INTRODUCTION TO HIV/AIDS PATHOLOGY

PROF. EA ROGENA

OBJECTIVES

- PATHOGENESIS OF HIV/ AIDS
- Clinico-pathologic manifestations of AIDS and WHO staging
- Pathogenesis of Kaposi's sarcoma and NHL associated with HIV/AIDS

Introduction- HIV/AIDS-Acquired Immunodeficiency Syndrome

- Retroviral disease: immunosuppression-cell-mediated immunity = manifestations, opportunistic infections, and neoplasms
- Sub-Saharan Africa: 25.8 million (23.8-28.9)(WHO-2005)

Introduction-KAIS 2012

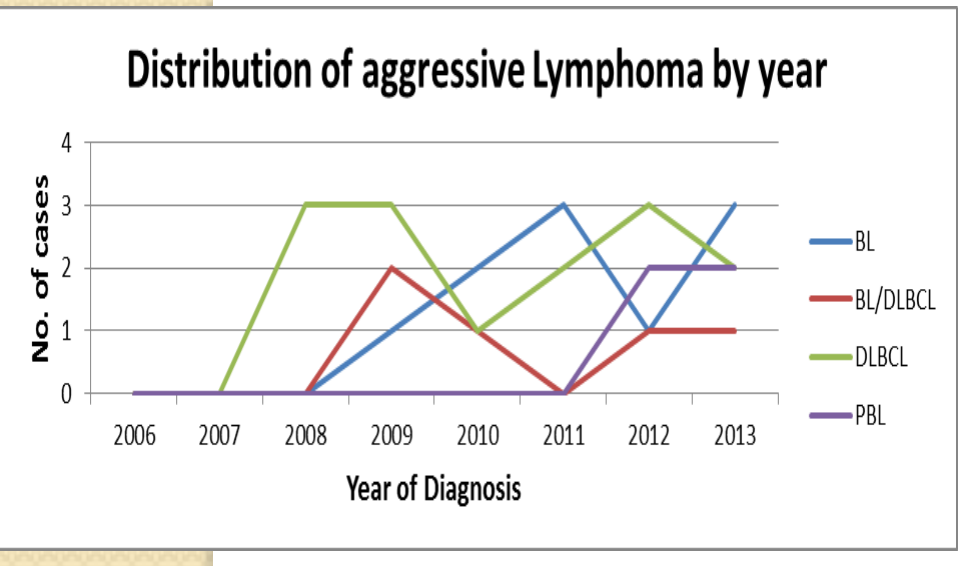
- HIV prevalence among adults aged 15 to 64 years decreased nationally from 7.2%, as measured in KAIS 2007 to 5.6% in 2012
- HIV prevalence among children aged 18 months to 14 years was 0.9%.
- HIV prevalence among adults varied by region, with the highest prevalence in Nyanza
- lowest prevalence in the Eastern North region
- Most regions showed a decreased prevalence from 2007, substantial drops were identified in the Coast, Nairobi and Rift Valley regions.
- Levels of HIV testing have increased with 72% of adults aged 15 to 64 years in 2012 , reporting ever having been tested for HIV, a significant increase from 34% in 2007.

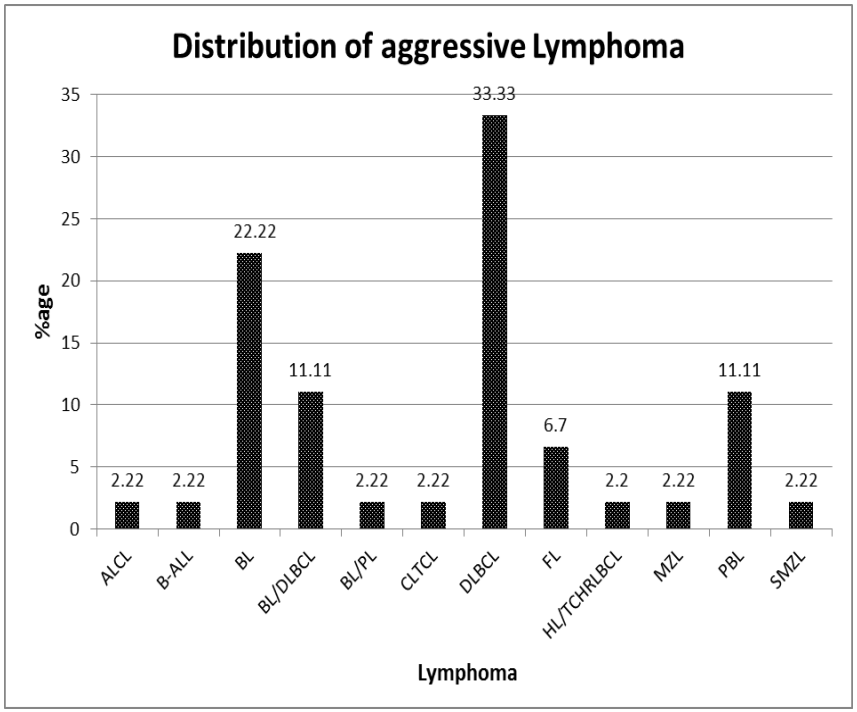
RISK FACTORS FOR AIDS

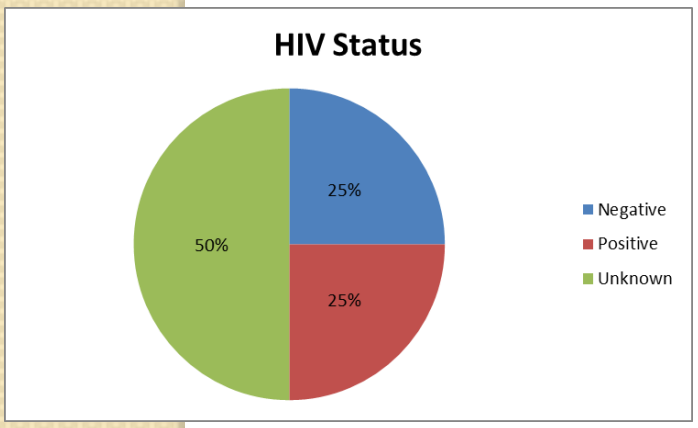
- Homosexual or bisexual men
- Heterosexual contacts with other high-risk individual(s)
- Intravenous drug users
- Hemophiliacs, especially who received factor VIII concentrates before 1985
- Recipients of blood and blood components.
- Infected mother to child transmission; high maternal viral load and low CD4 count, chorioamnionitis

ETIOLOGY OF AIDS

- HIV-1: U.S.A, Europe and East-Central Africa
- HIV-2 : West Africa



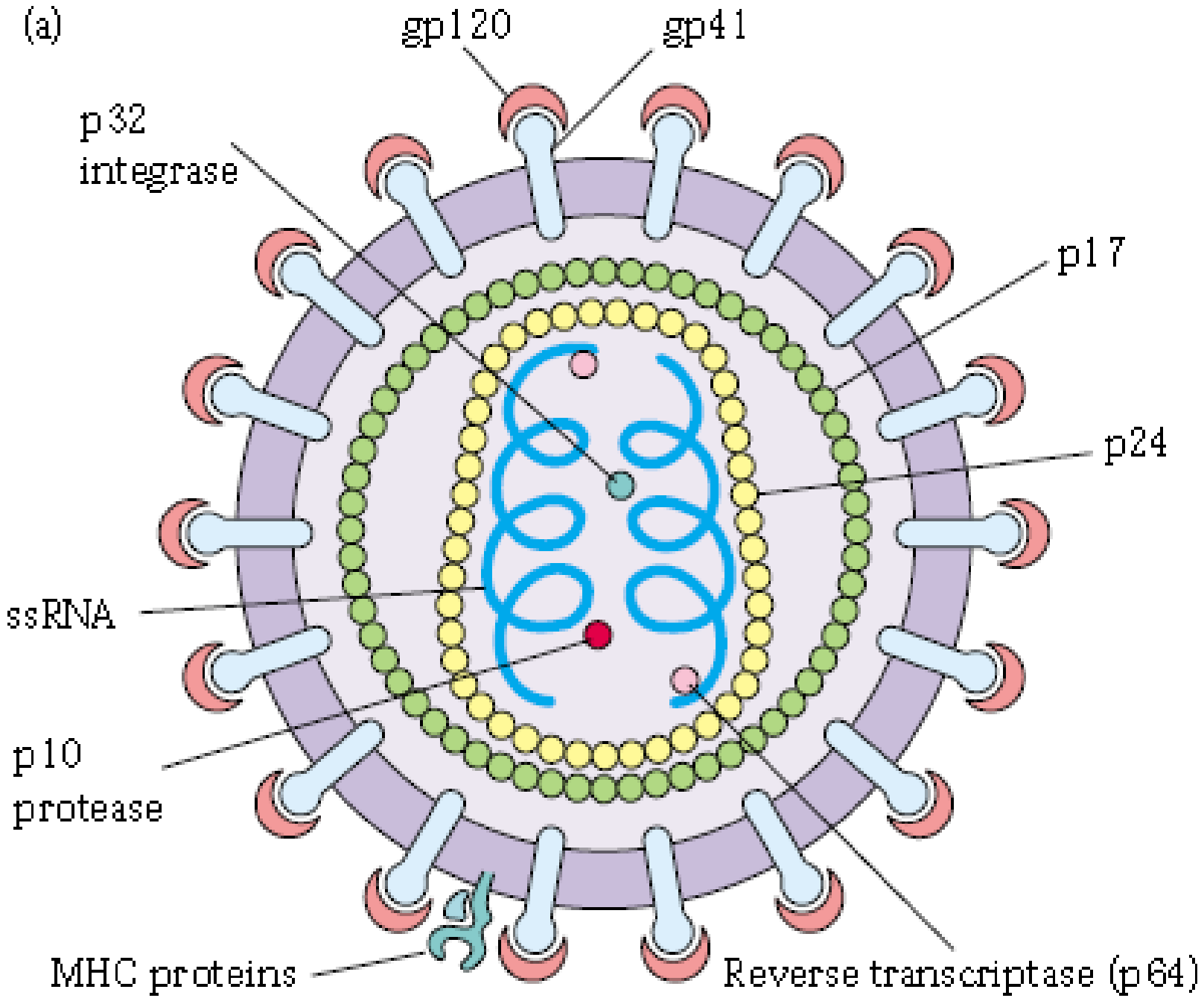




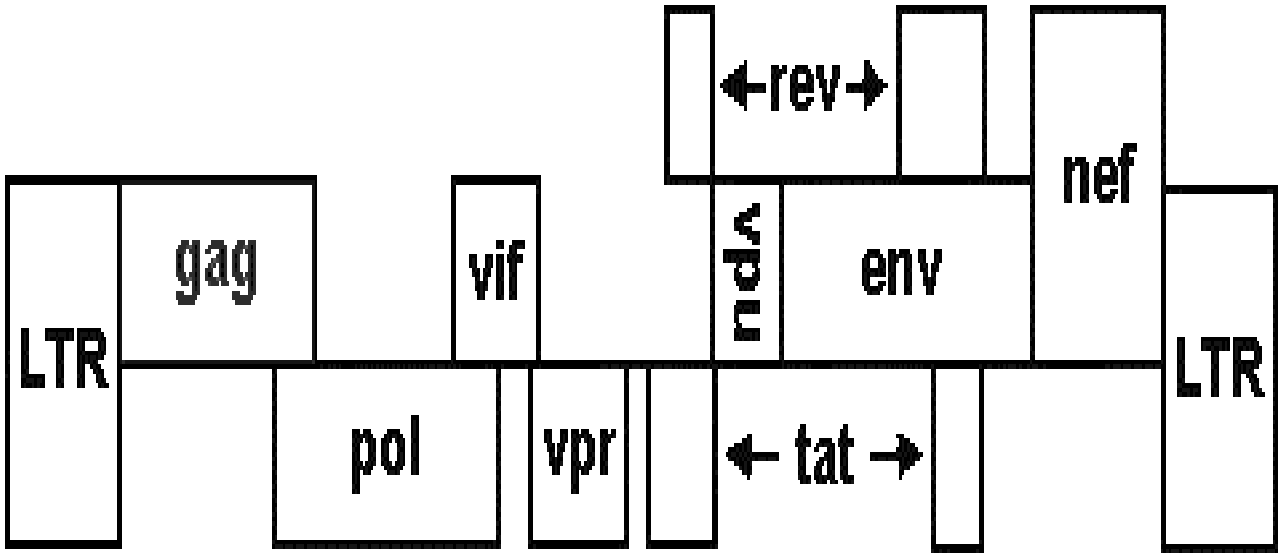
range 3 to 80 years
mean 40years ; median of 40 years.
male to female ratio was 1.53:1.
(60) 83% adults ; 12 (17%) minors.

