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# Improving HIV treatment in Africa

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Africa

Thanks to: The Ezintsha team, HE<sup>2</sup>RO, Sydney Rosen, Anna Grismrud, Phumla Sinxabi, Andrew Hill, Gary Maartens, Mohammed Ali, Mark Siedner, Elvin Geng, Aaloke Mody, Jeff Wing, Vince Marconi, Yogan Pillay, Liesel Page-Shipp, Thato Chidarikire

# Disclosures: Francois Venter

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Shout out...  
<https://i-base.info/>

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# HIV pipeline

2021  
New drugs in development

htb supplement: 2021 Vol 22:(1), August 2021

## CONTENTS

### HIV pipeline 2021: targets in the HIV lifecycle

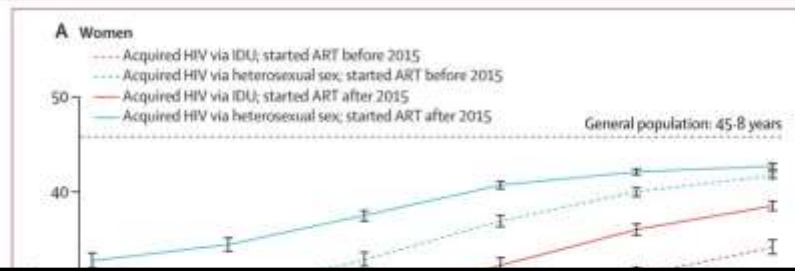
**Monoclonal antibodies (mAb)**

- IBS 407
- SPC8165 and SPC8745
- SBNC11745 and D-10745
- ECAP140, 10E6-Adidas
- PGT121 and PGT121-2
- MRG-019
- lenivimab, FRC-140

**Stages in the HIV lifecycle**

- 1 HIV attaches to a CD4 cell
- 2 HIV enters a CD4 cell and the viral RNA is released into the cell
- 3 The reverse transcriptase (RT) enzyme converts the viral RNA into DNA and integrase are released
- 4 Reverse transcriptase (RT) inserts HIV DNA into the host genome
- 5 HIV DNA enables HIV DNA to be used to produce new HIV particles
- 6 Entry and production of new HIV particles

# HIV treatment is VERY effective, if given early

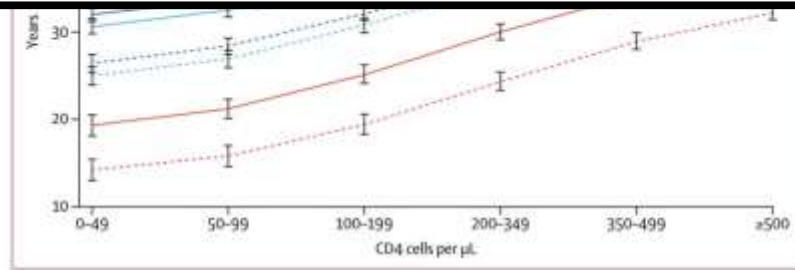


## Life expectancy after 2015 of adults with HIV on long-term antiretroviral therapy in Europe and North America: a collaborative analysis of cohort studies

Adam Trickey, Caroline A Sabin, Greer Burkholder, Heidi Crane, Antonella d'Arminio Monforte, Matthias Egger, M John Gill, Sophie Gribas, Jodie L Guest, Inma Jaram, Flana C Lampe, Niels Obel, Juliana M Reyes, Christoph Stephan, Timothy R Sterling, Ramon Teira, Giota Touloumi, Ian Christian Wainwright, Frederic Wit, Linda Wilkins, Robert Zangerle, Michael Sillman, Amy Justice, Jonathan A F Sterne



“...life expectancy was only a few years lower than that in the general population .... However, for people with low CD4 counts at the start of follow-up, life-expectancy estimates were substantially lower...”



(23.9–25.9) left if they started ART after 2015. The corresponding estimates for men were 18.2 years (17.1–19.4) and 23.7 years (22.7–24.8). Women with CD4 counts of at least 500 cells per µl had 40.2 years (39.7–40.6) of life left at age 40 years if they started ART after 2015. The corresponding estimates for men were 39.7 years (39.2–40.2) and 40.2 years (39.7–40.6) if they started ART before 2015.

**Interpretation** For people with HIV on ART and with high CD4 counts at the start of follow-up, life expectancy was only a few years lower than that of the general population if ART was started after 2015. However, for people with low CD4 counts at the start of follow-up, life expectancy was substantially lower than that of the general population if ART was started after 2015, emphasising the continuing importance of early ART.

