



HIV and obesity: remarkably similar epidemics



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.







HIV and Obesity



Overall: Obesity = HIV circa 1996





The HIV story



- "Treating diabetes is hard. Treating HIV is easy." endocrinologist, August 2023
- HIV 2023: Test once, start treatment same day with one tablet
- HIV 2003:
 - 2-3 formal blood tests to confirm HIV, results take up to a week to get back
 - 'Stage' with a CD4, results can take weeks
 - Drug one (d4T) one tablet in morning, one at night, dose adjusted for weight
 - Drug 2 (3TC), one in morning, one at night
 - Drug 3, depends on if you are a woman of 'child-bearing potential' (nevirapine) vs 'other' (efavirenz)
 - Drug 4 (cotrimoxazole) titrated away once stage improved >1 year





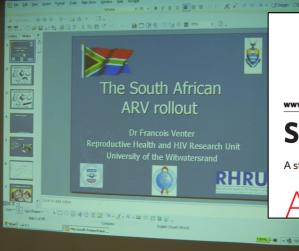
How bad was HIV? 1000 deaths/day



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	titute for	ATAT
		rARVS
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pensate for esting healthily	in Joburg.	FEEDBACK
"In the sume way, cat-	The report has already been	SMS your views to
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culosis we have to rely	The report is likely to rem-	suld the aim was to ensure that
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not mean that matels lowed inter-	Manie Tanatulaia Matmang.	ment get it.
vention had no role in the	mut the use of APVs actions	"The controversies about nutrition have been harmful,"
management of these infec-	Aids, but the is known - and	said the panel of scientists.
tions, especially where nutra-	Widely criticized - for her	They said the debate on the
The name included motor	strong emphasis on good nutri-	impact of natrition on immu-
tionists, immunologists hip.	non in carting Aids.	nity particularly in relation to
chemists, infections.disease	onotions conflict between the	the "two major concurrent opi- demics" of HIV infection and
physicians, passintricians, pol-	minister health neufossionals	TR, had resulted in serious dif-
icy experts and epidemi-	Aids activists and opposition	ferences in the approach to
B was chained by Destaurs		public policy dealing with the
Barry Mendelow of Wirs Ind.	Current government policy,	impact of these diseases.
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	South Africa 2007 2011, released	ously warned of the virulent effects of the combination of
chided Dr Mohamed Ali Dhan-	this year, emphasizes the need	the Alds and TB epidemics.
Say or the Medical Research	for ARV access and to integrate	This has become particularly
	HIV and TB care. ARV treat-	problematic with the smer-
nicable Discusses: and Dr Holen	ment is contrained at 40% of the	gence last year of extensively
Roes and Dr Francois Venter,		drug-resistant TB in South Africa.
	The first states and the	XDR TB, which is virtually
What the health	h maladada	incurable, has since been found
what the heard	n minister said	in all nine provinces.
		The minister of health
beetroot, shall I talk about lem	artic, shall I talk about	received a copy of the report two weeks ago.
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HIV/AIDS, TB AND NUTRITION



Vol 447 | Issue no. 7140 | 3 May 2007

www.nature.com/nature

South Africa's AIDS plan

A strategic plan has been developed to tackle the nation's HIV crisis — at last.

fter years of prevarication, the government of South Africa has finally adopted a sound and comprehensive strategy for managing the country's AIDS epidemic. The 160-page plan. inquiry into the nutritional influences nan immunity with special reference nfection and active TB in South Africa

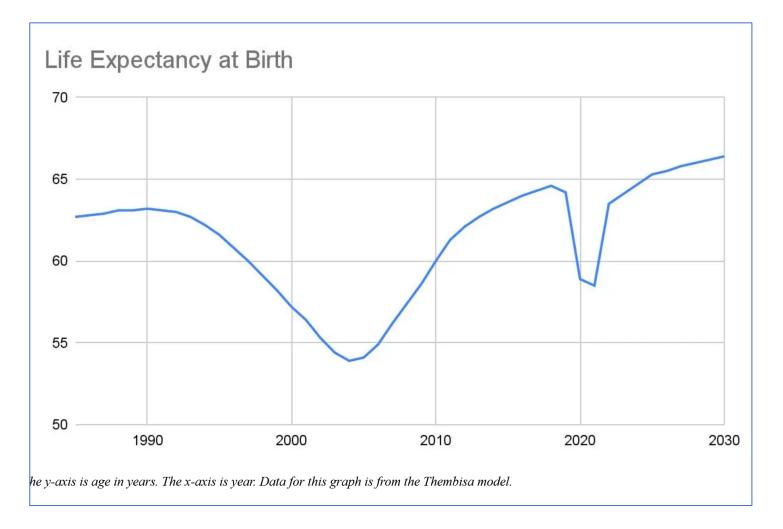
ASSAr Knowing & Helping

2008 – Zuma took power 2024 – about 6 million South Africans with HIV alive on world-class therapy





SA life expectancy



7

HIV treatment pre-2008 in LMICs was ugly

• Drugs toxic, fragile and twice daily





Price tag of HIV response to more than double by 2033

By Laura Lopez Gonzalez on June 12, 2015 in HIV - Antiretrovirals (ARVs), HIV/ALDS

