HIV Prevention Trials Network

Effect of Early versus Delayed Initiation of Antiretroviral Therapy (ART) on Clinical Outcomes in the HPTN 052 Randomized Clinical Trial

Beatriz Grinsztejn for the HPTN 052 Team

National Institute of Allergy and Infectious Diseases

NIMH National Institute of Mental Health

National Institutes of Health

U.S. Department of Health and Human Services

National Institutes of Health

NIDA National Institute on Drug Abuse

ACTG AIDS Clinical Trials Group

Background

- HIV-associated morbidity and mortality have declined in response to widespread ART
- Primary analyses of HPTN 052 showed that early ART
  - Reduces HIV transmission
  - Associated with a longer time to HIV disease progression and preservation of the immune system over 2 years
- Present analysis includes an additional 855 PY follow-up and a broader scope of clinical events

Objectives

- To examine the clinical outcomes of immediate versus delayed ART initiation in HPTN 052
  - Overall HIV related morbidity and mortality
  - Non-AIDS clinical events
  - Other adverse consequences

Methods

- HIV+ adults (CD4+350-550/µL) from Africa, Asia, and South America were randomized to ART immediately or after CD4+ <250/µL or AIDS (Delayed)
- Primary clinical event:
  - Death
  - WHO Stage 4
  - Tuberculosis
  - Severe bacterial infection
  - Targeted serious non-AIDS events
    - Serious cardiovascular/vascular disease, Serious liver disease, End stage renal disease, Non-AIDS malignancy, Diabetes mellitus
- All events were prospectively captured and underwent blinded independent review using standardized criteria
  - ACTG Diagnoses Appendix (Appendix 60) and WHO criteria

Statistical Analysis

- Time to first clinical event was estimated using Kaplan-Meier method
  - Treatment comparisons used log-rank tests
- Subgroup analyses and analyses evaluating risk factors for primary events used Cox proportional hazards models
- Incidence rates for combined primary and secondary events were estimated by arm (with 95% confidence intervals)
  - Robust standard errors accommodated repeated events

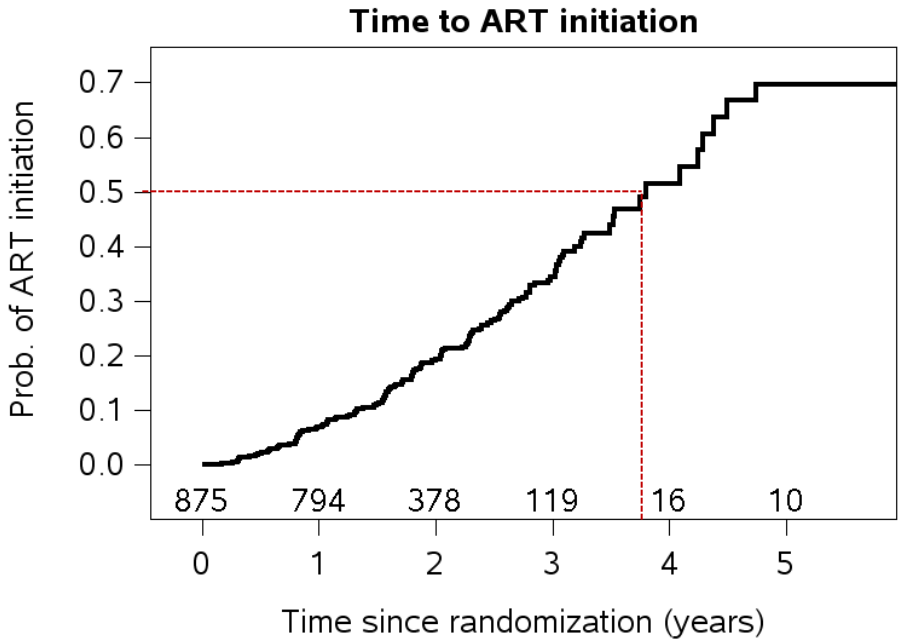
Baseline characteristics

		Delayed N=875	Immediate N=886
Female sex		50%	49%
Age	*18-25*	18%	16%
	26-40	62%	63%
	>40	19%	21%
Continent	*Asia*	30%	30%
	South America	16%	16%
	Africa	54%	54%
CD4 at baseline (cells/mm^3)*		428 (357 - 522)	442 (373 - 522)
HIV-1 RNA ($\log_{10}$ copies/ml) *		4.4 (3.9 – 4.9)	4.4 (3.8 – 4.9)
Prophylactic TMP/SMZ use		12%	11%
Prophylactic INH use		1%	<1%

**Median with interquartile range*

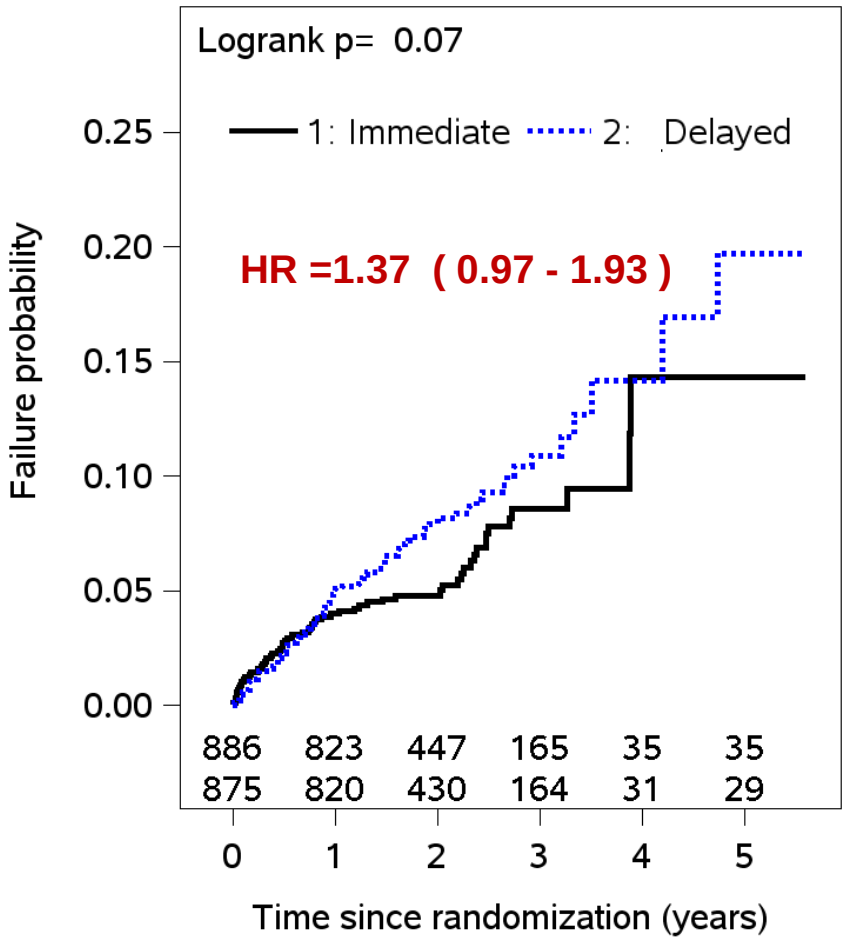
Follow-up & ART Initiation

- Overall median follow-up: 2.1 years (1.6 - 2.9)
- 213 individuals (24%) in the delayed arm initiated ART