**Funding** US National Institute on Alcohol Abuse and Alcoholism

ARTICLES | VOLUME 10, ISSUE 5, E255–E307, MAY 2023

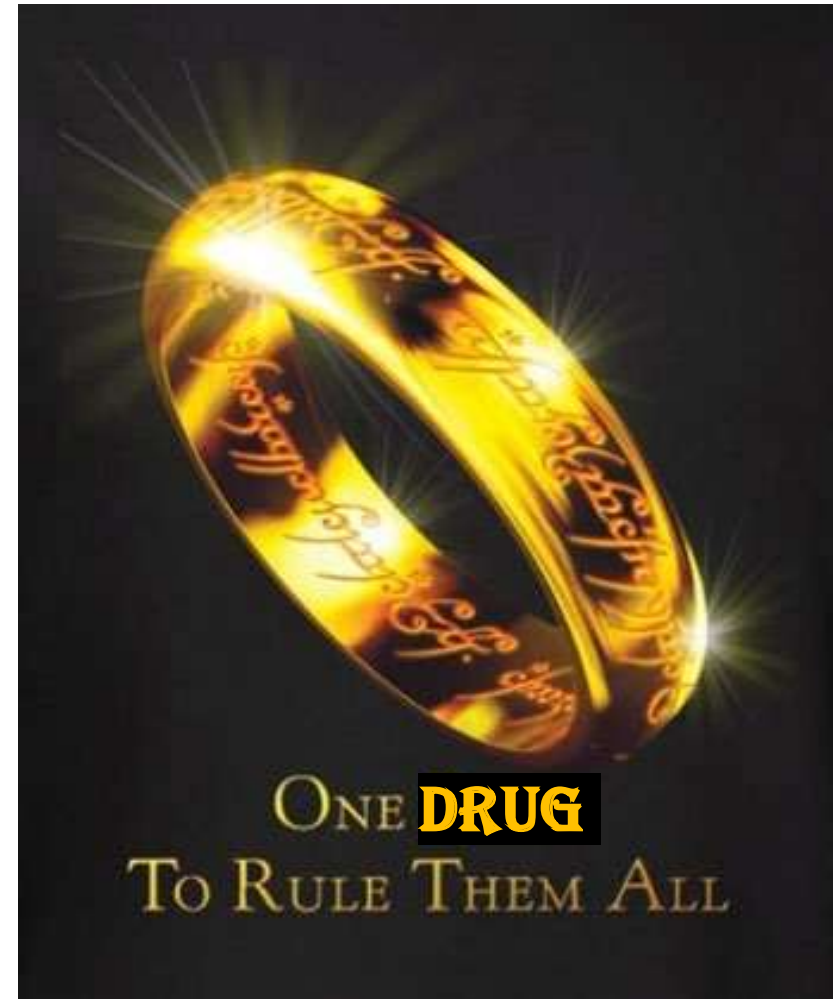
### Life expectancy after 2015 of adults with HIV on long-term antiretroviral therapy in Europe and North America: a collaborative analysis of cohort studies

Adam Trickey, PhD, • Prof Caroline A Sabin, PhD • Greer Burkholder, MD • Prof Heidi Crane, MD • Prof Antonella d'Arminio Monforte, PhD • Prof Matthias Egger, MD • et al. [Show all authors](#)

[Open Access](#) • Published: March 20, 2023 • DOI: [https://doi.org/10.1016/S2352-3018\(23\)00028-0](https://doi.org/10.1016/S2352-3018(23)00028-0)

# Big changes of last 5 years:

- Dolutegravir replaced efavirenz
  - Better side effects
  - Better persistence
  - Remarkable resistance profile
  - Cheaper?



# WHO 2019 guidelines: Dolutegravir

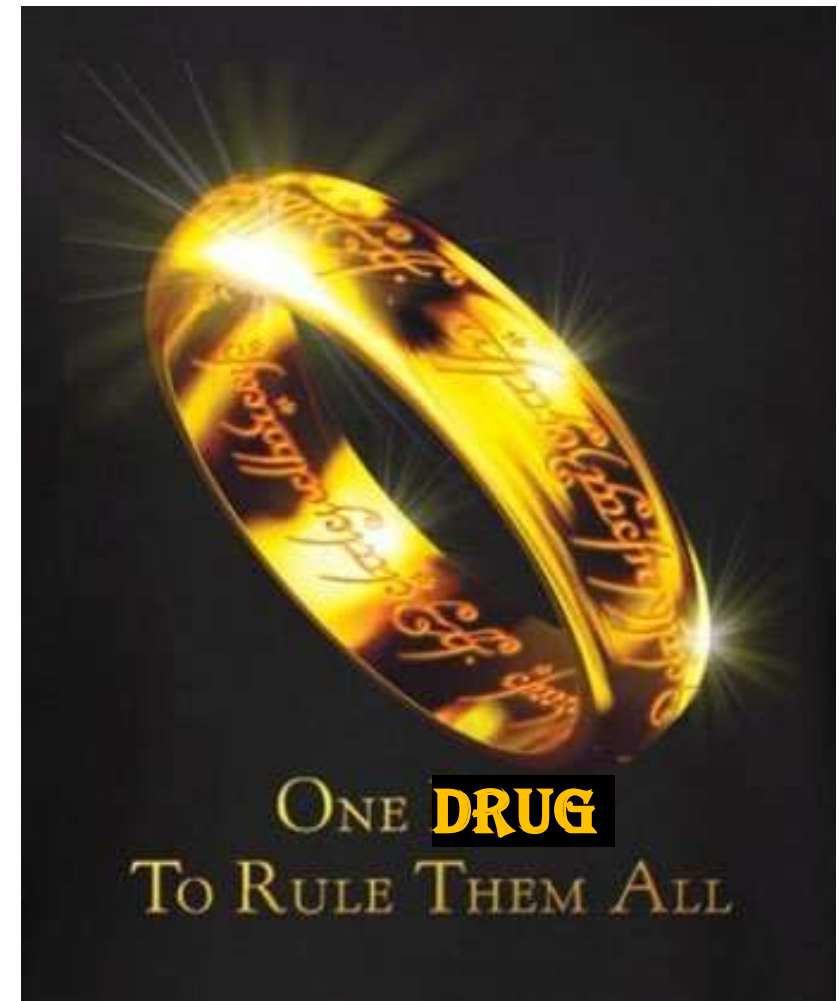
Population	First-line regimens	Second-line regimens	Third-line regimens
Adults and adolescents (incl. women of childbearing potential and pregnant women)	Two NRTIs + DTG	Two NRTIs + (ATV/r or LPV/r)	DRV/r + DTG + 1–2 NRTIs (if possible, consider optimisation using genotyping)
	Two NRTIs + EFV	Two NRTIs + DTG	
Children (0–10 years)	Two NRTIs + DTG	Two NRTIs + (ATV/r or LPV/r)	
	Two NRTIs + LPV/r	Two NRTIs + DTG	
	Two NRTIs + NNRTI	Two NRTIs + DTG	

