"The science of treatment and prevention – What do we know, what are the gaps".

2018 DCRID
Center for AIDS Res.

Advances in Treatment of HIV-1 infection

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Center for AIDS Research,
Kumamoto University, Kumamoto Japan

Today's topics

- Evolution of ART
- Current issues in treatment of HIV-1 infection
- Future of cure research

History of antiretroviral treatment (ART) against HIV-1/AIDS (33 years)

Development of new ARVs
- QD dosing (STR)
- Less side-effects
- Higher barrier for drug-resistance

Development of the NRTI

Introduction of cART /Drug resistance /Long-term toxicity

Discovery of AZT

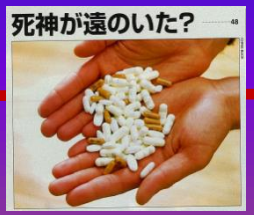
Discovery of HIV

Quantitate HIV-RNA
Viral dynamics in vivo

Outbreak of AIDS

STR: Single Tablet Regimen

1981 1983 1985 1990 1996-1997 2000 2007 2018



Newsweek p.48, Dec. 1996

Goals for antiretroviral therapy (ART)

1996～2007
Prevention of AIDS & death

- **Reduce AIDS-associated morbidity and prolong the duration and quality of survival**
- **Restore and preserve immunologic function**

2008～
Earlier treatment

- **Proof of earlier initiation of ART beneficial for preventing comorbidity related to premature aging**

2011～
ART for ALL
TasP

- **Maximally and durably suppress plasma HIV viral load and prevent HIV transmission as evidenced by HPTN052 (treatment as prevention; TasP)**

Earlier initiation of treatment such as Test and treat strategy has been considered as an ideal strategy of ART in terms of long-term treatment of the patients and prevention of new infection.

June 19, 2010 Vol. 24, No. 10
AIDS
Official Journal of the International AIDS Society

Life Expectancy of Recently Diagnosed Asymptomatic HIV-infected Patients Approaches that of Uninfected Individuals

A. van Sighem et al. on behalf of the ATHENA National Observational Cohort Study

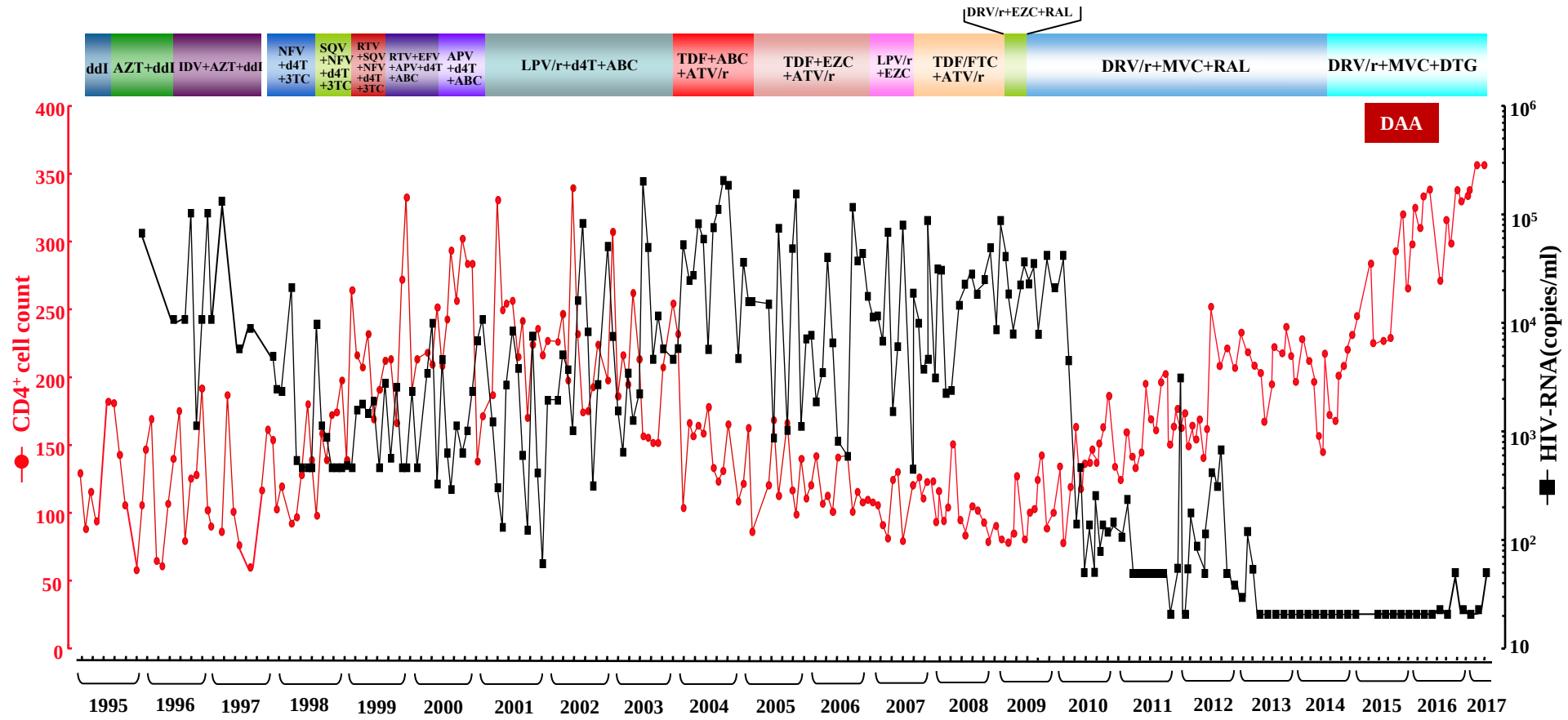
- **Life expectancy** for HIV-infected patients (without AIDS) aged 25 yrs at six months postinfection
  - **Men: an additional 52.7 yrs** (versus 53.1 yrs in general population)
  - **Women: an additional 57.8 yrs** (versus 58.1 yrs in general population)

Limitation of long-term ART

1) Adherence
   accumulation of drug-resistance mutations and treatment failure
2) Comorbidities associated with premature aging (long-term toxicity of ARVs)
3) Persistence of latent virus and residual replication in the presence of most effective ART

(cure is not a realistic goal?)

Clinical course of a case with triple class resistance due to insufficient adherence



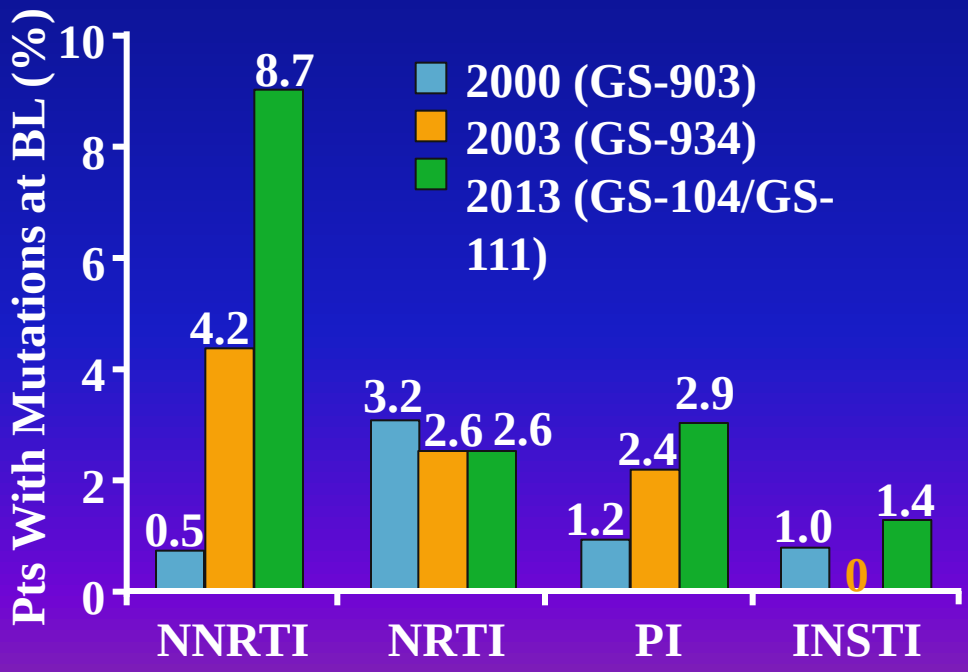
RT: : M41L, M184V, L2
10W, T215Y ,K103N
PR: M36I, I54V, A71V, G73S, V77I, L90M

