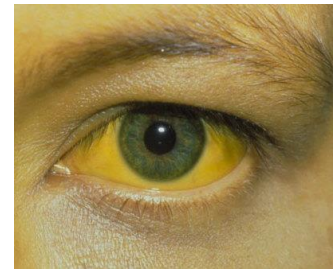
HIV

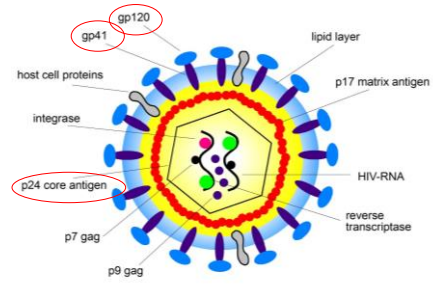
and

hepatitis viruses

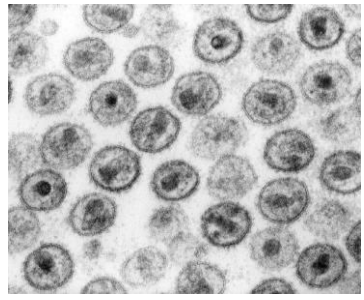


HIV – Human Immunodeficiency virus

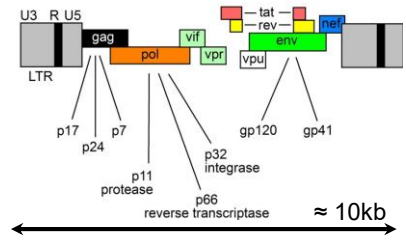
- Retrovirus
- coated ss RNA virus
- diameter 100 - 120 nm
- Not stabile
  in the environment
- Huge genome variability
  - instability



http://hivbook.files.wordpress.com/2011/11/figure-11.jpg?w=482&h=312

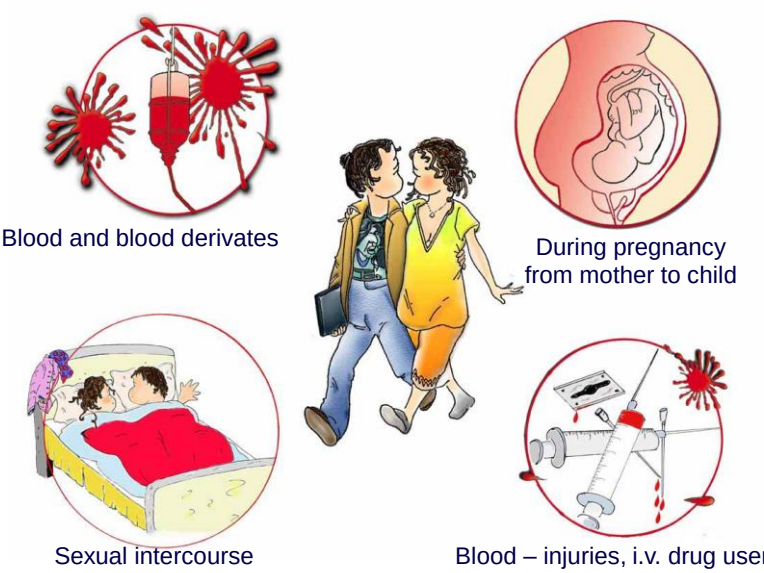


http://upload.wikimedia.org/wikipedia/commons/4/4c/HIV-1_Transmission_electron_micrograph_AIDS02bbb_lores.jpg



http://hivbook.files.wordpress.com/2011/11/figure-2.jpg?w=435&h=262

Transmission of HIV



Blood and blood derivates

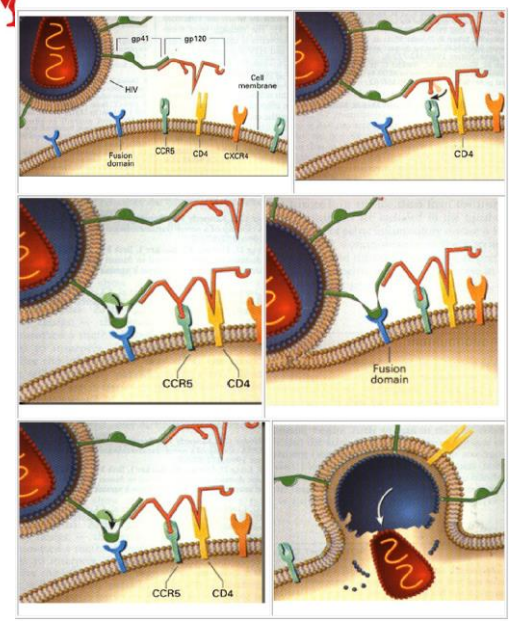
During pregnancy
from mother to child

Sexual intercourse
MSW, MSM, WSW

Blood – injuries, i.v. drug users

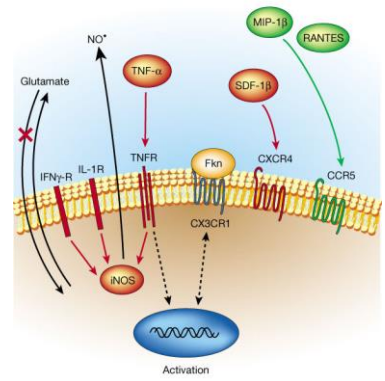
http://health.uml.edu/thc/HealthIssues/HIV%20NP/HIV_PresentationChinaLiuzhou8_061906.jpg

HIV – cell receptor



http://cdn.intechopen.com/pdfs/39816/InTech-Coreceptor_usage_in_hiv_infection.pdf

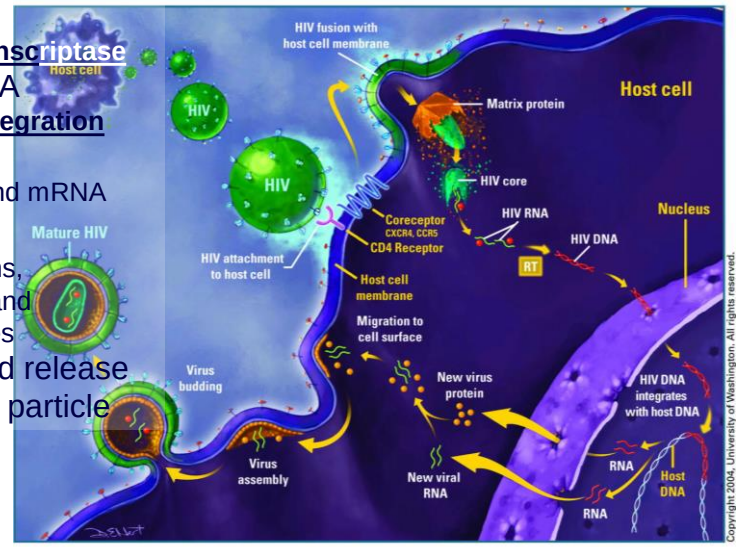
Natural resistance to HIV-1 throught delta 32 mutation in CCR5 (deletion of a part of gene). Homozygotes are resistant to M-tropic strains of HIV-1 infection



http://www.nature.com/nature/journal/v410/n6831/images/410988ac.2.jpg

HIV replication

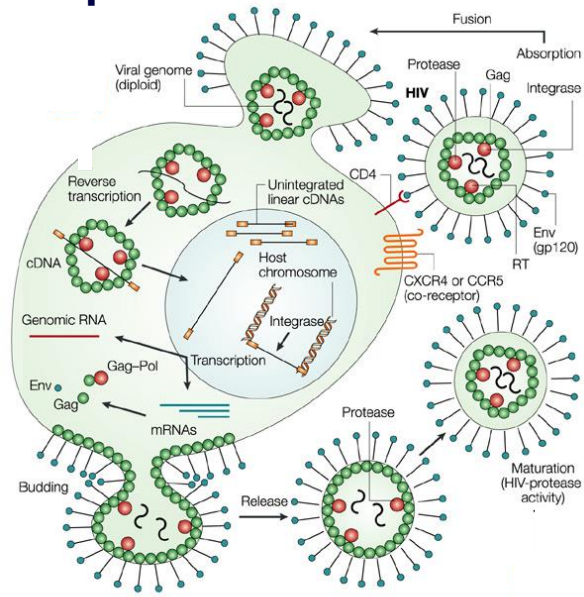
- viral RNA
  - **reverse transcriptase**
- proviral DNA
  - **genome integration**
- replication
  - viral RNA and mRNA
- translation
  - viral proteins, proteases and glycosidases
- Budding and release of new viral particle



http://home-hiv-tests.com/images/hiv_lifecycle.jpg

HIV replication

- viral RNA
  - **reverse transcriptase**
- proviral DNA
  - **genome integration**
- replication
  - viral RNA and mRNA
- translation
  - viral proteins, proteases and glycosidases
- Budding and release of new viral particle



http://www.nature.com/nrc/journal/v4/n11/box/nrc1479_BX1.html

Nature Reviews | Cancer

HIV – infected cells

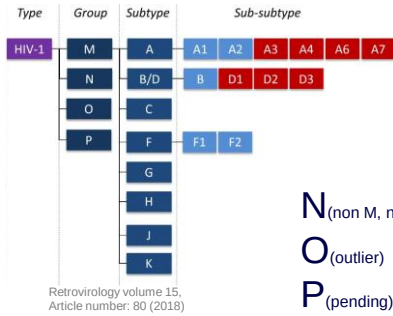
- **helper T cells** (specifically CD4+)
- **macrophages**
- **dendritic cells**
- **1st proliferation in lymphatic tissue – viraemia**
- **Latency**
- **Impact on cells**
  - ↓ counts of CD4+ T cells by:
    - apoptosis of uninfected bystander cells
    - direct viral killing of infected cells
    - killing of infected CD4+ T cells by CD8+ cytotoxic lymphocytes that recognize infected cells

http://www.topnews.in/health/files/hiv2.jpg

Observation of opportunistic infections

Types of HIV

- **HIV -1**



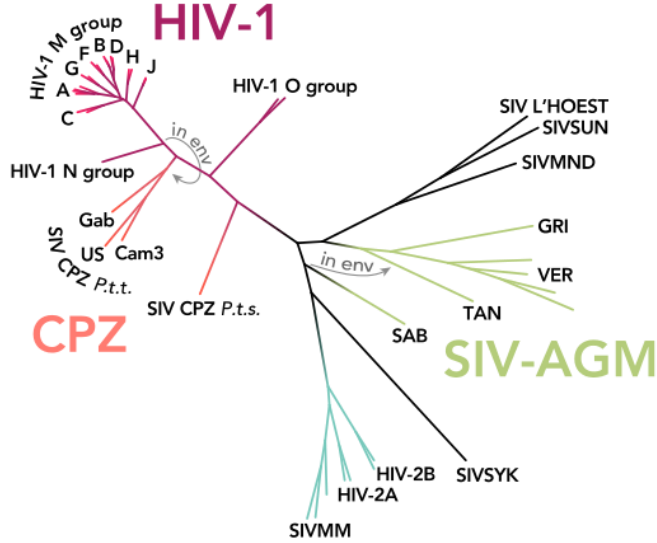
Retrovirology volume 15, Article number: 80 (2018)

M(major)	A	West and Central Africa
	B	Europe, North America, Thailand
	C	South Africa (especially Kongo), India
	D	Central Africa
	E	Central Africa, Thailand, India
	F	Zaire, Brazil, Romania
	G	Gabun, Zaire
	H	Cameroon, Gabun
	I	complex recombination CRF04_cpx
	J	North, Central and West Africa, Caribbean
	K	Democratic Republic of Congo, Cameroon
N(non M, non O)		Cameroon
O(outlier)		Central Africa
P(pending)		Cameroonian woman from France (similar to SIV (gorillas and chimpanzees)

