



EDCTP Stake Holders Meeting

Treatment and care III
Implementation research.



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The pandemic historically:

- *3000 people died in the 9/11 World Trade Center disaster and on that same day in Africa, 6500 people died of AIDS- just like the day before, and the day after, and the day after that....*



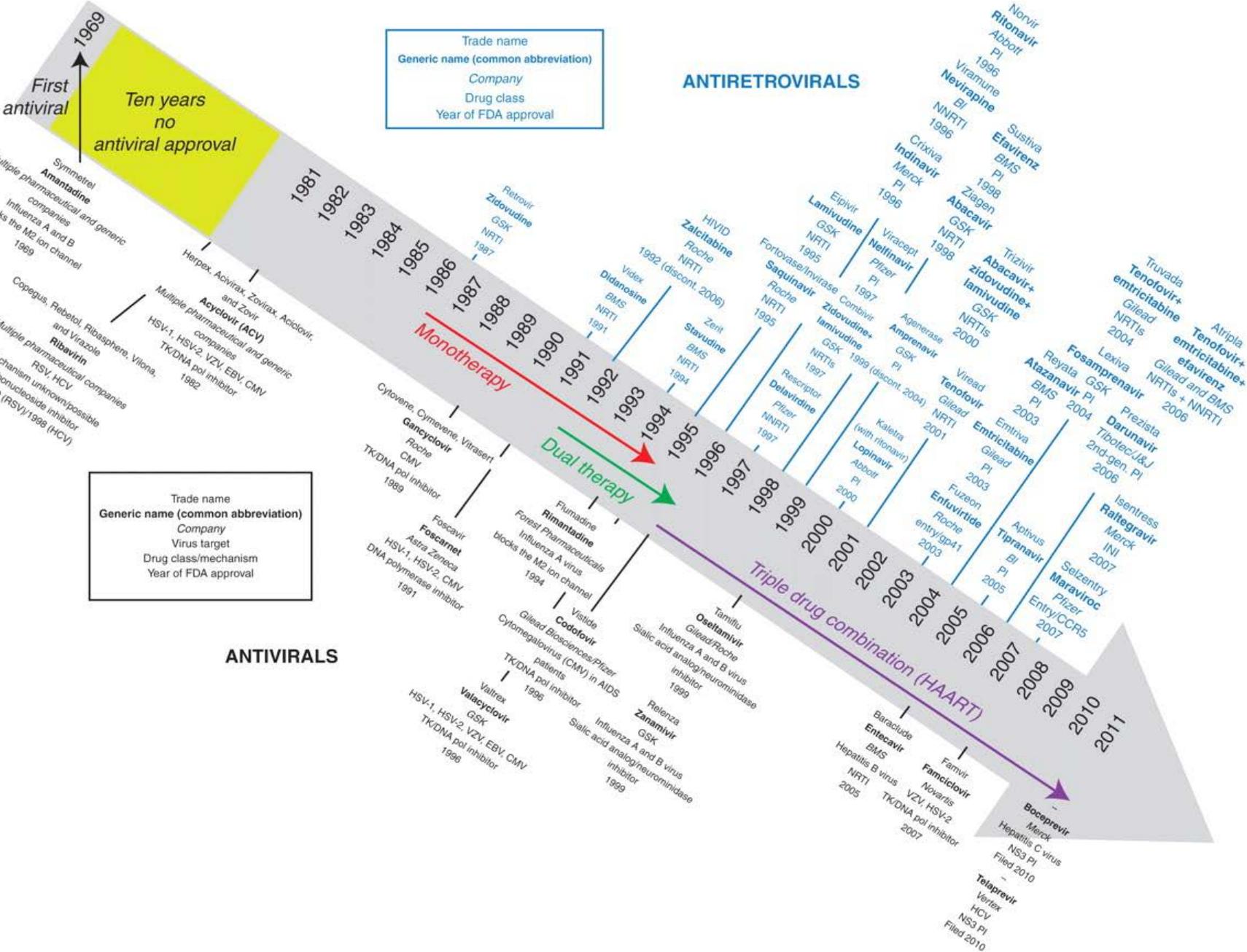
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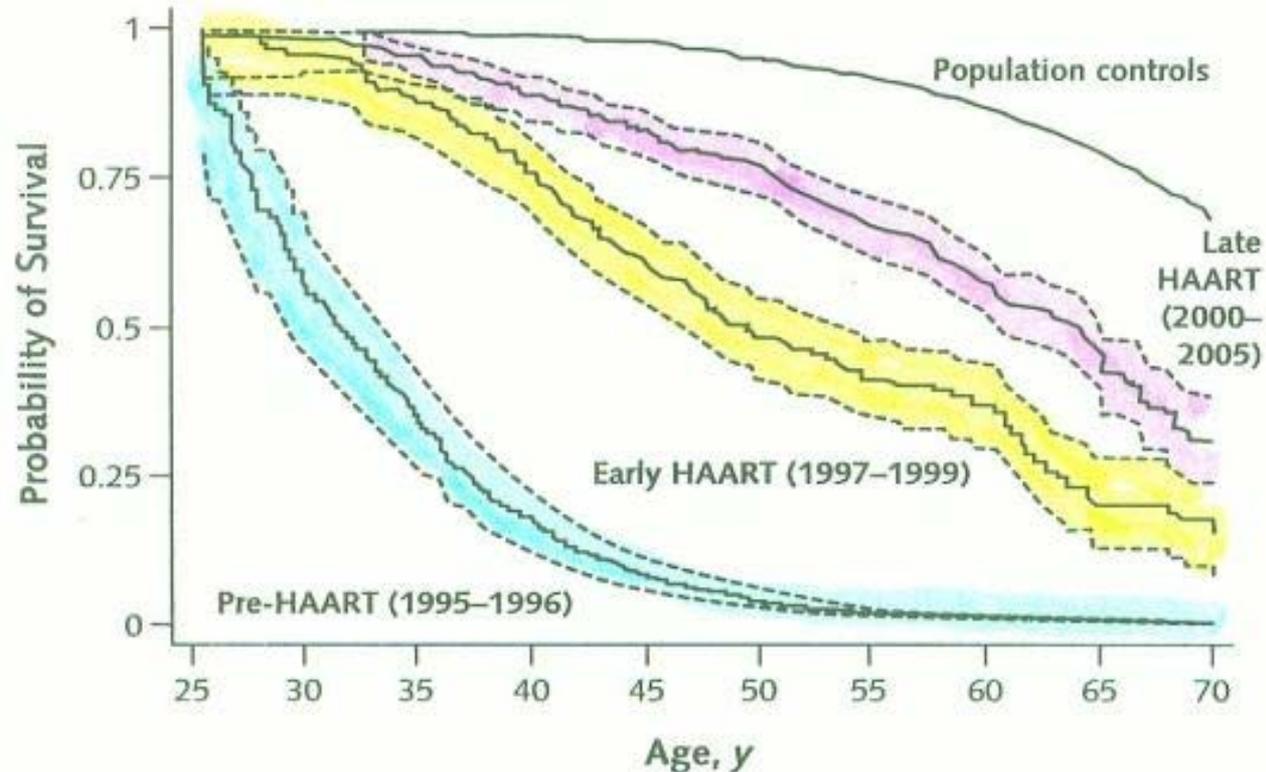
Trade name
 Generic name (common abbreviation)
 Company
 Drug class
 Year of FDA approval

ANTIRETROVIRALS



Trade name
 Generic name (common abbreviation)
 Company
 Virus target
 Drug class/mechanism
 Year of FDA approval

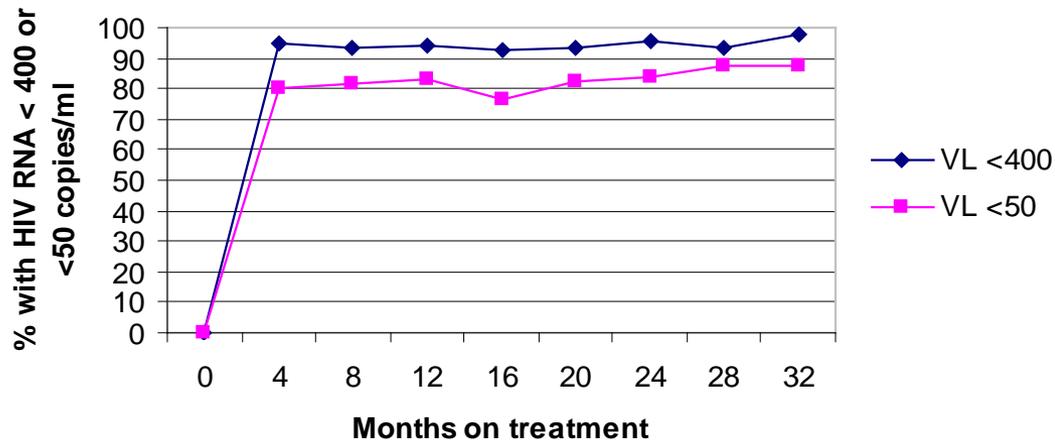
Figure. Survival from age 25 years.



Cumulative survival curve for HIV-infected persons (without hepatitis C coinfection) and persons from the general population. Persons with HIV infection are divided into 3 calendar periods of observation. Dashed lines indicate 95% CIs. HIV = human immunodeficiency virus; HAART = highly active antiretroviral therapy.

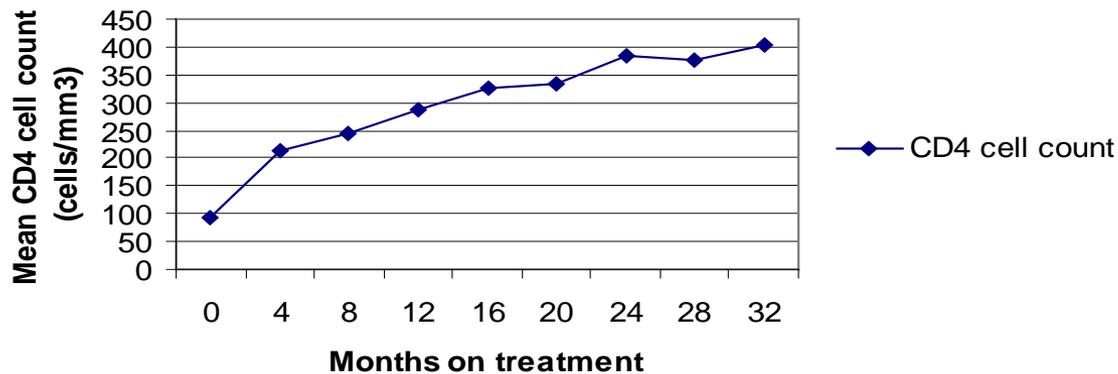
Virological suppression by duration on treatment

Figure 3:



HIV RNA level under 400 copies/ml (%)	0	94.8	93.6	94.3	93.0	93.2	95.7	93.1	97.5
HIV RNA level under 50 copies/ml (%)	0	80.2	81.7	82.8	76.7	82.4	83.8	87.5	87.5

Improvement in absolute CD4 cell count by duration on treatment



CD4 cell count > 200 cells/ml (%)	6.1	49.9	58.5	72.0	77.5	84.4	88.0	89.0	97.5
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WHO/UNAIDS initiatives

- 3 by 5 in 2003
 - 3 million on ART by 2005
 - Achieved this in 2007.....
 - 400,000 people in December 2003 to 1.3 million in December 2005. This included an eight-fold increase in sub-Saharan Africa.
- Eligibility: <200,
- 2010 : <350 and stage 3 and 4.



