SA HIV Clinicians Society Adult ART guidelines

In draft format

Graeme Meintjes
(on behalf of the guidelines committee)

Selected topics

- When to start ART
- First-line
- Second-line
- Third-line
- Patients with renal impairment

Key principles of guidelines

- South Africa 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 2 sectors for treatment.
- The guidelines are intended to reflect 'best practice' – while it is acknowledged that certain recommendations are aspirational for poorly resourced settings, the unavailability of diagnostic/monitoring tests should not be a barrier to providing ART to those in need.
- There has been a shift to view ARV treatment as a means of HIV prevention. The evidence base for this exists for serodiscordant couples; recommendations in this regard are included in these guidelines and additional data from community studies are awaited.

Question

- Would you prescribe ART for all patients with CD4 < 500?

CD4 threshold 500

- WHO guidelines 2013
- SA DOH guidelines from 1 Jan 2015

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

Haiti trial

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

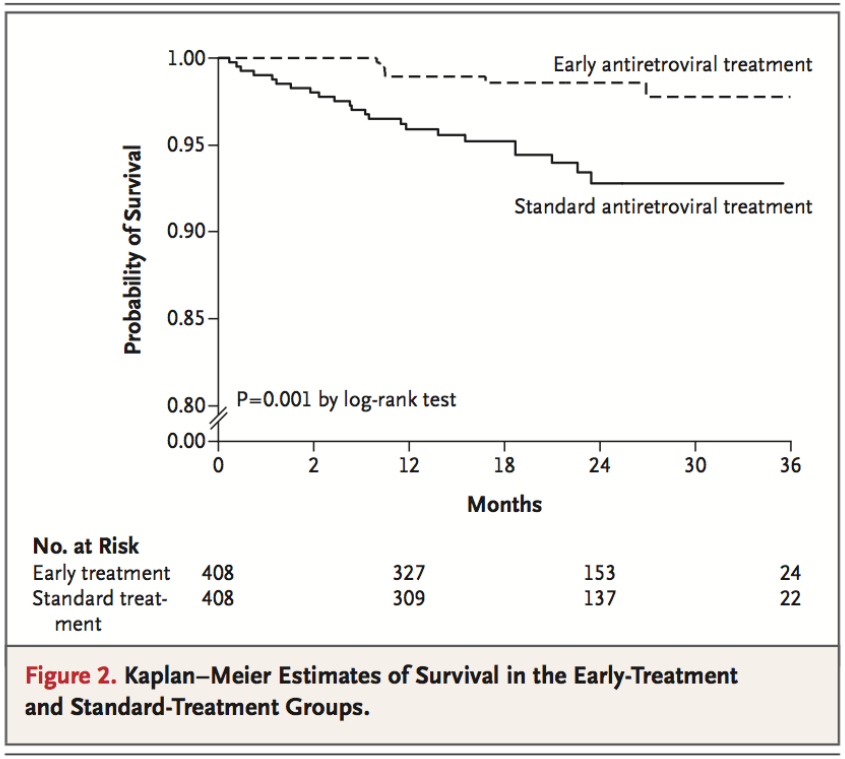


Figure 2. Kaplan–Meier Estimates of Survival in the Early-Treatment and Standard-Treatment Groups.

