Research priorities post-PEPFAR

Francois Venter

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Disclosures: Francois Venter

- Research Support: USAID; Unitaid; South African Medical Research Council; Bill and Melinda Gates Foundation; study drug donations from ViiV Healthcare, Merck and Gilead Sciences; study support Merck, ViiV, J&J
- Speaker's Bureau/Board Member/Advisory Panel: Gilead, ViiV, Mylan/Viatris, Merck, Adcock-Ingram, Aspen, Abbott, Roche, J&J, Sanofi, Boehringer Ingelheim, Thermo-Fischer and Virology Education
- The unit does investigator-led studies with Merck, J&J and ViiV providing financial support and is doing commercial drug studies for Merck and Novo. The unit performs evaluations of diagnostic devices for multiple biotech companies.

Wits

Ezintsha

INVESTIGATE INNOVATE ADVANCE

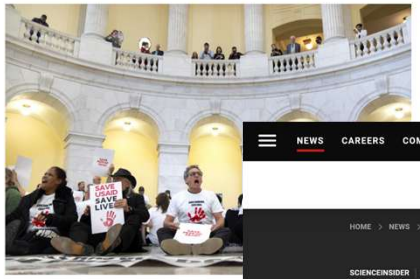
Resistance studies: See Durban

Tragic reason we are here

FOREIGN AFFAIRS

Trump administration says it's cutting 90% of USAID foreign aid contracts

The cuts would leave few surviving projects for advocates to try to save in ongoing court battles with the administration.



Demonstrators protest against cuts to American foreign aid spe
House Office Building on Capitol Hill on Wednesday. | AP Photo

By ASSOCIATED PRESS

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From Albania to Zambia: List of Cancelled USAID Projects Provides Insight into US Influence

Humanitarian Crises 14/03/2025 • Kerry Cullinan

The New York Times

OPINION

Musk Said No One Has Died Since Aid Was Cut. That Isn't True.

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SCIENCEINSIDER | HEALTH

Fear spreads that NIH will terminate grants involving South Africa

Trump has promised to cut off funding, claiming nation discriminates against white citizens

14 MAR 2025 • 5:40 PM ET • BY SARA REARDON

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Vincent Wong
7h ·

16 years at USAID - today the final stop at the office.

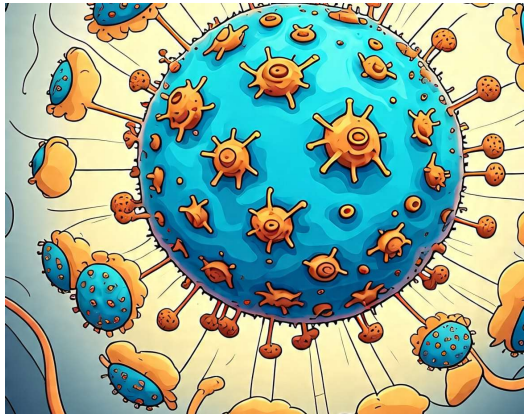
While we're all still coming to terms with the immensity of the loss...this morning was spent together with my fantastic colleagues - all federal workers - who gave their passion, intellect and energy to focusing your tax dollars into saving the most lives from HIV around the world. what an honor..

(Thanks to Alison Surdo Cheng for hiring me way back when!)

For today, a few snapshots (not all are mine).

Responses span extremes:

- “It’s time we stood on our own two feet”/ “Americans should not be blackmailing us like this”
- “HIV gets too much money anyway”
- “Treasury and private sector must fund PEPFAR programmes”
- “We must strengthen health systems and integrate HIV”
- “We’ll be OK”



Funding cuts extend beyond HIV

- Entire health systems
- Famine and disaster relief
- USAID and NIH research – estimated 70% of SSA's research budget
- Governance, climate, vaccines, FDA, CDC advice, air travel safety, earthquakes

