New adult ART guidelines

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University of Cape Town
Imperial College London

Port Alfred, 30 May 2015, SA HIV Clinicians Society CME

National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults

24 December 2014

GUIDELINE

Adult antiretroviral therapy guidelines 2014

By the Southern African HIV Clinicians Society

G Meintjes (*chairperson*)
J Black, F Conradie, V Cox, S Dlamini, J Fabian, G Maartens, T Manzini, M Mathe, C Menezes, M Moorhouse, Y Moosa, J Nash, C Orrell, Y Pakade, F Venter, D Wilson (*expert panel members*)

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Disclaimer: Specific recommendations provided here are intended only as a guide to clinical management, based on expert consensus and best current evidence. Treatment decisions for patients should be made by their responsible clinicians, with due consideration for individual circumstances. The most current version of this document should always be consulted.

These guidelines are intended as an update to those published in the *Southern African Journal of HIV Medicine* in 2012. Since the release of the previous guidelines, the scale-up of antiretroviral therapy (ART) in southern Africa has continued. Cohort studies from the region show excellent clinical outcomes; however, ART is still being initiated late (in advanced disease) in some patients, resulting in relatively high early mortality rates. New data on antiretroviral drugs have become available. Although currently few, there are patients in the region who are failing protease-inhibitor-based second-line regimens. To address this, guidelines on third-line therapy have been expanded.

S Afr J HIV Med 2014;15(4):121-143. DOI:10.7196/SAJHIVMED.1130

1. Key principles

While many antiretroviral therapy (ART) guidelines are available internationally, the current guidelines have been written to address issues relevant to southern Africa. The following general principles underpinned the writing process:

- South Africa (SA) is a middle-income country, whereas certain other countries in the region are low-income countries; therefore, affordability was taken into account.
- Only treatment and diagnostic options available in southern Africa were included.
- We recognised the need to bridge the gap in treatment recommendations between public and private sector programmes, considering that many patients transition between the two sectors for treatment.
- While it is acknowledged that certain recommendations are aspirational for poorly resourced settings, the unavailability of diagnostic/monitoring tests should not pose a barrier to providing ART to those in need.
- There has been a shift to view ART as a means of HIV prevention. The clinical trial evidence base for this exists for serodiscordant couples; recommendations in this regard are included in these guidelines and additional data from randomised community studies are awaited.

2. Goals of ART

The primary goals of ART are to:

- improve quality of life
- reduce HIV-related morbidity and mortality
- provide maximal and durable suppression of viral load (VL)
- restore and/or preserve immune function.

These goals are achieved by suppressing viral replication completely for as long as possible, using well-tolerated and sustainable treatment taken with good adherence. With prolonged viral suppression, the $CD4^+$ lymphocyte count usually increases, which is accompanied by a restoration of pathogen-specific immune function. For most patients, this results in a dramatic reduction in the risk of HIV-associated morbidity and mortality. It is still unclear whether immune function ever returns to full normality. Long-term cohorts show that patients who adhere well to ART have a near-normal life expectancy.[1]

3. Standard of care

Maximally suppressive ART regimens should be used in HIV-positive individuals to obtain the best results and to prevent resistance. However, non-suppressive regimens have a role in HIV prevention, e.g. in the prevention of mother-to-child transmission (PMTCT) (infant prophylaxis), in post-exposure prophylaxis (PEP) for healthcare workers following certain low-risk occupational exposures, and in pre-exposure prophylaxis (PrEP). Furthermore, these regimens are probably effective in HIV-negative individuals following low-risk sexual exposures. For further guidance see:

Southern African HIV Clinicians Society. Post-exposure prophylaxis. S Afr J HIV Med 2008;9(3):36-45. (An update will be published in 2015.)

OUTLINE

- When to start ART
- ART timing in patients with TB and CM
- First line issues
- Second line issues
- IPT
- Cryptococcal antigen screening
- Return to care after ART interruption
- Reducing CD4 count monitoring

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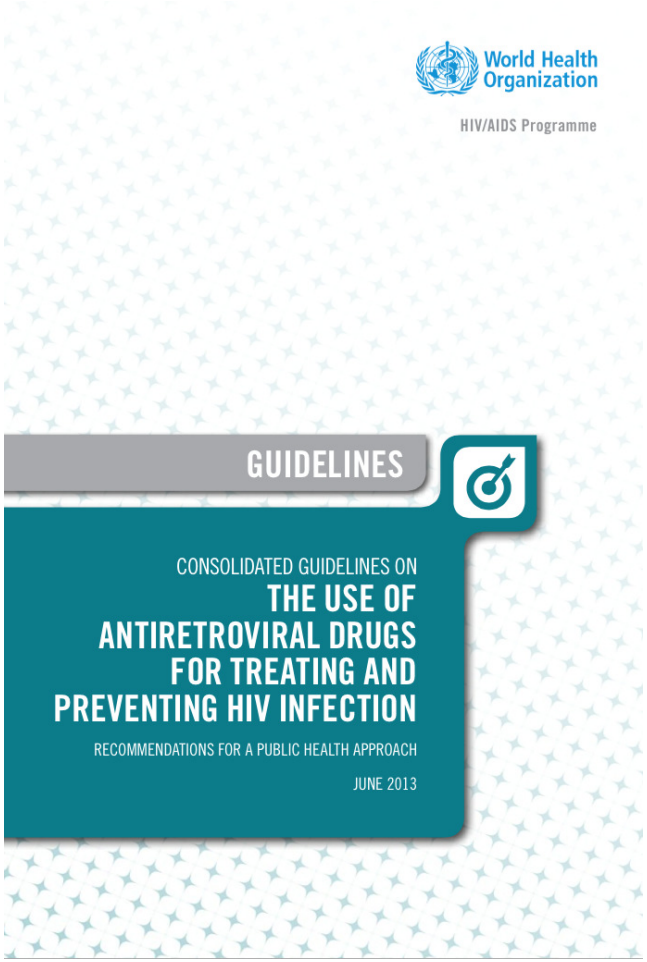
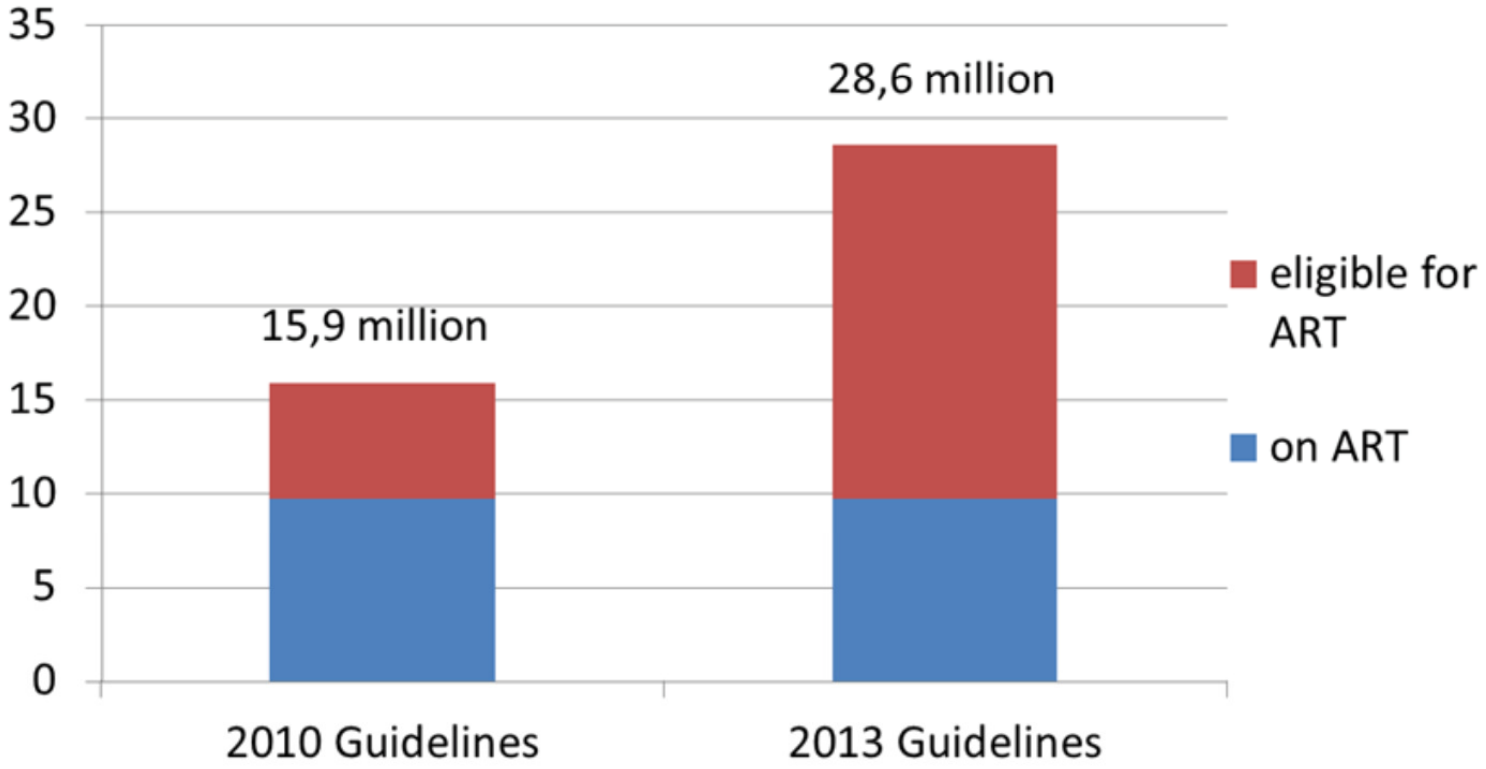
When to start ART?

- In 2013 the WHO increased the CD4 count threshold for starting ART to 500

- Also included all patients with TB, hepatitis B, pregnant women and HIV+ partner in serodiscordant couple as eligible



Number of people eligible for antiretroviral therapy in low- and middle-income countries based on the epidemic and response status at the end of 2012



Updated fig 1.23 (Global update on HIV treatment 2013: results, impact and opportunities: WHO report in partnership with UNICEF and UNAIDS, page 41).

World Health Organization

SA HIV Clinicians Society 2014

Table 3. Indications for ART*

Clinical diagnoses (irrespective of CD4 count)	
WHO clinical stage 3 and 4†	ART recommended
Other severe HIV-related disorders, e.g.:‡ Immune thrombocytopenia Thrombotic thrombocytopenic purpura Polymyositis Lymphocytic interstitial pneumonitis	ART recommended
Non HIV-related disorders:§ Malignancies (excluding localised malignancies) Hepatitis B¶ Hepatitis C	ART recommended
Any condition requiring long-term immunosuppressive therapy	ART recommended
CD4 counts	
<350 cells/µl	ART recommended
350-500 cells/µl (two counts in this range)	ART recommended if patient ready and motivated to start
>500 cells/µl	Defer ART
HIV-infected partner in serodiscordant relationship	
Regardless of CD4 count or clinical diagnoses	Offer ART and discuss safe sex (discussion must involve both partners)

HIV seroconversion added as indication for ART

SA DOH Guidelines
Implemented from 1 Jan 2015

Eligible to start ART
CD4 count ≤500 cells/µl irrespective of clinical stage (Prioritise those with CD4 <350 cells/µl) OR Severe or advanced HIV disease (WHO clinical stage 3 or 4), regardless of CD4 count OR Irrespective of CD4 count or clinical stage: • Active TB disease (including drug-resistant and EPTB) • Pregnant and breastfeeding women who are HIV-positive • Known hepatitis B viral (HBV)co-infection • Prioritise those with CD4 ≤350 cells/µl or advanced HIV disease

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 11, 2011 VOL. 365 NO. 6

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

HPTN 052 trial

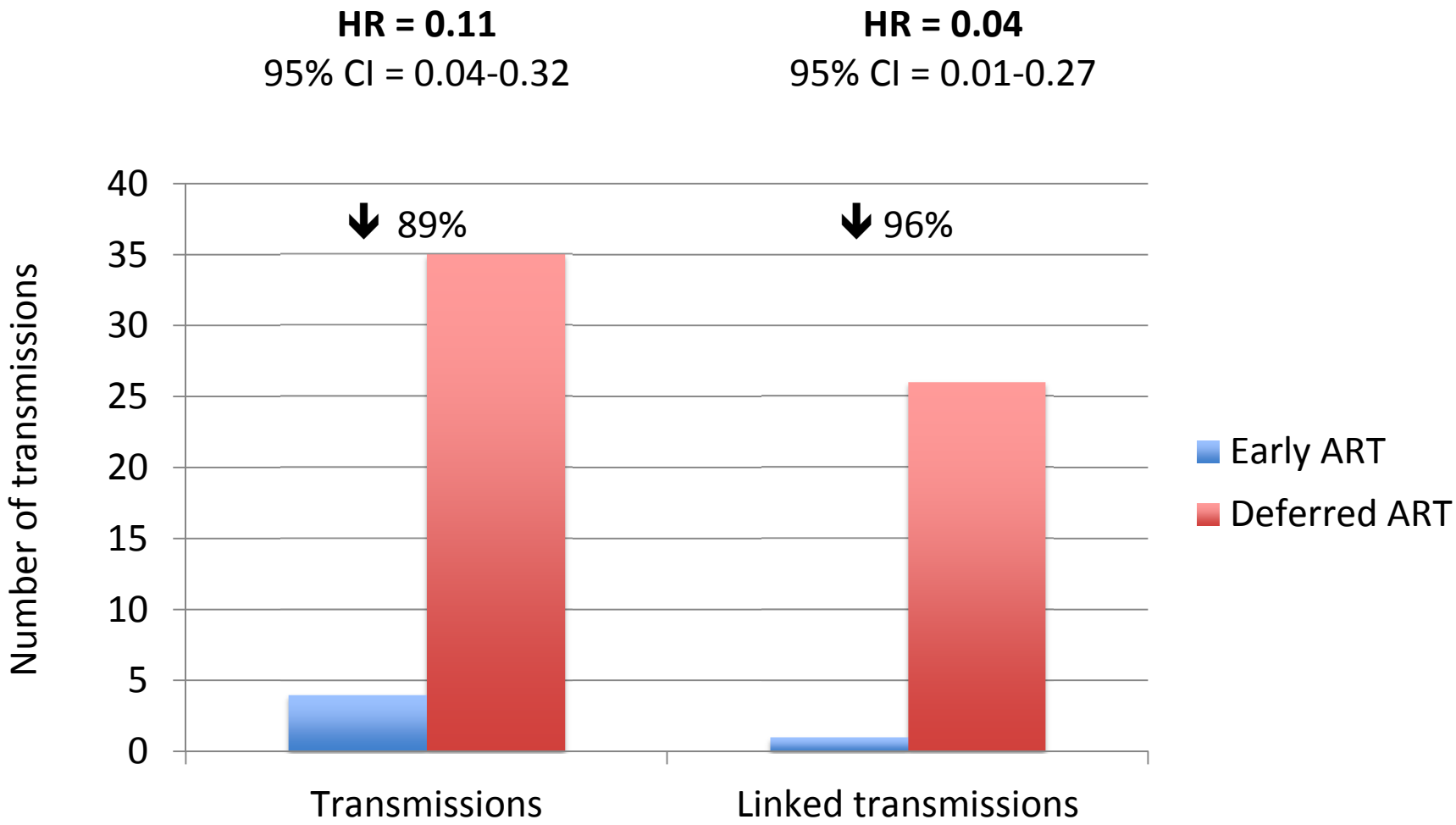
Botswana, Brazil, India, Kenya, Malawi, SA, Thailand, Zimbabwe, USA

1736 serodiscordant, sexually active couples with HIV+ partner having CD4 350-550 randomised 1:1 to:

- Immediate ART
- Delay ART until CD4 ≤ 250 or Stage 4 event

Cohen, NEJM 2011;365:493

Early ART reduced HIV transmission



Cohen, NEJM 2011;365:493

ART scale-up associated with lower HIV incidence in rural KZN

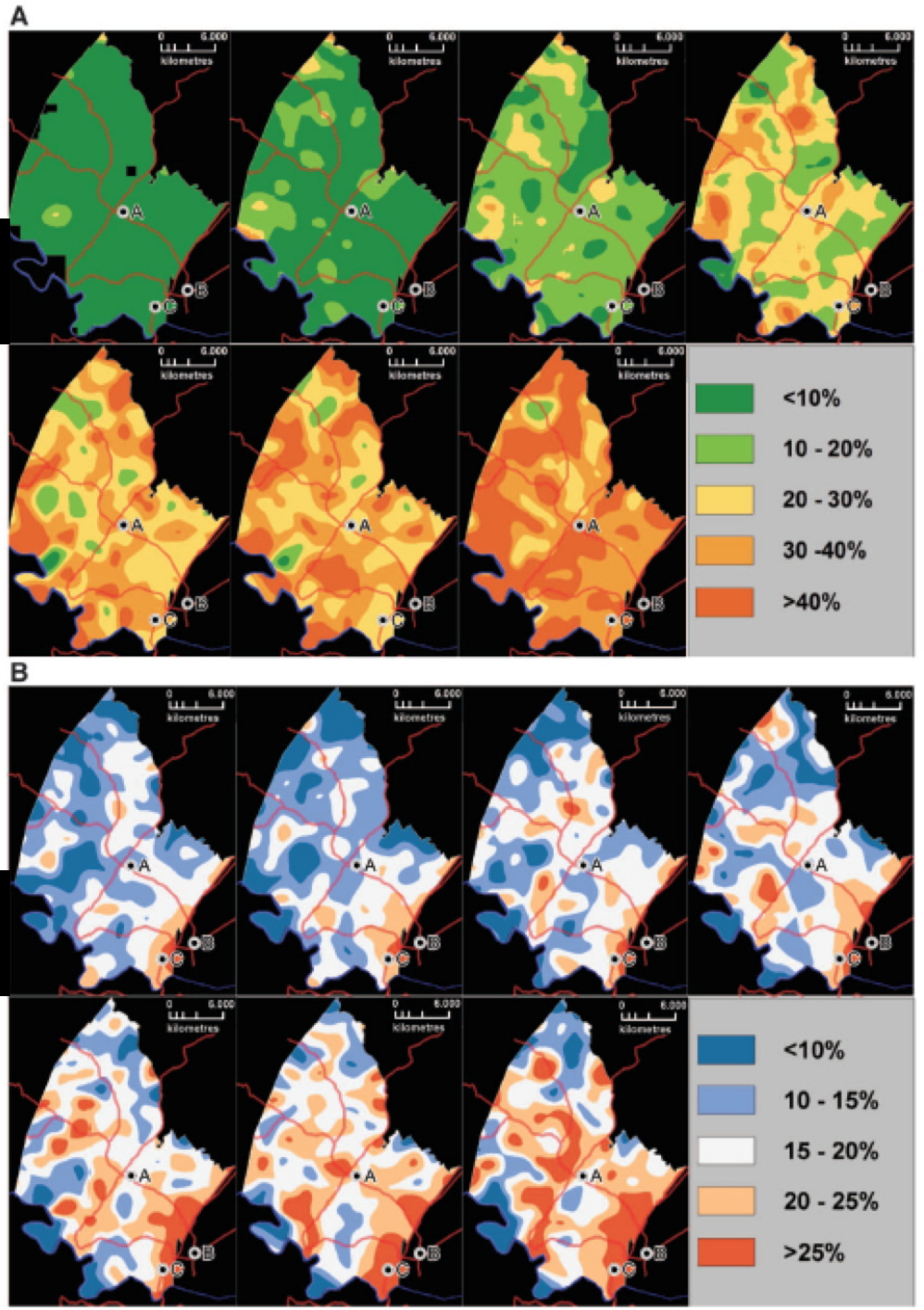
- 16,667 HIV-negative adults followed 2004-11
- Annual HIV prevalence and ART coverage in a 3km radius around each individual was calculated
- Hazard ratio for HIV seroconversion in relation to ART coverage calculated
  - Adjusted for gender, age, HIV prevalence and various HIV risk behaviours
- 1,413 seroconversions observed over 53,605 years of observation
  - Crude HIV incidence = 2.6/100 person-years