ZERIT

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Bristol-Myer

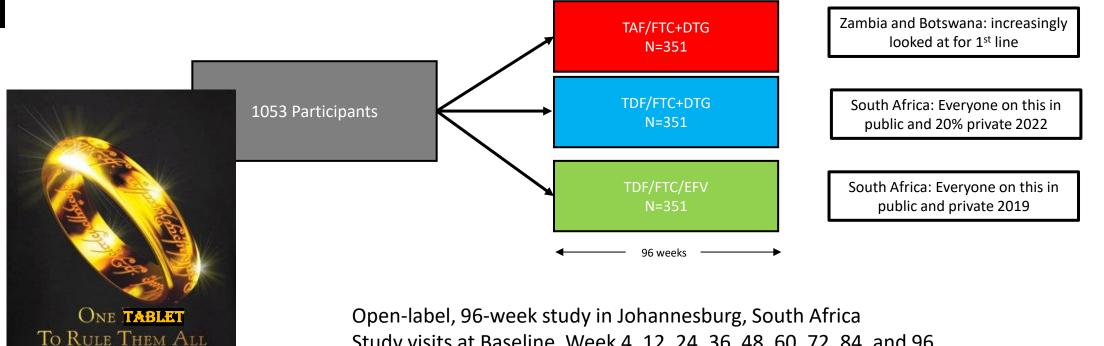
With 3.1 million people on antiretrovirals (ARV). South Africa has the world's largest ARV programme, but sustaining it – and the HIV response – will more than double in the next two decades, according to new research.



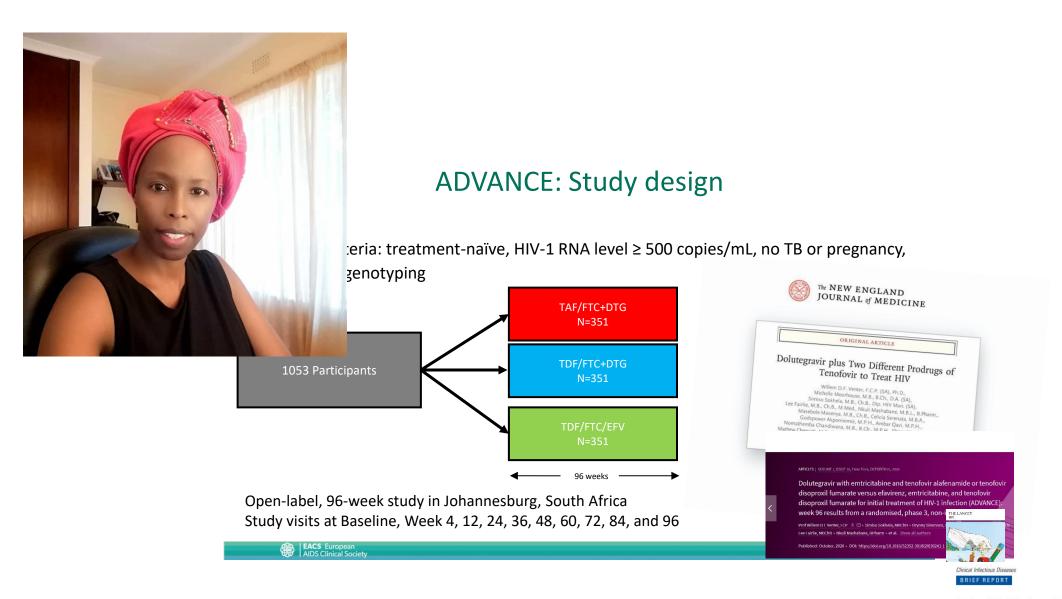
Then came ADVANCE - results April 2019

• Three different WHO regimens - cost and toxicity differences

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



Study visits at Baseline, Week 4, 12, 24, 36, 48, 60, 72, 84, and 96 Funders: Unitaid, USAID, SA MRC, ViiV, drugs Gilead, ViiV



Dr Simiso Sokhela (co-PI on ADVANCE): "Our patients are gaining weight!"

Weight and Metabolic Changes After Switching From Tenofovir Alafenamide/Emtricitabine (FTC) +Dolutegravir (DTG), Tenofovir Disoproxil Fumarate (TDF)/FTC + DTG, and TDF/FTC/Efavirenz to TDF/Lamivudine/DTG

of TDF and EPV on weight gain. EPV has been associated with significant side effects including neuropsychiatric side effects and increases in lipids and serum glucose levels (4). Weight loss is higher for people with cyclochrome polymorphisms, resulting in dower metabolism of the drug, which then confers other neurological and metabolic toxifies [5, 6], TDF has been associated with a higher risk of weight loss in a recent analysis of HIV-negative people taking preexposure prophylas: is therapy [5, 6].

