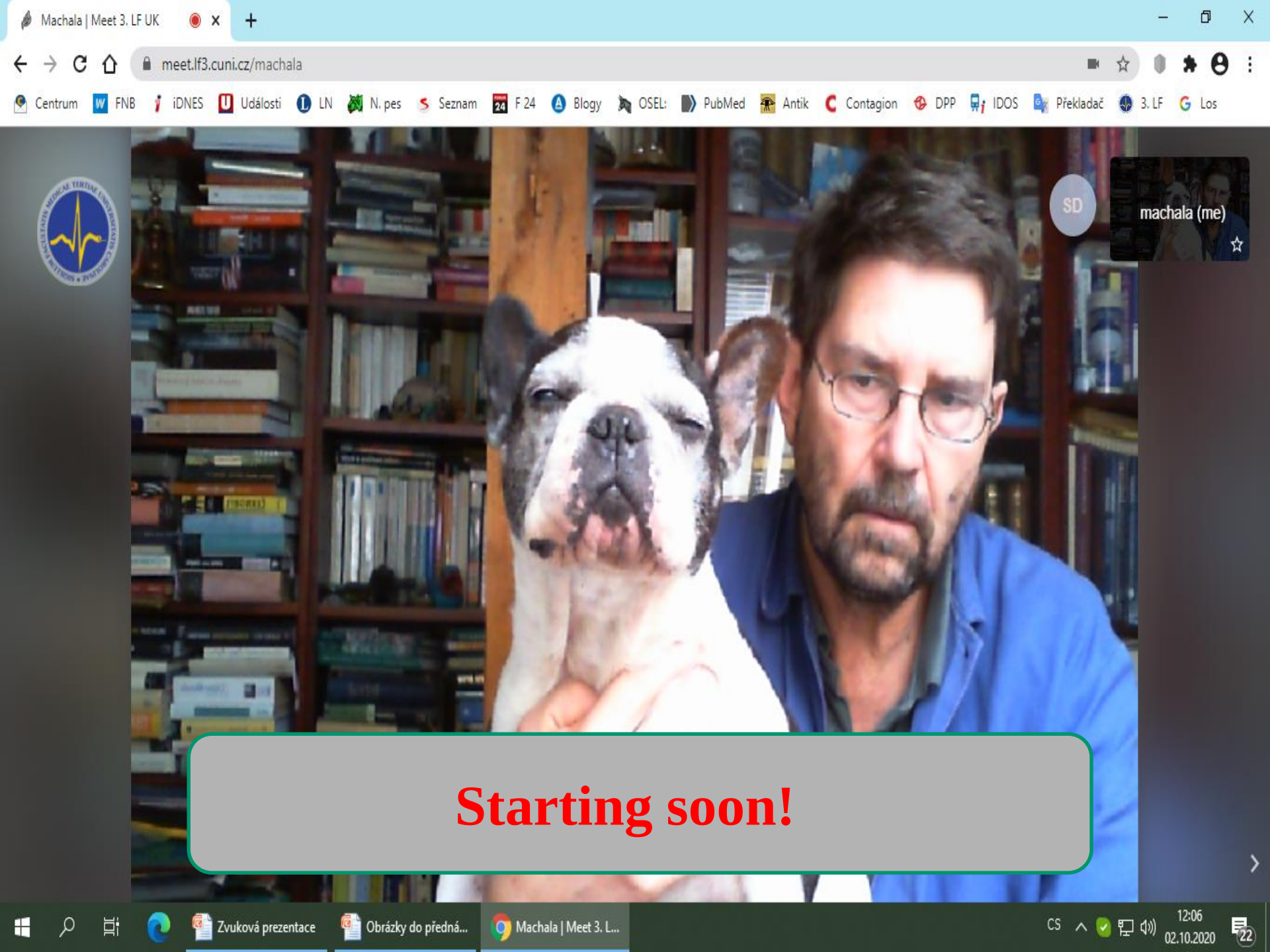

Machala | Meet 3. LF UK
meet.lf3.cuni.cz/machala
Centrum
FNB
iDNES
Události
LN
N. pes
Seznam
F 24
Blogy
OSEL:
PubMed
Antik
Contagion
DPP
IDOS
Překladač
3. LF
Los
SD
machala (me)
Starting soon!
Zvuková prezentace
Obrázky do předná...
Machala | Meet 3. L...
CS
12:06
02.10.2020

HIV/AIDS - history

1981 – AIDS

survival ~6 m

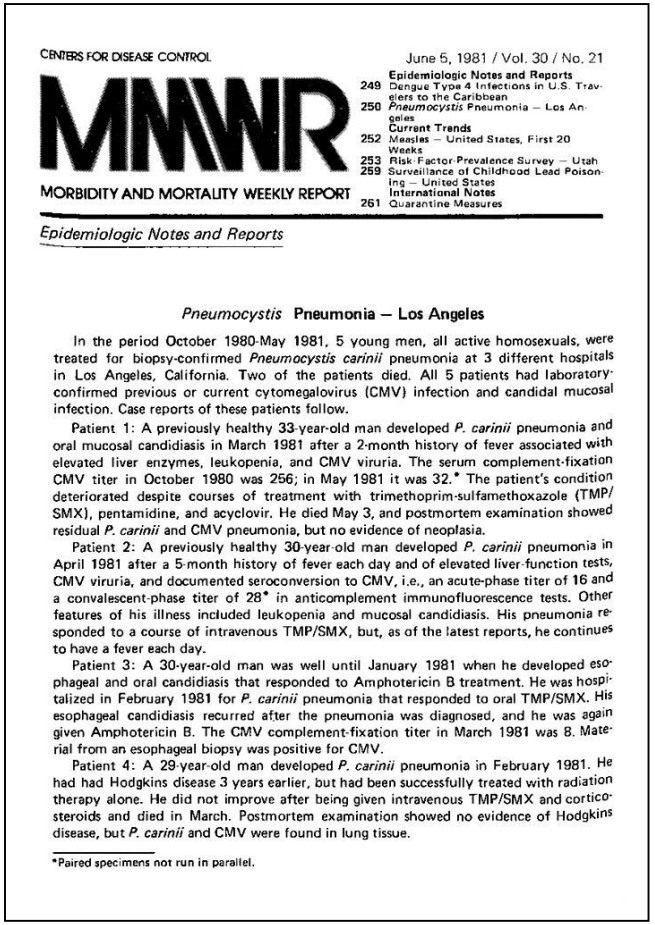
1983 – HIV discovery

1987 – zidovudine

survival ~1,5 y

1995 – combination therapy

(cART – *combination antiretroviral therapy*)



CENTERS FOR DISEASE CONTROL

June 5, 1981 / Vol. 30 / No. 21

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Epidemiologic Notes and Reports

Pneumocystis Pneumonia — Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viruria. The serum complement-fixation CMV titer in October 1980 was 256; in May 1981 it was 32.* The patient's condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole (TMP/SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination showed residual *P. carinii* and CMV pneumonia, but no evidence of neoplasia.

Patient 2: A previously healthy 30-year-old man developed *P. carinii* pneumonia in April 1981 after a 5-month history of fever each day and of elevated liver-function tests, CMV viruria, and documented seroconversion to CMV, i.e., an acute-phase titer of 16 and a convalescent-phase titer of 28* in anticomplement immunofluorescence tests. Other features of his illness included leukopenia and mucosal candidiasis. His pneumonia responded to a course of intravenous TMP/SMX, but, as of the latest reports, he continues to have a fever each day.

