



## Session 3 | Side Effects Related to INSTIs

# Weight Gain: What We Know and How to Manage



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# Weight gain: What we know and how to manage

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*Rio de Janeiro HIV Clinical Forum 2020  
Rio de Janeiro, 6 de novembro de 2020*

# Obesidade

- Obesity = BMI >30 kg/m<sup>2</sup>
- Global prevalence (2016)
  - 13% of adults (650 million adults)
  - 11% of men; 15% of women
  - nearly tripled since 1975
  - >30% in 7 countries
- Limited prevalence data for HIV+ adults
  - Botswana 17%
  - Ethiopia 21%
  - Nepal 39%
  - POPPY cohort ~15%
- 40% overweight (BMI >25 kg/m<sup>2</sup>)

Obesity	Prevalence
USA	36.2%
Turkey	32.1%
New Zealand	30.8%
Canada	29.4%
Australia	29.0%
South Africa	28.3%
United Kingdom	27.8%
Ireland	25.3%
Spain	23.8%
Russia / Norway	23.1%
Germany	22.3%
France	21.6%
Italy	19.9%
Nigeria	8.9%
China	6.2%
Japan	4.3%
India	3.9%
POPPY cohort	22.3%

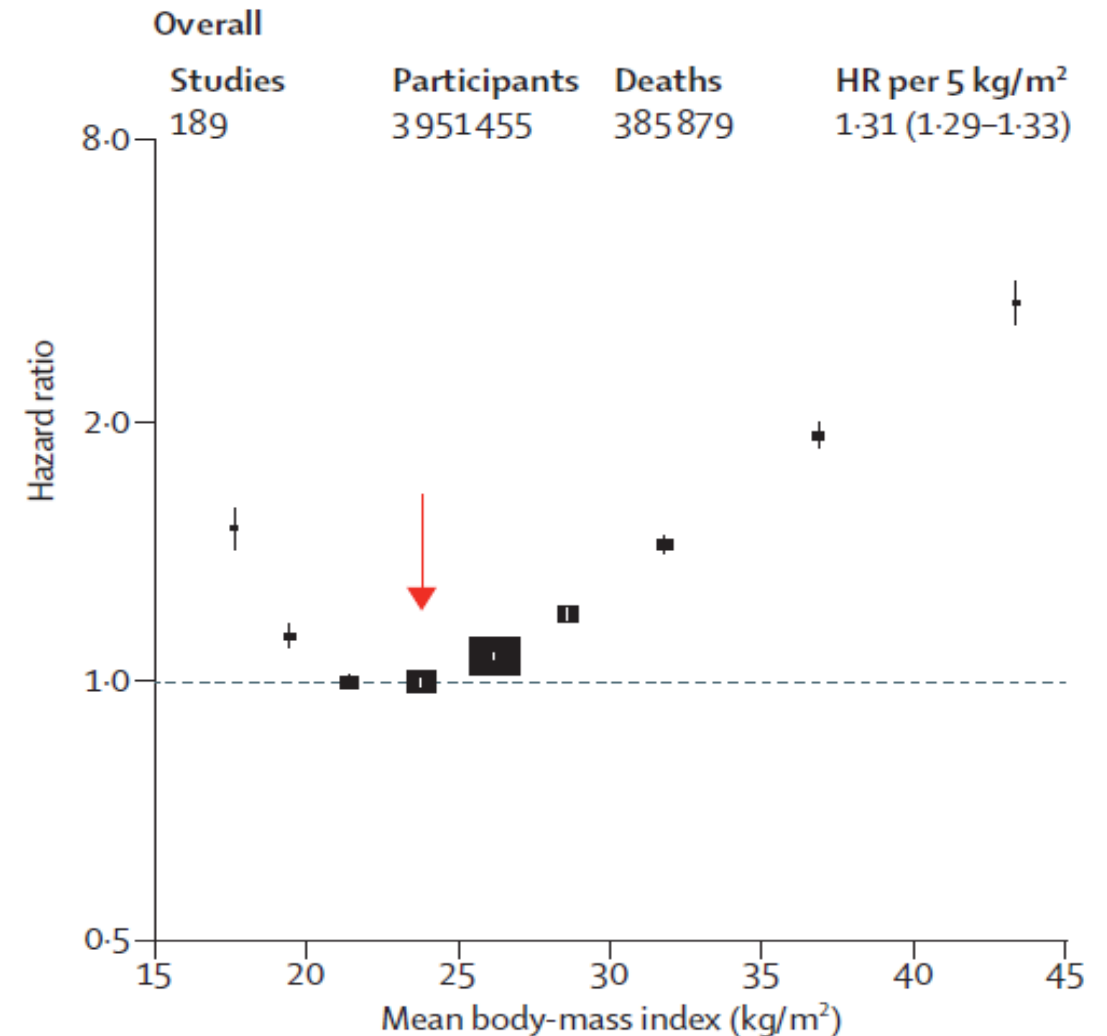
# Obesidade

Importância: múltiplas complicações

<b>Complicação</b>	<b>Consequências</b>
<b>Hipertensão</b>	<b>AVE demência insuficiência cardíaca Doença cardíaca isquêmica</b>
<b>Diabetes mellitus</b>	<b>Doença vascular retinopatia neuropatia periférica Doença renal crônica</b>
<b>Osteoartrite/artrose</b>	<b>Joelho, quadril, coluna</b>
<b>Cancer</b>	<b>endométrio, mama, ovário, próstata, fígado, vesícula biliar, rim e colon</b>
<b>Apnéia do sono</b>	<b>fadiga, demência</b>
<b>Esteatose hepática</b>	<b>insuficiência hepática</b>
<b>Gravidez</b>	<b>macrossomia, prematuridade</b>

# Obesidade

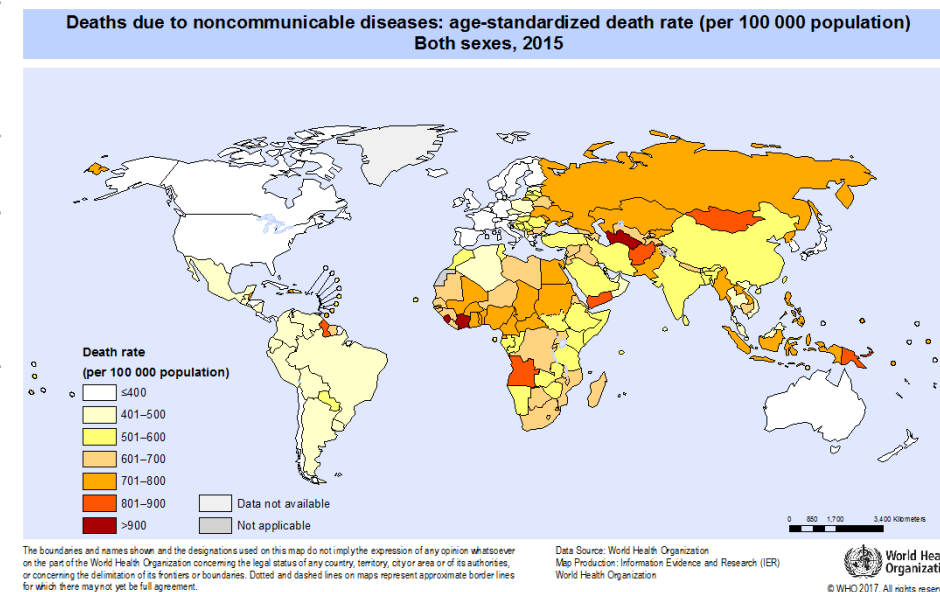
- Cada aumento de 5 kg/m<sup>2</sup> de IMC aumenta o risco de morte em ~30%
- Riscos semelhantes em todas as regiões
- HR
  - Homens 50% vs. Mulheres 30%
  - Idade <50 52% vs. 50-69 37% vs. 70-89 21%
- Não há razão para acreditar que seja diferente em pessoas com HIV



