NUH HIV PROGRAMME

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HIV and metabolic disease

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Singapore

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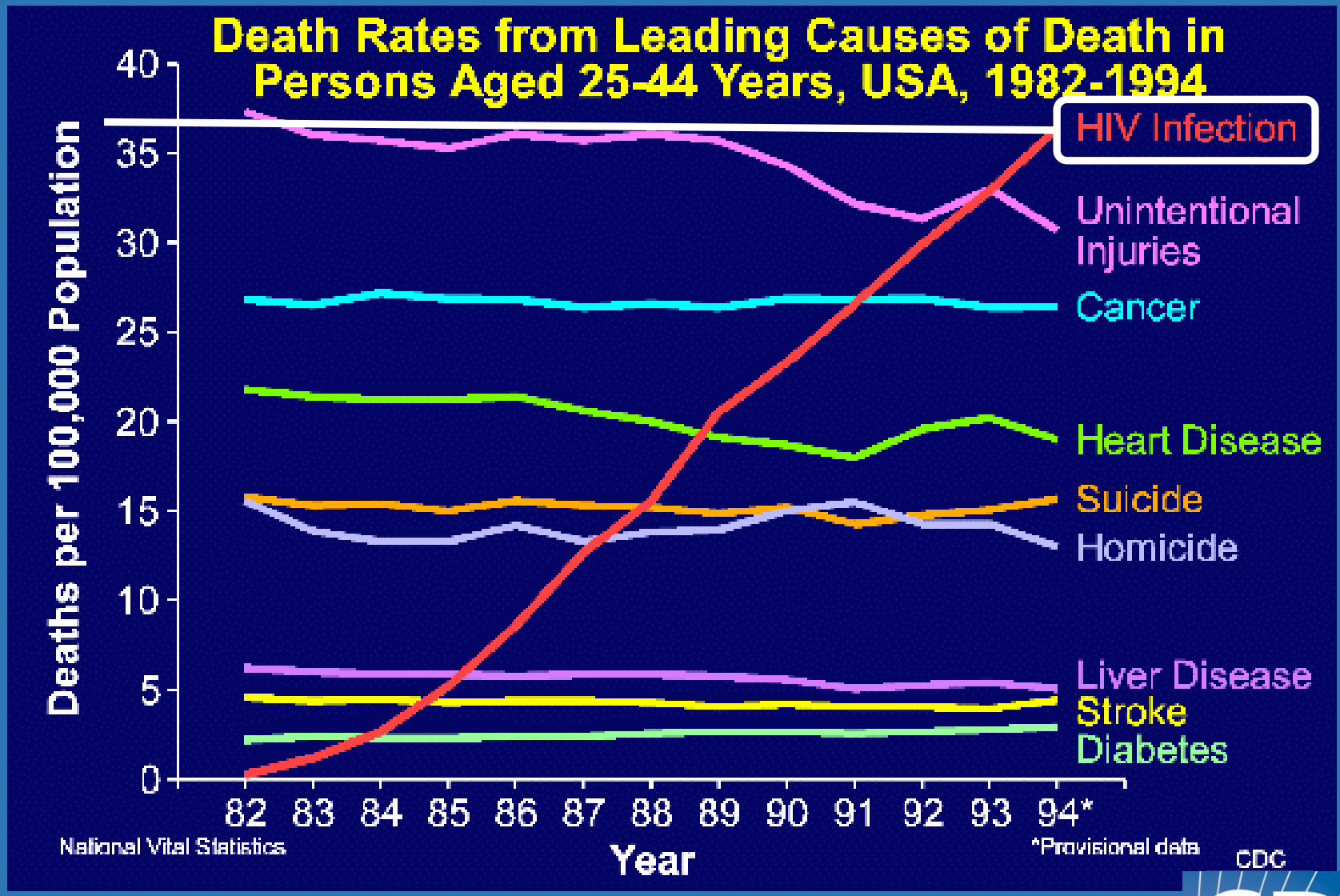
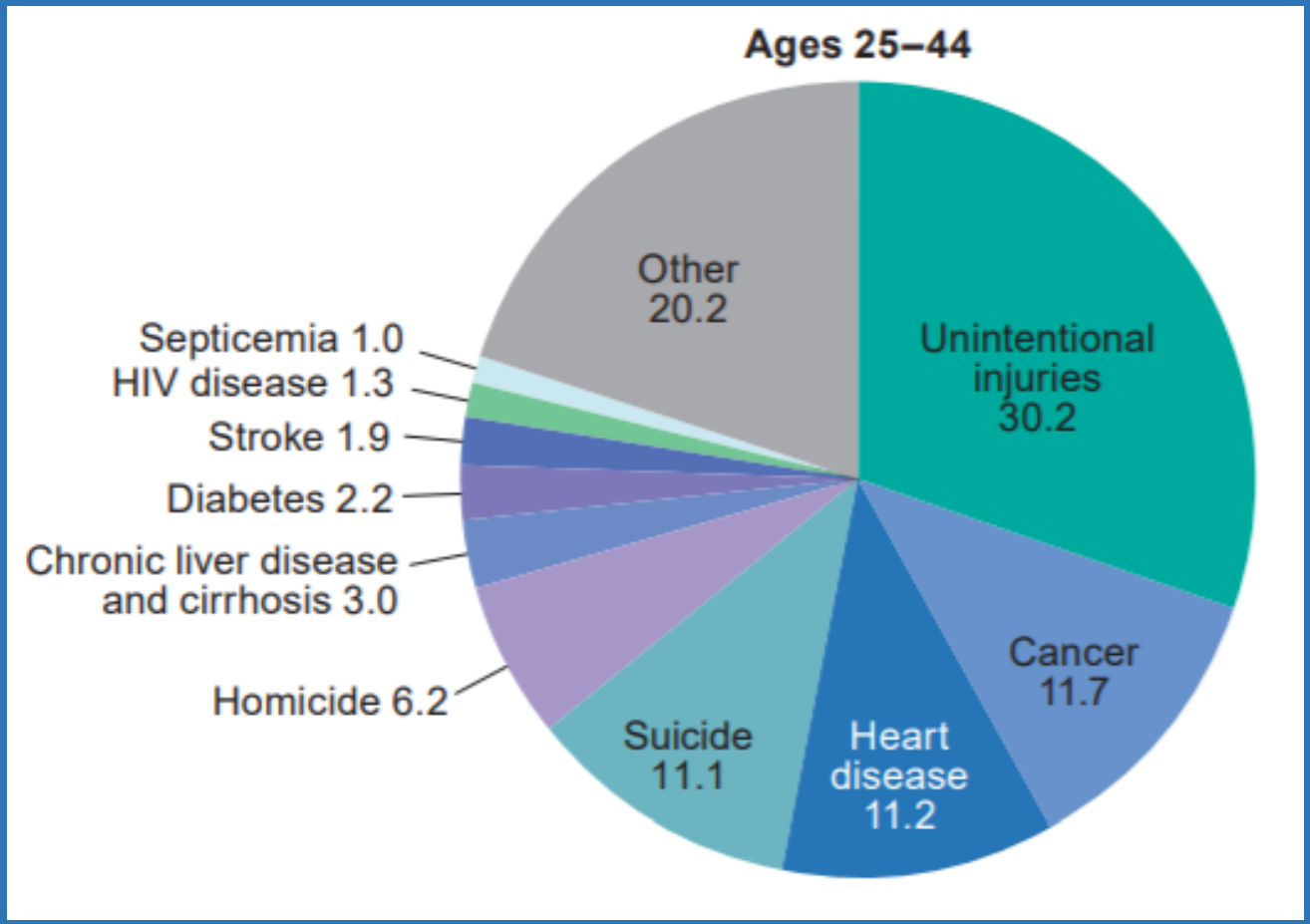
Disclosures

Travel and subsistence fees from:
World Health Organization (WHO)
Janssen / Johnson & Johnson

Introduction


Death Rates from Leading Causes of Death in Persons Aged 25-44 Years, USA, 1982-1994
Deaths per 100,000 Population
40
35
30
25
20
15
10
5
0
82 83 84 85 86 87 88 89 90 91 92 93 94*
Year
National Vital Statistics
*Provisional data
CDC
HIV Infection
Unintentional Injuries
Cancer
Heart Disease
Suicide
Homicide
Liver Disease
Stroke
Diabetes

Percentage distribution of 10 leading causes of death in the United States in 2015



Impact on life expectancy of HIV-1 positive individuals of $CD4^+$ cell count and viral load response to antiretroviral therapy

Margaret T. May[a], Mark Gompels[b], Valerie Delpech[c], Kholoud Porter[d], Chloe Orkin[e], Stephen Kegg[f], Phillip Hay[g], Margaret Johnson[h], Adrian Palfreeman[i], Richard Gilson[j], David Chadwick[k], Fabiola Martin[l], Teresa Hill[m], John Walsh[n], Frank Post[o], Martin Fisher[p], Jonathan Ainsworth[q], Sophie Jose[m], Clifford Leen[r], Mark Nelson[s], Jane Anderson[t], Caroline Sabin[m], for the UK Collaborative HIV Cohort (UK CHIC) Study

2014

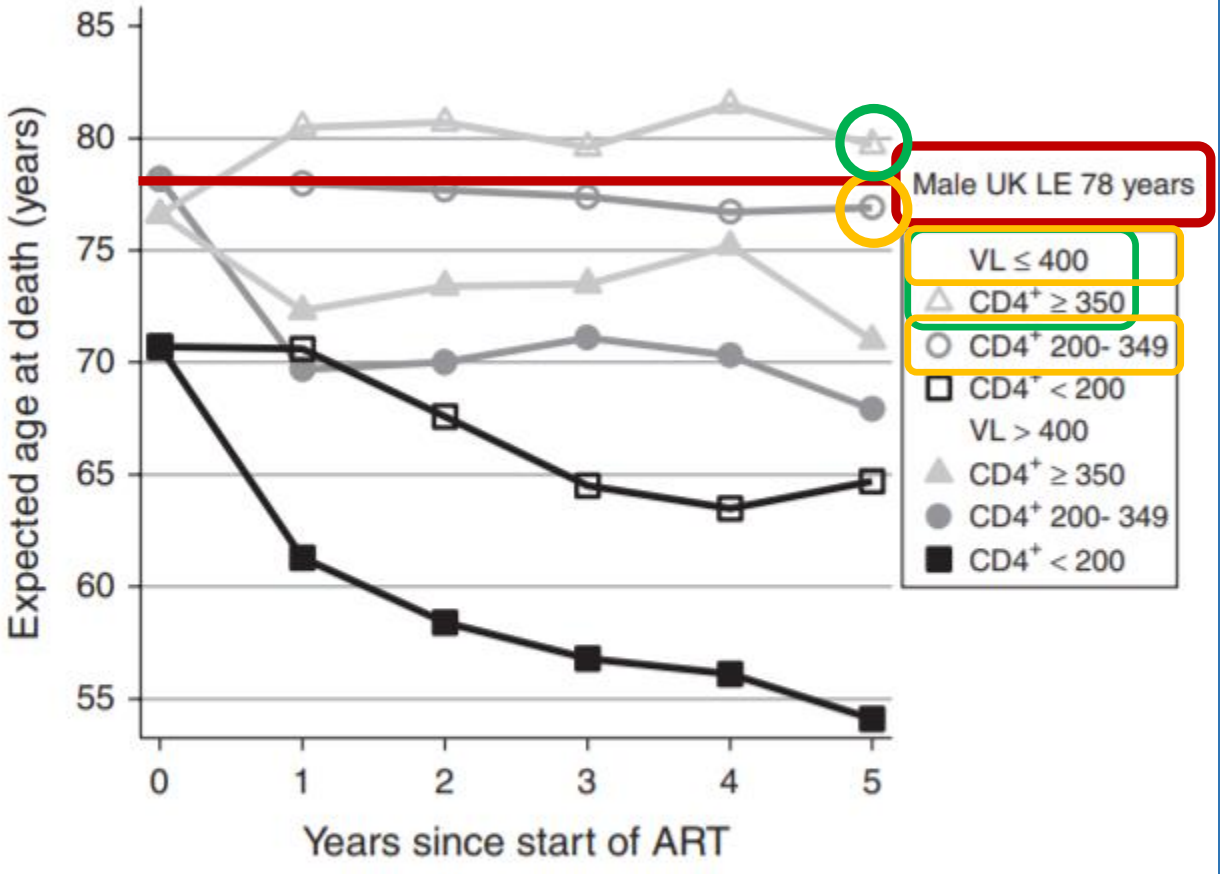


Fig. 1. Expected age at death of men aged 35 years at different durations of antiretroviral therapy according to current $CD4^+$ cell count and viral suppression compared with the general population.

