



# CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA



CAPRISA IS A UNAIDS  
COLLABORATING CENTRE  
FOR HIV PREVENTION RESEARCH

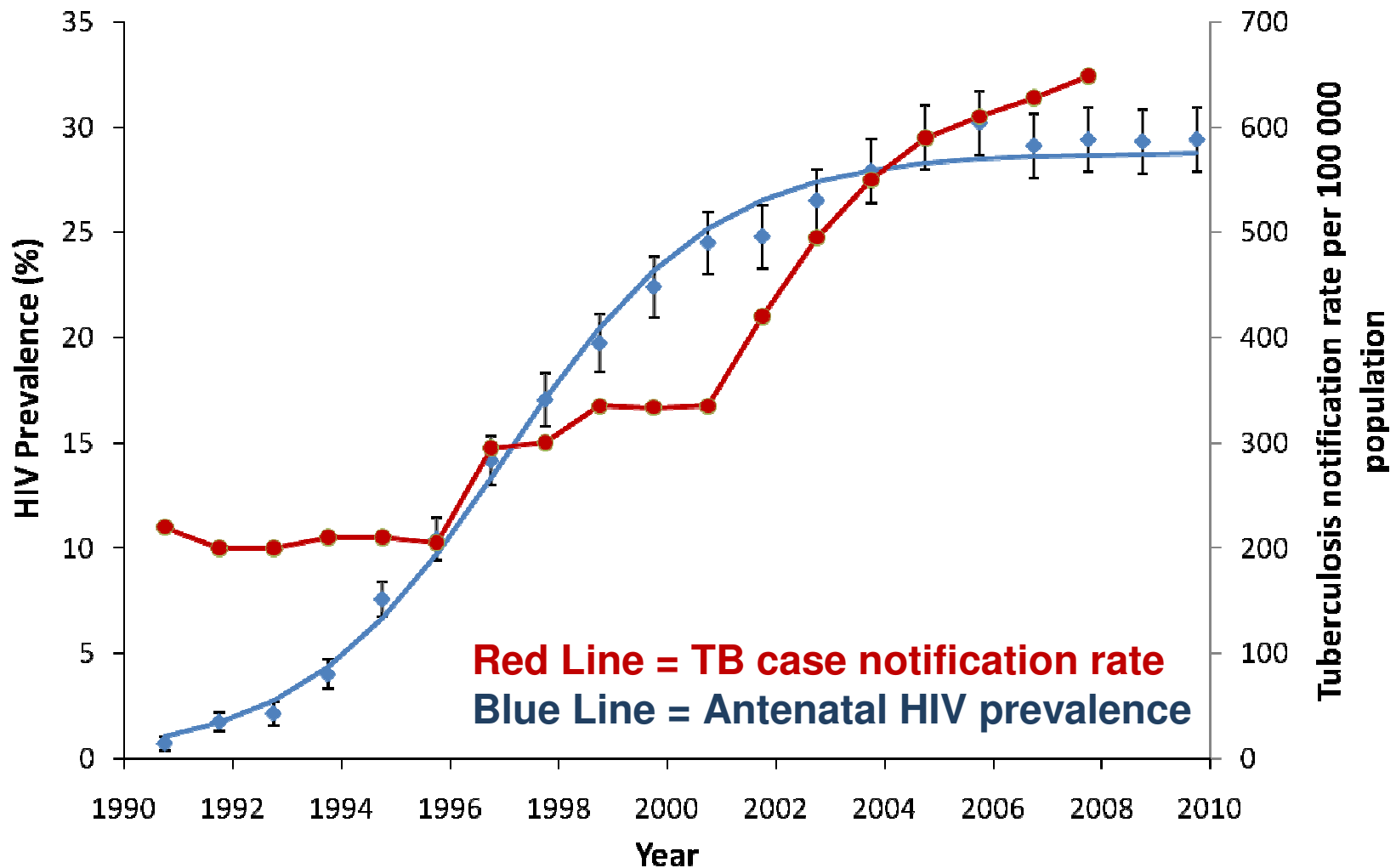
## Optimal timing of antiretroviral therapy during tuberculosis treatment: The SAPiT trial

