What's on the horizon for HIV?

Pharma Game of Thrones

François Venter

Wits Ezintsha, University of Witwatersrand

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.

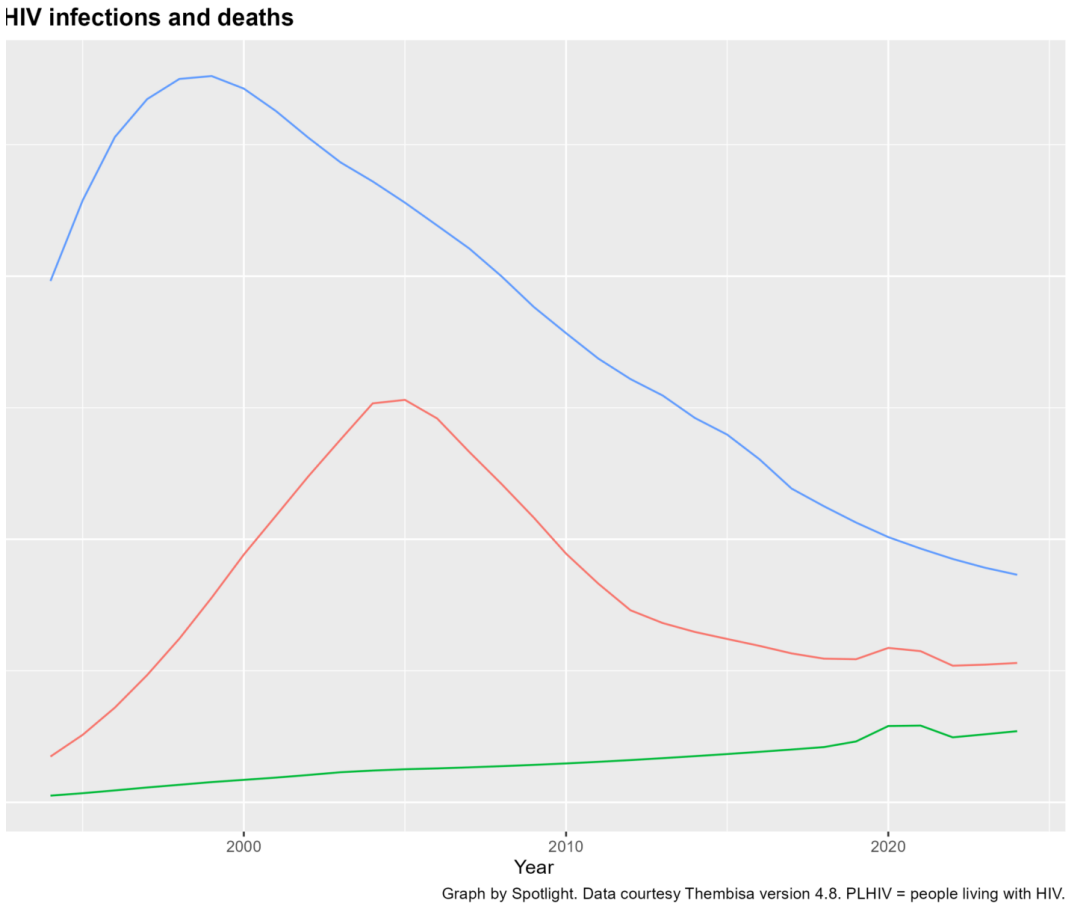
Wits

Ezintsha

INVESTIGATE INNOVATE ADVANCE

Quick SA numbers update…

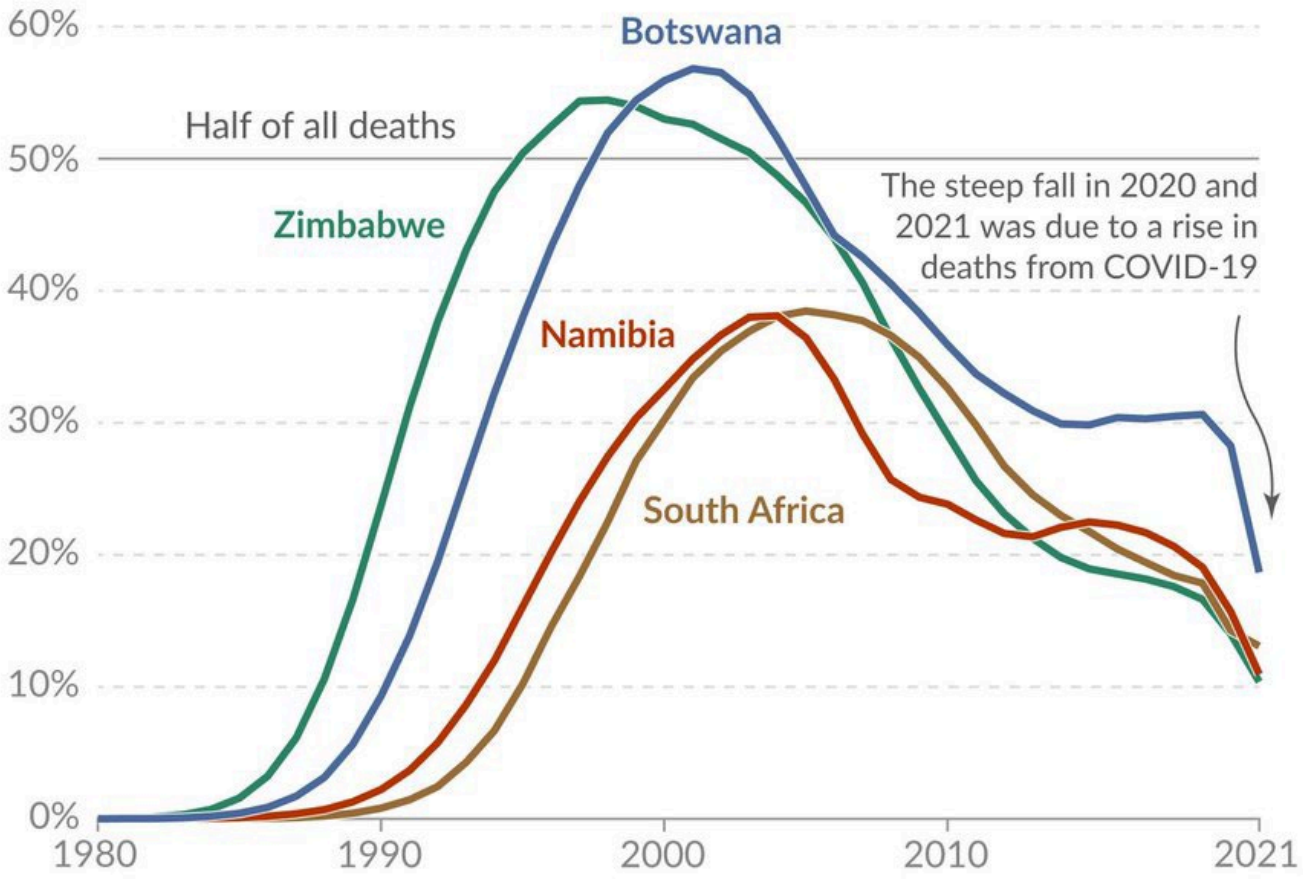
- 8 million with HIV/60 million, 12.8% of population
- 6 million on ART (2025 Thembisa)
- 150 000 on second line, about 3000 third line
- Dramatic reduction in paediatric numbers
- Life expectancy up a decade (dropped from #1 killer; although ?true - SAMRC)
- New infections dropping (remember incidence≠prevalence) – 170 000/year (2025)
- 105 000 people in 2024 died with HIV – 53 000 due to HIV-related diseases
- In 2023/4, 54 000 people with HIV started ART with CD4<200



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.

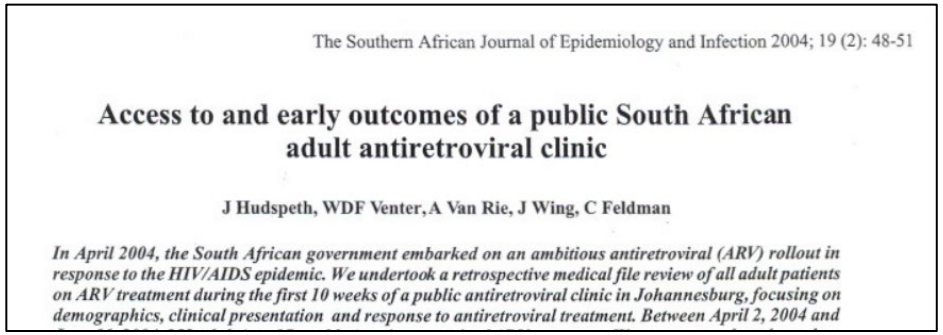


Data source: IHME, Global Burden of Disease (2024)

Then January 2025 came

South Africa and PEPFAR

- Initial grappling with huge wave of in-patient care – 2004-2008
- Case finding, specialised services key populations, programme simplification
- CD4 went from 80 cell/uL (2004-2009) to >400 at initiation now

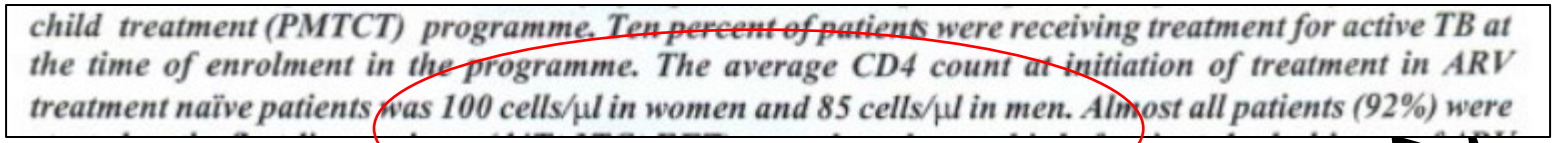


The Southern African Journal of Epidemiology and Infection 2004; 19 (2): 48-51

Access to and early outcomes of a public South African adult antiretroviral clinic

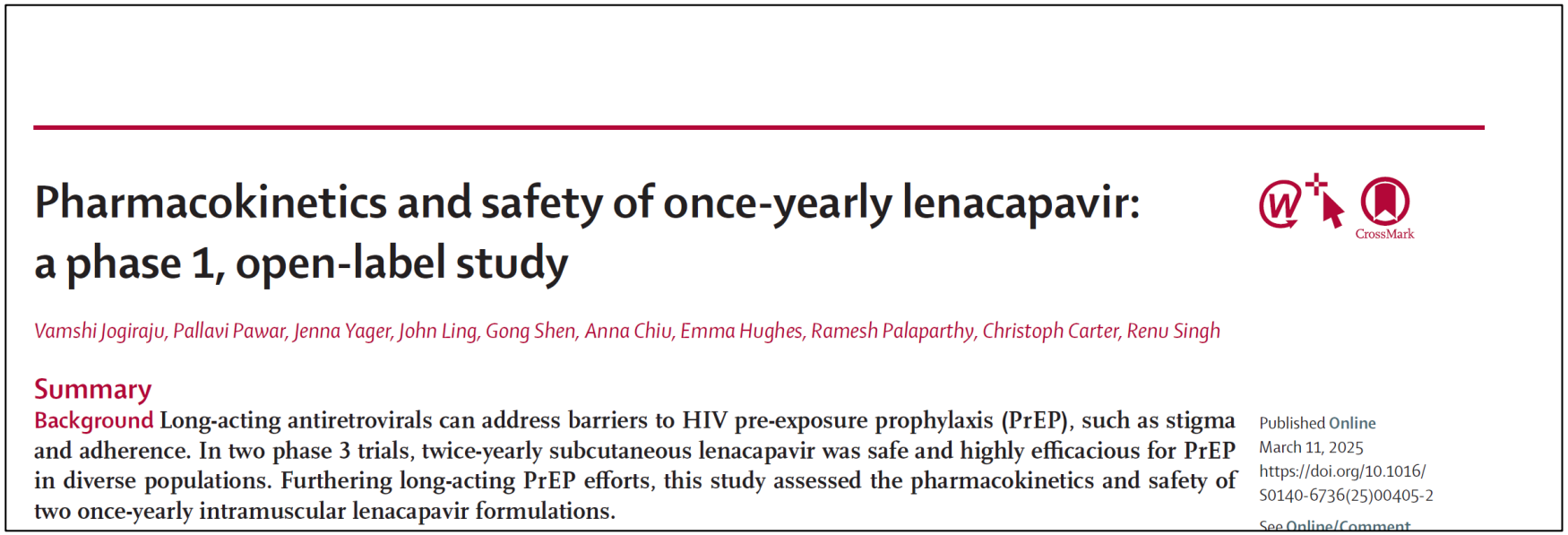
J Hudspeth, WDF Venter, A Van Rie, J Wing, C Feldman

In April 2004, the South African government embarked on an ambitious antiretroviral (ARV) rollout in response to the HIV/AIDS epidemic. We undertook a retrospective medical file review of all adult patients on ARV treatment during the first 10 weeks of a public antiretroviral clinic in Johannesburg, focusing on demographics, clinical presentation and response to antiretroviral treatment. Between April 2, 2004 and



child treatment (PMTCT) programme. Ten percent of patients were receiving treatment for active TB at the time of enrolment in the programme. The average CD4 count at initiation of treatment in ARV treatment naïve patients was 100 cells/μl in women and 85 cells/μl in men. Almost all patients (92%) were

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

See Online/Comment

Why must South Africa be scared?

