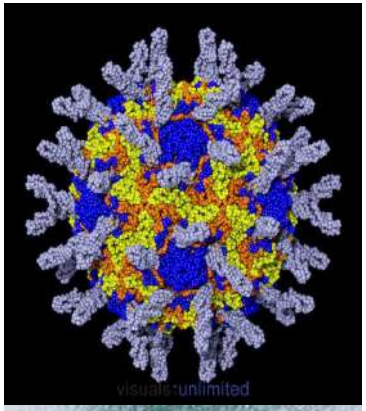
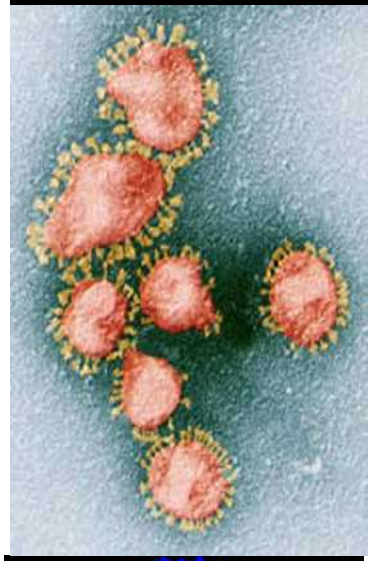
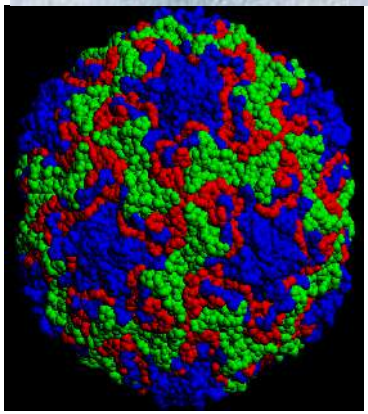




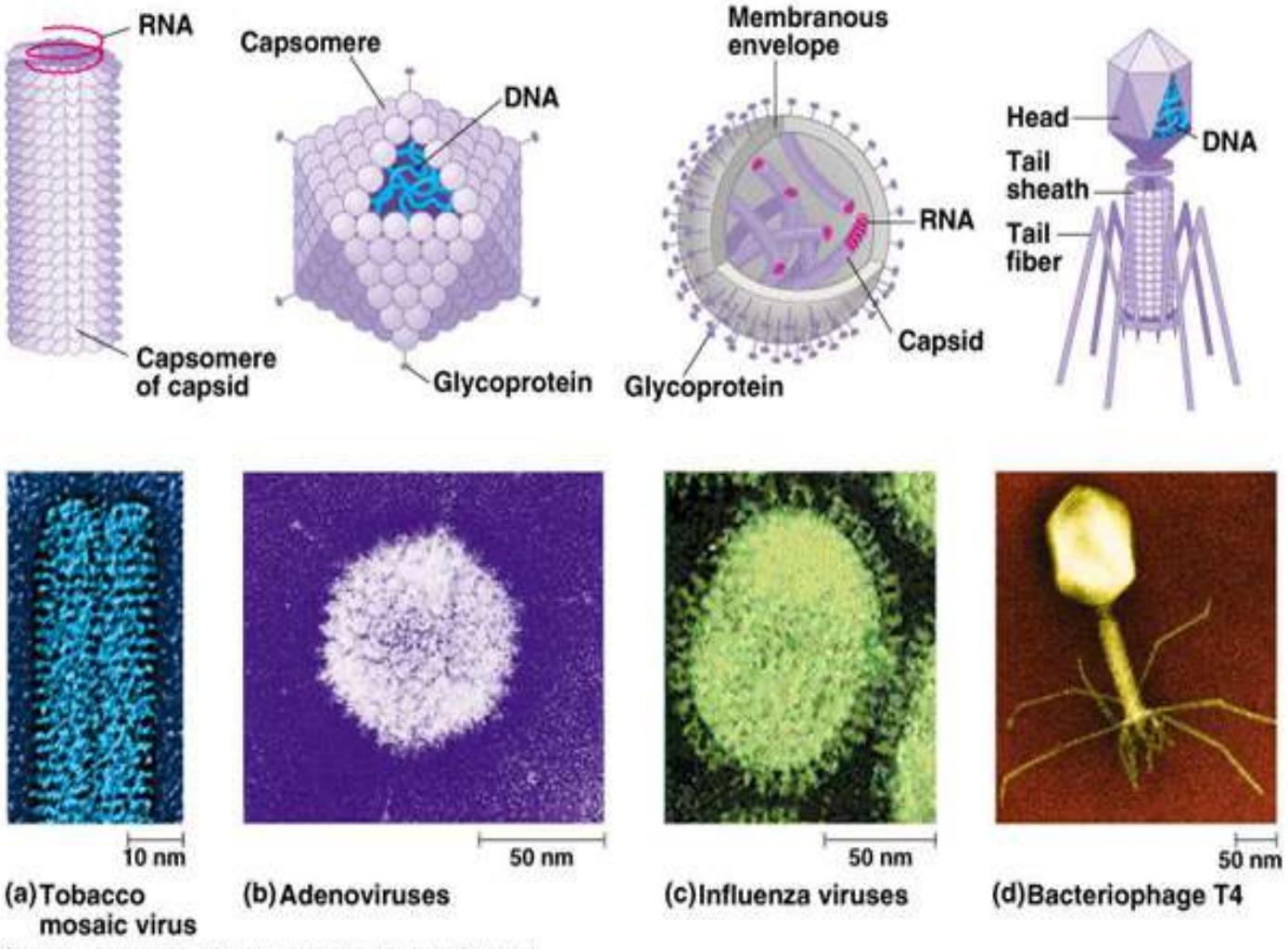


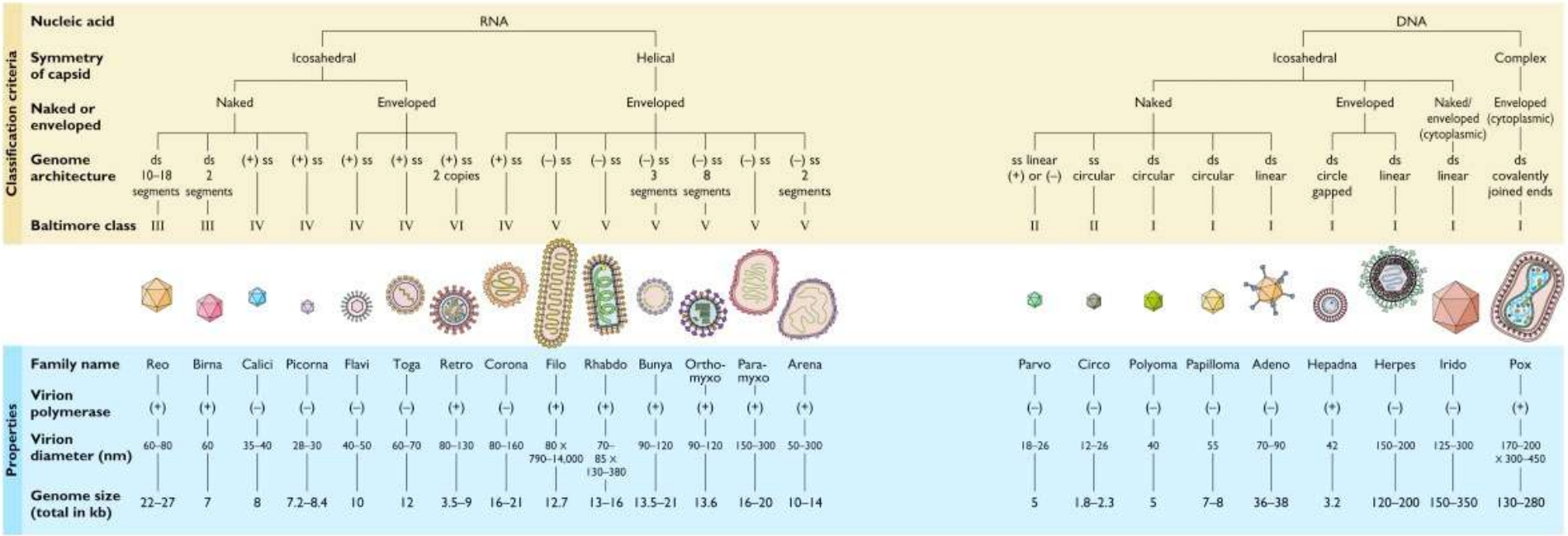
Virologia

BMM560

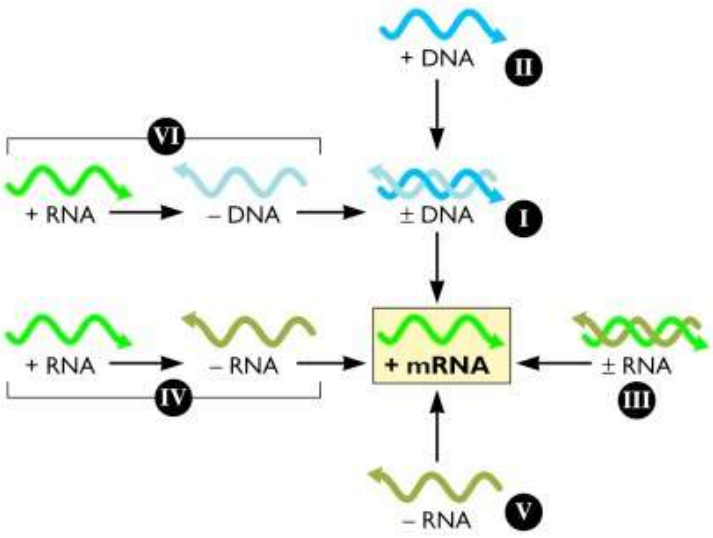
Paolo Zanotto
Departamento de Microbiologia
Laboratório de Evolução viral e Bioinformática
pzanotto@usp.br

Mini Revisão





Adapted from M. H. V. van Regenmortel et al. (ed.), *Virus Taxonomy: Classification and Nomenclature of Viruses. Seventh Report of the International Committee on Taxonomy of Viruses* (Academic Press, Inc., San Diego, Calif., 2000).




Virosphere 2002
dsDNA
ssDNA
dsDNA-RT
ssRNA-RT
dsRNA
ssRNA-
ssRNA+
Invertebrates
Vertebrates
Bacteria
Plants
Fungi
Donald Danforth Plant Science Center
copyright©2002 C.M.Fauquet
International Committee on Taxonomy of Viruses

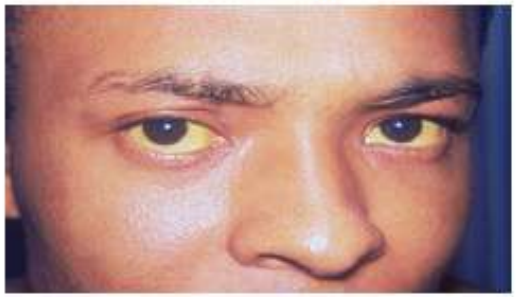
Parte 1

Hepatites Virais

Hepatite: definição

Manifestações clínicas

- Icterícia



- Falta de apetite
- Fezes claras
- Urina escura
- Prostração

Importância em Saúde pública: por quê?

Doença debilitante

Assintomática à óbito

Cronicidade

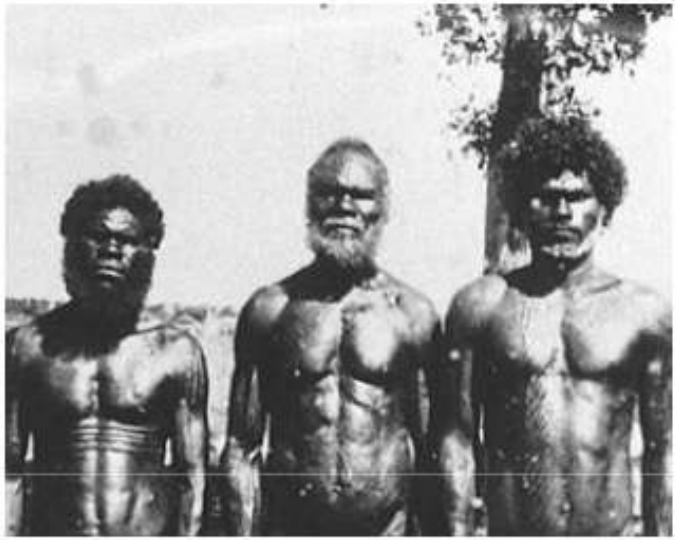
1947 - MacCallum

Hepatite A infecciosa

Hepatite B serica

1963 - Blumberg

Antígeno Austrália (Ag Au) - aborígenes



1968 - Prince, Okochi e Murakami

Antígeno de superfície do VHB (Ag HBs) corresponde ao Ag Au de Blumberg

Virus causadores de hepatite: tipos

A	Hepatite Infecciosa ou fecal-oral
B	Hepatite Sérica ou parenteral
C	Hepatite Não A-Não B
D	Hepatite Delta (Febre Negra de Lábrea)
E	Hepatite Não A- Não B
F	Hepatite F
G	Hepatite G (tipos GA e GB) Torque Teno Vírus (TTV) (comensal?)

Vírus Hepatite A (VHA)

Família *Picornaviridae*

Gênero *Hepatovirus*

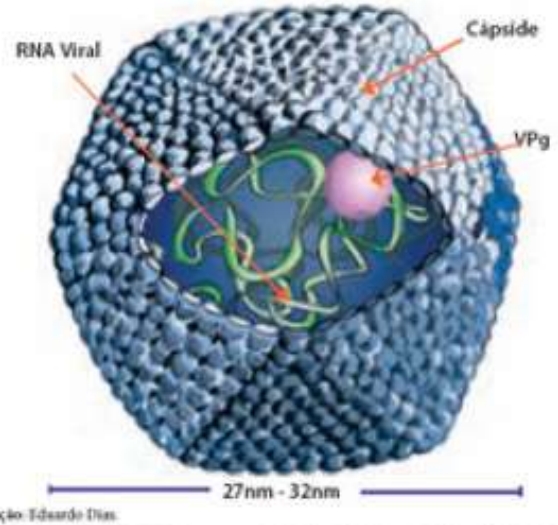
Tamanho 22 nm

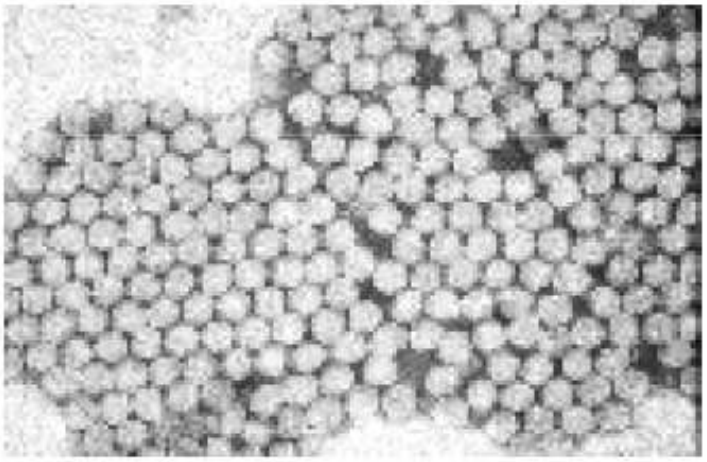
Capsídeo icosaédrico (Ag HA)

