HIV/AIDS -2022

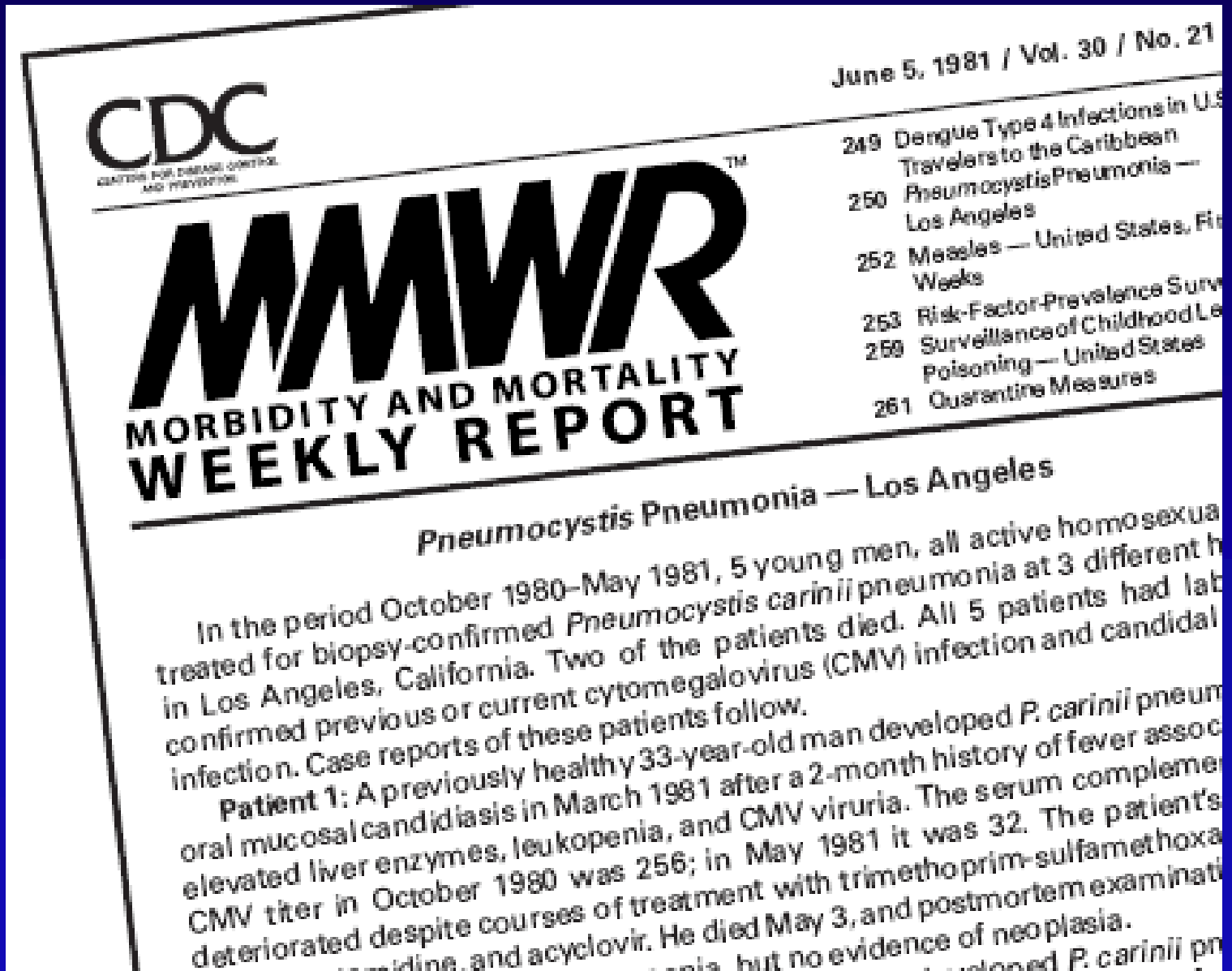
Martin S. Hirsch, M.D.

Conflicts and Learning Objectives

- I have no financial conflicts to report.

- Learning Objectives: To understand recent data and current concepts regarding the pathogenesis, epidemiology, treatment and prevention of HIV infection.

MMWR June 5, 1981



CDC

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

MORBIDITY AND MORTALITY WEEKLY REPORT

Pneumocystis Pneumonia — Los Angeles

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

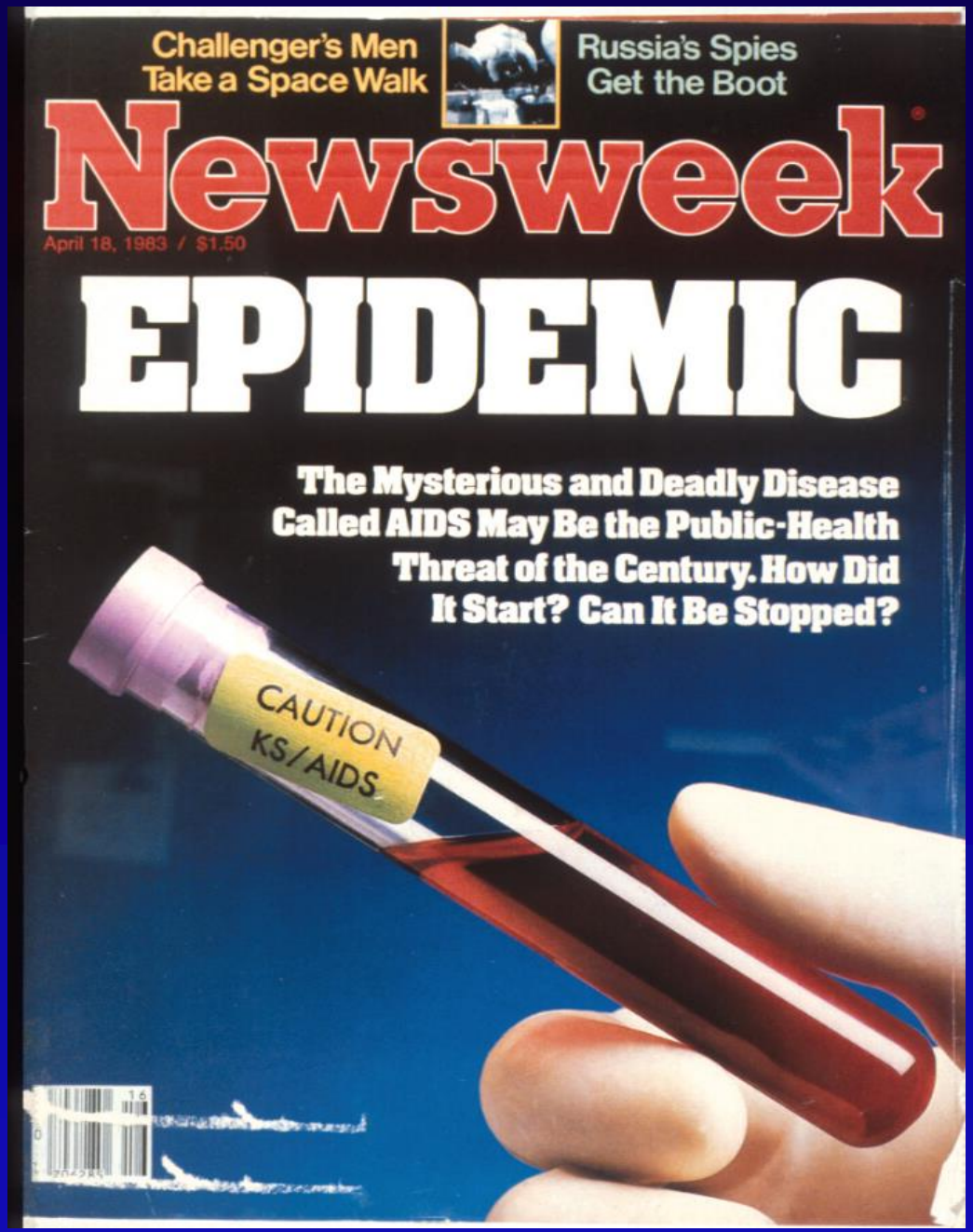
Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneum oral mucosal candidiasis in March 1981 after a 2-month history of fever assoc elevated liver enzymes, leukopenia, and CMV viruria. The serum compleme CMV titer in October 1980 was 256; in May 1981 it was 32. The patient's deteriorated despite courses of treatment with trimethoprim-sulfamethoxa and acyclovir. He died May 3, and postmortem examinati no evidence of neoplasia.

Initial Reports of AIDS

- CDC MMWR, June 5, 1981 – report of 5 previously healthy young men in LA with PCP, CMV and *Candida* infections

- Editorial note suggested a cellular-immune dysfunction related to a common exposure likely related to sexual contact

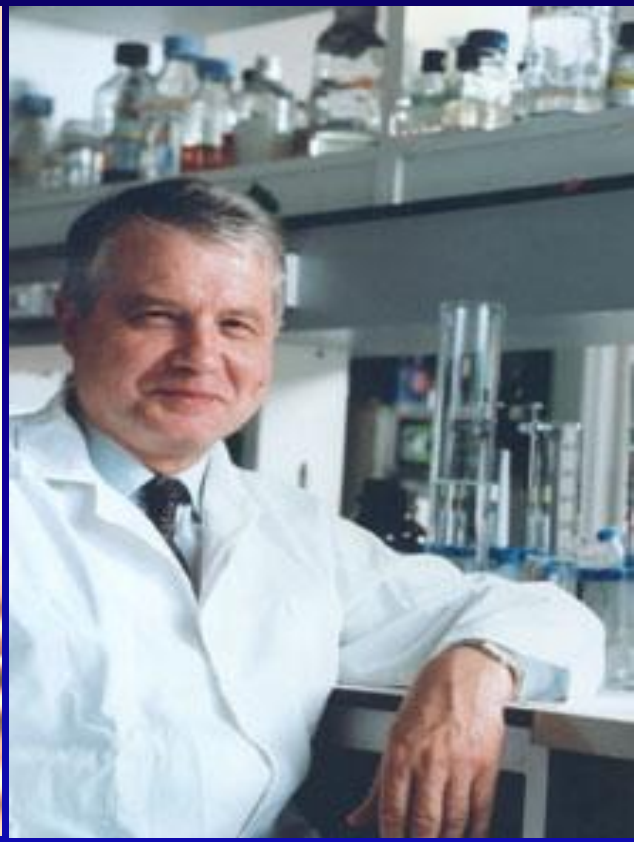
- Several MMWR reports of similar syndromes from other cities (NYC, SF) in ensuing weeks



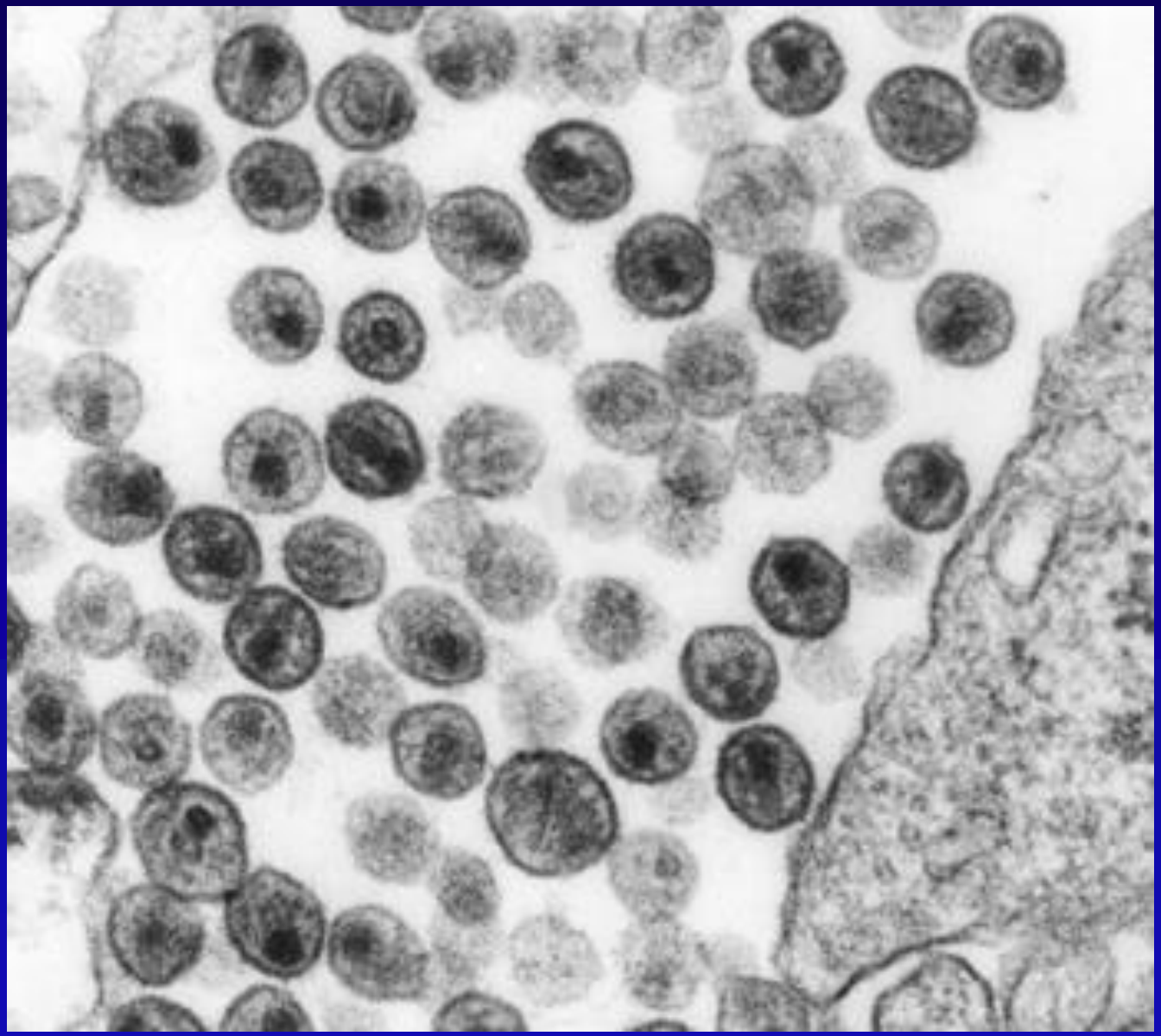
April 18, 1983

1981-83: Cases of *Pneumocystis* pneumonia and Kaposi's Sarcoma reported in gay men from major urban areas in the USA; shortly thereafter similar cases in women, injection drug users, blood product recipients, and internationally ("no risk factors")

