Can we improve first-line and second-line ART?

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Slide acknowledgements: Beatriz Grinsztejn, Joe Eron, WHO, UNAIDS, Clinical Care Options, CHAI, Celicia Serenata, Charley Flexner and others

Disclosures…

- Part of optimisation collaborations – grants to improve testing, new drug regimens, linkage to care
- Pharma (including drug donations for studies) and managed care

Beatriz Grinsztejn

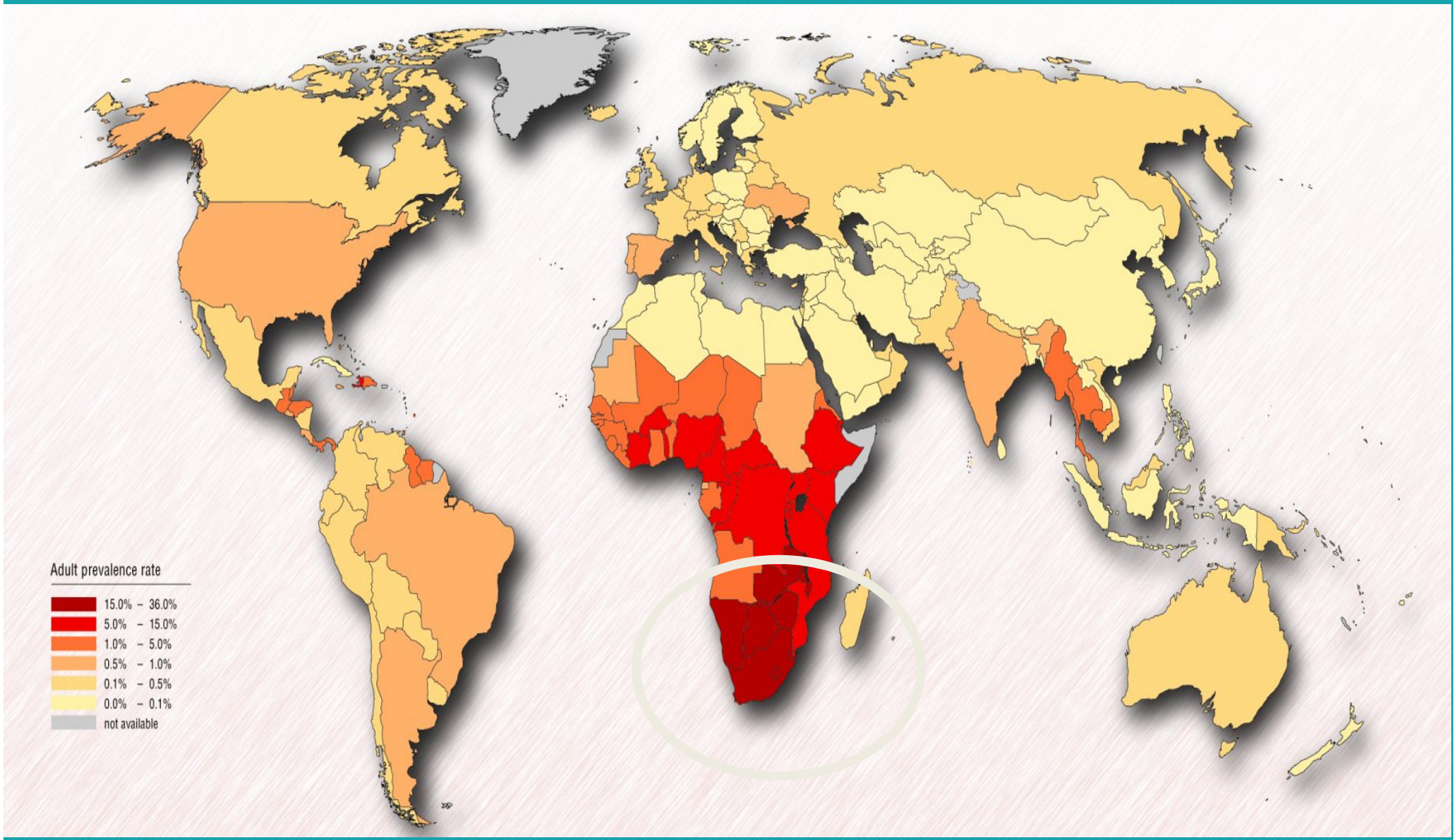
SOUTH AFRICANS AND AMERICANS IN PARTNERSHIP TO FIGHT HIV/AIDS
PEPFAR

USAID
FROM THE AMERICAN PEOPLE

UNITAID

MRC SOUTH AFRICA
SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

HIV and South Africa



South Africa: Why is it important? (and why is it different)?

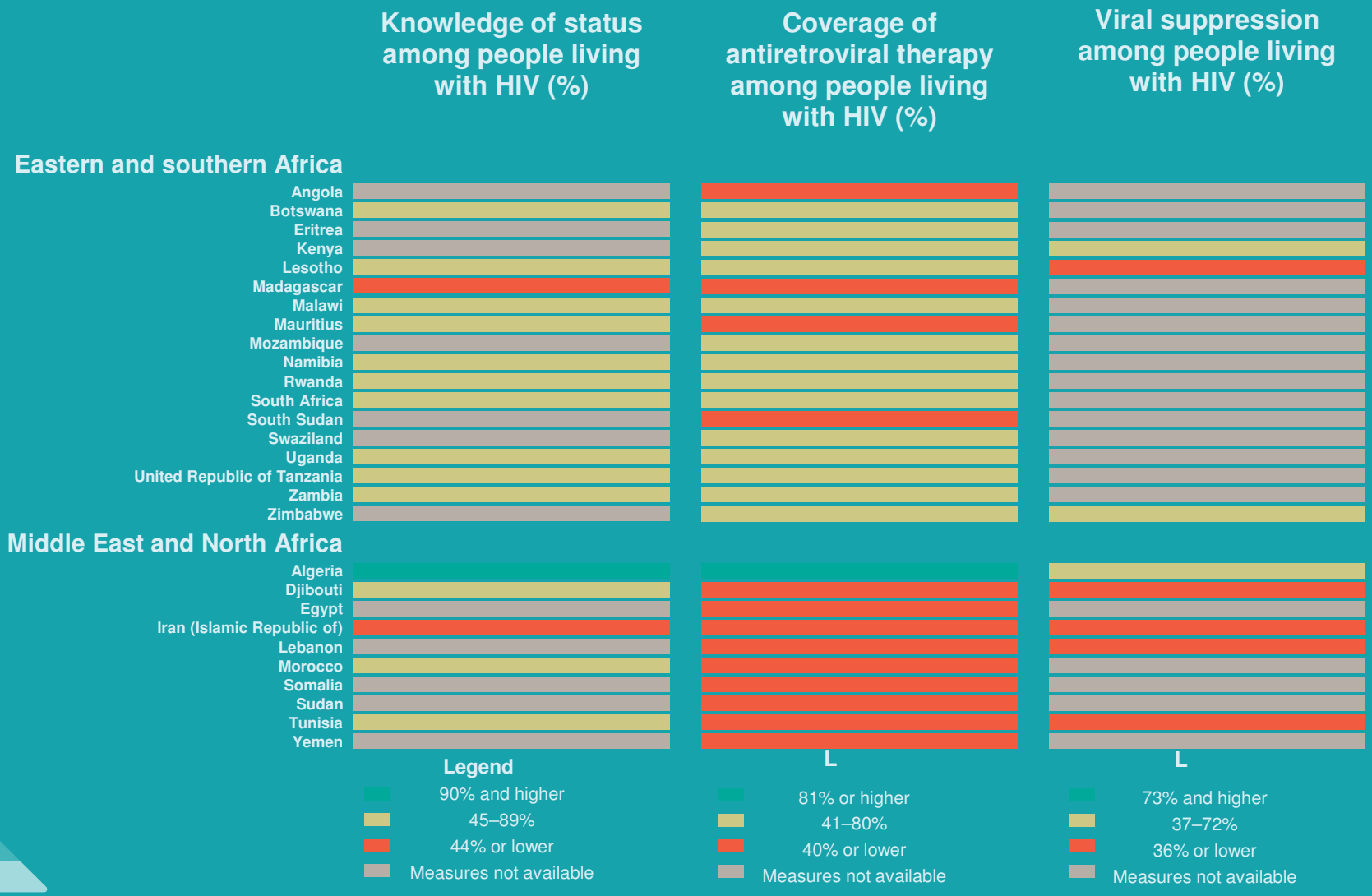
- Size of the country – 51 million people (2011), 5th largest in Africa
- Wealth – highest GDP in Africa, best infrastructure
- Size of HIV and TB problem

SA snapshot

- 3.4 million 1st line ($110/year)
- 145 000 2nd line ($350/year)
- 700 3rd line (roughly $1500/year, depends on regimen ($2000 if DRV/DTG/ETR))
- Bill 2014/2015: $350 million
- Sept 2016: Test and treat – theoretically doubling numbers
- SA drives the global market [SA=PEPFAR=Global Fund by ART volume]

Country status

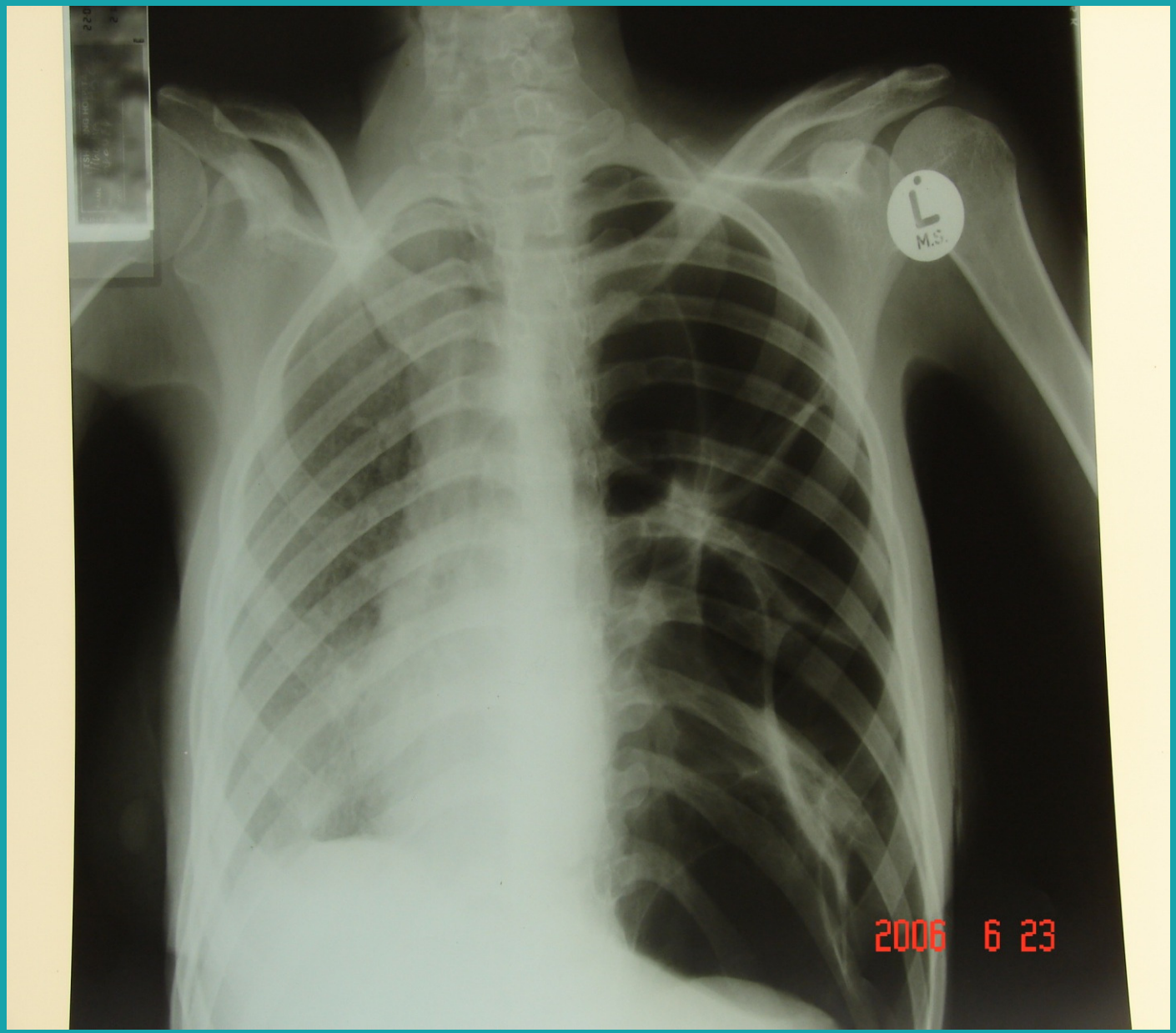
Progress toward the 90–90–90 targets, all ages, by country, 2015



For countries not shown, both measures are not available or under review.

Source: 2016 Global AIDS Response Progress Reporting; UNAIDS 2016 estimates.

TB…



Thanks: Braamie Variava

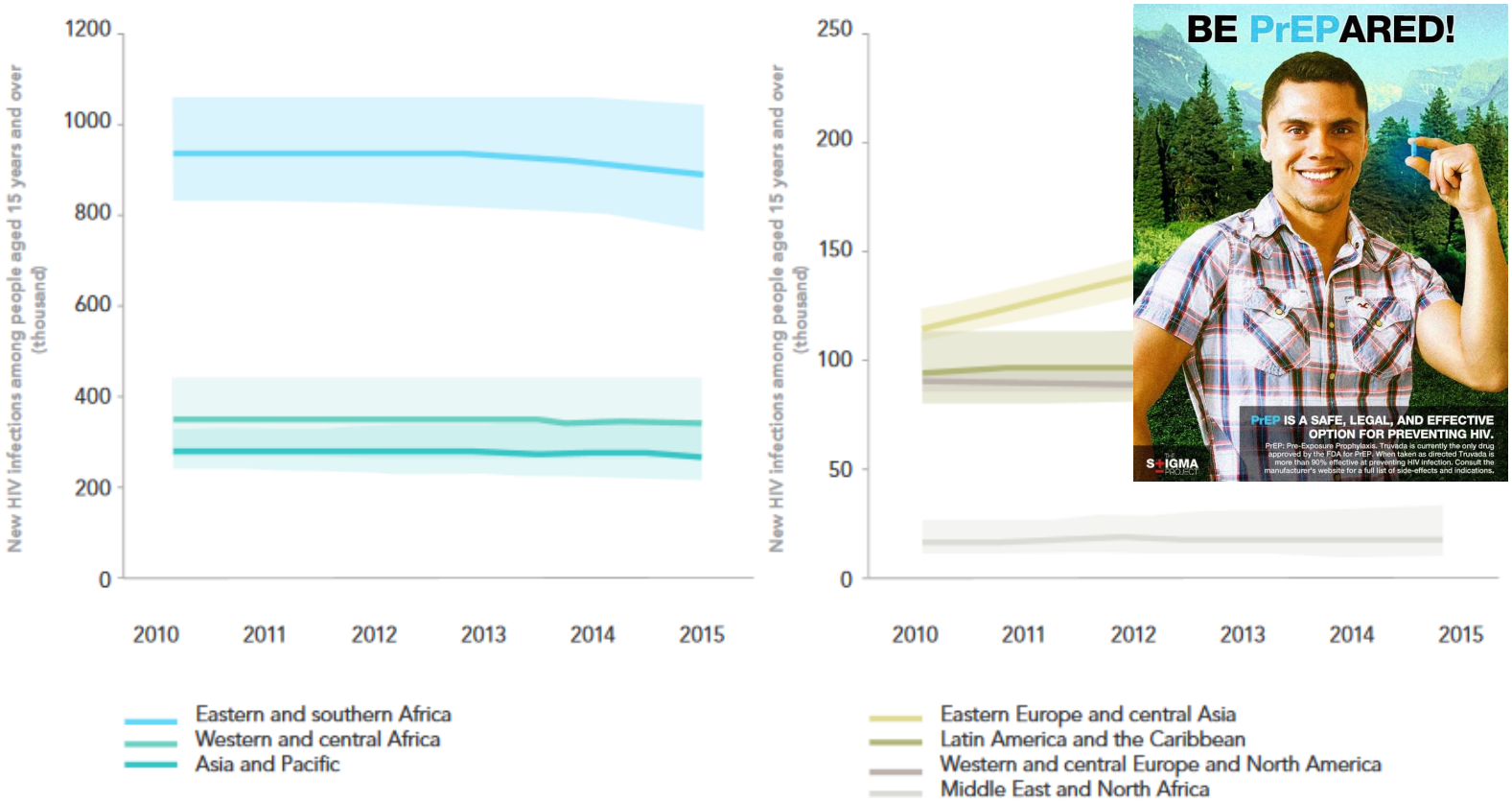
Mortality and causes of death in South Africa, 2013: Findings from death notification

Table 4.3: Number and percentage distribution of deaths by main groups of causes of death, 2013*

No.	Main groups of underlying causes of death (based on ICD-10)	Number	Percentage
1	Certain infectious and parasitic diseases (A00-B99)*	103 708	22,6
2	Neoplasms (C00-D48)	38 034	8,3
3	Diseases of the blood and immune mechanism (D50-D89)	10 357	2,3
4	Endocrine, nutritional and metabolic diseases (E00-E90)	28 974	6,3
5	Mental and behavioural disorders (F00-F99)	1 787	0,4
6	Diseases of the nervous system (G00-G99)	10 998	2,4
7	Diseases of the eye and adnexa (H00-H59)	18	0,0
8	Diseases of the ear and mastoid process (H60-H95)	58	0,0
9	Diseases of the circulatory system (I00-I99)	76 468	16,7

Incidence still remains stubbornly high…

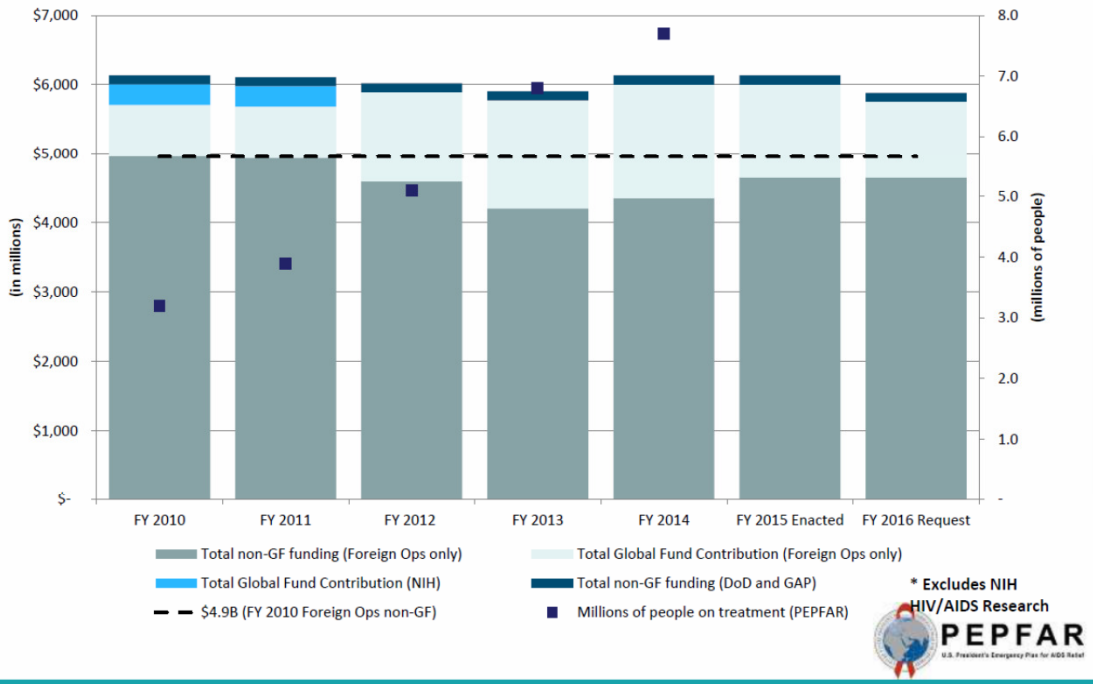
New HIV infections among people aged 15 years and over, by region, 2010–2015



Source: UNAIDS 2016 estimates.

