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Metabolic complications and Cancer in HIV

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February 2023

Overview

1. Cardiovascular disease
2. Weight gain
3. Bone disease
4. Cancer

Introduction

- Almost 30% of PLHIV in South Africa have at least one other comorbidity
- 20% hypertensive at ART initiation and almost 15% diagnosed with HPT at follow up
- SA adopted an Integrated Chronic Diseases Management (ICDM) model - 2011
  - Reorganising the facility to better manage bookings and patient flow
  - Expanding clinical management support by providing training and guidance
  - Providing assisted self-management
  - Prioritising health promotion and population screening

PLoS ONE 12(2): e0170983.
PLoS ONE 13(10): e0204020.
Asmal S, Mahomed O. Intergrated chronic disease management manual; 2016.

HIV-related cardiovascular disease

- PLHIV > 2x increased risk of cardiovascular disease overall.
  - Research predominantly from Europe and North America.
- Mechanisms for HIV-related CV disease are the same in all people with HIV
  - Distribution of CV risk factors varies by geographical location.
- Sub-Saharan Africa:
  - Younger population
  - Higher prevalence of hypertension
  - Lower tobacco smoking rates
  - Lower prevalence of elevated cholesterol
  - Unique exposures – indoor pollutants, repeated infections
- Profile of CV disease differs between geographic regions.

Disparities in cardiovascular care

- PWH less likely to receive
  - preventative medication like aspirin and statins
  - invasive procedures for myocardial infarction

- Disparities worsened in:
  - substance use disorders
  - female sex
  - among racial and ethnic minorities.

Burkholder GA, Tamhane AR, Salinas JL, et al. *Clin Infect Dis* 2012; **55:** 1550–57.
Pearce D, Ani C, Espinosa-Silva Y, et al. *Am J Cardiol* 2012; **110:** 1078–84.

HIV-related cardiovascular disease

Myocardial infarction

- 20% - 100% increase in RR
- Persists in virally suppressed

Stroke

- 80% ischaemic stroke
- HIV-associated in 15–25% of stroke cases in SSA

Heart failure

- Presentation evolved with ↑ access to ART
- HIV-ass. cardiomyopathy less common
- More HPT, RHD and CMP
- 62% ↑ mortality at 180 days after HF admission

Peripheral artery disease

- USA - 19% ↑ in risk of peripheral artery disease
- SA - Estimated prevalence 7% vs 3.9%

Risk factors for CV disease in PLHIV

HIV-associated factors

Viral related factors

ART-related factors

HIV associated risk factors

Viral related factors

1. Viral effects
   - Pro-inflammatory effects of HIV proteins
     - Biomarkers of chronic inflammation, monocyte activation, and altered coagulation ↑ in PWH
   - Direct viral effect → cardiomyopathy

1. CD4+ T-cell depletion
   - Increased OIs
   - Increased intestinal permeability with microbial translocation → chronic inflammation

1. Altered cholesterol metabolism → ↑ atherogenic lipid profiles

ART-related mechanisms

- ABC, lopinavir, and ritonavir
  - Alter glucose and lipid metabolism
  - Mitochondrial toxicity and subsequent cardiac myopathy, or impaired left ventricular function
- Dolutegravir or atazanavir more ‘cardiovascular safe’
- Weight gain after initiation of ART associated with incident diabetes
- Older PWH → risk of polypharmacy → prolonged QT intervals → 4x ↑ sudden cardiac death
- Any adverse effects on CVD risk - balance against life-preserving effects and ↓ HIV viraemia

Risk factors for CV disease in PLHIV

Non-HIV-associated factors

Traditional risk factors

Non-traditional risk factors

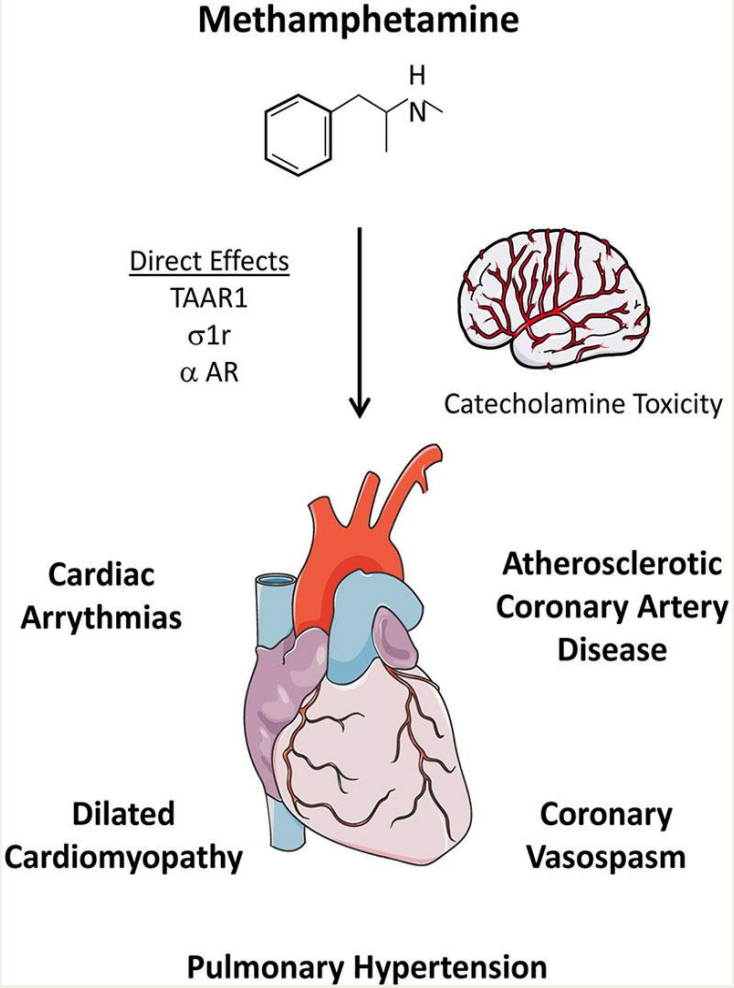
Non-HIV specific mechanisms

Traditional risk factors - smoking, diabetes, dyslipidaemia, hypertension, biological sex -

- Prevalence for PWH in LMIC varies
  - Hypertension (21%), elevated LDL cholesterol (23%), hypertriglyceridaemia (27%), low HDL cholesterol (52%), overweight (21%), and obesity (8%).
- Underdiagnosed:
  - 33–47% undiagnosed hypertension and 66% elevated cholesterol cases.
- Populations in some regions might have greater exposure to these risk factors.
- Women with HIV might have ↑ odds of developing metabolic syndrome
- When these risk factors are absent - absolute rates of acute MI are low BUT the relative risk is still 2x higher

