Antiretroviral treatment is Associated with increased Arterial Stiffness in Sub-Saharan African HIV-1 Infected Patients: A cross- Sectional Study

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Presentation outline

- Background
- Literature review
- Justification/rationale
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- Objectives
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- Summary & conclusion

- Acknowledgment

Background

- HIV infections have continued to rise since first cases were reported in early 1980's
- In Dec 2009, an estimated 33.3m persons were living with HIV/AIDS with 22.4m (68%) in the Sub-Saharan Africa (SSA). 2.6 million new infections and 1.8 million deaths, 260,000 being children. At the end 2013, an estimate 35m,among them 19m don't know their status worldwide.
- At the end 2013, 11.7m people worldwide was enrolled in the use of cART in the low and middle income countries.
- Long-term remission/suppression of HIV, can be achieved by use of combination therapy of ART(cART) agents.
- The increased use of these cART has led to increase in adverse effects

(UNAIDS AIDS epidemic update, 2010,2013,WHO, 2010, , Pornprasert et. al, 2010, Marfatia & Smita , 2005, Montessori et al.,2004

HIV in Tanzania

- HIV prevalence: 2013, 5.1%,2009 an estimate 5.7% lower compared to 7% (2005). females: 6.6% and males 4.6% (TACAIDS 2010);

- By 2009, TACAIDS estimated that 1.2 m were living with HIV (TACAIDS 2010)

- From 2004-2009, the no. of patients on cART has been increasing exponentially parallel with increase with new infections *(Bisimba J. 2009, TACAIDS 2010,)*
- At the end 2013,Tanzania mainland had a total of 512,555 HIV infected persons currently on cART

Global Antiretroviral therapy coverage in 2008 and 2009 compared

\	Dec. 2008	Dec. 2009
Children and adults receiving ART	4 ,053 ,000	**5, 254,000**
ART coverage in adults and children Based on 2009 WHO guidelines (<350 CD4 cells /uL)	28% [26–31%]	**36%** [33–39%]
ART coverage among children <15	22% [16–34%]	28% [21–43%]
Pregnant women receiving ART (PMTCT)	45% [37–57%]	53% [40–79%]