- Guidelines include recommendations on the selection of ARV drugs in response to high levels of DR<sup>1</sup>
  - Recommend countries consider changing their first-line ART regimens away from NNRTIs if levels of NNRTI DR reach 10%

1. <http://www.who.int/hiv/pub/arv/arv-2016/en/World Health Organization. HIV treatment interim guidance. Accessed August 2018>

# How has it panned out?

- Dolutegravir replaced efavirenz
  - Better side effects
    - Neural tube defect signal resolved
    - Diabetes - speculative
    - Weight gain – see next bit, but not dolutegravir
  - Better persistence
    - Definitely the case –PEPFAR, other cohorts
  - Remarkable resistance profile
    - Still awaiting any meaningful resistance – *years and tens of millions of patients in*
  - Cheaper
    - Price of annual treatment dropped from \$110 to \$75/year
- Dolutegravir has been a massive public health success!
- Except in the private sector





Clinical Infectious Diseases

MAJOR ARTICLE



# CYP2B6 Genotype and Weight Gain Differences Between Dolutegravir and Efavirenz

Rulan Griesel,<sup>1,2</sup> Gary Maartens,<sup>1,2</sup> Maxwell Chirehwa,<sup>1</sup> Simiso Sokhela,<sup>1</sup> Godspower Akpomemie,<sup>2</sup> Michelle Moorhouse,<sup>2</sup> Francois Venter,<sup>2</sup> and Phumla Sixxadi<sup>1,2</sup>

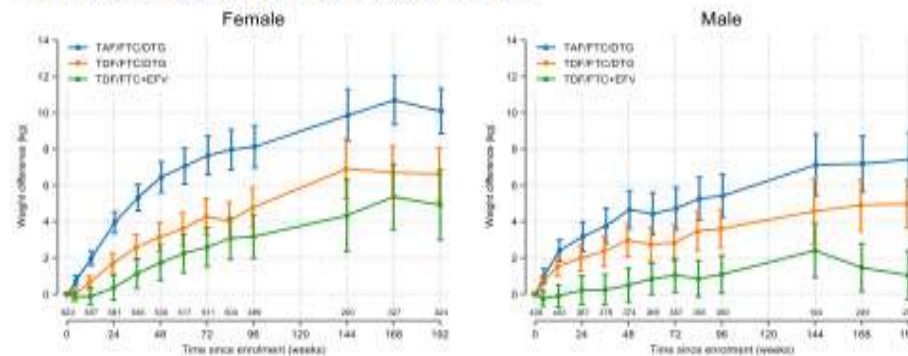
<sup>1</sup>Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa, and <sup>2</sup>Ezintsha, Witwatersrand, Johannesburg, South Africa

(See the Editorial Commentary by Conway on pages e3910-1.)

**Background.** Dolutegravir is associated with more weight gain result in higher efavirenz concentrations, which we hypothesized would result in higher efavirenz concentrations, which we hypothesized would result in higher efavirenz concentrations, which we hypothesized would result in higher efavirenz concentrations...

**Methods.** We studied ART-naive participants from the ADVANCE...

ADVANCE: Weight change from baseline over time





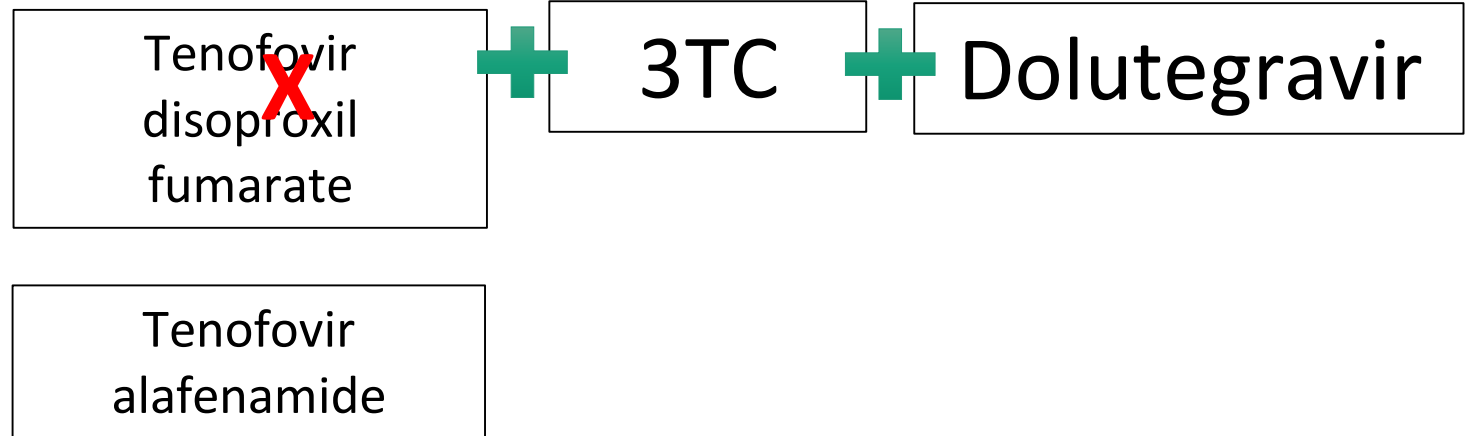
# WHO 2021 guidelines: Can we tinker?