Tanser, Science 2013;339:966

Researchers linked:
HIV surveillance database
ART clinics database

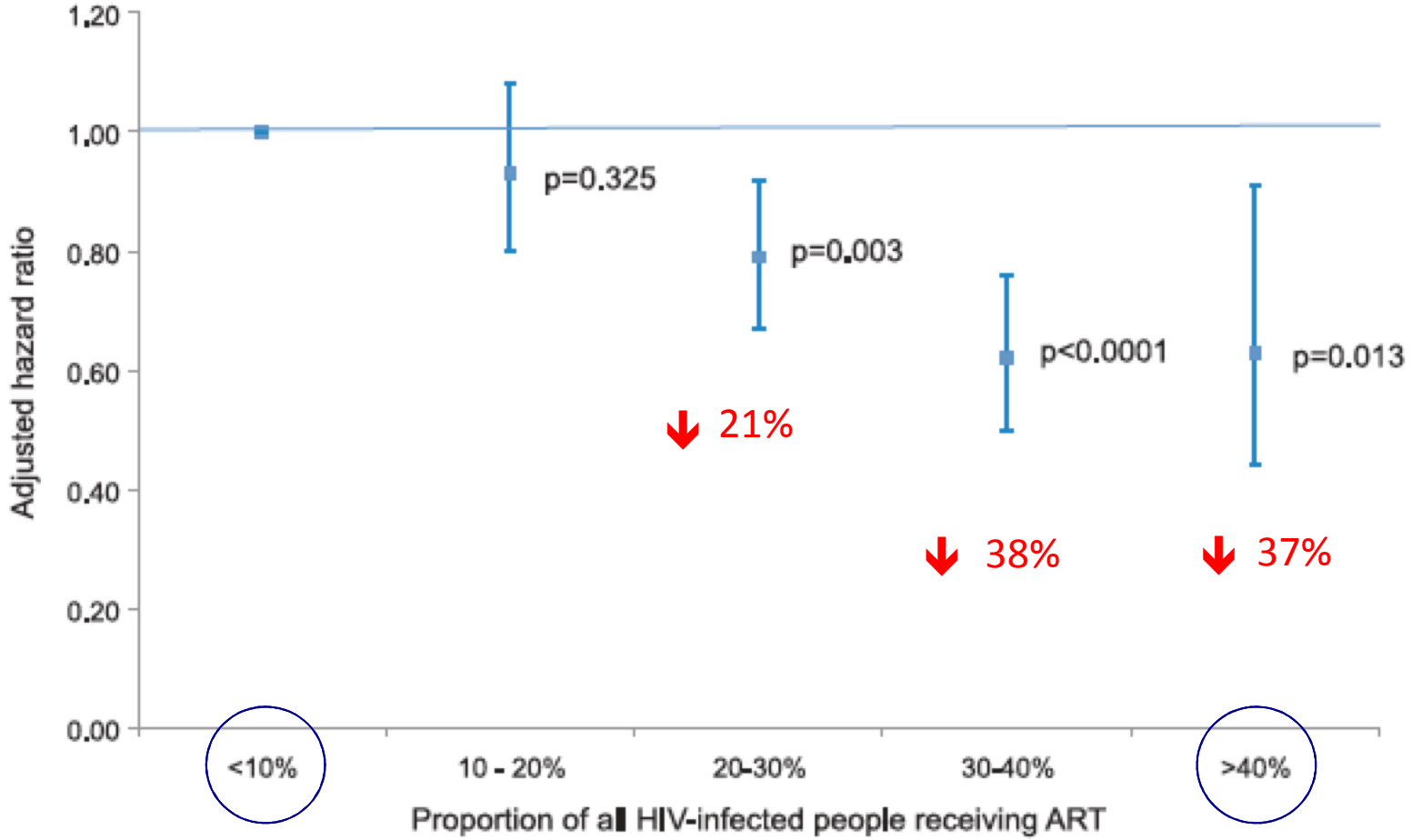
ART coverage
2005 - 2011

HIV prevalence
2005 - 2011



Tanser,Science 2013;339:966

Increased ART coverage associated with reduced HIV incidence (dose-response relationship)



Tanser,Science 2013;339:966

Haiti trial

Starting ART at CD4<350 vs CD4<200 or AIDS

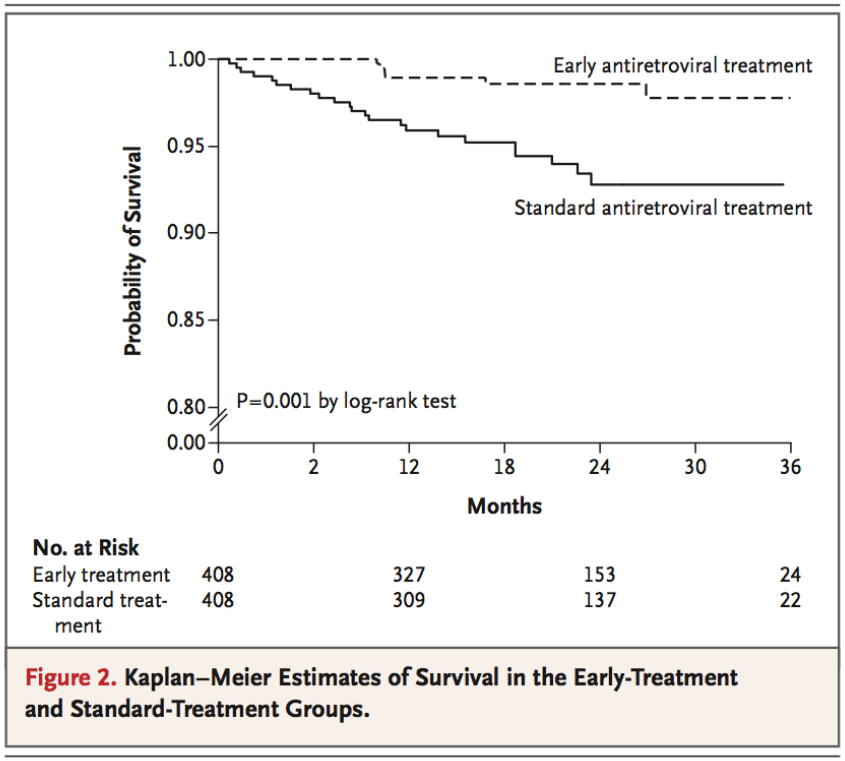


Figure 2. Kaplan–Meier Estimates of Survival in the Early-Treatment and Standard-Treatment Groups.

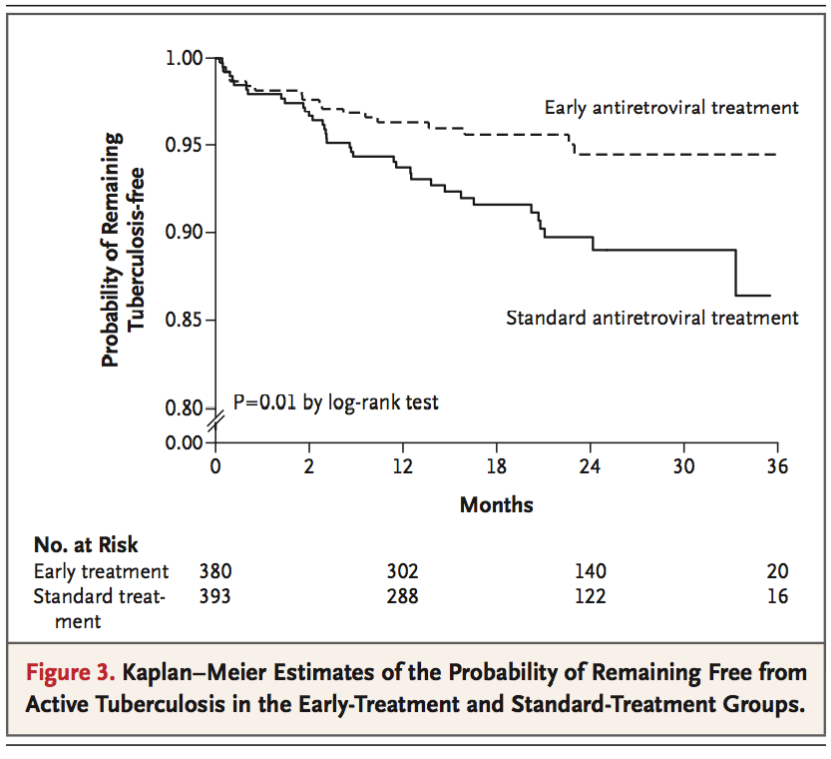


Figure 3. Kaplan–Meier Estimates of the Probability of Remaining Free from Active Tuberculosis in the Early-Treatment and Standard-Treatment Groups.

HR = 4.0

HR = 2.0

Severe, NEJM 2010

Early ART & IPT in HIV-Infected African Adults With High CD4 Count (Temprano Trial)

- Randomized 2x2 factorial superiority trial conducted in 9 HIV care centers in Côte d'Ivoire
  - Immediate ART vs WHO criteria
  - 6 months IPT vs no IPT
- March 2008 - January 2015
- Inclusion criteria were:
  - HIV-1 infection
  - Age >18 years
  - CD4 nadir <800/ul
  - No criteria for starting ART according to the most recent WHO guidelines
- 2076 randomised; 2056 included in analysis
  (median CD4 = 465)

Danel, CROI 2015, 115LB

Severe morbidity	N	TAR (PY)	Rate (/100PY)	AHR	(95% CI)
Overall					
WHOART	111	2,247	4.94		
EarlyART	64	2,310	2.77	0.56	(0.41 - 0.76)
No IPT	104	2,225	4.67		
IPT	71	2,332	3.04	0.65	(0.48 - 0.88)
Baseline CD4 >500/ul					
WHOART	38	918	4.14		
EarlyART	23	964	2.39	0.56	(0.33 - 0.93)
No IPT	37	918	4.03		
IPT	24	965	2.49	0.61	(0.37 - 1.02)

N: number of events. PY: person-years; TAR: time at risk; AHR: adjusted hazard ratio; CI: confidence interval

The primary endpoint was severe HIV morbidity (AIDS-defining diseases, non-AIDS-defining malignancy, or non-AIDS-defining invasive bacterial diseases), or any-cause mortality at 30 months .

START Study

Strategic Timing of AntiRetroviral Treatment Study

- Adult ART naïve patients with CD4 > 500
- Randomised to:
  - Immediate ART
  - Start when CD4 < 350
- 215 sites in 35 countries
- 4,685 patients enrolled
- Due to end late 2016
- Stopped early by DSMB and results announced on 27 May 2015 (average 3 years follow-up)

News Releases

2015
2014
2013
2012
Archive
By Topic

U.S. Department of Health and Human Services
NIH News
National Institutes of Health

National Institute of Allergy and Infectious Diseases (NIAID)
http://www.niaid.nih.gov

FOR IMMEDIATE RELEASE
Wednesday, May 27, 2015

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Starting Antiretroviral Treatment Early Improves Outcomes for HIV-Infected Individuals

NIH-Funded Trial Results Likely Will Impact Global Treatment Guidelines

A major international randomized clinical trial has found that HIV-infected individuals have a considerably lower risk of developing AIDS or other serious illnesses if they start taking antiretroviral drugs sooner, when their CD4+ T-cell count—a key measure of immune system health—is higher, instead of waiting until the CD4+ cell count drops to lower levels. Together with data from previous studies showing that antiretroviral treatment reduced the risk of HIV transmission to uninfected sexual partners, these findings support offering treatment to everyone with HIV.

The new finding is from the Strategic Timing of AntiRetroviral Treatment (START) study, the first large-scale randomized clinical trial to establish that earlier antiretroviral treatment benefits all HIV-infected individuals. The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, provided primary funding for the START trial. Though the study was expected to conclude at the end of 2016, an interim review of the study data by an independent data and safety monitoring board (DSMB) recommended that results be released early.

Event rate of primary endpoint

- Primary endpoint = AIDS, serious non-AIDS event* or death

- Early arm = 0.60/100 person years
- Deferred arm = 1.25/100 person years

- Hazard ratio = 0.47 (95%CI=0.32-0.68)

  (53% reduction in early arm)

* Serious non-AIDS event = Major CVS, renal or hepatic disease or non-AIDS cancer

Table 1a. Number of primary endpoint in each arm (15 May 2015)

	Number of events	
	Early arm (A)	Later arm (B)
Category 1:AIDS, serious non-AIDS, or death (primary).	41	86
Category 2:AIDS or AIDS death.	14	46
Category 3:Serious non-AIDS or non-AIDS death.	28	41

Tony Fauci (NIAID Director), 27 May 2015

"We now have clear-cut proof that it is of significantly greater health benefit to an HIV-infected person to start antiretroviral therapy sooner rather than later."

"Moreover, early therapy conveys a double benefit, not only improving the health of individuals but at the same time, by lowering their viral load, reducing the risk they will transmit HIV to others. These findings have global implications for the treatment of HIV."

NIH

→ Guidelines are likely to change soon

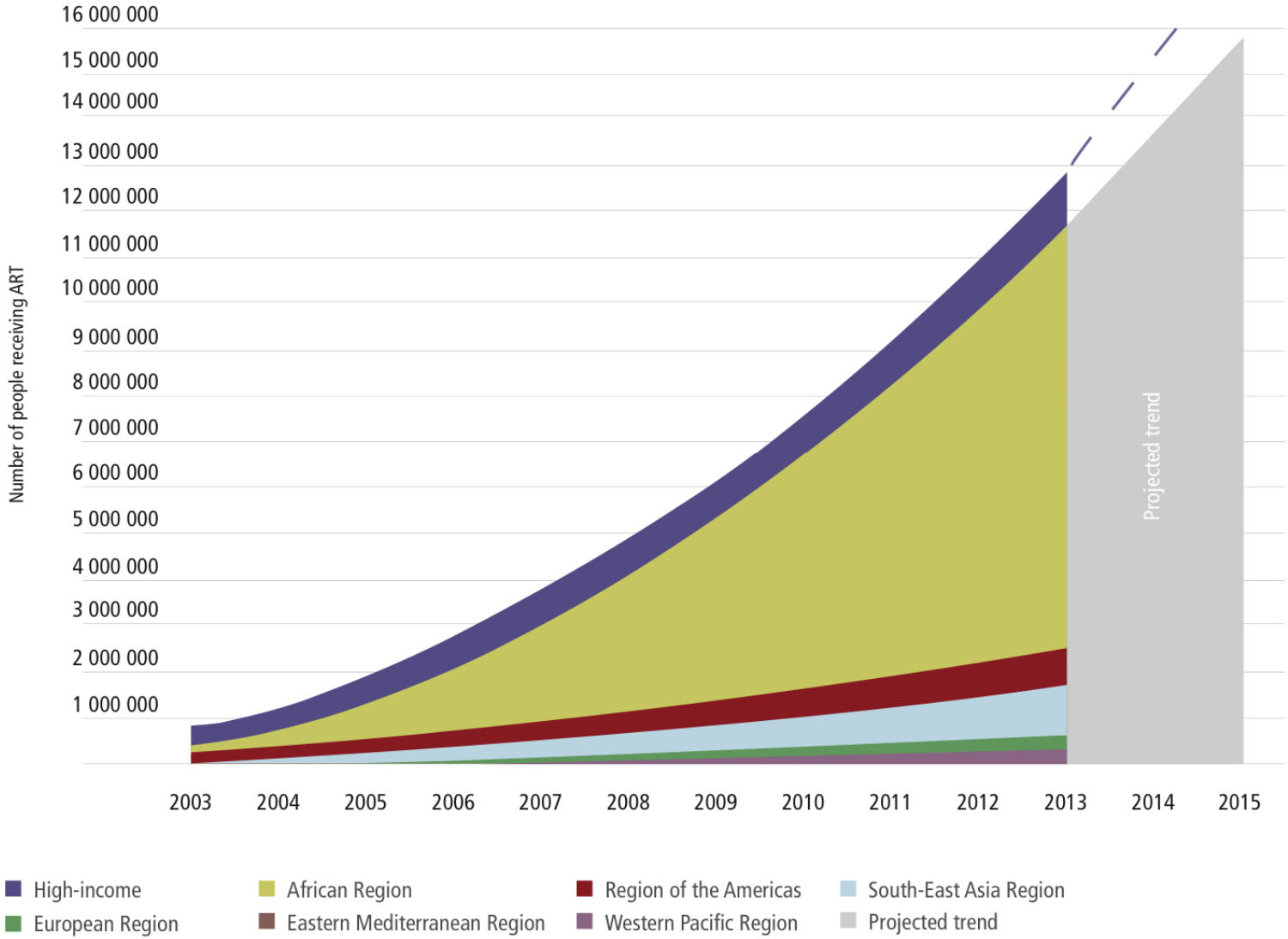
CD4 < 500

↓

All HIV+ patients regardless of CD4

Prioritise those with lowest CD4 counts
Patients must be motivated for lifelong ART

