Immune Reconstitution Inflammatory Syndrome - IRIS

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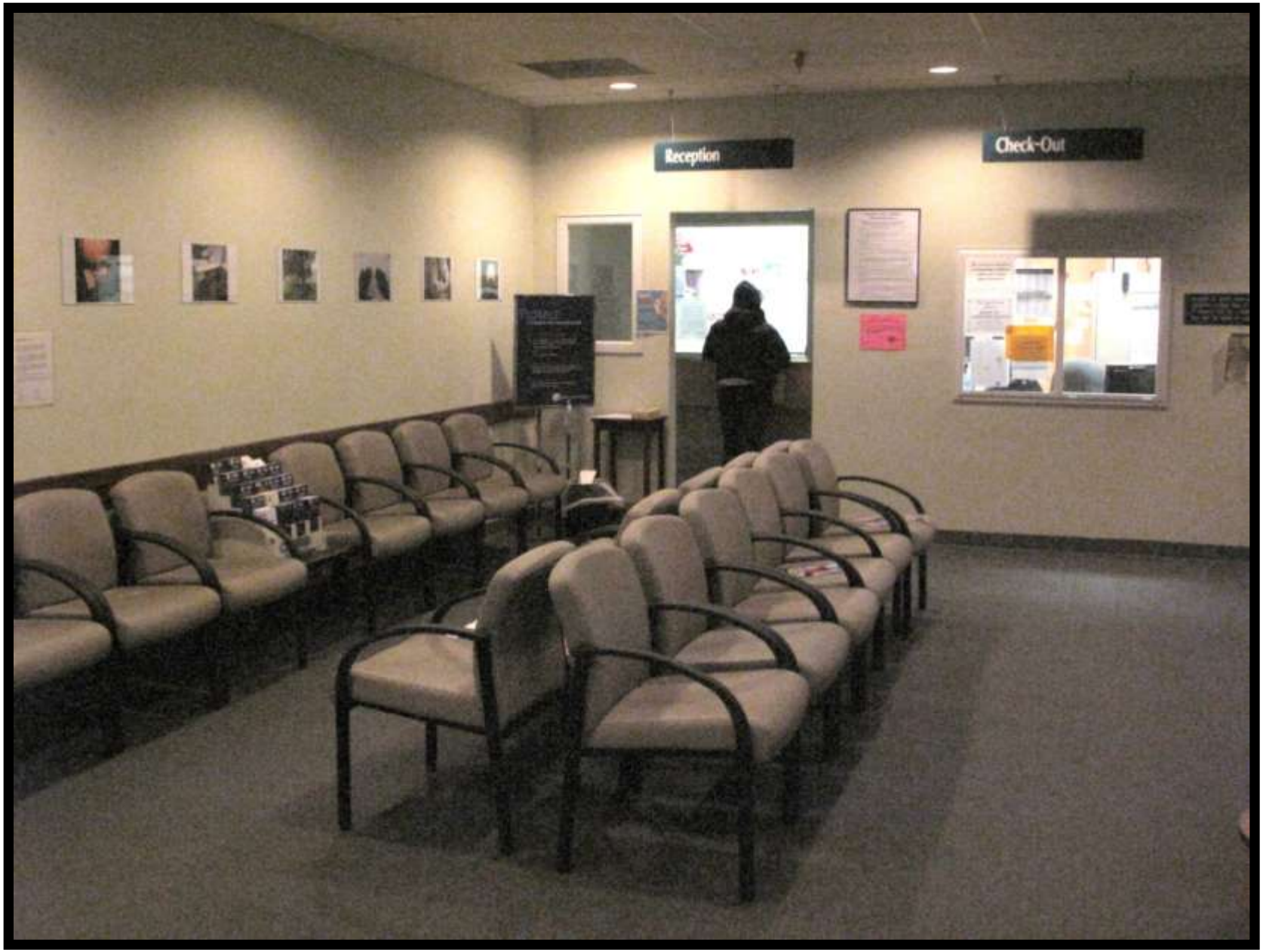

Reception
Check-Out

I-Tech: Thank you

- International Training and Education Center on HIV (I-TECH)
- Receives funding from the Health Resources and Services Administration (HRSA), the US Agency for International Development, the US Centers for Disease Control and Prevention (CDC)
- University of Washington in Seattle, and the University of California, San Francisco.