**17<sup>th</sup> Conference of Retroviruses and Opportunistic Infections  
Boston, 28 February 2011**

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# The HIV and TB epidemics in South Africa



Source: South African Department of Health

# Starting ART at 3 Points in TB

## The SAPiT Trial: CAPRISA 003

- **Purpose of study:** To determine the optimal time to initiate ART in TB patients
- **Design:** Open-label 3-arm randomized controlled trial
- **Sample size:** 642 HIV-TB co-infected patients
- **Study site:** CAPRISA eThekweni Clinic, Durban
- **Study Population:** Ambulatory TB smear +ve, HIV +ve (CD4 count < 500 cells/mm<sup>3</sup>) and on standard TB treatment regimens. Participants attended the clinic's TB-DOTS program.
- **Endpoints**
  - 1<sup>0</sup> All-cause mortality + AIDS defining illness
  - 2<sup>0</sup> Tolerability, Viral Load, TB outcomes & Immune Reconstitution Inflammatory Syndrome (IRIS)

**Sept 2008: Sequential arm of the SAPIT Trial stopped**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Timing of Initiation of Antiretroviral Drugs during Tuberculosis Therapy

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**56% lower mortality with integrated TB-HIV treatment**

# Continued the 2 integrated treatment arms\*: When to start ART during TB treatment?

- **Why initiate ART early during TB treatment?**
  - To halt HIV progression & avert high TB-HIV mortality
- **Why initiate ART later in TB treatment?**
  - Decreased risk of immune reconstitution syndrome
  - Lower pill burden / better tolerability – 3 ARVs + (4 vs 2 TB drugs)
- **Current treatment based on observational data, clinician judgement & expert opinion:**
  - High variability
  - WHO guidelines
    - *Pre-2009 : CD4<50 initiate early & CD4=50-200 initiate later*
    - *Since 2009: Start ART in all HIV-infected individuals with active TB, irrespective of CD4 cell count and start TB treatment first, followed by ART ASAP after starting TB treatment.*