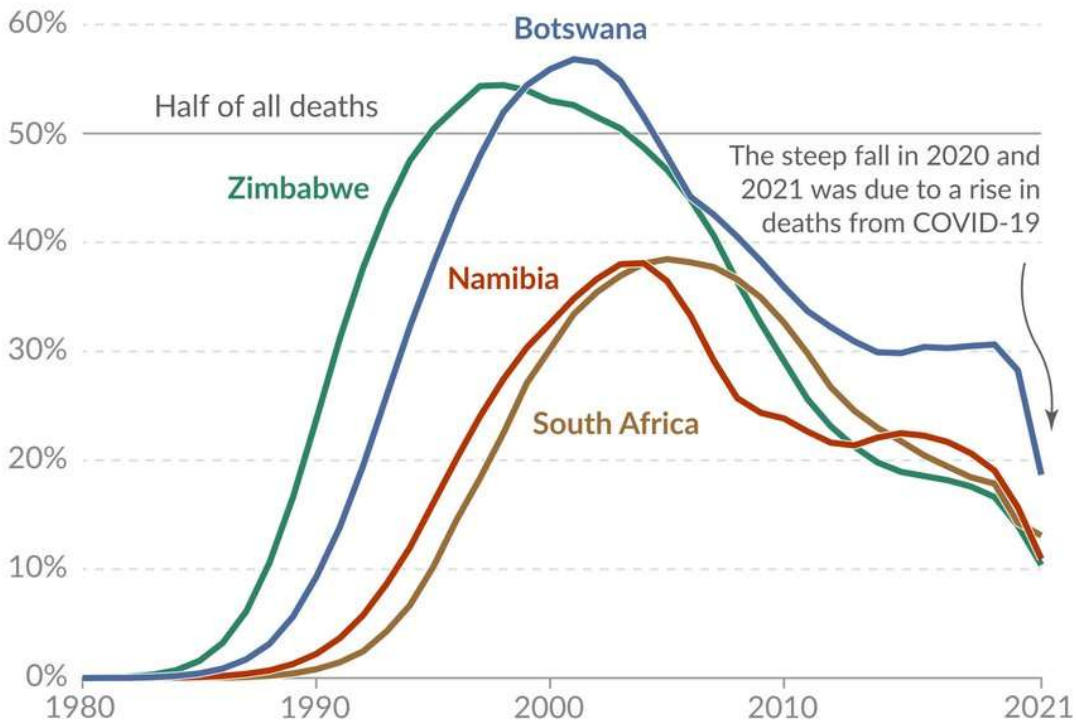
What did PEPFAR fund in South Africa?

- 17% of HIV budget – not consumables (almost none)
- Focused on 27 districts where 78% of people with HIV live
- Case finding – reason we have CD4>400
- TB screening and support
- Data systems – reason why system is managed well
- Support to National/provicial DoH - >200 technical experts
- Key populations programmes – LGBTQ+, sex workers, drug users
- Community monitoring of clinic service quality - https://ritshidze.org.za/the-model/

During the peak of the HIV epidemic, more than half of all deaths in some countries were caused by AIDS

Our World in Data

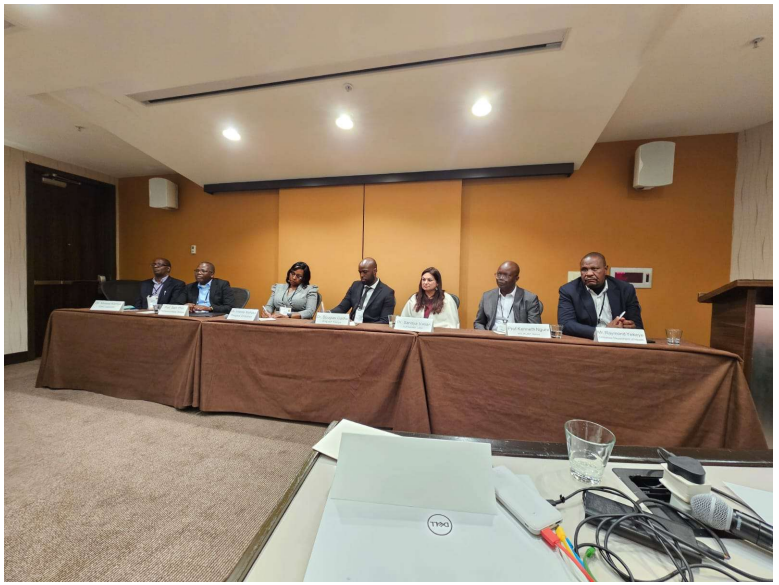
The share of all deaths caused by HIV/AIDS in some of the most-affected countries.



Data source: IHME, Global Burden of Disease (2024)

African impact has been mixed but devastating

- Overnight stoppage of programme, information freezes, spin
- Everywhere – HIV testing, key populations services stopped
- Kenya, Botswana, Lesotho, Eswatini, Mozambique, Zim, Uganda – different levels of collapse
- South Africa - spin, spin, spin



PEPFAR CROI discussion, 2025

It is almost unbearable – we were so close…

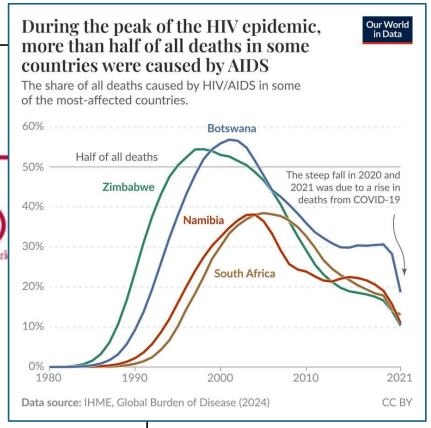
Pharmacokinetics and safety of once-yearly lenacapavir: a phase 1, open-label study

Vamshi Jogiraju, Pallavi Pawar, Jenna Yager, John Ling, Gong Shen, Anna Chiu, Emma Hughes, Ramesh Palaparthy, Christoph Carter, Renu Singh

Summary

Background Long-acting antiretrovirals can address barriers to HIV pre-exposure prophylaxis (PrEP), such as stigma and adherence. In two phase 3 trials, twice-yearly subcutaneous lenacapavir was safe and highly efficacious for PrEP in diverse populations. Furthering long-acting PrEP efforts, this study assessed the pharmacokinetics and safety of two once-yearly intramuscular lenacapavir formulations.

