

The Immune System and Complications of HIV Therapy

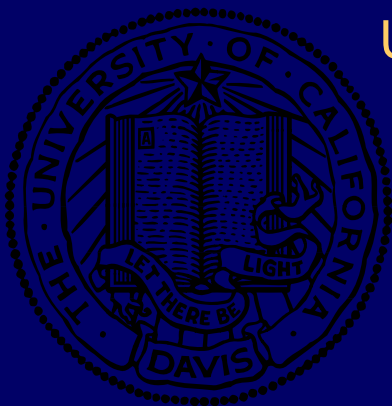
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IRIS

- Associated with an increase in CD4+ T-cell counts, decrease in HIV RNA, increase in signs or symptoms of an infection or inflammatory condition relative to initiation of ARV.
- Most often occurs within weeks of starting ARV
- Can occur up to 6 months
- Most common in those with <200 CD4+ T-cells
- Estimated to occur in 10-20%

Common Syndromes

1. MAC – occurs in those with prior documented or without a history of MAC. Fever, focal lymphadenitis , fistulas can occur at diffuse sites.
2. PML – MRI inflammation with contrast, biopsy with gliosis variable clinical course.
3. CMV- can occur in those with prior CMV retinitis or newly diagnosed. Increased inflammatory response and ocular changes.
4. MTb – occurs in 11-39% - new fevers, increased or thoracic adenopathy, pulmonary infiltrates or effusions
5. Cryptococcus – worsening meningitis, development of mediastinal or cervical lymphadenopathy, or cutaneous lesions

Common Syndromes (cont.)

6. PJP Pneumonia - worsening of pneumonia or rapid development of PCP after starting ART.
7. VZV – Herpes Zoster after starting HAART, maybe 2-5 fold higher in ART.
8. HSV – unusual presentations of chronic genital ulcers or proctitis.
9. Toxoplasmosis – rarely described
10. KS – Progression of KS lesions
11. HBV or HCV – increase in ALT or AST > 3 times baseline
12. HIV Dementia – worsening of symptoms after ART and no evidence of PML

IRIS Management

- Non steroidal anti-inflammatory compounds
Manage systemic symptoms – fever
- Prednisone – severe cases
MTb
MAC
PML
Sight threatening CMV retinitis
Cryptomenigitis
- Hold ARV
- ACTG 5164 – immediate vs. deferred ART, completely enrolled – N=283

Immune Reconstitution Inflammatory System (IRIS) Objectives (A5202)

1. To estimate the incidence of IRIS in subjects that initiate potent ARV therapy
2. To describe the presentation of IRIS and associated pathogens and/or inflammatory conditions
3. To evaluate the association of baseline CD4+ T-cell counts and plasma HIV-1 RNA levels and changes from baseline
4. To evaluate the association between the duration of prior OI treatment and/or prophylaxis with IRIS event
5. To explore the immunopathogenesis of IRIS by measuring markers of immune activation, LPA, plasma cytokines, induced cytokines and Tregs.

