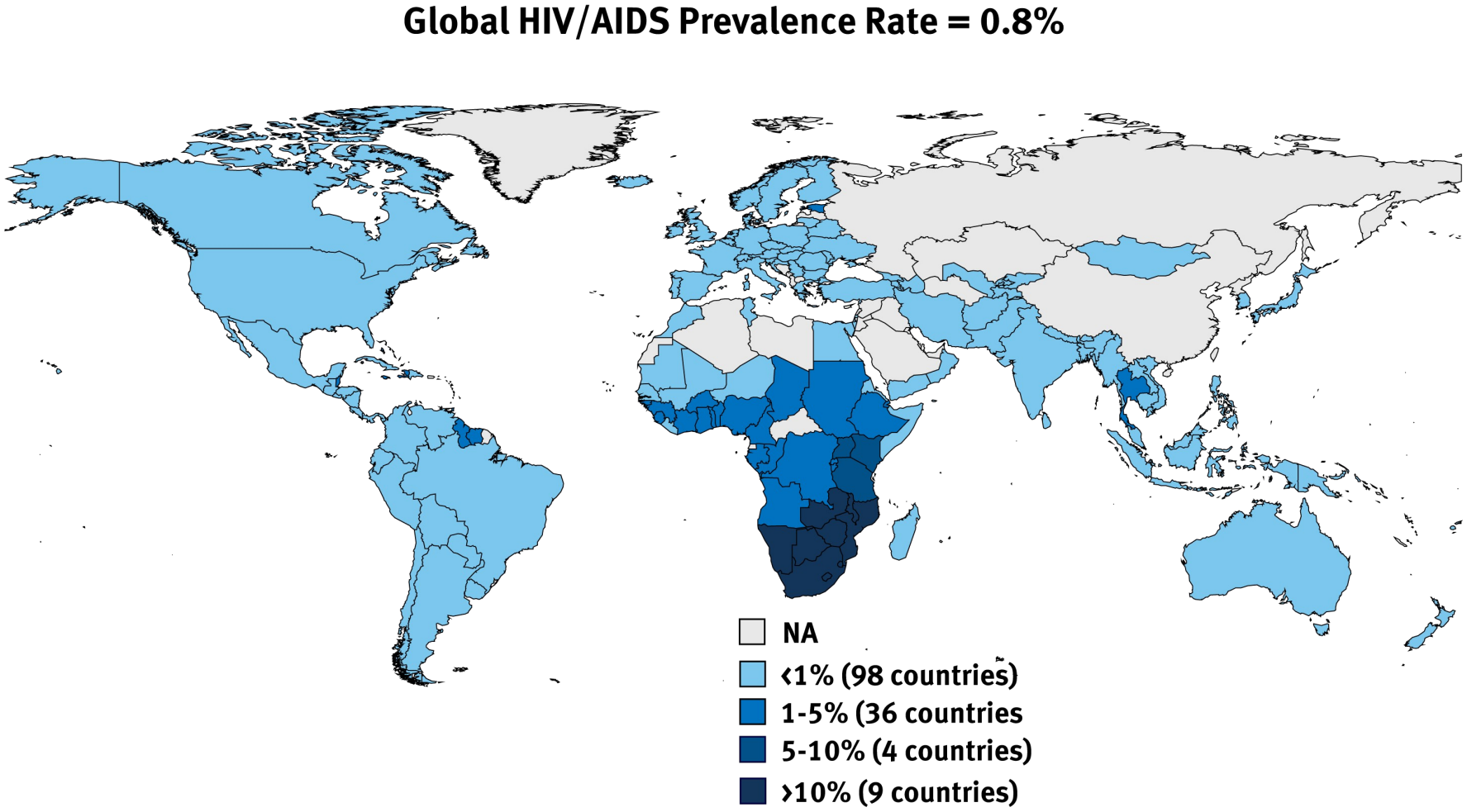
HIV
kroonilisest infektsioonist funktsionaalse paranemiseni