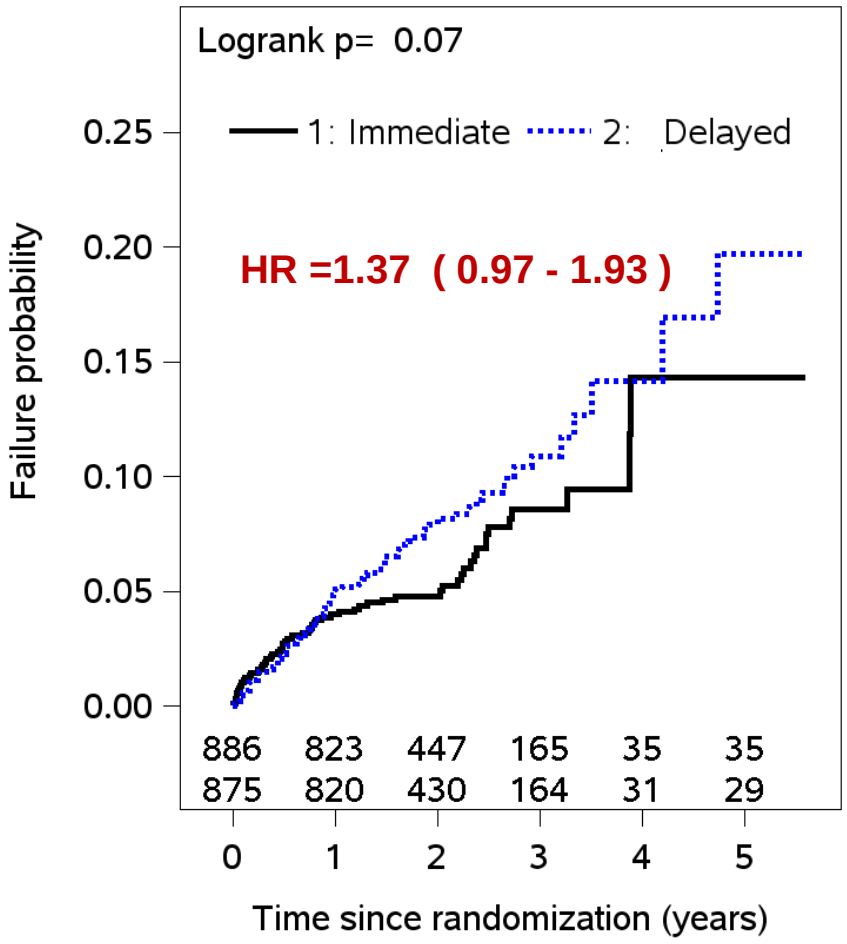
	N=213
CD4 at ART initiation (cells/mm^3)	229 (197 - 249)
HIV-1 RNA level at ART initiation (log_{10} copies/ml)	4.4 (3.9 – 4.9)
Median time to ART initiation (years)	3.8 (3.5 – 4.4)
Duration of ART exposure	1.0 (0.5 – 1.7)

Primary Events



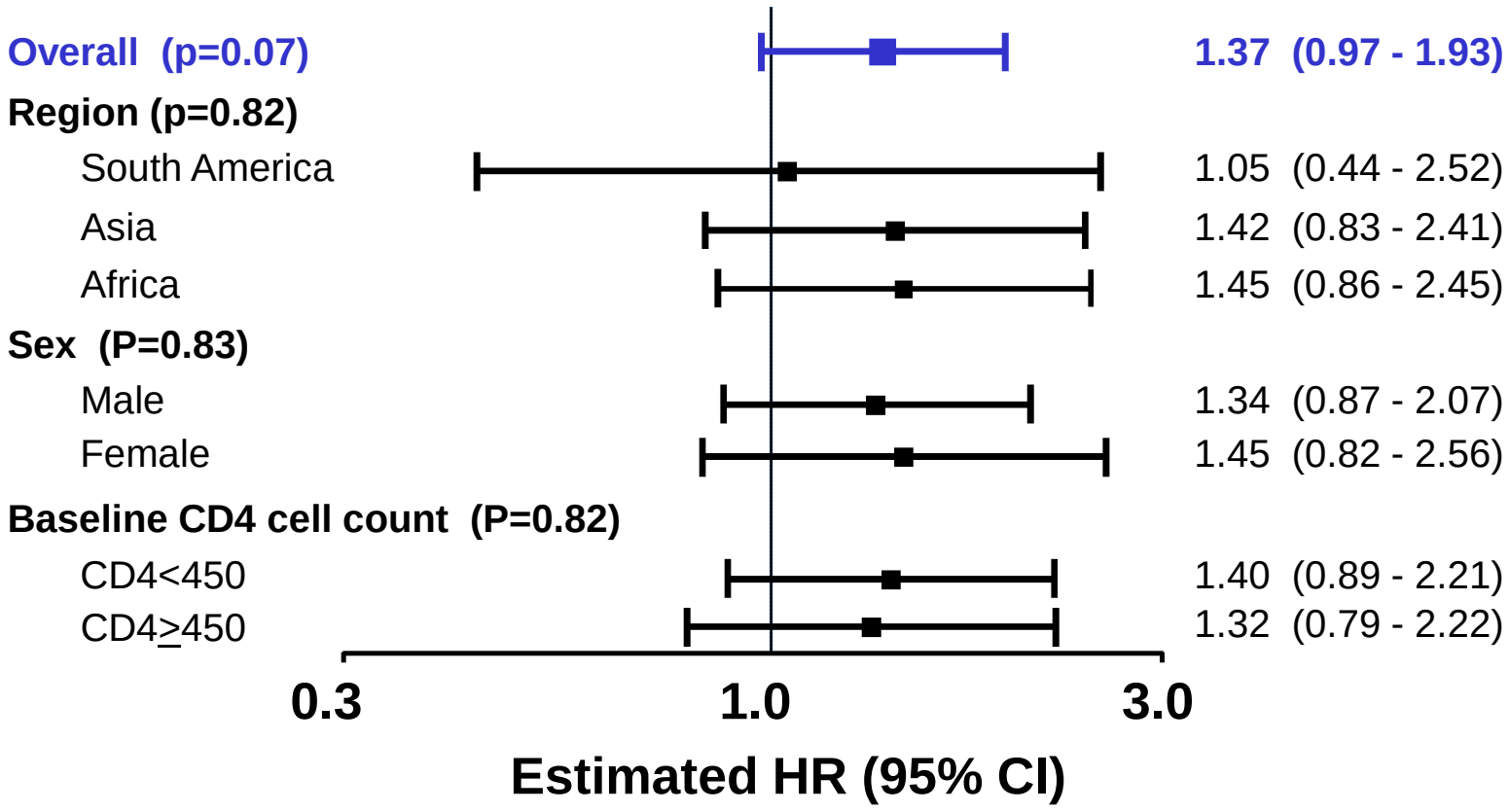
Number of subjects experiencing ≥1 event		
	Delayed	Immediate
Any Primary event	**77 (9%)**	**57 (6%)**
AIDS event	61	40
Deaths	15	11
Primary event associated	4	1
Deaths from other causes	11	10
Non-AIDS events	9	12

