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

17th Conference of Retroviruses and Opportunistic Infections
Boston, 28 February 2011

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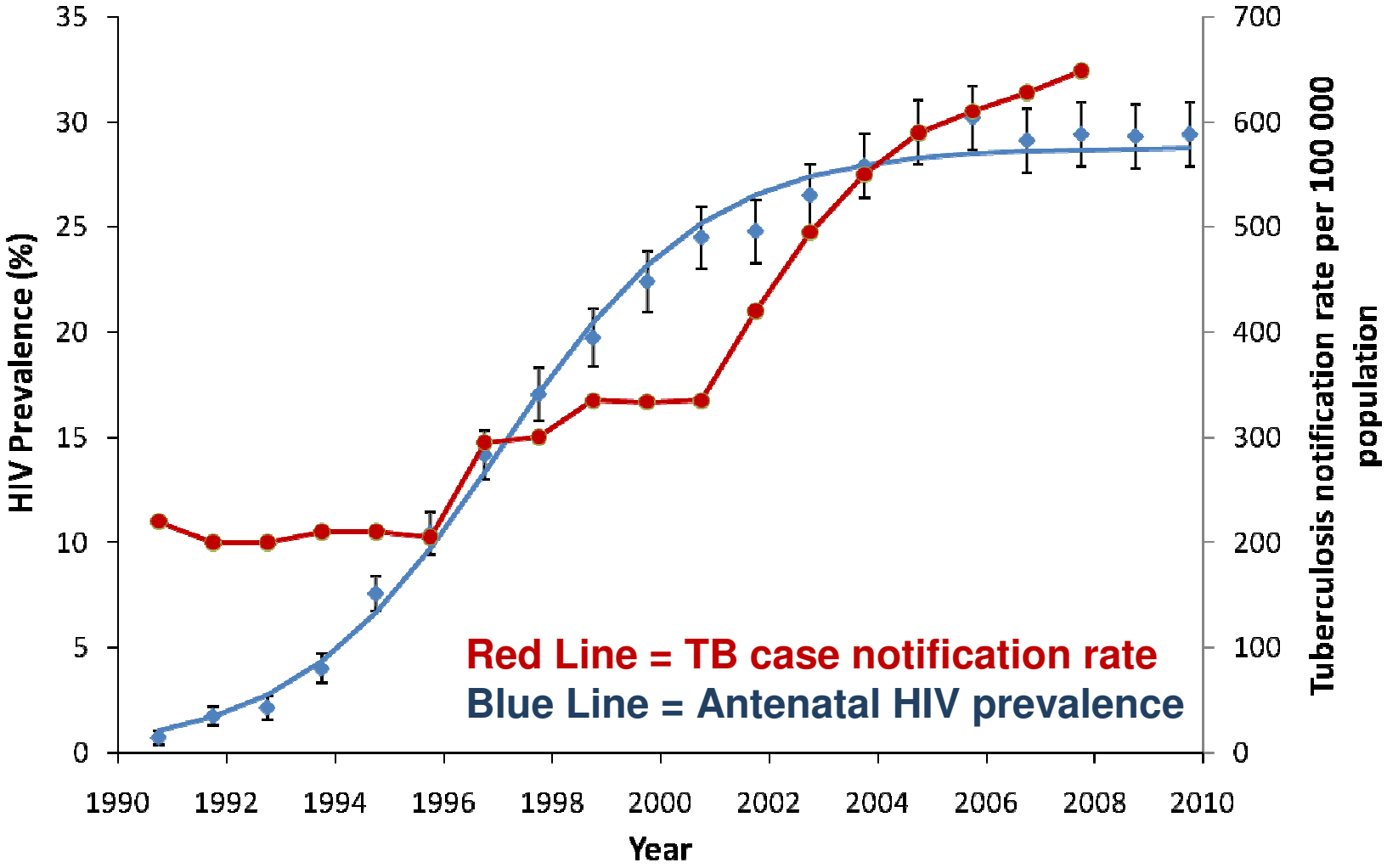
The HIV and TB epidemics in South Africa