Published Online
March 11, 2025
https://doi.org/10.1016/
S0140-6736(25)00405-2



EDITORIAL

Working at Cross-PURPOSEs to Ending HIV

Glenda E. Gray, M.B., B.Ch.,[1-3] and W.D. Francois Venter, M.B., B.Ch., Ph.D.[4,5]

SA if no funding...

- 2025-2028: 150,000-296,000 additional new HIV infections (29-56% increase) and 56,000-65,000 additional AIDS-related deaths (33-38%)

OPEN

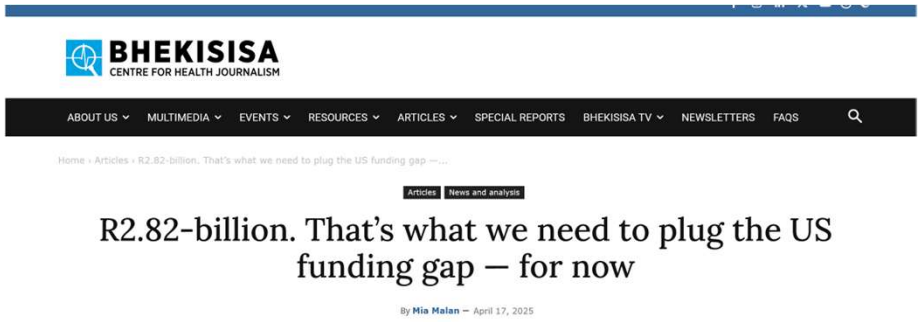
INFOGRAPHIC

CONCISE COMMUNICATION

The cost of the plunge: the impact and cost of a cessation of PEPFAR-supported services in South Africa

Gesine Meyer-Rath[a,b,c], Lise Jamieson[a,b], Edinah Mudimu[d], Jeffrey W. Imai-Eaton[e,f] and Leigh F. Johnson[g]

AIDS 39(10):p 1476-1480, August 01, 2025. |



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R2.82-billion. That's what we need to plug the US funding gap — for now

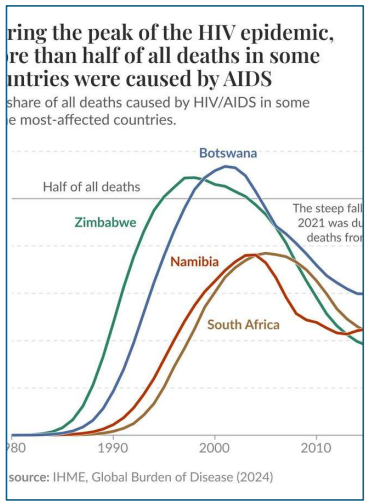
By Mia Malan — April 17, 2025

The U.S. President's Emergency Plan for AIDS Relief - PEPFAR

- Laser-like focus on HIV – often criticised
- In summary:
  - Efficiently found people with HIV and put them and kept them on treatment
  - And monitored and adapted as the programme changed
  - And managed the programme well
  - TB benefited
- My assessment? Brought the best (and the worst) of American programming to health – unbelievably efficient!
- The masterclass for NCDs – 'find & link & retain'

Why must South Africa be scared?

- No HIV testing, key pops programmes stopped
- Return to CD4=80, no TB screening
- In months, hospitalisations – return to 2007
- No key population programmes – no prevention, more illness
- No early-warning system – DoH has no systems in place
- Impact on economy: loss of >24 000 jobs, R20 billion/year (just PEPFAR)
- Impact on neighbours



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© 2025 The Authors http://dx.doi.org/10.5588/ijtldopen.25.0168

LETTER

Impact of US funding cuts and stop work orders on TB services and research in South Africa

Dear Editor,

Over the past decade, South Africa has made great strides and reduced the incidence of TB by 57%.[1] This inspiring reduction was driven by improved TB

exacerbated this uncertainty and will have significant and sustained health impacts.[7,8]

For 2024/2025, South Africa's NTP budget is US$244 million, US$164 million (67%) of which is