- **HIV 2** groups A-H — Central Africa

Not only human – FIV, SIV, …

Types of HIV

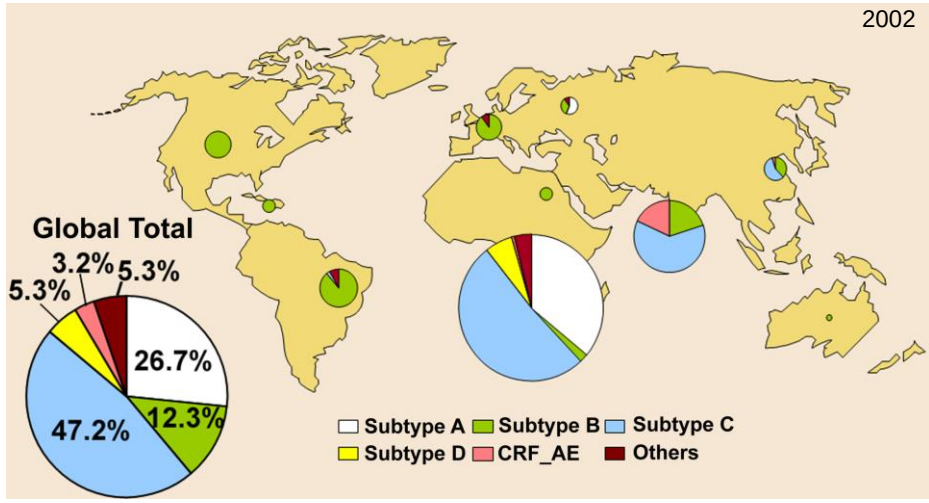


Not only human – FIV, SIV, …

0.10

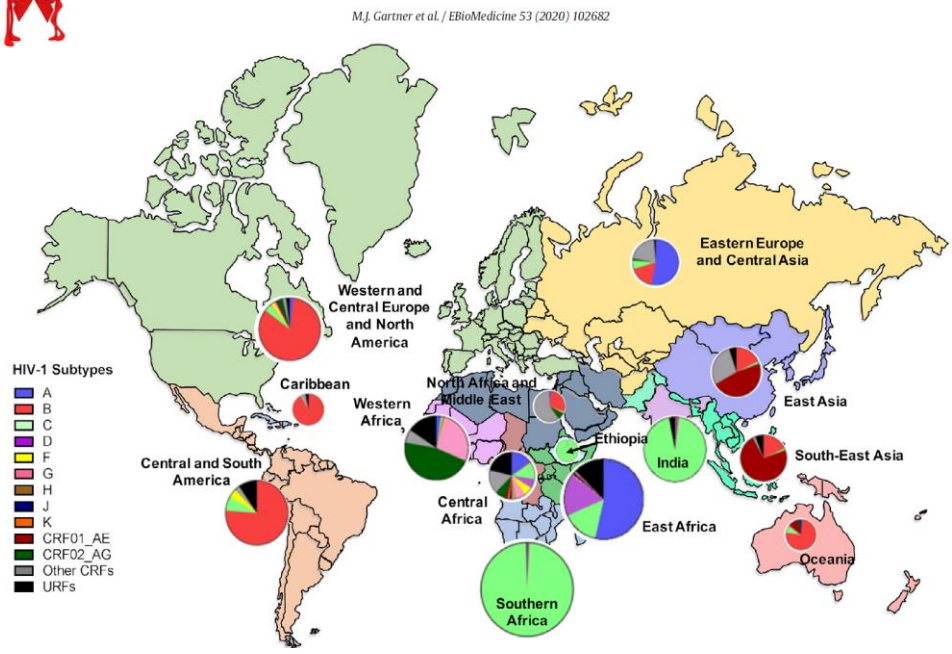
https://upload.wikimedia.org/wikipedia/commons/thumb/f/fb/HIV-SIV-phylogenetic-tree_straight.svg/180px-HIV-SIV-phylogenetic-tree_straight.svg.png

Types of HIV



http://en.wikipedia.org/wiki/File:HIV-1_subtype_prevalence_in_2002.png

Types of HIV - type C is dominating

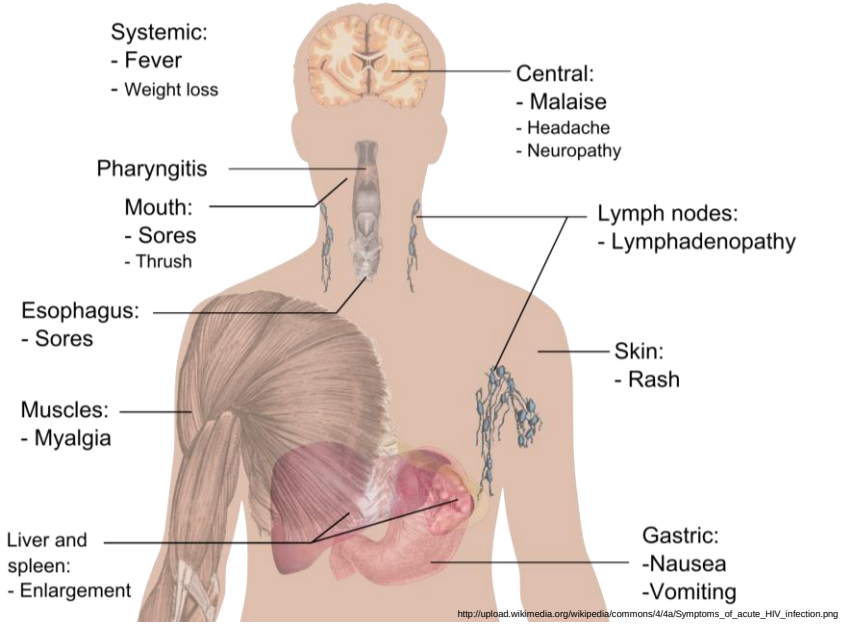


HIV pathogenesis

- **Clinical stages**
  Depends on infectious dose and genetic background of the patient
  - **A** - asymptomatic **(CD4+ > 500/µl)**
    (acute infection, benign lymfadenopathy)
  - **B** – light oportunistic infections **(CD4+ 200-500/µl)**
    (oropharyngeal or vulvovaginal candidiasis, diarrhea, „hairy“leucoplaky, peripheral neuropathy)
  - **C** - severe oportunistic infections **(CD4+ < 200/µl)**
    (CMV retinitis,pneumocystis pneumonia, toxoplasmosis or HIV encefalitis, tuberculosis, Kaposhi sarkoma, lymfoma, cryptococcus infection..)

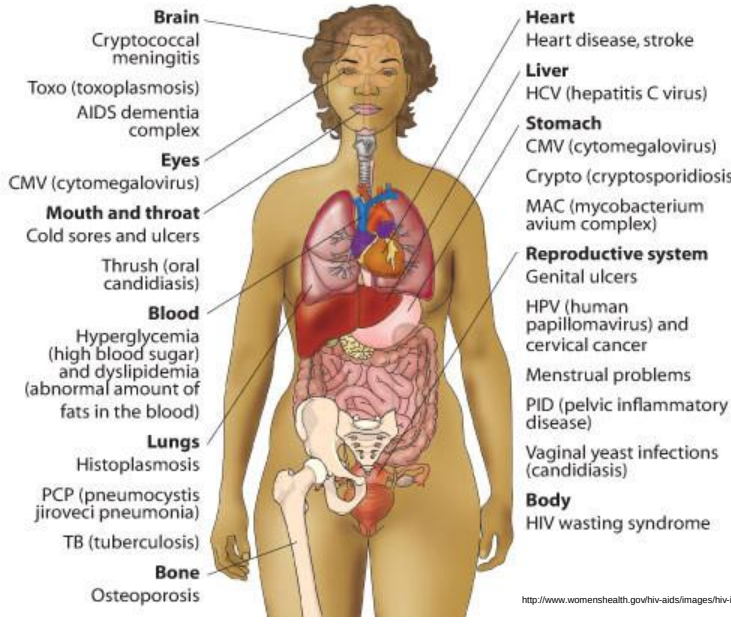
AIDS – Acquired Immunodeficiency Syndrome

Symptoms of acute HIV infection



http://upload.wikimedia.org/wikipedia/commons/4/4a/Symptoms_of_acute_HIV_infection.png

Symptoms of opportunistic infections



http://www.womenshealth.gov/hiv-aids/images/hiv-infections-diagram.jpg

Laboratory diagnostics
general

- Antigen detection **– antigen p24/25**
  - In acute phase
  - During active viral prolipheration
- Antibody detection
  - Basic screening technique **– anti p24/25**
- RNA (quantitative) detection
  - Quantification of viral load
- Detection of proviral integrated DNA

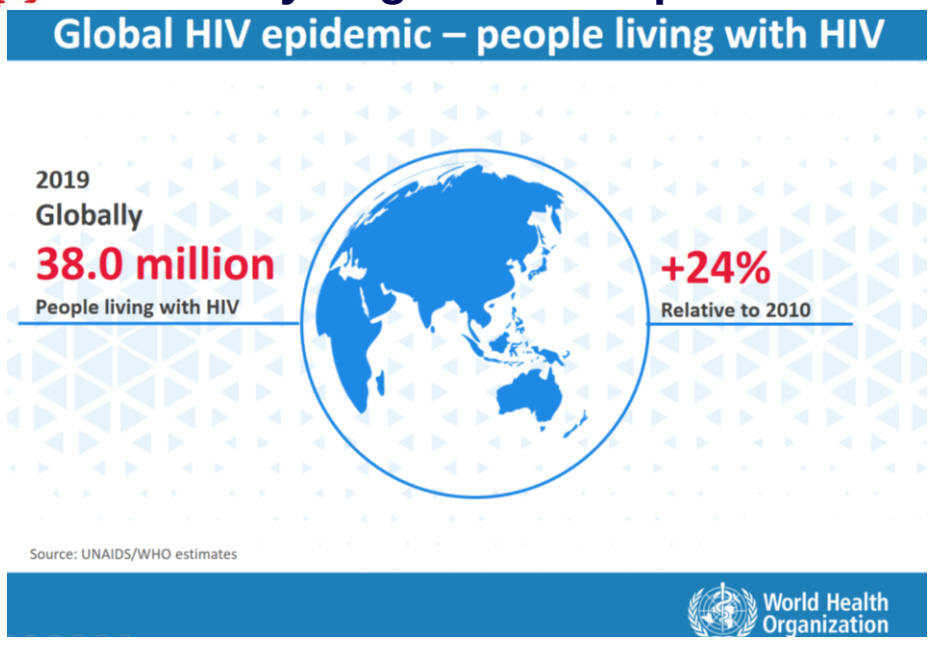
Laboratory diagnostics
detail

- Antibody detection
  - Mainly ELISA tests
  - Screening – necessity of confirmation
  - Positive at about 20 days post infection
- Antibody + antigen detection
  - Screening – necessity of confirmation
  - Positive at about 16-18 days post infection
- All test have to be confirmed

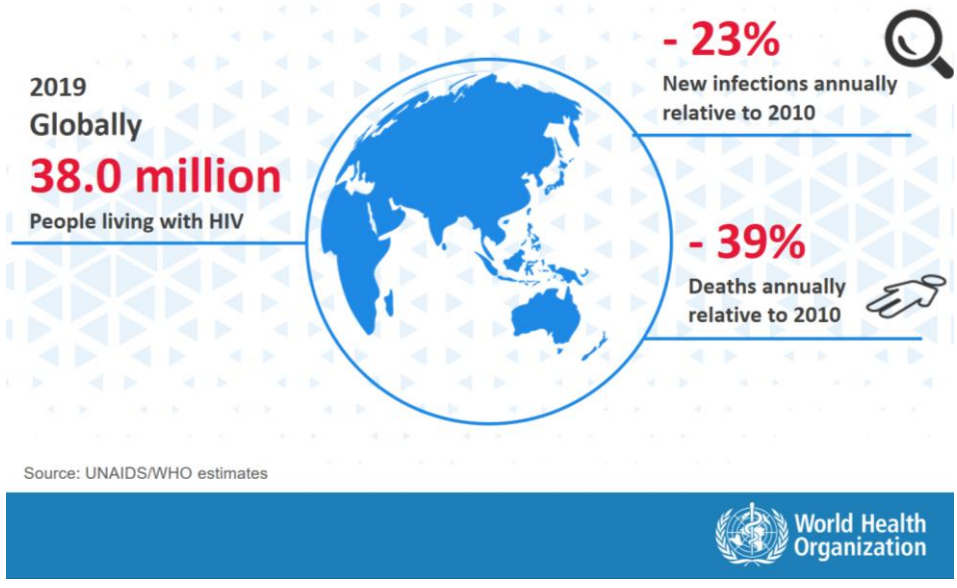
HIV epidemiology

- 1st „wave“
  - Blood transmission, MSM
  - 70-80 % of infected were men
  - North America and Europe
- 2nd „wave“
  - Infection mainly by MSW
  - Ratio of infected men and women 1:1
  - Africa, Asia and spread to other countries