# Obesidade

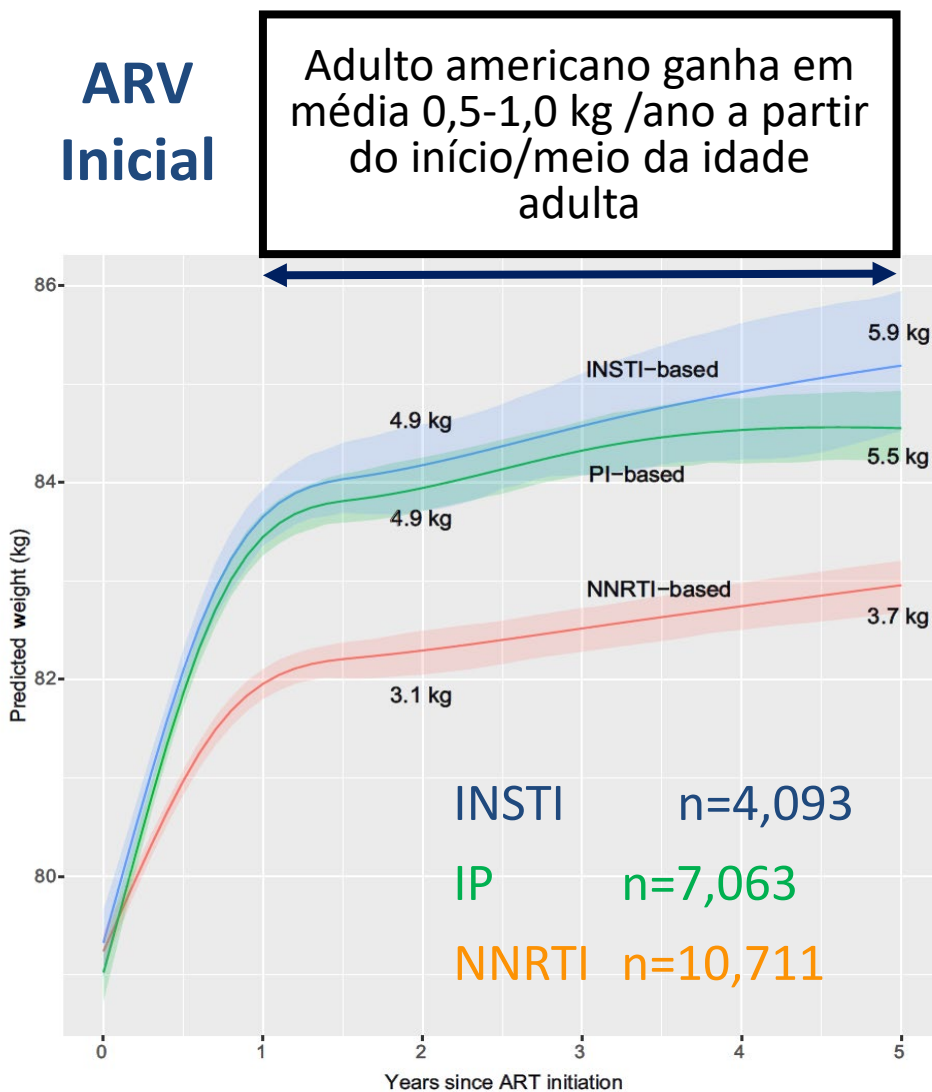
- Excesso de peso causou 4 milhões de mortes em 2015 (só 60% eram obesos)
- ~70% por DCV

Disease	Deaths	Δ2007-17	Years life lost	Δ2007-17
All	55,946,000	+9.3%	1,646,250	-9.0%
Infection	8,413,000	-22.2%	410,732	
AIDS	955,000	-50.3%	50,497	-51.2%
NCDs	41,071,000	+22.7%	872,602	+13.6%
CVD	17,791,000	+21.2%	330,173	+14.7%
Cancer	9,556,000	+25.4%	225,738	+19.6%
Diabetes	1,370,000	+34.7%	29,300	+29.9%
CKD	1,230,000	+33.7%	28,509	+21.0%