Triple class resistance

HCV:2a, SOF/Rib

Prevalence of Drug Resistance Mutations in Treatment-Naive Patients, 2000-2013

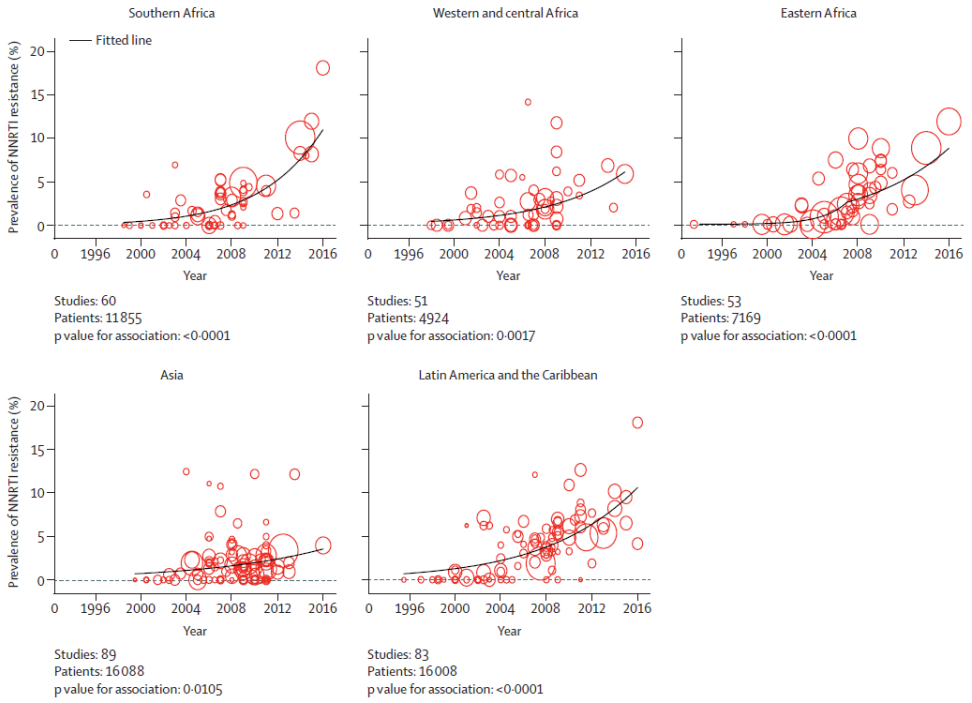
- Baseline plasma samples from 4 phase III trials (GS 903, 934, 104, 111)
  - 1617 samples analyzed for integrase mutations
  - 2531 analyzed for protease or RT mutations
- Substantial ↑ in prevalence of NNRTI resistance, modest ↑ in PI resistance
- Stable prevalence of NRTI resistance (mostly TAMs)
  - M184V/I ≤ 0.2%; K65R ≤ 0.2%
- Little evidence of transmitted INSTI resistance over period
  - Mostly T97A polymorphism



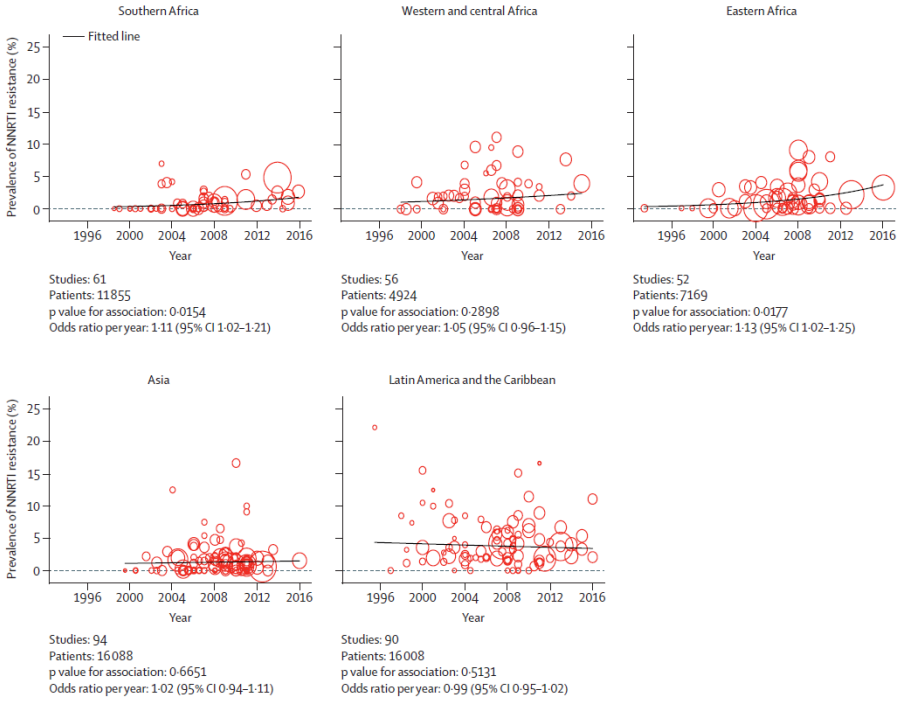
Margot NA, et al. CROI 2014. Abstract 578.

The prevalence of pretreatment NNRTI resistance is rising, with a significant annual increase in the odds of 23% in southern Africa, 17% in eastern, western and central Africa, and 11% in Asia and in Latin America and the Caribbean. By contrast, resistance to NRTI remained below 5%.

NNRTI



NRTI



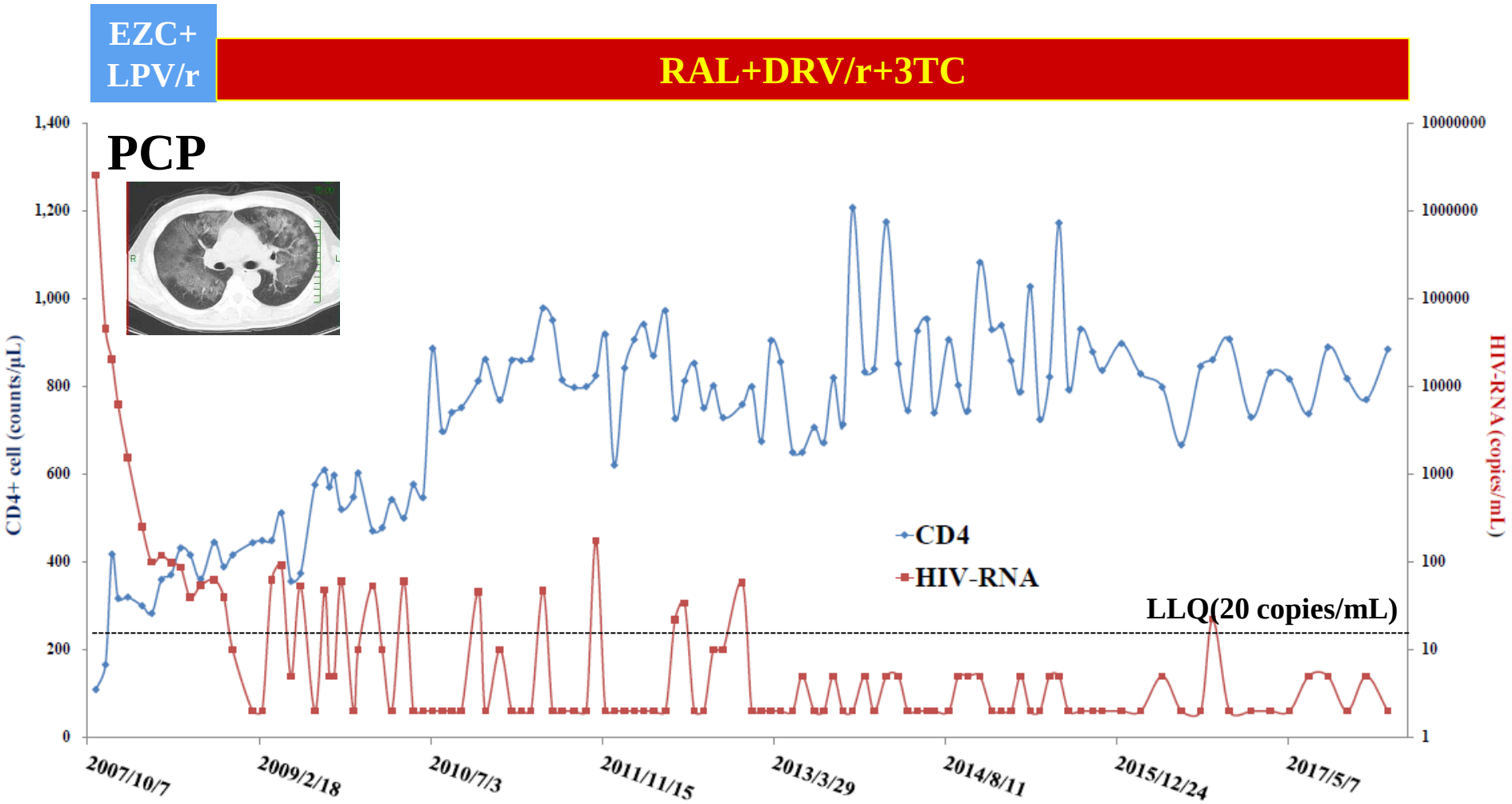
Gupta RK, Gregson J, Parkin N, et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. *Lancet Infect Dis* 2017; published online Nov 30. http://dx.doi. org/10.1016/S1473-3099(17)30702-8.

