Adult Guidelines

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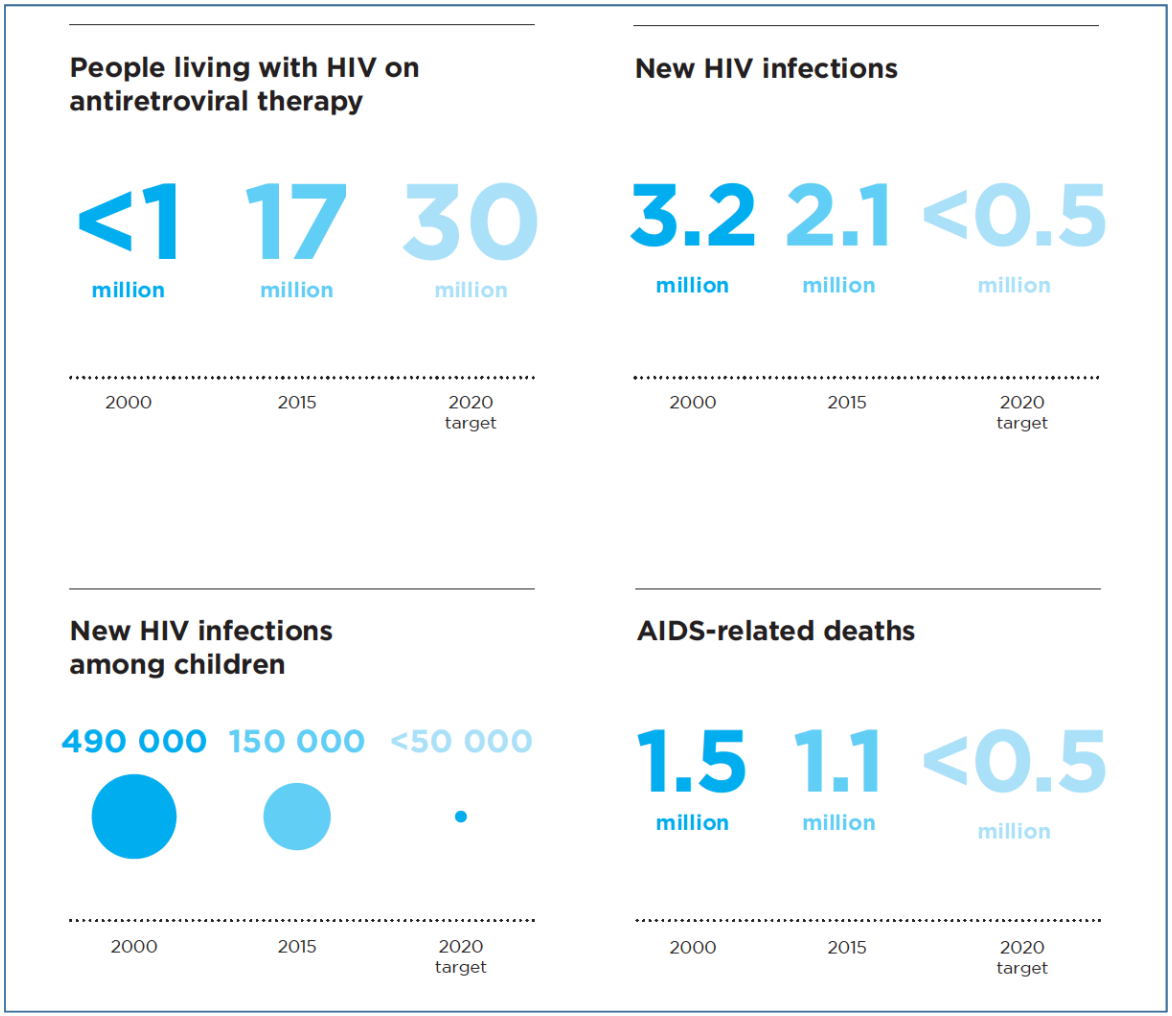
Rustenburg | 23rd June 2017 | Molokwane Lodge

Outline of talk

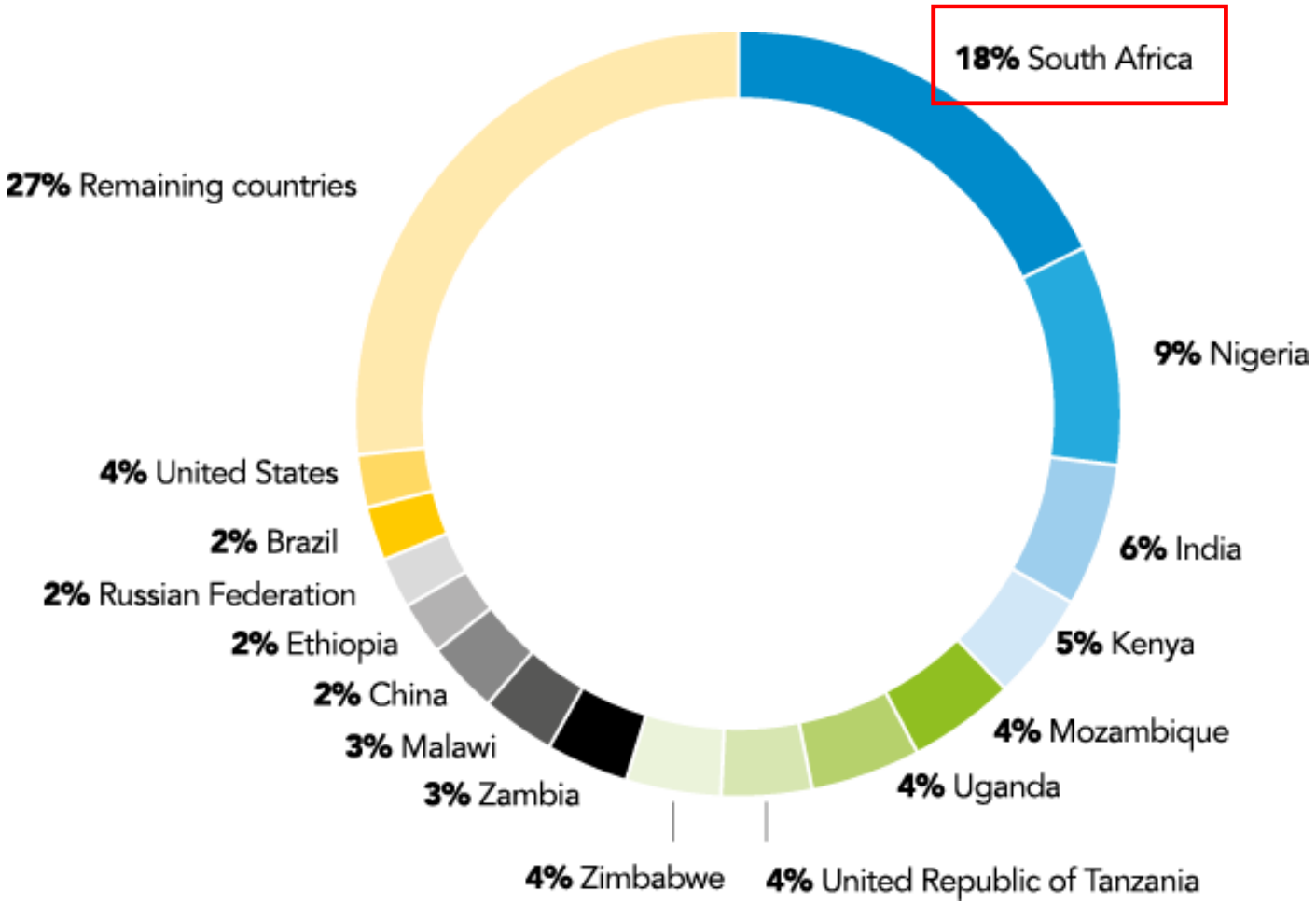
- Guidelines local versus International
- TEMPRANO Trial
- START Trial
- HPTN 052
- HIV Clinicians Society Guidelines -2017
- Isoniazid Preventative Therapy
- Conclusion

