV-infected children • Control Cohort: 227 perinatally HIV-exposed but uninfected children
Study Duration:	**The study is expected to last four or more years. Study participation for individual participants will end once they reach 18 years of age unless parent/legal guardian permission and/or youth assent is withdrawn prior to age 18.**
Evaluations:	Annual visits with medical, neurological, neurodevelopmental, behavioral, language, growth, metabolic, **mitochondrial,** cardiac, hearing, and laboratory studies.
Primary Objectives:	1. To define the impact of HIV infection and ART on growth and pubertal development (and their hormonal regulation), along with the cognitive, academic, and social development, of pre-adolescents and adolescents with perinatal HIV infection as they move through adolescence into adulthood. 2. To identify infectious and non-infectious complications of HIV disease, including the toxicities of antiretroviral therapy (ART). 3. To investigate: • Cognitive and behavioral changes over time, including medication adherence, family and social function, and high risk behaviors such as risky sexual behavior, licit and illicit drug use, and alcohol

	use; • Changes in language and hearing; **and** • Changes in glucose metabolism, body composition, bone mineralization **and mitochondrial function;** • Changes in lipid metabolism and other risk factors for cardiovascular disease; • Risk factors for secondary transmission of HIV; and • The occurrence and clinical course of cervical HPV infections among females.
Domain-Specific Aims:	Growth and sexual maturation To longitudinally track growth and sexual maturation and the factors that influence growth and maturation in HIV-infected children when compared to HIV-exposed but uninfected children. Metabolic risk factors for cardiovascular disease To characterize the emergence of abnormal glucose metabolism, lipid abnormalities, **mitochondrial abnormalities,** body composition and other risk factors for cardiovascular disease and identify the contributing influences in HIV-infected children when compared to HIV-exposed but uninfected children. Cardiac function To estimate the prevalence of cardiac structural and functional abnormalities in HIV-infected children and youth when compared to HIV-exposed but uninfected children. Bone mineral density To estimate the differences in bone mineral density of HIV-infected children when compared to HIV-exposed but uninfected children and to identify factors contributing to abnormal bone mineralization. Neurologic, neurodevelopment, language, and behavioral function • To examine cognitive and behavioral outcomes of HIV-infected children and adolescents, including high risk behaviors such as risky sexual behavior, licit and illicit drug use, and alcohol use, neurodevelopmental impairment, school achievement and to compare them with an HIV-exposed but uninfected control cohort. • To examine non-adherence to antiretroviral therapy and predictors of non-adherence among HIV-infected children receiving ART. • To examine family and psychosocial factors associated with emotional and behavioral problems. Adolescent gynecology and STI infection • To evaluate the incidence of and risk factors for acquiring STIs/vaginal infections (C. trachomatis, N. gonorrohea, T. vaginalis, syphilis, genital warts, HPV, and HSV) for males and

	females, and in addition bacterial vaginosis for females. • To evaluate the incidence, predictors, and outcomes of pregnancy.

STUDY SCHEMA



1.0 INTRODUCTION

1.1 Scientific Background

1.1.1 Impact of HIV Infection on Pre-adolescents and Adolescents

The advances in treatment to prevent maternal HIV transmission to neonates have been groundbreaking. As a result, the number of new perinatally-infected 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 previously infected American children have survived and are approaching adolescence. It is estimated that there are about 10,000 HIV-infected children and perinatally HIV-infected adolescents currently living with HIV in the U.S. with 15% between 6 and 10 years of age and 50% between 11 and 16 years of age. In the CDC Pediatric Spectrum of HIV Disease study, the median age of HIV-infected children is 11 years. 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. Therefore, there is a global cohort of children who have been living with HIV infection since birth who are aging into adolescence. Little is definitively known about the impact of HIV infection and its treatment on the maturation process in these children.

1.1.2 Growth, Maturation, and Body Composition in Pre-adolescents and Adolescents

Growth failure is a frequent manifestation of untreated pediatric HIV infection which can be improved by antiretroviral therapy (ART).[1,2,3,4,5] Although frank growth hormone (GH) deficiency is not commonly diagnosed in HIV-infected children, it has been suggested that the observed growth failure may be due, at least in part, to resistance to GH and/or to insulin-like growth factor-I (IGF-I), the physiological mediator of the growth-promoting action of GH.[6,7,8,9] A limited number of studies of GH treatment of short children with HIV infection have been reported.[10] High-dose GH, thought to be necessary to overcome endogenous GH resistance, has been shown to ameliorate HIV wasting after 12 weeks of administration to infected adults.[11,12] In addition to the impact of GH on growth, it is speculated that resistance to GH may contribute to immunodeficiency in HIV infection so that exogenous high-dose GH treatment could be a useful adjunctive therapy to aid immune reconstitution.[13] An additional effect of HIV infection that has been observed in perinatally-infected children and in transfusion-infected hemophiliacs is delayed sexual maturation.[14,15,16]

In addition to changes in growth and maturation, highly-active antiretroviral therapy (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.[17,18] The physiologic effect of the metabolic syndrome places patients at risk for cardiovascular (CV) disorders. There is controversy whether the metabolic syndrome in HIV-infected patients is exclusively related to ART exposure; other causes may include HIV itself (because many of the features of the metabolic syndrome pre-date HAART), underlying family risk factors, **mitochondrial abnormalities,** or a combination of all of these. Studies in children show similar although not identical findings, including abnormal body

composition, insulin resistance, and dyslipidemia, with increased risk at older age and longer duration of HAART.[19],[20],[21],[22],[23] The onset of puberty has been proposed as another factor causing these changes.[24] In adults with HAART-induced metabolic syndrome, growth hormone treatment at pharmacological doses has resulted in significant and sustained improvements in both lean body mass and fat compartments, although data on long-term outcomes are lacking.[25],[26]

Most previous studies of growth, puberty, and body composition in HIV-infected children have either been done in small numbers of participants, in mixed cohorts of vertically and horizontally acquired disease, or analyzed in a cross-sectional as opposed to a longitudinal manner. In addition, a well-matched control cohort is often lacking and a mechanistic component is usually not included. The power of the current proposal is that it allows for longitudinal study of a large, homogeneous population of perinatally HIV-infected children of pubertal age for study of relationships between disease status (e.g., immune deficiency), ART, and growth, puberty, and body composition. The results could lead to alterations of existing viral-specific therapeutic protocols, as well as to consideration of adjunctive treatments (e.g., human GH) to augment growth, improve immune function, and to counteract abnormal body composition and risk of metabolic syndrome.

1.1.3 Cardiovascular Risk Factors in Pre-adolescents and Adolescents

Several studies have investigated the relationship between HAART and atherosclerosis. In a report of 102 HIV-infected participants, a higher prevalence of carotid artery lesions was detected in patients receiving protease inhibitor (PI) therapy than among those receiving PI-sparing regimens or no therapy.[27] A large cohort study of 17,852 patients showed that adverse CV risk factors are associated with non-nucleoside reverse transcriptase inhibitors (NNRTI) and PI use.[28] Several studies have documented a 4 to 7 fold increase in annual incidence of myocardial infarction (MI) among HIV-infected patients after the introduction of HAART, when compared to the pre-HAART era.[29],[30] In a systematic review of the literature, Rhew et al. found that the majority of published studies showed that PI use is associated with lipid abnormalities and morphologic signs of CV disease.[31] These data suggest that exposure to PI therapy is an important risk factor for developing a MI. As HIV-infected children and youth live longer and have longer exposure to HAART, premature CV disease becomes an increasing concern.

One of the most significant mechanisms of atherosclerotic heart disease is vascular endothelial dysfunction and reduced flow mediated dilation. Vascular endothelial dysfunction is greater in HIV-infected children and adults when compared to controls, independent of known CV risk factors.[32],[33] Activation and/or injury of the endothelium can play a role in the development of vascular complications. Raised plasma levels of endothelial markers such as von Willebrand factor (vWF) antigen, soluble thrombomodulin and soluble vascular cell adhesion molecule-1 have a prognostic and/or diagnostic value. Cell adhesion proteins such as the selectins may be elevated as well.[34],[35] HIV-infected patients have conditions that may contribute to the activation or injury of the endothelium including dyslipidemia, insulin resistance, and chronic inflammation. Although HIV-infected children clearly demonstrate the features of lipodystrophy, very few investigations have focused on early CV risk in these children. In this study, we will

describe the prevalence and risk factors associated with fat redistribution in HIV-infected children.

HIV-infected children carry a number of metabolic risk factors that predispose them to early CV disease. In adults with HIV, the etiology of these complications is associated with mitochondrial dysfunction on ART. We hypothesize that the mitochondrial toxicities of ART and HIV itself are driven primarily by alterations in mitochondrial RNA and oxidative phosphorylation (OXPHOS) protein and enzyme activity levels, which, in turn, increase mitochondrial reactive oxygen stress and lactate levels, resulting in insulin resistance and lipodystrophy. OXPHOS protein and enzyme activities in PBMCs or buccal cells (cheek swabs) may correlate and predict the degree of the metabolic disease. In a subset of children enrolled in AMP, we will evaluate mitochondrial functions and other abnormalities in the context of metabolic dysfunction.

1.1.4. Cardiac Function

HIV-infected children exposed to ART

Abnormalities in left ventricular (LV) structure and function occur in HIV-infected children and are some of the strongest predictors of subsequent mortality.[36] These abnormalities are likely to result from multiple causes including infection of the myocardial cells with HIV, coinfection with cardiotropic viruses, autonomic dysfunction, and cardiotoxicity resulting from pharmacologic agents and inflammatory cytokines.[37] The abnormalities of LV structure and function associated with HIV cardiomyopathy can be related to depressed contractility, LV dilation, increased afterload (abnormal LV dimension: wall thickness), and abnormalities of heart rate and blood pressure. Similar abnormalities of LV structure and function are observed with ART that lead to cardiomyopathy in adults and animal models.

Children and young adolescents offer a unique opportunity to study the physiologic mechanisms of specific types of cardiomyopathy, as they are less likely than older adolescents and adults to be affected by such confounding factors as hypertension, tobacco smoking, obesity, diabetes mellitus and coronary atherosclerosis. In addition, the needs for future growth and longer survival in children suggest that subclinical abnormalities of cardiac structure and function may be more likely to result in subsequent symptomatic cardiomyopathy in children than in adults.

Cardiac dysfunction also occurs in HIV-exposed but uninfected children. The fact that LV dysfunction is found in both HIV-infected and uninfected children born to HIV-infected women suggest that the dysfunction is related in part to the intrauterine environment. One of the environmental factors may be *in utero* ART exposure.

The effects of ART on the cardiovascular system of HIV infected children are poorly understood. This is an important area of investigation for two reasons. First, HIV-infected children are routinely exposed to ART therapy for many years even as their cardiovascular system is developing and as HIV infection is affecting their overall development. The potential for ART to cause damage to the cardiovascular system is magnified by both the duration of

exposure and its occurrence during critical stages in a child's cardiovascular development. Second, the effects of ART and HIV on the cardiovascular system status of children may interact, given that both act on the cardiovascular system and on each other. Yet, the direction and magnitude of the effects of ART and HIV in combination are unknown.

Biomarkers of Myocardial Dysfunction

This study will include an assessment of blood biomakers of myocardial dysfunction such as N-terminal plasma N (amino)-terminal pro-brain natriuretic peptide (proBNP). ProBNP is a useful biomarker with high sensitivity and specificity for the diagnosis of ventricular dysfunction, heart failure, and coronary syndromes in adults, and also is a strong predictive marker for future cardiovascular events in adults and children.,[38],[39],[40] Age-related changes in proBNP have been observed.[41],[42],[43],[44] The biomarkers will be compared to the echocardiographic parameters of LV structure and function. We have found echocardiographic parameters of LV structure and function to be very sensitive for detecting asymptomatic cardiomyopathies in children with mitochondrial toxicity, a proposed mechanism of ART-associated cardiotoxicity.

In addition to studies of structure and function of the heart, studies are currently underway among ART-exposed children born to HIV-infected women to see if there is a link between LV dysfunction and mitochondrial DNA (mtDNA) mutations which are not present in controls.[45] Denaturing gradient gel electrophoresis screening of umbilical cord tissue from infants exposed *in utero* to zidovudine (ZDV) and lamivudine (3TC) (n=10) demonstrated a significant 3.7-fold increase in mtDNA mutations/sequence variants compared with unexposed controls (n=9) ($P<0.001$). Each ZDV-3TC exposed infant had eight additional sets of distinct mutations not found in controls. These data suggest "hotspots" for drug induced mtDNA mutations. Similar frequently occurring mtDNA mutations are observed in cord blood lymphocytes of infants exposed prepartum to ZDV-3TC, and in umbilical cords of newborns exposed *in utero* to ZDV as the only Nucleoside Reverse Transcriptase Inhibitor (NRTI) (V. Walker, personal communication, 2006). This, exposure to ART *in utero* may result in permanent changes in mitochondrial function that could have long-term adverse implications. Therefore, the association between *in utero* ART exposure, mtDNA mutations, and clinical cardiovascular abnormalities is an important area for further study.

1.1.5 Bone Mineralization in Pre-adolescents and Adolescents

HIV-infected children have lower bone mineral density (BMD) than healthy age-, sex- and race-matched controls.[46],[47] Yet very few of the HIV-infected children have had longitudinal follow-up of their BMD. During childhood and adolescence, bone mass increases extensively through longitudinal growth and changes in skeletal size and shape. By 18 years of age, as much as 90% of peak bone mass has been attained, and, by the end of the third decade of life, the acquisition of peak bone mass is complete.[48] Several factors influence the peak bone mass attained, including sex, ethnicity, genetics, weight-bearing physical activity, dietary intakes of calcium and vitamin D, and pubertal development through hormonal influences. Various risk factors for low BMD in HIV-infected children have been identified but no consistent pattern has emerged. These include low $CD4^+$ T-cell count, use of HAART, and lipodystrophy.[49] Tenofovir has been associated with a reduction in BMD in children. HIV-infected children receiving HAART and those with

calcium insufficiency also showed higher levels of bone resorption markers.[50] Some of these risk factors for low BMD in HIV-infected children are consistent with those identified among HIV-infected adults; these include high lactate levels, specific HAART regimens, $CD4^+$ T-cell count, visceral fat deposition, and glucose intolerance.[51],[52],[53] Indicators of decreased bone formation and increased bone resorption have also been observed. In addition, known risk factors for low BMD in the general population have been found in HIV-infected adults, including smoking, weight loss, low lean body mass, illicit drug and medication use, and perturbations of the hypothalamic-pituitary-gonadal axis. Many gaps remain in our understanding of low BMD in children and youth with perinatal HIV disease.

1.1.6 Pre-Adolescent and Adolescent Behavior

With the advent of ART, perinatally-infected children are reaching older childhood and adolescence in larger numbers. These youth are primarily of ethnic minority status living in low socioeconomic status urban communities and have many barriers to optimizing their mental and behavioral health.[54] Their problems are not only detrimental to themselves, but may place others at risk for HIV. Furthermore, there are many confounding factors related to the HIV infection, such as progression of HIV disease, neurocognitive deficits due to HIV, HIV stigma, and disclosure of infection status, which when combined with environmental factors such as substance use, poverty, inner-city stress, and disrupted family attachments due to substance use and illness, make adolescence a challenging period for these HIV-infected youth. Pre-adolescents and adolescents with HIV face additional unique complexities related to the impact of HIV on health, mental health, and normative developmental process such as school functioning, puberty, growth, peer relationships and sexuality.[55] As these youth reach adolescence, suboptimal adherence to complex medication regimens also becomes a prominent issue which can lead to viral resistance and treatment failure.[56],[57],[58],[59] Additionally, adolescence is a time of increased experimentation with sexual behavior and drug use which provides opportunities for transmission of HIV to others.

Studies of perinatally HIV-infected adolescents show high rates of: 1) psychiatric disorders including mood, anxiety, and behavioral problems,[60],[61] 2) high risk sexual behaviors and substance use, and 3) non-adherence to ART.[62],[63],[64],[65] The literature from studies of other populations of inner-city adolescents suggests that these youths are at high risk for poor outcomes through young adulthood, including difficulties functioning independently, engaging in risk behaviors, and developing multi-drug resistance to ART.

In most U.S. urban centers where pediatric HIV is most prevalent, pediatric AIDS represents a confluence of two major urban epidemics: HIV disease and substance abuse in the context of poverty. Early drug use exacerbates the problem of early sexual behavior through disinhibition and is associated with high rates of unprotected intercourse, teen pregnancy, and sexually transmitted infections (STIs).[66],[67] HIV-infected youth may be at even greater risk for contracting STIs due to their compromised immune functioning, and the presence of STIs, in turn, increases the chances of transmitting the virus to partners.[68] Thus, adolescence is a particularly vulnerable stage of development with profound physical, behavioral, and emotional consequences.[69],[70] Furthermore, youth entering adolescence with the burden of HIV infection have endured

perinatal deficits in growth, maturation, and neurodevelopment as well as years of less than optimal therapy and the psychosocial ramifications of HIV disease.[71],[72],[73],[74]

Therefore, understanding the behavioral dimensions of the youth is critical to understanding their outcomes and identifying potential points of intervention. The Adolescent Master Protocol (AMP) study will follow a large number of youth, with and without HIV infection, from the pre-adolescent era through completion of adolescence to evaluate the effect of HIV infection and the multiple confounding issues on their health and mental health outcomes.

1.1.7 Complications of HPV Infection in HIV-Infected Children and Youth

Among the STIs confronting sexually active adolescents, human papillomavirus (HPV) is perhaps the most important. 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. Other factors associated with cervical cancer development include smoking cigarettes and prolonged oral contraceptive use (> 6 years).[75] Certainly, nicotine and its metabolites can be detected directly from cervical mucous. Hence smoking may have direct carcinogenic effects or may alter immunologic responses in cervical mucous. Progesterone levels have also been associated with abnormal cell proliferation. Substance use has been shown to be associated with immune depression and may accelerate progression of HPV.[76] HPV is quite common in healthy adolescents and young women with up to 50% acquiring HPV within a few years after initiating intercourse.[77] Fortunately, the majority of infections in this age group are transient and benign.[78],[79] However, in HIV-infected adolescents and adults, HIV infection is associated with persistence of HPV.[80] This is not unexpected since HPV persistence has been linked to disordered cell mediated immune responses.[81],[82] A recent study of adolescents and young women from the REACH cohort showed that persistence of cervical HPV and the development of high-grade squamous intraepithelial lesions (HSIL) were extremely common.[83] Approximately 45% of the adolescent women 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 multivariate analysis, hormonal contraceptive use, high interleukin-12 (IL-12) concentrations of the cervical mucous, and persistent LSIL prior to HSIL were significantly associated with the development of HSIL. These factors were found to be independent of $CD4^+$ T-cell counts. The high IL-12 concentrations in cervical mucous associated with HSIL may be suggestive of a local immune dysregulation to HPV caused in part by HIV infection. The role of hormonal contraception as a risk factor 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 girls.[84]

The data regarding ART and HPV control is complicated. It appears that control of HIV replication and improved $CD4^+$ T-cell counts resulting from ART may lower the risk of developing HSIL. However, once HSIL develops, ART does not appear to strongly influence its

natural history.[85],[86] Unfortunately, little is known about the natural history of HPV in adolescents with perinatal HIV infection, limiting our ability to adequately care for this group.

The REACH study included only adolescents with behavioral acquisition of HIV who had been HIV-infected for a relatively short period of time. Most were not receiving ART. This study allows for HPV to be studied in the context of long-term perinatal HIV infection and ART.

1.2 Rationale

The advent of potent ART has resulted in the survival into adolescence of an increasing proportion of infants and children with perinatal HIV infection. At the same time, 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 pre-adolescents and adolescents. Some of these children represent long-term slow-progressors, while others have benefited from potent combination ART. The impact of HIV infection and its treatment on the growth and development of this cohort of children who have been living with HIV infection since birth is not fully known. The PHACS AMP protocol is designed to study the effect of HIV infection on key processes of maturation such as pubertal development, bone growth, fat distribution, and hepatic, renal and cardiovascular functions. The study will characterize adverse outcomes of HIV infection and its therapy, including end-organ disease, risk factors for cardiovascular disease, metabolic abnormalities, **mitochondrial abnormalities,** and malignancies. In addition, behavior in adolescents plays a major role in adherence to medications, treatment failure, evolution of viral resistance, and secondary transmission of HIV, including the transmission of resistant virus, to others. This knowledge can form the basis for interventions to improve the quality of life of infected children. Unfortunately, the number of HIV-infected infants, children and adolescents worldwide 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 the increasing number of infected youth worldwide.

1.3 Study Design

This study will establish a cohort of perinatally HIV-infected children from 7 years of age up to the 16th birthday at enrollment. This will be a fixed cohort of up to 600 participants. Recruitment and enrollment will close once the desired number of participants is enrolled. A control cohort of up to 200 HIV-uninfected children from 7 years of age (7th birthday) up to but not including the 16th birthday at enrollment with perinatal exposure to HIV will be enrolled. They will come from a similar sociodemographic background with a similar age distribution to that of the infected children, and most will have been exposed to ART *in utero.* This HIV-exposed but uninfected control cohort will be important in evaluating whether observed abnormalities are related to HIV infection and/or ART, since the groups should be well matched for other risk factors for behavioral, developmental, and health problems. Enrollment **into the main AMP Study** closed in **July** 2009 with the enrollment of 451 HIV-infected children and 227 HIV-exposed but uninfected children. **The Mitochondrial Determinants Component (MDC) was closed to**

accrual in August 2013 with 361 participants enrolled. Participant follow-up in MDC was completed in December 2014.

Participants will be evaluated prospectively according to an established schedule of evaluations. The study will prospectively document infectious and non-infectious complications of HIV and ART at each study visit. Events will be classified by diagnosis rather than by signs and symptoms, using standardized definitions. Some events will be further evaluated in future, separate, focused sub-studies designed to address specific scientific questions.

Certain abnormalities identified on protocol-specified clinical or laboratory evaluations will trigger specific additional evaluations. These include biochemical assessment of hypothalamic-pituitary-gonadal function and growth hormone insufficiency, oral glucose tolerance testing, testing of markers of bone formation and resorption.

2.0 OVERALL OBJECTIVES

1. To define the impact of HIV infection and ART on growth and pubertal development (and their hormonal regulation), along with the cognitive, academic, and social development, of pre-adolescents and adolescents with perinatal HIV infection as they move through adolescence into adulthood.

2. To identify infectious and non-infectious complications of HIV disease and evaluate their associations with ART. These include toxicities resulting from ART, including mitochondrial toxicity, lipid abnormalities, and end-organ damage.

3. To investigate:
   - Changes in glucose metabolism, body composition, and bone mineralization;
   - Changes in lipid metabolism, **mitochondrial function,** and other risk factors for cardiovascular disease;
   - Cognitive and behavioral changes over time, including medication adherence, family and social function, and high risk behaviors such as risky sexual behavior, licit drug abuse, illicit drug use, tobacco and alcohol use;
   - Changes in language and hearing;
   - Risk factors for secondary transmission of HIV; and
   - The occurrence and clinical course of cervical HPV infections among females.

3.0 DOMAIN-SPECIFIC AIMS AND HYPOTHESES

3.1 Growth and Sexual Maturation

Specific Aim

- To longitudinally track height, weight, body mass index (BMI), and sexual maturation in perinatally exposed HIV-infected and uninfected children and to correlate measurements with parental stature (if available), lifestyle (diet and physical exercise), and disease and treatment status.

Hypothesis:

- Perinatally HIV-infected children who reach adolescence manifest reduced growth, and delayed onset and altered trajectory of sexual maturation compared to HIV-exposed but uninfected children of similar socioedemographic background.

3.2 Metabolic Risk Factors for Cardiovascular Disease

Specific Aim

- To characterize the emergence and estimate the occurrence of insulin resistance and abnormal glucose tolerance, **mitochondrial dysfunction,** dyslipidemia, elevated blood pressure, and abnormal body composition and their relationship to HIV disease status and specific ART regimens in HIV-infected children over time.

Hypotheses

- Compared to non-infected children, there will be an increase in central adiposity or peripheral fat wasting prior to additional morbidity associated with lipodystrophy. The onset of puberty will be associated with progression of these changes. Specific ART regimens and classes of ART agents will have different effects on these metabolic and anthropometric outcomes.
- **HIV-infected children will have mitochondrial dysfunction compared to HIV-uninfected but exposed children, and these derangements will be associated with metabolic abnormalities.**
- Participants with insulin resistance will have a high likelihood of abnormal glucose tolerance, **mitochondrial dysfunction,** and increased total body and trunk fat. Participants with abnormal lipid levels will also have the greatest percentages of total and trunk fat and will have elevated **circulating levels of** vascular inflammatory markers. Together these factors have the potential to contribute to early atherosclerotic cardiovascular disease.

3.3 Cardiac Function

Specific Aims

- To identify abnormalities in cardiac function in perinatally HIV-infected children and youth and identify any relationship to age and to pre- and postnatal ART exposure.
    - To estimate the age and ART regimen specific prevalence and severity of cardiac abnormalities (specifically, cardiac systolic function, diastolic function, valvular function and pericardial effusion) in comparison to HIV-uninfected children;
    - To assess the utility of serum biomarkers as surrogate markers of cardiac dysfunction.
- To understand how changes in cardiac function over time relate to ART treatment regimens by therapeutic class.

Hypotheses

Primary Aims:

- The occurrence and severity of cardiac dysfunction among perinatally HIV-infected children and youth will be higher compared to HIV-uninfected children, will vary by type and duration of ART regimen, and will worsen over time. Specifically, left ventricular (LV) fractional shortening and ejection fraction will be decreased and LV mass and wall thickness will be increased by HIV infection and age and will vary by type and duration of prenatal and childhood ART regimen.

Secondary Aims:

- Serum biomarkers, such as proBNP, will correlate with LV dysfunction as measured by LV ejection fraction and noninvasive measures of LV diastolic function, and serum biomarkers will vary by type and duration of prenatal and childhood ART regimen.
- The occurrence and severity of other cardiac related abnormalities, including diastolic dysfunction, aortic and mitral insufficiency, and pericardial effusion, will be higher among perinatally HIV-infected children and youth, will be increased with age, and will vary by type and duration of prenatal and childhood ART regimen.

3.4 Bone Mineral Density

Specific Aims

- To estimate the differences in BMD of HIV-infected children when compared to HIV-exposed but uninfected children and normal healthy children from a pre-existing research database.
- To identify virologic, immunologic, therapeutic, hormonal, nutritional, and environmental factors associated with abnormal bone mineralization in HIV-infected and HIV-exposed, -uninfected children.

Hypotheses

- BMD of HIV-infected children, after adjusting for growth and pubertal status, will be significantly lower than HIV-exposed, -uninfected children and HIV-unexposed children of the same sex and age.
- For HIV-infected children, significant factors adversely affecting normal BMD will include delayed puberty, advanced HIV disease, and exposure to tenofovir or protease inhibitors. Factors associated with better BMD will include higher BMI, African-American race, and exposure to nevirapine or other NNRTIs.
- Participants with BMD z-score, corrected for bone age, < -1.5 will have evidence of increased bone resorption and decreased bone formation. Levels of calcium and vitamin D will not be related to a lower BMD.

3.5 Neurologic, Neurodevelopment, Language, Hearing, and Behavioral Function

Specific Aims

- To examine occurrence and patterns of change of the following cognitive and behavioral outcomes among HIV-infected and HIV-exposed but uninfected children:
  - Emotional and behavioral health problems;
  - High risk behaviors including risky sexual behavior, licit drug abuse, illicit drug use, and tobacco and alcohol use;
  - Neurodevelopmental impairment including cognitive function, academic achievement, executive function, adaptive functioning, hearing, and language development; and
  - Adherence to antiretroviral therapy among infected participants.
- To examine the association between HIV infection status and the rates and types of behavioral outcomes specified above (except non-adherence) by comparing perinatally HIV-infected youth to HIV-exposed but uninfected youth from similar backgrounds.
- To examine rates of non-adherence to ART and the predictors of non-adherence among HIV-infected participants, including youth factors (e.g., age, sex, mental health, sexual risk behavior, substance use, and neurodevelopment), caregiver factors (e.g., mental health, substance use, education, and cognitive function), and other sociodemographic factors.
- To examine the association between family and psychosocial factors (e.g., caregiver cognitive function, caregiver health, caregiver substance use and mental health, stressful life events, and caregiver-child relationships) and emotional and behavioral problems in the child.

Hypotheses

- Behavioral outcomes among HIV-exposed but uninfected children are better than those of children with perinatal HIV infection.
- There will be high rates of health risk behaviors among perinatally HIV-infected youth that increase with age and that are associated with each other (e.g., sexual and drug risk behaviors and non-adherence to treatment).
- Family and psychosocial factors (e.g., caregiver cognitive function, caregiver health, caregiver substance use and mental health, stressful life events, and caregiver-child relationships) and child factors (e.g., cognitive status, behavioral problems, and age) are associated with adherence.

