HIV & Cardiovascular Disease

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No relevant disclosures

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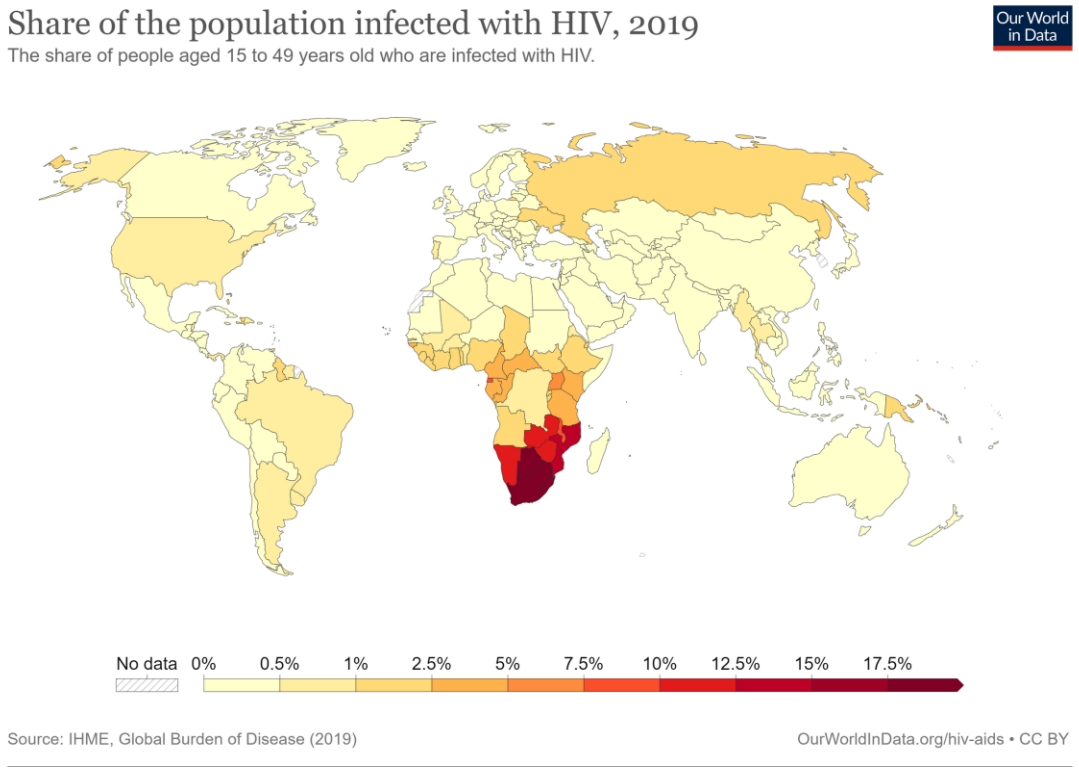
Overview

1. Epidemiology
2. Disease mechanisms
3. Myocardial disease
4. Heart failure
5. Coronary artery disease
6. Dyslipidaemia
7. Vasculopathy
8. Sex disparities
9. Why further research matters

Epidemiology

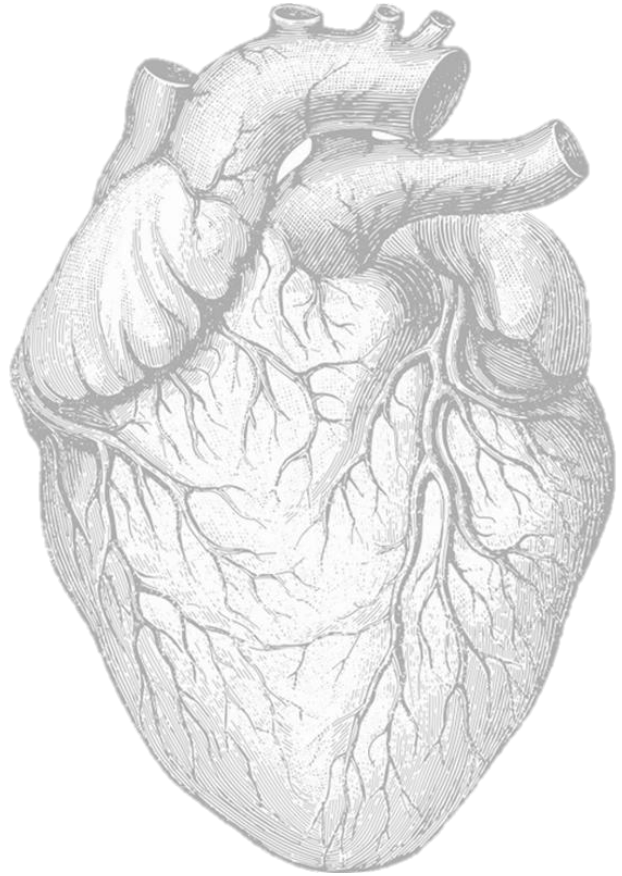
- At the end of 2022, 38.4 million people living with HIV globally, 69% of these in sub-Saharan Africa (19.5 million (53%) of global total on ART)
- Due to wide scale use & availability of ART, HIV-related mortality has decreased substantially
- AIDS deaths have fallen from 1.9 million in 2005 to 1 million in 2019 (the vast majority in SSA)
- Global target of 30 million people on ART by 2020 not reached: treatment scale-up needs to be accelerated
- WHO & UNAIDS aim to eradicate AIDS by 2030



Ntusi NAB, et al. *ESC Heart Failure* 2016;3(3):158-167.
WHO (https://www.who.int/data/gho/data/themes/hiv-aids)

Epidemiology

- HIV-associated CVD is present in up to 10-20% of hospitalised patients with HIV infection
- Can affect every segment of the cardiovascular axis
- Florid myocarditis & dilated LV with overt systolic dysfunction common in pre-ART era with high rates of mortality within 6 months
- ART has completely changed epidemiology: symptomatic myocarditis & cardiomyopathy uncommon, but diastolic dysfunction with preserved LV systolic function & size predominant phenotype



Ntusi NAB, et al. *ESC Heart Failure* 2016;3(3):158-167.
Sinha A, et al. *Prog Cardiovasc Dis* 2020;63(3):132-141.

Increasing disease burden

Burden of HIV-associated CVD is increasing due to:

1. **Growing population** of people living with HIV

2. **Late diagnosis**

   In 2016 in South Africa: 33% entered care with CD4<200 & 17% with CD4<100

3. **Disengagement from care**

   23% disengaged from ART care over 2 years in Khayelitsa

4. **Adherence problems & delays to switching to second line ART**

   Median 6 months (IQR 0–43) delay in eThekwini

Carmona, *Clin Infect Dis* 2018:66:S111
Kaplan, *PLoS Med* 14(11): e1002407
Narainsamy, *SA J HIV Med* 2017