Snapshot of the epidemic



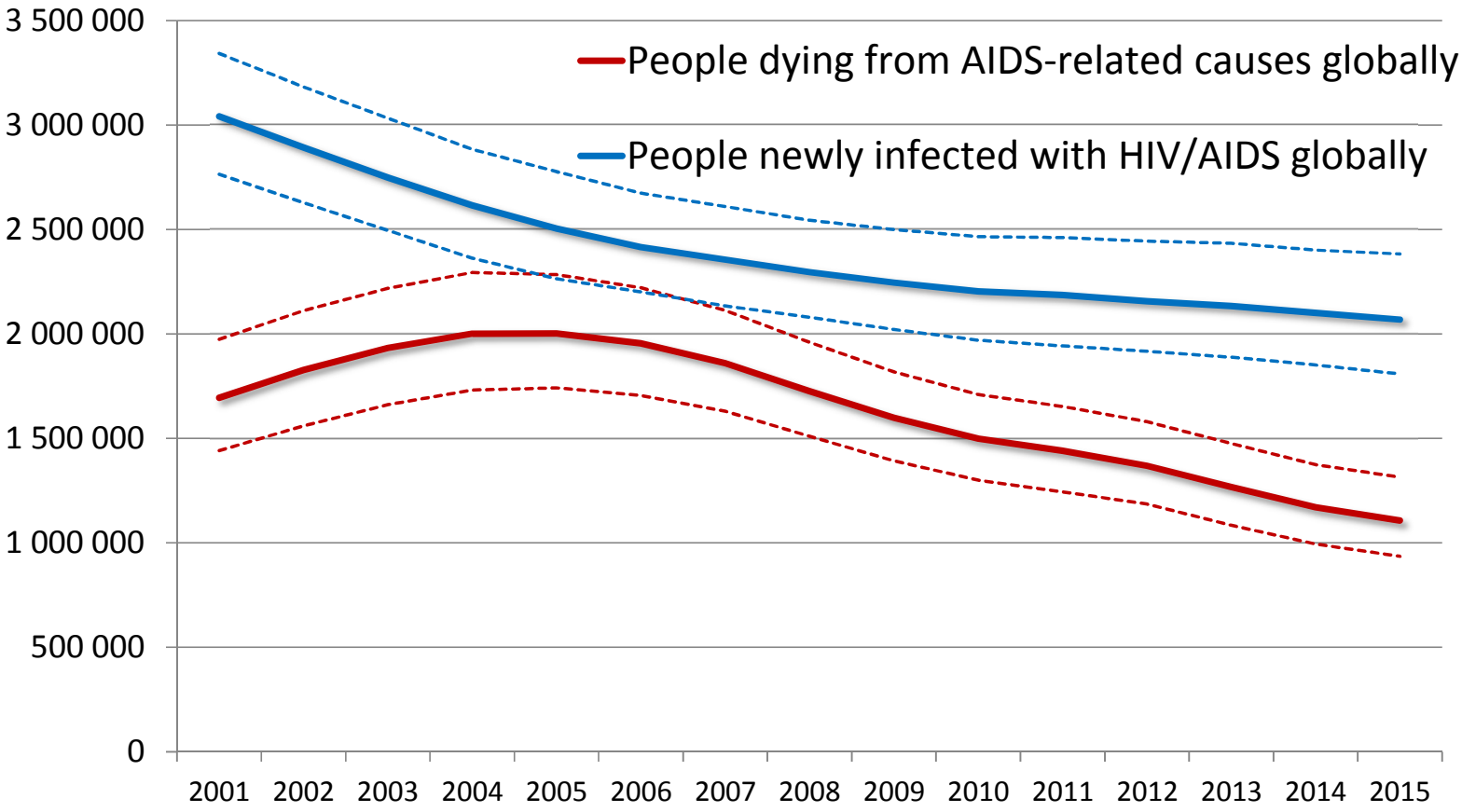
UNAIDS, 2016

People living with HIV by country



UNAIDS, 2014

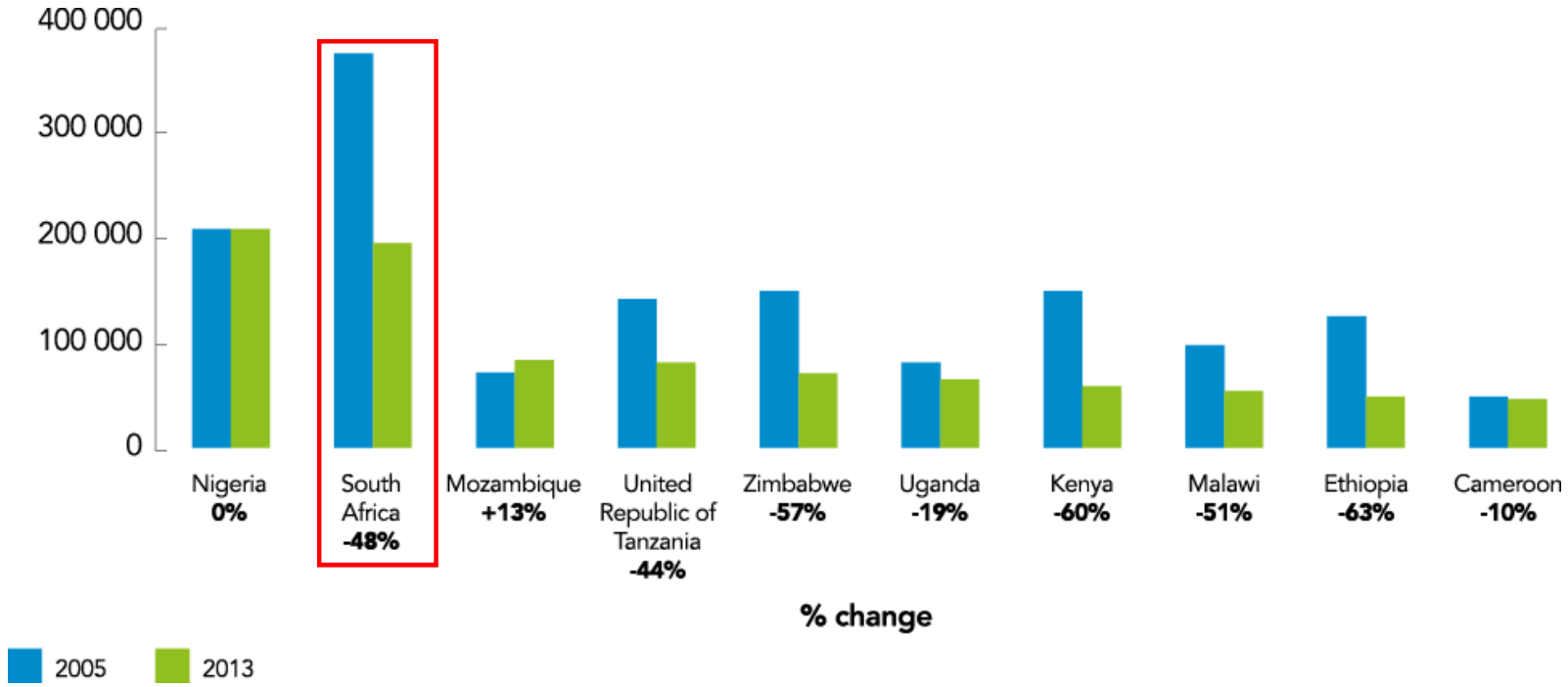
Decline in HIV incidence and mortality over time



Source: UNAIDS/WHO estimates.

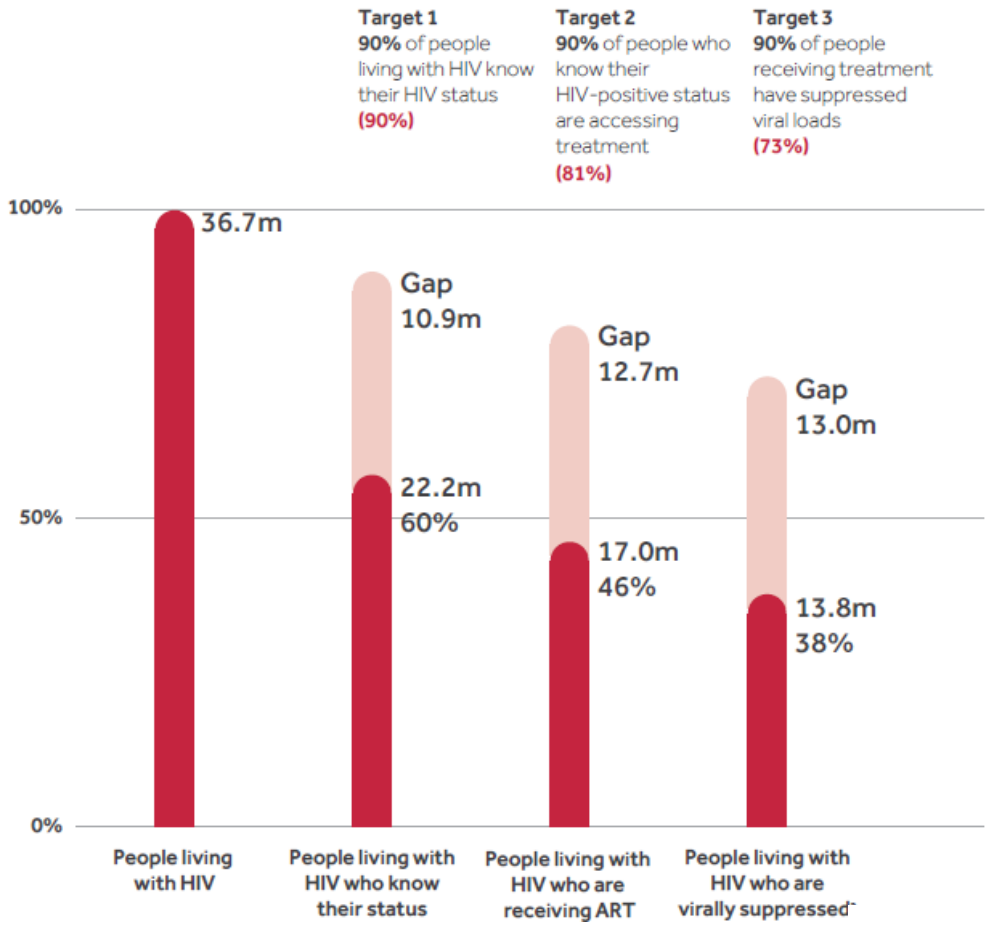
World Health Organization

Trends in AIDS-related deaths in SSA: 2005 versus 2013



UNAIDS, 2014

Improvements are needed at each stage of the cascade of HIV testing and treatment services, 2015