Target cells

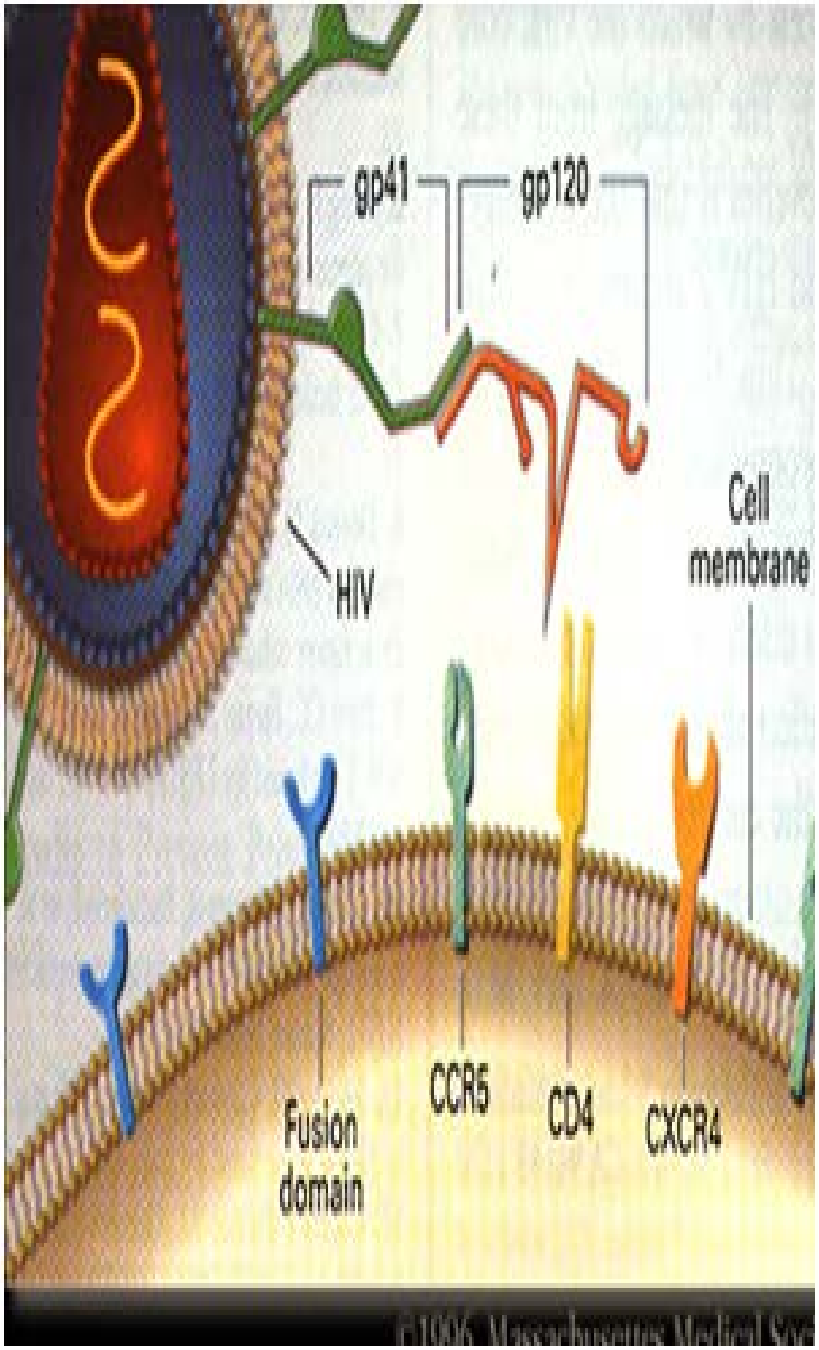
- CD4 lymphocytes
- Microglial cells
- Monocytes
- macrophages
- Follicular dendritic cells

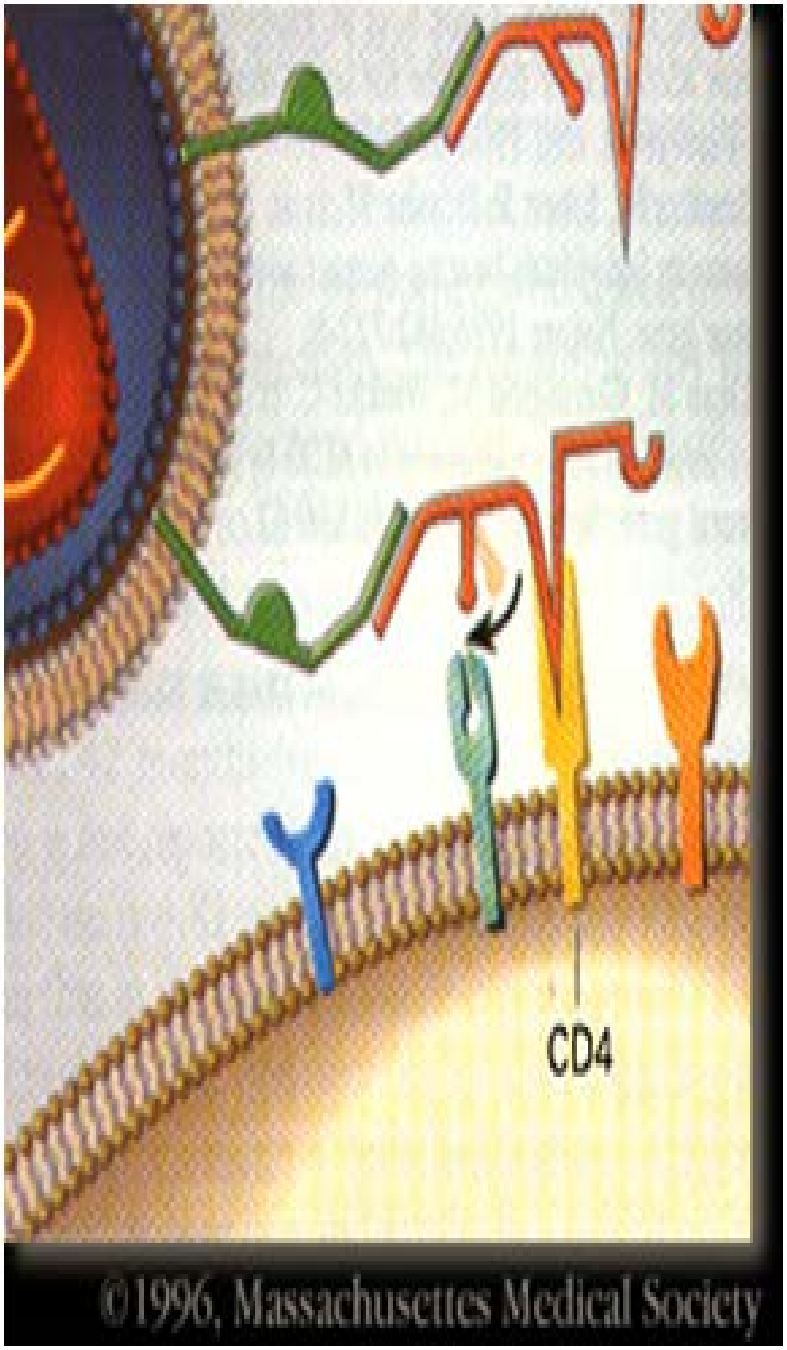

(a)
gp120
gp41
p32
integrase
p17
p24
ssRNA
p10
protease
MHC proteins
Reverse transcriptase (p64)