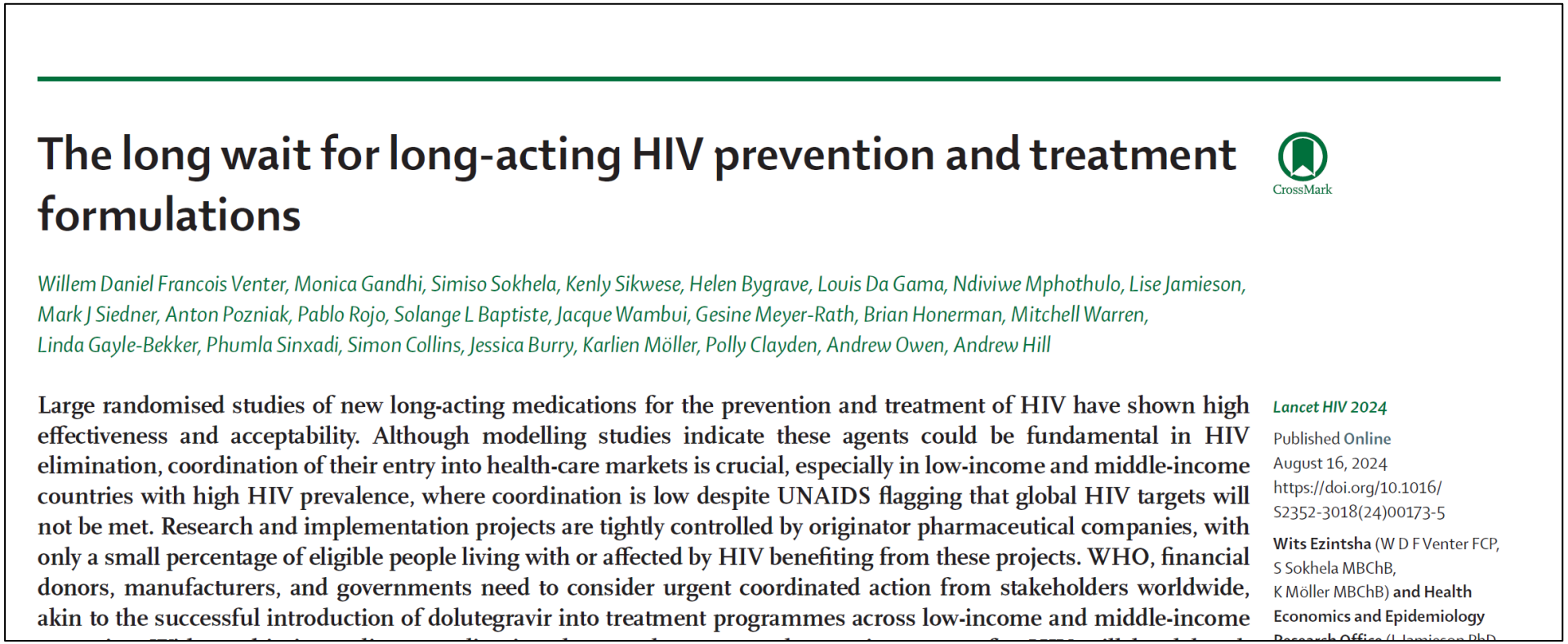
- No HIV testing, key pops programmes stopped, reports of stock outs
- Return to CD4=80, no TB screening – in months, hospitalisations – 2004
- No key population programmes – no prevention, more illness
- No early-warning system – DoH has no systems in place
- Impact on economy: loss of >24 000 jobs, R20 billion/year (just PEPFAR)
- But there is more: impact on neighbours

My epiphanies for 2024/5

- Ain’t gonna be injectable long-acting treatment anytime soon

My epiphanies on ARVs (1)

- Ain’t gonna be injectable long-acting treatment anytime soon (like a decade)
- Studies miles away



The long wait for long-acting HIV prevention and treatment formulations

Willem Daniel Francois Venter, Monica Gandhi, Simiso Sokhela, Kenly Sikwese, Helen Bygrave, Louis Da Gama, Ndiviwe Mphothulo, Lise Jamieson, Mark J Siedner, Anton Pozniak, Pablo Rojo, Solange L Baptiste, Jacque Wambui, Gesine Meyer-Rath, Brian Honerman, Mitchell Warren, Linda Gayle-Bekker, Phumla Sinxadi, Simon Collins, Jessica Burry, Karlien Möller, Polly Clayden, Andrew Owen, Andrew Hill

Large randomised studies of new long-acting medications for the prevention and treatment of HIV have shown high effectiveness and acceptability. Although modelling studies indicate these agents could be fundamental in HIV elimination, coordination of their entry into health-care markets is crucial, especially in low-income and middle-income countries with high HIV prevalence, where coordination is low despite UNAIDS flagging that global HIV targets will not be met. Research and implementation projects are tightly controlled by originator pharmaceutical companies, with only a small percentage of eligible people living with or affected by HIV benefiting from these projects. WHO, financial donors, manufacturers, and governments need to consider urgent coordinated action from stakeholders worldwide, akin to the successful introduction of dolutegravir into treatment programmes across low-income and middle-income

Lancet HIV 2024

Published Online
August 16, 2024
https://doi.org/10.1016/
S2352-3018(24)00173-5

Wits Ezintsha (W D F Venter FCP, S Sokhela MBChB, K Möller MBChB) **and Health Economics and Epidemiology**

My epiphanies on ARVs (2)

- Injectable ARV therapy is far more complicated than people think
- “Saturation complexity” – almost no sites > 100 with CAB/RILP - Glasgow November 2024
- Massive physician resistance – reimbursement, confidence

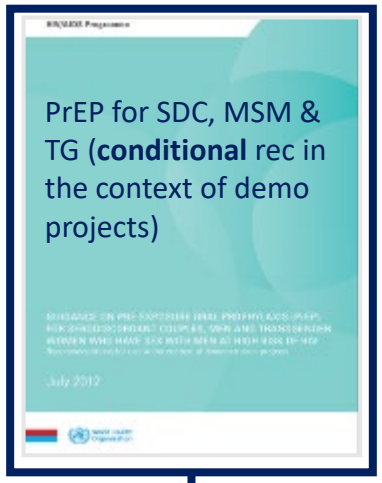
My epiphanies on ARVs (this week) (3)

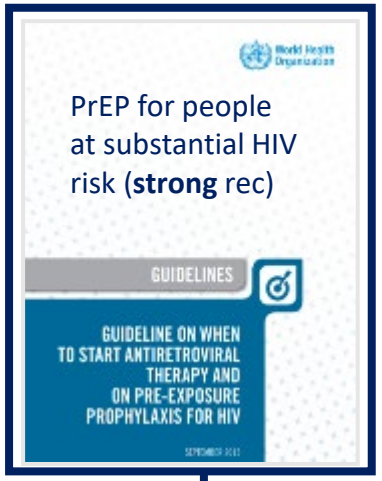
- Long-acting weekly treatment may be closer, more transformative

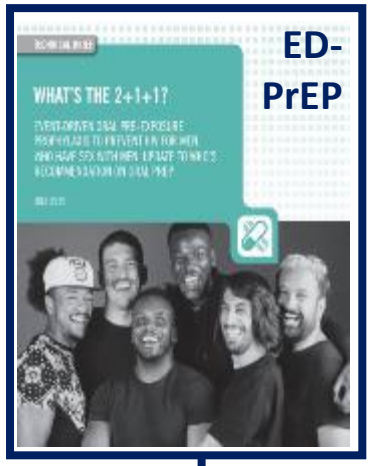
My epiphanies on ARVs (4)

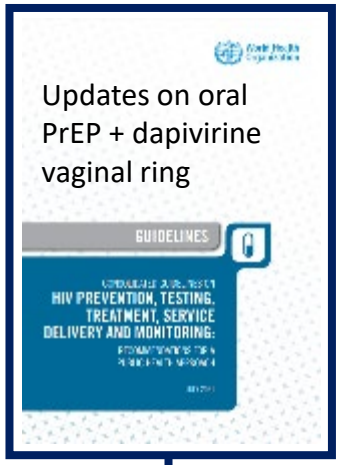
- Injectable PrEP going to change things
- BUT it is more complicated than I thought
- And weekly and monthly oral PrEP on its heels

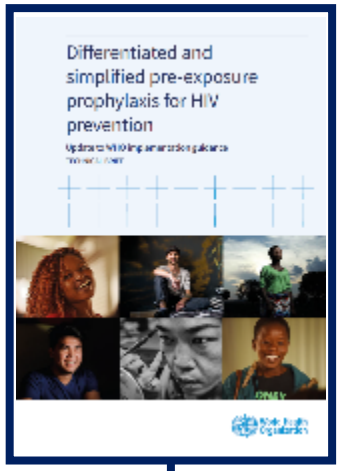
WHO PrEP recommendations and guidance

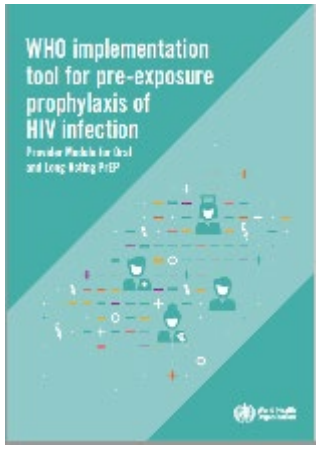




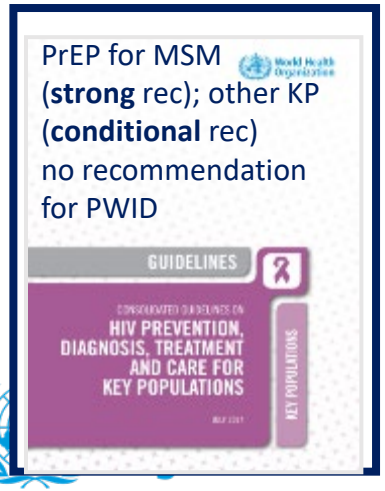


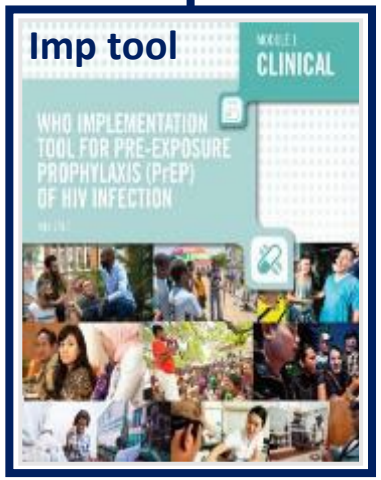






2012 2014 2015/16 2017 2019 2021 2022 2023/4

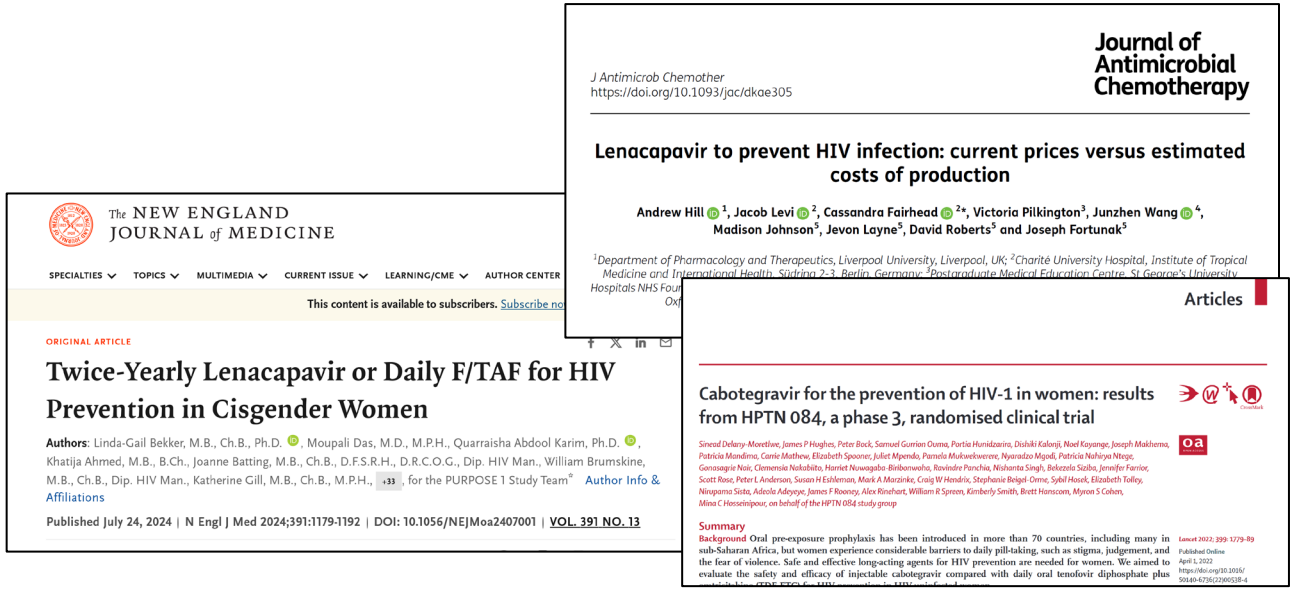




PEP Guidance Updated

(2024)

How PrEP look like?



J Antimicrob Chemother
https://doi.org/10.1093/jac/dkae305

Journal of Antimicrobial Chemotherapy

Lenacapavir to prevent HIV infection: current prices versus estimated costs of production

Andrew Hill[1], Jacob Levi[2], Cassandra Fairhead[2*], Victoria Pilkington[3], Junzhen Wang[4], Madison Johnson[5], Jevon Layne[5], David Roberts[5] and Joseph Fortunak[5]

[1]Department of Pharmacology and Therapeutics, Liverpool University, Liverpool, UK; [2]Charité University Hospital, Institute of Tropical Medicine and International Health, Südring 2-3, Berlin, Germany; [3]Postgraduate Medical Education Centre, St George's University Hospitals NHS Fou… Ox…

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ORIGINAL ARTICLE

Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women

Authors: Linda-Gail Bekker, M.B., Ch.B., Ph.D., Moupali Das, M.D., M.P.H., Quarraisha Abdool Karim, Ph.D., Khatija Ahmed, M.B., B.Ch., Joanne Batting, M.B., Ch.B., D.F.S.R.H., D.R.C.O.G., Dip. HIV Man., William Brumskine, M.B., Ch.B., Dip. HIV Man., Katherine Gill, M.B., Ch.B., M.P.H., +33, for the PURPOSE 1 Study Team* Author Info & Affiliations

Published July 24, 2024 | N Engl J Med 2024;391:1179-1192 | DOI: 10.1056/NEJMoa2407001 | VOL. 391 NO. 13

Articles

Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial

Sinead Delany-Moretlwe, James P Hughes, Peter Bock, Samuel Gurrion Ouma, Partia Hunidzarira, Dishiki Kalonji, Noel Kayange, Joseph Makhema, Patricia Mandima, Carrie Mathew, Elizabeth Spooner, Juliet Mpenda, Pamela Mukwekwerere, Nyaradzo Mgodi, Patricia Nuhleye Ntege, Gonasagrie Nair, Clemensia Nakabiito, Harriet Nuwagaba-Biribonwoha, Ravindre Panchia, Nishanta Singh, Bekezela Siziba, Jennifer Farrior, Scott Rose, Peter L Anderson, Susan H Eshleman, Mark A Marzinke, Craig W Hendrix, Stephanie Beigel-Orme, Sybil Hosek, Elizabeth Tolley, Nirupama Sista, Adeola Adeyeye, James F Rooney, Alex Rinehart, William R Spreen, Kimberly Smith, Brett Hanscom, Myron S Cohen, Mina C Hosseinipour, on behalf of the HPTN 084 study group

Summary

Background Oral pre-exposure prophylaxis has been introduced in more than 70 countries, including many in sub-Saharan Africa, but women experience considerable barriers to daily pill-taking, such as stigma, judgement, and the fear of violence. Safe and effective long-acting agents for HIV prevention are needed for women. We aimed to evaluate the safety and efficacy of injectable cabotegravir compared with daily oral tenofovir diphosphate plus

Lancet 2022; 399: 1779–89
Published Online April 1, 2022
https://doi.org/10.1016/S0140-6736(22)00538-4

- Oral PrEP >90% effective, dapi-ring lower but acceptable
- Injectable studies remarkable – injectables near 100% effective, brings ALL the promise off LAI over daily oral
- “Will electrify HIV prevention”, “LAI PrEP is a gamechanger “
- Except it isn’t – totally unavailable

Thanks, AVAC!

PrEP is a disaster

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SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

ORIGINAL ARTICLE

Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Authors: Robert M. Grant, M.D., M.P.H., Javier R. Lama, M.D., M.P.H., Peter L. Anderson, Pharm.D., Vanessa McMahan, B.S., Albert Y. Liu, M.D., M.P.H., Lorena Vargas, Pedro Goicochea, M.Sc., +28, for the iPrEx Study Team° Author Info & Affiliations

Published December 30, 2010 | N Engl J Med 2010;363:2587-2599 | DOI: 10.1056/NEJMoa1011205

VOL. 363 NO. 27

Country Overview: South Africa

LAST UPDATED: 5 SEPTEMBER 2024

Drug Registration Status

	APPROVED	NOT APPROVED	UNDER REVIEW	DATA NOT AVAILABLE
Gilead's Truvada (TDF/xTC*) Registration	2015			
Generic versions of TDF/xTC* for prevention	N/A			
ViiV's Apretude (CAB for PrEP) Registration	2022			
IPM's Dapivirine Vaginal Ring Registration	2022			

EST. CUMULATIVE INITIATIONS:

Total PrEP: 1,325,342

Oral PrEP: 1,322,867

Dapivirine Vaginal Ring: 790

Injectable PrEP: 1,685

World Health Organization

PrEP is a disaster

Country Overview: South Africa

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VS 5-6 million on TLD

World Health Organization

PrEP is a disaster

Country Overview: South Africa

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World Health Organization

OPINION “ FIRST OPINION

Tested in Africa, used in America

How can we end the practice of HIV wonder drug experimentation in Africa?