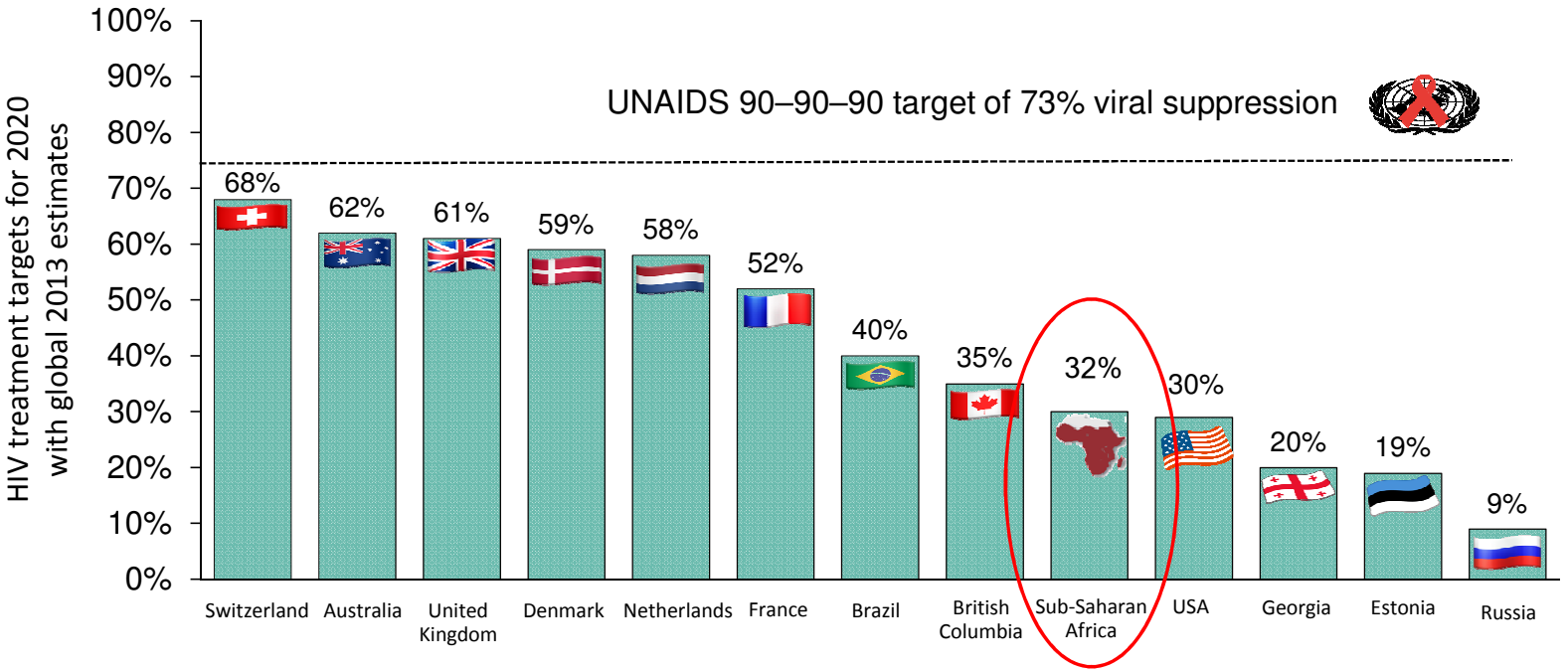


Source: UNAIDS/WHO estimates.

World Health Organization

UNAIDS 90–90–90 Target by 2020

Global HIV treatment cascades from 13 countries/regions: Switzerland, Australia, UK, Denmark, Netherlands, France, Brazil, Canada (BC), USA, Sub-Saharan Africa, Georgia, Estonia, Russia



- No country or region analysed so far met the UNAIDS 90–90–90 coverage target of 73% of HIV+ patients achieving undetectable HIV RNA

RNA = ribonucleic acid

Levi J, *et al.* IAS 2015. Vancouver, Canada. Oral Presentation MOAD0102

South Africa

- 6.4 million South Africans are HIV-infected
- 2.6 million have started ART
- Estimated ART coverage 42%

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Southern African HIV Clinicians Society adult antiretroviral therapy guidelines: Update on when to initiate antiretroviral therapy

Adult antiretroviral therapy guidelines 2014

Table 3. Indications for ART*

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
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)

Southern African HIV Clinicians Society adult antiretroviral therapy guidelines: Update on when to initiate antiretroviral therapy

Adult antiretroviral therapy guidelines 2015

We recommend initiation of lifelong ART for all patients diagnosed with HIV infection. The CD4 count and clinical stage of the patient should no longer be a consideration in the decision to start ART.

For patients who are asymptomatic with CD4 > 350 cells/µL, additional time (weeks to a few months) can be spent counselling and preparing the patient for lifelong ART with good adherence before starting. In those with CD4 < 350 cells/µL (and especially < 200 cells/µL), or with clinical indication for starting, there should not be undue delay.

Within ART programmes, it is important to factor in that the absolute benefit of ART is much greater at lower CD4 counts (there is a mortality benefit at CD4 < 350 cells/µL.[10†] Therefore, planners and clinicians should prioritise and fast-track those with low CD4 counts (especially < 200 cells/µL); this is particularly relevant where there are ART shortages or anticipated stock-outs.

S Afr J HIV Med. 2015;16(1), 4 pages

South African Department of Health

6.6.4 When to start: ART eligibility in late adolescents ≥15 years and adults living with HIV

Box 19: ART eligibility criteria

Eligible to start ART

CD4 count ≤500 cells/µl irrespective of clinical stage
(Prioritise those with CD4 ≤350 cells/µl)

OR

Severe or advanced HIV disease (WHO clinical stage 3 or 4), regardless of CD4 count

OR

Irrespective of CD4 count or clinical stage:

» Active TB disease (including drug-resistant and EPTB)

» Pregnant and breastfeeding women who are HIV-positive

» Known hepatitis B viral (HBV) co-infection

» Prioritise those with CD4 ≤350 cells/µl or advanced HIV disease

South African Department of Health (NDoH)

Eligibility Criteria for UTT:

- All HIV Positive children, adolescents and adults regardless of CD4 count will be offered ART treatment, prioritizing those with CD4 ≤ 350.
- Patients in the Pre-ART and Wellness programme shall be considered for UTT
- Willingness and readiness to start ART shall be assessed and patients who are not ready after assessment shall be kept in the wellness programme and continuous counseling
- Baseline monitoring of CD4 count will still be done as it is the key factor in determining the need to initiate Opportunistic Infection prophylaxis at CD4 ≤200, identify eligibility for CrAg at CD4 ≤100, prioritization at CD4 ≤350 and fast tracking at CD4 ≤200.

Timing of ART initiation:

ART should be started as soon as the patient is ready and within 2 weeks of CD4 count being Done

Immediate priority:

All HIV-positive pregnant or breastfeeding women, with no active TB or contraindication to FDC

Fast track initiation:

HIV stage 4

Patients with CD4 ≤200

6 Sept 2016

2014 Recommendations of the International IAS-USA-Society

Recommendations
• Clinicians should provide education about personal health benefits of ART and public benefits of prevention of transmission, and assess patients' readiness to initiate and adhere to long-term ART. **Rating: AIII**
• ART should be offered upon detection of HIV infection. **Rating: A1a**
• Strategies for adherence support should be implemented and tailored to individual patient needs or the setting. **Rating: AIa**
• Clinicians should be alert to the nonspecific presentation of acute HIV infection and urgently pursue specific diagnostic testing (plasma HIV viral load) if suspected. **Rating: AIIa**

Marrazzo et al, *JAMA*, 2014

Recommendation 1: When to start ART among people living with HIV			
Target population	**Specific recommendation**	**Strength of the recommendation**	**Quality of the evidence**
Adults[a] (>19 years)	ART should be initiated in all adults living with HIV at any CD4 cell count	*Strong*	*Moderate* NEW
	As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm^3	*Strong*	*Moderate*
Pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV at any CD4 cell count and continued lifelong	*Strong*	*Moderate* UPDATED

