AETC AIDS Education & Training Center Program Southeast

HIV, ARVs, and Weight Gain

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Objectives

- Discuss the history of cART and weight gain
- Review changes in HIV mortality
- Review most recent data discussing weight gain with current first line ARV regimens

A Historical Perspective

- Prior to widespread use of HAART PLWH struggled with wasting and lipoatrophy
- Often initial weight gain was viewed as “return to health” (reversal of catabolic effects of HIV)
- Older cART regimens were associated with lipodystrophy (stavudine, zidovudine, indinavir)

Vital Signs: Deaths Among Persons with Diagnosed HIV Infection, United States, 2010–2018

Weekly / November 20, 2020 / 69(46);1717–1724

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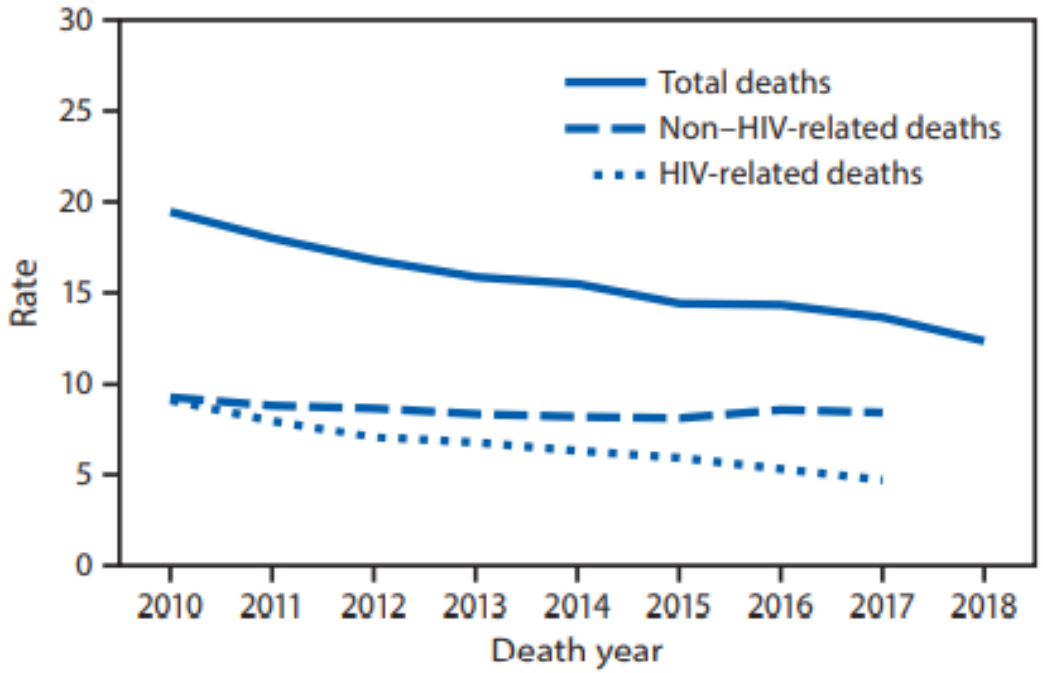
Methods

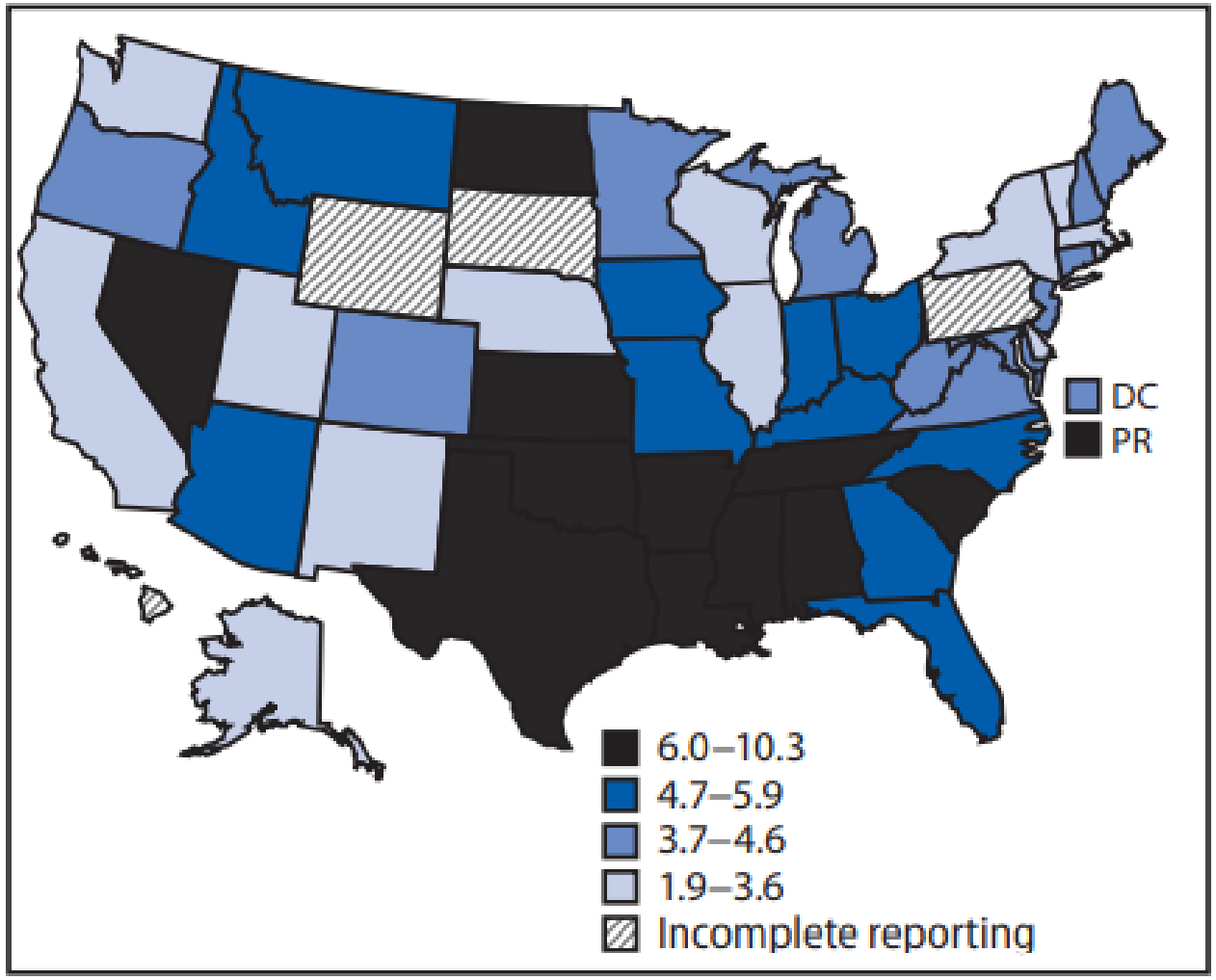
- Analysis of the National HIV Surveillance System death data from 2010 – 2018
- ICD-10 data
- Classified into HIV related, non-HIV related

FIGURE 1. Age-adjusted rates* of total deaths,† human immunodeficiency virus (HIV)–related deaths,§ and non–HIV-related deaths among persons aged ≥13 years with diagnosed HIV infection — United States, 2010–2018¶



* Rates per 1,000 persons with diagnosed HIV infection. Rates age-adjusted using the U.S. 2000 standard population.
† Deaths among persons with diagnosed HIV infection regardless of cause of death (n = 16,742 in 2010; n = 15,483 in 2018).
§ HIV-related deaths include deaths with an underlying cause with an *International Classification of Diseases, Tenth Revision*, code of B20-B24, O98.7, or R75. Non–HIV-related deaths include all other deaths with a known underlying cause.
¶ Deaths by cause available through 2017 because of reporting delays.

FIGURE 2. Age-adjusted rates* of human immunodeficiency virus (HIV)–related deaths among persons aged ≥13 years with diagnosed HIV infection, by area of residence at time of death — United States and Puerto Rico, 2017



Abbreviations: DC = District of Columbia; PR = Puerto Rico.

* Rates per 1,000 persons with diagnosed HIV infection. Rates age-adjusted using the U.S. 2000 standard population. HIV-related deaths include deaths with an underlying cause with an *International Classification of Diseases, Tenth Revision* code of B20–B24, 098.7, or R75. Other U.S. dependent areas are excluded because they do not report underlying cause of death information. Jurisdictions with striped shading are those with <85% of deaths in 2017 with a known underlying cause of death. Rates from Alaska, Idaho, Maine, Montana, Nebraska, New Hampshire, New Mexico, North Dakota, Rhode Island, Utah, Vermont, and West Virginia are calculated based on <12 deaths and should be interpreted with caution.

Despite success in reducing rates of HIV-related deaths among PWDH, differences still exist by gender, race/ethnicity, age, transmission category, and region. Variation in timely diagnosis and treatment initiation, along with ongoing treatment, likely contributes to differences in HIV-related deaths. During 2015, delays in HIV diagnosis were longer among non-White racial/ethnic groups and males with HIV infection attributed to heterosexual contact (*11*). Timely initiation of treatment, as measured by the proportion of persons with suppressed viral loads ≤6 months after diagnosis, and receipt of ongoing, recommended treatment, as measured by the proportion of PWDH with a suppressed viral load, varied during 2017 by gender, age, race/ethnicity, transmission category, and region (*8*,*12*); populations with higher rates of HIV-related deaths were less likely to have evidence of timely initiation of treatment and ongoing treatment as demonstrated through lower proportions of viral suppression in the population.