A lab technician working with vials of lenacapavir, the new HIV prevention injectable drug, at the Desmond Tutu Health Foundation's Masiphumelele Research Site, in Cape Town, South Africa. Nardus Engelbrecht/AP

By Mark Siedner and Rochelle Walensky Sept. 18, 2024

Siedner is an infectious disease clinician and associate professor of medicine at Harvard Medical

MOST POPULAR

S+ | 7 children developed blood cancer after Bluebird Bio gene therapy

https://www.statnews.com/2024/09/18/lenacapavir-cabotegravir-hiv-aids-clinical-trials-africa/

My epiphanies on ARVs (5)

- Can someone PLEASE sort out the integrase inhibitors?
- Multiple worrying signals

What happened with mass treatment?

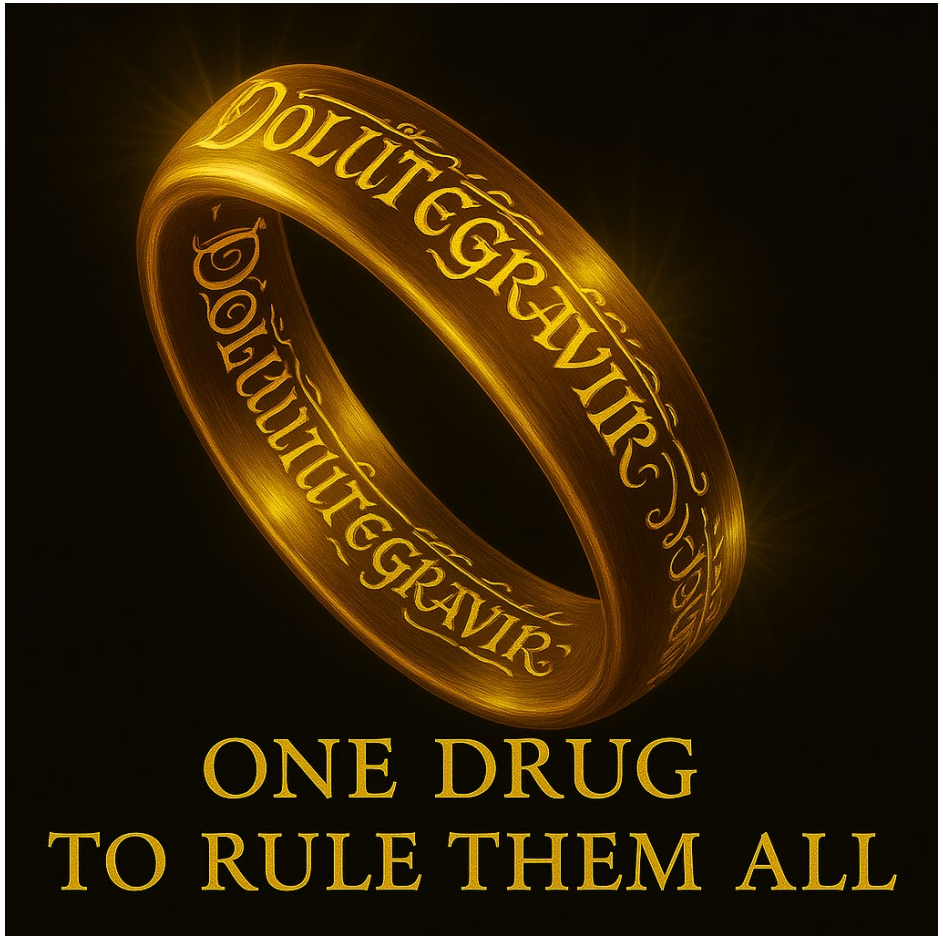
- We had an imperfect twice-daily oral formulation BD
  - 2 tablets am, 3 tablets pm – d4T plus 3TC plus efavirenz
- Muddled through – built delivery system as we went
- Initial rationing - via CD4, adherence visits, systems barriers
- Long acting drugs are paradigm-shifting –need similar mindset, initial offerings will not be perfect but allow us to test systems
- Waiting for perfect drug combinations delays this – suits pharma, government, donors

LAIs pose unique challenges to health systems

- If injections:
  - Do they need HCWs? (all current LAIs need this)
  - What about ‘bridges’ and extra tablets? Health systems hate complexity like that
- Do we have ‘choice’ – ie: more than one regimen?
  - Brings the old issues of supply lines, HCW prejudice, switching
- What about reminders and tails and LTFU?
  - Programmes don’t do that without PEPFAR
- We will need a LOT of muddling!

TLD has set a high bar in LMICs

- When dolutegravir replaced efavirenz…
  - Better side effects
    - Neural tube defect signal resolved
    - Diabetes, blood pressure, inflammation, weight gain concerns need better data
  - Better persistence
    - Compelling retention and VL data – PEPFAR, other cohorts
  - Remarkable resistance profile
    - Years and tens of millions of patients in, and still rare
  - Cheaper
    - Price of annual 1st line treatment dropped from $110 to $50/year
  - **Dolutegravir has been a massive public health success!**



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

- Patients love this!
- Conventional wisdom challenged
  - ‘men are scared of needles’
  - ‘patients don’t like injections’
  - ‘patients won’t come back’

Imagine

  - Giving a patient 28 tablets for 6 months?
  - Injections every 1, 2, 3, 4 or 6 months

- 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?’

What are we talking practically? Few LAI treatment agents currently

- Only 3 formulations registered by the FDA
- *Cabotegravir with rilpivirine* for treatment
- *Lenacapavir* subcutaneous 6-monthly for treatment - in highly experienced patients, with a lead-in oral dose, with optimized backbone
- All made by different companies, often with different global mandates
- Multiple other agents (*islatravir, mAbs, combinations*) under investigation in phase 2, phase 3; subcut TLD in phase 1

Agent 1: Cabotegravir (ViiV Healthcare)

- Next generation integrase inhibitor, high(ish) resistance barrier - <dolutegravir
- Monthly and 2-monthly dosing: CROI 2024 - ?longer – ViiV working on 4/12 with rilpivirine CROI 2025: ?longer
- Intramuscular injectable, (oral lead in - ?need)
- T ½ 21-50 days, studies found it detectable out to year!
- This 'tail' a double-edged sword – great for dosing, but lots of time to:
  - to get breakthrough HIV if on PrEP
  - and resistance if on other antiretrovirals for treatment
- Safety excellent (injection site reactions) (erythema, nodules, intravenous administration can be scary – Cape Town!))

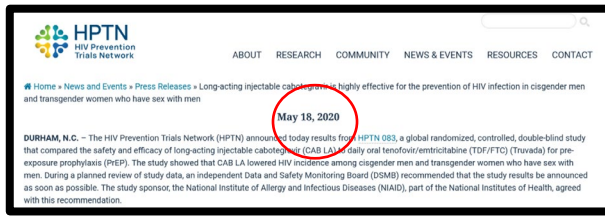
Cabotegravir IMI administration is complex

- Special training required to administer
- Separate injection, in a different buttock region, relatively large volume
- Special needle needed for people with obesity
- Other sites (thigh) being tested – similar pk, but patients largely preferred buttocks (CROI, 2023)
- Self-administration devices being tested (2023) ANS subcutaneous (minor-epiphany) with higher volumes – but painful

How effective is it as PrEP?

- Phase 1, 2, 3 studies completed – highly effective across all sexes, superior to oral TDF/3TC
- FDA approval 2022, SA 2022, EMA 2023, multiple other countries ince then (including 7 African countries (as of May 2024))
- Highly acceptable in multiple studies as PrEP (and treatment)

Politics of costs and access to CAB LA


HPTN
HIV Prevention Trials Network

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Home » News and Events » Press Releases » Long-acting injectable cabotegravir is highly effective for the prevention of HIV infection in cisgender men and transgender women who have sex with men

May 18, 2020

DURHAM, N.C. – The HIV Prevention Trials Network (HPTN) announced today results from HPTN 083, a global randomized, controlled, double-blind study that compared the safety and efficacy of long-acting injectable cabotegravir (CAB LA) to daily oral tenofovir/emtricitabine (TDF/FTC) (Truvada) for pre-exposure prophylaxis (PrEP). The study showed that CAB LA lowered HIV incidence among cisgender men and transgender women who have sex with men. During a planned review of study data, an independent Data and Safety Monitoring Board (DSMB) recommended that the study results be announced as soon as possible. The study sponsor, the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, agreed with this recommendation.

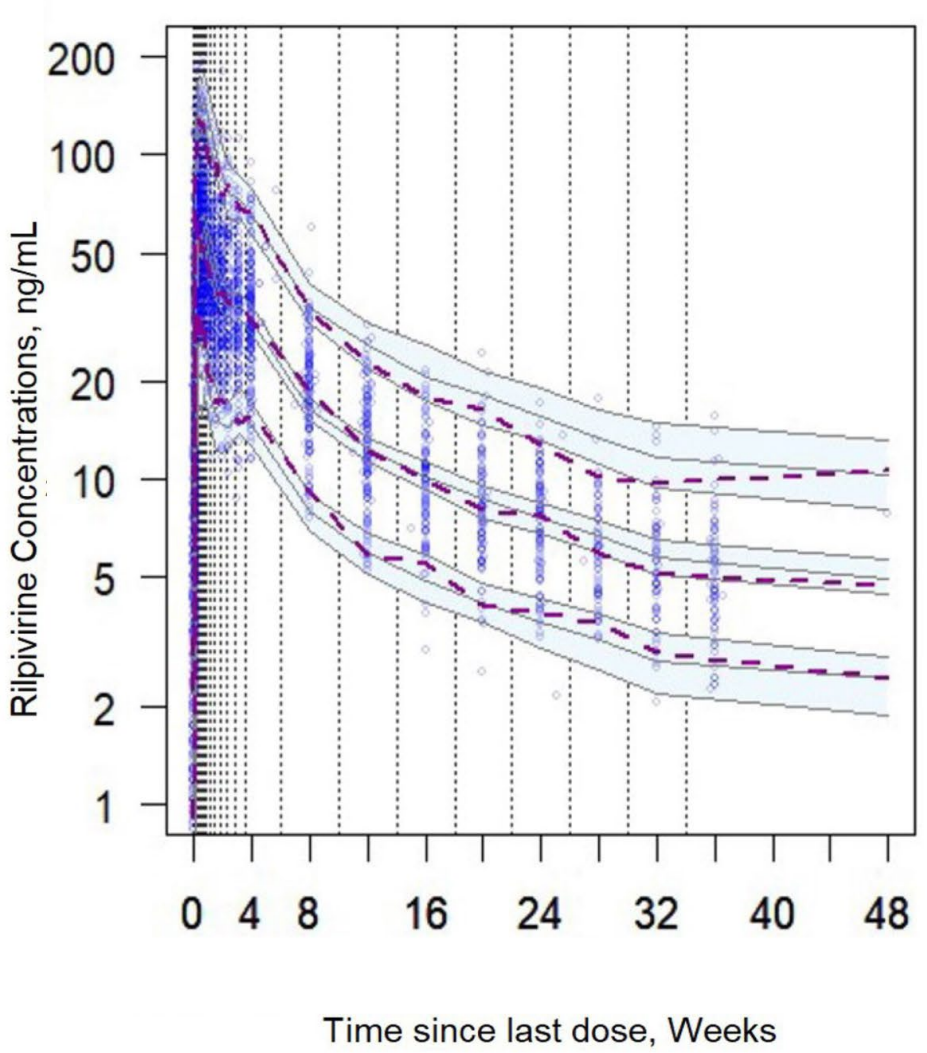
- ViiV initially announced it would make the world's CAB LA
- Immediate reaction was immediate and angry, ViiV changed position especially when clear could not cope with volume post PrEP results
- No immediate access plan, no immediate access price, restrictions on access to drug for implementation/investigator studies
- Initial cost of ViiV offering of CAB LA high - >$40/dose, now UK£29/dose, needs to to be $9-15 (CHAI: possible)
- Cabotegravir is complex to make
  - technology transfer
  - expensive manufacturing equipment
  - important QA processes
- Led to licencing to Medicine's Patent Pool (MPP) and granting of 3 licences (Cipla, Viatris, Aurobindo) – protracted process ?2027 – NOT for treatment
  (https://medicinespatentpool.org/licence-post/cabotegravir-long-acting-la-for-hiv-pre-exposure-prophylaxis-prep)

Agent 2: Rilpivirine (J&J/Jansen) – discussing injectable here

- Next generation non-nucleoside reverse transcriptase inhibitor
- Oral agent available for > decade as FDC, injectable IMI LA (oral ½ life 45-50 hours, IMI 13-28 weeks) separate injection with CAB
- Higher barrier to resistance vs older NNRTIs, but still vulnerable
- Dosed 2 monthly – CROI 2025: ? Longer achievable
- Given IMI, needs HCW training, needs cold chain, painful (very viscous), separate injection site from cabotegravir, new site each time
- Side effects – local reactions, but well tolerated
- In HIC, prior resistance/lack of resistance testing a contraindication

Rilpivirine LA IMI PK after stopping

EC90 12 ng/mL



Much shorter than CAB LA!

JAC 2021:76:3

Access?

- Munich IAS July 2024: “We won’t enforce the patent” – appears that J&J will cease developing/manufacturing the LAI drug
- No formal communication yet - ? What this means for ViiV
- Major implications for cabotegravir/rilpivirine combination for treatment

CAB/RILP for treatment

- Phase 3 – monthly and 2-monthly dosing non-inferior to oral Rx
- Lead-in optional (Orkin, LancetHIV, 2023)
- Occasional resistance
- EMA approval 2020, FDA 2021, others followed

CAB/RPV: Phase 3 Studies

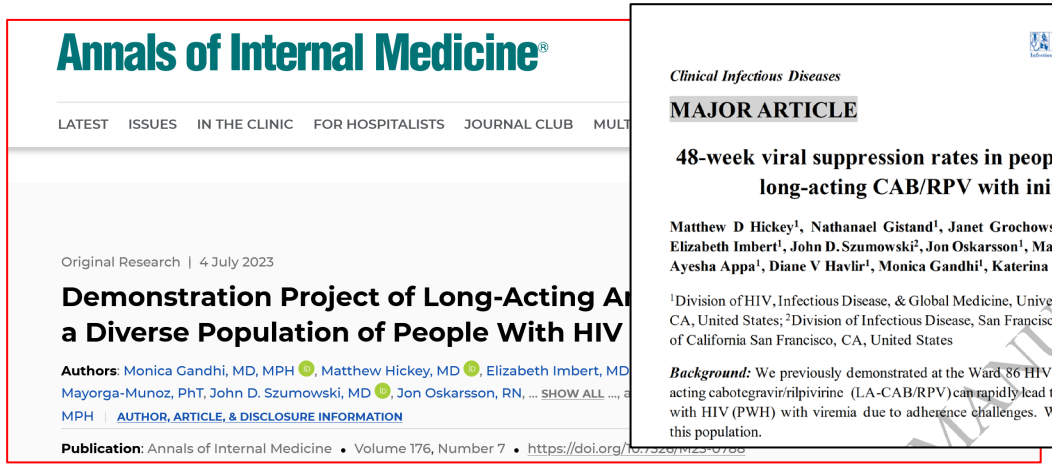
Study (reference)	Study population	Design	Result (week 48); f/u reference
FLAIR Orkin NEJM 2020;382:1124-1135	Rx-naïve adults (N=629)	ABC/3TC/DTG X 20 wks → CAB + RPV (oral X 4 wks, then IM monthly) or continue oral regimen (non-inferiority Δ6%)	VS >93%; CAB + RPV **non-inferior** to oral regimen Lancet HIV 2021;8:e668: 124 weeks IAS 2021: 144 wks
ATLAS Swindells NEJM 2020;382:1	Adults with VS on 2 NRTI + PI, NNRTI, or INSTI	continue ART or change to CAB + RPV (oral X 4 weeks, then IM monthly)	VS >92%; CAB + RPV **non-inferior** to oral regimen

Combination of CAB/RILP LA for treatment?

