UPDATES ON HIV IN THE HOSPITAL

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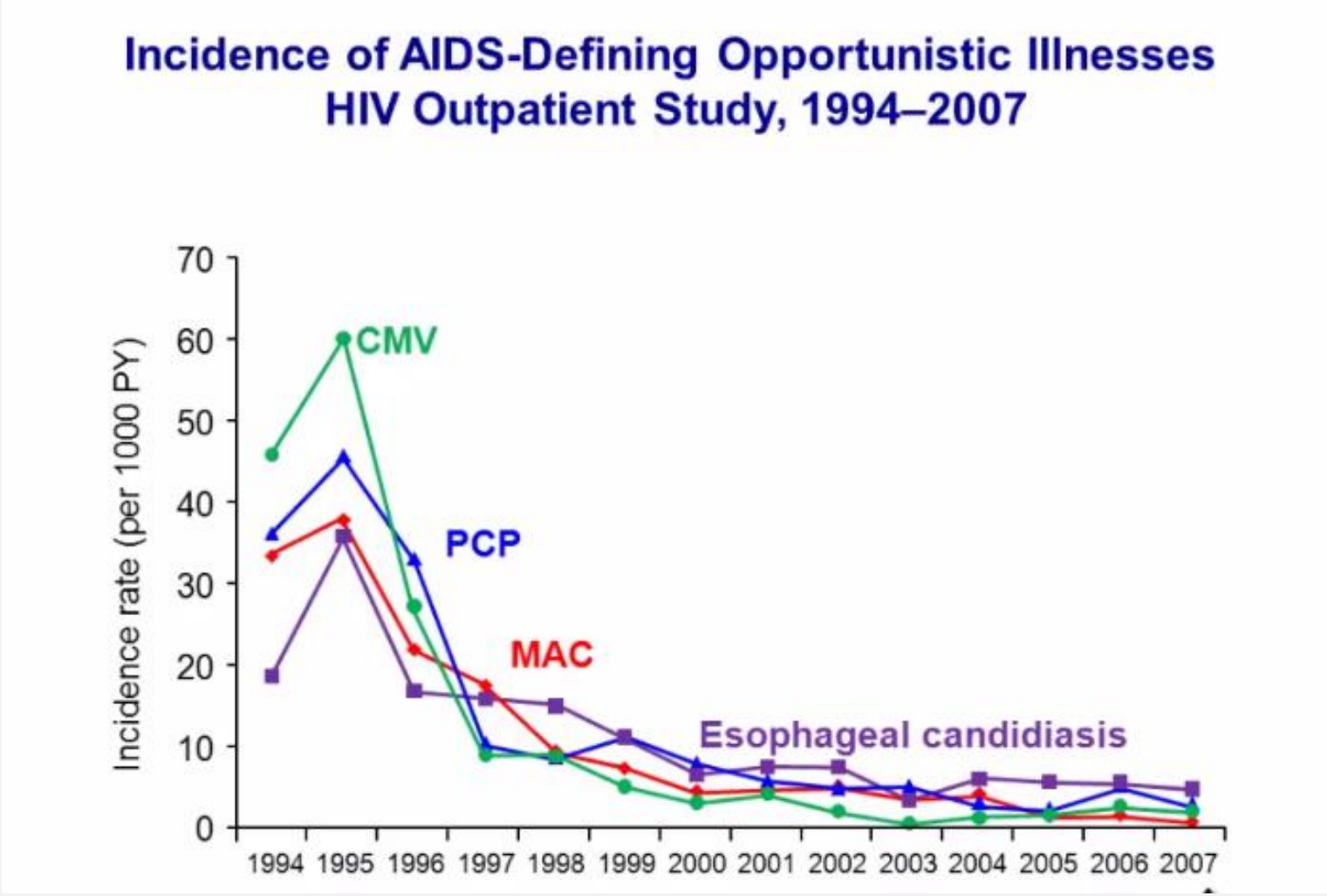
No disclosures or conflicts

OI DECLINE: THE WHOLE STORY?

- OI incidence has declined but is this the whole story?
  - Outpatient HOPS cohort (USA) →
- Data from national hospital discharge survey (NHDS) suggest a somewhat different view



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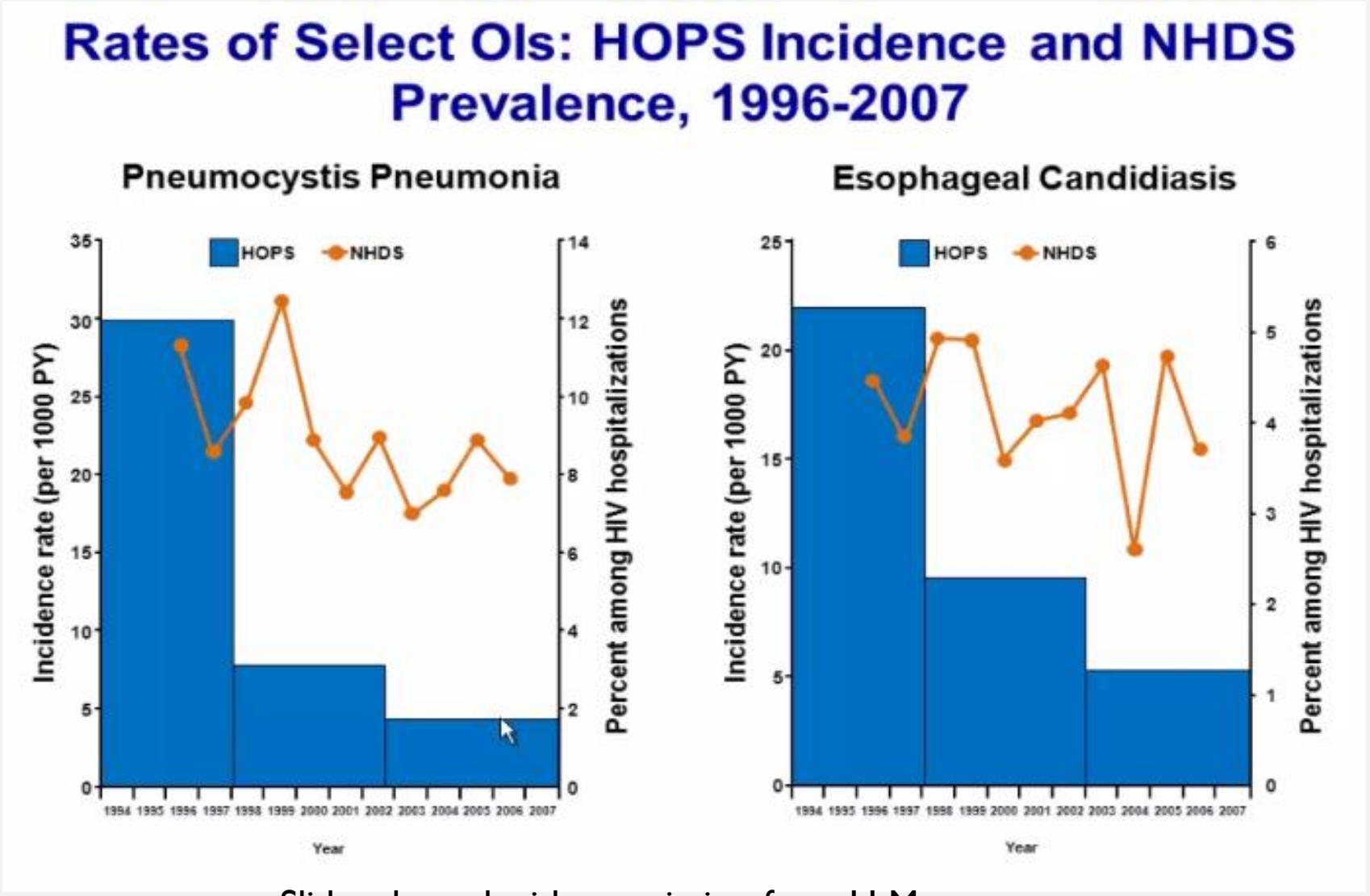
OI DECLINE: THE WHOLE STORY?

- OI decline less dramatic
- 2 main HIV-infected groups:
  - Aware of HIV and receiving ART
  - Unaware of HIV /aware not in care
- In 2014, an estimated 44,000 in the US were newly infected



Kamimoto Natl HIV Prevention Conference 2011

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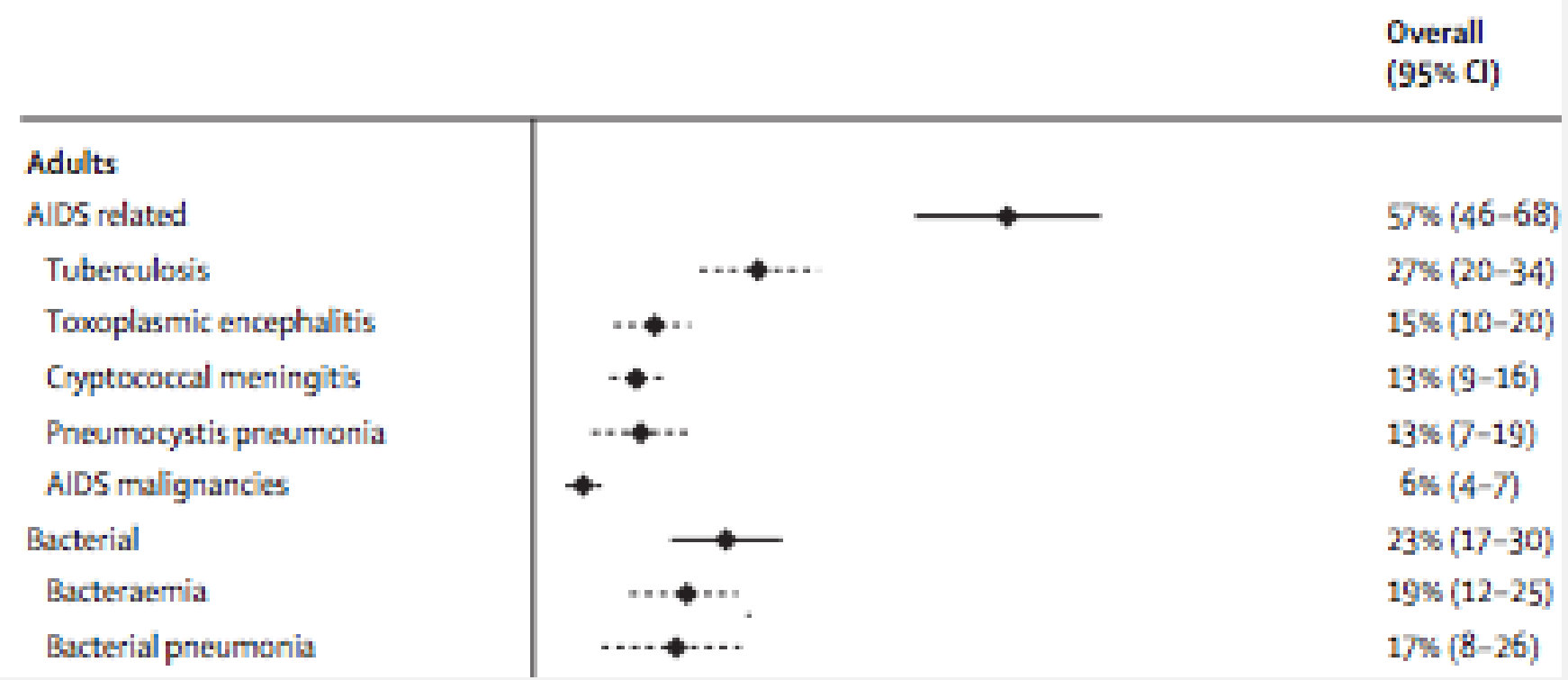
GLOBALLY: OI AND OTHER HOSPITALIZATIONS IN ADULTS WITH HIV