Population	Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents <sup>a</sup>	TDF <sup>b</sup> + 3TC (or FTC) + DTG <sup>c</sup>	AZT + 3TC + ATV/r (or LPV/r)	AZT + 3TC + DRV/r <sup>d</sup>
	TDF + 3TC (or FTC) + EFV (or NVP)	AZT + 3TC + DTG <sup>c</sup>	AZT + 3TC + ATV/r (or LPV/r or DRV/r) <sup>d</sup>
	AZT + 3TC + EFV (or NVP)	TDF <sup>b</sup> + 3TC (or FTC) + DTG <sup>c</sup>	TDF <sup>b</sup> + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r) <sup>d</sup>

Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO

Going to take a LOT to  
displace “TLD” – works  
great! But option 1....  
TAF

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# TDF vs TAF?

- Favours TDF
  - More pregnancy data
  - Less weight gain
  - Less impact on lipids
  - More safety data, more data from Africa
- Favours TAF
  - Less impact on kidneys, bone
  - May be cheaper
  - Less packaging, smaller tablet, less pharmaceutical

Going to take a LOT to displace  
“TLD” – works great! But option  
2.... Dump TDF altogether

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# Dual therapy – 'heresy'

3TC + Dolutegravir

- Clear data it works – even for initiation (dolutegravir is THAT powerful)
- Obvious cost benefits, but..
- Concerns:
  - Will it be durable in Africa?
  - Lose 'free' hepatitis B cover (note this will be an issue more and more)
    - And is the HIV programme now 'hostage' to hepatitis B? like it was to TB?

Going to take a LOT to displace “TLD” – works great! Option 3.... Replace dolutegravir

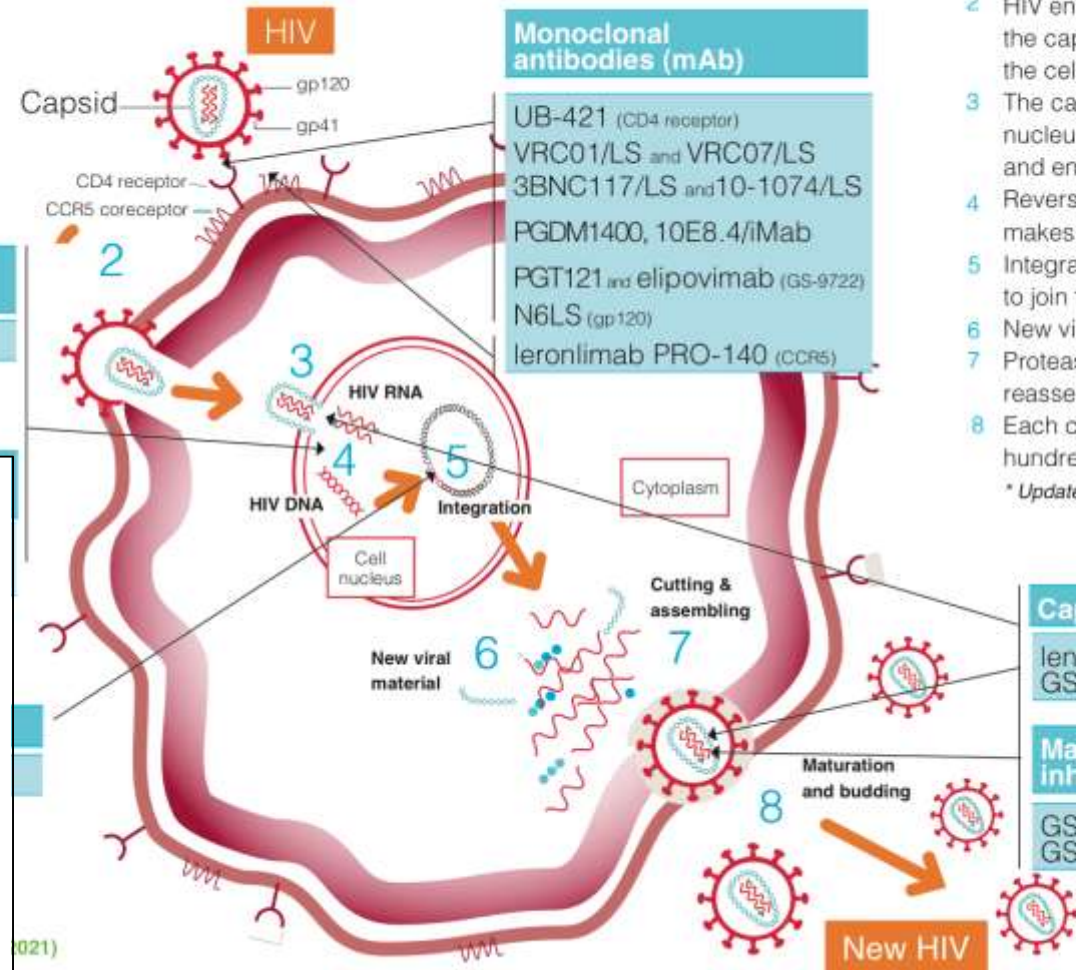


- Why would you want to?
- Candidates:
  - Bictegravir – carbon-copy with less pregnancy data
  - Doravirine – excellent non-nucleoside reverse transcriptase inhibitor, limited pregnancy data, any benefits over dolutegravir? Cant use in TB

# Enough with the tinkering!

- The great leap forward is – **long actings!**

## HIV pipeline 2021: targets in the HIV lifecycle



### Stages in the HIV lifecycle

- HIV attaches to a CD4 cell.
- HIV enters a CD4 cell and the capsid is released into the cell.
- The capsid enters the cell nucleus where HIV proteins and enzymes are released.
- Reverse transcriptase (RT) makes double strand HIV.
- Integrase enables HIV DNA to join the cell DNA.
- New viral material is made.
- Protease cuts and reassembles new HIV.
- Each cell produces hundreds of new virions.

