HIV 2023: An update for the family physician

(and how I sort of became one)

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Disclosures: Francois Venter

Before and after initiation of ARV therapy!

Before and after initiation of ARV therapy!

Paul Sax Aug 2023: "Major advances… have drifted away from an infectious diseases doctor's typical areas of focus"

My patient, 2019:

- **35-year-old woman**
- **On TAF/FTC/DTG – baseline BMI 23**
- **On <u>diet, exercising</u>, BMI 44**
- **Switched to TDF/FTC/EFV continues to gain weight**
- **In clinic, in tears, helpless – "I am doing everything you tell me to do"**
- **BMI now 60**

BMI classification	
Underweight	< 18.5
Normal range	18.5 - 24.9
Overweight	⩾ 25.0
Preobese	25.0 - 29.9
Obese	⩾ 30.0
Obese class I	30.0 - 34.9
Obese class II	35.0 - 39.9
Obese class III	⩾ 40.0

My advice for meaningful weight loss for this patient on ARVs was mainly diet and exercise:
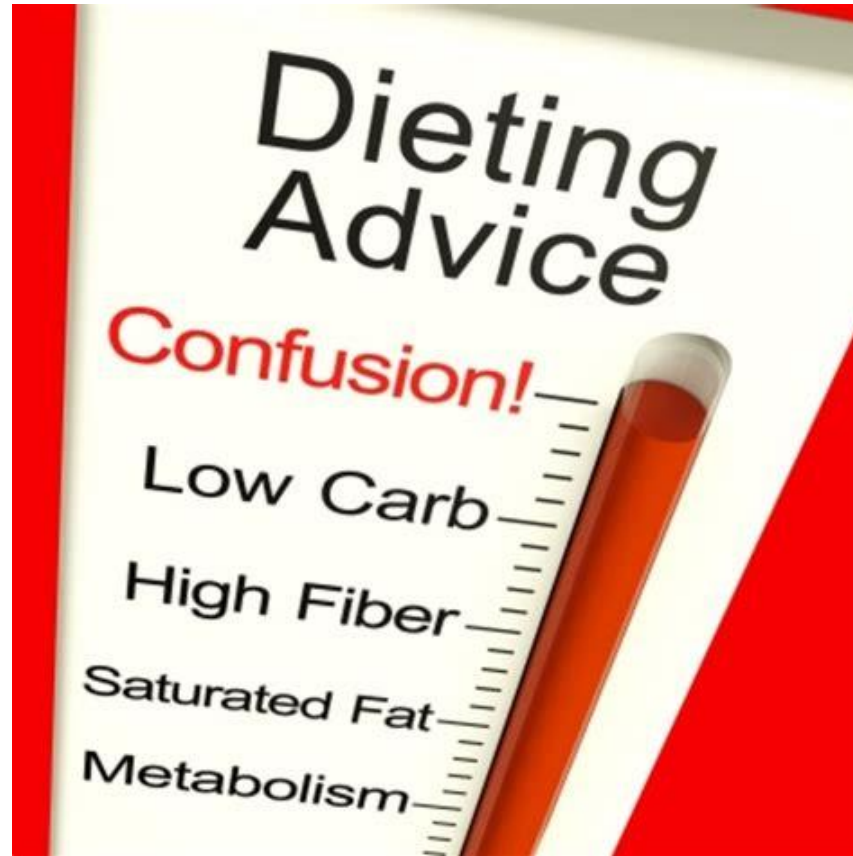
Quick SA numbers update…

- **7.9 million with HIV / 52 million**
- **Over 5 million people on ARVs in SA; 150 000 on second line, about 3000 third line, both 2nd/3rd dropiing**
- **Dramatic reduction in paediatric numbers**
- **Life expectancy up a decade!**

- Uganda/ US/ UK – 'higher life expectancy that matched populations"

1. Expect a normal life expectancy:
May et al. AIDS 2014

- UK CHIC: 21 388 people started ART 2000-2010

If 35 year old man started ART:

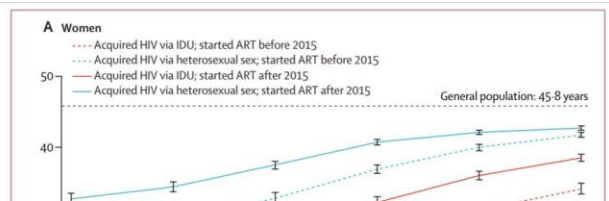|	life expectancy		
CD4	Baseline	1 year ART	5 years ART
<200	71		& VL>50 54
200-349	78	78	
>350	77	81	& VL<50 80
General population	78		

Conclusion: If diagnosed, in care and on effective ART: life expectancy is normal

Great information to give to people newly diagnosed and encourage good adherence

Thanks: Julie Fox, Guys
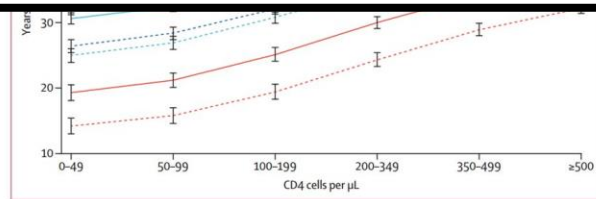
HIV treatment is VERY effective, if given early

A Women
- Acquired HIV via IDU; started ART before 2015
- Acquired HIV via heterosexual sex; started ART before 2015
- Acquired HIV via IDU; started ART after 2015
- Acquired HIV via heterosexual sex; started ART after 2015

General population: 45·8 years

CD4 cells per µL: 0–49, 50–99, 100–199, 200–349, 350–499, ≥500

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 Grabar, Jodie L Guest, Inma Jarrin, Fiona C Lampe, Niels Obel, Juliana M Reyes, Christoph Stephan, Timothy R Sterling, Ramon Teira, Giota Touloumi, Jan-Christian Wasmuth, Ferdinand Wit, Linda Wittkop, Robert Zangerle, Michael J Silverberg, Amy Justice, Jonathan A C Sterne

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

Interpretation For people with HIV on ART and with hi… 2015, life expectancy was only a few years lower than t… started. However, for people with low CD4 counts at the… lower, emphasising the continuing importance of early…

Funding US National Institute on Alcohol Abuse and Al…

(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 l… 40·2 years (39·7–40·6) of life left at age 40 years if they s… started ART after 2015. The corresponding estimates for…

TB...

Incidence dropping
TB <u>prevention very effective</u>

ISOLATED Doctors tell how they rescued TB timebomb

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D., Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

ABSTRACT

Thanks: Braamie Variava

South Africa changing epidemiology
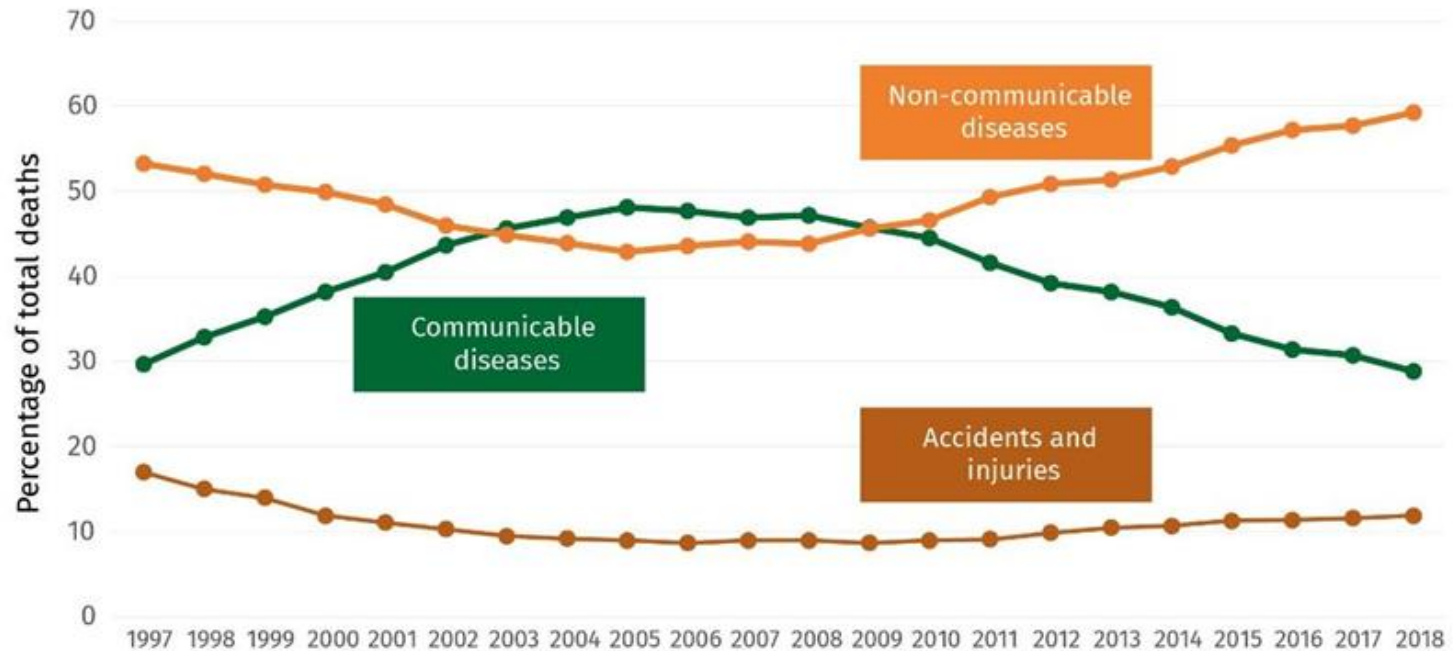
Changing Life-Expectancy

Chronic diseases

Infectious diseases eradicated

IDEAL

1950
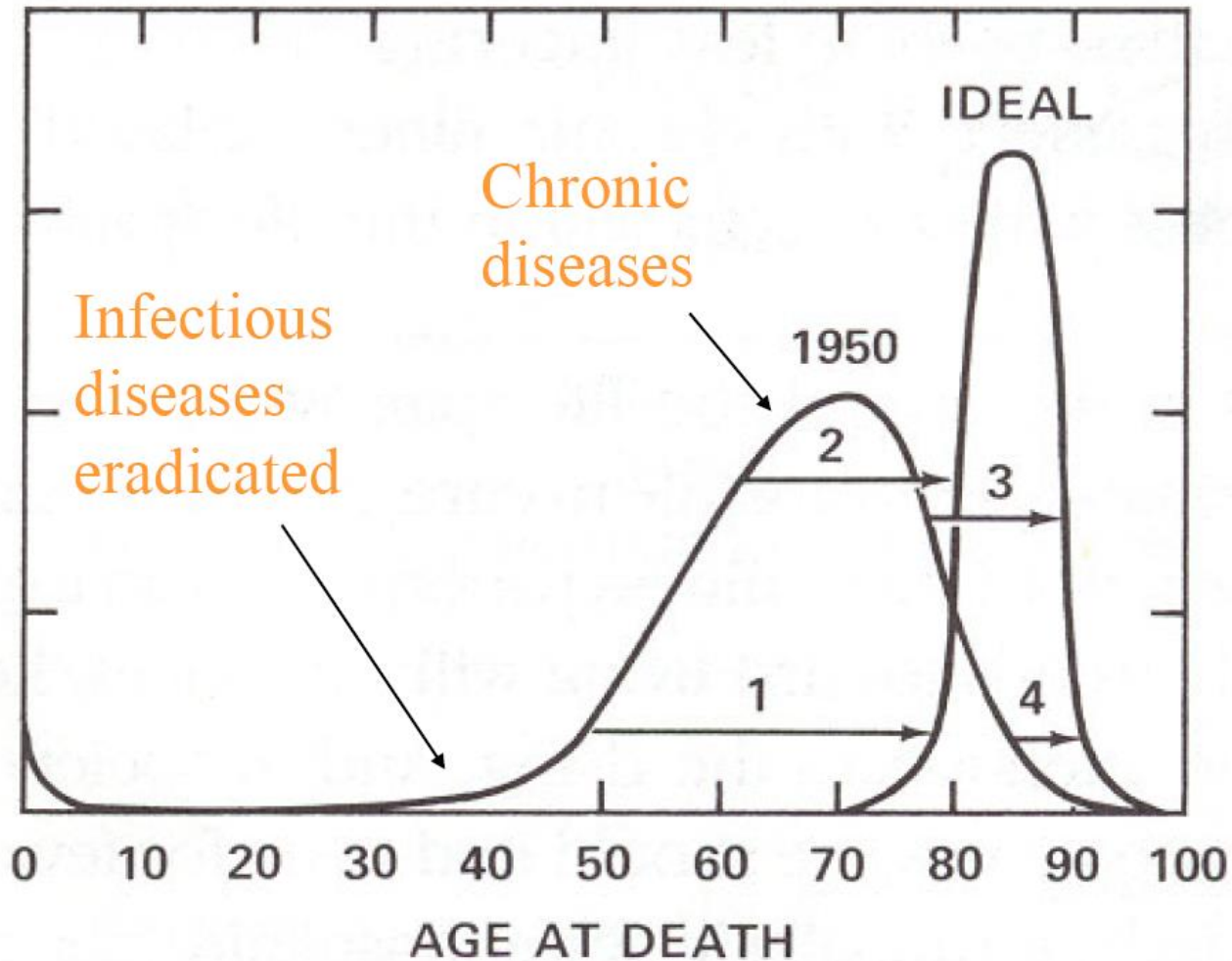
Uganda/ US/ UK – PLWHs higher life expectancy than general populations – people on ART will get older and gain weight and collect diseases