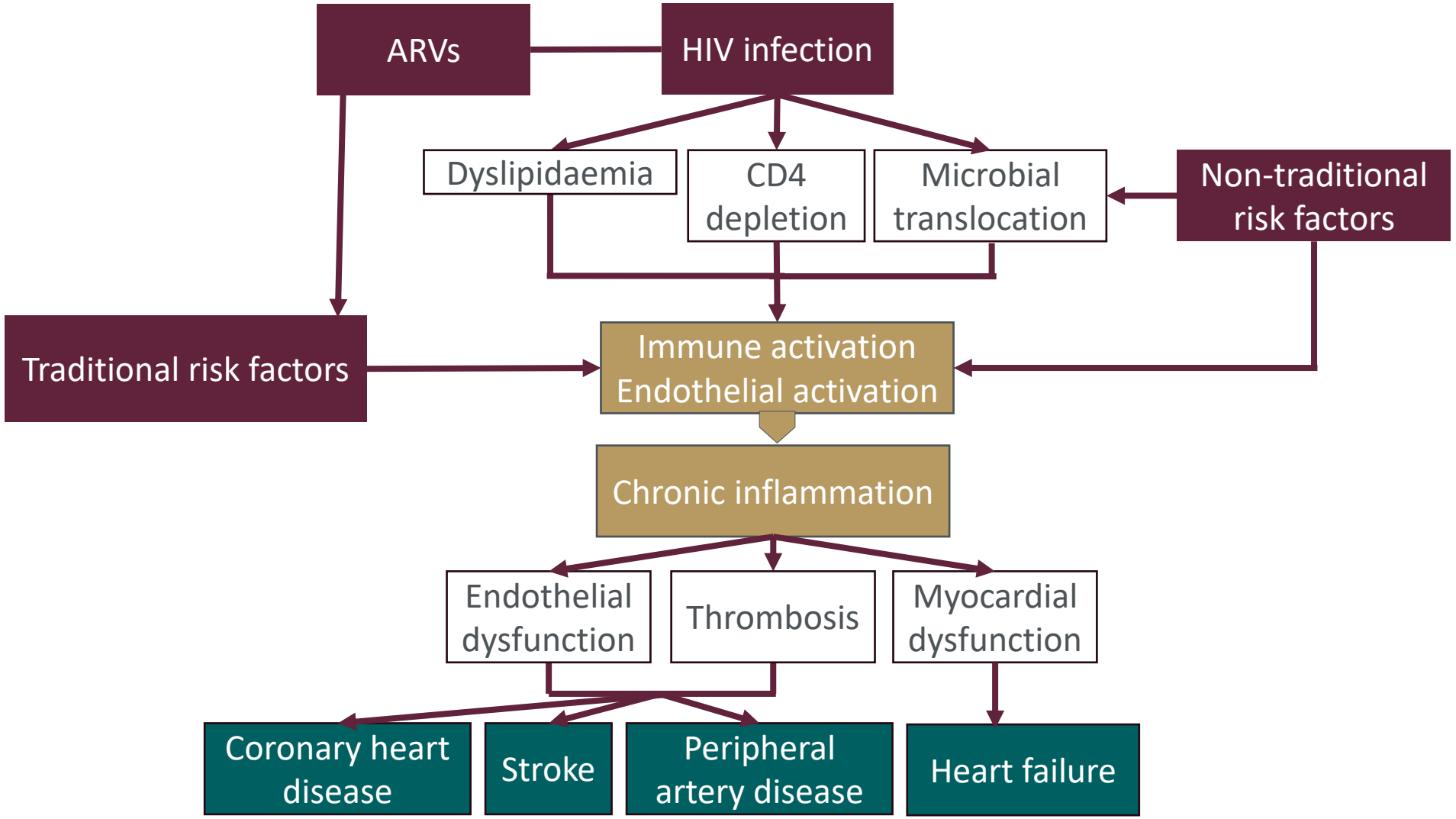
Non-traditional risk factors – accentuated in HIV -

- Unhealthy alcohol consumption → microbial translocation
- Substance use – cocaine, methamphetamine → multifactorial
- Hepatitis C
- Depression



Arteriosclerosis, Thrombosis, and Vascular Biology. Volume: 39, Issue: 9, Pages: 1739-1746,

Mechanisms of HIV-associated CV disease



Prevention of CV disease in PLHIV

1. HIV management
   - Suppress VL
   - Avoid high-risk ARVs
2. Traditional and non-traditional risk factor management
3. CV disease screening and referral

✓Using HIV platforms to incorporate comprehensive chronic-disease management and exploring population health approaches is key.

Recent examples from Malawi and Uganda

- Uganda - Population-based integrated HIV and non-communicable disease screening
  - People with HIV and hypertension referred to receive integrated care with
    - 45% successful linkage to care
    - BP control improved from 15% to 46%

- Malawi - HIV-care programme
  - 29 359 PWH screened for hypertension - 11% prevalence.
    - 85% received treatment, or lifestyle modification advice, or both
    - BP control rates at 6 months
      - 38% in people mild hypertension
      - 30% in people with moderate hypertension

Patel P, et al. *PLoS Med* 2018; **15:** e1002523.
Kwarisiima D, et al. *BMC Public Health* 2019; **19:** 511.

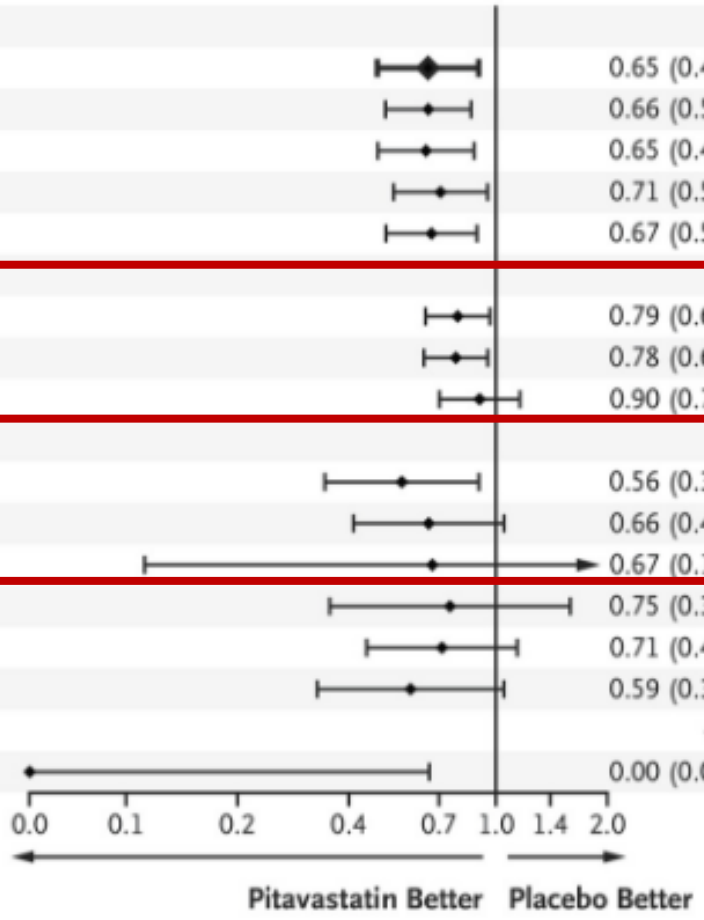
ORIGINAL ARTICLE

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Steven K. Grinspoon, M.D., Kathleen V. Fitch, M.S.N., Markella V. Zanni, M.D., Carl J. Fichtenbaum, M.D., Triin Umbleja, M.S., Judith A. Aberg, M.D., Edgar T. Overton, M.D., Carlos D. Malvestutto, M.D., M.P.H., Gerald S. Bloomfield, M.D., M.P.H., Judith S. Currier, M.D., Esteban Martinez, M.D., Ph.D., Jhoanna C. Roa, M.D., et al., for the REPRIEVE