Pilleriin Soodla
Tartu Ülikool
Eesti Infektsioonhaiguste Selts

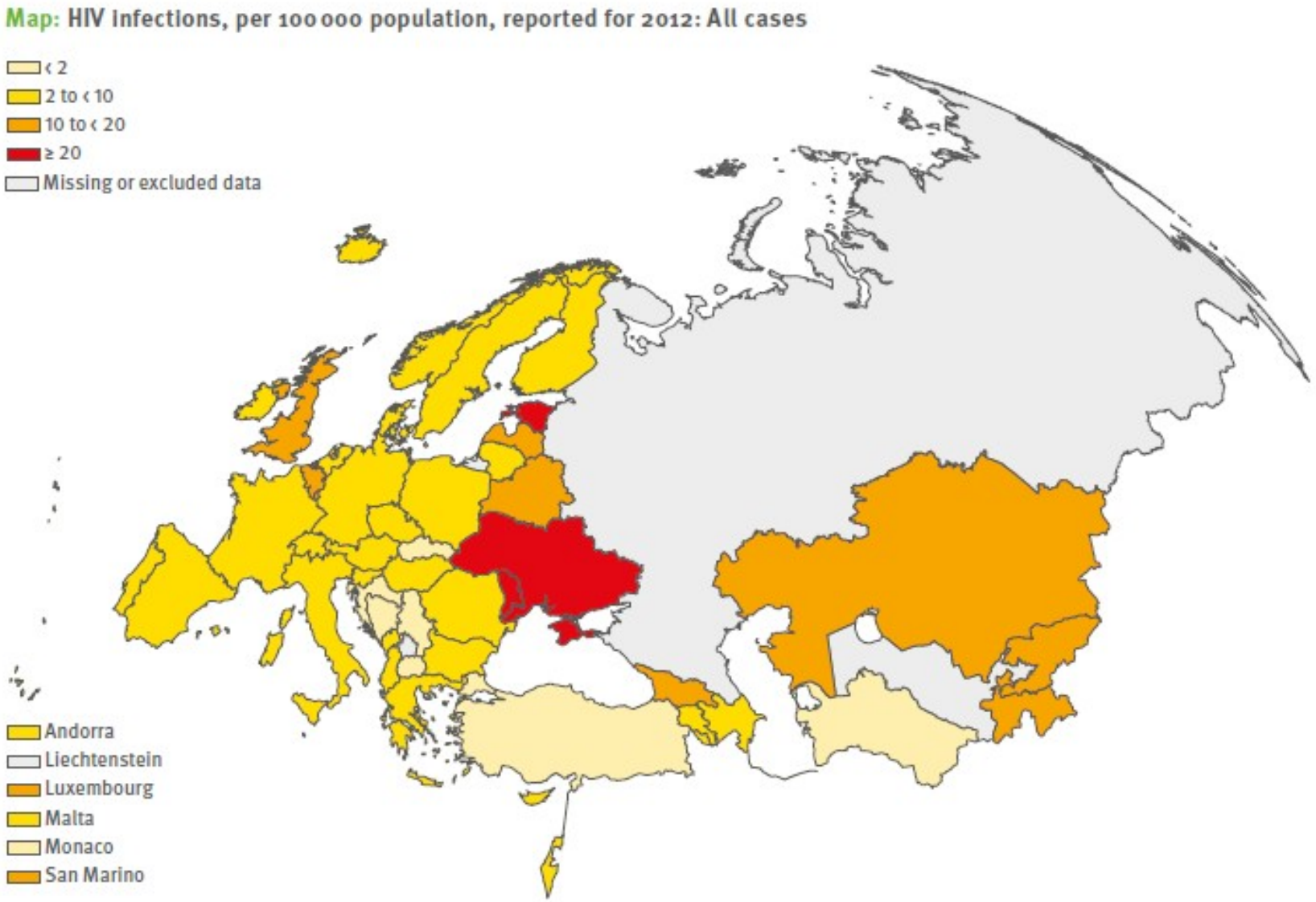
EAP 2014

Adult HIV Prevalence Rate, 2012



NOTES: Data are estimates. Prevalence rates include adults ages 15-49. The estimate for Sudan represents data for South Sudan. An estimate was not provided for Sudan.
SOURCE: Kaiser Family Foundation, www.GlobalHealthFacts.org, based on UNAIDS, Report on the Global AIDS Epidemic; 2013.