Some home truths…

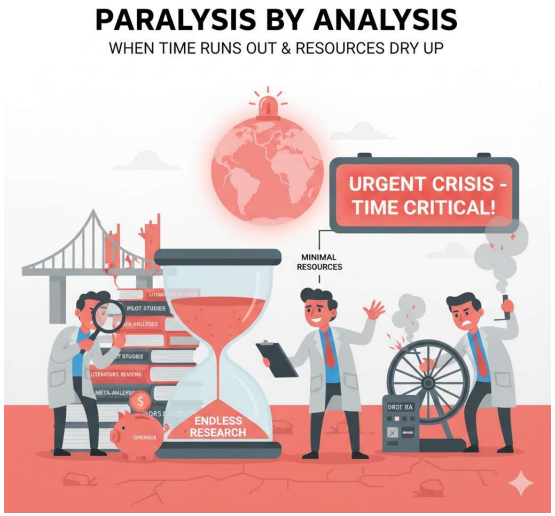
- Things are never going to be the same
  - Additional funding not attached to a clear SA plan - ?impact
  - South Africa unlikely to be a priority (?deserves to be a priority?)
  - No hero coming to plug the funding
    - No funder big enough
    - CDC patches a small %, temporary
    - Treasury allocations so far tiny, temporary
- SA was in big trouble pre-Trump – no budgets for key health staff, collapse of provinces

Summary….

No money
Health not only priority
Think differently

When DON’T we need research…

- Research (intervention research) is expensive, slooooooowww, and a precious resource
- Some programmes just need iterative course correction – PEPFAR taught us this!
- HIV programme – we largely know what to do, but we need resources
- And maybe more reflection on why so little research intervention data gets implemented



Some observations on PEPFAR (and our DoH system generally)

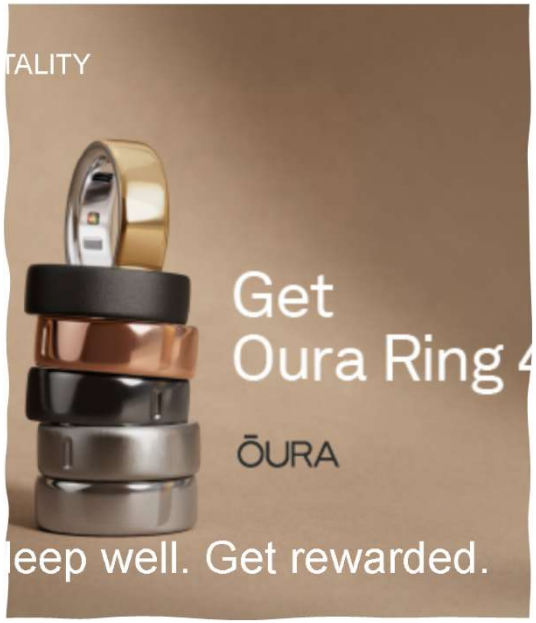
- "Integration" – systematic review: only PMTCT, TB screening, only in a handful of countries, and only small number of places
- We deliver services the same way, forever
  - Bricks and mortar clinic, see a nurse, pick up drugs every x months
  - Even key populations – bricks and mortar clinic with specialist nurses
  - CCMDD – started in 2014!
  - Mrs Mange…
- And yes, some things were expensive, complex, not scalable

Can we leapfrog?

- Same since I was a medical student, will be the same when I die
- Many outcomes remain stubbornly BAD – NCD screening and control, PrEP, mental health; others rolling back – vaccines, contraception, TB
- Penny wise, pound foolish: Dr Moran's case – the pregnant woman who got poor care and died
- Can we leapfrog – think the banking sector?
- Can we address root causes and fix other headaches? And play to South African strengths?

How can we better leverage new technologies and systems FAST?

