Challenges in the ART program and some solutions

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Southern African HIV Clinicians Society.

Disclaimer

- This is not a teaching lecture on FDCs or the new guidelines.
- Retrospective and introspective
- What must stay and what can go?

15 million accessing treatment

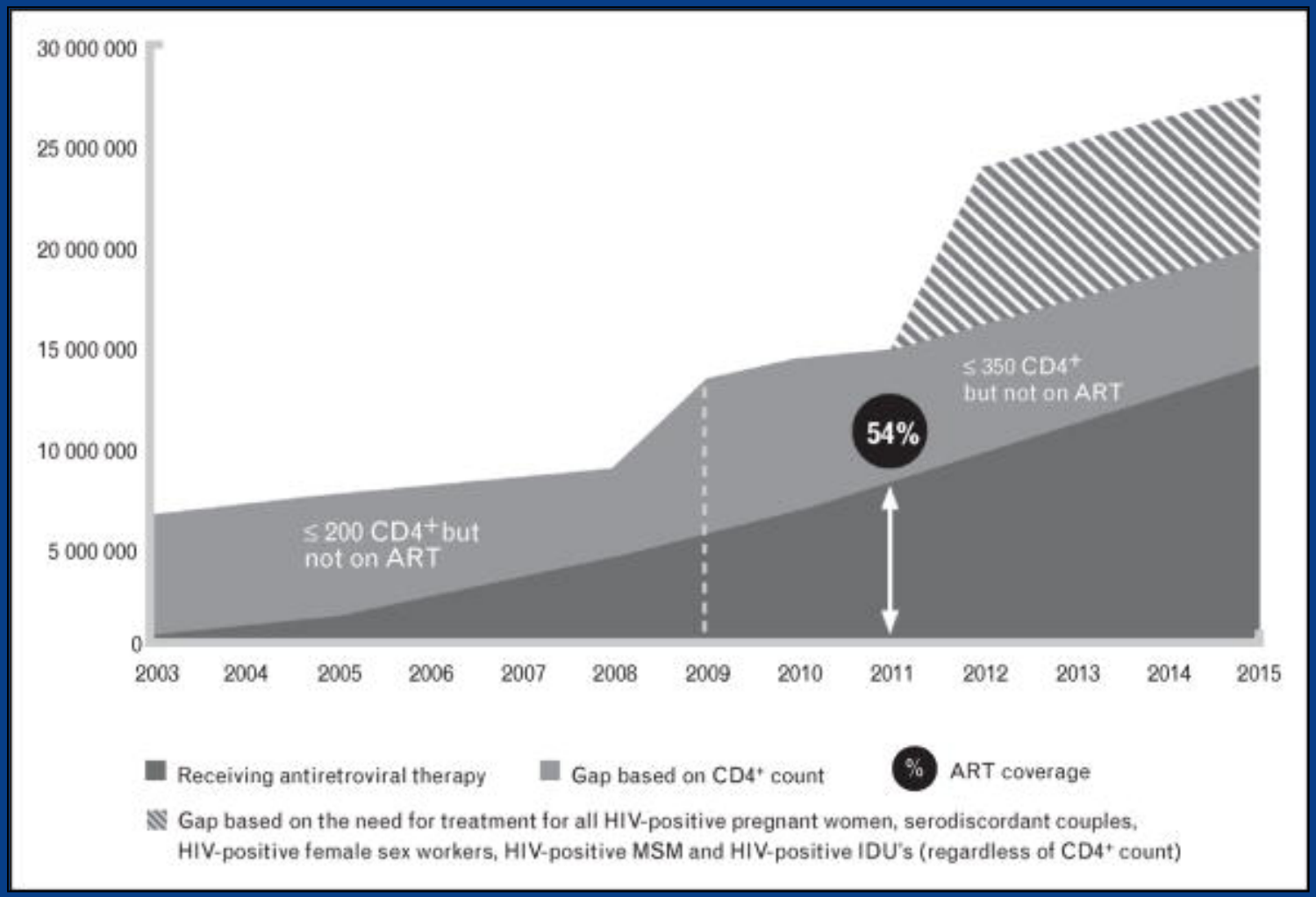
BOOKMARK + SHARE

THERE ARE ABOUT 9 MILLION PEOPLE LIVING WITH HIV STILL IN NEED OF TREATMENT WHO DO NOT HAVE ACCESS

Treatment 2.0

- Simplification
- Innovation
- Efficiency
- Effectiveness and cost -effectiveness
- Accessibility
- Equity
- Decentralization and integration
- Community involvement

How far are we?



Hereon lies the rub

- UNAIDS has estimated that the cost of putting 15 million people on ART by 2015 will be US$22–24 billion
- Less than 30% of people diagnosed with HIV infection the full cascade of care, from HIV testing through to initiation of ART and long-term retention in care

