New Adult ART Guidelines

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Cape Town, 20 June 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

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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.)

Topics

1. What CD4 threshold to start ART at?
2. Return to care after 1st line interruption
3. Patients with viraemia on 2nd line

4. Cryptococcal antigen screening

Topics

1. What CD4 threshold to start ART at?
2. Return to care after 1st line interruption
3. Patients with viraemia on 2nd line

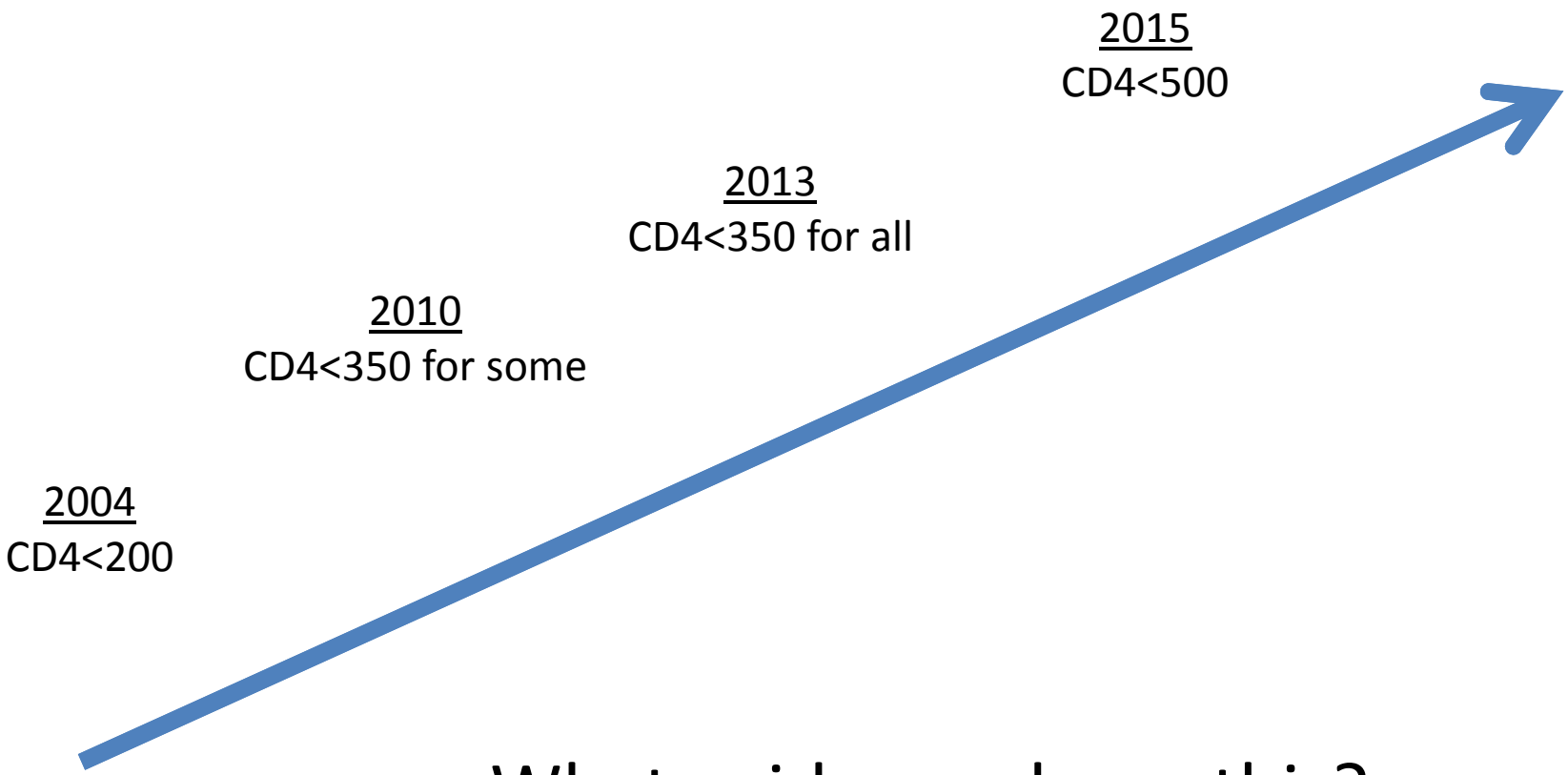
4. Cryptococcal antigen screening

Case scenario

- 28 yr man
- Newly diagnosed with HIV in HCT service
- CD4 count = 478
- Asymptomatic
- He asks you:

  “Why do I need to start ART now?”

Evolution of NDOH guidelines



What evidence drove this?

Haiti trial

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

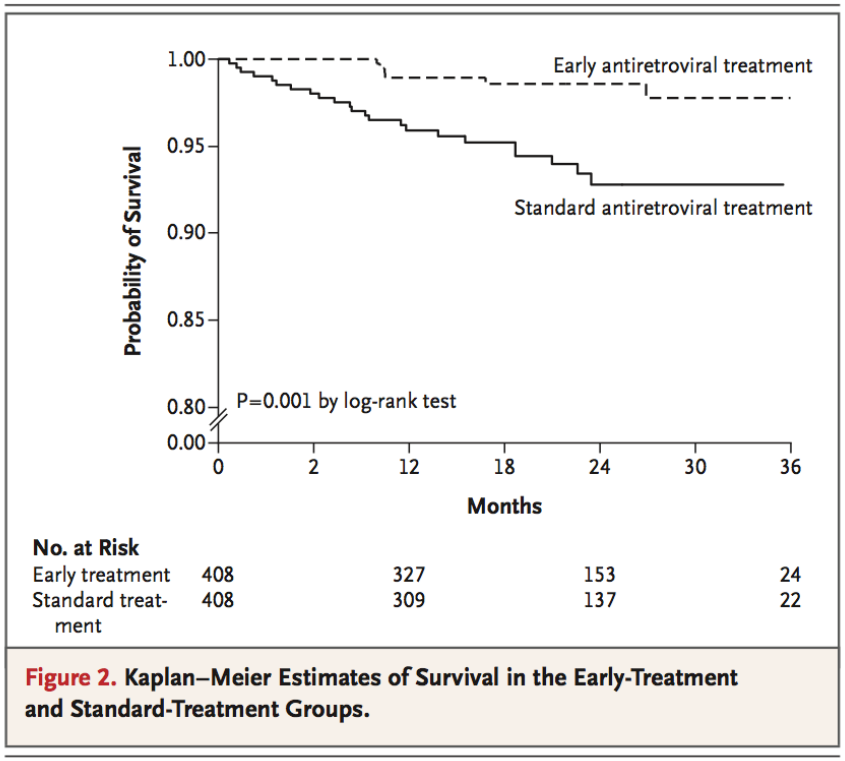


Figure 2. Kaplan–Meier Estimates of Survival in the Early-Treatment and Standard-Treatment Groups.

