Advanced Course in Clinical Parasitology (ACCP)

Barcelona, September 6th 2011

When to Start Antiretroviral Therapy in Patients with PCP and other Opportunistic Infections(OIs)

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Timing of cART in HIV-infected Patients with Opportunistic Infections (OIs)

Acute therapy	Maintenance therapy

Immediate cART

Deferred cART

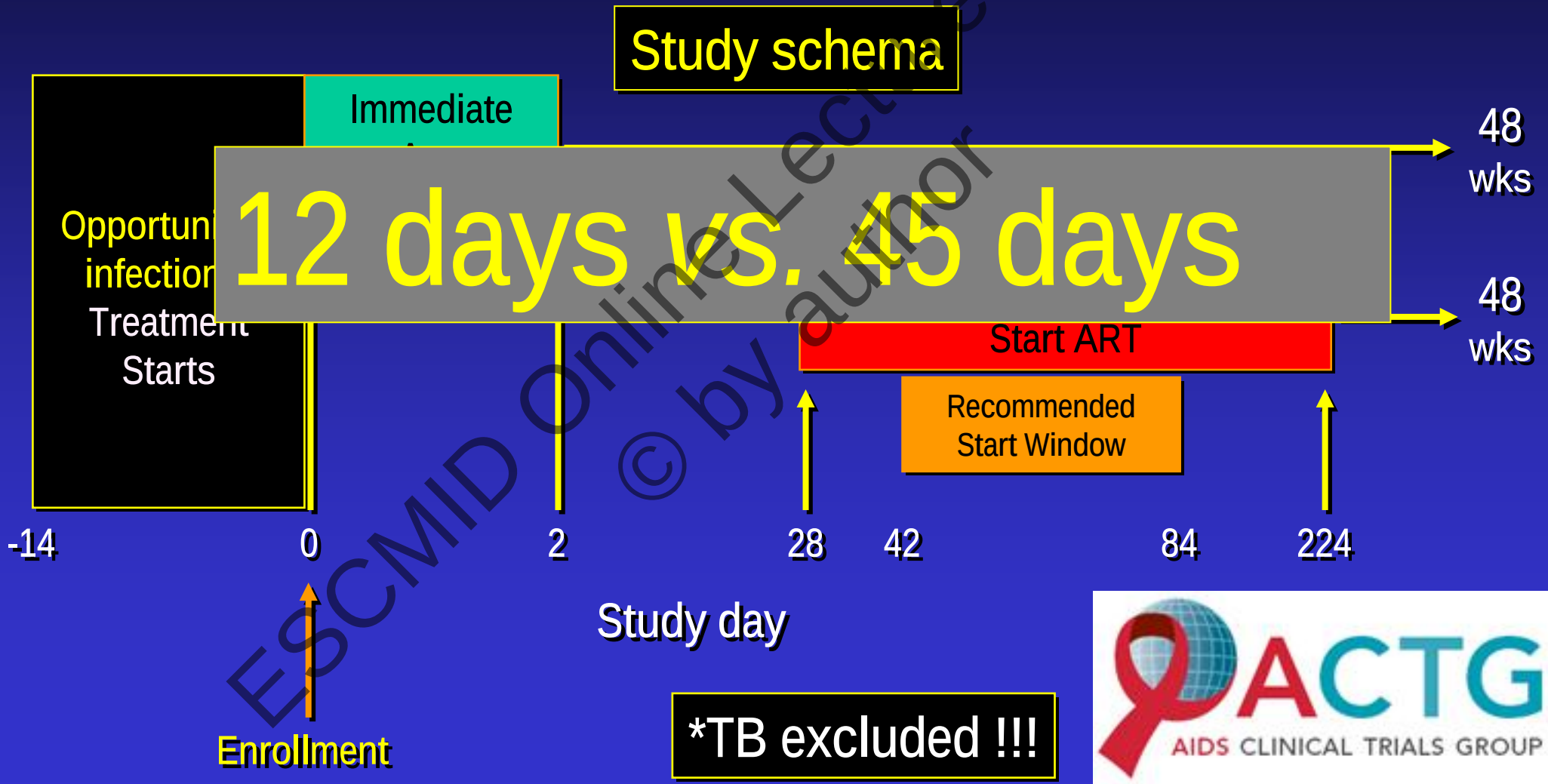
- High pill burden
- Overlapping side effects
- PK interactions
- Risk of IRIS

?

- High risk of HIV disease progression and death in patients with advanced disease (CD4<50 cells/mm^3)

Immediate *vs.* Deferred cART in the Setting of Acute AIDS-Related OIs (ACTG A5164)

Zolopa AR, et al. PLoS ONE. 2009;4(5):e5575. Epub 2009.



Immediate *vs.* Deferred cART in the Setting of Acute AIDS-Related OIs (ACTG A5164)

Zolopa AR, et al. PLoS ONE. 2009;4(5):e5575. Epub 2009.

Characteristics		Total	Immediate	Deferred
CD4 (cells/mm^3)	Median (IQR)	29 (10-55)	31 (12-54)	28 (10-56)
HIV RNA (log10)	Median (IQR)	5.07 (4.71-5.63)	5.07 (4.74-5.59)	5.08 (4.64-5.64)
No Prior ART	N (%)	259 (92)	131 (93)	128 (91)
PCP	N (%)	177 (63)	88 (62)	89 (63)
Bacterial infections	N (%)	34 (12)	17 (12)	17 (12)
Other OI	N (%)	71 (25)	36 (26)	35 (25)
Crypto / Histo	N (%)	45 (16)	20 (14)	25 (18)
Toxoplasmosis	N (%)	13 (5)	9 (6)	4 (3)
CMV	N (%)	6 (2)	4 (3)	2 (1)
MAC	N (%)	6 (2)	3 (2)	3 (2)
Multiple OI/BI	within 30 days	33%	32%	33%

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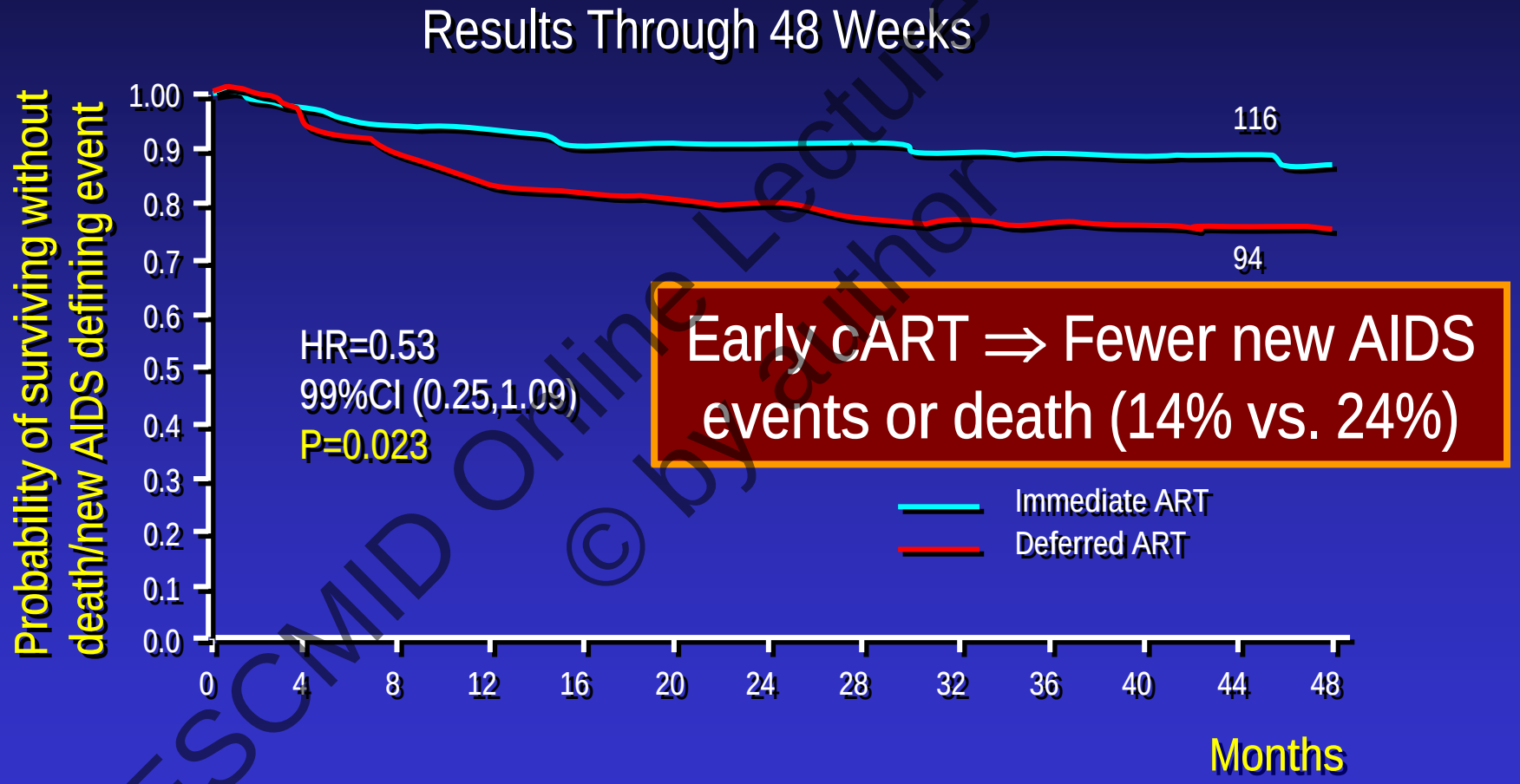