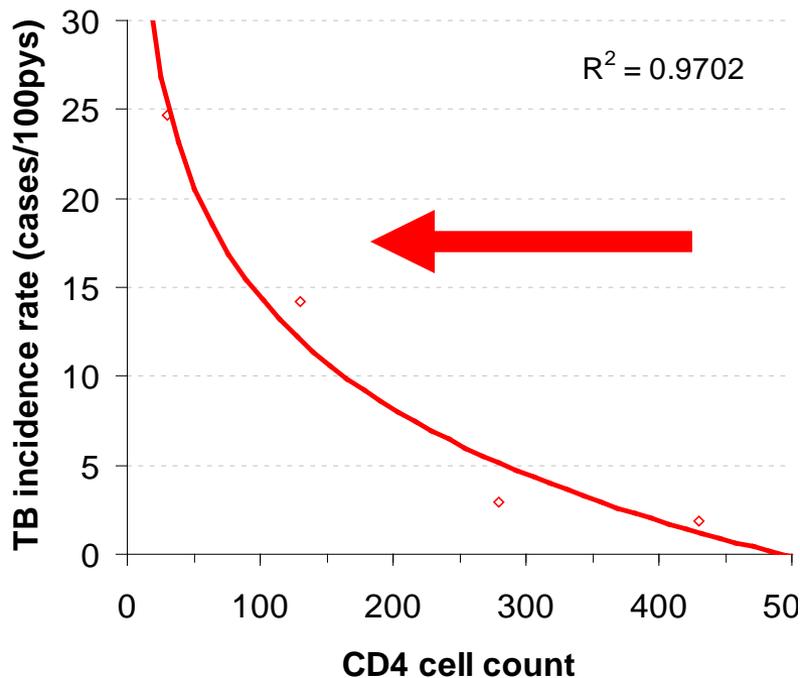
Universal access and MDG 6 by 2015

- reduce new infections by 50 percent among young people (15-24 years),
- reduce TB-related mortality by 50 percent,
- eliminate new infections in children,
- and reduce HIV-related mortality.

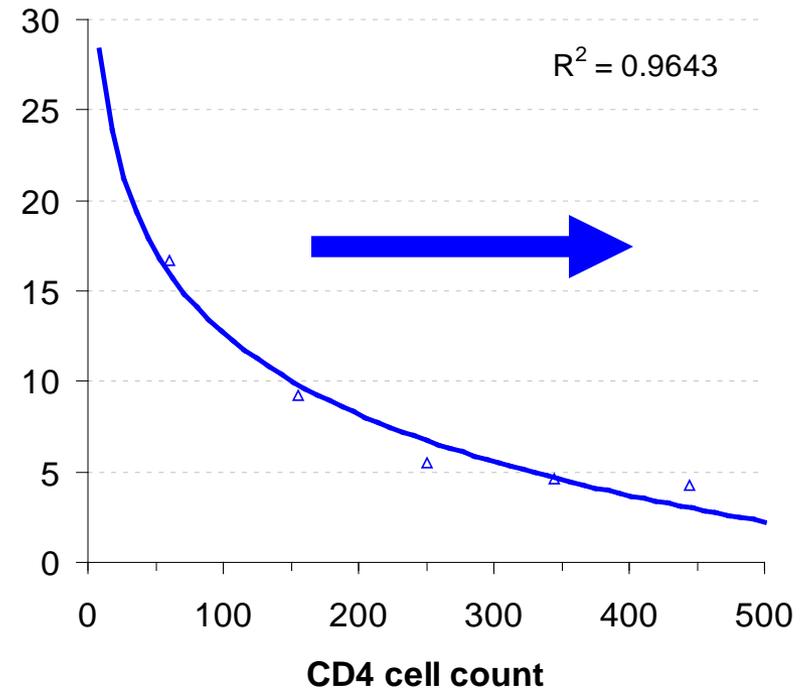
A:TB Incidence by CD4 without HAART

B: TB Incidence by CD4 with HAART

A: Cape Town AIDS Cohort



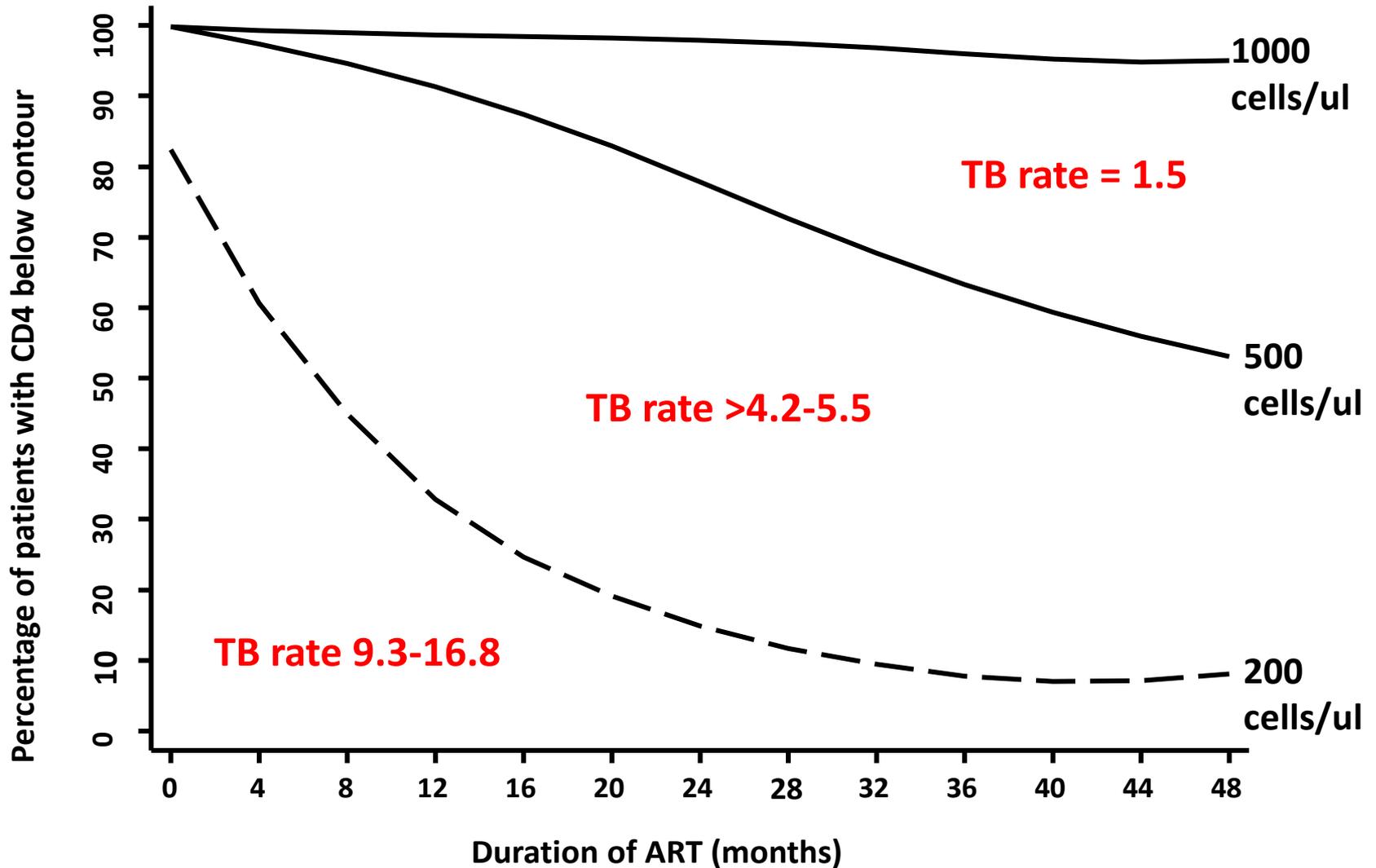
B: Cape Town ART Cohort



A: Holmes, Wood, Badri, *et al* JAIDS 2006

B: Lawn, Myers, Edwards Bekker, Wood. *AIDS* 2009

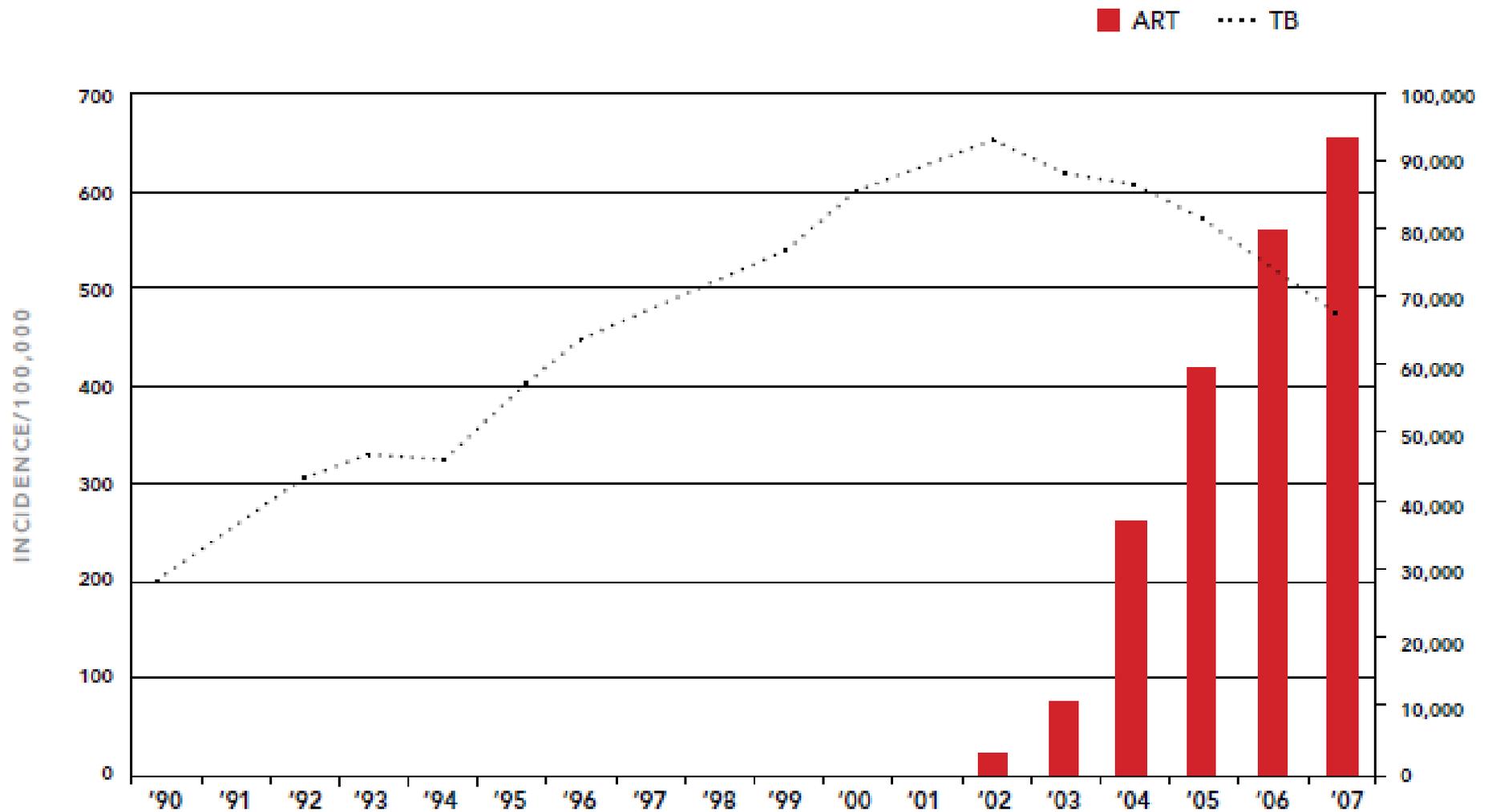
CD4 Count Recovery of ART Cohort



Antiretroviral therapy and TB incidence in Botswana

Source: Ministry of Health, Botswana.

Reported incidence of TB and number of people receiving antiretroviral therapy in Botswana, 1990–2007.



Treatment expansion

- Treatment access expanded extensively, increasing by 63 percent between 2009 and 2011.
- Treatment reached 8 million people in 2011, the first time the number of people being treated for HIV exceeded the number of those who were eligible but going without.