HIV/AIDS Funding trends:

FY 2010 Enacted - FY2016 President's Request

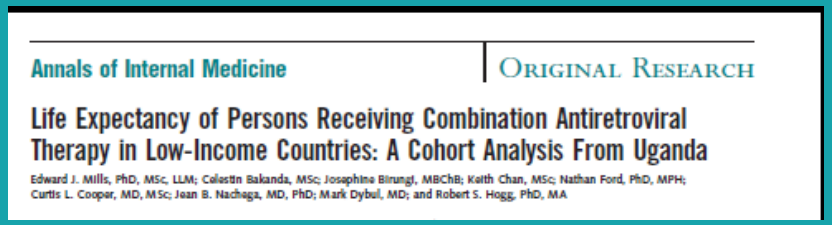


Before and after initiation of ARV therapy!

Before and after initiation of ARV therapy!

Thapelo

- Uganda/ US/ UK – ‘higher life expectancy that matched populations



Annals of Internal Medicine | ORIGINAL RESEARCH

Life Expectancy of Persons Receiving Combination Antiretroviral Therapy in Low-Income Countries: A Cohort Analysis From Uganda

Edward J. Mills, PhD, MSc, LLM; Celestin Bakanda, MSc; Josephine Birungi, MBChB; Keith Chan, MSc; Nathan Ford, PhD, MPH; Curtis L. Cooper, MD, MSc; Jean B. Nachega, MD, PhD; Mark Dybul, MD; and Robert S. Hogg, PhD, MA

1. Expect a normal life expectancy:
May et al. AIDS 2014

- UK CHIC: 21 388 people started ART 2000-2010

Annals of Internal Medicine | EDITORIAL

Life Expectancy in Africa: Back to the Future?

From 1950 to 1990, life expectancy in sub-Saharan Af- uals challenged global trade rules and regulations, ulti-

If 35 year old man started ART:

	life expectancy		
CD4	Baseline	1 year ART	5 years ART
<200	71		& VL>50 54
200-349	78	78	
>350	77	81	& VL<50 80
General population	78		

Conclusion: If diagnosed, in care and on effective ART: life expectancy is normal

Great information to give to people newly diagnosed and encourage good adherence

210 | 16 August 2011 | Annals of Internal Medicine | Volume 155 • Number 4

Thanks: Julie Fox, Guys

When to start debate solved in 2015: thanks to safer drugs

Table 1: Severe morbidity in TEMPRANO study at 30 months

	% events	n	Rate / 100 PY	adj HR	p
WHO ART	11.4%	111	4.9		
Early ART	6.6%	64	2.8	0.56	0.0002
No IPT	10.7%	104	4.7		
IPT	7.2%	71	3.0	0.65	0.005

Table 1. Primary endpoint and its components in open DSMB report (15 May 2015)

	Early ART (arm A)		Deferred ART (arm B)		Hazard Ratio
	N	rate/100 PY	N	rate/100 PY	Arm A/B (95% CI)
AIDS, serious non-AIDS, or death (primary)	41	0.60	86	1.25	0.47 (0.32 to 0.68)
AIDS or AIDS death	14	0.20	46	0.66	0.30 (0.17 to 0.55)
Serious non-AIDS or non-AIDS death	28	0.41	41	0.59	0.67 0.42 to 1.09) NS**

* PY = patient years, ** NS = non significant

Thanks: Simon Collins

Is sex safe? HPTN 052

And confirmed in Partners study

HR = 0.37 or 96.3% reduction in transmission

Major Guidelines for Initiation of Antiretroviral Therapy

Guideline	AIDS or HIV-Related Symptoms	CD4+ Cell Count < 200/mm³	CD4+ Cell Count 200-350/mm³	CD4+ Cell Count 350-500/mm³	CD4+ Cell Count > 500 cells/mm³
DHHS-USA, 2014	Yes	Yes	Yes	Yes[1]	Yes[2]
International AIDS Society-USA, 2014	Yes	Yes	Yes	Yes[1]	Yes[2]
Brazil, 2014	Yes	Yes	Yes	Yes[1]	Yes[2]
European AIDS Clinical Society, 2014	Yes	Yes	Yes	Consider[3]	Consider[3]
British HIV Association, 2014	Yes	Yes	Yes	Consider[3]	Defer[5]
World Health Organization, 2014	Yes	Yes	Yes	Yes[4]	Defer[5]

(1) Strong strength recommendation based on observational data (A-II)
(2) Moderate strength recommendation based on expert opinion (B-III).
(3) But treat all symptomatic patients, HIV+ pregnant women, HBV co-infection, HCV co-infection, HIVAN, HIV related neurocognitive disorders, ITP, non-AIDS cancers (including HPV) and serodiscordant couples
(4) Individuals with CD4 < 350 as a priority.
(5) But treat all HIV+ pregnant women ,TB co-infection with active disease and HBV co-infection with severe liver disease, and serodiscordant couples

SA HIV Clinicians Society 2014	Yes	Yes	Yes	Defer	Defer
SA Government , 2015	Yes	Yes	Yes	Yes	Defer

Do we have a resistance problem?

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THE LANCET Infectious Diseases

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Articles

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

*The TenoRes Study Group**

Summary

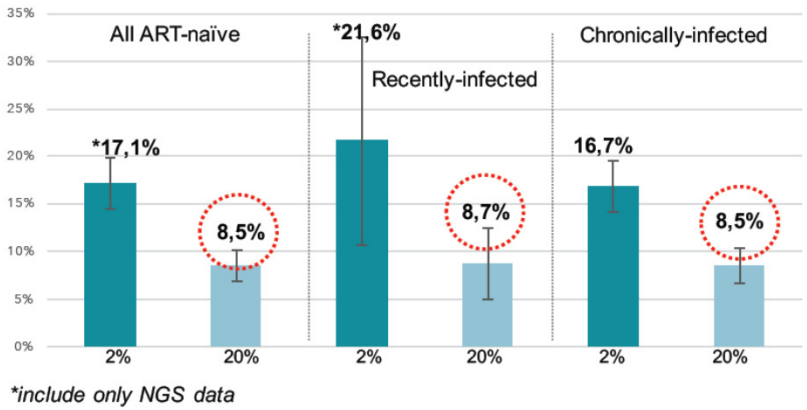
Background Antiretroviral therapy (ART) is crucial for controlling HIV-1 infection through wide-scale treatment as

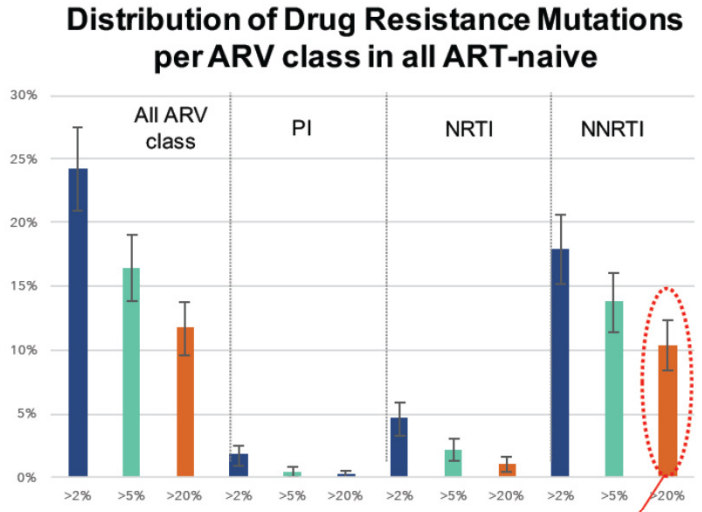
Lancet Infect Dis 2016

- “Researchers at University College London said the study could mean that, after a year of treatment, up to 15% of people in sub-Saharan Africa and 10% in South Africa were resistant to the drug.”

Resistance IS a problem….

Pretreatment Drug Resistance in TASP trial



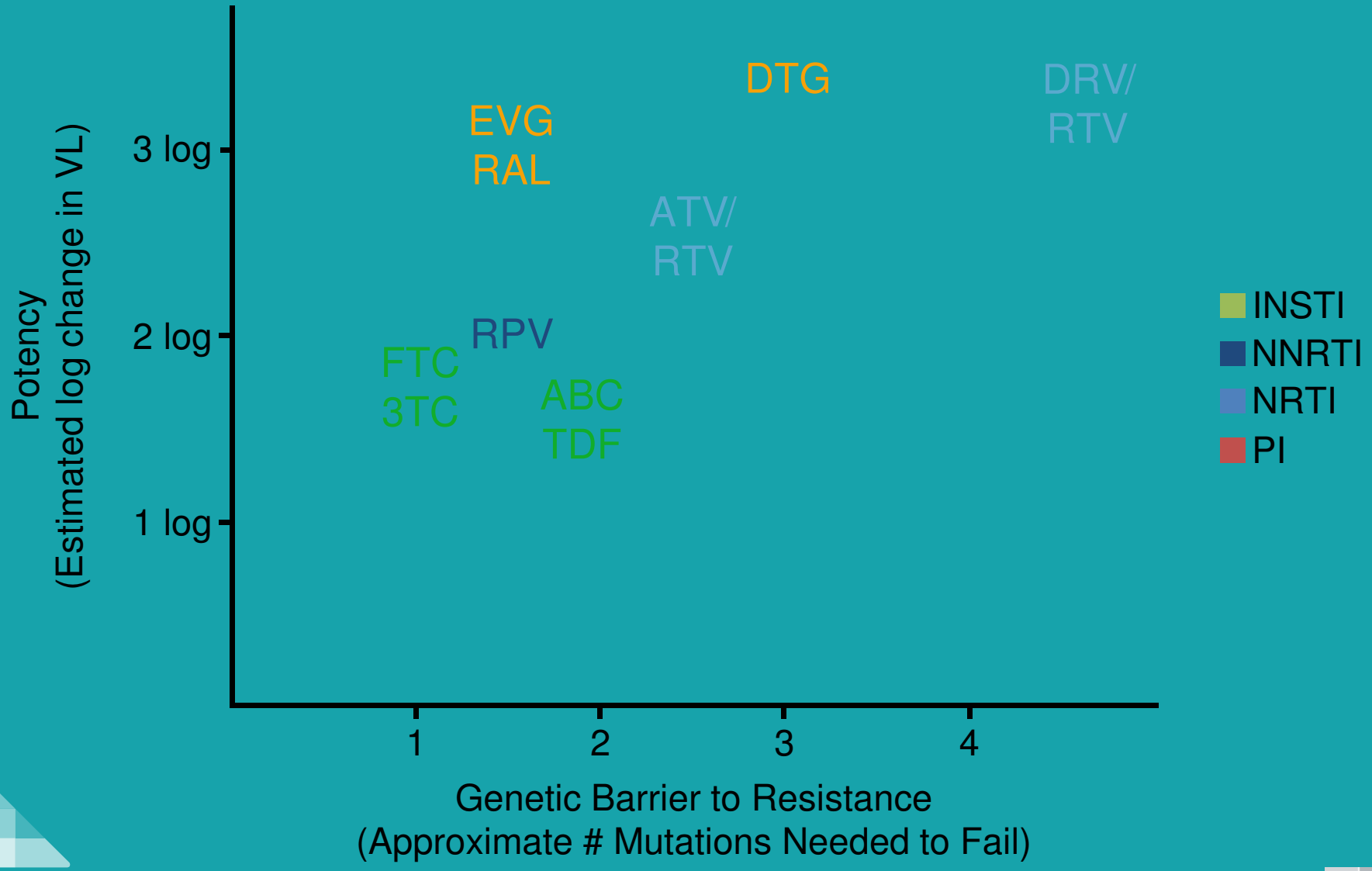


- PDR prevalence ~9% in both recently- and chronically infected participants
- 2x more low-level variants detected with NGS
- NNRTI mostly compromised by PDR, but NRTIs are still active

Mostly driven by K103N

Derache A et al. Croi 2017 – abstract# 43

Genetic Barrier to Resistance for Specific ARVs

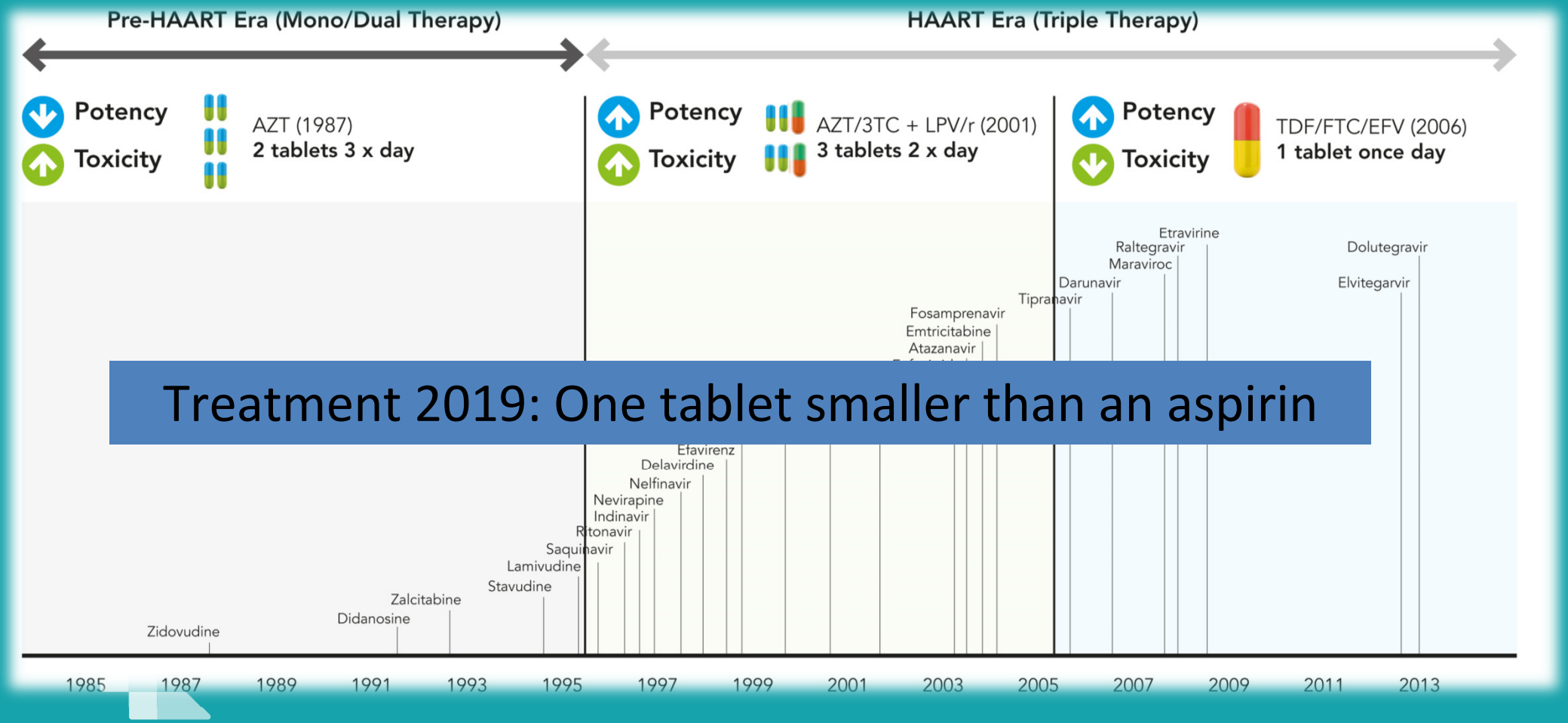


Clutter DS, et al. Infect Genet Evol. 2016;[Epub ahead of print].

