TB and HIV Co-infection, 2015

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TB and HIV Co-infection, 2015

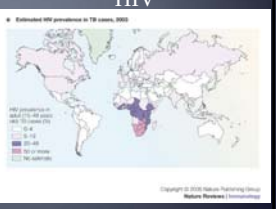
- Epidemiology
- Pathogenesis and effects of HIV on TB
- Treatment
- Drug interactions and preferred ART regimens
- IRIS

Epidemiology

Overlapping Epidemics

Tuberculosis

HIV



(Nunn, Nature Reviews, 2005)
(Harries, Int J Tuberc Lung Dis 2006;10:1306-11)

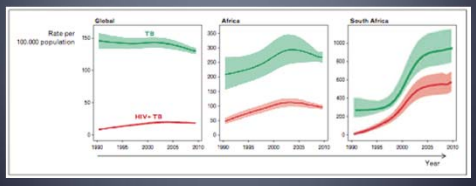
TB and HIV Facts, 2015

- At least 1/3 of all HIV infected patients are infected with TB and autopsy studies show evidence of TB in 30-50% of patients
- 2013
  - 25% of all TB deaths occur in HIV+ persons
  - TB was the leading cause of death in HIV+
  - In SSA: 41% of patients with TB have HIV
- 2011
  - 400,000 of 1.4 million TB deaths occurred in HIV infected individuals
  - USA: 10,521 TB cases; 7.9% HIV+

(Dirlikov, Ann Int Med 2015)
(WHO Global TB Control 2009 and 2011)
(Lawn, SD BMC Medicine 2013)

Epidemiology

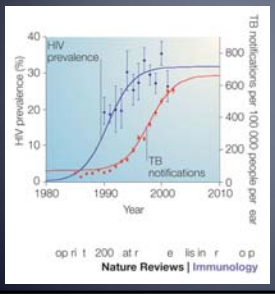
Overlapping Epidemics Centered in Africa



(Geldmacher, Curr Opin HIV AIDS, 2012)

Epidemiology

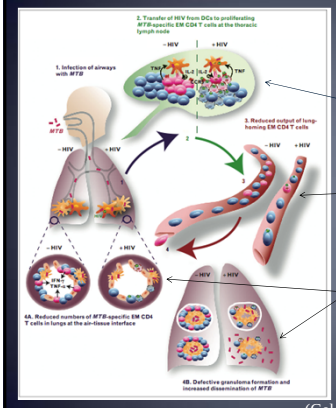
Africa is where the action is



TB epidemic is following the HIV epidemic. As HIV epidemic matures and people become more immunocompromised, TB incidence rises.

Nunn, Nature Reviews, 2005

Pathogenesis



HIV kills TB-specific CD4 cells
Impairs macrophage activation

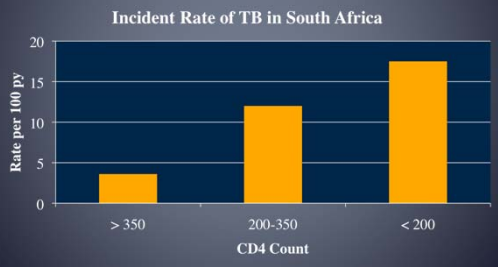
Reduced numbers lung-homing CD4 cells

Defective granuloma formation
Loss of control of infection

(Geldmacher, Curr Opin HIV AIDS, 2012)

Pathogenesis and Natural History

Active Disease Rates Driven by Degree of Immunosuppression



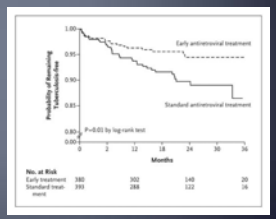
(Wood, Int J of TB + Lung Dis, 2010)

Pathogenesis and Natural History

Effect of ART on Tuberculosis: Haiti

- Randomized, open label study ARV (AZT+3TC+EFV) given when
  - CD4 cells were > 200 and < 350 cells/uL and no h/o AIDS Vs
  - CD4 cells were < 200 cells/uL or when patients had a clinical AIDS diagnosis
- N = 816 (408 in each group)
- Baseline CD4 ~ 280 in each group