- Globally late care presentation remains important cause of hospitalization + death
- Currently only ½ of HIV patients are receiving ART at the time of admission
- Cancers and NCDs rising in PLHIV but OIs and bacterial infections still the main cause of mortality in hospitalized HIV patients in Africa
- In-hospital mortality 31%



Causes of mortality in HIV patients admitted to hospital, globally

Ford et al Lancet HIV 2015

OI Updates

Pneumocystis pneumonia update

PCP IN AFRICA

- PCP once thought less common but more likely issue inadequate diagnostic capacity
- Recent systematic review of PCP in Africa revealed:
  - Median CD4 of patients with PCP 48 cells/ul
  - PCP prevalence: 24% of inpatients presenting with respiratory illness and 5% of outpatients
  - Beware ! Coinfections common in PCP patients
  - Empirical PCP treatment justified in advanced HIV + PCP syndrome & poor response to initial Rx
- Overall mortality 18%
- Prevalence may be declining but still important OI in those presenting late

Co-existent opportunistic disease (%, 95 % CI)	
- Overall	29.3 [25.4–33.6] (26 studies, $n = 474$)
- Tuberculosis	14.8 [11.8–18.5] (25 studies, $n = 431$)
- Bacterial pneumonia	8.7 [0.6–11.8] (22 studies, $n = 445$)
- Pulmonary cryptococcosis	1.4 [0.4–3.6] (17 studies, $n = 283$)
- Pulmonary Kaposi sarcoma	4.1 [2.4–6.6] (21 studies, $n = 410$)

Wasserman et al. BMC Infectious Diseases (2016)

CORTICOSTEROIDS IN PCP: AN RCT OF PREDNISONE V. PLACEBO IN PCP

TMP-SMX remains treatment of choice

What about the role of steroids?

- Primary outcomes: respiratory failure or death
- About 80% received TMP-SMX at 15-20 mg/kg/day
- Results at 31d f/u:
  - Respiratory failure 14% vs. 30%, death 16% vs. 26% (p=0.026), both favoring prednisone

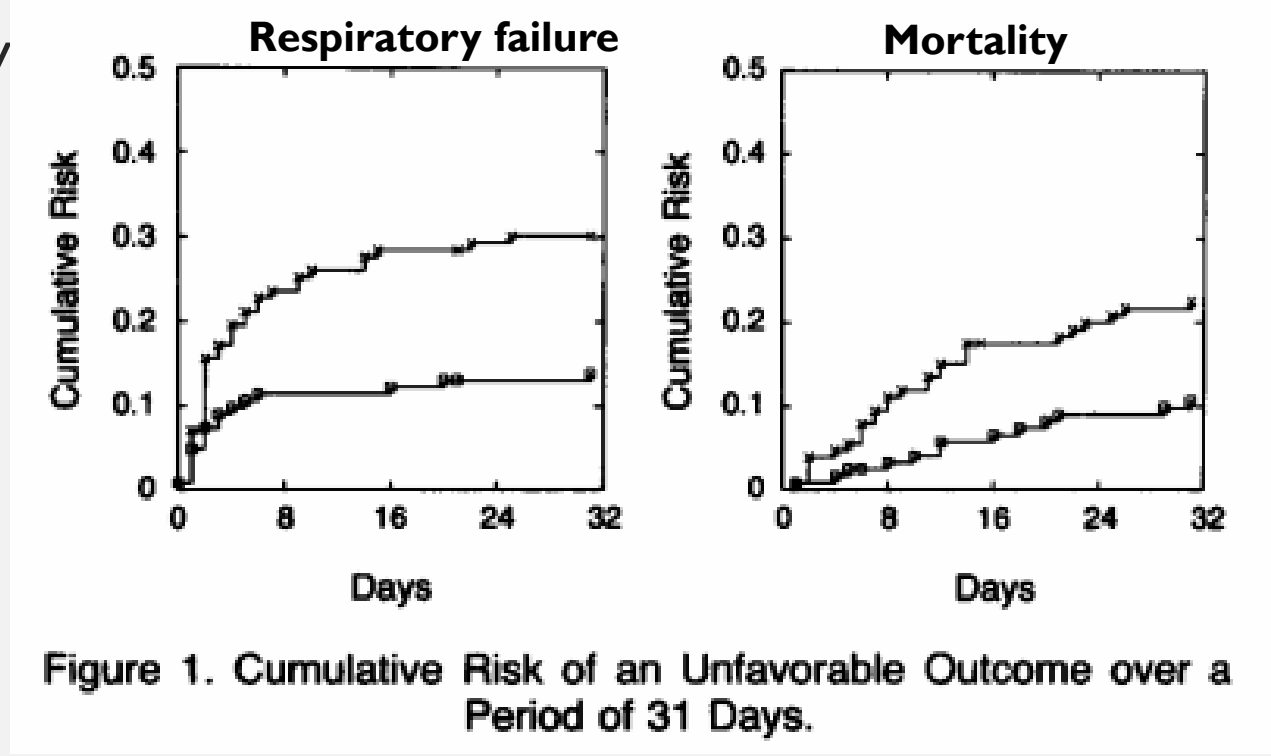


Figure 1. Cumulative Risk of an Unfavorable Outcome over a Period of 31 Days.

Sattler et al NEJM, 1990

Recommendation:

Steroids if PaO2 <70 mm Hg or A-a gradient ≥35

That is a saturation of 93% or less

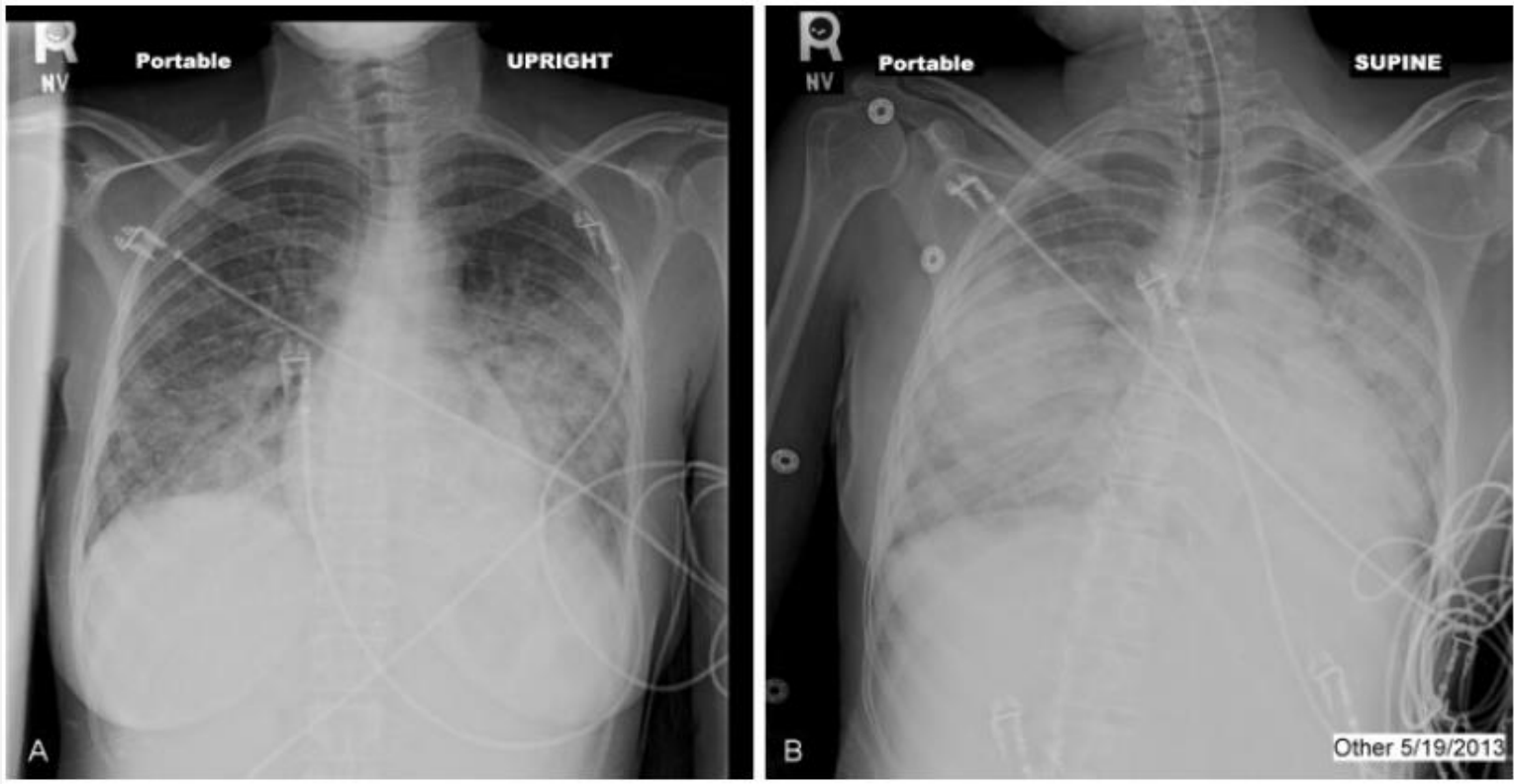
Regimen: 21 days

Prednisone 40mg q12 (day1-5), 40mg/day (day 6-10), 20 mg/day (days 11-21) ** or **

Methylprednisone IV at 75% of predn. dose

PCP IN ICU

- Respiratory decompensation common 48-72 hours into PCP treatment
- About 10% require mechanical ventilation (MV) and another 10% noninvasive positive press. ventilation
- Early in US epidemic there was reluctance to use MV
  - Survival in HIV patients with resp. failure from PCP requiring MV was ~20%
- DHHS guidelines endorse MV "if functional status is such that it would be otherwise appropriate," as with HIV uninfected.