Slide credit: clinicaloptions.com

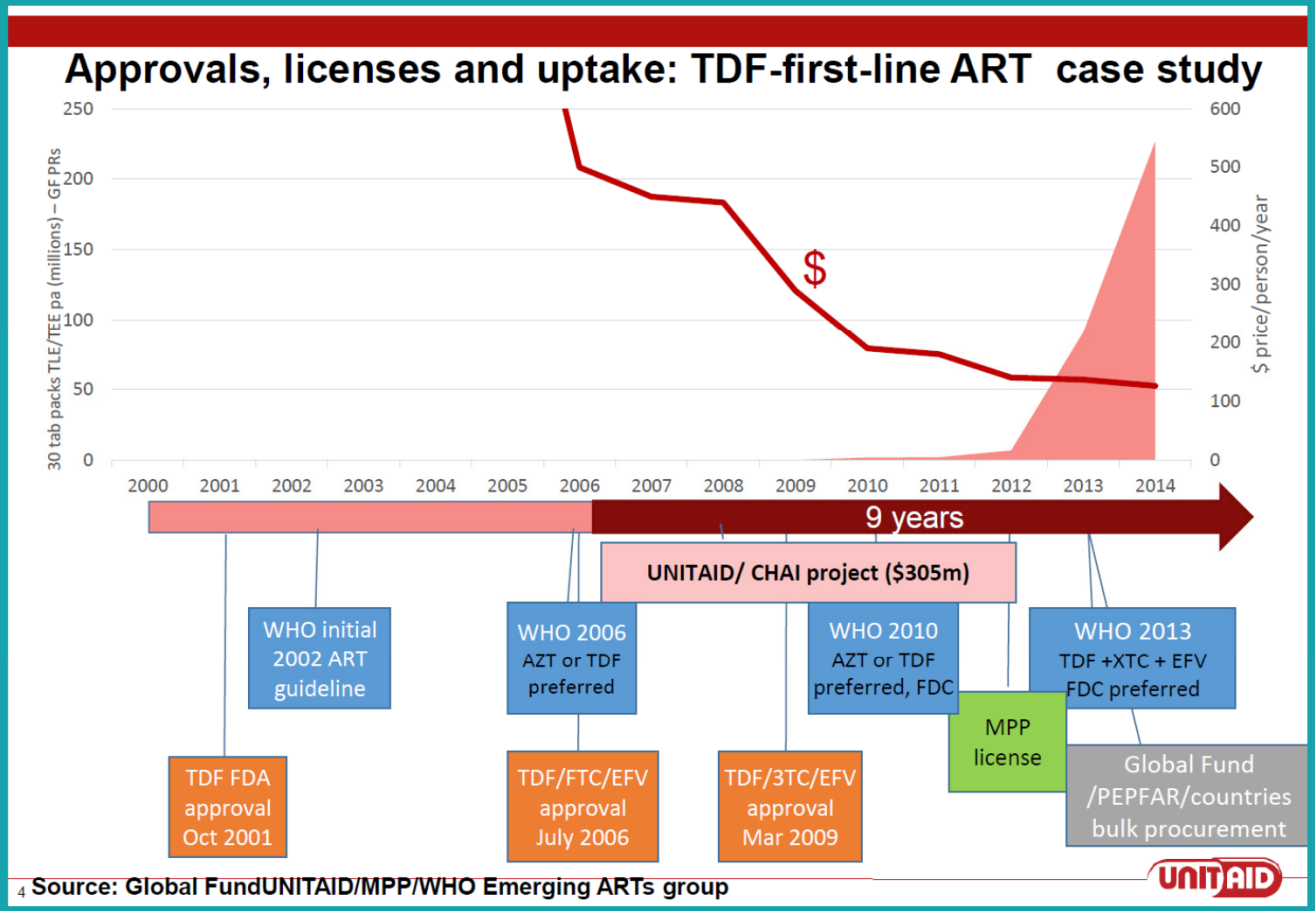
Drug optimization

Science evolved: smarter and better HIV treatment options are now available

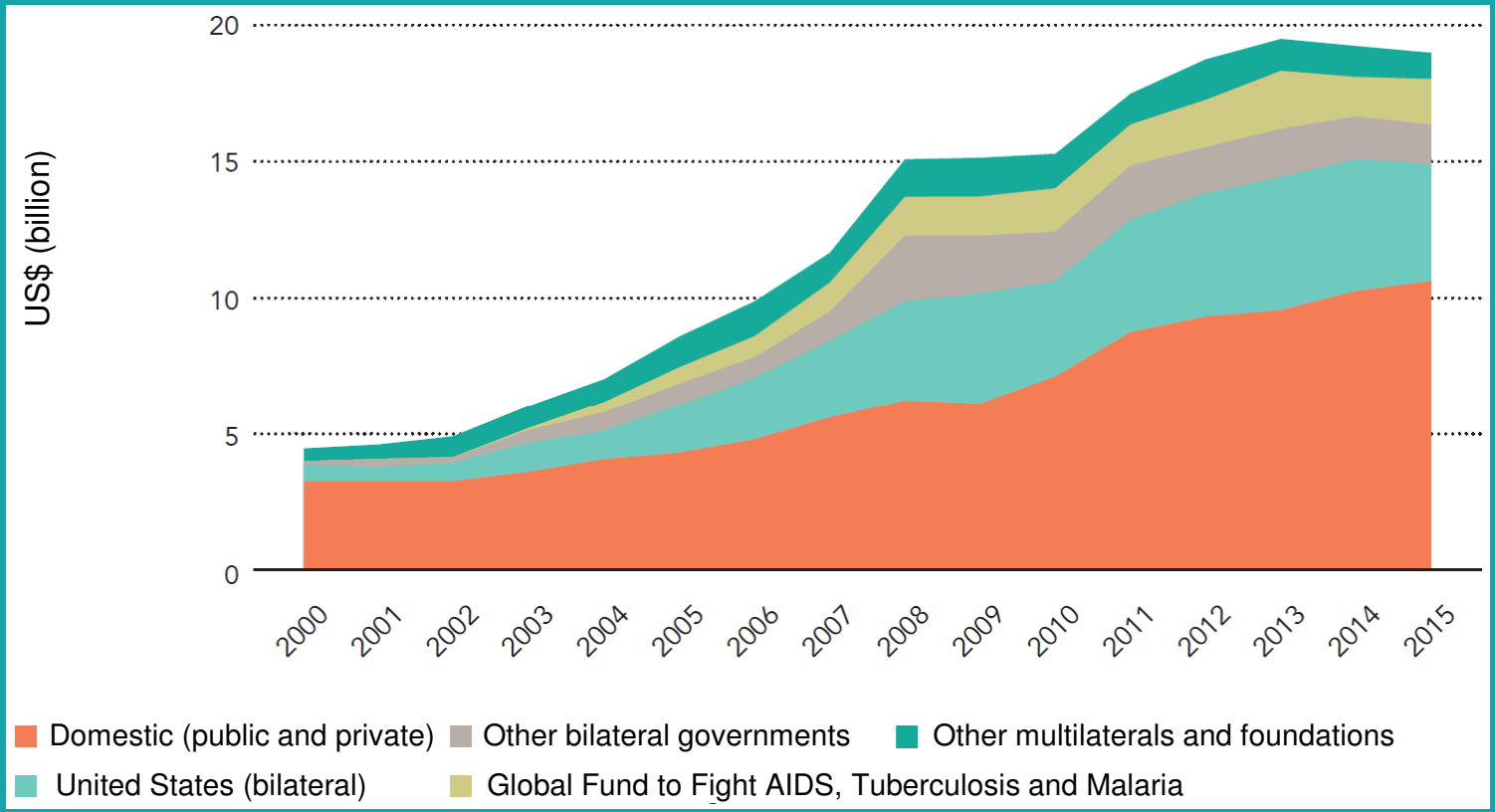


Treatment 2019: One tablet smaller than an aspirin

We need things to go faster

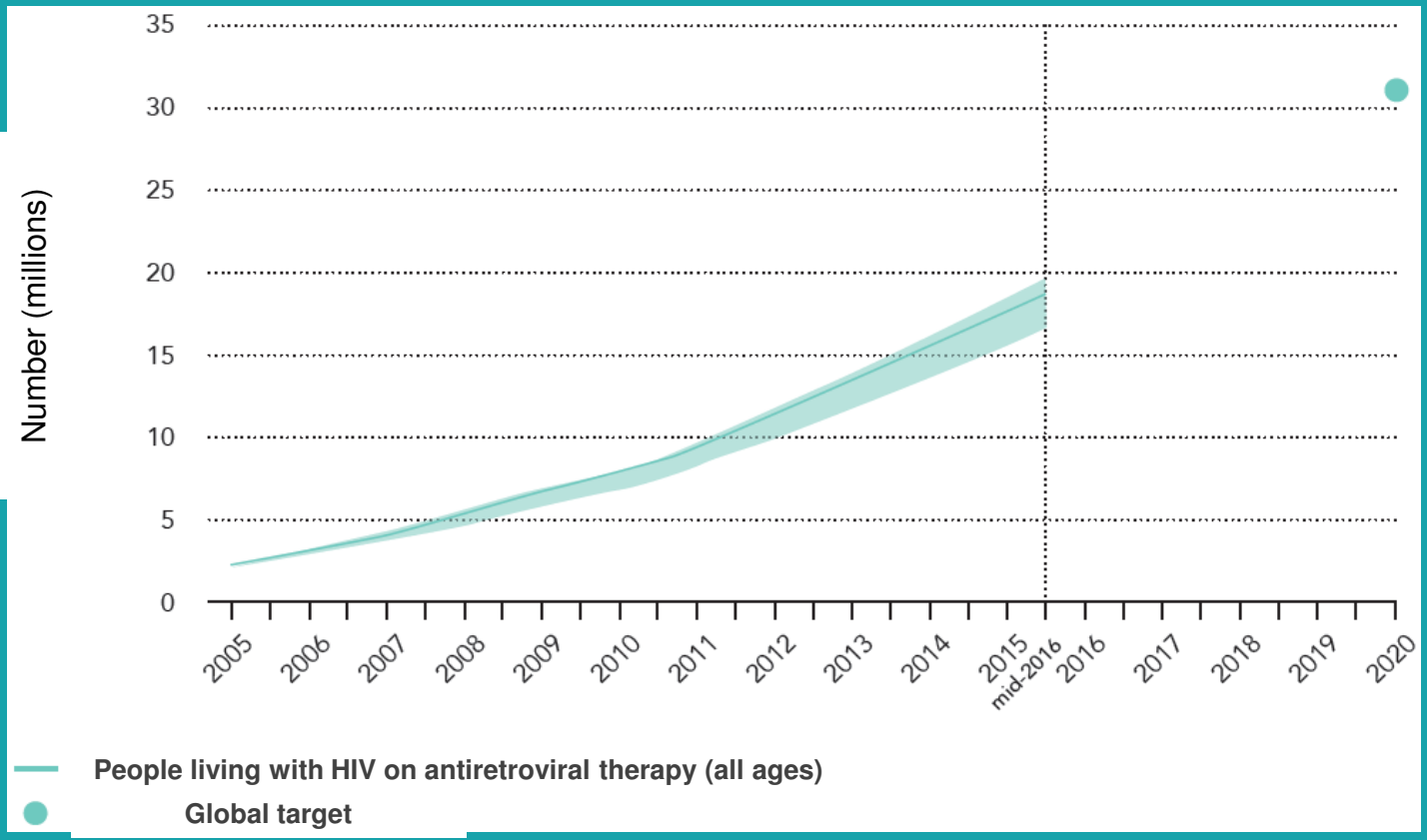


Investments in the AIDS responses of low- and middle-income countries, by source of funding, 2000–2015



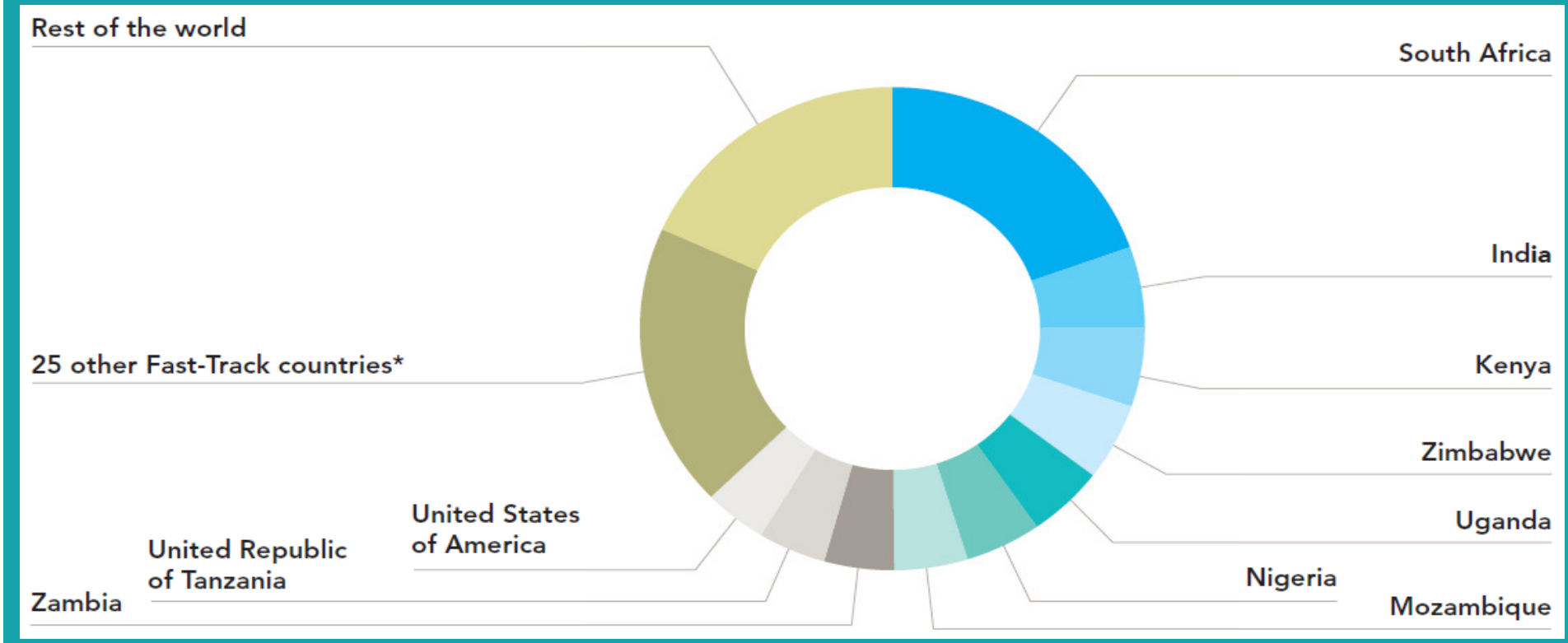
Source: UNAIDS estimates, June 2016 - UNAIDS-Kaiser Family Foundation. Financing the response to AIDS in low- and middle-income countries till 2015 - OECD CRS last accessed June 2016.

People living with HIV on antiretroviral therapy, all ages, global, 2010–July 2016



Source: Global AIDS Response Progress Reporting, 2016; UNAIDS 2016 estimates.

Distribution of antiretroviral therapy, by country, 2015

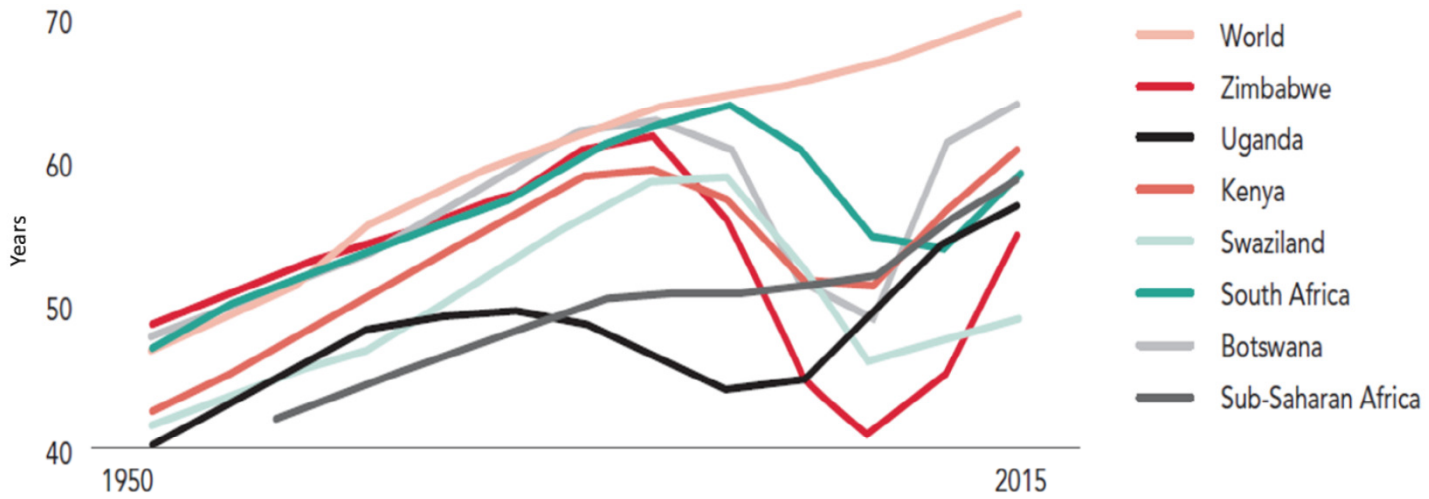


* The Fast-Track countries include the 10 displayed on this chart, plus Angola, Botswana, Brazil, Cameroon, Chad, China, Côte d'Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, Haiti, Indonesia, Iran (Islamic Republic of), Jamaica, Lesotho, Malawi, Mali, Myanmar, Namibia, Pakistan, South Sudan, Swaziland, Russian Federation, Ukraine and Viet Nam.

Sources: GARPR 2016; UNAIDS 2016 estimates

Impact of HIV response on life expectancy

Dramatic impact of HIV response on life expectancy, 1950-2015



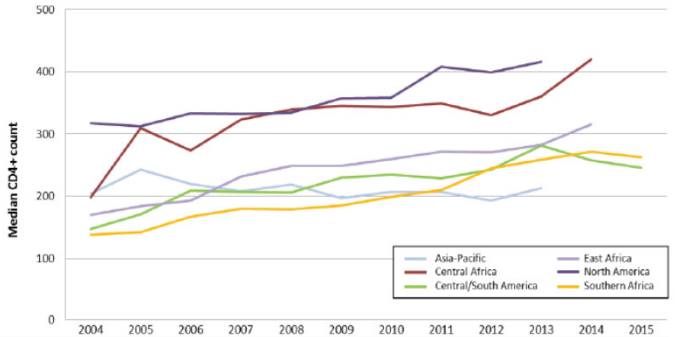
Source: United Nations Population Division, World Population Prospects, 2015 revision.