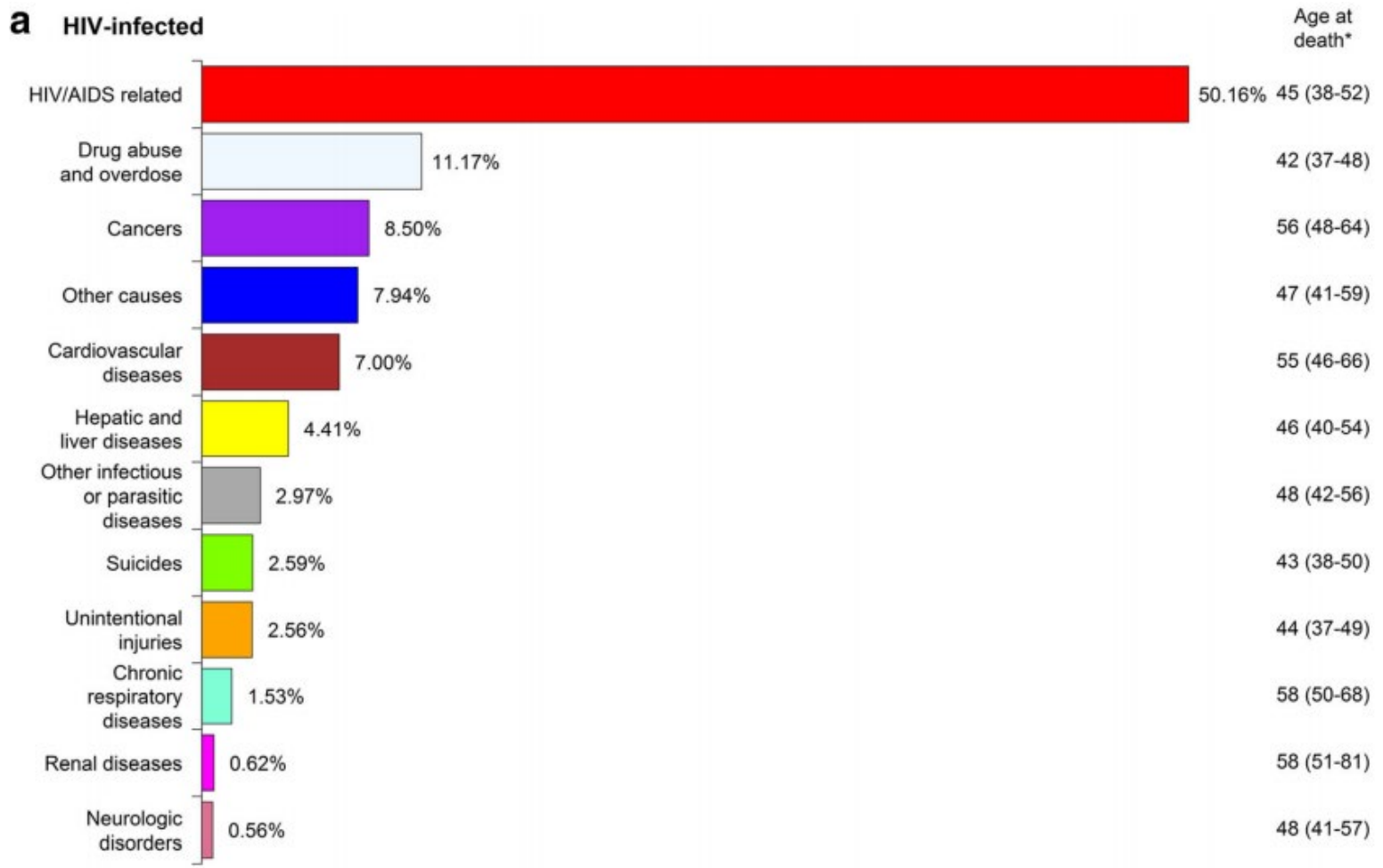
Changes in mortality rates and causes of death in a population-based cohort of persons living with and without HIV from 1996 to 2012

Oghenowede Eyawo[1,2], Conrado Franco-Villalobos[1], Mark W. Hull[1], Adriana Nohpal[3], Hasina Samji[4], Paul Sereda[1], Viviane D. Lima[1], Jeannie Shoveller[1,5], David Moore[1], Julio S. G. Montaner[1,6], Robert S. Hogg[1,2*] and for the Comparative Outcomes And Service Utilization Trends (COAST) study

COAST Cohort

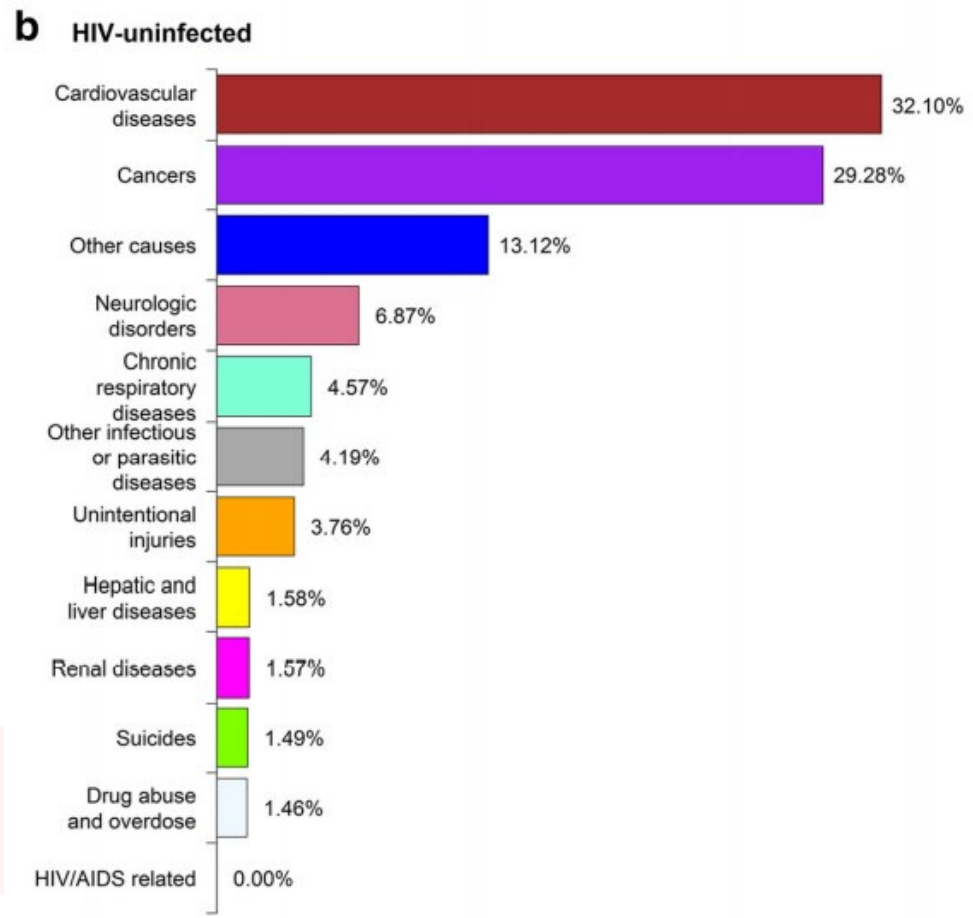
- Comparative Outcomes and Service Utilization Trends (COAST)
- Large population-based retrospective cohort study including longitudinal data of HIV-infected adults
- Population in British Columbia

HIV Causes of Mortality (2016)