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May et al. AIDS 2014

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If 35 year old man started ART:

CD4	Baseline	1 year ART	5 years ART
		life expectancy	
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Thanks: Julie Fox, Guys

Annals of Internal Medicine | ORIGINAL RESEARCH

Life Expectancy of Persons Receiving Combination Antiretroviral Therapy in Low-Income Countries: A   s From Uganda

Edward J. Mills, PhD, MSc, LLM; Celestin Bakanda, MSc; Josephine Birungi, MBChB; Keith Chan, MSc; Nathan Ford, PhD, MPH; Curtis L. Cooper, MD, MSc; Jean B. Nachega, MD, PhD; Mark Dybul, MD; and Robert S. Hogg, PhD, MA

Annals of Internal Medicine | EDITORIAL

Life Expectancy in Africa: Back to the Future?

From 1950 to 1990, life expectancy in sub-Saharan Af-   uals challenged global trade rules and regulations, ulti-

210 | 16 August 2011 | Annals of Internal Medicine | Volume 155 • Number 4

Pathophysiology

HIV and CVD
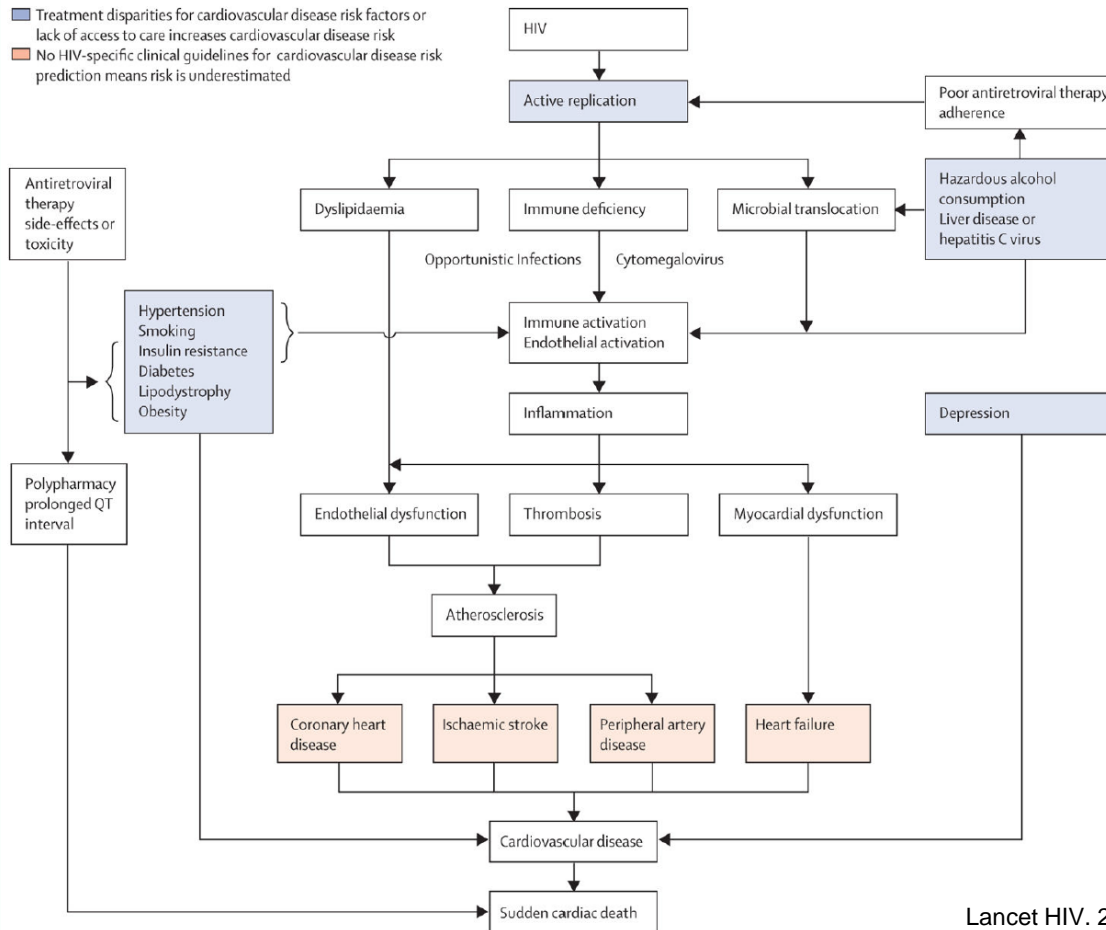
Lancet HIV. 2020. 7(4): e279–e293

Thanks: Joel Dave, UCT

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
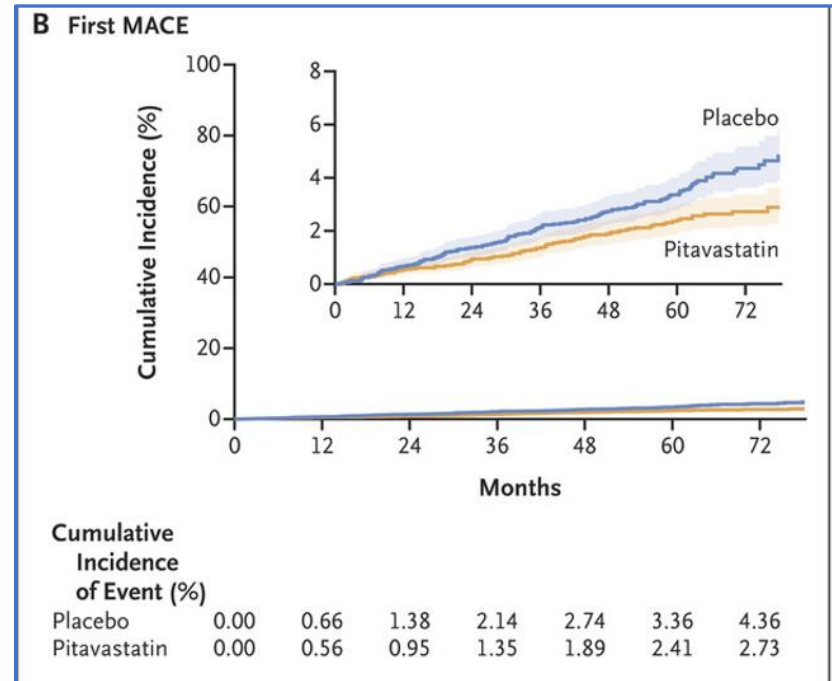
B First MACE

Vision... chronic care

Diagnosis and staging, good primary care that suits patients

Good ARV access, TB prophylaxis

Minimal hospitalization, chronic disease control

CD_4

8 to 10 years

prevention
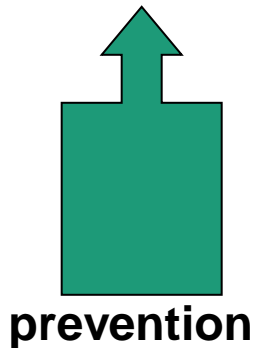
40 years

The importance of location and population

Legend:
- Young women
- Sex work
- People who inject drugs
- Men who have sex with men
- Transgender
- Migrants
- Prisoners
- Displaced
- Pregnant women
- 50+
- Disabled
- African-American women
- Intimate partners

People living with HIV (children and adults) are included as members of all of the featured populations. They are implicitly included in this map as they must have universal access to services.

In Africa, young women and girls are disproportionately affected by HIV

AT A GLANCE

In sub-Saharan Africa, three in four new HIV infections among 15–19-year-olds are among girls.

Source: UNAIDS 2017 estimates.

AIDS-related illnesses are the leading cause of death among 15–49-year-old females globally (hundred thousands)

- HIV — 241.9
- Ischaemic heart disease — 150.5
- Maternal conditions — 148.4
- Stroke — 139.5
- Breast cancer — 130.9
- Tuberculosis — 96.4

Source: Global health estimates 2015: deaths by cause, age, sex, by country and by region, 2000–2015. Geneva, World Health Organization; 2016.

10X
HIV INCIDENCE IS 10 TIMES HIGHER AMONG FEMALE SEX WORKERS THAN AMONG THE GENERAL POPULATION

Source: UNAIDS. Prevention gap report. Geneva: UNAIDS, 2016.

52%
of adolescent girls and young women in rural areas are unable to make decisions about their own health, compared with

47%
in urban areas.

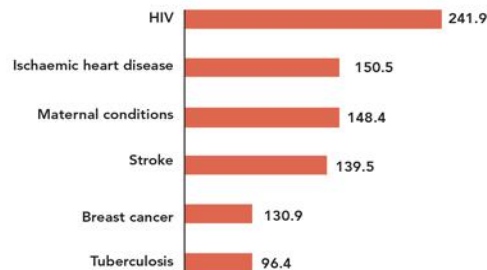Source: Population-based surveys, 2011–2016. The statistics are based on available data from 28 countries in which 83% of all women aged 15–24 in sub-Saharan Africa live.

IN SUB-SAHARAN AFRICA, **42%** OF WOMEN LIVING IN **URBAN** AREAS AGED 15–24 HAD A PREGNANCY BEFORE THE AGE OF 18. IN **RURAL** AREAS, MORE THAN **50%** OF WOMEN AGED 15–24 HAD A PREGNANCY BEFORE THE AGE OF 18.

Source: Population-based surveys, 2011–2016. The statistics are based on available data from 27 countries in which 80% of all women aged 15–24 in sub-Saharan Africa live.

42% of **urban** young women aged 15–24 who live in sub-Saharan Africa who have had sex and have had an HIV test.

30% of **rural** young women aged 15–24 who live in sub-Saharan Africa who have had sex and have had an HIV test.

Source: Population-based surveys, 2011–2016. The statistics are based on available data from 28 countries in which 83% of all women aged 15–24 in sub-Saharan Africa live.

