An update on Opportunistic Infections

Sanjay Bhagani
Royal Free Hospital/UCL
London

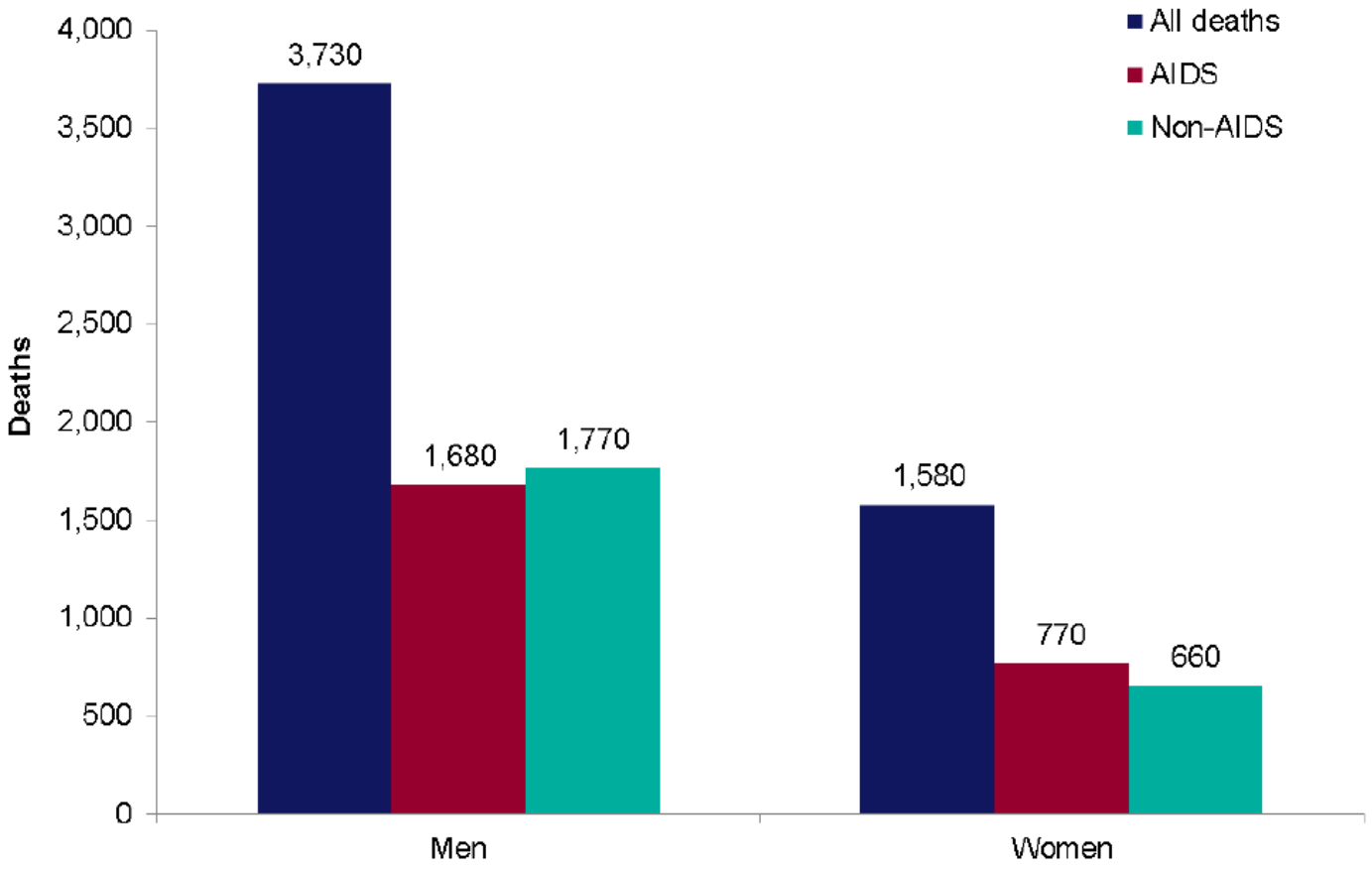
Royal Free London NHS Foundation Trust

NHS GreenShoots FOUNDATION

UCLPartners Academic Health Science Partnership

AIDS events still account for nearly 50% of deaths in the HIV population

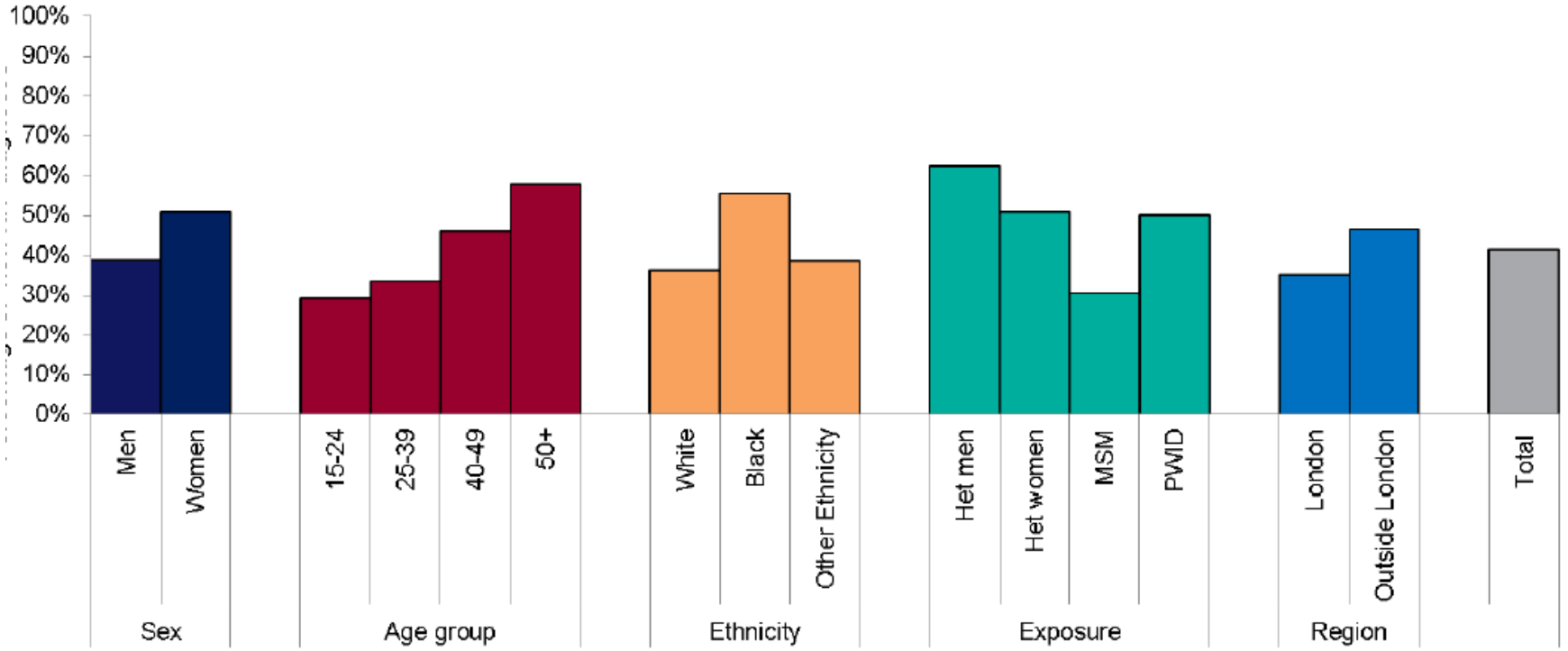
Figure 11: Deaths among adults diagnosed with HIV in the era of ART: England and Wales, 1997-2012



Yin Z, et al. HIV in the United Kingdom 2014 Report, PHE

Late diagnosis is still a major issue

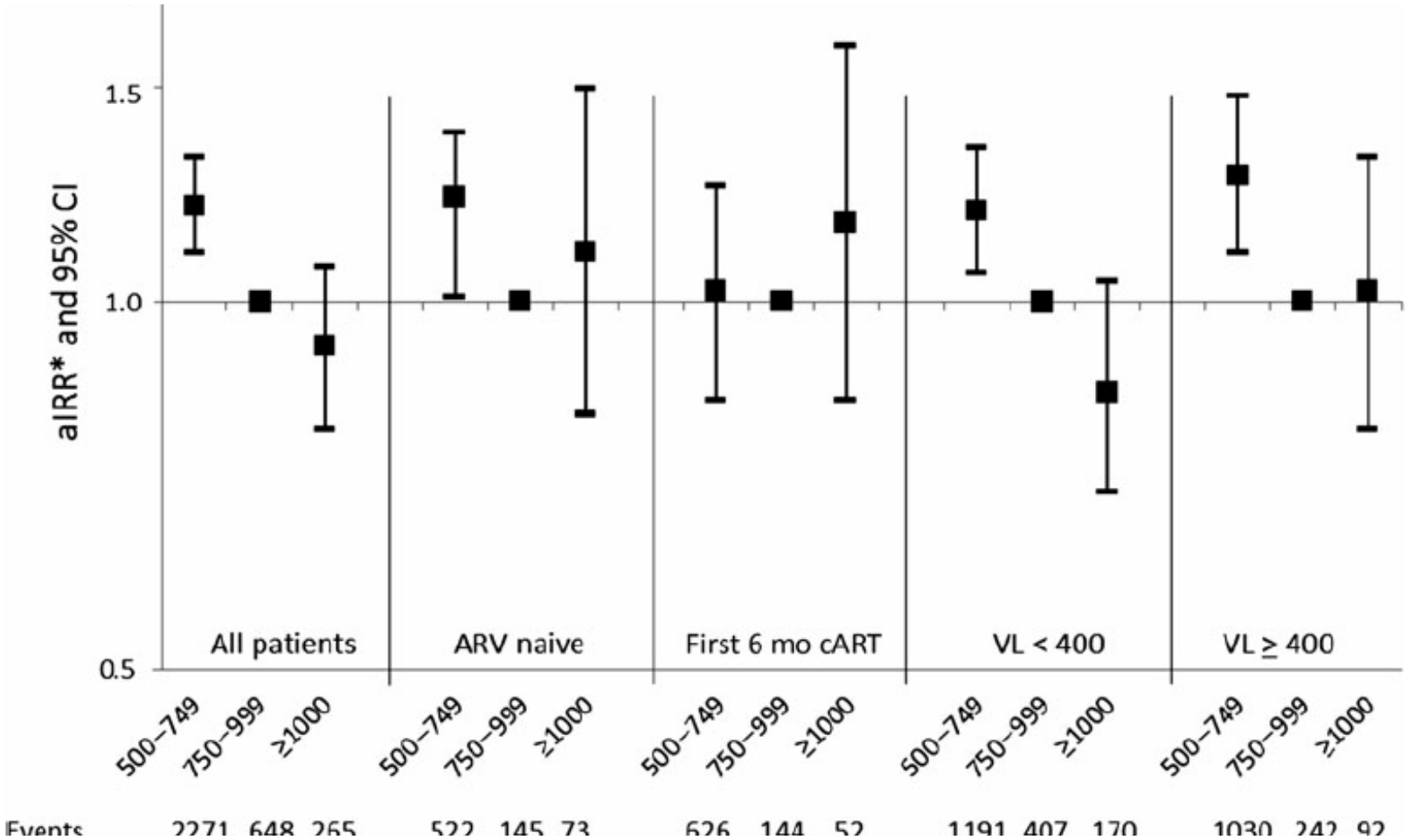
gure 9: Late diagnoses[1]: proportion of adults diagnosed with a CD4 count <350 lls/mm^3: UK, 2013



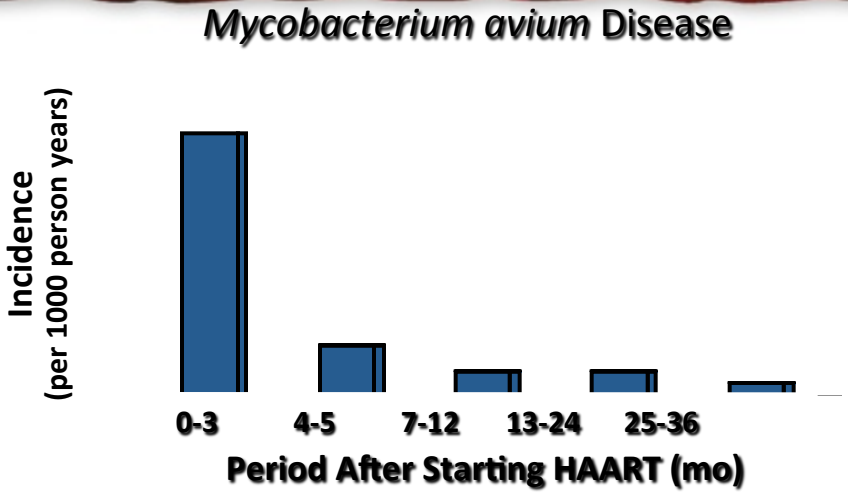
[1] CD4<350 cells/mm^3 within three months of diagnosis.