HIV GENOME



PATHOGENESIS


gp41
gp120
HIV
Cell membrane
Fusion domain
CCR5
CD4
CXCR4


CD4
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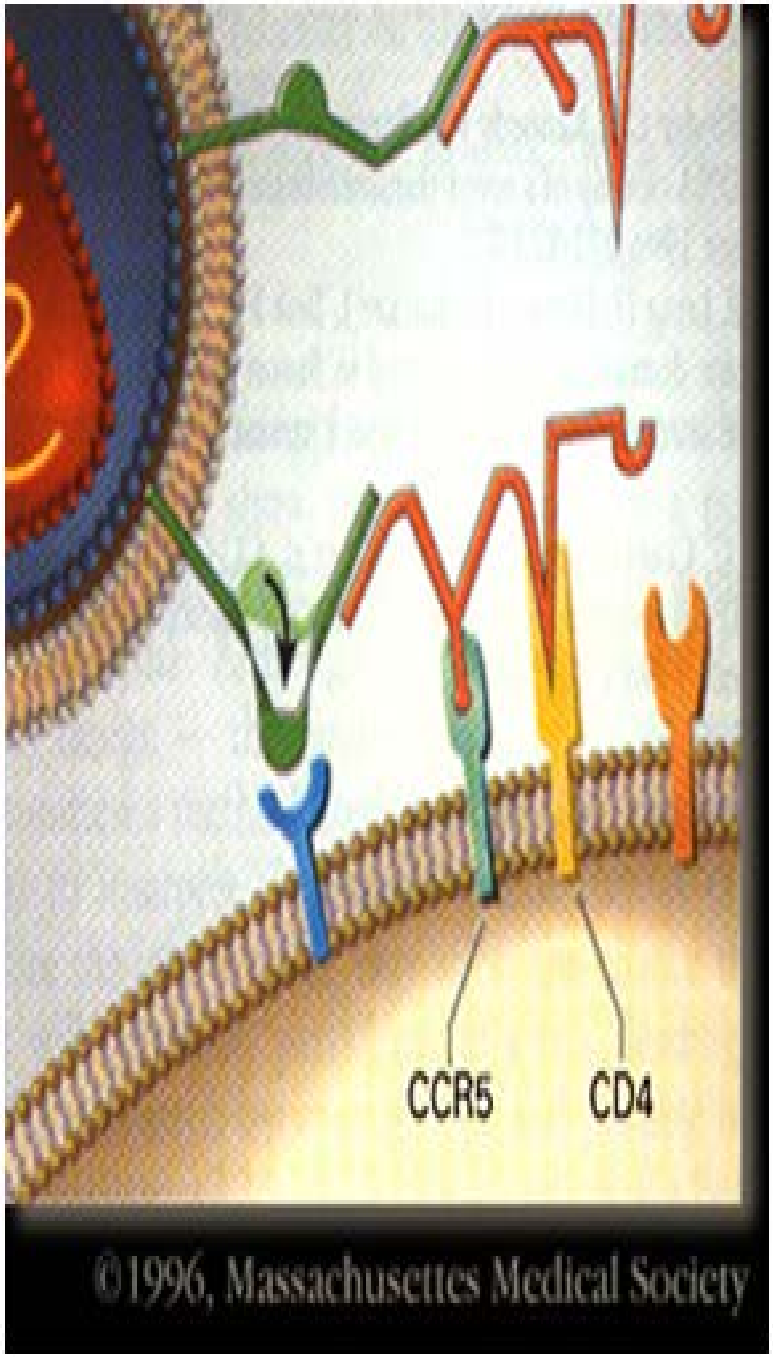
CCR5
CD4
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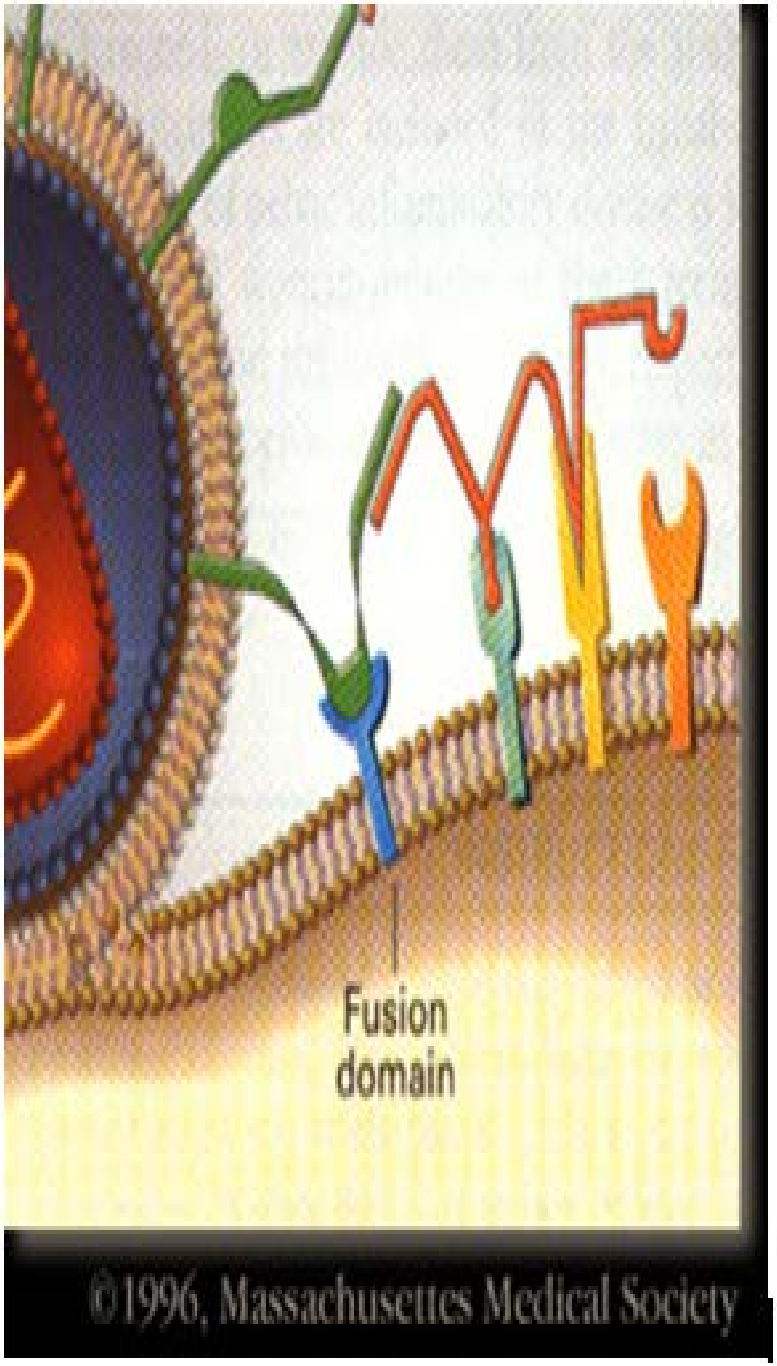
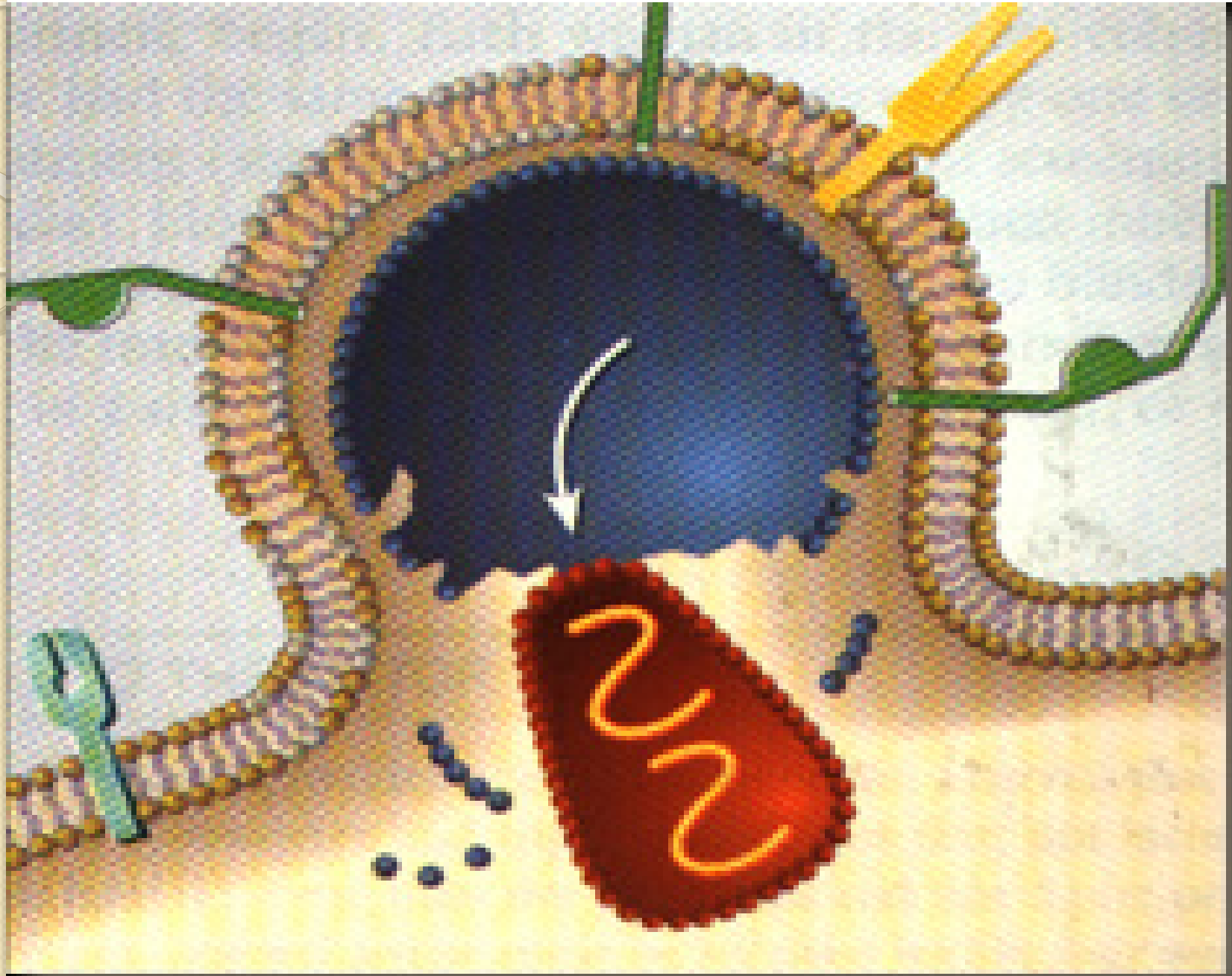

