ACTG A5221 STRIDE: An international randomized trial of immediate vs early antiretroviral therapy (ART) in HIV+ patients treated for tuberculosis

D Havlir, P Ive, M Kendall, A Luetkemeyer, S Swindells, J Kumwenda, J Rooney, S Qasba, E Hogg, J Andersen, I Sanne

ACTG SITE INVESTIGATORS

Mina Hosseinipour
Umesh Lalloo
Valdilea Veloso
Fatuma Some
N. Kumarasamy
Nesri Padayatchi
Breno Santos
Stewart Reid
James Hakim
Lerato Mohapi
Peter Mugyenyi

Constance Benson
Jorge Sanchez
Javier Lama
Jean William Pape
Fred Sattler
Aida Asmelash
Evans Moko
Frederick Sawe
Mauro Schechter
Thira Sirisanthana
Srikanth Tripathy
Judith Aberg

ACTG
AIDS CLINICAL TRIALS GROUP

BACKGROUND

- HIV-associated TB is a major cause of morbidity and mortality globally
- ART started prior to completion of TB therapy reduces mortality[1]
- However, the optimal time to start ART during TB treatment has not been established
- Clinicians often must decide when to start ART prior to the confirmation of TB

[1] Abdool Karim, NEJM, 2010

ACTG AIDS CLINICAL TRIALS GROUP

HYPOTHESIS

In patients starting treatment for TB, the immediate initiation of ART (within 2 weeks) could reduce mortality and morbidity compared to the early initiation of ART (8-12 weeks)