Global analysis of delays from eligibility to ART initiation among adults (2004-2015)

Median CD4 count at enrollment

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
N total	36,911	68,518	83,217	99,075	106,014	111,700	114,536	112,293	91,992	75,837	64,735	43,291
% missing enrollment CD4	28	25	26	25	24	23	23	26	31	39	43	53
Median CD4	167	167	183	199	198	201	217	228	254	266	280	263

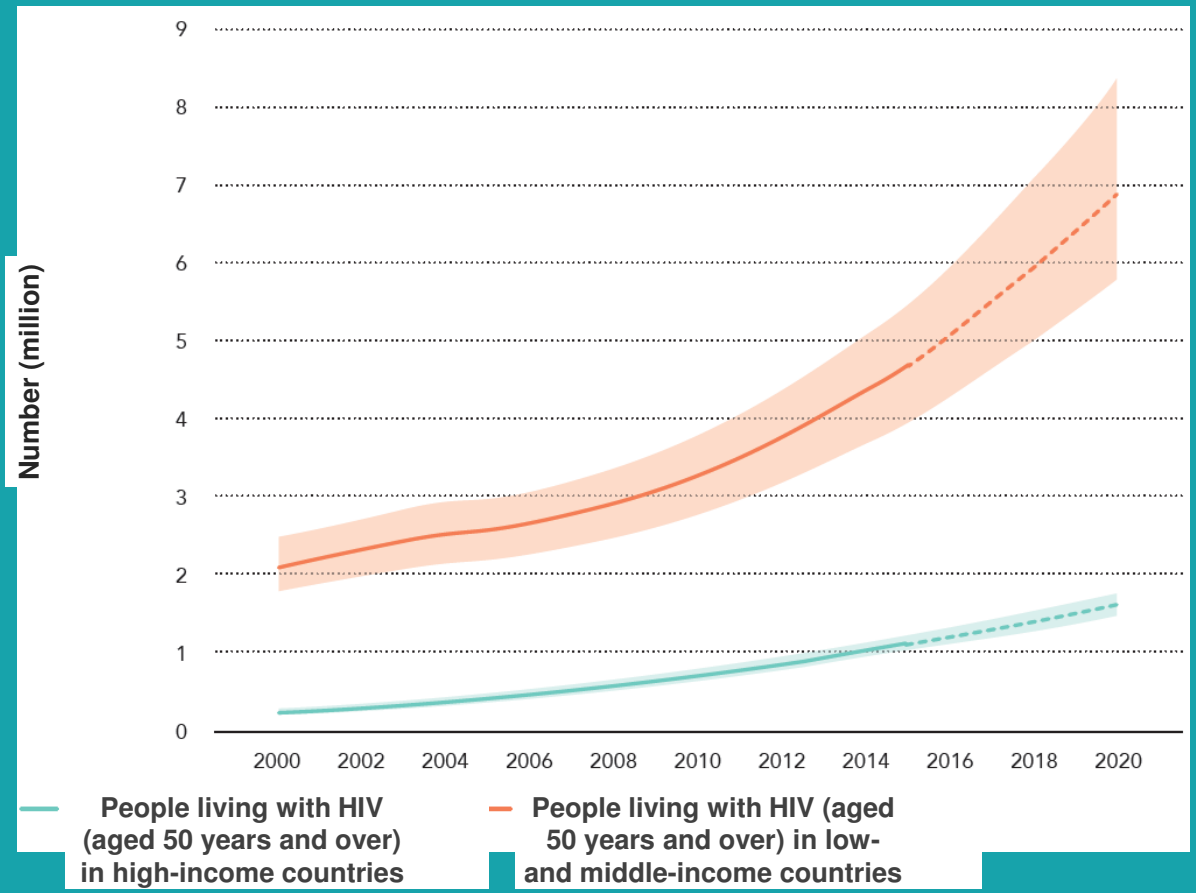
Median CD4 count at enrollment by region



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Overall N	36,911	68,518	83,217	99,075	106,014	111,700	114,536	112,293	91,992	75,837	64,415	42,601
% missing enrollment CD4	28	25	26	25	24	23	23	26	31	39	43	52

Courtesy of Olga Tymejczyk, on behalf of IeDEA. IeDEA-WHO Collaboration: Global analysis of delays from eligibility to antiretroviral treatment (ART) initiation among adults. Sep 2016.

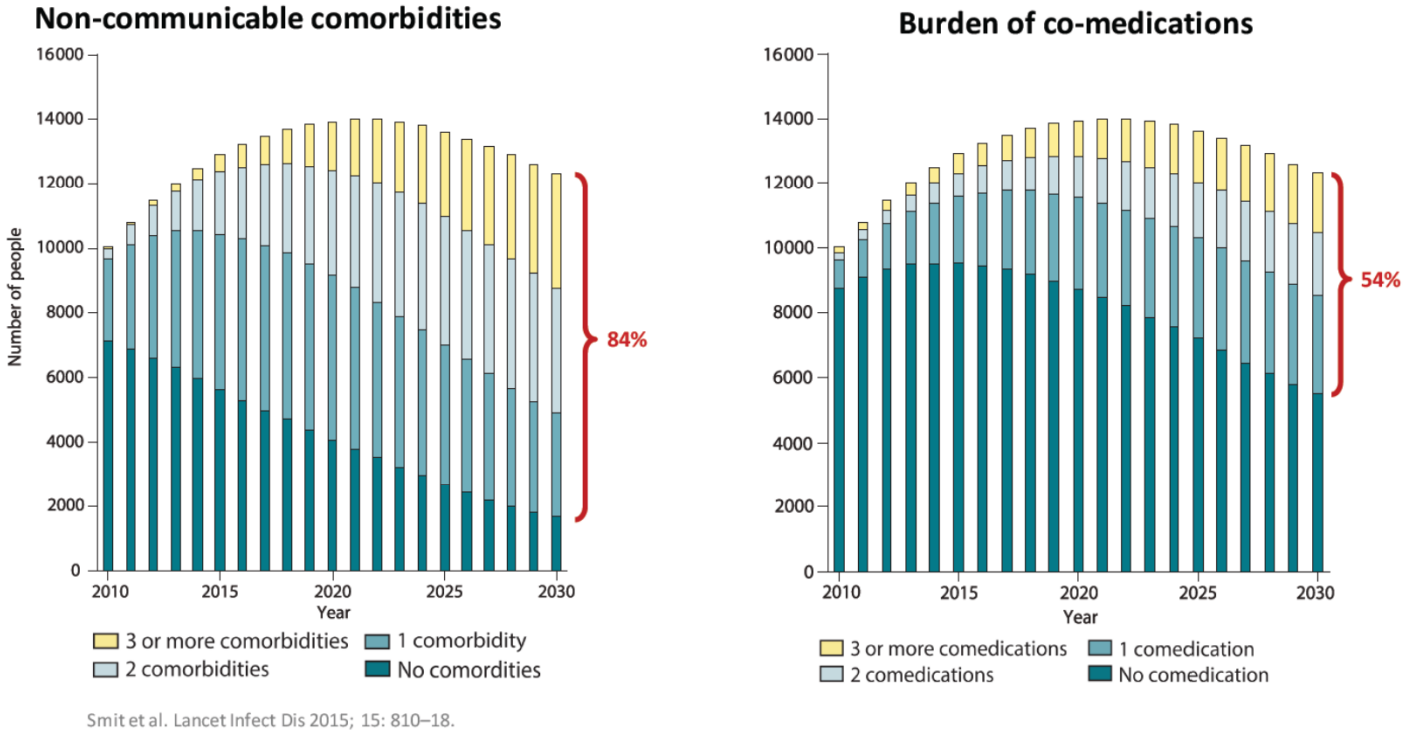
Number of people living with HIV (aged 50 years and over), high-income countries and low- and middle-income countries, 2000–2015 and projected to 2020



Source: UNAIDS 2016 estimates.

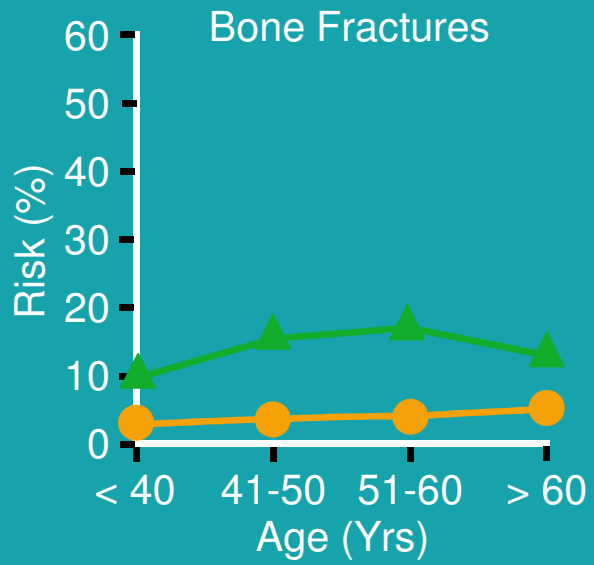
Note: Projections 2016–2020 are based on an assumption that scale up of antiretroviral treatment will reach 81% coverage of all people living with HIV by 2020. Country income classifications are from 2015.

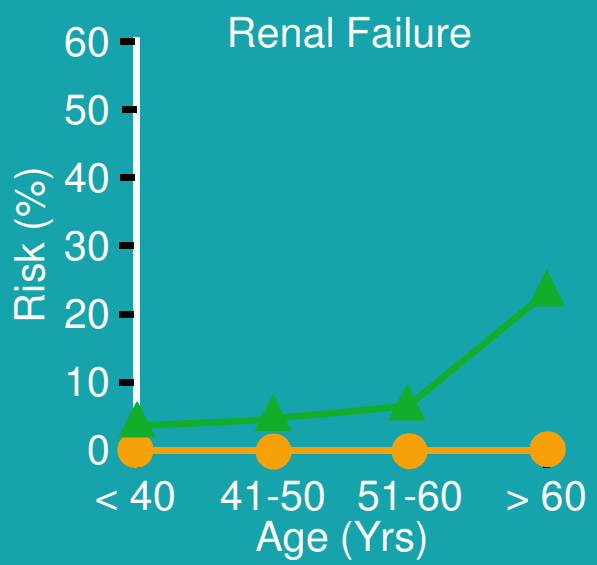
Aging with HIV infection-Athena Cohort

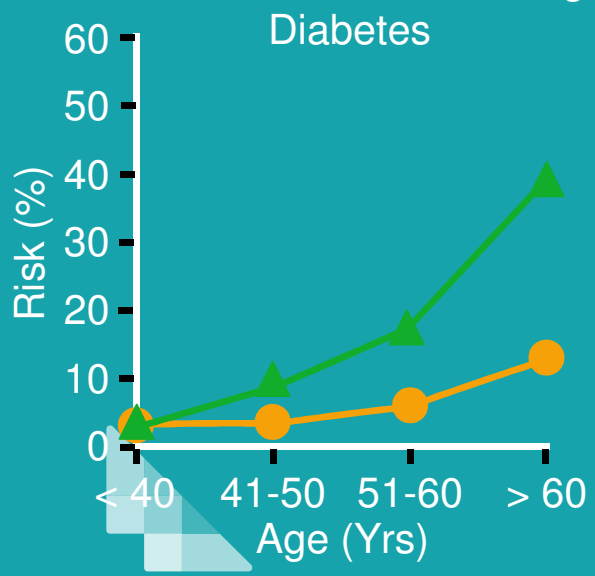


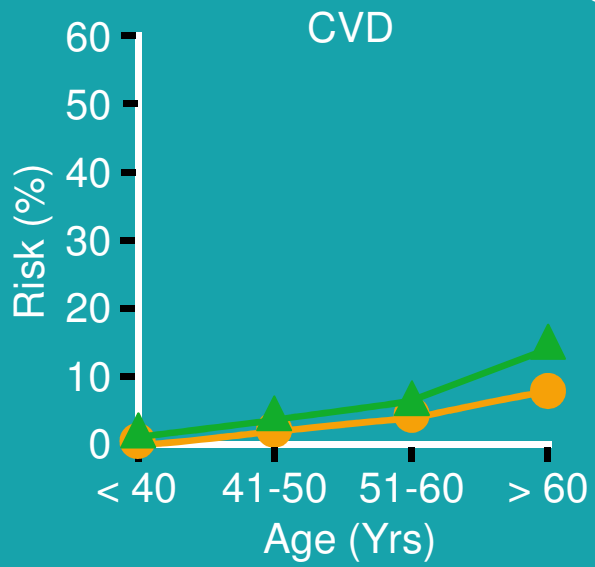
Smit et al. Lancet Infect Dis 2015; 15: 810–18.

HIV Pts More Likely to Experience Bone Fractures, CVD, Diabetes, Renal Failure





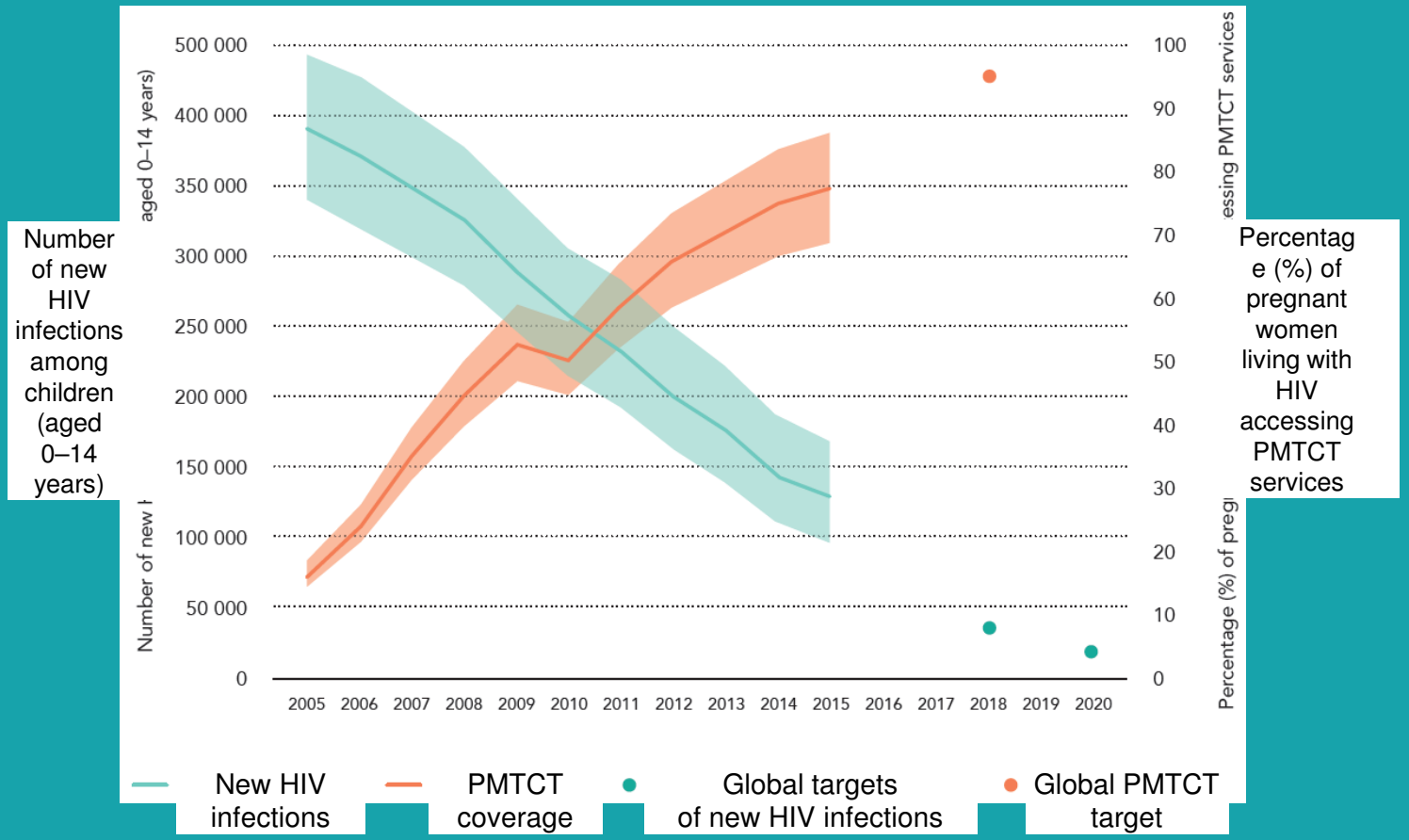




Guaraldi G, et al. Clinicoecon Outcomes Res. 2013;5:481-488.