Source: South African Department of Health

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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 eThekwini Clinic, Durban
- **Study Population:** Ambulatory TB smear +ve, HIV +ve (CD4 count < 500 cells/mm^3) and on standard TB treatment regimens. Participants attended the clinic's TB-DOTS program.
- **Endpoints**
  - 1^0 All-cause mortality + AIDS defining illness
  - 2^0 Tolerability, Viral Load, TB outcomes & Immune Reconstitution Inflammatory Syndrome (IRIS)

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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

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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

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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:** ddI + 3TC + efavirenz – once daily regimen
- **Once-a-day treatment** integrated with TB-DOT

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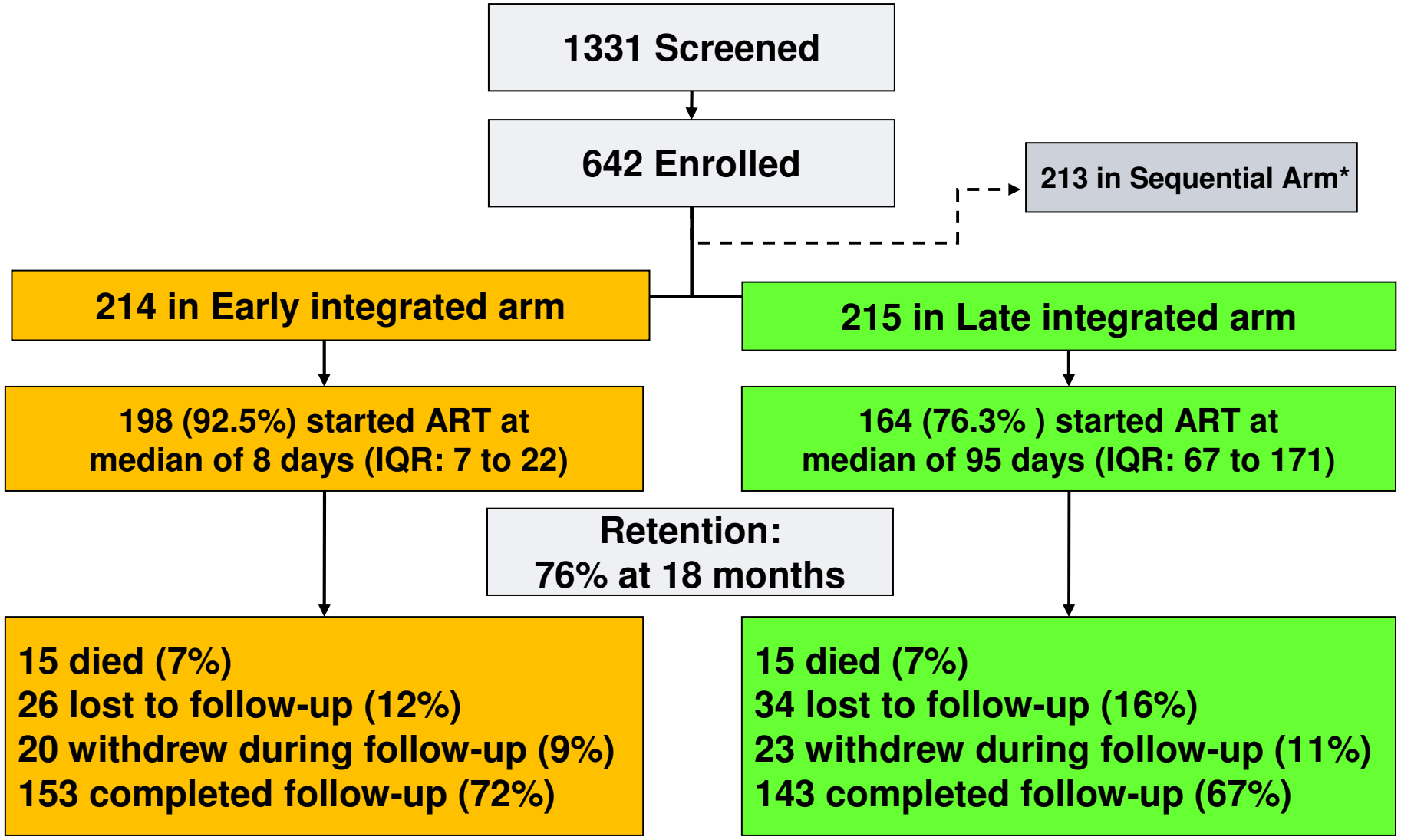
Enrollment and Outcomes