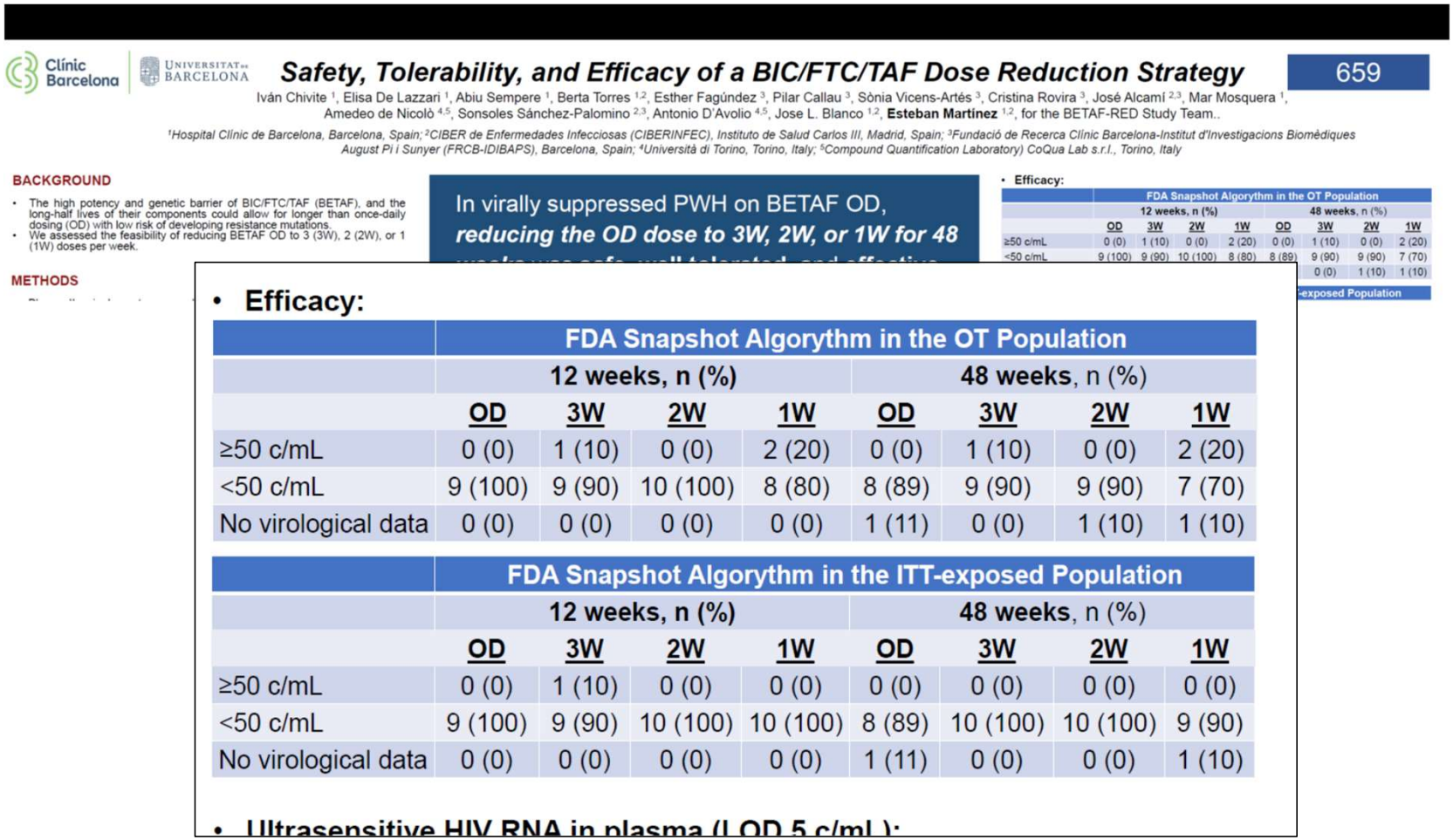
- Can we use wearables, home monitoring, new diabetes tech, pharmacy delivery systems, online ordering?
- What lessons from the private sector can easily come to the public sector?
- Leverage referral apps more effectively? Vula
- How can we use AI ethically, sustainable, safely FAST?
- Link incentives and new initiatives to existing systems eg: SASSA?
- Radically link to drug delivery systems - Dr Gama's presentation



Can we cut ART costs?

Cut dosing?

- Heresy – decrease doing intervals



Clínic Barcelona | Universitat de Barcelona

Safety, Tolerability, and Efficacy of a BIC/FTC/TAF Dose Reduction Strategy

659

Iván Chivite [1], Elisa De Lazzari [1], Abiu Sempere [1], Berta Torres [1,2], Esther Fagúndez [3], Pilar Callau [3], Sònia Vicens-Artés [3], Cristina Rovira [3], José Alcamí [2,3], Mar Mosquera [1], Amedeo de Nicolò [4,5], Sonsoles Sánchez-Palomino [2,3], Antonio D'Avolio [4,5], Jose L. Blanco [1,2], **Esteban Martínez** [1,2], for the BETAF-RED Study Team..

[1]Hospital Clínic de Barcelona, Barcelona, Spain; [2]CIBER de Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain; [3]Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer (FRCB-IDIBAPS), Barcelona, Spain; [4]Università di Torino, Torino, Italy; [5]Compound Quantification Laboratory) CoQua Lab s.r.l., Torino, Italy

BACKGROUND

- The high potency and genetic barrier of BIC/FTC/TAF (BETAF), and the long-half lives of their components could allow for longer than once-daily dosing (OD) with low risk of developing resistance mutations.
- We assessed the feasibility of reducing BETAF OD to 3 (3W), 2 (2W), or 1 (1W) doses per week.

