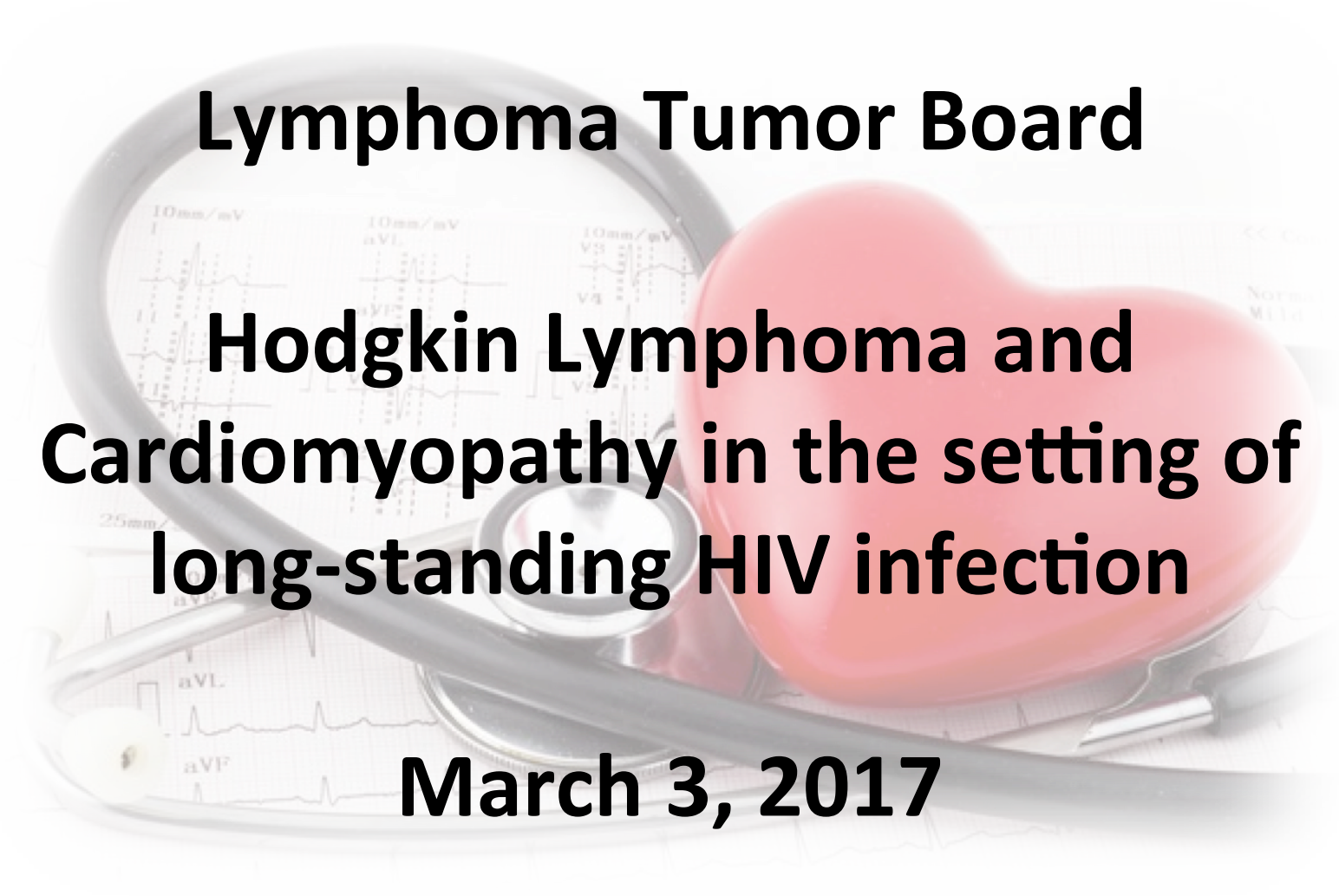


Lymphoma Tumor Board

Hodgkin Lymphoma and Cardiomyopathy in the setting of long-standing HIV infection

March 3, 2017

Cancers in HIV Disease

AIDS-Defining	Virus
• Kaposi's Sarcoma	HHV-8
• Non-Hodgkin's Lymphoma (systemic and CNS)	EBV, HHV-8
• Invasive Cervical Carcinoma	HPV
Non-AIDS Defining	
• Anal Cancer	HPV
• Hodgkin's Disease	EBV
• Leiomyosarcoma (pediatric)	EBV
• Squamous Conjunctival Carcinoma	HPV (?)
• Hepatoma	HBV, HCV

7 Notable Cancers in HIV

Cancer	Relative Risk in U.S. people with AIDS vs. general pop (SIR 1990-1995)	Estimated cases/yr in US based on 2004-7 HIV/Cancer Match Registry data	Etiologic agents	Relationship with immune suppression (CD4 or AIDS)
Kaposi sarcoma	22,100	735	KSHV	+++
Non-Hodgkin lymphoma	53	1146	EBV	+++
Cervical cancer	4.2	85	HPV	+
Lung cancer	3.3	324	Tobacco	+
Hodgkin lymphoma	13.6	174	EBV	++
Anal cancer	20.7	226	HPV	++
Liver cancer	4.0	90	HCV, HBV, alcohol	+

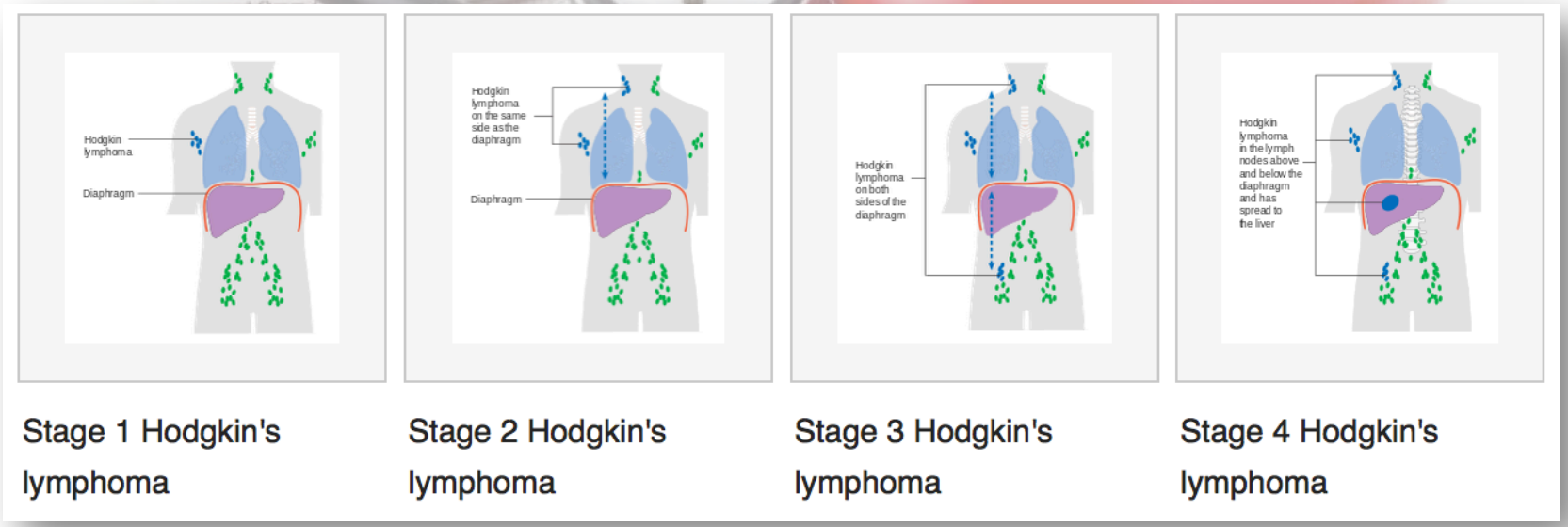
Refs: Engels *AIDS* 2006, Biggar *JNCI* 2007, Engels *Int J Cancer* 2008, Chaturvedi *JNCI* 2009, Guiguet *Lancet Oncol* 2009

