Why can TAF and DTG solve some implementation problems in LMICs?

July 2017

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WITS RHI

* Thanks Beatriz Grinsztejn

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

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/

- The international programme is doing well (from a drug choice perspective)! We need a lot of evidence to start tinkering with it
- Dolutegravir – potential game changer re resistance (and replace efavirenz)
- Tenofovir alafanemide (TAF)- lower dose, less toxic version of currently used tenofovir (TDF)

Summary Indicators | Provincial Comparison | Quarterly Trends | Map View

GROUPING: Quarter: Q1 2015

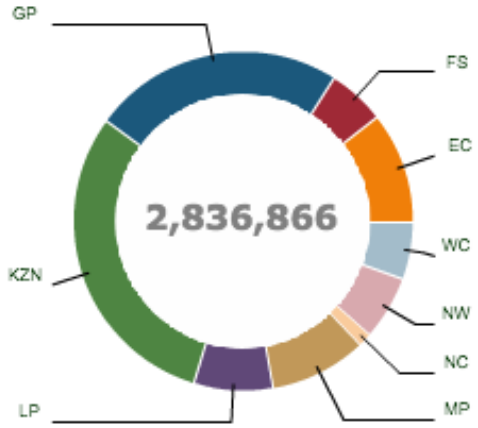
NATIONAL HEALTH LABORATORY SERVICE

Summary indicators for CCMT M&E in SA - Adults

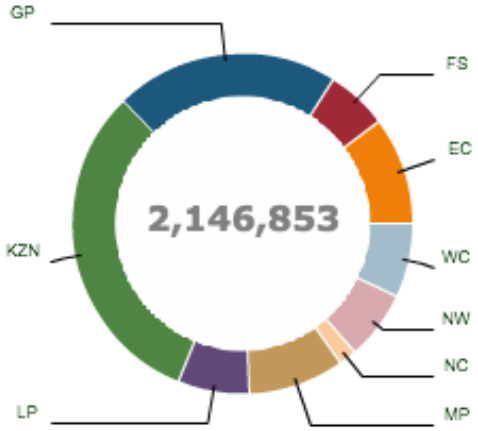
Period: from Q1 2012 to Q1 2015

Select Age Category: **Adults** | Children <15 years

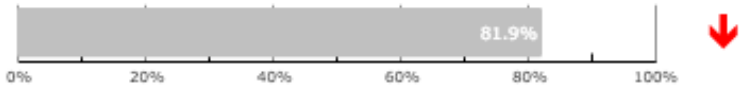
People on treatment (DHIS)



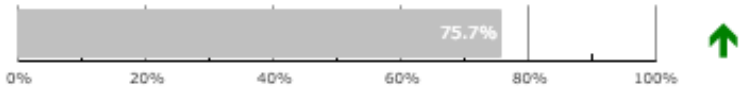
People with a VL test done in the last 12 months



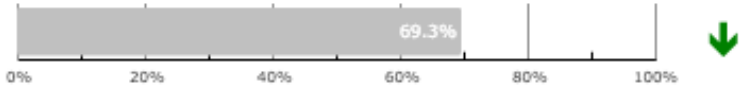
% People in care and on ART with a VL <= 1000 copies/ml



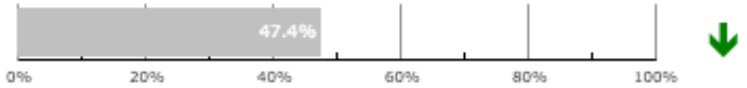
% People in care and on ART, who have a VL done at least annually



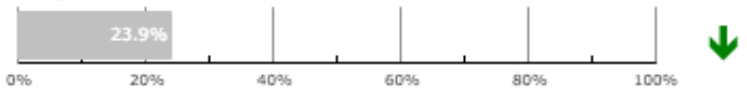
% People with CD4 tests done, with a CD4 count <= 500 cells/mm3



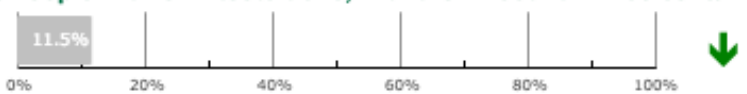
% People with CD4 tests done, with a CD4 count <= 350 cells/mm3