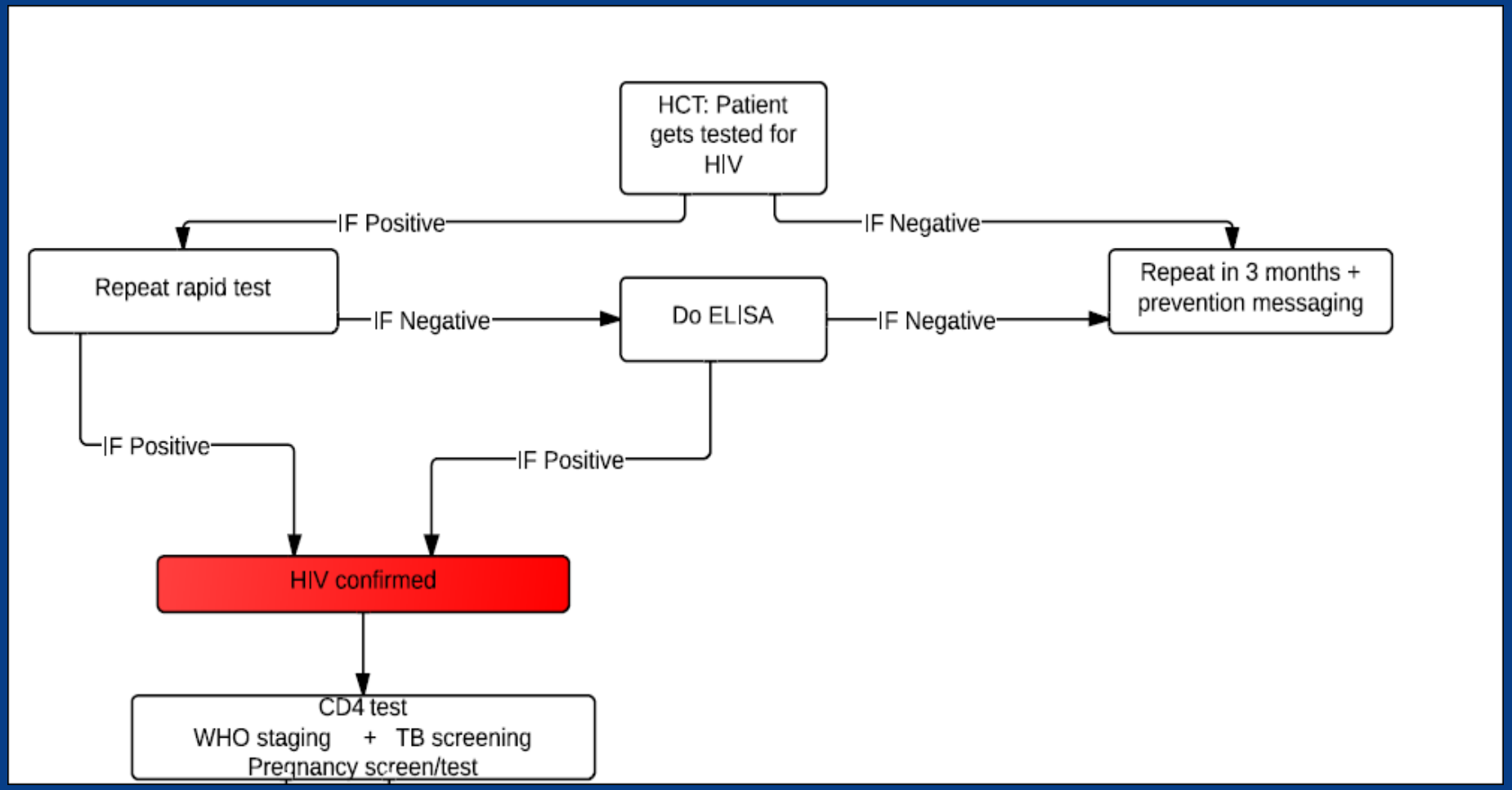
Topics to be covered

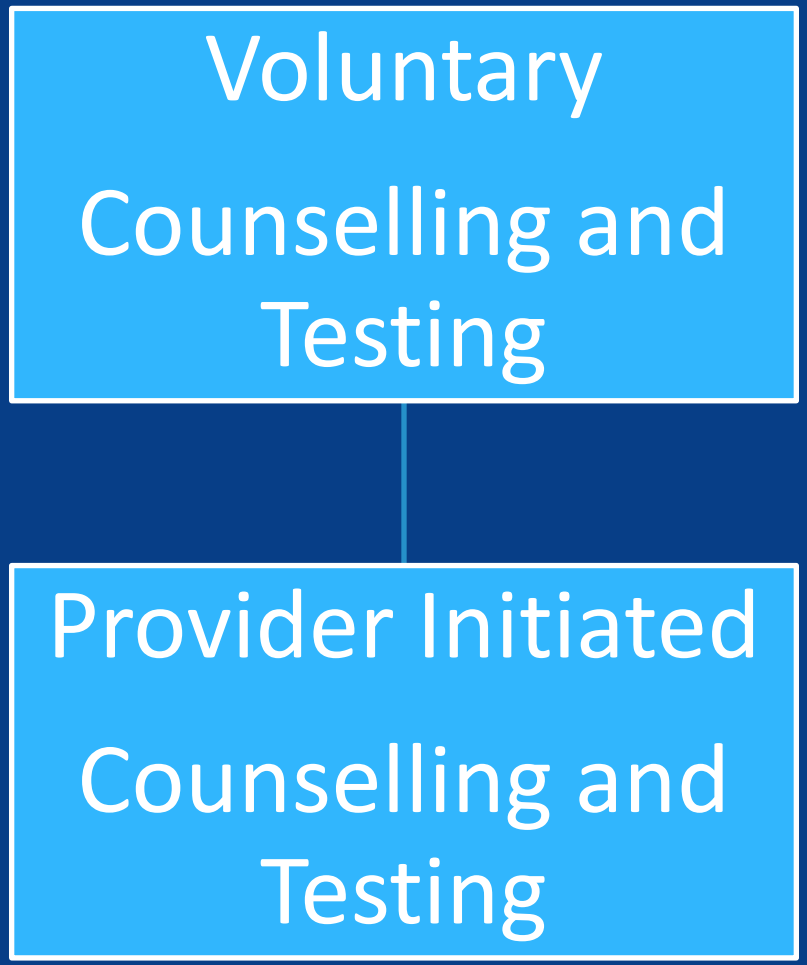
- HIV testing
- Linkage to care
- CD4+ vs. Viral load
- Safety and Efficacy measures
- Adherence
- Resistance