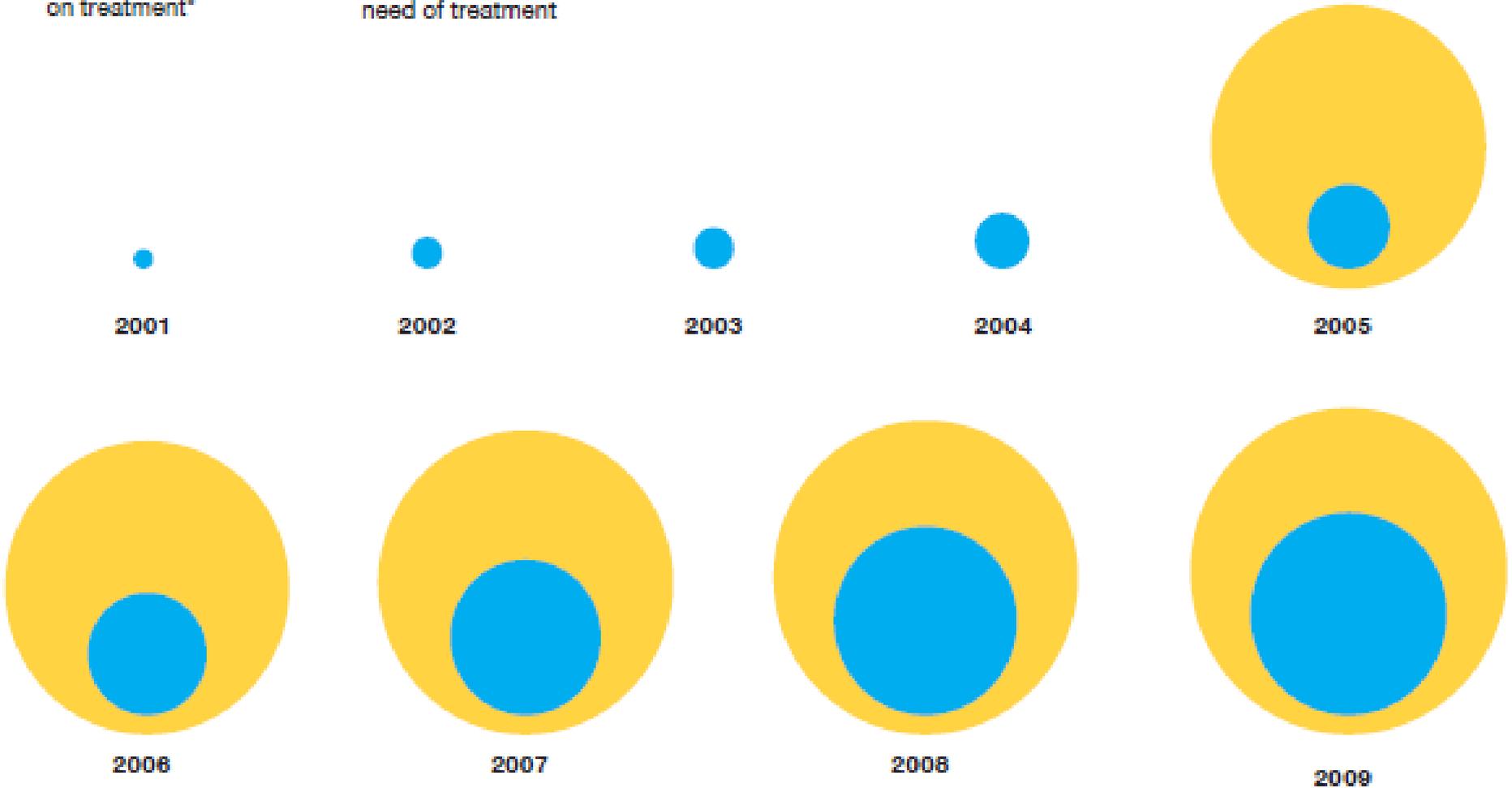
Treatment coverage in low- and middle-income countries

Population-adjusted averages for treatment coverage in low- and middle-income countries by geographical region in 2009 based on 2010 WHO guidelines: Millennium Development Goal target 6.B



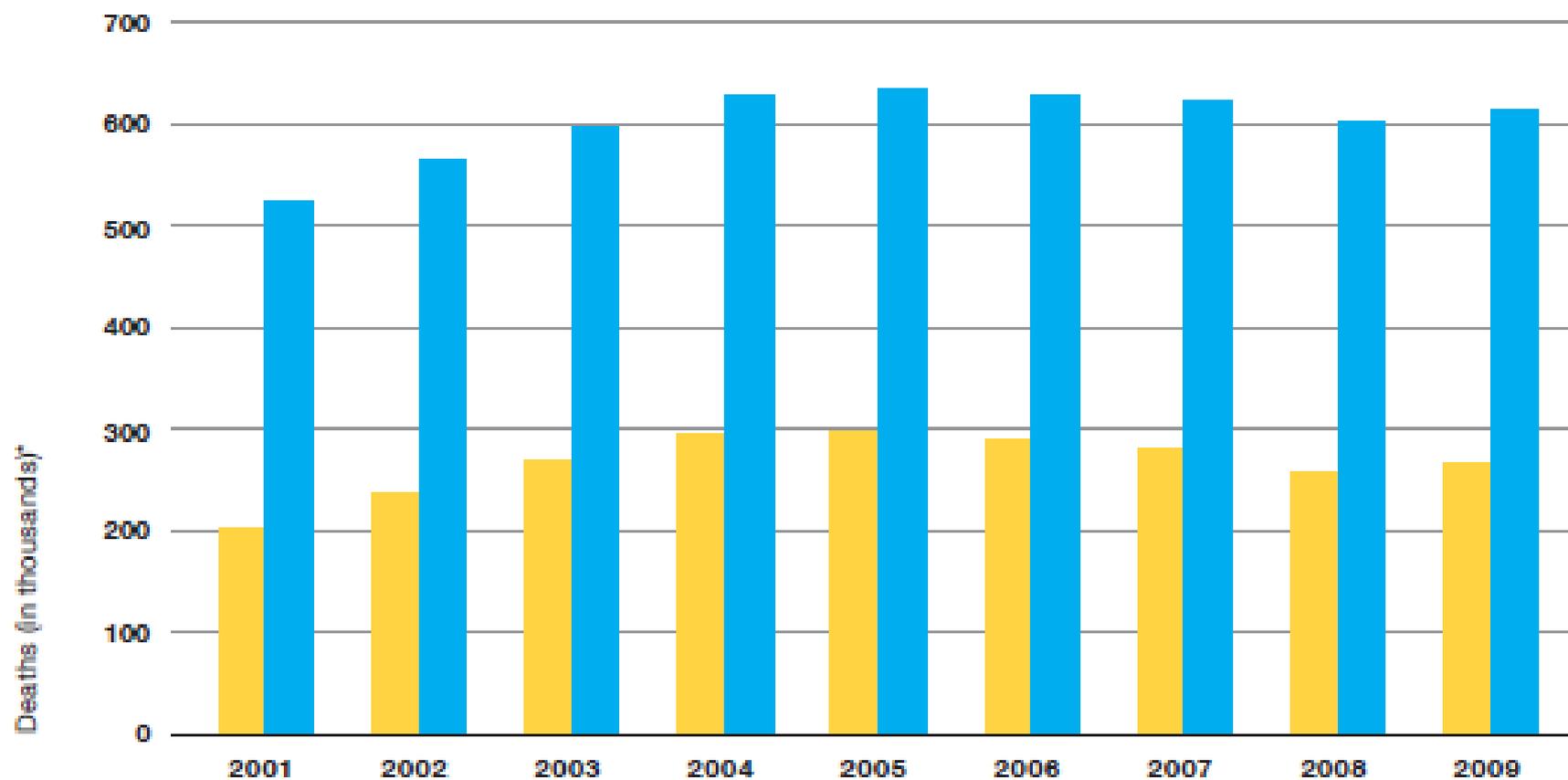
Treatment vs need in South Africa

● Estimated number on treatment* ● Estimated number in need of treatment



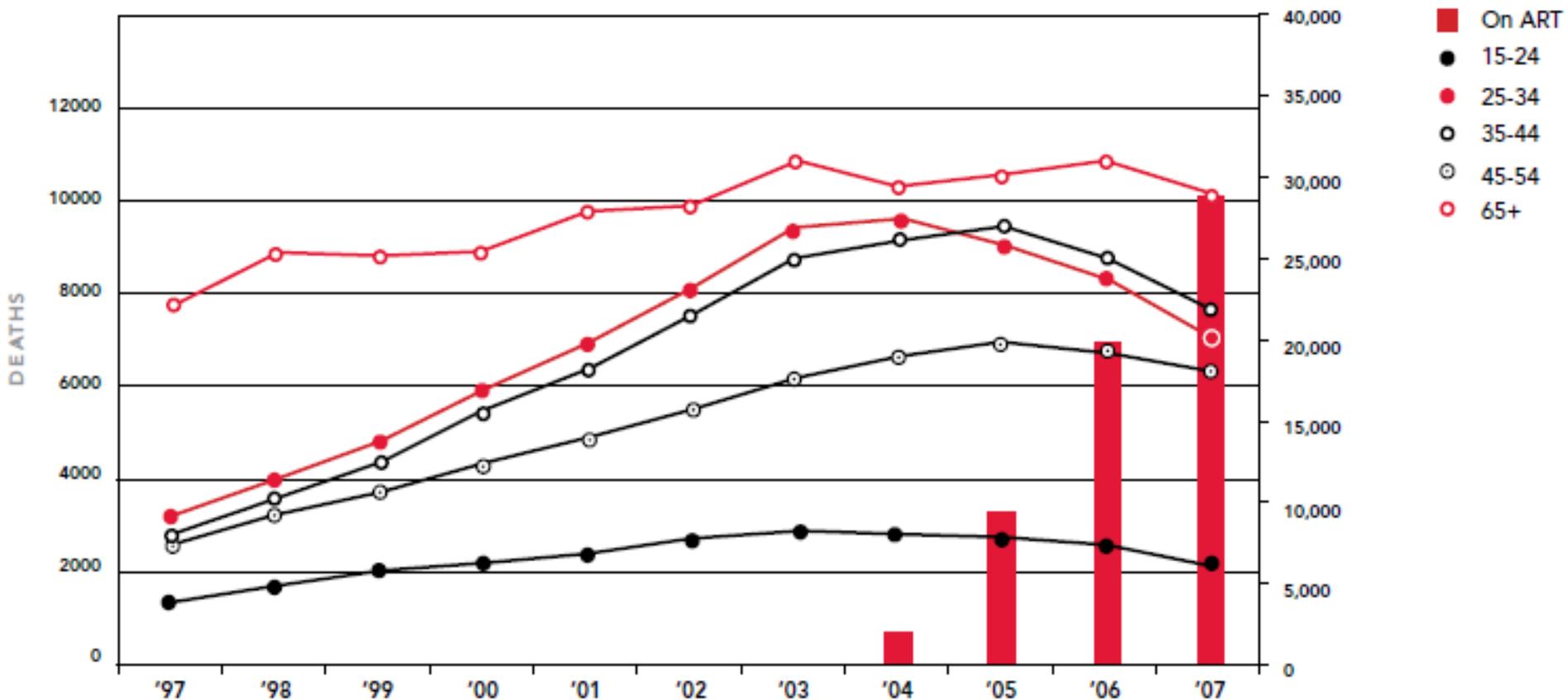
Causes of death in South Africa

■ AIDS-related deaths ■ Registered deaths (all causes)