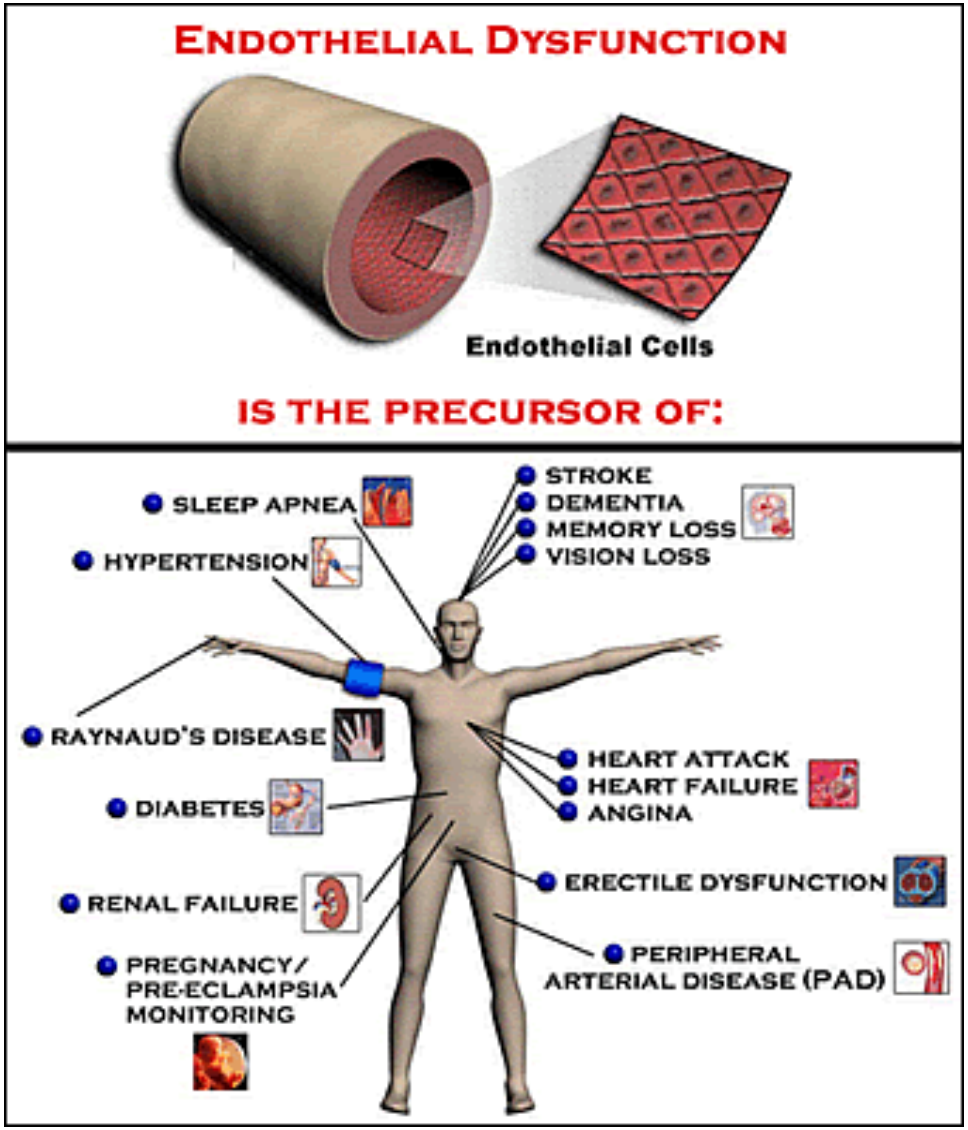
(WHO ,2010)

Use of cART improve significantly the health status of people living with HIV/AIDS;

- Suppression of viral duplication,
- Reinstatement of the immune response,
- Arresting the progression of disease
- Increased survival rates,
- Reduced morbidity and
- Improved quality of life

(Henderson et al, 2005)

- The increased use of these cART has led to increase in adverse effects among them;
- Cardiovascular complication
- Hypercholesterolemia (Dyslipidemia, Hyperlipidemia, high cholesterol)
- Lipodystrophy

