Clinical guidelines for the management of HIV/AIDS in adults and adolescents ≥15 years

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CAPRISA ACC –DOH ETHEKWINI PROJECT

HIV DR RESEARCH PROJECTS

Overview

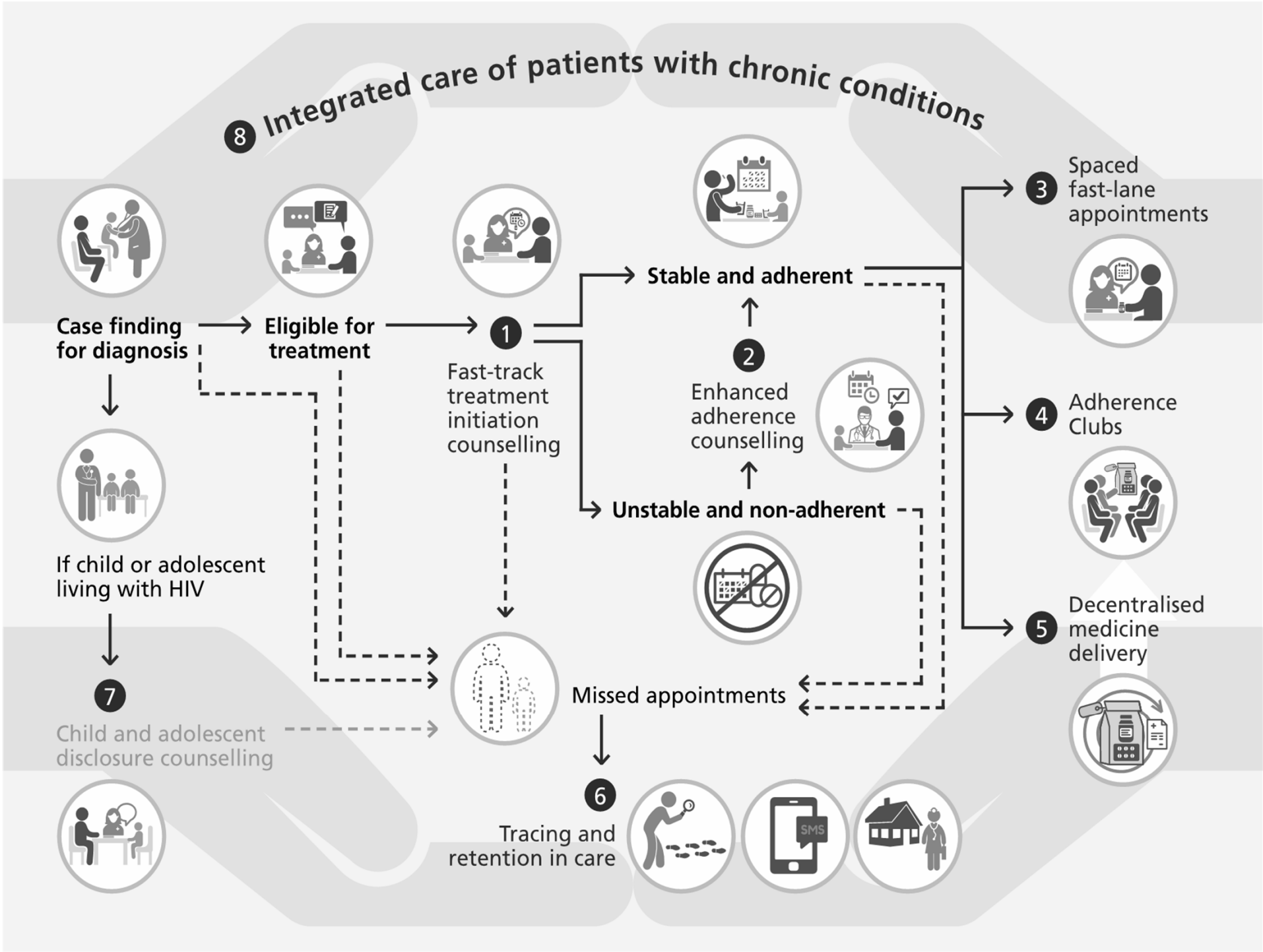
- HIV continuum of care
- ICDM
- What is NEW
- Co Infections
- ART adverse events
- Monitoring VL and DR

Antiretroviral Agents Approved

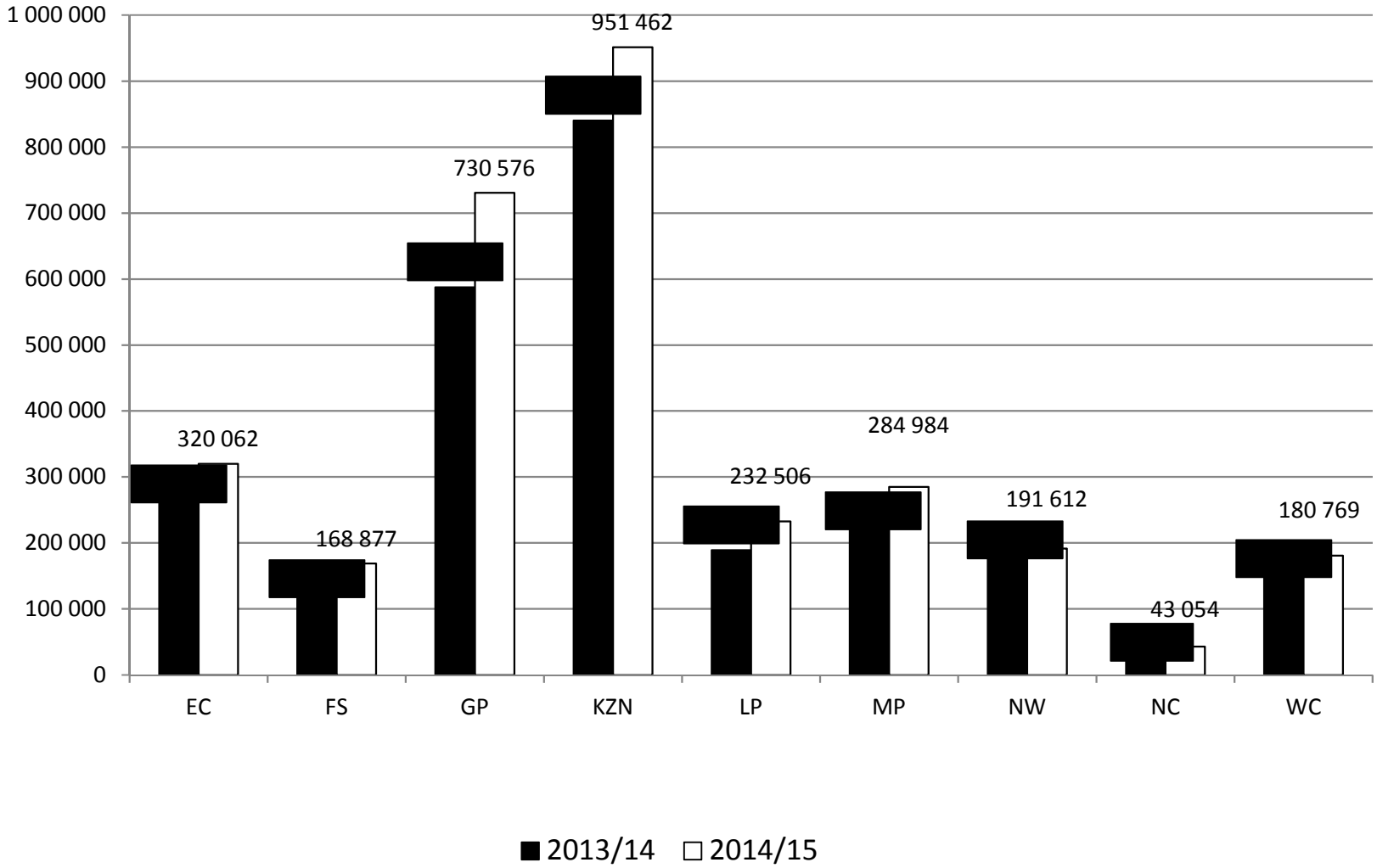
NRTIs	NNRTIs	PIs
zidovudine (AZT)	nevirapine (NVP), efavirenz (EFV)	saquinavir (SQV)
didanosine (ddI)	*Rilvipirine (RLP)*	indinavir (IDV)
zalcitabine (ddC)	etravirine (ETV)	ritonavir (RTV)
stavudine (d4T)	**Nucleotide RTIs**	nelfinavir (NFV)
lamivudine (3TC)	tenofovir DF (TDF)	lopinavir/ritonavir (LPV/r)
abacavir (ABC)	**Entry Inhibitors**	atazanavir (ATV)
emtricitabine (FTC)	enfuvirtide (ENF, T20) Maraviroc (CCR5)	fosamprenavir (FPV)
?TAF	**Integrase Inhibitors** Raltegravir (MK0518) Dolutegravir	tipranavir (TPV) Darunavir(DRV)

KZN - **ARV Update**

- The Ethekwini district has 121 fixed facilities offering ART.
- As at end of Q4/2015-16, there were 346 966 clients (I million in KZN)
- Out of 346 966 TROA, a total of 298 000 patients are on FDC (83%)
- District had a target of 104 459 ARV initiations and achieved 73 713 which was 71% of the target.
- Out of 73 713 total initiations, 70 616 were initiated on FDC which was 96%.


8 Integrated care of patients with chronic conditions
Case finding for diagnosis
Eligible for treatment
1
Fast-track treatment initiation counselling
Stable and adherent
2
Enhanced adherence counselling
Unstable and non-adherent
3
Spaced fast-lane appointments
4
Adherence Clubs
5
Decentralised medicine delivery
If child or adolescent living with HIV
7
Child and adolescent disclosure counselling
Missed appointments
6
Tracing and retention in care
SMS

Total Remaining on ART



What is new in these guidelines 2015?

Eligibility	• UTT (All eligible regardless of CD4/WHO stage) • Option B+
Regimens	• Use of FDCs for simplification • Harmonised ART regimens • Alternatives in second line for AEs • Third line drugs
Labs	• Routine CrAg screening in CD4 <100 cells/mm^3 • Use of VL for monitoring treatment • TST for IPT eligibility and duration

UTT Eligibility and Timing

UTT (All eligible regardless of CD4/WHO stage)

- All HIV+ children, adolescents and adults offered ART
- Pre-ART and wellness patients offered ART
- Assess willingness and readiness to start ART. If not ready continue wellness program and continuous counselling for ART.
- Baseline CD4 will still be done

ART should be started within 2 weeks after the CD4 count is done

Fast track:
HIV Stage 4
CD4 <200 cells/mm^3

Immediate Priority:
HIV+ pregnant and breastfeeding women
HIV+ children and adolescents
HIV+ Adults with CD4<350 cells/mm^3

TB/HIV co-infection:
Start TB Rx first then ART within 2-8 weeks
If CD4<50 initiate ART within 2 weeks of TB Rx

Cryptococcal/TB meningitis:
Defer ART for 4-6 weeks

Advanced disease

Low CD4 count <50

Different OIs with poor general medical condition and risk of high mortality –irrespective of CD4 count

CNS infections including CCM, Toxoplasmosis ,PML

Lung infections –PCP, severe PTB, Bacterial pneumonias

Extrapulmonary TB

HIV associated malignancies.

Dementia

Persistent diarrhoea

Renal failure

Cardiomyopathy

Life threatening ART adverse events

ICU admissions

Treatment failure –multiclass drug resistance

Acute OIs and Timing of ART

- Early ART outweighs risk
  - Esophageal candidiasis
  - Crypto/microsporidiosis
  - PML
  - KS
  - PCP
  - Serious bacterial infections
  - TB
- Early ART be beneficial or harmful
  - Toxoplasmosis
  - Tb meningitis
- Early ART is harmful
  - Crypto meningitis

SAHIVCS GUIDELINES-SEPT 2012

Starting ART in patients with TB

- CD4 count ≤50 cells/µl: - after 2 weeks of TB treatment when it is clear that the patient's TB symptoms are improving and that TB therapy is tolerated.

- CD4 count >50 cells/µl: - delayed until after the intensive phase of TB treatment (2 months) unless the patient has other serious HIV-related conditions (e.g. Kaposi's sarcoma or HIV encephalopathy, persistent diarrhoea etc)

- TB meningitis (TBM) - Recommend starting ART 2 - 8 weeks after TBM diagnosis.

Starting ART in patients with other OIs

Cryptococcal meningitis (CM)- Recommend starting ART before 3-4 weeks after antifungal treatment (preferably amphotericin B-based) is started

Pneumocystis pneumonia / bacterial pneumonia /Toxoplasmosis - within 2 weeks of starting treatment for that infection.