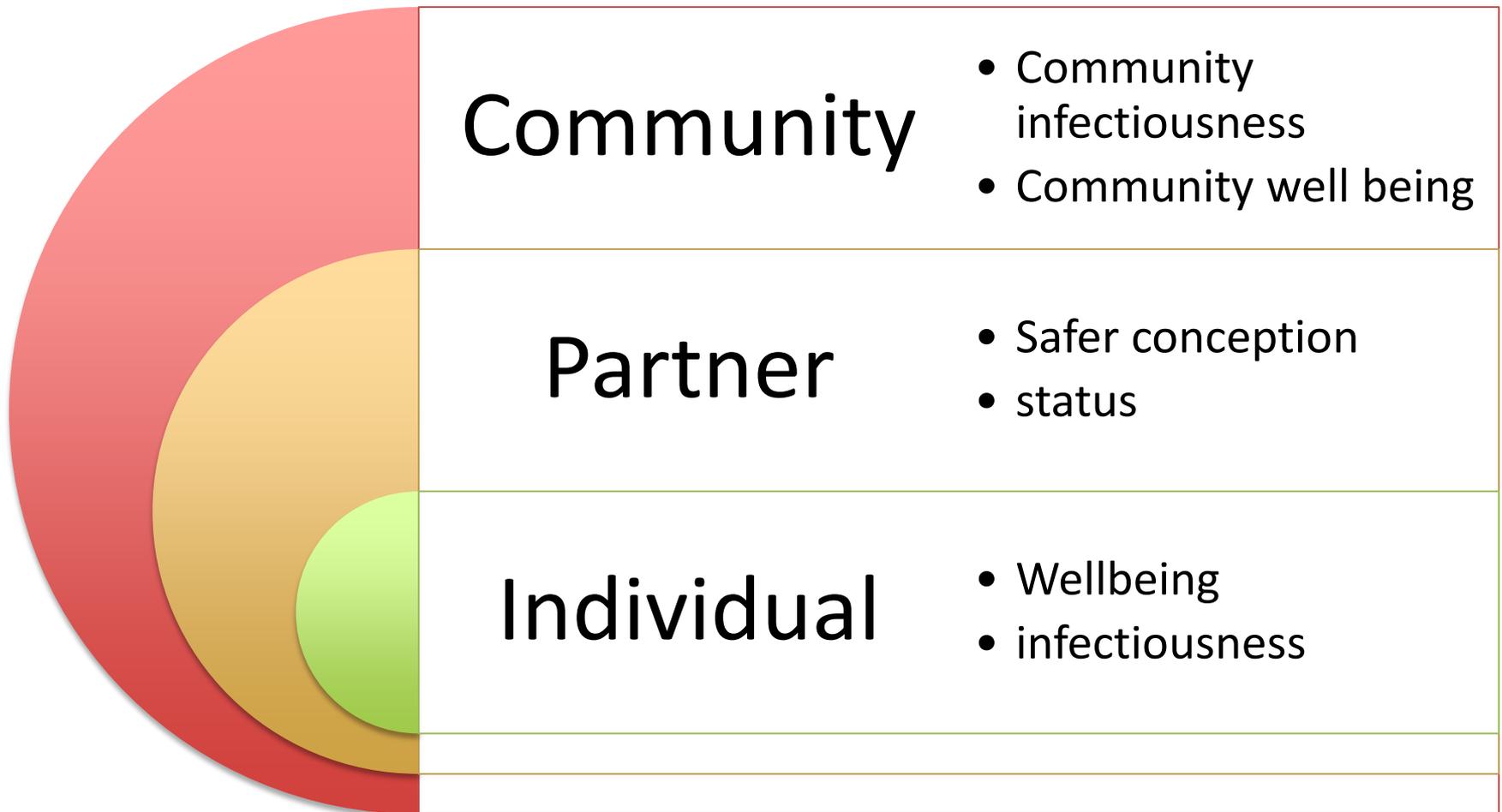
Antiretroviral therapy and mortality, Northwest Province, South Africa

Number of people ever receiving antiretroviral therapy and annual number of deaths by age group, Northwest Province, South Africa, 1997–2007.



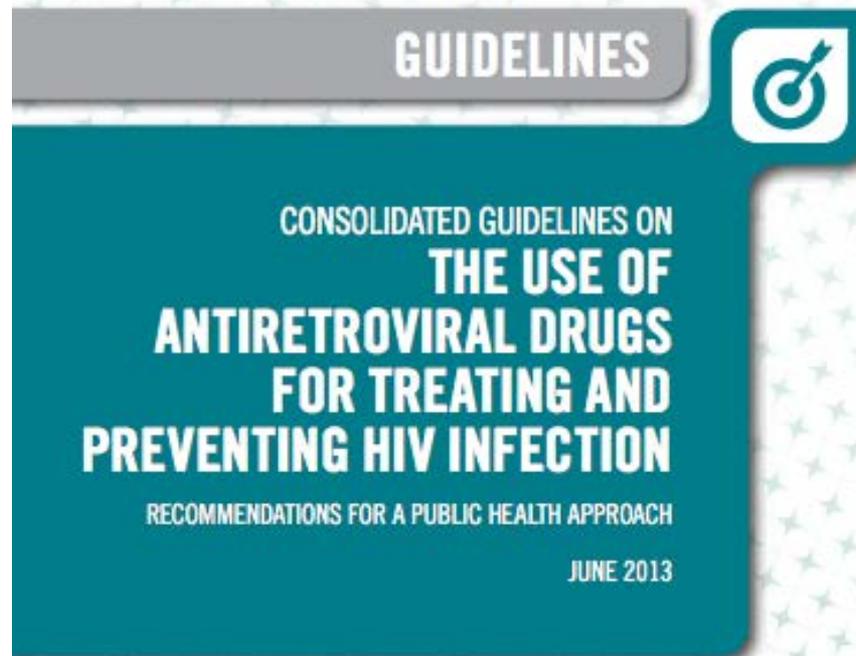
Source: Ministry of Health, South Africa.

ART beyond the individual



Eligibility : <500 CD4 Tcells with immediate ART for TB, pregnant women and discordant couples.

An estimated **17 million** people are eligible to take antiretroviral drugs, but under the new recommendations this number will increase to **26 million**.



LGB's ingredients of scale up

- widespread awareness of the value of testing and subsequent treatment even in the face of few symptoms.
- life-long commitment to antiretroviral drugs (ARVs) and supporting patients to adhere to a daily regimen
- adequate health infrastructure including health staff resourcing
- sustainable and reliable supply chains of effective drugs

IOMs ingredients.....

- Immediately introduce and scale up ART programs in resource-poor settings.
- Devise strategies to ensure high levels of patient adherence to complicated treatment regimens.
- Rapidly address human-resource shortages to avoid the failure of program implementation.
- Continuously monitor and evaluate the programs to form the most effective guidelines and treatment regimens for each population.
- Prepare to sustain ART for decades.

Tension

- Consolidate gains
- Ensure quality
- Optimise at current level

- **SCALE UP, SCALE UP, SCALE UP!!!**
 - With promise of less morbidity and mortality
 - Reduced force of infection and decreased transmission



Note...earlier start (WHO)

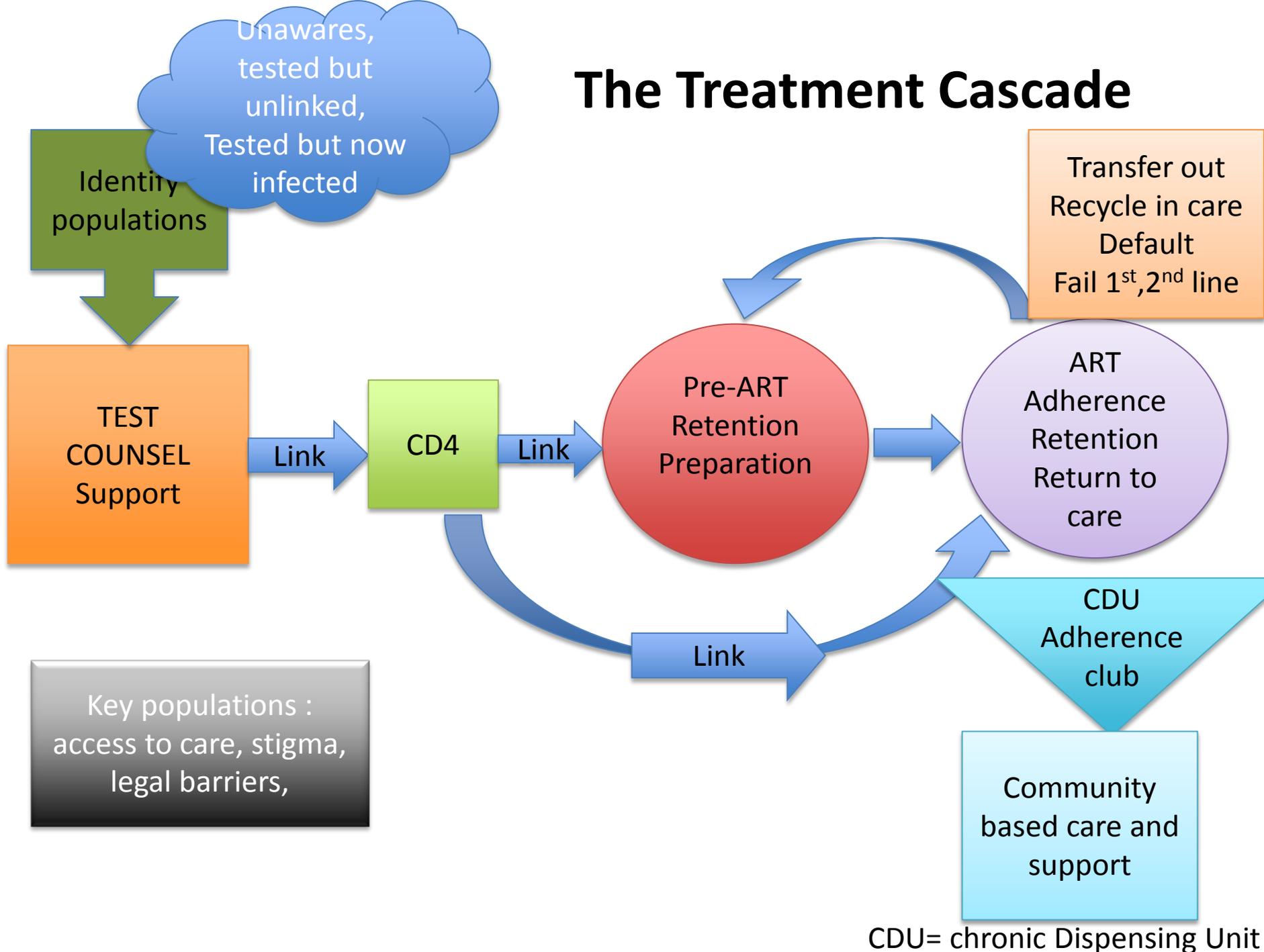
- Not all observational studies have consistently demonstrated the beneficial impact of initiating ART earlier on mortality
- and the incidence of non-AIDS events associated with chronic inflammation and ongoing viral replication,
- longer follow-up is needed to evaluate potential harms and benefits.
- The long-term safety profile of ART and the
- implications of earlier initiation on drug resistance and toxicity will also need to be closely monitored.

- START and TEMPRANO are in the field.