Fusion
domain
©1996, Massachusettes Medical Society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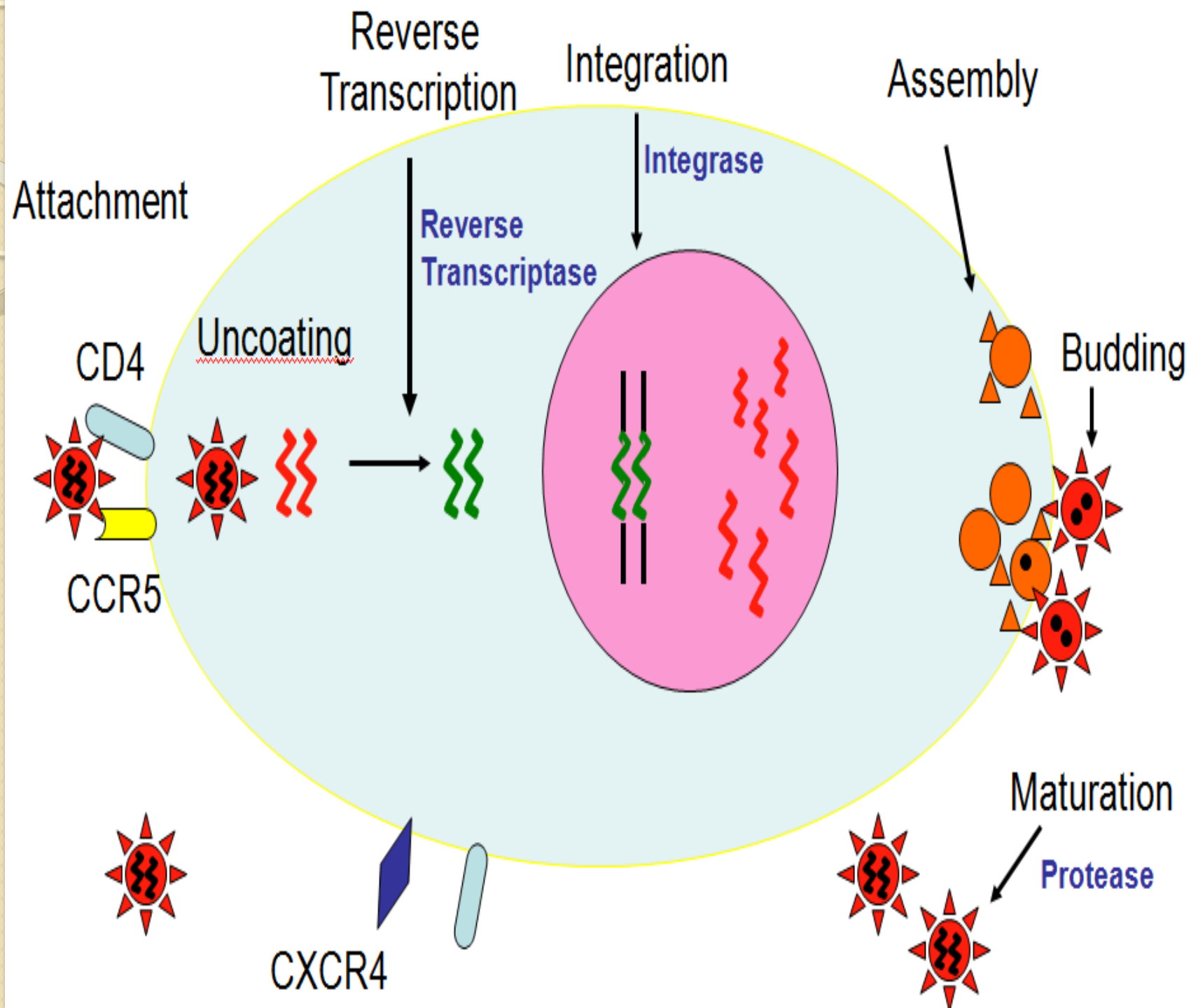
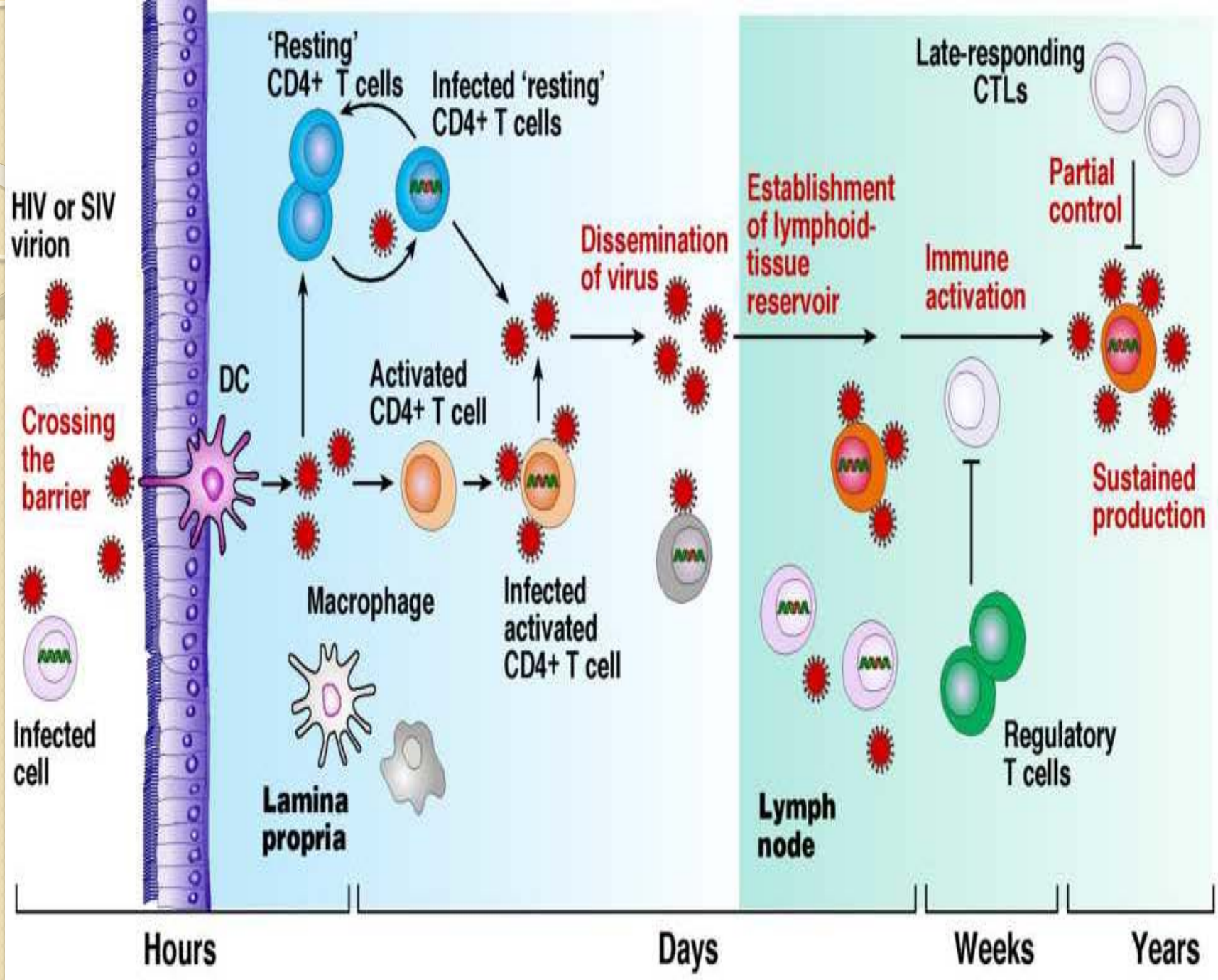
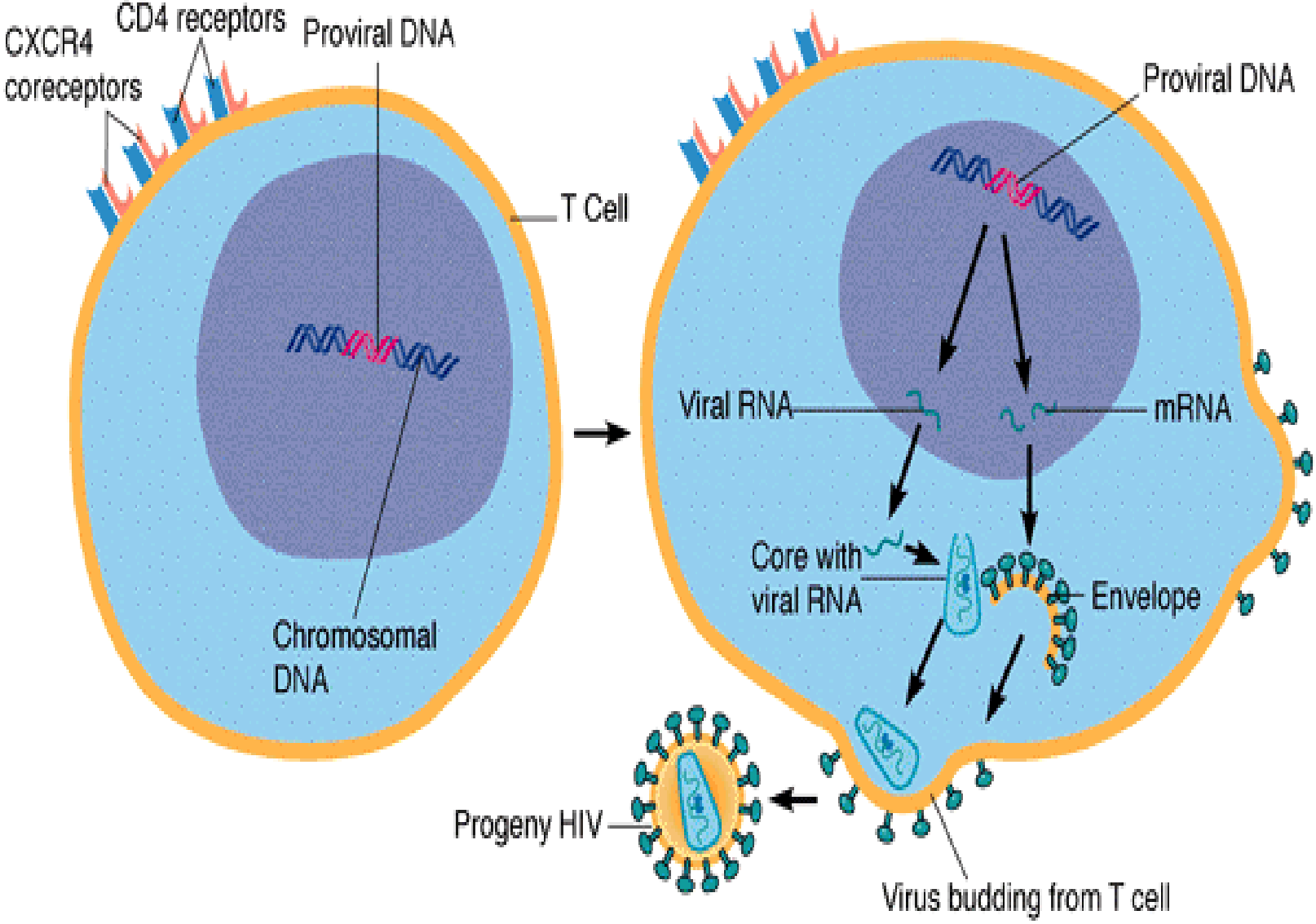

Reverse
Transcription
Integration
Assembly
Attachment
Integrase
Reverse
Transcriptase
Uncoating
CD4
Budding
CCR5
Maturation
Protease
CXCR4


'Resting' CD4+ T cells
Infected 'resting' CD4+ T cells
Late-responding CTLs
HIV or SIV virion
Dissemination of virus
Establishment of lymphoid-tissue reservoir
Partial control
Immune activation
DC
Activated CD4+ T cell
Crossing the barrier
Sustained production
Macrophage
Infected activated CD4+ T cell
Infected cell
Regulatory T cells
Lamina propria
Lymph node
Hours
Days
Weeks
Years