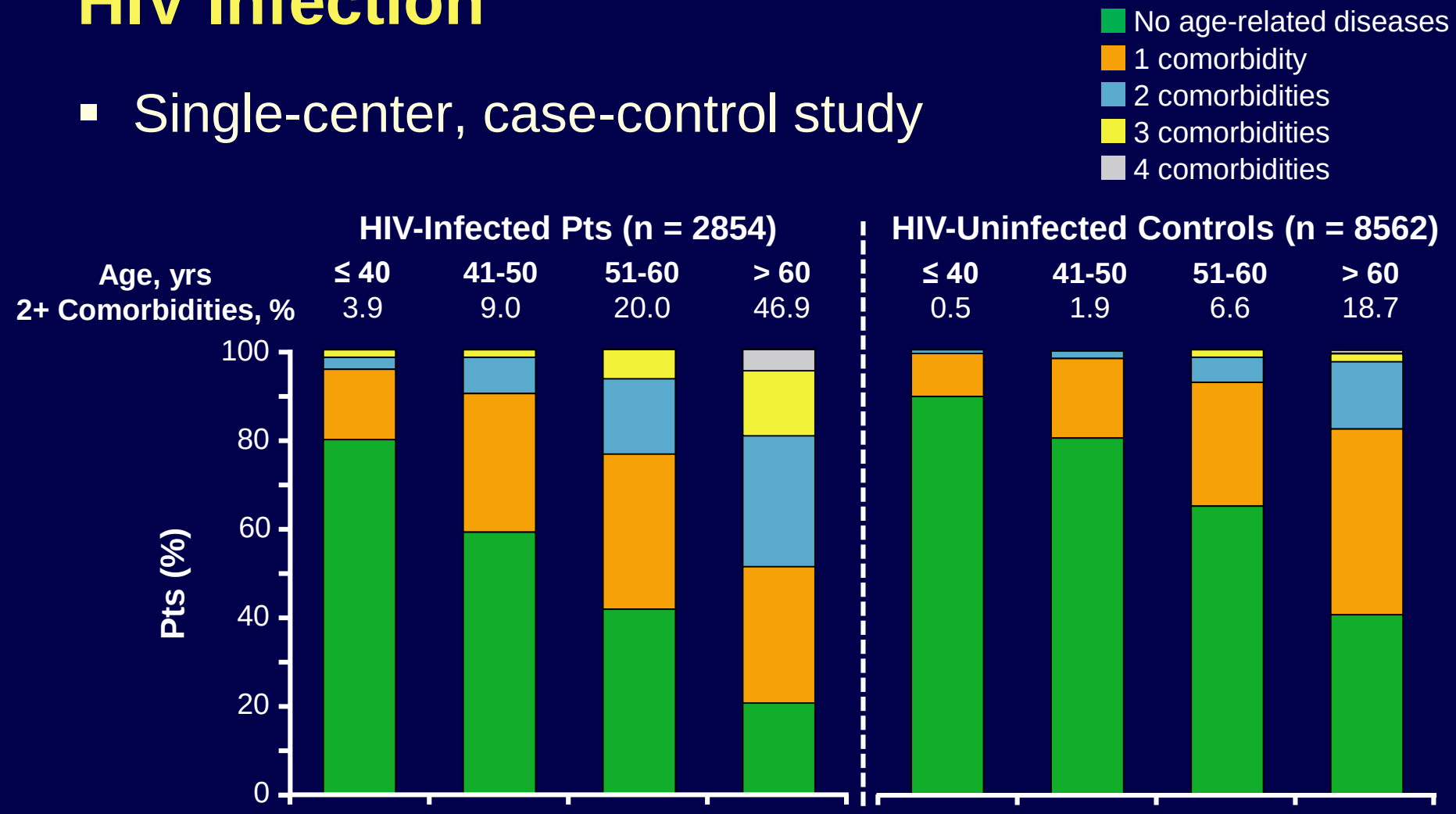
AIDS

Volume 26 Number 1 http://www.AIDSonline.com

UK CHIC Study, *2014*

Comorbidities Increase With Age and With HIV Infection

- Single-center, case-control study

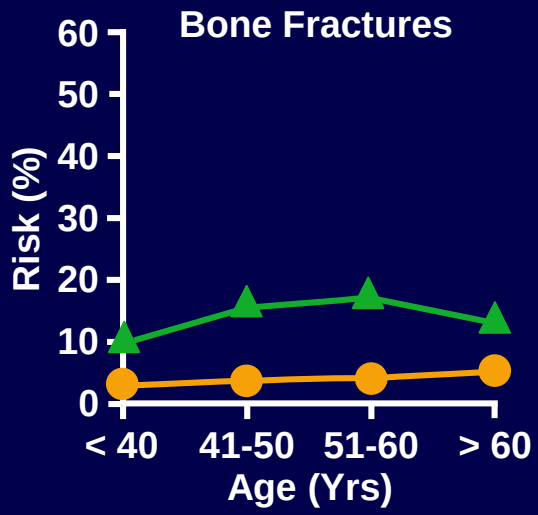


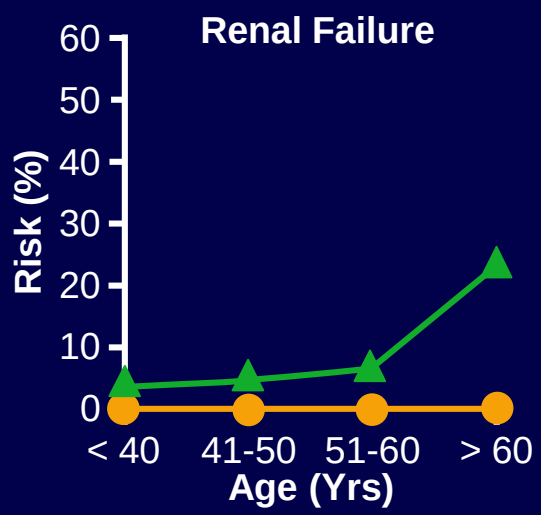
*Comorbidites: bone fractures, CVD, diabetes, HTN, hypothyroidism.

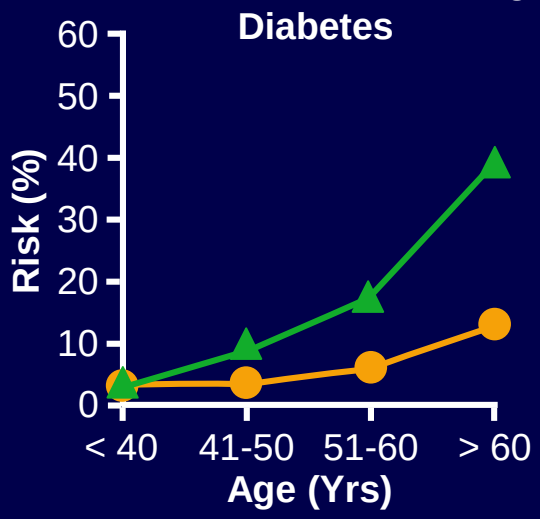
Guaraldi G, et al. Clin Infect Dis. 2011;53:1120-1126.

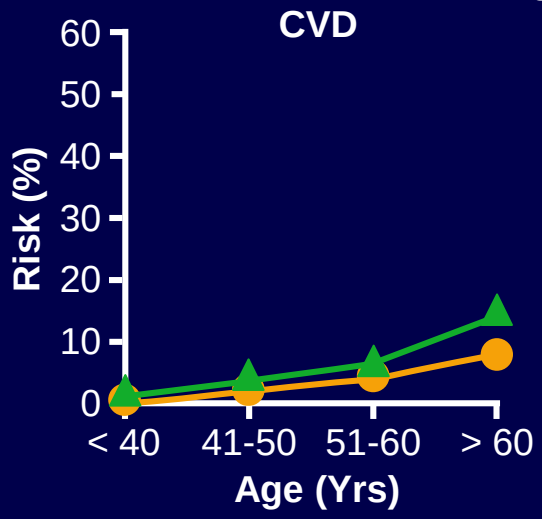
Slide credit: clinicaloptions.com

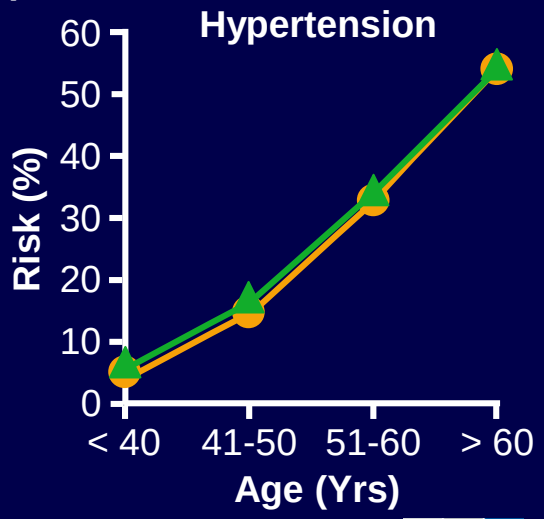
HIV Pts More Likely to Experience Bone Fractures, CVD, Diabetes, Renal Failure











Guaraldi G, et al. Clinicoecon Outcomes Res. 2013;5:481-488.

Slide credit: clinicaloptions.com

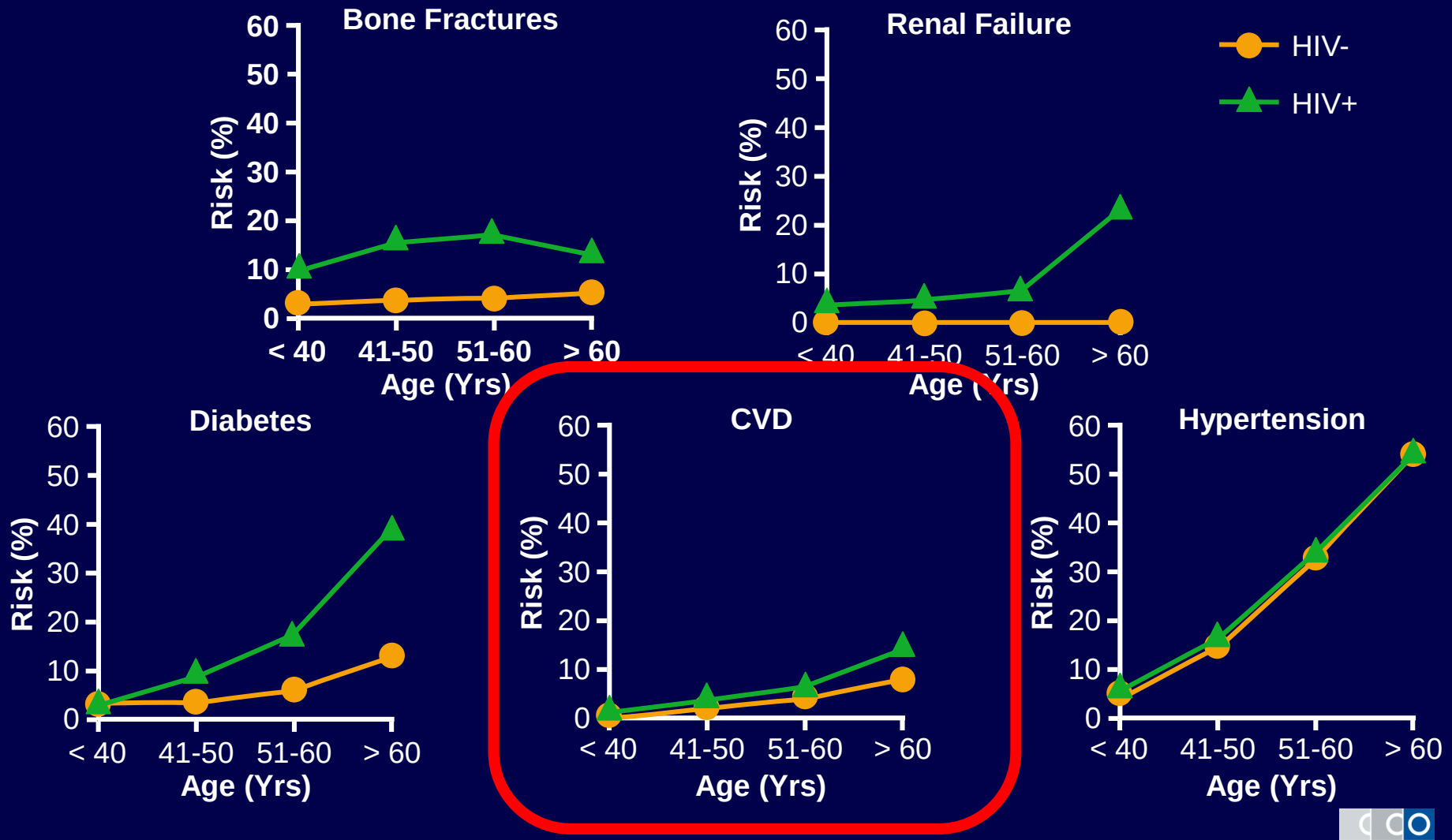
HIV care providers should be managing chronic conditions of their HIV patients.

Outline:

- cardiovascular disease and HIV/ART
- effects of ART on lipids / dyslipidemia
- prevention of CVD in PLHIVs
- hypertension
- DM / insulin resistance
- lactic acidosis
- HIV and bone health
- lipodystrophy

Cardiovascular Disease (CVD) and HIV

HIV Pts More Likely to Experience Bone Fractures, CVD, Diabetes, Renal Failure



Guaraldi G, et al. Clinicoecon Outcomes Res. 2013;5:481-488.

Slide credit: clinicaloptions.com

HIV and CVD

Most observational and retrospective data show that HIV infection is associated with an

- increase in CVD events
- accelerated atherosclerosis

Mechanisms are unclear, but likely related to ongoing inflammation mediated by HIV infection.