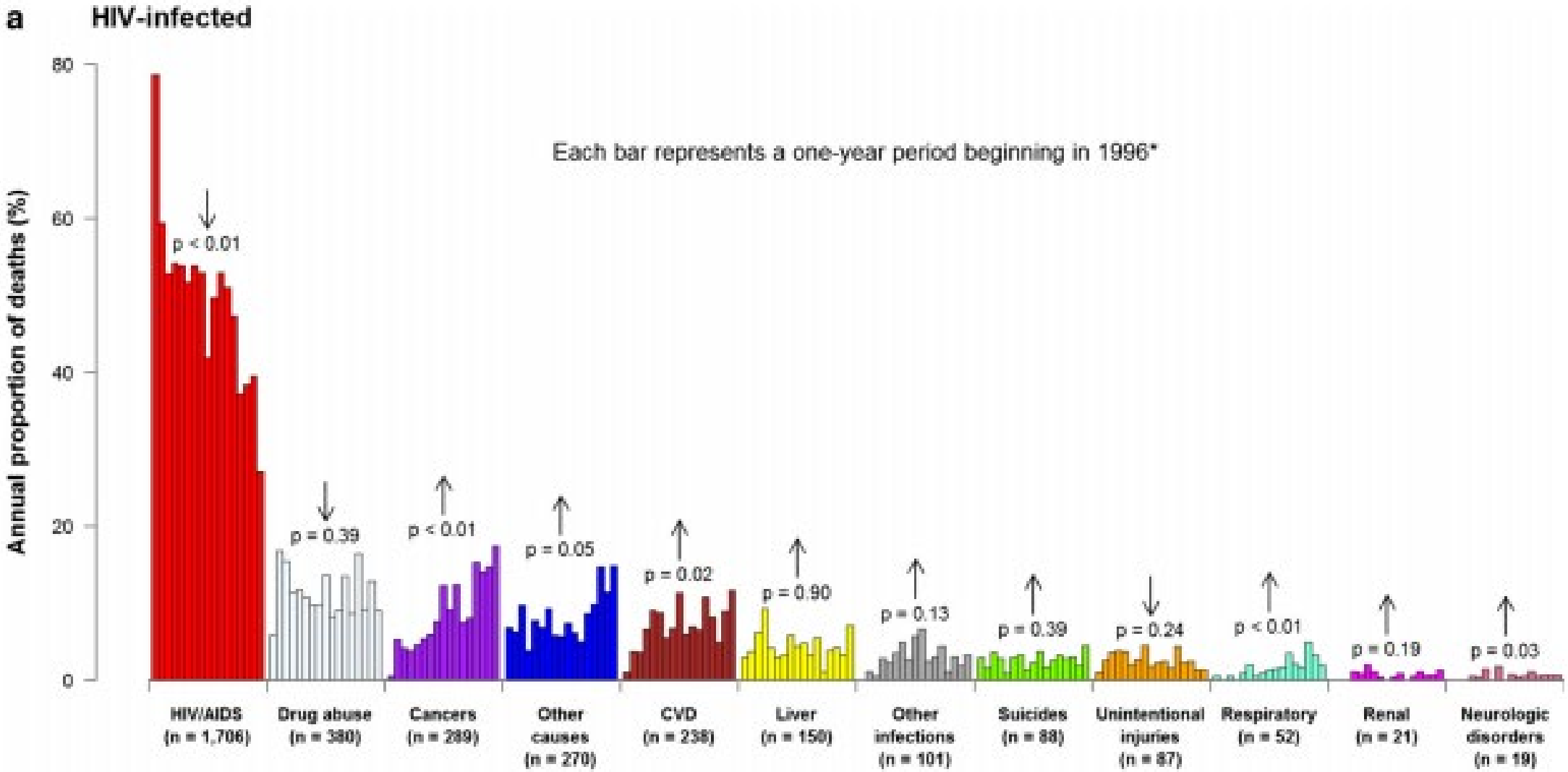
Eyawo et al COAST Study. 2017 17:174 DOI 100.1186/st12879-017-2254-7

Non-HIV Infected Causes of Mortality



Age at death*
83 (75-89)
74 (64-82)
81 (71-88)
85 (78-91)
81 (74-87)
86 (78-91)
65 (42-85)
62 (53-72)
85 (77-90)
49 (38-60)
47 (38-58)
NA

Eyawo et al COAST Study. 2017 17:174 DOI 100.1186/st12879-017-2254-7


a
HIV-infected
Each bar represents a one-year period beginning in 1996*
Annual proportion of deaths (%)
0
20
40
60
80
p < 0.01
p = 0.39
p < 0.01
p = 0.05
p = 0.02
p = 0.90
p = 0.13
p = 0.39
p = 0.24
p < 0.01
p = 0.19
p = 0.03
HIV/AIDS (n = 1,706)
Drug abuse (n = 380)
Cancers (n = 289)
Other causes (n = 270)
CVD (n = 238)
Liver (n = 150)
Other infections (n = 101)
Suicides (n = 88)
Unintentional injuries (n = 87)
Respiratory (n = 52)
Renal (n = 21)
Neurologic disorders (n = 19)

HIV and Cardiovascular Outcomes

	HIV-Infected Patients	Uninfected Controls
CVD hospitalization		
No. of Events	359	576
Person-years	33 394	97 449
IR (95% CI)*	10.8 (9.6–11.9)	5.9 (5.4–6.4)
Myocardial infarction		
No. of events	46	108
Person-years	33 873	98 135
IR (95% CI)*	1.4 (1.0–1.8)	1.1 (0.9–1.3)
Heart failure		
No. of events	116	107
Person-years	32 939	96 897
IR (95% CI)*	3.5 (2.9–4.2)	1.1 (0.9–1.3)
Stroke		
No. of events	46	47
Person-years	33 867	98 237
IR (95% CI)*	1.4 (1.0–1.8)	0.5 (0.3–0.6)
Peripheral artery disease		
No. of events	30	68
Person-years	33 304	96 942
IR (95% CI)*	0.9 (0.6–1.2)	0.7 (0.5–0.9)
Atrial fibrillation		
No. of events	116	281
Person-years	33 523	97 141
IR (95% CI)*	3.5 (2.8–4.1)	2.9 (2.6–3.2)

Alonso et al JAHA 2019;8:2012241

HIV and Diabetes Mellitus Type II

Table 1. Clinical characteristics of the 2005 and 2015 cohorts.

		2005 (n = 337)	2015 (n = 338)	*p*
GENDER	Male	77.2%	74.0%	0.335[a]
AGE (Years)	Median (IQR)	41 *(35–47)*	49 *(42–57)*	<0.001[b]
ETHNICITY	White	54.6%	49.7%	0.525[a]
	Black African	28.2%	31.7%	
	Black Caribbean	5.9%	7.7%	
	Other	11.3%	10.9%	
TYPE 2 DIABETES		6.8%	15.1%	0.003[a]
BMI (kg/m^2)	Median (IQR)	24.9 *(22.4–28.0)*	27.4 *(23.3–29.9)*	0.019[b]
WAIST (IDF DEFINITION)	Obese	47.7%	62.4%	0.024[a]
(cm)	Median (IQR)	91 *(83–98)*	95 *(86–104)*	0.055[b]
HYPERTENSION	%	19.6%	37.9%	<0.001[a]
LIPIDS (mmol/l)	Total Cholesterol (SD)	4.8 ±*1.0*	5.0 ±*1.1*	0.242[b]
	HDL: TG Ratio (SD)	1.59 ±*1.74*	1.39 ±*1.19*	0.180[b]
METABOLIC SYNDROME (IDF DEFINITION)	%	22.5%	31.8%	<0.001[b]
SMOKING	Current	35.6%	21.0%	0.019[a]
CARDIOVASCULAR DISEASE	(includes stroke)	2.7%	5.6%	0.055[a]
STATIN USE	Current	16.0%	27.2%	<0.001[a]
% 10-YEAR CVD RISK (Framingham)	Mean (SD)	4.4 ±*5.4*	12.1 ±*12.3*	<0.001[b]
HIV Duration (Years)	Mean (SD)	6.3 ±*0.9*	11.6 ±*0.9*	<0.001[b]
ANTIRETROVIRALS (ARVs)	Naïve	19.6%	8.0%	<0.001[a]
ARVs ASSOCIATED WITH T2D	Current or historic	23.4%	44.1%	<0.001[a]
LIPODYSTROPHY	Current or historic	27.3%	21.6%	0.007[a]
HEPATITIS B	Current	4.5%	9.2%	0.021[a]
HEPATITIS C	Current	3.6%	4.7%	0.433[a]

Duncan et al. Plos ONE 13(3):e0194199

Reviews/Commentaries/ADA Statements

Glucose Abnormalities in Patients with Hepatitis C Virus Infection

Epidemiology and pathogenesis

Albert Lecube, MD1, Cristina Hernández, MD1, Joan Genescà, MD2 and Rafael Simó, MD1

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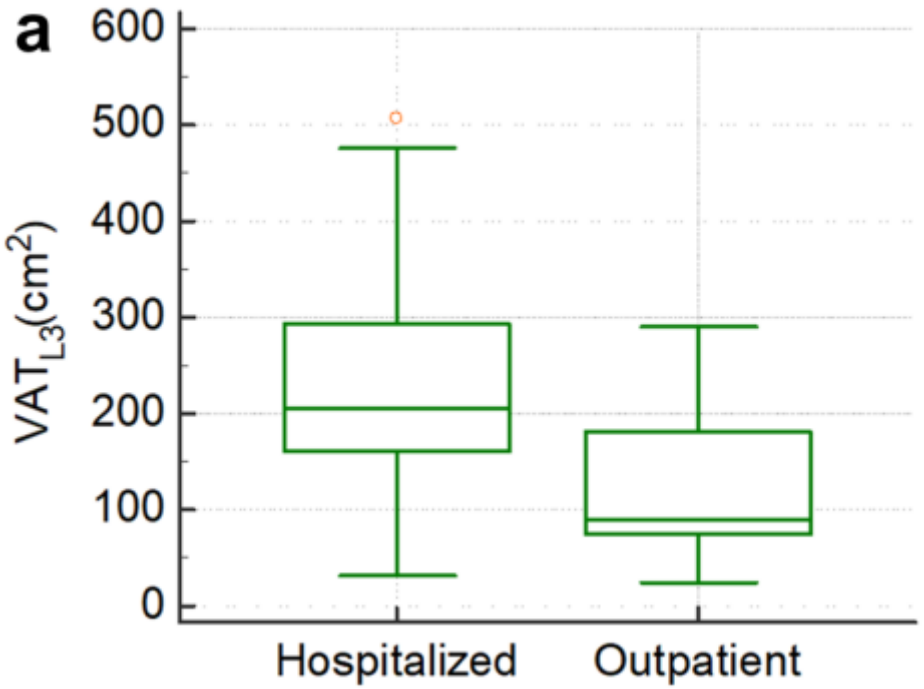
Visceral Abdominal Fat and COVID-19 Severity



- Previous studies have identified obesity as a risk factor for severity of COVID-19 symptoms, suggesting that body fat accumulation may be linked with greater infection severity and poor clinical outcomes.
- While these studies focus on BMI, an indirect marker of body fat, more recent studies had sought to differentiate the types of adipose tissue depots contributing to obesity.
- In a retrospective analysis assessing abdominal fat distribution in SARS-CoV-2- positive patients with different severity of COVID-19 infection, **higher VAT and VAT/TAT** were observed in COVID-19 patients that required hospitalized patients compared to outpatients ($p < 0.05$)[2].