- Initially dismissed for LMICs
  - Cost – 2 injections, likely to be $ >>> $ TLD
  - Resistance profile (background NNRTI resistance) and requirements for genotyping
  - Complexity of systems for administration (trained staff, cold chain, long needles, etc etc), risk stratifications (obesity, clades etc etc)
  - For suppressed patients? – the ones who least need it!
  - 4/12 in development

Renewed interest in CAB/RILP…

- Off-label use in viraemic and ARV-naïve patients – with excellent results
- And along came CARES (Kityo et al, CROI 2024, LancetID), 97% suppression in switch patients at 48 weeks! High acceptability, safety


Annals of Internal Medicine®

LATEST ISSUES IN THE CLINIC FOR HOSPITALISTS JOURNAL CLUB MULT

Original Research | 4 July 2023

Demonstration Project of Long-Acting A… a Diverse Population of People With HIV

Authors: Monica Gandhi, MD, MPH, Matthew Hickey, MD, Elizabeth Imbert, MD, Mayorga-Munoz, PhT, John D. Szumowski, MD, Jon Oskarsson, RN, … SHOW ALL …, … MPH | AUTHOR, ARTICLE, & DISCLOSURE INFORMATION

Publication: Annals of Internal Medicine • Volume 176, Number 7 • https://doi.org/10.7326/M23-0788

IDSA hivma OXFORD

Clinical Infectious Diseases

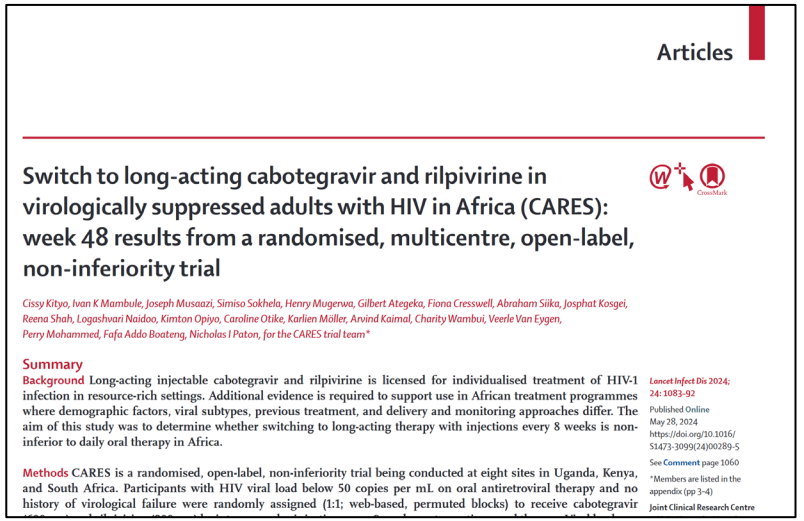
MAJOR ARTICLE

48-week viral suppression rates in people with HIV starting long-acting CAB/RPV with initial viremia

Matthew D Hickey[1], Nathanael Gistand[1], Janet Grochowski[1], Francis Mayorga-Munoz[1], Elizabeth Imbert[1], John D. Szumowski[2], Jon Oskarsson[1], Mary Shiels[1], Samantha Dilworth[1], Ayesha Appa[1], Diane V Havlir[1], Monica Gandhi[1], Katerina Christopoulos[1]

[1]Division of HIV, Infectious Disease, & Global Medicine, University of California, San Francisco, CA, United States; [2]Division of Infectious Disease, San Francisco VA Medical Center, University of California San Francisco, CA, United States

Background: We previously demonstrated at the Ward 86 HIV clinic in San Francisco that long-acting cabotegravir/rilpivirine (LA-CAB/RPV) can rapidly lead to viral suppression (VS) in people with HIV (PWH) with viremia due to adherence challenges. We now evaluate VS durability in this population.


Articles

Switch to long-acting cabotegravir and rilpivirine in virologically suppressed adults with HIV in Africa (CARES): week 48 results from a randomised, multicentre, open-label, non-inferiority trial

Cissy Kityo, Ivan K Mambule, Joseph Musaazi, Simiso Sokhela, Henry Mugerwa, Gilbert Ategeka, Fiona Cresswell, Abraham Siika, Josphat Kosgei, Reena Shah, Logashvari Naidoo, Kimton Opiyo, Caroline Otike, Karlien Möller, Arvind Kaimal, Charity Wambui, Veerle Van Eygen, Perry Mohammed, Fafa Addo Boateng, Nicholas I Paton, for the CARES trial team*

Summary

Background Long-acting injectable cabotegravir and rilpivirine is licensed for individualised treatment of HIV-1 infection in resource-rich settings. Additional evidence is required to support use in African treatment programmes where demographic factors, viral subtypes, previous treatment, and delivery and monitoring approaches differ. The aim of this study was to determine whether switching to long-acting therapy with injections every 8 weeks is non-inferior to daily oral therapy in Africa.

Methods CARES is a randomised, open-label, non-inferiority trial being conducted at eight sites in Uganda, Kenya, and South Africa. Participants with HIV viral load below 50 copies per mL on oral antiretroviral therapy and no history of virological failure were randomly assigned (1:1; web-based, permuted blocks) to receive cabotegravir

Lancet Infect Dis 2024; 24: 1083–92

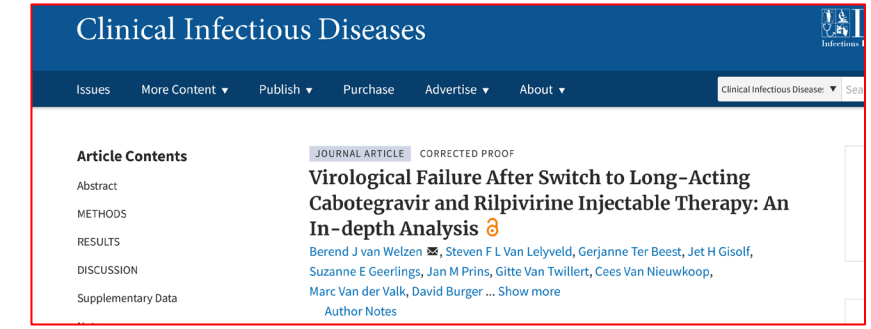
Published Online May 28, 2024 https://doi.org/10.1016/S1473-3099(24)00289-5

See Comment page 1060

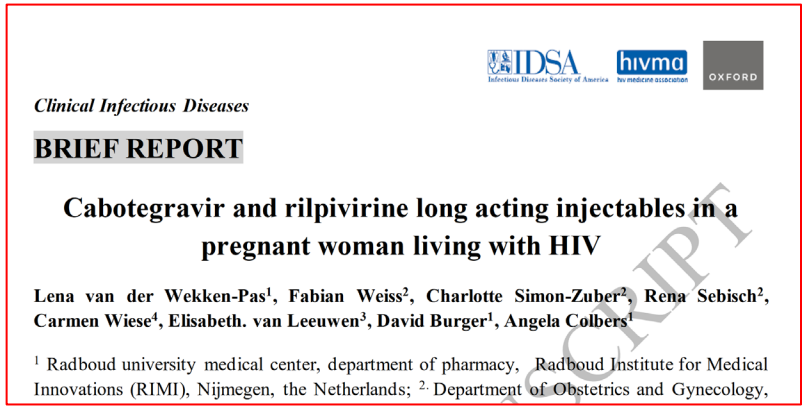
*Members are listed in the appendix (pp 3–4)

Joint Clinical Research Centre

Caveats are virological



- One patient on CARES with isolated INSTI mutation Q148R
- Dutch cohort failures – 5 with failure, despite no risk, low pk - Wensing, CID
- Failure in pregnancy case, RILP 70% lower, although no VF - van der Wekken-Pas, CID

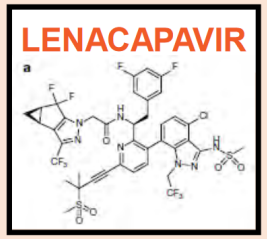


But immediate and urgent need:

- In unsuppressed patients – think adolescents, high-risk adults
- And the only combination to start testing implementation of LAIs in LMICs
- But:
  - Extremely limited access to either drug
  - No licencing agreement for either drug for treatment
  - Unclear patents for rilpivirine, and no pathway to make it viable for generic companies

Agent 3: Lenacapavir (Gilead Sciences)

Agent class:
HIV-1 capsid inhibitor



Dosing Strategy:
One injection every 6 months
(ARVs that you only need to take twice a year!)

- Capsid inhibitor
- Oral (daily, weekly) or subcutaneous (3, 6 monthly)
- Well tolerated (subcutaneous nodules?), resistance barrier high(ish)
- Approved for heavily pretreated ARV patients in small study, on optimised backbone – registered FDA/EMA 2022
- Don’t forget needs oral lead in!
- Manufacturing – technically not hard to make, but API complex to manufacture; having oral and subcutaneous formulations makes access complex

How is it available?

- Orally and subcutaneously
- Oral – 300mg tablet
- Subcutaneously – 3 and 6 monthly (?can be dosed other intervals), 1.5ml 463mg in each syringe, given as TWO injections
- NB: Subcut takes time to reach peak value, so needs a loading dose – has significant implications for programmes

Lenacapavir Dosing Schedule	
Initiation Option 1	
Day 1	927 mg by subcutaneous injection (2 x 1.5 mL injections) + 600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
Initiation Option 2	
Day 1	600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
Day 8	300 mg orally (1 x 300 mg tablets)
Day 15	927 mg by subcutaneous injection (2 x 1.5 mL injections)
Maintenance	
927 mg by subcutaneous injection (2 x 1.5 mL injections) every 6 months (26 weeks) from date of the last injection +/-2 weeks	
Missed dose: If more than 28 weeks since last injection and clinically appropriate to continue lenacapavir, restart initiation from Day 1, using either Option 1 or Option 2	

Source: Lenacapavir Prescribing Information

Access

- Opaque access plan from Gilead after prevention results – several generics licenced in internal arrangement Sept 2024
  - NOT for treatment beyond highly pre-treated patients!
  - Prevention volumes envisaged late 2027
  - ??? cost
  - Gilead says ‘will make enough drug for everyone’ till generics make it
  - Tiny ACTG study for LEN/CAB after > year pleading – concern is ‘asynchronous dosing’

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.

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S0140-6736(25)0040

See Online/Comment

The NEW ENGLAND JOURNAL of MEDICINE

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]

Almost 15 years ago, the results of the Preexposure Prophylaxis Initiative (iPrEx) trial, which showed the efficacy of oral antiretroviral agents as pre-exposure prophylaxis (PrEP), were reported in the *Journal*.[1] However, only 15% of persons who would benefit from PrEP currently receive it.[2] The recent modest fall in the global incidence of human immunodeficiency virus (HIV) infection obscures the ongoing epidemic among key populations in high-income, middle-income, and low-income countries, including continued high infection rates among young women in southern Africa. The United Nations 2030 prevention targets will not be met unless something different is done, and soon.

The results of the PURPOSE 2 trial, reported by Kelley et al. in this issue of the *Journal*,[3] essentially mirror those of the PURPOSE 1 trial, which was conducted in Uganda and South Africa. The PURPOSE 1 trial showed near-total protection from HIV infection among participants who received subcutaneous lenacapavir every 6 months.[4]

The PURPOSE 2 trial, which was conducted in the United States and six middle-income countries (Mexico, Argentina, Brazil, Thailand, Peru, and South Africa), recruited cisgender men and gender-diverse persons who were having condomless receptive anal sex with partners assigned male at birth. Recreational drug use and sexually transmitted infections (STIs) were common in the screened population.

Participants underwent randomization in a 2:1 ratio and were assigned to receive lenacapavir every 26 weeks or daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF). The incidence of HIV infection in the trial population was compared with the background incidence in the screened population.

The incidence of HIV infection was lower in the lenacapavir group than in the F/TDF group: of the 11 incident infections, 2 occurred in the lenacapavir group (0.10 per 100 person-years) and 9 occurred in the F/TDF group (0.93 per 100 person-years). The background incidence of HIV infection in the screened population was 2.37 per 100 person-years. The adherence to oral PrEP and the efficacy of PrEP were substantially higher in the PURPOSE 2 trial than in the PURPOSE 1 trial.

The two participants in the lenacapavir group who acquired HIV infection in the current trial had active STIs. Neither participant reported symptoms of HIV infection. The participants had presumed effective lenacapavir levels, and both participants were found to have the capsid inhibitor mutation N74D, indicating that long-term resistance monitoring for breakthrough cases is warranted. This finding has potential implications for treatment options under development.

The nine HIV infections in the F/TDF group were associated with low or undetectable levels of tenofovir (in eight participants) or discontinuation of the trial drug (in one participant). Drug monitoring suggested steadily decreasing adherence over time across this group.

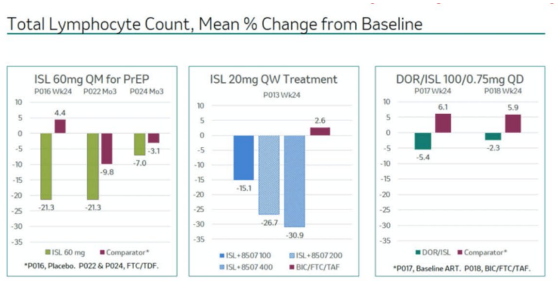
The near-total protection shown in the PURPOSE 1 and 2 trials is catalytic for HIV prevention. The long-acting injectable nature of lenacapavir addresses the major Achilles heel of oral PrEP: adherence. There is much to praise about these trials: the designs involved substantial

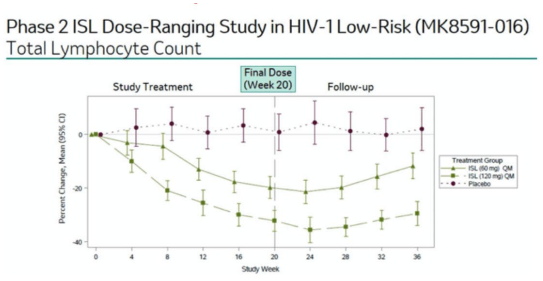
Do we need a lenacapavir/cabotegravir study for LMICs?

