

Managing HIV and Opportunistic Infections: What's New?

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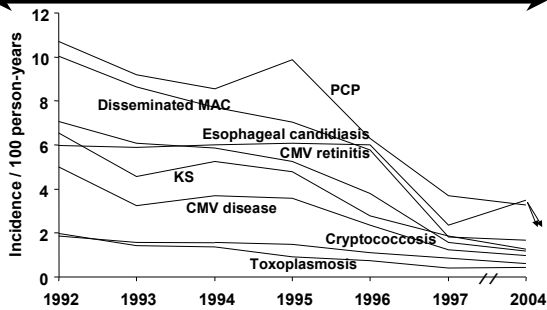
Impact of Potent Antiretroviral Therapy on Risk for OIs

Slide 2

- ♦ Rapid, sustained suppression of plasma HIV-1 RNA to < 50 copies/ml in > 90% of ART-naïve persons
- ♦ Second and third line regimens continue to improve with sustained suppression of viral load in >60%-80% of persons with drug-resistant HIV
- ♦ Sustained increase in CD4+ cell counts (memory and naïve subsets)
 - Improved pathogen-specific immune responses
 - Decreased risk for new or relapsed OIs

Incidence of AIDS-Defining OIs in Adults and Adolescents in the U.S.

Slide 3



Updated in: Morris A, et al. Emerging Infect Dis 2004; 10:1713

Decline in TB Incidence after Potent ART: South Africa

Slide 4

Incidence highest
BL CD4+ < 100
5.71/100 pt-yrs

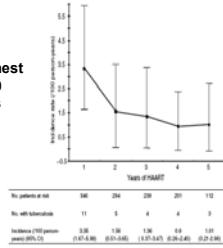


Fig. 1. Tuberculosis incidence density rates. $P = 0.02$ for trend; slope $y = -0.32x + 3.23$; $R^2 = 0.72$; CI, confidence interval.

Lawn S, et al. AIDS, 2005; 19:2109

Causes of Death in HIV-Infected Patients on ART: Clinical Trials vs Clinical Practice

Slide 5

- 453 deaths among 11,593 participants in 3 large RCTs 1999-2008 and 253 deaths among 4,471 pts 1997-2004 (Lifson AR, et al. HIV Clin Trials 2008; 9:177-85 and Martinez E, et al. HIV Med 2007; 8:251-258)

Cause of death	Clin Trials	Clin Prac
AIDS Defining Events	47 (10%)	95 (40%)
NADE-Malignancy (lung, liver)	93 (21%)	25 (11%)
Cardiac Disease (MI, CAD)	40 (9%)	14 (6%)
Liver Disease (HCV, HBV)	39 (9%)	53 (23%)
NADE-Serious Infections	36 (8%)	33 (14%)
Suicide	22 (5%)	3 (1%)
Trauma/Accident	23 (5%)	2 (1%)
Drug Overdose	20 (4%)	6 (3%)
Other	52 (11%)	

Case 1

Slide 6

- A 35-year-old man newly diagnosed with HIV infection presents with a 3-week history of cough, pleuritic chest pain, dyspnea and fever.
 - PHX: Smoker; uses crystal methamphetamine on weekends; incarcerated x 90 days 2 years previously
- Two weeks earlier a CD4+ count of was 58 cells/ μ L, and plasma HIV-1 RNA was 102,000 copies/ml
- A CXR shows bilateral interstitial infiltrates
- PaO₂ is 68 on room air

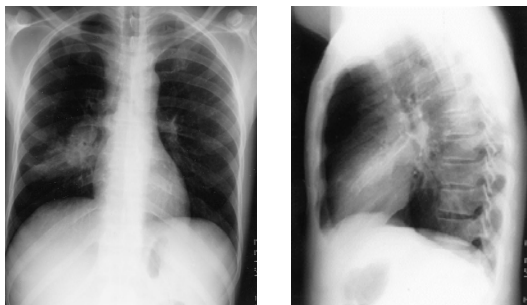
Case 1

- ◆ PCP treatment with adjunctive corticosteroids is administered; ART is deferred
- ◆ A tuberculin skin test is negative
- ◆ Symptoms improve over the next 5 days and he is discharged from hospital
- ◆ After completion of 21 days of PCP treatment, he is then started on fixed dose efavirenz + tenofovir + emtricitabine

Case 1

- ◆ He returns to the clinic in 3 weeks complaining of recurrent fevers, worsening dyspnea, increased cough, and a 10 pound weight loss
 - CD4+ cell count is 150 cells/ μ L
 - Plasma HIV-1 RNA is 9,000 copies/ml
 - A CXR is obtained

