DEPARTAMENTO DE
MICroBiologia
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ICB USP

Hepatites Virais

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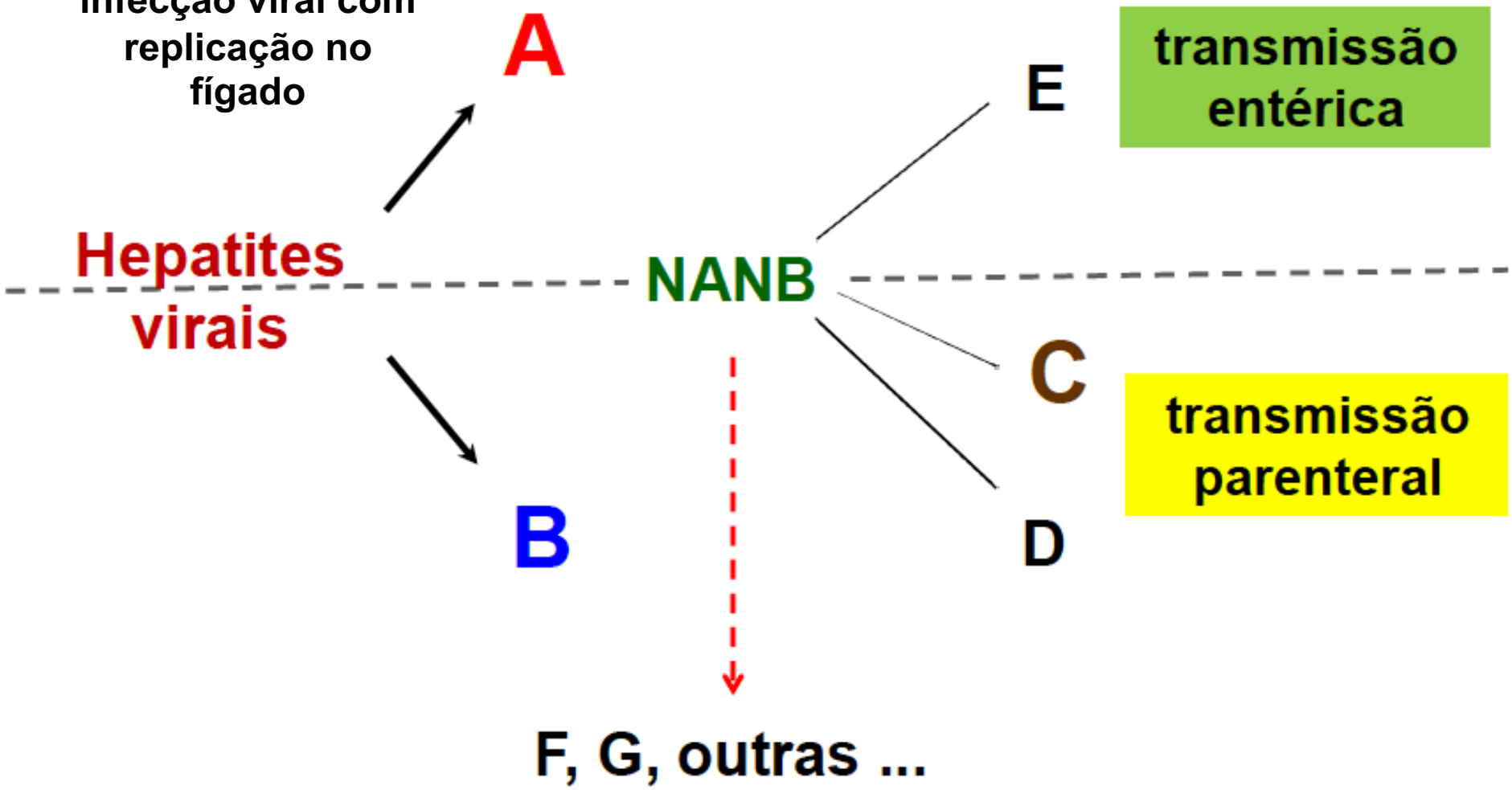
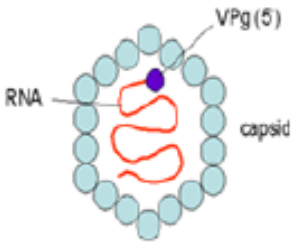
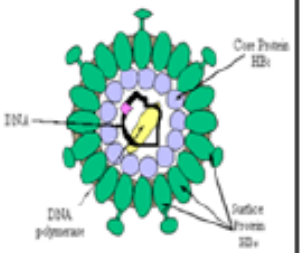
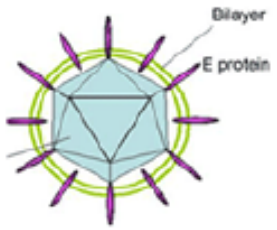
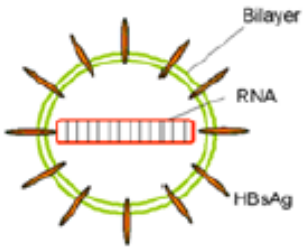
É uma virose...

Hepatites virais: infecção viral com replicação no fígado



Hepatites Virais

					
Name of Virus	Hepatitis A Virus (HAV)	Hepatitis B Virus (HBV)	Hepatitis C Virus (HCV)	Hepatitis D Virus (HDV)	Hepatitis E Virus (HEV)
Classification	Picornavirus	Hepadnavirus	Flavivirus	Deltavirus	Hepevirus
Viral genome	ssRNA	dsDNA	ssRNA	-ssRNA (-ve)	ssRNA
Transmission	Enteric	Parental	Parental	Parental	Enteric
Incubation period	15-45 days	45-160 days	15-150 days	30-60 days	15-60 days
Chronic Hepatitis	No.	Yes. 10% chance	Yes. >50% chance	Yes. <5% of coinfectious >80% of superinfectious	No.
Cure?	No cure. Treatments usually tackle the symptoms.	No cure. Treatments usually tackle the symptoms.	No cure. Treatments usually tackle the symptoms.	No cure. Treatment: Alpha interferon for 12 months.	No cure. Treatments usually tackle the symptoms

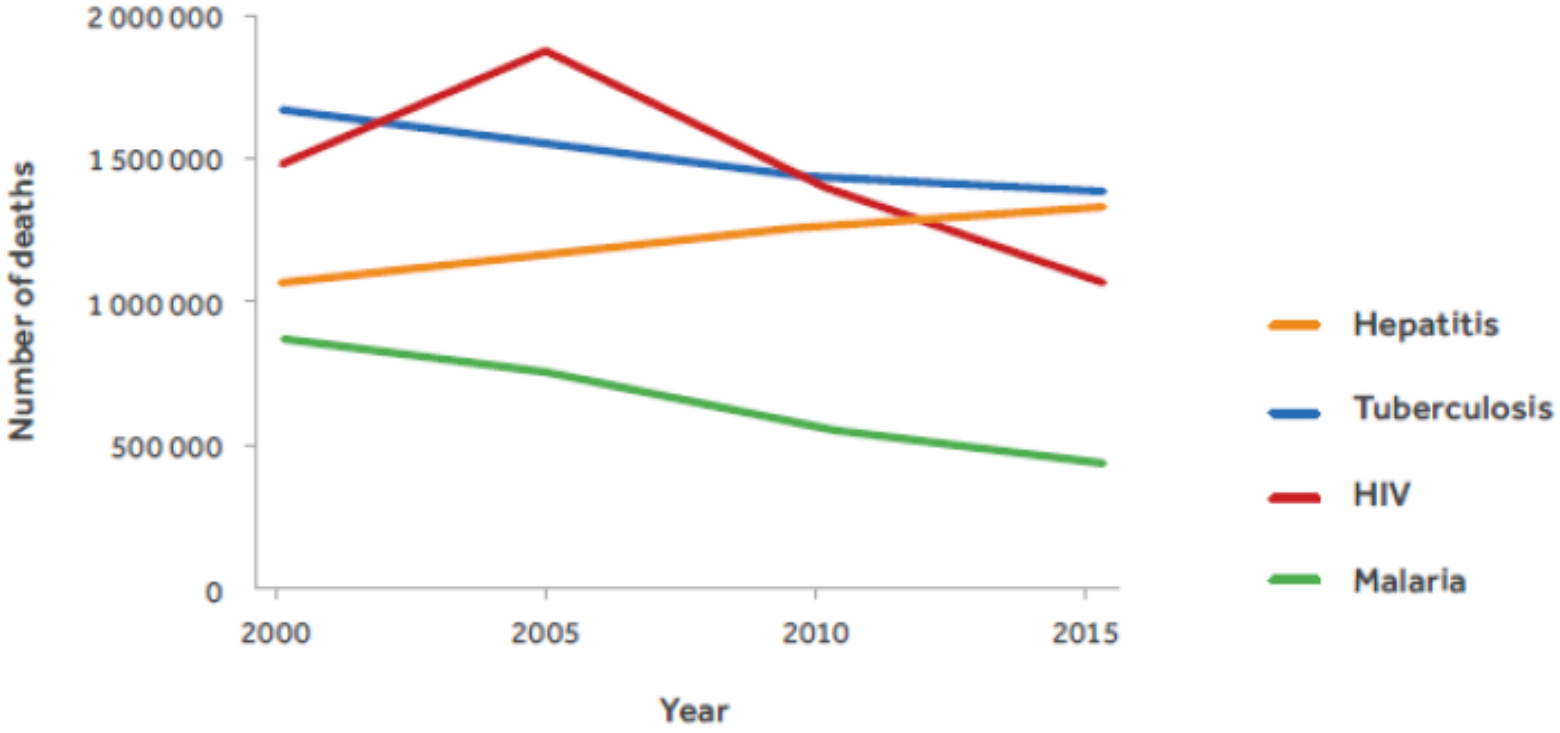
Hepatites Virais: impacto nas populações humanas

Estimativas da WHO (2015)

- 257 milhões de pessoas (3.5% da população mundial) estão infectados de maneira crônica pelo HBV.
- 5% das pessoas infectadas por HBV estão infectadas por HDV.
- 71 milhões de pessoas (1.0% da população mundial) estão infectados de maneira crônica pelo HCV.
- 20 milhões de pessoas/ano se infectam com o HEV (44.000 mortes em 2015 [3.3% das mortes por Hepatites virais]).
- Mais de 7.000 mortes por HAV em 2016 (taxa de hepatite fulminante varia de 0.14 – 0.35, portanto, 2 – 5 milhões de casos por ano).

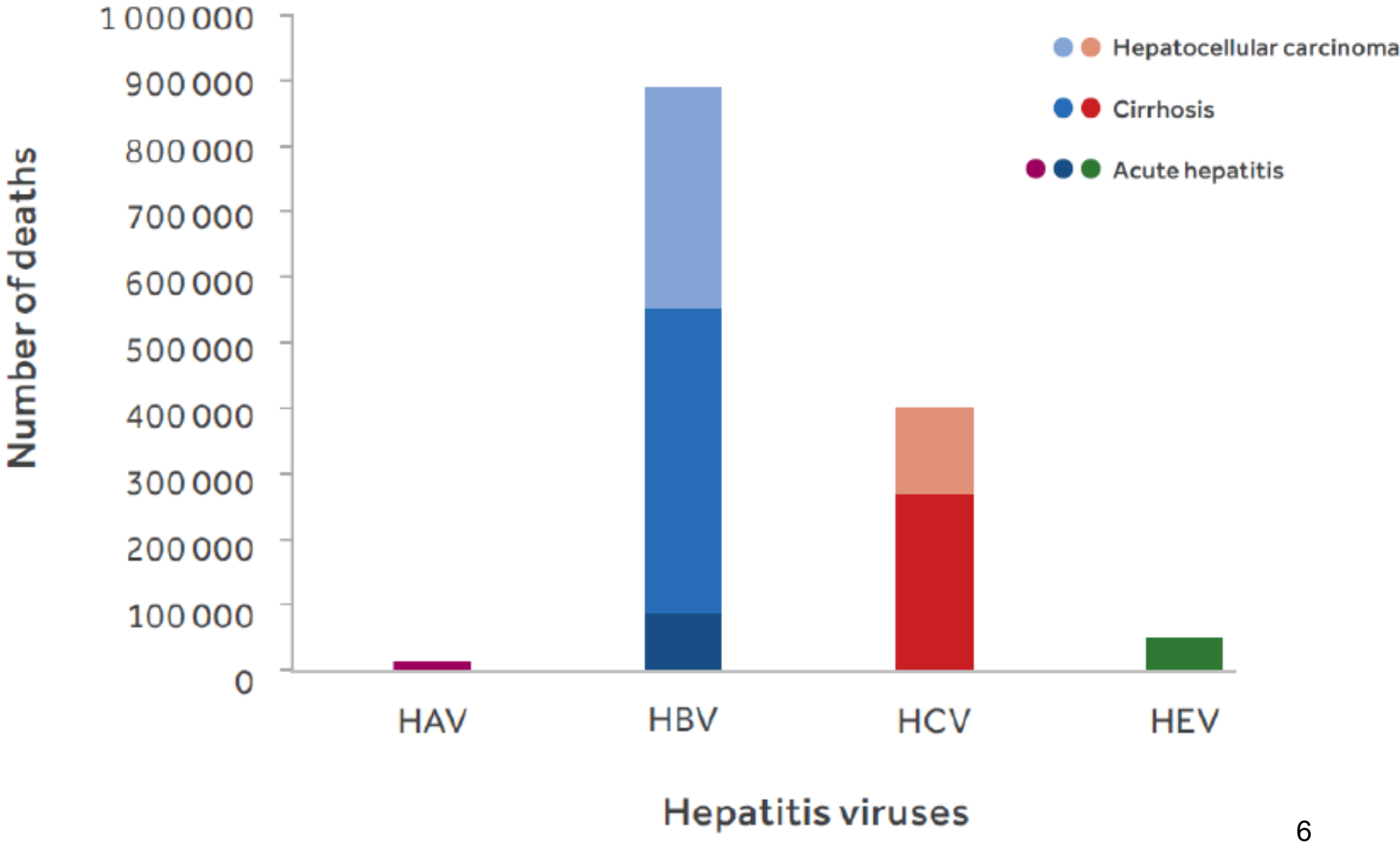
Hepatites Virais: impacto nas populações humanas

Fig. 2. Global annual mortality from hepatitis, HIV, tuberculosis and malaria, 2000–2015: unlike HIV, tuberculosis and malaria, the trend in mortality from viral hepatitis is increasing



Source: WHO global health estimates (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000-2015. Geneva: World Health Organization; 2016.)

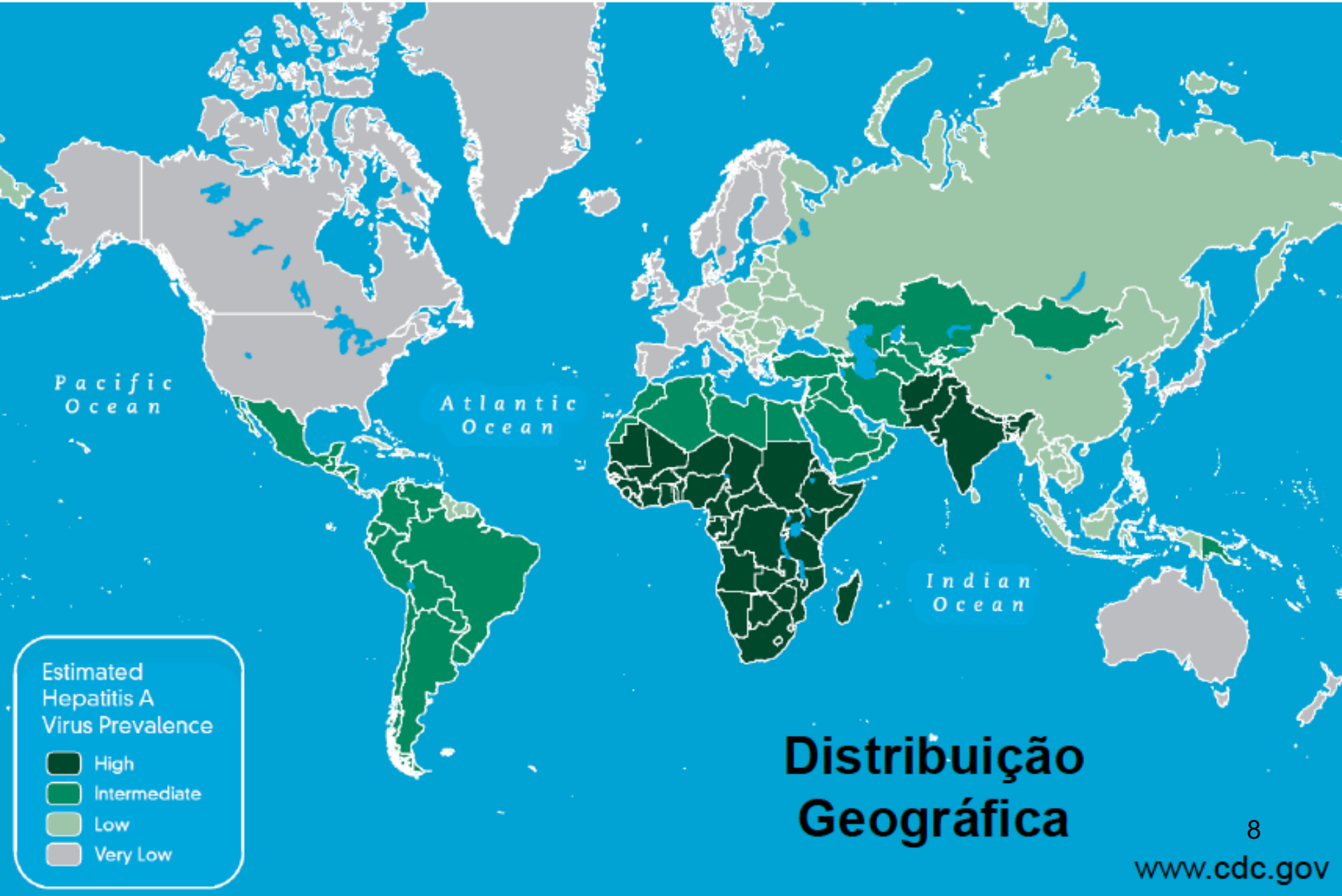
Hepatites Virais: impacto nas populações humanas



HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virusSource: WHO global health estimates for 2015 published in 2016 (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000–2015. Geneva: World Health Organization; 2016.)

Vírus de hepatite de transmissão entérica

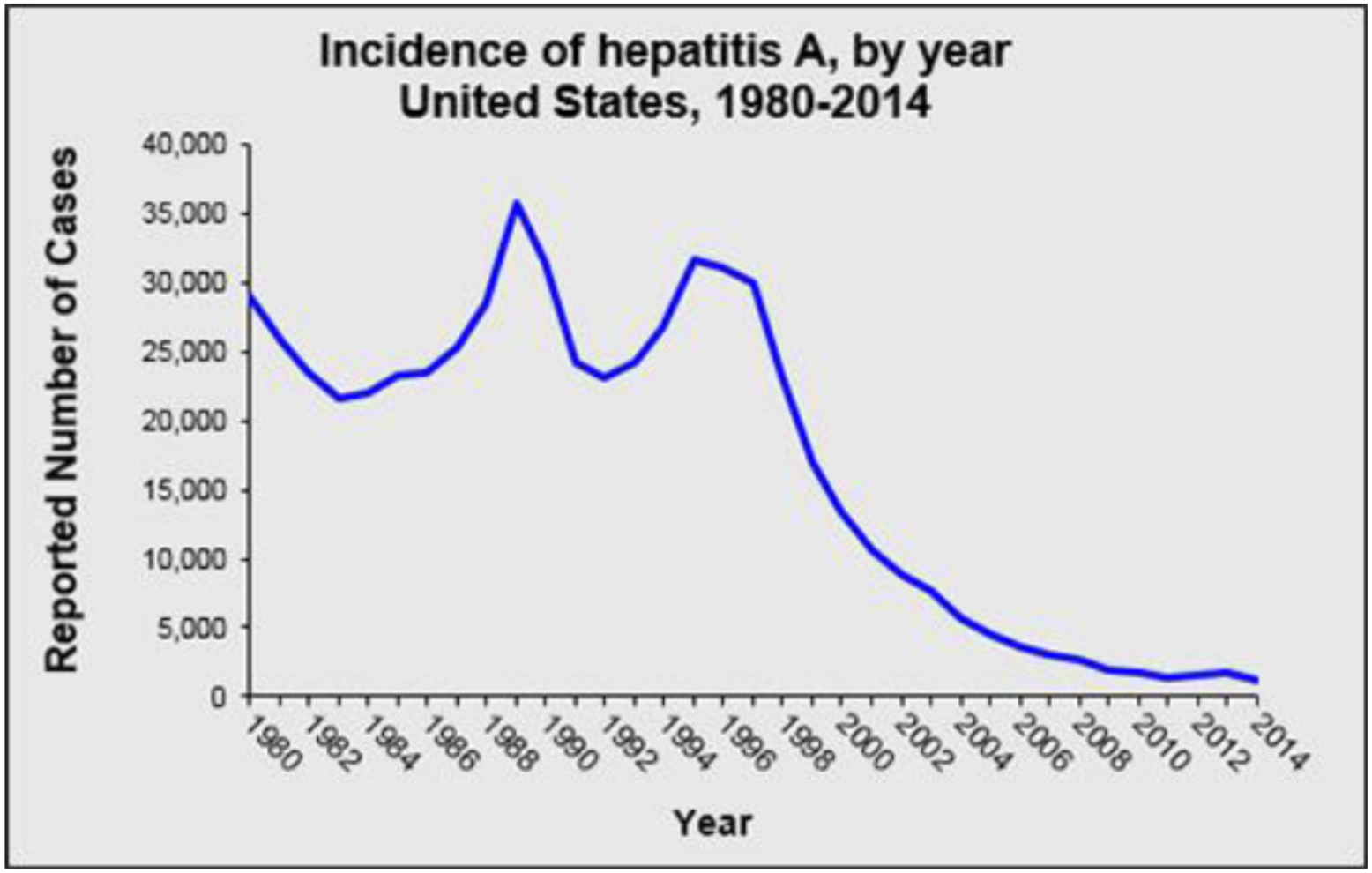
Hepatite A



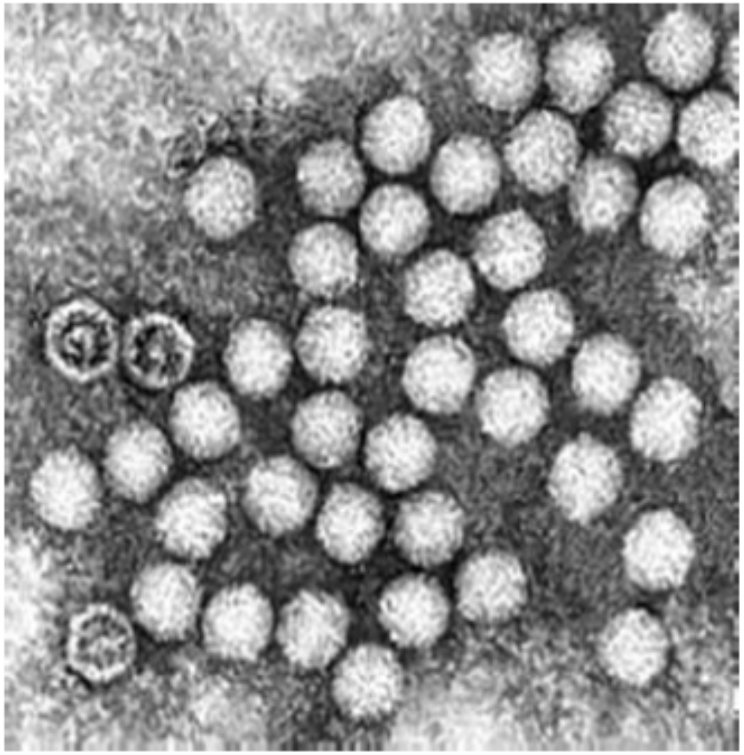
Distribuição Geográfica

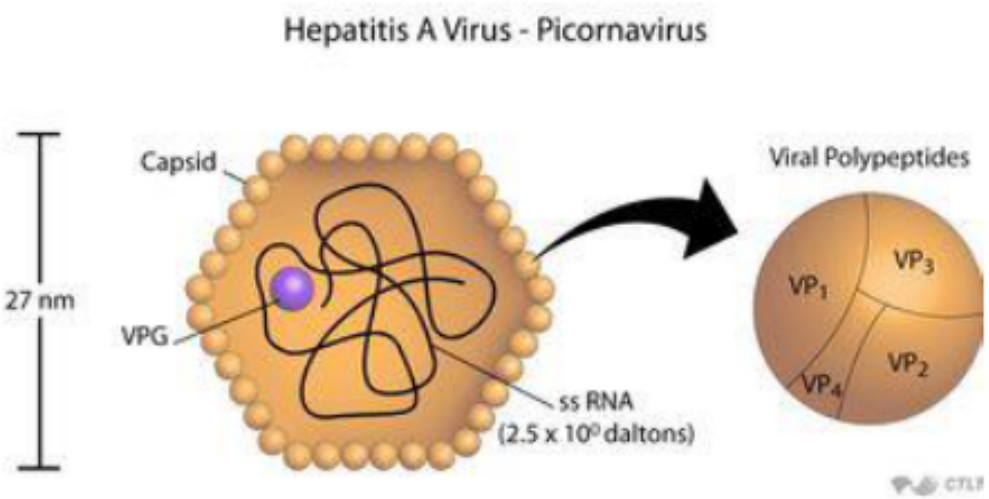
www.cdc.gov

Hepatite A


Incidence of hepatitis A, by year
United States, 1980-2014
Reported Number of Cases
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
1980
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014
Year