Learning Objectives

- Define diagnostic criteria for IRIS
- Pathogenesis
- Explain clinical spectrum & differential diagnosis of IRIS
- Discuss management of IRIS

Immune Reconstitution Inflammatory Syndrome (IRIS): Pathogenesis

- Improved cell-mediated immunity with restoration of both memory and naïve CD4 cells
- Increased CD4/CD8 cells detect hidden pathogens which were ignored with deficiency of immunity previously
- Result in inflammatory process at the area of occult / sub-clinical infections
- Usually improves with control of inflammation and specific treatment

Pathogenesis: Variables

- Underlying antigenic burden
- Degree of immune restoration following HAART
- Host genetic susceptibility

Murdoch DM et al. AIDS Research and Therapy 2007;4;9.

Early versus Delayed

- Early – “The first phase occurs within the first few weeks when the increase in CD4 T-cells is largely due to the redistribution of pre-existing memory T-cells.”

- Delayed – “The second phase of immune restitution occurs after 4 to 6 weeks and is a direct result of the proliferation of naive T-cells.”

McCombe JA *et al. Neurology* 2009;72:835– 841.

Types

- Unmasking of previously silent infection with HAART
  - Restoration of immune responses against pathogen-specific antigens.
    - French MA *CID* 2009;48:101-107.
  - Especially common and severe with tuberculosis and cryptococcal infections
- Autoimmune disease reactivation
  - Grave's disease & sarcoidosis
    - Median time to presentation 21 months for Grave's and may occur up to 3 years for sarcoidosis, after initiation of HAART
    - Similar reaction occurs after use of alemtuzumab, a monoclonal antibody to CD52 that induces extensive depletion of T and B cells

French MA *CID* 2009;48:101-107.

Defining IRIS

Required criterion	Supportive criterion
Worsening symptoms of inflammation/infection	Increase in CD4 cell count of > 25 cells/cmm
Temporal relationship with starting antiretroviral treatment	Biopsy demonstrating well-formed granulomatous inflammation or unusually exuberant inflammatory response
Symptoms not explained by newly acquired infection or disease or the usual course of a previously acquired disease	
> 1 log10 decrease in plasma viral load	

CID J 2006;June,42:1639-46.