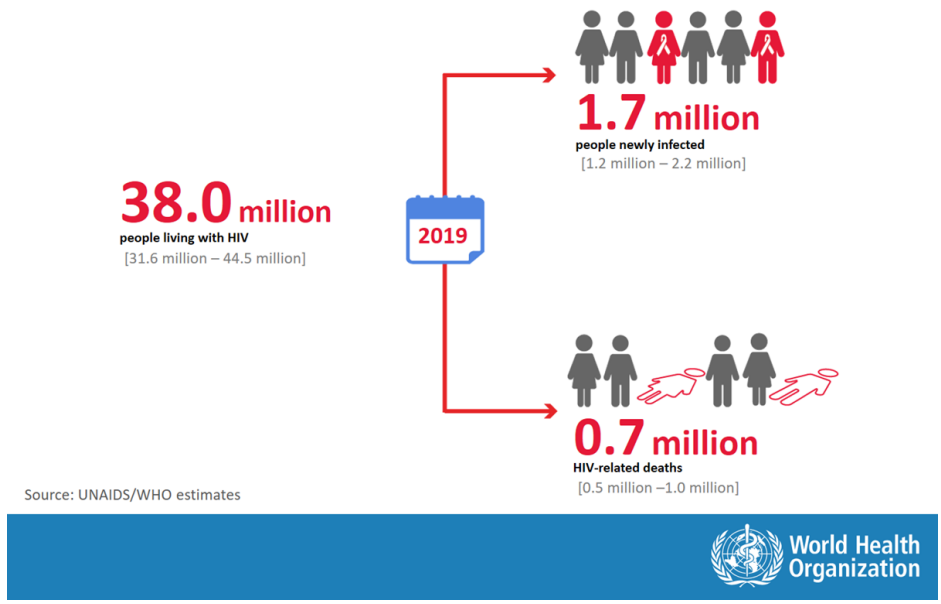
Summary of global HIV epidemic



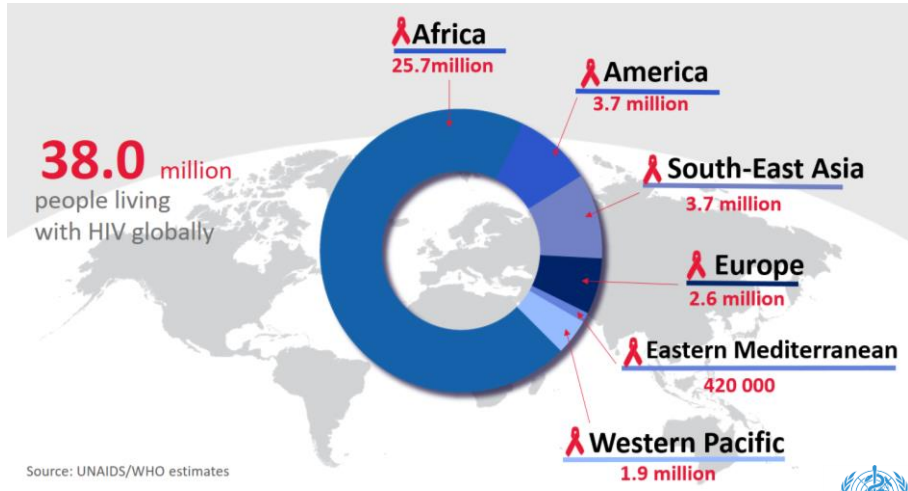
Summary of global HIV epidemic



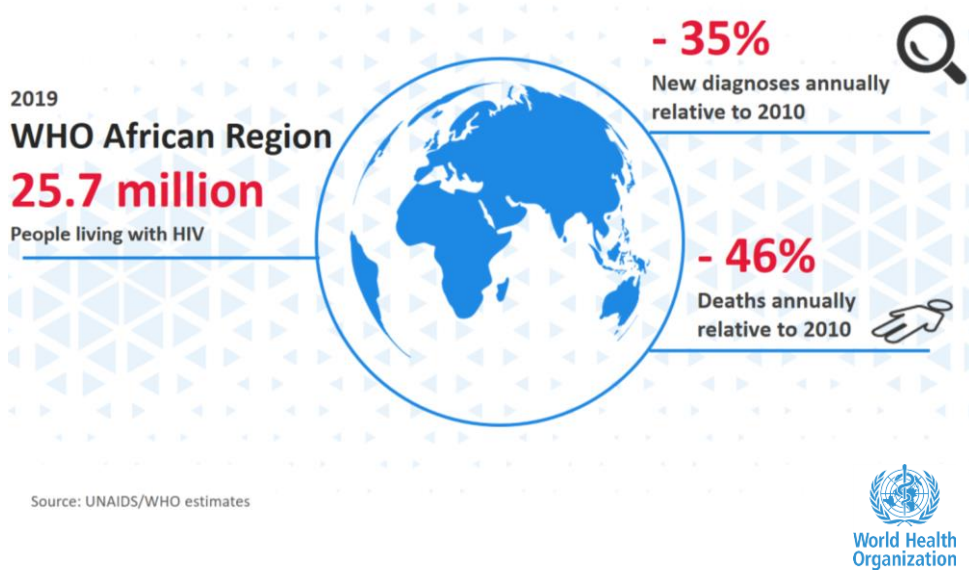
Summary of global HIV epidemic



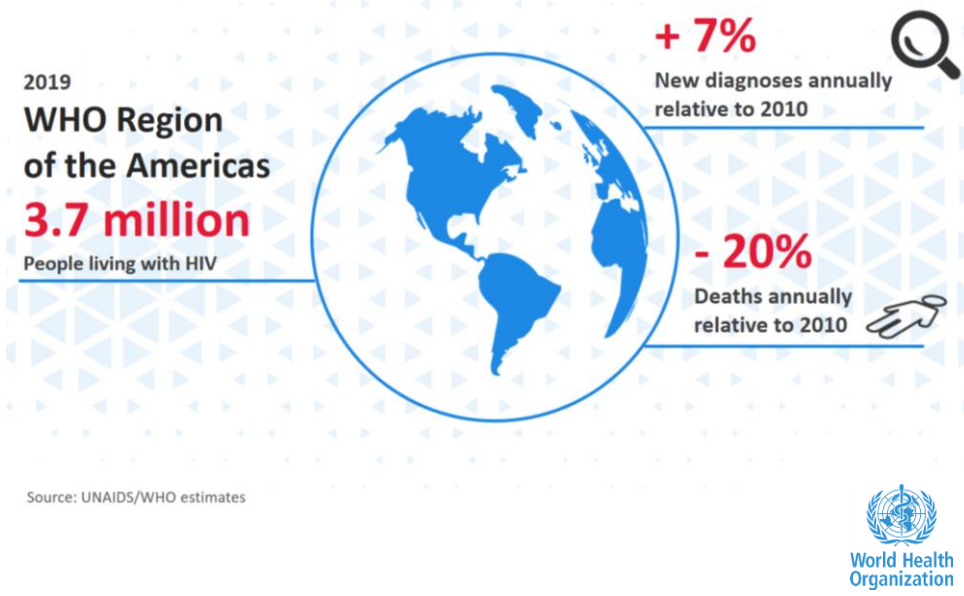
People living with HIV by WHO region
(2019)



Summary of regional HIV epidemic



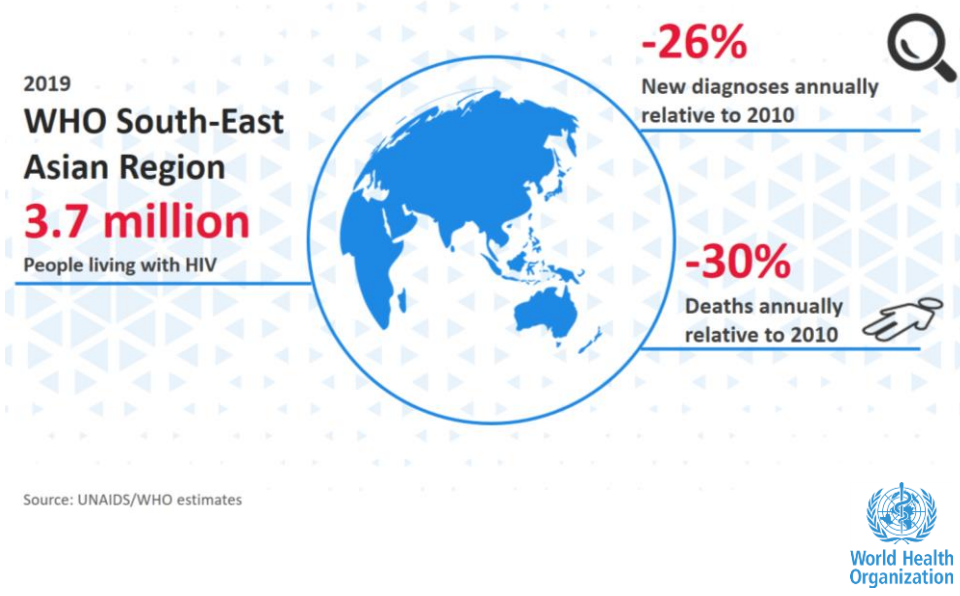
Summary of regional HIV epidemic



Source: UNAIDS/WHO estimates

World Health Organization

Summary of regional HIV epidemic



Source: UNAIDS/WHO estimates

World Health Organization

Summary of regional HIV epidemic

Source: UNAIDS/WHO estimates

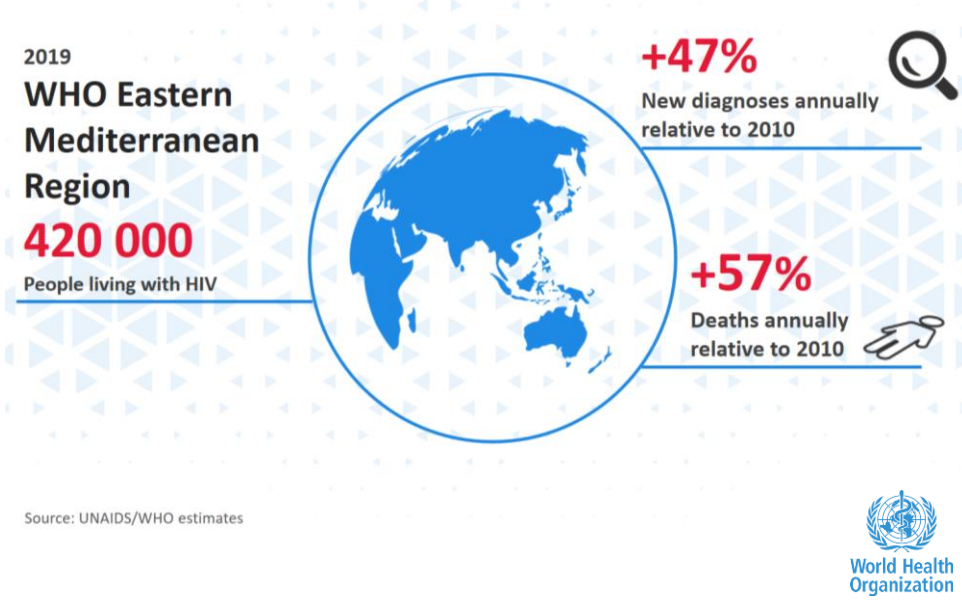
World Health Organization

Summary of regional HIV epidemic

Source: UNAIDS/WHO estimates

World Health Organization

Summary of regional HIV epidemic



Summary of global HIV epidemic (2019)

World Health Organization

	People living with HIV in 2019	People newly infected with HIV in 2019	HIV-related deaths in 2019
Total	38.0 million [31.6 million – 44.5 million]	1.7 million [1.2 million – 2.2 million]	690 000 [500 000 – 970 000 million]
Adults	36.2 million [30.2 million – 42.5 million]	1.5 million [1.1 million – 2.0 million]	600 000 [430 000 – 840 000]
Women	19.2 million [16.4 million – 22.2 million]	790 000 590 000 – 1.1 million]	300 000 [220 000 – 420 000]
Men	17.0 million [13.8 million – 20.4 million]	870 000 630 000 – 1.2 million]	390 000 [280 000 – 560 000]
Children (<15 years)	1.8 million [1.3 million – 2.2 million]	150 000 [94 000 – 240 000]	95 000 [61 000 – 150 000]

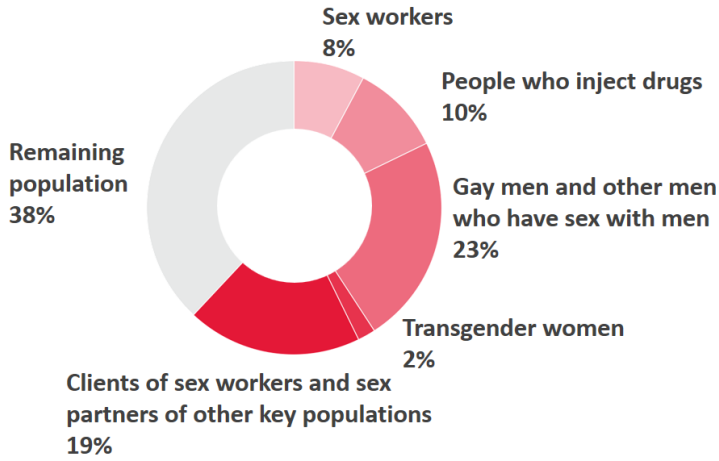
Source: UNAIDS/WHO estimates

World Health Organization

Source: UNAIDS/WHO estimates.