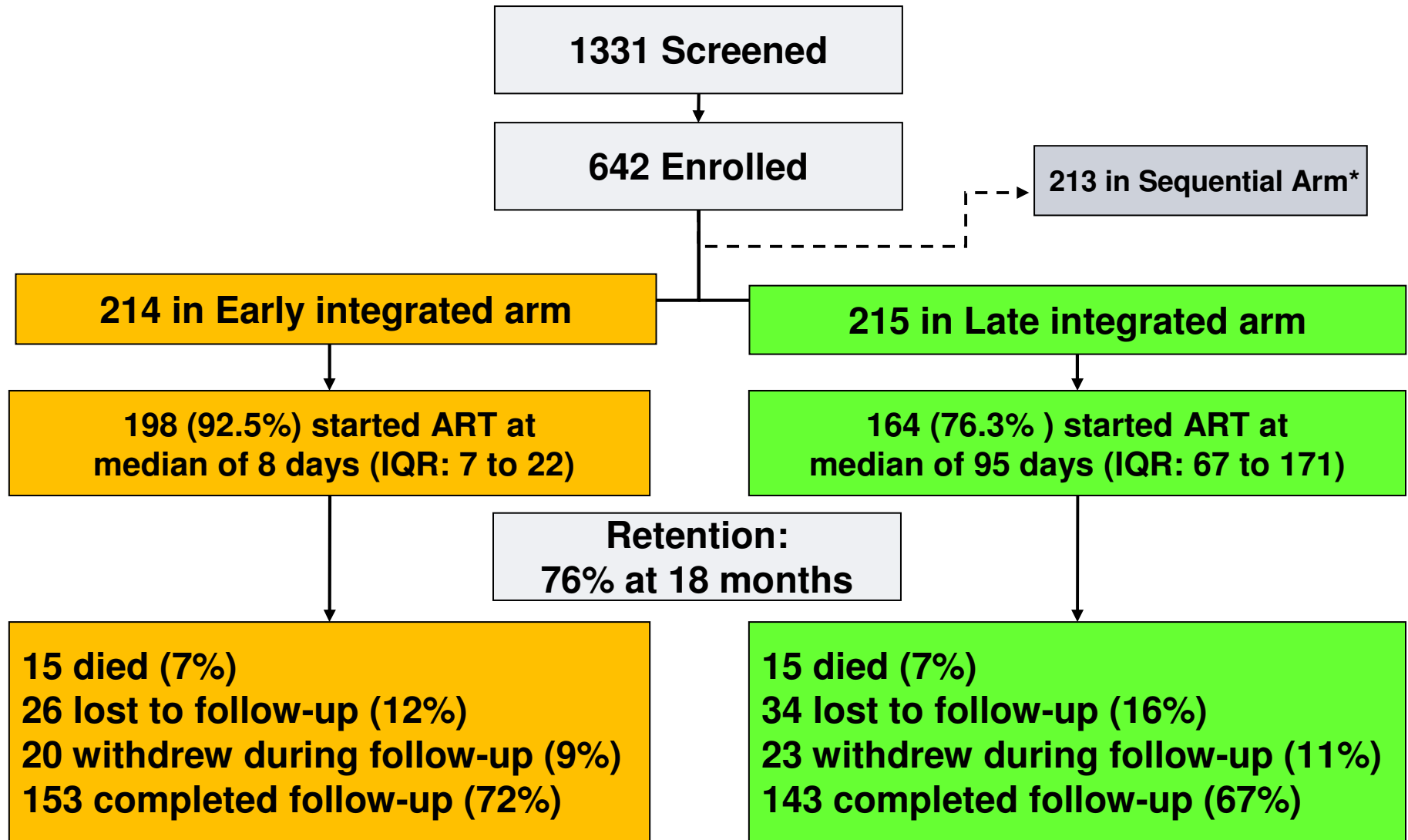
\*based on the trial's Safety Monitoring Committee recommendation

# Study intervention

(After Sept 2008, remaining 2 arms continued to end)

- **Randomized to one of 2 arms (continued to trial end):**
  - ***Early integrated-therapy arm-*** antiretroviral therapy to be initiated within 4 weeks of starting tuberculosis treatment,
  - ***Late integrated-therapy arm-*** antiretroviral therapy to be initiated within 4 weeks of completing the intensive phase of tuberculosis treatment, and
- **Cotrimoxazole prophylaxis:** provided to all patients
- **ART:** ddl + 3TC + efavirenz – once daily regimen
- **Once-a-day treatment** integrated with TB-DOT

# Enrollment and Outcomes



\*Safety Monitoring Committee review and recommended:  
 - Start ART immediately in all sequential arm patients but continue the two integrated treatment arms in the trial

# Results: Baseline Characteristics

Baseline characteristic	Early integrated arm (N =214)	Late integrated arm (N = 215)
Mean age in years (SD)	<b>34.3</b> ±8.0	<b>34.5</b> ±8.7
Gender - (% male)	<b>45.3</b>	<b>52.1</b>
Median CD4+ count, cells/mm <sup>3</sup> (IQR)	<b>154.5</b> (75 to 261)	<b>149</b> (77 to 244)
log viral load copies/ml (IQR)	<b>5.1</b> (4.5 to 5.6)	<b>5.2</b> (4.5 to 5.6)