Patient 3: A 30-year-old man was well until January 1981 when he developed esophageal and oral candidiasis that responded to Amphotericin B treatment. He was hospitalized in February 1981 for *P. carinii* pneumonia that responded to oral TMP/SMX. His esophageal candidiasis recurred after the pneumonia was diagnosed, and he was again given Amphotericin B. The CMV complement-fixation titer in March 1981 was 8. Material from an esophageal biopsy was positive for CMV.

Patient 4: A 29-year-old man developed *P. carinii* pneumonia in February 1981. He had had Hodgkins disease 3 years earlier, but had been successfully treated with radiation therapy alone. He did not improve after being given intravenous TMP/SMX and corticosteroids and died in March. Postmortem examination showed no evidence of Hodgkins disease, but *P. carinii* and CMV were found in lung tissue.

*Paired specimens not run in parallel.

HIV/AIDS - today

1981 – AIDS

survival ~6 m

1983 – HIV discovery

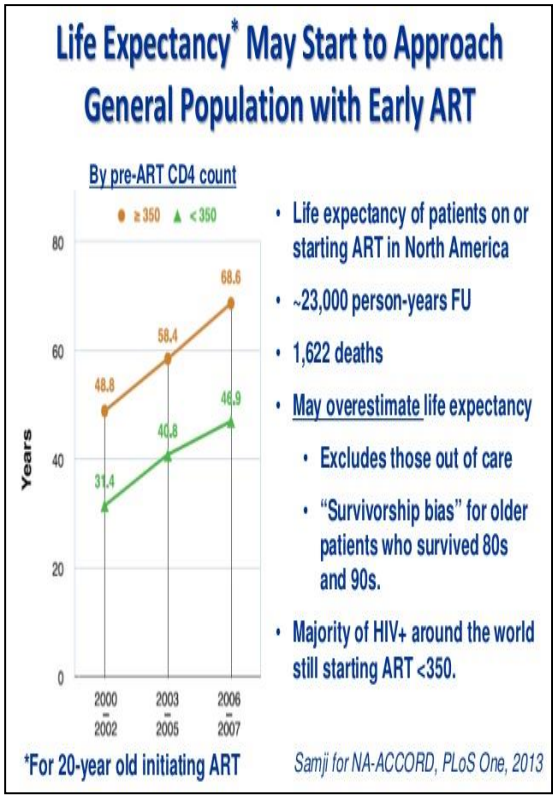
1987 – zidovudine

survival ~1,5 y

1995 – early cART

2010 – recent cART

expected survival = ± average life-span



HIV/AIDS - history

- **June 1981 - first 5 cases of pneumocystis pneumonia in Los Angeles**
- **autumn 1981 – first description of a new diseases - AIDS**
- **1983 isolation of the causative agent - virus HIV (Montagnier and Gallo)**
- **1986 isolation of HIV-2 (West Africa)**

L. Montagnier

R. Gallo

2020 estimate

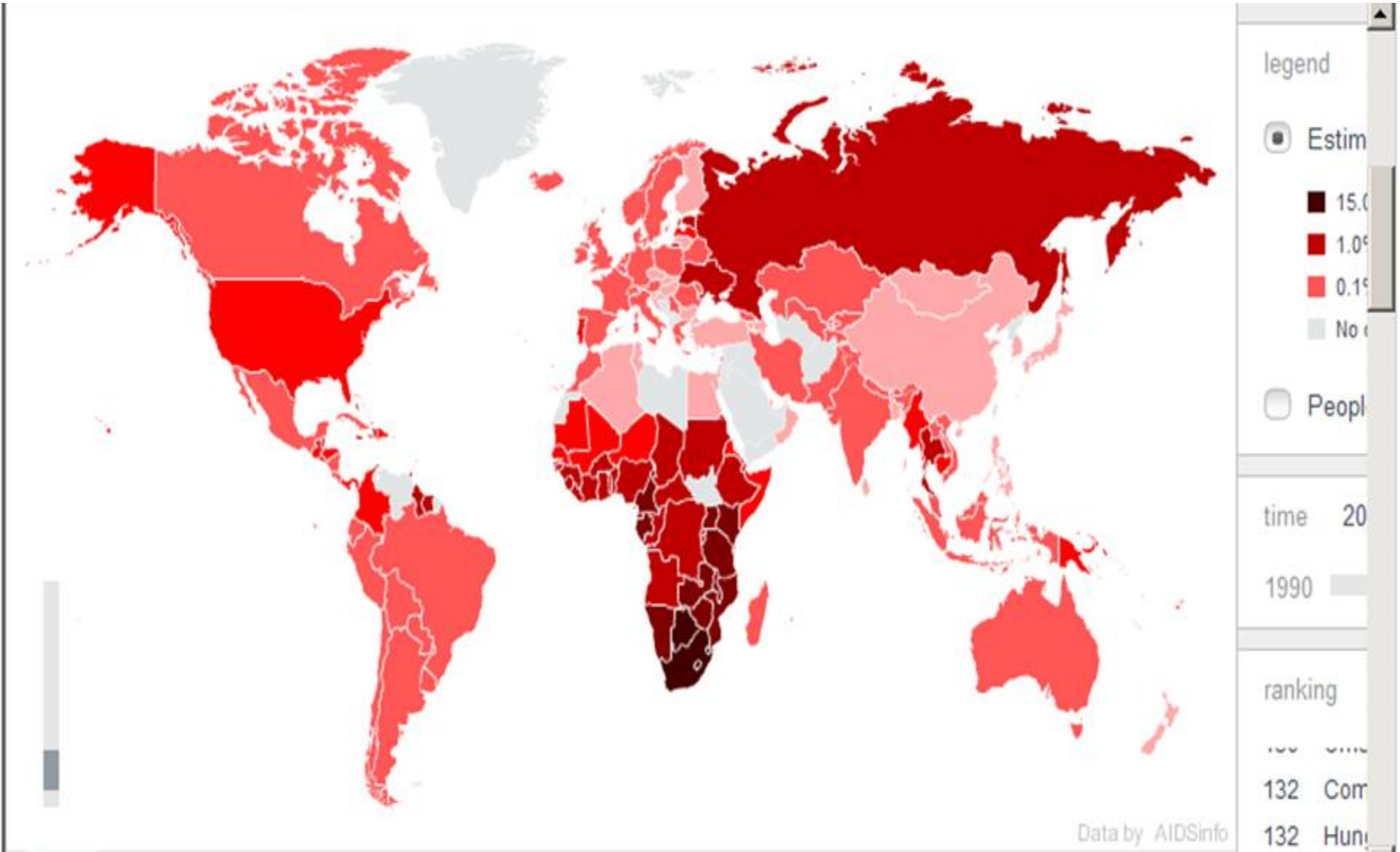
- **37.7 million living with HIV**
- **1.5 million newly infected**
- **0.68 million died**

