

# **HIV** Past, Present, & Future

Review some history of HIV

HIV in 2018 & what internists can do

Glimpse of the future

Interactive audience desired

On line handout succinct & “Board proof”

# Human Retroviruses

- HTLV-1      Adult T-cell Leukemia, HAM / TSP
- HTLV-2      Possible association with HAM / TSP
- HIV-1
- HIV-2      Extremely slow progression to AIDS



- HIV-1 Group M
- HIV-1 Group N
- HIV-1 Group O

SIV (Chimpanzee)



HIV-2

SIV (Sooty Mangabey)

# SIV in nonhuman primates

## Potential for new strains of HIV

- HIV-1 and -2 crossed species from nonhuman primates
- Assay of meat derived from butchered primates for SIV-type viruses
  - Meat from 17 species
  - 1096 samples assayed
- 14/17 species found to contain **SIV-like viruses** with range of positive samples 5–40%
- Significant potential for human exposure and resulting in HIV-3, HIV-4, HIV-5...

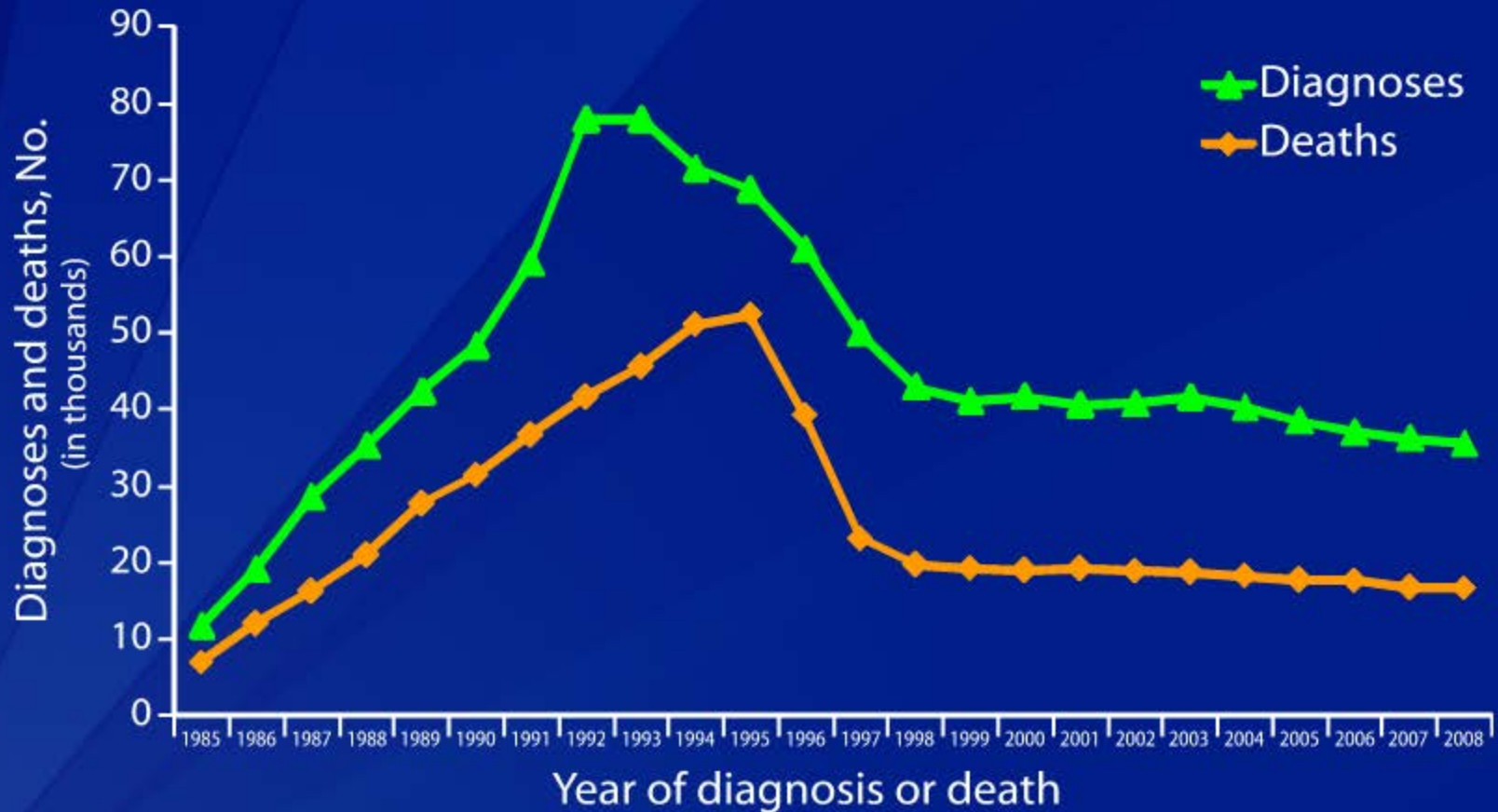


# Historical facts

- 1<sup>st</sup> HIV + on record ? In the USA ?
- Start of HIV epidemic in USA ?
- 1<sup>st</sup> identification of the virus ?
- 1<sup>st</sup> serologic test for HIV ?
- 1<sup>st</sup> anti retroviral therapy ?
- How many different ARTs are on market ?



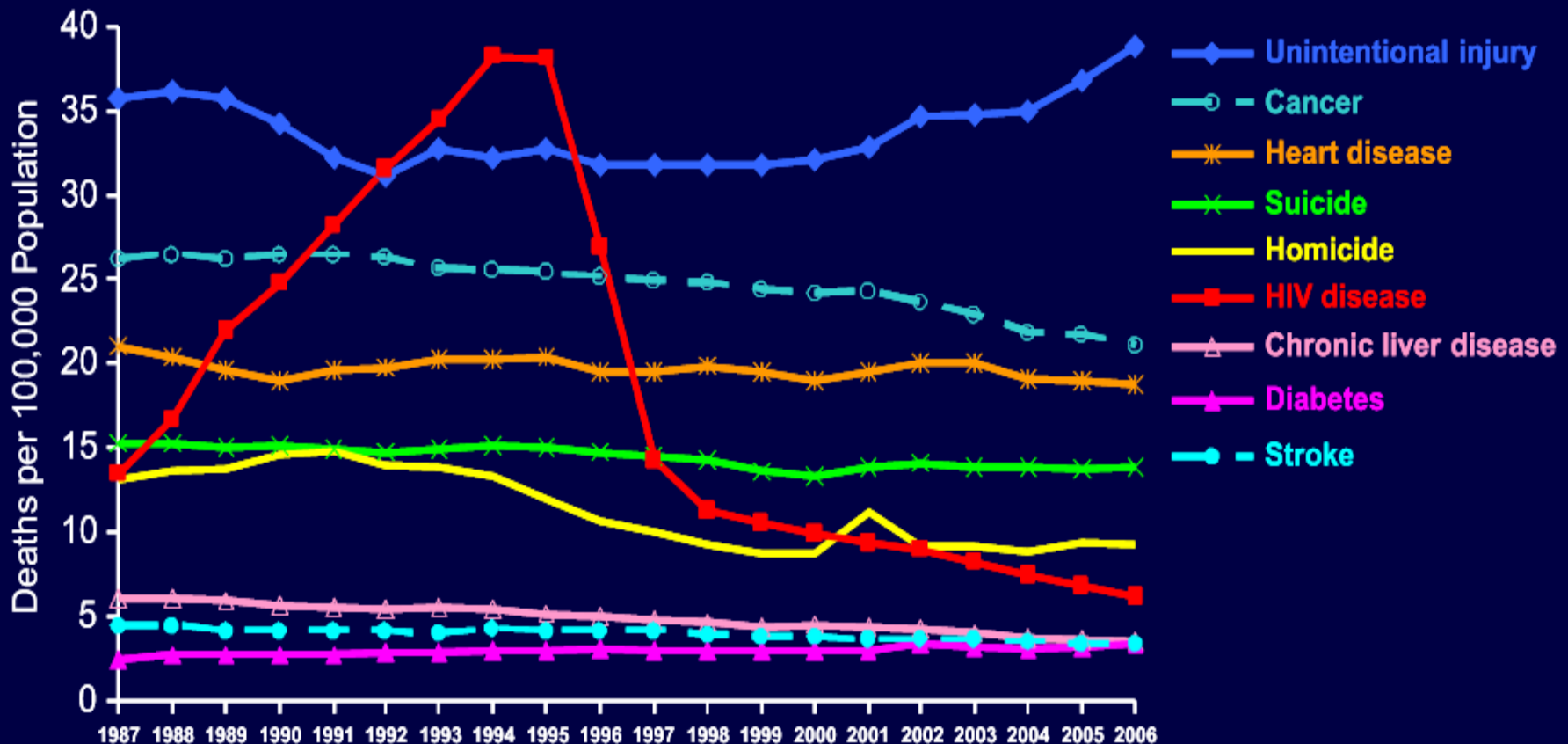
# AIDS Diagnoses and Deaths of Adults and Adolescents with AIDS, 1985–2008—United States and Dependent Areas



Note. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting. Deaths of persons with an AIDS diagnosis may be due to any cause.



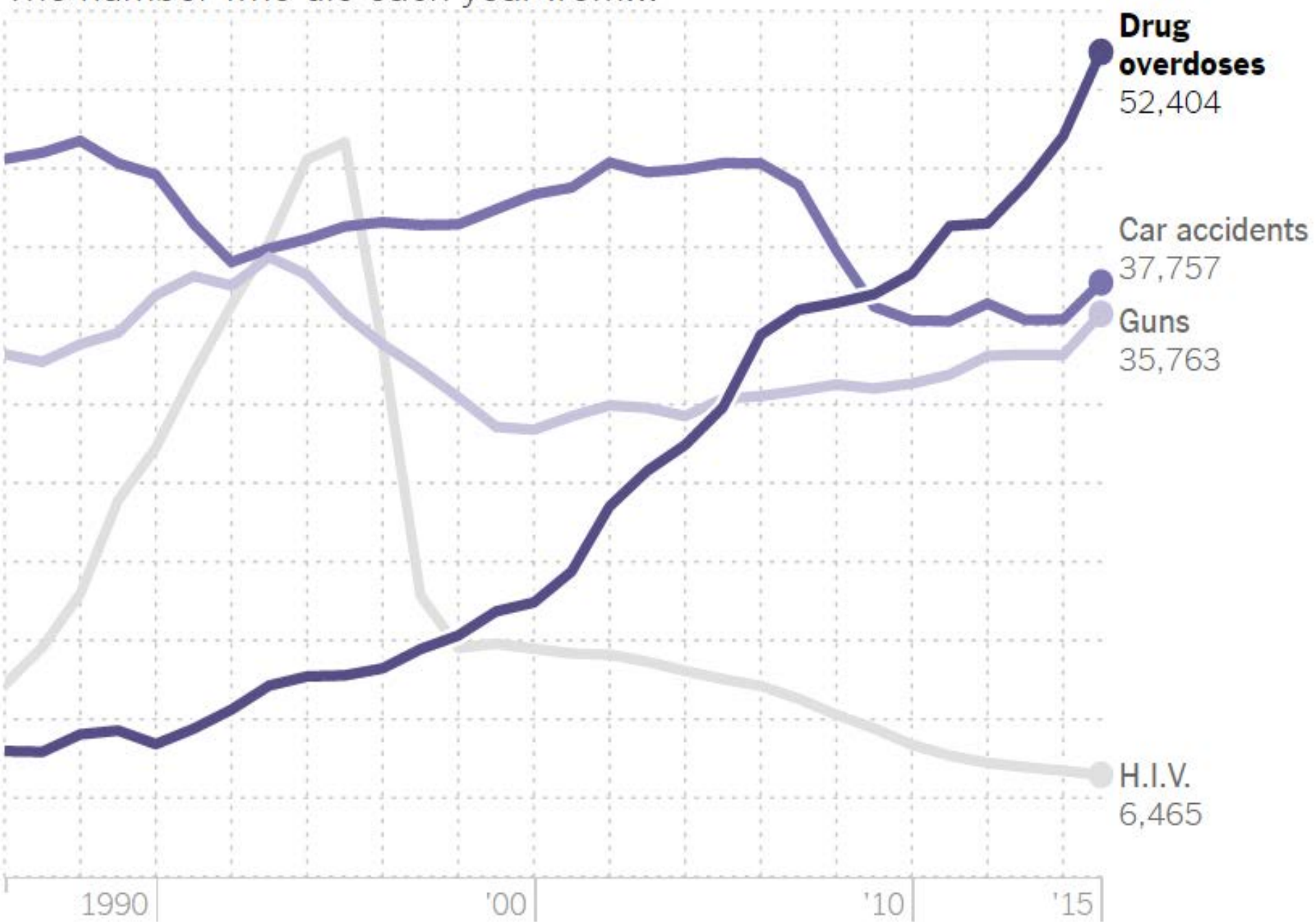
# Trends in Annual Rates of Death due to the 9 Leading Causes among Persons 25–44 Years Old, United States, 1987–2006



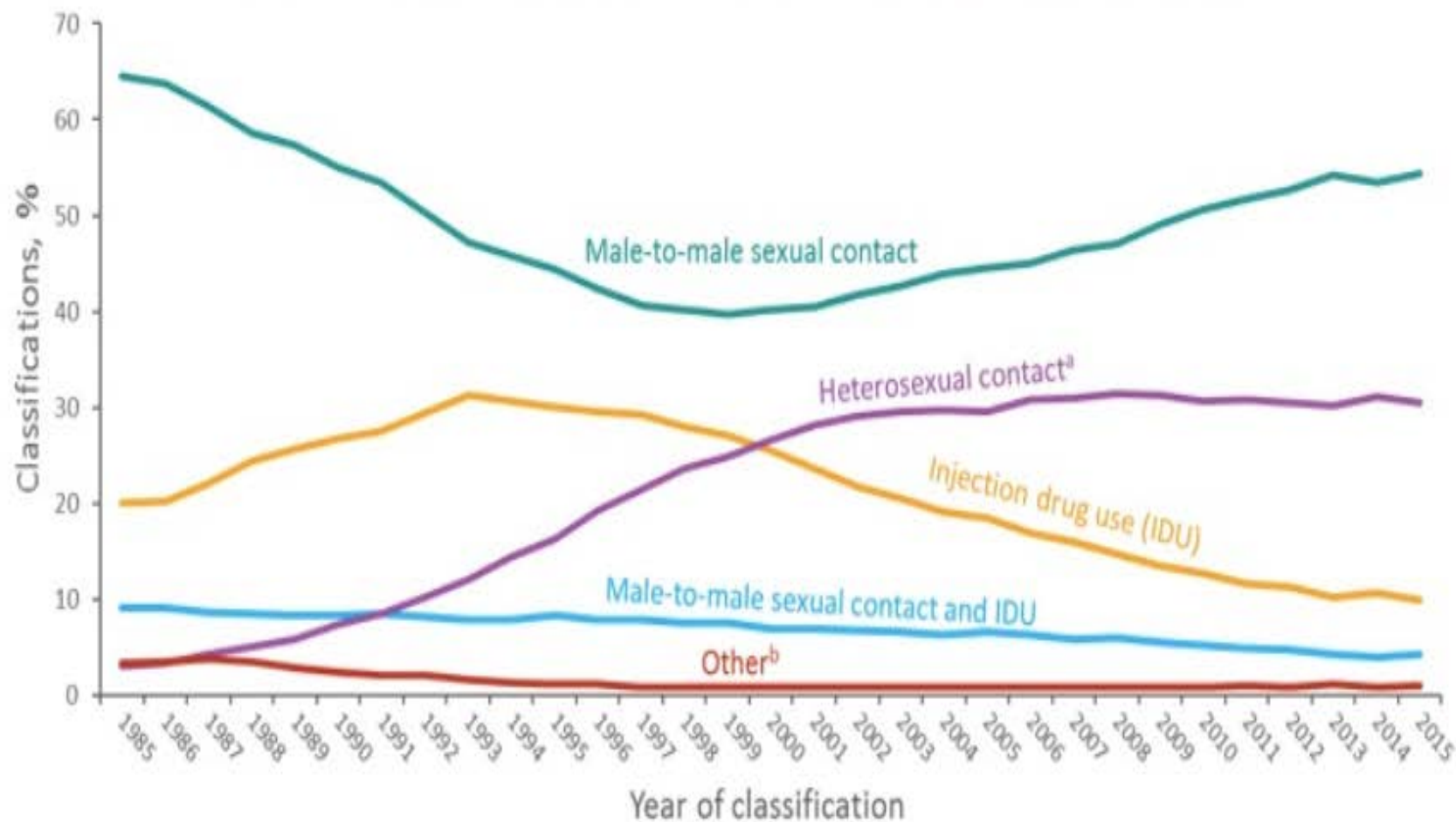
Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.



The number who die each year from...



# Percentages of Stage 3 (AIDS) Classifications among Adults and Adolescents with Diagnosed HIV Infection, by Transmission Category and Year of Classification 1985–2015—United States and 6 Dependent Areas



Note. Data have been statistically adjusted to account for missing transmission category.

