Where does rilpivirine fit in?

Francois Venter

March 2018

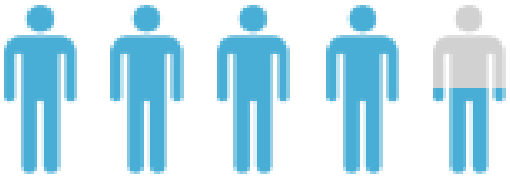
University of the Witwatersrand
WITS RHI

Thanks Michelle Moorhouse

UNIVERSITY OF THE WITWATERSRAND
JOHANNESBURG

90%

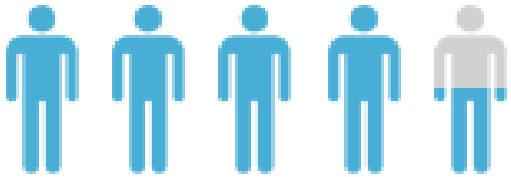
of all



living with HIV will know their HIV status

90%

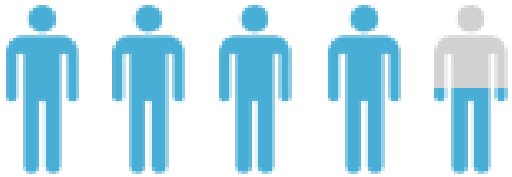
of all



living with HIV will receive sustained antiretroviral therapy

90%

of all



receiving antiretroviral therapy will have durable viral suppression

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SA Snapshot

- 4.2 million 1st line end 2017 ($110/year)
- 170 000 2nd line ($350/year)
- 1300 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]

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How has ART changed?

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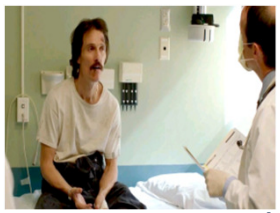
The Evolving HIV Treatment Paradigm

- 3TC=lamivudine; ZDV=zidovudine

HIV-1 discovered

1983



ZDV monotherapy

1987

ZDV/3TC

1995

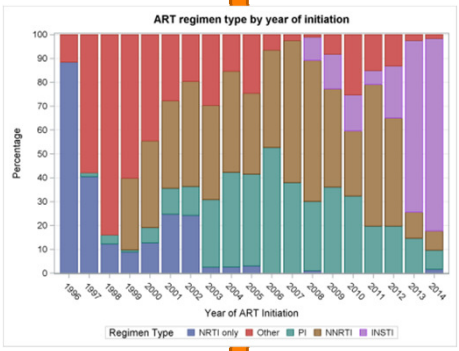
Triple-Drug Therapy

1996

Single-Tablet Regimens

2006

The Integrase Era



2012–2013

Long Acting Injectable?

2017

?????

2020

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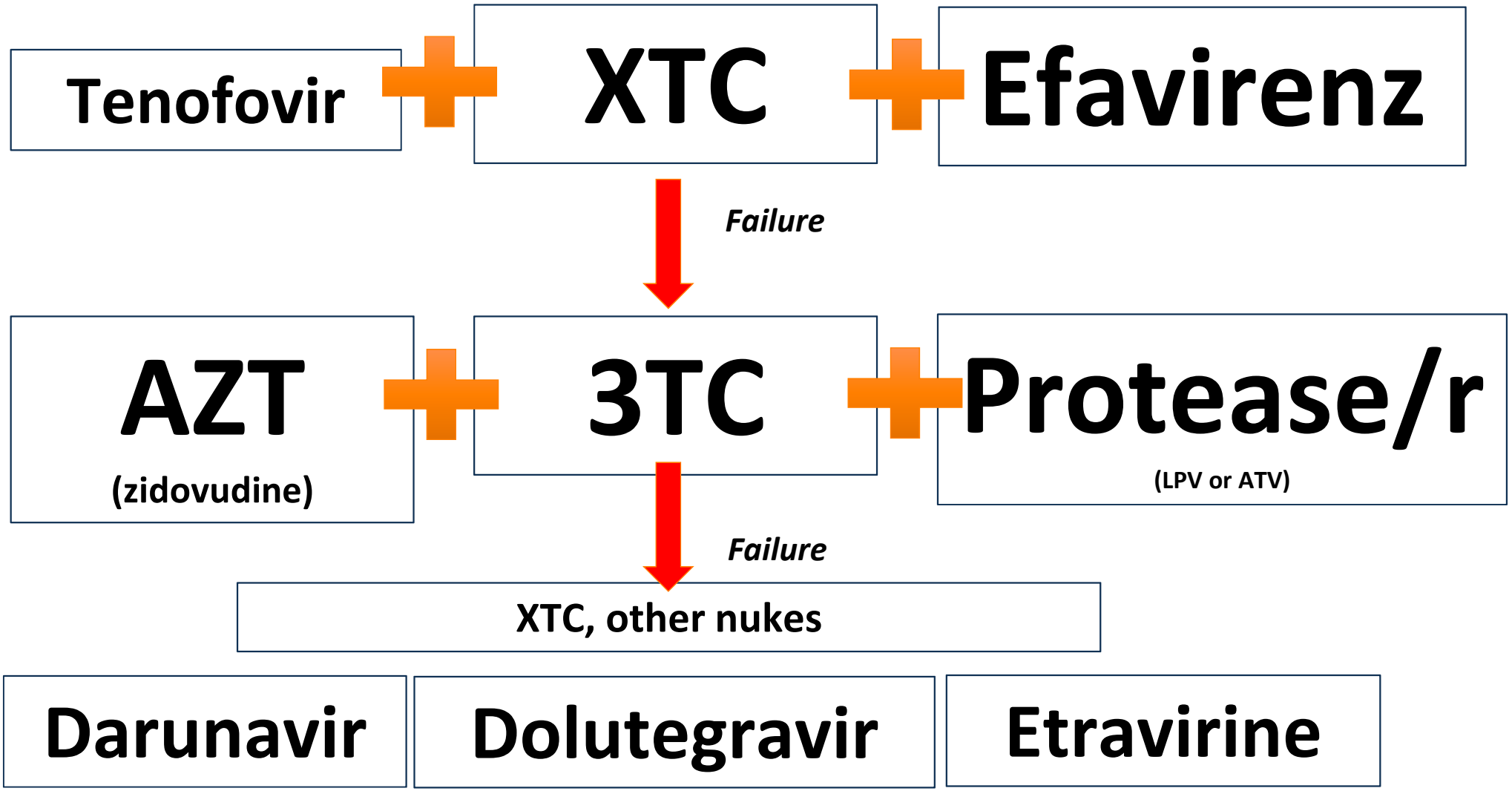
Current ART in SA