16% of **rural** currently married adolescent girls and young women who live in sub-Saharan Africa report using a modern contraceptive.

23% of **urban** currently married adolescent girls and young women who live in sub-Saharan Africa report using a modern contraceptive.

Source: Population-based surveys, 2011–2016. The statistics are based on available data from 28 countries in which 83% of all women aged 15–24 in sub-Saharan Africa live.

Globally, young women are twice as likely to acquire HIV as their male counterparts.

Source: UNAIDS 2017 estimates.

Each year, 12 million girls are married before the age of 18—married too soon, endangering their personal development and well-being.
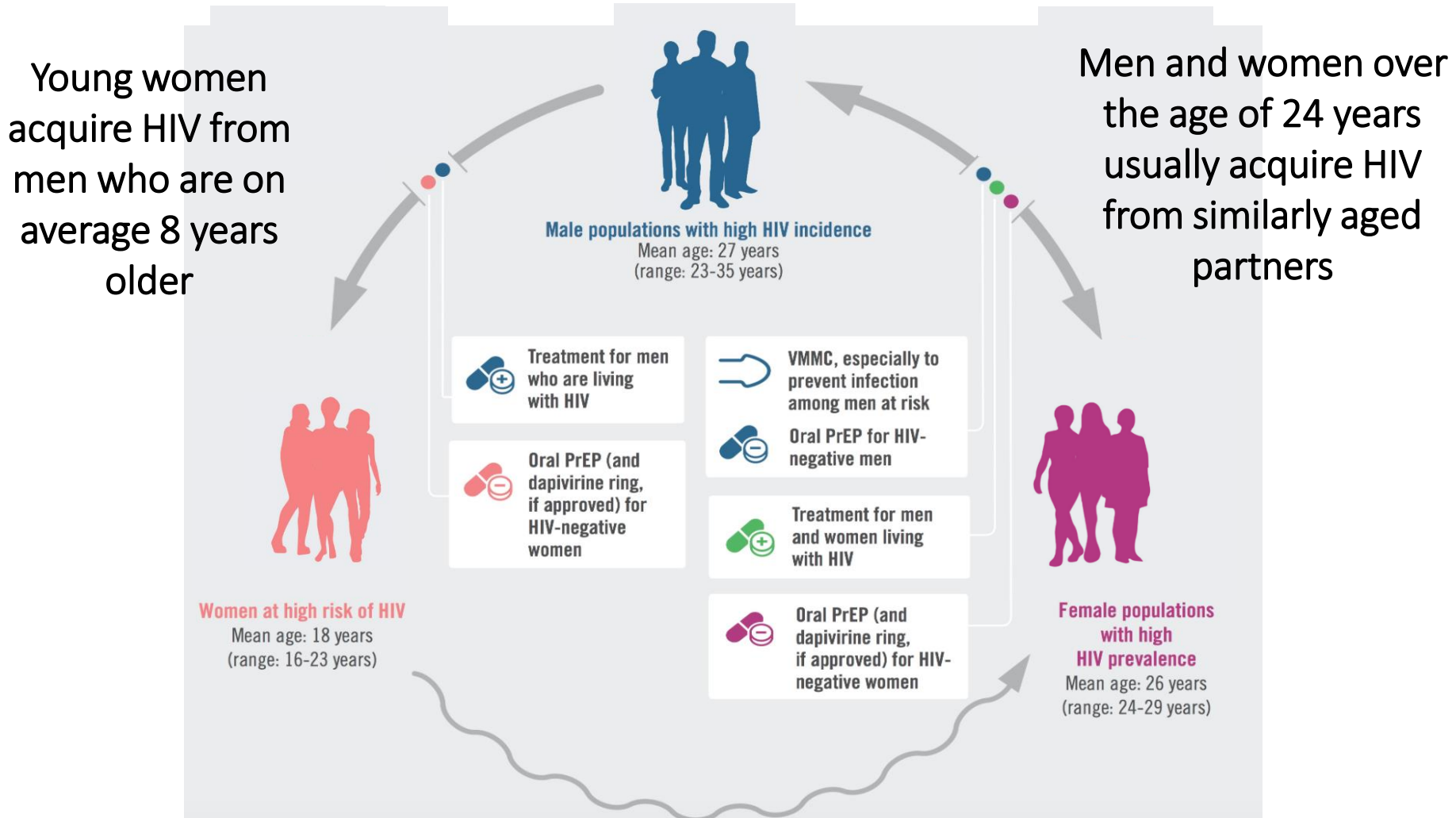
Source: UNICEF 2018 estimates.

AROUND 150
adolescents (10–19 years) died of AIDS-related illnesses every day in 2016.

Source: UNAIDS 2017 estimates.

Breaking the Cycle of Heterosexual Transmission

Young women acquire HIV from men who are on average 8 years older

Men and women over the age of 24 years usually acquire HIV from similarly aged partners

Male populations with high HIV incidence
Mean age: 27 years
(range: 23-35 years)

Treatment for men who are living with HIV

VMMC, especially to prevent infection among men at risk

Oral PrEP for HIV-negative men

Oral PrEP (and dapivirine ring, if approved) for HIV-negative women

Treatment for men and women living with HIV

Women at high risk of HIV
Mean age: 18 years
(range: 16-23 years)

Oral PrEP (and dapivirine ring, if approved) for HIV-negative women

Female populations with high HIV prevalence
Mean age: 26 years
(range: 24-29 years)

When teen women with HIV reach their mid-20s, if they aren't on effective ART, then they may transmit to partners of the same age—and vice versa

Sex is now safe

- PrEP/PEP: almost total protection
- As treatment: undetectable=untransmissable
- Partners study Sub-study of men-(Lancet Aug 2018)
  - who-have-sex-with-men (MSM)
  - Almost 77 000 unprotected anal sex acts – no transmission
  - WHO statement Aug 2023: 'No transmission"
- Intermittent PrEP for gay men
  - ''on-demand'' – 2 tabs 2-24 hours before sex, 1 tab at 24, then 48 hours
  - 1500 (mainly MSM) – no transmissions
- SA sex worker operational PrEP programme – no transmissions on PrEP
- Injectable PrEP– better than oral PrEP
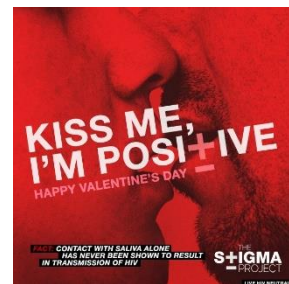
Reproduction is safe

- Near 0% transmission to sex partner or foetus

- NB. The 2012 results were re-calculated using the 2017 test parameters

- The overall HIV incidence has significantly dropped by 44%.

- The largest decline (56%) in incidence was among females.

- Among males the incidence declined by 18%
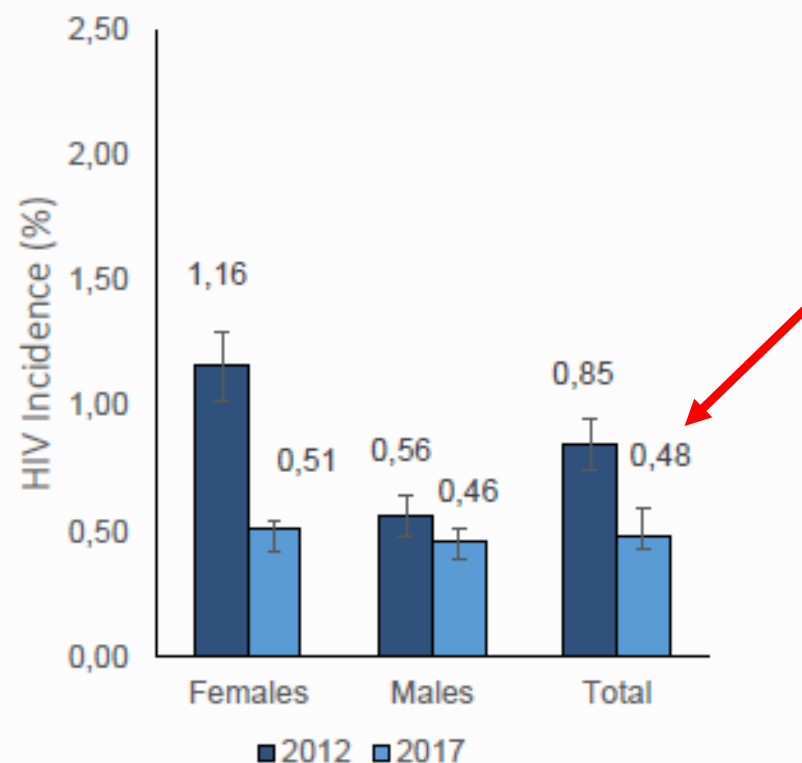
Prevention bearing fruit

- SA: 44% reduction– in only 5 years (2012-2017)!
- Similar in Swaziland
- Botswana – 30% (finally!)
- Melbourne, San Francisco also >50% drops
- US states with the highest PrEP use had greatest declines

Before and after initiation of ARV therapy!

Before and after initiation of ARV therapy!

Thapelo
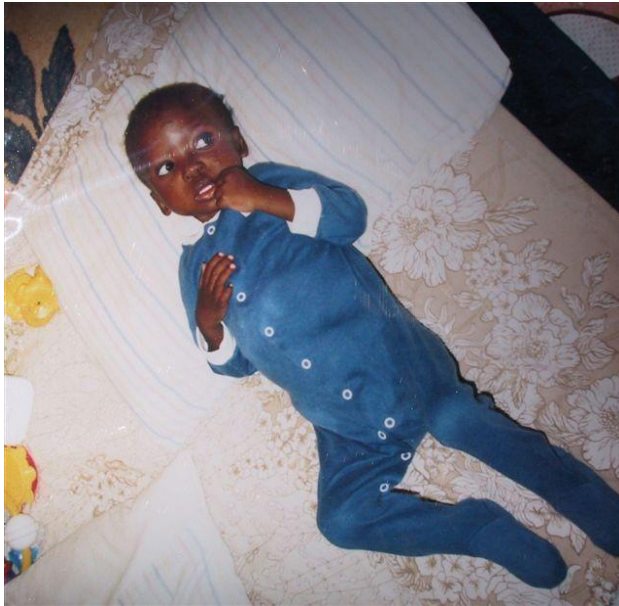
CD4: "When to start debate…"

- Occupied entire field for 20 years
- CD4 risk – terrible things below 350, especially 100; but lots above 350 cells/ul – worse if poor!
- Balance drug toxicity/cost vs risk of disease
- Drugs so safe, start immediately

"Treat All": From Policy to Action - What will it take?

