



The Role of Cohort Studies

ACTG

(IMPAACT, PHACS)

ACTG Studies with Cardiovascular Endpoints and/or Objectives

Overall comments:

- **ALL domestic ACTG** studies capture cardiovascular endpoints in Appendix 50 prospectively (reported on a clinical events form)
- All **multinational or international ACTG** studies capture cardiovascular endpoints in Appendix 60 prospectively (on a detailed diagnosis form, includes signs/symptoms, laboratory information, other confirmatory tests)
- All **domestic IMPAACT** studies capture cardiovascular endpoints in Appendix 40 prospectively, as they relate to women/children.
- Current efforts are underway to create a unified Appendix 100 used by these networks

STUDIES WITH HARD CARDIOVASCULAR ENDPOINTS:

1. **ALLRT MI project**
2. **A5257/A5260S –A Phase III Comparative Study of Three Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-Sparing Antiretroviral Regimens for Treatment-Naive HIV-1-Infected Volunteer**
3. **HPTN 052/A5245 –A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples and to Compare Survival and HIV Disease Progression**
4. **P1077HS / PROMISE –Promoting Maternal and Infant Survival Everywhere) Women who initiated HAART for MTCT are randomized to continue or stop ART after delivery and followed long-term**

STUDIES WITH HARD CARDIOVASCULAR ENDPOINTS:

- 5. A5202 – A Phase IIIB, Randomized, Trial of Open-Label Efavirenz or Atazanavir with Ritonavir in Combination with Double-Blind Comparison of Emtricitabine/Tenofovir or Abacavir/Lamivudine in Antiretroviral-Naive Subjects**
- 6. ACTG 362 –Initially a randomized trial evaluating need to continue MAC prophylaxis in adults with AIDS who had immune reconstitution. Trial was continued as observational follow-up to evaluate cardiovascular endpoints, metabolic effects, and neurologic outcomes**
- 7. ACTG 372A - A Randomized, Placebo-Controlled Trial of Abacavir Intensification in HIV-1 Infected Adults with Virologic Suppression on a Protease Inhibitor – Containing Regimen**

ALLRT MI Project (Heather Ribaud, Connie Benson)

Scientific goal: Identification of pre-treatment risk factors associated with MI and serious cardiovascular disease in subjects initiating ART in a randomized ACTG study (ACTG 384, ACTG 388, A5014, A5095, A5142), recent focus is on ABC-associated risk.

Status: analysis completed, manuscript submitted

Endpoints:

- **MI: 27 MIs over 3 years, 31 over 6 years**
- **Serious cardiovascular disease: N=55 events over 3 years, 75 over 6 years**

Identification/review: MIs reviewed by study chairs, serious cardiovascular events identified by MedDRA code from clinical and AE database, did not undergo chair review.

ALLRT MI Project (continued)

- **Risk factors:** family history of CHD, fasting lipids every 16 weeks, smoking at entry and updated, BP captured but not standardized
- **Statistical Methods:** ITT analysis using Cox proportional hazards models; IPCW used to adjust for potentially informative censoring. Note: Analysis is considered as competing risk framework with deaths censored, IPCW were not used to adjust for that censoring.
- **Prior Presentations:**
 - **HIV Cohorts Meeting 2008** – broader CHd outcomes including hypertension, chest pain, syncope, time-updated risk factors
 - **CROI 2009** – as treated analysis, baseline risk factors

A5257/A5260S –Jeff Lennox, Judy Currier, James Stein, Heather Ribaud

- **A Phase III Comparative Study of Three NNRTI-Sparing Antiretroviral Regimens for Treatment-Naive HIV-1-Infected Volunteers**
- **Status: Enrolling - 1063/1800**
- **Endpoints: Record all targeted non-AIDS events: diabetes mellitus, lipodystrophy, dyslipidemia, hypertension, MI, coronary artery disease, congestive heart failure, stroke, pulmonary embolism, deep vein thrombosis, and peripheral artery disease**
- **Risk Factors: Standardized BP, also dedicated Adult TP III data collection form**