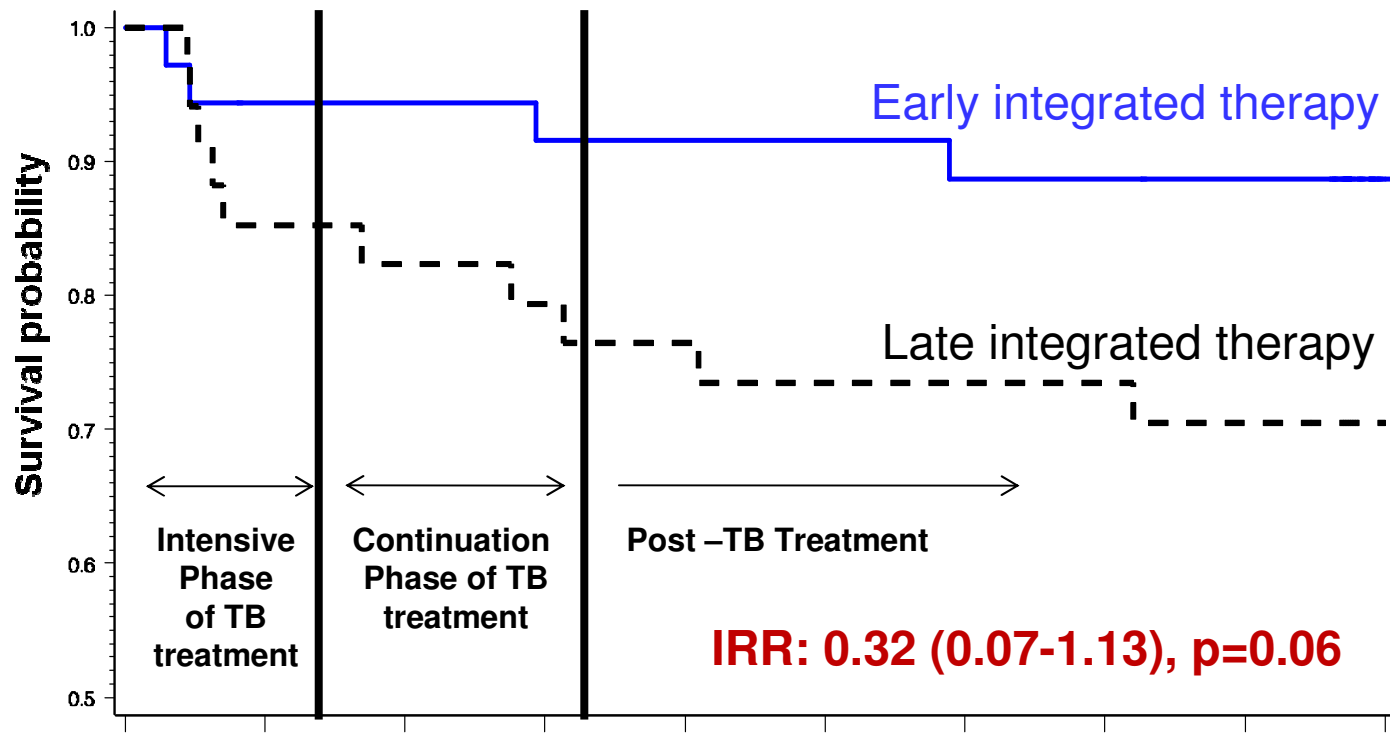
# Overall: AIDS defining illness or death

	Early Integrated arm n = 214	Late Integrated arm n = 215
Number of events	18	19
Person-years	259.4	244.2
<b>Event rate</b> (per 100 person-years)	<b>6.9</b>	<b>7.8</b>

