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HIV Basics: The History and Current State of the Epidemic

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University of Massachusetts Medical School

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USAID
FROM THE AMERICAN PEOPLE

University of Massachusetts
UMASS Medical School

HIV Basics: the History and Current State of the Epidemic

Steven Hatch, MD

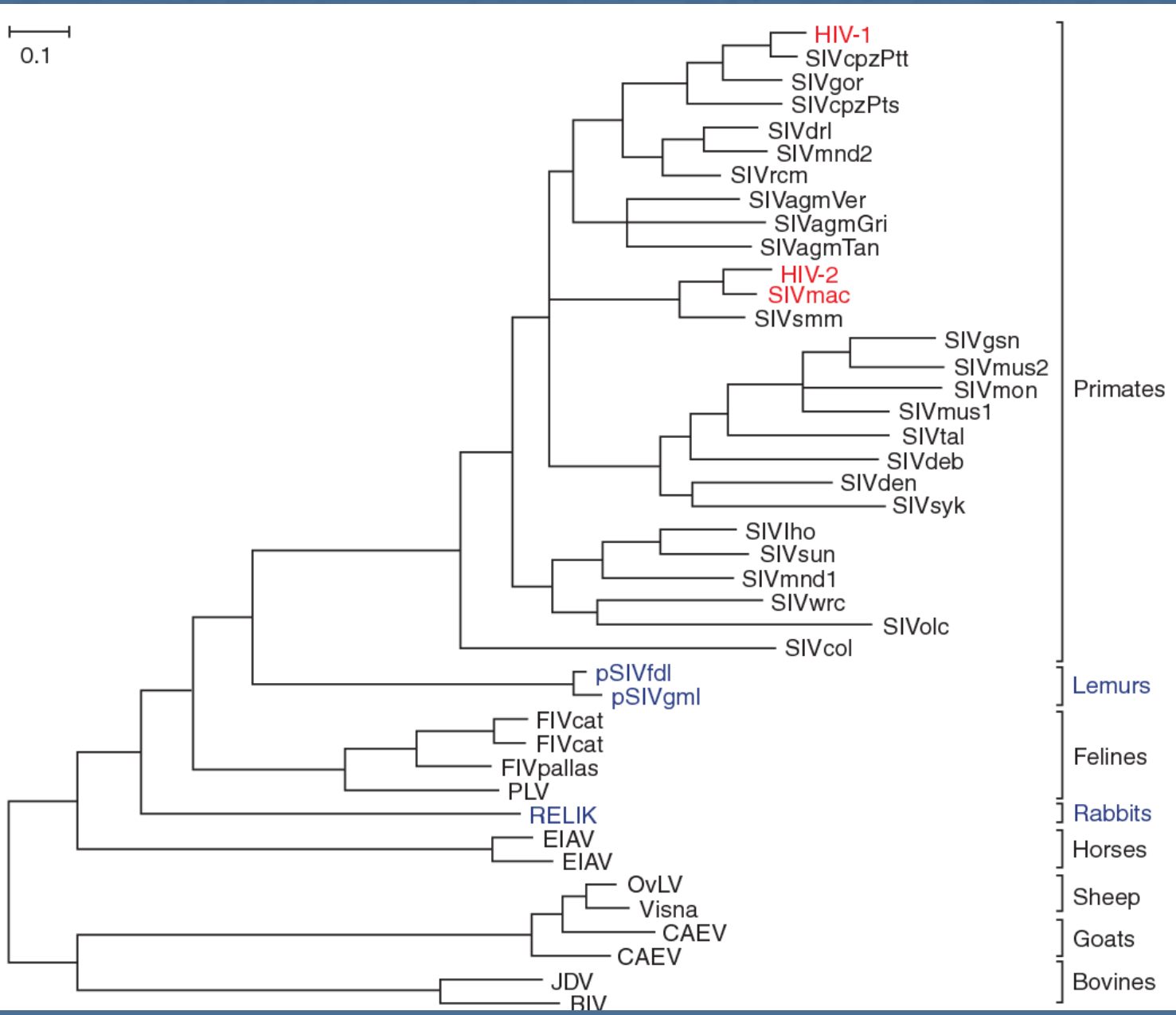
USAID PEER/Liberia ID Lecture Series

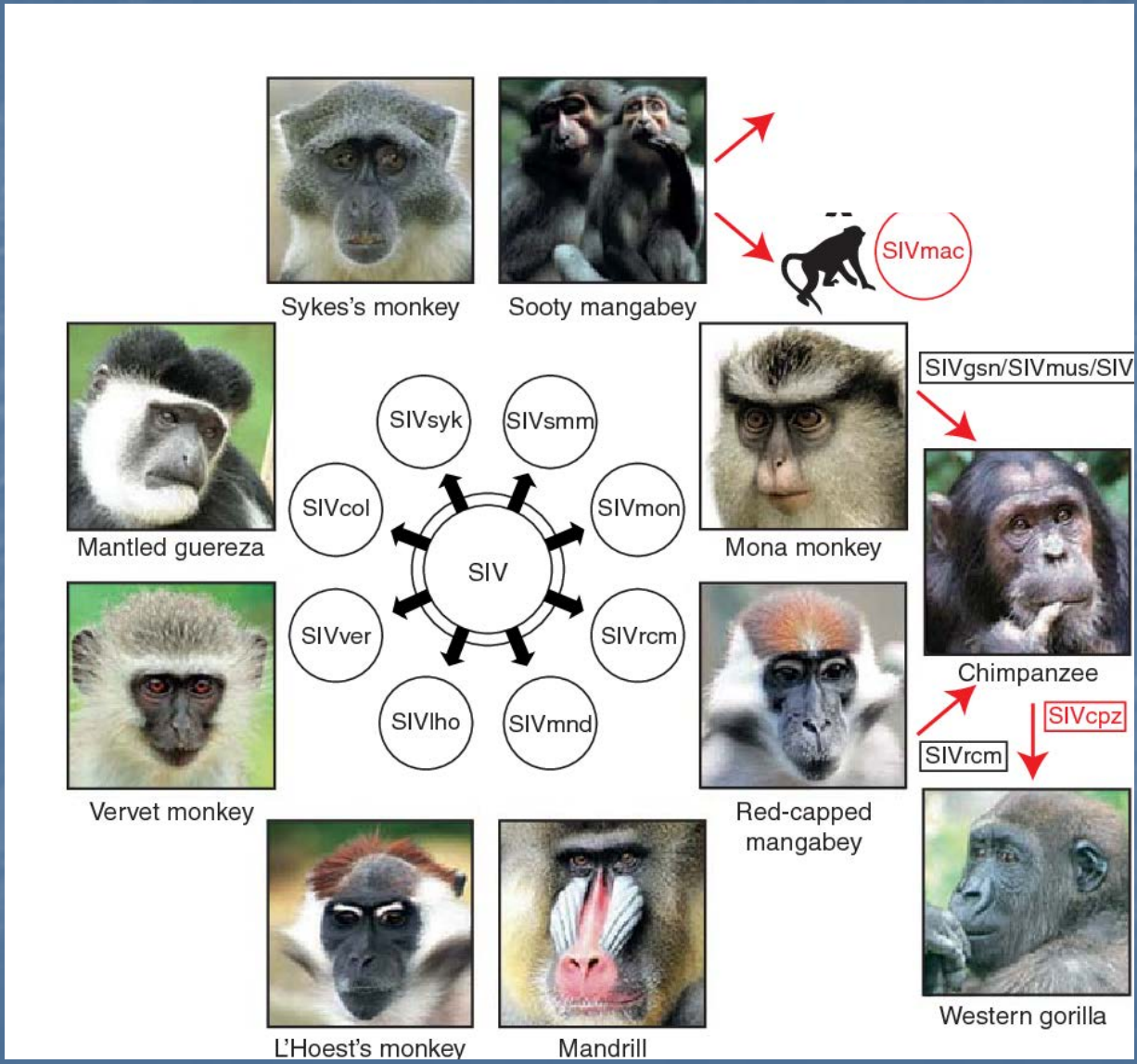
24 September 2020

Goals

- Provide HIV in brief historical context
- Illustrate life cycle of HIV and demonstrate effects of various drug classes on disruption of life cycle
- Discuss *basic* treatment strategies
- Highlight useful sources of information