HPTN 052/A5245 – Diane Havlir, Susan Swindells, Heather Ribaud

- **A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy plus HIV Primary Care versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 In Serodiscordant Couples and to Compare Survival and HIV Disease Progression**
- **Status: In follow-up, >1750 couples enrolled**
- **Endpoints: Targeted serious medical conditions prospectively captured and are reviewed by study chairs on an ongoing basis include: Diabetes mellitus, Lipodystrophy, Dyslipidemia, Hypertension, Myocardial infarction, Coronary artery disease, Congestive heart failure, Stroke.**

P1077HS / PROMISE – Judy Carrier, David Shapiro

- **HAART Standard Version of the PROMISE Study (Promoting Maternal and Infant Survival Everywhere)**
 - **Women who initiated HAART for MTCT are randomized to continue or stop ART after delivery and followed long-term**
- **Status: Enrolling - ??/2000**
- **Endpoints: Targeted serious medical conditions captured prospectively and reviewed by study chairs on an ongoing basis, including: Diabetes mellitus, Lipodystrophy, Dyslipidemia, Hypertension, Myocardial infarction, Coronary artery disease (not MI), Congestive heart failure, Stroke**

A5202 –

Paul Sax, Eric Daar, Camlin Tierney

- **A Phase IIIB, Randomized, Trial of Open-Label Efavirenz or Atazanavir with Ritonavir in Combination with Double-Blind Comparison of Emtricitabine/Tenofovir or Abacavir/Lamivudine in Antiretroviral-Naive Subjects**
- **Status: Completed, 1864 enrolled of 1800 target, published in NEJM 2009**
- **Endpoints: *There were no myocardial infarctions.***
- **Risk Factors: limitation was no smoking data**

ACTG 362 –

Paige Williams, Judy Currier

- **Initially a randomized trial evaluating need to continue MAC prophylaxis in adults with AIDS who had immune reconstitution. Study was continued as observational follow-up to evaluate cardiovascular endpoints, metabolic effects, and neurologic outcomes.**
- **Status: completed, manuscript published in HIV Med (2009)**
- **Study Size: 643 subjects**
- **Objective: evaluated incidence of metabolic syndrome, trends in fasting lipids, Framingham risk scores for serious cardiac disease, risk factors for cardiovascular disease**

ACTG 362 –

Paige Williams, Judy Carrier

- **Endpoints: MIs and serious cardiovascular events collected prospectively, verified by J Carrier, fasting lipids over 6 yrs**
- **Limitations: only 23 endpoints**
- **Statistical Methods: Cox proportional hazards models for baseline risk factors, mixed effect models for repeated lipid measurements over median of 6 years**

ACTG 372A – Scott Hammer, Roland Bassett, Heather Ribaudó

- **A Randomized, Placebo-Controlled Trial of Abacavir Intensification in HIV-1 Infected Adults with Virologic Suppression on a Protease Inhibitor – Containing Regimen**
- **Status: Completed, final manuscript submitted (hopefully)**
- **Study size: 229 subjects, median follow-up 4.4 years**
- **Endpoints: MedDRA-coded events, serious cardiovascular events**
- **Randomized to Combivir and IDV with or without abacavir**

ACTG 372A – Scott Hammer, Roland Bassett, Heather Ribaud

Following the D:A:D results, looked at cardiovascular diagnoses in the cohort. These are summarized in the final manuscript draft as follows:

- ***Eleven patients experienced serious cardiovascular events during study follow-up: 7 in the abacavir arm and 4 in the placebo arm. The median age at study entry of these 11 patients was 49 years and 10% were male. Myocardial infarction occurred in 4 and 3, unstable angina in 1 and 0, and cerebrovascular accident in 2 and 1 patients in the abacavir and placebo arms, respectively. One subject had discontinued study treatment 2 years prior to the event. For the remaining subjects, the time on study (and study treatment) at the time of the event was 99 and 163 weeks in the 2 arms, respectively.***

ACTG studies with Cardiac Biomarkers

- **A5087: CIMT in HIV+ (PI, non PI groups) and HIV-, published AIDS 2005**
- **A5152S: 3 class sparing regimens on endothelial functioning, published Amer College Cardiology 2008**
- **A5260S: Cardiovascular, Anthropometric, and Skeletal Effects of ART Initiation with FTC/TDF plus ATV/r, DRV/r, or RAL: Metabolic Substudy of A5257, enrolled 165 of 330 thus far, measuring BART FMD, CIMT, CT scan, plus inflammatory markers**