DHHS Guidelines 2016

Curtis et al Am J of Resp Crit Care Med 2000

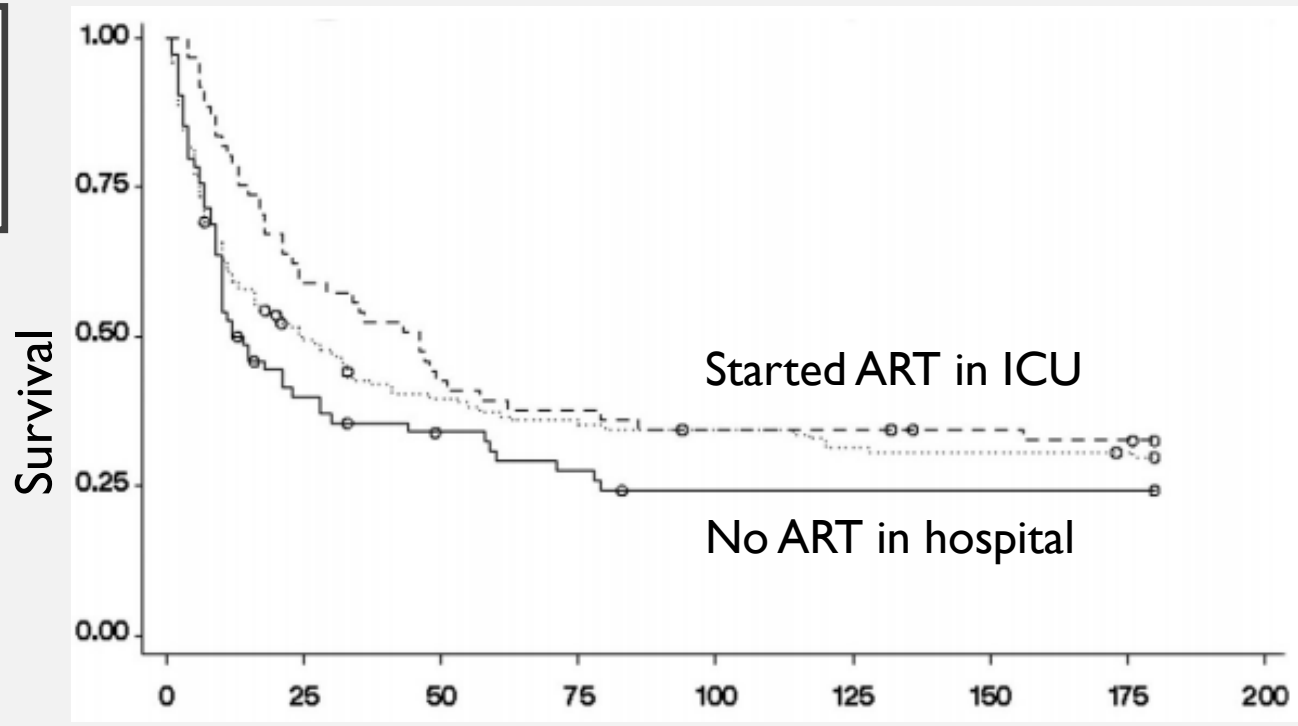
WHAT IS THE MODERN SURVIVAL IN HIV-ASSOCIATED PCP WITH RESP. FAILURE REQUIRING MECHANICAL VENTILATION?

- 0%
- 5%
- 20%
- 40%

PCP SURVIVAL IN ICU – ON THE INCREASE

Overall the survival for PCP patients requiring mechanical ventilation has improved to ~ 40-50%

- Use of corticosteroids in severe PCP widespread since 1990s so unlikely the cause
- New approaches to ventilating patients may have played a role
- A higher proportion of patients admitted with PCP are receiving or initiating ART in hospital



Year	Setting	Survival
Pre 2000	Multiple	~20%
2000	USA	44%
2006	UK	62%
2007	Thailand	57%
2008	France	85%
2014	China	60%

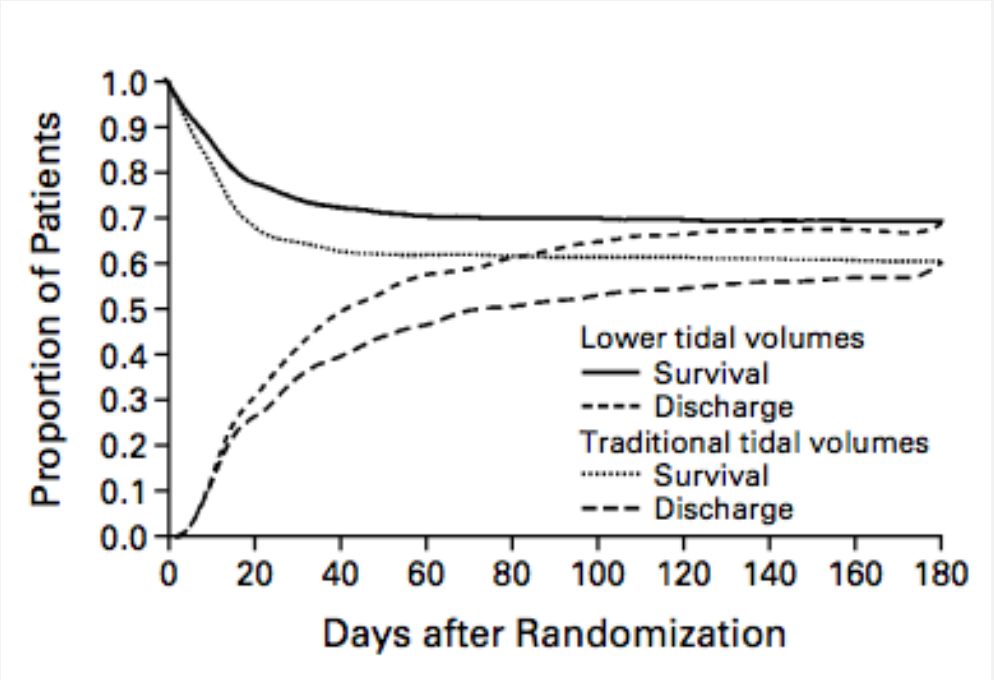
* Brazil retrospective study: Survival in PCP patient admitted to ICU better among among those initiating ART during ICU stay vs. those not receiving ART in hospital.

Miller *et al* Thorax 2006
Morris A *et al* AIDS 2003
Croda et al Crit Care Med 2009

FALLING MORTALITY OF PCP IN ICU

- A 2000 study showed improved mortality in all patients with ARDS using ventilation with low tidal volumes (TV)
  - San Francisco (2009): Survival of HIV patients with acute lung injury (PCP 36% of cohort) on MV better with low TVs.
- Italian study: Non-invasive positive pressure ventilation can avoid intubation in some PCP patients; those avoiding intubation have <u>improved</u> outcome
  - Included: PCP with acute respiratory failure
  - Excluded: shock, respiratory arrest, altered MS
  - 3/38 did not tolerate NIPPV and required MV but intubation avoided in 66% of NIPPV for whom survival was superior (100% vs. 38%; P=0.003) and few PTX.

Davis et al Thorax 2009



ARDSNet Study 2000 NEJM

Confalonieri Intensive Care Med 2002

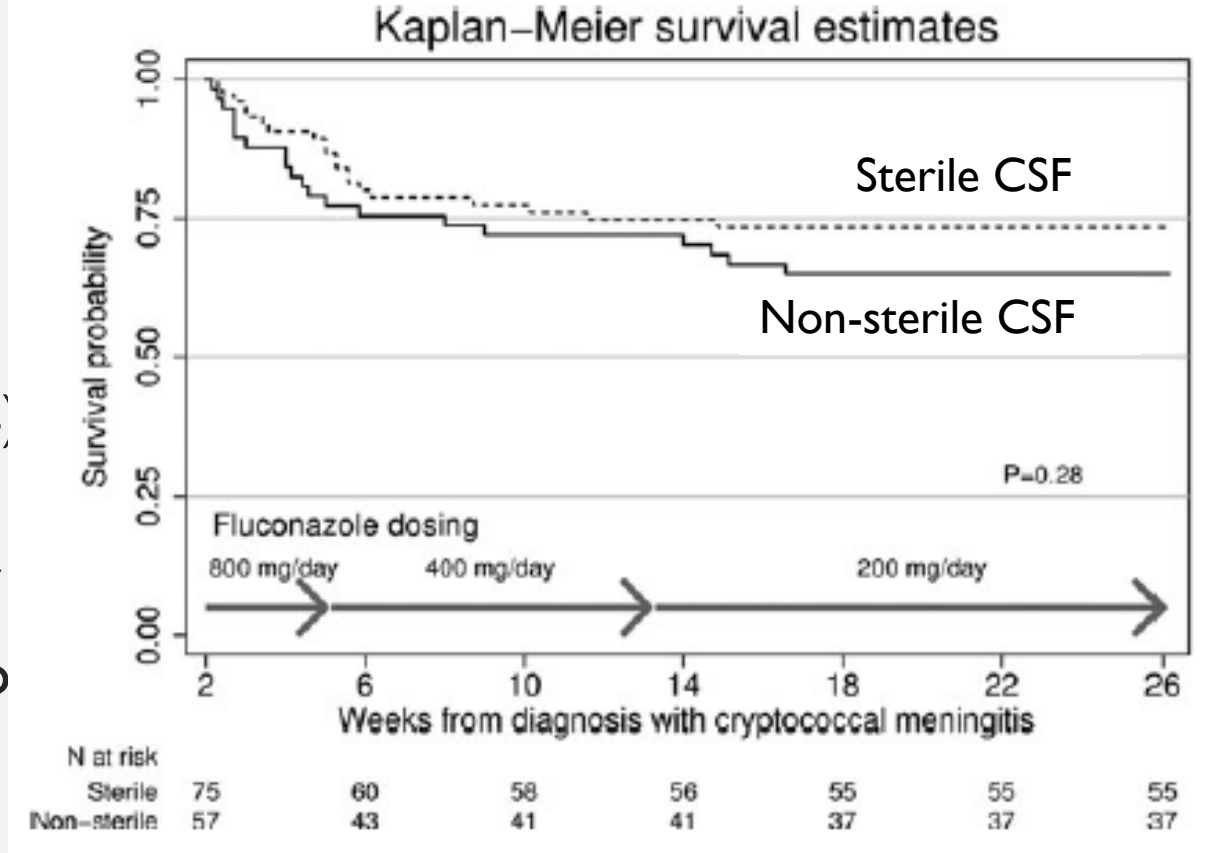
Cryptococcal meningitis updates

HOW COMMONLY IS THE CSF CULTURE POSITIVE AFTER 2 WEEKS OF AMPHOTERICIN-BASED THERAPY?

