Guidelines

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22 August 2015

ACKNOWLEDGEMENTS, DISCLAIMERS AND WARNINGS

What are guidelines?

"Statements that include recommendations intended to optimise patient care that are informed by a **systematic review** of evidence and an assessment of the benefits and harms of alternative care options"

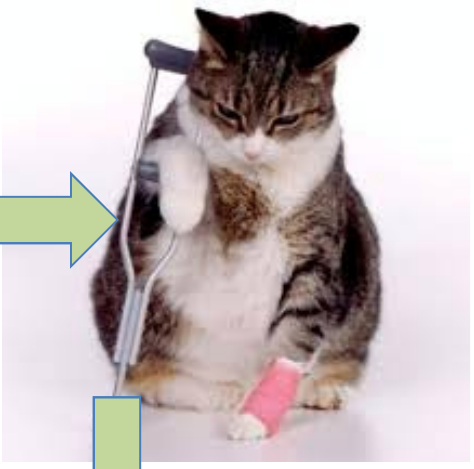
IOM 2011

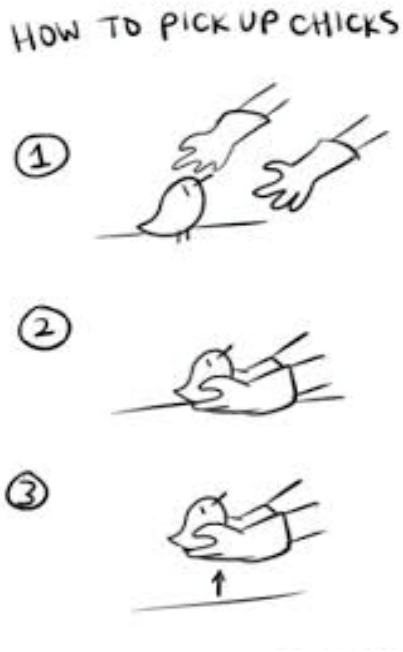
What are guidelines?

- "Clinical practice guidelines are **systematically** developed statements to assist practitioner and patient decisions about appropriate healthcare for **specific clinical circumstances**"

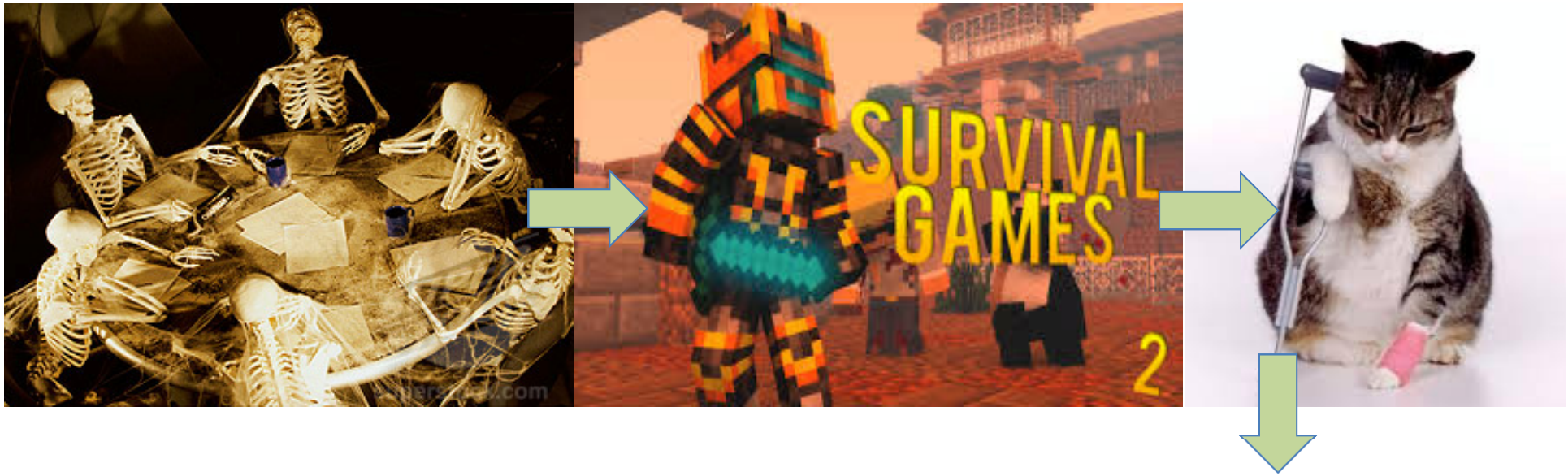
Field and Lohr 1990. page 38.