ART has also been associated with an increased risk of CVD

- cumulative exposure to LPV/r was associated with increased risk of MI after adjustment for lipids and other risk factors

Effect of CD4 count and viral load on CVD

CD4 count / HIV viral load and CVD

- Data are not consistent
- Most data suggest that lower CD4 count and higher viral loads are associated with higher CVD risk

JAIDS
JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROME

Immunodeficiency and Risk of Myocardial Infarction Among HIV-Positive Individuals With Access to Care

Silverberg, Michael J. PhD, MPH[*]; Leyden, Wendy A. MPH[*]; Xu, Lanfang MS[†]; Horberg, Michael A. MD, MAS[‡]; Chao, Chun R. PhD[†]; Towner, William J. MD[§]; Hurley, Leo B. MPH[*]; Quesenberry, Charles P. Jr PhD[*]; Klein, Daniel B. MD[‖]

TABLE 3. Risk Factors for MI Among HIV+ Subjects

	RR*	95% CI	*P*
Prior ART	1.26	0.83 to 1.91	0.28
Recent CD4 (per 100 cells/μL)	1.03	0.97 to 1.10	0.30
Nadir CD4 (per 100 cells/μL)	0.88	0.81 to 0.96	0.006
Recent HIV RNA (per 1 log)	1.03	0.97 to 1.08	0.38
HIV risk			
IDU vs. MSM	0.68	0.36 to 1.31	0.25
Heterosexual vs. MSM	1.28	0.85 to 1.91	0.23
Unknown vs. MSM	0.94	0.67 to 1.31	0.70
Years known HIV+			
≥10 vs. <5 yrs	0.92	0.67 to 1.27	0.60
5–9.9 vs. <5 yrs	1.05	0.77 to 1.45	0.75
Female sex	0.53	0.28 to 0.98	0.044
Age, yrs			
≥65 vs. 18–39	11.87	6.29 to 22.42	<0.001
50–64 vs. 18–39	5.94	3.35 to 10.56	<0.001
40–49 vs. 18–39	3.20	1.80 to 5.71	<0.001

CD4 nadir is the only HIV-related factor that is independently associated with MI risk

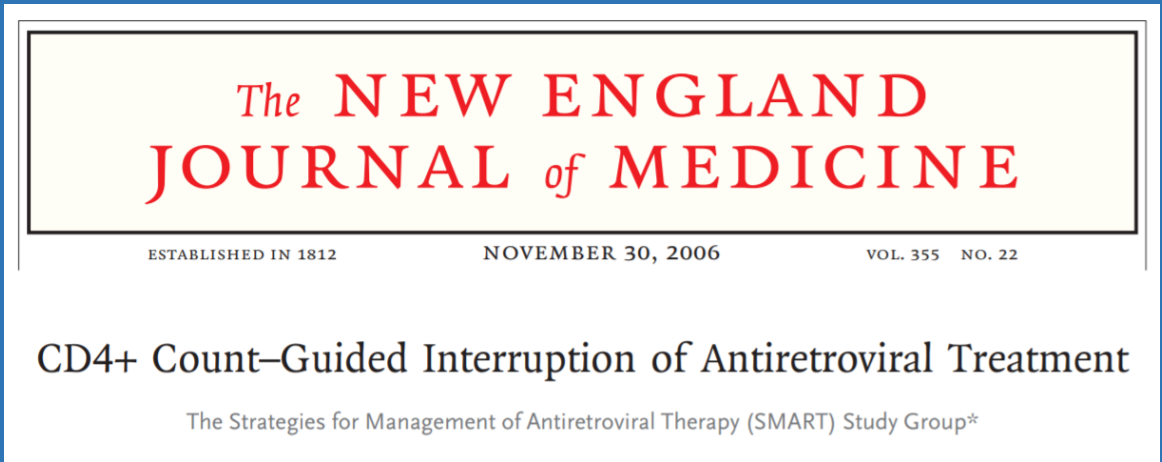
Silverberg, 2014

Effect of ART on cardiovascular disease

- Some ARVs are associated with increased risk of CVD (LPV)
- ART through virologic control and its effect on endothelial inflammation may modulate increased CVD risk in PLHIV

ART interruption and CVD

Interruption of ART is an important risk factor for cardiovascular disease in patients with low CD4 count nadir



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 30, 2006 VOL. 355 NO. 22

CD4+ Count–Guided Interruption of Antiretroviral Treatment

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group*

Increased risk of major CVD events in patients randomized to interrupt ART when their CD4+ cell count increased to >250 cells/mm^3 compared with patients who remained on ART

- marked elevations in inflammatory and coagulation biomarkers during follow-up compared with patients who maintained viral suppression

Abacavir
&
cardiovascular disease

Abacavir and CVD risk

D:A:D showed relationship between abacavir use and increased risk of myocardial infarction

Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) retrospective analysis of a large prospective cohort found an association between current and cumulative abacavir use and myocardial infarction

- 11 cohorts worldwide
- 339,108 person-years of follow-up as of January 31st 2012

D:A:D

Abacavir and CVD risk

Increased risk of MI or overall CVD events with ABC use shown in:

- large cohort studies
- RCTs
- case control studies

Range of risk estimates: 1.3-4.3 fold increase

- Friis-Moller N, et al. Eur J Cardiovasc Prev Rehabil. 2010;17:491-501.
- Friis-Moller N, et al. Eur J Prev Cardiol. 2016;23:214-223.
- SMART/INSIGHT Study Group. AIDS. 2008;22:F17-F24.
- Martin A, et al. Clin Infect Dis. 2009;49:1591-1601.
- Durand M, et al. J Acquir Immune Defic Syndr. 2011;57:245-253.
- Obel N, et al. HIV Med. 2010;11:130-136.
- Choi AI, et al. AIDS. 2011;25:1289-1298.
- Young J, et al. J Acquir Immune Defic Syndr. 2015;69:413-421.
- Rotger M, et al. Clin Infect Dis. 2013;57:112-121. .

Abacavir and CVD risk

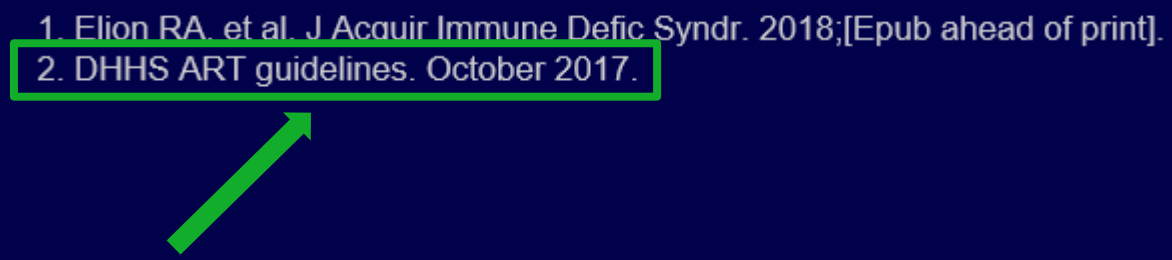
No increased risk of MI or overall CVD events with ABC use shown in:

- large cohort studies
- meta-analysis of RCTs
- case control studies

- Bedimo RJ, et al. Clin Infect Dis. 2011;53:84-91.
- Ribaudo HJ, et al. Clin Infect Dis. 2011;52:929-940.
- Lang S, et al. Arch Intern Med. 2010;170:1228-1238.
- Ding X, et al. J Acquir Immune Defic Syndr. 2012;61:441-447
- Palella F, et al. CROI 2015. Abstract 749LB.

NA-ACCORD: Recent ABC Use Associated With Risk of MI

- Analysis of 8265 ART recipients with 29,077 PYFU and 123 MI events in NA-ACCORD[1]
  - MI risk increased with recent ABC use (ie, in previous 6 mos)
  - Adjusted HR: 1.84 (95% CI: 1.17-2.91)
- DHHS: consider avoiding ABC in patients at elevated risk for CVD[2]



1. Elion RA, et al. J Acquir Immune Defic Syndr. 2018;[Epub ahead of print].
2. DHHS ART guidelines. October 2017.

Slide credit: clinicaloptions.com

Abacavir and CVD risk

- Data from an adequately powered, prospective, randomized trial are still lacking.
- Mechanism for any contribution of abacavir to MI risk remains unclear.

Treatment decisions on abacavir use should be individualized based on CVD risk and the risk-benefit ratio of other NRTI options

Dyslipidemia in PLHIVs

Studies consistently showed high prevalence of dyslipidemia in HIV:

- with ART
- without ART

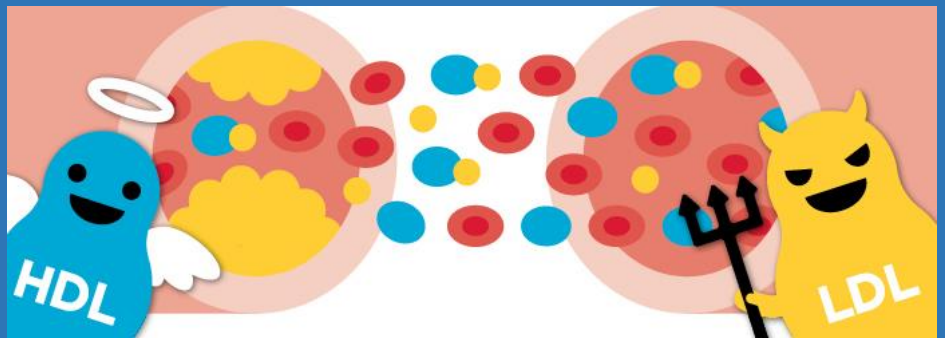
Natural history of dyslipidemia (while not on ART):

- low HDL- and low LDL-cholesterol
- increase in TG levels prior to developing AIDS

Mechanism is not understood.

ART initiation leads to:

- increase in LDL cholesterol
- no change in HDL cholesterol



High LDL cholesterol associated with CVD.

Lowering of LDL cholesterol decreases CVD risk.

Reverse is true for HDL cholesterol.

Triglycerides (TG) have not been shown to consistently predict CVD risk:

- no evidence that treatment of mild hypertriglyceridemia lowers CVD risk
- TG > 10 mmol/L increases risk of pancreatitis

Effect of ART on lipids

Protease Inhibitors and lipids

- Hypercholesterolemia
- Hypertriglyceridemia

Effect varies among PIs:

- **Ritonavir!!!**
- less in newer PIs (darunavir, atazanavir) which require less ritonavir boosting (only 100mg daily)
    - RTV 100mg BD, but not QD was associated with significant rise in TGs *(Collot-Teixeira S, e.a. Clin Pharmacol Ther, 2009)*

NNRTIs and lipids

- ↑ LDL
- ↑ HDL

<u>Effect varies among NNRTIs:</u>

- Efavirenz > Rilpivirine
  - but no difference in total cholesterol / HDL ration

NRTIs and lipids

Stavudine (d4T)

- ↑ total cholesterol and TGs

Tenofovir disoproxil fumarate (TDF)

- lower levels of total cholesterol, LDL and TGs compared to other NRTIs *(Crane HM, ea, AIDS 2011)*

Tenofovir alafenamide (TAF)

- compared to TDF, higher total cholesterol, LDL, and triglycerides when part of the single-dose combination

INSTIs and lipids

Raltegravir

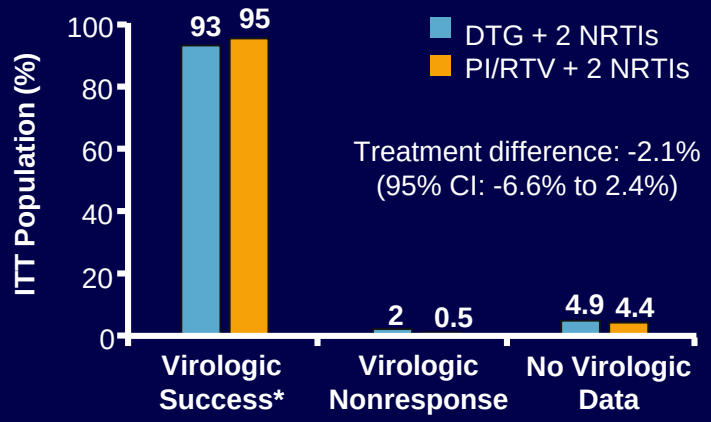
- lipid neutral

Dolutegravir

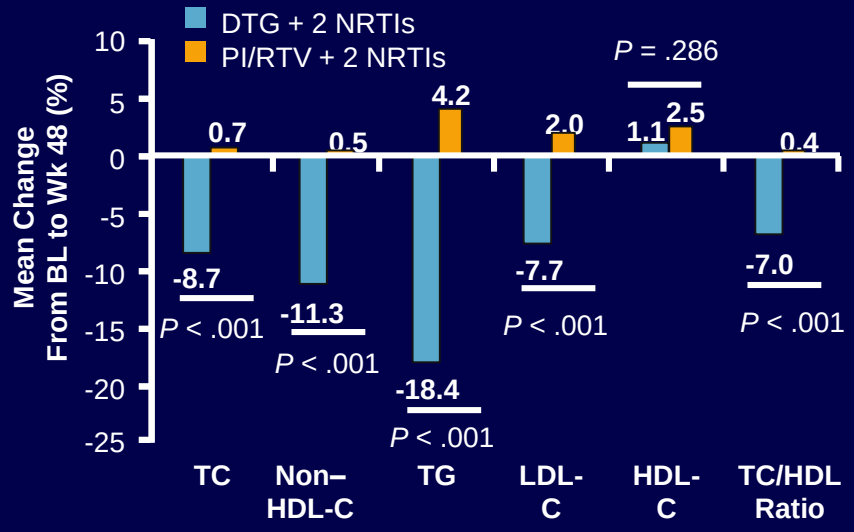
- lower levels of total cholesterol, LDL and TGs compared to other NRTIs *(Crane HM, ea, AIDS 2011)*

NEAT 022: Switch From Boosted PI to DTG in Suppressed Patients With High CV Risk

- Patients with stable HIV-1 RNA < 50 c/mL on PI/RTV + 2 NRTIs, high CV risk (> 50 yrs of age and/or Framingham risk score > 10% at 10 yrs), no resistance, no VF randomized to continue PI/RTV or switch to DTG (no change in NRTIs)



*HIV-1 RNA < 50 c/mL (coprimary endpoint with change in total plasma cholesterol).