Bob Gallo, Francoise Barre-Sinoussi, and Luc Montagnier; discoverers of HIV



HIV



HIV/AIDS – 2021 - UNAIDS/WHO

- >79 million people have been infected worldwide, with >36 million deaths; ~940,000 deaths per year
- ~ 37 million are currently living with HIV
- ~1.5 million new HIV infections/year
- In the USA, over 1.2 million living with HIV; 12-13% unaware of their infection
- Among those aged 15-49, HIV worldwide prevalence is 0.8%; in sub-Saharan Africa 4.2%

Good News

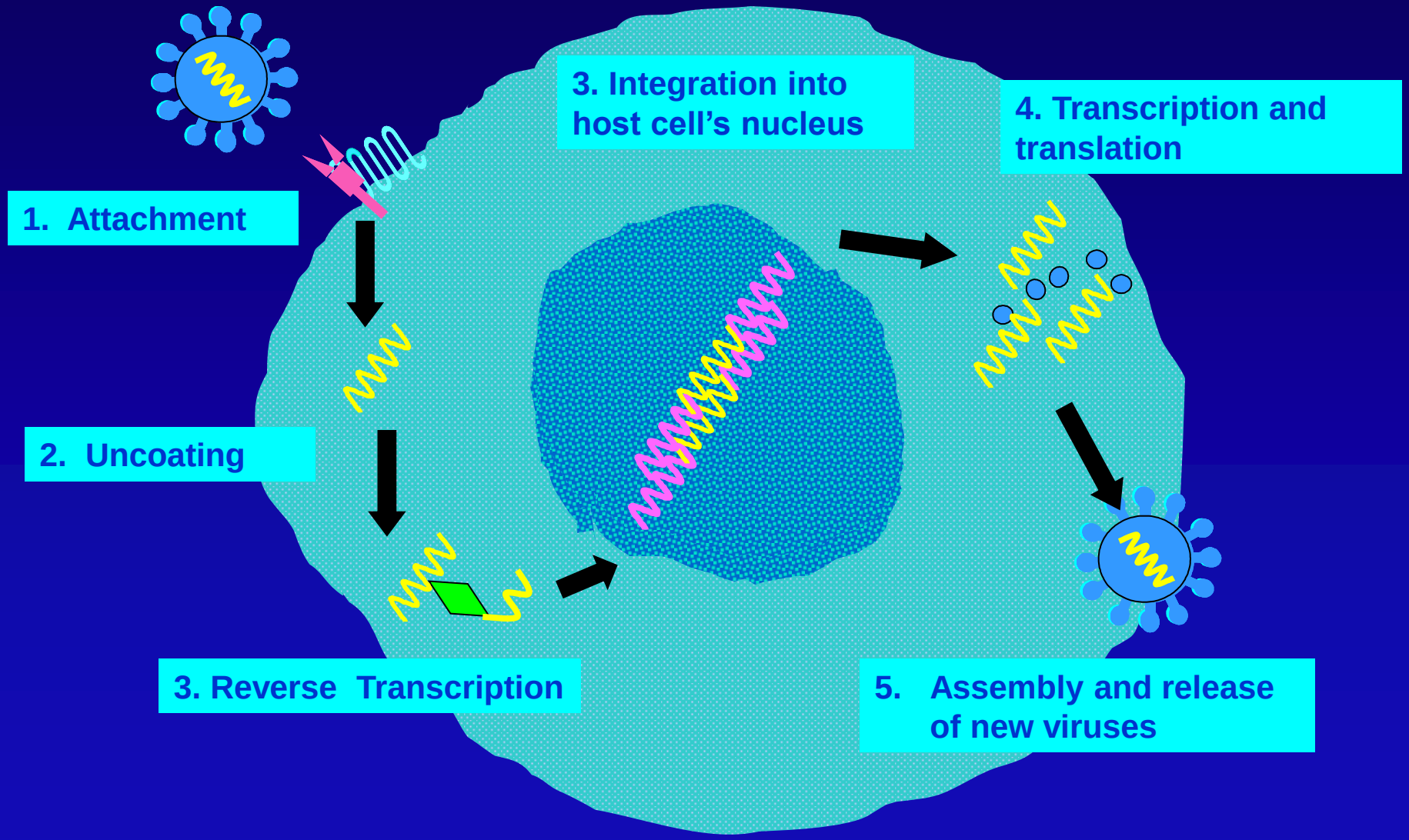
- New HIV infections have decreased 52% since peak year of 1997
- HIV/AIDS deaths have decreased 64% since peak year of 2004
- 73% of HIV-infected are receiving antiretroviral therapy

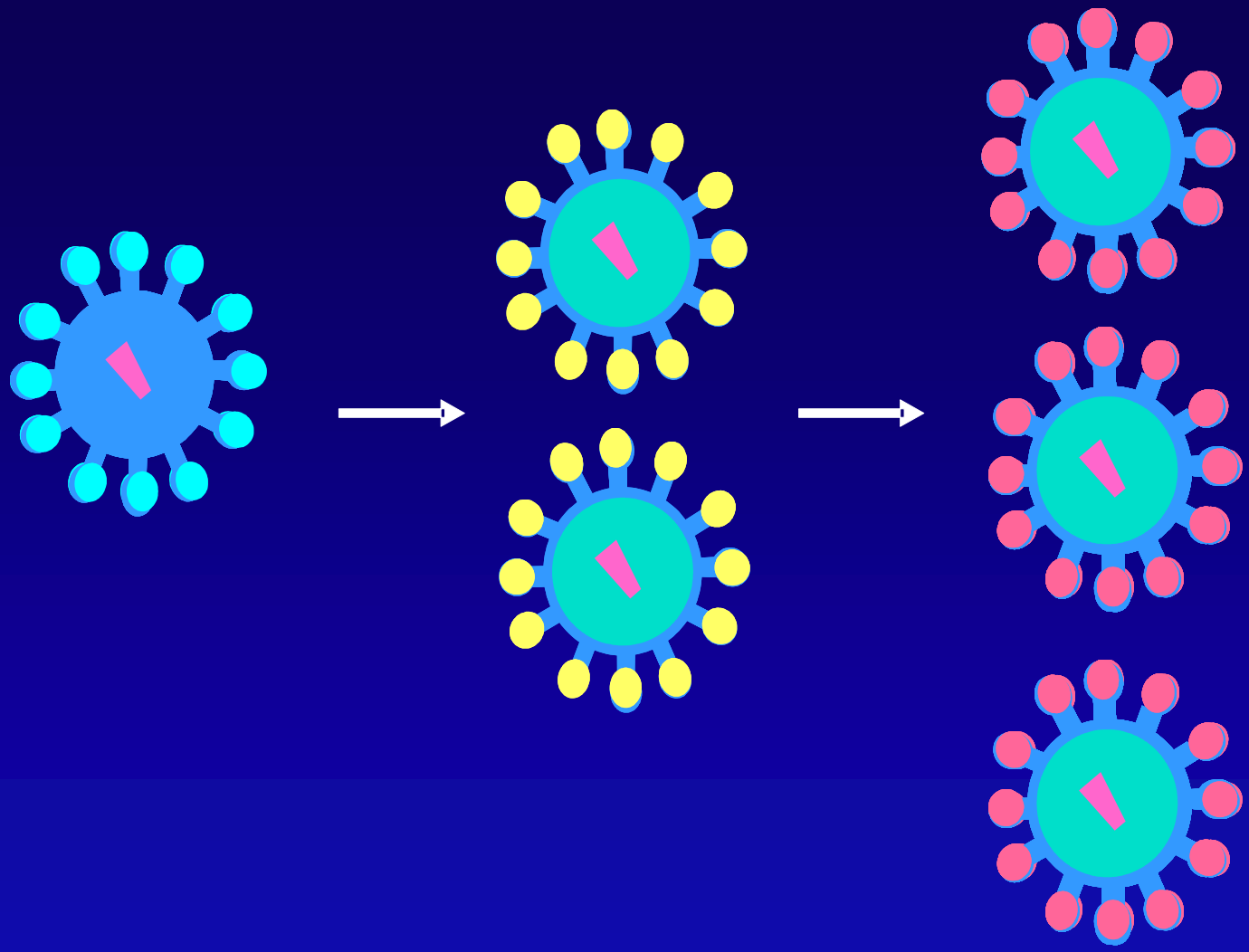
What Have We Learned?

- Since HIV was discovered 37 years ago, we've characterized the molecular structure of the virus, its replicative pathway, its mechanisms for inducing immune compromise, and have developed approaches to its treatment and prevention

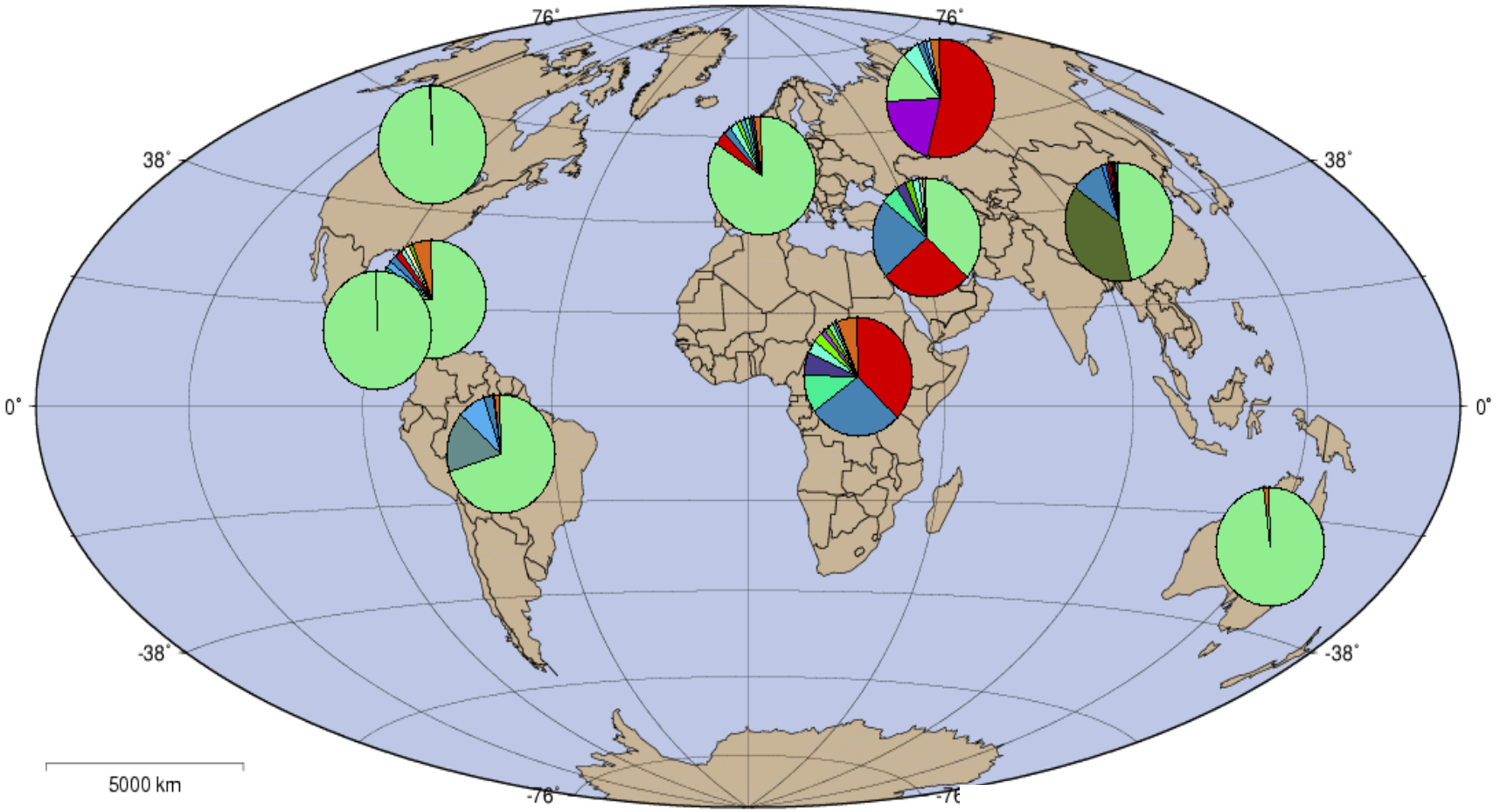
- These efforts have involved collaborative investigations by laboratories and clinics throughout the world

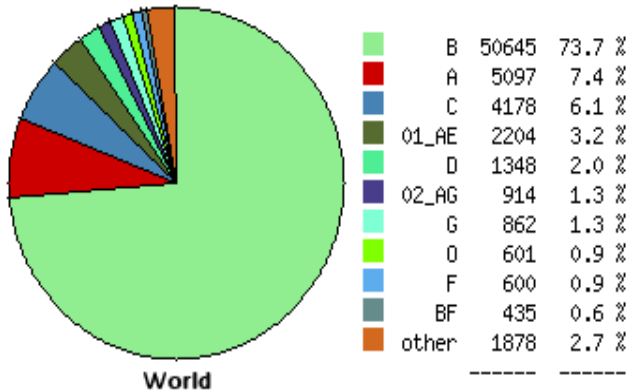
HIV-1 replication cycle in CD4 T lymphocytes