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First-line…

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

Cost driver
Toxicity

Desirable Property	EFV/TDF/FTC
High resistance barrier	No
Well tolerated	Not initially
No lab tox monitoring	TDF creat
Safe in pregnancy	Yes
Low pill burden	Yes FDC
Once a day	Yes
Use with TB (rif)	Yes

Toxicity driver
Pill size
Low genetic barrier
Cost

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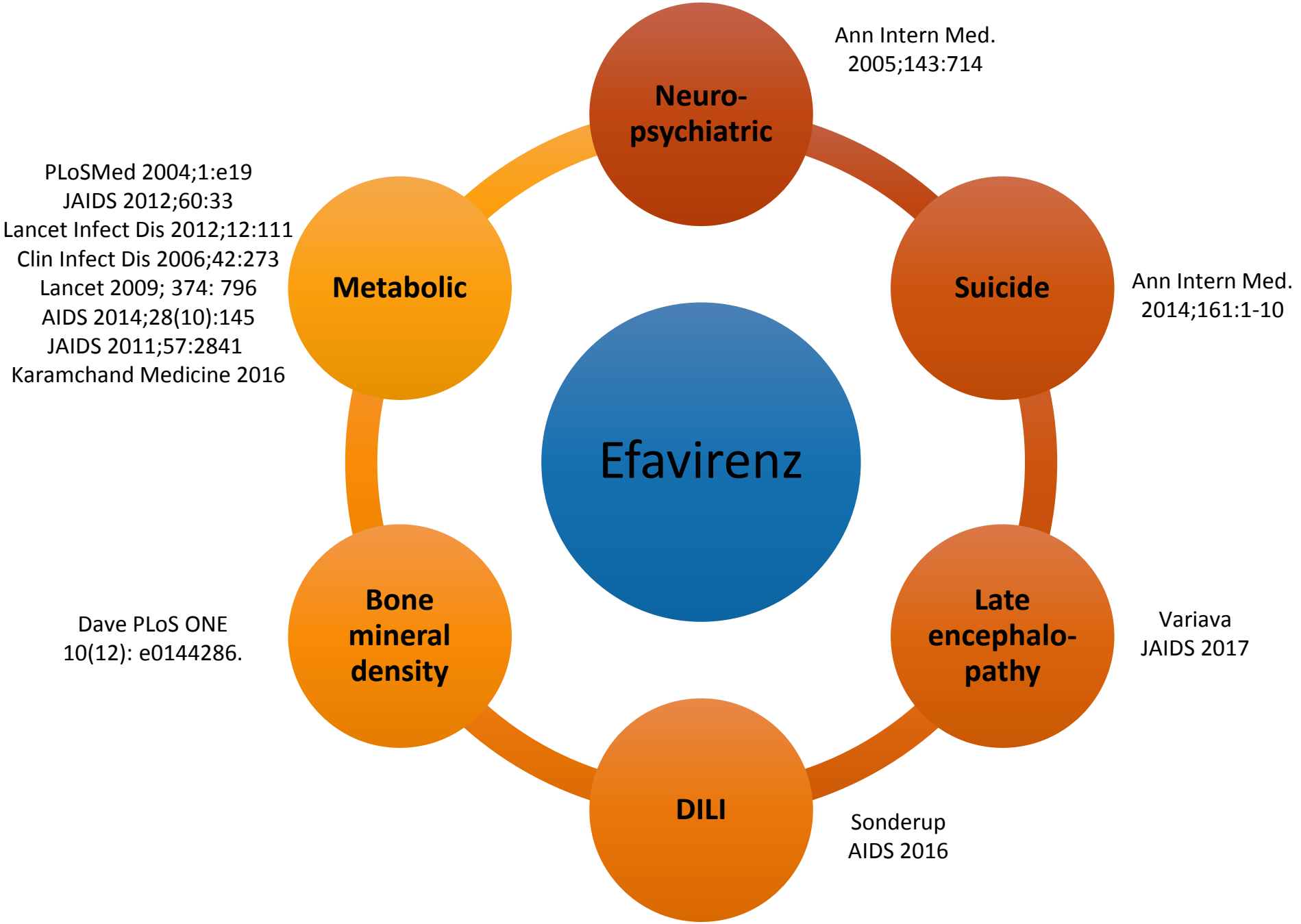
Efavirenz's side effects…



What are the ‘’third drug’’ options?