Epidemic drivers in SSA

New HIV infections

Poverty & challenging social circumstances

Age-disparate sexual partnering

Transactional sex

Multiple concurrent partnerships

Gender-based violence

Mobile populations

Vaginal microbiome & inflammation

HIV associated CVD

Success of ART

Duration of ART

Ageing population of PLHIV

Vertical & fragmented health systems

Epidemiological transition

Lifestyle/urbanisation

Obesity & other traditional risk factors

HIV-associated CVD

Hypertension

Metabolic syndrome

Dyslipidaemia

Coronary artery disease

Valvular heart disease

Pericarditis

Myocarditis

Coronary artery dissection

Cardiomyopathy

De novo arteriothrombosis

Myocardial fibrosis

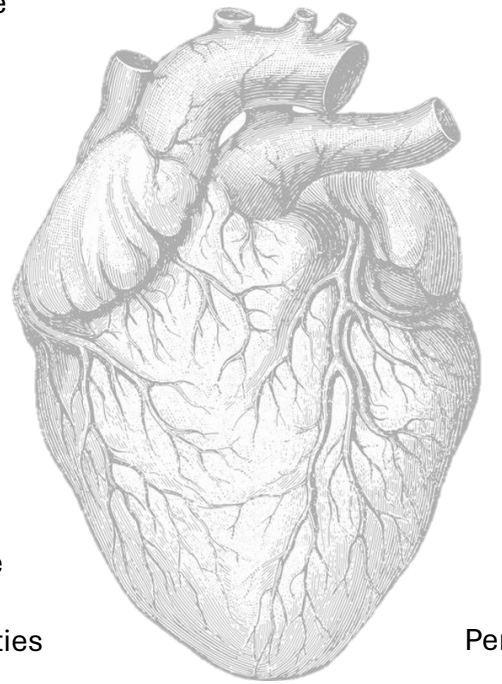
Autoimmunity

Myocardial lipidosis

Deep vein thrombosis

Treatment-related neuromuscular & cardiac toxicity

Lipodystrophy & pericardial adipose deposits



Cardiac amyloidosis

Heart failure

Cerebrovascular disease

Arterial stiffness

Conduction system abnormalities

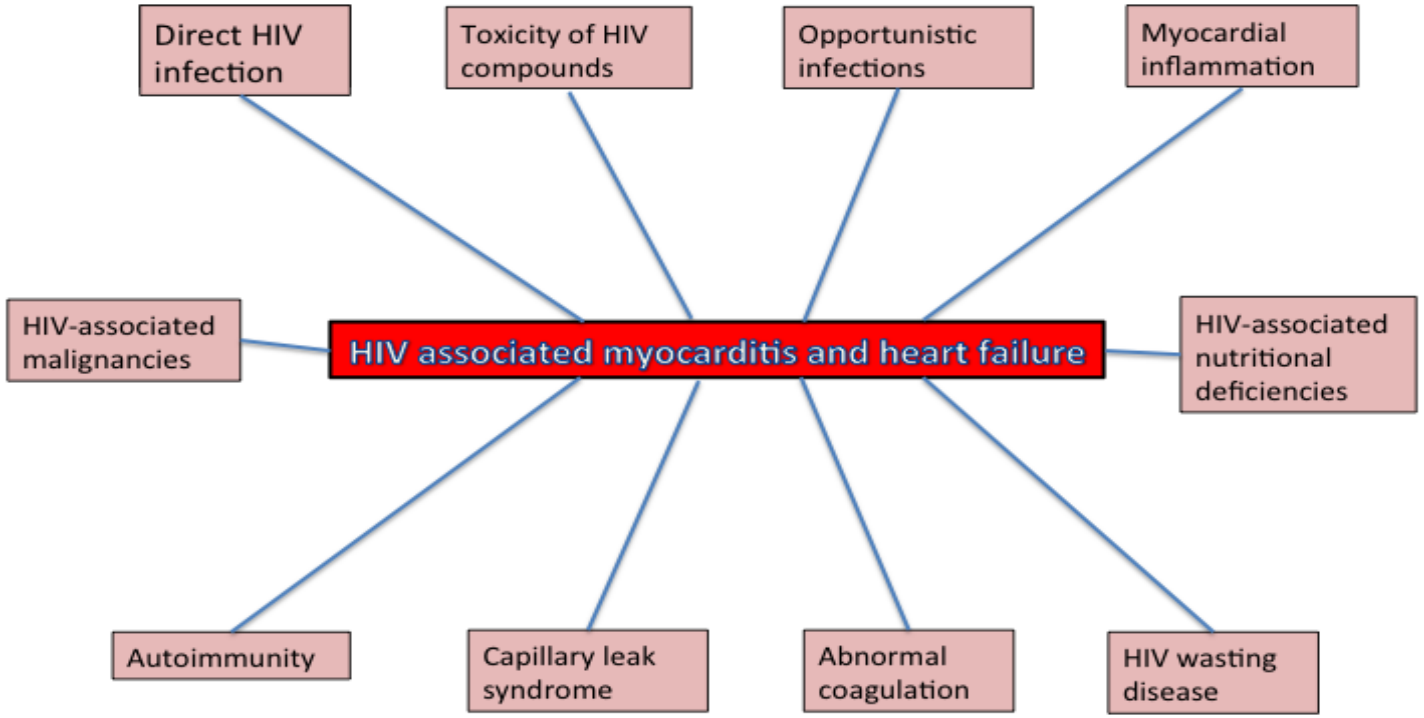
Peripheral vascular disease

Pulmonary hypertension

Vasculitis

HIV vasculopathy

Pathophysiology

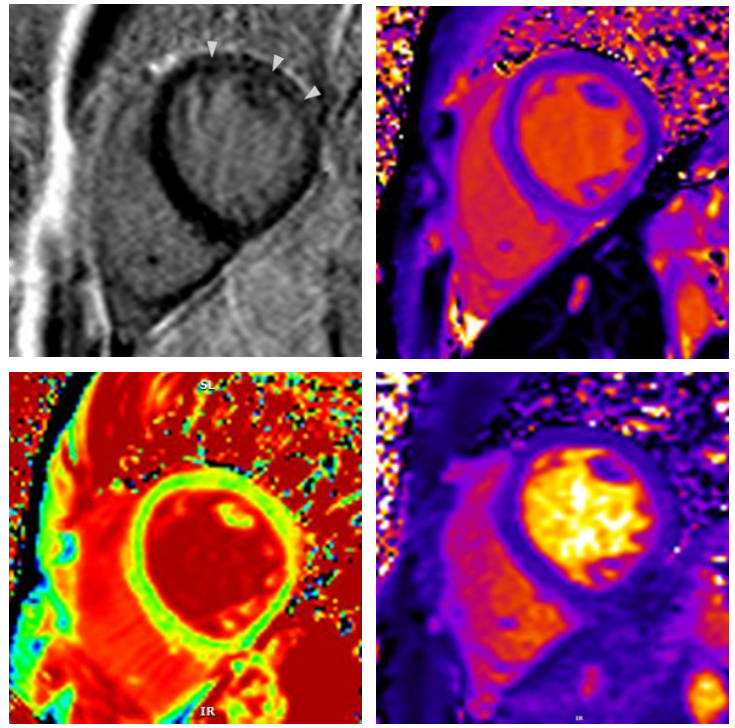


Ntusi NAB. *Curr Opinion HIV AIDS* 2017.