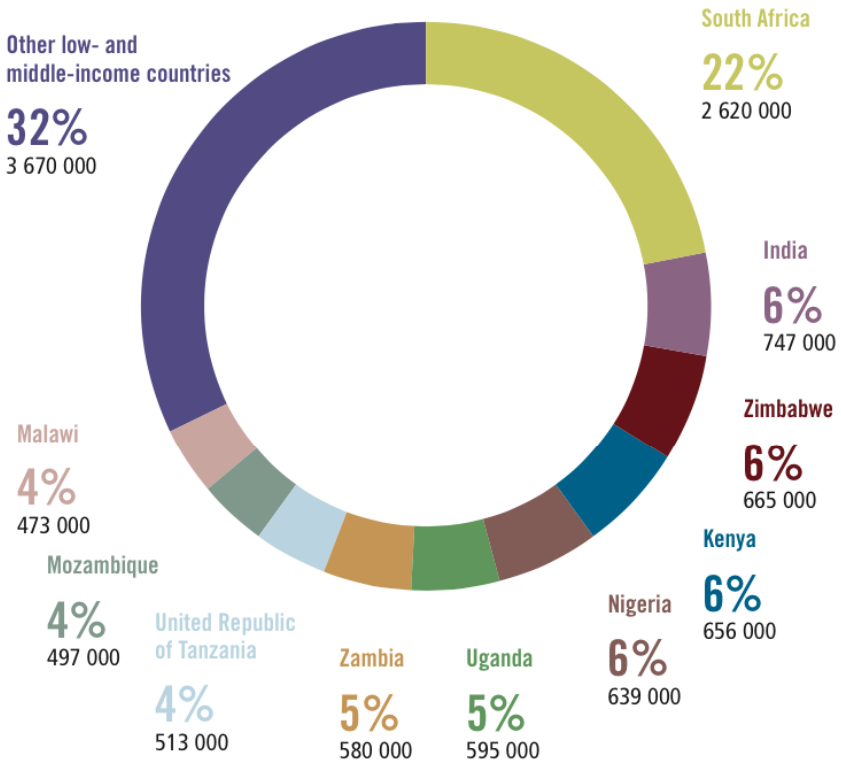
Fig. 5.1. Actual and projected numbers of people receiving antiretroviral therapy in low- and middle-income countries by WHO region and in high-income countries across WHO regions, 2003–2015[a]



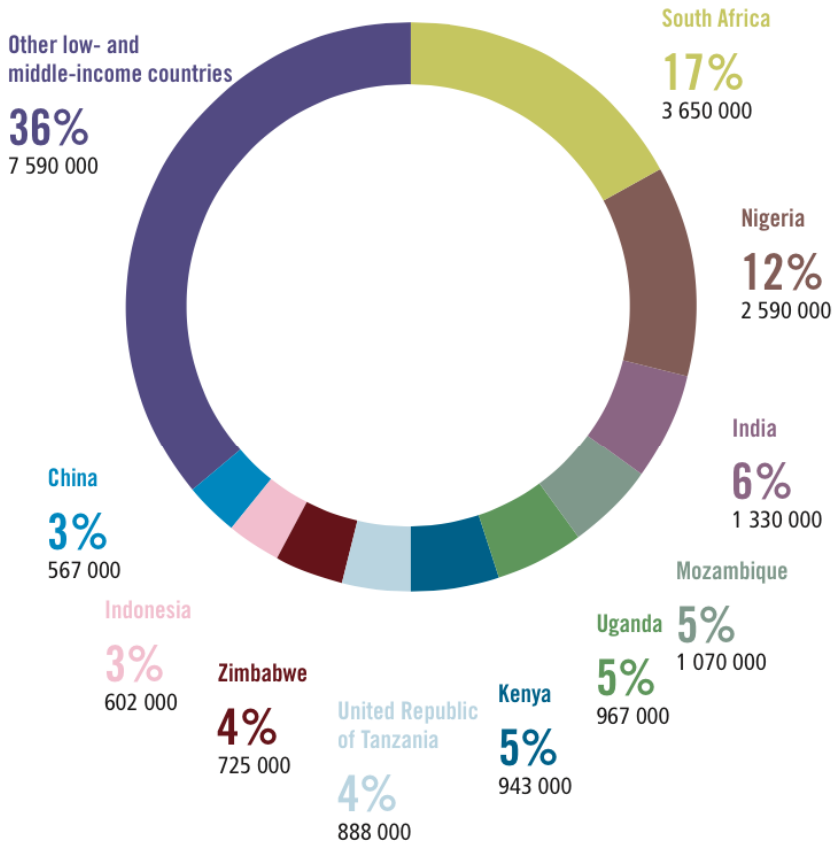
[a]Country income classification by the World Bank at the time of the 2011 Political Declaration on HIV and AIDS.

Source: Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS)

People living with HIV who were on ART as a percentage of all people on ART in low- and middle-income countries



People living with HIV who were not on ART as a percentage of all people not on ART in low- and middle-income countries



Source: Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS) and 2013 UNAIDS/WHO estimates.

By end of 2013

OUTLINE

- When to start ART
- ART timing in patients with TB and CM
- First line issues
- Second line issues
- IPT
- Cryptococcal antigen screening
- Return to care after ART interruption
- Reducing CD4 count monitoring

ART timing in patients with TB and CM

Timing of ART initiation

- ART should be started as soon as the patient is ready, and within at least 2 weeks of CD4 count being done
- In TB co-infection, start with TB treatment first, followed by ART as soon as possible and within 8 weeks
- If CD4 <50 cells/µl initiate ART within 2 weeks of starting TB treatment, when the patient's symptoms are improving and TB treatment is tolerated
- If CD4 >50 cells/µl initiate ART within 2-8 weeks of starting TB treatment
- In cryptococcal or TB meningitis: Defer ART initiation for 4-6 weeks

IMMEDIATE INITIATION: All HIV-positive pregnant or breastfeeding women, as long as no active TB

FAST TRACKING (within 7 days:)

- Patients with CD4 <200 cells/µl
- HIV stage 4, even if CD4 is not yet available

DOH guidelines

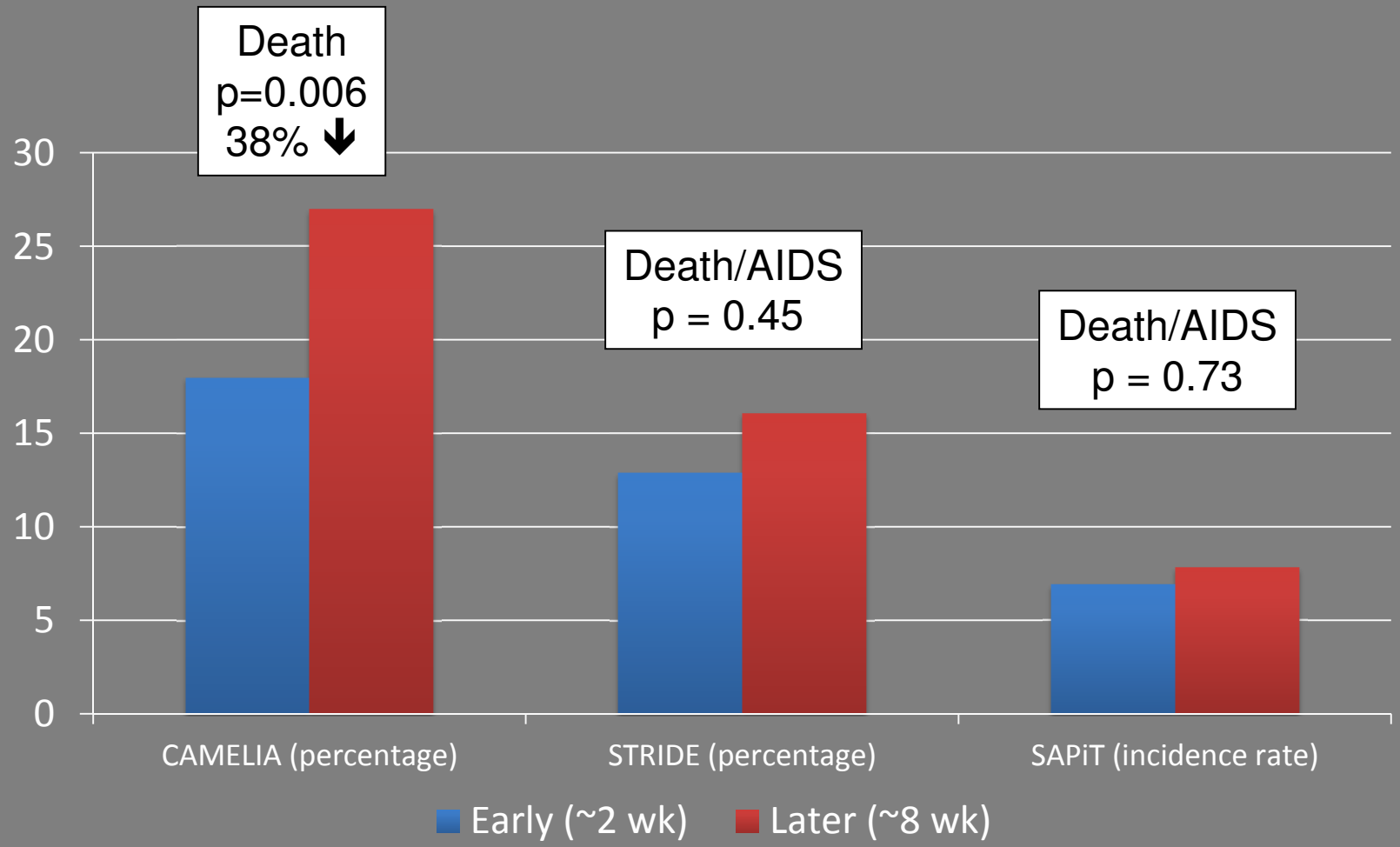
Randomised strategy trials of ART timing during TB treatment

Trial	Inclusion criteria	Early ART	Deferred ART
SAPiT* (South Africa)	Smear + PTB CD4 < 500	Within 4 weeks	8-12 weeks
STRIDE ACTG A5221 (Multi-country)	Smear + and – PTB CD4 < 250	Within 2 weeks	8-12 weeks
CAMELIA (Cambodia)	Smear + PTB and EPTB CD4 ≤ 200	2 weeks	8 weeks
TB meningitis trial (Vietnam)	TB meningitis	Within 1 week	8 weeks

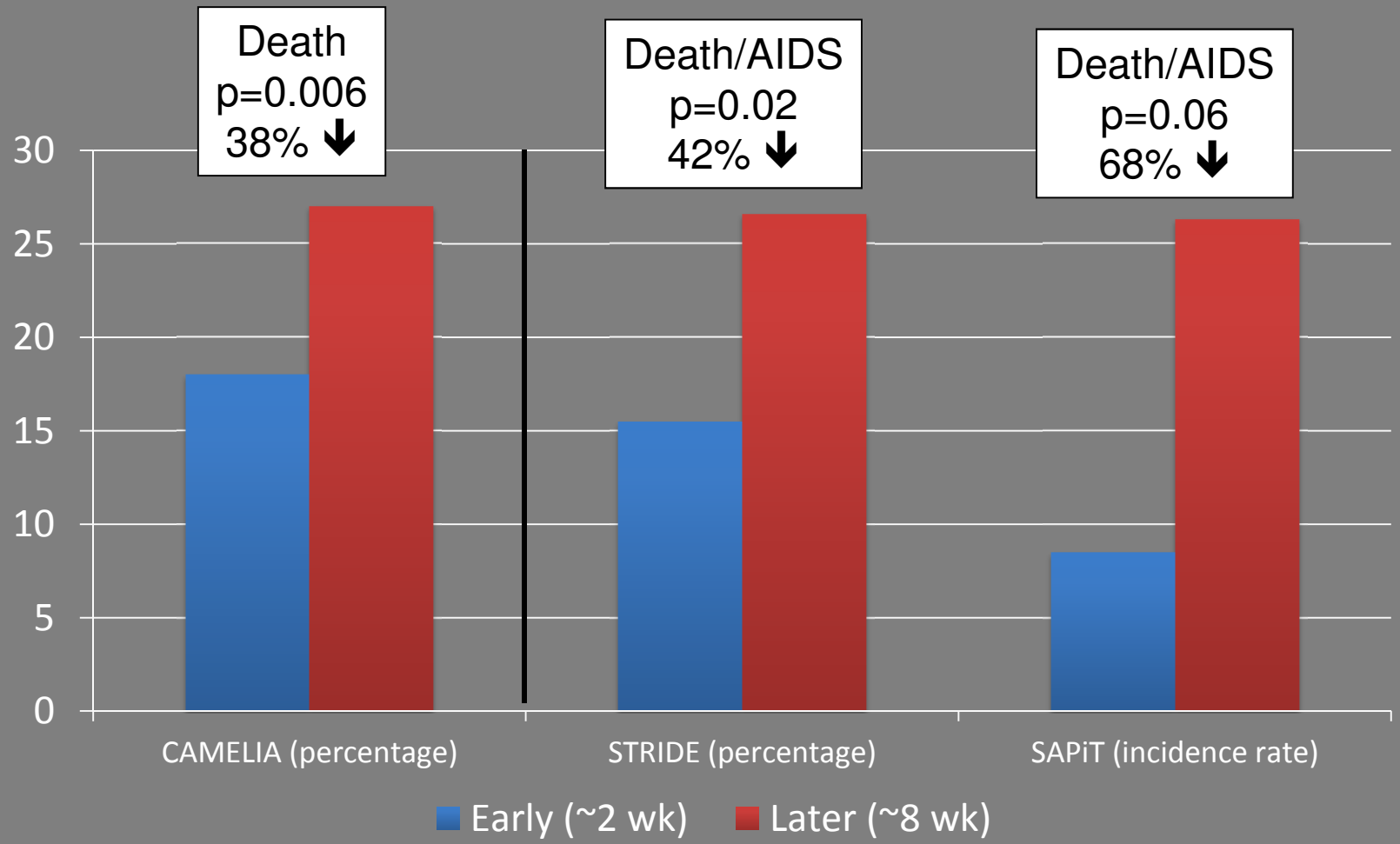
* SAPiT had 3rd arm (ART within 4 weeks of completing TB treatment) that was stopped early by DSMB due to significant excess mortality

Abdool Karim NEJM 2011;365:1492, Havlir NEJM 2011;365:1482, Blanc NEJM 2011;365:1471, Torok Clin Infect Dis 2011;52:1374, Abdool Karim NEJM 2010;362:697

ART timing and primary endpoints



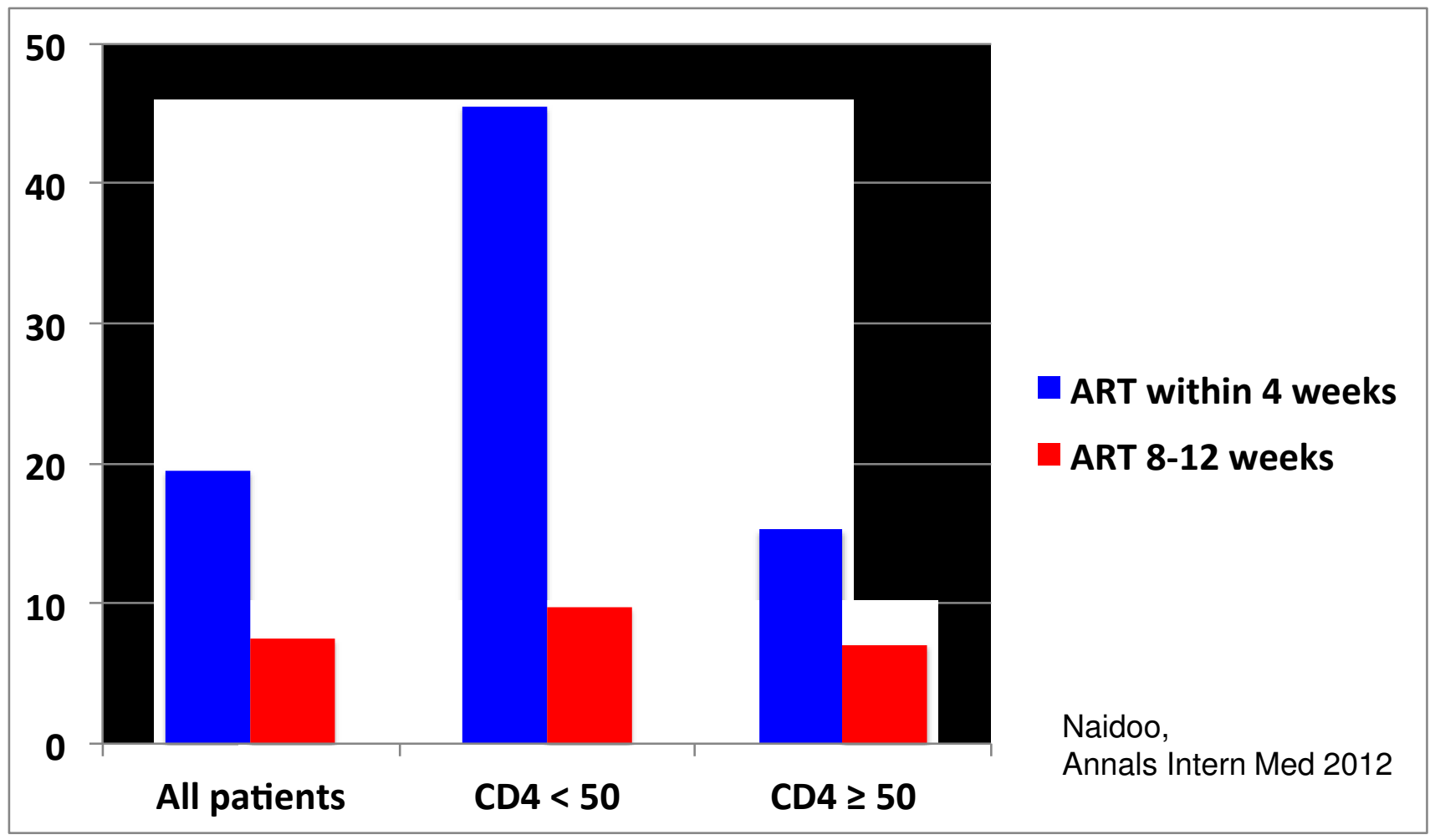
ART timing and primary endpoints in patients with CD4 < 50



* CAMELIA data represents all patients in trial, majority had CD4 < 50 (median CD4 =25)