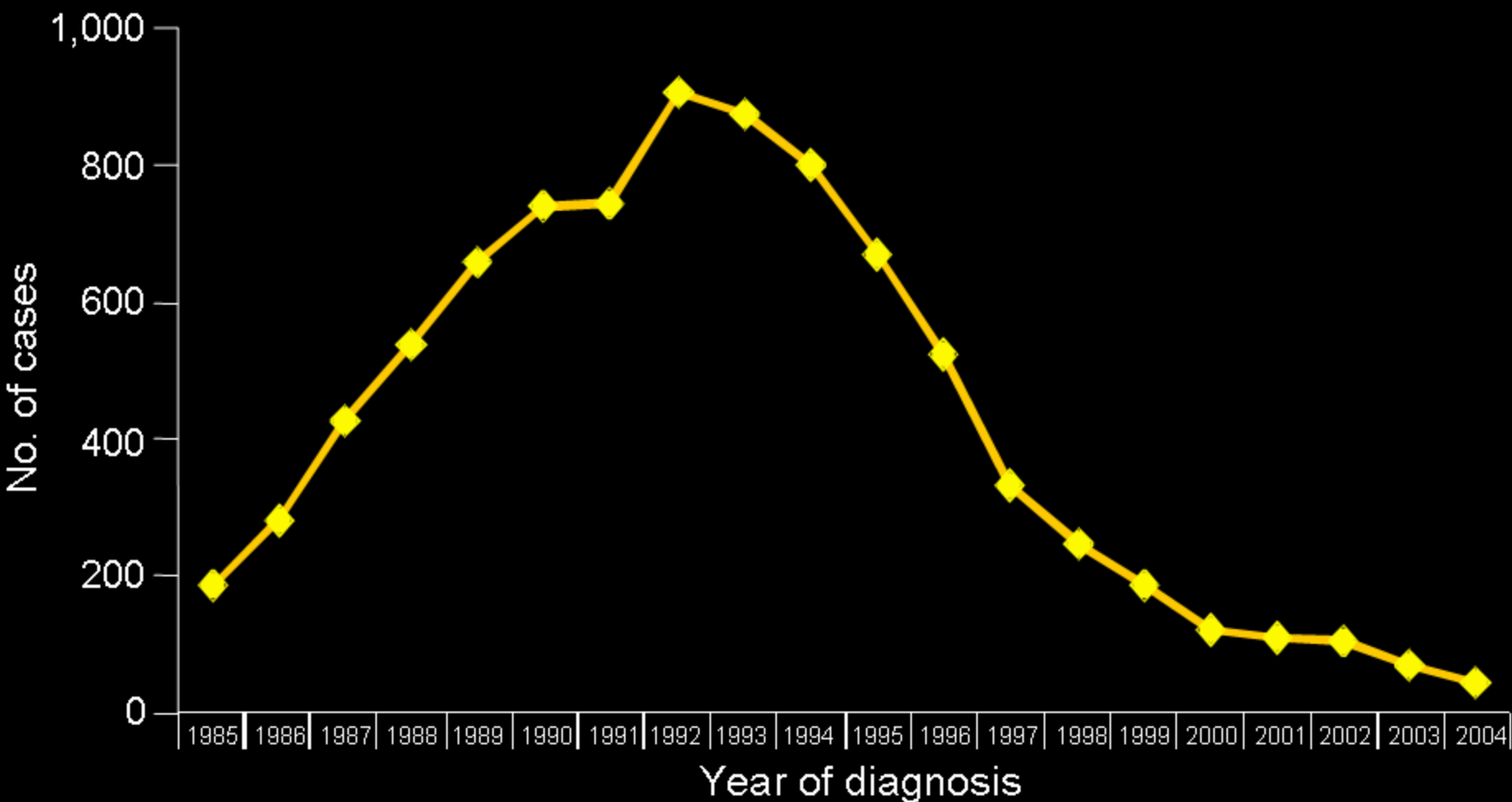
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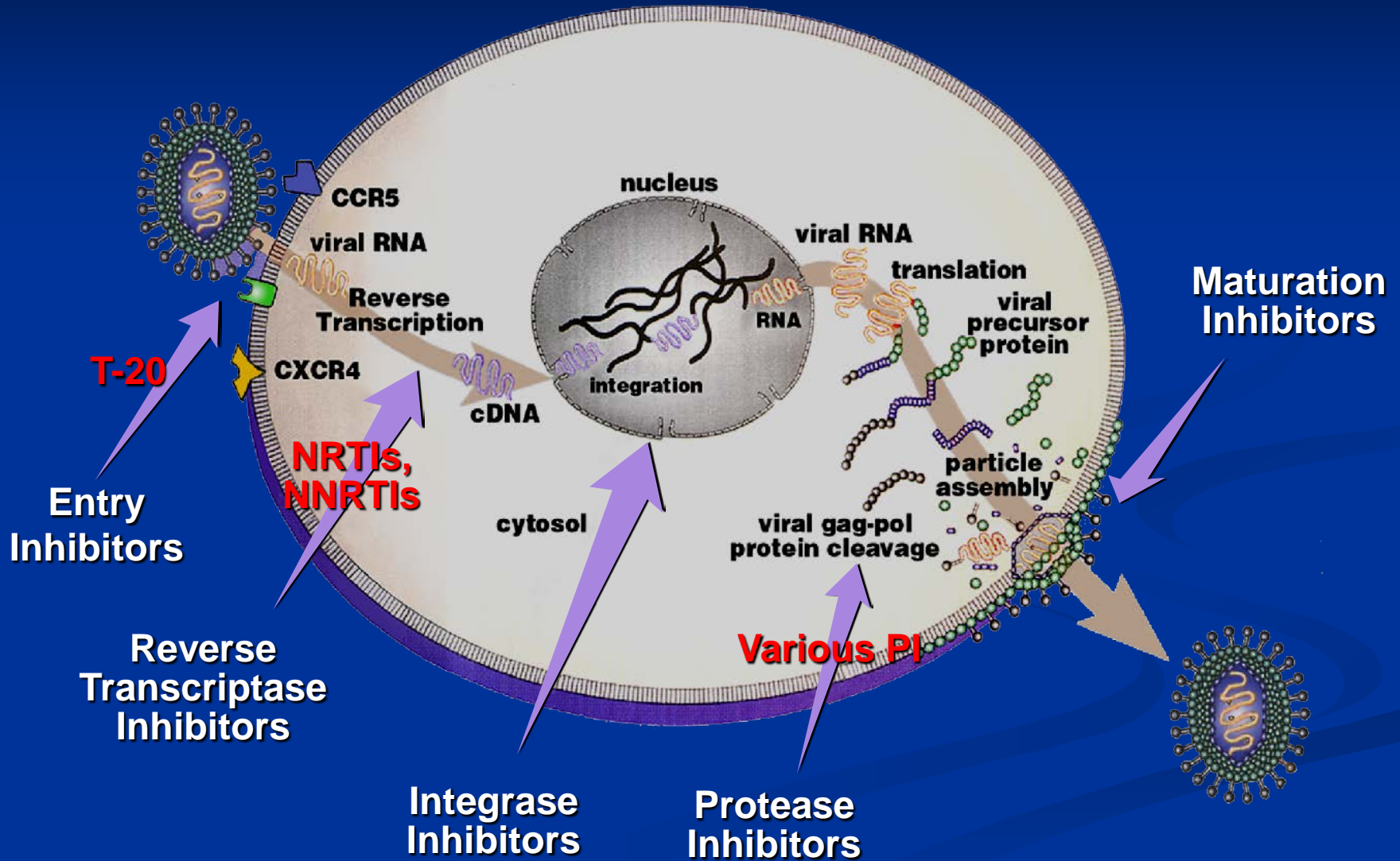
# Perinatally Acquired AIDS Cases, 1985-2004, United States



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

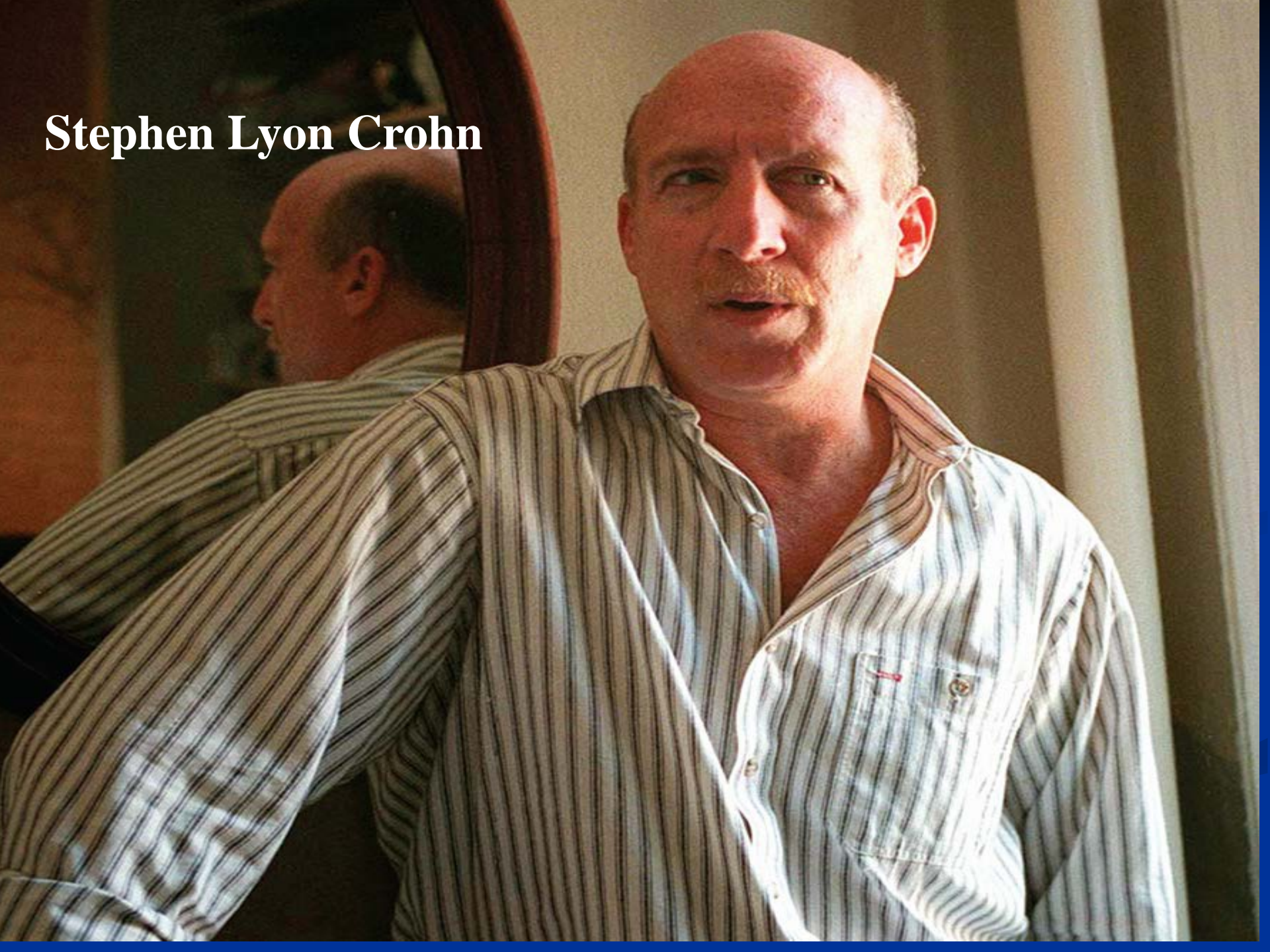


# Integrated Approaches to HIV Treatment





**Stephen Lyon Crohn**



# Work Towards a Cure

The New York Times

SCIENCE TIMES

TUESDAY, NOVEMBER 29, 2011

## New Hope of a Cure for H.I.V.

BY ANDREW POLLACK  
NOVEMBER 29, 2011



**VIRUS-FREE** Timothy Brown of San Francisco had two bone-marrow transplants to treat leukemia, and H.I.V. can no longer be detected in his body. (Heidi Schumann for The New York Times)

### Procedure and Events

- Ablative chemotherapy
- Total body XRT
- Graft vs. host
- Transplant with CCR5 $\Delta$ 32 homozygous donor

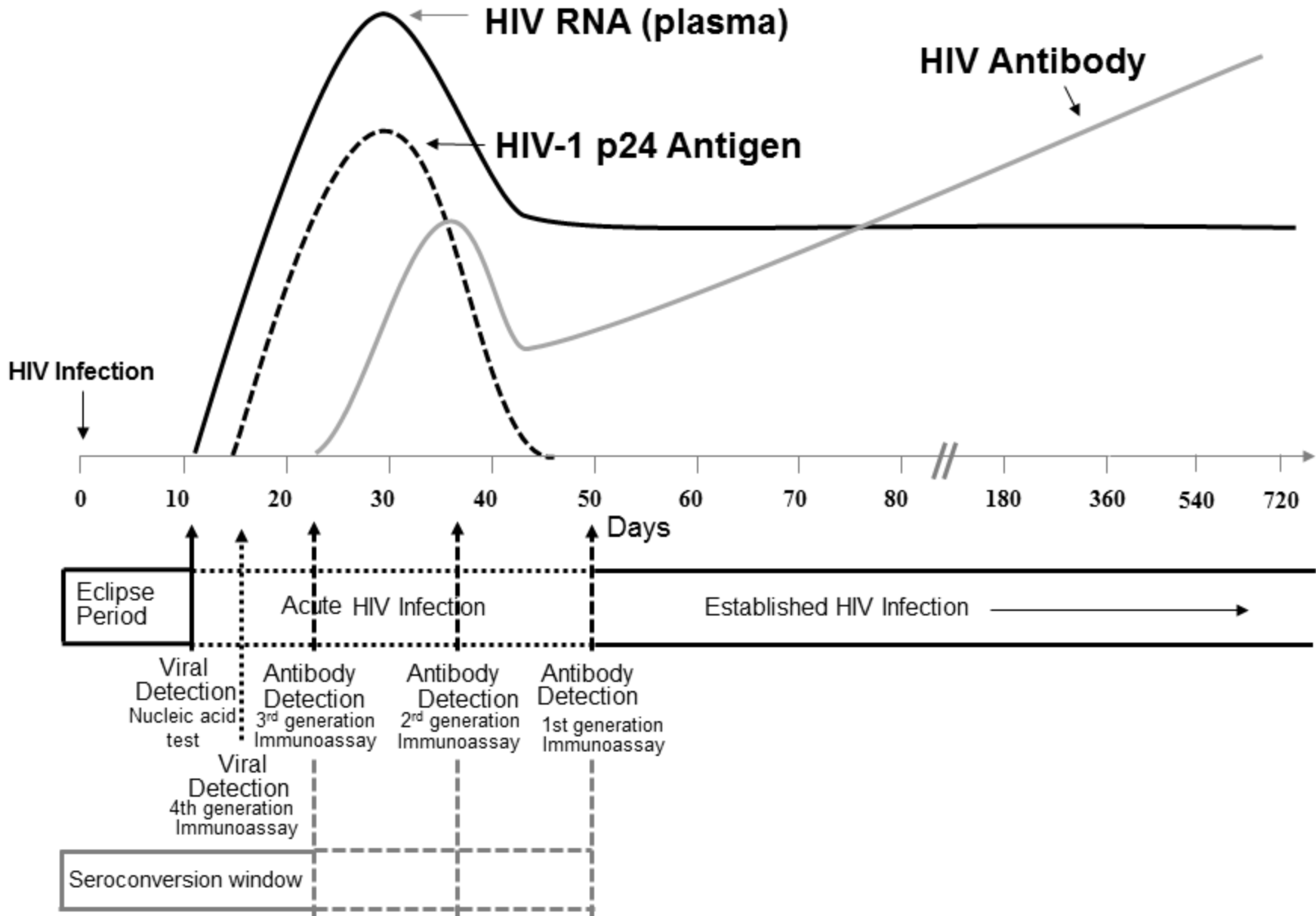


# Facts

- How many living with HIV in USA ?
- How many **new** cases of HIV yearly in USA ?
- How many HIV + do **NOT** know they are positive ?
- How many HIV + report no risk factors for HIV ?
- How many HIV + are engaged in therapy ?
- How many HIV + have **non** detectable viral loads ?
- What is the median age of HIV + people ?
- **Why** is the above important & **what** can we do ?

# Testing for HIV





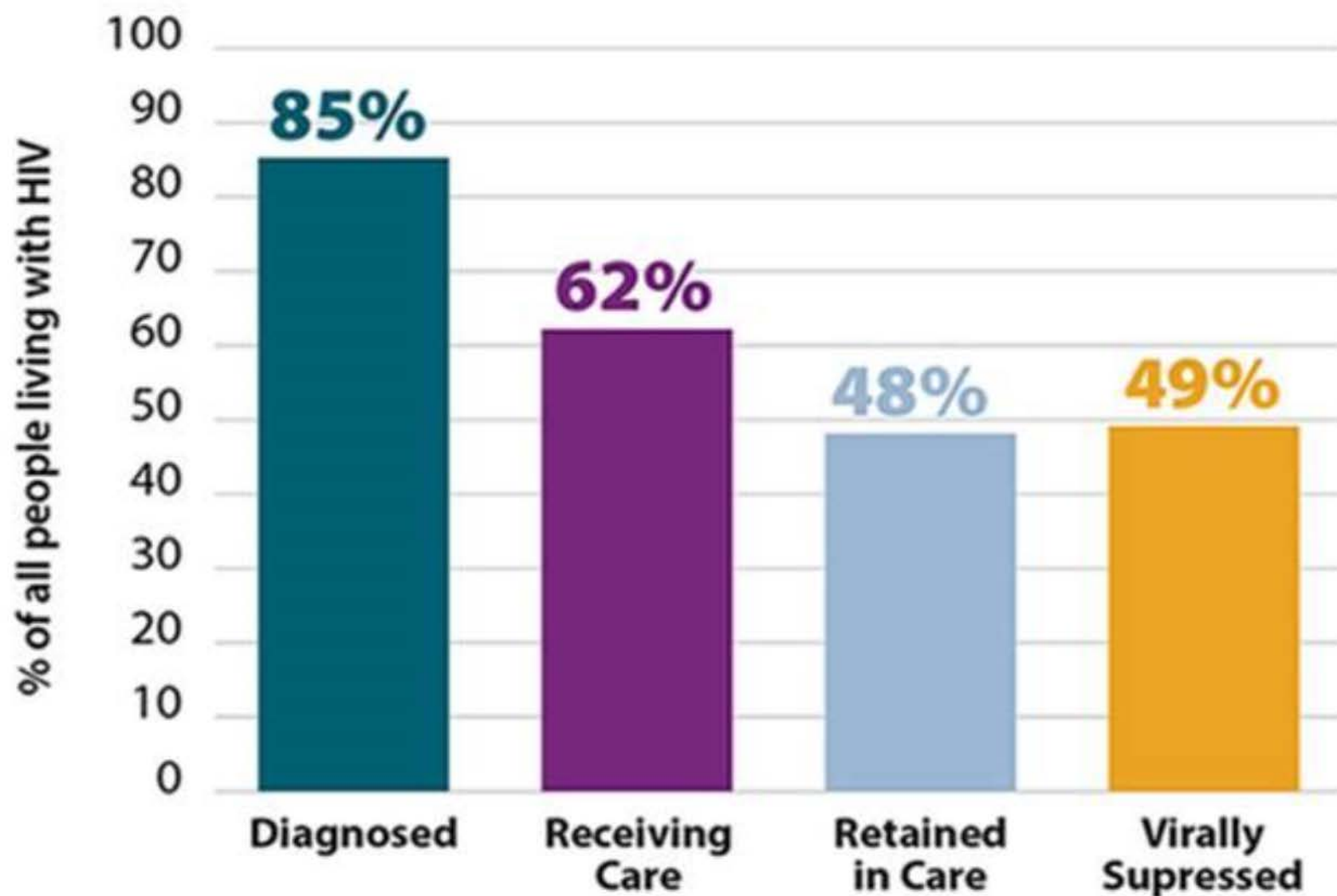
# Reasons why **routine** HIV testing is appropriate in 2018

- HIV = serious infection that can be detected early
- Reliable, inexpensive, non-invasive screening tests exist
- Infected persons can lead “normal” life span if viral load non detectable on Rx; early detection → better responses
- Awareness of HIV status can lead to behavior changes
- 20% to 26% of HIV + patients report no risk factors
- Infected people with **non detectable viral loads** are **not contagious, ergo, therapy is preventative**



# HIV Care Continuum, United States, 2014

An estimated 1.1 million people are living with HIV in the United States.



# Science

23 December 2011 | \$10

## BREAKTHROUGH OF THE YEAR

HIV Treatment as Prevention

AAAS

INSIDE THIS WEEK: TECHNOLOGY QUARTERLY

The  
Economist

JUNE 4TH - 10TH 2011

Economist.com

The trap for Turkey

Wall Street's plumbing problem

Lady Gaga, Mother Teresa and profits

Brazil's boiling economy

The farce that is FIFA

## The end of AIDS?



How 5 million lives have  
been saved, and a plague  
could now be defeated



F\*\*K  
W/OUT  
FEAR

PREP  
HERE



LOS  
ANGELES  
LGBT  
CENTER

ONE PREP PILL A DAY CAN PREVENT HIV.