EACS Guidelines 2017

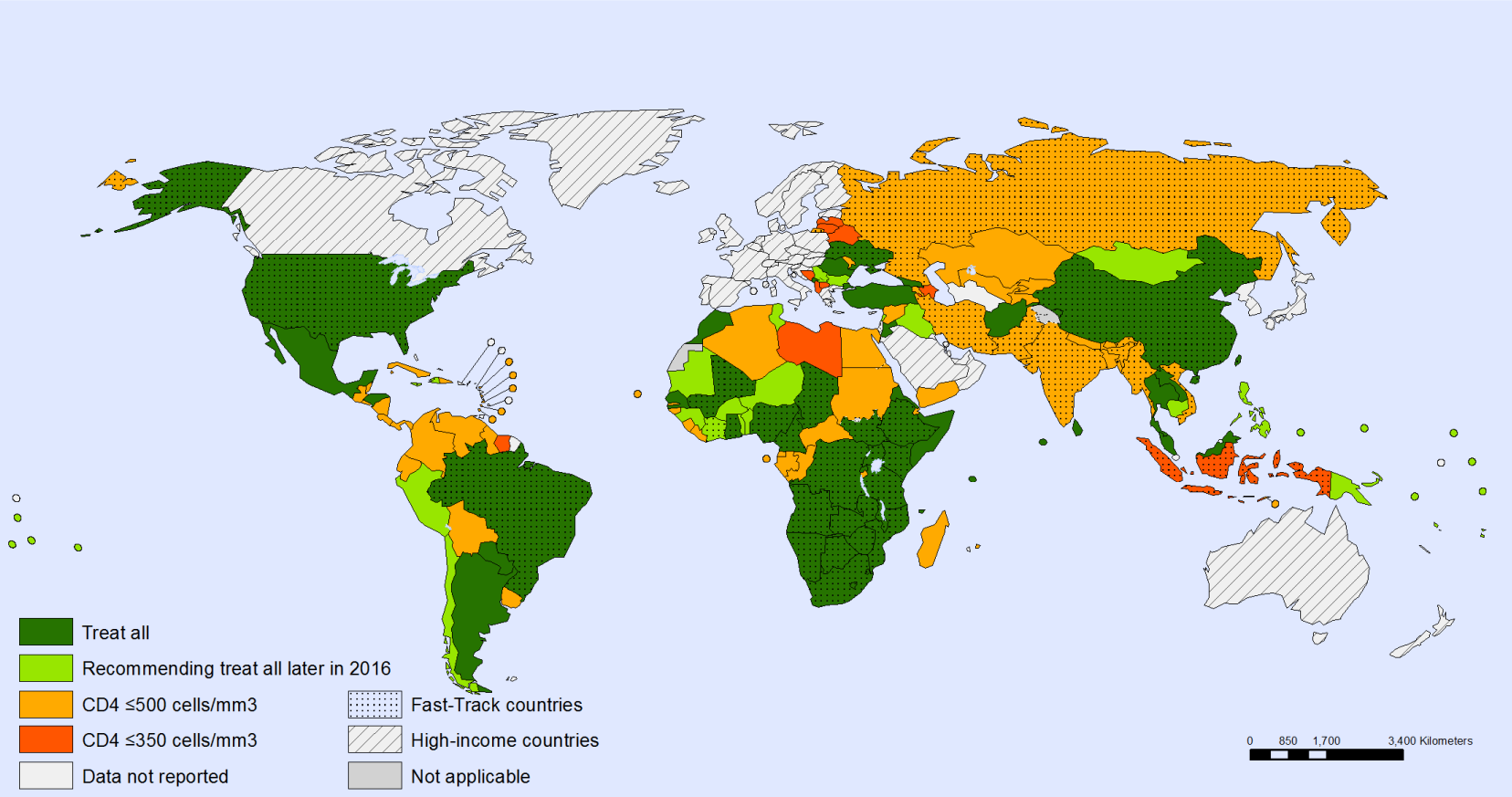
Assessing HIV+ Person's Readiness to start

- Pre-Contemplation: "I don't need it, I feel good."
- Contemplation: "I am weighing things…. and feel torn…"
- Preparation: "I want to start…"
- Action: "I will start now"

Recommendations for initiation of ART

ART is recommended in all adults with chronic HIV infection, irrespective of CD4 counts(i)

Adoption of the "treat all" recommendation among adults and adolescents living with HIV, October 2016



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization

World Health Organization

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TEMPRANO Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

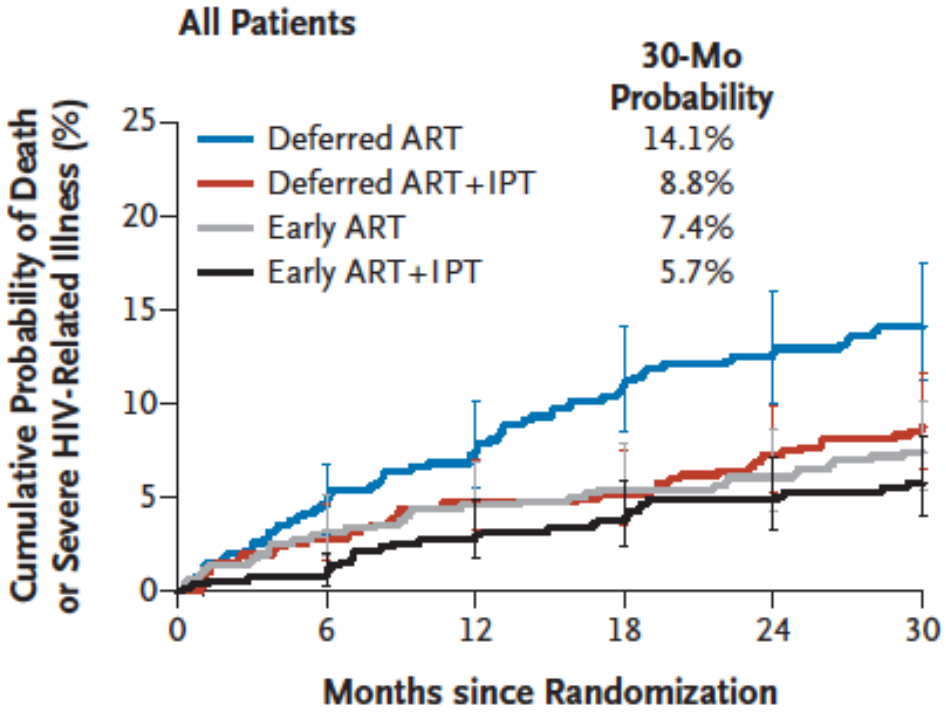
A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

The TEMPRANO ANRS 12136 Study Group*

July 20, 2015

- Study Site
  - Ivory Coast
- Trial design
  - Unblinded, multicenter, individual-randomized controlled 2-by-2 factorial trial.
- HIV positive with CD4 count < 800 cells/mm^3
- participants randomized to one of four groups
  - Deferred ART
  - Deferred ART plus IPT
  - Early ART
  - Early ART plus IPT