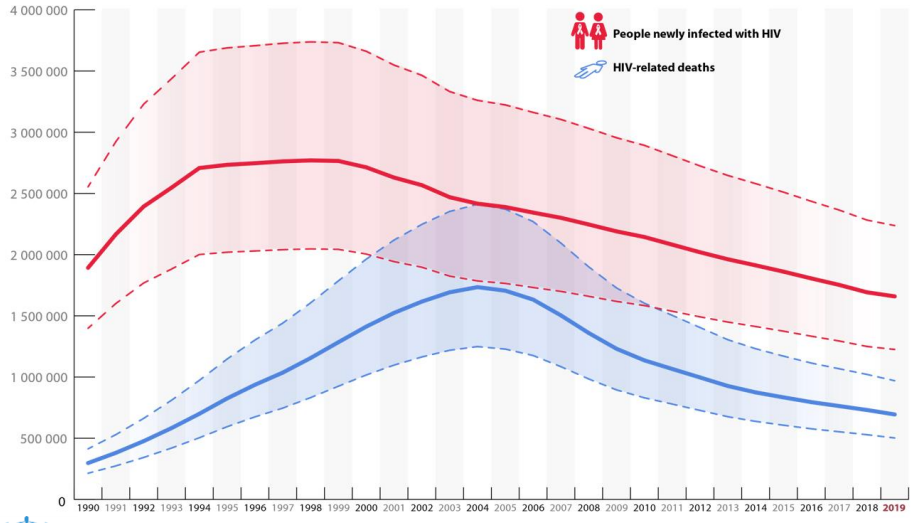
Distribution of new HIV infections by key population, global (2019)

World Health Organization



Source: UNAIDS special analysis, 2020

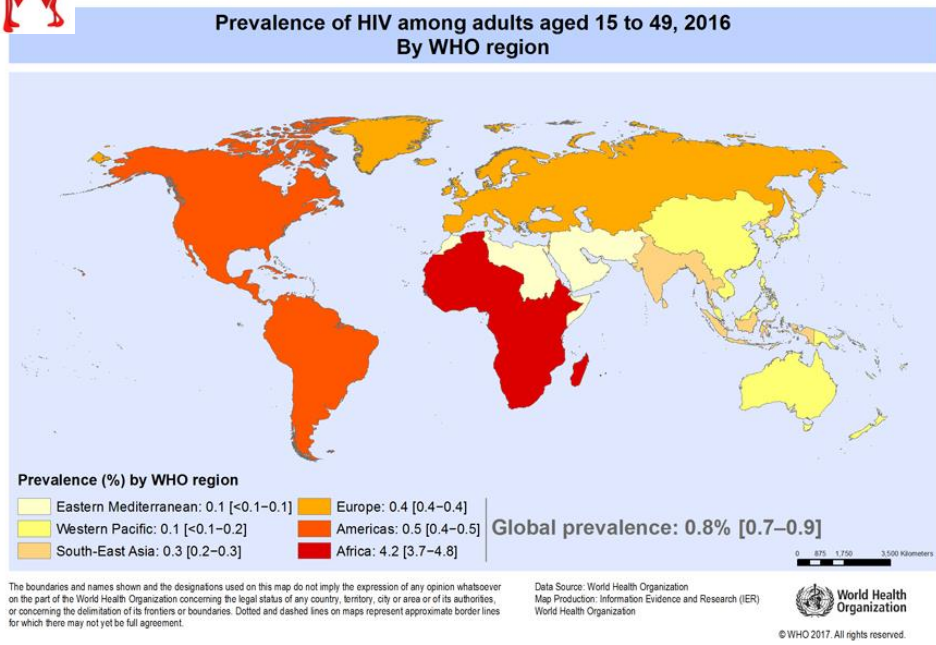
Decline in HIV incidence and mortality over time



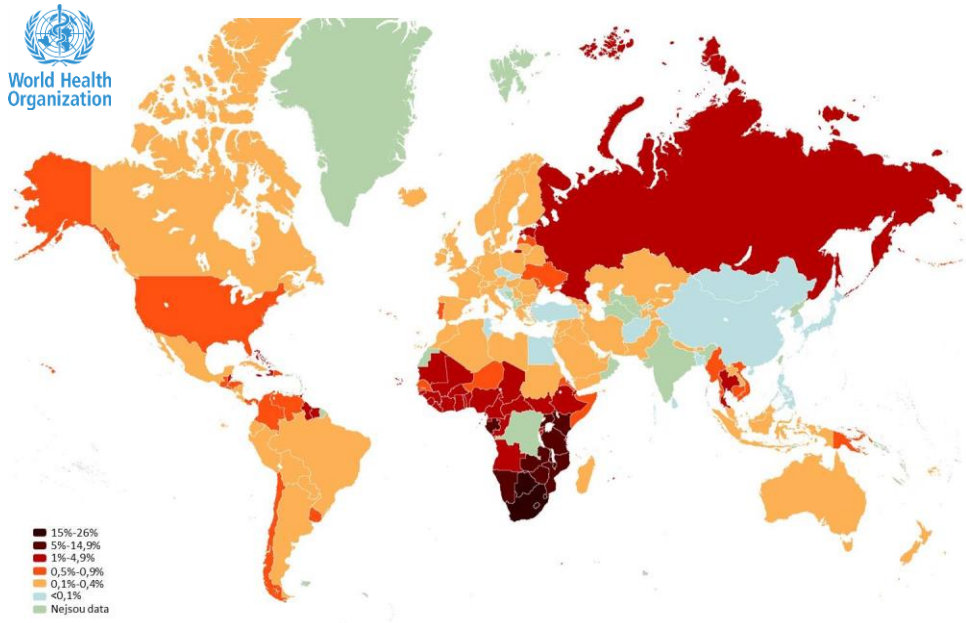
World Health Organization

Source: UNAIDS/WHO estimates.

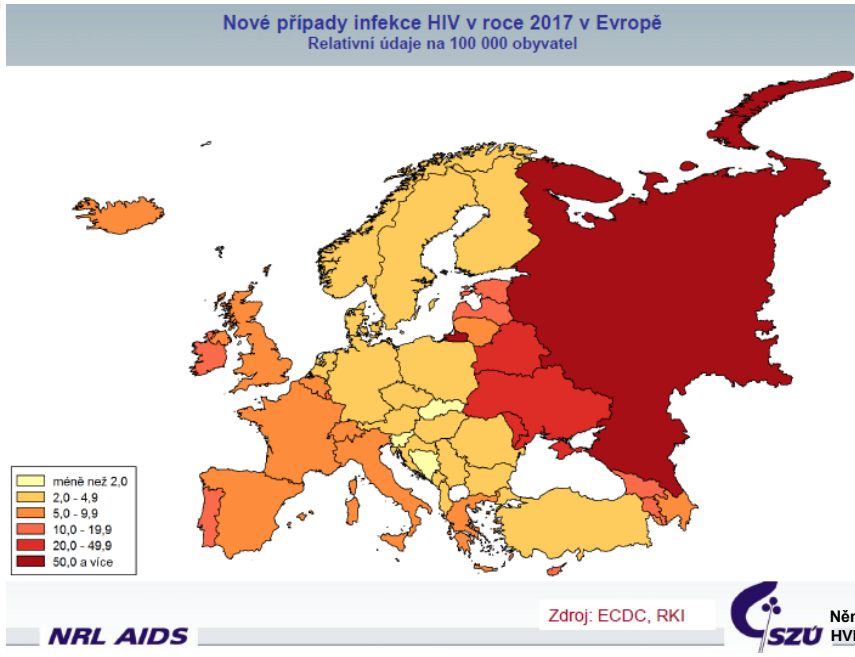
HIV prevalence



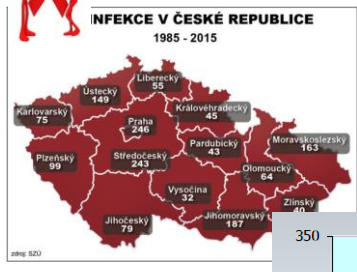
HIV prevalence (2014)



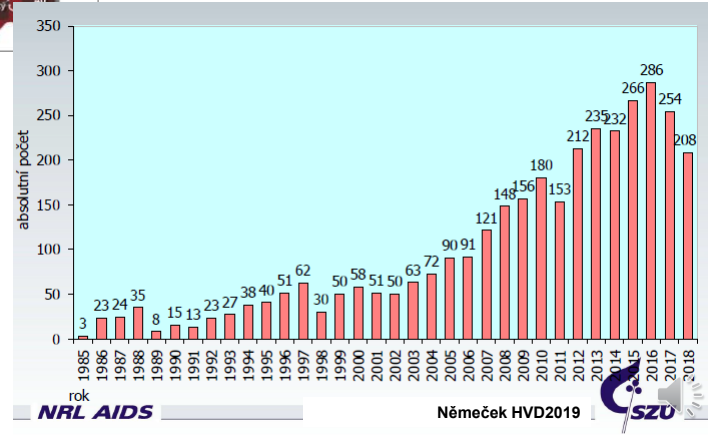
New cases of HIV infection 2017



Epidemiological HIV data CR



Cumulative data f new HIV+ cases up to 31.8.2019



Epidemiological HIV data CR
HIV/AIDS 1985-31.8.2019

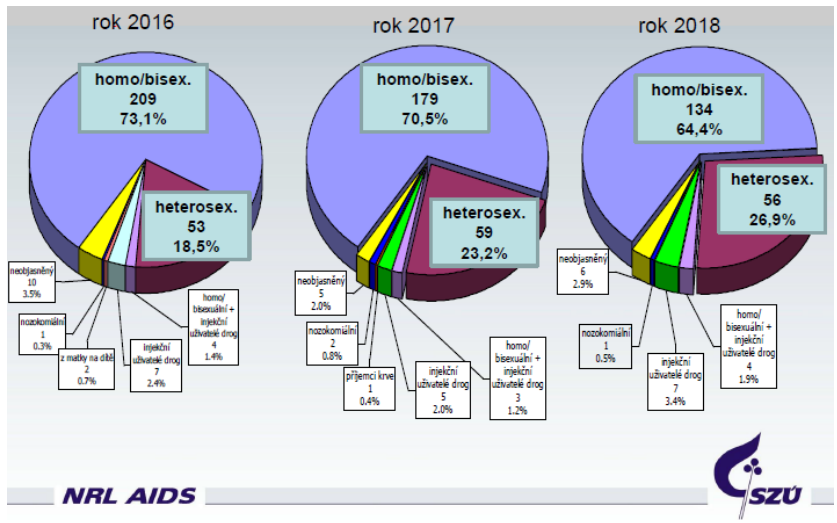
Total No. of HIV+	**3536**	
	M F	3056 (86.4%) 480 (13.6%)
AIDS (658)	M F	538 (81.8%) 120 (18.2%)
Deceased with AIDS (308)	M F	251 (81.5%) 57 (18.5%)
Deceased from another reason (147)	M F	130 (88.4%) 17 (11.6%)

NRL AIDS SZÚ

Němeček HVD2019

Epidemiological HIV data CR

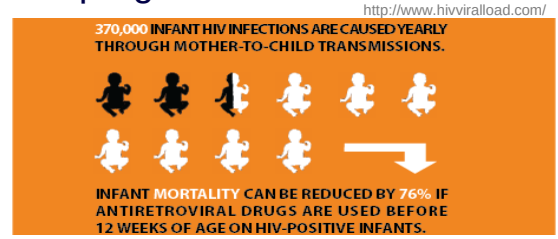
New cases according to the transmission 2016-2019



Němeček HVD2019

HIV prevention

- Prevention of exposition
  - Health education for people
  - Control of blood and blood derivates
  - Babies of the HIV+ mothers
- Stop of spreading of the infection in the body
  - Vaccines (so far in development)
  - Limitation of Mother to child transmission
- Decrease of the illness progression
  - Virostatic treatment



Possible HIV vaccines

- Typ of vaccine
  - Surface antigen (subunit)
  - Control of blood and blood derivates
- Attenuated virus
- Poxvirus expressing the HIV antigens

- Possible problems
  - Virus variability
  - Long time for development of immunity
  - Risky for children

HIV treatment

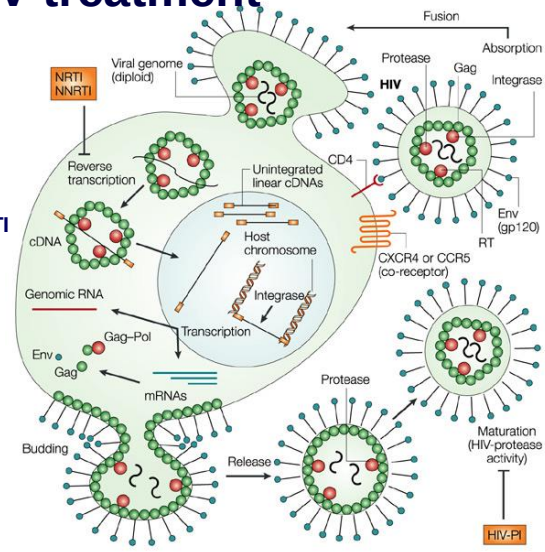
- Receptor neutralisation — Solution of anti-CD4; Neutralizing antibody; CD4+ imunoadhesins
- Reverse transcriptase inhibitors (RTIs) — AZT(Retrovir), ddI(Videx) 3TC(Epivir)…
- Inhibitors of integrase
- Inhibitors of transcription — Ribavirine
- Protease inhibitors (PI) — Saqinavir, Ritonavir...
- Antiglycosidase

HAART – Highly Active AntiRetroviral Therapy

usual HAART regimen combines 3 or more different drugs such as 2 nucleoside RTIs and PI, 2 nucleoside RTIs and a non-nucleoside reverse transcriptase inhibitor (NNRTI) or other such combinations