3.6 Adolescent Gynecology and STI Infections

Specific Aims

- In perinatally HIV-infected and HIV-exposed but uninfected participants, to evaluate the incidence of and risk factors for acquiring STIs/vaginal infections (C. trachomatis, N. gonorrohea, T. vaginalis, syphilis, HPV, and HSV) for males and females, and in addition bacterial vaginosis for females.
- To estimate the rate of regression of LSIL.
- To determine the incidence, predictors, and outcomes of pregnancy.

Hypotheses

Adolescents will be at particularly high risk for acquiring STIs/vaginal infections specifically C. trachomatis, T. vaginalis, bacterial vaginosis and HPV.

- The risk of developing HPV-associated LSIL and HSIL is higher in HIV-infected youth than that reported for HIV-uninfected youth. Risk factors for LSIL and HSIL will include low $CD4^+$ T-cell counts, smoking, substance use, and oral contraceptive use.
- LSIL is less likely to regress among perinatally HIV-infected youth than among HIV-uninfected youth. Risk factors for HPV persistence will include smoking, immunosuppression, and oral contraceptive use. Infection at multiple sites reflects global immune failure at mucosal sites reflected by a lower rate or regression.

4.0 SELECTION AND ENROLLMENT OF STUDY POPULATION

4.1 Eligibility Criteria and Target Enrollment

4.1.1 HIV-Infected Cohort

Inclusion criteria

- Perinatal HIV infection as documented in the medical record.

- Age 7 years (7th birthday) up to but not including the 16th birthday at enrollment.
- Engaged in care and ART history is available.
- Either: Previous or current enrollment in any of the studies included on the list of approved studies allowing for enrollment into AMP. Children participating in other studies may be enrolled with approval of the Protocol Team. Additional approved protocols will be listed on the PHACS website.

  Or: Available medical record documentation since birth of:

  - ART exposure history
  - Opportunistic Infection (OI) prophylaxis exposure history
  - Viral load and CD4 count history
  - Major medical events history
- Willingness to participate and provide parental/legal guardian permission with assent. Children who do not know their HIV infection status will not be excluded.

Exclusion criteria

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

Target enrollment

- N = up to 600. (Enrollment closed at N=451)

4.1.2 HIV-Uninfected, HIV-Exposed Control Cohort

Inclusion criteria

- HIV-uninfected and born to an HIV-infected mother as documented in the medical record.
- Age 7 years (7th birthday) up to but not including the 16th birthday at enrollment.
- Previous or current enrollment in any of the studies included on the list of approved studies allowing for enrollment into AMP. Children participating in other studies may be enrolled with approval of the Protocol Team. Additional approved protocols will be listed on the PHACS website.

  Or: Available medical record documentation since birth of:

  - ART exposure history
  - Major medical events history
- Willingness to participate and provide parental/legal guardian permission with assent.
- Co-enrollment in the PHACS SMARTT protocol is allowed.

Target enrollment

- N = up to 200. (Enrollment closed at N=227)

4.1.3 Mothers

Inclusion criteria

- Biologic mother of child enrolled in this study.
- Willingness to participate and provide written informed consent.

Exclusion criteria

- Prisoner status.

Target number participating

- N = up to but not to exceed 800.

4.1.4 Primary Caregivers Other than Mother

Inclusion criteria

- Primary caregiver of child enrolled in this study.
- Willingness to participate and provide written informed consent.

4.1.5 Participants in MDC

Inclusion criteria

- **Enrolled in the main AMP study**
- **Willingness to participate and provide written informed consent or parental/legal guardian permission with assent**

Exclusion criteria

- **Known mitochondrial abnormalities, Type I diabetes, or liver dysfunction (alanine aminotransferase (ALT) > 3 times the upper limit of normal)**
- **Other conditions known to affect mitochondrial function or serum lactate levels, e.g., acute infection, malignancy, and ischemic condition**

Exclusion criteria

- Prisoner status.

Target number participating

- N = up to 800 or more. Since a child may, over time, have more than one caregiver, the number of caregivers may exceed the number of children.

Enrollment of mothers/primary caregivers of enrolled children will continue for mothers/ primary caregivers not formerly enrolled who opt to enroll later in the study and in cases where there is a change in the primary caregiver.

4.2 Study Registration Procedures

The AMP protocol is one of two multicenter studies supported through the National Institutes of Health (NIH)-sponsored PHACS. Prior to implementation of AMP, sites in the PHACS network must have the protocol approved by their local institutional review board (IRB) and must register with the Data and Operations Center (DOC) for the AMP Study at Harvard School of Public Health. Confirmation of site registration must occur before any participant is enrolled. Original approval documents must be maintained at the site. The procedures for registration are outlined in the PHACS Manual of Operations.

4.3 Participant Recruitment and Enrollment Procedures

Clinical staff members such as case managers and/or healthcare providers at clinical sites will be made aware of the eligibility criteria of the AMP study. Potential participants will be identified and referred to the clinical research team for potential enrollment. A research staff member will contact the potential participants and provide an overview of the study to see if they are interested in participating. The majority of the potential participants will have already interacted with the research staff through their clinic visits. If a patient is new to the clinic and appears to be eligible, the case manager/social worker or healthcare provider will make the initial introduction of the patient to the research staff member. Clinical research teams will be encouraged to contact current and former participants from the list of approved co-enrollable studies for their interest in participating in the AMP study.

Once it is determined that a participant may qualify for the protocol, written parental/legal guardian permission will be obtained before any study-related medical abstraction or evaluation is performed. When older children are considered able to understand participation in the study, assent will be obtained with written parental/legal guardian permission. Written informed consent will also be obtained from the mother or primary caregiver for their personal participation. Please note that it is not a requirement that the mother and/or primary caregiver be enrolled in order for the child to participate.

Prior to study enrollment, participants will receive an assigned patient identification number (PID) from the list provided to the site. When a participant qualifies for the study, 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 patient and eligibility information. The SES will then generate a study identification number (SID) specific to the AMP study for participants who are confirmed eligible.

Enrollment **into the main AMP study** closed in 2009 with 451 HIV-infected participants and 227 HIV-exposed but uninfected participants enrolled. **The MDC will be open to enrollment for those participants already enrolled in the main AMP study.**

Site research teams will be informed about the MDC and the specific eligibility criteria. They will approach AMP participants who fit the eligibility criteria and provide an

overview to see if they are interested in participating. Written informed consent or parental/legal guardian permission with assent for participation in the MDC will be obtained prior to collection of specimens for the MDC assessments.

4.4 Co-enrollment Guidelines

Enrollment of AMP participants into other studies (with or without similar goals/ data collection as AMP) where no data sharing will occur is at the discretion of the local principal investigator. However, s/he must take into account any issues (such as blood volume and study burden) that enrollment in the additional study may require and which may compromise the site's ability to fulfill the requirements of PHACS.

Participants may co-enroll in both the PHACS AMP and PHACS SMARTT protocols. When such co-enrollment occurs, the patient ID number (PID) will remain the same for both protocols, but a separate SID will be assigned for each protocol. Sites are requested to notify both protocol teams when a child is co-enrolled in AMP and SMARTT.

5.0 CLINICAL AND LABORATORY EVALUATIONS

5.1 Study Schedules

All participants will have study visits at entry, at six months, 1 year, 2 years, 2.5 years, and 3 years on study and then once a year thereafter **until participants reach 18 years of age**. Details of evaluations can be found in the schedules of evaluations in Appendices I – VII.

Study visits were every 6 months in versions 1.0 through 3.0 of the protocol.

5.2 Abnormal Values as Triggers for Further Evaluation

This study has predefined clinical and laboratory abnormalities that automatically lead to further evaluation (See Appendix V). Parents or legal guardians will be asked during the original consent process for permission to progress to a more in-depth evaluation when a designated abnormality is identified ("triggered") if the more in-depth evaluation involves similar procedures without additional risk – which includes all of the evaluations in this section. Examples of triggered tests that do not require additional consent include medical subspecialty evaluations, additional neurodevelopmental testing or additional laboratory studies that require modest amounts of additional blood or studies using stored blood specimens. Parental/legal guardian permission will be obtained for additional in-depth evaluations that introduce greater risk or are of a different nature (none currently specified in the protocol).

5.2.1 Growth and Sexual Maturation Triggers

Delayed onset of puberty

In children (infected participants and uninfected control cohort) showing delayed onset of puberty by Tanner staging (defined as Tanner stage 1 at or beyond the 12th birthday for girls and at or beyond the 13th birthday for boys), biochemical assessment of hypothalamic-pituitary-gonadal function will be performed by obtaining serum in the morning for measurements of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and testosterone for both males and females. Specimens are sent to the repository for later testing.

Delayed growth

In children (infected participants and uninfected control cohort) who have EITHER:

(1) an absolute height z-score of less than -1.88 SD (< 3rd percentile) based on the CDC/NCHS 2000 growth reference, unless mid-parental height z-score is available and is less than -1.65 SD OR

(2) a decrease in height growth z-score of more than 1.3 SD over 6 months **or more** (approximately corresponding to weight or height growth downwardly crossing two or more lines on the growth chart),

the following laboratory studies should be obtained during the study visit (fasting is not required):

1) IGF-I;
2) IGFBP-3; and
3) Growth hormone binding protein (GHBP).

However, for children meeting the first criteria above, laboratory testing will not be required and this trigger will not be considered to be met if it can be demonstrated that the mid-parental height z-score is < -1.65 SD (i.e., short stature of child is related to parents' short stature).

Note that GHBP is derived from the extracellular binding domain of the GH receptor, which is shed from cell surfaces into the bloodstream; GHBP levels correlate with the number of GH receptors.[88] The samples for IGF-I, IGFBP-3, and GHBP will be shipped by the site directly to Esoterix for testing in real time.

If IGF-I is low for age and gender, refer the participant to the local pediatric endocrinologist (see below). If IGF-I is normal for age and gender, re-evaluate growth at the next scheduled study visit. If the interval growth shows a positive change in height z-score, continue to evaluate changes per protocol; if height z-score is unchanged or worse, refer to the endocrinologist (see below).

If participant is referred to a pediatric endocrinologist for further evaluation, and the endocrinology evaluation supports the need for a growth hormone (GH) stimulation test, the preferred GH secretogogue for this protocol is glucagon as described in Section 7.1.6. Glucagon is preferred as its administration also allows assessment of the integrity of the hypothalamic-pituitary-adrenal axis.[93] However, another common stimulus (e.g., clonidine, carbi-dopa, arginine, or insulin) can be used alone or in combination at the discretion of the endocrinologist.

5.2.2 Metabolic Risk Factors for Cardiovascular Disease Triggers

Abnormal glucose metabolism

Fasting plasma glucose and serum insulin levels will be determined annually in all infected and uninfected participants using a central reference laboratory. For infected children, if the calculated homeostatic model assessment insulin resistance (HOMA-IR = (fasting insulin in mcU/mL x fasting glucose in mmol/L)/22.5) is greater than 2.5 in children (Tanner stage 1), or greater than 4.0 in adolescents (Tanner stage greater than or equal to 2), then a 2-hour oral glucose tolerance test (OGTT) and an HbA1c will be obtained.[87] (See 7.1.6). There is no triggered assessment for uninfected participants.

Dyslipidemia

In children (infected participants only, not uninfected control cohort) with dyslipidemia, as defined by any of the abnormalities in fasting serum lipids noted in the table below (modified from the National Cholesterol Education Program (NCEP) criteria[88]) fasting serum and plasma will be banked for future measurement of endothelial dysfunction (I, E, P-selectins; V, I-CAM-1; endothelin-1 (ET-1), highly sensitive c-reactive protein (hs-CRP), homocysteine, apolipoprotein B, lipoprotein (a), vWF antigen) in order to evaluate the relation of body composition, metabolic outcomes, anti-retroviral therapy, and HIV disease status to changes in endothelial function.

Category	Trigger
Total cholesterol	>200 mg/dL
LDL cholesterol	>130 mg/dL
Triglycerides	
0-9 years	>110 mg/dL
10-19 years	>150 mg/dL
HDL cholesterol	<35 mg/dL

5.2.3 Bone Mineral Density Triggers

In children (infected participants and the uninfected control cohort) with abnormal BMD (defined as a z-score of < -1.5, adjusted for bone age) the following evaluations will be performed in the local lab: TSH, calcium, 25-hydroxy-vitamin D, bone-specific alkaline phosphatase (isoenzyme) (as a marker of bone formation), and parathyroid hormone (PTH). In addition, plasma and serum will be obtained and stored in the repository for subsequent

testing for pro-inflammatory cytokines (IL-1, IL-6, and TNF-alpha). Serum will be sent to the repository for measurement of N-terminal telopeptide of type I collagen (as a marker of bone resorption).

5.2.4 Cardiology Triggers

There will be no additional AMP protocol studies triggered by study echocardiograms or biomarker assessments.

6.0 DATA AND SPECIMEN COLLECTION AND SITE MONITORING

6.1 Records to Be Kept

Case report forms (CRF) 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 SID numbers assigned by AMP.

6.2 Data Collection

Instructions on recording study data on the CRFs and the entry of data into the computerized database will be provided by the DMC.

6.3 Clinical Site Monitoring and Record Availability

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

The site investigator will make study documents (e.g., consent forms and CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the NIH, the Office of Human Research Protection (OHRP), and the site monitors acting on behalf of the National Institute of Child Health and Development (NICHD) to confirm the study data and regulatory compliance.

6.4 Temporary Specimen Storage

Laboratory evaluations specified in the AMP protocol will be performed in real time unless specified otherwise. Some specimens will be held locally and subsequently shipped in batches to the PHACS Repository for temporary storage prior to testing in a central lab. Examples include the annual fasting glucose and insulin and the cardiac biomarkers. In addition, some specimens are shipped directly to a specific laboratory for central testing. These specimens will be catalogued using the Laboratory Data Management System (LDMS).

6.5 Repository Storage

AMP will also store repository specimens for future studies that are currently undetermined. This storage will be at an agency institutionally distinct from the PHACS sites and will be governed by the PHACS Repository Policy (See Appendix VIII). Parental/legal guardian permission will be obtained separately for this storage.

7.0 PARTICIPANT AND STUDY MANAGEMENT

7.1 Participant Management

The study entry procedures are described in Section 4.3. Informed consent procedures are described in Section 11.0. Other participant management issues are discussed below.

7.1.1 Recruitment

It is expected that a majority of participants will be former or current participants in any of the studies included on the list of approved studies allowing enrollment into AMP. If a site proposes enrolling a participant from another longitudinal cohort study, it must obtain approval from the Protocol Team. The major criterion for approval is the completeness of documentation of ART exposure history. Sites are encouraged to re-contact and attempt to enroll former participants who may have participated in any of these studies.

Enrollment will remain open until the required number of participants is enrolled or until enrollment is closed by the Protocol Team and PHACS Executive Committee (EC) in order to allow adequate duration of follow-up of participants. The age distribution of the two study cohorts will be monitored by the Protocol Team to ensure that they are balanced. It may be necessary to close enrollment of certain age groups in order to ensure a comparable age distribution in the two cohorts.

Enrollment closed in 2009 with 451 HIV-infected participants and 227 HIV-exposed but uninfected participants enrolled.

7.1.2 Retention

Participant retention will be a challenge and is considered a high priority. Retention and participation in study visits will be monitored carefully. The target retention rate, excluding unavoidable causes of loss (e.g., move out of the area and death), for infected and uninfected participants will be 96% and 94% per year, respectively. These targets will be periodically re-evaluated based on ongoing experience. For those participants who move out of the area to a location that has an AMP site, the originating site personnel will make every effort to encourage transfer of the participant to a PHACS site at the new location.

Retention at 1 and 2 years on study are 94% and 91%, respectively, for the infected cohort and 98% and 92%, respectively, for the uninfected cohort.

7.1.3 Discontinuing Study Participation

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

- The participant or parent/legal guardian withdraws permission;
- The participant or parent/legal guardian fails to comply with the study requirements so as to cause harm to the participant or seriously interfere with the validity of the study results and the site investigator believes that compliance is unlikely to improve;
- The site investigator determines that further participation would be detrimental to the participant's health or well-being;
- If an uninfected participant becomes HIV infected, the participant will be discontinued from the study and referred for care and counseling;
- The study is stopped by a governmental agency, including the NIH or Department of Health and Human Services; or
- The clinical site is terminated for significant participant safety concerns, study integrity, poor performance issues, or lack of funding.

7.1.4 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 AMP. Permission to obtain outside records will be obtained from the parent/legal guardian. If a child 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.

7.1.5 Test- and Evaluation-specific Management Medical, ART, and Social History

Start and stop dates for all antiretroviral therapy will be recorded. Use of other medications will also be captured except for short courses of over-the-counter medications (less than 2 weeks duration). Results of any HIV resistance testing performed (genotype or phenotype testing) will be recorded if available. Diet and physical activity will be obtained using the Block Dietary Questionnaire and the Physical Activity Screener for children and adolescents from Block Dietary Data Systems.

Blood Pressure

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

Neurodevelopment and Neurobehavioral Testing

Some testing will require a trained psychologist to administer. Other tests may be administered by a trained non-psychologist (Non-P) operating under the direction of the psychologist. The specifications for each test are shown in Appendix VI. Training will be conducted for the psychologist and a protocol will be developed for monitoring performance. The psychologist will be responsible for training and performance of the non-psychologist, if used. For some measures, the psychologist must review the results before the child leaves (e.g., BASC-II Parent Rating Scale, BRIEF-Parent Rating Scale, and ABAS-II) if they are administered by a Non-P. Testing will be done, whenever possible, prior to blood drawing. However, ND testing can be deferred until the blood draw is obtained as long as the child is comfortable when testing begins, has recovered from blood work, and has had breakfast/snack after fasting. If child is not fasting, ND evaluations should be scheduled and done prior to blood draw if possible. The psychologist should reschedule testing if any child is ill or appears to be tiring prior to or during the evaluation.

Neurodevelopmental and behavioral measures can only be administered to English-speaking or Spanish-speaking children and caregivers; they are not available in other languages. Further, not all measures are available as a Spanish translation. Thus, for monolingual Spanish-speaking participants, some of the cognitive and language tests will not be administered. If the participant is competent in English, the measures should be administered in English.

Translators may not be used to administer any standardized tests; on site translation of measures can lead to invalid and unreliable results. Furthermore, the psychologist/examiner who administers the Spanish version of a measure must be fluent in Spanish. If the examiner is not fluent in Spanish, they may not use a Spanish-speaking translator to administer the measure. However, Spanish-speaking staff, such as a Spanish-speaking research assistant or study nurse, can administer specific questionnaires or interviews that do not require administration by the psychologist.

The following tests/questionnaires/interviews are available in Spanish and must be administered by a Spanish-speaking psychologist:

WISC-IV
CELF-IV
BASC-II-Child/Adolescent Self-Report
Children's Color Trails Test (Spanish language administration directions are available)
CDQ
Trail Making

While the Spanish translation of the WAIS-IV is not approved for use in AMP, the EIWA-III can be used under the conditions outlined below:

WAIS-IV - administer the EIWA-III in place of the WAIS-IV ONLY to participants ≥ 17 and < 18 years of age who are primarily Spanish speaking and whose parental/

family heritage is Puerto Rican; for all other Spanish-speaking participants, do not administer the WAIS-IV subtests.

The following tests/questionnaires can be administered by a Spanish-speaking trained non-psychologist under the supervision of the site psychologist (the psychologist must review the results before the child leaves if they are administered by a Non-P):

ABAS-II
BASC-II-Parent Rating Scale
BRIEF-Parent Rating Scale

The following tests which require administration by a psychologist are not available in Spanish and should not be administered to monolingual Spanish-speaking participants. **If Spanish language versions become available in the future, PHACS will begin to use the Spanish versions of these assessments as well.**

(For WAIS-IV, see note above regarding use of EIWA-III)
WASI
WIAT-II
BRIEF-Child/Adolescent Self-Report
Woodcock Reading Mastery Test

The following questionnaires and interviews have been translated into Spanish and must be administered by a Spanish-speaking psychologist or trained non-psychologist:

Life Events Checklist
Monitoring the Future
Quality of Life
ACASI
Adherence (cannot be administered by any staff involved in the medical care of the child)
PCRI

The following questionnaires have been translated into Spanish and can be administered by a Spanish-speaking trained non-psychologist and do not require ongoing supervision by a psychologist:

Caregiver Health
Demographics
Substance Use During Pregnancy

<u>Cardiac Function</u>

Transthoracic echocardiograms will be performed including 2-D, Doppler, color Doppler, M-mode, and tissue Doppler imaging. Sedation will not be used unless required for a clinically-indicated study as described below. The technical details of performing the study and transmitting the data to the core lab are presented in more detail in the manual of procedures.

The core lab analysis of echocardiograms without a clinical interpretation will be returned to the site once completed, but may be delayed for several months. If the sites require a rapid interpretation, they should have one done locally. If a clinically indicated echocardiogram is performed within the window for the protocol-specified echocardiogram, the clinical echocardiogram can be used as the study echocardiogram as long as it is performed according to the specifications of the study echocardiogram.

Audiological Evaluation – Infected and Uninfected Participants

All children will have a single full audiological evaluation performed. The full audiological evaluation will be conducted by an audiologist. The assessment will include tympanometry, pure-tone, air conduction threshold determination at 250, 500, 1000, 2000, 4000, and 8000 Hz, and bone-conduction threshold testing if needed based on the air-conduction thresholds.

Blood Test (See Appendices III & IV)

Some of the required tests may be performed as part of routine clinical care of the child. These routine laboratory tests will be performed in the local clinical laboratory (CAP or similarly approved). Tests that are not part of routine care or are not clinically indicated and are specified in the AMP protocol will be done as part of the study. The anticoagulant for specific tests is critically important. For tests performed in the local laboratory, please follow the specifications of the local lab. For tests performed at Esoterix, please follow the specifications provided by Esoterix, which can be found on the PHACS website.

For repository specimens, see below and Appendix III for specimen collection specifications.

Fasting

Fasting is required for some specimens. The duration of fasting is 8 hours. Water and medications are allowed during fasting.

Specimens to be sent to the PHACS Repository for Temporary Storage/Future Testing

Site personnel will be responsible for ensuring that the specimens for the PHACS Repository are appropriately processed for storage. In the case of serum specimens, the serum must be separated within 24 hours of the draw unless otherwise specified, aliquoted as per protocol, labeled using the LDMS system, and frozen at -70° C. Blood for cell pellets (PBMCs) should be collected in **either CPT or EDTA** tubes and may be held at room temperature for up to 2 hours prior to processing. **If** the blood **is** collected in an EDTA tube (lavender top) and the PBMCs separated on Ficoll-Hypaque, **plasma should be saved** (see ACTG Lab Manual, Chapter 12, section 6.1). The cells should be frozen as dried PBMC pellets (LDMS specimen code = BLD/PEL; see ACTG Lab Manual, Chapter 12, section 6.2). **For participants enrolled in MDC, two 8-ml CPT or EDTA tubes for viable PBMCs and 3 buccal cell brushes for buccal cells will be collected and processed (refer to the laboratory processing instructions specific to the MDC).** Shipping will occur on a regularly scheduled basis. See Appendix IV of the protocol for more detailed repository specimen collection specifications. See the AMP Lab Processing Summary chart and the ACTG Lab Manual (Chapter 12) for details on specimen processing.

Tanner Staging and Testicular Volume

Training will be provided with regular updates for Tanner staging and use of the orchidometer for males.

HPV and STI Testing

Screening for STIs include urine screening for C. trachomatis and N. gonorrohea, self-collected or provider-collected vaginal swabs for C. trachomatis, N. gonorrhea, T. vaginalis and bacterial vaginosis, culture/DFA or PCR or serology for HSV, and HIV testing (for the HIV-uninfected cohort). Occurrence of genital warts is usually determined through simple visual screening. Syphilis is screened through a blood test. Cytology for cervical cancer screening requires a pelvic examination. When the occurrence of any of these examinations is ascertained through medical record review (urine, swab, genital visual exam, speculum aided exam, blood), a copy of cervical cytology and/or STI testing results will be obtained. If the participant has an abnormal cytology and is referred to colposcopy, a record of the histology results will also be obtained. It is expected that the diagnoses of atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSIL), or high-grade squamous intraepithelial lesions (HSIL) will be made according to the Bethesda system for cervical cytological diagnosis by the local institution's laboratory accredited by the Colleges of American Pathology. Permission will be obtained for all females at enrollment for future temporary release and central review of cytology and pathology slides obtained during routine pelvic exams and colposcopy if performed.

Type of test (swab, urine, blood) and the result of the test (positive or negative) will be recorded. The results of the clinical examinations will be abstracted for AMP at the entry and Q12 month visits.

Buccal Cells

Buccal cell swabs will be collected annually on those participants enrolled in the MDC. Refer to the laboratory processing instructions specific to the MDC.

7.1.6 Management of Triggered Evaluations

All triggered laboratory studies should be completed within 6 weeks of identification that a trigger has been met. Site staff do not need prior approval from the protocol team to schedule triggered laboratory studies further than 6 weeks from the date of the identification of a trigger. The site should key the required triggered form within 6 weeks of the identification of the trigger indicating when the assessment is expected to be done. Site should complete the assessment as soon as possible; document in study record which assessments were done more than 6 weeks from identification of trigger, including date of completion and reason why assessment was administered late. If a triggered evaluation has not been completed before the next scheduled study visit, it be considered missed. If a triggered evaluation is missed and the same trigger is met at the next or any subsequent study visit, the triggered laboratory studies should be

completed at that time. Once a triggered laboratory evaluation is completed once, it should not be repeated if the same trigger is met at a subsequent visit.

Recommended Protocol for Growth Hormone Stimulation Test with Sex Steroid-Priming

Regardless of the secretagogue chosen by the endocrinologist, sex steroid-priming should be performed for adolescent participants as follows. For boys at or beyond their 11th birthday, administer testosterone enanthate (200 mg/cc) as a single dose of 50 mg (0.25 cc) intramuscularly 1 wk before the test. For girls at or beyond their 10th birthday, estrogen in the form of Premarin® at a dose of 5 (five) mg should be given PO between 6:00 pm and 10:00 pm the night before and a second 5 (five)-mg dose should be given PO between 6:00 am and 10:00 am the morning of the GH stimulation test assuming that the test will be started between 8:00 am and 10:00 am. Note that the morning dose of Premarin® should be given 2-4 hr before the secretagogue is administered in the GH stimulation test.[92]

A glucose determination (point-of-care) should be checked before administering the glucagon and testing should not continue if the glucose is <70 mg/dL. The participant should be NPO for 8 hours prior to and during testing. Blood should be obtained for point-of-care blood glucose (bedside meter), plasma glucose (local laboratory), serum growth hormone (to Esoterix), and serum cortisol (to Esoterix) prior to the glucagon administration (0.1 mg/kg SC, maximum dose 1.0 mg) and at the following times following administration: 90 min; 120 min; 150 min; and 180 min. If IV fluid is used to maintain venous access, it should not contain glucose. Participants should be allowed to eat following the 180-min blood draw. Following testing, participants can be discharged 30 min after eating.

Oral Glucose Tolerance Test

Participants should have a normal diet for three days prior to the test, with a carbohydrate intake of no less than 150 g/day. Participants should not be sick or hospitalized, and they should avoid exercise and emotional stress during the testing. Testing should be performed between 7 AM and noon following an 8-hour overnight fast. Plasma glucose (local lab) and serum insulin levels (to repository) will be obtained at baseline and at 2 hours after ingestion of 1.75 g/kg (maximum 75 g) of an oral glucose solution (not a mix of mono- and disaccharides). Abnormalities of glucose tolerance include either an impaired fasting plasma glucose concentration between 111-125 mg/dL or impaired glucose tolerance, defined as a 2-hr post-glucose load plasma glucose between 141-200 mg/dL. Participants will also have HbA1c levels determined (local lab).

Table 7.1 American Diabetes Association criteria for the diagnosis of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes mellitus

	IFG	**IGT**	**Diabetes**
FPG*	≥ 110 to 125		≥ 126
2-hr PG*		≥ 140 and < 200	≥ 200

*FPG = fasting plasma glucose; 2-hr PG = 2-hr plasma glucose concentration during a standard OGTT [1.75 g/kg (maximum 75 g) of an oral glucose solution].

7.2 Study Management

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

7.2.1 Protocol Query Management

For the integrity of the study and the welfare of the participants, it is important for the site staff to have ready access to the Protocol Team. A team logon has been established to receive study-related queries or reports. It is expected that queries will be responded to within 2 working days of receipt by the Protocol Team. The categories of queries and the appropriate team member for responding are as follows:

- Protocol violations or adverse participant, staff, or community experiences related to the protocol (see Section 9.0): these should be reported to the Protocol Team and to the NICHD program scientist via the team logon, and to the local IRB as stipulated in their guidance.
- Study management issues requiring clarification: these should be reported via the team logon and managed by the protocol specialist.
- Participant management issues that fall outside the protocol parameters: these should be reported via the team logon and managed by the Protocol Team.