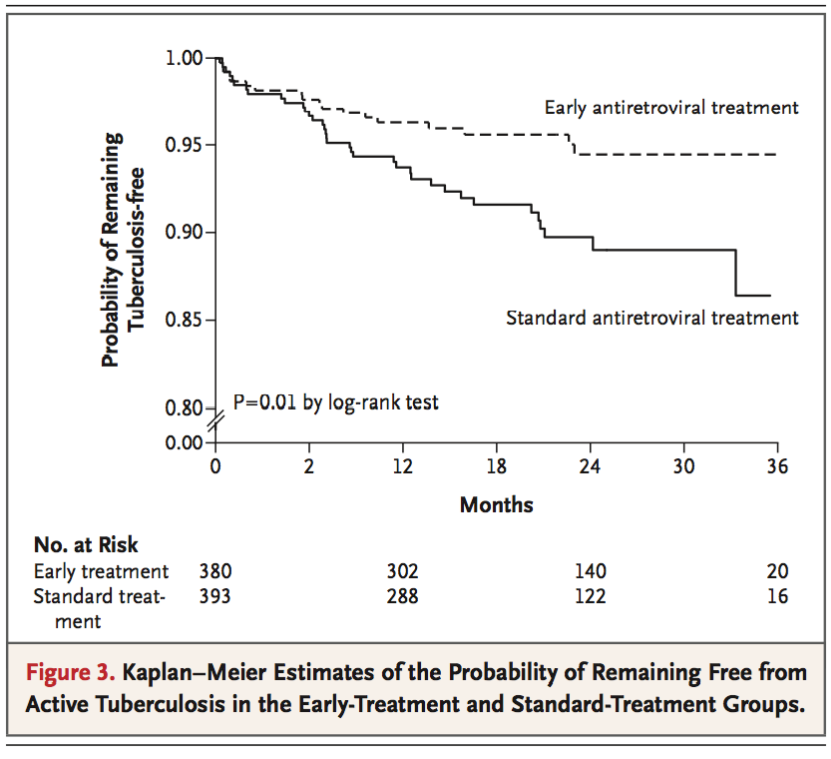


Figure 3. Kaplan–Meier Estimates of the Probability of Remaining Free from Active Tuberculosis in the Early-Treatment and Standard-Treatment Groups.

HR = 4.0

HR = 2.0

Severe, NEJM 2010

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

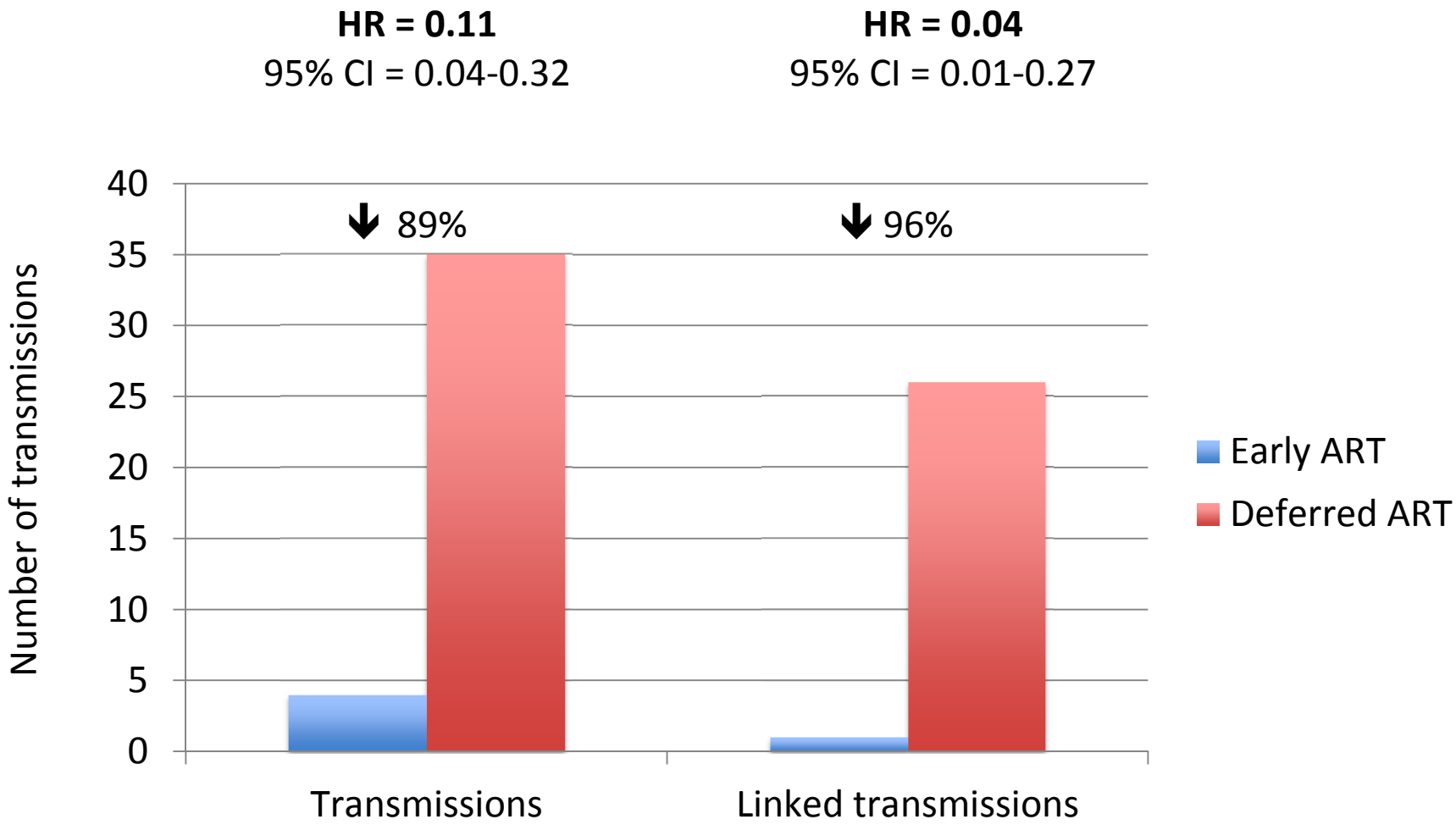
Botswana, Brazil, India, Kenya, Malawi, SA, Thailand, Zimbabwe, USA