hivmo

gain, worsened lipid profile, equivalent renal and bone toxicit

and virological potency when compared to unboosted TDF, as

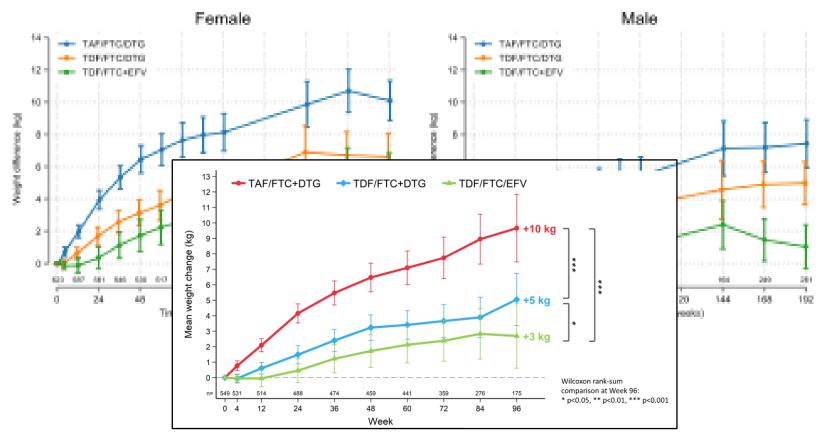
well as concerns regarding drug interactions, unknown preg-

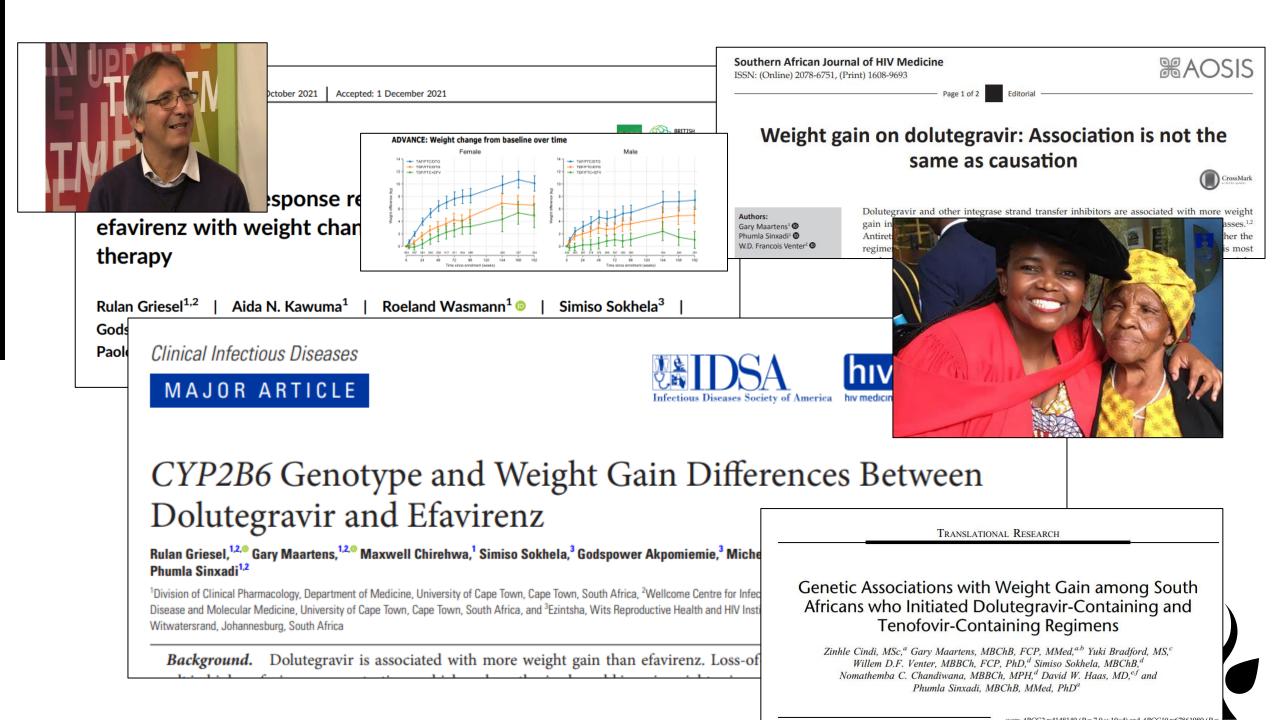
nancy outcomes, and high cost [2, 3]. In contrast, some studies have observed the mitigating effect

UAIDSA

• Immediate reaction: New drugs caused weight gain

ADVANCE: Weight change from baseline over time





But why did you not notice?