Subtype Distribution of Collected HIV-1 Sequences

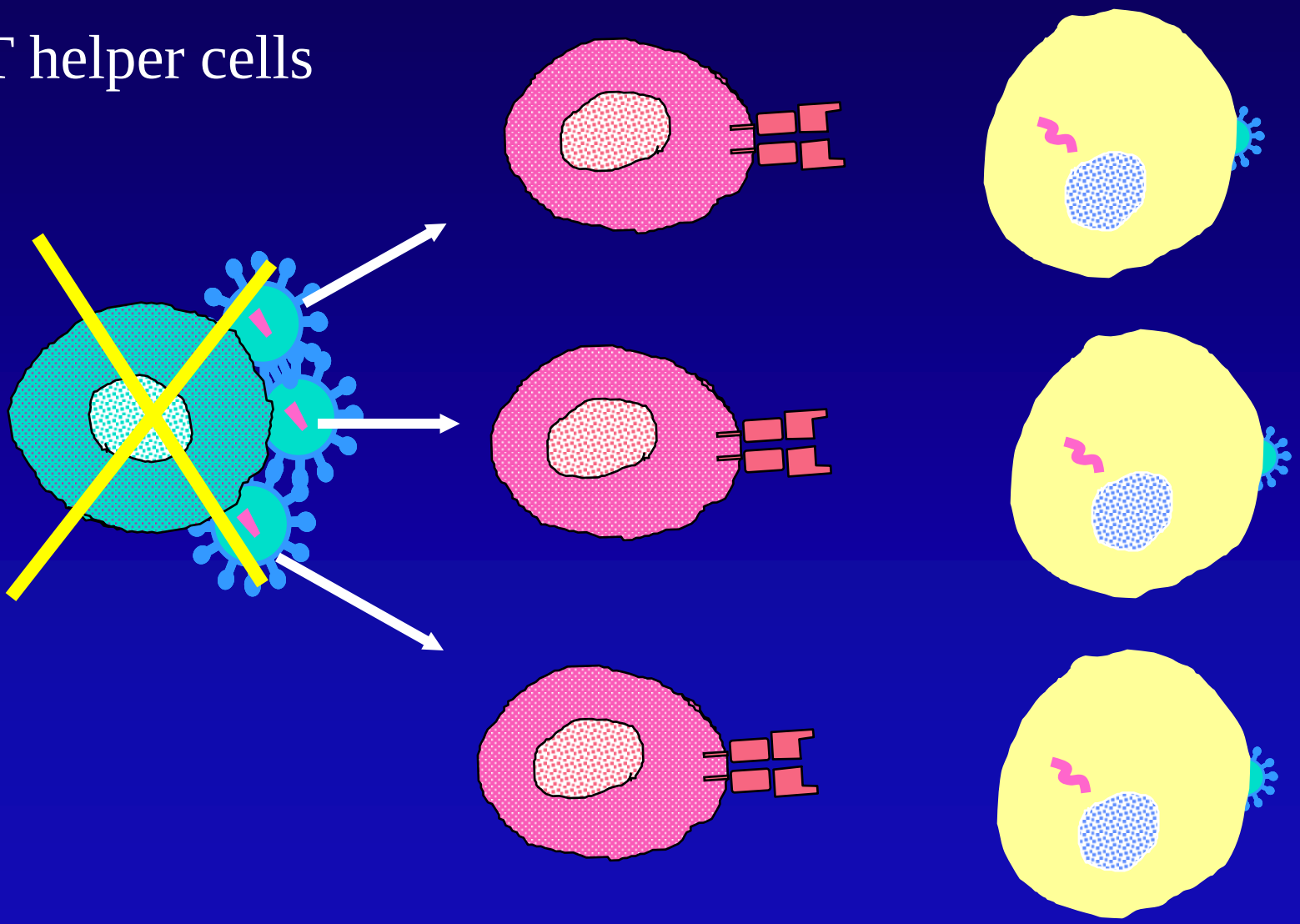




CTLs

Infected cells

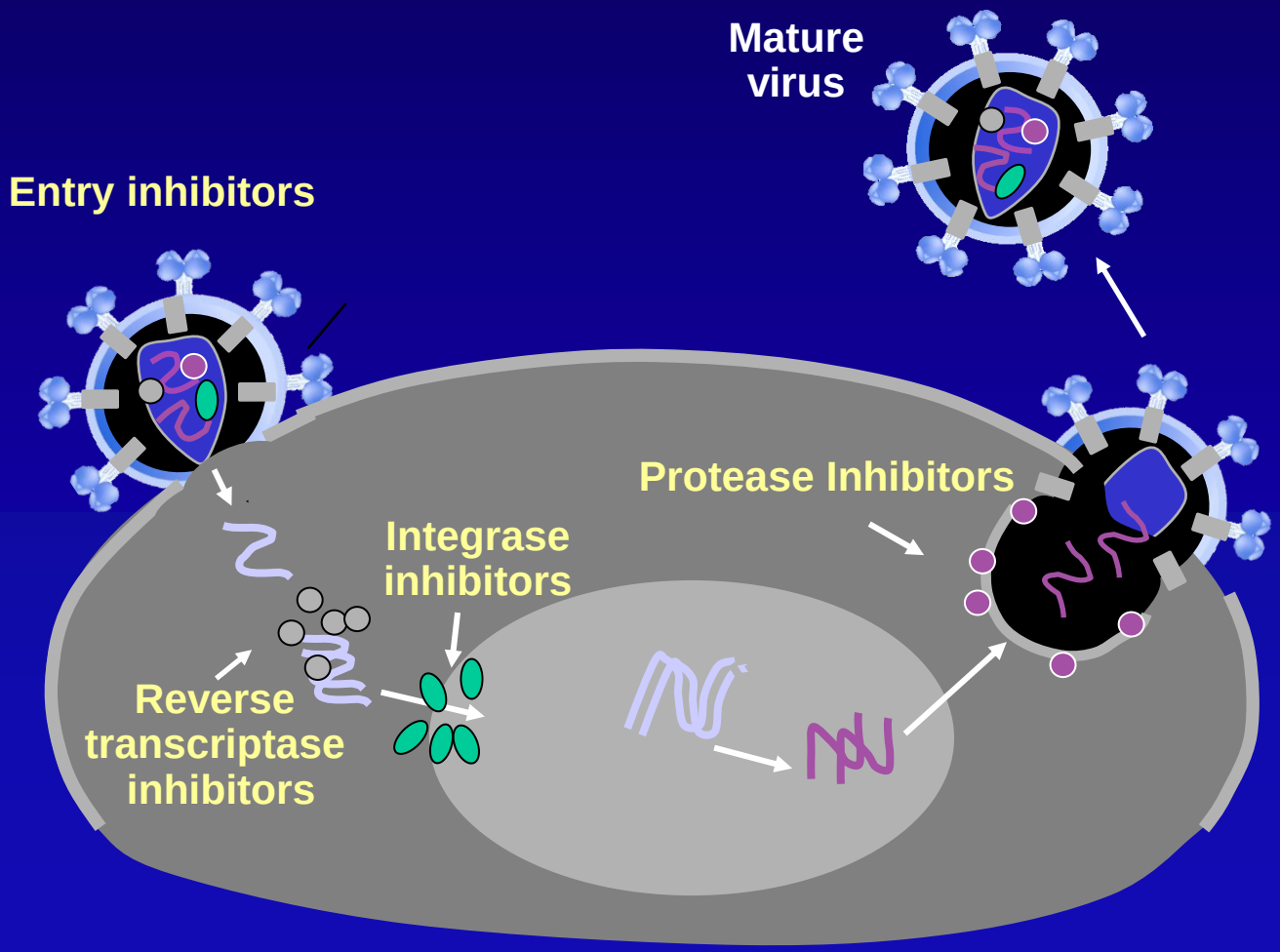
T helper cells



How can we interrupt this lethal infectious cycle?

Antiretroviral Therapy

Antiretroviral Sites of Attack



Approved Antiretroviral Agents in 2022

Nucleoside RTIs
- Zidovudine (ZDV)
- Didanosine (ddI)
- ~~Stavudine (d4T)~~
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)

Nucleotide RTI
- Tenofovir DF (TDF)
- Tenofovir AF (TAF)

Nonnucleoside RTIs
- Nevirapine (NVP)
- Delavirdine (DLV)
- Efavirenz (EFZ)
- Etravirine (ETV)
- Rilpiverine (RPV)
- Doravirine (DOR)

Integrase Inhibitors
- Raltegravir (RAL)
- Elvitegravir (EVG)
- Dolutegravir (DTG)
- Bictegravir (BTG)
- Cabotegravir (CAB)

Protease Inhibitors
- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- ~~Lopinavir/r (LPV/r)~~
- Atazanavir (ATV)
- Fosamprenavir (Fos-APV)
- Tipranavir (TPV)
- Darunavir (DRV)

Fusion Inhibitor
- Enfuvirtide (T-20)

Entry Antagonists
- Maraviroc (MVC)
- Ibalizumab (IBA)
- Fostemsavir (FTR)

N.B.: Several fixed-dose combinations are approved, including: ZDV + 3TC; ZDV + 3TC + ABC; ABC + 3TC; FTC + TDF; FTC + TAF; LPV + RTV; TDF + FTC + EFV; TDF + FTC + RPV; TDF + FTC + EVG + Cobicistat; DTG + ABC + 3TC; DRV + Cobi; ATV + Cobi; TAF + FTC + EVG + Cobi; TAF + FTC + RPV; TAF + FTC + BTG; CAB + RPV

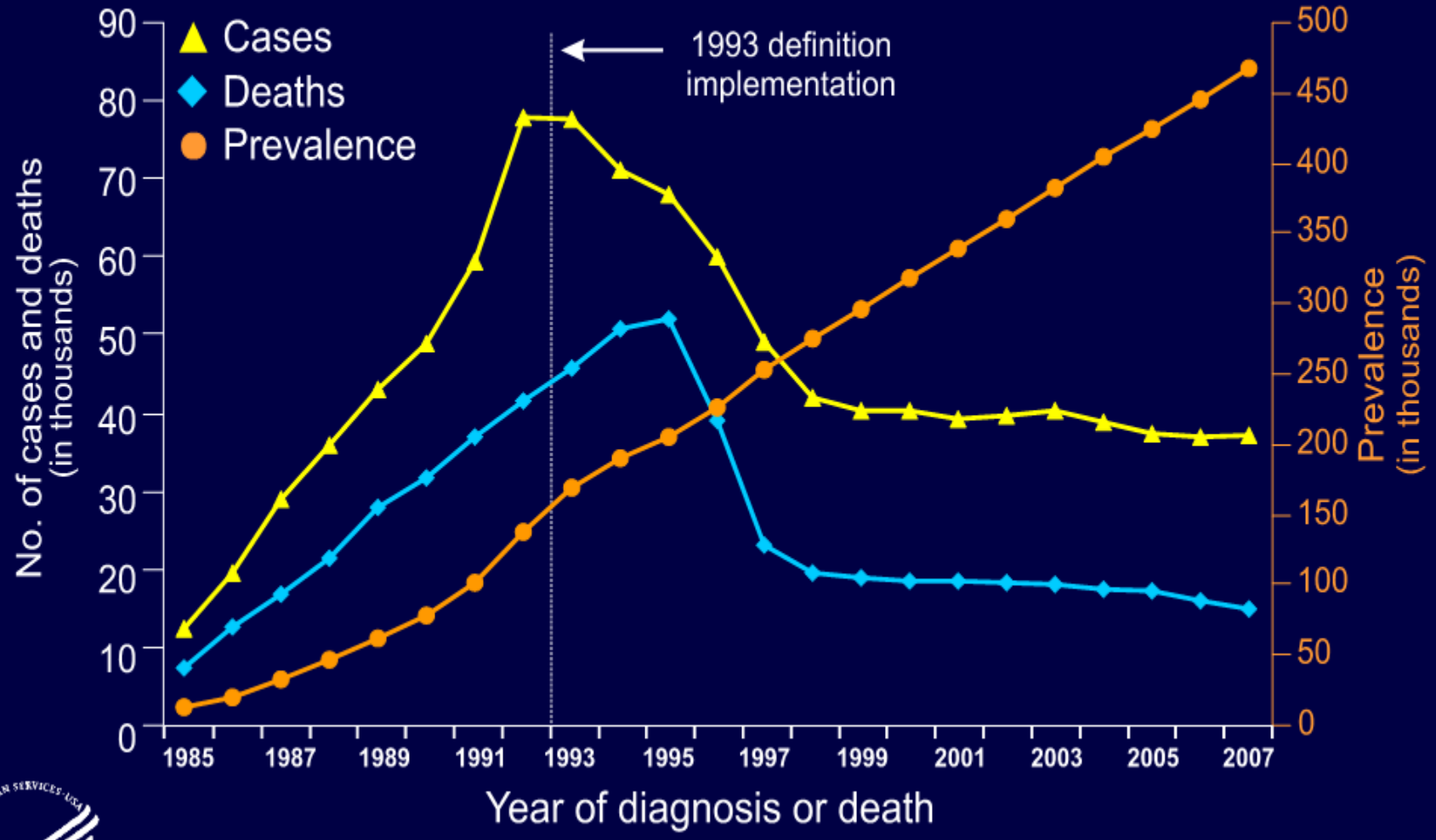
ART 2022

Easier, less toxic, and more potent; multiple single tablet regimens approved by the FDA

Potential Advantages and Disadvantages of Single-Tablet Regimens

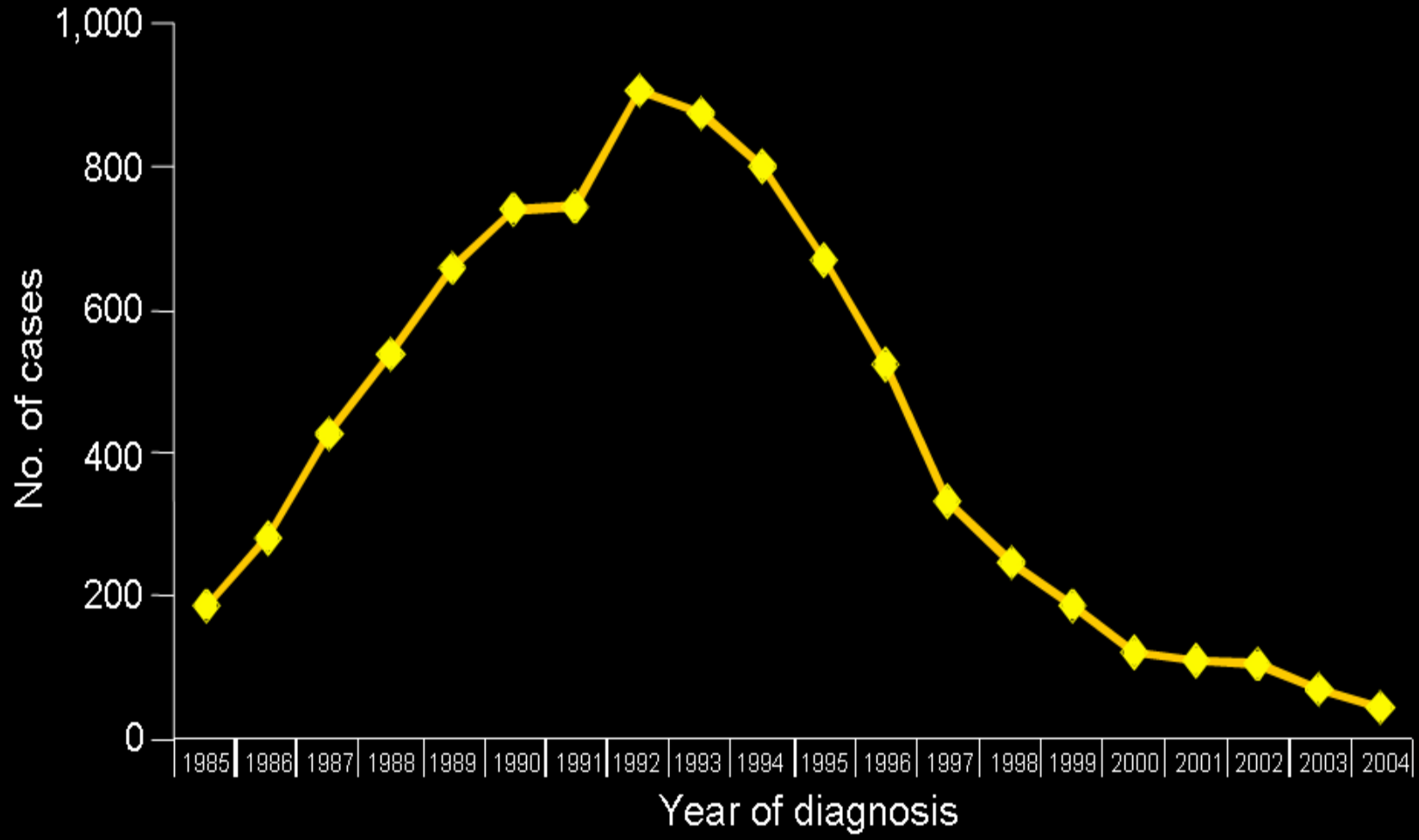
Advantages	Disadvantages
▪ Simplicity ▪ Convenience ▪ Fewer copays ▪ Reduces selective nonadherence to components of regimen	▪ Inability to adjust dosages of components if needed ▪ Not available for all ART regimens