Origins

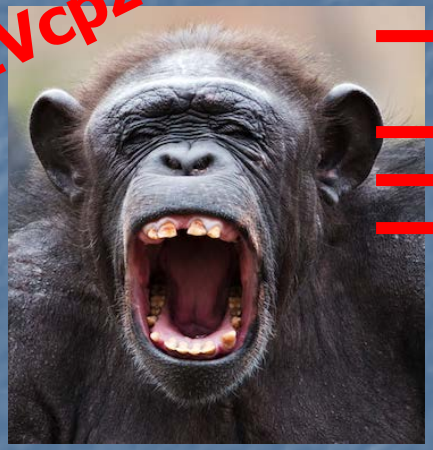

0.1
HIV-1
SIVcpzPtt
SIVgor
SIVcpzPts
SIVdrl
SIVmnd2
SIVrcm
SIVagmVer
SIVagmGri
SIVagmTan
HIV-2
SIVmac
SIVsmm
SIVgsn
SIVmus2
SIVmon
SIVmus1
SIVtal
SIVdeb
SIVden
SIVsyk
SIVlho
SIVsun
SIVmnd1
SIVwrc
SIVolc
SIVcol
pSIVfdl
pSIVgml
FIVcat
FIVcat
FIVpallas
PLV
RELIK
EIAV
EIAV
OvLV
Visna
CAEV
CAEV
JDV
BIV
Primates
Lemurs
Felines
Rabbits
Horses
Sheep
Goats
Bovines


Sykes's monkey
Sooty mangabey
SIVmac
Mantled guereza
SIVsyk
SIVsmm
SIVcol
SIVmon
SIV
SIVver
SIVrcm
SIVlho
SIVmnd
Mona monkey
SIVgsn/SIVmus/SIV
Chimpanzee
SIVcpz
SIVrcm
Vervet monkey
Red-capped mangabey
L'Hoest's monkey
Mandrill
Western gorilla

“The Hunter” Theory

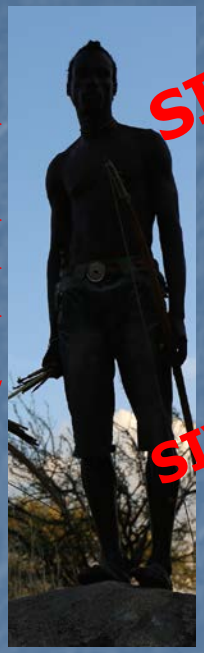
Chimp

SIVcpz



Sooty Mangabey

SIVsmm



SIVcpz

SIVsmm

HIV-1

HIV-2

STRAINS
HIV-1 M
HIV-1 N
HIV-1 O

HIV-1 P from gorillas
Maybe HIV-1 O too

MOST CASES OF HIV ARE HIV-1 M (minimal clinical significance)

Late 1800s - 1981

- HIV spreads ~1920-1950 along the Congo river: Brazzaville to Leopoldville (now Kinshasa)
- Haitian professionals training in Congo in mid-1960s return
- From there, virus jumps to US ~1969
- See Faria N et al, “The early spread and epidemic ignition of HIV-1 in human populations,” *Science* 346 (6205): 56-61.
- By 1960s, African doctors note rise in OIs and wasting in urban areas (eg Kinshasa/Brazzaville)
- Then…

CENTERS FOR DISEASE CONTROL

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

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Epidemiologic Notes and Reports

249 Dengue Type 4 Infections in U.S. Travelers to the Caribbean

250 *Pneumocystis* Pneumonia - Los Angeles

Current Trends

252 Measles - United States, First 20 Weeks

253 **Risk-Factor-Prevalence Survey - Utah**

259 **Surveillance of Childhood Lead Poisoning - United States**

International Notes

261 **Quarantine Measures**

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.

The 1980s: "And The Band Played On"

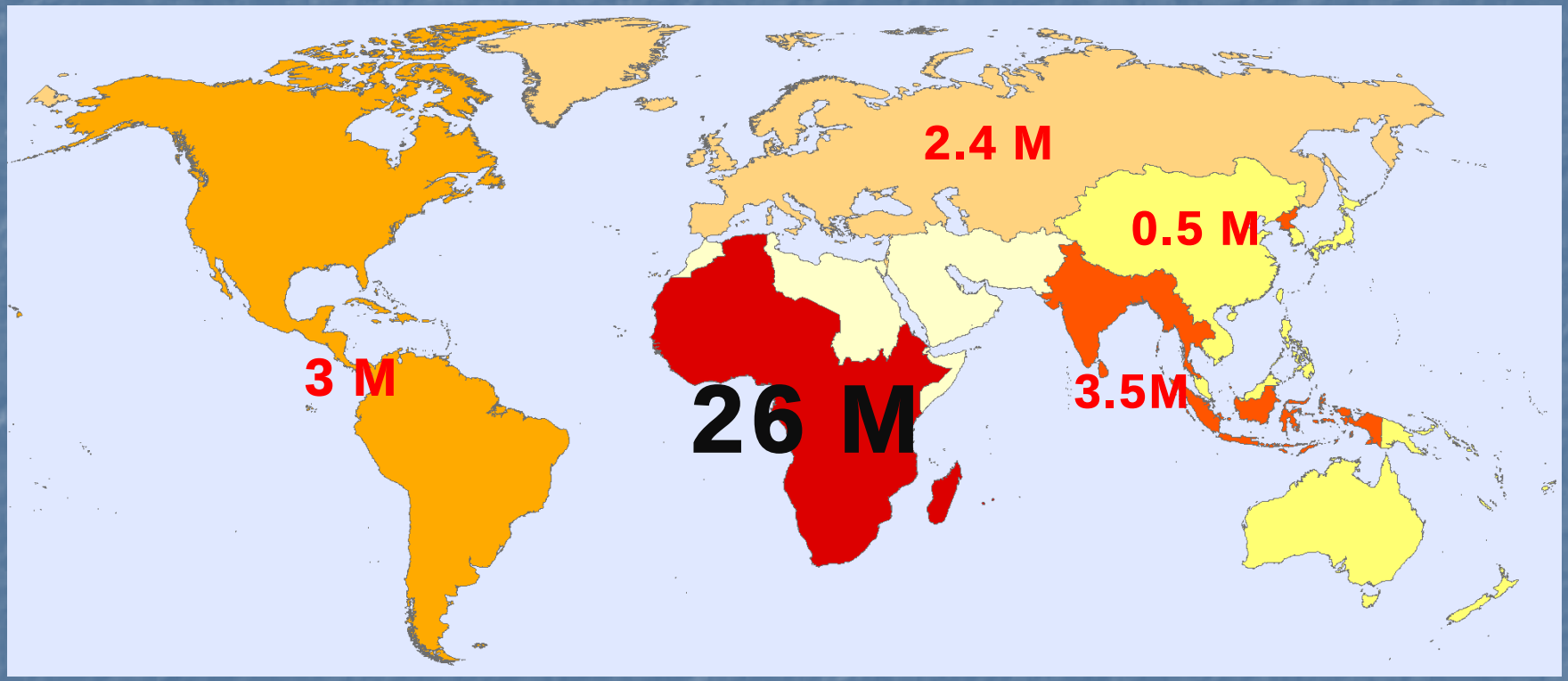
- Initially called "GRID"—Gay Related Immune Syndrome
- Mult causal etiologies espoused, including "poppers," gay lifestyle; several scientists understood quickly that it was likely STV
- Also known as "4H Syndrome"—Homosexuals, Hemophiliacs, Haitians, and Heroin users
- AIDS coined July 1982

1980s con't

- 1984: virus is identified (Gallo/Montagnier)
- 1985: China reports AIDS; last major populated region on earth to do so
- 1987: AZT approved
- By end of 1980s, **~8 million people** with HIV infection
- For more: *And The Band Played On*, Randy Shilts of San Francisco Chronicle (USA epidemic)