Sem envoltório

Genoma RNA fita simples

polaridade mensageira

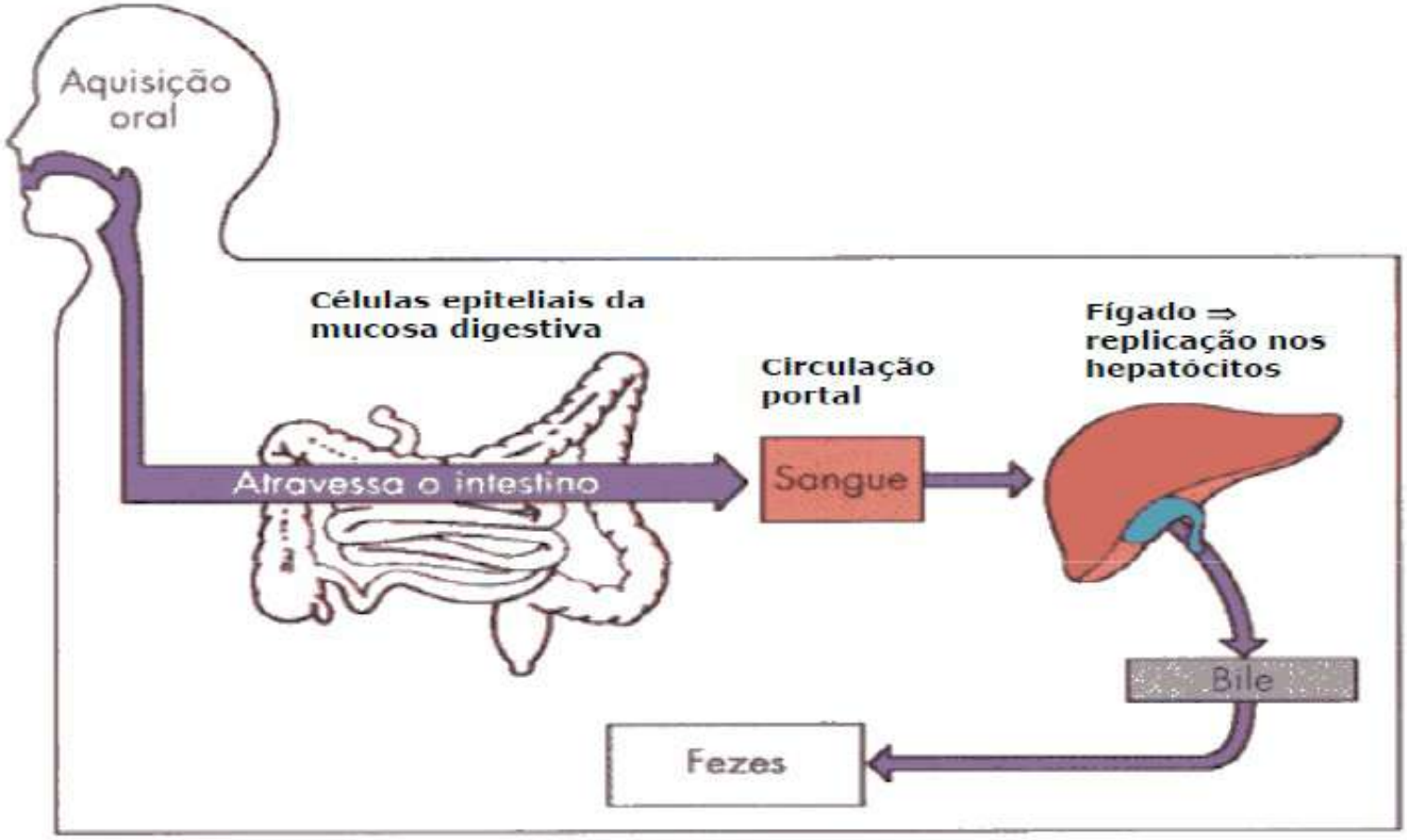




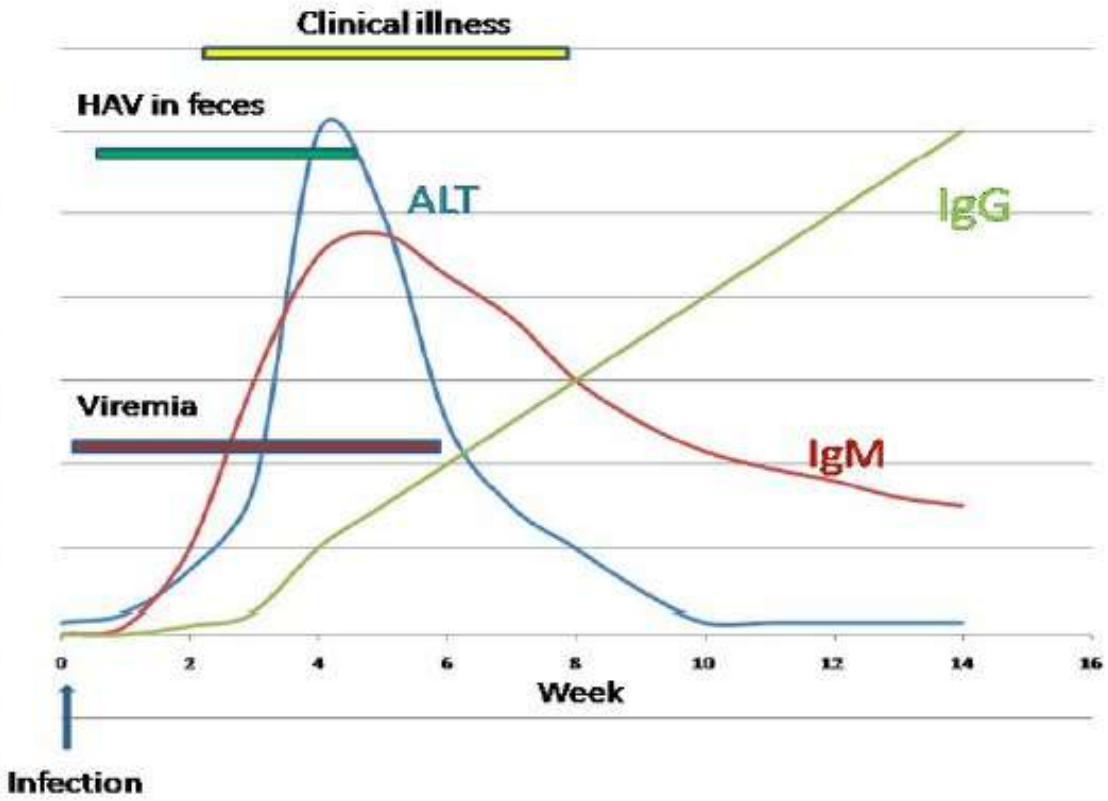
Vias de transmissão - VHA

Fecal-oral	Ingestão de água e alimentos contaminados com material fecal
Contato direto pessoa-pessoa	Saliva Hábitos inadequados de higiene
Veiculação por objetos pessoais e utensílios (fômites)	

Patogenese HAV



Infecção aguda – marcadores da infecção



Profilaxia :

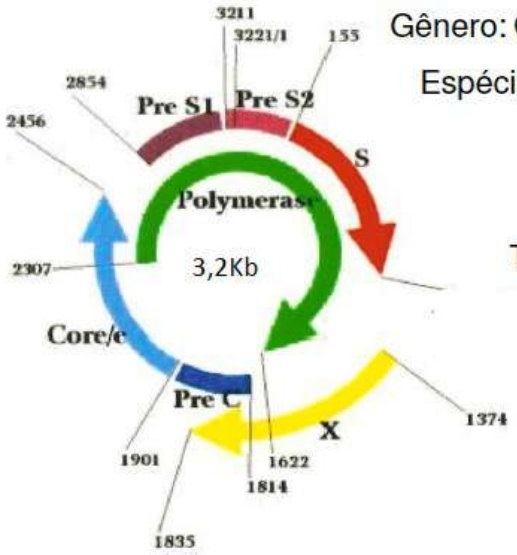
Higiene e Vacinas

Hepatite A: HAVRIX

2 doses

(intervalo de 6 meses a 1 ano)

Vírus da Hepatite B (VHB)



Família *Hepadnaviridae*

Gênero: Orthohepadnavirus

Espécie: Hepatitis B Virus

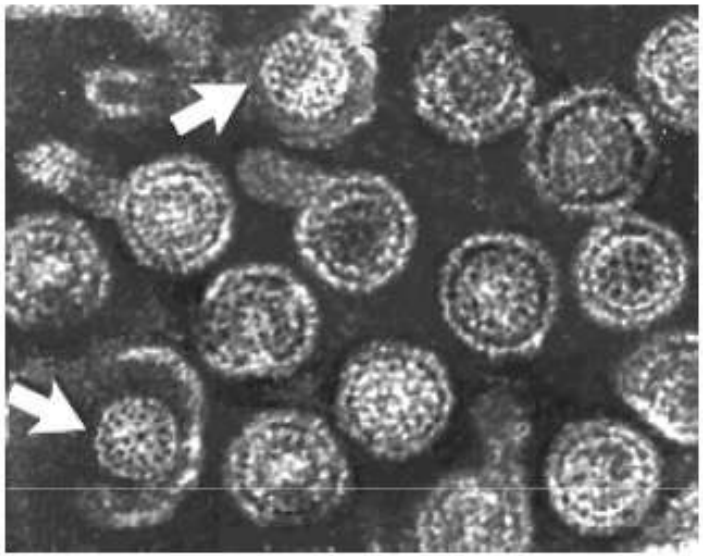
Tipos (A-G)

4 subtipos

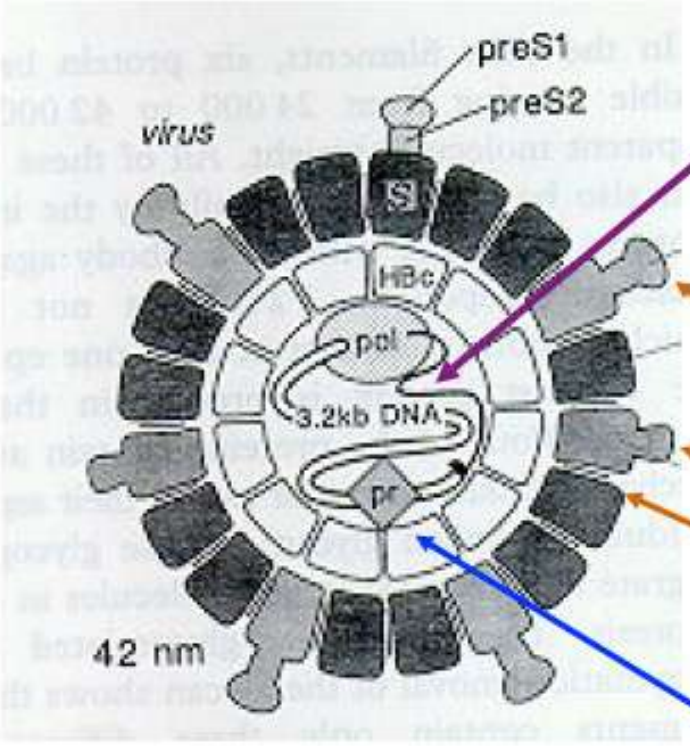
Tamanho 48-52 nm

Capsídeo esférico

Envoltório protéico



Estrutura da partícula viral infecciosa (Dane) e seus marcadores*



DNA viral (genoma)

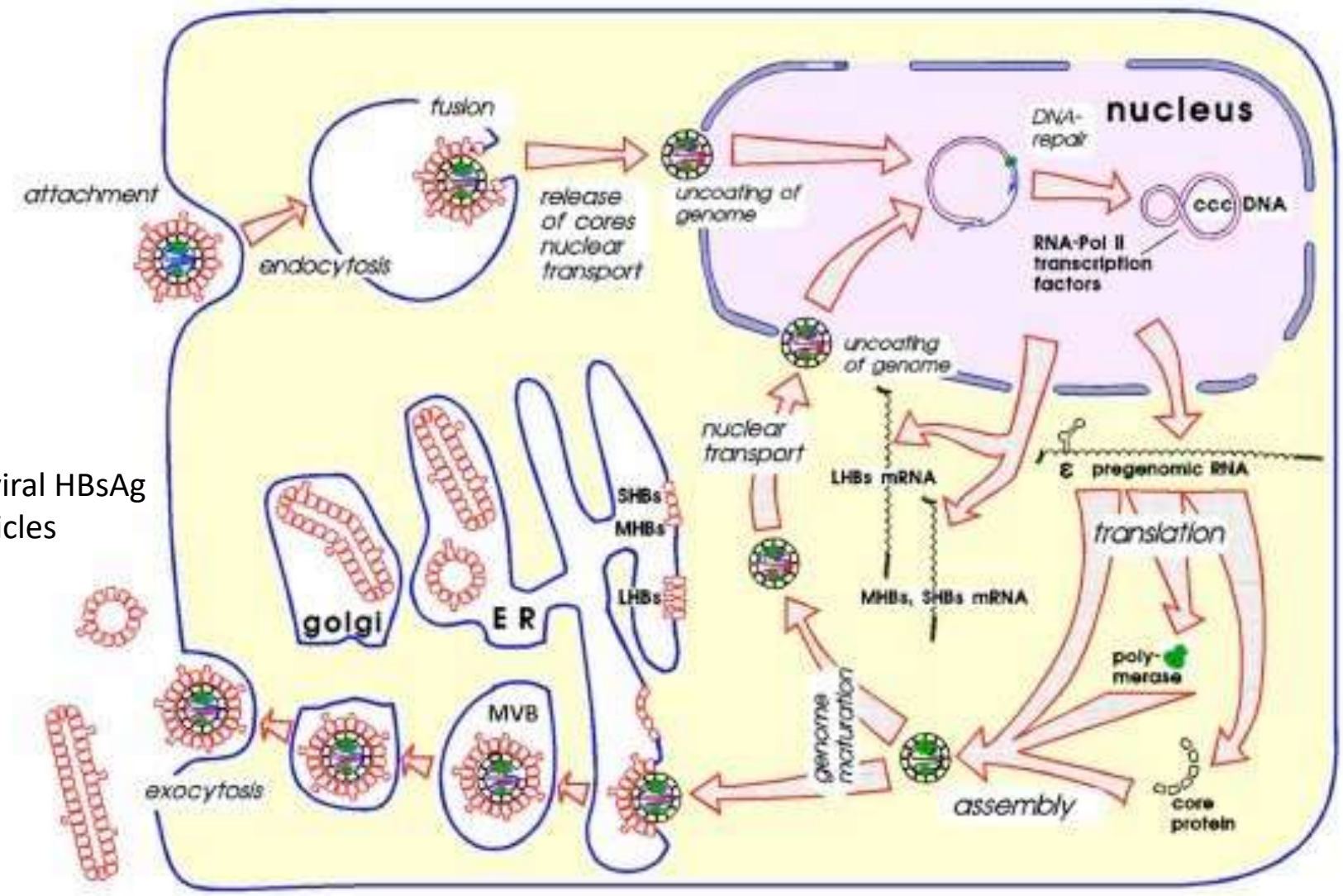
Antígeno HBs (superfície – envoltório viral)
LHBs (Large)
MHBs (Medium)
SHBs (Small)

Antígeno HBc (core - capsídeo)

* Incluem também os anticorpos específicos

Ac anti-HBs, Ac anti-HBc, Ac anti-Hbe)

Life cycle of HBV

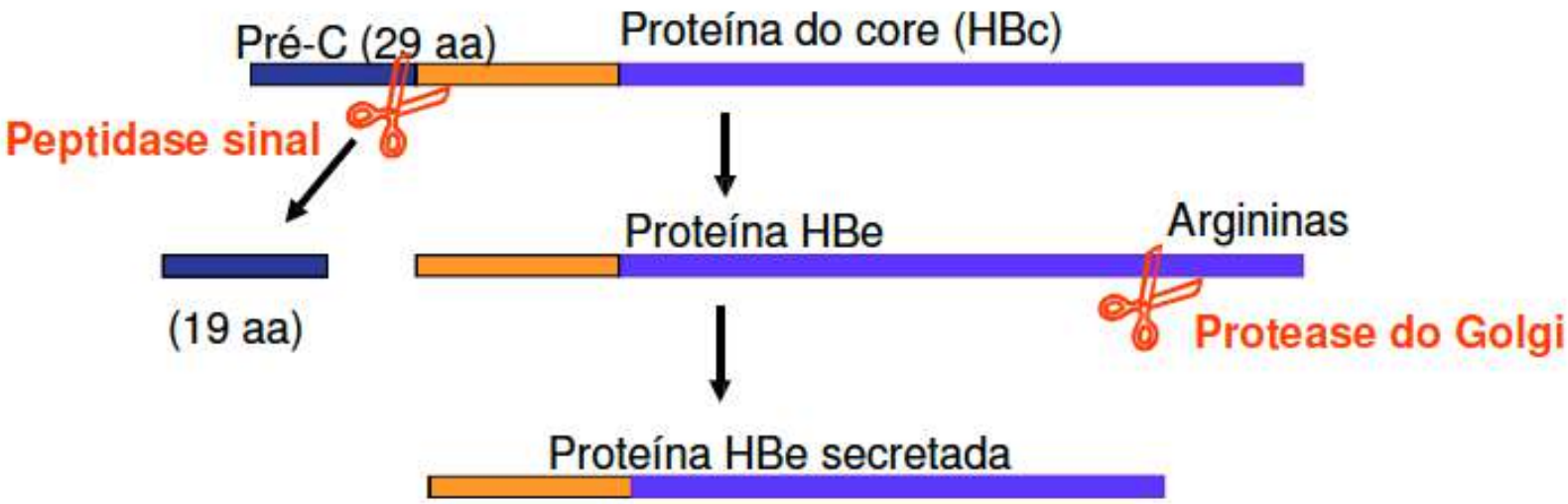


subviral HBsAg particles

covalently closed circular (ccc) DNA

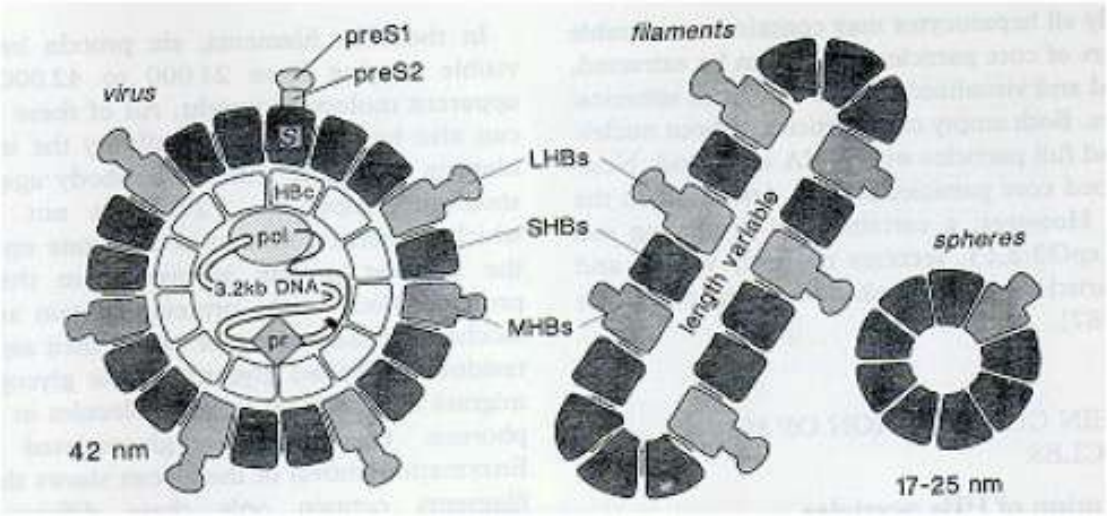
Estrutura da partícula viral infecciosa (Dane) e seus marcadores

Proteína não estrutural – Antígeno *e* (AgHBe)