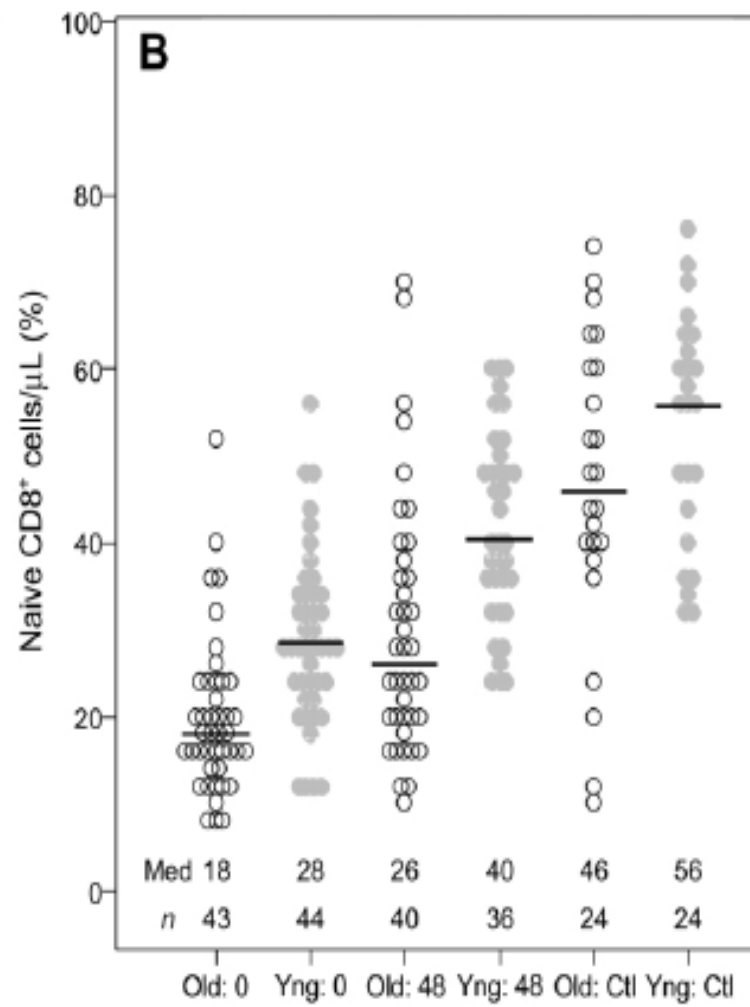
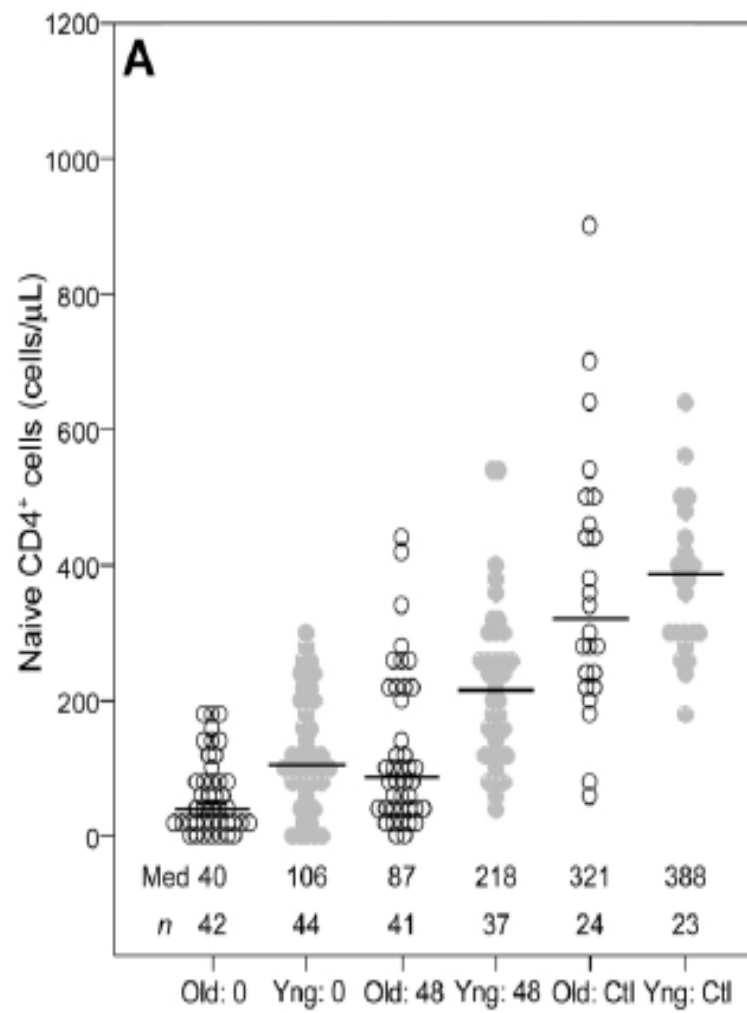
Immunologic Non-Responders

- Failure to increase by 100 cells over baseline in naives
- Multiple trials and cohorts identify 10-20% who are virologic successes and immunologic failures
- In ACTG 384 13% were virologic successes between weeks 24-144 but were immunologic failures
- The immunologic failures were older, age 42 vs 35 years $P=0.005$

Proportion of subjects with >100 CD4 cell count increase by baseline CD4 stratum and study week

CD4 Stratum	Week 24	Week 48	Week 96	Week 144
1	54.7%	82.8%	95.2%	92.3%
2	61.1%	77.2%	93.6%	90.9%
3	67.9%	77.8%	87.5%	100%
4	55.2%	73.3%	84.6%	95.2%
5	55.1%	72.7%	79.0%	73.9%
p-value ^a	0.729	0.170	0.0027	0.101

^aCochran-Armitage trend test



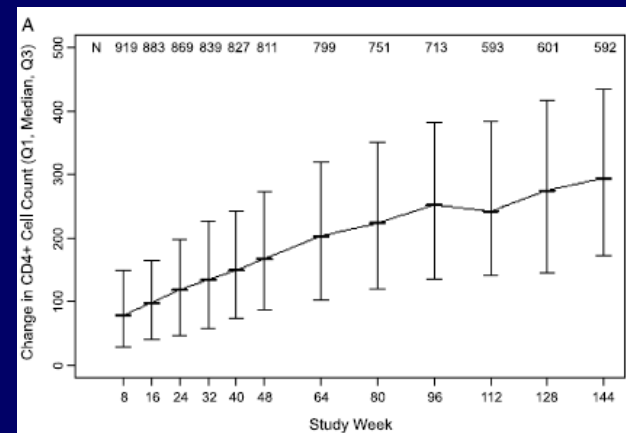
Baseline Characteristics

Characteristics	Entire 384 Cohort (n=980)	Comprehensive Immunologic Assessments (n=623)
Age (median), y	36	36
Sex (% male), %	82	83
H/O IDU, %	9	8
CD4 cell count/mm ³ (median)	279	280
HIV-1 RNA log ₁₀ copies/mL (median)	4.94	4.94