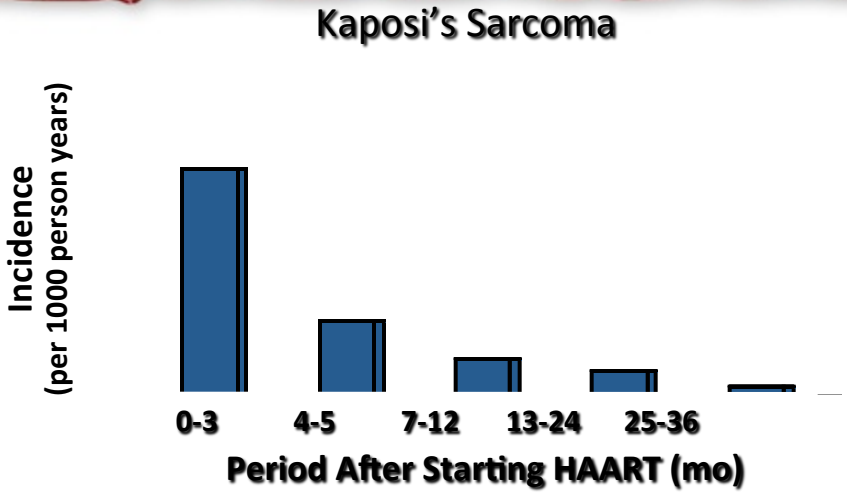
Yin Z, et al. HIV in the United Kingdom 2014 Report, PHE

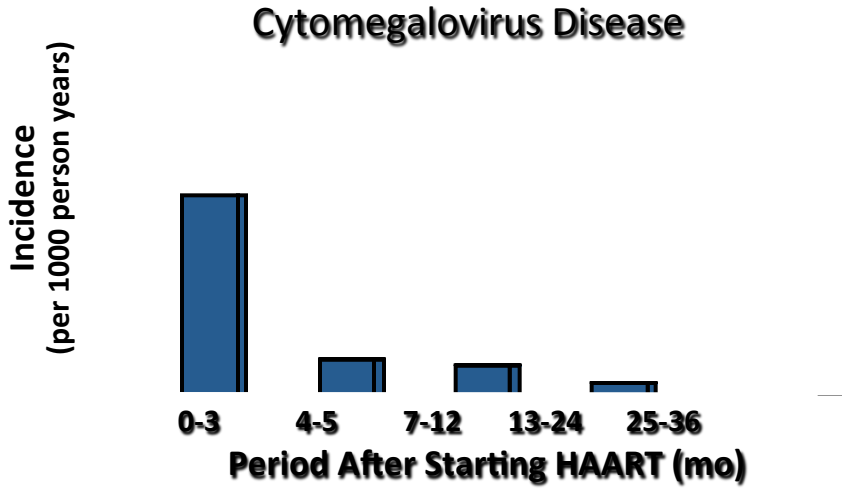
ADIs and OIs – not just a problem of late presentation

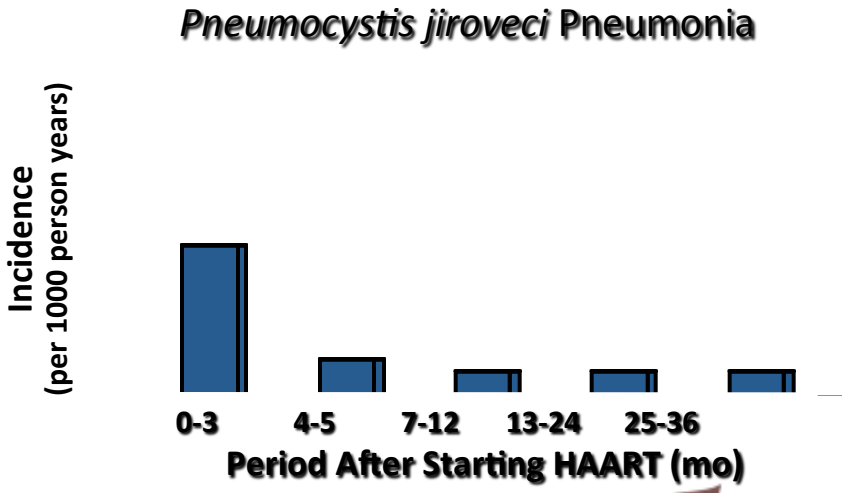


Incidence of AIDS-Defining Events After Initiation of cART









ART-CC: d'Arminio Monforte *et al. Arch Intern Med.* 2005

Managing OIs and prophylaxis

AIDSinfo

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

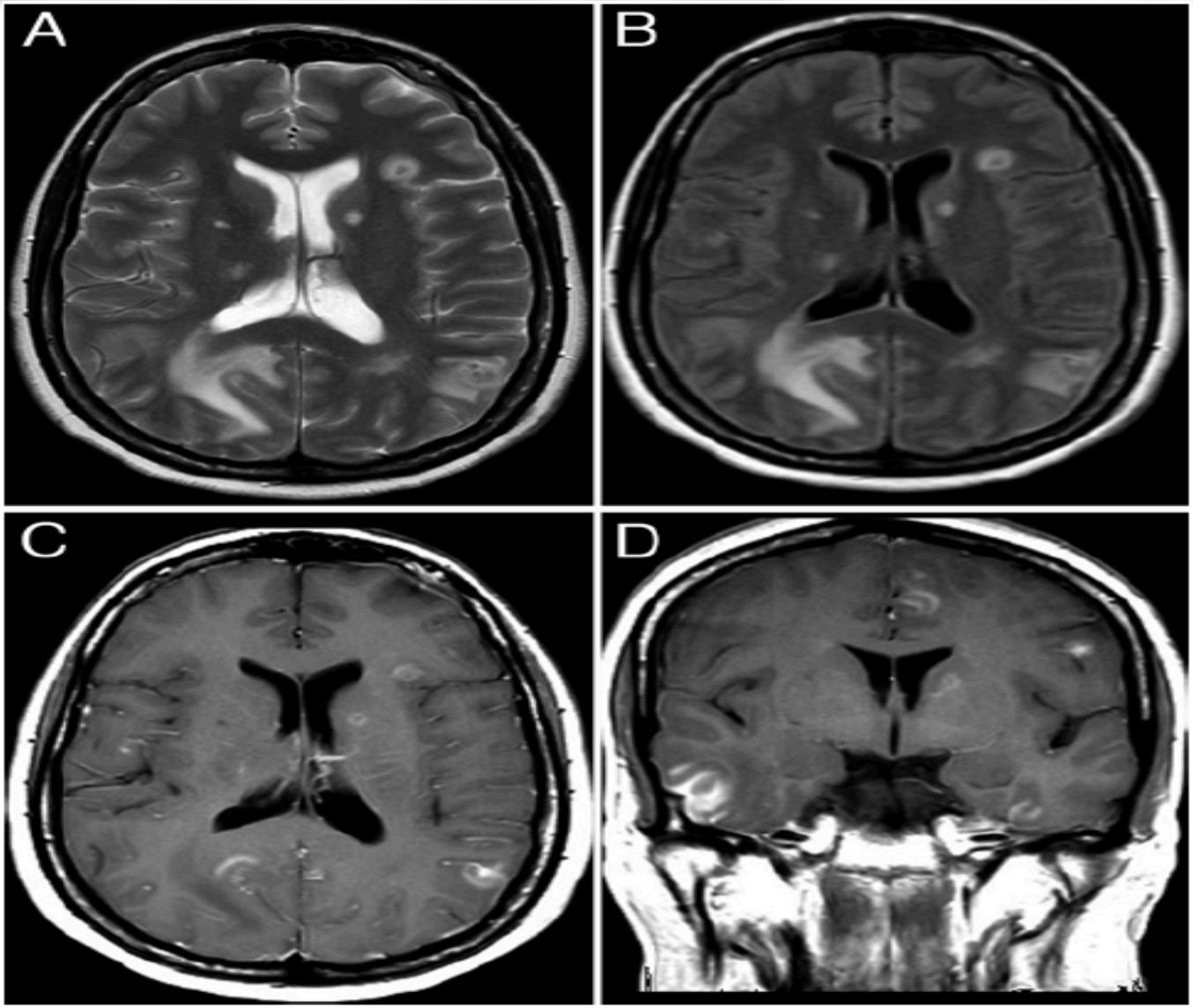
Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

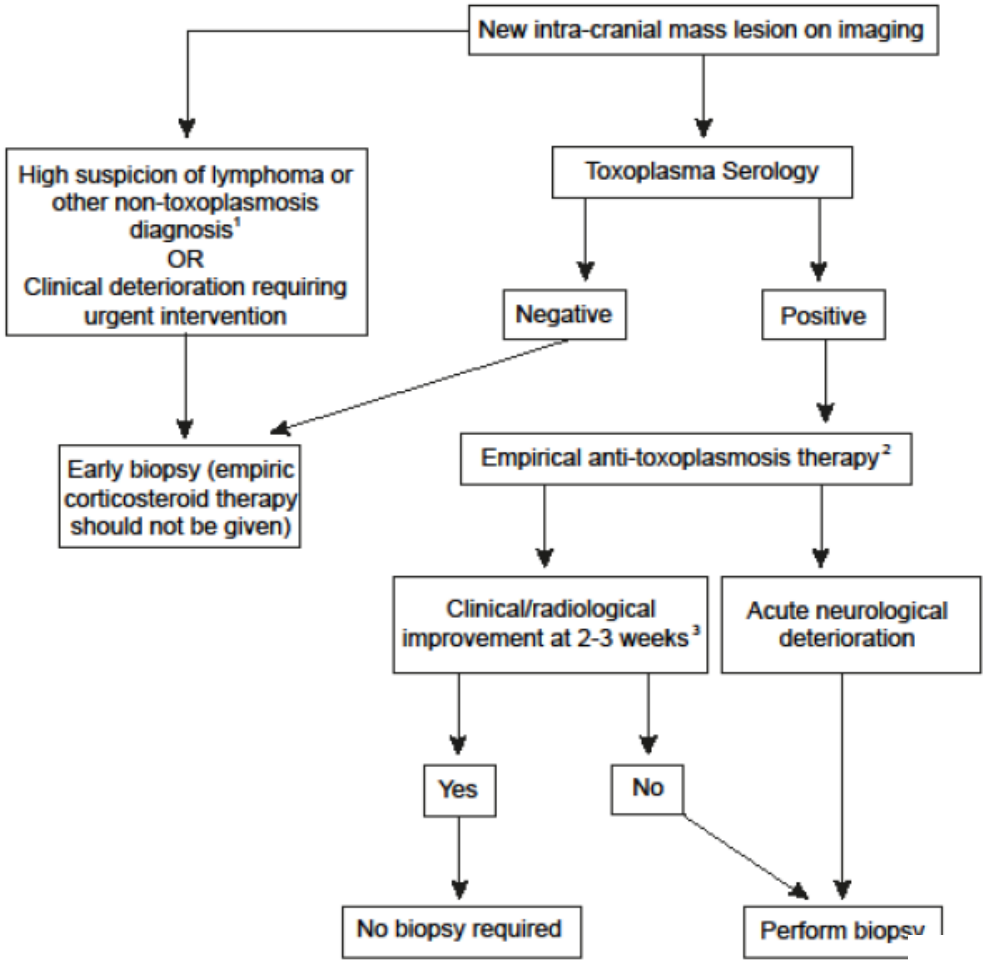
DOI: 10.1111/j.1468-1293.2011.00944.x
HIV Medicine (2011), 12 (Suppl. 2), 1–5

British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011

Empirical Rx or biopsy?



Managing CNS mass lesions – a neurosurgeon's perspective



Major Criteria

- Atypical imaging for toxoplasmosis
- Patient history atypical for cerebral toxoplasmosis

Minor Criteria

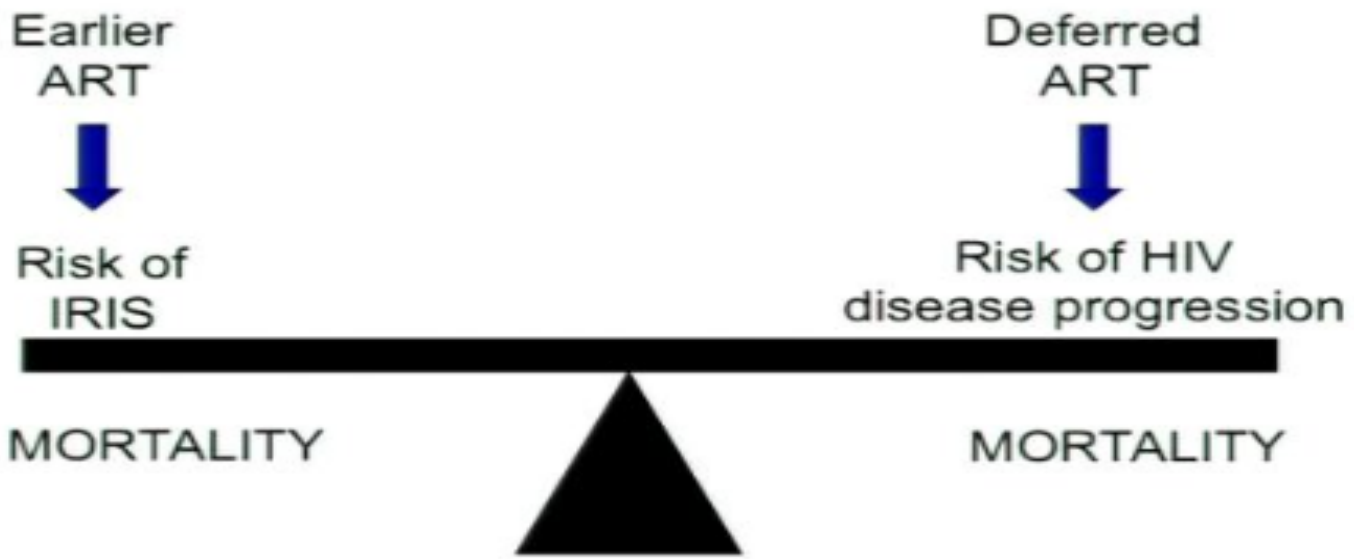
- Currently on Sulpha based Pneumocystis prophylaxis
- Positive CSF JC virus PCR
- Positive CSF EBV PCR
- CD4 count >200

Henderson, et al (J Neurosurgery 2016)

Key emerging issues

- Timing of cART in the context of OIs
  - CNS vs. non-CNS OIs
  - Focus on TB meningitis and cryptococcal meningitis
- Pre-emptive therapy to prevent morbidity/ mortality
  - Cryptococcal meningitis
  - CMV end-organ disease