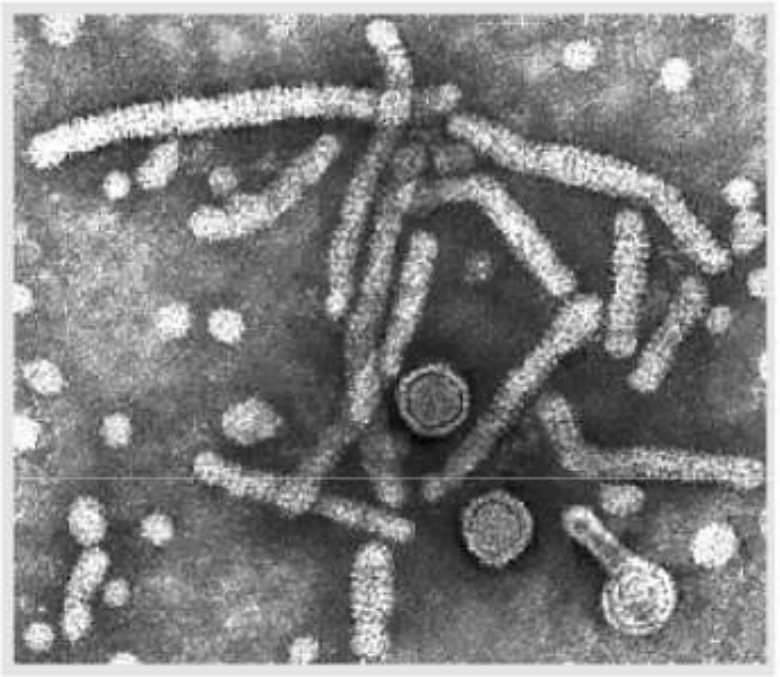


Indica multiplicação viral em andamento no fígado

Tipos de partículas virais

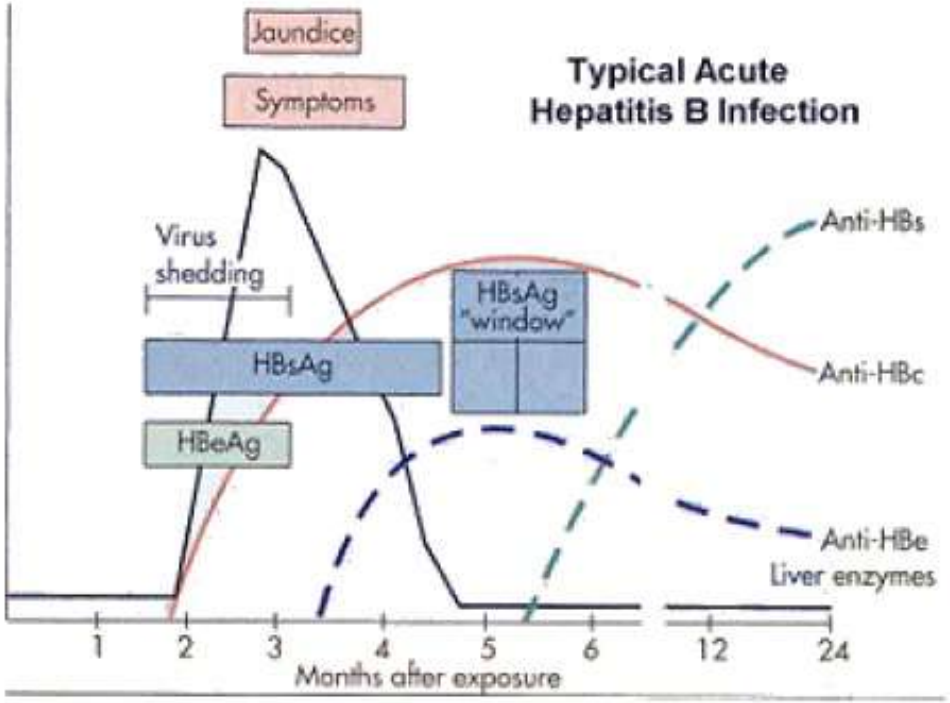


Dane

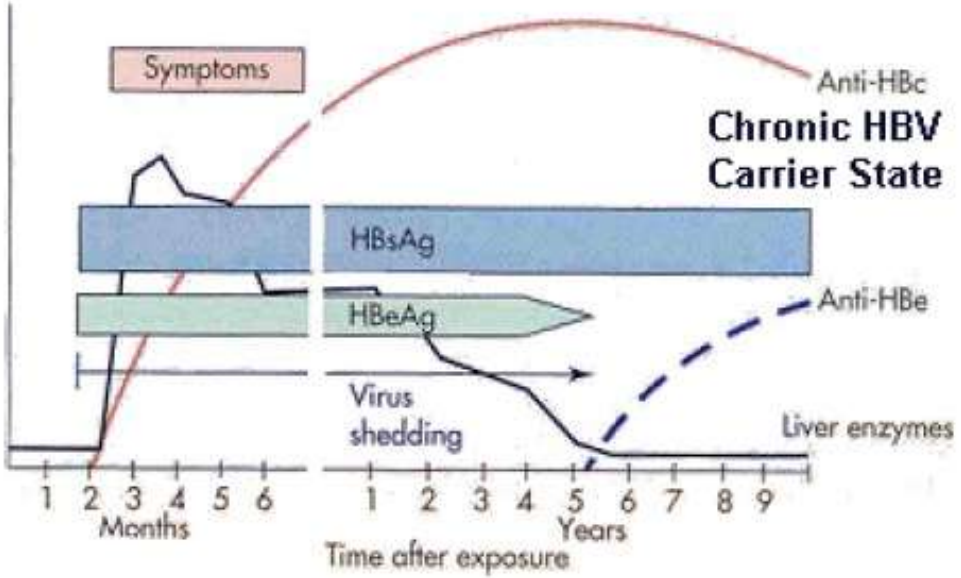


Filamentosas e globulares

Evolução do quadro clínico baseado na análise dos marcadores virais

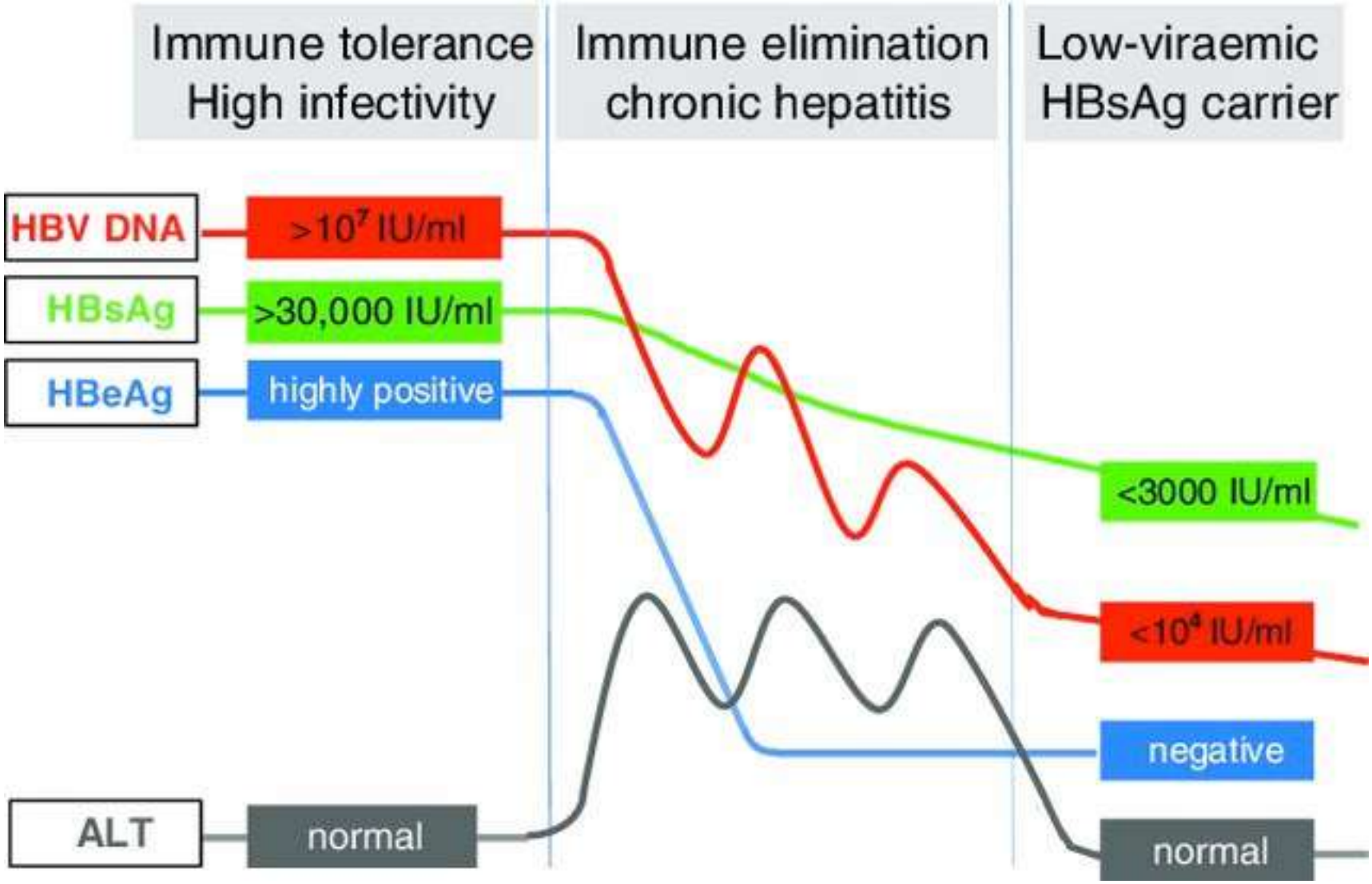


Infecção aguda



Infecção crônica

The three phases of chronic HBV infections.



Vias de transmissão

Sangüínea:

- Uso de drogas injetáveis
- Transplantes e fatores coagulantes (VIII e IX)
- Hemodiálise
- Transfusão sangüínea (controle adequado)
- Profissionais da área de saúde - 1 a 2%
- Tatuagens e *piercings* - risco indeterminado

Sexual ➡ risco médio

dependente de outros fatores

Perinatal ➡ parto (cesárea/normal)

(mães sabidamente positivas - risco 5 a 6%)

➡ aleitamento

(não documentado)

Contato

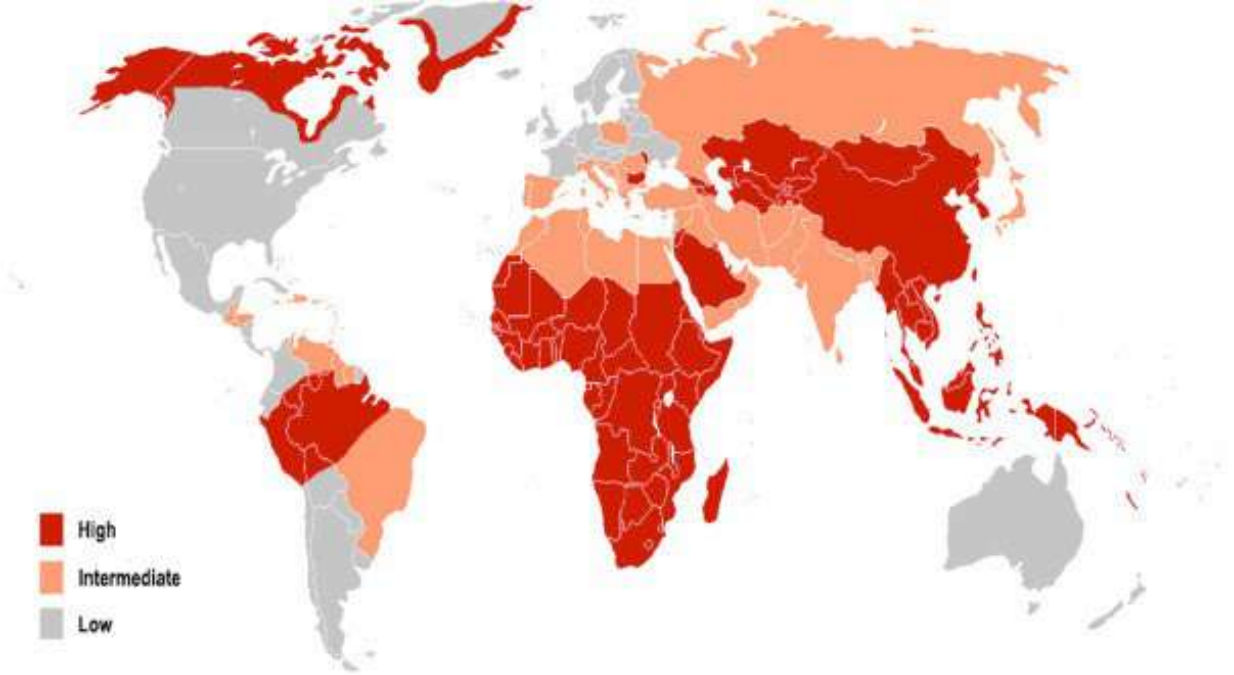
Pessoa-pessoa

Objetos pessoais e utensílios

Saliva

Prevalência (superior) e distribuição genotípica (inferior) das infecções pelo HBV.

O HBV subgenótipo A2, presente nas vacinas mais populares contra a hepatite B, só é predominante nas regiões de baixa endemia das Américas e da Europa. Isto significa que >99% de todos os portadores do VHB possuem outros subgenótipos do VHB.



Vírus da Hepatite B

Inativação por agentes físicos e químicos

Agentes físicos:

Calor: Autoclavação a 121 °C por 20 min
Calor seco (estufa) 160 °C por 1 h.
Radiação: UV

Agentes químicos:

Hipoclorito de sódio (500 mg cloro livre por L) 10 min,
2% Glutaraldeído em T.A. por 5 min,
5% de formalina em água,
Álcool isopropílico a 70%
β-propriolactone

http://www.who.int/csr/disease/hepatitis/whocdscsrlyo20022/en/index2.html#stability

Tratamento

Hepatite viral crônica B:

Interferon:

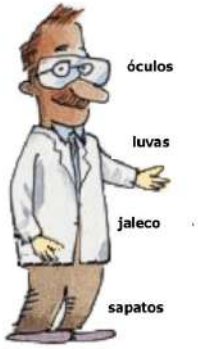
- interferon-alfa,
- peg-interferon-alfa (interferon peguilado)

Drogas antivirais:

- lamivudina,
- adefovir,
- entecavir,
- telbivudina
- tenofovir.

Equipameto de Proteção Individual (EPI)

Proteção da saúde e integridade física do trabalhador



Profilaxia Hepatite B

Administração de gamaglobulina

Vacinação

Uso de preservativos

Cuidados no consultório

Atenção às Normas de Biossegurança

Uso de EPI

Agente da Hepatite D - vírus satélite

- Genoma: RNA fita simples circular - 1,7 kb

  ribozyme - autoclivagem e re-ligação
- Envoltório protéico: AgHBs (VHB)
- Antígeno específico: AgHD (nucleoproteína)

  2 formas: P24 (fase aguda) e P27 (fase crônica)

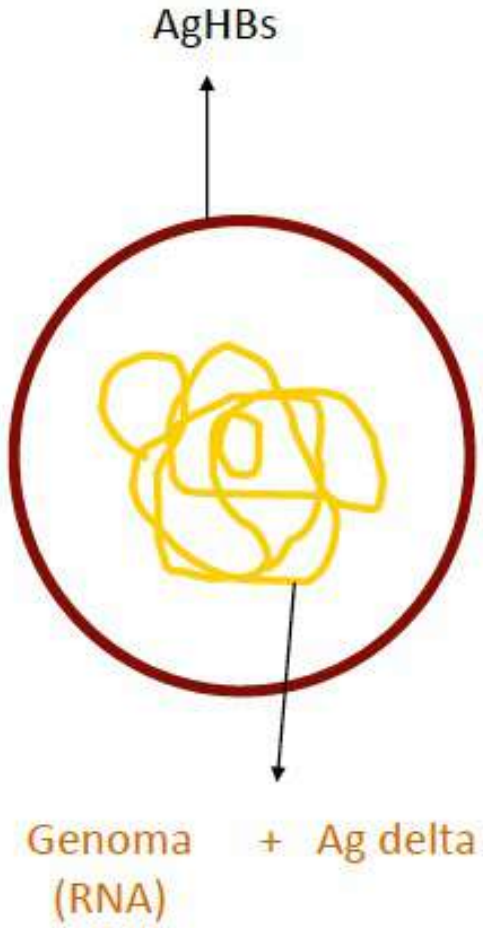
Infecção:

- Co-infecção: HBV/VHD
- Super-infecção:

  HBV pré-existente nos hepatócitos

Hepatite fulminante

Efeito citotóxico da proteína P24 no núcleo do hepatócito.