Process for GL development





Process for GL development



GUIDELINE

Adult antiretroviral therapy guidelines 2014

By the Southern African HIV Clinicians Society

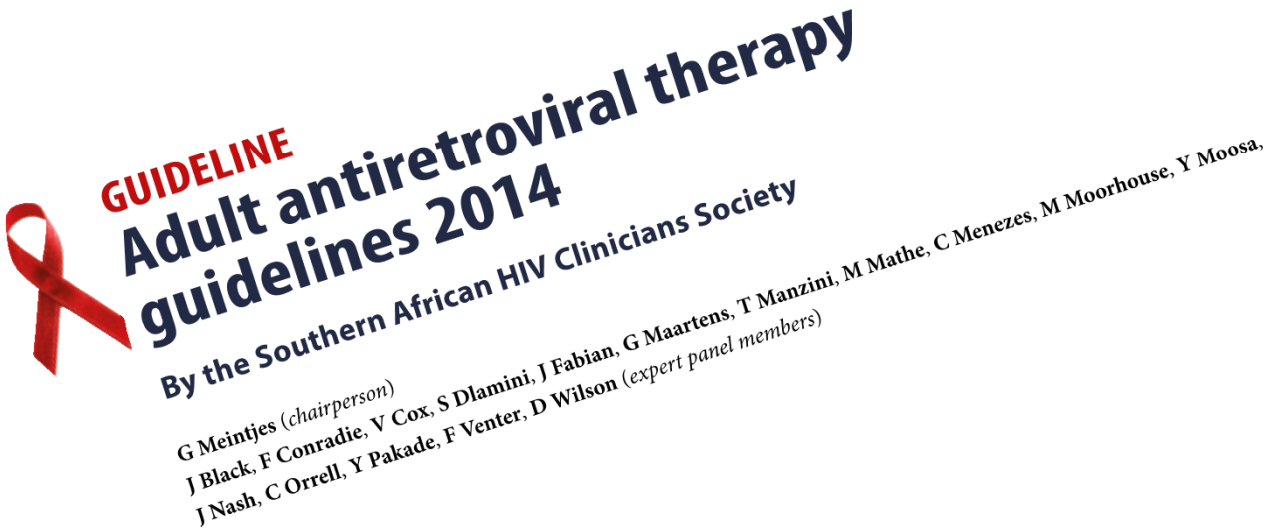
G Meintjes (*chairperson*)
J Black, F Conradie, V Cox, S Dlamini, J Fabian, G Maartens, T Manzini, M Mathe, C Menezes, M Moorhouse, Y Moosa, J Nash, C Orrell, Y Pakade, F Venter, D Wilson (*expert panel members*)

Selected topics

- When to start ART
- What ART to start?
- When to switch?
- Switch to which?
- Third line ART
- Patients with renal impairment

Updated GL: underlying philosophy

- Affordability considered
- Only treatment and diagnostic options available in Southern Africa were considered
- Bridge gap between public and private sectors
- Intended to reflect “best practice”
- Shift to view ART as prevention



When to start ART: diagnosis based

Clinical diagnosis (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 co-infection¶ • hepatitis C co-infection	ART recommended
Any condition requiring long-term immunosuppressive therapy	ART recommended

When to start ART: CD4-based/other

CD4⁺ counts	
<350 cells/μL	ART recommended
350 - 500 cells/μL (two counts in this range)	ART recommended if patient is 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 should ideally involve all partners)