Primary Events



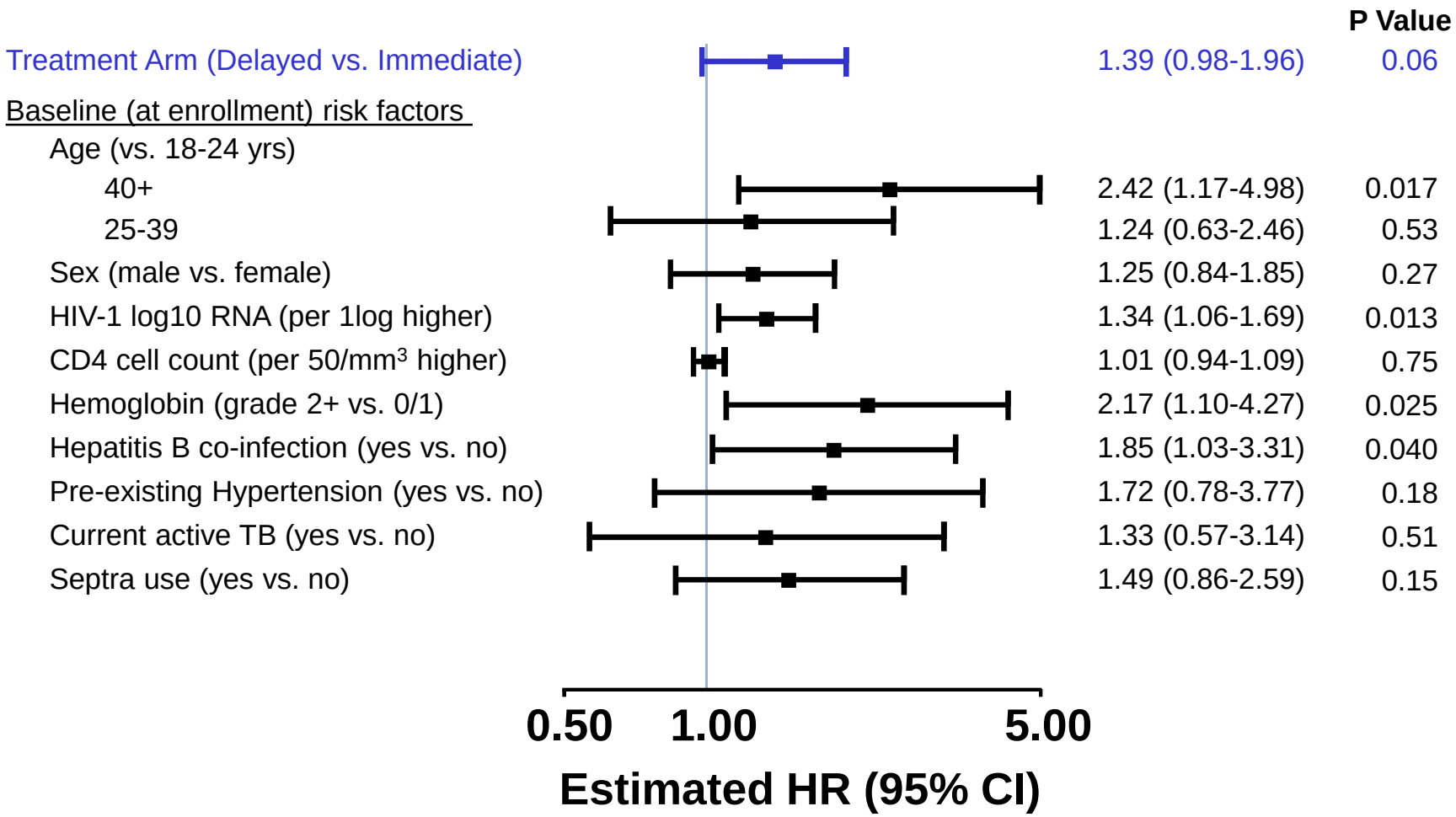
Number of subjects experiencing ≥1 event	Delayed	Immediate
Any Primary event	**77 (9%)**	**57 (6%)**
AIDS event	61	40
Deaths	15	11
Primary event associated	4	1
Deaths from other causes	11	10
Non-AIDS events	**9**	**12**
Diabetes mellitus	5	4
Non AIDS malignancy	3	3
Cardiovascular/Vascular	1	3
Serious liver disease	0	2
End stage renal disease	0	0