Estimated Numbers of AIDS Cases, Deaths, and Persons Living with AIDS, 1985–2007—United States and Dependent Areas



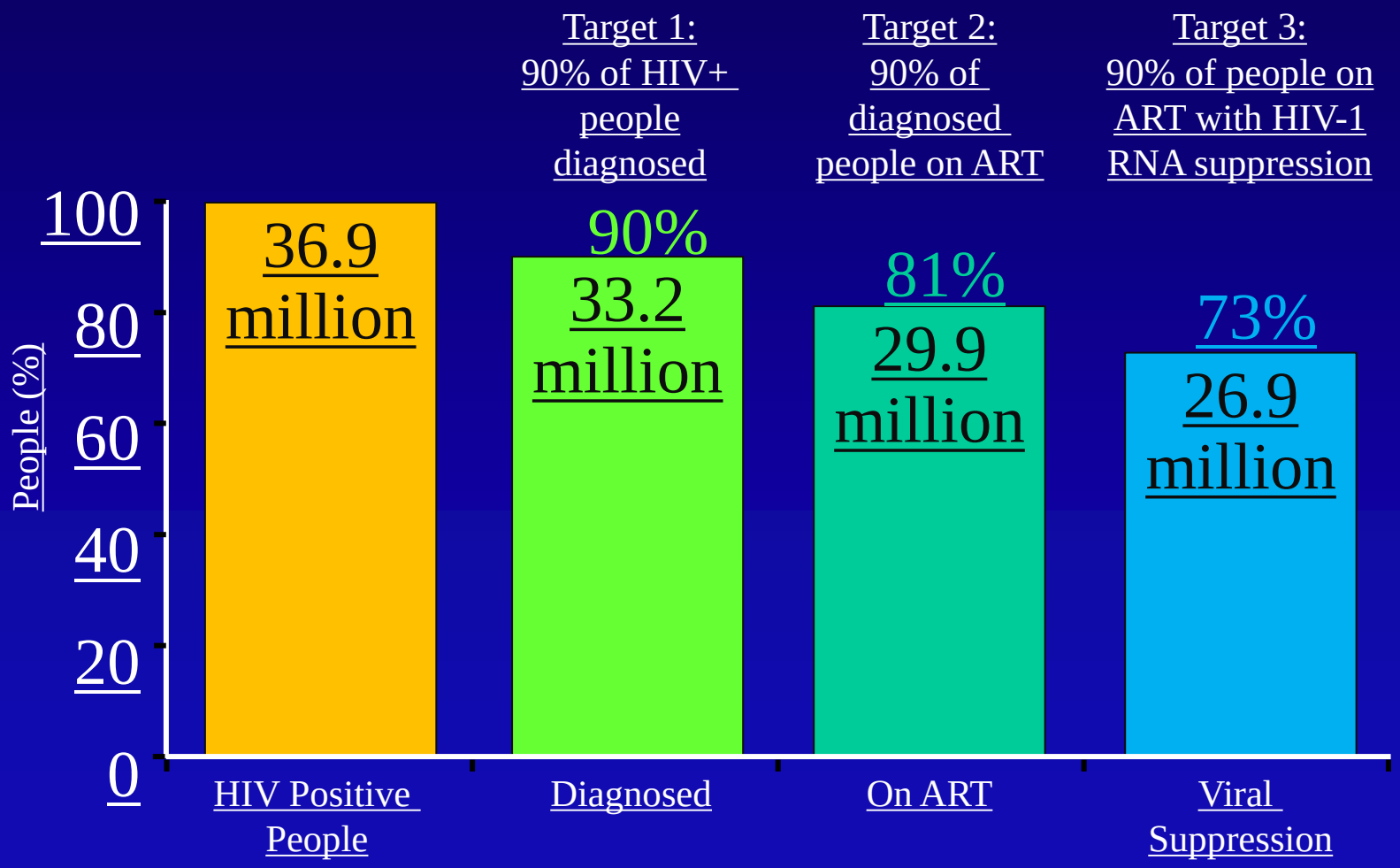
Note. Data have been adjusted for reporting delays.

Perinatally Acquired AIDS Cases, 1985-2004, United States



Note. Data have been adjusted for reporting delays and cases without risk factor information were proportionally redistributed.

UNAIDS: 90-90-90 Targets for 2020



Actual Worldwide Results of 90-90-90

- Overall, 84% know status, 73% on ARV, 66% virologically suppressed

- Some countries (e.g., Australia, Botswana) have met the goal. USA has not

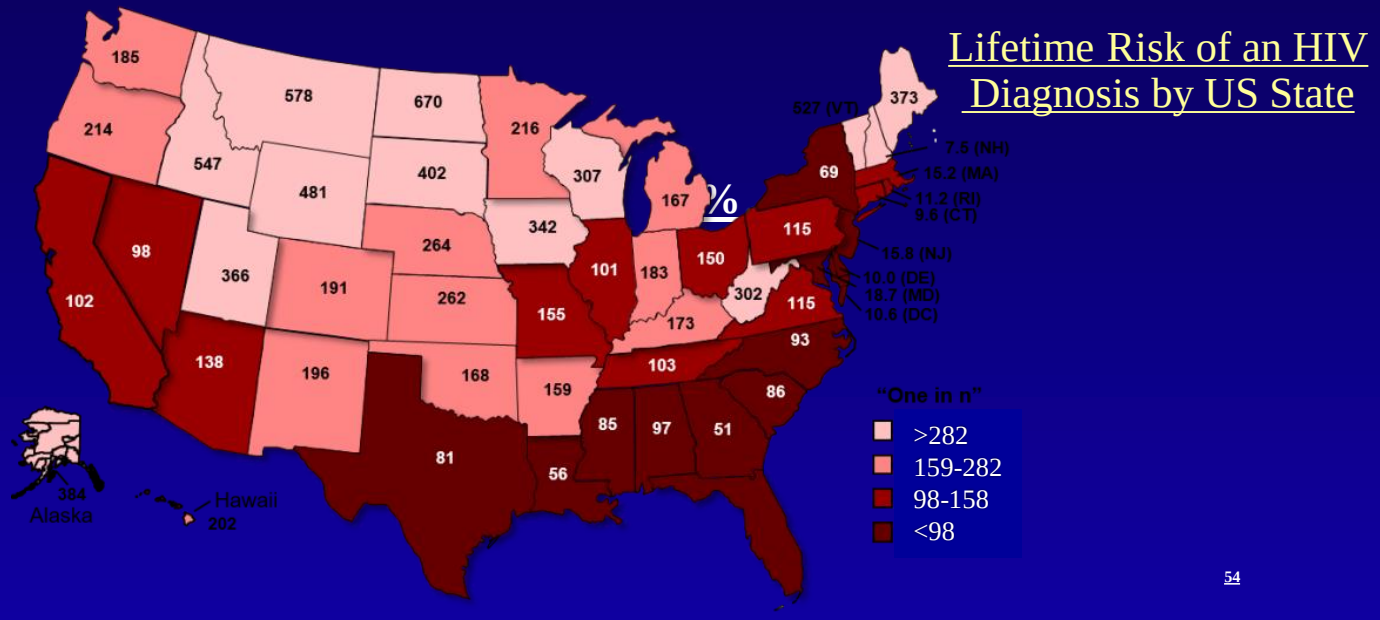
U.S. HIV Implementation Plan

- Focus on high-incidence geographic areas
  - 48 counties targeted plus Washington, DC; San Juan, Puerto Rico; 7 US states with high rural HIV burdens, mostly in south
- Emphasize early Dx, Rx
  - Reduce transmission
  - Increase viral suppression from 63% to at least 95%
- Expand PrEP
  - Increase use by at-risk population to at least 50% by 2025
- Rapid response to emerging HIV clusters
  - Monitor for early detection of clusters
  - Treat each new diagnosis as a "sentinel event"

National HIV Surveillance System Census Data

Lifetime U.S. Risk of HIV Diagnosis

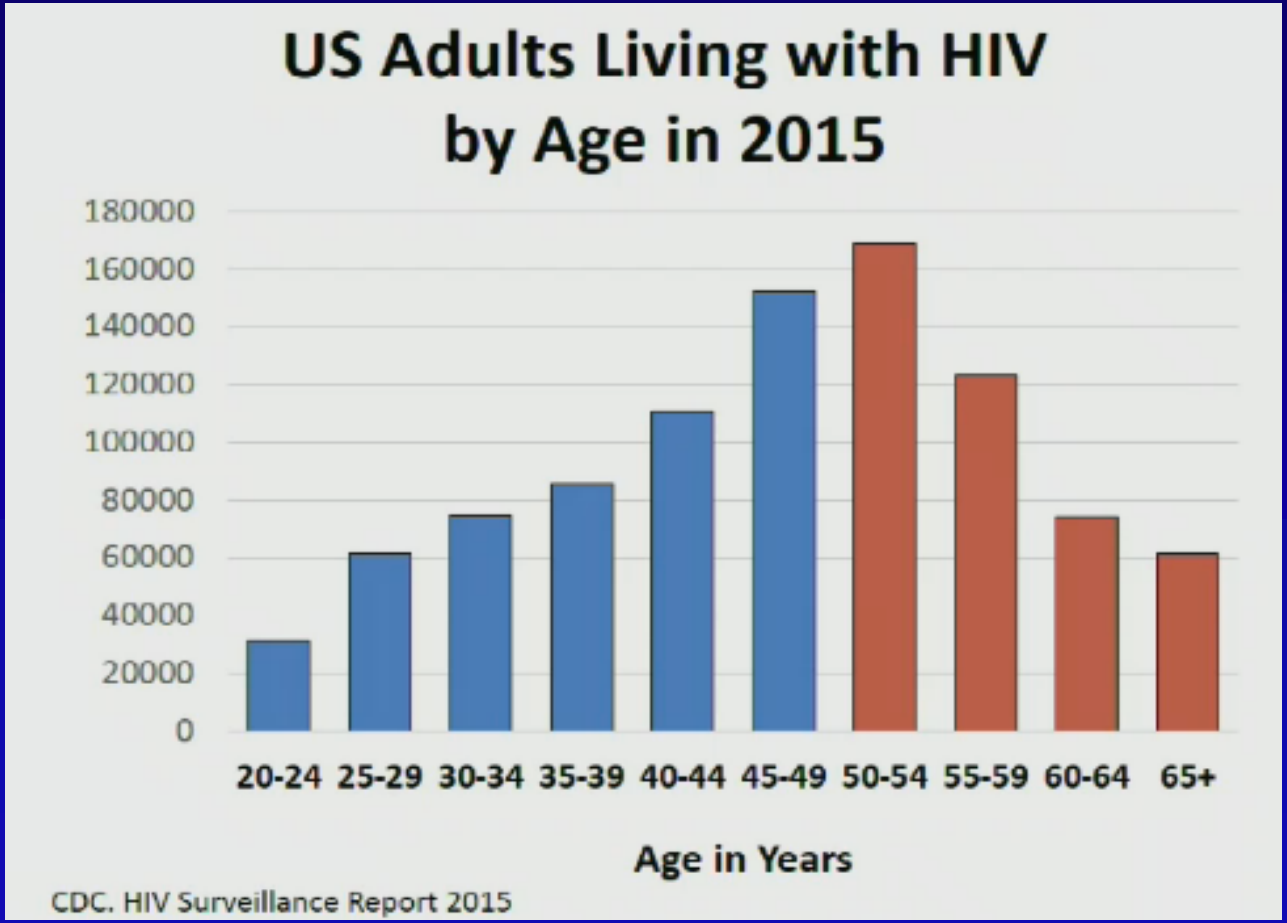
Singh et al. CROI 2022



Results: Lifetime Risk of Acquiring HIV:

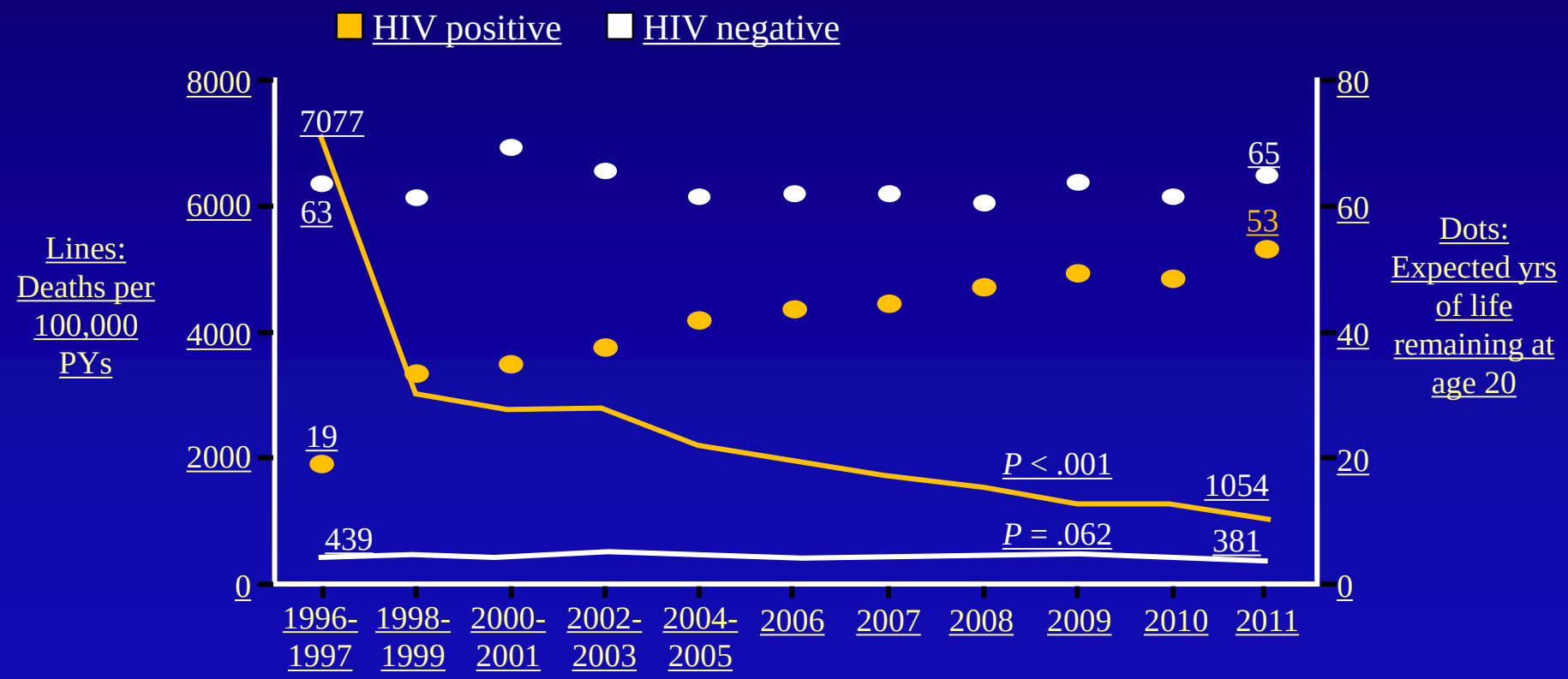
- Overall in USA: 1 in 120; 1 in 76 in men, 1 in 309 in women
- Risks among men: 1 in 27 Black; 1 in 50 Hispanic; 1 in 171 White; 1 in 187 Asian

Aging of U.S.Population with HIV



Kaiser Permanente: Life Expectancy in HIV-Infected vs Uninfected Persons

- Life expectancy in 24,768 HIV-infected and 257,600 HIV-uninfected adult pts in KP California 1996-2011; groups matched for age, sex, year



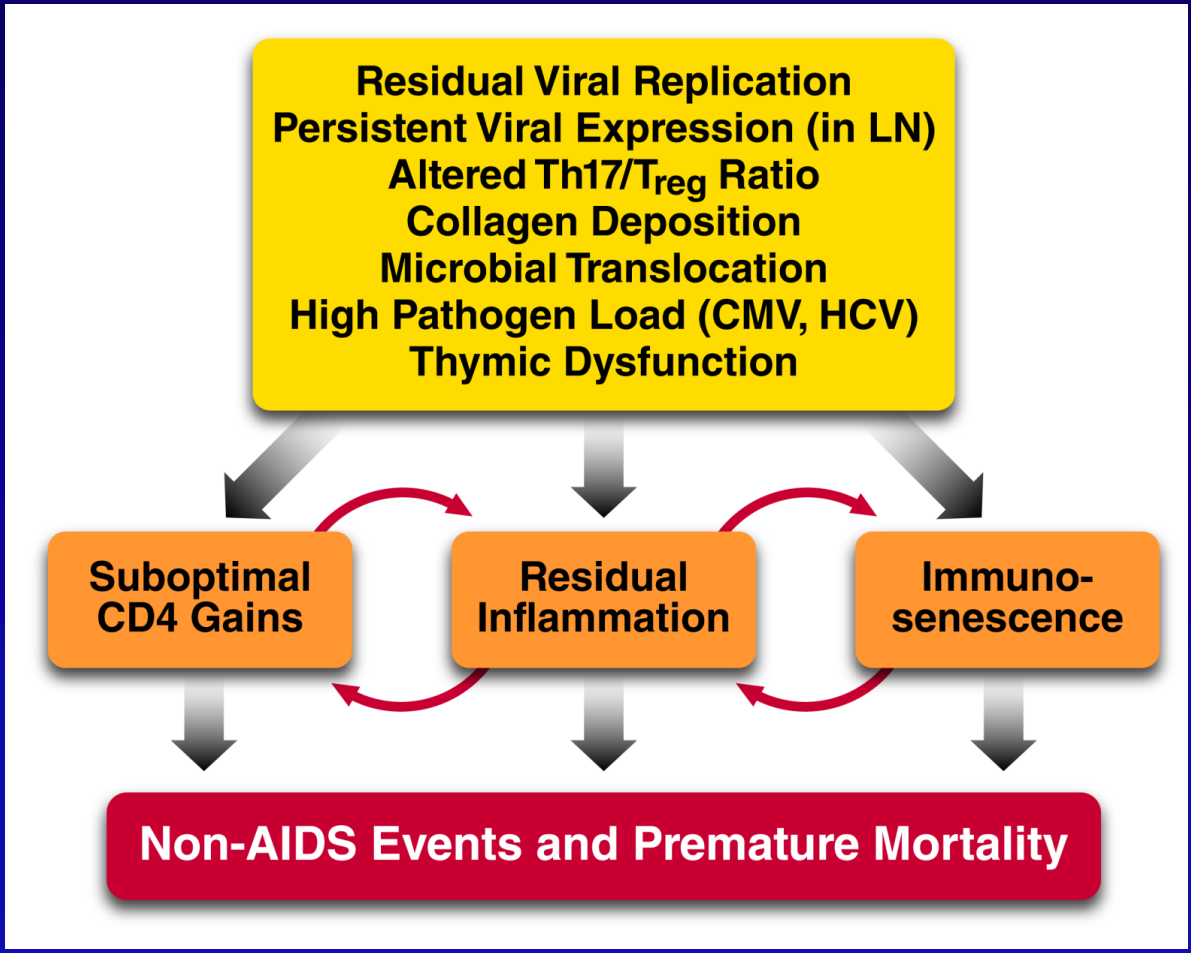
Marcus JL, et al. *JAIDS* 2016.

Challenges: Increased Frequency of "non-AIDS-related" Complications

- Cardiovascular disease[1-4]
- Metabolic syndrome and diabetes
- Cancer (non-AIDS)
- Bone fractures/osteopenia [5,6]
- Liver failure[7]
- Renal disease
- Peripheral neuropathy
- Cognitive decline [8]
- Frailty[9]

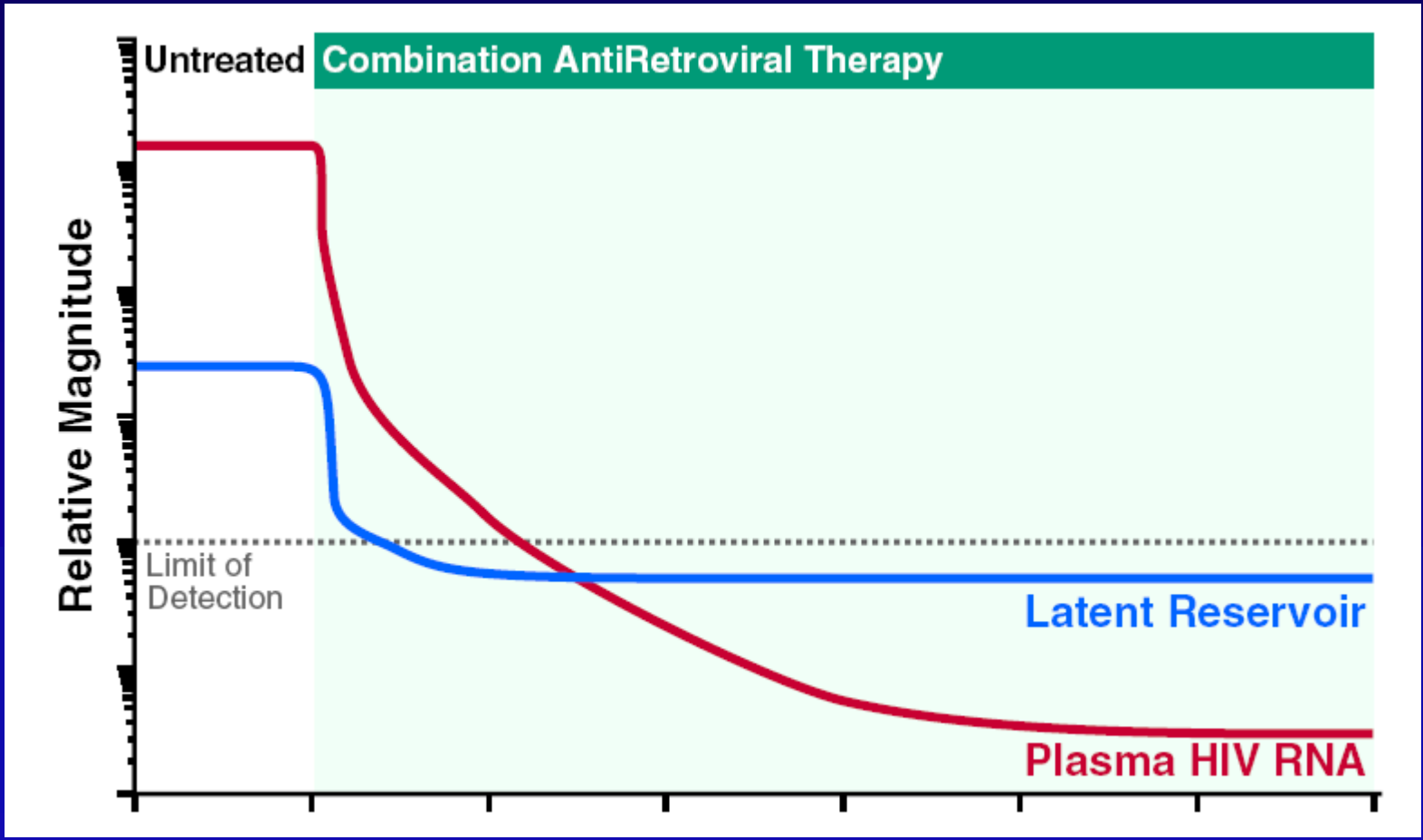
1. Klein D, et al. *JAIDS*. 2002;30:471-477. 2. Hsue P, et al. *Circulation*. 2004;109:316-319. 3. Mary-Kraus M, et al. *AIDS*. 2003;17:2479-2486. 4. Grinspoon SK, et al. *Circulation*. 2008;118:198-210. 5. Triant V, et al. *J Clin Endocrinol Metab*. 2008;93:3499-3504. 6. Arnsten JH, et al. *AIDS*. 2007 ;21:617-623. 7. Odden MC, et al. *Arch Intern Med*. 2007;167:2213-2219. 8. McCutchan JA, et al. *AIDS*. 2007 ;21:1109-1117. 9. Desquilbet L, et al. *J Gerontol A Biol Sci Med Sci*. 2007;62:1279-1286

Pathogenesis of non-AIDS complications



Volberding and Deeks, *Lancet* 2010

ART decreases HIV RNA levels in blood, but the latent reservoir persists



Volberding and Deeks, *Lancet* 2010

When to Start Therapy?

When to Start Therapy: Balance in Favor of Earlier Initiation

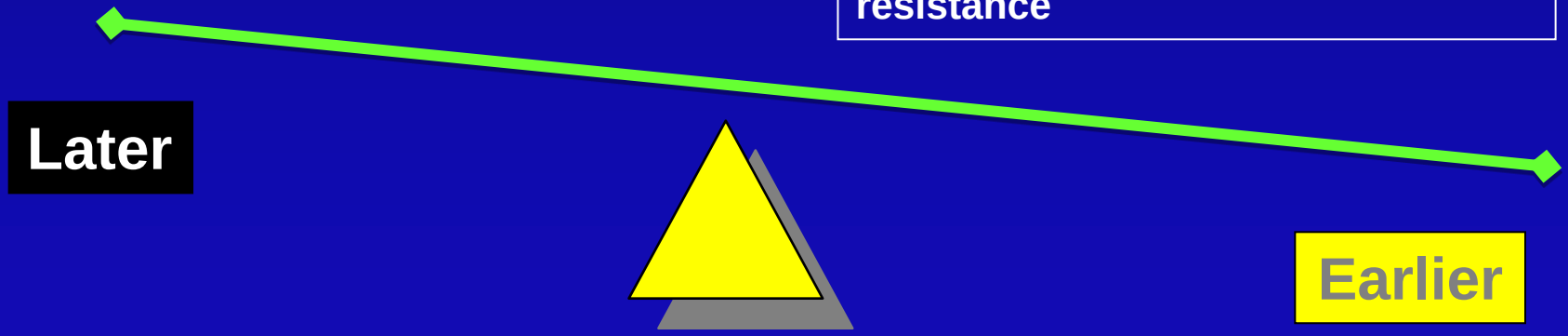
Harmful effects of uncontrolled viremia at all CD4 levels