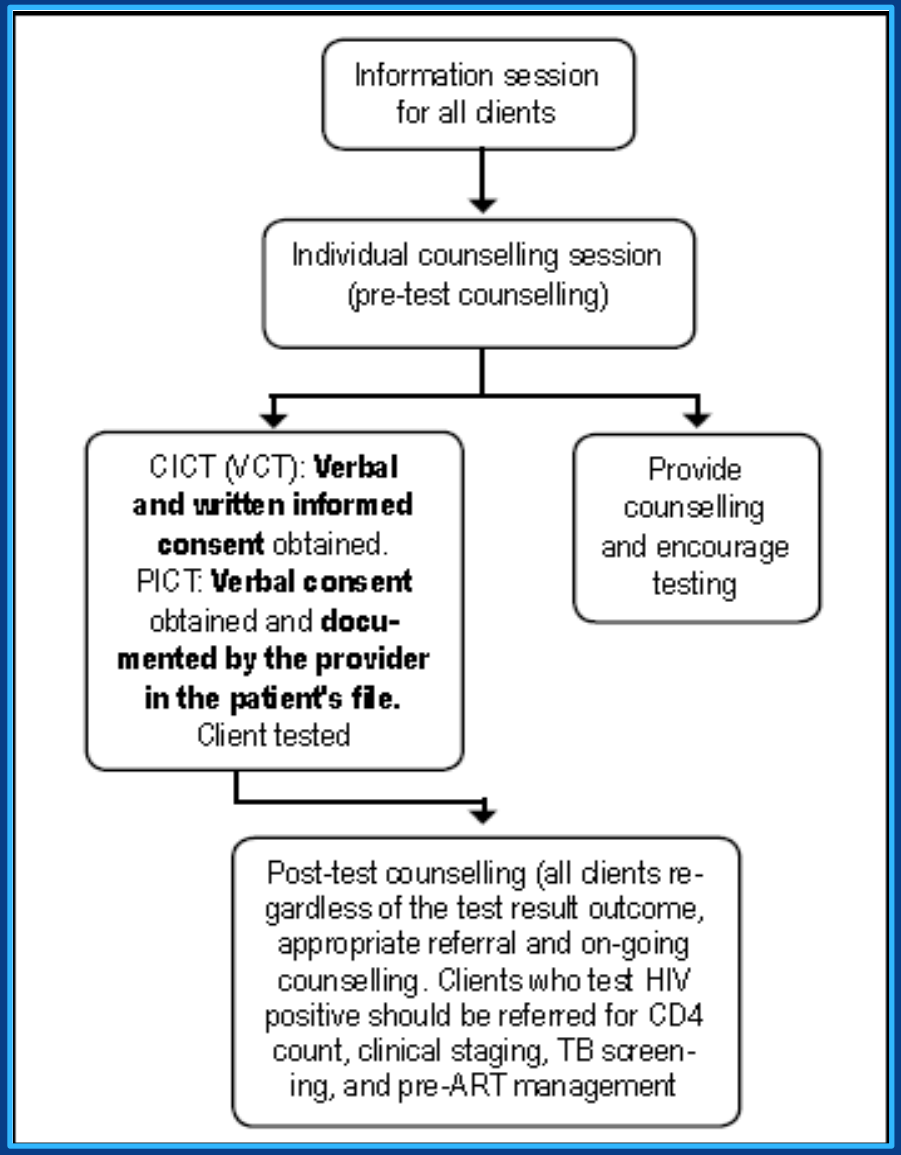
HIV testing

- HIV-1 infection, documented by a rapid HIV test or any licensed ELISA test kit, and confirmed by a repeat ELISA, Western blot, or plasma HIV-1 RNA

National Algorithm




Voluntary
Counselling and Testing
Provider Initiated
Counselling and Testing



- National Department of Health. HCT Policy Guidelines March 2010. Pretoria: NDoH, 2010.

Self testing for HIV

ISSUES IN PUBLIC HEALTH

Home self-testing for HIV: AIDS exceptionalism gone wrong

Marlise Richter, W D Francois Venter, Andy Gray

Risks of Home testing

- There is increased risk of unmanaged anxiety, with potential for suicide
- Counselling is a vital component of HIV tests and is bypassed by self-testing
- Testing could be coerced in a home environment
- Accuracy of test

Recommendations

- Legal and policy framework should be amended
- The information sheet should contain detailed but simple information on HIV testing
- Self-testing kits should clearly display the accuracy of the test
- Toll-free helpline for counselling
- Clear warnings that it is illegal to test other people for HIV

First Rapid Home-Use HIV Kit Approved for Self-Testing

Accuracy of rapid tests

- False negative results -window period
- False positive results
  - Cross reactivity of other antibodies.
  - No other confirmation of HIV infection
  - CD4+ entry criteria

  - Massive implications for Option B+

Table 1 Performance characteristics of HIV RDTs

RDT	Sensitivity% (n = 150)		Specificity% (n = 150)			
	Manufacturer's SEN*	SEN†	Manufacturer's SPE*	SPE (95% CI)†	NPV% (95% CI)†	PPV% (95% CI)†
Determine	100	100	99.9	85.2 (77.4, 91.1)	100 (96.3, 100)	67.3 (52.9, 79.7)
STAT-PAK	100	100	100	99.1 (95.3, 99.9)	100 (96.8, 100)	97.2 (85.5, 99.9)
Uni-Gold	100	100	99.7	97.4 (92.6, 99.5)	100 (96.8, 100)	92.1 (78.6, 98.3)
First Response	100	100	99.2	97.4 (92.6, 99.5)	100 (96.8, 100)	92.1 (78.6, 98.3)
Advanced Quality	100	100	100	100 (96.8, 100)	100 (96.8, 100)	100 (90.0, 100)

PPV = positive predictive value; NPV = negative predictive value; CI = confidence interval; RDT = rapid diagnostic test; SEN = sensitivity; SPE = specificity

*Manufacturers' test characteristic performance (kit inserts) on serum; PPV and NPV dependent on the prevalence of population tested

