Effects of Early versus Delayed Initiation of Antiretroviral Therapy (ART) on HIV Clinical Outcomes: Results from the HPTN 052 Randomized Clinical Trial

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HIV Prevention Trials Network

National Institute of Allergy and Infectious Diseases

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Background

- Controversy around best time to initiate antiretroviral therapy (ART)
- CIPRA Haiti showed delayed disease progression and increased survival at CD4 cell counts 250-350 compared to <200 CD4 cell count
- At higher CD4, observational studies from developed countries suggested a benefit from earlier initiation of ART
  - Benefit relative to toxicity complications and risk viral resistance is less clear
- ART associated costs present a challenge in the resource limited settings
- HPTN 052 provides an opportunity to address “when to start” ART in a randomized population with CD4 cell counts 350-550

Primary Clinical Endpoint

- Death, WHO stage 4 clinical event, pulmonary TB or severe bacterial infection
- All events underwent blinded independent review using standardized criteria
  - ACTG Diagnoses Appendix (Appendix 60)
  - Classified as confirmed or probable
- The primary clinical endpoint
  - Time to first primary clinical event, including death

Baseline Characteristics

		Immediate N=886	Delayed N=877
Female sex		49%	50%
Age	*18-25*	16%	18%
	26-40	63%	62%
	>40	21%	19%
Continent	*Asia*	30%	30%
	North/South America	16%	16%
	Africa	54%	54%
CD4 cell counts (cells/mm^3)		442 (373 – 522)*	428 (357 – 522)*
HIV-1 RNA (log_{10} copies/ml)		4.4 (3.8 – 4.9)*	4.4 (3.9 – 4.9)*
Prophylactic Septra use		7%	7%
Prophylactic INH use		4%	4%

** Median (Q1 – Q3)*

Results

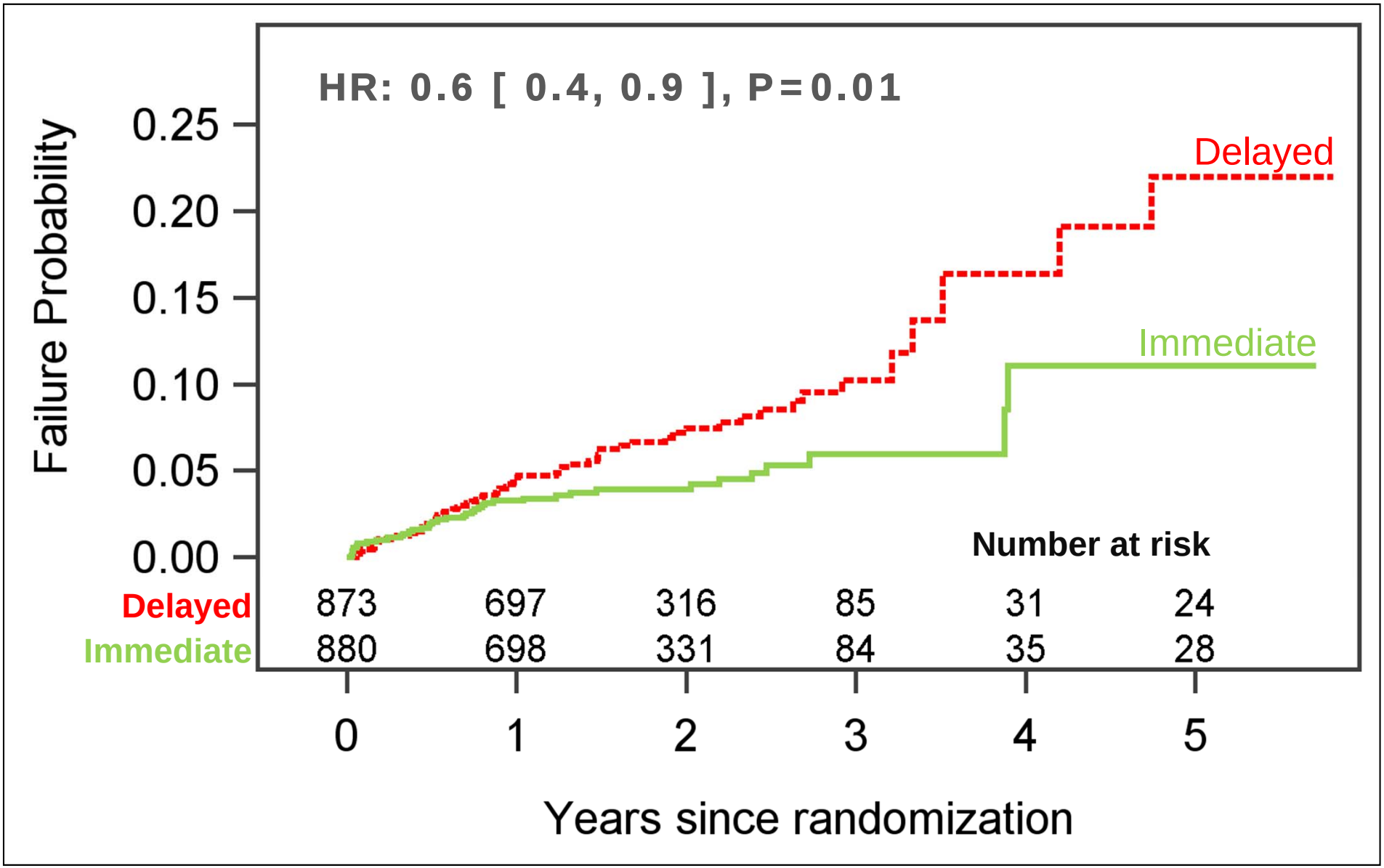
- Median follow-up: 1.7 years
- 105 individuals experienced at least one primary clinical endpoint event
  - 40 immediate arm
  - 65 delayed arm