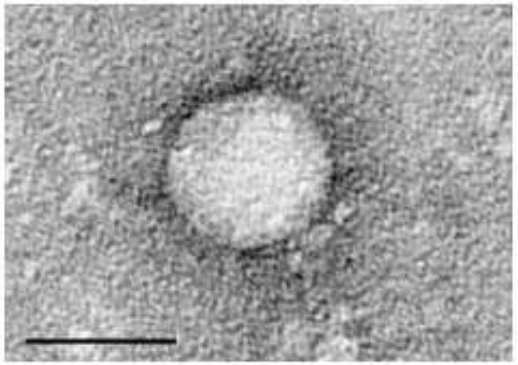


Vírus da Hepatite C (HCV)

Família *Flaviviridae*

Gênero Hepacivirus

Espécie: Hepatite C vírus

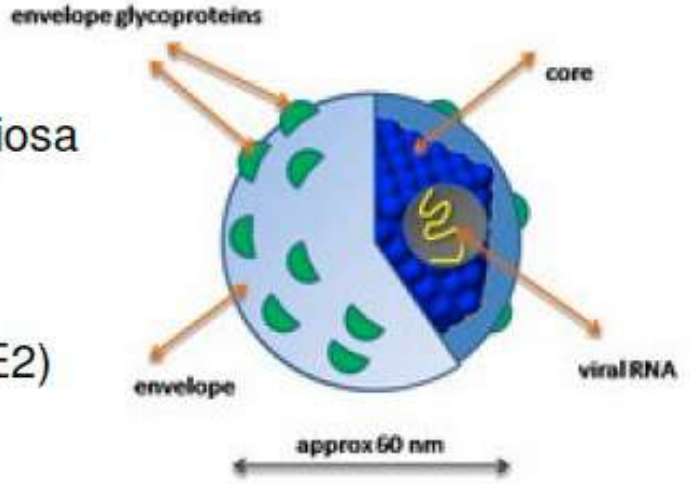


Genótipos 1 a 11
Alta variabilidade genética

Vírus RNA fita simples positiva infecciosa

Tamanho de 55 a 65 nm

Com envoltório (glicoproteínas E1 e E2)



Structure of Hepatitis C Virus

Vírus da Hepatite C (HCV)

Inativação por agentes físicos e químicos

- exposição a solventes lipídicos

- Temperatura 60 °C por 10 h ou
  100 °C por 2 min em solução aquosa

- formaldeído (1:2000) a 37 °C por 72 h

- ß-propriolactona

- radiação UV

http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index2.html#morphology

Vírus da Hepatite C (HCV)

Alta cronicidade

Maioria das infecções subclínicas

Diagnóstico laboratorial (RT-PCR)

Não ocorre transmissão por vetores como na febre amarela

Não há vacina

Vírus da Hepatite C (HCV)

Tratamento clássico:

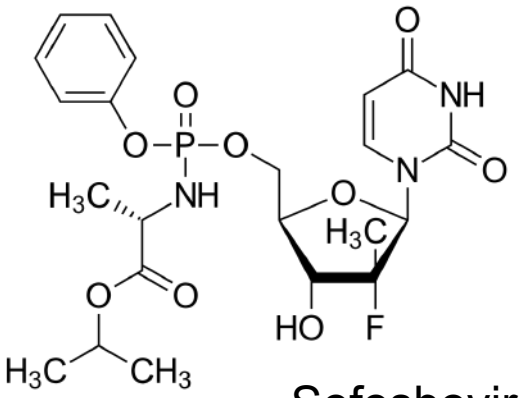
Interferon-α tratado com PEG ("pegylated interferon-α)
+
Ribavirina

Tipos 1 e 4 (mais resistentes) - duração de 48 semanas

Tipos 2 e 3 e demais – duração de 24 semanas

Profilaxia

Idem para Hepatite B



Sofosbovir

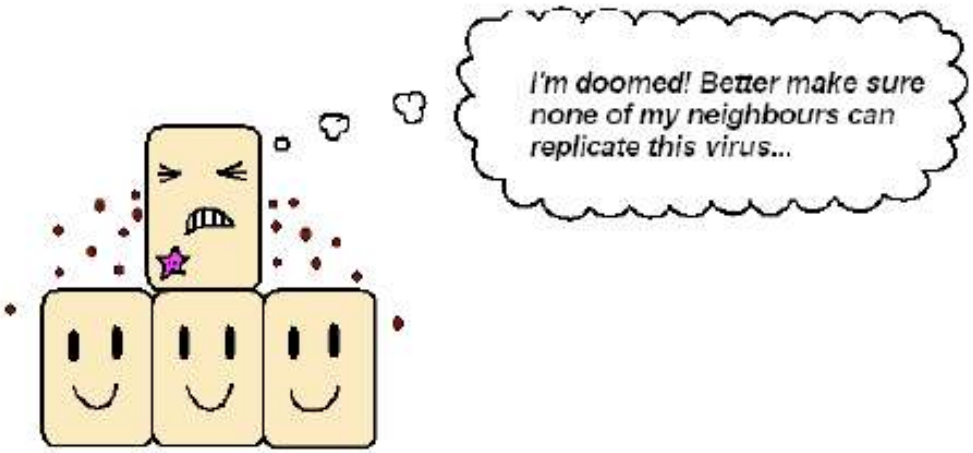
Interferons

são glicoproteínas produzidas por células infectadas por vírus.

três tipos:

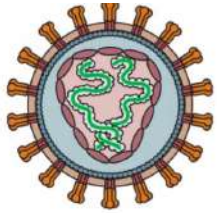
- alfa, produzido por linfócitos B e monócitos,
- beta, por fibroblastos
- gama, por linfócitos T-helper e NK.

O **interferon-alfa-2b** (IFN-alfa) age diretamente contra o vírus e também aumenta a resposta imune (tem atividade antiviral, antiproliferativa e imunomoduladora).

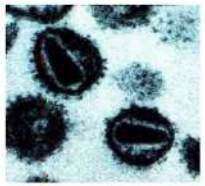


Parte 2

HIV como modelo de patogênese viral

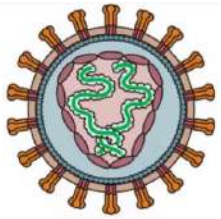


HIV is a lentivirus



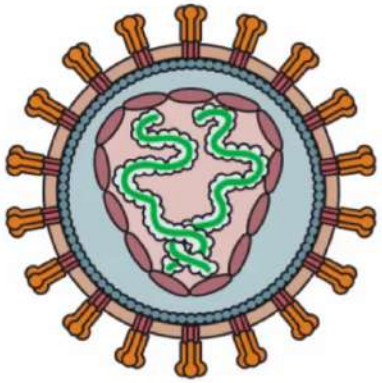
- First isolated in 1983 from the lymph node of a patient with lymphadenopathy in Paris; 2008 Nobel to Montagnier & Barré-Sinoussi
- 1984 blood test developed
- Electron microscopy and sequence analysis revealed HIV to be a lentivirus, known group of retroviruses

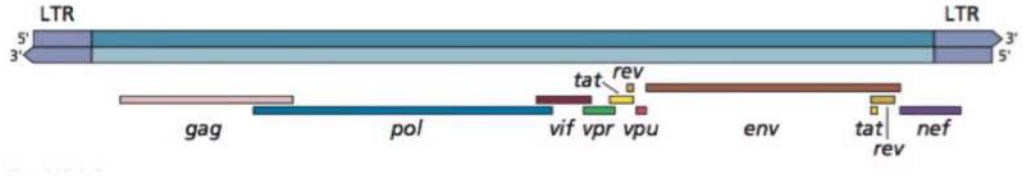
Retroviridae



- *Orthoretrovirinae (subfamily)*
  - *Alpharetrovirus (Avian leukosis virus)*
  - *Betaretrovirus*
  - *Gammaretrovirus*
  - *Deltaretrovirus (Human T cell lymphotropic virus 1, 2 ,3)*
  - *Epsilonretrovirus (Walleye dermal sarcoma virus)*
  - *Spumavirus*
  - *Lentivirus (Human immunodeficiency virus 1, 2)*

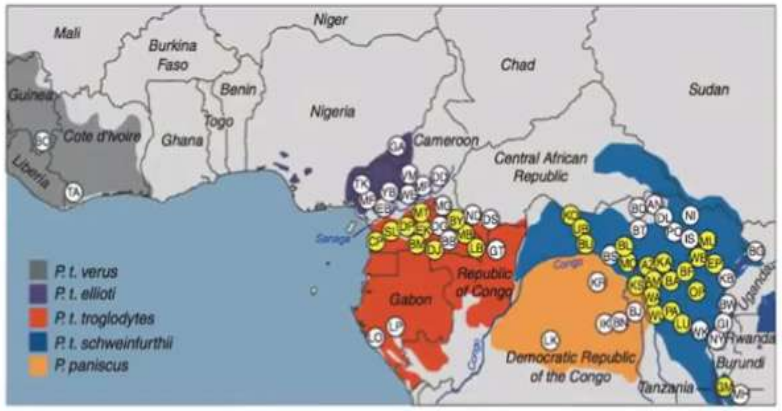
Mapa físico do HIV-1. Genoma de um retrovírus complexo.





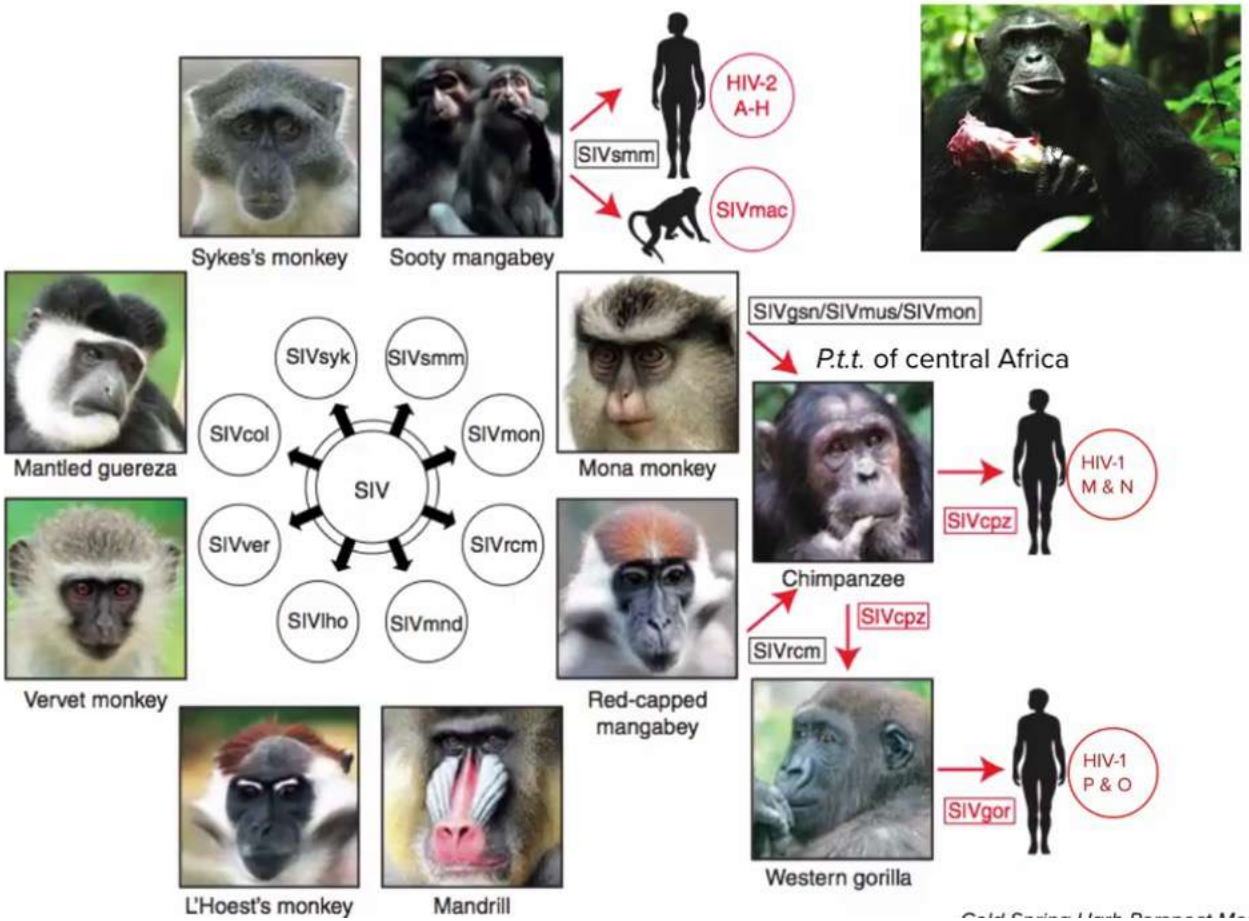
What was the source of HIV-1?

- SIV first isolated from chimpanzee in 1989 (SIVcpz)
- Analysis of >7,000 chimpanzee fecal samples from 90 field sites confirmed natural SIVcpz reservoir
- Only *Pan troglodytes troglodytes* and *P. T. schweinfurthii* harbor SIVcpz



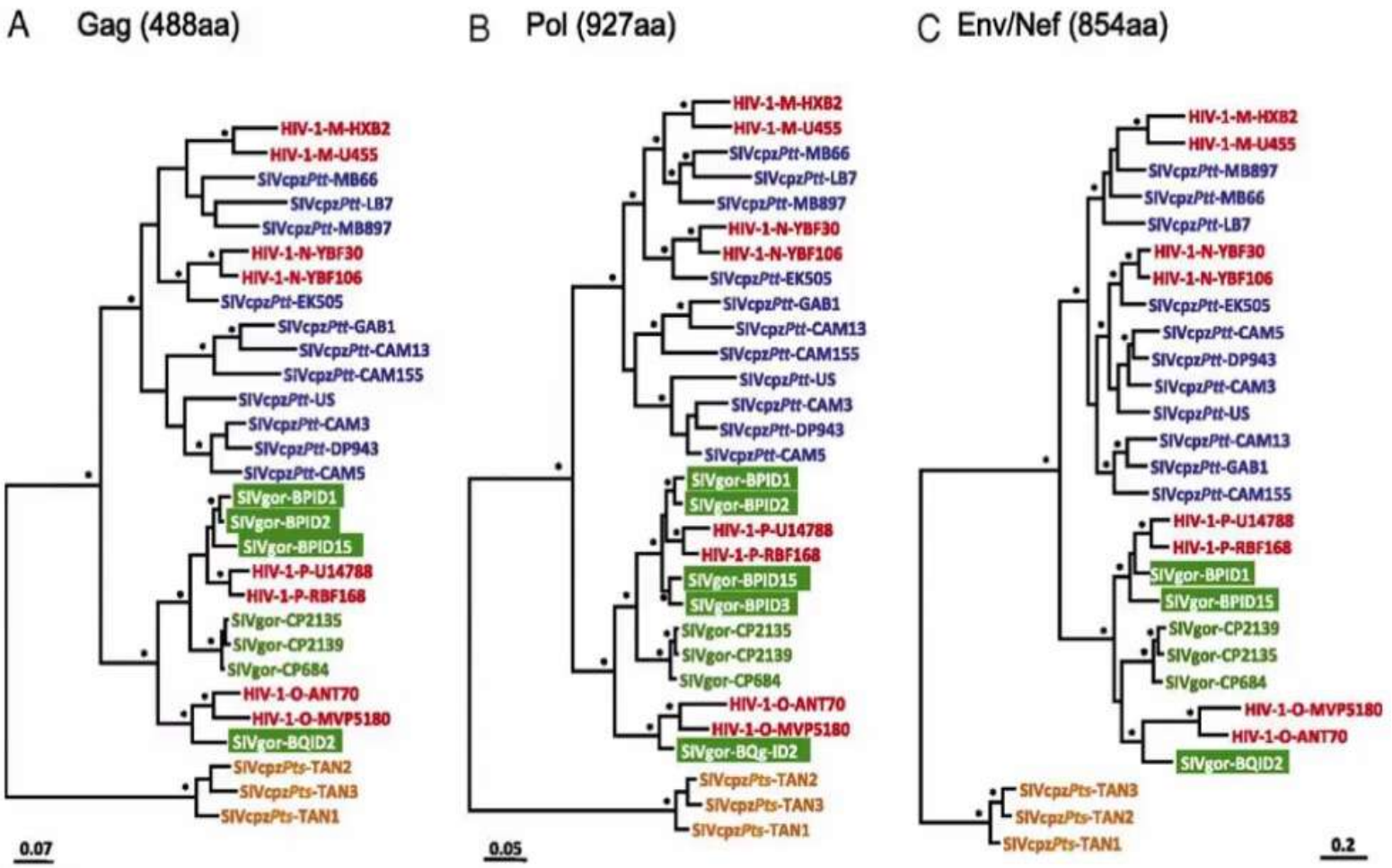
Urina e fezes foram usadas para isolar SIVcpz pela Dra. Beatrice Han. Pontos amarelos são positivos por SIV. O mais próximo do HIV foi o do Congo (área vermelha no Oeste da África).

HIV: de zoonoze para pandemia



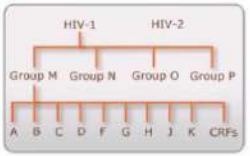
Macacos do velho mundo infectados há muito tempo por SIVs. SIVcpz (HIV-1) é um recombinante entre Mona monkey SIV e o Red-capped mangabey SIV. P&O são infrequentes em humanos e vem do SIVcpz de gorila. M&N, P&O são 4 introduções independentes em humanos.