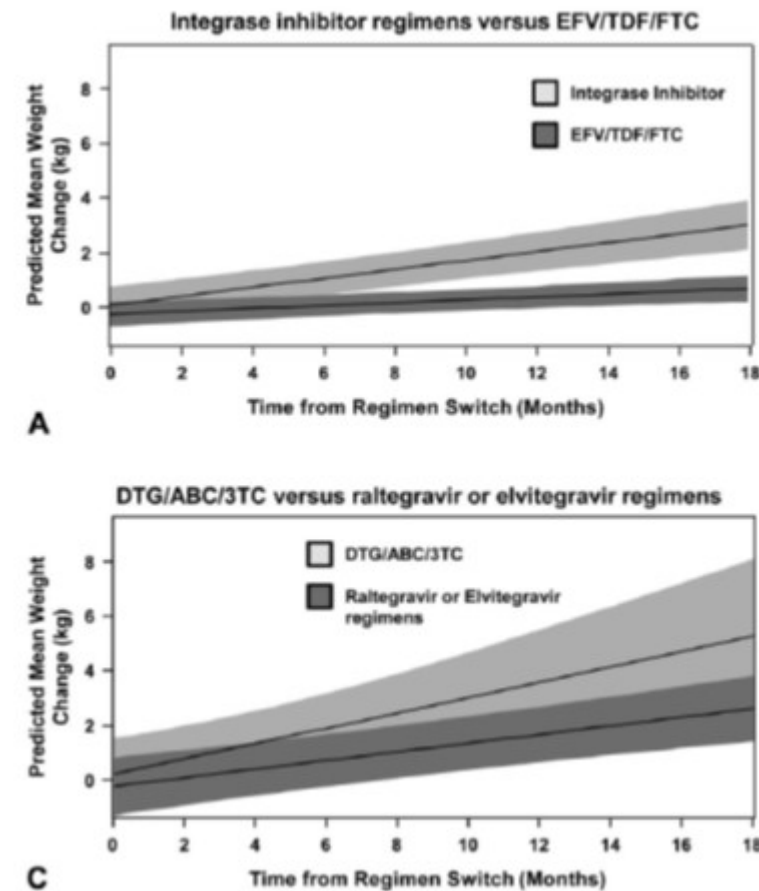


>85% of NCD deaths occur in low-  
middle income countries

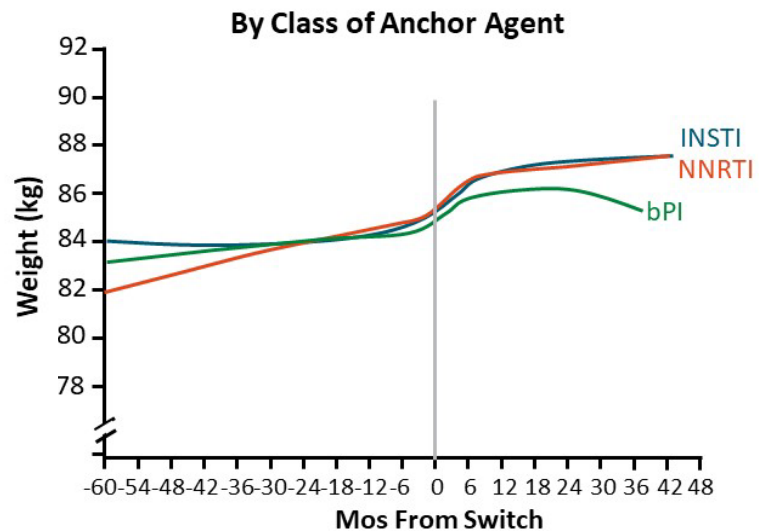
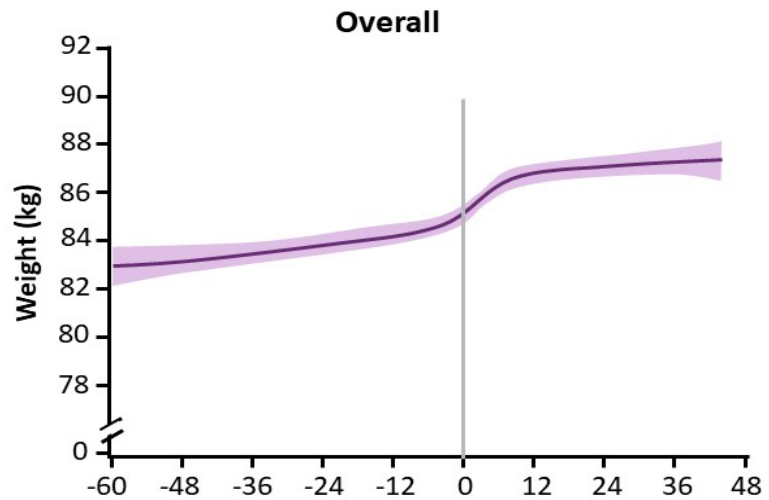
# Antirretrovirais e Ganho de Peso



## Switching



# Antirretrovirais e Ganho de Peso



## Troca de TDF para TAF (OPERA)

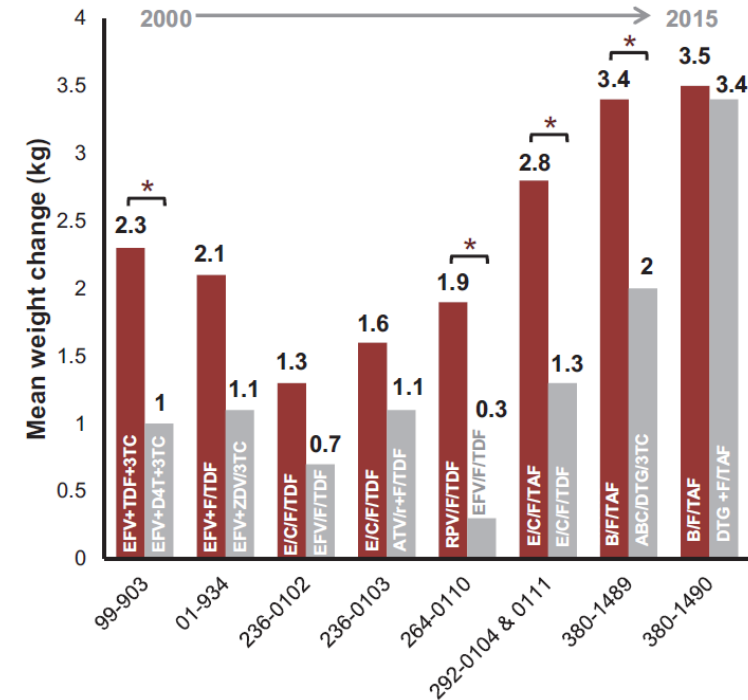
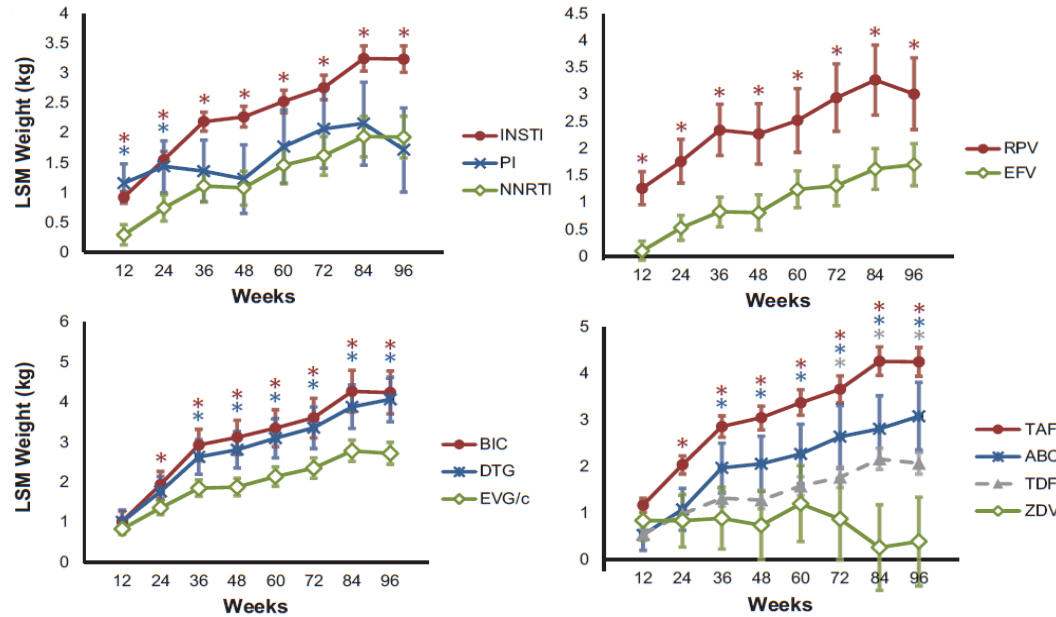
- Todos com CV indetectável
- Troca só TDF para TAF ou também não-INSTI para INSTI

Tempo até a troca (meses)	INSTI (n=3281)	NNRTI (n=1452)	IPx (n=746)
-60 to 0	0.42	0.66	0.31
0 to 9	2.64	2.25	1.98
9+	0.29	0.20	-0.11