Limitation of long-term cART

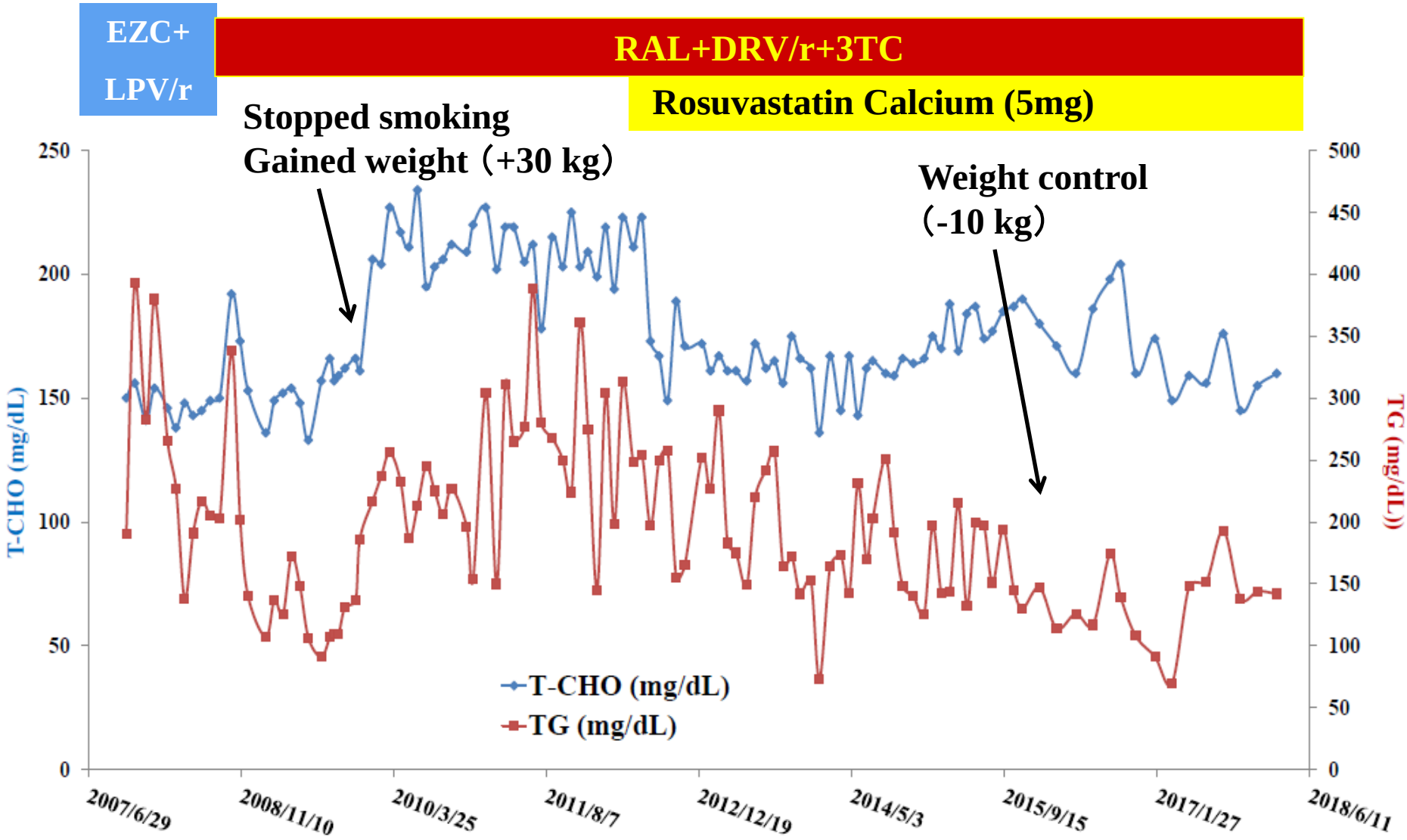
1) Adherence
   accumulation of drug-resistance mutations and treatment failure
2) Comorbidities associated with premature aging (long-term toxicity of ARVs)
3) Persistence of latent virus and residual replication in the presence of most effective cART

(cure is not a realistic goal)

Recovery from full-blown AIDS by ART



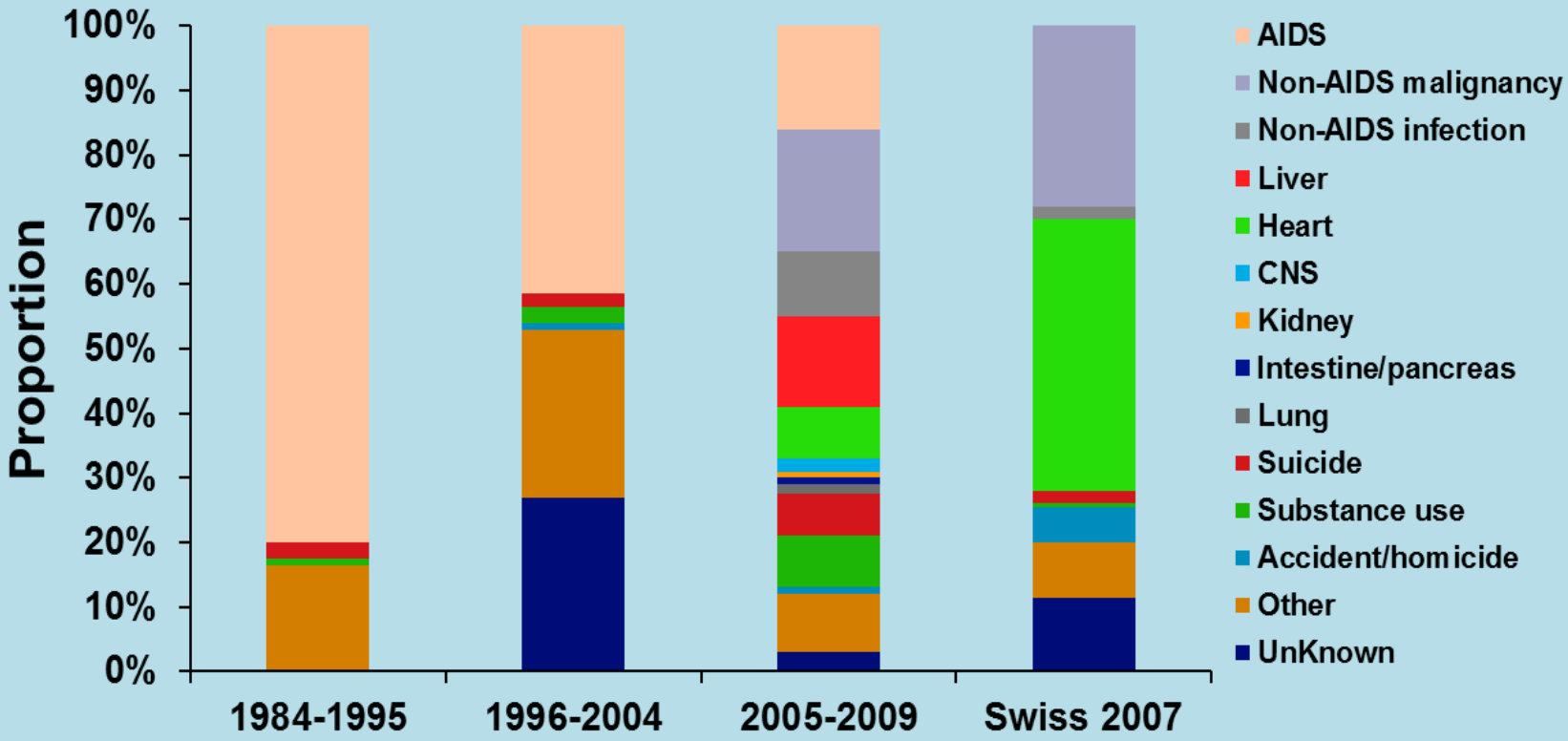
Improvement in lipid profile in the patient



(Comorbidities; 加齢や長期のARTと関連した慢性合併症;
CVD, CKD, Osteoporosis & fracture, etc)

Non-AIDS cancers

Changing the Causes of Death Swiss Cohort (SHCS)