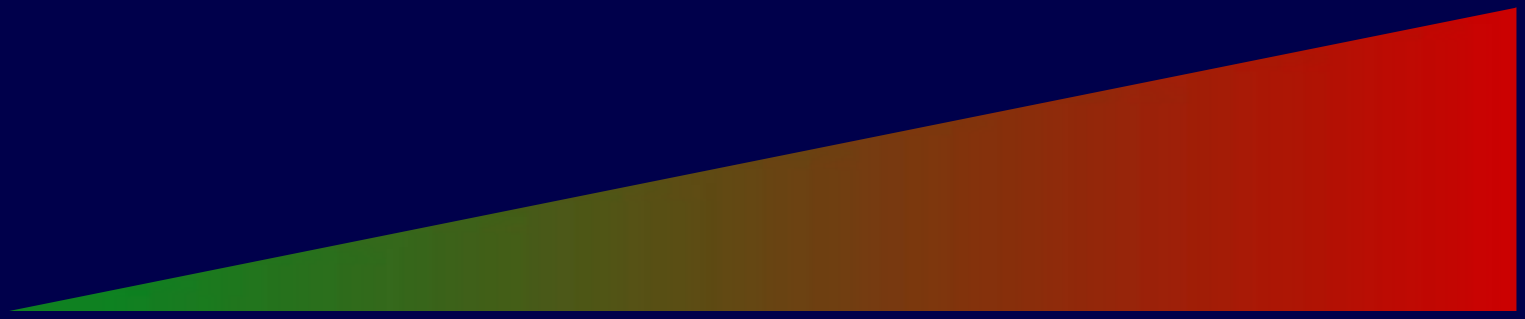


- No emergent resistance in patients with VF

Gatell JM, et al. AIDS. 2017;31:2503-2514.

Slide credit: clinicaloptions.com

ART and Effects on Lipids



TDF	TAF RAL DTG BIC	RPV ETV	ABC	EFV	ATV/RTV or ATV/COBI DRV/RTV or DRV/COBI EVG/COBI

Slide credit: clinicaloptions.com

Treatment of dyslipidemia in people with HIV

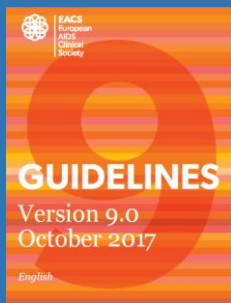
Treatment of dyslipidemia

- Undisputable evidence that lowering LDL cholesterol reduces CVD risk
- Statins are preferred first line agents to reduce LDL cholesterol
- Different statins have different capacity to lower LDL cholesterol, but once desired LDL level is achieved, one statin is as good as any other.
- Statins are recommended for 10-year CVD risk of ≥ 7.5%

Drug class	Drug	Dose	Side effects	Advise on use of statin together with ART	
				use with PI/r	use with NNRTIs
Statin[i,ix]	atorvastatin[ii]	10-80 mg qd	Gastrointestinal symptoms, headache, insomnia, rhabdomyolysis (rare) and toxic hepatitis	Start with low dose[v] (max: 40 mg)	Consider higher dose[vi]
	fluvastatin[iii]	20-80 mg qd		Consider higher dose[vi]	Consider higher dose[vi]
	pravastatin[iii]	20-80 mg qd		Consider higher dose[vi,vii]	Consider higher dose[vi]
	rosuvastatin[ii]	5-40 mg qd		Start with low dose[v] (max: 20 mg)	Start with low dose[v]
	simvastatin[ii]	10-40 mg qd		Contraindicated	
Intestinal cholesterol absorption inhibitor↓[i,viii]	ezetimibe[iv]	10 mg qd	Gastrointestinal symptoms	No known drug-drug interactions with ART	
PCSK9-inhibitor[x]	evolocumab	140 mg 2 weekly or 420 mg monthly	Nil	No drug-drug interactions anticipated	

- Simvastatin, but not atorvastatin has to be given before sleep
- Simvastatin **contraindicated with PIs**
- Maximum atorvastatin dose with PIs is 40mg daily
- When combined with NNRTIs (Efavirenz), higher doses of simvastatin or atorvastatin may be needed

Monitoring of liver function (LFT) or creatinine kinase (CK) not routinely required.



Rosuvastatin in Asian patients

- start with low dose (5mg daily)
- max dose in Asians 20mg daily

Pharmacokinetics:

Specific Populations

Race

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group.

8.8 Asian Patients

Pharmacokinetic studies have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls. CRESTOR dosage should be adjusted in Asian patients *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

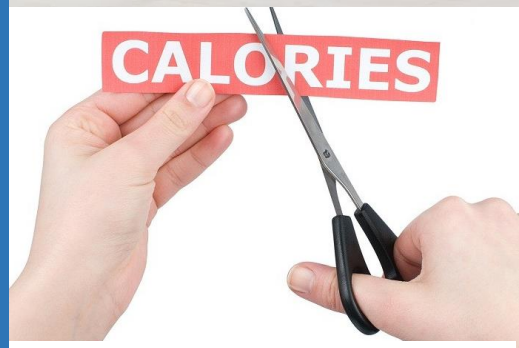
Rosuvastatin Prescribing information (AstraZeneca)

Increasing HDL

- physical exercise
- less calories
- reduction in body weight

Decreasing TG levels

- less calories
- eating fish
- reduction in alcohol consumption



Drug–Drug Interactions With First-line ART and Lipid-Lowering Therapy

Antiretroviral	Contraindicated	Titrate Dose	No Dose Adjustment
EFV		Atorvastatin Simvastatin Pravastatin	Pitavastatin Rosuvastatin
RPV			Atorvastatin Pitavastatin
ATV/RTV	Lovastatin Simvastatin	Atorvastatin Pravastatin Rosuvastatin	Pitavastatin
ATV/COBI	Atorvastatin Lovastatin Simvastatin	Pravastatin Rosuvastatin	Pitavastatin
DRV/RTV DRV/COBI	Lovastatin Simvastatin	Atorvastatin Pravastatin Rosuvastatin	Pitavastatin
EVG/COBI/FTC/**TAF**	Lovastatin Simvastatin	Atorvastatin Rosuvastatin	
EVG/COBI/FTC/**TDF**	Lovastatin Simvastatin	Atorvastatin Rosuvastatin	
DTG or RAL			All

DHHS Adult Guidelines. October 2017. US Food and Drug Administration.

Slide credit: clinicaloptions.com

Statin Dosing in the Setting of ART

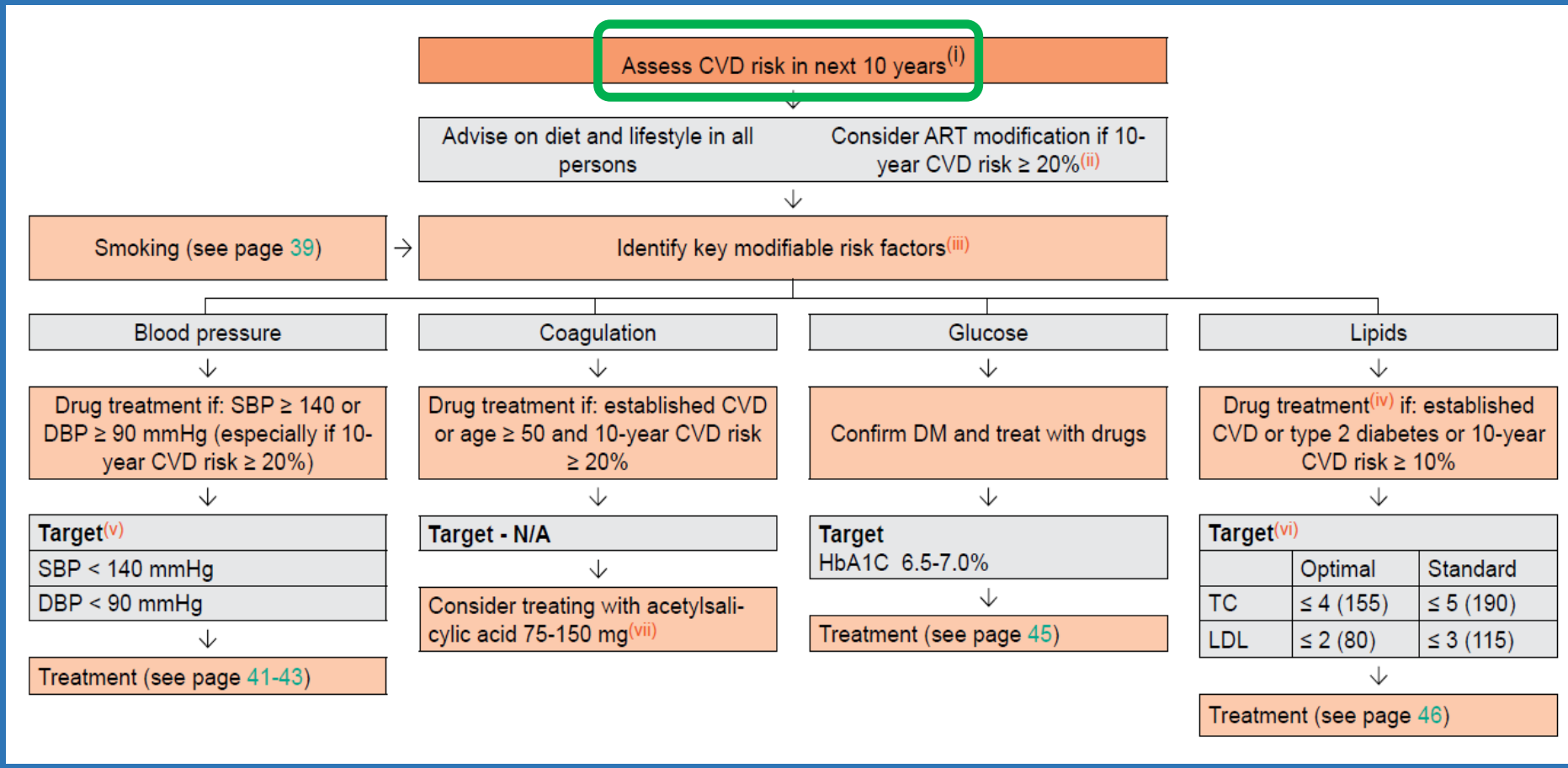
PI- or COBI-Containing Regimens		
High-Intensity Statin	**Moderate-Intensity Statin**	**Low-Intensity Statin**
Atorvastatin 20 mg	Atorvastatin 10 mg	Pravastatin 10-20 mg
Rosuvastatin 10-20 mg	Rosuvastatin 5 mg	Fluvastatin 20-40 mg
	Pravastatin 40-80 mg*	Pitavastatin 1 mg
	Pitavastatin 2-4 mg	
Simvastatin and lovastatin are contraindicated for patients receiving a PI or COBI *With darunavir, reduce pravastatin to 20-40 mg		
NNRTI-, RAL-, or DTG-Containing Regimens		
High-Intensity Statin	**Moderate-Intensity Statin**	**Low-Intensity Statin**
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Pravastatin 10-20 mg
Rosuvastatin 20 mg	Rosuvastatin 10 mg	Fluvastatin 20-40 mg
	Pravastatin 40-80 mg	Pitavastatin 1 mg
	Pitavastatin 2-4 mg	Lovastatin 20 mg
	Lovastatin 40 mg	Simvastatin 10 mg
	Simvastatin 20-40 mg	

All doses daily.

Dubé MP. Lipid management. 2015. p. 241-255.

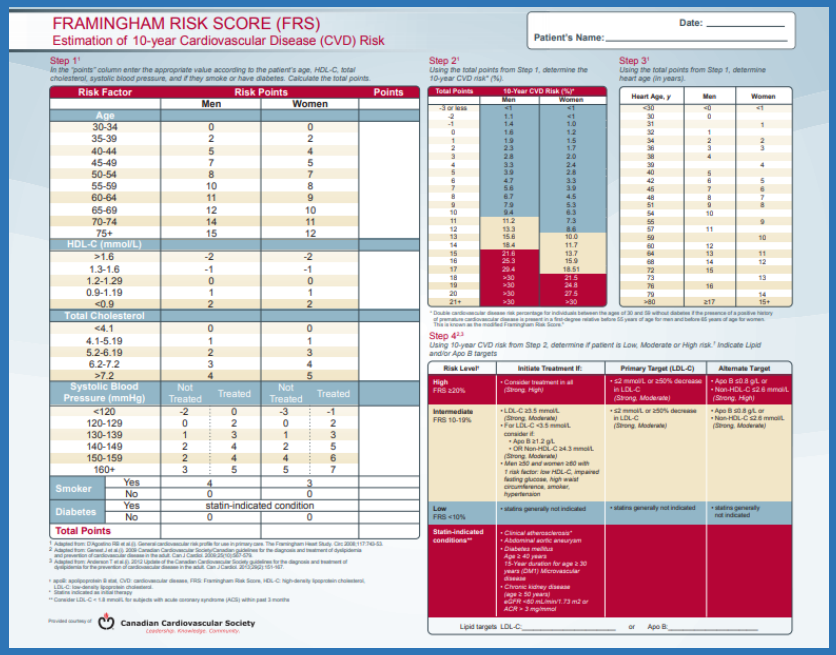
Slide credit: clinicaloptions.com

Prevention of CVD in PLHIV



Accessing CVD risk in PLHIV

…but which risk calculator to choose?