Onset of IRIS in 57 Patients

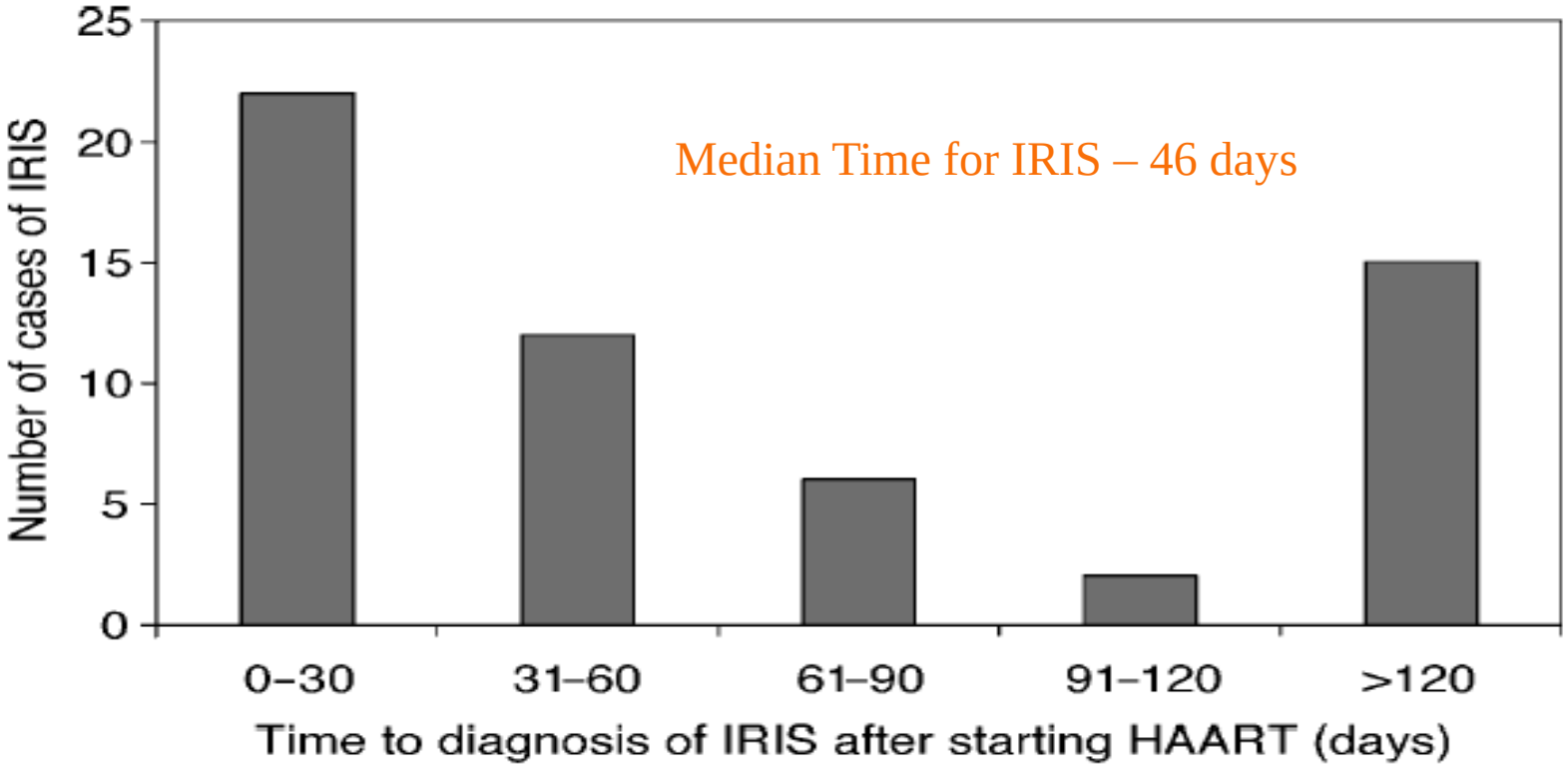


Fig. 1. Time to diagnosis of IRIS after starting HAART. IRIS, immune reconstitution inflammatory syndrome; HAART, highly active antiretroviral therapy.

Shelburne SA *et al. AIDS* 2005; Vol 19, No4 :399-406.