A Estimated Treatment Effect

Subgroup	Pitavastatin (N=3888) no./1000 person-yr (no. of events)	Placebo (N=3881) no./1000 person-yr (no. of events)	Hazard Ratio (95% CI)
Primary outcome and supporting analyses			
First MACE	4.81 (89)	7.32 (136)	0.65 (0.48 to 0.90)
First MACE including vital status follow-up	4.75 (90)	7.22 (137)	0.66 (0.50 to 0.86)
First confirmed MACE	3.83 (71)	5.92 (110)	0.65 (0.48 to 0.87)
First MACE (as-treated analysis)	4.44 (77)	6.25 (107)	0.71 (0.53 to 0.95)
First MACE (per-protocol analysis)	4.54 (80)	6.77 (120)	0.67 (0.50 to 0.89)
Secondary outcomes and supporting analyses			
First MACE or death	9.18 (170)	11.63 (216)	0.79 (0.65 to 0.96)
First MACE or death including vital status follow-up	9.13 (173)	11.70 (222)	0.78 (0.64 to 0.95)
Death from any cause	6.17 (116)	6.83 (129)	0.90 (0.70 to 1.16)
Individual components of MACE			
First cardiac ischemia or myocardial infarction	1.40 (26)	2.51 (47)	0.56 (0.34 to 0.90)
First cerebrovascular event (stroke or TIA)	1.56 (29)	2.36 (44)	0.66 (0.41 to 1.05)
First peripheral arterial ischemia	0.11 (2)	0.16 (3)	0.67 (0.11 to 4.02)
Death from cardiovascular causes	0.64 (12)	0.85 (16)	0.75 (0.36 to 1.59)
Death from cardiovascular or undetermined causes	1.60 (30)	2.24 (42)	0.71 (0.45 to 1.14)
First cardiac catheterization or revascularization	0.97 (18)	1.66 (31)	0.59 (0.33 to 1.05)
First carotid or cerebrovascular revascularization	0.00 (0)	0.00 (0)	—
First peripheral arterial revascularization	0.00 (0)	0.32 (6)	0.00 (0.00 to 0.66)



N Engl J Med 2023; 389:687-699.

Weight gain and HIV treatment

Historical perspective on changes in weight and fat distribution in PLWH:

- 1980s
  - Severe weight loss a very common symptom of HIV infection.
  - Starting ART → weigh gain – *aka* 'return to health' effect of treatment
    - Still seen today in people lost weight before starting ART.

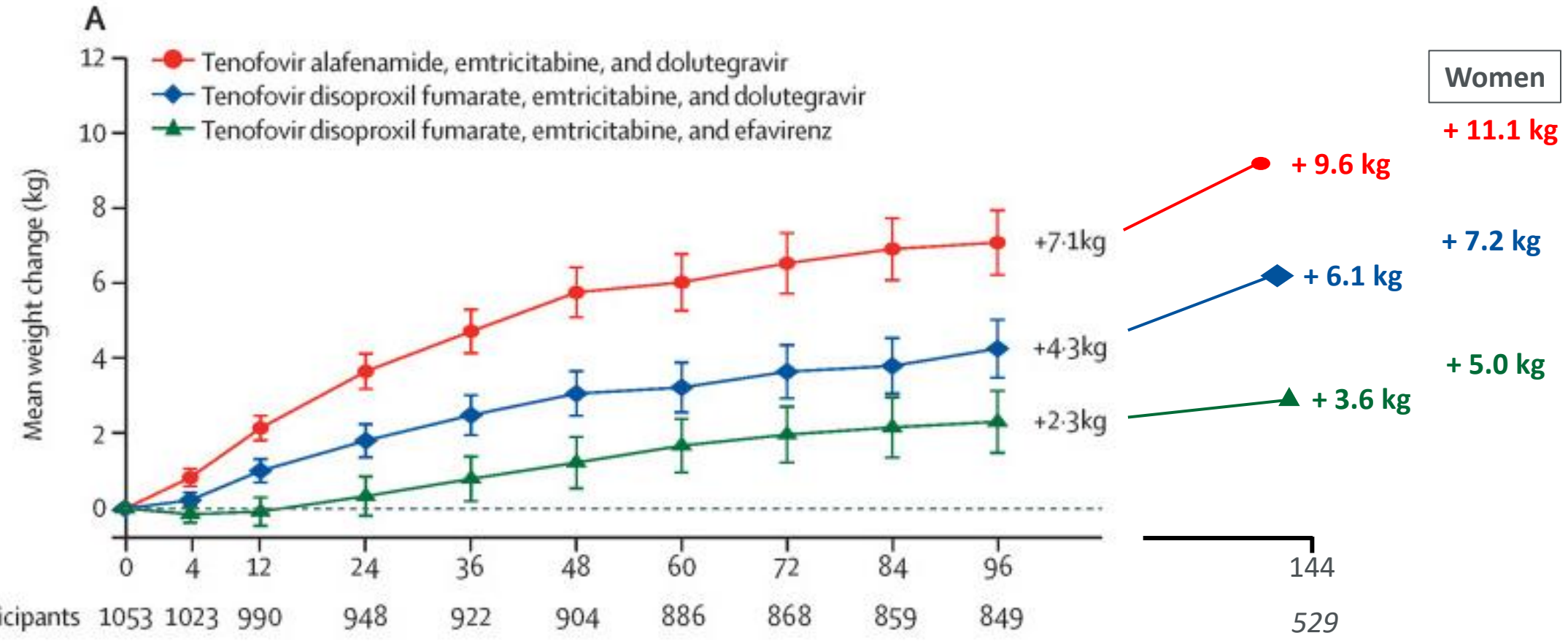
- 1996-2006
  - Fat loss from limbs and abdominal fat gain in PWH on ART *aka* lipodystrophy syndrome.
    - **Fat loss** associated with the NRTIs **stavudine and zidovudine**.
    - **Fat gain** associated with PIs like **indinavir, nelfinavir or ritonavir**.
  - Modern ARVs NOT associated with lipodystrophy syndrome

How does weight gain in the modern era look like?

- Recent studies - excessive weight gain in people starting modern ART regimens.
  - Not everyone gains weight and the amount of weight gained varies.
  - **ADVANCE** study compared 3 different drug combinations.
    - People gained between **3.6kg and 9.6kg over 144 weeks**.
  - Meta-analysis of 8 clinical trials:
    - **17% of participants gained at least 10% over 1-2 years**.
      - **On average, 2kg over 2 years with most in the 1st year.**
  - Studies looking at progress from a normal weight → overweight or obese after starting ART.
    - Large study in North America:
      - **Over 20% of people: normal weight → overweight after 3 years**
      - **Similar proportion: overweight → obese over the same time.**

N Engl J Med. 2019;381:803-815.
The Lancet HIV. 2020, 7; e666-e676.
IAC 2020. Abstract OAXLB0104.

ADVANCE trial



Women

+ 11.1 kg

+ 9.6 kg

+ 7.2 kg

+ 6.1 kg

+ 5.0 kg

+ 3.6 kg

Who is more likely to gain weight?

1. People with low CD4 counts and high viral load.
   - As CD4 counts goes up on treatment, so did body weight.
2. Women gained more weight than men.
3. Black people gained more weight than other ethnic groups.
4. People with higher baseline weight.
5. Older people ?

