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CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

CAPRISA IS A UNAIDS COLLABORATING CENTRE FOR HIV PREVENTION RESEARCH

Addressing challenges in treating TB-HIV co-infected patients

The SAPiT Trial: Starting Antiretroviral therapy at three Points in TB

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On behalf of :

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Global & South African TB and HIV epidemics in 2007

HIV

- **Globally:**
  33 million HIV +ve
- **South Africa:**
  5.4 million HIV +ve

TB

- **Globally:**
  9.2 million cases of TB
- **South Africa:**
  341,165 cases of TB

TB - HIV co-infection

- **Globally:**
  700 000 cases & 230 000 deaths
- **South Africa:**
  ~250 000 cases (HIV-TB co-infection = 70%)

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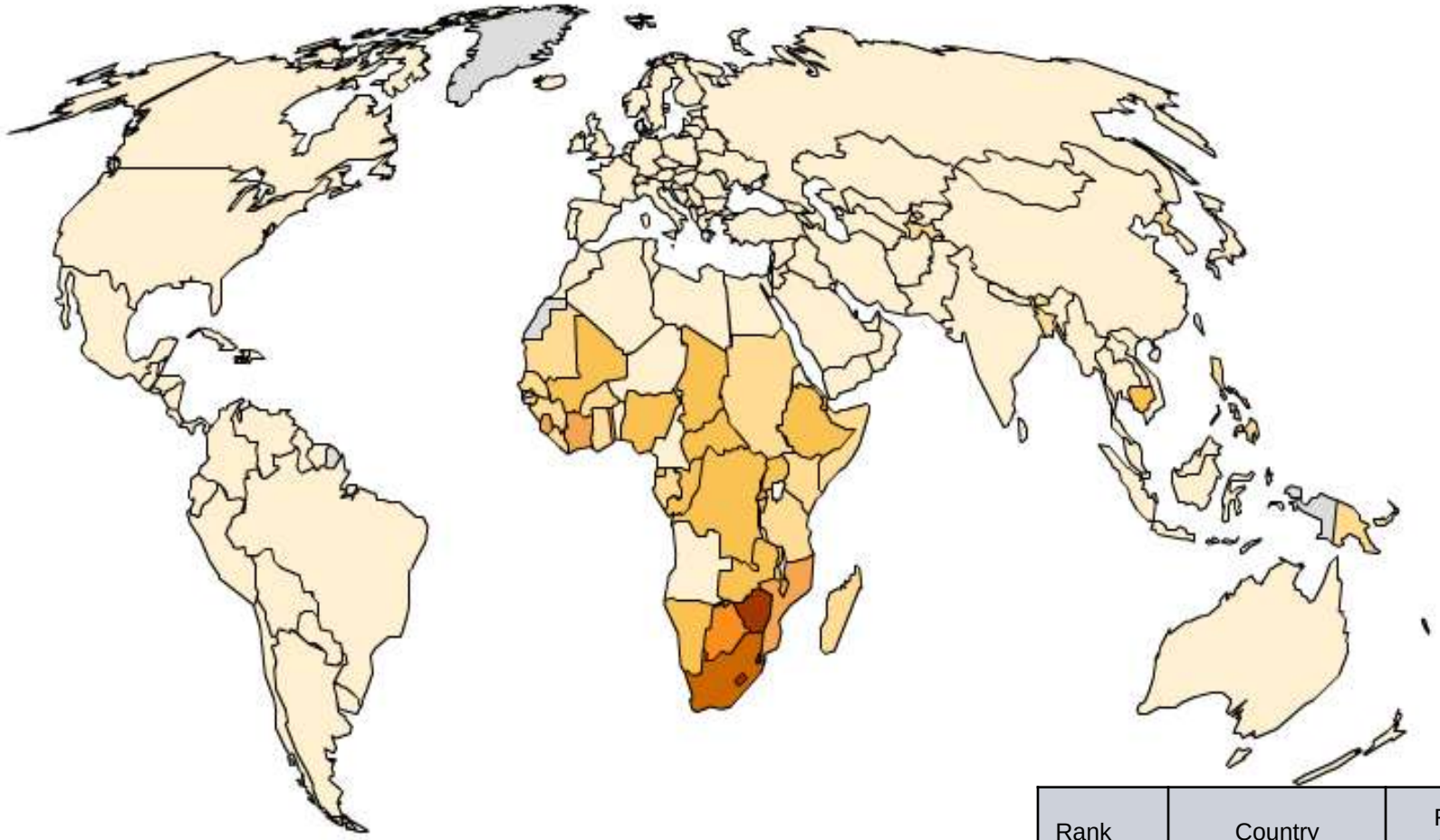
TB deaths per 100,000 population - 2007