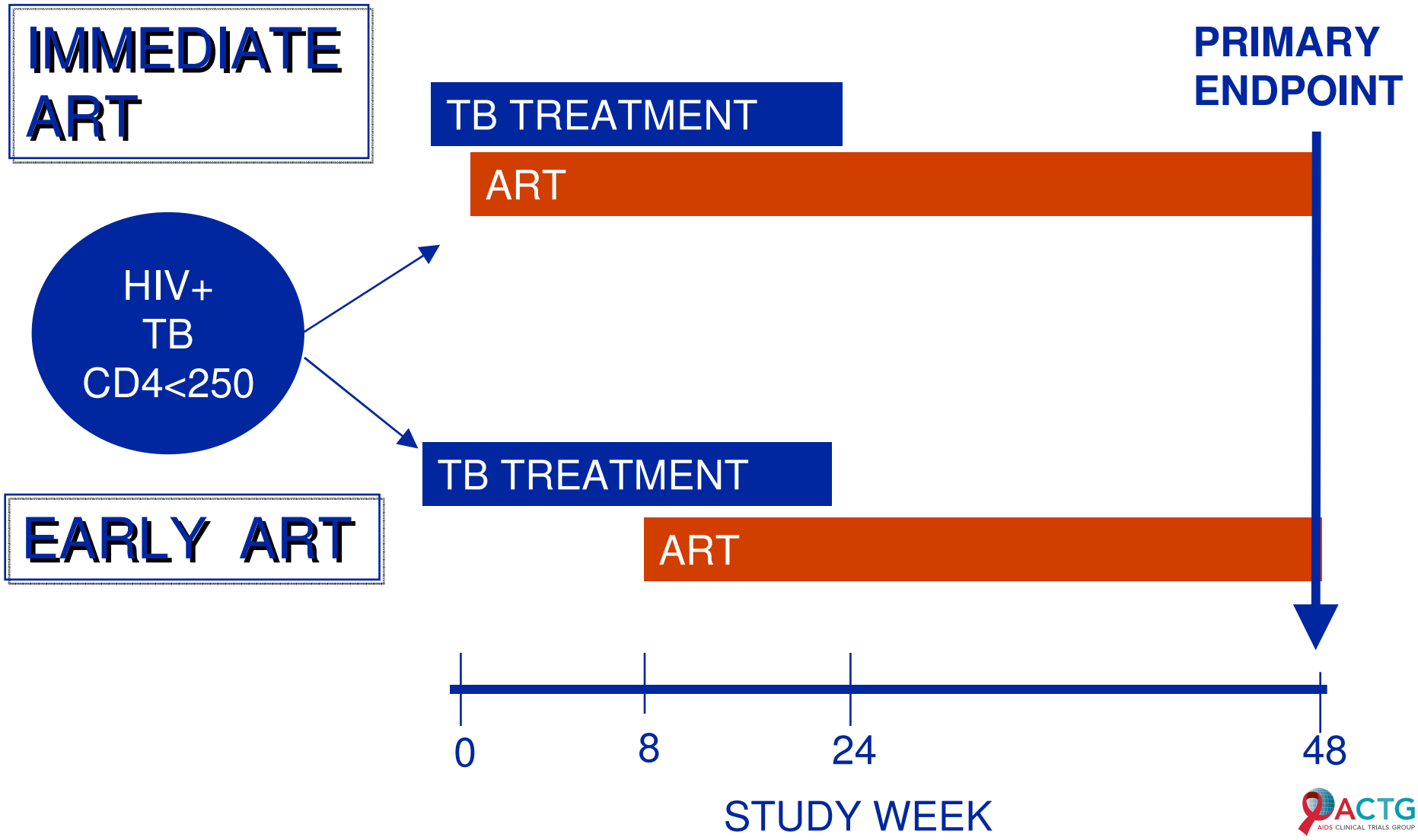
ACTG
AIDS CLINICAL TRIALS GROUP

STUDY DESIGN

- Phase IV, randomized, open-label strategy study
- HIV+ adults with confirmed or presumed TB
- CD4 <250
- Two arms: immediate ART (<2 weeks) vs. early ART (8-12 weeks)
- ART regimen: EFV + TDF/FTC
- TB treatment regimen: rifampin based, country approved

ACTG
AIDS CLINICAL TRIALS GROUP

STUDY SCHEMA



STUDY ENDPOINTS

- **Primary: all-cause mortality and new AIDS-defining illnesses by 48 weeks**
  - Proportions estimated using the Kaplan-Meier method
  - Stratified analysis by weighting by the inverse of the Greenwood's variance in each CD4 stratum
- **Secondary:**
  - **Safety**
  - **CD4, HIV RNA changes**
  - **TB IRIS[1]**
  - **TB outcomes**

[1] Required 1 major or 2 minor criteria Meintjes, Lancet ID, 2008

ACTG AIDS CLINICAL TRIALS GROUP

RESULTS: Baseline characteristics

	Treatment arm		
	Immediate N=405	Early N=401	All N=806
Study Site			
Africa	275	279	554
Asia	29	23	52
N. America	21	18	39
S. America	80	81	161
Confirmed TB	48%	45%	46%
Median CD4 cells/mm^3 (IQR)	70 (34,146)	82 (40,144)	77 (36, 145)
Median $\log_{10}$ HIV RNA	5.39	5.50	5.43
EVF/TDF/FTC	98%	96%	97%
Median time to ART	10 days	70 days	n.a.