When should we start ARVs in the context of an OI



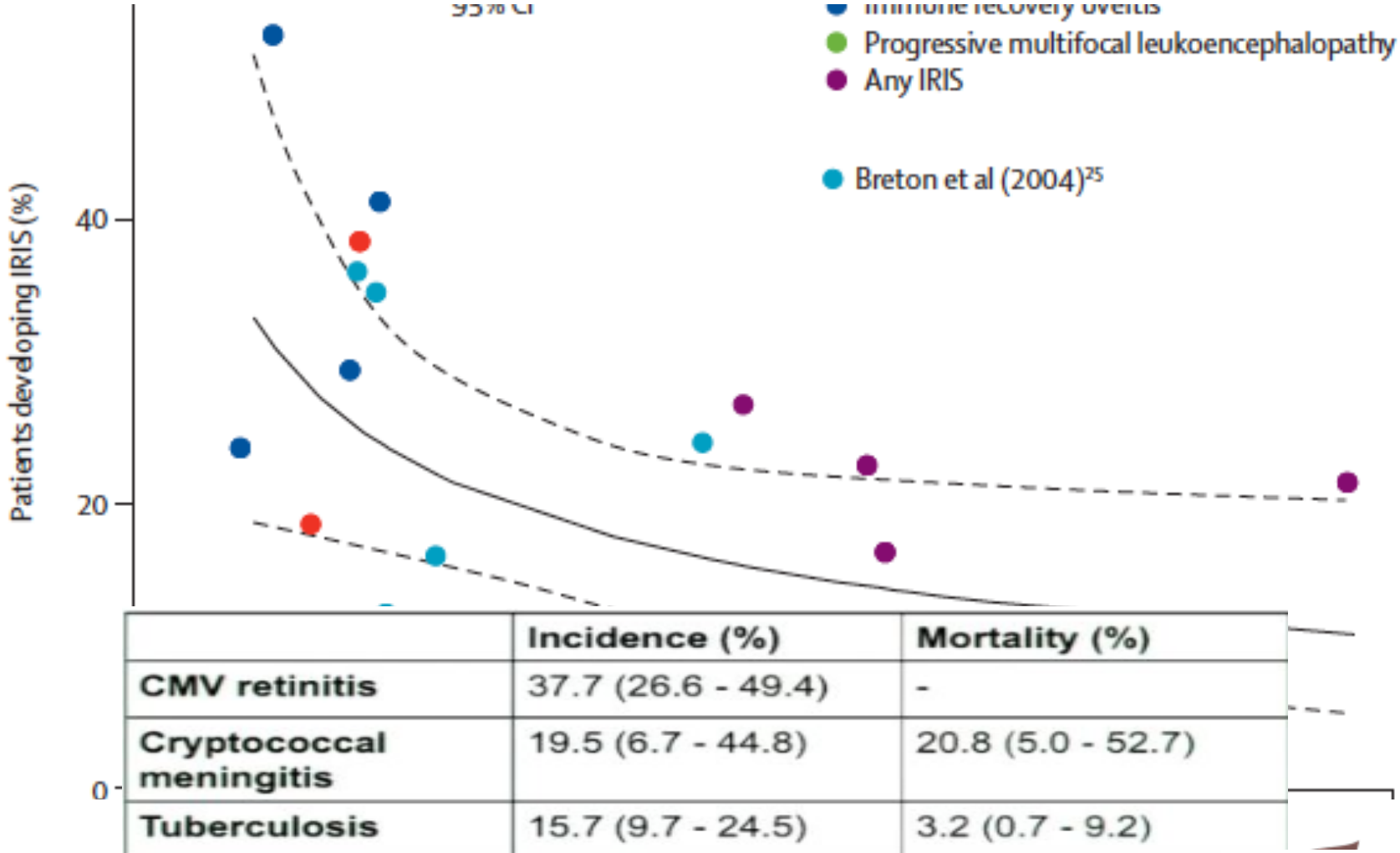
When to start ART after recent diagnosis of OI?

Box 1. Immune reconstitution inflammatory syndrome (IRIS): definitions [11]

- Early IRIS: appears during the first 3 months after the initiation of cART
- Late IRIS: appears from 3 months up to years after the initiation of cART
- Paradoxical IRIS: worsening of symptoms of a previously diagnosed OI for which the patient is receiving treatment
- Unmasking (or cART-related) IRIS: diagnosis of a new OI with inflammatory characteristics after the initiation of cART
- cART-associated OIs: diagnosis of a new OI after initiation of cART, but without clinical criteria for IRIS
- Infectious IRIS: atypical presentation of an already diagnosed or undiagnosed OI after the initiation of cART
- Sarcoid IRIS: granulomatous inflammation of the lungs, skin, kidney, liver or other organs with the characteristics of sarcoidosis; it is important to rule out infectious IRIS
- Autoimmune IRIS: autoimmune disease presenting for the first time or exacerbating after the initiation of cART

cART: Combined antiretroviral treatment; IRIS: Immune reconstitution inflammatory syndrome; OIs: Opportunistic infections.

Risk of IRS and IRS associated deaths

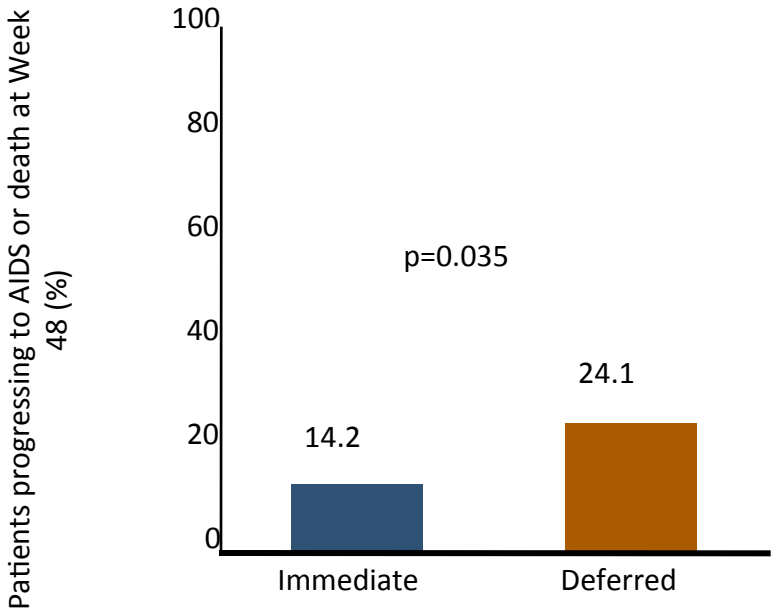


	Incidence (%)	Mortality (%)
CMV retinitis	37.7 (26.6 - 49.4)	-
Cryptococcal meningitis	19.5 (6.7 - 44.8)	20.8 (5.0 - 52.7)
Tuberculosis	15.7 (9.7 - 24.5)	3.2 (0.7 - 9.2)
PML	16.7 (2.3 - 50.7)	-

Lancet ID, 2010: 10: 251

ACTG 5164: Improved outcomes with immediate ART during acute OI

- 92% treatment naïve
  - Median baseline CD4+ cell count 29 cells/mm^3; HIV-1 RNA 5.07 log_{10} copies/mL
- OIs with effective antimicrobial therapy only: PCP, bacterial infections, cryptococcal disease, MAC, toxoplasmosis
- Median duration from start of OI treatment to initiation of HAART
  - Immediate group: 12 days
  - Deferred group: 45 days



- Week 48 virologic outcomes similar between groups
- Safety and incidence of IRIS similar between groups

Adapted from: Zolopa A, et al. CROI 2008; Abstract 142

Timing of Initiation of ART for Patients with TB and HIV

SAPIT trial

- Concurrent TB and HIV treatment reduces mortality
- Improved survival in patients with high or low CD4 counts

CAMELIA, STRIDE, and SAPIT trials

- Starting ART within 2 weeks of TB treatment may reduce risk of mortality or AIDS-defining illnesses
- Benefit seen among those with CD4<50 cells/mm^3

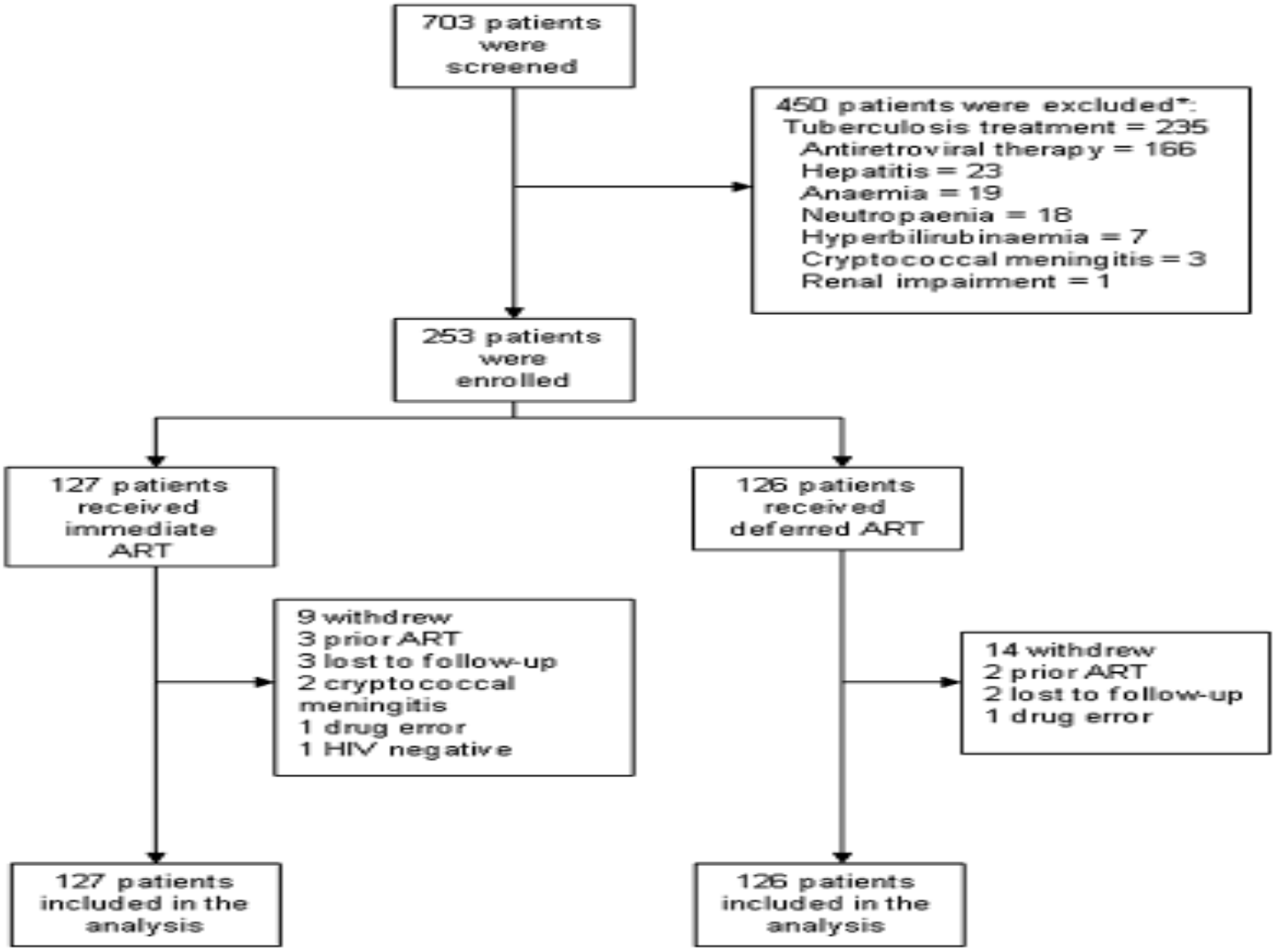
Abdool Karim S et al. (2010) NEJM 362: 697;
NEJM (2011) 365 – Blanc et al., Havlir et al., Abdool Karim et al.

When to start HAART in TB/ HIV

CD4 count, cells/µL	When to start HAART
<100	As soon as practical
100–350	As soon as practical, but can wait until after completing 2 months TB treatment especially when there are difficulties with drug interactions, adherence and toxicities
>350	At physician discretion