1. Petrilli, et al Diabetes Care 2020 2. Chandarana, et al. Abdominal Radiology, 2020

Visceral fat associated with increased risk of ICU admission patients with COVID-19

- In a recent study of 144 hospitalized COVID-19 patients, abdominal fat distribution characterized **by increased visceral and lower subcutaneous fat increased the risk of ICU admission for COVID-19**, independent of BMI.
  - VAT thickness and VAT/SAT ratio were associated with increased risk of ICU[1] admission.
  - ICU-COVID-19 patients had 30% thicker visceral fat than nICU-COVID-19 and non-COVID-19 patients.
  - Subjects with COVID-19 had thicker VAT than subjects without COVID-19.
- Excess visceral adipose tissue (VAT) is a metabolically more active tissue that promotes hyper inflammation, potentially exacerbating disease severity.
- The direct role of adipose tissue in disease pathogenesis remains unclear, however additional research is needed to understand whether fat distribution can predict mortality in patients with COVID-19.

1. Battisti, et al. Diabetes Care 2020.

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- BIC/TAF/FTC **(AI)**
- DTG/ABC/3TC **(AI)—if HLA-B*5701 negative**
- DTG plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
- RAL plus (TAF or TDF)[a] plus (FTC or 3TC) (**BI** for TDF/[FTC or 3TC], **BII** for TAF/FTC)

INSTI plus 1 NRTI:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

Clinical Infectious Diseases

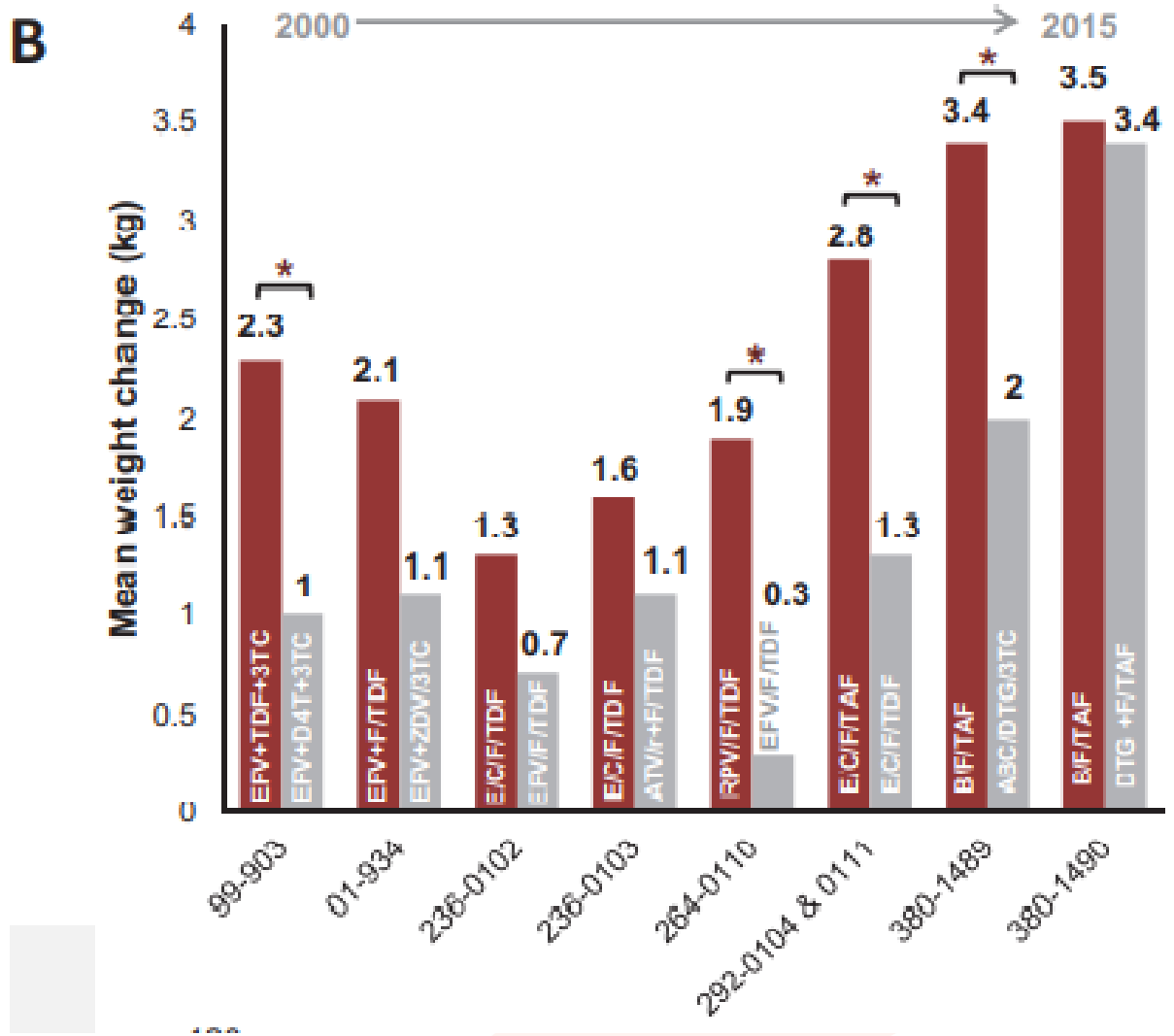
MAJOR ARTICLE

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

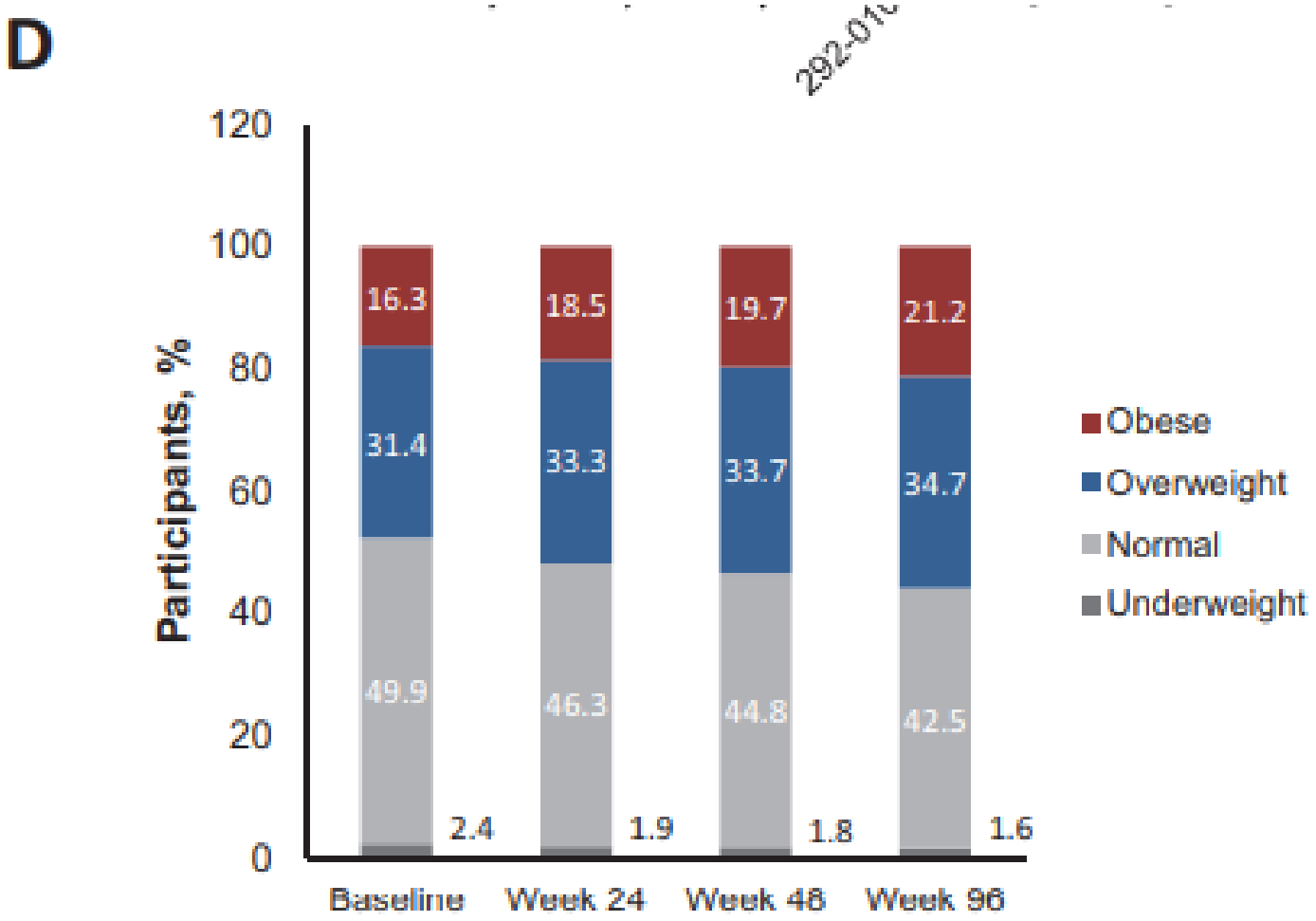
Paul E. Sax,[1] Kristine M. Erlandson,[2] Jordan E. Lake,[3] Grace A. McComsey,[4] Chloe Orkin,[5] Stefan Esser,[6] Todd T. Brown,[7] Jürgen K. Rockstroh,[8] Xuelian Wei,[9] Christoph C. Carter,[9] Lijie Zhong,[9] Diana M. Brainard,[9] Kathleen Melbourne,[9] Moupali Das,[9] Hans-Jürgen Stellbrink,[10] Frank A. Post,[11] Laura Waters,[12] and John R. Koethe[13]

