

# Risk Factor Analyses for Immune Reconstitution Inflammatory Syndrome and Mortality during a Randomized Trial of Early versus Deferred ART in the Setting of Acute Opportunistic Infections (ACTG A5164)

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## Abstract

### Background

Immune Reconstitution Inflammatory Syndrome (IRIS) complicates ART initiation in 10-40% of patients. Despite ART, patients with advanced HIV remain at increased risk for mortality. Few prospective studies have evaluated risk factors for IRIS and mortality in this setting.

### Methods

A5164 randomized subjects with OIs (excluding TB) to ART at entry (E-ART) vs. ART delayed ≥28 days from entry (D-ART). Associations between IRIS and baseline characteristics, entry OIs, and laboratory values were evaluated using Wilcoxon and Fisher's tests. Multivariate analyses of the time from ART initiation to IRIS were performed using Cox models with time-varying covariates. Risk factors for mortality were determined using Cox models.

### Results

Of 282 subjects (median CD4 29 cells/μL, HIV viral load (VL) 5.1 log c/mL) enrolled, 262 initiated ART (23/282 (8.2%) died, 20/262 (7.6%), 95% CI 4.7%, 11.8%) developed IRIS after a median of 33 days (QR 26, 72) on ART, 8/135 on E-ART and 12/127 on D-ART (p=0.35). No baseline variables were associated with IRIS. There was no difference in IRIS between subjects who received corticosteroids during their OI and those who did not: p=0.59 (6.0%) vs. 11/112 (9.8%), p=0.35. However, no subjects developed IRIS while still receiving corticosteroids. Log VL decline at 4 weeks was associated with IRIS (-2.48 vs. -2.07, p=0.04) but change in CD4 was not. In Cox models controlling for VL change, subjects with fungal infections had a hazard ratio (HR) of 2.9 for developing IRIS (p<0.02). In univariate analyses, entry mycobacterial infections (HR=5.9, p<0.01), OI number (HR=2.2 for each additional OI, p<0.01), hospitalization (HR=3.7, p<0.01), low albumin (HR=3.6, p=0.02), low hemoglobin (HR=2.8, p=0.03), and low CD4 (HR=1.3 for each 10 cells/μL decrement, p=0.02) were associated with mortality. In multivariate analysis, entry mycobacterial infection (HR=4.6, p<0.01), hospitalization (HR=3.2, p<0.01), and low CD4 (HR=1.2 for each 10 cells/μL decrement, p=0.04) predicted mortality.

### Conclusion

Predictors who will develop IRIS at ART initiation are different. E-ART does not lead to an increase in IRIS in non-TB OI. Change in VL, but not CD4, predicted IRIS. Corticosteroids, as used in this study, do not appear to prevent IRIS but may delay its presentation. Risk factors for increased mortality in the pre-ART era including low albumin, hemoglobin and CD4 remain important in patients with an OI initiating ART. Mycobacterial infections are associated with high rates of mortality despite ART.

## Background

- Reported prevalence of IRIS ranges from 10-40%
- Majority of studies are retrospective and include patients without OIs at baseline
- Two retrospective studies have shown an association between "early" ART and IRIS but confounders such as adherence may have biased results
- ART is sometimes deferred in patients with an acute OI because of fear of IRIS, despite the limitations of the data
- Patients with acute OI initiating ART remain at significant risk for mortality
- Few prospective studies evaluate the risk factors for IRIS and mortality
- Primary study, ACTG A5164 presented at CROI 2008 (Zolopa, et al; abstract#142) showed decreased AIDS progression/death with early ART in acute OI (14% vs 24%; p=0.04)

## Methods

### ACTG A5164 Design

- ACTG A5164 randomized subjects with OIs (excluding TB) or serious bacterial infections to ART at entry versus ART delayed ≥28 days from entry
- Allowable entry OIs included *Pneumocystis jirovecii* pneumonia (PCP), other fungal infections (including cryptococcus, histoplasma, and aspergillus), toxoplasmosis, cytomegalovirus, and non-tuberculous mycobacteria

### Case Definitions

- IRIS cases were prospectively identified at the study site and verified centrally by a study chair
- Study chairs also reviewed study records of subjects who were prescribed anti-inflammatories during the study in an attempt to diagnose additional cases of IRIS
- IRIS was defined as: "Evidence of an increase in CD4+ cell count and/or a decrease in the HIV-1 viral load in response to starting ART with symptoms that are consistent with an infectious/inflammatory condition and temporally related to initiation of ART but cannot be explained by a newly acquired infection, the expected clinical course of a previously recognized infectious agent, or the side effects of ART itself."

•For mortality analysis, participants who were alive at last contact were censored at that contact date, with one exception; one subject died of a cocaine overdose after week 48 and was categorized as "Alive" and censored at week 48

### Statistical Methods

- IRIS risk factor analysis limited to those subjects who started ART and had at least one follow-up visit after the initiation of ART with baseline considered date of ART initiation
- Associations between IRIS and baseline characteristics, entry OIs, and laboratory values were evaluated using the Wilcoxon rank-sum and Fisher's exact tests.
- Analyses of the time from ART initiation to IRIS were performed using Cox models
- Risk factors for mortality were determined using Cox models
- Limited multivariate analyses for mortality to no more than 3 dependent variables to avoid overfitting