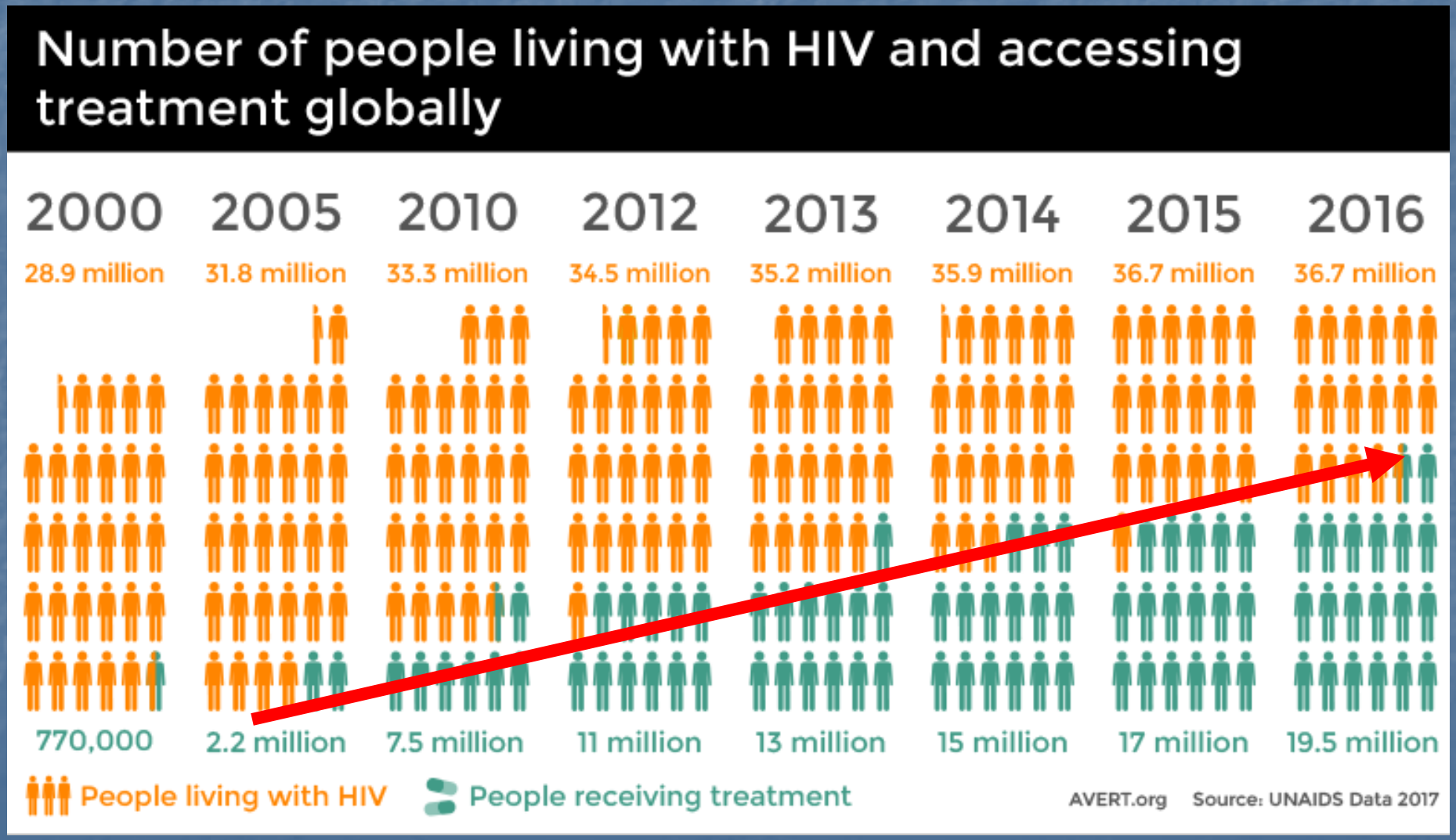
Where things stand now

2016 Estimated Prevalence ~37 M



~700,000 deaths/year

Fortunately it's not all bad news

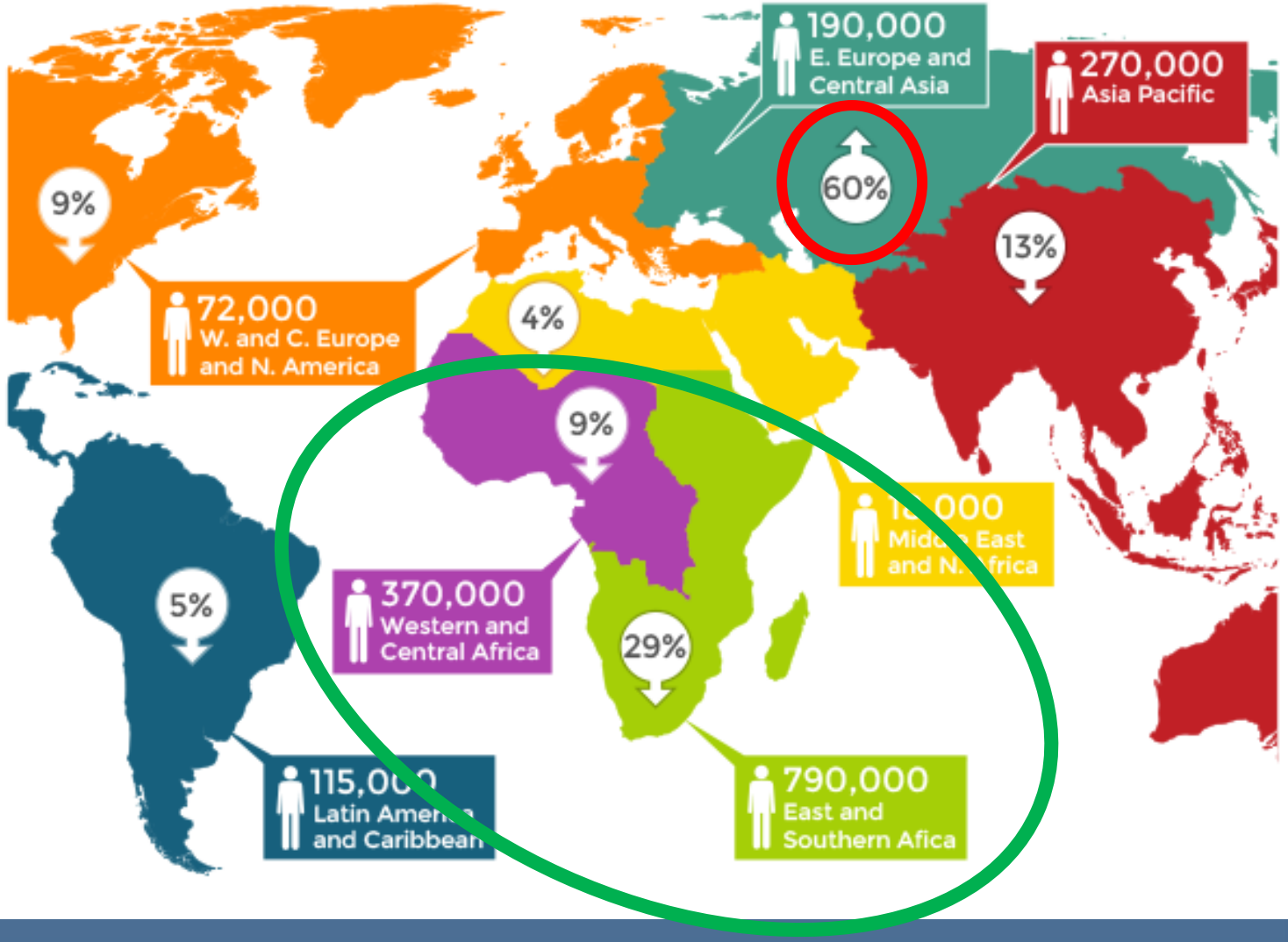


Number of new HIV infections in 2016 and change since 2010

1.8 million people newly infected in 2016 globally

Decrease in number of new infections across the global population each year since 2010