More treatment options: improved potency, tolerability, durability, simplicity

Increased ability to suppress virus with multidrug resistance

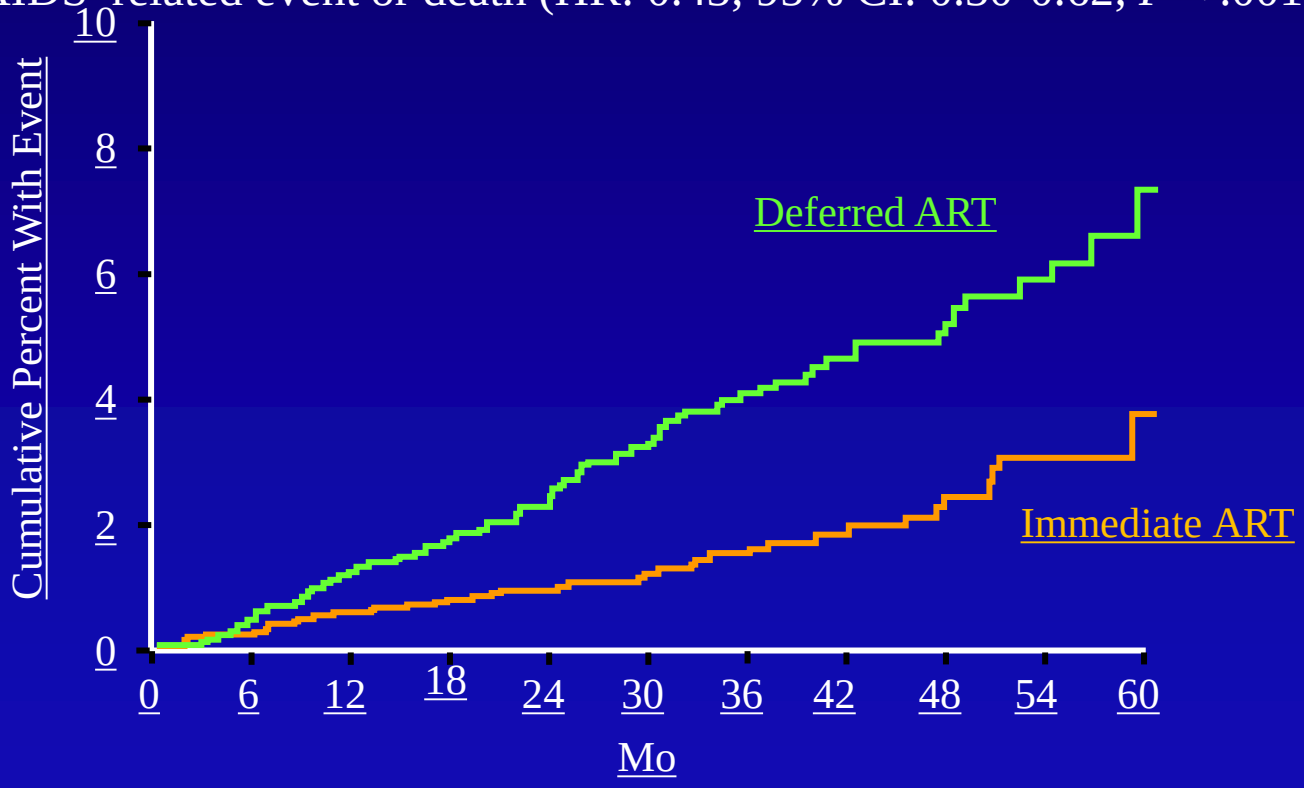
Diminished emergence of resistance

Drug toxicity
Preservation of treatment options
Cost



START: 57% Reduced Risk of Serious Events or Death With Immediate ART

- 4.1% vs 1.8% in deferred vs immediate arms experienced serious AIDS or non-AIDS–related event or death (HR: 0.43; 95% CI: 0.30-0.62; *P* < .001)



INSIGHT START Group. *N Engl J Med*. 2015;373:795. Lundgren J, et al. IAS 2015. Abstract MOSY0302.

Can Antiretroviral Therapy Influence Transmission?

Treatment to Prevent Transmission

- NIH Partners Study (HPTN 052)
- 1763 serodiscordant couples (97% heterosexual) in Africa, Asia, South America and the USA
- HIV-infected partners randomly assigned to immediate ART or deferral of therapy until CD4 <250/mm^3 or an AIDS-defining event occurred
- 28 partner-related HIV transmissions, 27 in the deferral group (96% reduction by early ART)

Cohen MS et al. *NEJM* 2011;365:493
Cohen MS et al. *NEJM 2016;375:830*

"When should I start treatment?"
→You should start now!

When to Start

ART recommended for all HIV+ individuals, regardless of CD4 cell count

CD4 Cell Count	Recommendation
• ≤ 350	AI
• 350-500	AI
• >500	AI

AI: strong recommendation, data from randomized clinical trials

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents – **2019.**

Institution of ART Upon HIV Diagnosis

- Benefits of immediate ART initiation include:
  - Higher rates of rapid viral suppression
  - Reduced risk of complications, serious events and death
  - Reduced loss-to-followup
  - Reduced risk of HIV transmission

Potential Risks of Rapid ART

- Missing conditions: TB or cryptococcal disease → increased risk of Immune Reconstitution Inflammatory Syndromes (IRIS)
- Severe liver or renal disease should ideally be managed before initiating ART
- Potential for patients to feel coerced to start when they are not psychologically ready
- Potential for insufficient time to discuss regimen considerations with women of childbearing potential

WHO Guidelines. 2017; Ford. *AIDS*. 2018; Müller. *Lancet Infect Dis*. 2010

Recommendations for Starting ART

DHHS, IAS-USA, and WHO guidance panels all recommend ART for persons with HIV, regardless of CD4 cell count

ART initiation recommended as soon as possible; same day where feasible

Take-home Message: Do not delay treatment!

1. INSIGHT START Study Group. *N Engl J Med*. 2015;373:795. 2. Cohen MS, et al. *N Engl J Med*. 2016;375:830. 3. DHHS Guidelines. 2019. 4. Saag MS, et al. *JAMA.* 2018;320:379. 5. WHO. July 2017.

What to Start?

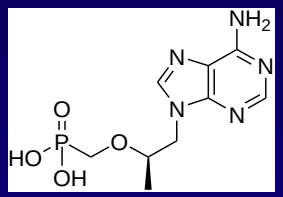
What to Start : Current Dogma

- Regimens should ideally contain 2 NRTI, one of which is lamivudine (3TC) or emtricitabine (FTC)
- The “third drug” should generally be an INSTI or, less commonly, a boosted PI (PI/r or PI/c)
- Two choices need to be made:
  - which NRTI combination to use
  - which 3rd drug to use with 2 NRTI

What is the preferred NRTI backbone?

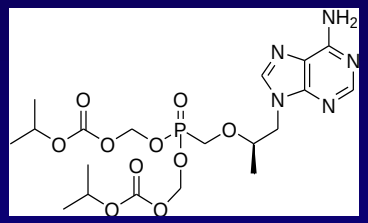
Tenofovir Alafenamide (TAF)

Next Generation Prodrug of Tenofovir



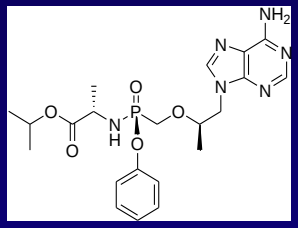
TFV

Tenofovir



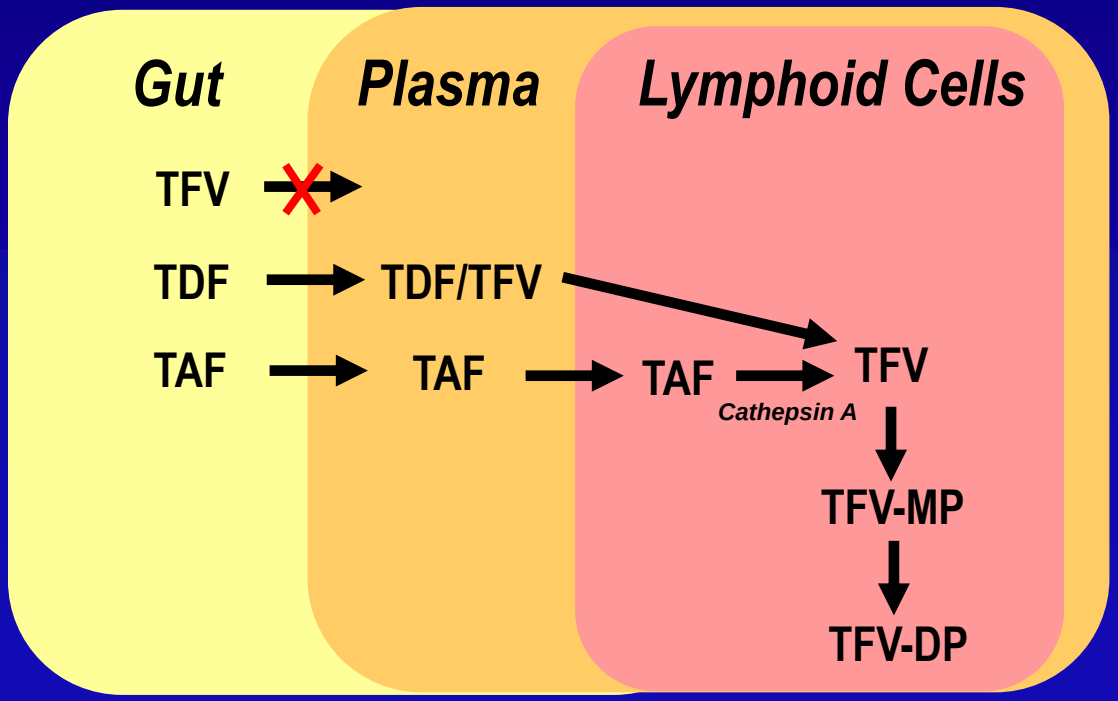
TDF

Tenofovir Disoproxil Fumarate



TAF

Tenofovir Alafenamide



TAF vs TDF -Conclusions

- TAF has equivalent or better antiviral activity, higher intracellular TFV-DP, and lower circulating plasma TFV
- Favorable Phase 3 TAF results (initiating or switching therapy), with decreased renal and bone toxicity
- TAF use is associated with increased weight gain and lipid levels, compared to TDF

What should be the third drug be?

INSTI Summary

- INSTI-based regimens are preferred for first-line ART because of efficacy, safety, and tolerability in randomized comparisons with other options
- Once-daily INSTI-based single tablet regimens are available
- Dolutegravir and Bictegravir are the preferred INSTIs;

Best Initial Regimens for Therapy in 2022

tenofovir AF/emtricitabine

dolutegravir

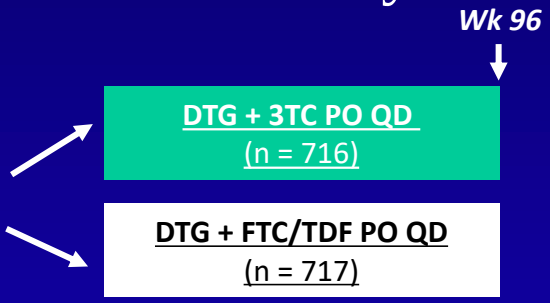
OR

bictegravir/tenofovir AF/emtricitabine

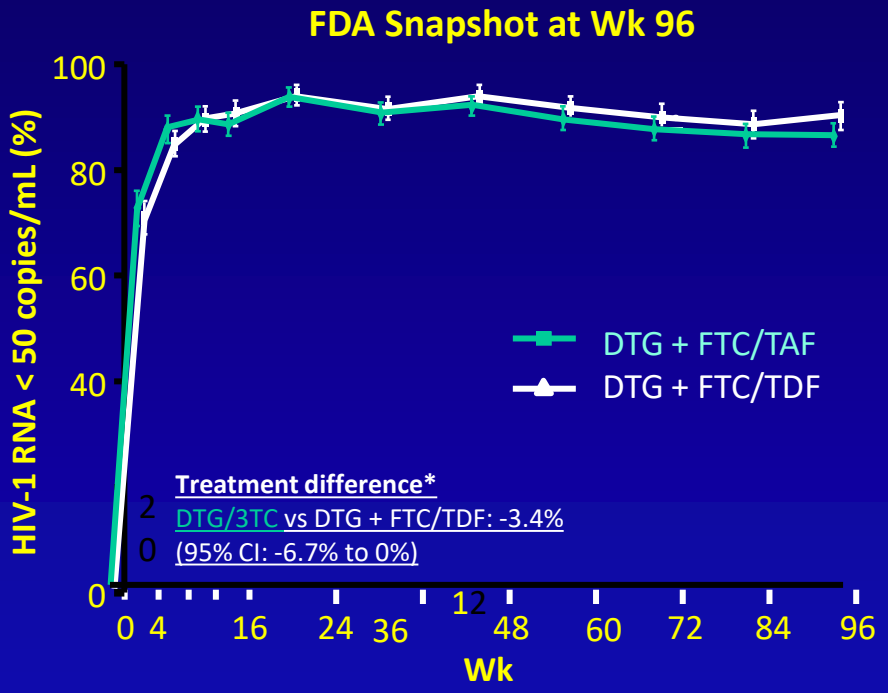
- Reasons
  - Once daily administration of small tablets
  - Clinically significant drug resistance rare
  - Well-tolerated and taken with or without food
  - Reduced renal and bone toxicity c/w TDF
  - Active vs hepatitis B
  - Ideal for same-day institution of ART

GEMINI-1 and -2: DTG + 3TC in ART-Naive Adults

- Randomized, double-blind phase III noninferiority studies



- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48



*Adjusted for BL HIV-1 RNA, BL CD4+ cell count, and study.

Slide credit: clinicaloptions.com

Cahn P et al. *JAIDS* 2020

2022 HIV Treatment Recommendations

- Bictegravir/TAF/FTC
- Dolutegravir plus
  - TAF/FTC or
  - TDF/FTC or
  - TDF/3TC
- DTG/3TC, with caveats - Not recommended for pts with chronic hepatitis B or HIV RNA above 500,000 copies/mL, and perhaps a CD4 cell count below 200/µL, Close monitoring for adherence and virologic response is needed. Not recommended for those being treated for an active opportunistic infection.

Challenging Issues in HIV Treatment

- What is the best treatment in pregnancy or for non-pregnant women of childbearing potential?
- When should one switch a regimen that's working?
- What to do about ART-related weight gain?