Years of Death of HIV+ Persons Versus Swiss Population

Weber R, et al. HIV Med. 2013;14:195-207

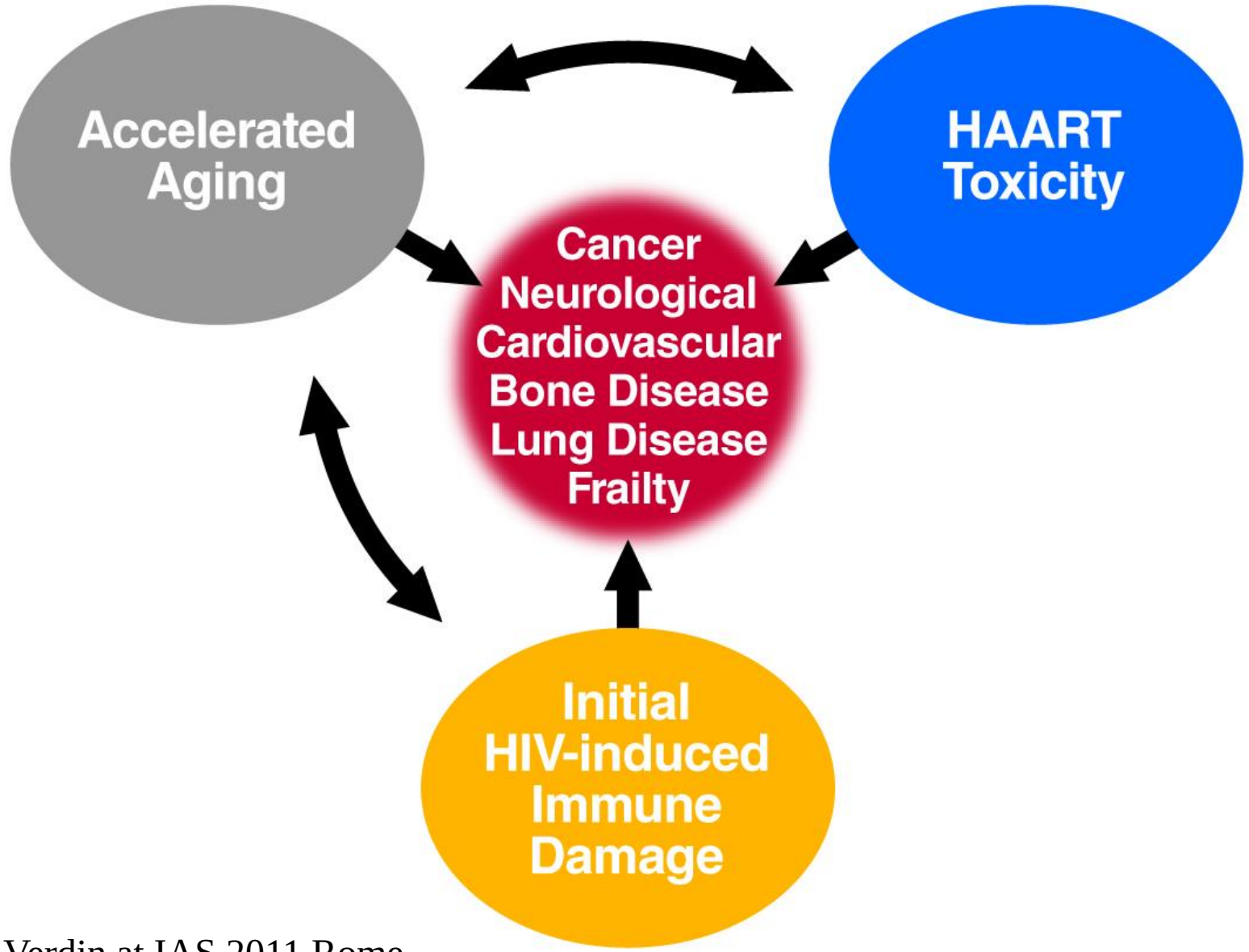
Chronic liver disease

COPD

Chronic renal disease

IAS 2011

Patients on HAART Show Significant Morbidity



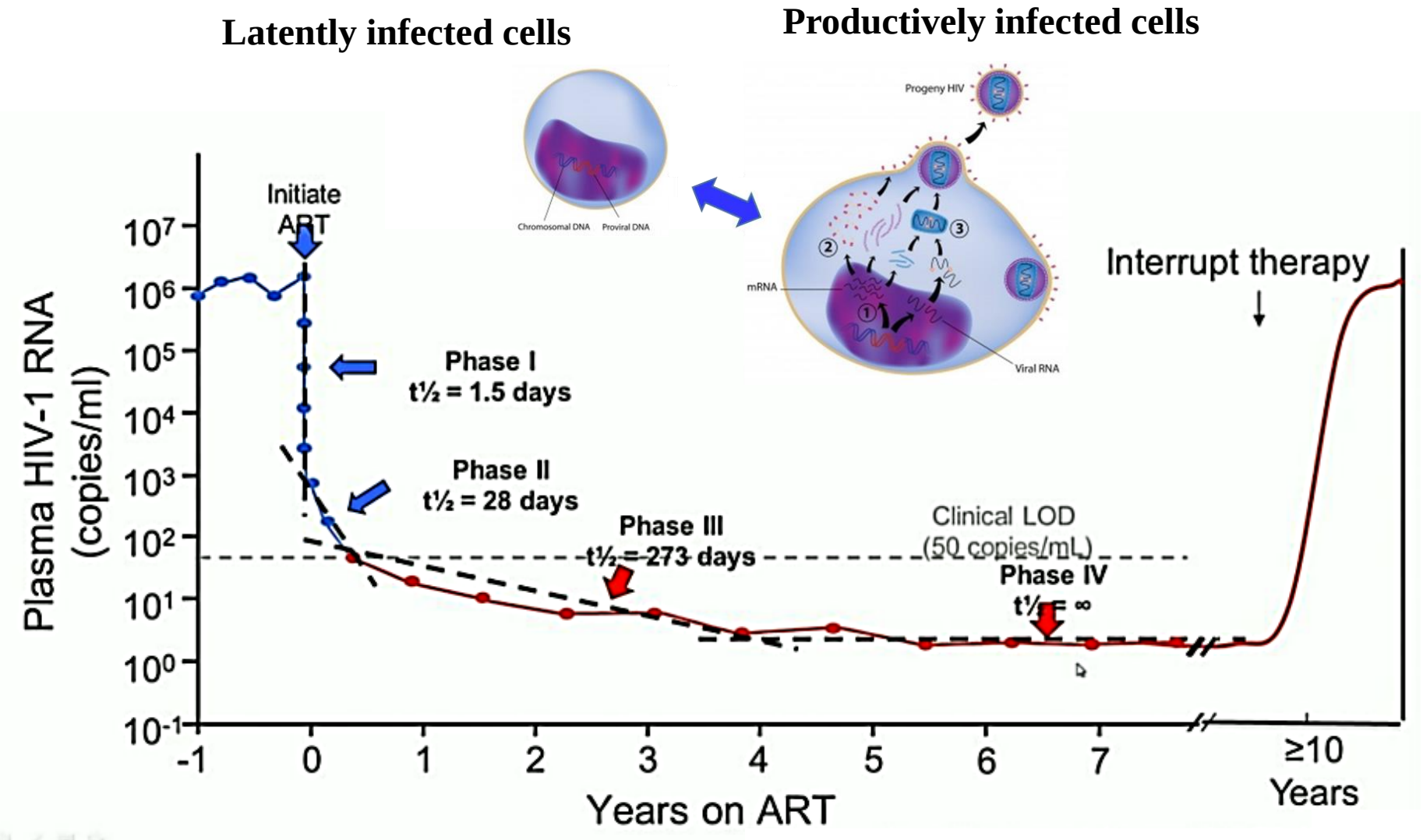
Dr. Eric Verdin at IAS 2011 Rome

Current issue in the treatment of HIV-1 infection

- 薬剤耐性 (drug resistance)
- Agingに関連した慢性合併症(Comorbidities)の増加
- 重複感染 (co-infections; TB, HBV, HCV etc)
- 薬剤相互作用 (ARV/drug-drug interaction)
- ART アクセス　(HIV care cascade)
- 全員治療時代のコスト (ART cost in all-treat era)

- ARTは一生継続 (maintain a lifelong adherence)

ART suppress HIV-1 replication but does not eliminate HIV-infected cells



Towards an HIV cure: a global scientific strategy

The International AIDS Society Scientific Working Group on HIV Cure

Priority areas for research towards an HIV cure.