HIV treatment

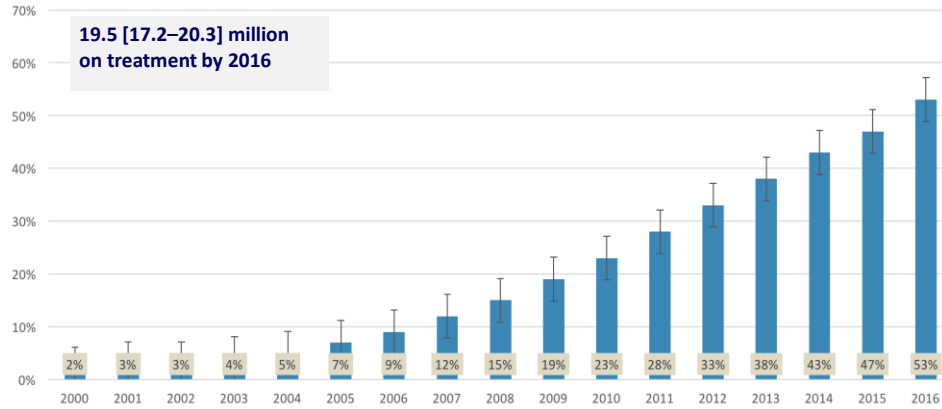
- Receptor neutralisation
- Reverse transcriptase inhibitors (RTIs) – **NRTI a NNRTI**
- Inhibitors of integrase
- Inhibitors of transcription
- Protease inhibitors (PI)
- Antiglycosidase



HAART

usual HAART regimen combines 3 or more different drugs such as 2 nucleoside RTIs and PI, 2 nucleoside RTIs and a non-nucleoside reverse transcriptase inhibitor (NNRTI) or other such combinations

ART coverage over time



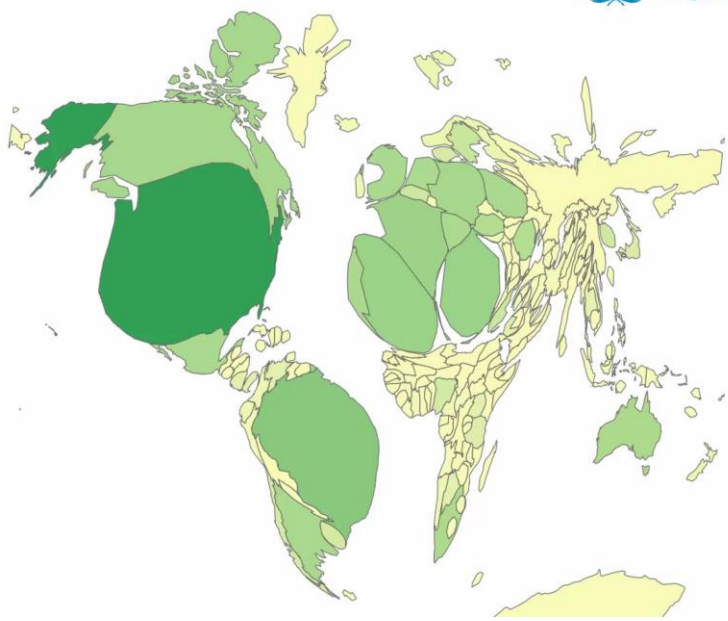
Source: UNAIDS/WHO estimates.

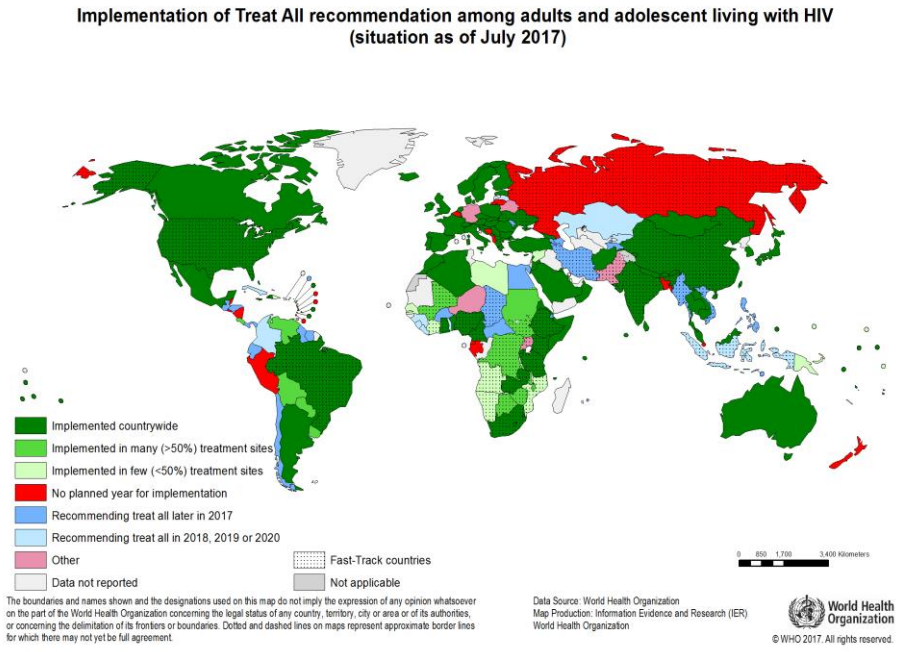
19.5 millions (17 in 2015) of people had access to antiretroviral therapy

HAART

- 2 nucleoside RTIs and PI
- 2 nucleoside RTIs and a NNRTI
- …

Countries with size proportional to people on ART, 2000-2016





Factors influencing the survival

- ↓ of viral load – primoinfection therapy
- Treatment of the opportunistic infections
- Careful use of common vaccines
- Treatment during decrease of CD4 lymfocyte count

After HAART
IRIS –
Immune Reconstitution Inflammatory Syndrome can be observed.

Viral hepatitis

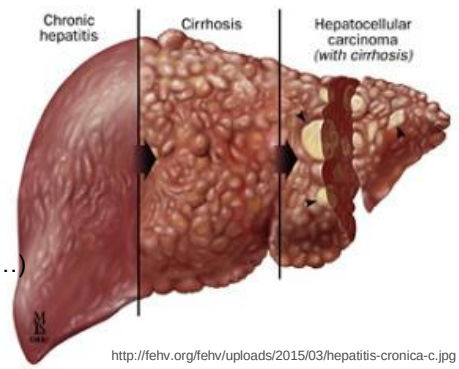
- A RNA virus Picornaviridae /Heparnavirus
- B DNA virus Hepadnaviridae/Hepadnavirus
- C RNA virus Flaviviridae/Flavivirus
- D RNA virus HBV dependent/Deltavirus
- E RNA virus Hepeviridae
- G RNA virus Flaviviridae
- TTV DNA virus Anelloviridae

Hepatitis

Hepatitis is a disease of the liver characterized by the presence of inflammatory cells in the tissue of the organ. Hepatitis may occur without symptoms, but can lead to jaundice (a yellow discoloration of the skin, mucous membranes, and conjunctiva of the eyes), poor appetite, and fatigue. (Wikipedia)

- acute – chronic
- cirhosis – fibrosis
- potencially lethal

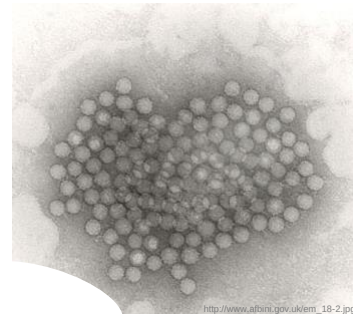
- treatment
  - hepatoprotective drugs
  - liver-protective food (no/low fat…)



http://fehv.org/fehv/uploads/2015/03/hepatitis-cronica-c.jpg

Hepatitis A Virus (HAV)

- small RNA virus (27-30 nm)
- non-enveloped - Picornavirus
- genetically homogenous
- resistant to environment
- transmission fecal-oral route through GIT
- release in stool
- human restricted pathogen

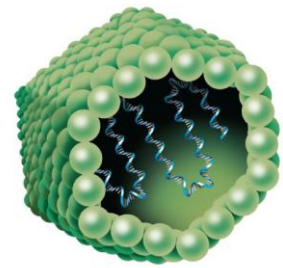


http://www.afbini.gov.uk/em_18-2.jpg

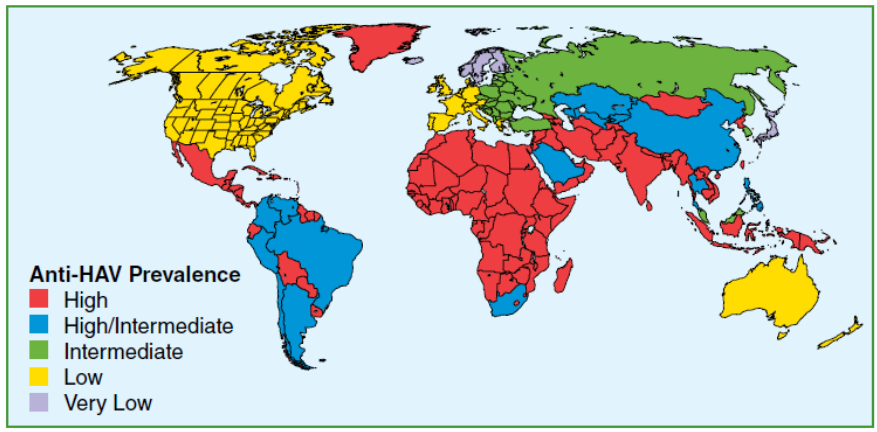
http://www.healthsym.com/wp-content/uploads/2013/01/JAUNDICE.jpg

Hepatitis A Virus (HAV) Pathogenesis

- Incubation period 15-45 days
- Primary proliferation in enterocytes
- Short viremia
- Subsequently infects hepatocytes and release to the stool through bile
- No ability to chronic infection



Hepatitis A Virus (HAV) Geographic distribution

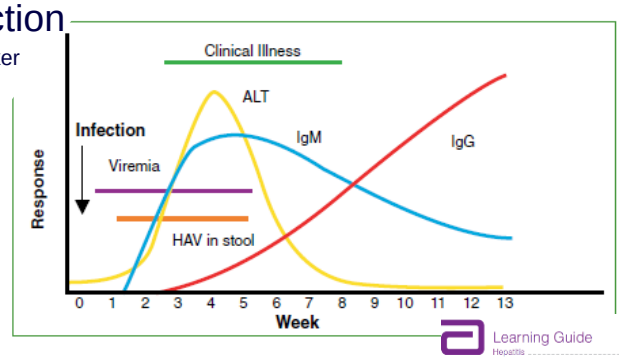


*Note: This map has been generalized from available data.

Learning Guide Hepatitis

Hepatitis A Virus (HAV) Diagnostics

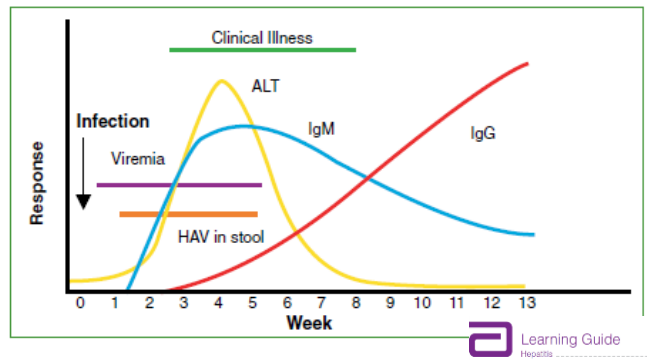
- Electronmicropy in stool
  - In the 2nd part of incubation period, shortly after start of the clinical symptoms
- Antigen and RNA detection
  - In stool, similar to EM
- Antibody detection
  - Main diagnostic marker



Learning Guide Hepatitis

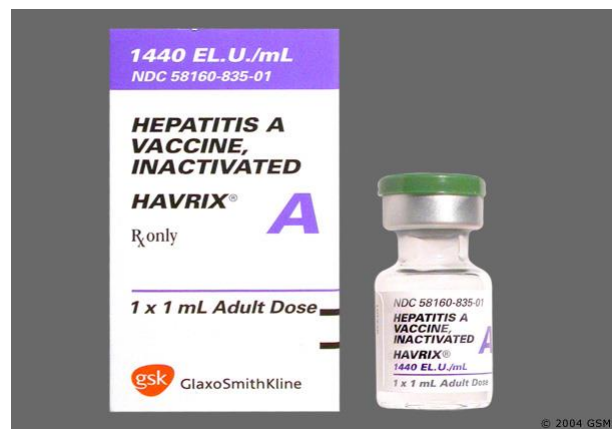
Hepatitis A Virus (HAV) Diagnostics - antibody

- Total Immunoglobuline (Ig)
  - Acute infection
  - Post infection immunity
  - Post vaccination immunity
- Specific IgM
  - Acute infection
  - Convalescence (even > 1 yr)



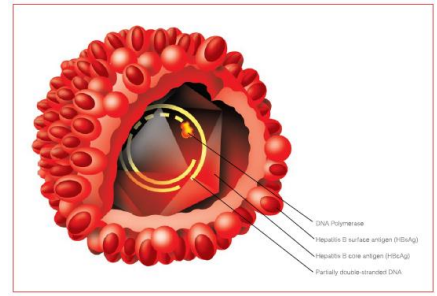
Hepatitis A Virus (HAV) Therapy and prevention

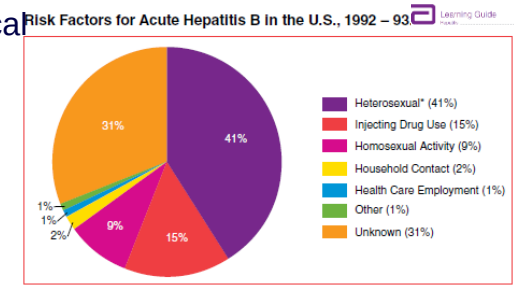
- No specific treatment
- Prophylaxis with human immunoglobuline
- Vaccination
  - (Havrix..)