Slide credit: clinicaloptions.com

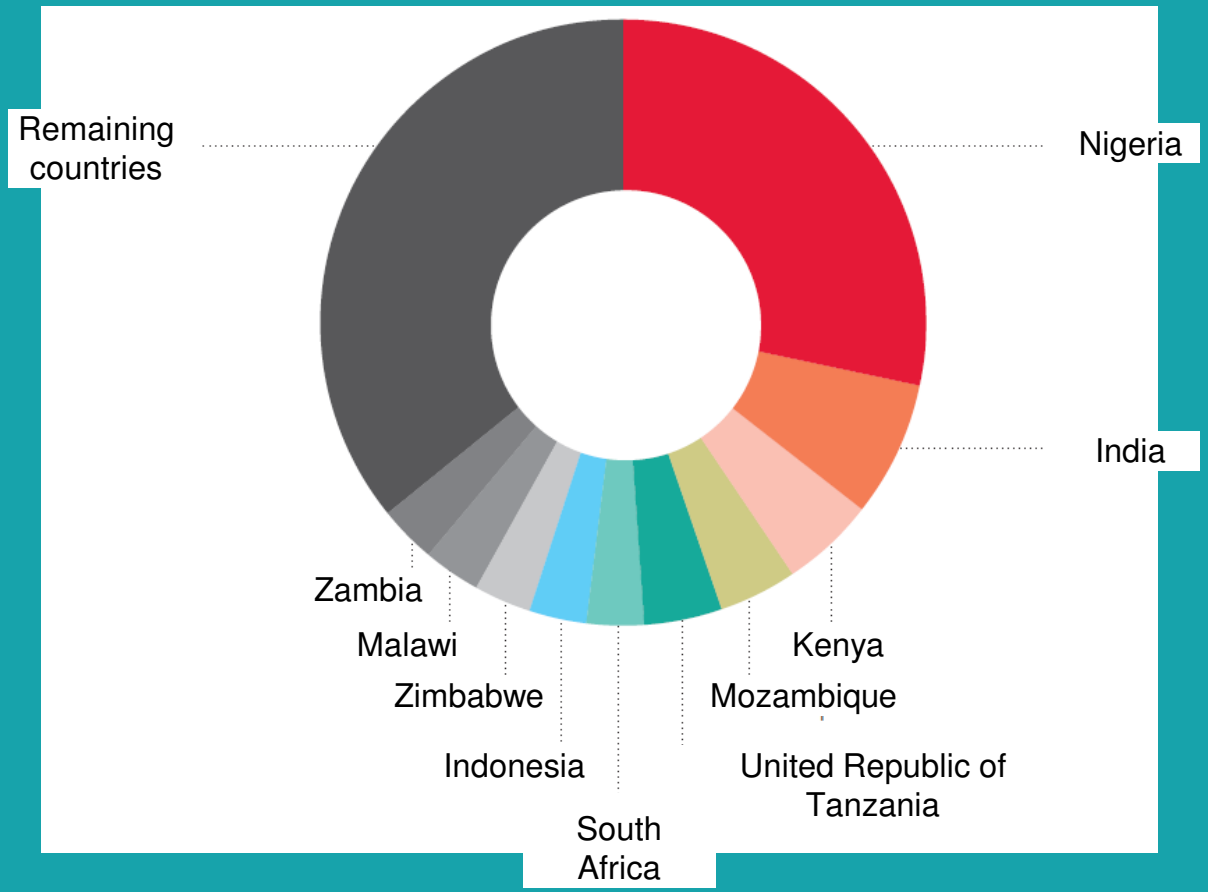
New HIV infections among children (aged 0–14 years) and percentage of pregnant women living with HIV receiving antiretroviral medicines (either prophylaxis or lifelong therapy) to prevent mother-to-child transmission, global, 2005–2015



Source: UNAIDS 2016 estimates.

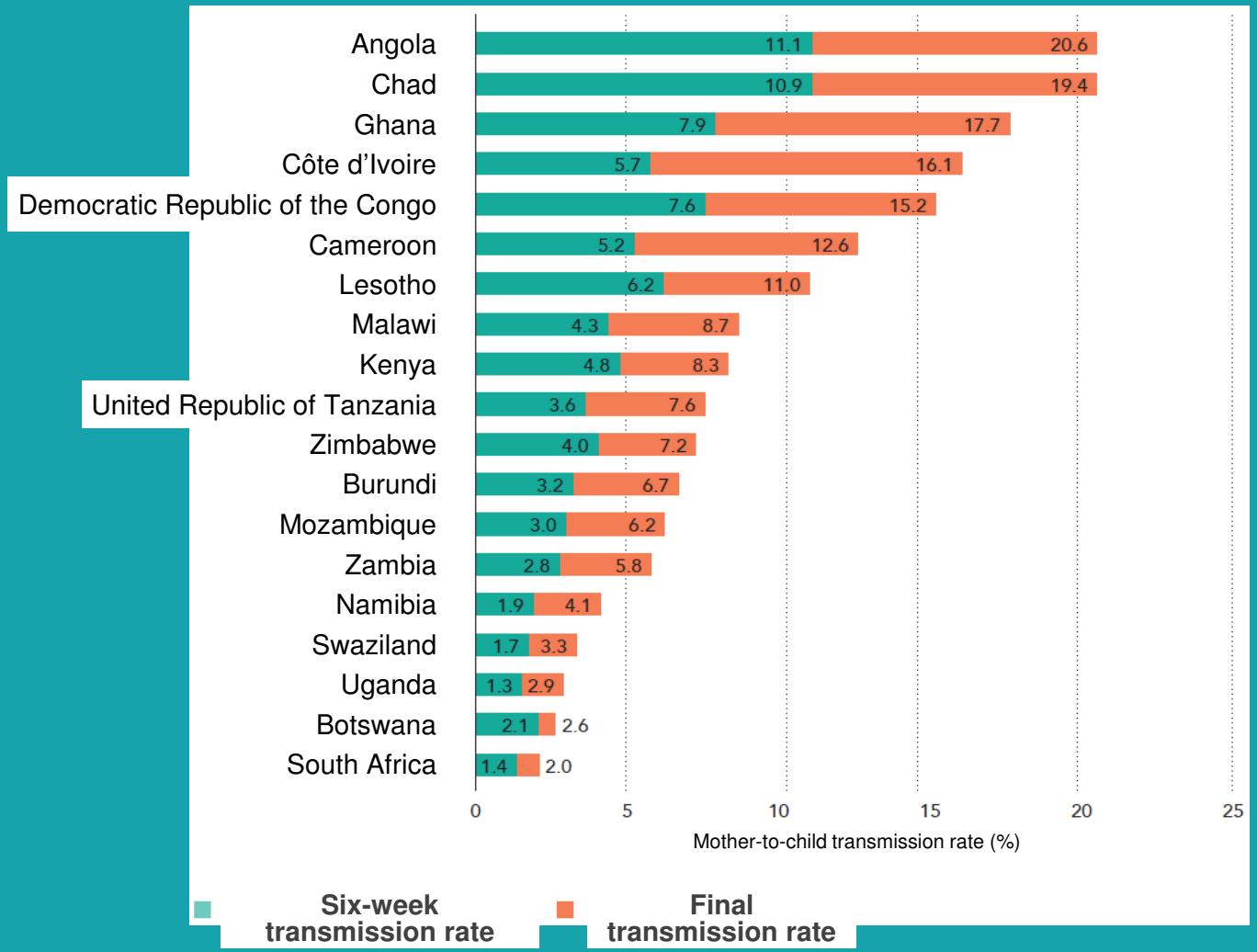
Note: In 2010, single-dose nevirapine was no longer included in ARV coverage as an effective regimen for the prevention of mother-to-child transmission.

Distribution of new HIV infections among children (aged 0–14 years), global, 2015



Source: UNAIDS 2016 estimates.

Six-week and final mother-to-child transmission rates, by country, 2015



Source: UNAIDS 2016 estimates

WHO ARV Guidelines Evolution 2002 to 2015

Topic	2002	2003	2006	2010	2013	2015
When to start	CD4 ≤200	CD4 ≤200	CD4 ≤200 – Consider 350 – CD4 ≤350 for tuberculosis (TB)	CD4 ≤350 – Regardless CD4 for TB and hepatitis B virus (HBV)	CD4 ≤500 – Regardless CD4 for TB, HBV PW and SDC – CD4 ≤350 as priority	**Toward Treat All adolescents age band**
Earlier initiation						
First-Line ART	8 options – AZT preferred	4 options – AZT preferred	8 options – AZT or TDF preferred – d4T dose reduction	6 options and FDCs – AZT or TDF preferred – d4T phase out	1 preferred option and FDCs – TDF and EFV preferred across all populations	**Continue with FDC and harmonization across age bands**
Simpler treatment						
Second-Line ART	Boosted and non-boosted PIs	Boosted PIs – IDV/r LPV/r, SQV/r	Boosted PI – ATV/r, DRV/r, FPV/r LPV/r, SQV/r	Boosted PI – Heat stable FDC: ATV/r, LPV/r	Boosted PIs – Heat stable FDC: ATV/r, LPV/r	**Greater number of options**
Less toxic, more robust regimens						
Third-Line ART	None	None	None	DRV/r, RAL, ETV	DRV/r, RAL, ETV	**Encourage HIV DR to guide**
Viral Load (VL) Testing	No	No (desirable)	Yes (tertiary centers)	Yes (phase-in approach)	Yes (preferred for monitoring, use of PoC, DBS)	**Support for scale up of VL using all technologies**
Better and simpler monitoring						

2016 WHO ART Guidelines

What to use in first-line therapy in adults	ARV regimen*,†
Preferred option	**TDF + XTC‡ + EFV_{600}**
Alternative options	AZT + 3TC + EFV_{600}
	AZT + 3TC + NVP
	TDF + XTC‡ + NVP
	TDF + XTC‡ + DTG§ **NEW**
	TDF + XTC‡ + EFV_{400}§ **NEW**

DTG=dolutegravir

*ARV regimens as fixed-dose combinations is the preferred approach because of clinical, operational, and programmatic benefits

†Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities

‡XTC = 3TC or FTC

§These alternative regimens are expected to be available only in 2017. Safety data PLHIV with TB co-infection and in HIV+ pregnant women still pending

Courtesy of M Vitoria: WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection Recommendations for a public health approach - Second edition. June 2016. Available at: http://www.who.int/hiv/pub/arv/arv-2016/en/

TOWARD AN IDEAL **ANTIRETROVIRAL** REGIMEN FOR THE **GLOBAL EPIDEMIC**

Beatriz Grinsztejn, MD, PhD
Evandro Chagas National Institute of Infectious Diseases – Fiocruz

What are the requirements for an ideal regimen?

Efficacy	Safety and tolerability	Convenience
Special populations HIV/TB Pregnant women Children/Adolescents Acute infection Aging	Access	Global Affordability

TDF + **XTC** + **EFV**

AZT + **XTC** + **PI** (lopinavir or atazanavir)

XTC, other nukes

Darunavir | **Raltegravir or dolutegravir** | **Etravirine**

1st line….

TDF + **XTC** + **EFV**

Cost driver

Side effect (and size) driver, resistance weak link

TDF + XTC + EFV

AZT + XTC + PI (lopinavir or atazanavir)

XTC, other nukes

Darunavir

Raltegravir

Etravirine

Tenofovir has taken over the world!

- 1st line recommendation by WHO; feature in EVERY guideline (some have ABC)
- Well tolerated, FDCs galore, daily
- Cheap (only alternative that is cheaper is d4T)
- Hep B for free
- Renal, bone concerns

TDF + **XTC** + **EFV**

AZT + **XTC** + **PI** (lopinavir or atazanavir)

XTC, other nukes

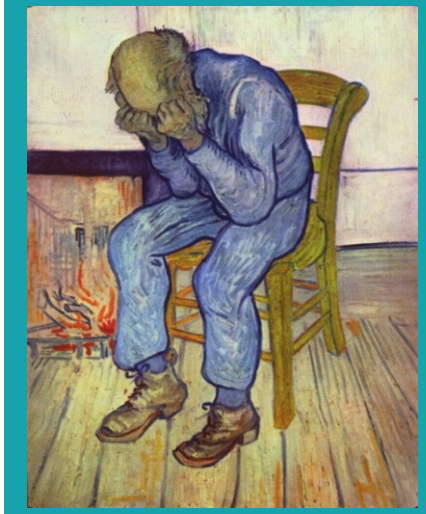
Darunavir **Raltegravir** **Etravirine**

Efavirenz

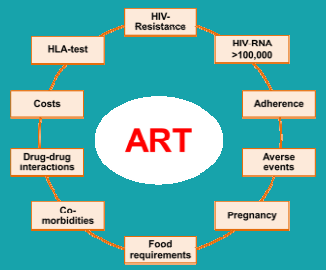
- Daily, cheap, co-formulated, huge experience base, TB (and most everything else)-friendly
- EFV side effects predictable, treatable, substitutions easy

BUT…

- Increasing recognition of CNS side effects - ?Africans stoic? More nb in asymptomatics
- Rash, hepatitis, gynaecomastia, lipids
- 2016: serious and fatal rare CNS side effects, hepatic events
- ENCORE (Lancet 2013): 400mg vs. 600mg

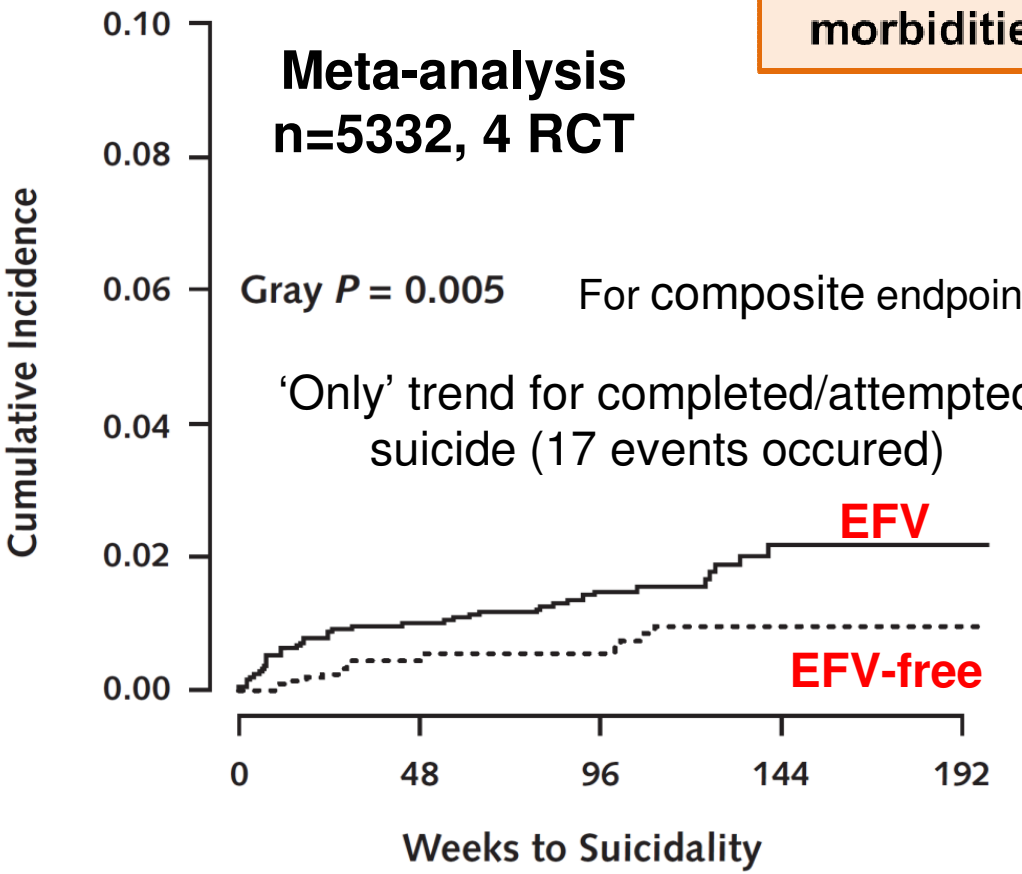


Depression



Co-morbidities

- **Efavirenz** (6%)
  2x higher risk for suicidality
- **Rilpivirine** (8%)
- **Elvitegravir/COBI** (5%)
- **Raltegravir** (6%)
- **Atazanavir/r** (2%)



Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study #O315 Wednesday 5 November

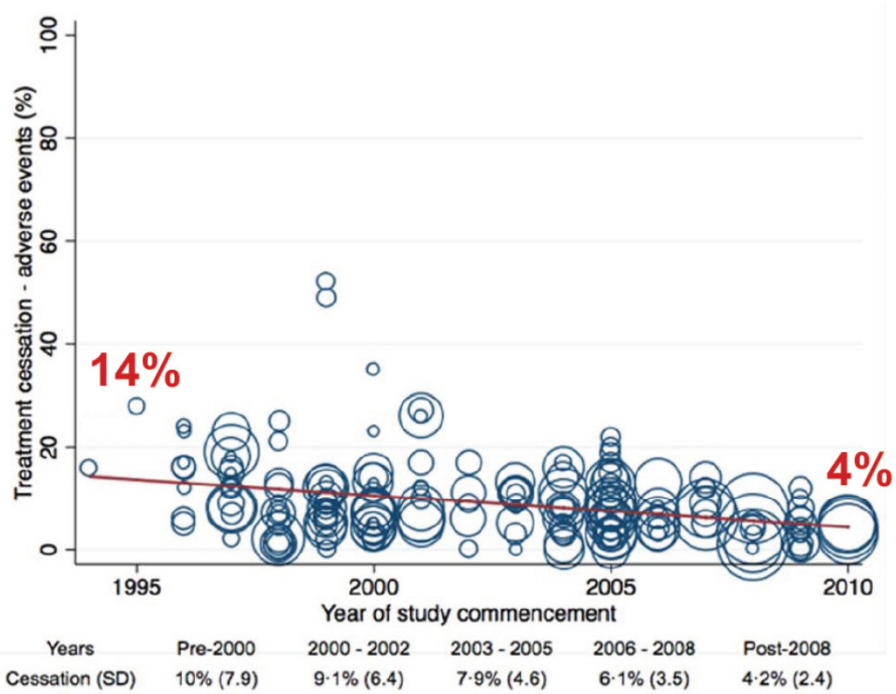
C. Smith; L. Ryom; A. d'Arminio Monforte; P. Reiss; A. Mocroft; W. El-Sadr; R. Weber; M. Law; C. Sabin; J. Lundgren.