ORIGINAL RESEARCH

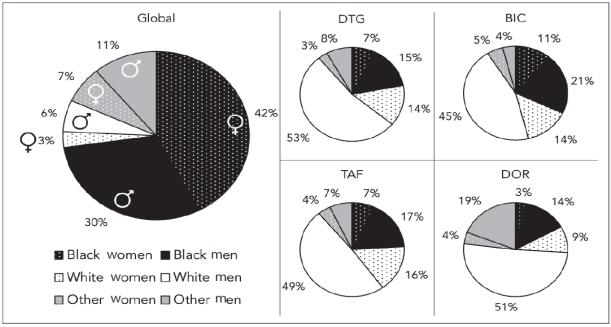
Journal of Virus Eradication 2020; 6: 70-73

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

Toby Pepperrell¹, Andrew Hill^{2*}, Michelle Moorhouse³, Polly Clayden⁴, Kaitlyn McCann⁵, Simiso Sokhela³, Celicia Serenata⁶, Willem Daniel Francois Venter³

¹Faculty 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

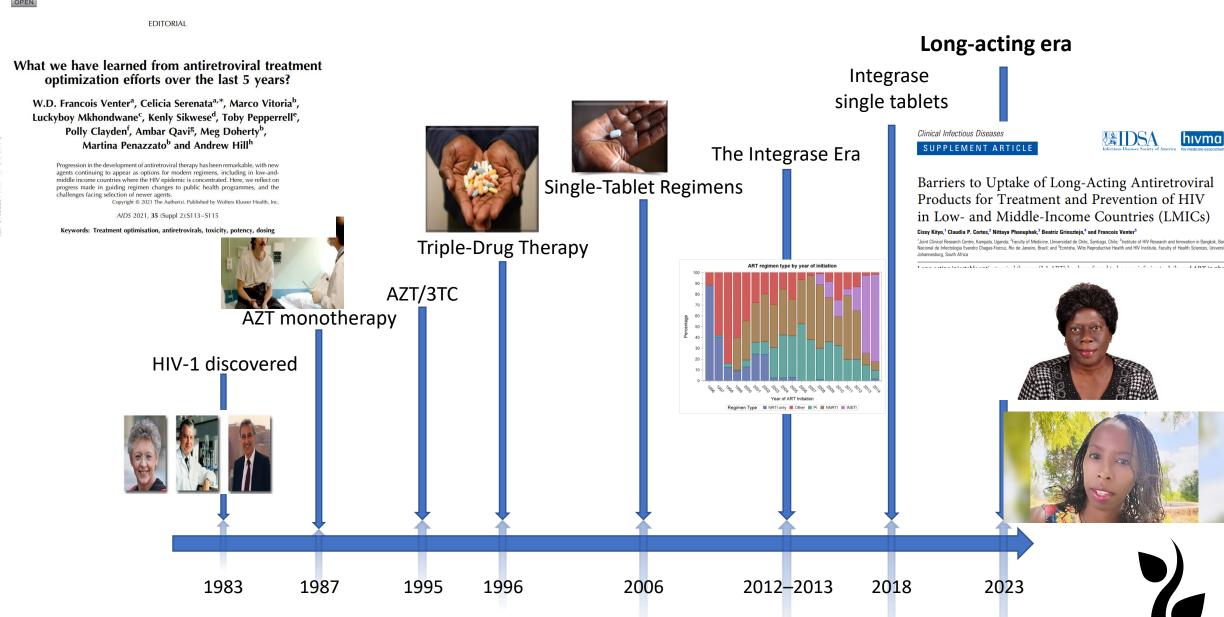




TDF/XTC/DTG

Risks and benefits of TAF versus TDF

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.