FRAMINGHAM RISK SCORE (FRS)

Estimation of 10-year Cardiovascular Disease (CVD) Risk

Date: _____

Patient's Name: _____

Step 1[1]

In the "points" column enter the appropriate value according to the patient's age, HDL-C, total cholesterol, systolic blood pressure, and if they smoke or have diabetes. Calculate the total points.

Risk Factor	Risk Points				Points
	Men		Women		
Age					
30-34	0		0		
35-39	2		2		
40-44	5		4		
45-49	7		5		
50-54	8		7		
55-59	10		8		
60-64	11		9		
65-69	12		10		
70-74	14		11		
75+	15		12		
HDL-C (mmol/L)					
>1.6	-2		-2		
1.3-1.6	-1		-1		
1.2-1.29	0		0		
0.9-1.19	1		1		
<0.9	2		2		
Total Cholesterol					
<4.1	0		0		
4.1-5.19	1		1		
5.2-6.19	2		3		
6.2-7.2	3		4		
>7.2	4		5		
Systolic Blood Pressure (mmHg)	Not Treated	Treated	Not Treated	Treated	
<120	-2	0	-3	-1	
120-129	0	2	0	2	
130-139	1	3	1	3	
140-149	2	4	2	5	
150-159	2	4	4	6	
160+	3	5	5	7	
Smoker Yes	4		3		
Smoker No	0		0		
Diabetes Yes	statin-indicated condition				
Diabetes No	0		0		
Total Points					

Step 2[1]

Using the total points from Step 1, determine the 10-year CVD risk (%).*

Total Points	10-Year CVD Risk (%)*	
	Men	Women
-3 or less	<1	<1
-2	1.1	<1
-1	1.4	1.0
0	1.6	1.2
1	1.9	1.5
2	2.3	1.7
3	2.8	2.0
4	3.3	2.4
5	3.9	2.8
6	4.7	3.3
7	5.6	3.9
8	6.7	4.5
9	7.9	5.3
10	9.4	6.3
11	11.2	7.3
12	13.3	8.6
13	15.6	10.0
14	18.4	11.7
15	21.6	13.7
16	25.3	15.9
17	29.4	18.51
18	>30	21.5
19	>30	24.8
20	>30	27.5
21+	>30	>30

Step 3[1]

Using the total points from Step 1, determine heart age (in years).

Heart Age, y	Men	Women
<30	<0	<1
30	0	
31		1
32	1	
34	2	2
36	3	3
38	4	
39		4
40	5	
42	6	5
45	7	6
48	8	7
51	9	8
54	10	
55		9
57	11	
59		10
60	12	
64	13	11
68	14	12
72	15	
73		13
76	16	
79		14
>80	≥17	15+

* Double cardiovascular disease risk percentage for individuals between the age of 30 and 59 without diabetes if the presence of a positive history of premature cardiovascular disease is present in a first-degree relative before 55 years of age for men and before 65 years of age for women. This is known as the modified Framingham Risk Score.[3]

Step 4[1,2]

Using 10-year CVD risk from Step 2, determine if patient is Low, Moderate or High risk.† Indicate Lipid and/or Apo B targets

Risk Level†	Initiate Treatment If:	Primary Target (LDL-C)	Alternate Target
High FRS ≥20%	• Consider treatment in all *(Strong, High)*	• ≤2 mmol/L or ≥50% decrease in LDL-C *(Strong, Moderate)*	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L *(Strong, High)*
Intermediate FRS 10-19%	• LDL-C ≥3.5 mmol/L *(Strong, Moderate)* • For LDL-C <3.5 mmol/L consider if: • Apo B ≥1.2 g/L • OR Non-HDL-C ≥4.3 mmol/L *(Strong, Moderate)* • *Men ≥50 and women ≥60 with 1 risk factor: low HDL-C, impaired fasting glucose, high waist circumference, smoker, hypertension*	≤2 mmol/L or ≥50% decrease in LDL-C *(Strong, Moderate)*	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L *(Strong, Moderate)*
Low FRS <10%	• statins generally not indicated	• statins generally not indicated	• statins generally not indicated
Statin-indicated conditions††	• *Clinical atherosclerosis*‡ • *Abdominal aortic aneurysm* • *Diabetes mellitus Age ≥ 40 years 15-Year duration for age ≥ 30 years (DM1) Microvascular disease* • *Chronic kidney disease (age ≥ 50 years) eGFR <60 mL/min/1.73 m2 or ACR > 3 mg/mmol*		

Lipid targets LDL-C:_____ or Apo B:_____

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† apoB: apolipoprotein B (old), CVD: cardiovascular disease, FRS: Framingham Risk Score, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol

‡ Statins indicated as initial therapy

†† Consider LDL-C < 1.8 mmol/L for subjects with acute coronary syndrome (ACS) within past 3 months

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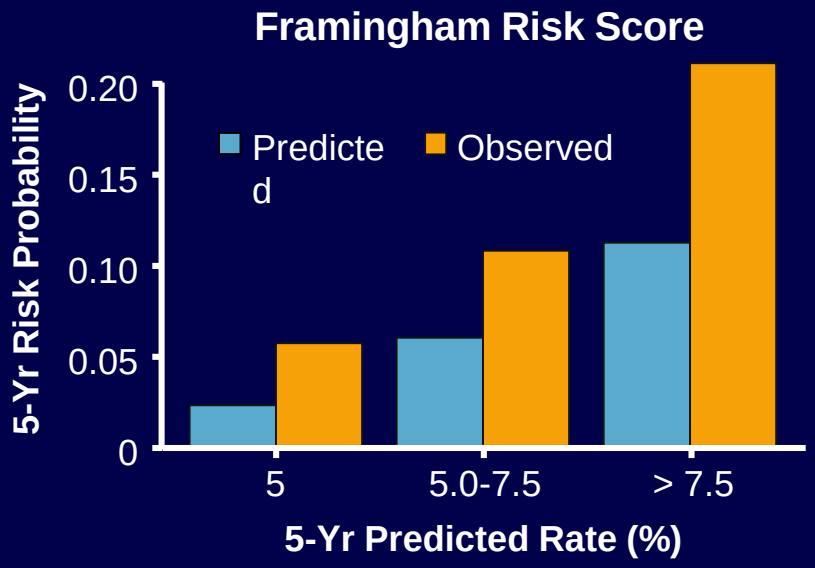
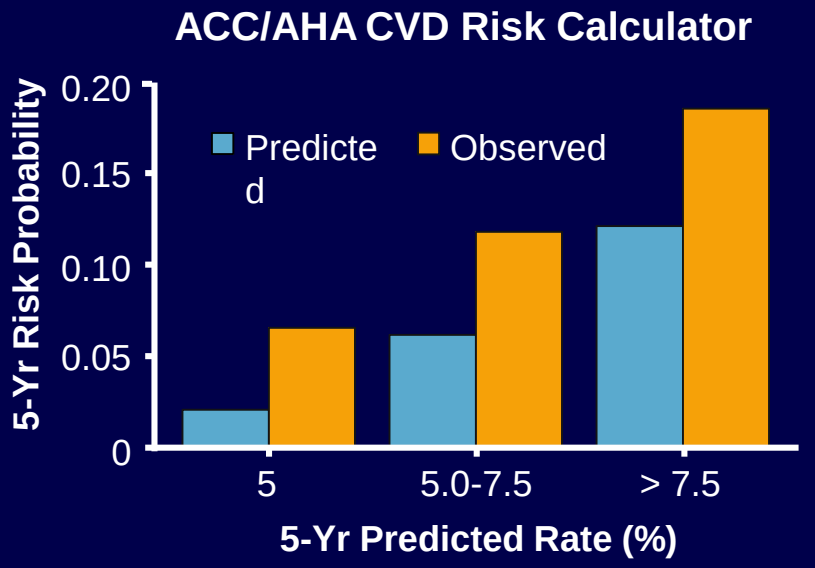
CVD Outcomes Underestimated in HIV-Positive Patients by Risk Calculators

- CVD risk scores calculated with data from 1/1/2006 to 12/31/2008 for patients in Partners HealthCare System HIV Cohort (N = 1280 men; median f/u: 4.4 yrs)



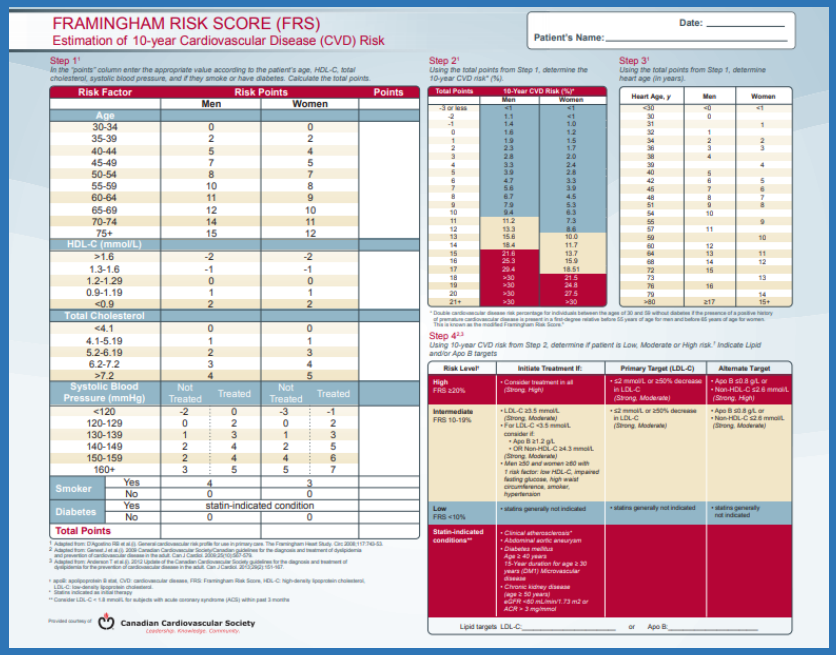


Triant VA, et al. Circulation. 2018;[Epub ahead of print].

Slide credit: clinicaloptions.com

Accessing CVD risk in PLHIV

…but which risk calculator to choose?



FRAMINGHAM RISK SCORE (FRS)

Estimation of 10-year Cardiovascular Disease (CVD) Risk

Date: _____

Patient's Name: _____

Step 1[1]

In the "points" column enter the appropriate value according to the patient's age, HDL-C, total cholesterol, systolic blood pressure, and if they smoke or have diabetes. Calculate the total points.

Risk Factor	Risk Points				Points
	Men		Women		
Age					
30-34	0		0		
35-39	2		2		
40-44	5		4		
45-49	7		5		
50-54	8		7		
55-59	10		8		
60-64	11		9		
65-69	12		10		
70-74	14		11		
75+	15		12		
HDL-C (mmol/L)					
>1.6	-2		-2		
1.3-1.6	-1		-1		
1.2-1.29	0		0		
0.9-1.19	1		1		
<0.9	2		2		
Total Cholesterol					
<4.1	0		0		
4.1-5.19	1		1		
5.2-6.19	2		3		
6.2-7.2	3		4		
>7.2	4		5		
Systolic Blood Pressure (mmHg)	Not Treated	Treated	Not Treated	Treated	
<120	-2	0	-3	-1	
120-129	0	2	0	2	
130-139	1	3	1	3	
140-149	2	4	2	5	
150-159	2	4	4	6	
160+	3	5	5	7	
Smoker Yes	4		3		
Smoker No	0		0		
Diabetes Yes	statin-indicated condition				
Diabetes No	0		0		
Total Points					

Step 2[1]

Using the total points from Step 1, determine the 10-year CVD risk (%).*

Total Points	10-Year CVD Risk (%)*	
	Men	Women
-3 or less	<1	<1
-2	1.1	<1
-1	1.4	1.0
0	1.6	1.2
1	1.9	1.5
2	2.3	1.7
3	2.8	2.0
4	3.3	2.4
5	3.9	2.8
6	4.7	3.3
7	5.6	3.9
8	6.7	4.5
9	7.9	5.3
10	9.4	6.3
11	11.2	7.3
12	13.3	8.6
13	15.6	10.0
14	18.4	11.7
15	21.6	13.7
16	25.3	15.9
17	29.4	18.51
18	>30	21.5
19	>30	24.8
20	>30	27.5
21+	>30	>30

Step 3[1]

Using the total points from Step 1, determine heart age (in years).