Thursday, 9 June, 13.00 – 14.30
Conference Room 11, United Nations

WHO: 2019 recommendations first-line ART regimens - <u>DOLUTEGRAVIR</u>

POLICY BRIEF

UPDATED RECOMMENDATIONS ON FIRST-LINE AND SECOND-LINE ANTIRETROVIRAL REGIMENS AND POST-EXPOSURE PROPHYLAXIS AND RECOMMENDATIONS ON EARLY INFANT DIAGNOSIS OF HIV

JULY 2018

HIV TREATMENT — INTERIM GUIDANCE

World Health Organization

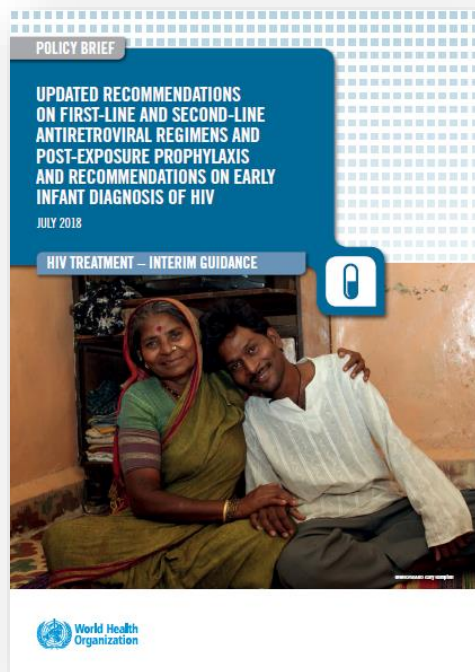**BOX 1. RECOMMENDATIONS: FIRST-LINE ARV DRUG REGIMENS**

1. A DTG based regimen may be recommended as a preferred first-line regimen for people living with HIV initiating ART *(conditional recommendation)*

   – Adults and adolescents *(moderate-certainty evidence)*

   – Women and adolescent girls of childbearing potential[a] *(very-low-certainty evidence)*

   – Infants and children with approved DTG dosing[b] *(low-certainty evidence)*

Old ART

| Tenofovir | ➕ | XTC | ➕ | Efavirenz |

Failure

| AZT | ➕ | 3TC | ➕ | Protease/r |
| (zidovudine) | | | | (LPV or ATV) |

Failure

XTC, other nukes

| Darunavir | Dolutegravir | Etravirine |

New ART

Tenofovir ➕ **3TC** ➕ **Dolutegravir**

Fa... ✖

AZT ➕ 3TC ➕ Protease/r
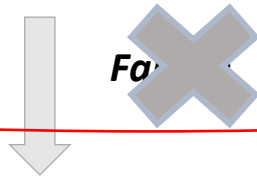
- **Incredibly well tolerated**
- **Almost no resistance**
- **Safe in pregnancy**
- **HOTP: UCT – may be OK in TB**

Darunavir   Dolutegravir

ONE **TABLET** TO RULE THEM ALL
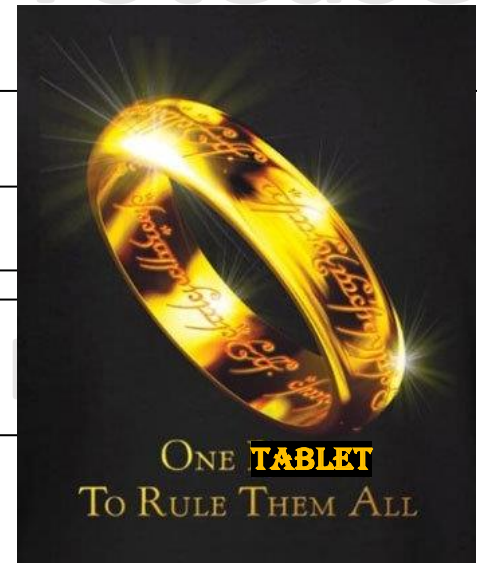
The Evolving HIV Treatment Paradigm

?????

- 3TC=lamivudine; ZDV=zidovudine

Long Acting Injectable?

Single-Tablet Regimens

The Integrase Era

Triple-Drug Therapy

AZT/3TC

AZT monotherapy
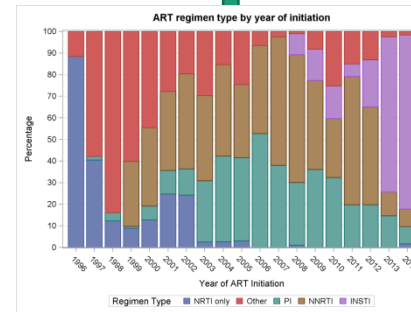
HIV-1 discovered

1983

1987

1995

1996

2006

2012–2013

2020

2023

CLINICAL UPDATE

Cutting the cost of South African antiretroviral therapy using newer, safer drugs

W D F Venter,[1] FCP (SA), MMed; B Kaiser,[2] MPH, PharmD, BCPS; Y Pillay,[3] PhD; F Conradie,[4] MB BCh; G B Gomez,[5] PhD; P Clayden;[6]
M Matsolo;[7] C Amole,[8] BA; L Rutter,[7] BA; F Abdullah,[9] M
M Barnhart,[12] MD, MPH; A Pillay,[13] PhD; A Pozniak,[14] M
M Moorhouse,[1] MB BCh; M Chersich,[1] MB BCh, PhD; C

[1] Wits Reproductive Health and HIV Institute, University of t
[2] Formerly UNITAID, Geneva, Switzerland
[3] HIV/AIDS, TB and Maternal, Child and Women's Health i
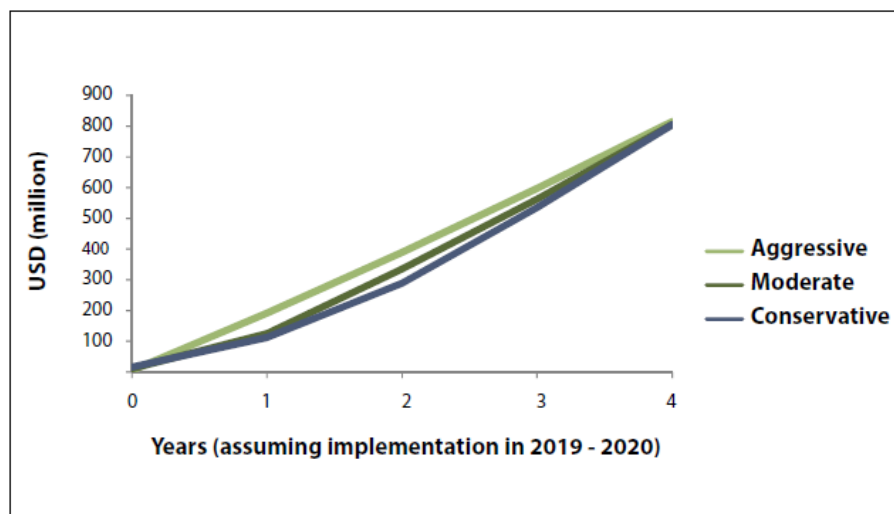
Fig. 2. Estimated crude savings on antiretroviral drugs (assuming implementation of new regimen in 2019 - 2020). Cumulative savings compared with status quo (conservative = 300 000 annually, transition from old regimen to new over 3 years; moderate = new regimen, 400 000 annually, transition over 2 years; aggressive = new regimen, 500 000 annually, transition over 1 year).

Most boring study ever: ADVANCE – results April 2019

- **Three different WHO regimens - EFV vs DTG, TAF vs TDF**
- **Cost and toxicity differences**

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

	TAF/FTC+DTG N=351	Zambia and Botswana: increasingly looked at for 1st line
1053 Participants	**TDF/FTC+DTG** N=351	South Africa: Everyone on this in public and 50% private 2023
	TDF/FTC/EFV N=351	South Africa: Everyone on this in public and private 2019
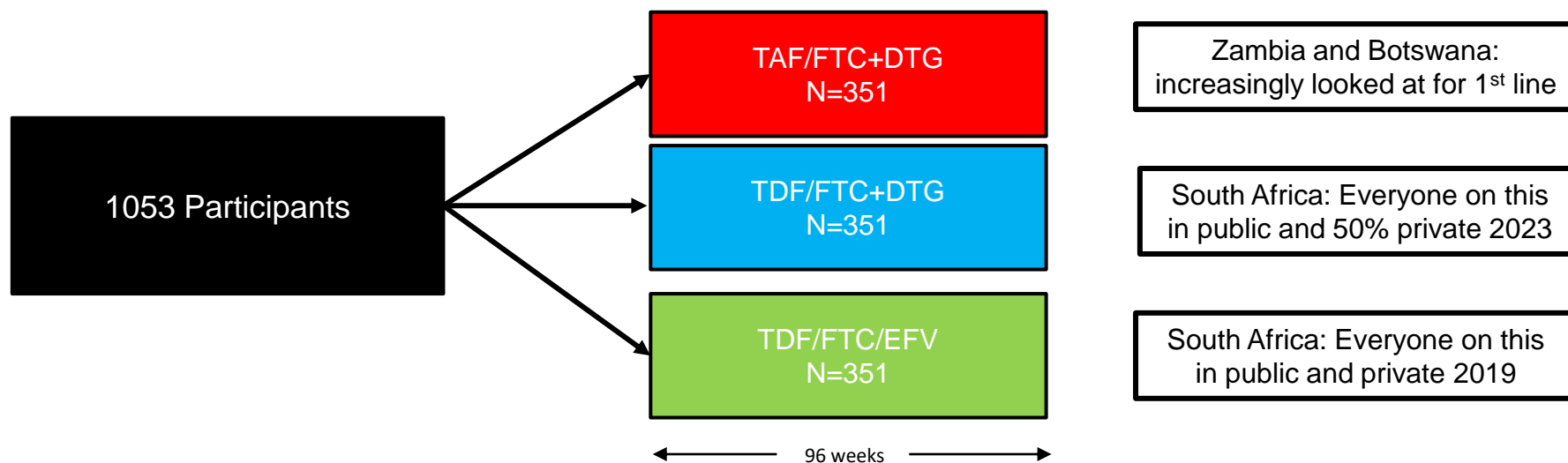
96 weeks

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

Are new antiretroviral treatments increasing the risks of clinical obesity?

Andrew Hill[1]*, Laura Waters[2] and Anton Pozniak[3]

[1] Department of Translational Medicine, University of Liverpool, UK
[2] Central and North West London NHS Trust, Mortimer Market Centre, London, UK
[3] Chelsea and Westminster Hospital, London, UK; London School of Hygiene and Tropical Medicine, UK

Table 1. Effects of raltegravir, dolutegravir and bictegravir on body weight in randomised trials

Study [ref]	Design	Results
Raltegravir		
NEAT 001 [12] (naïve, n=126)	DRV/r+RAL DRV/r + TDF/FTC	DEXA sub-study: trunk fat 7.3% higher DRV/r/RAL *vs* TDF/FTC/RAL at week 96 (P=0.021)
ACTG 5260s [10,11] (naïve, n=126)	TDF/FTC/RAL TDF/FTC/DRV/r TDF/FTC/ATV/r	Higher risk of severe weight gain for RAL vs ATV/r
Dolutegravir		
NEAT 022 [13] (switch, n=415)	NRTIs + DTG NRTIs + PI/r	+1 kg increase in body weight to week 48 (P=0.002)
SPRING-1 [13] (naïve, n=204)	TDF/FTC/EFV TDF/FTC/DTG	Increases in body weight higher in DTG arms
Gilead 1490 [15] (naïve, n=645)	TAF/FTC/DTG TAF/FTC/BIC	+3.9 kg increase in body weight to week 96 +3.5 kg increase in body weight to week 96
MONODO [9] (naïve, n=8)	DTG monotherapy	+4.1 kg increase in body weight to week 24

ATV/r; atazanavir/ritonavir; BIC: bictegravir; DRV/r: darunavir/ritonavir; DTG: dolutegravir; FTC: emtricitabine; NRTI: nucleoside reverse transcriptase inhibitors; PI/r: ritonavir-boosted protease inhibitor; RAL: raltegravir; TAF: tenofovir AF; TDF: tenofovir DF.