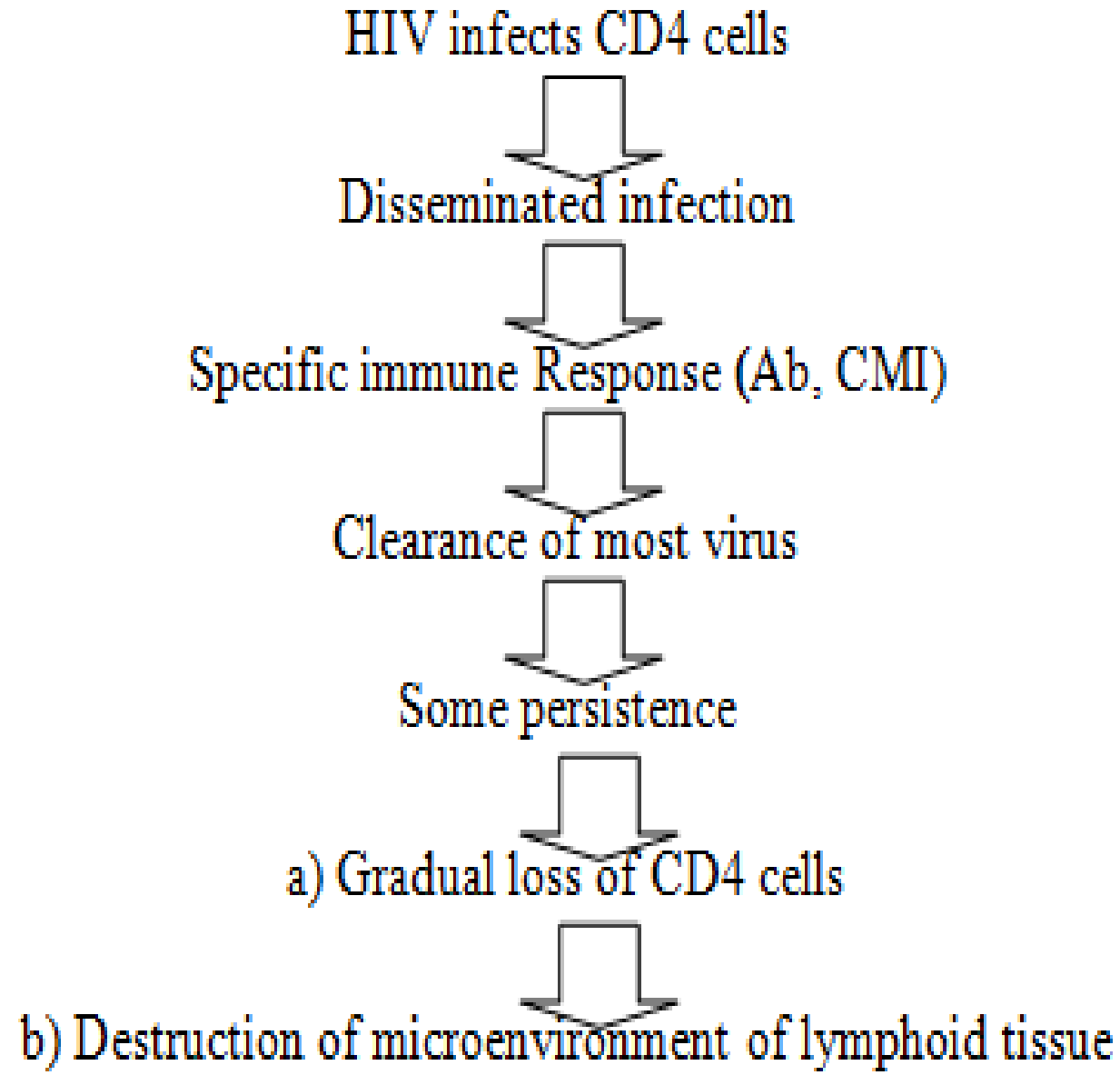
(a) Latent infection

(b) Active infection

EFFECTS-
1. CD4 CELLS

- IMMUNOPATHOGENICITY OF HIV-1 VIRUS

Figure 6: Simplified model of the immunopathogenicity of HIV-1 virus

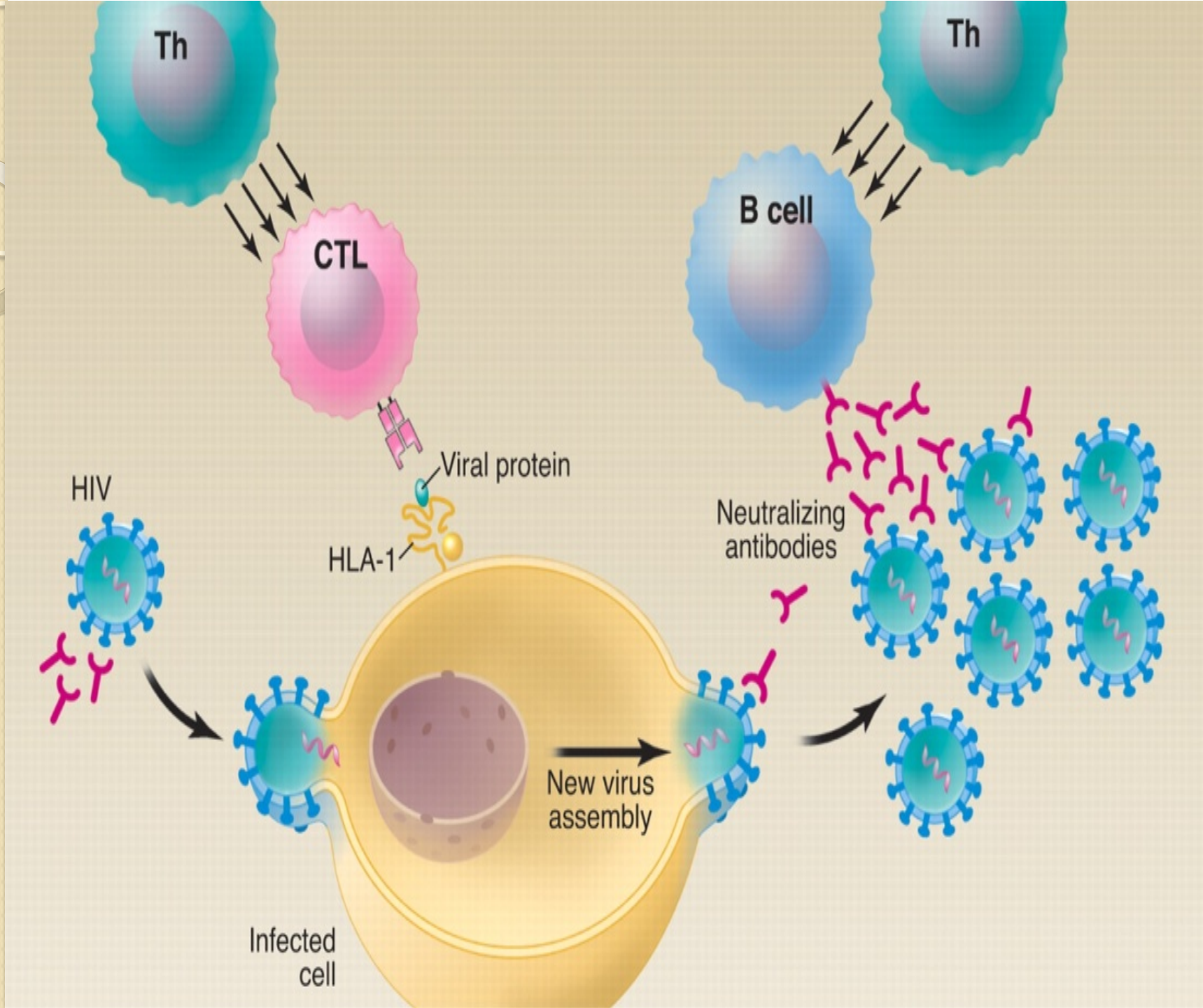


NK cells

- Innate immunity: Natural Killer Cells

Abnormal B cell function

- Abnormality of B-cell function


Th
Th
CTL
B cell
Viral protein
HIV
HLA-1
Neutralizing
antibodies
New virus
assembly
Infected
cell

Lack of HIV-specific T cell responses

- Clonal deletion
- Anergy
- Ag-induced apoptosis
- Defect in Ag presentation

Other effects

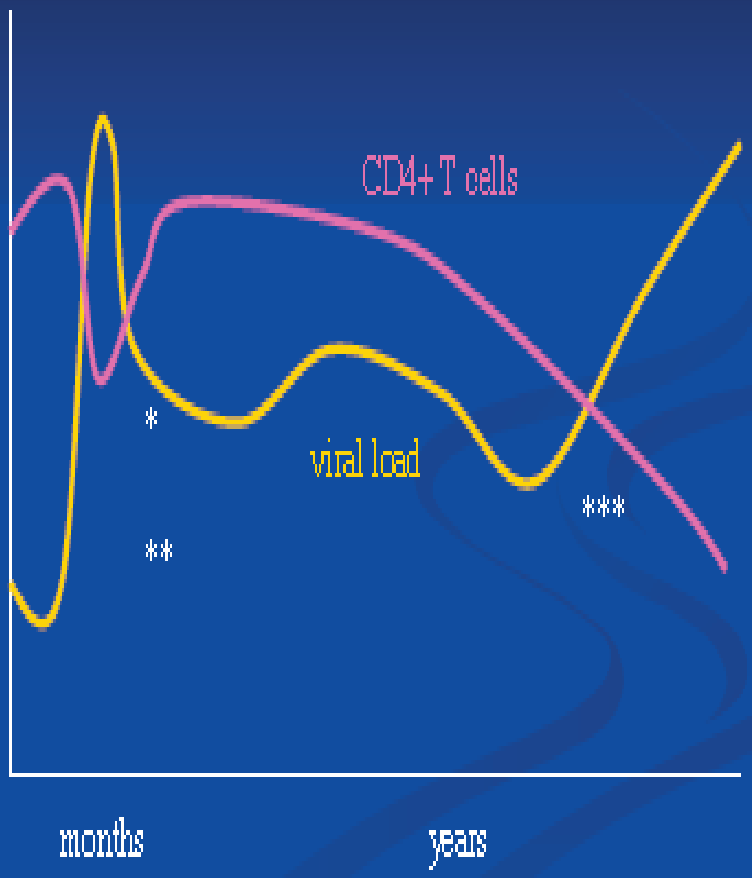
- Cytokines-TNF
- Constant inflammation associated with neoplasms etc

- Micro RNA increase
- Large pool of proliferating B cells- risk of neoplasms

CNS INFECTION

- Causes of neurological deficit:
  - Soluble gp 120 (direct)
  - Viral products & soluble factors produced by microglia (indirect)
  - Soluble neurotoxins trigger excessive Ca2+ entry into neurons through glutamate-activated ion channels

Time points in HIV Infection



Important events

- *Set-point viremia (weeks):
  - stabilization of viral load in early infection
  - predicts progression
- **Seroconversion (weeks -> 6 months):
  - positive for HIV antibodies
  - can be accompanied by flu-like symptoms
- ***AIDS (2-30+ years):
  - blood CD4 count < 200 /ul
  - appearance of opportunistic infections

WHO- CLINICAL STAGING OF AIDS

Clinical Stage	Symptoms
I(mild)	Asymptomatic, or persistent generalized lymphadenopathy Performance scale 1: asymptomatic, normal activity
II(moderate)	Weight loss <10% of body weight Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis) Herpes zoster within the last five years Recurrent upper respiratory tract infections (i.e. bacterial sinusitis)

	And/or performance scale 2: symptomatic, normal activity
III(severe)	*Weight loss > 10% of body weight*
	Unexplained chronic diarrhoea, > 1 month
	Unexplained prolonged fever (intermittent or constant), > 1 month
	Oral candidiasis
	Oral hairy leucoplakia
	Pulmonary tuberculosis
	Severe bacterial infections (i.e. pneumonia, pyomyositis)
	And/or performance scale 3: bedridden < 50% of the day during last month

IV(very severe)	HIV wasting syndrome (weight loss of >10% of body weight, + either unexplained chronic diarrhoea (>1 month) or chronic weakness and unexplained prolonged fever (>1 month))
	Pneumocystic carinii pneumonia
	Toxoplasmosis of the brain
	Cryptosporidiosis with diarrhoea >1 month
	Cryptococcosis, extrapulmonary
	Cytomegalovirus disease of an organ other than liver, spleen or lymph node (e.g. retinitis)
	Herpes simplex virus infection, mucocutaneous (>1 month) or visceral
	Progressive multifocal leucoencephalopathy
	Any disseminated endemic mycosis
	Candidiasis of esophagus, trachea, bronchi

Atypical mycobactenosis, disseminated or pulmonory

Non-typhoid Salmonella septicemia

Extrapulmonary tuberculosis

Lymphoma

Kaposi's sarcoma

HIV encephalopathy (clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition, other than HIV infection, which could explain the finding)

And/or performance scale 4: bedridden >50% of the day during last month

Neoplasms associated with HIV/AIDS

AIDS DEFINING

- Kaposi's sarcoma*
- Primary cerebral lymphoma*
- High-grade non-Hodgkin lymphoma*
- Carcinoma (invasive) of the cervix*
- Anorectal squamous cell carcinoma