Incident Tuberculosis

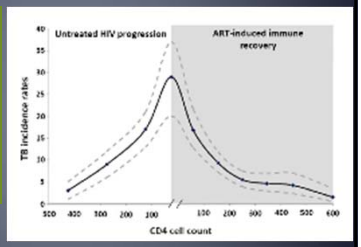


(Severe, et.al NEJM, 2010;263:257-65)

Pathogenesis and Natural History

Effect of ARV

- Incidence of tuberculosis is decreased by 70 to 90% over time
- ART reduces mortality 64-95%



1. Lederberger, JAMA, 1999
2. Girardi, AIDS, 2000
3. Jones Int J Tuberc Lung Dis, 2000
4. Santoro-Lopez, CID, 2002
5. ARV Rx Cohort Collab, CID, 2005
6. Lawn, Clin Chest Med, 2009)

(Lawn, JID, 2011)

Pathogenesis and Natural History

Effect of HIV on TB

TB acquisition

Progressive, primary infection 10% (up to 37%)

LTBI 90%

Reactivation TB
10% annual risk, 30% lifetime

Early HIV disease
Disease similar to HIV negative pts

Late HIV disease
At least 50% EPTB

Tuberculosis in Patients Dying in Zambia

Autopsy Study: Zambia

- 125 autopsies on patients who died in University Hospital in Lusaka, Zambia 2012-13

	Overall (n=125)	HIV+ (n=101)	HIV- (n=24)	p value
TB (all forms)*	78 (62%)	66 (65%)	12 (50%)	0·16
Extrapulmonary†	35 (28%)	33 (33%)	2 (8%)	0·017
Pulmonary only	43 (34%)	33 (33%)	10 (42%)	0·40

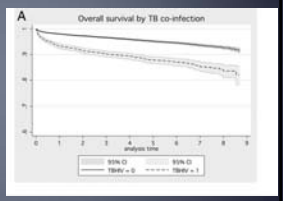
- 65% of HIV patients died with TB
- 26% not diagnosed ante-mortem

Bates, Lancet ID, 2015

Tuberculosis in HIV+ Patients in the UK

The United Kingdom

- Between 2000-08
- 3188 cases of TB among 44,050 with HIV
- TB co-infection was present in 18% of all deaths and 79% of deaths in the first year after HIV diagnosis
- HR for death for TB/HIV co-infected persons: 4.77



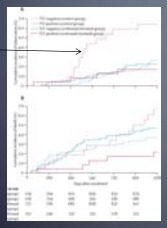
(Zenner, Thorax, 2015)

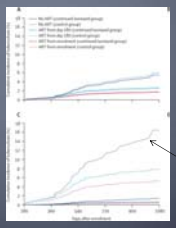
A Word on Prevention

High prevalence country: Botswana

- 6 months Vs 36 months of INH in HIV+ patients
- 36 months superior to 6 months – effect of re-infection
- ART protective

TST+
6 m INH





TST+, CD4 < 200

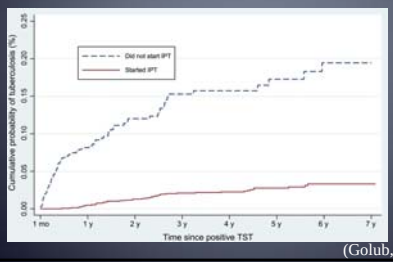
No ART
6 months INH

(Samandari, Lancet, 2011)

A Word on Prevention

Medium prevalence country: Brazil

- Cluster randomized trial of 6 months of INH in HIV+ patients with +TST
- Sustained benefit of INH – limited re-infection



(Golub, Clin Infect Dis, 2015)

Clinical Presentation

- Presentation depends on immune status
- Extra-pulmonary disease occurs in 40 to 80%
- CNS TB develops in 5 to 10% of HIV+ patients (< 2% of HIV- patients)
- Bacteremia occurs in 26 to 42%

Clinical Presentation

Atypical presentations of TB are common

- Kenya: acute pneumonia – 9% are TB
- Malawi: cough for > 3 weeks – 35% are TB
- Tanzania: fever in HIV+ patients – 23% are TB
- Kenya: diarrhea in HIV+ patients – 13% are TB
- Cote d'Ivoire and Congo: autopsy series – 38 to 47% COD is TB (< 50% diagnosed with TB ante-mortem)