Severe Kaposi's sarcoma and lymphoma, - ART counselling should be expedited and ART should be started as soon as possible.

Starting ART in patients with PTB

- CD4 ≤50
  - ART within 2/52 of TB treatment
  - reduces AIDS progression & mortality
- CD4 >50⇒ ART after intensive phase
  - Reduced shared toxicity
  - Reduce risk of IRIS

NEJM 2011; 365:1482–1491., NEJM 2011;365:1471-81, CID 2011;52:1374–1383

TB while on ART

- On First-line regimen
  - Continue ART with TB treatment.
  - No change ART

- On Second-line regimen:
  - Double dose LPV/r
  - Monitor ALT monthly.
  - Reduce LPV/r to standard dose 2/52 after stopping TB treatment

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First line regimen

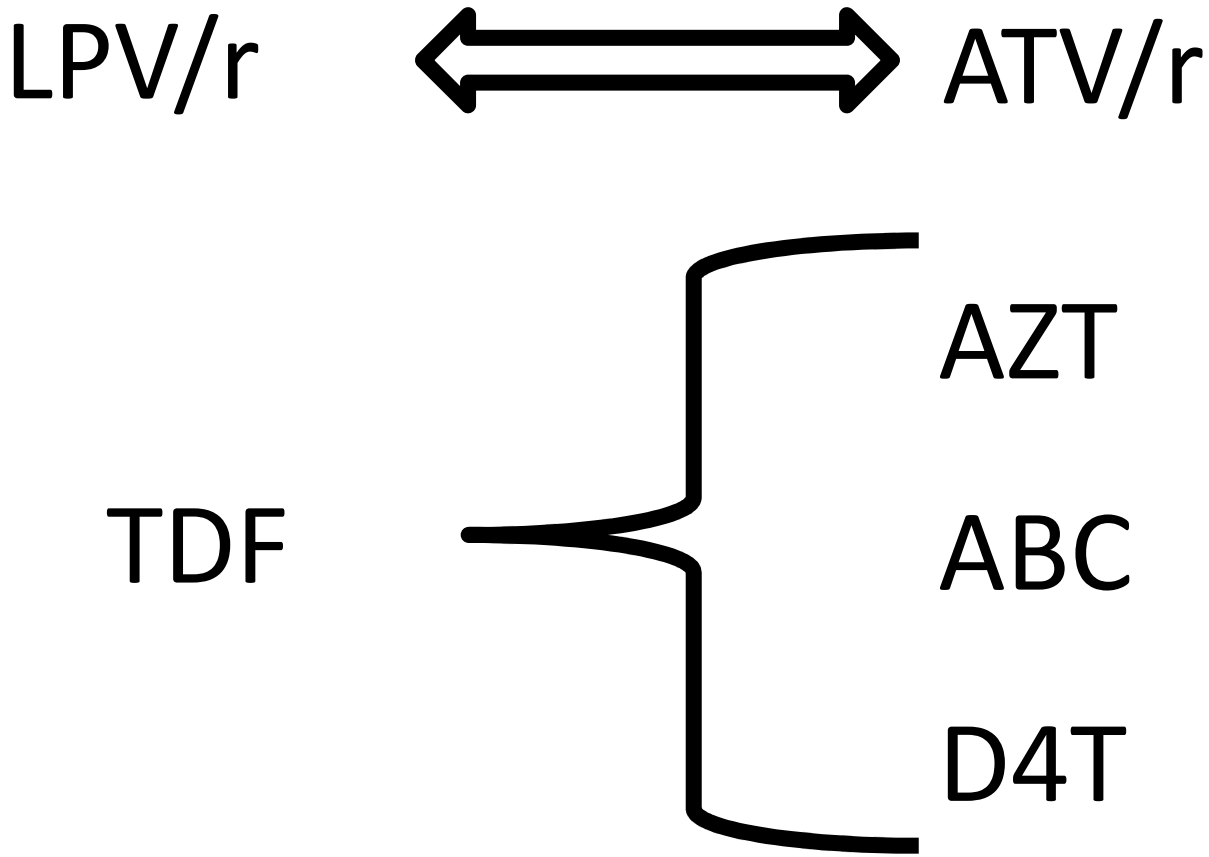
Who?	What?	Comments
• Adults • Pregnant and breastfeeding women • TB co-infection • HBV co-infection • HIV-positive partner in serodiscordant couple • Adolescents >15 years and weighing >40kg	TDF + FTC (or 3TC) + EFV (FDC preferred)	Replace EFV with NVP if significant psychiatric comorbidity or intolerance to EFV and where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. shift workers. . Remember CD4 count restrictions for NVP Evidence supports the efficacy and safety equivalence of 3TC and FTC
• Adolescents <40kg	ABC + 3TC + EFV	If adolescent's weight <40kg, align with paediatric regimen

Substituting contraindicated drugs in first line

Contraindicated drug	Substitute	Comments
EFV	TDF + FTC (or 3TC) + NVP	Replace EFV with NVP if significant psychiatric comorbidity or intolerance to EFV and where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. shift workers. Remember CD4 count restrictions for NVP
NVP	TDF + FTC (or 3TC) + LPV/r	Avoid NVP in women if CD4 count >250 cells/mm^3, and men with CD4 count >400 cells/mm^3
TDF	ABC + 3TC + EFV (or NVP)	Renal disease or the use of other nephrotoxic drugs, e.g. aminoglycosides MDR treatment
Currently on d4T	TDF + FTC (or 3TC) + EFV FDC preferred	d4T to be discontinued in all patients, even if well tolerated. If patient is not virally suppressed, consider switching to second line

Second-Line Regimen

- AZT/3TC/LPV/r



Drugs for Third-line

- Lamivudine
- Tenofovir
- Raltegravir
- Boosted Darunavir
- Etravirine

Combinations

TDF/3TC/DAR

DAR/RAL/ETR

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

National 3rd-line committee

- ~n=163 patients
- Median age 40 years
- DRV/r +3TC/FTC+AZT/TDF ± RAL ± ETR
- Facility completes motivation form and submits to:
  - the Secretariat: Third Line ARV Peer Review Committee (PRC)
  - TLART@health.gov.za

Reintroducing ART after Interruption

- If defaulted - restart old regimen- VL after 3/12
  - Not suppressed - 2nd line
- Multiple episodes of interruption
  - switch to 2nd line
- Do genotypic resistance test while on ARV's

Monitoring at diagnosis/baseline

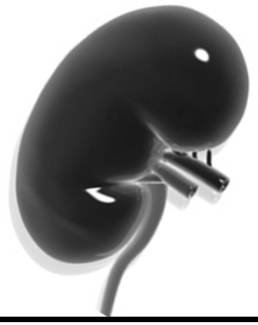
What?	Why?
Confirm HIV result with rapid antibody test if no test results are available	To confirm HIV-positive status in patients who present without proof of status
WHO clinical staging if HIV-positive	For ART fast tracking and OI management
Screen for TB symptoms using the TB screening tool	To identify TB suspects and refer for investigation; assess IPT eligibility
Screen for pregnancy or ask if planning to conceive	To identify women who need ART for PMTCT and offer family planning services
Screening for STIs	To identify and treat STIs
Blood pressure and glycosuria	Screen for comorbidities
Weight and height in adolescents	To determine which ARVs to use

Monitoring at diagnosis/baseline

What?	Why?
CD4 count	Identify prioritisation (CD4 <350 cells/mm^3) eligibility Identify cotrimoxazole (CD4 <200 cells/mm^3) eligibility Identify CrAg eligibility (CD4 <100 cells/mm^3)
Screen for HBV (HBsAg)	HBV co-infection management
CrAg test if CD4 <100 cells/mm^3	Assess if there is disseminated cryptococcal infection and fluconazole therapy is indicated
Creatinine if pt requires TDF ALT if pt requires NVP FBC if patient requires AZT	Assess renal sufficiency Exclude liver disease Detect anaemia or neutropenia
Fasting cholesterol and triglycerides if LPV/r required	Identify patients at risk of LPV/r related hyperlipidaemia. If >6 mmol/L, give ATV/r instead of LPV/r

Monitoring on ART

What?	When?	Why?
TB screen	Every visit	TB infection / IPT eligibility
WHO staging		New OIs
Ask about SEs		ARV toxicity
CD4 count	At 12 months on ART	Immune response
Viral load	Months 6 and 12 on ART; then 12 monthly	Treatment failure / adherence problems
Creatinine	Months 3, 6 and 12 if on TDF; then 12 monthly	TDF toxicity / renal impairment
FBC	Months 3 and 6 if on AZT; then 12 monthly	AZT toxicity
ALT	If on NVP and develops rash or symptoms of hepatitis	NVP toxicity
Fasting TC and TG	At month 3 if on LPV/r	LPV/r toxicity



General management: Creatinine clearance

TDF can only be used in patients with creatinine clearance >50 mL/min and creatinine <100 umol/L

Serum creatinine gives indication of renal function, but poor indicator in some cases:

- Elderly
- Low body weight
- Acute illness

Calculate creatinine clearance:

- Age >50 years
- Weight <50 kg
- Serum creatinine >100 umol/L
- Comorbidities that affect renal function (HPT; DM)
- Medications that may impair renal function

Don't forget dose adjustment of certain ARVs when used in renal impairment

Don't forget to readjust doses as renal impairment improves!

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PREVENTION AND MANAGEMENT OF OPPORTUNISTIC INFECTIONS

Cotrimoxazole preventive therapy (CPT)

When to start

WHO stage 2, 3 and 4

HIV/TB co-infection

Reduces hospitalisation and morbidity

Protects against PCP, toxoplasmosis, malaria and bacterial infections

Benefit outweighs risk in pregnancy therefore continue in pregnant women

Maculopapular rash most common SE. Continue or stop and restart for mild rash

When to stop?

CD4≥350 on 2 occasions

160/800 mg daily

(2 tablets)

When to restart

CD4 drops < 350

ART fails

New OI

Monitor clinically at 3 monthly intervals

Safety of CPT

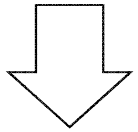
Neutropenia is rare SE. Routine FBC monitoring not required

Can use dapsone 100 mg unless severe reaction (cross reactivity) Less cover

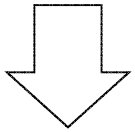
Do not delay ART in favour of cotrimoxazole initiation

Isoniazid Preventive Therapy (IPT)