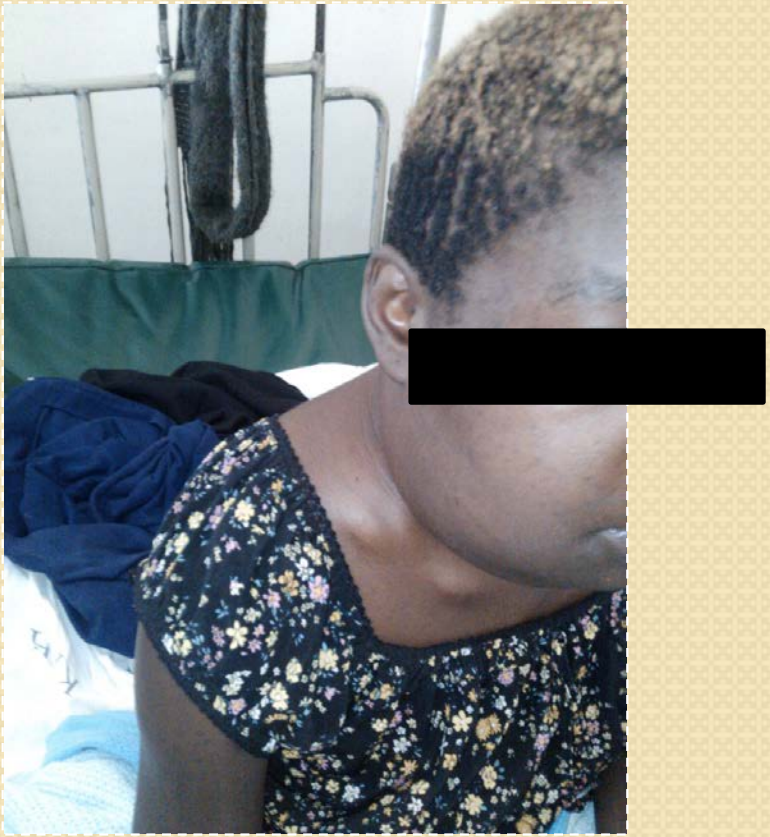
AIDS RELATED

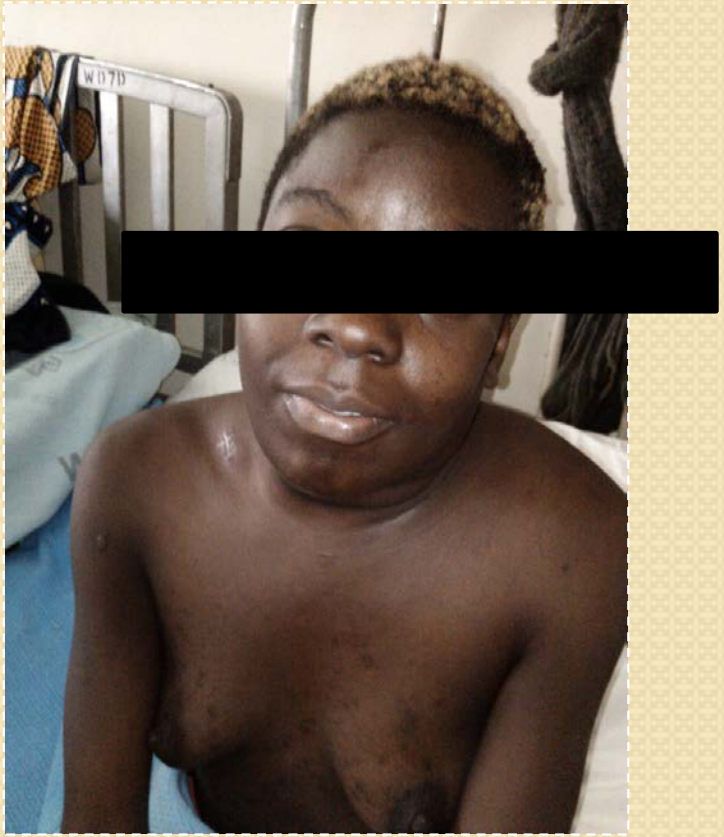
- Carcinoma of the conjunctiva
- T-cell lymphoma
- Hodgkin's disease
- Lymphoproliferative disease,

BEFORE RX

AFTER RX

26yr old female, HIV positive on HAART with Superior Vena Cave Syndrome and respiratory distress





B-cell Non Hodgkin Lymphoma in the context of HIV

- Increased risk of NHL in HIV infection correlated to the severity of the underlying immunodeficiency
- Damage to B Cell and activation of B Cell
- Roles of immunosuppression and viruses : EBV, HHV8
- Roles of HIV proteins : Env, **Tat**, Nef

AIDS related B-cell lymphoma : specificity at different levels

Epidemiology

Clinical features

Pathological findings

Histogenetic profiles

Molecular, Genetic and Epigenetic aspects

B-Cell dysfunction, HIV infection and Lymphoma

Number and magnitude of B-cell alterations leading to lymphoma result from complex and multiple interactions

HIV

- Polyclonal activation
  virion binding to CD21/cytokines **environment**
- Elevated class switch
  gp120, CD40-CD40L
- Nef and increased AID level **cells**
- Tat protein
  Transgenic mice Tat lymphoma
- VEGF mimetic
- DNA repair to double strand DNA breaks
  cell cycle/ chromatin remodeling

Damage to B Cell
Microgenerative

Perturbation of naive/memory cells
B cell exhaustion
Increased transitional B

CD38+, SIgD+, CD10+

- **EBV**

EBER and latency proteins

EBV driven lymphoproliferations

Genetic/Epigenetic abnormalities (miRNA)

B cell NHL in the context of HIV infection

From the french data base (ANRS CO4)

- NHL are the first cause of death from cancer among HIV infected patients
- Drastic decrease of Primary Brain Lymphoma since combined Anti retroviral Therapy (cART)
- Incidence of Hodgkin Lymphoma is 5 -15 fold higher in HIV infected patients than in general population
- Not decreased in the cART era

French ANRS CO16 LYMPHOVIR
Cohort study :105 cases of HIV associated lymphomas

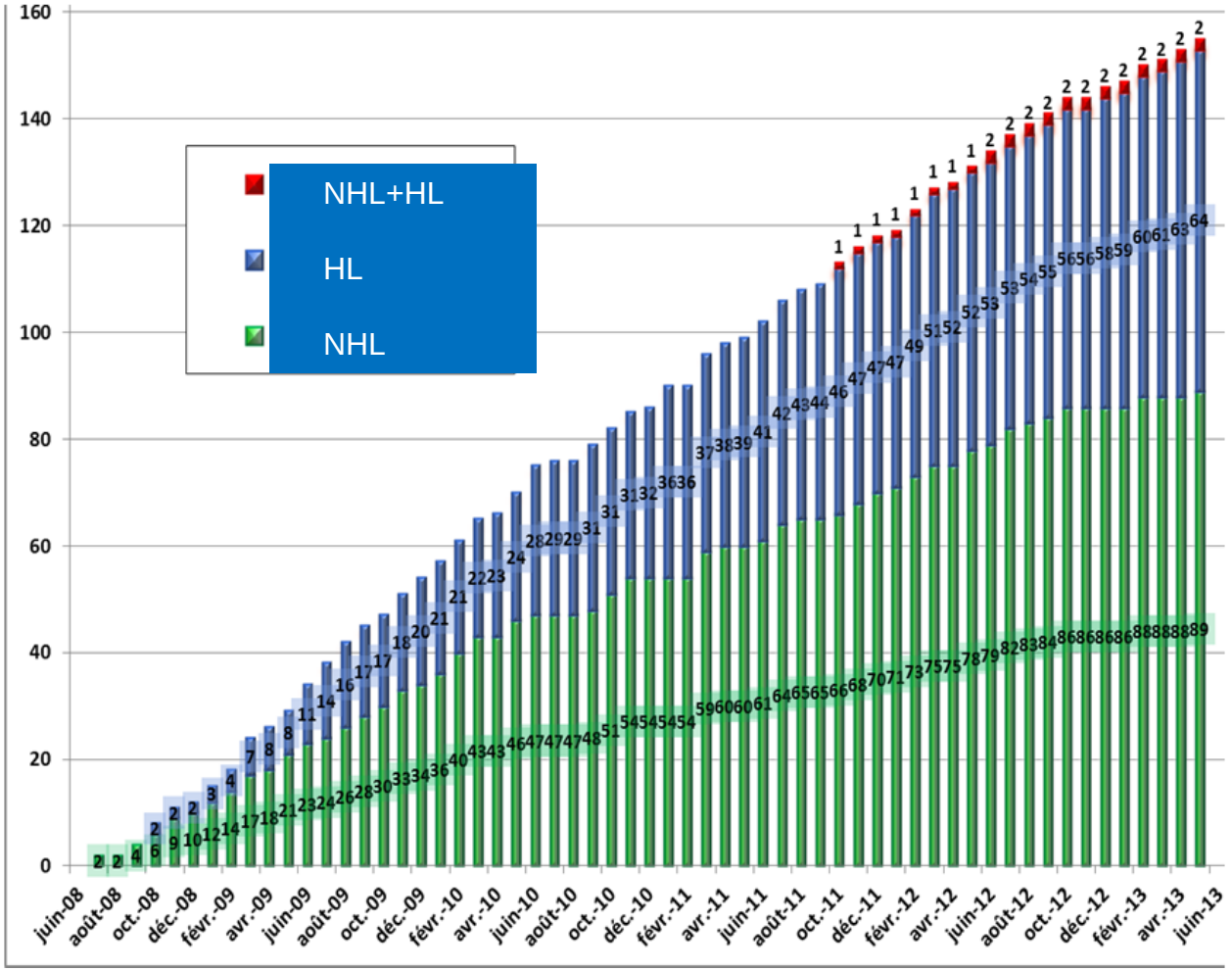
Observational
prospective
French cohort

- Adult patients with HIV infection (+/- HBV/HCV Infection) at diagnosis of HL or NHL

- Blood and tissue banking

NHL : 57%

HL : 43%



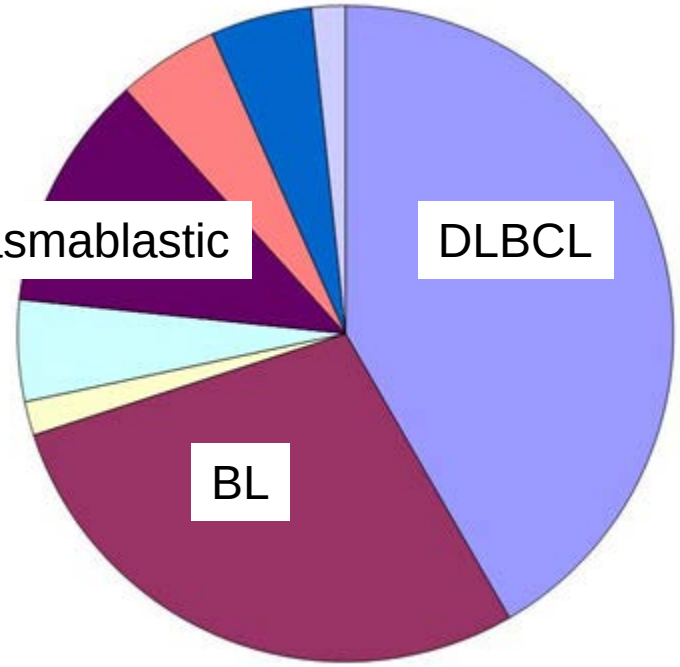
Histological distribution of B cell NHL (60 cases)