1. 5%
2. 20%
3. 50%
4. 90%

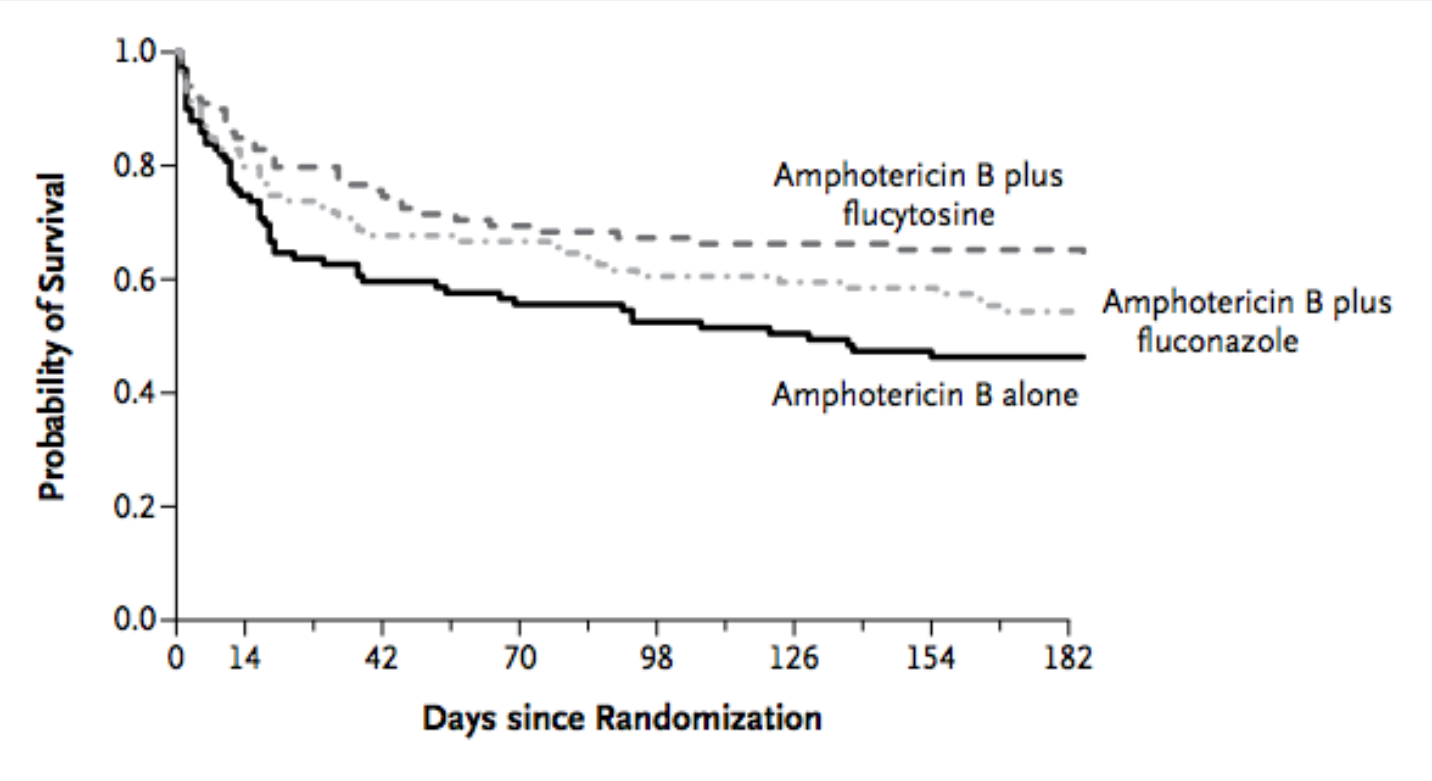
CRYPTOCOCCAL MENINGITIS

- Viable *Cryptococcus neoformans* present in 50% at end of amphotericin treatment
- Positive culture at end of induction associated with poor outcomes including incr. risk of IRIS and mortality
  - In SA, hi mortality linked with (+) CSF culture end of consolidation (14% mortality sterile CSF vs 26%)
- In the COAT trial, fluconazole 800 mg/day – not 400 mg/day – was given as consolidation therapy
- High dose fluconazole consolidation appeared to improve outcomes in culture (+) patients
- Without routine cultures, optimal duration of high dose fluconazole remains unclear.



Rolfes et al Open Forum ID 2015

ACCESS TO FLUCYTOSINE FOR CM



Day JN et al NEJM 2013

- Induction therapy in South Africa: amphotericin B + fluconazole
- In large trial, mortality higher among patients receiving amphotericin B + fluconazole vs. amphotericin B + flucytosine
- Flucytosine is an old, generic antifungal drug (1957).
  - It is not highly toxic or difficult to monitor at doses used in CM

<u>Barriers</u>:

- (1) Not registered in most of Africa; previously marketed in SA by Roche
- (2) Current FDA-approved sources are very expensive with 2 generic producers
- (3) Market failure of insufficient supply of an old generic drug

Govender et al SAMJ 2014

ADJUNCTIVE DEXAMETHASONE IN CM?

Mortality in some types of meningitis is improved with corticosteroids

- This trial in SE Asia and Africa randomized HIV-infected patients treated with CM receiving amphotericin + fluconazole to tapering dexamethasone or placebo.
- 40% of patients were receiving ART at admission and median CD4 cell count 20 cells/ul

Outcomes

- Fungal clearance in cerebrospinal fluid was slower in the dexamethasone group
- Dexamethasone associated with more disability and AEs and the trial was stopped early.

	"Good" outcome (lack disability)	10 week Mortality
Dexamethasone	13%	47%
Placebo	25% (P<0.001)	41% (P=0.20)

Beardsley et al NEJM 16

OPENING PRESSURE MANAGEMENT

Opening pressure

- 50% patients > 250 mm H2O

- But most patients do not undergo therapeutic lumbar punctures despite reduction in mortality by 50%
  - COAT trial substudy:
    - No therapeutic LP: mortality 18%

      Therapeutic LP performed: mortality 7%
    - Adj. risk of mortality with therapeutic LP 0.31
  - Recommended: Daily LP if > 250 mm H2O and removal of up to 25cc until pressure <200 mm

- No significant risk of herniation; the problem is not edema and shift but obstruction of outflow

- In absence of manometry, recommend qd LP until symptoms well controlled.

J AIDS & Hum Retrovirol. 1998

CID 2014; 4: 59 (11)

Tuberculosis meningitis updates

TB-MENINGITIS AND DISMAL OUTCOMES

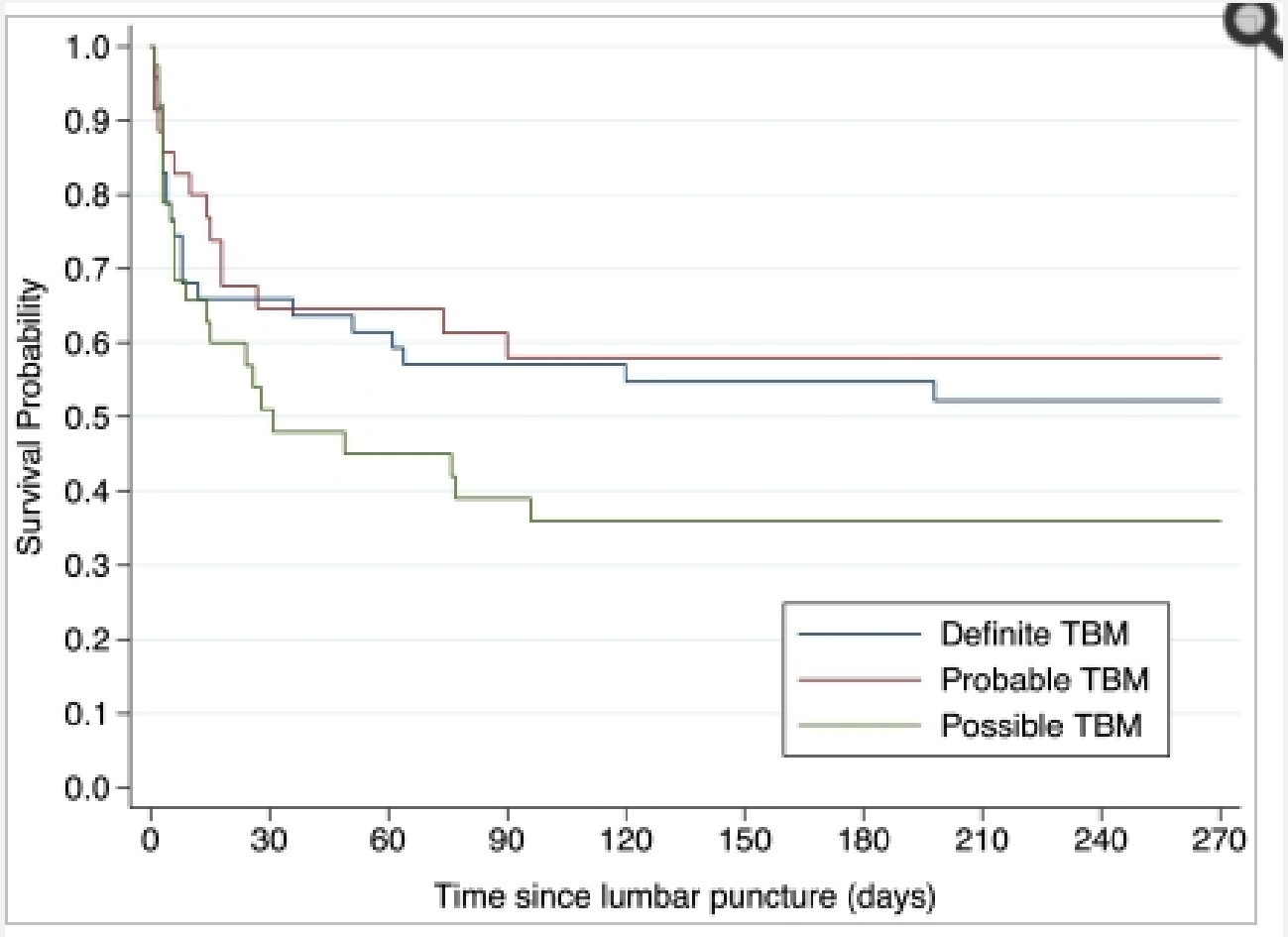
Empirical treatment in HIV based on suspicion:

- CSF:
  - Lymphocyte pleocytosis
  - Depressed glucose, elevated protein
  - Negative CrAg and cryptococcal culture
- TB evident elsewhere (i.e. CXR or smear)

Therapy:

- RHZE for 2 months, RH for 4-7 months further + corticosteroids for first 4-6 weeks

TB-M is a grave diagnosis for which we have weak diagnostic and treatment strategies. →



Kaplan-Meier survival curves of patients with definite, probable and possible tuberculous meningitis (TBM) in Cape Town, 2011

XPERT MTB/RIF FOR DIAGNOSIS OF TB-M

- In a UK study, the retrospectively evaluated CSF specimens known to be culture positive with the XPERT MTB/RIF assay
- The quantity of CSF available was small
- Overall sensitivity was 55% but specificity very high (few false positives)
  - Sensitivity may as high as 72% with large CSF volume 10ml + centrifuge (Uganda, 2015)

When positive, XPERT MTB/RIF CSF testing can "rule-in" TB-M – and identify drug-resistant TB – but a negative test does not exclude TB-M when suspicion is high

UK Retrospective Study

	No. of samples		
Xpert MTB/RIF result	Culture positive	Culture negative	Total
Positive	25	3[a]	28
Negative	20	687	707
Total	45	690	735

Pink et J of Clinical Micro 2016

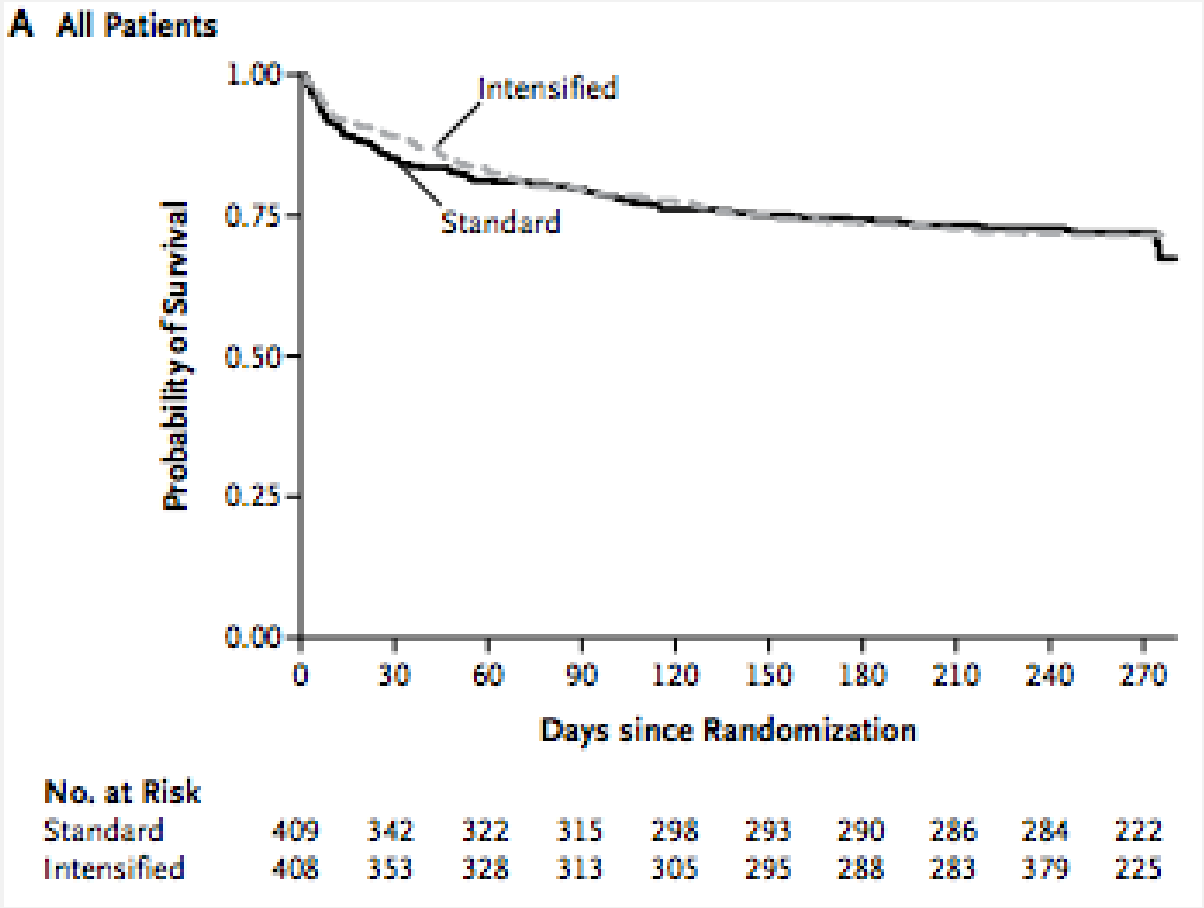
MANAGEMENT: TB-MENINGITIS

Role of adding levofloxacin + hi dose rif ?