ACTG studies with Cardiac Biomarkers

- **A5292: A Randomized Controlled Trial to Compare the Effects of HAART Versus Statin Therapy on Endothelial Function and Markers of Inflammation/Coagulation In HIV-Infected Individuals with High CD4 cell Count, in design**
- **A5293: Effect of HDL-Raising Therapies on Endothelial Function, Lipoproteins, and Inflammation in HIV-infected Subjects with Low HDL Cholesterol: A Randomized Trial of Extended Release Niacin vs. Fenofibrate, in design**
- **Other studies measuring inflammatory markers: A5095, A8286, A5274, NWCS302, NWCS305**

Pediatric (IMPAACT or PHACS) Studies with Cardiac Endpoints

P2C2 and CHAART:

Scientific goals:

- Evaluate HIV-infected children using serial echocardiograms to identify cardiovascular toxicity and assess any potential association with antiretroviral therapy
- Evaluate HIV-uninfected children born to HIV-infected mothers using serial echocardiograms to evaluate potential cardiotoxic effects of HIV and *in utero* ARV exposure

Status: several papers published (NEJM, Circulation, Lancet)

Populations:

P2C2 – mostly unexposed, or mono-therapy with ZDV

CHAART – over 80% exposed in utero to CART

Pediatric (IMPAACT or PHACS) Studies with Cardiac Endpoints

Endpoints:

- **Abnormal echocardiogram parameters: contractility, ejection fraction, fractional shortening are key functional measures of cardiac functioning, additional measures of interest are structural parameters such as LV wall thickness and LV Dimension (diastolic and systolic); abnormal functioning or structure defined as z-scores >2 (or <2 for function)**
- **Also evaluated cardiac deaths among HIV-infected**

Statistical Methods: Cox proportional hazards model for time to death as a function of echo z-score for wall thickness or fractional shortening, comparison of percent mortality by abnormal echo status, linear regression with z-scores as outcome

PHACS Echocardiogram Studies

- **HIV+ vs HIV- (AMP)**: have about 440 of target 520 echos completed at a single time in 7-16 year olds, significant differences detected both in percent abnormal and in adjusted mean z-scores. Preliminary results presented at AHA meeting plenary session.
- **HIV-uninfected (SMARTT)**: have about 250 echos of 400 target, completed at a single time in 3-5 year olds born to HIV+ mothers, preliminary results presented at the IWHOD 2010 Meeting.

IMPAACT NWCS 102: Cardiomyopathy

- **Analysis of risk and protective factors for development of cardiac dysfunction in children**
- **Status: Will be presented in oral session at IAS 2010**
- **Study Size: 3095 perinatally HIV+, 147 cases of cardiac dysfunction (8.3 cases per 1000 children-years)**
- **Endpoints: Cardiac dysfunction defined as cardiomyopathy or use of cardiac medications.**
- **Statistical Methods: Cox proportional hazards model for time to cardiomyopathy, and logistic regression models for risk factors measured up to the time of censoring or case status in nested case-control study.**

Pediatric Studies of Cardiac Biomarkers

- **P1045: lipids and insulin resistance in 386, AIDS 2009**
- **P1010: change in lipids, growth, IGF1, IGF BP1 and IGF BP3 over 1 year in 97 HIV+ children starting ARV therapy, 3 publications (Chantry, Hughes, Cervia, et al)**
- **P219/219C:**
 - Prevalence of hypercholesterolemia, 13%, PIs as risk factors
 - Incidence of hypercholesterolemia, 13%, PIs again
 - Management of high cholesterol in 240 with incident high cholesterol to evaluate time to resolution, changes in ARV
- **P1063: Atorvastatin dose-escalation study, PK with ARVs.**
- **PHACS: Metabolic and Cardiovascular Working groups, measuring lipids, insulin resistance, body composition, vascular biomarkers, cardiac biomarkers**