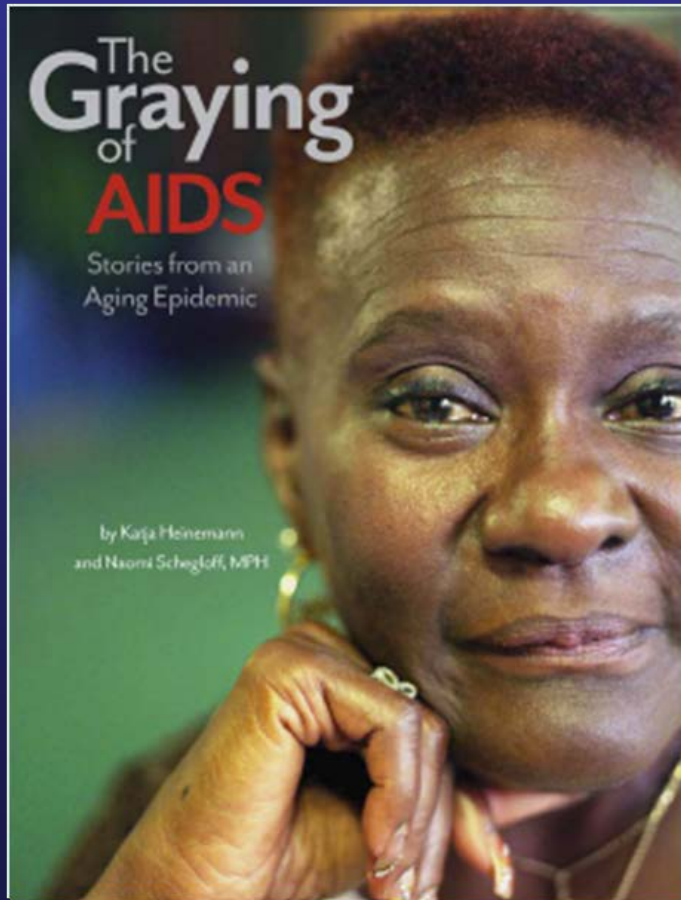
PREPHERE.ORG

PREVENT STDs WITH A CONDOM

↓  
SAFE  
CAR WASH

# Older patients account for 17% of new HIV diagnoses

- Up from 13% in 2001



**I didn't know...**

...she could be at risk

...she was clueless

...she only met her once

Carlos, 59/Bronx, NY

**AgeisnotaCondom.org**

Get informed. Be safe. Get tested for HIV.

NYS 800-541-AIDS    NYC 800-TALK-HIV  
800-541-2437    800-825-5448

20 YEARS ACRIA

**NYC**

# Acute HIV presents how ?

How many acute HIV /year & significance ?



## Acute HIV presentation

Fever, night sweats, fatigue, rash

Headache, viral meningitis, GB syndrome

Nausea, vomiting, diarrhea

Sore throat, lymphadenopathy

Myalgia or arthralgia

Oral ulcers, genital ulcers

Thrombocytopenia

Just like EBV, CMV, Parvovirus, et al

How many acute HIV /year & significance ?



# HIV Never Occurs in a Vacuum

- HIV care is complicated by:
  - Multi drug regimens susceptible to non-adherence, resistance, & toxicity
  - Polypharmacy
  - Co infections (HCV, HBV, TB, STIs)
  - Socio-economic issues: stigma, substance addiction, incarceration, homelessness, under nutrition, poverty, psycho-social issues, etc
  - **Public health funding issues**
- Aging → multiple chronic non-infectious diseases
- Nearly **1 in 5 HIV +** people > 50 years of age have **not** received a diagnosis of HIV infection<sup>1</sup>
- HIV **accentuates & accelerates** aging → inflammatory markers ↑

1. Kirk JB et al. *Am Geriatr Soc.* 2009;57:2129–2138

# An AIDS free generation

- Scientifically, we can end the HIV/AIDS pandemic
- Eliminate vertical & neonatal transmission
- Interventions = **Rx as prevention**, condoms, male circumcision, microbicide rings, PrEP (pre-exposure prophylaxis), mother to child prevention
- Focus on MSM, IVDA, prisons, & the marginalized
- Cure will likely require drugs that draw the virus from memory reservoirs in T cells & other tissues
- An effective vaccine would be of enormous value



## *The* NEW ENGLAND JOURNAL *of* MEDICINE

### **The Quest for an HIV-1 Vaccine — Moving Forward**

Dan H. Barouch, M.D., Ph.D.

Related article, p. 2083

**V**accines have historically been the most effective biomedical interventions for controlling global infectious diseases. The development of a safe and effective vaccine against human immuno-

cise types of immune responses that need to be induced by a vaccine are not well understood. Fourth, although a series of broad and potent neutralizing mono-

There are clear reasons for optimism in the quest to develop an HIV-1 vaccine. The modest protection achieved in the RV144 study provides the proof of concept that an HIV-1 vaccine is in fact possible.

November 28, 2013

# The Benefit of ARTs





# Caveats in the care of HIV+ patients

Diagnosis early, therapy early

Drug-drug interactions are common. Be pro-active.

Compliance is essential to keep resistance at bay.

Diseases of age will accelerate & accentuate even with non detectable viral loads.

TB **worldwide** is found in at least 1/3<sup>rd</sup> of HIV infected patients. (8-10% of HIV infected develop clinical TB every year)

Costs

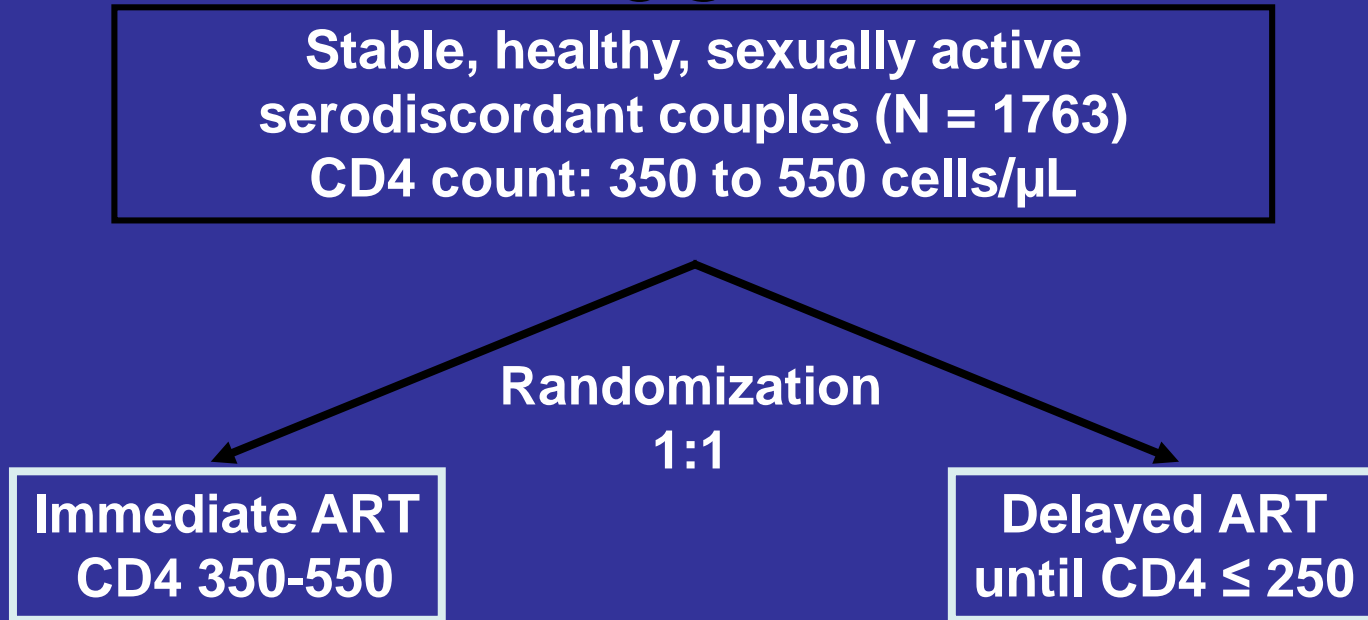
# Testing for HIV



**I WANT YOU  
TO GET A HIV TEST**

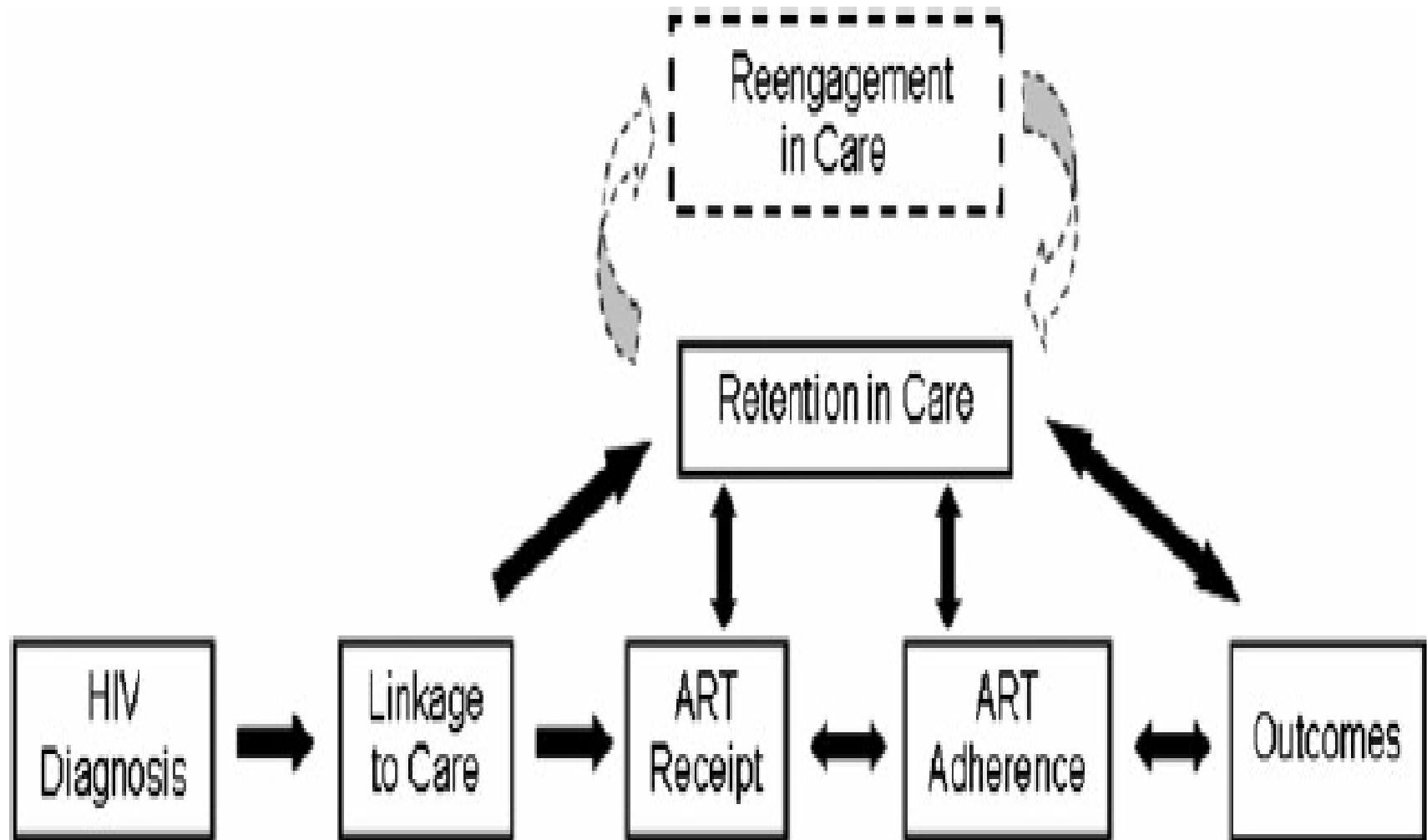


# Treatment as Prevention: HPTN 052

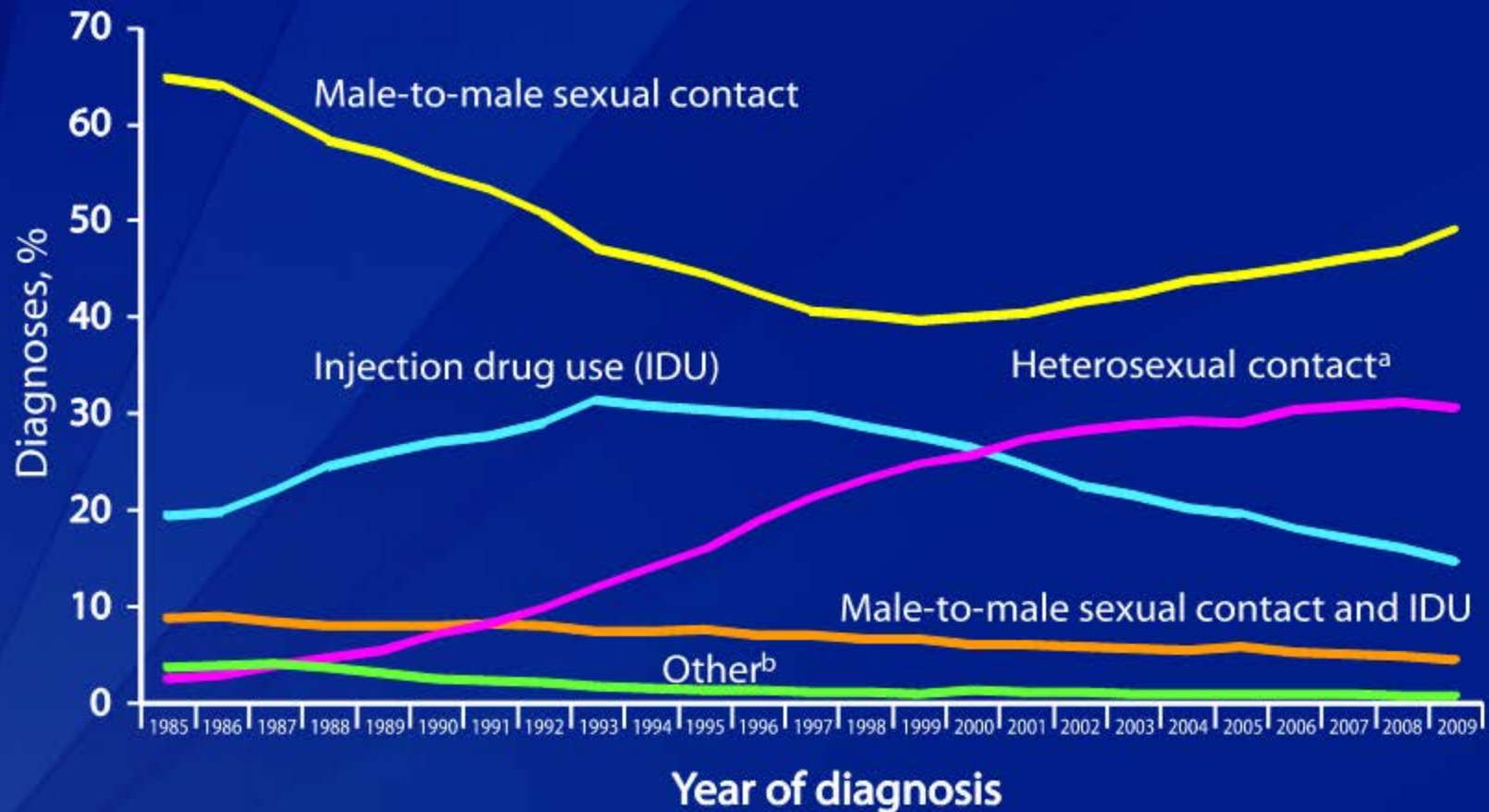


- **Primary transmission end point:** virally linked transmission events
- **Results:** 39 total HIV transmission events (28 linked events)
  - Immediate ART: 1 linked transmission
  - Delayed ART: 27 linked transmissions
  - **96% reduction in risk of HIV transmission** ( $P < .001$ )

# Our task to end the HIV pandemic



## AIDS Diagnoses among Adults and Adolescents, by Transmission Category and Year of Diagnosis, 1985–2009—United States and Dependent Areas



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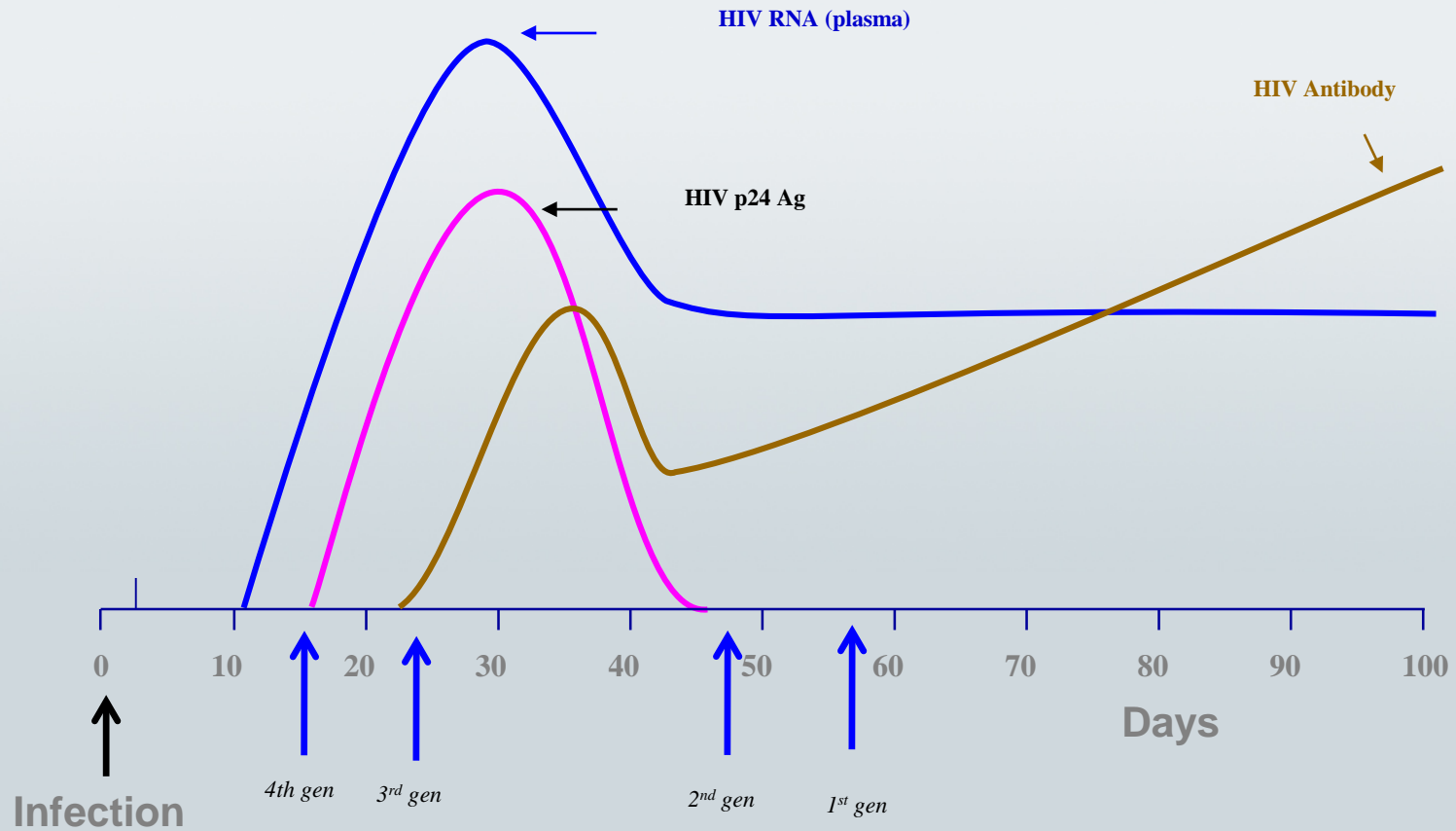