7.2.2 Data Management

Instructions concerning the recording of study data on CRFs will be provided by the PHACS DMC. Each site is responsible for keying the data in a timely fashion according to standards set by the PHACS Network. The CRF 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 Laboratory Data Management System (LDMS) will be used to manage and track specimens collected in the PHACS Network.

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

7.2.3 Collaboration with Outside Studies

It will be useful for the AMP 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 EC and a memorandum of understanding (MOU) about the extent and nature of the sharing as well as a data use agreement will be executed for all collaborations.

The MOU will include an understanding of the control of the use of the data, publication rights, and authorship rights as well as address the human participant's confidentiality issues.

For participants co-enrolled in the PHACS SMARTT Study or the CDC LEGACY study, permission from the parent/legal guardian will be obtained in order to share data between the two studies so as to decrease burden on the study participants.

8.0 DRUG-ASSOCIATED ADVERSE EVENT REPORTING

Children enrolled in AMP may develop common pediatric conditions requiring treatment during the course of the study period. PHACS AMP 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. AMP is not a treatment study and will not monitor such adverse events. However, site investigators will be encouraged to use the FDA's MedWatch system to report any possible drug-associated events.

9.0 STUDY IMPACT AND SAFETY MONITORING

Participant-level or community-level untoward events will be monitored by the study team, NIH program officials, and local IRB panels. Monitoring will consider the impact of the study on the welfare of three groups of people:

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

Reporting of participant or staff-level negative study impact events to the team and program officials will result in the reexamination 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-level 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.

9.1 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-level events will not be graded but will be addressed as they occur.

9.2 Reporting Requirements

All moderate and major impact events involving study participants or staff are to be reported to the team through the query system 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 or uncovered during interview or sessions (e.g., current suicidal or homicidal ideation, physical or sexual abuse, depression, and inadvertent disclosure of HIV diagnosis); and
- 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.

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

- Inadequate preparation for management of research-related events; and
- 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.

Examples of events for the community include:

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

9.3 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).

10.0 ANALYTIC CONSIDERATIONS

The AMP study design includes an infected group of 451 participants and a control cohort of 227 perinatally-exposed participants. The control cohort is expected to consist mostly of children exposed to antiretrovirals *in utero*, but children unexposed to antiretrovirals will not be excluded, just as they are not excluded from the infected group. Ideally, the control cohort will come from the same population as the infected group for comparability on many non-HIV measures that also influence outcomes of interest. Prenatal ART exposures in both groups will exhibit a time-confounding effect because of changes in clinical practice which cannot be controlled.

Evaluation of several stated AMP hypotheses will involve comparison of the distributions of outcomes between the perinatally HIV-infected children and the HIV-exposed but uninfected comparison children. These comparisons will allow us to assess whether the outcomes are different between HIV-infected and ART-exposed children overall versus uninfected and postnatally ART-unexposed children. For some hypotheses, for example growth, neurocognitive measures, and HPV prevalence, the control cohort will provide a control cohort from a similar socioeconomic background and home environment. However, a limitation of our study design is that we will have little ability to separate out the effects of HIV infection from post-natal ART exposure. It should be noted that many of our primary hypotheses for evaluating the impact of ART regimens on outcomes in AMP will be evaluated by comparing assessments across subgroups of the HIV-infected children; these analyses will not include the control cohort.

Since all participants enrolled in AMP are expected to have previous data collected from WITS, PACTG 219C, or a comparable cohort providing detailed ART exposure information, most analyses described below will use the existing historical data from these studies in evaluating the hypotheses of this study. These data will be merged for the WITS or PACTG 219C participants who enroll into PHACS from the corresponding study databases. In addition to information on post-natal ART history, we will utilize existing information from WITS, PACTG 219C, or other approved studies on *in utero* ART exposure, growth and puberty assessments, prior neurocognitive measures, health status (CD4%, viral load), and caregiver history, along with other important covariates described below in the analysis plans or in the hypotheses.

10.1 Power and Sample Size Consideration

In the context of this study, we will be measuring many targeted outcomes, some continuous (e.g., BMD, BMI, and height and weight z-scores) and some binary (puberty onset, insulin resistance, and neurodevelopmental impairment). For relatively rare events, the calculations for binary outcomes can serve as good approximations for survival outcomes, and for more common outcomes they often serve as an upper bound (i.e., a survival analysis would have greater power than comparison of proportions of events at a fixed time). All of the following calculations were conducted using PASS 2002[89] with the exception of specified simulation studies.

10.1.1 Comparisons between Perinatally-Infected and Uninfected (comparison) Children

For continuous outcomes, the enrolled sample size of 451 perinatally-infected versus 227 uninfected participants provides 80% power to detect a difference in means of 0.228 standard deviations based on a 2-sample t-test (assuming normality holds), and 0.234 based on a non-parametric Wilcoxon ranksum test at alpha = 0.05. For example, if we were comparing the full-scale IQ scores of HIV infected vs. uninfected participants and assumed a standard deviation of 15 points, we could detect a difference of 3.5 points or more in the mean IQs. If we allow for possible loss to follow-up and/or incomplete/missing assessments of 4% per year for infected and 6% per year for uninfected participants for three years after enrollment was completed, then an adjusted sample size of 400 HIV infected vs. 188 uninfected participants provides 80% power to detect a difference of 0.254 standard deviations, or 3.8 points in mean IQ scores. Once we adjust for potential confounders, we will typically lose some power so the minimum detectable difference will usually increase.

For binary outcomes, the table below shows the minimum difference we can detect in proportions in terms of the Odds Ratio (OR) based on comparing HIV infected vs. uninfected, at 80% power with a 0.05 significance level. For this type of outcome, the detectable differences depend on the underlying rate of the event in the control cohort. For simplicity here, it is assumed that event rate increases in the HIV-infected group.

Table 10.1 Minimum detectable ORs between HIV-infected and uninfected children at 80% power and a 0.05 significance level for various event rates in the control cohort

Sample Size for HIV+	Sample Size for Uninfected Control cohort	Event rate in Control cohort	Minimum Detectable OR	Detectable Rate in HIV+ Group
451	227	4%	2.65	10.0%
		5%	2.45	11.4%
		10%	1.99	18.1%
		20%	1.72	30.1%
		30%	1.63	41.2%
400	188	4%	2.84	10.6%
		5%	2.61	12.1%
		10%	2.10	18.9%
		20%	1.80	31.0%
		30%	1.70	42.2%

10.1.2 Comparisons within HIV-Infected Children

For the second type of comparison, we are looking at subgroups of just the HIV-infected participants. We can consider breaking the population into 2 groups, 3 groups, or 4 groups based on ART or other exposure. The table below summarizes the detectable differences in means relative to the standard deviation that can be detected assuming 451 HIV-infected participants or

400 participants (under an assumption of 4% loss per year) when only 2 subgroups of the HIV-infected participants are being compared.

Table 10.2 Detectable differences in means (relative to SD) between subgroups of HIV-infected participants

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 = 451	N = 400
50%	50%	0.27	0.29
40%	60%	0.28	0.29
30%	70%	0.30	0.31
20%	80%	0.34	0.36
10%	90%	0.46	0.48

N = number of HIV-positive participants with assessments

Last of all, to consider differences between proportions of participants with events confining our interest to the HIV-infected participants, we may collapse our exposure groups into two categories, e.g., HAART with PI vs. HAART without PI, or use of a specific ARV drug vs. unexposed to that drug. The following table provides the minimum detectable differences in terms of ORs.

Table 10.3 Detectable differences in ORs based on logistic regression models comparing two subgroups of HIV-infected participants with N = 451 participants or N = 400

Percent in Each group		**Event Rate in Group 2**	**OR for Given Sample Size**	
Group 1	Group 2		N = 451	N = 400
50%	50%	4%	2.94	3.11
		5%	2.70	2.84
		10%	2.15	2.25
		20%	1.84	1.91
		40%	1.71	1.77
40%	60%	4%	2.95	3.11
		5%	2.70	2.85
		10%	2.17	2.26
		20%	1.86	1.92
		40%	1.73	1.79
30%	70%	4%	3.07	3.24
		5%	2.81	2.96
		10%	2.25	2.35
		20%	1.92	2.00
		40%	1.80	1.87
20%	80%	4%	3.39	3.60

Percent in Each group		Event Rate in Group 2	OR for Given Sample Size	
		5%	3.10	3.28
		10%	2.46	2.58
		20%	2.08	2.17
		40%	1.96	2.05
10%	90%	4%	4.37	4.66
		5%	3.96	4.22
		10%	3.07	3.25
		20%	2.56	2.70
		40%	2.50	2.66

10.1.3 Sample Size Considerations for Evaluating Cardiac Function and Structure

To evaluate the power of detecting differences between HIV-infected and uninfected participants in AMP, we assume that we will obtain echocardiograms on between 405-542 participants (approximately 60-80% of the total of 678 enrolled participants). With these sample sizes, we will be able to detect an overall difference between mean z-scores for HIV-infected and uninfected children at 80% power of 0.26-0.30 standard deviations, as shown in the table below. All of these detectable effects are of small to moderate magnitude. In addition, in conducting a one-sample t-test of whether the mean z-score for each echocardiogram parameter is different from 0 (a comparison to the control group assembled at the central echocardiogram reading center), we will have 80% power to detect a difference in mean echocardiogram z-score of 0.12-0.14.

Table 10.4 Detectable differences in mean echocardiogram Z-scores between HIV-infected participants versus HIV-uninfected participants

Percent with Echocardiograms Conducted and Evaluable	Comparison Between HIV-infected and HIV-uninfected Participants in AMP		Detectable Differences in Mean Echocardiogram Z-scores
	Number HIV+	Number HIV-	
60%	270	135	0.30
70%	316	158	0.27
80%	361	181	0.26

Finally, to evaluate the effect of ARV treatment and HIV disease severity measures on echocardiogram z-scores within the HIV-infected participants, the detectable differences in mean z-scores will depend on the percentage of participants with echocardiograms who are considered "exposed". For example, if 70% of the HIV+ participants are on a PI-based regimen, as compared to 30% without a PI, then we will have 80% power to detect a mean difference in echo z-scores of 0.37 for N=270 echocardiograms and 0.32 for N=360 echocardiograms. Other detectable differences are summarized in Table 10.5 below, assuming a total number of 270 or 361 echocardiograms obtained and evaluable within the HIV+ participants.

Table 10.5 Detectable differences in means echocardiogram Z-scores between subgroups of HIV-infected participants

Sample Size with Echocardiograms	Percent Exposed to ARV drug class or individual drug of interest	Comparison between exposed and unexposed		Detectable Differences in Mean Echocardiogram Z-scores
		Number Exposed	Number Unexposed	
270	50%	135	135	0.341
	40% (or 60%)	108	162	0.348
	30% (or 70%)	81	189	0.372
360	50%	180	180	0.295
	40% (or 60%)	144	216	0.301
	30% (or 70%)	108	252	0.322

10.2 Domain-specific Statistical and Analytic Considerations

10.2.1 Growth and Sexual Maturation

Absolute height, weight, and BMI measurements will be normalized for age and sex by conversion to z-scores using the most recent data set from the National Center for Health Statistics.[90] Relationships between specific ART regimens and selective associations with growth and timing of puberty onset will be investigated. In investigating the association of ART regimens with growth (i.e., height, weight, and BMI z-scores and changes in z-scores), we will first consider each outcome separately in a linear regression model as a function of ART regimen and other potential covariates including parental stature (when available), diet, physical activity, immune status, and socioeconomic status. Secondly, mixed effect models will be used to evaluate the height, weight, and BMI over multiple study visits, to increase power by incorporating repeated measures taken on the same participant, and to account for correlation between such repeated measurements. These types of models also allow modeling of the trajectory of growth within an individual child (i.e., growth curve models) and evaluation of the association of ART with growth trajectories.

In evaluating puberty onset, we have at least two possible indicators. For the males, we will use orchidometers to measure testicular volume. For females, we will collect the age at menarche. These gender-specific outcomes are considered the "gold standard" for defining progression through puberty. In addition, for both males and females, we will have the more standard indicator of puberty onset based on attainment of Tanner stage 2 or higher. We will evaluate the consistency of these two measures of puberty onset, but primarily rely on testicular volume for males and age at menarche for females as indicators of puberty onset. Similarly, for both males and females, progression of puberty will be defined as advancement from Tanner stage 2 to 5, and sexual maturation will be defined as attainment of Tanner stage 5. Relatively straightforward analyses can be conducted by considering each of these outcomes as binary, and we can thus fit a logistic regression model for each of these outcomes to evaluate the differences between ART regimens controlling for other potential confounders. The evaluations for pubertal progression would be restricted to those with puberty onset based on Tanner stage 2.

More sophisticated analyses of the impact of ART on puberty onset may also be conducted which treat puberty onset as an interval censored outcome.[91] In other words, we will not know exactly when puberty onset has occurred, but whether it has occurred or not since the previous visit. There are several approaches which are available for such outcomes, including Turnbull's method,[92] pooled logistic regression, and GEE approaches.[93],[94] The pooled logistic regression approach considers the outcomes as "grouped" survival data. In this sense, we evaluate the proportion of children who start at age "x" without puberty onset and then attain puberty onset by age "x + 1". Both this approach and the GEE approach allow adjustment for changing values of covariates over time such as $CD4^+$ T-cell % and plasma viral load. Other time-varying covariates of interest include the height, weight, and BMI. However, some care must be taken in including measurements such as BMI which may reflect intermediate effects in the pathway between ART exposure and pubertal development. Consistency of results across these three approaches will strengthen any conclusions drawn from the results.

In evaluating the relationship between ART regimens and growth, we may also want to control for the Tanner stage, which is known to be a strong predictor of growth rates. By controlling for sexual maturation in our regression model, we will be able to evaluate whether there is an effect of ART exposure on growth rates after adjustment for sexual maturation. By employing methods for evaluating effects of intermediate events,[95] we can evaluate whether the effects of ART regimens on growth rates is mostly explained by resulting changes in sexual maturation, or whether there are other potential pathways affected by ART exposure.

10.2.2 Metabolic Cardiac Risk Factors

We are interested in estimating the prevalence and incidence of insulin resistance, abnormal glucose tolerance, dyslipidemia, elevated blood pressure, **mitochondrial dysfunction,** and abnormal body composition, as well as evaluating the association of HIV disease status and specific ART regimens with these outcomes.

Insulin resistance, abnormal glucose tolerance, dyslipidemia, and elevated blood pressure as binary outcomes

Insulin resistance, abnormal glucose tolerance, elevated blood pressure, tobacco use, and dyslipidemia (considering each of fasting total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides separately) will be considered as binary variables. Elevated systolic and diastolic blood pressure will be determined using American Academy of Pediatrics standards for age using the 95^{th} percentile cutoffs. Systolic and diastolic blood pressure percentile, lipid levels, and the abnormal body composition measures (waist, upper-mid arm and hip circumferences, and percent body fat from DXA measurements) will be considered as continuous outcomes.

We will estimate the prevalence of each binary metabolic risk factor (insulin resistance, abnormal glucose tolerance, dyslipidemia and elevated blood pressure) at the baseline visit among HIV-infected children and compare them to a subset of HIV-uninfected children. Prevalence will be calculated as the number of children with the specific outcome at baseline, divided by the total number of children who are tested and have a measure for each outcome at

the baseline visit. We will also calculate the 95% confidence intervals for each prevalence estimate.

We will evaluate the association of each metabolic outcome with specific ART regimens (particularly PIs and NRTIs, which have been implicated in various metabolic disorders) 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. Race, gender, age, $CD4^+$ count, viral load and BMI will be included in each model as potential confounders. In addition, Tanner stage and CDC classification have been associated with insulin resistance and will also be included in models for that outcome.

We will estimate the incidence rate of each metabolic risk factor among HIV-infected children. The incidence rate will be calculated by dividing the number with new development of each metabolic risk factor by the total person-time contributed by children initially free of the risk factor at baseline. The 95% confidence limits for these incidence rates will be calculated using the Poisson distribution.

Among children who are HIV infected, we will estimate the association between specific ART regimens and incidence of each metabolic risk factor. The incidence of each outcome (with the possible exception of elevated blood pressure) 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% confidence intervals, adjusting for other risk factors for the outcome. As for the analysis of factors associated with prevalent outcomes, Tanner stage, CDC classification, BMI, age, race and gender will be included in our models as potential confounders. For metabolic risk factors that are observed to occur less frequently, Poisson regression models may be used to compare incidence rates.

Abnormal glucose tolerance as binary outcome

Children and adolescents with insulin resistance (defined as having a HOMA-IR $\geq$ 2.5 in children (Tanner stage =1) and > 4.0 in adolescents (Tanner stage 2 or higher) will undergo oral glucose tolerance testing and have HbA1c levels tested, to detect the presence of abnormal glucose tolerance.

We will estimate the prevalence of glucose intolerance among children who are insulin resistant at baseline. Prevalence will be calculated by dividing the number of cases of prevalent glucose intolerance by the total number of children who were found to be insulin resistant at baseline.

We will estimate the incidence rate of glucose intolerance by dividing the number of new cases of glucose intolerance by the total person-time at risk contributed by children who were initially found to be glucose intolerant. At each study visit, children who are insulin resistant but not yet glucose intolerant will contribute person-time.

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

Systolic and diastolic blood pressure and lipid levels (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) will be considered as continuous outcomes. The abnormal body composition measures (waist, upper-mid arm and hip circumferences, as well as percent body fat from DXA measurements) will be considered only as continuous outcomes. These measures will be normalized for age and sex by conversion to z-scores.

There is evidence that ARTs, particularly PIs and NRTIs (especially stavudine) are associated with lipodystrophy and dyslipidemia. We will first investigate the association of PI-containing and NRTI-containing regimens with each outcome, in models restricted to HIV-infected children, by using linear regression. Covariates that will be included in the blood pressure models will include BMI, race, physical activity, tobacco use, and diet. BMI and race will be included in models for abnormal body composition. To examine the effect of ART regimens with changes in z-scores over time (using z-scores measured over multiple study visits), we will use mixed effects models, which will account for the correlations between these repeated measures. Similarly, linear regression and mixed effects models will be used to compare HIV-infected children to the HIV-exposed but uninfected control cohort on these continuous outcomes (except lipid levels).

10.2.3 Cardiac Function

Design and rationale for evaluating changes in cardiac function over time and between HIV+ children and controls

The two primary purposes of this study are to detect the presence and progression of cardiac abnormalities in children with HIV-infection, and to understand whether these abnormalities relate to their treatment regimens. To accomplish these goals as efficiently as possible within the time constraints of the PHACS study, we propose to perform a single echocardiogram and collect sera to measure biomarkers on 405-542 HIV-infected children in the AMP cohort (between 60-80% of the total cohort). Our primary assessment of this echocardiogram results will thus be cross-sectional, but accounting for age at the time of echocardiogram (from 7 years old to 15 years old). This 8-year time span should be long enough to provide data on the prevalence of cardiac abnormalities as children with HIV infection age and accumulate more years of antiretroviral treatment. Although an original goal of the study was to evaluate progression over time in cardiac parameters, it will be necessary to secure outside funding in order to allow conduct of a second echocardiogram at a future time point for youth in the AMP study. Such additional funding may be limited to assessing those with indications of cardiac dysfunction based on their first echocardiogram, or if possible may address all those with a first echocardiogram to allow assessment of incidence of new cardiac dysfunction as children age.

In addition, we will capture echo and blood biomarker data from 200 HIV-uninfected AMP children (of whom we anticipate 150 will provide the requisite data). By comparing outcome measures between the infected and uninfected cohorts, we will be able to assess the combined effect of ART therapy and HIV disease. Subgroup comparisons within the infected cohort

(divided according to treatment intensity as was done in the CHAART II study) will further allow us to examine the impact of therapeutic regimen classes.

Standardization of Echocardiographic Endpoints

Initially, all echocardiographic endpoints will be converted to standardized z-scores using normative data from a Boston control group. This will adjust for the normally anticipated age and growth-related changes in cardiac size and structure, as well as allow some interpretability as to whether these cardiac measures are abnormally elevated (i.e., z-scores above +2), abnormally depressed (i.e., z-scores below –2) or essentially normal (i.e., z-scores within ± 2). Unfortunately, as we have learned through experience with the CHAART study, the Boston norms cannot serve as the sole point of comparison because the socio-demographics of the HIV-infected mothers in the PHACS study are not comparable to those of the Boston norms, and these factors can have substantial impact on cardiac outcomes, independent of HIV-status and ART therapy.

Comparison of HIV-infected to uninfected children and youth

We will compare the echocardiographic z-scores from the HIV-infected AMP cohort to the z-scores from the HIV-uninfected AMP cohort in order to establish whether the presence of abnormalities can be attributed to the combination of HIV-disease and its treatment. A linear regression model will be used to compare HIV-infected versus uninfected, controlling for age along with possible interactions between age and infection status. The model will also include any maternal or child characteristics which may confound the primary predictors, although since all of the children were HIV-exposed, we would hope for rough comparability on many of the demographic and maternal factors. We will also explore using the P2C2 study and CHAART II as control cohorts.

Occurrence of Cardiac Abnormalities

To evaluate whether children in AMP are more likely to have abnormal cardiac outcomes, we will develop clinically meaningful cutoffs, based on the literature, that define abnormal function for each cardiac outcome (e.g. left ventricular (LV) fractional shortening, ejection fraction, etc.). For each outcome, we will compare the prevalence of abnormal scores in the PHACS cohort with the prevalence in the Children's Hospital database and with the AMP HIV-negative controls using Fisher's exact test. We will also compute the incidence rate of cardiac abnormality, for each outcome, among those without that abnormality at baseline.

ART and Cardiac Function

The last primary analysis will focus again on only the HIV-infected children. For each child, the intensity of their treatment regimen will be classified. We will compare echocardiogram z-scores for the primary targeted measures of cardiac function and structure by type of antiretroviral regimen (HAART with PI, HAART without PI, other ARV, or no ARV) and control for measures of disease severity at the time of the echocardiogram or prior to the initiation of HAART (if available) to control for possible confounding by indication. Specific ARV drugs, alone or in combination and used by at least 10% of the AMP HIV+ participants will be evaluated for association with echocardiogram z-scores. These analyses will help us

determine whether certain therapies are more highly associated with the development of cardio-toxic effects.

Among all AMP participants, levels of serum biomarkers will be collected as a marker of cardiac function and compared to cardiac function as determined using an M-mode echocardiogram. Correlation coefficients will be calculated to assess the association between levels of serum biomarkers and the estimated M-mode echocardiogram z-scores. This will provide a validation of levels of serum biomarkers as a marker of cardiac function. In addition, based on various thresholds for each biomarker, we will evaluate the sensitivity and specificity of the biomarker for detecting cardiac abnormalities. Differences in levels of biomarkers across prenatal and childhood ART regimens will also be evaluated to evaluate consistency with findings based on echocardiograms.

Additional Analyses

We will explore the relationships between the cardiac outcomes in this proposal and other disease endpoints (i.e., immune function; neurodevelomental outcomes; etc.). We will identify predictors for subgroups of children who progress poorly in terms of cardiac measures.

10.2.4 Bone Mineral Density

Reference data from normal children is available in several research databases which provide BMD z-scores with adjustment for age, gender, and other covariates. Using one or more of these extensive datasets, BMD z-scores of HIV-infected children will be evaluated relative to the general U.S. population of normal, healthy children, and the z-scores for HIV-infected children will also be compared to those for the HIV-exposed but uninfected control cohort.

The overall distribution of BMD z-scores for the HIV-infected participants can be examined to serve as a comparison with the normal U.S. population. If the mean z-score is significantly lower than zero, this would suggest that the HIV-infected participants have a lower BMD than the general pediatric population. For example, based on the assumption that the reference U.S. population follows a standard normal distribution, we would expect about 16% of the HIV-infected participants to have a BMD z-score < -1.0, and 6.7% to have a BMD z-score < -1.5. The proportion of participants with BMD z-score < -1.5 will be compared between HIV-infected children and the control cohort (HIV-exposed but uninfected) using a chi-square test.

Since the HIV-exposed but uninfected control cohort is expected to have a more similar socioeconomic background, they are expected to serve as a more appropriate control cohort to the HIV-infected group. Linear regression models will be used with the BMD z-score as the outcome and an indicator of HIV-infection as the main predictor. In addition, to adjust comparisons for individual growth, the potential confounders of height and weight (or of BMI) z-scores will be added to the crude linear regression model as continuous variables. Tanner stage and bone age will also be added as a categorical variable to further adjust for pubertal status. Although it is expected that the z-scores will follow a normal distribution, this assumption of the linear regression model will be verified and regression diagnostics will be used to assess the fit of the model and identify potential outliers.

In order to evaluate virologic, immunologic, therapeutic, hormonal, nutritional, and environmental factors associated with abnormal bone mineralization among HIV-infected children, the study population will be restricted to HIV-infected children. The factors considered as potential predictors of BMD z-scores in this population will include race, HIV-1 viral load, $CD4^+$ T-cell count, CDC clinical category, PI-containing ART regimen, tenofovir containing ART regimen, NNRTI-containing ART regimen, nevirapine containing ART regimen, Tanner stage, height and weight z-scores (or BMI z-score), calcium, vitamin D and multivitamin use intake, smoking and substance abuse, insulin resistance, waist-to-hip ratio, physical activity, and lipodystrophy. In addition, age and gender will be evaluated as potential predictors, although they should not need to be included due to the adjustment for age and gender in the initial z-score calculation. Each potential risk factor will be first examined as a predictor of BMD in a univariate linear regression model. The factors found to be associated with BMD z-scores at the $p = 0.20$ significance level will be considered for inclusion in the final prediction model for BMD. This model will be built using a step-wise model building procedure. Since we will have repeated measures of BMD, we can increase power by incorporating repeated measures taken on the same participant using mixed effects models that take into account the correlation between the repeated measures. The same procedure of identifying univariate predictors and then building a prediction model can be undertaken. In addition, based on measurements of BMD collected over time, the change from baseline in BMD can be calculated and summarized overall and by various subgroups of interest.

Further laboratory assessments of bone metabolism will be conducted only among those with BMD z-scores < -1.5. Thus, our ability to directly compare laboratory measures of bone resorption and formation between the two study groups and national standards will depend on the number of participants undergoing these extensive evaluations in each of the groups. If there are enough participants, the difference in the mean levels of TSH, calcium and vitamin D, bone-specific alkaline phosphatase, PTH, pro-inflammatory cytokines, and N-terminal telopeptide of type I collagen, can be compared by considering each measure separately in a linear regression model with study group as the main predictor, and age, gender, and other measures of body size as confounders. We will also calculate the mean levels of TSH, calcium and vitamin D, bone-specific alkaline phosphatase, PTH, pro-inflammatory cytokines, and N-terminal telopeptide of type I collagen in our population. These means can then be compared to standard levels observed previously among children with normal BMD.

10.2.5 Neurologic, Neurodevelopmental, Language, and Behavioral Function

The analysis of neurobehavioral outcomes will focus on estimating the prevalence at study entry and over follow-up of emotional and behavioral health problems, high risk behaviors (risky sexual behavior, licit and illicit drug use, tobacco and alcohol use), neurodevelopmental impairment (cognitive function, academic achievement, executive function, and language), impaired hearing or language development, and non-adherence to ART. We will also evaluate the changes over time in these outcomes both in terms of incidence of new neurobehavioral outcomes among participants free of these at study entry, along with resolution of such outcomes which are observed to be prevalent at entry. 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% confidence intervals. Incidence estimates based on follow-up data will be calculated under a Poisson distribution based on participant-years of follow-up.

The prevalence of mental health problems, high risk behaviors including risky sexual behavior, licit and illicit drug use, tobacco and alcohol use, neurodevelopmental impairment, and impaired hearing will be compared between the HIV-infected participants versus the HIV-exposed, -uninfected control cohort using chi-square tests as crude analyses and using logistic regression models for each separate outcome as a function of HIV status controlling for important family and psychosocial factors (demographic characteristics, caregiver characteristics including type of caregiver, caregiver education level and cognitive function, and caregiver mental and physical health and substance use, and socioeconomic factors.

To evaluate whether high risk behaviors tend to occur together, we will summarize the co-occurrence of sexual, drug, and tobacco and alcohol risk behaviors and consider each as a potential predictor of the other risk behaviors. For example, a logistic regression model for risky sexual behavior may include risky drug behavior as a predictor. Among the subset of HIV-infected and uninfected participants identified to have an emotional or behavioral health problem, we will also compare the types of mental health problems by infection status.

Among just the HIV-infected participants, we will conduct logistic regression analyses to evaluate the association of behavioral and emotional health outcomes with age, ART regimen, and family and psychosocial factors (caregiver cognitive function, caregiver mental health, stressful life events, and caregiver-child relationships). Secondly, we will consider ART medication adherence as an outcome in a logistic regression model and evaluate the association of this outcome with youth factors (age, sex, mental health, sexual risk behavior, illicit drug use, licit drug abuse, and neurodevelopment), caregiver factors (mental health, physical health, stressful life events, substance use, education, and cognitive function), and other sociodemographic factors.