- **36.3 million together died**

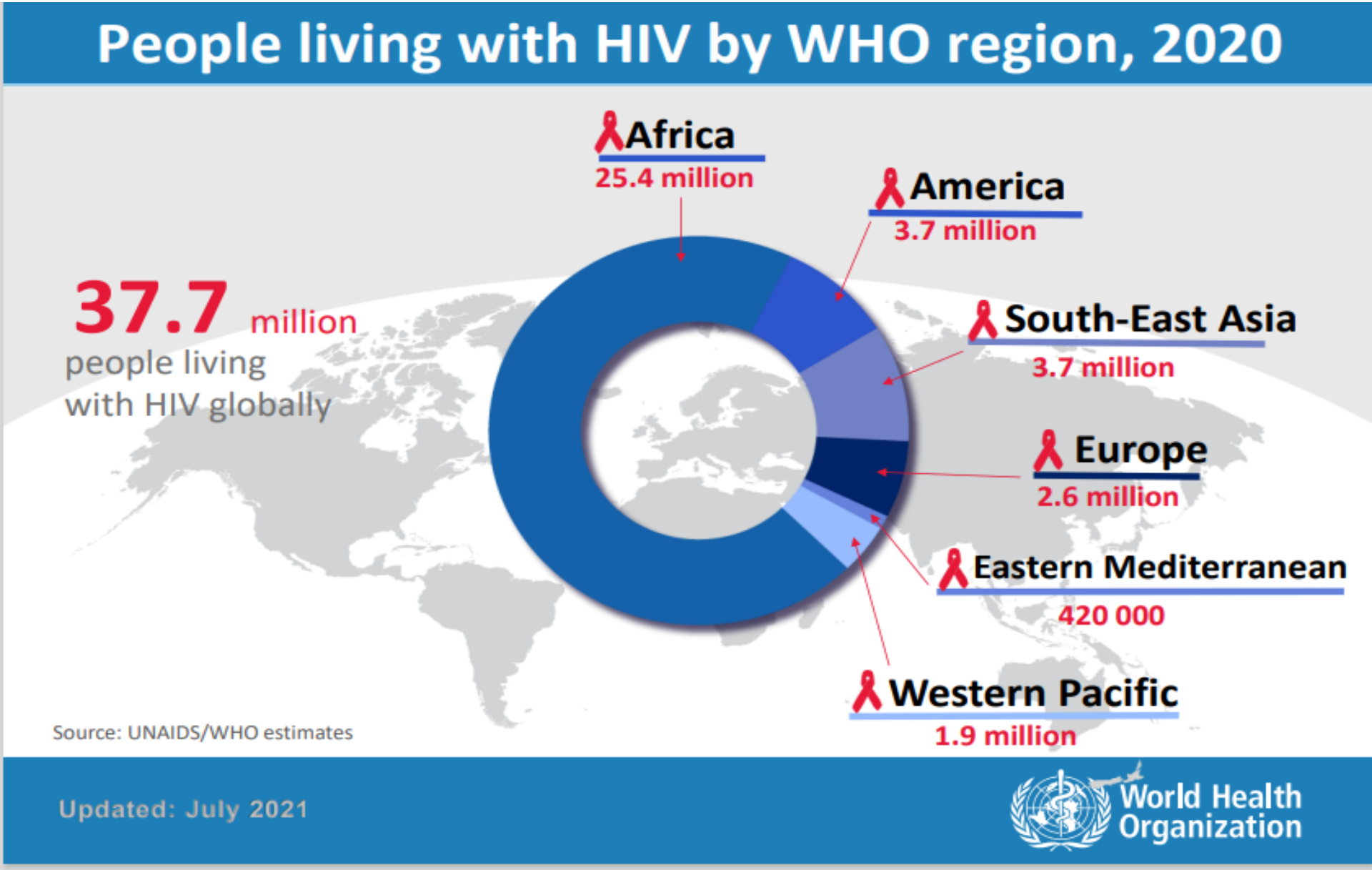
HIV/AIDS - epidemiology

- **90% of all HIV+ in the most poor parts of the world**
- **huge socio-economic problem**
- **Africa**
- **only 73% of all HIV+ people have access to cART**

HIV - world


legend
Estim
15.
1.0
0.1
No
Peopl
time
20
1990
ranking
132
132
Data by AIDSinfo

HIV - world


People living with HIV by WHO region, 2020
Africa
25.4 million
America
3.7 million
South-East Asia
3.7 million
Europe
2.6 million
Eastern Mediterranean
420 000
Western Pacific
1.9 million
37.7 million
people living
with HIV globally
Source: UNAIDS/WHO estimates
Updated: July 2021
World Health Organization

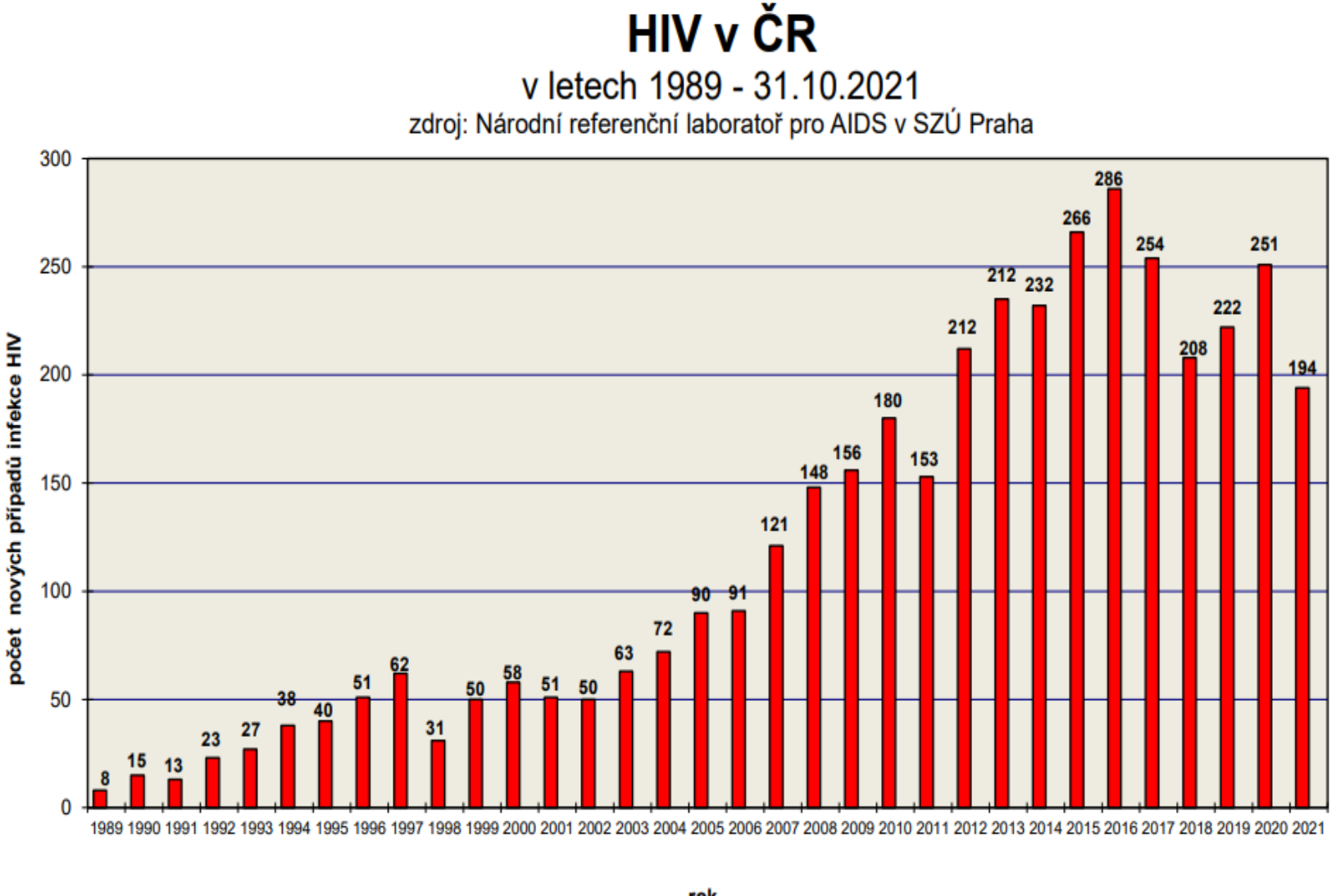
HIV - ČR

- first case1985
- 31.10.2021
  - 4034 HIV+
    - 3456 ♂
    - 578 ♀
  - 763 AIDS
    - 348 died
  - 502 HIV+ foreigners
    - 350 ♂
    - 152 ♀
  - 213 deliveries HIV+ women
    - 9 babies HIV+
- incidence 2/100 000
- estinate
  - in ČR live ~ 3500-4000 HIV+