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

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Results: Baseline Characteristics

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

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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
Event rate (per 100 person-years)	**6.9**	**7.8**

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

Similar rates of AIDS defining illness or death

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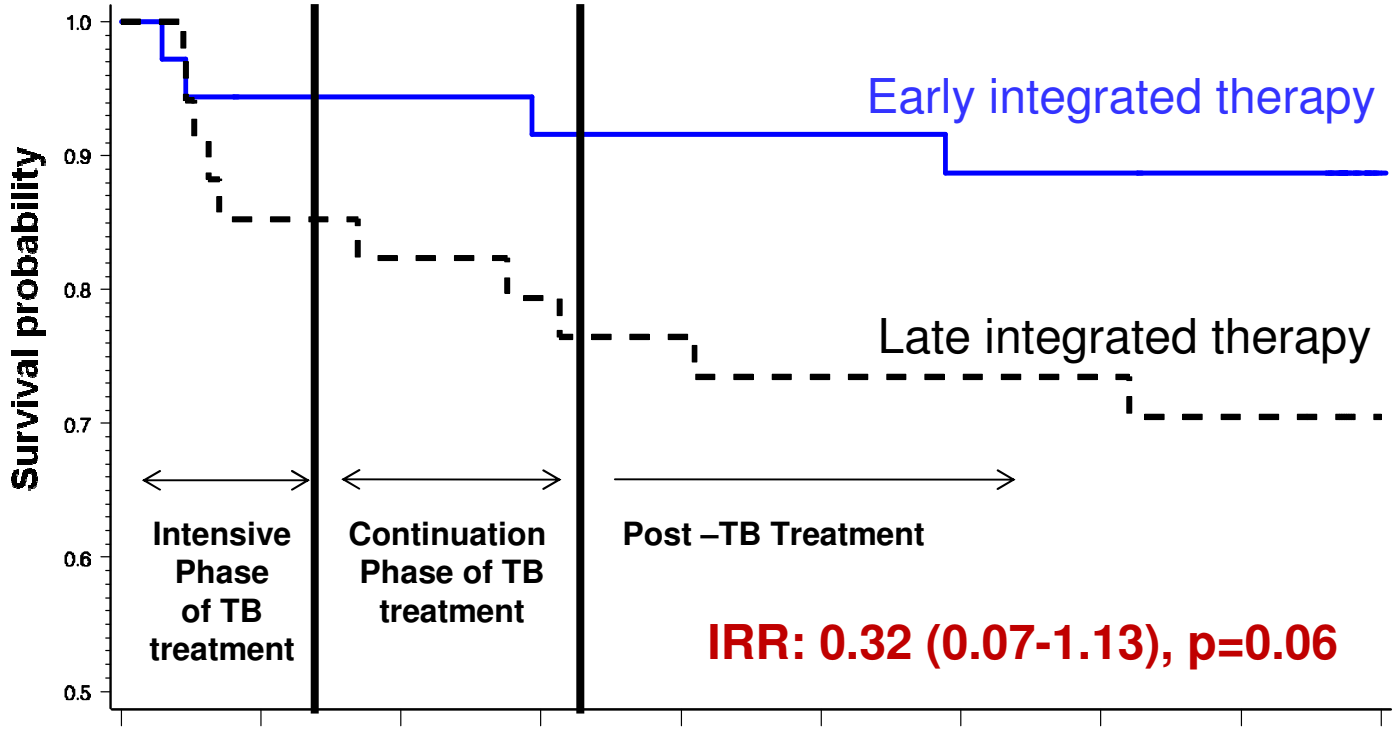
Kaplan-Meier curve for AIDS or death in patients with CD4 <50 cells/mm^3