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Alternatives…

- Protease inhibitors – toxic, expensive, not discussed
- Integrase inhibitors
- Rilprivine

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What about: Dolutegravir

- Wunderkind of the moment
- 50 mg once-daily (in naïve patients)
- Very good efficacy
- Minimal toxicity
- Pregnancy category B
- Superior to EFV at 48 weeks in naïve patients– SINGLE study (compared ABC/3TC/DTG with TDF/FTC/EFV.) – but safer, not virologically better
- Potential to be low cost and co-formulated
- Some concerns about resistance claims, creat clearance
- **CHOICE of DoH!**

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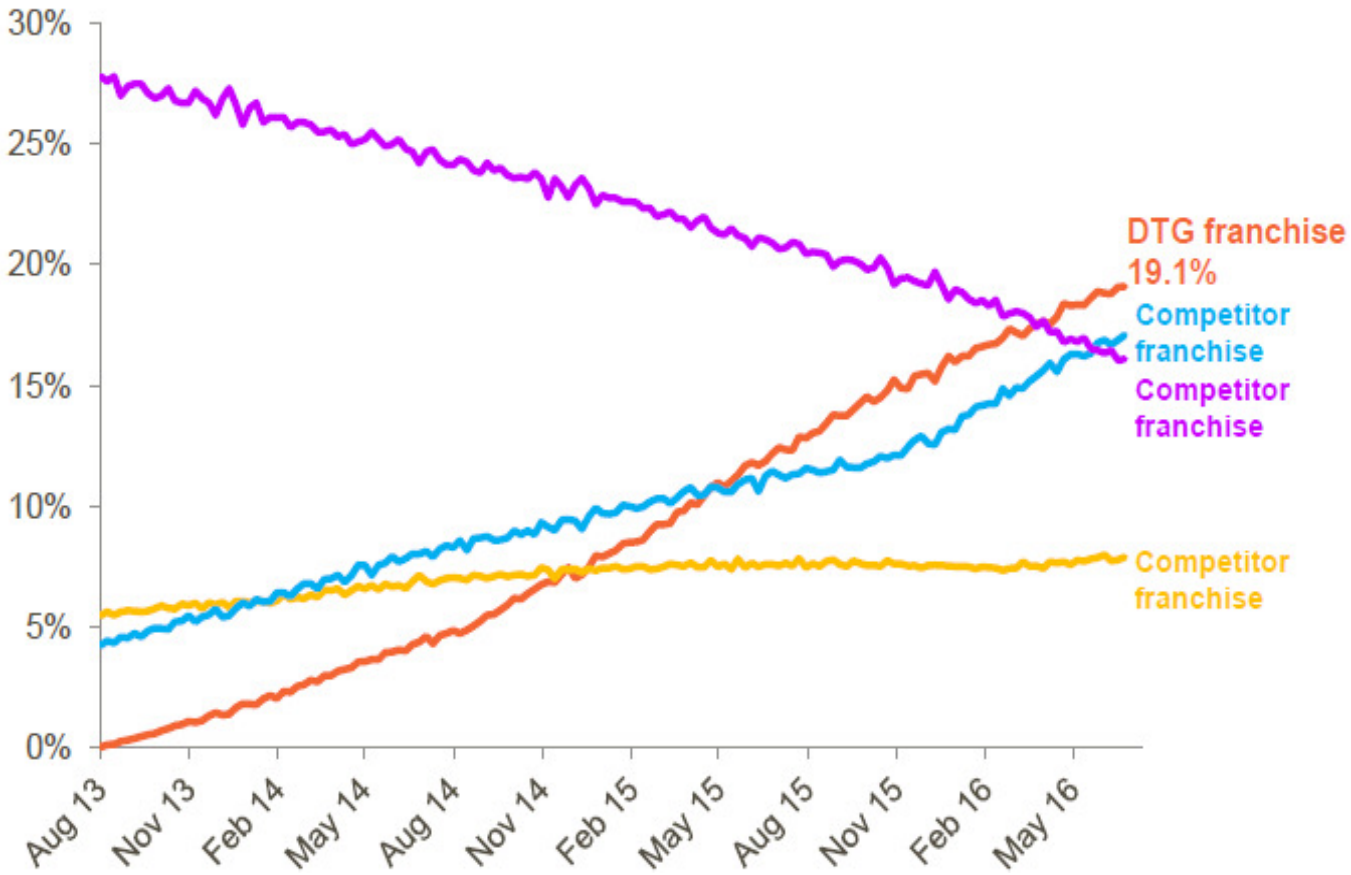
US Weekly Treatment Market Share Since DTG Launch