- Molecular biology of HIV latency
- Immunology of HIV persistence
- Models for HIV cure or sustainable remission
- Remission in the pediatric population
- Gene and cell therapy
- Novel biomarkers to quantify HIV persistence
- Social-science and health-systems research

Nature Reviews Immunology **volume12, pages607–614(2012)**
Deeks S., Lewin SR, Zacks J. et al, International AIDS Society global scientific strategy: towards an HIV cure 2016, Nat. Med. 22(8), p839-850, 2016

N Engl J Med. 2009; 360:692-8

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Mußig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

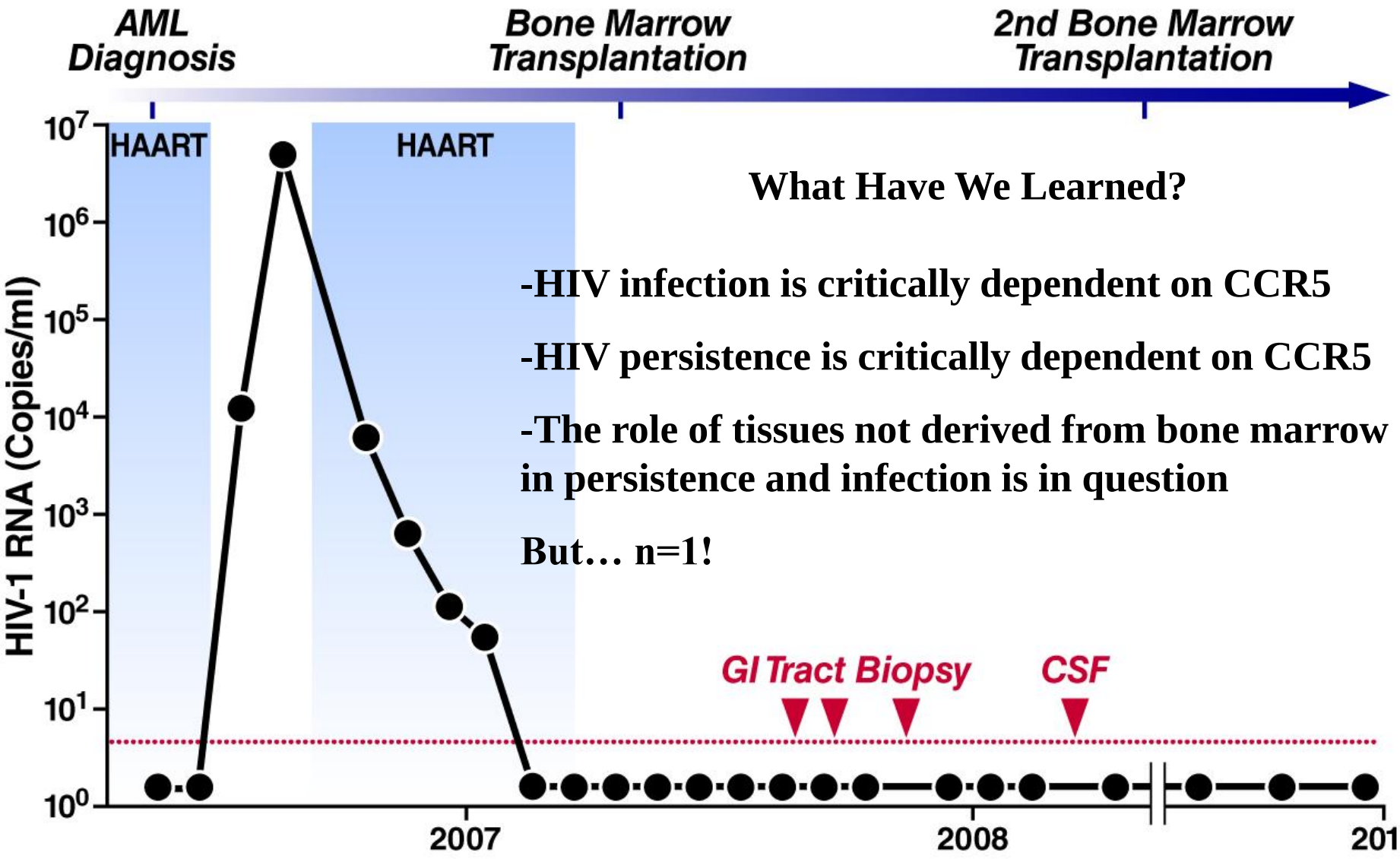
SUMMARY

Infection with the human immunodeficiency virus type 1 (HIV-1) requires the presence of a CD4 receptor and a chemokine receptor, principally chemokine receptor 5 (CCR5). Homozygosity for a 32-bp deletion in the *CCR5* allele provides resistance against HIV-1 acquisition. We transplanted stem cells from a donor who was homozygous for *CCR5* delta32 in a patient with acute myeloid leukemia and HIV-1 infection. The patient remained without viral rebound 20 months after transplantation and discontinuation of antiretroviral therapy. This outcome demonstrates the critical role *CCR5* plays in maintaining HIV-1 infection.

Allers et al. Evidence for the cure of HIV infection by CCR5Δ32/Δ32 stem cell transplantation. Blood 2011: 117:2791-9

The 'Berlin Patient,' Timothy Brown, has been cured of HIV since 2007. His story has renewed interest in cure research.

Sterilizing Cure for HIV Infection: Δ32/Δ32 Stem Cell Transplantation



What Have We Learned?

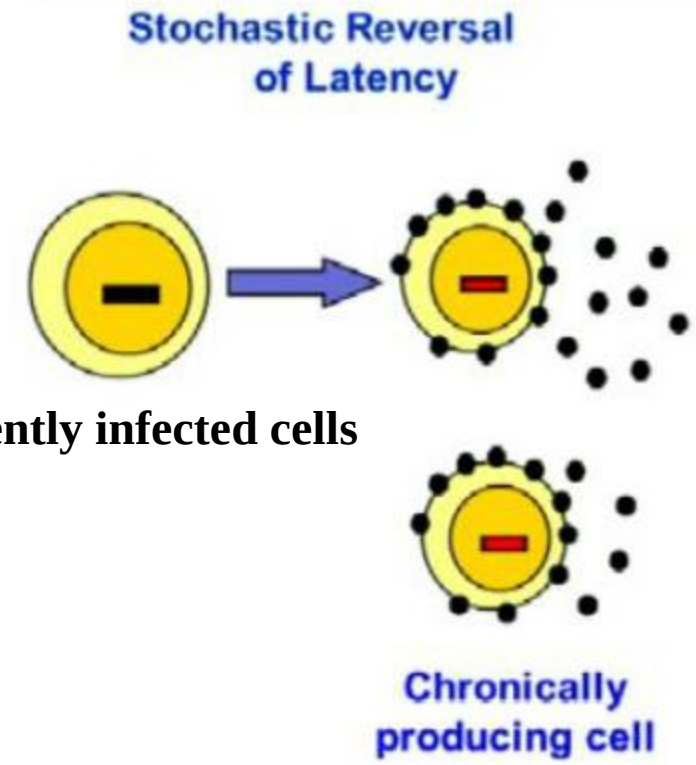
-HIV infection is critically dependent on CCR5

-HIV persistence is critically dependent on CCR5

-The role of tissues not derived from bone marrow in persistence and infection is in question

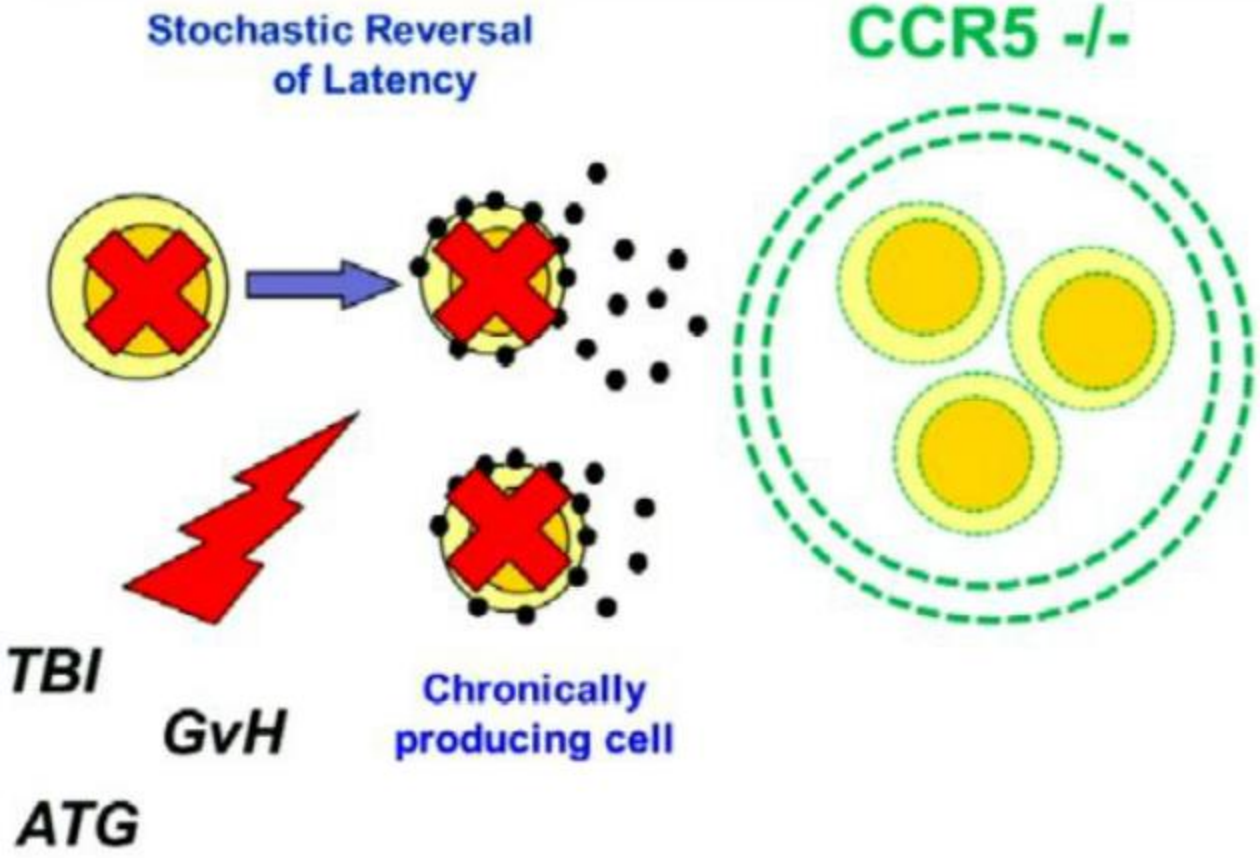
But… n=1!