In virally suppressed PWH on BETAF OD, ***reducing the OD dose to 3W, 2W, or 1W for 48 weeks was safe, well tolerated, and effective***

METHODS

- **Efficacy:**

	FDA Snapshot Algorythm in the OT Population							
	12 weeks, n (%)				48 weeks, n (%)			
	OD	3W	2W	1W	OD	3W	2W	1W
≥50 c/mL	0 (0)	1 (10)	0 (0)	2 (20)	0 (0)	1 (10)	0 (0)	2 (20)
<50 c/mL	9 (100)	9 (90)	10 (100)	8 (80)	8 (89)	9 (90)	9 (90)	7 (70)
No virological data	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	1 (10)	1 (10)

	FDA Snapshot Algorythm in the ITT-exposed Population							
	12 weeks, n (%)				48 weeks, n (%)			
	OD	3W	2W	1W	OD	3W	2W	1W
≥50 c/mL	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<50 c/mL	9 (100)	9 (90)	10 (100)	10 (100)	8 (89)	10 (100)	10 (100)	9 (90)
No virological data	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	0 (0)	0 (0)	1 (10)

- **Ultrasensitive HIV RNA in plasma (LOD 5 c/mL):**

Problem is, most of the world does not use BIC/FTC/TAF; also, this was a pilot

Interestingly, answers come largely from rich countries…

- ART treatment is super-expensive – many high-income countries still use EFV>DTG

Methods

PubMed, MEDLINE, ClinicalTrials.Gov
Randomised controlled trials of triple ART 3-6 days/week versus daily

- **Efficacy: HIV VL ≥50 copies/mL**
  Meta-analysis; Random Effects Model

Additional outcomes, where available:

- Viral suppression
- Highly-sensitive viral load
- Inflammation: interleukin-6, d-dimer, hsCRP
- Treatment-emergent drug resistance
- Adherence
- Acceptability