HIV Euroopas

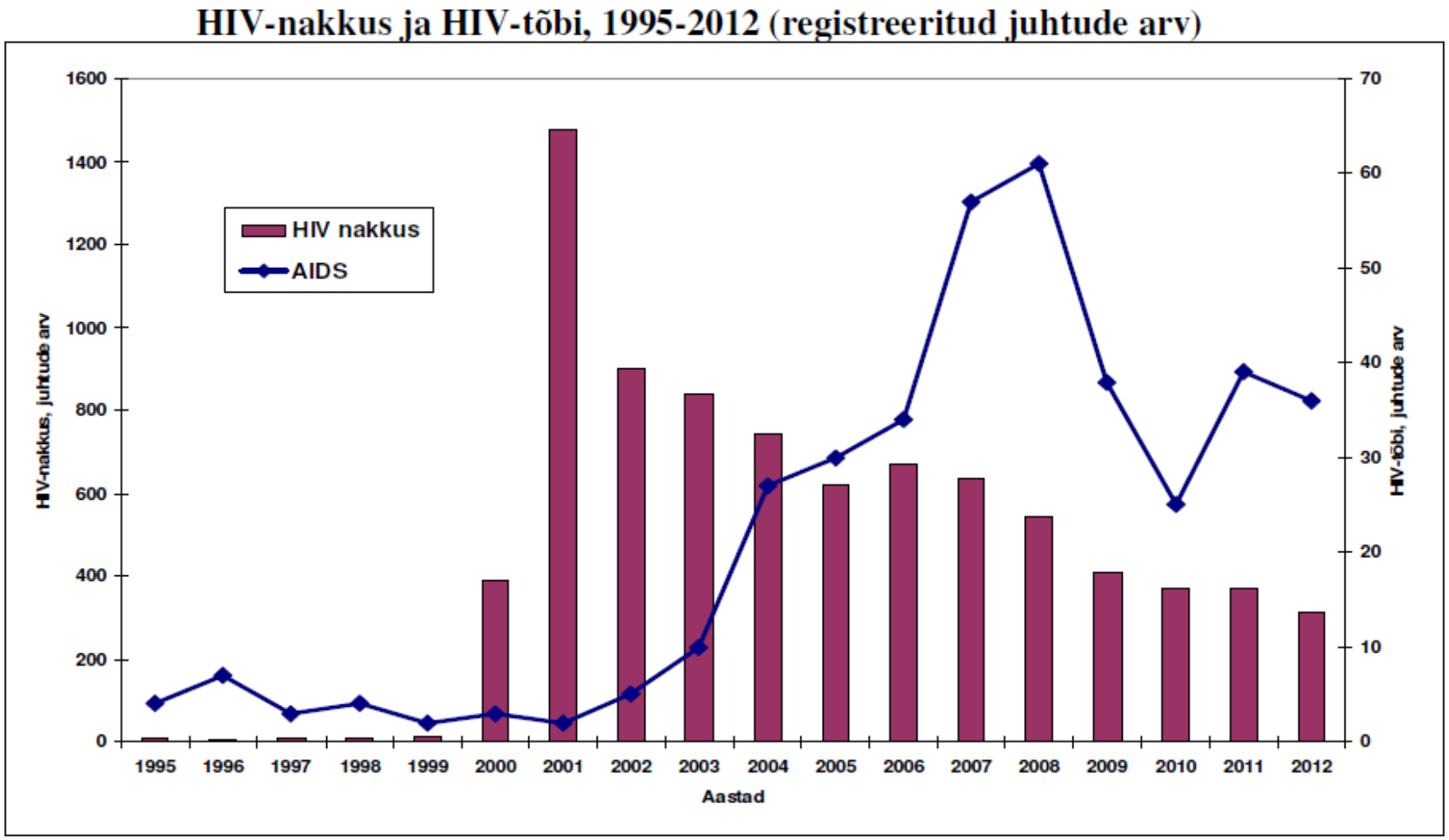


HIV/AIDS surveillance in Europe 2012

Terviseameti andmetel on 2014. aasta

28. märtsi seisuga diagnoositud Eestis kokku 8780

HIV positiivset, sealhulgas AIDS 421 inimesel



Ajalugu

AIDS kui surmaga lõppev haigus

CDC

MMWR™

MORBIDITY AND MORTALITY WEEKLY REPORT

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

Pneumocystis Pneumonia — Los Angeles

In the period October 1980–May 1981, 5 young men, all active homosexual, 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 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, pentamidine, and acyclovir. He died May 3, and postmortem examination showed pneumonia, but no evidence of neoplasia.

RARE CANCER SEEN IN 41 HOMOSEXUALS

Outbreak Occurs Among Men in New York and California —8 Died Inside 2 Years

By LAWRENCE K. ALTMAN

Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often rapidly fatal form of cancer. Eight of the victims died less than 24 months after the diagnosis was made.

The cause of the outbreak is unknown, and there is as yet no evidence of contagion. But the doctors who have made the

1981

Antiretroviirusravi ajastu

cART

HIV kui krooniline infektsioon

Colorado AIDS Education and Training Center • University of Colorado at Denver and Health Sciences Center •
4200 E. Ninth Ave., Box A089 • Denver, CO 80262 TEL: 303-315-2512 • FAX: 303-315-2514 • www.mpaetc.org/colorado.htm •
Developed by MeriLou Johnson, MSW, MPA and Steven Johnson, MD

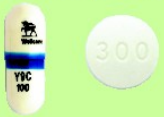
HIV Medication Chart

Nucleoside/Nucleotide Analogue Reverse Transcriptase Inhibitors (NRTI)

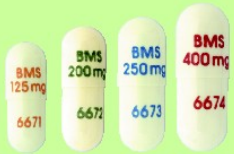
Emtriva®* (emtricitabine, FTC)

Epivir®* (lamivudine, 3TC)

Retrovir®* (zidovudine, AZT, ZDV)

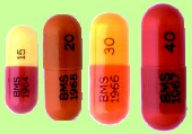


Videx EC® (didanosine, ddl)



Viread® (tenofovir, TDF)*

Zerit®* (stavudine, d4T)



Ziagen®* (abacavir, ABC)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

Rescriptor® (delavirdine, DLV)

Sustiva®* (efavirenz, EFV)

Viramune®* (nevirapine, NVP)

FDA Pregnancy Category D

Fixed Dose Combinations

Atripla® (TDF + FTC + EFV)

FDA Pregnancy Category D

Combivir® (AZT plus 3TC)

Epzicom® (ABC plus 3TC)

Trizivir® (AZT plus 3TC plus abacavir)

Truvada® (TDF plus FTC)

®The brands listed are the registered trademarks of their respective owners.

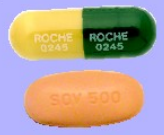
*Also available in liquid form.

Protease Inhibitors (PI)

Aptivus® (tipranavir, TPV)

Crixivan® (indinavir, IDV)

Invirase® (saquinavir hard gel capsules, SQV)

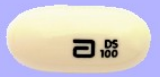


Kaletra®* opinavir/ritonavir, LPV/r)

Lexiva® (fosamprenavir, FPV)

Prezista® (darunavir, DRV)

Norvir®* (ritonavir, RTV)

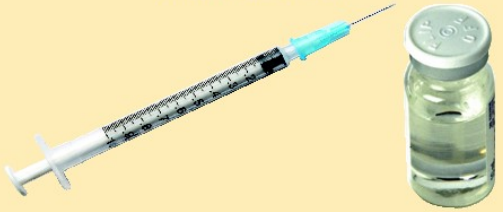


Reyataz® (atazanavir, ATV)

Viracept® (nelfinavir, NFV)

Fusion Inhibitors

Fuzeon® (enfuvirtide, T-20)



All pills shown in actual size except Fuzeon® which is shown at 50%.