Dolutegravir therapy at conception and neural tube defects

- Summer 2017: Reports from a prospective Botswana study cited a 0.9% prevalence of neural tube defects in babies born to mothers who conceived while receiving DTG

- Data updates July 2020/21: Neural tube defect prevalence no longer significantly higher with DTG than with other ART

What to Start in Pregnancy: DHHS Guidelines 2022

Two NRTIs

TAF/FTC, TAF/3TC *(now preferred in pregnancy and for those trying to conceive)* or

TDF/FTC, TDF/3TC

Plus

Integrase inhibitor:

Raltegravir (twice daily) or

Dolutegravir (*Preferred ARV throughout pregnancy and for those trying to conceive*)

or

Protease inhibitor:

Darunavir/ritonavir (twice daily) or

Atazanavir/ritonavir

Bictegravir (limited data)
Elvitegravir/cobi (PK concerns)
DRV/cobi (PK concerns)
ATV/cobi (PK concerns)
DOR (no data)
Fostemsavir (limited data)
Oral or IM CAB/RPV (insufficient data)

https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new-guidelines

Reasons to Consider Regimen Switching Even With Viral Suppression

- To manage drug associated adverse events and tolerability
- To reduce pill burden and dosing frequency in order to optimize adherence
- To minimize or address drug interaction concerns
- To reduce costs

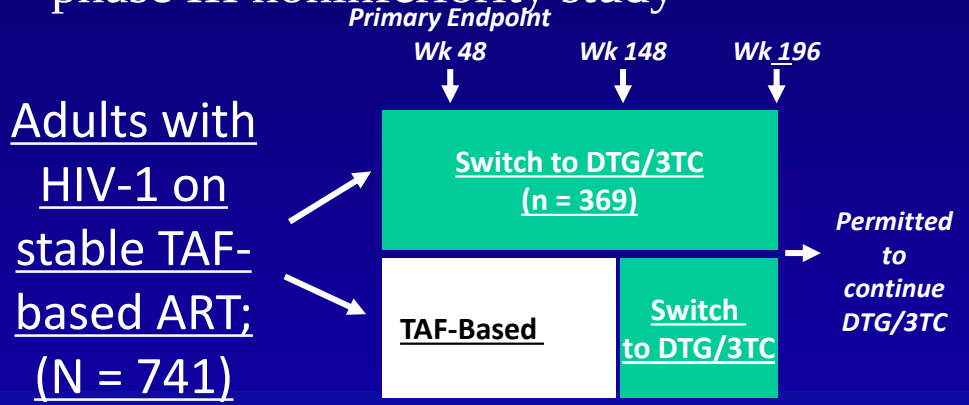
Cardinal Principles of Regimen Switching

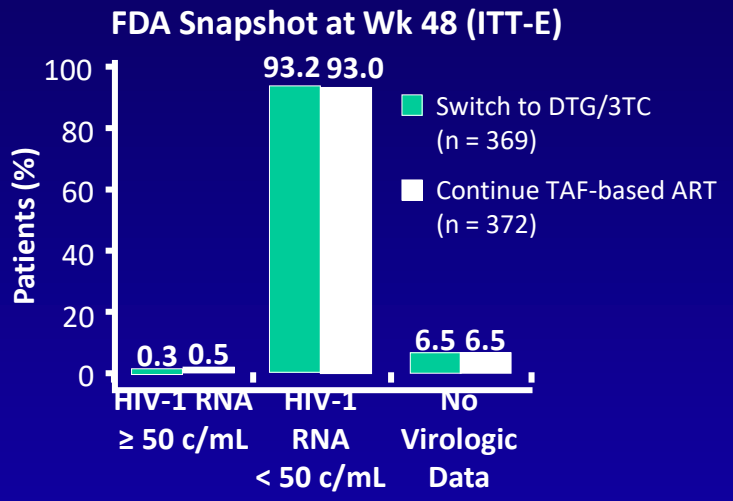
- Maintain virologic suppression since inappropriate switches can lead to virologic rebound, new resistance mutations, and a need for more complex regimens

- If it ain't broke, don't fix it!

TANGO: Switch to DTG/3TC in Virologically Suppressed Adults on Stable TAF-Based ART

- Multicenter, randomized, open-label phase III noninferiority study

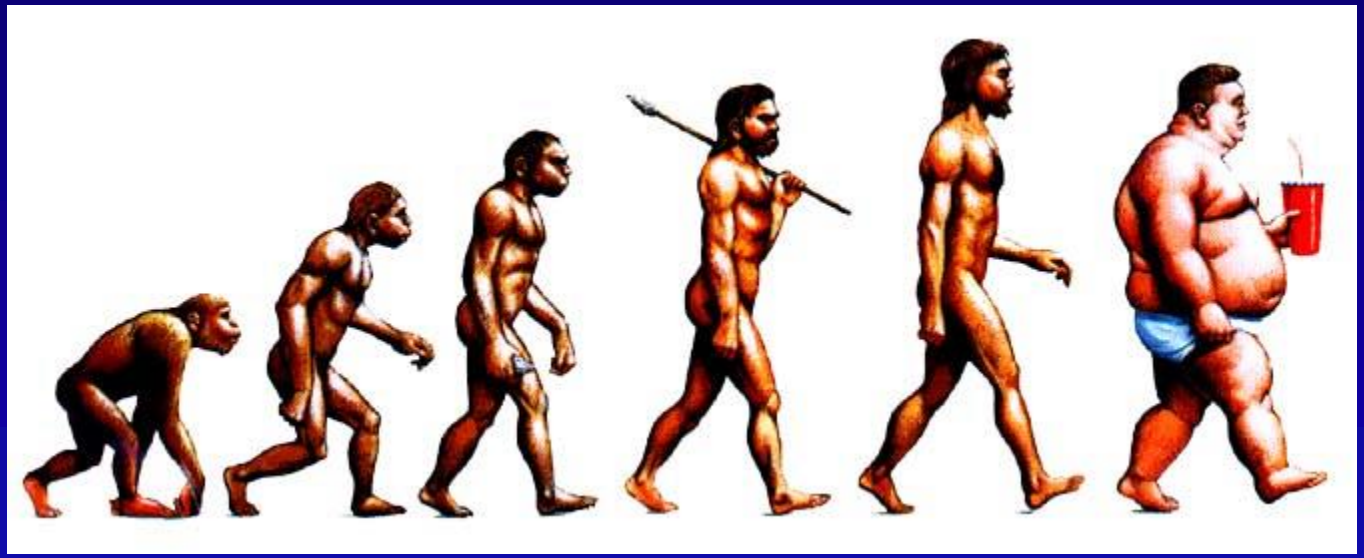




- Primary endpoint: HIV-1 RNA ≥ 50 copies/mL at Wk 48 by FDA Snapshot

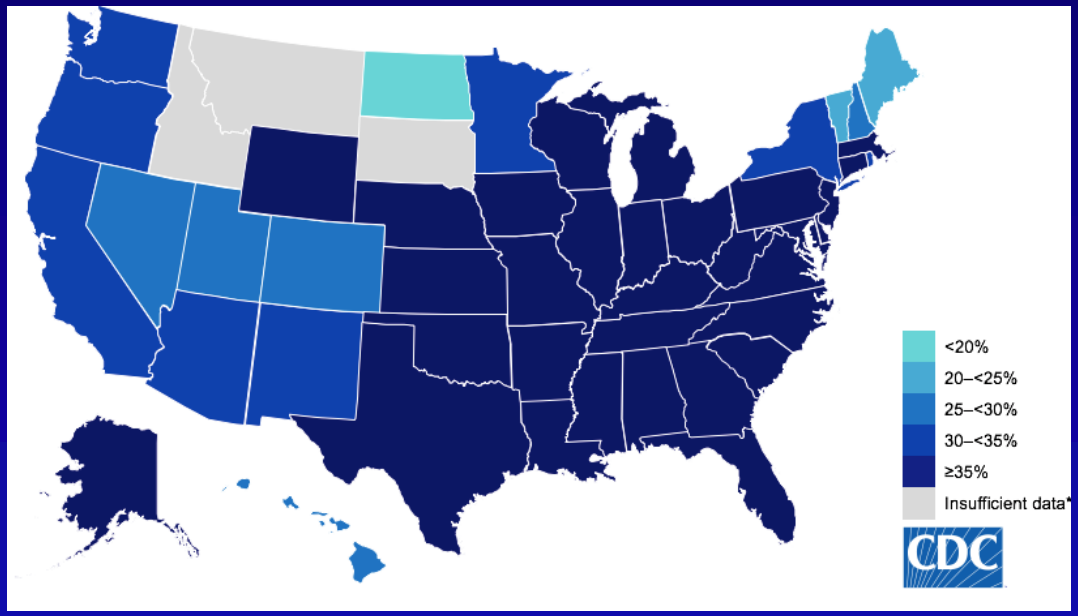
Van Wyk et al. *CID* 2020

Obesity, HIV Therapy, and Weight Gain – What is the Evidence?



Factors Driving Increased Obesity Among People with HIV

- Geographic region
- Sex
- Race
- Poverty
- Food insecurity
- Antiretrovirals?



Weight Gain on ART: What We Know

- Initiation of any ART may lead to weight gain and may be desirable in some recipients
- Initially low CD4 cell count and high plasma HIV RNA associated with the greatest ART-associated weight gains
- High person to person variability in weight gain on ART
- Variability among individual agents and regimens

DHHS Guidelines: Weight Gain and ART

- Weight gain appears greater with INSTIs than with other drug classes; mechanisms for this are unclear
- Greater weight gains with TAF than with TDF
- ART-associated weight gain may contribute to increased cardiometabolic risk, particularly in older individuals with co-morbidities

Some key remaining questions

- Do TAF and the INSTIs *cause* weight gain or do TDF and EFV *suppress* weight gain? Or is it some combination of these contrasting effects?
- What are the mechanisms involved?
- Is there a reversal in weight gain by switching ART regimens? Probably not, but these studies are ongoing.

HIV Treatment – Take Home Points

- Current standard of care is two NRTIs (TAF/FTC best) with one integrase inhibitor (preferably DTG or BIC)
- Same-day ART initiation feasible and recommended
- Maintain virologic suppression when switching ART
- Be aware about weight gain with certain regimens

Global Access to ART

- Concerted efforts to rollout ART programs and monitoring in resource-limited countries (PEPFAR, WHO, UN-AIDS, Clinton Fdn, etc.)
- 2002: 300,000 people on ART worldwide
- 2019: >23 million people on ART (WHO)
- Several million who should be on ART are not

What's New in Therapy?

Unmet Need? Long-acting ART

- Poor adherence over time is common
- Long-acting ART offers the possibility of directly observed therapy, and is an attractive option for those with “pill fatigue”
- May provide better protection of health privacy
- Reduces HIV-related stigma – taking oral meds may be a daily reminder that a person has HIV

Cabotegravir (CAB)

- Dolutegravir derivative, a long-acting (LA) INSTI for depot injection or oral administration

- Two drug combination of injectable LA CAB and LA Rilpiverine q4 or q8 weeks is as effective as a daily oral 3 drug regimen

- The FDA has approved q 1 mo. or q 2 mo i.m. injections following a 1 mo. lead in with oral drugs

Andrews et al., *Science* 2015; Margolis et al., *Lancet ID 2017;* Swindells et al. *NEJM* 2020; Orkin et al. *NEJM* 2020

Summary and Implications for Long-Acting Cabotegravir + Rilpivirine

- In people with VL suppression, and no history of resistance
- High incidence of injection site reactions, but few serious
- High patient satisfaction in surveys, but may be biased

- Questions:
  - How many will want this treatment?
  - Are clinics OK with more patient visits?
  - How to choose the right candidates?

Why search for a cure?

- Need for life-long ART
  - Side-effects and long-term toxicities
  - Burden of life-long adherence
  - Cost
  - Sustainability
- Adverse effects of HIV-1 persistence
  - Inappropriate immune activation
  - Cardiovascular, CNS, other end-organ damage
- Potential risk for transmission
- Ongoing stigma of HIV infection

Barriers to Cure

- Latently infected cells
  - *resting CD4+ T cells*
  - *other (potential) cell types*
  - *reservoir may be much larger than previously thought*
- Long-lived cells (macrophages, microglia)
- Inadequacy of HIV-specific immunity and generalized immune dysfunction

Approaches to HIV cure

- Hematopoietic stem cell transplantation
- Immediate initiation of ART in acute infection
- Genetically modified CD4+ T-cells
- Induce HIV expression from latently infected cells
- Immune-based interventions

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

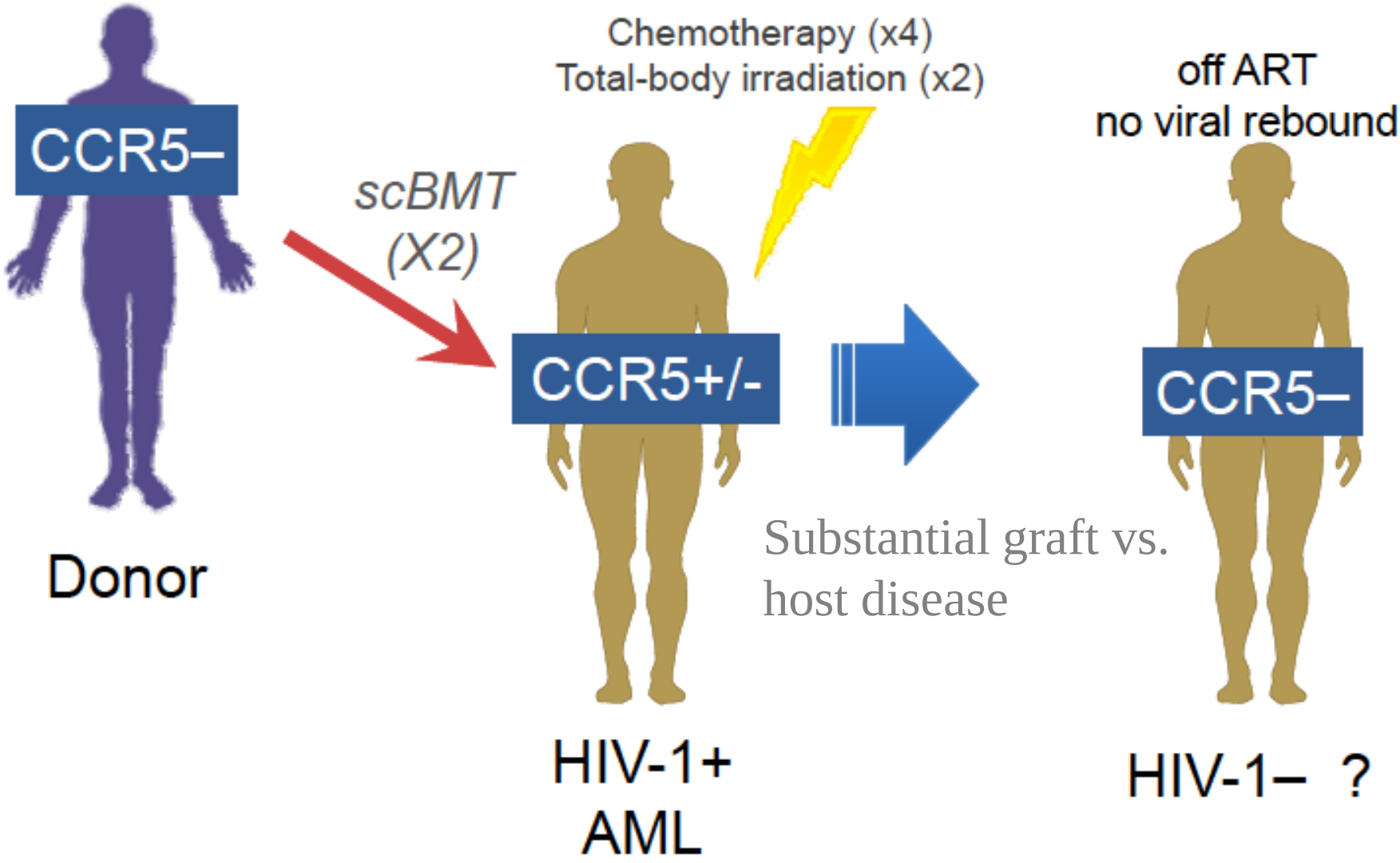
BRIEF REPORT

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 Müßig, 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.