CMR & MRS consistently reveal high burden of myocardial disease in HIV

Comprehensive CMR & MRS reveal high burden of myocardial disease in HIV

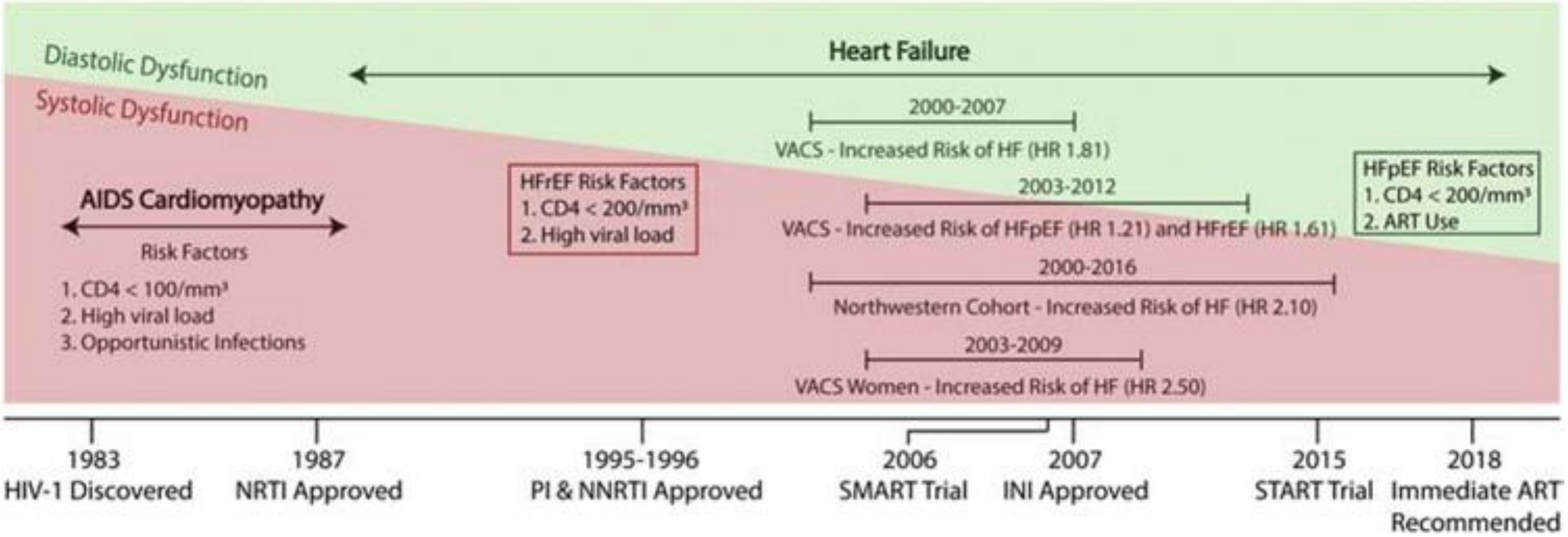
- Lower global longitudinal function
- Impairment in systolic & diastolic strain rates
- Increased focal fibrosis in LGE imaging
- Higher native T1 parametric mapping values
- Higher ECV values
- Higher myocardial steatosis
- Higher serum triglycerides
- Higher frequency of pericardial effusions
- Higher T2 STIR signal intensity ratios



Chronic subclinical inflammation drives fibrosis, as well as diastolic & systolic dysfunction.

Holloway CJ, Ntusi NAB, et al. *Circulation* 2013;128:814-822.
Ntusi NAB, et al. *Circulation Cardiovasc Imaging* 2016; 9(3):e004430.
Jao J, et al. European Heart Journal 2023;44:ehad655.2736..

Diastolic dysfunction has become the predominant functional impairment



Sinha A, et al. *Prog Cardiovasc Dis* 2020;63(3):132-141.
Shuldiener S, et al. *Open Forum Infect Dis* 2020;8(1):ofaa600.
Petersen T, et al. *ESC Heart Failure* 2020;7(5):3246-3251.

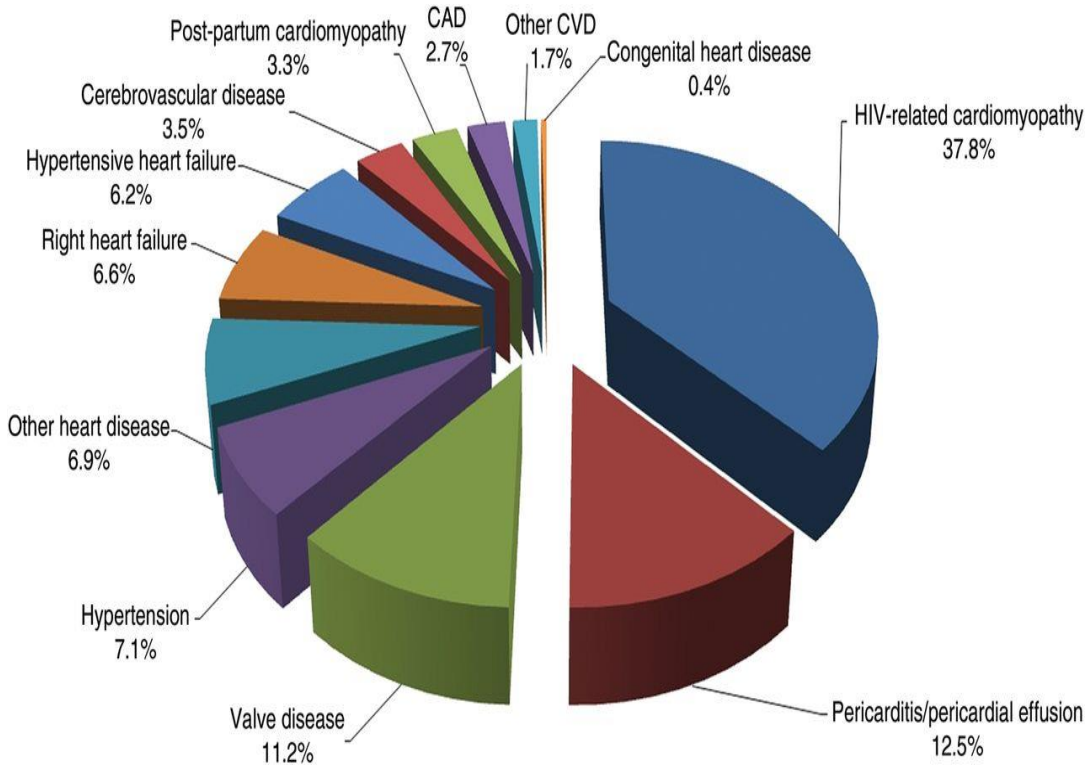
Heart Failure

Heart failure in SSA (1957 – 2008_ caused by:

1. Hypertension
2. Cardiomyopathy
3. RHD

HIV accounted for less than 5% of causes of HF

38% of HIV-infected individuals presented in HF



Ntusi NAB, et al. *Expert Rev Cardiovasc Ther* 2009; Dis 2009;7(2):169-180.
Sliwa K, et al. *Eur Heart J* 2012;33(7):866-874.

Heart Failure

An analysis of 25 studies from Africa, Asia, North America & Europe confirm that, between 2000 & 2018, there was a nearly **2-fold increased risk of HF** in HIV-infected persons. This association persisted in those with & without coronary artery disease

Risk factors for HF in HIV include:

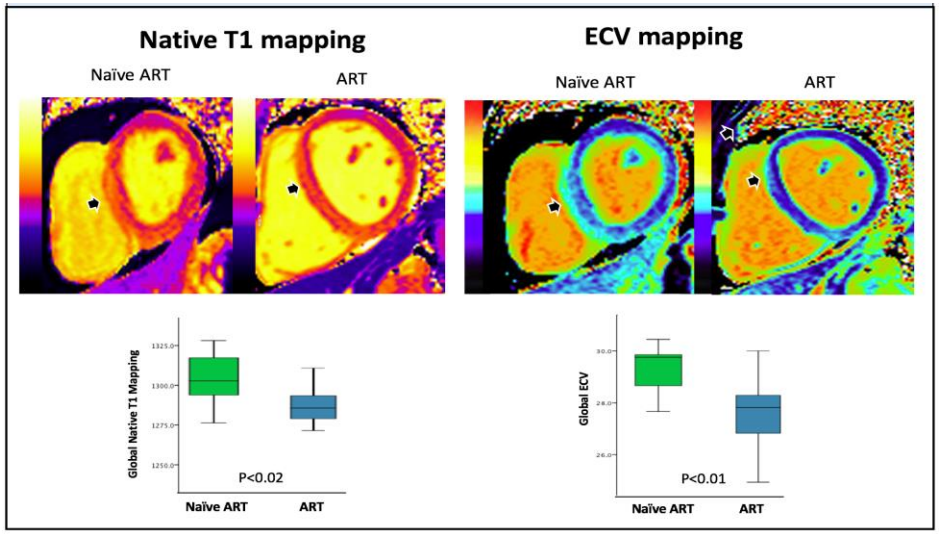
- Elevated VL
- Low nadir CD4 count
- Low current CD4 count
- Presence of traditional CV risk factors
- Female sex