8/06

Antiretroviirusravi

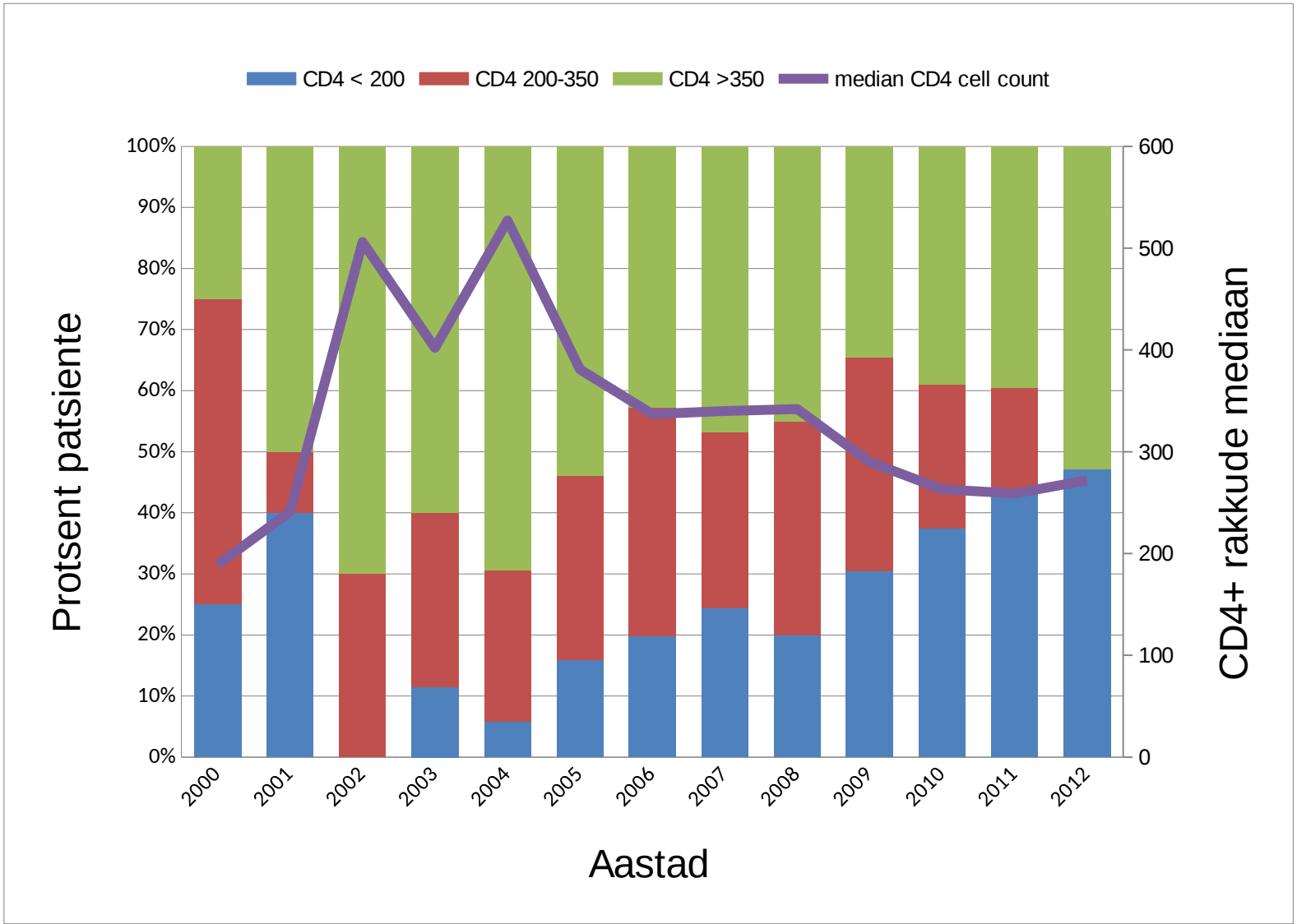
- Ravi on efektiivne, parandab elukvaliteeti ning pikendab eluiga
- Väheneb ülekandeoht

- Ravimeid tuleb võtta igapäevaselt kogu elu
- Kõrvaltoimed (kiired, hilised)
- Maksumus

Antiretroviirusravi Eestis seisuga 31.12.2013

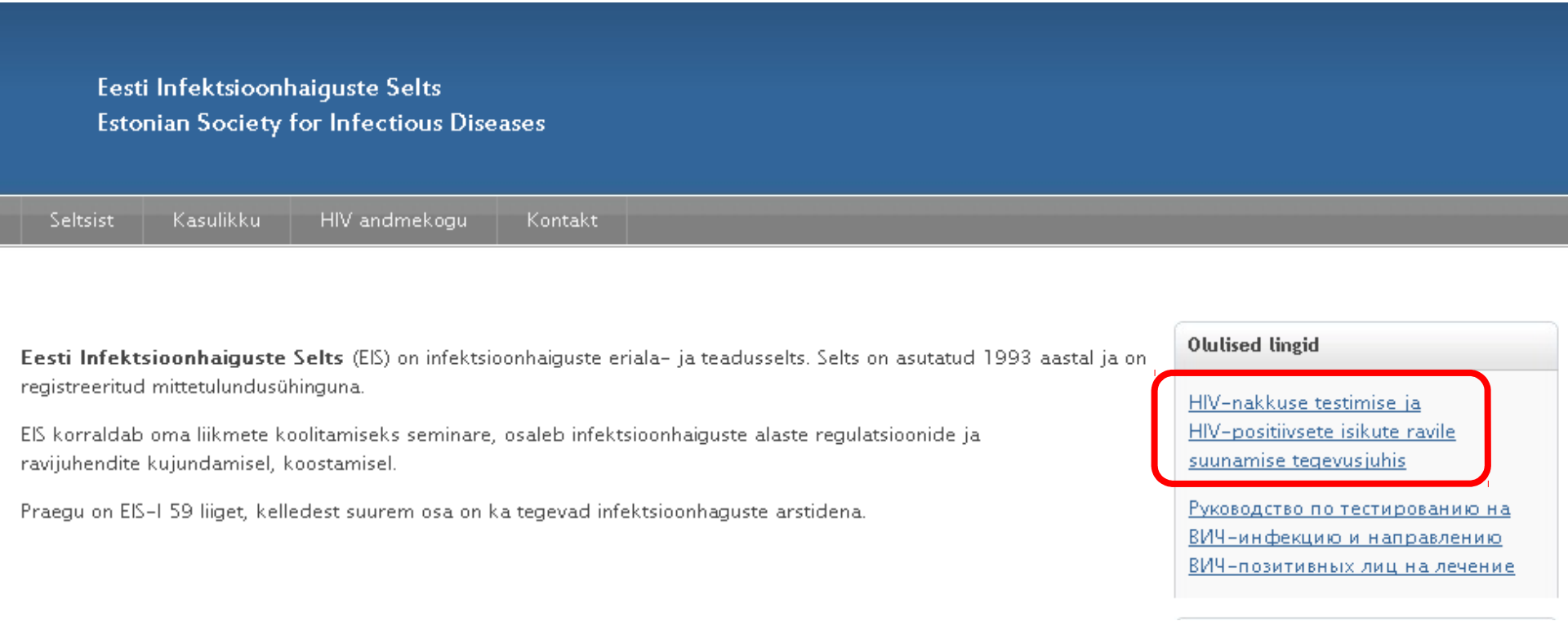
- Arsti juures jälgimisel 5192 patsienti, lapsi 36
- 2013. aastal külastas arsti 3517 patsienti
- Ravil 2691 patsienti