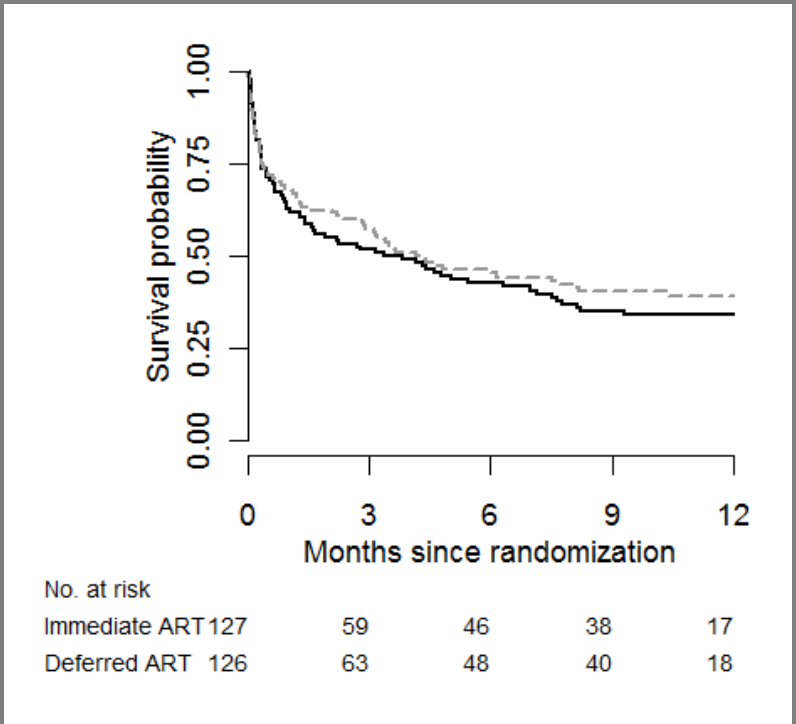
SAPiT IRIS incidence

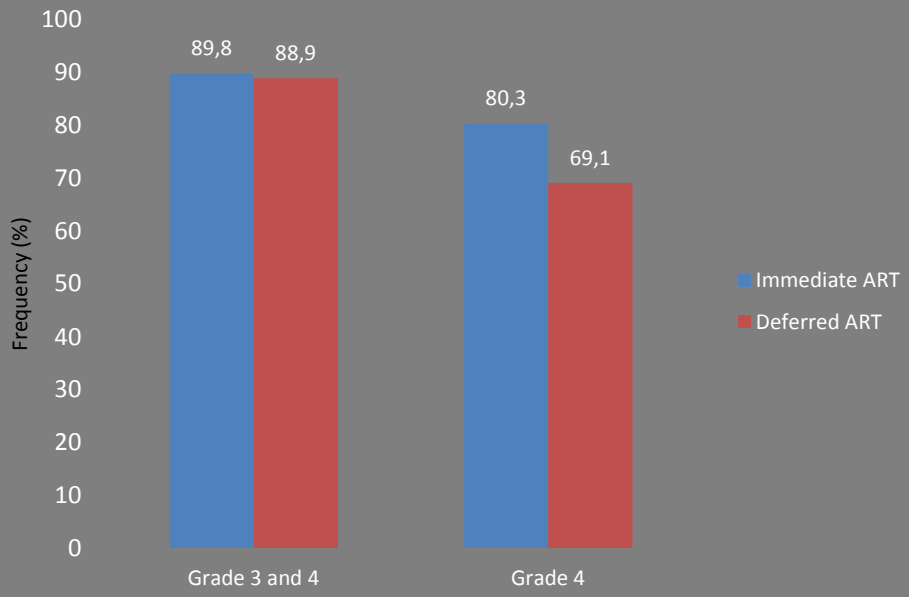
(IRIS cases/100 person years)



TBM trial, Vietnam

Immediate ART (within 1 week) vs Deferred ART (8 weeks)





"These data support deferred initiation of ART in HIV-associated TBM, particularly in resource-limited settings"

Torok Clin Infect Dis 2011;52:1374

ART Timing in TB patients

- CD4 < 50
  - Start at 2 weeks
  - Increased TB-IRIS risk (2-5x)
  - *PredART clinical trial evaluating prednisone to prevent TB-IRIS*
- CD4 > 50
  - Can defer up to 8 weeks
  - Unless clinical reasons to start earlier
- CD4 > 220
  - Can defer longer but for programmatic reasons start by 8 weeks
- TBM
  - Defer 4-6 weeks

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Timing of Antiretroviral Therapy after Diagnosis of Cryptococcal Meningitis

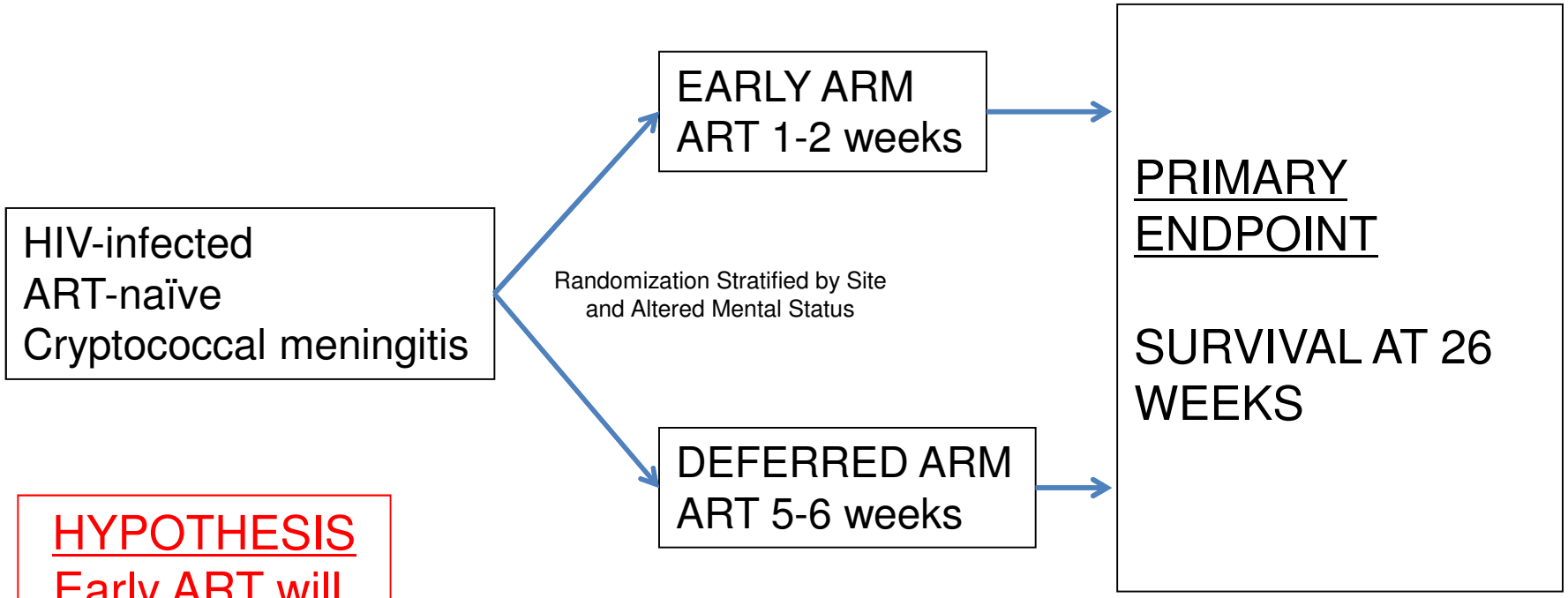
David R. Boulware, M.D., M.P.H., David B. Meya, M.Med., Conrad Muzoora, M.Med., Melissa A. Rolfes, Ph.D., Katherine Huppler Hullsiek, Ph.D., Abdu Musubire, M.Med., Kabanda Taseera, M.Med., Henry W. Nabeta, M.B., Ch.B., Charlotte Schutz, M.B., Ch.B., M.P.H., Darlisha A. Williams, M.P.H., Radha Rajasingham, M.D., Joshua Rhein, M.D., Friedrich Thienemann, M.D., Ph.D., Melanie W. Lo, M.D., Kirsten Nielsen, Ph.D., Tracy L. Bergemann, Ph.D., Andrew Kambugu, M.Med., Yukari C. Manabe, M.D., Edward N. Janoff, M.D., Paul R. Bohjanen, M.D., Ph.D., Graeme Meintjes, M.B., Ch.B., Ph.D., for the COAT Trial Team*

N Engl J Med 2014;370:2487-98.

Randomized Strategy Trial

Cryptococcal Optimal ART Timing (COAT) Trial

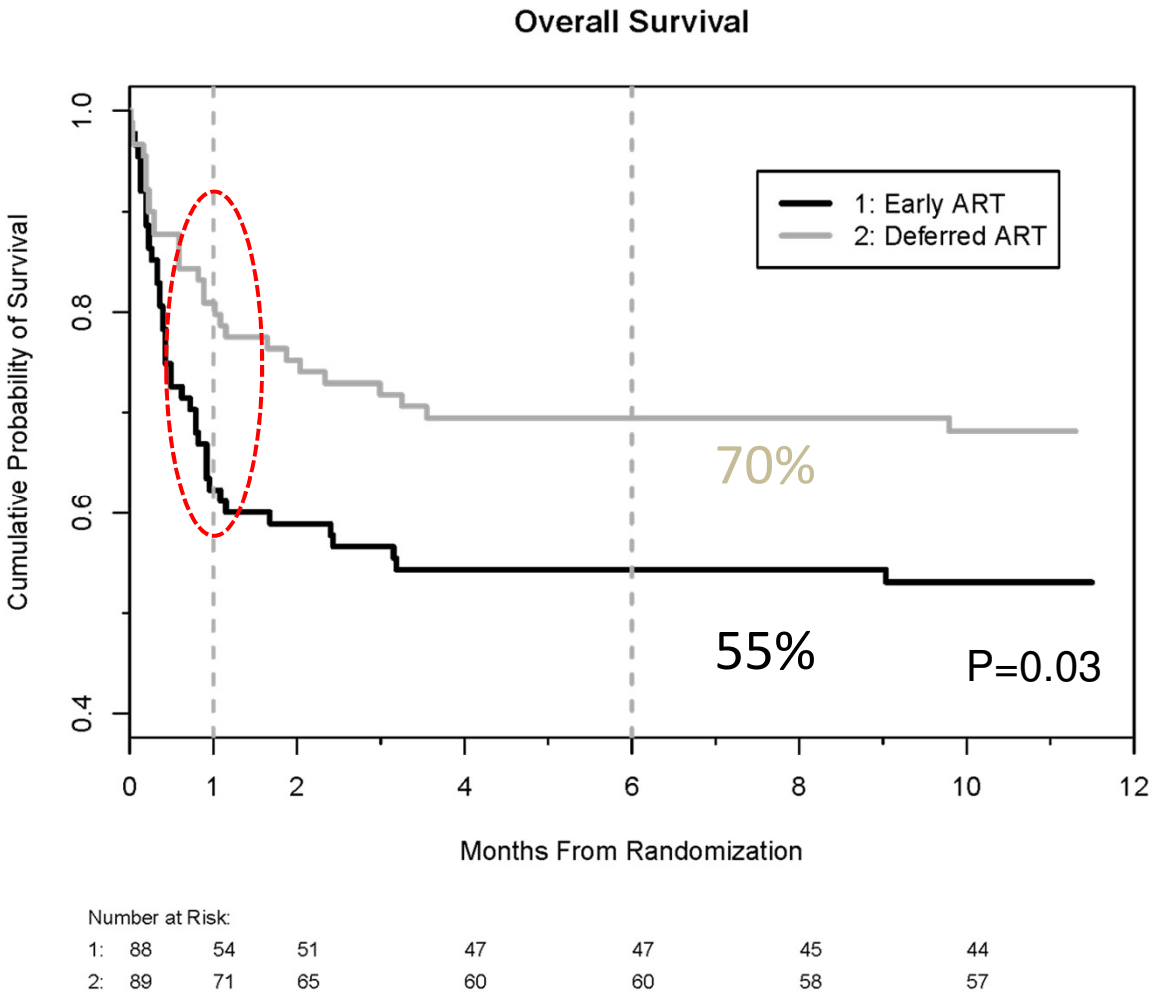
Uganda and South Africa



HYPOTHESIS
Early ART will reduce mortality

Target enrollment = 500
177 participants enrolled
Enrollment halted after 17 months by NIAID Africa DSMB

Boulware et al, NEJM 2014



Hazard ratio [HR] = 1.7
(95% CI = 1.1-2.8)

Early ART:
↑ 70% mortality

Recognised cryptococcal IRIS events
Early ART = 17/87 (20%)
Deferred ART = 9/69 (13%) p=0.32

Boulware et al, NEJM 2014

OUTLINE

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- Return to care after ART interruption
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First line ART

	1	2	3
Recommended	**TDF**	**FTC/3TC**	**Efavirenz**
Alternatives	ABC AZT Short term D4T	-	Rilpivirine Nevirapine

Raltegravir or PI/r to be used as 3rd drug when NNRTI contra-indicated
eg. life-threatening hypersensitivity reaction

SA HIV Clinicians Society 2014

TDF and the kidney: Meta-analysis

- 17 studies
  - 9 RCT
  - 8 Observational
- Tenofovir vs other regimens
  - Mean difference in calculated CrCl: -3.9 ml/min
  - Risk difference for ARF: 0.7%
- But many studies exclude higher risk patients

Cooper, Clin Infect Dis 2010

First line ART & renal function

- Assess creatinine clearance at baseline
  - MDRD or modified Cockgraft-Gault formula
  - Avoid TDF if < 50ml/min
  - Could later use TDF if normalises
- Monitor Creatinine on TDF
  - Timepoints: month 3, 6 and 12 then annually
  - If creatinine rises: recalculate creatinine clearance
- Generally avoid TDF while on injectable for MDR TB

The modified Cockroft-Gault equation:

$$\textbf{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{ideal weight}}{\text{serum creatinine}}$$

*For women, multiply the total by 0.85

NDOH 1st line if TDF contra-indicated

TDF contraindication: Creatinine clearance of <50 mL/min	ABC+ 3TC + EFV (or NVP)	Renal disease or the use of other nephrotoxic drugs e.g. aminoglycosides MDR treatment

Abacavir Drug Hypersensitivity (1)

- Features
  - Fever (usually 39-40 degrees)
  - Rash in 70% (maculopapular or urticarial)
  - Fatigue, malaise
  - GI symptoms (N&V, diarrhoea, abdominal pain)
  - Arthralgias
  - Cough, dyspnoea, pharyngitis
  - Usually > 1 system
  - Temporally related to taking dose

- Timing
  - Median onset 9 days
  - 90% in first 6 weeks

Abacavir Drug Hypersensitivity (2)

- Incidence
  - 4-8% in people of European descent
  - Much less common in people of African descent
  - Strongly associated with HLA-B5701
    - White Americans 8%
    - African-Americans 2.5%
    - Africa < 1%
- Can be fatal
  - 3/10,000 people on abacavir-based ART (trial data)
  - Rechallenge is an important risk

Use of Abacavir in 30 HIV-infected Children From Durban, South Africa

Report From a Pilot Study

To the Editors:

We report on the use of Abacavir from a pilot study conducted between February 3, 2004 and August 29, 2006 at King Edward VIII Hospital in Durban, South Africa. Ethical approval was obtained from the University of KwaZulu Natal.

Thirty ART (antiretroviral therapy) naive children aged between 2 and 12 years with vertically transmitted HIV-1 infection were enrolled in the study to assess the use of structured treatment interruptions.

The children received a combination of 3 nucleoside reverse transcriptase inhibitors, namely Zidovudine, Lamivudine, and Abacavir. The use of a triple nucleoside regimen was based on the unavailability of protease inhibitors at the time of the study, as well as on the possible risk of resistance developing if a non-nucleoside reverse transcriptase inhibitor was used in the interrupted subjects. ART was received for a mean of 84.27 weeks (2–96 weeks). Follow-up was done at regular intervals and the children were monitored for side effects.

During the course of the study, there were no significant adverse events. There was one instance of suspected hypersensitivity. This occurred in a 5-year-old child, who presented with fever and a rash 2 weeks after starting ART. A septic workup and skin biopsy were done on the child. All investigations were normal and the histopathology of the biopsy was nonspecific. It was therefore unclear whether the rash was drug related or due to an intercurrent viral infection. The rash cleared on stopping Abacavir and was therefore not recommenced. The child remained well on follow-up.

All children on the study had molecular class I HLA (human leukocyte antigen) typing done at baseline through the South African National Blood Bank. The most prevalent allele in this cohort was HLA-B*1503. No patient, including the child with the suspected hypersensitivity, had the HLA-B*5701 allele.

Abacavir has been recommended for use in both first and second line therapy.[1] However, there are safety concerns; as hypersensitivity to Abacavir can present with idiosyncratic symptoms.[1] Reintroduction can be potentially fatal.

Studies have shown a strong association between the presence of the (HLA) B*5701 allele and Abacavir hypersensitivity.[1] HLA-B*5701 is more prevalent among Caucasians.[1]

In an HIV-1 infected clade C Zulu/Xhosa population of both children and adults in Durban, South Africa, there was zero prevalence of *B5701.[2–4] Prospective screening for HLA-B*5701 has a positive predictive value of 100% in preventing hypersensitivity reactions to Abacavir.[1] It has been suggested that patients be screened for possible hypersensitivity prior to treatment; however these tests are prohibitively expensive, and possibly not indicated in patients of African origin.

This is the first report on the use of Abacavir in African children. It appears to be safe in a population of children where the prevalence of HLA-B5701 is low, however, it would be prudent to maintain surveillance in view of some reports of Abacavir hypersensitivity in the absence of HLA-B*5701.[5]

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4. Thobakgale CF, Prendergast A, Crawford H, et al. Impact of HLA in mother and child on disease progression of pediatric human immunodeficiency virus type 1 infection. *J Virol*. 2009;83:10234–10244.