Holloway CJ, Ntusi NAB, et al. *Circulation* 2013;128:814-822. Ntusi NAB, et al. *Circulation Cardiovasc Imaging* 2016; 9(3):e004430. Jao J, et al. European Heart Journal 2023;44:ehad655.2736. Al-Kindi SG, et al. *Int J Cardiol* 2016;218:43-46. Feinstein MJ, et al. *J Am Heart Ass* 2018;7(21):e009985. Freiberg MS, et al. *JAMA Cardiol* 2017;2(5):536-546. Ntsekhe M, et al. *Nat Clin Pract Cardiovasc Med* 2009;6(2):120-127. Butt AA, et al. *Archives Int Med* 2011;171(8):737-7432017;24(16):1746-1758. Steverson AB, et al. *Eur J Prevent Cardiol* 2017;26(16):1746-1758. Yen YF, et al. *J AIDS* 2019;80(3):255-263. Womack JA, et al. *J Am Heart Ass* 2014;3(5):e001035. Janjua SA, et al. *JACC* 2017;69(1):107-108. Erqou S, et al. *JACC Heart failure* 2019;7(2):98-108.

ART modulation of myocardial abnormalities

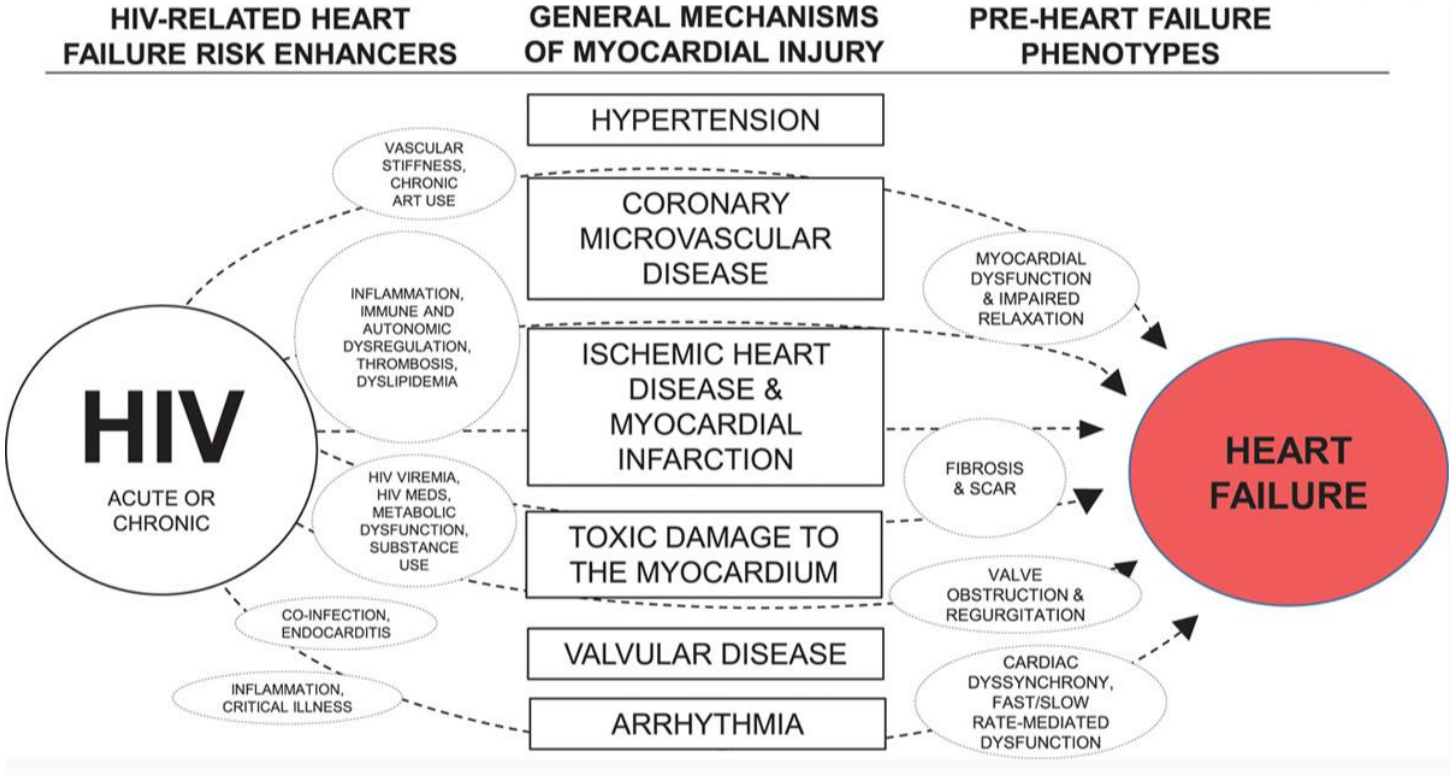
When compared to ART-naïve HIV+, those on ART showed:

- Reduced levels of systolic & diastolic dysfunction
- Reduced myocardial strain
- Less fibrosis
- Less oedema
- Reduced LV remodeling in perinatally-infected adolescents



Menacho K, et al. *JACC Cardiovasc Imaging* 2020.
Saad H, et al. Unpublished data.
Magodoro I, et al. *Circ Res* 2021.
Magodoro I, et al. *Int J Cardiol* 2023

Proposed mechanisms of myocardial dysfunction & HF



<u>Mechanistic drivers of HF in HIV:</u>

Myocardial fibrosis

Subclinical immune activation

Myocardial steatosis

Diastolic dysfunction

Pericardial constriction

Elevated hsTnT & NT-proBNP

Ischaemia/CAD

Arrhythmias

Pulmonary hypertension

Pericardial constriction

Feinstein MJ, et al. Circulation 2019;140:e98-e124. Shuldiner SR, et al. *Open Forum Infect Dis* 2020;8(1):ofa600, Holloway CJ, Ntusi NAB, et al. *Circulation* 2013;128:814-822, Ntusi NAB, et al. *Circulation Cardiovasc Imaging* 2016; 9(3):e004430, Ntusi NAB, et al. *J Cardiovasc Magn Reson* 2016;18(Suppl1):Q29., Petersen T, et al. *ESC Heart Failure* 2020;7(5):3246-3251.