†Evaluation findings

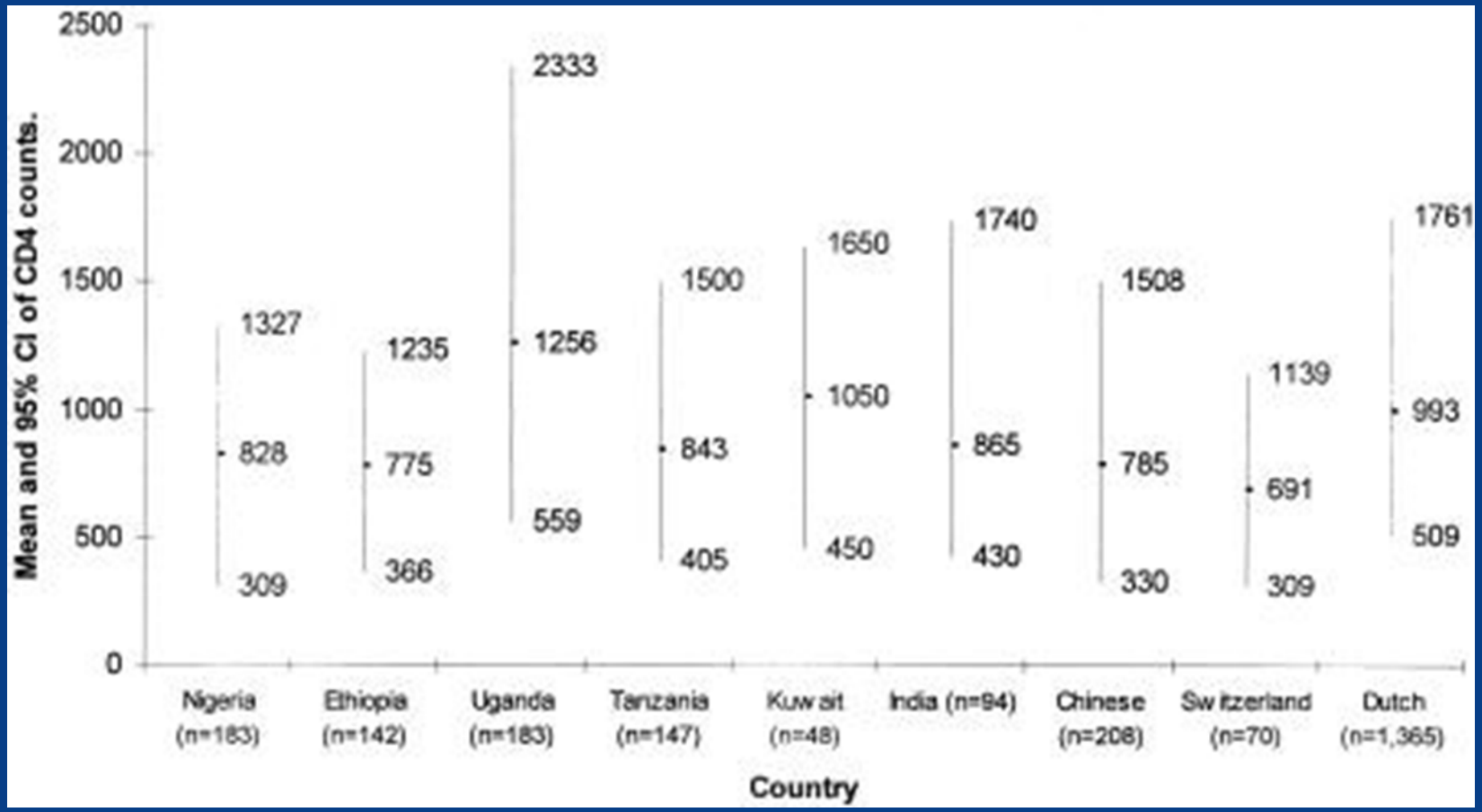
- S C Kagulire Int Journal of STD AIDs

CD4+

- Our security blanket
- Immunological failure
- Immunological non- response
- When to stop cotrimoxazole?
- When to stop fluconazole?

Entry levels of CD4+

Aina Clin Diagn Lab Immunol. 2005



Immunological failure

- Fall of CD4 count to baseline (or below)

OR

- 50% fall from on-treatment peak value

OR

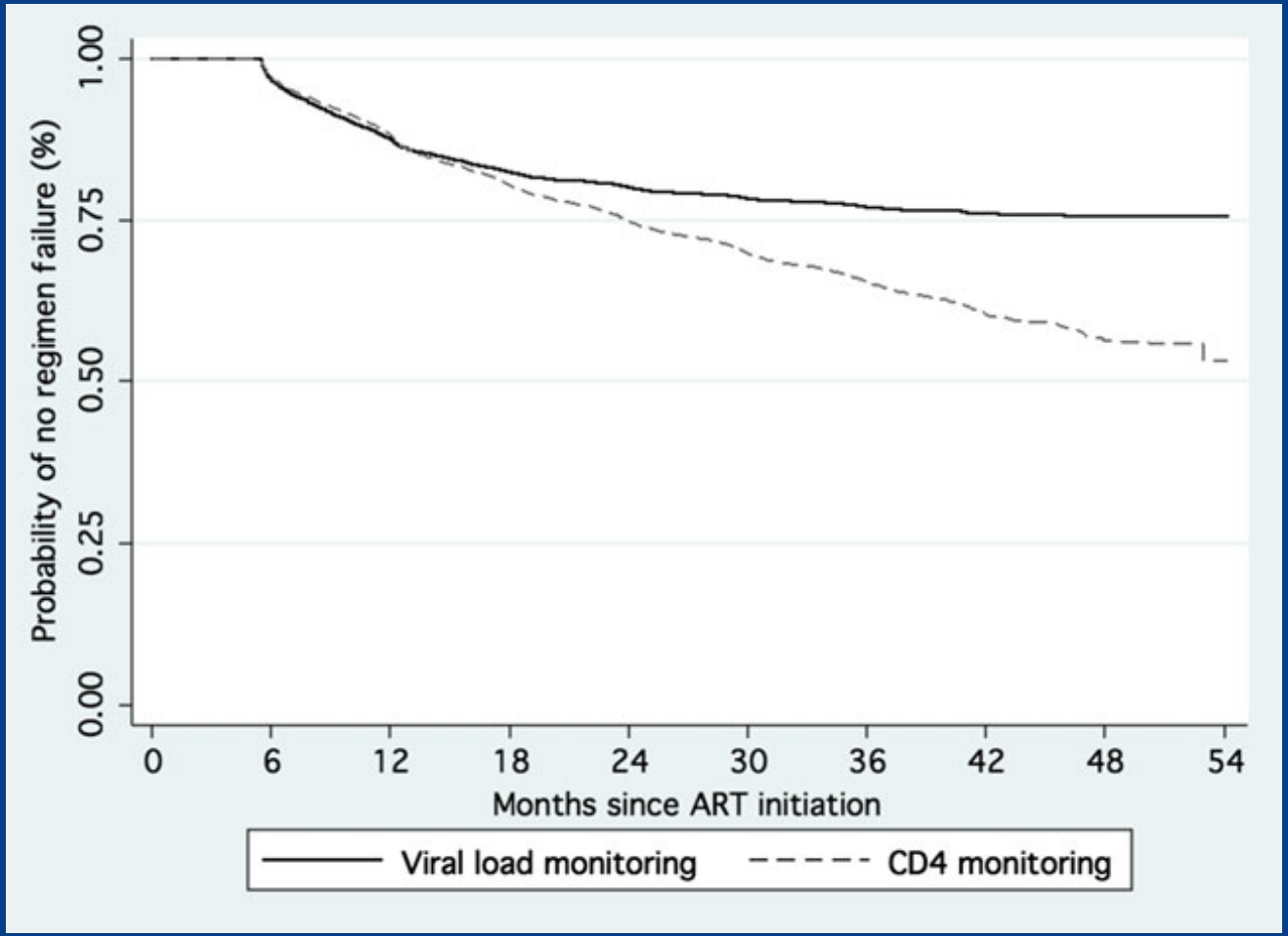
- Persistent CD4 levels below 100 cells/mm3

Table 3. Comparison of Performance of CD4 Failure Criteria[a] to Various Definitions of Virologic Failure

Viral load failure definition	Failure				Sensitivity%	Specificity%	PPV%	NPV%
	Immunologic and virologic	Immunologic only	Virologic only	None				
Confirmed VL >5000 copies/mL (WHO-defined viral failure)	880	2242	449	6119	66.2	73.2	28.2	93.2
Confirmed VL >1000 copies/mL (protocol-defined viral failure)	1225	1897	872	5696	58.4	75.0	39.2	86.7
Confirmed VL >400 copies/mL	1440	1682	1301	5267	52.6	75.9	46.1	80.2

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; VL, viral load; WHO, World Health Organization.