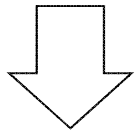
Exclude active TB



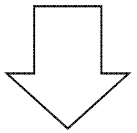
Confirm IPT eligibility



TST to determine duration



Start IPT and pyridoxine



Monitor adherence and SEs
Screen for TB at every visit

Exclude active TB

TB symptom screen

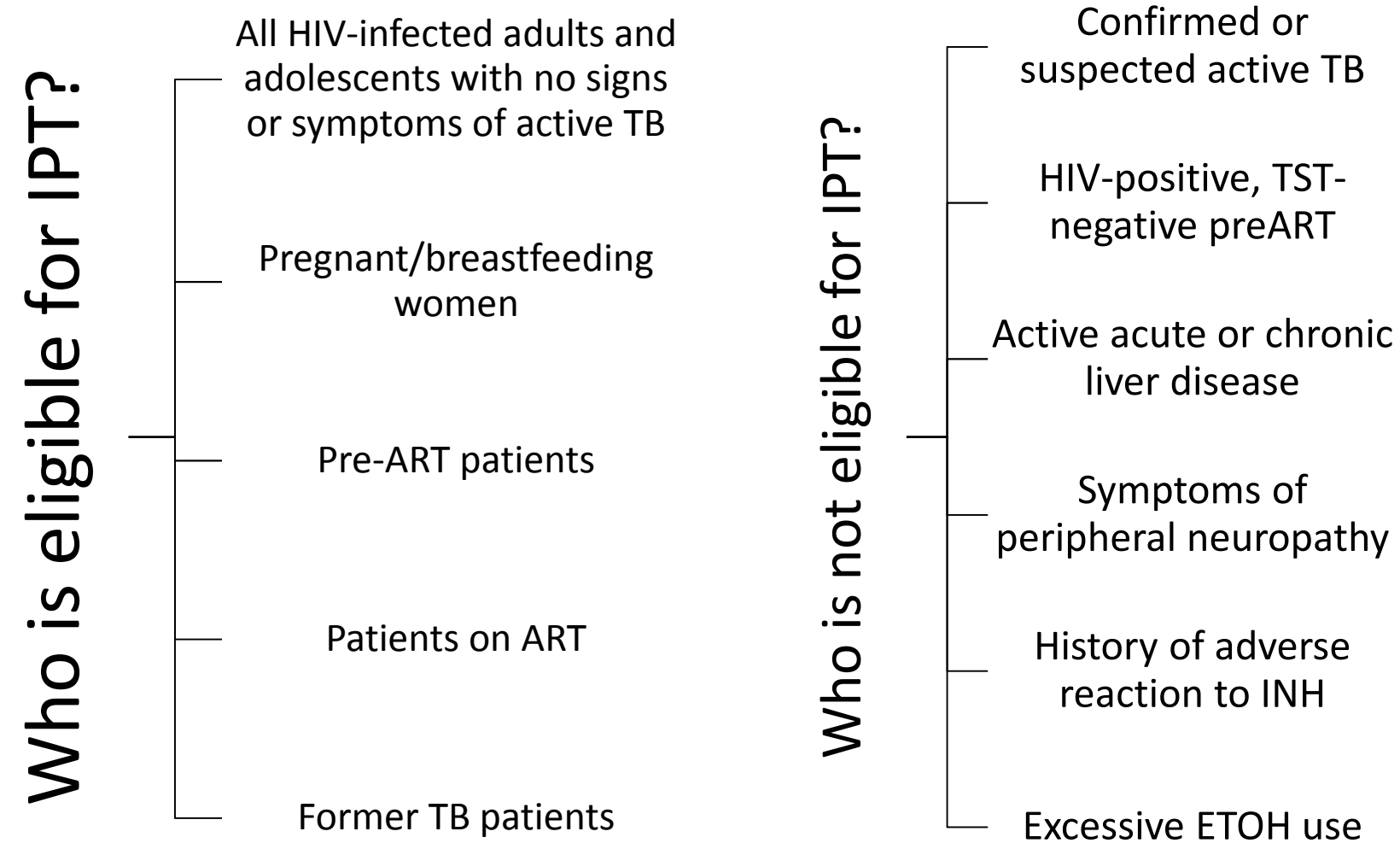
Investigate for TB if ≥1 symptoms

No TB, do not give IPT

Reassess for IPT eligibility after 3 months

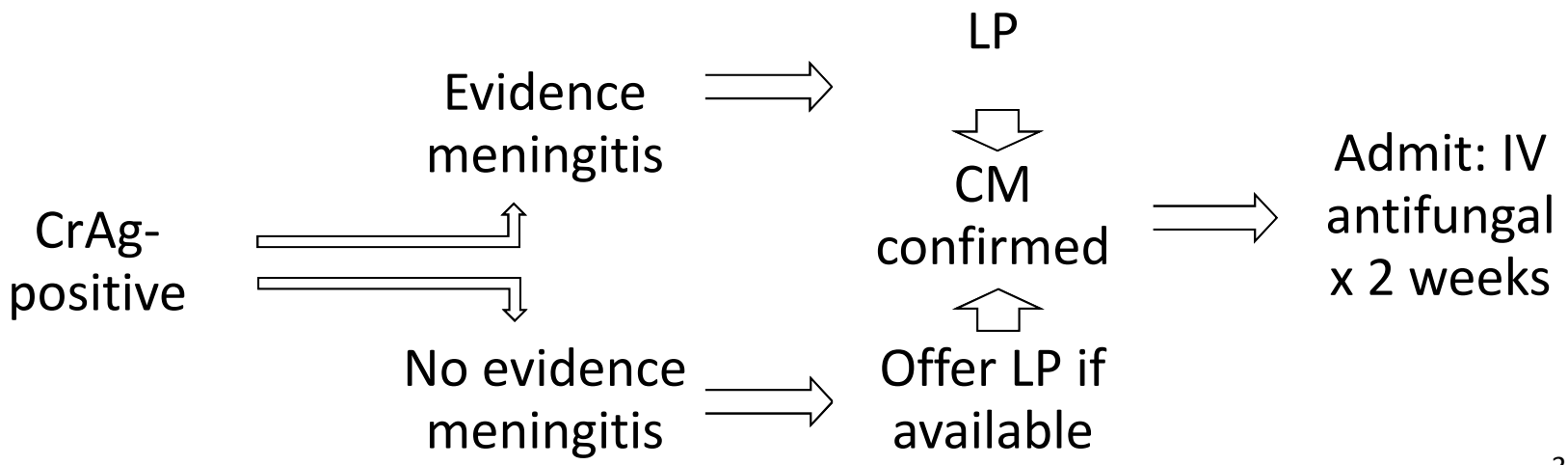
TB symptom screen
Current cough, any duration
Persistent fever >2 weeks
Unexplained weight loss
Drenching night sweats

IPT eligibility



Cryptococcus

- Screen patients with CD4 count <100 cells/mm^3 for cryptococcal disease BEFORE initiating ART (CrAg)
  - Currently clinician initiated
- CrAg-positive indicates disseminated cryptococcal disease
  - Evaluate for symptoms/signs of meningitis



Cryptococcus

Summary recommendations		
Clinical picture	**Antifungal treatment**	**ART**
CrAg-positive but no evidence of meningitis	Oral fluconazole (800mg/day x 2 weeks; standard consolidation and maintenance antifungal treatment	Start after 2 weeks antifungal treatment
CrAg-positive with evidence of meningitis	IV antifungal treatment x 2 weeks; standard consolidation and maintenance antifungal treatment	Start after 4-6 weeks antifungal treatment

- WOCBA: if CrAg-positive, do pregnancy test before starting fluconazole (teratogenic)
- All CrAg-positive PREGNANT women should be offered LP
  - Discuss with expert before deciding management
- Fluconazole may cause liver injury
  - Monitor patients with evidence of liver disease carefully

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Adverse events

Life Threatening

- **Hypersensitivity reaction** (ABC, NVP)
- Pancreatitis (ddI, ddC, d4T)
- **Lactic acidosis** (NRTIs)
- **Hepatitis** (NNRTIs, PIs, d4T/ddI)
- SJS (NVP)

Acute/Early

- Gastrointestinal (ZDV, ddI, PIs)
- Jaundice (ATV, IDV)
- Renal stones (IDV)
- **Anemia, neutropenia** (ZDV)
- Asthenia (ZDV)
- **Central Nervous System** (EFV)
- Rash (NNRTIs)

Chronic/Long term

- **Peripheral Neuropathy** (ddC, d4T, ddI)
- Metabolic – glucose intolerance, lactate, lipids, fatty liver, osteoporosis (PIs, d4T, TDF)
- **Morphologic** – fat loss, fat gain (d4T, PIs?)
- **Rena**l (TDF)

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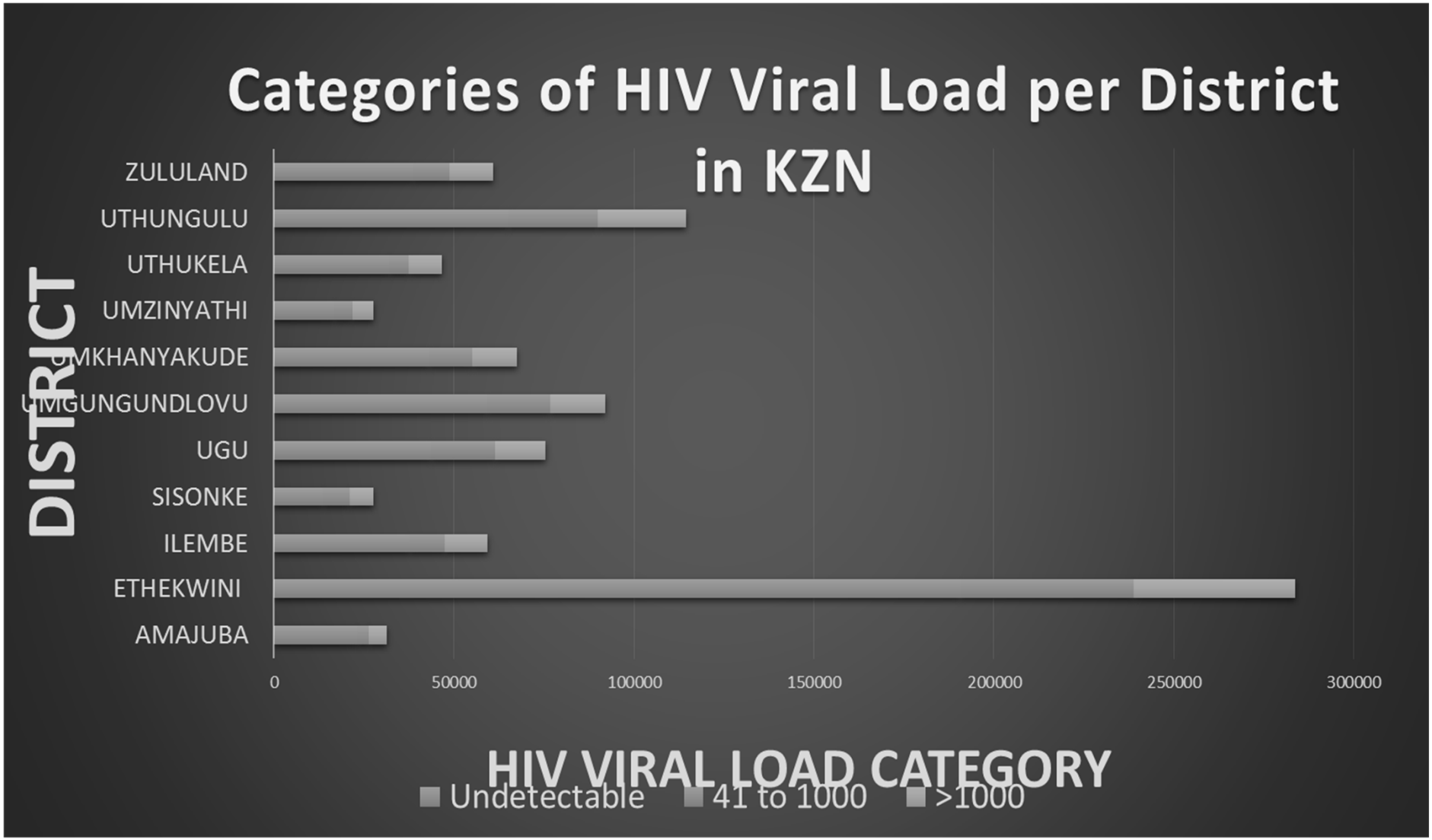
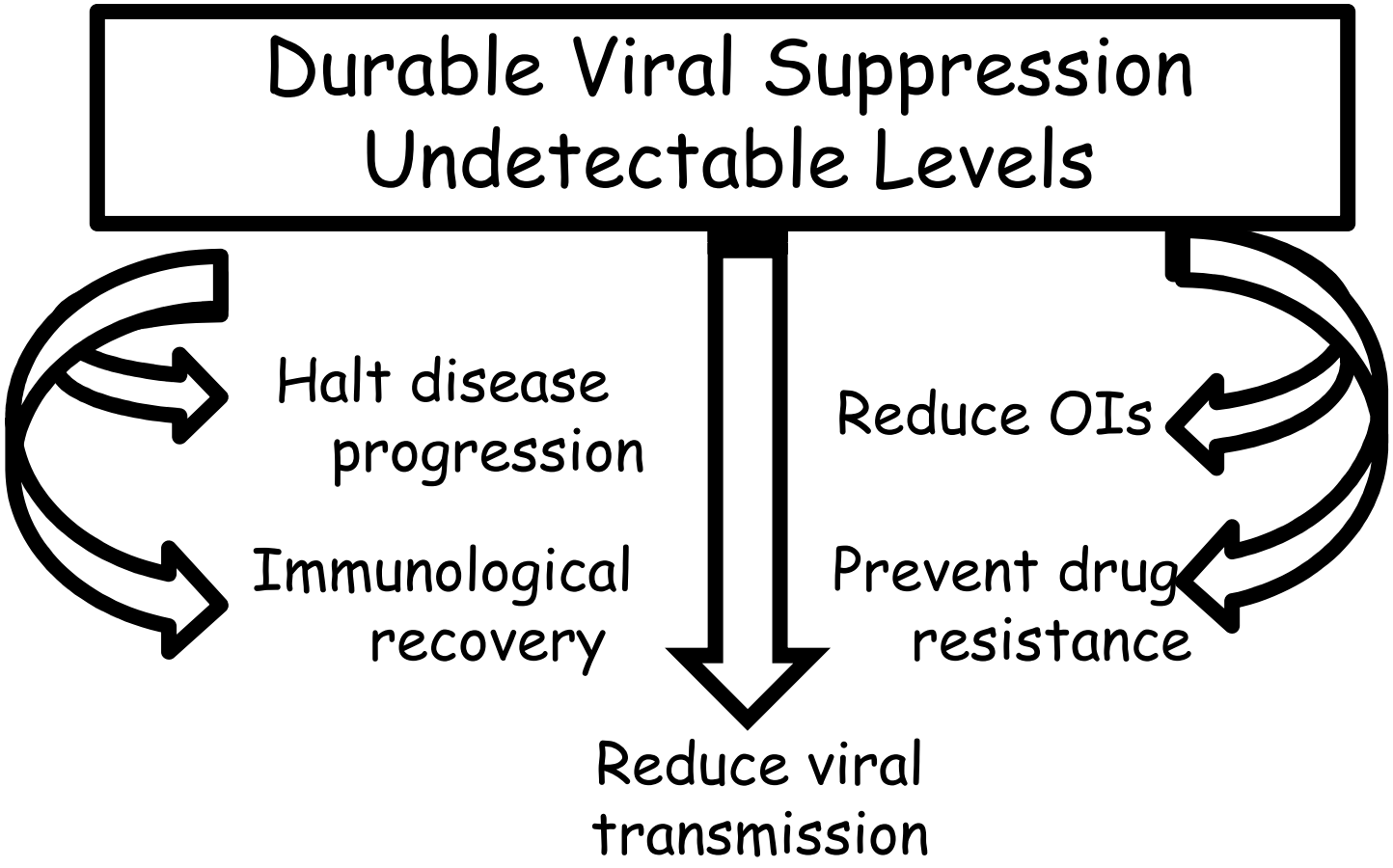