Tim Brown: Eradication Cure

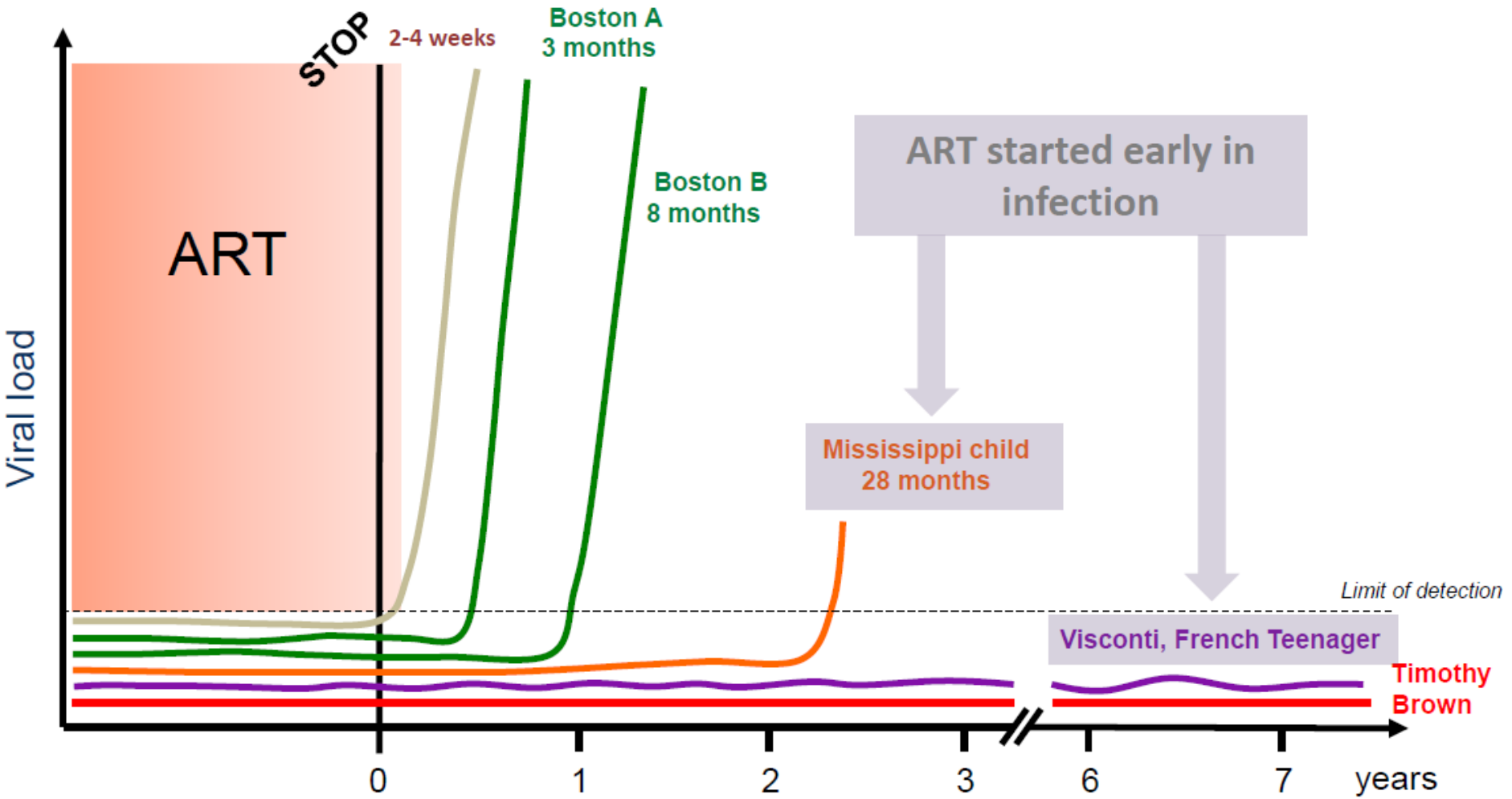


Source of residual virus replication consisted of viruses reactivated from latently infected cells and viruses produced by persistent infected long-lived cells.

Tim Brown: Eradication Cure



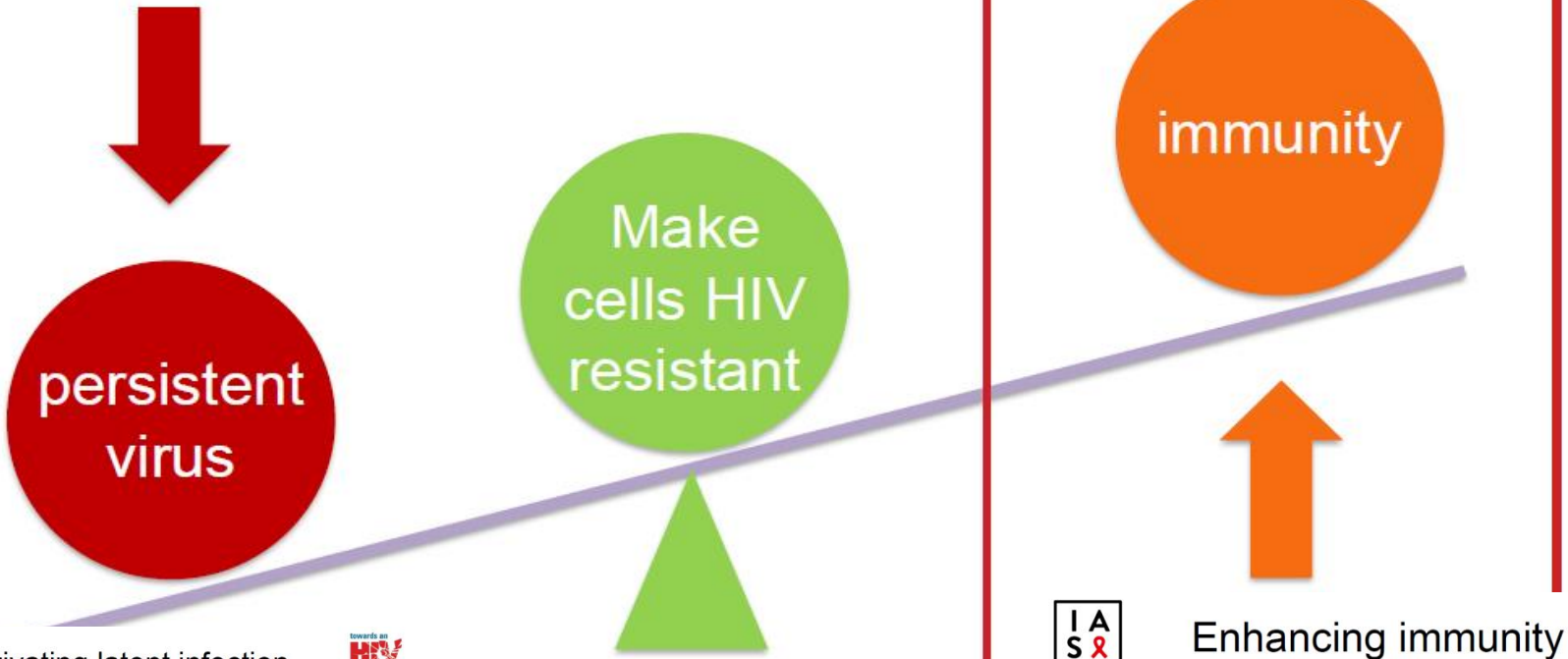
Achieving HIV remission



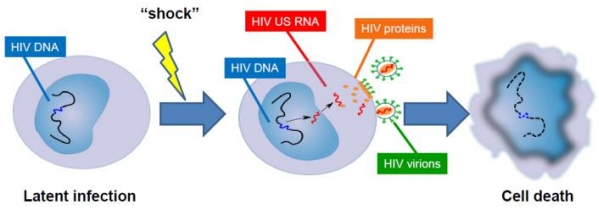
Deeks S., Lewin SR, Zacks J. et al, International AIDS Society global scientific strategy: towards an HIV cure 2016, Nat. Med. 22(8), p839-850, 2016