10.2.6 HPV Infection

The cumulative incidence of 1) LSIL and 2) HSIL will be estimated using the Kaplan-Meier Product Limit Method; only adolescent females with a first Pap smear indicative of normal cervical cytology and at least one subsequent Pap smear examination will be included. Associations between putative risk factors (e.g. CD4 %, HIV viral load, ART use, CDC disease classification, contraceptive use, number of sexual partners, and smoking) and the occurrence of 1) LSIL and 2) HSIL will be estimated using Cox Proportional Hazards regression.

The rate of regression of LSIL to normal cervical cytology will be estimated using the Kaplan-Meier Product Limit Method; only adolescent females with an incident LSIL will be included. Time zero will be defined as the date of the Pap smear examination of the incident LSIL. If there are too few adolescents with incident LSIL to accurately estimate the rate of regression, descriptive case data will be reported.

11.0 HUMAN SUBJECTS

11.1 AMP as 45 CFR § 46.404

It is the judgment of the Protocol Team that the AMP protocol belongs in Category One Research under 45 CFR § 46 Subpart D: Research not involving greater than minimal risk. This judgment is premised on the definition of minimal risk found at 45 CFR § 46.102 (i):

> *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

The principal risks in this study result from the disclosure of sensitive maternal information and the risks inherent in the routine examinations the children and adolescents will receive. These are discussed in more detail in the following sections but in essence are medical and psychological examinations employed in routine clinical evaluation

11.2 Prisoner Participation

The PHACS and NICHD concluded that this protocol does not meet Federal requirements governing recruitment of prisoners for participation in research and should NOT be considered by local IRBs for this purpose. Participants recruited from the general population who, subsequent to enrollment, become incarcerated or are placed in detention, may not continue study participation while incarcerated.

11.3 Participant Confidentiality

All participants enrolled into the PHACS Network will be assigned a unique PHACS patient identifier (PID). A unique study identifier (SID) number will also be assigned by the Subject Enrollment System when the participants are successfully enrolled onto a PHACS Protocol. Although a new SID will be issued for each PHACS study (substudy) a patient enrolls onto, each patient will only be assigned one PID number to be used on all PHACS protocols. The PID and SID 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. A list linking the participant names with the PID and SID numbers will be stored at the clinical site under double locks, separate from all other research records. All research records will be stored in a secured area in locked files.

All 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 protocol team investigators and collaborators are required to sign data use agreements pledging not to seek the identity of study participants.

Research staff will work with parents or legal guardians to fashion a list of contact people (friends or family) 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 had become 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 will conduct a National Death Index (NDI) search. The NDI is a government service using national vital record databases. Since the CFR applies to living participants only, consent for this procedure will not be required. If the location or vital status of lost participant cannot be ascertained, AMP also intends to conduct a 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 consent (permission) process. Application to the NDI is governed by several layers of confidential assurances 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). To preserve the coded nature of the AMP 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 research staff at the PHACS clinical sites and the central NDI staff to accomplish the NDI searches. Searches will only be conducted on those participants who become lost to follow-up and for whom the site has consent/permission and HIPAA authorization. Westat will receive information from the NDI if a match is successful. This information will be confidentially provided by designated Westat staff to the research staff at the site who, in turn, will code the vital status and diagnostic information and submit it to the AMP database. No personally identifying information will be known to or incorporated into the AMP database.

Personally identifying information will not be released by the sites without written permission of the participant's parent or legal guardian, except as necessary for monitoring by Westat or the NICHD or as consented and authorized for NDI searches. To the extent possible, clinically obtained evaluations such as echocardiograms and cervical cytology/histology specimens will be stripped of identifiers and coded with the AMP PID prior to centralized reads. However, it is acknowledged that this may not be possible in all situations and therefore all parents/legal guardians will be asked to consent and authorize the release of such evaluations when and if their release becomes applicable. The protocol team members who would be responsible for these central reads will be institutionally distinct from the DOC where the AMP database is secured and will sign specific user agreements outlining their responsibilities to protect participant identities. No personally identifying information will be known to or incorporated into the AMP database

To further protect the privacy of the study participants, the PHACS has obtained a Certificate of Confidentiality from the U.S. Department of Health and Human Services. With this Certificate in place, the PHACS researchers cannot be forced to turn over identifying information about a study participant in any Federal, State, or local criminal, administrative, legislative, or other proceedings. This Certificate does not prevent a parent or legal guardian of a study participant from volunteering to turn over research information nor does it prevent researchers from

providing research-related information to others when requested by the study participant's parent or legal guardian.

The site investigator 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.

11.4 Mothers and Primary Caregivers as Study Participants

It is important to include the mother or the primary caregiver, if the child is not living with the mother, as a study participant in AMP. The child's environment has a dramatic impact on many parameters that are being assessed in AMP. For example, growth, nutrition, educational achievement are significantly impacted by the mother or caregiver's status. Substance abuse or disordered physical or mental health by the mother or primary caregiver has a deleterious effect on psychosocial development and behavior in children as well as adherence to medical recommendations. Therefore, data will be collected from the mother/primary caregiver on key parameters that may have an impact on the child. In addition, mothers or primary caregivers will be asked about their observations of the children under their care. Mothers and/or primary caregivers will be consented separately as research participants themselves.

Mothers will also be asked to give permission for AMP study personnel to obtain the records of their pregnancy and perinatal course. Since most participants will have been previously enrolled in WITS or PACTG 219C, information will usually be available from the research databases. Mothers will also be asked to give permission for AMP to obtain repository specimens from other pediatric HIV studies in which they were previously or currently enrolled. The information may be useful in evaluating abnormalities that may have resulted from or been influenced by prenatal exposures. If the birth mother is alive and is the legal guardian of the child, but the child resides with another person who is the primary caregiver, the birth mother should consent for the child's participation and use of data and specimens from her pregnancy and perinatal course and the primary caregiver should consent for his/her own participation as the primary caregiver.

11.4.1 Risks and Benefits for Mothers/Primary Caregivers

The principal risk to the mother/caregiver is a breach of confidentiality thereby disclosing potentially damaging information. We believe that PHACS has adequate protective safeguards in place to dramatically minimize this risk (see Section 11.3).

There is no direct benefit to mothers/caregivers who consent for their personal information to be used other than knowing that their contribution may make the management of HIV-infected adolescents better. Future children may benefit from their participation.

PHACS staff will take precautions to prevent inadvertent disclosure of maternal HIV infection status to the children participating in this study. However, parents/legal guardians will be informed in the consent/permission forms that this cannot be guaranteed since children will

interact with other study children who do know; they will also be exposed to the clinical area where displayed HIV material may raise their awareness.

11.4.2 Mothers Unavailable for Consent

Some HIV-infected mothers may be unavailable to consent to the use of their personal information existing in available research databases. Some may be deceased; for these, the provisions of the CFR requiring consent do not apply and their data may be used. Others may be unengaged in their children's lives and legal guardians have custody of their children. In this circumstance we are asking the IRB to grant access to the mother's study data for the following reasons.

The maternal information from the WITS and PACTG study databases are identified only by study code. This code carries no personally identifying data. The identities of the mothers will not be ascertainable by the PHACS investigators who are in different institutions without access to the research files of the clinical sites where linking information is retained. Non-disclosure forms are required of all research staff at the sites; data use agreements are required of all PHACS investigators. See http://www.hhs.gov/ohrp/policy/index.html#biol.

For those PHACS investigators who do belong to institutions with PHACS clinical sites where participants are enrolled, the identities of the mothers are theoretically ascertainable. In these situations, we request the IRB to grant a waiver of the requirement for informed consent under 45 CFR § 46.116 (d):

> An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provide the IRB finds and documents that:
>
> - the research involves no more than minimal risk to the participants;
> - the waiver or alteration will not adversely affect the rights and welfare of the participants;
> - the research could not practicably be carried out without the waiver or alteration; and
> - whenever appropriate, the participants will be provided with additional pertinent information after participation.

The research involved in this study involves no more than minimal risk (see Section 11.1). Protective safeguards are in place to keep personal data confidential. The research could not be practicably carried out without access to the previously-collected (and consented) information.

11.5 Children as Participants: Procedures, Risks, and Benefits

11.5.1 Procedures, Risks, and Benefits for All Participants

The measurements that are involved in this study require: venipuncture, clinical assessment, neurodevelopmental and behavioral testing, anthropometric evaluation, dual-energy x-ray

absorptiometry (DXA), and a fasting period (not to exceed 8 hours) for laboratory studies. Possible risks resulting from the study include:

- Venipuncture to collect blood specimens may cause local discomfort, bleeding, or bruising; rarely a small clot or infection can occur at the blood draw site.
- Distress resulting from knowing about the result of a clinical or laboratory assessment.
- Anthropometric evaluation is obtained through the external grasping of skin and underlying adipose tissue with calipers; it can cause some temporary discomfort and redness at the point of contact.
- DXA uses a small x-ray exposure (the amount of radiation used is extremely small, less than one-tenth the dose of a standard chest x-ray) to determine the density of bone.
- An M-mode 2-D echocardiogram is non-invasive and carries no additional risks.
- An x-ray of the hand or arm will be performed for determination of bone age. This involves a small amount of x-ray exposure.
- Fasting periods will not exceed 8 hours and should present little risk. Some participants may feel hunger, irritability, and lightheadedness as a result of fasting.
- Disclosure of confidential information obtained through behavioral testing. Some of the information that the youth provide during interviews will not be shared with the parent or caregiver and 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 medication adherence, quality of life, and mental health.

While there is no guarantee of direct benefit to the children who participate in this study, benefiting from participating is possible. If the parents or legal guardians choose, the information obtained in this study can be made available to their children's health care providers and may inform their primary health care. Parents or legal guardians of study participants will be encouraged to do this in order to maximize the potential for benefits.

Note: Sites should ensure that their institutional HIPAA authorization form permits this release of protected health information to the clinical provider.

Since children entering this study may reach the age of legal majority in their respective state or jurisdiction during the course of this study, research staff will track the status of older enrolled participants as they age. When a child reaches legal majority, informed consent will be obtained from him/her to continue participation in the study. The policy of AMP is that data previously collected under the permission (consent) of the mother or legal guardian will continue to be available to the study.

11.5.2 Determining Sexual Activity

Information on the sexual activity reported by participants in the confidential AMP ACASI will not be disclosed to the PHACS site research staff or to the clinicians responsible for their health

care. If a participant is unable to complete the ACASI independently due to technical challenges, a research staff member may assist with this process as needed while making every effort to maintain confidentiality.

Results of screenings for sexually transmitted infections (STIs) done as part of routine care will be obtained from the medical record. For females, results of pelvic exams and pap smears and histology, if applicable, performed as standard of care will be obtained from the medical record.

Parental/legal guardian permission will anticipate the possibility of pelvic exams performed as standard of care and the consent will seek permission for obtaining the results from the medical record and for temporary release and central review of cytology and pathology slides obtained during any pelvic exams and colposcopy performed as part of primary care during the study.

11.5.3 Procedures, Risks, and Benefits for HIV-Infected Children Only

The potential risks for HIV-infected participants include inadvertent disclosure of the child's HIV status to the child who does not yet know about the infection.

11.5.4 AMP Abnormality-Triggered Evaluations

Children followed in this study will be screened for abnormalities using low-technology and low-cost measures when possible. Abnormal values on these screening measures will "trigger" more extensive evaluation. (See section 5.2.) When this evaluation consists of additional measures that are of the same nature (neurodevelopmental testing) or can be performed on stored biologic samples, the investigators will move immediately to this evaluation within the original protocol consent process. If additional blood drawing is required by the triggered evaluation, its impact on the permissible blood volume per visit will be assessed and the triggered evaluation will be scheduled when adequate recovery time has elapsed if the maximum allowed volume has been exceeded. Consent will be obtained at the time of the future evaluation for any triggered evaluation that increases risk to the participant.

11.6 Repository Policy

The PHACS Repository Policy and samples of the consent forms for the PHACS Repository can be found in Appendix VIII. Participants may participate without agreeing to the repository specimens.

11.7 45 CFR § 160 and 164 Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule" pursuant to the Health Insurance Portability and Accountability Act- HIPAA)

11.7.1 AMP Database

Specific protected health information (PHI) will be needed to create the AMP 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 data center and PHACS site monitors;
- PHACS investigators and their collaborators;
- Child's primary care provider if so desired by parent or legal guardian;
- NIH; and
- Westat for the purpose of a NDI search, to be referred to as "national health department database search" to prevent dismay from the use of "death".

11.7.2 PHACS Repository

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.

11.8 Study Discontinuation

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

APPENDIX I
Schedule of Evaluations: HIV-Infected Cohort

	Entry (completed)	2.5 years after entry	Q 12 mo after entry	Other
Medical, ART and social history[1]	X		X	
Physical exam[2]	X		X	
Family history[3]	X			And year 3 on study
Diet and physical activity[4]	X			Every 2 years
Adherence questionnaire				See Appendix VI and VII
ACASI[5]				See Appendix VI and VII
Diagnoses	X		X	
Tanner stage[6]	X		X	
Body measurements[7]	X		X	
Neurodevelopment and behavior assessments	X	X	X	See Appendix VI and VII
DXA Scan	X			2nd at 2 years after first DXA; 3rd at Tanner 5 and at least 2 years after the 2nd DXA. Do not do a 3rd DXA if child was Tanner 5 at 2nd DXA[10]
Bone age	X			At same time as DXA unless Tanner 5. See [10]
Echocardiogram including 2-D, Doppler, color Doppler, M-mode, and tissue Doppler imaging				If not already done. See [11]
Full audiological evaluation				If not already done as a result of a language/hearing trigger, do at the first visit under Version 4.0 that is a year 2 or later study visit
Laboratory				
Abstract CBC [9]	X		X	
Abstract Chemistries (BUN, creatinine, lipase, AST, ALT, CPK)[9]	X		X	
Abstract all interval results of STI testing performed as part of routine care[8]	X		X	
Abstract results of urinalysis performed as part of routine care[9]	X		X	
Abstract all interval Lymphocyte subsets (CD3, CD4, and CD8)[9]	X		X	
Abstract all interval HIV RNA viral load and resistance testing results[9]	X		X	
Urine for protein/creatinine ratio	X			Deleted in Version 4.0
Fasting lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)	X		X	
Dip stick urine test in real time for glucose, protein, ketones, blood, bilirubin, etc.	X		X	Point-of-care testing in clinic
Venous lactate/pyruvate[15]				At first visit under Version 4.0
Held in Repository: Serum for cardiac biomarkers				See [11]

	Entry (completed)	2.5 years after entry	Q 12 mo after entry	Other
(at time of echocardiogram)				
Repository – fasting serum[13], EDTA plasma, and fasting NaF/K oxalate plasma[14]	X		X	
Repository - frozen cell pellets	X		X	
Repository – urine[12]	X		X	
Testing at local lab for MDC – Venous lactate/pyruvate[16]			**X**	**Annually after first visit under Version 4.0 until 3 visits are completed[19]**
Repository for MDC – frozen viable cell pellets[17]			**X**	
Repository for MDC – buccal cells[18]			**X**	

Note: The visit window will be ± 3 months for all visits including the echocardiogram. Q6 month evaluations no longer performed, refer to Version 3.0 protocol for Q6 month evaluations.

(Note: Footnote 10 regarding saliva collection in Oragene device and Footnote 14 regarding POC lactate collection were deleted per CM #13 and CM #10, respectively. The remaining footnotes were renumbered.)

[1] Include CV risk history, contraception use, results of HIV resistance testing **and history of bone fractures.** (Contraception use **is** collected in **the** ACASI **– see Appendix VII for schedule**).

[2] If physical exam is not performed as a part of routine care, a checklist will be completed to indicate that the components of the exam performed and the findings will be recorded in the clinical record. Only diagnoses will be collected on the AMP CRF. Blood pressure will be measured and recorded twice at each visit.

[3] Family history should include parental height and weight, history of hypertension, diabetes mellitus, early atherosclerotic heart disease, and stroke.

[4] Diet and physical activity will be collected using the Block Food Frequency and Physical Activity questionnaires; for participants age 7 at entry, do not administer until the 1-year visit at age 8 and then administer every 2 years.

[5] ACASI will be conducted for sexual behavior and substance use for participants ≥ 10 years of age.

[6] Tanner staging - stop when Tanner 5. For males, use orchidometer and check for gynecomastia.

[7] Includes height and weight, skinfold thickness with calipers (TSF, biceps, suprailiac, subscapular), upper mid arm, waist and hip circumferences.

[8] At entry, obtain from the parent/guardian of all girls a release for the future central review of routine histology and cytology slides. For males and females, abstract all interval results of STI testing performed as part of routine care, including results of pelvic exams and pap smears for females.

[9] Results to be captured from routine clinical testing, i.e., abstract from chart. CBC should include differential and platelets. Report all interval lymphocyte subset, viral load, and HIV resistance testing results. Report CBC, chemistry, and urinalysis results obtained twice a year, i.e., results available from **the** first 6 months after the last study visit should be reported in addition to results in the 6 months immediately prior to the current visit. **If there are no results available from routine care since the last visit for the following tests, they should be done as part of the current study visit: CBC, chemistry, lymphocyte subset, and viral load. If at least one result is available since the last visit, there is no need to perform the test at the current visit.**

[10] Both Tanner stages must be Tanner 5 (breast and pubic hair in girls; pubic hair and testicular volume in boys). Bone age should be done at the same time as DXA unless the participant is Tanner stage 5.

[11] If not already performed under a prior version, an echocardiogram and repository serum collection for cardiac biomarkers will be performed once within 3 months either side of the first protocol visit under version 4.0 at which the participant's age is an odd number of years. These evaluations will be discontinued once an adequate number have been performed; sites will be notified when they are discontinued.

[12] Clean catch urine collected after first void urine of the day.

[13] Two tubes of blood should be drawn for serum while fasting.

[14] Included are serum for insulin and NaF/K oxalate plasma for glucose which are specimens to be held temporarily in the Repository for central testing. These specimens should be collected for all participants including those who did not sign the repository consent.

[15] A blood sample for venous lactate and pyruvate will be collected for all participants only at the first visit under version 4.0.

[16] For participants enrolled in MDC, collect 4 ml of fasting blood in a NaF/K oxalate (grey-top) tube annually after the first visit under version 4.0. Venous lactate levels will be drawn in a grey-top tube (NaF/K oxalate) and processed at the site within 30 minutes. Participants will be fasted at rest for 30 minutes without fist-clenching prior to the blood draw. Samples will be placed on ice and transported immediately to the local laboratory for testing. Abnormal lactate will be defined as any level > 2.0 mmol/L. Participants with a lactate level > 2.0 mmol/L will require a repeat lactate for confirmation.

[17] For participants enrolled in MDC only - 2 8-ml tubes of blood should be drawn while fasting to isolate and store the PBMCs as viable cells. These will be held temporarily in the repository and then shipped for central testing.

[18] For participants enrolled in MDC only - 3 cytobrushes will be used to obtain buccal (cheek) cells. Cytobrushes will be obtained from the University of Hawaii. These samples will be held temporarily in the repository before being shipped for central testing.

[19] Per CM #6 dated March 25, 2014, no 4th MDC visit should be conducted as of March 31, 2014. Participants will be taken off study after completing the 3rd MDC visit.

APPENDIX II
Schedule of Evaluations: HIV-Exposed, Uninfected Control Cohort

	Entry (completed)	2.5 years after entry	Q 12 mo after entry	Other
Medical and social history[1]	X		X	
Physical Exam[2]	X		X	
Family history[3]	X			And year 3 on study
Diet and physical activity[4]	X			2nd at age 12 or at first visit under Version 4.0 (whichever comes first)
ACASI[5]				See Appendix VI and VII
Diagnoses	X		X	
Tanner stage[6]	X		X	
Body measurements[7]	X		X	
Neurodevelopment and behavior assessment	X	X	X	See Appendix VI and VII
DXA Scan				See [10]
Bone age				See [10]
Echocardiogram including 2-D, Doppler, color Doppler, M-mode, and tissue Doppler imaging				If not already done. See [9]
Full audiological evaluation				If not already done as a result of a language/hearing trigger, do at the first visit under Version 4.0 that is a year 2 or later study visit
Laboratory				
Abstract all interval results of STI testing performed as part of routine care[8]	X		X	
Abstract results of urinalysis performed as part of routine care[14]	X		X	
Dip stick urine test in real time for glucose, protein, ketones, blood, bilirubin, etc.	X		X	Point-of-care testing in clinic
Venous lactate/pyruvate[15]				At first visit under Version 4.0
Repository – fasting serum[12], EDTA plasma, and fasting NaF/K oxalate plasma[13]	X		X	
Held in Repository: Serum for cardiac biomarkers (at time of echocardiogram)				See [9]
Repository – frozen cell pellets	X		X	
Repository – urine[11]	X		X	
Test at local lab for MDC - Venous lactate/pyruvate[16]			**X**	**Annually after first visit under version 4.0 until 3 visits are completed[19]**
Repository for MDC – frozen viable cell pellets[17]			**X**	
Repository for MDC – buccal cells[18]			**X**	

Note: The visit window will be ± 3 months for all visits including the echocardiogram. Q6 month evaluations no longer performed, refer to Version 3.0 protocol for Q6 month evaluations.

(Note: Footnote 9 regarding saliva collection in Oragene device and Footnote 13 regarding POC lactate collection were deleted per CM #13 and CM #10, respectively. The remaining footnotes were renumbered.)

[1] Include **CV** risk history, contraception use, **and history of bone fractures.** (Contraception use **is** collected in **the** ACASI **– see Appendix VII for schedule**).

[2] If physical exam is nfot performed as a part of routine care, a checklist will be completed to indicate that the components of the exam performed and the findings will be recorded in the clinical record. Only diagnoses will be collected on the AMP CRF. Blood pressure will be measured and recorded twice at each visit.

[3] Family history should include parental height and weight, history of hypertension, diabetes mellitus, early atherosclerotic heart disease, and stroke.

[4] Diet and physical activity will be collected using the Block Food Frequency and Physical Activity. questionnaires; it should be done at entry AND repeated when the participant turns 12 years of age or at the first visit under version 4.0 if not yet 12 years of age at that time (and not already done a second time). For participants age 7 at entry, do not administer until the 1-year visit at age 8.

[5] ACASI will be conducted for sexual behavior and substance use for participants ≥ 10 years of age.

[6] Tanner staging - stop when Tanner 5. For males, use orchidometer and check for gynecomastia.

[7] Includes height and weight, skinfold thickness with calipers (TSF, biceps, suprailiac, subscapular), waist and hip circumferences.

[8] At entry, obtain from the parent/guardian of all girls a release for the future central review of routine histology and cytology slides. For males and females, abstract all interval results of STI testing performed as part of routine care, including results of annual pelvic exam and pap smears for females.

[9] If not already performed under a prior version, an echocardiogram and repository serum collection for cardiac biomarkers will be performed once within 3 months either side of the first protocol visit under version 4.0 at which the participant's age is an odd number of years. These evaluations will be discontinued once an adequate number have been performed; sites will be notified when they are discontinued.

[10] Bone age and DXA, should be performed at entry if age 12 or older at entry, or when the participant turns 12 years of age, or at the first visit under version 4.0 if not yet 12 years of age at that time (and not already done). However, the bone age should not be done if the participant is Tanner stage 5 at the time the bone age due. The DXA should still be performed on participants who are Tanner stage 5 at the time that it is due.

[11] Clean catch urine collected after first void urine of the day.

[12] Two tubes of blood should be drawn for serum while fasting.

[13] Included are serum for insulin and NaF/K oxalate plasma for glucose which are specimens to be held temporarily in the Repository for central testing. These specimens should be collected for all participants including those who did not sign the repository consent.

[14] Abstract urinalysis results obtained twice a year.

[15] **A blood sample for venous lactate and pyruvate will be collected for all participants only at the first visit under version 4.0.**
For participants not enrolled in MDC, if lactate is > 3.0 mmol/L, but lactate/pyruvate ratio is ≤ 20, then repeat lactate/pyruvate with careful attention to blood-drawing technique.
For participants enrolled in MDC, if lactate is > 2.0 mmol/L, but lactate/pyruvate ratio is ≤ 20, then repeat lactate/pyruvate with careful attention to blood-drawing technique.

[16] **For participants enrolled in MDC, collect 4 ml of fasting blood in a NaF/K oxalate (grey-top) tube annually after the first visit under version 4.0. Venous lactate levels will be drawn in a grey-top tube (NaF/K oxalate) and processed at the site within 30 minutes. Participants will be fasted at rest for 30 minutes without fist-clenching prior to the blood draw. Samples will be placed on ice and transported immediately to the local laboratory for testing. Abnormal lactate will be defined as any level > 2.0 mmol/L. Participants with a lactate level > 2.0 mmol/L will require a repeat lactate for confirmation.**

[17] **For participants enrolled in MDC only - 2 8-ml tubes of blood should be drawn while fasting to isolate and store the PBMCs as viable cells. These will be held temporarily in the repository and then shipped for central testing.**

[18] **For participants enrolled in MDC only - 3 cytobrushes will be used to obtain buccal (cheek) cells. Cytobrushes will be obtained from the University of Hawaii. These samples will be held temporarily in the repository before being shipped for central testing.**

[19] **Per CM #6 dated March 25, 2014, no 4th MDC visit should be conducted as of March 31, 2014. Participants will be taken off study after completing the 3rd MDC visit.**

APPENDIX III
Routine Sample Collection Specifications for Specimens Sent to the Repository

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

Test	Volume of draw	Anticoagulant (tube color)
Serum biomarkers for cardiac function	2 ml	Separator or red top tube
Fasting serum – 2 tubes	12-14 ml	Separator or red top tube
Frozen cell pellet/plasma	8 ml	CPT tube[1]
EDTA plasma	6-7 ml	EDTA (lavender top)
Fasting NaF/K oxalate plasma	4 ml	NaF/K oxalate (grey top)
MDC: Viable cell pellet[1,2]	**16 ml**	**CPT or EDTA**
MDC: buccal cells[2]	**3 cytobrushes**	**Brushes supplied by the University of Hawaii**
Urine	10 ml	Sterile container

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

[1] EDTA (lavender top). PBMCs to be separated using ficoll-hypaque as an alternative to using the CPT tube. See Repository Specimens in section 7.1.5. **Refer to the laboratory processing instructions specific to MDC.**

[2] Collected for only those participants enrolled in MDC.

APPENDIX IV
Sample Collection Specifications for Triggered Laboratory Studies

("Batched" repository samples are sent to the repository every month.)

For Delayed Onset of Puberty (5.2.1):

Sent to Repository (Batched)

LH	serum
FSH	serum
Estradiol	serum
Testosterone	serum

Collect one 6-7 mL SST or red top tube = 6-7 aliquots @ 0.5 mL

For Delayed Growth (5.2.1, 7.1.6):

Sent to Esoterix for testing in real time:

IGF-I	serum
IGFBP-3	serum
GHBP	serum

Collect one 6-7 mL SST or red top tube = 6-7 aliquots @ 0.5 mL

For Growth Hormone Stimulation Test - Done locally using tubes specified by local lab:

Glucose	plasma

For Growth Hormone Stimulation Test - Sent to Esoterix for testing in real time:

Growth hormone	serum
Cortisol	serum

Collect one 6-7 mL SST or red top tube = 6-7 aliquots @ 0.5 mL

For Abnormal Glucose Metabolism (5.2.2, 7.1.6):

For Glucose tolerance test. Done locally using tubes specified by local lab:

Glucose	plasma
HbA1c	anticoagulated whole blood

For Glucose tolerance test. Sent to Repository (Batched)

Insulin	serum

For Dyslipidemia (5.2.2):

Sent to Repository (Batched)

I, E, P-Selectins	EDTA plasma
Homocysteine	EDTA plasma
Lipoprotein (a)	EDTA plasma

Endothelin-1	EDTA plasma
CAM's (I, V)	Citrated plasma (ACD)
vWF antigen	Citrated plasma (ACD)
hs-CRP	serum
Apolipoprotein B	serum

Collect: One 6-7 mL EDTA tube = 6-7 aliquots @ 0.5 mL
One 6 mL ACD tube = 6 aliquots @ 0.5 mL
One 6-7 mL serum tube = 6-7 aliquots @ 0.5 mL

For the Bone Mineral Density Trigger (5.2.3):

Done locally using tubes specified by local lab:

TSH	serum
Calcium	serum
25-OH Vitamin D	serum
Bone-specific alk phos	serum
PTH	serum

Sent to Repository (Batched)

IL-1	EDTA plasma
IL-6	EDTA plasma
TNF	EDTA plasma
N-terminal telopeptide of type I collagen	Serum

Collect: One 6-7 mL EDTA tube = 6-7 aliquots @ 0.5 mL
One 6-7 mL serum tube = 6-7 aliquots @ 0.5 mL

APPENDIX V
Triggered Evaluation of Participants in AMP
(See Section 5.2)

NOTE: TRIGGERED EVALUATION IS DONE THE FIRST TIME THE TRIGGER IS MET AND NOT REPEATED IF MET AGAIN AT A LATER VISIT.