} **Descriptive analysis**

Randomised trials

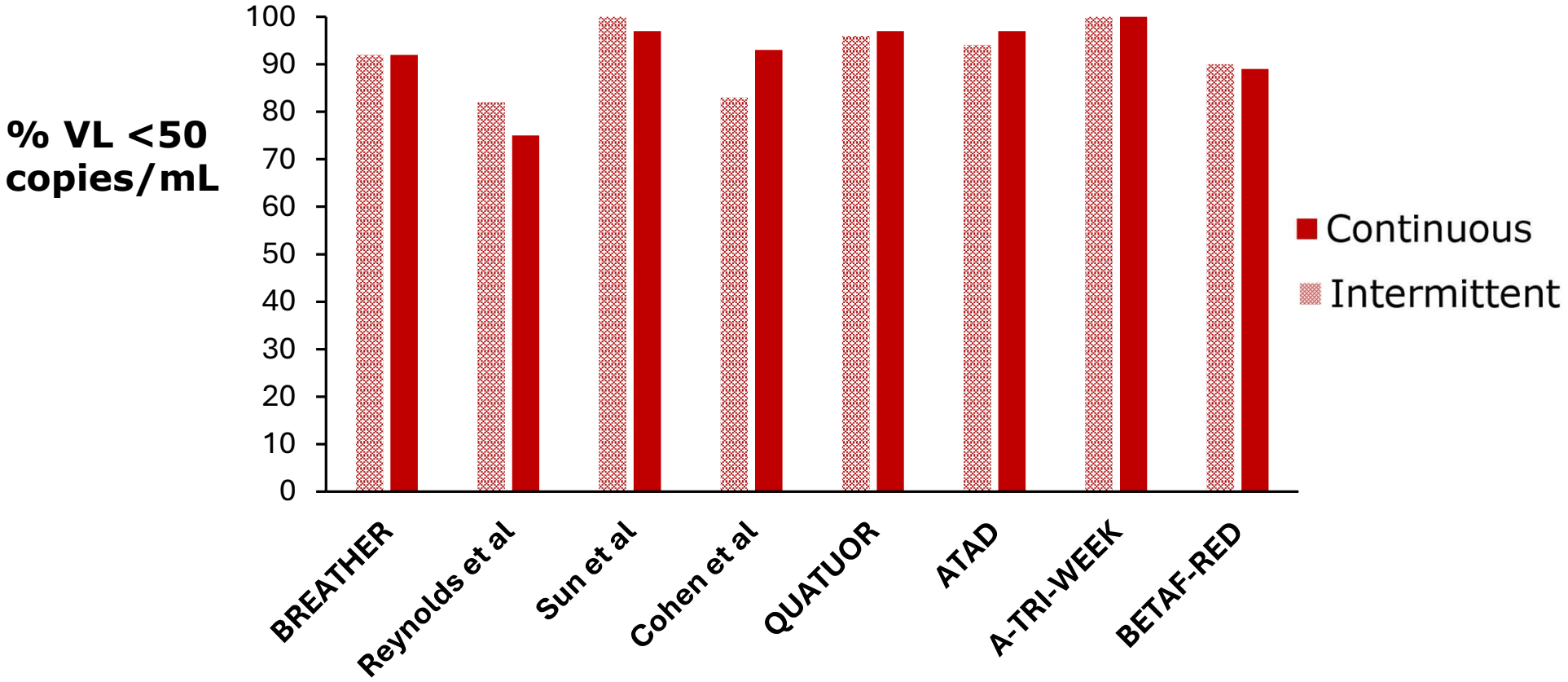
1346 individuals

22% female

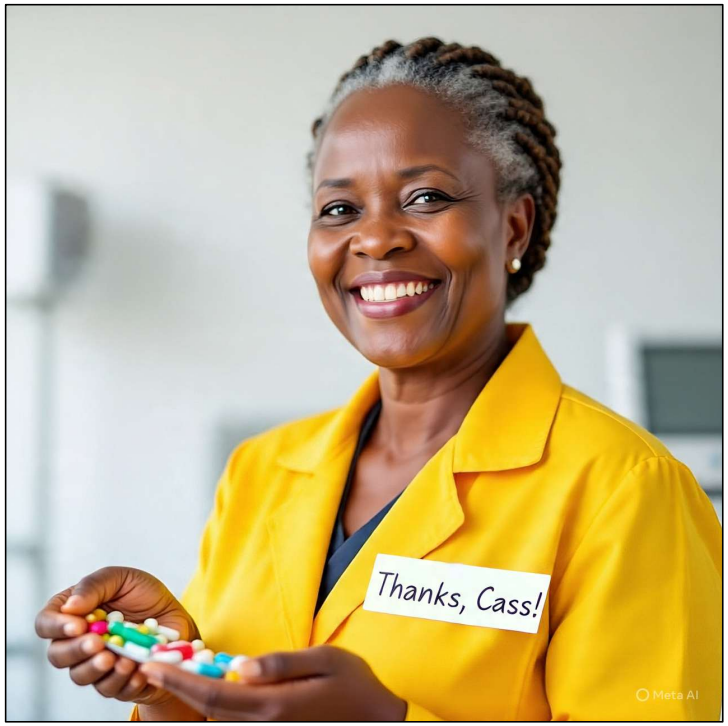
	Location	Sample size	Length, weeks	Regimen	Median age, years	Average time on ART, years
BREATHER	11 countries	199	48	TDF/FTC/EFV	14	6.1
Reynolds et al	Uganda	113	72	EFV plus 2NRTI	38	1
Sun et al	Taiwan	60	52	BIC/FTC/TAF	ND	NR
Cohen et al	USA	60	24	TDF/FTC/EFV	44	NR
QUATUOR	France	636	48	Two NRTIs + PI or NNRTI or INSTI	50	7
ATAD	Italy	197	48	TDF/FTC/EFV	43	4.9
A-TRI-WEEK	Spain	61	24	TDF/FTC/EFV	49	NR
BETAF-RED	Spain	19	48	BIC/FTC/TAF	42	8

	Dosing	M	T	W	T	F	S	S
BREATHER	5 on, 2 off	✓	✓	✓	✓	✓	✗	✗
Reynolds et al	5 on, 2 off	✓	✓	✓	✓	✓	✗	✗
Sun et al	5 on, 2 off	✓	✓	✓	✓	✓	✗	✗
Cohen et al	5 on, 2 off	✓	✓	✓	✓	✓	✗	✗
QUATUOR	4 on, 3 off	✓	✓	✓	✓	✗	✗	✗
ATAD	Alternate	✓	✗	✓	✗	✓	✗	✓
A-TRI-WEEK	3 on, 4 off	✓	✗	✓	✗	✓	✗	✗
BETAF-RED	3 on, 4 off	✓	✗	✓	✗	✓	✗	✗

HIV VL <50 copies/mL at 48 weeks, ITT analysis



Problem solved!



And just when we thought we could…

BREATHER

- A randomised open label two-arm, 96 week trial evaluating the efficacy, safety and acceptability of short cycle (five days on, two days off) dolutegravir/tenofovir based triple antiretroviral therapy (ART) compared to daily dolutegravir/tenofovir based triple ART in virologically suppressed HIV infected adolescents aged 12 to 19 years

Breather plus dosing

	Dosing	M	T	W	T	F	S	S
BREATHER	5 on, 2 off	✓	✓	✓	✓	✓	✗	✗
Reynolds et al	5 on, 2 off	✓	✓	✓	✓	✓	✗	✗
Sun et al	5 on, 2 off	✓	✓	✓	✓	✓	✗	✗
Cohen et al	5 on, 2 off	✓	✓	✓	✓	✓	✗	✗
QUATUOR	4 on, 3 off	✓	✓	✓	✓	✗	✗	✗
ATAD	Alternate	✓	✗	✓	✗	✓	✗	✓
A-TRI-WEEK	3 on, 4 off	✓	✗	✓	✗	✓	✗	✗
BETAF-RED	3 on, 4 off	✓	✗	✓	✗	✓	✗	✗