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

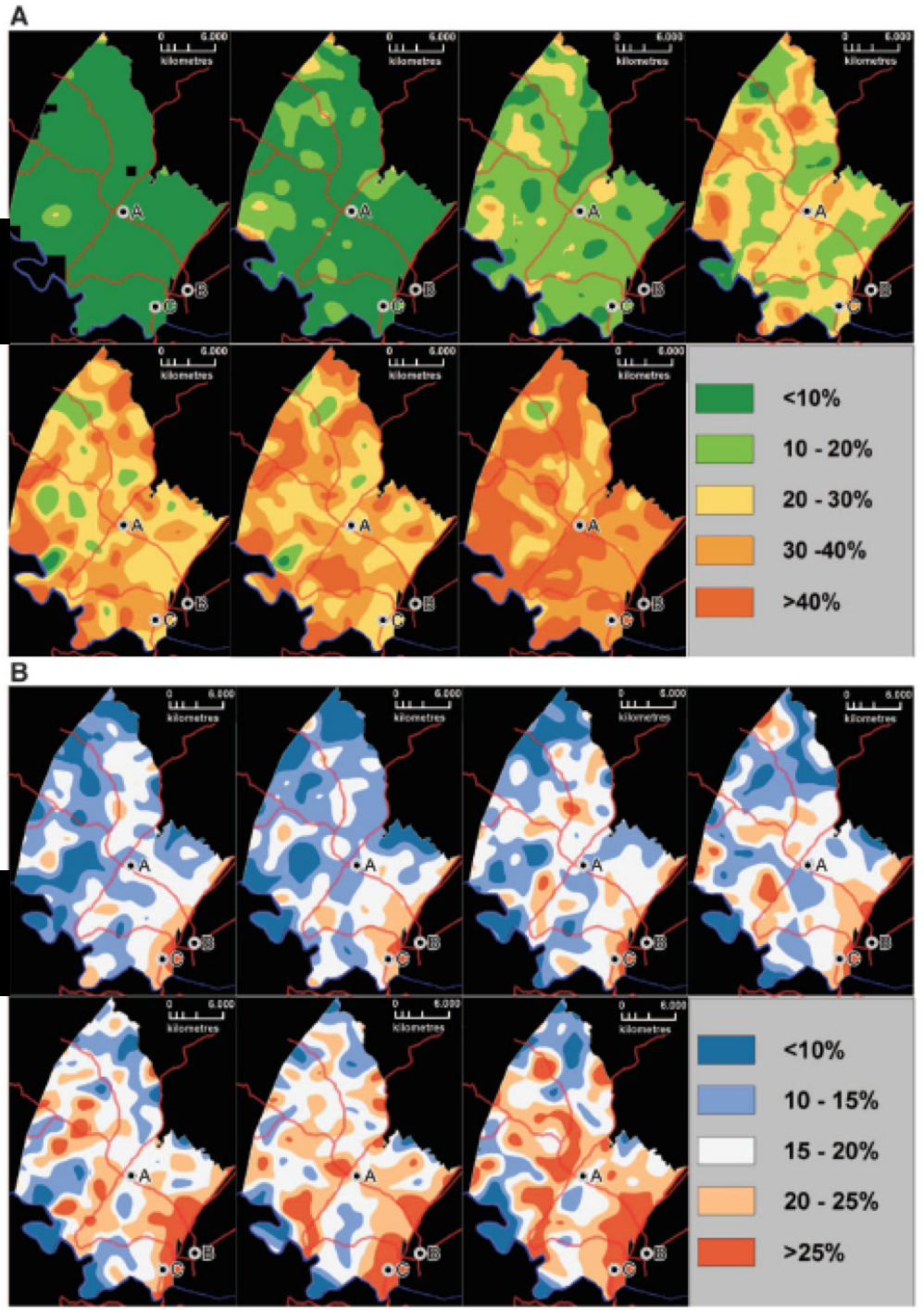
- 16,667 HIV-negative adults followed 2004-11
- Annual HIV prevalence and ART coverage in a 3km radius around each individual was calculated
- Hazard ratio for HIV seroconversion in relation to ART coverage calculated
  - Adjusted for gender, age, HIV prevalence and various HIV risk behaviours
- 1,413 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