**Incidence Rate Ratio: 0.89 (95% CI: 0.44 to 1.79); p=0.73**

**Similar rates of AIDS defining illness or death**

# Kaplan-Meier curve for AIDS or death in patients with CD4 <50 cells/mm<sup>3</sup>

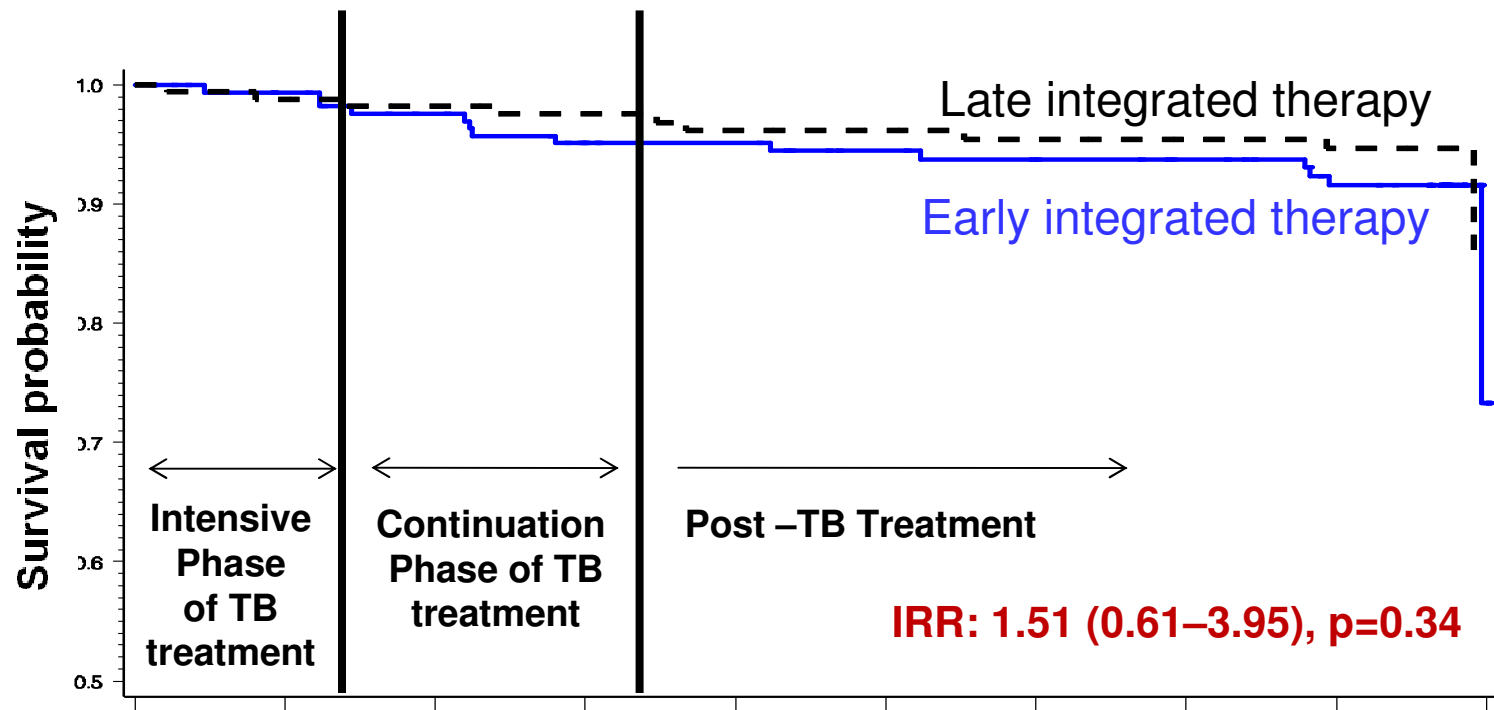


**IRR: 0.32 (0.07-1.13), p=0.06**

Months of follow-up	0	6	12	18
Early – Events / # at risk	0/37	2/33	4/31	4/29
Late – Events / # at risk	0/35	7/27	9/24	10/21