Current Clinical Strategies

Latency Reverting Agents : LRA



Activating latent infection



Release the brake on latency
Eg., HDACi

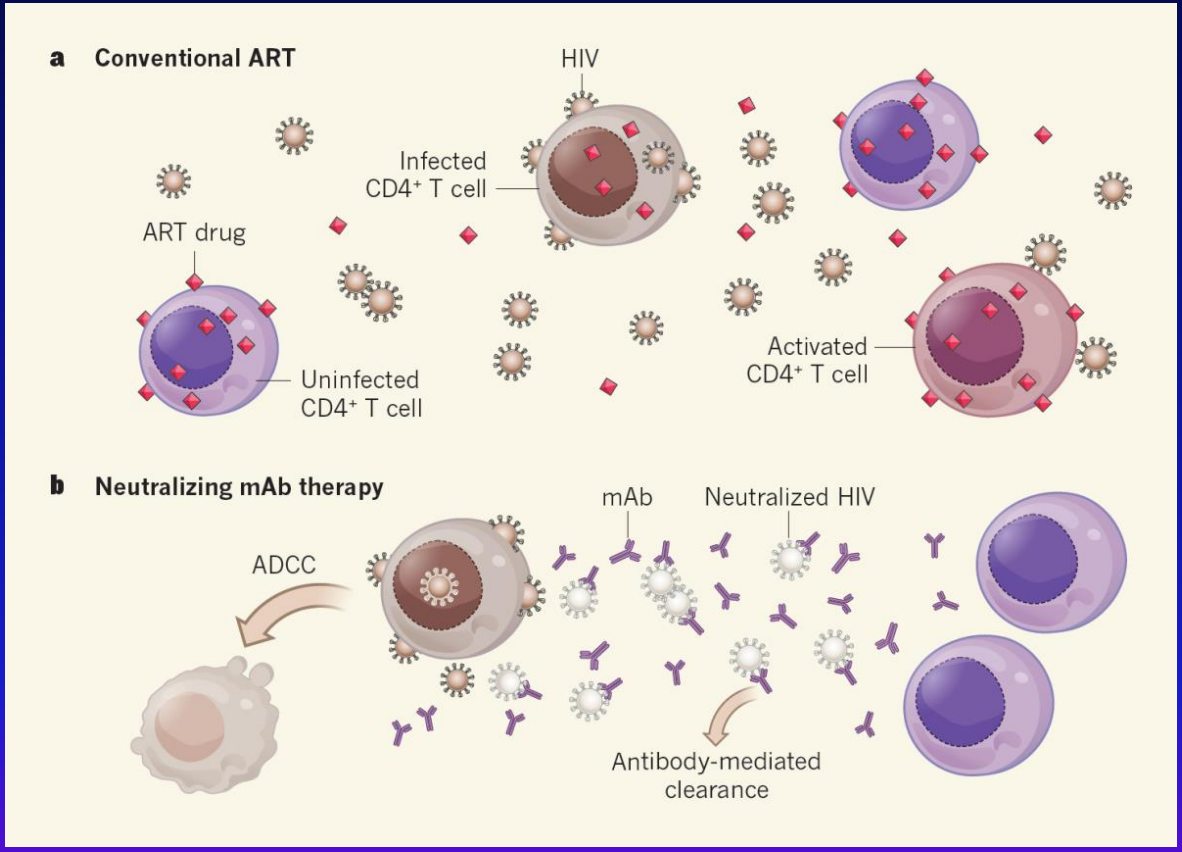
Floor the accelerator
Eg., disulfiram, TLR agonists

- Knock out genes
  - Eliminate CCR5
    - Autologous T-cells
    - Allogeneic cord blood
    - Stem cells
  - HIV
- Knock in genes
  - Restriction factors

Enhancing immunity

- Antibodies
  - Broadly neutralising Ab
  - (Bi-specific Ab)
  - (Antibody dependent cell cytotoxicity)
- T-cell vaccines
  - (CMV vaccines)
- Dendritic cell vaccines
- Immunomodulation

Neutralizing antibodies may contribute to sustainable remission by attacking HIV-infected cells (Fc-mediated functions)



Functions of nAbs

Neutralization

ADCC/ADCVI

Antibody-mediated immune-enhancing effects

Picker L, Deeks S. HIV: Antibodies advance the search for a cure. Nature 503, 207–208, 2013.
Caskey M et al., Broadly neutralizing antibodies for HIV prevention or immunotherapy. N Engl J Med 375;21, 2016

CRU,CAR
Kumamoto Univ.

KAKETSUKEN

QUINTILES

OA4-3LB

International AIDS Society
Stronger Together Against HIV

Passive transfer of neutralizing monoclonal antibody KD-247 reduces plasma viral load in patients chronically infected with HIV-1: a phase-1b clinical study of a humanized monoclonal antibody KD-247 (KD-1002)

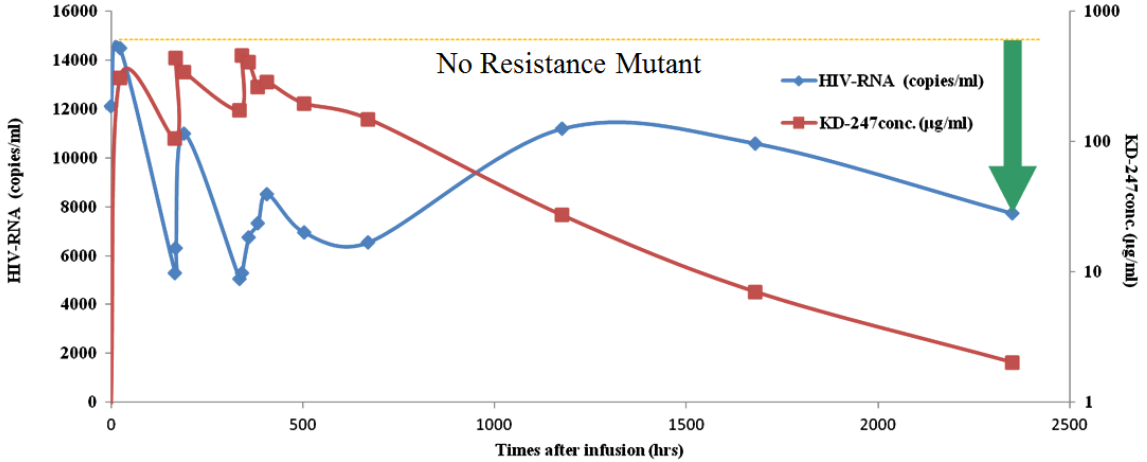
Shuzo Matsushita[1], Kazuhisa Yoshimura[1,2], Toshihiro Maeda[3], Toshio Murakami[3] , KD-1002 Principal Investigators and The Protocol Team of Quintiles

Center for AIDS Research, Kumamoto University[1], AIDS Research Center, National Institute of Infectious Diseases[2], The Chemo-Sero-Therapeutic Research Institute[3]