- **Burkitt L** **28%**
- **DLBCL** **42%**
- Anaplastic 1,5%

- **HIV specific** :
  PEL (primary effusion) 1,5%
  Plasmablastic 12%

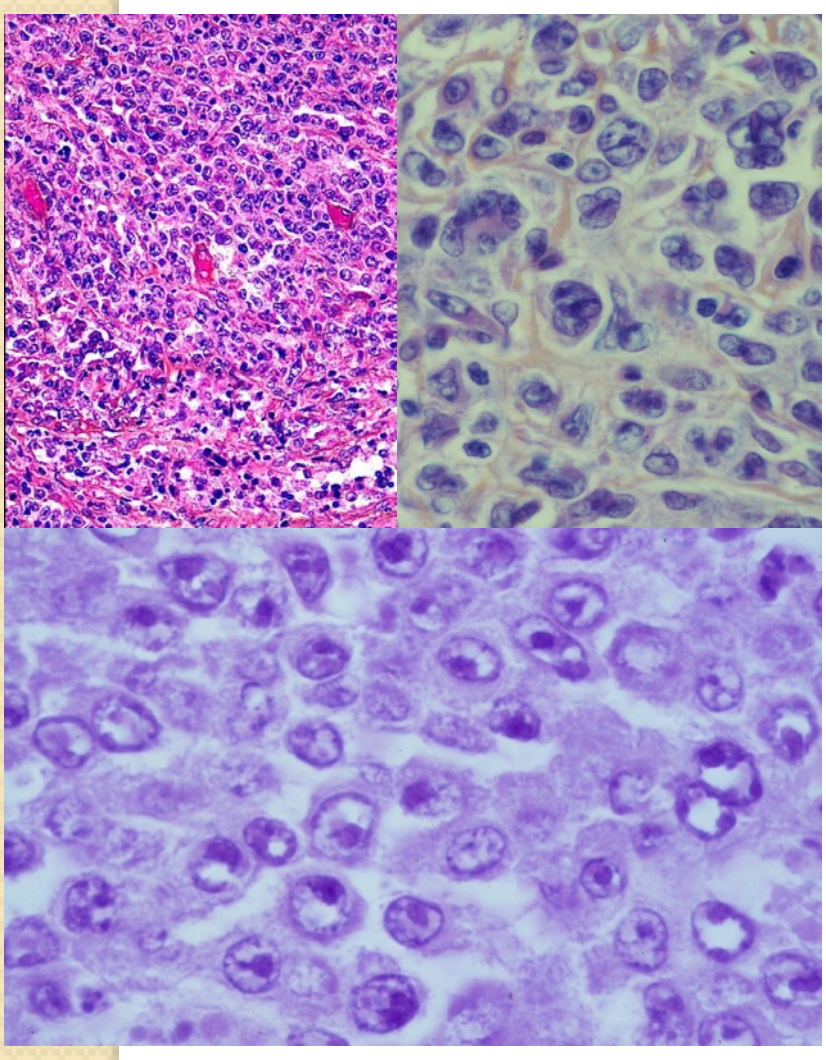
- **Immunocompromised** :
  PTLD-like 5%

• 3 «small cell» : marginal zone 5% lymphoma/Malt (HIV/HCV+)

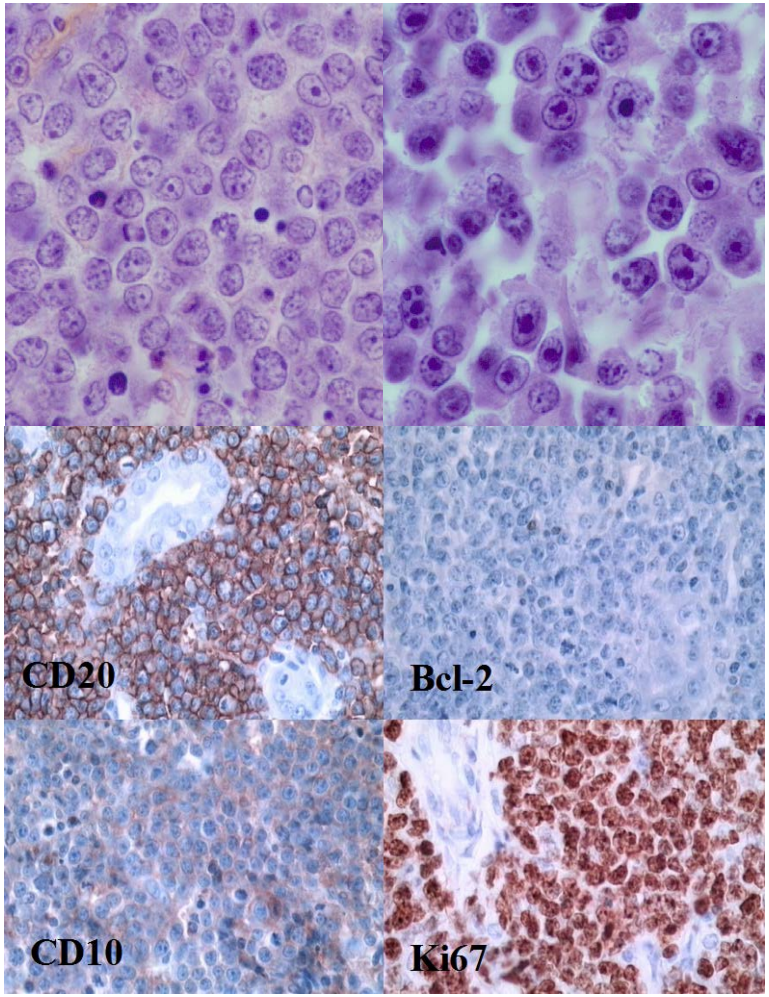


From Sohie Prevot
ANRS, Lymphovir Cohort

DLBCL
Centroblastic
Immunoblastic



Burkitt Lymphoma



KAPOSI'S SARCOMA

- Angioproliferative lesion, low-grade malignant potential-Kaposi sarcoma-associated herpesvirus/ human herpesvirus 8 (KSHV/HHV8) infection: skin lesions
- Epidemiology

PATHOGENESIS OF KAPOSI'S SARCOMA

Etiology: **Kaposi sarcoma-associated herpesvirus** (KSHV), also known as **human herpesvirus 8** (HHV-8)

Phases of infection:

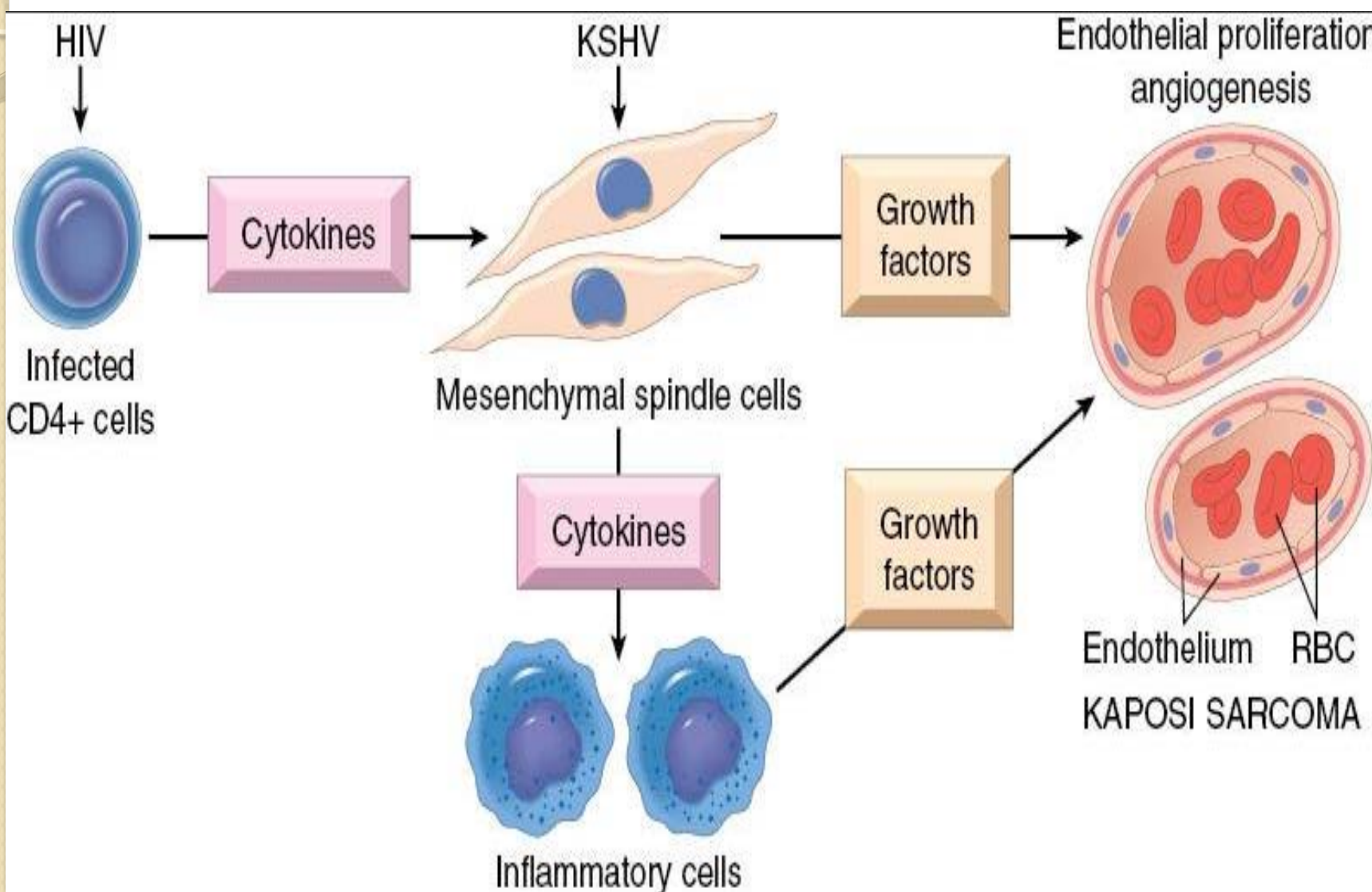
i) **Lytic phase-** replicates in infected cells, which results in cell lysis

ii) **Latent phase-** virus does not replicate, although cells harbor viral episomes and express several proteins, such as latency-associated nuclear antigens (LANA1 and LANA2)