- Weight gain is less frequent after switching treatment compared to starting treatment.

Weight gain after switching to TLD

172 participants in the ADVANCE cohort - switched to open-label TLD - evaluated at 52 weeks

- 70 switched from **TAF**/FTC/**DTG**
  - Lost 1.2 kg
- 31 switched from **TEE**
  - Gained 2.9 kg

CID 2023. 76; 1492–1495.

Which drugs have been linked to weight gain?

- Consistently shown in people taking newer generation ARVs introduced in the last 10 years; i.e. integrase inhibitors, TAF.

- Greatest weight gain (starting or switching) - **dolutegravir and TAF**

Why do people gain weight after starting ART ?

- Reasons unclear but several explanations proposed.
  1. **Weight gain is a result of immune recovery.**
  - Restoration of weight to what it might have been, had the person not had HIV.
  - May 'overshoot' if prone to obesity for dietary / genetic reasons

  2. **Some drugs most often used in the past – efavirenz and TDF – suppressed weight gain.**
  - Replaced by drugs that do not suppress weight gain (TAF, DTG) → effect of immune recovery on weight more obvious.
  - Effects more pronounced in Black people
    - Gene that results in higher levels of efavirenz → greater suppression of weight gain.

Are there long-term consequences to weight gain?

- Weight gain in people previously underweight → **reduces the risk of death**.
  - I.e. 'return to health' effect.

however

- Weight gain in people with normal or ↑ body weight → may **increase risk of CVD & DM**

- Excessive weight gain during pregnancy
  - ↑ **risk of complications of pregnancy** incl. high BP, pre-eclampsia and gestational diabetes.
  - ↑ **risk of stillbirth and premature delivery**.

Lancet HIV 2020; 7: e663–65.

Is weight gain reversible if people change treatment?

- Uncertain if changing to different ARVs might slow down or reverse weight gain.

- INSTIs are preferred 1st-line agents:
  - more reliable in suppressing viral load
  - less likely to cause drug resistance
  - have fewer side effects than NNRTIs and PIs

- Reserve TAF for patients with renal failure and osteoporosis

Key points on weight gain in PLWH starting ART

- One in 6 people starting ART gain at least 10% over 1-2 years.
- More common in women, Black people and those with advanced HIV disease.
- Associated with specific ARVs namely INSTIs and tenofovir alafenamide (TAF).
  - Association is not the same as causation
- The reasons for weight gain are unclear and multifactorial:
  - Overshoot of 'return to health' effect in people prone to obesity
  - Absence of drugs supressing weight gain
- Weight gain may increase risk for DM and cardiovascular disease.
  - Integration of NCD screening and management in HIV clinics is overdue!
  - Ongoing programmatic surveillance of any weight associated adverse events on ART

Impact of Integrase inhibitors and tenofovir alafenamide on weight gain in people with HIV. Lake, Jordan, et.al. Current Opinion in HIV and AIDS16(3):148-151, May 2021

Recommended approach

- Be aware of the potential risks of weight gain:
  - Starting or switching to an INSTI-based regimen
  - Black women with advanced HIV
- Keep an eye on the literature/guidelines for new developments
- For now:
  - Benefits of TLD outweighs the potential risks.
  - Monitor weight and HbA1c
  - Address modifiable factors
  - Be culturally sensitive
  - Allow patients to partake in decision making

Bone disease in HIV

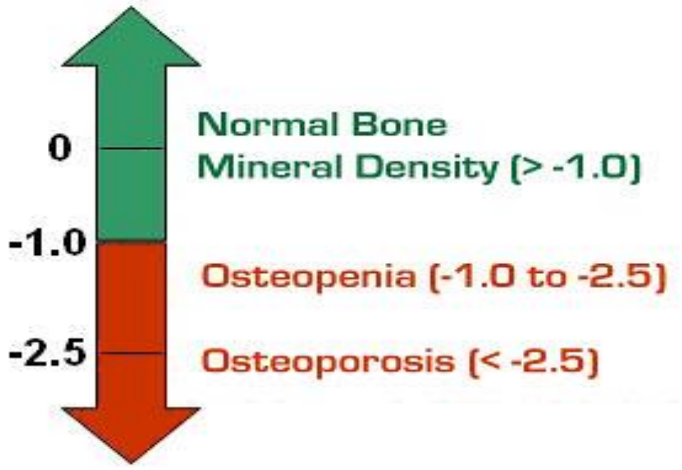
1) Osteonecrosis / Avascular necrosis:
   - Due to temporary or permanent loss of blood supply to the bone

2) Osteopenia and osteoporosis:
   - Reduced bone mass and bone quality leading to an increased risk of fractures

Osteopaenia & osteoporosis

- Risk factors:
  1. HIV (for > 7 years)
  2. ART – Tenofovir (TDF)
  3. Smoking
  4. Alcohol abuse
  5. Corticosteroids
  6. Prolonged bedrest
  7. Severe weight loss
  8. Sedentary lifestyle
  9. Vitamin D deficiency
  10. Hypogonadism

- Diagnosis
  - DEXA scan - T score



Cancers associated with HIV infection

AIDS-defining cancers (ADC)

1. Kaposi Sarcoma
2. Non Hodgkin Lymphoma
3. Invasive Cervical cancer

+

Non-AIDS defining cancers (but ↑ incidence)

1. Hodgkin Lymphoma
2. Lung cancer
3. Anogenital cancers
4. Head & Neck cancers
5. Hepatocellular cancer
6. Cutaneous cancers
7. Soft tissue malignancies

HIV-associated cancers

Robert Yarchoan, Thomas S. Uldrick. HIV-Associated Cancers and Related Diseases. N Eng J Med. 2018 Mar 15;378(11):1029-1041.

How high is the risk for cancer in HIV compared with the general population?

- Kaposi sarcoma:
  - 500x more likely
- Non-Hodgkin lymphoma:
  - 12x more likely
- Cervical cancer:
  - 6x more likely
- Anal cancer:
  - 19x more likely
- Hodgkin lymphoma:
  - 8x more likely
- Liver cancer:
  - 3x more likely
- Lung cancer:
  - 2-4x more likely
- Oral cavity/pharynx cancer:
  - 2-3x more likely

Why are people with HIV at risk of developing cancer?

Multiple factors:

1. Immunosuppression
2. Chronic inflammatory state
3. Co-infection with oncogenic viruses:
   a. HHV-8 (KSHV): *Kaposi's sarcoma, Castleman's, Body cavity lymphoma*
   b. HPV: *Cervix Ca, Anal Ca, Nasopharyngeal Ca*
   c. EBV: *Lymphoma*
   d. HBV & HCV : *Liver cancer*
   e. Merkel cell polyoma virus: *Merkel cell Ca*
4. Environmental oncogenic stimuli
   - Tobacco, Alcohol

Robert Yarchoan and Thomas S. Uldrick. HIV-Associated Cancers and Related Diseases. N Eng J Med. 2018 Mar 15;378(11):1029-1041.