Domain	Condition	If condition is:	Triggered Evaluation
Growth and sexual maturation (5.2.1)	Onset of puberty (infected and uninfected)	Females: Tanner stage 1 at or beyond the 12th birthday Males: Tanner stage 1 at or beyond the 13th birthday	Hypothalamic-pituitary-gonadal function: morning LH, FSH, estradiol, and testosterone in both males and females.
	Height (infected and uninfected)	Either: (1) Absolute height z-score of less than -1.88 SD (< 3rd percentile) unless mid-parental height z-score is available and is less than -1.65 SD; or (2) decrease in height z-score of more than 1.3 SD over 6 months **or more**.	IGF-I, IGFBP-3, and GHBP. If IGF-I is low for age and gender, refer participant to local pediatric endocrinologist for further evaluation. If the endocrinology evaluation supports the need for a growth hormone stimulation test, perform the test (See 7.1.6). If IGF-I is normal for age and gender, re-evaluate growth at the next scheduled visit. If the interval growth shows a positive change in height z-score, continue to evaluate changes per protocol; if height z-score is unchanged or worse, refer to the endocrinologist.
Metabolic risk factors for CV disease (See 5.2.2)	Insulin resistance (infected only)	Fasting glucose and insulin levels (results from central lab using specimens sent to repository) show HOMA-IR greater than 2.5 in children (Tanner stage 1) or greater than 4.0 in adolescents (Tanner stage ≥ 2)	Oral glucose tolerance test, HbA1c levels, and repository insulin (See 7.1.6)
	Dyslipidemia (infected only)	Elevated serum lipids: Total cholesterol > 200 mg/dL, LDL cholesterol > 130 mg/dL, Triglycerides for ages 0-9 years > 110 mg/dL; for ages 10-**17** years > 150 mg/dL, and HDL cholesterol < 35 mg/dL	Collect and store samples for future measurements of endothelial dysfunction (I, E, P-selectins: V, I-CAM-1, endothelin-1, hs-CRP, homocysteine, apolipoprotein B, lipoprotein (a), and vWF antigen)

Domain	Condition	If condition is:	Triggered Evaluation
Bone mineral density (see 5.2.3)	Abnormal BMD by DXA (infected and uninfected)	z-score of less than -1.5 SD after adjusting for bone age	TSH, calcium, 25-hydroxy-vitamin D, bone-specific alkaline phosphatase, and PTH in real time and repository specimens for assay of pro-inflammatory cytokines (IL-1, IL-6, TNF-α) Serum for N-terminal telopeptide of type I collagen to the repository.

APPENDIX VI
NEURODEVELOPMENT AND BEHAVIOR ASSESSMENTS

CAREGIVER

Caregiver Functioning	
IQ	• WASI*: 6 months, **10 years (if never completed by caregiver during AMP participation)**
Mental Health and Substance Use[1]	• Clinical Diagnostic Questionnaire (CDQ)*: 6 months, 2.5 years, 5 and 8 years • Substance using during pregnancy: 6 months
Family Environment	
Family Functioning	• Parent-Child Relationship Inventory[2,3] (PCRI): 6 months, 2.5 years, 5 **and 8 years**
Demographics	Entry, 1, 2, 3, 4, 5, 6, 7, **8, 9, and 10** years
Caregiver Health[1]	• Entry, 1, 2, 2.5, 4, 5, 6, 7, **8, 9, and 10** years

* Indicates measures that must be administered by a psychologist or psychometrician.
Note: Entry, 6 months, **1-, 2-, 2.5-, 3-, 4-, 5-**, and **6**-year evaluations already performed and no longer applicable are grayed out.

[1] The CDQ and Caregiver Health Screen require caregiver consent and enrollment.
[2] The psychologist must provide training, supervision/oversight to those administering the PCRI.
[3] The PCRI will only be administered to caregivers of youth < 16 years of age.

CHILD

Neurodevelopment	
IQ	• WISC-IV* (if youth is < 17 years): Entry and 3 years • WAIS-IV* (if youth is ≥ 17 years): 3 years Note: For Spanish-speaking only participants, the Spanish version of the WAIS-III should be used instead of the WAIS-IV
Language	• Clinical Evaluation of Language Fundamentals (CELF), Version 4*: the Core Language Domain assessment: 6 months and 2 years • Woodcock Reading Mastery Test (Form H)*: Word Identification and Word Attack subtests: 6 months and 2 years
Executive Function	• Behavior Rating Inventory of Executive Function (BRIEF)* - Child Report beginning at Age 11: 1, 3, 5, 7 **and 9** years • BRIEF[1] - Parent Report for entire age range: 1, 3, 5, 7 **and 9** years • Children's Color Trails Test* (age 8-16) or Trail Making Test Forms A and B* (age ≥ 17 years and < 18 years): 1, 3, 5, 7 **and 9** years
Achievement	• WIAT-II screener*: 1, 3 and 5 years. WIAT II - Abbreviated: Word Reading, Numerical Operations, Spelling subtests at 7 **and 9** years
Working Memory and Processing Speed Subtests	WISC-IV for those < 17; WAIS-IV for those ≥ 17 and < 18 at 5, 7 **and 9** years: • Working Memory **(3 subtests**): Digit Span, Letter Number Sequencing, Arithmetic • Processing Speed **(3 subtests):** Coding, Symbol Search, Cancellation **Note: EIWA-III for participants ≥ 17 and < 18 who are primarily Spanish speaking and whose parental/family heritage is Puerto Rican at 5, 7, and 9**

	years. Participants who are primarily Spanish speaking and of Mexican or other non-Puerto Rican heritage should not be administered the WAIS-IV subtests. • Working Memory (**3 subtests**): Digit Span, Letter-Number Sequencing, Arithmetic Processing Speed (**2 subtests):** Coding, Symbol Search
Adaptive Functioning	• Adaptive Behavior Assessment System-2nd Edition (ABAS-II)[1] - Parent Report: Entry, 3, 5, **and 7** years
Risk Behaviors	
Sexual Behavior and Substance Use	• ACASI[1]: 6 months, 2.5, 4, 5, 6, 7, 8, **9, and 10** years
Adherence[2]	• Self- and parent-report questionnaire[1]: 6 months, 2.5, 4, 5, 6, 7, 8, **9, and 10** years
Mental Health	
Behavior	• Behavior Assessment System for Children, Version 2 (BASC-2)* – Child Report – younger child version (7 years old) or older child version (8-11 years old) or adolescent version (≥ 12 years old): Entry, 2, 2.5, 4, 6, 8, **and 10** years • BASC-2 - Parent Report[1]: Entry, 2, 2.5, 4, 6, 8, **and 10** years
Quality of Life	• QOL[1] - Parent Report: 1, 2, 3, 4, 6, 8, **and 10** years • QOL[1] - Child Report starting at Age 12: 1, 2, 3, 4, 6, 8, **and 10** years • Life Events Questionnaire[1] - Child: 1, 2, 3, 4, 6 and 8 years (only for children ages 8-15 (i.e., < 16)
Future Orientation/ Vocation and Family Planning	• Monitoring the Future Questions[1] (for youths ≥ 14 years old): 2, 4, 6, 8, **and 10** years

* Indicates measures that must be administered by a psychologist or psychometrician.

Note: The Entry, 6 months, 1-, 2-, 2.5-, 3-, **4-, 5-,** and **6**-year evaluations are grayed out to indicate that all visits at those time points have been completed.

[1] The psychologist must provide training, supervision/oversight those administering these measures. Non-psychologists must have prior training in administering mental health or psychosocial measures.

[2] Adherence questionnaire must be administered by someone who is not involved in the medical care of the participant.

APPENDIX VII
Schedule of Evaluations: Neurodevelopment and Behavior

ENTRY VISIT								
	7 yrs	8-9 yrs	10 yrs	11 yrs	12 yrs	13-15 yrs	16-18 yrs	19+ yrs
Neurodevelopment								
WISC-IV	X	X	X	X	X	X		
Mental Health								
BASC-2-Child/Adol.	X	X	X	X	X	X		
BASC-2-Parent	X	X	X	X	X	X		
ABAS-Parent	X	X	X	X	X	X		
Family Environment								
Demographics -Household & Family Demographics -Subject Demog./Neuropsych. Assess.	X	X	X	X	X	X		
Caregiver Health	X	X	X	X	X	X		

Note: Participants who enter having completed a WISC-IV within the six preceding months will not repeat the WISC-IV at entry but use the results from the previous evaluation in place of the entry evaluation. Otherwise, participants who enter AMP without having completed a WISC-IV within the six preceding months will undergo WISC-IV evaluation within two months.
Entry and 6 months evaluations already performed and no longer applicable are grayed out.

6 MONTH VISIT								
	7 yrs	8-9 yrs	10 yrs	11 yrs	12 yrs	13-15 yrs	16-18 yrs	19+ yrs
Neurodevelopment								
Language: CELF-IV Woodcock Reading Mastery Test (Form H): Word ID & Word Attack	X	X	X	X	X	X	X	
Risk Behaviors								
Sex & Drugs: ACASI			X	X	X	X	X	
Adherence (caregiver & child/adolescent)	X	X	X	X	X	X	X	
Caregiver Functioning								
WASI	X	X	X	X	X	X	X	
CDQ	X	X	X	X	X	X	X	
Substance Use Pregnancy	X	X	X	X	X	X	X	
Family Environment								
PCRI	X	X	X	X	X	X	X	

Note: Entry and 6 months evaluations already performed and no longer applicable are grayed out.

1 YEAR VISIT									
	7 yrs	8-9 yrs	10 yrs	11 yrs	12 yrs	13-15 yrs	16 yrs	17-18 yrs	19+ yrs
Neurodevelopment									
BRIEF (Child/Adolescent)				X	X	X	X	X	
BRIEF (Parent)		X	X	X	X	X	X	X	
Executive Functioning Color Trails (8-16) Trailmaking (17+)		X	X	X	X	X	X	X	
WIAT-II		X	X	X	X	X	X	X	
Mental Health									
QOL (Adolescent)					X	X	X	X	
QOL (Parent)		X	X	X	X	X	X	X	
Life Events (Child)		X	X	X	X	X			
Family Environment									
Demographics -Household & Family Demographics -Subject Demog./Neuropsych. Assess.		X	X	X	X	X	X	X	
Caregiver Health		X	X	X	X	X	X	X	

Note: The 1-year visit table is grayed out to indicate that all visits at this time point have been completed.

2 YEAR VISIT									
	7 yrs	8-9 yrs	10 yrs	11 yrs	12 yrs	13-15 yrs	16 yrs	17-18 yrs	19+ yrs
Neurodevelopment									
Language: CELF-IV Woodcock Reading Mastery Test (Form H): Word ID & Word Attack		X	X	X	X	X	X	X	
Mental Health									
BASC-2 (Child/Adolescent)		X	X	X	X	X	X	X	
BASC-2 (Parent)		X	X	X	X	X	X	X	
QOL (Adolescent)					X	X	X	X	
QOL (Parent)		X	X	X	X	X	X	X	
Life Events (Child)		X	X	X	X	X			
Monitoring the Future (14+)						X	X	X	
Family Environment									
Demographics -Household & Family Demographics -Subject Demog./Neuropsych. Assess.		X	X	X	X	X	X	X	
Caregiver Health		X	X	X	X	X	X	X	

Note: The 2-year visit table is grayed out to indicate that all visits at this time point have been completed.

2.5 YEAR VISIT									
	7 yrs	8-9 yrs	10 yrs	11 yrs	12 yrs	13-15 yrs	16 yrs	17-18 yrs	19+ yrs
Risk Behavior									
Sex and Drugs: ACASI			X	X	X	X	X	X	
Adherence (caregiver & child/adolescent)		X	X	X	X	X	X	X	
Mental Health									
BASC-2 (Child/Adolescent)		X	X	X	X	X	X	X	
BASC-2 (Parent)		X	X	X	X	X	X	X	
Caregiver Functioning									
CDQ		X	X	X	X	X	X	X	
Family Environment									
PCRI		X	X	X	X	X	X	X	
Caregiver Health		X	X	X	X	X	X	X	

Note: The 2.5-year visit table is grayed out to indicate that all visits at this time point have been completed.

3 YEAR VISIT									
	7 yrs	8-9 Yrs	10 yrs	11 yrs	12 yrs	13-15 yrs	16 yrs	17-18 yrs	19+ Yrs
Neurodevelopment									
WISC-IV (< 17th birthday)			X	X	X	X	X		
WAIS-IV (17 years and older) (or WAIS-III Spanish version if Spanish-speaking only, until Spanish version of WAIS-IV becomes available)								X	X
BRIEF (Child/Adolescent)				X	X	X	X	X	
BRIEF (Parent)			X	X	X	X	X	X	
WIAT-II			X	X	X	X	X	X	X
Executive Functioning Color Trails (8-16) Trailmaking (17+)			X	X	X	X	X	X	X
ABAS-II (Parent)			X	X	X	X	X	X	X
Mental Health									
QOL (Adolescent)					X	X	X	X	X
QOL (Parent)			X	X	X	X	X	X	X
Life Events (Child)			X	X	X	X			
Family Environment									
Demographics -Household & Family Demographics -Subject Demog./Neuropsych. Assess.			X	X	X	X	X	X	X

Note: The 3-year visit table is grayed out to indicate that all visits at this time point have been completed.

4 YEAR VISIT								
	7 yrs	8-9 yrs	10 yrs	11 yrs	12 yrs	13-15 yrs	16 yrs	**17 yrs**
Risk Behaviors								
Sex and Drugs: ACASI				X	X	X	X	X
Adherence (caregiver & child/adolescent)				X	X	X	X	X
Mental Health								
BASC-2 (Child/Adolescent)				X	X	X	X	X
BASC-2 (Parent)				X	X	X	X	X
QOL (Adolescent)					X	X	X	X
QOL (Parent)				X	X	X	X	X
Life Events (Child/Adolescent)				X	X	X		
Monitoring the Future (14+)						X	X	X
Family Environment								
Demographics -Household & Family Demographics -Subject Demog./Neuropsych. Assess.				X	X	X	X	X
Caregiver Health				X	X	X	X	X

Note: The 4-year visit table is grayed out to indicate that all visits at this time point have been completed.

5 YEAR VISIT								
	7 yrs	8-9 yrs	10 yrs	11 yrs	12 yrs	13-15 yrs	16 yrs	**17 yrs**
Risk Behavior								
Sex and Drugs: ACASI					X	X	X	X
Adherence (caregiver & child/adolescent)					X	X	X	X
Neurodevelopment								
WIAT-II					X	X	X	X
BRIEF (Child/Adolescent					X	X	X	X
BRIEF (Parent)					X	X	X	X
Executive Functioning Color Trails (8-16) Trailmaking **(≥ 17 and < 18)**					X	X	X	X
ABAS-II (Parent)					X	X	X	X
WISC-IV Working Memory and Processing Speed subtests[1]					**X**	**X**	**X**	
WAIS-IV Working Memory and Processing Speeds subtests[1,2]								**X**
Mental Health								
Caregiver Functioning								
CDQ					X	X	X	X
Family Environment								
Demographics -Household & Family Demographics -Subject Demog./Neuropsych. Assess.					X	X	X	X
PCRI					X	X		
Caregiver Health					X	X	X	X

[1] **Complete the following subtests: (1) Working Memory: Digit Span, Letter-Number Sequencing, Arithmetic; and (2) Processing Speed: Coding, Symbol Search, Cancellation.**

[2] **For participants who are primarily Spanish speaking and whose parental/family heritage is Puerto Rican,** complete the following **EIWA-III** subtests: (1) Working Memory: Digit Span, Letter-Number Sequencing, Arithmetic; and (2) Processing Speed: Coding, Symbol Search. **For participants who are primarily Spanish speaking and are of Mexican or other non-Puerto Rican heritage, do not administer the WAIS-IV subtests.**

Note: The 5-year visit table is grayed out to indicate that all visits at this time point have been completed.

6 YEAR VISIT								
	7 yrs	**8-9 yrs**	**10 yrs**	**11 yrs**	**12 yrs**	**13-15 yrs**	**16 yrs**	**17 yrs**
Risk Behavior								
Sex and Drugs: ACASI						X	X	X
Adherence (caregiver & child/adolescent)						X	X	X
Mental Health								
BASC-2 (Child/Adolescent)						X	X	X
BASC-2 (Parent)						X	X	X
QOL (Adolescent)						X	X	X
QOL (Parent)						X	X	X
Life Events (Child/Adolescent)						X	.	
Monitoring the Future (14+)						X	X	X
Family Environment								
Demographics -Household & Family Demographics -Subject Demog./Neuropsych. Assess.						X	X	X
Caregiver Health						X	X	X

Note: The 6-year visit table is grayed out to indicate that all visits at this time point have been completed.

7 YEAR VISIT								
	7 yrs	**8-9 yrs**	**10 yrs**	**11 yrs**	**12 yrs**	**13-15 yrs**	**16 yrs**	**17 yrs**
Risk Behavior								
Sex and Drugs: ACASI						**X**	**X**	**X**
Adherence (caregiver & child/adolescent)						**X**	**X**	**X**
Neurodevelopment								
WIAT-II, Abbreviated: Word Reading, Numerical Operations and Spelling substets						**X**	**X**	**X**
BRIEF (Child/Adolescent)						**X**	**X**	**X**
BRIEF (Parent)						**X**	**X**	**X**
Executive Functioning Color Trails (8-16) Trailmaking (≥17 and < 18)						**X**	**X**	**X**
ABAS-II (Parent)						**X**	**X**	**X**
WISC-IV Working Memory and Processing Speed subtests[1]						**X**	**X**	
WAIS-IV Working Memory and Processing Speeds subtests[2]								**X**
Family Environment								

7 YEAR VISIT								
	7 yrs	8-9 yrs	10 yrs	11 yrs	12 yrs	13-15 yrs	16 yrs	17 yrs
Demographics **-Household & Family Demographics** **-Subject Demog./Neuropsych. Assess.**						X	X	X
Caregiver Health						X	X	X

[1] **For <17, WISC-IV: Working Memory subtests (Digit Span, Letter-Number Sequencing, Arithmetic) and Processing Speed subtests (Coding, Symbol Search, Cancellation).**

[2] For ≥ 17 and < 18, WAIS-IV: Working Memory subtests (Digit Span, Letter-Number Sequencing, Arithmetic) and Processing Speed subtests (Coding, Symbol Search, Cancellation). **Note: For participants ≥ 17 years and <18 years who are primarily Spanish speaking and whose parental/family heritage is Puerto Rican,** complete the following **EIWA-III** subtests: Working Memory (Digit Span, Letter-Number Sequencing, Arithmetic) and Processing Speed (Coding, Symbol Search). **For participants who are primarily Spanish speaking and of Mexican or other non-Puerto Rican heritage, do not administer the WAIS-IV subtests.**

8 YEAR VISIT								
	7 yrs	8-9 yrs	10 yrs	11 yrs	12 yrs	13-15 yrs	16 yrs	17 yrs
Risk Behavior								
Sex and Drugs: ACASI						X	X	X
Adherence **(caregiver & child/adolescent)**						X	X	X
Mental Health								
BASC-2 (Child/Adolescent)						X	X	X
BASC-2 (Parent)						X	X	X
QOL (Adolescent)						X	X	X
QOL (Parent)						X	X	X
Life Events (Child/Adolescent)						X		
Monitoring the Future (14+)						X	X	X
Caregiver Functioning								
CDQ						X	X	X
Family Environment								
Demographics **-Household & Family Demographics** **-Subject Demog./Neuropsych. Assess.**						X	X	X
PCRI						X		
Caregiver Health						X	X	X

9 YEAR VISIT	7 yrs	8-9 yrs	10 yrs	11 yrs	12 yrs	13-15 yrs	16 yrs	17 yrs
Risk Behavior								
Sex and Drugs: ACASI							X	X
Adherence (caregiver & child/adolescent)							X	X
Neurodevelopment								
WIAT-II, Abbreviated: Word Reading, Numerical Operations and Spelling subtests							X	X
BRIEF (Child/Adolescent)							X	X
BRIEF (Parent)							X	X
Executive Functioning Color Trails (8-16) Trailmaking (≥ 17 and < 18)							X	X
WISC-IV Working Memory and Processing Speed subtests[1]							X	
WAIS-IV Working Memory and Processing Speeds subtests[2]								X
Family Environment								
Demographics -Household & Family Demographics -Subject Demog./Neuropsych. Assess.							X	X
Caregiver Health							X	X

[1] For < 17, WISC-IV: Working Memory subtests (Digit Span, Letter-Number Sequencing, Arithmetic) and Processing Speed subtests (Coding, Symbol Search, Cancellation)

[2] For ≥ 17 and < 18, WAIS-IV: Working Memory subtests (Digit Span, Letter-Number Sequencing, Arithmetic) and Processing Speed subtests (Coding, Symbol Search, Cancellation). Note: For participants ≥ 17 years and < 18 years who are primarily Spanish speaking and whose parental/family heritage is Puerto Rican, complete the following EIWA-III subtests: Working Memory (Digit Span, Letter-Number Sequencing, Arithmetic) and Processing Speed (Coding, Symbol Search). For participants who are primarily Spanish speaking and of Mexican or other non-Puerto Rican heritage, do not administer the WAIS-IV subtests.

10 YEAR VISIT	7 yrs	8-9 yrs	10 yrs	11 yrs	12 yrs	13-15 yrs	16 yrs	17 yrs
Risk Behavior								
Sex and Drugs: ACASI								X
Adherence (caregiver & child/adolescent)								X
Mental Health								
BASC-2 (Child/Adolescent)								X
BASC-2 (Parent)								X
QOL (Adolescent)								X
QOL (Parent)								X
Monitoring the Future (14+)								X
Caregiver Functioning								

10 YEAR VISIT								
	7 yrs	8-9 yrs	10 yrs	11 yrs	12 yrs	13-15 yrs	16 yrs	17 yrs
WASI[1]								X
Family Environment								
Demographics -Household & Family Demographics -Subject Demog./Neuropsych. Assess.								X
Caregiver Health								X

[1] Complete if never completed by caregiver during AMP participation.

APPENDIX VIII
Pediatric HIV/AIDS Cohort Study 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 written 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 written 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.

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 (PAMAB), 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

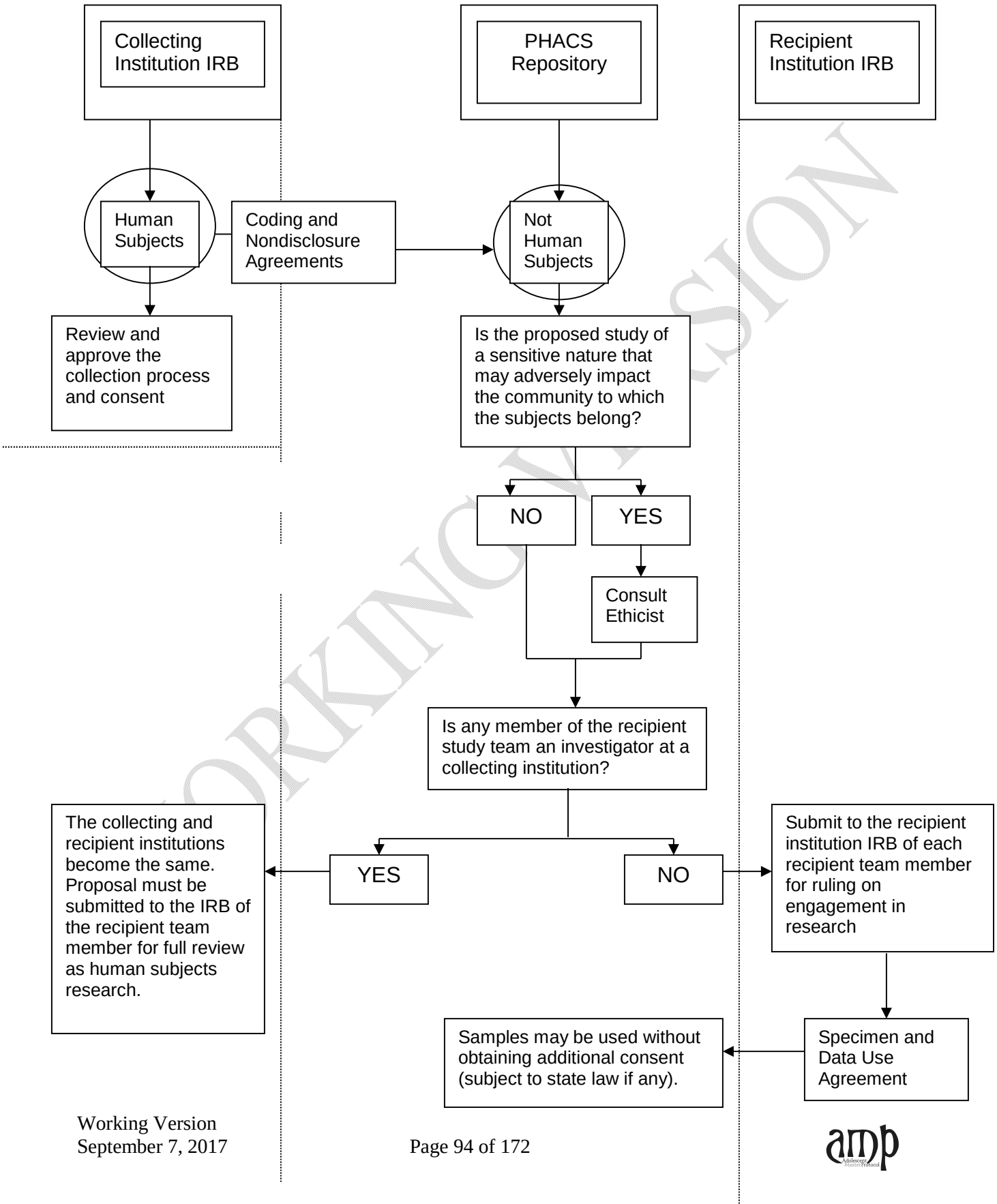
Prior to accessing specimens stored in the PHACS Repository, the following procedure must be followed:

- 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 (PAMAB) the Repository Policy Adherence and Specified Data Use Agreement;
- Once the proposal is approved, NICHD (PAMAB) 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. Oversight of the PHACS Repository Activities



Attachment A

PHACS Repository Policy Adherence and Non-disclosure 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 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

Attachment C (Revised November 13, 2013)

(Note:Saliva collection for the study was discontinued as of May 10, 2017 per Clarification Memo (CM) #13, however this template consent form remains unchanged given that the removal of saliva collection does not impact the risk/benefit ratio for study participants.)

FACT SHEET and TEMPLATE CONSENT FORM for Specimen Storage at PHACS Repository

Template Permission Form for Parent/Legal Guardian

Your child has been participating in the AMP study. We are asking for you to agree to allow some specimens that the doctor or nurse will take from your **child's** body to be stored in a repository. A repository is a special lab with freezers where samples like blood, tissue cells and body fluids are kept. There are no names on these samples, only a special study number. The people who run the repository lab do not know your **child's** name. You can decide not to have your **child's** samples stored in the repository. Even if you agree to have them stored now, you can change your mind later and stop at any time.

Why have a repository?

As time goes by, laboratory tests may get better or new tests may be developed. Researchers may also find new, important questions that need to be answered that weren't identified at the start of the study. When study volunteers agree to put samples in the repository for future use, researchers can use these samples to take advantage of the new tests or answer the new questions. When they do this, more information is learned.

How will my child's privacy be protected?

Your **child's** rights and privacy will be protected in any new studies that use **his/her** samples. The only record that shows that **your child** is in AMP is locked away at the clinic where **he/she has his/her** study visits. It is kept separate from your **child's** health records.

The samples will have the same special study code used on your **child's** information in AMP. None of the samples or your **child's** study information will have **his/her** name on it. Only a few study staff at the clinic where your **child has his/her** study visits can link the special study code with **his/her** name.

Do I have to agree to store my child's samples in the repository?

No, you do not have to agree to store your **child's** samples in the repository for future tests in order **for him/her** to continue taking part in this study. **Your child** will not lose any benefits to which **he/she is** entitled if you **do** not **agree** to store **his/her** samples. If **your child** previously had samples stored, those samples will stay there and be used for testing. If you don't want them

to be used, you must tell the clinic staff. Even if they aren't used for testing, **your child's** samples will stay in the repository unless you ask us to remove them.

What if I give permission now to store my child's samples in the repository but then change my mind?

You can agree to have **your child's** samples stored now and change your mind later. Again, at that time, if you don't want the samples that were already collected used for testing, you must tell the clinic staff. Even if they aren't used for testing, **your child's** samples will stay in the repository unless you also ask us to remove them.

How would a researcher get to use the samples in the repository?