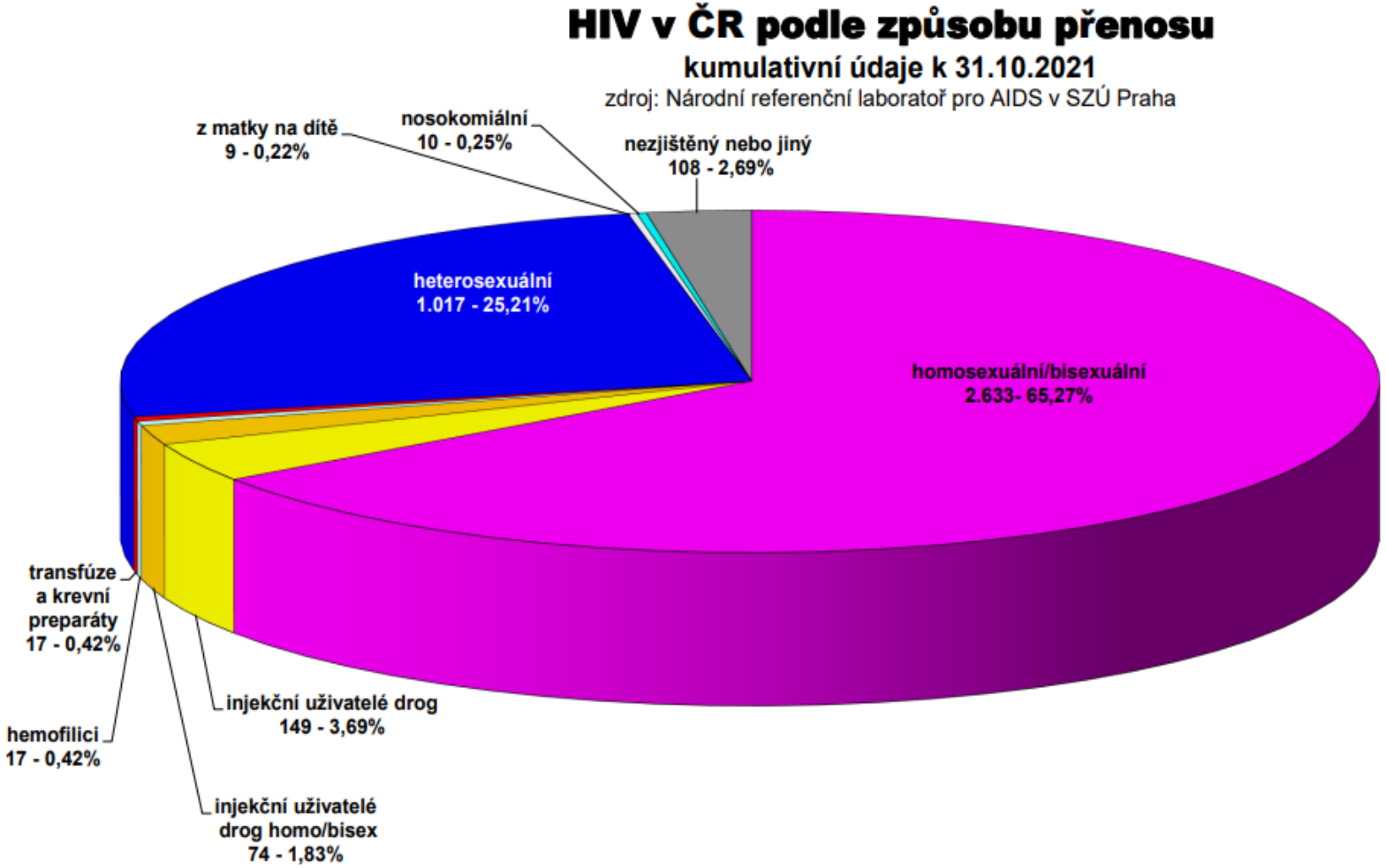
Centra poskytující péči HIV+ pacientům

Zdroj: Národní referenční laboratoř pro AIDS, Státní zdravotní ústav Praha

HIV - ČR


HIV v ČR
v letech 1989 - 31.10.2021
zdroj: Národní referenční laboratoř pro AIDS v SZÚ Praha
počet nových případů infekce HIV
0
50
100
150
200
250
300
8
15
13
23
27
38
40
51
62
31
50
58
51
50
63
72
90
91
121
148
156
180
153
212
212
232
266
286
254
208
222
251
194
1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021

HIV - ČR


HIV v ČR podle způsobu přenosu
kumulativní údaje k 31.10.2021
zdroj: Národní referenční laboratoř pro AIDS v SZÚ Praha
z matky na dítě
9 - 0,22%
nosokomiální
10 - 0,25%
nezjištěný nebo jiný
108 - 2,69%
heterosexuální
1.017 - 25,21%
homosexuální/bisexuální
2.633- 65,27%
transfúze
a krevní
preparáty
17 - 0,42%
hemofilici
17 - 0,42%
injekční uživatelé drog
149 - 3,69%
injekční uživatelé
drog homo/bisex
74 - 1,83%