Study Arm	Follow-up	Incidence /100 PY [95% CI]
Immediate	1662 PY	2.4 [1.7 – 3.3]
Delayed	1641 PY	4.0 [3.1 - 5.0]

***Person-years specific for clinical events**

Probability of Primary Clinical Event

(Death, WHO stage 4 clinical event, pulmonary TB or severe bacterial infection)



All Primary Clinical Events (N = 129)

17 subjects experienced >1 primary clinical event

	Immediate		Delayed	
Total (N=129)	**53**		**76**	
Tuberculosis	**17**		**33**	
Severe bacterial infection	**16**		**11**	
Death	**10**		**13**	
Chronic herpes simplex	**3**		**7**	
Bacterial pneumonia (recurrent)	**2**		**2**	
Oesophageal candidiasis	**2**		**2**	
Cervical carcinoma	**0**		**2**	
Kaposi's sarcoma	**1**		**1**	
Wasting syndrome	**0**		**2**	
Other*	**2**		**3**	

** Extrapulmonary crypto, HIV-related encephalopathy, lymphoma, PCP, septicemia (recurrent)*

CD4 at Clinical Event

	Immediate		Delayed	
	N	Median CD4	N	Median CD4
Total (N=129)	53	**506 (409 - 625)**	76	**340 (283 – 418)**
Tuberculosis	17	**518**	33	**316**
Severe bacterial infection	16	**551**	11	**337**
Death	10	**476**	13	**372**
Chronic herpes simplex	3	**753**	7	**413**
Bacterial pneumonia (recurrent)	2	**445**	2	**220**
Oesophageal candidiasis	2	**301**	2	**256**
Cervical carcinoma	0	**--**	2	**445**
Kaposi's sarcoma	1	**459**	1	**364**
Wasting syndrome	0	**--**	2	**366**
Other	2	**488**	3	**217**