# Suggested Wholesale Price (SWP) of ART

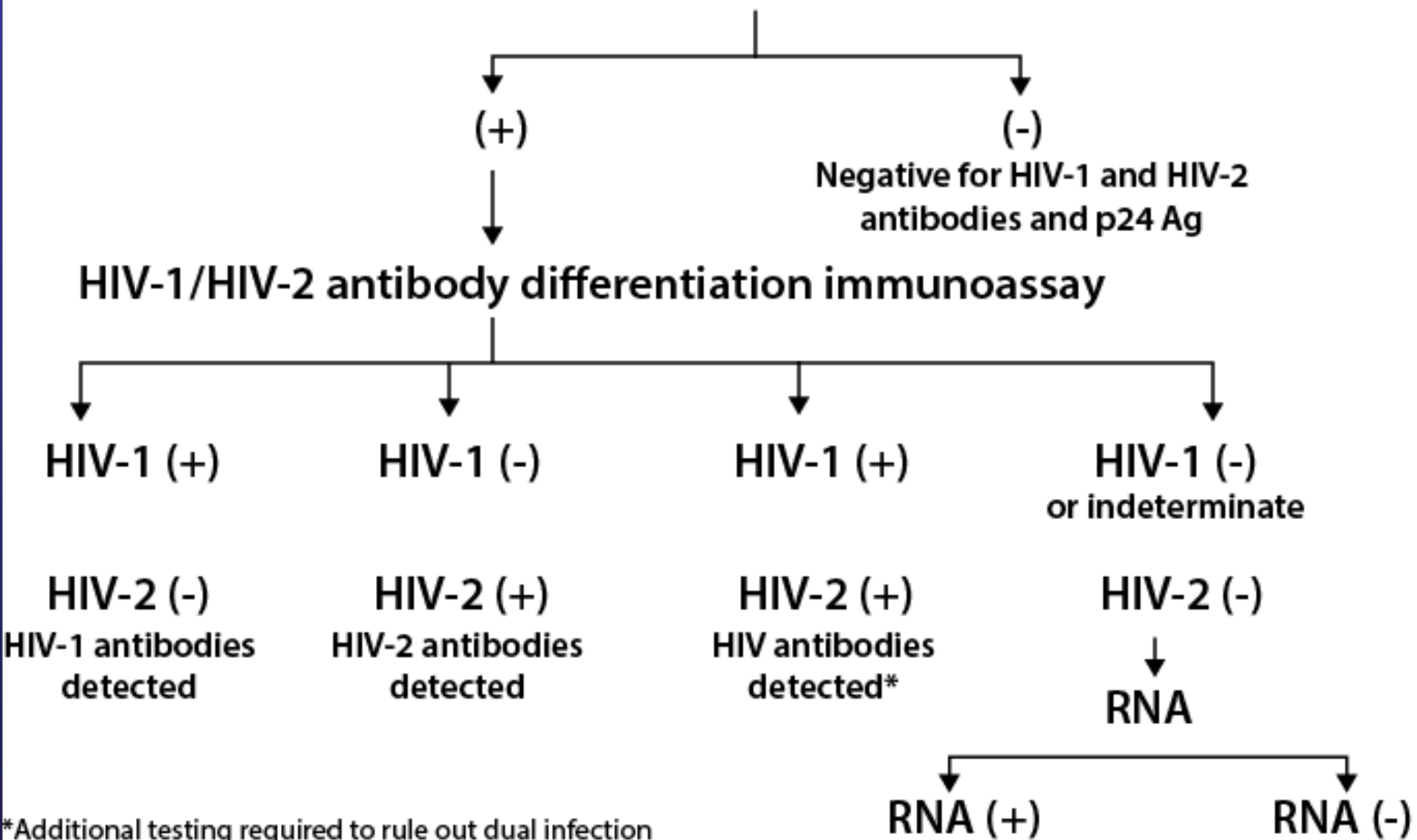
Drug or Combination	SWP of 30-day supply
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# HIV Infection and Laboratory Markers

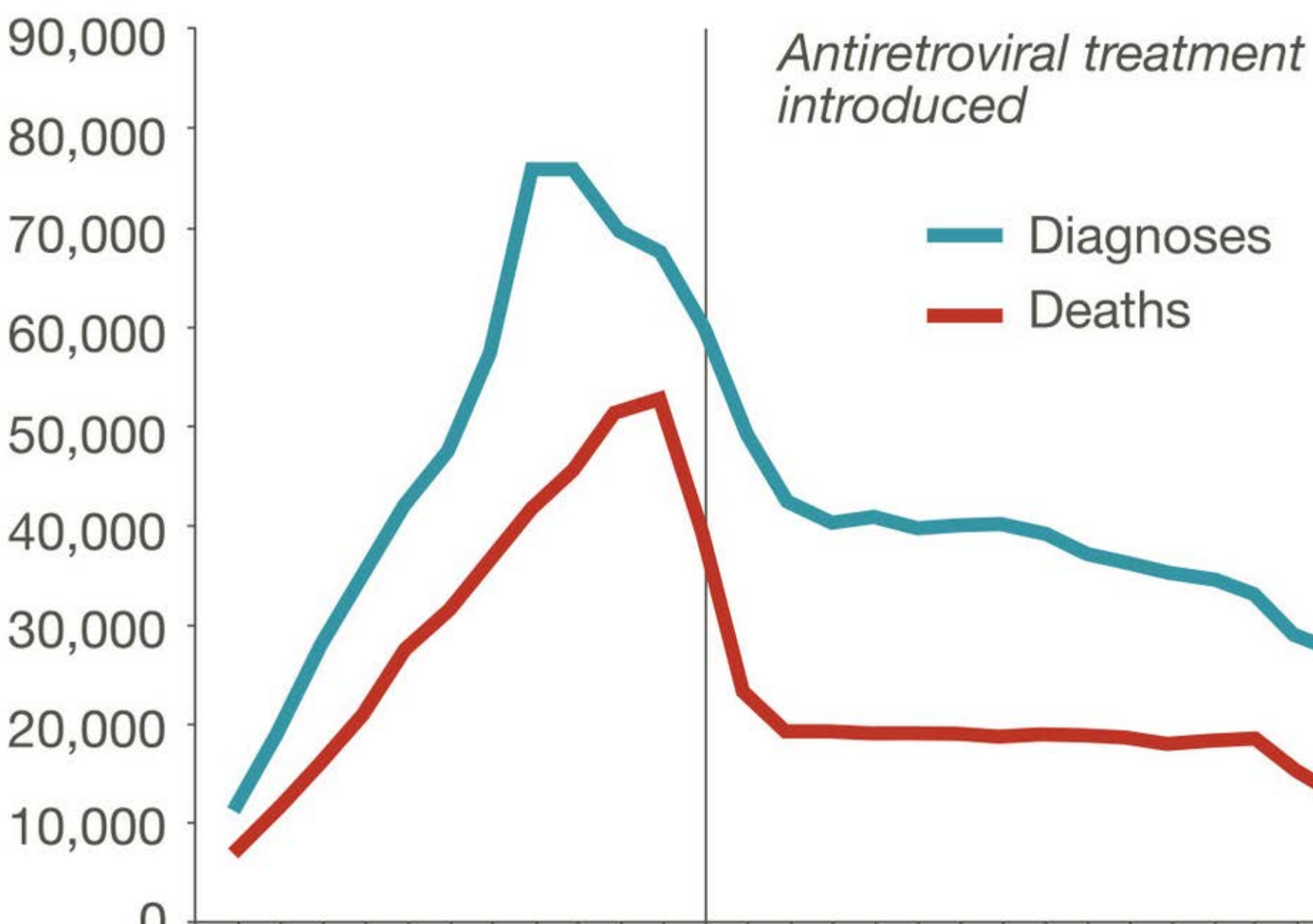


# 4th generation HIV-1/2 immunoassay



\*Additional testing required to rule out dual infection

# AIDS Diagnoses and Deaths, 1985-2012



# An Increasing Proportion of the HIV Population Is Older

Percentage of Persons in the US Living With Diagnosed HIV Infection  
Age 50 Years or Older, by Year (Estimated)<sup>1</sup>



**By 2015, 50% of people in USA with HIV will be 50 years or older<sup>2</sup>**



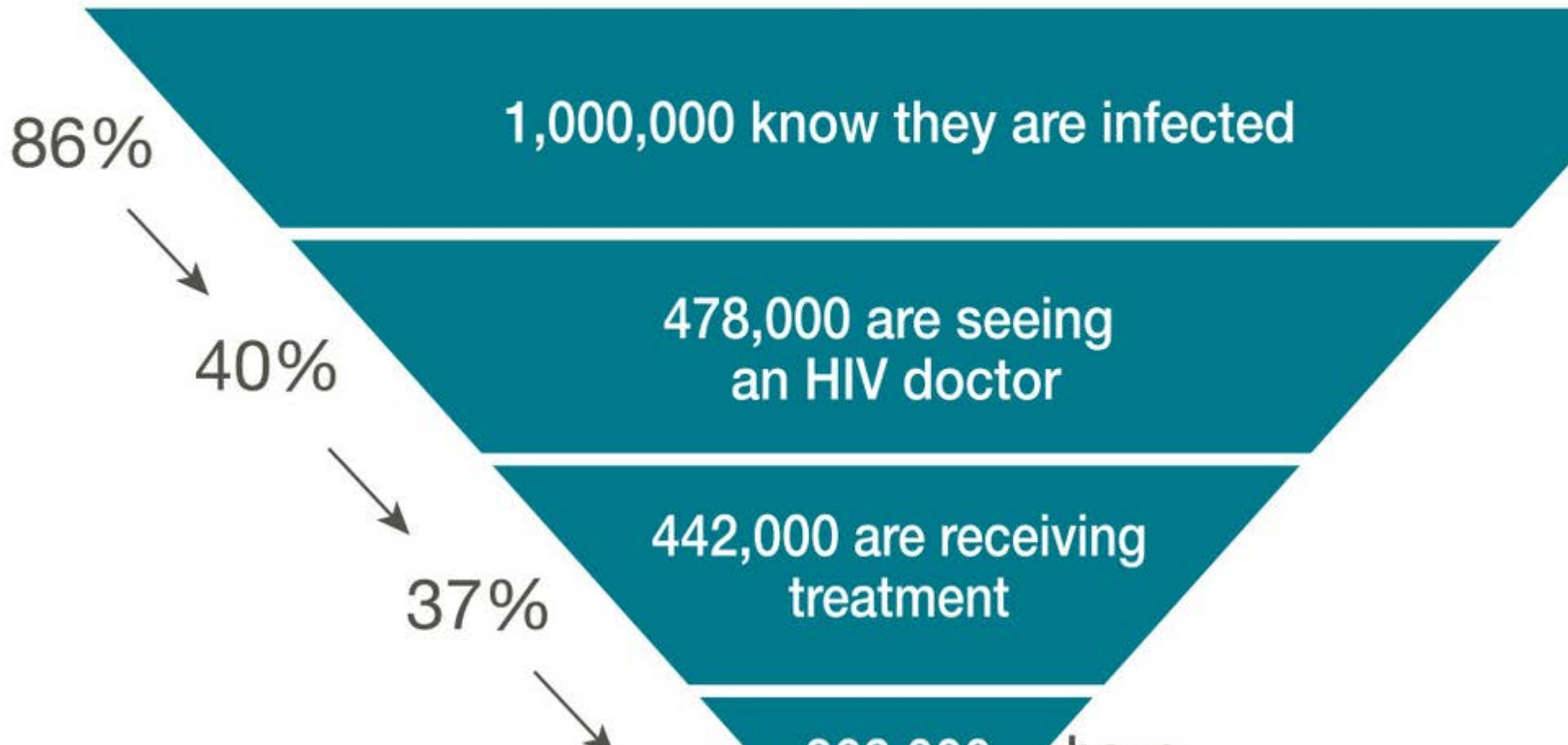
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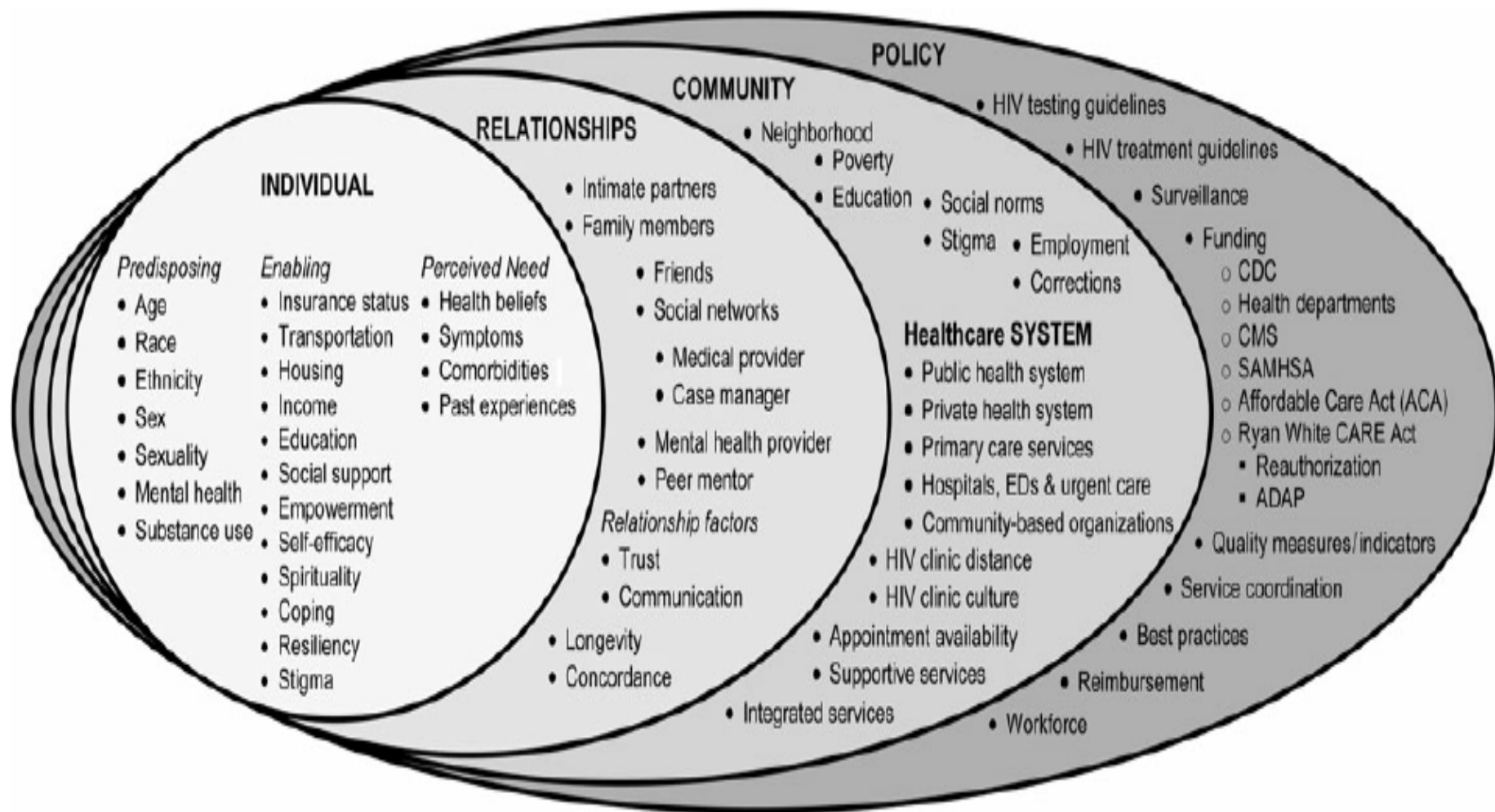
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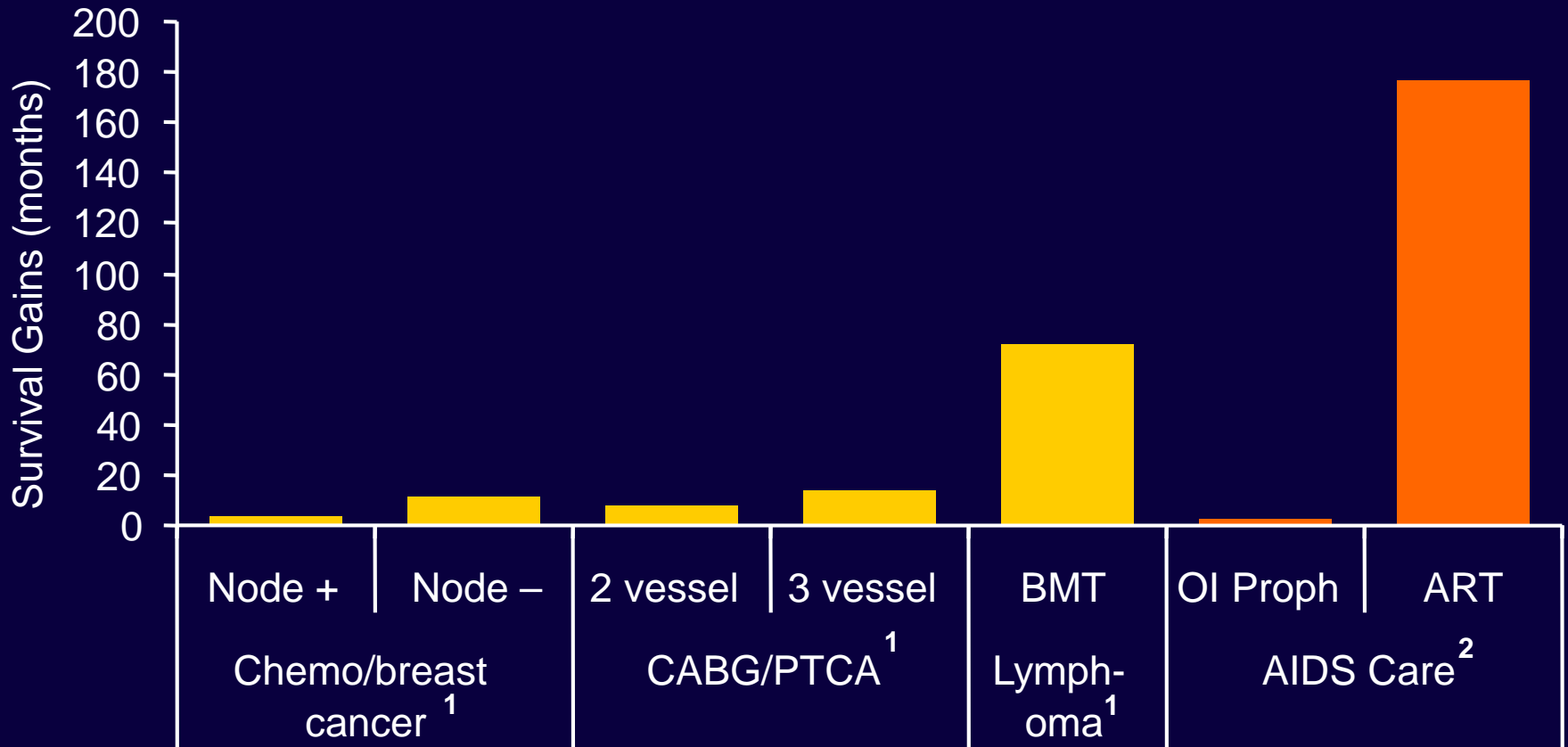
# Percentage of HIV-Infected Individuals Engaged in Selected Stages of the Continuum of HIV Care, 2011