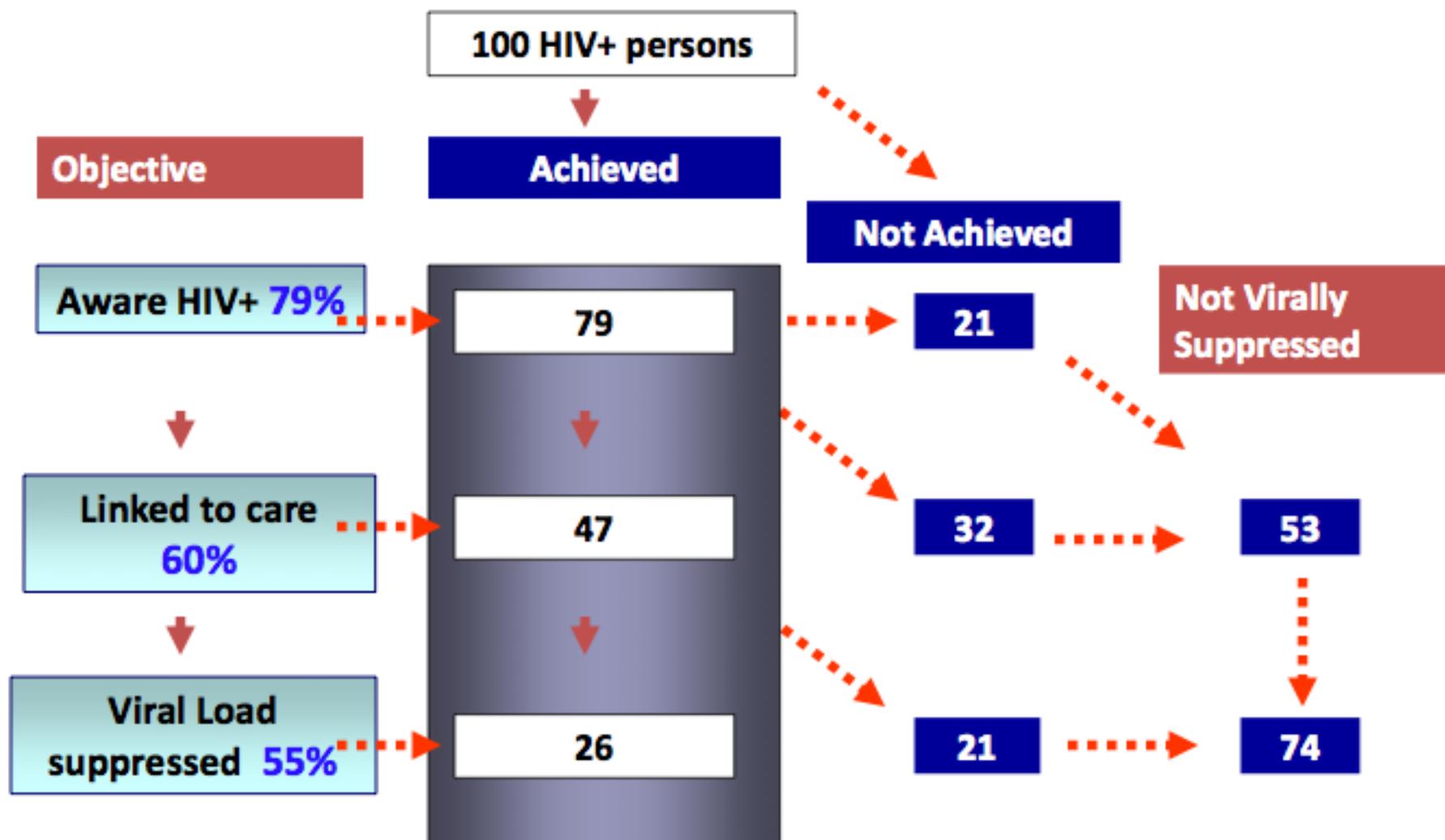
Where are we??

- End of 2011 on 2010 guideline eligibility :
- 54% coverage (8 million)
- Range per region 15-68%
- 9 LMIC with coverage >80%
- 68 countries < 50% coverage
- Median CD4 <350 in most settings incl high income

The Treatment Cascade



Cascade Effect: Diminishing Returns

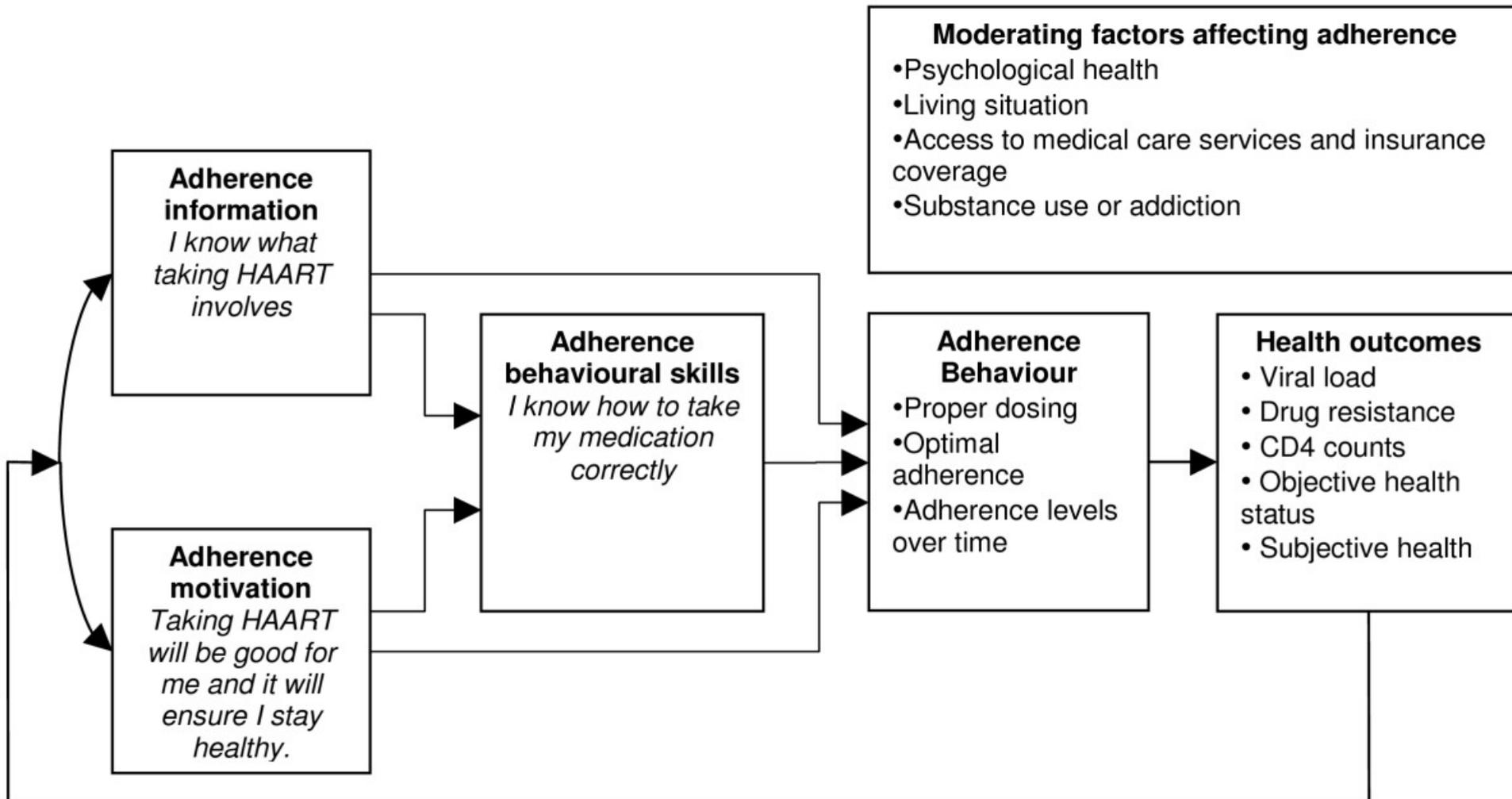


Overall: ~26% of HIV+ persons were in care and estimated to have a viral load <500 copies/ml

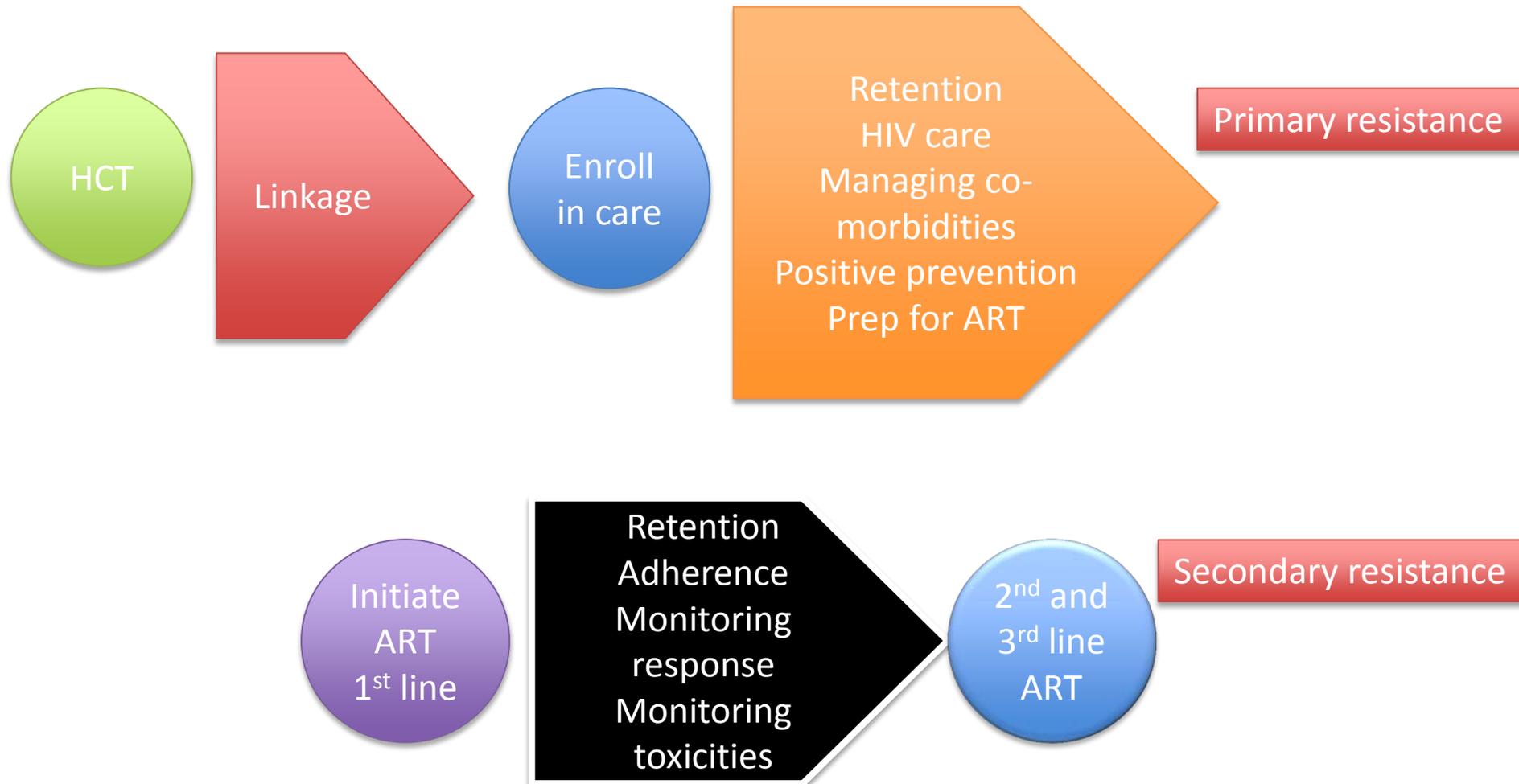
Adherence to any medication- consequences of ART non-adherence



Situated IMBs model applied to ART



Opportunities for translational research



Testing

Activity	recommendation	evidence
Community based in GE	strong	Low
Community based KP	strong	low
Adolescents in GE	strong	low
Adolescents KP	strong	Very low
Adolescents in low and conc E	conditional	Very low

When to start

Activity	recommendation	evidence
<350 stage 3/4	strong	moderate
>350 <500	strong	moderate
Any in TB	strong	low
Any in HepB	strong	low
Any if discordant	strong	high

What to start

Activity	recommendation	evidence
TNF, 3TC, EFV	strong	moderate
AZT for TNF	strong	moderate
NVP for EFV	strong	moderate
Discontinue Stavudine	strong	moderate
Adolescents go to ABC	strong	Very low

2nd line consists of heat stable LPV/r or ATV/r – Strong with moderate evidence
DRV is not heat stable.