Tuberculosis

	Immediate		Delayed	
	N [incidence]	Median CD4	N [incidence]	Median CD4
Total	**17** [1 /100PY]	**518**	**33** [1.9 /100PY]	**316**
Pulmonary TB	**14** [0.8 /100PY]	**521**	**16** [0.9 /100PY]	**295**
Extrapulmonary TB	**3** [0.2 /100PY]	**443**	**17** [1 /100PY]	**342**
Peripheral Lymph Nodes	2	432	4	492
Abdominal	0	--	8	324
Pleural	1	443	3	316
Skeletal	0	--	1	417
Meningeal	0	--	1	302

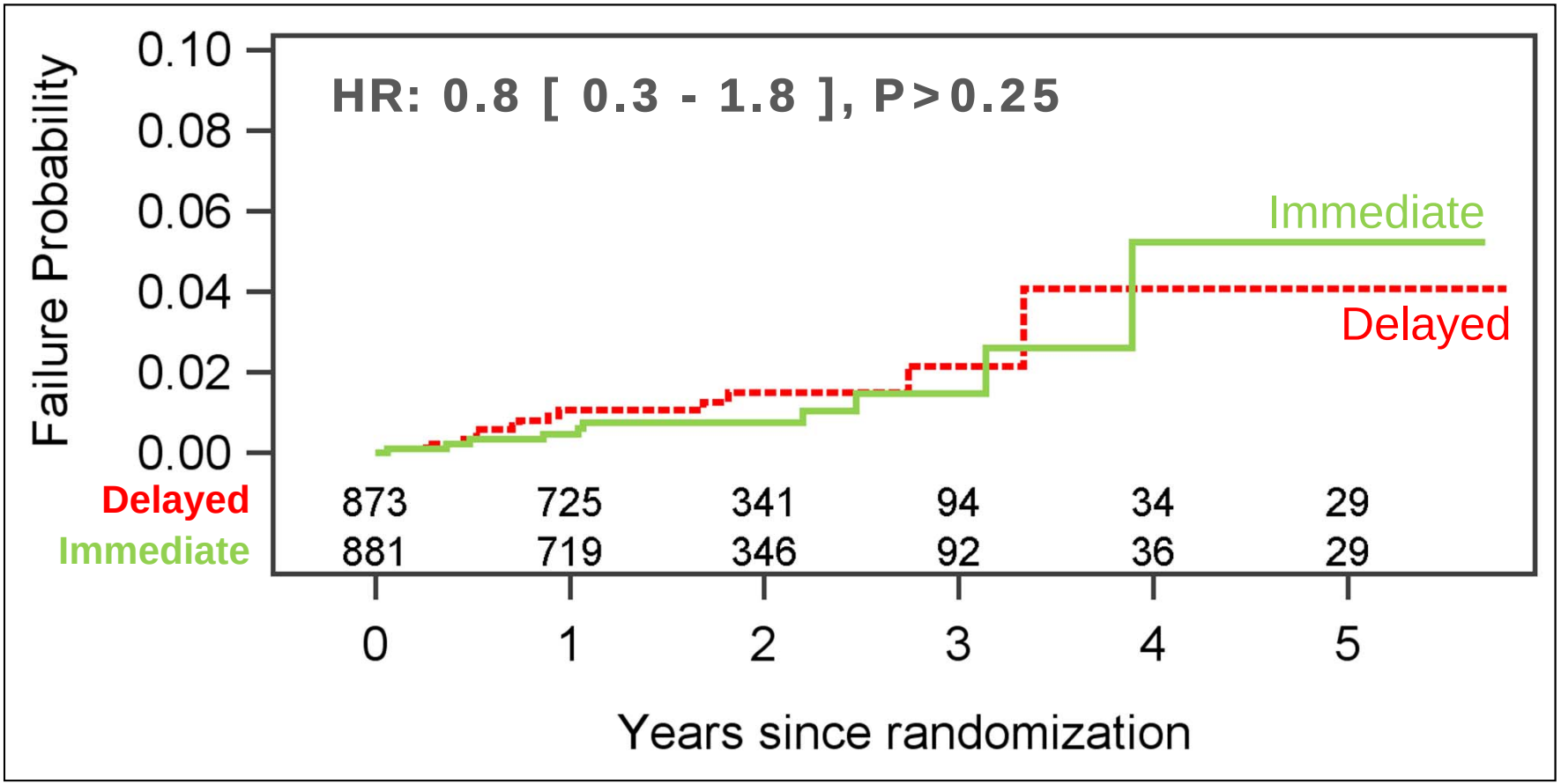
Bacterial Infections

	Immediate		Delayed	
	N [Incidence]	Median CD4	N [Incidence]	Median CD4
Total	**19** [1.1 /100PY]	**551**	**13** [0.8 /100PY]	**337**
Pneumonia	11	511	10	336
Meningitis	2	392	1	480
Sepsis	4	551	0	--
Cellulitis	1	635	2	256
Pelvic inflammatory disease	1	668	0	--

- 3 subjects experienced >1 infection
  - All in the immediate arm

Deaths

- 23 deaths during the course of the study
  - 10 in the immediate arm
  - 13 in the delayed arm



Causes of Death

		Immediate	Delayed
Total (N=23)		**10**	**13**
Infections		3	2
	Tuberculosis	1	1
	Sepsis	1	1
	Leptospirosis	1	-
Other medical conditions		1	2
	Stroke	-	1
	Gastroenteritis	1	
	Adenocarcinoma	-	1
Suicide		3	-
Accidental death (MVA)		-	2
Unknown		3	6

Laboratory Abnormalities

- 403 participants had a severe or life-threatening laboratory abnormality
  - 27% immediate arm
  - 18% delayed arm

	Immediate		Delayed	
	Grade 3	Grade 4	Grade 3	Grade 4
Neutrophils	8%	2%	4%	1%
Phosphate	6%	<1%	6%	<1
Total Bilirubin	5%	1%	<1%	<1%
ALT	1%	<1%	1%	<1%
AST	1%	1%	1%	<1%
Hemoglobin	1%	1%	<1%	1%

Only events reported for ≥1% of participants are shown

Adverse Events

- Events coded using the MedDRA System
- 246 participants had one or more severe or life-threatening adverse events
  - 14% immediate arm
  - 14% delayed arm

	Immediate	Delayed
Infections	5%	6%
Psychiatric disorders	3%	<1%
Nervous system disorders	2%	1%
Metabolism and nutrition disorders	2%	2%
Gastrointestinal disorders	1%	2%

Only events reported for >1% of participants are shown

Conclusions