# Antirretrovirais e Ganho de Peso

## 8 estudos em terapia inicial



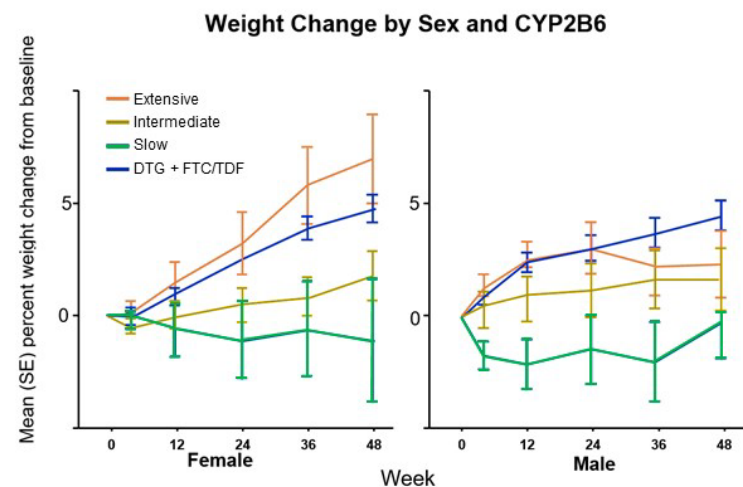
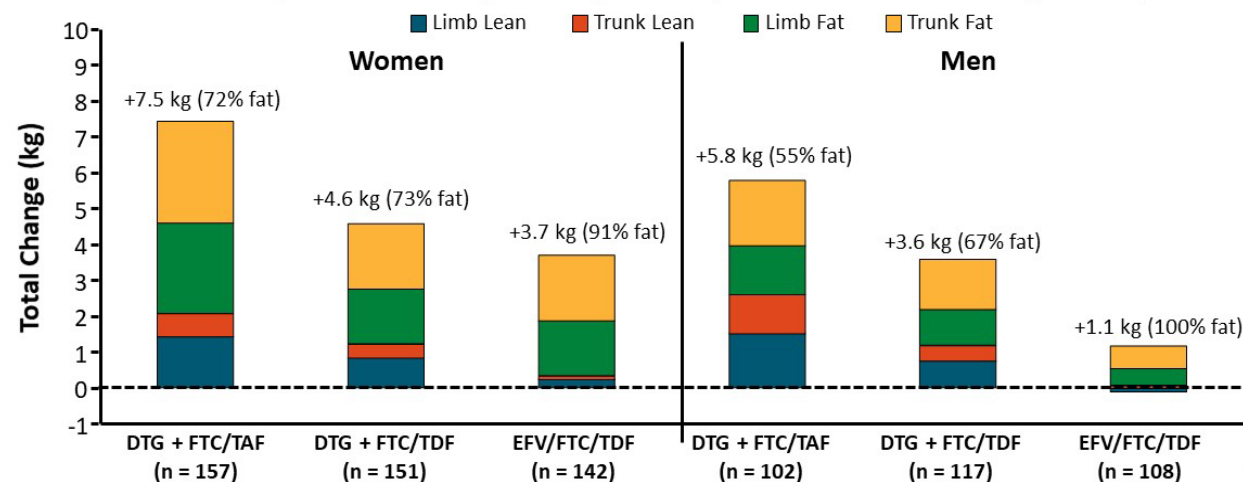
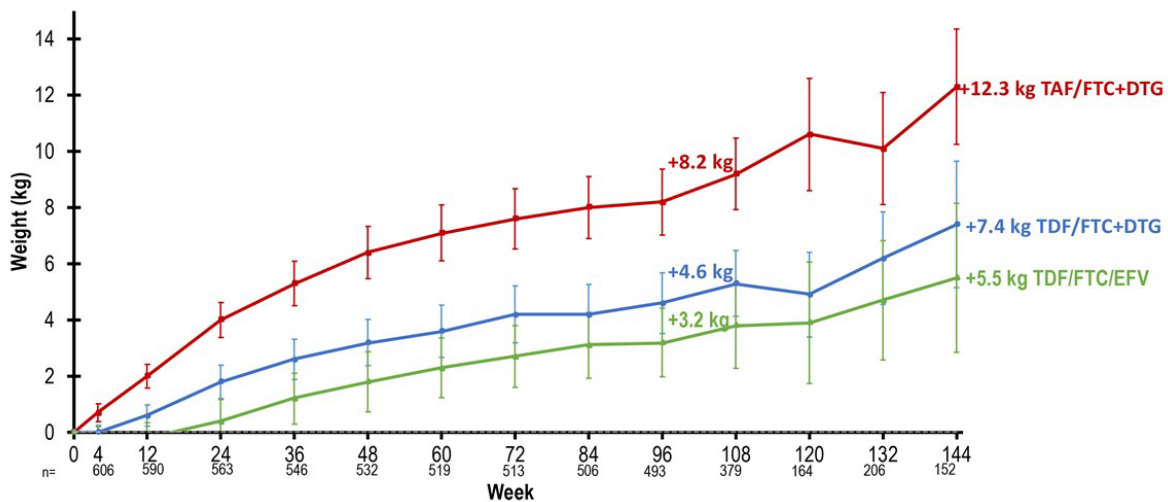
Fator de risco	Odds ratio
CD4 <200	4.36
RNA >100,000	1.98
IMC >25, >30	1.54, 1.66
Mulheres	1.54
Negros	1.32

Fator de risco	Odds ratio
BIC / DTG vs. EFV	1.82
RPV vs. EFV	1.51
TAF vs. ABC	1.90
TAF vs. TDF	1.47