Haiti trial

Starting ART at CD4<350 vs. CD4<200 / AIDS

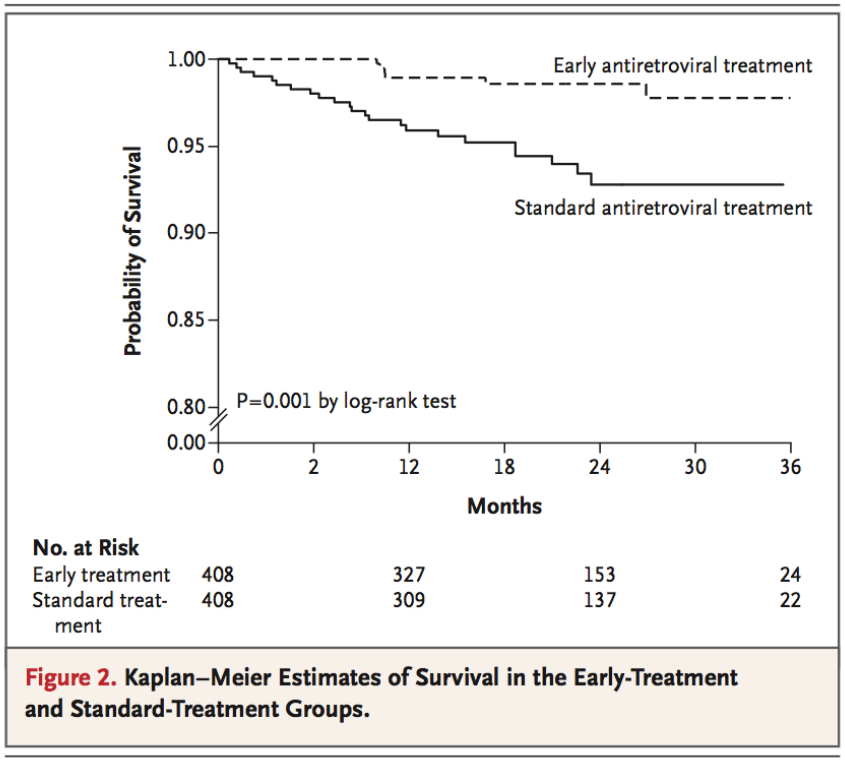


Figure 2. Kaplan–Meier Estimates of Survival in the Early-Treatment and Standard-Treatment Groups.

HR = 4.0

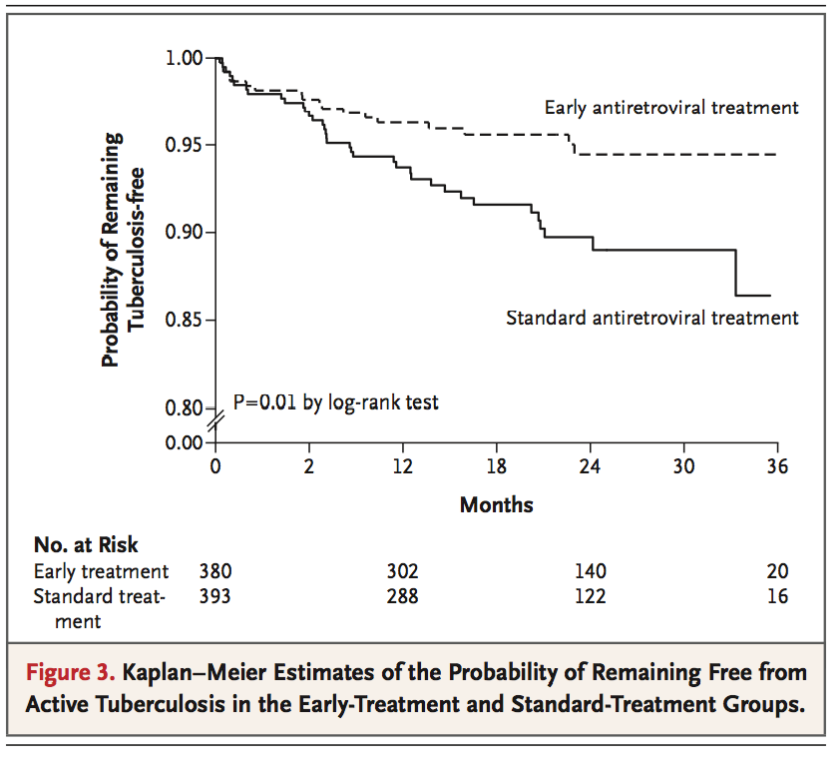


Figure 3. Kaplan–Meier Estimates of the Probability of Remaining Free from Active Tuberculosis in the Early-Treatment and Standard-Treatment Groups.

HR = 2.0

Severe, NEJM 2010

The evidence

CD4 >350 cells/mm^3

- No clinical trial shown improved patient survival >350 cells/mm^3
- Observational data: reduced MM associated with earlier ART
- RCT HPTN 052: reduced morbidity but not mortality
- HIV-related events >350 cells/mm^3 rare
- Await evidence from START and TEMPRANO

CD4 350-500 cells/mm^3

RECOMMENDATIONS:

- Reduces transmission in serodiscordancy
- Wider cover: reduce transmission community level (Hlabisa)
- Individualised approach: may be well; start lifelong ART with possible SEs
- If not ready, defer until CD4 <350 cells/mm^3

One more eligibility criterion…

Patients diagnosed during seroconversion, if adherence requirements are met

- Recent studies suggest that ART initiation during serconversion associated with slower disease progression
- At least 3 years; consider lifelong
- Limits size of reservoir
- Diagnosis: recent negative HIV test that becomes positive on subsequent test

What ART to start?