Autocrine/Paracrine mechanisms

Direct transformation

Simplified model of the pathogenesis of KS

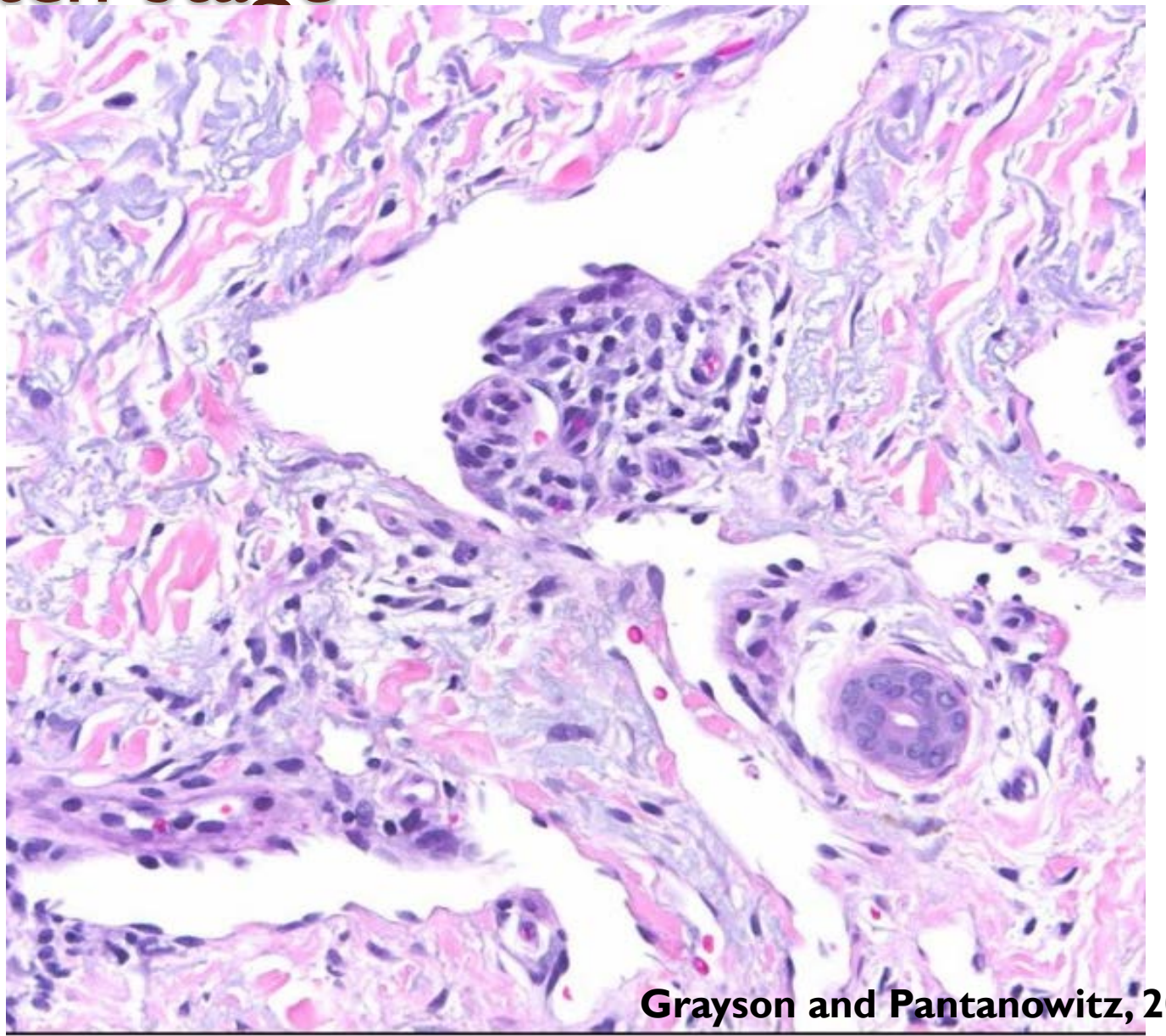


Immunohistochemistry for KS

- Viral Cyclin D
- LANA
- Flip & BCL2 activated
- VGCPR
- Cytokines

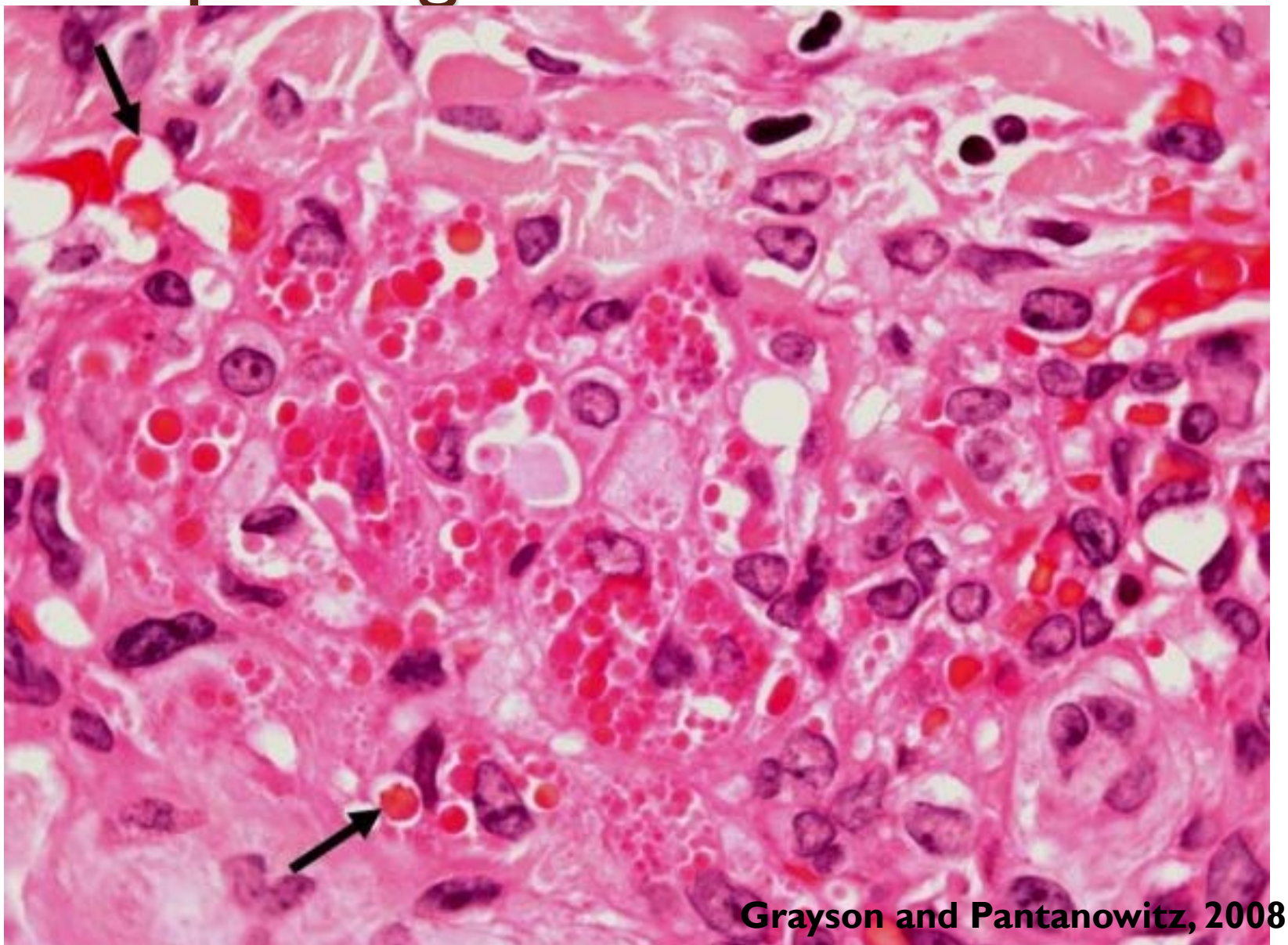
Patch stage

Patch stage



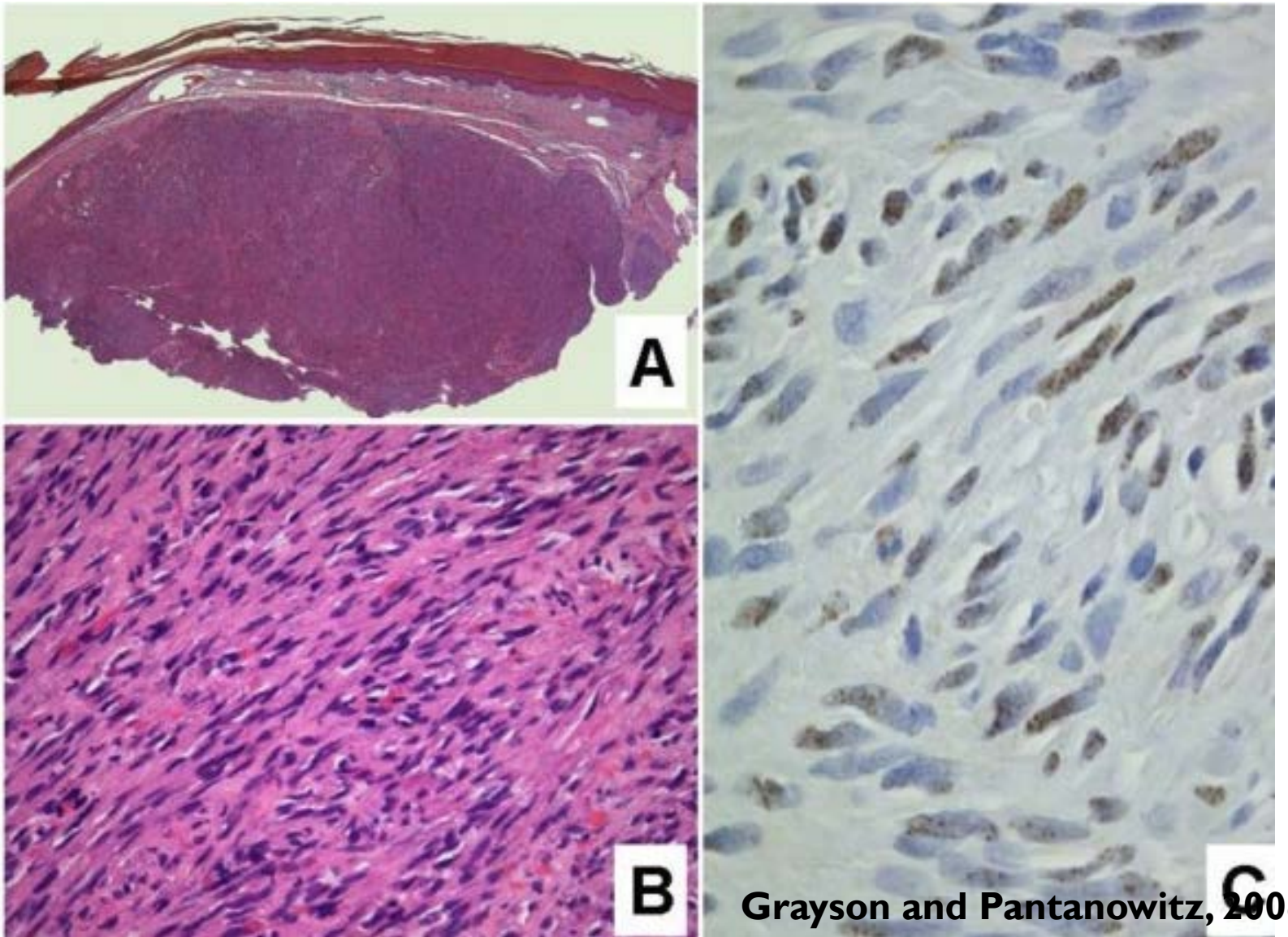
Grayson and Pantanowitz, 2008

Plaque stage



Grayson and Pantanowitz, 2008

Nodular stage



Grayson and Pantanowitz, 2008

Other histological variants of KS

- Anaplastic KS
- Lymphangioma-like KS
- Bullous KS
- Telangiectatic KS
- Hyperkeratotic (Verrucous) KS
- Keloidal KS
- Micronodular KS
- Pyogenic granuloma-like KS
- Ecchymotic KS
- Regressing KS

Other conditions associated with HIV/AIDS

- HIV-wasting syndrome* (fever, weight loss, diarrhoea)
- HIV-associated dementia*
- Various dermatitis patterns (e.g. pruritic rash, eosinophilic folliculitis)
- Skeletal myopathy
- Peripheral and autonomic neuropathy
- Cardiomyopathy
- Pulmonary hypertension
- Vasculitis
- HIV-associated nephropathy (HIVAN)
- Haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopaenic purpura (TTP)
- Oral and oesophageal ulcers
- Dyshaemopoiesis and marrow serous atrophy

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4. Goldsby RA, Kindt TJ, Osborne BA. *Kuby immunology by Macmillan Higher Education*, 2000.
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6. **French ANRS CO16 LYMPHOVIR**
7. Main opportunistic diseases associated with HIV infection, seen in AIDS- **Sabastian Lucas**

THANK YOU