Out of the more than 1.2 million Americans with





# Survival gains of ART compared with other disease interventions





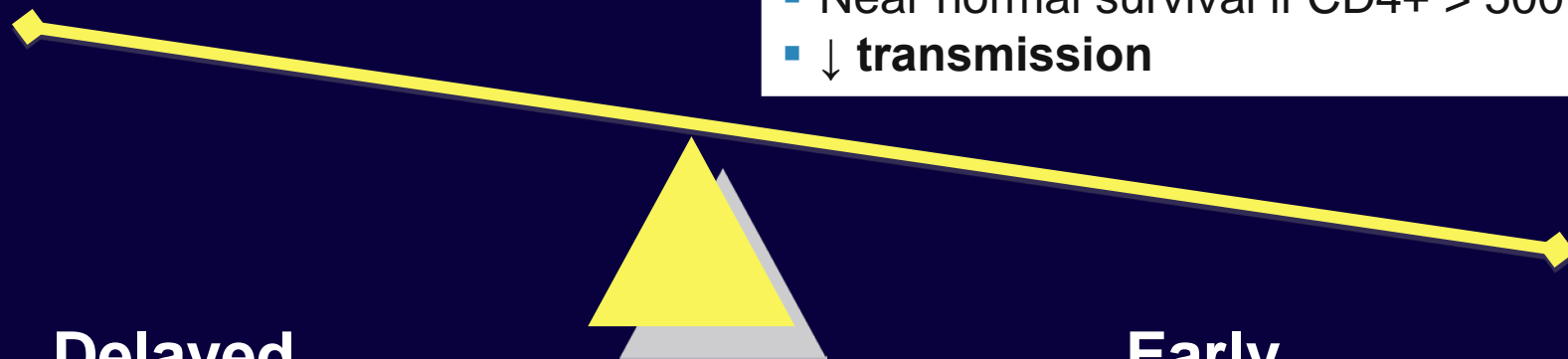
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- Drug toxicity
- Preservation of limited Rx options
- Risk of resistance (and transmission of resistant virus)

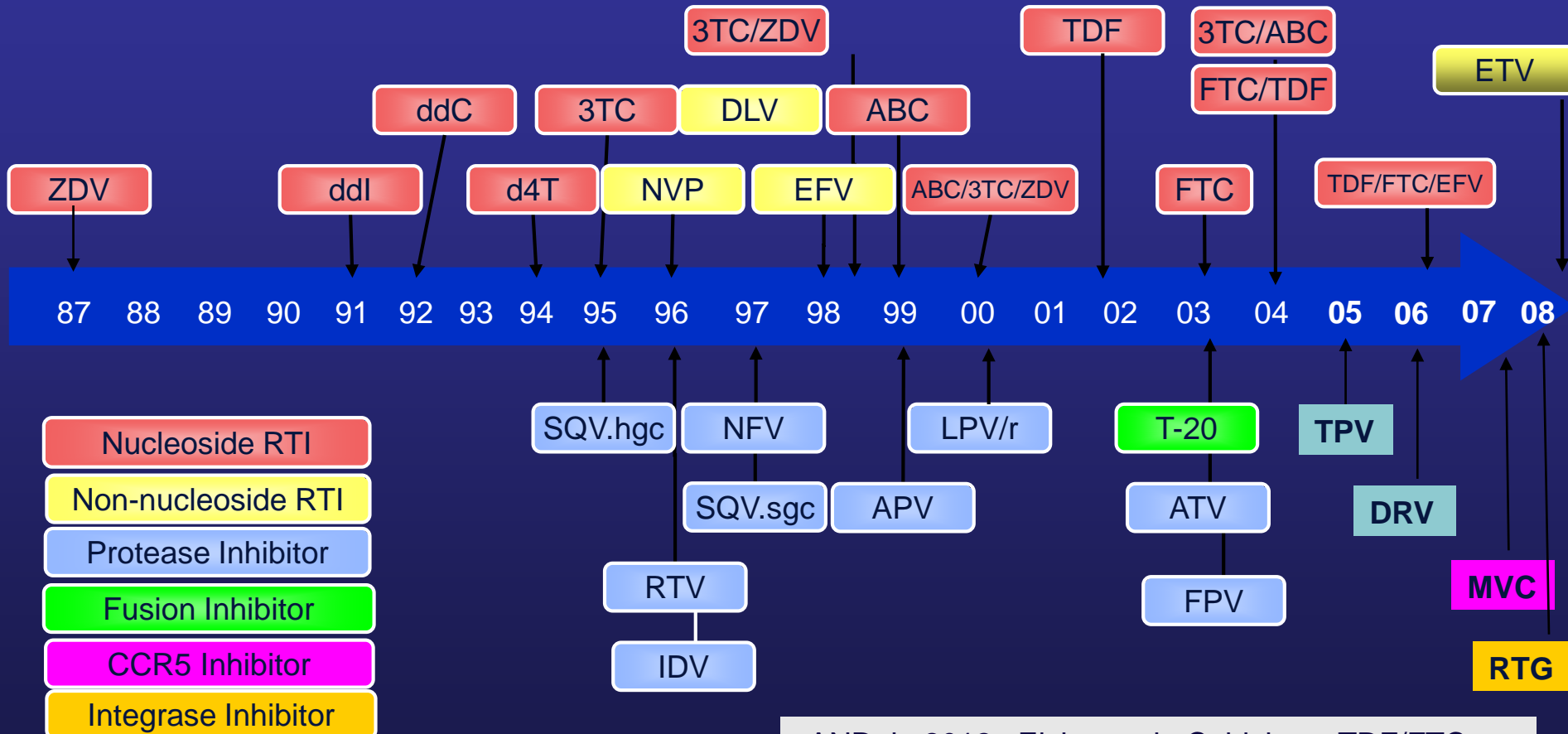
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**Delayed  
Antiretroviral Therapy**

**Early  
Antiretroviral Therapy**



# Approved Antiretroviral Agents 1987-2013

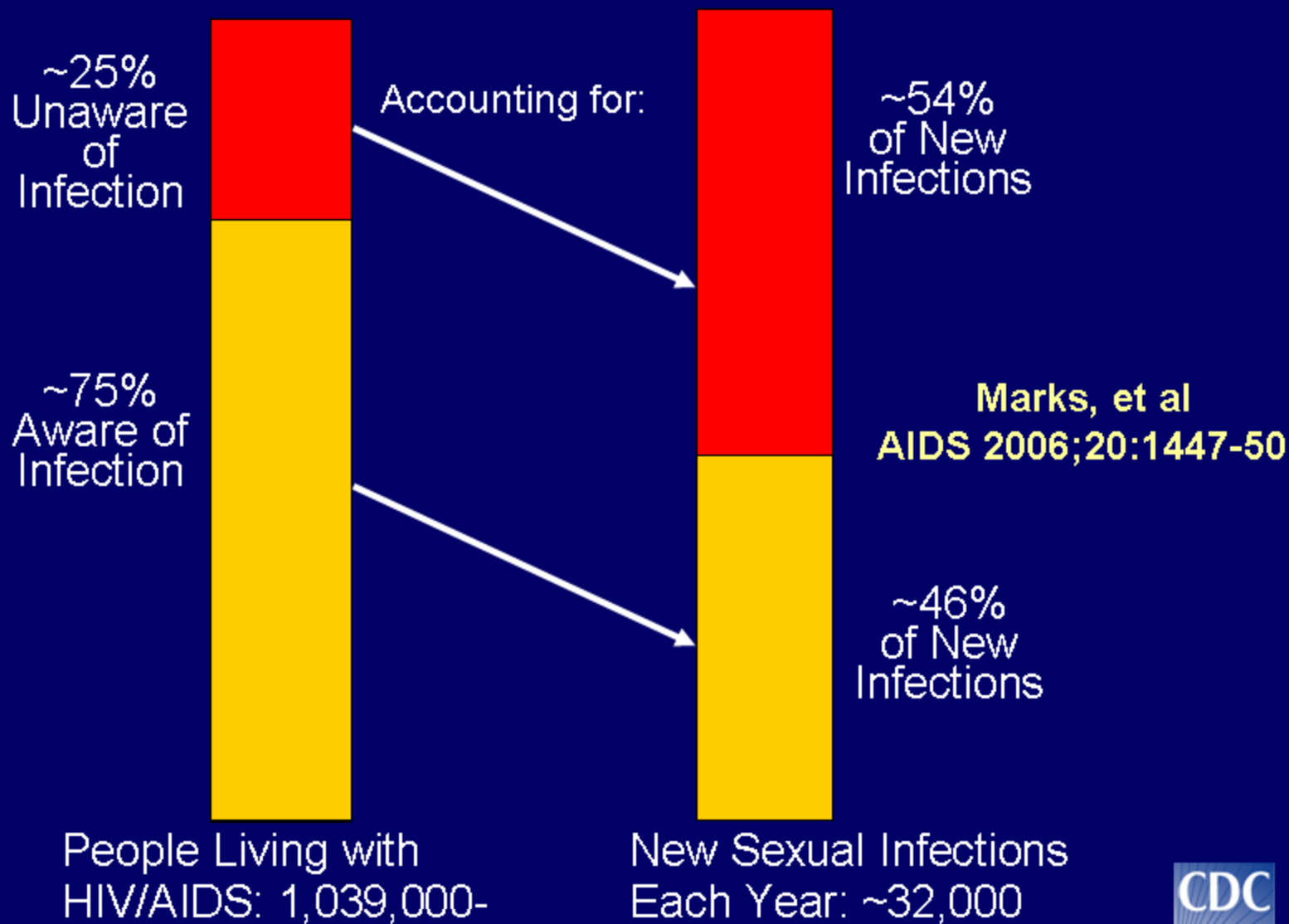


AND, in 2011: rilpivirine (RPV) and TDF/FTC/RPV fixed dose (Complera)

AND, in 2012: Elvitegravir, Cobicistat, TDF/FTC as a Single Tablet Regimen (STRIBILD)

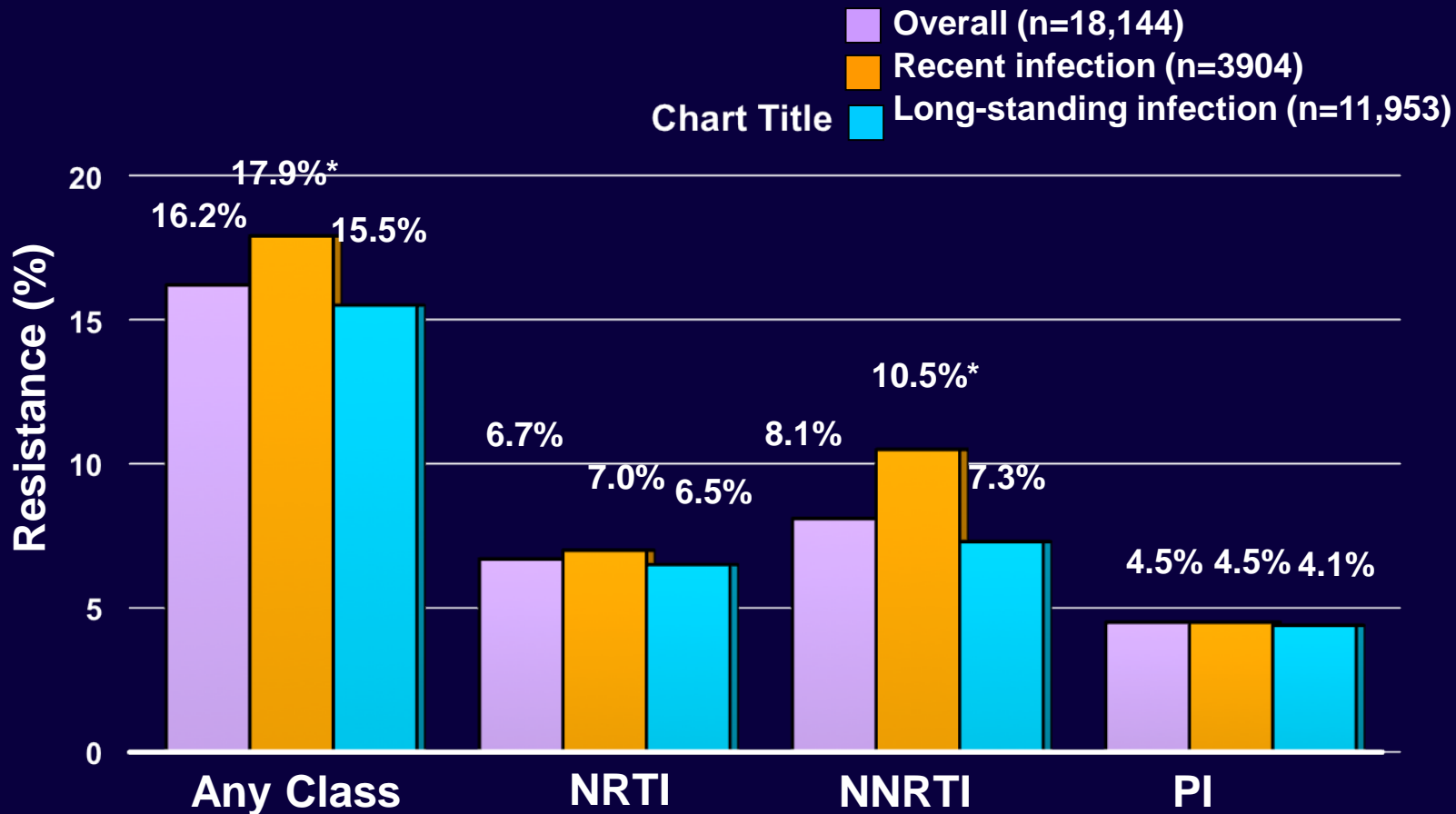
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# Awareness of Serostatus Among People with HIV and Estimates of Transmission



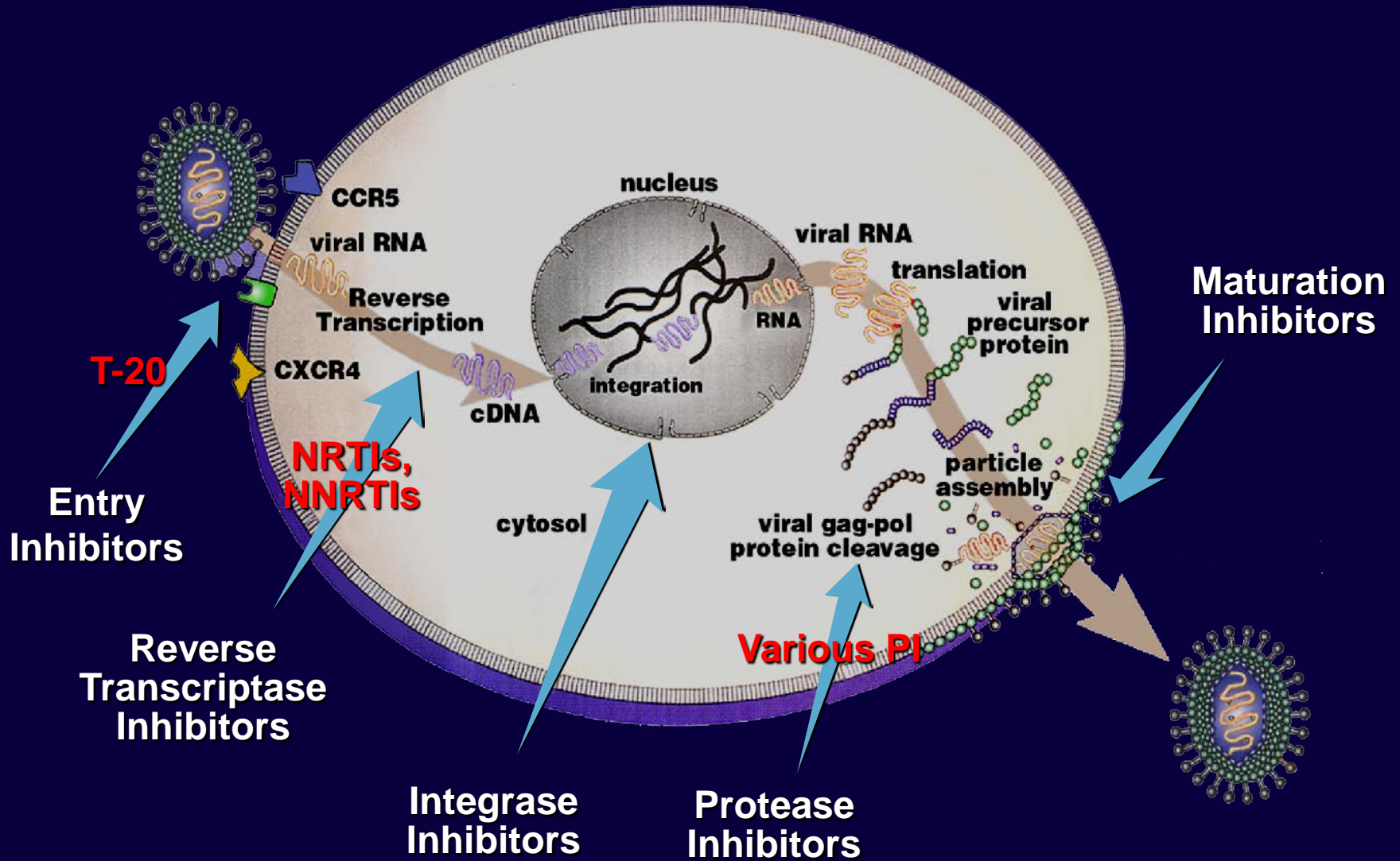
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## 10 HIV Surveillance Areas in US