- No difference in primary endpoint of virologic suppression
- No difference in IRIS (10 immediate, 13 deferred) or need for ART switches

Immediate vs. Deferred cART in the Setting of Acute AIDS-Related OIs (ACTG A5164)

Zolopa AR. PLoS ONE. 2009. 4(5): e5575. doi:10.1371/journal.pone.0005575

Outcome		Immediate	Deferred	p-value
HIV VL < 50 @ wk 48	ITT analysis	71 (50%)	72 (51%)	ns
ART Adherent @ wk 48	"took most or all ART in past 4 days"	95%	93%	ns
ART Changes	Includes: switches, interruptions and D/Cs	42%	35%	0.19

Immediate vs. Deferred cART in the Setting of Acute AIDS-Related OIs (ACTG A5164)

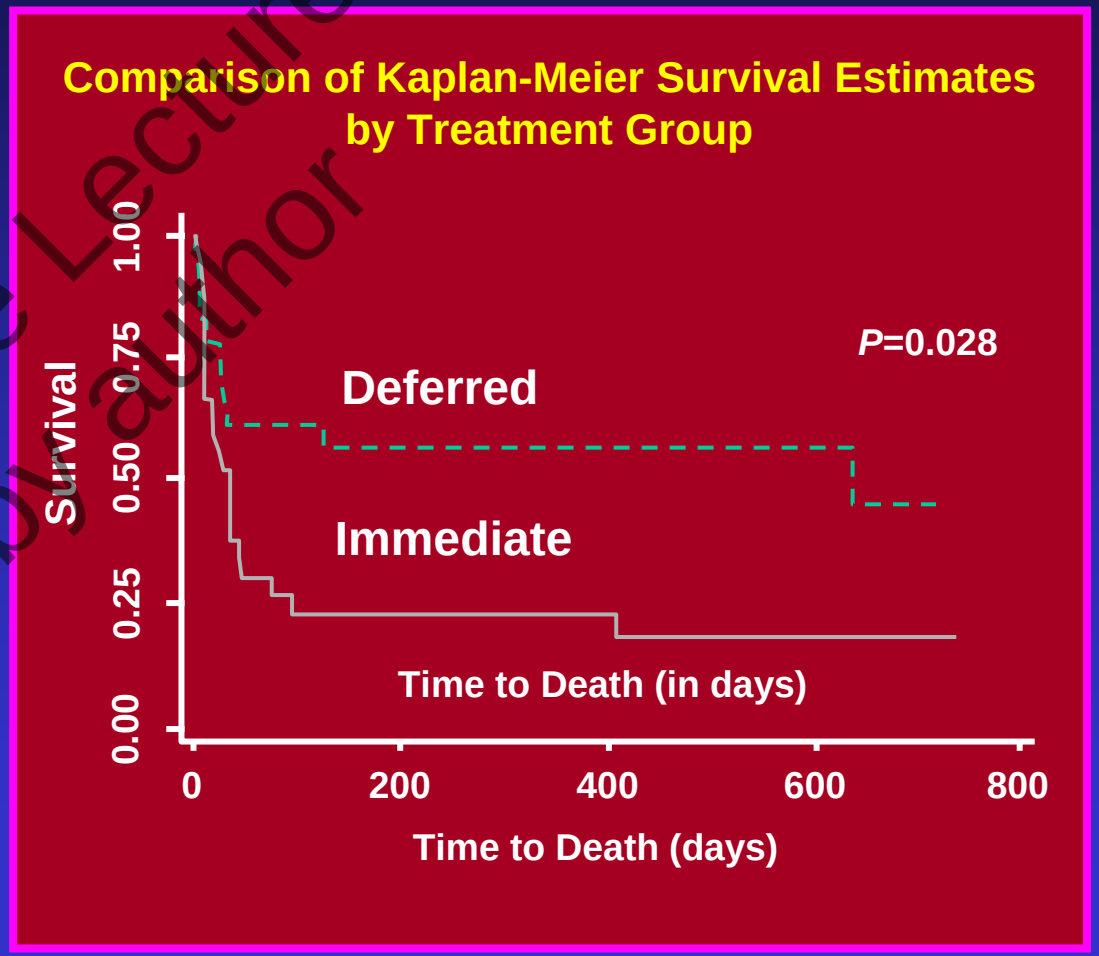
Zolopa AR. PLoS ONE. 2009. 4(5): e5575. doi:10.1371/journal.pone.0005575

Outcome	Immediate	Deferred	*p-value*
IRIS reported	10	13	
IRIS confirmed	**8 (6%)**	**12 (8.5%)**	**NS**
Lab AEs Grades 2-3-4	31 - 39 - 20	36 - 45 - 21	0.77
Clinical AEs Grades 2-3-4	14 - 40 - 7	34 - 29 - 6	0.87
Hospitalizations (>30 d.)			
Patients	39%	36%	0.63
Hospital days (median)	5	6	0.79

HIV-associated Cryptococcal Meningitis: Immediate *vs.* Deferred cART

Makadzange A, et al. Clin Infect Dis. 2010; 50:1532-8

- Immediate *vs.* Deferred (10 weeks) cART in Cryptococcal Meningitis (N=54)
  - Rx: Fluconazole 800 mg daily and d4T/3TC/NVP
  - No use of amphotericin or management of raised intracranial pressure
- Mortality: 87% immediate *vs.* 37% delayed (*P*=0.002)
  - Most deaths in immediate ART group occurred within the first month, possibly due to IRIS
  - Fluconazole-NVP drug interaction postulated



Abdool Karim SS. N Engl J Med. 2010;362:697-706.

CAPRISA

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

Salim S. Abdool Karim

Director: CAPRISA
Pro Vice-Chancellor (Research): University of KwaZulu-Natal
Professor in Clinical Epidemiology, Columbia University

On behalf of :
Kogieleum Naidoo, Anneke Grobler, Nesri Padayatchi, Andrew Gray, Jacqueline Pienaar, Tanuja Gengiah, Gonasagrie Nair, Sheila Bamber, Aarthi Singh, Munira Khan, Wafaa El-Sadr, Gerald Friedland and Quarraisha Abdool Karim

Columbia University MAILMAN SCHOOL OF PUBLIC HEALTH

UNIVERSITY OF KWAZULU-NATAL

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

Abdool Karim SS. N Engl J Med. 2010;362:697-706.

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Outcome at halt of sequential arm: Mortality rates