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)

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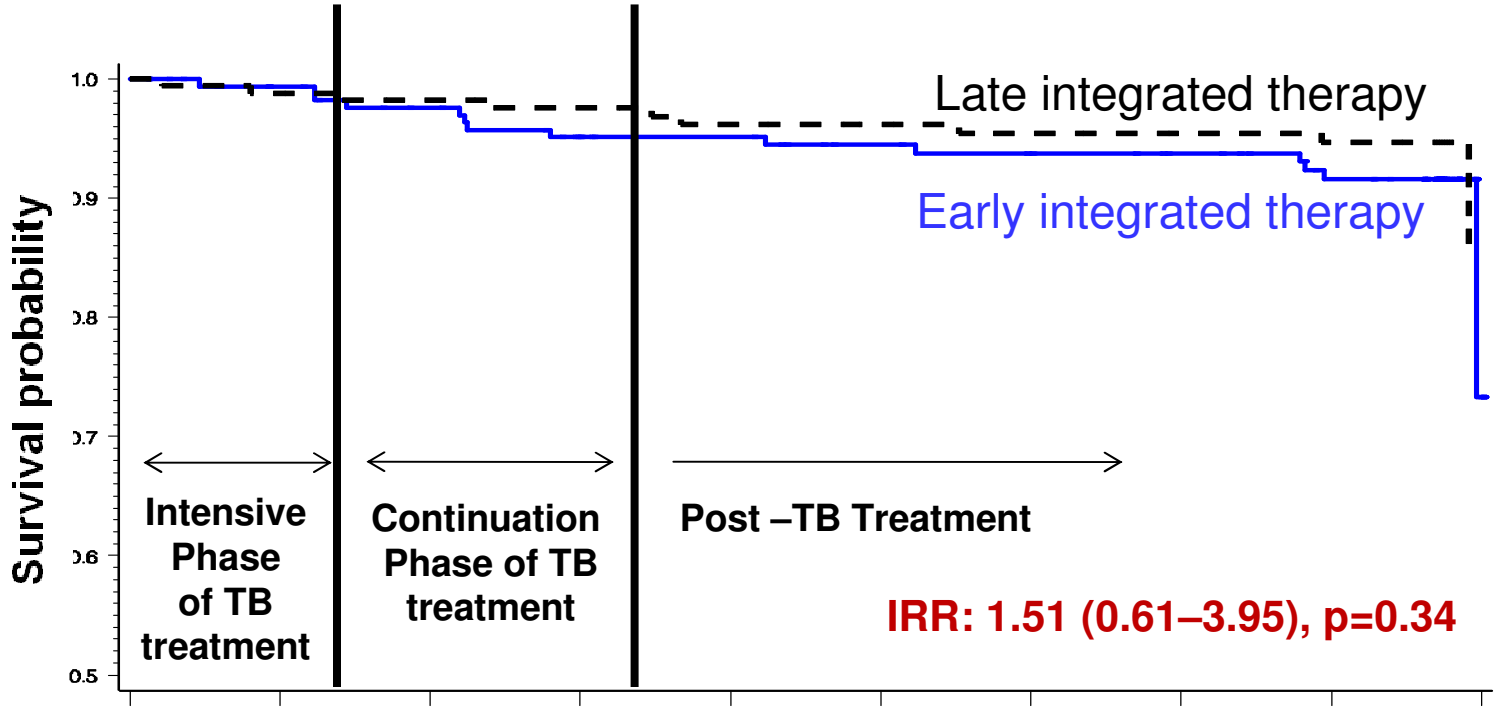
Kaplan-Meier curve for AIDS or death in patients with CD4 ≥50 cells/mm^3