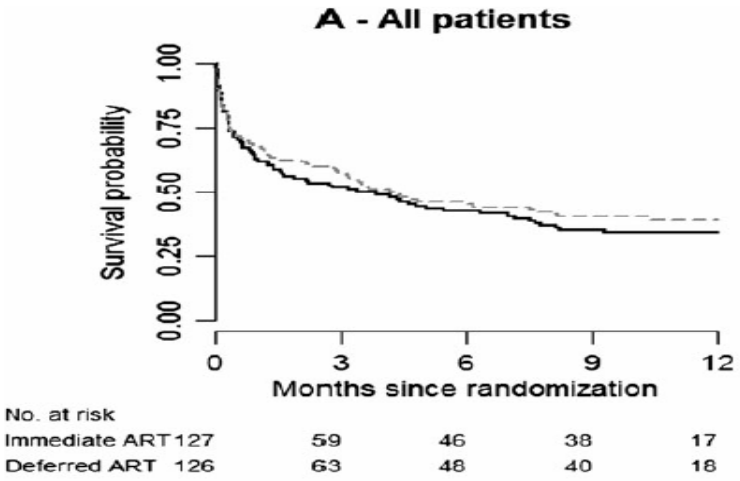
BHIVA TB-coinfection Guidelines, 2011

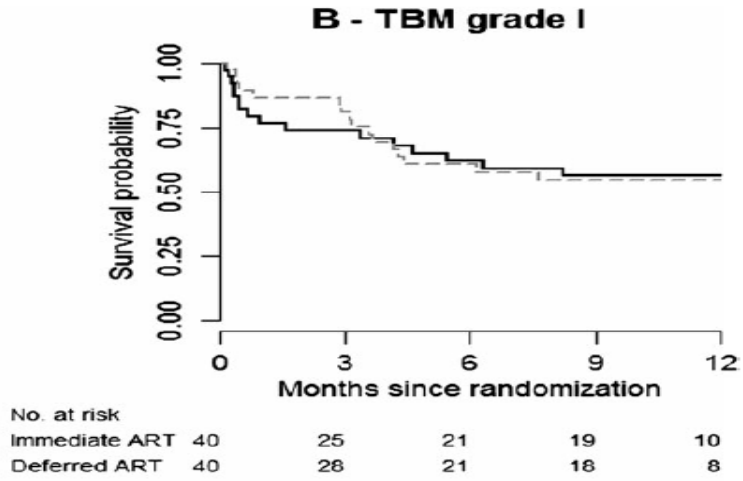
TB Meningitis – Vietnam RCT

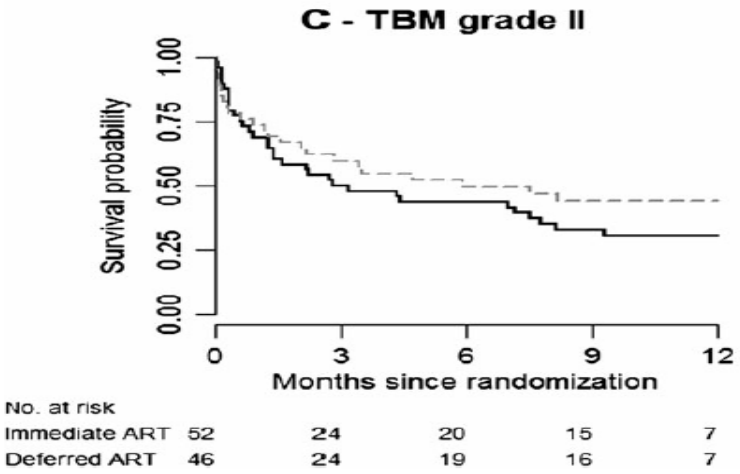


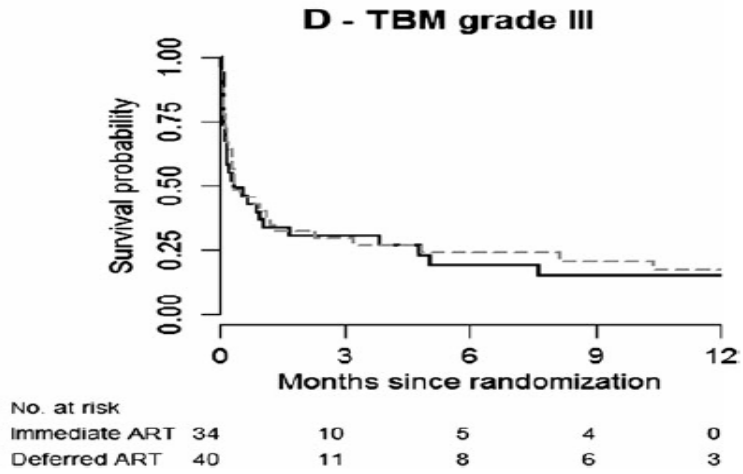
Torok, et al. CID 2011; 52: 1374

TB meningitis – the Vietnam experience





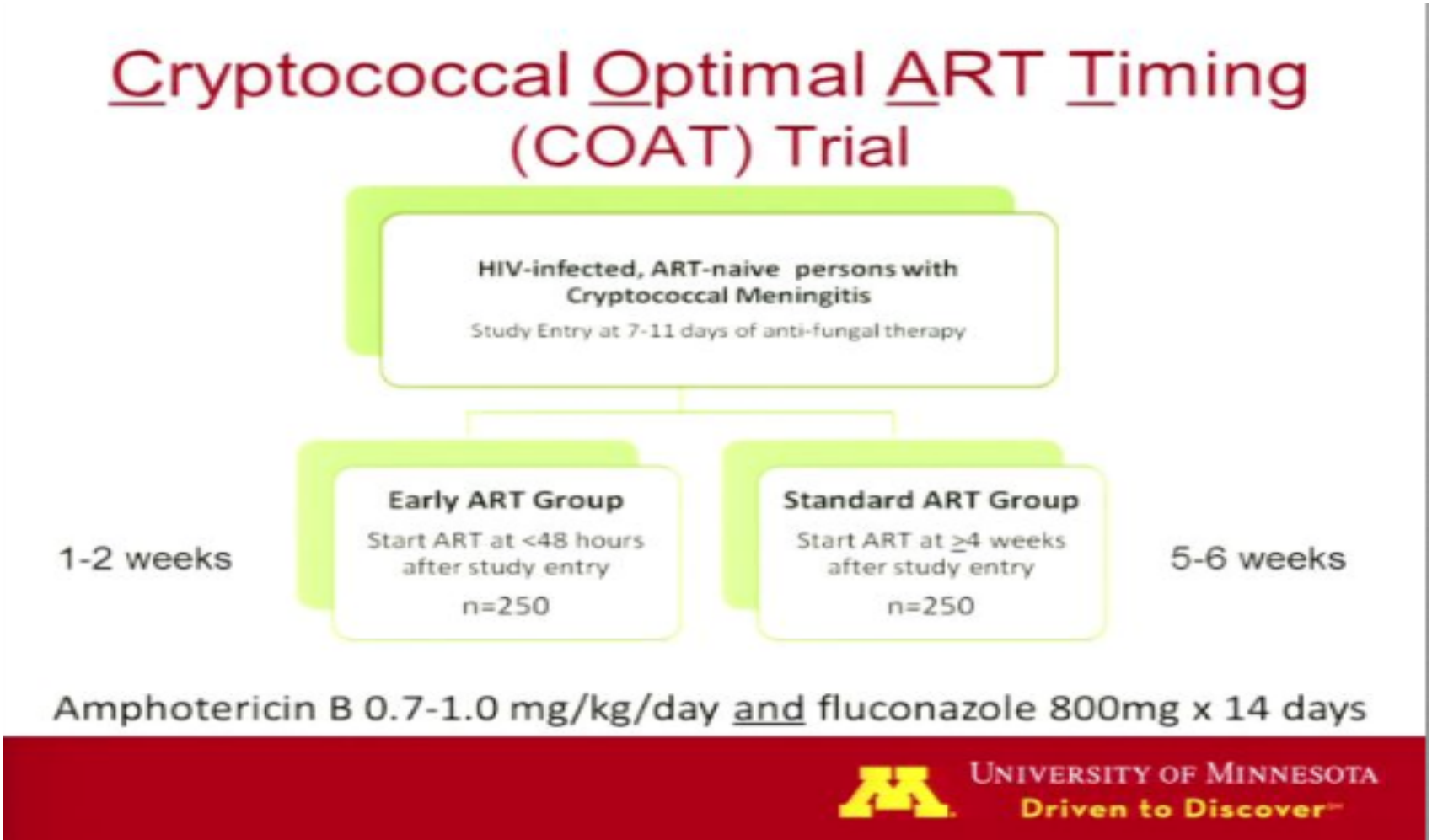




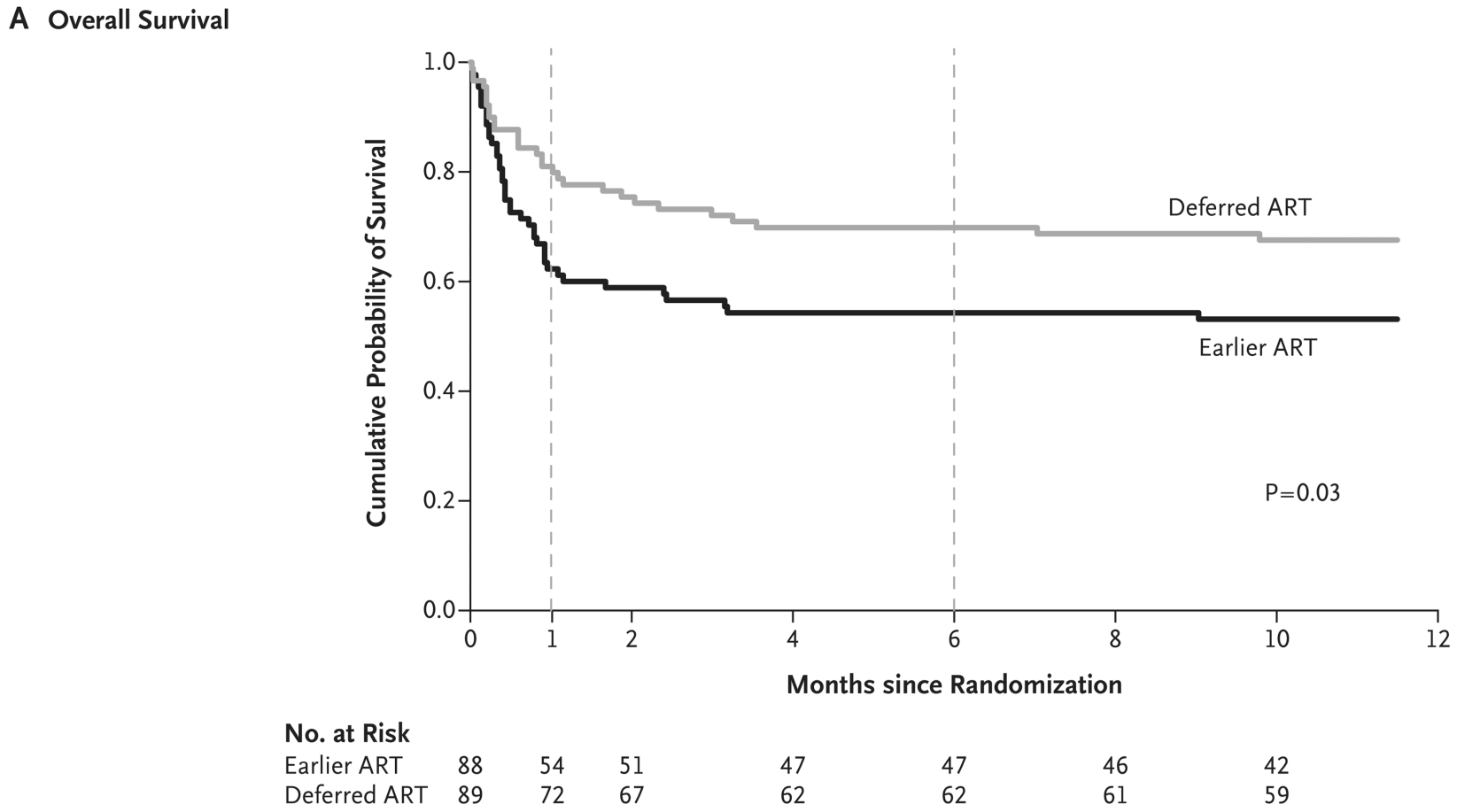
Torok, et al. CID 2011; 52: 1374

Published in final edited form as:
N Engl J Med. 2014 June 26; 370(26): 2487–2498. doi:10.1056/NEJMoa1312884.