Methods

- Pooled analysis of 8 Gilead Sciences-sponsored trials of participants initiating ART (2003 – 2015) that satisfied the selection criteria:
  - Phase 3 stage
  - Active-controlled design
  - Enrollment of treatment naïve participants
  - Follow up duration of 96 weeks



Mean weight change observed at the 48-week time point for the indicated trials, which are organized by date of initiation.



Body mass index category distributions over time in 8 pooled clinical trials

Table 3. Risk Factors for Any Weight Gain in Individuals Initiating Antiretroviral Therapy

Variable	Difference, kg	(95% CI)	*P* Value
CD4 count (<200 vs ≥200 cells/μL)	2.97	(2.81–3.13)	<.001
IV drug use (no vs yes)	1.41	(.97–1.85)	<.001
Race (black vs non-black)	0.99	(.87–1.11)	<.001
HIV RNA (>100K vs ≤100K copies/mL)	0.96	(.84–1.08)	<.001
Symptomatic HIV (yes vs no)	0.51	(.36–.65)	<.001
Sex (female vs male)	0.23	(.07–.4)	.006
Age (<50 vs ≥50 y)	0.22	(.07–.37)	.004
BMI			
Obese vs normal	0.21	(.06–.36)	.005
Overweight vs normal	0.24	(−.36 to −.13)	<.001

Stepwise model selection was used to identify baseline risk factors associated with weight gain in individuals initiating antiretroviral therapy, resulting in the inclusion of the above 8 baseline risk factors in the mixed-effect model. Difference, 95% CI, and *P* values were determined from the mixed-effect model including these 8 baseline risk factors and visit as fixed effects and participants as a random effect.

Abbreviations: BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; IV, intravenous.

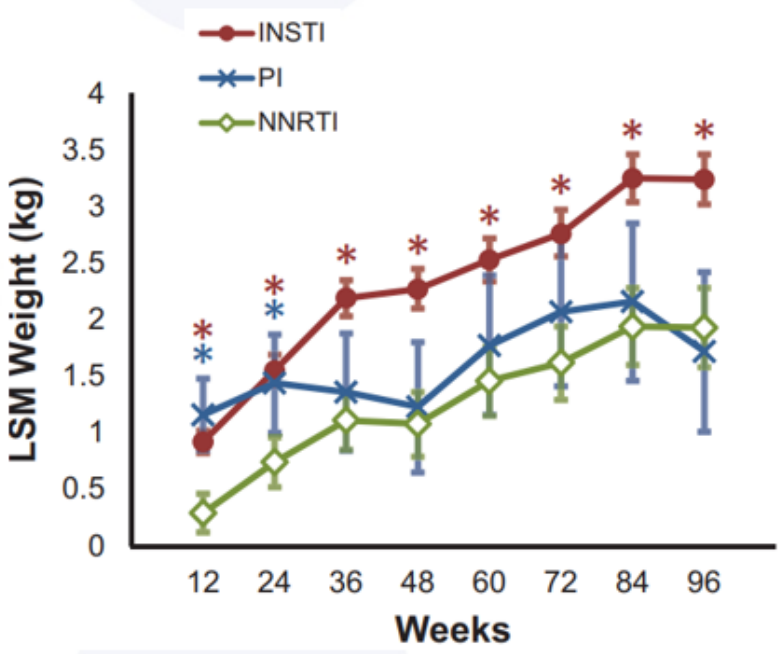
Table 5. Risk Factors for Significant (≥10%) Weight Gain in Individuals Initiating Antiretroviral Therapy

Variable	OR	(95% CI)	*P* Value
CD4 count (<200 vs ≥200 cells/all)	4.36	(3.6–5.27)	<.001
HIV RNA (>100K vs ≤100K copies/mL)	1.98	(1.65–2.37)	<.001
BMI			
Normal vs overweight	1.54	(1.27–1.87)	<.001
Normal vs obese	1.66	(1.29–2.15)	<.001
Sex (female vs male)	1.54	(1.21–1.96)	<.001
Race (black vs non-black)	1.32	(1.10–1.59)	.003
Third ART agent			
BIC/DTG vs EFV	1.82	(1.24–2.66)	.002
EVG/c vs EFV	1.36	(1.04–1.78)	.026
RPV vs EFV	1.51	(1.03–2.20)	.035
ATV/r vs EFV	0.92	(.59–1.45)	.73
NRTI			
TAF vs ZDV	1.75	(1.04–2.95)	.034
TDF vs ZDV	1.19	(.76–1.87)	.44
ABC vs ZDV	0.93	(.47–1.8)	.82
TAF vs ABC	1.9	(1.25–2.88)	.003
TDF vs ABC	1.29	(.79–2.11)	.31
TAF vs TDF	1.47	(1.14–1.90)	.003

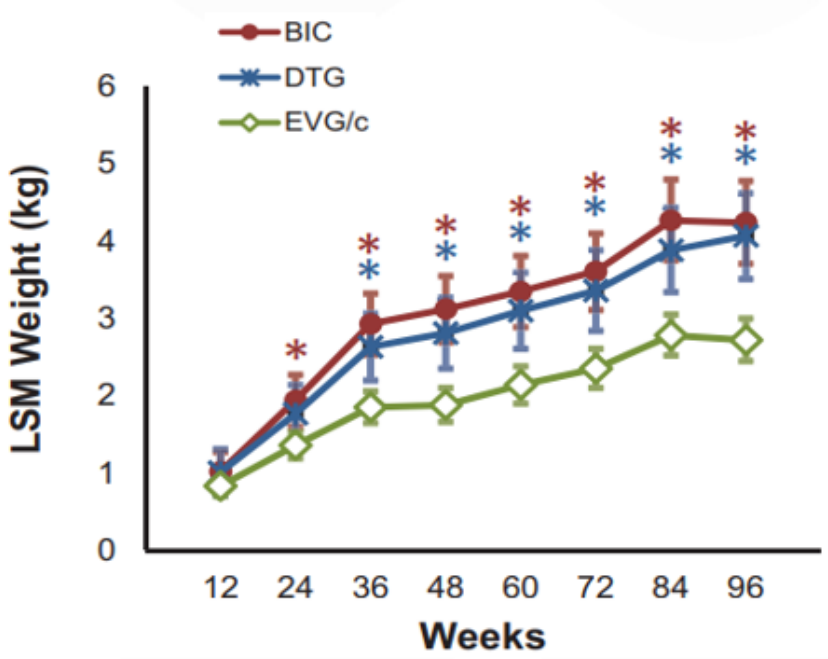
Evidence of Weight Gain in PWH initiating ART