HAART & HIV RNA Levels

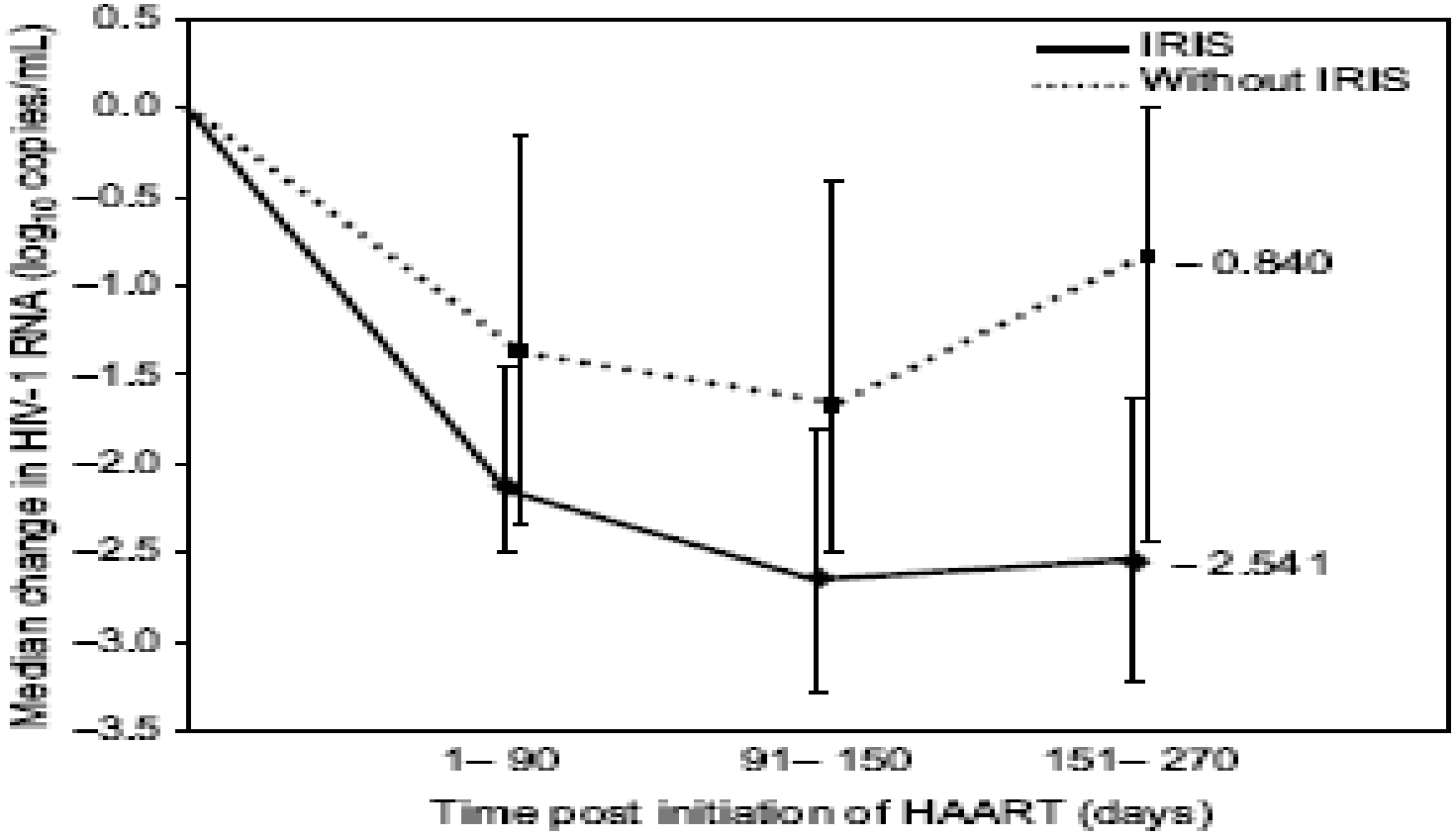


Fig. 2. Time course of HIV-1 RNA levels in response to HAART. IRIS, immune reconstitution inflammatory syndrome; HAART, highly active antiretroviral therapy; Error bars represent 25–75th percentiles.

Shelburne SA *et al. AIDS* 2005; Vol 19, No4 :399-406.

IRIS & Non-IRIS Response to HAART

Table 2. Comparison of the IRIS and non-IRIS response to HAART.

Variables at time after starting HAART	Patients with IRIS ($n = 57$)	Patients without IRIS ($n = 123$)	Difference/relative risk*	*P* value for difference
1–90 days				
Median CD4 cell count increase ($\times 10^6$ cells/l)	43	14	29	0.102
Median log10 HIV-1 RNA level decrease	−2.11	−1.37	−0.74	<0.001
91–150 days				
Median CD4 cell count increase ($\times 10^6$ cells/l)	65	31	34	0.047
Median log10 HIV-1 RNA level decrease	−2.63	−1.67	−0.96	<0.001
151–270 days				
Median CD4 cell count increase ($\times 10^6$ cells/l)	73	33	40	0.007
Median log10 HIV-1 RNA level decrease	−2.54	−0.84	−1.70	<0.001
0–12 months				
Hospital admissions (mean)	1.67	0.54	1.13	<0.001
Invasive procedures (mean)	2.93	0.41	2.52	<0.001
24 months				
HIV RNA-1 level < 400 copies/ml (yes/total)	31/40	26/72	3.32*	<0.001
CD4 cell count increase < 100 $\times 10^6$ cells/l (yes/total)	29/40	32/73	2.24*	0.003
Alive (alive/total)	40/46	73/100	1.95*	0.061

IRIS, immune reconstitution inflammatory syndrome; HAART, highly active antiretroviral therapy.

Shelburne SA *et al*. *AIDS* 2005; Vol 19, No4 :399-406.

Clinical Spectrum

- Heterogeneous
- Onset; early/delayed
- Atypical symptoms; generalized/local
- Varying severity
- Infectious agents/site of infection

Differential Diagnosis

- New opportunistic infections or tumors
- Drug side effects

Risk Factors

- Risk factors at base line:
  - Lower CD4 count prior to start of ART
  - Higher HIV-1 RNA levels at baseline
  - Initiating ART in close proximity to starting therapy for an OI
- Response to therapy & the development of IRIS:
  - Rapid fall in HIV-1 RNA level during the first 3 months of therapy

Shelburne SA, Montes M and Hamill RJ. *Journal of Antimicrobial Chemotherapy* 2006; 57:,67-170.

Risk Factors – ACTG A5164

- Multivariate analysis controlling for confounding factors found as independent predictors of mortality:
  - Mycobacterial infection (HR 4.6; P < 0.002),
  - Hospitalization (HR 3.2; P = 0.007)
  - Low CD4 count (HR 1.2 for each 10 cells/ mm3 decrement; P = 0.04)

Grant P et al. 16th Conference on Retroviruses and Opportunistic Infections. Montreal, Canada. February, 2009; Abstract 775.