Timing of Antiretroviral Therapy after Diagnosis of Cryptococcal Meningitis



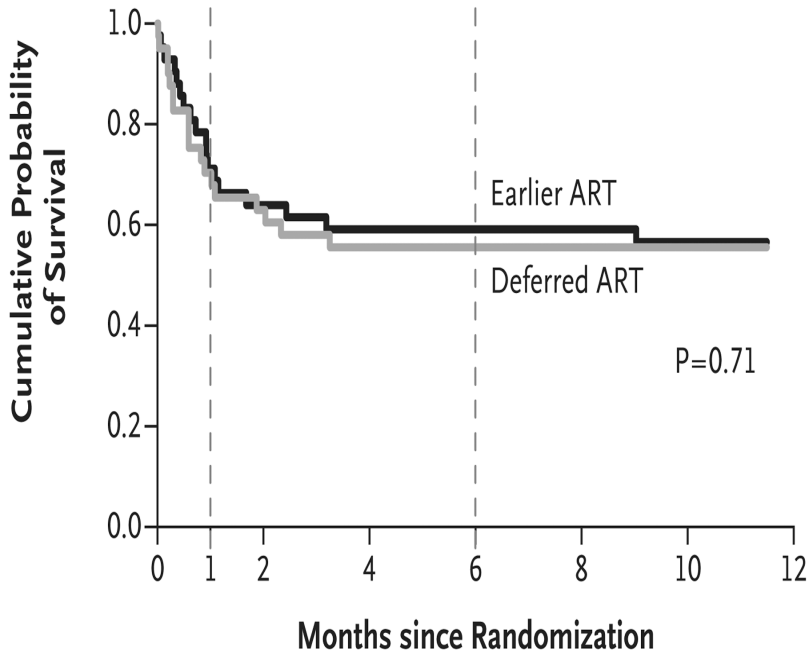
COAT – overall survival



Boulware et al. NEJM 2014; 37: 2487

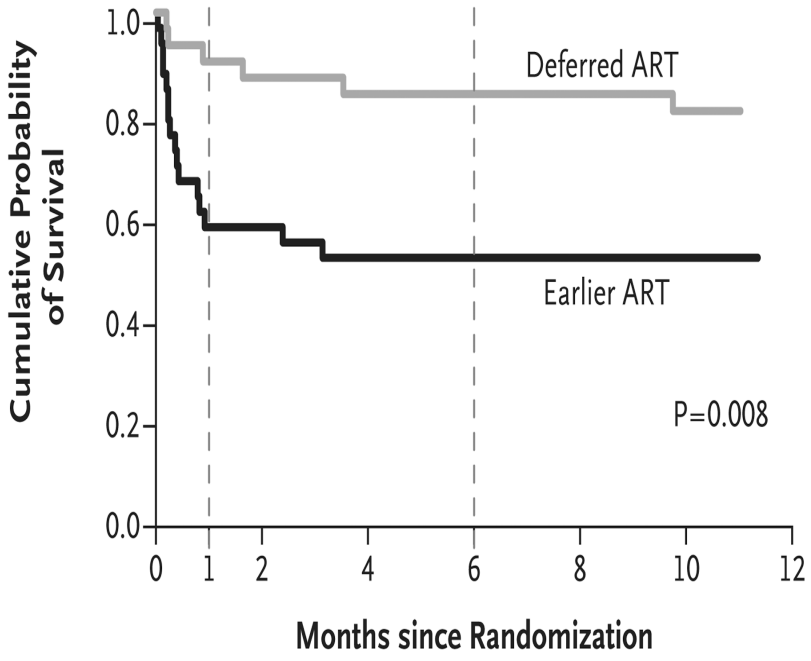
Only significant predictor of mortality

B Survival in Those with CSF White-Cell Count ≥5 Cells per mm^3 at Randomization



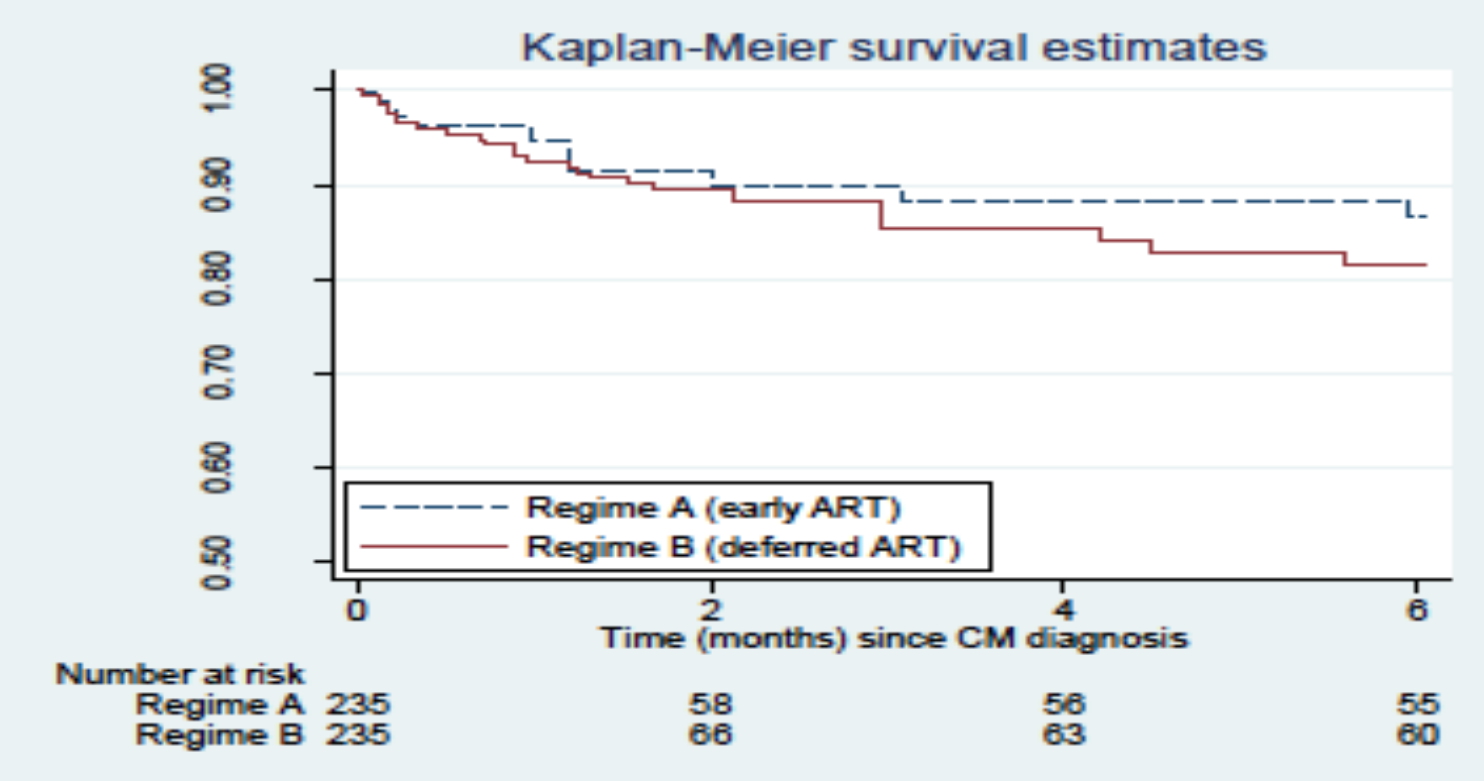
No. at Risk							
Earlier ART	42	29	26	24	24	23	21
Deferred ART	40	28	25	22	22	22	22

C Survival in Those with CSF White-Cell Count <5 Cells per mm^3 at Randomization



No. at Risk							
Earlier ART	33	19	19	17	17	17	16
Deferred ART	31	28	27	26	26	26	24

Retrospective review of European/USA cohorts – early vs. deferred ART



Ingle, et al. CROI 2015, P837

Retrospective review of European/USA cohorts – early vs. deferred ART

Time since starting ART	N	Number of deaths (%)	Rate per person-year (95% CI)
0-13 days	62	7 (11.3)	0.24 (0.12,0.51)
14-56 days	67	7 (10.5)	0.22 (0.10,0.45)
>56 days	21	4 (19.1)	0.41 (0.16,1.10)
Never	85	24 (28.2)	0.73 (0.49,1.09)
Total	**235**	**42**	**0.41 (0.30,0.55)**

Ingle, et al. CROI 2015, P837

Results not consistent across studies

			Early ART	Deferred ART	ETA	DTA	ETA	DTA	ETA	DTA	ETA	DTA
ACTG A5164	USA/South Africa	NA	≤2 weeks	≥4 weeks	13	22	29 (10–55)	31 (12–54)	1 (7.7)	3 (13.6)	0 (0)	2 (15.3)
Makadzange *et al.*	Zimbabwe	Fluconazole 800 mg once a day 2 weeks	≤72 h	≥10 weeks	28	26	27 (17–69)	51 (25–69)	NA	NA	23 (82.1)	12 (46.1)
Bisson *et al.*	Botswana	Amphotericin B 2 weeks	≤1 week	≥4 weeks	13	14	36 (25–44)	14 (4–50)	7 (54)	0 (0)	2 (15)	5 (36)
COAT trial	Uganda/ South Africa	Amphotericn B + Fluconazole 2 weeks or until CSF culture is negative	≤48 h	≥4 weeks	88	89	19 (9–69)	28 (11–76)	14 (16.2)	7 (10.1)	40 (55)	28 (30)
Ingle *et al.*†	Europe and North America	NA	≤2 weeks	15–56 days	62	88	NA	NA	NA	NA	7 (11)	11 (12)

What have we learnt about timing of cART in CNS OIs

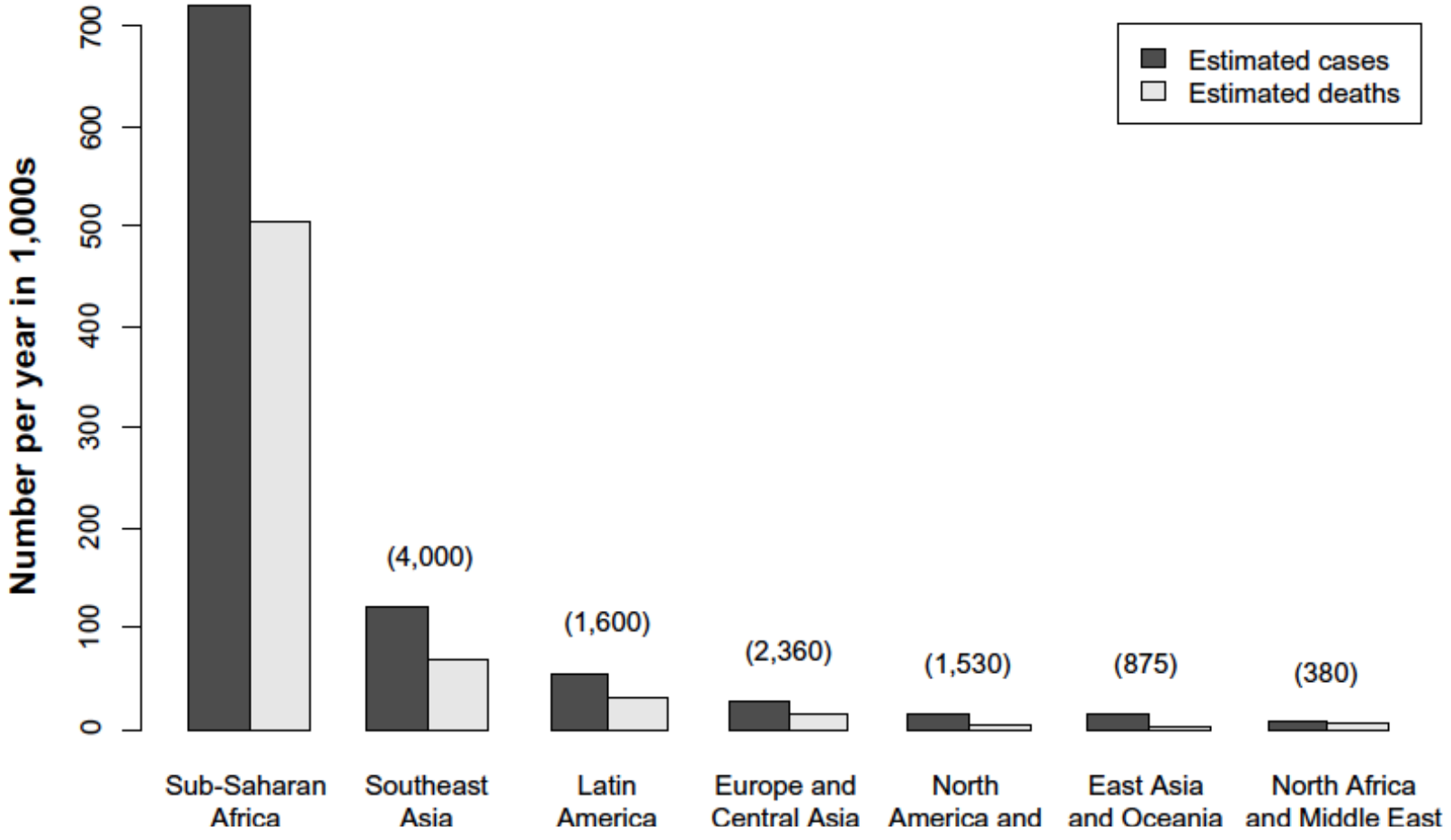
- TB Meningitis
  - Optimal timing of cART not clear
  - Vietnam study – high mortality irrespective of early vs. deferred cART AND increased SAEs in the early treatment arms
  - Does recommended use of corticosteroids prevent serious IRS related morbidity in early cART?

- Cryptococcal meningitis
  - 2-4 weeks seems optimal
  - Need to define sub-groups most at risk with early cART (?high uncontrolled pressure, low CSF wcc, slow anti-fungal response)

- Toxoplasmosis
  - No (little) data – but early (within 2 weeks) seems appropriate