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

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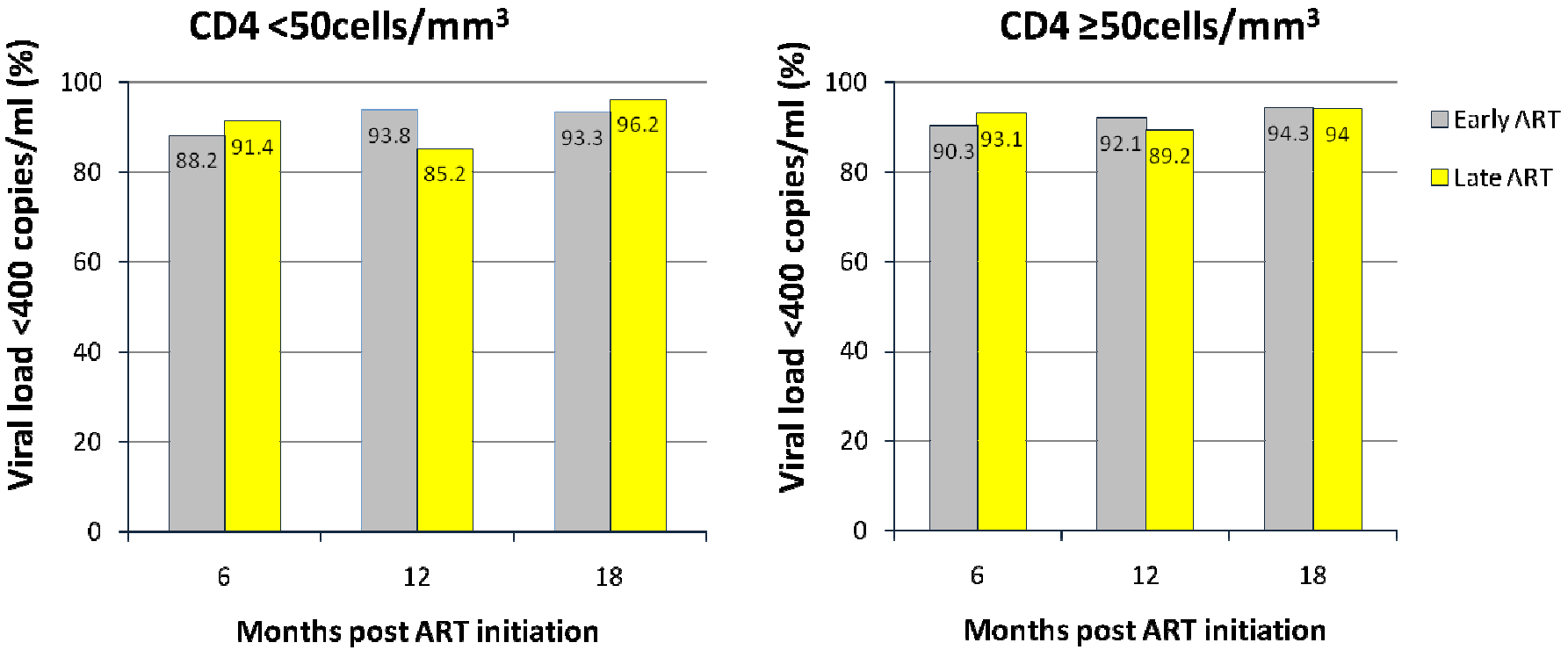
HIV treatment outcomes