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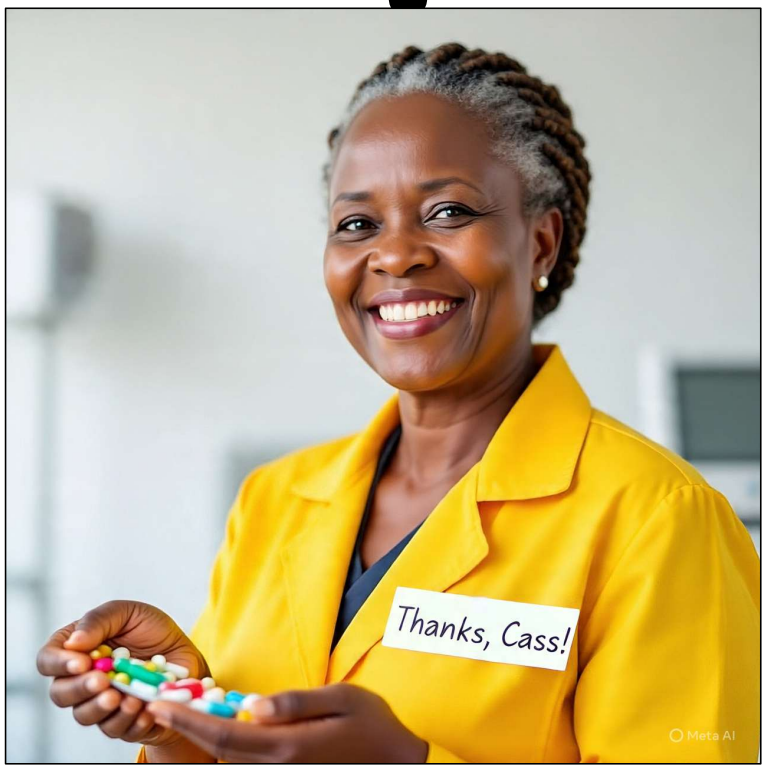
Thanks, Cass!
Meta AI

So:

- Seems we can relatively safely decrease dosing TLD
- Does the adolescent data extrapolate to adults? Does it matter?
- Still major systems complexity
  - Dosing messaging, adherence
  - Supply lines, packaging, pick-ups
- Does not solve the underlying medium-term crisis – funding ART

Simplify treatment with
long actings?

So then why all this excitement about long-actings? Especially injections?

- Patients love this!
- Adherence has been a huge issue in PrEP, in adolescents in treatment, in certain key-populations (drug users, ‘chaotic lives’)
- But even everyday people don’t like tablets – ‘when can I get them?’

Few LAI treatment agents currently

- Only 3 formulations registered by the FDA, all made by different companies, often with different global mandates
- *Cabotegravir with rilpivirine* for treatment
  - Cold-chain issues, expensive, special needles needed if obesity, ?genotypes, concerning resistance reports
  - Special training to inject
  - 'Tail' issues if fall out of care
  - CAB, rilpivirine being developed beyond 2/12 – CAB may bet to 4, 6, 12/12
  - Used in non-suppressed people
- *Lenacapavir* subcutaneous 6-monthly for treatment - in highly experienced patients, with a lead-in oral dose, with optimised backbone

Do we need a lenacapavir/cabotegravir study for LMICs?

- Most obvious combination
  - Pregnancy data
  - Plenty safety, acceptability data
  - TB/hep B unfriendly
  - CAB may be amenable to 3, 4, 6, 12 monthly dosing, more ‘synchronous’
- Cost likely to approach TLD if administration devices kept simple, volumes high, HCW approach kept simple
- But:
  - Extremely limited access to either drug
  - No licensing agreement

Oral weekly therapy – the next blockbuster?

- Len plus islatravir – phase 2 2024, 2025 looks good - safety, virological
- Other combinations:
  - Gilead – LEN + LAI INSTI – tanked ☠️
  - Merck – LAI NNRTI + islatravir
- Same number of tablets for 6 months as usually provided monthly
- Concerns:
  - Adherence for weekly dosing unfamiliar Pregnancy data,
  - TB and hep B issue
  - How big a step forward is this really for LMICs? Why not wait for injectables?

Other agents: Mabs and things

- >17 antibodies evaluated – good safety, but resistance a major issue; cost and dose
- Also: long-acting TAF, new Merck ‘islatravir’
- Industry products that aren’t in the sunlight
- Injectable TLD LA

Current situation for treatment access

- We need:
  - Studies of different drugs in different combinations
  - Switch studies, naïve studies, unsuppressed studies, pk studies, special population studies
- And THEN we need to start working how to scale in LMIC health systems

Last thoughts on research and new projects

- We need something radical to happen – not tinkering, not disease specific – to health delivery
- Need to guard against ‘too expensive’, ‘won’t work’ thinking
- New technologies, financial crunches, may be what finally forces new thinking


BUILDING
C