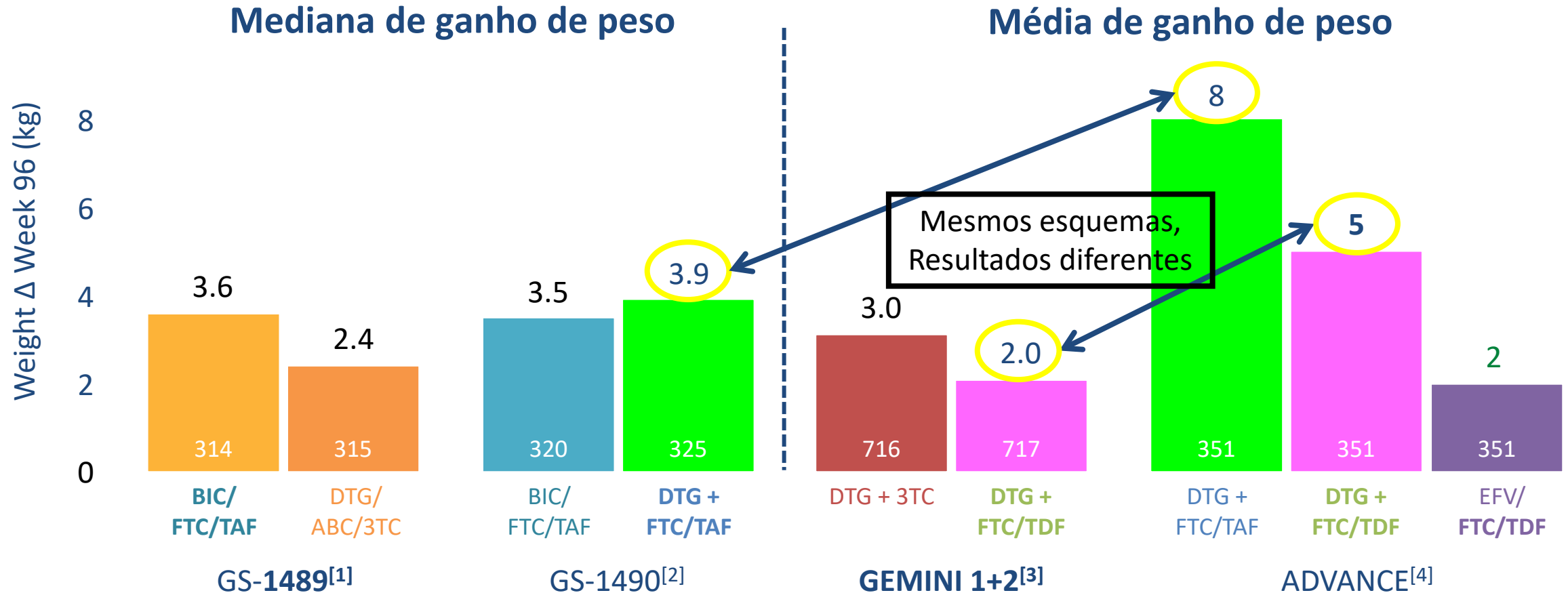
# Antirretrovirais e Ganho de Peso

## Dolutegravir, TAF/TDF and efavirenz

### ADVANCE



# Antirretrovirais e Ganho de Peso

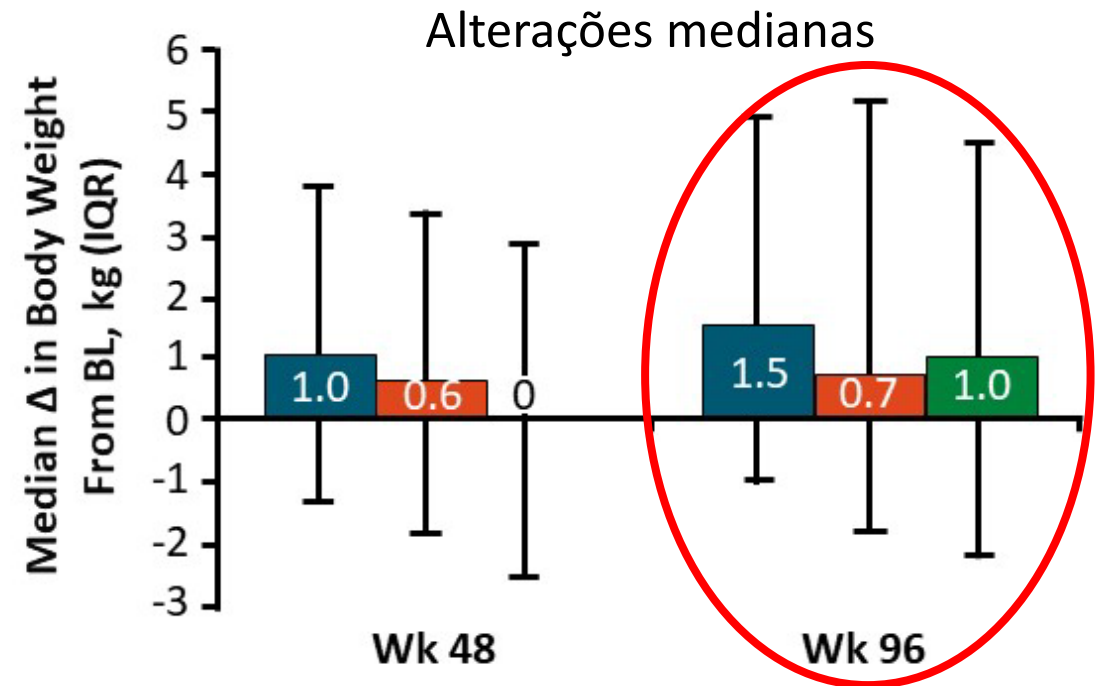
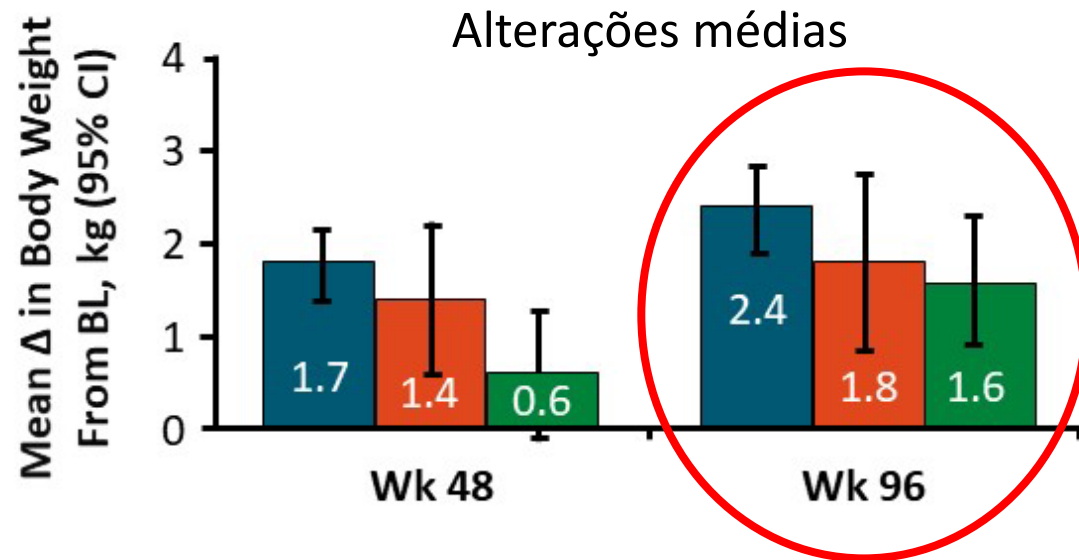