3rd line: conditional recommendation- new agents.

Monitoring response and toxicities

activity	recommendation	evidence
Viral load	strong	low
If no VL, CD4/clinical	strong	moderate
toxicities	strong	low

Integration of care

- Where possible ART should be commenced in setting of initial care, eg.
 - ANC setting, TB clinic, methadone clinics.
 - Strong recommendation, very low evidence!

Methods to improve adherence

- Mobile phone technology
 - Strong recommendation, moderate quality
- Ways to measure adherence



Decentralisation of services

- Move from hospitals to peripheral clinics
- Initiate and maintain from peripheral clinics
 - Strong recommendation and low quality evidence
- Initiate in peripheral clinics and maintain at community level
 - Strong recommendation and moderate evidence

Task shifting

- Trained Non-physician clinicians, nurses, midwives can initiate and maintain ART and trained and supervised community health workers can dispense ART between clinic visits
 - Strong recommendation and moderate quality evidence

Key populations

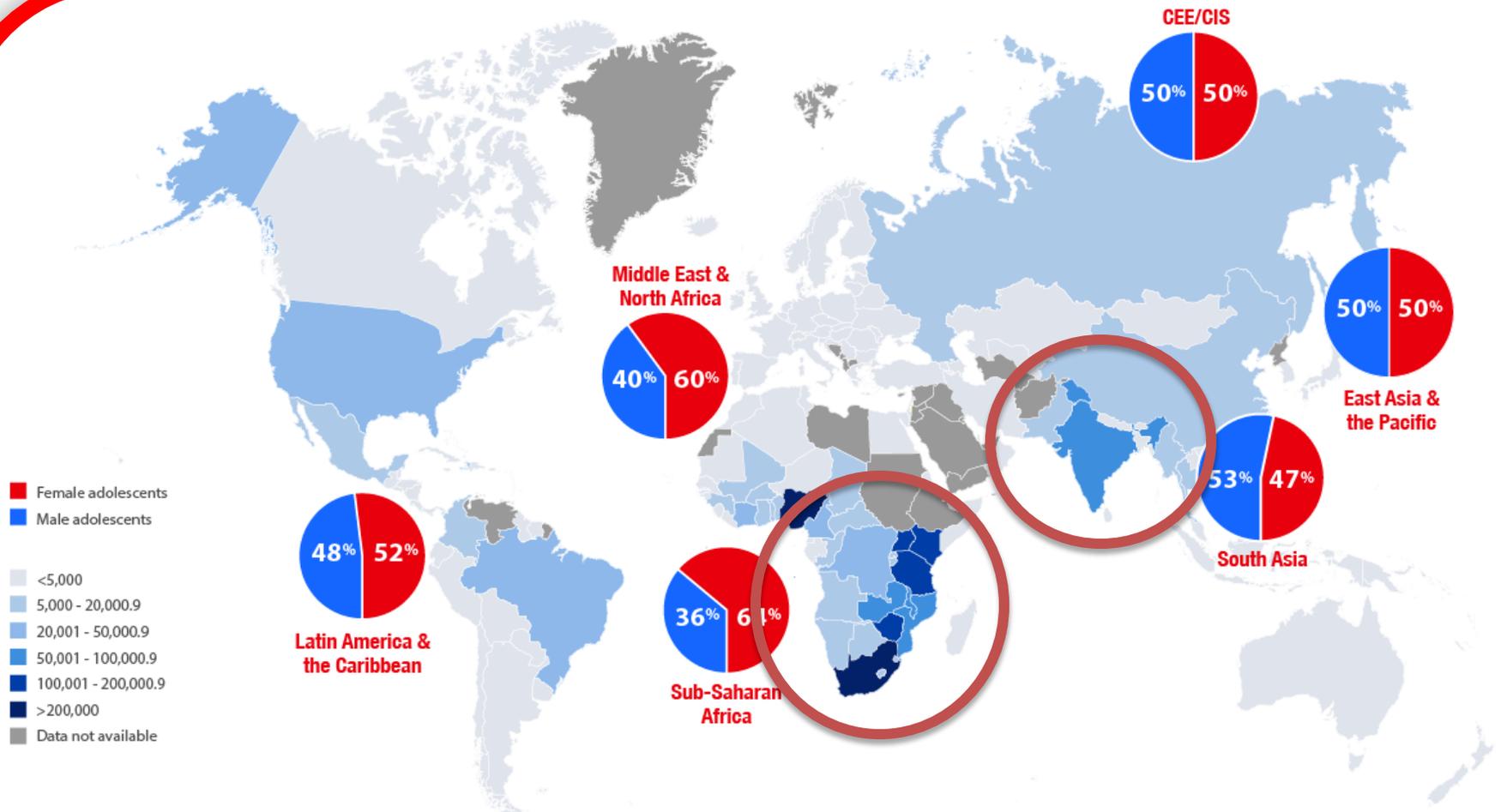
- Drug users
- Incarcerated populations
- MSM
- TB co-infected
- Sex workers
- adolescents



Key populations

Adolescents (10 – 19) Living with HIV

2.1 million [1.6 million – 2.6 million] of whom 60% are girls (2011)



Note: The map is stylized and not to scale. It does not reflect a position on the part of UNICEF on the legal status of any country or territory or the delimitation of any frontiers.

Source:

- Regional summaries by gender: UNICEF, Progress for Children, 2012 derived from 2010 estimates
- Country data: UNAIDS 2009 estimates



Two populations-



Perinatally infected youth, pHIVa

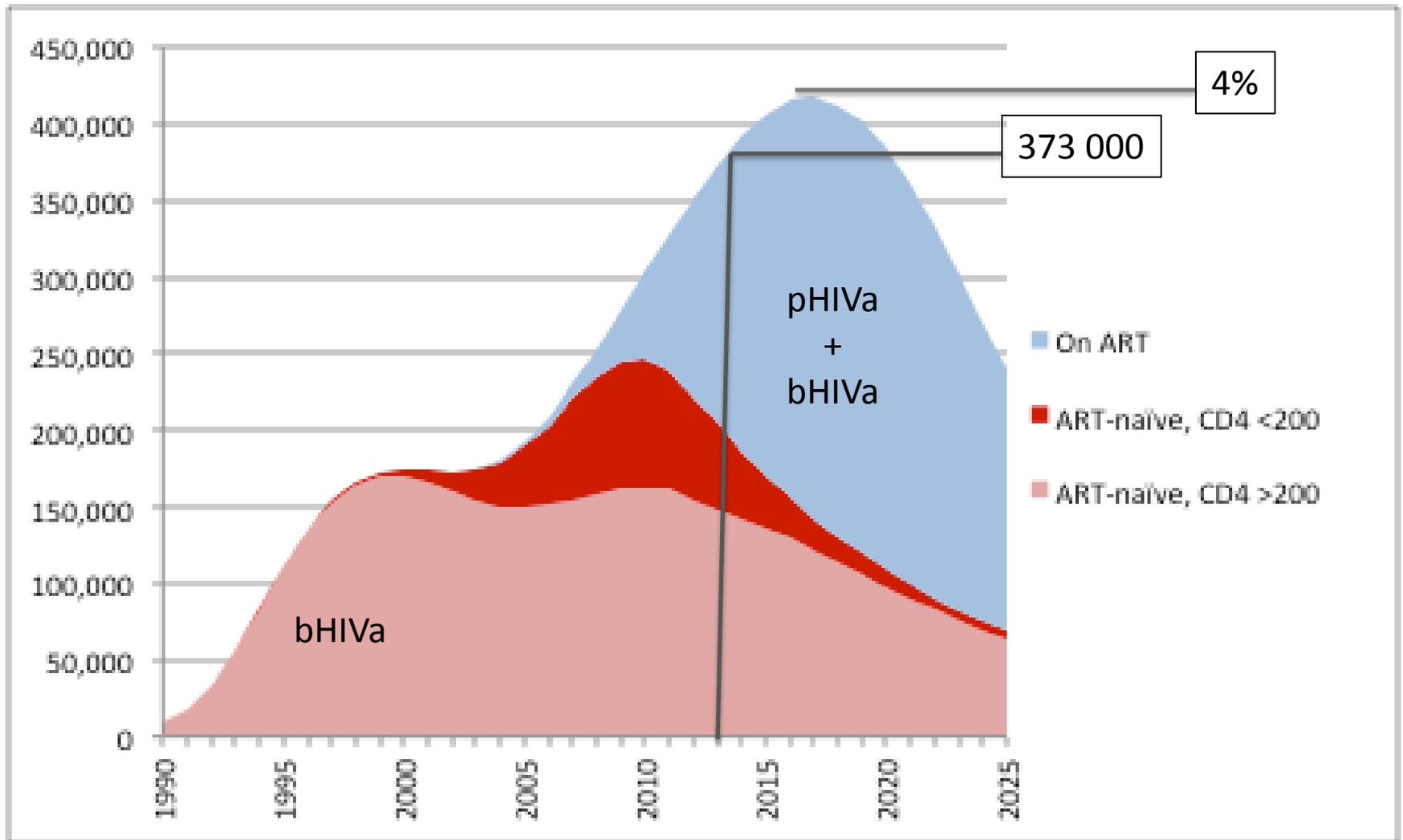
- F=M
- Younger
- Developmental stunting
- >treatment experienced
- Unaware of status
- Transitioned ex Paediatric Care
- Transition into Adult Care

Sexual and IDU Transmission, bHIVa

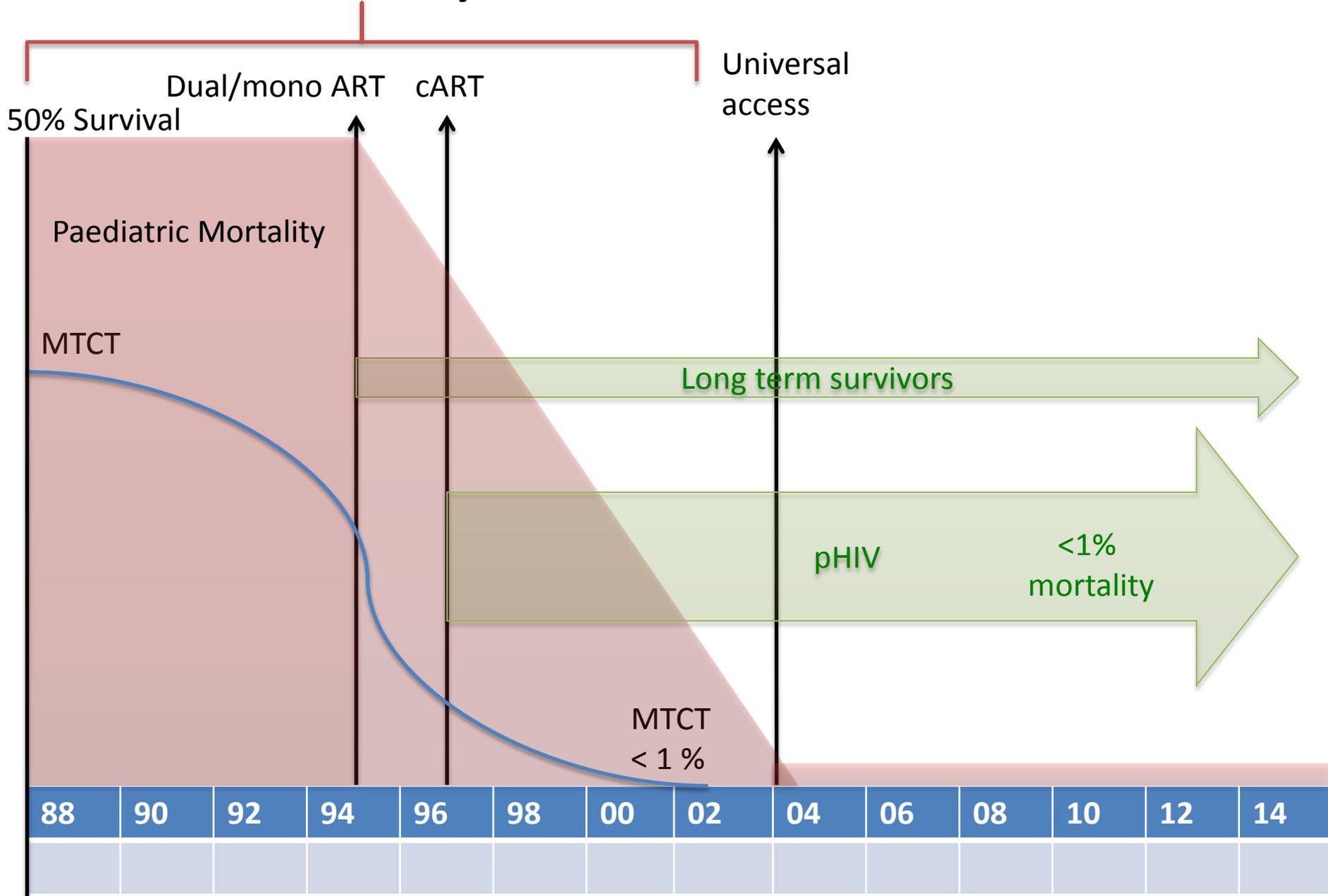
- F > M in Africa
- M>F elsewhere
- Older
- Treatment naïve
- Aware of status
- Transition into adult care

Adolescents (10-19yo) living with HIV: South Africa.