\* Updated in 2021.

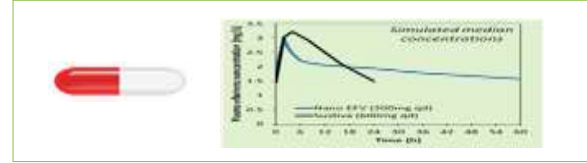
C. Fleuter, A. Owen, M. Scrocci et al. International Journal of Antimicrobial Agents 57 (2021) 106220

**Table 1**  
Long-acting drugs in development for human immunodeficiency virus (HIV) prevention (Px) and treatment (Tx) by infusion, injection or implant.

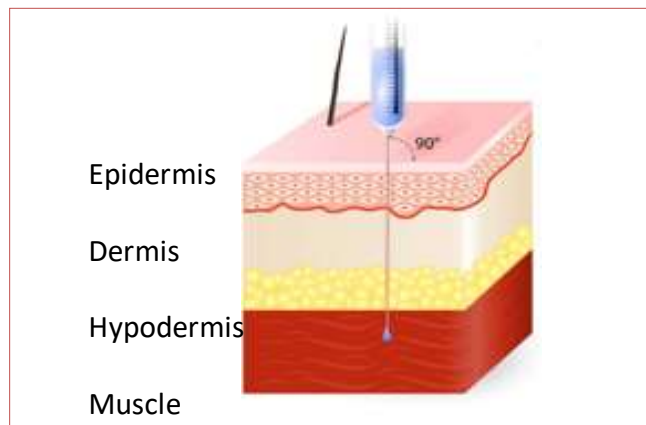
Antiretroviral class/agent	Formulation	Development stage
<b>Nucleoside reverse transcriptase inhibitors (NRTI)</b>		
Islatravir (MR-8591)	Implant/Oral	Phase 1/2 (Px)
TAF	Implant	Phase 1/2 (Px)
GS-9131	Implant	Preclinical
<b>Non-nucleoside reverse transcriptase inhibitors (NNRTI)</b>		
Rilpivirine	Injectable	Phase 3/NDA
Esofavirine	Injectable	Preclinical
<b>Protease inhibitors (PI)</b>		
Atazanavir	Injectable	Preclinical
Ritonavir	Injectable	Preclinical
<b>Integrase strand transfer inhibitors (INSTI)</b>		
Cabotegravir	Injectable	Phase 3/NDA, phase 2/3 (Px)
Dolutegravir	Implant	Preclinical (Px)
Raltegravir	Injectable	Preclinical
<b>Entry inhibitors</b>		
Ibalizumab	Intravenous	FDA-approved (Tx)
Leronlimab (PRO 140)	Intravenous and injectable	Phase 3
Albuviride	Intravenous and injectable	Approved in China
bnAbs (e.g. VRC01, VRC07)	Intravenous	Phase 1/2/3
Combivectin	Intravenous	Phase 1
<b>Capsid inhibitors</b>		
Lenacapavir (GS-6207)	Injectable	Phase 2

NDA, New Drug Application; FDA, US Food and Drug Administration; bnAbs, broadly-neutralising antibodies.

# Some concepts



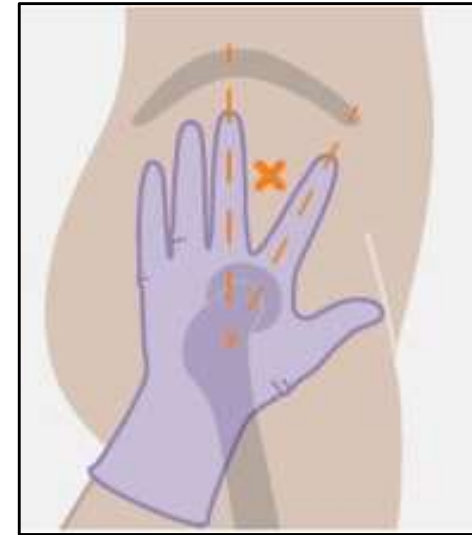
- 'Long acting' – loose term for anything lasting a week or more
- Can be oral, injectable (intramuscular or subcutaneous), or implantable





# What are we talking practically?

- Only 3 formulations registered by FDA
- Cabotegravir for prevention – one intramuscular injection 2 monthly by skilled health care worker
- Cabotegravir with rilpivirine for treatment – 2 separate (painful, different sites, cold chain, by trained health workers, expensive) intramuscular injections
- Lenacapavir subcutaneous 6-monthly for treatment – but WITH daily tablets in highly experienced patients
- Studies with lenacapavir – but battling to find a partner drug!
- Islatravir weekly tablet for treatment (monthly dropped) paired with daily tablet, including lenacapavir
- Many, many other compounds – none near completion, so at least 2-3 years before registration