- 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

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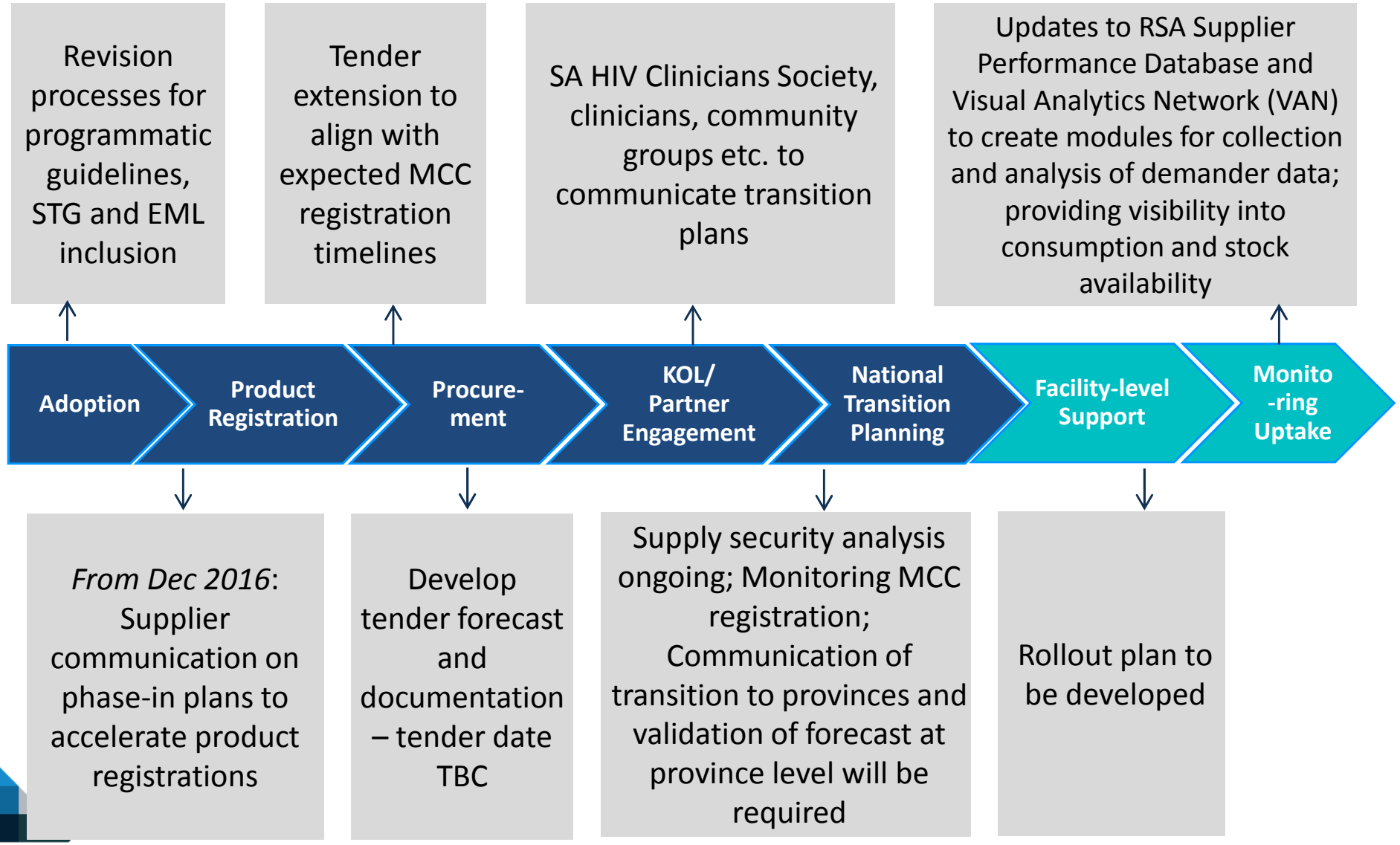
USAID FROM THE AMERICAN PEOPLE
SOUTH AFRICANS AND AMERICANS IN PARTNERSHIP TO FIGHT HIV/AIDS
PEPFAR
Unitaid Innovation in Global Health
saMRC advancing life

Significant technical/programmatic work is required for full transition to TLD in 2018



Elvitegravir

- Integrase inhibitor
- Requires boosting
  - ritonavir
  - cobicistat
- Co-formulated with a booster, TDF and FTC
- Renal monitoring, drug interactions

- QUAD-Stribild

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Raltegravir

- Integrase inhibitor, very well tolerated, price dropping
- Very heavily studied
- TB friendly
- Expensive, no co-formulations, low resistance barrier

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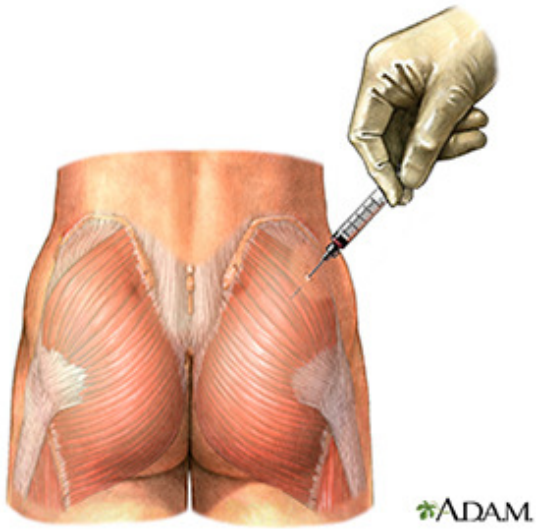
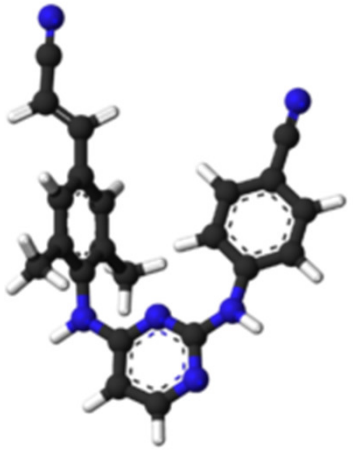
What about: Rilpivirine