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

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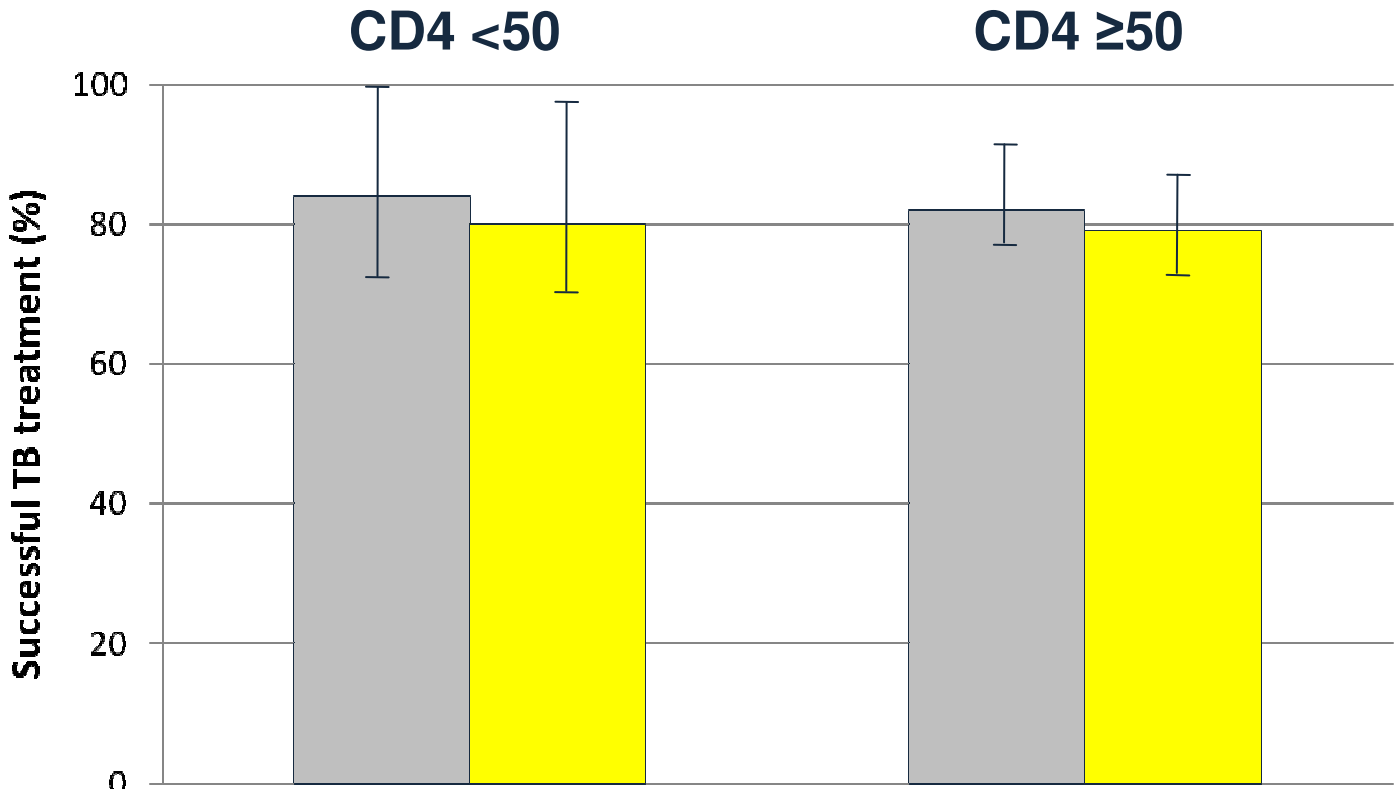
Successful TB treatment completion



	CD4 <50		CD4 ≥50	
n/N	31/37	28/31	148/180	140/177
%	83.8	80.0	82.2	79.1
P value	0.78		0.60	