Case 1



Question 1



♦ **What is your working diagnosis?**

1. Relapsed PCP
2. Immune reconstitution inflammatory syndrome (IRIS)
3. Unmasked TB
4. Relapsed PCP + unmasked TB
5. Something else

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents



Recommendations from the CDC, the National Institutes of Health and the HIV Medicine Association of the Infectious Disease Society of America

Kaplan JE, Holmes KK, Benson CA, Pau A, Brooks JT, Masur H
MMWR 2009; 57 (RR XX) (In Press)

“What’s New in This Document”



- ♦ Updates and combines both prevention and treatment guidelines
- ♦ Greater emphasis on ART for prevention and treatment of OIs, particularly those for which there is no effective therapy
- ♦ IRIS diagnosis and management
- ♦ Use of IFN-γ release assays for latent TB detection
- ♦ Update drug interactions particularly with rifampin used for TB
- ♦ New sections on TB and HBV
- ♦ Addition of malaria as a geographic OI of interest; updated info on other geographic OIs

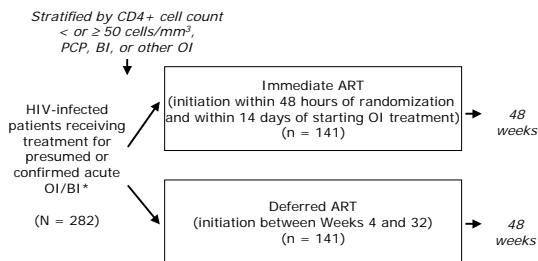
Question 2

- ◆ When do you start ART in your treatment-naïve patients who present with an acute OI?
 1. Immediately, concomitant with OI treatment
 2. Wait until completion of OI treatment
 3. Delay for two weeks or until the patient has improved or recovered
 4. It depends on the OI

Initiation of ART in the Setting of an Acute OI

- ◆ “With the exception of patients with newly diagnosed TB, unless compelling contraindications are present, early initiation of ART at or near the time of initiation of OI treatment should be considered for all patients.”
- ◆ “In cases of cryptosporidiosis, microsporidiosis, PML, Kaposi’s sarcoma, PCP, and invasive bacterial infections...ART should be started as soon as possible.”

ACTG A5164: Immediate vs Deferred ART in Patients With Acute OIs

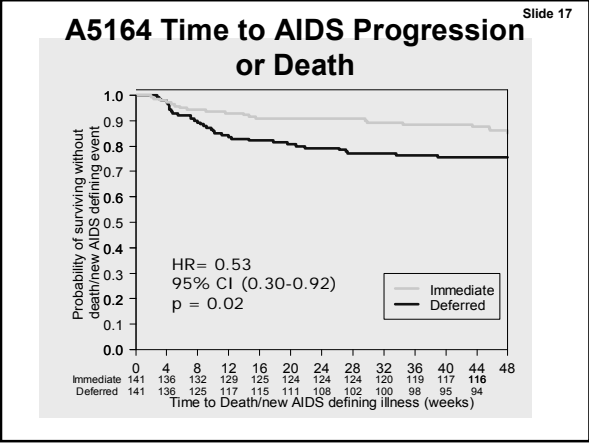


*Patients with TB excluded.

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ACTG A5164: Improved Outcomes With Immediate ART During Acute OI

- ◆ Median duration from start of OI treatment to initiation of ART (12 d for immediate group vs 45 d for deferred)
- ◆ No significant difference between groups in composite primary endpoint (virologic response, clinical progression, and death; $P = .215$)
- ◆ Immediate treatment associated with significant reduction in clinical progression or death through Week 48 ($P = .035$)
 - 14.2% vs 24.1%, respectively; OR: 0.51 (99% CI: 0.23-1.15)
- ◆ Safety, incidence of immune reconstitution events similar between groups





Slide 18

SAPIT: Starting Antiretroviral therapy (ART) in three Points In TB

Primary Objectives:

- Whether to initiate ART during or after TB treatment?
- Whether to start ART during TB intensive phase (first 2 months) or during TB continuation phase (months 3 & 4)?

Patient Population and Study Design

- Confirmed HIV infection with CD4 count < 500
- Sputum AFB smear positive & receiving standard anti-TB therapy regimens
- TB treatment: Standard TB regimen (DOT)
- All patients provided with cotrimoxazole prophylaxis
- ART: Didanosine + Lamivudine + Efavirenz once daily
- Randomized to one of 3 arms (N=645):
 - 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



Interim trial outcome: Mortality rates

55% lower mortality in integrated TB-HIV treatment

Hazard Rate: 0.451 (95% CI: 0.26 to 0.79); p = 0.0049

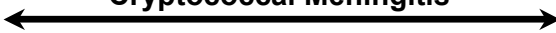
	Integrated Treatment Arm n = 431	Sequential Treatment Arm n = 214
Time to start ART after TB Treatment initiation	67d	261d
Number of deaths	24	26
Person-years of follow-up	469	224
Mortality rate per 100 person-years	5.1	11.6