- Most obvious combination
  - Pregnancy data
  - Plenty safety, acceptability data
  - TB less of an issue, hep B will need resolution with any LAI without TDF/3TC
- CAB may be amenable to 3, 4, 6 monthly dosing, more ‘synchronous’
- Cost likely to approach TLD if administration devices kept simple, volumes high, HCW approach kept simple

Agent 4: Islatravir (MSD/Merck)

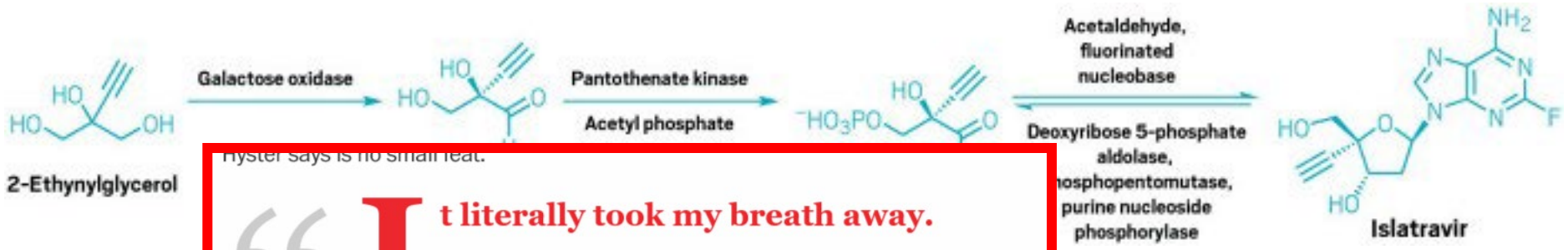
- Nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- Derived from soy sauce flavouring
- Developed by Merck/MSD when bought in 2012
- Oral – daily, weekly; monthly (PrEP/implant paused due to side effects)
- High resistance barrier, very well tolerated, very low dose





Pure enzyme synthesis

- Traditional small molecule synthesis – multiple steps, time consuming, complex, with significant waste and environmental hazard
- Islatravir – manufactured using 'biocatalysis'- pure enzymatic reaction, biochemist awe
- High volume, no waste, possible revolutionary mechanism to manufacture drugs



Hyster says is no small feat.

"It literally took my breath away.

— **Alison Narayan,** *assistant professor, University of Michigan*

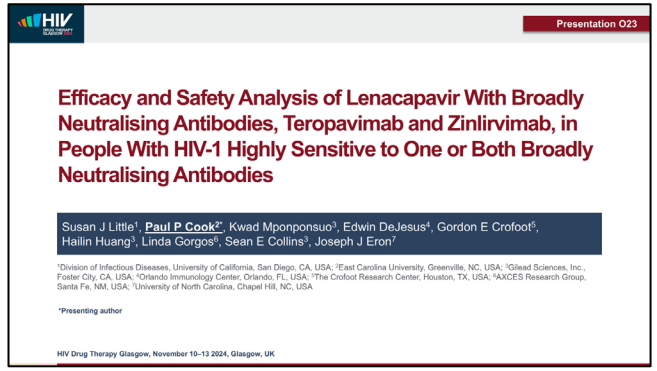
https://cen.acs.org/pharmaceuticals/process-chemistry/Scientists-made-HIV-drug-using/97/web/2019/12

Islatravir continued

- Current plan is oral weekly combo with LEN – preliminary data from CROI 2024 phase 2 promising, also plans for oral daily with doravirine
- 2025: long-acting treatment back on the table
- No access discussions, minimal pregnancy data
- Combination is potentially very cheap to make, and package
- Provisional safety and resistance data very encouraging

Other agents: Mabs and things

- >17 antibodies evaluated – good safety, but resistance a major issue; cost and dose – Gilead's LEN pairing strategy
- Lots of optimism in the field, not many results yet
- Also: long-acting TAF, new Merck 'islatravir'
- Industry products that aren't in the sunlight
- Injectable TLD LA – in primates, s/c 4 weekly, pk adequate (AIDS 2023) – intriguing data suggesting alternative to current approaches


HIV DRUG THERAPY GLASGOW

Presentation O23

Efficacy and Safety Analysis of Lenacapavir With Broadly Neutralising Antibodies, Teropavimab and Zinlirvimab, in People With HIV-1 Highly Sensitive to One or Both Broadly Neutralising Antibodies

Susan J Little[1], Paul P Cook[2*], Kwad Mponponsuo[3], Edwin DeJesus[4], Gordon E Crofoot[5], Hailin Huang[3], Linda Gorgos[6], Sean E Collins[3], Joseph J Eron[7]

[1]Division of Infectious Diseases, University of California, San Diego, CA, USA; [2]East Carolina University, Greenville, NC, USA; [3]Gilead Sciences, Inc., Foster City, CA, USA; [4]Orlando Immunology Center, Orlando, FL, USA; [5]The Crofoot Research Center, Houston, TX, USA; [6]AXCES Research Group, Santa Fe, NM, USA; [7]University of North Carolina, Chapel Hill, NC, USA

*Presenting author

HIV Drug Therapy Glasgow, November 10–13 2024, Glasgow, UK

The rise of weekly tablets…

Once-Weekly Islatravir Plus Lenacapavir in Virologically Suppressed PWH: Week 48 Safety, Efficacy, and Metabolic Changes

Amy E. Colson[1], Gordon E. Crofoot[2], Peter J. Ruane[3], Moti N. Ramgopal[4], Alexandra W. Dretler[5], Ronald G. Nahass[6], Gary I. Sinclair[7], Mezgebe Berhe[8], Fadi Shihadeh[9], Shan-Yu Liu[9], Stephanie Klopfer[10], Sharline Madera[9], Hadas Dvory-Sobol[9], Martin S. Rhee[9], Elizabeth G. Rhee[10], Jared Baeten[9], Joseph Eron[11]

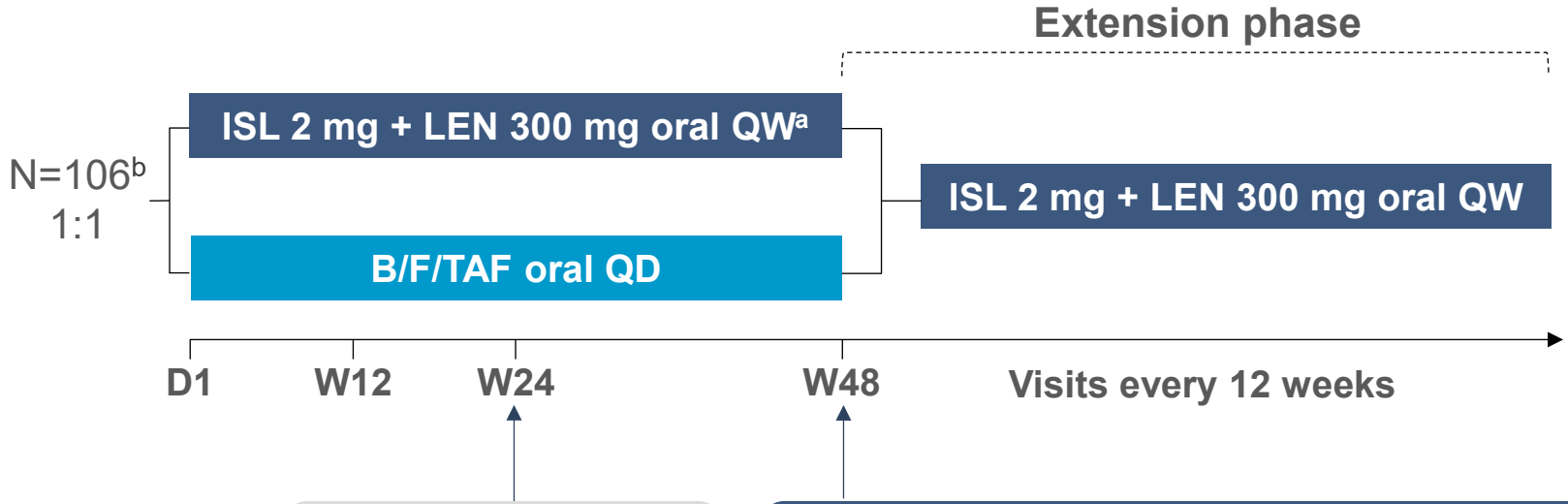
[1]Community Resource Initiative, Boston, Massachusetts, USA; [2]The Crofoot Research Center, Houston, Texas, USA; [3]Ruane Clinical Research, Los Angeles, California, USA; [4]Midway Immunology & Research Center, Fort Pierce, Florida, USA; [5]Metro Infectious Disease Consultants, Decatur, Georgia, USA; [6]IDCare, Hillsborough, New Jersey, USA; [7]Prism Health North Texas, Dallas, Texas, USA; [8]North Texas Infectious Diseases Consultants, Dallas, Texas, USA; [9]Gilead Sciences, Foster City, California, USA; [10]Merck & Co., Inc., Rahway, New Jersey, USA; [11]University of North Carolina, Chapel Hill, North Carolina, USA

HIV Drug Therapy Glasgow 2024, November 10–13, Glasgow, United Kingdom

Methods

A Phase 2, Open-label, Active-Controlled Study in Virologically Suppressed PWH

Eligibility criteria
- Aged ≥18 years
- On B/F/TAF for >6 months
- HIV-1 RNA <50 c/mL for >6 months
- No history of virologic failure
- CD4+ T-cell count ≥350 cells/µl
- Lymphocyte count ≥900 cells/µl
- No HBV infection



Primary endpoint:[1]
- Proportion with HIV-1 RNA ≥50 c/mL at Week 24 per FDA Snapshot Algorithm

Secondary endpoints included in this presentation:
- Proportion with HIV-1 RNA ≥50 c/mL at Week 48
- Proportion with HIV-1 RNA <50 c/mL at Week 48
- Change from baseline in CD4+ T-cell count
- AEs leading to study drug discontinuation

Other assessments:
- Change in BMI, body weight, and adherence

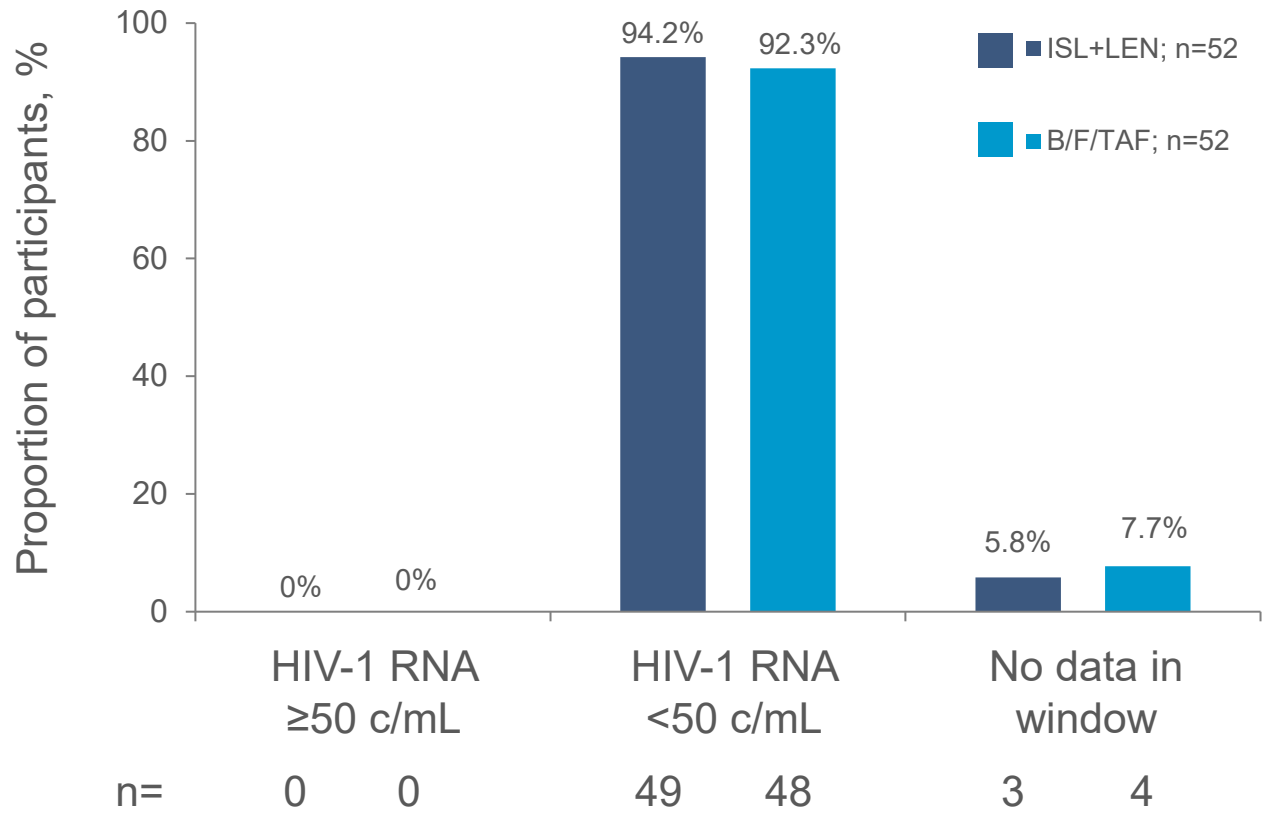
[a]600 mg of LEN was given on Day 1 and Day 2 for pharmacologic loading. [b]Randomised, N=106; dosed, n=104.
AE, adverse event; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **BMI**, body mass index; **c/mL**, copies/ml; **D**, Day; **FDA**, Food and Drug Administration; **HBV**, hepatitis B virus; **ISL**, islatravir; **LEN**, lenacapavir; **PWH**, people with HIV-1; **QD**, daily; **QW**, weekly; **W**, Week.
1. Colson A, et al. CROI 2024; Abstract 208.

Baseline Demographic and Disease Characteristics

	ISL+LEN (n=52)	B/F/TAF (n=52)	Total (N=104)
Median (range) age, years	40 (28–67)	40 (26–76)	40 (26–76)
Assigned female at birth, n (%)	10 (19.2)	9 (17.3)	19 (18.3)
Gender identity, n (%)			
Transgender female	1 (1.9)	0	1 (1.0)
Non-binary/third gender	0	1 (1.9)	1 (1.0)
Race, n (%)			
White	25 (48.1)	27 (51.9)	52 (50.0)
Black	21 (40.4)	16 (30.8)	37 (35.6)
Asian	2 (3.8)	1 (1.9)	3 (2.9)
American Indian or Alaska Native	1 (1.9)	2 (3.8)	3 (2.9)
Native Hawaiian or Pacific Islander	0 (0)	1 (1.9)	1 (1.0)
Other	3 (5.8)	5 (9.6)	8 (7.7)
Hispanic or Latinx ethnicity, n (%)	13 (25.0)	17 (32.7)	30 (28.8)
Mean (SD) CD4+ T-cell count, cells/μL	755 (223.6)	818 (271.3)	786 (249.5)
Mean (SD) lymphocyte count x 10^3 cells/μL	1.94 (0.445)	1.95 (0.652)	1.94 (0.556)
Median (IQR) body weight, kg	79.3 (70.4–87.4)	83.2 (76.1–92.5)	80.5 (74.4–88.7)
Median (IQR) BMI, kg/m^2	26.9 (23.8–30.0)	27.2 (25.5–29.3)	27.1 (24.5–29.4)

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **BMI**, body mass index; **IQR,** interquartile range; **ISL**, islatravir; **LEN**, lenacapavir.