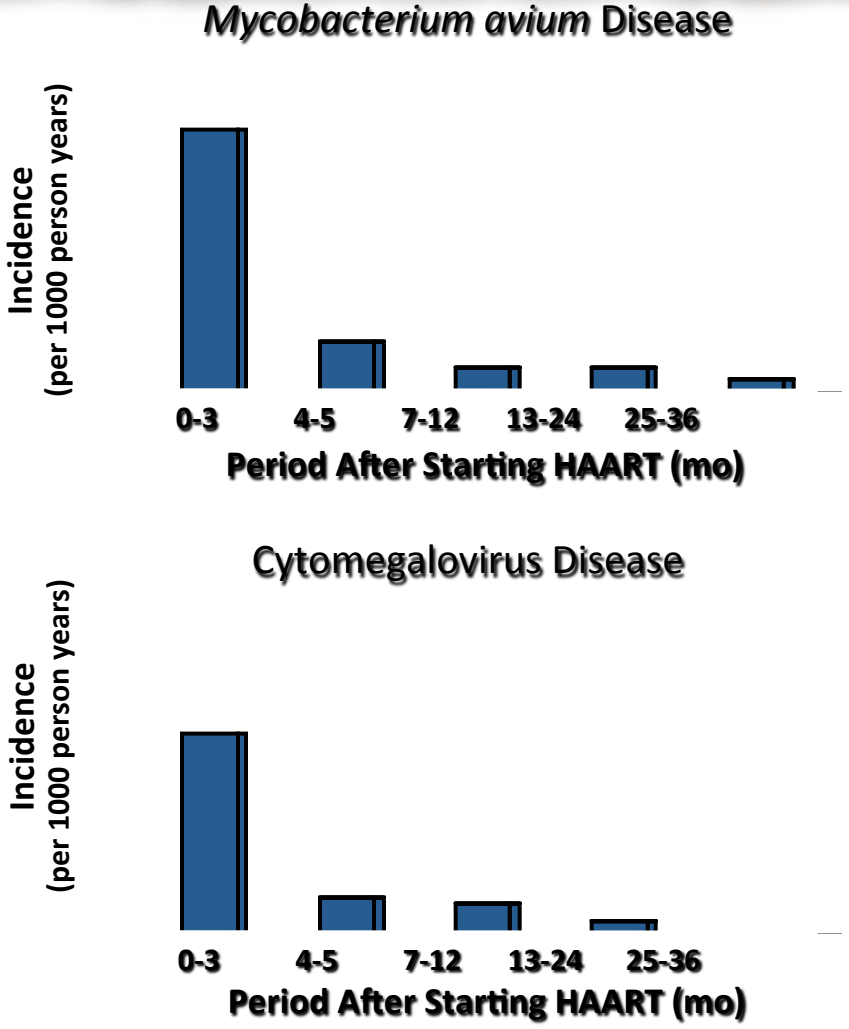
- PML
  - Early cART recommended

Cryptococcal meningitis – the burden of disease



Sloan and Parris, Clin Epidemiol 2014; 6: 169

Incidence of AIDS-Defining Events After Initiation of cART



ART-CC: d'Arminio Monforte *et al. Arch Intern Med.* 2005

Principals of pre-emptive therapy

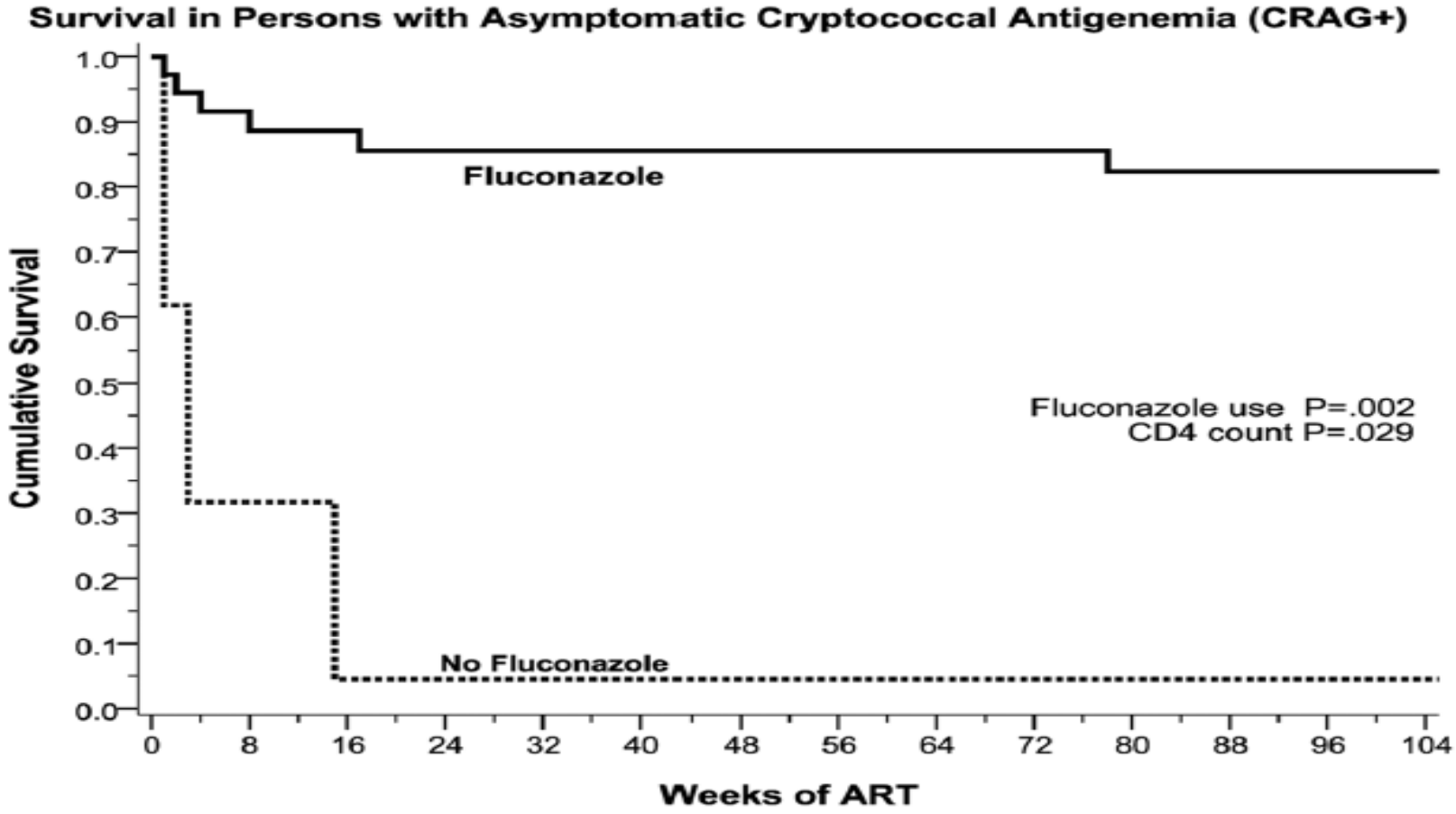
- End organ disease – high morbidity/mortality, difficult/ expensive to treat, and appears pre-/peri-cART initiation
  - 8-26% of patients in sub-Sharan Africa die within one year of starting cART
  - 20% associated with cryptococcal meningitis
  - Typically occurring 4-6 weeks post cART in patients with CD4 <100

- Biomarker that predicts development of disease
  - A positive serum CrAg – HR 3.2 (1.5 – 6.6) for death
  - A negative serum CrAg has 100% negative predictive value for development of cryptococcal meningitis

Jarvis, et al. JAIPAC 2012; 11: 374

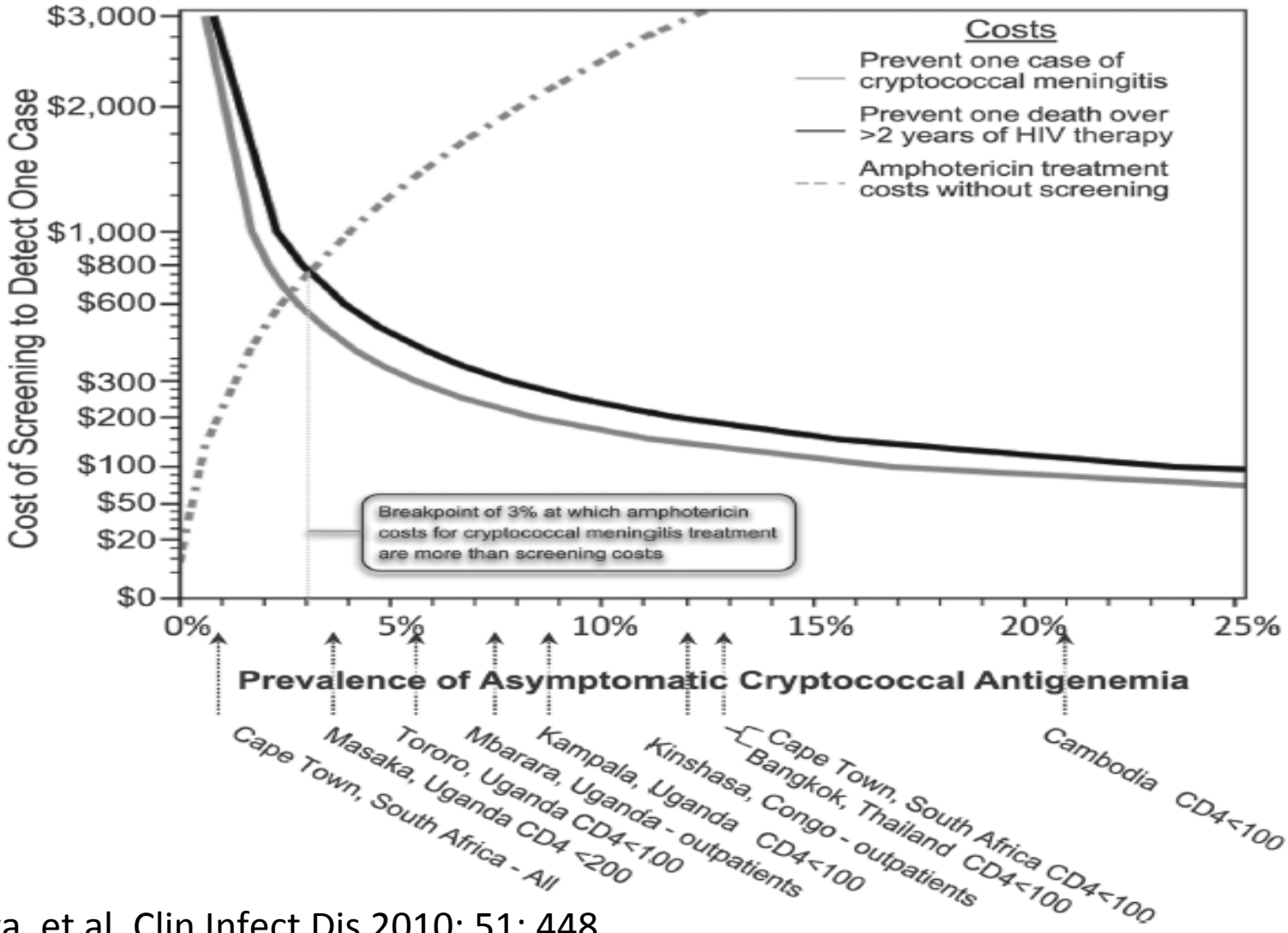
Cost-Effectiveness of Serum Cryptococcal Antigen Screening to Prevent Deaths among HIV-Infected Persons with a $CD4^+$ Cell Count $\leqslant$100 Cells/μL Who Start HIV Therapy in Resource-Limited Settings

David B. Meya,[1,2,4] Yukari C. Manabe,[1,3] Barbara Castelnuovo,[1] Bethany A. Cook,[4] Ali M. Elbireer,[1,3] Andrew Kambugu,[1,4] Moses R. Kamya,[1,2] Paul R. Bohjanen,[4] and David R. Boulware[4]