Change in body weight after switch from TDF to TAF – German cohort study
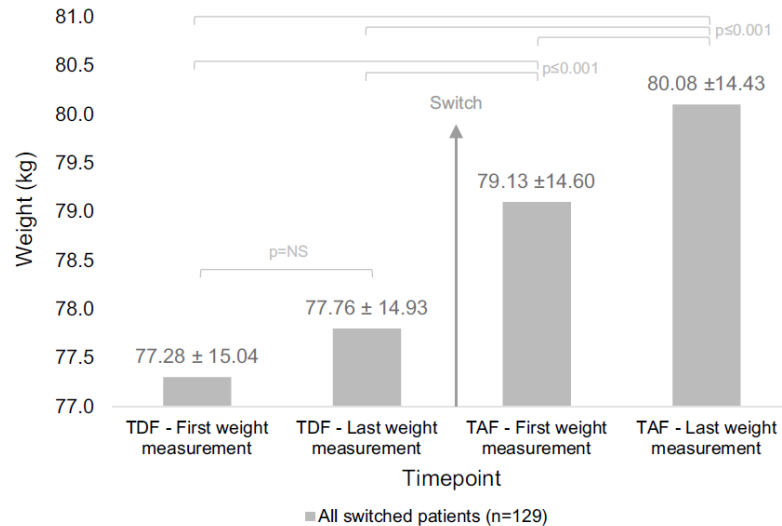
Only switch patients are shown, "TDF (TAF)—first/last weight measurement" denotes the first/last weight measured on TDF (TAF) treatment; results shown for weight in kg; *NS* not statistically significant

Gomez et al. Weight Gain switching TDF to TAF. Infection 2018

Then came the integrase inhibitors….
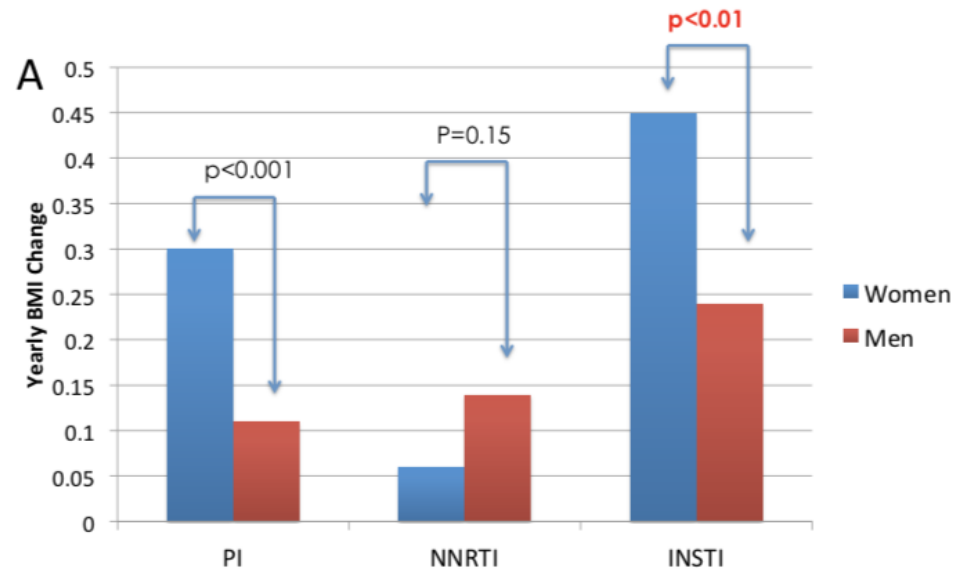
- **Rapidly became standard of care <u>globally</u>**
- **2 years later (2019), at CROI – <u>weight</u> raised in themed discussion**
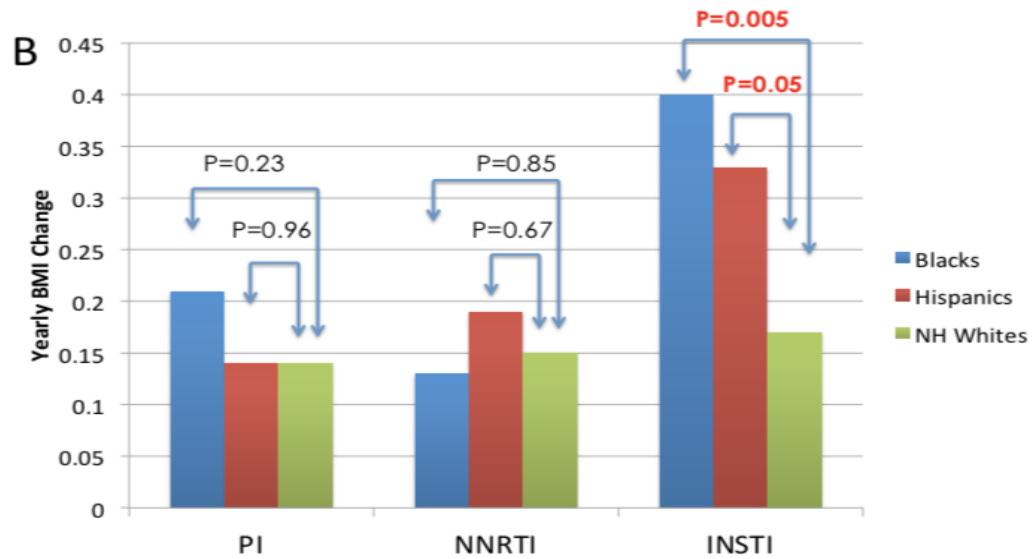
Weight gain themed discussion : CROI 2019 http://www.croiwebcasts.org/s/2019croi/TD-08

Weight gain on classes – women gain 2x more than men (US cohort study)

Weight gain on INSTI – black people gain 2x more than whites (US cohort study)

IDSA — Infectious Diseases Society of America

hivma — hiv medicine association

OXFORD

Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials

Paul E. Sax,[1] Kristine M. Erlandson,[2] Jordan E. Lake,[3] Grace A. McComsey,[4] Chloe Orkin,[5] Stefan Esser,[6] Todd T. Brown,[7] Jürgen K. Rockstroh,[8] Xuelian Wei,[9] Christoph C. Carter,[9] Lijie Zhong,[9] Diana M. Brainard,[9] Kathleen Melbourne,[9] Moupali Das,[9] Hans-Jürgen Stellbrink,[10] Frank A. Post,[11]

Table 5. Risk factors for significant (≥10%) weight gain in individuals initiating ART.

Variable	OR	95% CI	p value
CD4 (<200 vs. ≥200/µL)	4.36	3.6, 5.27	<0.001
HIV RNA (>100k vs. ≤100k c/mL)	1.98	1.65, 2.37	<0.001
BMI (normal vs. overweight)	1.54	1.27, 1.87	<0.001
BMI (normal vs. obese)	1.66	1.29, 2.15	<0.001
Sex (female vs. male)	1.54	1.21, 1.96	<0.001
Race (black vs. non-black)	1.32	1.1, 1.59	0.003
Third agent (BIC/DTG vs. EFV)	1.82	1.24, 2.66	0.002
Third agent (EVG/c vs. EFV)	1.36	1.04, 1.78	0.026
Third agent (RPV vs. EFV)	1.51	1.03, 2.2	0.035
Third agent (ATV/r vs. EFV)	0.92	0.59, 1.45	0.73
NRTI (TAF vs. AZT)	1.75	1.04, 2.95	0.034
NRTI (TDF vs. AZT)	1.19	0.76, 1.87	0.44
NRTI (ABC vs. AZT)	0.93	0.47, 1.8	0.82
NRTI (TAF vs. ABC)	1.9	1.25, 2.88	0.003
NRTI (TDF vs. ABC)	1.29	0.79, 2.11	0.31
NRTI (TAF vs. TDF)	1.47	1.14, 1.9	0.003

Sax, CID, 2019
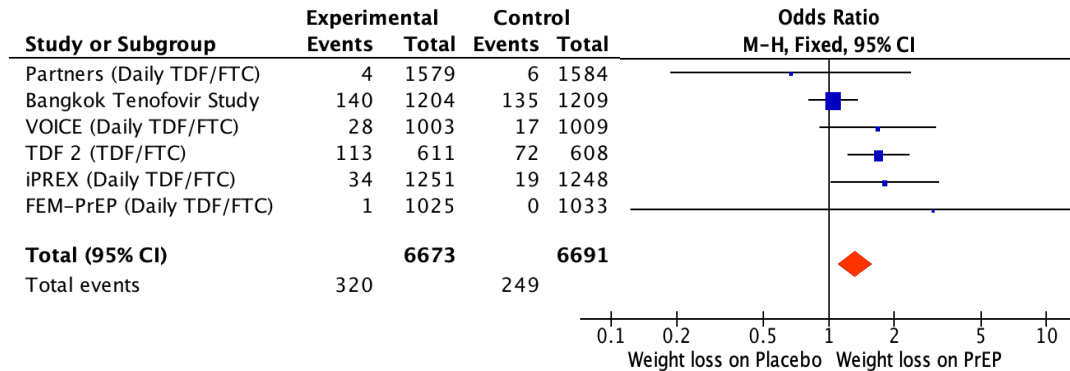
IDSA | hivma | OXFORD

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Table 5. Risk factors for significant (≥10%) weight gain in individuals initiating ART.

Variable	OR	95% CI	p value
CD4 (<200 vs. ≥200/µL)	4.36	3.6, 5.27	<0.001
HIV RNA (>100k vs. ≤100k c/mL)	1.98	1.65, 2.37	<0.001
BMI (normal vs. overweight	1.54	1.27, 1.87	<0.001
BMI (normal vs. obese)	1.66	1.29, 2.15	<0.001
Sex (female vs. male)	1.54	1.21, 1.96	<0.001
Race (black vs. non-black)	1.32	1.1, 1.59	0.003
Third agent (BIC/DTG vs. EFV)	1.82	1.24, 2.66	0.002
Third agent (EVG/c vs. EFV)	1.36	1.04, 1.78	0.026
Third agent (RPV vs. EFV)	1.51	1.03, 2.2	0.035
Third agent (ATV/r vs. EFV)	0.92	0.59, 1.45	0.73
NRTI (TAF vs. AZT)	1.75	1.04, 2.95	0.034
NRTI (TDF vs. AZT)	1.19	0.76, 1.87	0.44
NRTI (ABC vs. AZT)	0.93	0.47, 1.8	0.82
NRTI (TAF vs. ABC)	1.9	1.25, 2.88	0.003
NRTI (TDF vs. ABC)	1.29	0.79, 2.11	0.31
NRTI (TAF vs. TDF)	1.47	1.14, 1.9	0.003

Sax, CID, 2019

TDF as PrEP: weight loss >5%

	Experimental		Control		Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**M–H, Fixed, 95% CI**
Partners (Daily TDF/FTC)	4	1579	6	1584	
Bangkok Tenofovir Study	140	1204	135	1209	
VOICE (Daily TDF/FTC)	28	1003	17	1009	
TDF 2 (TDF/FTC)	113	611	72	608	
iPREX (Daily TDF/FTC)	34	1251	19	1248	
FEM–PrEP (Daily TDF/FTC)	1	1025	0	1033	
Total (95% CI)		**6673**		**6691**	
Total events	320		249		