Subtypes of Hodgkin Lymphoma (HL)

- Nodular sclerosing HL
  - Most common subtype
  - Composed of large tumor nodules
  - Nodules show scattered lacunar classical Reed Sternberg (RS) cells that are reactive
- Mixed-cellularity subtype
  - Common subtype
  - Composed of numerous classic RS cells with inflammatory cells
  - Frequently associated with EBV infection
  - Can be confused with “cellular” phase of nodular sclerosing CHL.
- Lymphocyte-rich
  - Rare subtype
  - Has most favorable prognosis
- Lymphocyte-depleted
  - Rare subtype
  - Composed of large numbers of pleomorphic RS cells with intermixed with reactive lymphocytes, which can be confused with DLBCL

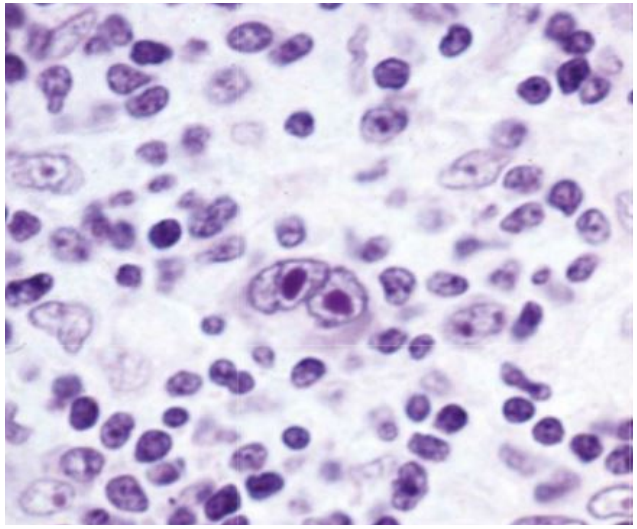
Staging of Hodgkin Lymphoma (HL)

- Stage I
  - Involvement of single lymph node region
  - Typically, cervical or single extralymphatic site
- Stage II
  - Involvement of two or more lymph node regions on same side of diaphragm
  - Or one lymph node region and a contiguous extralymphatic site (IIe)
- Stage III
  - Involvement of lymph node regions on both sides of the diaphragm
  - Can include spleen (IIIs) and/or limited contiguous extralymphatic organ sites (IIIe, IIIes)
- Stage IV
  - Disseminated involvement of one or more extralymphatic organs