- Trial of TB meningitis in Vietnam (42% HIV-infected, median CD4 38)
- No advantage of adding – to RIPE and dexamethasone– levofloxacin and high dose rifampin during first 8 weeks

Role of linezolid ?

- Small (n=33) study showed more rapid improvement of GCS, fever, and CSF parameters when linezolid 1200 mg/day added to standard regimen
- No mortality data provided. Larger trial needed.



Sun et al AAC 2014

NEJM 2016; 374:124-34

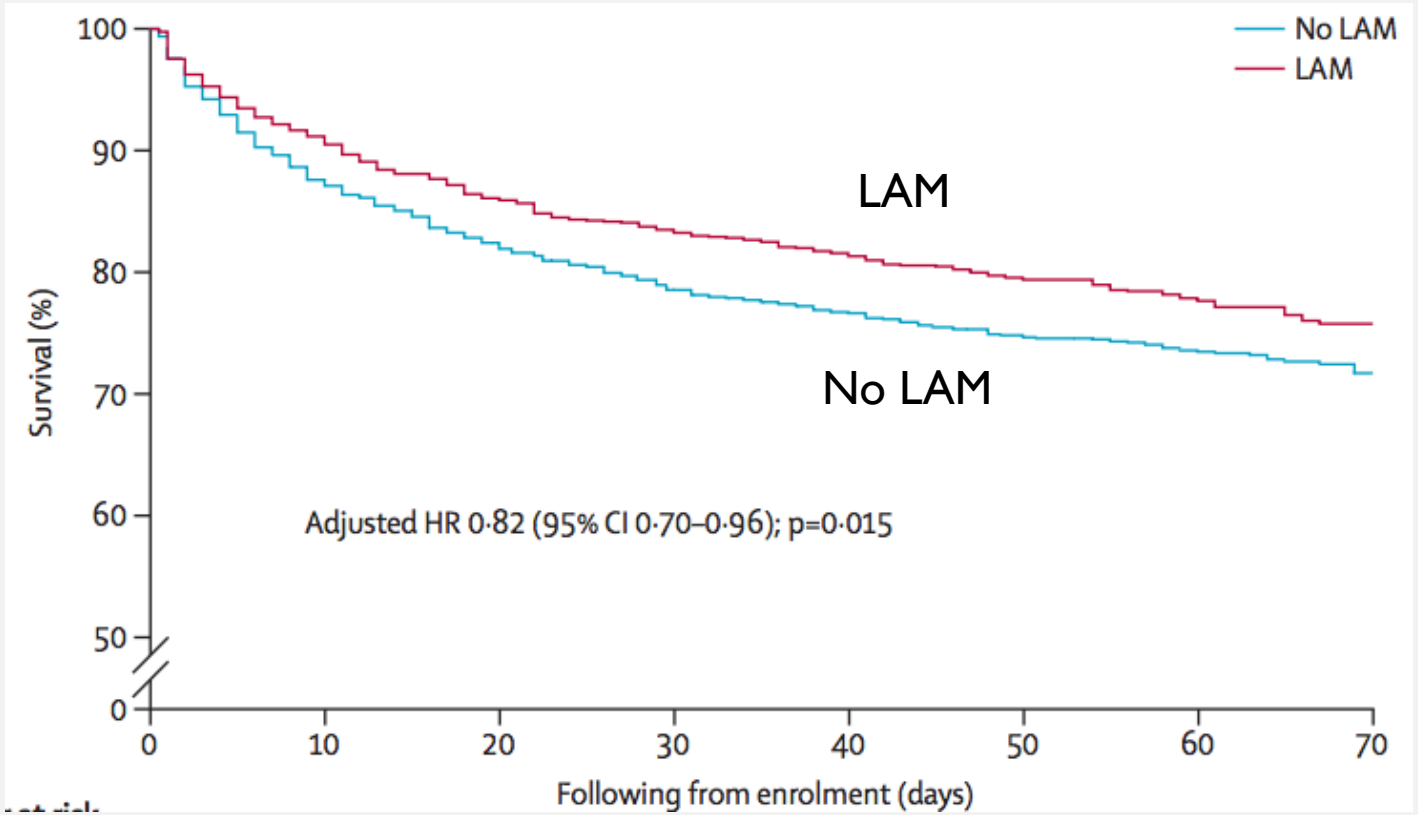
TB updates

TB DIAGNOSTICS IN ADVANCED HIV

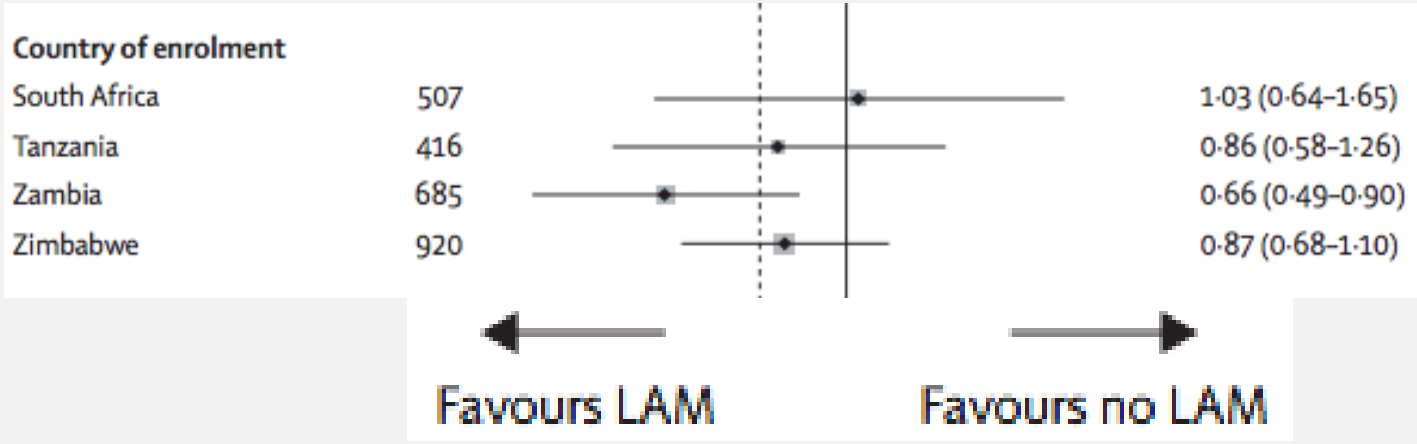
- It is difficult to diagnose TB in inpatients with advanced HIV however post mortem studies show that many with HIV still die with TB
- Alere Determine TB Ag lateral flow strip test is a bedside diagnostic using 60 ul of urine to detect lipoarabinomannan (LAM), a cell wall Ag
  - It is most sensitive at CD4 count <200 cells/ul
  - At <200 cells/ul = 50% sensitivity, 90% specificity
- HIV-infected TB suspected admitted to hospital
- In treatment arm, LAM added to routine TB work-up (smear, Xpert-MTB/RIF, and culture)
- By end of hospital day 1, in LAM group 55% started TB therapy vs 40% in no LAM group

Peter J et al Lancet 2015

Mortality improved by ~4% with LAM (8 w mort. 25% vs 21%)

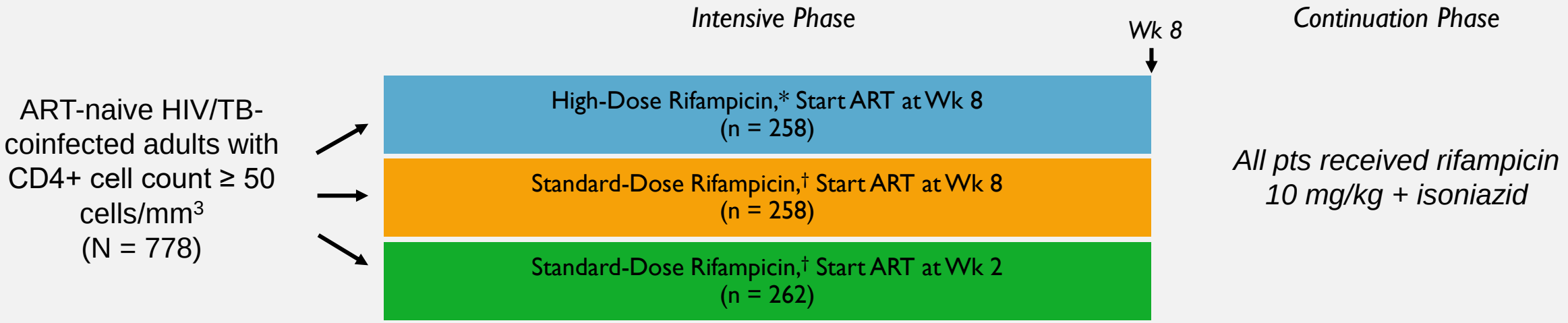


Effect size by country of implementation



RAFA: ART WITH STANDARD- VS HIGH-DOSE RIFAMPICIN IN HIV/TB-COINFECTED PTS

- Multicenter, open-label, randomized phase III trial
  - Pts in Benin, Guinea, and Senegal
  - Primary outcome: mortality at 12 mos post-randomization