0.1   0.2   0.5   1   2   5   10

Weight loss on Placebo   Weight loss on PrEP
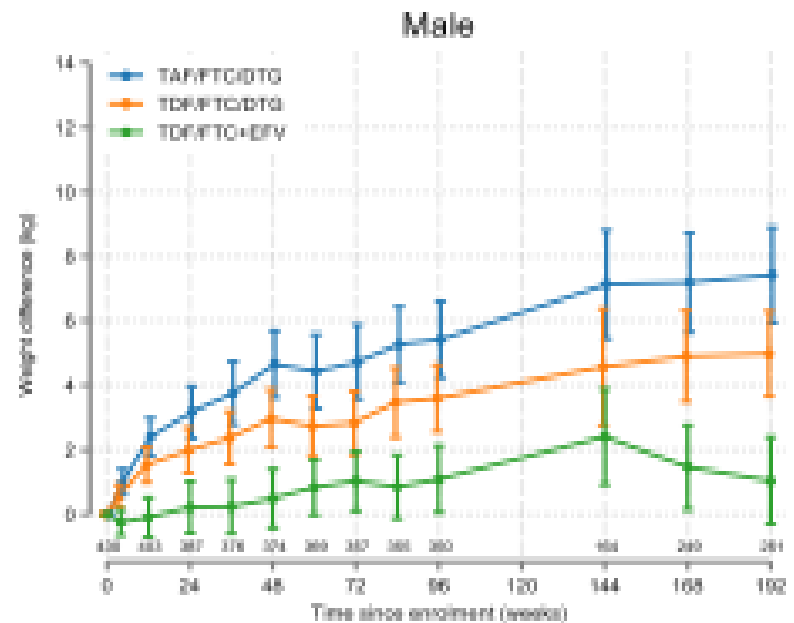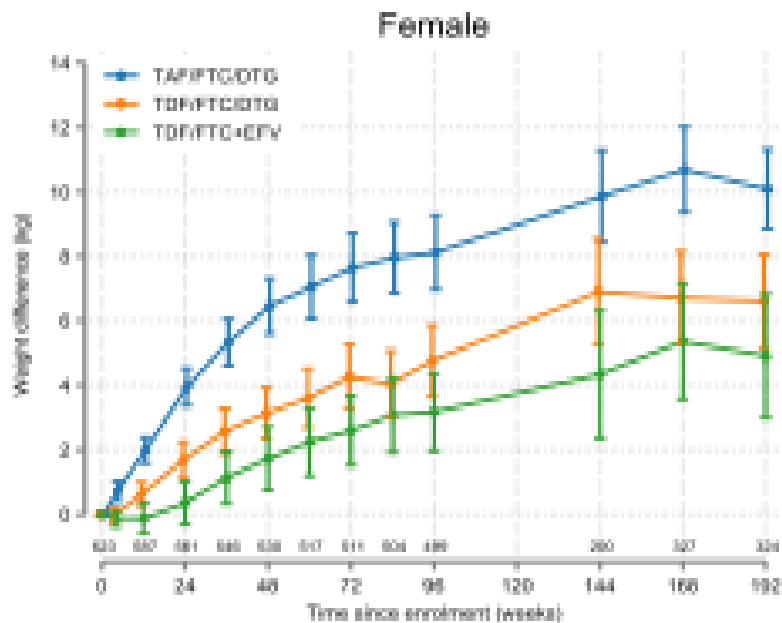
Odds Ratio = 1.32 (1.11 to 1.58)

P = 0.002

And PIs and EFV associated with weight loss

- **Immediate reaction: DTG, TAF caused weight gain**

ADVANCE: Weight change from baseline over time
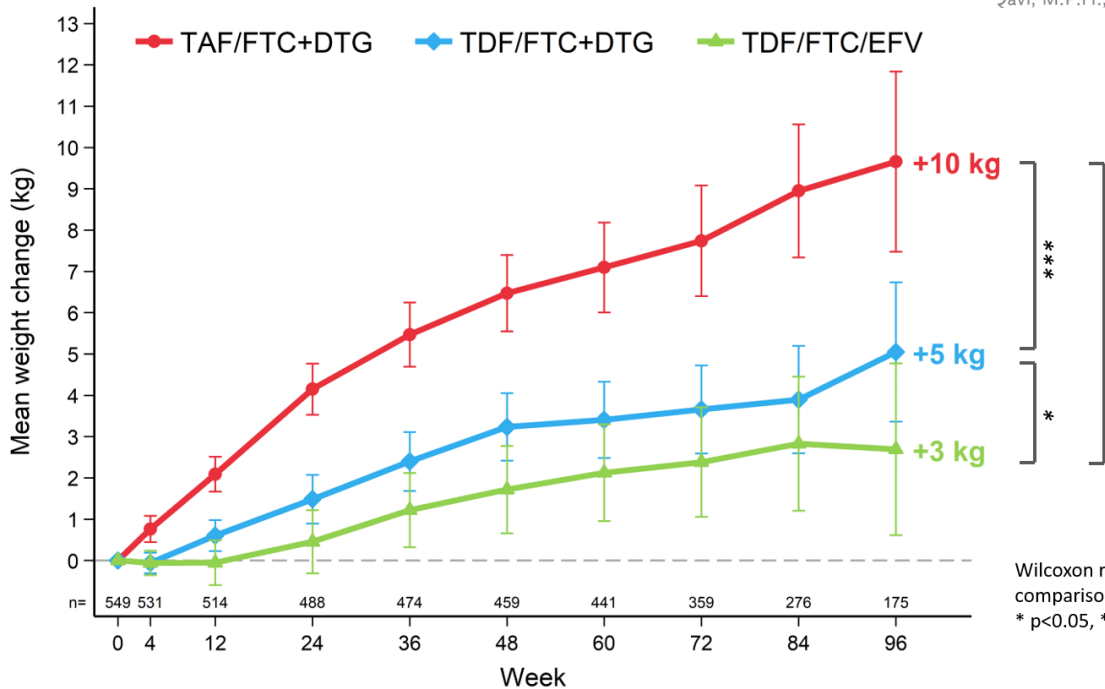
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV

Willem D.F. Venter, F.C.P. (SA), Ph.D.,
Michelle Moorhouse, M.B., B.Ch., D.A. (SA),
Simiso Sokhela, M.B., Ch.B., Dip. HIV Man. (SA),
Lee Fairlie, M.B., Ch.B., M.Med., Nkuli Mashabane, M.B.L., B.Pharm.,
Masebole Masenya, M.B., Ch.B., Celicia Serenata, M.B.A.,
Davi, M.P.H.,

Ezintsha
INVESTIGATE INNOVATE ADVANCE

Mean weight change (kg)

- TAF/FTC+DTG
- TDF/FTC+DTG
- TDF/FTC/EFV

+10 kg ***
+5 kg ***
+3 kg *

| n= | 549 | 531 | 514 | 488 | 474 | 459 | 441 | 359 | 276 | 175 |

Week: 0 4 12 24 36 48 60 72 84 96

Wilcoxon rank-sum comparison at Week 96:
* p<0.05, ** p<0.01, *** p<0.001

Full set of disclosures at nejm.org

But…

- **Little change in glucose, lipids, blood pressure after 192 weeks (and now after 6 years) – except for EFV**
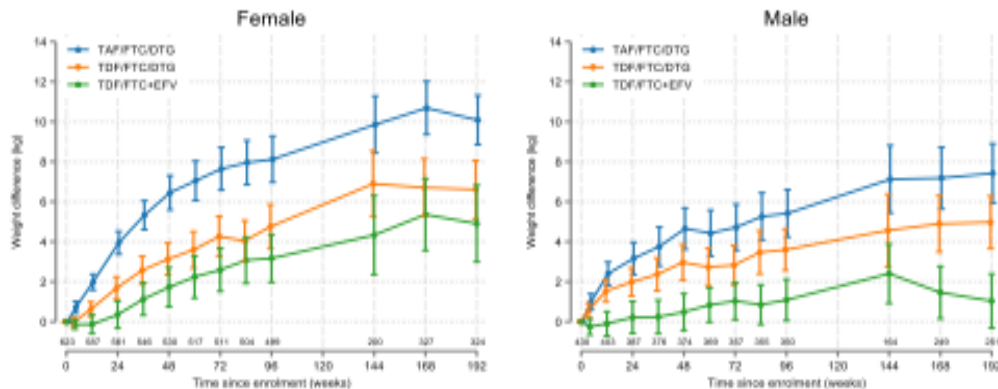
CYP2B6 Genotype and Weight Gain Differences Between Dolutegravir and Efavirenz

Rulan Griesel, Gary Maartens, Simiso Sokhela, Godspower Akpomiemie, Francois Venter, Michelle Moorhouse, Phumla Sinxadi

Slow metabolisers of EFV LOST all the weight – medium/fast metabolisers of EFV = DTG for weight gain!!

CID, 2020

ADVANCE: Weight change from baseline over time

But why did you not notice?

Phase 3 trials of new antiretrovirals are not representative of the global HIV epidemic

Toby Pepperrell[1], Andrew Hill[2]*, Michelle Moorhouse[3], Polly Clayden[4], Kaitlyn McCann[5], Simiso Sokhela[3], Celicia Serenata[6], Willem Daniel Francois Venter[3]

[1] Faculty of Medicine, Imperial College London, UK
[2] Department of Translational Medicine, Liverpool University, Pharmacology, Liverpool, UK

- **Most registration studies done in white males for almost all newer antiretrovirals**
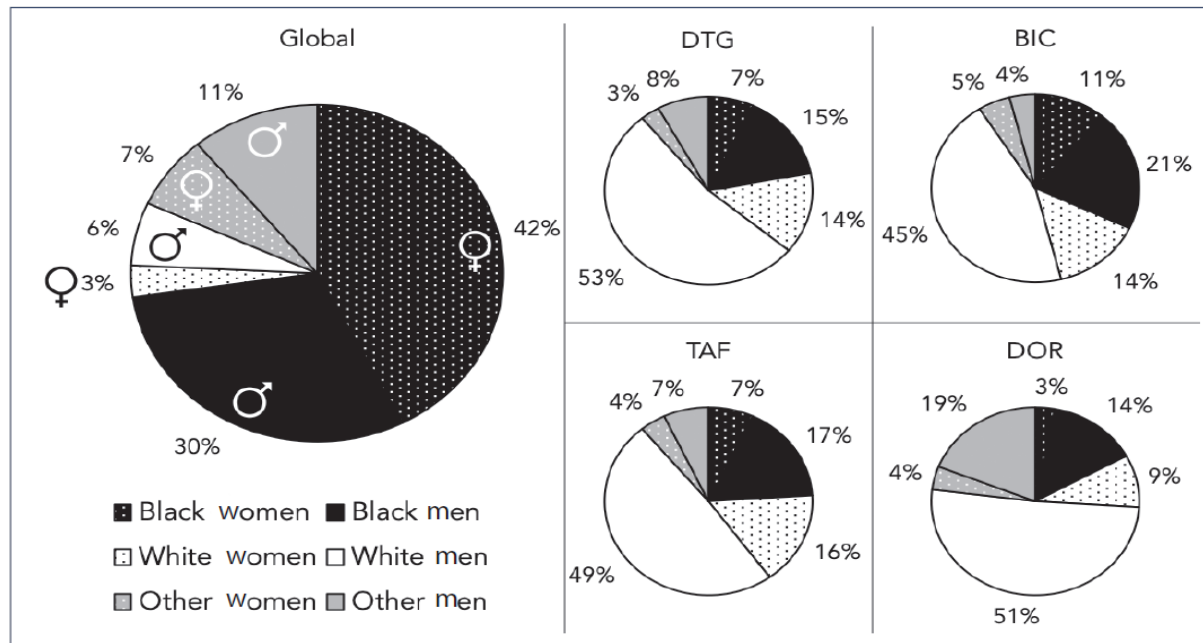
Figure 1. Estimated global demographics of PLWH vs RCT demographics. Percentages may be rounded up to make 100. Data are given as percentage. BIC: bictegravir; DOR: doravirine; DTG: dolutegravir; PLWH: people living with HIV; RCT: randomised controlled trial; TAF: tenofovir alafenamide.
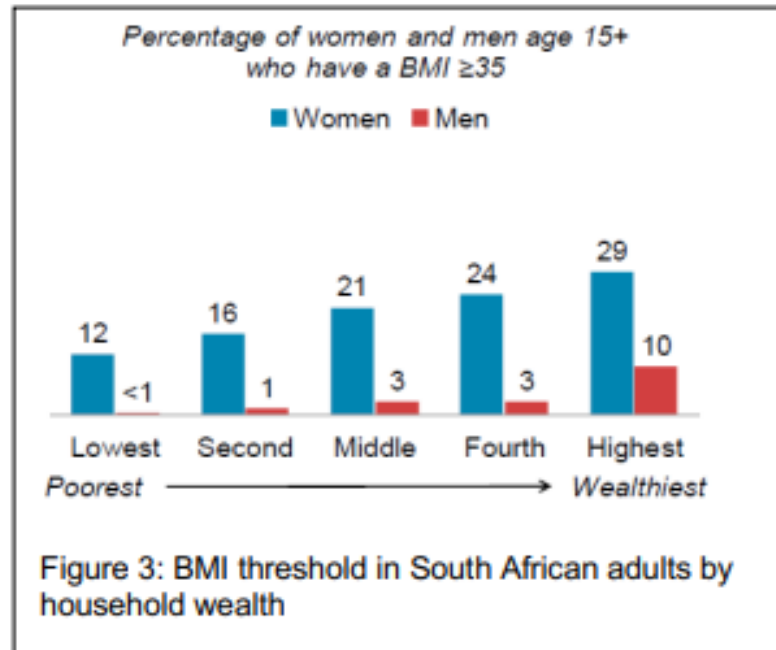
So where have we landed with weight and ARVs?