Categories of HIV Viral Load per District in KZN
DISTRICT
ZULULAND
UTHUNGULU
UTHUKELA
UMZINYATHI
UMKHANYAKUDE
UMGUNGUNDLOVU
UGU
SISONKE
ILEMBE
ETHEKWINI
AMAJUBA
0
50000
100000
150000
200000
250000
300000
HIV VIRAL LOAD CATEGORY
Undetectable
41 to 1000
>1000

Goal of HAART



Consequences of viraemia

- Poor immunological recovery- risk of recurrent OIs and increase mortality
- Increased risk of transmission of infection – poor prevention and control of the epidemic
- Risk of resistance to ART and need to change to more expensive regimens
- Increased risk of transmission of resistant virus
- Disease progression – increased risk of comorbidities viz. DM; HPT; IHD due to chronic immune activation with increasing age

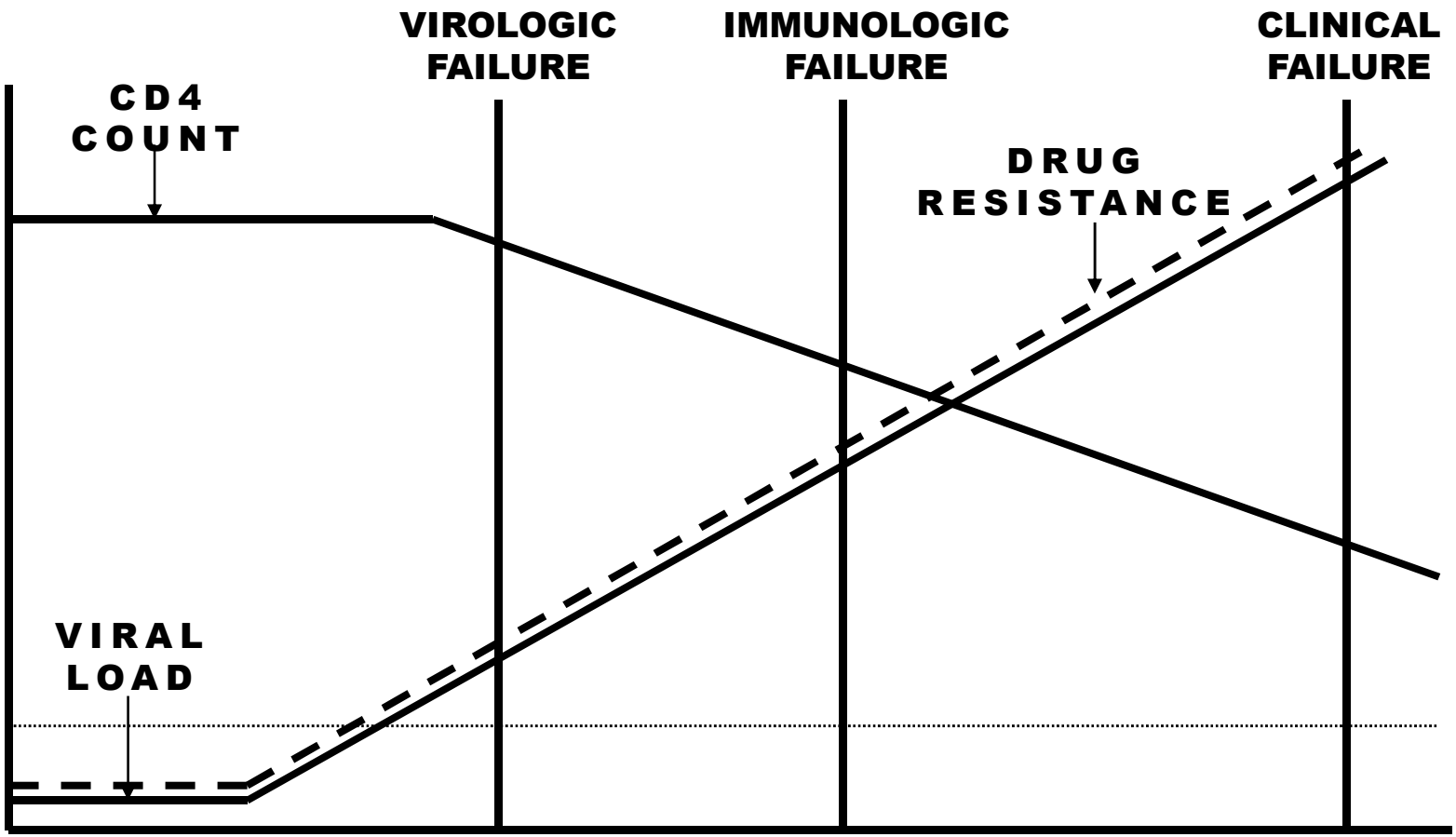
Viral Load

Plasma HIV RNA load is the most representative and sensitive laboratory test for monitoring:

- Response to antiretroviral therapy
- Failure of treatment from any cause

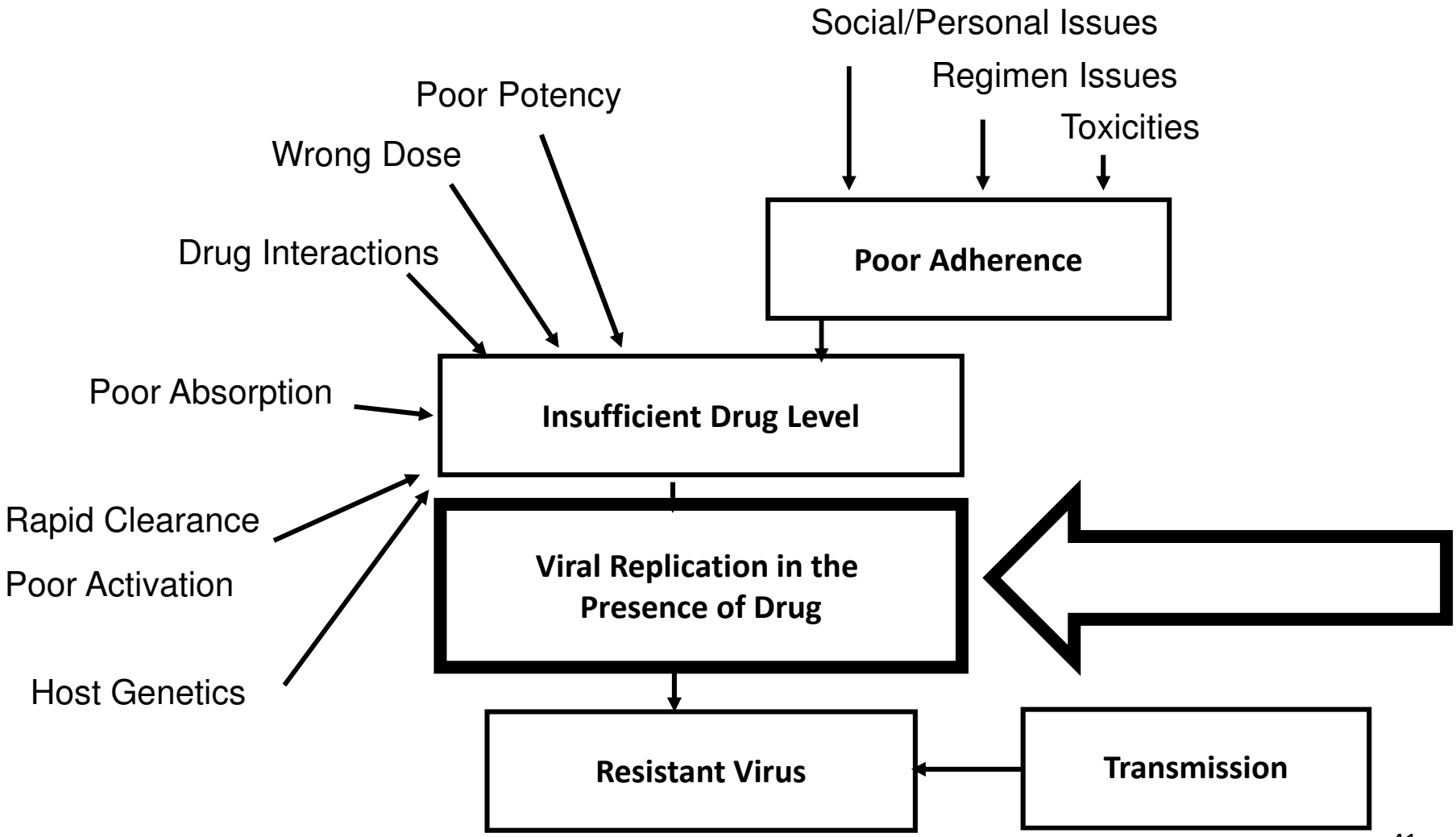
1. Drug resistance
2. Adherence

Virological failure –first warning sign



Murri R, *et al. JAIDS*. 2006;41:23-30.
Losina E *et al, 15th CROI* 2008, #823
Pillay D, *et al. 14th CROI*, Los Angeles 2007, #642

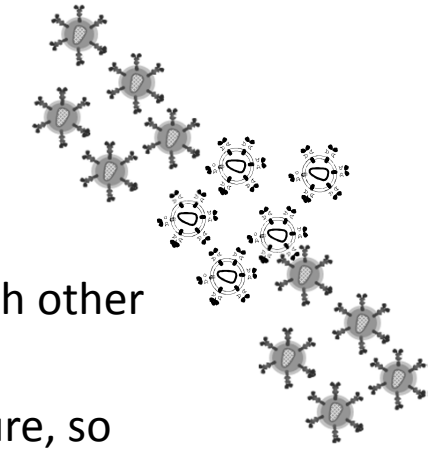
Factors that contribute to the Development of Resistance



Virology failure (SA)

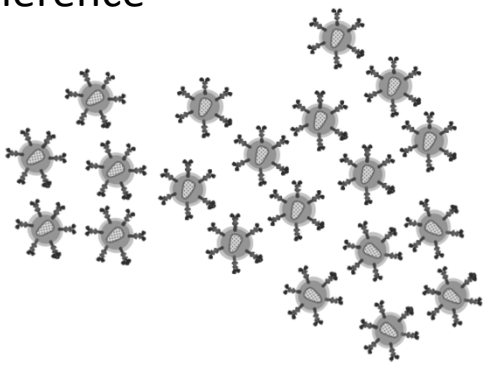
- HIV RNA >1000 check for:
  - Adherence
  - Tolerability
  - Dosing schedule
  - Drug interactions
- Repeat VL in 2 months
- Repeat VL >1000 change regimen

Adherence monitoring:



Use the viral load.

- WHO recommends **VL monitoring** with other adherence measures.
- Raised viral load indicates a risk of failure, so **DO** something.
- 56-68% can re-suppress with an adherence intervention.



CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

UNAIDS

CAPRISA is the UNAIDS Collaborating Centre for HIV Research and Policy

Improving Viral Load Monitoring and Outcome
File and facility Audit
2 hospitals/3 CHCs/5 PHCs

PROVINCE OF KWAZULU-NATAL
ISIFUNDAZWE SAKWAZULU-NATALI

DEPARTMENT OF HEALTH & HUMAN SERVICES-USA

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

CAPRISA
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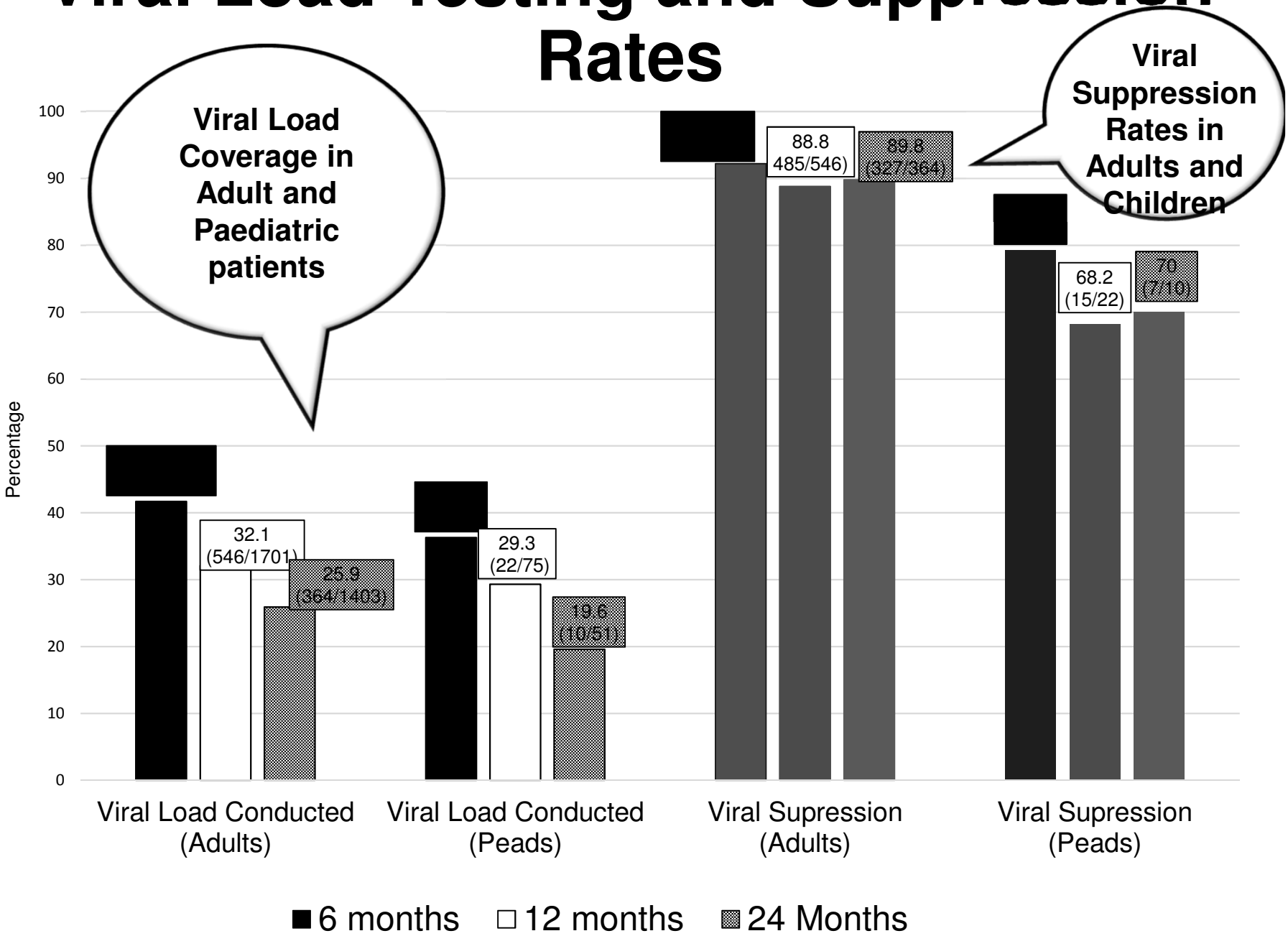
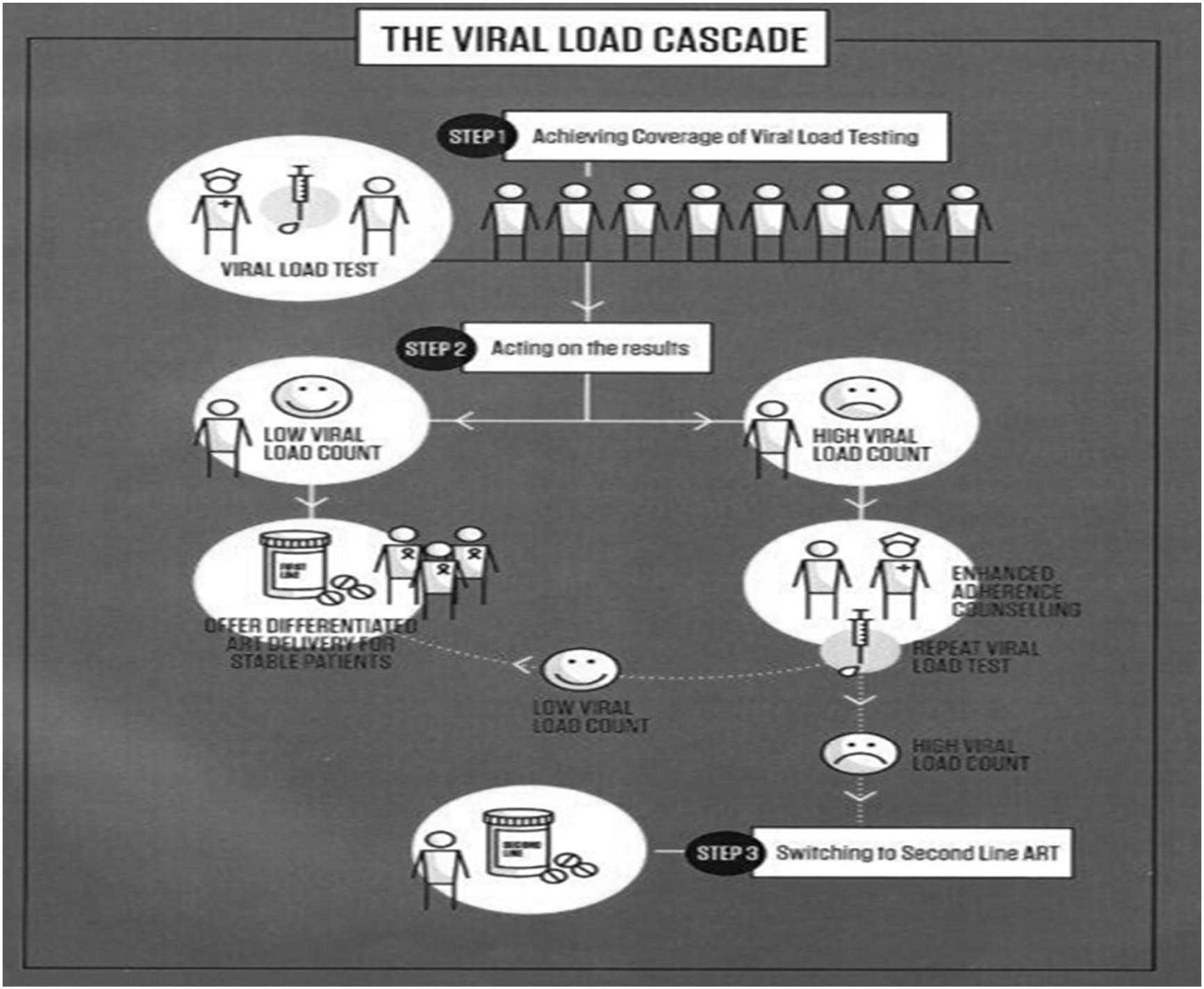
Viral Load Testing and Suppression Rates



MAKING VL ROUTINE

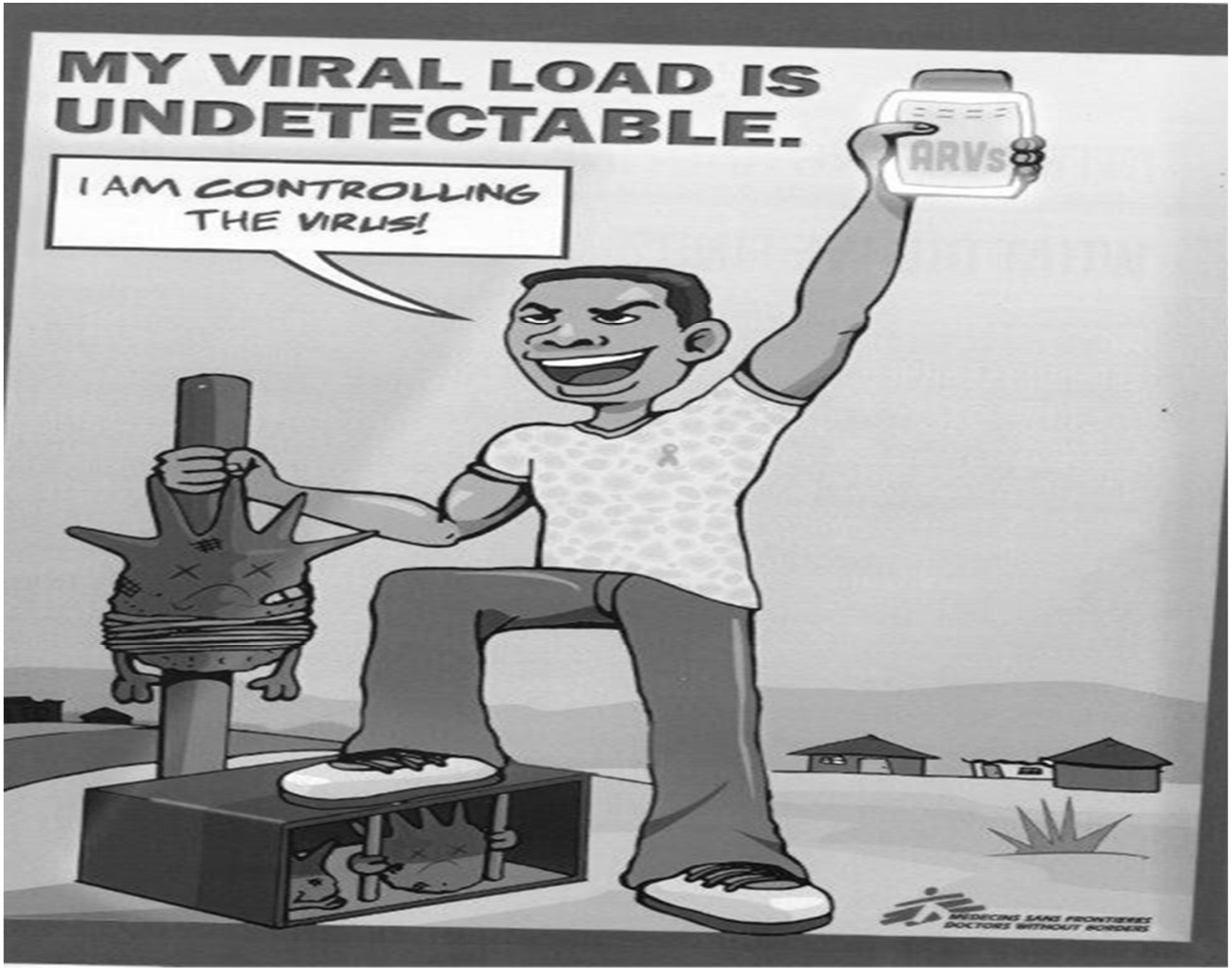

THE VIRAL LOAD CASCADE
STEP 1
Achieving Coverage of Viral Load Testing
VIRAL LOAD TEST
STEP 2
Acting on the results
LOW VIRAL LOAD COUNT
HIGH VIRAL LOAD COUNT
OFFER DIFFERENTIATED ART DELIVERY FOR STABLE PATIENTS
ENHANCED ADHERENCE COUNSELLING
REPEAT VIRAL LOAD TEST
LOW VIRAL LOAD COUNT
HIGH VIRAL LOAD COUNT
STEP 3
Switching to Second Line ART