Reduction in mortality in the Integrated arm is statistically significant in patients with both CD4 ≤ 200 and > 200



Early vs. Deferred ART in Cryptococcal Meningitis



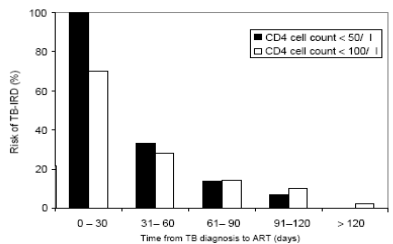
- ♦ RCT in Parirenyatwa Hospital, Harare, Zimbabwe (Makadzange A, et al. Abstr. 36cLB, CROI 2009)
 - 54 pts with CM treated with oral fluconazole and randomized within 72 h of diagnosis to immediate vs deferred (after 10 wks of fluconazole) ART with stavudine, lamivudine and nevirapine
 - Overall mortality 62%; 82% in the early ART arm vs 37% in the deferred arm (median duration of survival 35d vs 274d (P = 0.028)
 - ♦ HR 2.36 (95% CI 1.12, 4.97)

Managing IRIS

Paradoxical Reactions and “Unmasking” IRIS in HIV-Infected Patients

- ◆ Paradoxical reactions generally reported in patients with TB
 - Paradoxical reaction - worsening of TB signs and symptoms shortly after initiation of ART
- ◆ “Unmasking” IRIS – emergence of signs and symptoms of TB or OI that was subclinical or undiagnosed at the time ART was started
 - Generally observed within 2-4 weeks of ART initiation
 - Risk factors:
 - ◆ Shorter interval between initiation of TB or OI treatment and ART
 - ◆ Low CD4+ (< 100 cells/μL) with or without high viral load

Risk of IRIS Based on Time from TB Diagnosis to Initiation of ART



Time from TB diagnosis to ART (days)	0-30	31-60	61-90	91-120	> 120
Patients with IRIS	6	4	1	1	0
Total no. in stratum	6	12	7	15	17

Lawn SD, et al. AIDS 2007; 21:335-41

Management of IRIS

- ◆ Double-blind, placebo-controlled RCT in South Africa (Meintjes G, et al. Abstr. 34, CROI 2009)
 - 109 pts with TB-IRIS were randomized to receive prednisone 1.5 mg/kg/d x 2 weeks then 0.75 mg/kg/d x 2 weeks (N=55) or placebo (N=54)
 - ◆ Pts deteriorating after starting study drug could switch to open label prednisone
 - ◆ Median age 32; CD4+ 53 cells/ μ L; 6 pts LTFU in placebo arm

Management of IRIS

Parameter	Prednisone	Placebo	P-value
Median hospital days	1	3	0.05
Cumulative hospital days	282	463	0.05
Deaths	3	2	0.70
# switched to open label	5	19	0.001
Steroid AEs	9	3	0.07
Symptoms improved (5 point score)	-----	-----	0.003
Rifampin resistance	5	7	0.50

Management of IRIS

- ◆ Rule out relapse or recurrence of underlying OI or malignancy
- ◆ Continue antiretroviral therapy
- ◆ Pathogen-specific therapy as appropriate
- ◆ NSAIDs as initial adjunctive therapy for inflammatory symptoms
- ◆ Use corticosteroids in severe cases; 40-60 mg prednisone/day x 2 weeks then taper as signs and symptoms allow

Issues in Treatment of Specific OIs

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Preferred Treatment for HIV-Related Opportunistic Infections - 2009

- ◆ PCP
 - TMP-SMX
- ◆ CMV
 - Ganciclovir ocular implant +/-
 - Oral valganciclovir
- ◆ DMAC
 - Clarithromycin + ethambutol +/- rifabutin
- ◆ Tuberculosis
 - INH/RIF/PZA/EMB x 2 mos then INH/RIF x 4 mos
- ◆ Cryptosporidiosis
 - Initiate or optimize ART
- ◆ Toxoplasmic encephalitis
 - Pyrimethamine + sulfadiazine + leucovorin
- ◆ Cryptococcal meningitis
 - Amphotericin B (standard or liposomal) + flurouracil x 2 wks then fluconazole x 8 wks
- ◆ Candidiasis
 - Azoles
- ◆ HBV
 - (3TC or FTC) + TDF if ART required
 - Adefovir or PEG-IFN α if not on ART
- ◆ HCV
 - PEG-IFN α + ribavirin