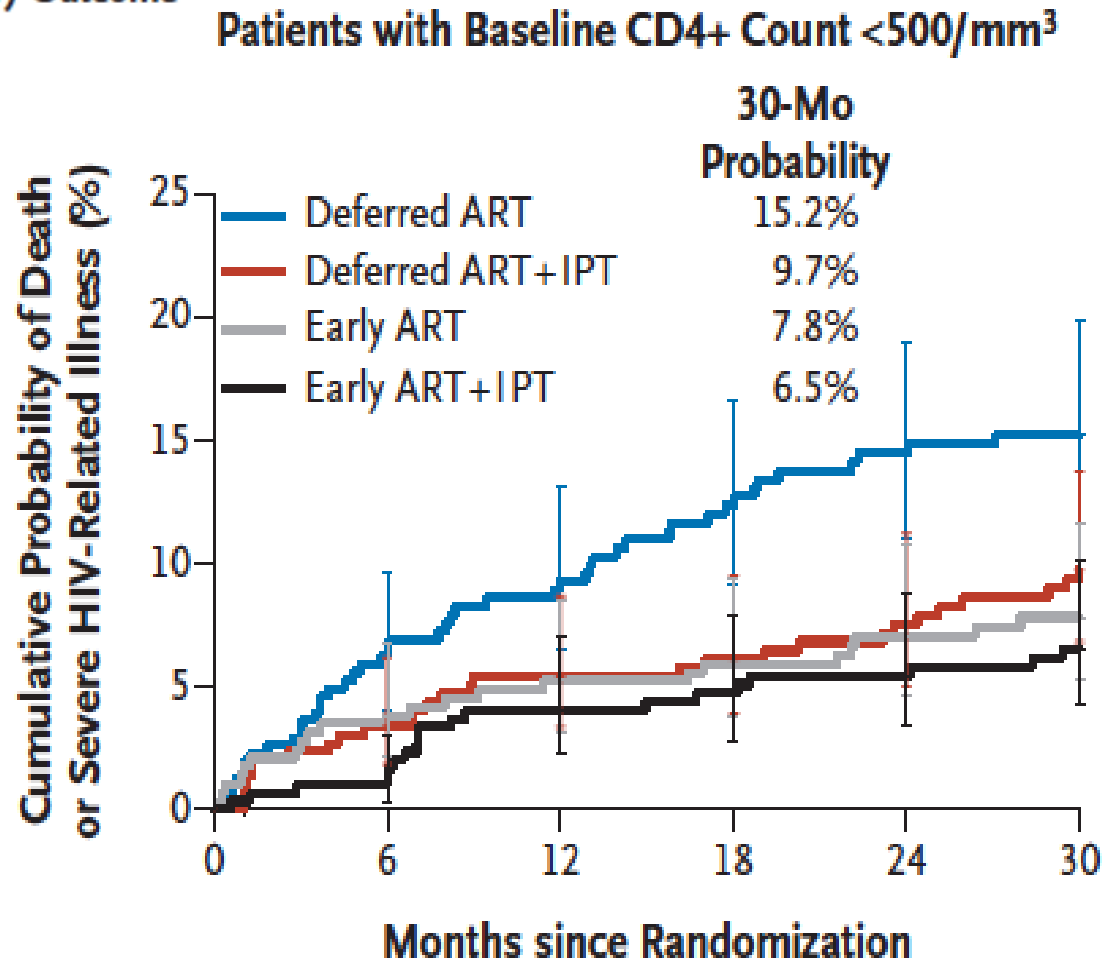
A Primary Outcome

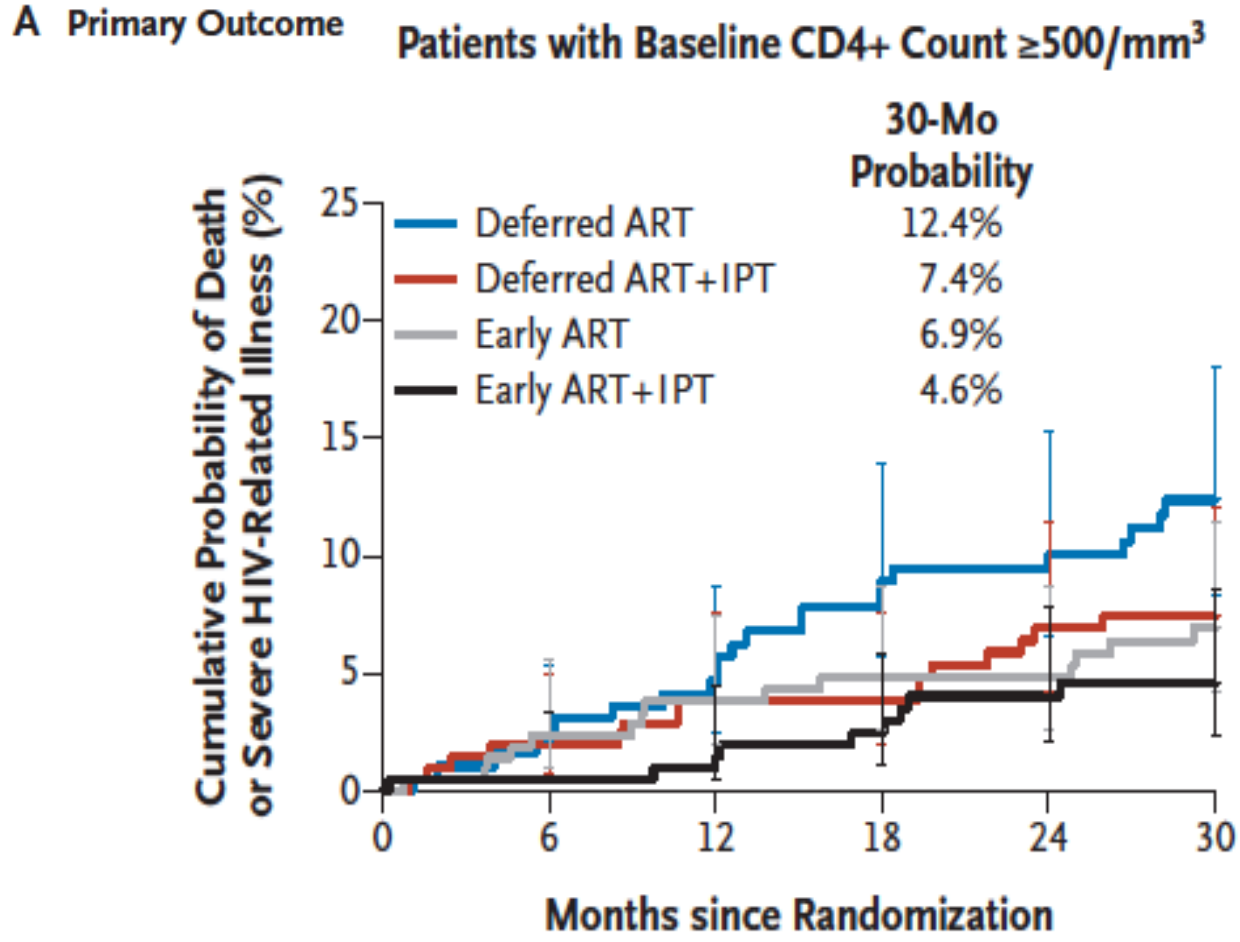


No. at Risk

Deferred ART	511	473	448	418	400	366
Deferred ART+IPT	512	489	473	459	440	419
Early ART	515	481	463	452	432	403
Early ART+IPT	518	501	478	459	445	418

A Primary Outcome




A Primary Outcome
Patients with Baseline CD4+ Count ≥500/mm3
30-Mo Probability
Deferred ART 12.4%
Deferred ART+IPT 7.4%
Early ART 6.9%
Early ART+IPT 4.6%
Cumulative Probability of Death or Severe HIV-Related Illness (%)
25
20
15
10
5
0
0
6
12
18
24
30
Months since Randomization

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The START Trial

The NEW ENGLAND JOURNAL of MEDICINE

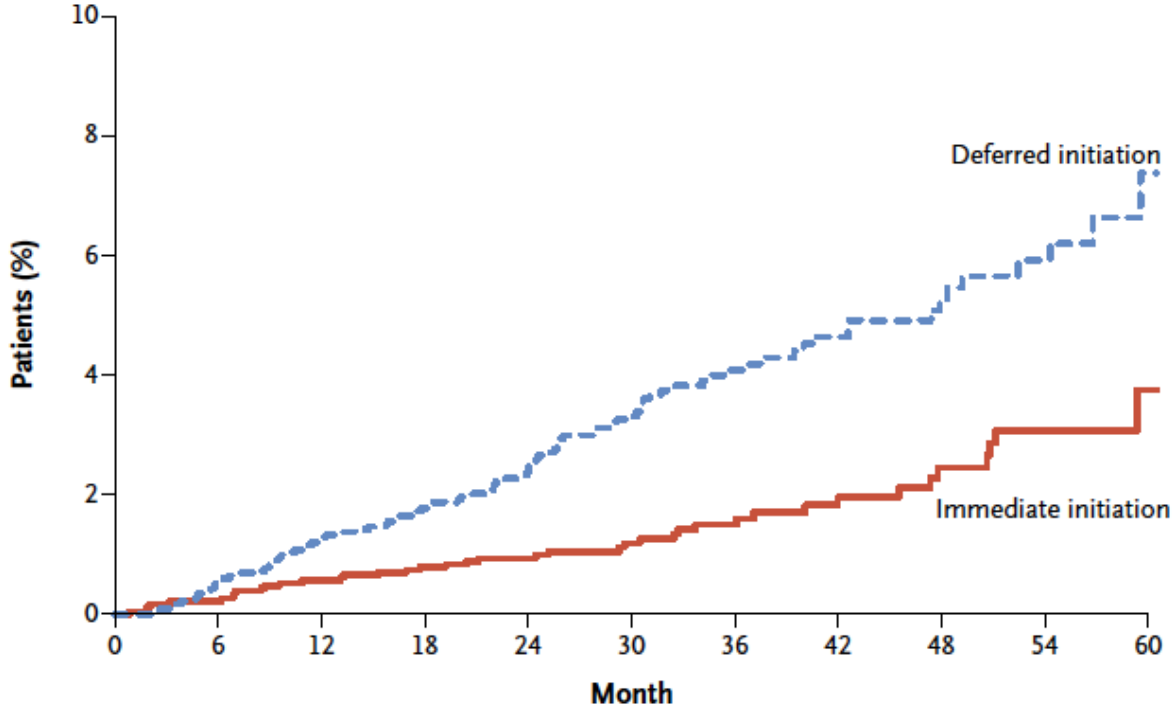
ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