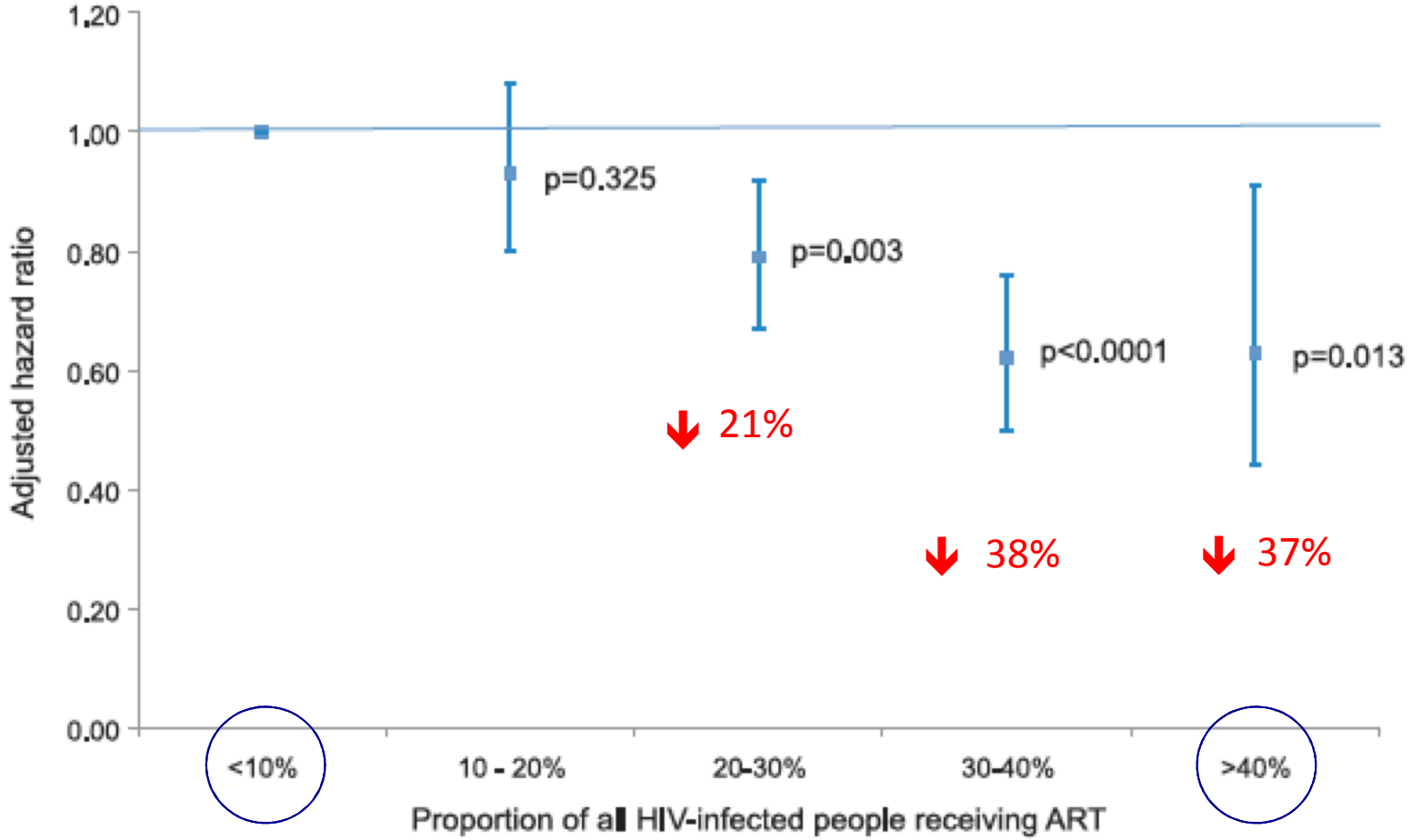
ART coverage
2005 - 2011

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

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

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 .

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

CD4 < 500

↓

All HIV+ patients regardless of CD4

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

Topics

1. What CD4 threshold to start ART at?
2. Return to care after 1st line interruption
3. Patients with viraemia on 2nd line

4. Cryptococcal antigen screening

Case scenario

- Baseline CD4 = 180
- Viral load suppressed on 1st line for 18 months
- Family crisis, stops ART and only returns to care 11 months later
- No TB symptoms and generally well
- What do you do?

SA HIV CLINICIANS SOCIETY (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

SA HIV CLINICIANS SOCIETY (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

DEPARTMENT OF HEALTH

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.

SA NDOH guidelines

General points

- Issues to consider
  - History of adherence prior to default episode
  - Viral load measures prior to default episode
  - CD4 nadir and current CD4
  - Current clinical status
- In most cases restart 1st line
  - Do not want to unnecessarily switch to 2nd line (less well tolerated)
- Some exceptions
  - Not wanting to restart patient on failing regimen if very immunosuppressed and/or very unlikely to be effective
- 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

Virological Failure and Drug Resistance in Patients on Antiretroviral Therapy After Treatment Interruption in Lilongwe, Malawi

Julia Luebbert,[1,2] Hannock Tweya,[3,5] Sam Phiri,[3] Thom Chaweza,[3] Johnbosco Mwafilaso,[3] Mina C. Hosseinipour,[4] Heribert Ramroth,[1] Paul Schnitzler,[2] and Florian Neuhann[1]

133 patients

Mean duration of ART prior to interruption 14 months

After a minimum of 2 months following ART resumption:

- VL was undetectable in 81 (60.9%)
- 400–1000 copies/mL in 12 (9.0%)
- ≥1000 copies/mL in 40 (30.1%)

Drug-resistance testing successful for 36 of 40 patients

- NNRTI mutations in 32 of 133 (24.1%)
- NNRTI + NRTI mutations in 27 of 133 (20.3%)

Clin Infect Dis 2012

Topics

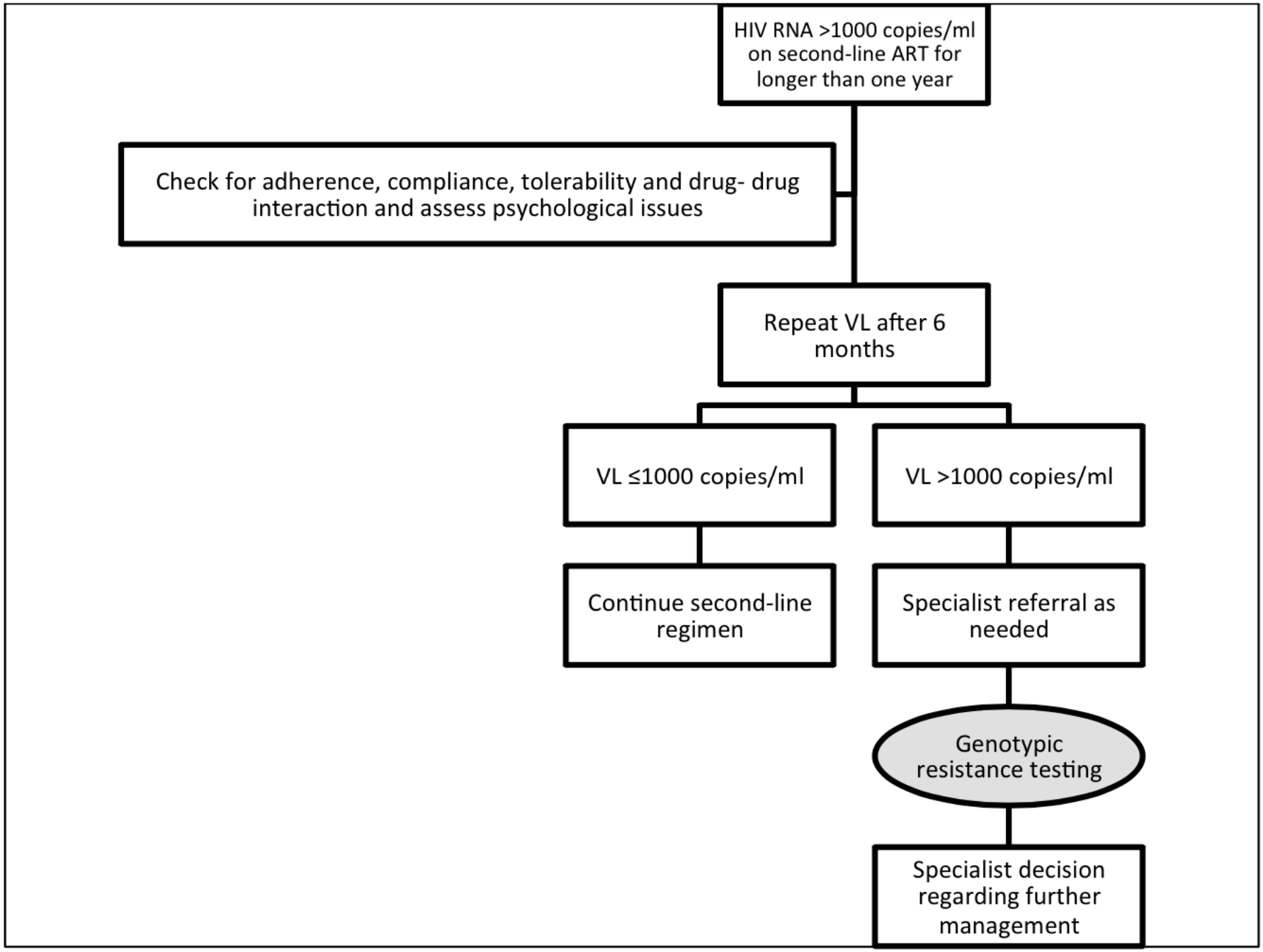
1. What CD4 threshold to start ART at?
2. Return to care after 1st line interruption
3. Patients with viraemia on 2nd line