Hazard of Primary Event
Subgroup Analyses



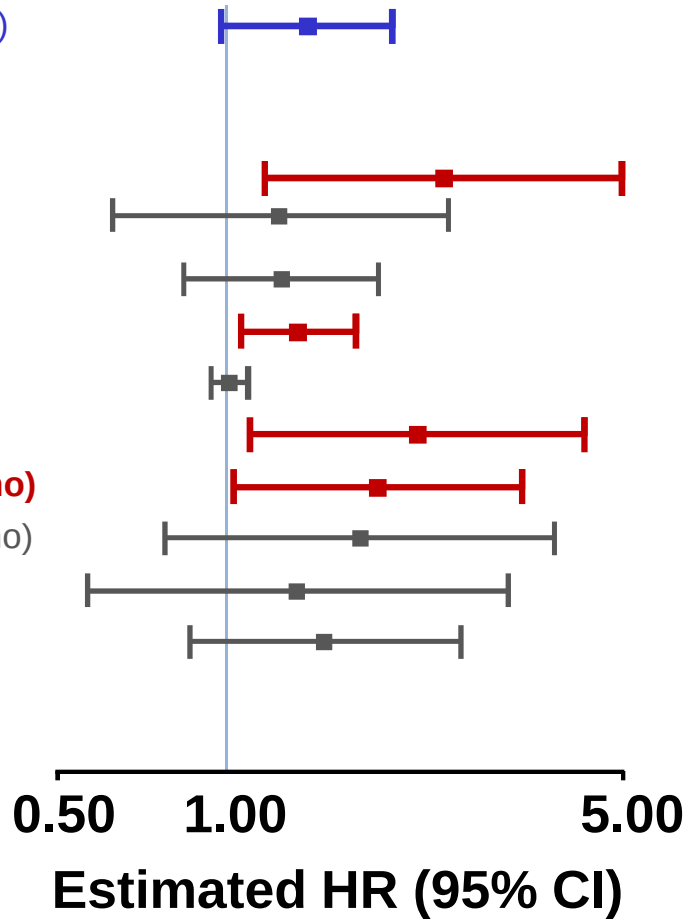
Risk Factors for Primary Event

Multivariable analysis



Risk Factors for Primary Event

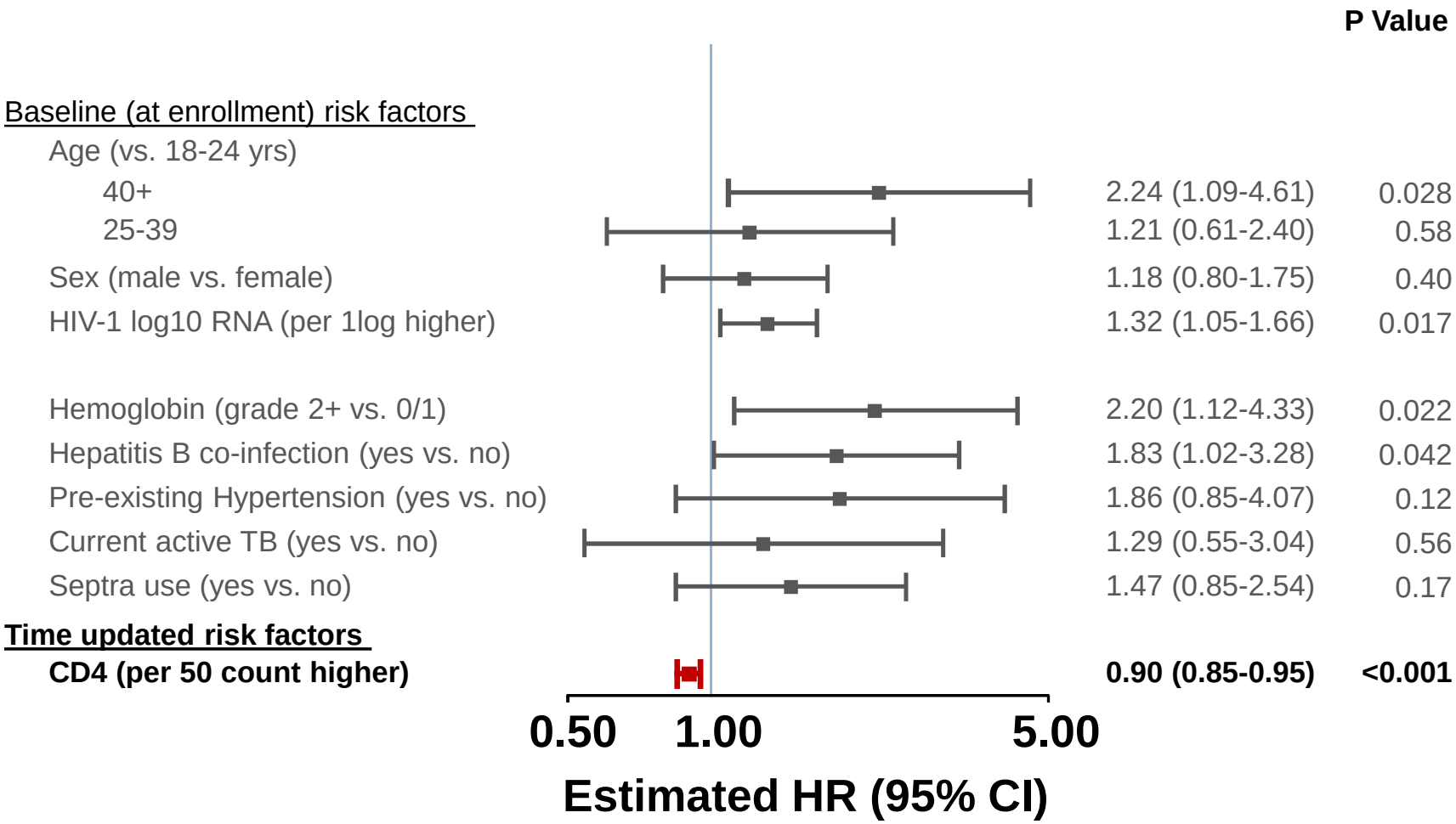
Multivariable analysis



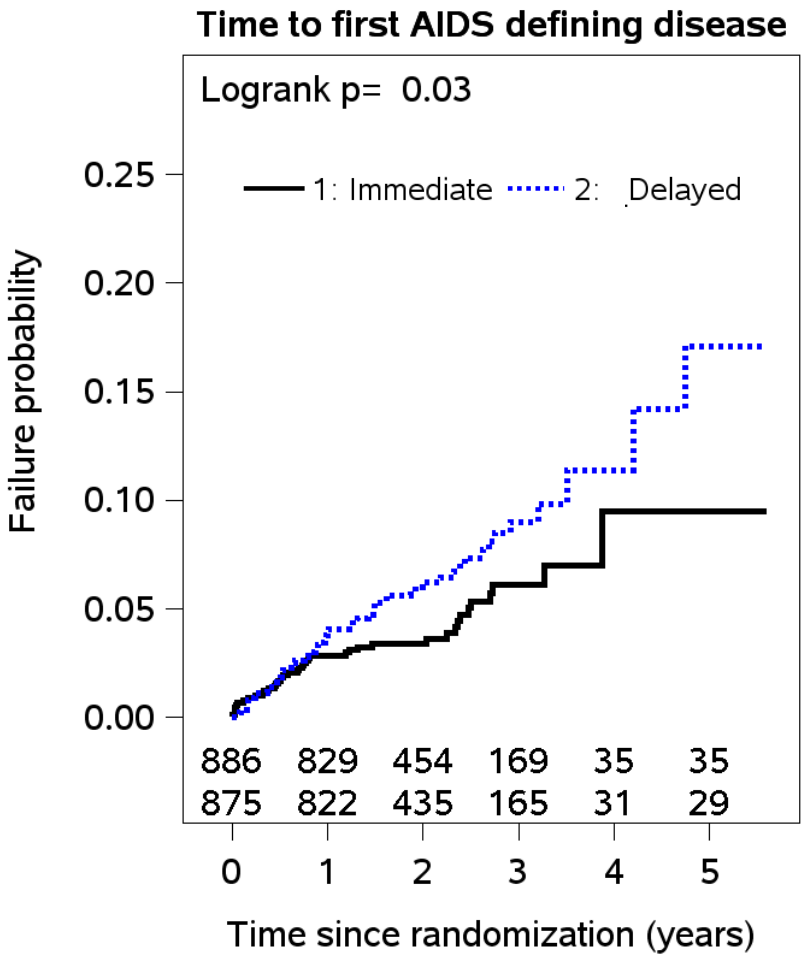
		P Value
Treatment Arm (Delayed vs. Immediate)	1.39 (0.98-1.96)	0.06
Baseline (at enrollment) risk factors		
Age (vs. 18-24 yrs)		
40+	**2.42 (1.17-4.98)**	**0.017**
25-39	1.24 (0.63-2.46)	0.53
Sex (male vs. female)	1.25 (0.84-1.85)	0.27
HIV-1 log10 RNA (per 1log higher)	**1.34 (1.06-1.69)**	**0.013**
CD4 cell count (per 50/mm^3 higher)	1.01 (0.94-1.09)	0.75
Hemoglobin (grade 2+ vs. 0/1)	**2.17 (1.10-4.27)**	**0.025**
Hepatitis B co-infection (yes vs. no)	**1.85 (1.03-3.31)**	**0.040**
Pre-existing Hypertension (yes vs. no)	1.72 (0.78-3.77)	0.18
Current active TB (yes vs. no)	1.33 (0.57-3.14)	0.51
Septra use (yes vs. no)	1.49 (0.86-2.59)	0.15