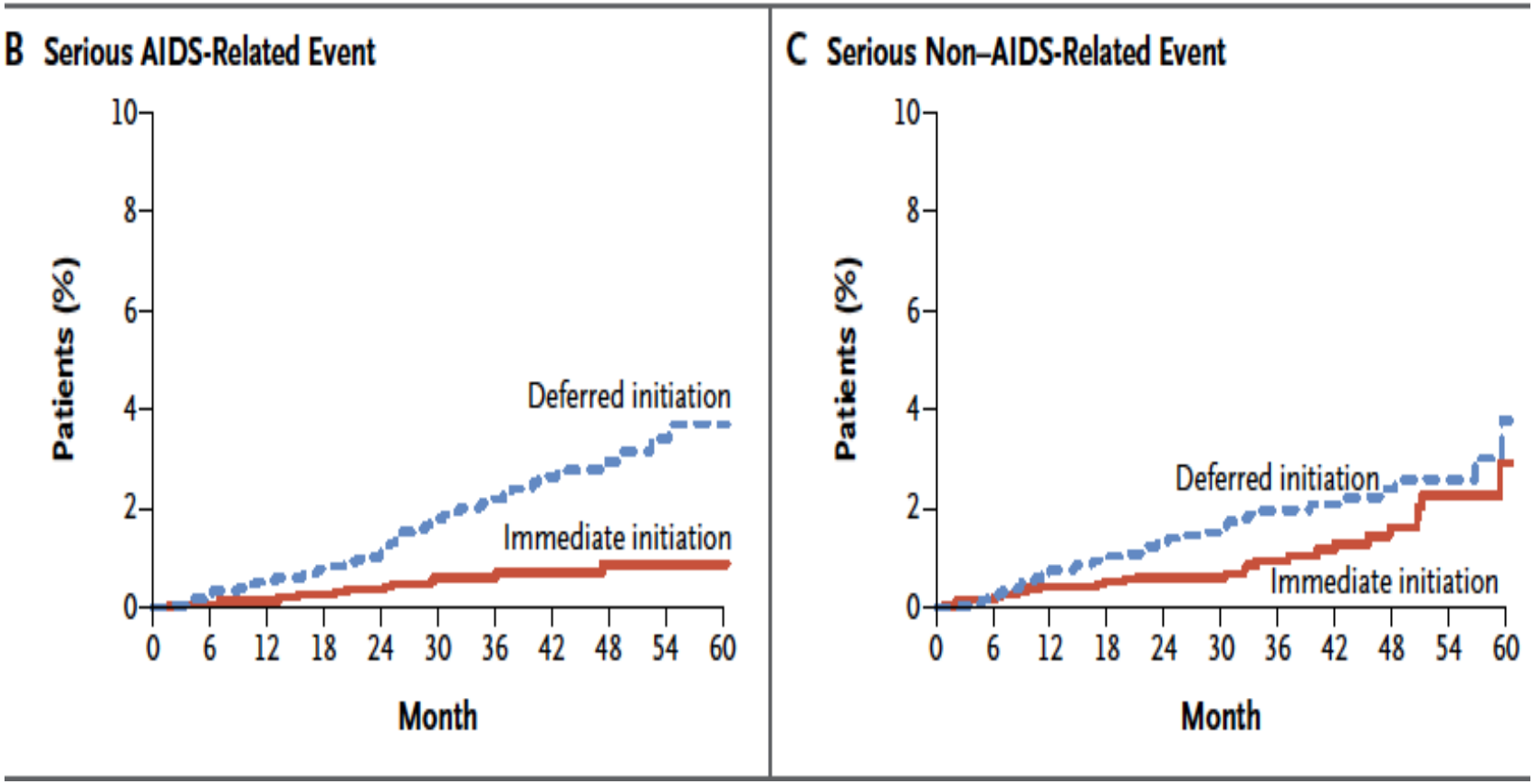
Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

- Multicontinental randomized trial
  - 215 sites in 35 countries
- Study participants
  - HIV positive > 18 years
  - Not yet initiated on ART with no history of AIDS
  - CD4+ counts >500 cells/mm^3
  - Pregnant and breast feeding women not eligible
- Randomized to
  - Immediate ART or
  - Deferred initiation until the CD4+ count declined to 350 cells/mm^3

A **Time to First Primary Event**




B Serious AIDS-Related Event
Patients (%)
10
8
6
4
2
0
Deferred initiation
Immediate initiation
0 6 12 18 24 30 36 42 48 54 60
Month
C Serious Non–AIDS-Related Event
Patients (%)
10
8
6
4
2
0
Deferred initiation
Immediate initiation
0 6 12 18 24 30 36 42 48 54 60
Month

D Death from Any Cause

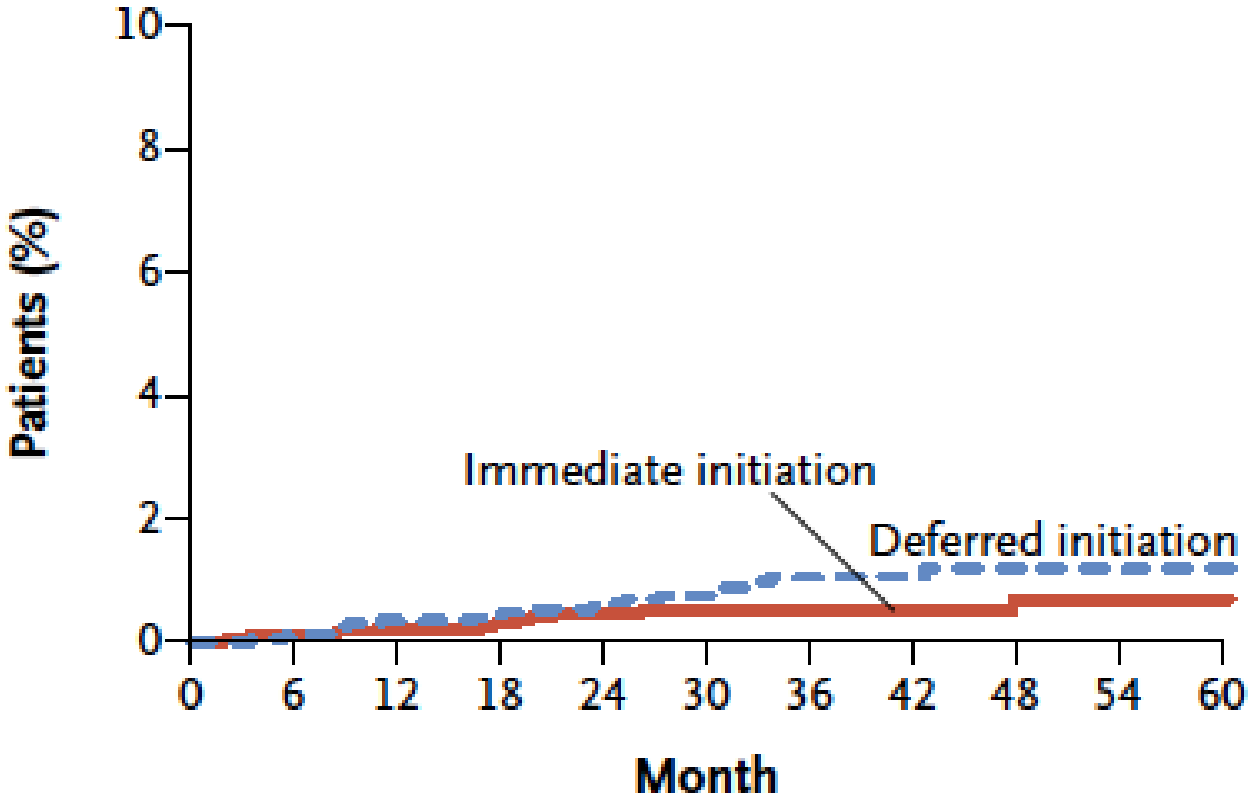


TABLE 1: Summary of design, conduct and findings of the Strategic timing of antiretroviral therapy and TEMPRANO ANRS 12136 (Early antiretroviral treatment and/or early isoniazid prophylaxis against tuberculosis in HIV-infected adults) randomised controlled trials.

Trial	TEMPRANO	START
Countries	Cote d'Ivoire	35 countries (21% of participants enrolled in Africa)
Enrolment years	2008–2012	2009–2013
Number of participants	2056	4685
Inclusion criteria	≥ 18 years old	≥ 18 years old
	HIV-1 (or dual HIV-1 and 2)	ART naive
	CD4 < 800	No history of AIDS
	Not meeting WHO criteria for starting ART at the time (these criteria changed during the course of the trial)	General good health
	-	2 CD4 counts > 500
Comparison arms	*Immediate* ART	*Immediate* ART
	ART *deferred* until WHO criteria for starting ART met (these criteria changed over the course of the trial)	ART *deferred* until CD4 ≤ 350, AIDS diagnosis or other indication for ART (e.g. pregnancy)
Composite primary endpoint	AIDS, non-AIDS cancer, non-AIDS invasive bacterial disease or death	Serious AIDS-related event, serious non-AIDS-related event or death
Duration of follow-up	30 months for each participant	Mean 3.0 years (trial stopped early by DSMB)
Number of primary events	Immediate arm: 64	Immediate arm: 42
	Deferred arm: 111	Deferred arm: 96
Primary endpoint finding	44% reduction with immediate ART (aHR = 0.56, 95% CI = 0.41–0.76)	57% reduction with immediate ART (HR = 0.43, 95% CI = 0.30–0.62)
	Among patients with baseline CD4 ≥ 500, there was also a 44% in primary endpoint (aHR = 0.56, 95% CI = 0.33–0.94)	-
Main contributors to finding	Reduction in AIDS events (50%, mainly TB [50%]) and invasive bacterial disease (61%)	Reduction in AIDS events (72%, including TB [71%]), serious non-AIDS events (29%), cancers (64%) and bacterial infections (62%)
Deaths	Immediate arm: 21	Immediate arm: 12
	Deferred arm: 26	Deferred arm: 21
	Not significant: aHR = 0.60, 95% CI = 0.34–1.09	Not significant: $p = 0.13$
Viral load suppression	Viral load < 100 at 12 months on ART	Viral load < 200 at 12 months on ART
	Immediate arm: 84%	Immediate arm: 98%
	Deferred arm: 80%	Deferred arm: 97%
Adverse events	Overall, the 30-month probability of a Grade 3 or 4 AE did not differ between arms although it was 2.6 times higher in the immediate ART arm for the first 6 months	No difference between arms in terms of grade 4 events and hospitalisations for reasons other than AIDS

Note: In the TEMPRANO trial, there was a separate randomisation of participants to 6 months isoniazid preventive therapy (IPT) versus no IPT.
WHO, World Health Organization; DSMB, Data and Safety Monitoring Board; aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; AE, adverse event.