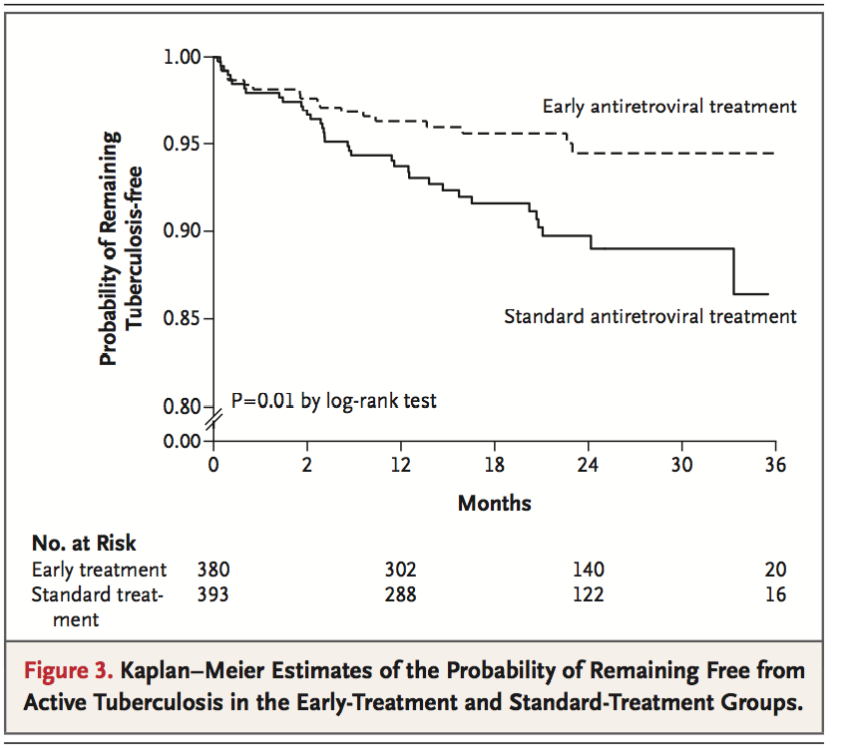


Figure 3. Kaplan–Meier Estimates of the Probability of Remaining Free from Active Tuberculosis in the Early-Treatment and Standard-Treatment Groups.

HR = 4.0

HR = 2.0

Severe, NEJM 2010

Evidence for starting at CD4 > 350

- Evidence that increasing the CD4 count threshold for starting to 500 results in individual patient benefit is less clear.
- No clinical trial has shown improved patient survival from starting at a CD4 count higher than 350.
- Some observational data suggest reduced morbidity and mortality associated with starting ART earlier.
- If there is benefit to patients starting ART at CD4 counts >350, the benefit is likely to be small, since HIV-related events at high CD4 counts are rare.
- A randomised controlled trial (RCT) (HPTN052) showed reduced morbidity but not mortality associated with starting ART at a CD4 count of 350 – 550 (compared with <250). Absolute benefits were small.
- Definitive evidence regarding earlier ART initiation is awaited from ongoing RCTs, the START trial and TEMPRANO trial.

Recommendations if CD4 350-500

- Starting ART at higher CD4 counts reduces HIV transmission within couples where one partner is HIV negative (HPTN052)
- Wider ART coverage appears to reduce the risk of HIV transmission at a community level (Hlabisa)
- Thus consideration should be given to starting patients whose CD4 counts are between 350-500.
- However, it must be remembered that many of these patients (CD4 350-500) are completely well and starting lifelong medication that needs to be taken with 100% adherence, and also may have side effects in some patients, may be a difficult undertaking.
- We thus support an individualised approach in patients with a CD4 count 350-500: after a discussion about the potential benefits, uncertainties, side effects and need for impeccable adherence patients should only be prescribed ART in this CD4 range if they are motivated for lifelong ART with the required adherence.

- If they do not feel ready yet, ART should be deferred until their CD4 count is below 350 with a plan in place for ongoing follow-up and CD4 monitoring.

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

NNRTI in first line

- **Avoid EFV if**
  - active psychiatric illness
  - history of severe psychiatric disease
  - night shift workers and those operating heavy machinery or vehicles.

- **Rilpivirine**
  - Inexpensive (R47/month)
  - RPV should not be used in patients with viral load > 100,000 copies/ml as clinical trials have shown that RPV-based regimens have higher virological failure rates in these patients compared with EFV (Cohen AIDS 2013;27:939).
  - In patients with viral load ≤ 100,000 copies/ml outcomes are comparable overall to EFV-based regimens, with RPV being better tolerated (Molina, HIV Med 2014;15:57)

- **Avoid NVP**
  - CD4 > 250 in women and > 400 in men
  - Liver disease or LFT derangement

Efavirenz and pregnancy

- In a meta-analysis, the incidence of neural tube defects and all congenital abnormalities among women exposed to EFV in the first trimester 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 on contrast to our previous guidance.
- The FDA category D classification should be discussed with women, explaining that this was based on animal studies, human cohort studies have not demonstrated an increased risk of congenital abnormalities, but that there is a background low risk of congenital abnormalities in all pregnancies unrelated to drugs.