Disease-specific IRIS

IRIS due to Tuberculosis

- Pre-HIV era, paradoxical CNS worsening of tuberculosis was well described in HIV-negative patients

- Among 43 HIV+ TB patients, IRIS occurred at median of 12 – 15 days after initiation of HAART
  - Range 2 – 114 days

Murdoch DM *et al*. *AIDS Res and Ther* 2007; 4(9).

Management of Tuberculous IRIS

- In HIV-negative patients with tuberculous meningitis
  - Steroids decreased neurologic sequelae and improved survival over standard therapy alone.

- HIV-positive patients
  - Risk greatest in first 2 months of TB therapy
  - When CD4 < 100 cells/cmm

Dooley DP *et al. Clin Infect Dis* 25(4)872-887. Thwaites GE *et al. N Engl J Med* 2004, 351(17)1741-51. *MMWR* April 10, 2009;58(RR-4); www.aidsinfo.nih.gov

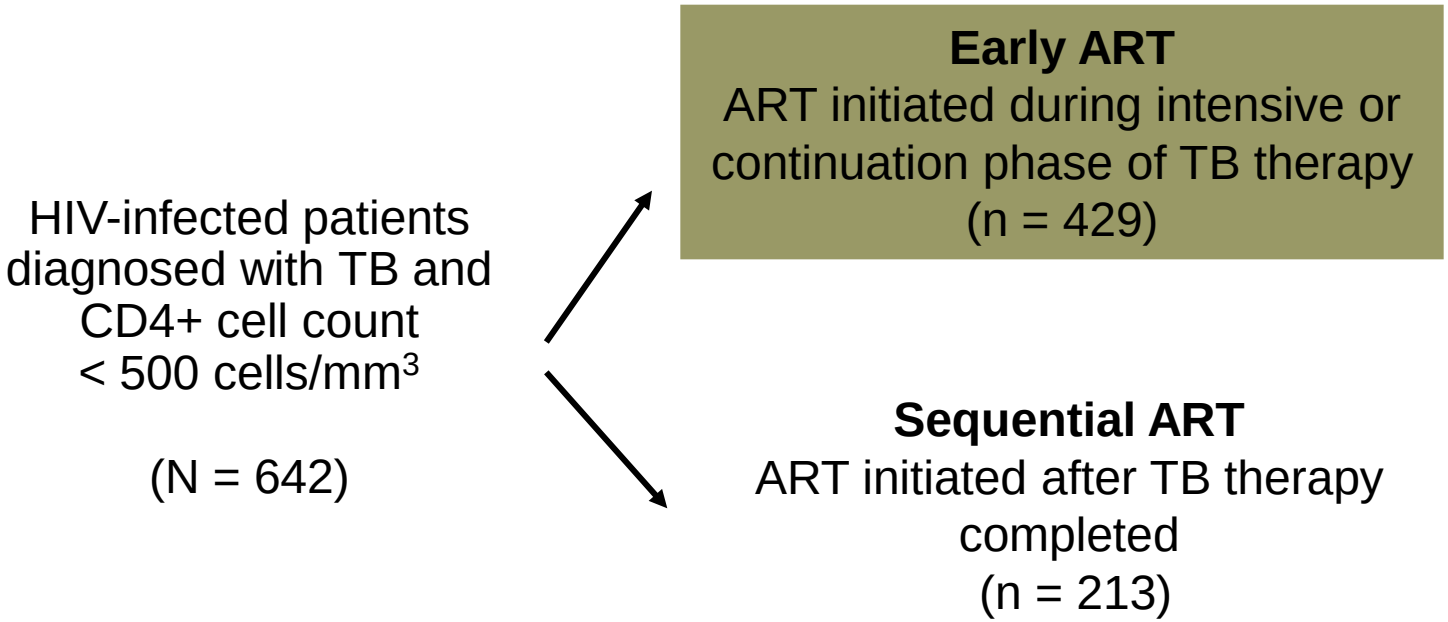
Starting Antiretrovirals at 3 Points in Tuberculosis - SAPiT

- 642 HIV-infected adults in South Africa who had smear-positive TB and a CD4 count <500 cells/mm3 were randomized 1:1:1 to three treatment groups:
  - Early integrated therapy: Patients started ART within 4 weeks after starting TB treatment.
  - Late integrated therapy: Patients started ART within 4 weeks after completing the intensive phase of TB treatment.
  - Sequential therapy: Patients did not begin ART until they had completed all TB treatment (2 months of intensive therapy, followed by 4 months of continuation therapy).