Rank	Country	Rate per 100,000
1	Swaziland	317
2	Zimbabwe	265
3	Lesotho	263
4	South Africa	230

Source: GLOBAL TUBERCULOSIS CONTROL WHO REPORT 2009

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- **TB - leading cause of morbidity and mortality in HIV/AIDS patients**

Prevalence of HIV and HIV-related diseases in the adult medical wards of a tertiary hospital in Durban, South Africa

International Journal of STD & AIDS 2001; **12**: 386–389

M Colvin MS MBChB[1], **S Dawood** MBChB FCP[2], **I Kleinschmidt** MSc[1], **S Mullick** MSc MBChB[3] and **U Lallo** MBChB MD[2]

[1]*Medical Research Council, Durban, South Africa,* [2]*Medical School, University of Natal Durban and* [3]*Reproductive Health Research Unit, Durban, South Africa*

- **Higher TB associated CFR in HIV pos vs HIV neg despite effective chemotherapy**

Factors associated with an increased case-fatality rate in HIV-infected and non-infected South African gold miners with pulmonary tuberculosis

INT J TUBERC LUNG DIS 4(8):705–712

G. J. Churchyard,* I. Kleinschmidt,† E. L. Corbett,‡ J. Murray,§¶ J. Smit,** K. M. De Cock‡

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- **Effective mechanism of identifying patients eligible for HAART**
- **Several solvable challenges in TB-HIV integration**

Implementing antiretroviral therapy in resource-constrained settings: opportunities and challenges in integrating HIV and tuberculosis care

Salim S. Abdool Karim[a,b], Quarraisha Abdool Karim[a,b], Gerald Friedland[c], Umesh Lalloo[a] and Wafaa M. El Sadr[b,d] on behalf of the START project*

AIDS 2004, 18:975–979

- **20 TB patients started on ART**
- **Good adherence and clinical response**
- **Pilot show integration of TB and HIV treatment is feasible**

A Pilot Study of Once-Daily Antiretroviral Therapy Integrated With Tuberculosis Directly Observed Therapy in a Resource-Limited Setting

Christopher Jack, MBChB, Umesh Lalloo, MBChB, MD,* Quarraisha Abdool Karim, PhD,* Salim Abdool Karim, MBChB, PhD,* Wafaa El-Sadr, MD, MPH,† Sharon Cassol, PhD,*‡ and Gerald Friedland, MD§*

(*J Acquir Immune Defic Syndr* 2004;36:929–934)

Summary: To determine the feasibility and effectiveness of integrating highly active antiretroviral therapy (HAART) into existing tuberculosis directly observed therapy (TB/DOT) programs, we par-

Tuberculosis (TB) is a major cause of morbidity and mortality among persons with HIV disease worldwide, particularly in resource-poor settings. The province of KwaZulu

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TB and HIV Integration Challenges