Cohen et al., Lancet 2011; Molina et al, Lancet 2011; Elion et al., JAIDS 2013; Mollan et al, Ann Intern Med, 2014

EFV 400mg

- Studies currently underway – pregnancy and TB
- Likely results: 2017
- Then, probable mass switch to 400mg; cost saving ≈ 5-10%
- Other option: rilpivirine: but TB, VL, food issues

ART discontinuation for AE



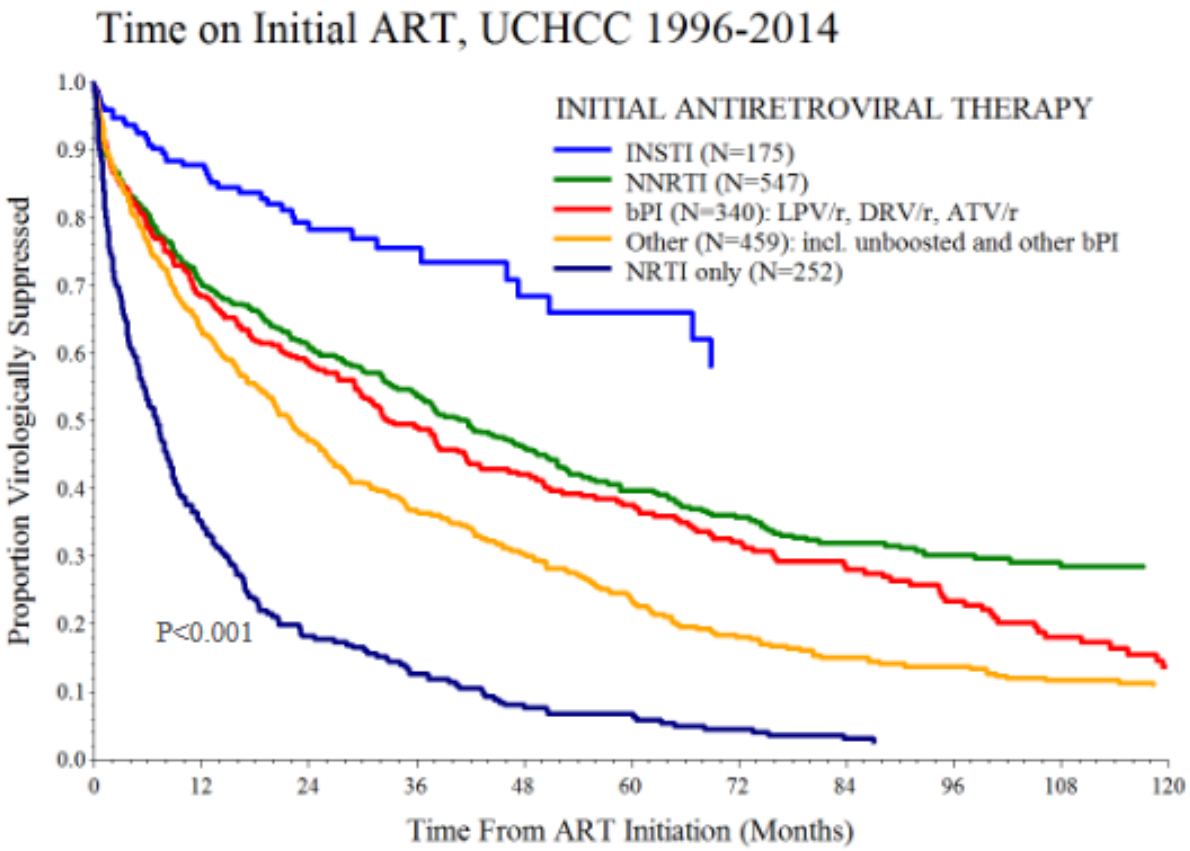
Years	Pre-2000	2000 - 2002	2003 - 2005	2006 - 2008	Post-2008
Cessation (SD)	10% (7.9)	9·1% (6.4)	7·9% (4.6)	6·1% (3.5)	4·2% (2.4)

Carr A (2014). PLoS ONE 9(5): e97482.

The Integrase inhibitor era!

UCHCC: UNC CFAR HIV Clinical Cohort

Persistence of Initial ART



In CNICS cohort integrase inhibitor use was strongly associated with HIV RNA suppression

Thanks Joe Eron

What about: Dolutegravir

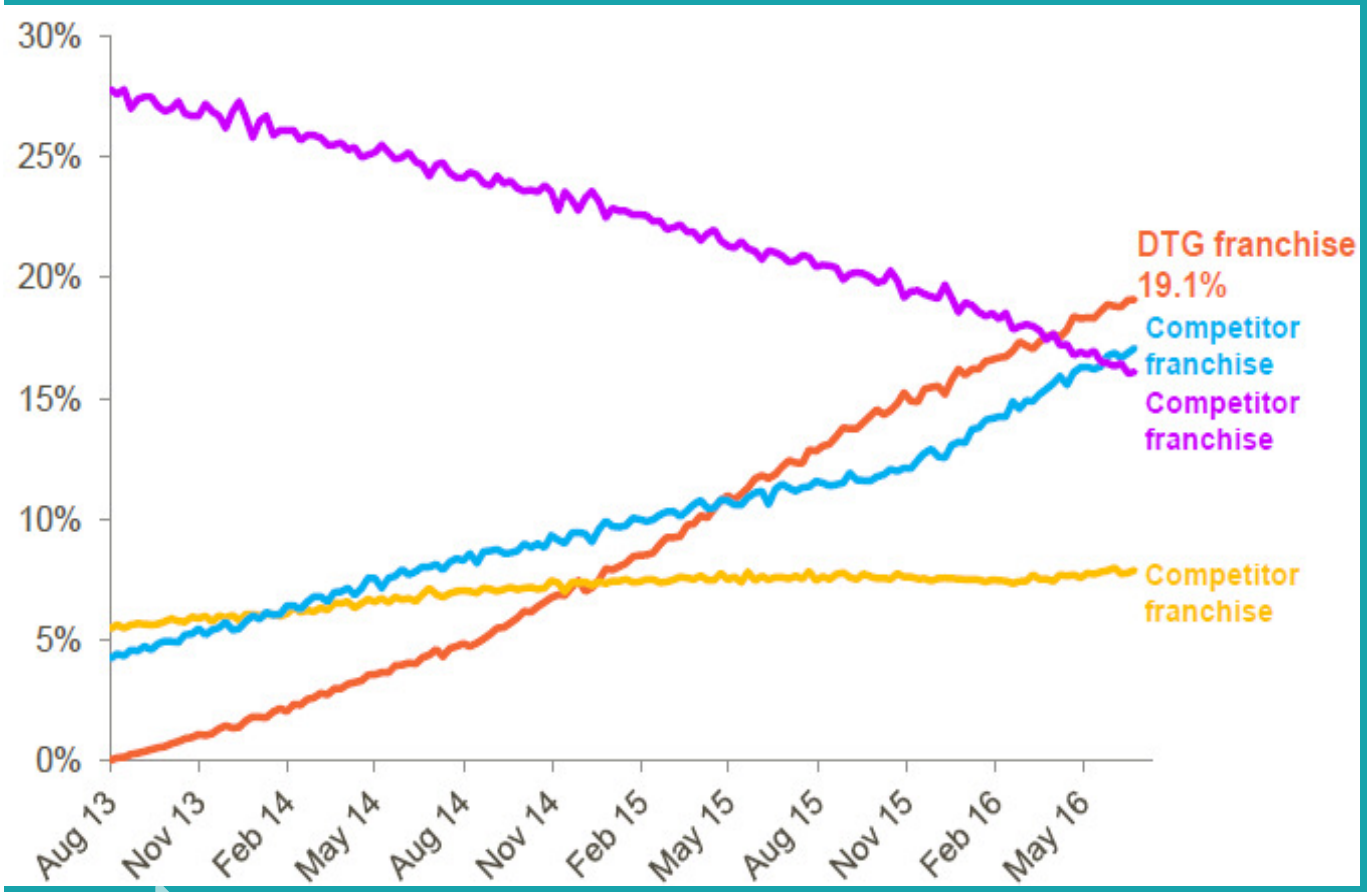
- (raltegravir and elvitegravir expensive)
- Wunderkind of the moment – almost unbreakable!
- 50mg once-daily (in naïve patients)
- Very good efficacy
- Minimal toxicity – but NEW data re CNS
- Pregnancy category B
- Potential to be low cost and co-formulated

EFV 600 vs. DTG

Major parameters	EFV 600	DTG
Occurrence of SAEs	comparable	
Better virologic suppression		✓
Better CD4 recovery		✓
Less treatment discontinuation		✓
Less occurrence of subjective side effects		✓
Lower potential for drug–drug interactions		✓
Efficacy in HIV-2 infection		✓
Efficacy in **TB coinfection**	✓	?
Efficacy and safety in **pregnant/breastfeeding women**	✓	
Availability as **generic formulations**	✓	

In US and EU, DTG-based regimens have become the top prescribed ARVs, affirming DTG's clinically superior profile

US Weekly Treatment Market Share Since DTG Launch



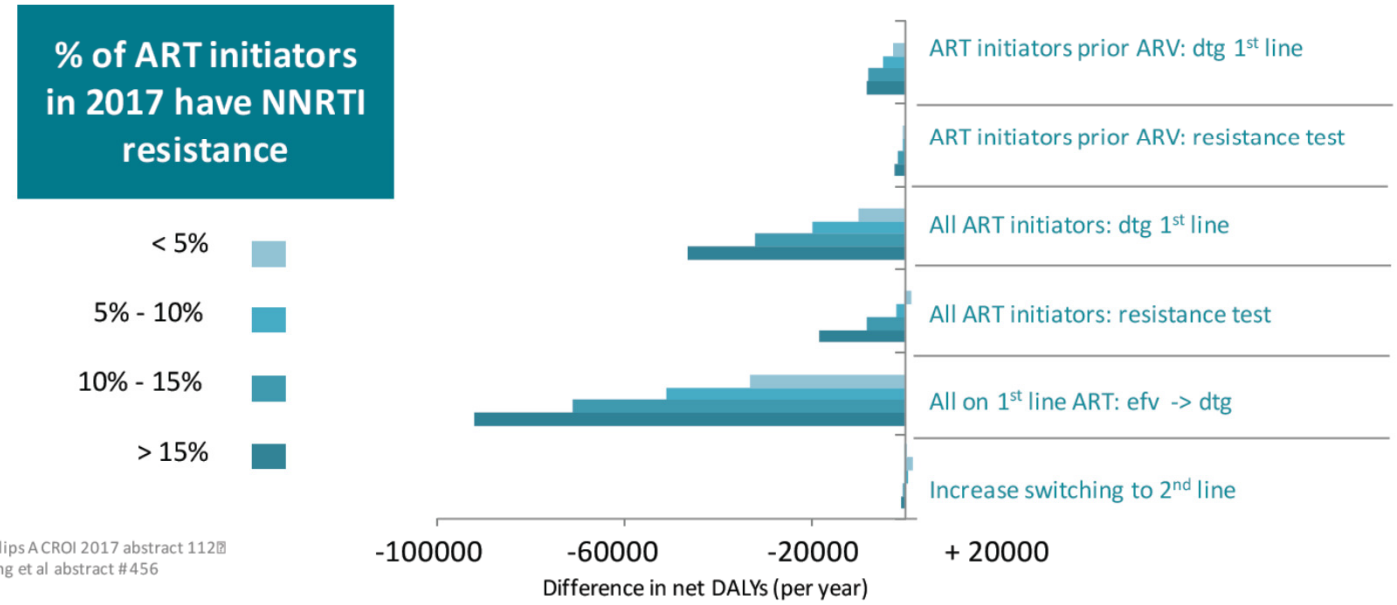
- In Feb **2013, the US** Health and Human Services Guidelines on ARVs recommends **INSTI-based regimens as the preferred** for ART-naïve patients
  - EFV no longer included in DHHS guidelines
- As of 2Q16, DTG treatment volume of >21,000 patients weekly, with nearly **1 in 5 patients on a DTG regimen in the US**
- DTG now leads US/EU markets:
  - US: #1 core agent in treatment share and volume
  - EU: #2 prescribed regimen in treatment-naïve patients

The US and EU has long moved on from EFV-based treatment

Source: GILD and GSK earnings.
Note: Graph depicts single tablet regimen plus core agent market

Difference in net DALYs compared with no change in policy, according to % of ART initiators with NNRTI resistance in 2017

Net DALYS take into account DALYs and costs simultaneously.
The strategy with the lowest net DALYs is the most cost effective.

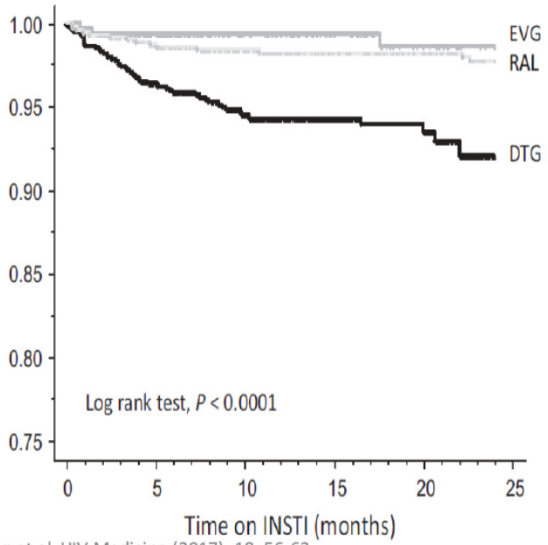


Phillips A CROI 2017 abstract 112
Zheng et al abstract #456

Dolutegravir: discontinuation due to AE

Germany (2 cohorts), 1950 INSTI-based therapies

Discontinuation due to neuropsychiatric AE



Hoffman et al. HIV Medicine (2017), 18, 56-63
Libre et al.CROI 2017 abstract# 651

Factors associated with DTG discontinuation

	RH	95% CI	*P*
Any AE			
Female, *vs.* male gender	2.81	1.46–5.41	0.002
Older age (> 60 years), *vs.* younger age	2.88	1.56–5.34	< 0.001
ABC with DTG initiated, *vs.* no ABC	2.63	1.61–4.29	0.0001
DTG start in 2016, *vs.* in 2014/2015	8.93	3.76–21.28	< 0.0001
Neuropsychiatric AEs			
Female, *vs.* male gender	2.64	1.23–5.65	0.01
Older age (> 60 years), *vs.* younger age	2.86	1.42–5.77	0.003
ABC with DTG initiated, *vs.* no ABC	2.42	1.38–4.24	0.002
DTG start in 2016, *vs.* in 2014/2015	11.36	4.31–29.41	< 0.0001

Hsu et al CROI 2017 abstract #664

CLINICAL UPDATE

Cutting the cost of South African antiretroviral therapy using newer, safer drugs

W D F Venter,[1] FCP (SA), MMed; **B Kaiser**,[2] MPH, PharmD, BCPS; **Y Pillay**,[3] PhD; **F Conradie**,[4] MB BCh; **G B Gomez**,[5] PhD; **P Clayden**;[6] **M Matsolo**;[7] **C Amole**,[8] BA; **L Rutter**,[7] BA; **F Abdullah**,[9] MB ChB, FCPHM, BSc Hons (Epi); **E J Abrams**,[10] MD; **C P Casas**,[11] MSc; **M Barnhart**,[12] MD, MPH; **A Pillay**,[13] PhD; **A Pozniak**,[14] MD, FRCP; **A Hill**,[14] PhD; **L Fairlie**,[1] FCPaed (SA); **M Boffito**,[14] MD, PhD; **M Moorhouse**,[1] MB BCh; **M Chersich**,[1] MB BCh, PhD; **C Serenata**,[1] MBA; **J Quevedo**,[8] BS; **G Loots**[15]

[1] *Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa*
[2] *Formerly UNITAID, Geneva, Switzerland*
[3] *HIV/AIDS, TB and Maternal, Child and Women's Health in the South African National Department of Health, Pretoria, South Africa*

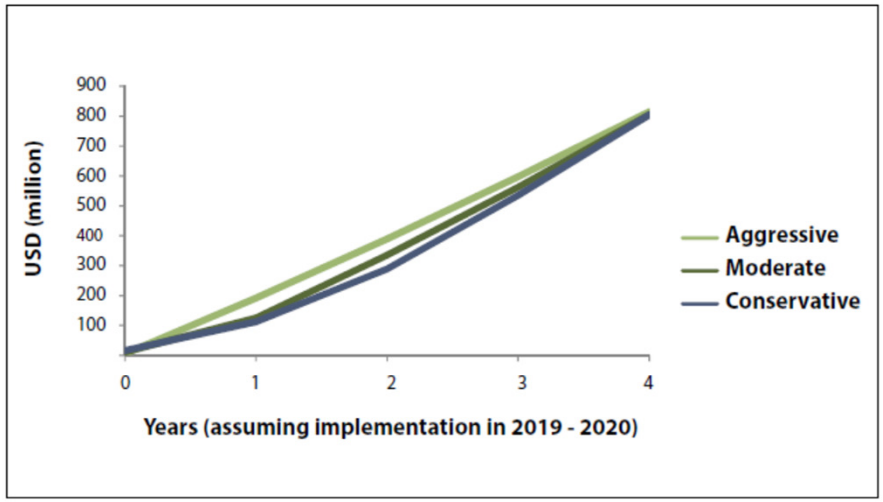
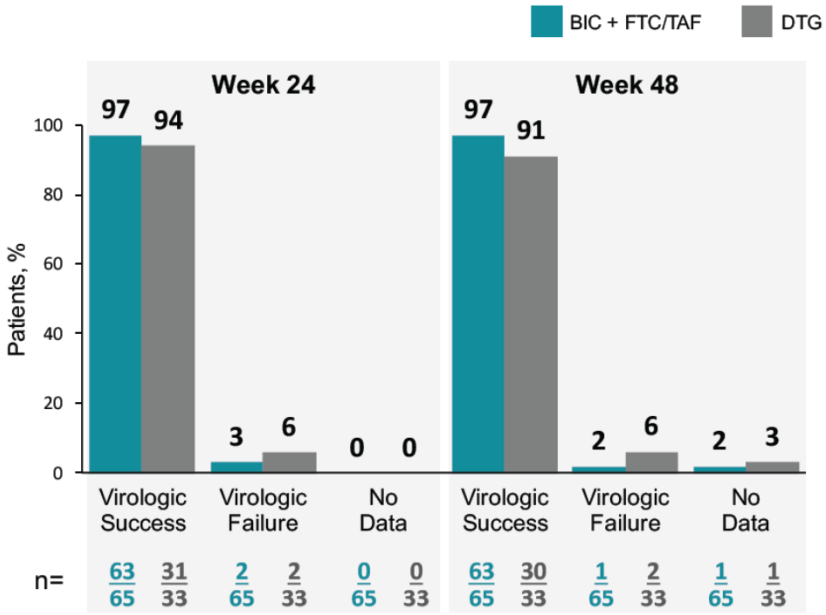
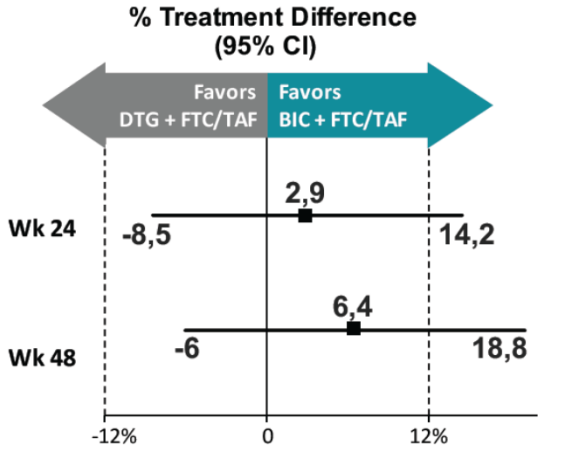


Fig. 2. Estimated crude savings on antiretroviral drugs (assuming implementation of new regimen in 2019 - 2020). Cumulative savings compared with status quo (conservative = 300 000 annually, transition from old regimen to new over 3 years; moderate = new regimen, 400 000 annually, transition over 2 years; aggressive = new regimen, 500 000 annually, transition over 1 year).