If a researcher wants to do a test on samples from the PHACS repository, he or she will write up the idea. A committee will review the idea to make sure that the research is worthwhile. If the idea is approved, then coded samples and coded information will be given to the researcher. The researcher will not know your **child's** name, address or phone number.

Will I find out the results of research using my **child's samples?**

No, you will not receive the results of research done with your **child's** samples. This is because research can take a long time. Your **child's** samples can stay in the freezer for many years. There is no time limit to when studies could be done in the future. This means results from research using your **child's** samples may not be ready for many years. When studies are first done, it is not always clear how the information from the study can be used to change the health care that people receive. So the results from the study are unlikely to affect your **child's** care right now. They may be helpful to people like **your child** in the future.

Would I ever be contacted in the future about research using my **child's samples?**

POSSIBLY. You are being asked to agree that certain tests can be done **on your child's samples** in the future without anyone contacting you to ask permission. All of the studies done on **his/her** samples in the repository will likely be for the reasons that you agreed to now. Every study that plans to use repository samples from AMP will be reviewed by a committee. This is to determine if the planned study is the kind of study that you agreed to. If it is, then the study will go ahead since you agreed that these types of tests could be done **on your child's samples** without anyone contacting you to get your permission.

If the study to be done is not like the kind of tests you agreed to, then the committee will decide if you need to be contacted to give permission for the new study. If so, someone at your site will contact you. No one doing these tests would ever contact you or your **child's** doctor or nurse about the tests they are running.

What type of research will be done with my child's samples?

As part of the AMP study, you are being asked to **agree to** have some blood (no more than 3 tablespoons at a visit), saliva (spit), and urine collected **from your child**. Many different kinds of studies use these samples. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new tests or drugs. If this happens and these tests or drugs make money, there are no plans to share that money with the people who gave the samples.

What about samples from other studies my child has participated in?

Your child may have participated in IMPAACT, PACTG, WITS, the HIV Research Network or other Department of Health and Human Services (DHHS) funded pediatric HIV studies, and had repository samples stored in those studies. In the future, PHACS may have the opportunity to perform tests on samples collected **from your child** in those studies. We would like to get your permission now to do that.

What are the <u>general</u> studies that can be done with the repository samples?

The general studies that can be done will help researchers to understand if and how HIV infection and HIV drugs may cause disease and complications. They also want to figure out how to treat or prevent these complications. To do these studies, they need samples from children and young people who have HIV infection and those who do not but may have been exposed to HIV drugs before they were born. Sometimes the samples can be used to learn about new problems that children and young people with HIV infection have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your **child's** DNA or genes).

Benefits: There are no direct benefits to **your child**. You **and your child** will be helping researchers learn more about how to help other children and young people who have HIV infection.

Risks: The samples would be collected as part of your **child's** study visits. Blood and urine would be collected no more than once a year. Once the samples are in the repository, there are few risks. Your **child's** name will not be available to the repository or to the scientists who may be doing any future test.

I agree to have samples collected **from my child** during the AMP study to use for the purposes stated in the above section (general tests).

☐ Yes, I agree

☐ No, I refuse

_____
Participant's Name (print)

_____	_____	_____
Parent/Legal Guardian Name (print)	Parent/Legal Guardian Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date
_____	_____	_____
Study Staff Member Conducting IC Process (print)	Study Staff Member Conducting IC Process Signature	Date

I give permission for the use of my **child's** stored samples collected in IMPAACT, PACTG, WITS, the HIV Research Network, or other DHHS funded pediatric HIV studies: (*insert name of study*) for the purposes stated in the above section (general tests).

☐ Yes, I agree

☐ No, I refuse

☐ N/A (non-applicable – participant not on prior study)

_____		
Participant's Name (print)		
_____	_____	_____
Parent/Legal Guardian Name (print)	Parent/Legal Guardian Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date
_____	_____	_____
Study Staff Member Conducting IC Process (print)	Study Staff Member Conducting IC Process Signature	Date

What are the <u>special</u> studies that can be done with the repository samples?

The special studies that can be done will look at how to treat or prevent HIV disease and its complications through looking at each person's genetic makeup (DNA or genes). A person's genetic makeup can either protect them or put them at greater risk. To do these studies, researchers need samples from children and young people who have HIV infection and those who do not and may have been exposed to HIV drugs before they were born.

Benefits: There are no direct benefits to **your child**. You **and your child** will be helping researchers learn more about how to help children and young people with HIV infection.

Risks: The samples would be collected as part of your **child's** study visits. Blood and saliva (spit) would be collected no more than once a year. Once the samples are in the repository, there are few risks. Your **child's** name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored samples, you will not receive any information on your **child's** genetic makeup.

I agree to have samples collected **from my child** during the AMP study to use for the purposes stated in the above section (special tests).

☐ Yes, I agree

☐ No, I refuse

_____		
Participant's Name (print)]		
_____	_____	_____
Parent/Legal Guardian Name (print)	Parent/Legal Guardian Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date
_____	_____	_____
Study Staff Member Conducting IC Process (print)	Study Staff Member Conducting IC Process Signature	Date

I give permission for the use of my **child's** stored samples collected in IMPAACT, PACTG, WITS, the HIV Research Network, or other DHHS funded pediatric HIV studies: (*insert name of study)* for the purposes stated in the above section (special tests).

☐ Yes, I agree

☐ No, I refuse

☐ N/A (non-applicable – participant not on prior study)

_____		
Participant's Name (print)		
_____	_____	_____
Parent/Legal Guardian Name (print)	Parent/Legal Guardian Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date
_____	_____	_____
Study Staff Member Conducting IC Process (print)	Study Staff Member Conducting IC Process Signature	Date

What if I have more questions?

If you have any questions about the repository, about storage, or the use of your **child's** samples, contact (Study personnel) at (phone).

If you have questions about giving **permission** or your **child's** rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

Attachment D

FACT SHEET and TEMPLATE CONSENT FORM for Use of Mother's Stored Specimens from Previous Studies

CONSENT FORM FOR MOTHERS IN AMP

You and your child are participating in the AMP study. We are now asking for your consent to allow the AMP study researchers to use samples that were collected from you and stored in a repository in studies in which you participated in the past. A repository is a special lab with freezers where samples like blood, tissue cells and body fluids are kept. There are no names on these samples. There's only a special study code.

You may have participated in IMPAACT, PACTG, WITS, the HIV Research Network or other Department of Health and Human Services (DHHS) funded HIV studies, and had repository samples stored as part of those studies. As part of AMP, we may have the opportunity to perform tests on those samples to help us better understand what we will learn in AMP about your child. We would like to get your permission to use your samples for these tests. We want you to decide if you want your stored samples from previous studies to be used in AMP. We will answer any questions you may have.

Why have a repository?

As time goes by, laboratory tests may get better or new tests may be developed. Researchers may also find new, important questions that need to be answered that weren't identified at the start of the study. When study volunteers agree to put samples in the repository for future use, researchers can use these samples to take advantage of the new tests or answer the new questions. When they do this, more information is learned. By allowing the AMP study researchers to use your stored samples, we may be able to learn information about you that will help us better understand what we will learn about your child.

How will my privacy be protected?

Your rights and privacy will be protected in any studies that use your samples. The only record that shows that you have stored samples from previous studies you participated in is locked away at the clinic where you participated in the studies and had your study visits.

If you give us permission to use your samples, your samples and any information we learn will have a special study code. None of the samples or information we learn will have your name on it. Only a few study staff at the clinic where you had your study visits can link the special study code with your name.

Do I have to agree to allow AMP to use my stored samples from studies in which I previously participated?

No, you do not. You and your child may take part in AMP regardless of what you decide about your stored samples. You and your child will not lose any benefits to which you are entitled if you decide not to allow us to use your stored samples.

What if I give permission now for my stored samples to be used but then change my mind?

You can agree to allow us to use your samples now and change your mind later. At the time when you decide you don't want AMP to use your stored samples, you should tell the clinic staff. Even if they aren't used for testing, the samples will stay in the repository unless you specifically tell us to destroy them.

How would a researcher get to use the samples in the repository?

If a researcher wants to do a test on samples from the repository, he or she will write up the idea. A committee will review the idea to make sure that the research is worthwhile. If the idea is approved, then coded samples and coded information will be given to the researcher. The researcher will not know your name, address or phone number.

Will I find out the results of research using my samples?

No, you will not receive the results of research done with your samples. This is because research can take a long time. Your samples can stay in the freezer for many years. There is no time limit to when studies could be done in the future. This means results from research using your samples may not be ready for many years. When studies are first done, it is not always clear how the information from the study can be used to change the health care that people receive. So the results from the study are unlikely to affect you or your child's care right now. They may be helpful to people like you and your child in the future.

Would I ever be contacted in the future about research using my samples?

POSSIBLY. You are being asked to agree that certain tests can be done in the future without anyone contacting you to ask permission. All of the studies done on your samples in the repository will likely be for the reasons that you agreed to now. Every study that plans to use repository samples from AMP will be reviewed by a committee. This is to determine if the planned study is the kind of study that you agreed to. If it is, then the study will go ahead since you agreed that these types of tests could be done without anyone contacting you to get your permission.

If the study to be done is not like the kind of tests you agreed to, then the committee will decide if you need to be contacted to give permission for the new study. If so, someone at your site will

contact you. No one doing these tests would ever contact you or your doctor or nurse about the tests they are running.

What type of research will be done with my samples?

As part of the AMP study, you are being asked to allow the AMP researchers to use your stored samples from previous studies in which you participated. Many different kinds of studies may use these samples. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new tests or drugs. If this happens and these tests or drugs make money, there are no plans to share that money with the people who gave the samples.

What are the <u>general</u> studies that can be done with the repository samples?

The general studies that can be done will help researchers to understand if and how HIV infection and HIV drugs may cause disease and complications. They also want to figure out how to treat or prevent these complications. To do these studies, they need samples from mothers of children and young people who have HIV infection and those who do not but may have been exposed to HIV drugs before they were born. Sometimes the samples can be used to learn about new problems that children and young people with HIV infection have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your DNA or genes).

Benefits: There are no direct benefits to you or to your child. You will be helping researchers learn more about how to help children and young people who have HIV infection.

Risks: There is little risk. The requested samples and any information we learn will have a special study code. You and your child's name will not be on the samples or any information we learn. Your name, address, telephone number will not be available to the repository or to the scientists who may be doing any future test.

I give permission for the use of my stored samples collected in IMPAACT, PACTG, WITS, the HIV Research Network, or other DHHS funded HIV studies: (*<u>insert name of study</u>)* for the purposes stated in the above section (general tests).

☐ Yes, I agree ☐ No, I refuse ☐ N/A (non-applicable)

_____	_____	_____
Participant Name (print)	Participant Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date
_____	_____	_____
Study Staff Member Conducting IC Process (print)	Study Staff Member Conducting IC Process Signature	Date

What are the special studies that can be done with the repository samples?

The special studies that can be done will look at how to treat or prevent HIV disease and its complications through looking at each person's genetic makeup (DNA or genes). A person's genetic makeup can either protect them or put them at greater risk of being infected with HIV or having complication of HIV. To do these studies, researchers need samples from mothers of children and young people who have HIV infection and those who do not and may have been exposed to HIV drugs before they were born.

Benefits: There are no direct benefits to you or to your child. You will be helping researchers learn more about how to help children and young people with HIV infection.

Risks: There is little risk. The samples and any information we learn will have a special study code. You and your child's name will not be on the samples or any information we learn. Your name, address, telephone number will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored samples, you will not receive any information on your genetic makeup.

I give permission for the use of my stored samples collected in IMPAACT, PACTG, WITS, the HIV Research Network, or other DHHS funded HIV studies: (*insert name of study)* for the purposes stated in the above section (special tests).

☐ Yes, I agree ☐ No, I refuse ☐ N/A (non-applicable)

_____	_____	_____
Participant Name (print)	Participant Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date
_____	_____	_____
Study Staff Member Conducting IC Process (print)	Study Staff Member Conducting IC Process Signature	Date

What if I have more questions?

If you have any questions about the repository, about storage, or the use of your samples, contact (Study personnel) at (phone).

If you have questions about giving consent or your rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

APPENDIX IX.A (REVISED NOVEMBER 13, 2013)

Sample Permission Form for Parent/Legal Guardian: Participation in Study Cohort

(Note: The point-of-care (POC) lactate test was discontinued as of August 6, 2015 per Clarification Memo (CM) #10 and saliva collection was discontinued as of May 10, 2017 per CM #13. However, this sample consent form remains unchanged given that these changes do not impact the risk/benefit ratio for study participants.)

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 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 (AMP), Version 4.0

PRINCIPAL INVESTIGATOR: _____

PHONE: _____

Your child has been participating in the AMP study. We are asking **for your child** to continue to participate in this research study. We want to tell you about AMP and answer questions you have so that you can decide if you want **your child** to continue being in the study. You can decide not to **have your child** continue in the study. Even if you agree to **have your child** continue in the study now, you can change your mind later and **have your child** stop being in the study at any time.

What will my child need to do?

We are asking **for your child** to continue to be in a research study that will try to better understand how HIV infection and the medications used to treat HIV affect the growth and development of people infected since birth. We want to see if there are any problems with how children grow and develop in their teens and into adulthood.

Why is my child being asked to participate?

We are asking for **your child** to help with this research because:

- **Your child was** between 7 and 16 years of age at study entry;
- Your **child's** medical record shows that **he/she has** been HIV-infected since birth; and
- **Your child is** already participating in the study **and is under 18 years of age**.

Why are you doing this research?

There are about 10,000 children in the United States who have been living with HIV infection since birth and taking HIV medications for most of their lives. Little is known about the effects of HIV infection and its treatment on the growth and development of these children. Children with HIV face challenges related to their health, well-being, and development such as how they do in school and get along with other children. For adolescents and young adults coping with HIV, little is known about how or when they make decisions about continued education, work, family, sexual behavior, and alcohol or drug use. In this study, we will try to find out the effects of HIV infection and its treatment on children, adolescents and young adults. We will use the information to develop ways to improve the quality of life for this group of young people.

Does my child have to be in this research study?

No, you can decide not to **let your child** be in this research study.

You make the decision about **your child** being in the research study using the information in this informed consent form and talking to our research staff.

If you decide to **let your child** be in the research study, we will ask you to sign this form. Signing this form shows that you got this information and that you want **your child** to be in the research study. You will get a copy of the signed paper to keep

Even if you agree to **let your child** be in the research study now and sign this form, you can still change your mind later and stop **your child from** being in the study at any time.

Your child will get **his/her** regular health care at **his/her** regular clinic no matter what you decide.

What will happen to my child in this study?

Your child will have the following kinds of exams:

- We will check your **child's** medical records to see how **your child has** been doing with **his/her** regular exams/care.

- We will look at the kinds of HIV medications **your child has** been taking and how well **he/she is** able to take them.
- We will ask about your **child's** diet and physical activity.
- We will collect information on your **child's** family: for example, if family members have high blood pressure, diabetes, or heart disease.
- We will record your **child's** physical exam. We will check your **child's** height and weight, measure parts of **his/her** body, and see how far **your child has** matured.
- DXA (dual energy x-ray absorptiometry) scans will be done. This is a type of x-ray to measure how strong the bones are. For these DXA scans, **your child's** will be asked to lie down on a table with **his/her** hand palms down next to the body. The scan will take about 30 minutes. It will not cause **your child** any pain. **No more than three** DXA scans **will** be done with at least 2 years between the scans.
- **Your child** will also have an x-ray of **his/her** wrist to see if the bone shows that **your child is** still growing. This x-ray will be done at the same time when the DXA scan is done unless **your child has** stopped growing.
- **Your child** will be asked questions to see how well **he/she is** thinking, feeling, solving problems, using words to express **himself/herself, and managing daily life tasks**. These questions will be asked by a **psychologist or** trained interviewer in private.
- If **your child is** 10 years of age or older, **your child** will also be asked some questions about use of alcohol and drugs and sexual behavior. These questions will be asked using an ACASI (**A**udio **C**omputer-**A**ssisted **S**elf-**I**nterview). ACASI uses a computer and voice recordings so **your child can** hear (through headphones) and see (on the screen) each question and the answer choices for that question. **Your child enters his/her** answer right into the computer. When the interview is over, the computer "locks in" your **child's** answers so no one at the clinic can see them. The interview is set up to ask simple questions first. These questions can tell if **your child has not** started to have sex or use drugs or alcohol. **Your child** will not be asked any more questions about sex, drugs or alcohol if your **child's** answers to the simple questions show **he/she hasn't** done these things.
- We will test your **child's** blood to see if routine things like the number of cells and the blood's makeup is normal. We will take no more than two tablespoons of blood from a vein in your **child's** arm at each visit. For one test we will prick your **child's** finger to take blood.
- We will also collect your **child's** urine to check for levels of glucose, protein, blood, and other chemicals.
- We will also test your **child's** hearing.
- We will check your **child's** medical records for results of screenings for sexually transmitted infections (STIs) done as part of routine care. In addition, if **your child is** female and **receives** gynecologic (GYN) exams with PAP smears as part of routine care, we will review the results from **her** medical records. We will ask you to sign a form to

allow this hospital to release samples collected during the exam to the AMP researchers for review.

Some abnormal test results will need us to do additional studies. If that happens, we will come to you again to tell you everything you need to know and get your permission to go ahead.

We will also store some of your **child's** blood, saliva, and urine for tests in the future. This will be explained in another paper and we will ask for your permission separately.

How often will my child have these visits? Will all visits include the exams just described?

Your **child** will come into the clinic once every year **until he/she turns 18 years old**. All visits will have the same kind of exams that were just explained. However, not all of them will be performed at every visit. We will try to keep visits from taking more than a few hours.

How many children will be in this study?

We enrolled 451 HIV-infected children born to HIV-infected mothers in this study and are following them. We also enrolled 227 HIV-uninfected children born to HIV-infected mothers and are following them.

How long will this study last?

This study is planned to last at least 4 years.

What if I decide to take my child out of the study?

You can always decide to take **your child** out of the study. If you make this decision, it will not change any benefits at the clinical site that **your child is** entitled to. Your **child's** care at the clinical site will not be affected.

What kinds of bad things could happen to my child?

The blood tests may hurt a little. **Your child** might feel a little pain, have some bleeding, or a bruise where the needle enters the skin to draw the blood from **his/her** arm. Sometimes people feel like they might faint. In one test we will prick your **child's** finger to take blood. In a small number of cases, we may have to do it more than once.

Your child will have to fast (not eat) for some of the blood tests. This shouldn't be for more than 8 hours and **your child** can have sips of water during fasting. Sometimes people feel like they might faint when they have been fasting.

Your child may get tired or feel uncomfortable, embarrassed or upset with the questions asking about **his/her** thoughts and feelings, use of alcohol and drugs, and sexual behavior.

If **your child has** a DXA scan, **he/she** will be exposed to a small amount of radiation. The amount of radiation from this procedure is approximately 5% the amount of natural radiation a person receives each year. The risk from this radiation exposure is too small to measure.

If **your child has** a wrist x-ray, **he/she** will be exposed to a small amount of radiation.

What kinds of good things could come from being in this study?

This study will look at the effects of HIV infection and HIV medications on your **child's** development and growth. It is possible that you **and your child** will get nothing **yourselves** out of taking part. You **and your child** will be helping to develop new treatments or programs for other children and teens infected with HIV.

There will be some evaluations that might help you make sure **your child is** growing and developing as **he/she** should. This is information that can reassure you if the exams are normal. It can also help you decide to seek new services **for your child** if the exams are not normal.

*If you give us permission, we will share the medical information from this study with your **child's** doctor to guide the health care **your child receives**.

What will I and/or my child be told about the study?

If we learn anything during the study that might make you change your mind about **letting your child** staying in it, we will let you know as soon as possible.

At the end of the study, we will tell you when the study results will be ready and how to learn about them.

What are the alternatives to participating in this study?

You may choose not to **let your child continue in** this study. You can **have him/her** stop **being in the study** at any time. Whether you **let your child stay in the study** or not, your decision will not affect your **child's** regular health care at **his/her** regular clinic. If you decide not to **let your child be in** this research study, **he/she** will receive standard clinical care outside of this study. Your decision will not affect your **child's** participation in other studies **he/she** may be enrolled in now or would like to enroll in the future.

Could my child be asked to leave the study before it ends even if I don't want to leave?

Your child could be asked to leave the study for the following reasons:

- **Your child** cannot keep study appointments when **he/she is** supposed to;

- The site investigator determines that further participation could be harmful to your **child's** health or well-being.
- The study is stopped by the agency doing 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 decide to take **your child** out of the study early, your **child's** health information that has already been collected may be used or released as needed for this study or any follow-up activities related to the study. If **your child is** removed from the study the research staff will explain why **your child was** removed and also explain the options that are available to **your child**.

Will being in this study cost me any money?

You will not have to pay for any study visits, physical exams, or tests that are done in the study.

You or your child's insurance company will have to pay for any treatment or exams done for **his/her** medical care outside the study.

Will my child be paid for taking part in this study?

Your child (will/will not) be compensated for the study. (Site enters compensation type and/or payment, if applicable.)

Who will know about my child being in this study and about the information you get about my child during the study?

- If the results of this research are published or presented, only group information will be given. Your **child's** name will not be used.
- Your **child's** research records, including lab tests, will be kept confidential, unless the law says some information must be shared. For example, we must report if **your child tells** us that **he/she is** planning on hurting **himself/herself** or others. Otherwise, your **child's** personal information will not be released without your written permission.
- We have a paper from the government, saying that we do not have to share information about people in this study with state, federal or civil courts. If you want to share the research information with someone, like your **child's** doctor or an insurance company, then we will do that. We will not share your **child's** information with someone unless you tell us to in writing. Some of the information **your child tells** us will not be shared with your **child's** doctor without your **child's** permission. This includes information on how well **your child takes his/her** medications, how **he/she feels** about **his/her** life and future, and **his/her** mental health. This paper does not prevent us from reporting suspected or known sexual or physical abuse, or if we feel that there is a significant risk

of harming others. Such information will be reported to the appropriate authorities. Also, any evidence of threatened suicide or threatened violence by **your child** to **himself/herself** or others will be reported to a member of the research staff. We will make every effort to maintain **your child's** confidentiality, unless any of the above situations are suspected.

- The information we get from **your child**, including lab tests, will be stored under a code number, not under your **child's** name. The link between the code number and your **child's** name is locked away. It can only be seen by the research staff.
- However, some people will look at study records and may see your **child's** name. These people may be from the agency doing the research, the site's Institutional Review Board (IRB), the National Institutes of Health (NIH), the Office of Human Research Protection (OHRP), or from Westat, a research group helping the NIH to run this study.
- If the study staff at this site lose contact with you, they will confidentially give your **child's** name, sex, date and city of birth to Westat. Westat will conduct a computer match with health department records to check your **child's** status. As soon as the computer match is finished, your **child's** information will be destroyed. This match will only happen if you and the research staff lose contact. The computer match is private and will be kept secret. It will not be used to find you **or your child**.

What will happen to the information on my child that was collected in WITS, PACTG studies like PACTG 219, and (*insert study*)?

It is important to this study to have as complete a picture of your **child's** health that we can get. Information collected already in studies like WITS, PACTG studies like PACTG 219, and (*insert study*) would be very useful in this study. We have made an arrangement with those studies to work together. If **your child was** on those studies, we need your permission for us to use that information. You will be asked to give us that permission.

*INCLUDE FOLLOWING IF THE CDC LEGACY STUDY IS BEING OR WAS CONDUCTED AT THE SITE:

There is also another study sponsored by the CDC, called LEGACY, which looks at some of the same things as AMP. If **your child is** enrolled in both studies, we want to be able to make it easier for **your child** and for our staff by doing the things required by both studies just one time. We will ask your permission for the AMP study and LEGACY study to share your **child's** information. This way, we don't have to ask **your child** or our staff to do things twice.

What happens if my child gets hurt from being in the study?

If **your child is** hurt as a result of being in this study, the (insert the name of the clinic) will give **your child** any treatment **he/she needs** right away. The cost of this treatment will be charged to **you or your child's** insurance company. Your clinic will then tell you **or your child** where you can get more treatment, if **he/she needs** it. No payment will be made to you **or your child** either by the research clinic or the agency that is sponsoring this research.

Who can I call for information about this study?

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

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

There is a group of doctors and researchers whose job it is to see that research is done carefully. They also ensure that people in research are treated fairly and made as safe as possible. If you have any questions about these things, you can call (name and title of IRB member), who is a member of this group, at (telephone number).

Statement of consent:

Information about this study has been given to you. You have had a chance to ask any questions you have about the study. We have told you that it is your decision whether or not to **let your child** be in the study. **Your child** should be in the research study only if you want **him/her** to be. You can decide not to **let your child** be in the study. You can change your mind about **your child** being in the study without changing your **child's** care at this hospital or changing the way people who work for the hospital treat **your child**. If, at this time, you voluntarily agree to **let your child** take part 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.)

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

_____
Participant's Name (print)

_____	_____	_____
Parent/Legal Guardian Name (print)	Parent/Legal Guardian Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date
_____	_____	_____
Study Staff Member Conducting IC Discussion (print)	Study Staff Member Conducting IC Discussion Signature	Date

SIGNATURES TO SHARE STUDY INFORMATION WITH YOUR DOCTOR
(This is only a suggested Signature format. Sites may use their own signature page.)

If you have read the informed consent (or if you have had it explained to you) and understand the information, and you want the medical information from the study to be shared with your **child's** doctor, please sign your name below.

I give permission for medical information from this study to be shared with my **child's** doctor.

☐ Yes, I agree ☐ No, I refuse

_____
Participant's Name (print)

_____	_____	_____
Parent/Legal Guardian Name (print)	Parent/Legal Guardian Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date
_____	_____	_____
Study Staff Member Conducting IC Discussion (print)	Study Staff Member Conducting IC Discussion Signature	Date

SIGNATURES TO USE STUDY INFORMATION COLLECTED ON YOU IN WITS, PACTG STUDIES LIKE PACTG 219, or (*insert study number*)

If you have read the informed consent (or if you have had it explained to you) and understand the information, and if **your child was** in WITS, PACTG studies like 219, or (*insert study number*) and you want the research staff to be able to use information already collected on **your child** to help this study, please sign your name below.

I give permission for information collected from **my child** in the studies stated above to help this study.

☐ Yes, I agree ☐ No, I refuse ☐ N/A (non-applicable)

_____
Participant's Name (print)

_____	_____	_____
Parent/Legal Guardian Name (print)	Parent/Legal Guardian Signature	Date

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

SIGNATURES TO SHARE STUDY INFORMATION COLLECTED ON YOUR CHILD IN AMP AND LEGACY

If you have read the informed consent (or if you have had it explained to you) and understand the information, and you want the research staff to be able to share information collected in AMP and LEGACY studies to make it easier on **your child** and our staff, please sign your name below.

I give permission for information collected from **my child** in AMP and LEGACY to be shared.

☐ Yes, I agree ☐ No, I refuse ☐ N/A (non-applicable)

Participant's Name (print)

Parent/Legal Guardian Name (print)	Parent/Legal Guardian Signature	Date
Witness Name (print)	Witness Signature	Date
Study Staff Member Conducting IC Discussion (print)	Study Staff Member Conducting IC Discussion 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 IX.B (REVISED NOVEMBER 13, 2013)

Sample Permission Form for Parent/Legal Guardian: Participation in Control Cohort

(Note: The point-of-care (POC) lactate test was discontinued as of August 6, 2015 per Clarification Memo (CM) #10 and saliva collection was discontinued as of May 10, 2017 per CM #13. However, this sample consent form remains unchanged given that these changes do not impact the risk/benefit ratio for study participants.)

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 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 (AMP), Version 4.0

PRINCIPAL INVESTIGATOR: _____

PHONE: _____

Your child has been participating in the AMP study. We are asking **for your child** to continue to participate in this research study. We want to tell you about AMP and answer questions you have so that you can decide if you want **your child** to continue being in the study. You can decide not to **have your child** continue in the study. Even if you agree to **have your child** continue in the study now, you can change your mind later and **have your child** stop being in the study at any time.

What will my child need to do?

We are asking for **your child** to continue to be in a research study that will try to better understand how HIV infection and the medications used to treat HIV affect the growth and development of people infected since birth. We want to see if there are any problems with how children grow and develop in their teens and into adulthood. **Your child** is not infected with HIV. The study needs individuals who are not infected in the study so we can compare the information we learn.

Why is my child being asked to participate?

We are asking for **your child** to help with this research because:

- **Your child was** between 7 and 16 years of age at study entry;
- Your **child's** medical record shows that **he/she** was not infected with HIV at birth; and
- **Your child is** already participating in the study **and is under 18 years of age**.

Why are you doing this research?