	SAHIVSOC	SA NDOH	WHO
NRTIs Recommended Alternative	**TDF + FTC/3TC** ABC AZT Short term d4T	**TDF + FTC/3TC** ABC	**TDF + FTC/3TC** AZT ABC Short term d4T
Third drug Recommended Alternative	**EFV** RPV NVP (RAL) (PI/r)	**EFV** NVP LPV/r (ATV/r)	**EFV** NVP PI/r

What ART to start? NNRTIs

EFV	RPV	NVP
Avoid if • Active psychiatric illness • History severe psych disease • Nightshifts / heavy machinery / driving **Common/severe ADRs** • CNS symptoms (vivid dreams, problems with concentration, dizziness, confusion, mood disturbance, psychosis) • Rash • Hepatitis • Gynaecomastia	**Avoid if** • VL >100 000 copies/mL **Common/severe ADRs** • Rash • Hepatitis • CNS symptoms (all uncommon) **Inexpensive**	**Avoid if** • CD4 >250 in women and >400 in men • Liver disease or LFT derangement **Common/severe ADRs** • Rash • Hepatitis

Efavirenz and pregnancy

- In a meta-analysis, the incidence of NTDs and all congenital abnormalities among women exposed to EFV in T1 was similar to that of the general population
- Based on the accumulated evidence we endorse the WHO guidance that EFV can be used in pregnancy and women who intend to fall pregnant
- This is in contrast to our previous guidance
- The FDA category D classification should be discussed with women
  - based on animal studies
  - human cohort studies have not demonstrated an increased risk of congenital abnormalities
  - background low risk of congenital abnormalities in all pregnancies (unrelated to drugs)

EFV and birth defects

General US pop	General South Africa pop	1st trimester exposure to any ARV	2nd/3rd trimester exposure to any ARV	1st trimester exposure to EFV	2nd/3rd trimester exposure to EFV	1st trimester exposure to EFV Meta analysis
3%	5.3%	2.9%	2.8%	2.4%	2.0%	2.0%
95% CI :		(2.5 - 3.4)	(2.5 - 3.2)	(1.4 - 3.9)	(0.4 – 5.8)	(0.82-3.18)
Numbers:		195/6666	237/8394	18/735	3/149	39/1437

Relative risk 1st trimester EFV to non EFV ART was 0.87 (0.61-1.24, p=0.45)

Neural tube defects

South African general population estimate = 0.23 - 0.36%

Meta-analysis (2011) = 0.07% **(95% CI = 0.002 - 0.39)**

Pillay, SA J HIV Med, March 2012;28

Ford, AIDS 2011;25:2301

The Antiretroviral Pregnancy Register Interim (2013)

Global Report of Birth Defects

When to switch?

- Two VL >1000 copies/mL
- 2-3 months apart
- At least 4 weeks **adherence intervention** in between

Low level viraemia (200 – 1000 copies/mL)

- Prolonged (>1 year)

OR

- With persistently low CD4 counts (<100 cells/mm^3)

Despite **adherence interventions**

Switch to which?

SAHIVSOC		SA NDOH		WHO	
First line NRTI	**Switch to**	**First line NRTI**	**Switch to**	**First line NRTI**	**Switch to**
AZT d4T	TDF	AZT d4T	TDF	TDF	AZT
TDF ABC	AZT	TDF ABC	AZT	AZT d4T	TDF

EARNEST trial suggested that NRTIs have important role in second line with PI/r even when there is NRTI resistance present

Third drug options

SAHIVSOC	SA NDOH	WHO
ATV/r LPV/r DRV/r*	LPV/r (ATV/r)	ATV/r LPV/r

* When 800/100mg daily available

ATV/r 300mg/ 100mg daily

Advantages

- Once daily
- Fewer GI SEs than LPV/r
- More favourable lipid profile

Disadvantages

- No FDC in SA
- RTV capsules not heat-stable
- Cannot be co-administered with rifampicin

Exceptions

- Not tolerated eg jaundice
- Patients who don't own fridge
- Patients on rifampicin

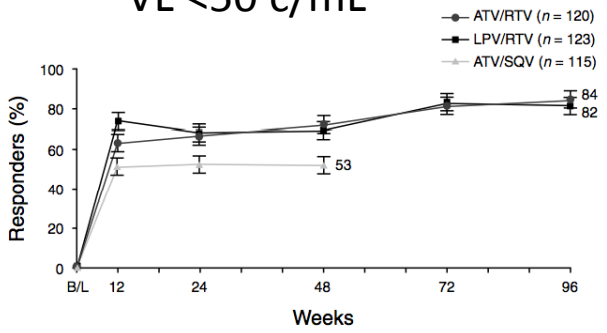
BMS 045: 96 week results

LPV/r vs. ATV/r in treatment-experienced patients

Table 3. Adverse events (AEs) and laboratory abnormalities up to week 96.