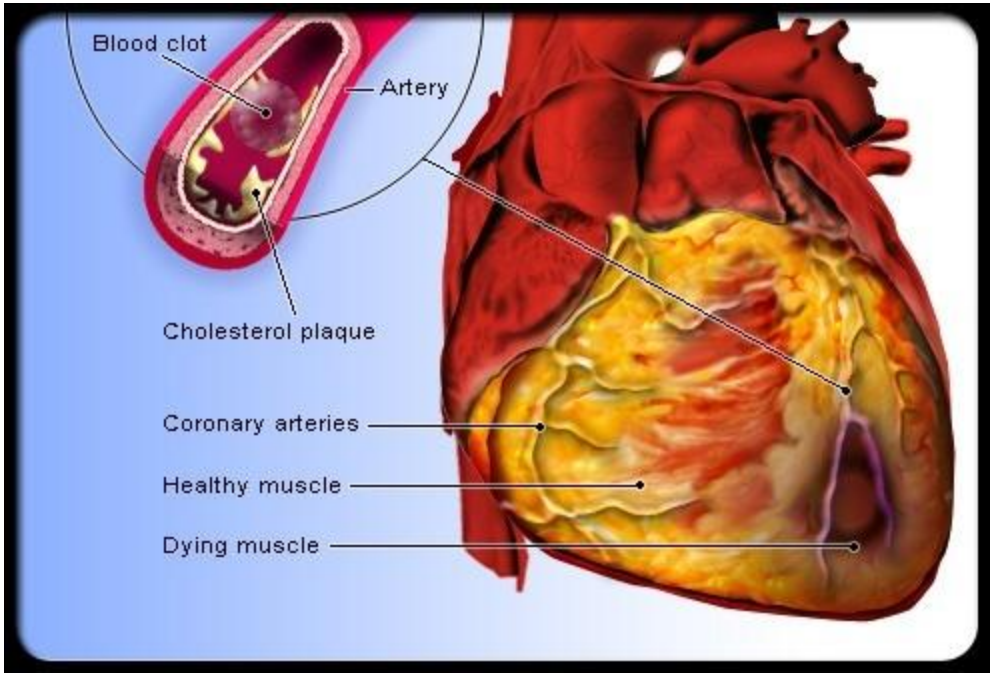

ENDOTHELIAL DYSFUNCTION
Endothelial Cells
IS THE PRECURSOR OF:
SLEEP APNEA
HYPERTENSION
RAYNAUD'S DISEASE
DIABETES
RENAL FAILURE
PREGNANCY/ PRE-ECLAMPSIA MONITORING
STROKE
DEMENTIA
MEMORY LOSS
VISION LOSS
HEART ATTACK
HEART FAILURE
ANGINA
ERECTILE DYSFUNCTION
PERIPHERAL ARTERIAL DISEASE (PAD)