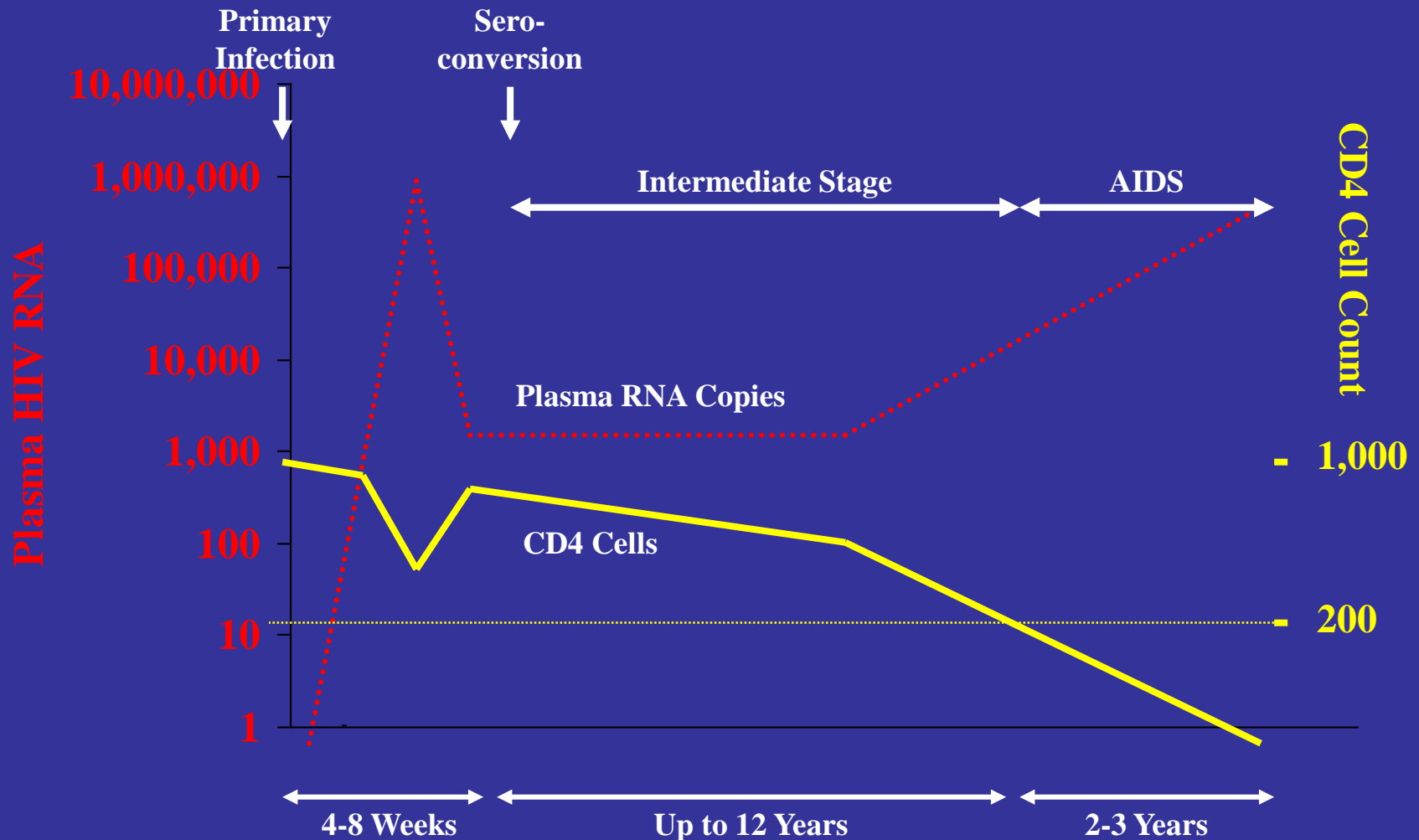


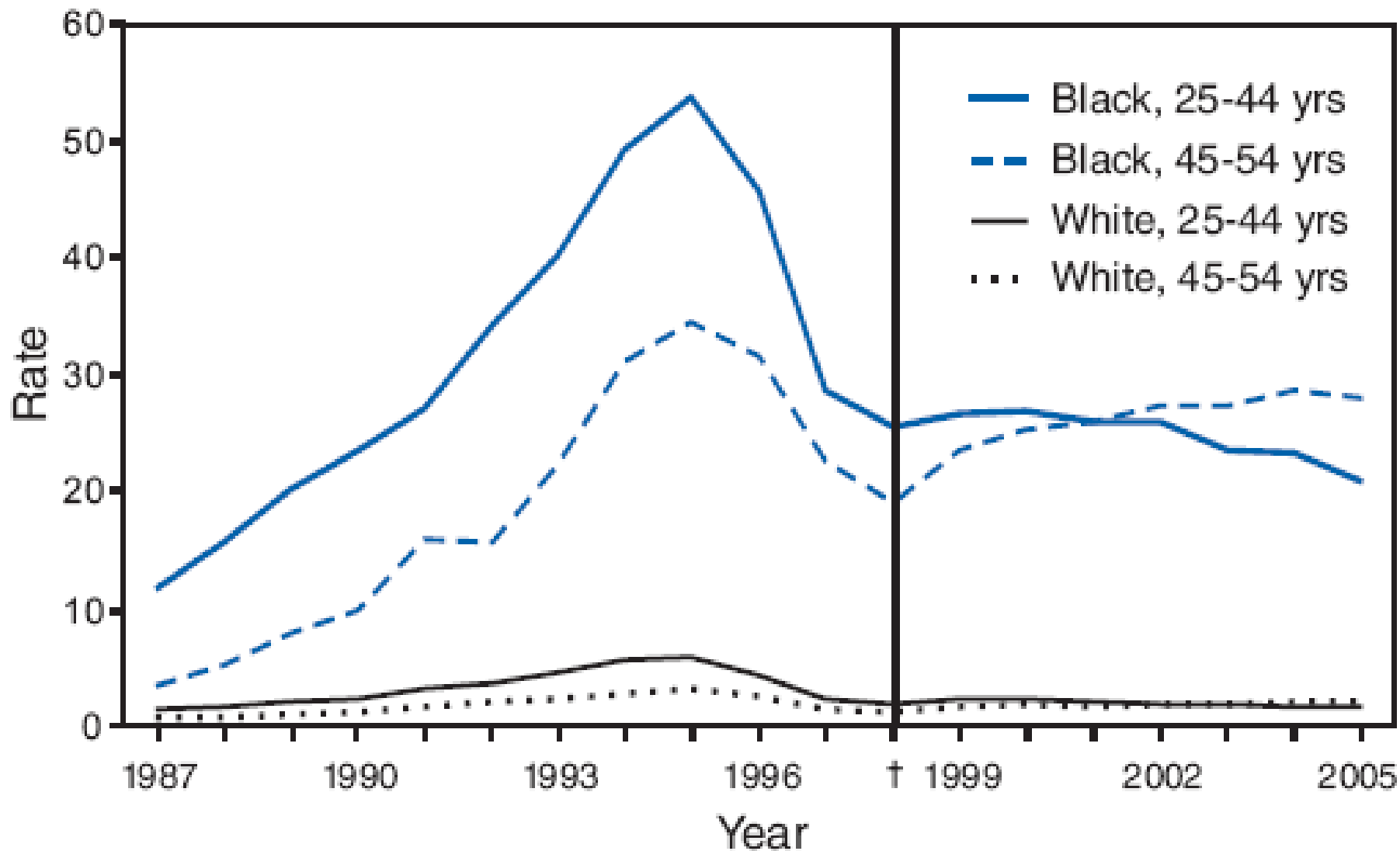


# Integrated Approaches to HIV Treatment

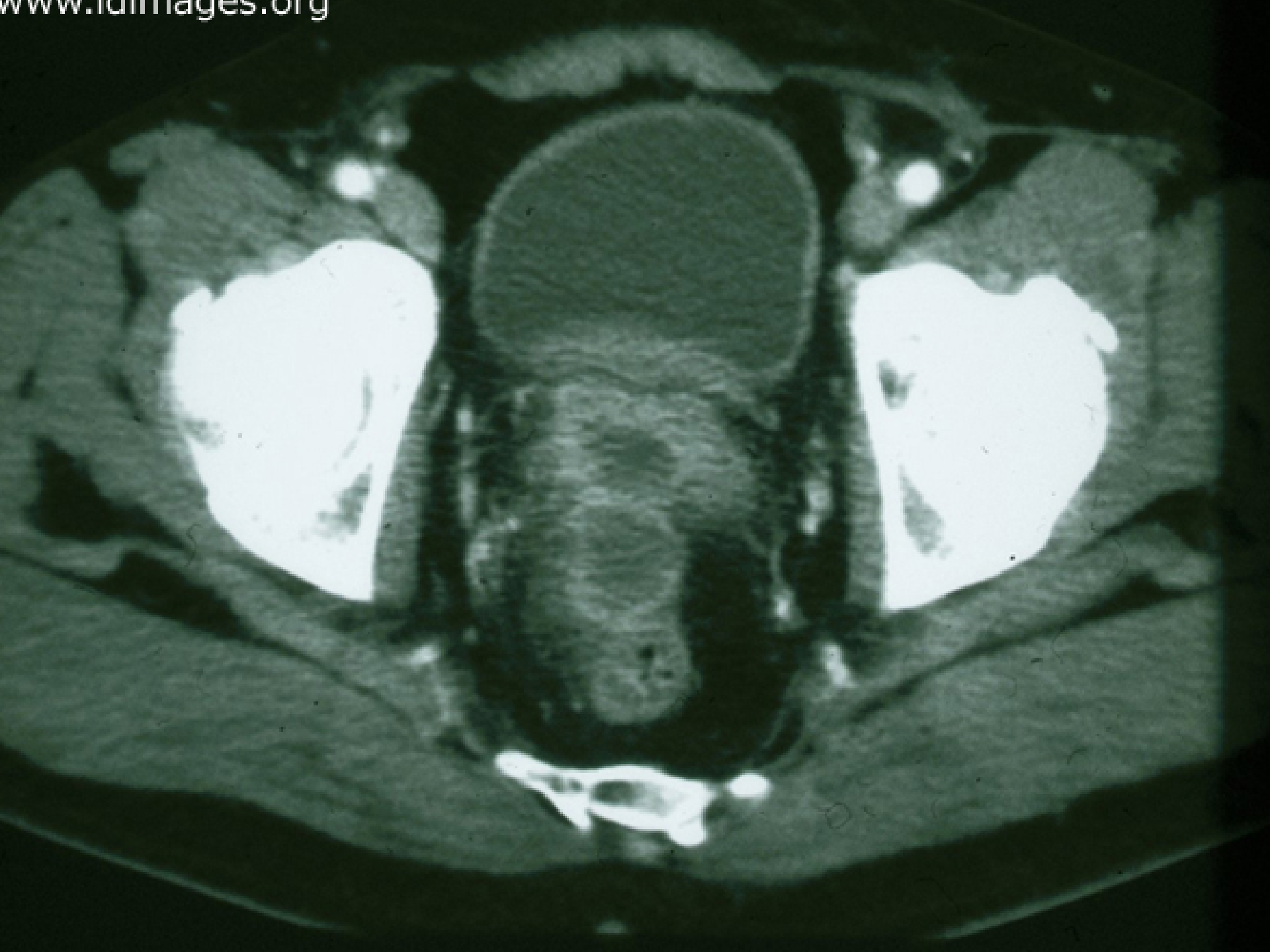


# Natural Course of HIV Infection

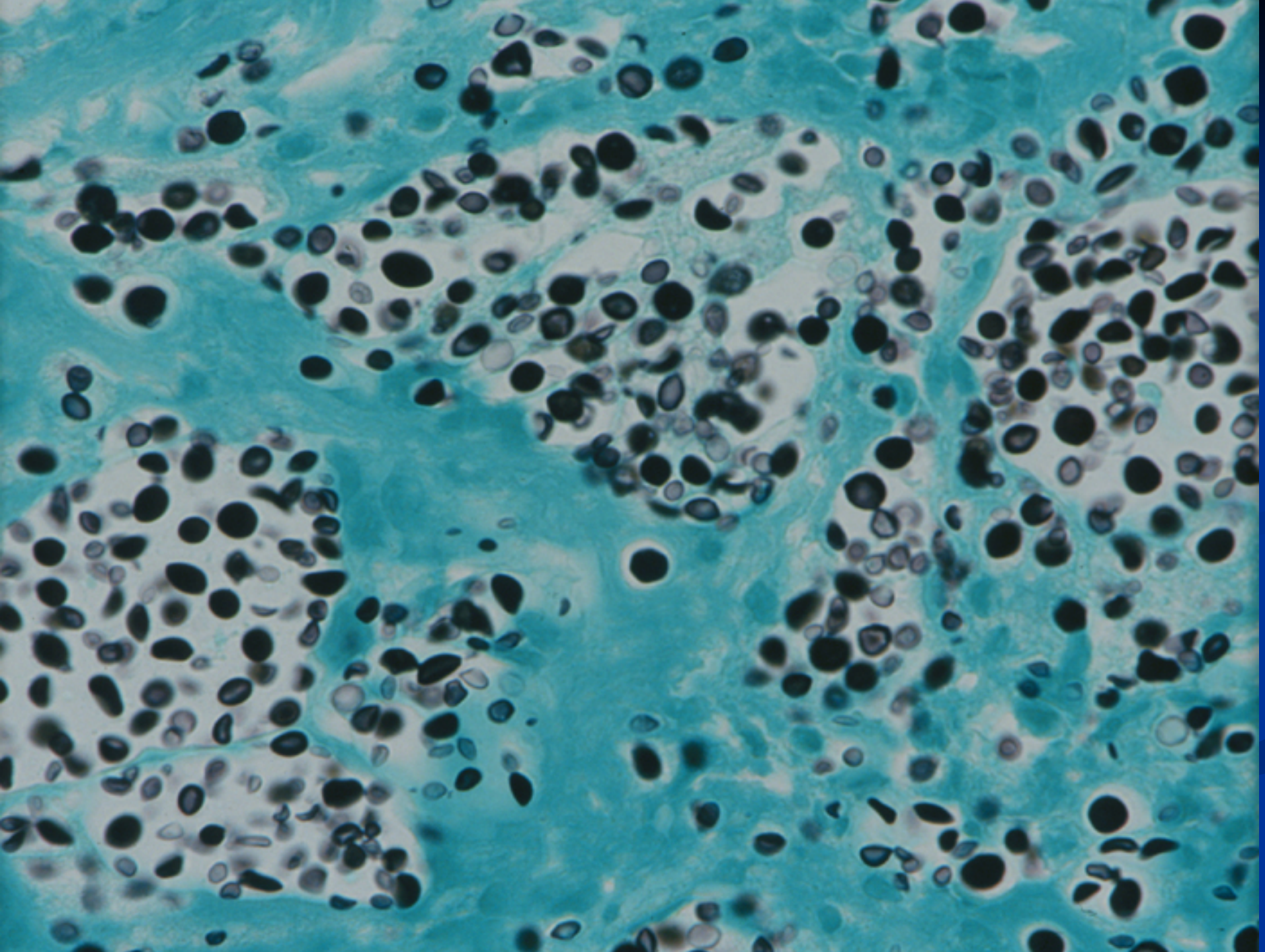




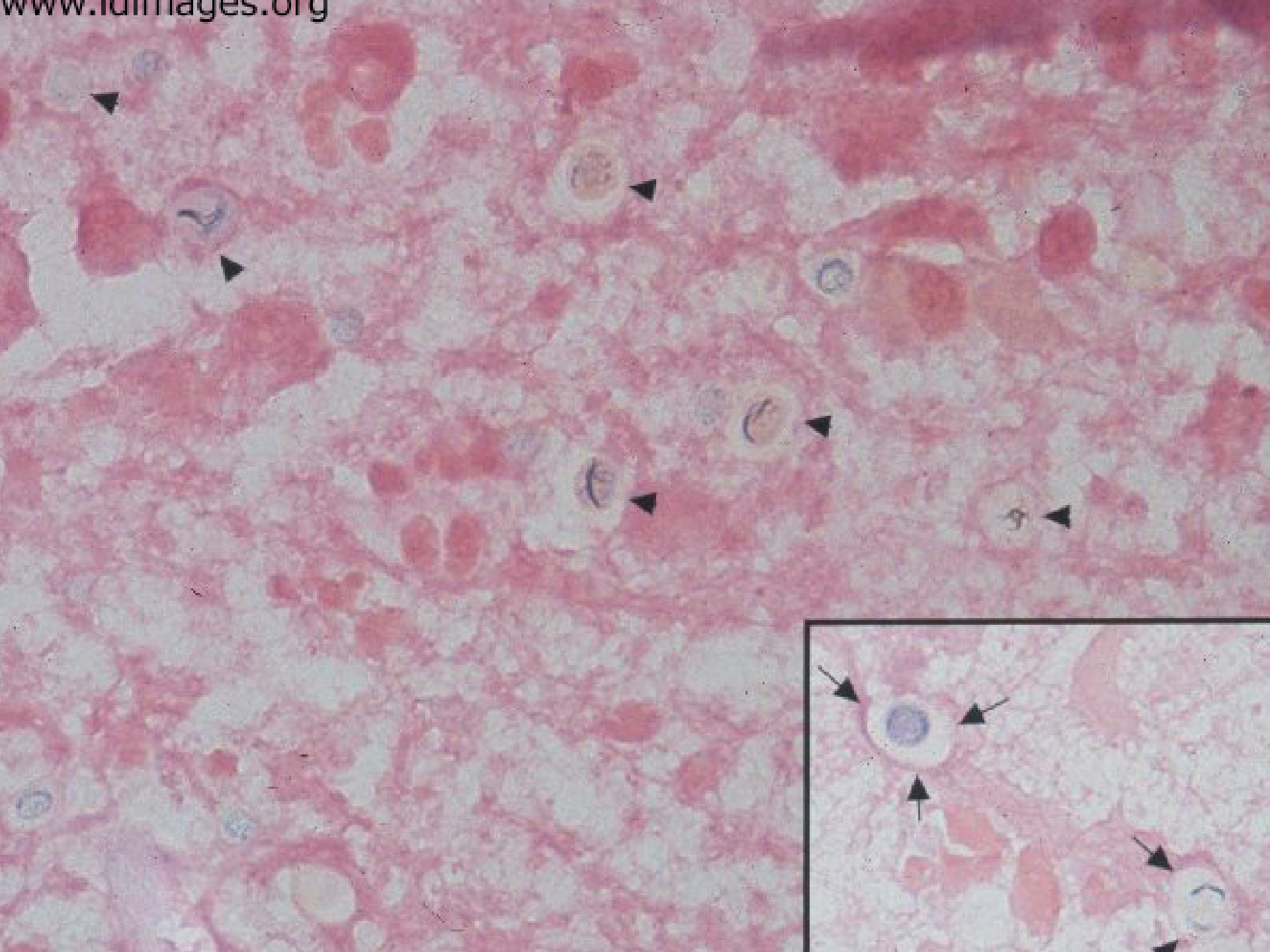
Rate per 100,000 population for HIV disease as **underlying cause of death**.  
 For **women** by **Race and Age Group** USA 1987--2005