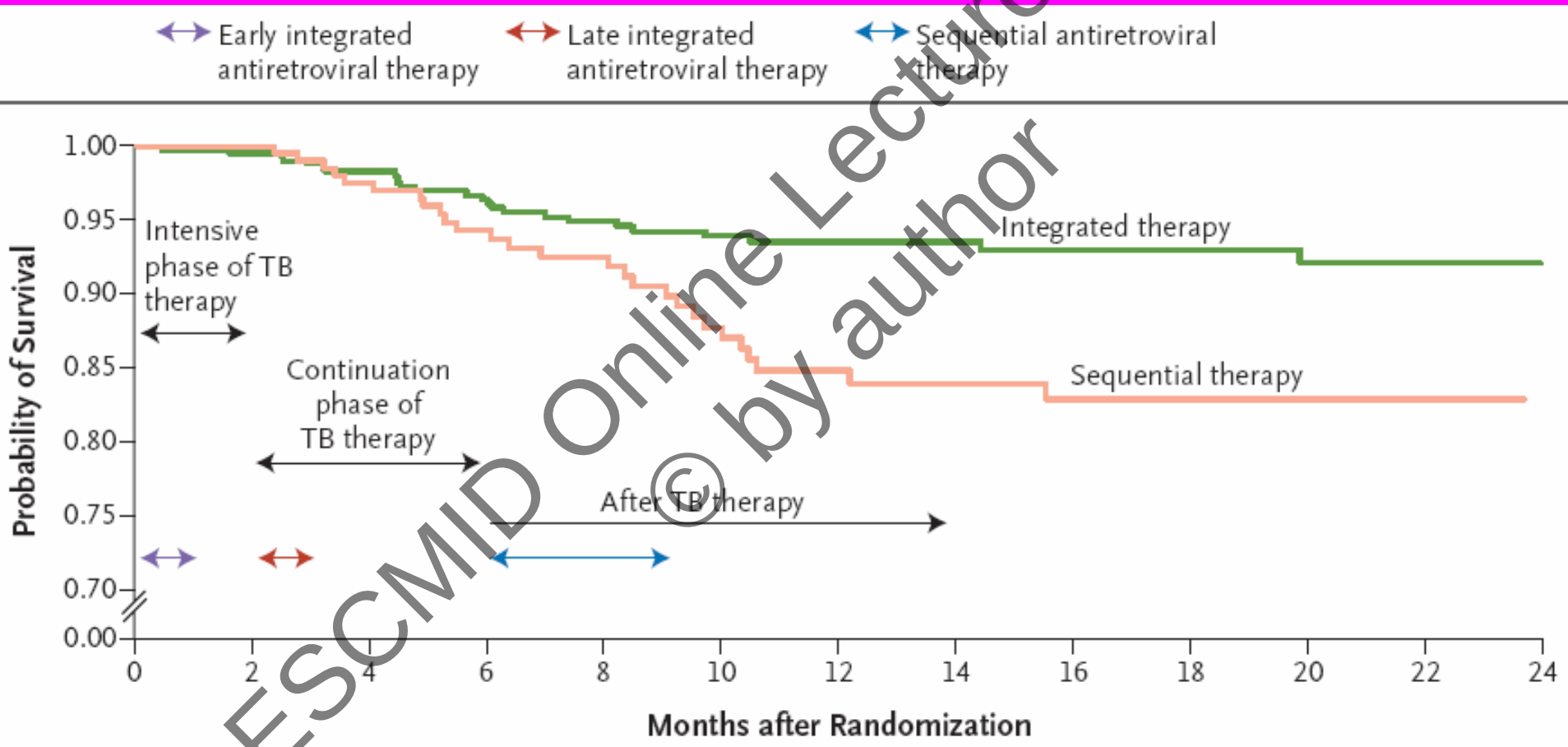
	Integrated Treatment Arm n = 429	Sequential Treatment Arm n = 213
Number of deaths	25	27
Person-years of follow-up	466	222
Mortality rate per 100 person-years	5.4	12.1

Sept 2008: DSMB stopped sequential arm and recommended that all patients begin cART

Abdool Karim SS. N Engl J Med. 2010;362:697-706.

Kaplan–Meier Survival Curves in SAPIT Trial: Integrated *vs.* Sequential Therapy.

Abdool Karim SS. N Engl J Med. 2010;362:697-706.



SAPIT Trial: Incidence of IRIS in Integrated *vs.* Sequential Therapy

Abdool Karim SS. N Engl J Med. 2010;362:697-706.

ART adherence & TB and AIDS treatment outcomes

	Integrated arm	Sequential arm
ART Adherence > 95% pill count	**90.4%** (311/344)	**87.1%** (115/132)
Viral load <1000 at 12 mths #	**91.0%** (201/221)	**80.0%** (72/90)
TB treatment successful	**78.4%** (258/331)	**73.3%** (121/165)
Incidence of IRIS #	**12.1%** (52/429)*	**3.8%** (8/213)*
Mortality in MDR-TB patients	**20%** (3/15)	**71%** (5/7)

# p<0.05

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

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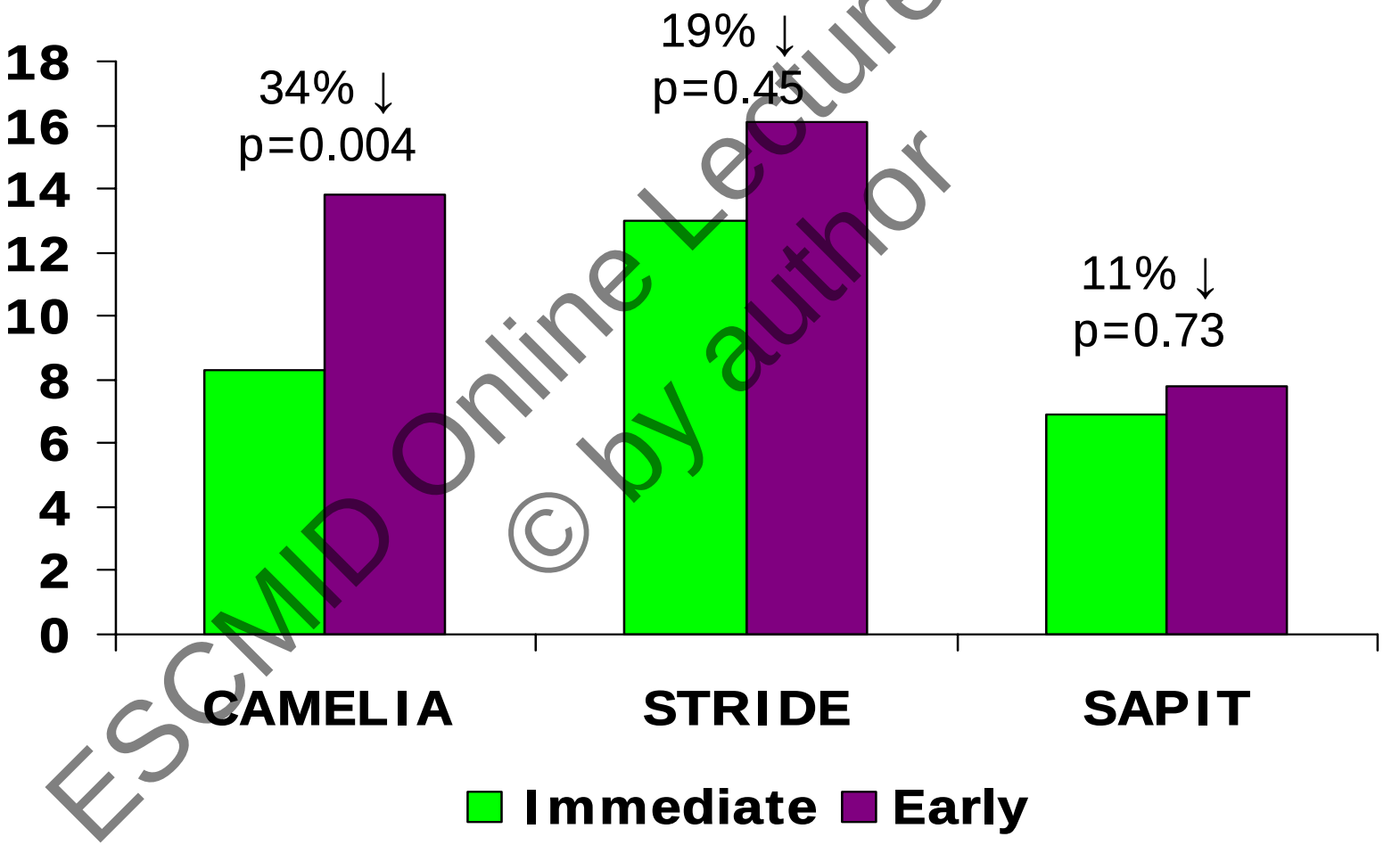
When to Start cART During TB Treatment

	A5221/STRIDE	CAMELIA	SAPIT
No.	800/800	660/660	215/215
Sites	Africa, Asia, SA, NA	Cambodia	South Africa
Arms	Imm *vs.* 8-12 wk	Imm *vs.* 8 wk	Imm *vs.* 8-24 wk
Endpoints	Death, AIDS	Death	Death