Virologic Outcomes at Week 48 by FDA Snapshot Algorithm



Participants with no data in window:

ISL+LEN (n=3)

- Two participants discontinued due to AEs not related to study drug
- One participant discontinued due to other reasons not related to study drug
- All participants had HIV-1 RNA <50 c/mL at study discontinuation

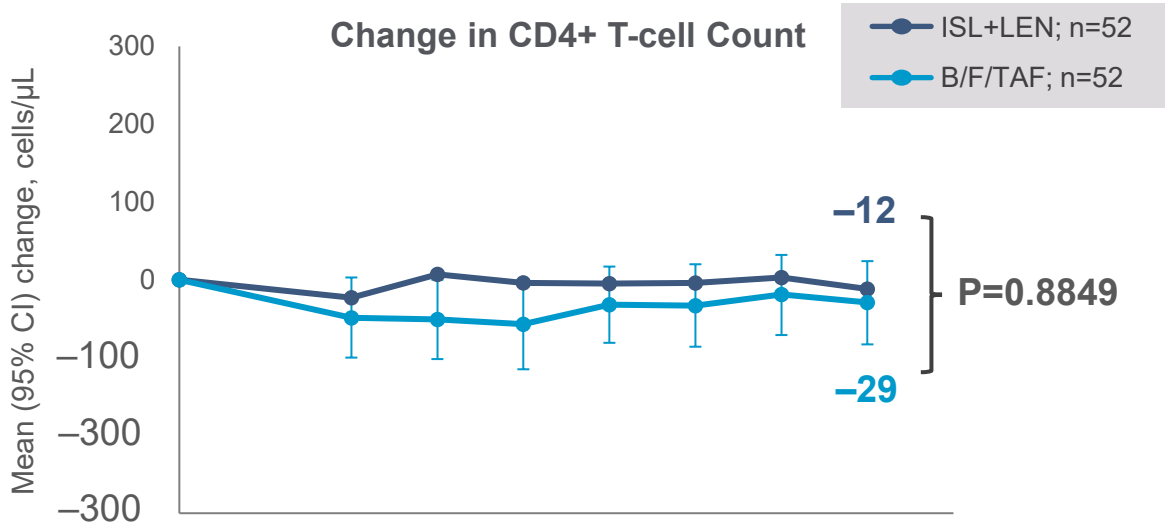
B/F/TAF (n=4)

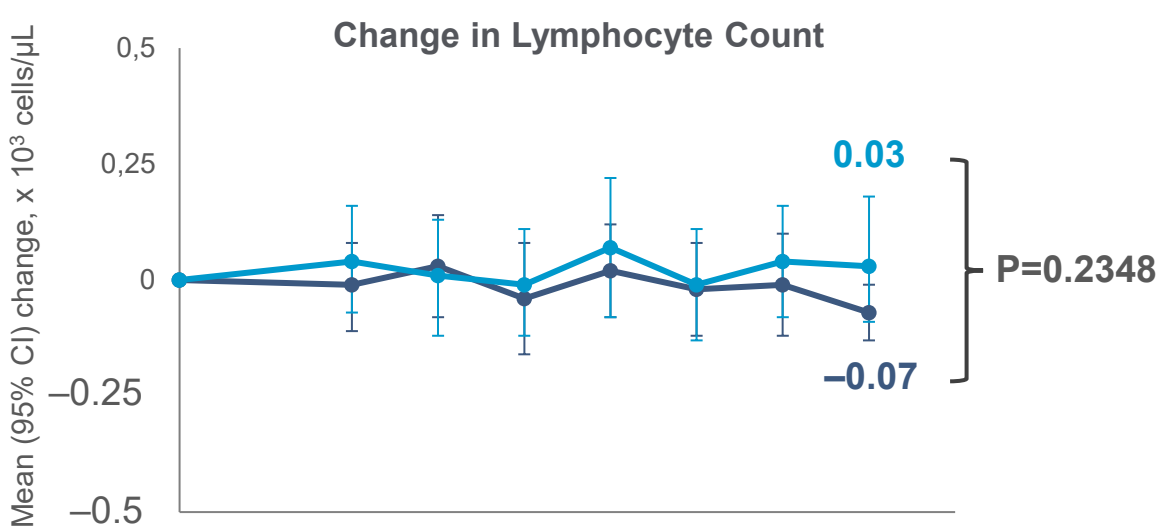
- Three participants discontinued due to other reasons not related to study drug and had HIV-1 RNA <50 c/mL at study discontinuation
- One participant had missing data during window, but remained on study drug

Participants in both treatment groups maintained high rates of virologic suppression

AE, adverse event; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **c/mL**, copies/mL; **FDA**, Food and Drug Administration; **ISL**, islatravir; **LEN**, lenacapavir.

CD4+ T-cell and Lymphocyte Count Changes Through Week 48





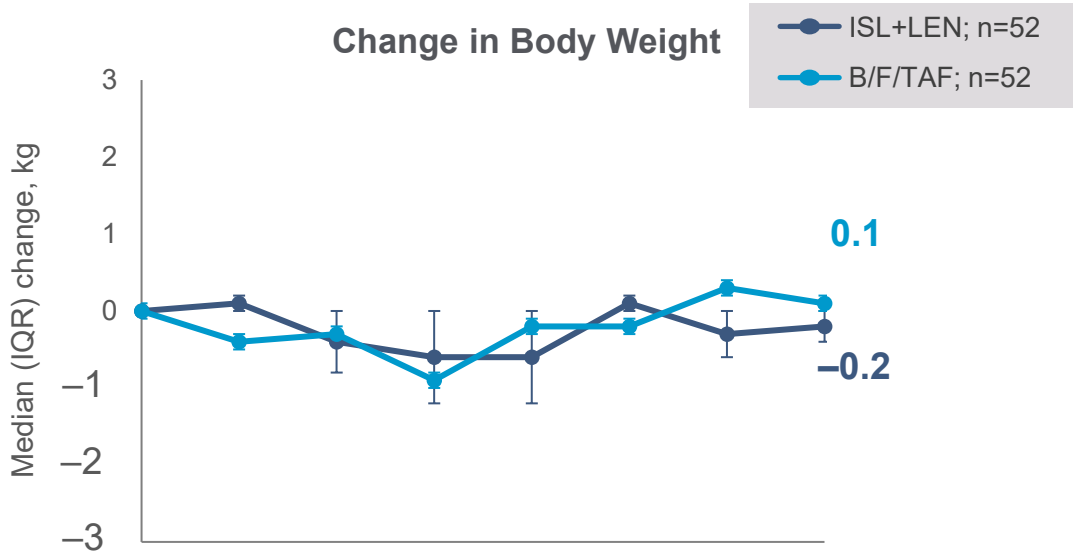
Mean Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	755	732	766	755	754	756	761	746
B/F/TAF	818	758	767	761	785	783	797	787

Mean Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	1.94	1.94	1.98	1.92	1.96	1.94	1.93	1.88
B/F/TAF	1.95	1.99	1.97	1.96	2.03	1.96	2.00	1.99

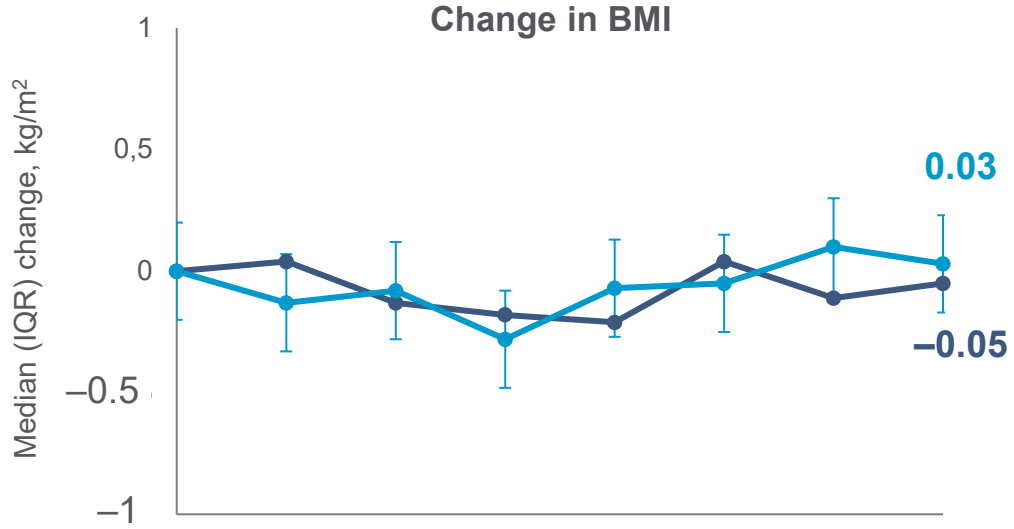
- There were no significant differences between groups in mean change from baseline in CD4+ T-cell or lymphocyte counts at Week 48
- No participants discontinued due to a decrease in CD4+ T-cell or lymphocyte counts

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **BL**, baseline; **ISL**, islatravir; **LEN**, lenacapavir; **W**, Week.

Body Weight and BMI Changes Through Week 48



Median Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	79.3	79.1	77.2	77.9	77.7	78.8	77.9	77.6
B/F/TAF	83.2	83.4	82.8	82.0	84.7	84.7	84.2	84.0



Median Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	26.9	26.8	26.9	26.6	27.2	27.1	26.6	26.7
B/F/TAF	27.2	27.4	27.3	27.3	27.4	27.9	27.6	27.7

No between-group differences in median change in body weight and BMI at Week 48

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **BL**, baseline; **BMI**, body mass index; **IQR**, interquartile range; **ISL**, islatravir; **LEN**, lenacapavir; **W**, Week.

Dual therapy continued – the next blockbuster?

- Other combinations:
  - Gilead – LEN + LAI INSTI
  - Merck – LAI NNRTI + islatravir
- Same number of tablets for 6 months as usually provided monthly
- Concerns:
  - Adherence for weekly dosing unfamiliar in HIV world
  - Pregnancy data, TB and hep B issue
  - How big a step forward is this really for LMICs? Why not wait for injectables?
  - Do we work on this as a side-project?

Current situation for treatment access

- No access to promising agents for necessary studies – for changing guidelines or demonstration projects
- Even if all drug companies allowed instant access today, 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

EXCLUSIVE

STAT+

Doctors Without Borders is closing its widely regarded access-to-medicines campaign

By Ed Silverman June 20, 2024

Reprints

ADOBE

In a surprise move, Doctors Without Borders is closing down its access-to-medicines campaign, which has been credited with ensuring needed drugs and vaccines have been made available to countless patients in low-income countries around the world.

aighd AMSTERDAM INSTITUTE FOR GLOBAL HEALTH & DEVELOPM

AVAC Advocacy. Access. Equity.

And finally…

- Just when you thought the weight nonsense was over….

PASO-DOBLE (GeSIDA 11720): Switch to DTG/3TC vs BIC/TAF/FTC in Virologically Suppressed Persons With HIV

CCO Official Conference Coverage

of *AIDS 2024, the 25th International AIDS Conference; July 22-26, 2024; Munich, Germany*

Provided by Clinical Care Options, LLC
Produced in partnership with the International AIDS Society.

Supported by educational grants from Gilead Sciences, Inc. and ViiV Healthcare.

IAS

CCO

powered by cea

PASO-DOBLE: Study Design

- Multicenter, randomized, open-label phase IV trial in Spain

Adults with HIV-1 RNA <50 c/mL for ≥24 wk; current ART with ≥1 pill/day including either COBI booster, EFV, or TDF; no earlier VF or ART resistance; no previous use of DTG or BIC; no chronic HBV
(N = 553)

Stratified by TAF use at baseline, sex at birth

Randomized 1:1

DTG/3TC
(n = 277)

BIC/FTC/TAF
(n = 276)

- Primary endpoint: plasma HIV-1 RNA ≥50 c/mL at Wk 48 by FDA Snapshot with noninferiority margin of 4%
- Key secondary endpoints: efficacy, safety, tolerability, weight change

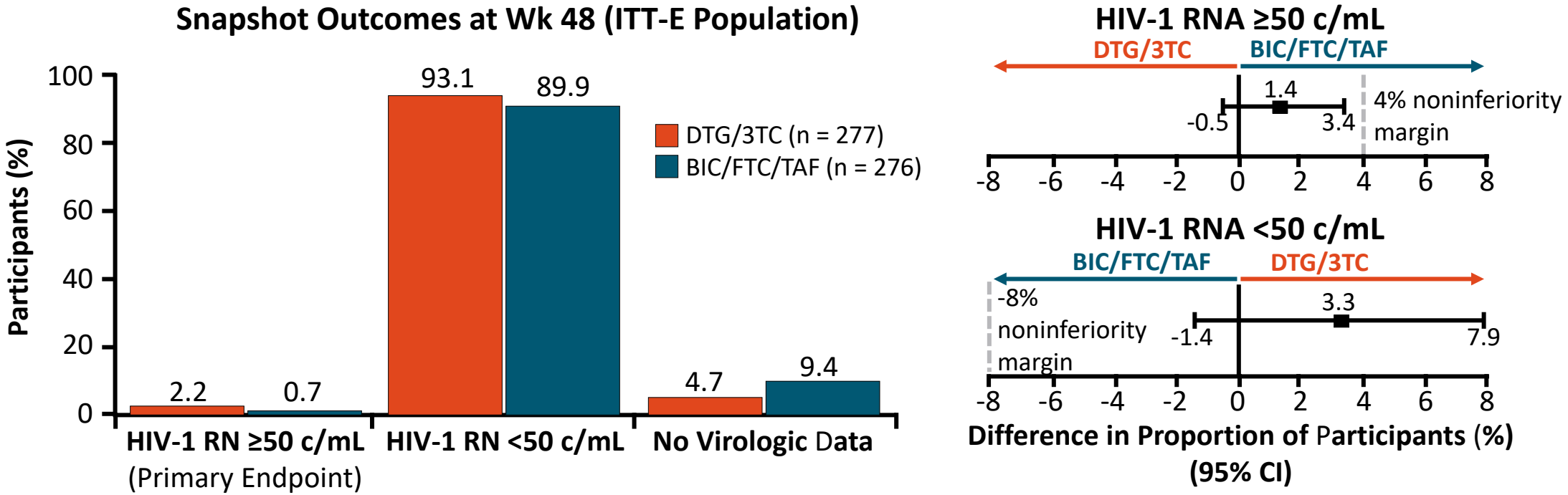
Martinez. AIDS 2024. Abstr OAB3606LB.

PASO-DOBLE: Baseline ART Regimens

Agent/Class, n (%)	DTG/3TC (n = 277)	BIC/FTC/TAF (n = 276)
NRTI 1		
▪ TAF	77 (27.8)	78 (28.3)
▪ ABC	59 (21.3)	52 (18.8)
▪ TDF	92 (33.2)	103 (37.3)
▪ No NRTI 1	49 (17.7)	43 (15.6)
NRTI 2		
▪ 3TC	70 (25.3)	64 (23.2%)
▪ FTC	182 (65.7)	190 (68.8%)
▪ None	25 (9.0)	22 (8.0%)
Core drug		
▪ NNRTI only	138 (49.8)	141 (51.1)
▪ INSTI only	44 (15.9)	49 (17.8)
▪ PI only	93 (33.6)	82 (29.7)
▪ >1 core drugs	2 (0.7)	4 (1.4)

Martinez. AIDS 2024. Abstr OAB3606LB.