**Table 1: Baseline Characteristics of Subjects in ACTG A5164**

Gender	Male	85% (241/282)
	Female	15% (41/282)
Race/Ethnicity	Black	37% (103/282)
	Hispanic	36% (101/282)
	White	23% (64/282)
	Other	5% (14/282)
Median Age (IQR)		38 (32-44)
Median CD4+ (cells/μL) (IQR)		29 (10-55)
Median HIV RNA (log10) (IQR)		5.07 (4.71-5.63)
Entry OIs	PCP	64% (181/282)
	Bacterial Infection	15% (41/282)
	Cryptococcus	15% (41/282)
	Mycobacterial infection	6% (18/282)
	Toxoplasmosis	5% (15/282)
	CMV	4% (11/282)
	Histoplasmosis	4% (10/282)

**Table 2: Univariate Analyses of Baseline Characteristics vs. IRIS**

Variable	Relative Risk of IRIS (95% CI)	P-value
Early ART	0.63 (0.27, 1.5)	0.28
Age ≥40	1.2 (0.52, 2.8)	0.67
ART-Native	0.78 (0.20, 3.2)	0.73
Steroids +/- 14 days ART Start	0.60 (0.26, 1.4)	0.23
Entry Mycobacterial Infection	1.8 (0.47, 7.2)	0.39
<b>Entry Fungal Infection (not PCP)</b>	<b>2.6 (1.1, 6.1)</b>	<b>0.03</b>
Entry PCP Infection	1.2 (0.49, 3.1)	0.64
Hospitalized at Entry	1.7 (0.74, 4.0)	0.21
ART initiation CD4+ < 29 cells/μL	1.3 (0.57, 3.1)	0.52
ART initiation viral load ≥100,000 c/mL	1.1 (0.46, 2.6)	0.85

## Results

**Table 3: Change in T-cell subsets and Viral Load versus IRIS**

Variable	IRIS	Not IRIS	P-value
Median 4 week change in CD4+ (cells/μL) (IQR)	82 (34, 187)	70 (30, 140)	0.21
Median 8 week change in CD4+ (cells/μL) (IQR)	96 (51, 168)	98 (50, 156)	0.80
<b>Median 4 week change in CD4% (IQR)</b>	<b>6.0 (3.5, 10.5)</b>	<b>4.0 (2.0, 7.0)</b>	<b>0.02</b>
Median 8 week change in CD4% (IQR)	7.0 (3.0, 8.0)	4.0 (2.0, 7.0)	0.14
<b>Median 4 week change in log viral load (IQR)</b>	<b>-2.5 (-2.8, -2.1)</b>	<b>-2.1 (-2.6, -1.5)</b>	<b>0.04</b>
Median 8 week change in log viral load (IQR)	-3.0 (-3.7, -2.2)	-2.6 (-3.2, -2.0)	0.11

**Table 4: Univariate Cox Models for Baseline Characteristics vs. Mortality**

Variable	Hazard Ratio (95% CI)	P-value
Early ART	0.66 (0.29-1.5)	0.34
Age≥40	0.64 (0.27-1.5)	0.30
<b>Entry Mycobacterial Infection</b>	<b>5.9 (2.3-14.9)</b>	<b>&lt;0.001</b>
Entry Cryptococcal Infection	2.0 (0.80-5.2)	0.13
<b>Entry PCP Infection</b>	<b>0.42 (0.19-0.97)</b>	<b>0.04</b>
<b>Number of OIs at entry</b>	<b>2.2 (1.4-3.5)</b>	<b>0.001</b>
<b>Hospitalized at entry</b>	<b>3.7 (1.6-8.5)</b>	<b>0.002</b>
<b>Albumin &lt;2.5 mg/dL</b>	<b>3.6 (1.3-10.1)</b>	<b>0.02</b>
<b>Hemoglobin &lt;10 g/dL</b>	<b>2.8 (1.1-6.7)</b>	<b>0.02</b>
<b>Lymphocytes &lt;600 cells/μL</b>	<b>4.8 (1.7-13.3)</b>	<b>0.002</b>
<b>CD4+ count (per 10 cell/μL decrement)</b>	<b>1.3 (1.0-1.5)</b>	<b>0.02</b>
HIV RNA>100,000 c/mL	2.6 (0.97-7.0)	0.06

**Table 5: Multivariate Cox Model for Mortality**

Variable	Hazard Ratio (95% CI)	P-value
<b>Entry Mycobacterial Infection</b>	<b>4.6 (1.8-12.0)</b>	<b>0.002</b>
<b>Hospitalized at Entry</b>	<b>3.2 (1.4-7.4)</b>	<b>0.007</b>
<b>Baseline CD4 (per 10 cell/μL decrement)</b>	<b>1.2 (1.0-1.5)</b>	<b>0.04</b>

## Conclusions

### IRIS Secondary Analysis

- Retrospective reports likely overestimate the incidence of IRIS
- The 7.6% incidence of IRIS in this study is similar to the 10.4% estimate from a large prospective cohort from South Africa (Murdoch, et al)
- In patients with an acute OI, it is difficult to predict who will develop IRIS from baseline characteristics, although those with fungal disease (other than PCP) may be at increased risk of IRIS.
- Corticosteroids, as used in this study, do not appear to prevent IRIS but may delay its presentation
- Change in viral load and change in CD4% at 4 weeks are both clearer predictors of IRIS than change in CD4+ count
- In subjects with non-TB OIs, early initiation of ART does not increase the incidence of IRIS, and concern for IRIS should not be a reason to defer ART
- The previous association found in retrospective studies between early ART initiation and IRIS may have been due to biases inherent in their study designs

### Mortality Secondary Analysis

- Risk factors for increased mortality in the pre-ART era including low albumin, hemoglobin, total lymphocytes and CD4+ count remain important predictors in patients with an acute OI initiating ART
- CD4+ counts obtained at baseline during an acute OI should not be discounted as they predict survival, with lower values associated with an increased risk of death
- Mycobacterial infections are associated with high rates of mortality despite ART