Corbett, Lancet, 2006

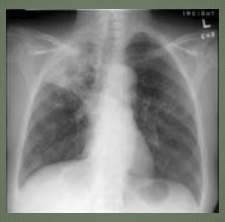
Clinical Presentation

	Late HIV (CD4 < 200)	Early HIV
PTB:EPTB	50:50	80:20
Presentation	Resembles primary TB	Resembles reactivation
CXR		
LNs	Common	Rare
Lower lobes	Common	Rare
Cavitation	Rare	Common
Anergy	Common	Rare
Smear +	Less common	Common
Adverse drug reactions	Common	Rare
Relapse	Common	Rare

Case 1

- A 38 yo South African male presents with a 10 kg weight loss, 3 weeks of cough and intermittent fever. He has no past medical history.
- On exam he is thin, T 38.8 C, BP 100/70, HR 104, RR 20. He has prominent cervical adenopathy, oral thrush and course breath sounds over his R upper and mid lung zones.

Case 1



- An HIV test is + and Sputum smear stains 3+ for AFB

Tuberculosis and HAART

The NEW ENGLAND JOURNAL of MEDICINE

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Earlier versus Later Start of Antiretroviral Therapy in HIV-Infected Adults with Tuberculosis

François-Xavier Blanc, M.D., Ph.D., Thim Sok, M.D., Didier Laureillard, M.D., Laurence Borand, Pharm.D., Claire Rekacewicz, M.D., Eric Nerrienet, Ph.D., Yoann Madec, Ph.D., Olivier Marcy, M.D., Sarin Chan, M.D., Narom Prak, M.D., Chindamony Kim, M.D., Khemarin Kim Lak, M.D., Channoeum Hak, M.D., Bunnet Dim, M.D., Chhun Im Sin, M.D., Sath Sun, M.D., Bertrand Guillard, M.D., Borann Sar, M.D., Ph.D., Sirenda Vong, M.D., Marcelo Fernandez, M.D., Lawrence Fox, M.D., Ph.D., Jean-François Delfraissy, M.D., Ph.D., and Anne E. Goldfeld, M.D., for the CAMELIA (ANRS 1295–CIPRA KH001) Study Team*

ORIGINAL ARTICLE

Integration of Antiretroviral Therapy with Tuberculosis Treatment

Salim S. Abdool Karim, M.B., Ch.B., Ph.D., Kogieleum Naidoo, M.B., Ch.B., Anneke Grobler, M.Sc., Nesri Padayatchi, M.B., Ch.B., Cheryl Baxter, M.Sc., Andrew L. Gray, M.Sc.(Pharm.), Tanuja Gengiah, M.Clin.Pharm., M.S.(Epi.), Santhanalakshmi Gengiah, M.A.(Res.Psych.), Anushka Naidoo, M.Med.Sci.(Pharm.), Niraksha Jithoo, M.B., Ch.B., Gonasagrie Nair, M.B., Ch.B., M.P.H., Wafaa M. El-Sadr, M.D., M.P.H., Gerald Friedland, M.D., and Quarraisha Abdool Karim, Ph.D.

ORIGINAL ARTICLE

Timing of Antiretroviral Therapy for HIV-1 Infection and Tuberculosis

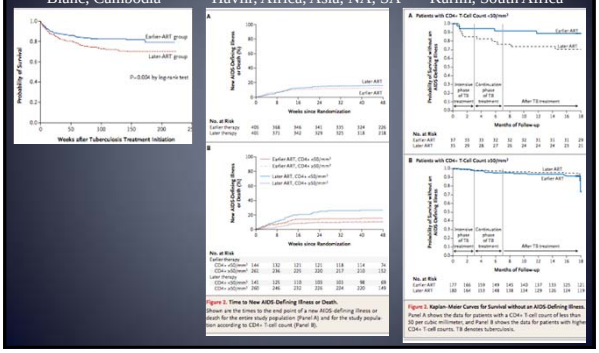
Diane V. Havlir, M.D., Michelle A. Kendall, M.S., Prudence Ive, M.D., Johnstone Kumwenda, M.B., B.S., Susan Swindells, M.B., B.S., Sanjini S. Qasba, M.D., Anne F. Luetkemeyer, M.D., Evelyn Hogg, B.A., James F. Rooney, M.D., Xingye Wu, M.S., Mina C. Hosseinipour, M.D., Umesh Lalloo, M.B., Ch.B., Valdilea G. Veloso, M.D., Fatuma F. Some, M.B., Ch.B., N. Kumarasamy, M.D., Nesri Padayatchi, M.D., Breno R. Santos, M.D., Stewart Reid, M.D., James Hakim, M.B., Ch.B., Lerato Mohapi, M.D., Peter Mugyenyi, M.D., Jorge Sanchez, M.D., Javier R. Lama, M.D., Jean W. Pape, M.D., Alejandro Sanchez, M.D., Aida Asmelash, M.D., Evans Moko, M.B., Ch.B., Fred Sawe, M.B., Ch.B., Janet Andersen, Sc.D., and Ian Sanne, M.D., for the AIDS Clinical Trials Group Study A5221*