4. Cryptococcal antigen screening

Case scenario

- Patient on 2nd line for 3 years has viral load of 450,000 copies/ml after being undetectable

- When would you do genotype resistance test?


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

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

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.

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)*

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

Topics

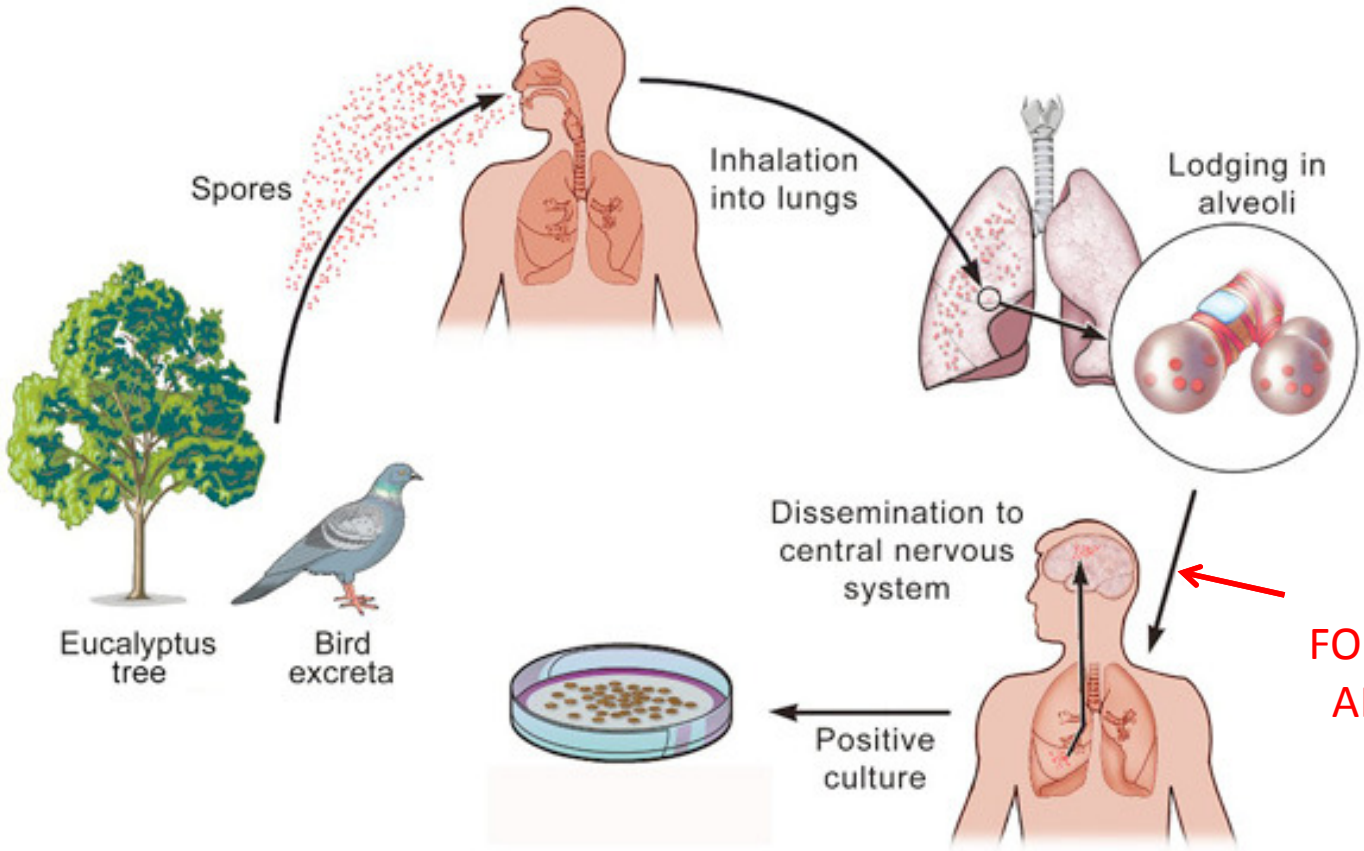
1. What CD4 threshold to start ART at?
2. Return to care after 1st line interruption
3. Patients with viraemia on 2nd line

4. Cryptococcal antigen screening

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)

Case scenario

- ART naïve patient with CD4 = 55
- Attends ART clinic and tested for serum cryptococcal antigen = POSITIVE
- What do you do?