% People with CD4 tests done, with a CD4 count <= 200 cells/mm3

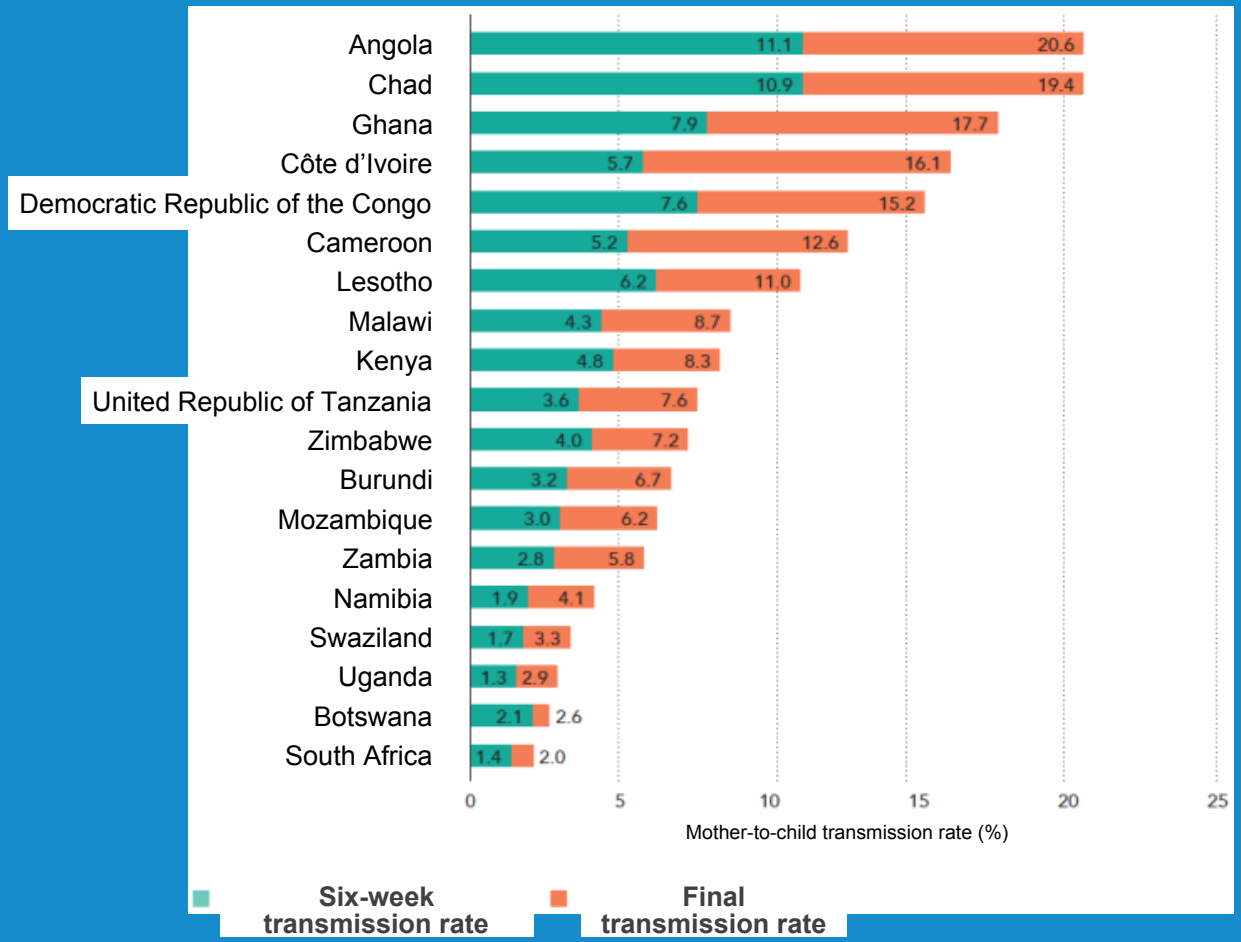


% People with CD4 tests done, with a CD4 count <= 100 cells/mm3



EC - Eastern Cape, FS - Free State, GP - Gauteng, KZN - KwaZulu Natal, LP - Limpopo, MP - Mpumalanga, NW - North West, NC - Northern Cape, WC - Western Cape