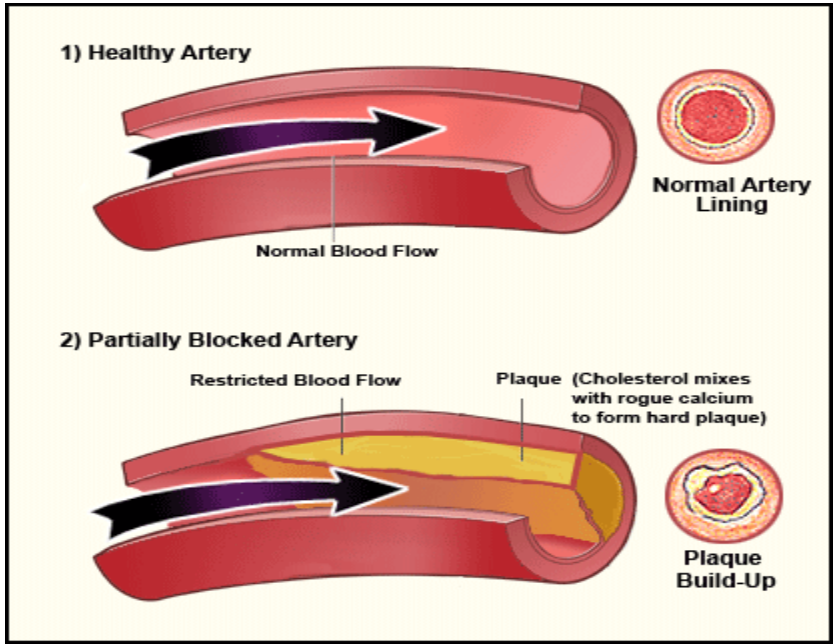
Myocardial Infarction in HIV

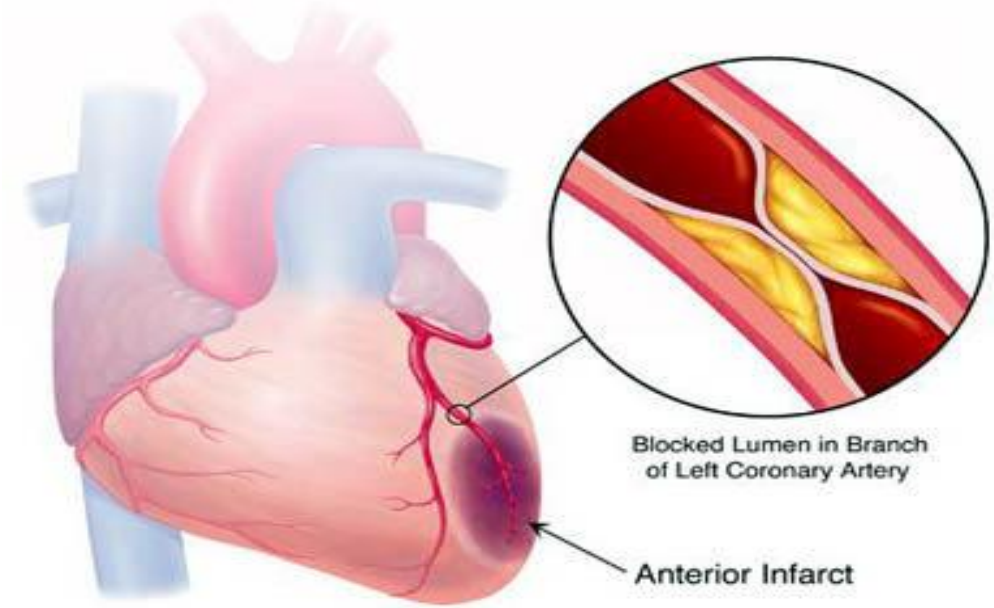
Age 33-44	rates	Infected	10%
		Uninfected	3%
Age 45-54		Infected	19%
		Uninfected	8%
Age 65-74		Infected	78%
		Uninfected	25%

- Overall risk of MI in HIV estimated 10-18% and 26% increase risk with cART
- Prevalence of some risk factor may be higher in HIV population

Judith S Currier et al.,2004


Blood clot
Artery
Cholesterol plaque
Coronary arteries
Healthy muscle
Dying muscle


1) Healthy Artery
Normal Blood Flow
Normal Artery Lining
2) Partially Blocked Artery
Restricted Blood Flow
Plaque (Cholesterol mixes with rogue calcium to form hard plaque)
Plaque Build-Up


Blocked Lumen in Branch of Left Coronary Artery
Anterior Infarct

Justification/rationale

- Number of people using cART is increasing each year and there is an increase in vascular and metabolic complications in HIV-infected patients receiving cART

- The relative burden of HIV and its therapies on vascular and metabolic changes in patients with HIV infection is not properly addressed in Tanzania

- Need to assess and compare the efficacy of cART in achieving viral load suppression and recovery in CD4

Hypothesis

- The chronic inflammatory state associated with HIV contributes to structural arterial changes, whereas cART causes metabolic derangements, such as dyslipidemia and hyperglycaemia

- Hypothesis for the chronic inflammation is translocation of bacteria from the gut to the blood causing a low grade inflammatory reaction.

Broad Objectives

We want to follow up(3 yrs) HIV negative controls, pre-cART HIV-infected, and individuals on cART to determine

- Arterial stiffening by measuring AoI and PWV by using SphygmoCor device
- The Framingham score
- Inflammatory markers CRP and bacterial DNA in blood

Specific objectives

To relate the vascular changes and the Framingham score to:

- The response to cART (CD4, Plasma HIV RNA)
- Anthropometric changes
- Clinical/demographic parameters

Research Questions

- Is AoI and CAR-FEM PWV accelerated during HIV-infection? Is there a relationship between the stiffness measurements and the Framingham score?
- Does cART attenuate the rate of AoI and CAR-FEM PWV
- Is cART associated with worsening of the metabolic profile (lipids, glucose metabolism) compared to the pre-cART period?
- Is therapy failure related to worsening of arterial stiffening and/or Framingham score?
- Do patients with signs of lipoatrophy/ lipohypertrophy have worsening arterial stiffness and/or Framingham score?