Quatro ramos (taxa em vermelho) indicam as entradas independentes do SIV em humanos



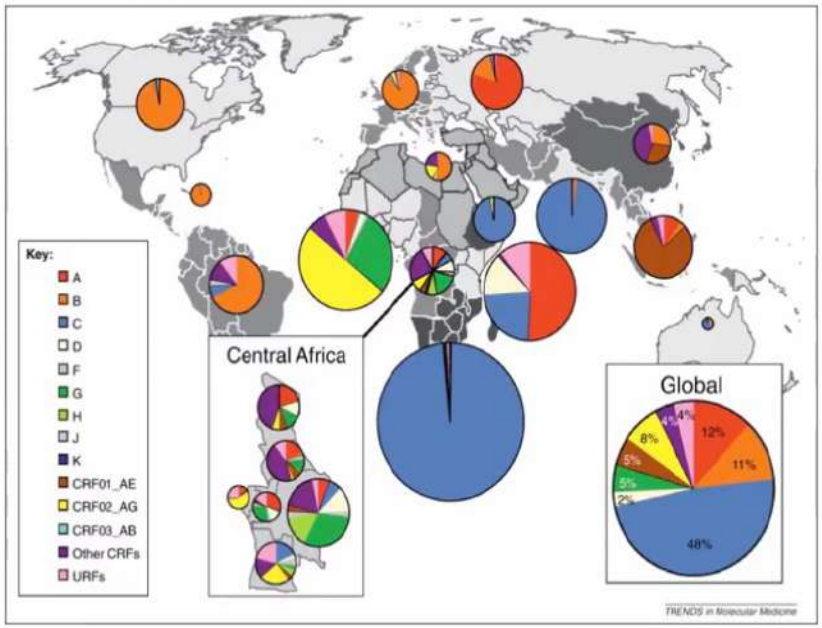
PNAS 112(2015) doi: 10.1073/pnas.1502022112

HIV-1 diversity



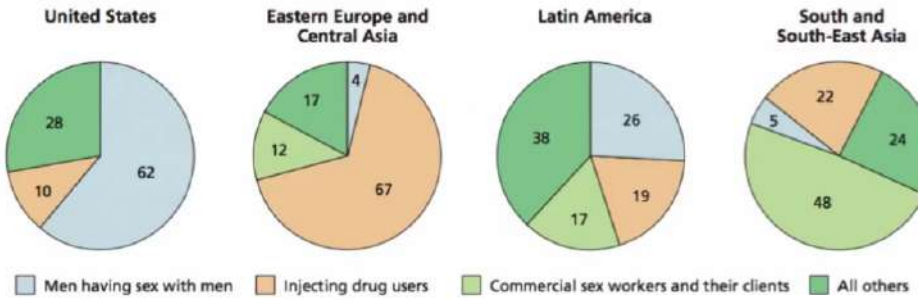
- Four groups based on sequence alignment
- Group M (main): 99% of all HIV-1 infections
- Group O (outlier): <1% of infections, limited to Cameroon, Gabon, neighboring countries
- Group N: Only 13 cases, Cameroon
- Group P: Only 2 cases, Cameroon
- *Each from an independent transmission event of SIV to humans*

- Subtype C (50%), B and A (10-12%), G (6%), CRF02_AG (5%), CRF01_AE (5%), D (2.5%) of all HIV-1 infections
- Subtypes F, H, J, K limited transmission (<1%)



Transmission

- HIV is not a particularly infectious virus, not contagious like measles virus (R_0 2-5)
- Not spread by respiratory, alimentary, or vector routes



Risk of transmission of HIV-1

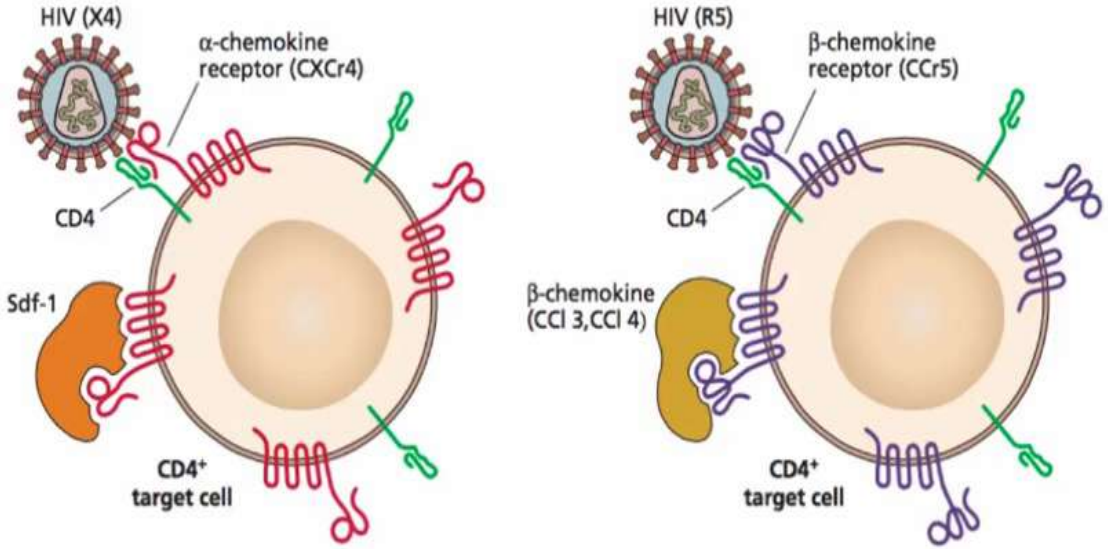
Mode	Risk
Sexual transmission	
Female-to-male	1 in 700 to 1 in 3,000
Male-to-female	1 in 200 to 1 in 2,000
Male-to-male	1 in 10 to 1 in 1,600
Parenteral	
Transfusion of infected blood	95 in 100
Needle sharing	1 in 150
Needle stick	1 in 200
Needle stick /AZT PEP	1 in 10,000
Mother to infant	
Without AZT	1 in 4
With AZT	<1 in 10

Isolation of infectious HIV-1 from body fluids

Fluid	Virus isolation[b]	Estimated quantity of virus[c]
Cell-free fluid		
Cerebrospinal fluid	21/40	10–10,000
Ear secretions	1/8	5–10
Feces	0/2	None detected
Milk	1/5	<1
Plasma	33/33	1–5,000[d]
Saliva	3/55	<1
Semen	5/15	10–50
Sweat	0/2	None detected
Tears	2/5	<1
Urine	1/5	<1
Vaginal-cervical	5/16	<1
Infected cells		
Bronchial fluid	3/24	Not determined
PBMC	89/92	0.001–1%[d]
Saliva	4/11	<0.01%
Semen	11/28	0.01–5%
Vaginal-cervical fluid	7/16	Not determined

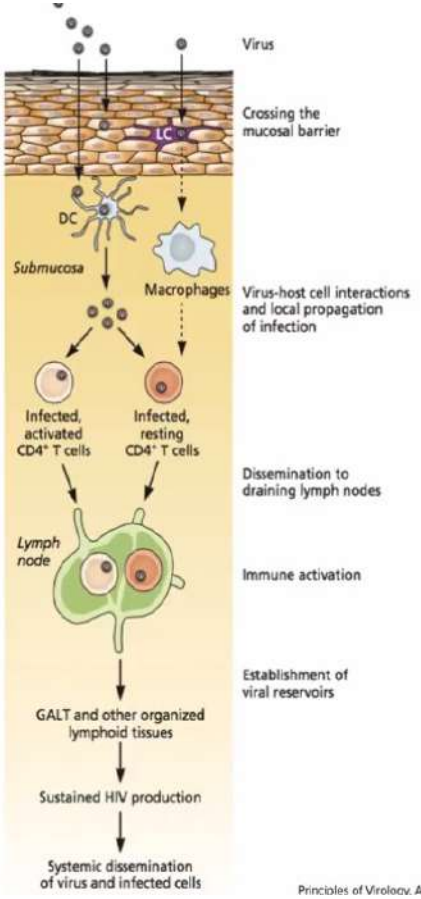
Primary HIV Infection: Clinical characteristics

- 50-90% of infections are symptomatic
- Symptoms generally occur 5-30 days after exposure
- Symptoms and signs
  - Fever, fatigue, malaise, arthralgias, headache, nausea, vomiting, diarrhea
  - Lymphadenopathy, pharyngitis, rash, weight loss, mucocutaneous ulcerations, aseptic meningitis
  - Leukopenia, thrombocytopenia, elevated liver enzymes
- Median duration of symptoms: 14 days



Primary HIV Infection

- Virus-dendritic cell interaction (no activation)
  - Infection typically with CCR5 binding strains
  - Importance of DC-SIGN (dendritic cell-specific, Icam-3 grabbing nonintegrin)
- Delivery of virus to lymph nodes
- Active replication in lymphoid tissue
- High levels of viremia and dissemination
- Down-regulation of virus replication by immune response
- Viral set point reached after ~6 months

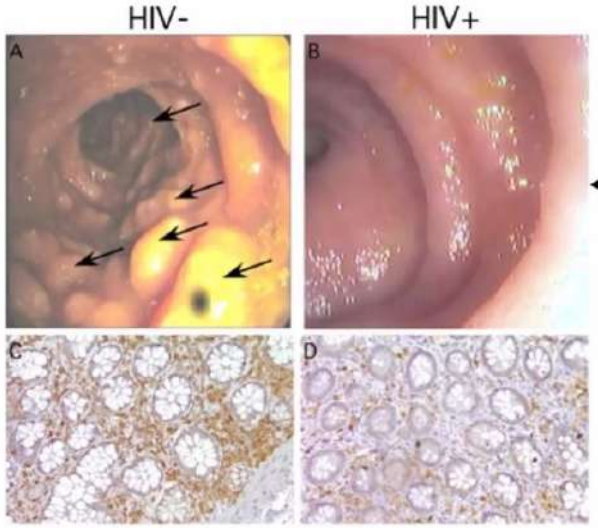


Vírus introduzido no sangue faz contato com DC-SIGN (integrina específica de células dendríticas). As integrinas são proteínas de adesão presentes na membrana celular inseridas de forma transmembrânica, com uma extremidade externa que se liga a componentes da matriz e outra extremidade que se liga, através da proteína talina à porção do citoesqueleto constituído de actina. GALT “gut-associated lymphatc tissue”

Primary HIV Infection: Clinical characteristics

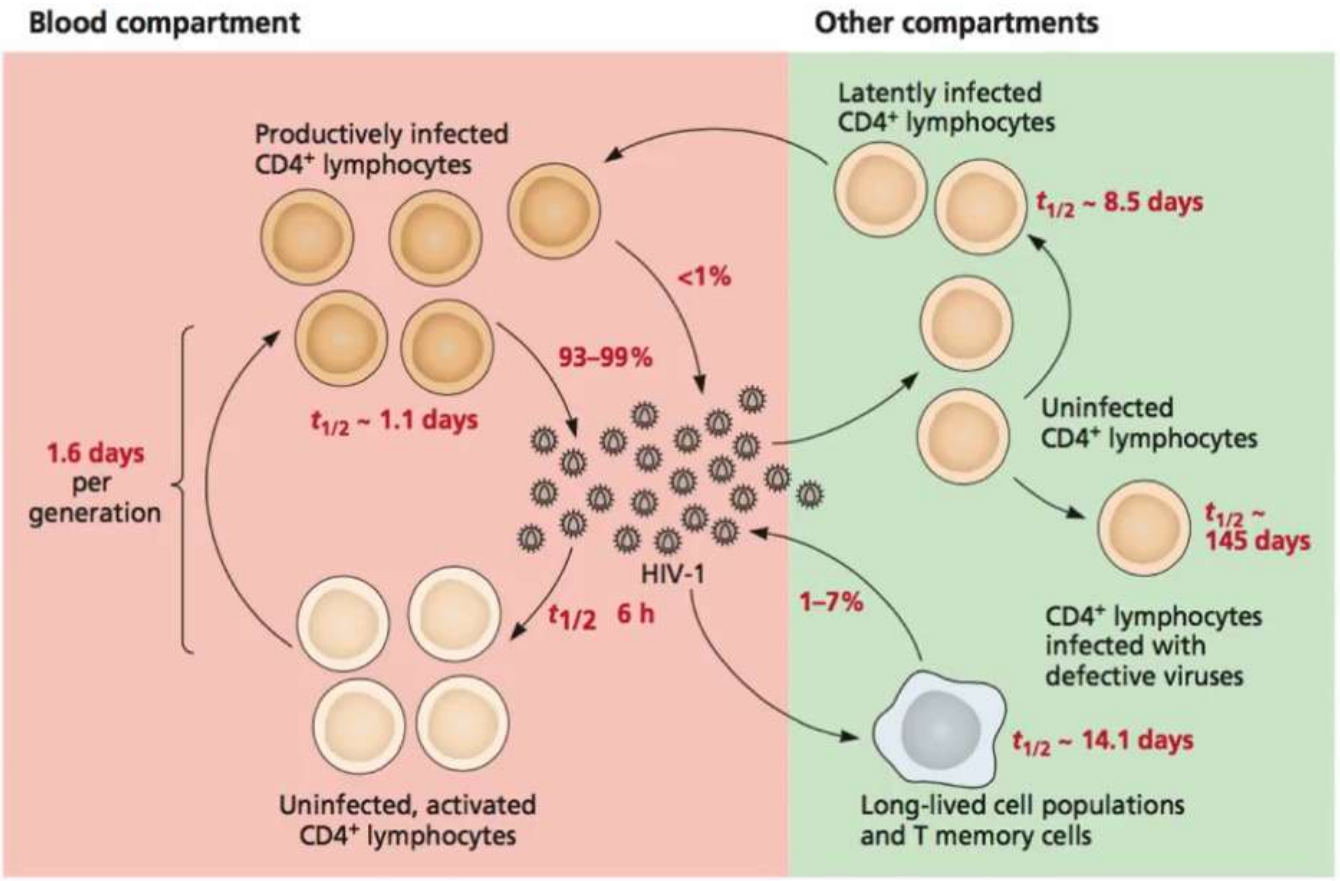
- 50-90% of infections are symptomatic
- Symptoms generally occur 5-30 days after exposure
- Symptoms and signs
  - Fever, fatigue, malaise, arthralgias, headache, nausea, vomiting, diarrhea
  - Lymphadenopathy, pharyngitis, rash, weight loss, mucocutaneous ulcerations, aseptic meningitis
  - Leukopenia, thrombocytopenia, elevated liver enzymes
- Median duration of symptoms: 14 days

GI associated lymphoid tissue following acute infection



Absence of lymphoid cell aggregates in terminal Ileum

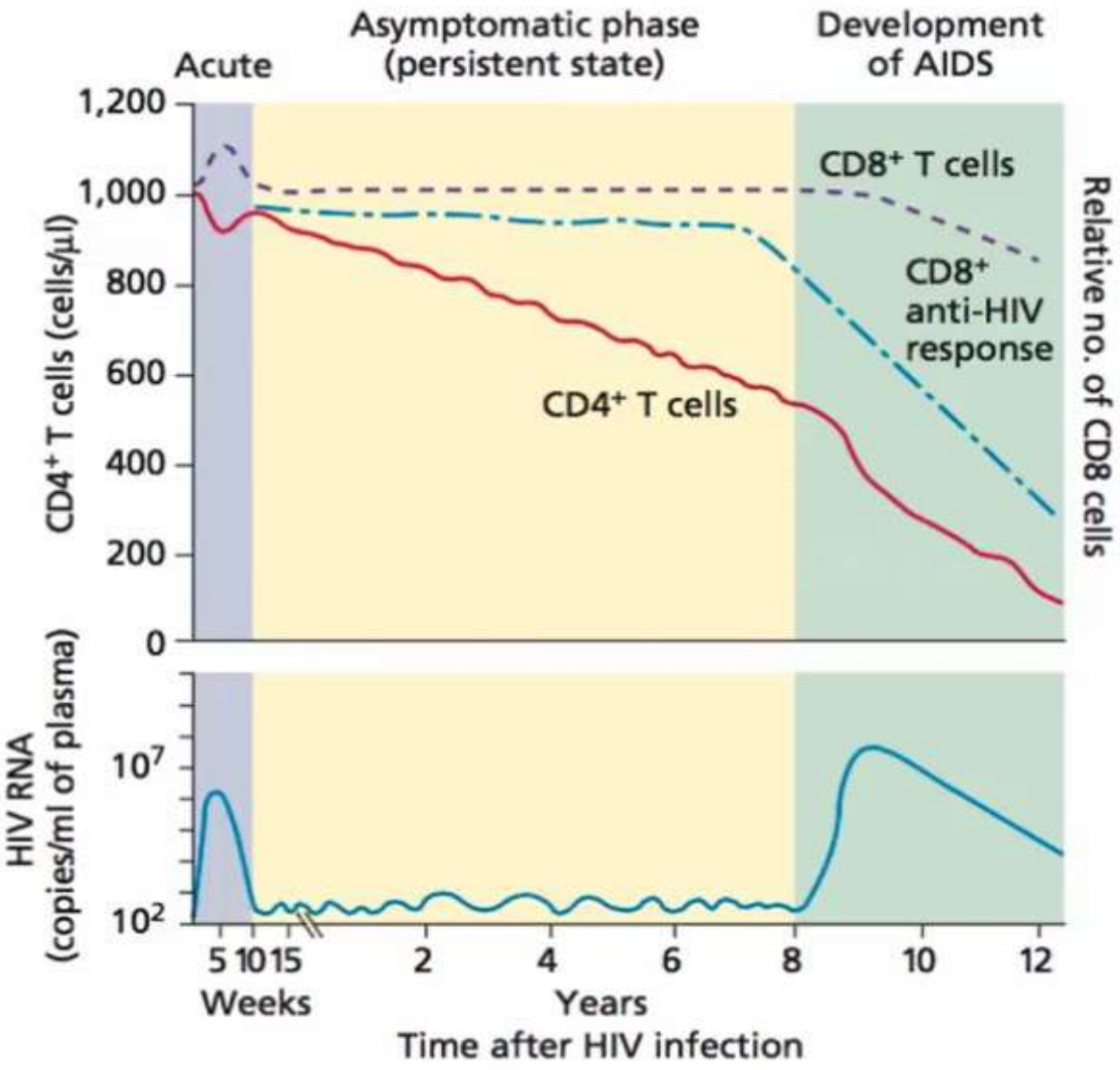
Santuários & Reservatórios



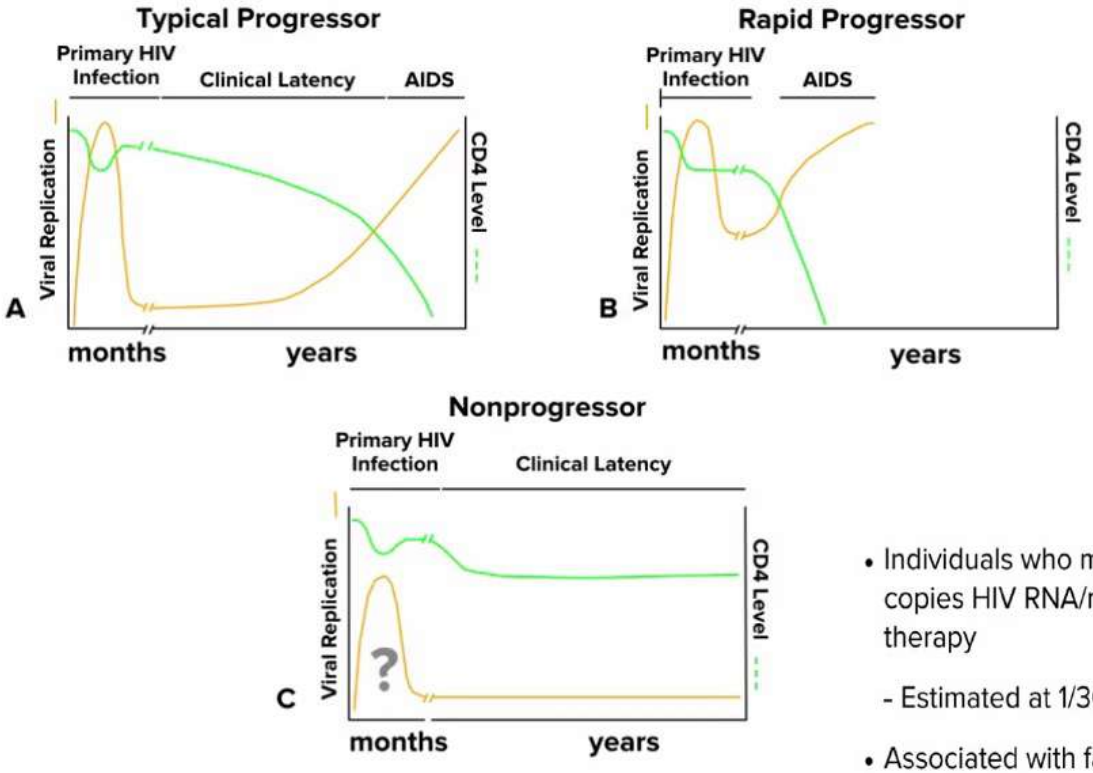
Multipotent hematopoietic progenitor cells - latent reservoir

HIV-1 replica em linfócitos CD4+ células ativados. Outros compartimentos são infectadas como: (*i*) o tecido linfóide associado ao intestino e (*ii*) células de memória que residem na medula e podem manter infecção latente por HIV-1 pela vida toda do portador.