Risk Factors for Primary Event

Multivariable analysis – Time updated CD4

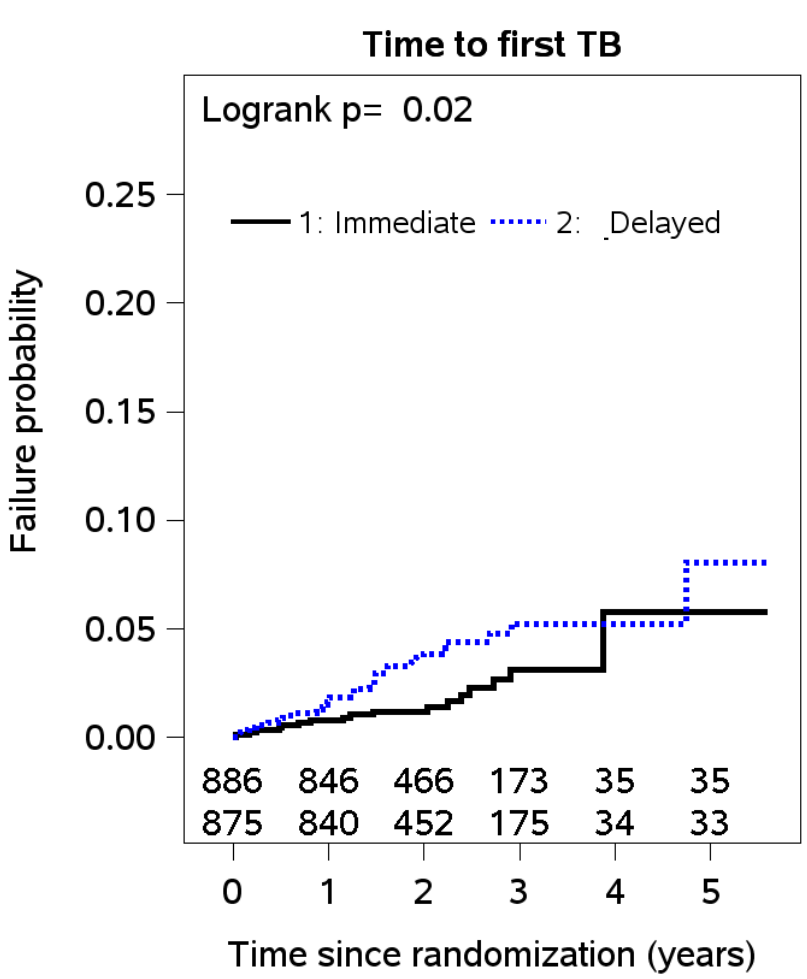


AIDS Events



Number of subjects experiencing ≥1 event	Delayed	Immediate
Tuberculosis	**34 (4%)**	**17 (2%)**
Serious bacterial infection	**13 (1%)**	**20 (2%)**
WHO Stage 4 event	**19 (2%)**	**9 (1%)**
Oesophageal candidiasis	2	2
Cervical carcinoma	2	0
Cryptococcosis	0	1
HIV-related encephalopathy	1	0
Herpes simplex, chronic	8	2
Kaposi's sarcoma	1	1
CNS Lymphoma	1	0
Pneumocystis pneumonia	1	0
Septicemia	0	1
HIV Wasting	2	0
Bacterial pneumonia	1	2

Tuberculosis



	Delayed	Immediate
Number of subjects experiencing ≥1 event	34	17
Number of events	37	17

Note: Includes both confirmed and probable cases

Secondary Endpoints

- In addition to serious (primary) clinical events, secondary analyses included the following ***secondary clinical events***
  - WHO Stage 2/3
  - Malaria
  - Renal insufficiency
  - Hepatic transaminitis
  - Lipodystrophy
  - Dyslipidemia
  - Hypertension
  - Peripheral neuropathy
  - Lactic acidosis
  - Thrombocytopenia
- WHO Stage 2/3 events did not undergo case review

Most Prevalent Secondary Events

Number of subjects experiencing ≥1 event	Delayed (N=317)	Immediate (N=298)
Upper respiratory tract infection	87	72
Moderate unexplained weight loss	61	76
Popular puritic eruption	52	33
Herpes zoster	53	17
Smear positive malaria	49	49
Oral Candidiasis, persistent	47	22
Unexplained severe weight loss	21	37
Dyslipidemia	7	23
Peripheral neuropathy	14	15
Seborrhoeic dermatitis	18	7
Hypertension	8	12
Oral ulcerations	9	10

Most Prevalent Secondary Events

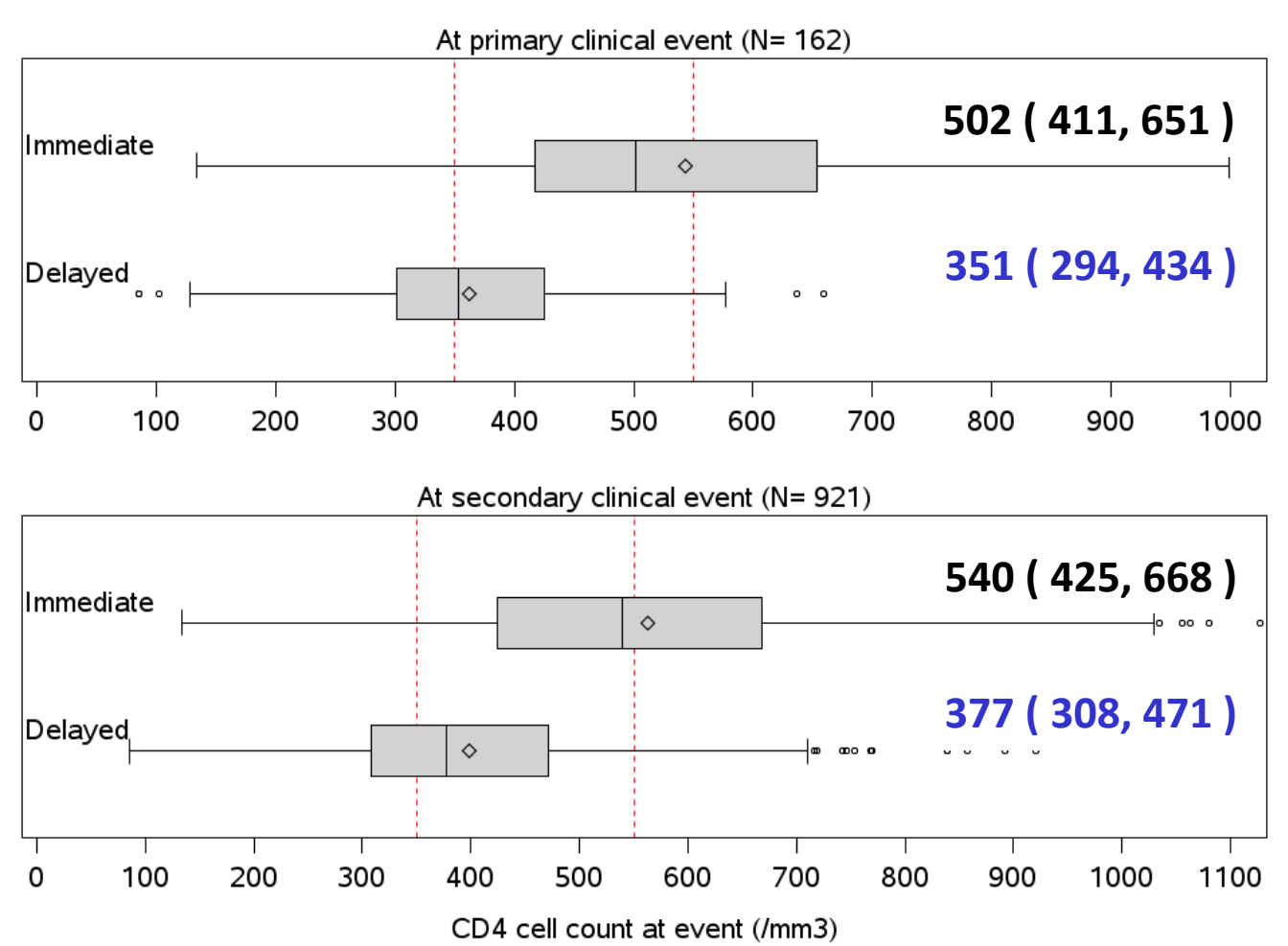
Number of subjects experiencing ≥1 event	Delayed (N=317)	Immediate (N=298)
Upper respiratory tract infection	87	72
Moderate unexplained weight loss*	61	76
Popular puritic eruption	52	33
Herpes zoster	**53**	**17**
Smear positive malaria	49	49
Oral Candidiasis, persistent	**47**	**22**
Unexplained severe weight loss	21	37
Dyslipidemia	7	23
Peripheral neuropathy	14	15
Seborrhoeic dermatitis	**18**	**7**
Hypertension	8	12
Oral ulcerations	9	10