- **Programmatic**
  - Is it feasible and practical
  - Case finding & case holding
  - Contact tracing
  - HCW & patients perspectives
- **Therapeutic**
  - When to start?
  - Which ARVs to start with?
  - Adherence
  - Drug- Drug interactions
- **Clinical**
  - Additive toxicities
  - Immune Reconstitution (IRIS)
  - Changing TB clinical features
- **TB Diagnostics**
  - Smear negative TB
  - Rapid diagnosis (resistance)
  - Extra-pulmonary TB
- **TB Prevention**
  - Better vaccines
  - Effective prophylaxis
  - Infection control
- **TB Therapy**
  - Shorter duration
  - New drugs
- **Policy and Planning**
  - Resource allocation
  - Practical implementation

Challenges in TB-HIV co-infection: When to start ART in relation to TB treatment?

- **Why initiate ART during TB treatment?**
  - To halt HIV progression & avert high TB-HIV mortality
- **Why not initiate ART in TB treatment?**
  - Drug interactions bet Rifampin & some ARVs
  - Pill burden / tolerability – 4 TB drugs + 3 ARVs
  - Multiple and overlapping toxicities
  - Increased risk of immune reconstitution syndrome
- **Current treatment based on observational data, clinician judgement & expert opinion:**
  - High variability & lack of integration of TB-HIV care
  - Country guidelines based on WHO guidance

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SAPiT: Starting Antiretroviral therapy (ART) in three Points in TB

Primary Objective:

- To determine the optimal time to initiate ARVs in TB patients

Inclusion Criteria:

- Smear +ve & on standard TB treatment regimens
- HIV positive with CD4 count < 500 cells/mm^3
- Women must agree to use contraception – (efavirenz)

Endpoints

- 1^0 All-cause mortality
- 2^0 Tolerability, Toxicity, Viral Load, TB outcomes & Immune Reconstitution Inflammatory Syndrome (IRIS)

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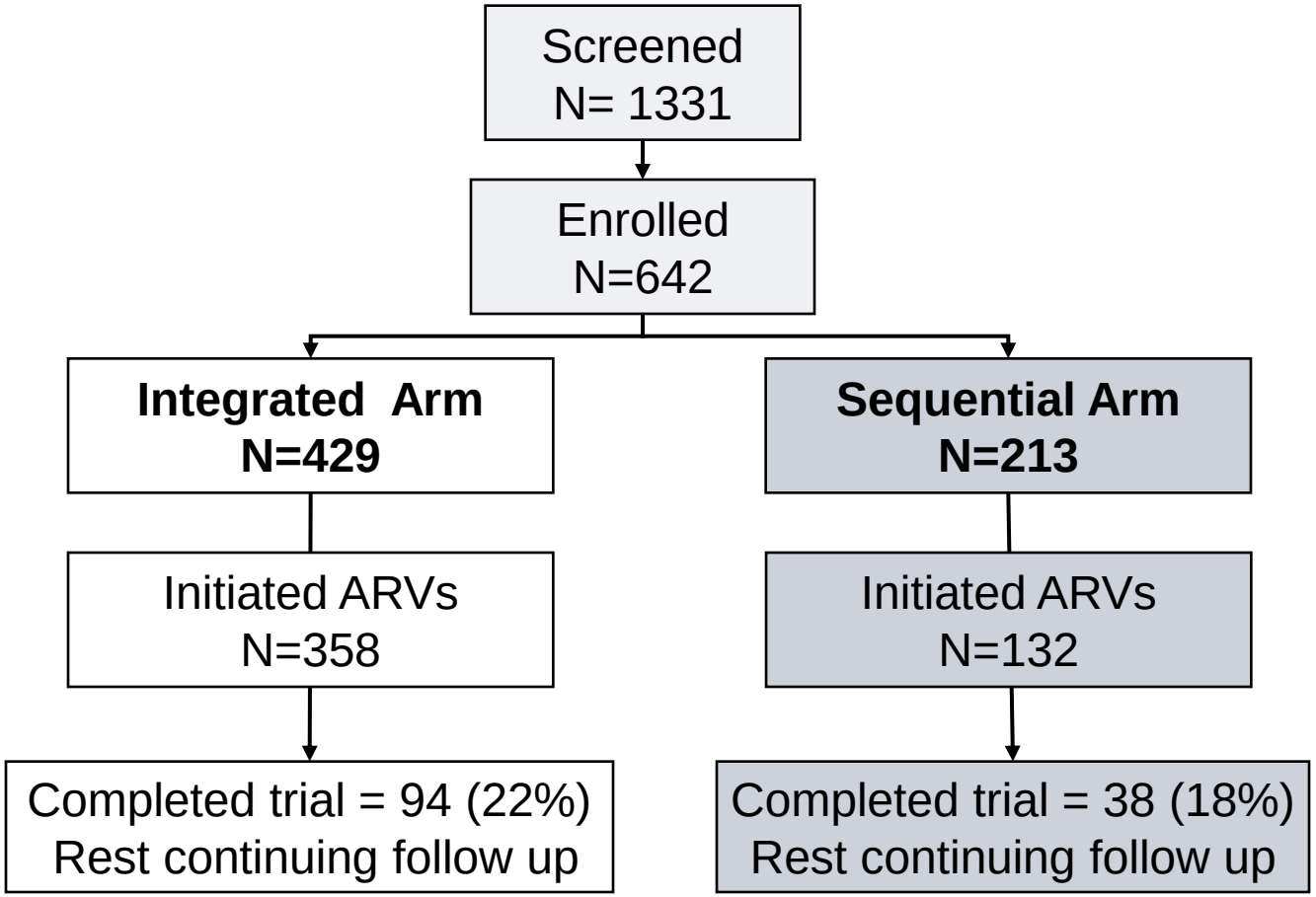
Study design and intervention