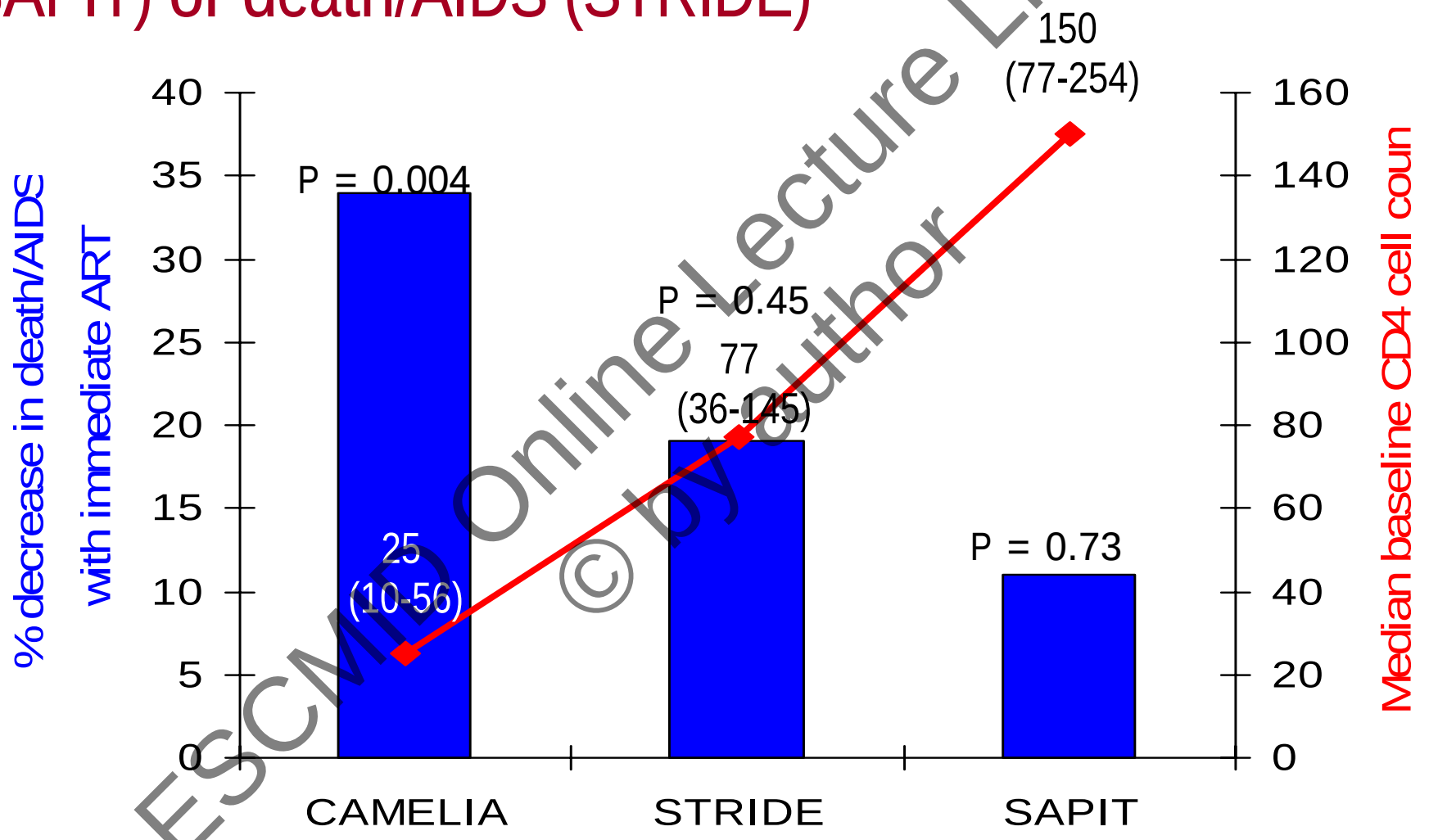
Immediate = First 2 weeks.

Effect of ART timing on death (CAMELIA, SAPIT) or death/AIDS (STRIDE)



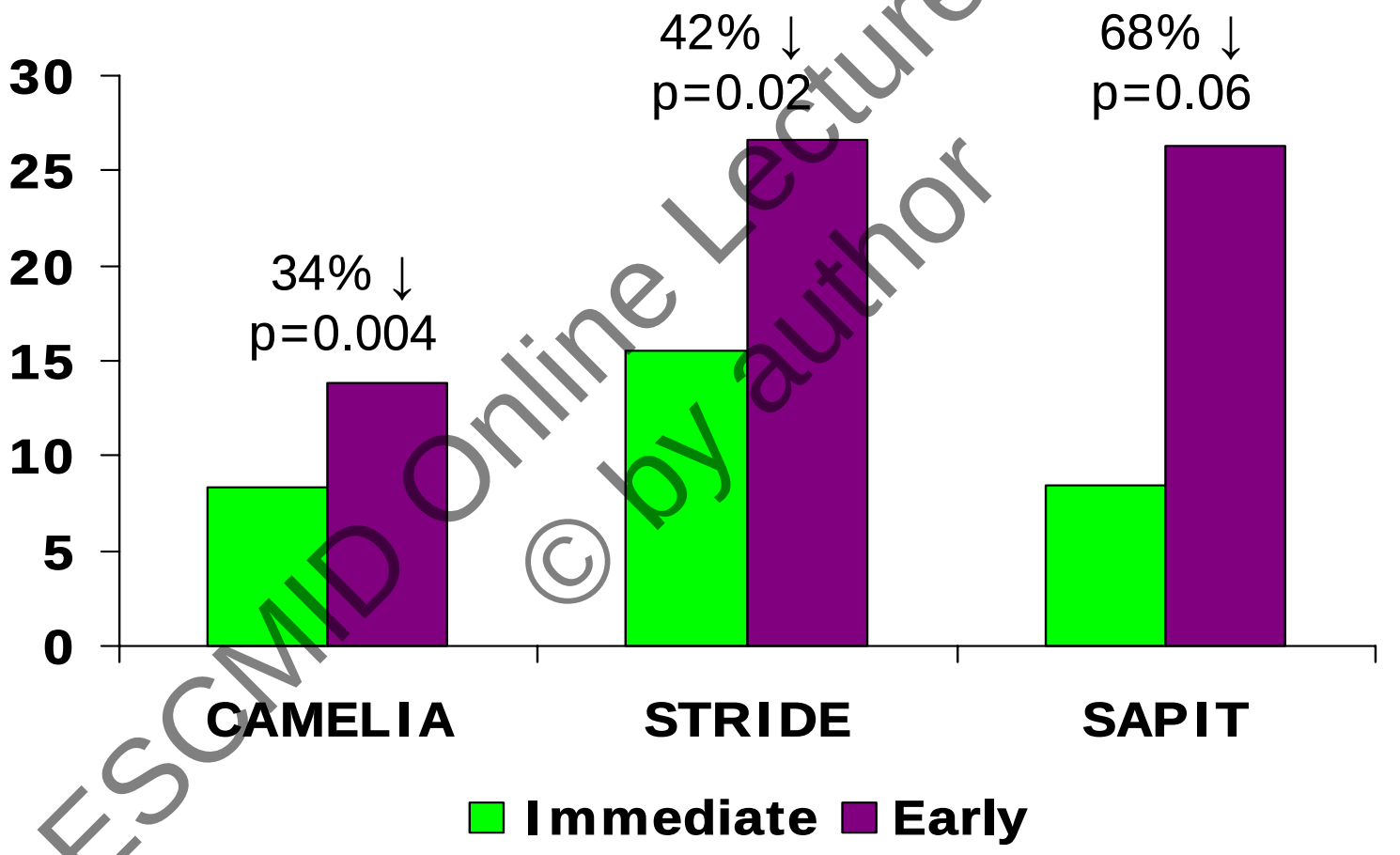
AIDS 2010 abstract THLBB106, CROI 2011 abstract 38, CROI 2011 abstract 39LB

Relationship between median baseline CD4 count and the effect of immediate ART on death (CAMELIA, SAPIT) or death/AIDS (STRIDE)



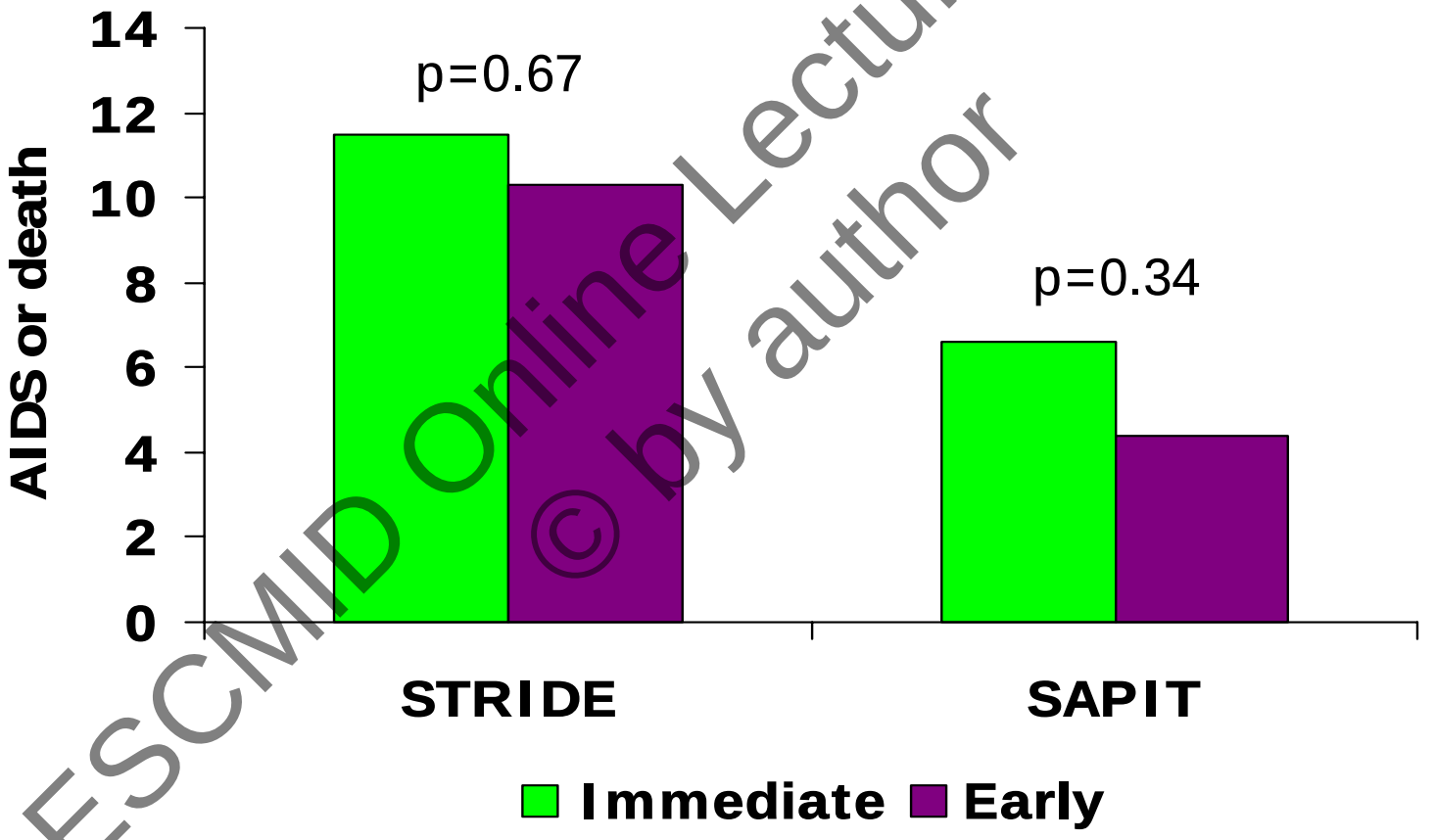
AIDS 2010 abstract THLBB106, CROI 2011 abstract , CROI 2011 abstract