Leigh Johnson 2013



Our 11-24 year olds : 1989-2002

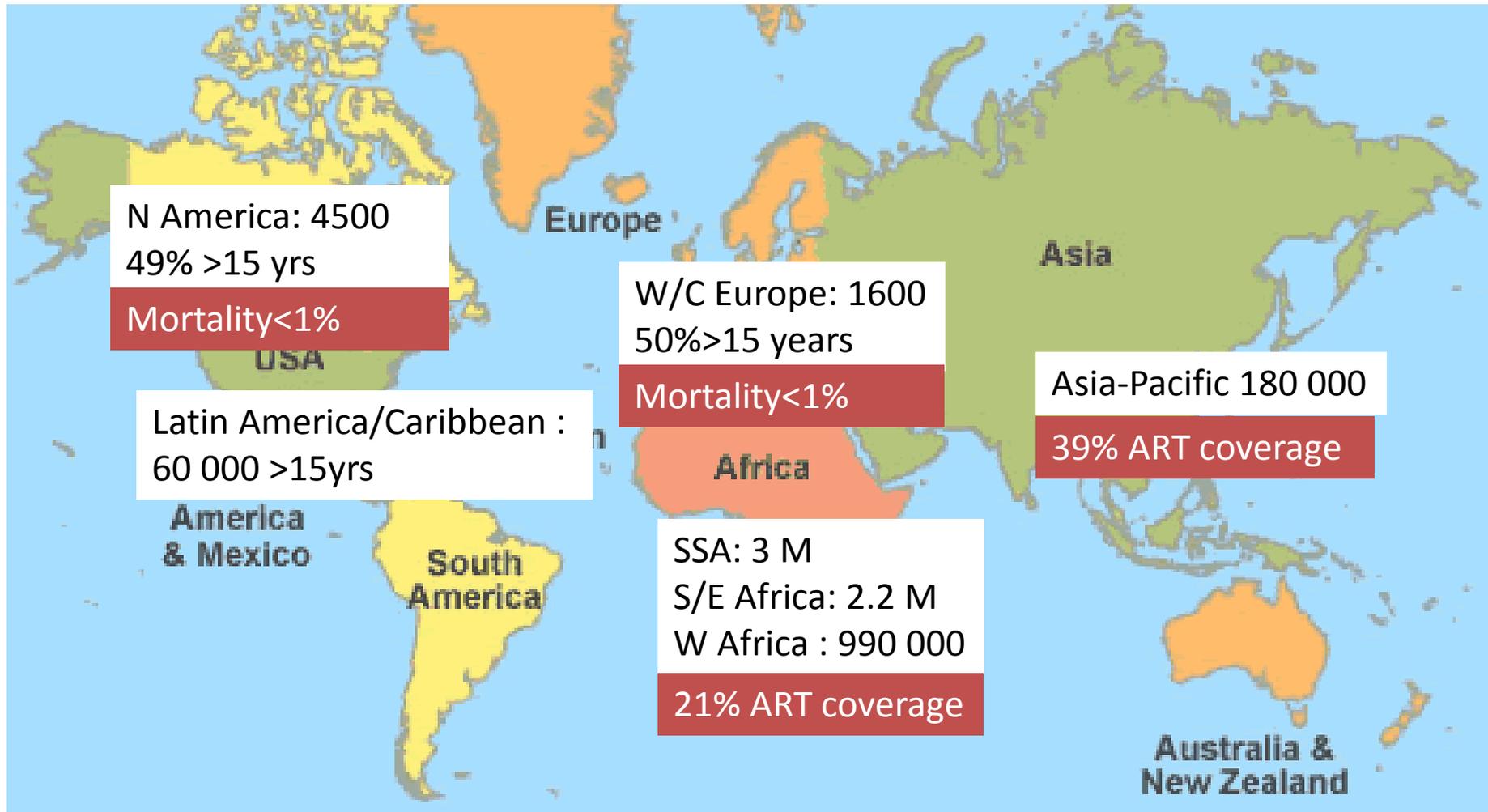


The paediatric HIV legacy



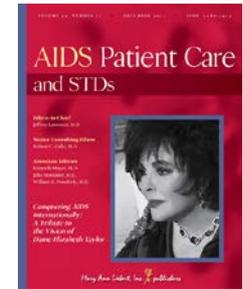
- In resource rich settings:
 - ART experienced (mean > 10 years)
 - Suboptimal regimens before (mono-dual-)
 - PHACS cohort :
 - 10-20% cART as first regimen
 - Mean exposure: 7 antiviral agents
- In resource-limited settings:
 - Present later
 - More cART at initiation (delay in access)
 - But this is changing with new guidelines and universal access.

Burden of HIV infection: children <15 yrs



The Paediatric legacy for Adult services:

Collaborative HIV Paediatric Study cohort
(CHIPS)(UK and Ireland- 1996-2007)



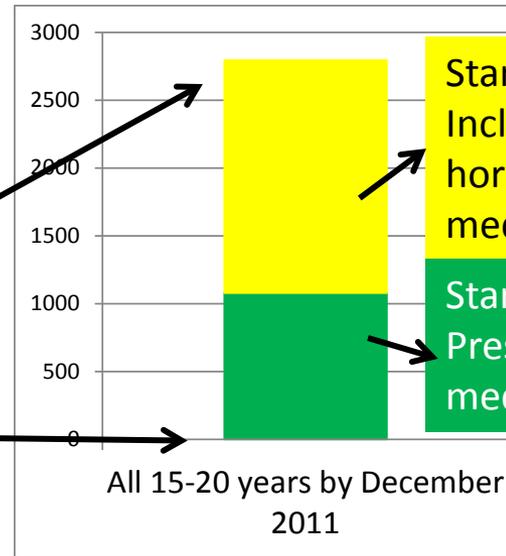
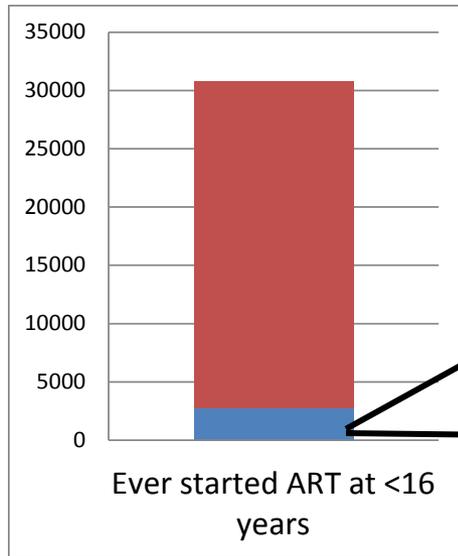
654 perinatally infected (76% Black African)

- 64% on ART (mean 10 years)
- CD4 < 200 : 27.2%
- 518 on ART:
 - 47% triple class experienced
 - 78% virally suppressed





Adolescents in care in leDEA Southern Africa – December 2011



Started ART at ≥12 years of age
Includes perinatally & horizontally infected;
median time on ART **28 months**

Started ART at <12 years of age
Presumed perinatal infection
median time on ART **65 months**

Characteristics at last visit

Median BMI-for-age z-score (IQR)	-0.72 (-1.61 to 0.08)
Median CD4 (IQR)	513 (320 - 711)
CD4 <200 (%)	11%
Viral load >400 at last visit (%)	39%

The Young and the Resistant

Canada: 45 youth transferred to adult services

- 38/45 resistance testing:
 - 73% resistance to single drug
 - 31.6% resistant to 3 classes

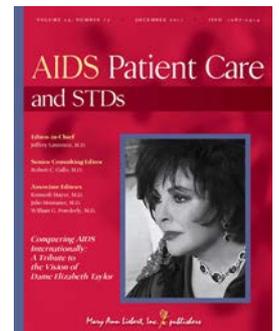
Van der Linden D, et al J Paed Inf Dis Soc 2012



CHIPS Cohort : 166 resistance assays

52% Dual class resistance
12% Triple class resistance

Foster C, et al AIDS Patient Care and STDs 2009



Hanan-Crusaid Clinic, CT : 78 children on 2nd line,
20% failed -TAMS : 62% ; PR : 50% in those on full dose Rtvr

Orrell C, et al Ped IDJ 2013



There is a need for

HEALTH CARE TRANSITION
from child to adult
services....

That is safe and effective

Multiple position papers...

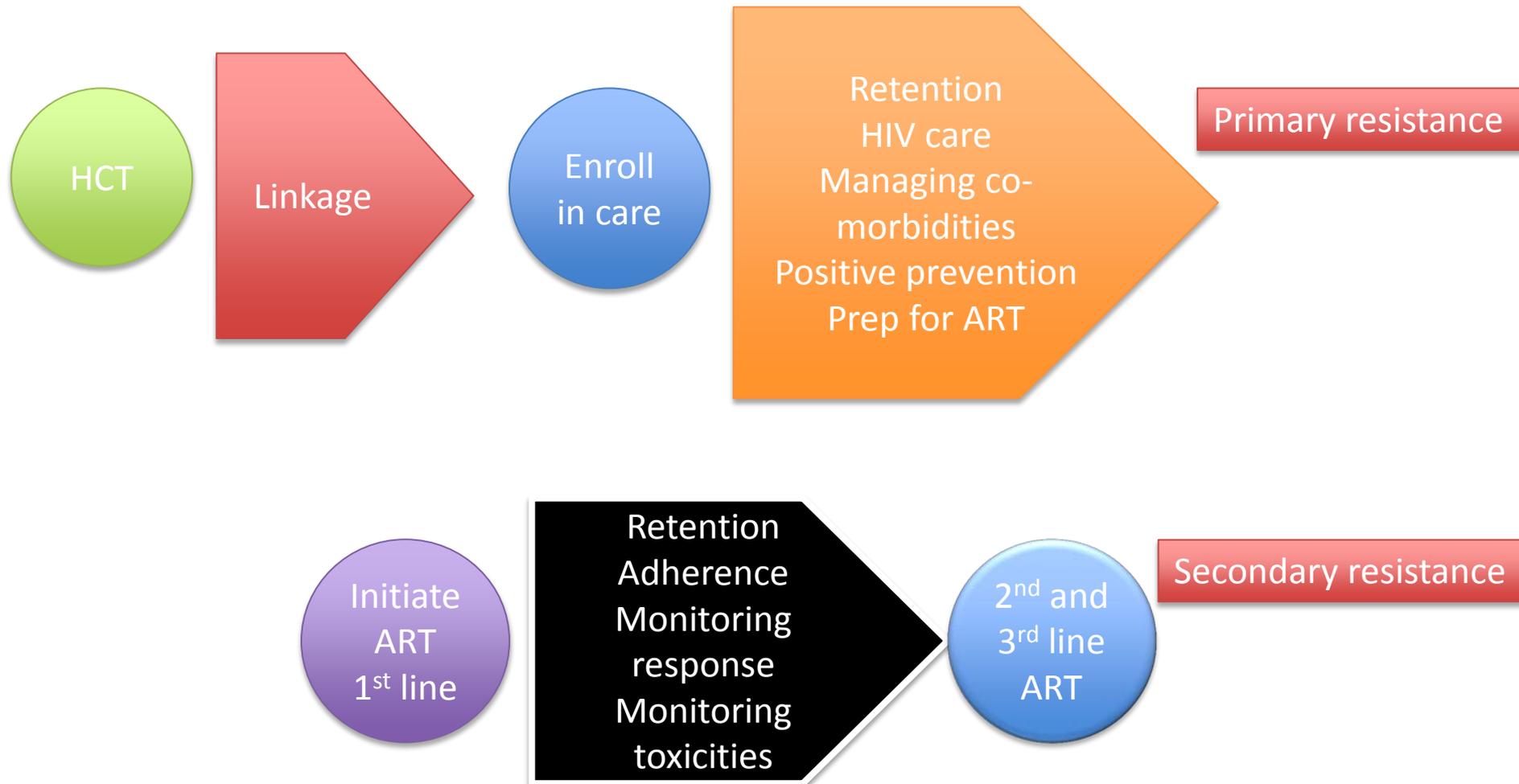
All agree:

Continuous, coordinated, culturally appropriate, compassionate, collaborative, family centred.....