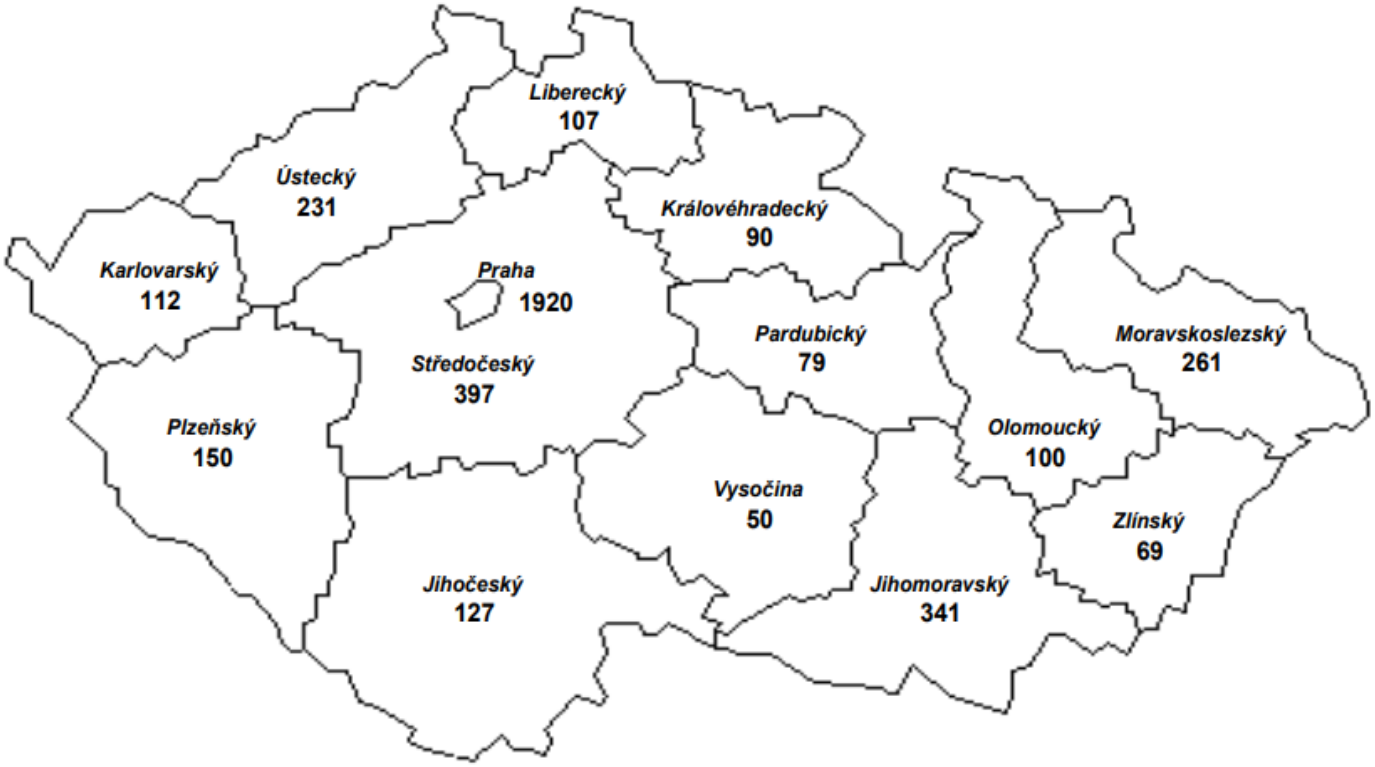
HIV - ČR

HIV INFEKCE V ČESKÉ REPUBLICE - občané ČR a cizinci s trvalým pobytem

rozdělení podle kraje bydliště v době první diagnózy HIV

kumulativní údaje za období 1.10.1985 - 31.10.2021

zdroj: Národní referenční laboratoř pro HIV/AIDS v SZÚ Praha



HIV infekce celkem: 4.034

HIV - ČR

HIV POZITIVNÍ CIZINCI V ČR
PODLE PŮVODU - GEOGRAFICKÉ OBLASTI
Kumulativní údaje za období
1.10.1985 - 31.10.2021

Geografická oblast	Muži	Ženy	Celkem	Způsob přenosu								
				HO	ID	IH	HF	TR	HT	MD	NO	NE
ZÁPADNÍ EVROPA	64	13	**77**	12	5	0	0	0	6	0	0	54
STŘEDNÍ EVROPA	53	16	**69**	12	1	0	0	0	18	0	1	37
VÝCHODNÍ EVROPA	101	67	**168**	16	30	0	0	0	58	0	0	64
SUBSAHARSKÁ AFRIKA	64	50	**114**	0	0	0	0	0	21	1	0	92
SEVERNÍ AFRIKA A BLÍZKÝ VÝCHOD	6	0	**6**	0	1	0	0	0	1	0	0	4
JIŽNÍ A JIHOVÝCHODNÍ ASIE	22	4	**26**	2	5	0	0	0	4	0	0	15
VÝCHODNÍ ASIE A OCEÁNIE	2	1	**3**	1	1	0	0	0	0	0	0	1
AUSTRÁLIE A NOVÝ ZÉLAND	1	0	**1**	1	0	0	0	0	0	0	0	0
SEVERNÍ AMERIKA	20	0	**20**	8	0	0	0	0	3	0	0	9
KARIBSKÁ OBLAST	5	0	**5**	1	0	0	0	0	2	0	0	2
JIŽNÍ AMERIKA	12	1	**13**	3	0	0	0	0	1	0	0	9
CELKEM	**350**	**152**	**502**	**56**	**43**	**0**	**0**	**0**	**114**	**1**	**1**	**287**

Způsob přenosu:

HO homosexuální / bisexuální ID injekční uživatelé drog

HIV/AIDS - etiology

- **RNA viruses HIV-1, HIV-2**
- **family *Retroviridae***
  - **subfamily *Lentivirinae***
- **other human retroviruses**
  - **HTLV-I – adult leukemia from T cells, tropical spastic paraparesis (myelopathy)**
  - **HTLV-II – probably hairy-cell leukemia**

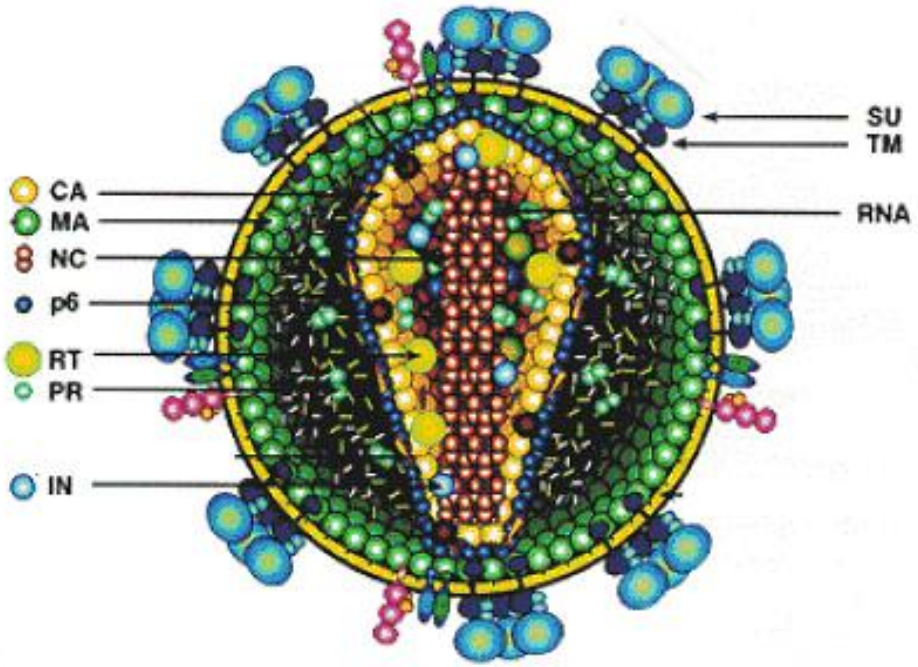
HIV/AIDS - etiology

HIV-1 and HIV-2 - differences

- different antigenic structure
  - HIV-1
    - responsible for the world pandemic
    - several genotypes - A, B, C, D, E, F…M, 0
  - HIV-2
    - occurs mainly in West Africa
    - less infective and virulent

HIV/AIDS – etiology

HIV - 1



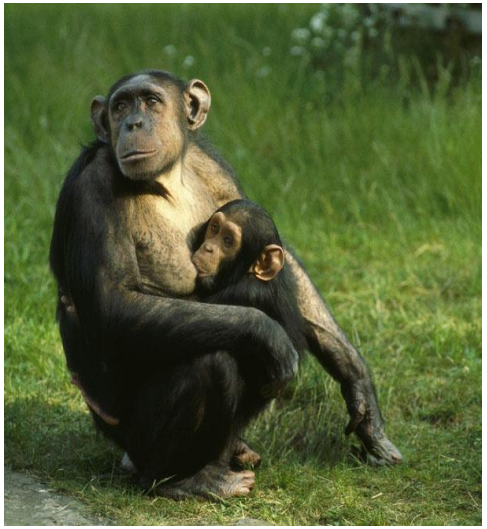
CA - capsid
MA - matrix
NC - nucleocapsid
SU - glycoprotein gp120
TM - glycoprotein gp41

RT - reverse transcriptase
IN - integrase
PR - protease

HIV/AIDS - etiology

<u>Origin of HIV</u> – probably natural evolution from monkey retroviruses SIV in Central and East Africa

HIV-1 from chimpanzee (*Pan troglodytes*)



HIV-2 from green monkey (*Cercocebus atys*)