Ischaemic heart disease in HIV

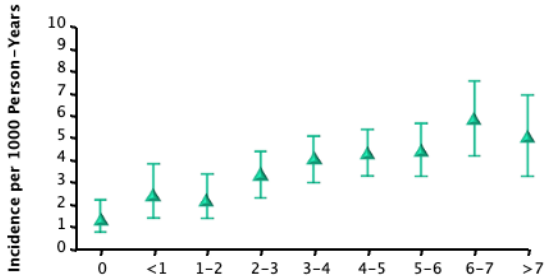
Increasing impact of ASCVD on morbidity & mortality in HIV relative to AIDS-related diagnoses

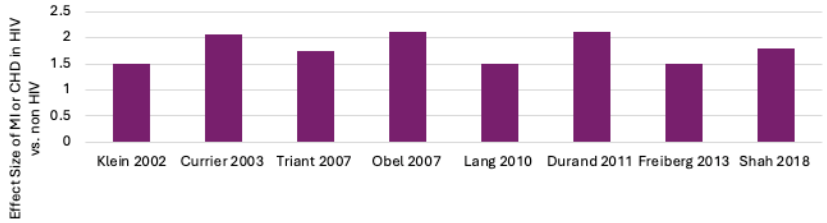
Risk of MI/CAD is increased in PLHIV & the incidence of MI increases with duration of ART use

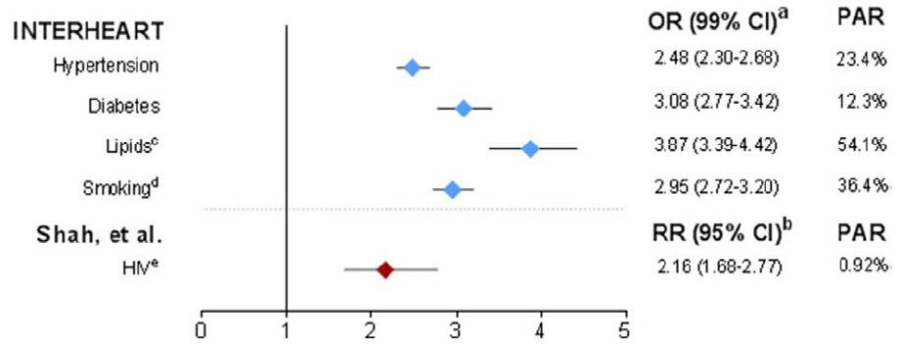
Increased risk of CAD is **beyond** that predicted by traditional risk factors

1.5 to 2-fold increased risk of IHD conferred by HIV, with specific risk varying by sex & virologic/immunologic status

Specific ART may increase CVD risk, yet the net effect of ART with viral suppression is beneficial with regard to CVD risk







Friis-Moller N, et al. *AIDS* 2003;17:1179-1193.
SMART Study Group. *NEJM* 2006;355:2283-2296.

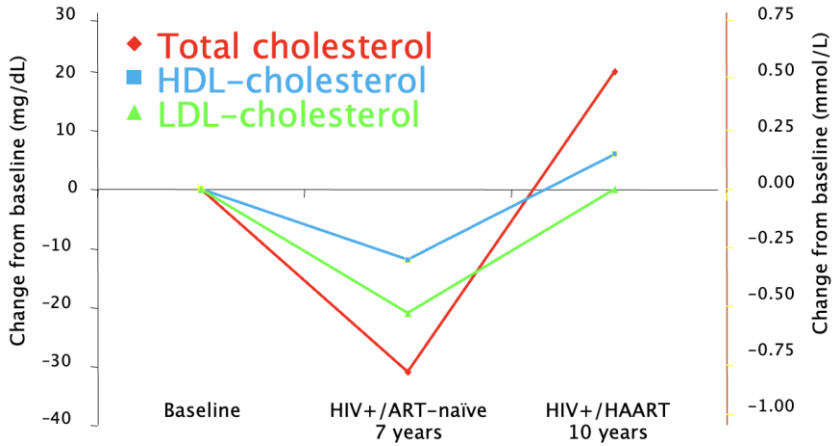
HI viraemia perturbs plasma lipids

Analysis in 13,698 PLWH: pooled prevalence of **moderate-high cardiovascular risk** through random-effect modeling was **20.41%** (95% CI: 16.77-24.31)

The most prevalent concomitant cardiovascular risk factor was dyslipidemia (39.5%)

Dyslipidemia is a key driver of ASCVD in PLHIV

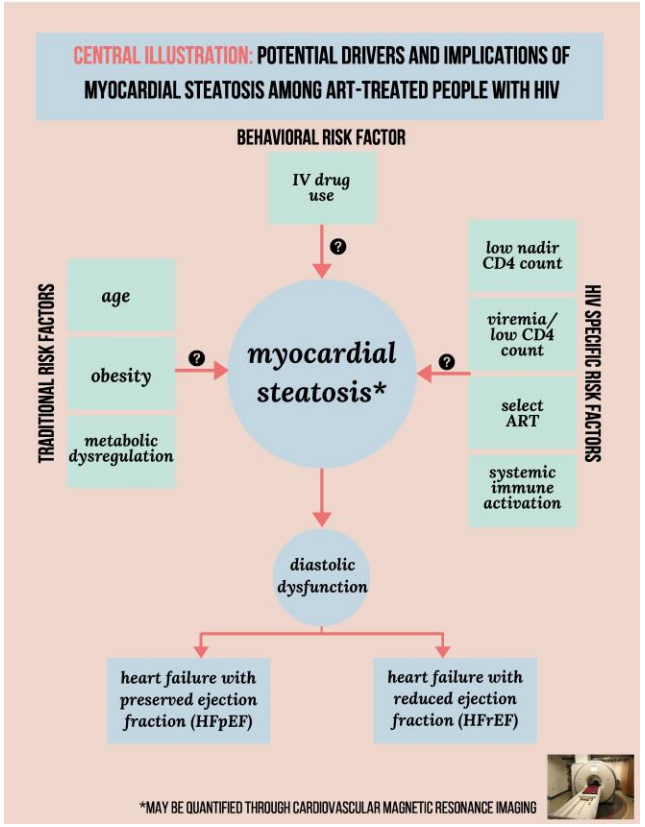
Consistent use of lipid lowering therapy in HIV infections is associated with lowered risk for major cardiovascular events & mortality



Drug	HDL-c	LDL-c	TG	TC
PIs				
Ritonavir-boosted PIs	↓	↑	↑↑	↑↑
Lopinavir/ritonavir	↓	↑	↑↑↑	↑↑↑
Fosamprenavir/ritonavir	↓	↑	↑↑↑	↑↑↑
Darunavir/ritonavir	↓	↑	↑↑	↑↑
Atazanavir/ritonavir	↓	↑	↑↑	↑↑
Nelfinavir	[a]/↓		↑	↑
Saquinavir	↑/[a]		↑	↑
NNRTIs				
Efavirenz			↑↑	↑↑
Nevirapine			↑	↑
NRTIs				
Stavudine		↑↑↑	↑↑↑	
Zidovudine		↑↑	↑↑	
Abacavir		↑	↑	

Riddler SA, et al. *JAMA* 2003;289:2978-2982.
Bloomfield & Leung. Cardiol Clin 35 (2017) 59–70, http://dx.doi.org/10.1016/j.ccl.2016.09.003
Catapano AL, et al. Eur Heart J 2016;37:2999–3058. 2. Mach F, et al. Eur Heart J 2019;41:111–88.
Grinspoon, Douglas *Am Heart J* 2019