Evidence based.....

Little data on best practices and even fewer on outcomes.

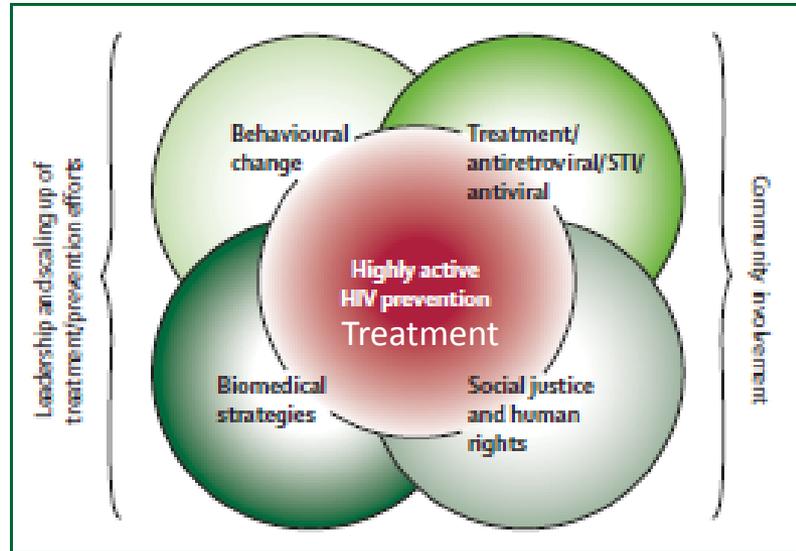
Opportunities for translational research



Research gaps : Testing and LTC

- Reaching “unawares” for testing- risk perception and regular HIV testing
- Recognition of the need/desire for treatment even when asymptomatic.
- Linkage to care beyond HIV testing
 - point of care diagnostics and strategies
 - Cell phone, cash incentives, navigators, etc
- to identify and “follow” newly diagnosed individuals into care (identification systems).

HIV Counselling and Testing



Prevention Cascade



Treatment Cascade



Research gaps : HIV care

- Retention in HIV care
 - indentifiers
- **Quality of HIV Care**
- Positive prevention
- Safer conception
- Fertility intent and safer contraception
- Management of co-morbidities
- Discordant couples ? Identification and management
- Special needs of key populations
 - Health care sensitization, incarcerated LTC.

Research gaps :

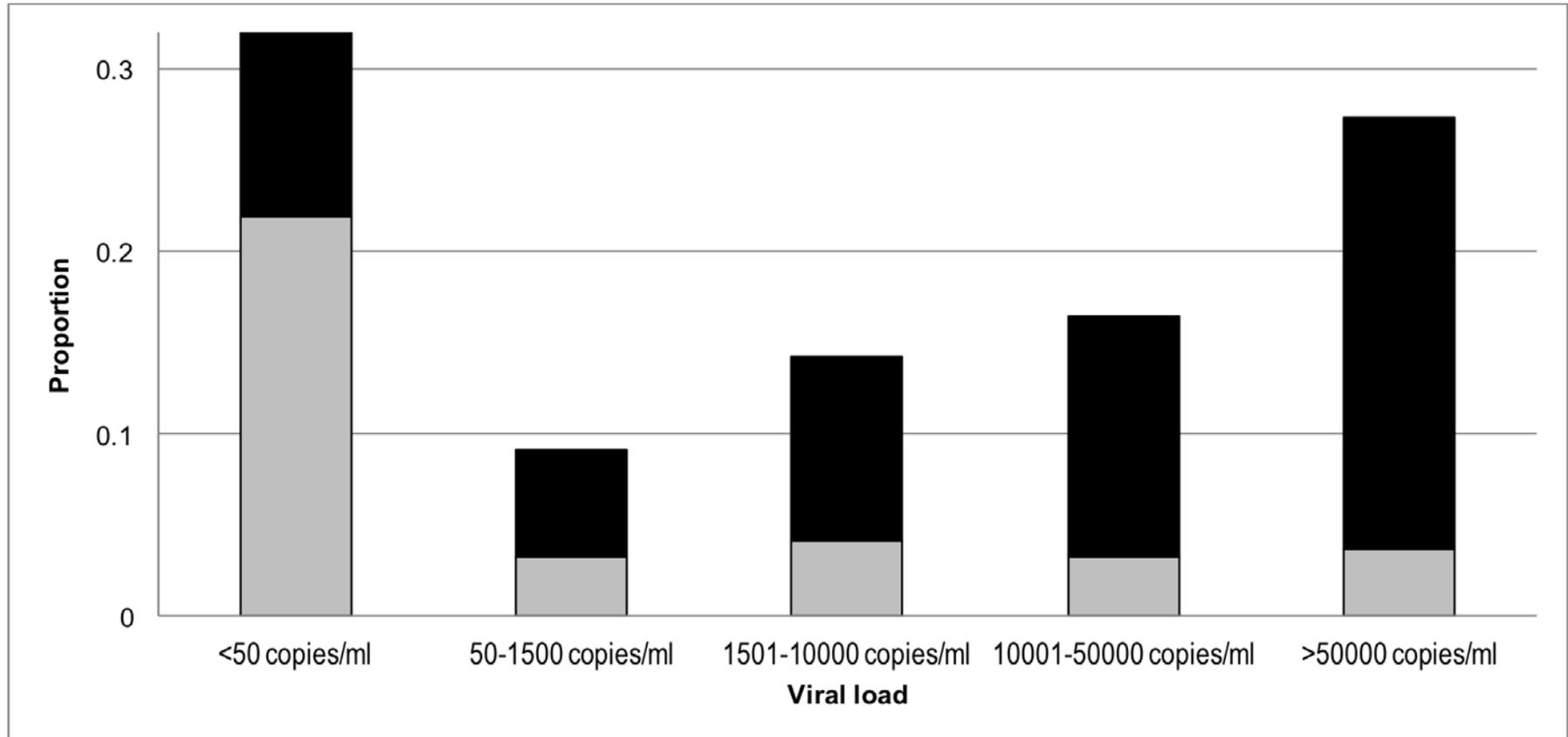
- ART optimisation
- Reduction of time at low CD4
- Reduction of uncontrolled viraemia
- Monitoring ART performance
 - Frequency, platform
- Monitoring ART toxicity
 - Frequency, key population (TDF in adolescents)
- Task shifting
- Resistance surveillance
- Community well being and viral load

Community CD4 and VL survey

CD4 count	Total (N=219)			On ART (N=79)			Not yet on ART (N=140)		
	N	%	95% CI	N	%	95% CI	N	%	95% CI
≤200 cells/μl	33	13.0	0.09; 0.18	10	11.5	0.06; 0.20	22	13.6	0.09; 19.8
201-350 cells/μl	72	28.5	0.23; 0.34	26	29.9	0.21; 0.41	44	27.2	0.20; 0.35
351-500 cells/μl	60	23.7	0.19; 0.29	19	21.8	0.14; 0.32	41	25.3	0.19; 0.33
>500 cells/μl	88	34.8	0.29; 0.41	32	36.8	0.27; 0.48	55	34.0	0.27; 0.42

VL in community

Figure 1: Viral load distribution by self-reported treatment status



Viral loads of individuals receiving ART are displayed in grey, viral loads of individuals not yet receiving ART are displayed in black.

Research gaps : on ART programs

- Retention in care
 - Logistics, motivations.
 - Personal identifiers
- Adherence to drug
 - Monitoring performance
 - Strategies/interventions
 - Early identification
- Recognition and Management of failure
 - Viral load test frequency, platform, resistance testing
- Task shifting
- Decentralisation of care
- Integration into TB, ANC, PHC, oncology services
- ART program performance
- Resistance surveillance

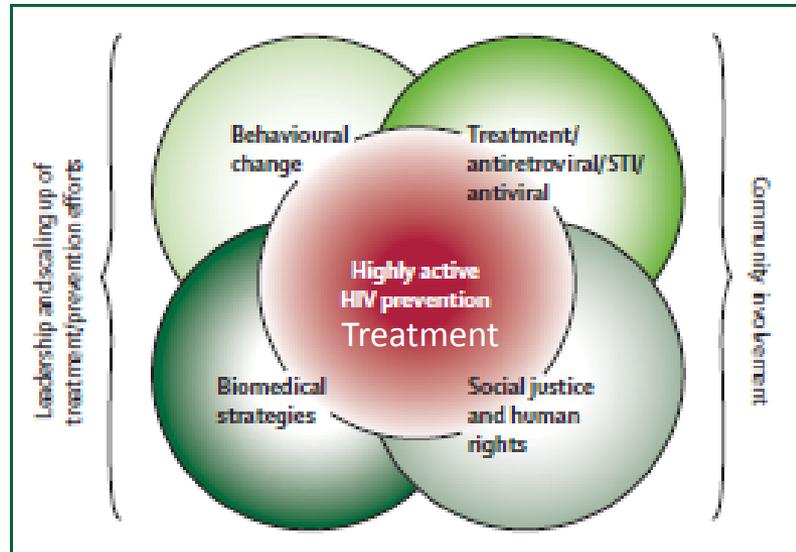
Research gaps: long term follow up and after first line....

- Management of failure: 1st and 2nd line
- Retention in care
 - Cycling, defaulters, return to care, migration
- Long term toxicities
- Ongoing morbidities
 - Cancer, metabolic, age related.
- Aging on ART
- Adherence fatigue
- Facility decongestion, task shifting
- Community based drug distribution
- Community well being and viral load

Novel research gaps

- Integrating the double helix of the prevention and Treatment cascades

HIV Counselling and Testing



Prevention Cascade



Treatment Cascade



Novel research gaps

- Integrating the double helix of the prevention and Treatment cascades
- Reducing viral reservoirs
- Working towards viral cure.....
 - Visconti, Berlin, Mississippi- patients
 - Kampala, Dakar, Chang Mai patients??

Thanks

- My Gurus : Graeme Meintjies, Marc Mendelsohn, Francois Venter, Richard Kaplan, Catherine Orrell, Robin Wood
- WHO 2013 ART Guidelines
- Carlie Williams, IDEAA, others whose slides were borrowed
- Add my thanks to Europe and EDCTP- in this time of Economic downturn when There us still SO much to do!!