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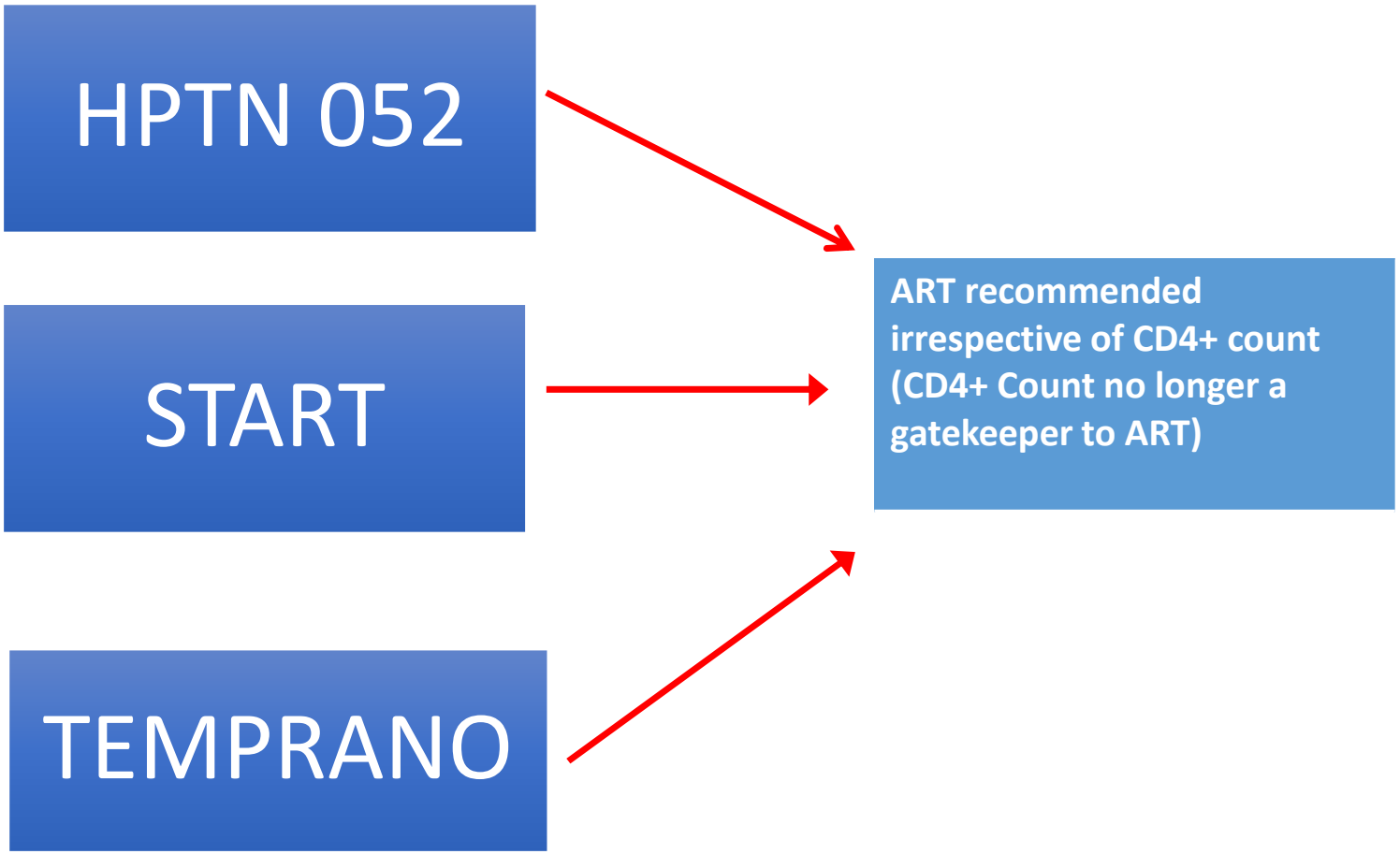
HPTN 052

- Worldwide multicentre randomized controlled trial
  - Early versus delayed ART
  - HIV infected adults with CD4 counts of 350-550 cells/mm^3
- 93% reduction in HIV transmission to sexual partner
- Delayed time to AIDS events with early treatment

Summary


HPTN 052
START
TEMPRANO
ART recommended irrespective of CD4+ count (CD4+ Count no longer a gatekeeper to ART)

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First Line Regimens

Initial ART Regimens for the previously untreated patient
The preferred First-line regimens
FTC (or 3TC) **plus** **tenofovir** **plus** **dolutegravir OR efavirenz OR rilpivirine**
Rilpivirine cannot be used with rifampicin & dolutegravir requires dose adjustment with rifampicin

Baseline resistance test

- Only recommend baseline resistance test for following situations
  - Pre-exposure prophylaxis (PrEP)- in last 6 months
  - History of sexual exposure to a person with known drug resistant HIV or who is known to have failed an ART regimen

Starting ART at the first clinic visit

- Several studies have demonstrated that it is possible to initiate ART safely on the same day as HIV diagnosis or receipt of CD4 count result.
  - These studies have demonstrated **less overall loss to follow-up** when ART is initiated immediately in selected patients.
- Now that treatment is recommended irrespective of CD4 count this same-day strategy should be considered as a means to improve retention in care.

Starting ART at the first clinic visit

- The patient should be motivated to start immediately.
- Same day initiation is not an adherence support “short cut’’; ongoing support can occur in the days and weeks immediately after initiation.
- Patients starting TDF (which are the majority) should be contactable in the event of a creatinine clearance < 50ml/min, and told to return to the clinic immediately.
- Screen for cryptococcal meningitis with CrAg if CD4<100 cells/µL. The patient should be the contactable in the event of a positive CrAg, and advised to return to the clinic immediately.
- Patients with TB symptoms (cough, night sweats, fever, recent weight loss) should first be investigated for TB before ART initiation.

Commencing ART in patients with TB or OIs

- CM and TBM
  - Start 4-6 weeks
- PCP and other OIs
  - Start within 2 weeks
- TB if CD4 < 50
  - Start within 2 weeks
- TB if CD4 > 50
  - Start 2-8 weeks
  - IRIS risk and operational issues

When should you check a viral load?

	SA Dept. Health	SA HIV Clin. Soc.	DHHS (USA)
At initiation	✗	✓	✓
Before 6 months	✗	3 months	At 2-8 weeks, then every 4-8 weeks until suppressed
6 months	✓	✓	✓
12 months	✓	✓	✓
Thereafter	Every 12 months	Every 6 (-12) months	Every 3-6 months

Why check viral loads before 6 months?

- Enables early detection of virological failure (usually due to poor adherence), before resistance develops, or worsens.
- At 3 months, most patients will be virally suppressed, but a small group of people who started with a very high viral load may still have detectable viraemia… although they'll still show at least a 2 $\log_{10}$ drop from their initiation viral loads.

When should you check a CD4 count?

- At baseline
  - Why? Allows for identification of patients at risk of OIs (and hence who will benefit from Bactrim prophylaxis, etc.)
- Every 6 months until CD4 > 200
- Can stop checking CD4 if > 200, provided that viral load is suppressed and remains suppressed

Second-line regimens

Recommend a regimen of 2 NRTIs and a ritonavir (RTV)- boosted (/r) PI
The preferred PI in Second-line regimens
Atazanavir (ATV) 300 mg / RTV 100mg daily **OR**
Lopinavir (LPV)/r BD
NRTI combinations advised for second-line regimens:
AZT + 3TC (if TDF- or ABC-based first line) **or**
TDF + 3TC (if AZT- or d4T-based first line)
Drawbacks of ATV: **-cannot be used with rifampicin- based TB therapy** **- Important drug interactions with drugs that reduce stomach acidity such as proton pump inhibitors**

Choice of second-line NRTIs in relation to first-line NRTIs used	
First-line NRTIs used	**Second-line NRTI combination advised**
AZT + 3TC	**TDF + 3TC***
d4T +3TC	**TDF + 3TC***
TDF + 3TC*	**AZT + 3TC**
ABC + 3TC	**AZT + 3TC**