Alternative Treatment for Opportunistic Infections - 2009

- ◆ PCP
 - TMP-dapsone
 - Pentamidine
 - Atovaquone
 - Primaquine + clindamycin
- ◆ CMV
 - IV ganciclovir or foscarnet
 - IV cidofovir
- ◆ MAC
 - Azithromycin + ethambutol +/- rifabutin, amikacin, streptomycin, cipro, moxifloxacin, levofloxacin
- ◆ Cryptosporidiosis
 - Trial of nitazoxanide
- ◆ Toxoplasmic encephalitis
 - Pyrimethamine + clindamycin
 - Trimethoprim + sulfadiazine or sulfamethoxazole
 - Atovaquone + pyrimethamine + leucovorin
 - Azithromycin + pyrimethamine + leucovorin
- ◆ Cryptococcosis
 - Ampho B + fluconazole
 - Fluconazole + flucytosine
- ◆ Candidiasis
 - Amphotericin B, voriconazole, caspofungin, micafungin
- ◆ HBV
 - 3TC of FTC + adefovir, entecavir

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Tuberculin Skin Testing vs Interferon- γ Release Assays

Operational Characteristics	TST	Quantiferon-Gold	T-Spot TB
Sensitivity	~70%	76-80%	87-88%
Specificity	56-95%	97%	92%
Cross-reactivity with BCG	Yes	No	No
+ test and risk of subsequent TB	Moderate to strong association	Insufficient data	Insufficient data
Boosting	Yes	No	No
Adverse reactions	Yes	No	NO
Patient visits	2	1	1
Cost	Low	Moderate	High
Lab infrastructure	No	Yes	Yes
Turn around time	48-72 hours	24-48 hours	24-48 hours

- Slide 35
- ### Novel Regimens for Treating Latent TB in HIV-Infected Patients
- ◆ RCT in 1150 HIV-infected, TST+, South African adults block randomized 2:2:1:2 to
 - Rifapentine 900 mg + INH 900 mg once per week x 12 weeks
 - Rifampin 600 mg + INH 900 mg twice weekly x 12 weeks
 - INH 300 mg daily
 - INH 300 mg daily for 6 months

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Novel Regimens for Treating Latent TB in HIV-Infected Patients

Outcome	RPT/INH-3 (N = 329)	RIF/INH-3 (N = 329)	INH-cont (N = 164)	INH-6 (N = 328)
Median F/U (yrs)	3.98	3.99	3.81	3.78
TB Cases	23	24	8	20
TB Incidence Rate Ratio	1.94	1.97	1.43	1.77
95% CI	1.10 0.57 – 2.1	1.11 0.59 – 2.1	0.81 0.31 – 1.9	1 (ref)
TB or death Rate Ratio	3.03	2.87	2.67	3.53
95% CI	0.86 0.53 – 1.4	0.81 0.50 – 1.3	0.76 0.39 – 1.4	1 (ref)

Conclusions: Alternative, short course, rifamycin-based regimens and continuous INH were as effective as INH for 6 months; development of RIF-resistance and MDRTB higher in RPT/INH arm of concern

Discontinuation of Prophylaxis

Criteria for Discontinuing & Restarting Primary OI Prophylaxis



Disease	CD4+ to Stop	CD4+ to Restart
PCP	> 200 cells/μL for > 3 months in response to ART	< 200 cells/μL
Toxoplasmosis	> 200 cells/μL for > 3 months in response to ART	< 100-200 cells/μL
MAC	> 100 cells/μL for ≥ 3 months in response to ART	< 50 cells/μL

Criteria for Discontinuing & Restarting Secondary OI Prophylaxis



Disease	CD4+ to Stop	CD4+ to Restart
PCP	> 200 cells/μL for ≥ 3 months on ART	< 200 cells/μL or if PCP recurred at CD4+ > 200 cells/μL
Toxoplasmosis	Asymptomatic after completing initial Rx and > 200 cells/μL for > 6 months on ART	< 200 cells/μL
MAC	Asymptomatic after completing 12 mos of Rx and > 100 cells/μL for ≥ 6 mos on ART	< 100 cells/μL
Cryptococcal meningitis	Asymptomatic after completing initial Rx and ≥ 200 cells/μL for 6 mos on ART	< 200 cells/μL
CMV retinitis	CD4+ > 100 cells/μL for > 3-6 mos on ART; ophthalmologist monitoring every 3 mos	< 100 cells/μL

HIV-Associated OIs: What Does the Future Hold?



- ◆ New drug development
 - TB, PCP, malaria, OIs of geographic significance (leishmaniasis)
- ◆ Continue optimizing initiation of ART in the setting of an acute OI
 - Management of IRIS
- ◆ Prevention
 - OI vaccines available - HBV, HPV, VZV, BCG
 - OI vaccines in development - TB, malaria, HCV