EFZ and birth defects

TABLE 3. PREVALENCE OF BIRTH DEFECTS

General US pop[18]	General South African pop[19]	1st trimester exposure to any ARV[18]	2nd/3rd trimester exposure to any ARV[18]	1st trimester exposure to EFV[18]	2nd/3rd trimester exposure to EFV[18]	1st trimester exposure to EFV[17]
3%	5.3%	2.9%	2.7%	2.7%	2.9%	2.0%
95% CI:		(2.5 - 3.4)	(0.88 - 1.32)	(1.6 - 4.3)	(0.3 - 10.0)	(0.82 - 3.18)
Numbers:		164/5 555	205/7 483	17/643	2/70	39/1 437

Relative risk 1st trimester EFV to non-EFV ART was 0.85 (0.61 - 1.20)[17]

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 (January 2011)
Global Report of Birth Defects

Question

- After a patients fails TDF/FTC/EFZ, what is your preferred second line regimen?

Second line ART

- 2 NRTIs and boosted PI

- Boosted PI's
  - Atazanavir/ritonavir (preferred)
  - Lopinavir/ritonavir
  - Darunavir/ritonavir (when 800/100mg daily is available)

Atazanavir 300mg/ritonavir 100mg daily

- Advantages:
  - Once daily
  - Fewer GI side effects than lopinavir/ritonavir
  - More favorable lipid profile

- Disadvantages:
  - No fixed-dose combination currently in SA
  - Ritonavir capsules not heat-stable
  - Cannot be co-administered with rifampicin

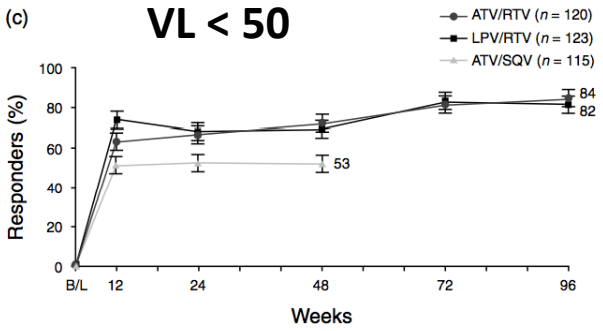
- Exceptions:
  - Not tolerated (eg. cosmetically unacceptable jaundice) then use lopinavir/ritonavir
  - Patients who do not own a fridge (to store ritonavir capsules)
  - Patients on rifampicin-based TB treatment -(double dose lopinavir/ritonavir should be used while on the TB treatment)

BMS045: 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



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

Atazanavir and jaundice

- 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

Choice of 2nd line NRTIs

1st line NRTIs	2nd line NRTIs
AZT/3TC	TDF/3TC*
D4T/3TC	TDF/3TC* (preferably after genotype)
TDF/3TC*	AZT/3TC
ABC/3TC	AZT/3TC

*3TC interchangeable with FTC

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

Third line/ART salvage

- Patient failing 2nd line (2 x VL > 1000)
- Check adherence (claims + self-report)
- Genotype resistance test
- Salvage if significant lopinavir/atazanavir resistance
- Use Stanford database resistance test analysis + treatment history to design salvage regimen

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/

Salvage regimens

- Darunavir/ritonavir 600/100mg bd
- Raltegravir 400mg bd (future: Dolutegravir)
- NRTIs based on genotype (usually 2)
  - cf. EARNEST findings

- ?Etravirine (genotype cannot reliably inform regarding susceptibility if done at 2nd line failure)
- ?Maraviroc (extremely expensive and requires tropism tests - CCR5 tropic virus)