Hepatite A (HAV)





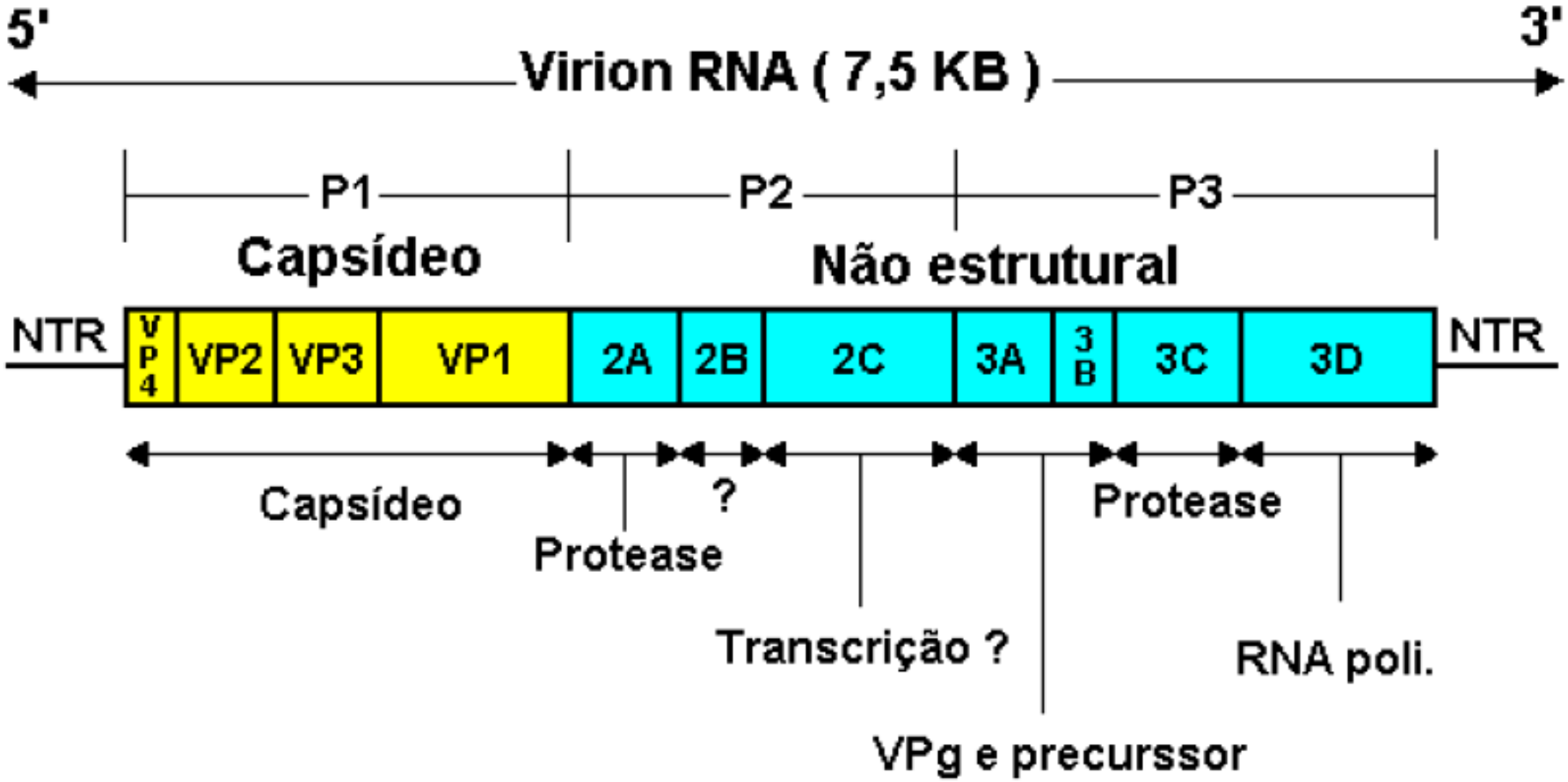
Hepatite A

Família: *Picornavidae*
Gênero: Hepatovírus

- Capsídeo icosaédrico, não envelopado, de 27-32nm.
- Resistente ao calor, frio, condições ácidas e relativa resistência à desinfecção.
- Genoma de RNA linear, de fita simples, (+).
- Genótipos I,II e III infectam humanos
- Transmissão via oral-fecal e parentérica (Crianças = fonte de infecção)

Hepatite A

Organização genômica



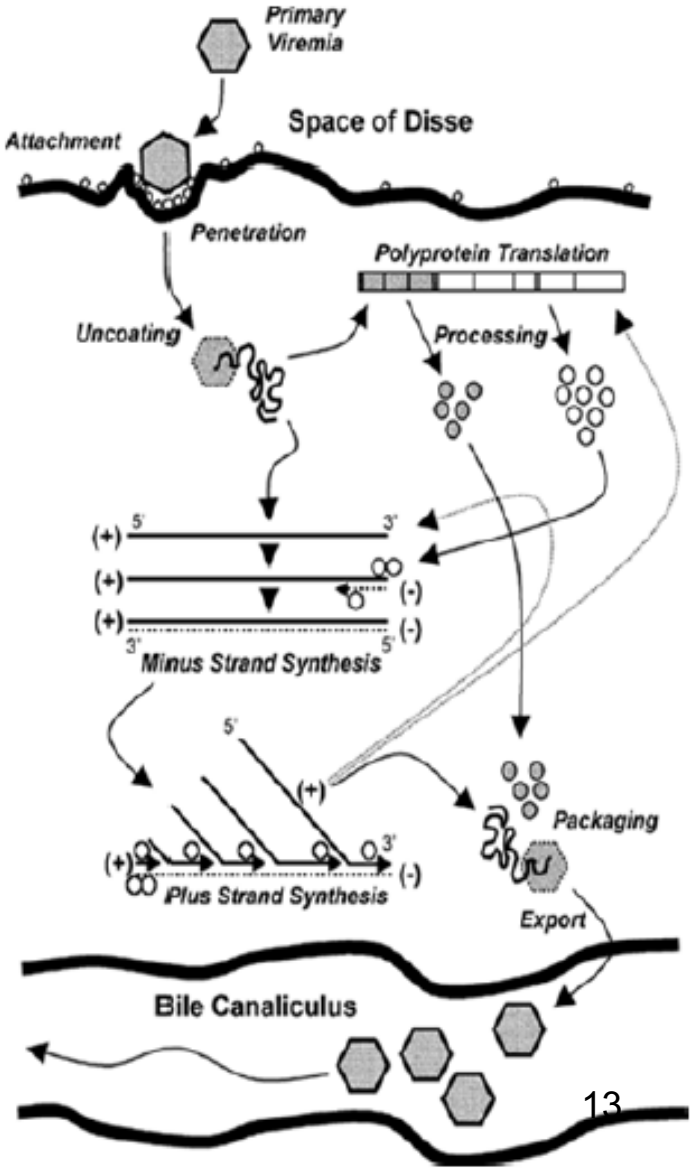
Hepatite A

Multiplicação

- Transmissão por água e alimentos.
- Porta de entrada pela via oral.
- Replicação viral primária no intestino delgado e migração por veia porta até o fígado.
- Excretado por bile e pelas fezes.

Na célula:

- entrada por endocitose
- genoma RNA+ vai para os ribossomos
- formação de poliproteína
- clivagem por protease viral
- replicação do genoma viral
- montagem no citoplasma
- liberação por lise



Hepatite A

Diagnóstico Laboratorial

- Ensaios imunoenzimáticos
  - pesquisa de anticorpos
- Imunomicroscopia eletrônica
  - antígeno nas fezes
- Técnicas de biologia molecular
  - PCR, sequenciamento (tipagem dos vírus circulantes)

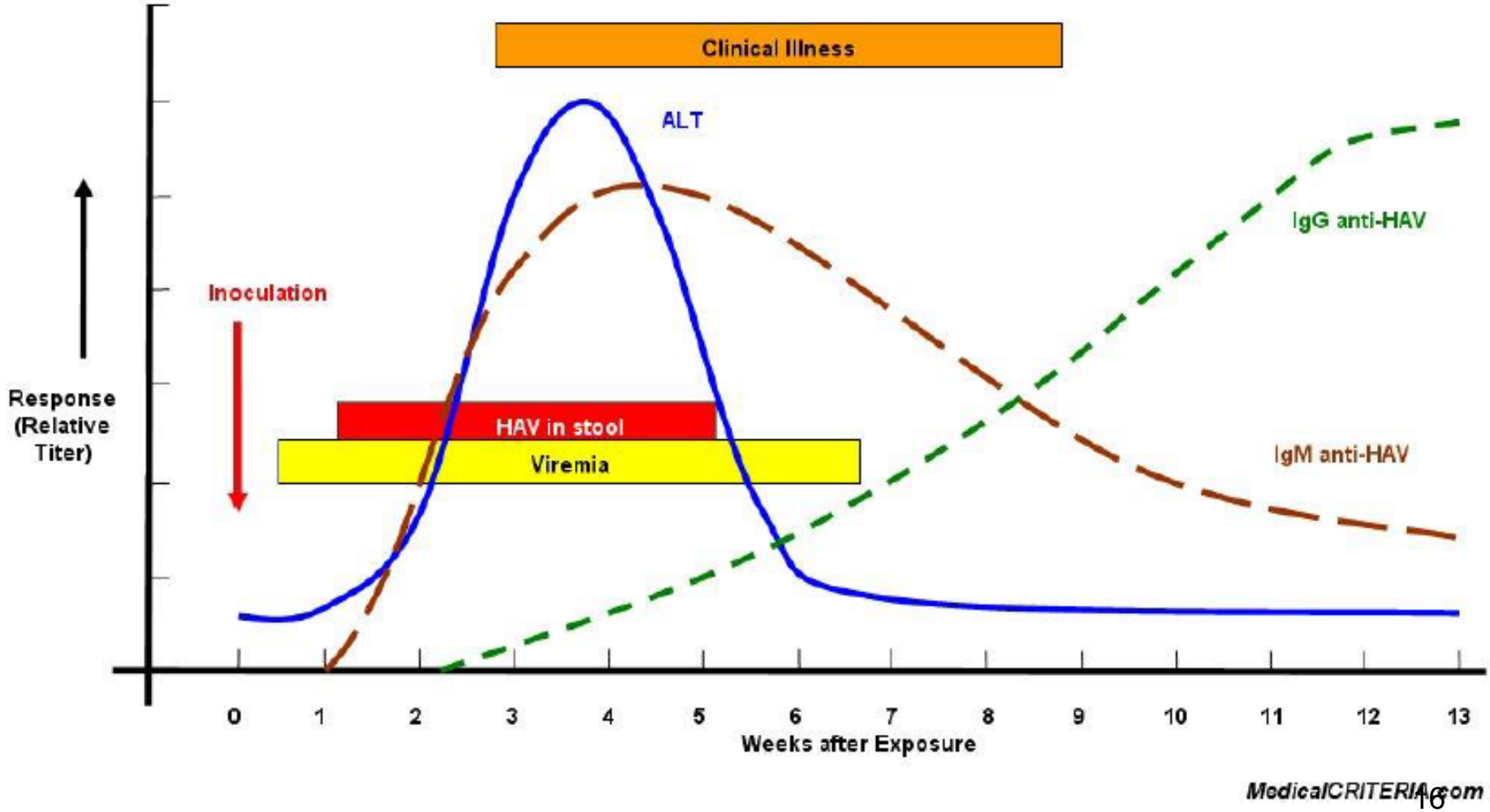
Hepatite A

Pesquisa de anticorpos

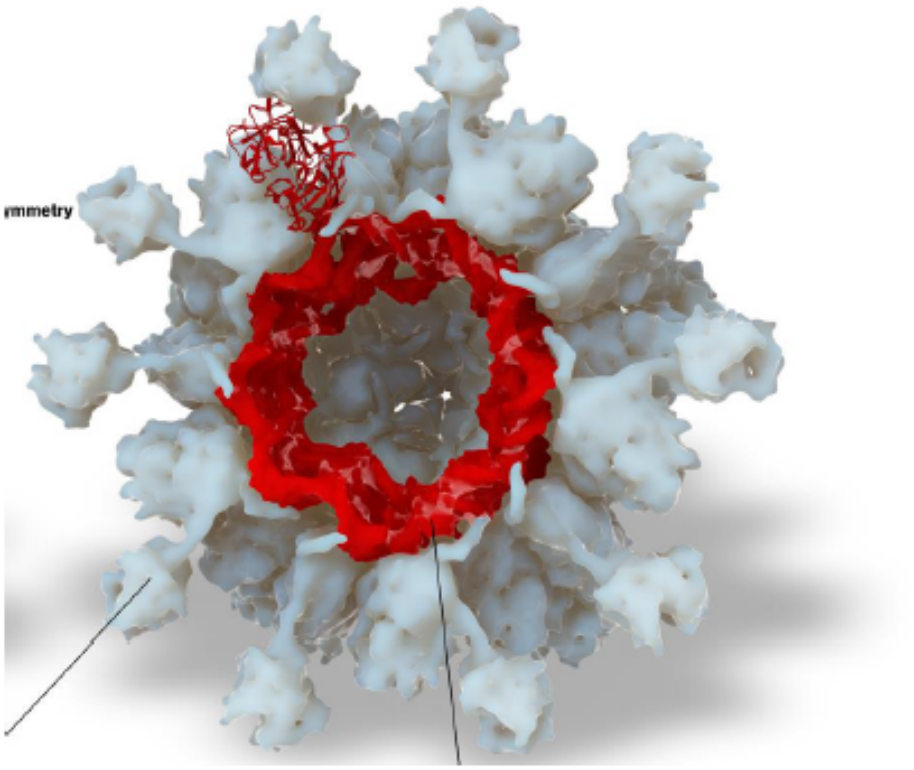
- **anti-VHA IgM**
  - marcador de infecção recente
- **anti-VHA IgG**
  - conferem imunidade duradoura
  - marcador soroepidemiológico
  - indicador de contato prévio
- **amostra clínica**
  - soro
  - saliva
  - sangue - polpa digital

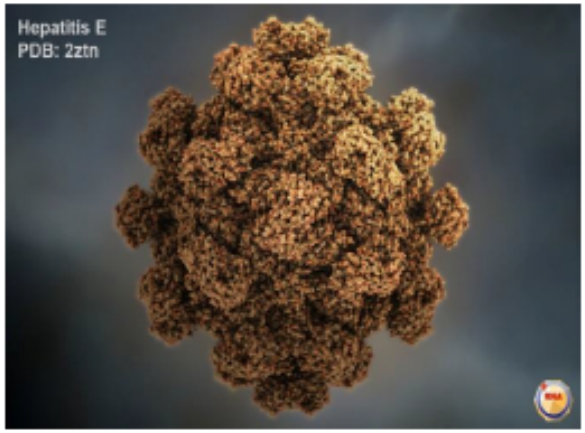
Hepatite A

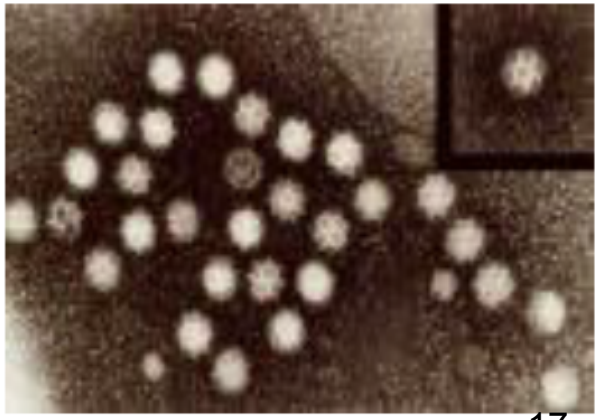
Sorologia da infecção



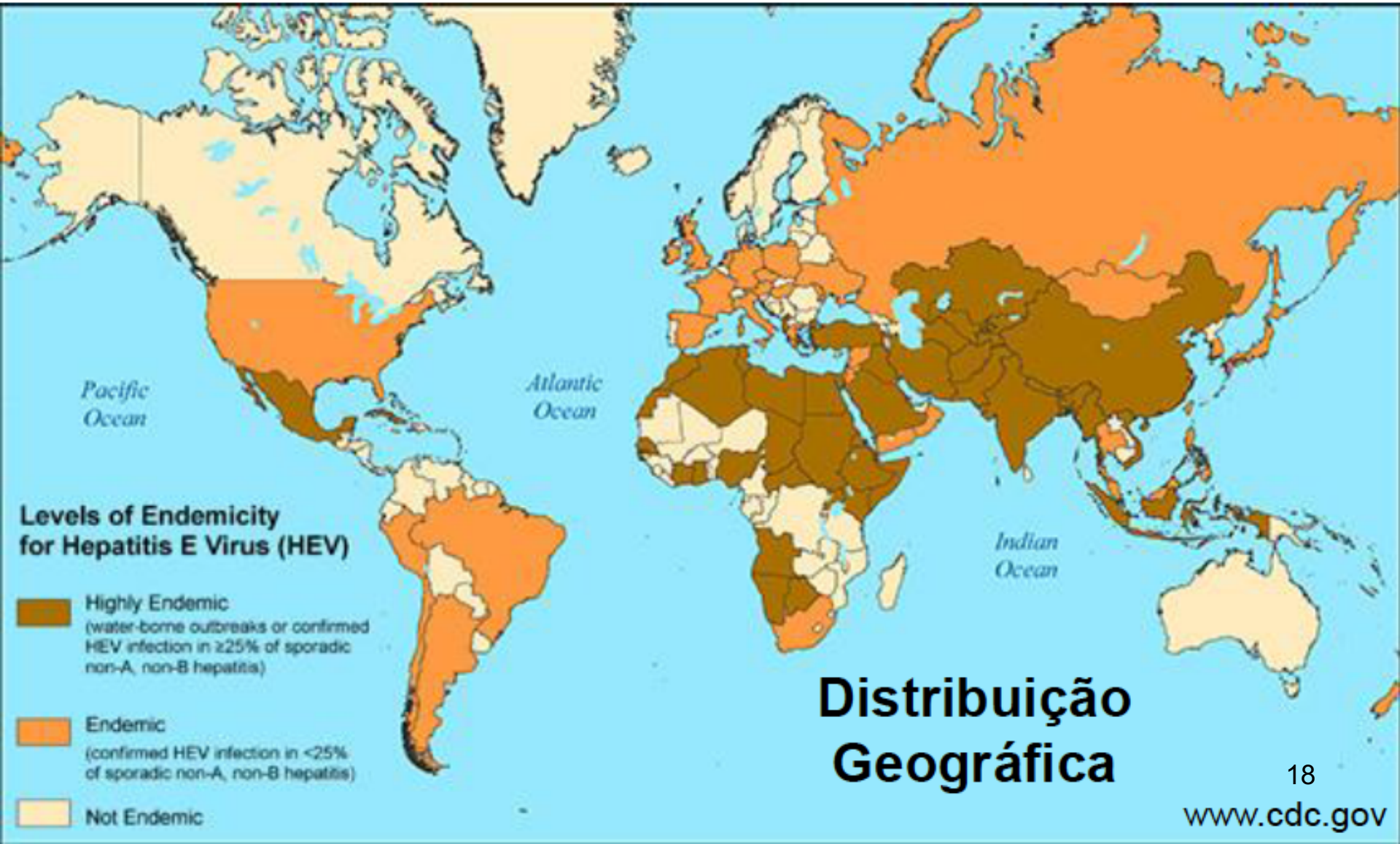
Hepatite E (HEV)







Hepatite E



Distribuição Geográfica

www.cdc.gov

Hepatite E

Epidemiologia

- Maioria dos surtos associados a consumo de água contaminada com fezes
- Transmissão pessoa-a-pessoa mínima
- Casos descritos em áreas endêmicas ou em pessoas que viajaram para estas regiões

Hepatite E

Família: Hepeviridae
Gênero: Hepevírus

- Capsídeo: icosaédrico, esférico, não envelopado, 27-34nm.
- Genoma de RNA com leitura positiva com 7,2 kb 3 ORF.
- transmissão fecal-oral e água contaminada (zoonose - suínos).
- Endêmico no Sudeste Asiático e Índia.
- Mortalidade de até 20%, especialmente em grávidas.