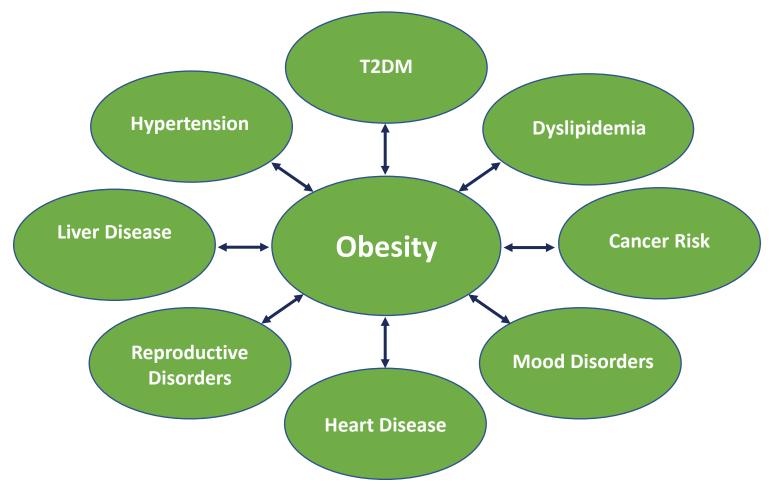


3TC=lamivudine; AZT=zidovudine

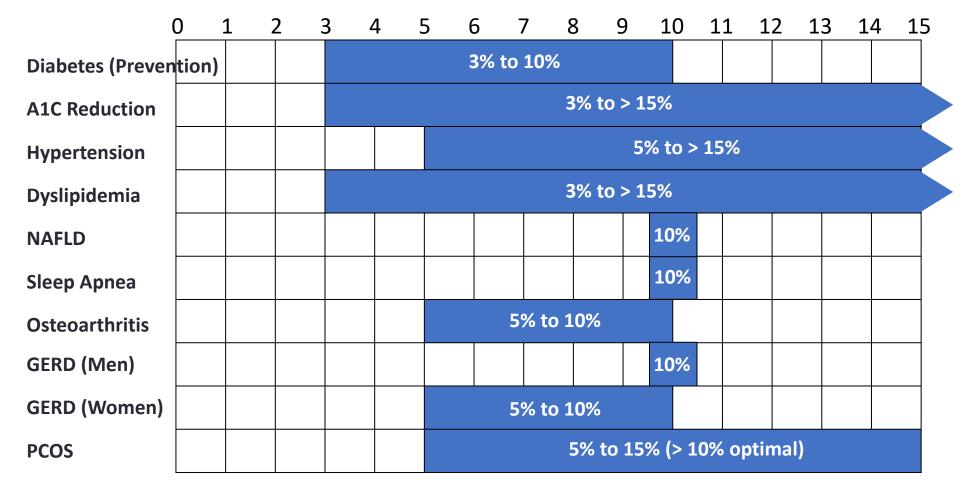
OPEN

Similarly, for obesity: The drugs are revolutionising everything

Health Consequences of Obesity



Weight Loss Required for Therapeutic Benefit



Cefalu. Diabetes Care. 2015;38:1567.

Lifestyle changes are <u>bleak</u> for weight loss

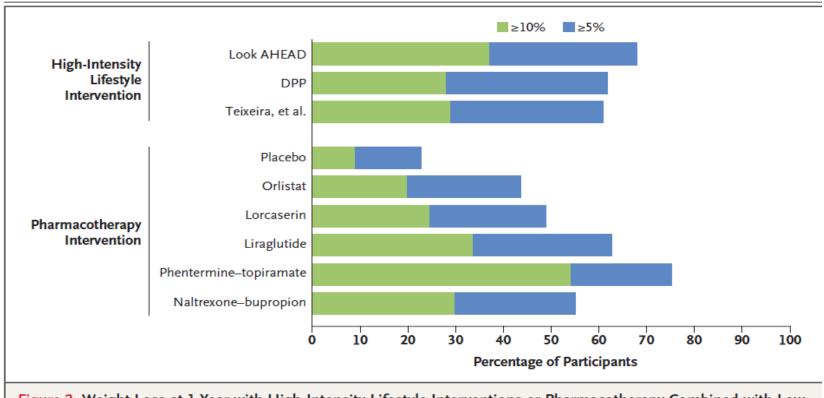


Figure 2. Weight Loss at 1 Year with High-Intensity Lifestyle Interventions or Pharmacotherapy Combined with Lowto-Moderate-Intensity Lifestyle Counseling.

Longo, NEJM, 2017

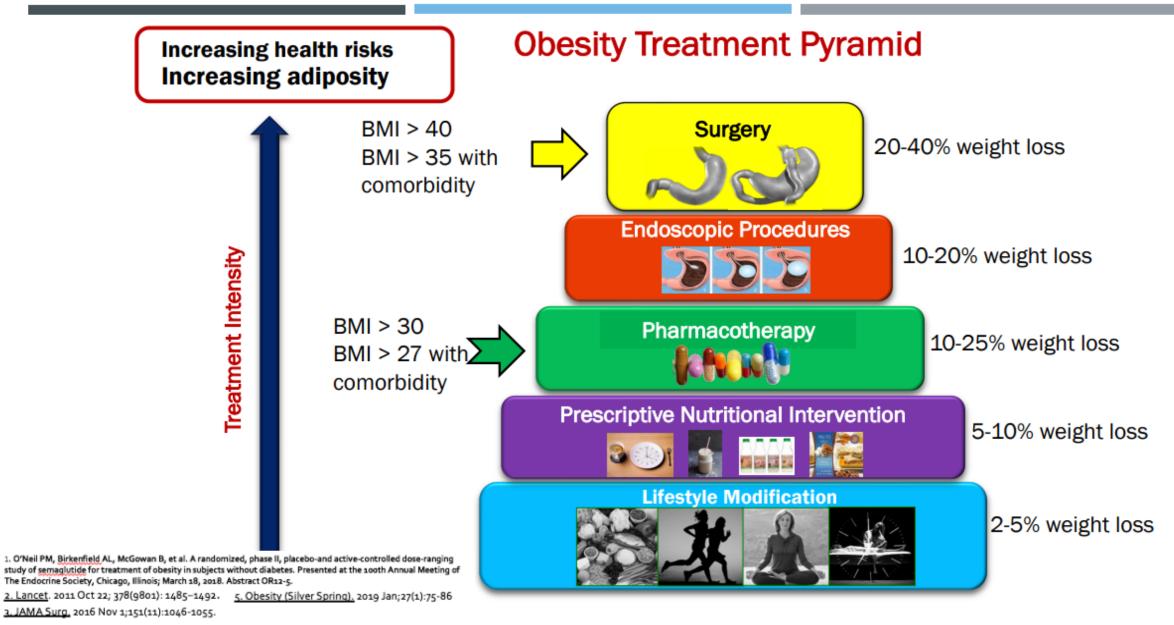
People make a LOT of money from making you feel horrible about your body - implicated in everything from depression to anorexia