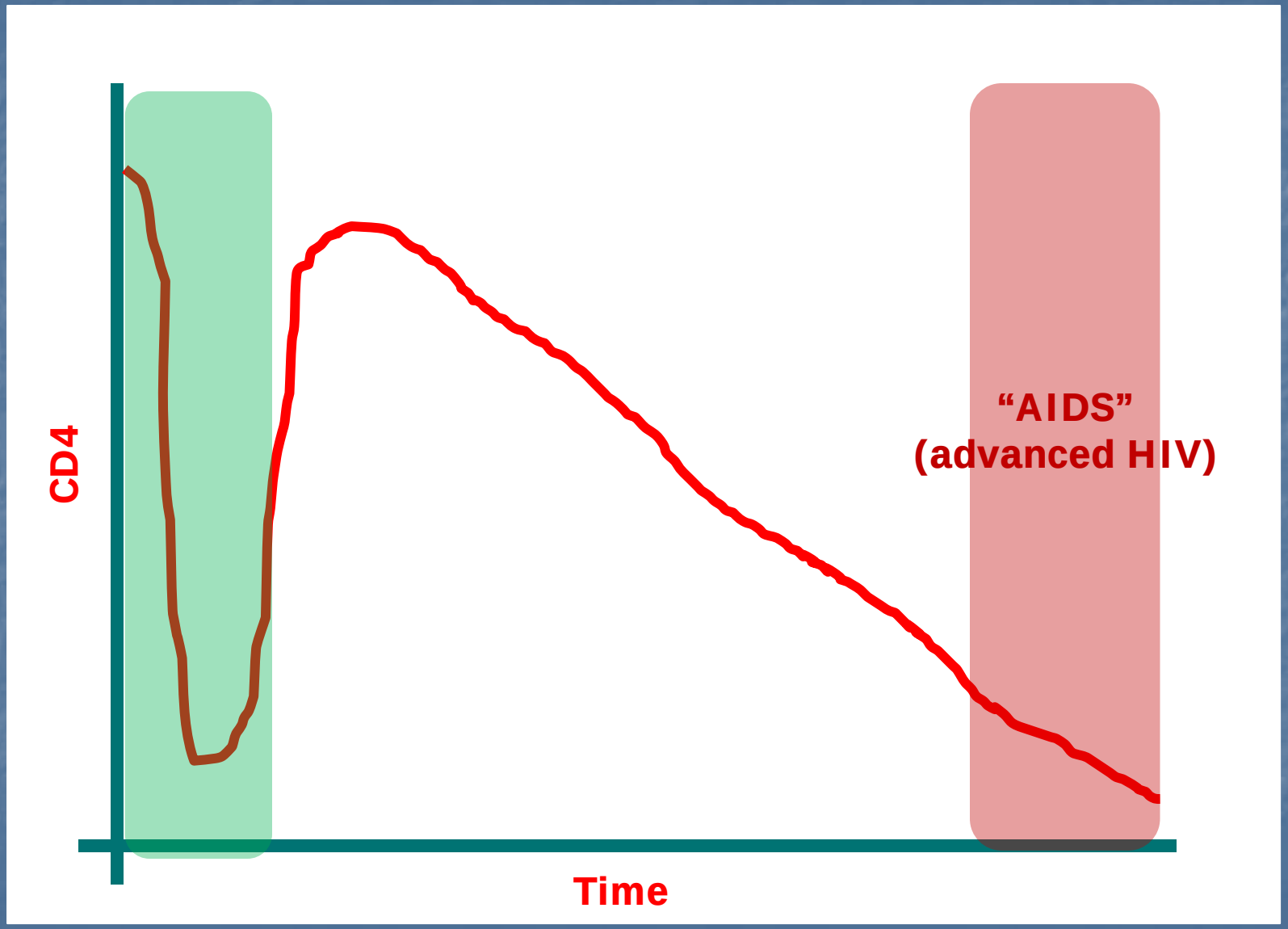
16%

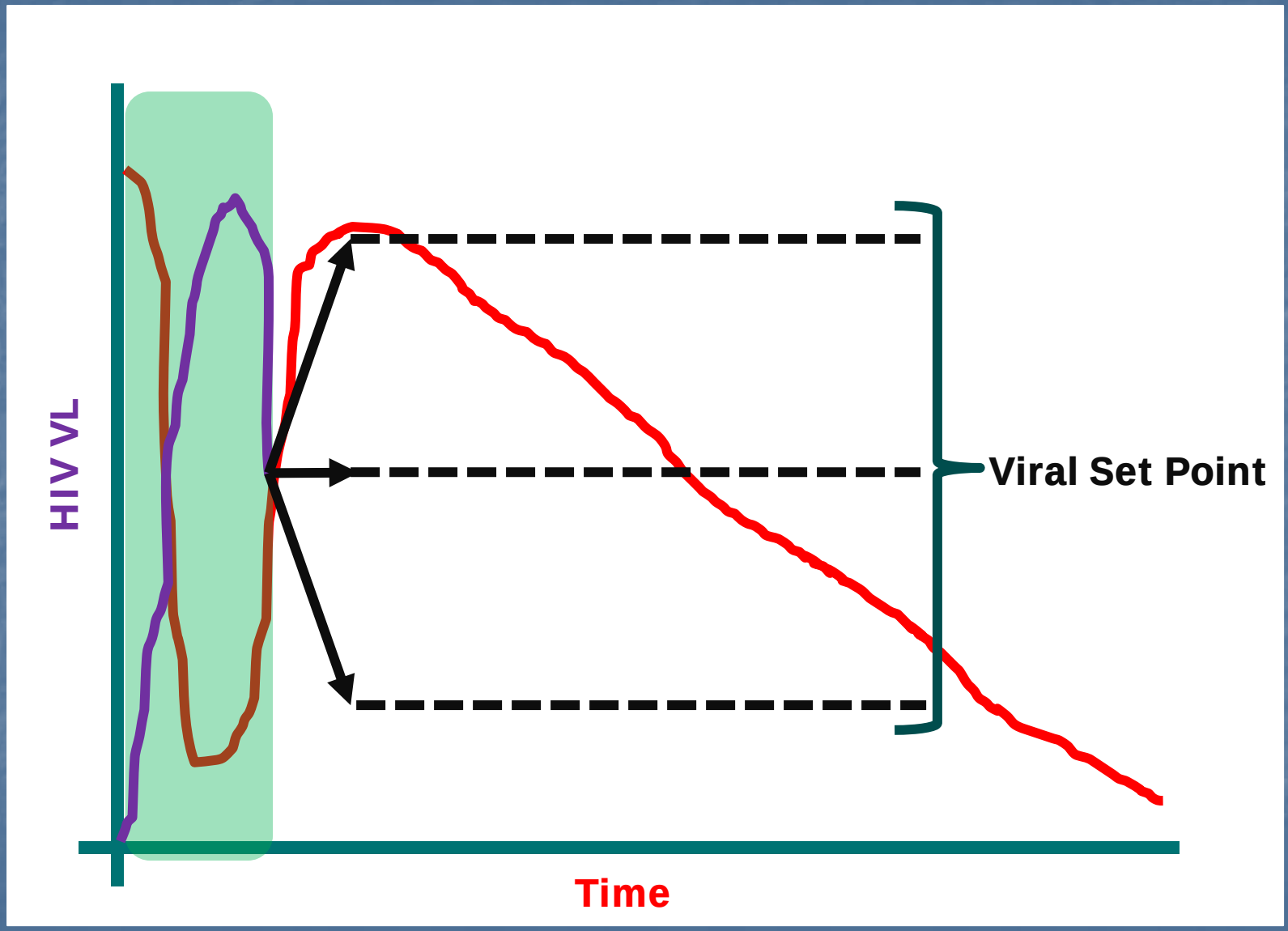


AVERT.org
Source: UNAIDS Data 2017

What does infection look like

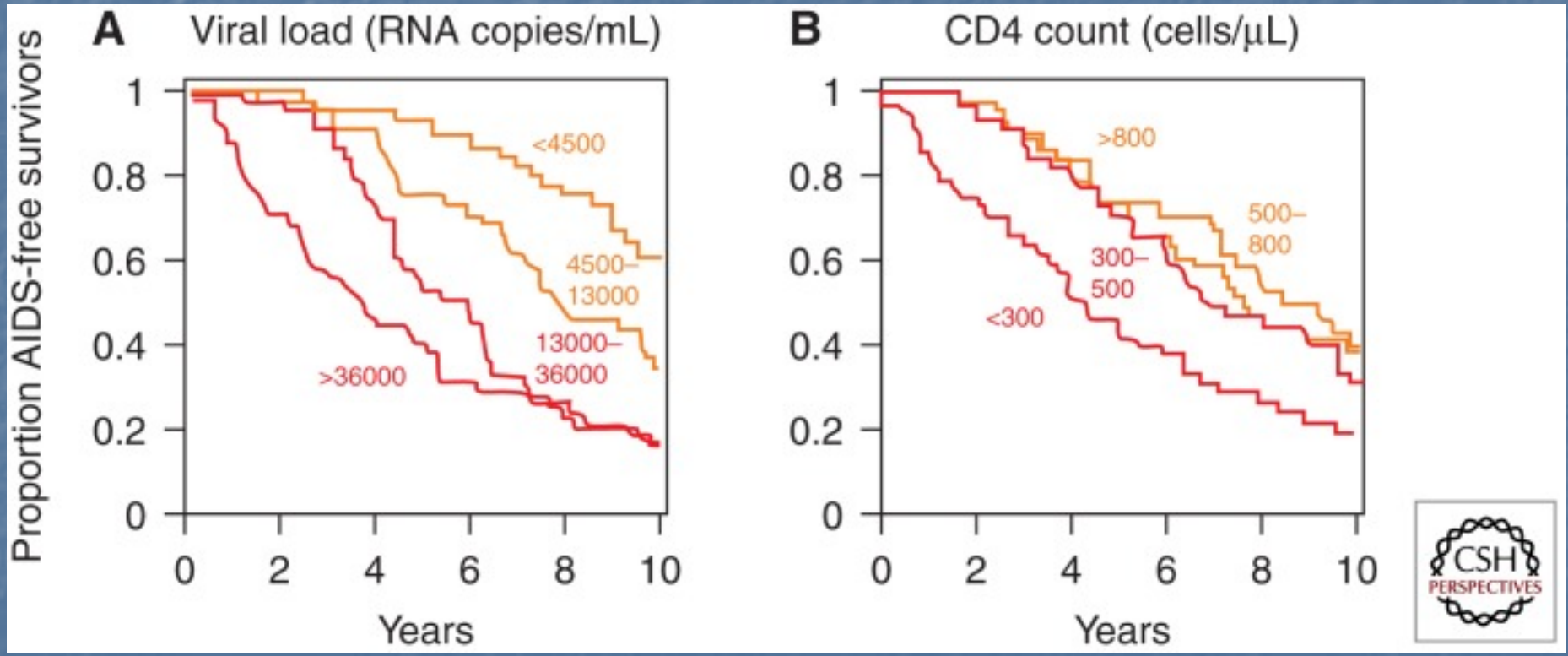
Acute Retroviral Syndrome (~1-3 months)