# Antirretrovirais e Ganho de Peso

Antirretrovirais: ganho de peso não é uniformemente distribuído

## TDF-3TC-DOR vs TDF-3TC-DRVc (DRIVE)

■ Combined DOR ■ DRV + RTV ■ Combined EFV

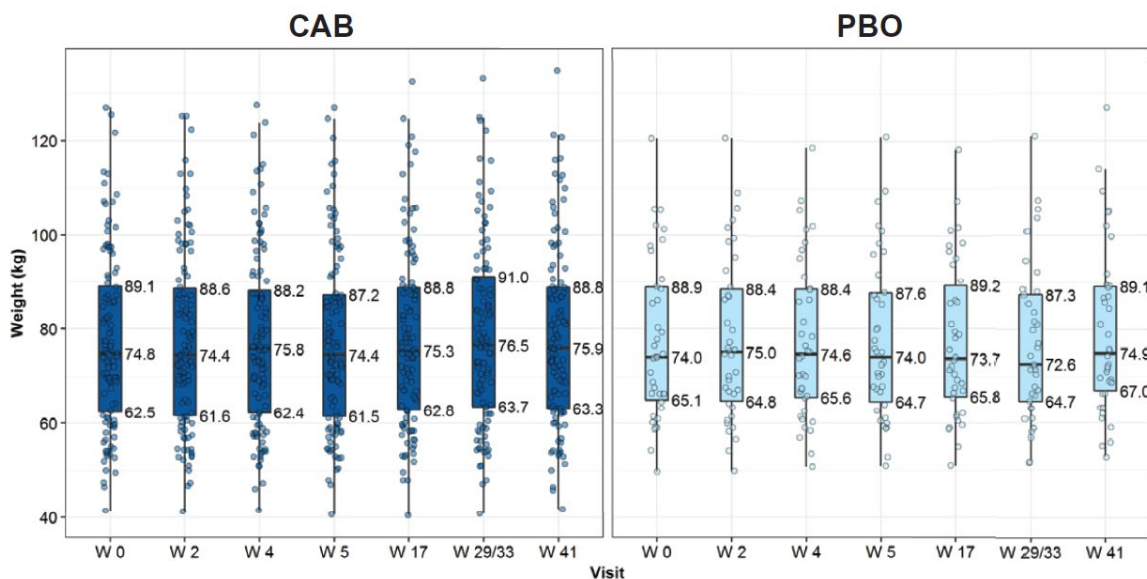


# Antirretrovirais e Ganho de Peso

## Cabotegravir vs. placebo ou TDF – PrEP

### Cabotegravir vs. Placebo (HPTN077)

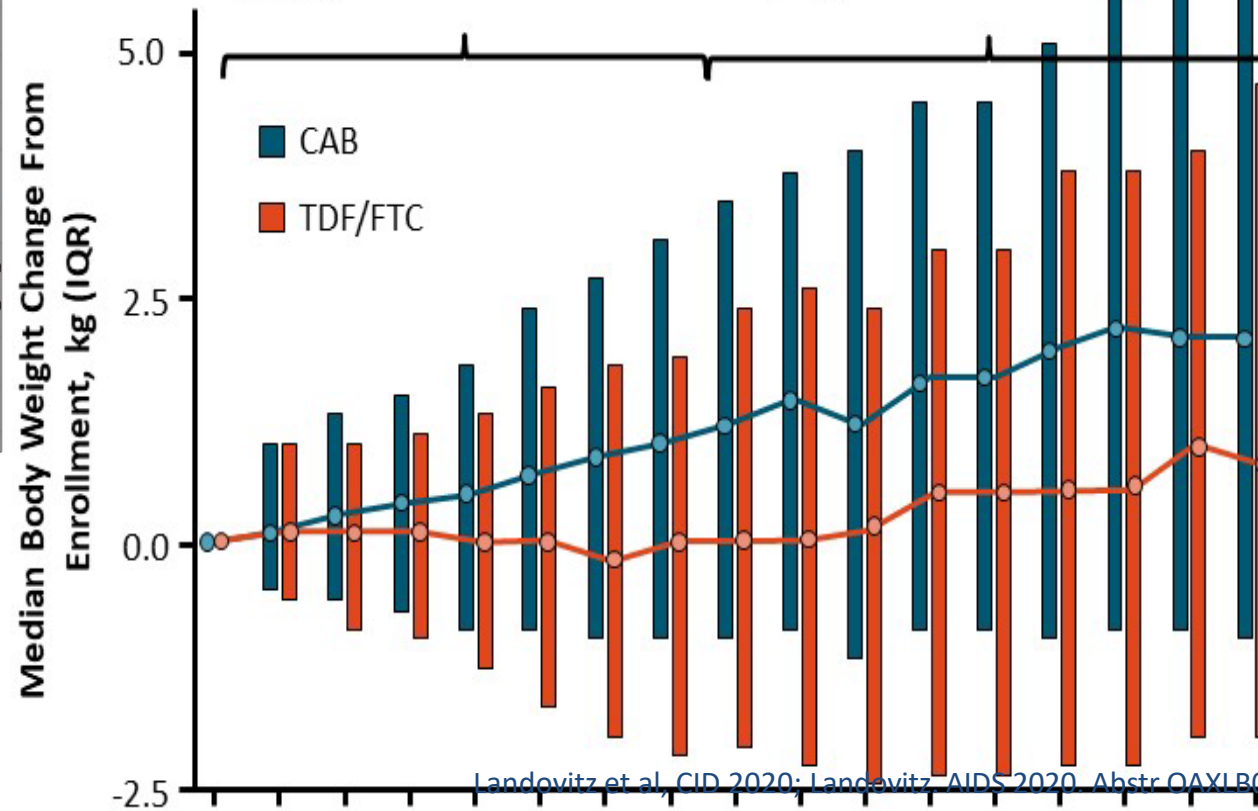
CAB: +1.1kg, Pbo: +1.0, P=0.66



### Cabotegravir vs. TDF-FTC (HPTN083)

CAB: +1.3kg, TDF-FTC: +0.3, P<0.001

CAB +1.54 kg/yr (95% CI: 1.00-2.00) CAB +1.07 kg/yr (95% CI: 0.61-1.50)  
 TDF/FTC -0.51 kg/yr (95% CI: -0.80 to -1.22) TDF/FTC +1.06 kg/yr (95% CI: 0.79-1.30)  
 P < .001 P = .93