Tuberculosis and HAART

Study	Patients	ARV timing	IRIS	Outcome
Blanc (Cambodia)	N = 661 Median CD4 = 25	2 weeks Vs 8 weeks	HR 2.51 (for early ARVs)	HR for death 0.62 (for early ARVs)
Havlir (Africa, Asia, NA, SA)	N = 809 Median CD4 = 77	Median of 10 Vs 70 days	Early 11% Late 5%	Death rate: Overall 12.9% Vs 16.1% (NS) CD4 < 50: 15.5% Vs 26.6% (P=0.02)
Karim (S. Africa)	N = 642 Median CD4 = 150	Median of 21 Vs 97 days	HR of 2.62 (for early ARVs)	AIDS or Death: Overall: No difference CD4 < 50: 8.5 Vs 26.3 per 100 py (P=0.06)

Tuberculosis and HAART

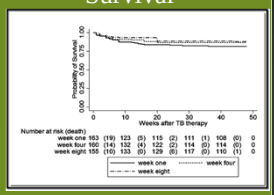
Blanc, Cambodia | Havlir, Africa, Asia, NA, SA | Karim, South Africa

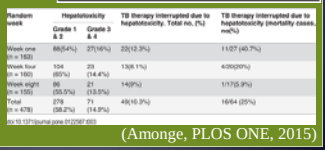


Tuberculosis and HAART

- R, open-label trial of HIV+ patients with TB.
- Started on EFV-based ART: 1, 2, 8 weeks into TB therapy
- Median CD4 73
- No difference in mortality between arms
- More hepatotoxicity in the group starting ART within the first week

Survival





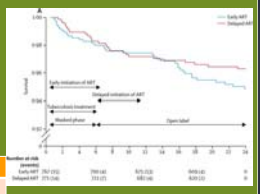
(Amonge, PLOS ONE, 2015)

Tuberculosis and HAART

- R, PC trial in Africa of HIV+ patients with pulmonary TB
- Started on ART at 2 weeks into TB treatment or at 6 months
- CD4 > 220
- Primary endpoint: combination of TB Rx failure, TB recurrence and death at 12 months

	Early (N=767)	Late (N=771)
Primary endpoint	8.5%	9.2% (p=0.9)
Grade 4-5 AE	18%	21% (p=0.37)
IRIS	10%	10%

Survival

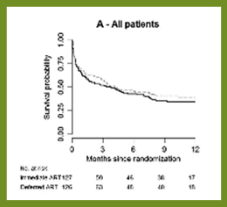


(Mfinanga, Lancet ID, 2014)

TB Meningitis and HAART

- R, DB, PC trial of 253 pts with TB meningitis
- All received RIPE + Dex
- ART (3TC/AZT/EFV) was given either
  - Immediately (~ 1 week)
  - After 2 months of TB Rx
- *Results*
  - *No difference in mortality or new AIDS dx between groups*
  - *More grade 4 AE in the immediate group*
  - *No difference in neurological events between groups*

Survival



(Torok, CID, 2011)

WHO HIV and Tb Treatment Recommendations

- Anti-retroviral therapy (ART) is indicated for all HIV+ patients with TB
- ART should be started as soon as possible within the first 8 weeks of TB Rx
- For patients with CD4 counts < 50, ART should be started within the first 2 weeks of TB Rx
- Efavirenz-based ART is preferred

TB/HIV Co-infection: Principles of Treatment

- Treatment generally the same as in HIV- patients (4 drugs for 2 months and 2 drugs for 4 months)
- Sub-optimal response (culture + after 2 months) – give 9 months, skeletal TB – 6 to 9 months, CNS TB – 9 to 12 months
- If using regimens without INH or a rifamycin - duration should be 12 to 15 months