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Journal of Antimicrobial Chemotherapy

Virological efficacy of abacavir: systematic review and meta-analysis

Mario Cruciani[1]*, Carlo Mengoli[2], Marina Malena[1], Giovanni Serpelloni[1], Saverio G. Parisi[2], Graeme Moyle[3] and Oliviero Bosco[1]

Findings

- In a meta-analytical pooling of RCTs with a direct comparison of ABC/3TC and TDF/FTC at 48 weeks (6 trials, 4118 patients) proportion with VL < 50 similar in
  - in overall comparison (RR 0.98; 95% CI 0.94–1.03),
  - in the low baseline VL strata (RR 1.01; 95% CI 0.99–1.03)
  - in the high baseline VL strata (RR 0.96; 95% CI 0.90–1.03)

- Similar virological results were found at 96 weeks (4 trials, 2003 patients)

48 weeks

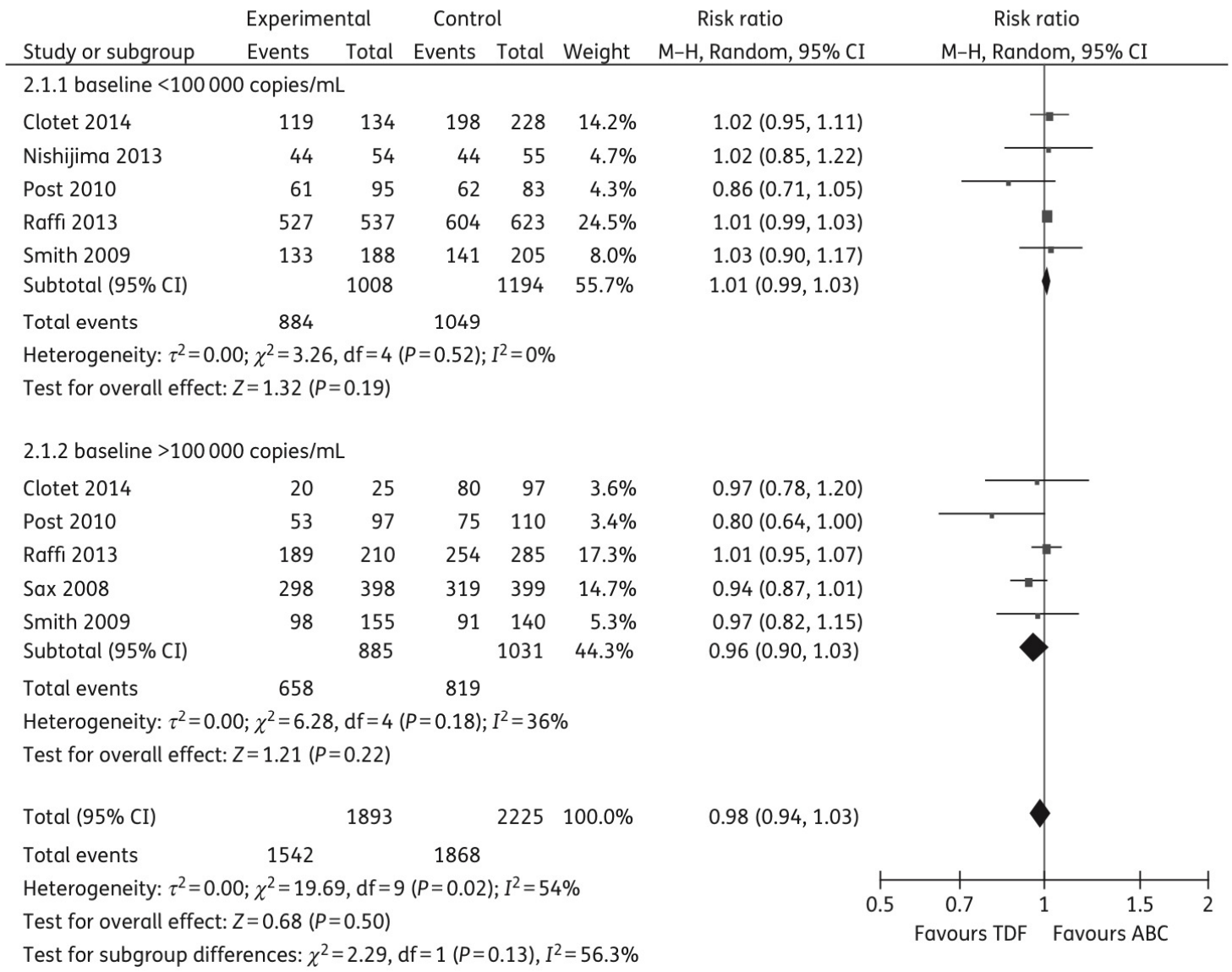

Figure 4. Forest plot of comparison: rates of patients with VL <50 copies/mL at 48 weeks and 96 weeks in studies comparing abacavir (ABC) and tenofovir (TDF) according to baseline VL values. Cumulative results and subgroup analyses based on screening values: <100000 copies/mL (analyses 2.1.1 and 2.2.1) or >100000 copies/mL (analyses 2.1.2 and 2.2.2).

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2nd line

1st LINE	2nd LINE
TDF + FTC + NNRTI →	AZT + 3TC + Lopinavir/ritonavir
AZT/D4T + 3TC + NNRTI →	TDF + FTC + Lopinavir/ritonavir

If on rifampicin-based TB treatment: Double dose lopinavir/ritonavir

Contra-indication or Intolerance

Dyslipidaemia (total cholesterol >6 mmol/L) or diarrhoea associated with LPV/r	Switch LPV/r to ATV/r
Anaemia and renal failure	Switch to ABC

Atazanavir

- Causes mild unconjugated hyperbilirubinaemia in up to 50% of patients
- Competitive inhibition of uridine diphosphate-glucuronosyl transferase (UGT) 1A1 enzyme similar to Gilbert's syndrome
- If other LFTs normal and no hepatitis symptoms then this does not represent liver injury
- Cannot be used with Rifampicin

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IPT guidelines

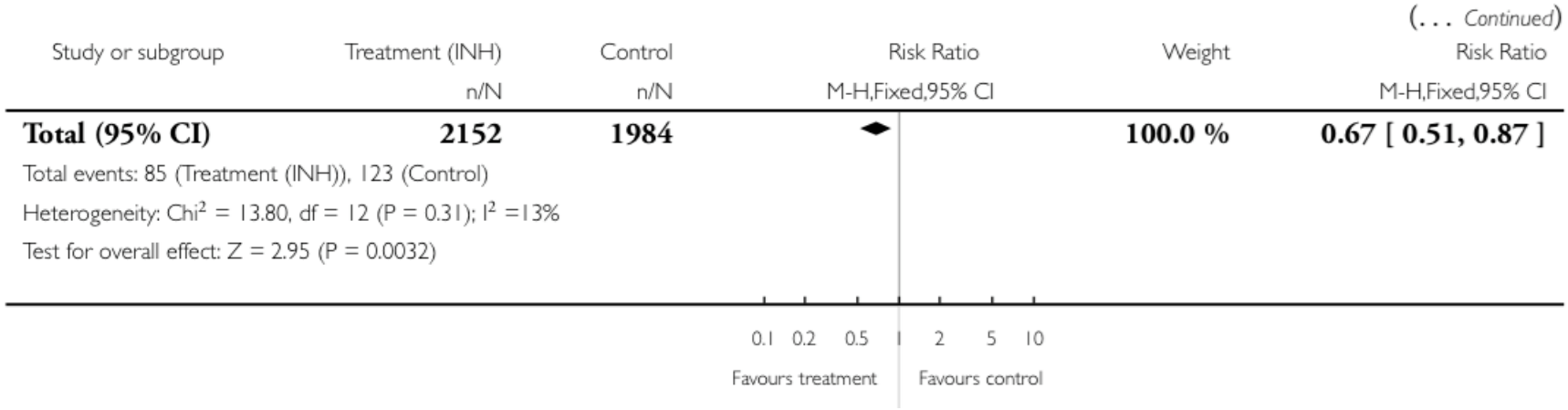
Table 13. Indications for and duration of IPT

TST	Pre-ART	On ART
Not done	IPT for 6 months	IPT for 12 months
Negative	IPT not indicated	IPT for 12 months
Positive	IPT for at least 36 months	IPT for at least 36 months

IPT = isoniazid preventive therapy; TST = tuberculin skin test; ART = antiretroviral therapy.

SA HIV Clin Soc guidelines, 2014

Cochrane meta-analysis: IPT in HIV+



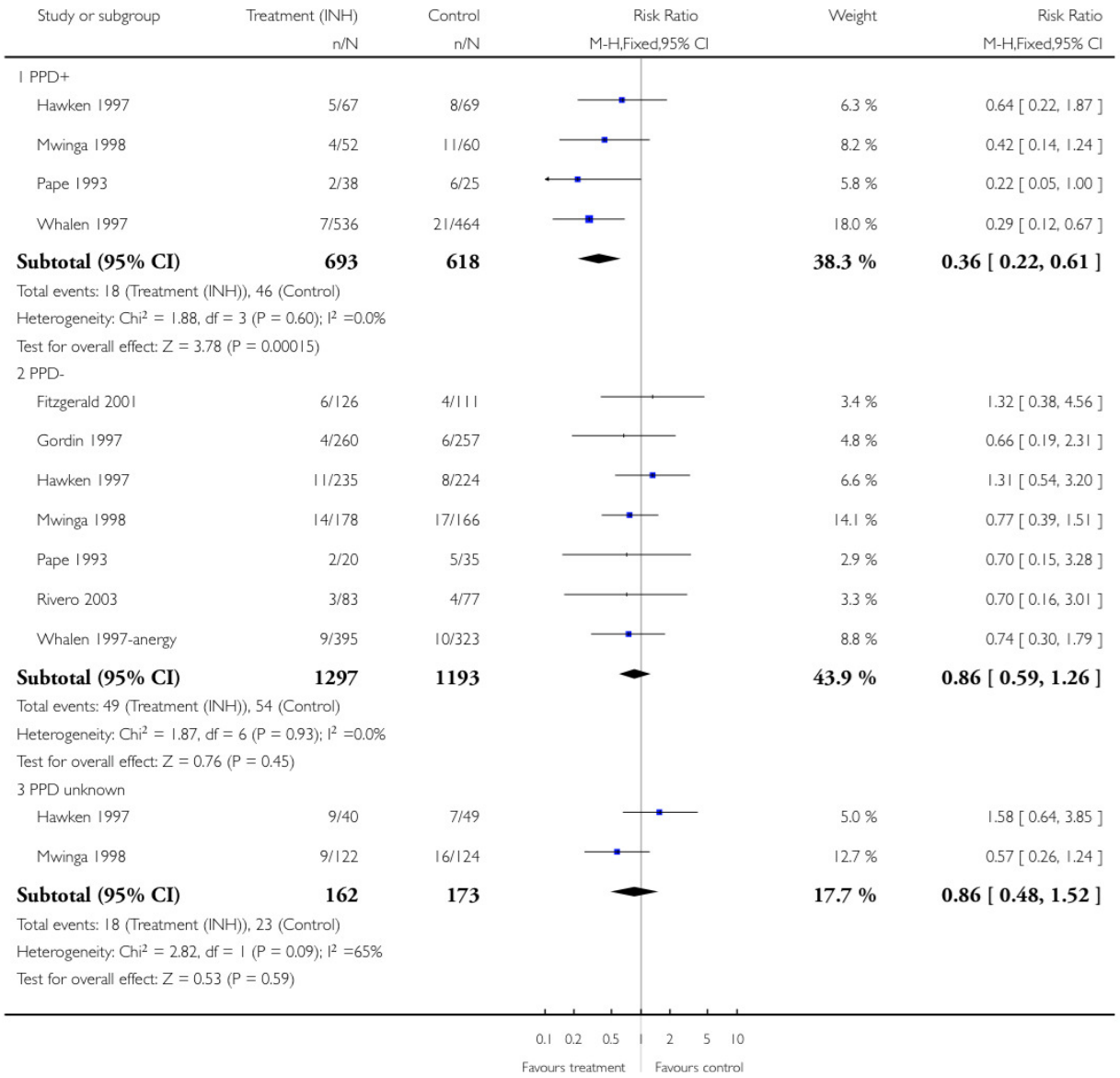
Akolo, 2010

Analysis 2.1. Comparison 2 Isoniazid vs placebo, Outcome 1 Incidence of active TB (confirmed, probable or possible).

Review: Treatment of latent tuberculosis infection in HIV infected persons

Comparison: 2 Isoniazid vs placebo

Outcome: 1 Incidence of active TB (confirmed, probable or possible)



6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial

Taraz Samandari, Tefera B Agizew, Samba Nyirenda, Zegabriel Tedla, Thabisa Sibanda, Nong Shang, Barudi Mosimaneotsile, Oaitse I Motsamai, Lorna Bozeman, Margarett K Davis, Elizabeth A Talbot, Themba L Moeti, Howard J Moffat, Peter H Kilmarx, Kenneth G Castro, Charles D Wells

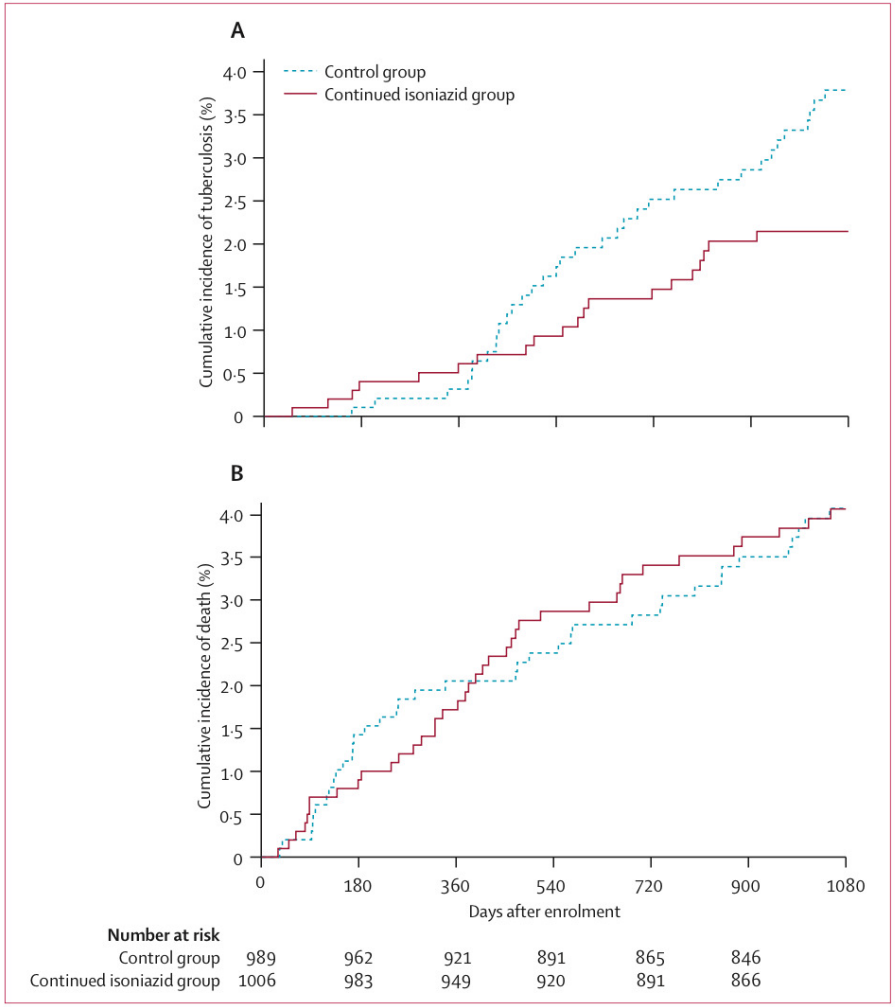


Figure 2: Cumulative incidence of tuberculosis (A) and death (B) in participants receiving 6 months' open-label isoniazid and 30 months' masked placebo (control group) or isoniazid (continued isoniazid group)

Overall (n=1995)

- 43% reduction in TB

TST positive

- 74% reduction in TB

TST negative

- No significant reduction in TB
- Unexplained increased mortality (21 vs 7 deaths after 5 months)

Lancet 2011; 377: 1588–98

Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial

Molebogeng X Rangaka, Robert J Wilkinson, Andrew Boulle, Judith R Glynn, Katherine Fielding, Gilles van Cutsem, Katalin A Wilkinson, Rene Goliath, Shaheed Mathee, Eric Goemaere, Gary Maartens

1329 patients starting ART/on ART randomised to 12 months IPT vs placebo

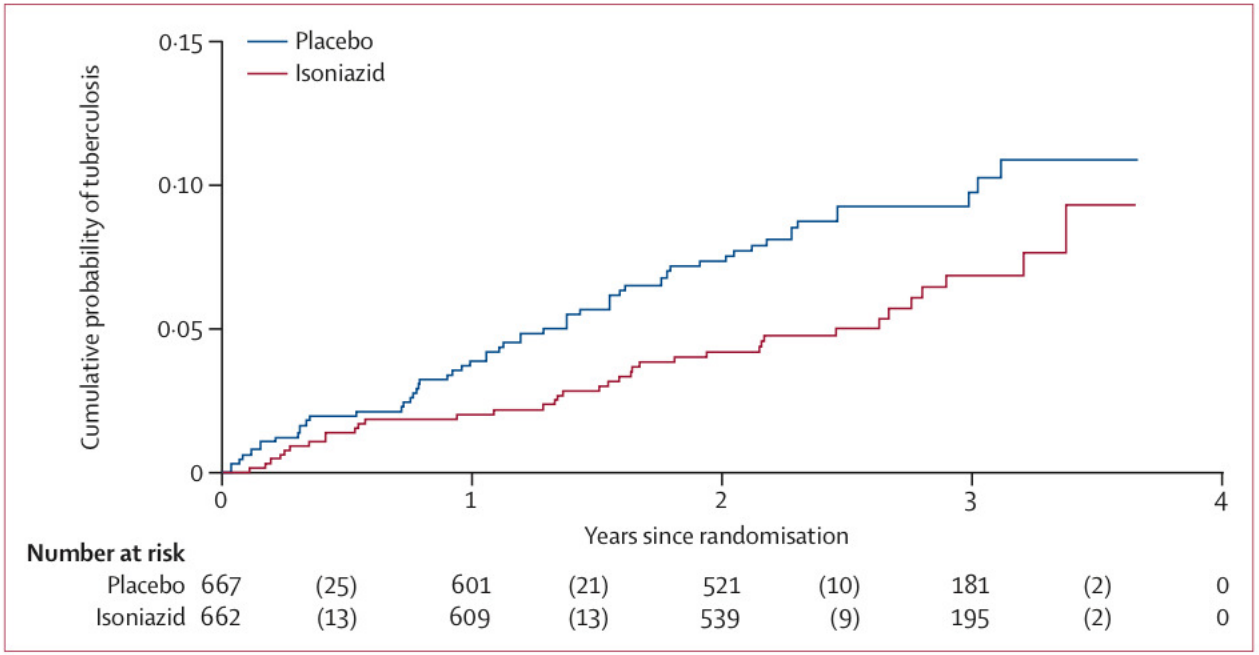
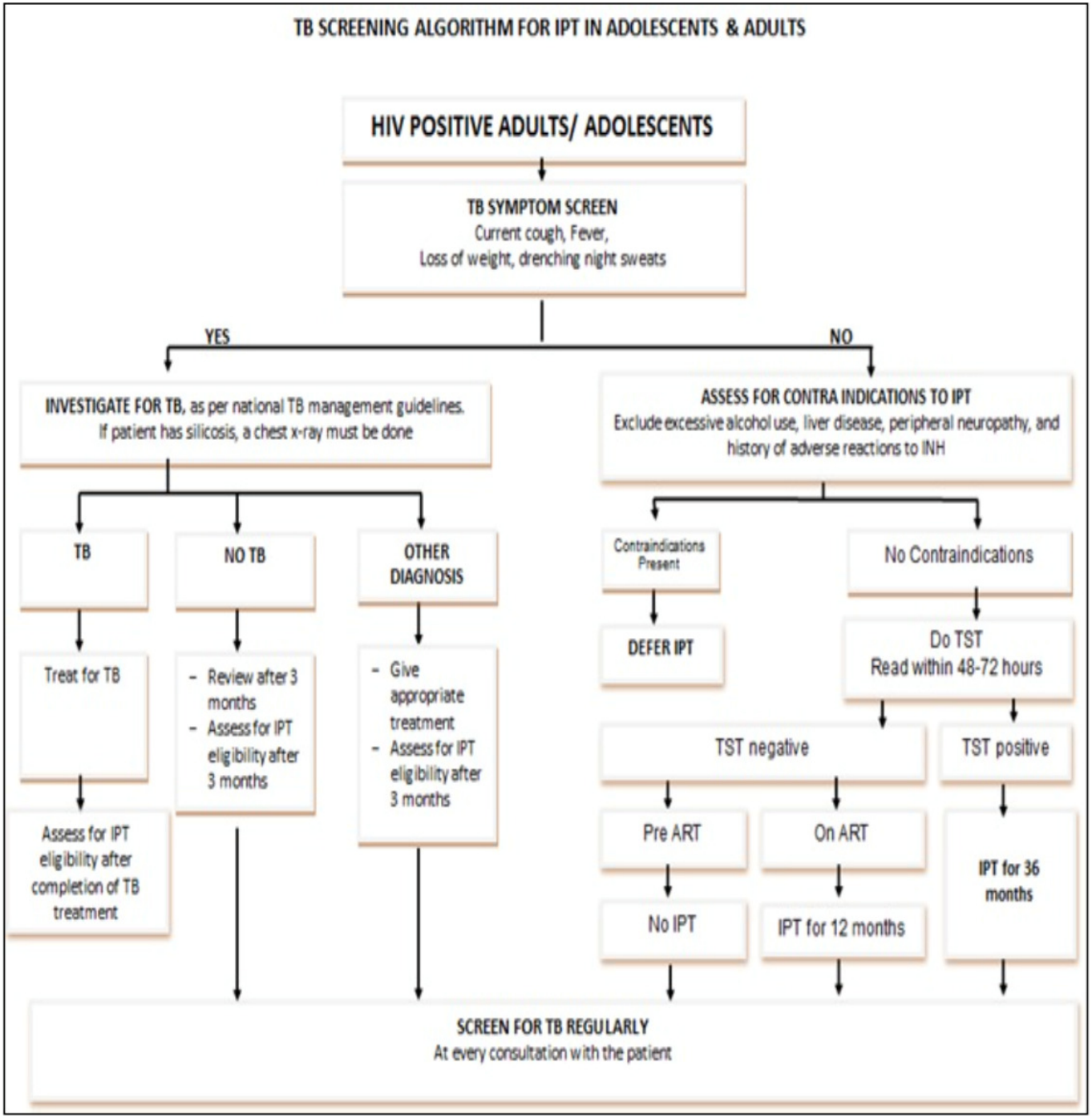


Figure 2: **Time to tuberculosis from randomisation**
The placebo group was given antiretroviral therapy plus placebo and the isoniazid group was given antiretroviral therapy plus isoniazid. Numbers show the number of participants followed up at each timepoint, and the numbers in parentheses show new tuberculosis cases in each period. Log-rank test p value for equality of survival curves=0·02.