Effects of ART timing on outcomes in CAMELIA and patients with CD4 < 50 in STRIDE and SAPIT



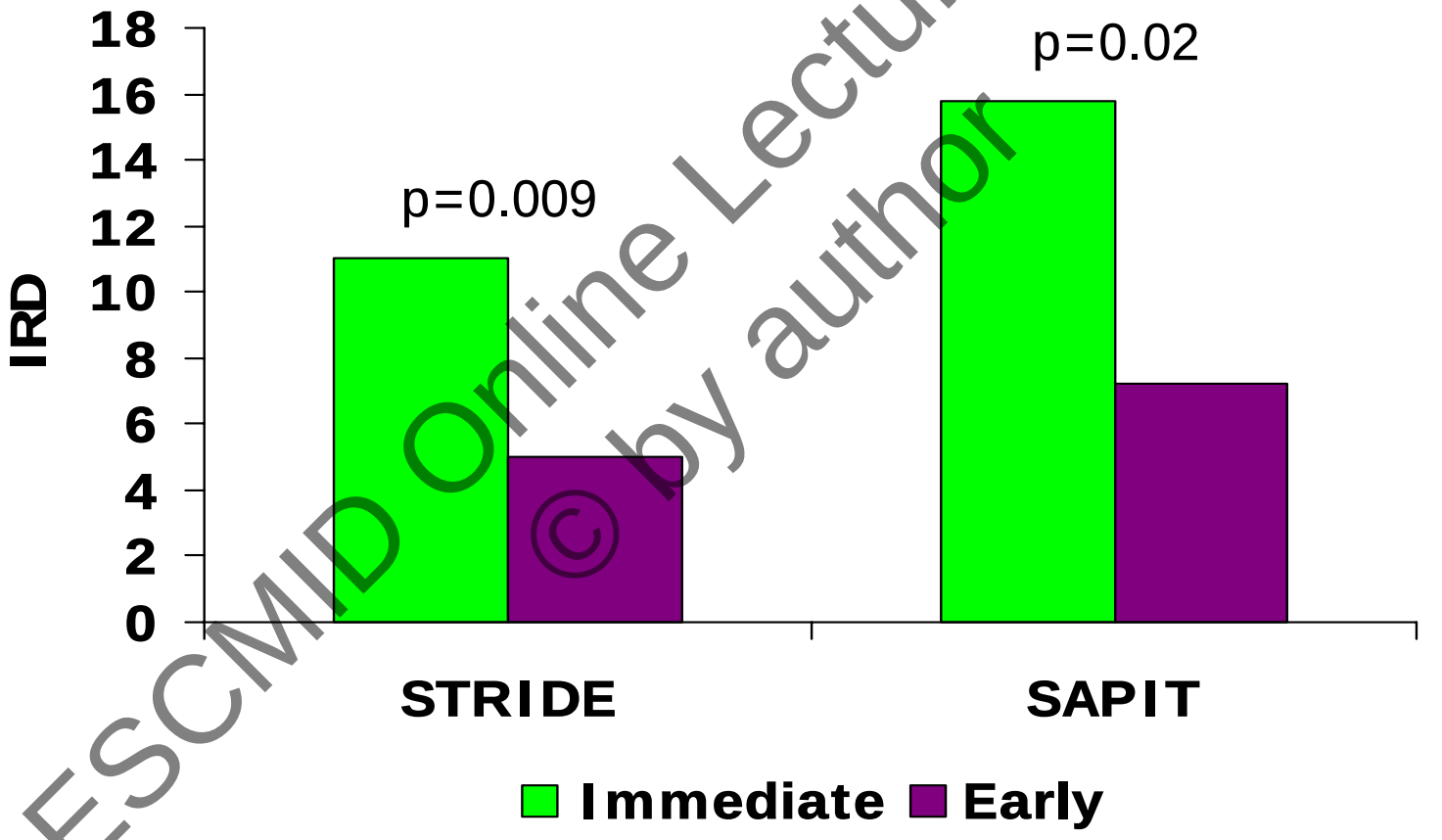
AIDS 2010 abstract THLBB106, CROI 2011 abstract 38, CROI 2011 abstract 39LB

Effects of ART timing on death/AIDS among patients with CD4 > 50 in STRIDE and SAPIT



CROI 2011 abstract 38, CROI 2011 abstract 39LB

Effects of ART timing on TB-IRIS among patients in STRIDE and SAPIT trials



CROI 2011 abstract 38, CROI 2011 abstract 39LB

HIV-associated Tuberculous Meningitis: Immediate *vs*. Deferred cART

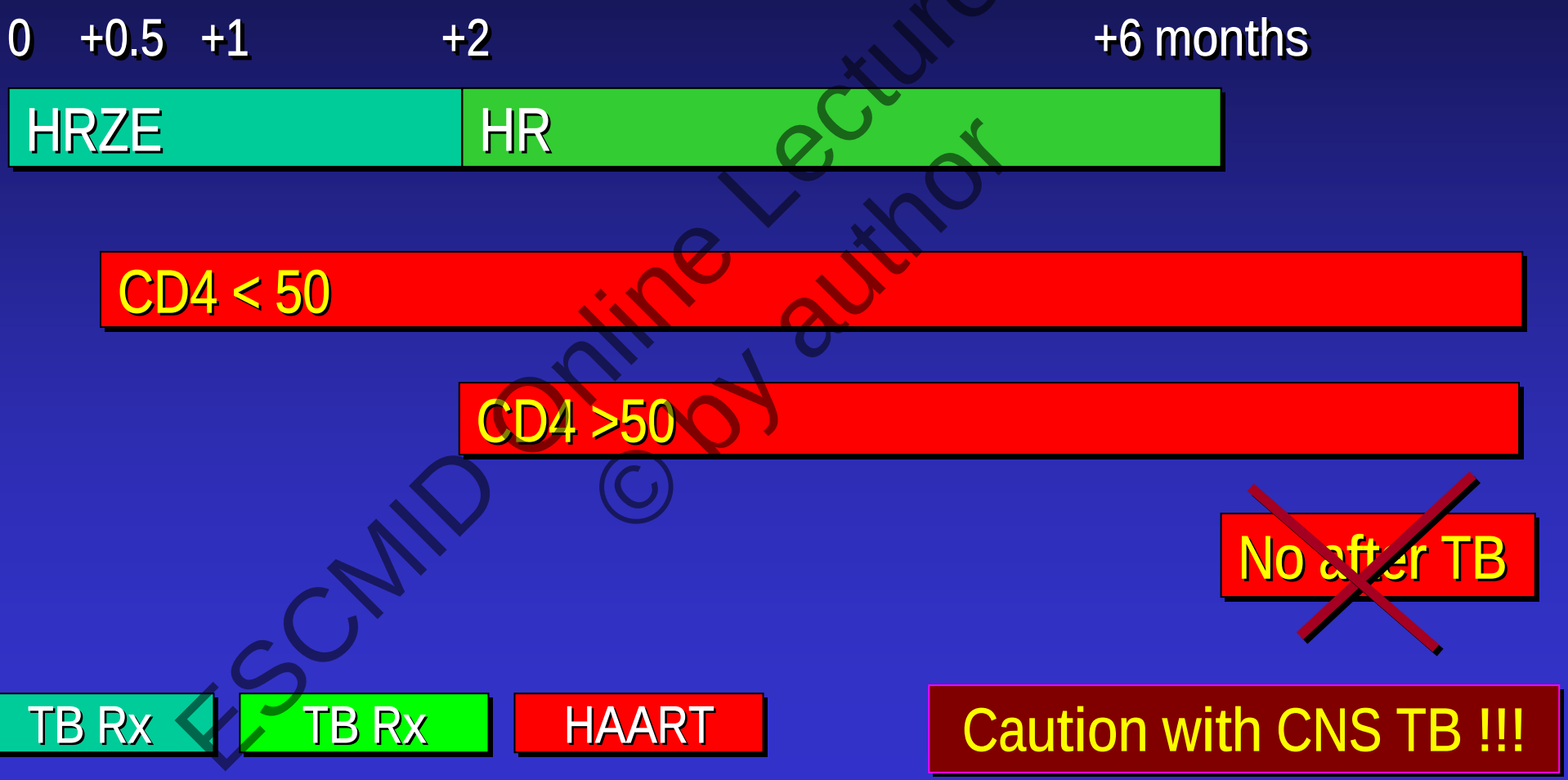
Torok ME et al. 41st Union World Conference on Lung Health, Berlin Nov 2010