	ATV/RTV ($n = 119$)[a]	LPV/RTV ($n = 118$)[a]
Adverse events leading to discontinuations, *n* (%)	10 (8)	9 (8)
Serious adverse events, *n* (%)[b]	16 (13)	13 (11)
Grade 2–4 AEs ≥ 3%[c]		
Diarrhoea	3[d]	13
Nausea	3	2
Jaundice	7[e]	0
Scleral icterus	3	0
Myalgia	4	0
Lipodystrophy	3	3
Grade 3–4 laboratory abnormalities (%)[f]		
ALT elevation	5	3
AST elevation	3	4
Total bilirubin elevation	53[g]	< 1
Neutropenia	8	10
Thrombocytopenia	5	5

VL <50 c/mL

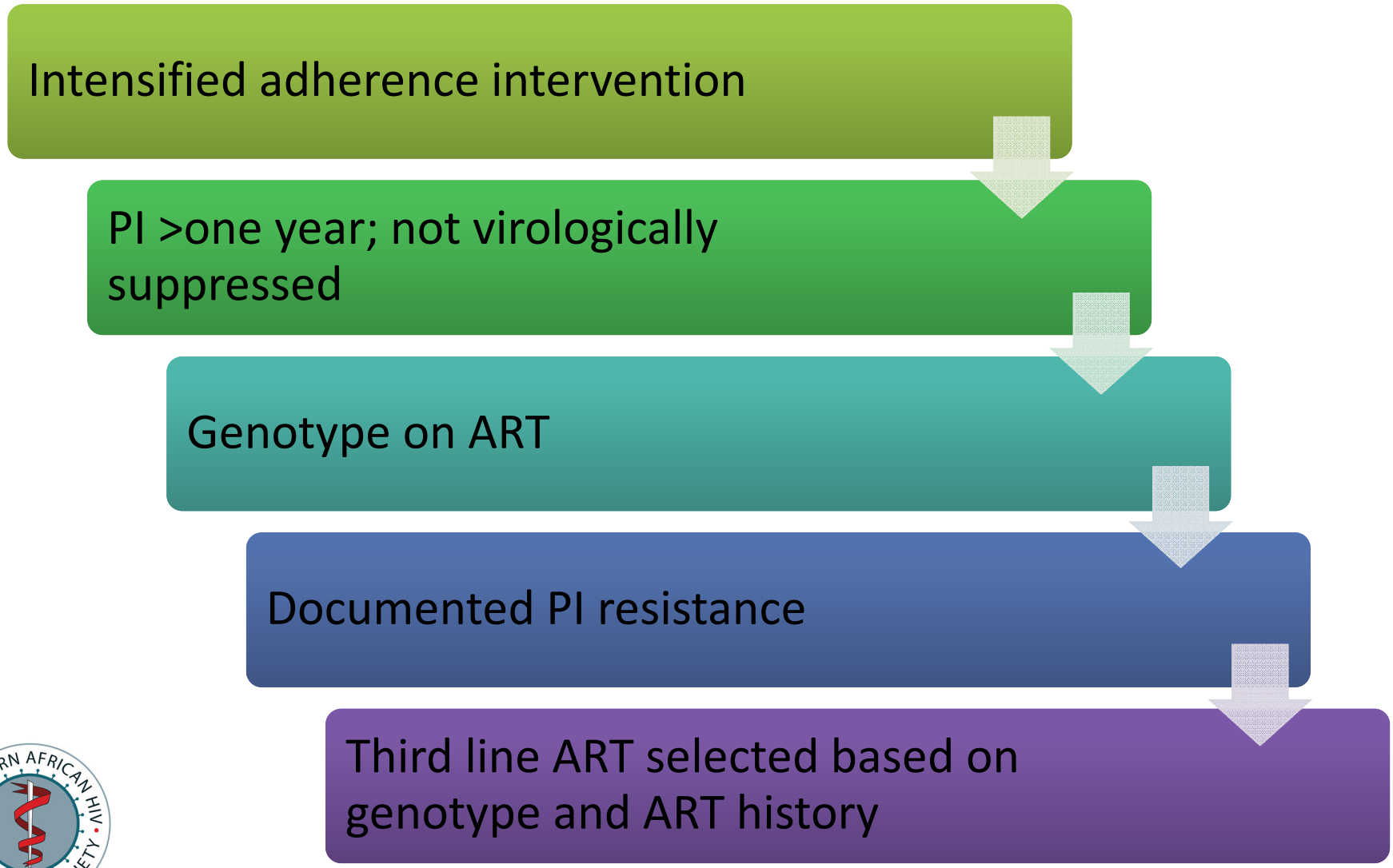