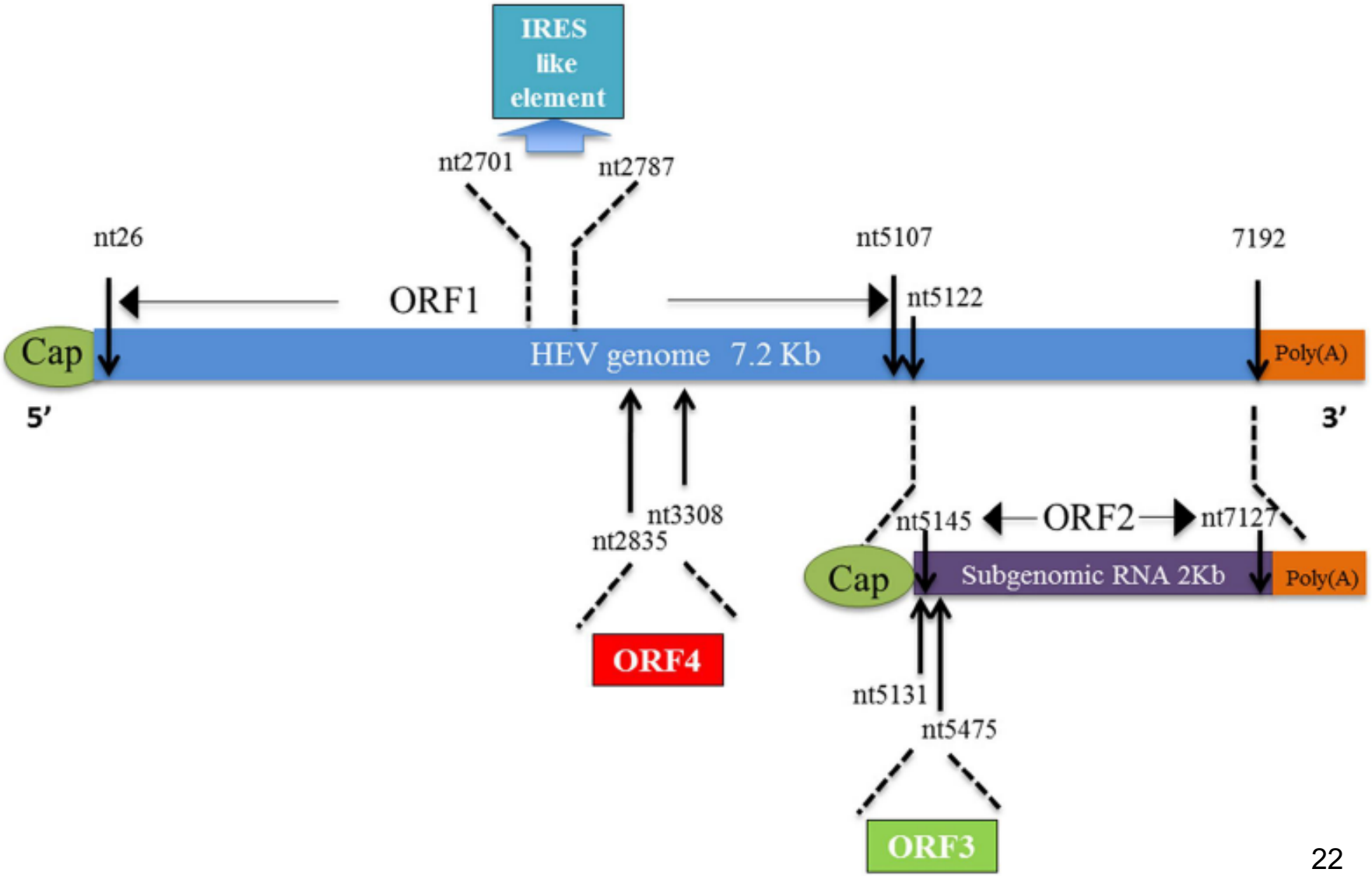
Hepatite E

Table 1 Comparison of the four hepatitis E virus genotypes by select characteristics

Characterstics	Genotype 1	Genotype 2	Genotype3	Genotype 4
Viral discovery	1983	1986	1995	2003
Geographic distribution	Developing countries	Mexico, West Africa	Developed countries	China, Taiwan, Japan
Food-borne transmission	No	No	Yes	Yes
Fecal-oral transmission	Yes	Yes	?	No
Water-borne transmission	Yes	Yes	?	No
Person-to-person transmission	Yes	Unknown	Yes	Unknown
Zoonotic transmission	No	No	Yes	Yes
Occurrence of epidemics	Common	Smaller scale epidemics	No epidemics	Uncommon
Highest attack rate	Young adults	Young adults	Persons ⩾ 40 yr of age	Young adults
Gender	Male preponderance	Not discriminatory	Mostly male	Not discriminatory
Mortality rate	0.5%-3%	0.5%-3%	Not determined	0.5%-3%
Mortality among pregnant women	High	High	Not determined	High
Chronic infection	None	None	Yes	None
Severe disease among immuno-compromised	Not reported	Not reported	Yes	Not reported
Interspecies transmission	Only humans and non-human primates	Only humans and non-human primates	Humans Pigs	Humans Pigs
Subtypes	5	2	10	7

Hepatite E

Organização genômica



doi.org/10.3389/fmicb.2016.01419

Hepatite E

Diagnóstico Laboratorial

- ensaios imunoenzimáticos

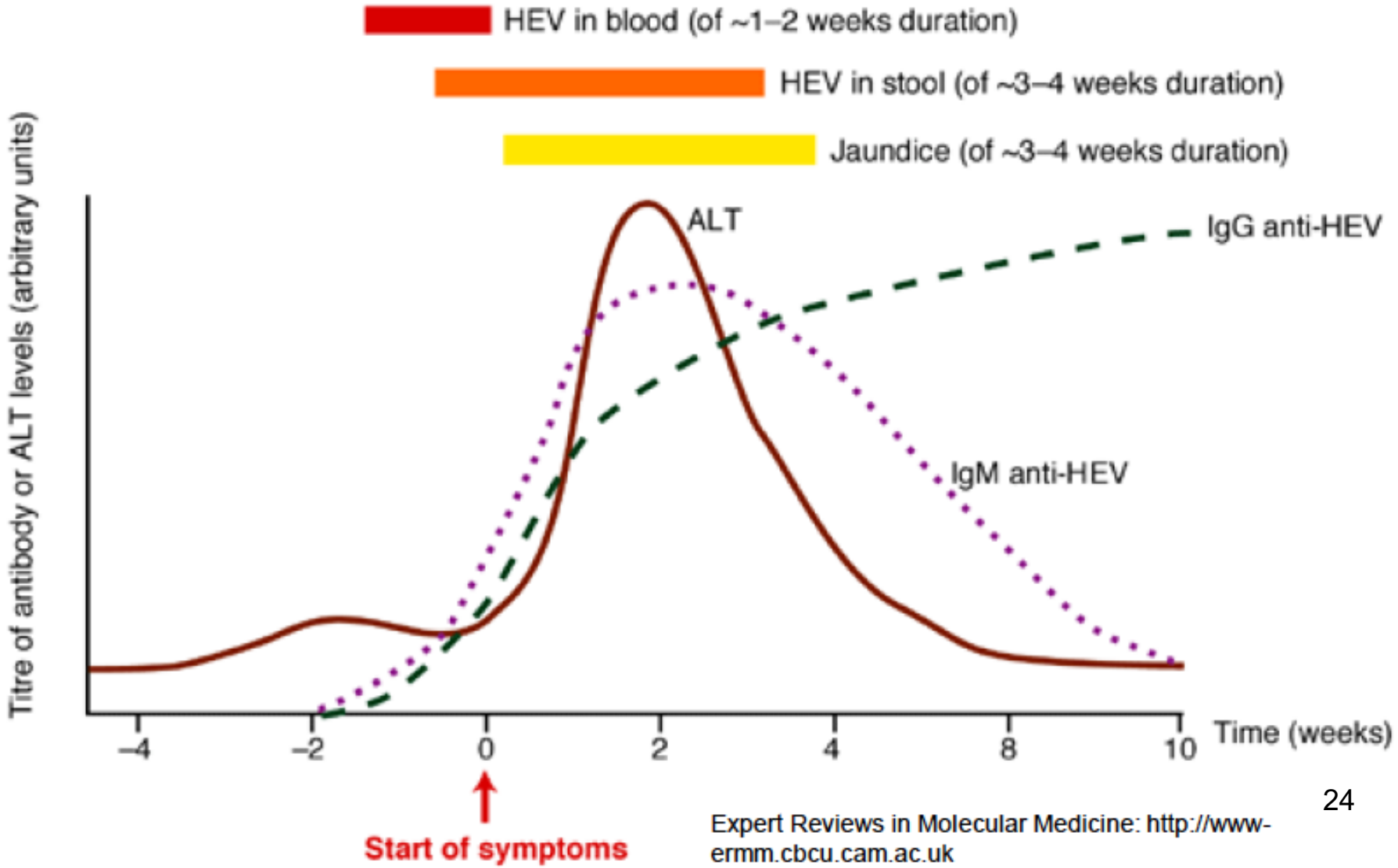
  Pesquisa de anti-VHE (IgM ou IgG) - ELISA

  - ELISA
  - IMUNOBLOT

- técnicas de biologia molecular

Hepatite E

Sorologia da infecção



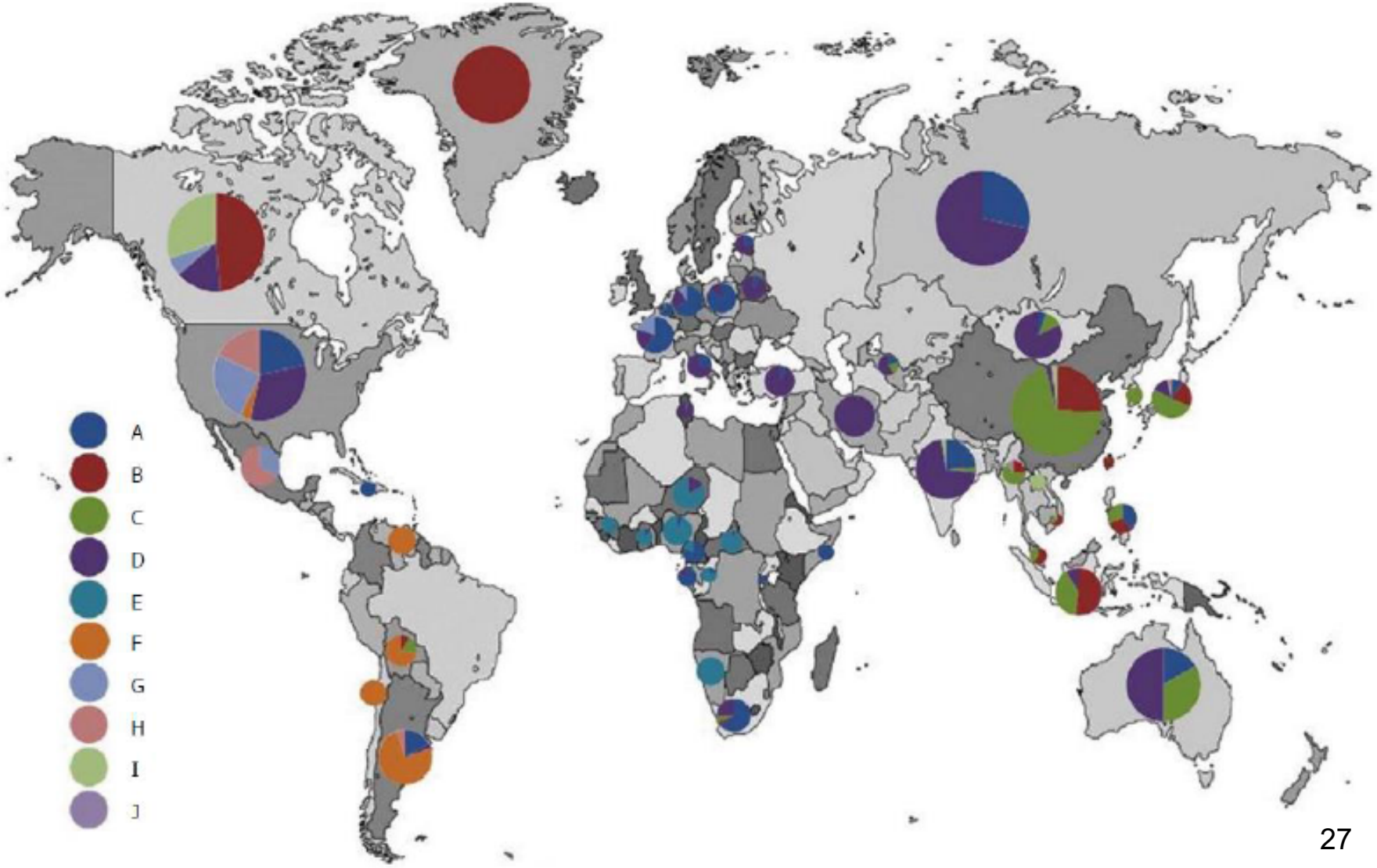
Expert Reviews in Molecular Medicine: http://www-ermm.cbcu.cam.ac.uk

Vírus de hepatite de transmissão parenteral (sexual?)

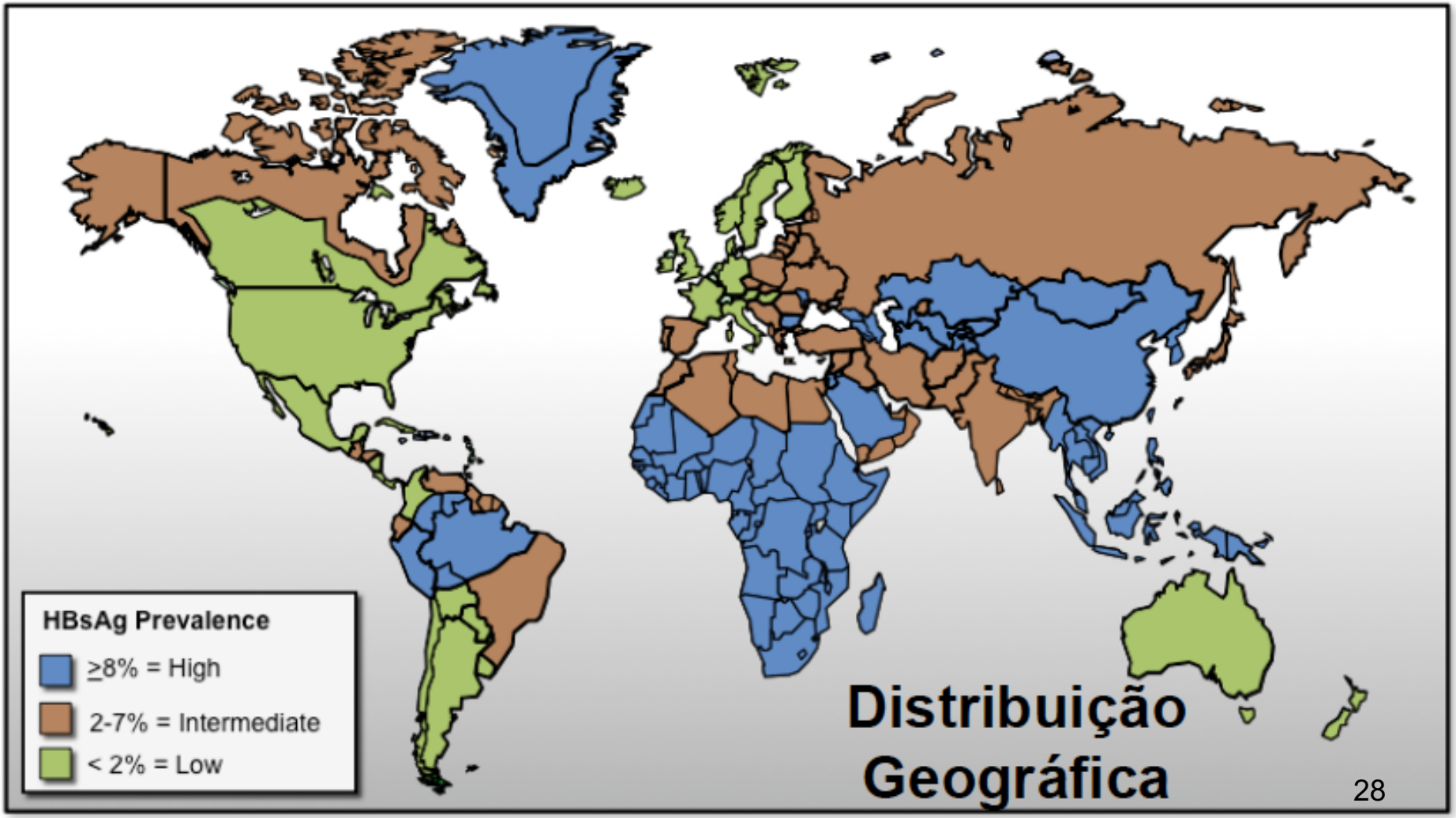
Hepatite B (HBV)

Hepatite B

Dez genótipos

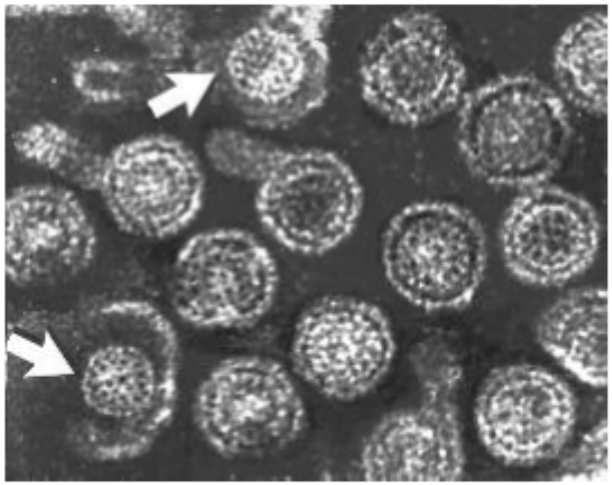


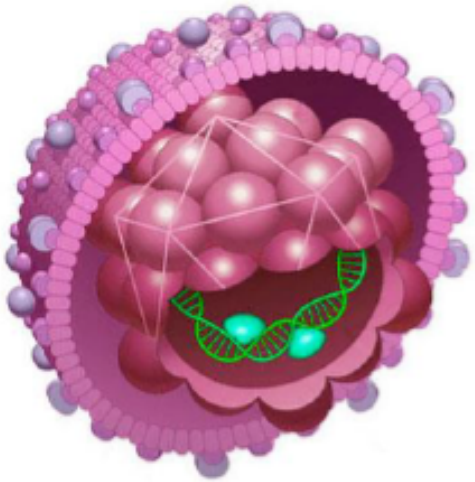
Hepatite B



www.cdc.gov

Hepatite B





Familia : *Hepadnaviridae*
Gênero: *Orthohepadnavírus*

- Pararetrovírus

Vírus pequenos de DNA envelopados (~45 nm)

DNA circular dupla-fita parcial (~3,5 kpb)

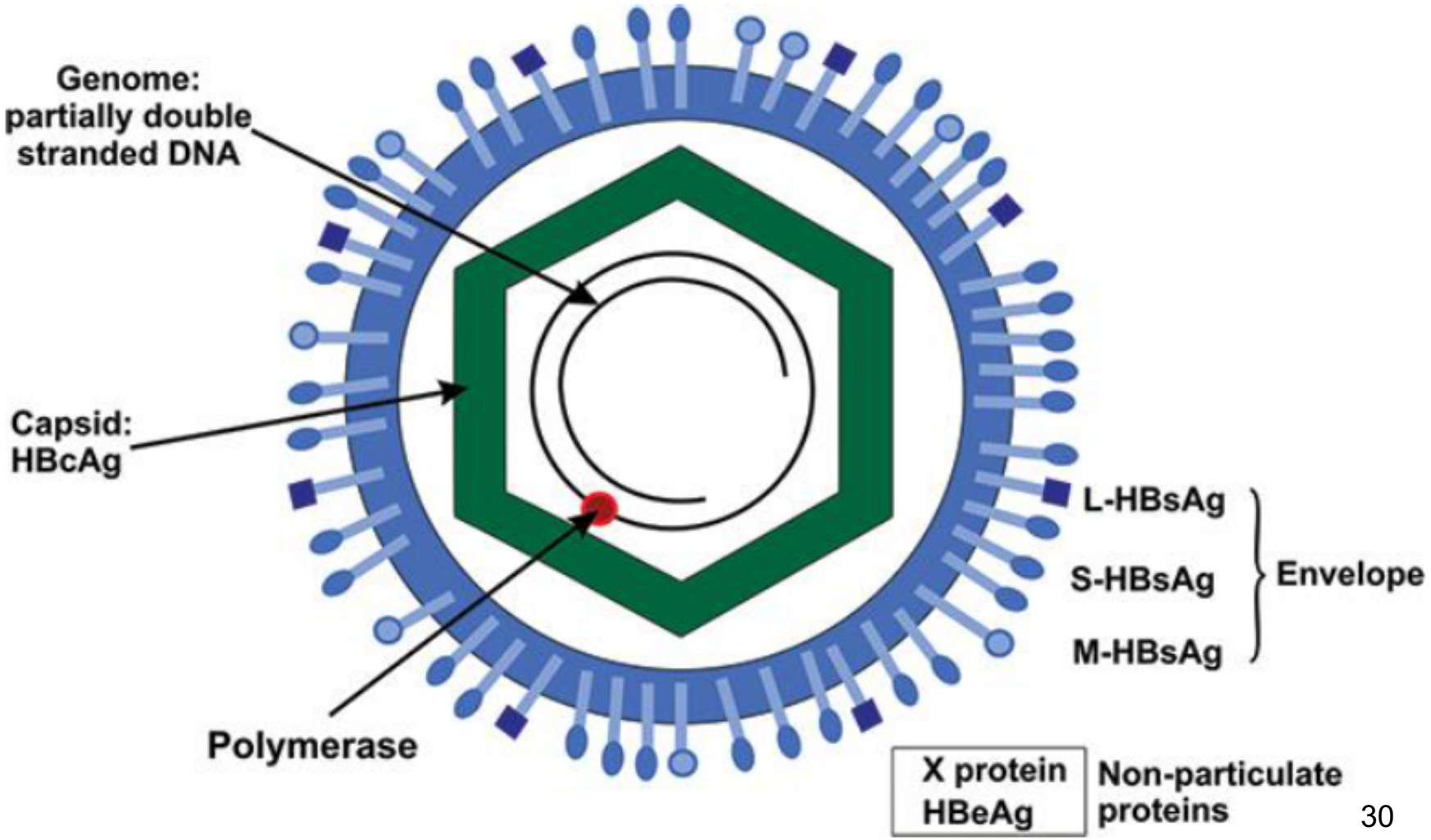
Célula alvo: hepatócitos

Etiologicamente associado com:

- Hepatite
- Cirrose
- Carcinoma hepatocelular

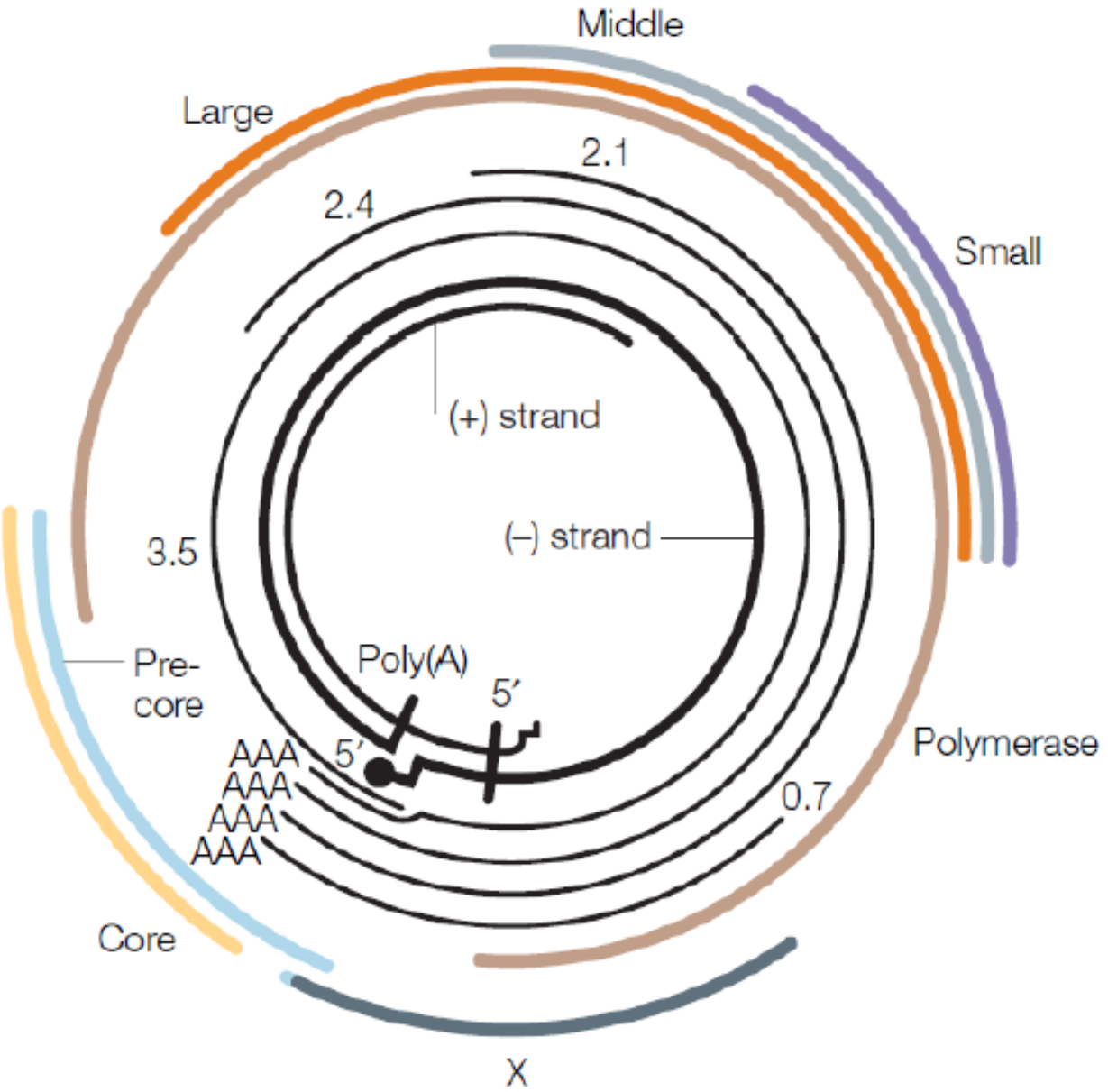
Hepatite B

Antígenos virais



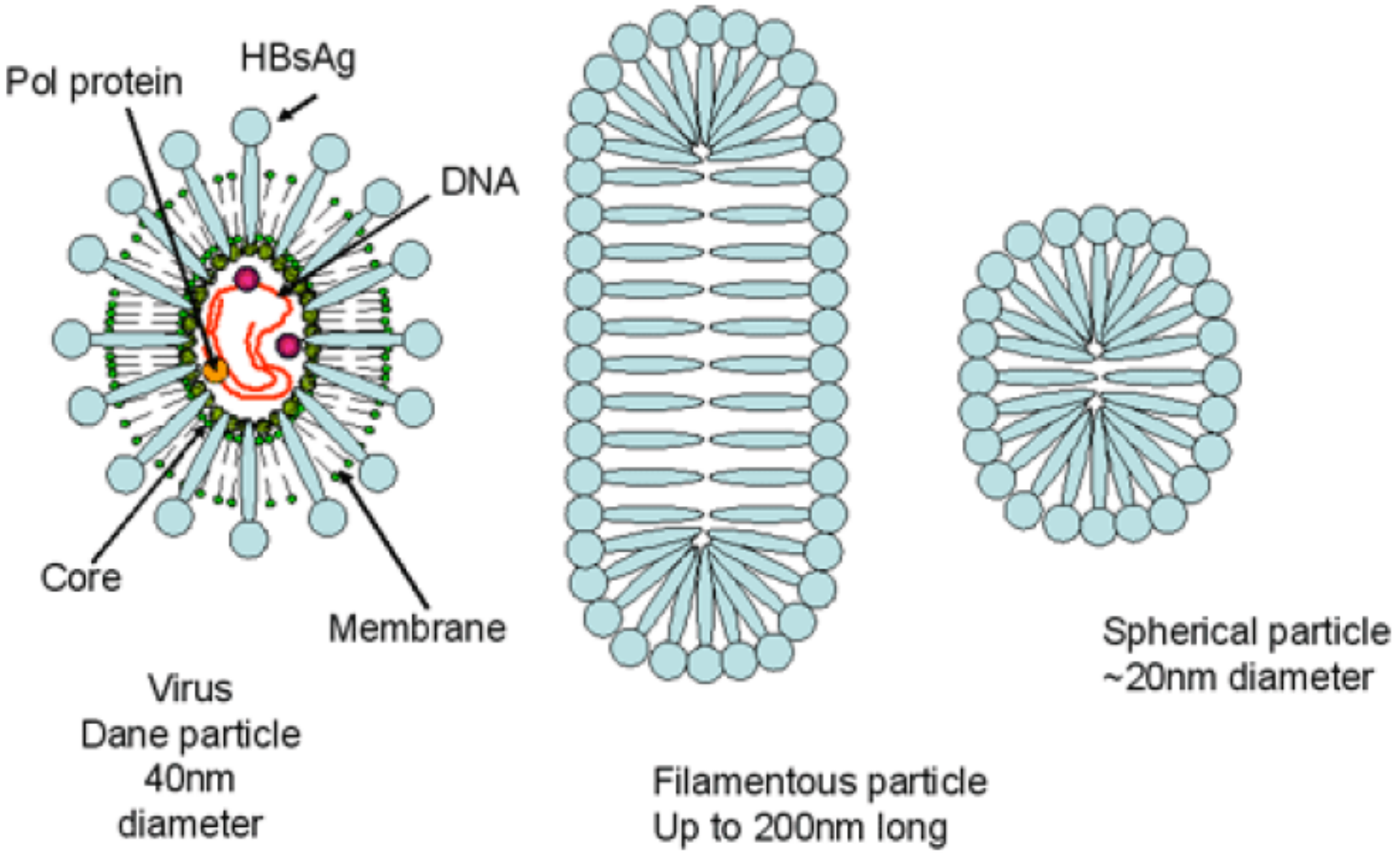
Hepatite B

Organização genômica



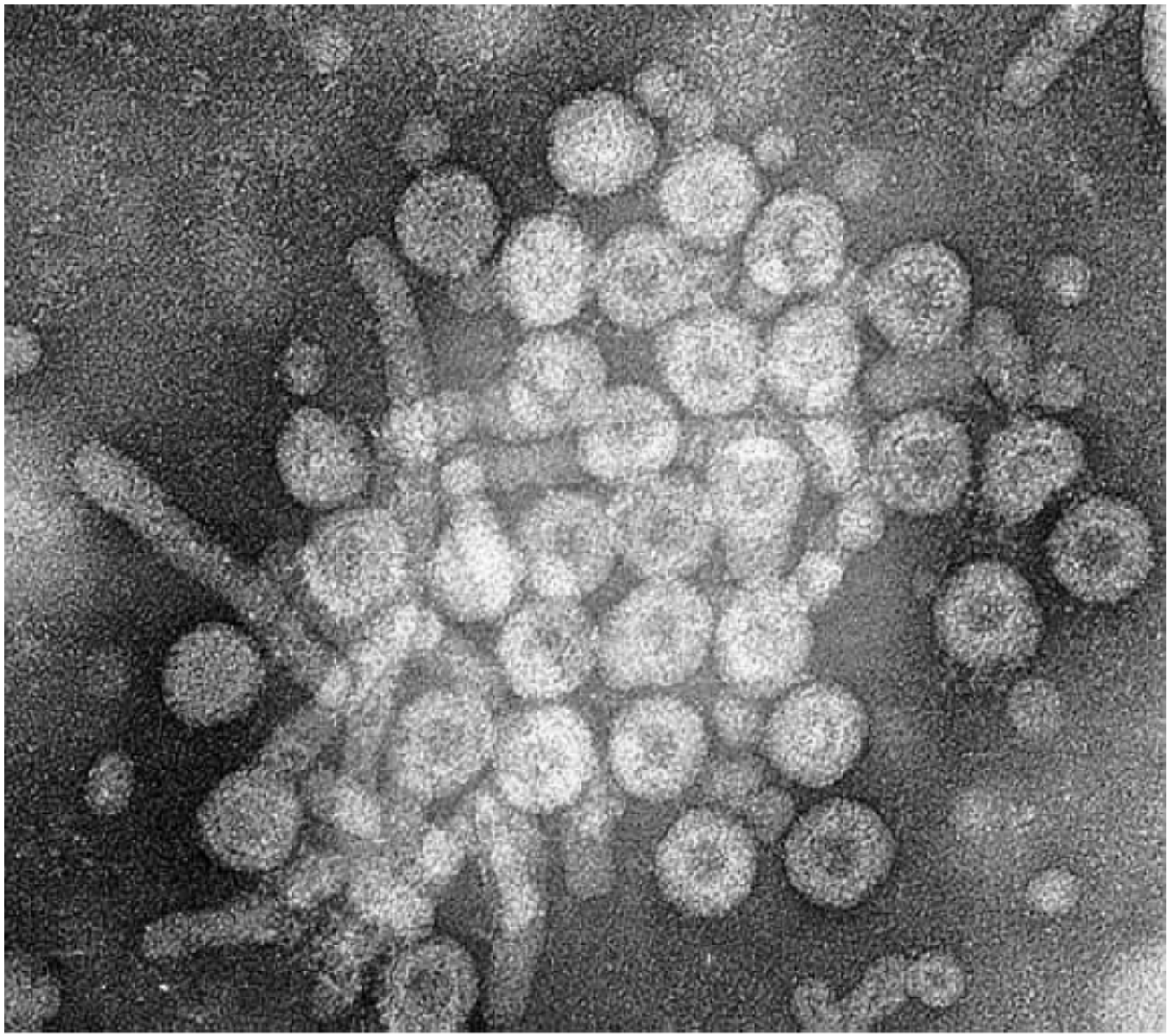
Hepatite B

Antígenos virais



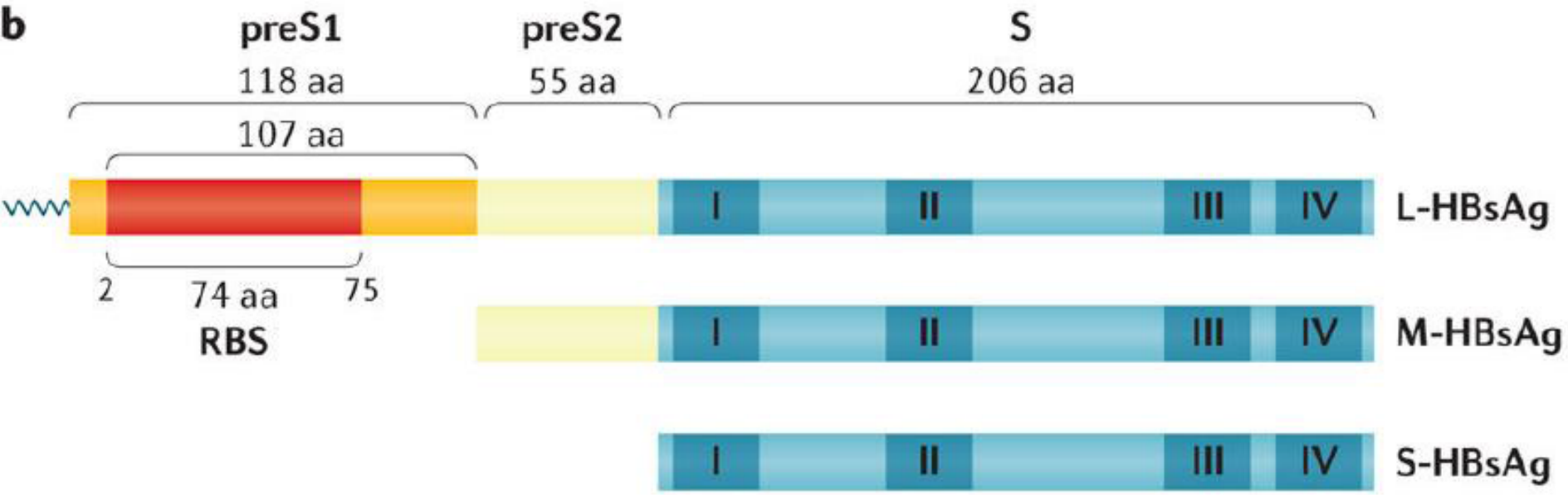
Hepatite B

Antígenos virais



Hepatite B

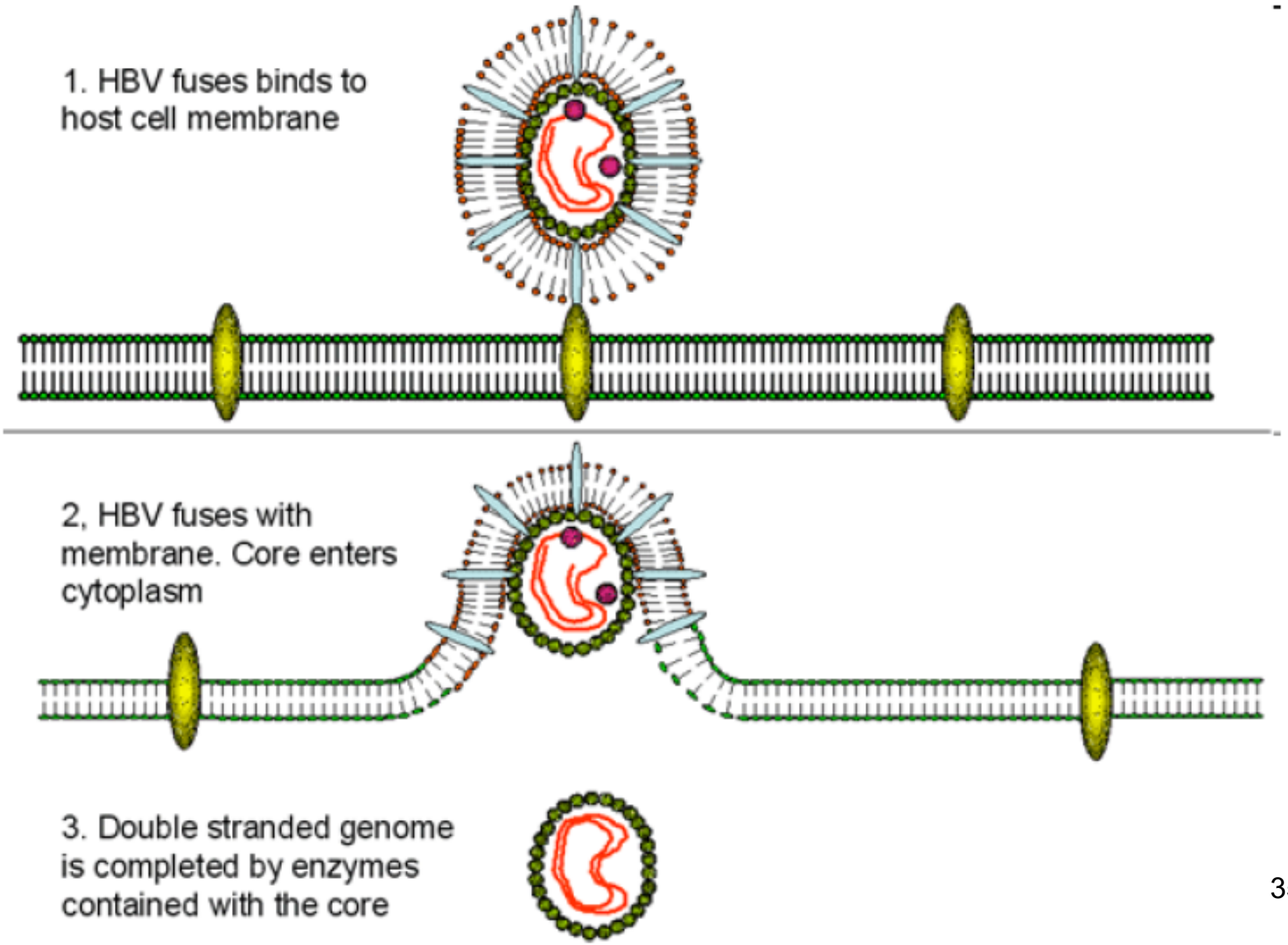
Antígenos virais



doi:10.1038/nrgastro.2016.126

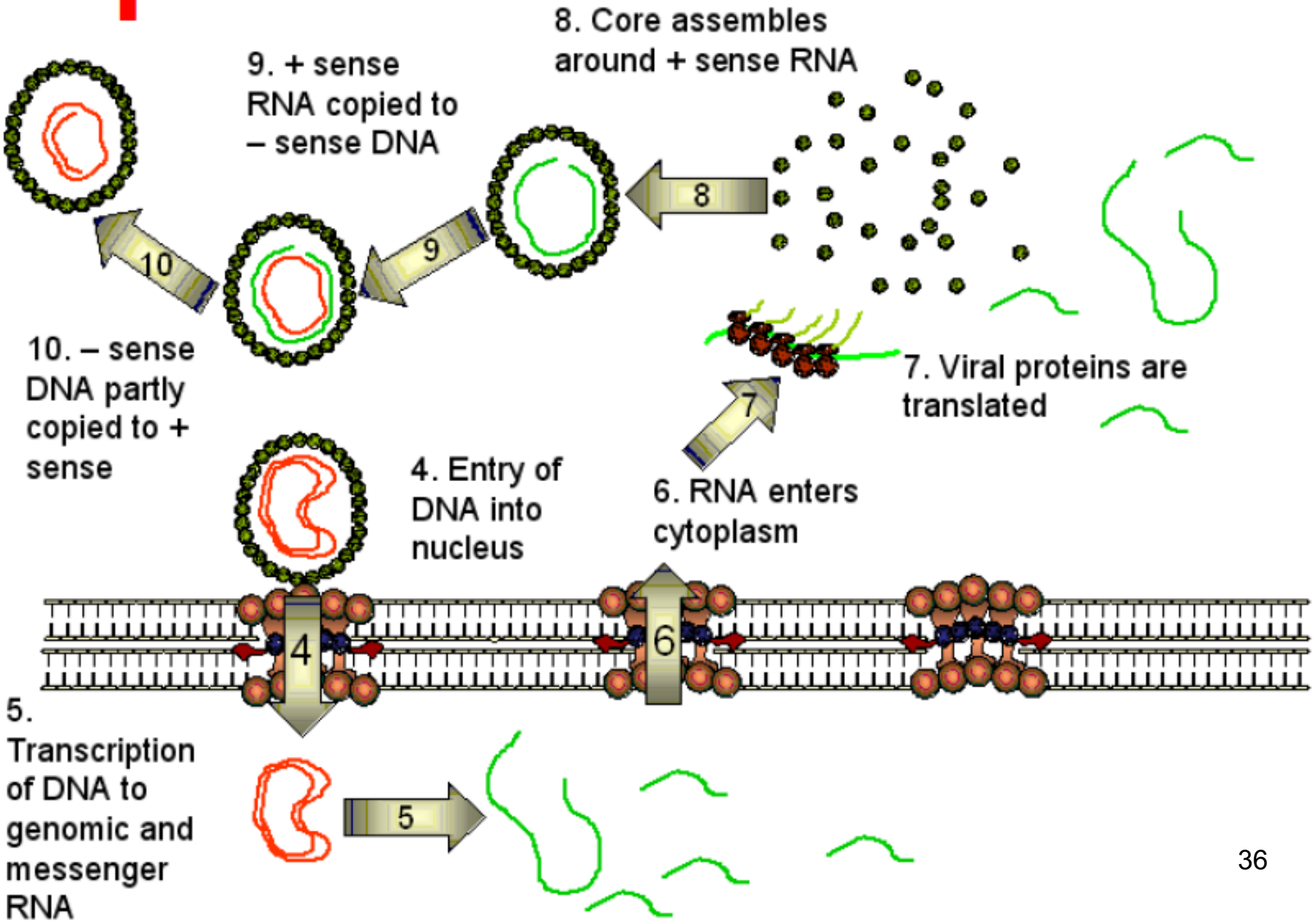
Hepatite B

Ciclo Viral



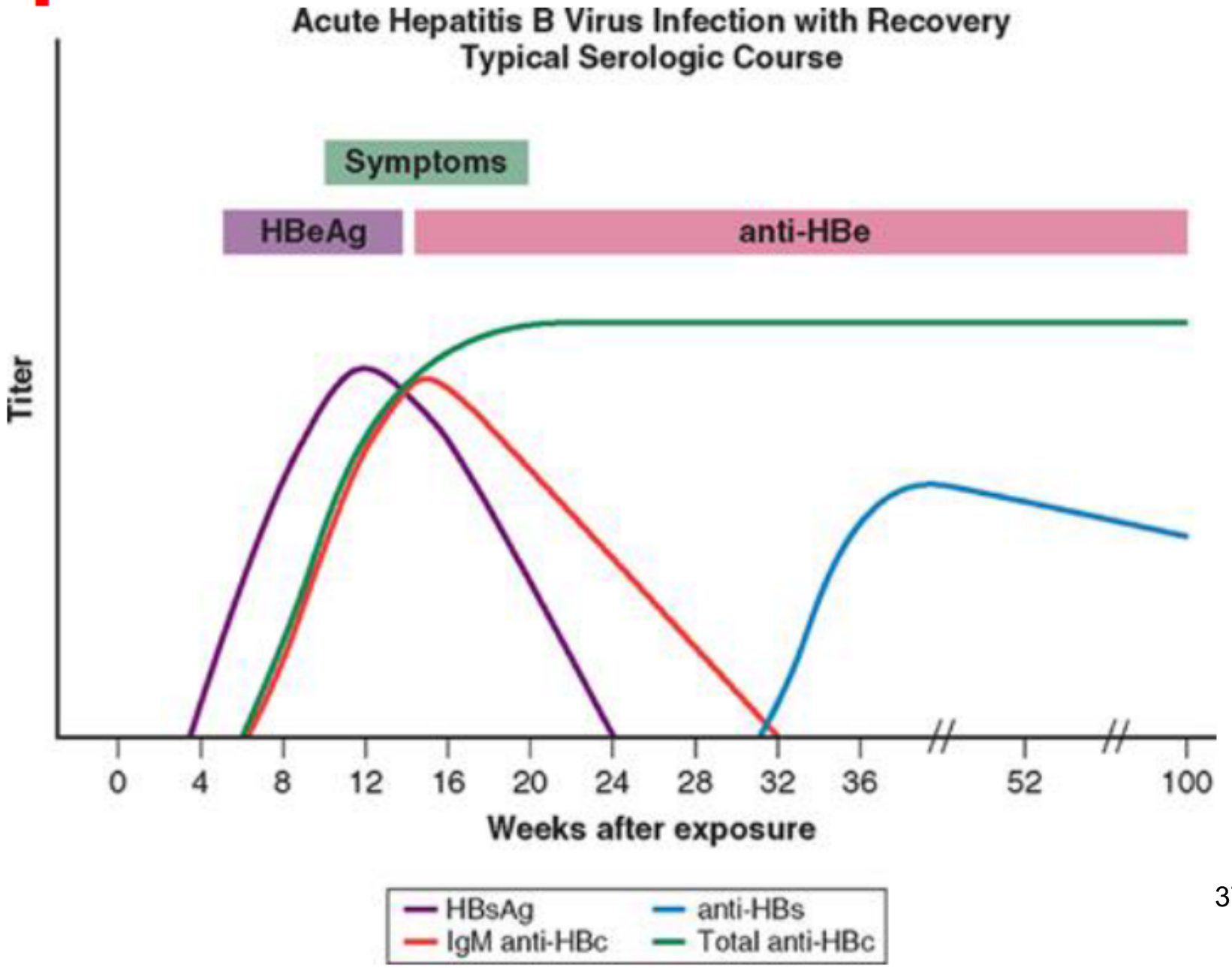
Hepatite B

Ciclo Viral



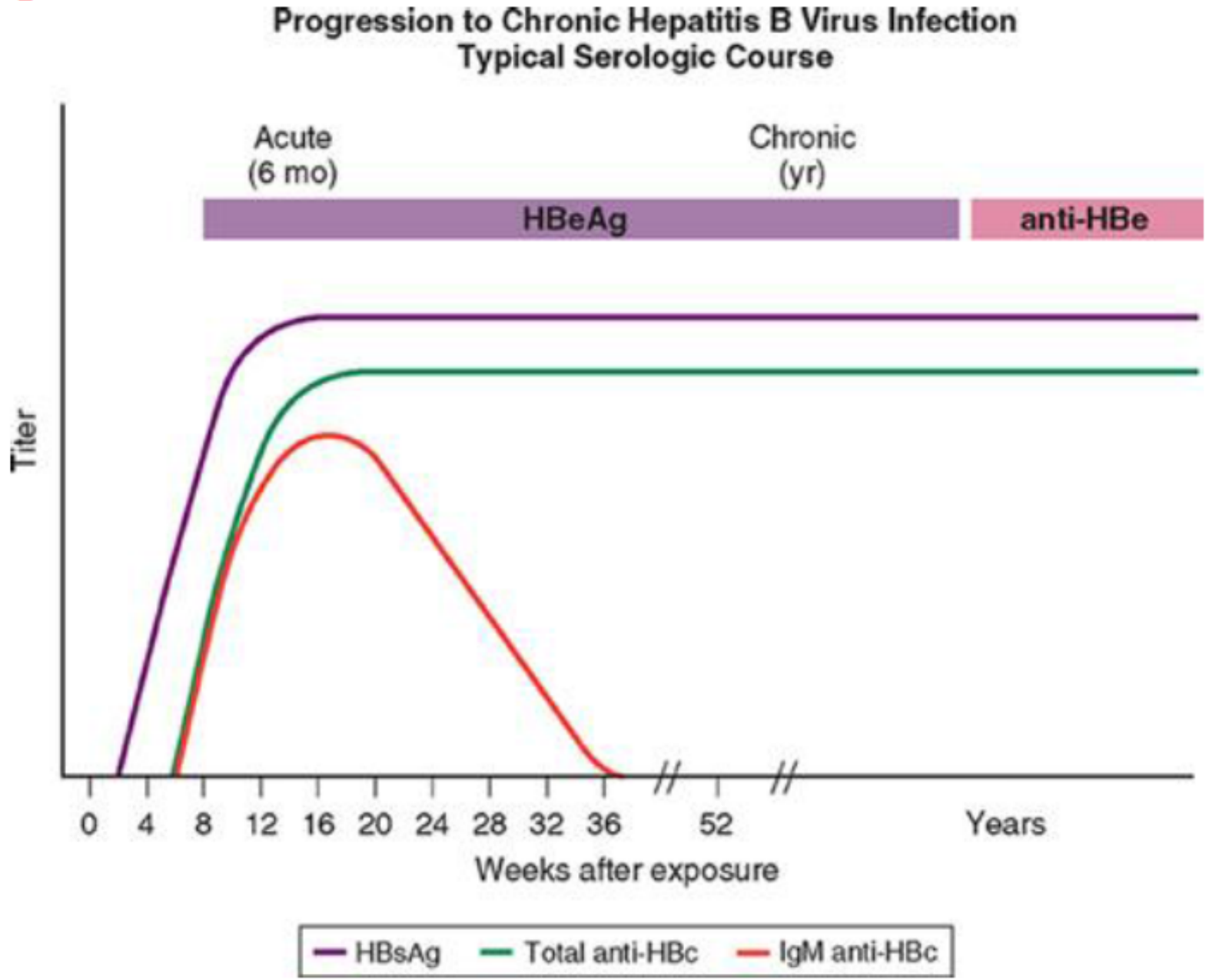
Hepatite B

Antígenos virais



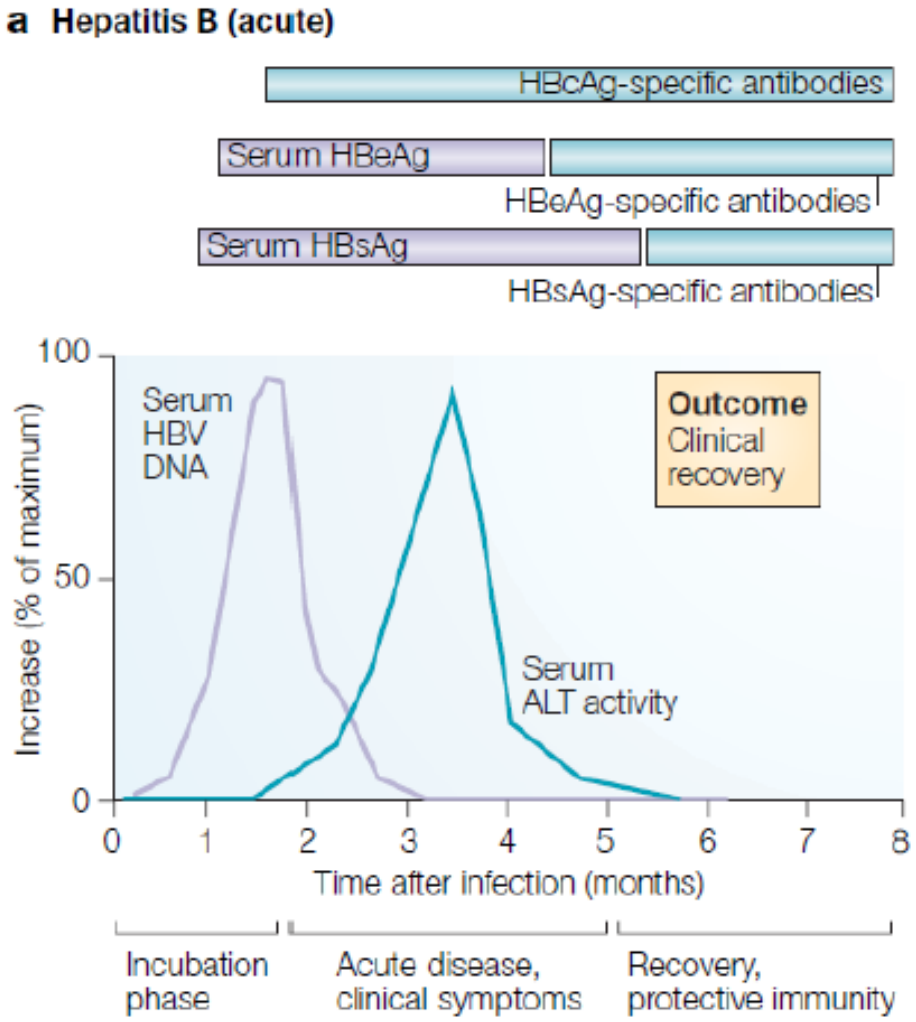
Hepatite B

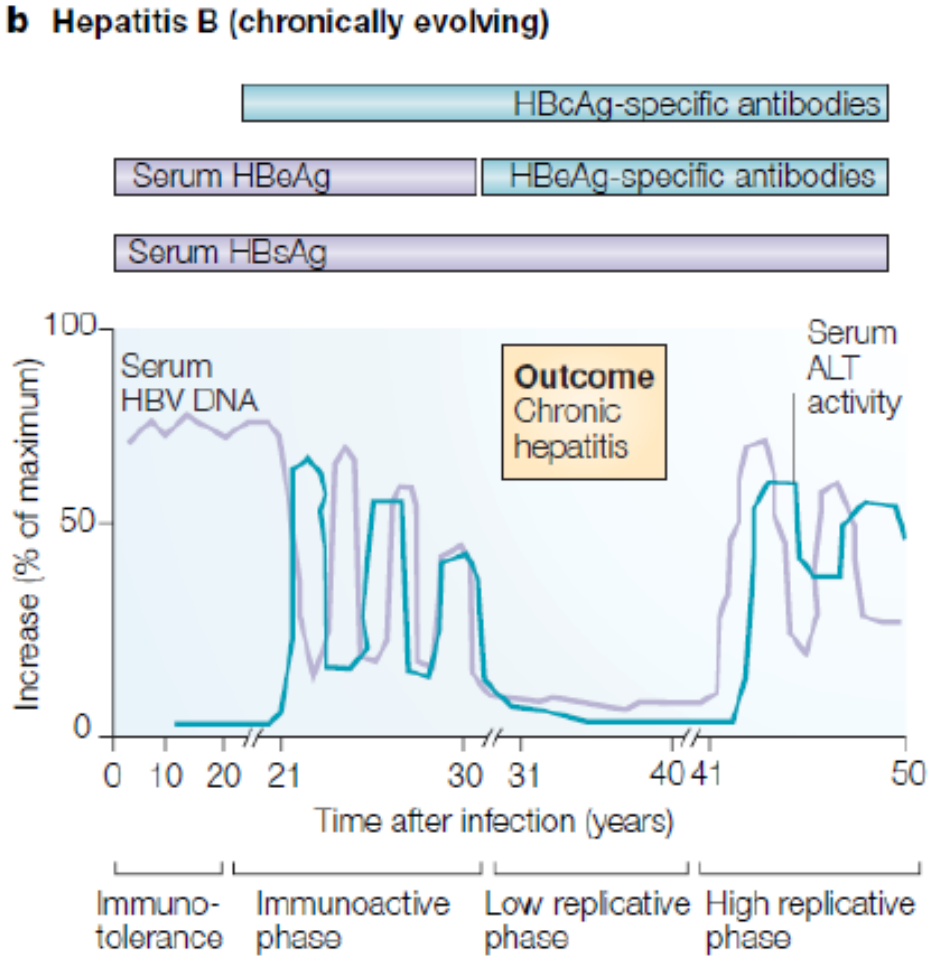
Antígenos virais



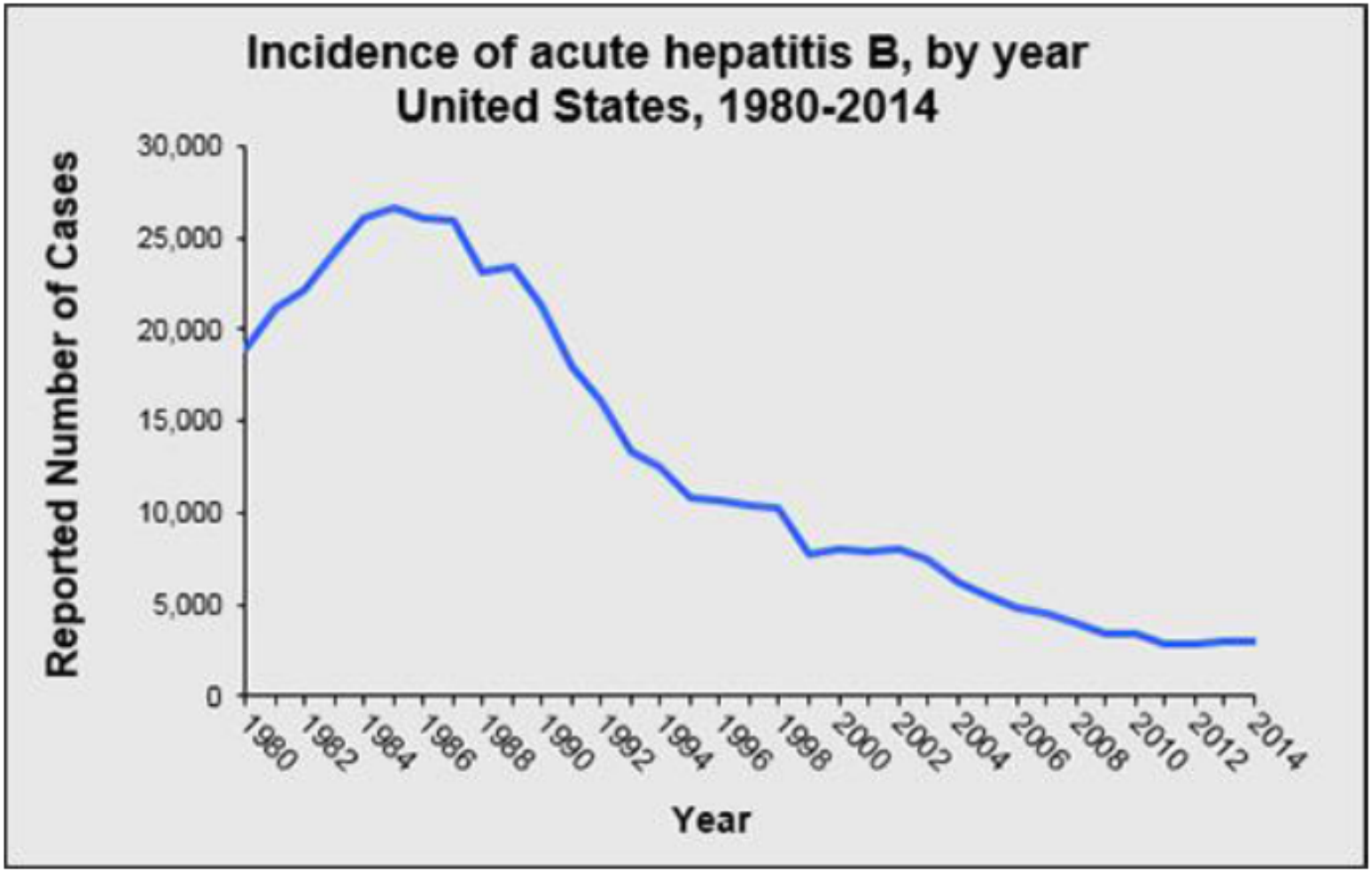
Hepatite B

Antígenos virais



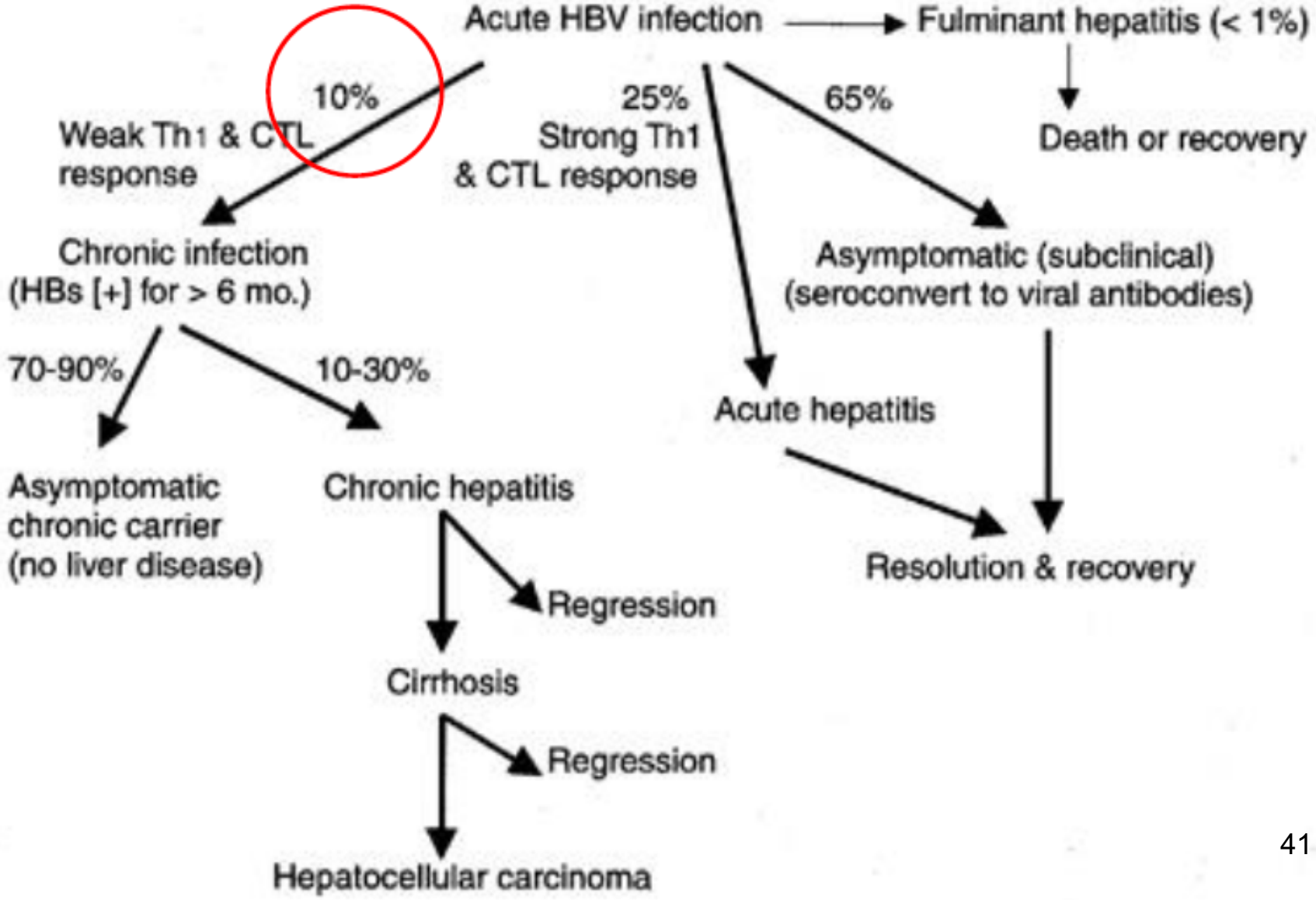


Hepatite B