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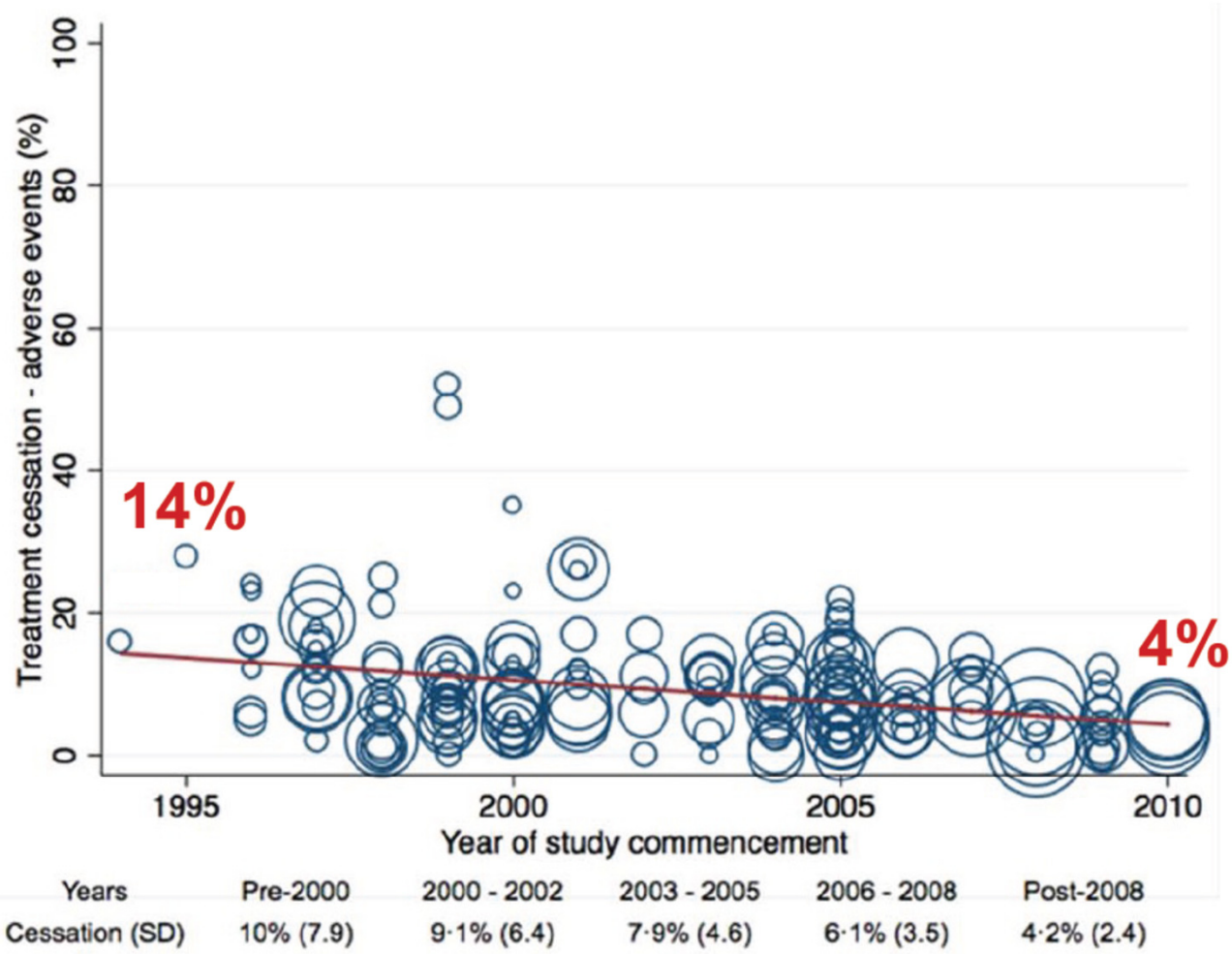
NNRTI history and rilpivirine

- ''First generation" – nevirapine (1996 licenced by FDA), delavirdine (1997), efavirenz (1998)
- Rilpivirine licenced by FDA in 2011 (including as a single (Edurant), fixed dose combination (Complera, with TDF/FTC)
- TAF/FTC/rilpivirine (Odefsey) licenced in 2016
- Injectables being explored
- Dolutegravir/rilpivirine (Juluca) Nov 2017 – <u>for switch</u>
- Only the single in SA at the moment

What are the considerations?

- Once/day
- Higher resistance barrier than first generation NNRTIs
- Indicated > age 12, >35kg
- Pregnancy category B (although few exposures in pregnancy registry)
- Very cheap

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)

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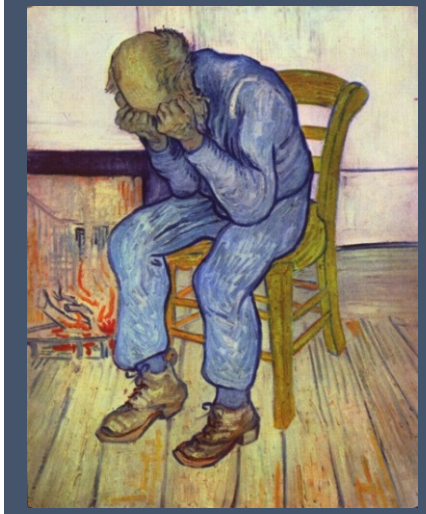
Carr A (2014). PLoS ONE 9(S): e97482

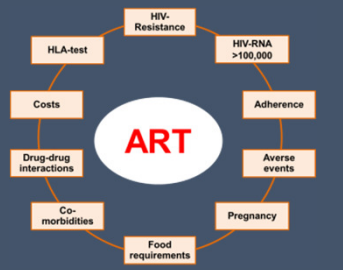
Better than efavirenz re side effects (ECHO and THRIVE)