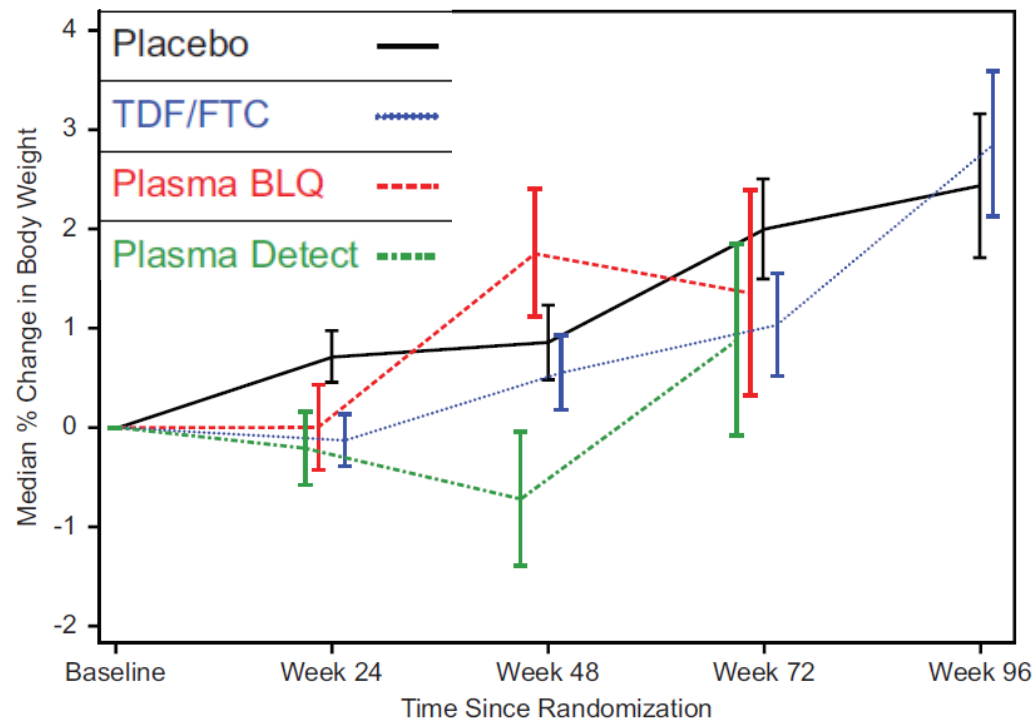


# Antirretrovirais e Ganho de Peso

## TDF vs. placebo ou TAF – PrEP

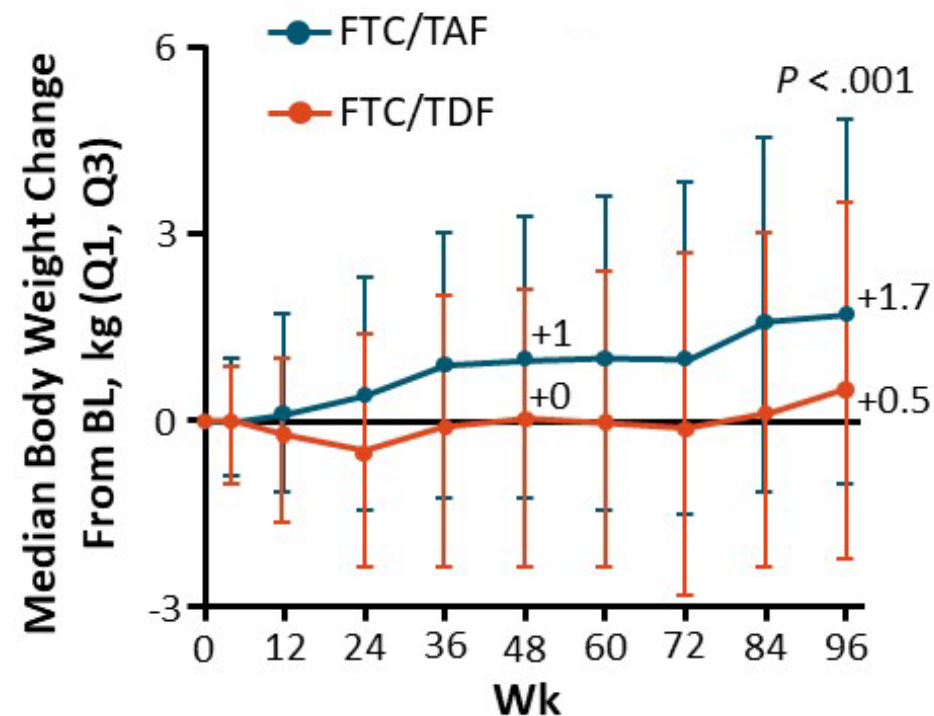
### TDF-FTC vs. Placebo (iPrEx)

Difference = -0.8%, P=0.02



### TAF-FTC vs. TDF-FTC (DISCOVER)

TAF-FTC: +1.7kg, TDF-FTC: +0.5, P<0.001



Difference greater for fat than for lean mass

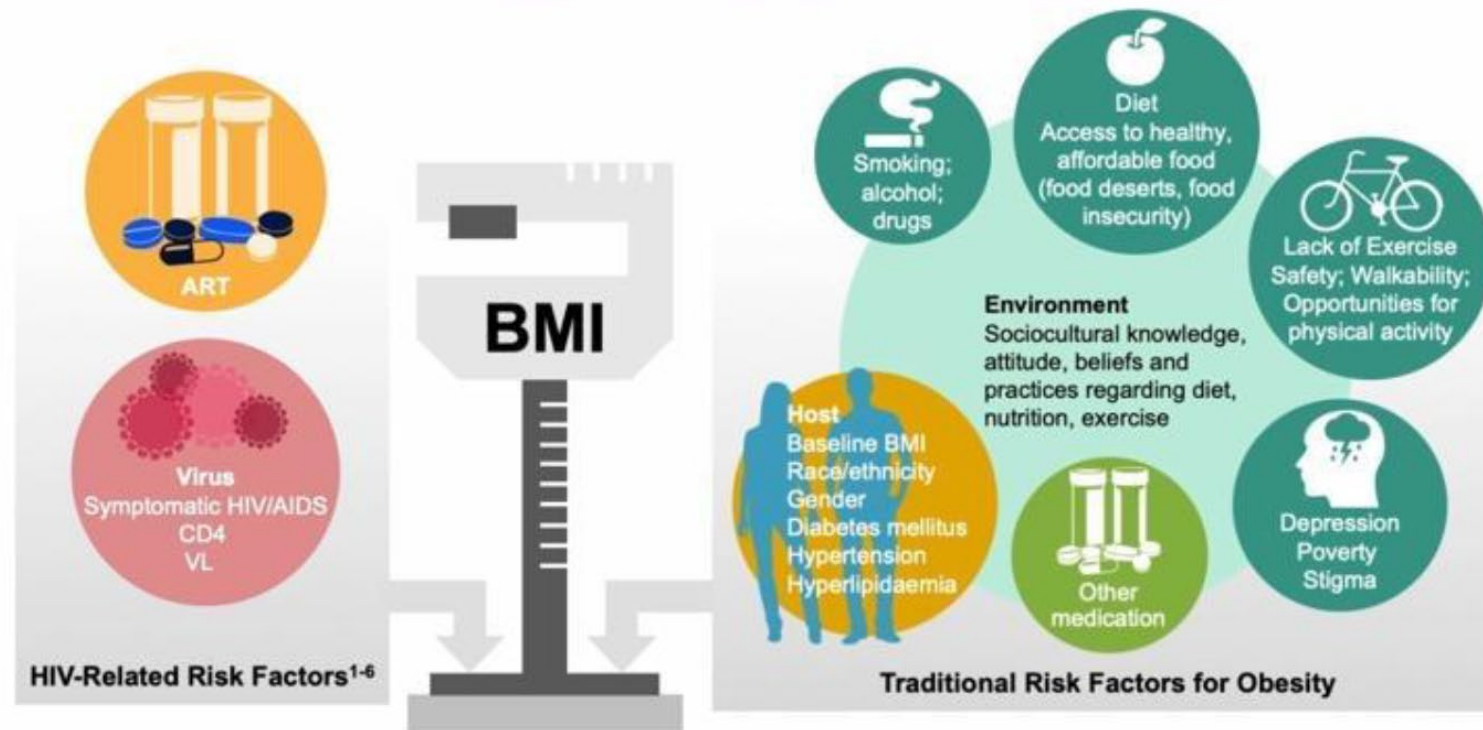
# Antirretrovirais e Ganho de Peso

Randomised trial	Study	TDF/F-3TC	TAF/FTC	INSTI	ABC/3TC	Cont/Pbo
ART-naïve: INSTI	NEAT-001	+1.4				DRVr: +3.1
	Spring-1			+2.1		EFV: 0
	1489		+3.6		+2.4	
	1490		+3.5, +3.9			
	ADVANCE	+5.0	+8.0			EFV: +2.0
	FLAIR			+1.3	+1.5	
	GEMINI	+2.1		+3.1		
ART-naïve: NNRTI	DRIVE	+2.4, +1.6				DRVc: +1.8
ART switch	STEAL	+0.7			+1.9	
	TANGO		+0.8			+0.8
	NEAT-022			(+0.8)		(Plr: +0.3)
	ATLAS			+1.8		+0.3
	BRAAVE			+0.9		+0.2
PrEP	HPTN-077			+1.1		Pbo: +1.0
	iPrEx	(+0.1)				(Pbo: +1.6)
	HPTN-083	+0.3		+1.3		
	DISCOVER	+0.5	+1.7			

TDF/EFV: less than comparator
  TAF: greater than comparator
  INSTI: greater than comparator

# Antirretrovirais e Ganho de Peso

Weight gain in PLHIV is a multifactorial process driven by the interplay among virus, ART, host and environment-specific risk factors