www.cdc.gov/hepatitis/hbv/hbvfaq.htm#a3

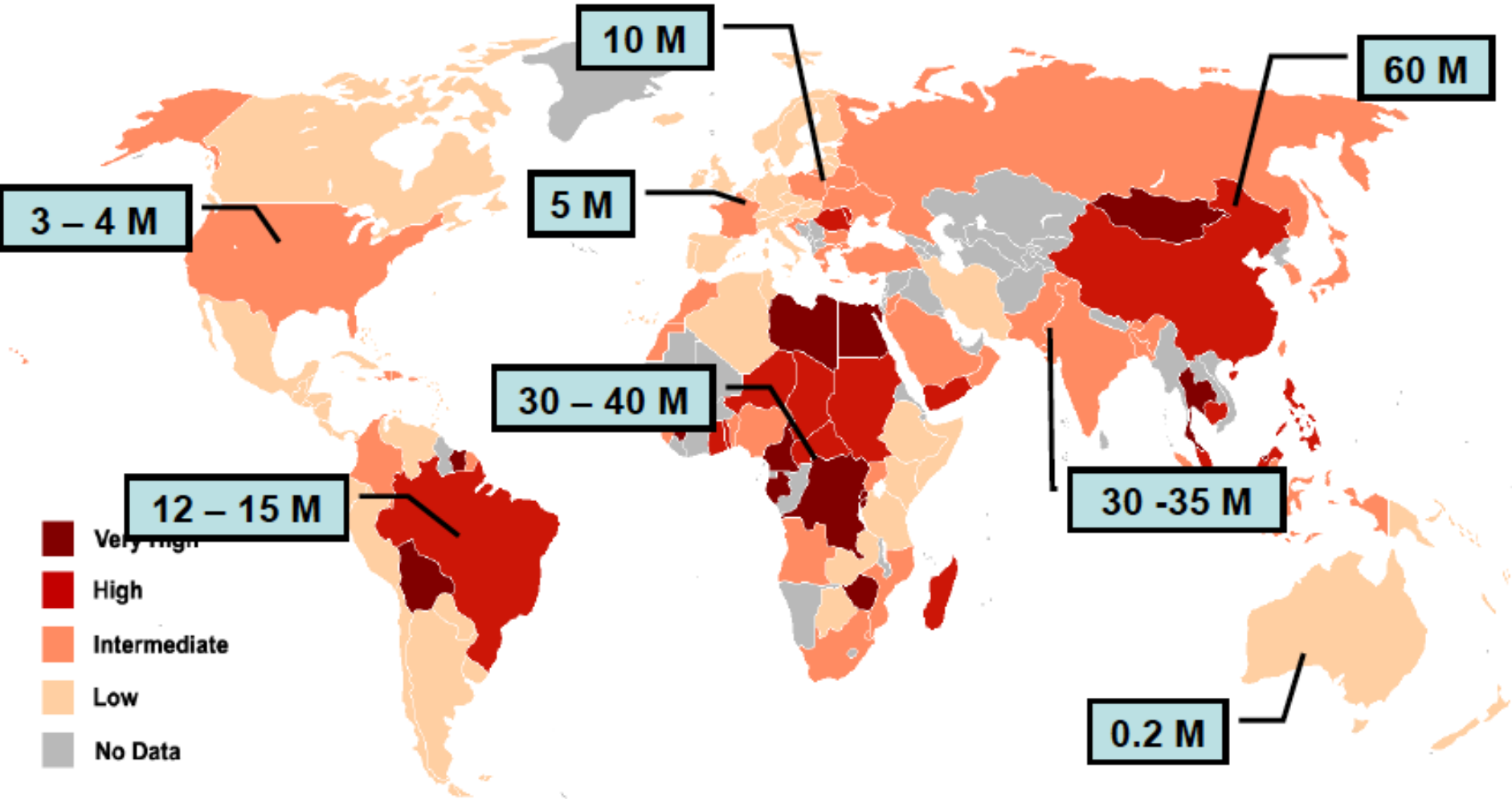
Hepatite B


Acute HBV infection
Fulminant hepatitis (< 1%)
10%
Weak Th1 & CTL response
25%
Strong Th1 & CTL response
65%
Death or recovery
Chronic infection (HBs [+] for > 6 mo.)
Asymptomatic (subclinical) (seroconvert to viral antibodies)
70-90%
10-30%
Acute hepatitis
Asymptomatic chronic carrier (no liver disease)
Chronic hepatitis
Resolution & recovery
Regression
Cirrhosis
Regression
Hepatocellular carcinoma

Hepatite C (HCV)

Hepatite C

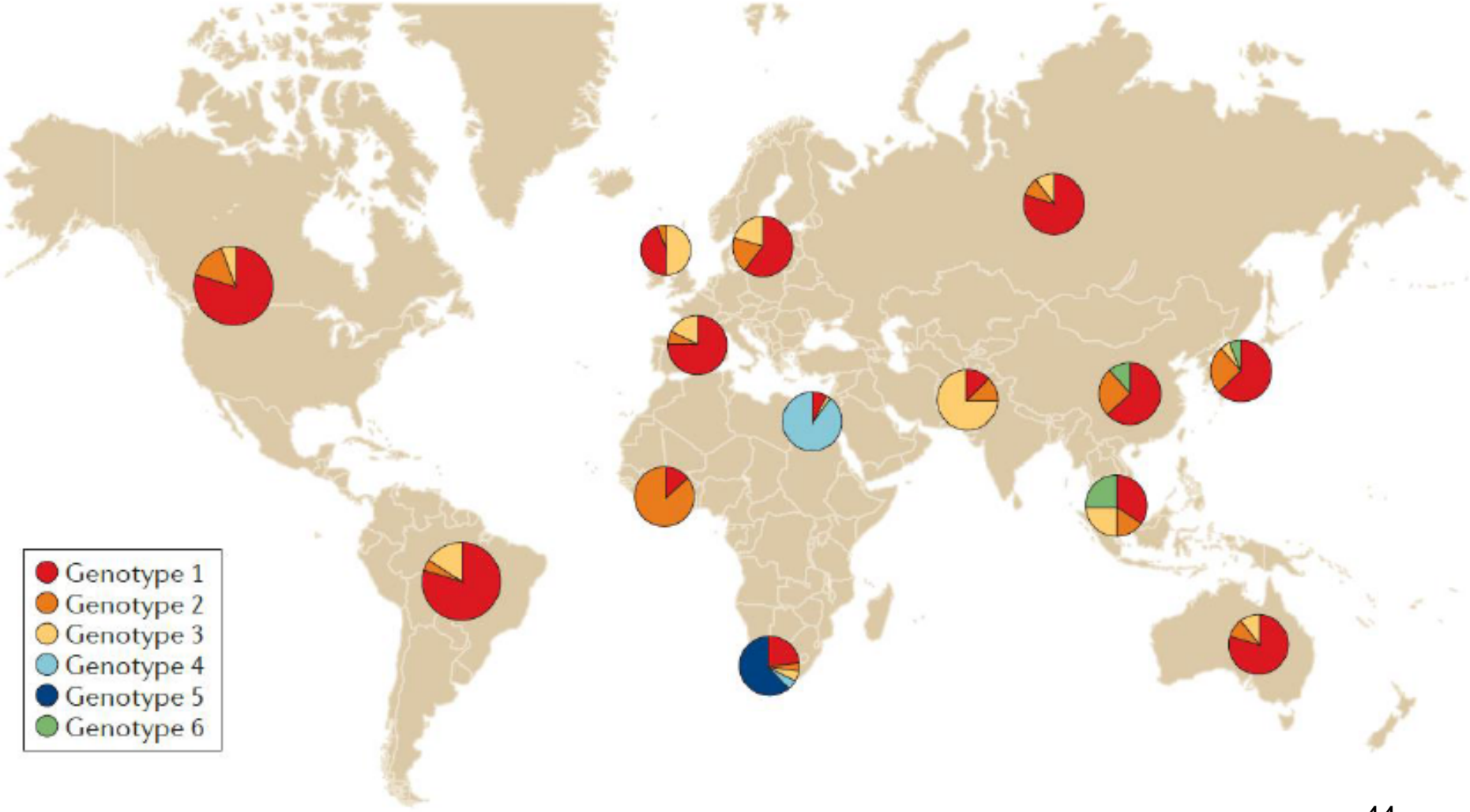
170 – 200 milhões de portadores no Mundo todo



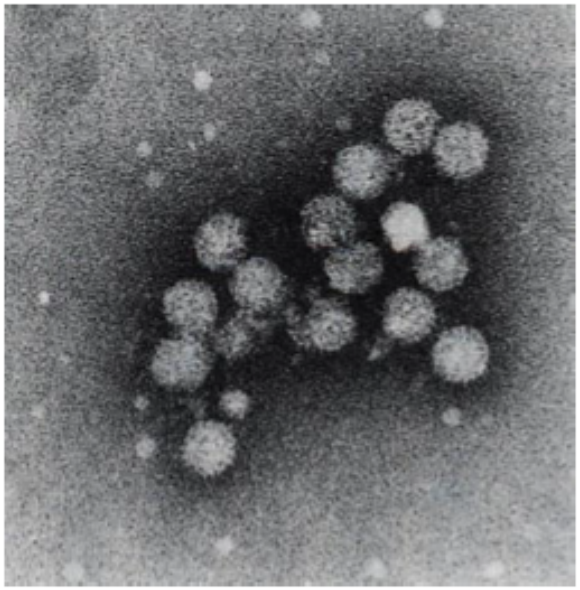
www.cdc.gov // www.who.int 2007

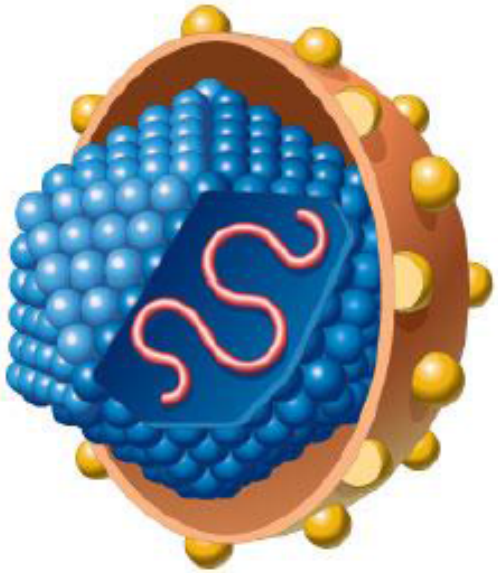
Hepatite C

170 – 200 milhões de portadores no Mundo todo



Hepatite C





Familia : *Flaviviridae*
Gênero: *Hepacivírus*

Vírus pequenos de RNA envelopados (~45 nm)