Probleemiks CD4+ rakkude arv diagnoosimisel



Testimine

- HIV-nakkuse testimise ja HIV-positiivsete isikute ravile suunamise tegevusjuhis



XXI sajand

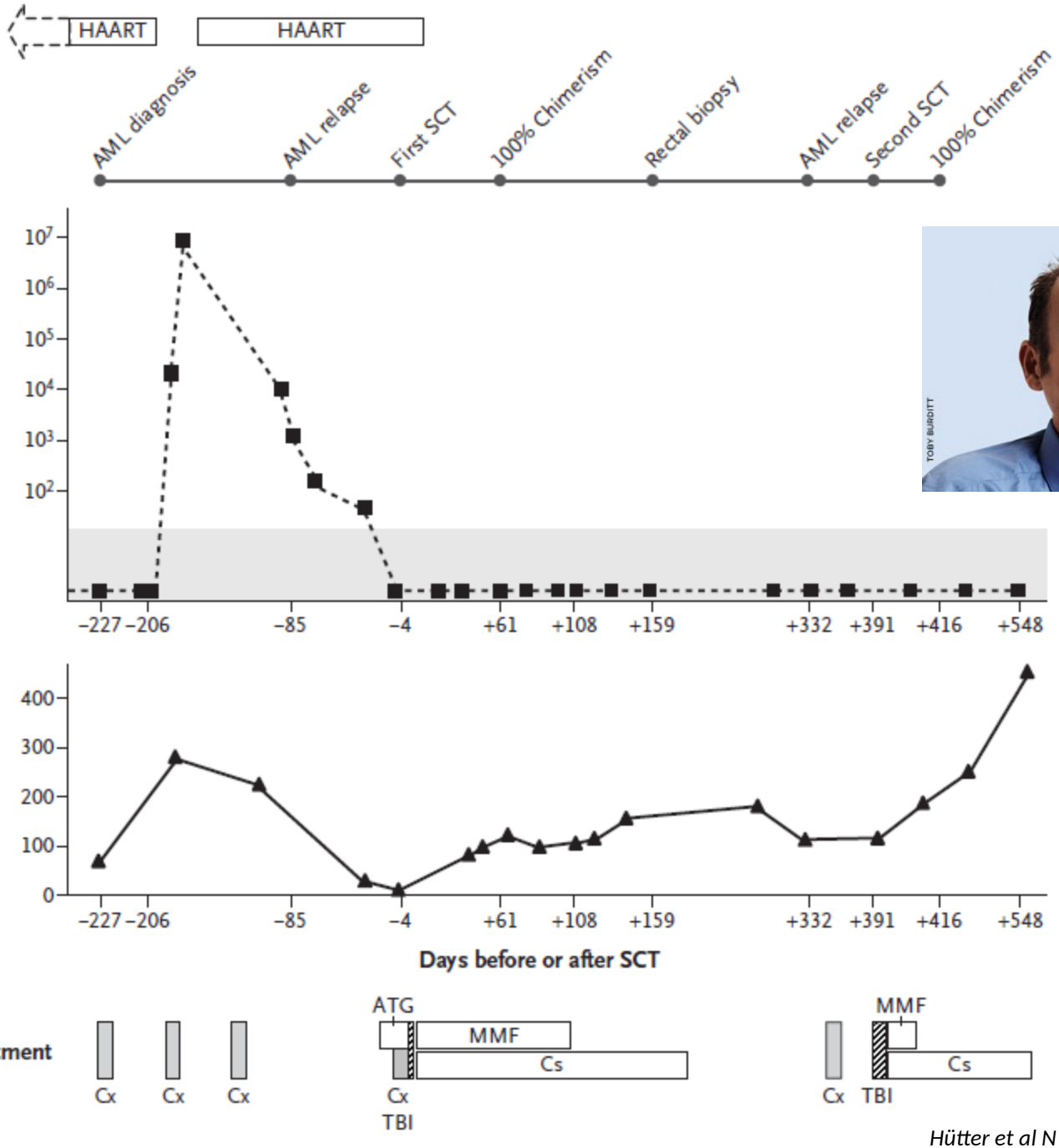
Paranemine?!

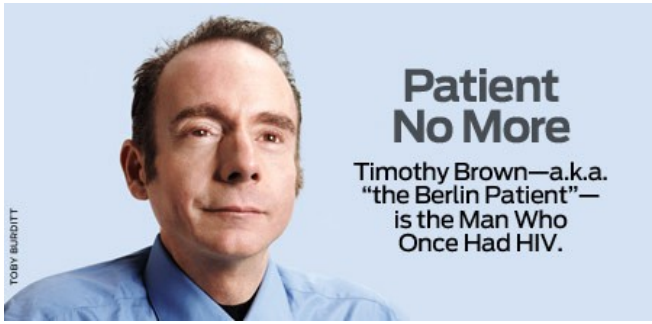
HIV paranemine

- Funktsionaalne paranemine (*functional cure*)
  - Viiruse paljunemine püsib ravimiteta kontrolli all
- Täielik paranemine (*sterilising cure*)
  - HIV DNA ei ole määratav