- Randomized, double-blind, placebo-controlled, phase IV trial of immediate vs. deferred cART in HIV patients with tuberculous meningitis, to determine whether immediate cART reduced the risk of death during 9 months of follow-up.
- Antiretroviral drugs (zidovudine, lamivudine and efavirenz) were started either at study entry (Immediate arm) or two months post-randomization (Deferred arm).

	Immediate cART N=127	Deferred cART N=126	*P*
- AEs (grade3/4)	90%	89%	NS
- AEs (<2 months)	86%	75%	.04
- Death	60%	56%	NS

Immediate cART was not significantly associated with 9-month mortality (hazard ratio (HR) 1.12, 95% confidence interval (CI) 0.81 to 1.55, p=0.50)

Timing of cART in HIV-infected Patients with TB According to CD4+ T-cell Count



Immune Restoration Induced by HAART

French MA et al, AIDS. 2004;18:1615-27

Immune reconstitution inflammatory syndrome (IRIS)

Baseline characteristics of OIs

- Clinical (disseminated) or subclinical infection before cART
- Low baseline $CD4^+$ T-cell count

cART

- Early initiation of cART (short interval between OI and cART)
- Effective cART (↑ CD4+ T-cells; ↓ Plasma HIV RNA VL [BDL])

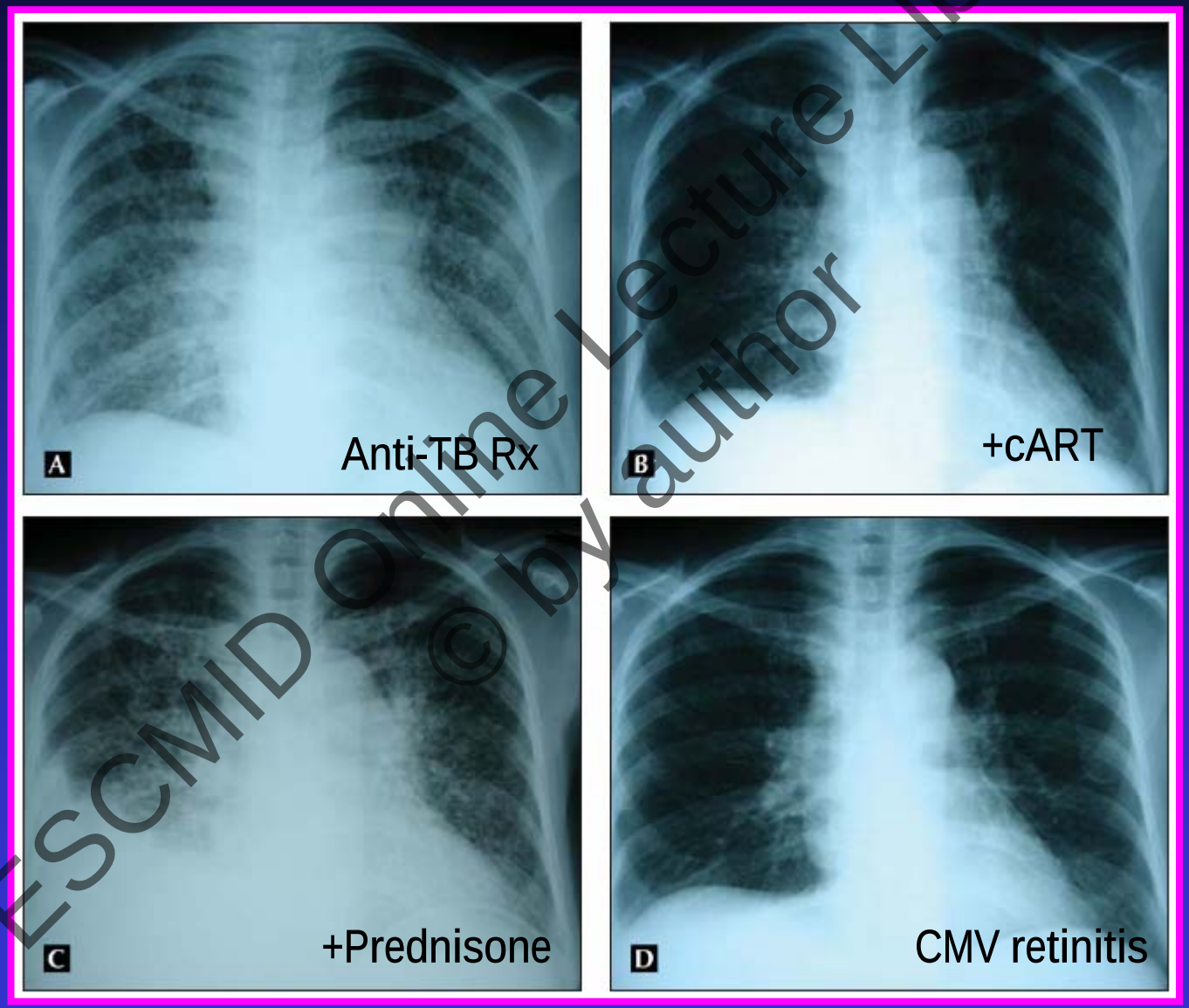
Clinical OI evolution

- Clinical worsening without Rx failure/toxicity or new diagnosis
- Restoration of Ag-specific T-cell responses induced by cART

Breen RA et al, *Thorax* 2004;59:704 ; Kumarasamy N et al, *JAIDS* 2004;37:1574; Breton G et al, *CID* 2004;39:1709; Shelburne SA et al, *AIDS* 2005;19:399; Lortholary O et al, *AIDS* 2005;19:1043; Manosuthi W et al, *J Infect* 2006;53:357; Lawn S et al, *AIDS* 2007;21:335.