Heart Age, y	Men	Women
<30	<0	<1
30	0	
31		1
32	1	
34	2	2
36	3	3
38	4	
39		4
40	5	
42	6	5
45	7	6
48	8	7
51	9	8
54	10	
55		9
57	11	
59		10
60	12	
64	13	11
68	14	12
72	15	
73		13
76	16	
79		14
>80	≥17	15+

* Double cardiovascular disease risk percentage for individuals between the age of 30 and 59 without diabetes if the presence of a positive history of premature cardiovascular disease is present in a first-degree relative before 55 years of age for men and before 65 years of age for women. This is known as the modified Framingham Risk Score.[3]

Step 4[1,2]

Using 10-year CVD risk from Step 2, determine if patient is Low, Moderate or High risk.† Indicate Lipid and/or Apo B targets

Risk Level†	Initiate Treatment If:	Primary Target (LDL-C)	Alternate Target
High FRS ≥20%	• Consider treatment in all *(Strong, High)*	• ≤2 mmol/L or ≥50% decrease in LDL-C *(Strong, Moderate)*	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L *(Strong, High)*
Intermediate FRS 10-19%	• LDL-C ≥3.5 mmol/L *(Strong, Moderate)* • For LDL-C <3.5 mmol/L consider if: • Apo B ≥1.2 g/L • OR Non-HDL-C ≥4.3 mmol/L *(Strong, Moderate)* • *Men ≥50 and women ≥60 with 1 risk factor: low HDL-C, impaired fasting glucose, high waist circumference, smoker, hypertension*	≤2 mmol/L or ≥50% decrease in LDL-C *(Strong, Moderate)*	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L *(Strong, Moderate)*
Low FRS <10%	• statins generally not indicated	• statins generally not indicated	• statins generally not indicated
Statin-indicated conditions††	• *Clinical atherosclerosis*‡ • *Abdominal aortic aneurysm* • *Diabetes mellitus Age ≥ 40 years 15-Year duration for age ≥ 30 years (DM1) Microvascular disease* • *Chronic kidney disease (age ≥ 50 years) eGFR <60 mL/min/1.73 m2 or ACR > 3 mg/mmol*		

Lipid targets LDL-C:_____ or Apo B:_____

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† apoB: apolipoprotein B (old), CVD: cardiovascular disease, FRS: Framingham Risk Score, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol

‡ Statins indicated as initial therapy

†† Consider LDL-C < 1.8 mmol/L for subjects with acute coronary syndrome (ACS) within past 3 months

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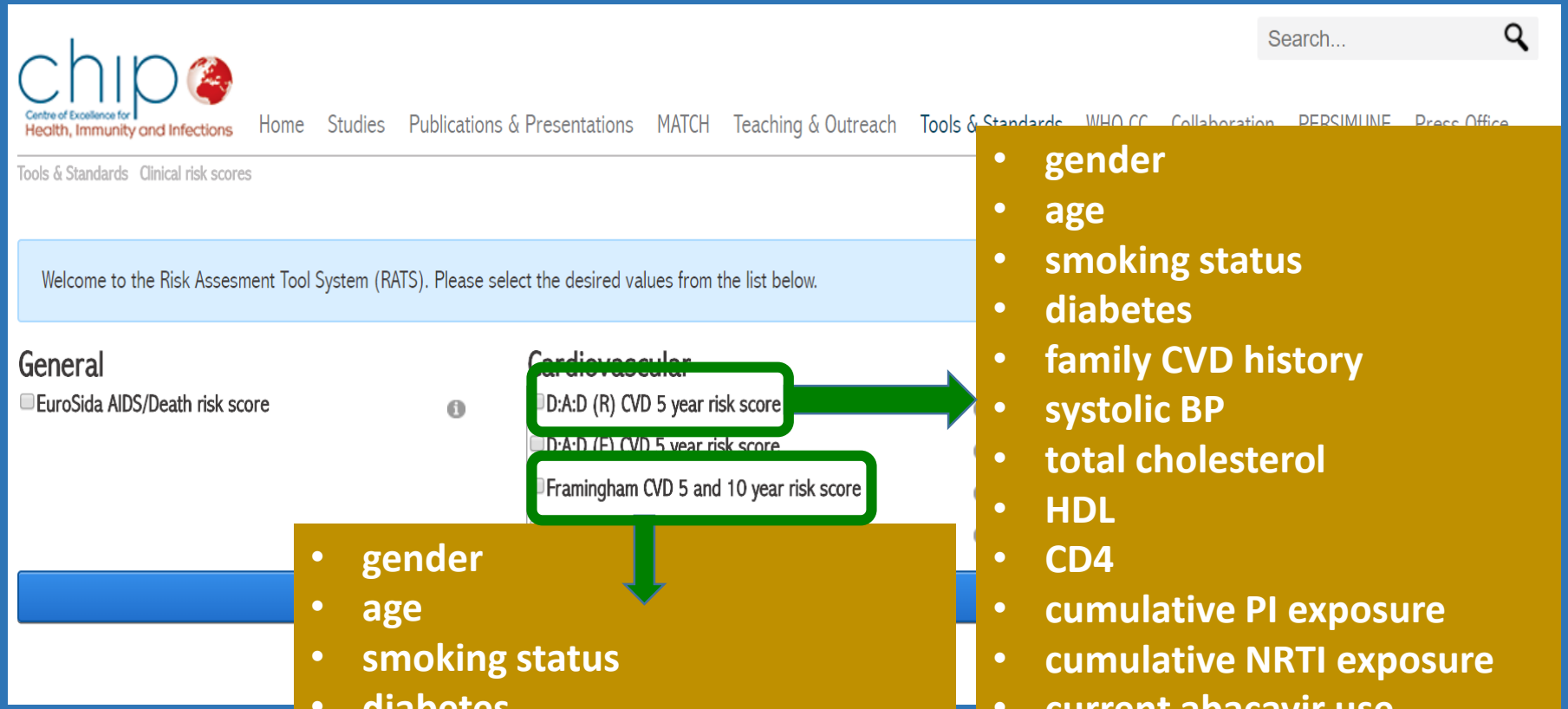
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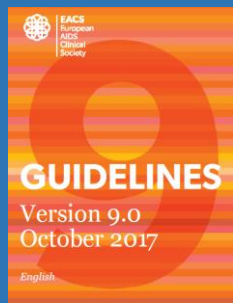
Cardiovascular
D:A:D (R) CVD 5 year risk score
D:A:D (E) CVD 5 year risk score
Framingham CVD 5 and 10 year risk score
• gender
• age
• smoking status
• diabetes
• family CVD history
• systolic BP
• total cholesterol
• HDL
• CD4
• cumulative PI exposure
• cumulative NRTI exposure
• current abacavir use
• gender
• age
• smoking status
• diabetes
• systolic BP(antihypertensive treatment)
• total cholesterol
• HDL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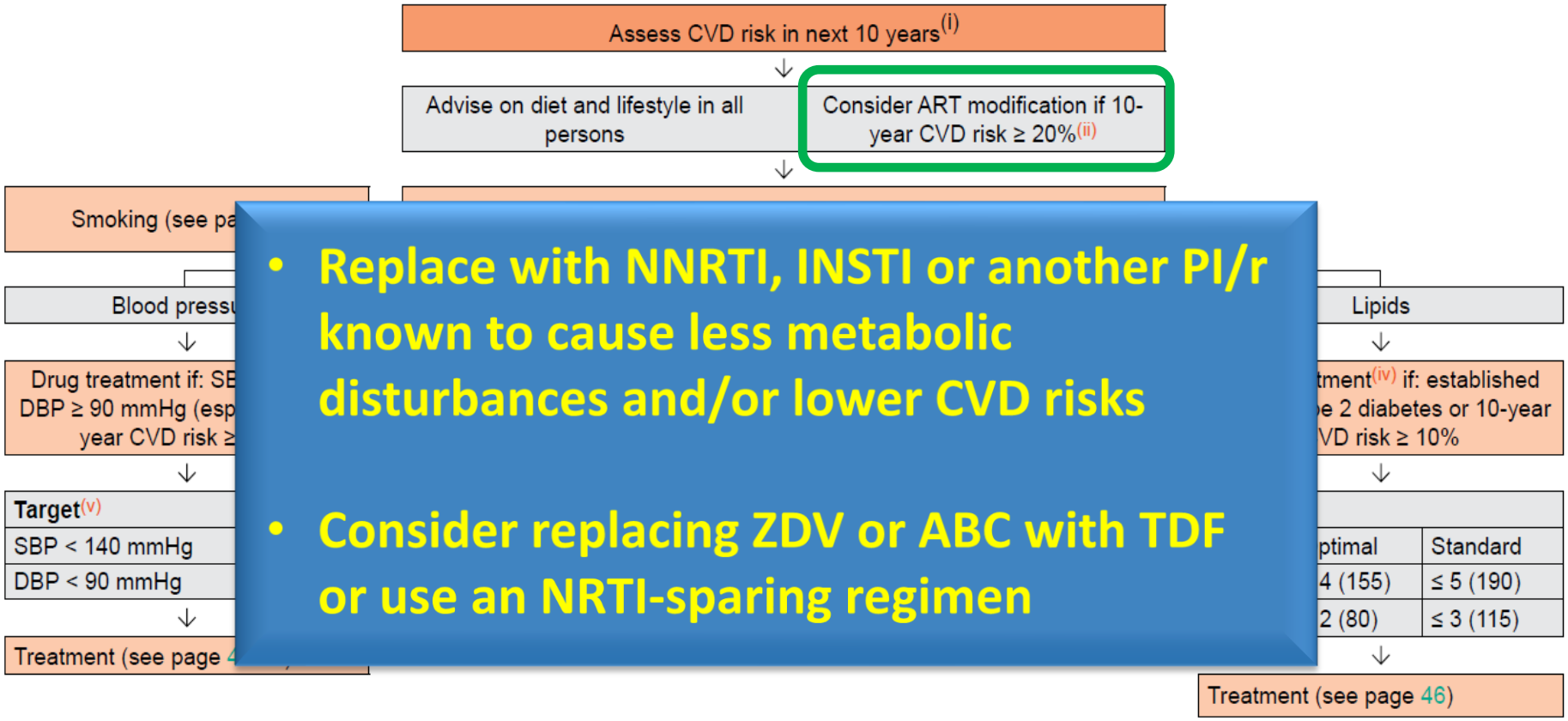