All Events (Primary & Secondary)

	Number of subjects experiencing ≥1 event		Total events Incidence (/100PY) [95% CI]	
	Delayed	Immediate	Delayed	Immediate
Any event	**347 (40%)**	**326 (37%)**	**585 29 [26, 32]**	**498 25 [22, 27]**
			P=0.02	
Primary event	272 (31%)	220 (25%)	91 4.5 [3.6, 5.7]	71 3.5 [2.7, 4.7]
			P=0.18	
Secondary event	317 (36%)	298 (34%)	494 25 [22, 27]	427 21 [19, 24]
			P=0.05	

- Most frequently reported events
  - Upper respiratory tract infections, moderate and severe unexplained weight loss, smear positive malaria, papular puritic abruptions, herpes zoster, persistent candidiasis, tuberculosis, and serious bacterial infections

CD4 at Clinical Event



Summary

- This is the first RCT to examine benefits of ART initiated at CD4 count between 350 – 550 compared to <250
- There was a trend towards a shorter time to a primary clinical event (AIDS and non-AIDS defining) with delayed compared to immediate therapy (HR=1.4, p=0.07)
  - Delayed therapy was associated with a significantly shorter time to AIDS events and TB
  - Non-AIDS defining events were rare and similar between arms
- The overall incidence of clinical events was significantly lower in patients on immediate therapy (IRR=0.8, P=0.02)
  - This difference was driven by clinical events directly related to HIV infection (e.g. TB, HSV, Zoster, Candida and skin conditions)

HPTN 052: Not Done Yet

- The study is ongoing
- All HIV infected subjects offered ART
  - 93% index cases are now on ART
- Retention is 96% among the index cases and 85% for the discordant couples
- Questions remain:
  - What is the durability of the prevention benefit?
  - What are the consequences of delayed ART on clinical outcomes over a longer follow up?

Conclusions

- Early ART significantly delayed the time to AIDS defining events and TB, and significantly decreased the incidence of clinical events
- **We conclude that the combined treatment and prevention benefits of ART support early initiation**
- **Cost-effectiveness analysis of early ART using these results will be presented by Dr Rochelle Walensky at the LB session tomorrow**

HPTN 052 Recognition

U.S. Sponsors:
- National Institutes of Health (NIH)
- Division of AIDS (DAIDS), U.S. National Institute of Allergy and Infectious Diseases (NIAID)

HIV Prevention Trials Network (HPTN):
- Network Laboratory, Johns Hopkins University
- Statistical Center for HIV/AIDS Research & Prevention (SCHARP) and University of Washington
- Coordinating and Operations Center, Family Health International (FHI)
- HPTN Leadership

AIDS Clinical Trials Group (ACTG):
- ACTG Leadership and Investigators
  - Statistical leadership for the present analyses from ACTG Statistics and Data Analysis Center

Pharmaceutical Companies:
- Abbott Laboratories
- Boehringer Ingelheim Pharmaceuticals, Inc.
- Bristol-Myers Squibb
- Gilead Sciences, Inc.
- GlaxoSmithKline
- Merck & Co., Inc.

Sites (Investigators of Record):
- Porto Alegre, Brazil (Breno Santos)
- Rio de Janeiro, Brazil (Beatriz Grinsztejn)
- Boston, United States (Kenneth Mayer)
- Chennai, India (N. Kumarasamy)
- Pune, India (Sheela Godbole)
- Chiang Mai, Thailand (Suwat Chariyalertsak)
- Gaborone, Botswana (Joseph Makhema)
- Kisumu, Kenya (Lisa Mills)
- Blantyre, Malawi (Johnstone Kumwenda)
- Lilongwe, Malawi (Mina Hosseinipour)
- Johannesburg, South Africa (Ian Sanne)
- Soweto, South Africa (Guy De Bruyn)
- Harare, Zimbabwe (James Hakim)

The Study Participants!!

HIV Prevention Trials Network

ACKNOWLEDGEMENTS

- Sponsored by NIAID, NIDA, NIMH under Cooperative Agreement # UM1 AI068619

National Institute of Allergy and Infectious Diseases

NIMH National Institute of Mental Health

National Institutes of Health

U.S. Department of Health and Human Services
NATIONAL INSTITUTES OF HEALTH
NIDA National Institute on Drug Abuse