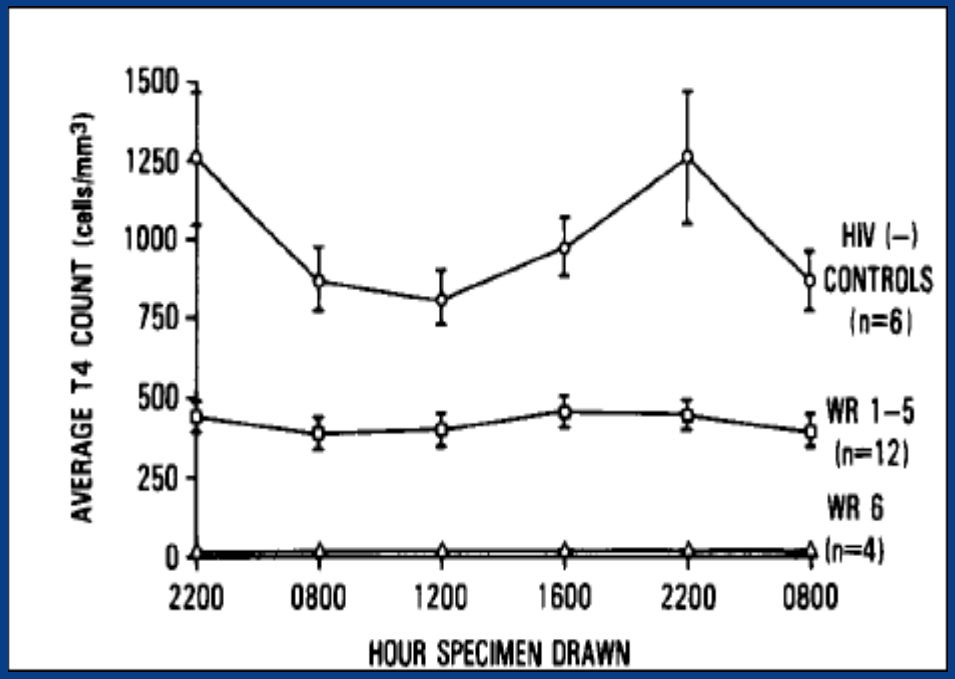
[a] Immunologic failure defined in this table as meeting any of the 3 WHO CD4 failure definitions (unconfirmed by a second CD4 value).


Probability of no regimen failure (%)
0.00
0.25
0.50
0.75
1.00
0
6
12
18
24
30
36
42
48
54
Months since ART initiation
Viral load monitoring
CD4 monitoring

Variations in CD4+

Journal of Acquired Immune Deficiency Syndromes
3:144–151, 1990 Raven Press, Ltd., New York

- Diurnal variation



Immunological non-responder

- 15%–30% of patients on ART
  - lack of increase in the CD4+ T cell count
  - full suppression of HIV replication.

Treatment intensification with Raltegravir in subjects with sustained HIV-1 viraemia suppression: a randomized 48-week study

- *Libre, Antiviral Therapy* 2012; **17**:355-364

Table 1. Changes in virological parameters after 48 weeks of intensification with raltegravir

Parameter	Control (*n*=22)	Intensification (*n*=45)	*P*-value between groups
Total HIV-1 DNA			
Median at baseline, copies per million PBMCs (IQR)	14.1 (3.1–61.3)	10.3 (4.5–38.3)	0.713[a]
Median at week 48, copies per million PBMCs (IQR)	54.6 (11.5–367.1)	19.6 (1.4–104.9)	0.043[a]
P-value within group, baseline versus week 48[b]	0.002	0.914	–
Linear mixed models, coefficient (SE)[c]	2.8 (0.49)	-0.42 (0.39)	<0.0001[d]
P-value[e]	<0.0001	0.277	–
Integrated HIV-1 DNA			
Median at baseline, copies per million PBMCs (IQR)	1.9 (0–41.7)	0 (0–7.4)	0.229[a]
Median at week 48, copies per million PBMCs (IQR)	0.4 (0–19.3)	0 (0–3.3)	0.061[a]
P-value within group, baseline versus week 48[b]	0.459	0.406	–
Linear mixed models, coefficient (SE)[c]	0.85 (0.41)	0.09 (0.21)	0.065[d]
P-value[e]	0.039	0.653	–
Ultrasensitive plasma viral load			
Median at baseline, copies/ml (IQR)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.334[f]
Median at week 48, copies/ml (IQR)	0.5 (0.2–2.7)	0.4 (0.01–2.8)	0.737[f]
P-value within group, baseline versus week 48[g]	0.782	0.977	–

Table 2. Changes in $CD4^+$ T-cell parameters after 48 weeks of intensification with raltegravir

Parameter	Control (*n*=22)	Intensification (*n*=45)	*P*-value between groups
Median absolute $CD4^+$ T-cell count at baseline, cells/μl (IQR)	503 (371–600)	530 (434–786)	0.333[a]
Median absolute $CD4^+$ T-cell count at week 48, cells/μl (IQR)	583 (420–744)	654 (462–795)	0.381[a]
P-value within group, baseline versus week 48[b]	0.027	0.005	–
Linear mixed models, coefficient (SE)[c]	1.65 (0.44)	1.73 (0.41)	0.902[d]
P-value[e]	0.0003	<0.0001	–
Median $CD45RA^-$ at baseline, % of $CD4^+$ (IQR)[f]	65.9 (63.6–74.2)	68.6 (43.0–80.2)	0.943[a]
Median $CD45RA^-$ at week 48, % of $CD4^+$ (IQR)[f]	72.1 (57.5–77.4)	68.5 (56.5–78.1)	0.838[a]
P-value within group, baseline versus week 48[b]	0.677	0.608	–
Linear mixed models, coefficient (SE)[c]	-0.337 (0.05)	-0.033 (0.04)	0.273[d]
P-value[e]	0.488	0.354	–