HIV – diagnostic tests

- **informed consent**
- **routine screening**
  - **antibodies anti-HIV – after 4-6 w**
  - **antigen p-24 – after 2 w**
- **blood donors screening**
  - **antibodies anti-HIV**
  - **antigen p-24**
  - **PCR HIV RNA – after 1 w**
- **anonymous testing**

HIV - transmisson

HIV in body fluids

- blood
- sperma
- vaginal secretion

way of transmission

- blood
- sexually

Exposure – risk estimates

Exposure	risk %
transfusion HIV+ blood	>99,9
intact mucosa	0,009
percutaneous injury	0,3
i.v. exposuree – i.v. drugs	0,67
receptiva anal	0,5
insertive anal	0,065
receptive vaginal ♀	0,01
insertive vaginal ♂	0,005
vertical perinatal	15

HIV – transmission

<u>blood</u>

- **transfusion (window period)**
- **invasive procedures (needle < 0,5%)**
- **injection drugs**
- **vertical transmission mother ➔ baby (15 - 25%)**

HIV - transmission

sexually

- **homosexually**
- **heterosexually**

0,005%

♀ ⇄ ♂

0,01%

solution - „safer“ sex

- **non-promiscuous sexual behavior**
- **and/or barrier protection condom/femidom**
- **PrEP**

HIV/AIDS – clinical course

chronic disease

- not definitive cure
- but effective treatment

- 3 stages - clinical categories CDC 1993
  - A - asymptomatic stadium
  - B - early symptomatic stadium
  - C - advanced symptomatic stadium - AIDS

HIV infection – clinical course

incubation **4 – 6 w**

primary (acute) HIV infection - 85%

- **„febrile „virosis“**
  - **positive PCR – high HIV RNA (viral load)**
  - **positive p24 antigen**
  - **seroconversion – anti-HIV AB**

clinical category A - asymptomatic - latention about 10,5 y

- **normal clinical finding**
- **normal labory parameters**
  - **CD4+ T lymphocyte = 600 – 1100/mm^3**
  - **anti-HIV AB positive**
  - **viral load - low HIV RNA**
  - **antigen p24 negative**

HIV/AIDS – clinical course

clinical category B - early symptomatic

- **oropharyngeal candidiasis**
- **recurrent candidal vulvovaginitis**
- **bacillary angiomatosis**
- **oral leukoplakia (EBV)**
- **herpes zoster**
- **fever > 38,5˚C, diarrhea >4 weeks**
- **thrombocytopenic purpura (ITCP)**
- **cervical dysplasia (*ca in situ*)**
- **recurrent adnexitis**
- **listeria meningitis**
- **peripheral neuropathy**

HIV/AIDS – clinical course

clinical category C - AIDS

- **pneumocystis pneumonia (PCP)**
- **toxoplasmic encephalitis**
- **candidal esophagitis**
- **CMV retinitis, generalized CMV**
- **HS infection (respiratory, mucocutaneous)**
- **bacterial pneumonia >2x / year**

HIV/AIDS – clinical course

clinical category C - AIDS

- **salmonella sepsis**
- **TBC**
- **mycobacterial inf. (MAI etc.)**
- **cryptococcosis extrapulmonary**
- **cryptosporidiosis chronic**
- **coccidioidomycosis disseminated (USA)**

HIV/AIDS – clinical course

clinical category C - AIDS

- **histoplasmosis disseminated (USA)**
- **isosporosis chronic**
- **PMLE**
- **cervical ca invasive**
- **Kaposi sarcoma (HHV 8)**
- **malignant lymphoma (non-Hodgkin B)**

HIV/AIDS – clinical course

<u>clinical category C - AIDS</u>

- **primary brain lymphoma**
- **HIV encephalopathy (AIDS dementia)**
- **wasting syndrome (slim disease)**

USA: CD4+ lymphocytes < 200/mm^3

cART - goals

individual

- **suppression of HIV replication**
  - ***restitution of imunne function***
    - **life prolongation**
    - **life quality improvement (?)**

epidemiological

- ***reduction of HIV transmission***
  - **horizontally ~ 1000x**
  - **vertically ~ 10x**

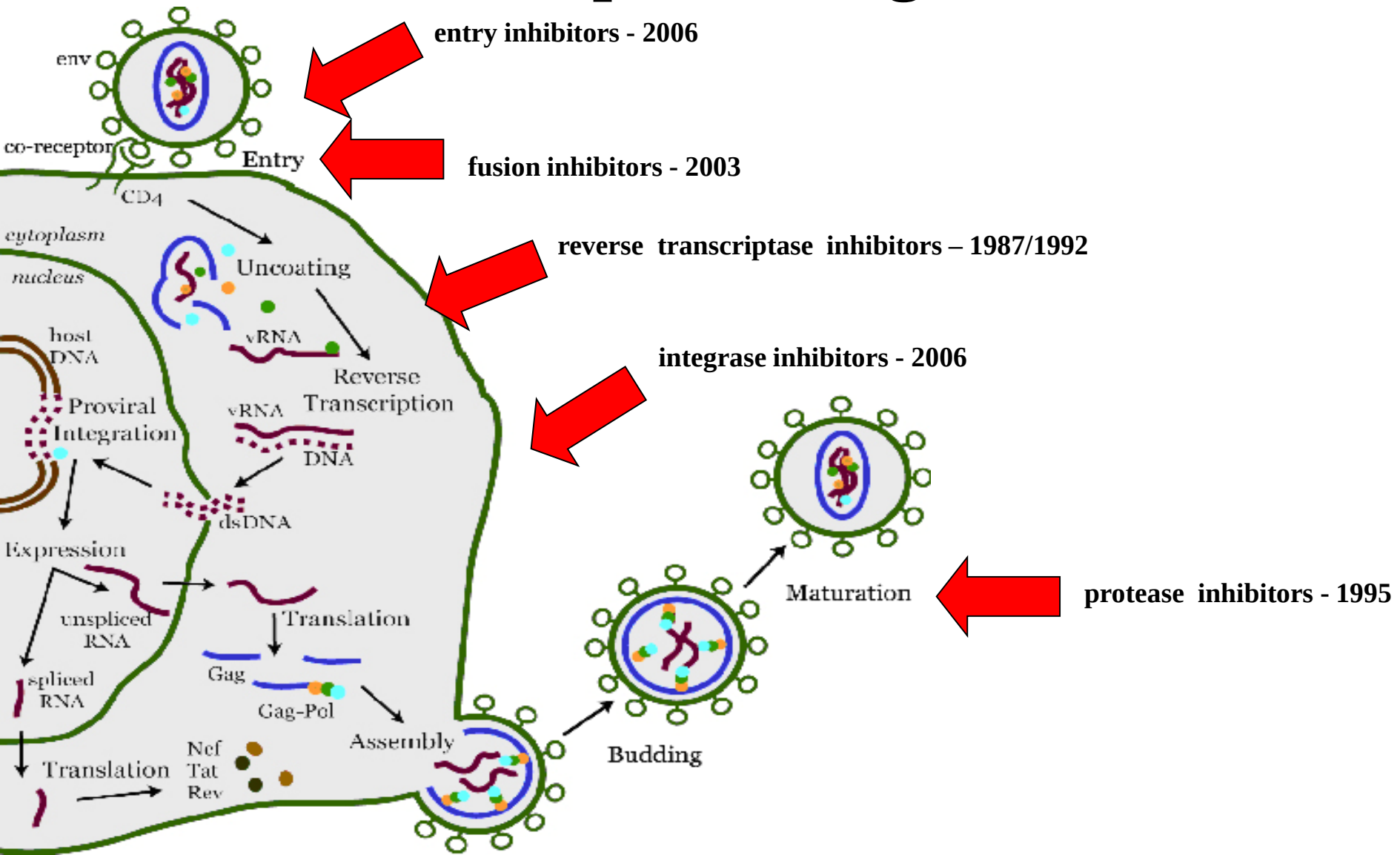
U = U

Undetectable = Untransmittable

cART indications

- **all HIV cases**
- **chronic HIV infection**
  - **symptomatic (B and C category)**
  - **asymptomatic (A category)**
    - **CD4+ T lymphocytes ≤ 500/μl**
    - **viral load > 10^5 copies HIV RNA/ml**
- **post-exposure prophylaxis**
- **vertical transmission prophylaxis**