Myocardial steatosis in HIV

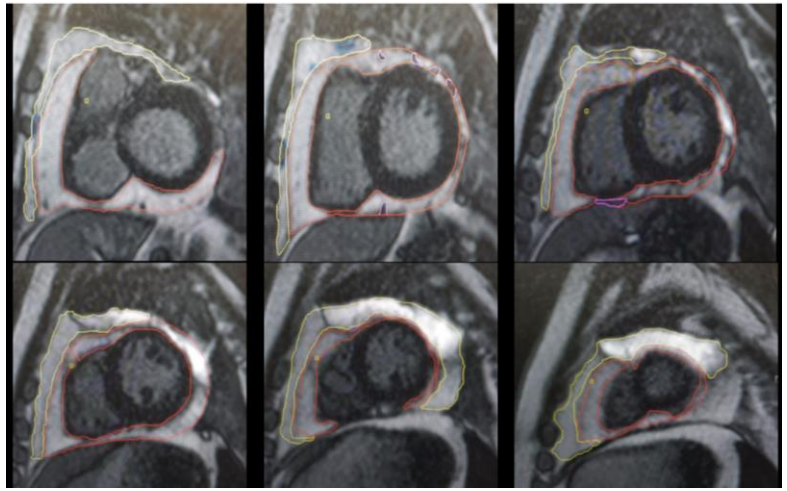


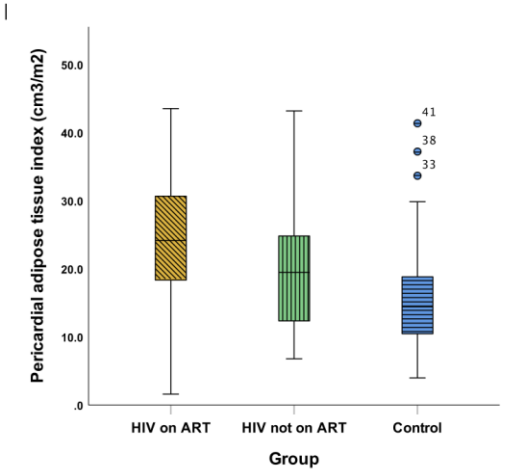
Covariates of myocardial steatosis:

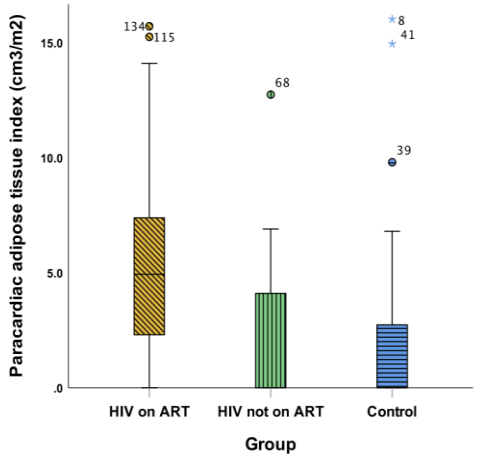
- Age
- Body mass index
- History of intravenous drug use
- Nadir CD4 count
- Select ART use

Neilan TG, et al. *J Infect Dis* 2020;222(Suppl 1):S63-S69.

Pericardial & paracardiac fat in HIV







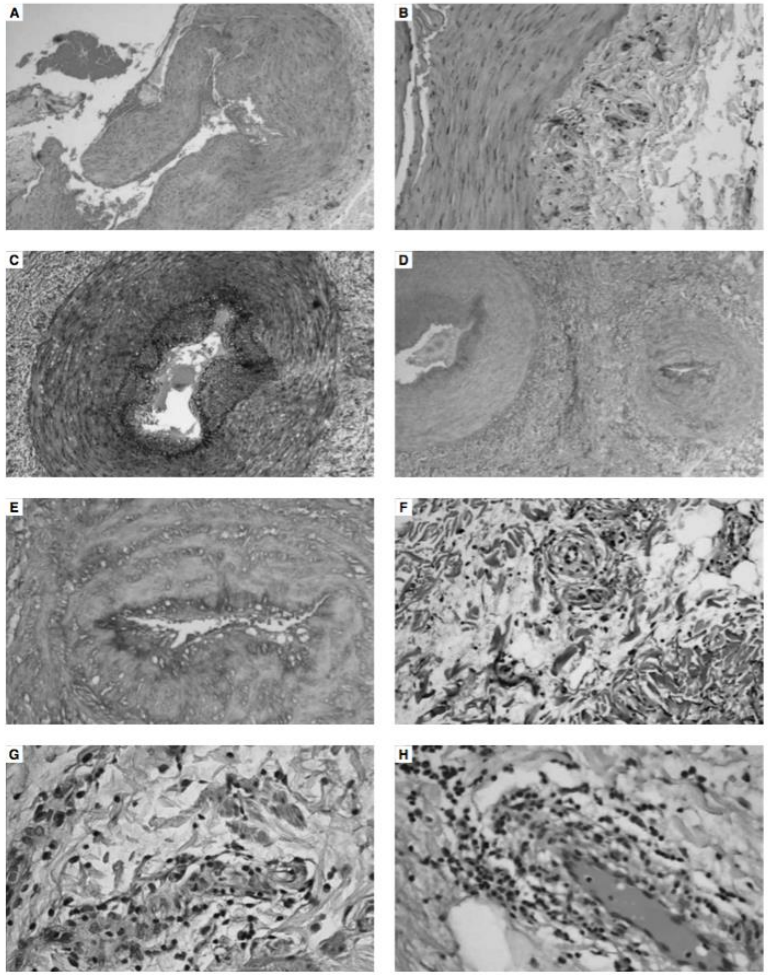
- Demonstrate a gradient of PAT & ParaAT volume, which is greatest in PLHIV on ART, has an intermediate phenotype in untreated PLHIV, & is lowest in HIV uninfected persons

- Abnormalities in strain, strain rate, LVM, myocardial inflammation & fibrosis are commonest in untreated PLHIV compared to PLHIV on ART & uninfected controls

- Both PAT & ParaAT showed weak correlations with indices of myocardial function & tissue characteristics

Maishi P, et al. ISMRT 2023.

HIV vasculopathy



- Thickened vessels
- Prominent adventitial capillaries
- **Lymphocyte infiltration**
- **Reduplication of the lamina**
- Mucopolysaccharide deposition in vessel wall
- **Fragmented stromal collagen**
- **Plexiform changes**
- **Thrombosis**
- **Aneurysm formation**

Ntusi NAB, et al. *Cardiovasc J Afr* 2011;22(4):197-200.

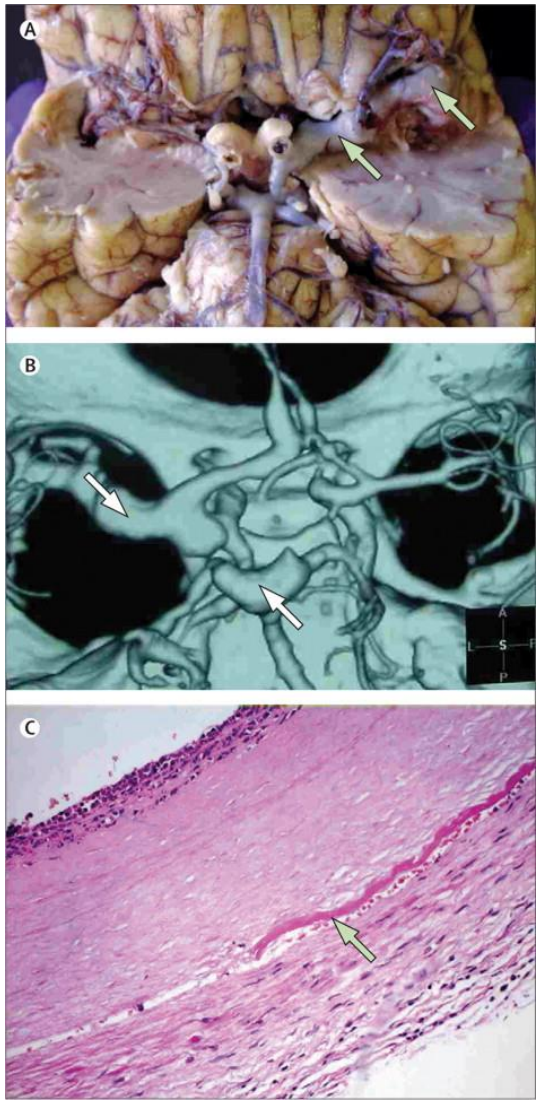
HIV & stroke

Mechanisms include:

- Vasculopathy
- Opportunistic infection
- Cardioembolism
- Coagulopathy

HIV-associated vasculopathy describes various cerebrovascular changes, including **stenosis & aneurysm formation, vasculitis, & accelerated atherosclerosis**

ART is clearly beneficial, but can be atherogenic & may increase stroke risk (OR reduced from 3.4 to 1.6)



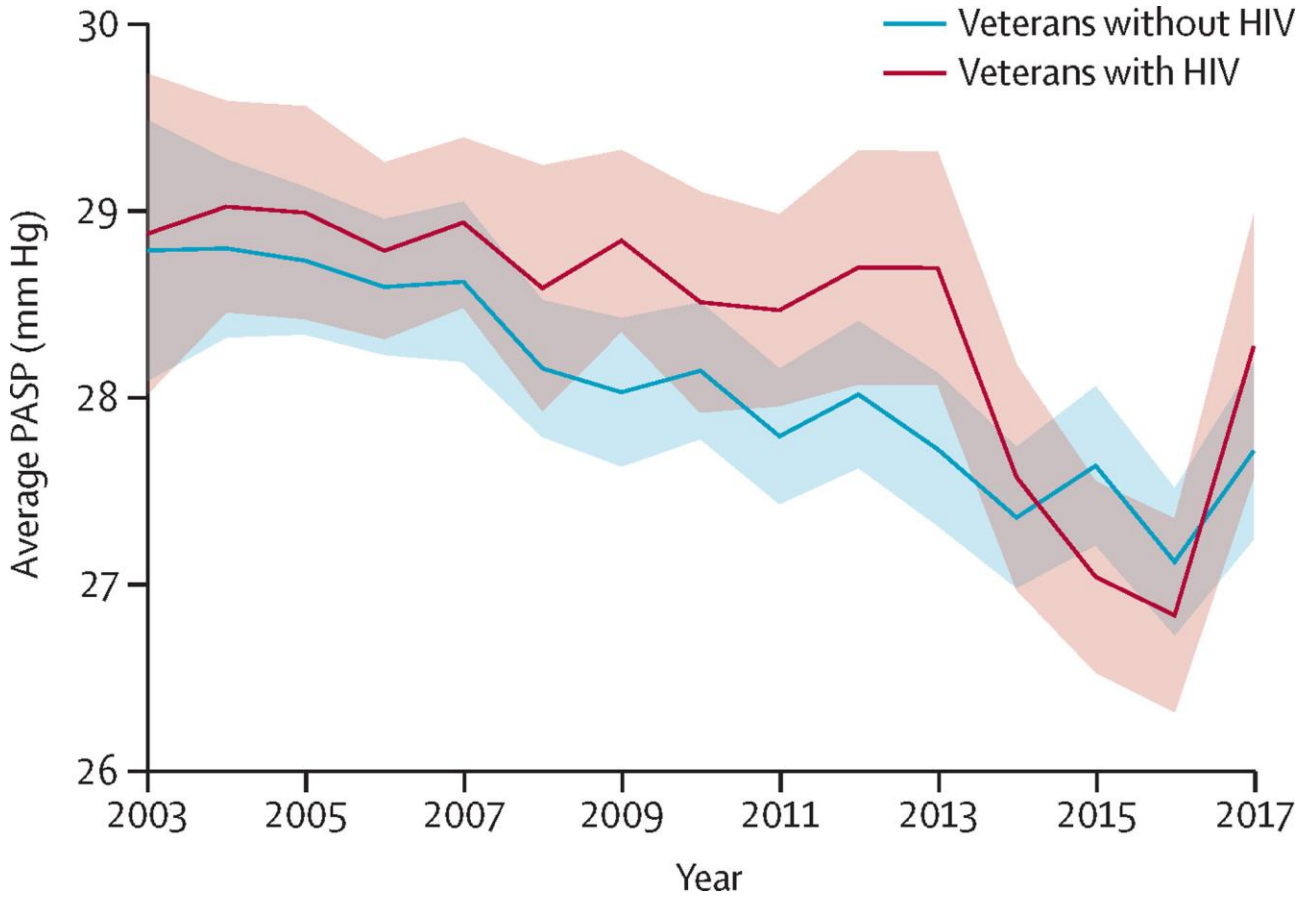
Benjamin LA, et al. *Lancet Neurol* 2012;11(10): 878-890.
Benjamin LA, et al. *Neurol Neuroimmunol Neuroinflamm* 2016;3(4):e254.

HIV-associated primary pulmonary hypertension

A life-threatening condition characterised by pulmonary vascular remodelling, elevated pulmonary arterial pressure & right heart failure

PLHIV have a higher incidence of pulmonary hypertension than the general population

Incidence reduced by use of ART



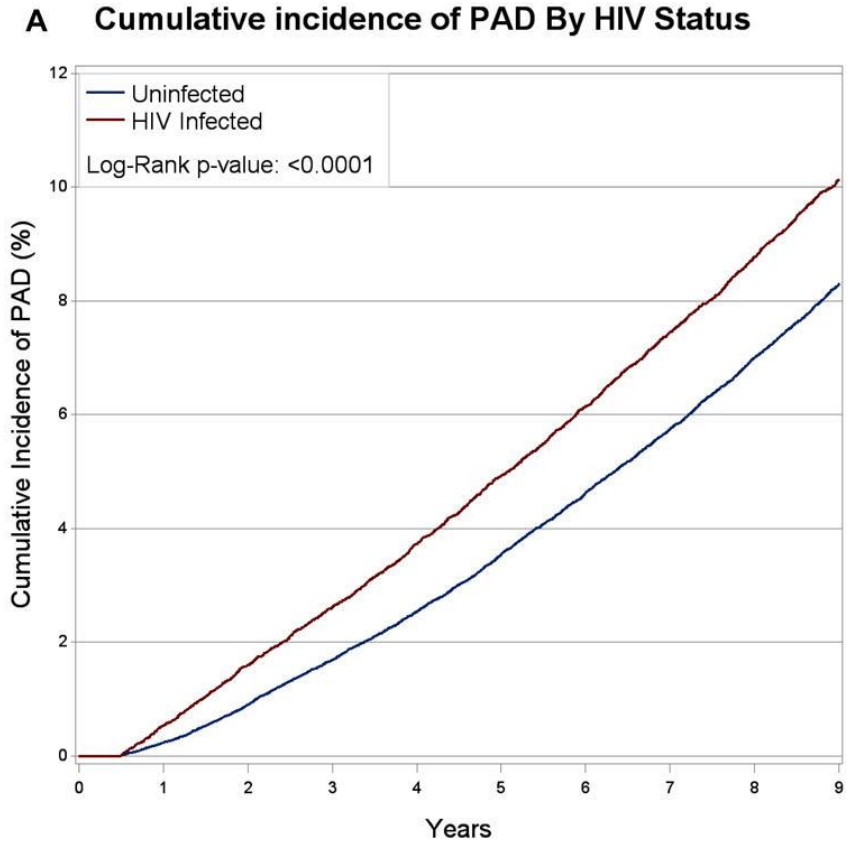
Duncan MS, et al. *Lancet Healthy Longev*. 2021

HIV-associated peripheral arterial disease

Established relationship between HIV & vascular system characterized by clinical expression of **aneurysmal & occlusive disease** that emanate from a **common pathological process**

Infection with HIV is associated with a **19% increased risk of PAD** beyond that explained by traditional atherosclerotic risk factors.