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



Source: UNAIDS 2016 estimates

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

~4 YEAR LAG BETWEEN SCALE UP OF ART AND DECLINE IN MTB INCIDENCE

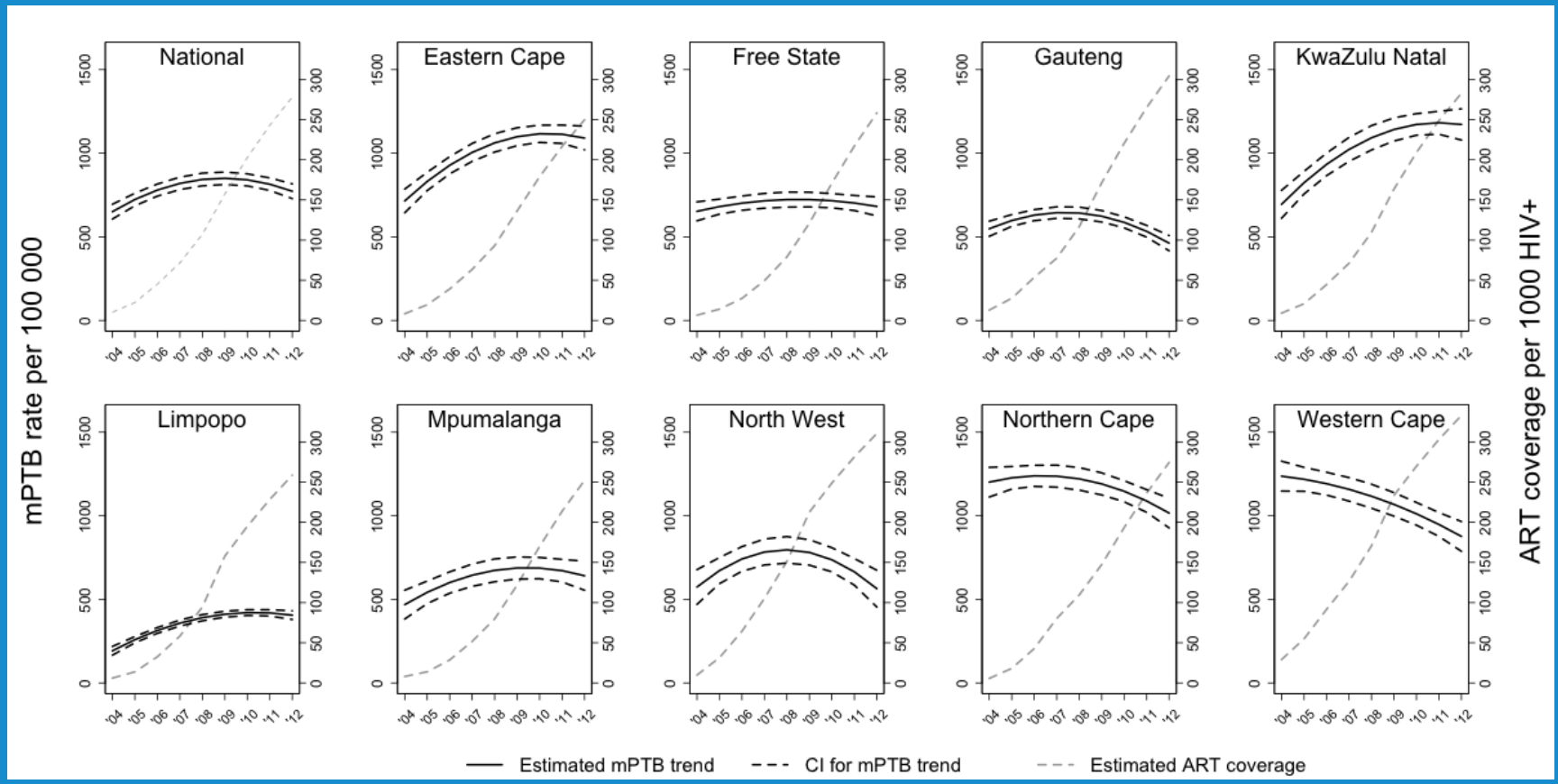
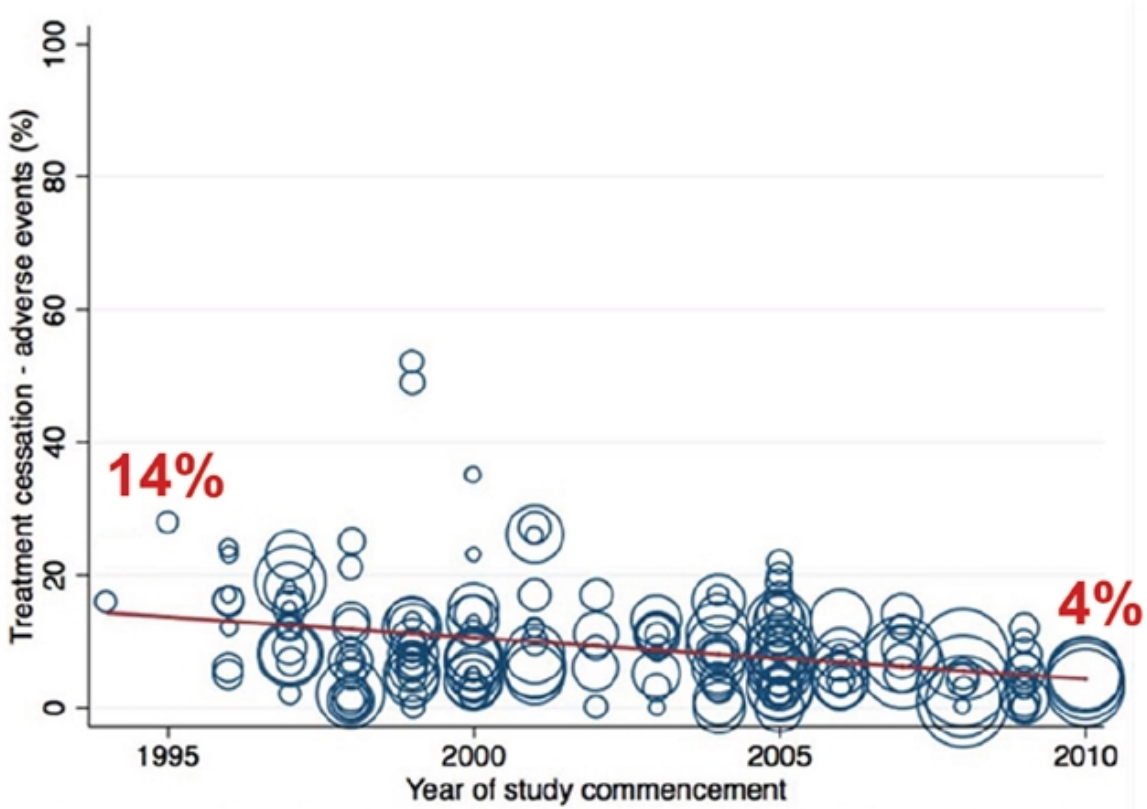