Primary Outcome

- AoI and CAR-FEM PWV might be accelerated during HIV-infection due to the inflammation response in the vascular wall

- cART may attenuate the rate of AoI and CAR-FEM PWV parameters of arterial stiffening

- cART might be associated with worsening of the metabolic profile (lipids, glucose metabolism) compared to the pre-ART period

Methodology

- Cross sectional

- **Population**

  - Adult person M/F
  - Age 40-60
  - Follow up during 0,1,2 &3 years

- **Sample size**

  - 3 groups of 75 participants@

- **Individual groups**

  - Patients tested HIV negative (at t= 0 and t= 3 years) without cardiovascular co morbidity, HT, or diabetes

- **Inclusion**
  - Age 40-60 years (male and female)
  - HIV patients with CD4 count > 500/ul and not on cART
  - HIV patients started on first line-cART consistent of AZT-3TC-NVP and suppressed viral load for > 3 months

- **Exclusion**
  - Central obesity.
  - Hyperlipidemia
  - Diabetes mellitus or fasting plasma glucose >6.9mmol/l
  - Hypertension (BP >140/90) or cardiovascular disease
  - Use of cardiovascular drugs or statins.
  - Smoking
  - Evidence of IHD

Measurements which will be done for each group in 3 years: 0 (screening), 12, 24, 36 months

- Lipid panel:(HDL, LDL,TG,FBG)
- Immunologic studies
- Virologic studies: Plasma HIV RNA
- Anthropometric assessments (weight, height and skin-fold thickness)
- Inflammatory markers (CRP, bacterial DNA)
- Vascular measurements

Sample collection and processing

- 2x 7 cc ml of whole blood/EDTA
- **Plasma separation**
  - Plasma will be separated within 8 hours of blood collection
  - Serum and whole blood will be stored at -80^{0}C

- Ethical clearance was obtained from KCM College Research Ethical committee
- Permission was obtained from IDC clinic and medical department
- Informed written consent will be sought from all participants
- Subject has the right to discontinue from the study without consequences for their treatment

Statistical analysis

- All data were analysed by use of the SPSS statistical package.
- Descriptive data were expressed as means ±SD or median-range, as appropriate .
- All *P* values less than 0.05 were considered to indicate significance.

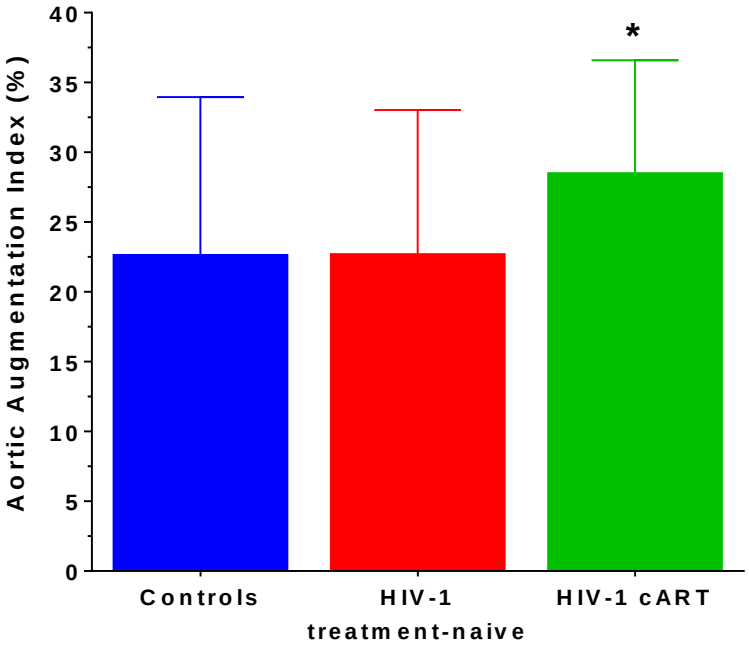
- Data dissemination
  - PhD thesis
  - Publication in the International journals