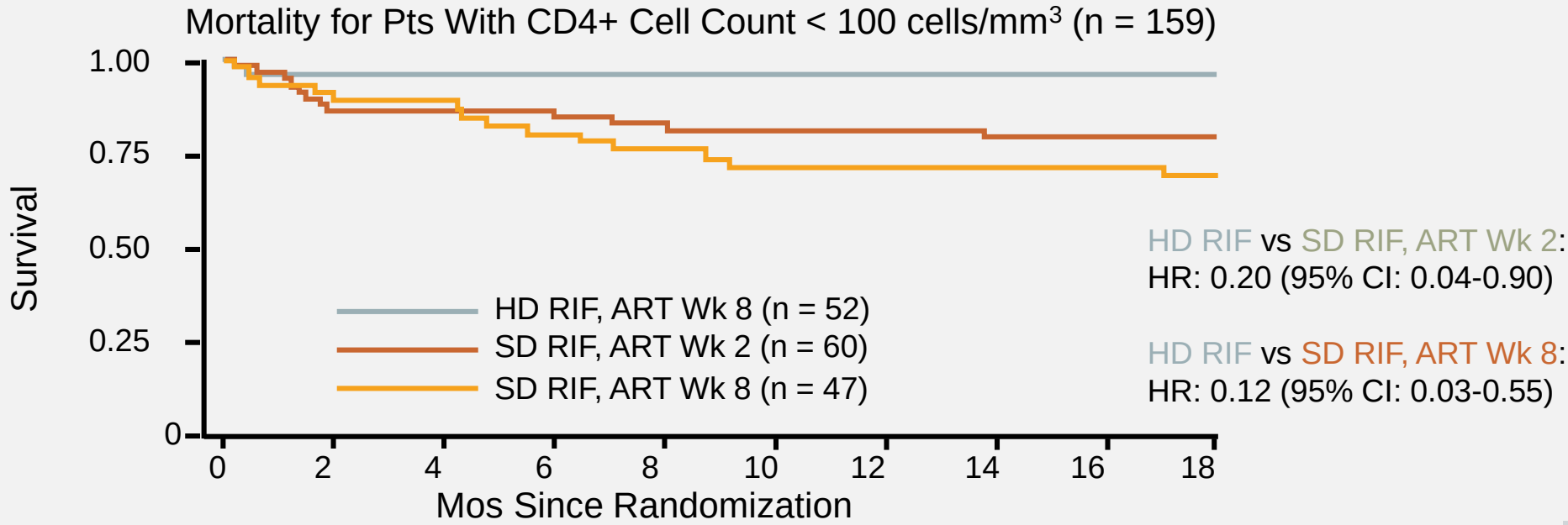
*Rifampicin 15 mg/kg plus ethambutol, isoniazid, pyrazinamide.
†Rifampicin 10 mg/kg plus ethambutol, isoniazid, pyrazinamide.
ART regimen: EFV 600 mg + 2 NRTIs.

Merle CS, et al. AIDS 2016. Abstract WEAB0205LB.
Pactr.org. PACTR201105000291300. EDCTP Project Portfolio.

RAFA: SURVIVAL OUTCOMES WITH HIGH- VS STANDARD-DOSE RIFAMPICIN

- Overall survival not improved, but high-dose rifampicin may benefit severely immunocompromised pts

Overall Survival, %	HD RIF, ART Wk 8 (n = 249)	SD RIF, ART Wk 8 (n = 247)	SD RIF, ART Wk 2 (n = 251)
12 mos	90	86	89
18 mos	90	85	88



Merle CS, et al. AIDS 2016. Abstract WEAB0205LB.
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Slide credit: clinicaloptions.com

Bacterial pneumonia updates

WHAT IS THE MOST COMMON CAUSE OF BACTERIAL PNEUMONIA IN HIV?

1. *Streptococcus pneumoniae*
2. *Staph. aureus*
3. *Pseudomonas aeruginosa*
4. *Legionella* spp.

PROSPECTIVE STUDY OF PNEUMONIA IN HIV-INFECTED PATIENTS ADMITTED IN MALAWI

- HIV-infected patients with pneumonia and symptoms of <14 days prospectively enrolled
- Patients underwent a protocolized work-up
- Median CD4 ~100 cells/ul

Figure 1. Overview of study procedures

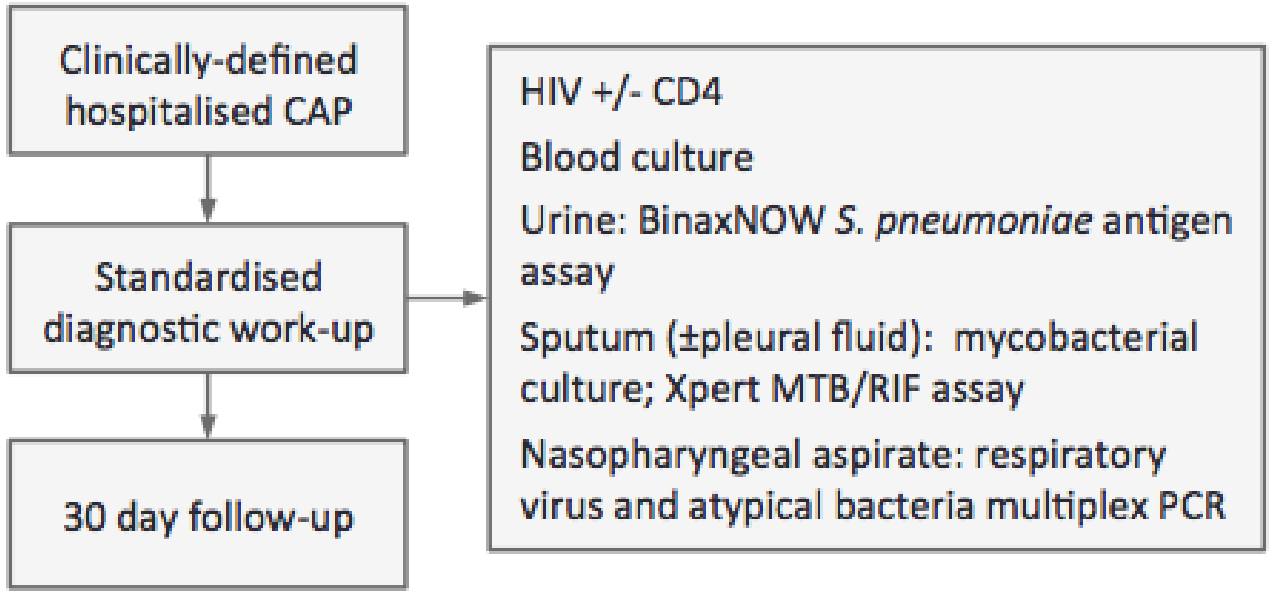
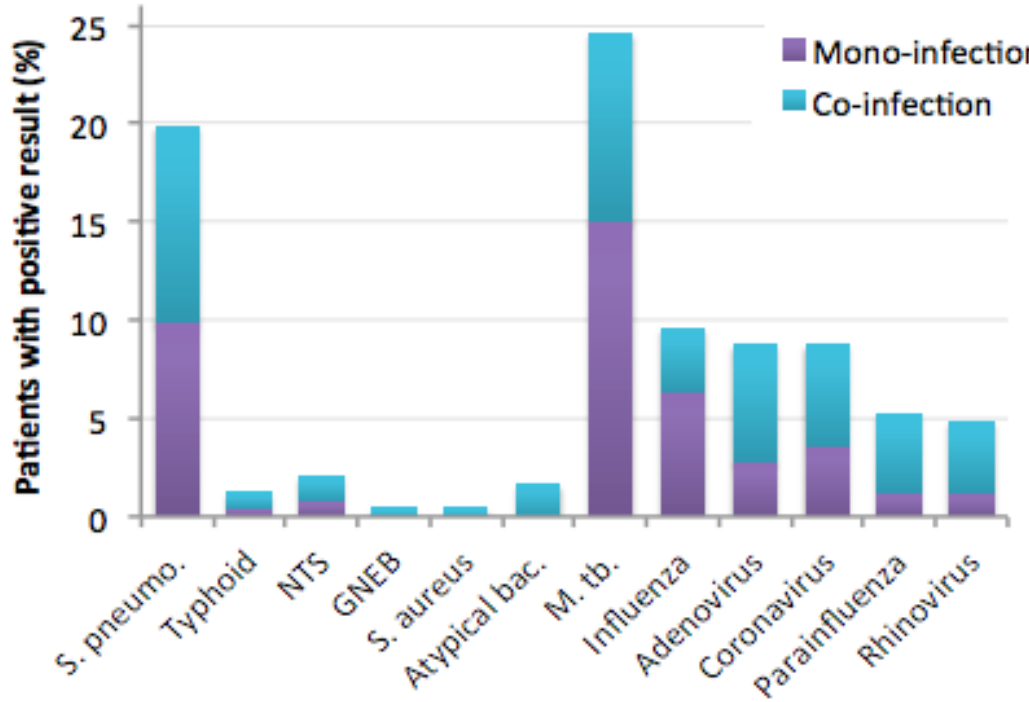


Figure 3. Frequency of specific organism detection alone or in combination



- The top 3 etiologies were *S. pneumoniae* (19%), *M. tuberculosis* (25%) and influenza (9%). Coinfection was common.
- 2/3 are potentially vaccine preventable
- *M. tuberculosis* is an important cause of <u>acute</u> presentations and linked with incr. 30 d mortality
  - Patients with *S pneumoniae* or influenza had low mortality

CROI 2015 Aston et. al.

DISTINGUISHING BACTERIAL PNEUMONIA

Features favoring bacterial pneumonia:

- Leukocytosis
  - Most patients have leukocytosis or relative leukocytosis
- Lobar or segmental infiltrates most common
  - Hilar or other LAN uncommon
  - Bilateral infiltrates with reduced O2 saturation occurs but less common
- AFB, XPERT MTB/RIF and urine LAM negative

If no response in 48 hours, consider:

- Patient not receiving drug
- Coinfection such as TB, PCP, or fungi
- Infected collection (e.g. empyema)
- Antibiotic resistant or difficult bug (e.g. MRSA, ESBL-producer, *Pseud.*)
- Non infectious (e.g lymphoma or KS, VTE)

McCord Hospital ward

MANAGEMENT OF COMMUNITY ACQUIRED PNEUMONIA: A BETA-LACTAM ALONE?

- Guidelines have for years recommended a beta-lactam + macrolide (BLM) or fluoroquinolone (FQ) based on limited data
- In the Netherlands a trial compared: (1) beta-lactam monotherapy (2) BLM and (2) FQ for non ICU patients admitted with pneumonia
- Crude mortality for 90 days of follow-up:
  - Beta-lactam monotherapy 9%
  - Beta-lactam + macrolide 11.1%
  - FQ 8.8%
- Results indicated non-inferiority at 3% margin.
- *But nearly 40% of patients in the beta-lactam monotherapy group received coverage for atypical organisms during hospital period*

<u>Management initially?</u>

- Beta-lactam +/- macrolide
  - Ex. ceftriaxone 2 g/day +/- azithromycin 500 mg/day
- Avoid FQs given potential for misleading initial improvement in TB and risk for acquired resistance (10%)
- If PCP is considered: combination of beta-lactam PLUS high dose TMP-SMX PLUS corticosteroids reasonable
- If neutropenia or very severe pneumonia, coverage for *Pseudomonas* +/- MRSA reasonable

Postma D et al NEJM 2015

TRIAGE AND MANAGEMENT

- Most patients with with HIV and pneumonia should be admitted, especially in presence of abnormal vitals or hypoxemia.
- Validated prediction tools for HIV patients admitted with LRTI in developing countries lacking
- Role for procalcitonin? May be a strong independent predictor of inpatient mortality in HIV
  - In Uganda, admitted HIV patients (N=241, median CD4 47) underwent smear, x-ray and if initial tests (-), bronchoscopy
  - Final diagnoses: TB 72%, bacterial pneumonia 12%, fungal pneumonia or PCP 6%, pulmonary KS 3%