# So why all this excitement?

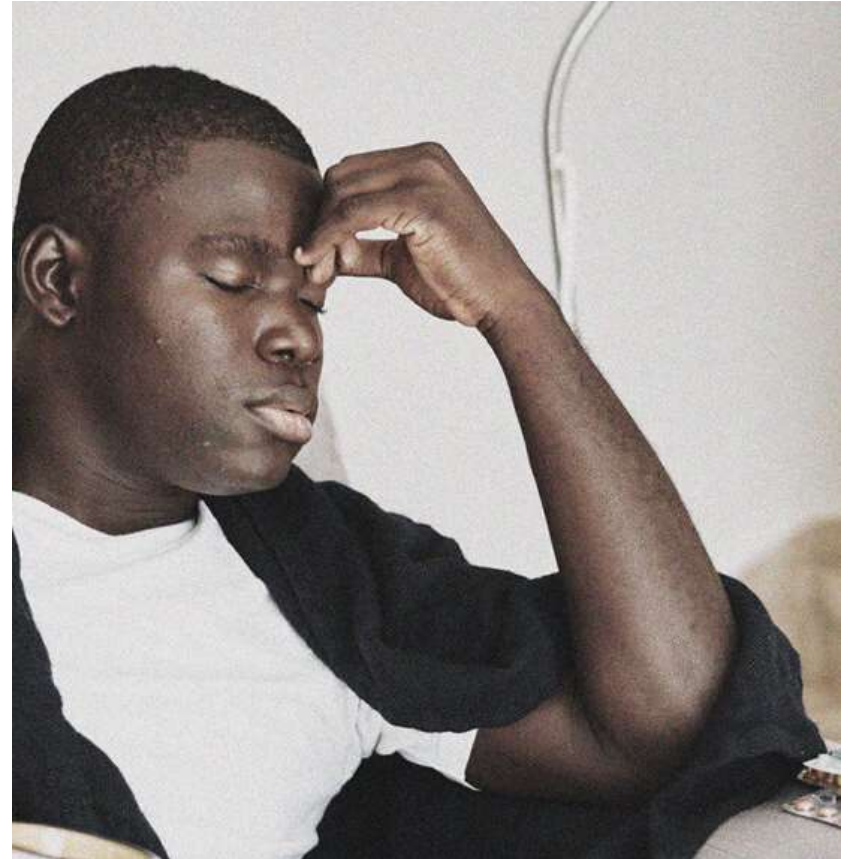
- People with HIV love this! Despite pain. And includes men.
- Imagine giving a patient 28 tablets for 6 months? Or 6 tablets! Or one injection! Or an implant for a year!
- Showing success in drug-using populations
- Operational questions – will they ‘love’ coming more often?



# Big thorns

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- Usual intellectual property issues – cabotegravir and ViiV, lenacapavir and Gilead, rilpivirine and J&J
- Cost issues being sorted out – modelling, MPP, advocacy, generics, tenders, PEPFAR
- Women still deprioritised in research (luckily, PrEP studies giving us pregnancy data) – so some drugs will lack safety data
- Long tails – integrase resistance and cabotegravir – studies addressing this



# Immediate HUGE thorn for long-actings

- Deeply flawed access plans left in the hands of originators
  - Cabotegravir access – trickle in 2027, ?if generic access even happening
  - ?access plan from Gilead re LEN
  - No combinations for treatment
  - Taken together – no access till deep 2030s for Africa
- Resistance Conference 2023: Breakthrough resistance on:
  - TLD – small numbers, but it is there – how do we deal with it?
  - Rilpivirine/cabotegravir – including in ‘perfect cases’

# But the biggest challenges are systemic



- Health system that does not like complexity
  - What if injections are complex?
  - Tolerance for more than one regimen is low
- BUT important – we have time! We can test with cabotegravir PrEP
  - We must learn, and we must learn fast
- And advocacy needs to happen! Otherwise, we can wait for a decade or more

# Getting old (and large) with HIV

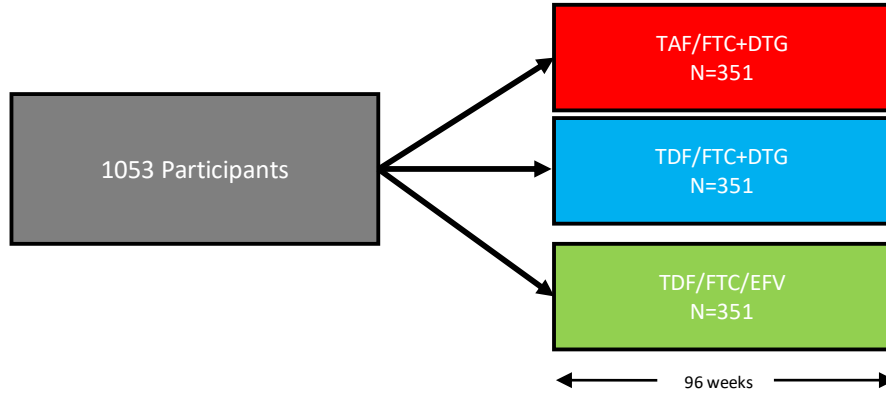
“...life expectancy was only a few years lower than that in the general population  
.... However, for people with low CD4 counts at the start of follow-up, life-  
expectancy estimates were substantially lower...”