8 randomized phase III clinical trials of treatment-naïve PWH initiating ART

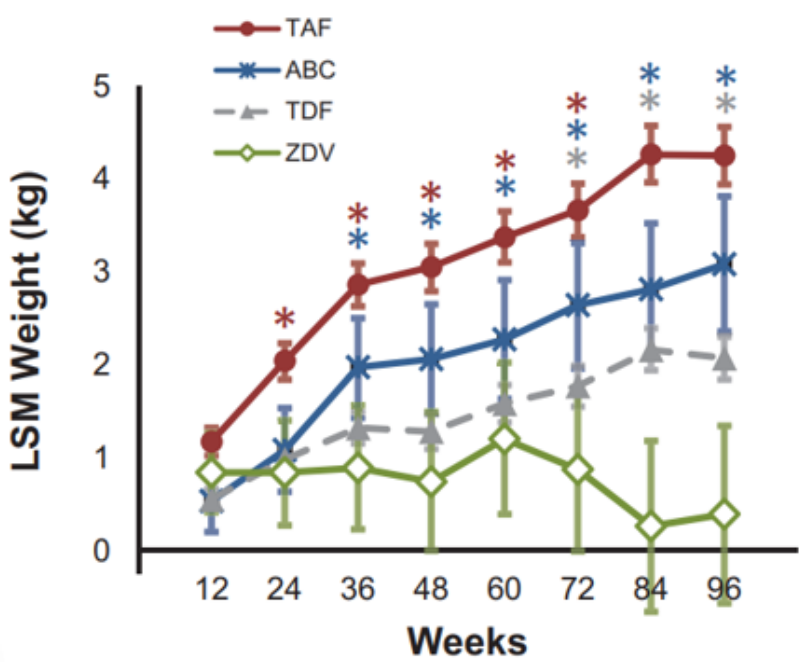
Stratified by 3rd Agent Class



Stratified by INSTI



Stratified by NRTI

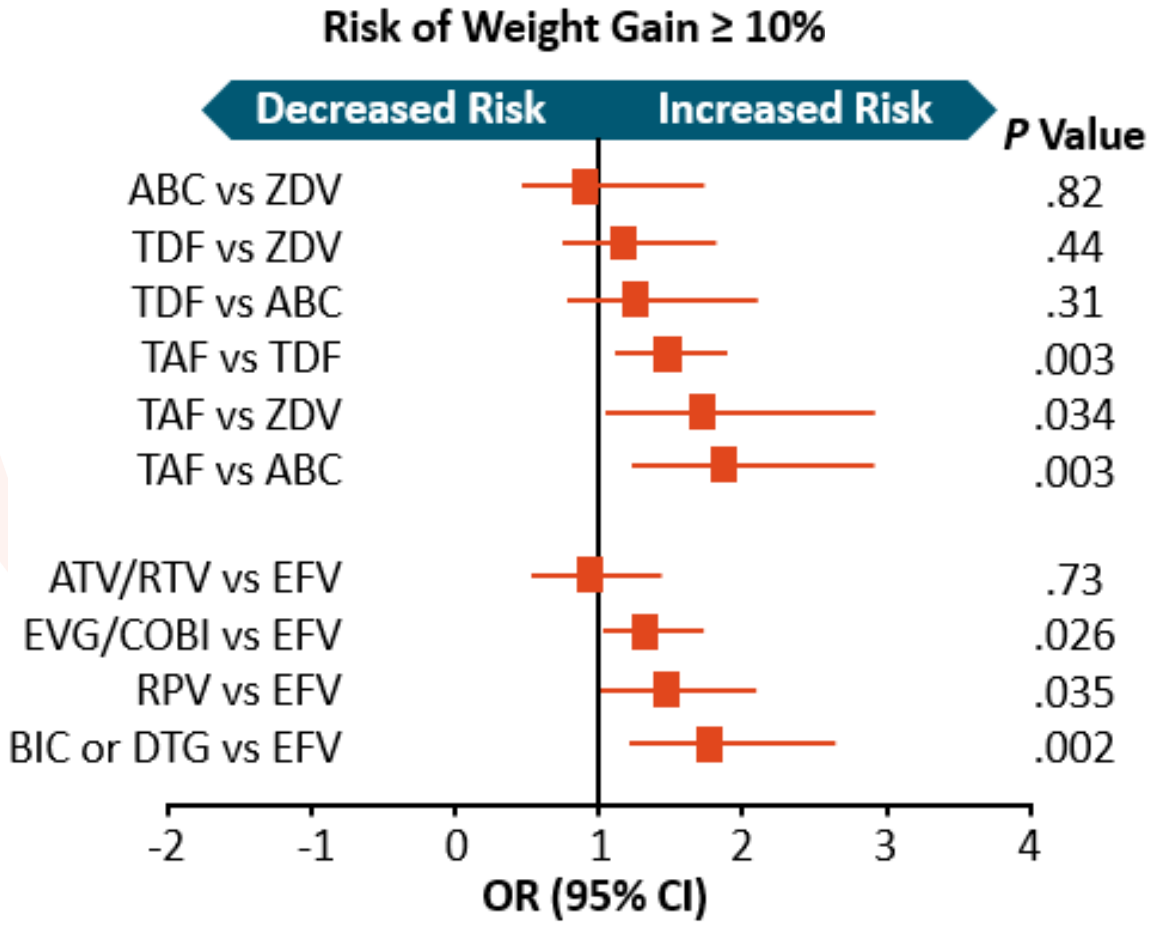


- TAF was associated with greater weight gain at 96 weeks compared to any other NRTI (ABC, ZDV $p < 0.001$, TDF $p = 0.001$).
- Similar weight gain among PWH initiating INSTIs bictegravir or dolutegravir

3. Sax, et al. CID 2020

Association between ARVs and weight gain

INSTIs and TAF Associated with Greater Weight Gain vs. Other ARVs



Risk Factors for Significant (≥10%) Weight Gain in Individuals Initiating Antiretroviral Therapy

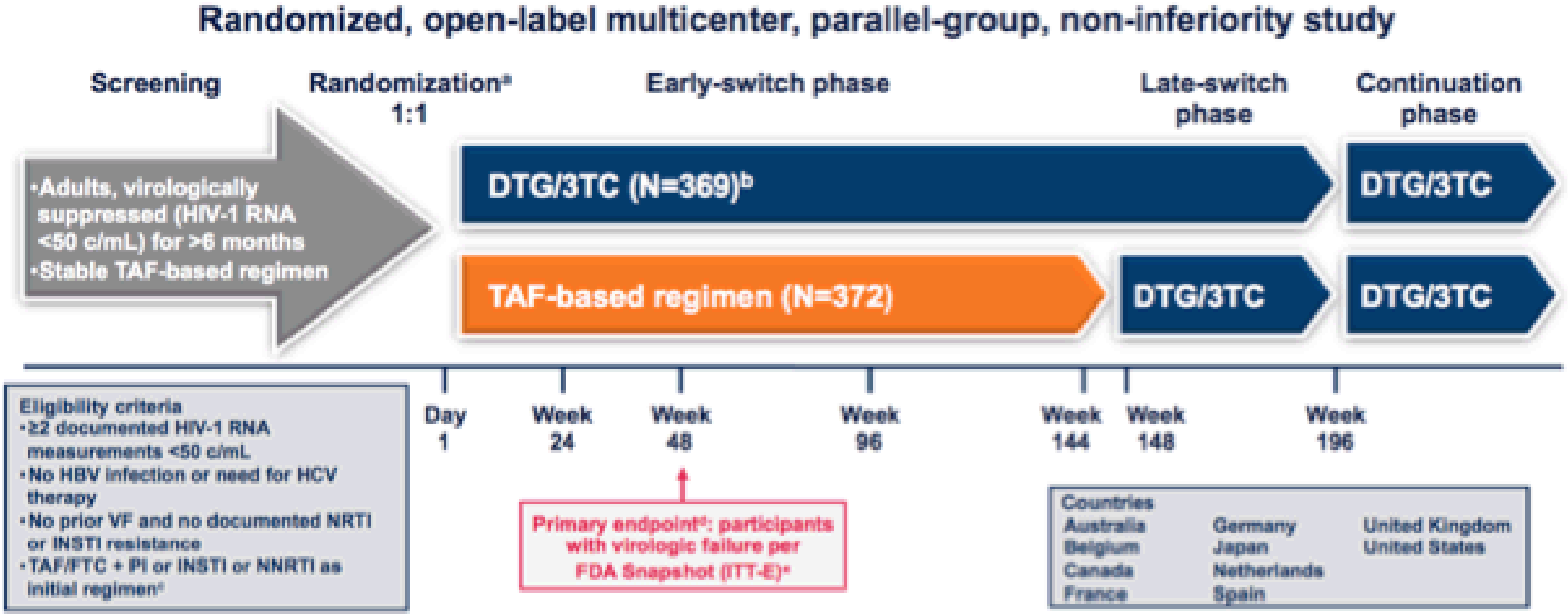
- **NRTIs:** TAF was associated with an increased risk of ≥10% weight gain compared to ABC, TDF and ZDV
- **3rd Agent:** Compared to EFV, the initiation of BIC or DTG, EVG/c and RPV was associated with an increased risk of ≥10% weight gain

3. Sax, et al. CID 2020

DISCOVER – TAF for PREP

- Phase 3 , blinded trial to look at the safety and efficacy of PReP with TAF vs TDF
- Emtricitabine and tenofovir alafenamide was associated with weight gain when compared with emtricitabine and tenofovir disoproxil fumarate (mean 1·2 kg difference in bodyweight change between groups at week 48)

TANGO Phase III Study Design



van Wyk et al. *Clin Infect Dis*. 2020 [Epub ahead of print].

