Long-term follow-up of ACTG study subjects

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A5001

ACTG Longitudinal Linked Randomized Trials (ALLRT) Cohort

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Origins of ALLRT

- Recognition in 1998/9 that longer-term follow-up of subjects participating in ACTG trials would be informative
- Desire to maintain a cohort of clinical trials participants for future study

A5001: Introduction

- **Primary Objectives:**
  - To evaluate the long-term (5+ years) outcomes of potent combination ART
    - Virological
    - Immunological
    - Pharmacological/pharmacogenomic
    - Clinical endpoints and adverse effects
    - Quality of life, resource utilization
    - Neurological/cognitive

A5001: Introduction

- **Prospectively planned series of meta-analyses and cross-protocol analyses of subjects enrolled in ACTG trials that:**
  - Provide randomized ART or immune-based treatment regimens
  - Include ART-naïve or ART-experienced patients

A5001: Methods

- **Enrollment in a qualifying "parent" study**
- **Data collection at entry:**
  - Medical History
    - Prior OIs, AIDS defining events
    - FHx, CVD risk factors
    - Gynecologic diagnoses
    - Metabolic complications (DM, CVD, hyperlipidemia)
    - Hepatitis B, C serology
    - Nadir CD4+ count and pre-Rx HIV-1 RNA
    - Pre-Rx lipid levels

A5001: Methods

- **Evaluations on study (Q16 weeks):**
  - Physical Examination
    - Anthropometric measures
    - Gyn, Neurological assessments Q48 wks
  - CBC, liver chemistries, serum creatinine, U/A, urine microalbumin
  - Lipid profile (fasting repeat if abnormal), FBS
  - CD4+ cell counts and subsets; activation markers (from 2000-2003, then discontinued)
  - Plasma HIV-1 RNA level
  - Hepatitis serology (at entry if not previously positive)
  - PBMC, plasma, serum

A5001 Overall Accrual

- Current Accrual = 3,695 (as of 5/06)
- Mean F/U from parent study entry:
- ~ 3.7 yrs ART-naïve (max 8.9 yrs)
- ~ 4.9 yrs ART-exp. (max 9 yrs)
- (Data as of 3/15/06)

Baseline Demographics of A5001 Subjects

- Age (mean) 38 yrs
- Current/prior IDU 8%
- Female 17%
- ART-naïve 66%
- CD4+ count 218 cells/μL
- HIV RNA 152,000 c/ml

Baseline Demographics of A5001 Subjects

Race/Ethnicity	%
White	50
Black	23
Hispanic	19
Asian/Pacific Islander	2
Native Am/Alaskan	1
Other	5

Baseline CD4+ Cell Counts of A5001 Subjects

CD4+ (cells/uL)	%
Median	218
<=50	16
51 - 200	24
201 - 350	26
351 - 500	16
500+	17

Baseline HIV-1 RNA of A5001 Subjects

RNA (copies/mL)	%
Median	152,000 c/ml
<=10,000	28
10,000-100,000	38
>100,000	35

Status of Stored Specimens
(6/04)

- **BRI Repository**
  - Plasma 192,010
  - Serum 100,247
  - Viable PBMC 99,764
- **Non-BRI (Sites)**
  - Plasma 43,564
  - Serum 10,583
  - Viable PBMC 25,709
- **Overall BRI total 414,409**
- **Overall Non-BRI 84,279**
- **Total 498,688**

Status of Analyses

- **Neurology, QoL, 3-yr treatment response, OI endpoints, influence of HCV on lipid levels analyses completed; manuscripts published/submitted**
- **Additional planned analyses:**
  - Clinical events, AEs associated with therapy (including sex differences)
  - Durability of VL and CD4+ responses after 4+ years
  - Influence of specific drug regimens/regimen type
  - Genomics analyses
  - Participation in NA-ACCORD Database

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Diagnosed Opportunistic Infections

	Total N = 519	Major n = 163	Minor n = 356
Parasitic	**18 (3%)**	**7 (4%)**	**11 (3%)**
Fungal	**224 (43%)**	**70 (43%)**	**154 (43%)**
Bacterial	**51 (10%)**	**47 (29%)**	**4 (1%)**
Viral	**209 (40%)**	**22 (13%)**	**187 (53%)**
Malignancy	**17 (3%)**	**17 (10%)**	**--**

Major OI Diagnoses (N = 163 OIs in 116 Subjects)

- Most Common:
- Pneumocystis jiroveci Pneumonia (20%)
- Esophageal Candidiasis (17%)
- MAC (17%)
- CMV (7%)
- Kaposi's Sarcoma (6%)
- Time of Diagnosis, post ART Initiation
- < 24 weeks: N=79 (48%)
- ≥ 24 weeks: N=84 (52%)

116 Subjects with Major OI Diagnoses

- **CD4+ counts did not increase substantially from baseline to time of 1st OI diagnosis**
  - Median baseline CD4+ count: 37 cells/μL
  - Median CD4+ count at 1st OI diagnosis: 62 cells/μL
- **76% of subjects had a VL > 50 copies/ml just prior to major OI diagnosis**

Conclusions

- **OIs continue to occur among ART-naïve individuals treated with potent combination ART**
  - Half of all OIs occur more than 24 weeks after starting ART
- **As with other studies, high pre-treatment VL and low CD4 count were associated with increased risk of OI after starting ART**
  - Lack of increase in CD4+ cell count after starting ART also contributes
- **Unique association of female sex with increased risk of OI**
- **Evaluation of additional variables (including predictors of risk after 24 weeks), and interactions among variables, is underway**

Some pitfalls

- Subject and investigator fatigue
- Less useful for monitoring a placebo control group
- Although well-distributed across the US, not all ACTUs are within reach of a CCR5 inhibitor trial site

A5001 Protocol Team

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