HIV Prevention Trials Network

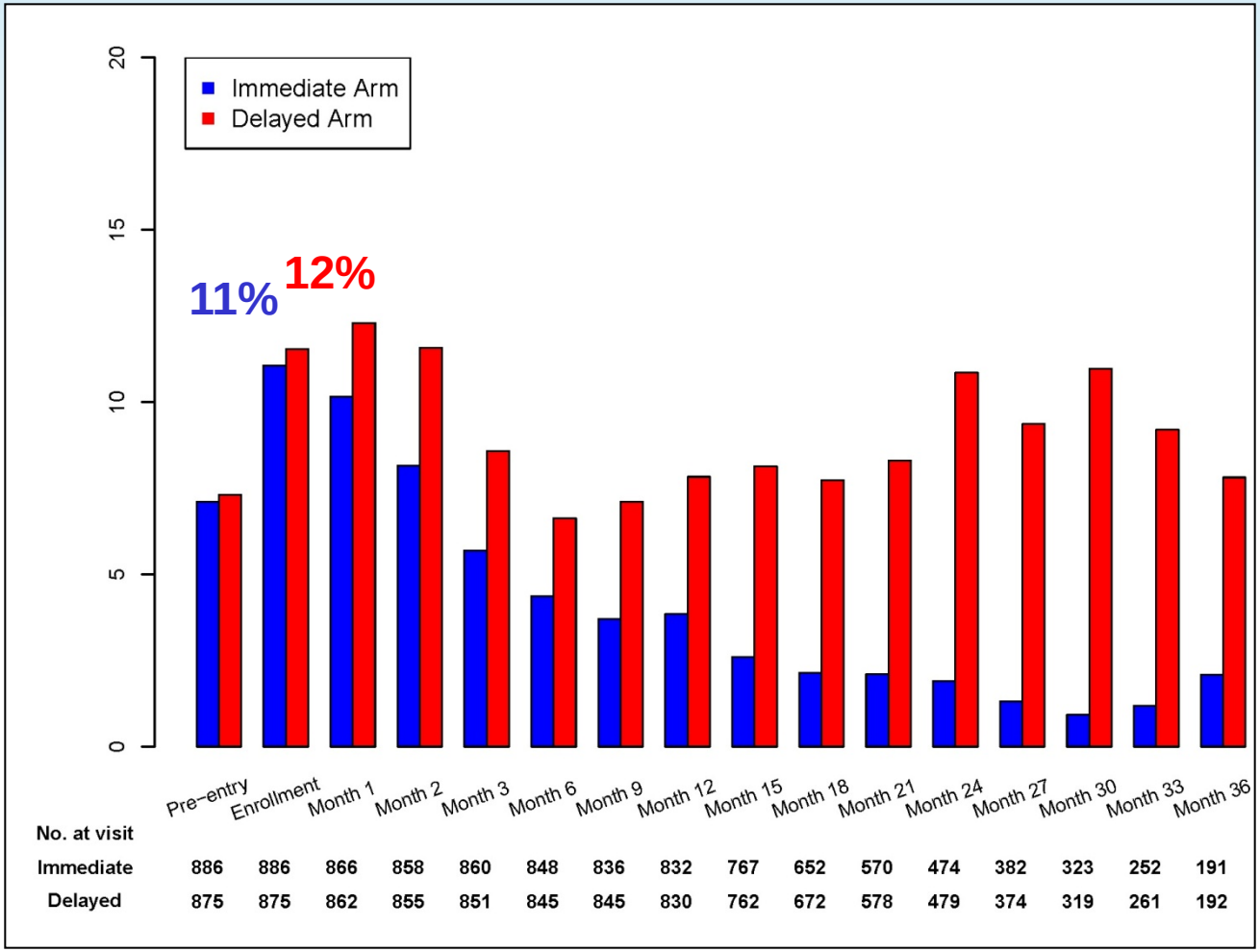
ACTG AIDS Clinical Trials Group

Back-up Slides

Causes of Death

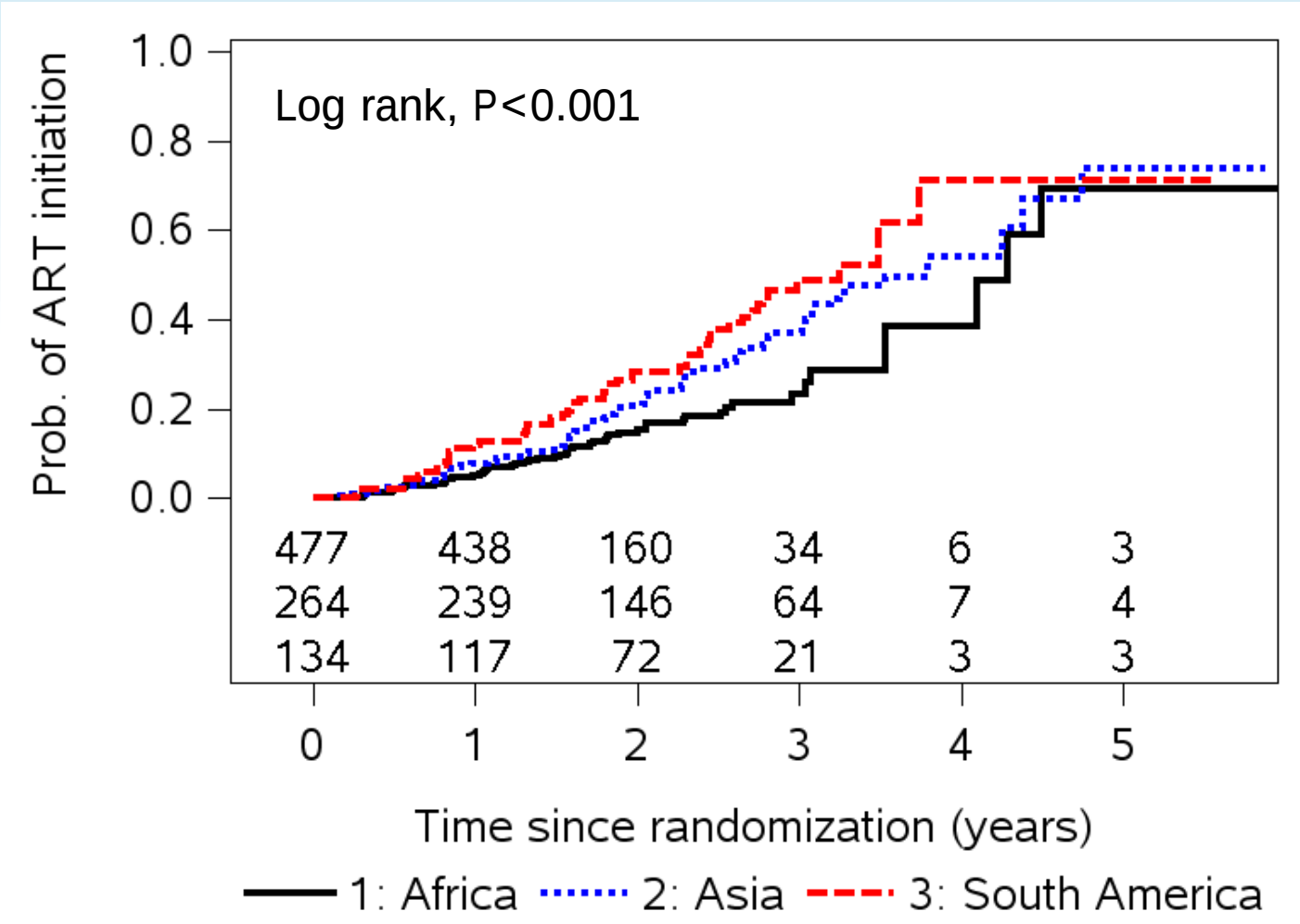
	Delayed	Immediate
Total (N=26)	**15**	**11**
Primary Events		
Bacterial infection	1	0
Tuberculosis	2	0
Non-AIDS Malignancy	1	0
Septicemia, recurrent	0	1
Other Causes (non-primary or unconfirmed)	11	10
Suicide	0	3
Accidental	2	1
Leptospirosis	0	1
Probable Miliary tuberculosis (pre-existing)	0	1
Circulatory failure due to acute gastroenteritis	0	1
Cardiac arrest probably due to illicit liquor consumption	1	0
Undefined	8	3