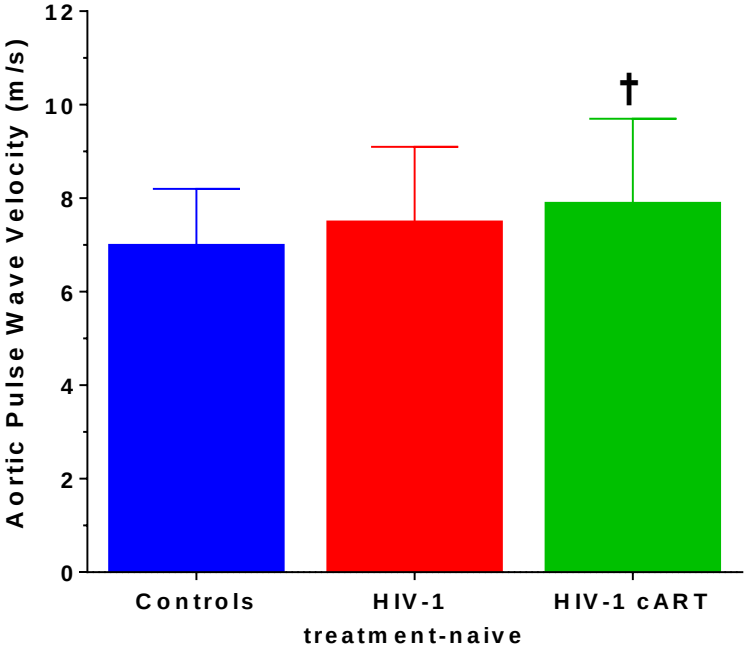
I. Subject characteristics

Variable	Controls (n=40)	HIV-1 treatment-naïve (n=47)	HIV-1 cART (n=34)
Age, year	45±5	45±6	45±4
Sex, men/women	25/15	11/36*	6/28*
Body mass, kg	69.1±12.4	66.8±11.2	63.3±12.3
BMI, kg/m^2	25.5±4.2	25.1±3.9	24.8±4.1
Body fat, %	33±8	37±6	36±7
Waist circumference, cm	86±10	85±9	86±12
Systolic BP, mmHg	126±12	128±10	122±11†
Diastolic BP, mmHg	75±6	77±5	74±8
MAP, mmHg	92±7	94±6	90±8†
LDL-cholesterol, mmol/l	2.9±0.1	2.6±0.1	2.8±0.1
HDL-cholesterol, mmol/l	1.2±0.1	1.0±0.1	1.4±0.1†
Triglycerides, mmol/l	1.0±0.1	1.1±0.1	1.2±0.1
Glucose, mmol/l	4.7±0.1	4.6±0.1	4.7±0.1
CD4, cells/μL	---	663±136	491±226†
Months HIV-1, median	---	21.7	38.7
Months cART, median	---	---	32.4

Values are means ± standard deviation unless otherwise noted. M, men; W, women; BMI, body mass index; BP, blood pressure; MAP, mean arterial pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; cART, combination antiretroviral treatment; *P=0.001 by χ^2 for sex distribution in HIV-1 patients; †P < 0.05 vs. HIV-1

II. Aortic AIx (A) was 26% higher in HIV-1 cART compared to treatment-naive HIV-1 patients and controls. Aortic PWV was 13% higher in HIV-1 cART subjects compared to controls. *P<0.05 versus controls and HIV-1 treatment-naïve; †P<0.05 versus controls.





Summary and Conclusions

- Untreated HIV-1 infection in sub-Saharan African patients was not associated with increased large arterial stiffness.
- However, cART for more than one year was associated with increased arterial stiffness in HIV-1 patients. Duration of HIV-1 infection and cART accounted for a large portion of the variance in arterial stiffness.

Acknowledgements

- NUFFIC Scholarship Programme-The Netherland
- Vje Universtait Medical Centre-Amsterdam
- KCM College
- KCMC Hosp.
- Supervisors
- Study participants