Phase 2 Bictegravir or Dolutegravir with FTC/TAF for Initial HIV Therapy
Virologic Outcomes at Weeks 24 and 48 by FDA Snapshot





No resistance to study medications was detected in either arm

Sax P et al CROI 2017 abstract# 41

Integrase inhibitors and IRIS

- Results from the Athena cohort that integrase inhibitors use in HIV-1 late presenters is an independent risk factor for IRIS.
- Data from the French Dat'AIDS cohort show higher risk for IRIS among individuals who started ART with a integrase-based regimen
- Case reports emerging from Botswana and the UK of TB-IRIS with first-line with integrase-based treatment.
- This could increase the burden on health care workers and hospital/ clinical costs.

Wijting et al. Croi 2017 – abstract# 731
Dutertre et al. Croi 2017 - abstract #732
Personal communication Anton Pozniak

Safety and Efficacy of INSTIs and EFV_{400} in First-Line ART (NMA)

Major outcomes	INSTI vs. EFV_{600}	DTG vs. other INSTI	DTG vs. EFV_{600}	DTG vs. EFV_{400}	EFV_{400} vs. EFV_{600}	Quality of evidence
Viral suppression	**INSTI better**	**DTG better**	**DTG better**	comparable*	comparable	**moderate**
CD4 recovery	**INSTI better**	**DTG better**	**DTG better**	comparable	**EFV_{400} better**	**moderate**
Treatment discontinuation	**INSTI better**	**DTG better**	**DTG better**	comparable	**EFV_{400} better**	**moderate**
Mortality	comparable	comparable	comparable	comparable	comparable	low
AIDS progression	comparable	comparable	comparable	comparable	comparable	low
SAE	comparable	comparable	comparable	comparable	comparable	**moderate**

*Estimated effects favored DTG, but statistical analysis not significant

WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection – What's New Policy Brief, November 2015. Available at http://www.who.int/hiv/pub/arv/policy-brief-arv-2015/en/

New Studies with DTG & TAF in PLHIV

(adults & children)

M Vitoria, Nov 2016

DTG & TAF STUDIES IN PLHIV

Study	Drug	Intervention	Major outcomes	N	Study Countries	Expected Completion
NAMSAL (ANRS 12313)	**DTG**	Safety/efficacy of DTG vs EFV in initial ART of PLHIV in RLS (TDF/3TC + DTG vs TDF/3TC + EFV)	VL at 24 and 48 weeks, CD4 changes, disease progression, treatment discontinuation, AEs; HIVDR, time to viral suppression	**606**	Cameroon	**Q3 2018**
ADVANCE (WRHI 060)	**DTG TAF**	Safety/efficacy of DTG and TAF in initial ART (TDF+FTC+ DTG vs TAF + FTC + DTG vs TDF + FTC + EFV)	VL at 24 and 48 weeks, CD4 changes, disease progression, treatment discontinuation, AEs; HIVDR,	**1050**	South Africa	**Q4 2019**
DAWNING	**DTG**	Safety/efficacy of DTG vs LPV/r in PLHIV failing 1st line ART (2NRTI + DTG vs 2NRTI + LPVr)	VL at 96 weeks, CD4 changes, disease progression, treatment discontinuation,	**612**	Argentina, Brazil, Chile, China, Colombia, Kenya, Mexico, Peru, Romania, Russia, South Africa, Thailand, Ukraine	**Q4 2018**
ODYSSEY (PENTA 20)	**DTG**	2NRTI + DTG vs SoC in children/ young adults (6-18 yrs) with HIV starting 1st line or switching to 2nd line ART	VL at 24 and 48 weeks, CD4 changes, disease progression, treatment discontinuation, AEs	**700**	Argentina, Austria, Belgium, Brazil, Denmark, France, Ireland, Germany, Italy, Netherlands, Poland, Portugal, Romania, Spain, Sweden, Switzerland, Thailand, Uganda, UK, Ukraine, USA,	**Q3 2019**
ARIA	**DTG**	Safety/efficacy of DTG vs ARTV/r in initial ART of women with HIV (ABC/3TC/DTG vs TDF/3TC + ATV/r)	VL at 24 and 48 weeks, CD4 changes, disease progression, treatment discontinuation, AEs HIVDR,	**495**	Belgium, Dominican Republic, France, Italy, Mexico, Portugal, Puerto Rico, Russia, Thailand, Uganda, UK, USA,	**Q4 2020**

New ARVs and TB drugs: Current Studies

M Vitoria, Nov 2016

DTG, EFV_{400} & TAF STUDIES IN TB

Study	Drug	Intervention	Major outcomes	N	Study Countries	Expected Completion
SSAT 062	**EFV_{400}**	EFV 400 mg pK in PLHIV in presence of RIF and INH, with and without TB	pK data, AEs, treatment discontinuation, influence of genetic polymorphism and EFV exposure	**35**	Uganda and UK	**Q2 2017**
INSPIRING (ING117175)	**DTG**	Safety /efficacy of DTG vs EFV in PLHIV with TB confection using RIF (50 mg DTG twice daily vs 600 mg EFV once daily during TB treatment)	VL at 24 and 48 weeks, CD4 changes, treatment discontinuation, AEs; HIVDR	**125**	Argentina, Brazil, Mexico, Peru, Russian Federation, South Africa, Thailand	**Q4 2017**
SSAT 075	**TAF**	TAF and TDF pK in presence of RIF (HIV negative patients)	TDF DP levels	**20**	South Africa	**Q4 2017**

New ARVs in Pregnancy: Current Studies

M Vitoria, Nov 2016

DTG, EFV_{400} ^ TAF STUDIES IN PREGNANT WOMEN

Study	Drug	Intervention	Major outcomes	N	Study Countries	Expected Completion
SSAT 063	EFV_{400}	EFV 400mg pK and safety in pregnant women with HIV using ARV regimen containing EFV at standard dose	pK data 3rd trimester and post partum; maternal and infant AEs, adverse pregnancy outcomes; genetic polymorphisms influence on EFV pK	25	Uganda, UK	Q2 2017
DOLPHIN 1	DTG	DTG pK in pregnant women with HIV	pK data in 3rd trimester and 2 weeks postpartum; maternal VL at delivery	60	South Africa Uganda	Q4 2017
DOLPHIN 2	DTG	DTG safety/efficacy/ tolerability in pregnant women with HIV	pK data 3rd trimester and 18 weeks post partum, maternal VL at delivery, breast milk sterilization	250	South Africa Uganda	Q1 2021
ING200336	DTG	DTG pK and safety in unintended pregnancies in ARIA study (DTG/ABC/3TC vs ATV/r+ TDF/FTC)	pK data in 2nd and 3rd trimester; pK in neonates, maternal and infant adverse events; adverse pregnancy outcomes, maternal disease progression and fetal transmission	25	Spain, Russia, UK, USA	Q1 2019
WAVES OLE	TAF	TAF safety/efficacy/ tolerability in pregnant women with HIV (TAF/FTC/EVGc vs ATV/r +TDF/FTC)	Maternal VL at 48 weeks	583	Belgium, Dominican Republic, France, Italy, Mexico, Portugal, Puerto Rico, Russia, Thailand, Uganda, USA, UK	Q2 2017
IMPAACT P1026s	DTG TAF	DTG and TAF pK in women with HIV on ART > 20 weeks of pregnancy and post partum	pK data (during pregnancy and post partum), pK data in neonates, maternal:cord blood ration, maternal and infant AEs, adverse pregnancy outcomes	100	Argentina, Botswana, Brazil, Puerto Rico, South Africa, Thailand, Uganda, USA	Q3 2017
IMPAACT P2010	DTG TAF	DTG and TAF safety/efficacy in women with HIV starting ART at 14-28 weeks of pregnancy (DTG+ TAF/FTC vs DTG/TDF/FTC vs EFV/TDF/XTC)	Maternal VL at delivery, adverse pregnancy outcomes, maternal toxicity, SAB, foetal deaths, infant AEs, mother-infant ARV transfer at birth and from breast milk	549	Argentina, Botswana, Brazil, Puerto Rico, South Africa, Tanzania, Thailand, USA, Zimbabwe	Q3 2018
PANNA	DTG TAF	DTG and TAF safety/efficacy in women with HIV receiving ART and < 33 weeks of pregnancy	PK data in week 33 of pregnancy and 4-6 weeks after delivery, pK data in neonates; maternal VL and fetal transmission; maternal and infant AEs; adverse pregnancy outcomes	32	Belgium, Germany, Ireland, Italy, Netherlands, Spain, UK	Q4 2020

Clinical trials: Children and adolescents

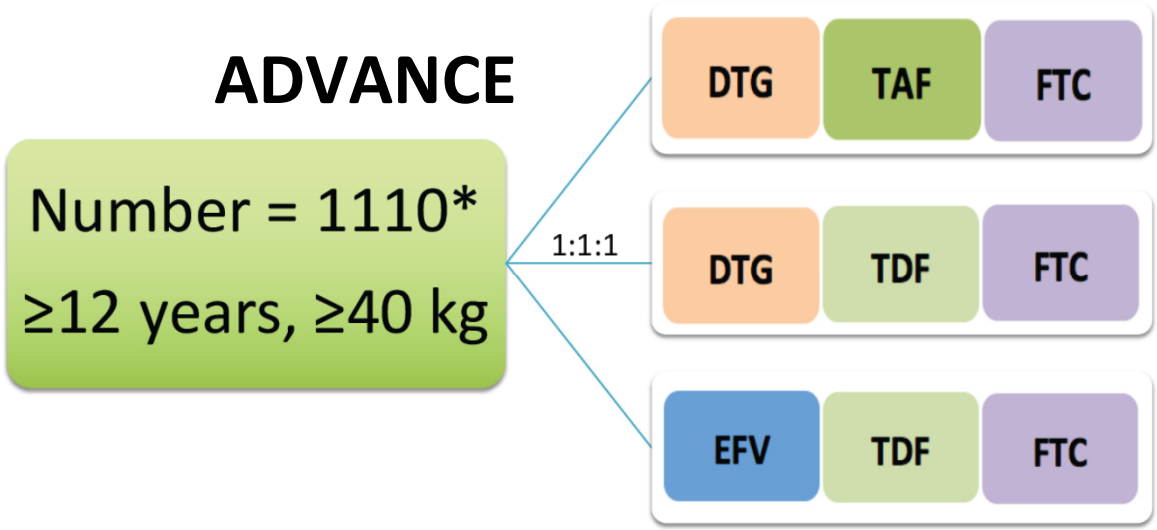
	Phase	Regimen	Age	Expected completion
GS-US-183-0160 (NCT01923311)	II/III	EVG/r	Up to 17 years	Q1 2017
CR108265 (NCT02993237)	I	DRV/c swallowing tablets DRV/c/FTC/TAF swallowing tablets	12-17 years	Q2 2017
GS-US-292-1515 (NCT02276612)	II/III	EVG/c/FTC/TAF	12-17 years	Q3 2017
GS-US-236-0112 (NCT01721109)	II/III	EVG/c/FTC/TDF	12-17 years	Q3 2017
IMPAACT P1093 (NCT01302847)	I/II	DTG film-coated tablets DTG granules for suspension	Up to 17 years	Q2 2018
ING114916 (NCT01536873)	III	DTG 50 mg (expanded access)	> 12 years	Q3 2018
SMILE (PENTA 17) (NCT02383108)	II/III	EVG + DRV/r	6-17 years	Q3 2018
GS-US-380-1474 (NCT02881320)	II/III	Bictegravir/FTC/TAF	6-17 years	Q4 2018
ODYSSEY (PENTA 20) (NCT02259127)	II/III	DTG	6-18 years	Q2 2019
GS-US-311-1269 (NCT02285114)	II/III	TAF	6-17 years	Q1 2020
GS-US-216-0128 (NCT02016924)	II/III	ATV/c DRV/c	3m-17years	Q4 2020
GS-US-292-0106 (NCT01854775)	II/III	EVG/c/TAF/FTC	6-17 years	Q4 2021
IMPAACT 2006*	II	DTG	1m – 3Y	In development

Clinicaltrials.gov *www.impaactnetwork.org/studies

TAF/FTC/DTG

- Almost unbreakable – 600 000 people on first-line DTG, no resistance (well one case, no second, third-line)
- DTG slightly cheaper than EFV, TAF much cheaper than TDF – generics: immediate 20% price reduction, CHAI ?closer to 50%
- Possibility of harmony for >12 years (and possibly below)
- ?Move second-line patients BACK to 1st line

ADVANCE



- Non inferiority of 2 new combinations to current treatment
- Open label, randomised, single site study over 48 weeks
- * n=1110, with 90-120 in age group 12-18 years

Reformulation of existing ARV's

Shao J, et al. *Nanomedicine (Lond.) 2016;* 11: 545

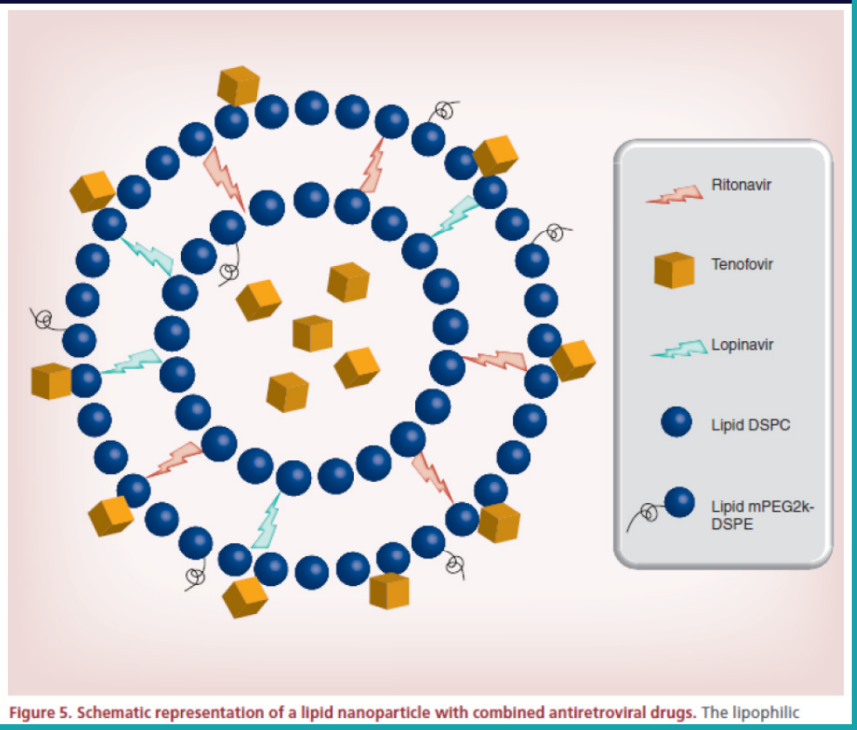
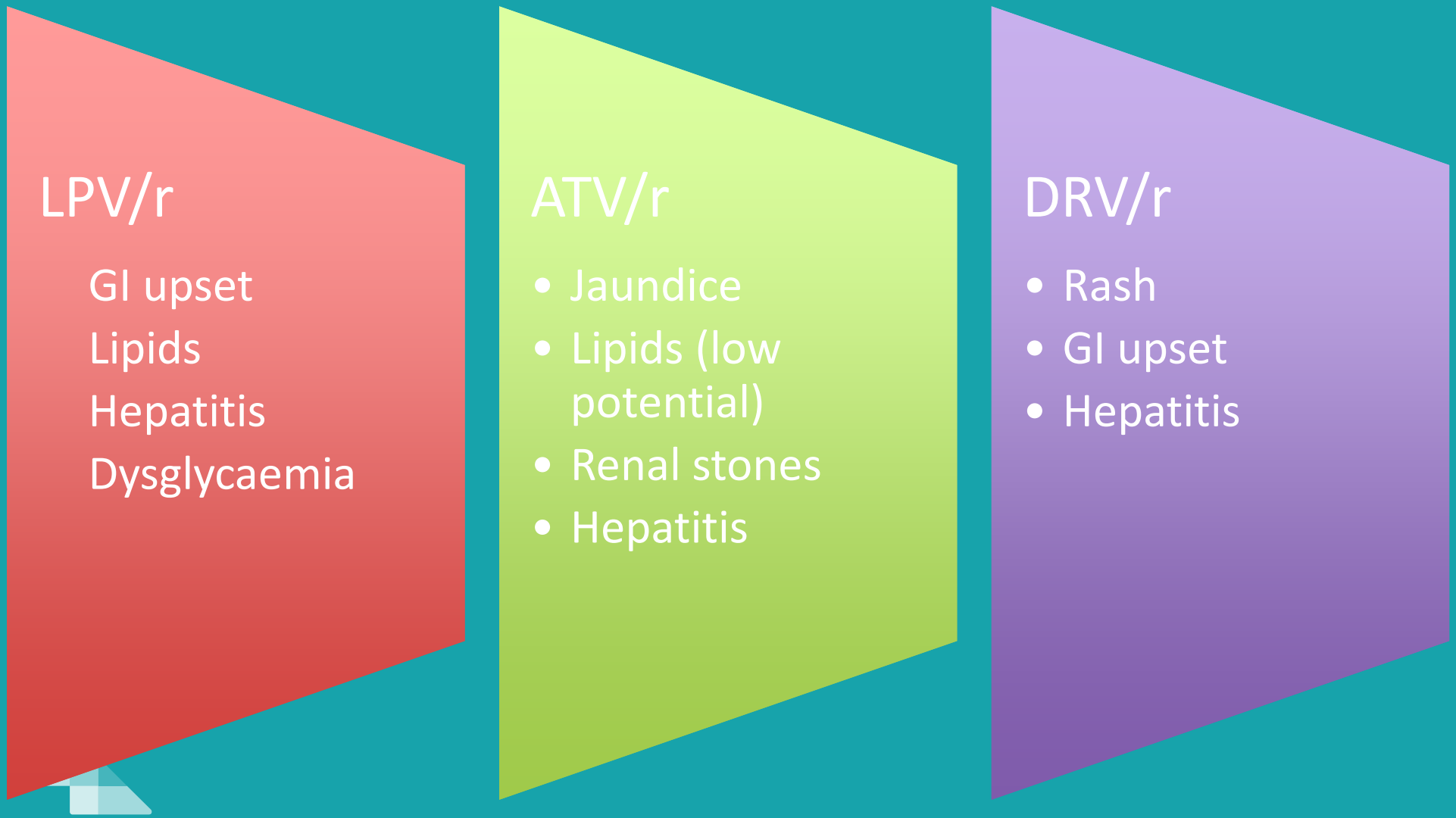