**68% reduction of AIDS / death (p=0.06)**

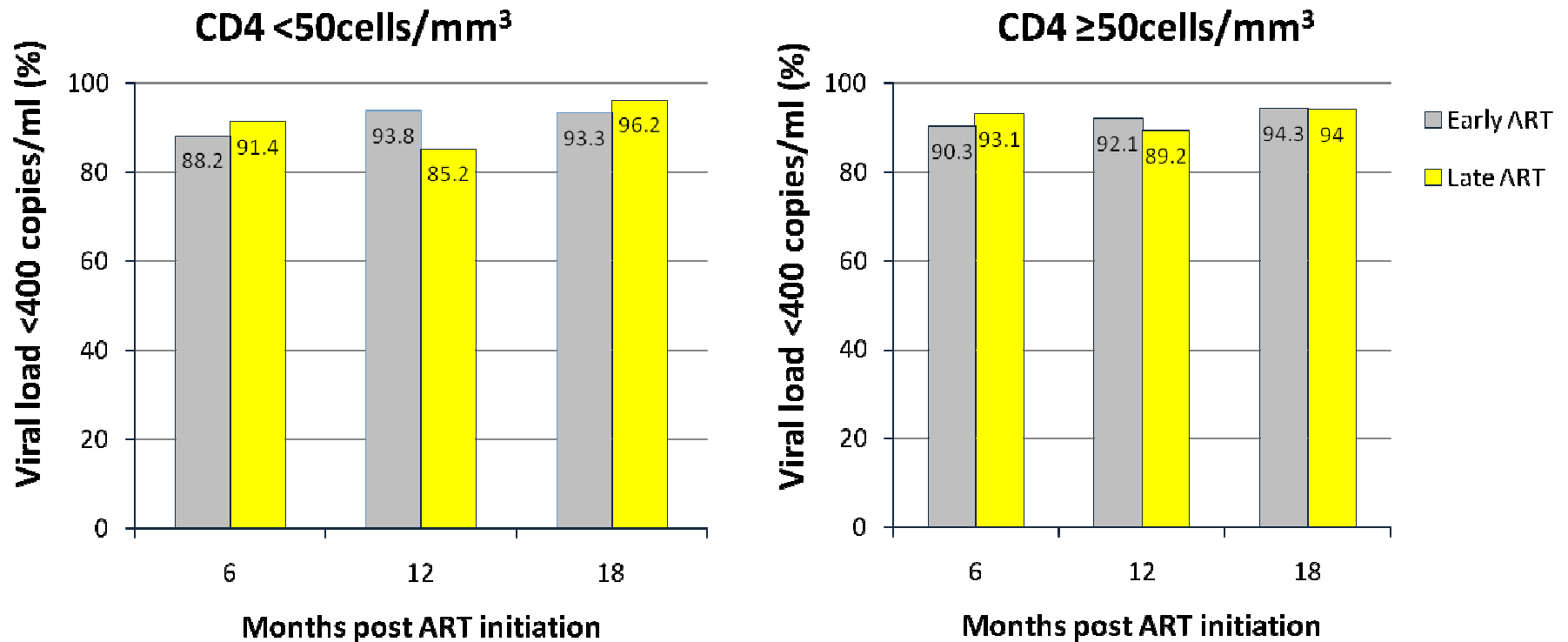
# Kaplan-Meier curve for AIDS or death in patients with CD4 $\geq 50$ cells/mm<sup>3</sup>



Months of follow-up	0	6	12	18
Early – Events/ # at risk	0/177	8/149	10/137	14/121
Late – Events / # at risk	0/180	4/48	7/129	9/121