Viral load

Dried Blood Spot Specimens Are a Suitable Alternative Sample Type for HIV-1 Viral Load Measurement and Drug Resistance Genotyping in Patients Receiving First-Line Antiretroviral Therapy

- (Rottinghaus CID 2012:54 (15 April))

Table 1. Concordance Between DBS, DPS, and Plasma Specimens in Identifying Virological Failure

Specimen Type and VL, copies/mL	Plasma Specimens: VL ≥1000 Copies/mL	Plasma Specimens: VL <1000 Copies/mL	Plasma Specimens: Total	κ Value, Mean ± SE (95% Confidence Interval)	*P*	Performance of DBS and DPS Specimens, %[a]
DBS				0.78 ± 0.08 (0.62–0.94)	<.001	Sensitivity, 77.8; specificity, 98.1; PPV, 82.3; NPV, 97.4
≥1000	14	3	17			
<1000	4	152	156			
Total	18	155	173			
DPS				0.83 ± 0.07 (0.69–0.98)	<.001	Sensitivity, 77.8; specificity, 99.4; PPV, 93.3; NPV, 97.5
≥1000	14	1	15			
<1000	4	154	158			
Total	18	155	173			

Viral failure was defined as plasma viral RNA levels ≥1000 copies/mL.

Abbreviations: DBS, dried blood spot; DPS, dried plasma spot; NPV, negative predictive value, PPV, positive predictive value; SE, standard error; VL, viral load.

[a] PPV and NPV were calculated using a 10.4% prevalence of virological failure

Table 2. Dried Fluid Spot Genotyping Efficiency and Pairwise Nucleotide Identity Compared to Plasma Specimens

Plasma VL Group	Genotyping Efficiency for Plasma Specimens, % (No.)	DBS Specimens		DPS Specimens	
		Genotyping Efficiency, % (No.)	Nucleotide Identity to Plasma, % Mean ± SD (95% CI)	Genotyping Efficiency, % (No.)	Nucleotide Identity to Plasma, % Mean ± SD (95% CI)
<1000 copies/mL	87.5 (7/8)	50.0 (4/8)	98.6 ± 1.2 (96.7–100.5)	12.5 (1/8)	98.9[a]
≥1000 copies/mL	100 (18/18)	100 (18/18)	98.8 ± 0.83 (98.4–99.2)	38.9 (7/18)	98.2 ± 1.1 (97.2–99.2)

Abbreviations: CI, confidence interval; DBS, dried blood spot; DPS, dried plasma spot; SD, standard deviation; VL, viral load.

[a] This value represents the VL of a single DPS sample and is not a mean

When to stop cotrimoxazole?

- Very cheap intervention so just carry on for another year.

UNDETECTABLE

HOW VIRAL LOAD MONITORING
CAN IMPROVE HIV TREATMENT
IN DEVELOPING COUNTRIES

Linkage to care

- Patients
  - Stigma-related issues
  - Feared discrimination
  - Inconvenient clinic hours
  - Long queues
  - Difficulty in appointment scheduling
  - Disrespect from staff

Linkage to care

- Rapid Point-of-Care CD4 Testing at Mobile HIV Testing Sites to Increase Linkage to Care: An Evaluation of a Pilot Program in South Africa

Testing Group	Not Offered POC CD4 Test	Offered POC CD4 Test	Relative Risk of Offered POC CD4 Test*	95% CI
Sample Size	197	311	—	—
Female, n (%)	109 (55.3)	194 (62.4)	1.14	0.99 to 1.32
Tested previously for HIV, n (%)	92 (46.7)	185 (59.4)	0.87	0.75 to 1.00
Age, mean (SD), yrs*	34.3 (11.8)	34.0 (10.7)	—	—
Age < 30 yrs, n (%)	78 (40.00)	116 (37.54)	1.00	—
Age 30–39 yrs, n (%)	58 (29.74)	112 (36.25)	1.15	0.98 to 1.35
Age 40–49 yrs, n (%)	37 (18.97)	52 (16.83)	1.01	0.82 to 1.25
Age 49+ yrs, n (%)	22 (11.28)	29 (9.39)	0.97	0.76 to 1.26

*Age is missing for 4 patients (total) (2 patients in each testing group). These 4 patients are excluded from all multivariate analyses. Adjusted relative risks of being offered the POC CD4 test estimated using a modified Poisson approach (female, tested previously, and age categories as covariates).[15]

Outcomes*	Successful Follow-up (Yes/No)		Completed Referral Visit (Yes/No), ITT Analysis†		Completed Referral Visit (Yes/No), TOT Analysis‡	
No. patients (total) in analysis	504	—	316	—	286	—
Number with outcome (yes)	316	—	172	—	158	—
	Relative Risk§	95% CI	Relative Risk	95% CI	Relative Risk	95% CI
Offered POC CD4 test	**1.01**	**0.88** to **1.16**	**1.25**	**1.00** to **1.57**	**1.31**	**1.04** to **1.64**
Female	1.21	1.04 to 1.40	1.22	0.97 to 1.54	1.14	0.90 to 1.43
Tested previously for HIV	1.01	0.88 to 1.16	1.14	0.93 to 1.40	1.09	0.88 to 1.35
Age < 30 yrs	1	—	1	—	1	—
Age 30–39 yrs	0.97	0.83 to 1.14	0.87	0.67 to 1.13	0.94	0.72 to 1.22
Age 40–49 yrs	0.95	0.78 to 1.16	1.26	0.99 to 1.62	1.26	0.97 to 1.64
Age 49+ yrs	0.91	0.70 to 1.16	0.97	0.68 to 1.39	0.94	0.65 to 1.38

*Successful follow-up means the patient was successfully contacted by phone 8 weeks after HIV testing.

†ITT is intention to treat, which uses the full sample of patients contacted and offered the POC CD4 test.

‡TOT is treatment on treated, which uses the full sample of patients contacted and offered the POC CD4 test and then excludes those who declined the test or the site experienced a technical failure with the test.