TABLE 3. Summary of Treatment-Emergent AEs and Laboratory Abnormalities at the Time of the Week-48 Analysis

	RPV 25 mg Once Daily, N = 686	EFV 600 mg Once Daily, N = 682
Median (range) treatment duration (wks)	56 (0–87)	56 (0–88)
AE, n (%)		
Any AE	616 (90)	629 (92)
Any treatment-related AE ≥ grade 2	109 (16)*	212 (31)
AE leading to permanent discontinuation	23 (3)	52 (8)
Any serious AE (including death)	45 (7)	55 (8)
Death	1 (0.1)	4 (1)
Most common treatment-related AEs ≥grade 2 and occurring in ≥2% of patients in either group†		
Rash‡	7 (1)*	56 (8)
Dizziness	4 (1)	43 (6)
Abnormal dreams/nightmares	9 (1)	25 (4)
Headache	11 (2)	15 (2)
Insomnia	12 (2)	16 (2)
Nausea	5 (1)	17 (2)
Most common treatment-related AEs of interest (all grades) occurring in ≥10% of patients in either group†,§		
Any neurologic AE‖	117 (17)*	258 (38)
Dizziness	55 (8)*	179 (26)
Any psychiatric AE¶	102 (15)#	155 (23)
Abnormal dreams/nightmares	56 (8)**	87 (13)
Rash‡	21 (3)*	93 (14)
Treatment-emergent grade 2–4 laboratory abnormalities occurring in ≥5% of patients in either group, n (%)		
Any grade 2–4 laboratory abnormality		
Hypophosphatemia	62 (9)	69 (10)
Increased pancreatic amylase	42 (6)	60 (9)
Hyperglycemia (fasted)	37 (5)	30 (4)
Grade 2–3 increased LDL-cholesterol (fasted)††	38 (6)	102 (15)
Grade 2–3 increased total cholesterol (fasted)	34 (5)	122 (18)
Increased aspartate amino transferase	33 (5)	60 (9)
Increased alanine amino transferase	35 (5)	66 (10)