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

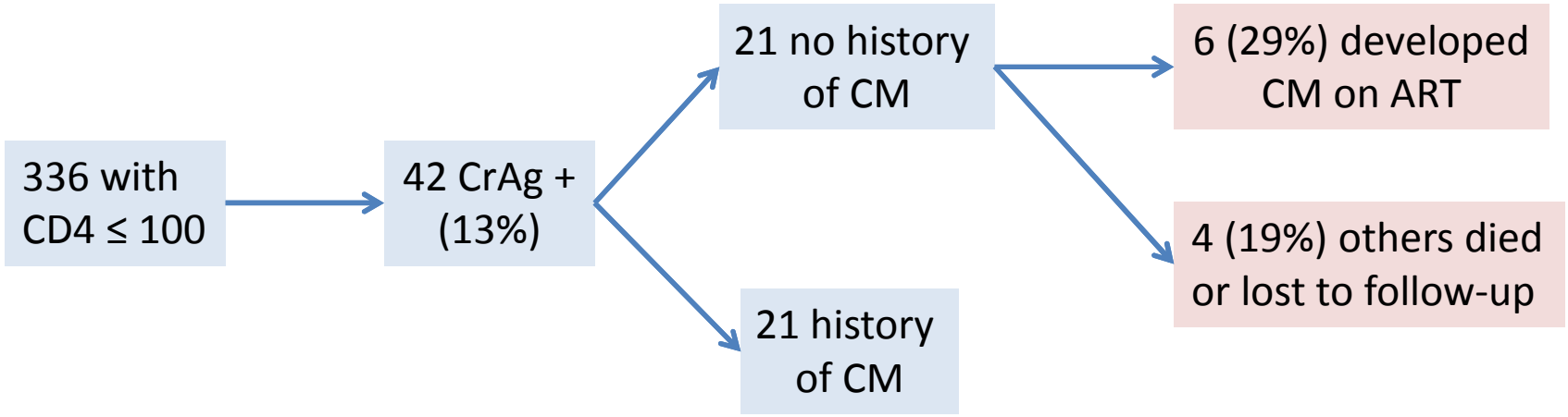
French, AIDS 2002;16:1031

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

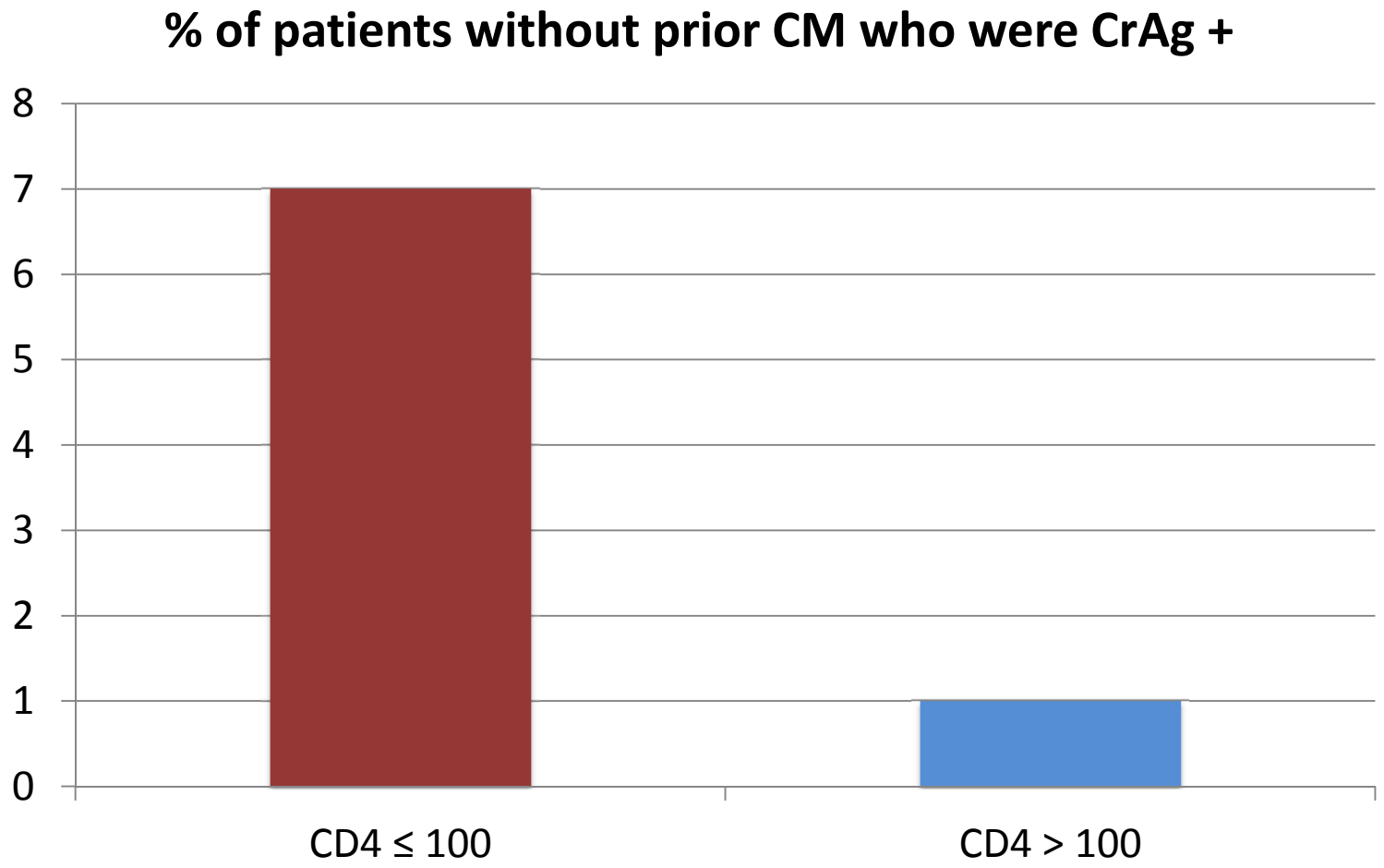
Joseph N. Jarvis,[1,2,3,4] Stephen D. Lawn,[1,5] Monica Vogt,[1] Nonzwakazi Bangani,[1] Robin Wood,[1] and Thomas S. Harrison[1,4]