ACTG AIDS CLINICAL TRIALS GROUP

RESULTS: Proportion with AIDS/Death

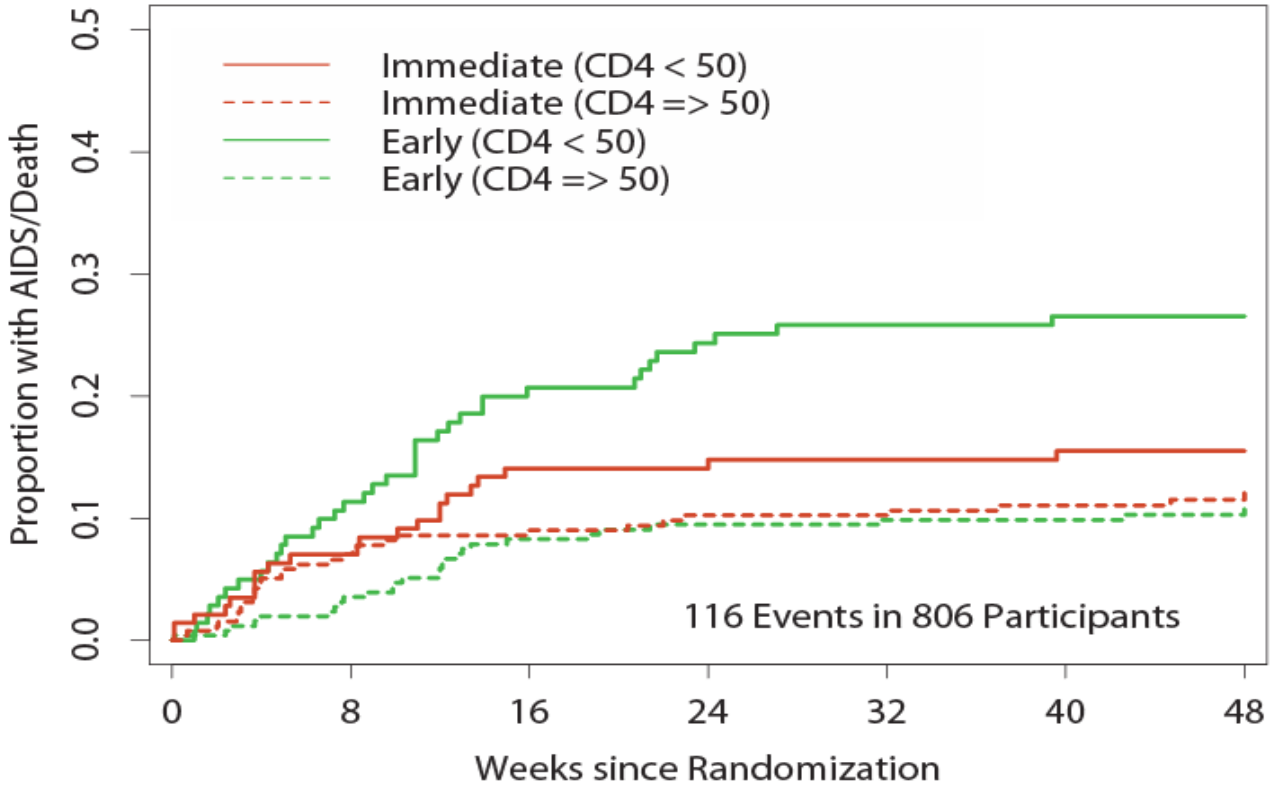
	Immediate	Early	P (95% CI for difference)
All Subjects	**12.9%**	**16.1%**	**0.45 (-1.8, 8.1)**
CD4 <50 cells/mm^3	15.5%	26.6%	0.02 (1.5, 20.5)
CD4 ≥50 cells/mm^3	11.5%	10.3%	0.67 (-6.7, 4.3)

ACTG
AIDS CLINICAL TRIALS GROUP

RESULTS: Proportion with AIDS/Death

	Immediate	Early	P (95% CI for difference)
All Subjects	12.9%	16.1%	0.45 (-1.8, 8.1)
CD4 <50 cells/mm^3	15.5%	26.6%	0.02 (1.5, 20.5)
CD4 ≥50 cells/mm^3	11.5%	10.3%	0.67 (-6.7, 4.3)

Time-to-New AIDS-Defining Illness or Death by CD4 Stratum



N at risk						
Immed 405	368	346	341	335	324	226
Early 401	371	342	329	325	318	218

Primary Endpoint: AIDS

AIDS Illness	Immediate ART (N=26)	Early ART (N=37)	Total (N=63)
Cryptococcal Disease	6	7	13
Esophogeal Candidiasis	4	8	12
Kaposi's Sarcoma	3	8	11
Pneumocystis pneumonia	3	3	6
Toxoplasmosis	2	3	5
Cytomegalovirus	2	2	4
Non-TB Mycobacteria	2	1	3
Other	4	5	9

ACTG AIDS CLINICAL TRIALS GROUP

Deaths

Cause	Immediate	Early	Total
	(N=31)	(N=37)	(N=68)
Tuberculosis	14	7	21
AIDS Related			
Bacterial infection	3	7	10
Cryptococcus	2	3	5
CMV	1	1	2
MAC	1	1	2
Lymphoma	0	1	1
Toxoplasmosis	0	1	1
Non AIDS	6	10	16
Trauma/suicide/ingestion	2	2	4
Unknown	2	4	6