TB/HIV Co-infection: Principles of Treatment

High Incident Settings

- Zaire: treatment with an additional 6 months of INH + rifampin (after standard 6 month therapy) reduced the relapse rate from 9% to 1.9%. No effect on survival
- Haiti: treatment with INH for 12 months (after standard 6 month therapy) reduced the recurrent rate of tuberculosis from 7.8 to 1.4/100 py

(Perriens, NEJM, 1995, Fitzgerald, Lancet, 2000)

Principles of Treatment: Its All About Rifampin

Drug Interactions: The P450 system

- Isoform CYP 3A is induced by NNRTIs (NVP, EFV, ETR, RLP)
- Isoform CYP 3A is inhibited by Protease Inhibitors
- Rifamycins: Induce CYP 3A
  - Rifampin > rifapentine > rifabutin
  - Rifampin is not metabolized by CYP 3A (level not affected by other drugs that influence CYP 3A)
  - Rifabutin is metabolized by CYP 3A (level is affected by other drugs that also affect CYP 3A)

Principles of Treatment: Its All About Rifampin

- Treatment with NON rifamycin-containing regimens is associated with:
  - Higher relapse rates
  - Higher mortality

Wallis, et al. (1996) Tuber Lung Dis 77:516-23
Hawken, et al. (1993) Lancet 342:332-38
Perriens, et al. (1991) AM Rev Resp Dis 144:750-55
Korwnromp, et al. (2003) CID 37:101-12

Principles of Treatment: Its All About Rifampin

Intermittent Rifamycin Dosing: A Bad Idea

- Randomized study of weekly INH-rifapentine vs 2X/week INH-rifampin (cont phase)
  - Relapse in 5/30 (17%) vs 3/31 (10%)
  - 4/5 relapses in rifapentine arm were R to rifampin
  - These patients had lower CD4 count (16), more extra-pulmonary TB and more azole exposure
- Other studies of acquired rifampin resistance: all patients have CD4 < 100 and all patients on intermittent dosing in intensive phase of Rx

Vernon, et al. (1999) Lancet 353:1843-47.
Li, et al. (2005) CID 41:87-91

Principles of Treatment: Its All About Rifampin

Protease Inhibitors and Rifampin

- Rifampin will reduce the level of PIs by 75-90%
  - Super-boost or double LPV/r: increased hepatotoxicity in health volunteers and high d/c rate
  - DON'T DO IT!!!!
- Rifabutin may be substituted for rifampin but:
  - Need to dose reduce to avoid ribabutin toxicity (uveitis and cytopenias) but…..
  - Lower dose ribabutin (150 mg QOD) has been associated with relapsed TB and the development of rifampin resistance: *use 150mg Q day*
  - If patients interrupts ARV treatment – they will be on insufficient doses of rifabutin

(Jenny-Avital, CID, 2009)
(Lawn SD, BMC Medicine, 2013)

Principles of Treatment: Its All About Rifampin

ARV agent	Rifampin	Rifabutin
Efavirenz	Yes: EVF at 600mg/d US: increase to 800mg/d if > 50 kg	Increase RFB to 450mg/d
Neviripine	Inferior to EFV; Risky: No NVP lead-in	OK
Eravirine	No data, Not recommended	OK
Rilpivirine	NO	Increase rilpivirine?
Protease Inhibitors	Generally NO Super-boost or DD LPV/r - toxic	Decrease RFB to 150mg QD
Raltegravir	Increase Raltegravir to 800 mg BID	Probably OK?
Dolutegravir	Use BID dosing (50mg)	OK at 50 mg Q day
Maraviroc	Increase Maraviroc	No data

Rifampin Vs Rifabutin

- Retrospective review of HIV+ patients with TB cared for at HIV centers in London between 1999 and 2011
- N = 171, Rifabutin 41, Rifampin 130

	Rifabutin	Rifampin
Completed TB Rx	88%	97%
Interrupted TB Rx due to AE	25%	18%
IRIS	29%	12%
Recurrent TB at 24 months	5%	4%
Died	2 (1 from TB)	5 (2 from TB)

(Rawson, J Acquir Immune Defic Syndr, 2015)