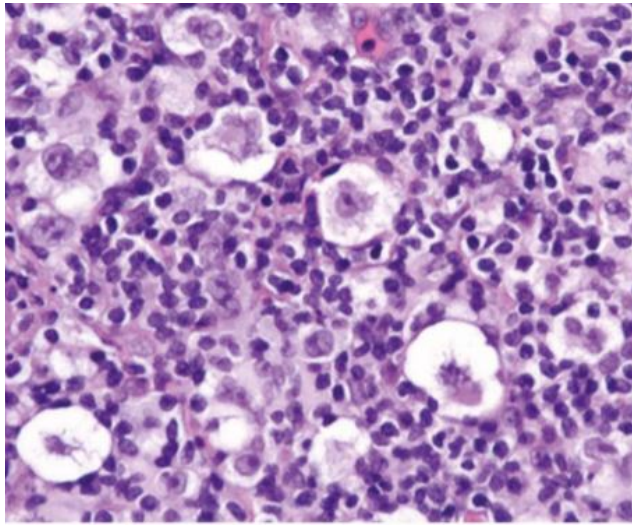


Classic HL - RS Cell Variants

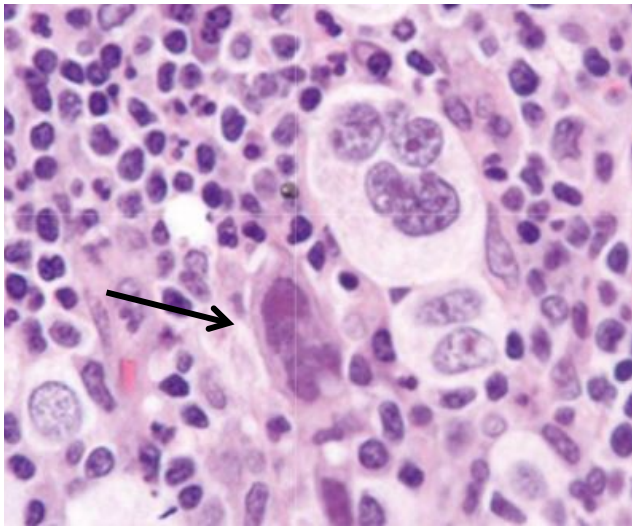
Classic RS Cell



Lacunar Cells

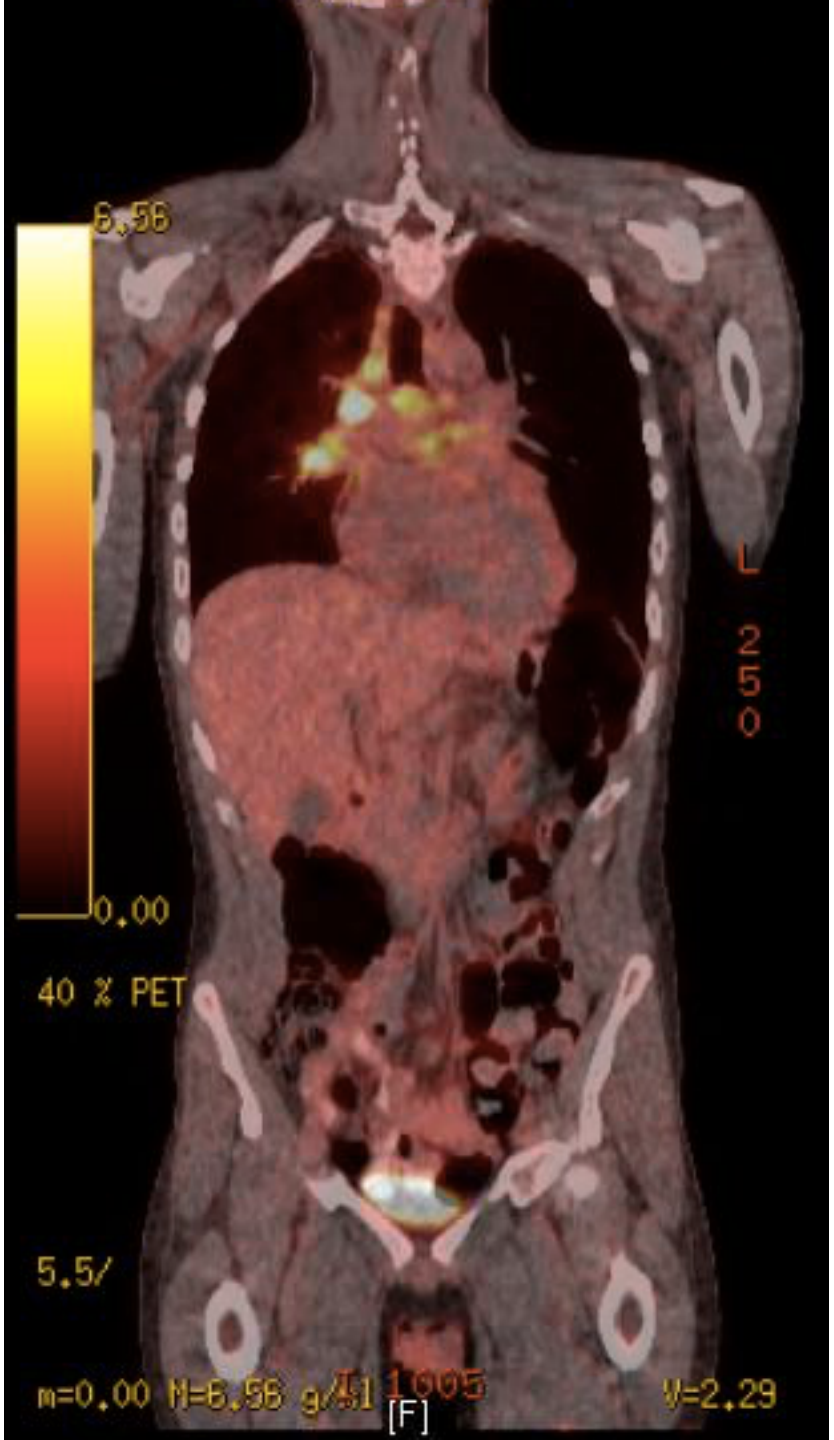


Mummified Cell



Emily Glynn

Hsi ED and Golblum JR. Foundations in Diagnostic Pathology: Hematopathology. 2nd Ed. 2012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250
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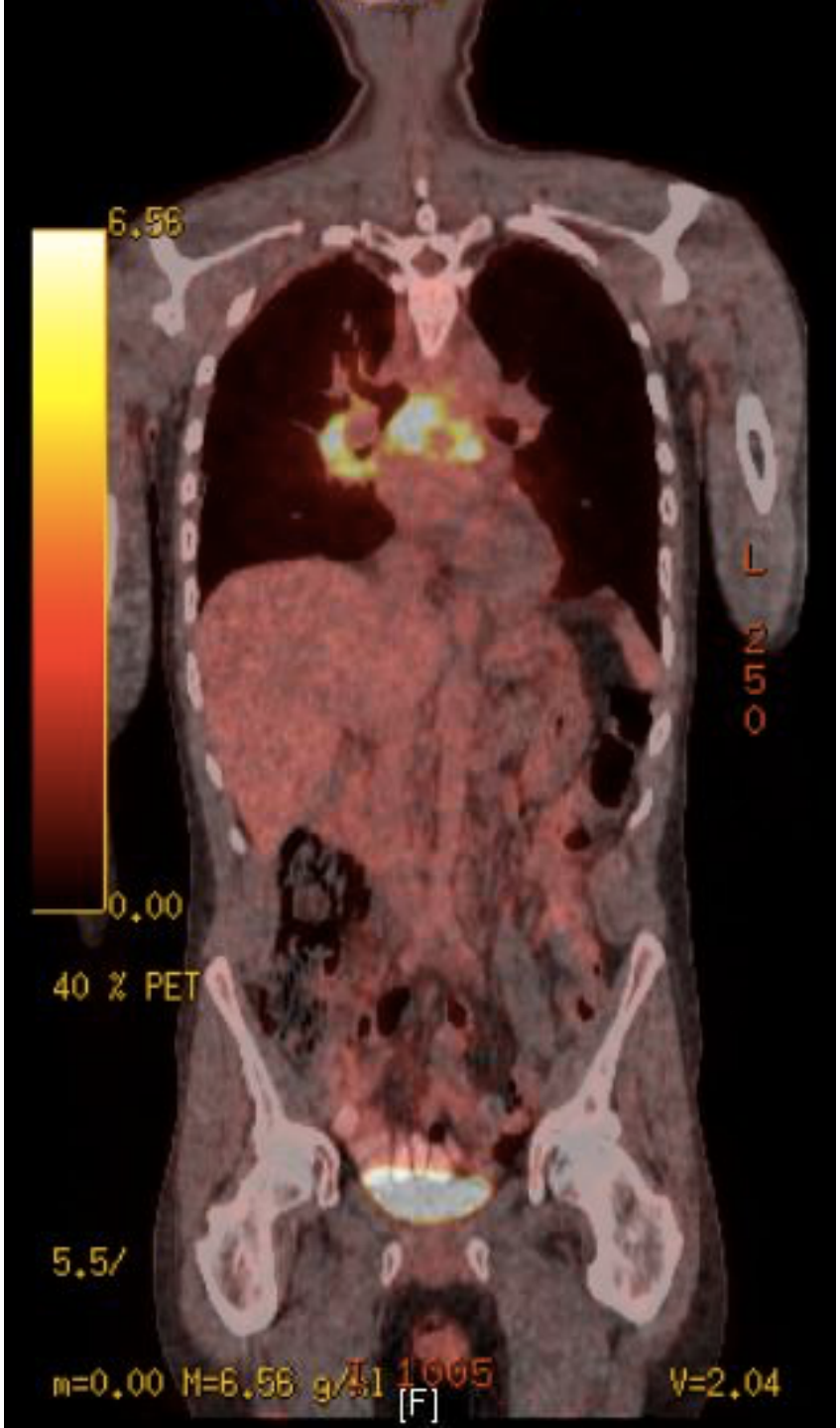
6.56
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m=0.00 M=6.56 g/ml 1005
[F]
V=2.04

Treatment of Hodgkin Lymphoma (1)

- Depends on the patient's age, performance status, stage of disease, and choice

First Line Therapy

- **ABVD** - Adriamycin, bleomycin, vinblastine, and dacarbzine
  - Standard treatment of HL in the US
  - Takes between 6-8 months

- **MOPP** – [Nitrogen] Mustard, Oncovin, Prednisone and Procarbazine
  - Administered in four week cycles, often for 6 cycles.
  - *Not often used, but a reasonable option for those with relapse or other complications.*

- **Stanford V regimen** - typically takes half as long as ABVD, but more intense chemotherapy schedule, and incorporates radiation.

- **BEACOPP** - treatment for stages > II, mainly used in Europe
  - Approximately 10-15% higher with standard ABVD in advanced stages.
  - More expensive due to use of G-CSF, more intense and more toxic

- Rituximab is not routinely used due to lack of CD20 surface expression on RS cells

Treatment of Hodgkin Lymphoma (2)