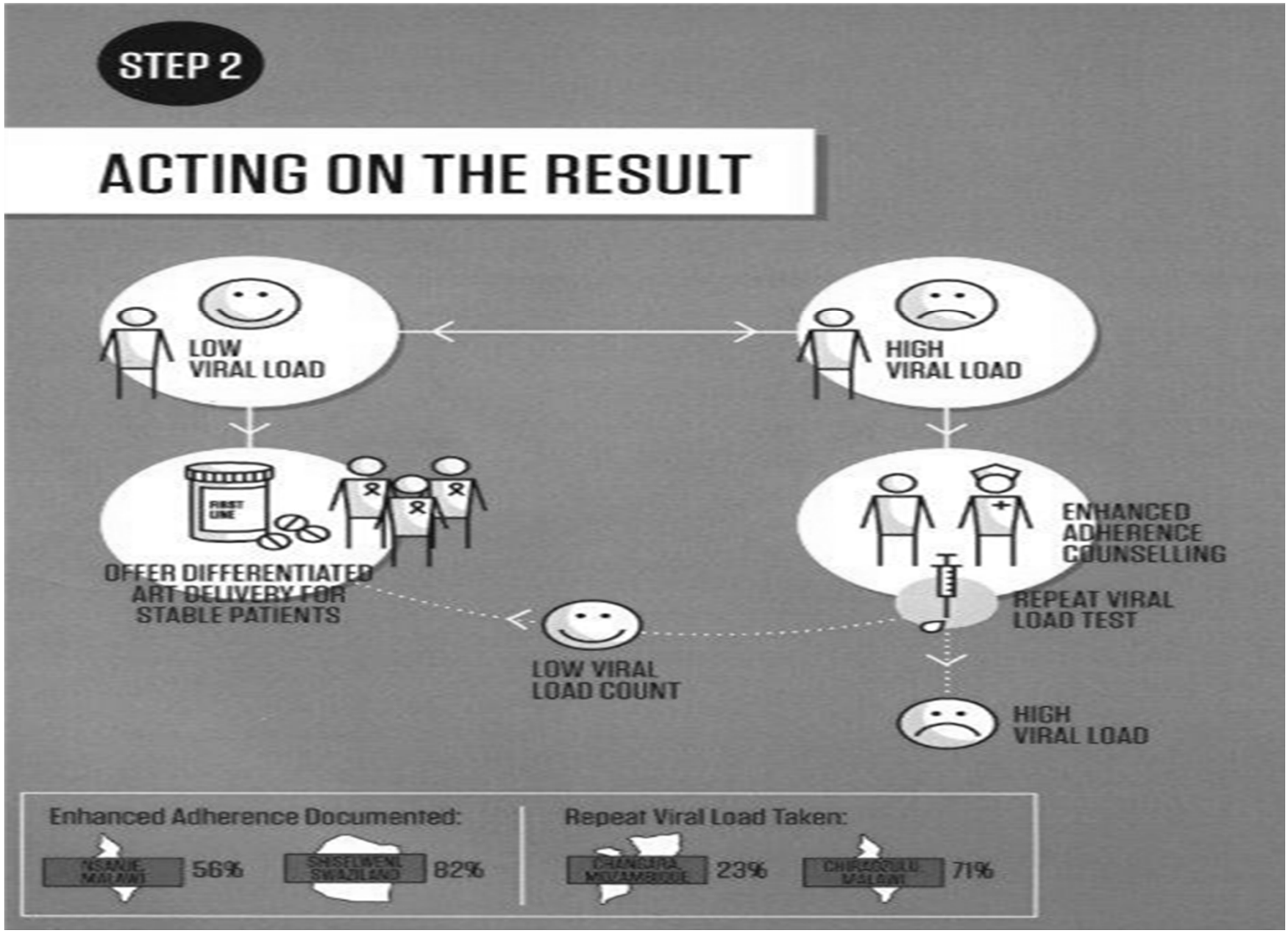
STEPS TO AN IDEAL ART SERVICE SITE

1. HAST Clinical Manager And VL Champ in each CHC/hospital and VLC in each ART site assisted by QA teams	**1. Terms of reference identified for overall supervision of process.** **2. Responsible for facility reports to DOH** **3. Manage exit plan with partners in 2018 so that M&E takes over.**
2. Make viral load monitoring routine	1. Increase demand by pt. education and HCW education 2. Institute VL anniversary concept 3. Implement gate keeping not to issue repeat scripts without VL
3. Synergise data sources so that TIER.NET is optimally functional and totally reliable	1. Create a high VL register for 1st and 2nd line ART from all data sources – routine clinic VL records, NHLS weekly dashboard, TIER.NET records, pharmacy records, complete file audit of all active patients. 2. Ensure that VL results are entered into clinical charts daily so that TIER.NET can be updated. 3. Clean and update TIER.NET for recording and reporting –will improve after catch up phase 4. Catch up phase to account for every patient every seen in clinic and not accounted for on TIER.NET. 5. Finally depend on TIER reports only.
4. Start VL priority clinic on specific day/ dedicated team working daily	Trained EAC team work with trained doctor to manage complex VF in first line and all second line VF Ensure that all patients receive care by a MDT
5. Support PHCs in the area	VLC in each PHC to be mentored and supported by local CHC/hospital. Manage all first line VF and refer all second line VF Standardise referral forms for VF and data required for 3RD line ART

CREATING DEMAND FOR VIRAL LOAD TESTING

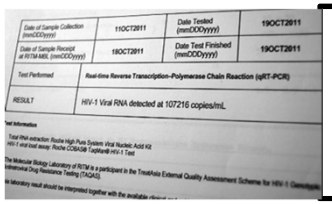
- Programmes should invest in the training of counsellors and development of educational material to ensure quality patient education on VL,
- Funding for civil society organisations to support VL awareness campaigns should be integrated into national VL scale-up plans.


MY VIRAL LOAD IS UNDETECTABLE.
I AM CONTROLLING THE VIRUS!
ARVs
MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS


STEP 2
ACTING ON THE RESULT
LOW VIRAL LOAD
HIGH VIRAL LOAD
FIRST LINE
OFFER DIFFERENTIATED ART DELIVERY FOR STABLE PATIENTS
ENHANCED ADHERENCE COUNSELLING
REPEAT VIRAL LOAD TEST
LOW VIRAL LOAD COUNT
HIGH VIRAL LOAD
Enhanced Adherence Documented:
56%
82%
Repeat Viral Load Taken:
23%
71%

NHLS Track Care

Data Capturer



VL Result Printout

Data Capturer

File in Patient Chart

Doctor

HAST Flow Sheet in Patient Chart

Data Capturer

Tier.Net

Tier.Net

IALH

Sample Log

Nurse or delegate or counselor

Nurse or Phlebotomist

Email Weekly List of High VL to Clinic Manager

High VL Register

Patient Navigator

First Line

Second Line

Clinical Manager or ARV Clinic Director

Weekly Group Session

Daily Individual Session

Patient Navigator (Adherence Counselor)

Nurse for Care (Viral Load Champ)

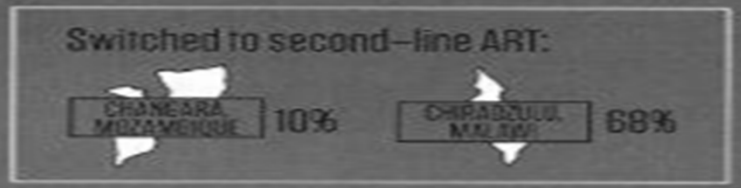
Adherence Counseling

Unsuppressed to Doctor

Suppressed Follow Up

STEP 3

SWITCHING TO SECOND-LINE ART



* LESSONS LEARNED

- Rates of switch to second-line ART remain low in most sites
- Where patients are well or where adherence is not optimal, clinicians are reluctant to switch and 'give more time' for adherence support
- The optimal duration to allow for suppression before switch is not clear but may depend on the first VL result
- Factors that facilitated switch to second-line ART included:
  - *Decentralisation of second-line initiation*
  - *Task-shifting of second-line initiation to non-physician cadres*
  - *M-health strategies to allow remote clinical decision support for switching*
- Ensuring second-line drugs are available where the patient is accessing their first-line therapy should be a priority
- Ongoing adherence support following the switch to second-line ART is essential

Resistance tests serve two purposes:

- *(i)* a fully sensitive pattern may imply that the patient is not adhering to treatment or has completely interrupted ART; and
- *(ii)* if resistance mutations are present, then the clinician, preferably together with an expert, can decide on the most appropriate second-line (and now third line) regimen.

HIVDR testing algorithm

VL >1000 copies/mL on PI-based ART >1 year

Adherence; compliance; tolerability; drug interactions; psychological issues

Repeat VL after 6 months

VL ≤1000 copies/mL

Continue second-line

VL>1000 copies/mL

Specialist referral

GENOTYPE

Specialist decision re further management

Criteria for referral

1. FIRST LINE VF- after counselling for two months ,if the repeat VL 1000 copies/ml and now requires second line ART
a. The patient has multimorbidity – renal ,cardiac,liver pathology
b. The patient needs TB treatment or review of Tb treatment
c. There are existing drug toxicities or concerns about drug interactions
d. The patient has been commenced on second line ART and continues to be intolerant of the drugs –vomiting etc
e. The patient has proven hyperlipidemia as per guidelines and requires another PI
f. All pts with complex psychosocial problems that need intervention by trained EAC teams
2. SECOND LINE VF- REFER FROM LOCAL CLINIC LINKED TO SITE
a. ALL patients that have 2 high viral loads (>1000 copies/ml) 6 months apart after the high viral load done at 12 months review. **Pt A has a high VL at 6 months on second line ART –then has counselling and repeat VL 6 months later (12 months on ART) – NOW the pt will be seen 6 months later and have another VL (18 months on ART). If this VL is >1000 copies/ml then refer this patient.** **Patient A will then have EAC at the referral site by the team and another Vl will be done 6 months later (24 months on ART).If that VL is high –a GRT will be ordered by the senior clinical advisor at the referral site**
b. HBV positive patients that have renal failure
c. All pts on second line ART that have multimorbidities ot drug toxicities
d. WITHIN A REFERRAL SITE ALL SECOND LINE ART PATIENTS WITH A HIGH VIRAL LOAD CAN BE REFERRED IMMEDIATELY FOR ONGOING MANAGEMENT and remain in the clinic till further discussions about the follow up are resolved .

Overview

- HIV continuum of care
- ICDM
- What is NEW
- Co Infections
- ART adverse events
- Monitoring VL and DR

Putting resistance in perspective

- Drug resistance depends on:
  - Adherence
  - Health systems
  - Potency of regimens

Evidende: Swiss cohort 11 084 patients on ART between 1999 and 2013

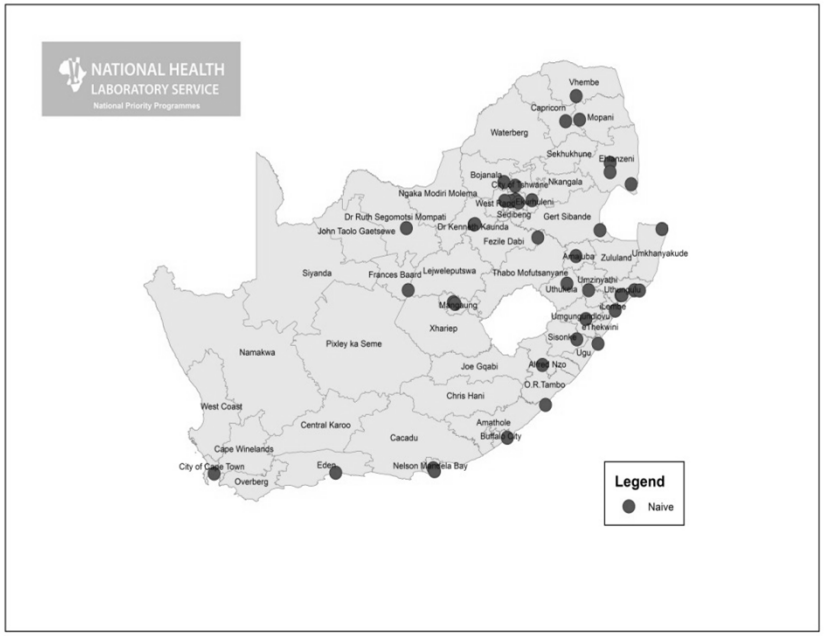
  - 56% resistance in patients initiating ART before 1999
    - dual/mono ART
  - 20% resistance in patients initiating ART between 1999 and 2006
    - early NNRTI or 1st generation boosted PI
  - 10% resistance in patients initiating ART after 2007

Scherrer et al. CID 2016

ART naïve survey

Are patients initiating treatment susceptible to the 1st line ART regimen?