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

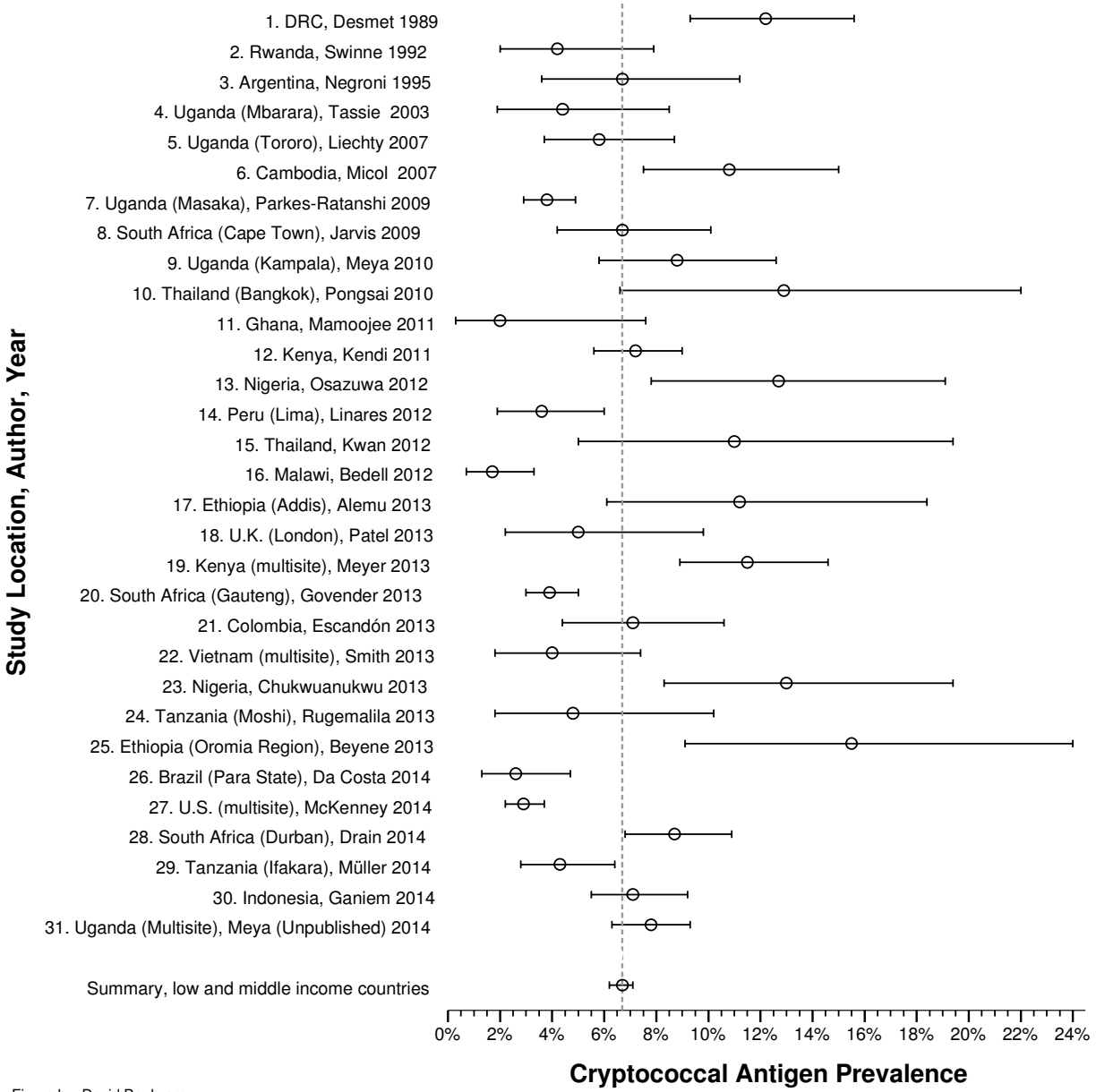
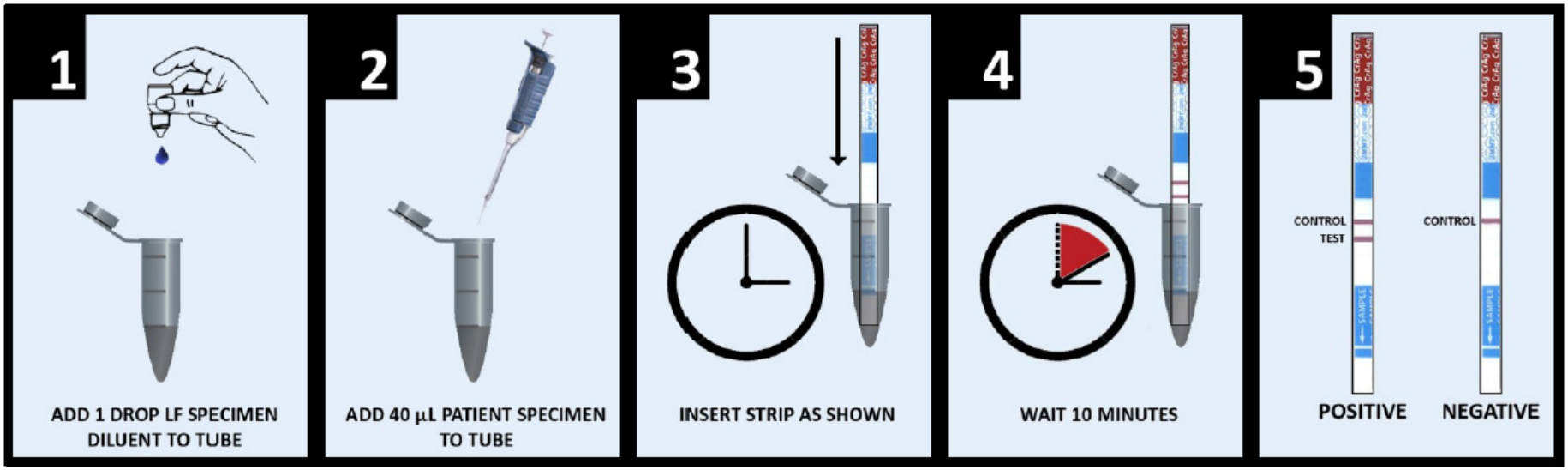
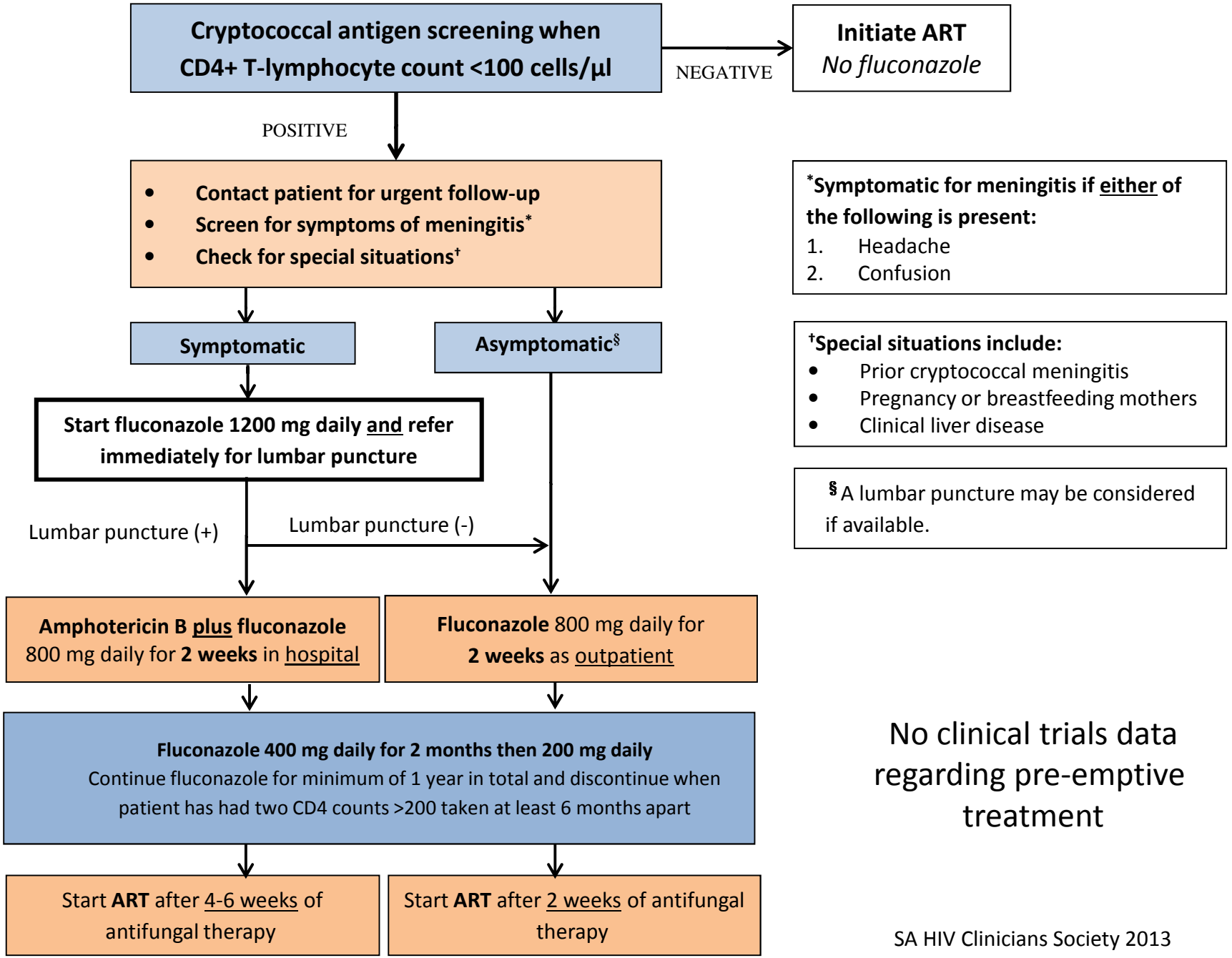