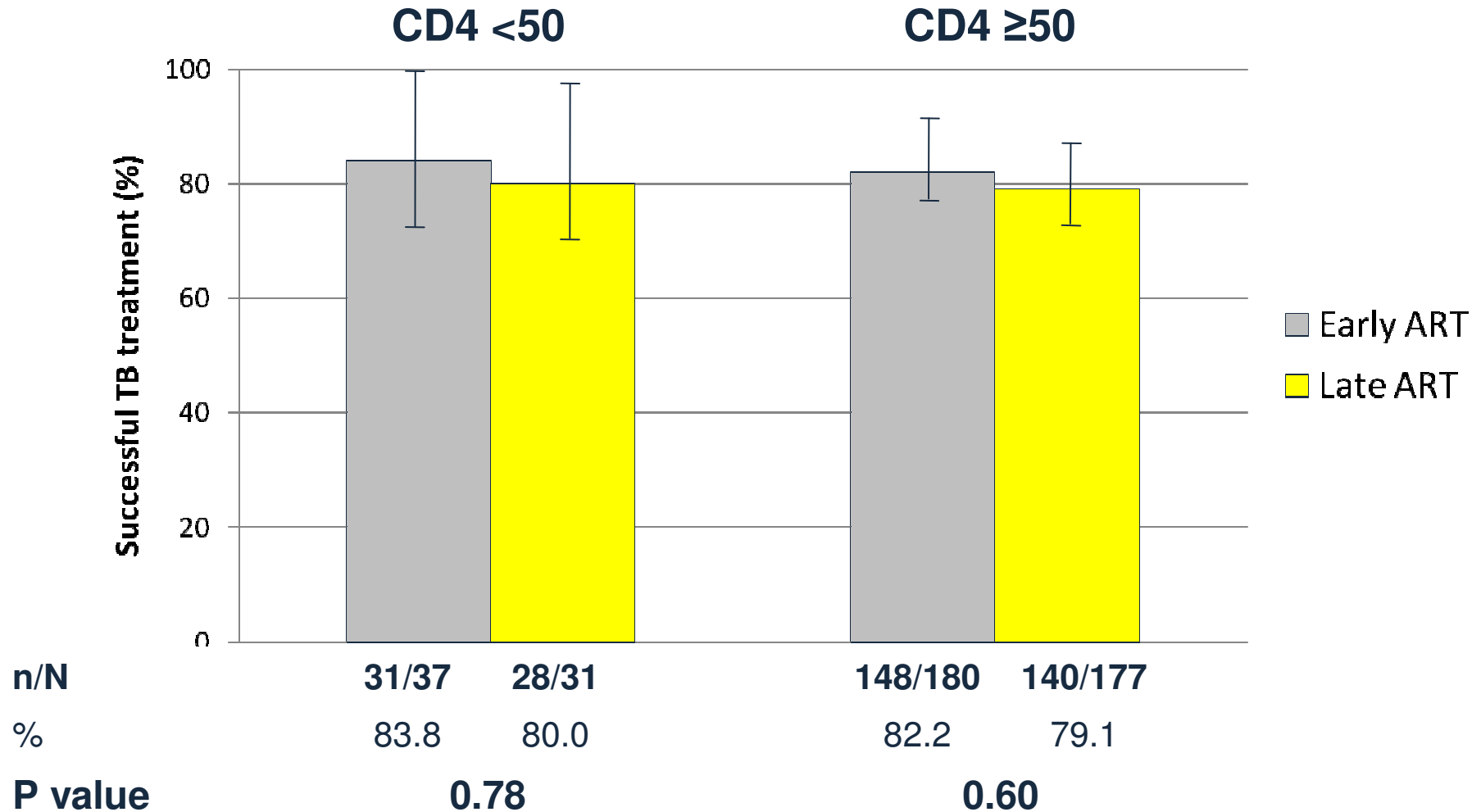
**No discernable differences in AIDS / death**

# HIV treatment outcomes



**HIV suppression >90% after 18 months**  
**No difference between arms irrespective of CD4 status**

# Successful TB treatment completion



**TB treatment successfully completed in ~80% of the patients with no significant differences across groups**

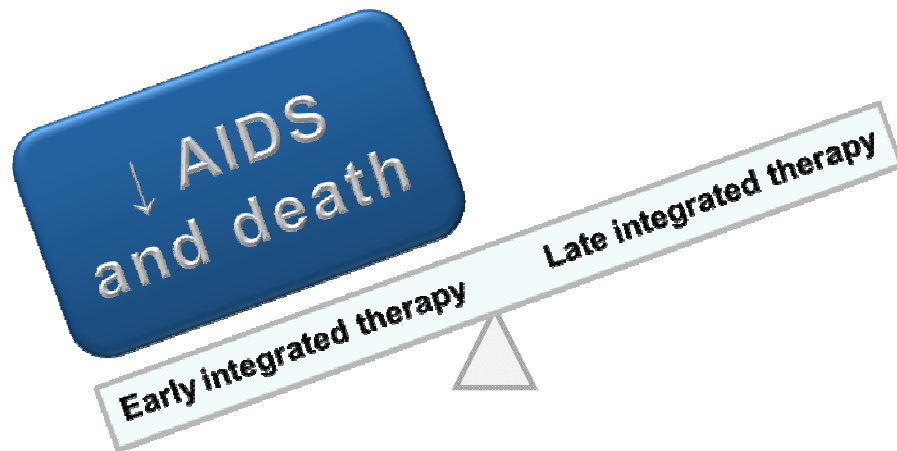
# AIDS / death, IRIS rates, and drug switches stratified by CD4+ count