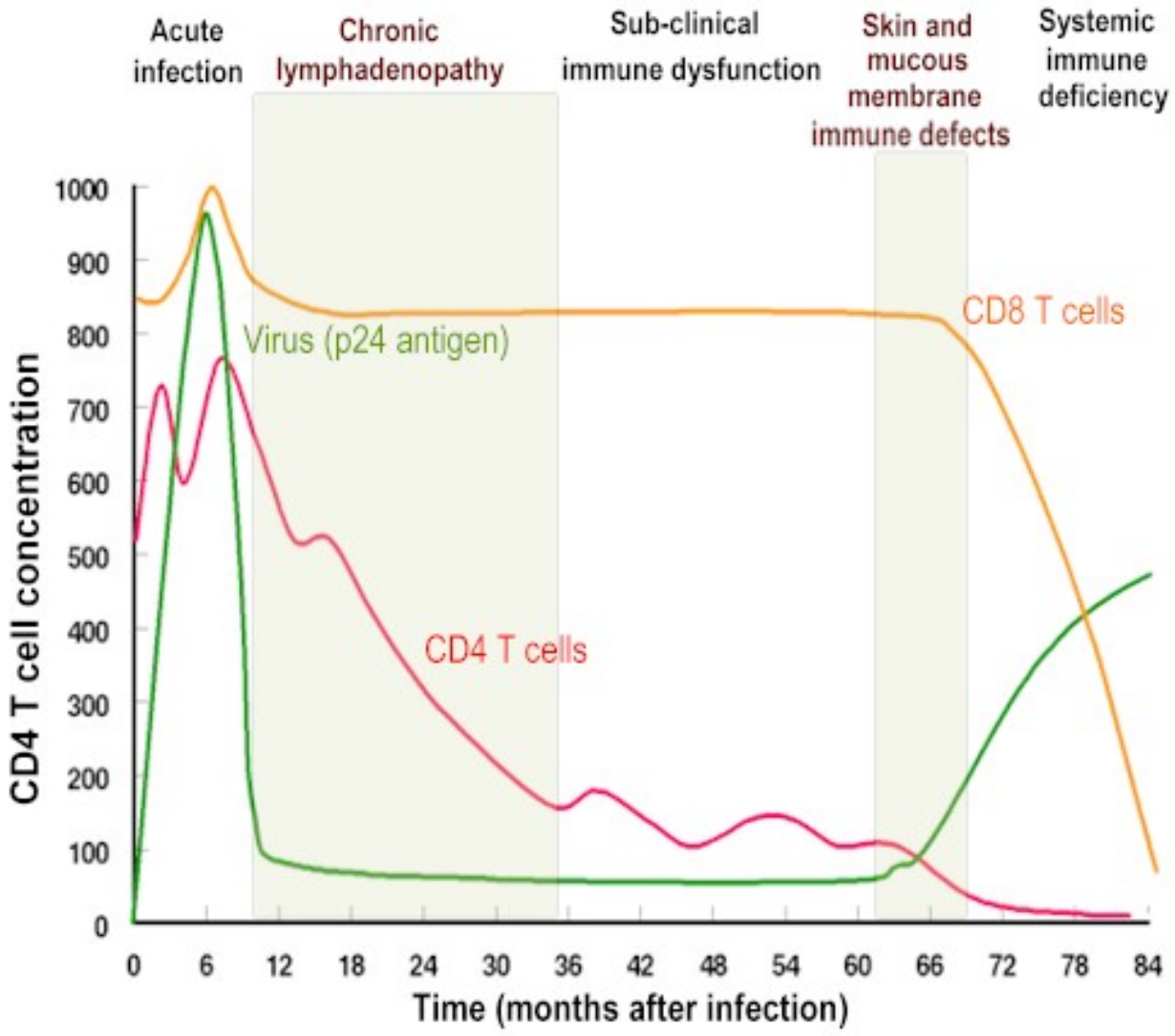

HIV VL
Viral Set Point
Time

Inverse correlation between viral load & CD4 decline

Untreated HIV is a train heading toward a cliff:
CD4 count = distance to the cliff (immune collapse);
Viral Load = speed of the train



Fauci AS, Desrosiers RC 1997. Pathogenesis of HIV and SIV. In Retroviruses (ed. Coffin JM, et al.), pp. 587–635 Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.

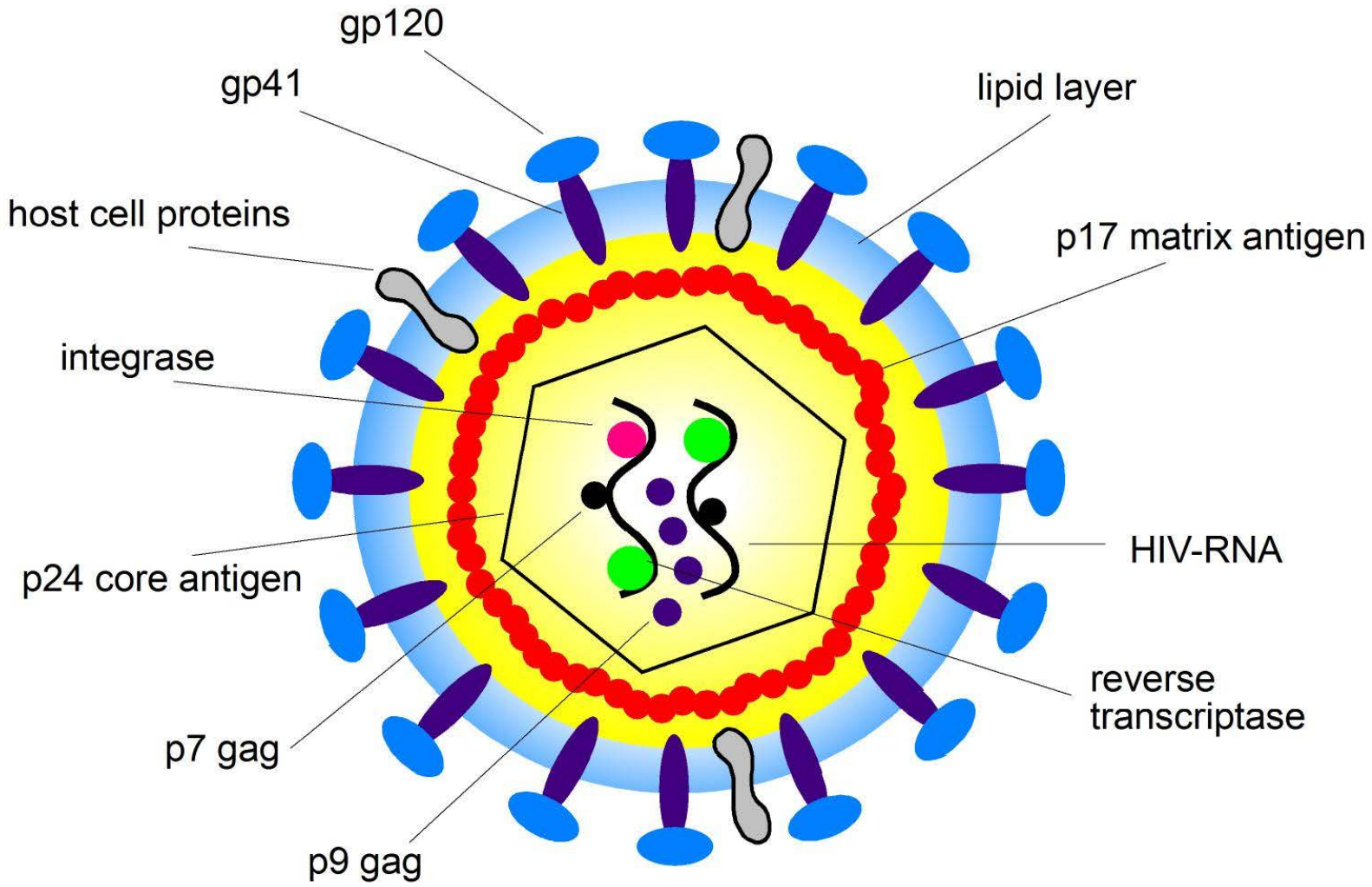

Acute infection
Chronic lymphadenopathy
Sub-clinical immune dysfunction
Skin and mucous membrane immune defects
Systemic immune deficiency
CD4 T cell concentration
1000
900
800
700
600
500
400
300
200
100
0
Virus (p24 antigen)
CD8 T cells
CD4 T cells
0
6
12
18
24
30
36
42
48
54
60
66
72
78
84
Time (months after infection)