Oxygen saturation <90%	Respiratory rate ≥30 breaths/minute	Procalcitonin ≤0.5ng/ml		Procalcitonin >0.5ng/ml		p-value
		Mean PP* (95%CI)	n	Mean PP* (95%CI)	n	
No	No	1% (0.3–6)	51	10% (6–17)	98	0.004
Yes	No	4% (1–19)	5	26% (11–49)	8	0.32
No	Yes	3% (1–13)	15	19% (10–33)	36	0.25
Yes	Yes	9% (2–30)	7	42% (24–62)	17	0.17

ART INITIATION IN THE HOSPITAL

ART IN ADVANCED HIV
PRACTICAL FACTORS TO CONSIDER

- Drug-drug interactions between OI treatment and ART
  - Particularly with boosted PIs
  - Univ. of Liverpool has nice interaction algorithm: http://www.hiv-druginteractions.org
- Ability to swallow pills
  - There are few fully liquid regimens however potential options exist
  - See Univ. of Liverpool web site for dosing liquid formul. dosing in adults
- Renal impairment
  - Patients with renal impairment at increased risk for TDF-induced nephrotoxicity.
- Attributing causation when adverse events arise
  - Ex. A patient receiving RIPE for TB develops hepatitis after ART initiation (EFV-TDF-FTC)
  - Ex. A patient receiving high dose TMP-SMX develops rash after ART initiation (EFV-TDF-FTC)

TIMING OF ART AFTER OI

*There is some clear guidance from randomized trials * :*

	When to start ART?
• TB (non CNS) in patients with CD4< 50 cells/ul *	Within 2 weeks
• PCP,* bacterial pneumonia	Within 2 weeks or in ICU
• OI with no effective specific therapy (Ex. chronic diarrhea)	Within 2 weeks
• Lymphoma or KS anticipating chemotherapy	Within 2 weeks
• TB in patients with CD4> 50 cells/ul*	Within 4 weeks

CNS OIs

• Cryptococcal meningitis *	Defer until 5 weeks
• TB meningitis	Unknown, consider defer until 5 wks

OI Guidelines DHHS 2016

OUTCOMES AMONG PATIENTS ADMITTED WITH ACUTE OI: MCCORD HOSPITAL 2006-7

- Consecutive ART naïve HIV-infected patients discharged after OI prospectively followed
- The median CD4 cell count was 42 cells/ul

Prevalent OIs:

- Extrapulm. TB (38%)
- Pulmonary TB (28%)
- *Pneumocystis* pneumonia (8%)
- Chronic diarrhea (8%)
- Crypto. meningitis (6%)
- *Toxoplasmosis gondii* (4%)
- Other/unknown (8%)

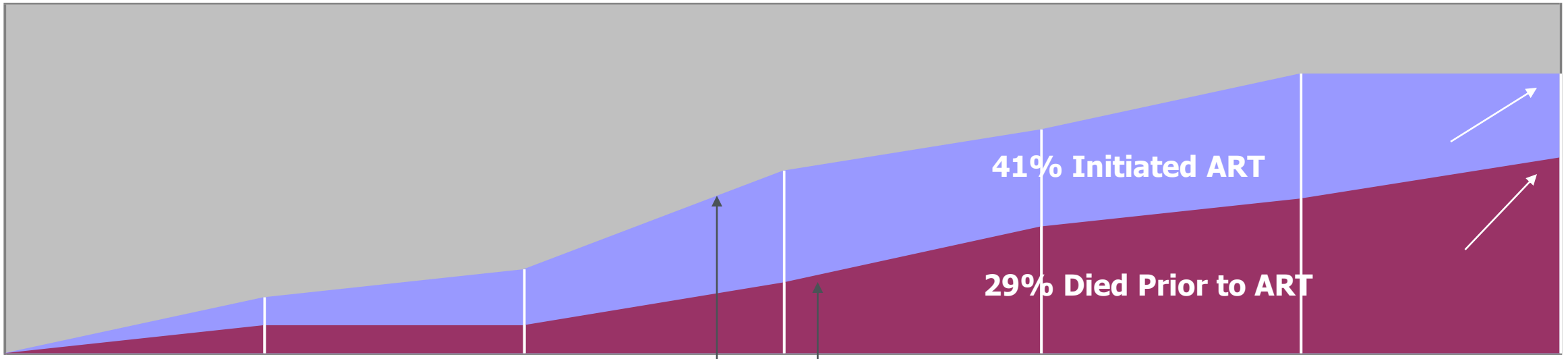
Results:

- ART initiation by 6 months associated with less advanced HIV infection;
- CD4 < 50 associated with not initiating ART within 6 months of discharge.

Sunpath H *et al* Int J TB Lung 2011

WHAT HAPPENED TO HIV PATIENTS AFTER ACUTE OI IN 2007?

Trajectory After Discharge, McCord Hospital, Durban



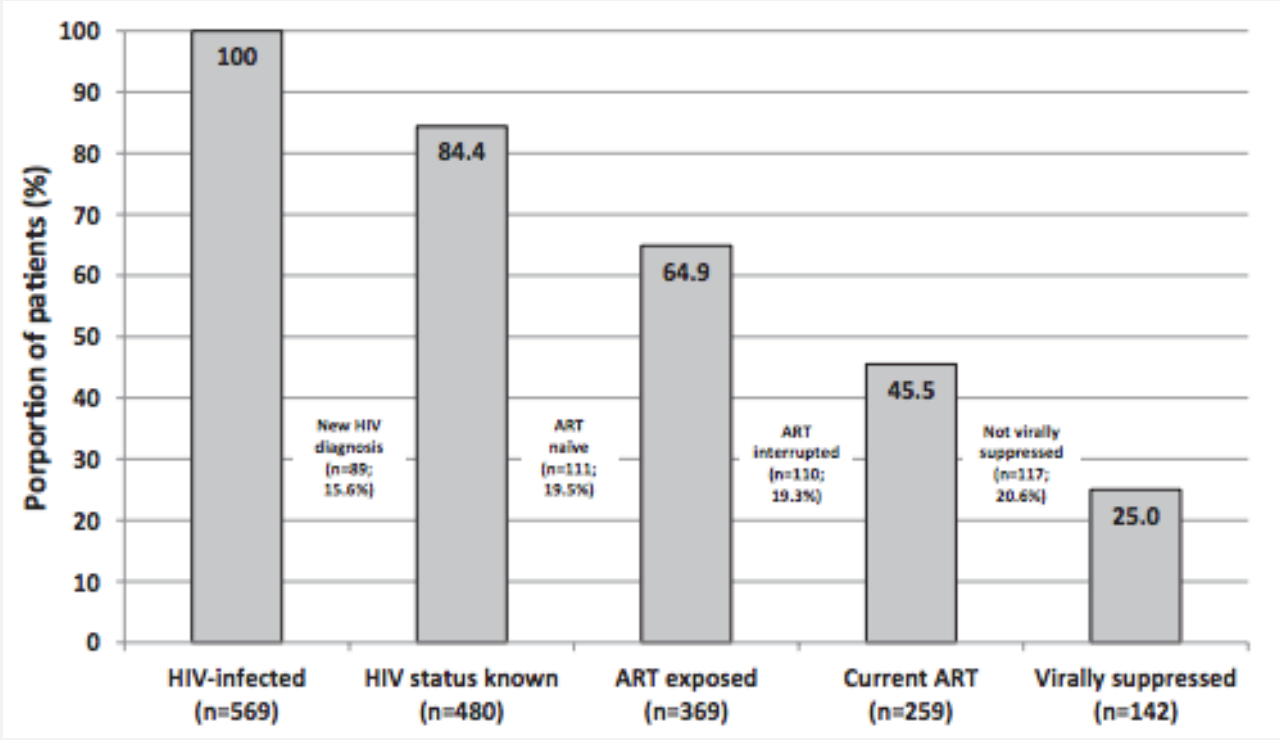
Sunpath H *et al* Int J TB Lung 2011

CF JOOSTE HOSPITAL EXPERIENCE 2012-13

- Follow-up of hospitalized HIV patients recruited day 4
- Most common condition was newly diagnosed TB
  - 15% had a neurological diagnosis most often TB-M or CM
  - Clinical deterioration on or AE to TB therapy also common
- 45% were receiving ART at admission
- About 15% had a new HIV diagnosis; median CD4 cell count in this group was 123 cells/ul
- 6 m mortality: CF Jooste 18%
- Mortality RFs: low Hb, reduced GFR and OI other than TB – especially neurological diagnosis

Meintjes G, *et al.* Medicine (Baltimore) 2015

Status in the care cascade on the day of admission



SIYAPHILA: AN INPATIENT ART PROGRAM

Patients admitted with HIV and concurrent TB or other OI initiated on early inpatient ART (N=382).

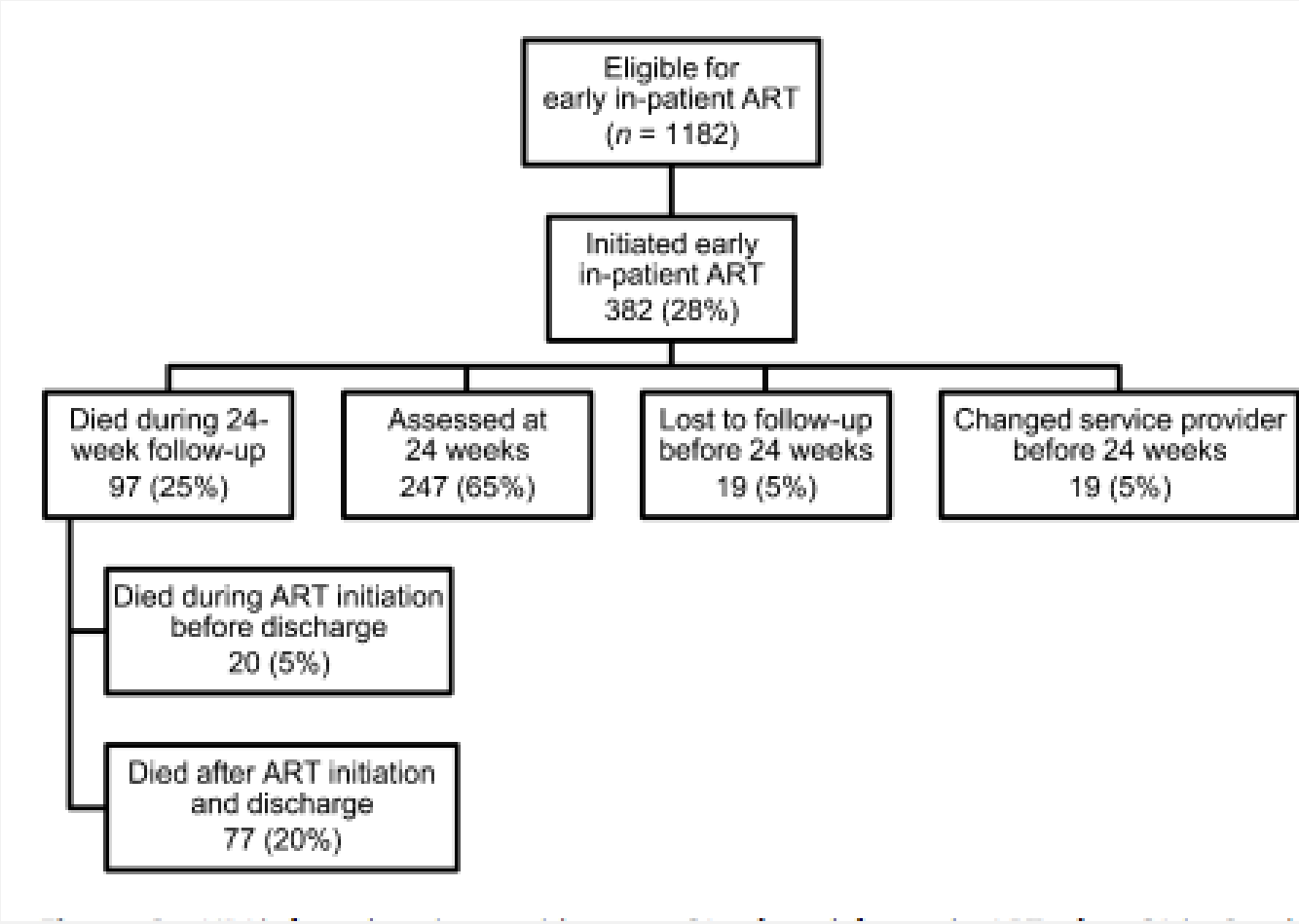
- 48% women with median CD4 count 33 cells/ul
- The median time from admission to ART start was 14 days (range 4–32, IQR 11–18)

<u>Outcomes:</u>

At 24 weeks of follow-up:

- Virol. suppression 93% with median change in CD4 count of +100 cells/ul
- Overall 24-week mort. was 25% with 5% LTFU

- Risk factors for mortality: >21 day delay prior to ART and age > 40 years



Sunpath H, Int J Tuberc Lung Dis. 2012 Jul;16(7):917-23.