Berliini patsient
Timothy Brown

- Ainus inimene, kes on vabanenud viirusest





Hütter et al N Engl J Med 2009

Bostoni patsiendid

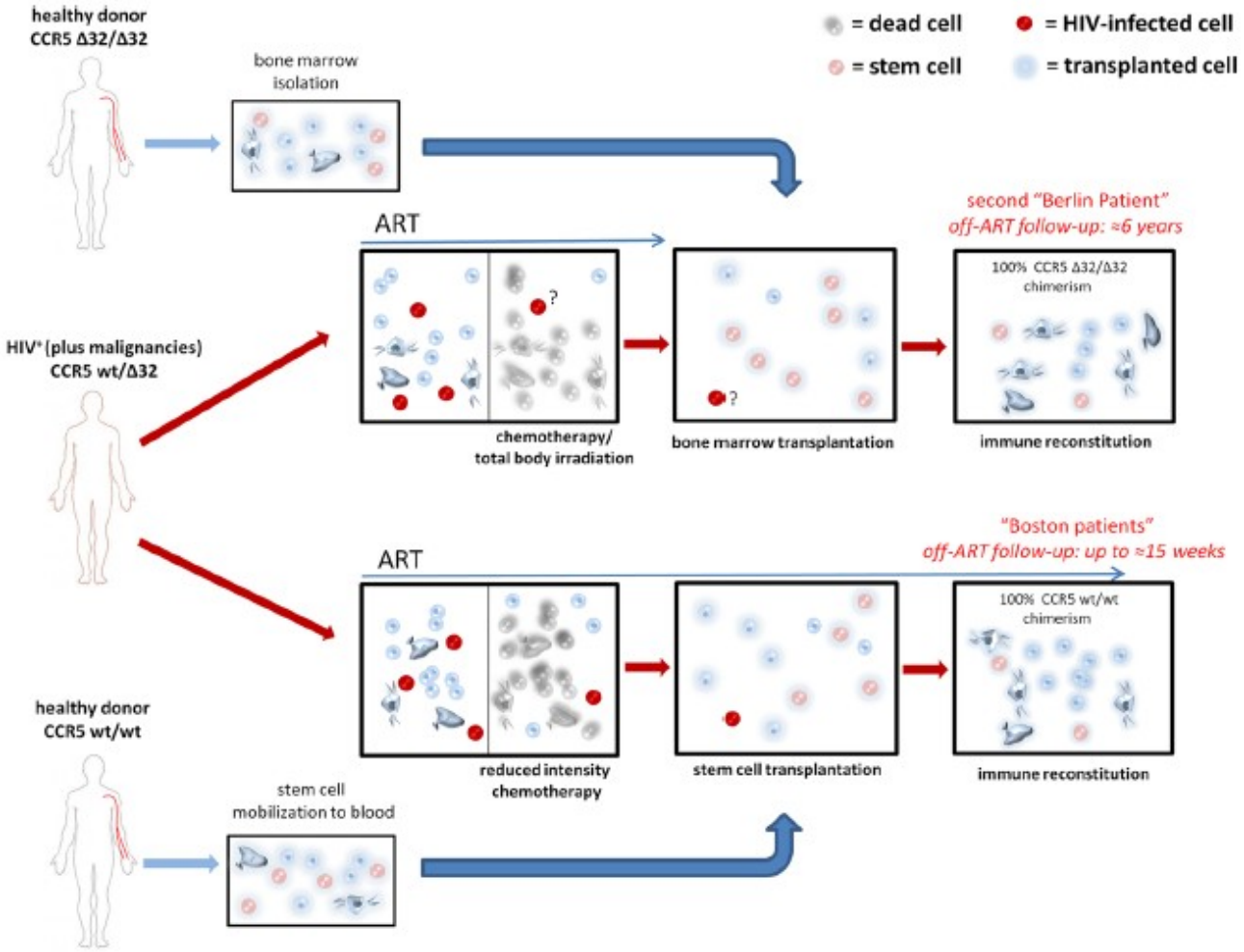


Figure 2 Schematic representation of the therapeutic interventions received by the second "Berlin patient" and the "Boston patients". Although the second "Berlin patient" had received two stem cell transplants, only one is shown for clarity purposes. Note that the length of the arrows indicating the period under ART is meant to provide a qualitative comparison between the ART and transplantation schedules and is not in scale.

Shytaj and Savarino Retrovirology 2013

Mississippi beebi

Table 1. Timeline of the Mississippi baby case.

Age of baby	Event
Prenatal	Child's mother was HIV infected and received no prenatal care Child was born at 35 weeks of gestation
30 h	Initiated on a three-drug regimen of nevirapine, zidovudine and lamivudine before confirmation of HIV infection Positive HIV DNA PCR test
31 h	HIV RNA quantity of 19,812 c.p.m
6 days	HIV RNA quantity of 2617 c.p.m
7 days	Switched from nevirapine to a ritonavir-boosted lopinavir (LPV/r) regimen
11 days	HIV RNA quantity of 516 c.p.m
19 days	HIV RNA quantity of 265 c.p.m
29 days	HIV RNA quantity <48 c.p.m
29 days to 18 months	Remained on ART
18–23 months	Lost to follow-up, missed clinic appointments Off ART
23 months	Returned to clinic, remained off ART No detectable HIV RNA quantity by standard clinical assay
24 months	No detectable HIV RNA quantity by standard clinical assay HIV RNA quantity of 1 c.p.m using ultrasensitive assay Negative HIV DNA PCR test HIV proviral DNA detected near limit of detection but not in resting $CD4^+$ T cells No replication-competent HIV detected in resting $CD4^+$ T cells Negative antibody test
26 months	No detectable HIV RNA quantity using ultrasensitive assay HIV proviral DNA detected near limit of detection but not in resting $CD4^+$ T cells Negative antibody test
28 months	Negative antibody test
30 months	Case reported No viral rebound