- **Design:** Open-Label Randomized Controlled Trial
- **Randomized to one of 3 arms:**
  - ***Arm 1:*** *ART initiated during intensive phase of TB treatment*
  - ***Arm 2:*** *ART initiated after intensive phase of TB treatment*
  - ***Arms 1 & 2 combined:*** *Integrated TB-HIV treatment*
  - ***Arm 3:*** *Sequential treatment - ART initiated after TB treatment completed*
- **TB treatment:** Standard TB regimen
- **Cotrimoxazole prophylaxis:** provided to all patients
- **ART:** Didanosine (ddI) + Lamivudine (3TC) + Efavirenz

  Once-a-day treatment integrated with TB-DOT

Status of the trial at Safety Monitoring Committee review (September 2008)



Safety Monitoring Committee review and recommended:

- *Start ART iimmediately n all sequential arm patients (ie. to halt the sequential treatment arm)*
- *Continue the two integrated treatment arms in the trial*

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Results: Baseline Characteristics

Baseline Characteristic	Integrated Arm	Sequential Arm	p-value
Age in years (SD)	**34.4** (8.38)	**33.9** (8.18)	0.48
Gender - % male	**48.7%**	**52.1%**	0.45
CD4 count cells/mm^3 (SD)	**181** (136.2)	**167** (124.1)	0.22
Log viral load (SD)	**5.00** (0.91)	**5.12** (0.74)	0.12
WHO stage 4	**4.9%** (n=21)	**4.7%** (n=10)	1.00
MDR-TB cases (%)	**3.5%** (n=15)	**3.3%** (n=7)	1.00

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Outcome at halt of sequential arm: Mortality rates

	Integrated Treatment Arm n = 429	Sequential Treatment Arm n = 213
Number of deaths	25	27
Person-years of follow-up	466	222
Mortality rate per 100 person-years	5.4	12.1