There are about 10,000 children in the United States who have been living with HIV infection since birth and taking HIV medications for most of their lives. Little is known about the effects of HIV infection and its treatment on the growth and development of these children. Children with HIV face challenges related to their health, well-being, and development such as how they do in school and get along with other children. For adolescents and young adults coping with HIV, little is known about how or when they make decisions about continued education, work, family, sexual behavior, and alcohol or drug use. In this study, we will try to find out the effects of HIV infection and its treatment on children, adolescents and young adults. We will use the information to develop ways to improve the quality of life for this group of young people. To do this, we need children and teens who are infected with HIV and those who are not.

Does my child have to be in this research study?

No, you can decide not to **let your child** be in the research.

You make the decision about **your child** being in the research study using the information in this informed consent form and talking to our research staff.

If you decide to **let your child** be in the research study, we will ask you to sign this form. Signing this form shows that you got this information and that you want **your child** to be in the research study. You will get a copy of the signed paper to keep

Even if you agree to **let your child** be in the research study now and sign this form, you can still change your mind later and stop **your child from** being in the study at any time.

Your child will get **his/her** regular health care at **his/her** regular clinic no matter what you decide.

What will happen to my child in this study?

Your child will have the following kinds of exams:

- We will check your **child's** medical records to see how **he/she has** been doing with regular exams/care.
- We will record your **child's** physical exam. We will check your **child's** height and weight, measure parts of **his/her** body, and see how far **your child has** matured.
- **Your child** will be asked questions to see how well **he/she is** thinking, feeling, solving problems, using words to express **himself/herself, and managing daily life tasks**. These questions will be asked by a **psychologist or** trained interviewer in private.
- If **your child is** 10 years of age or older, **your child** will also be asked some questions about **his/her** use of alcohol and drugs and sexual behavior. These questions will be asked using an ACASI (**A**udio **C**omputer-**A**ssisted **S**elf-**I**nterview). ACASI uses a computer and voice recordings so **your child can** hear (through headphones) and see (on the screen) each question and the answer choices for that question. **Your child enters his/her** answer right into the computer. When the interview is over, the computer "locks in" your **child's** answers so no one at the clinic can see them. The interview is set up to ask simple questions first. These questions can tell if **your child has** not started to have sex or use drugs or alcohol. **Your child** will not be asked any more questions about sex, drugs or alcohol if **his/her** answers to the simple questions show **he/she hasn't** done these things.
- We will test your **child's** blood to see if the blood's makeup is normal. We will take no more than one tablespoon of blood from a vein in your **child's** arm at each visit. For one test we will prick **his/her** finger to take blood.
- We will also collect your **child's** urine to check for levels of glucose, protein, blood, and other chemicals.
- We will also test your **child's** hearing.
- We will check your **child's** medical records for results of screenings for sexually transmitted infections (STIs) done as part of routine care. In addition, if **your child is** female and **receives** gynecologic (GYN) exams with PAP smears as part of routine care, we will ask you to sign a form to allow this hospital to release samples collected during the exam to the AMP researchers for review.

Some abnormal test results will need us to do additional studies. If that happens, we will come to you again to tell you everything you need to know and get your permission to go ahead.

We will also store some of your **child's** blood, saliva, and urine for tests in the future. This will be explained in another paper and we will ask for your permission separately.

How often will my child have these visits? Will all visits include the exams just described?

Your **child** will come into the clinic once every year **until he/she turns 18 years old**. All visits will have the same kind of exams that were just explained. However, not all of them

will be performed at every visit. We will try to keep visits from taking more than a few hours.

How many children will be in this study?

We enrolled 451 HIV-infected children born to HIV-infected mothers in this study and are following them. We also enrolled 227 HIV-uninfected children born to HIV-infected mothers and are following them.

How long will this study last?

This study is planned to last at least 4 years.

What if I decide to take my child out of the study?

You can always decide to take **your child** out of the study. If you make this decision, it will not change any benefits at the clinical site that **your child is** entitled to. Your **child's** care at the clinical site will not be affected.

What kinds of bad things could happen to my child?

The blood draw for the storage may hurt a little. **Your child** might feel a little pain; have some bleeding, or a bruise where the needle enters the skin to draw the blood from **his/her** arm. Sometimes people feel like they might faint. In one test we will prick your **child's** finger to take blood. In a small number of cases, we may have to do it more than once.

Your child will have to fast (not eat) for some of the blood tests. This shouldn't be for more than 8 hours and **your child** can have sips of water during fasting. Sometimes people feel like they might faint when they have been fasting.

Your child may get tired or feel uncomfortable, embarrassed or upset with the questions asking about **his/her** thoughts and feelings, use of alcohol and drugs, and sexual behavior.

What kinds of good things could come from being in this study?

This study will look at the effects of HIV infection and HIV medications on the development and growth of children infected with HIV. It is possible that you **and your child** will get nothing **yourselves** out of taking part. You **and your child** will be helping to develop new treatments or programs for children and teens infected with HIV.

There will be some evaluations that might help you make sure **your child is** growing and developing as **he/she** should. This is information that can reassure you if the exams are normal. It can also help you decide to seek new services **for your child** if the exams are not normal.

*If you give us permission, we will share medical information from this study with your **child's** doctor to guide the health care **your child receives**.

What will I and/or my child be told about the study?

If we learn anything during the study that might make you change your mind about **letting your child stay** in it, we will let you know as soon as possible.

At the end of the study, we will tell you when the study results will be ready and how to learn about them.

What are the alternatives to participating in this study?

You may choose not to **let your child continue in** this study. You can **have him/her** stop **being in the study** at any time. Whether you **let your child stay in the study** or not, your decision will not affect your **child's** regular health care at **his/her** regular clinic. If you decide not to **let your child continue in** this research study, **your child** will receive standard clinical care outside of this study. Your decision will not affect your **child's** participation in other studies **he/she** may be enrolled in now or would like to enroll in the future.

Could my child be asked to leave the study before it ends even if I don't want to leave?

Your child could be asked to leave the study for the following reasons:

- **Your child** cannot keep study appointments when **he/she is** supposed to;
- The site investigator determines that further participation could be harmful to your **child's** health or well-being.
- The study is stopped by the agency doing 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 decide to take **your child** out of the study early, **his/her** health information that has already been collected may be used or released as needed for this study or any follow-up activities related to the study. If **your child is** removed from the study, the research staff will explain why **he/she was** removed and also explain the options that are available to **your child**.

Will being in this study cost me any money?

You will not have to pay for any study visits, physical exams, or tests that are done in the study.

You or your child's insurance company will have to pay for any treatment or exams done for **his/her** medical care outside the study.

Will my child be paid for taking part in this study?

Your child (will/will not) be compensated for the study. (Site enters compensation type and/or payment, if applicable.)

Who will know about my child being in this study and about the information you get about my child during the study?

- If the results of this research are published or presented, only group information will be given. Your **child's** name will not be used.
- Your **child's** research records, including lab tests, will be kept confidential, unless the law says some information must be shared. For example, we must report if **your child tells** us that **he/she is** planning on hurting **himself/herself** or others. Otherwise, your **child's** personal information will not be released without your written permission.
- We have a paper from the government, saying that we do not have to share information about people in this study with state, federal or civil courts. If you want to share the research information with someone, like your **child's** doctor or an insurance company, then we will do that. We will not share your **child's** information with someone unless you tell us to in writing. Some of the information **your child tells** us will not be shared with **you or** your **child's** doctor without your **child's** permission. This includes information on how well **your child takes his/her** medications, how **he/she feels** about **his/her** life and future, and **his/her** mental health. This paper does not prevent us from reporting suspected or known sexual or physical abuse **of your child**, or if we feel that there is a significant risk of harming others. Such information will be reported to the appropriate authorities. Also, any evidence of threatened suicide or threatened violence by **your child** to **himself/herself** or others will be reported to a member of the research staff. We will make every effort to maintain **your child's** confidentiality, unless any of the above situations are suspected.
- The information we get from **your child**, including lab tests, will be stored under a code number, not under **his/her** name. The link between the code number and your **child's** name is locked away. It can only be seen by the research staff.
- However, some people will look at study records and may see your **child's** name. These people may be from the agency doing the research, the site's Institutional Review Board (IRB), the National Institutes of Health (NIH), the Office of Human Research Protection (OHRP), or from Westat, a research group helping the NIH to run this study.
- If the study staff at this site lose contact with you, they will confidentially give your **child's** name, sex, date and city of birth to Westat. Westat will conduct a computer match with health department records to check your **child's** status. As soon as the computer match is finished, your **child's** information will be destroyed. This match will only happen if you and the research staff lose contact. The computer match is private and will be kept secret. It will not be used to find you **or your child**.

What will happen to the information on my child that was collected in WITS, PACTG studies like 219, and (*insert study*)?

It is important to this study to have as complete a picture of your **child's** health that we can get. Information collected already in studies like WITS, PACTG studies like PACTG 219, and (*insert study*) would be very useful in this study. We have made an arrangement with those studies to work together. If **your child was** on those studies, we need your permission to use that information. You will be asked to give us that permission.

*INCLUDE FOLLOWING IF THE PHACS SMARTT STUDY IS BEING CONDUCTED AT THE SITE:

There is also another study sponsored by the PHACS Research Network, calledSMARTT, which looks at some of the same things as AMP. If **your child is** enrolled in both studies, we want to be able to make it easier for **your child** and for our staff by doing the things required by both studies just one time. We will ask your permission for the AMP and SMARTT studies to share your **child's** information. This way, we don't have to ask **your child** or our staff to do things twice.

What happens if my child gets hurt from being in the study?

If **your child is** hurt as a result of being in this study, the (insert the name of the clinic) will give **your child** any treatment **he/she needs** right away. The cost of this treatment will be charged to **you or your child's** insurance company. Your clinic will then tell you where **your child** can get more treatment, if **he/she needs** it. No payment will be made to you **or your child** either by the research clinic or the agency that is sponsoring this research.

Who can I call for information about this study?

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

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

There is a group of doctors and researchers whose job it is to see that research is done carefully. They also ensure that people in research are treated fairly and made as safe as possible. If you have any questions about these things, you can call (name and title of IRB member), who is a member of this group, at (telephone number).

Statement of consent:

Information about this study has been given to you. You have had a chance to ask any questions you had about the study. We have told you that it is your decision whether or not to **let your child** be in the study. **Your child** should be in the research study only if you want **him/her** to be. You can decide not to **let your child** be in the study. You can change your mind about **your child** being in the study without changing your **child's** care at this hospital or changing the way people who work for the hospital treat **your child**. If, at this time, you voluntarily agree to **let your child** take part 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.)

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

_____
Participant's Name (print)

_____	_____	_____
Parent/Legal Guardian Name (print)	Parent/Legal Guardian Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date
_____	_____	_____
Study Staff Member Conducting IC Discussion (print)	Study Staff Member Conducting IC Discussion Signature	Date

---

SIGNATURES TO SHARE STUDY INFORMATION WITH YOUR CHILD'S DOCTOR
(This is only a suggested Signature format. Sites may use their own signature page.)

If you have read the informed consent (or if you have had it explained to you) and understand the information, and you want the medical information from the study to be shared with your **child's** doctor, please sign your name below.

I give permission for medical information from this study to be shared with my **child's** doctor.

☐ Yes, I agree ☐ No, I refuse

_____
Participant's Name (print)

Parent/Legal Guardian Name (print)	Parent/Legal Guardian Signature	Date
Witness Name (print)	Witness Signature	Date
Study Staff Member Conducting IC Discussion (print)	Study Staff Member Conducting IC Discussion Signature	Date

SIGNATURES TO USE STUDY INFORMATION COLLECTED ON YOUR CHILD IN WITS, PACTG STUDIES LIKE PACTG 219, or (*insert study*)

If you have read the informed consent (or if you have had it explained to you) and understand the information, and if **your child was** in WITS, PACTG studies like 219 or (*insert study*) and you want the research staff to be able to use information already collected on **your child** to help this study, please sign your name below.

I give permission for information collected from **my child** in the studies stated above to help this study.

☐ Yes, I agree ☐ No, I refuse ☐ N/A (non-applicable)

Participant's Name (print)

Parent/Legal Guardian Name (print)	Parent/Legal Guardian Signature	Date
Witness Name (print)	Witness Signature	Date
Study Staff Member Conducting IC Discussion (print)	Study Staff Member Conducting IC Discussion Signature	Date

SIGNATURES TO SHARE STUDY INFORMATION COLLECTED ON YOUR CHILD IN AMP AND SMARTT

If you have read the informed consent (or if you have had it explained to you) and understand the information, and you want the research staff to be able to share information collected in AMP and SMARTT studies to make it easier on **your child** and our staff, please sign your name below.

I give permission for information collected from **my child** in AMP and SMARTT to be shared.

☐ Yes, I agree ☐ No, I refuse ☐ N/A (non-applicable)

_____
Participant's Name (print)

_____	_____	_____
Parent/Legal Guardian Name (print)	Parent/Legal Guardian Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date
_____	_____	_____
Study Staff Member Conducting IC Discussion (print)	Study Staff Member Conducting IC Discussion 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 IX.C

Simplified Sample Informed Consent Form for Mother: Personal Participation in Study or Control Cohort

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 along with the 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 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 (AMP), Version 4.0

PRINCIPAL INVESTIGATOR: _____

PHONE: _____

What am I being asked to do?

We are doing a research study that will try to better understand the effects of HIV infection and anti-HIV medications on children who became infected before or during birth. To do this, we need children who are infected with HIV and those who are not. We want to tell if there are any problems with how these children grow and develop as they move through their teens into adulthood. You have already given permission for your child to be in this study. We are asking you to provide personal information to help us better understand what we will learn about your child.

Why am I being asked to join?

We are asking you to help with this research because:

- Your child **was** between 7 and 16 years of age at study entry;
- Your child's records show that you were infected with HIV when pregnant with him/her;
- You have already give permission for your child to be in this study; and

- Your personal information will help us understand better how your child is growing and developing.

Why are you doing this research?

There are about 10,000 children who have been living with HIV infection since birth and taking anti-HIV medications for almost as many years in the United States. Little is known about the effects of HIV infection and its treatment on the growth and development of these children. Children with HIV face additional difficulties because of HIV with their health, well-being and development such as how they do in school and get along with other children and teens. In this study, we will try to find out the effects of HIV infection and its treatment on children and use the information to develop ways to improve the health and quality of life for this group of children.

Do I have to be in the research?

No, you can decide not to take part in the research.

Your decision not to be in the research study will not affect your child being in the research study.

You make the decision about being in the research yourself, using this information and talking to our research staff.

If you decide to take part in the research, we will ask you to sign this form, to show that you got this information and that you want to be in the research. You will get a copy of the signed paper to keep.

Even if you agree to take part in the research now and sign this form, you can still change your mind later and stop being in the research.

You will get your regular health care at your regular clinic no matter what you decide.

What will happen to me in this study?

We will ask you questions about your own development since children often develop just like their parents did so we will ask for your height and weight as well as those of the child's father We will also ask about when you were pregnant with this child. We want to know about your health and if you had any problems with the pregnancy. We will ask you questions about how you think or solve problems. We also want to know if you were smoking cigarettes, drinking alcohol, or taking street drugs while you were pregnant. We need to be able to tell if the any problems we see in the study are from these kinds of things or from HIV or the drugs used to treat HIV.

We will ask you some questions to see how you are feeling, for example, if you are depressed/sad or anxious/nervous. We will also ask some questions about your home life and your relationship with your child and if you are taking drugs now.

We are also asking your consent to look at your pregnancy and childbirth records here in this hospital if this is where you had care during pregnancy or gave birth.

Whenever your child has a visit, we will ask you about how your child is doing.

How often will I have these visits?

We will ask questions about how you are feeling, your home life including whether you are using drugs, and your relationship with your child once a year throughout the study.

The visits in your child's study are once every year except for the second year, when your child will come in twice.

How many children and mothers will be in this study?

We enrolled 451 HIV-infected children born to HIV-infected mothers in this study and are following them. We also enrolled 227 HIV-uninfected children born to HIV-infected mothers and are following them. We enrolled 562 mothers/caregivers in this study. Enrollment of mothers of enrolled children who opt to enroll later on in the study will continue.

How long will this study last?

Your child's study is planned to last at least 4 years and this would be the same for you.

What if I decide to stop taking part in the study?

You can decide to stop taking part in the study at any time. If you make this decision, it will not change any benefits at the clinical site that you entitled to. Your care at your regular clinic will not be affected. Your child can stay in the study if you want him/her to continue even if you yourself want to stop.

What kinds of bad things could happen to me if I take part?

The information you would share with us, particularly about any drug use, needs to be kept private. If it got out, you could be hurt. We will keep all this information locked up. Your name will not be on any of the papers with your answers, only a code number. All the research staff people have signed a pledge to protect your information.

What kinds of good things could come from being in this study?

This study is designed to look at the effects of HIV infection and anti-HIV medications on the development and growth of children. It is possible that you and your child will get nothing yourselves out of taking part. You will be helping to develop new treatment or programs for children infected with HIV.

What will I and/or my child be told about the study?

If we learn anything during the study that might make you change your mind about staying in the study or letting your child stay in it, we will let you know as soon as possible.

At the end of the study, we will tell you when the study results will be ready and how to learn about them.

What are the alternatives to participating in this study?

You may choose not to join this study or stop participating at any time. Whether you decide to participate or not, your decision will not affect your regular health care at your regular clinic. If you decide not to participate in this research study, your will receive standard clinical care outside of this study. Regardless of your decision, it will not affect your participation in other studies may be enrolled in now or would like to enroll in the future.

Could I be asked to leave the study before it ends even if I don't want to leave?

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

- Your cannot keep study appointments when you are supposed to;
- The site investigator determines that further participation could be harmful to your child's health or well-being.
- The study is stopped by the agency doing this study, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institutes of Health; or
- If the study has to be stopped for other administrative reasons.

If you decide to leave the study early, your health information that has already been collected may be used or released as needed for this study or any follow-up activities related to the study. If you are removed from the study or if you decided to take yourself off the study, the research staff will explain why you were removed and also explain the alternatives that are available to you.

Will being in this study cost me any money?

You will not have to pay for the study visits, physical exams or tests that are done as part of the study.

Your insurance company will have to pay for any treatment or exams done for your medical care outside the study.

Will I be paid for taking part in this study?

You (will/will not) be compensated for each study visit in the amount of (site enters compensation type and/or payment, if applicable.)

Who will know about me being in this study and about the information you get about me during the study?

- If the results of this research are published or presented, only group information will be given, not names of people in the study.
- Your research records will be kept confidential, unless the law says some information must be shared. For example, we must report if you tell us that your child is being abused or neglected. Also, if you tell us that you are planning to hurt yourself or others, we will need to report that to find you help.
- Otherwise, your personal information will not be released without your written permission
- We have a paper from the government, saying that we do not have to share information about people in this study with State or federal or civil courts. But, if you want to share the research information with someone, like an insurance company, then we will do as you say. We will not share your information with someone unless you tell us to in writing.
- The information we get from you will be stored under a code number, not under your name. The link between the code number and your name is locked away and can only be seen by the research staff
- However, some people will look at study records to make sure the study is following the rules and may see your name. These people may be from the agency doing the research, the site's Institutional Review Board (IRB), the National Institutes of Health (NIH), the Office of Human Research Protection (OHRP), or from Westat, a research group helping NIH to run this study.

What will happen to the information on my pregnancy that was collected in WITS, PACTG studies like 219, and (*insert study*)?

It will be important to this study to have as complete a picture of your child's health that we can get. Information collected already within studies like WITS, PACTG studies like PACTG 219, and (*insert study*) would be very useful in this study. We have made an arrangement with those studies to work together. But we need your permission to use that information on you that they have. You will be asked to give us that permission.

What happens if being in the study upsets me?

If you are upset as a result of being in this study, the (insert the name of the clinic) will give you the counseling you need right away. Your clinic will then tell you where you can get more counseling, if you need it. You would be responsible for paying for any extra counseling. No payment will be made to you either by the research clinic or the agency that is sponsoring this research.

Who can I call for information about this study?

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

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

There is a group of doctors and researchers whose job it is to see that research is done carefully and that people in the research are treated fairly and made as safe as possible. If you have any questions about these things, you can call (name and title of IRB member) at (telephone number).

Statement of consent:

Information about this study has been given to you and you have had a chance to ask any questions you have had about the study. We have told you that it is your decision about whether or not to be in the study. You can be in the research only if you want to be, and you can decide not to be in the research, or change your mind about being in the research without changing your care at this hospital, or changing the way people who work for the hospital treat you. If, at this time, you voluntarily agree to take part 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.)

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

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

SIGNATURES TO USE STUDY INFORMATION COLLECTED ON YOU IN WITS, PACTG STUDIES LIKE PACTG 219, OR (*insert study*)

If you have read the informed consent (or if you have had it explained to you) and understand the information, and you want the research staff to be able to use information already collected on you in WITS, PACTG studies like PACTG 219, or (*insert study*) to help this study, please sign your name below.

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.

APPENDIX IX.D

Simplified Sample Informed Consent Form for Primary Caregiver Other Than Mother Personal Participation in Study or Control Cohort

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 along with the 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 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 (AMP), Version 4.0

PRINCIPAL INVESTIGATOR: _____

PHONE: _____

What am I being asked to do?

We are doing a research study that will try to better understand the effects of HIV infection and anti-HIV medications on children who became infected before or during birth. To do this, we need children who are infected with HIV and those who are not. We want to tell if there are any problems with how these children grow and develop as they move through their teens into adulthood. Your child already has permission to be in this study. We are asking you to provide personal information to help us better understand what we will learn about your child.

Why am I being asked to join?

We are asking you to help with this research because:

- Your child was between 7 and 16 years of age at study entry;
- Your child's records show that the child's mother was infected with HIV when pregnant with him/her;
- Your child already has permission to be in this study; and

- Your personal information will help us understand better how your child is growing and developing.

Why are you doing this research?

There are about 10,000 children who have been living with HIV infection since birth and taking anti-HIV medications for almost as many years in the United States. Little is known about the effects of HIV infection and its treatment on the growth and development of these children. Children with HIV face additional difficulties because of HIV with their health, well-being and development such as how they do in school and get along with other children and teens. In this study, we will try to find out the effects of HIV infection and its treatment on children and use the information to develop ways to improve the health and quality of life for this group of children.

Do I have to be in the research?

No, you can decide not to take part in the research.

Your decision not to be in the research study will not affect your child being in the research study.

You make the decision about being in the research yourself, using this information and talking to our research staff.

If you decide to take part in the research, we will ask you to sign this form, to show that you got this information and that you want to be in the research. You will get a copy of the signed paper to keep.

Even if you agree to take part in the research now and sign this form, you can still change your mind later and stop being in the research.

You will get your regular health care at your regular clinic no matter what you decide.

What will happen to me in this study?

We will ask you questions about how you are feeling, for example, if you are depressed/sad or anxious/nervous. We will ask you questions about how you think or solve problems. We will also ask some questions about your home life and your relationship with your child and if you are using alcohol or any drugs.

Whenever your child has a visit, we will ask you about how your child is doing.

How often will I have these visits?

We will ask you about how you are feeling, your home life, and your relationship with your child once a year throughout the study.

The visits in your child's study are once every year except for the second year, when your child will come in twice.

How many children and caregivers will be in this study?

We enrolled 451 HIV-infected children born to HIV-infected mothers in this study and are following them. We also enrolled 227 HIV-uninfected children born to HIV-infected mothers and are following them. We enrolled 562 mothers/caregivers in this study. Enrollment of new primary caregivers of enrolled children will continue.

How long will this study last?

Your child's study is planned to last at least 4 years and this would be the same for you.

What if I decide to stop taking part in the study?

You can decide to stop taking part in the study at any time. If you make this decision, it will not change any benefits at the clinical site that you entitled to. Your care at your regular clinic will not be affected. Your child can stay in the study if you want him/her to continue even if you yourself want to stop.

What kinds of bad things could happen to me if I take part?

The information you would share with us, particularly about any drug use, needs to be kept private. If it got out, you could be hurt. We will keep all this information locked up. Your name will not be on any of the papers with your answers, only a code number. All the research staff people have signed a pledge to protect your information.

What kinds of good things could come from being in this study?

This study is designed to look at the effects of HIV infection and anti-HIV medications on the development and growth of children. It is possible that you and your child will get nothing yourselves out of taking part. You will be helping to develop new treatment or programs for children infected with HIV.

What will I and/or my child be told about the study?

If we learn anything during the study that might make you change your mind about staying in the study or letting your child stay in it, we will let you know as soon as possible.

At the end of the study, we will tell you when the study results will be ready and how to learn about them.

What are the alternatives to participating in this study?

You may choose not to join this study or stop participating at any time. Whether you decide to participate or not, your decision will not affect your regular health care at your regular clinic. If you decide not to participate in this research study, your will receive standard clinical care outside of this study. Regardless of your decision, it will not affect your participation in other studies may be enrolled in now or would like to enroll in the future.

Could I be asked to leave the study before it ends even if I don't want to leave?

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

- Your cannot keep study appointments when you are supposed to;
- The site investigator determines that further participation could be harmful to your child's health or well-being.
- The study is stopped by the agency doing this study, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institutes of Health; or
- If the study has to be stopped for other administrative reasons.

If you decide to leave the study early, your health information that has already been collected may be used or released as needed for this study or any follow-up activities related to the study. If you are removed from the study or if you decided to take yourself off the study, the research staff will explain why you were removed and also explain the alternatives that are available to you.

Will being in this study cost me any money?

You will not have to pay for the study visits, physical exams or tests that are done as part of the study.

Your insurance company will have to pay for any treatment or exams done for your medical care outside the study.

Will I be paid for taking part in this study?

You (will/will not) be compensated for each study visit in the amount of (site enters compensation type and/or payment, if applicable.)

Who will know about me being in this study and about the information you get about me during the study?

- If the results of this research are published or presented, only group information will be given, not names of people in the study.
- Your research records will be kept confidential, unless the law says some information must be shared. For example, we must report if you tell us that your child is being abused or neglected. Also, if you tell us that you are planning to hurt yourself or others, we will need to report that to find you help.
- Otherwise, your personal information will not be released without your written permission
- We have a paper from the government, saying that we do not have to share information about people in this study with State or federal or civil courts. But, if you want to share the research information with someone, like an insurance company, then we will do as you say. We will not share your information with someone unless you tell us to in writing.
- The information we get from you will be stored under a code number, not under your name. The link between the code number and your name is locked away and can only be seen by the research staff
- However, some people will look at study records to make sure the study is following the rules and may see your name. These people may be from the agency doing the research, the site's Institutional Review Board (IRB), the National Institutes of Health (NIH), the Office of Human Research Protection (OHRP), or from Westat, a research group helping NIH to run this study.

What happens if being in the study upsets me?

If you are upset as a result of being in this study, the (insert the name of the clinic) will give you the counseling you need right away. Your clinic will then tell you where you can get more counseling, if you need it. You would be responsible for paying for any extra counseling. No payment will be made to you either by the research clinic or the agency that is sponsoring this research.

Who can I call for information about this study?

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

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

There is a group of doctors and researchers whose job it is to see that research is done carefully and that people in the research are treated fairly and made as safe as possible. If you have any questions about these things, you can call (name and title of IRB member) at (telephone number).

Statement of consent:

Information about this study has been given to you and you have had a chance to ask any questions you have had about the study. We have told you that it is your decision about whether or not to be in the study. You can be in the research only if you want to be, and you can decide not to be in the research, or change your mind about being in the research without changing your care at this hospital, or changing the way people who work for the hospital treat you. If, at this time, you voluntarily agree to take part 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.)

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

_____	_____	_____
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.

APPENDIX IX.E (REVISED NOVEMBER 13, 2013)

Simplified Sample Assent Form: Assent for Older Child for Participation in Study Cohort

(Note: The point-of-care (POC) lactate test was discontinued as of August 6, 2015 per Clarification Memo (CM) #10 and saliva collection was discontinued as of May 10, 2017 per CM #13. However, this sample consent form remains unchanged given that these changes do not impact the risk/benefit ratio for study participants.)

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 the older adolescents to be enrolled in this study.

TITLE OF STUDY: Adolescent Master Protocol (AMP), Version 4.0

PRINCIPAL INVESTIGATOR: _____

PHONE: _____

You have been participating in the AMP study. We are asking you to continue to participate in this study. You can decide not to continue in the study. Even if you agree to continue in the study now, you can change your mind later and stop being in the study at any time.

What am I being asked to do?

We are asking you to continue to be in a study that will look at how children and youth grow and develop.

Why am I being asked to join?

You were over 7 years of age when you entered the study and you **are under 18 years of age now**.

Why are you doing this research?

We want to find out how children and youth do as they grow into teens with their health, well-being, and development such as how they do in school and get along with other children and teens. We want to use the information to develop ways to improve the quality of life for other children and youth.

Do I have to be in the research study?

No, you can decide not to continue in the research.

You should decide to continue in the research study, using this information and talking to our research staff.

If you decide to be in the research study, we will ask you to sign this form, to show that you got this information and that you agree to continue in the research study. You will get a copy of the signed paper to keep.

Even if you agree to join the study now and sign this form, you can still change your mind later and stop being in the research study.