PASO-DOBLE: Virologic Efficacy



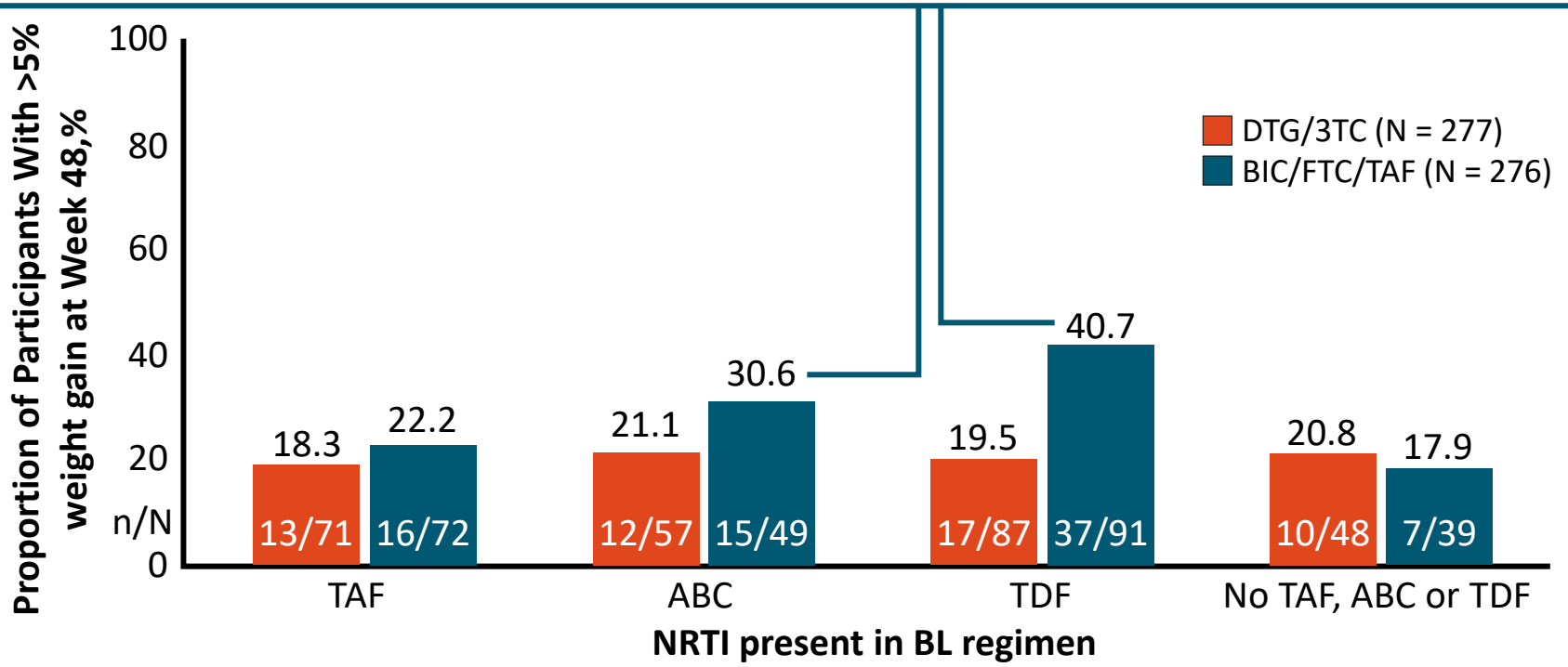
- By Wk 48, ≥1 virologic blip in 5.8% (16/277) receiving DTG/3TC and in 9.4% (26/276) receiving BIC/FTC/TAF; *P* = .106
  - Through Wk 48, 98 vs 152 total blips in those receiving DTG/3TC and BIC/FTC/TAF, respectively
- Confirmed virologic failure through Wk 48 in 1 participant receiving BIC/FTC/TAF vs 0 in those receiving DTG/3TC; no cases of emergent resistance in either arm

Martinez. AIDS 2024. Abstr OAB3606LB.

Slide credit: clinicaloptions.com

PASO-DOBLE: Body Weight Outcomes by Baseline NRTI

- Change in weight with BIC/TAF/FTC may depend on NRTI of previous regimen
  - In **DTG/3TC** arm, proportion with >5% weight gain was similar regardless of BL NRTI
  - In **BIC/FTC/TAF** arm, proportion with >5% weight gain was highest after switch from TDF or ABC



Martinez. AIDS 2024. Abstr OAB3606LB.

Slide credit: clinicaloptions.com

ADVANCE 192-week data

Open Forum Infectious Diseases

MAJOR ARTICLE

Final 192-Week Efficacy and Safety Results of the ADVANCE Trial, Comparing 3 First-line Antiretroviral Regimens

Simiso Sokhela,[1,©] Willem D. F. Venter,[1,©] Bronwyn Bosch,[1] Joana Woods,[1] Kaitlyn McCann,[2] Godspower Akpomiemie,[1] Nomathemba Chandiwana,[1] Nkuli Mashabane,[1] Angela Tembo,[1] Bryony Simmons,[3] Samanta Lalla-Edward,[1] Mark J. Siedner,[4,5] Phumla Sinxadi,[6,7] Lucas Hermans,[1,8] Lee Fairlie,[9] Alinda Vos,[1,10] Elaine Abrams,[11] Jennifer M. Manne-Goehler,[12] Michelle Moorhouse,[13] Polly Clayden,[14] Shane Norris,[15] Ambar Qavi,[2] Matthew Chersich,[8] Masebole Masenya,[8] Natasha Arulappan,[1] and Andrew Hill[16]

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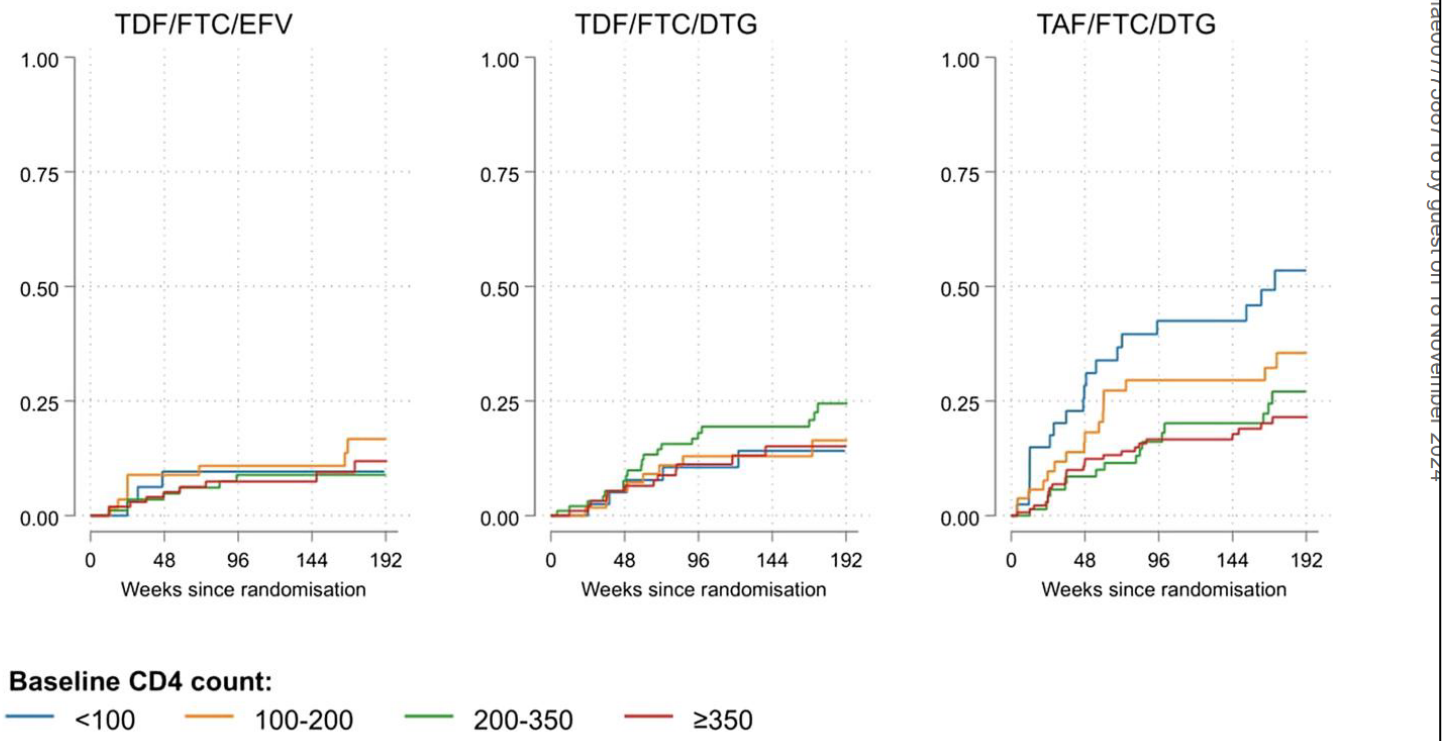


Figure 2. Time to clinical obesity by treatment arm and baseline CD4 count. DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Slide credit: clinicaloptions.com

Improvement in insulin sensitivity after switching from an integrase inhibitor-based regimen to doravirine/tenofovir disoproxil fumarate/lamivudine in people with significant weight gain

Improved insulin resistance associated with decreased waist circumfence and improved cardiometabolic profile

TABLE 2 Immunological, virological, and biological results 12 months after the switch to doravirine/lamivudine/tenofovir disoproxil fumarate.

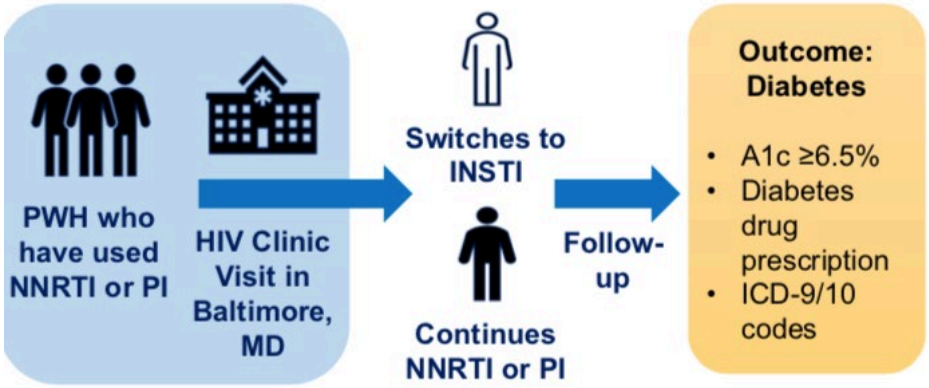
Variable	Total	*p* value[a]
Enrolled patients (*n*)	81	
Treatment failures		
Discontinuations due to AEs	2 (2.4)	0.339
Virological failures	1 (1.2)	0.501
Loss to follow-up, missing data, or withdrew consent	4 (4.9)	0.639
Virological successes (patients with HIV RNA < 20 copies/mL)		
ITT analysis (%)	74/81 (91.3)	0.592
PP analysis (%)	74/75 (98.7)	0.478
Change from baseline in CD4+ lymphocyte count (cells/mm^3)	+55 (+10 to +109)	0.729
Change from baseline in glucose (mg/dL)	−7.2 (−16.8 to +6.2)	0.438
Change from baseline in insulin (mcrUI/L)	−3.54 (−4.22 to −2.87)	0.012
Change from baseline in HOMA-IR index	−0.54 (−0.91 to −0.18)	0.021
Patients with HOMA-IR index >2.5	28 (34.6)	
Change from baseline in serum lipids (mg/dL)		
Total cholesterol	−25.2 (−40.3 to −11.6)	0.039
LDL cholesterol	−14.6 (−29.2 to −6.5)	0.042
HDL cholesterol	−2.1 (−4.4 to +1.4)	0.473
Triglycerides	−37.6 (−61.4 to −11.5)	0.189
Weight change from baseline (kg)	−1.09 (−2.11 to −0.35)	0.175
BMI change from baseline (kg/m^2)	−0.35 (−0.48 to −0.23)	0.329
Change from baseline in abdominal circumference (cm)	−2.8 (−3.7 to −1.8)	0.087

60.4% at baseline

L Calza HiV Med 2024

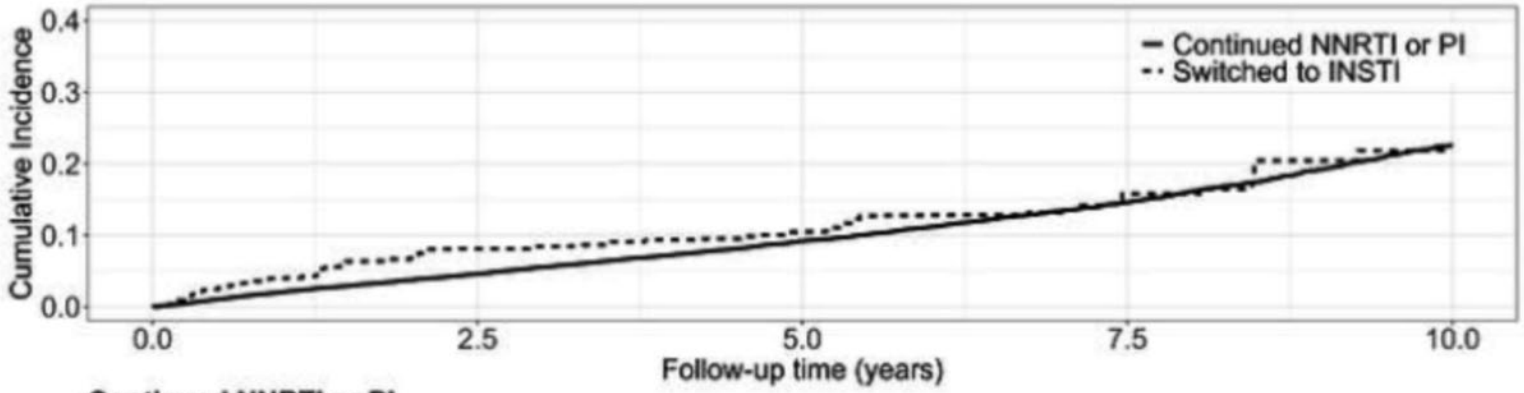
Association between switching to integrase strand transfer inhibitors and incident diabetes in people with HIV: a longitudinal cohort study

2,075 PWH who attended 22,116 visits where they continued NNRTI or PI and 631 visits where they switched to INSTI.
Globally, switching to INSTI was associated with a weighted HR of 1.11 for incident diabetes (NS).
Increased risk of incident diabetes in the first two years (wHR: 1.79)
If no weight gain occured during the first two years wHR: 1.22 (NS).