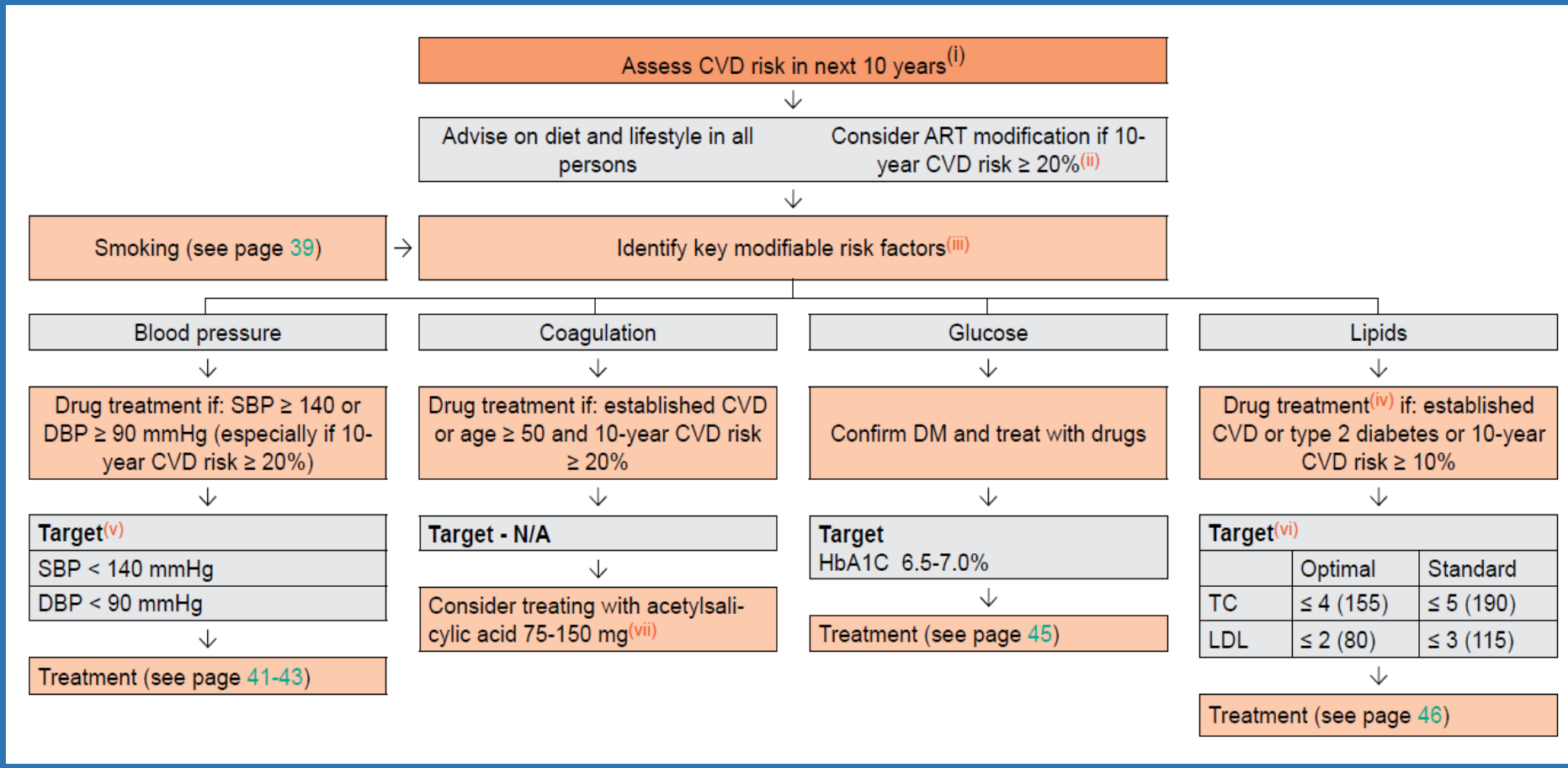

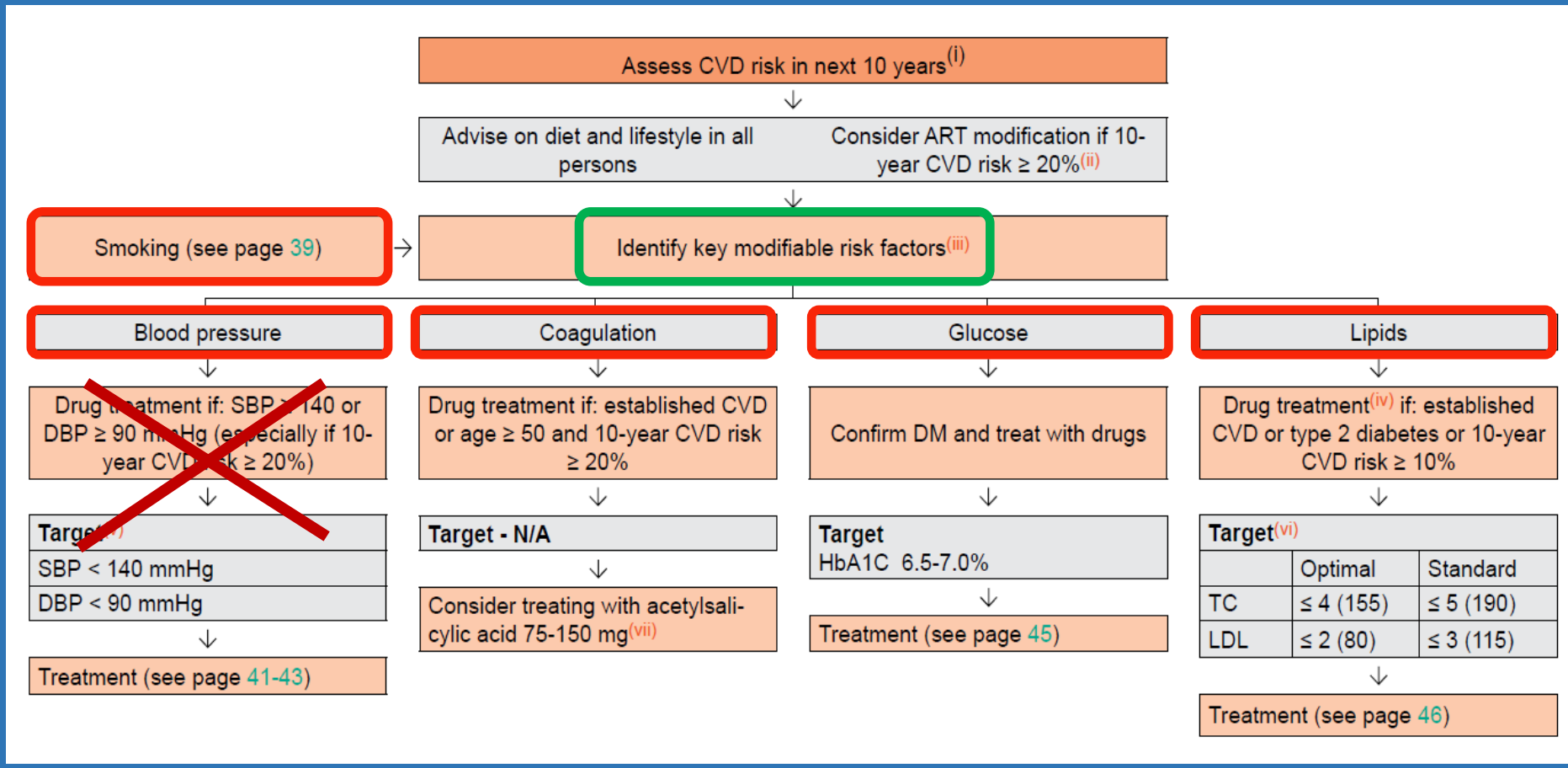

Hypertension in PLHIV

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2017 Guideline for High Blood Pressure in Adults

normal BP: <120/<80 mm Hg

elevated BP: 120-129/<80 mm Hg

hypertension stage 1: 130-139 or 80-89 mm Hg
hypertension stage 2: is ≥140 or ≥90 mm Hg

Prior to labeling a person with hypertension, it is important to use an average based on ≥2 readings obtained on ≥2 occasions to estimate the individual's level of BP.

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2017 Guideline for High Blood Pressure in Adults

In adults with an untreated systolic BP (SBP) >130 but <160 mm Hg or diastolic BP (DBP) >80 but <100 mm Hg, it is reasonable to screen for the presence of white coat hypertension using either daytime ABPM or HBPM prior to diagnosis of hypertension.

In adults with elevated office BP (120-129/<80) but not meeting the criteria for hypertension, screening for masked hypertension with daytime ABPM or HBPM is reasonable

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2017 Guideline for High Blood Pressure in Adults

A 20 mm Hg higher SBP and 10 mm Hg higher DBP are each associated with a **doubling in the risk of death** from stroke, heart disease, or other vascular disease.

In persons ≥30 years of age, higher SBP and DBP are associated with increased risk for CVD, angina, myocardial infarction (MI), heart failure (HF), stroke, peripheral arterial disease, and abdominal aortic aneurysm.

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2017 Guideline for High Blood Pressure in Adults

It is important to screen for and manage other CVD risk factors in adults with hypertension:

- smoking,
- diabetes,
- dyslipidaemia,
- excessive weight,
- low fitness,
- unhealthy diet,
- psychosocial stress,
- sleep apnea

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2017 Guideline for High Blood Pressure in Adults

Basic testing for primary hypertension:

- fasting blood glucose
- complete blood cell count,
- lipids,
- basic metabolic panel,
- thyroid function,
- urinalysis,
- electrocardiogram with optional echocardiogram,
- uric acid,
- urinary albumin-to-creatinine ratio.

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2017 Guideline for High Blood Pressure in Adults

Blood pressure targets in hypertension:

For adults with *known CVD or 10-year ASCVD event risk of 10% or higher:*

- BP target of <130/80 mm Hg is recommended.

For adults *without CVD or markers of increased CVD risk:*

- BP target of <130/80 mm Hg is recommended as reasonable.

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2017 Guideline for High Blood Pressure in Adults

Management:

elevated BP or stage 1 HT with low ASCVD risk

- Repeat BP after 3-6 months of lifestyle interventions

Therapy

stage 1 HT with CVD or >10% 10-year ASCVD risk

- Initiate both lifestyle interventions and pharmacologic therapy (1 drug) and repeat BP after 1 month

stage 2 HT

- Initiate both lifestyle interventions and pharmacologic therapy (2drugs) and repeat BP after 1 month

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2017 Guideline for High Blood Pressure in Adults

Targets in special groups

- CKD : <130/80 mm
- CVD: <130/80 mm

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2017 Guideline for High Blood Pressure in Adults

Secondary prevention following a stroke (CVA) or transient ischemic attack (TIA):

- restart treatment after the first few days of the index event
- if not previously treated for hypertension; if BP ≥140/90 mm Hg; begin antihypertensive therapy a few days after CVA/TIA
- ACE inhibitor or ARB with thiazide diuretic is useful

For those with an ischemic stroke and no previous treatment for hypertension, there is no evidence of treatment benefit if the BP is <140/90 mm Hg.

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2017 Guideline for High Blood Pressure in Adults

Patients with DM

- Start antihypertensive drug treatment if BP ≥130/80 mmHg
- treatment goal of <130/80 mmHg

- All first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective
- ACE inhibitors or ARBs may be considered in the presence of albuminuria.

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2017 Guideline for High Blood Pressure in Adults

Hypertension and elderly patients

Treatment is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age), with an average SBP ≥130 mm Hg with SBP treatment goal of <130 mm Hg.

For older adults (≥65 years of age) with hypertension and a high burden of comorbidity and/or limited life expectancy, clinical judgment, patient preference, antihypertensive drugs. BP lowering is reasonable to prevent cognitive decline and dementia.

ART and insulin resistance / DM

Diagnosis

Exposure to ART associated with insulin resistance and increased incidence of DM

At least annual screening for DM/insulin resistance required in all PLHIV, particularly if on ART

Hyperlactataemia & Lactic Acidosis

…a rare, but potentially life-threatening situation

Risk factors

- ddI > d4T > ZDV
- HCV/HBV co-infection
- use of ribavirin
- liver disease
- low CD4 count
- pregnancy
- female sex
- obesity

Diagnosis

Avoid d4T + ddI combination

Routine monitoring of serum lactate levels not recommended - does not predict risk of lactic acidosis

Measurement of serum lactate, bicarbonate, arterial blood gases and pH indicated in case of symptoms suggestive of hyperlactataemia

Close monitoring for symptoms if > 1 risk factor

Symptoms of lactic acidosis

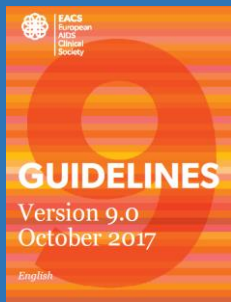
- hyperlactataemia: unexplained nausea, abdominal pain, hepatomegaly, elevated ALT and/or AST, weight loss
- acidaemia: asthenia, dyspnoea, arrhythmias
- Guillain-Barré-like syndrome

Approach to hyperlactataemia

Serum lactate (mmol/L)	Symptoms	Action
> 5[(i)]	Yes/No	• Repeat test under standardised conditions to confirm & obtain arterial pH and bicarbonate[(i)] • If confirmed, exclude other causes – Arterial pH ↓ and/or bicarbonate ↓[(i)]: Stop NRTIs – Arterial pH and/or bicarbonate normal: Consider switch from high to low-risk NRTI & monitor carefully OR stop NRTIs
2-5	Yes	Exclude other causes; if none found: watchfully follow up OR consider switch from high to low-risk NRTI, OR stop NRTI
2-5	No	Repeat test If confirmed, watchfully follow up
< 2		None

Lactic acidosis (no matter how high lactate levels):

- admit patient
- stop NRTIs
- give iv fluids



HIV and bone health

HIV and osteoporosis

Osteoporosis is common in people with HIV

- Up to 10-15% prevalence of osteoporosis
- Aetiology multifactorial
- Loss of BMD observed with ART initiation
- Greater loss of BMD with initiation of certain ARVs

TDF and bone disease

Greater loss of BMD observed with initiation of regimens containing TDF

Gains in BMD observed with switch away from TDF-containing ARV regimens,

Clinical relevance to fracture risk not determined.

Consider switching from TDF to another NRTI or TAF if:

- Osteoporosis / progressive osteopenia
- History of fragility fracture
- FRAX score for major osteoporotic fracture > 10%
- Use of a PI/r as third agent
- Expert opinion, pending clinical

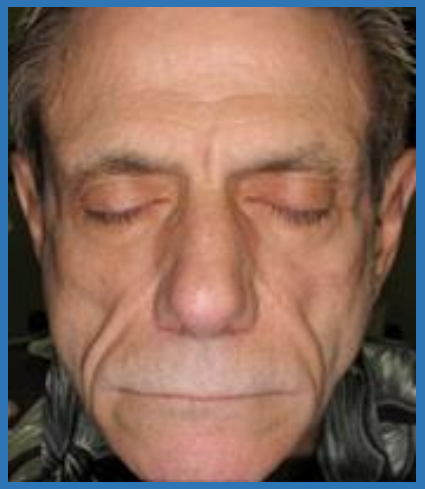
Lipodystrophy syndrome

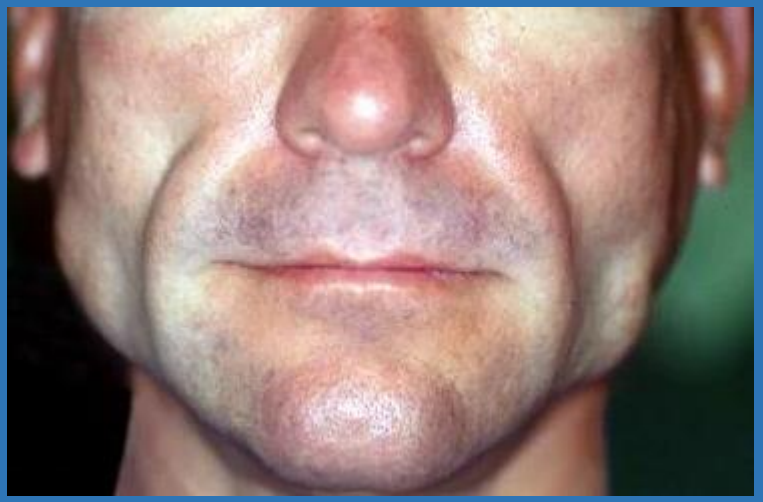
Abnormal fat redistribution with lipoatrophy and/or lipohypertrophy

…often associated with

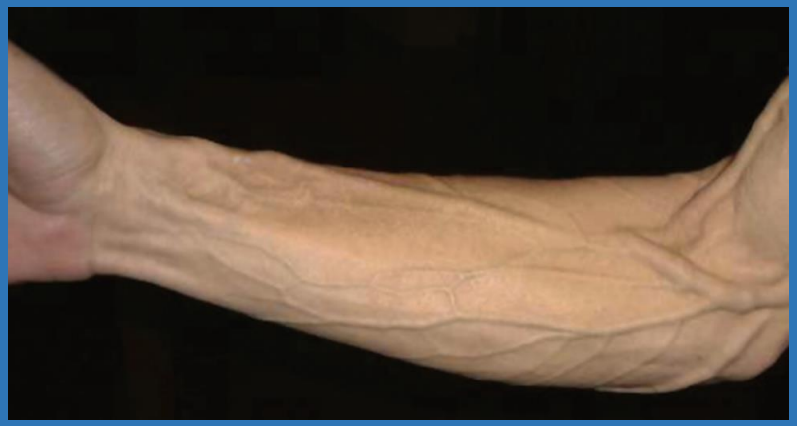
- dyslipidaemia
- insulin resistance
- increased CVD risk