You will get your regular health care at your regular clinic no matter what you decide.

What will happen to me in this study?

You will have the following kinds of exams:

- We will check your medical records to see how you have been doing with your regular exams/care.
- We will ask about your diet and physical activity.
- We will collect information on your family: for example, if family members have high blood pressure, diabetes, or heart disease.
- If you have additional medical tests performed as part of your regular medical care, we will obtain the results of these tests. We will also look at any microscope slides that are made during any of these exams.
- We will record your physical exam. We will check your height and weight, measure around your hip and waist, and see how far you have matured.
- DXA (dual energy x-ray absorptiometry) scans will be done. This is a type of x-ray to measure how strong your bones are. For these DXA scans, you will be asked to lie down on a table with your hand palms down alongside the body. The scans will take approximately 30 minutes and will not cause you any pain. **No more than three** DXA scans may be done with at least 2 years between scans.
- You will also have an x-ray of your wrist to see if the bone shows that you are still growing. This x-ray will be done at the same time when the DXA scan is done unless you've stopped growing.
- You will be asked questions to see how well you are thinking, solving problems, and using words to express yourself. We will also test your memory and attention. We will also ask questions about your feelings, behaviors, relationship with parents or caregivers, experiences, and how well you adhere to your medications. These questions will be asked by a trained interviewer in private.
- If you are 10 years of age or older, you will also be asked some questions about sexual behavior, alcohol and drugs. These questions will be asked using a computer interview

called ACASI (**A**udio **C**omputer-**A**ssisted **S**elf-Interview). ACASI uses a computer and voice recordings so that you will hear (through headphones) and see (on the screen) each question and the answers for that question. You would enter your answer right into the computer. When the interview is complete, the computer "locks in" your answers so no one at the clinic can see what you have said. [THIS PARAGRAPH CAN BE DELETED FOR USE IN CHILDREN LESS THAN 10 YEARS OF AGE]

- We will test your blood to see if routine things like the number of cells and the blood's makeup is normal. We will take no more than two tablespoons of blood from a vein in your arm at each visit. For one test we will prick your finger to take blood.
- We will also collect your urine to check for levels of glucose, protein, blood, and other chemicals.
- We will also test your hearing.
- We will check your medical records for results of screenings for sexually transmitted infections (STIs) done as part of routine care. In addition, if you are female and received gynecologic (GYN) exams with PAP smears as part of routine care, we will review the results from your medical records. We will ask you to sign a form to allow this hospital to release samples collected during the exam to the AMP researchers for review.

Some abnormal test results will need us to do additional studies. If that happens, we will come to you again to tell you everything you need to know and get your permission to go ahead.

We will also store some of your blood, saliva, and urine for tests in the future but this will be explained in another paper.

How often will I have these visits? Will all visits include the exams just described?

You will come into the clinic once every year **until you turn 18 years old**. All visits will have the same kind of exams that were just explained. But not all of them will be performed at every visit. We will try to keep visits from taking more than a few hours.

How many other teens will be in this study?

We enrolled 451 children and teens like you in this study and are following them.

How long will this study last?

This study is planned to last at least 4 years.

What if I decide to stop being in the study?

You can always decide to stop being in the study. If you make this decision, it will not change any benefits at the clinical site that you are entitled to. Your care at the clinical site will not be affected.

What kinds of bad things could happen to me?

The blood tests may hurt a little. You might feel a little pain, have some bleeding, or a bruise where the needle enters the skin to draw the blood from your arm. Sometimes people feel like they might faint. In one test we will prick your finger to take blood. In a small number of cases, we may have to do it more than once.

You will have to fast (not eat) for some of the blood tests. This shouldn't be for more than 8 hours and you can have sips of water during fasting. Sometimes people feel more like they might faint when they have been fasting.

You may get tired or feel uncomfortable, embarrassed or upset with the questions asking about your thoughts and feelings, use of alcohol and drugs, and sexual behavior.

If you have a DXA scan, you will be exposed to a small amount of radiation. The amount of radiation from this procedure is approximately 5% the amount of natural radiation a person receives each year. The risk from this radiation exposure is too small to measure.

If you have a wrist x-ray, you will be exposed to a small amount of radiation.

What kinds of good things could come from being in this study?

This study will look at how children and youth develop and grow. It is possible that you will get nothing yourself out of taking part. You will be helping to develop new treatment or programs for other children and youth.

There will be some evaluations that might help you make sure you are growing and developing as you should. This is information that can reassure you if the exams are normal or help you decide to seek new services if the exams are not normal.

What will I be told about the study?

If we learn anything during the study that might make you change your mind about staying in the study, we will let you know as soon as possible.

At the end of the study, we will tell you when the study results will be ready and how to learn about them.

What are the alternatives to participating in this study?

You may choose not to join this study. You can stop participating at any time. Whether you decide to participate or not, your decision will not affect your regular health care at your regular clinic. If you decide not to participate in this research study, your will receive standard clinical care outside of this study. Regardless of your decision, it will not affect your participation in other studies may be enrolled in now or would like to enroll in the future.

Could I be asked to leave the study before it ends even if I don't want to leave?

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

- You cannot keep study appointments when you are supposed to;
- The site investigator determines that further participation could be harmful to your health or well-being.
- The study is stopped by the agency doing 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 has to be stopped for other administrative reasons.

If you decide to leave the study early, your health information that has already been collected may be used or released as needed for this study or any follow-up activities related to the study. If you are removed from the study or if you decided to take yourself off the study, the research staff will explain why you were removed and also explain the options that are available to you.

Will being in this study cost any money?

You or your family will not have to pay for any of the study visits, physical exams, or tests that are done in the study.

Your family or your insurance company will have to pay for any treatment or exams done for your medical care outside the study.

Will I be paid for taking part in this study?

You (will/will not) be compensated for each study visit in the amount of (site enters compensation type and/or payment, if applicable.)

Who will know about me being in this study and about the information you get about me during the study?

- If the results of this research are published or presented, only group information will be given, not names of people in the study.

- Your research records, including lab tests, will be kept confidential, unless the law says some information must be shared. For example, we must report if we are told that you are being abused or neglected or if you tell us that you are planning to hurt yourself or others.
- Otherwise, your personal information will not be released without your parent/legal guardian's written permission.
- We have a paper from the government, saying that we do not have to share information about people in this study with State or federal or civil courts. But, if your parent/legal guardian wants to share the research information with someone, like your doctor or an insurance company, then we will do as your parent/legal guardian says. We will not share your information with someone unless we are told to in writing. Some of the information that you share with us, such as your responses to questionnaires and interviews, will not be shared with your parent/legal guardian or doctor without your permission. This includes information on how well you take your medicines, how you feel about your life and your future, and your mental health. This paper does not prevent us from reporting suspected or known sexual or physical abuse, or if we feel that there is a significant risk of you harming others. Such information will be reported to the appropriate authorities. Also, any evidence of threatened suicide, threatened violence by you to yourself or others will be reported to a member of the research staff. However, we will make every effort to maintain confidentiality, unless any of the above situations are suspected.
- The information we get from you, including lab tests, will be stored under a code number, not under your name. The link between the code number and your name is locked away and can only be seen by the research staff.
- However, some people will look at study records and may see your name. These people may be from the agency doing the research, the site's Institutional Review Board (IRB), the National Institutes of Health (NIH), the Office of Human Research Protection (OHRP), or from Westat, a research group helping the NIH to run this study.
- If the study staff at this site lose contact with you, they will confidentially give your name, sex, date and city of birth to Westat so that a computer match can be conducted with health department records to check your status. As soon as the computer match is finished, your information will be destroyed. This match will only happen if you and the research staff lose contact. The computer match is private and will be kept secret. It will not be used to find you.

Who can I call for information about this study?

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

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

There is a group of doctors and researchers whose job it is to see that research is done carefully and that people in the research are treated fairly and made as safe as possible. If you

have any questions about these things, you can call (name and title of IRB member) at (telephone number).

Statement of assent:

Information about this study has been given to you and you have had a chance to ask any questions you have had about the study. We have told you that it is your decision about whether or not 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 about being in the research 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 take part 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.)

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

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

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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 IX.F (REVISED NOVEMBER 13, 2013)

Simplified Sample Assent Form: Assent for Older Child for Participation in Control Cohort

(Note: The point-of-care (POC) lactate test was discontinued as of August 6, 2015 per Clarification Memo (CM) #10 and saliva collection was discontinued as of May 10, 2017 per CM #13. However, this sample consent form remains unchanged given that these changes do not impact the risk/benefit ratio for study participants.)

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 the older adolescents to be enrolled in this study.

TITLE OF STUDY: Adolescent Master Protocol (AMP), Version 4.0

PRINCIPAL INVESTIGATOR: _____

PHONE: _____

You have been participating in the AMP study. We are asking you to continue to participate in this study. You can decide not to continue in the study. Even if you agree to continue in the study now, you can change your mind later and stop being in the study at any time.

What am I being asked to do?

We are asking you to continue being in a study that will look at how children and youth grow and develop.

Why am I being asked to join?

You were over 7 years of age when you entered the study and you **are under 18 years of age now**.

Why are you doing this research?

We want to find out how children and youth do as they grow into teens with their health, well-being, and development such as how they do in school and get along with other children and teens. We want to use the information to develop ways to improve the quality of life for other children and youth.

Do I have to be in the research study?

No, you can decide not to continue in the research.

You should decide to continue in the research study, using this information and talking to our research staff.

If you decide to be in the research study, we will ask you to sign this form, to show that you got this information and that you agree to continue in the research study. You will get a copy of the signed paper to keep.

Even if you agree to join the study now and sign this form, you can still change your mind later and stop being in the research study.

You will get your regular health care at your regular clinic no matter what you decide.

What will happen to me in this study?

You will have the following kinds of exams:

- We will check your medical records to see how you have been doing with your regular exams/care.
- We will record your physical exam. We will check your height and weight, measure around your hip and waist, and see how far you have matured.
- You will be asked questions to see how well you are thinking, feeling, solving problems, and using words to express yourself. We will also test your memory and attention. These questions will be asked by a trained interviewer in private.
- If you are 10 years of age or older, you will also be asked some questions about use of alcohol and drugs and sexual behavior. These questions will be asked using a computer interview called ACASI (Audio Computer-Assisted Self-Interview). ACASI uses a computer and voice recordings so that you hear (through headphones) and see (on the screen) each question and the answers for that question. You will enter your answer right into the computer. When the interview is complete, the computer "locks in" your answers so no one at the clinic can see what you have said. [THIS PARAGRAPH CAN BE DELETED FOR USE IN CHILDREN LESS THAN 10 YEARS OF AGE.]
- We will test your blood to see if the blood's makeup is normal. We will take no more than one tablespoon of blood from a vein in your arm at each visit. For one test we will prick your finger to take blood.
- We will also collect your urine to check for levels of glucose, protein, blood, and other chemicals.
- We will also test your hearing.

- We will check your medical records for results of screenings for sexually transmitted infections (STIs) done as part of routine care. In addition, if you are female and received gynecologic (GYN) exams with PAP smears as part of routine care, we will review the results from your medical records. We will ask you to sign a form to allow this hospital to release samples collected during the exam to the AMP researchers for review.

Some abnormal test results will need us to do additional studies. If that happens, we will come to you again to tell you everything you need to know and get your permission to go ahead.

We will also store some of your blood, saliva, and urine for tests in the future but this will be explained in another paper.

How often will I have these visits? Will all the visits include the exams just described?

You will come into the clinic once every year **until you turn 18 years old**. All visits will have the same kind of exams that were just explained. But not all of them will be performed at every visit. We will try to keep visits from taking more than a few hours.

How many children will be in this study?

We enrolled 227 children and teens like you in this study and are following them.

How long will this study last?

This study is planned to last at least 4 years.

What if I decide to stop the study?

You can always decide to stop being in the study. If you make this decision, it will not change any benefits at the clinical site that you are entitled to. Your care at the clinical site will not be affected.

What kinds of bad things could happen to me?

The blood tests may hurt a little. You might feel a little pain, have some bleeding, or a bruise where the needle enters the skin to draw the blood from your arm. Sometimes people feel like they might faint. In one test we will prick your finger to take blood. In a small number of cases, we may have to do it more than once.

You will have to fast (not eat) for some of the blood tests. This shouldn't be for more than 8 hours and you can have sips of water during fasting. Sometimes people feel like they might faint when they have been fasting.

You may get tired or feel uncomfortable, embarrassed or upset with the questions asking about your thoughts and feelings, use of alcohol and drugs, and sexual behavior.

What kinds of good things could come from being in this study?

This study will look at how children and youth grow and develop. It is likely that you will get nothing yourself out of taking part. You will be helping to develop new treatment or programs for other children and youth.

There will be some evaluations that might help you make sure you are growing and developing as you should. This is information that can reassure you if the exams are normal or help you decide to seek new services if the exams are not normal.

What will I be told about the study?

If we learn anything during the study that might make you change your mind about staying in the study, we will let you know as soon as possible.

At the end of the study, we will tell you when the study results will be ready and how to learn about them.

What are the alternatives to participating in this study?

You may choose not to join this study. You can stop participating at any time. Whether you decide to participate or not, your decision will not affect your regular health care at your regular clinic. If you decide not to participate in this research study, your will receive standard clinical care outside of this study. Regardless of your decision, it will not affect your participation in other studies may be enrolled in now or would like to enroll in the future.

Could I be asked to leave the study before it ends even if I don't want to leave?

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

- You cannot keep study appointments when you are supposed to;
- The site investigator determines that further participation could be harmful to your health or well-being.
- The study is stopped by the agency doing 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 has to be stopped for other administrative reasons.

If you decide to leave the study early, your health information that has already been collected may be used or released as needed for this study or any follow-up activities related to the study. If you are removed from the study or if you decided to take yourself off the study, the research staff will explain why you were removed and also explain the options that are available to you.

Will being in this study cost me any money?

You or your family will not have to pay for any of the study visits, physical exams, or tests that are done in the study.

Your family or your insurance company will have to pay for any treatment or exams done for your medical care outside the study.

Will I be paid for taking part in this study?

You (will/will not) be compensated for each study visit in the amount of (site enters compensation type and/or payment, if applicable.)

Who will know about me being in this study and about the information you get about me during the study?

- If the results of this research are published or presented, only group information will be given, not names of people in the study.
- Your research records, including lab tests, will be kept confidential, unless the law says some information must be shared. For example, we must report if we are told that you are being abused or neglected or if you tell us that you are planning to hurt yourself or others.
- Otherwise, your personal information will not be released without your parent/legal guardian's written permission.
- We have a paper from the government, saying that we do not have to share information about people in this study with State or federal or civil courts. But, if your parent/legal guardian wants to share the research information with someone, like your doctor or an insurance company, then we will do as your parent/legal guardian says. We will not share your information with someone unless we are told to in writing. Some of the information that you share with us, such as your responses to questionnaires and interviews, will not be shared with your parent/legal guardian or doctor without your permission. This includes information on how well you take your medicines, how you feel about your life and your future, and your mental health. This paper does not prevent us from reporting suspected or known sexual or physical abuse, or if we feel that there is a significant risk of you harming others. Such information will be reported to the appropriate authorities. Also, any evidence of threatened suicide, threatened violence by you to yourself or others will be reported to a member of the research staff. However, we will make every effort to maintain confidentiality, unless any of the above situations are suspected.
- The information we get from you, including lab tests, will be stored under a code number, not under your name. The link between the code number and your name is locked away and can only be seen by the research staff.
- However, some people will look at study records and may see your name. These people may be from the agency doing the research, the site's Institutional Review Board (IRB), the National Institutes of Health (NIH), the Office of Human Research Protection (OHRP), or from Westat, a research group helping the NIH to run this study.

- If the study staff at this site lose contact with you, they will confidentially give your name, sex, date and city of birth to Westat so that a computer match can be conducted with health department records to check your status. As soon as the computer match is finished, your information will be destroyed. This match will only happen if you and the research staff lose contact. The computer match is private and will be kept secret. It will not be used to find you.

Who can I call for information about this study?

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

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

There is a group of doctors and researchers whose job it is to see that research is done carefully and that people in the research are treated fairly and made as safe as possible. If you have any questions about these things, you can call (name and title of IRB member) at (telephone number).

Statement of assent:

Information about this study has been given to you and you have had a chance to ask any questions you have had about the study. We have told you that it is your decision about whether or not 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 about being in the research 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 take part 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.)

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

_____	_____	_____
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.

APPENDIX IX.G (REVISED NOVEMBER 13, 2013)

Simplified Sample Assent Form: Assent for Younger Child for Participation in Study

(Note: The point-of-care (POC) lactate test was discontinued as of August 6, 2015 per Clarification Memo (CM) #10 and saliva collection was discontinued as of May 10, 2017 per CM #13. However, this sample consent form remains unchanged given that these changes do not impact the risk/benefit ratio for study participants.)

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 the older adolescents to be enrolled in this study.

TITLE OF STUDY: Adolescent Master Protocol (AMP), Version 4.0

PRINCIPAL INVESTIGATOR: _____

PHONE: _____

JOINING THE AMP STUDY

What do I have to do?

We are asking you to continue to be in a research study of how you are growing and developing.

Why me?

You were over 7 years old when you started the study **and you are under 18 years old now**.

Why are the scientists doing this research?

Scientists want to see if children have any problems in growing and developing. If they find these problems, they want to be able to figure out ways to prevent them.

Do I have to be in the research?

No, you can decide that you don't want continue to be in this study.

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

If you decide to stop being in the study early, 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 if you decided to stop being in the study, they will explain the options that are available to you.

What will happen to me in this study?

We want children who were already taking part in studies like this (the WITS and PACTG 219C, for example) to join this study so we can continue to follow how they grow.

We will need to know about your health so we will look at your health record here in clinic. We will also measure your height and weight. We will do "talking" exams that tell us how you think, feel, behave, solve puzzles, and how well you take your medications. We may take some x-rays, but will only do this if it hasn't been done already in the study. We will prick your finger to get blood for one test. We will also take a small amount of blood from your arm (no more than two tablespoons at each visit) and urine (pee) for special laboratory tests. And we want to store some of your blood, saliva (spit) and urine (pee) for the time that scientists have new tests or new questions in the future. In addition to all of this, we will ask you questions about how you feel, behave and how well you take medications.

If any of these tests are not normal, we will want to do extra tests. Most of these are more blood tests.

How often will I have these visits? Will all the visits be like the one just described?

The visits in this study are one time a year **until you turn 18 years old**. All the visits will have the same kind of exams that were just explained to you. We will try to keep visits from taking more than a few hours.

How many other children will be in this study?

We enrolled 678 children and teens like you in the study and are following them.

How long will this study last?

This study is planned to last at least 4 years.

What kinds of bad things could happen to me if I join the study?

The blood tests may hurt a little. You might feel a little pain, have some bleeding, or a bruise where the needle goes in. Sometimes people feel like they might faint. In a small number of children, we may have to do the finger prick more than once.

What kinds of good things could come from being in this study?

This study will watch how you grow. You may not get anything yourself by being in the study. But you may help the scientists figure out ways to help other children.

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

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 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

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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 IX.H (NEW AS OF FEBRUARY 8, 2011)

Sample Permission Form for Parent/Legal Guardian or Informed Consent Form for Minors Who Reached the Age of Majority: Participation in the Mitochondrial Determinants Component of the AMP 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 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 their next encounter, with all new participants prior to involvement, or as the local IRB may otherwise additionally require.

TITLE: Adolescent Master Protocol (AMP), Version 4.0 - Mitochondrial Determinants Component (MDC)

PRINCIPAL INVESTIGATOR: _____

PHONE: _____

If you are a parent or legal guardian of a potential participant on this Mitochondrial Determinants Component (MDC) of the AMP study, in the rest of the document, "you" refers to "your child."

What am I being asked to do?

We are asking you to join another part of the AMP study, called the Mitochondrial Determinants Component (MDC). We will refer to it as the MDC in the rest of this form. We are trying to better understand how HIV infection and the medications used to treat HIV may affect mitochondria, the parts of cells in the body that are the batteries of your body, like those in a car, that manage how the body makes energy. Problems with mitochondria may affect the body's metabolism (energy use), leading to insulin resistance/diabetes (trouble with blood sugar) and, possibly, heart attacks and strokes in the future.

Why am I being asked to join in the research?

We are asking for you to help with this research because:

- You are participating in the AMP study.

Why are you doing this research?

Children with HIV are living longer, healthier lives because of better medical treatments. HIV infection and the medications used to treat the infection have been known to cause health issues for some people. These include insulin resistance/diabetes (trouble with blood sugar) and other changes that may increase the risk for heart attacks and strokes. This research will try to find out how medications used to treat HIV infection may contribute to these health issues.

Do I have to join the research?

No, you can decide not to join.

You make the decision about being in the MDC using the information in this informed consent form and talking to our research staff.

We will answer any questions you have so that you can decide if you want to join. If you do decide to join, we will ask you to sign this form. Signing this form shows that you got this information and that you want to join the MDC. You will get a copy of the signed paper to keep.

Even if you agree to join now and sign this form, you can still change your mind later and stop being in the MDC at any time.

What will happen to me in the MDC?

You will have the following samples collected:

- Three tubes of blood (up to 2 tablespoons) will be drawn from a vein in your arm; and
- Some cells from the inside of your cheek will be collected. This will be done by gently scraping the inside of your cheeks with a sterile nylon brush. This will be done three times to collect three brushes.

If there are any samples remaining after the MDC research tests are done, we would like to store them in the PHACS repository for future use. You can decide not to have your remaining samples stored in the repository. Even if you agree to have them stored now, you can change your mind later and stop at any time.

How often will I have these visits? Will all visits include the evaluations just described?

The samples will be collected when you come to the clinic once every year for your AMP visits. All visits will have the same evaluations that were just explained.

How many children will be in the MDC?

We will try to enroll 400 children, 300 HIV-infected and 100 HIV-uninfected.

How long will the MDC last?

The MDC is planned to last at least 5 years.

What if I decide to take myself out of the MDC?

You can always decide to take yourself out of the MDC. If you make this decision, it will not change any benefits at the clinical site that you are entitled to. Your care at the clinical site will not be affected.

What kinds of bad things could happen to me?

The blood draw may hurt a little. You might feel a little pain or have some bleeding or a bruise where the needle enters the skin to draw the blood from your arm. Sometimes people feel like they might faint. There is no discomfort or risk with the collection of cells from the inside of your cheeks.

What kinds of good things could come from being in this research?

The MDC of the AMP study will look at the effects of HIV infection and HIV medications on the health of children infected with HIV. It is possible that you will get nothing out of taking part just for yourself.

What are the alternatives to participating in the MDC?

You may choose not to join the MDC. You can stop participating at any time once you joined. Whether you join or not, your decision will not affect your regular health care at your regular clinic. Your decision will not affect your participation in the AMP study. If you decide not to join, you will receive standard clinical care. Your decision will not affect your participation in other studies you may be enrolled in now or would like to enroll in the future.

Could I be asked to leave the MDC before it ends even if I don't want to leave?

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

- You are taken off the AMP study for any reason;
- The site investigator determines that further participation could be harmful to your health or well-being;

- The MDC is stopped by the agency doing the research, the ***Eunice Kennedy Shriver*** National Institute of Child Health and Human Development (NICHD) and the National Institutes of Health (NIH); or
- If the MDC is stopped for other administrative reasons.

If you decide to take yourself out of the MDC early, your health information that has already been collected may be used or released as needed for this research or any related follow-up activities. If you are removed from the MDC, the research staff will explain why you were removed and also explain the options that are available to you.

Will being in the MDC cost me any money?

You will not have to pay for any visits or tests that are done for the MDC.

Will I be paid for taking part in the MDC?

You (will/will not) be compensated for your participation. (Site enters compensation type and/or payment, if applicable.)

Who can I call for information about this research?

If you have questions or an injury or problem that you think was caused by this research, you can call (name of investigator) at (telephone number).

Who can I call for information about my rights as someone in the MDC?

There is a group of doctors and researchers whose job it is to see that research is done carefully. They also ensure that people in research are treated fairly and made as safe as possible. If you have any questions about these things, you can call (name and title of IRB member), who is a member of this group, at (telephone number).

Statement of Consent:

Information about the MDC of the AMP study has been given to you. You have had a chance to ask any questions you have had about this research. We have told you that it is your decision whether or not to join. You should join only if you want to. You can decide not to join. You can change your mind about participating 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 take part, please sign your name below. All other information contained in the main AMP study consent you signed also applies to this MDC consent.

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

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

_____
Participant's Name (print) [If parent/legal guardian signing]

_____	_____	_____
Parent/Legal Guardian/ Participant Name (print)	Parent/Legal Guardian/ Participant Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date
_____	_____	_____
Study Staff Member Conducting IC Discussion (print)	Study Staff Member Conducting IC Discussion Signature	Date

SIGNATURES TO SHARE RESEARCH INFORMATION WITH YOUR DOCTOR
(This is only a suggested Signature format. Sites may use their own signature page.)

If you have read the informed consent (or if you have had it explained to you) and understand the information, and you want the medical information from the research to be shared with your doctor, please sign your name below.

I give permission for medical information from this research to be shared with my doctor.

☐ Yes, I agree ☐ No, I refuse

_____
Participant's Name (print) [If parent/legal guardian signing]

_____	_____	_____
Parent/Legal Guardian/ Participant Name (print)	Parent/Legal Guardian/ Participant Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date
_____	_____	_____
Study Staff Member Conducting IC Discussion (print)	Study Staff Member Conducting IC Discussion Signature	Date

SIGNATURES TO STORE REMAINING SAMPLES STORED IN THE PHACS REPOSITORY FOR FUTURE USE

I agree to have any samples that remain after the MDC research tests are done to be stored in the PHACS Repository for future use.

☐ Yes, I agree ☐ No, I refuse

_____
Participant's Name (print) [If parent/legal guardian signing]

_____	_____	_____
Parent/Legal Guardian/ Participant Name (print)	Parent/Legal Guardian/ Participant Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date
_____	_____	_____
Study Staff Member Conducting IC Discussion (print)	Study Staff Member Conducting IC Discussion Signature	Date

Note: This permission/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 IX.I (NEW AS OF FEBRUARY 8, 2011)

Sample Assent Form for Older Children: Joining the Mitochondrial Determinants Component (MDC) of the AMP Study

What do I have to do?

We are asking you to be in another part of the AMP study that we are calling the MDC. The MDC will look at problems in metabolism such as insulin resistance and diabetes (trouble with blood sugar) and mitochondrial changes that may lead to heart disease. Mitochondria are the batteries in your body, like the batteries in a car, that manage how the body makes energy.

Why me?

You are already participating in the AMP study.

Why are the scientists doing this research?

Scientists want to look at problems such as insulin resistance/diabetes (trouble with blood sugar) and other changes that may increase the risk for heart attacks and strokes. They want to try to find out the possible causes of these problems.

Do I have to be in the MDC?

No, you can decide that you don't want to be in the MDC.

Even if you agree to be in the MDC, you can still change your mind later and stop being in the MDC. It's up to you. You should decide whether or not to be in the MDC, using this information and talking to our research staff.

If you decide to be in the MDC, we will ask you to sign this form, to show that you got this information and that you agree to join the MDC. You will get a copy of this signed paper to keep.

What will happen to me in the MDC?

We will ask you to give us some blood (up to 2 tablespoons) from a vein in your arm.

We will also need to collect some cells from the inside of your cheek. This will be done by gently scraping the inside of your cheeks with a soft brush. This will be done three times to collect three brushes.

If there are any samples remaining after the MDC research tests are done, we would like to store them in the PHACS repository for future use. You can decide not to have your remaining samples stored in the repository. Even if you agree to have them stored now, you can change your mind later and stop at any time.

How often will I have these visits?

The samples will be collected when you come to the clinic once every year for your AMP visits. All visits will have the same two collections that were just explained.

How many other children will be in the MDC?

We want to have as many as 400 children like you in the MDC.

How long will the MDC last?

This MDC is planned to last at least 5 years.

What kinds of bad things could happen to me if I join the MDC?

The blood draw may hurt a little. You might feel a little pain, have a little bleeding, or a bruise where the needle goes in. Sometimes people feel like they might faint. It shouldn't hurt when you have the cells taken from the inside of your cheeks.

What kinds of good things could come from being in the MDC?

You may get nothing out of taking part for yourself.

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

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

I understand what being in the MDC means and I got answers for all the questions I had.
I agree to be in the MDC.

_____	_____	_____
Participant's Name (print)	Participant's Signature	Date
_____	_____	_____
Study Staff Member Conducting IC Discussion (print)	Study Staff Member's Signature	Date
_____	_____	_____
Witness' Name (print)	Witness' Signature	Date

SIGNATURES TO STORE REMAINING SAMPLES STORED IN THE PHACS REPOSITORY FOR FUTURE USE

I agree to have any samples that remain after the MDC research tests are done to be stored in the PHACS Repository for future use.

☐ Yes, I agree ☐ No, I refuse

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

Note: This assent 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.

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