***3TC is interchangeable with FTC.**

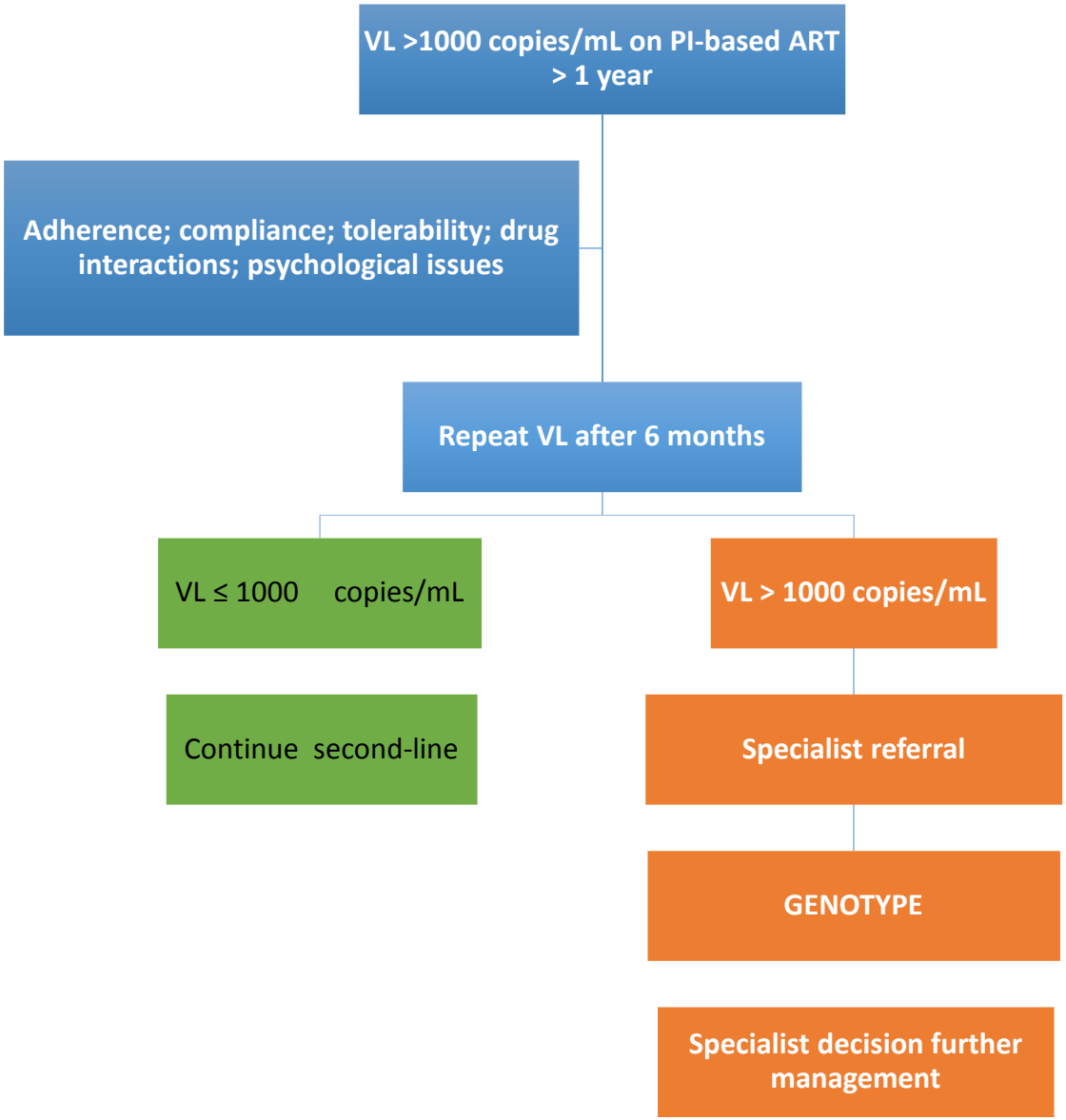
TB co-infection

Drug	Change in concentration	Dose with RIF
NRTIs	No significant interactions	Normal dose
EFV	Mild reduction	Normal dose
NVP	Moderate reduction	Omit lead-in dose phase (start at 200 mg 12-hourly)
ETV/RPV	Marked reduction	Don’t use with RIF
LPV/r	Significant reduction	Double LPV/r dose (risk of hepatotoxicity)
Other PIs	Marked reduction	Don’t use with RIF
RAL	Reduction, but significance unclear	? Double dose (800 mg 12-hourly) ? Standard dose (400 mg 12-hourly)

Dosing of ART drugs and rifabutin when prescribed concomitantly		
ART drug	**ART dosage**	**Rifabutin dosage**
EFV	No change	**Increase to 450 mg/day**
NVP	No change	**300 mg/day**
ATV or RTV-boosted PIs	No change	**Decrease to 150 mg/day (monitor ALT, neutrophils and visual symptoms at least monthly)**

Third-line ART Regimens

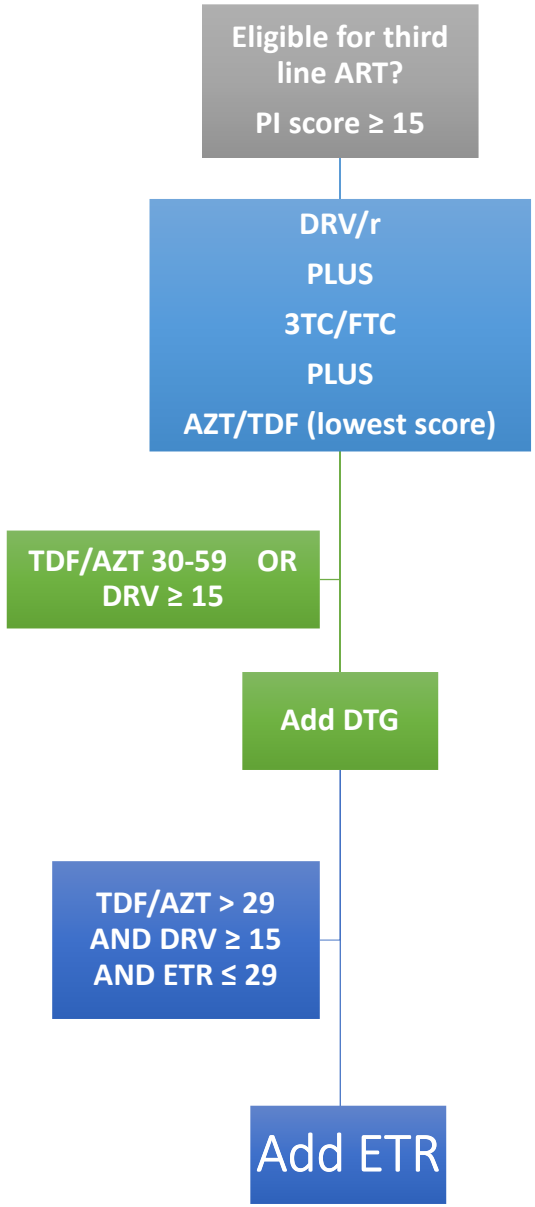
- Indicated for patients with documented PI resistance
- Requires resistance testing before regimen chosen
- Must have been on PI-based second line regimen for longer than 1 year
- Criteria for resistance testing on second-line ART
  - 2 or 3 VL > 1000 copies/mL in 6 month period
  - Exception- error of not double dosing of LPV/r with rifampicin


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
VL > 1000 copies/mL
Continue second-line
Specialist referral
GENOTYPE
Specialist decision further management

Drugs available for third-line ART

PI	Darunavir (DRV)
InSTI	Dolutegravir (DTG)
InSTI	Raltegravir (RAL)
NNRTIs	Etravirine (ETR) Rilpivirine (RPV)
CCR5 blocker	Maraviroc (MVC)

First-generation NNRTIs (NVP & EFV) have no place in third-line therapy as they do not impair viral fitness


Eligible for third line ART?
PI score ≥ 15
DRV/r
PLUS
3TC/FTC
PLUS
AZT/TDF (lowest score)
TDF/AZT 30-59 OR DRV ≥ 15
Add DTG
TDF/AZT > 29 AND DRV ≥ 15 AND ETR ≤ 29
Add ETR

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Isoniazid Preventive Therapy (IPT)

- TEMPRANO : separate randomisation to 6 months of IPT
  - addition of IPT to ART- provided added protection against active TB disease
  - Benefit to patients with relatively high CD4 counts
- Khayelitsha study- placebo-controlled
  - 12 months of IPT to patients on ART
  - reduced TB incidence by 37%

Indications for and duration of IPT		
TST	**Pre-ART***	**On ART**
Not done	IPT for 6 months	**IPT for 12 months**
Negative	IPT not indicated	**IPT for 12 months**
Positive	IPT for at least 36 months	**IPT for at least 36 months**

IPT = isoniazid preventive therapy; TST = tuberculin skin test; ART = antiretroviral therapy.

***This would only apply in the case of a patient wishing to defer ART initiation.**

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Conclusion

- $CD4^+$ count no longer a barrier to ART initiation
- Earlier ART benefits all HIV-infected individuals
  - reduces risk of disease progression
  - prevents HIV transmission
- Benefits to early ART in developing countries
  - reduce TB rates
- IPT for all patients on ART