Replication cyclus of HIV with therapeutic targets



HIV/AIDS - therapy

22 remedies from 6 groups

- **nucleoside reverse transcriptase inhibitors - NRTI**
- **non-nucleosidové reverse transcriptase inhibitors - NNRTI**
- **protease inhibitors - PI**
- **fusion inhibitors – FI**
- **integrase inhibitors**
- **entry inhibitors**

HIV/AIDS - therapy

NRTI since 1987

- **false basis for formation of proviral DNA inhibition of HIV reverse transcriptase**
- **relatively toxic**
  - **inhibition of mitochondrial DNA polymerase**
- **cross-resistance**

HIV/AIDS - therapy

NRTI

- **azidothymidine (AZT)**
- **didanosine (ddI)**
- **zalcitabine (ddC)**
- **stavudine (d4T)**
- **lamivudine (3TC)**
- **abacavir (ABC)**
- **tenofovir (TDF)**
- **emtricitabine (FTC)**

prof. A. Holý
Institute of organic chemistry and biochemistry, Prague

HIV/AIDS - therapy

NNRTI since 1992

- binding near to catalytic site of RT
- penetrate to CNS
- similar pharmacodynamic → cross resistance
- similar side effects

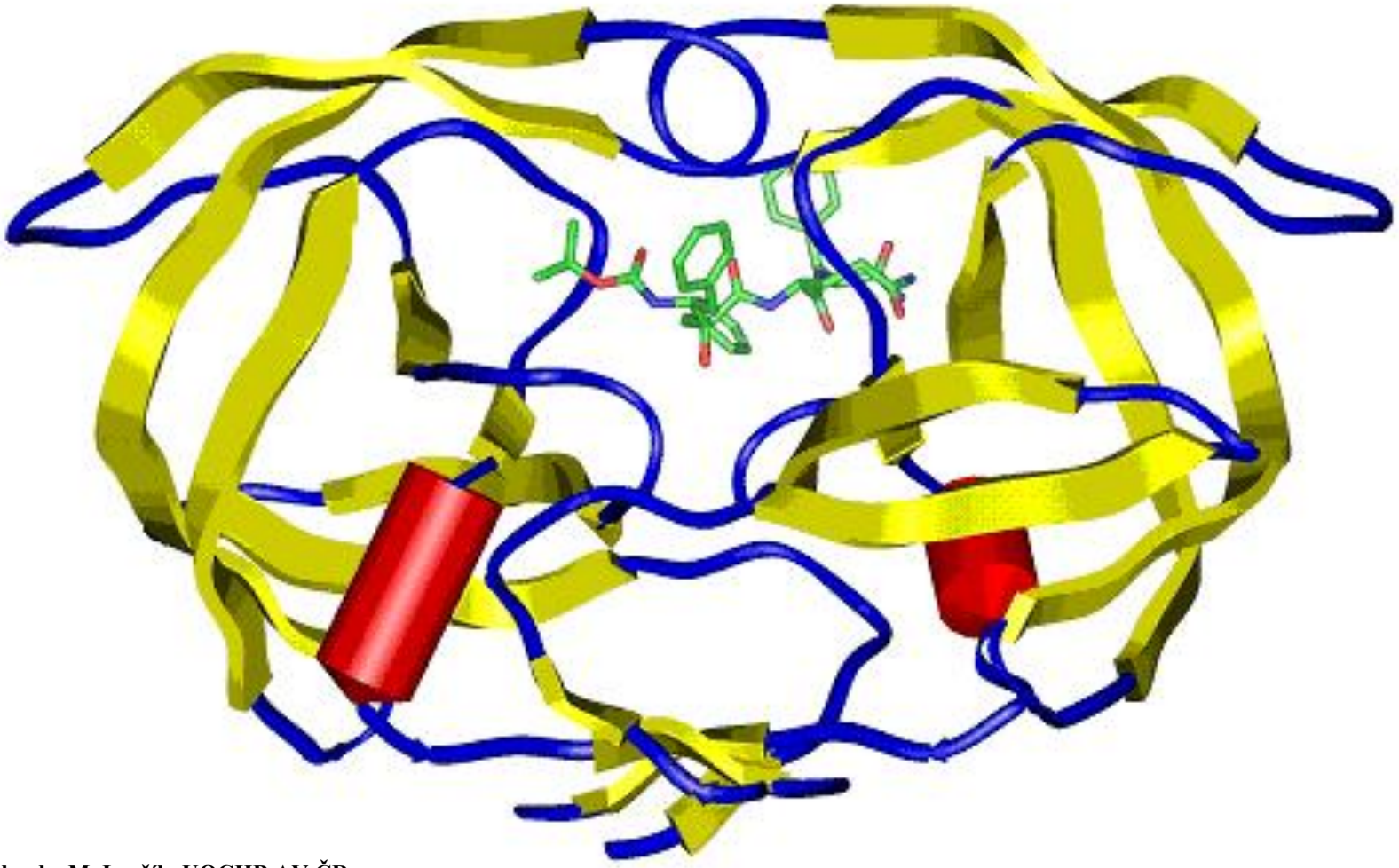
- efavirenz
- etravirine
- rilpivirine

HIV/AIDS - therapy

PI since 1995

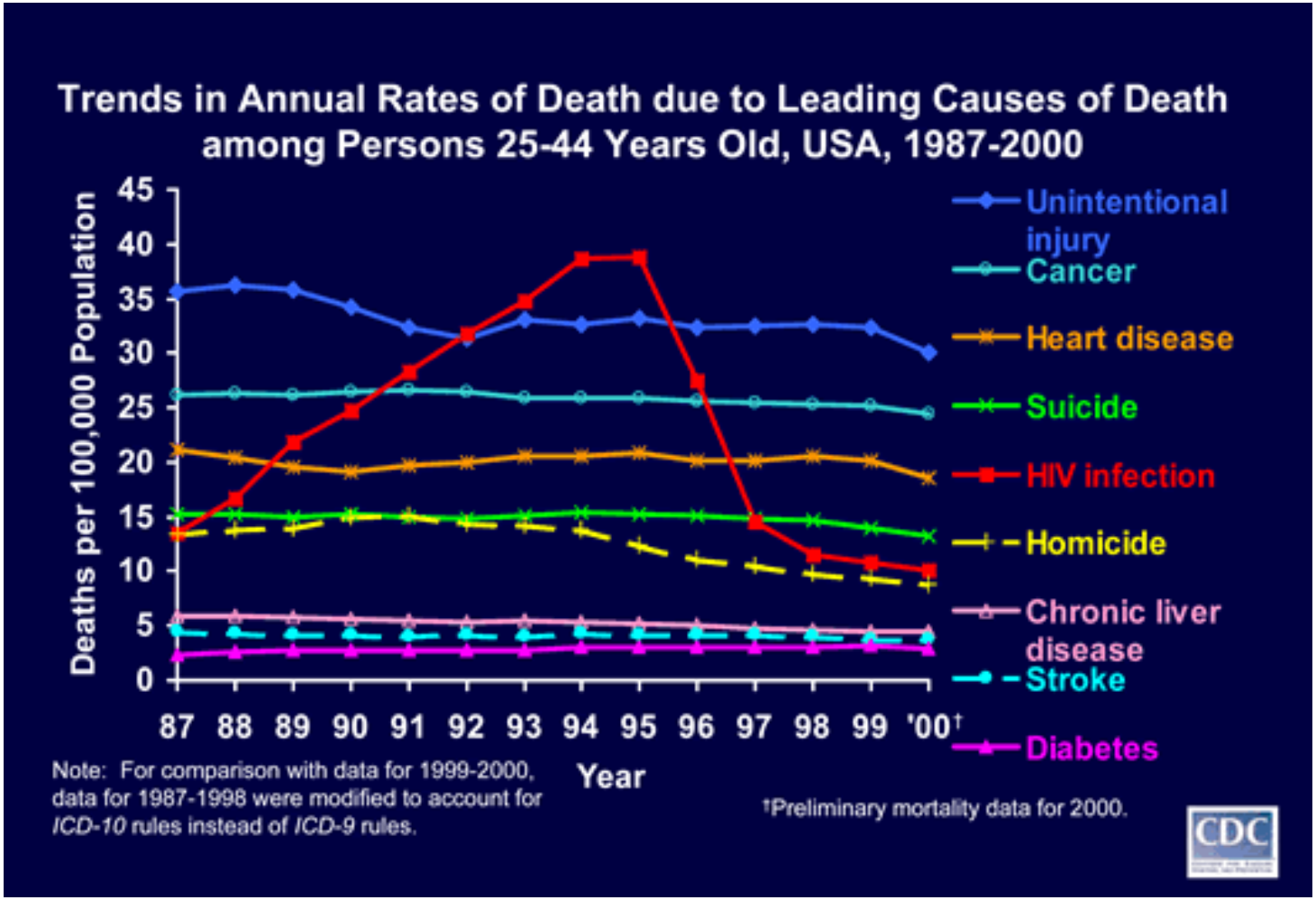
- **highly effective - 1000x than NRTI**
- **very expensive - 18 000.-Kč/month**
- **inhibition of HIV protease**
- **several side-effects:**
  - **lipodystrophy**
  - **diabetes mellitus**
  - **cytochrome P450 – incompatibility with many drugs**

HIV protease + inhibitor



Model created by dr. M. Lepšík, UOCHB AV ČR.

Impact of introduction of PIs on HIV mortality



HIV/AIDS - therapy

PI

- **ritonavir (RTV)**
- **lopinavir/r (LPV/r)**
- **amprenavir (APV) (fos-amprenavir)**