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

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

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

* Rates calculated as events per 100 person-years

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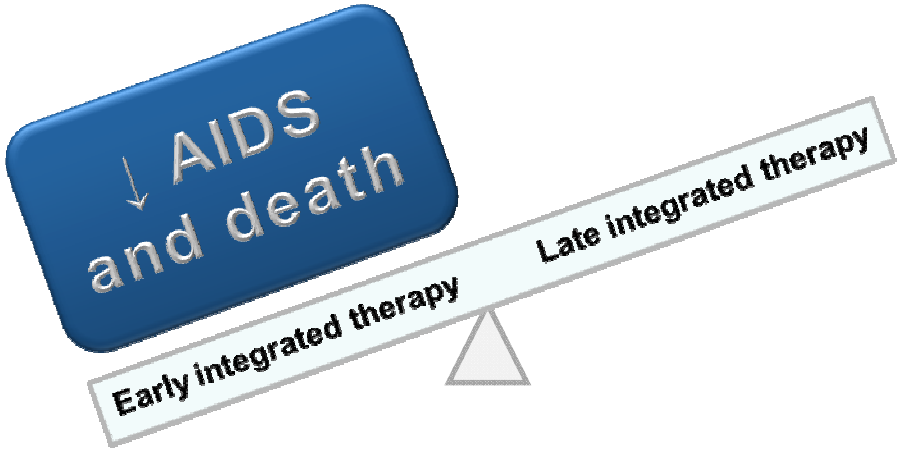
Balance of risks and benefits

For CD4 count <50 cells/mm^3

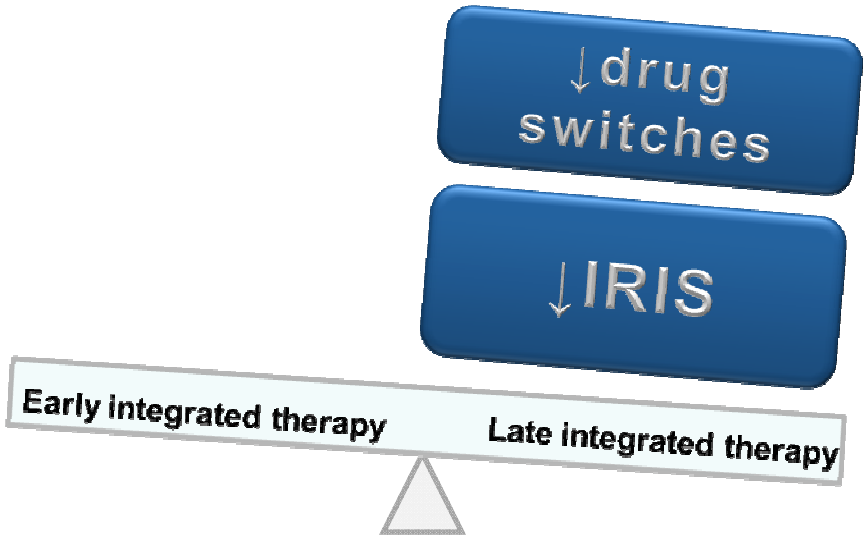


Early integrated therapy has:

68% lower AIDS /death rate overshadows

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

For CD4 ≥50 cells/mm^3



Early integrated therapy has:

No discernable benefit in AIDS /death rate

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

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Conclusions

- **Findings support integration of TB and HIV treatment**
- **Recommend:**
  - *Patients with CD4+ counts <50 cells/mm^3:*
    - Early ART initiation as soon as possible after TB treatment initiation
  - *Patients with CD4 counts ≥ 50 cells/mm^3:*
    - 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

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Acknowledgements

- **The patients in the study**
- President's Emergency Plan for AIDS Relief (PEPfAR)
- **Global Fund & Enhancing Care Initiative**
- eThekwini Metro & staff of Prince Cyril Zulu clinic
- **CAPRISA SAPiT Team & Community Support Group**
- The SAPiT Safety Monitoring Committee
- **KwaZulu-Natal Provincial Department of Health**
- KwaZulu-Natal, Yale & Columbia Universities
- **CAPRISA was established by the Comprehensive International Program of Research on AIDS of the US National Institutes of Health (grant# AI51794)**

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