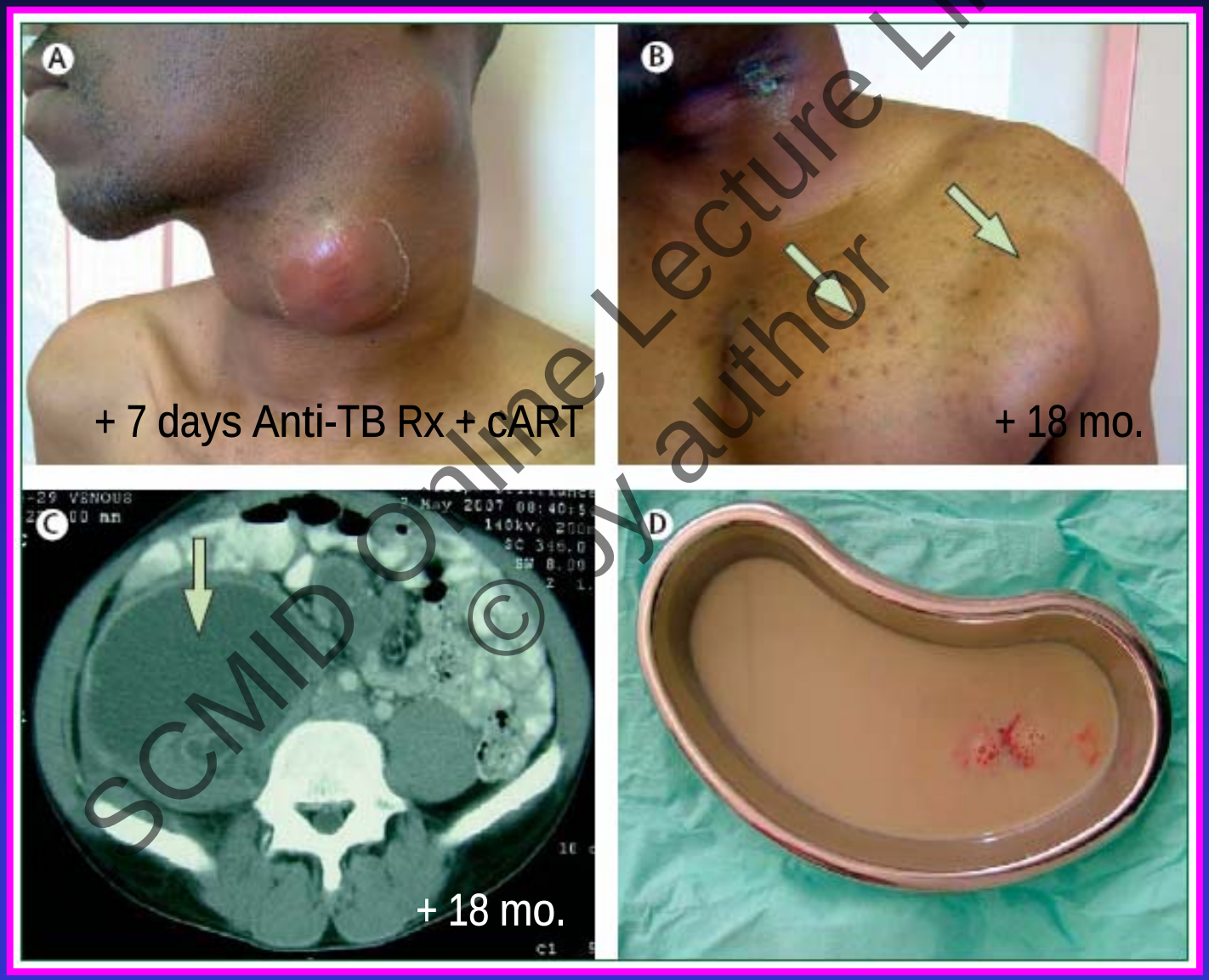
Illustrative Cases of Paradoxical TB-associated IRIS

Marais S et al. Current HIV/AIDS Reports 2009, 6:162–171



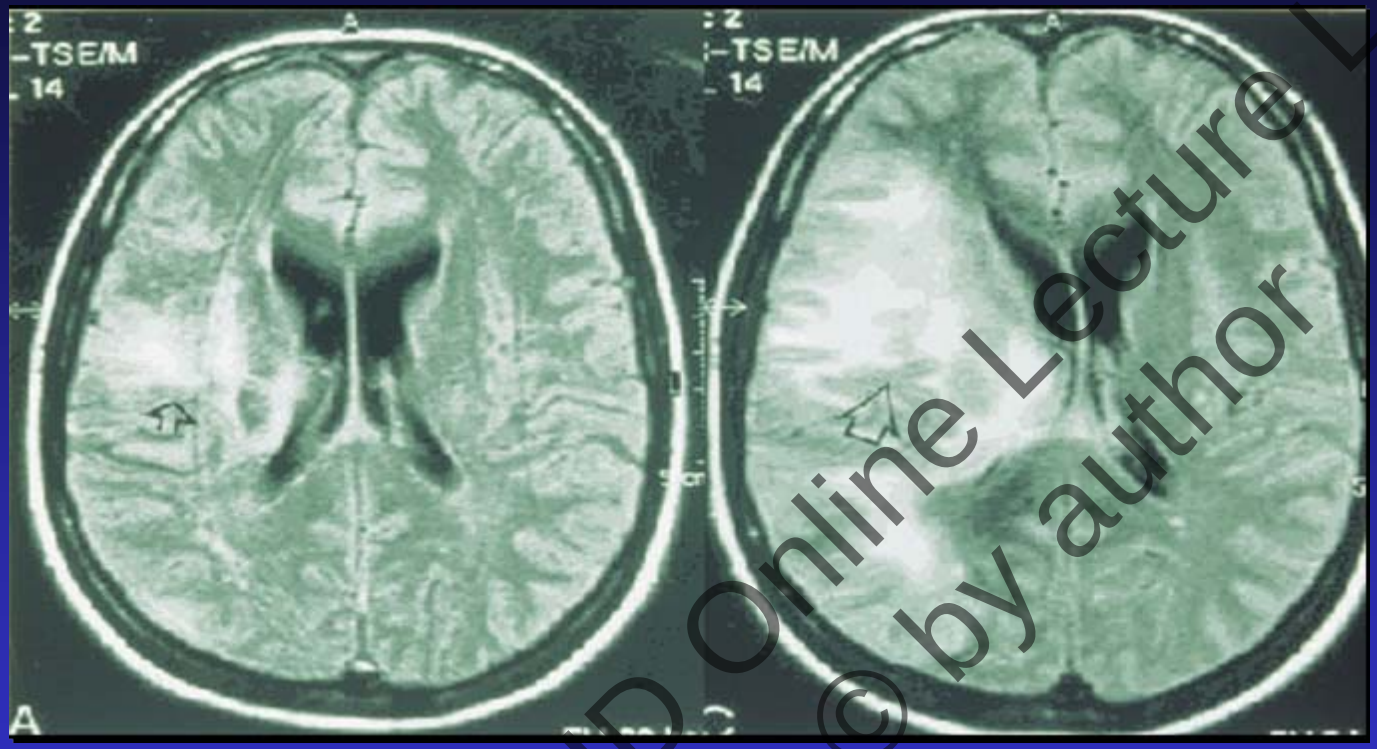
Illustrative Cases of Paradoxical TB-associated IRIS

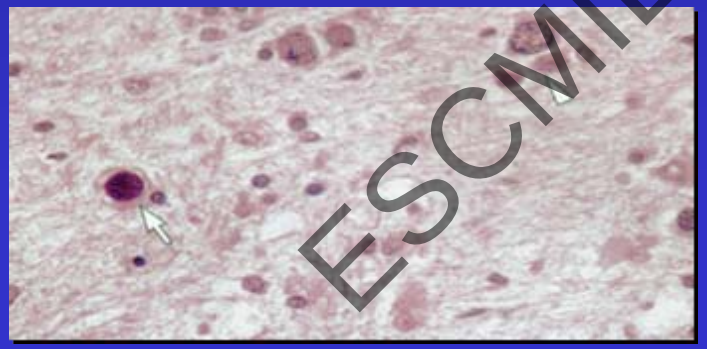
Meintjes G et al. Lancet Infect Dis 2008; 8: 516–23

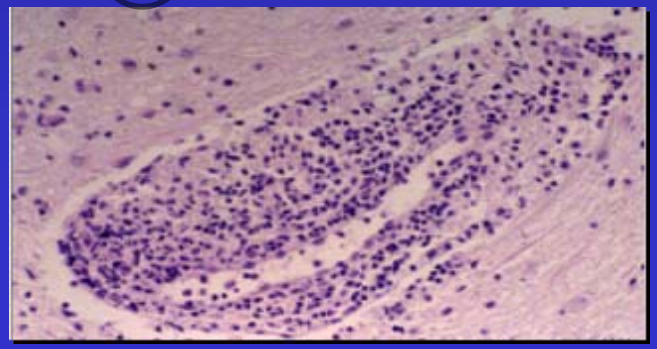


Illustrative Case of IRIS PML

Miralles P et al. AIDS. 2001; 15: 1900-02







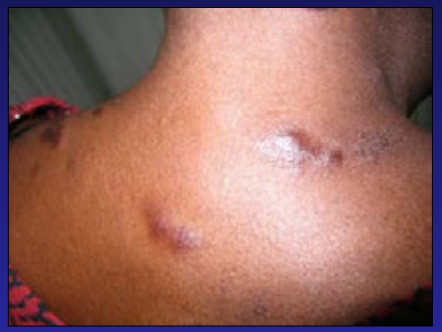
"Inflammatory" PML after cART

JCV IRIS associated with a perivascular $CD8^+$ T-cell infiltrates

Illustrative Case of IRIS KS

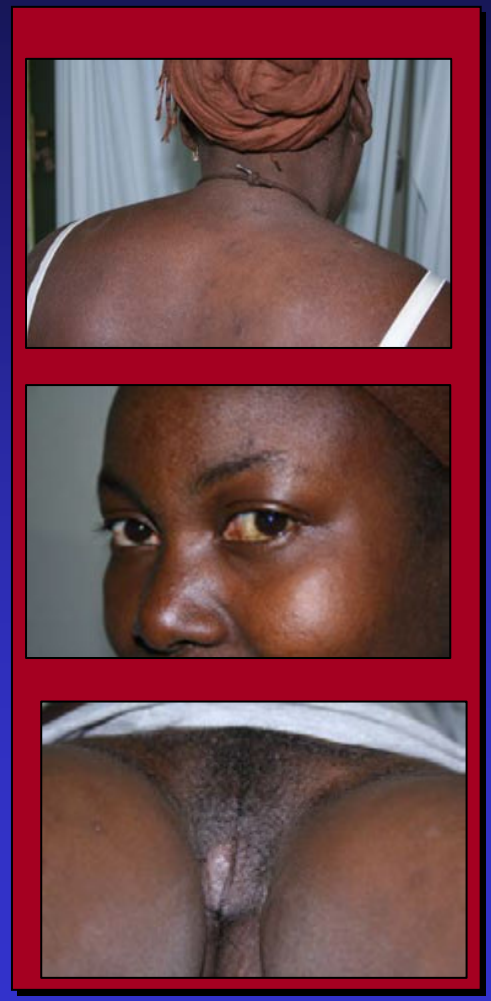
Courtesy of Dr. E. Letang

KS



cART
+ 17 wk

cART + Chemotherapy
+ 21 wk



IRIS Management / Treatment

1.- OI Treatment: To rule out microbiological failure, resistance or toxicity.