Hepatitis B Virus (HBV)

- DNA virus with complicated life cycle
- enveloped
- genus – Hepadnavirus
- Antigen structures important for diagnostics
- HBV subtypes without clinical importance
- Sensitive to environmental conditions
- Blood and sexually transmitted
- human restricted pathogen





Source: Centers for Disease Control and Prevention Sentinel Counties Study of Viral Hepatitis

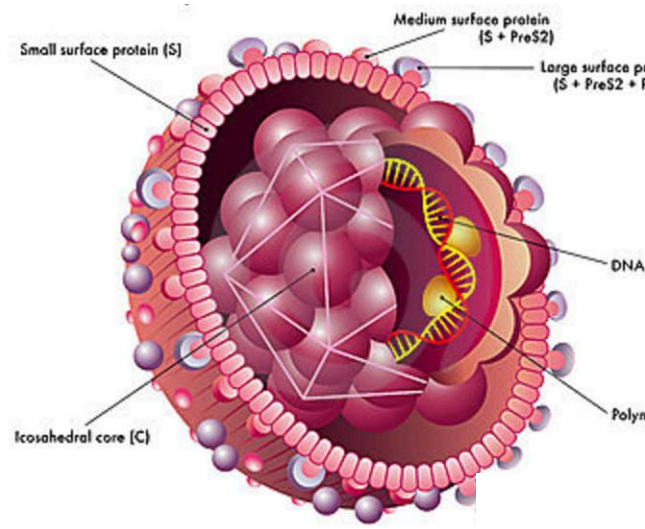
**Includes sexual contact with acute cases, carriers, and multiple partners*

Hepatitis B Virus (HBV) Genome structure

- circular DNA, not fully double-stranded
- one end of the full length strand linked to the viral DNA polymerase
- genome 3020–3320 nucleotides long (full-length strand) and 1700–2800 nucleotides long (short length-strand)

http://upload.wikimedia.org/wikipedia/commons/thumb/0/00/HBV_Genome.svg/425px-HBV_Genome.svg.png

Hepatitis B Virus (HBV)
Viral structure



HBsAg – surface antigen

HBeAg – enhanced infectivity

HBcAg – core antigen

http://thumbs.dreamstime.com/z/hepatitis-b-virus-22144156.jpg

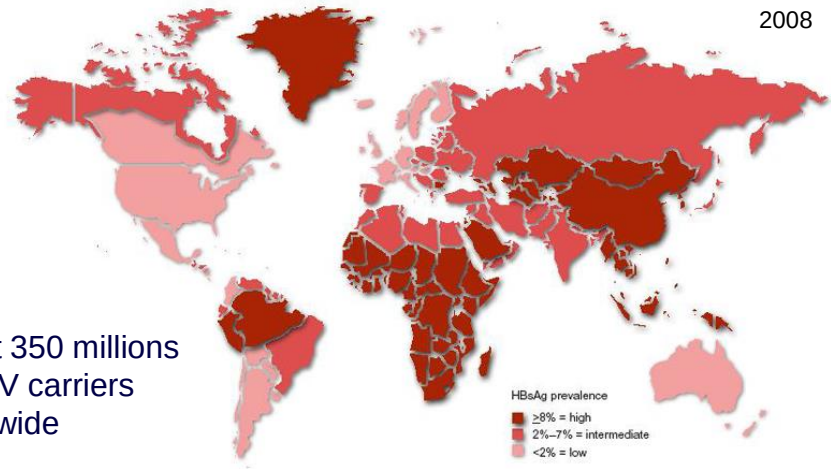
Hepatitis B Virus (HBV)
Clinical symptoms

- acute illness
- history of blood administration
- incubation period 2-6 months
- long lasting infection
- switch to chronicity in 5-10%
  - Hepatic fibrosis

http://www.google.cz/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&cad=rja&docid=rQwLNq8-Wn1SeM&tbnid=STc4TtPRL8qMYM:&ved=&url=http%3A%2F%2Faquilathp.blogspot.com%2F2013%2F08%2Fcirrhosis.html&ei=N_9WUqycJleS5ATqqYCoAw&bvm=bv.53899372,d.bGE&psig=AFQjCNG575vNjxajKUy5GPU0YNHCYVq4tQ&ust=1381519543978090

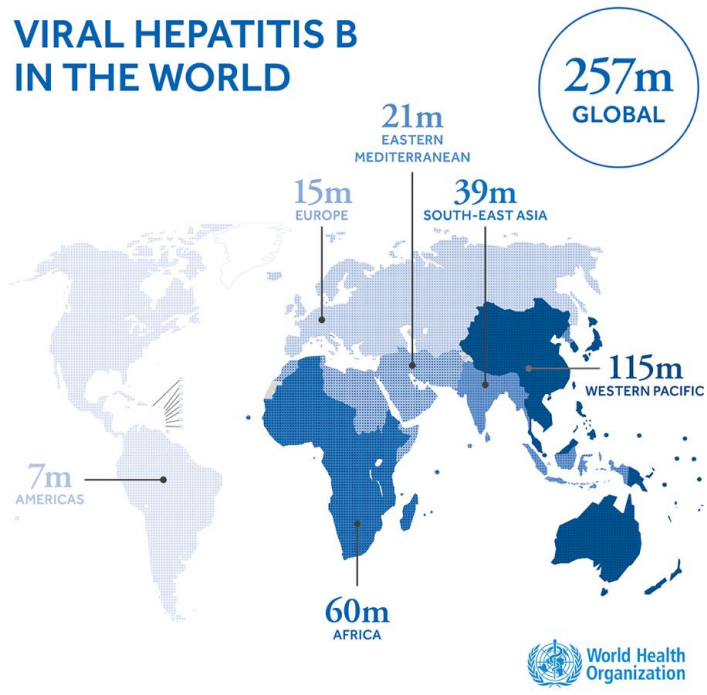
Hepatitis B Virus (HBV) Geographic distribution

2008



About 350 millions of HBV carriers worldwide

* For multiple countries, estimates of prevalence of hepatitis B surface antigen (HBsAg), a marker of chronic HBV infection, are based on limited data and might not reflect current prevalence in countries that have implemented childhood hepatitis B vaccination. In addition, HBsAg prevalence might vary within countries by subpopulation and locality.
Source: CDC. Travelers' health; yellow book. Atlanta, GA: US Department of Health and Human Services, CDC; 2008. Available at http://wwwn.cdc.gov/travel/yellowbookch4-HepB.aspx.
http://img.medscape.com/fullsize/migrated/editorial/casecme/2008/17750/figure.png



2017

Hepatitis B Virus (HBV) Diagnostic markers

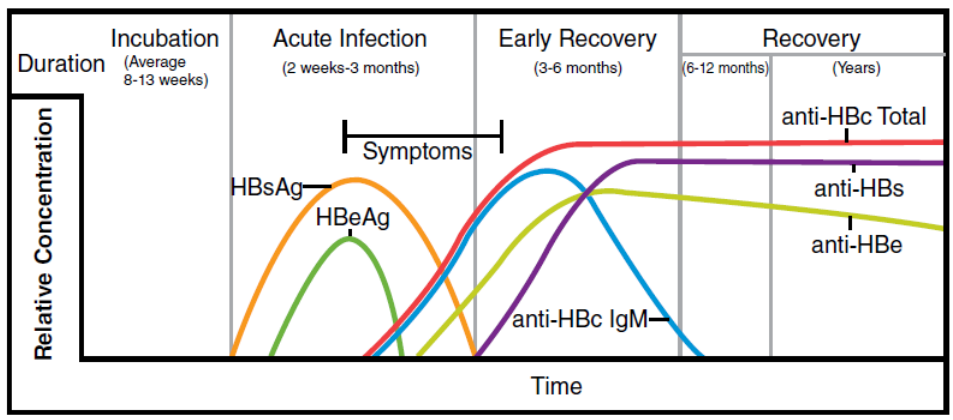
- Antigens
- HBs Ag
  - high amounts
  - in acute and chronic
  - sign of carrier
- HBe Ag
  - marker of acute and active infection
- DNA
  - Qualitative
  - Quantitative

    (treatment monitoring)

- Antibodies
- anti HBs
  - in convalescence
  - after vaccination
- anti HBe
  - in convalescence
- anti HBc
  - lifelong evidence of infection

Hepatitis B Virus (HBV) Antibody response

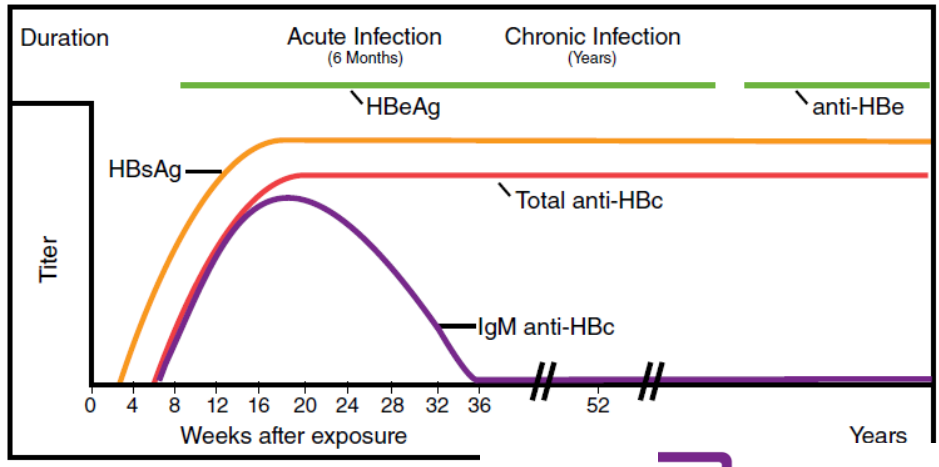
Acute Hepatitis B Diagnostic Profile



Learning Guide
Hepatitis

Hepatitis B Virus (HBV) Antibody response

Progression to Chronic HBV Infection Typical Serologic Course

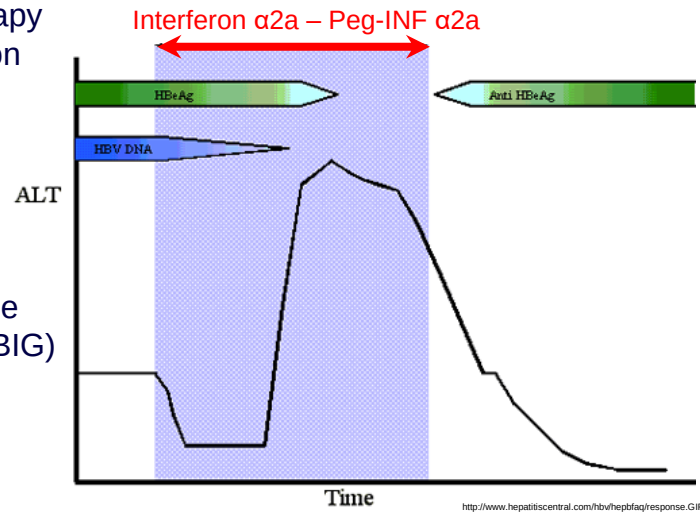


Learning Guide
Hepatitis

Hepatitis B Virus (HBV) Therapy and prevention

- Immunotherapy with interferon
- Virostatics (lamivudine, adefovir)
- Vaccine
  - Engerix..
- Hyperimmune globuline (HBIG)

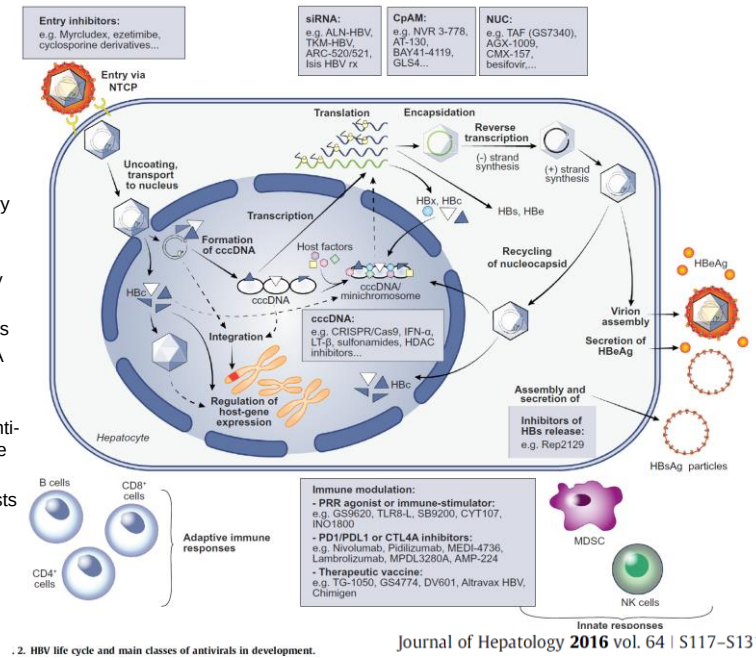
BUT…



Hepatitis B Virus (HBV) New therapy

DAA

- inhibitors of viral entry
- new polymerase inhibitors
- capsid and assembly inhibitors
- virus release blockers
- disruptors of cccDNA formation and transcription
- Agents enhancing anti-HBV specific immune responses
- including TLR agonists
- checkpoint inhibitors
- therapeutic vaccines

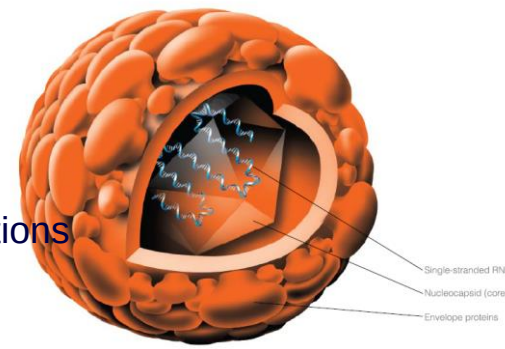


. 2. HBV life cycle and main classes of antivirals in development.