§Relative risk is adjusted relative risks of successful contact using a modified Poisson approach (offered POC CD4 test, female, tested previously, and age categories as covariates).[13]

Blood tests (2004- 2013)

	2004	2010	2013
CD4+	Initiation, 6 monthly	Initiation, annually	At initiation and at one year
VL	Initiation, 6 monthly	6 months, annually	6 months, annually
ALT	Initiation, 6 monthly (2 and for weeks for NVP)	Initiation for NVP, closely monitor	Initiation for NVP
Creatinine	Never	Initiation, 3 and 6 months, annually	Initiation, 3 and 6 months, annually
FBC (AZT)	Initiation, Month 1, 2, 3 , then 6 monthly	Month 1, 2, 3 and 6 6 monthly	Initiation, month 3 and 6
Fasting cholesterol and triglycerides	Baseline, 6 months, annually	3 month on PI	3 month on PI
Fasting glucose	Baseline,	Never	Never

Adherence

- What have we done so far?
  - Decentralization of services
  - Task-shifting aspects of care to nurses and non-clinical staff
  - NIMART
  - 3 monthly supply given, when possible.

Adherence Clubs (MSF)

- Clinically stable adult patients
- On ART for at least 18 months.
- CD4 count of more than 200 cells/ml in the previous six months
- Sustained viral load suppression.
- Groups of 15 to 30 patients
- Medicines are pre-packaged for each participant and brought to the group by a counselor

Adherence Clubs (MSF)

- Any patients reporting symptoms referred back to the clinic to be assessed by a nurse.
- The counselor or experienced patients lead short group discussions
- A nurse attends these groups annually to draw blood for viral load and CD4 count testing.
- Effectiveness of Patient Adherence Groups as a Model of

- Care for Stable Patients on Antiretroviral Therapy in Khayelitsha, Cape Town, South AfricaMiguel Angel Luque-Fernandez PlosOne Feb 2013

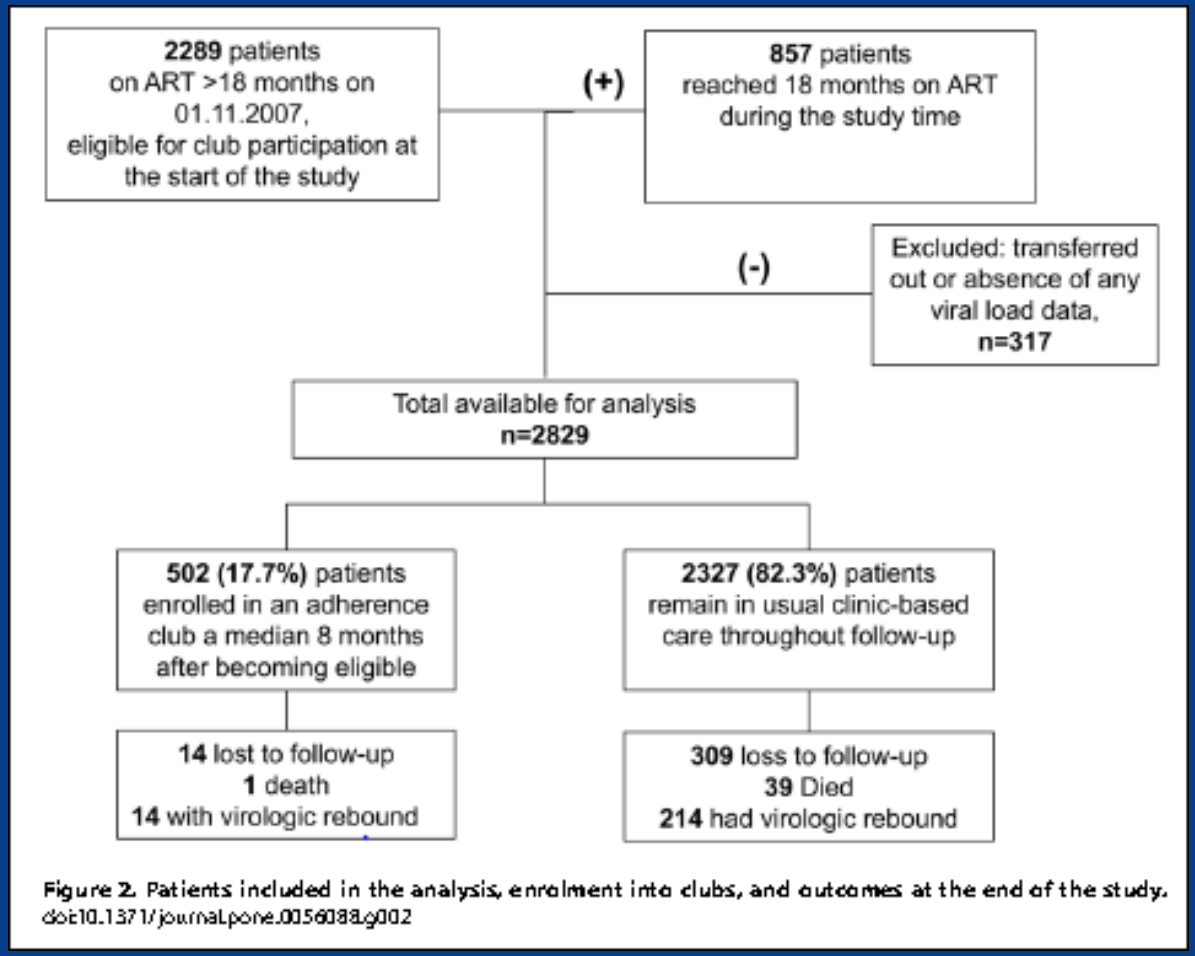


Figure 2. Patients included in the analysis, enrolment into clubs, and outcomes at the end of the study.
doi:10.1371/journal.pone.0056088.g002

Resistance

GUIDELINES

GUIDELINES

The 2012 southern African ARV drug resistance testing guidelines

by the Southern African HIV Clinicians Society

F Conradie, D Wilson (Chairpersons of the Resistance Testing Guidelines Committee), **A Basson, T de Oliveira, G Hunt, D Joel, M Papathanasopoulos, W Preiser, J Klausner, D Spencer, W Stevens, F Venter, C van Vuuren** (Expert Panel Members), **L Levin, G Meintjes, C Orrell, H Sunpath, T Rossouw, G van Zyl** (Reviewers)

Corresponding author: *F Conradie (fconradie@witshealth.co.za)*

Drug resistance refers to a **reduction** in the **ability** of a particular **drug** or combination of drugs **to cure a disease** or **block replication** of **pathogens**