Weighted cumulative incidence of diabetes after switching to an INSTI compared to continuing an NNRTI or PI

N at risk and N of events represent weighted values



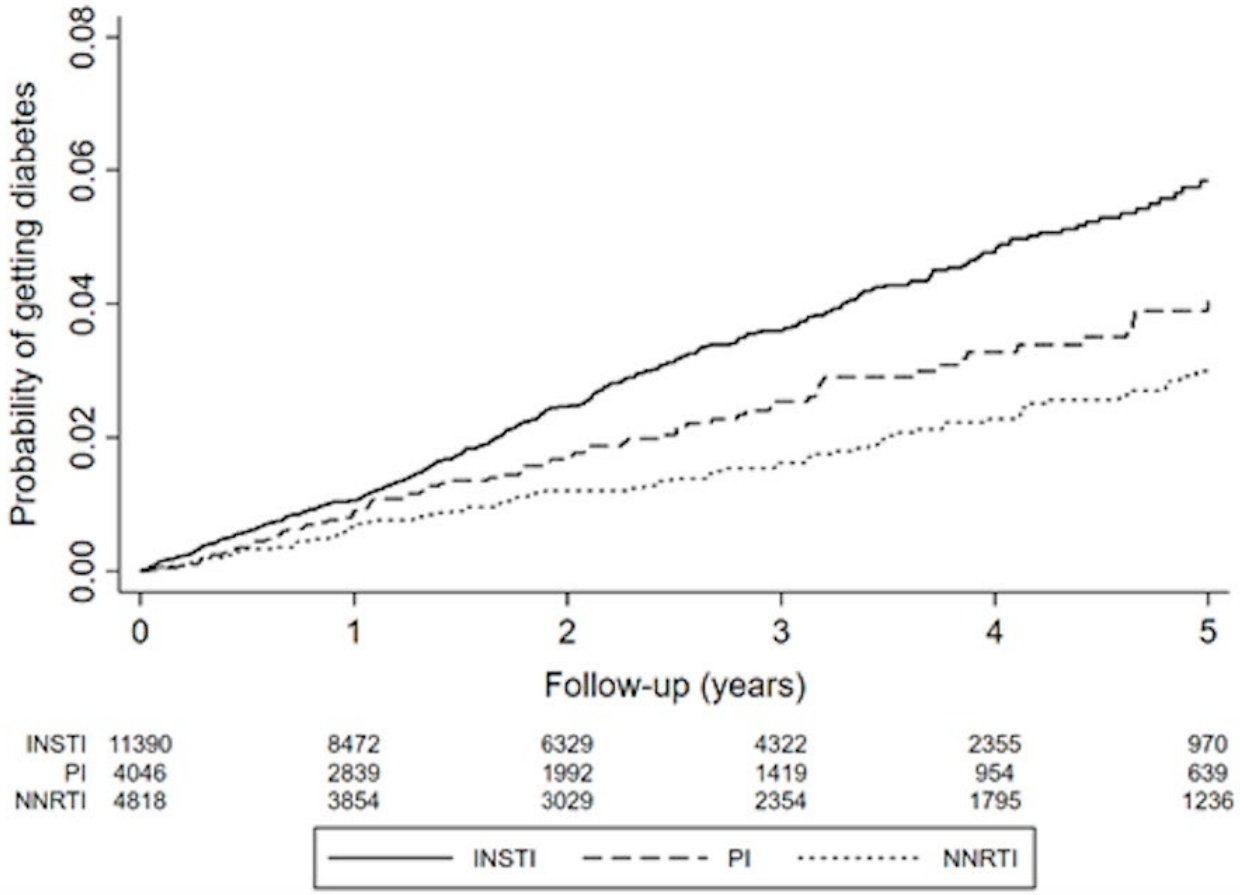
Continued NNRTI or PI					
N at risk	22133	13115	7206	3516	1573
N of events	0	831	485	312	235
Switched to INSTI					
N at risk	584	413	273	183	85
N of events	0	43	9	13	10

YJ Hwang CROI 2924 #805, AIDS 2024

INSTI-related changes in BMI and risk of diabetes: a prospective study from the RESPOND cohort consortium

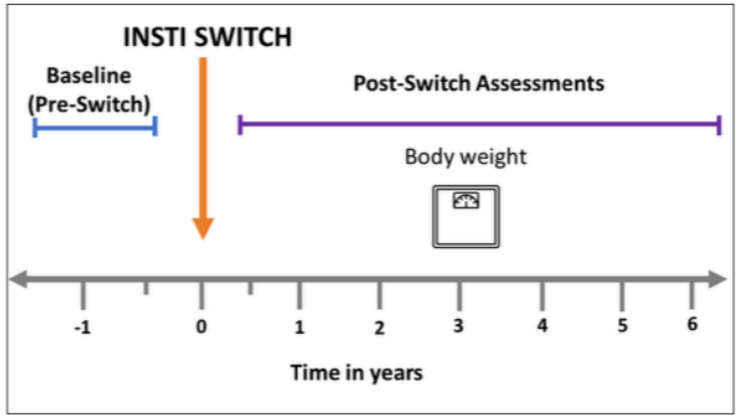
- Among 20,865 PWH (74% male, 73% white)
- baseline age 45y, median BMI 24,
- 785 DM diagnosed with a crude rate 7.3/1000 PYFU
- Ln(BMI) strongly associated with DM incidence rate ratio: 16.54
- Current INSTI use associated with increased DM risk: 1.58 in years 1 to 3
- Only partially attenuated when adjusted to ln(BMI): 1.48

Figure 2b: Kaplan Meier demonstrating the time to DM event from the start of drug class



D Rupasinghe CID 2024 in press

Short and long-term body weight gain following switch to integrase inhibitors differs by sex



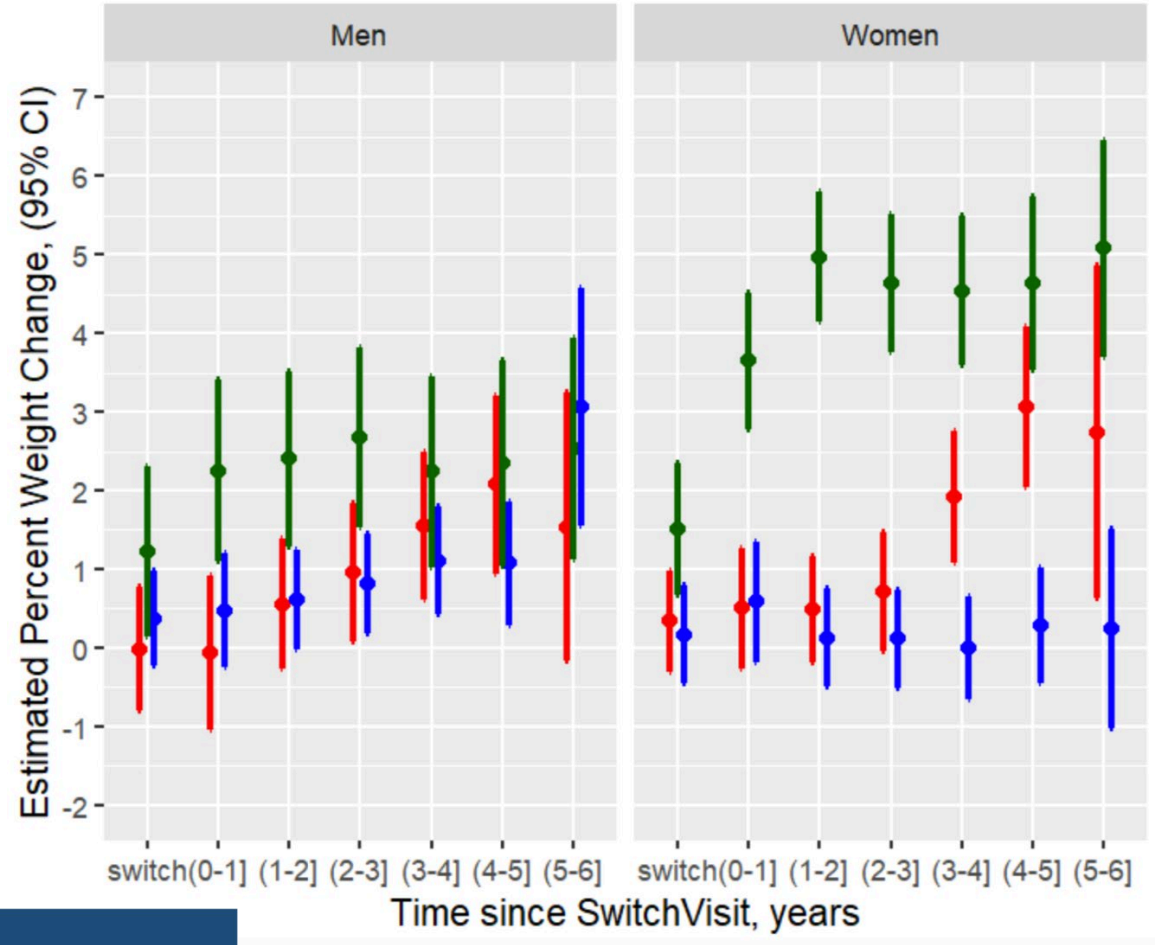


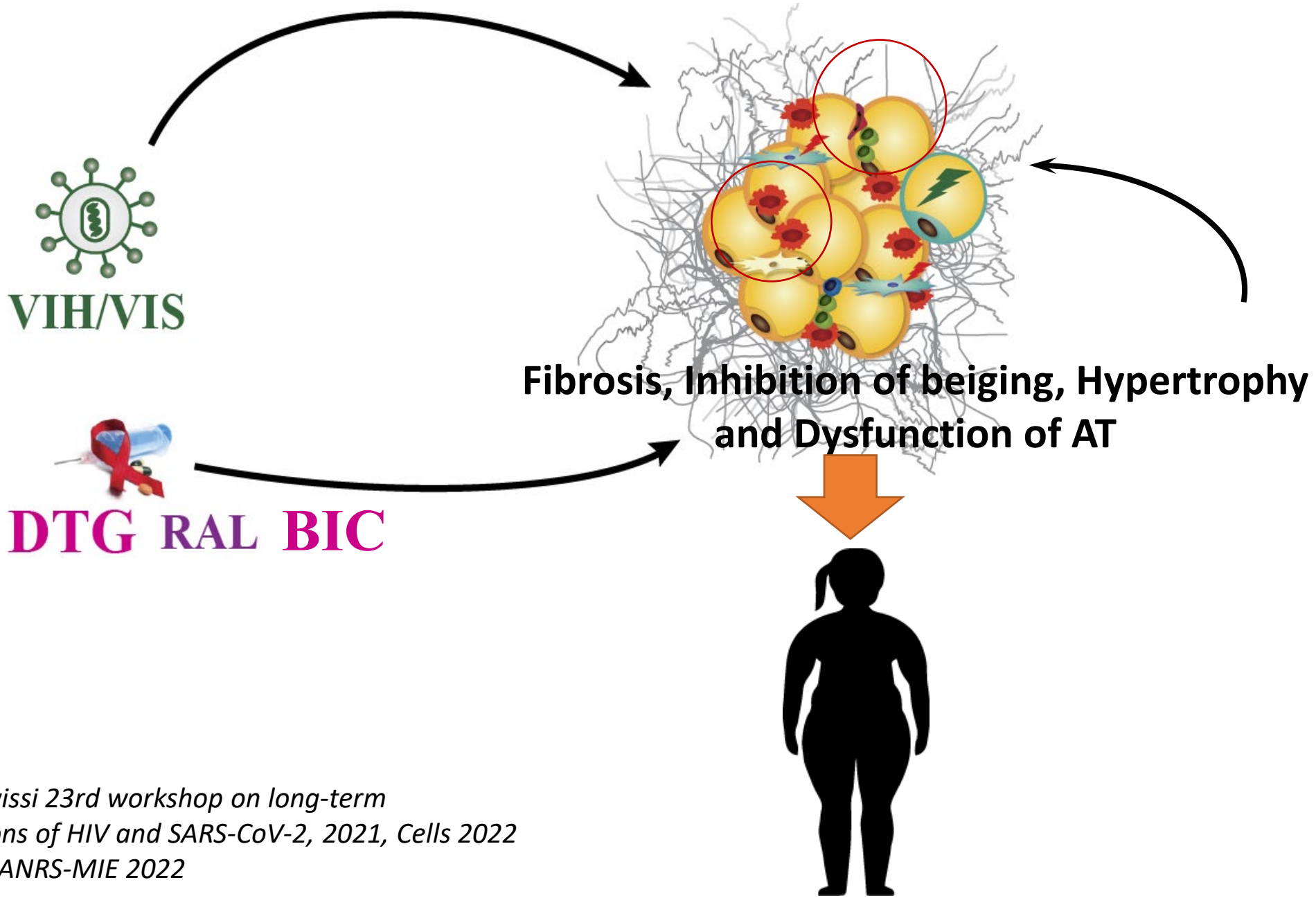
Figure 2. Model-estimated mean percent weight change among men and women with and without HIV in the MWCCS, stratified by study group and years since switch. Models adjusted for age, race/ethnicity, socioeconomic status, diabetes. Sex*group*years interaction term, p<0.0001

Compared with men, women with HIV switching to INSTIs experienced greater amount and longer duration of body weight gain relative to non-INSTI and HIV seronegative controls

MWCCS
MACS/WIHS COMBINED COHORT STUDY

CD Lahiri CROI 2024 #823

Deleterious impact of INSTIs on adipose tissue functions



K Ngono Ayissi 23rd workshop on long-term complications of HIV and SARS-CoV-2, 2021, Cells 2022
J Gorwood ANRS-MIE 2022

As for HIV: The drugs are revolutionising everything

The New York Times

Account

We Know Where New Weight Loss Drugs Came From, but Not Why They Work

The empty auditoriums, Gila monsters, resistant pharmaceutical executives and enigmas that led to Ozempic and other drugs that may change how society thinks about obesity.

FORECAST

How Long Til We're All on Ozempic?

Greg Justice

Over 100 million Americans, and possibly many more, could benefit from GLP-1 drugs. When can they expect to get them?

Obesity medication has something of a troubled past. Fen-phen, a weight-loss drug combination popular in the 1990s, was pulled after it was found to cause heart valve problems. Sibutramine, sold under the brand name Meridia, was prescribed until it was discovered to lead to adverse cardiovascular events including strokes in 2010.

But the market for an effective weight-loss drug is too big and the potential profits too

Weight Loss Required for Therapeutic Benefit

Diabetes (Pre

A1C Reductio

Hypertensior

Dyslipidemia

NAFLD

Sleep Apnea

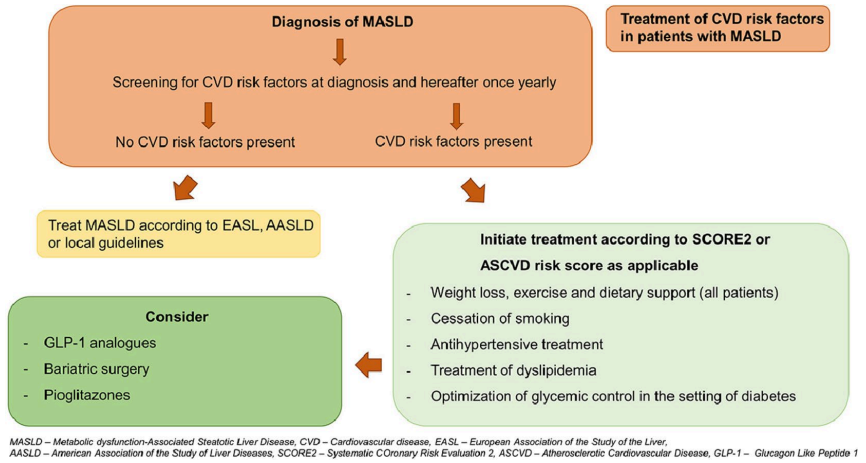
Osteoarthriti

GERD (Men)

GERD (Wome

PCOS

Explosion in indications – from renal to liver to heart failure (to addiction)

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https://www.astralcodexten.com/p/why-does-ozempic-cure-all-diseases

Cefalu. Diabetes Care. 2015;38:1567.


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C


he Dark Side