Lipoatrophy

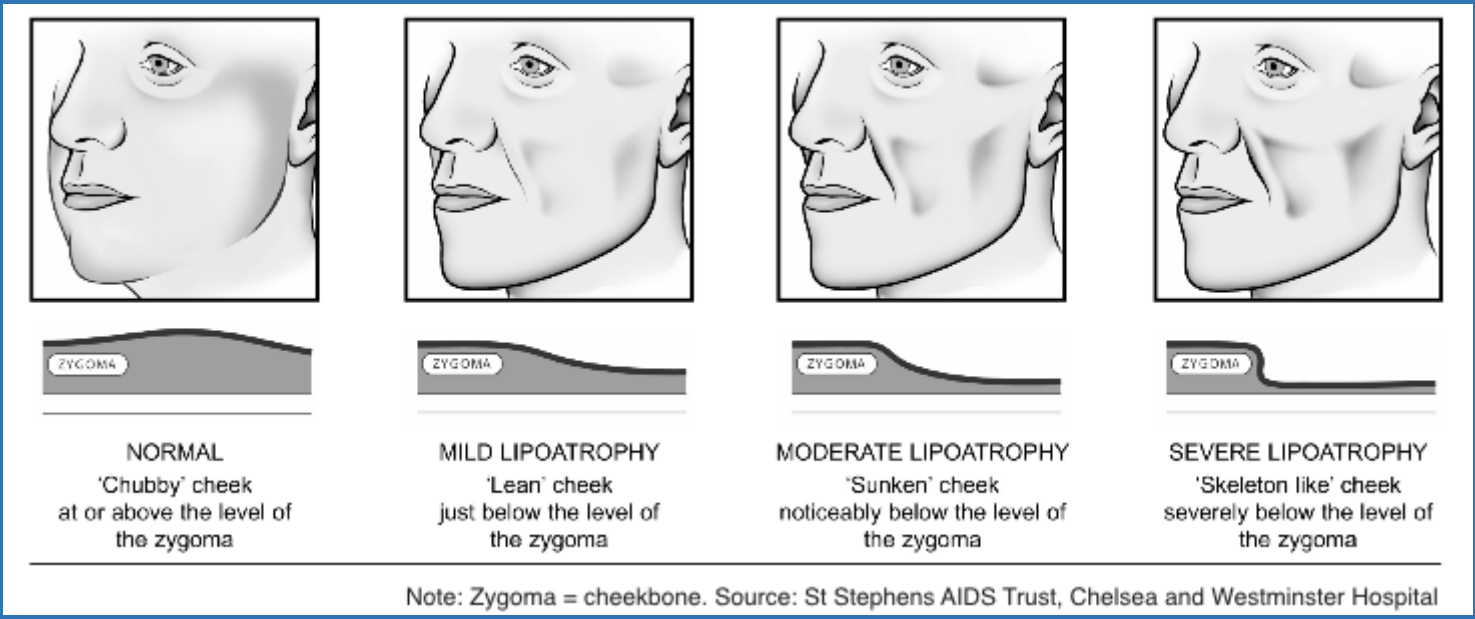


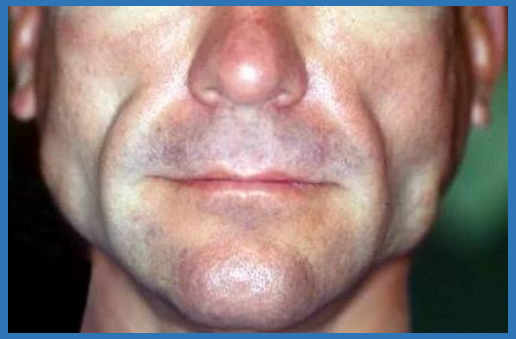


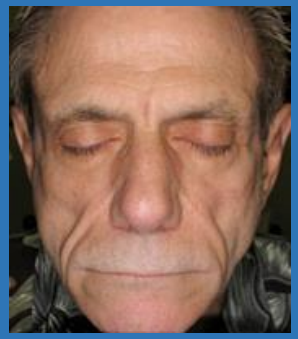
- multiple facial shadows
- sunken temples and cheeks
- prominent bone landmarks



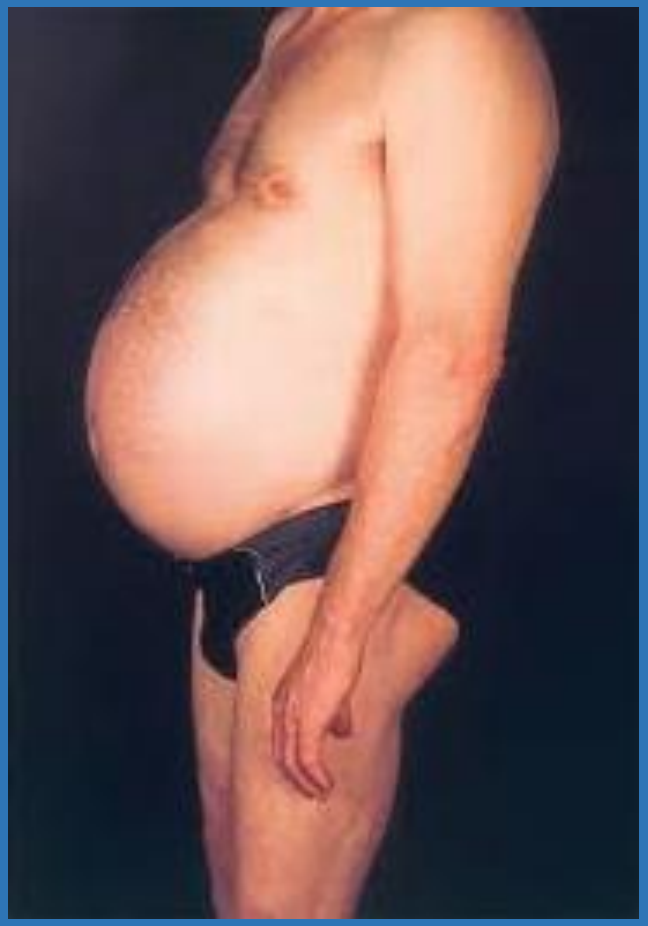
Lipoatrophy

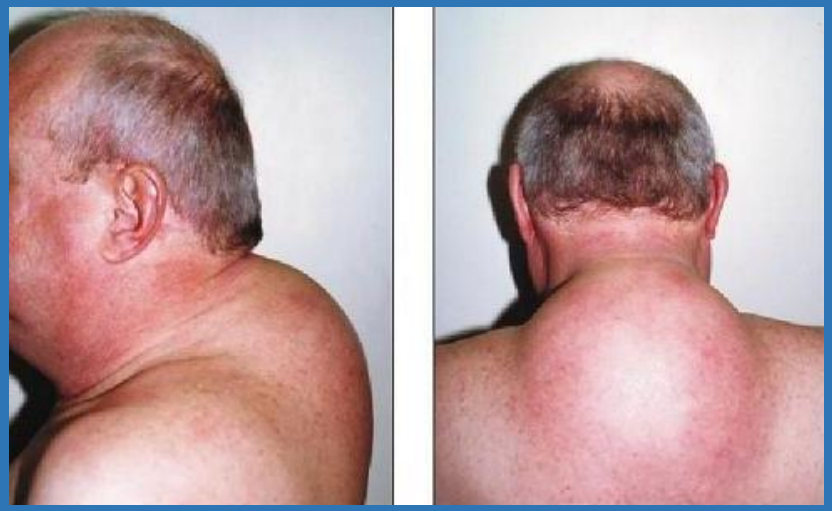






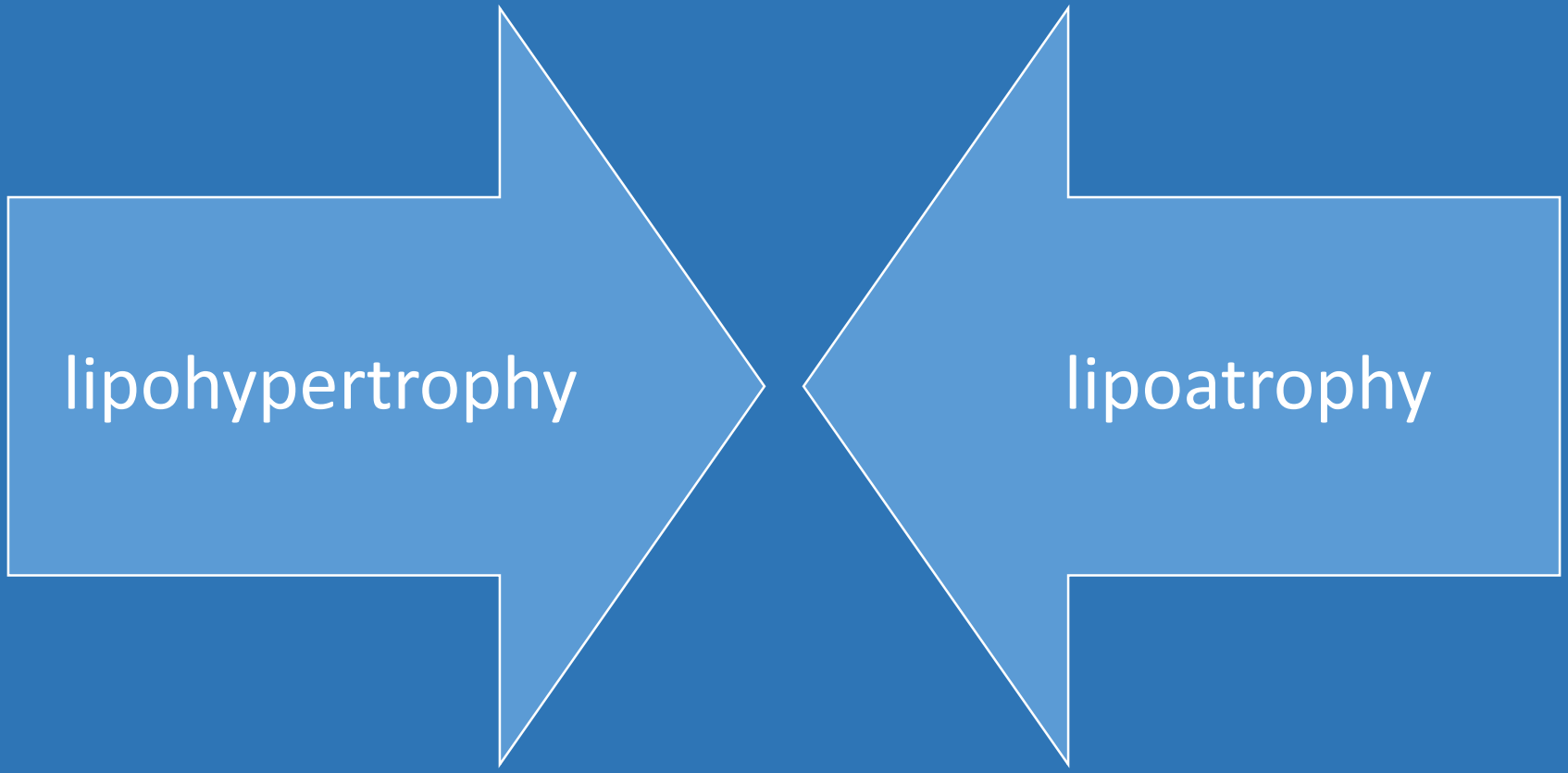
Lipohypertrophy





- abdominal obesity
- “Buffalo” hump
- gynecomastia

Lipodystrophy syndrome



Lipodystrophy

d4T most commonly implicated in lipoatrophy, but also AZT

Management:

- ART modification (reversal of symptoms may be only gradual)
- Liposuction (lipohyperatrophy)
- Recombinant GH-RH analogue (lipohyperatrophy)
- Injectable fillers (lipoatrophy)

HIV & Metabolic Disease

Take Home Messages

As people with HIV live longer, there is increased burden of (multiple) comorbidities.

Caution still advised with abacavir in patients with CVD or high risk for CVD.

ART interruption in patients with low CD4 count leads to cardiovascular events.

PLHIVs have increased risk of dyslipidemia.

Both HIV and ART each may contribute to such dyslipidemia.

Conventional CVD risk calculators underestimate CVD risk in PLHIV (but by how much?).

Consider potential impact on CVD risk, lipids, DDIs with statins when starting ART.

Multiple interventions are effective in decreasing CVD risk in people with HIV.

Do not diagnose hypertension based on one or two BP measurements in your office.

Newest guidelines define hypertension at ≥130 / ≥80 mmHg.

BP target for most hypertensive patients is now <130/80 mmHg.

Do not miss lactic acidosis in your patients on d4T or AZT.

TDF is associated with bone loss, but does it lead to fractures?

Do not miss lipodystrophy in your patients. You may not have injectable fillers or rGH-GF, but you can switch their ART.

Thank you!