The clinical, imaging & pathological observations position HIV-associated large-vessel vasculopathy as a **unique entity**



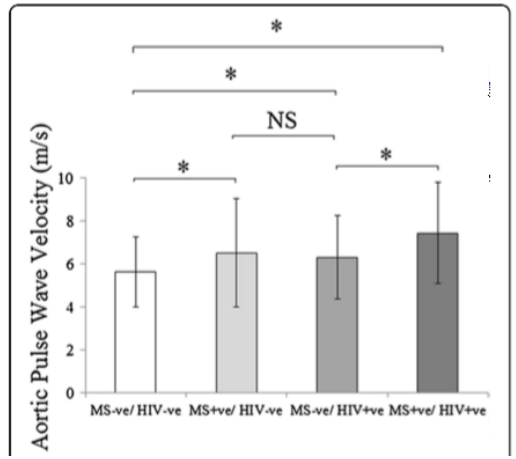
Beckman JA, et al. Circulation 2018;138(3):255-265.
Pillay B, et al. Cardiovasc J Afr 2015;26(2):70-81.

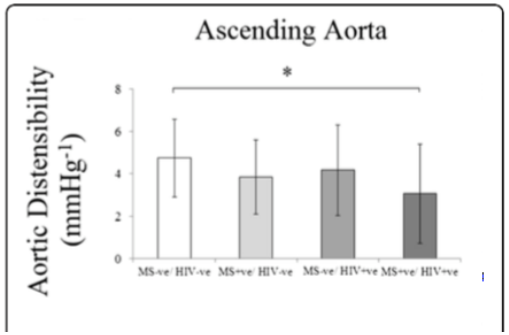
Aortic distensibility & vascular dysfunction

HIV is an independent predictor of aortic stiffness & vascular dysfunction

HIV infected patients had:

- Higher pulse wave velocity
- Lower aortic distensibility
- Vascular stiffness most impaired in those with HIV infection & metabolic syndrome
- HIV uninfected & with no metabolic syndrome have the least impairments in vascular elasticity





Rider O, et al. *J Cardiovasc Magn Reson* 2014;16:57.

Sex-disparities in HIV-associated CVD

Female sex has been shown to be a risk-factor for HF in PWHIV with

- 2-2.8 times higher risk compared to woman without HIV
- 1.5-2 times higher risk compared to men with HIV infection

Among those with HF, women with HIV have higher rates of:

- HF hospitalization
- Longer HF hospital stays
- Higher rates of CVD mortality compared to uninfected women

Coronary artery disease incidence is about 1.5-2-fold higher in women with HIV

Al-Kindi SG, et al. *Int J Cardiol* 2016;218:43-46. Feinstein MJ, et al. *J Am Heart Ass* 2018;7(21):e009985. Freiberg MS, et al. *JAMA Cardiol* 2017;2(5):536-546. Ntsekhe M, et al. *Nat Clin Pract Cardiovasc Med* 2009;6(2):120-127. Butt AA, et al. *Archives Int Med* 2011;171(8):737-7432017;24(16):1746-1758. Steverson AB, et al. *Eur J Prevent Cardiol* 2017;26(16):1746-1758. Yen YF, et al. *J AIDS* 2019;80(3):255-263. Womack JA, et al. *J Am Heart Ass* 2014;3(5):e001035. Janjua SA, et al. *JACC* 2017;69(1):107-108. Erqou S, et al. *JACC Heart failure* 2019;7(2):98-108.

Sex-disparities in HIV-associated CVD

Postulated that this may be due to:

- Sex-specific responses to the virus & to immunomodulatory agents due to higher levels of systemic immune activation
- Social & behavioural factors
- Comorbid conditions
- Perturbations in the hypothalamic-pituitary-gonadal axis

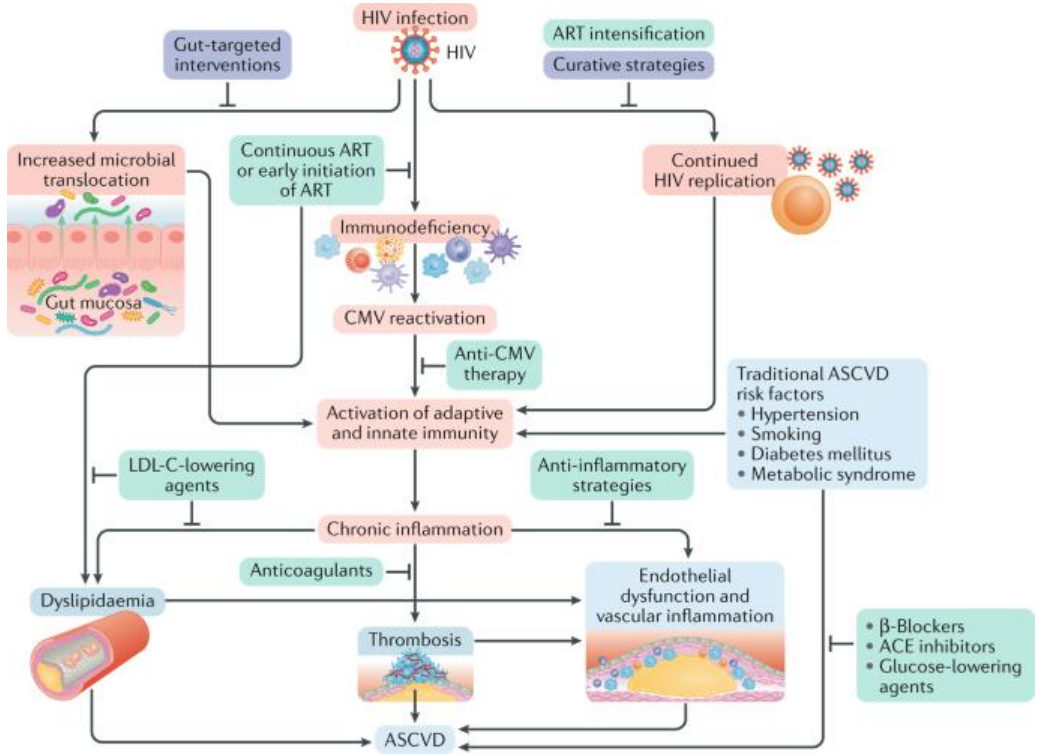
Raghavan, A., et al. *Current Hiv/Aids Reports*. 2017;*14*, pp.220-228.
Foldyna, Borek, et al. *JAIDS. 2018;*78:4, pp.421-428

Challenges in management of HIV-associated CVD

Limited understanding of the mechanisms & treatment strategies for CVD specific to PLHIV

Newer studies suggest the importance of inflammation & immune dysfunction as non-traditional disease mechanisms & hence risk factors/markers

Current recommendations for prevention of CVD in PWH are non-specific & do not consider the unique pathophysiology of atherosclerosis in this population



Hsue PY, et al. *Nature Rev Cardiol* 2019;16:745-759.

Why further research matters

Africa, whilst representing the youngest & fastest growing population in the world, has the oldest & most diverse genome in the world

Africa carries 20% of global burden of disease, however its scientific output represents less than 1% of the world's share

Burden of disease rapidly shifting from communicable to non-communicable & the interplay between these becomes important.

World-class facilities & expertise for the study of disease epidemiology, natural history, mechanisms, management, outcomes & prognosis

Thank you

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