- People with HIV fall out of and re-enter the (unfriendly) system
- They get chronic diseases – like we all do
- They gain weight – like we all do (except more)

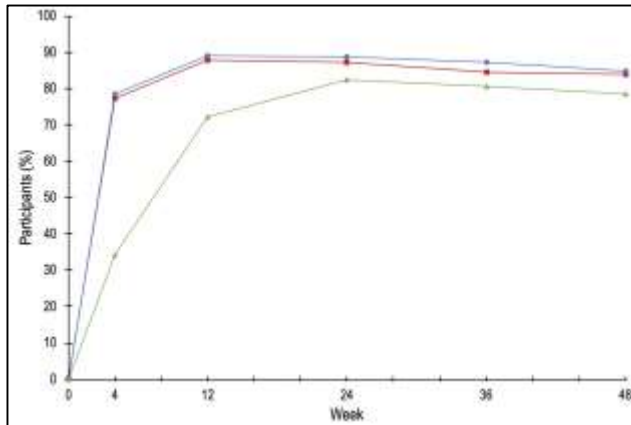


# ADVANCE: Study design

Inclusion criteria: treatment-naïve, HIV-1 RNA level  $\geq 500$  copies/mL, no TB or pregnancy, no baseline genotyping



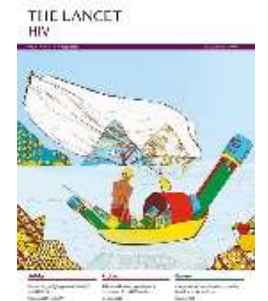
Open-label, 96-week study in Johannesburg, South Africa  
Study visits at Baseline, Week 4, 12, 24, 36, 48, 60, 72, 84, 96, 144, 192



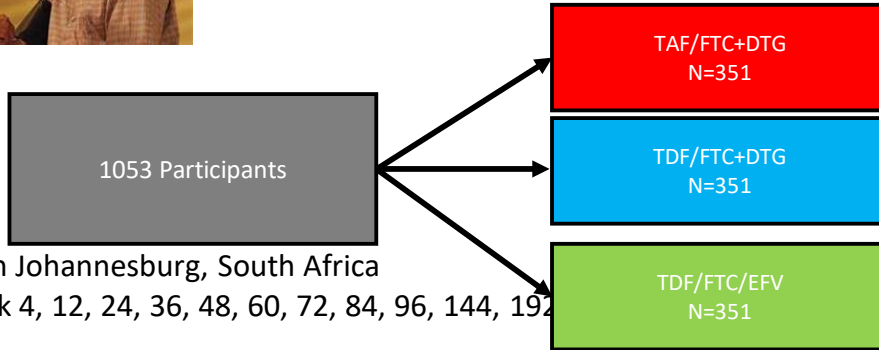
DTG/TDF/FTC, 84.9%

DTG/TAF/FTC, 83.8%

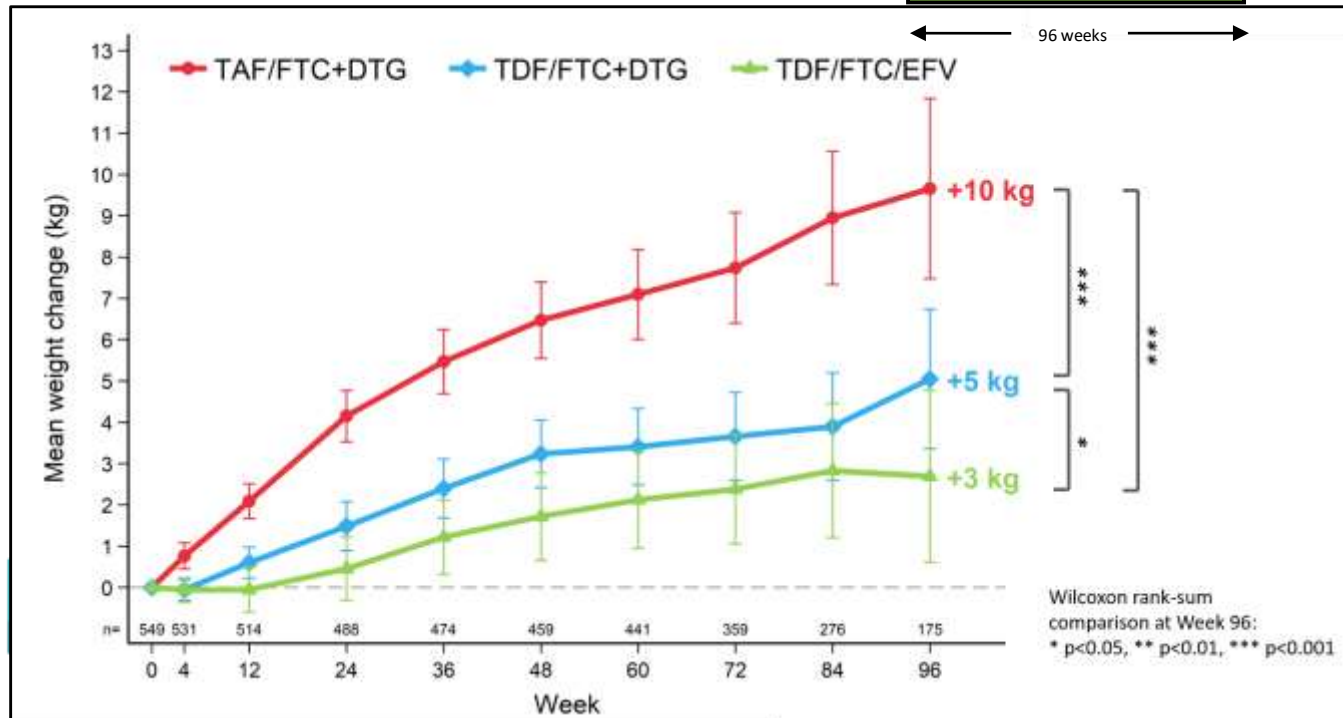
EFV/TDF/FTC, 78.6%



# ADVANCE: Study design



Open-label, 96-week study in Johannesburg, South Africa  
 Study visits at Baseline, Week 4, 12, 24, 36, 48, 60, 72, 84, 96, 144, 192