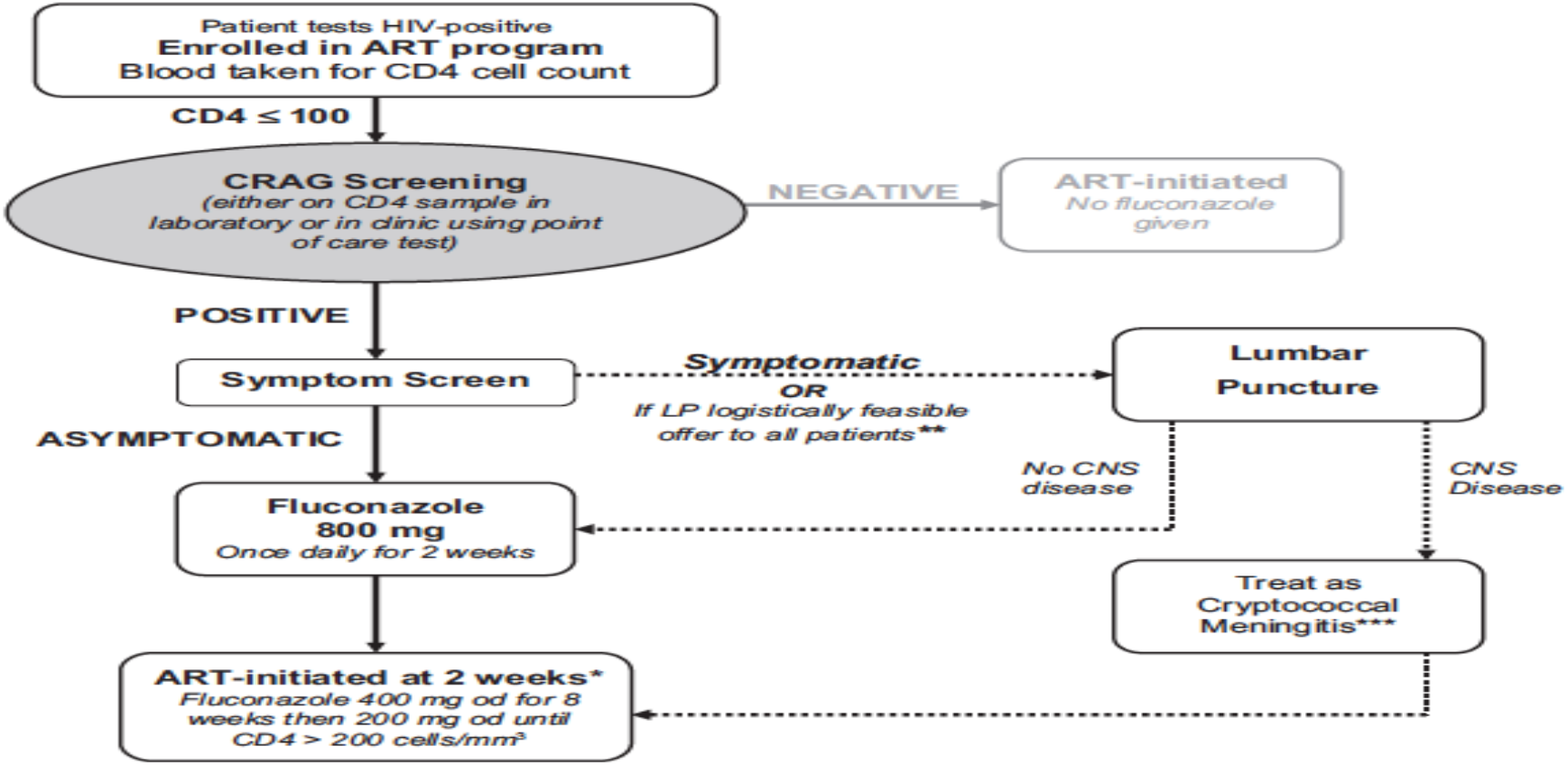
Clin Infect Dis 2010; 51: 448

Cost-effective

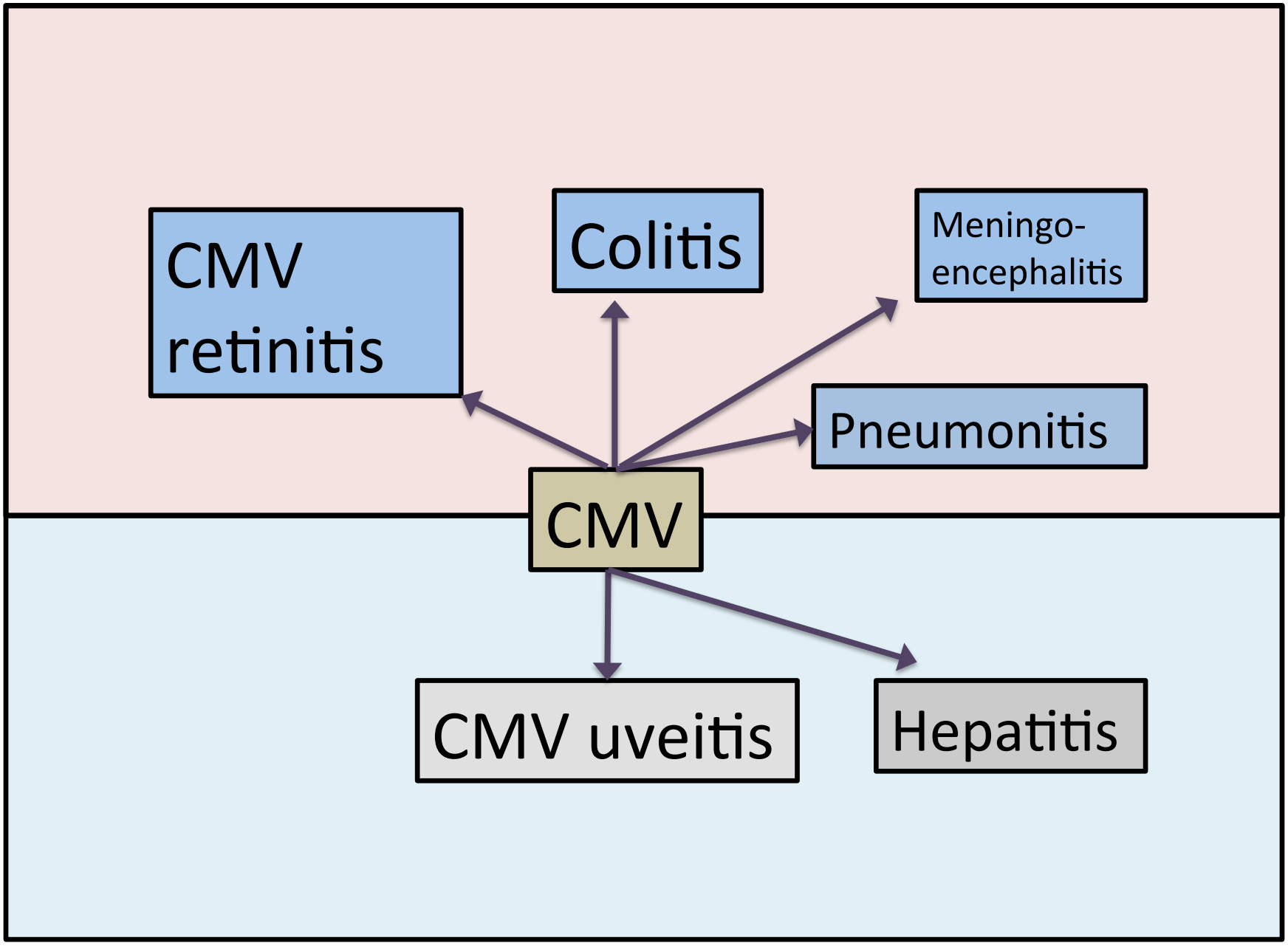


Meya, et al. Clin Infect Dis 2010; 51: 448

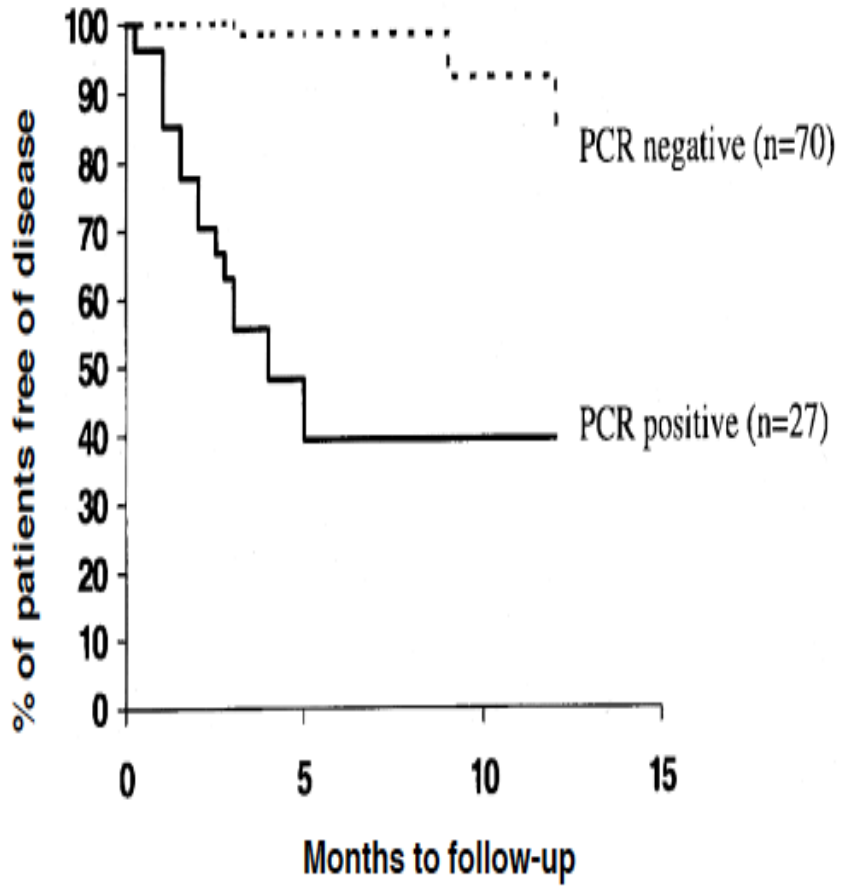
Screening and pre-emptive Rx algorithm

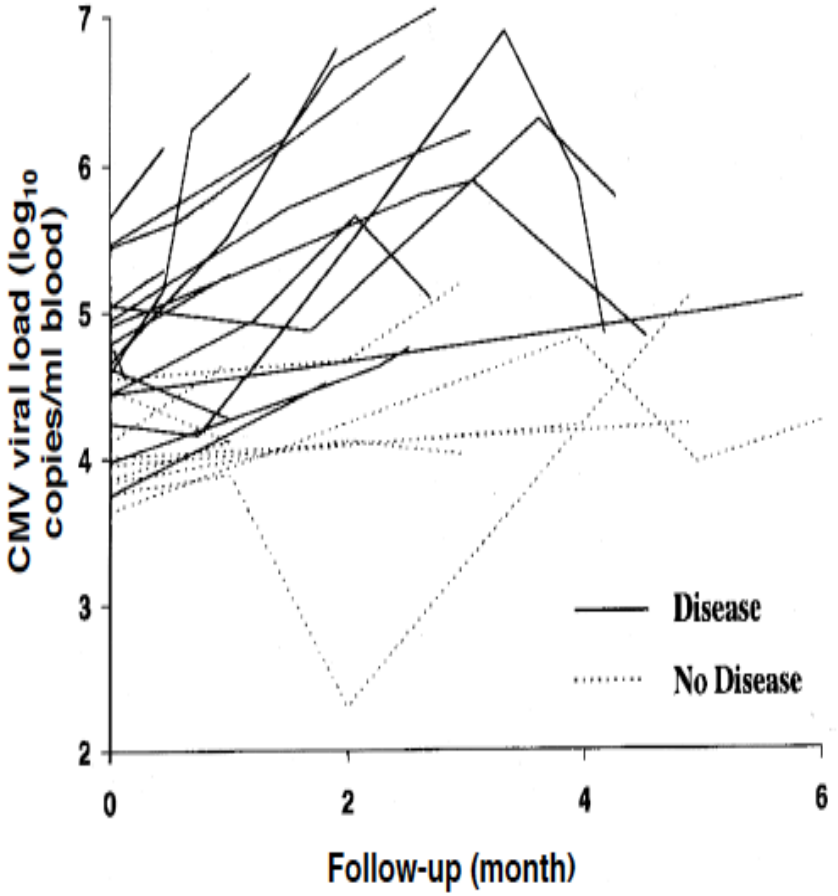


Jarvis, et al. JAIPAC 2012; 11: 374


CMV retinitis
Colitis
Meningo-encephalitis
Pneumonitis
CMV
CMV uveitis
Hepatitis

Peripheral blood and CMV viraemia predicts development of retinitis





Bowen, et al. AIDS 1997; 11: 889

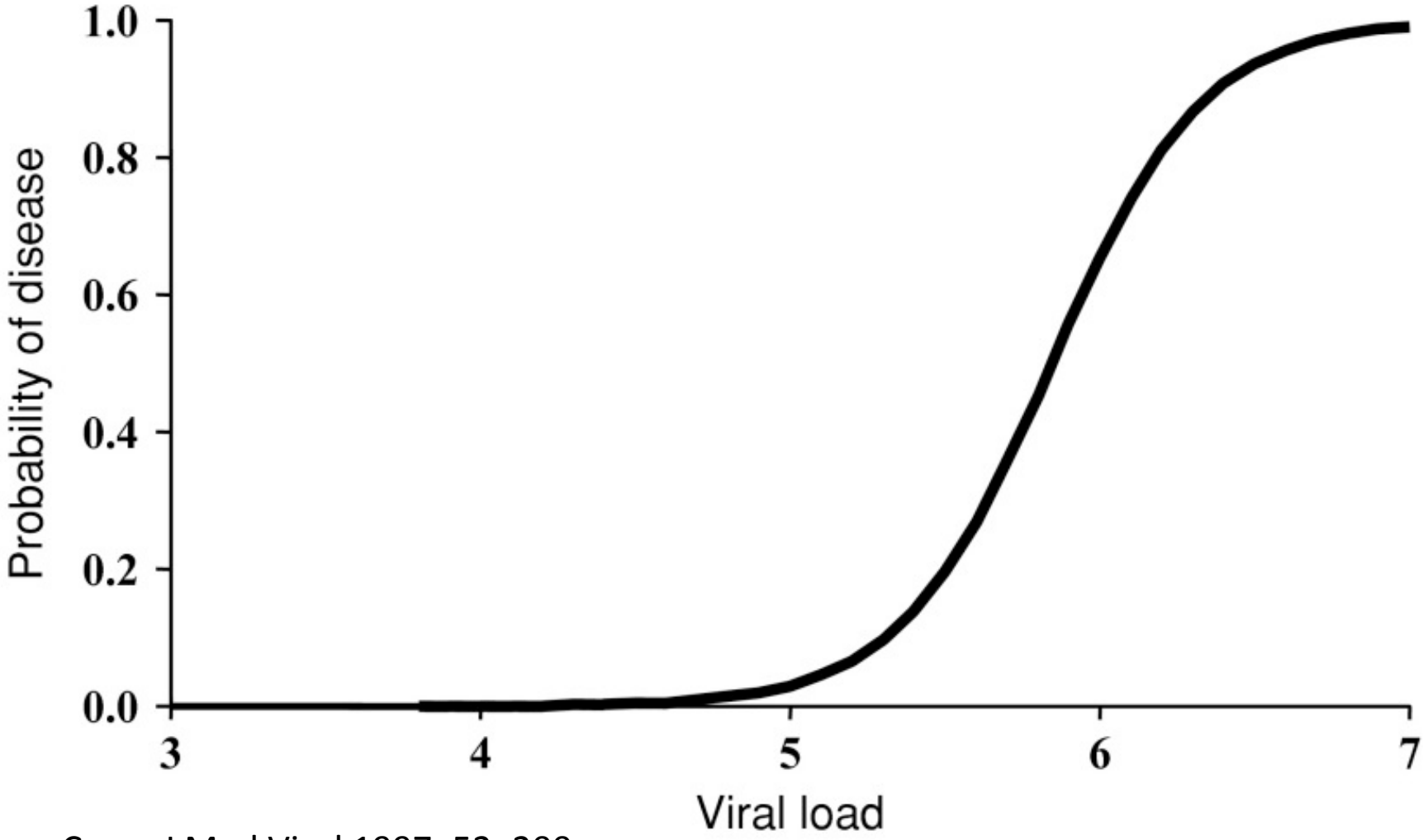
CMV viraemia – an independent predictor of death and AIDS

Factor	Univariate models		Multivariate: baseline covariates		Multivariate: covariates measured over follow-up	
	Relative rate (95% CI)	p	Relative rate (95% CI)	p	Relative rate (95% CI)	p
Cytomegalovirus PCR positive						
At baseline	2·11 (1·25–3·55)	0·005	1·79 (1·03–3·13)	0·04		
During follow-up	4·97 (2·98–8·30)	0·0001			2·22 (1·27–3·88)	0·005
CD4-cell count (per $\log_2$ per μL higher)						
At baseline	0·88 (0·79–0·97)	0·02	0·94 (0·83–1·06)	0·32		
During follow-up	0·71 (0·65–0·78)	0·0001			0·83 (0·74–0·93)	0·001
HIV RNA (per $\log_{10}$ copies per mL higher)						
At baseline	1·51 (1·23–1·85)	0·0001	1·48 (1·19–1·83)	0·0003		
During follow-up	1·77 (1·50–2·10)	0·0001			1·44 (1·19–1·75)	0·0002