 And we've made many people rich, and health workers have colluded

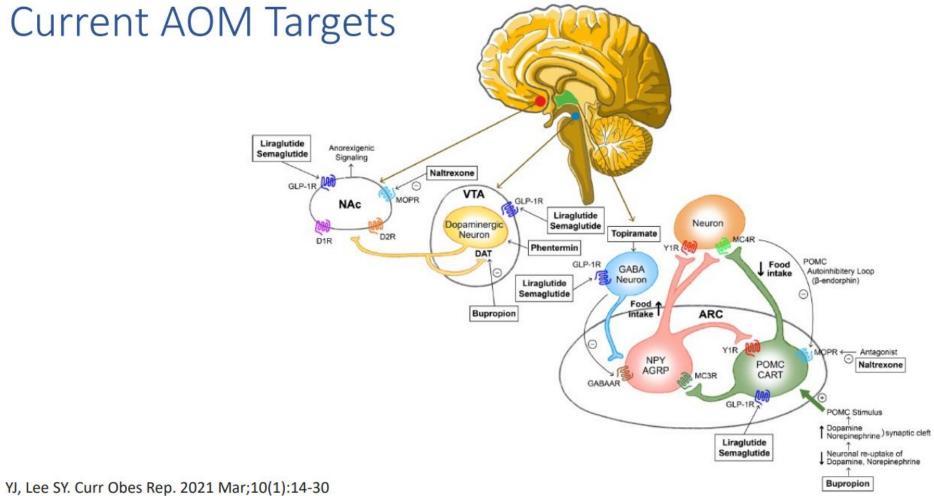








4. Obesity (Silver Spring). 2011 Jan; 19(1): 110-120.



New agents

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 (^{JPS} 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	5			
HM15211 (^{LAPS} 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 (^{APS} 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 ("APSGlucagon Analog)	Hanmi Pharmaceutical	Phase I	Obesity	See Related links
Leptin sensitizers				
Withaferin A	Academic, non-commercial	Phase I	Obesity, T2D	298
Celastrol	Academic, non-commercial	Preclinical	Obesity, T2D	294
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

Table 2 Weight loss drugs in clinical developmen

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

The NEW ENGLAND JOURNAL of MEDICINE

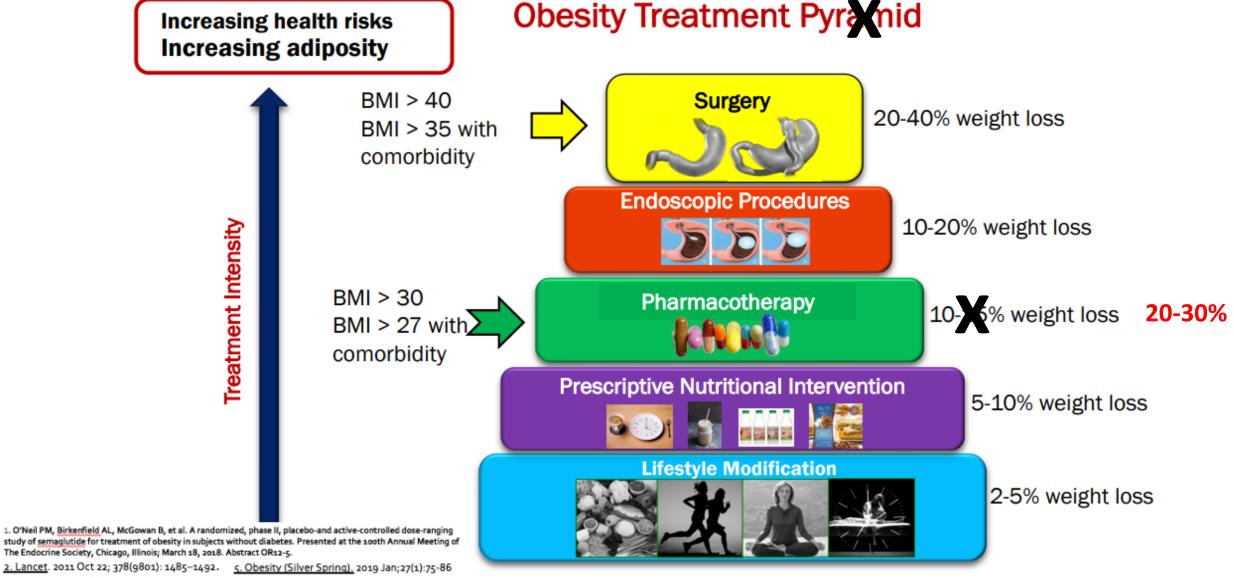
REVIEW ARTICLE

Julie R. Ingelfinger, M.D., Editor

Reassessing Human Adipose Tissue

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

prinology, and istitute of Dialney Diseases, th, Bethesda, contacted at the Diabe



3. JAMA Surg. 2016 Nov 1;151(11):1046-1055.

Obesity (Silver Spring). 2011 Jan; 19(1): 110–120.