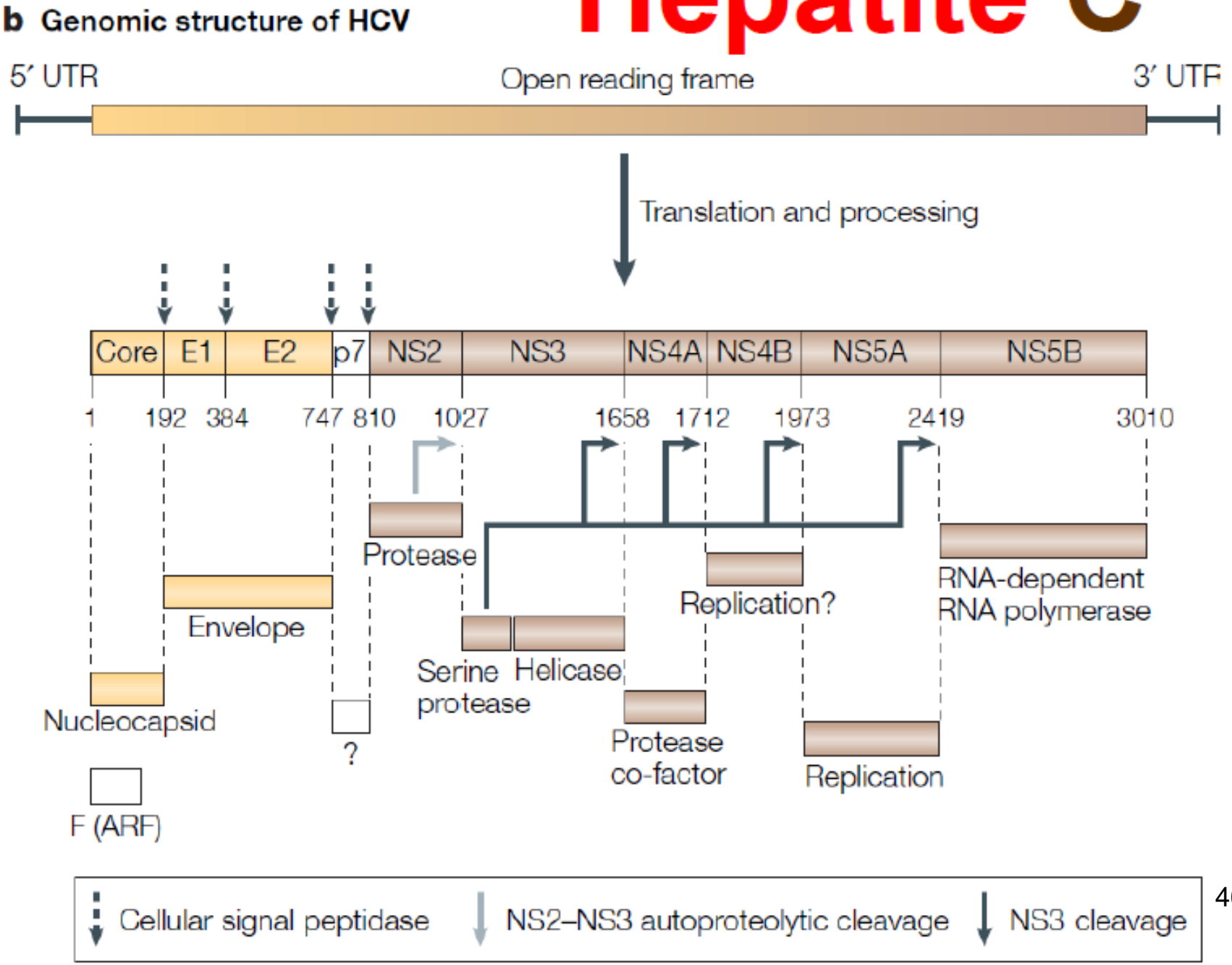
RNA linear simples-fita (~9,4 kpb)

Célular alvo: hepatócitos

Etiologicamente associado com:

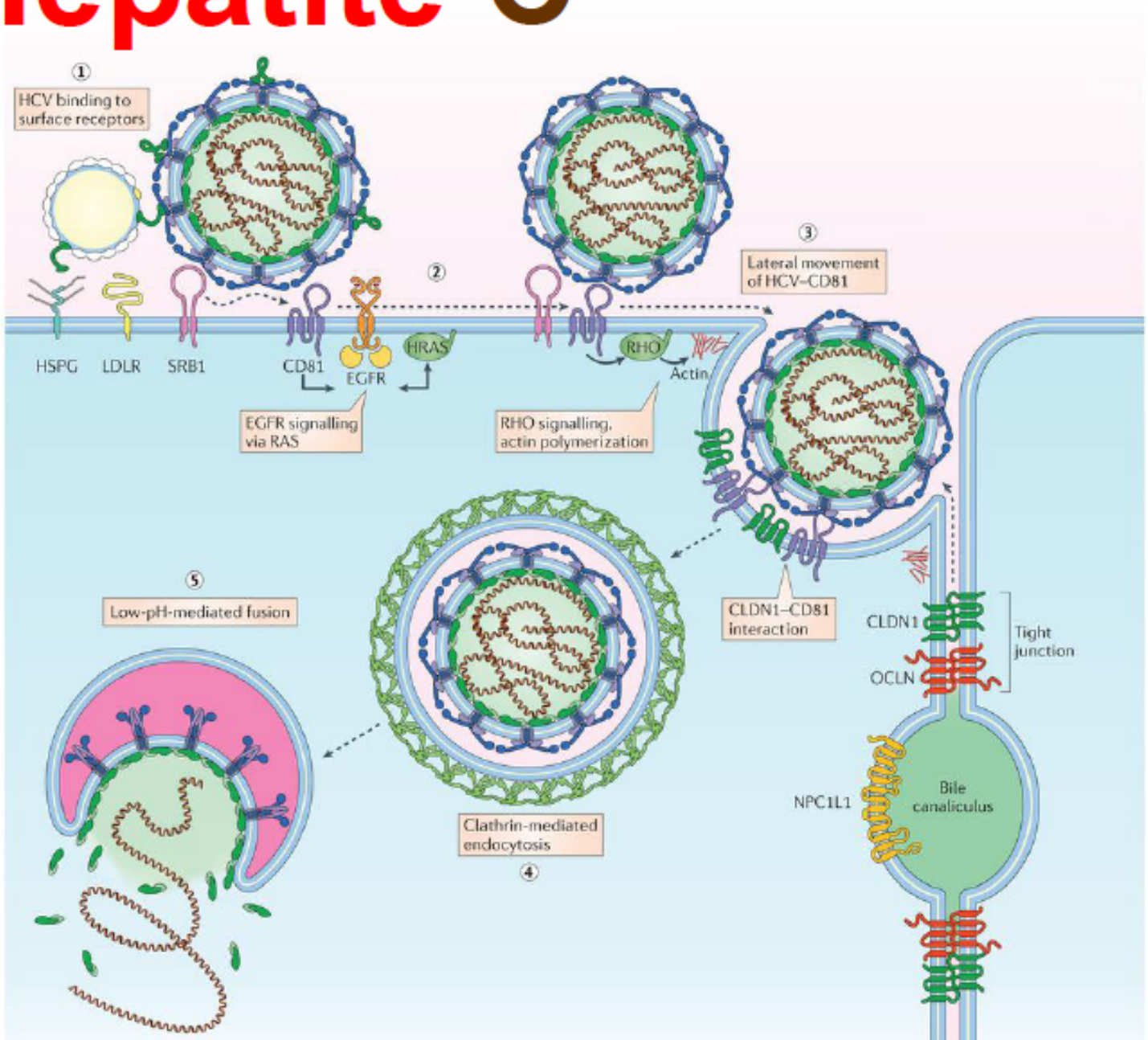
- Hepatite
- Cirrose
- Carcinoma hepatocelular

Hepatite C

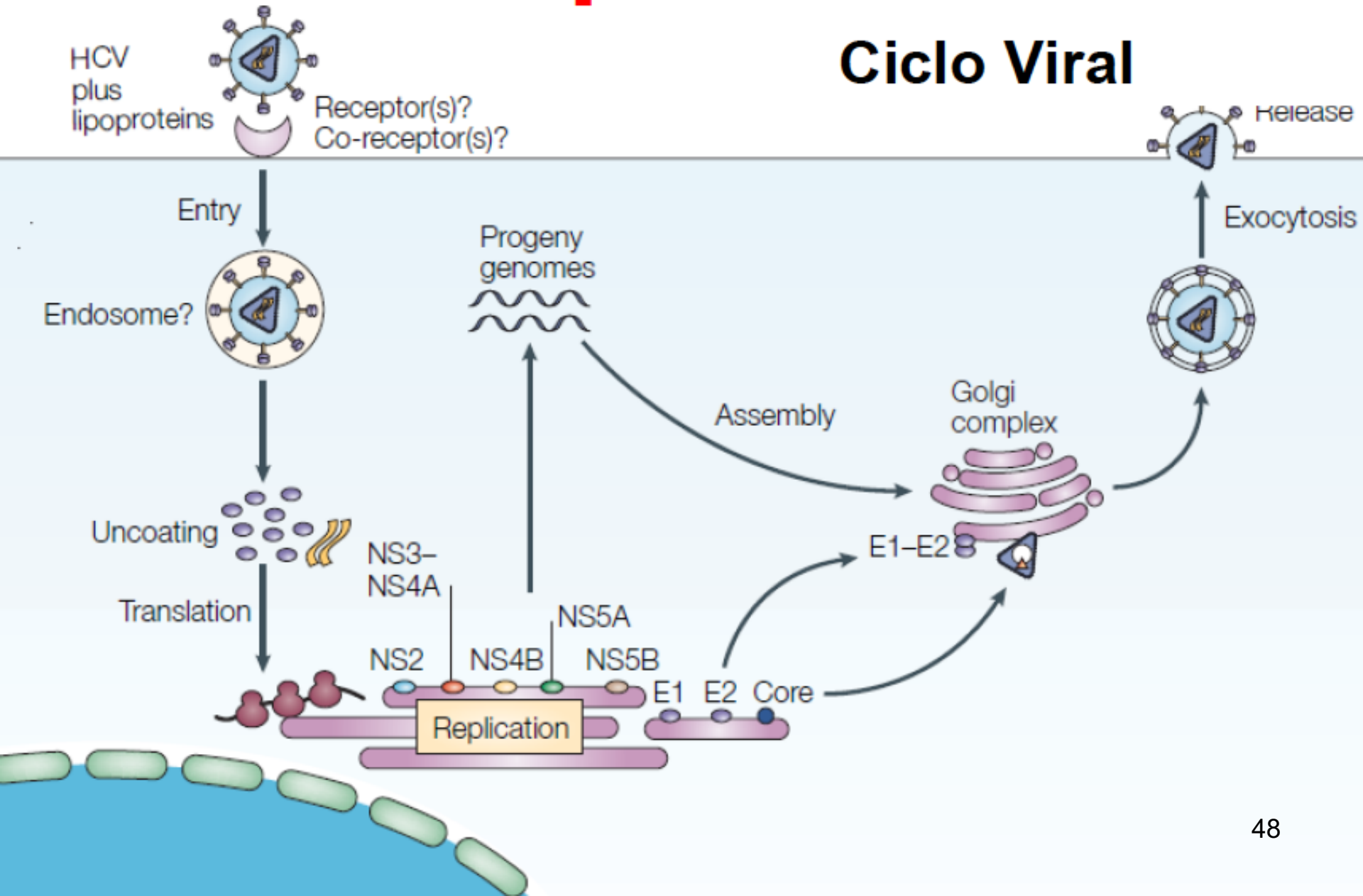

b Genomic structure of HCV
5′ UTR
Open reading frame
3′ UTR
Translation and processing
Core
E1
E2
p7
NS2
NS3
NS4A
NS4B
NS5A
NS5B
1
192
384
747
810
1027
1658
1712
1973
2419
3010
Protease
Envelope
Replication?
RNA-dependent
RNA polymerase
Serine
protease
Helicase
Nucleocapsid
?
Protease
co-factor
Replication
F (ARF)
Cellular signal peptidase
NS2–NS3 autoproteolytic cleavage
NS3 cleavage

Hepatite C

Ciclo Viral

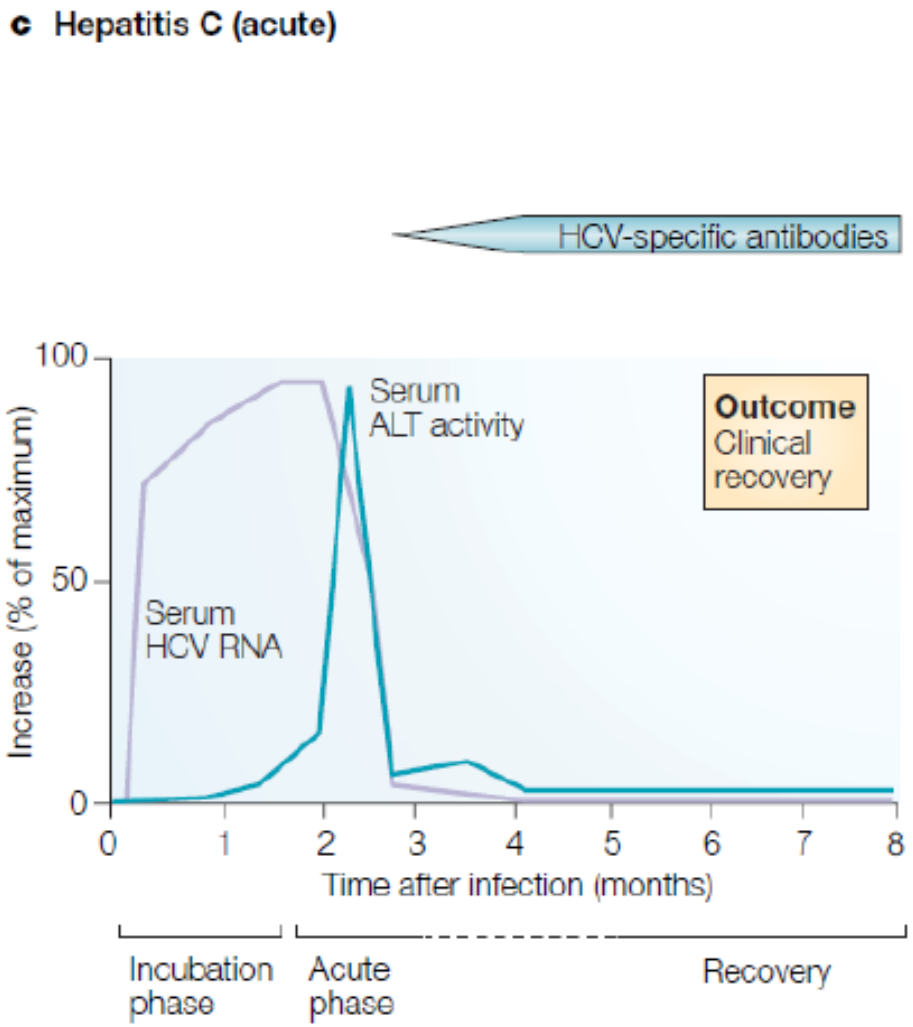


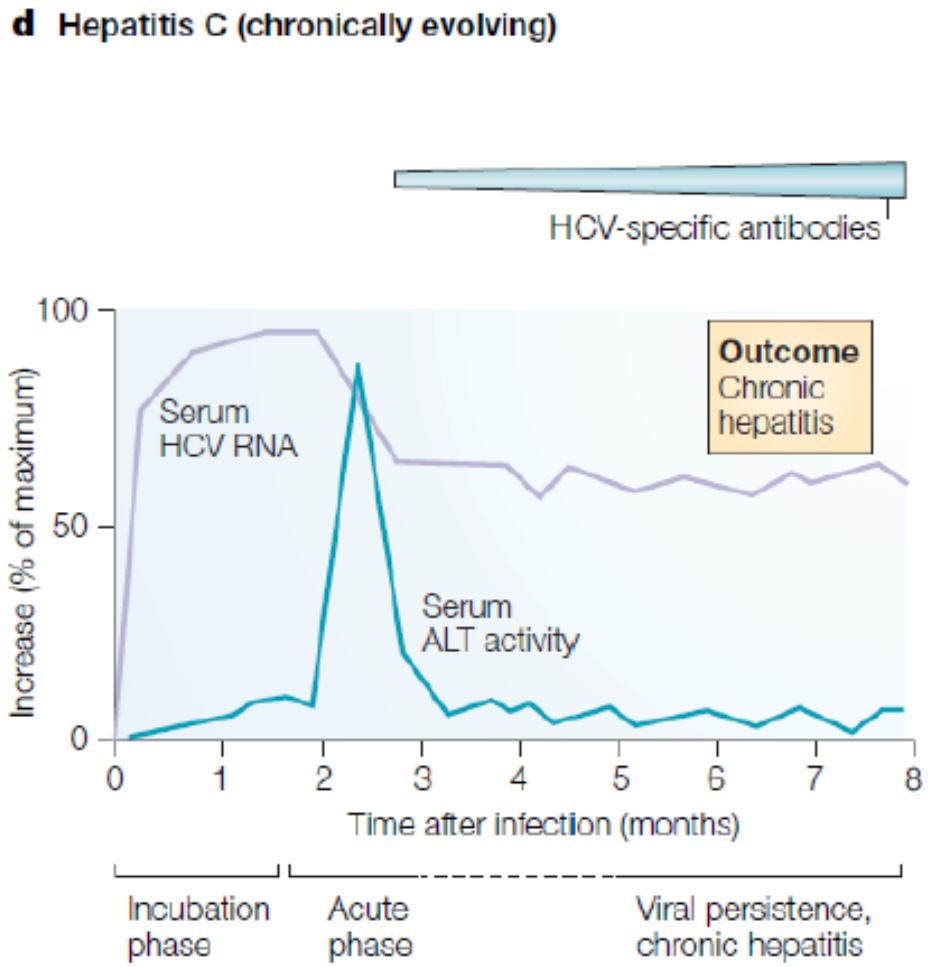
Hepatite C


Ciclo Viral
HCV
plus
lipoproteins
Receptor(s)?
Co-receptor(s)?
Entry
Endosome?
Uncoating
Translation
NS3–
NS4A
NS2
NS4B
NS5A
NS5B
E1
E2
Core
Replication
Progeny
genomes
Assembly
Golgi
complex
E1–E2
Exocytosis
Release

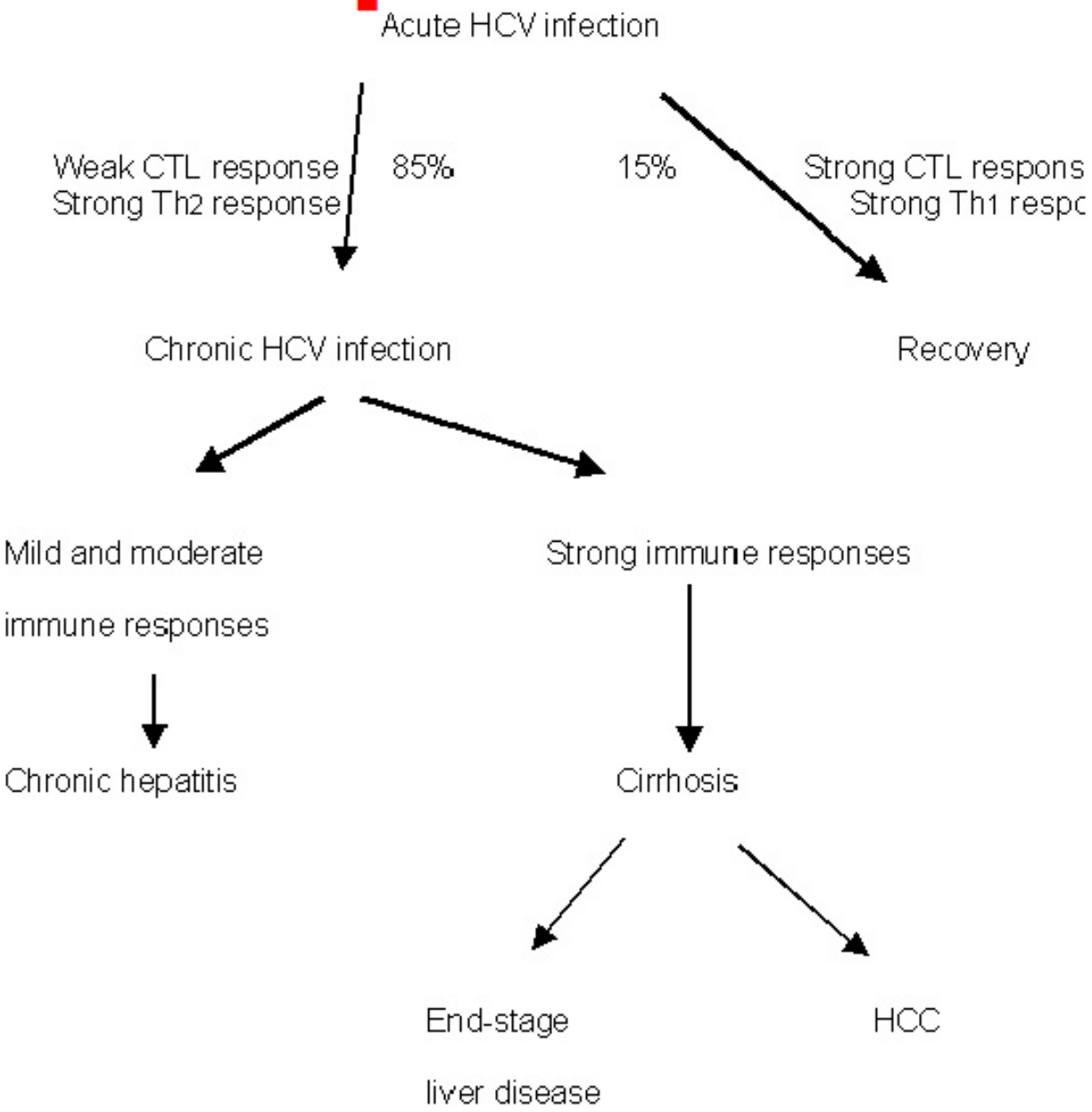
Hepatite C

Antígenos virais



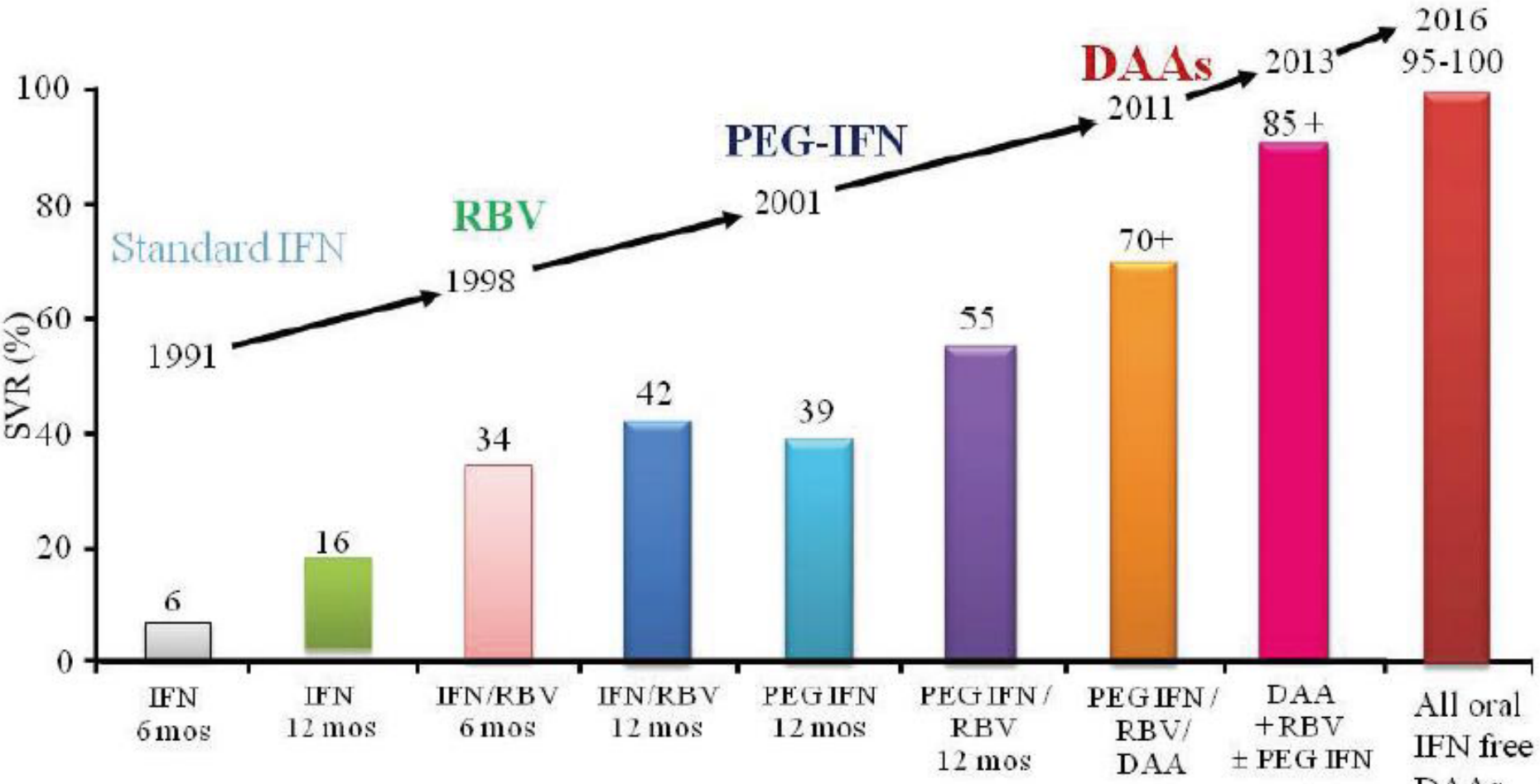


Hepatite C


Acute HCV infection
Weak CTL response
Strong Th2 response
85%
15%
Strong CTL respons
Strong Th1 respc
Chronic HCV infection
Recovery
Mild and moderate
immune responses
Strong immune responses
Chronic hepatitis
Cirrhosis
End-stage
liver disease
HCC