[a]Stratified by baseline third agent class (PI, INSTI, or NNRTI). [b]Two participants excluded who were randomized but not exposed to study drug. [c]Participants with initial TDF treatment who switched to TAF ≥3 months before screening, with no changes to other drugs in their regimen, were also eligible. [d]4% non-inferiority margin. [e]Includes participants who changed a background therapy component or discontinued study treatment for lack of efficacy before Week 48, or who had HIV-1 RNA ≥50 c/mL in the 48-week window.

Weight Changes From Baseline at Week 48 Were Small and Comparable Between Treatment Groups

- Adjusted[a] mean (SE) change from baseline in weight (kg) in the DTG/3TC and TAF-based regimen arms, respectively, was 0.81 (0.27) and 0.88 (0.25) in the boosted subgroup and 0.81 (0.45) and 0.40 (0.44) in the unboosted subgroup

Weight parameter	DTG/3TC (N=343)	TAF-based regimen (N=343)
Adjusted[b] change from baseline, mean (SE), kg	0.81 (0.23)	0.76 (0.22)
Prior TAF duration <1 y[c]	1.45 (0.46)	1.35 (0.47)
Prior TAF duration ≥1 y[d]	0.60 (0.26)	0.60 (0.25)
Increased from baseline, n (%)		
≥10%	11 (3)	13 (4)

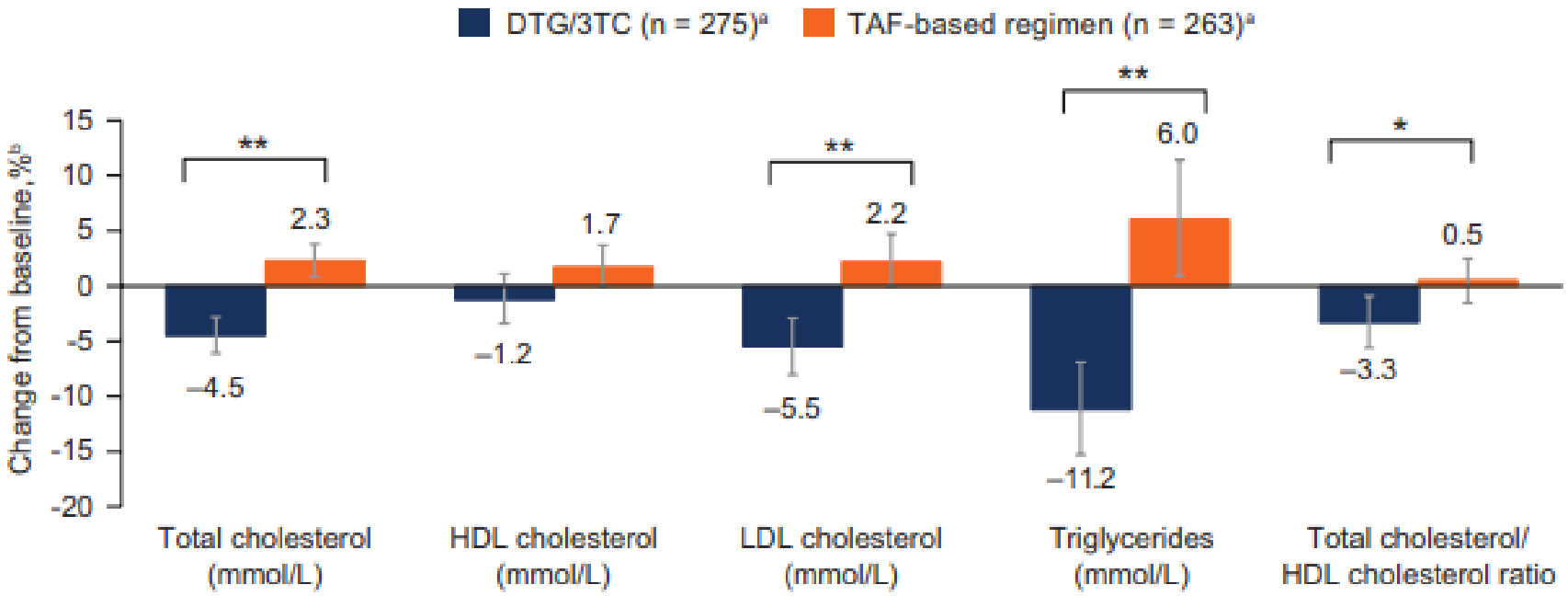


Figure 6. Change from baseline in serum or plasma lipids at week 48. [a]n = number of participants with nonmissing fasting lipid data at baseline and week 48, removing those with lipid-modifying agent administered at baseline (lipid data collected after initiation of a lipid-modifying agent were censored and a last observation carried forward method was applied so that the last available fasted, on-treatment lipid value before initiation of a lipid-modifying agent was used). [b]Percent change from baseline based on adjusted ratio (week 48 to baseline) in each group calculated from a repeated measures model applied to change from baseline in $\log_e$-transformed data adjusting for the following: treatment, visit, baseline third agent class, CD4+ cell count (continuous), $\log_e$-transformed baseline value (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor. *P = .017. **P < .001. Abbreviations: 3TC, lamivudine; DTG, dolutegravir; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TAF, tenofovir alafenamide.

Risk Factors and Metabolic Implications of Integrase Inhibitor Associated Weight Gain

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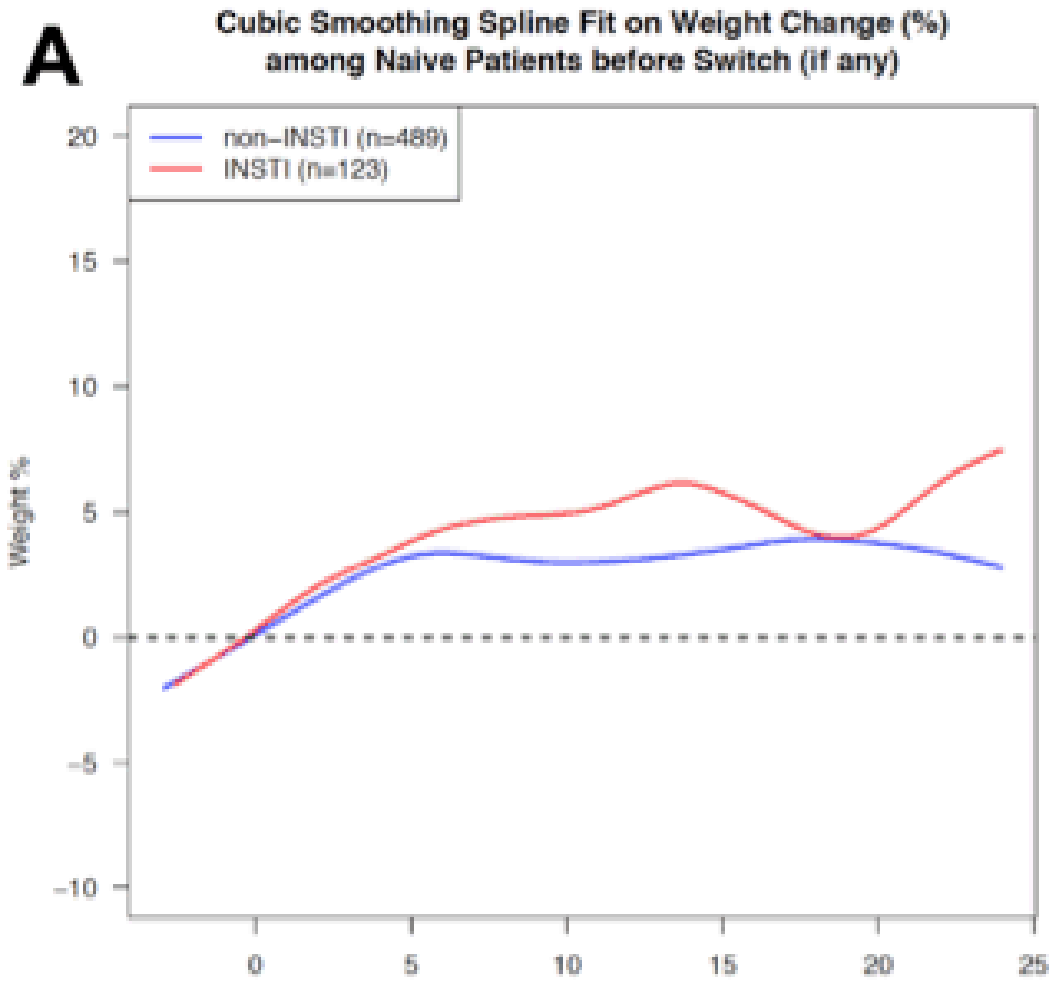
1. Cohort baseline characteristics of ART-naïve patients