TMP-SMX Prophylaxis



No. at visit																
Immediate	886	886	866	858	860	848	836	832	767	652	570	474	382	323	252	191
Delayed	875	875	862	855	851	845	845	830	762	672	578	479	374	319	261	192

Time to ART initiation by Region



Primary Event Incidence

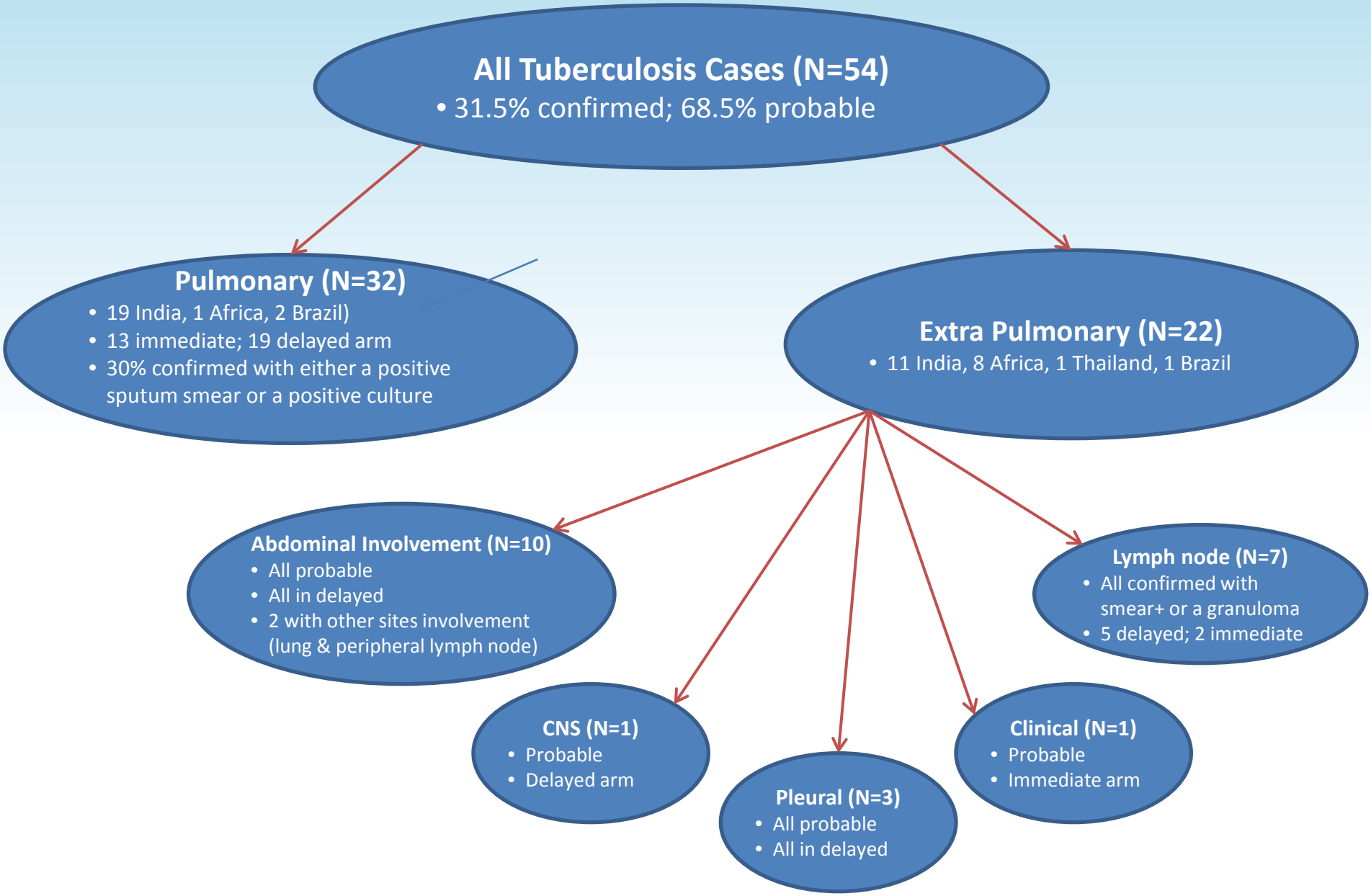
	Total events Incidence (/100PY) [95% CI]	
	Delayed	Immediate
Any Primary event*	**91** **4.5% [3.6%, 5.7%]**	**71** **3.5% [2.6%, 4.7%]**
	P=0.18	
AIDS event**	71 3.5% [2.7%, 4.5%]	49 2.4% [1.7%, 3.4%]
	P=0.08	
Non-AIDS event	9 0.4% [0.2%, 0.9%]	12 0.6% [0.3%, 1.0%]
	P=0.51	
Tuberculosis	37 1.8% [1.3%, 2.6%]	17 0.8% [0.5%, 1.3%]
	P=0.009	

**Primary clinical event: Death,WHO Stage 4,Tuberculosis, Severe bacterial infection,Serious cardiovascular/vascular disease,Serious liver disease,End stage renal disease,Non-AIDS malignancy,Diabetes mellitus,*

***AIDS events: WHO stage 4 events, tuberculosis, serious bacterial infections*

Tuberculosis (N=54)

- 31.5% confirmed; 68.5% probable
- Pulmonary TB
  - Total number of cases: 32 (11 Africa,19 India, 2 Brasil)
  - 13 cases on the immediate arm; 19 cases on the delayed arm
  - 30% confirmed with either a positive sputum smear or a positive culture
- Extrapulmonary TB
  - Total number of cases: 22 (11 India,8 Africa,1 Thailand,1 Brasil)
- TB cases with abdominal involvement –All probable
  - Total number of cases: 8
  - All of them in the delayed arm,2 with other sites of involvement-lung and peripheral lymph node
- Lymph node TB (all confirmed with either a smear+ or a granuloma)
  - Total number of cases: 7 (5 delayed;2 immediate)
- CNS- 1 case
  - Delayed arm/Probable
- Pleural- 3 cases
  - All delayed arm/all Probable
- Clinical-1 case
  - Immediate/Probable


All Tuberculosis Cases (N=54)
• 31.5% confirmed; 68.5% probable
Pulmonary (N=32)
• 19 India, 1 Africa, 2 Brazil)
• 13 immediate; 19 delayed arm
• 30% confirmed with either a positive sputum smear or a positive culture
Extra Pulmonary (N=22)
• 11 India, 8 Africa, 1 Thailand, 1 Brazil
Abdominal Involvement (N=10)
• All probable
• All in delayed
• 2 with other sites involvement (lung & peripheral lymph node)
Lymph node (N=7)
• All confirmed with smear+ or a granuloma
• 5 delayed; 2 immediate
CNS (N=1)
• Probable
• Delayed arm
Pleural (N=3)
• All probable
• All in delayed
Clinical (N=1)
• Probable
• Immediate arm