ATV/RTV	120	115	113	93	72	67
LPV/RTV	123	115	112	105	70	65
ATV/SQV	115	102	96	80		

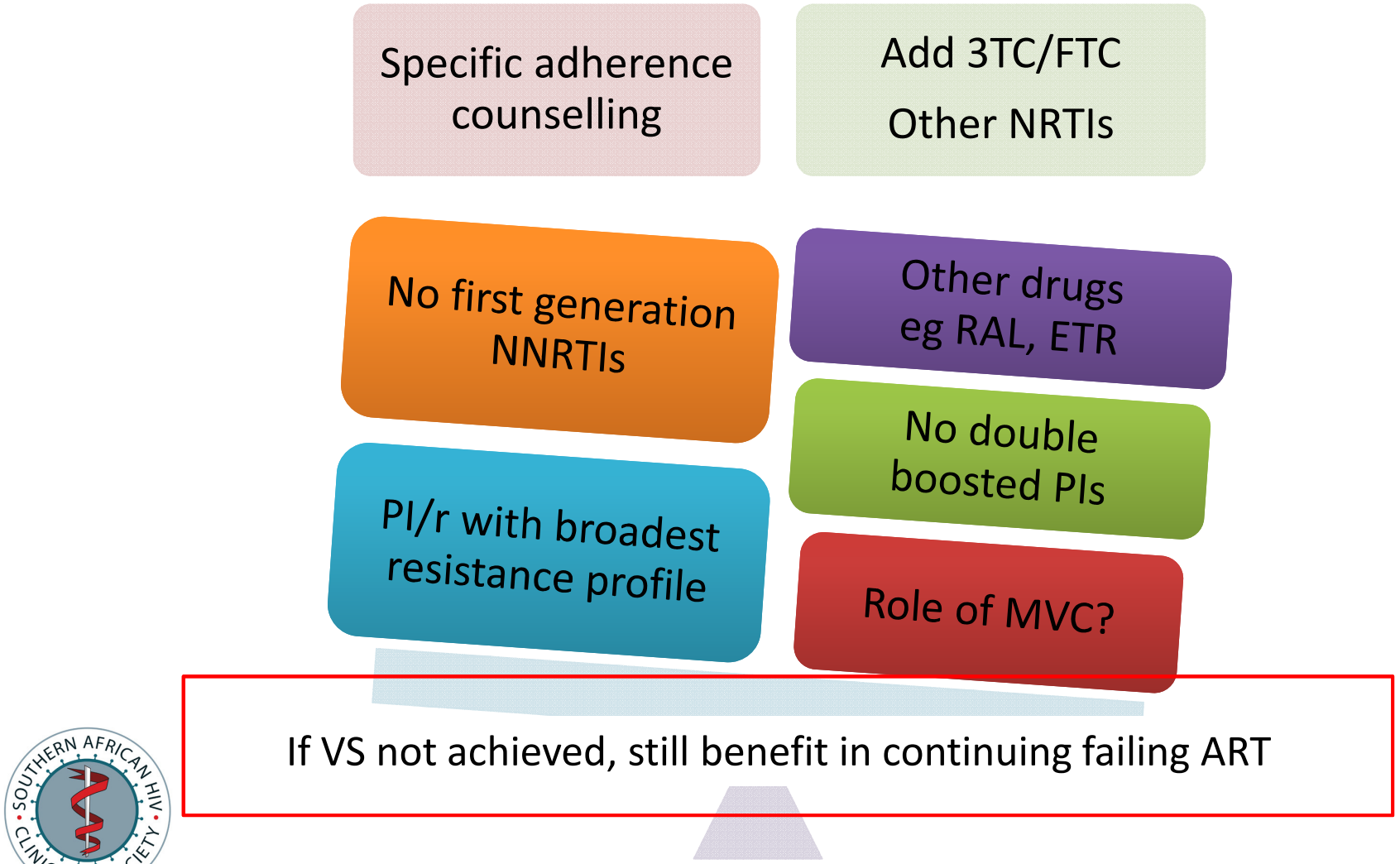
By end of trial:
20% in LPV/r arm
9% in ATV/r
on lipid lowering Rx

Johnson, AIDS 2006

Patients failing on second line ART



Third line regimen: principles



Outcomes


EVALUATE CLINICAL GUIDELINES
YES...I DON'T UNDERSTAND! BUT HIS BACK STIL HURTS
I LOVE MASSAGE...


RIP
"He had it coming to him - he didn't follow government guidelines."

VS on salvage ART:

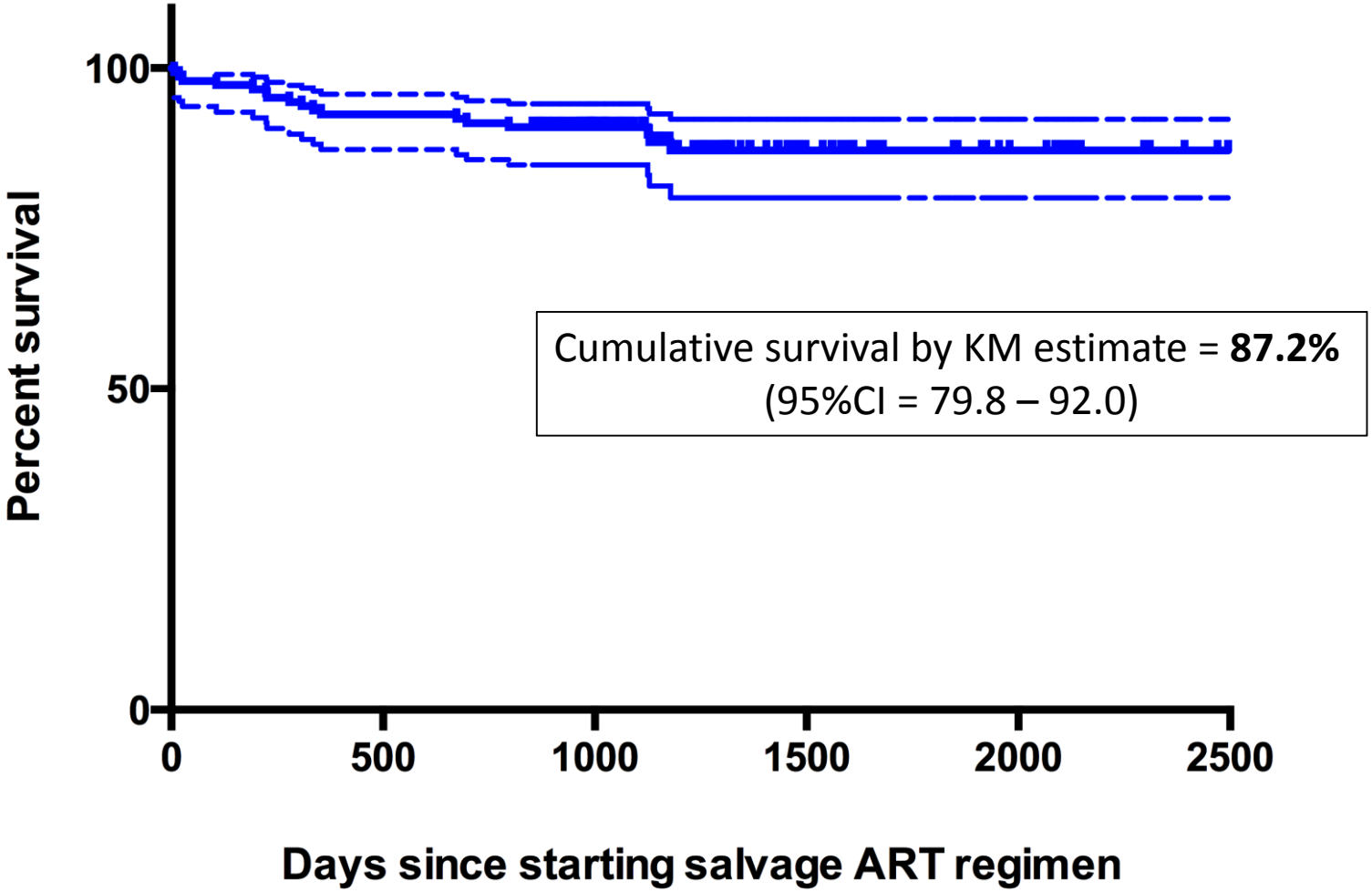
AfA programme (n=152)

145 (95.4%) 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 copies/mL	126	86.9%	82.9%
Suppressed <50 copies/mL	108	74.5%	71.1%

Dunn, unpublished

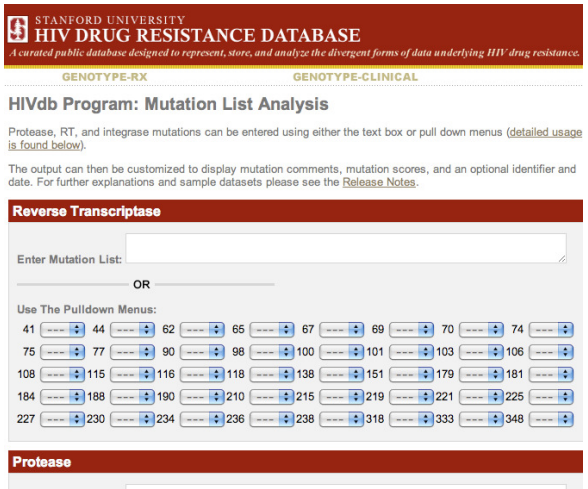
Kaplan Meier curve: Survival proportions



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

Resistance testing

- At first line failure if resources permit
  - Differentiate adherence issues from resistance
  - Informative ETR/RPV mutations (third line)
  - Which NRTIs?
- Patients receiving PI-based first line who are failing
- Second line failure



ART when renal impairment

Acute and chronic kidney injury

- ABC standard dose + 3TC (adjust dose based on CrCl) + EFV
- If renal impairment resolving readjust to standard doses

Chronic dialysis

- First line
  - ABC 600mg daily
  - 3TC 50mg x 1 dose then 25mg daily (given after dialysis session)
  - EFV 600mg nocte
- Second line
  - LPV/r (twice-daily) plus 2 NRTIs selected based on resistance test and tolerability considerations