Principles of Treatment: Overlapping Toxicities

Adverse effect	ART	Anti-TB therapy
Gastrointestinal	AZT, ddI, PIs	R,I,P, ethionamide, PAS, Clofazamine, linezolid
Hepatotoxicity	NVP, EFV, PIs, NRTIs	R,I,P, ethionamide, quinolones, PAS
Neuropathy	D4T, ddI	I, ethionamide, cycloserine, linezolid
Renal dysfunction	TDF	Aminoglycosides and capreomycin
Neuropsychiatric	EFV	Cycloserine, ethionamide, quinolones, INH
Rash	NVP, EFV, ABC	R,I,P,E, streptomycin, quinolones, PSA, clofzamine
Cytopenia	AZT, 3TC	R,I, Linezolid, rifabutin
Cardiac conduction	PIs	Bedaquiline, quinolone, clofazamine
Pancreatitis	D4T, ddI	Linezolid
Lactic acidosis	D4T, ddI	Linezolid

(adapted from Lawn, BMC Medicine, 2013)

Principles of Treatment: Overlapping Toxicities

- Upon re-challenge >90% patients tolerate medications without a recurrence of the adverse effect
- Hepatotoxicity: when ALT < 2 X ULN: restart rifampin, then INH; avoid PZA

(Sharma SK, CID, 2010)
(ATS guidelines)

Principles of Treatment: Its All About ART!

- 2010 WHO recommendations:
  - Rifamycins for 6 months
  - Every day dosing for the intensive phase
  - ART
- Meta-analysis 2012:
  - Risk of relapse with > 9 mos of RIF Vs 6 mos: - 9.1%
  - OR for relapse 2 mos RIF Vs > 8 mos: 5.0
  - OR for relapse 6 mos RIF Vs > 8 mos: 2.5
  - OR for relapse No ARV Vs ARV: 14.3
  - *Restricting the analysis to ARV studies: nothing else mattered*

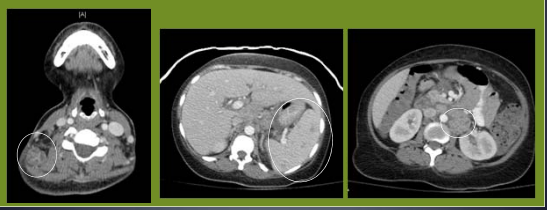
(WHO, 2010 and Khan, CID, 2010 and 2012)

Case 2

- 31 yo woman from Tanzania arrived in the US and was diagnosed with HIV (CD4 15) and latent TB.
- She was started on ART (r/DRV + TDF/FTC) and INH but presented 12 days later with cough, dyspnea, fever, headache and pancytopenia and was diagnosed with disseminated TB (sputum +, BM: granulomas).
- Started on RifabutinIPE and prednisone and discharged
- Presented 2 days later with HA, nausea, and altered mental status. CSF benign (normal OP, 10 WBC, nl protein/glucose, negative cultures and stains and CRAG). Brain MR – volume loss.
- Medication change: r/DRV was changed to dolutegravir to allow rifabutin change to rifampin

Case 2

- Altered MS continued: INH briefly changed to moxifloxacin – then changed back. Prednisone tapered quickly → fever to 41, cervical adenopathy, delirium



Case 2

- The cervical LNs were biopsied showing necrotizing granulomas and AFB
- Steroids were increased with resolution of fever after several days.
- The case is ongoing: fevers return periodically with delirum. Repeat CSF sampling revealed 150 copies of CMV

Immune Reconstitution Inflammatory Syndrome

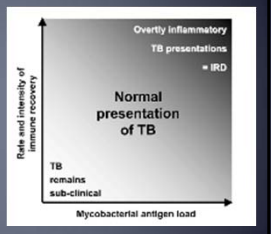
An illness…

- Occurring in an HIV + person
- With a temporal relationship to ARV initiation
- Associated with a decline in plasma HIVRNA and a rise in CD4 count
- Presentation with an unusual inflammatory course
- Exclusion of alternative causes (e.g., progression of an OI, drug toxicity, etc)

Immune Reconstitution Inflammatory Syndrome

Two Versions

- Paradoxical: IRIS occurring when an OI, responding to treatment before ARV therapy, deteriorates after initiating ARVs
- Unmasking: disease that was cryptic prior to starting ARVs, presents after starting ARVs with florid, inflammatory symptoms
- Not all illnesses represent IRIS: need overtly inflammatory disease