New Proposed HIVDR guidelines
HIV Clinician's Society Guideline in South Africa

Patient group	Recommendation for HIV resistance testing	Comments
Recent infection		
Infants under the age of two years or within two years of stopping daily NVP or any form of ARV or infants less than 2 years where PMTCT is uncertain	Recommended	As soon as HIV is diagnosed.
Documented recent infection	Recommended	Information on circulating strains
HIV diagnosis		
Patients without documented seroconversion presenting for routine clinical care	Not recommended	background prevalence of transmitted resistance is low
ARV initiation		
Children above the age of 2 years about to start first-line ART	Not recommended	Unless within 2 years of stopping daily NVP
Pregnant women about to start first-line ART	Not recommended	Pregnant women should have a viral load measured three months after triple therpayr ARV initiation .Detectable >1000 copies/ml viraemia should be treated as a medical emergency (see below)
Adults about to start first-line ART	Not recommended	
Failure of NNRTI-based ART		
Adults and children with two viral load measurements>1,000** copies per ml and a <2 logs drop in viral load (at least 4-weeks apart) while taking NNRTI-based ART	Recommended	Adherence* issues should be comprehensively addressed between the two measurements. Resistance testing should be done while the patient is taking the failing regimen, or within 4 weeks of discontinuation.
Failure of a boosted protease-inhibitor based regimen		
Adults and children with two viral load measurements >1,000** copies/ ml and a < 2 log drop in viral load, > 4weeks apart while taking	Recommended	Adherence* issues should be comprehensively addressed between the two measurements. Resistance testing should be done while the patient is taking the failing regimen, or within 4

Other Resistance Guidelines

	SA[2012]	IAS-USA[2012]	DHHS[2011]	British HIV Assoc[2011]
Primary/acute	Recommend	Recommend	Recommend	Recommend
Chronic, Rx naive		Recommend	Recommend	Recommend
Failure 1st, 2nd	Recommend	Recommend	Recommend	Recommend
Pregnancy	Increase monitoring	Recommend	Recommend	Recommend
Pediatric (<2yrs or within 2yrs stopping daily NVP)	Recommend		Recommend	Recommend

2 viral load measurements >1000c/ml ,
4 weeks apart for NNRTI's and longer period for PI's

European guidelines are even more aggressive

NATIONAL HEALTH LABORATORY SERVICE
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

National HIV Drug Resistance Working Group

Incorporation now required in the SA national ARV treatment guidelines in an appropriate, feasible, affordable and cost-effective manner?

A working group was formed by the NDoH in late 2012 with relevant stakeholders and consensus reached on way forward (NDoH, clinicians, public, academic and private sector labs etc.)

A Steering committee formed based on the following four pillars/needs to ensure success:

4 pillars (led by NDoH)

1) Clinical team,
2) Laboratory group NHLS/NICD;
3) Epidemiology stream;
4) Database development team

Ambitious Goals:

- One guideline
- Standardized testing strategies
- Increased laboratory capacity
- Appropriate surveillance surveys
- One national database

HIV-1 drug resistance in antiretroviral-naive individuals in sub-Saharan Africa after rollout of antiretroviral therapy: a multicentre observational study

Lancet , 2011

*Raph L Hamers, Carole L Wallis, Cissy Kityo, Margaret Siwale, Kishor Mandaliya, Francesca Conradie, Mariette E Botes, Maureen Wellington, Akin Osibogun, Kim C E Sigaloff, Immaculate Nankya, Rob Schuurman, Ferdinand W Wit, Wendy S Stevens, Michèle van Vugt, Tobias F Rinke de Wit, for PharmAccess African Studies to Evaluate Resistance (PASER)**

- Cross-sectional analysis of ARV naïve individuals in 2007-2009 in 11 regions in Kenya(2), Uganda(3), Nigeria, South Africa (3), Zambia (3)
- 2436(94%) of 2590, 57% women, CD4 median: 133 CD4 cells/ul; >18 years
- Sample weighted drug prevalence of resistance was: **5.6%: ranged from 1.1% in Pretoria (SA) to 12.3% in Kampala (Uganda)**
- Pooled prevalence for 3 sites in Uganda was 11.6% compared to 3.5% for all other sites
- 2.5% NRTI, 3.3% for NNRTis, 1.3% for PI's and 1.1% for dual NRTI and NNRTI
- Odds ratio for drug resistance- associated with each additional year since ART rollout was 1.3 (95% CI: 1.13-1.68)

Interpretation The higher prevalence of primary drug resistance in Uganda than in other African countries is probably related to the earlier start of ART roll-out in Uganda. Resistance surveillance and prevention should be prioritised in settings where ART programmes are scaled up.

South African studies of drug resistance in adults with virological failure on first-line ART

Author	Location	Criteria	N	Duration ART (months)	No drug resistance (%)	NRTI resistance (%)	NNRTI resistance (%)	Complex NRTI resistance* (%)
Barth	Limpopo (one rural clinic)	1 x VL>1000	21	9.0	9.5	52.4	85.8	nil
Marconi	Durban (two hospitals)	1 x VL>1000	115	10.8	16.5	70.4	78.3	15.7
Orrell	Cape Town (eight clinics)	1 x VL>1000	110	8.9	6.0	82.7	88.2	10.9
Hoffmann	Johannesburg (workplace clinic)	1 x VL>1000	68	-	33.8	36.8	61.8	nil
Wallis	Johannesburg (two hospitals)	2 x VL>1000 or 2 x VL>5000	226	-	16.8	72.1	77.9	16.4
El-Khatib	Soweto (one hospital)	ART >12M; VL>400	94	-	-	63.8	80.8	1.0
Sigaloff	Johannesburg (one hospital)	2 x VL>5000	43	22.0	11.6	81.4	86.1	25.6
Van Zyl	Western Cape (one hospital & one CHC)	1 x VL>400	167	13.5	16.8	60.5	82.0	6.6
Murphy	Durban (two hospitals)	1 x VL>1000	141	>6	13.5	-	-	-
Singh	Durban (one hospital)	ART>6M; VL>5000	43	29.0	4.7	91.0	95.0	16.3
Manasa	Hlabisa (rural primary health programme)	2 x VL>1000	240	42.0	13.3	81.3	82.9	23.3

South African studies of drug resistance in adults with virological failure on second-line ART

Author	N	Criteria for genotype	Duration on second-line ART (median)	Drug resistance
Wallis	75	2 x VL >5000	16 months	39% no major DRAM 7% major PI mutations
Levison	33	2 x VL >1000	10 months	67% no major DRAM No major PI mutations
Sigaloff	15	1 x VL >1000	>12 months	40% no major DRAM 7% major PI mutations

Re-cap

- Testing
- Linkage to care
- CD4+ and VL
- Adherence
- Resistance