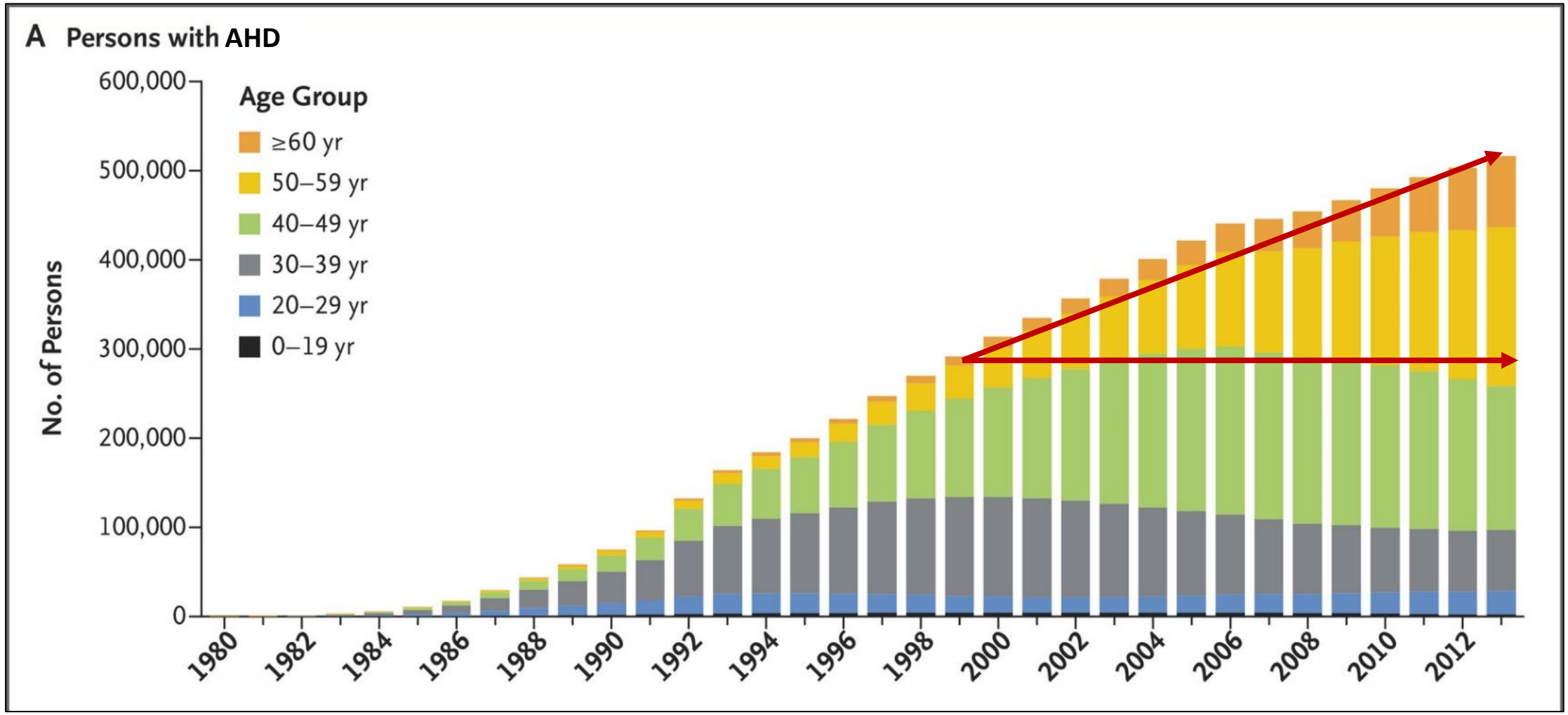
Changing epidemiology of HIV-associated cancers in ART era

- Spectrum changing in areas where ART used extensively
  - NHL ↓↓
  - KS ↓ / ↔
  - Cervix cancer ↔
  - **Relative ↑ in NADC**

NADCs are increasingly contributing to mortality in people with HIV

Tanaka LF, et al. Trends in the incidence of AIDS-defining and non-AIDS-defining cancers in people living with AIDS: a population-based study from São Paulo, Brazil. Int J STD AIDS. 2017 Oct;28(12):1190-1198.
Robert Yarchoan and Thomas S. Uldrick. HIV-Associated Cancers and Related Diseases. N Eng J Med. 2018 Mar 15;378(11):1029-1041.

Epidemiology of HIV-Associated Cancers



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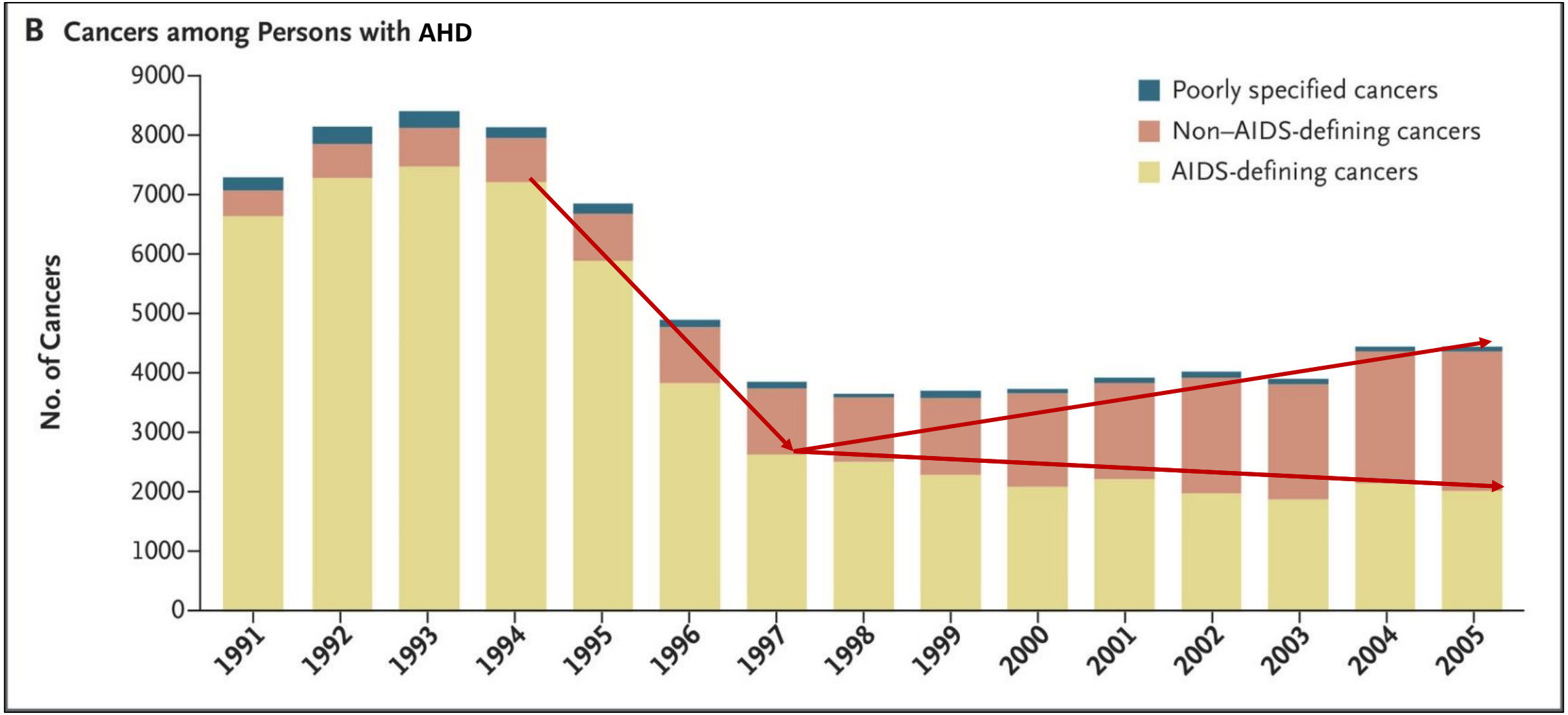
Epidemiology of HIV-Associated Cancers



Robert Yarchoan and Thomas S. Uldrick. HIV-Associated Cancers and Related Diseases. N Eng J Med. 2018 Mar 15;378(11):1029-1041.