)RIGINAL ARTICLE 🔂 Open Access 🕝 😯 😒

Estimated minimum prices and lowest available national prices for antiobesity medications: Improving affordability and access to treatment

IMPROVING AFFORDABILITY AND ACCESS TO TREATMENT

Jacob Levi 🔀, Junzheng Wang, Francois Venter, Andr

First published: 23 February 2023 | https://doi.org/

TABLE 1 Comparison of antiobesity medications showing treatment effect from RCTs, highest and lowest available national prices, and estimated minimum price per course

Drug (route) [course duration]	Average weight loss on treatment vs. placebo, % (kg) [study duration]	Highest national price	Lowest national price	Estimated minimum price
Oral treatments				
Orlistat (PO) [120 mg TDS for 30 days]	Treatment -8.8% (-8.7 kg) vs. placebo -5.7% (-5.8 kg) [after 52 weeks] [20]	\$100 (US VETS)	\$1 (Vietnam)	\$7
Naltrexone-bupropion (PO) [8 mg/90 mg QDS for 30 days]	Treatment -6.4% (-6.2 kg) vs. placebo -1.9% (-1.3 kg) [after 56 weeks] [21]	\$326 (US PHARM)	\$56 (South Africa)	\$54
Topiramate-phentermine (PO) [92/15 mg/d for 30 days]	Treatment -9.8% (-10.2 kg) vs. placebo -1.2% (-1.4 kg) [after 56 weeks] [22]	\$199 (US PHARM)	\$1.3 (Kenya)	\$1.4-\$5
Semaglutide (PO) [14 mg/d for 30 days]	$\begin{array}{l} \mbox{Treatment} -5.3\% \ (-5.0 \ \mbox{kg}) \ \mbox{vs. placebo} \\ -1.3\% \ (-1.2 \ \mbox{kg}) \ \mbox{[after 20 \ \mbox{mg OD for} $$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$$	\$578 (US VETS)	\$65 (India)	NA
Subcutaneous treatments				
Semaglutide (S/C) [2.4 mg/wk, price calculated for 10.25 mg per 30 days]	Treatment -14.9% (-15.3 kg) vs. placebo -2.4% (-2.6 kg) [after 68 weeks] [10, 24],	\$804 (US PHARM)	\$95 (Turkey)	\$40
Liraglutide (S/C) [3 mg OD for 30 days]	Treatment -8.0% (-8.4 kg) vs. placebo -2.8% (-2.8 kg) [after 3 mg OD for 56 weeks] [25]	\$1418 (US PHARM)	\$252 (Norway)	\$50
Tirzepatide (S/C) [15 mg once weekly, price calculated for 12.67 mg per 30 days]	Treatment –20.9% (–21.4 kg) vs. placebo –3.1% (–3.2 kg) [after 72 weeks] [11]	\$1100.70 (US PHARM)	\$715.56 (US VETS)	NA



HEALTH

Ozempic users say weight loss 'wonder drug' curbs cravings for booze, cigarettes, gambling Alcohol intake

By Marc Lallanilla

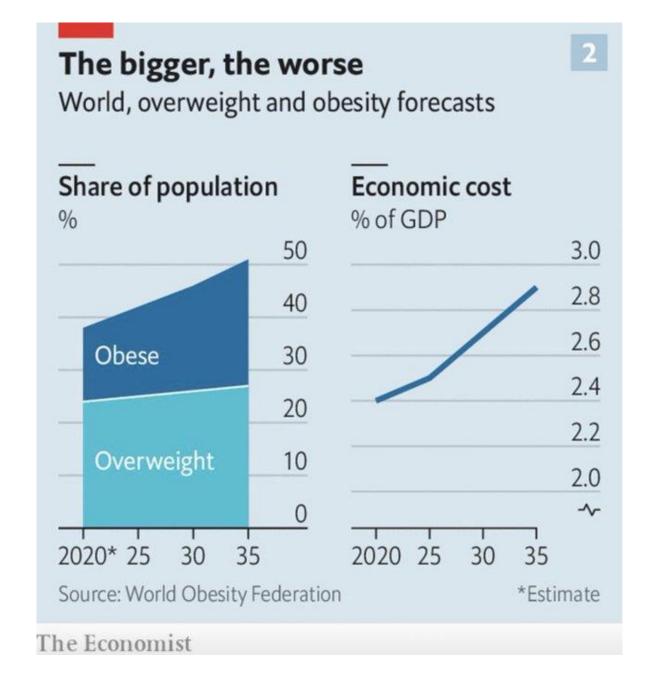
Published Aug. 28, 2023 Updated Aug. 29, 2023, 1:26 p.m. ET



- Binge eating and impulse snacking
- Cigarette smoking, use of other tobacco products
- Use of vaping products
- Impulse and "shopaholic" buying
- Nail biting
- Opioid use
- Gambling

HIV and Obesity: New epidemics







South African epidemic



Percentage of women and men age 15+ who have a BMI ≥35 ■Women ■Men 29 24 21 12 10 3 3 <1Middle Fourth Highest Lowest Second Poorest Wealthiest

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











HIV and Obesity: Big impact on SA health

Taylor & Francis

* Type II diabetes # 1 killer of women; TB #1 killer of men



Estimating the healthcare cost of overweight and obesity in South Africa

Micheal Kofi Boachie, Evelyn Thsehla, Mustapha Immurana, Ciaran Kohli-Lynch & Karen J Hofman

.... equivalent to 0.67% of GDP. Annual per person cost of overweight and obesity is ZAR2,769.