Second Line Therapy

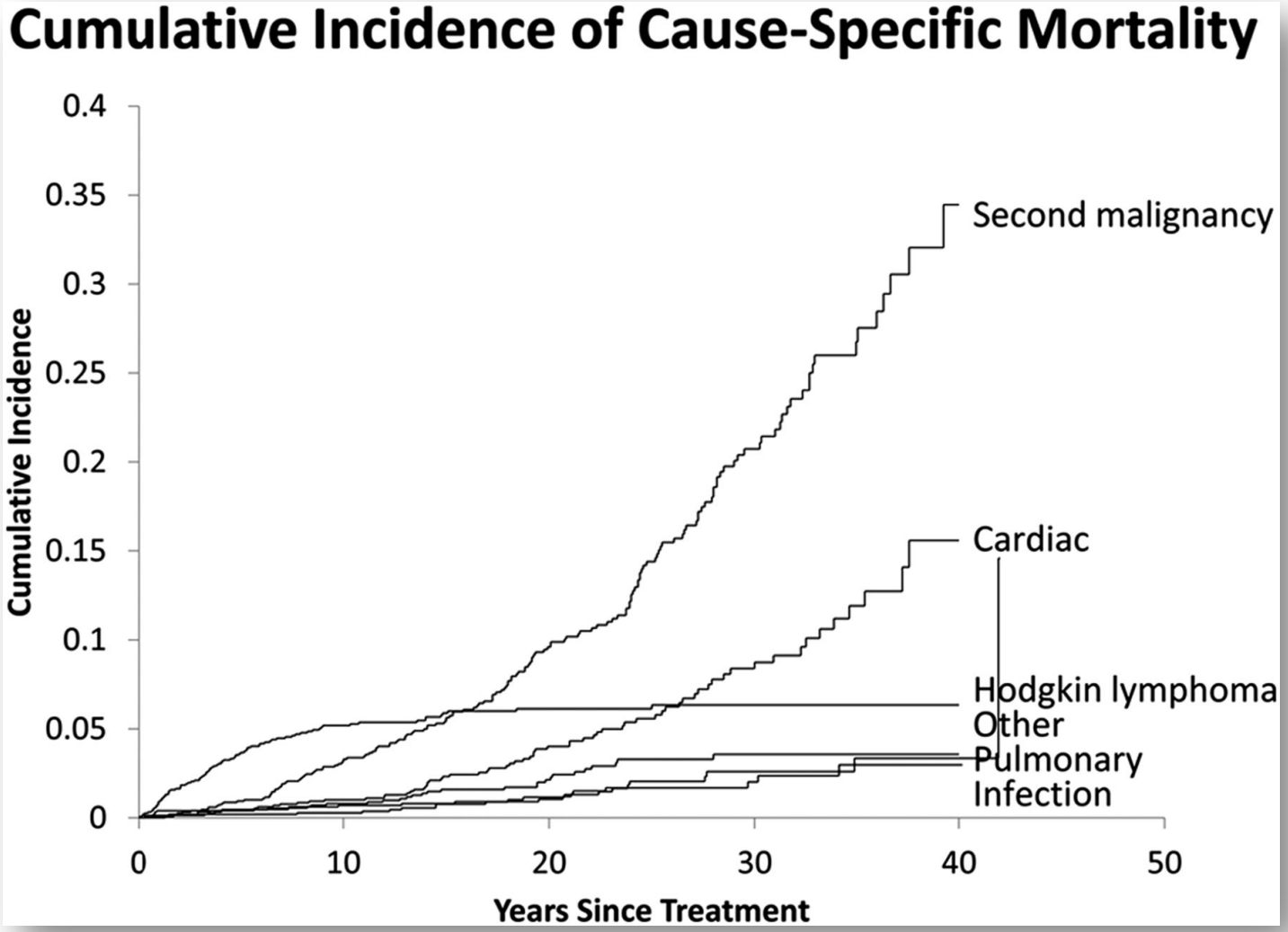
- **ICE**: Ifosfamide (Ifex), carboplatin (Paraplatin), and etoposide
  - Given every 2 or 3 weeks for 2-4 cycles.

- **ESHAP or DHAP**: Etoposide, methylprednisolone (Solu-Medrol), high-dose cytarabine, (Cytosar-U), cisplatin (Platinol);
  - OR, dexamethasone, high-dose cytarabine, and cisplatin.
  - ESHAP or DHAP regimens are given every 3 weeks for 2 to 3 months.

- **GVD, Gem-Ox, or GDP**: Gemcitabine (Gemzar), vinorelbine (Navelbine), doxorubicin; OR gemcitabine and oxaliplatin (Eloxatin);
  - OR gemcitabine, dexamethasone, and cisplatin.
  - Gemcitabine-based regimens are either given 2 weeks in a row, followed by an off-week, or every other week.

- **Brentuximab vedotin (Adcetris)**: Brentuximab vedotin (Adcetris) is an antibody-drug conjugate – anti-CD30 coupled to monomethyl auristatin A
  - Brentuximab vedotin is usually given every 3 weeks for up to 16 cycles, although sometimes it is given every 4 weeks.

Cumulative incidence of cause-specific mortality in long-term HL survivors



Andrea K. Ng Blood 2014;124:3373-3379

blood

Table 1. Dose Related Risk of Doxorubicin-Induced Congestive Heart Failure (Based on Data from (9))

Cumulative Dose (mg/m^2)	Patients with CHF (%)
150	0.2
300	1.6
450	3.3
600	8.7

Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin. Cancer 2003; 97(11): 2869-79.

Table 2. Factors Associated with Increased Risk of Anthracycline-Induced Cardiotoxicity

Age >65 years or <4 years
Female gender
Hypertension
Preexisting cardiac disease
Mediastinal radiation
Treatment with cyclophosphamide, paclitaxel, or trastuzumab
Cumulative anthracycline dose
Higher individual anthracycline doses

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Eur Heart J. 2013;34(46):3538-3546. doi:10.1093/eurheartj/eht388

Cardiac manifestations of HIV infection

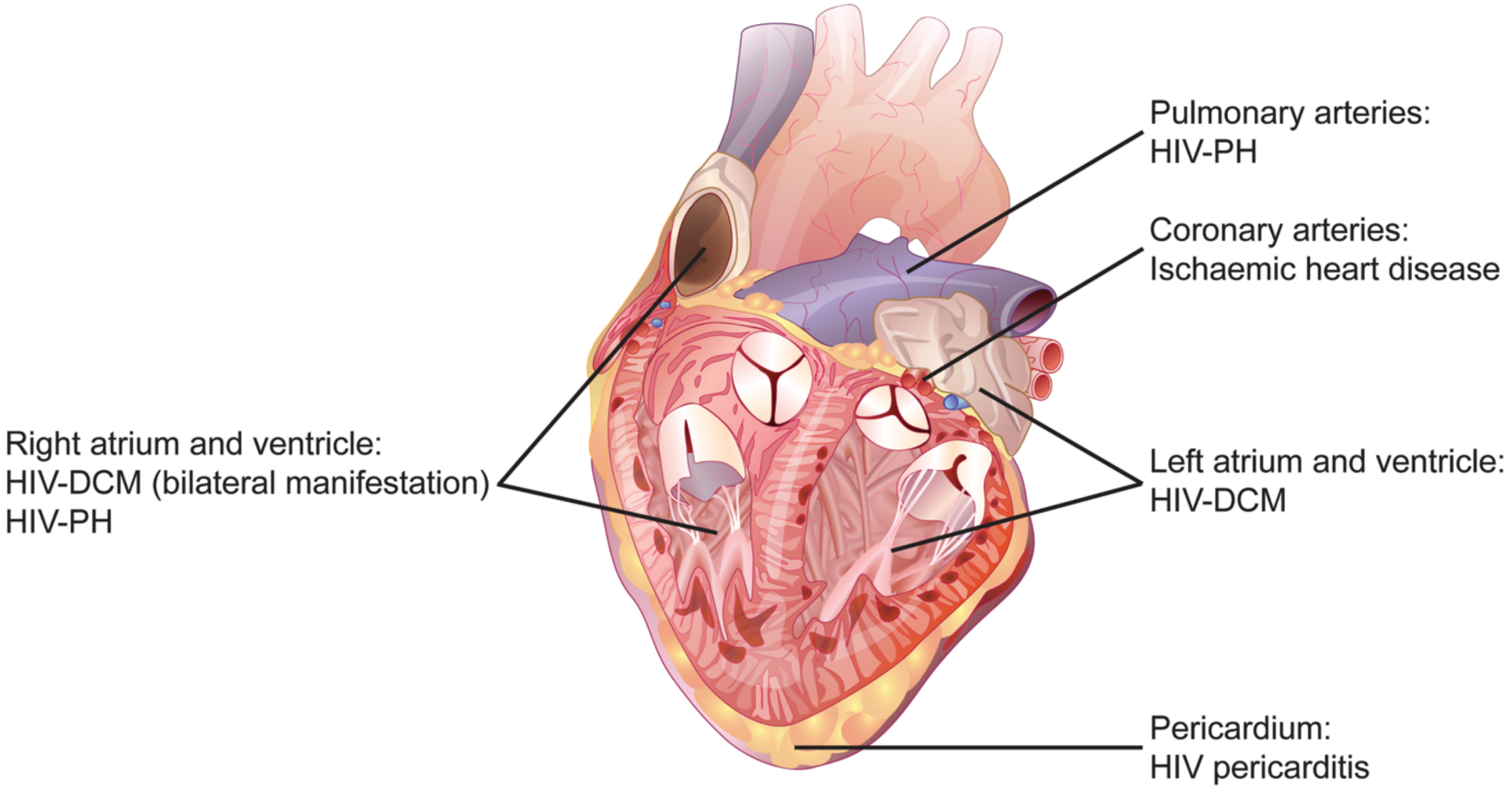


Figure Legend:
Cardiac manifestations of human immunodeficiency virus infection. HIV-PH, HIV-associated pulmonary hypertension, HIV-DCM, HIV-associated dilated cardiomyopathy.