- All received once daily didanosine, lamivudine & efavirenz

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

SAPiT: Optimal Time to Initiate ART in HIV/TB-Coinfected Patients

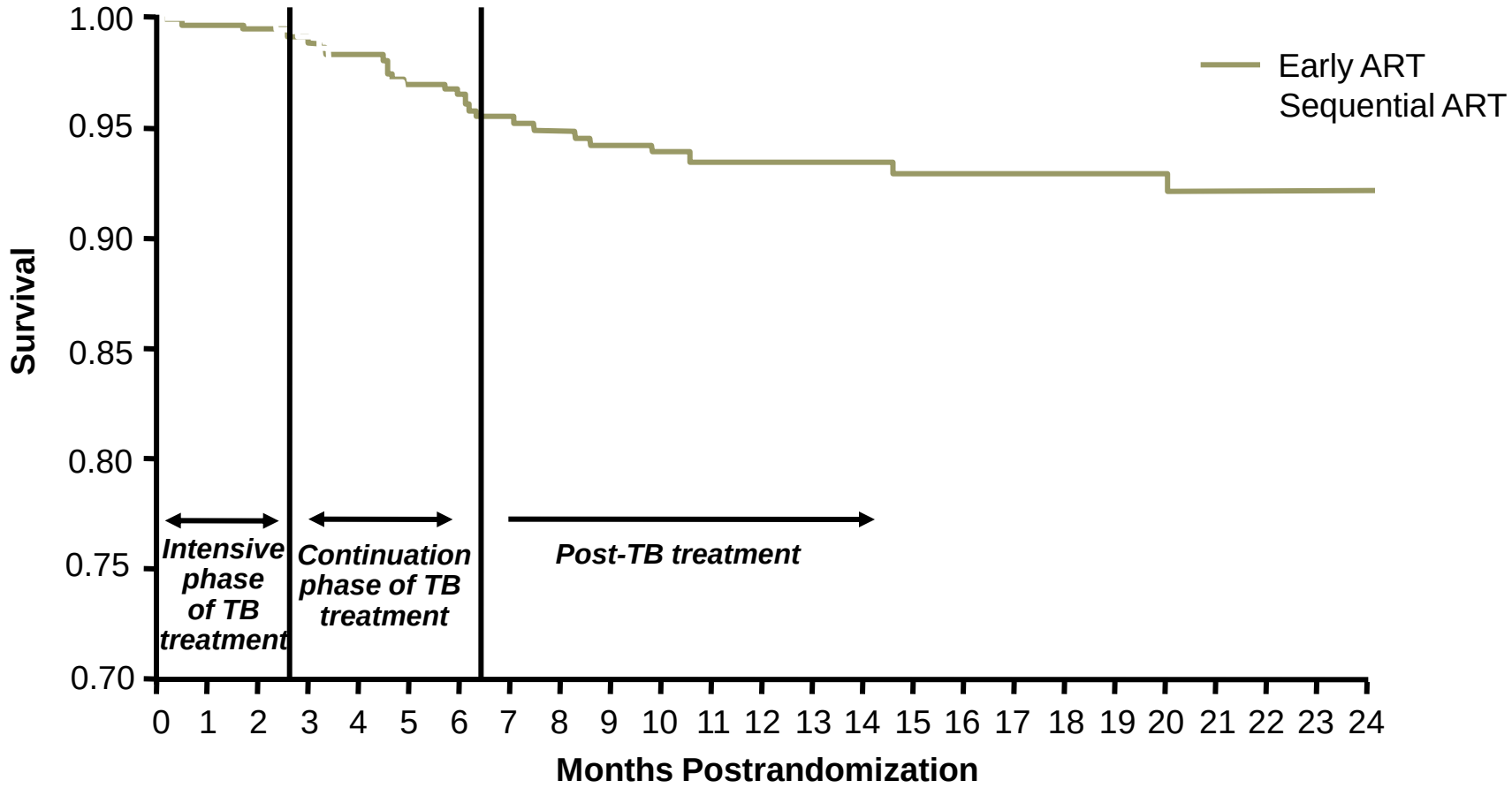


Primary endpoint: all-cause mortality

Abdool Karim SS *et al.* CROI 2009. Abstract 36a. Graphic reproduced with permission.

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

SAPiT: Increased Survival With Concurrent HIV and TB Treatment



Abdool Karim SS *et al.* CROI 2009. Abstract 36a. Graphic reproduced with permission. Abdool Karim SS *et al. N Engl J Med* 2010; 362:697-706.