- **atazanavir (ATV)**
- **darunavir**

HIV therapy - entry inhibitor

- **maraviroc 2x 300 mg p.o.**
  - **inhibition of binding gp120 to CCR5**
  - **test HIV tropisms**
- **low toxicity**
    - **rash**
    - **cefalea**
    - **hepatotoxicity**
    - **cardiotoxicity**

HIV therapy – integrase inhibitors INSTIs

Inhibition of v-DNA integration ➔ host genome

- **low toxicity**
  - **rash**
  - **cefalea**
  - **vertigo**

- **raltegravir**
- **elvitegravir**
- **dolutegravir**

HIV/AIDS - therapy

FI since 2003 - only for salvage therapy

- **enfuvirtide**
  - **inhibition of fusion of HIV with target cell**
  - **only for parenteral administration**
  - **different toxicity and resistance**

Preferred cART regimens

NRTI „*back-bone*“ = tenofovir + emtricitabine

+

INSTI **dolutegravir**

PI **darunavir/r**

HIV/AIDS - therapy

<u>prophylaxis after needle exposure (or sex)</u>

- **up to 36 (72) hours after exposure**
  - **basic - 2 NRTI**
  - **expanded - 2 NRTI + 1 PI**
- **efficacy about 95% (after sex lower)**
- **administered l month**

prophylaxis does not substitute non-risky behaviour

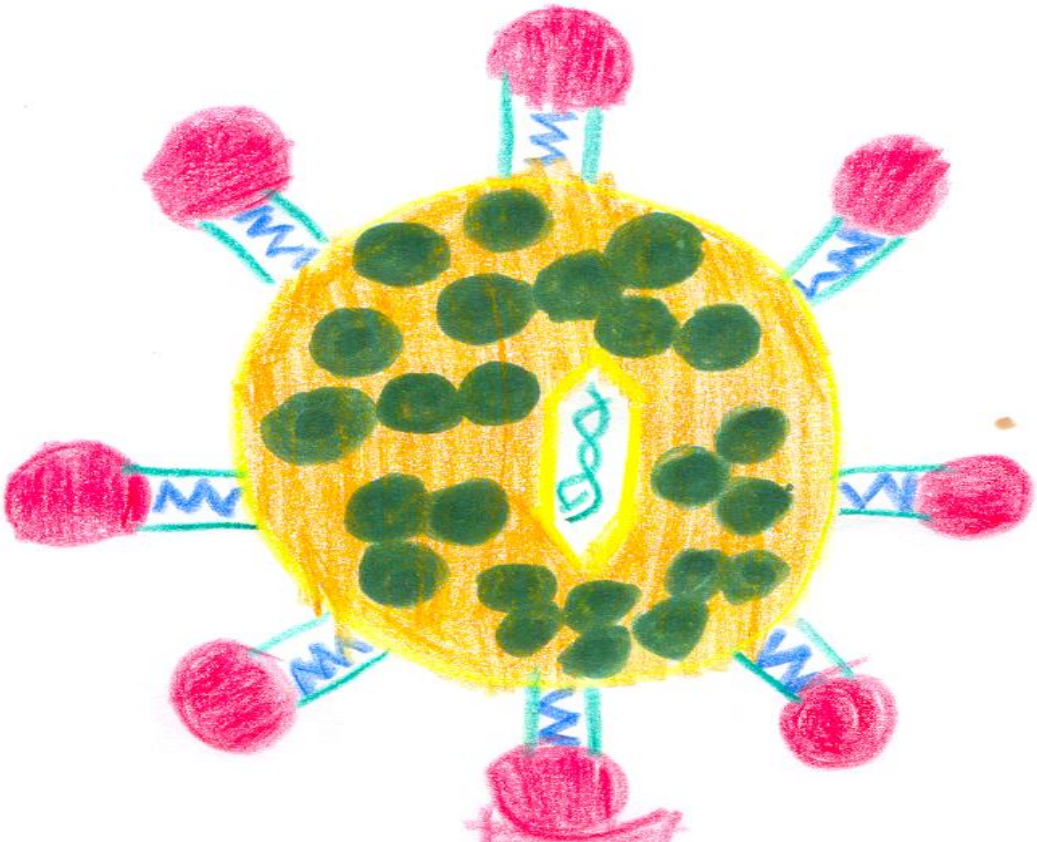
!!! **!!!**

HIV/AIDS - therapy

<u>prophylaxis in pregnancy</u>

- **without prophylaxis risk 20 - 25%**
- **with profylaxis risk 2%**
- **from 12th week AZT + 3TC**
- **during delivery AZT 2x 300 mg i.v.**
- **delivery – usually *caesarian section***
- **no breast-feeding**
- **infant - AZT suspension for 6 weeks**

HIV model designed by daughter Lily Caroline Louise *Pássaro* Carvalho Machala, pupil of 2nd grade elementary school Unhošť



Thanks for your attention