Figure 1: Incidence of microbiologically-confirmed pulmonary tuberculosis (per 100,000 population) and antiretroviral treatment coverage rates in HIV-infected individuals nationally in South Africa nationally and provincially from 2004 to 2012

The solid black line represents the estimated trend in PTB incidence per 100,000 population over the study period and the dotted black line the corresponding 95% confidence interval. The overlaid dotted grey line is the ART coverage per 1000 HIV positive individuals based on data from the ASSA 2008 model.

Nanoo A, Izu A, Ismail, NA, Ihekweazu C, Abubakar I, Mametja D, Madhi SAM. 2015. Nationwide and regional decline in incidence of microbiologically-confirmed pulmonary tuberculosis in South Africa: a time series analysis from 2004 to 2012. The Lancet Infectious Diseases, In press

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)

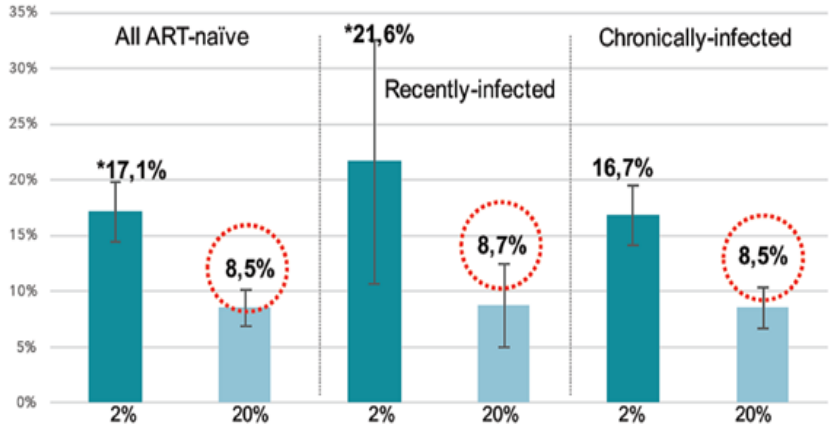
Carr A (2014). PLoS ONE 9(5): e97482.