Figure 5. Schematic representation of a lipid nanoparticle with combined antiretroviral drugs. The lipophilic

Safety issues with PIs



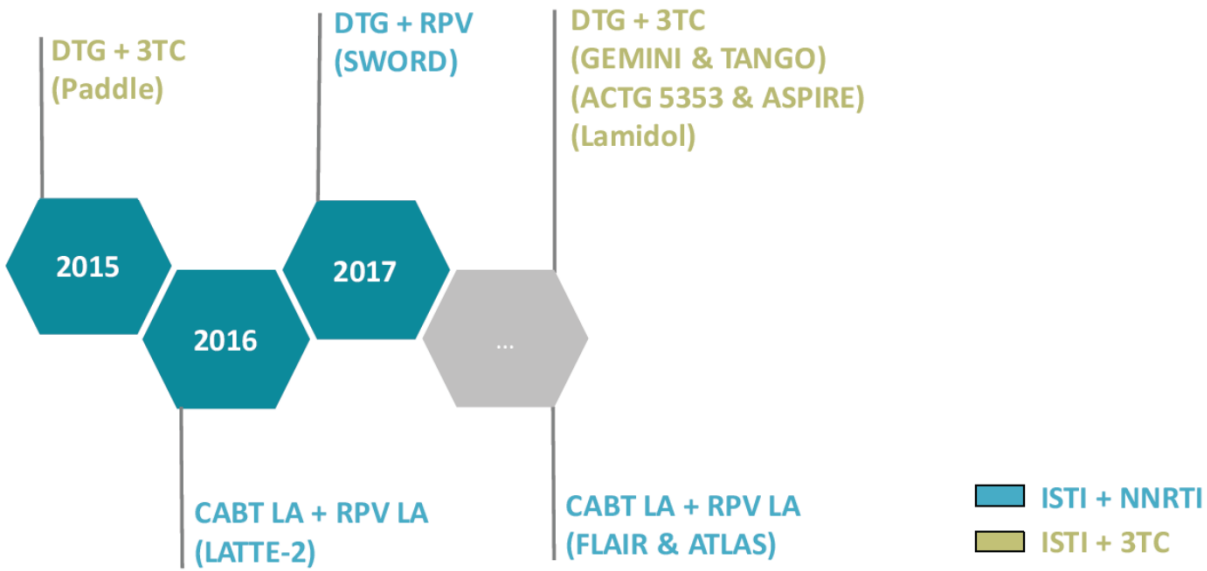
How do we make PIs safer?

- New molecules
- Prodrugs of current PIs
  - Improve bioavailability
  - Reduce side effects
- New formulations of existing PIs
- Different pharmacokinetic boosters
- Use existing PIs in a different ways
  - Lower doses
  - Different combinations e.g. nuke sparing

Some new approaches…

- Dual (and mono) therapy!
- Injectables
- And new classes, immunoglobulins

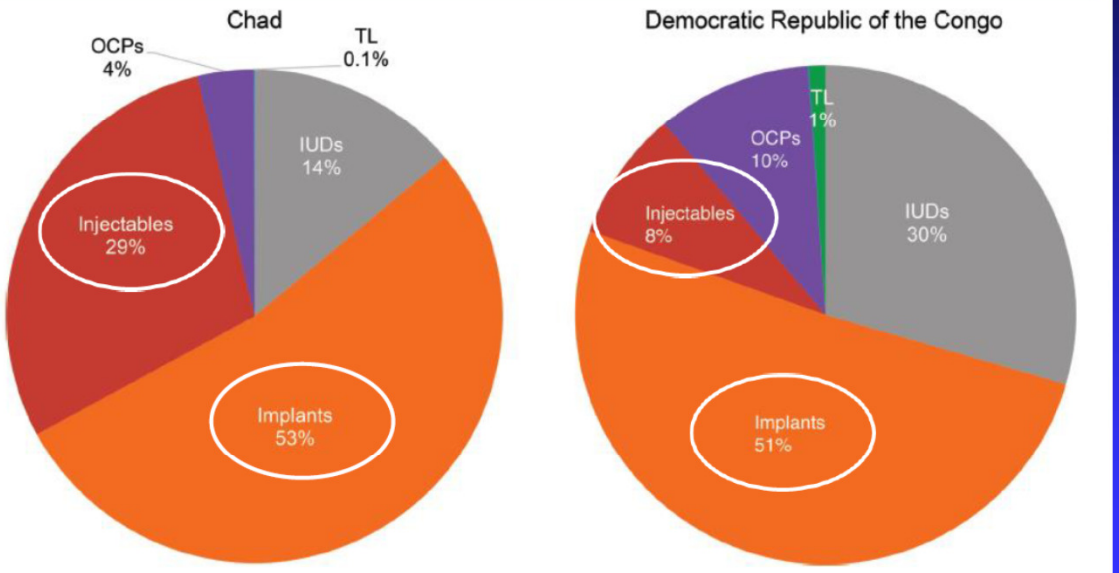
Reduced drug regimens in suppressed and naive patients. Simplicity 2.0



Courtesy Jose Arribas

Uptake of contraceptive implants in SSA

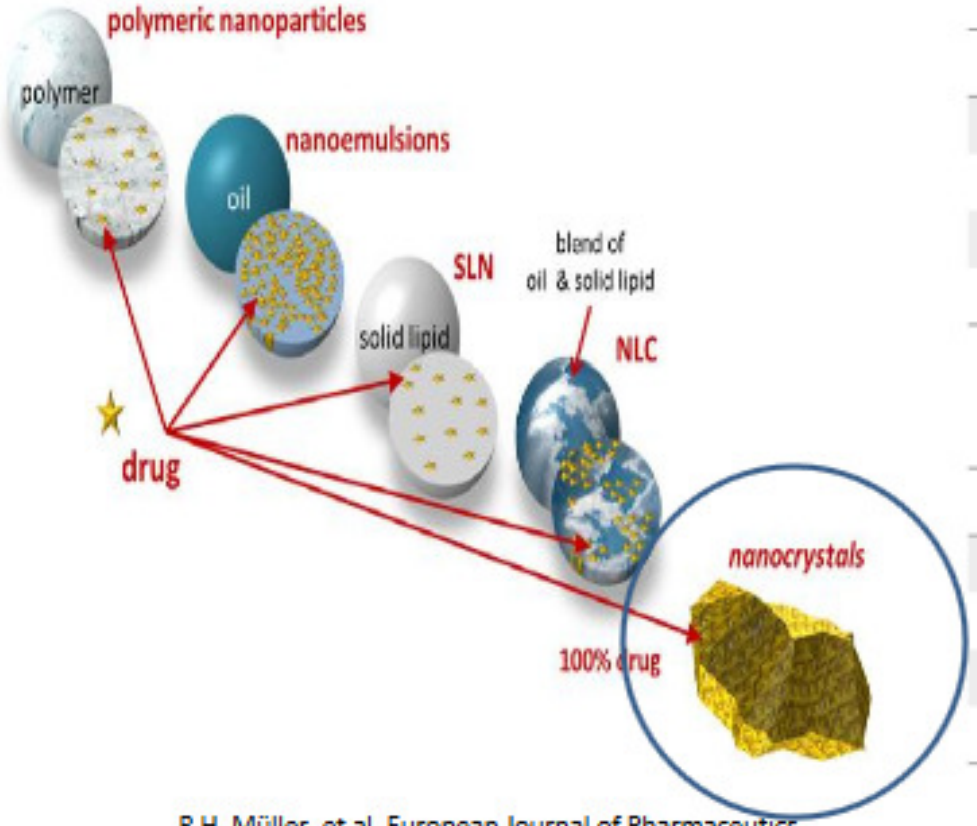
FIGURE 1. Contraceptive Method Mix Among New Family Planning Users in Program Areas in Chad[a] and DRC, June 2011 to November 2015



- Rattan J et al., *Global Health: Sci Prac* 2016; 4: Suppl 2

Cabotegravir LA and Rilpivirine LA Nanosuspensions

- Drug nanocrystal suspended in liquid = nanosuspension
- Nanomilled to increase surface area and drug dissolution rate
- Allows ~100% drug loading vs. matrix approaches for lower inj. volumes



R H. Müller, et al. European Journal of Pharmaceutics and Biopharmaceutics 78 (2011) 1-9

GSK744 200mg/mL

Component	Function
GSK1265744 (d50 ~200 nm)	Active
Mannitol	Tonicity agent
Surfactant System	Wetting/Stabilizer
Water for Injection	Solvent

TMC278 300mg/mL

Component	Function
TMC278 (d50 ~200 nm)	Active
Glucose	Tonicity agent
Surfactant System	Wetting/Stabilizer
Water for Injection	Solvent

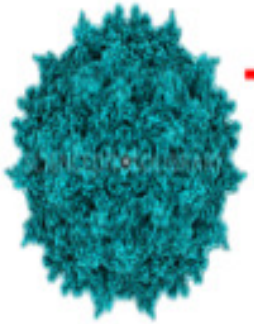
Spreen et al. IAS 2013; Kuala Lumpur. Abstract WEAB0103.

Antiretroviral Therapy: The Next Generation?

- Implantable (and removable) combination antiretrovirals

- Vectored delivery of combinations of antibody-based therapy or protein based therapy

Recombinant AAV (rAAV) features



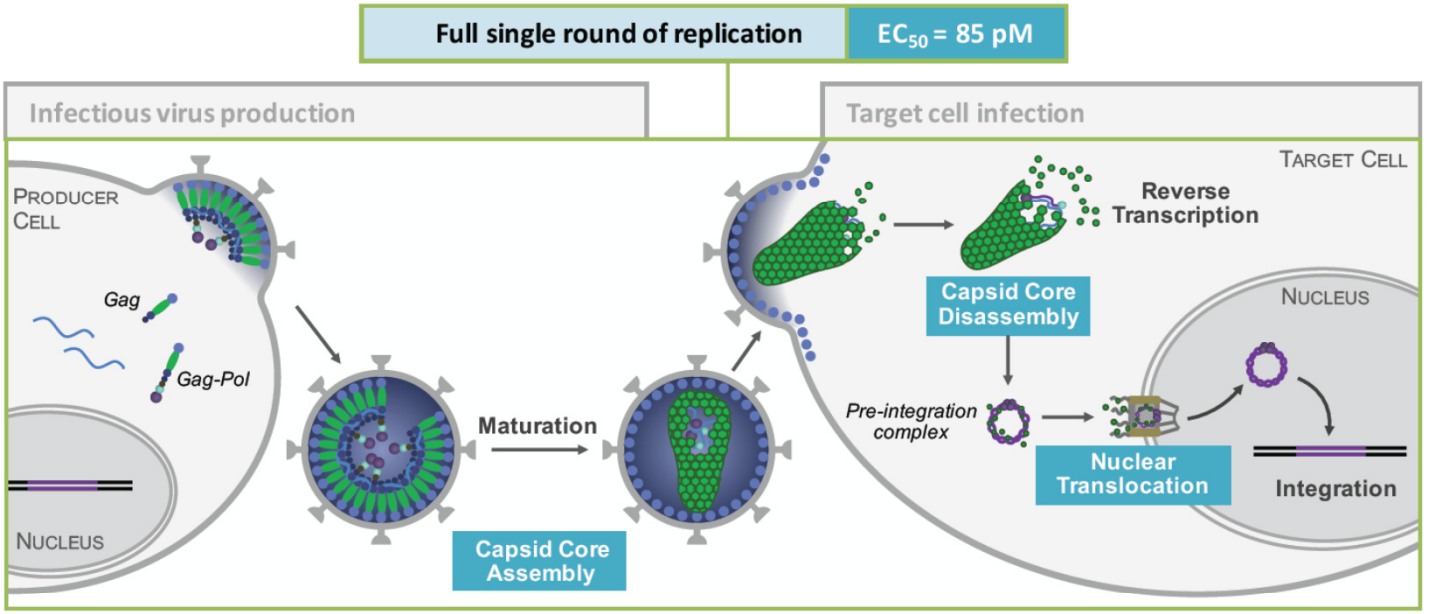
- Transfects both dividing & non-dividing cells
- No host-genome integration & Stable Expression
- Ease to produce at high viral titer (Helper Free)
- Do not elicit significant immune response *in vivo*
- Can be used for in vivo gene deliveries

2016

And nanoparticles….

First-in-Class Capsid Inhibitor GS-CA1
GS-CA1 Inhibits Multiple Steps in HIV Replication Cycle

Dissect replication cycle for points of GS-CA1 action:



Tse el al. Croi 2017 - abstract 38

Vision… chronic care

Diagnosis and staging, good primary care that suits patients

Minimal hospitalisation

Good ARV access

CD4

8 to 10 years

Prevention

40 years

NSP INDICATOR	WHAT THE INDICATOR MEASURES	STATISTICS 1	STATISTICS 2	STATISTICS 3	HOW OFTEN IS IT MEASURED	NSP TARGET BY 2016	WAS THE TARGET MET?	SPOTLIGHT AND SANAC COMMENTS
HIV Incidence	Actual number of new HIV infections in the population	1.47 [CI 1.23-1.72]. (2012): SANAC's 2016 NSP Progress Report on NSP 2012-2016	0.7% (2015): Health Indicators; Health Systems Trust	0.87% (2014): Joint Review of HIV, TB, & PMTCT Programmes in South Africa Main Report April 2014	Periodic	0.47%	NO	*18% decline based on updated and corrected baseline data. HIV incidence remains above the desired target for the adult population. – SANAC* *While the downward trend in HIV incidence is not rapid enough – there is hope that increasing treatment coverage, the continued rollout of VMMC, together with other prevention methods may lead to continued reductions. – Spotlight*
HIV Mortality	Success of HIV and TB Programmes	5.1% (2013): SANAC's 2016 NSP Progress Report on NSP 2012-2016	43.6% (2014): Joint Review of HIV, TB, & PMTCT Programmes in South Africa Main Report April 2014		Annually	21.8%	NO	*According to UNAIDS (2013), HIV mortality has declined. This is a major achievement due to improved reporting. - SANAC* *HIV mortality is still much higher than hoped for in 2016. - Spotlight*
MTCT rate (6 weeks and 18 months)	Success of the Prevention of Mother to Child Transmission Programme, by determining the percentage of babies born HIV positive	1.5% (6 weeks); less than 5% (18 months (2015) SANAC's 2016 NSP Progress Report on NSP 2012-2016			Annually	2% (6 weeks) 5% (18 months)	YES	*Target exceeded for MTCT at 6 weeks. Target met for MTCT at 18 months (at follow up). - SANAC* *Very little data exists at the 18 month age: failure to track this data well makes it almost impossible to measure the success of the programme or set new targets for the future. - Spotlight*
Patients alive and on treatment	Retention in care	12mo=75.0% 60mo=52.3% (2015): SANAC's 2016 NSP Progress Report on NSP 2012-2016			Quarterly	12mo=96% 24mo=88% 36mo=82% 48mo=76% 60mo=70%	NO	*Retention on ART is below target for each cohort due to absence of a unique identifier - high chances of under-reporting. In addition unrecorded viral loads done lead to under-reporting. - SANAC* *In addition to factors identified by SANAC, health system dysfunction, long queues, medicines stockouts, lack of community healthcare workers and lay councillors likely contributes to these shockingly poor retention in care figures. – Spotlight*
Male condom distribution	Reach of condom distribution programme	723,799,877 (2014/15): SANAC's 2016 NSP Progress Report on NSP 2012-2016						
Number of men circumcised, medically (MMC) and traditionally (TMC)	Reach of male circumcision (MC) programmes	508,404 (2014/15): Department of Health; Annual Report 2015	482,272 (2014): AIDS Info-UNAIDS	514,991 (2012/13): SANAC's NSP Progress Report 2014				
Percent of people per year who become eligible and receive ART	Coverage of the ART programme	73% (adults), 75% (children) (2014): SANAC's 2016 NSP Progress Report on NSP 2012-2016	82% (2013): Joint Review of HIV, TB, & PMTCT Programmes in South Africa 2013					
Number of people reached by prevention communication at least twice a year	Reach of communications	82% (2012): SANAC's 2016 NSP Progress Report on NSP 2012-2016						
Stigma Index	Trends of stigma and discrimination experienced by those with HIV or TB	35% external stigma among PLHIV 43% internal stigma among PLHIV 36.3% TB related stigma (2015): SANAC's 2016 NSP Progress Report on NSP 2012-2016						

National Strategic Plan coming end of this year!

NSP INDICATORS

Are we meeting the NSP targets?

Compiled by Kristanna Peris & Marcus Low

The National Strategic Plan for HIV, STIs, and TB 2012-2016 (NSP) set a number of ambitious targets for South Africa to have reached by 2016. While 2016 data will not be available for another year or two, the available data (mostly from 2014 and 2015) is nevertheless illuminating.

So, lifetime treatment means…

- Less and less tolerance for ‘’nuisance’’ side effects
- Far less focus on the initiation period, sickness
- Interest in contribution of ARVs & HIV to other non-communicable disease risk factors
- Focus on costs – especially of drugs
- Focus on longer-acting injectables, implantables
- Interest in ‘’cure’’
- Unacceptable to have ‘’lesser’’ drugs in lower-income countries – complex!
- Harmonisation between paeds and adults

Thank you

USAID, UNITAID, WHO, HIV i-Base, CHAI, Mylan, ICAP, MPP, Andrew Hill, Anton Pozniak, Marta Boffito, Michelle Moorhouse

OPTIMIZE

Save the Date

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JOHANNESBURG, SOUTH AFRICA,
6 - 8 NOVEMBER 2017

XXVI INTERNATIONAL WORKSHOP ON HIV DRUG RESISTANCE AND TREATMENT STRATEGIES
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