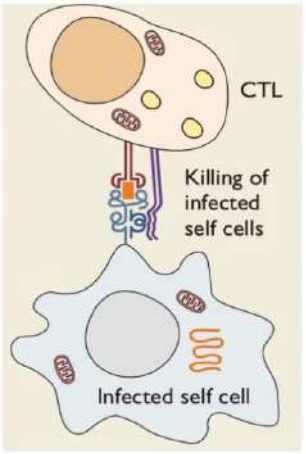
Progressão


Acute
Asymptomatic phase (persistent state)
Development of AIDS
1,200
1,000
800
600
400
200
0
CD4+ T cells (cells/μl)
CD8+ T cells
CD8+ anti-HIV response
CD4+ T cells
Relative no. of CD8 cells
HIV RNA (copies/ml of plasma)
10^7
10^2
5 10 15
Weeks
2
4
6
8
10
12
Years
Time after HIV infection

The variable course of HIV-1 infection



Virus susceptibility mapping to MHC



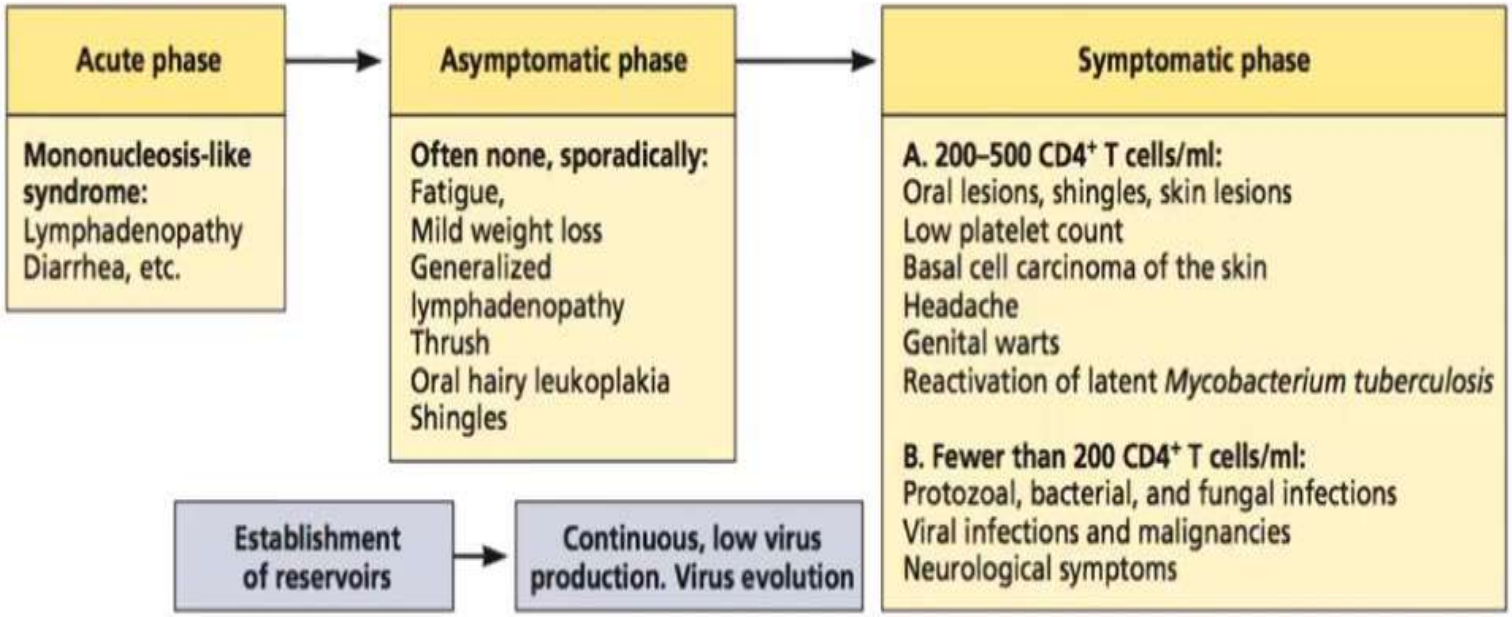
Elite HIV Controllers

- Individuals who maintain normal CD4 counts and undetectable viral loads (1-30 copies HIV RNA/ml of plasma) for >10 years in the absence of antiretroviral therapy
  - Estimated at 1/300 infected persons
- Associated with favorable HLA (MHC) types (esp HLA B57 and B27) and T-cell responses (CD4 and CD8) to Gag
- Not associated with attenuated viruses

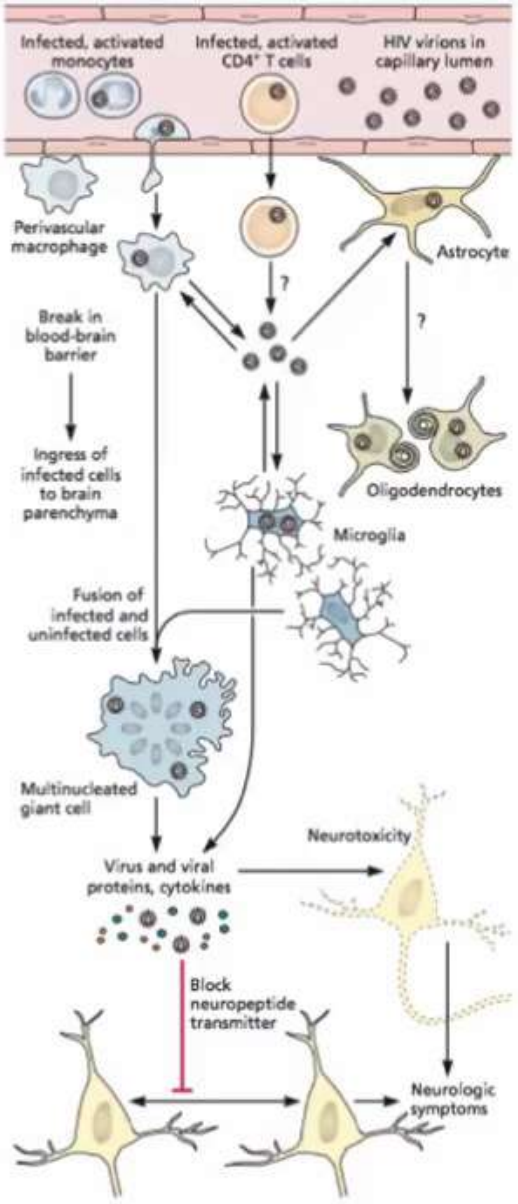
Sistema antígeno leucocitário humano HLA (sigla em inglês: Human leukocyte antigen), é um complexo genético que codifica o complexo principal de histocompatibilidade (MHC) humano. Situa-se no locus 21 do braço curto (p) do Cromossoma 6. Os genes HLA são altamente polimórficos (diversificados em forma e com muitos alelos diferentes) permitindo a grande especificidade do sistema imune adaptativo.

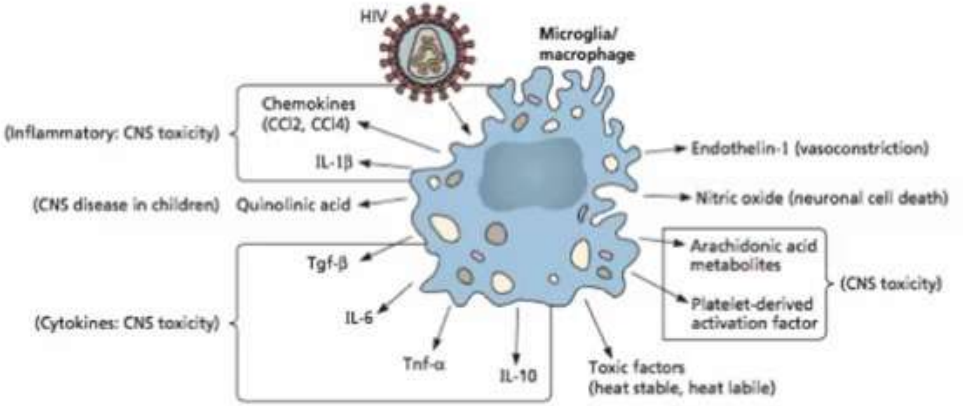
AIDS

- <200 CD4+ T cells/ml
- Protozoal: *Pneumocystis*, *Toxoplasma*, *Isospora*, *Cryptosporidium*, microsporidia
- Bacterial: *Mycobacterium*, *Treponema*
- Fungal: *Candida*, *Cryptococcus*, *Histoplasma*
- Viral: CMV, HSV
- Immune activation: HIV replicates better in activated T cells
- Malignancies: EBV lymphoma, Kaposi's sarcoma, anogenital carcinoma
- Neurological symptoms: aseptic meningitis, myelopathies, neuropathies, AIDS dementia complex



Neurological symptoms





Monócitos e linfócitos T ativados e infectados passam pela barreira hematocefálica. Liberam partículas virais que podem infectar astrócitos e talvez oligodendrócitos.

Monócitos fundem com célula da micróglia formando células gigantes multinucleadas.

Neurônios não são infectados mas sofrem neurotoxidade, bloqueio de neuro transmissores peptídicos e morte causados por partículas virais, proteínas virais e citocinas infectadas.

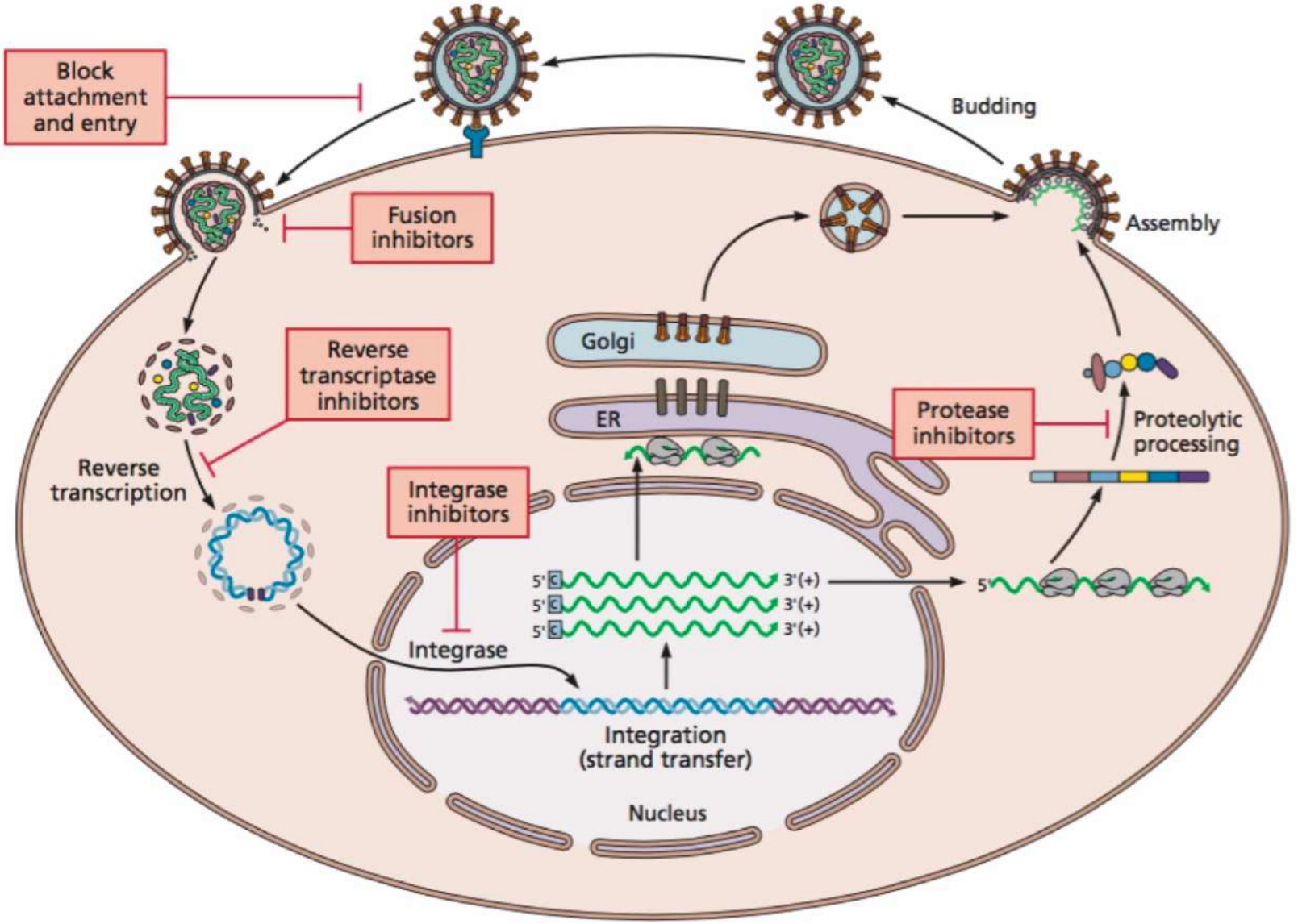
HIV and cancer

- HIV-1 infection leads to increase incidence of malignancy: 40% of infected individuals
- An indirect effect of dysregulation of the immune system
  - Absence of proper immune surveillance
  - High levels of cytokines leads to inappropriate cell proliferation, replication of oncogenic viruses (EBV, HHV8, HPV), angiogenesis

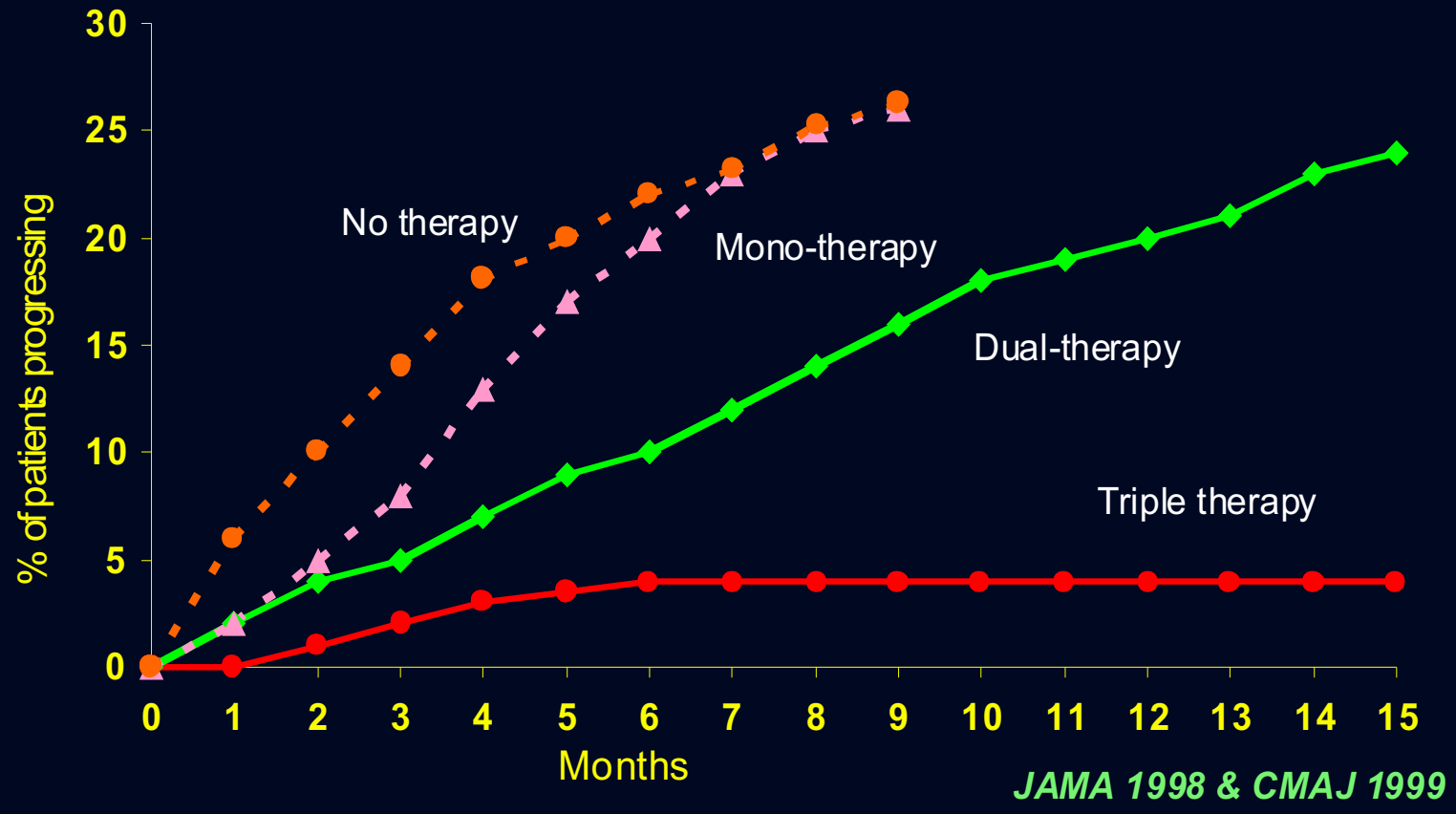
Kaposi's sarcoma

- Described 1872 by Hungarian physician
- Pre-AIDS: mainly in older Mediterranean men
- Occurs in 20% of HIV-1 infected homosexual men, 2% of HIV-1 infected women, transfusion recipients
- Infection with human herpesvirus 8 is necessary for development of KS