Shiau & Kuhn

Expert Rev. Anti Infect. Ther 2014

Los Angelese beebi

- Teine võimalik HIV ravijuht lapsel
- Lapsel alustati neljandal elutunnil antiretroviirusravi
- 8-kuuselt ei ole võimalik enam paljunemisvõimelist viirust määrata
- Hetkel saab veel viirusvastast ravi

CROI 2014

Viiruse reservuaari piiramine
Varajane antiretroviirusravi

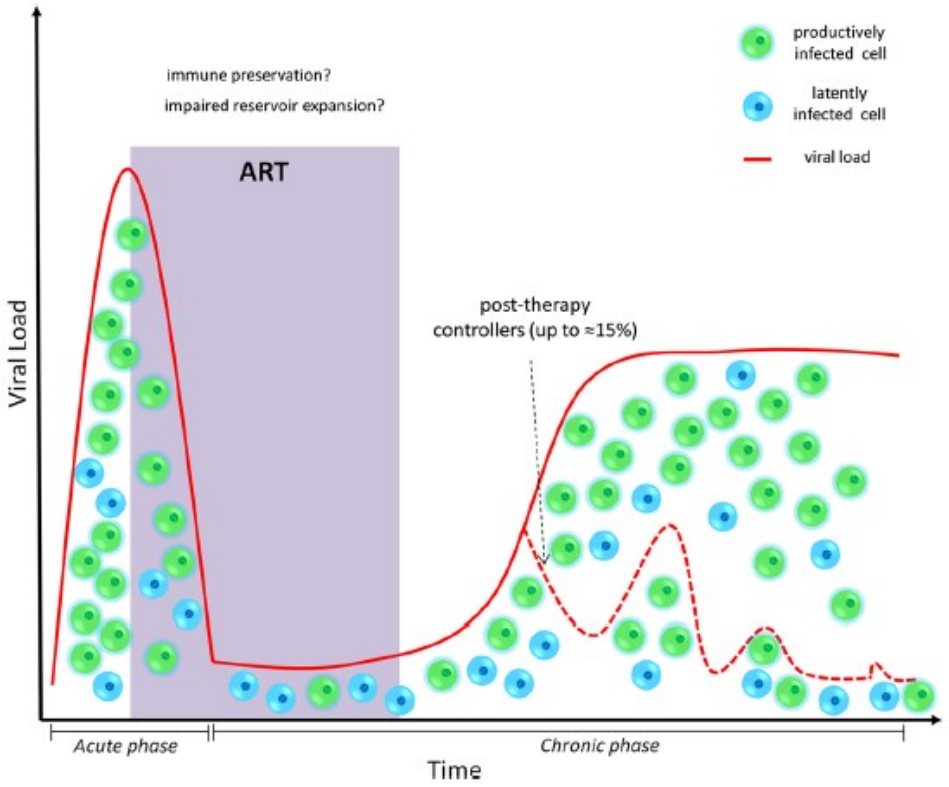


Figure 1 ART administration during acute infection results in spontaneous control of viral load in a minority of individuals following therapy suspension. The dotted line depicts representative viral load dynamics of patients controlling the infection following ART withdrawal, as compared to non controllers (solid line). The upper limit of the percentage of controllers is taken from [27]).

Shytaj and Savarino Retrovirology 2013

Viiruse reservuaari piiramine
Latentse viiruse aktiveerimine

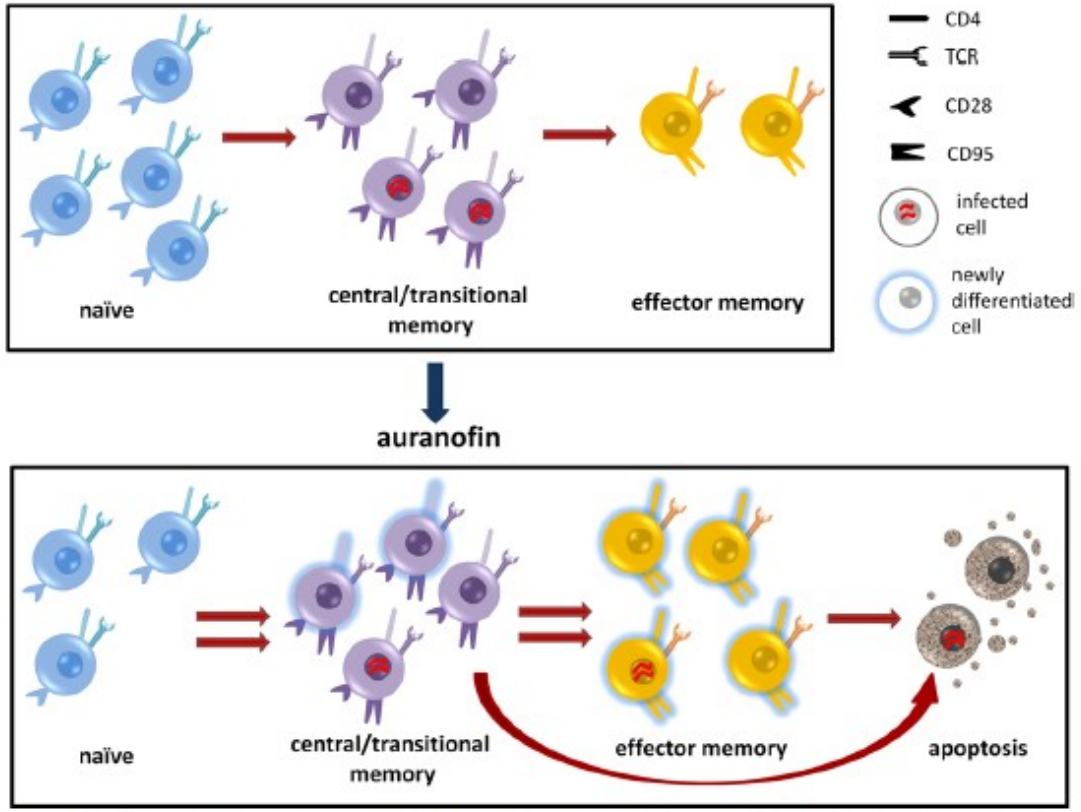


Figure 3 Treatment with auranofin increases the turnover of CD4$^+$ T-cell subsets and induces a partially selective apoptosis of the memory compartment. The cell subsets are identified by the expression of the surface markers CD28 and CD95 (naïve: CD28$^+$ CD95$^-$; central and transitional memory: CD28$^+$ CD95$^+$; effector memory: CD28$^-$ CD95$^+$).