Do we have a resistance problem?

Pretreatment Drug Resistance in TASP trial

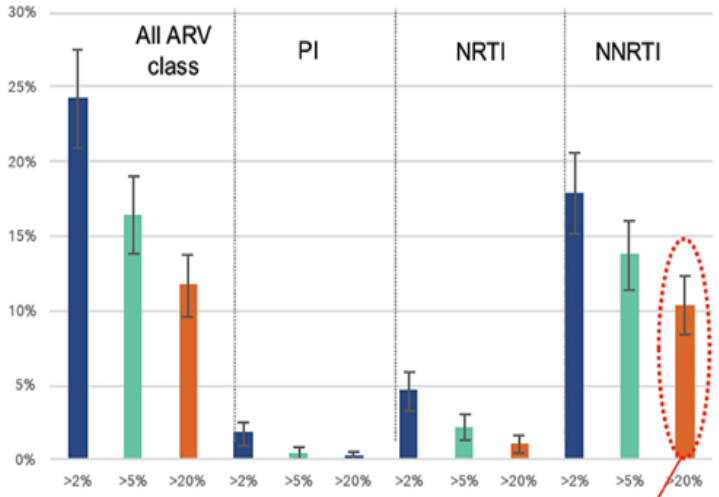
AHRI AFRICA HEALTH RESEARCH INSTITUTE

Prevalence of PDR in TASP



*include only NGS data

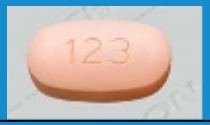
Distribution of Drug Resistance Mutations per ARV class in all ART-naive



- 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



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

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

XTC, other nukes

Darunavir **Raltegravir** **Etravirine**

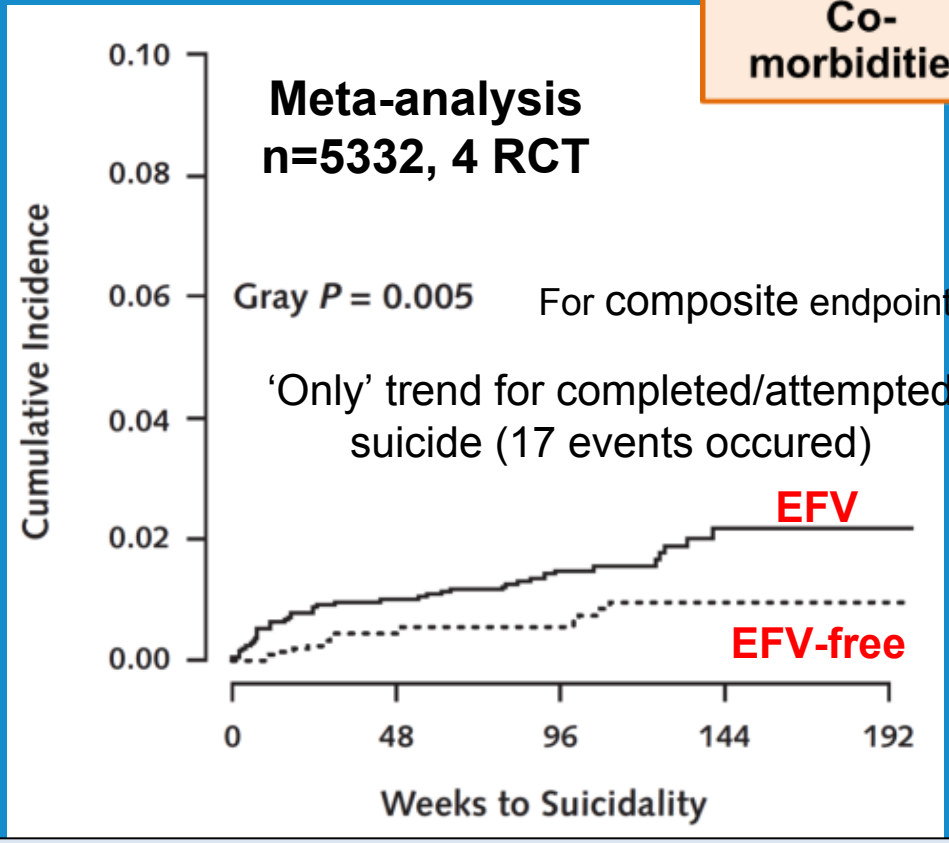
Efavirenz

- Daily, cheap, co-formulated, huge experience base, TB (and most everything else)-friendly
- EFV side effects predictable, treatable, substitutions easy
- Increasing recognition of CNS side effects
- Rash, hepatitis, gynaecomastia, lipids
- 2016: serious and fatal rare CNS side effects, hepatic events