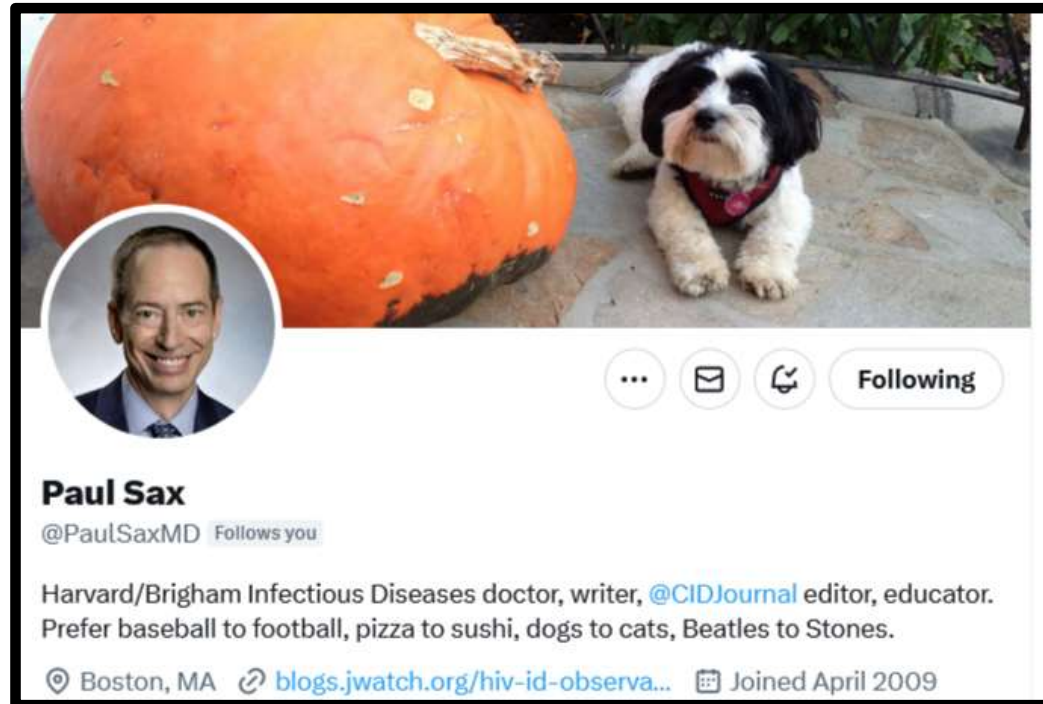
One patient on ADVANCE, BMI>60: “I have done everything you told me, please help me”.



# Weight gain and obesity

- Traditional medical advice: “*move more and eat less*” – which do not work for weight loss by themselves
- New medications (and old medications) – 15-20% weight loss routinely after 14-15 months
- But need to address food industry
- Civil society alliances forcing government to action



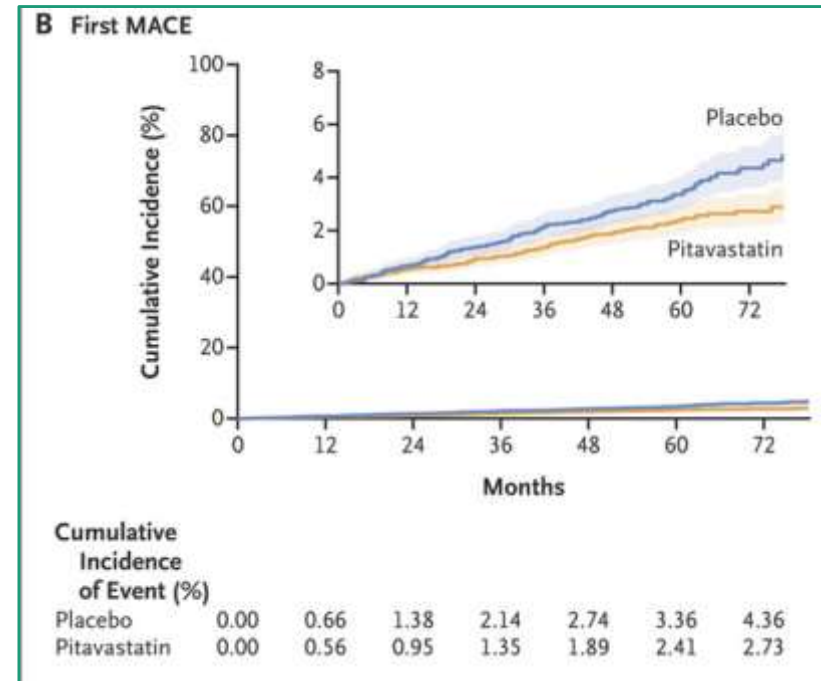


**Paul Sax Aug 2023:** “Major advances... have drifted away from an infectious diseases doctor’s typical areas of focus”

# Hot off the press...

- REPRIEVE – statins for primary prevention in low-medium
- ?applies to us – but the way the field is going

Grinspoon, NEJM, 2023



# Getting old (and large) with HIV

- People with HIV fall out of and re-enter the (unfriendly) system
- They get chronic diseases – like we all do
- They gain weight – like we all do (except more)
- Social determinants, issues like mental health, become more and more important
- **FINALLY:** successful integrated models are not found at scale – long actings may kick start this





# Finally

- New drugs are exciting but are not going to fix systems
- Need strong advocacy for long acting
- Long-acting formulations will stress inflexible primary care
- Need a plan for weight gain
- Need creativity and activism for integration, better systems