- Specimens collected from 45 health care facilities, in 34 districts and all 9 provinces
- Sample size of 336 calculated, using PPS sampling
- 277 sequences included in analysis (82.4% of target)
- 25 out of 277 patients presented with ≥ 1 surveillance drug resistance mutation (SDRM, WHO 2009)



- Prevalence of SDRM 9.0% (95% CI: 6.1-13.0%)
  - NNRTI mutations most common, n=23
  - NRTI mutations, n=7
  - PI mutations, n=2
  - In 4 patients ≥ 4 SDRMs detected, which might indicate they were not truly ART-naïve

Steegen K et al, IAS 2015: TUPEB232

ART naïve survey: Conclusion

- Although routine VL monitoring is available in South Africa, effort in earlier management of VL is important.

- Regular assessment of pre-treatment drug resistance levels in all regions are recommended.

1st-line failure survey: results

- 3.7% of patients presented with wild-type virus (indication for non-adherence)

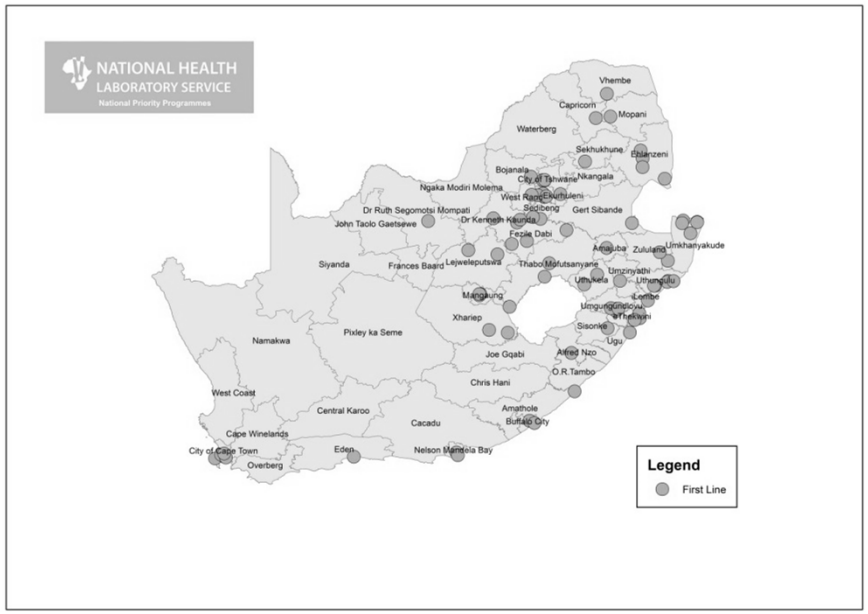
- Most common NNRTI mutations:
  - K103N (48.8%), V106M (34.9%), Y181C (26.2%), G190A (21.7%)

- Most common NRTI mutations:
  - M184V/I (82.7%), K65R (45.8%)
  - **K65R in TDF-exposed patients: 57.5%**
  - ≥ 1 TAM :27.2%
  - ≥ 3 TAMs: 6.4%

ART-experienced survey

Are patients who fail 1st line treatment susceptible to the 2nd line ART regimen?

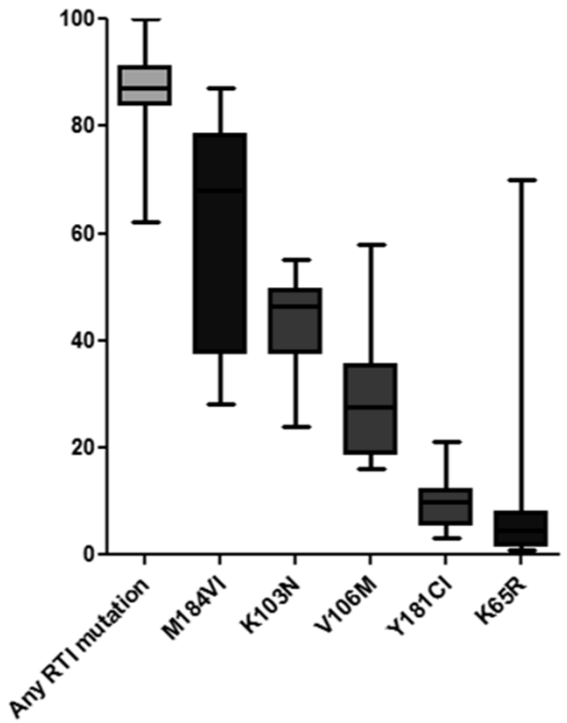
- Specimens collected from 91 health care facilities, in 37 districts and 8 provinces (excl NC).
- 793 sequences included in analysis (88.1% of target 900)
- VL 4.7log cp/ml
- Median time on ART: 36 months
- 3.7% of patients presented with wild-type virus (indication for non-adherence)



- Most common NNRTI mutations: K103N (48 (21.7%)
- Most common NRTI mutations: M184V/I (82.7%), K65R (45.8%)
- K65R in TDF-exposed patients: 57.5%

Steegen K et al, IAS 2015: TUPEB238

Resistance mutations among 1st-line failures in SA



Pillay, ARHR 2008: n=26 2000-03 GP

Marconi, CID 2008: n=115 2005-06 KZN

Hoffmann, CID 2009: n=68 2002-06 GP

Orrell, AT 2009: n=120 2002-07 WC

Wallis, JAIDS 2010: n=226 2005-09 GP

Murphy, AIDS 2010: n=141 2005-09 KZN

El Khatib, AIDS 2010: n=129 2008 GP

Singh, JAIDS 2011: n=45 <2010 KZN

Sunpath, AIDS 2012: n=33 2010-11 KZN

Sigaloff, ARHR 2012: n=43 2006-09 GP

Manasa, POne 2013: n-242 2010-2012 KZN

It’s all about context

- TenoRes study:
  - Prevalence of TDF resistance was highest in Sub-Saharan Africa (57%) → K65R and subtype C
  - Only 20% in Europe → mainly subtype B and more frequent VL monitor
  - Prevalence detected in patients

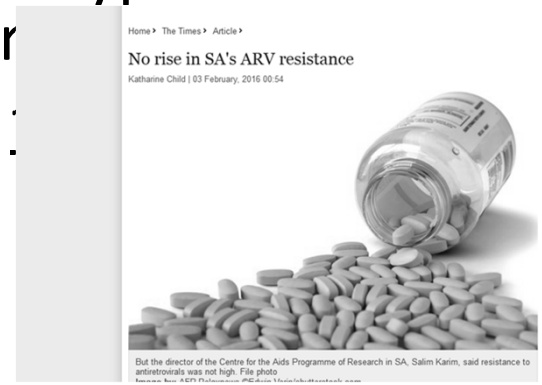
Latest news | News by topic | HIV update | News feeds | Conference news

RESISTANCE

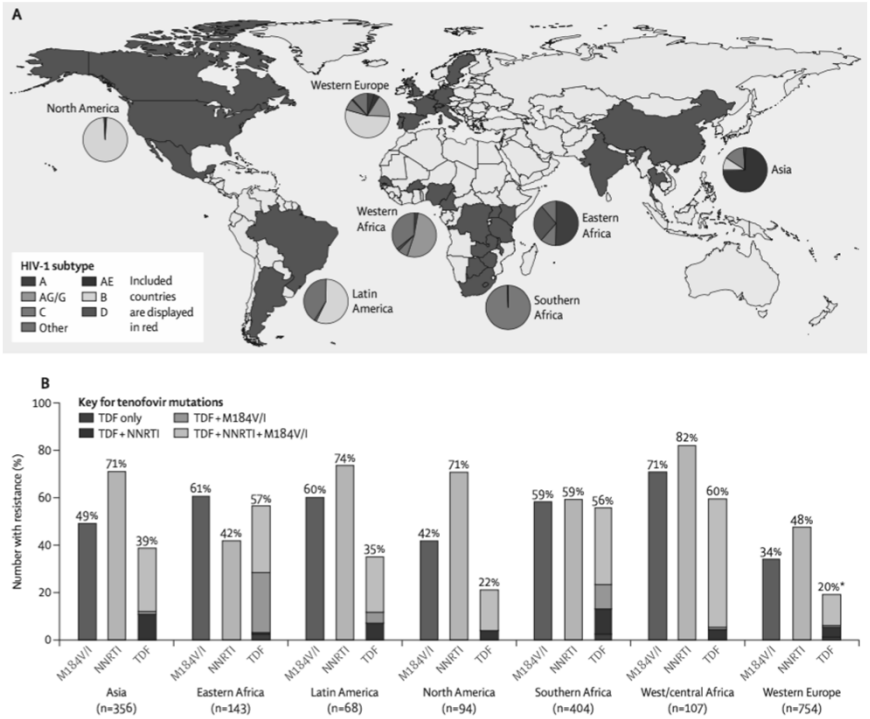
Tenofovir resistance may develop in more than half of patients failing treatment in sub-Saharan Africa

Keith Alcorn
Published: 01 February 2016

% of South Africans on ART
.2 million people on ART with 10-20% failure rate)



Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multicentre retrospective cohort study



***Lancet Infect Dis* 2016**

- 1926 patients from 36 countries with ***treatment failure*** between 1998 and 2015.
- ***Prevalence*** of tenofovir resistance was highest in sub-Saharan Africa (370/654 [57%]).
- Pre-ART CD4 cell count was the covariate most strongly associated with the development of tenofovir resistance (odds ratio [OR] 1·50, 95% CI 1·27–1·77 for CD4 cell count <100 cells per µL).

1st-line failure survey: results

- 1/3 patients retain full susceptibility to 2nd-generation NNRTIs
  - ETR: 36.3%
  - RPV: 27.1%

- Cross-resistance of NRTIs was often observed but,
  - 82.6% of all patients remained susceptible to AZT
  - 92.0% of TDF-exposed patients remained susceptible to AZT

The NEW ENGLAND JOURNAL of MEDICINE

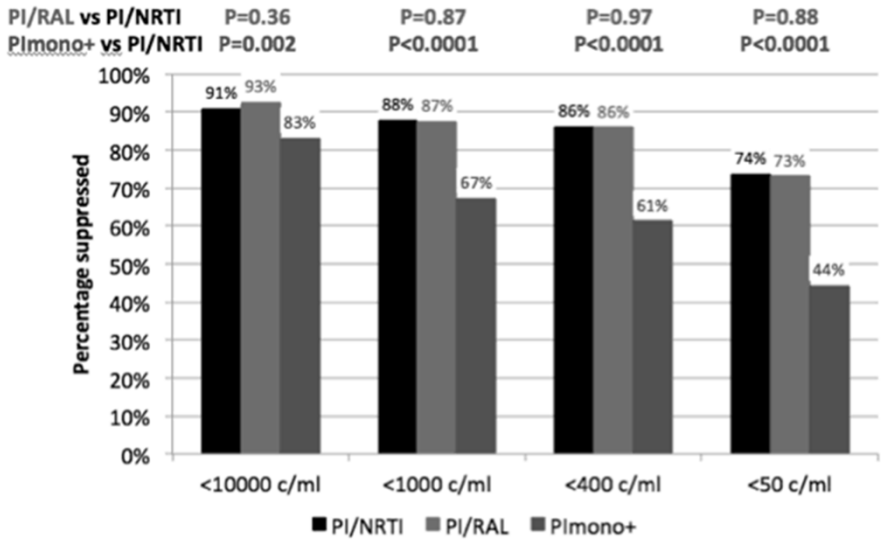
ORIGINAL ARTICLE

Assessment of Second-Line Antiretroviral Regimens for HIV Therapy in Africa

Nicholas I. Paton, M.D., Cissy Kityo, M.Sc., Anne Hoppe, Ph.D., Andrew Reid, M.R.C.P., Andrew Kambugu, M.Med., Abbas Lugemwa, M.D., Joep J. van Oosterhout, Ph.D., Mary Kiconco, M.P.H., Abraham Siika, M.Med., Raymond Mwebaze, M.Med., Mary Abwola, M.Med., George Abongomera, M.Sc., Aggrey Mweemba, M.Med., Hillary Alima, M.P.H., Dickens Atwongyeire, M.B., Ch.B., Rose Nyirenda, M.Sc., Justine Boles, M.Sc., Jennifer Thompson, M.Sc., Dinah Tumukunde, M.P.H., Ennie Chidziva, Dipl.G.N., Ivan Mambule, M.B., Ch.B., Jose R. Arribas, M.D., Philippa J. Easterbrook, M.D., James Hakim, F.R.C.P., A. Sarah Walker, Ph.D., and Peter Mugyenyi, F.R.C.P., for the EARNEST Trial Team*