Eur Heart J. 2013;34(46):3538-3546. doi:10.1093/eurheartj/eht388

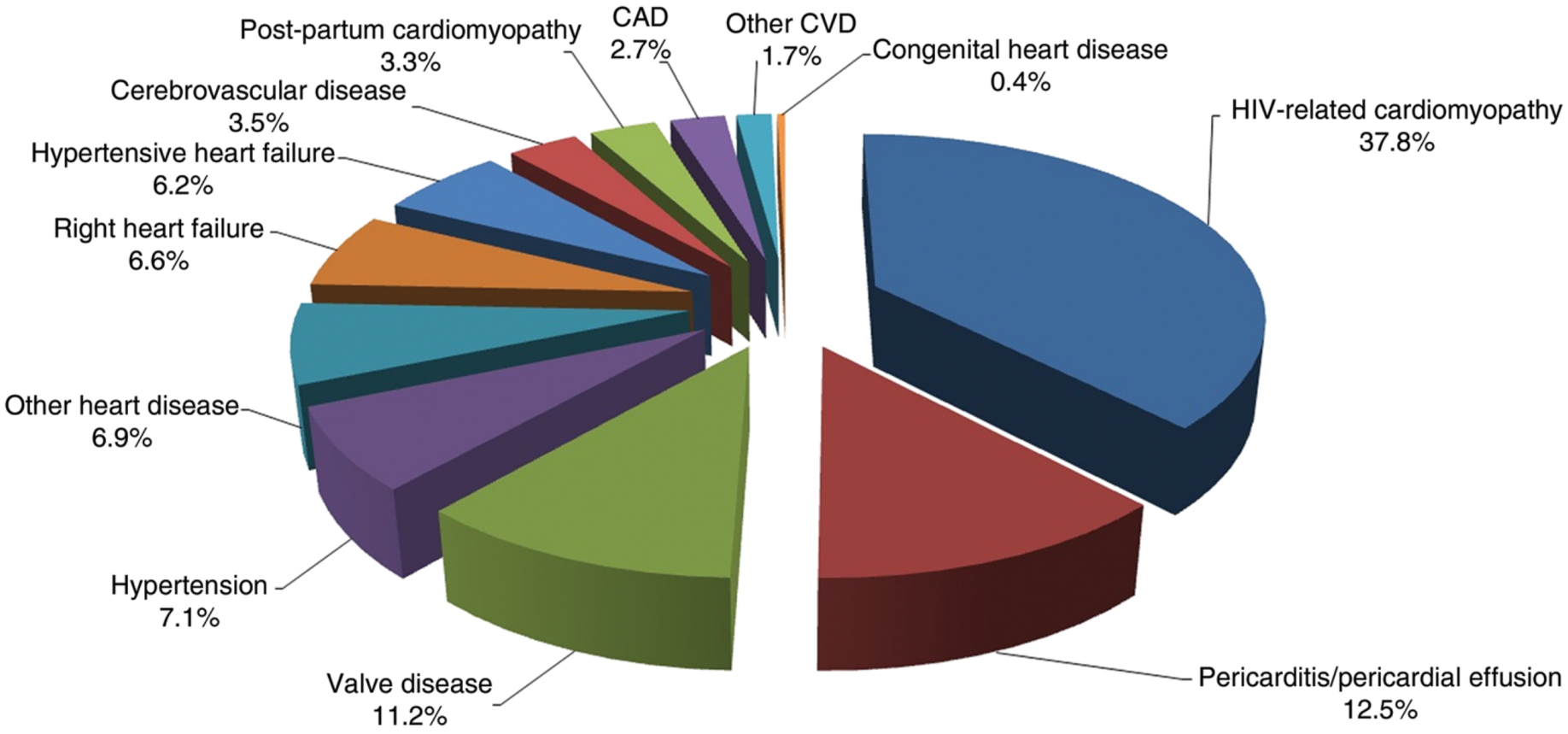
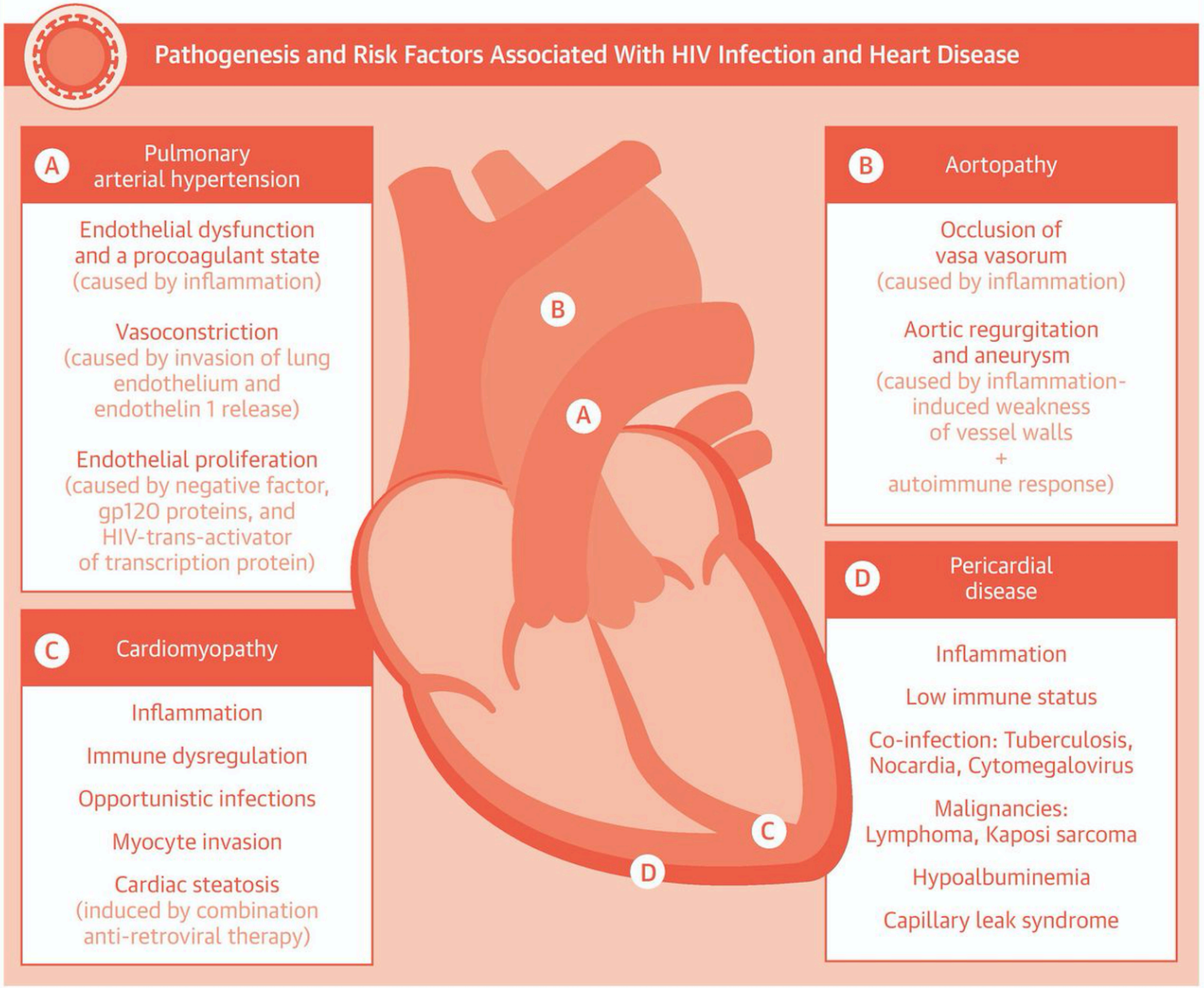