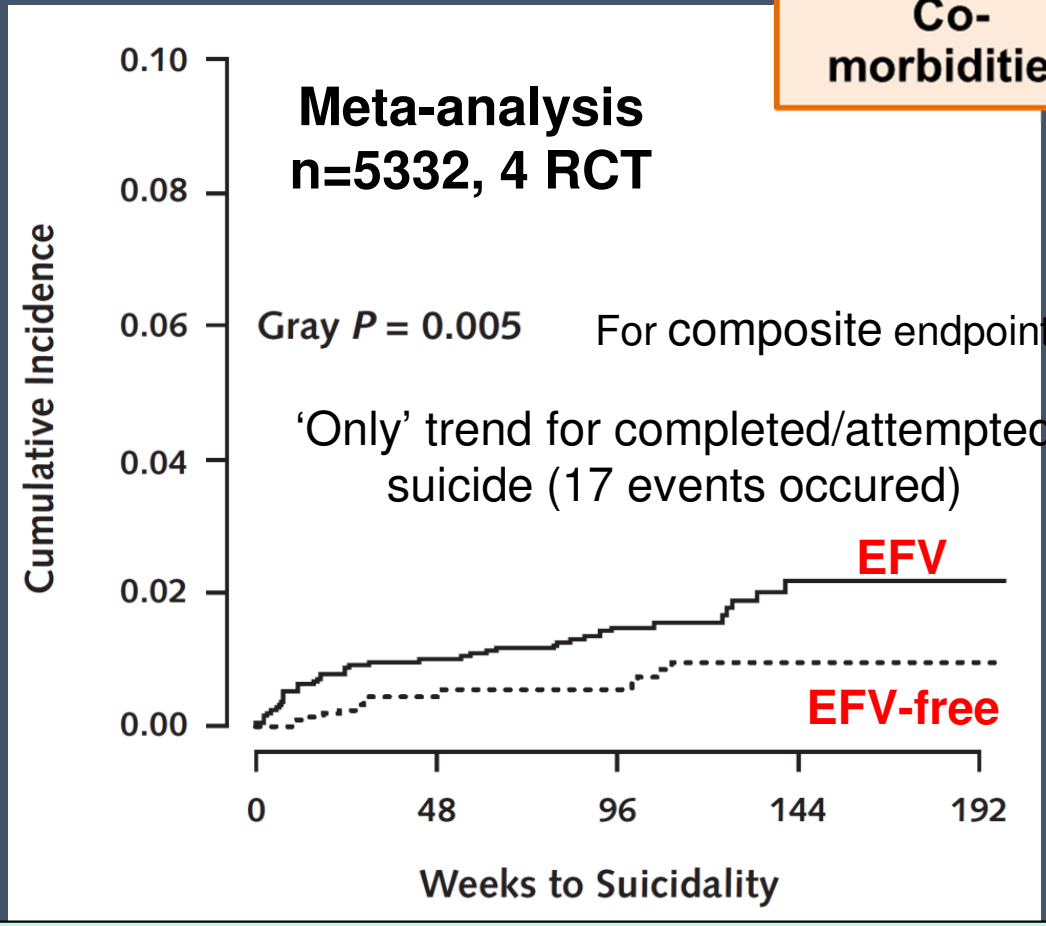


Depression



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

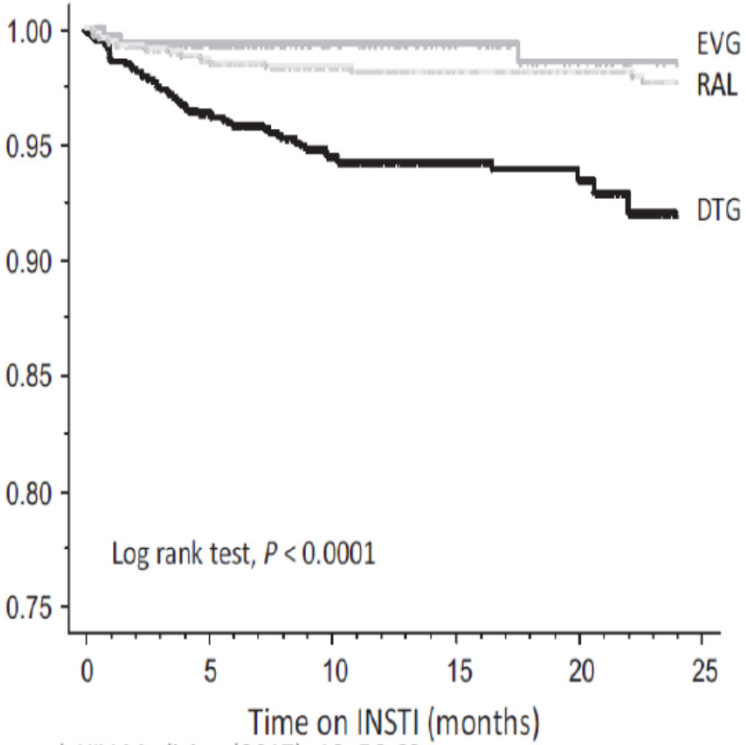
C. Smith; L. Ryom; A. d'Arminio Monforte; P. Reiss; A. Mocroft; W. El-Sadr; R. Weber; M. Law; C. Sabin; J. Lundgren.

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

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

Why isn’t it used everywhere????

- Can’t use with rifampicin OR rifabutin
- Food restriction – need to take with a meal
- Lack of available co-formulation
- Appears to fail more often if VL>100 000 copies (vs. efavirenz) – 2-3x risk virological failure and resistance emerging
  - Does NOT apply if using as switch, if started >100 000 on original regimen
  - May be an issue with other NNRTIs too
  - Note: still works in majority (83%) of patients if VL>100 000

Other issues to consider

- Little data on ABC/3TC with rilpivirine
- CI if PPI; absorption generally an issue
- Is it an alternative to people who can't tolerate efavirenz or dolutegravir? Excellent in SALIF
- Several studies suggesting good durability
- First line choice in a healthy person with low VL initiating ART? No study vs. dolutegravir yet (in fact, used in combination! Network analysis suggests dolutegravir superior)
- And an option for PEP (but ?benefit over FDC?)

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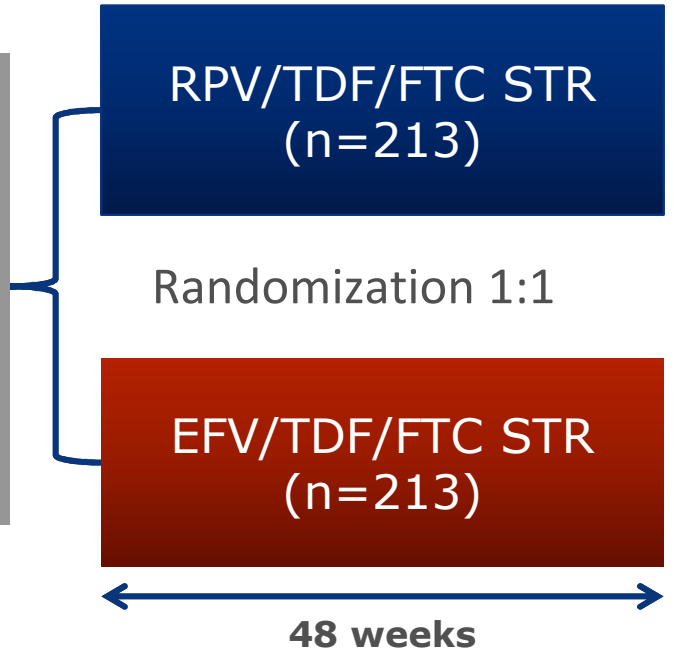
SALIF – Study design

Switching **A**t **L**ow HIV-1 RNA **I**nto **F**ixed Dose Combinations

- A 48-week randomized, open-label study of RPV/TDF/FTC STR as an appropriate "switch" option for virologically suppressed HIV-1 infected patients in low- and middle income countries on stable NNRTI-based therapies

Key entry criteria:

- On first-line ART with **EFV** or **NVP** for ≥1 year*
- Plasma HIV-1 RNA <50 copies/mL
- CD4 >200 cells/mm^3
- No history of virologic or immunologic failure during ART
- No known primary N[t]RTI or NNRTI mutations



- Randomization stratified by NNRTI at screening (EFV or NVP)
- Key **exclusion** criteria:

TB requiring rifampicin based treatment or CrCl <50 mL/min

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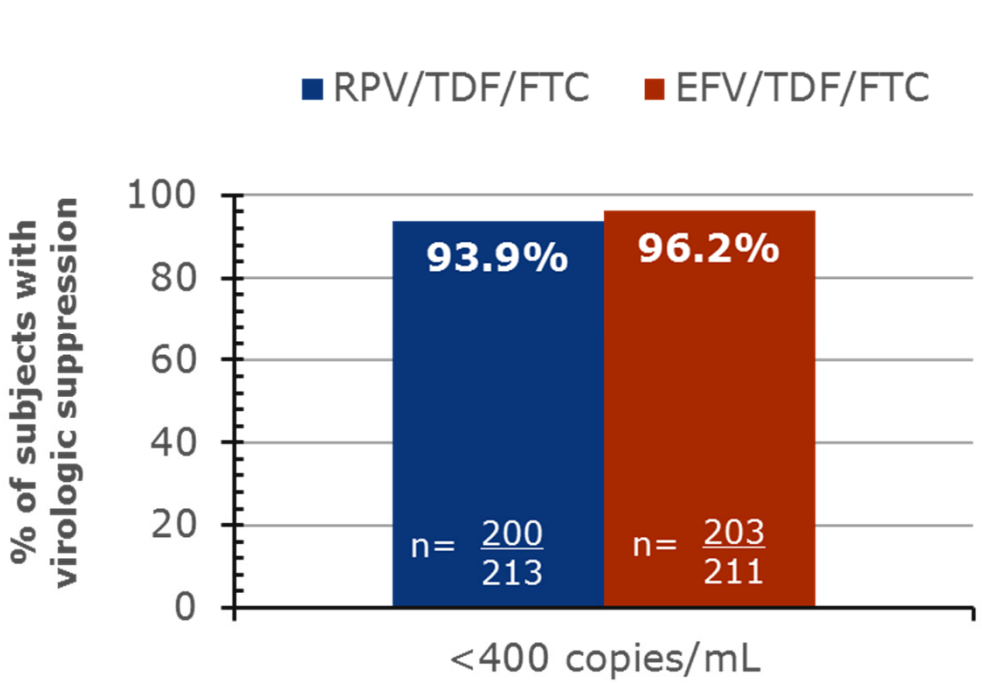
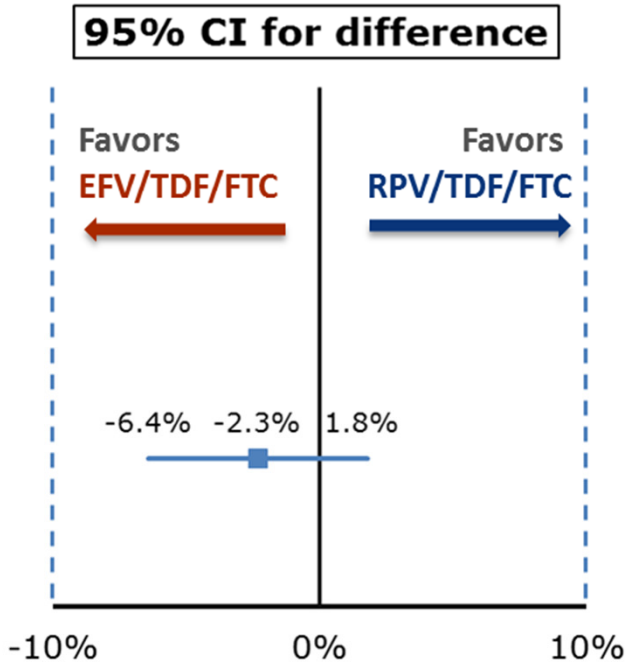
Munderi et al. AIDS 2016; Durban, South Africa. #THAB104

*Switch from NVP to EFV allowed but not vice versa

SALIF – Virological suppression

HIV-1 RNA <400 copies/mL (FDA Snapshot at week 48, ITT)





- RPV/TDF/FTC as a switch option is **non-inferior** to EFV/TDF/FTC regardless of suppression cut-off of <400 or <50 copies/mL
- 1 confirmed virologic failure ≥400 copies/mL in each study arm (0.5%)
  No ARV resistance observed - preserved future ARV options

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Munderi et al. AIDS 2016; Durban, South Africa. #THAB104

SALIF – Safety

Number of Subjects with	**RPV/TDF/FTC (n=213)**	**EFV/TDF/FTC (n=211)**
SAE	16 (7.5%)	11 (5.2%)
At least possibly related	3 (1.4%)	1 (0.5%)
Fatal SAE (MI, unrelated)*	1 (0.5%)	0
AE, grade 3 or 4	40 (18.8%)	56 (26.5%)
At least possibly related	13 (6.1%)	4 (1.9%)
AE of interest (all cause)		
Rash	32 (15.0%)	23 (10.9%)
Neuropsychiatric	60 (28.2%)	63 (29.9%)
Headaches	38 (17.8%)	29 (13.7%)
Dizziness	7 (3.3%)	14 (6.6%)
Insomnia	10 (4.7%)	6 (2.8%)
Nightmare/abnormal dreams	4 (1.9%)	10 (4.7%)
Potential QT prolongation	3 (1.4%)	3 (1.4%)
AE leading to permanent stop study medication	8 (3.8%)†	1 (0.5%)

Munderi et al. AIDS 2016; Durban, South Africa. #THAB104

* MI = myocardial infarction; 55 year old, Asian male, with no known risk factors

† Includes 1 virologic failure

Finally, as an injectable….

- In combination with cabotegravir, 4-8 weekly
- Exciting for ‘’difficult adherence groups’’ – long road ahead for registration, likely to be expensive, but exciting
- ? Role in PrEP!

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Finally…

- Where does rilpivirine fall in an INSTI-dominated era?
- Tussle now re two and three drug regimens (DTG/3TC vs DTG/rilpivirine vs. TAF/FTC/BIC vs. ABC/3TC/DTG) in high income countries
- And between NRTI and non-NRTI regimens

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