2.- IRIS treatment

Mild/Moderate: Nonsteroidal anti-inflammatory drugs (NSAIDs)

Severe: Corticosteroids, consider other therapies.

3.- Other therapeutic procedures: Surgical drainage or needle aspiration of cold abscesses.

4.- cART: Could be stopped in some life-threatening cases.

Meintjes G et al. AIDS. 2010; 24:2381-90.

Randomized Placebo-controlled Trial of Prednisone for the TB-Immune Reconstitution Inflammatory Syndrome

Graeme Meintjes[1,2], Robert J Wilkinson[1,2,3,4], Chelsea Morroni[1], Dominique Pepper[1,2], Kevin Rebe[1,2], Molebogeng Rangaka[1], Tollulah Oni[1,3], Gary Maartens[1]

1. University of Cape Town, 2. GF Jooste Hospital, 3. Imperial College London, 4. National Institute for Medical Research (UK)

Meintjes G et al. AIDS. 2010; 24:2381-90.

Study Design

- Hypothesis: 4 week course of prednisone would reduce need for medical interventions without excess adverse events
- Study drug
  - Prednisone or placebo, randomized, double-blind
  - 1.5mg/kg for 2 weeks then 0.75mg/kg for 2 weeks
- Follow up assessments at 1, 2, 4, 8 and 12 weeks
- Open-label prednisone at physician discretion if clinical deterioration/relapse
- Predefined primary endpoint*
  - Cumulative number of days hospitalized and outpatient therapeutic procedures counted as 1 additional day

*Trial registered: http://www.controlled-trials.com/ISRCTN21322548/maartens

Meintjes G et al. AIDS. 2010; 24:2381-90.

Primary endpoint

Cumulative number of days hospitalized and outpatient therapeutic procedures (counted as 1 additional day), ITT analysis

	Placebo arm N = 55	Prednisone arm N = 55	P-value
Total days hospitalized	463	282	-
Total number outpatient procedures	31	27	-
Cumulative primary endpoint (median, IQR)	**3 (0-9)**	**1 (0-3)**	**0.046**

Anti-inflammatory and Immunomodulatory Therapies for IRIS

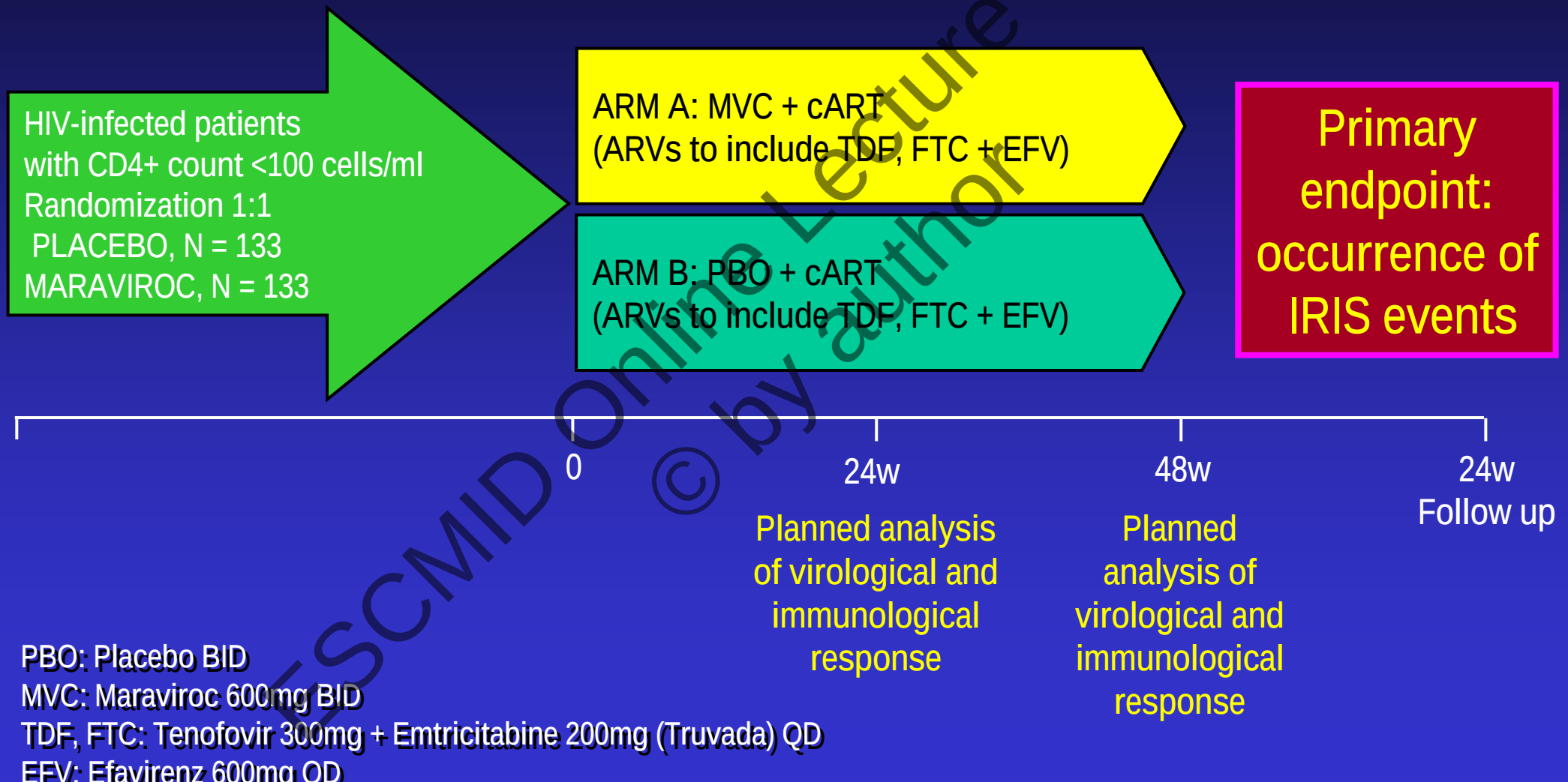
- NSAIDs
- Corticosteroids
- Thalidomide
- Pentoxifylline
- Hydrochloroquine

- Leukotriene receptor antagonists*
- Tumor Necrosis Factor-α inhibitors**
- Other medical treatments***

* Montelukast and Zafirlukast; ** Infliximab, Etanercept, Adalimumab or Certolizumab; *** G-CSF, GM-CSF, IL-2, iv Immunoglobulin.

Maraviroc (CCR5) Antagonism to Decrease the Incidence of the IRIS in HIV-Infected Patients (CADIRIS)

Sierra Madero JG et al. ClinicalTrials.gov# NCT00988780



Conclusions (I)

- cART should not be delayed in patients with AIDS defining diseases.
- The best time for starting cART in patients with PCP is 2 weeks after starting Rx for PCP. The same rule may be applied for all other OIs except cryptococcosis.
- In TB patients, cART must be started within the first 2 weeks of Rx for TB in patients with <50 CD4+ T cells/mm3 and at the maintenance phase (>8 weeks) in patients with >50 CD4+ T cells/mm3. However, it is not known when it should be started in patients TB meningitis.

Conclusions (II)

- A significant proportion of patients who started effective cART after an OI will present a paradoxical worsening known as IRIS.
- The lack of evidence-based treatment guidelines poses challenges in the management of IRIS. Guidelines recommended continuing with specific treatment against OIs and cART.
- Adjuvant NSAIDs and corticosteroids are commonly used. Corticosteroids have demonstrated their usefulness in a recent clinical trial in TB patients.