Figure Legend:

Primary cardiovascular diagnosis of all human immunodeficiency virus patients (%) presenting with de novo heart disease at a tertiary cardiac service in South Africa (n = 518). CAD, coronary artery disease; CVD, cardiovascular disease. Source: Sliwa et al.[9]

CENTRAL ILLUSTRATION: HIV and Nonischemic Heart Disease: Pathogenesis of HIV-Associated Cardiomyopathy, Pericardial Disease, Pulmonary Arterial Hypertension, and Aortopathy



Manga, P. et al. J Am Coll Cardiol. 2017;69(1):83-91.

Table I **Cause of pericardial disease in human immunodeficiency virus with risk stratification by CD4 count**

Type	Infectious and non-infectious cause	CD4 count[a] (cells/μL)
Bacteria	*Staphylococcus aureus*	Any CD4 count
	Streptococcus pneumoniae	
	Proteus sp.	
	Nocardia sp.	
	Pseudomonas aeruginosa	
	Klebsiella sp.	
	Enterococcus sp.	
	Listeria monocytogenes	
Mycobacteria	*Mycobacterium tuberculosis*	<500
	Atypical mycobacteria	<50
Viruses	HIV	Any CD4 count
	Herpes simplex virus I/II	<300
	Cytomegalovirus	<50
Fungi	*Histoplasma capsulatum*	<50
	Cryptococcus neoformans	<50
	Candida sp.	<300
Protozoa	*Toxoplasma gondii*	<100
Malignancies	Kaposi's sarcoma	Any CD4 count
	Non-Hodgkin's lymphoma	<200
Other	Immune reconstitution inflammatory syndrome	<50
	Left ventricular dysfunction (ejection fraction <50%)	Any CD4 count

[a]Risk of HIV-associated pericardial disease increases in incidence as CD4 count declines.

Table 2 **Epidemiology of cardiovascular disease in human immunodeficiency virus and the impact of combination antiretroviral therapy**

Cardiovascular disease	cART-naive patients, pre-cART era, or countries with limited access to cART	Patients on cART, cART era, or countries with unlimited access to cART
Pericardial disease	Incidence of 11% per annum in advanced HIV In one-third a cause other than HIV can be established Tuberculosis is most common cause of pericardial disease Pericardial effusion predictor of mortality	Pericardial disease is rare Prevalence <1% in patients on cART
Dilated cardiomyopathy (DCM)	Incidence of 1.6–5.0% per annum Risk factors: low CD4 count, high HIV viral load, advanced HIV In one-fifth a cause other than HIV can be established Cardiotrophic viruses, Epstein-Barr virus, toxoplasmosis, Cryptococcus neoformans, or malnutrition can cause myocarditis Tuberculosis can cause perimyocarditis Poor prognosis	Prevalence of HIV-DCM dropped by 30% in countries with unlimited access to cART
Pulmonary hypertension (PH)	Prevalence of HIV-PH 0.6–5.0% No association between HIV-PH and CD4 count, HIV viral load, or stage of disease	Prevalence of HIV-PH 0.5% No change in incidence of HIV-PH since the advent of cART
Coronary artery disease (CAD)	HIV-infection amplifies risk for CAD, but data inconclusive	Exposure to specific antiretroviral drugs may also increase risk for CAD

cART, combination antiretroviral therapy.

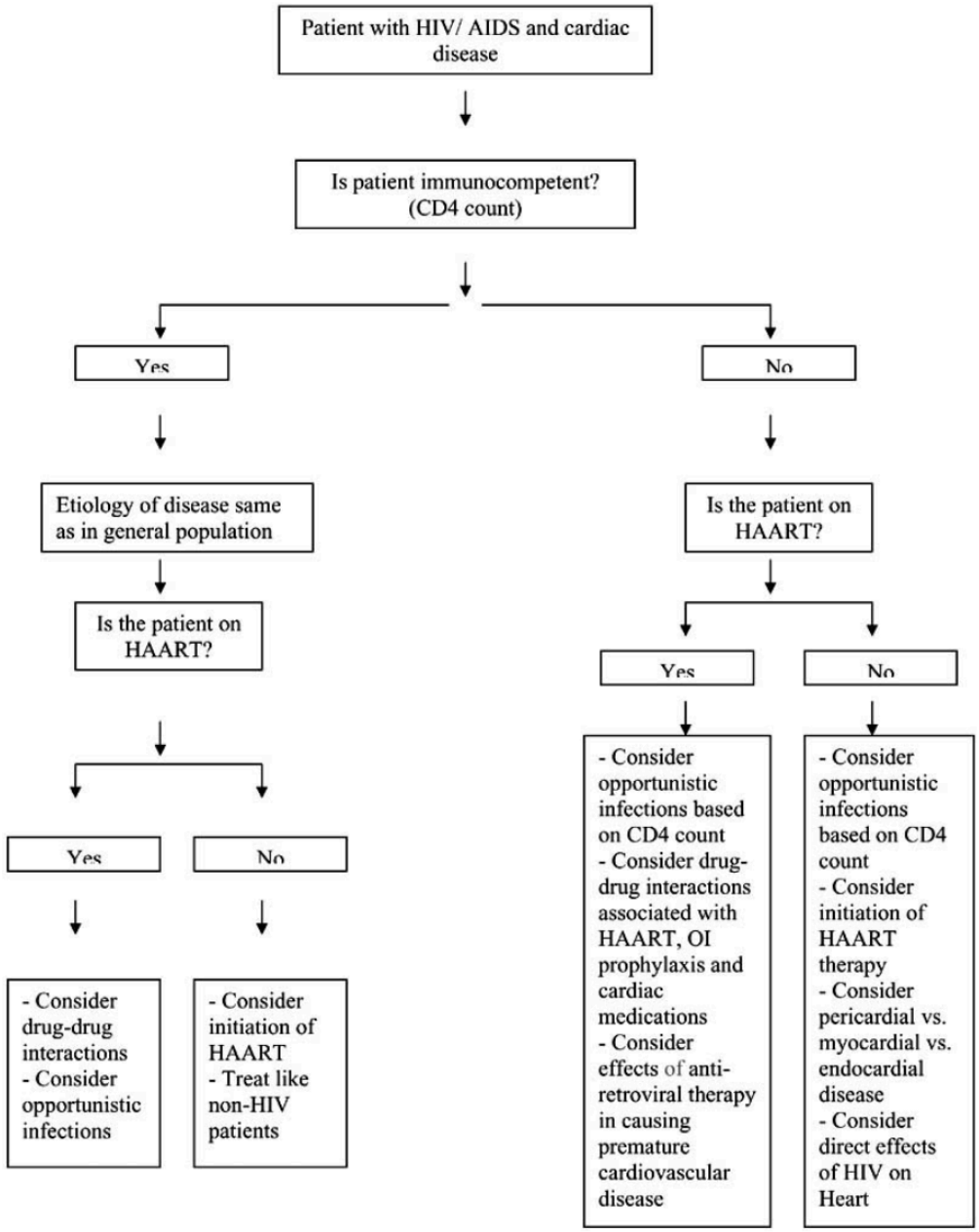


Fig. (1). An algorithmic approach to cardiac problems in HIV/AIDS.