Clinical implications of cancer in HIV

- Malignancies in HIV positive patients are characterized by:
  - Earlier age at onset
  - Atypical pathology (higher tumour grade)
  - More aggressive clinical behaviour
  - More advanced stage at presentation
  - Poorer outcome, with rapid progression
  - High rate of relapse
  - Worse response to treatment
  - More aggressive screening and treatment needed

Deeken JF, et al. Clin Infect Dis. 2012;55(9):1228.

Principles of treatment

- Same general principles as for HIV negative patients
  - PLUS: START ALL PATIENTS ON ART

- Early-stage disease
  - **Manage with curative intent (as in HIV-uninfected individuals)**

- Challenges in the management of cancer in PLWH:
  1. Cytotoxic chemotherapy
     - Additive cytotoxicity
     - Drug-drug interactions
     - Further immunosuppression
  2. Poor performance status = poor cancer survival
  3. Risk of postoperative infections
     - Only in advanced HIV disease
     - Early-stage disease - surgical risks similar

Prognosis of HIV associated cancer

- There is a higher cancer-specific mortality PWH
  - Independent of cancer stage or receipt of cancer treatment

- This is related to immunosuppression, leading to:
  - Decreased tolerance of cancer treatments
  - Promotion of tumour progression
  - Poor baseline performance status

Key messages:

Start antiretroviral therapy early

Treat early cancer with curative intent

Coghill AE, Shiels MS, Suneja G, Engels EA. Elevated Cancer-Specific Mortality Among HIV-Infected Patients in the United States. J Clin Oncol 2015; 33:2376.

How does KS present in people with HIV?

- any CD4 count; more common and severe with lower CD4 counts -

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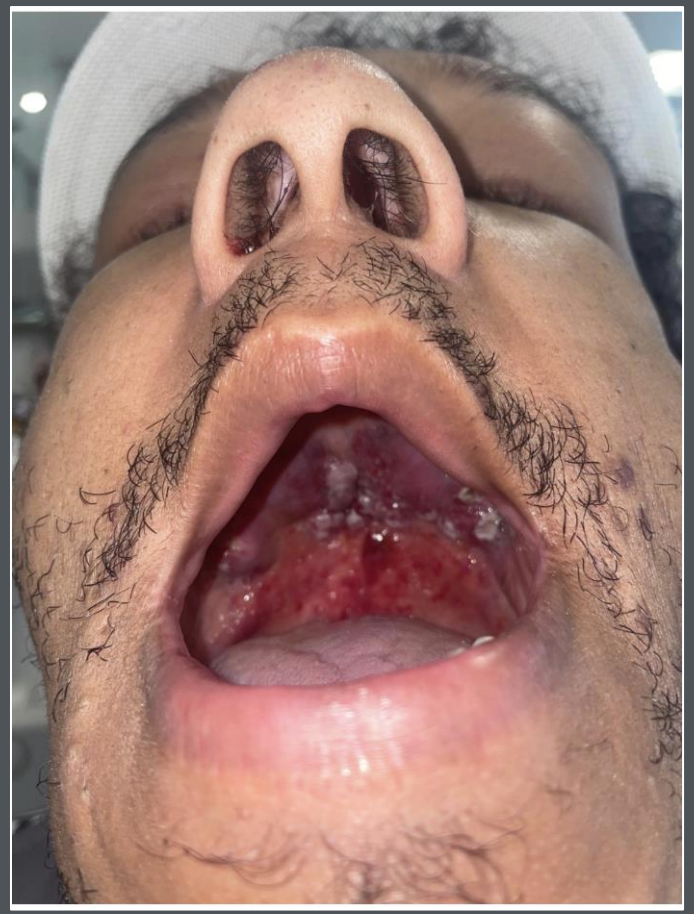
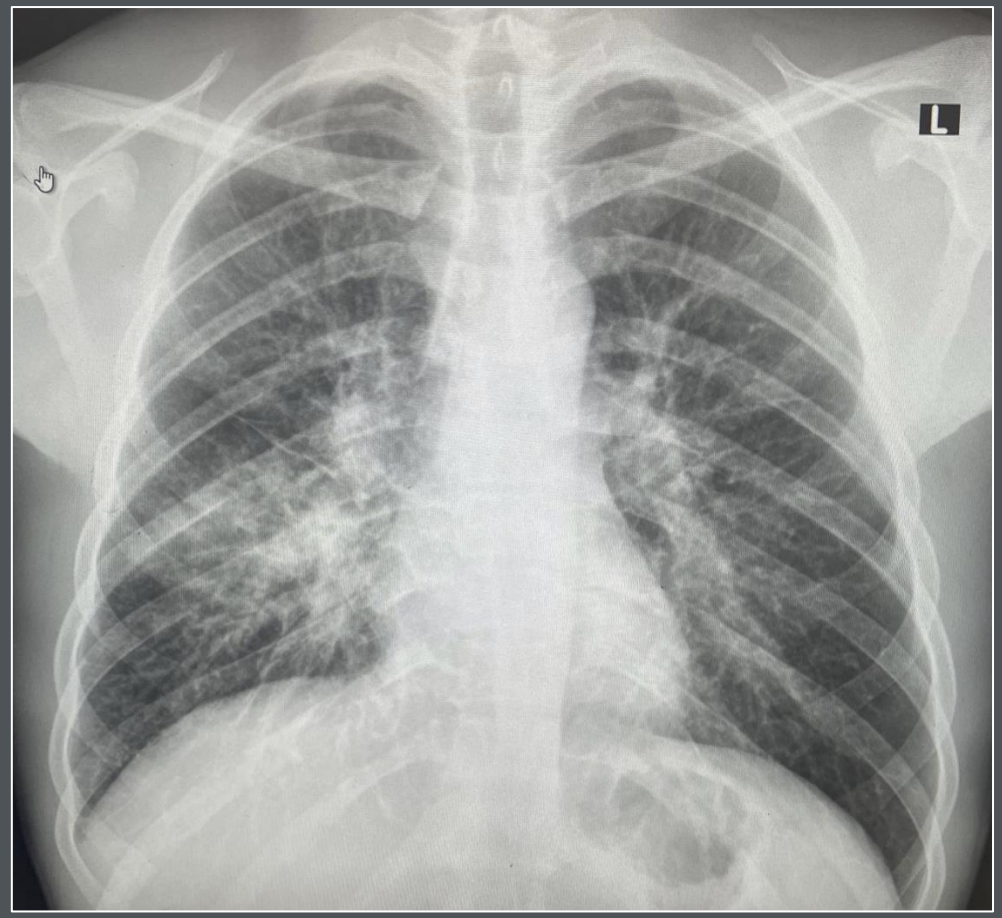
1. Skin (most common)
   - Lower limbs, trunk (front and back), face and genitalia
2. Mouth (30%)
   - Hard palate and gums
3. Lymph nodes
4. Lungs (± pleura)
   - Strong association with oral lesions
   - Differentiate from TB, PJP, LRTI
5. GIT
   - May be silent, any GI symptoms, upper or lower GIT bleeding