Hepatite C

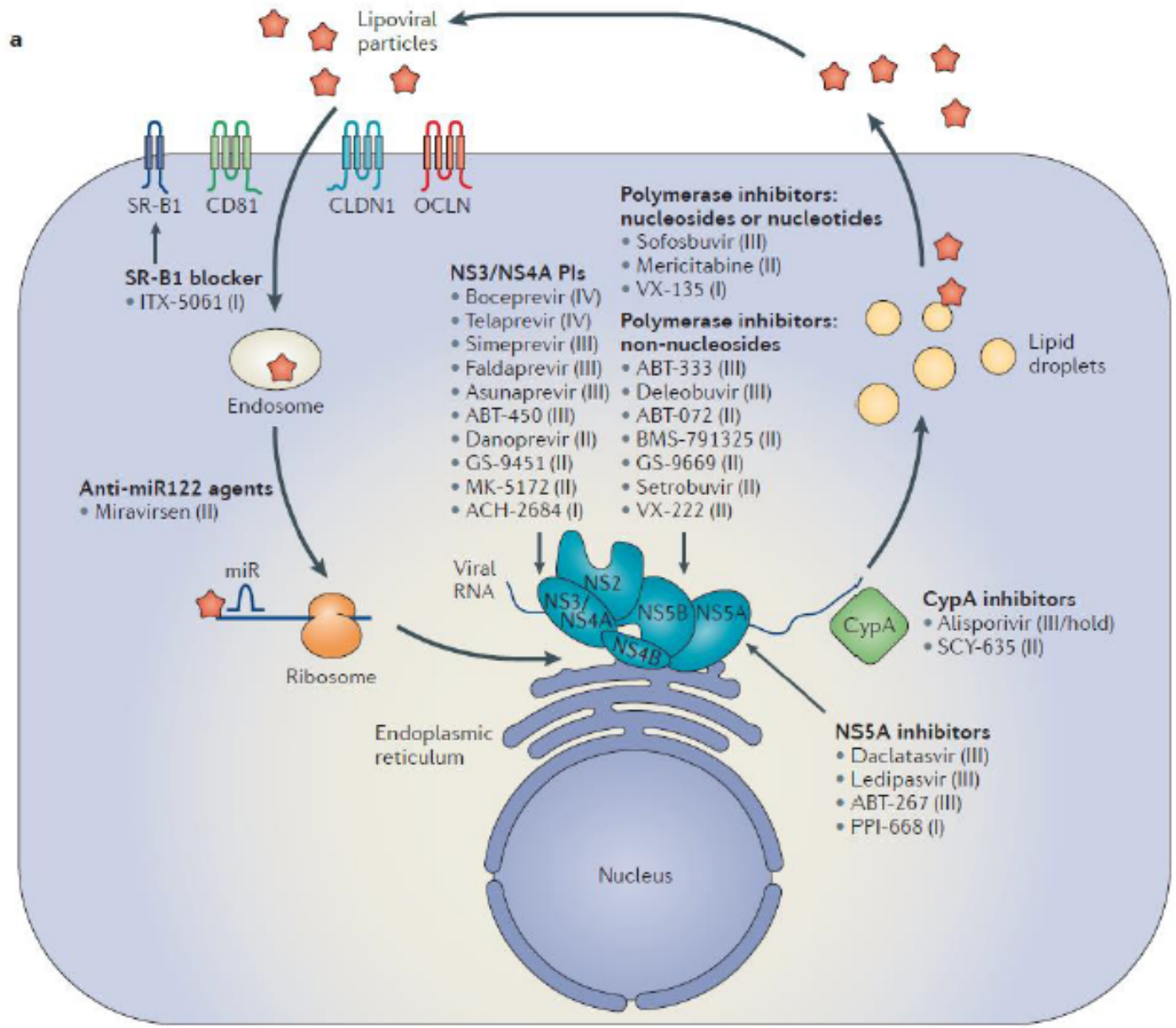
Evolução das terapias contra HCV

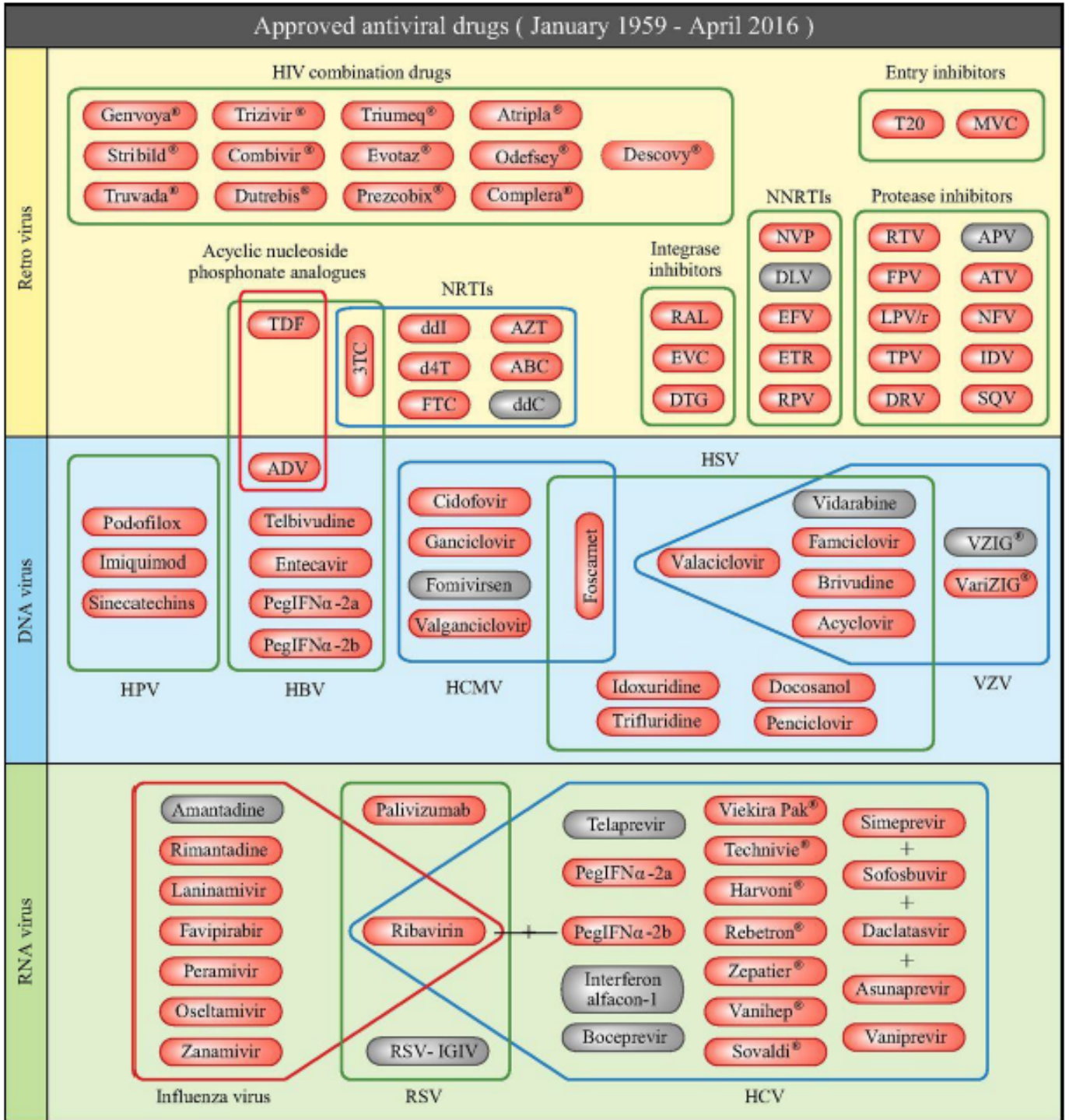


sustained virologic response (SVR) – RNA de HCV não detectável após 24 semanas de finalizado o tratamento.

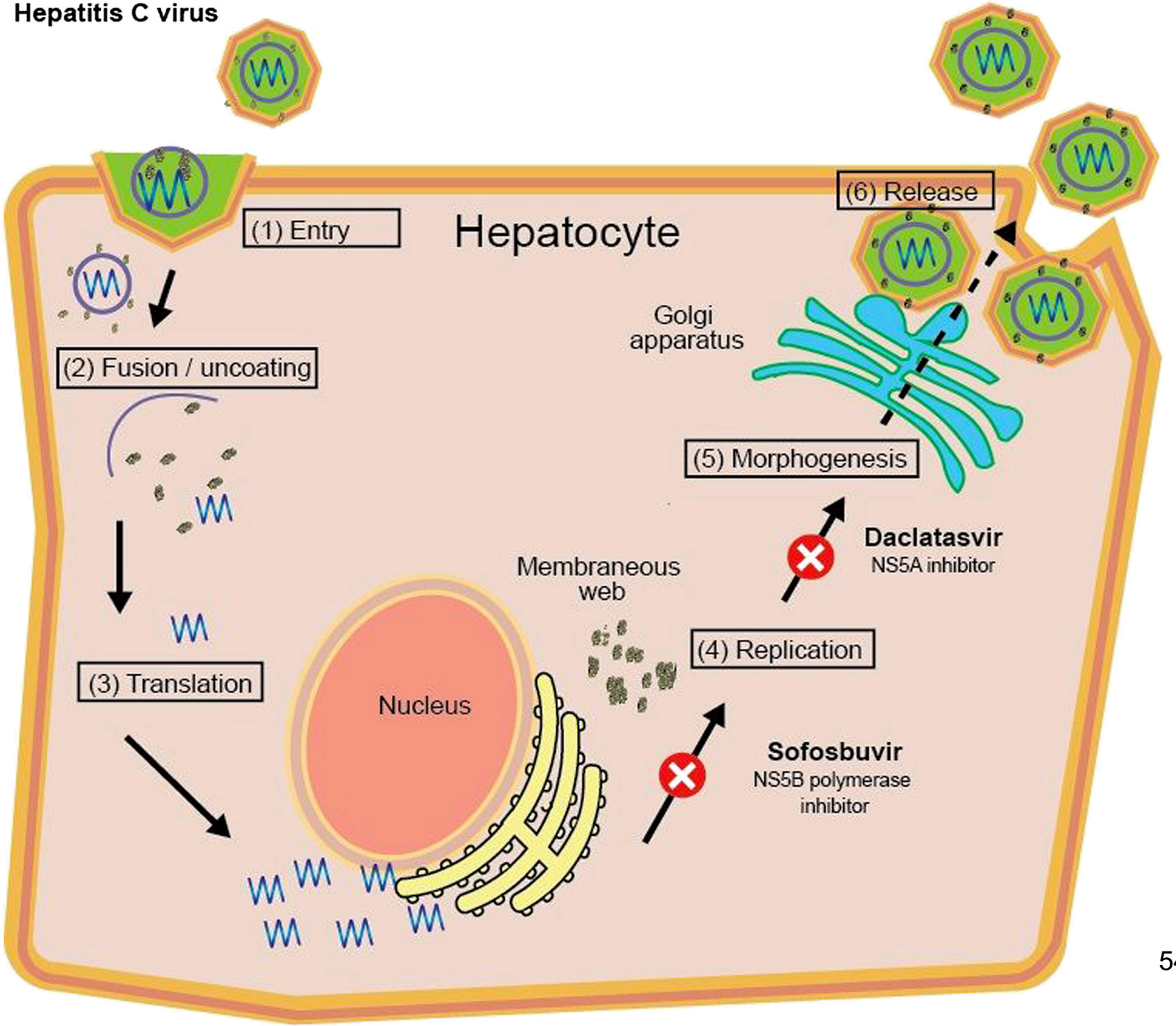
dx.doi.org/10.5772/66719

Hepatite C Profilaxia

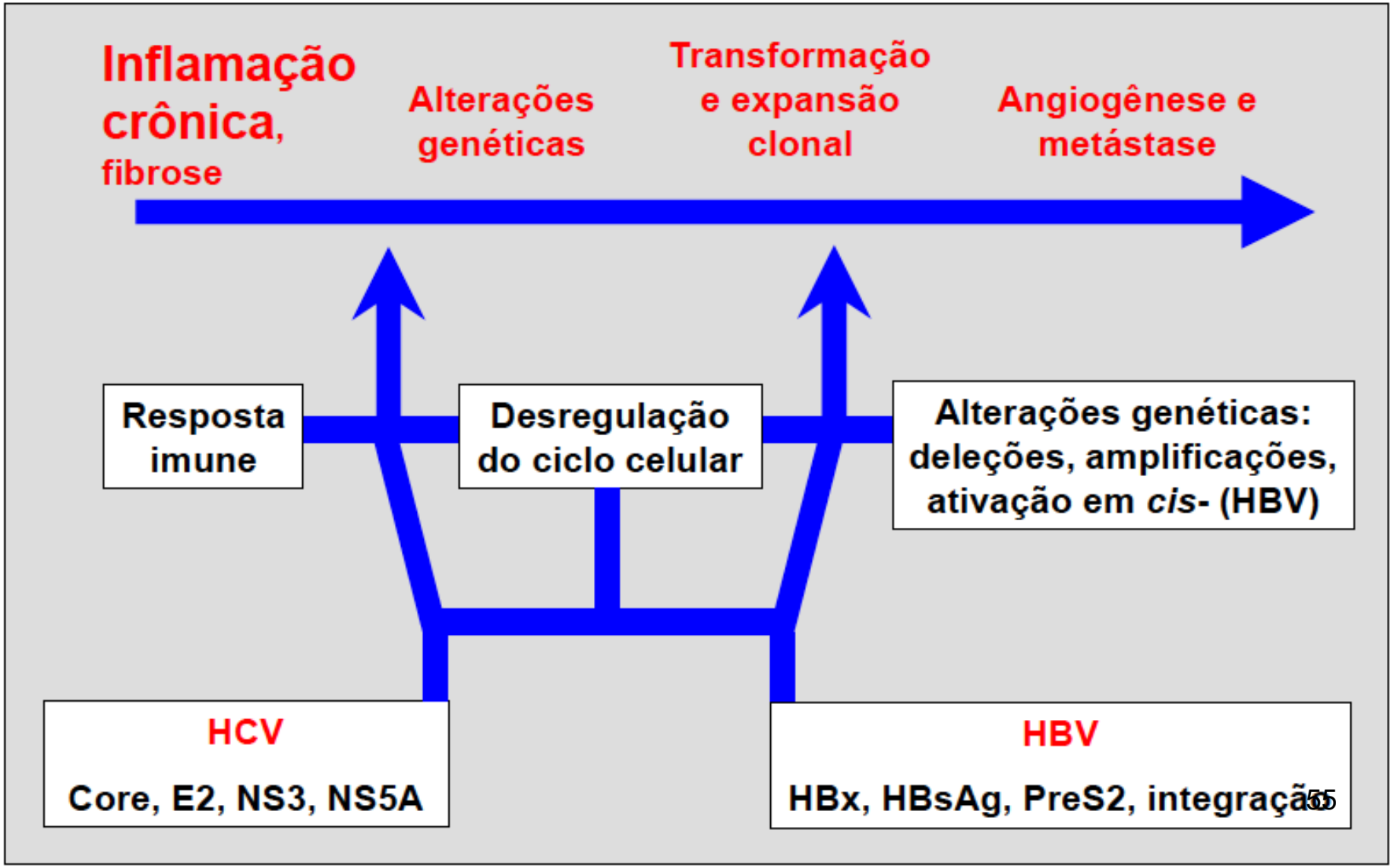



Approved antiviral drugs (January 1959 - April 2016)
Retro virus
HIV combination drugs
Genvoya®
Trizivir®
Triumeq®
Atripla®
Stribild®
Combivir®
Evotaz®
Odefsey®
Descovy®
Truvada®
Dutrebis®
Prezcobix®
Complera®
Entry inhibitors
T20
MVC
NNRTIs
NVP
DLV
EFV
ETR
RPV
Protease inhibitors
RTV
APV
FPV
ATV
LPV/r
NFV
TPV
IDV
DRV
SQV
Acyclic nucleoside phosphonate analogues
TDF
NRTIs
3TC
ddI
AZT
d4T
ABC
FTC
ddC
Integrase inhibitors
RAL
EVC
DTG
DNA virus
ADV
Podofilox
Imiquimod
Sinecatechins
Telbivudine
Entecavir
PegIFNα-2a
PegIFNα-2b
HPV
HBV
HSV
Cidofovir
Ganciclovir
Fomivirsen
Valganciclovir
Foscarnet
Valaciclovir
Vidarabine
Famciclovir
Brivudine
Acyclovir
VZIG®
VariZIG®
Idoxuridine
Trifluridine
Docosanol
Penciclovir
HCMV
VZV
RNA virus
Amantadine
Rimantadine
Laninamivir
Favipirabir
Peramivir
Oseltamivir
Zanamivir
Palivizumab
Ribavirin
RSV- IGIV
Telaprevir
PegIFNα-2a
PegIFNα-2b
Interferon alfacon-1
Boceprevir
Viekira Pak®
Technivie®
Harvoni®
Rebetron®
Zepatier®
Vanihep®
Sovaldi®
Simeprevir
+
Sofosbuvir
+
Daclatasvir
+
Asunaprevir
Vaniprevir
Influenza virus
RSV
HCV

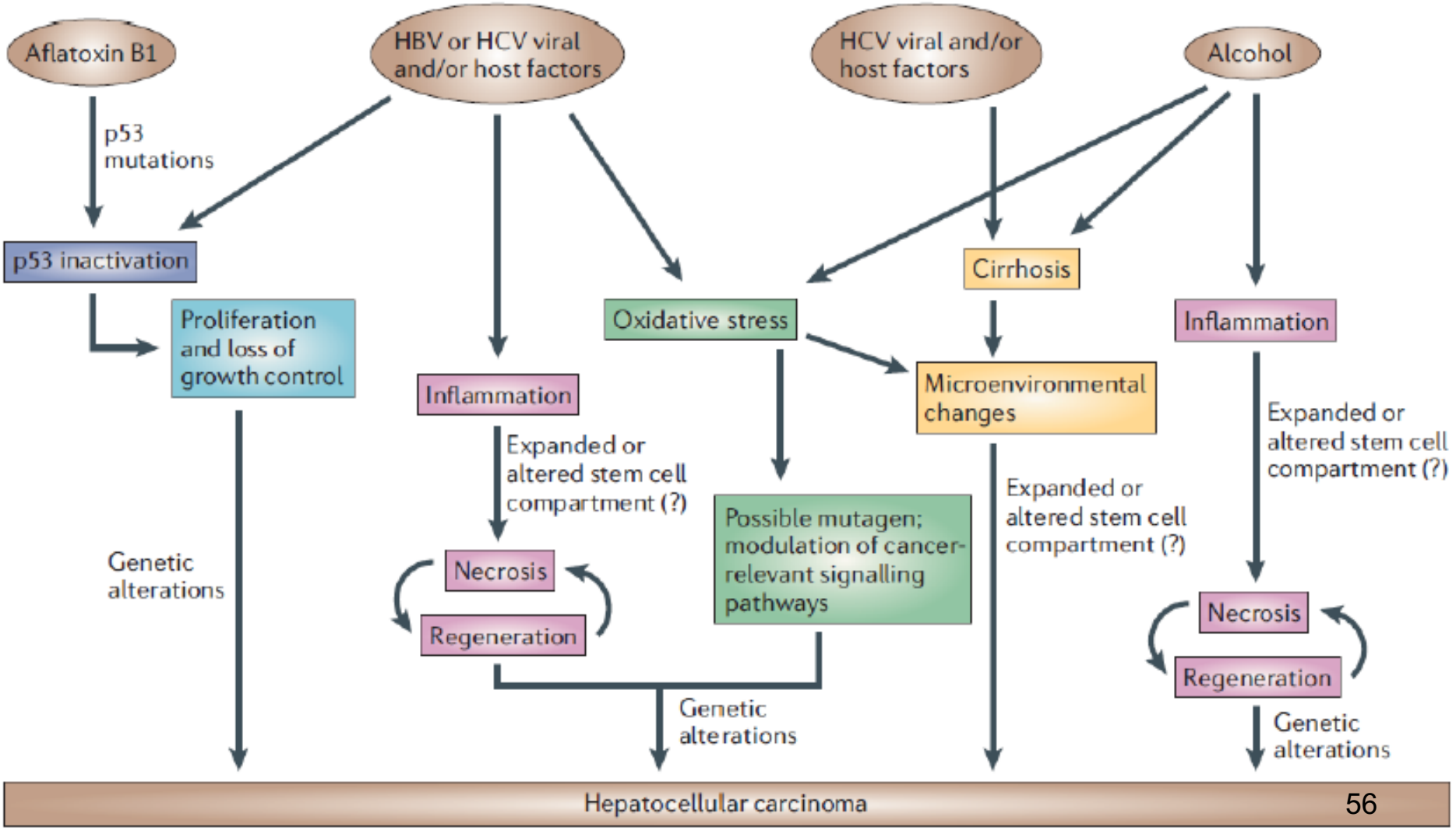
Hepatitis C virus



Transformação celular por HBV e HCV



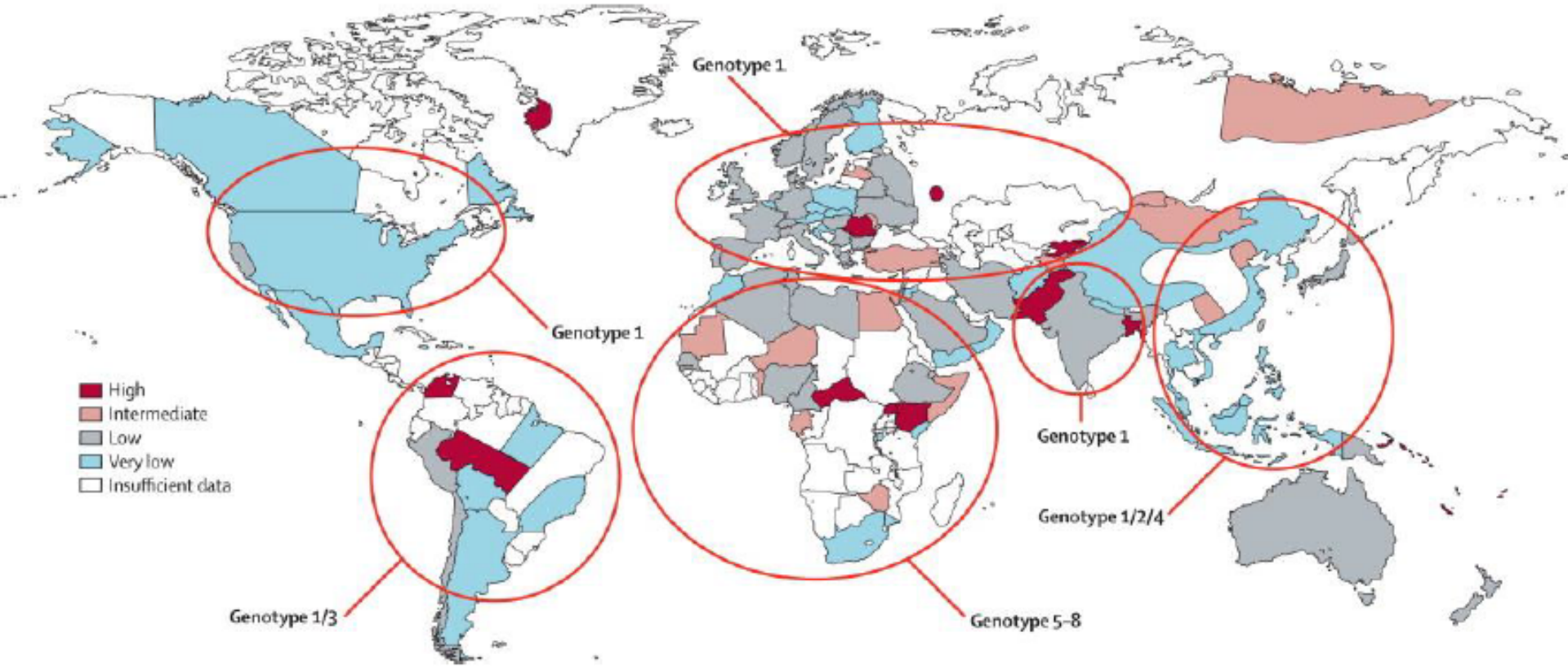
HCC: Co-fatores



Hepatite Delta (HDV)