Significantly Improved Outcomes With Integrated HIV & TB Treatment

- 56% lower rate of death associated with concurrent ART and TB treatment (early ART)
- Mortality: HR: 0.44 (95% CI: 0.25-0.79; *P* = .003)
  - Early ART: 5.4/100 person-yrs
  - Sequential ART: 12.1/100 person-yrs

Outcome, %	Early ART	Sequential ART
HIV-1 RNA <1000 copies/mL at 12 mos	91.0*	80.0
TB treatment successful	78.4	73.3
Incidence of IRIS	12.4*	3.8†
Mortality in MDR-TB patients	20	71

*$P < .05$
† $P < 0.001$

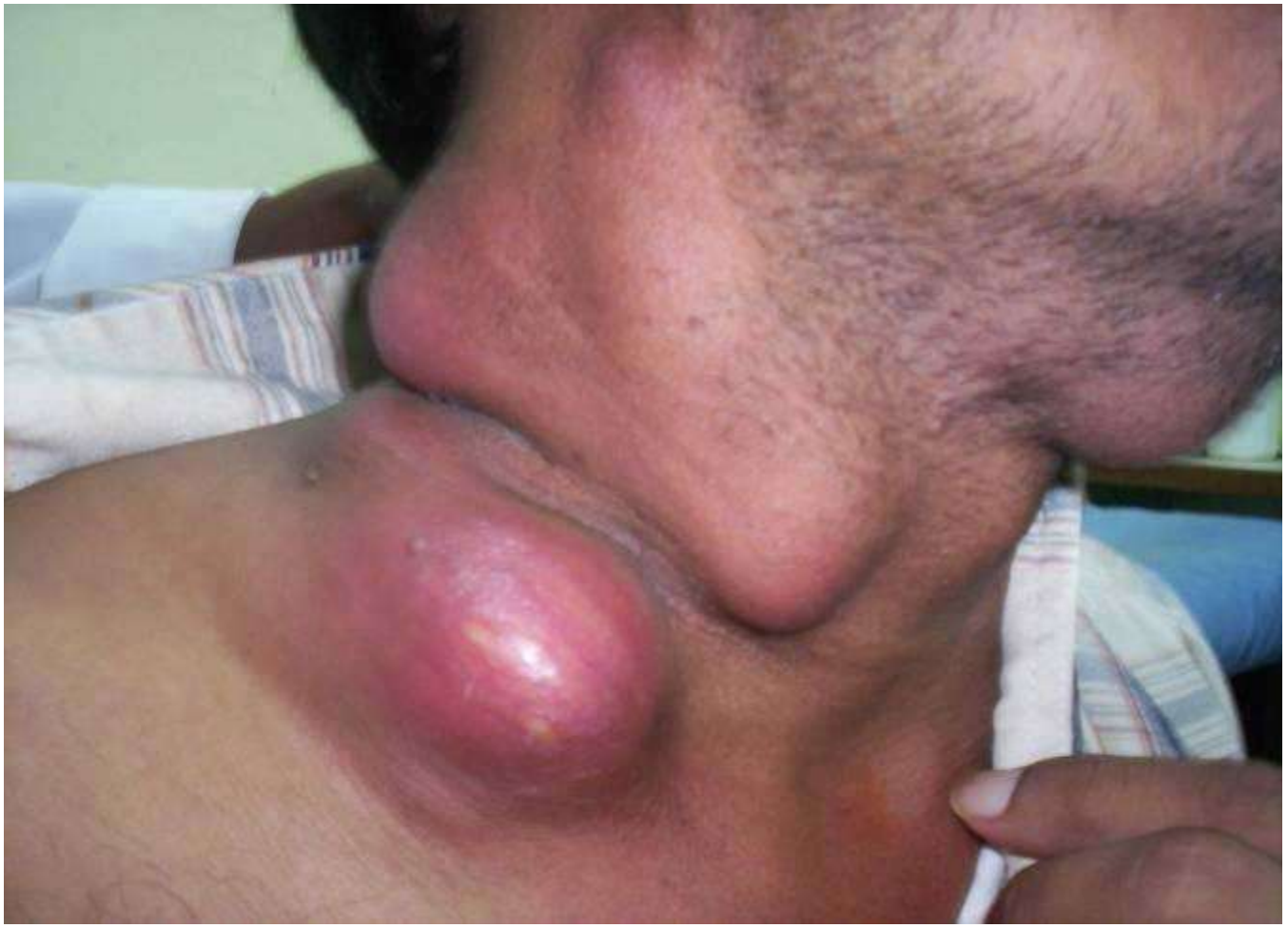
Abdool Karim SS *et al.* CROI 2009. Abstract 36a. Graphic reproduced with permission. Abdool Karim SS *et al. N Engl J Med* 2010; 362:697-706.