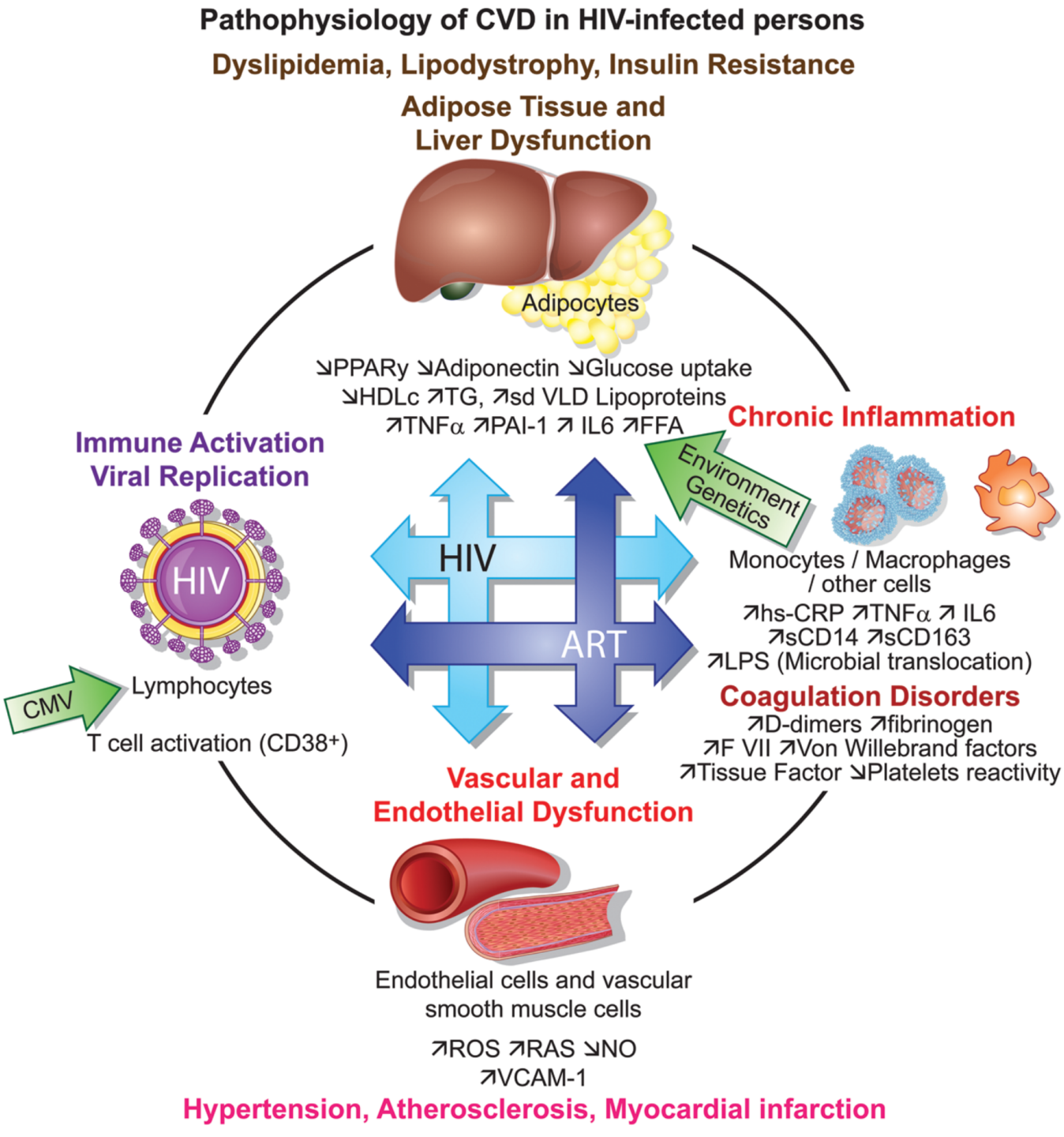

Pathophysiology of CVD in HIV-infected persons
Dyslipidemia, Lipodystrophy, Insulin Resistance
Adipose Tissue and
Liver Dysfunction
Adipocytes
↘PPARγ ↘Adiponectin ↘Glucose uptake
↘HDLc ↗TG, ↗sd VLD Lipoproteins
↗TNFα ↗PAI-1 ↗ IL6 ↗FFA
Chronic Inflammation
Environment
Genetics
Monocytes / Macrophages
/ other cells
↗hs-CRP ↗TNFα ↗ IL6
↗sCD14 ↗sCD163
↗LPS (Microbial translocation)
Coagulation Disorders
↗D-dimers ↗fibrinogen
↗F VII ↗Von Willebrand factors
↗Tissue Factor ↘Platelets reactivity
Immune Activation
Viral Replication
HIV
HIV
ART
CMV
Lymphocytes
T cell activation (CD38+)
Vascular and
Endothelial Dysfunction
Endothelial cells and vascular
smooth muscle cells
↗ROS ↗RAS ↘NO
↗VCAM-1
Hypertension, Atherosclerosis, Myocardial infarction

Table 2. Cardiovascular Drugs Interacting with Antiviral Therapy [49]

Cardiovascular medications that interact with anti-retrovirals
Dihydropyridine calcium-channel blockers
Sildenafil
β-Blockers, digoxin, and non-dihydropyridine calcium-channel blockers
Statins Metabolized by CYP3A4: atorvastatin, lovastatin, simvastatin, Not metabolized by CYP3A4: fluvastatin, pravastatin
Anticoagulants- warfarin, antiarrhythmics- amiodarone, antiplatelets- ASA, clopidogrel
Drugs used in HIV positive individuals that interact with cardiovascular drugs
Protease Inhibitors (PI's)- some act as substrates, CYP enzyme inhibitor/ inducers
Nucleoside reverse transcriptase inhibitors (NRTI)-some act as substrates. CYP enzyme inhibitor/ inducers
Non-nucleotide reverse transciptase inhibitors (NNRTI)- some act as substrates. CYP enzyme inhibitor/ inducers
Antibiotics- Cotrimoxazole, anti-virals- class of acyclovir, anti-fungals- azoles
Anti-tuberculous therapy

Table 4 **Drug–drug interactions between antiretroviral and cardiovascular drugs**

		Atazanavir	Darunavir	Lopinavir	Ritonavir[2*]	Efavirenz	Etravirine	Rilpivirine	Navirapine	Maraviroc	Raltegravir	ELV/c
CARDIOVASCULAR DRUGS	atorvastatin	↑	↑	↑	↑	↓	↓	↔	↓*	↔	↔	↑*
	fluvastatin	↔*	↔*	↔*	↔*		↑*	↔		↔*	↔*	↔*
	pravastatin	↔*	↑	↔	↔	↓	↓*	↔	↔*	↔	↔	↔*
	rosuvastatin	↑	↑*	↑	↑	↔	↑*	↔	↔	↔	↔	↑*
	simvastatin	↑	↑	↑	↑	↓	↓*	↔	↓*	↔	↔	↑*
	amlodipine	↑*[(3)]	↑*	↑*	↑*	↓*	↓*	↔	↓*	↔*	↔	↑*
	diltiazem	↑[(3)]	↑*	↑	↑	↓	↓*	E*	↓	E*	↔	↑*
	metoprolol	↑*	↑*	↑*	↑*	↔*	↔*	↔	↔*	↔*	↔*	↑*
	verapamil	↑*[(3)]	↑*	↑*	↑*	↓*	↓*	↔	↓*	E*	↔*	↑*
	warfarin	↑ or ↓*	↓	↓	↓	↑ or ↓*	↑*	↔	↑ or ↓*	↔*	↔*	↓*

[a]Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent.