Lancet, 2014


TB SCREENING ALGORITHM FOR IPT IN ADOLESCENTS & ADULTS
HIV POSITIVE ADULTS/ ADOLESCENTS
TB SYMPTOM SCREEN
Current cough, Fever,
Loss of weight, drenching night sweats
YES
NO
INVESTIGATE FOR TB, as per national TB management guidelines.
If patient has silicosis, a chest x-ray must be done
ASSESS FOR CONTRA INDICATIONS TO IPT
Exclude excessive alcohol use, liver disease, peripheral neuropathy, and history of adverse reactions to INH
TB
NO TB
OTHER DIAGNOSIS
Contraindications Present
No Contraindications
Treat for TB
- Review after 3 months
- Assess for IPT eligibility after 3 months
- Give appropriate treatment
- Assess for IPT eligibility after 3 months
DEFER IPT
Do TST
Read within 48-72 hours
Assess for IPT eligibility after completion of TB treatment
TST negative
TST positive
Pre ART
On ART
IPT for 36 months
No IPT
IPT for 12 months
SCREEN FOR TB REGULARLY
At every consultation with the patient

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Development of a Standardized Screening Rule for Tuberculosis in People Living with HIV in Resource-Constrained Settings: Individual Participant Data Meta-analysis of Observational Studies

Haileyesus Getahun[1]*, Wanitchaya Kittikraisak[2], Charles M. Heilig[3], Elizabeth L. Corbett[4], Helen Ayles[4,5], Kevin P. Cain[3], Alison D. Grant[4], Gavin J. Churchyard[6], Michael Kimerling[7], Sarita Shah[8], Stephen D. Lawn[4,9], Robin Wood[9], Gary Maartens[10], Reuben Granich[1], Anand A. Date[3], Jay K. Varma[2,3]

The best performing rule was the presence of any one of:

- current cough (any duration)
- fever
- night sweats
- or weight loss

The overall sensitivity was 78.9% and specificity was 49.6%

Published 2011

OUTLINE

- When to start ART
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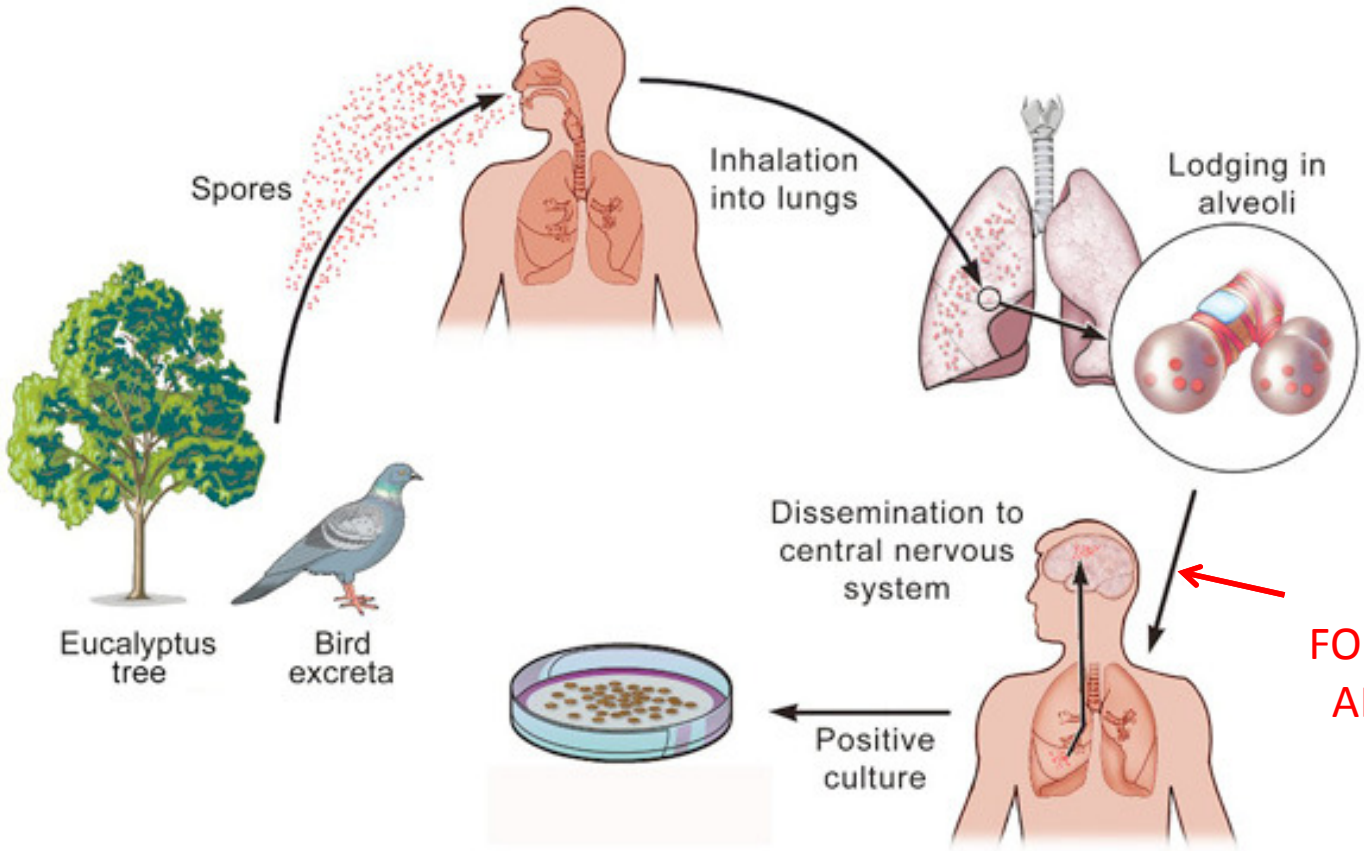
- Reducing CD4 count monitoring

Phase of HIV management	Purpose
HIV diagnosis	
Confirm HIV result with rapid antibody test if no test results are available	To confirm HIV-positive status in patients who present without documented proof of positive HIV status
WHO clinical staging if HIV-positive	To assess eligibility for ART and timing of initiation
CD4 count	To identify eligibility for ART (CD4 <500/µl) To identify eligibility for prioritisation (CD4 <350/µl) To identify eligibility for fast-tracking (CD4 <200/µl) To identify eligibility for Cotrimoxazole (CD4 <200/µl) To identify eligibility for CrAg or CLAT (CD4 <100/µl)
Screen for pregnancy or ask if planning to conceive	To identify women who need ART for PMTCT and offer appropriate family planning
Assessment of hypertension and diabetes with blood pressure and urine glycosuria	To identify any concomitant chronic diseases
Screen for TB symptoms using the TB screening tool	To identify those suspected of TB and refer them for investigation and to assess eligibility for INH
Screen for HBV (HBsAg)	To identify those co-infected with HBV so that they can be initiated on ART regardless of CD4 count
Screening for STIs and syphilis	To identify and treat STIs
Weight and height in adolescent	To check if the weight is above or below 40kg to determine which ARV drugs to use
Cryptococcus Antigen (CrAg) test if CD4 <100 cells/µl	To assess if there is disseminated Cryptococcal infection and if fluconazole treatment/prophylaxis is indicated
Do Hb or FBC if requires AZT Creatinine if requires TDF ALT if requires NVP	To detect anaemia or neutropenia To assess renal sufficiency To exclude liver dysfunction
Fasting cholesterol and triglycerides if requires LPV/r	To identify at risk of LPV/r related hyperlipidaemia. If above 6 mml/L, consider (ATV/r) instead of LPV/r (if available)



In a Ugandan study: Antigenaemia preceded meningitis by median 22 days (>100 days in 11%)

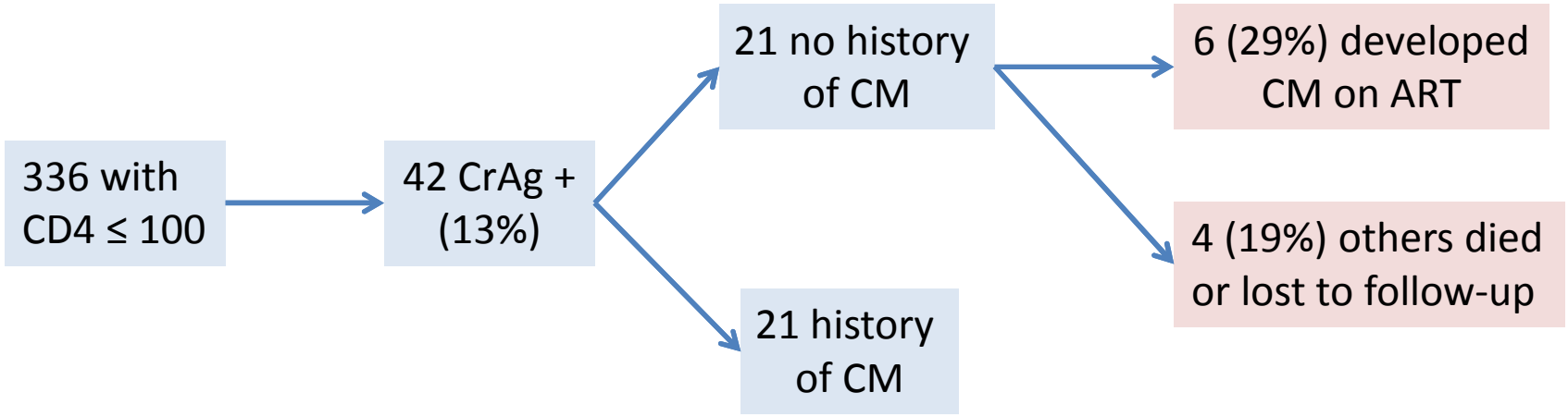
French, AIDS 2002;16:1031

Screening for Cryptococcal Antigenemia in Patients Accessing an Antiretroviral Treatment Program in South Africa

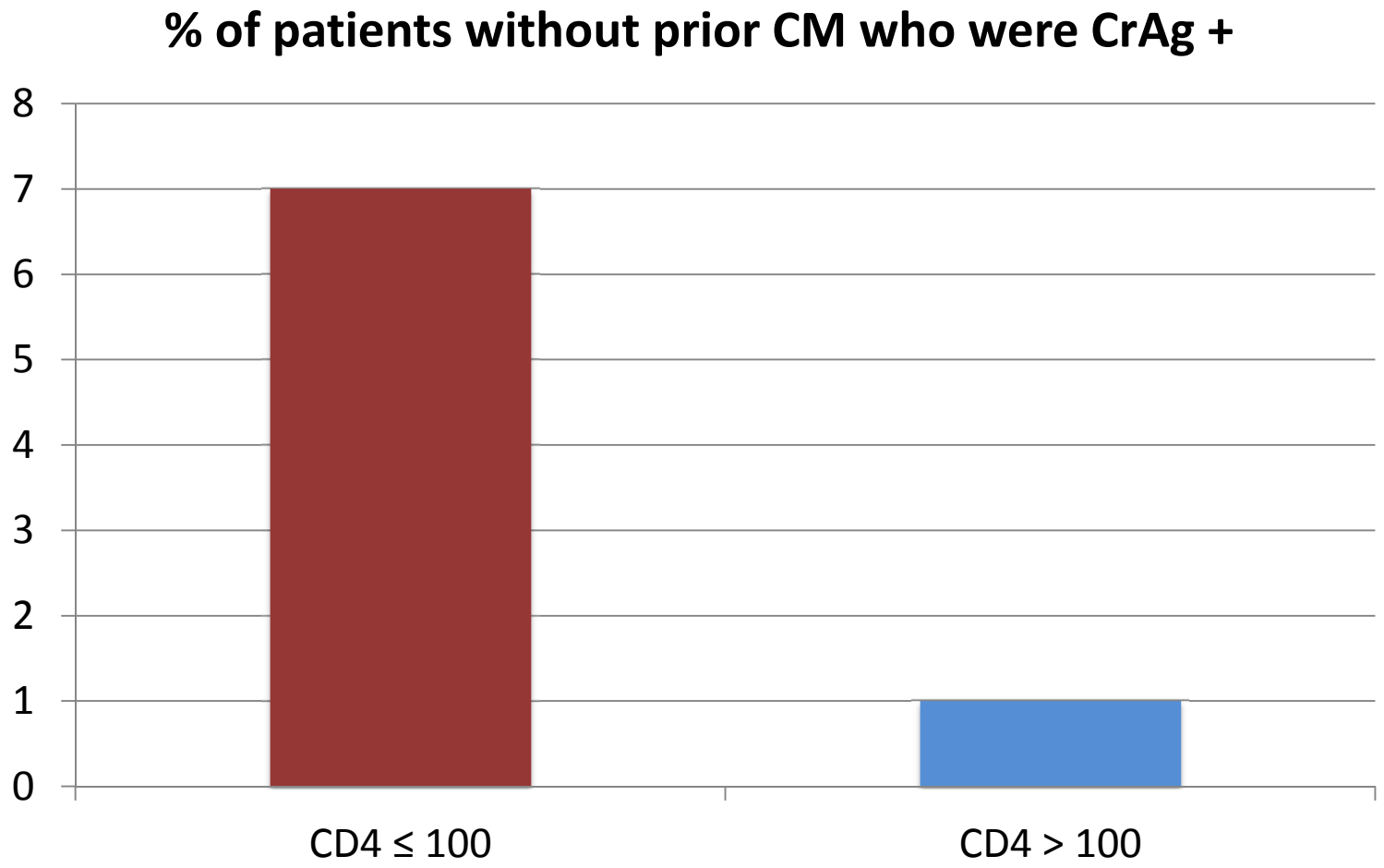
Joseph N. Jarvis,[1,2,3,4] Stephen D. Lawn,[1,5] Monica Vogt,[1] Nonzwakazi Bangani,[1] Robin Wood,[1] and Thomas S. Harrison[1,4]