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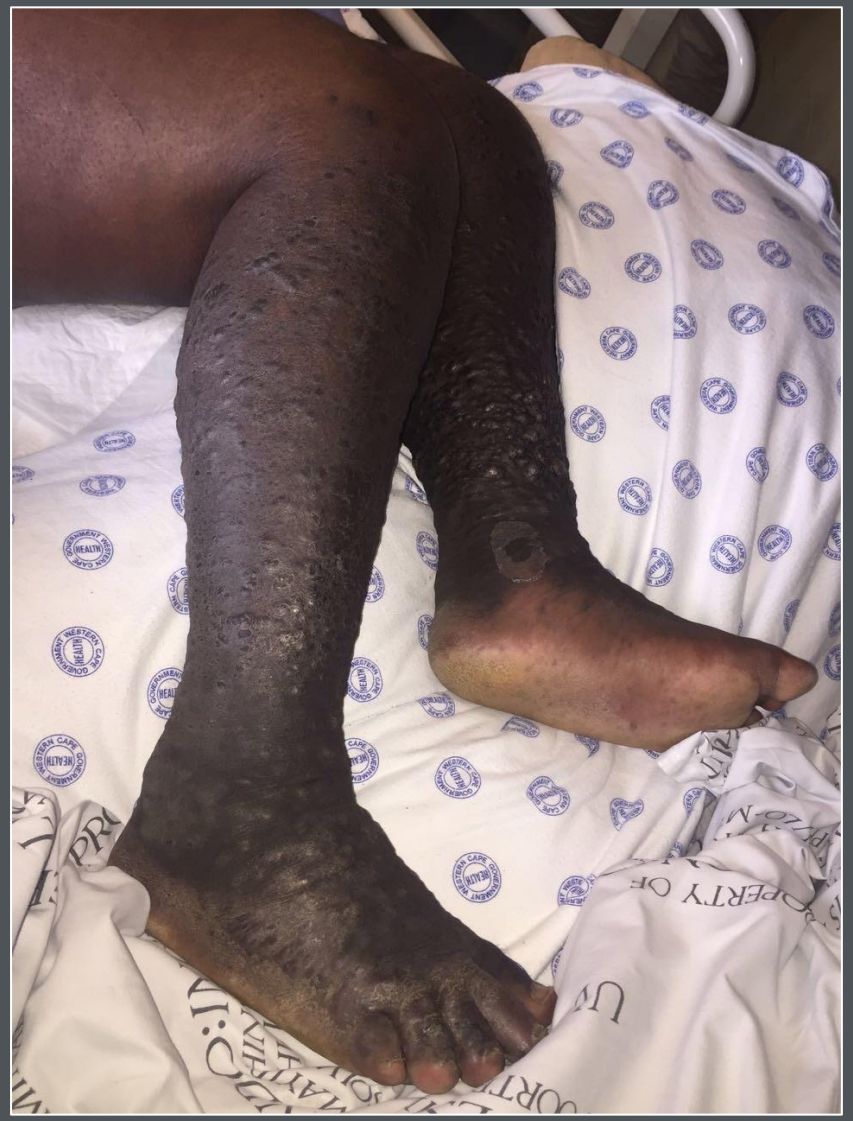

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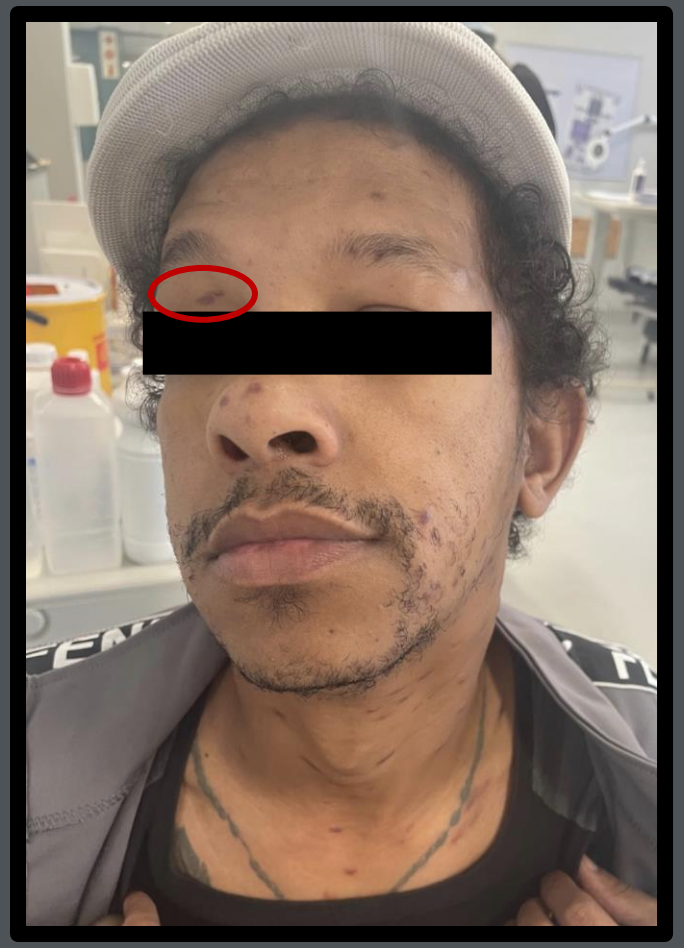