Hazard Ratio: 0.44 (95% CI: 0.25 to 0.79); p = 0.003

56% lower mortality with integrated TB-HIV treatment

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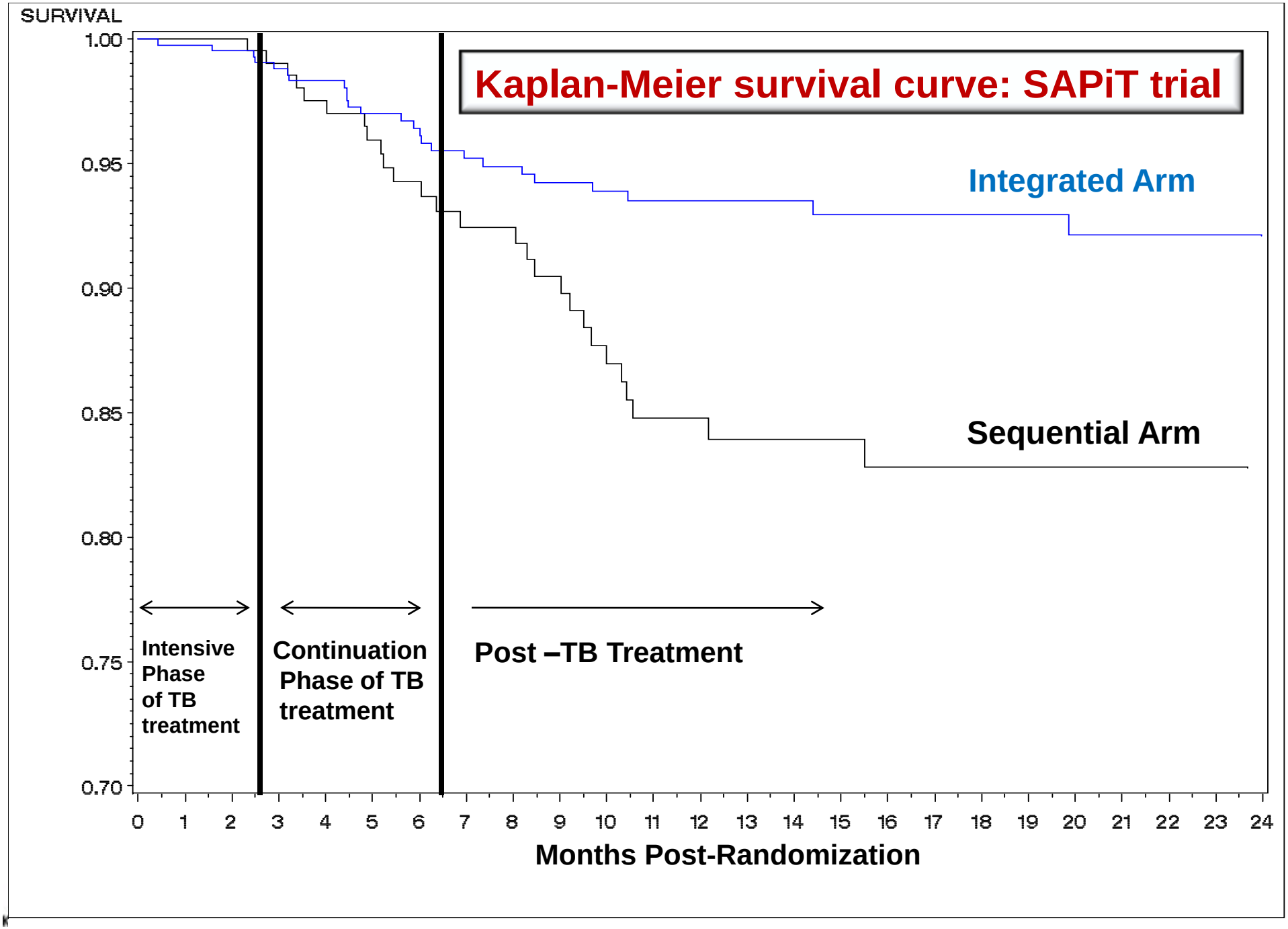
SURVIVAL
1.00
0.95
0.90
0.85
0.80
0.75
0.70
Kaplan-Meier survival curve: SAPiT trial
Integrated Arm
Sequential Arm
Intensive Phase of TB treatment
Continuation Phase of TB treatment
Post –TB Treatment
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Months Post-Randomization