HIV and Obesity: Science understanding is evolving



What is a "healthy diet"?

- move away from processed foods with additives

- all diets associated with weight loss, all temporary





Our pets are also getting larger...







- "Even animals that aren't eating too much or exercising too little are getting fat."
- "The worldwide prevalence of pet obesity lies between 22% and 44%, and rates seem to be rising."

VetRecord

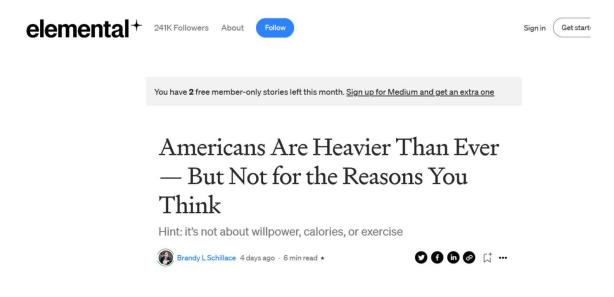
Letters and notices a previous and previous and previous trends in pet obesity Alexander J. German & Georgiana R. T. Woods, Shelley L. Holden, Louise Brennan, Caroline Burke First published: 06 January 2018 | https://doi.org/10.1136/vr.k2 | Citations: 42

HIV and Obesity: Prevention is (very) complicated



Reasons for obesity

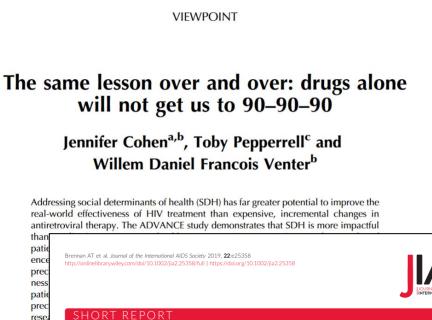
- Lay public and most health workers: poor self control, laziness, not enough exercise – <u>its your fault</u>
- Obesity experts social determinants, genes, modern food – <u>it's the</u> <u>environment, stupid</u>



HIV : Genes, environment

 HIV and targets: Professor Jennifer Cohen, Global and Intercultural Studies at Miami University: "Its capitalism, stupid".





SHORT REPOR

per-

Who is seeking antiretroviral treatment for HIV now? Characteristics of patients presenting in Kenya and South Africa in 2017-2018

Alana T Brennan^{1,2,3*}, Mhairi Maskew^{3*}, Bruce A Larson¹^{§*} (b), Isaac Tsikhutsu^{4,5}, Margaret Bii^{4,5}, Lungisile Vezi³, Matthew P Fox^{1,2,3}, Willem DF Venter⁶, Peter Ehrenkranz⁷ (b) and Sydney Rosen^{1,3*}

⁶Corresponding author: Bruce A Larson, 801 Massachusetts Avenue, Boston, MA 02118, USA. Tel: +1 617 414 1267. (blarson@bu.edu) These authors have contributed equally to the work Clinical Trial Number: NCT02891135 and NCT033150

Obesity: Genes, environment

 Professor Jeff Wing, endocrinologist: "Choose your parents carefully"



 Growing consensus that obesity due to food constituent change



Obesity

• Not a single country has reversed it's epidemic



HIV and Obesity: Denialism in government and society is a major issue



"Those of us who live affluent lives, well-attended by medical care and treatment, should not ask how Germans or white South Africans could tolerate living in proximity to moral evil. We do so ourselves today, in proximity to the impending illness and death of many millions of people with AIDS." **Edwin Cameron**



ORIGINAL ARTICLE

Similar for obesity...

Outbreak of Listeriosis in South Africa Associated with Processed Meat

J. Thomas, N. Govender, K.M. McCarthy, L.K. Erasmus, T.J. Doyle, M. Allam, A. Ismail, N. Ramalwa, P. Sekwadi, G. Ntshoe, A. Shonhiwa, V. Essel, N. Tau, S. Smouse, H.M. Ngomane, B. Disenyeng, N.A. Page, N.P. Govender, A.G. Duse, R. Stewart, T. Thomas, D. Mahoney, M. Tourdjman, O. Disson, P. Thouvenot, M.M. Maury, A. Leclercq, M. Lecuit, A.M. Smith, and L.H. Blumberg







RE: HEALA Technical Public Comment - Draft Regulation Relating to the Labelling and Advertising of Foodstuffs (R3337)

Dear Director General of Health

HEALA applauds the National Department of Health (NDoH) for taking proactive steps toward improving South Africa's health by empowering all consumers to understand what is in their food to avoid making unhealthv food choices. Food policies¹ that help prevent and

So how are HIV and obesity similar?

- Common, complex, hugely important health issues
- Both are preventable but need government intervention
- Both highly dependent on external social factors
- Black women highly vulnerable
- Stigma and blame
- New drugs transformative
- Delivery systems will be the Achilles heel as they already are in rich countries