Table 1: **Factors associated with progression to a new AIDS-defining event**

Deayton, et al. Lancet 2004; 363: 2116

CMV viraemia and end-organ disease in solid-organ transplant recipients



Cope, J Med Virol 1997; 52: 200

CMV viraemia usually resolves following cART

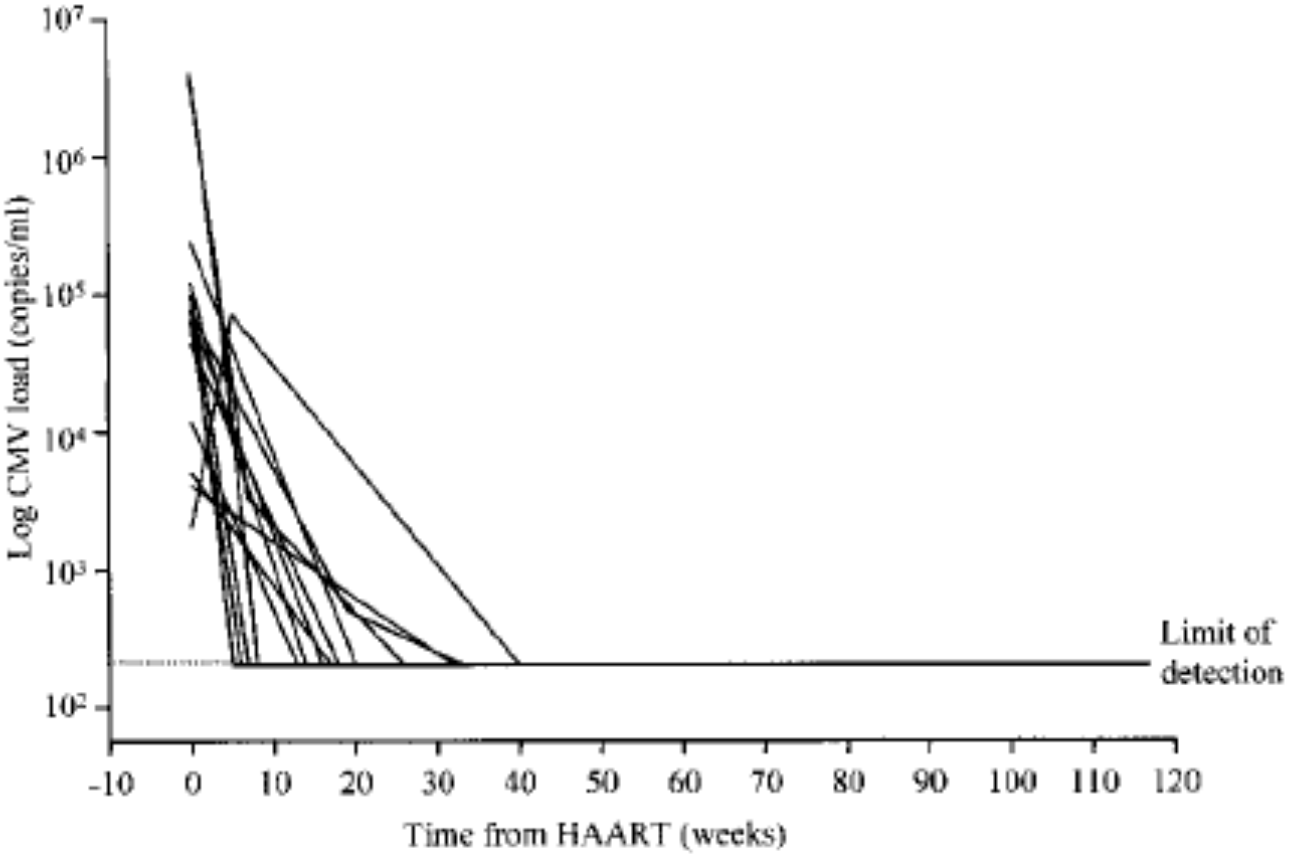
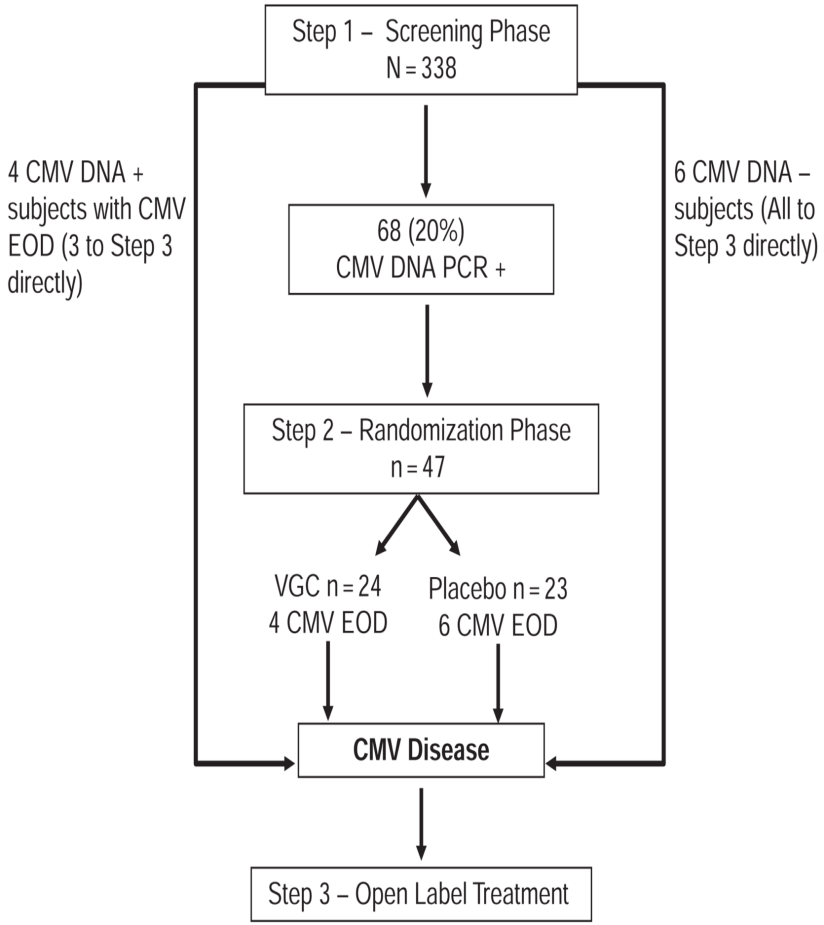


Fig. 1. CMV loads following HAART in patients remaining CMV negative.

Deayton et al. AIDS 1999; 13: 1203 - 1206

ACTG 5030 study – pre-emptive VGC

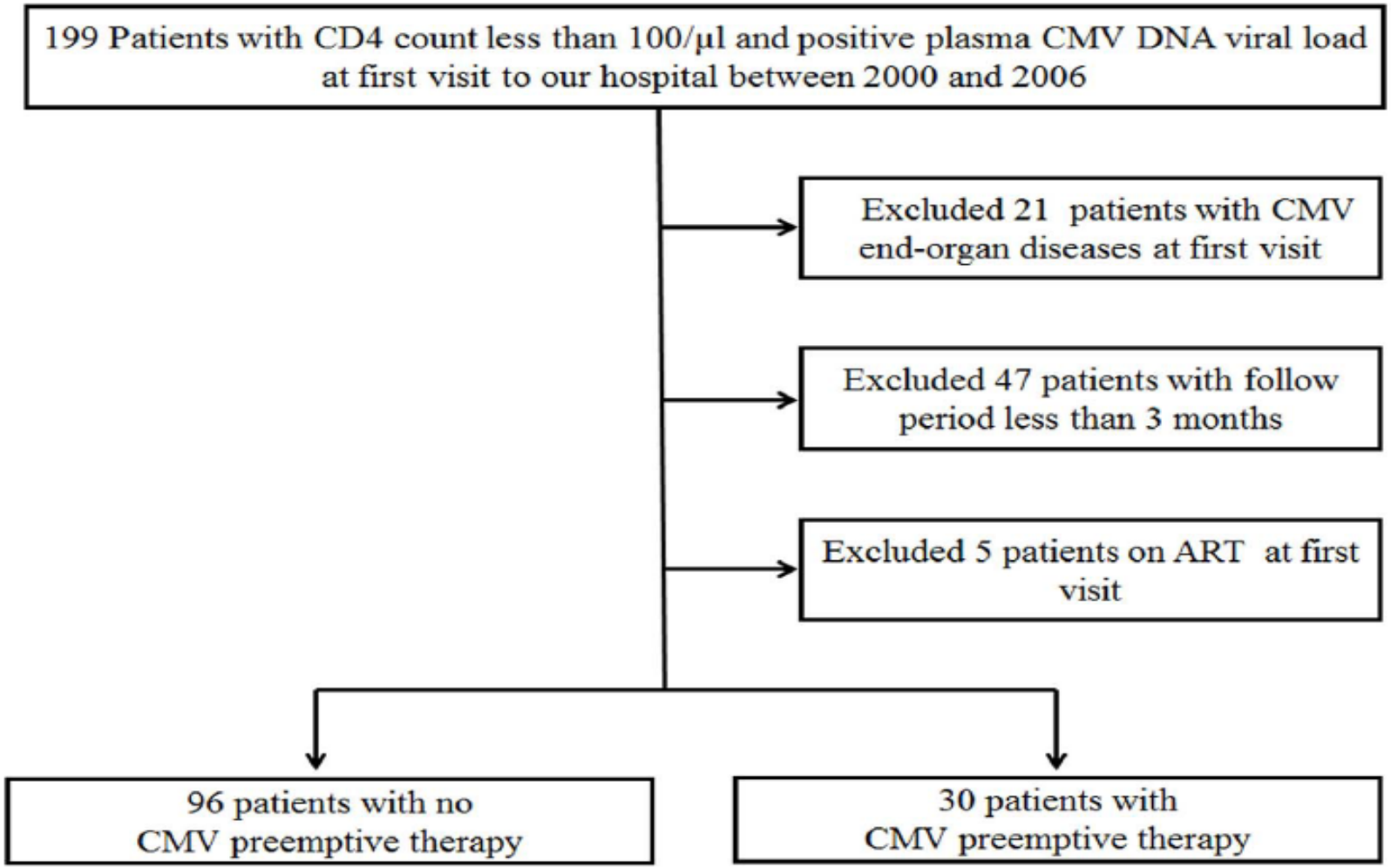


- Trial terminated early
- Too few events to justify continuing

- Note: majority already on cART
  - Many viraemic and low CD4 counts because of failing regimens
  - High mortality associated with non-CMV AIDS events

Wohl, et al. HIV Clinical Trials, 2009; 10(3): 143

Preemptive Therapy Prevents Cytomegalovirus End-Organ Disease in Treatment-Naïve Patients with Advanced HIV-1 Infection in the HAART Era



Mizushima, et al. PLOS one 2013; 8(5): e65348

CMV pre-emptive therapy

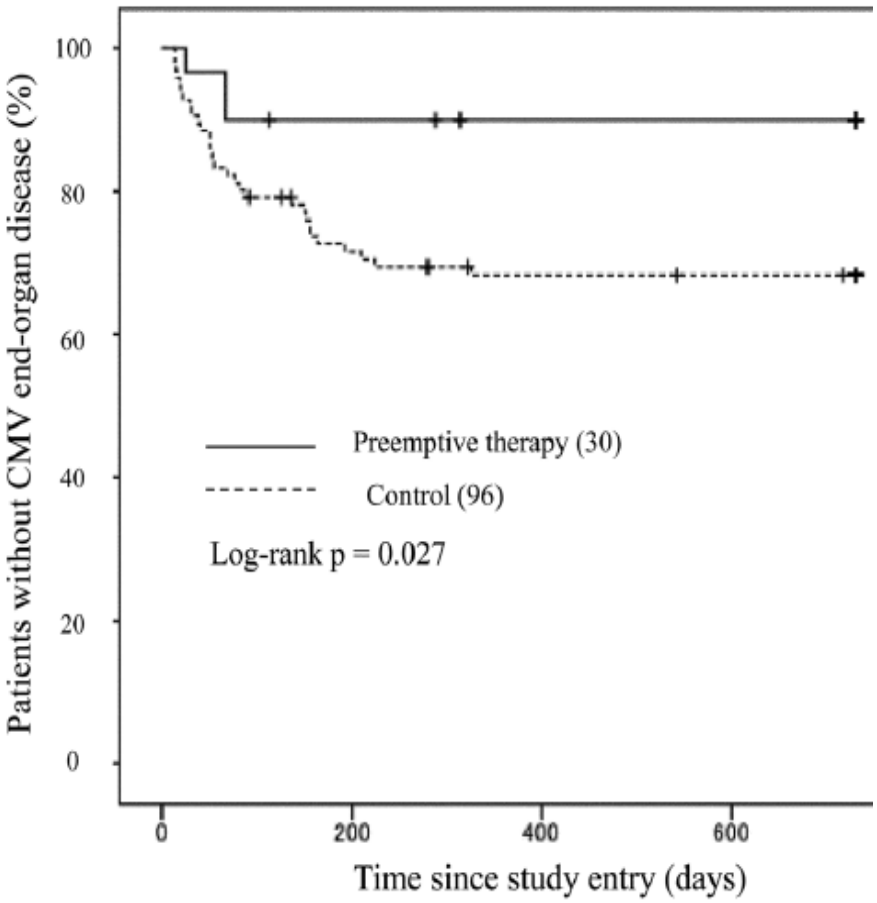


Table 2. Results of univariate analysis to estimate the risk of various factors in inducing CMV end-organ disease.

	Hazard ratio	95% CI	P value
CMV preemptive therapy	0.286	0.087–0.939	0.039
Female	1.284	0.392–4.209	0.680
Age per 1 year	0.982	0.951–1.013	0.240
CD4 count per 1/μl decrement	1.001	0.989–1.013	0.867
HIV viral load per log10/ml	1.875	0.905–3.884	0.091
CMV viral load per log10/ml	1.450	0.984–2.136	0.060
Use of steroid	0.716	0.356–1.439	0.348
Chemotherapy	1.390	0.488–3.955	0.537
Concurrent AIDS	0.703	0.290–1.704	0.436

Mizushima, et al. PLOS one 2013; 8(5): e65348

Pre-emptive therapy

- Well-established for mTB (Isoniazid chemo-preventative therapy)
- Increasing adoption of CrAg screening and pre-emptive fluconazole therapy for patients with CD4 <100
- Managing asymptomatic CMV viraemia is a bit more difficult
  - Early effective cART and careful monitoring for CMV-EOD
  - May be effective for patients with added immune suppressive therapy
  - ?viral load cut-off
  - ?regimen and length of therapy

Conclusions

- OIs remain significant contributors to morbidity and mortality in HIV+ patients
- Prophylaxis and effective treatment are essential knowledge
- cART is beneficial
  - Timing may be different in CNS vs. non-CNS OIs
- Pre-emotive therapy may be beneficial for some OIs

Questions?

GreenShoots
FOUNDATION