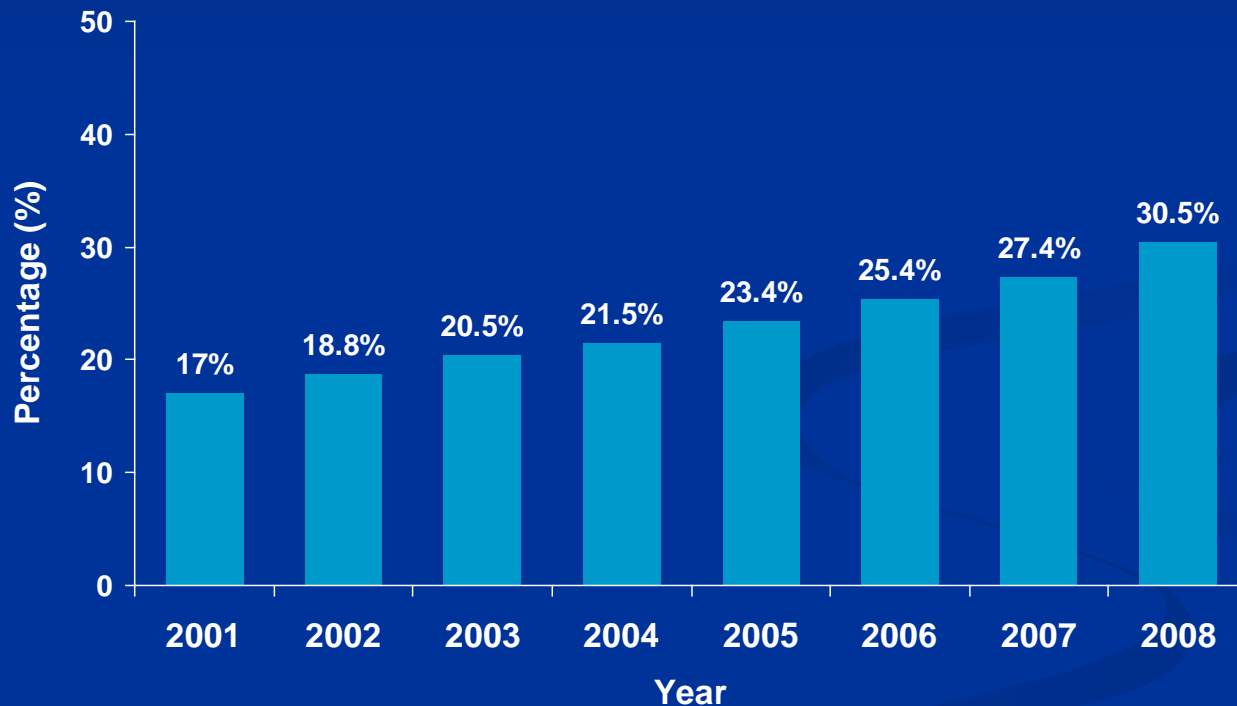


## Fruit bats for sale in Cameroon market



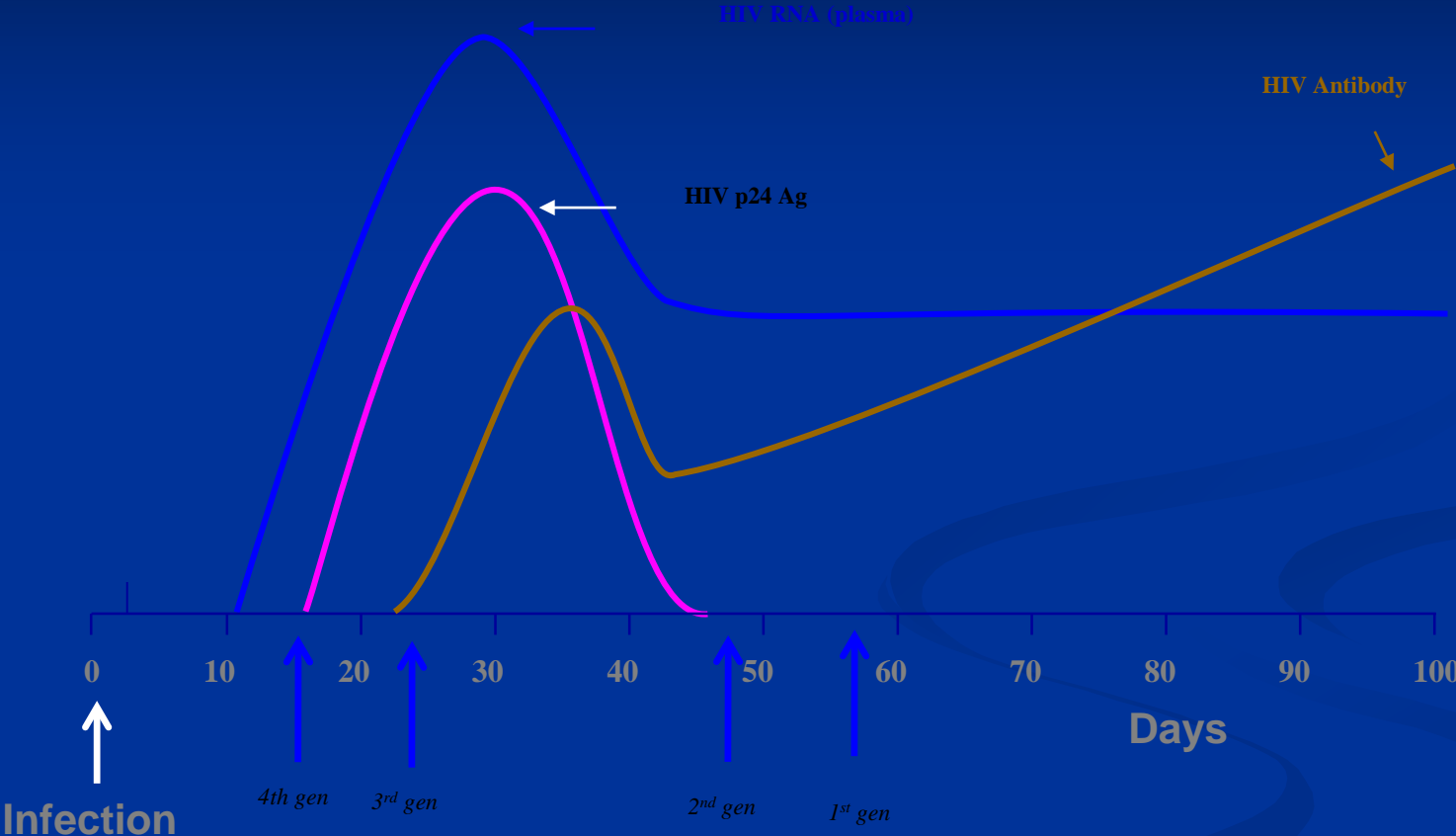
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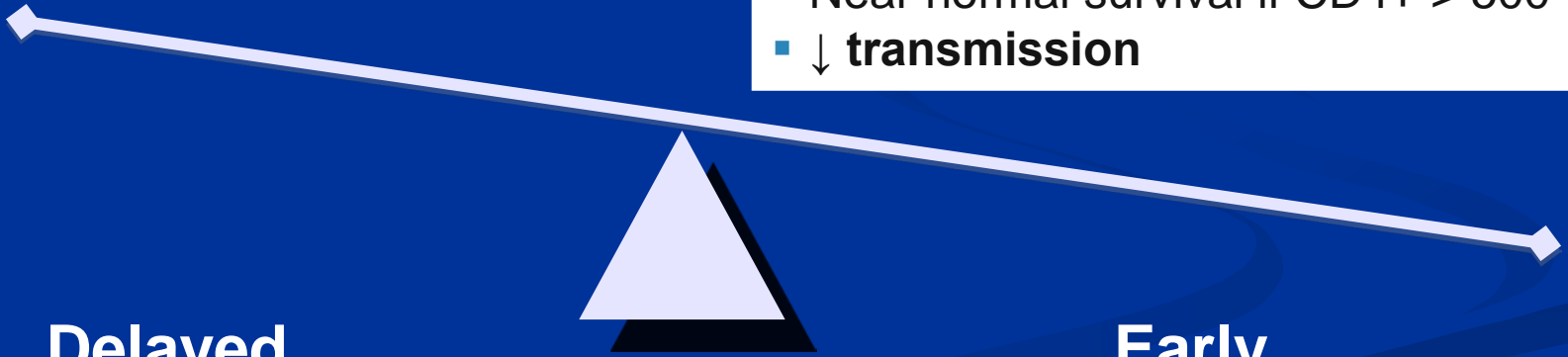
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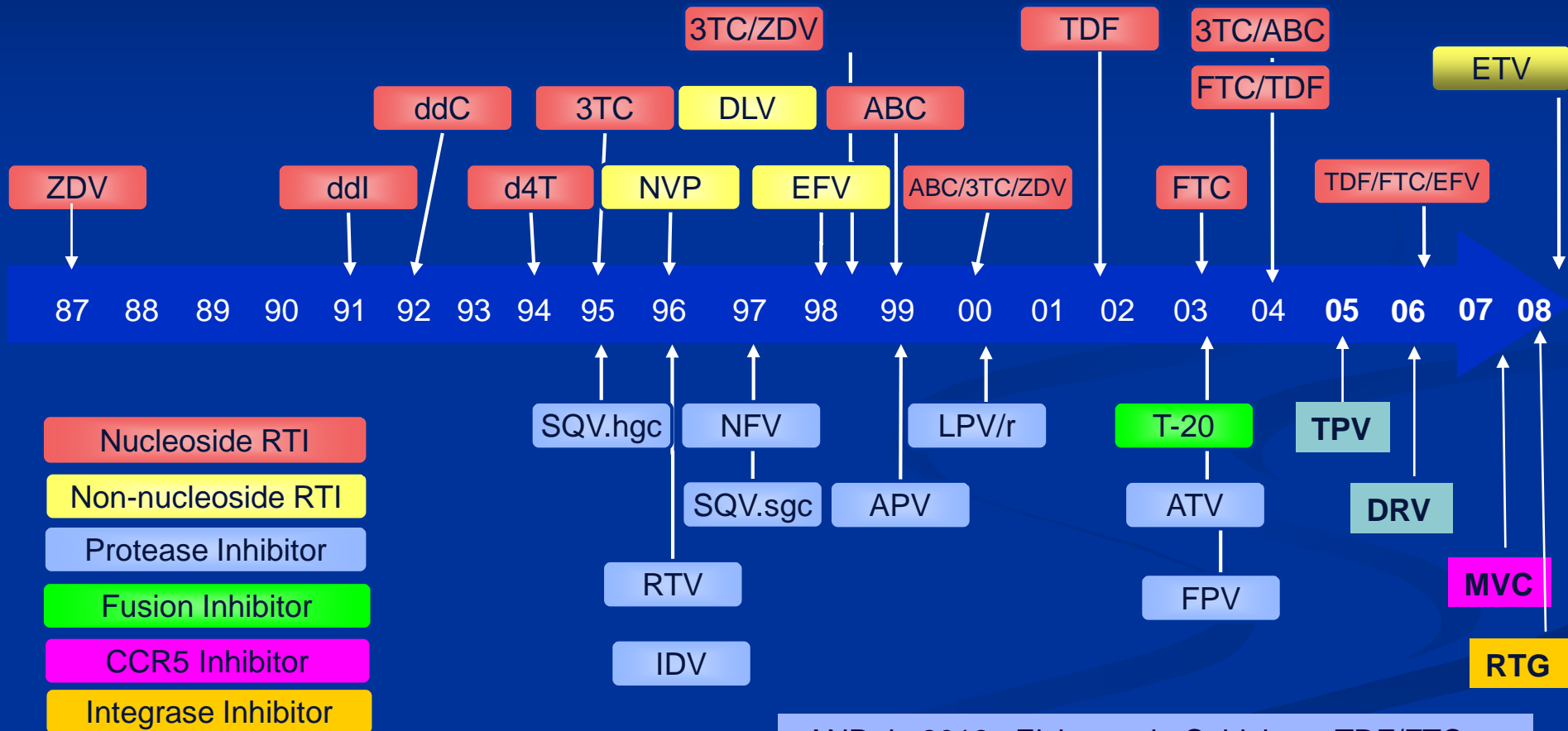
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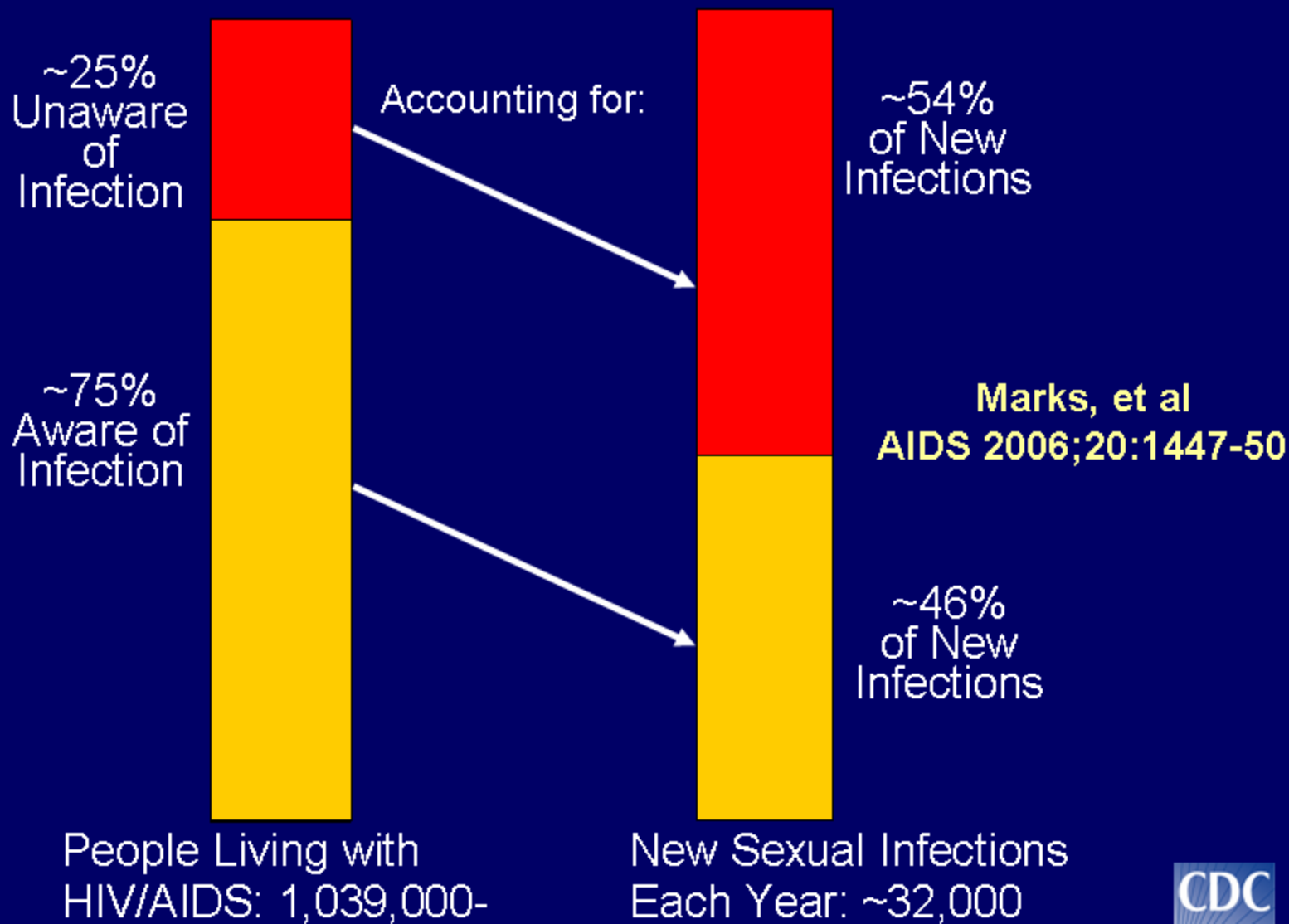


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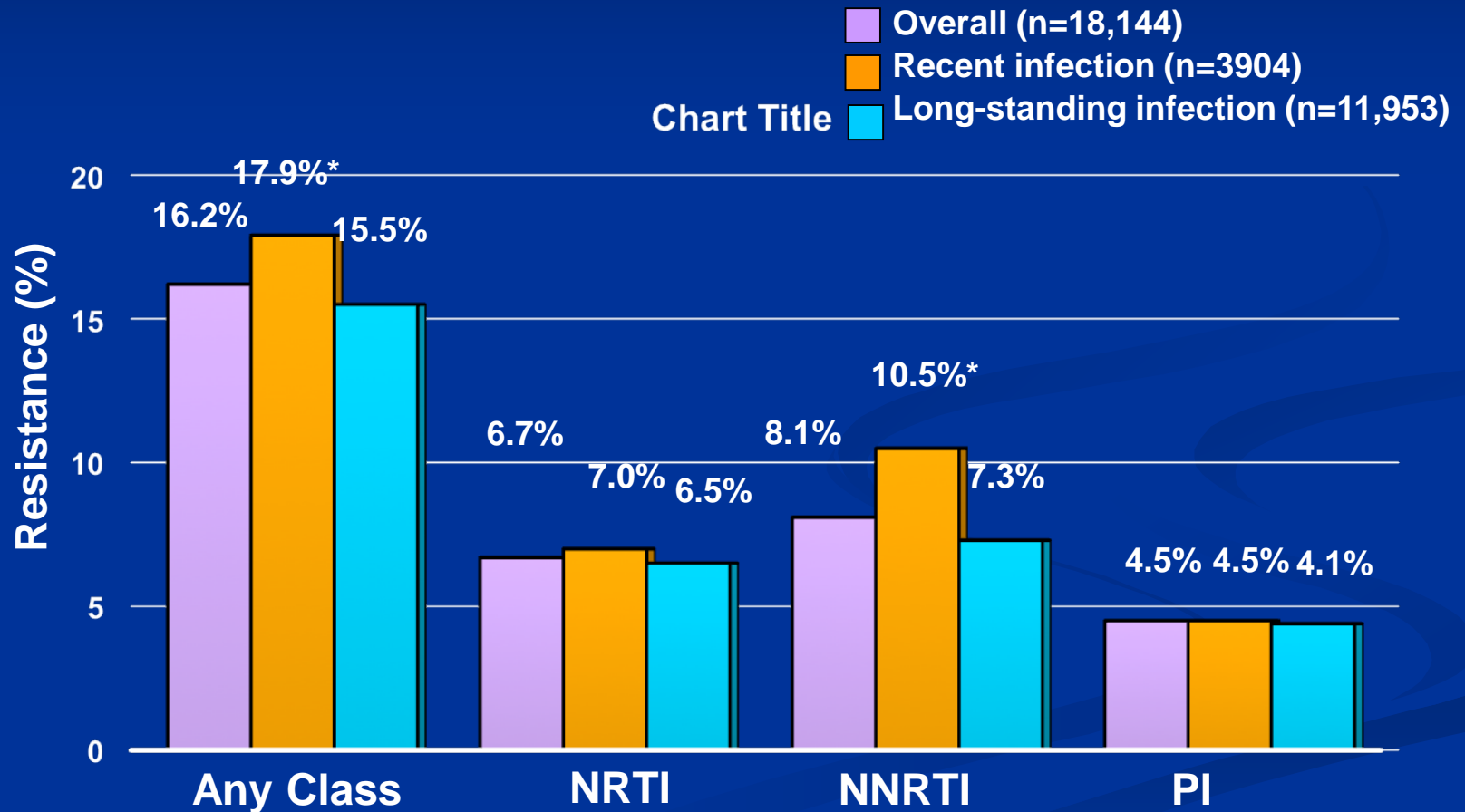
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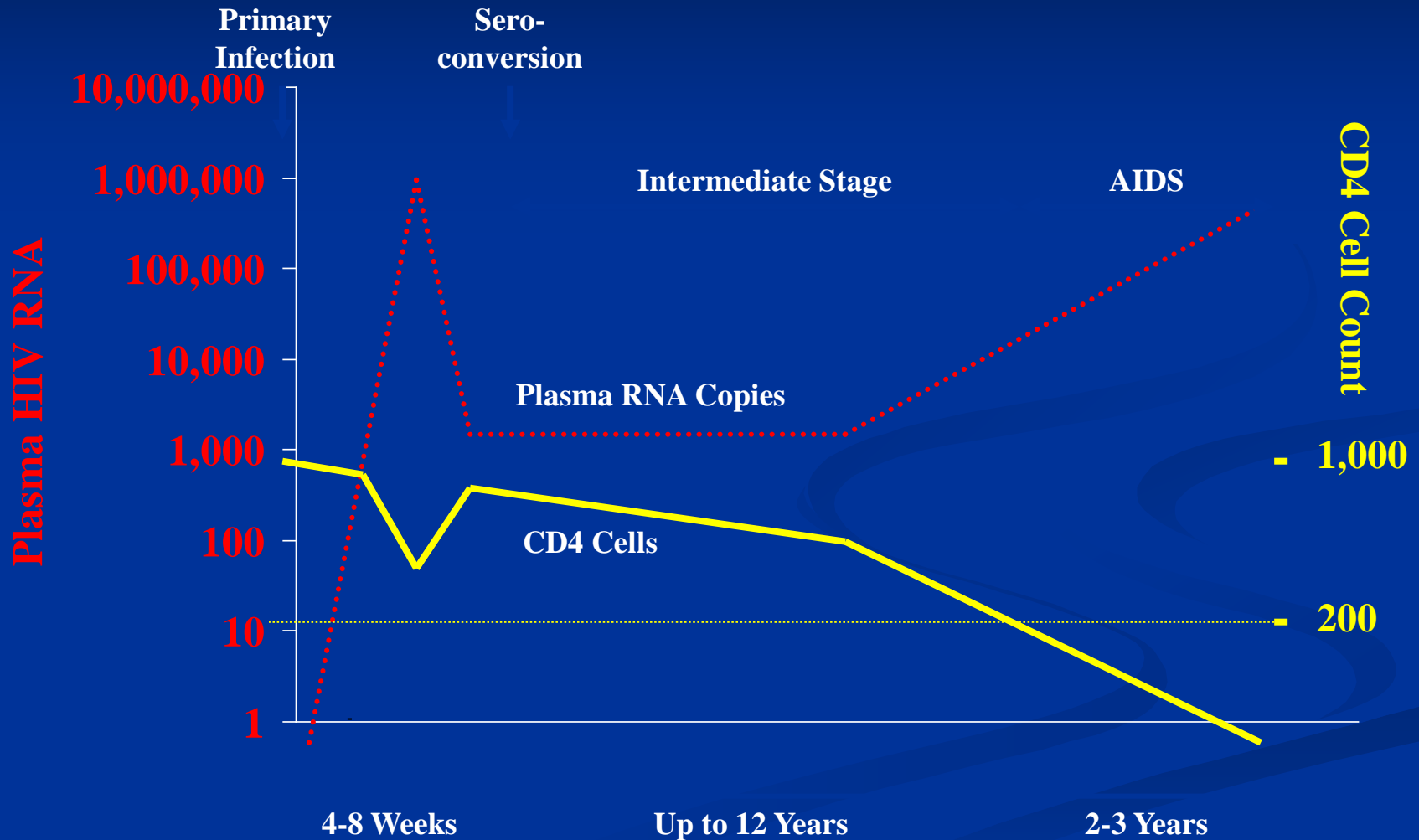