Viral replication, kinetics & resistance

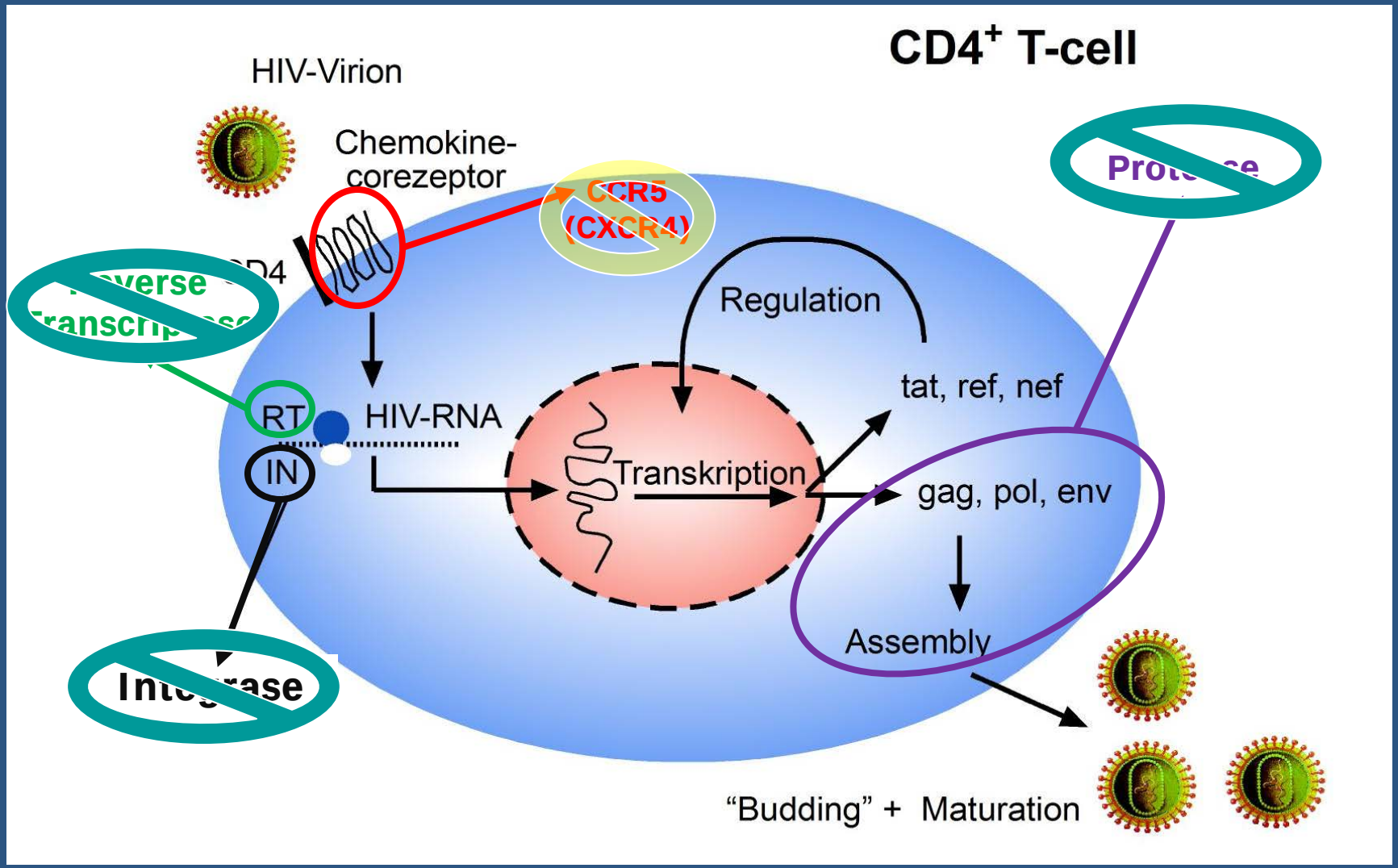
HIV Replication and Mutation

(highly simplified)

- Suppose 10^4 virions/mL (ie VL = 10,000)
- RNA Pol error rate ~1 every 10^4 nucleotides
- HIV genome is 10^4 ~nucleotides long
- HIV replication produces 10^8 virons/day
- ***Given replication kinetics, <u>all</u> possible point mutations can be produced <u>each day</u> in untreated pts***


gp120
gp41
lipid layer
host cell proteins
p17 matrix antigen
integrase
HIV-RNA
p24 core antigen
reverse
transcriptase
p7 gag
p9 gag

Principal Events in HIV Replication



One additional agent (enfuvirtide) blocks entry from a different mechanism than CCR5 inhibition

Treatment options as of 2020 by class

Reverse Transcriptase Inhibitors (NRTI, "Nukes")

3TC (lamivudine)
FTC (emtricitabine)
TDF/TAF (tenofovir)

ABC (abacavir)

also: ddI, d4T, AZT (ZDV)

Reverse Transcriptase Inhibitors (NNRTI, or "Non-Nukes")

EFV (efavirenz)
RPV (rilpiverine)*
DOR (doravirine)
ETR (etravirine)

also: NVP (nevirapine)

Integrase Inhibitors

DTG (dolutegravir)

RAL (raltegravir)
EVG (elvitegravir)
BIC (bictegravir)
CAB (cabotegravir)*

Entry Inhibitors

MVC (maraviroc)

Fusion Inhibitors

T20 (enfuvirtide)—SubQ

Protease Inhibitors

ATV (atazanavir)
DRV (darunavir)

also: FPV (fosamprenavir), LPV/r (lopinavir), TPV (tipranavir), SQV (saquinavir), NFV (nelfinavir)

"Boosters"

r (ritonavir)
c (cobicistat)

HIV Replication and Mutation, reconsidered

- RNA Pol error rate ~1 every 10^4 nucleotides
- HIV replication produces 10^8 virons/day
- ***One "pressure point" (ie, active medication) is not enough; virus will develop resistance mutations almost immediately***
- This is the reasoning behind HAART

HAART basics

- Basic strategy: pressure virus at *three* separate points
  - 2 nukes + integrase inhibitor (eg TDF/FTC + DTG), or
  - 2 nukes + protease inhibitor (eg TDF/FTC + DRV/r), or
  - 2 nukes + non-nuke (eg TDF/FTC + EFV—*but* this is 2nd line)
- OR:
- Truvada plus Dolutegravir;
- Truvada plus Atazanavir;
- Truvada plus Efavirenz (or in one pill as Atripla)