Clin Infect Dis 2009;48:856

Retrospective testing of plasma of 707 patients who started ART 2002-2005



Among those who were CrAg negative none developed CM



Jarvis et al, Clin Infect Dis 2009;48:856

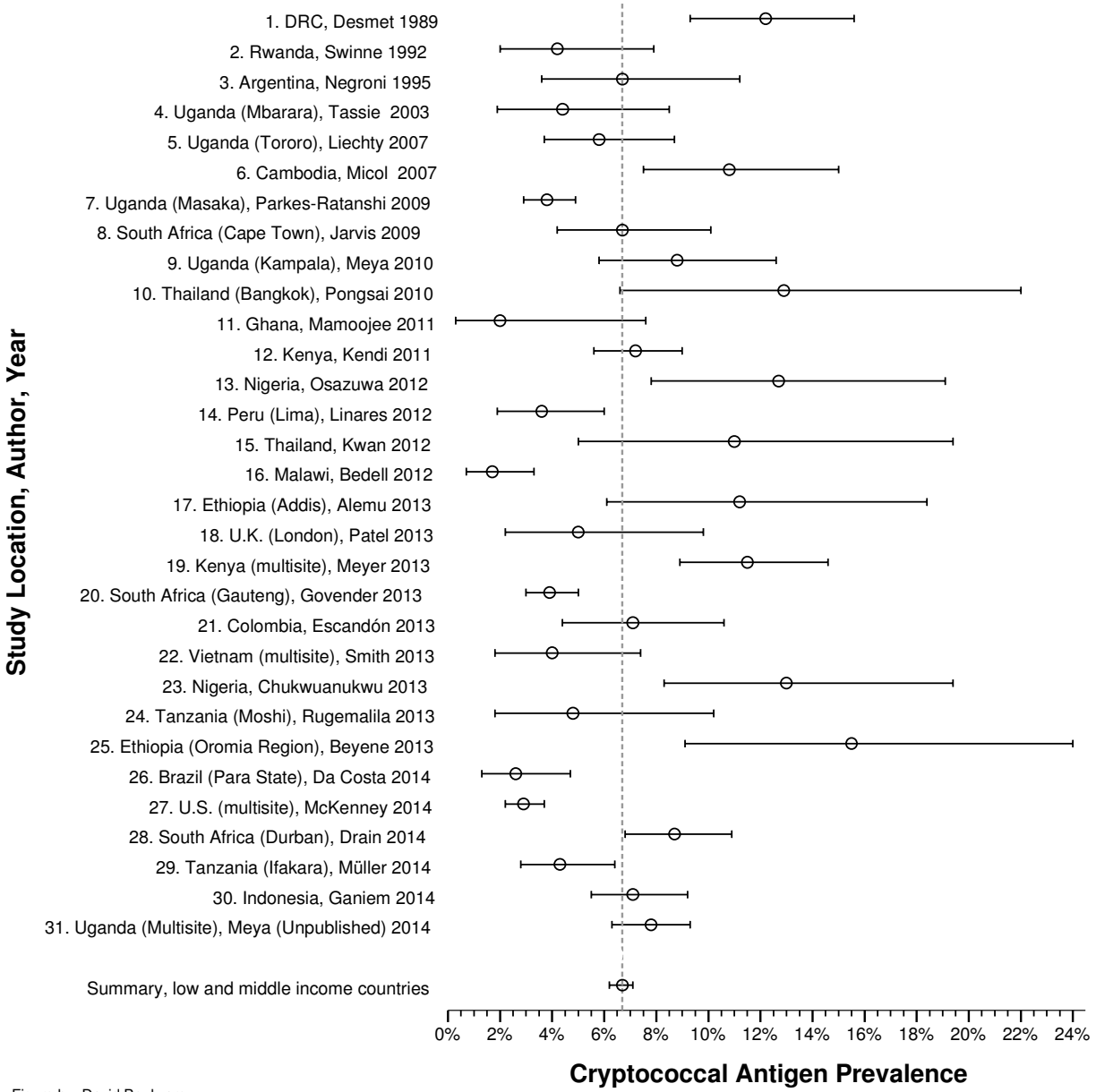
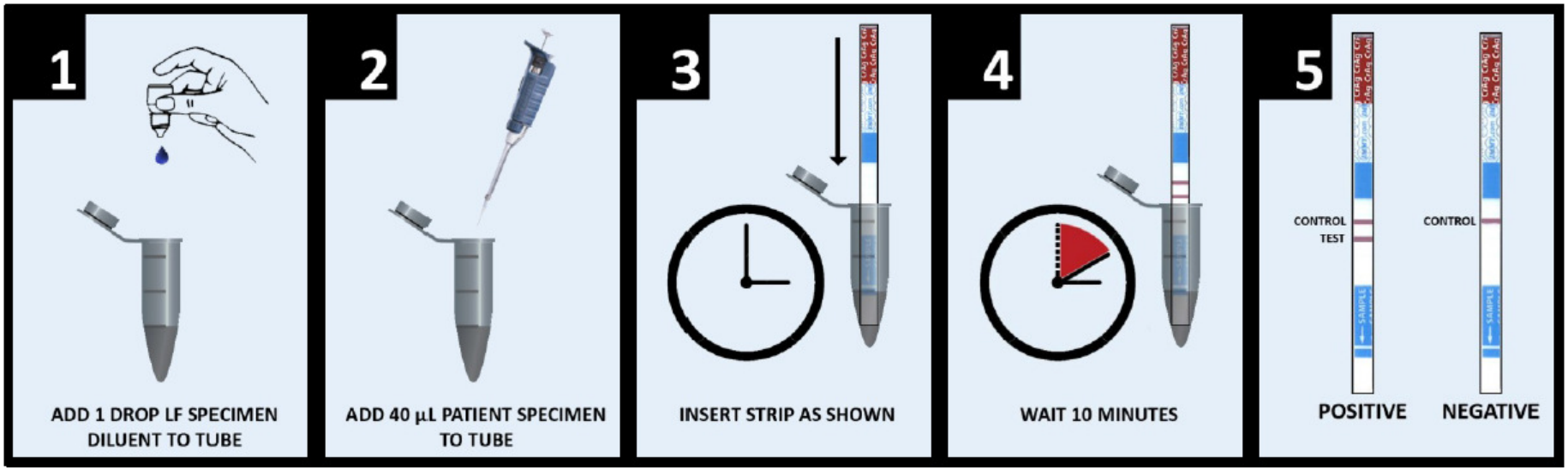
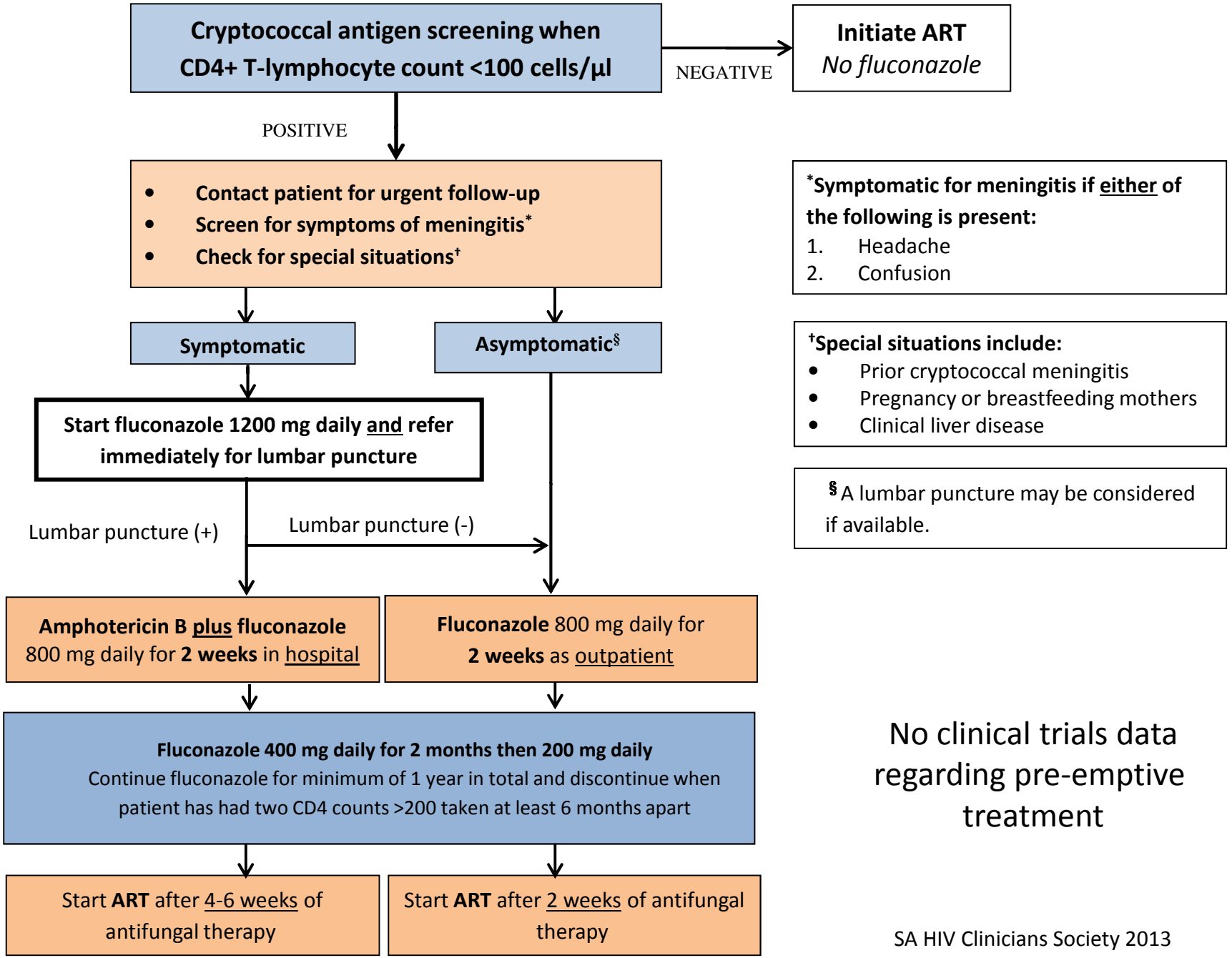


Figure by: David Boulware

CrAg Lateral Flow Assay



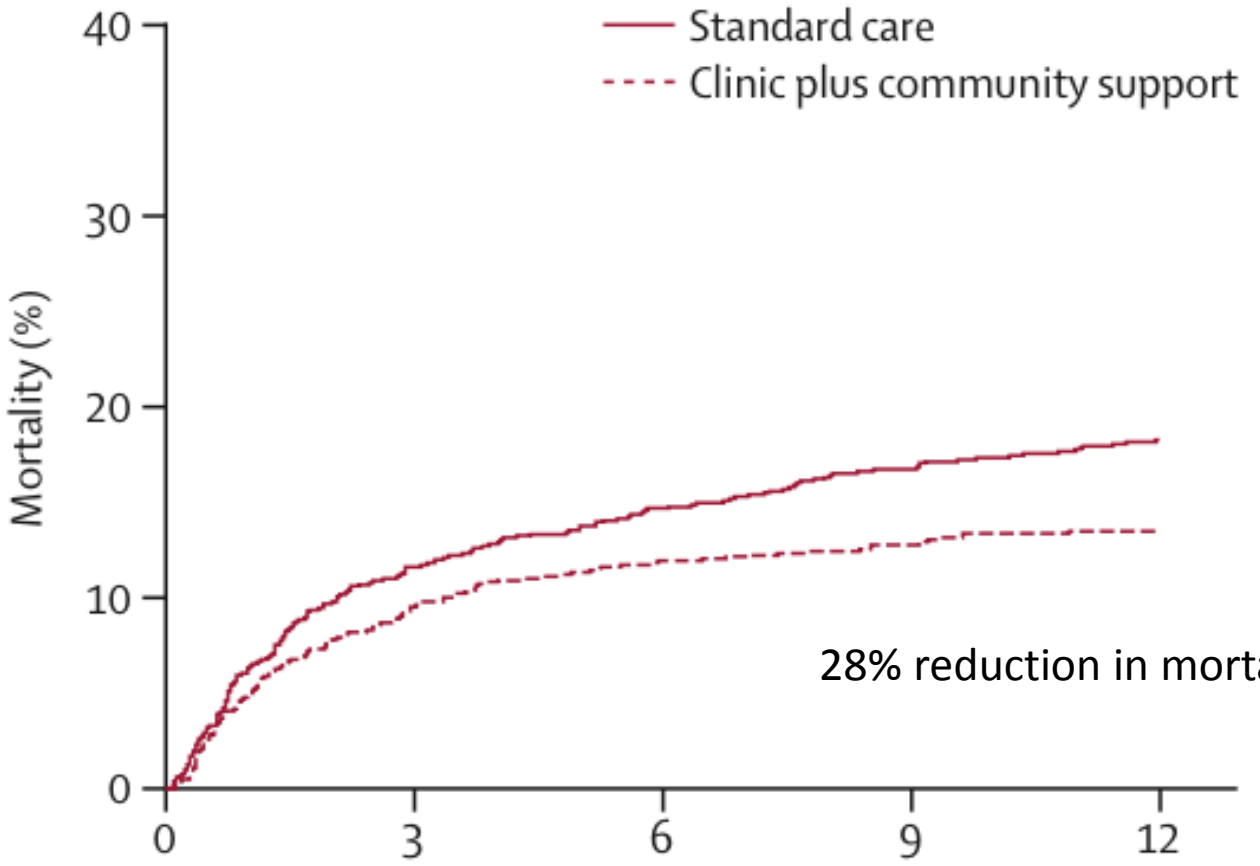
Source: Immy CrAg LFA package insert


Cryptococcal antigen screening when CD4+ T-lymphocyte count <100 cells/µl
NEGATIVE
Initiate ART
No fluconazole
POSITIVE
Contact patient for urgent follow-up
Screen for symptoms of meningitis*
Check for special situations†
Symptomatic
Asymptomatic§
Start fluconazole 1200 mg daily and refer immediately for lumbar puncture
Lumbar puncture (+)
Lumbar puncture (-)
Amphotericin B plus fluconazole 800 mg daily for 2 weeks in hospital
Fluconazole 800 mg daily for 2 weeks as outpatient
Fluconazole 400 mg daily for 2 months then 200 mg daily
Continue fluconazole for minimum of 1 year in total and discontinue when patient has had two CD4 counts >200 taken at least 6 months apart
Start ART after 4-6 weeks of antifungal therapy
Start ART after 2 weeks of antifungal therapy
*Symptomatic for meningitis if either of the following is present:
1. Headache
2. Confusion
†Special situations include:
• Prior cryptococcal meningitis
• Pregnancy or breastfeeding mothers
• Clinical liver disease
§ A lumbar puncture may be considered if available.
No clinical trials data regarding pre-emptive treatment
SA HIV Clinicians Society 2013

Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial

*Sayoki Mfinanga, Duncan Chanda, Sokoine L Kivuyo, Lorna Guinness, Christian Bottomley, Victoria Simms, Carol Chijoka, Ayubu Masasi, Godfather Kimaro, Bernard Ngowi, Amos Kahwa, Peter Mwaba, Thomas S Harrison, Saidi Egwaga, Shabbar Jaffar, on behalf of the REMSTART trial team**

Lancet, published online March 10,2015



28% reduction in mortality

Number at risk

Clinic plus community support	1001	899	869	854	842
Standard care	998	869	834	811	794

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Return to care after 1st line interruption

- Issues to consider
  - History of adherence prior to default episode
  - Viral load measure prior to default episode
  - CD4 nadir and current CD4
  - Current clinical status
- Individualised decision weighing up
  - Not wanting to unnecessarily switch to 2nd line (less well tolerated)
  - Not wanting to restart patient on failing regimen if very immunosuppressed
- If restart first line (especially in patients with CD4 < 200)
  - Do viral load when restart then at 2-3 months, anticipate > 2 log drop if adherent and no resistance
  - Most will have VL < 1000 by 3 months

Return to care after interruption (1)

- We recommend restarting the same regimen if patients return to care after defaulting therapy.
- A VL should preferably be performed before restarting. We then recommend that the VL is measured 3 months after restarting ART; switching to a second-line regimen should be considered if the VL is not <1 000 copies/mL at this point.
- In patients with multiple episodes of interruption, particularly beyond the first year of ART, many clinicians would consider switching to a second- line regimen, making the assumption that the multiple interruptions resulted in first-line resistance.
- Reasons for defaulting should be addressed and adherence support increased.

SA HIV Clin Soc guidelines, 2014

Return to care after interruption (2)

- Hospitalisation with an AIDS-defining condition and a CD4+ count of <50 cells/µL represents another situation where a patient may be restarted immediately on second-line ART when returning to care after defaulting
- The reason being that the patient is considered to be at high risk of mortality if restarted on a first-line therapy to which their virus may be resistant, and that they require a guaranteed effective ART regimen immediately.
- This decision should usually be taken by the clinicians at a hospital level.

SA HIV Clin Soc guidelines, 2014

6.6.9 Management of patients previously on ART

If a patient is referred in (e.g. from the private sector), and **is still on ART**and the regimen is successful (VL undetectable and no side-effects), where possible, the patient should be continued on the same regimen.

If the patient **has interrupted treatment** and was on a previous regimen as above, or where the prior regimen is unknown, take a full history to establish why the treatment was stopped. If the interruption was NOT due to toxicity or clear virological failure, check the VL and restart first line treatment as above, and **repeat the VL after 2 months.**

If patients **have failed a previous regimen**, initiate appropriate second line treatment.

If patient was **previously on ART but has interrupted treatment,** establish the cause of the interruption. If it is due to social or psychological factors, address these and follow up on interventions. If the patient stopped as a result of side effects, evaluate other drug choices and offer appropriate options. If the interruption was due to drug supply issues, and there were no non-adherence, resistance or toxicity issues, the previous ART regimen should be reinitiated as soon as possible.

NB: If NVP is restarted after an interruption of >1 week, re-commence with the 2 week lead-in dose and check the ALT if the patient becomes symptomatic.

SA NDOH guidelines

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Monitoring on ART

On ART	Purpose
Screen for TB symptoms at each visit	To identify TB/HIV co-infected
WHO clinical staging at every visit	To identify new OIs
Ask about side effects at each visit	To identify ARV related toxicity
CD4 at 1 year on ART	To monitor immune response to ART
VL at month 6, month 12 on ART and then every 12 months	To identify treatment failures and problems with adherence
ALT if on NVP and develops rash or symptoms of hepatitis	To identify NVP toxicity
FBC at month 3 and 6 if on AZT and	To identify AZT toxicity
then every 12 months	
Creatinine at month 3 and 6, month 12, then every 12 months if on TDF	To identify TDF toxicity
Fasting cholesterol and triglycerides at month 3 if on LPV/r	To identify LPV/r toxicity

SA NDOH guidelines

The future role of CD4 cell count for monitoring antiretroviral therapy

Nathan Ford, Graeme Meintjes, Anton Pozniak, Helen Bygrave, Andrew Hill, Trevor Peter, Mary-Ann Davies, Beatriz Grinsztejn, Alexandra Calmy, N Kumarasamy, Praphan Phanuphak, Pierre deBeaudrap, Marco Vitoria, Meg Doherty, Wendy Stevens, George K Siberry

For more than two decades, CD4 cell count measurements have been central to understanding HIV disease progression, making important clinical decisions, and monitoring the response to antiretroviral therapy (ART). In well resourced settings, the monitoring of patients on ART has been supported by routine virological monitoring. Viral load monitoring was recommended by WHO in 2013 guidelines as the preferred way to monitor people on ART, and efforts are underway to scale up access in resource-limited settings. Recent studies suggest that in situations where viral load is available and patients are virologically suppressed, long-term CD4 monitoring adds little value and stopping CD4 monitoring will have major cost savings. CD4 cell counts will continue to play an important part in initial decisions around ART initiation and clinical management, particularly for patients presenting late to care, and for treatment monitoring where viral load monitoring is restricted. However, in settings where both CD4 cell counts and viral load testing are routinely available, countries should consider reducing the frequency of CD4 cell counts or not doing routine CD4 monitoring for patients who are stable on ART.