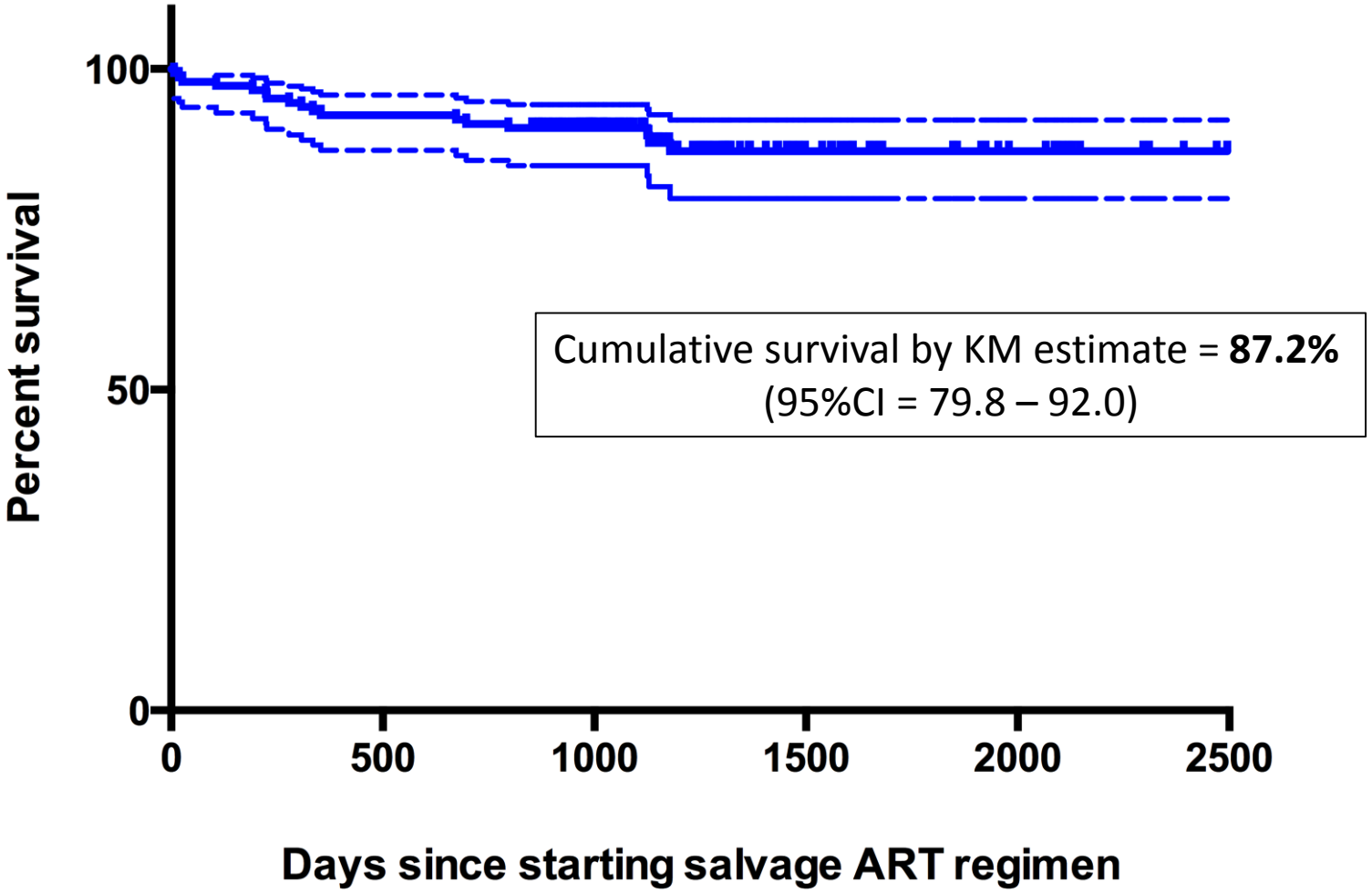
Virological suppression on salvage ART, AfA programme (n=152)

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	126	86.9%	82.9%
Suppressed < 50	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)

Question

- In a patient on chronic dialysis, what is your preferred first line regimen?

ART when renal impairment

- Acute and chronic kidney injury
  - Abacavir standard dose + 3TC (adjust dose based on CrCl) + Efavirenz
  - If renal impairment resolving readjust to standard doses

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