	Early Integrated Therapy	Late Integrated Therapy	IRR (95% CI)	P-Value
<b>CD4 &lt;50 cells/mm<sup>3</sup></b>	n=37	n=35		
AIDS / death*	8.5	26.3	<b>0.32</b> (0.1-1.1)	<b>0.06</b>
IRIS*	46.8	9.9	<b>4.7</b> (1.5-19.6)	<b>0.01</b>
# drug switches	3	0	-	-
<b>CD4 ≥50 cells/mm<sup>3</sup></b>	n=177	n=180		
AIDS / death*	6.6	4.4	<b>1.51</b> (0.6-4.0)	<b>0.34</b>
IRIS*	15.8	7.2	<b>2.2</b> ( 1.1-4.5)	<b>0.02</b>
# drug switches	7	1	<b>6.8</b> (0.8-55)	<b>0.04</b>

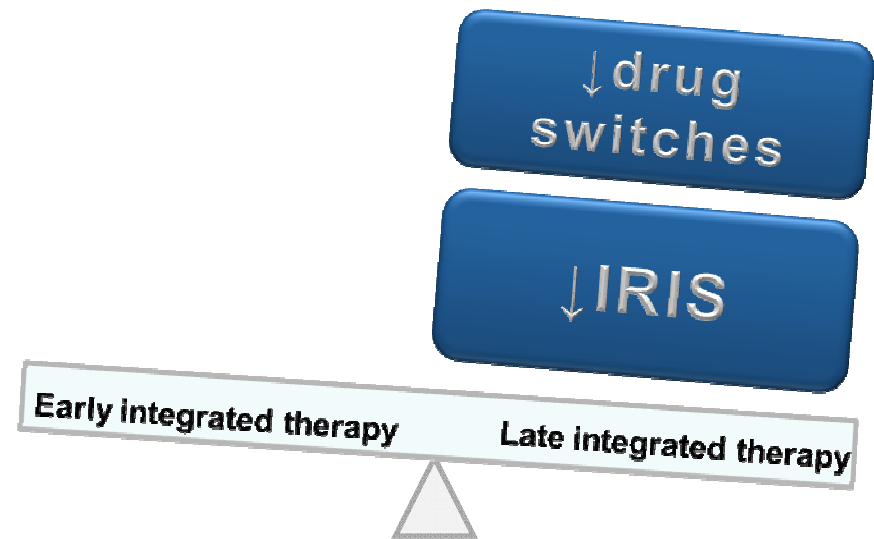
\* Rates calculated as events per 100 person-years

# Balance of risks and benefits

For CD4 count  $<50$  cells/mm<sup>3</sup>



For CD4  $\geq 50$  cells/mm<sup>3</sup>



## Early integrated therapy has:

68% lower AIDS /death rate overshadows

- 5-fold higher risk of IRIS
- Increasing trend in drug switches

## Early integrated therapy has:

No discernable benefit in AIDS /death rate

- 2-fold higher risk of IRIS
- ↑ drug switches

# Conclusions

- Findings support integration of TB and HIV treatment
- Recommend:
  - *Patients with CD4+ counts <50 cells/mm<sup>3</sup>:*
    - Early ART initiation as soon as possible after TB treatment initiation
  - *Patients with CD4 counts ≥ 50 cells/mm<sup>3</sup>:*
    - ART initiation can be deferred to start of the continuation phase of TB treatment
    - Decision on early or late initiation: use clinical judgement of capacity to manage IRIS & toxicities



# Acknowledgements

- **The patients in the study**
- President's Emergency Plan for AIDS Relief (PEPFAR)
- **Global Fund & Enhancing Care Initiative**
- eThekweni Metro & staff of Prince Cyril Zulu clinic
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- The SAPIt Safety Monitoring Committee
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