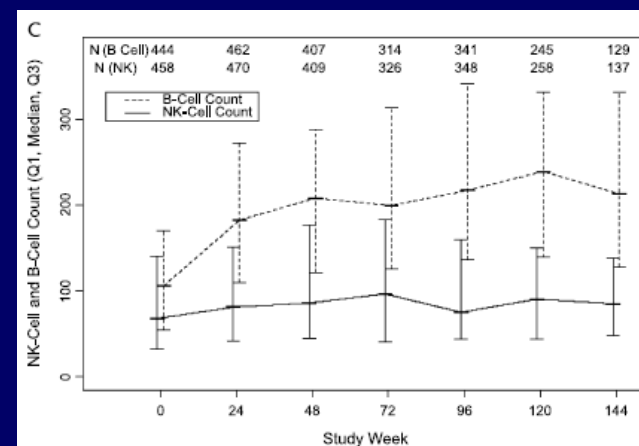
Change in lymphocyte counts after starting ART

- Median increase in CD4 cells at wk 144 of 294
- B cells increased substantially
 - From 106 at baseline to 213 at wk 144
- CD8 and NK cells essentially flat

CD4 cells



B cells and NK cells

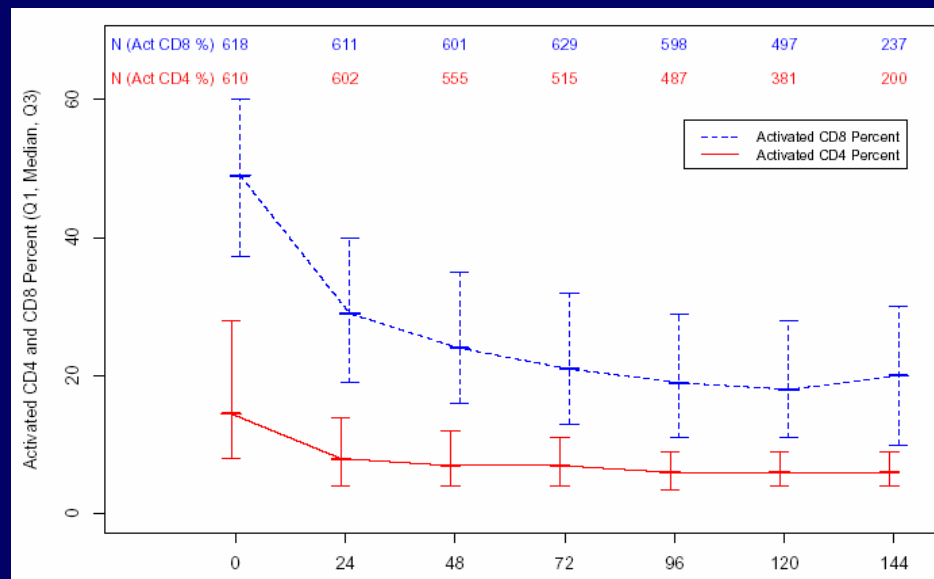


Univariate & Multivariable Analysis of Baseline-and Treatment-Related Factors and CD4 Cell Recovery

	<u>Univariate Analysis</u>		<u>Multivariable Analysis</u>	
	Median Change in CD4 Count Baseline to Wk 48	<i>P</i>	Coefficient Estimate	<i>P</i>
Age, y				
≤40	182	0.0005	-1.9 (Continuous)	0.0014
>40	135			
Sex				
Male	164	0.009	-53 (Male)	0.0004
Female	205			
Virus load				
VL ≤50	176	0.0006	46 (VL ≤ 50)	0.0008
VL >50	127			
Baseline CD4 count	ND		-0.02	0.60
Baseline log ₁₀ VL	Coefficient est=25	0.0002	34	<0.0001

T cell activation

- Rapid decline in CD8 & CD4 activation after ART initiation
 - No difference by initial treatment assignment
- Subjects who had higher levels of persistent T cell activation after starting ART had smaller increases in CD4 cell counts



Conclusions

1. Immune Reconstitution Syndrome occurs with variable frequency across groups of patients beginning antiretroviral therapy
2. Exact pathogenesis remains unclear- restoration of pathogen specific immune responses or broaden immune reconstitution
3. Subgroups of patients are immunologic failures while being virologically suppressed
4. Age is one identified risk factor and others are being examined
5. Individuals with more advanced disease as manifested by lower CD4 counts fail to reconstitute
6. Activation markers remain elevated despite successful virologic suppression