## Intervenções em nível individual

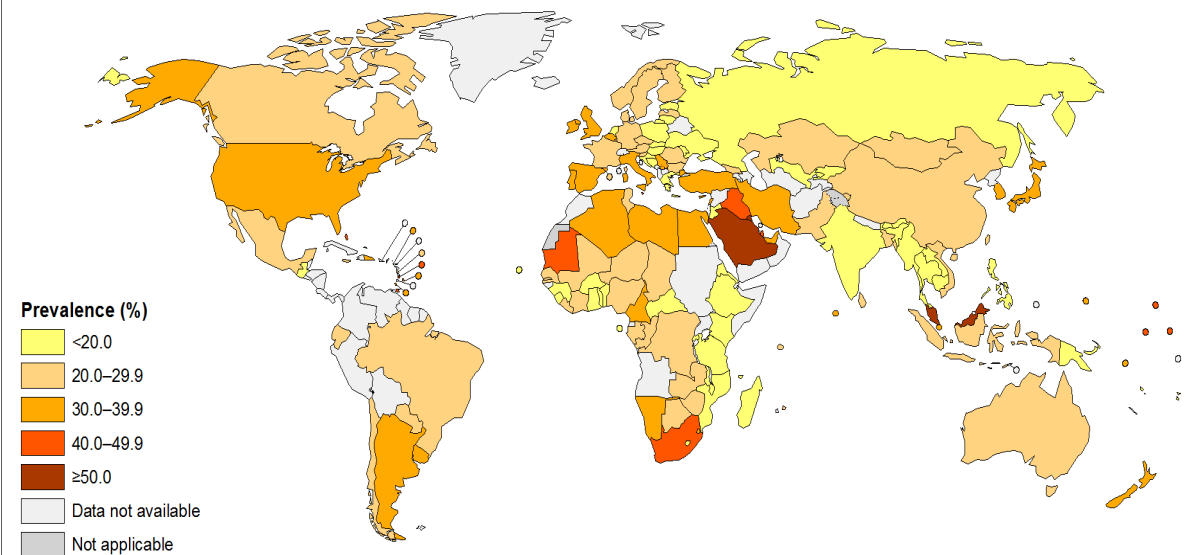
- Restrição calórica (nutricionista)
- +
  - Aumento de atividade física
- Considerar
  - Trocar INSTI ou TAF???
  - Medicação – não há dados

# Antirretrovirais e Ganho de Peso

## Intervenções em nível populacional (OMS)

- **Estimular aumento das atividades físicas**
- **150 minutos de exercícios distribuídos pela semana**
  - Redução de trabalho sedentário
  - Mudar meios de transporte
  - Reduzir trânsito / poluição
  - Mais espaços públicos para exercícios

## Inatividade física 2010

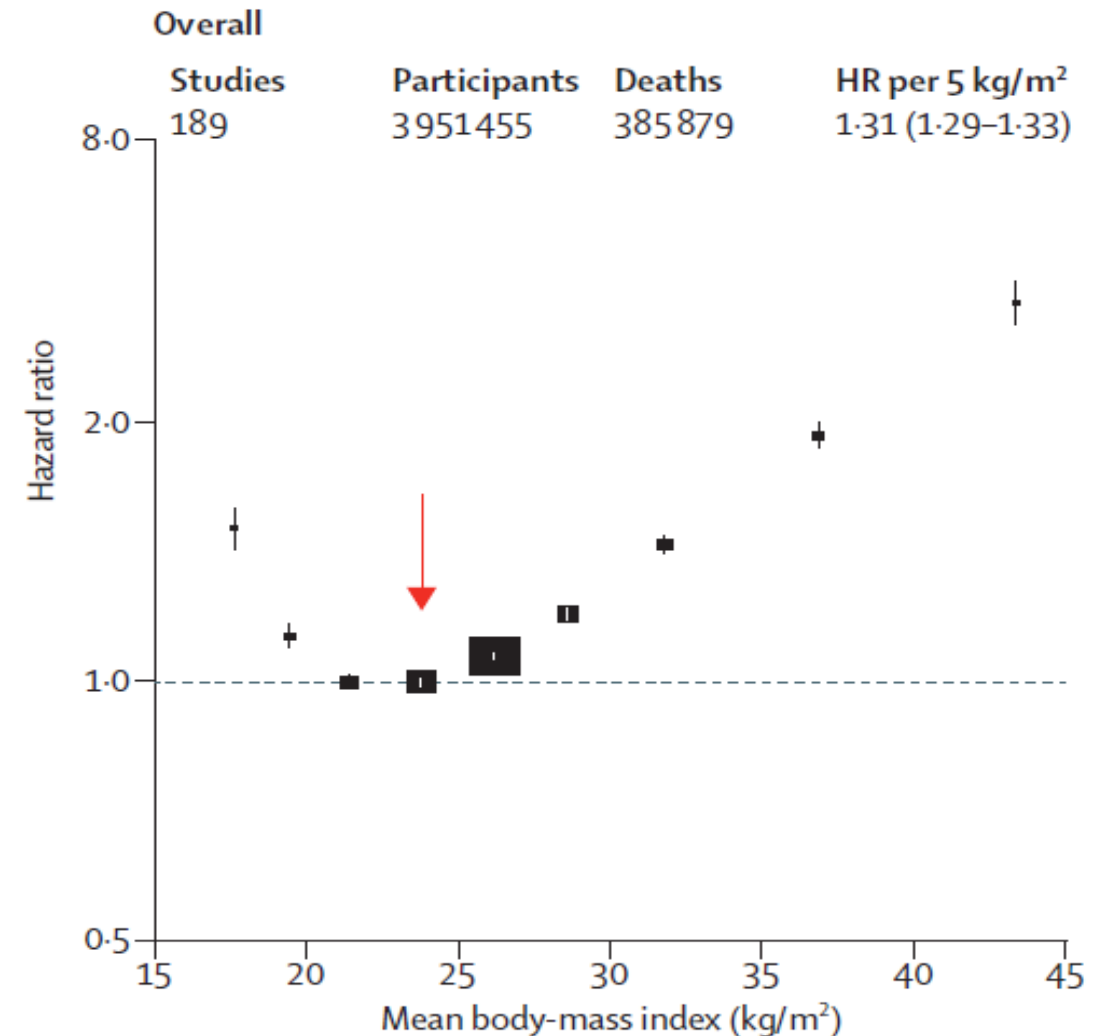


## Lições históricas: HIV e lipodistrofia

Year	HIV lipodystrophy	Year	HIV weight gain
1996	<b>ART is safe</b>	2014	<b>Modern ART is safe</b>
1997	<b>Features reported; largely ignored</b>	2017	<b>Reports of generalised weight gain</b>
1998	Syndrome recognised; <b>attributed to PIs</b>		
1999-	Also attributed to tNRTIs	2018	Larger cohorts – INSTI link
2001	PI and NRTI mechanisms proposed		RCT of DTG switching
	PI switching+++	2019	<b>“TAF / DTG cause fat gain”</b>
2002	Partially reversible with tNRTI switch		<b>“TDF / EFV prevent fat gain”</b>
2003	Prospective confirmation	2020+	3 drug classes?
	Prevented with initial TDF/ABC		Mechanism(s)?
2004	Treatment: glitazones not very effective		Biology of risk factors?
2005	<b>Mitochondrial mechanism</b>		Hierarchy in drug classes?
2008	<b>PI (LPVr) did <u>not</u> cause LD in RCT</b>		Does weight gain stabilise?
			Reversibility / treatment?
			Clinical consequences?

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# Agradecimentos

- Andrew Carr
- Marcia Rachid
- Tânia Vergara



**Obrigado !!!!!**