	Median (IQR / %)			
	Total (N=612)	non-INSTIs (N=489)	INSTIs (N=123)	P-value[1]
Age	41.56 (32.8-49.7)	41.79 (33.0-49.5)	39.23 (32.3-51.1)	0.7
Sex: Female	237 (38.7%)	195 (39.9%)	42 (34.1%)	0.3
Race: White	119 (19.4%)	90 (18.4%)	29 (23.6%)	
Race: Black/African American	339 (55.4%)	276 (56.4%)	63 (51.2%)	0.6
Race: Asian	10 (1.6%)	8 (1.6%)	2 (1.6%)	
Ethnicity: Hispanic or Latino	121 (19.7%)	99 (20.1%)	22 (17.9%)	0.7
Year of ARV initiation	2011 (2009-2013)	2010 (2009-2012)	2015 (2014-2016)	<0.001
INSTI agent at ARV initiation				
Raltegravir			30 (24.4%)	
Dolutegravir			78 (63.4%)	
Elvitegravir			15 (12.2%)	
Weight (lbs)	164.95 (143.7-186)	165 (145-185.8)	164.02 (141-187.4)	0.7
BMI	25.55 (22.9-28.9)	25.57 (23.0-29.0)	25.54 (22.7-28.6)	0.8
HbA1C (%)	5.65 (5.5-6.1)	5.8 (5.5-6.2)	5.35 (5.1-5.6)	0.1
HIV Viral Load (copies/mL)	0 (0-4300.8)	0 (0-1629)	185 (0-19771)	0.4
CD4 Count (cells/mL)	352 (179-523)	354 (210-516.5)	337 (33-580)	0.7

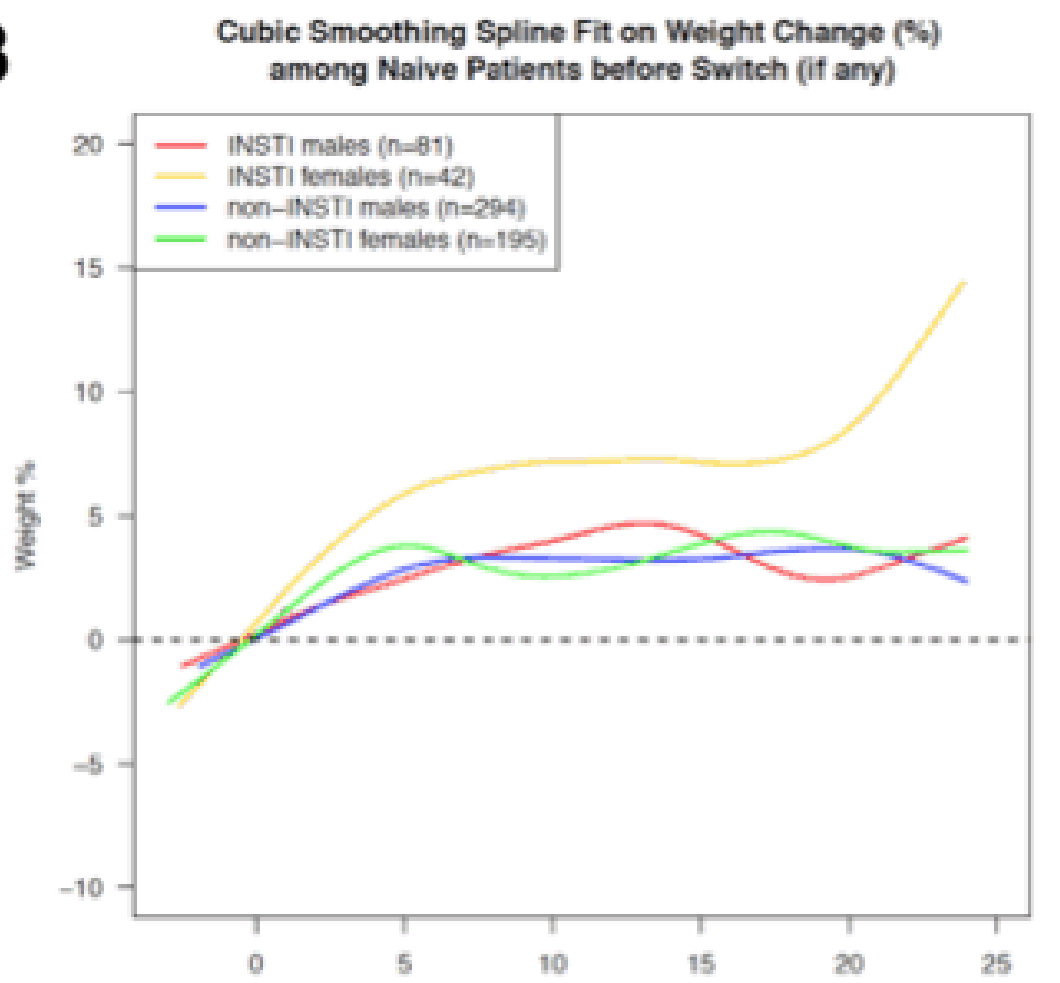
[1]P-value for continuous variables were obtained using two-sample Student t-test; p-value for categorical variable obtained using two-sided Fisher's exact test

2. Percent weight gain in first 24-months post-ART initiation by ART type alone (A) and by gender (B)

A



B

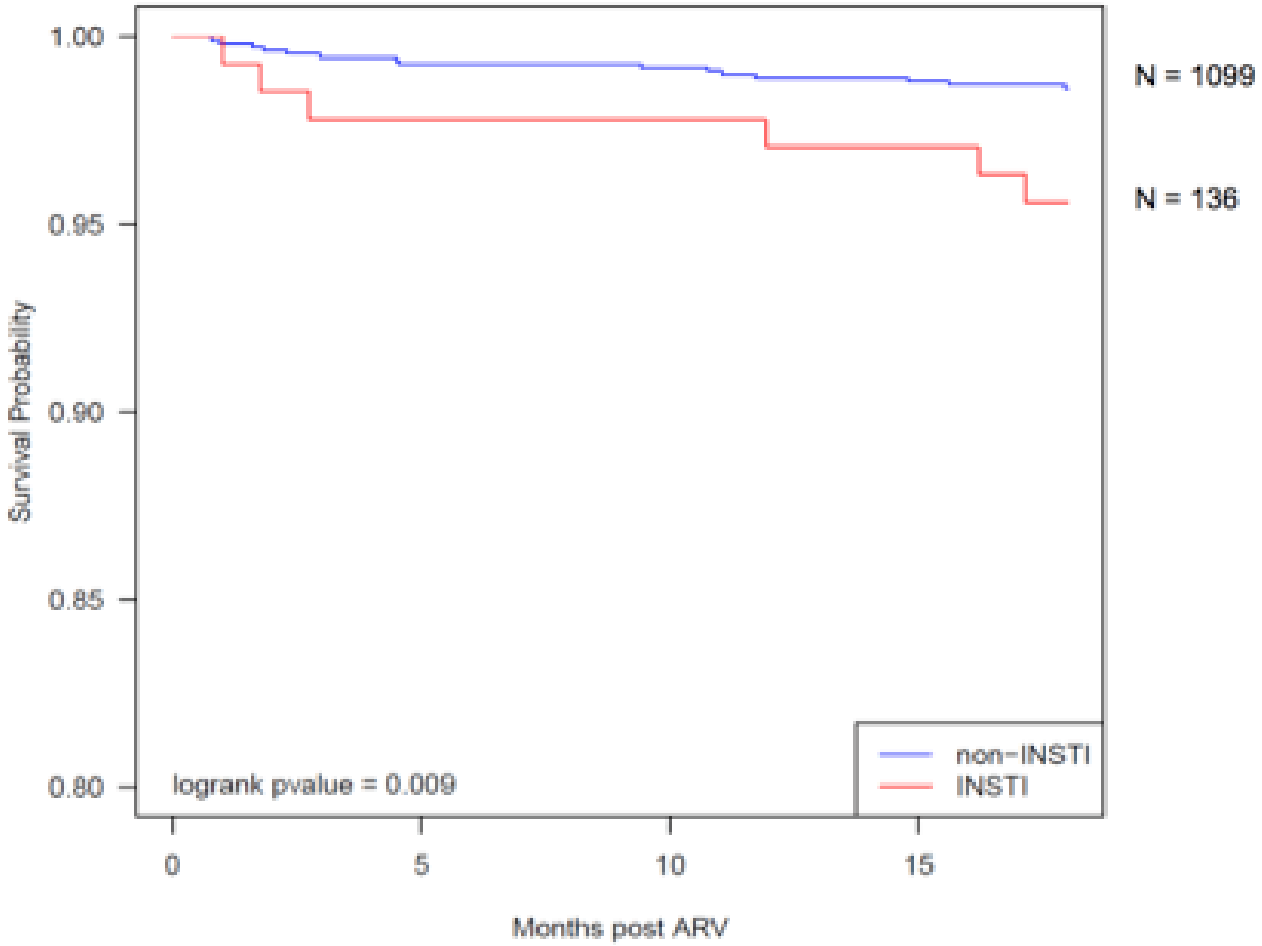


3. Adjusted multivariable analysis of 24-month weight gain due to InSTIs

Cohort Characteristic	Weight Gain (%)	95% Confidence Interval
Males		
White	1.68	-3.88, 7.24
Non-white	2.08	-2.52, 6.68
Females		
White	10.62	2.83, 18.41
Non-white	11.02	5.17, 16.88

*INSTI effect after adjusting ARV initiation year, age at baseline, ethnicity, NRTI, CD4 and viral load at baseline.

4. Incidence of Diabetes Diagnosis (ICD code) by type of ART in first 18 months post-initiation



Conclusions

- HIV care paradigms have shifted over time
- Long term side effects of ARVs should be a part of regimen choice