ACTG
AIDS CLINICAL TRIALS GROUP

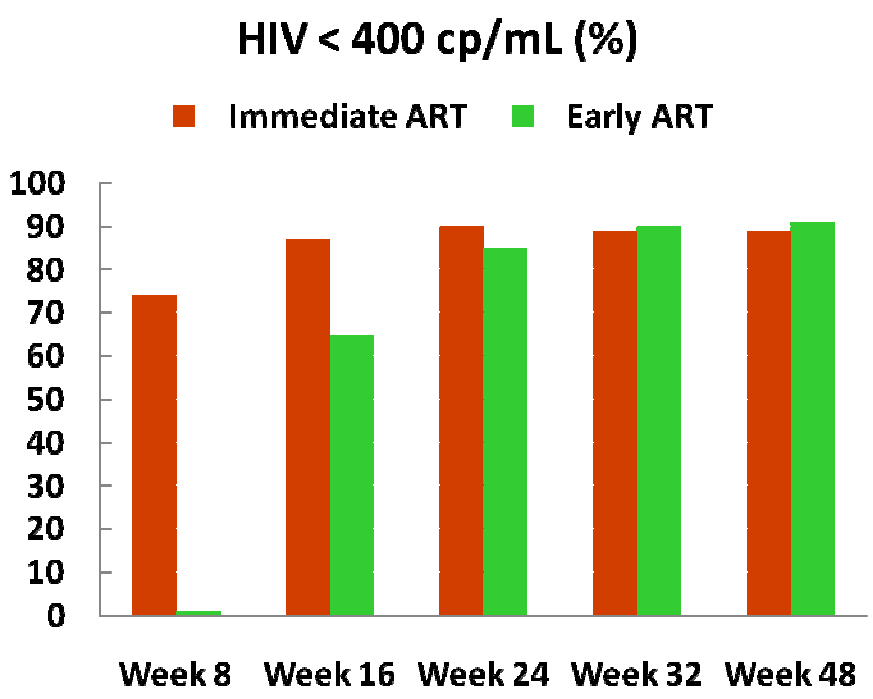
Grade 3 or 4 Clinical Events or Laboratory Abnormalities

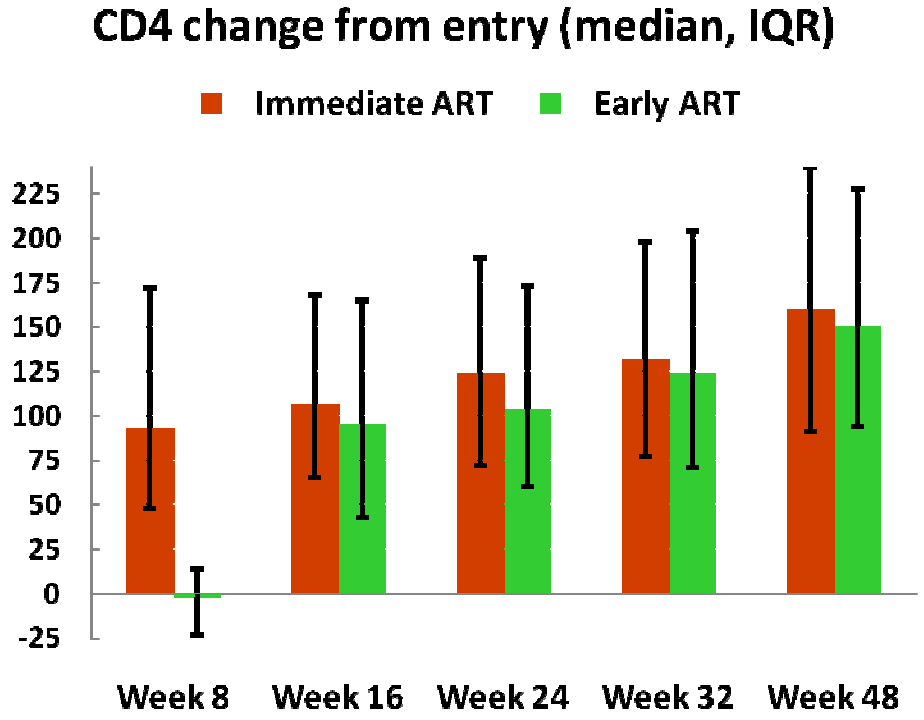
Event	Immediate	Early	Total
Constitutional	8%	8%	8%
Respiratory	4%	4%	4%
Cardiac/Circulatory	3%	2%	2%
Gastrointestinal	4%	5%	5%
Skin	3%	3%	3%
Neurological	5%	7%	6%
ANC < 750/mm^3*	9%	17%	13%
Hemoglobin	7%	5%	6%
Platelets <50,000/mm^3 *	<1%	3%	2%
Liver transaminase > 5x ULN	6%	10%	8%
ANY	44%	47%	46%