Hepatite D

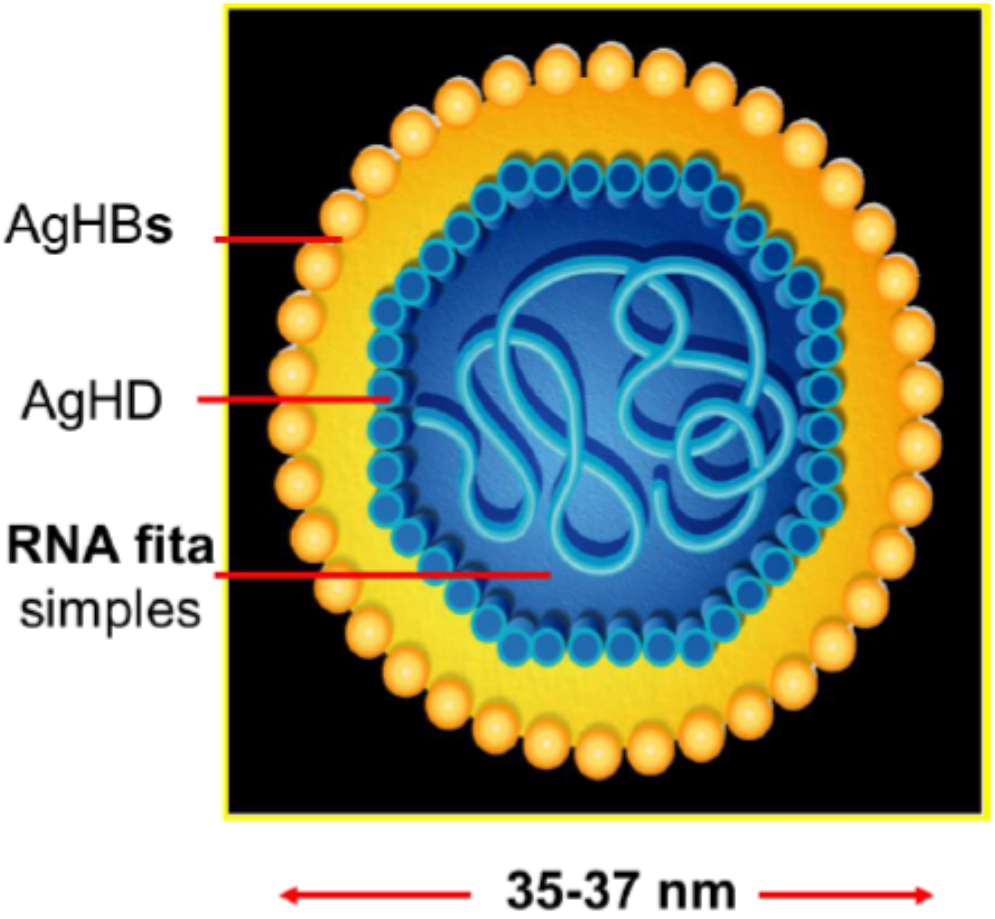
Oito genótipos

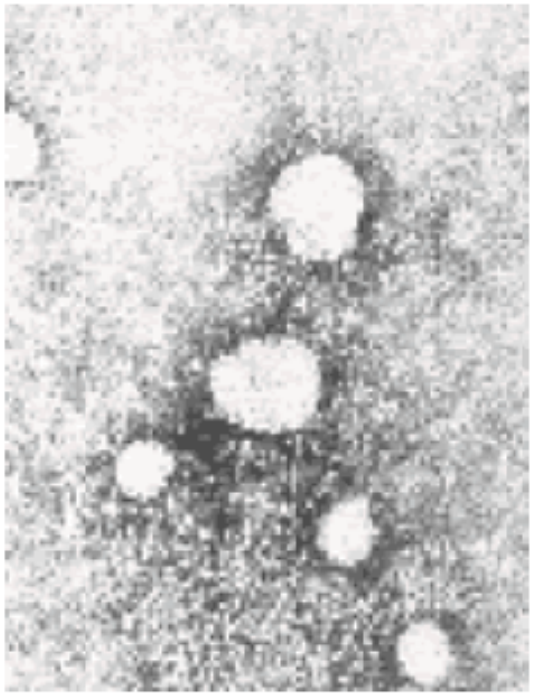


Hepatite D

- Similar a viróides de plantas
- codifica proteínas (S-HDAg/replicação e L-HDAg/montagem)
- RNA com 1,7Kb, circular, negativo, dobrado sobre si mesmo
- Infecção concomitante com HBV, mas com multiplicação independente
- Citopático, 3 genótipos
- Antígeno + RNA envelopado por capsídeo codificada por HBsAg

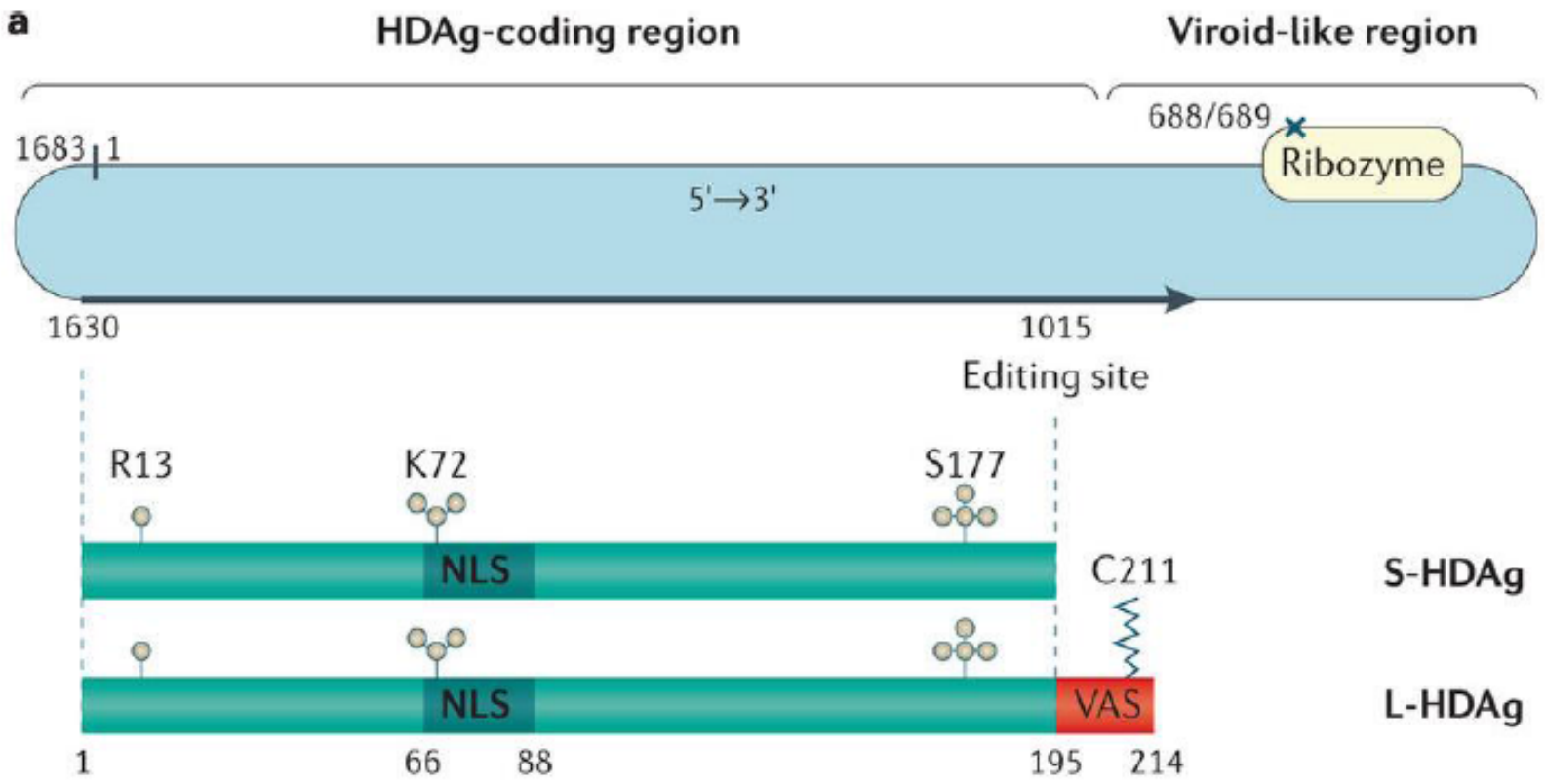
Hepatite D

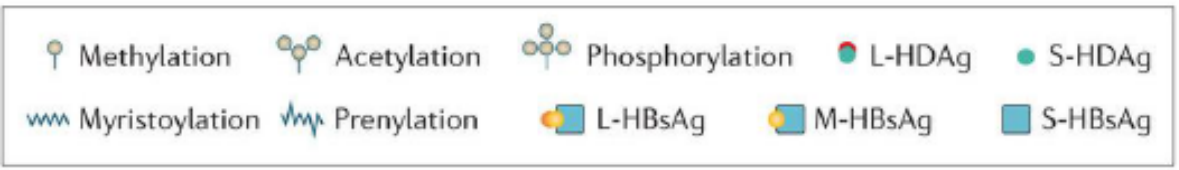




Hepatite D

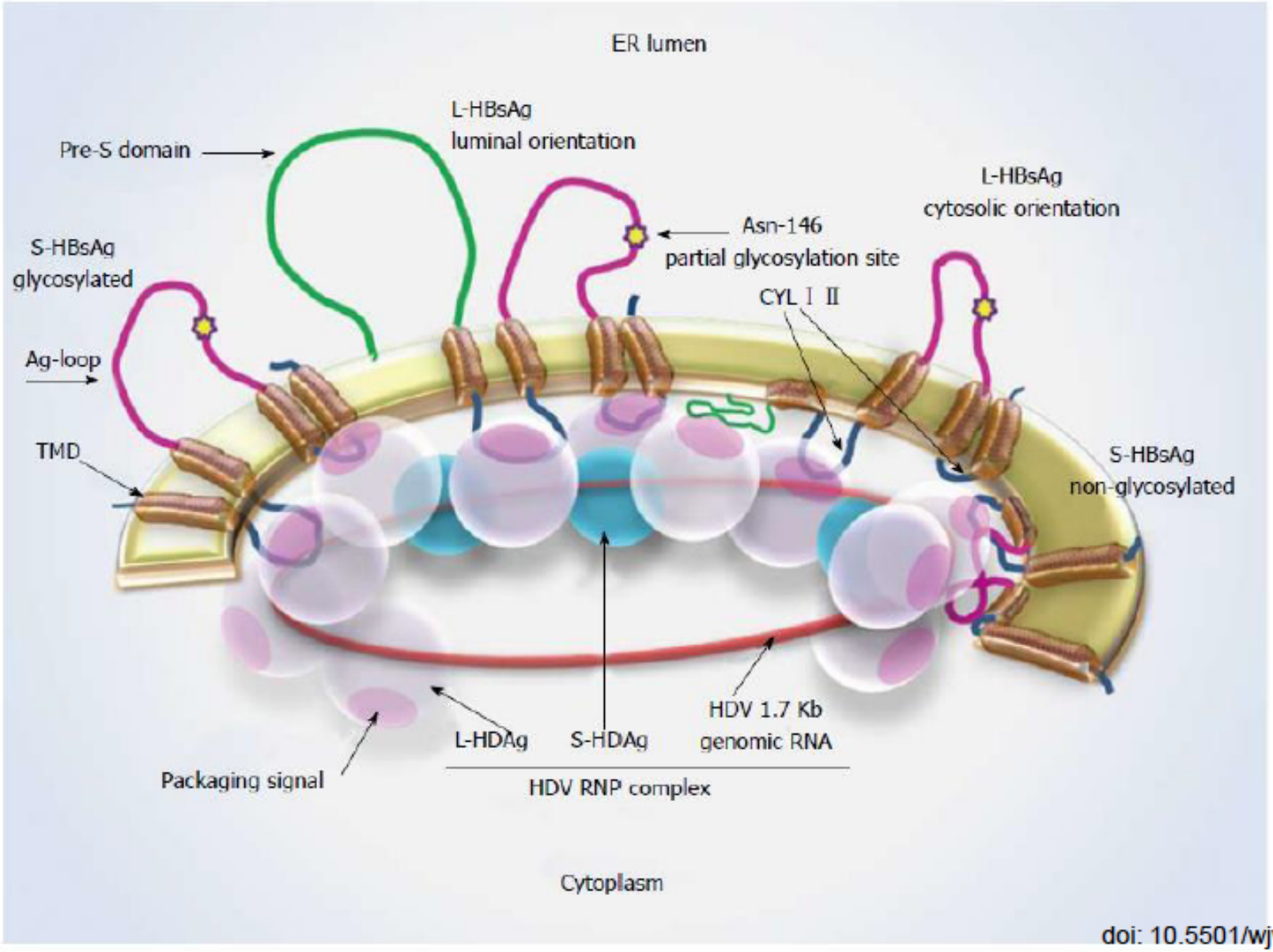
Organização genômica





doi:10.1038/nrgastro.2016.126

Hepatite D



doi: 10.5501/wjv.v4.i2.36

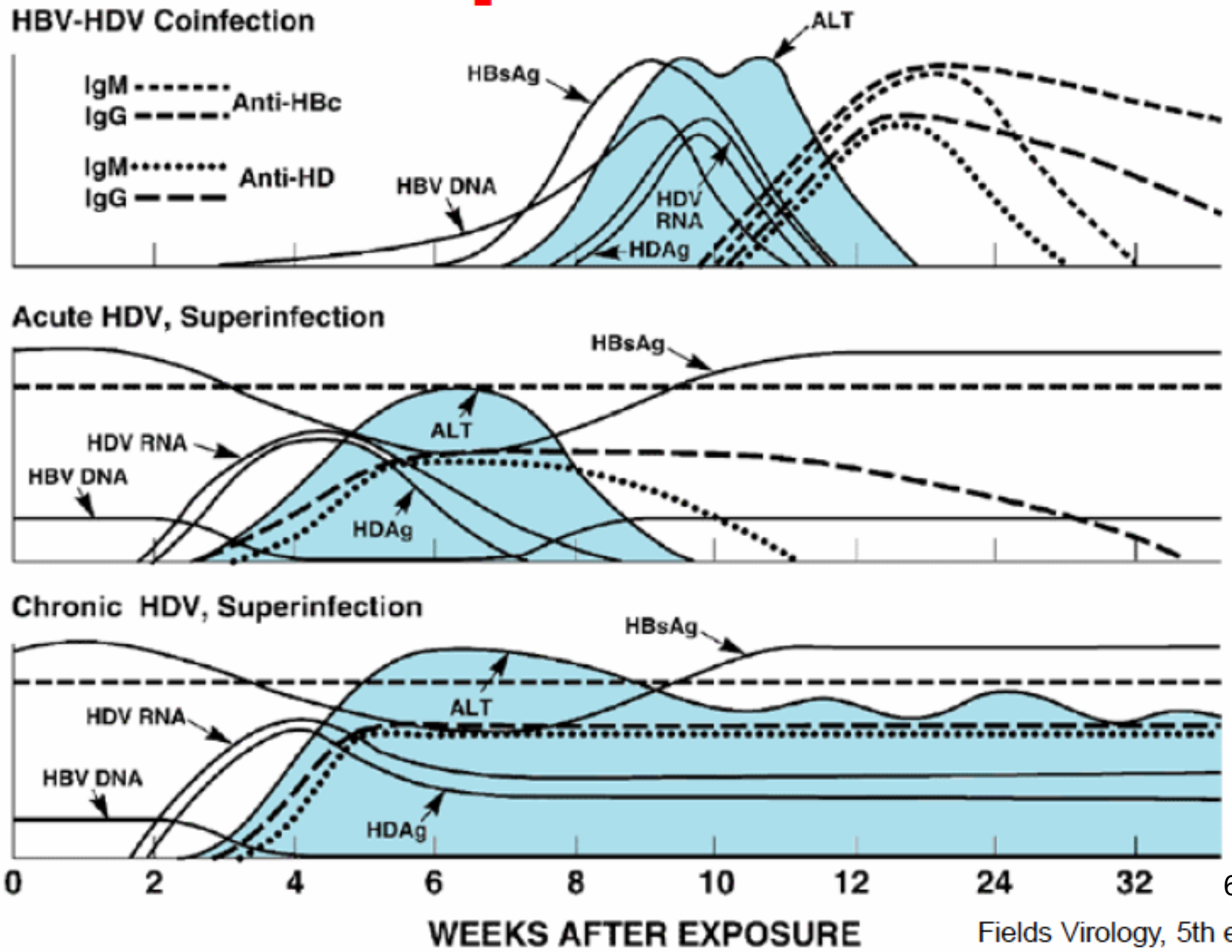
Hepatite D

Características clínicas

- Co-infecção
  - Doença aguda severa - hepatite fulminante
  - Baixo risco de infecção crônica

- Super-infecção
  - Geralmente desenvolve infecção crônica por HDV
  - Alto risco de doença crônica grave

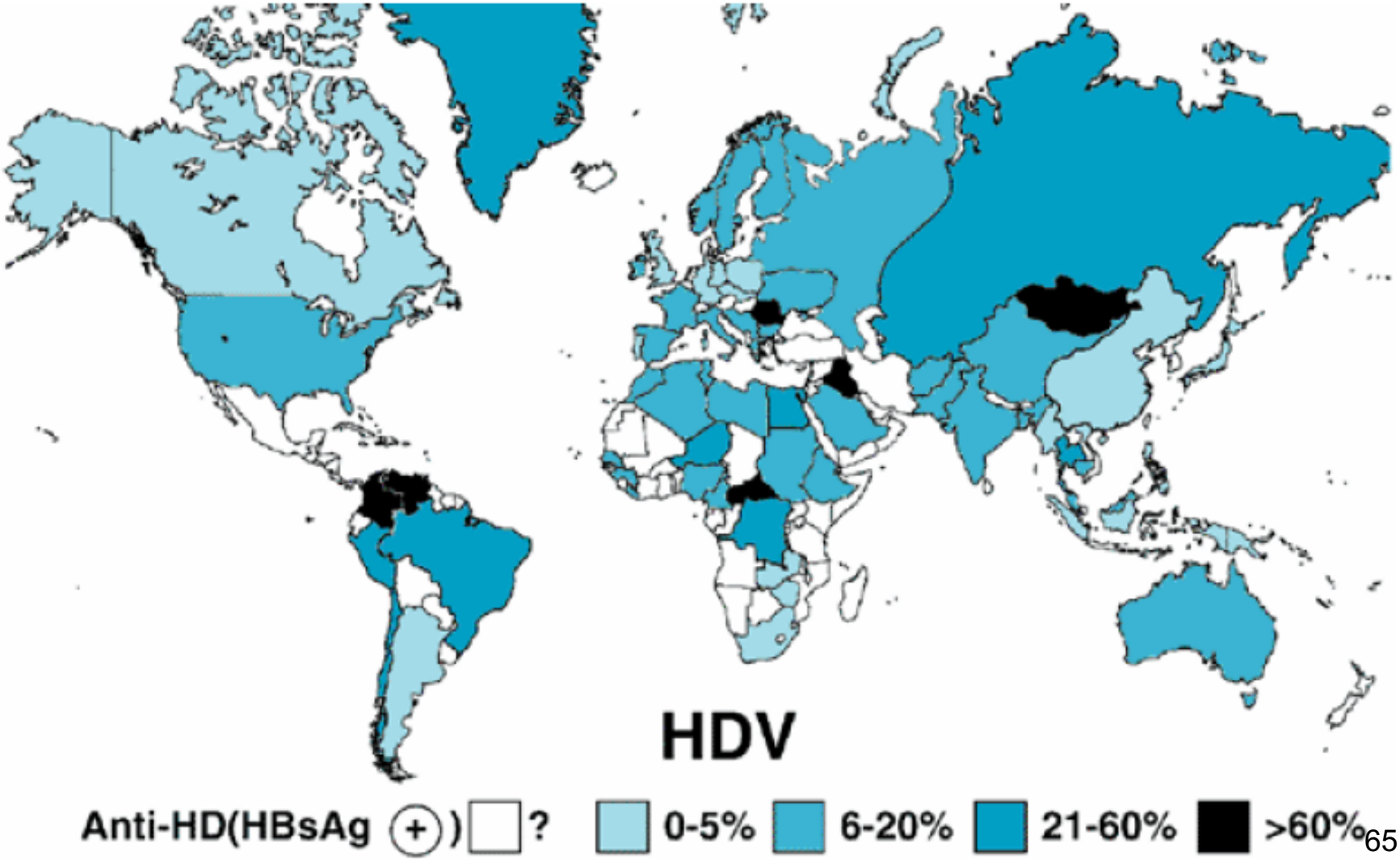
Hepatite D



Fields Virology, 5th ed

Hepatite D

Prevalência de anti-HD em indivíduos positivos para HBsAg



Fields Virology, 5th ed

Hepatite D

Diagnóstico Laboratorial

- Marcador Sorológico:
  - VHB (Ag e Ac)
  - Anti-VHD IgM
  - Anti-VHD IgG
- Marcador Molecular: RNA
  - RT-PCR / “nested” PCR

Table 1 | A summary of diagnostic tests for the evaluation of patients with HDV infection

Test	Purpose	Remarks
Anti-HDV IgG antibody	Detects IgG antibodies against HDV, indicates previous or ongoing contact with HDV	Should be the first diagnostic screening test employed and should be performed in all HBsAg-positive patients
Anti-HDV IgM antibody	Detects IgM antibodies against HDV, indicates acute HDV infection or chronic HDV infection with disease activity	Can be used to determine disease activity in patients who test positive for anti-HDV IgG antibodies. Available tests are not standardized
HDV RNA qualitative	Detects HDV RNA Indicates HDV replication and active infection	Gold standard to determine HDV infection. Test can be false-negative if primers are not optimized for all HDV genotypes
HDV RNA quantitative	Determines the level of HDV RNA in the blood	Can be useful in the context of antiviral treatment to predict treatment response. There is no association between serum HDV RNA levels and the grade or stage of liver disease
HDV genotyping	Determines the HDV genotype	Different HDV genotypes may be associated with distinct clinical courses
HBsAg quantitative	Determines the level of HBsAg in the blood	HBsAg is associated with HDV RNA levels. HBsAg clearance is associated with HDV eradication and thus HBsAg monitoring can be useful during antiviral treatment
HBeAg/anti-HBe antibody	Determines the presence of the HBeAg and the presence of anti-HBe antibodies	About 15–20% of patients with HDV infection test positive for HBeAg, which can be associated with HBV replication. Treatment with HBV polymerase inhibitors might be indicated if IFN-α treatment is not possible
HBV DNA quantitative	Determines the level of HBV DNA in the blood	Indication for treatment with HBV polymerase inhibitors depends on the amount of HBV DNA detectable in the blood
Anti-HCV antibody/HCV RNA	Determines the presence of the antibodies against HCV and the presence of HCV RNA	Up to one third of patients in Europe with HDV infection are coinfected with HCV. Screening for HCV should be performed at least once. HCV RNA is frequently suppressed by coinfection
Liver biopsy	Histological evaluation of and grading or staging of liver disease	Should be performed in all patients with hepatitis D as noninvasive markers of liver fibrosis are not proven to be able to accurately predict the stage of liver disease in patients with HDV infection

Abbreviations: HBsAg, hepatitis B surface antigen; HBe; hepatitis B early antigen; HBeAg, hepatitis B e antigen; HDV, hepatitis D virus.