Mortality rates in CD4 count strata

- **Reduction in mortality in the Integrated arm is present in patients with CD4 <= 200 and patients with CD4 > 200 cells/mm^3**

	CD4 count	
	≤ 200 cells/mm^3	**> 200 cells/mm^3**
Integrated arm:		
# dead/ py (n)	23/281 (273)	2/186 (156)
Mortality rate (95% CI)	**8.2** (5.2 - 12.3)	**1.1** (0.1 - 3.9)
Sequential arm:		
# dead / py (n)	21/137 (138)	6/86 (75)
Mortality rate (95% CI)	**15.3** (9.57 - 23.5)	**7.0** (2.6 -15.3)
Rate Ratio (95% CI)	**0.53** (0.28-1.01) **p=0.051**	**0.15** (0.02-0.86) **p=0.022**

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Incidence of IRIS and ART adherence

	Integrated arm	Sequential arm
% with IRIS #	**12.1%** (52/429)	**3.8%** (8/213)*
Hospitalization due to IRIS	10/52	0/8
Viral load <1000 at 12 mths #	**91.0%** (201/221)	**80.0%** (72/90)
ART Adherence (pill count)	(n = 344)	(n = 132)
< 90%	**3.2%** (11)	**5.3%** (7)
90-95%	**6.4%** (22)	**7.6%** (10)
>95%	**90.4%** (311)	**87.1%** (115)

 # p<0.05

*Note: 83% Integrated arm vs 62% Sequential arm patients had initiated ART – data provisional

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TB outcomes in SAPiT trial

TB Outcome	Integrated arm n = 331 % (# cases)	Sequential arm n = 165 % (# cases)
Cure	60.7% (201)	59.4% (98)
Successful completion	17.5% (58)	13.9% (23)
Successfully treated	**78.2% (259)**	**73.3% (121)**
Died	5.7% (19)	9.7% (16)
Treatment interruption	3.9% (13)	7.9% (13)
Treatment failure	0.6% (2)	0.6% (1)
Unknown	11.5% (38)	8.5% (14)

p-value = 0.26

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Conclusions

- **Clinical trial evidence for combining TB & HIV treatment -** reduces mortality by 56% in co-infected patients with CD4 < 500
- **IRIS cases and hospitalizations increased** by initiation of ART during TB treatment
- **TB outcomes similar in both arms** - mortality in the sequential treatment arm occurs late - mainly after TB treatment is completed, hence TB program is not aware
- **Viral suppression (VL<1000) at 12 months higher** in the Integrated treatment arm
- **When to start ART during TB treatment?**

  Awaiting completion of the SAPiT trial - the 2 integrated treatment arms are continuing……

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Limitations

- **All-cause mortality- underestimates the potential impact of integrated HIV-tuberculosis treatment on deaths related only to tuberculosis and HIV**
- **Ambulant adult patients enrolled**
- **Focus on smear pulmonary PTB**
- **Empiric confirmation of results required in patients with SNTB, EPTB, and in patients with more severe form of TB eg admitted patients, disseminated TB etc**

Implications of the findings

- **Programmatic implementation implications:**
  - All TB patients should be offered an HIV test & CD4 count
  - TB-HIV co-infected patients with CD4 <500 should be initiated on ART during TB treatment
  - Vigilance for the diagnosis and management of IRIS & toxicities
  - Monitor the proportion of TB-HIV patients on ART as an indicator of the performance of ART rollout programs
- **Implementation in South Africa:**
  - ~150,000 more TB patients initiated on ART annually
  - ~10,000 deaths averted

Acknowledgements

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- **University of KwaZulu-Natal & Columbia University**

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- University of Kwa bia University

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