IRIS with *M. tuberculosis*…

- Six patients required the use of corticosteroids
  - Five in the integrated-therapy group and one in the sequential-therapy group.
- No deaths were attributable to IRIS.
- No changes in HAART required.

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

Illustration



Source: CMC, Vellore

I-TECH

Atypical Mycobacteria

- Particularly *Mycobacterium avium complex*
- Lymphadenitis most common presentation
- May also present as respiratory failure, pyomyositis with cutaneous abscess, leprosy, intra-abdominal disease, or involvement of joints, skin, soft tissue or spine.

Murdoch DM *et al. AIDS Res and Ther* 2007; 4(9).

Cryptococcal Meningitis

- Estimates that 30% of patients develop IRIS after initiation of HAART.
- Risk factors include being ARV naive, and having high HIV RNA viral loads.
- Consider delaying ART until the 2 weeks of induction therapy completed, especially if patient has elevated intracranial pressure. (CIII – expert opinion)
- Severely symptomatic IRIS – some experts recommend steroids (BIII), in addition to frequent lumbar punctures.

MMWR April 10, 2009;58(RR-4); www.aidsinfo.nih.gov

Cytomegaloviral Infection

- Retrospective cohort - 6/33 (18%) cases
  - French MA *et al. HIV Med* 2000,1(2):107-115.
- Prospective cohort - symptomatic vitritis occurred in 63% of ART responders with previous diagnosis of CMV but inactive disease at initiation of ART
  - Karavellas MP *et al. J Infect Dis* 1999;179(3):697-700.
- Treatment may require anti-CMV therapy and/or systemic or ocular steroids

Neuro-IRIS

- 7 of 461 pts from 1999 – 2007 in retrospective review in Alberta, Canada with Neuro-IRIS
  - All men – median age 35, with timefame 2-25 weeks
  - Median CD4 30 cells/cmm
  - 4 pts with new events, and 3 with worsening of:
    - PML, toxoplasmosis encephalitis and cryptococcal meningitis, one each
    - New patients had HIV encephalopathy and 1 pt had pulmonary TB
  - One patient died

McCombe JA *et al. Neurology* 2009;72:835– 841.

IRIS has occurred with…

- Skin eruptions including Molluscum contagiosum
- Hepatitis B and C – hepatitis flares
- Bartonellosis – lymphangitis; splenic inflammation
- Herpes simplex – erosions
- Leshmaniasis – skin or visceral disease; uveitis
- Pneumocystis jiroveci – ARDS; granulomatous pneumonia
- *Strongyloides stercoralis* – disseminated disease
- Genital HPV – expanding lesions

Bartlett JG *et al. 2009-2010 Medical Management of HIV.* 2009;503.

IRIS: Non-infectious Causes

Condition	Clinical Expression
Autoimmune disorders	Hyperthyroidism, Grave's Disease, Rheumatoid Arthritis, Lupus
Malignancies	Kaposi's Sarcoma Non-Hodgkin's Lymphoma
Miscellaneous	Sarcoidosis, Guillain Barre, Tatto Ink, Lymphoid Interstitial Pneumonitis

Bartlett JG *et al. 2009-2010 Medical Management of HIV.* 2009;503.

Management

- Mild form (with ongoing ART)
  - Observation
- Localized IRIS (with ongoing ART)
  - Local therapy such as minor surgical procedures for lymph node abscesses – aspiration or excision
- Most of the situations (with ongoing ART)
  - **Unmasking &/or Recognition of ongoing infections:**
    - Antimicrobial therapy to reduce the antigen load of the triggering pathogen;
  - **Reconstituting immune reaction to non-replicating antigens:**
    - No antimicrobial therapy. Short term therapy with corticosteroids or non-steroidal anti inflammatory drugs to reduce the inflammation.

Management may require:

- Prednisone in 60-80 mg doses per day.
  - May have to use slow taper over months

- Temporary cessation of ART has to be considered only if potentially life-threatening forms of IRIS develop.

Bartlett JG *et al. 2009-2010 Medical Management of HIV.* 2009;503.