Dosage adjustment in renal failure

Drug	CrCl (mL/min)[‡§] 10 - 50	CrCl (mL/min)[‡§] <10	Haemodialysis (dose after dialysis)	Peritoneal dialysis
TDF	AVOID	AVOID	300 mg once weekly	Unknown
ABC	Unchanged	Unchanged	Unchanged	Unchanged
3TC	150 mg daily	50 mg daily[†]	50 mg first dose and thereafter 25 mg daily[†]	50 mg first dose and thereafter 25 mg daily[†]
AZT	Unchanged	300 mg daily	300 mg daily	300 mg daily
d4T	15 mg 12-hourly	15 mg daily	15 mg daily	Unknown
ddI	>60 kg body weight: 200 mg daily <60 kg body weight: 150 mg daily	>60 kg body weight: 125 mg daily <60 kg body weight: 75 mg daily	>60 kg body weight: 125 mg daily <60 kg body weight: 75 mg daily	>60 kg body weight: 125 mg daily <60 kg body weight: 75 mg daily

No dosage adjustments needed for NNRTIs, PIs and InSTIs

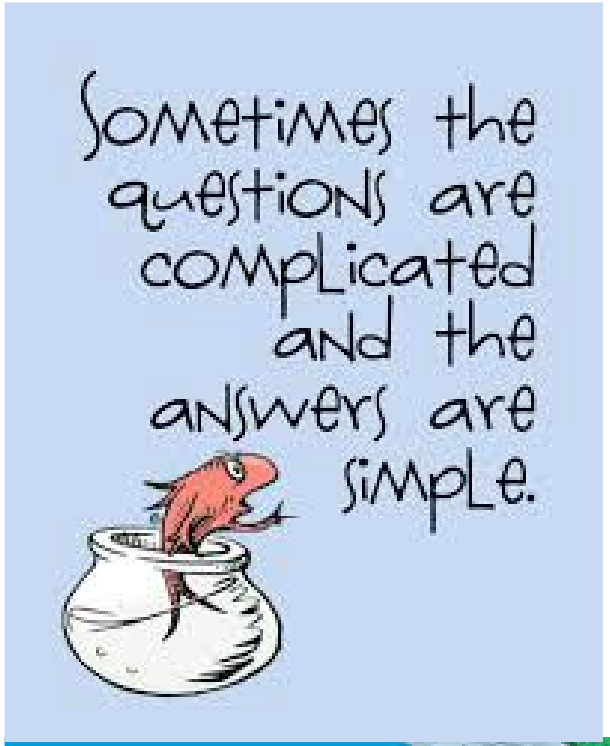
What else?

Unchanged

- Investigations prior to ART initiation
- Laboratory monitoring on ART
- Minimal changes in ARV toxicity monitoring and management

New

- Confirm HIV diagnosed on 2 rapids with lab test
- Do CD4 if virological or clinical failure
- IPT included in GL



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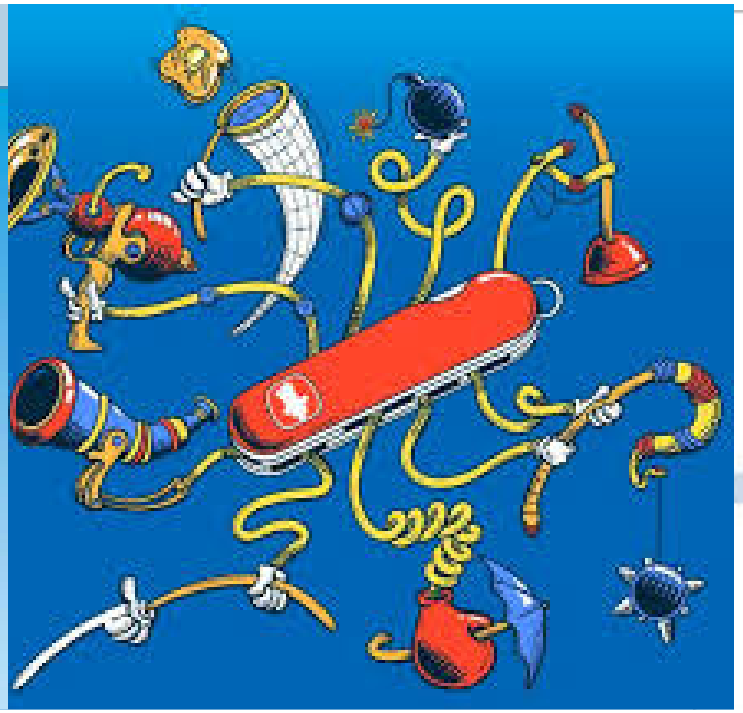

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Mar 2015