- **Efavirenz slow-metabolisers are the one's who have less weight gain and associated with side effects** – <u>not</u> a good switch option
- **DTG not driving weight gain**
- **No data to firmly support any switch strategy from INSTI-regimens for weight gain (yet)** – watch islatravir and lenocapavir vs Bictarvy data!
- **?role of TAF in weight gain –** most KOLs think not
- **Clear TDF mitigates weight gain** – but modest
- **Weight gain significant if ART started in:**
  - Advanced disease – low CD4, high VL
  - Black
  - Women
  - **VERY important** – <u>including in switch patients</u> (the majority of the world)
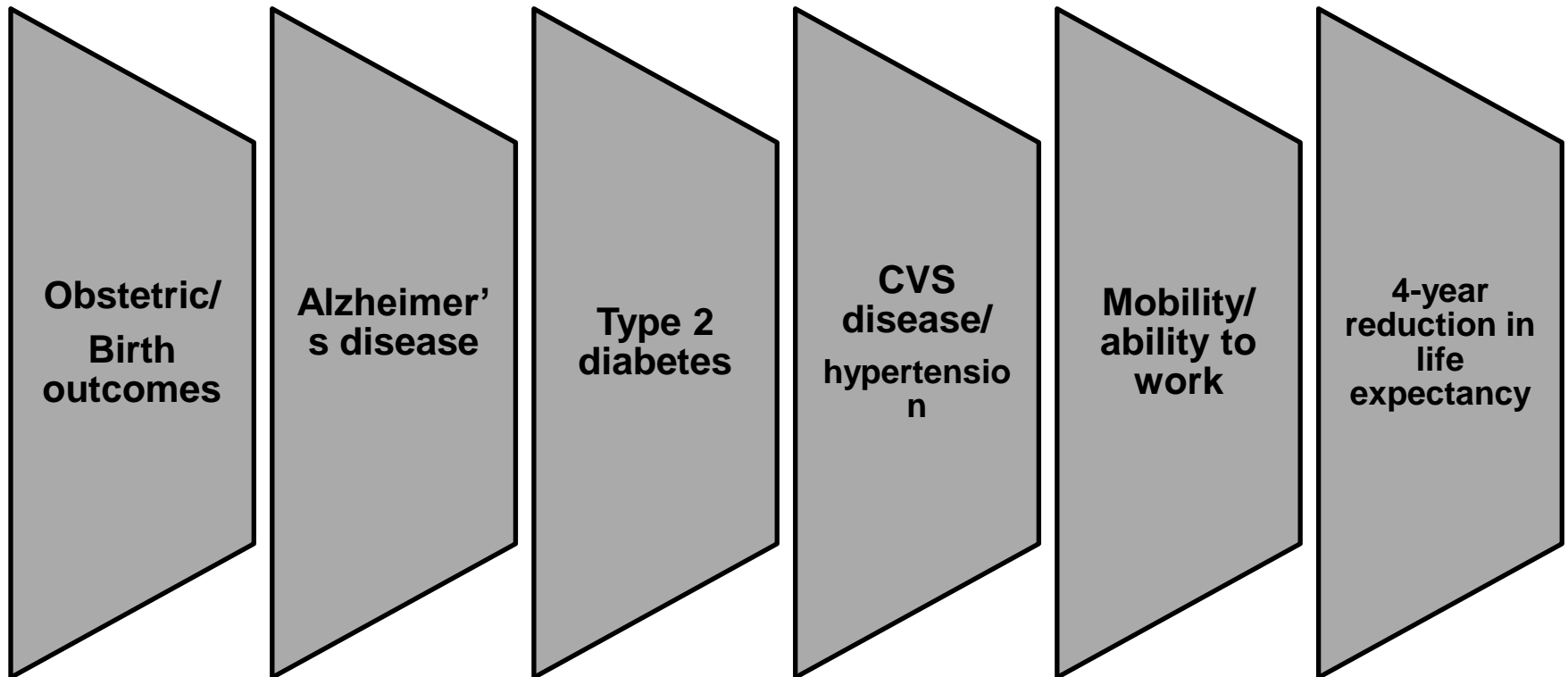
Pretty scary scenario possible…

- **Obesity occurs on <u>ALL modern ART</u> – scary in midst of existing epidemic**
- **Obesity physiologist at CROI 2019: Obesity a predictable response to suppression of inflammation**
- **Did we miss all this with d4T, TDF and EFV?**

Percentage of women and men age 15+
who have a BMI ≥35

■ Women ■ Men

| | 12 | 16 | 21 | 24 | 29 |
| Men | <1 | 1 | 3 | 3 | 10 |

Lowest   Second   Middle   Fourth   Highest
Poorest ──────────────────────────→ Wealthiest

Figure 3: BMI threshold in South African adults by household wealth

Clinical implications of obesity in HIV-negative (BMI ≥ 30kg/m2)

Obstetric/ Birth outcomes

Alzheimer's disease

Type 2 diabetes

CVS disease/ hypertension

Mobility/ ability to work

4-year reduction in life expectancy

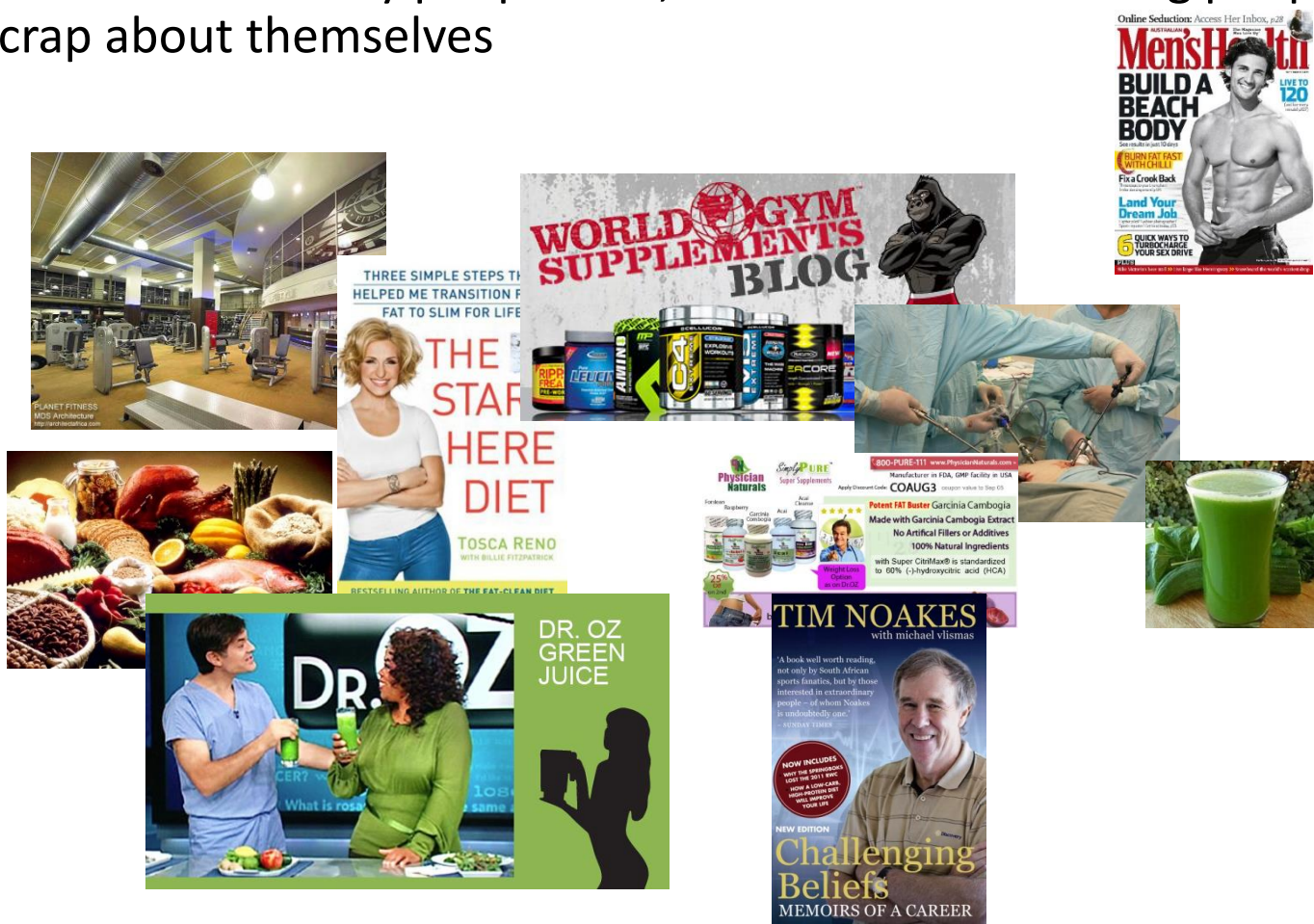M Kivimaki *et al*. Lancet Public Health 2017; K Bhaskaran et al. Lancet Diabetes Endocrinol 2018

People make a LOT of money from making you feel horrible about your body – implicated in everything from depression to anorexia

- And we've made many people rich, and colluded in making people feel crap about themselves

HIV and obesity sound a lot alike…

- **THIS physician has had to re-learn everything he knew**
- **Obesity = HIV in many ways; stigma, drugs, treatment approaches**
- **Obesity=diabetes: progressive, lifelong**
- **Field has changed vastly**
  - World of controversy
  - Pathways, hormones, understandings of mechanisms of weight gain
  - Language – mind your p's and q's
  - And new drugs and hope (and politics!)
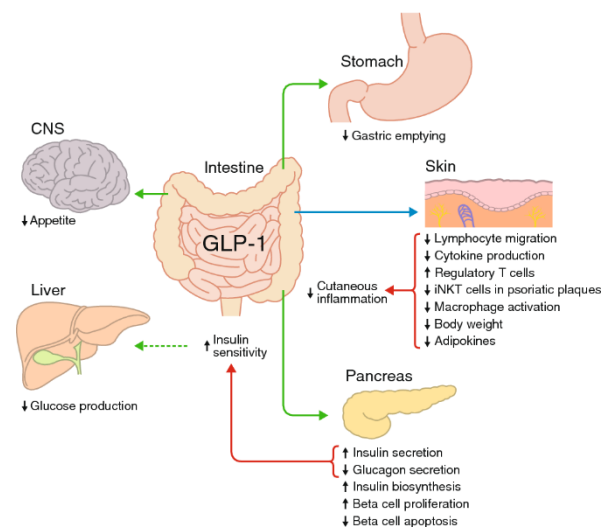
Flegal KM, Kit BK, Orpana H, Graubard BI, Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013 Jan 2;309(1):71-82

Flawed methods and inappropriate conclusions f͟ health policy on overweight and obesity: the Glo͟ BMI Mortality Collaboration meta-analysis

Katherine M Flegal [1], John P A Ioannidis [1][2][3][4], Wolfram Doehner [5][6][7]

NCHS Data Brief ■ No. 82 ■ January 2012

Prevalence of Obesity in the United States, 2009–2010

Cynthia L. Ogden, Ph.D.; Margaret D. Carroll, M.S.P.H.; Brian K. Kit, M.D., M.P.H.; and Katherine M. Flegal, Ph.D.