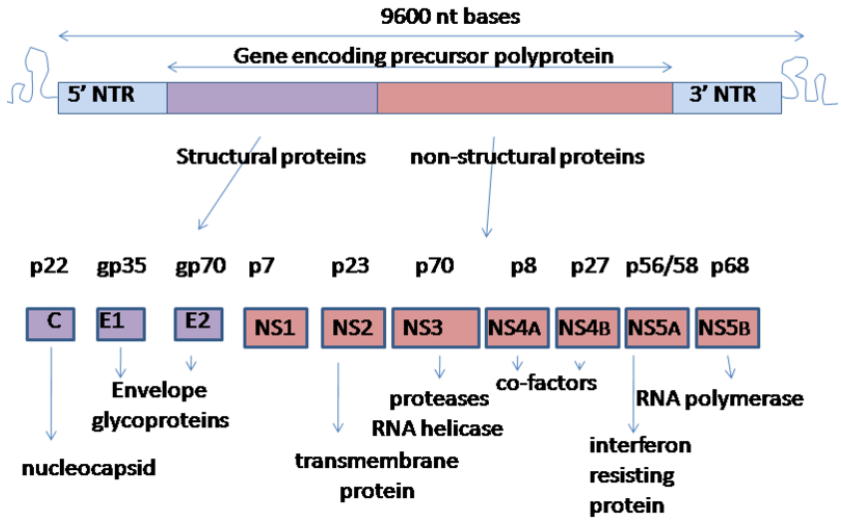
Journal of Hepatology **2016** vol. 64 | S117–S131

Hepatitis C Virus (HCV)

- ss RNA virus (uncultivateable)
- Flavivirus
- 6 types and about 40 subtypes
- Sensitive to environmental conditions
- Blood and sexually transmitted
- Human restricted pathogen



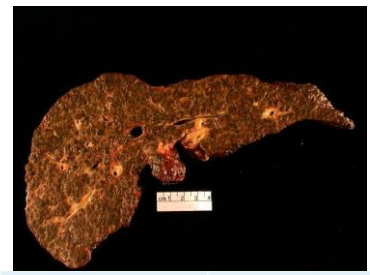
Hepatitis C Virus (HCV) Genome structure

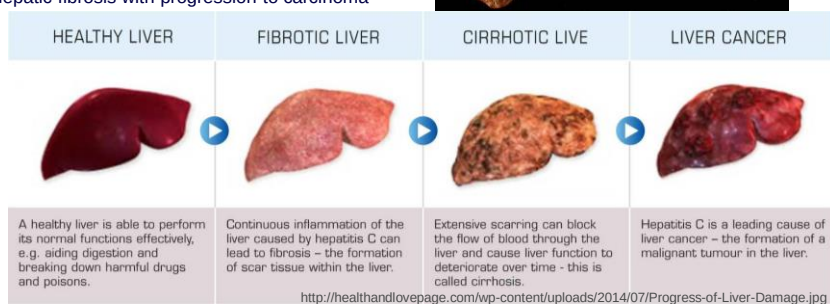


http://upload.wikimedia.org/wikipedia/commons/thumb/c/c0/HCV_genome.png/800px-HCV_genome.png

Hepatitis C Virus (HCV) Clinical symptoms

- discreet start of illness
- often unicteric form 60-70%
- incubation period 2-7 wks (2-26 wks)
- long lasting infection
- switch to chronicity up to 80%
  - Hepatic fibrosis with progression to carcinoma

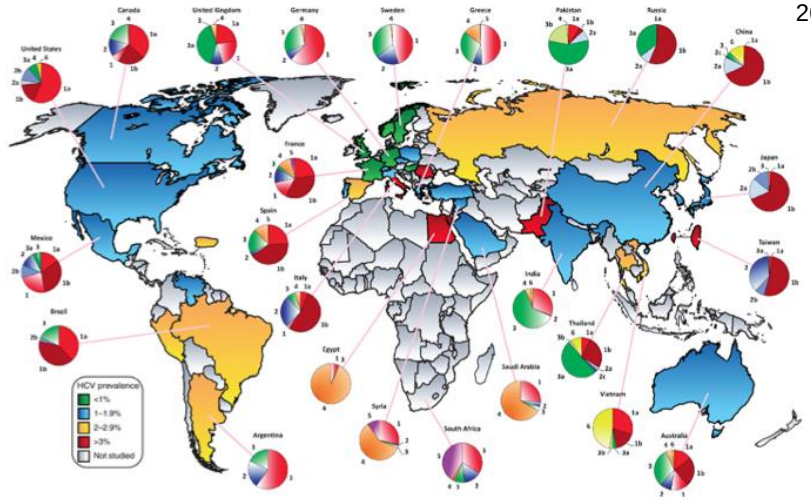




http://healthandlovepage.com/wp-content/uploads/2014/07/Progress-of-Liver-Damage.jpg

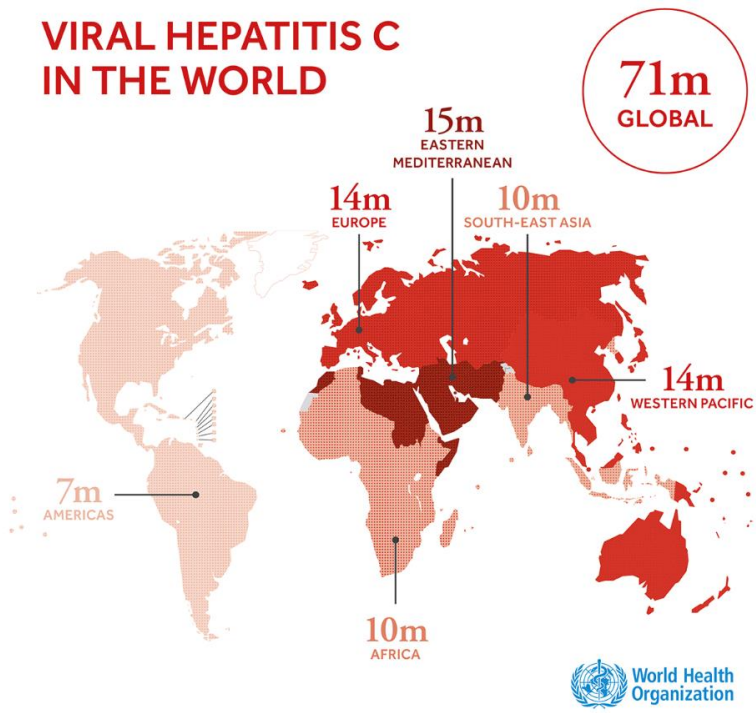
Hepatitis C Virus (HCV) Geographic distribution

2011



About 170 millions of HCV carriers worldwide

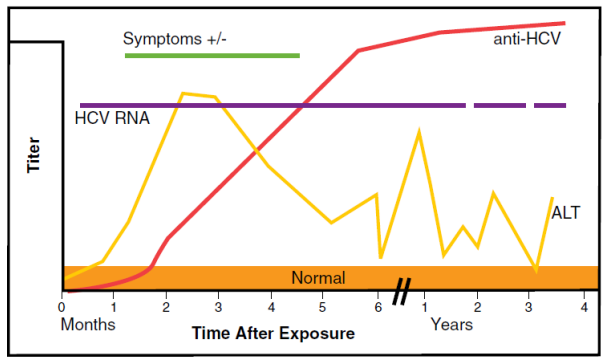
http://lloydbelcher.files.wordpress.com/2011/07/hcv-global-prevalence.png



2017

Hepatitis C Virus (HCV) Diagnostics

- RNA
  - Qualitative or quantitative
    (treatment monitoring)
- Antibody detection anti-HCV (ELISA)
  - in infection and convalescence
    - < 3 months

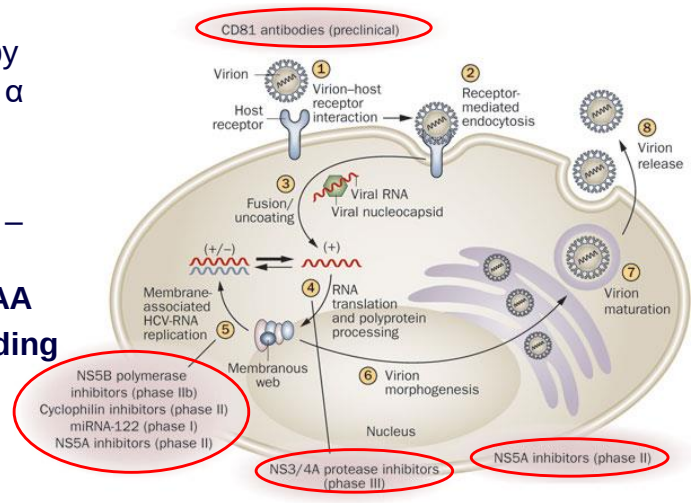


Serologic Pattern of Acute HCV Infection With Progression to Chronic Infection

Learning Guide Hepatitis

Hepatitis C Virus (HCV) Therapy and prevention

- Immunotherapy with interferon α
- Virostatics (ribavirine)
- Combined Th. – **Direct acting antivirals - DAA**
- **Differs according to the type of HCV**
- No Vaccine



http://www.nature.com/nrgastro/journal/v8/n2/images/nrgastro.2010.219-f1.jpg

Hepatitis C Virus (HCV) Therapy and prevention

- **Direct acting antivirals – DAA**
  - nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs)
    telaprevir a **boceprevir**
  - NS5B nucleoside polymerase inhibitors (NPIs)
    grazoprevir, **paritaprevir** a **simeprevir**, **sofosbuvir**
  - NS5B non-nucleoside polymerase inhibitors (NNPIs)
    dasabuvir
  - NS5A inhibitors
    edipasvir, **ombitasvir**, **elbasvir** a **daclatasvir**
  - **In some drugs, there are fixed combination of virostatics**

STANDARDNÍ DIAGNOSTICKÝ A TERAPEUTICKÝ POSTUP CHRONICKÉ INFEKCE VIREM HEPATITIDY C (HCV)

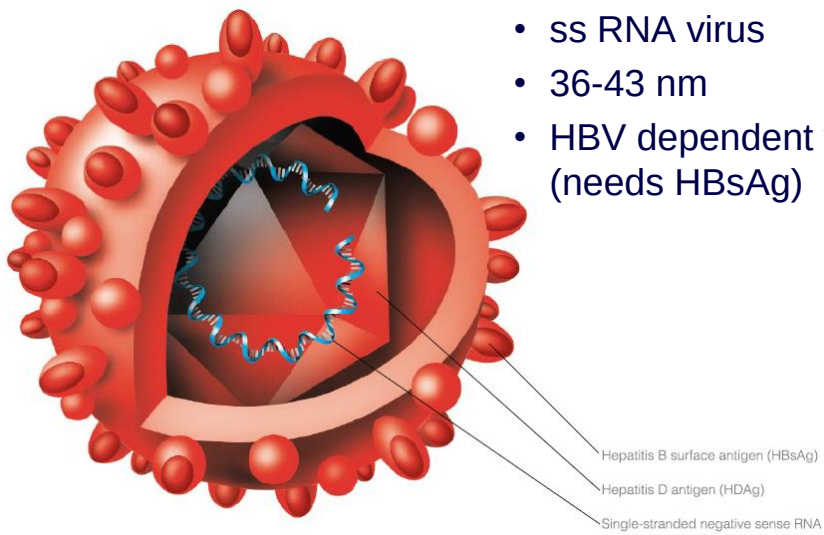
Pracovní skupina pro virové hepatitidy České hepatologické společnosti České lékařské společnosti Jana Evangelisty Purkyně
Pracovní skupina pro virové hepatitidy Společnosti infekčního lékařství České lékařské společnosti Jana Evangelisty Purkyně