Targets for intervention: HIV replication



PROGRESSION TO AIDS/DEATH



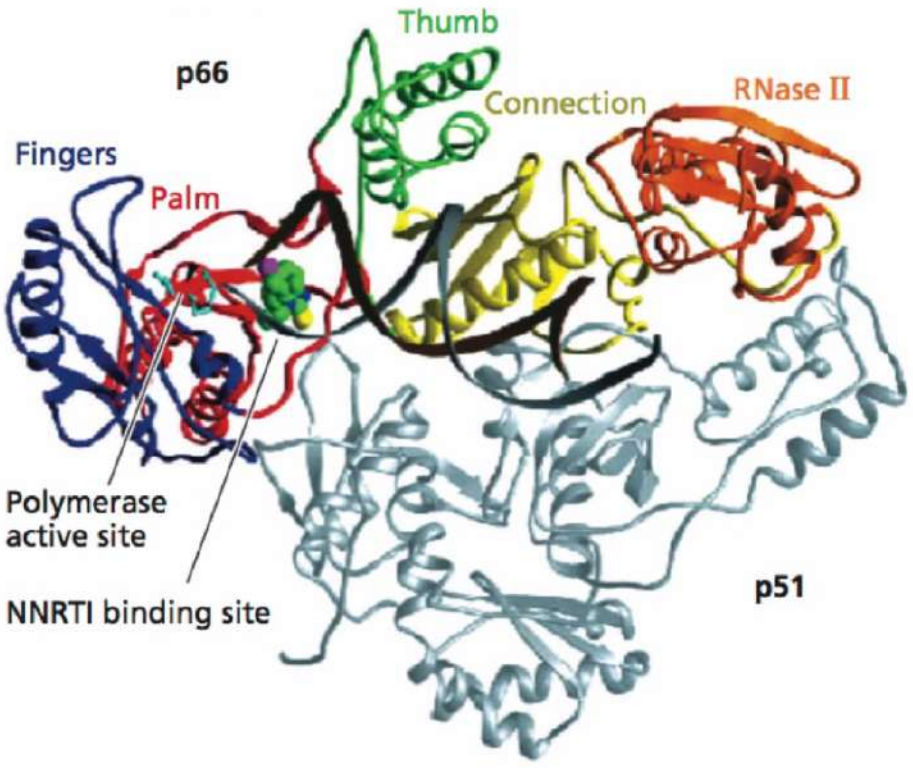
JAMA 1998 & CMAJ 1999

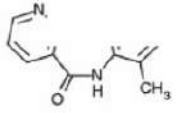
Brand name	Generic name(s)	Manufacturer name	Approval date	Time to approval
Nucleoside reverse transcriptase inhibitors (NRTIs)[a,b]				
Retrovir	Zidovudine, azidothymidine, AZT, ZDV	GlaxoSmithKline (original sponsor Burroughs-Wellcome)	19 March 1987	3.5 months
Videx	Didanosine, dideoxyinosine, ddI	Bristol Myers-Squibb	9 October 1991	6 months
Hivid	Zalcitabine, dideoxycytidine, ddC (no longer marked as of December 31, 2006)	Hoffmann-La Roche	19 June 1992	7.6 months
Zerit	Stavudine, d4T	Bristol Myers-Squibb	24 June 1994	5.9 months
Epivir	Lamivudine, 3TC	GlaxoSmithKline	17 November 1995	4.4 months
Combivir	Lamivudine and zidovudine	GlaxoSmithKline	27 September 1997	3.9 months
Ziagen	Abacavir sulfate, ABC	GlaxoSmithKline	17 December 1998	5.8 months
Videx EC	Enteric coated didanosine, ddI EC	Bristol Myers-Squibb	31 October 2000	9 months
Trizivir	Abacavir, zidovudine, and lamivudine	GlaxoSmithKline	14 November 2000	10.9 months
Viread	Tenofovir disoproxil fumarate, TDF	Gilead Sciences	26 October 2001	5.9 months
Emtriva	Emtricitabine, FTC	Gilead Sciences	02 July 2003	10 months
Epzicom	Abacavir and lamivudine	GlaxoSmithKline	02 August 2004	10 months
Truvada	Tenofovir disoproxil fumarate and emtricitabine	Gilead Sciences	02 August 2004	5 months
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)[c]				
Viramune	Nevirapine, NVP	Boehringer Ingelheim	21 June 1996	3.9 months
Rescriptor	Delavirdine, DLV	Pfizer	4 April 1997	8.7 months
Sustiva	Efavirenz, EFV	Bristol Myers-Squibb	17 September 1998	3.2 months
Intelence	Etravirine	Tibotec Therapeutics	18 Jane 2008	6 months
Protease inhibitors (PIs)				
Invirase	Saquinavir mesylate, SQV	Hoffmann-La Roche	6 December 1995	3.2 months
Norvir	Ritonavir, RTV	Abbott Laboratories	1 March 1996	2.3 months
Crixivan	Indinavir, IDV,	Merck	13 March 1996	1.4 months
Viracept	Nelfinavir mesylate, NFV	Agouron Pharmaceuticals	14 March 1997	2.6 months
Fortovase	Saquinavir (no longer marketed)	Hoffmann-La Roche	7 November 1997	5.9 months
Agenerase	Amprenavir, APV	GlaxoSmithKline	15 April 1999	6 months
Kaletra	Lopinavir and ritonavir, LPV/RTV	Abbott Laboratories	15 September 2000	3.5 months
Reyataz	Atazanavir sulfate, ATV	Bristol-Myers Squibb	20 June 2003	6 months
Lexiva	Fosamprenavir calcium, FOS-APV	GlaxoSmithKline	20 October 2003	10 months
Aptivus	Tipranavir, TPV	Boehringer Ingelheim	22 June 2005	6 months
Prezista	Darunavir	Tibotec, Inc.	23 June 2006	6 months
Fusion inhibitors				
Fuzeon	Enfuvirtide, T-20	Hoffmann-La Roche and Trimeris	13 March 2003	6 months
Entry inhibitors—CCR5 co-receptor antagonists				
Selzentry	Maraviroc	Pfizer	06 August 2007	8 months
HIV integrase strand transfer inhibitors				
Isentress	Raltegravir	Merck & Co., Inc.	12 October 2007	6 months
Multi-class combination products				
Atripla	Efavirenz, emtricitabine and tenofovir disoproxil fumarate	Bristol-Myers Squibb and Gilead Sciences	12 July 2006	2.5 months

Resistance to AZT

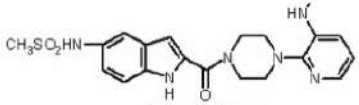
- Mutants resistant to AZT arose immediately after drug was licensed
- Single aa changes at one of four sites in RT
- Altered RT do not bind phosphorylated AZT
- New nucleoside analogs developed: Didanosine (ddI), Zalcitabine (ddC), Stavudine (d4T), Lamivudine (3TC)
- This lead to combination therapy, use of two antiviral drugs to combat resistance
- Mutants resistant to two drugs arose <1 yr

Non-nucleoside RT inhibitors (NNRTI)

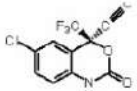




nevirapine (Viramune)



delavirdine



efavirenz

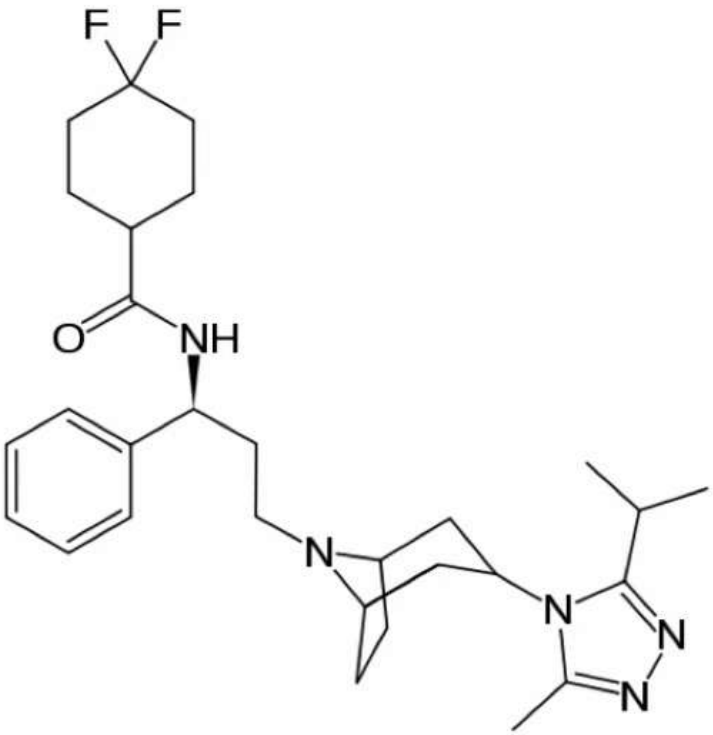
11-cyclopropyl-4-methyl-5,11-dihydro-6*H*- dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one

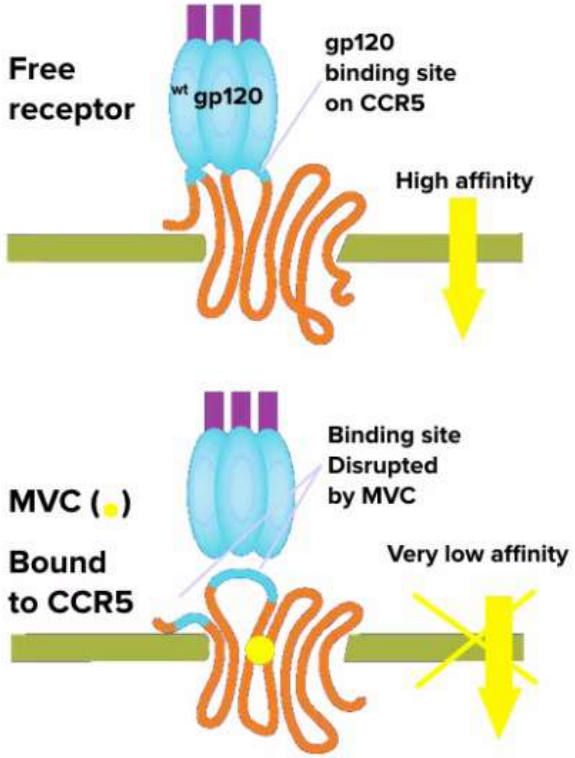
Resistance to NNRTIs

NNRTI não se ligam ao sítio ativo da RT e tem efeito "alostérico"

- Resistant mutants are selected rapidly
- Amino acid substitutions in any of seven residues that line binding sites on enzyme confer resistance
- Cannot be used alone for treatment of AIDS
- Now used largely in combination therapy

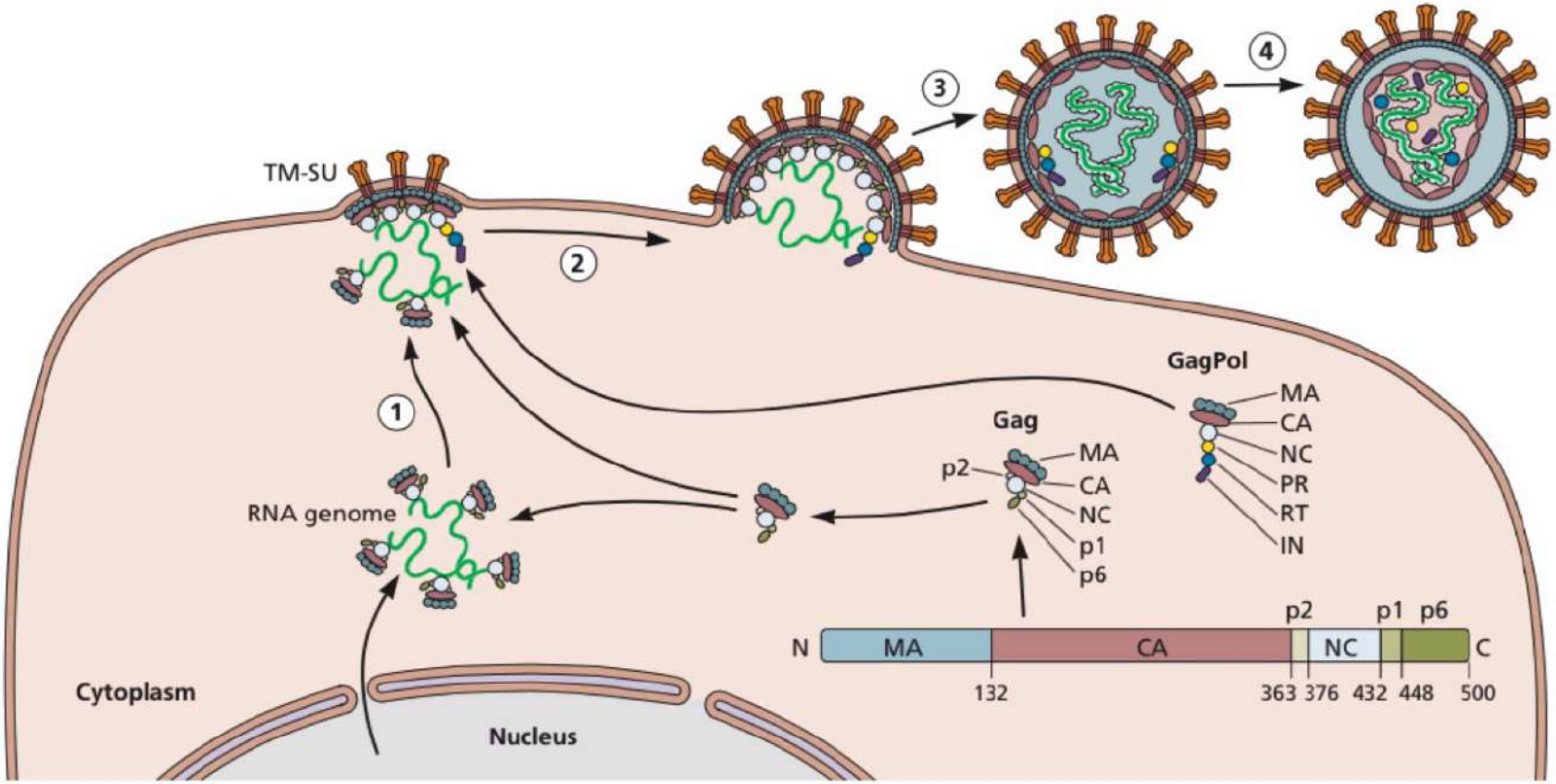
Maraviroc: CCR5 inhibitor





Antiviral drugs that target HIV protease

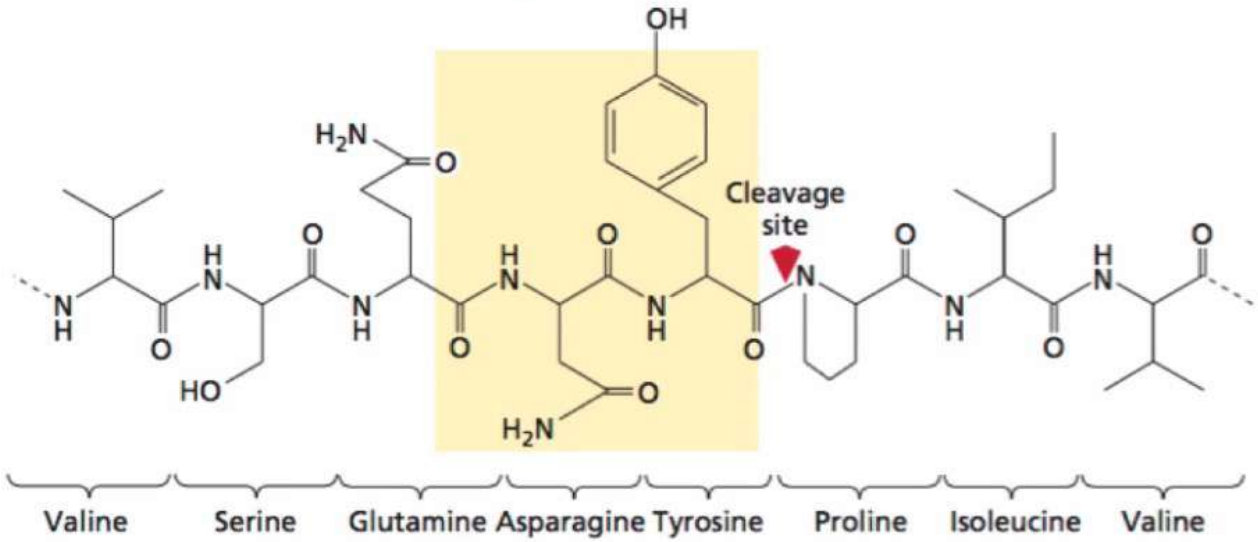
HIV protease absolutely required for production of infectious virions