[b]ECG monitoring recommended; *, prediction based on metabolic profiles of drugs only, no clinical data from interaction study; absence of * indicates that clinical data are available; ↑, elevated exposure of cardiovascular drug; ↓, decreased exposure of cardiovascular drug; ↔, no significant effect; E, elevated exposure of antiretroviral drug; D, decreased exposure of antiretroviral drug; ELV/c, Elvitegravir/cobicistat (cobicistat is used as pharmacokinetic enhancer without anti-HIV activity). Adopted from European AIDS Clinical Society (EACS).

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Eur Heart J. 2013;34(46):3538-3546. doi:10.1093/eurheartj/eht388

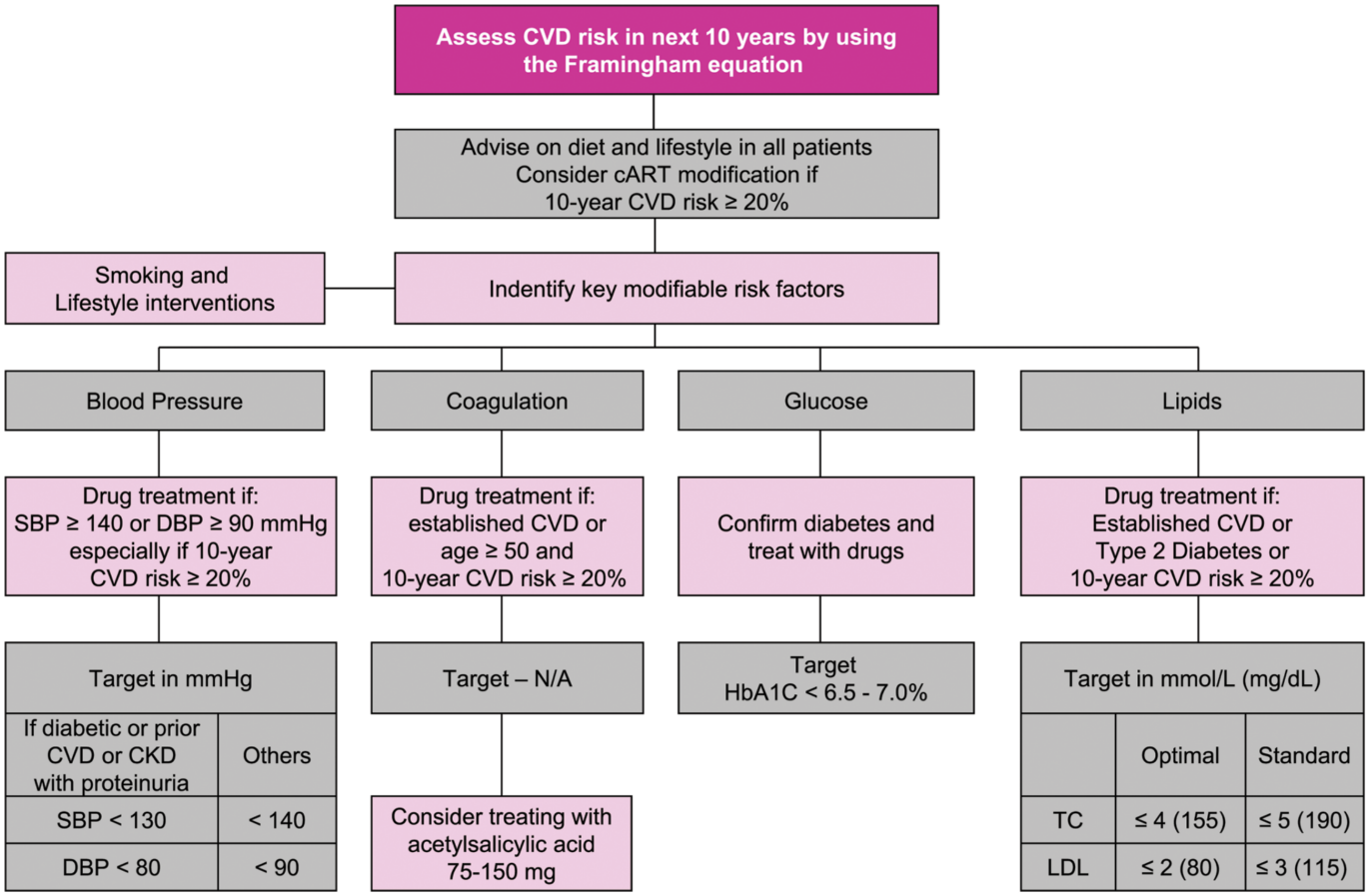


Figure Legend:

Algorithm for the prevention of cardiovascular diseases. CVD, cardiovascular disease; cART, combination antiretroviral therapy; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidneys disease; TC, total cholesterol; LDL, low-density lipoprotein. Source: European AIDS Clinical Society.

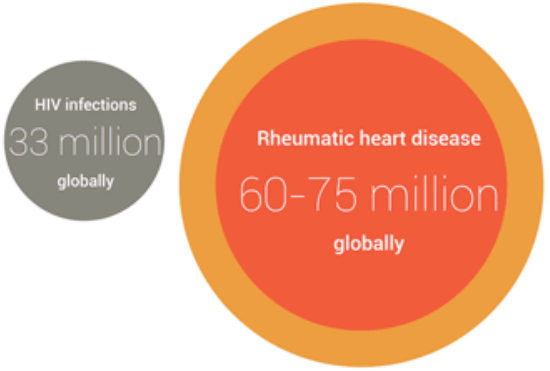
The disease

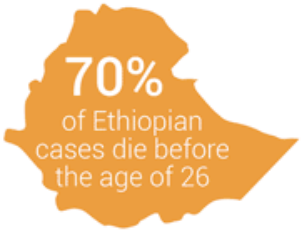
Symptoms of **strep throat** disappear after 14–25 day

Rheumatic Heart Disease symptoms appear **years later**

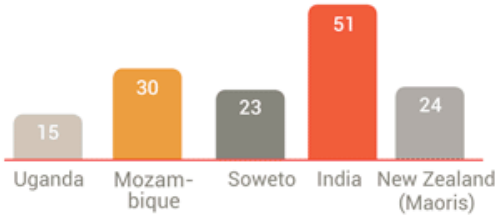
Rheumatic Heart Disease primarily affects poor, young people between the ages of 5 and 15

The global picture





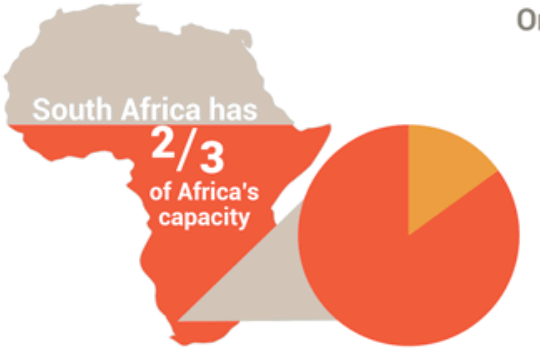
Levels of incidence per 1000



Treatment

Available cardiac surgery facilities in Africa

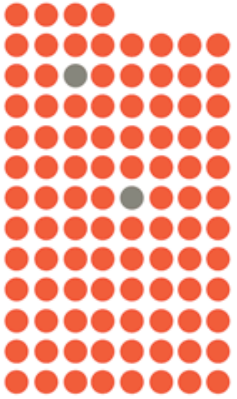
- Egypt
- Ghana
- Algeria
- Namibia
- Kenya
- Sudan



But only 15% of this is for indigent RHD sufferers

As a Result

Only 2 in 100 get treated



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