- **Immediate ART was associated with 41% reduction in HIV-related clinical events**
- **ART therapy was well tolerated in this wide range of high CD4 population**
- **Rates of serious lab abnormalities and adverse events were low**
  - **More extensive analyses of WHO stage 1-3 and non-AIDS events will follow**

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Heather Ribaudo, Diane Havlir, Susan Swindells,
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HPTN 052: Summary

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HPTN 052: Session Highlights

- ART prevented linked transmission of HIV
- Unlinked transmissions were noted despite intensive couples counseling
- HIV infected participants had reduced numbers of clinical events
- Regional differences in HIV transmission associated with ART were noted

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ORIGINAL ARTICLE

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

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HPTN 052: Implications

- The HIV prevention effect demonstrated in HPTN 052 is the proof of a concept

- These results could inform
  - The “Test and Treat” strategies
  - Management of HIV discordant couples

HPTN 052 Recognition

U.S. Sponsors:

- National Institute of Allergy and Infectious Diseases (NIAID) / U.S. National Institutes of Health (NIH)

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

Pharmaceutical Companies:

- Abbott Laboratories
- Boehringer Ingelheim Pharmaceuticals, Inc.
- Bristol-Myers Squibb
- Gilead Sciences, Inc.
- GlaxoSmithKline/ViiV Healthcare
- Merck & Co., Inc.

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- Chiang Mai, Thailand (Suwat Chariyalertsak)
- Gaborone, Botswana (Joseph Makhema)
- Kisumu, Kenya (Lisa Mills)
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- Johannesburg, South Africa (Ian Sanne)
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Study Participants!

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