(Lawn, Am J Respir & Crit Care Med, 2008)
(Meintjes, Lancet Infect Dis 2008)

IRIS: Pathogenesis

HIV-Immunodeficiency-Opportunistic Infection

ART

Immune recovery

Activated IFN+ Effector-memory CD4+ T-cells	CD8+ T-cells	Macrophages GD-T-cells NK cells

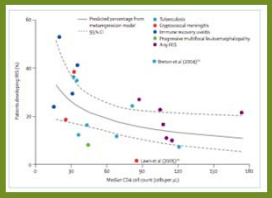
Defect in regulatory T-cells

IRS

Martin-Blondel, Curr Opin Infect Dis, 2012

IRIS: Epidemiology

- Paradoxical
  - Tuberculosis 17% (range 8-45%)
  - Cryptococcus 20% (range 4-49%)
  - PML 17%
  - KS 7-31 %
- Unmasking
  - Tuberculosis 1-5%
  - Cryptococcus 1-2%



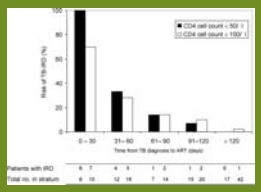
Haddow, PLoS One, 2012 and Muller, Lancet Infectious Diseases 2010

IRIS: Timing

TB-associated IRIS in South Africa

- 160 patients receiving Rx for TB at the time HAART initiated
- Median CD4 68
- IRS in 12% overall, 32% in those who started HAART within 2 months of TB Rx

TB-IRS, CD4 and HAART



(Lawn, AIDS 2007;21:335-41)

IRIS: Risk Factors

Advanced HIV	Low CD4 count High HIV RNA
High pathogen or antigen burden	Disseminated infection
Strong response to ARVs	Large drop in plasma HIVRNA Marked increase in CD4 count
Short interval between treatment of OI and initiation of ARVs	
Other factors	Host genetics, ARV naïve, low hemoglobin, PI-based ARV

Martin-Blondel, Curr Opin Infec Dis, 2012

IRIS: Clinical Symptoms and Predicting Tests

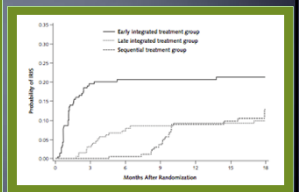
- Symptoms
  - New or worsening adenopathy (TB, MAC, KS)
  - Hepatitis (HBV, HCV)
  - Pulmonary infiltrates (TB and fungi)
  - Vitritis (CMV)
  - Multi-organ symptoms (TB, MAC, fungi, KS)
  - CNS symptoms (JCV, Cryptococcus)
- Predicting Tests
  - Elevated plasma levels of IL-2, INF, TNF, IL-17, IL-8

Grant (for ACTG 5164), JID, 2012, Achenbach, CID, 2012

TB-IRS

SAPiT Trial

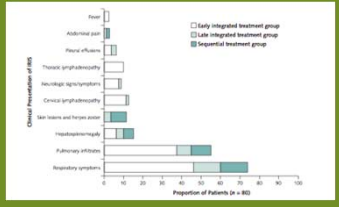
- Starting ARV at Three Points in TB
  - Starting ARVs within 4 wks of TB Rx (group 1)
  - Starting ARVs within 4 wks of completing the intensive phase of TB Rx (group 2)
  - Starting ARVs within 4 wks of completion of TB Rx (group 3)
  - N = 642
  - TB IRIS = 85
    - Group 1 = 43
    - Group 2 = 18
    - Group 3 = 19



(Naidoo, Ann Int Med, 2012)

SAPiT Trial

Symptoms of TB-IRIS



(Naidoo, Ann Int Med, 2012)

SAPiT Trial

Clinical Features and Outcomes

	Early ARV	Integrated ARV	Sequential ARV
Median time to IRIS from ART initiation (days)	17.5	17	28
Median time to IRIS resolution (days)	70.5	34	23.5
IRIS associated death	2	0	0

(Naidoo, Ann Int Med, 2012)

Tuberculous Meningitis

- Prospective, observational study of 34 HIV+ patients with tuberculous meningitis (TBM)
- TBM-IRIS in 16/34
- TBM-IRIS associated with increased rate of culture + CSF (94% vs 33%)
- TBM-IRIS associated with higher median CSF WBC count (50 Vs 3)
- Combination of high CSF TNF and low IFN; predicted the development of TBM-IRIS