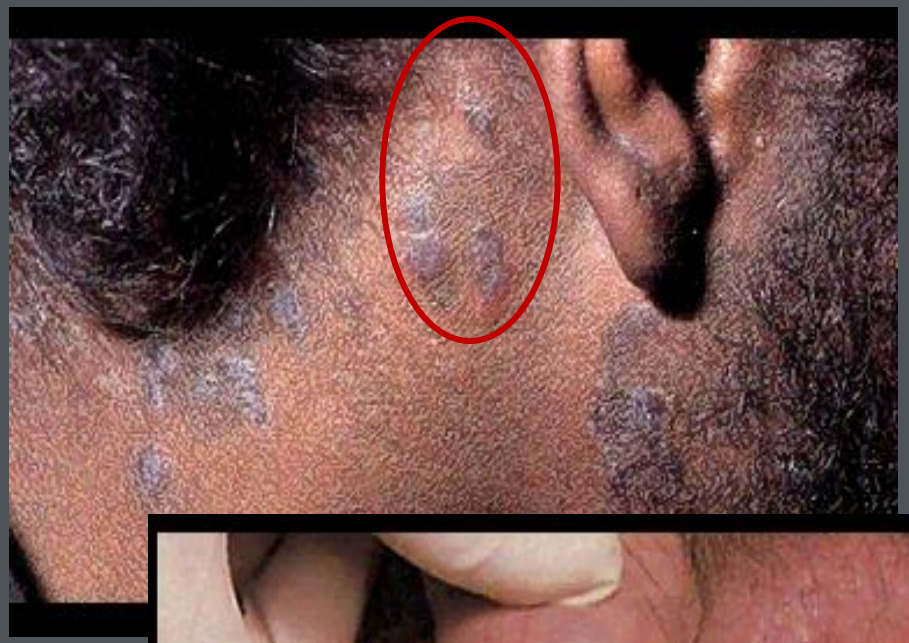

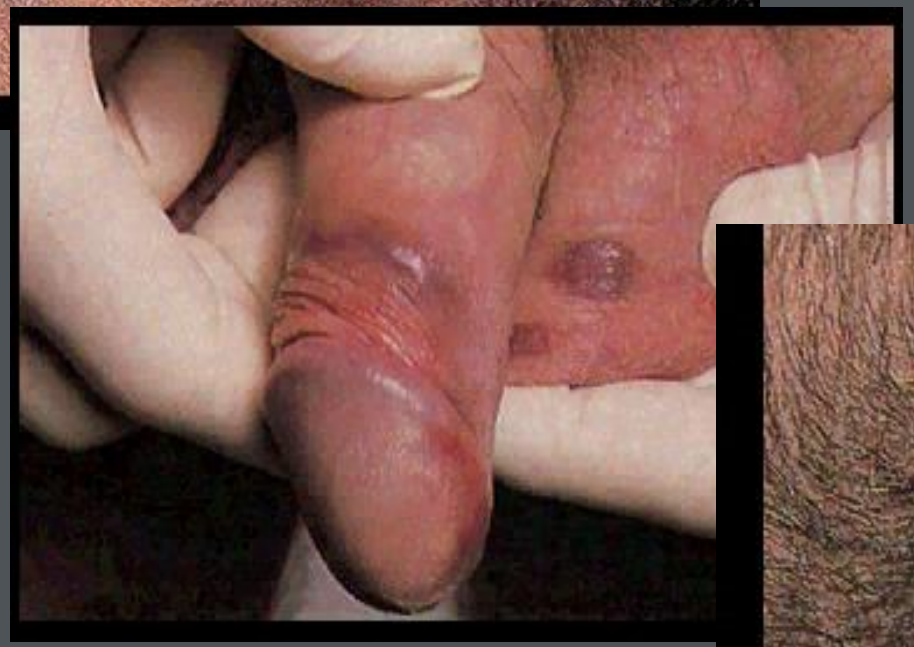

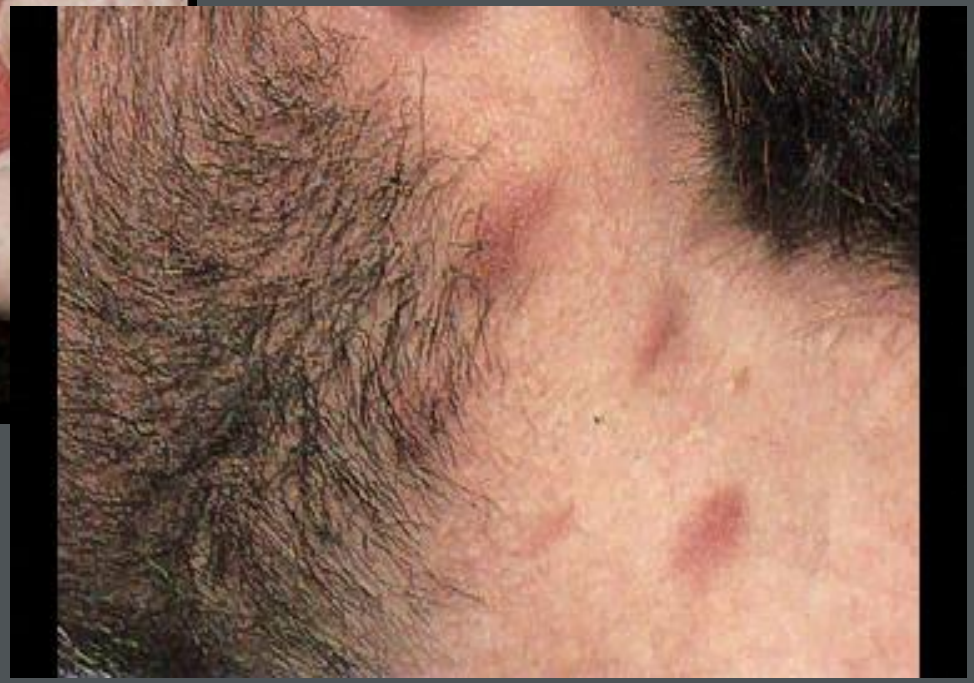

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WHO staging of Kaposi's sarcoma

	Good risk (all of the following)	Poor risk (any of the following)
Tumour (T)	**T0:** • Confined to skin and/or lymph nodes *and/or* • Minimal oral disease - non-nodular & confined to palate	**T1:** • Tumour-associated oedema or ulceration • Extensive oral KS • KS in other non-nodal viscera e.g., GIT or Lung KS
Immune system (I)	**I0:** • CD4 cell count >150/µL	**I1:** • CD4 cell count <150/µL
Systemic illness (S)	**S0:** • No history of OI /thrush • No "B" symptoms* • Karnofsky performance status >70	**S1:** • History of OI and/or oral thrush • "B" symptoms* present • Karnofsky performance status <70 • Other HIV-related illness

***unexplained fever, night sweats, <10 percent involuntary weight loss, or diarrhoea persisting more than 2 weeks**

Treatment of KS

- ART must always be started asap (irrespective of stage)
  - Mild disease will respond to ART only

±

- Systemic chemotherapy indicated for:
  1. Visceral disease (usually Lung & GIT)
  2. Painful or ulcerated lesions
  3. Oedema – limb, face
  4. Extensive cutaneous disease
  5. Rapidly progressive disease

Key points on cancer in PLWH

"People with HIV have a substantially **higher risk of some types of cancer** compared to people of the same age without HIV"

"People with HIV have a substantially **higher risk of dying from cancer** compared to people of the same age without HIV"

"**Cancer screening and prevention measures** must be integrated into HIV management programmes"

"Outcomes improve significantly, with **early diagnosis and treatment** of HIV and cancer"

2 take home messages

The 10 keys to healthy aging

1. Control blood pressure
2. Regulate blood glucose
3. Regulate lipids
4. Stop smoking
5. Be active
6. Screen for cancer
7. Get regular vaccinations
8. Prevent bone loss & muscle weakness
9. Combat depression
10. Maintain social contact

The 11 keys to healthy aging in HIV

1. Control blood pressure
2. Regulate blood glucose
3. Regulate lipids
4. Stop smoking
5. Be active
6. Screen for cancer
7. Get regular vaccinations
8. Prevent bone loss & muscle weakness
9. Combat depression
10. Maintain social contact
11. Early diagnosis & sustainable viral suppression

Integrated chronic care model is essential

- Challenges
  - Lack of staff capacity
  - Unclear guidelines on the delivery of integrated care for patients with HIV chronic comorbidities
  - Pill burden
  - Non-disclosure
  - Financial burden
  - Poor knowledge of treatments
  - Relocation of patients
  - Access to treatment.

Thank you

Godongwana et al. BMC Health Services Research (2021) 21:647