Depression

Co-morbidities

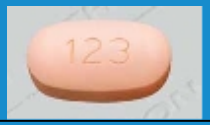
- **Efavirenz** (6%)
  2x higher risk for suicidality
- **Rilpivirine** (8%)
- **Elvitegravir/COBI** (5%)
- **Raltegravir** (6%)
- **Atazanavir/r** (2%)



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



TDF + **XTC** + **DTG**

AZT + **3TC** + **PI** (lopinavir or atazanavir)

XTC, other nukes

Darunavir **Raltegravir** **Etravirine**

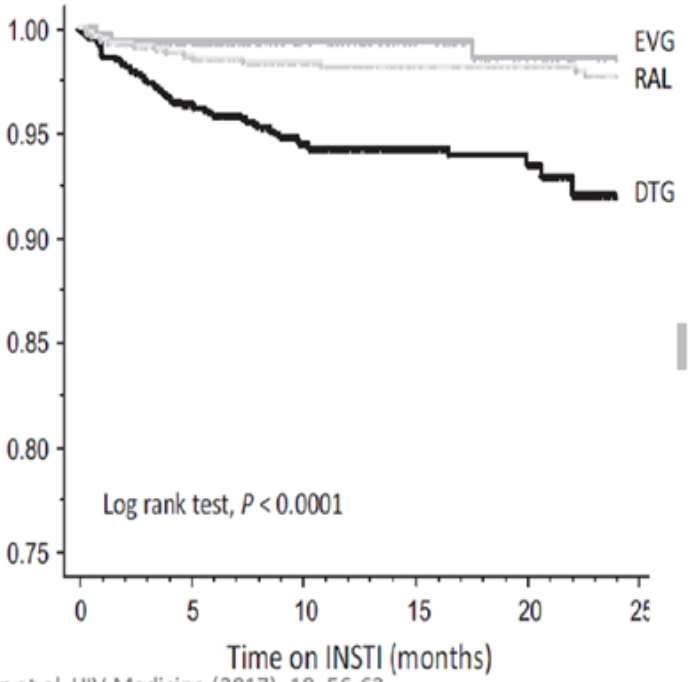
DTG near unbreakable….

- And cheaper than EFV is many countries!
- Very well tolerated

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

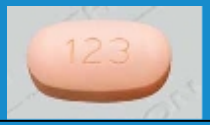
Factors associated with DTG discontinuation

	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

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

TAF +  XTC + DTG

AZT + XTC + PI (lopinavir or atazanavir)

XTC, other nukes

Darunavir

Raltegravir

Etravirine

TAF

- Safer (laboratory)
- Cheaper than TDF

But

- TAF and DTG are made by commercial competitors
- Need data before moving millions of people over

New Studies with DTG & TAF in PLHIV

(adults & children)

M Vitoria, Nov 2016

DTG & TAF STUDIES IN PLHI V

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

What is the cost if we switch to DTG/TAF?

- Millions of patients will need to be switched (assuming stable patients on EFV will move, seems likely) – huge undertaking – and the manufacturing changes will likely be slightly chaotic
- Moving from EFV to DTG unlikely to be a big deal (?VL) ; reverse a problem
- TAF to TDF not an issue
- ?harmonisation between and within different countries
- Pregnancy – limited data
- TB – studies are needed
- Studies largely done in men
- Hep B=major problem when considering DTG/3TC dual therapy

So…

- DTG may mean second and subsequent regimens are unusual – huge implications for focus on VL and adherence and genotyping
- May mean we can transition all second line back to first
- TAF very important for cost, long-term toxicity
- Hep B a constant challenge; hep C coming

WITS RHI

Thank you

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

Save the Date

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CONFERENCE 2018

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JOHANNESBURG, SOUTH AFRICA,
6 - 8 NOVEMBER 2017

www.HIVresistance2017.co.za