*P<0.05 for ANC and platelets, all other NS

ACTG AIDS CLINICAL TRIALS GROUP

HIV RNA and CD4 Responses





HIV RNA suppression 74% at 48 weeks
No difference between arms

CD4 change 156 cells: entry to week 48
No difference between arms

ACTG
AIDS CLINICAL TRIALS GROUP

Frequency and Predictors of MTB IRIS

	Frequency[1] # MTB IRIS
Immediate ART	43 (11%)
Early ART	19 (5%)

[1]P=0.002

Predictor	Hazard (95% CI)[1]	P Value
Immediate ART	**2.5 (1.4, 4.2)**	**0.001**
HIV RNA Higher	**1.8 (1.2, 2.7)**	**0.007**
Confirmed TB[2]	**3.6 (2.0, 6.6)**	**<0.001**

[1]Cox analysis, multivariate analysis
[2]versus probable/not TB

ACTG AIDS CLINICAL TRIALS GROUP

Summary

- Overall, immediate ART did not reduce AIDS-defining illnesses and death compared to early ART
- However, for persons with CD4+ counts< 50/mm^3, immediate ART reduced mortality/AIDS
- Grade 3 or 4 toxicities did not differ between arms
- No differences in HIV RNA suppression rates (74%) or CD4 rise between arms
- TB IRIS was higher in immediate vs early arms

ACTG
AIDS CLINICAL TRIALS GROUP

When to Start ART in TB – Building on previous studies

	A5221/ STRIDE	CAMELIA[1]	SAPIT[2]
N	806	660	429
Sites	Africa, Asia, S Am, N Am	Cambodia	S. Africa
Arms	Imm vs 8-12 wk	Imm vs 8 wk	Early vs 24 wk
Endpt	↓Death/AIDS <50 CD4	↓Death	↓Death
CD4 (IQR)	77 (36,145)	25 (11,56)	150 (77, 254)

[1] Blanc, IAC, 2010 [2]Abdool Karim, NEJM, 2010

ACTG AIDS CLINICAL TRIALS GROUP

Conclusions

- Both immediate and early ART strategies are safe and do not jeopardize CD4 or viral suppression rates
- In patients with CD4 <50, ART should be started within 2 weeks- delays increase AIDS/death
- TB IRIS is more common in those receiving immediate ART, but does not increase mortality
- Implementation of these findings should be a high priority in HIV and TB programs and will require coordination with hospital and outpatient programs

ACTG
AIDS CLINICAL TRIALS GROUP

Acknowledgments

- Study patients, families and care providers
- Other 5221 STRIDE team members: Fran Aweeka, Eva Purcelle, Ana Martinez, Travis Behm, Patricia Anthony, Janet Nicotera, Margaret Mensah-King, Stephanie Warner, Christina Blanchard, Xingye (Shirley) Wu
- Carol Suckow and Lynne Jones, Data Managers
- HIV and TB care programs
- Veronica Miller, Forum for Collaborative Research
- NIAID, Richard Hafner
- Members of the DSMB
- Gilead Sciences and Merck Pharmaceuticals

ACTG
AIDS CLINICAL TRIALS GROUP