N Engl J Med 2009; 360:692-698 | February 12, 2009

Long-term control of HIV by CCR5 Δ32/Δ32 stem cell transplantation: T. Brown, the Berlin Patient



Courtesy of J Martinez Picado

Hütter. NEJM. 2009; Allers. Blood. 2010

Update on "Berlin Patient"

- Blood and gut mucosa reconstituted with cells expressing only CXCR4 receptor
- Plasma HIV RNA remained negative using ultra-sensitive techniques
- No evidence of HIV in gut mucosa, bone marrow, or cerebrospinal fluid
- Patuebt died of recurrent leukemia in 2020 with no evidence of recurrent HIV

Allers et al, *Blood*. 2011;117:2791-9;
Brown TR *AIDS Research Human Retroviruses* 2015


REALITY
CHECK
AHEAD

HIV-1 Remission With CCR5 Delta 32 Haplo-Cord Transplant in a Woman

- 59-year-old woman with HIV in 2013 and AML in 2017
- 2017: CCR5Δ32/Δ32 cord blood transplant + PBMC from a relative (to aid engraftment)
- Day 100: full remission of AML
- ART stopped 37 months post-transplant;14 months off ART with no viral rebound, loss of HIV specific antibody responses; undetectable HIV DNA, no detectable replication competent latent reservoir

Bryson Y, et al. CROI 2022. Abstract 65.

Conclusions Regarding Cure Research

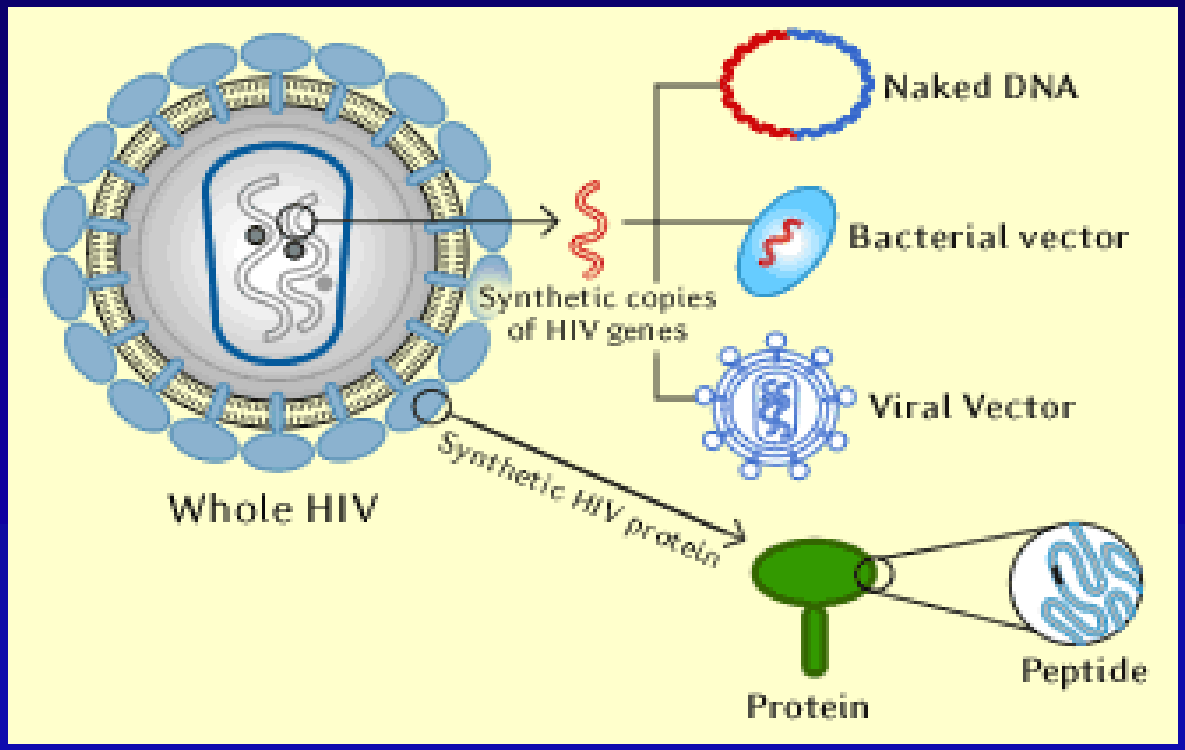
- Purging the HIV-1 reservoir may require both virologic and immunologic interventions
- Novel approaches and better tools are needed
- Ethical and regulatory issues must be addressed
- Stakeholder expectations must be realistic

Margolis D et al. Perspectives in HIV Cure Research, *J Infect Dis Suppl* 2017

PREVENTION OF HIV INFECTION

What about vaccines?

Past and Current Vaccine Strategies



Is an HIV Vaccine on the Horizon?

- Great progress against other viruses (e.g., smallpox, polio, measles, hepatitis A, rabies, SARS-CoV-2)

- Obstacles

  HIV mutation rate and multiple subtypes

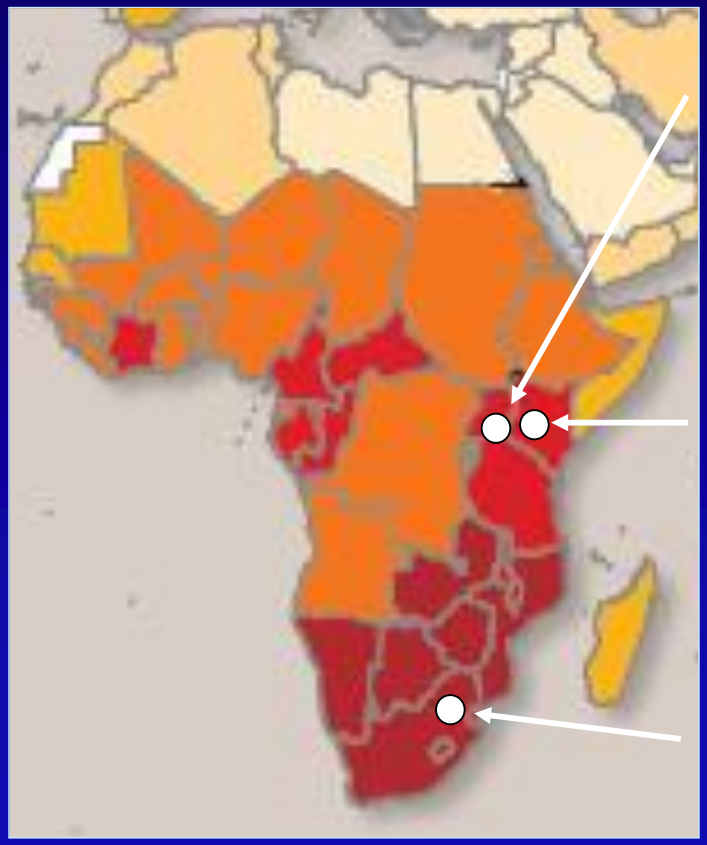
  Immune cells activation may enhance HIV infection

- Large, controlled trials have been negative (STEP, HVTN 505, HVTN 702); others still underway

Gray *NEJM* 2021; Feinberg *NEJM* 2021

Circumcision and HIV

Randomized controlled trials of male circumcision to reduce HIV infection



Rakai, Uganda

Gray *et. al.* (2007) *Lancet*;
51% reduction in transmission

Kisumu, Kenya

Bailey *et. al.* (2007) *Lancet*;
53% reduction

Orange Farm, South Africa

Auvert *et. al.* (2005) *PLoS Med*;
60% reduction

UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
UNHCR UNODC
UNICEF ILO
WFP UNESCO
UNDP WHO
UNFPA WORLD BANK

World Health Organization

Paris/Geneva, 28 March 2007

WHO and UNAIDS Announce Recommendations from Expert Consultation on Male Circumcision for HIV Prevention

- Male circumcision should now be recognized as an additional, important intervention to reduce the risk of heterosexually acquired HIV infection in men.
- Male circumcision should be part of a comprehensive HIV prevention package.
- Adequate training, hygiene, monitoring, counseling are critical.
- Modeling studies suggest that male circumcision in sub-Saharan Africa could prevent 5.7 million new cases of HIV infection and 3 million deaths over 20 years.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Pre-Exposure Prophylaxis (PrEP)

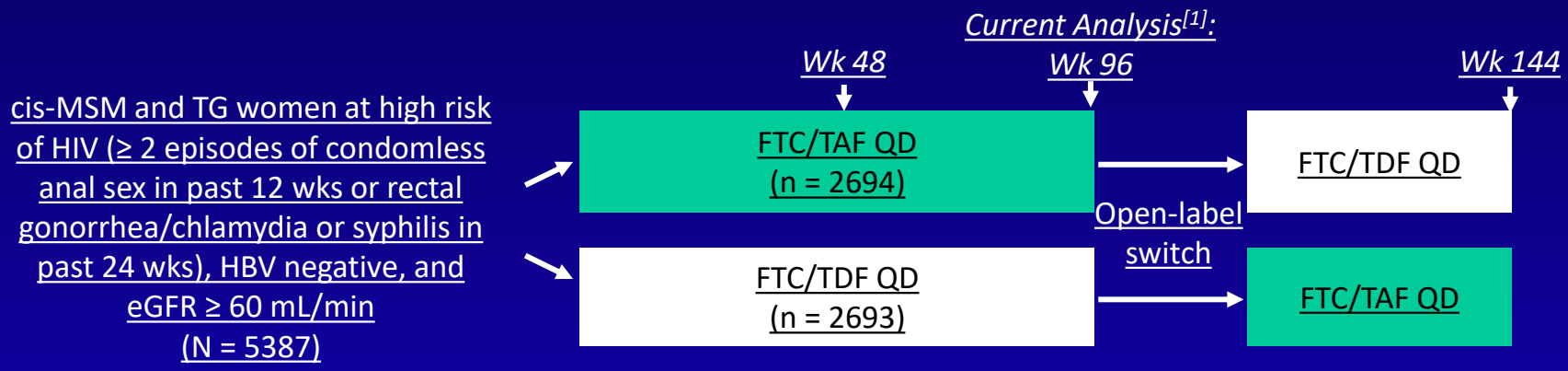
Preexposure Prophylaxis (PrEP) with Oral TDF/FTC (iPrEx study)

- Placebo-controlled trial of once daily TDF/FTC in 2499 uninfected MSM
- 44% reduction in infections over median of 1.2 yrs
- Detectable blood levels strongly correlated with the prophylactic effect
- Mild reversible creatinine increases on TDF/FTC

Grant et al. *NEJM* 2010;363:2587-2599.

DISCOVER: FTC/TAF vs FTC/TDF Oral PrEP in cis-MSM and Transgender Women

- Randomized, double-blind phase III noninferiority trial in Europe and North America



- Primary endpoint: HIV incidence/100 PY
- **FTC/TAF noninferior to FTC/TDF** for HIV infection endpoint
- **FTC/TAF** had less effect on renal function
- **FTC/TAF** led to more weight gain and no lipid lowering effect

1. Ogbuagu. CROI 2020. Abstr 92. 2. Hare. CROI 2019. Abstr 104LB. 3. Ruane. EACS 2019.

HPTN 083 and 084 PrEP Trial Results

- Long acting Cabotegravir i.m. q 2 months vs daily TDF/FTC in MSM and transgender women who have sex with men; 4566 participants (HPTN 083)
- Study stopped on DSMB recommendation
- 12 HIV infections in CAB arm vs 38 in TDF/FTC arm (0.38% vs 1.21%); 66% reduction by CAB, p=0.00051)
- Companion study in women in Africa (HPTN 084) showed similar results

Landovitz *NEJM* 2021; Marzinke *JID* 2021; Delany-Moreltwe *Lancet* 2022; Eshleman *JID* 2022

Take-home Points on PrEP

- The 2021 CDC guidelines now recommend that PrEP be discussed with all sexually active patients
- Injectable cabotegravir superior to FTC/TDF for PrEP in men and women and is FDA approved
- Selection of p.o. or i.m. PrEP requires careful evaluation discussion with potential candidates

Summary: HIV Prevention by PrEP

- PrEP is effective in high-risk individuals.
- Although oral PrEP use in US has increased, it is not at levels desired. Only 5% of who have indications for PrEP are receiving it.
- PrEP-to-need ratio lowest in South, in non-Medicaid expansion states, and in young people

HIV/AIDS and SARS-CoV-2/COVID-19

- Conflicting data on risk of acquisition and severity of COVID in PWH.

- This may be related to confounding factors, e.g., control of viral infection, CD4 cell counts, co-morbid conditions.

- Vaccines reduce COVID in the immunocompromised, but not to the degree that they do in immunocompetent persons

Lee et al. *BMJ* 2022; Sun et al. *JAMA Intern Med* 2022; Brown et al. *Curr Opin HIV AIDS* 2021; Lesko et al. *Am J Epi* 2021;\

Take Home Messages and Expectations

- Enormous progress has been made in ART, with great improvements in disease-free life spans
- Future advances in pre- and post-exposure prophylaxis will lead to reductions in new infections
- Continued efforts required to develop prophylactic and therapeutic vaccines and immunotherapies

The Economist: June 4-10th, 2011

Thanks!

- Rachel Erdil
- Paul Sax
- Raj Gandhi
- Bruce Walker
- Tom Quinn
- The Audience !!