Marquis, CID, 2013

Observational Study of TB-IRIS

Retrospective Analysis of 34 Patients with TB-IRIS treated In Paris Hospitals between 1996-2008

	No Rx (N = 10)	**ART interruption (N = 13)**	**ART interruption + steroids (N = 3)**	**Steroids alone (N = 8)**
Favorable outcome	10 (100%)	11 (85%)	3 (100%)	8 (100%)
Relapse	1 (10%)	6 (46%)	0 (0%)	4 (50%)

1. First IRIS: median steroid dose: 50 mg/day for median of 55 days
2. Relapse: 16 episodes in 11 patients, median of 47 days later, 9 episodes were treated with steroids at 30 mg per day for a median of 64 days
3. CD4 recovery: No steroids: +274 cells, Yes steroids: +146 cells

(Breton G, Int J Tuberc Lung Dis, 2012)

Randomized Placebo-Controlled Trial of Prednisone for TB-IRIS

- Double-blind placebo controlled RCT
- Intervention: Prednisone 1.5 mg/kg (100 mg daily for 70 kg adult) for 2 weeks then 0.75 mg/kg (50 mg daily for 70 kg adult) for 2 weeks
- Assessments: 1, 2, 4, 8 and 12 weeks
- Could switch to open label prednisone at MD discretion if deterioration/relapse

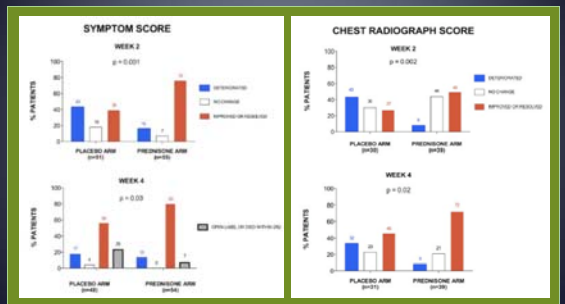
(Meintjes, AIDS, 2010)

Randomized Placebo-Controlled Trial of Prednisone for TB-IRIS

	Prednisone	Placebo	P value
Number	55	55	
Duration of TB RX before ART	66	43.5	0.02
Death	3 (5%)	2 (4%)	0.65
Severe infection	2 (4%)	4 (7%)	0.40
Infection	36 (65%)	30 (55%)	0.24
Steroid AE	8 (15%)	3 (5%)	0.11
Primary endpoint			
Total hospital days	282	463	
Outpatient procedures	27	31	
Median number of hospital days	1 (0-3)	3 (0-9)	0.046

(Meintjes, AIDS, 2010)

Randomized Placebo-Controlled Trial of Prednisone for TB-IRIS



(Meintjes, AIDS, 2010)

Randomized Placebo-Controlled Trial of Prednisone for TB-IRIS

Conclusions

- Prednisone reduced need for medical interventions (hospitalization and outpatient procedures)
- Consistent benefit of symptoms and radiographic evaluations
- Benefit despite cross over to open label
- No excess steroid toxicity or infection
- Optimal Duration? -- 4 weeks too short for some

(Meintjes, AIDS, 2010)

TB and HIV Co-infection, 2015

Conclusions

- TB and HIV have an bad influence on one another
- Africa is bearing the brunt of these co-epidemics
- HAART is decreasing the incidence of and mortality due to TB but is also expanding the pool of patients especially vulnerable to TB
- Atypical (primary and extra-pulmonary) presentations of TB predominate in HIV-TB co-infected persons
- Response to anti-tuberculous is excellent as long as you use daily dosing and watch out for drug interactions

TB and HIV Co-infection, 2015

Conclusions

- Starting HAART soon after anti-tubercular therapy improves survival, especially in those with very low CD4 counts
- Preferred ART is a standard-dosed Efavirenz-anchored regimen. Alternative regimens require substitution of rifabutin for rifampin and/or dose adjustments of both ART and anti-TB drugs. Integrase inhibitors are promising new agents anti-HIV medications with few TB drug interactions
- Concerns regarding the development of IRS should not interfere with the early initiation of HAART
- TB-IRS can be effectively managed with anti-inflammatory therapy but relapses are common and often require prolonged steroid courses