Reasons for obesity

- **Lay public and most health workers: poor self control, laziness, not enough exercise – <u>its your fault</u>**
- **Obesity experts – social determinants, genes, modern food – <u>it's the environment, stupid</u>**

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Americans Are Heavier Than Ever — But Not for the Reasons You Think

Hint: it's not about willpower, calories, or exercise

Brandy L Schillace 4 days ago · 6 min read ★

Weight gain and obesity

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

OK, that is all bleak, what you got?

Figure 2. Weight Loss at 1 Year with High-Intensity Lifestyle Interventions or Pharmacotherapy Combined with Low-to-Moderate-Intensity Lifestyle Counseling.

OK, that is all bleak, what you got?

Figure 2. Weight Loss at 1 Year with High-Intensity Lifestyle Interventions or Pharmacotherapy Combined with Low-to-Moderate-Intensity Lifestyle Counseling.

Longo, NEJM, 2017

OK, that is all bleak, what you got?

Figure 2. Weight Loss at 1 Year with High-Intensity Lifestyle Interventions or Pharmacotherapy Combined with Low-to-Moderate-Intensity Lifestyle Counseling.

Surgery

Tirzepatide – 20.9% vs placebo 3.1% at 72 weeks

Longo, NEJM, 2017

New agents

- ?how long do we take the drugs?
- Side effects of new agents?
- Will people take injections? Titrations are complex
- Cost $$$$

Table 2 | Weight loss drugs in clinical development

Agent	Company	Development stage	Indication	ClinicalTrials.gov ID/ref.*
GLP1/glucagon dual agonists				
Cotadutide (MEDI0382)	AstraZeneca	Phase II	T2D, NASH	NCT04019561 NCT03235050
BI 456906	Boehringer Ingelheim	Phase II	Obesity, T2D	NCT04153929
Efinopegdutide (^{MED}GLP/GCG)	Hanmi Pharmaceutical	Phase II	NASH	NCT03486392
OXM	Eli Lilly	Phase I	T2D	See Related links
GIP/GLP1 dual agonists				
Tirzepatide	Eli Lilly	Phase III	Obesity, T2D	NCT04657003
GIP/GLP peptide I	Eli Lilly	Phase I	T2D	See Related links
GIP/GLP peptide II	Eli Lilly	Phase I	T2D	See Related links
NN9709	Novo Nordisk	Discontinued	Obesity, T2D	See Related links
GIP/GLP1/glucagon tri-agonists				
HM15211 (^{MED}Triple Agonist)	Hanmi Pharmaceutical	Phase II	NASH	NCT04505436
GGG tri-agonist	Eli Lilly	Phase I	T2D	See Related links
NN9423	Novo Nordisk	Discontinued	Obesity, T2D	See Related links
GIPR agonists				
GIPR agonist long acting	Eli Lilly	Phase I	T2D	See Related links
ZP 6590	Zealand Pharma	Preclinical	Obesity	See Related links
GLP1R agonists				
Efpeglenatide (^{MED}Exd4 Analog)	Hanmi Pharmaceutical	Phase III	T2D	NCT03353350 NCT03496298
Rybelsus	Novo Nordisk	Phase III	Obesity	NCT03919929
Danuglipron (PF-06882961)	Pfizer	Phase II	Obesity, T2D	NCT04707313 NCT03985293
GLPR-NPA	Eli Lilly	Phase I	T2D	See Related links
PF-07081532	Pfizer	Phase I	T2D	NCT04305587
Glucagon analogue				
HM15136 (^{MED}Glucagon Analog)	Hanmi Pharmaceutical	Phase I	Obesity	See Related links
Leptin sensitizers				
Withaferin A	Academic, non-commercial	Phase I	Obesity, T2D	[29]
Celastrol	Academic, non-commercial	Preclinical	Obesity, T2D	[29]
Leptin/amylin	Amylin Pharmaceuticals	Discontinued	Obesity, T2D	See Related links
Y2R agonists				
PYY analogue	Eli Lilly	Phase I	T2D	See Related links
NN9748 (NN9747)	Novo Nordisk	Phase I	Obesity, T2D	NCT03574584
NNC0165-1875 + semaglutide	Novo Nordisk	Phase II	Obesity, T2D	NCT04969939
Amylin/calcitonin dual agonists				
KBP-089	Nordic Biosciences	Phase I	T2D	NCT03907202
KBP-042	Nordic Biosciences	Discontinued	T2D	NCT03230786
Davalintide	Amylin Pharmaceuticals	Discontinued	Obesity, T2D	See Related links
Amylin analogues				
Cagrilintide	Novo Nordisk	Phase II	Obesity, T2D	NCT04940078 NCT04982575
ZP 8396	Zealand Pharma	Preclinical	Obesity	See Related links

REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

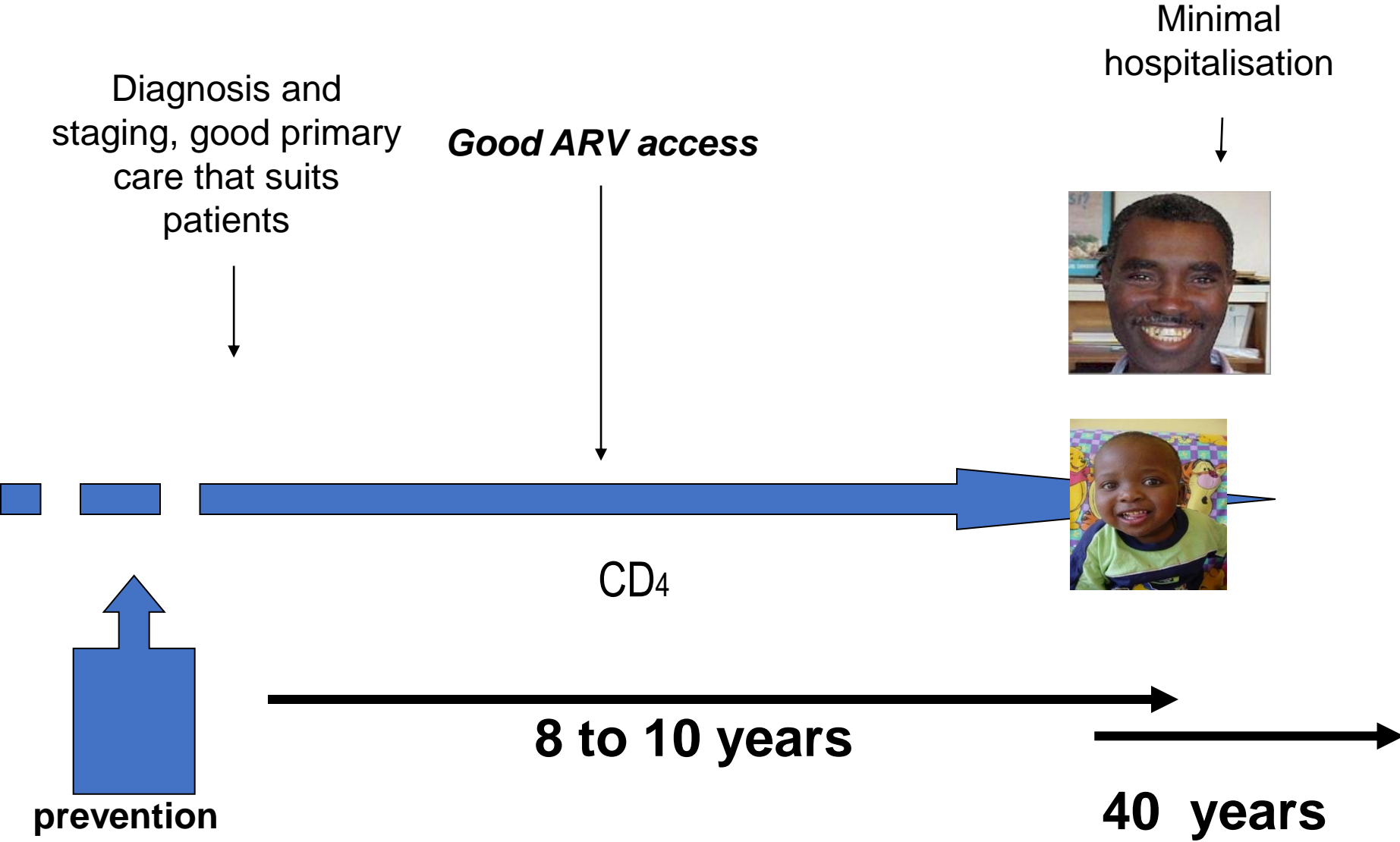## Reassessing Human Adipose Tissue

Aaron M. Cypess, M.D., Ph.D.

...rinology, and ...stitute of Dia-...lney Diseases, ...lth, Bethesda, ...contacted at ...at the Diabe-

ADIPOSE TISSUE IS AN UNDERAPPRECIATED AND MISUNDERSTOOD ORGAN. Capable of more than doubling in mass and then returning to baseline,[1] white adipose tissue (WAT) continues to play an essential role in the development of humans. WAT efficiently stores sufficient energy to free us from con-

Vision... chronic care

Diagnosis and staging, good primary care that suits patients

Good ARV access

Minimal hospitalisation

CD$_4$

8 to 10 years

prevention

40 years

August 28, 2015

People Worldwide Living Longer, but Not Necessarily in Good Health

By Kelly Young

Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition

GBD 2013 DALYs and HALE Collaborators*

Summary

Background The Global Burden of Disease Study 2013 (GBD 2013) aims to bring together all available epidemiological data using a coherent measurement framework, standardised estimation methods, and transparent data sources to enable comparisons of health loss over time and across causes, age–sex groups, and countries. The GBD can be used to generate summary measures such as disability-adjusted life-years (DALYs) and healthy life expectancy (HALE) that make possible comparative assessments of broad epidemiological patterns across countries and time. These summary measures can also be used to quantify the component of variation in epidemiology that is related to sociodemographic development.

How to live a long and healthy life by abstaining from anything that brings you joy
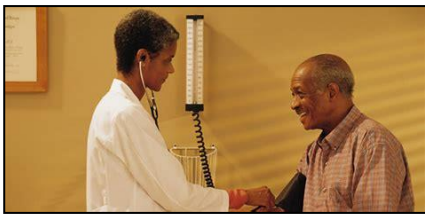
Final thoughts for HIV management

- Basics – adherence, adherence, adherence – rather than ARV selection
- Don't forget TB prevention, reproductive choices – easy now
- Anticipate weight gain: Encourage exercise and good diet but don't link to weight loss
- Unlikely ART switches will make a differences
- Thoughtful management of metabolic complications – lipids, glucose, blood pressure
- Watch the obesity therapeutics space – coming!
- Focus on quality of life

REMEMBER THE TWENTY EXTRA YEARS YOU ADDED TO YOUR LIFE THROUGH CLEAN, HEALTHY LIVING? - WELL, THESE ARE THEM.