Lancet Infect Dis 2014

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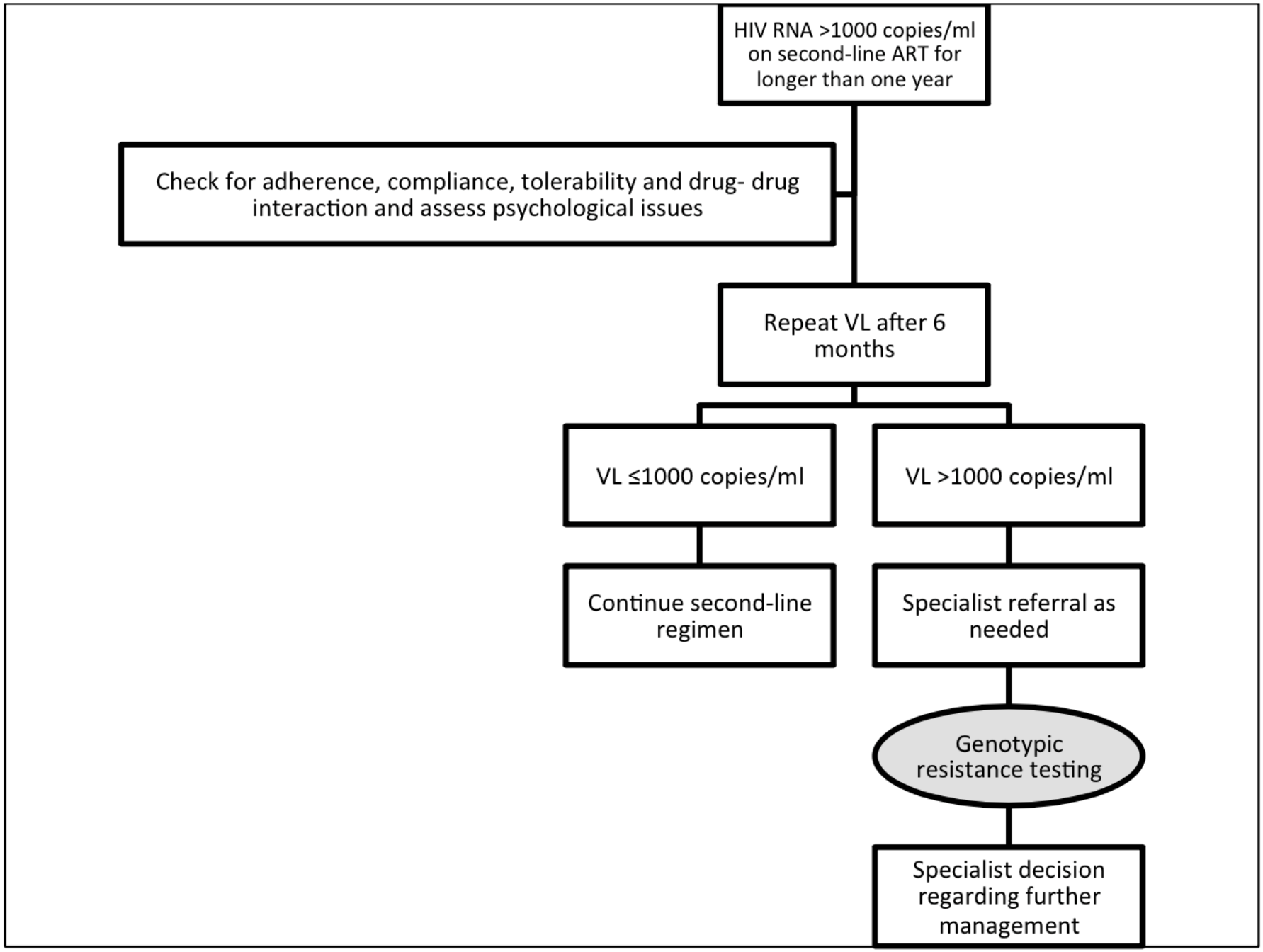
Department of HIV/AIDS, World Health Organization, Geneva, Switzerland (N Ford PhD, M Vitoria MD, M Doherty PhD); **Clinical Infectious Diseases Research Initiative, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South**

Consideration for Genotype & 3rd line

- Repeated VL > 1000 on 2nd line ART
- On 2nd line > 1 year
- Of those with virological failure on 2nd line majority do not have resistance*
- Critical to ensure adherence
  - Pharmacy claims records for the last 6 months is objective method (specific but not sensitive)
- Adherence counseling and address side effects
- Ask re previous exposure to rifampicin without lopinavir/ritonavir dose adjustment

*Van Zyl, PLoSONE 2013; Wallis, AIDS Res and Treatment 2011


HIV RNA >1000 copies/ml on second-line ART for longer than one year
Check for adherence, compliance, tolerability and drug- drug interaction and assess psychological issues
Repeat VL after 6 months
VL ≤1000 copies/ml
VL >1000 copies/ml
Continue second-line regimen
Specialist referral as needed
Genotypic resistance testing
Specialist decision regarding further management

Third line options

- NRTIs with best resistance profile
- New generation NNRTIs
  - Etravirine (and rilpivirine)
  - NNRTI genotype unreliable at 2nd line failure
- **Ritonavir-boosted darunavir**
- **Raltegravir**

- *Maraviroc (cost+++, only if purely CCR5 tropic)*
- *Dolutegravir (to be registered later this year)*

STANFORD UNIVERSITY

HIV DRUG RESISTANCE DATABASE

A curated public database designed to represent, store, and analyze the divergent forms of data underlying HIV drug resistance.

GENOTYPE-RX GENOTYPE-CLINICAL

HIVdb Program: Mutation List Analysis

Protease, RT, and integrase mutations can be entered using either the text box or pull down menus (detailed usage is found below).

The output can then be customized to display mutation comments, mutation scores, and an optional identifier and date. For further explanations and sample datasets please see the Release Notes.

Reverse Transcriptase

Enter Mutation List:

OR

Use The Pulldown Menus:

41 ---	44 ---	62 ---	65 ---	67 ---	69 ---	70 ---	74 ---
75 ---	77 ---	90 ---	98 ---	100 ---	101 ---	103 ---	106 ---
108 ---	115 ---	116 ---	118 ---	138 ---	151 ---	179 ---	181 ---
184 ---	188 ---	190 ---	210 ---	215 ---	219 ---	221 ---	225 ---
227 ---	230 ---	234 ---	236 ---	238 ---	318 ---	333 ---	348 ---

Protease

http://hivdb.stanford.edu/

Mutation Scoring

PR	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
M46I	10	0	10	10	10	20	5	5
I54V	15	0	10	15	15	20	15	20
L76V	-5	20	60	30	30	0	-5	-5
V82A	15	0	15	30	30	30	15	0
L10IV	0	0	0	0	0	0	0	0
Q58E	5	0	0	0	0	5	0	15
A71I	5	0	5	0	0	5	5	0
L76V+M46I	-	-	-	10	10	10	-	-
I54V+V82A	10	-	10	10	10	10	10	-
V82A+M46I	10	-	10	10	5	10	-	-
Total:	65	20	120	115	110	110	45	35

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
D67N	0	5	15	15	5	0	5	-	-	-	-
T69DN	0	0	5	10	30	0	0	-	-	-	-
K70R	0	10	30	15	10	0	10	-	-	-	-
M184V	60	15	-10	-10	10	60	-10	-	-	-	-
K219Q	0	5	10	10	5	0	5	-	-	-	-
A98G	-	-	-	-	-	-	-	10	10	30	15
F227L	-	-	-	-	-	-	-	15	0	30	0
D67N+K70R+K219Q	10	10	10	10	10	10	10	-	-	-	-
Total:	70	45	60	50	70	70	20	25	10	60	15

MUTATION SCORING

Mutation scoring

The mutation penalty score for an antiretroviral drug is obtained by adding together the scores of each mutation associated with resistance to that drug. The scores are titrated to fall within the following ranges:

0-9: Drug susceptible

10-14: Potential low level resistance

15-29: Low level resistance

30-59: Intermediate resistance

>60: High level resistance

HIVdb: Genotypic Resistance Interpretation Algorithm

Report: Date: 18-Feb-2010 00:23:42 PST

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	**M41L, K70R, Q151M**
NNRTI Resistance Mutations:	None
Other Mutations:	None

Nucleoside RTI		Non-Nucleoside RTI	
lamivudine (3TC)	Low-level resistance	**delavirdine (DLV)**	Susceptible
abacavir (ABC)	Intermediate resistance	**efavirenz (EFV)**	Susceptible
zidovudine (AZT)	High-level resistance	**etravirine (ETR)**	Susceptible
stavudine (D4T)	High-level resistance	**nevirapine (NVP)**	Susceptible
didanosine (DDI)	High-level resistance		
emtricitabine (FTC)	Low-level resistance		
tenofovir (TDF)	Intermediate resistance		

RT Comments

NRTI

- M41L usually occurs with T215Y. Together these mutations confer intermediate-to-high level resistance to AZT and d4T and a lower level of resistance to ddI, ABC, and TDF.
- K70R causes low-level AZT, d4T, and possibly TDF resistance.
- By itself, Q151M causes intermediate-to-high level resistance to AZT, ddI, d4T, and ABC; and low-level resistance to TDF. With changes at the associated positions 75, 77, and 116, Q151M confers high-level resistance to AZT, ddI, d4T, and ABC; intermediate resistance to TDF, and low-level resistance to 3TC and FTC.

CASE 1: GT while failing 2nd line

Class	Mutations
NRTIs	M184V
NNRTIs	K103N
PIs	Mo major mutations

- Explanation?
- Management?

CASE 2: GT while failing 2nd line

Class	Mutations
NRTI	D67N, K70R, K219Q, M184V
NNRTI	A98G, F227L
PI	**M46I, I54V, L76V, V82A**, L10IV, Q85E, A71I

Mutation Scoring

PR	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
M46I	10	0	10	10	10	20	5	5
I54V	15	0	10	15	15	20	15	20
L76V	-5	20	60	30	30	0	-5	-5
V82A	15	0	15	30	30	30	15	0
L10IV	0	0	0	0	0	0	0	0
Q58E	5	0	0	0	0	5	0	15
A71I	5	0	5	0	0	5	5	0
L76V+M46I	-	-	-	10	10	10	-	-
I54V+V82A	10	-	10	10	10	10	10	-
V82A+M46I	10	-	10	10	5	10	-	-
Total:	65	20	120	115	110	110	45	35

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	EFV	ETR	NVP	RPV
D67N	0	5	15	15	5	0	5	-	-	-	-
T69DN	0	0	5	10	30	0	0	-	-	-	-
K70R	0	10	30	15	10	0	10	-	-	-	-
M184V	60	15	-10	-10	10	60	-10	-	-	-	-
K219Q	0	5	10	10	5	0	5	-	-	-	-
A98G	-	-	-	-	-	-	-	10	10	30	15
F227L	-	-	-	-	-	-	-	15	0	30	0
D67N+K70R+K219Q	10	10	10	10	10	10	10	-	-	-	-
Total:	70	45	60	50	70	70	20	25	10	60	15

Management?

Management

- 3rd line:
  - TDF/FTC + Raltegravir + Darunavir/ritonavir

- Follow-up viral loads:
  - Less than 40 for over 2 years

Efficacy of third line ART in Africa: outcomes on ART salvage regimens in the Southern African private sector

Liezl Dunn[1], Marla Coetsee[1], Michael Hislop[1],
Leon Regensberg[1], Gary Maartens[1,2], Graeme Meintjes[1,2]

[1]Aid for AIDS
[2]University of Cape Town

7th EDCTP Forum, Berlin, 1 July 2014

Resistance patterns

185 resistance tests in 152 patients
111/113 were subtype C

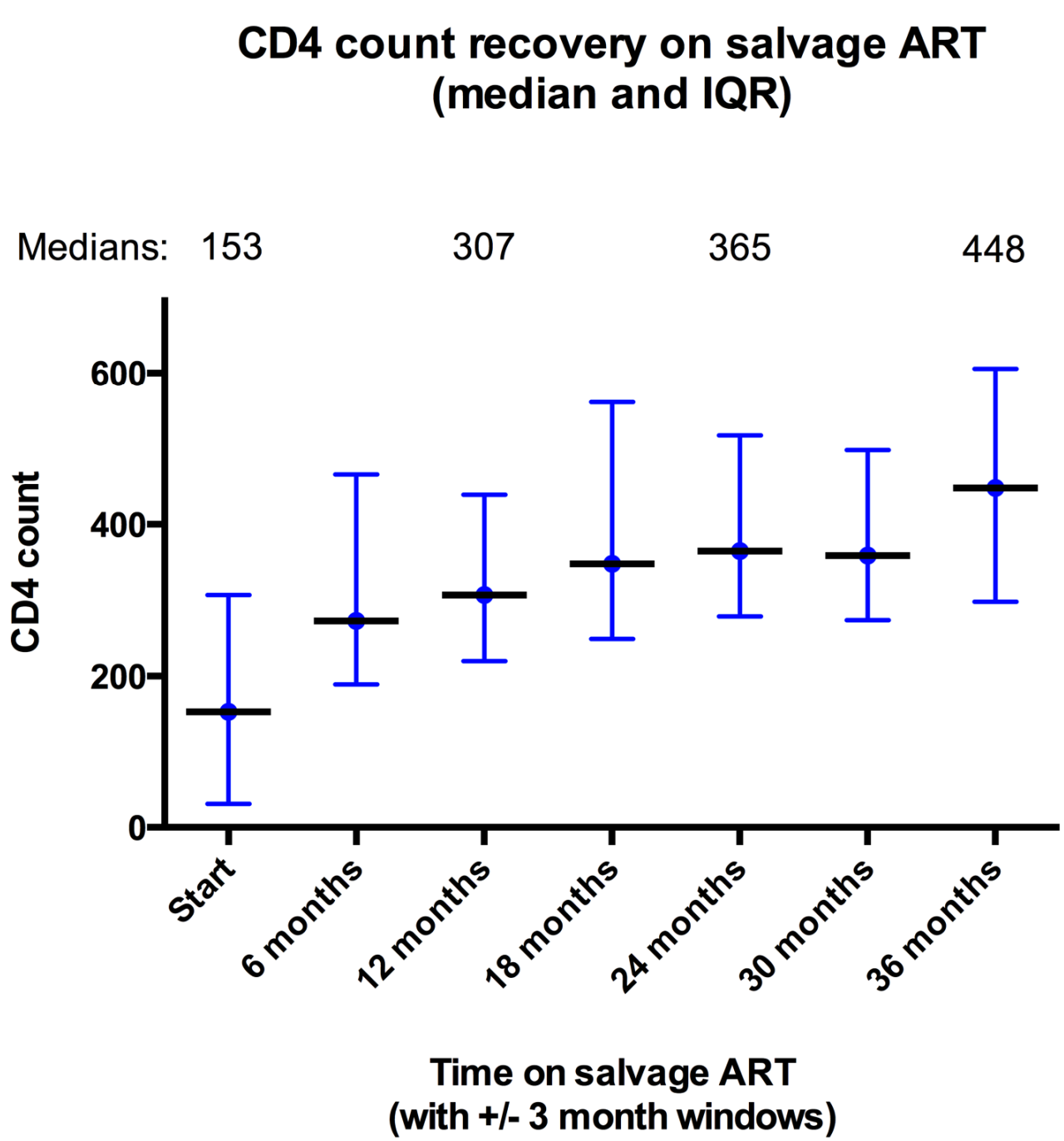
Mutations	n	%
No TAMs	45	30%
1-2 TAMs	35	23%
≥ 3 TAMs	72	47%
No major PI mutations	0	0%
1-2 major PI mutations	38	25%
≥ 3 major PI mutations	114	75%

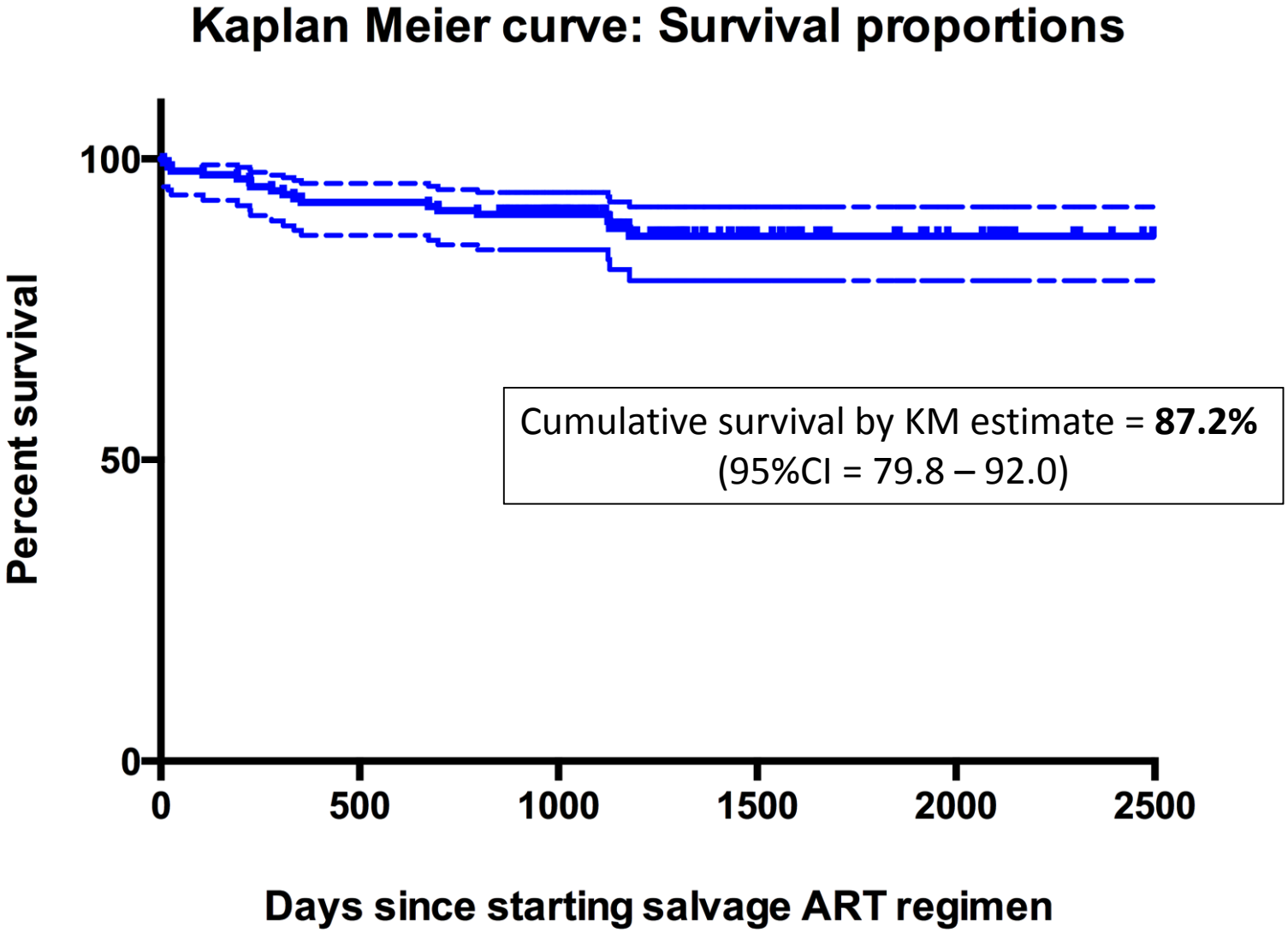
TAMs = Thymidine analogue mutations

Virological suppression

145 (95.4%) of 152 had at least one viral load performed on salvage ART

	n	% of those who had VL performed (n=145)	% of whole cohort (n=152)
Suppressed < 400	126	86.9%	82.9%
Suppressed < 50	108	74.5%	71.1%


CD4 count recovery on salvage ART
(median and IQR)
Medians: 153 307 365 448
CD4 count
600
400
200
0
Start
6 months
12 months
18 months
24 months
30 months
36 months
Time on salvage ART
(with +/- 3 month windows)



Vital status available for all patients on administrative censor date (30 April 2014)