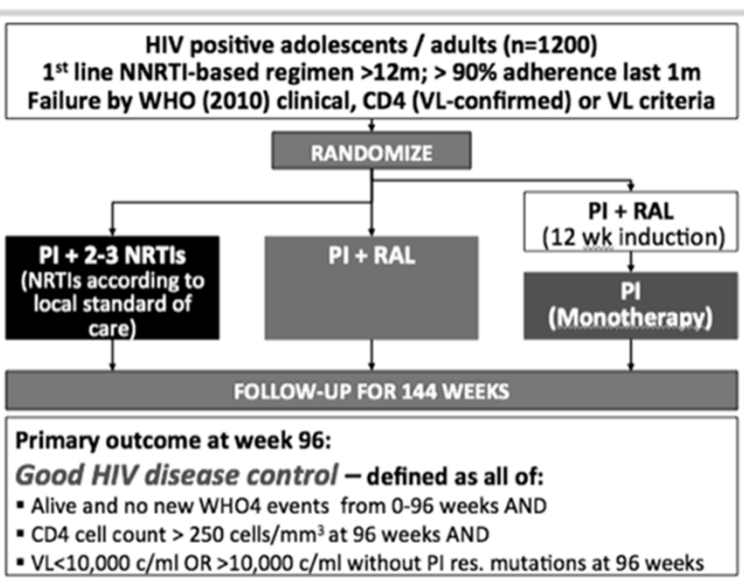
Paton NI et al, NEJM 2014

VL suppression at 96 weeks

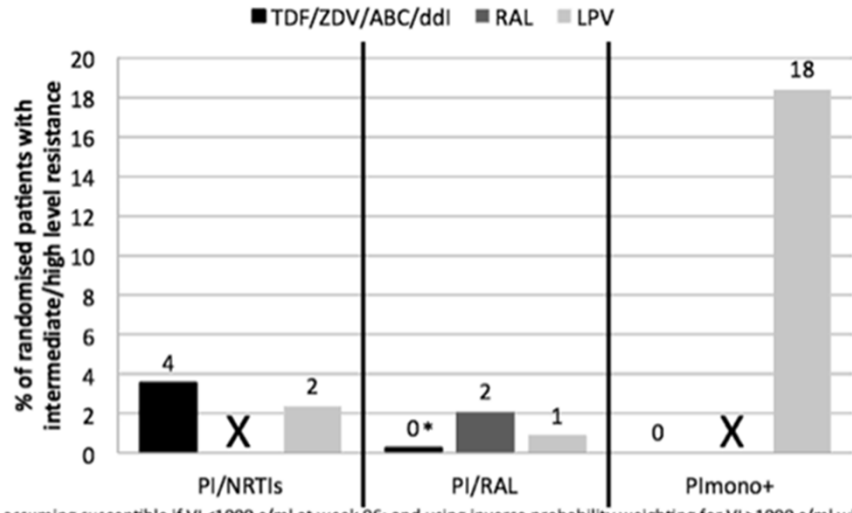


12

Trial design (1)



Resistance at 96 weeks
(predicted in whole population)



Note: assuming susceptible if VL<1000 c/ml at week 96; and using inverse probability weighting for VL>1000 c/ml with missing genotype at week 96 based on those with observed genotypes
*One patient in RAL/PI with intermediate/high level resistance to TDF had moved to 3TC TDF ALV at week 4 due to rash

13

1st-line failure survey

- Studies have shown that residual activity of NRTI-backbone in combination with PI is sufficient to supress virus in most patients when switched to 2nd-line (Paton 2014, Boyd 2013, Sigaloff 2012)
- The more mutations are seen, the more likely the patient is to supress provided good adherence
- ***Empirical switch to standard 2nd-line without drug resistance testing is still ok***
- ***Regimens recommended in South Arica for 1st and 2nd-line are still suitable***

- Similar rates of adverse events in NRTI group compared to other groups
- Recycling of NRTI's not harmful
  - this has also been confirmed in the SECOND-LINE study
- Algorithmic NRTI drug selection and appropriate adherence measures are likely to achieve optimal outcomes in standardized PI/NRTI second-line therapy in RLS
- Resistance testing to select NRTIs is of little value.

Role of resistance testing in South Africa

- Public Health monitoring: surveys
- Patient monitoring
  - HIVDR testing at 1st-line not required (EARNEST and Second-Line studies)
  - HIVDR testing at 2nd-line required
    - Identify patients that are not adherent
    - Identify patients with PI-mutations to tailor 3rd-line regimen
    - Uptake of HIVDR at 2nd-line failure very slow
  - HIVDR testing in pregnant women on PI-regimen
  - HIVDR testing in infants who's mother was exposed to Pis

- **Expand VL monitoring to identify failure early and act on VL results>1000 copies/ml**

Acknowledgements

- The Epicentre team led by Cherie Cawood
- The 11 facilities that participated in the File and Facility Audit
- The CAPRISA ACC Statistics & Data Management Team
- Dr Henry Sunpath (eThekwini District Specialist Clinical Team Leader)

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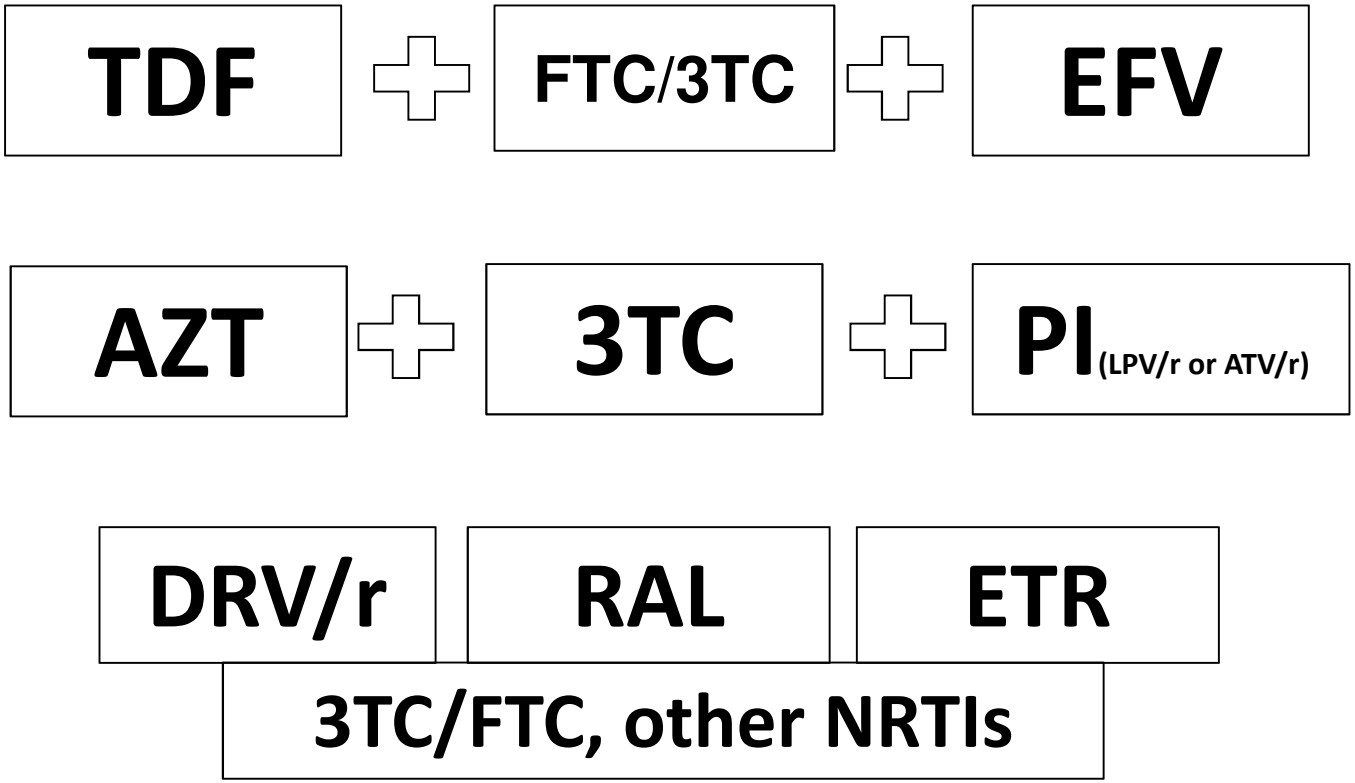
Partners

- Harvard Medical School
- Emory University
- SA HIV clinicians Society
- MEDICATE –AIDS T/A AWACC

Questions

Current regimens in SA

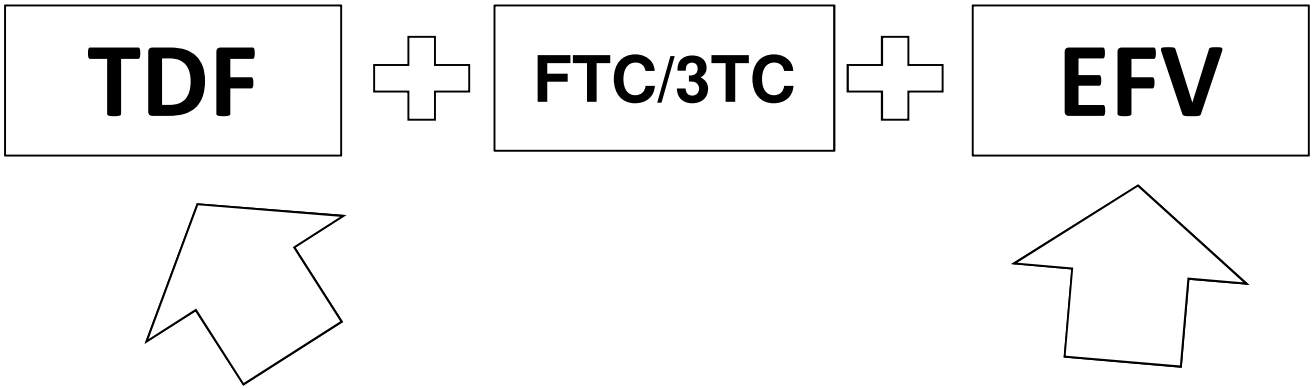


Alternatives for current regimens?

- Dolutegravir (DTG)
- Tenofovir alafenamide fumerate (TAF)
- EFV 400 mg once daily
- Two-drug combinations
  - DRV/r+RAL
  - LPV/r+3TC

Vitoria et al. JIAS 2016

Issues with current 1st-line



Cost driver

Side effects (and size) driver
Low barrier to resistance

Can TAF replace TDF?

- Low dose (10mg with ritonavir or cobicistat OR 25mg unboosted) → ***small pill size and cheap***
- No difference in efficacy at 48 and 96 weeks between TDF and TAF
- No difference in risk of treatment related resistance (K65R in subtype C?)
- Slightly better ***safety profile*** than TDF (10 or 25mg vs 300mg)
- Current studies included TAF/FTC/DRV/cobi or TAF/FTC/EVG/cobi → too expensive for RLS
- Rifampicin interaction!
- RHI plans a study on TAF, including pregnant women

Wohl et al. JAIDS 2016
Mills et al. JAIDS 2015
Sax et al. JAIDS 2014

Is Dolutegravir the wonder drug?

- Similar VL suppression rates compared to EFV-regimens, but fewer adverse events (SINGLE study)
- No documented case of resistance when used as 1st-line
  - Resistance is possible when previously exposed to other INIs
- Potential to be low-cost and co-formulated
- No FDC yet
- Minimal toxicity but neurotoxicity might be concern
- Limited data in pregnant women
  - Planned studies: RHI and NIH (NCT02245022)

  Increased Metformin levels with DTG
- Limited data in patients on rifampicin (double dose DTG required?)
  - Planned studies: RHI and NIH (NCT02178592)
- Limited data on long term use with TDF/FTC, no data with
- TAF/FTC
  - Planned studies RHI

Walmsley SL et al. N Engl J Med 2013;369:1807-1818.
Walmsley et al. CROI 2014, poster 543
Wainberg and Mesplede, JIAS 2015
Dooley et al. JAIDS 2013

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

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- National HIV Drug Resistance Working Group and Steering Group including all members and affiliates
- National Health Laboratory Service
- National Institute for Communicable Diseases

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

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UNIVERSITY OF KWAZULU-NATAL

CDC

11TH ANNUAL WORKSHOP ON ADVANCED CLINICAL CARE (AWACC) – AIDS 07& 08 September 2017-Durban.

Dr. Henry Sunpath – MEDICATE –AIDS NPC
Prof. Yunus Moosa - ID Unit - Nelson Mandela School of Medicine, UKZN
Prof. Raj Gandhi - ID Unit - Mass General Hospital – Harvard Medical School
Prof Tulio de Oliveira –SATURN (Southern African Treatment Resistance Network)

Elangeni Tsogo Sun in Durban

To view programme and register visit www.awacc.org