Shytaj and Savarino Retrovirology 2013

Viiruse reservuaari piiramine
Latentse viiruse aktiveerimine

	Drug	n	Design	Results
Lehrman et al,[37] 2005	Valproic acid	4	Proof of concept study—treatment analysis of infectious units per million cells	Reduced viral reservoir with antiretroviral inte
Siliciano et al,[38] 2007		9	Observational study of patients on combined antiretroviral therapy and valproate	No differences in infect
Sagot-Lerolle et al,[39] 2008		11/13	Case-control study	No effect
Archin et al,[40] 2010		3	Follow-up of Lehrman et al[37] at 48 and 96 weeks	No long-term effect of
Routy et al,[41] 2012		56	Randomised study (27 given valproate in weeks 0–16, 29 given valproate in weeks 16–32)	No effect on infectious
NCT01319383	Vorinostat	30	400 mg single dose; later investigation to use 400 mg daily for 3 consecutive days per week (maximum 8 weeks)	Initial analysis[35] of single increase in cell-associate
NCT01365065		20	400 mg daily for 14 days; initial follow-up to 24 weeks	NA
NCT01680094 (CLEAR study)	Panobinostat	16	20 mg on days 1, 3, and 5, every other week for 8 weeks; viral load, proviral DNA, and infectious units per million cells recorded for 32 weeks	NA
NCT01286259	Disulfiram	20	500 mg daily for 1 month	NA

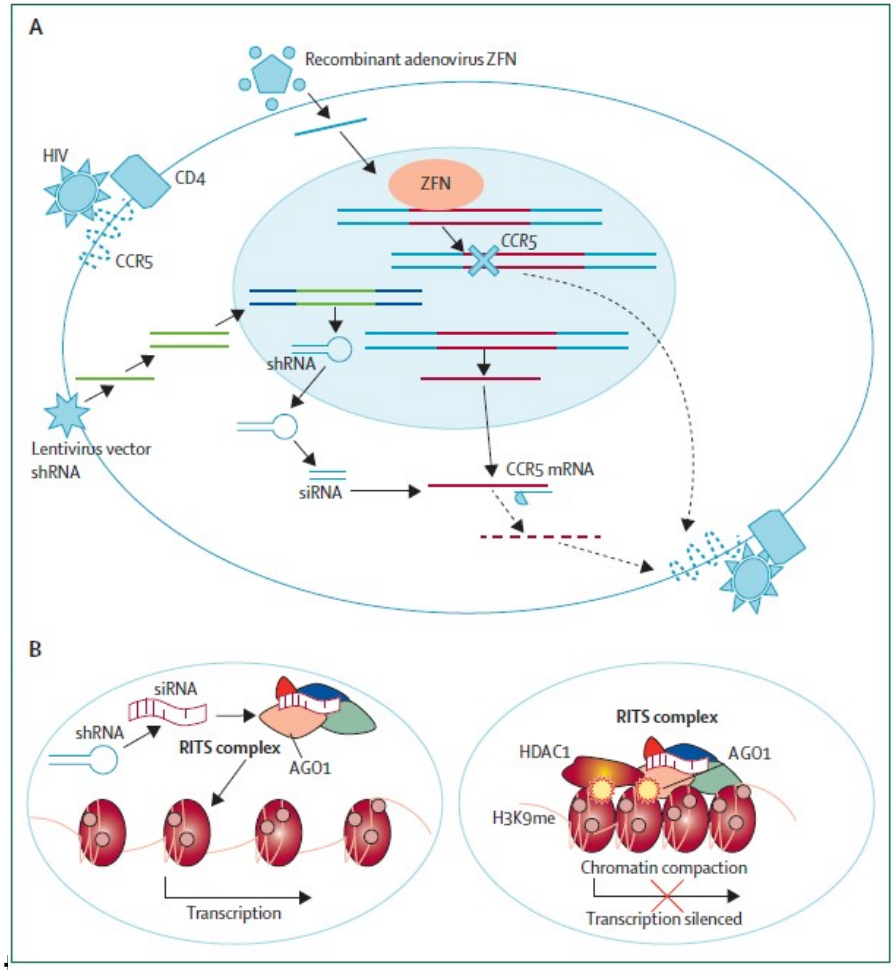
Table: **Clinical studies of drugs to reduce viral latency by activating the latent virus**

Kent et al Lancet Infect Dis 2013

Geeniteraapia

DNA-d muutvad ensüümid:

- *Zinc-finger nucleases*
- *Transcription activator-like effector nucleases*
- *Homing endonucleases*



- Eesmärgiks kustutada viirus nakatunud rakust või muuta rakud HIV-resistentseks

Kent et al Lancet Infect Dis 2013

Kokkuvõte

HIV

- Surma-haigusest ravimitega kontrollitavaks krooniliseks infektsiooniks
- Efektiivse raviga: eluiga, elukvaliteet ülekanderisk
- Oluline leida nakatunud varakult

- Lähitulevikus paranemine HIV-infektsioonist?