Autoři
Doc. MUDr. Petr Urbánek, CSc.
Prof. MUDr. Petr Husa, CSc.
MUDr. Jan Šperl, CSc.
Doc. MUDr. Stanislav Plíšek, Ph.D.
Doc. MUDr. Luděk Rožnovský, CSc.
MUDr. Petr Klimpel

www.ces-hep.cz
www.infekce.cz

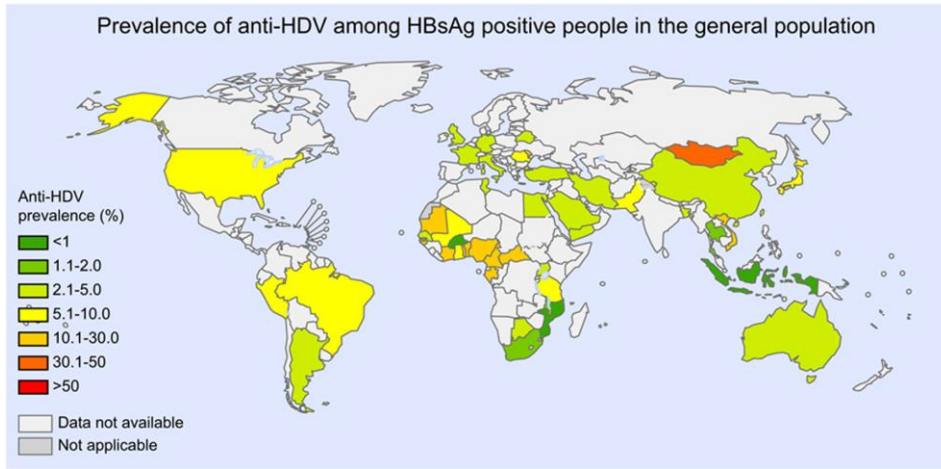
Datum: 29.10. 2014

Hepatitis D Virus (HDV)



- ss RNA virus
- 36-43 nm
- HBV dependent virus (needs HBsAg)

Hepatitis D Virus (HDV) Geographic distribution

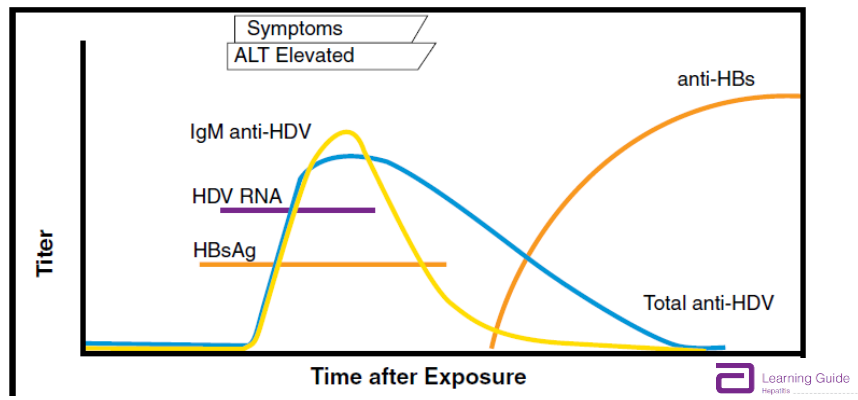


Journal of Hepatology 2020 73523-532DOI: (10.1016/j.jhep.2020.04.008)

EASL JOURNAL OF HEPATOLOGY

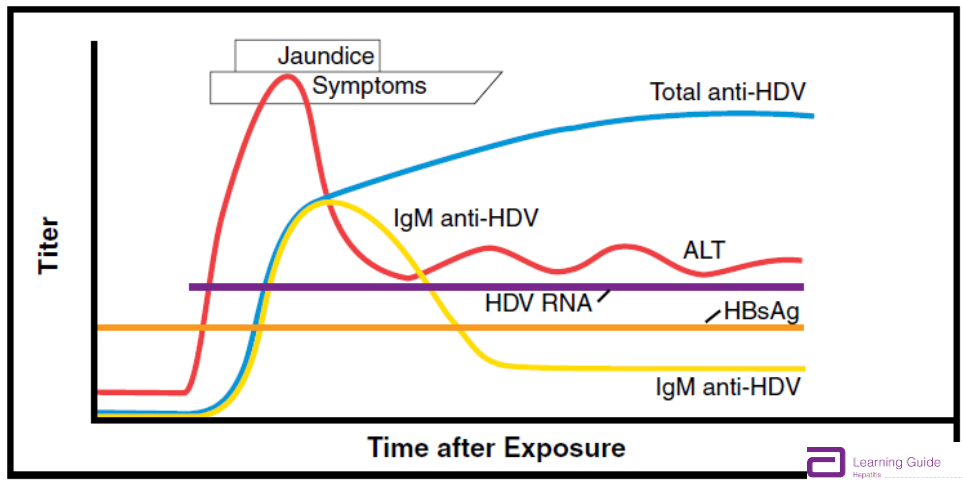
Hepatitis D Virus (HDV) Clinical symptoms

- **Co-infection** with HBV; transmission similar
- Incubation period 21-49 days; abrupt start
- More severe clinical course



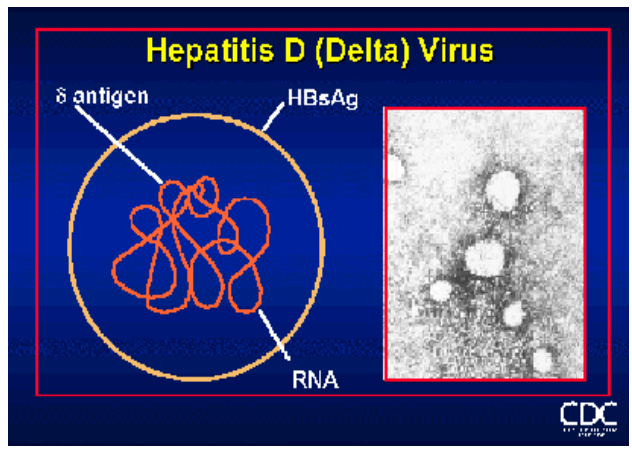
Hepatitis D Virus (HDV) Clinical symptoms

- Often chronic HBV **super-infection** (80%)



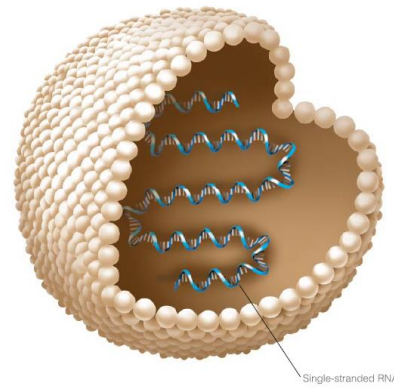
Hepatitis D Virus (HDV) Diagnostics

- RNA
- Antibody detection – IgM and IgG



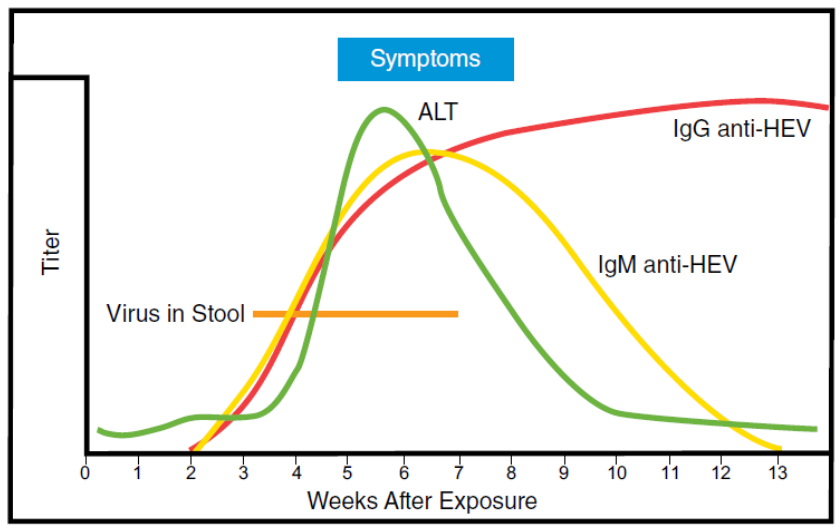
Hepatitis E Virus (HDV)

Virus Family	Hepeviridae
Route of Transmission	Fecal-oral (especially contaminated water)
Onset	Usually abrupt
Incubation	15 – 60 days, average 40 days
Chronicity	None reported
Mortality	About 1 – 3%, 15 – 25% in pregnant women



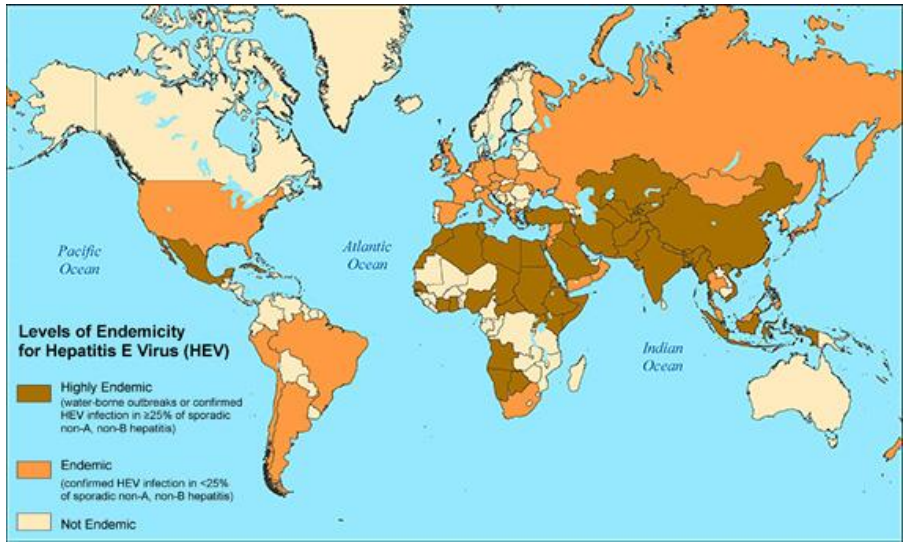
Learning Guide

Hepatitis E Virus (HEV) Diagnostics



Learning Guide

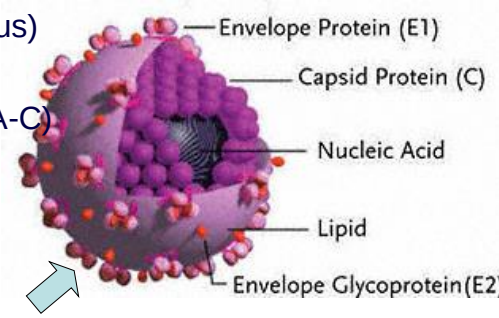
Hepatitis E Virus (HEV) Geographic distribution



http://www.cdc.gov/hepatitis/HEV/images/Map5_4_HepatitisE_sml.jpg

Hepatitis G Virus (HGV)

- RNA viry similar to HCV (Flavivirus- genus Pegivirus)
- several types
- different HGV and GBV (A-C)
- Blood transmission
- Also in health population
- Patogenic likely **GBV-C**

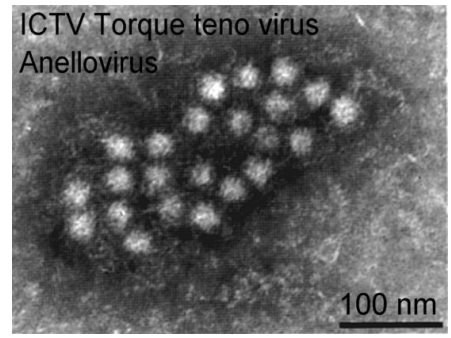


http://www.prn.org/images/uploads/gbv-c_3d_high.jpg

- **Diagnostics mainly PCR** (Antibody non reliable)

Torque Teno Virus (TTV)

- DNA virus
- Uncertain pathogenity
- Blood transmission
- Also in health population

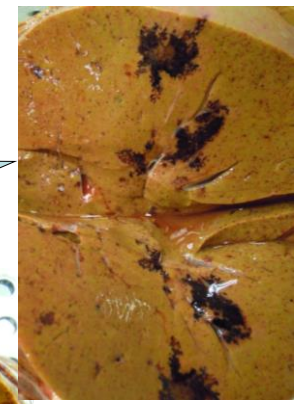


http://ictvdb.bio-mirror.cn/WIntkey/Images/em_anell_ICTV.jpg

- **Diagnostics only PCR**

Other viruses associated with hepatitis/hepatopathy

- **CMV**
- **EBV** (hepatopathy)
- **HSV**
- **adenovirus**
- **enterovirus**
- **Influenza**



- **From exotic viruses – yellow fever virus, dengue fever virus and more…**


Thank you for your attention