WHAT IS MOST EFFECTIVE INITIAL ART FOR PATIENT WITH RECENT OI WITH CD4<200 AND VIRAL LOAD > 100,000 COPIES?

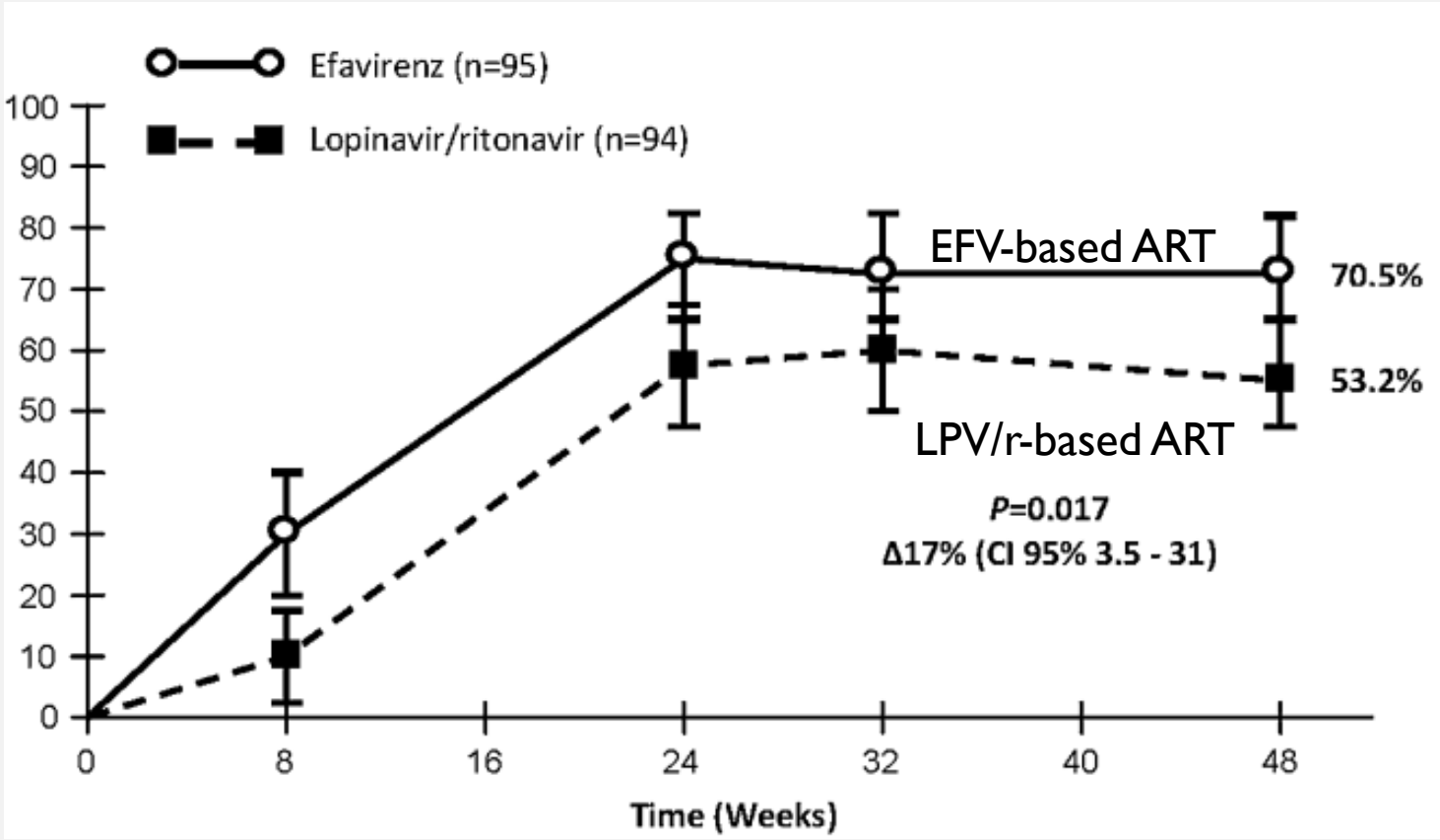
1. Boosted-PI regimen
2. NNRTI-based regimen
3. Triple NRTI regimen

BOOSTED PI OR EFV-BASED ART IN ADVANCED DISEASE?

Clinicians commonly reach for boosted protease inhibitor-based regimens in advanced HIV

What is actual data?

- ART naïve CD4 < 200 randomized to AZT/3TC + LPV/r or EFV
- Median CD4 64 cells/ul, VL > 75,000 in majority
- If OI present, ART initiated after OI therapy. TB patients excluded.
- At week 48, 70% of EFV and 53% of LPV/r patients achieved <50 copies/mL (P = 0.013)

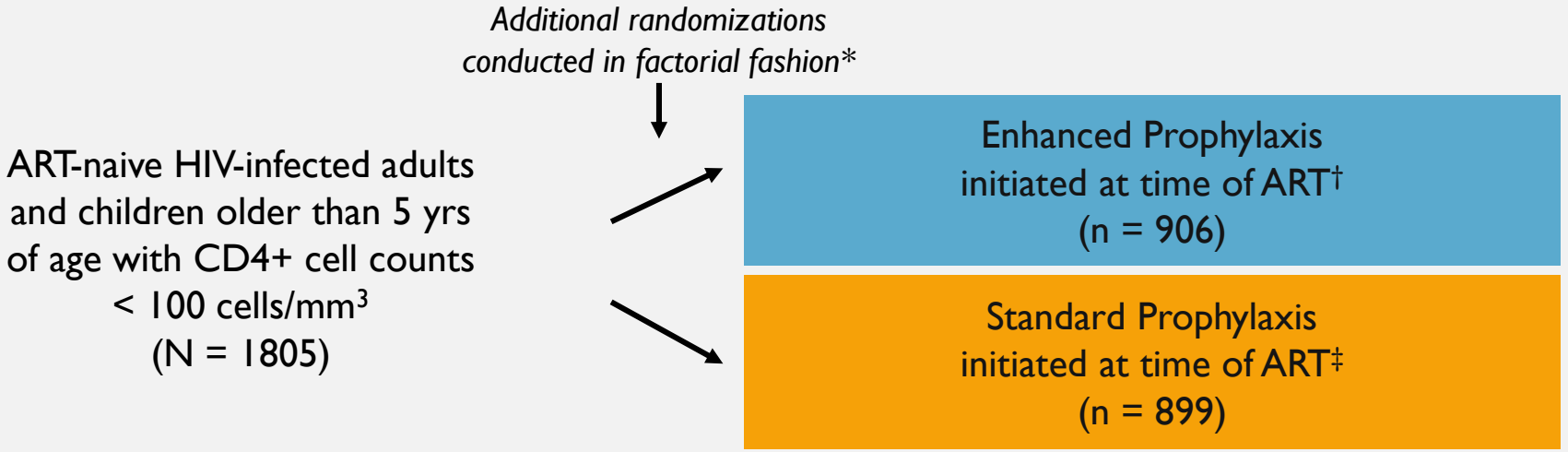


Sierra-Madero J et al JAIDS 2010

OI prophylaxis updates

REALITY: ENHANCED OI PROPHYLAXIS AT ART INITIATION IN IMMUNOCOMPROMISED PTS

- Prospective, randomized trial conducted in Zimbabwe, Malawi, Uganda, and Kenya
  - Primary endpoint: mortality at 24 wks
- Enhanced prophylaxis: STD + fluconazole 100 mg/day, azithromycin 500 mg/day x 5 days, albendazole x 1



*Raltegravir added to ART for 12 wks; food supplementation for 12 wks.
†Cotrimoxazole, isoniazid/vitamin B6 300/25 mg/day for 12 wks (IPT), fluconazole 100 mg/day for 12 wks, azithromycin 500 mg/day for 5 days, albendazole 400 mg (single dose).
‡Cotrimoxazole, IPT added after 12 wks (except in Malawi).
In both prophylaxis regimens, cotrimoxazole and IPT given at half doses if younger than 12 yrs of age.

Hakim J, et al. AIDS 2016. Abstract FRAB0101LB.

Slide credit: clinicaloptions.com

REALITY: MORTALITY BENEFIT WITH ENHANCED OI PROPHYLAXIS FOR PTS INITIATING ART

Deaths, %[1]	Enhanced Prophylaxis (n = 906)	Standard Prophylaxis (n = 899)	HR (95% CI)	*P* Value
Wk 24*	8.9	12.2	0.73 (0.54-0.97)	.03
Wk 48	11.0	14.4	0.75 (0.58-0.98)	.04

*Primary endpoint.

- 3.3 lives saved for every 100 treated with enhanced prophylaxis[1]

1. Hakim J, et al. AIDS 2016. Abstract FRAB0101LB.
2. Kityo C, et al. AIDS 2016. Abstract FRAB0102LB.

PREVENTING PNEUMONIA

- Pneumococcal vaccination:
  - *For vaccine-naïve patients:*
    - Prevnar (PCV13) followed after 8 weeks by PPV23
  - *For vaccine-experienced patients:*
    - A single dose of Prevnar (PCV13) should be given ≥1 year after PPV23
- Influenza vaccination yearly
- TMP-SMX prophylaxis and ART also both reduce pneumonia risk considerably

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TAKE - AWAYS

- We continue to see OIs as initial HIV presentation and in those lost from care
- PCP patients with resp failure have survival ~50% with mechanical ventilation and – if performance status good – should be offered intensive care
- For CM, consider fluconazole 800 mg/day as consolidation therapy
- For CM, ICP management with therapeutic LPs is essential
- TB-M still difficult to diagnose / treat but CSF XPERT a promising diagnostic
- Enhanced OI prophylaxis improves survival if starting ART with CD4<100
- Early ART – including ART prior to hospital discharge – should be considered in PCP, TB, bacterial pneumonia, and chronic diarrhea or in HIV-associated malignancies but not in CNS OIs.
  - The first 6 months after discharge continues to be a very high risk period in SA

Thank you