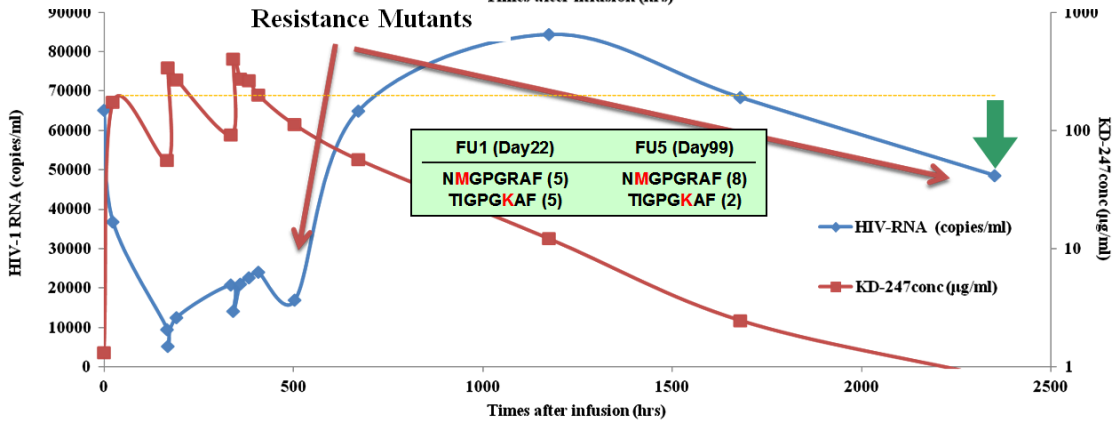
IAS 2013 Towards an HIV Cure Symposium

Long-term viral suppression effect in 16mg/kg cohort

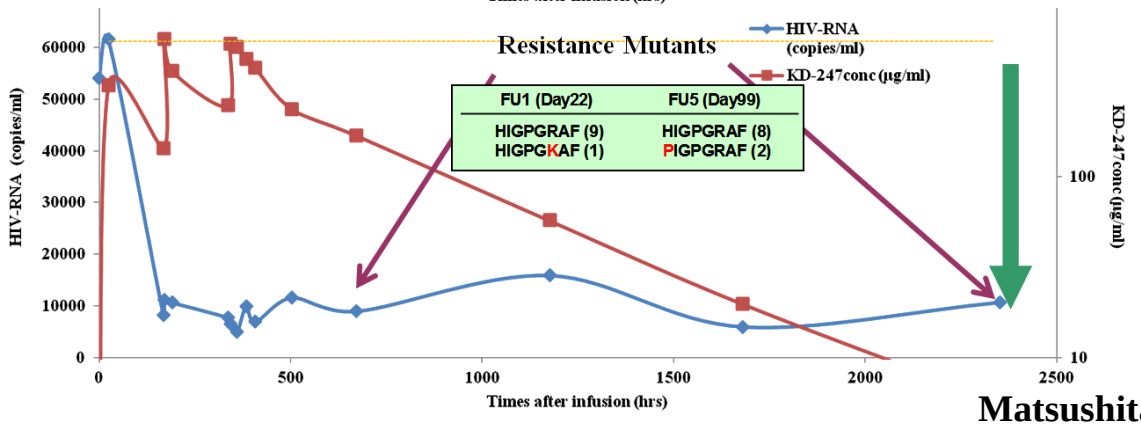
Case#10012



Case #03017

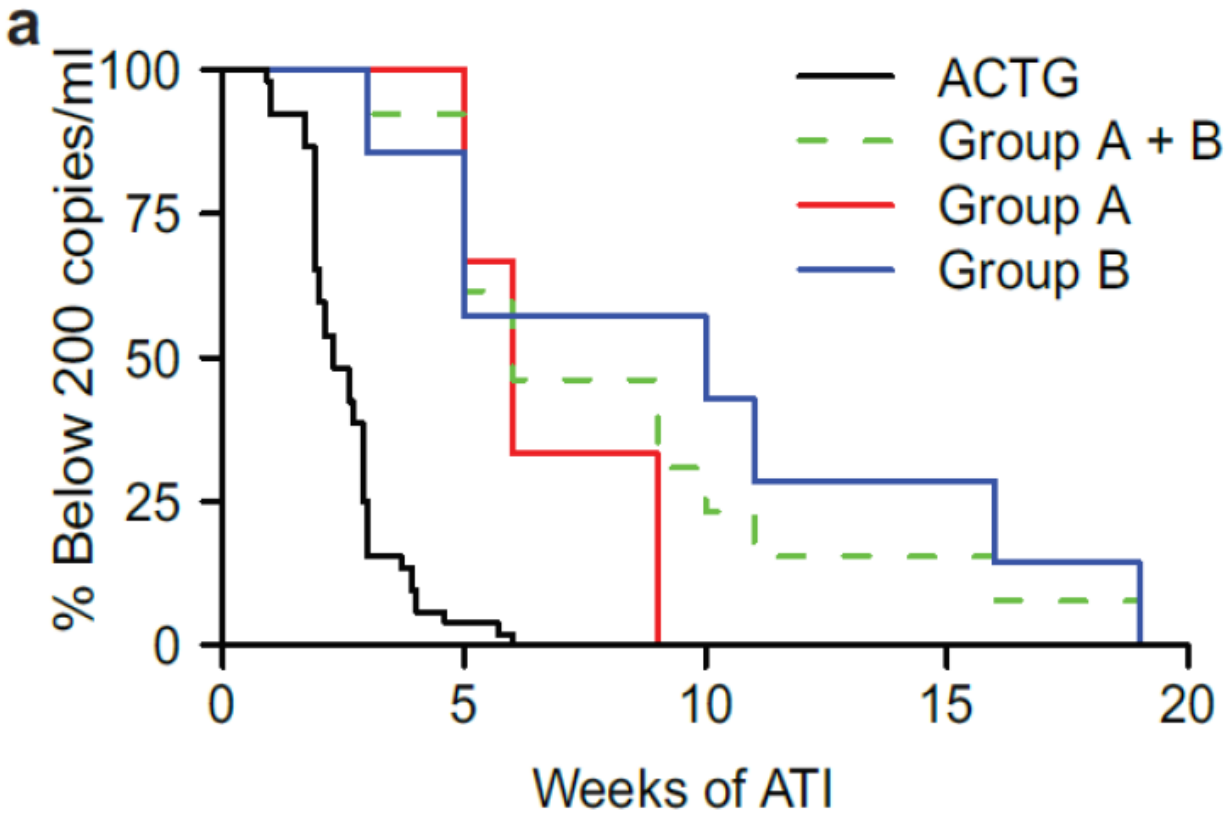


Case#12044



Matsushita s. et al., AIDS 2015

Broadly neutralising antibodies prolong time to rebound



Group A = 3BNC1017 x2 infusions; Group B = 3BNC1017 x 4 infusions

Scheid et al., Nature 2016

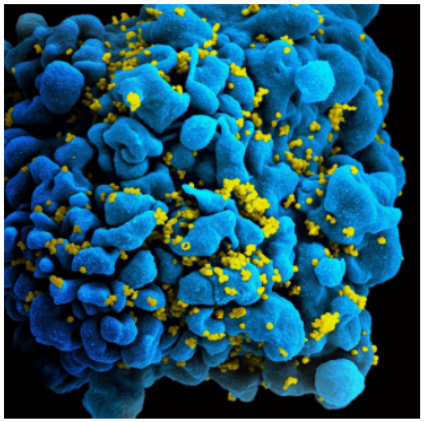
PGT121 Combined with GS-9620 Delays Viral Rebound in SHIV-Infected Rhesus Monkeys. E Borducchi, *et al*. Conference on Retroviruses and Opportunistic Infections, March 6, 2018.

Monday, March 5, 2018

Broadly neutralizing antibody treatment may target viral reservoir in monkeys

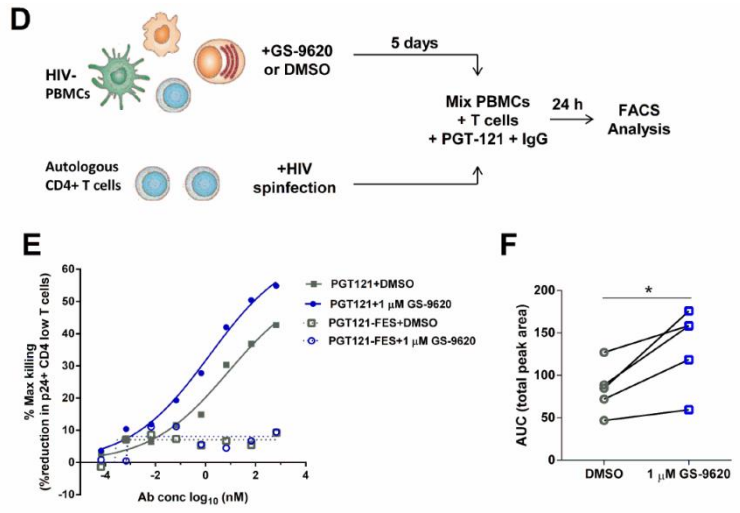
NIH-supported scientists find combination therapy suppresses HIV-like virus in primates.

After receiving a course of antiretroviral therapy for their HIV-like infection, approximately half of a group of monkeys infused with a broadly neutralizing antibody to HIV combined with an immune stimulatory compound suppressed the virus for six months without additional treatment, according to scientists supported in part by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. The therapy may have targeted the viral reservoir — populations of long-lived, latently infected cells that harbor the virus and that lead to resurgent viral replication when suppressive therapy is discontinued.



HIV-infected T cell. *NIAID*

The new findings may inform strategies that attempt to achieve sustained, drug-free viral remission in people living with HIV. Researchers discussed their results today at a press conference at the 25th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston.



GS-9620 (TLR7 agonist): best in class LRA + PGT121 (bNAb) reduced viral reservoir in monkey model

Summary

- With advances in antiviral therapy (ART), HIV-1 infection has become a controllable chronic infection.
- ART is a treatment that requires continuation for a lifetime.
- Overcoming chronic complications refereed as comorbidities related to aging and drug resistance in the course of long-term treatment is becoming a global problem.
- Research toward an HIV cure is progressing. Even though elimination of HIV is difficult, research aimed at "long-term remission state" which does not require ART for a long time is being conducted.

Thank you for your attention

Amakusa

Mt. ASO

Kumamon

Collaborators

C-AIDS Res.

Kumamoto Univ.

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2019年5月7日(火)～6月28日(金)

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