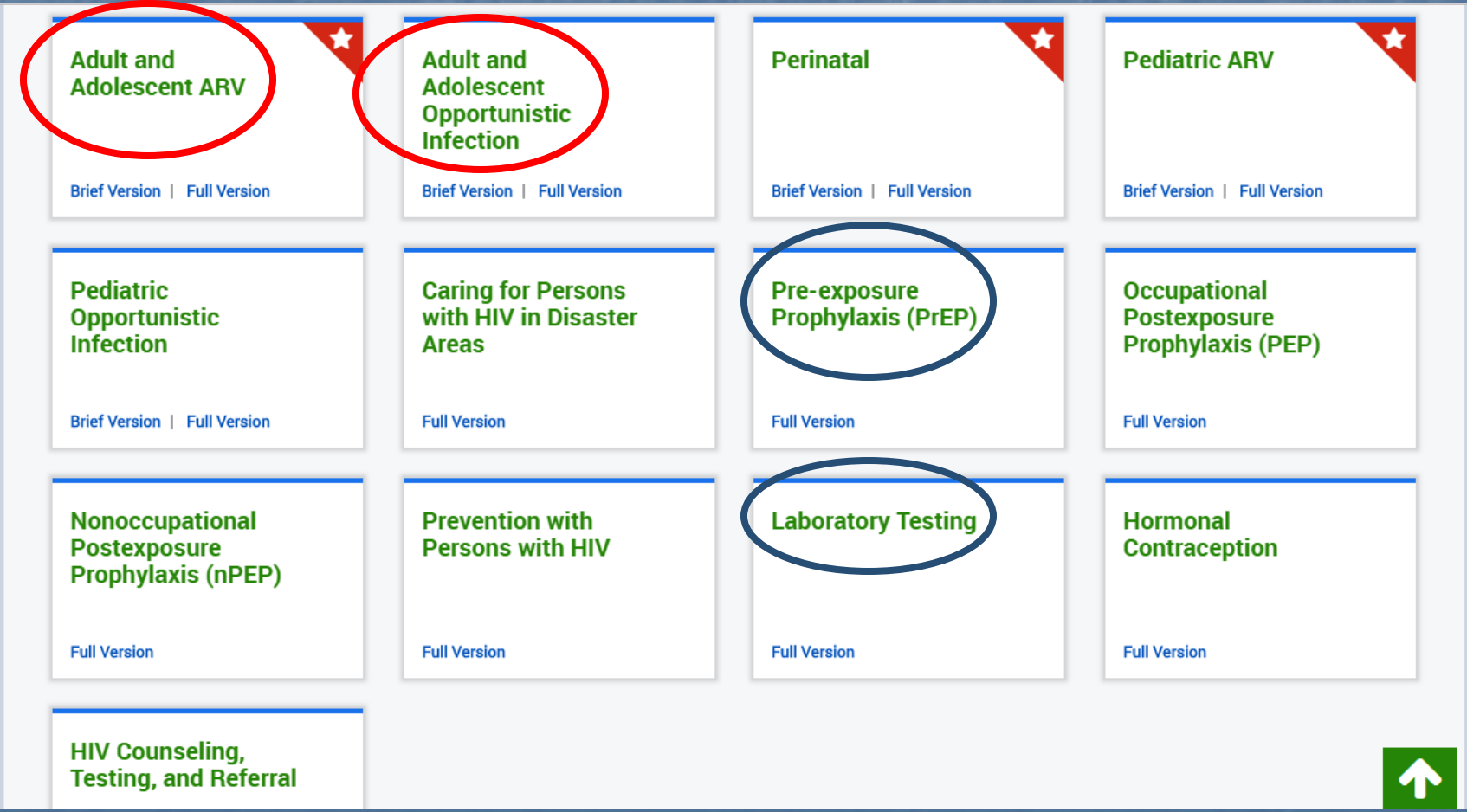
HAART basics con't

- Integrase Inhibitors favored over Protease Inhibitors because of once-daily dosing/combo pills
- Must consider many variables when prescribing
- For example: Hep B status, VL >100K, HLA status, CKDz, psych illness, cirrhosis, QTc, TB on rif, osteoporosis, other

Selected HIV web resources

You will need them.
Over and over.

aidsinfo.nih.gov



eg Table 6

https://aidsinfo.nih.gov/contentfiles/lvguidelines/AA_Tables.pdf

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI + 2 NRTIs:

- DTG/ABC/3TC[a] **(AI)**—if HLA-B*5701 negative
- DTG + tenofovir[b]/FTC[a] (**AI** for both TAF/FTC and TDF/FTC)
- EVG/c/tenofovir[b]/FTC (**AI** for both TAF/FTC and TDF/FTC)
- RAL[c] + tenofovir[b]/FTC[a] (**AI** for TDF/FTC, **AII** for TAF/FTC)

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable, but have some disadvantages when compared with the regimens listed above, or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

Boosted PI + 2 NRTIs: (In general, boosted DRV is preferred over boosted ATV)

- (DRV/c or DRV/r) + tenofovir[b]/FTC[a] (**AI** for DRV/r and AII for DRV/c)
- (ATV/c or ATV/r) + tenofovir[b]/FTC[a] **(BI)**
- (DRV/c or DRV/r) + ABC/3TC[a] **—if HLA-B*5701–negative (BII)**
- (ATV/c or ATV/r) + ABC/3TC[a] **—if HLA-B*5701–negative and HIV RNA <100,000 copies/mL** (**CI** for ATV/r and **CIII** for ATV/c)

NNRTI + 2 NRTIs:

- EFV + tenofovir[b]/FTC[a] (**BI** for EFV/TDF/FTC and **BII** for EFV + TAF/FTC)
- RPV/tenofovir[b]/FTC[a] **(BI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3**

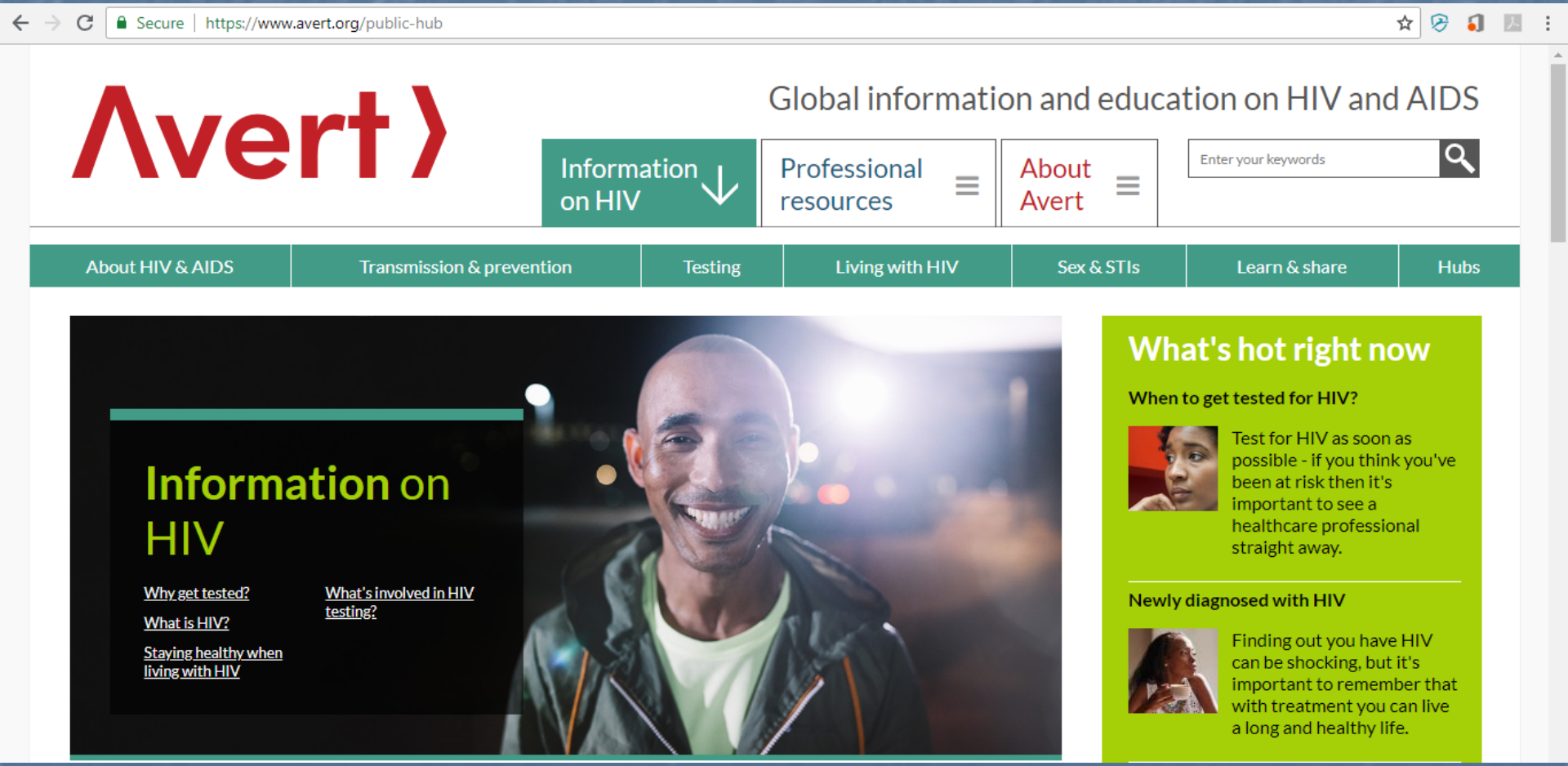
INSTI + 2 NRTIs:

- RAL[c] + ABC/3TC[a] **(CII)—if HLA-B*5701–negative and HIV RNA < 100,000 copies/mL**

Regimens to Consider when ABC, TAF, and TDF Cannot be Used:[d]

- DRV/r + RAL (BID) **(CI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3**
- LPV/r + 3TC[a] (BID)[e] **(CI)**

Avert.org


Secure | https://www.avert.org/public-hub
Avert
Global information and education on HIV and AIDS
Information on HIV
Professional resources
About Avert
Enter your keywords
About HIV & AIDS
Transmission & prevention
Testing
Living with HIV
Sex & STIs
Learn & share
Hubs
Information on HIV
Why get tested?
What is HIV?
Staying healthy when living with HIV
What's involved in HIV testing?
What's hot right now
When to get tested for HIV?
Test for HIV as soon as possible - if you think you've been at risk then it's important to see a healthcare professional straight away.
Newly diagnosed with HIV
Finding out you have HIV can be shocking, but it's important to remember that with treatment you can live a long and healthy life.

avert.org/professionals/hiv-around-world/sub-saharan-africa/overview

Global statistics

Global response
- Funding
- Global targets

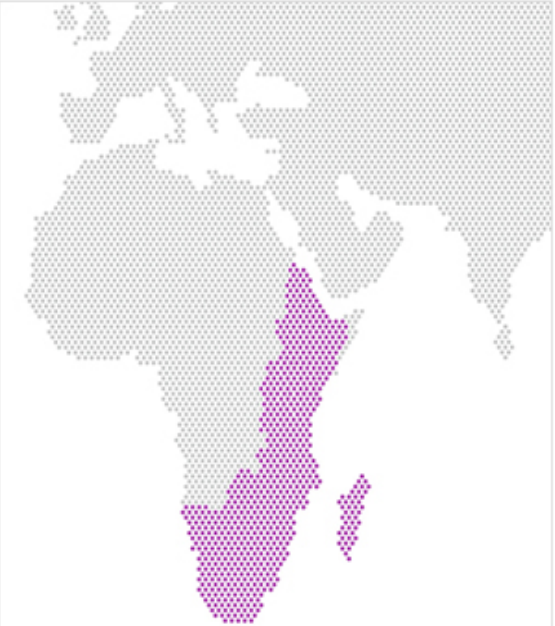
History
- History of HIV & AIDS overview
- HIV origins
- Timeline

East and Southern Africa
- Regional overview
- Botswana
- Kenya
- Lesotho
- Malawi
- South Africa
- Eswatini
- Tanzania
- Uganda
- Zambia
- Zimbabwe

West and Central Africa

Asia & the Pacific

HIV AND AIDS IN EAST AND SOUTHERN AFRICA REGIONAL OVERVIEW



East and Southern Africa (2019)

20.7m people living with HIV

6.7% adult HIV prevalence (ages 15-49)

730,000 new HIV infections

300,000 AIDS-related deaths

73% adults on antiretroviral treatment*

58% children on antiretroviral treatment*

*All adults/children living with HIV

Source: UNAIDS Data 2020

KEY POINTS

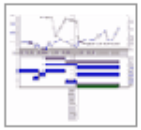
- East and Southern Africa is the region most affected by HIV in the world and is home to the largest number of people living with HIV.
- The HIV epidemic in this region is generalised but young women, men who have sex with men, transgender people, sex workers, prisoners and people who inject drugs are at an increased vulnerability to infection.

Stanford Database

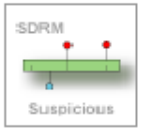
STANFORD UNIVERSITY
HIV DRUG RESISTANCE DATABASE
A curated public database designed to represent, store, and analyze the divergent forms of data underlying HIV drug resistance.

HOME | GENOTYPE-RX | GENOTYPE-PHENO | GENOTYPE-CLINICAL | HIVdb PROGRAM

Three new programs launched: ART-AiDE, eCARE, and CPR



Antiretroviral Therapy - Acquisition and Display Engine (ART-AiDE) makes it possible to generate a permanent electronic and graphical record of a patient's antiretroviral treatment (ARV) history, plasma HIV-1 RNA levels,... More »



GENOTYPE-TREATMENT CORRELATIONS

- Retrieve sequences (and/or mutations) from persons receiving selected HIV drugs
- Retrieve sequences and treatments from viruses with specific mutations

GENOTYPE-CLINICAL CORRELATIONS

- Summaries of genotype-clinical outcome studies
- Genotype-clinical outcome datasets (download)

GENOTYPE-PHENOTYPE CORRELATIONS

- Retrieve drug susceptibility data for isolates with selected mutations
- Download genotype-phenotype research datasets

REFERENCES

- Published drug resistance studies in HIVRT&PrDB
- Published studies by Stanford database group

NEW SUBMISSIONS

- Church, et al. NVP Mutations in Treatment-naive Patients with

SURVEILLANCE

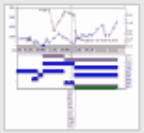
- World Health Organization 2008 Mutation List

HIVdb PROGRAM Genotype Resistance Interpretation

This program interprets user-entered mutations to infer the level of resistance to NRTIs, NNRTIs, PIs. Web Service is available.

ART-AiDE

Antiretroviral Therapy - Acquisition & Display Engine
» Go To Program



HIVseq Program

Provides mutation frequencies by subtype.
» Go To Program

HIValg Program

Compare HIVdb, ANRS, Rega, or create your own algorithm.
» Go To Program

Drug Resistance Summaries

Clinical Care Options

Address http://clinicaloptions.com/HIV.aspx Go Links

CLINICAL CARE OPTIONS
HIV

Register Login

Browse by Topics OR Enter search terms Search

Conference Coverage | Journal Options | Management Series | Treatment Updates | Annual Updates | Interactive Cases | Resources

CCO > HIV

Tuesday, July 08, 2008

Join us in this unique video classroom in which faculty members guide you through the management of 2 complex cases

Now Available from CCO HIV

MANAGEMENT SERIES

Clinical Studies of Integrase Inhibitors: A Comprehensive Review

Martin Markowitz, MD, discusses recent data from clinical studies involving the use of the integrase inhibitors raltegravir and elvitegravir. Click here to start.

Treatment Update

Integrating New Antiretroviral Agents Into Therapeutic Strategies for Treatment-Experienced Patients

Newly Available!

Interactive Virtual Presentation:
Watch, listen, and make treatment decisions as Eric S. Daar, MD, leads you through a series

Browse HIV

Topics

- Adverse Effects and Comorbidities
- Antiretroviral Management
- Epidemiology and Natural History
- Opportunistic Diseases and Coinfection
- Pharmacology
- Resistance
- Special Populations

Resources

- Advanced Search
- Animations
- Case Challenges
- Free Bookstore
- Live Events
- Slide Download Library
- Interactive Tools

Medscape

Medscape HIV/AIDS from WebMD

RESOURCE CENTERS

- Antiretroviral Drug Resistance and Testing
- Antiretroviral Therapy
- HIV Pathogenesis
- HIV Transmission & Prevention
- Immune Reconstitution
- More »

>> All Resource Centers

HIV/AIDS JOURNALS

- AIDS
- AIDS Clinical Care
- Future HIV Therapy
- HIV Medicine
- JAIDS

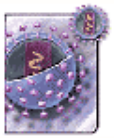
HIV/AIDS NEWS

From Medscape Medical News, TheHeart.org, Reuters and more

- IL-7 Therapy Boosts Immune Response in Cancer Patients
- Bush Urges Congress to Pass AIDS Funds
- HIV-Related Mortality Near Normal in First 5 Years on HAART
- CME FDA Safety Changes: Atripla, Halcion, Restoril
- CME CVD Is a "Major Killer" in HIV+ Patients, but Underrecognized by Doctors

>> More HIV/AIDS News | Sign Up for Daily News Emails

HIV/AIDS FEATURES



Immune Activation and AIDS Pathogenesis What causes immune activation in HIV infection?
AIDS, July 9, 2008

CME NY Course 2008: Recent Additions to ART Classes
Medscape HIV/AIDS, July 9, 2008

Other Specialties...

HIV/AIDS CME

- CME NY Course 2008: Recent Additions to ART Classes
- CME NY Course 2008: Pharmacology of Antiretrovirals
- CME NY Course 2008: HIV Resistance Issues
- CME NY Course 2008: Progress in Antiretroviral Therapy
- CME NY Course 2008: Host-Related Issues

>> More CME | Sign Up for CME Alerts

Lots of stuff to do.

Go and learn.