Figure by: David Boulware

CrAg Lateral Flow Assay



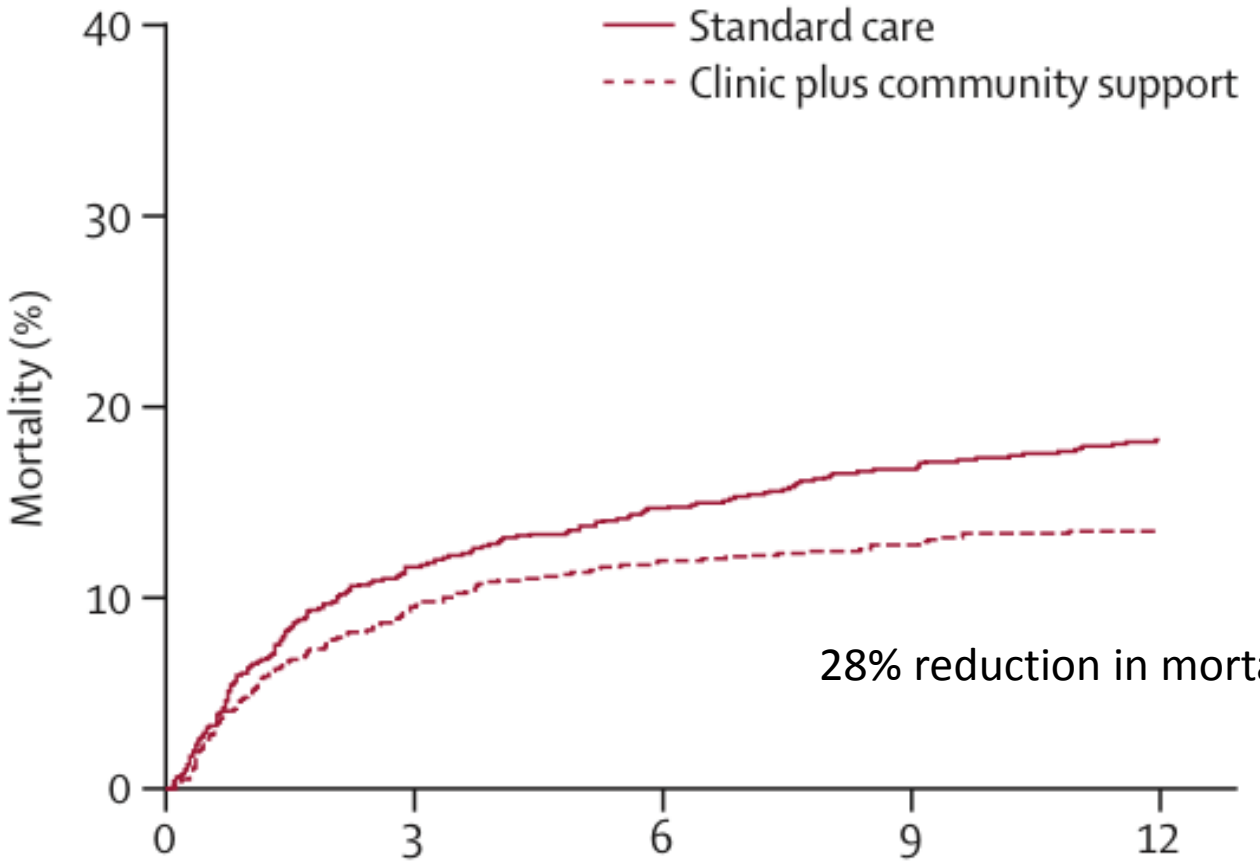
Source: Immy CrAg LFA package insert


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

Take home messages

1. Now evidence of individual clinical benefit from initiating ART even at CD4 counts > 500.
2. If patient defaults 1st line and returns, generally restart 1st line and monitor VL closely. There are exceptions.
3. First evaluate adherence objectively before considering genotype and 3rd line in patients failing 2nd line.
4. Cryptococcal antigen screening and pre-emptive fluconazole reduces mortality at a programmatic level.

Steve Andrews

9 June 1970 – 27 June 2009

Friend, colleague, teacher and stalwart of the Clinicians Society