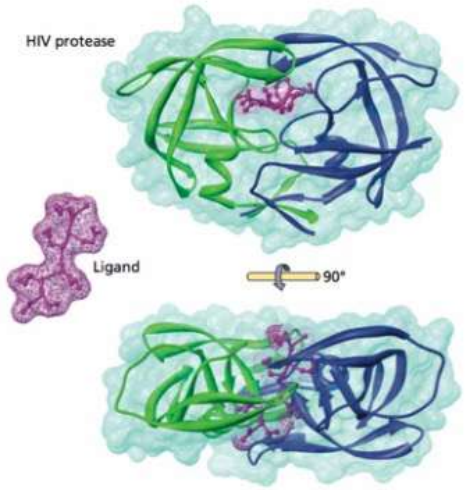


Antiviral drugs that target HIV protease

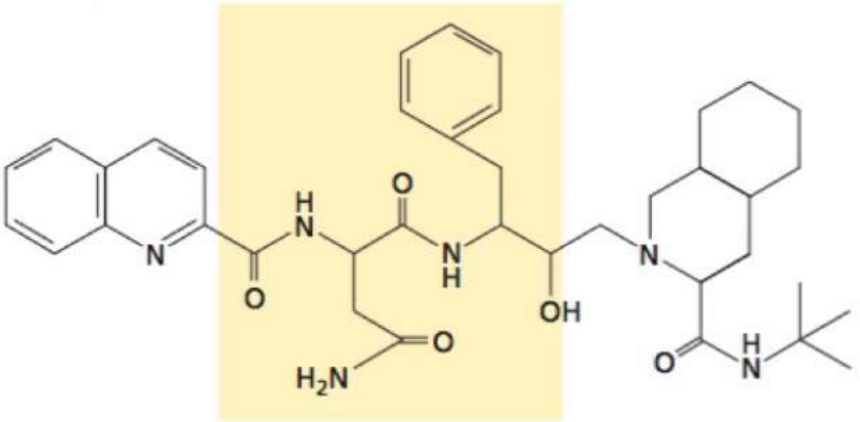
Key finding: HIV protease recognizes and cleaves small synthetic peptides

A Natural substrate of the HIV-1 protease

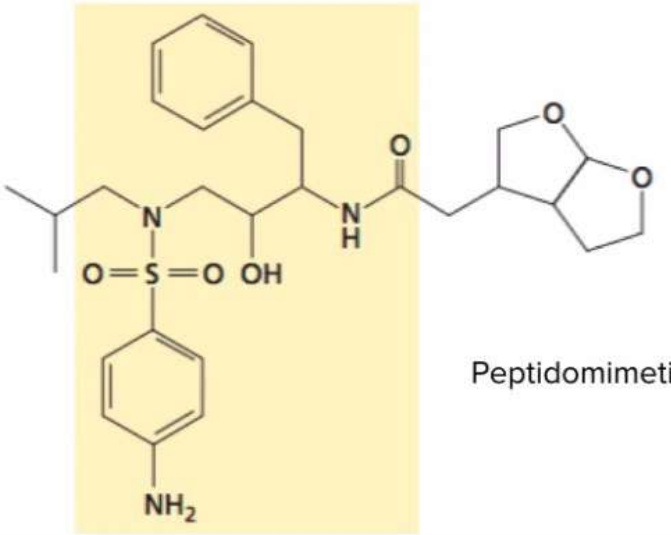




B Saquinavir

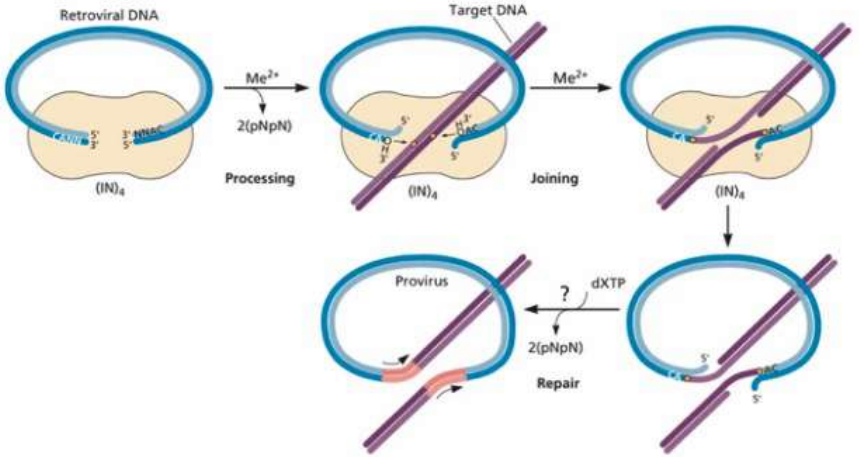


C Darunavir

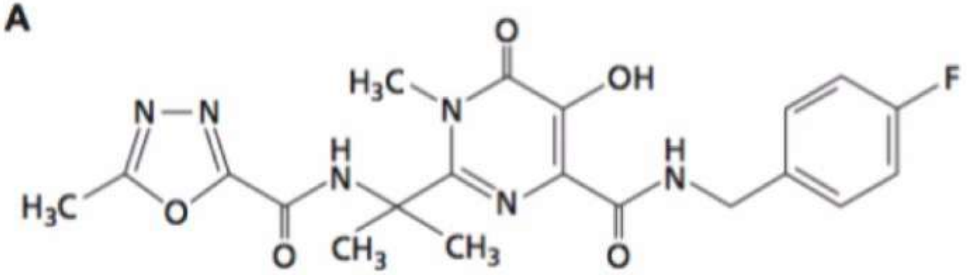


Peptidomimetic

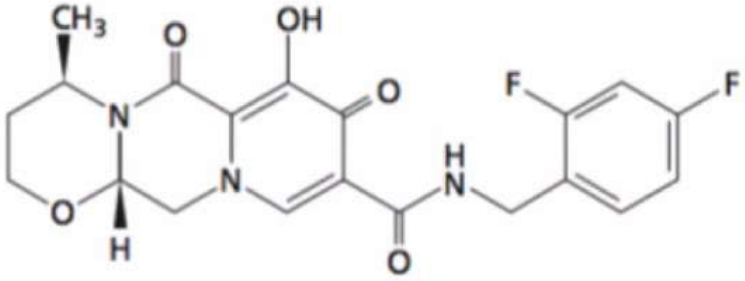
IN inhibitors



A

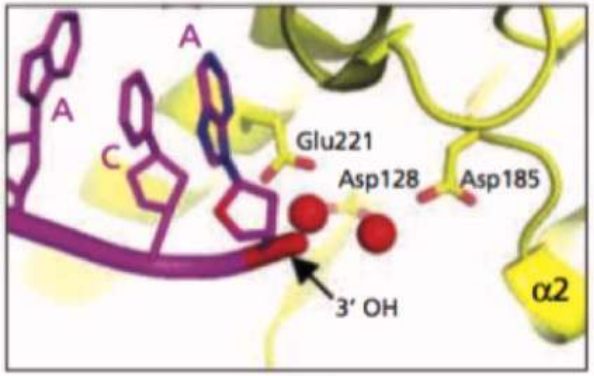


RAL

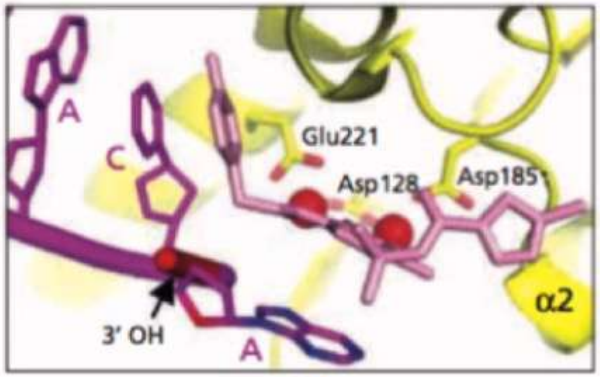


DTG

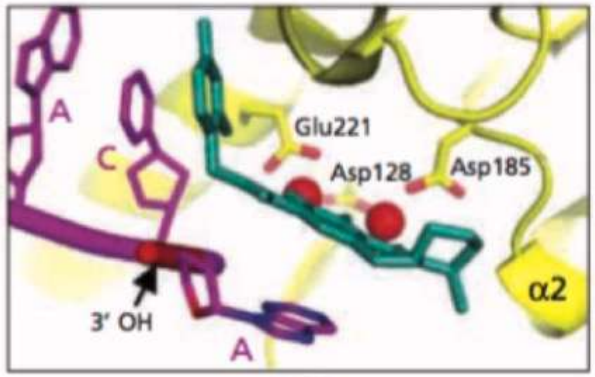
B



No Drug

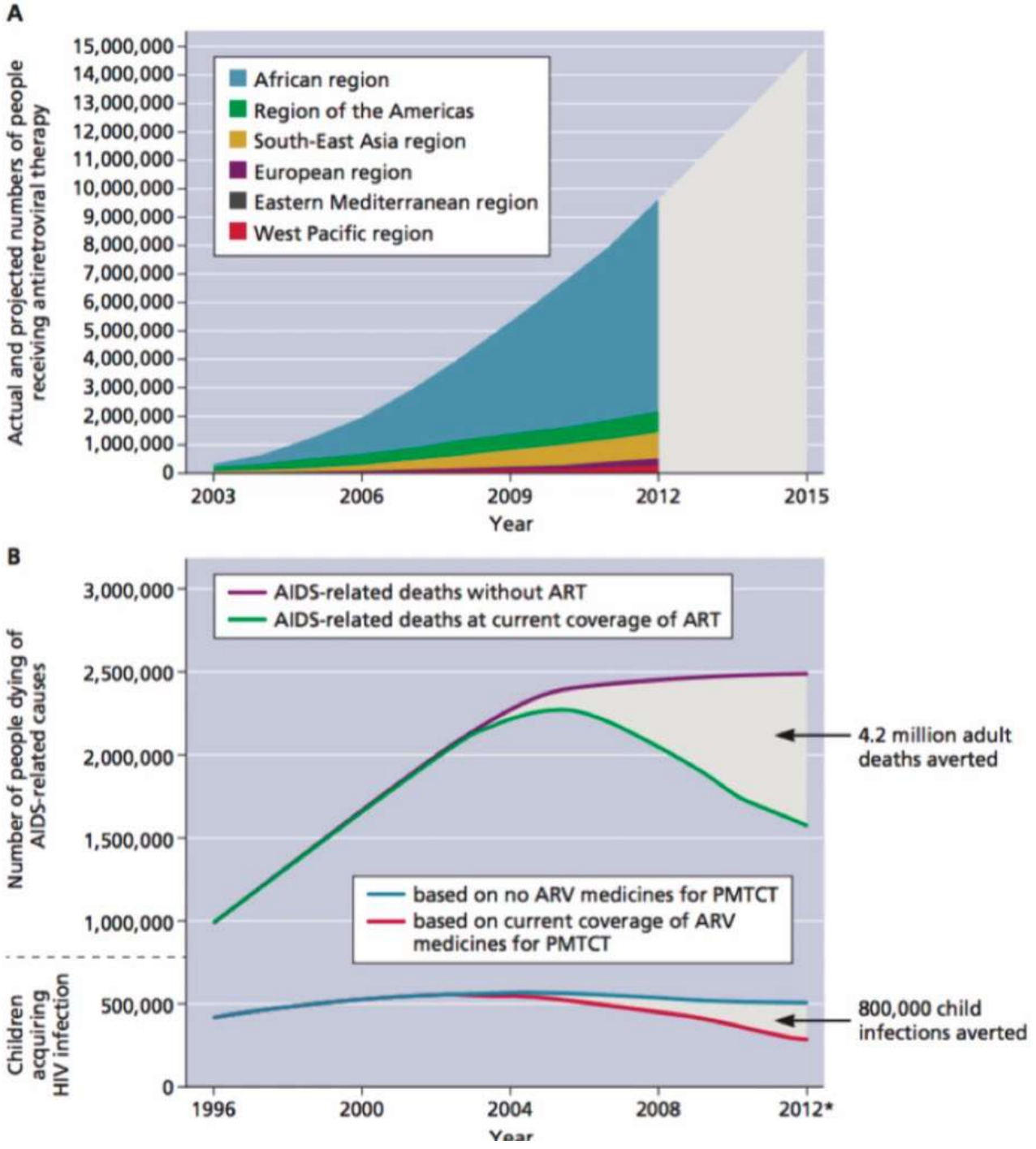


RAL



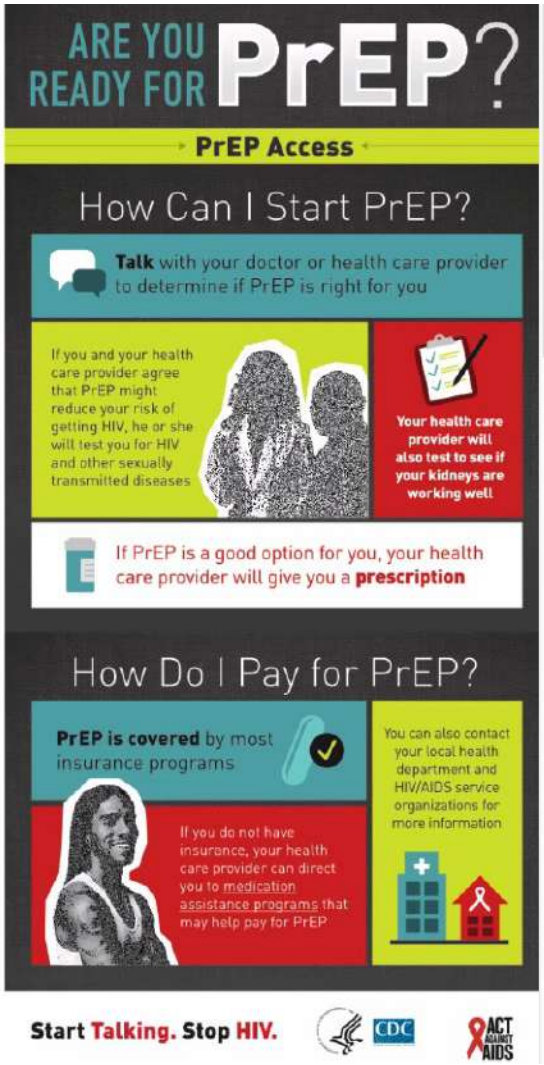
DTG

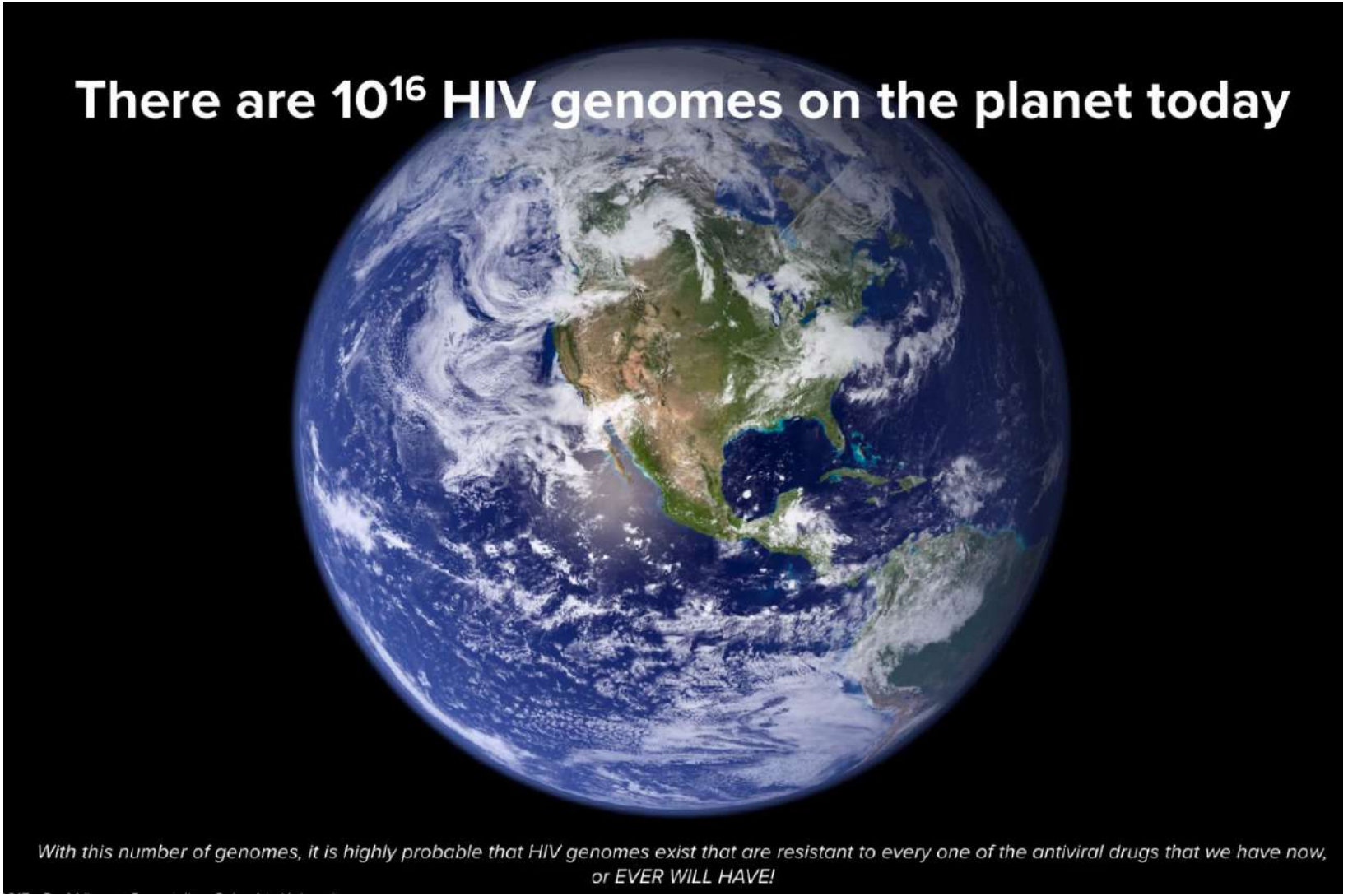
ART saves lives



Pre-exposure prophylaxis (PrEP)

- Daily double therapy (tenofovir and emtricitabine) for those at high risk for HIV infection
- Reduces risk of sexual transmission of HIV-1 by >90%
- Reduces risk of transmission by IVDU by >70%
- No resistance in trials, but real world?
- https://www.ncbi.nlm.nih.gov/pubmed/27391094





Até logo!!!!!

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