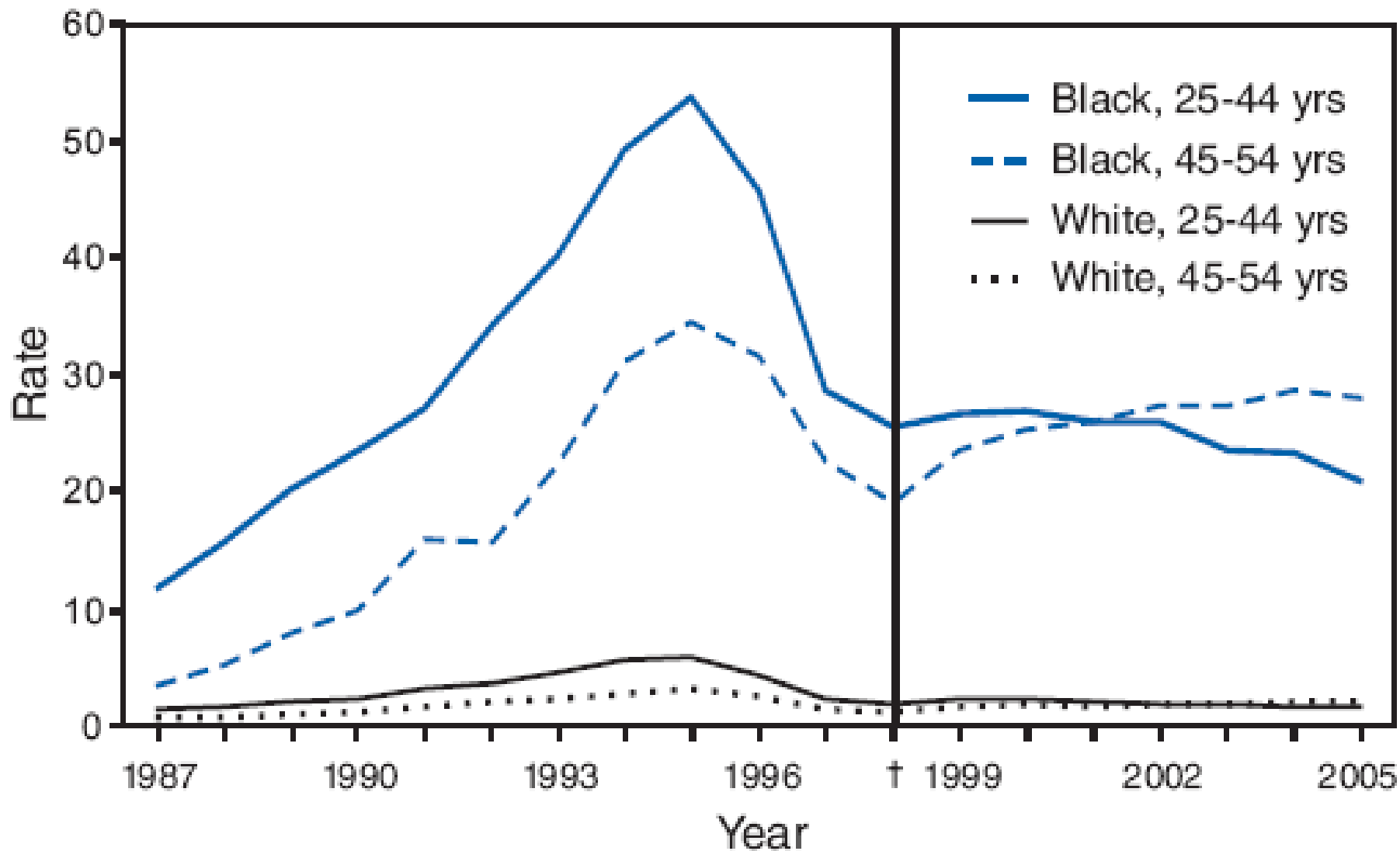
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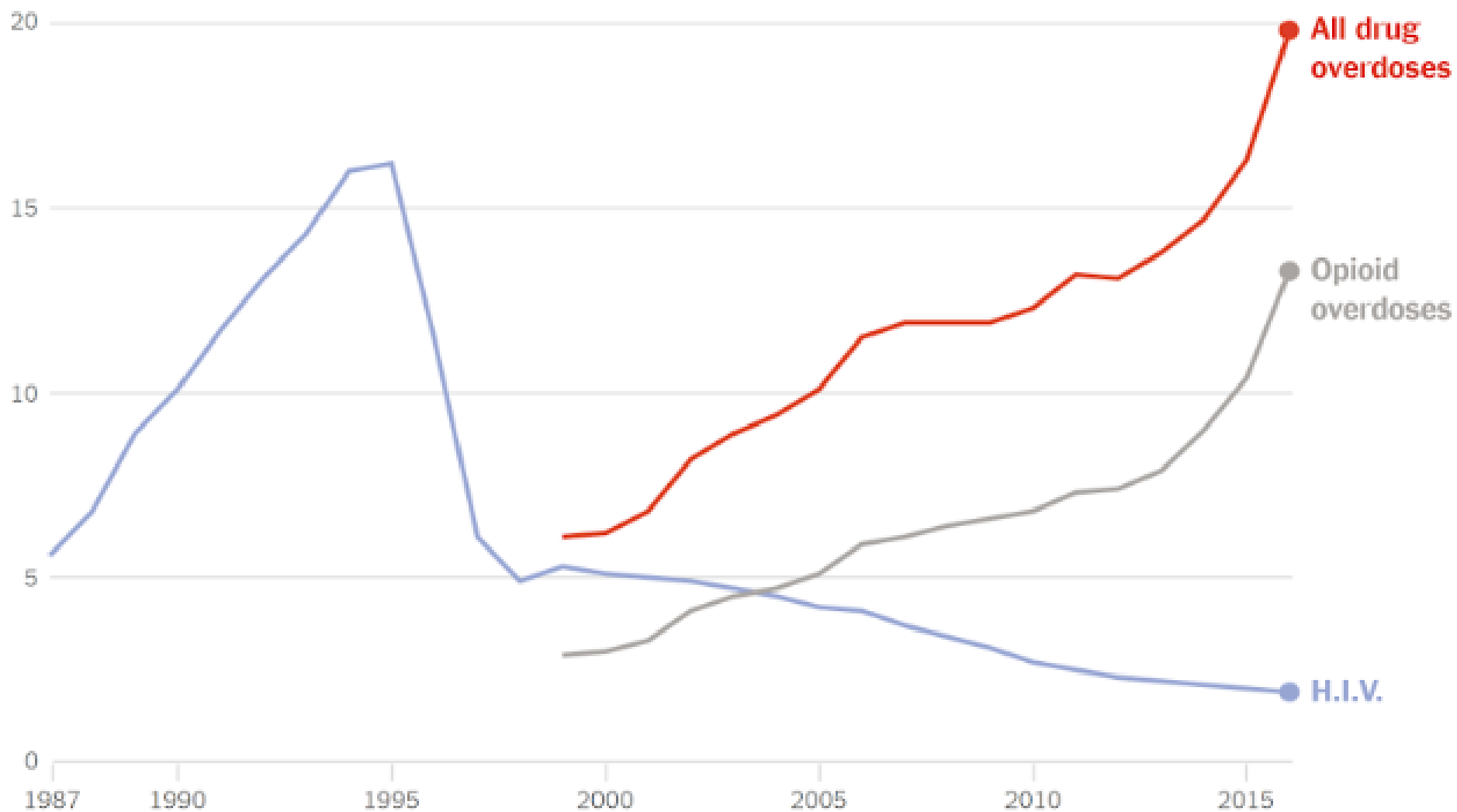




Rate per 100,000 population for HIV disease as **underlying cause of death**.  
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# Lost Lives

Deaths in the U.S. per 100,000 people



Note: Drug overdose data available since 1999. Source: Centers for Disease Control and Prevention

# HIV Screening in Older Adults

## Underdiagnosed population?

- HCPs are less likely to offer HIV testing to older adults<sup>1</sup>
  - Screening rate 25.4%<sup>2</sup>
- It is estimated that nearly 1 in 5 HIV-positive people over the age of 50 have not received a diagnosis of HIV infection<sup>1</sup>
  - In many older people, HIV infection is diagnosed only when infection is advanced
- **CDC recommendations: Routine screening specified in adults up to age 64<sup>3</sup>**
  - Persons aged 64 and over should be counseled to receive HIV testing if they have risk factors for HIV infection
  - Making testing routine in older patients can help open discussions between HCPs and patients
- Cost-effectiveness of screening in patients age 55 to 75 years compares favorably with that of other accepted health care interventions<sup>4</sup>
  - In the US population, 1-time routine screening of patients age 55 to 64 years could save a total of more than 120,000 years of life among nearly 170,000 people

CDC = Centers for Disease Control and Prevention; HCP = health care provider.

1. Kirk JB et al. *Am Geriatr Soc*. 2009;57:2129–2138. 2. Oluwatoyosi, et al. *PLOS One*. 2012;7:8. 3. HIV/AIDS Among Persons Aged 50 and Older. Centers for Disease Control and Prevention Web site. <http://www.cdc.gov/hiv/topics/over50/resources/factsheets/pdf/over50.pdf> Accessed May 13, 2011. 4. Sanders GD et al. *Ann Intern Med*. 2008;148:889–903.



# Why is he smiling?





# The Benefit of ARVs



# Summary

- Despite optimal ART, HIV is associated with an increase in chronic diseases associated with aging
- Immune activation/inflammation persist despite ART and predict many of these morbidities
- Targeted interventions directed at the underlying causes of inflammation may hold promise
- Investigations regarding MT toxicity and effect on physical decline hold promise

# Integrase Inhibitors in DHHS Guidelines

	Preferred Regimens	Alternative Regimens
NNRTI	<ul style="list-style-type: none"> <li>▪ EFV/TDF/FTC</li> </ul>	<ul style="list-style-type: none"> <li>▪ EFV + ABC/3TC</li> <li>▪ RPV/TDF/FTC or RPV + ABC/3TC</li> </ul>
Boosted PI	<ul style="list-style-type: none"> <li>▪ ATV/RTV + TDF/FTC</li> <li>▪ DRV/RTV + TDF/FTC</li> </ul>	<ul style="list-style-type: none"> <li>▪ ATV/RTV + ABC/3TC</li> <li>▪ DRV/RTV + ABC/3TC</li> <li>▪ FPV/RTV + (TDF/FTC or ABC/3TC)</li> <li>▪ LPV/RTV + (TDF/FTC or ABC/3TC)</li> </ul>
INSTI	<ul style="list-style-type: none"> <li>▪ RAL + TDF/FTC</li> <li>▪ EVG/COBI/TDF/FTC</li> <li>▪ DTG + ABC/3TC</li> <li>▪ DTG + TDF/FTC</li> </ul>	<ul style="list-style-type: none"> <li>▪ RAL + ABC/3TC</li> </ul>

- All 3 integrase inhibitors are now part of preferred first-line regimens

# Evolution of Easier & More Compact Therapy for HIV Infection

- Easier, more potent, and less toxic therapy





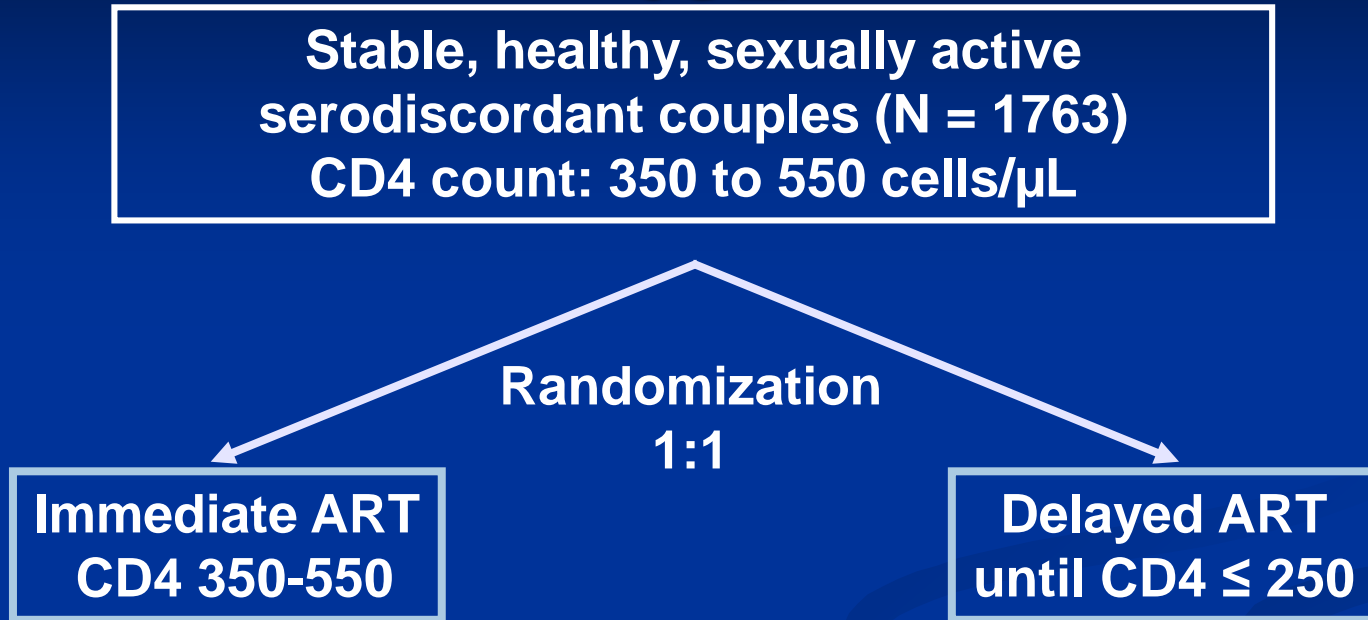
# When to Start Antiretroviral Therapy (1998-2013)

CD4 Cell Count, cells/ $\mu$ L	1998	2001	2006	2008	2009	2013
> 500	Offer if VL > 20,000	Offer if VL > 55,000	Consider if VL $\geq$ 100,000	Consider in certain groups	Consider	Treat
350-500	Offer if VL > 20,000	Consider if VL > 55,000	Consider if VL $\geq$ 100,000	Consider in certain groups	Treat	Treat
200-350	Offer if VL > 20,000	Offer, but controversy exists	Offer after discussion with patient	Treat	Treat	Treat
< 200 or symptomatic disease	Treat	Treat	Treat	Treat	Treat	Treat

**DHHS 2013: Antiretroviral therapy (ART) recommended for all patients with HIV infection regardless of their CD4 cell count or HIV viral load to reduce the risk for disease progression and prevent HIV transmission.**

# Treatment as Prevention: HPTN

## 052



- **Primary transmission end point:** virally linked transmission events
- **Results:** 39 total HIV transmission events (28 linked events)
  - Immediate ART: 1 linked transmission
  - Delayed ART: 27 linked transmissions
  - **96% reduction in risk of HIV transmission ( $P < .001$ )**

# Reasons to Delay ART Initiation

- Effects of long-term exposure to ART still unknown
  - Some studies point to potential for emergent cardiovascular, renal, and bone abnormalities associated with ART use
- Patients who initiate ART must be ready to adhere to lifelong treatment
  - Treatment non-adherence may result in virologic failure with emergent drug resistance
  - If possible, address factors affecting adherence prior to treatment initiation
    - Mental health issues
    - Substance/alcohol use
    - Other socioeconomic concerns

# Work Towards a Cure

The New York Times

SCIENCE TIMES

TUESDAY, NOVEMBER 29, 2011

## New Hope of a Cure for H.I.V.

BY ANDREW POLLACK  
NOVEMBER 29, 2011



**VIRUS-FREE** Timothy Brown of San Francisco had two bone-marrow transplants to treat leukemia, and H.I.V. can no longer be detected in his body. (Heidi Schumann for The New York Times)

### Procedure and Events

- Ablative chemotherapy
- Total body XRT
- Graft vs. host
- Transplant with CCR5 $\Delta$ 32 homozygous donor



## NEW YORK

# Another Kind of AIDS Crisis

Left: Russell Steinke. Age: 56 / HIV: 23 years / Has suffered from: memory loss, nerve damage in feet, lipodystrophy, fatigue.

Right: Enrico McLane. Age: 52 / HIV: 17 years / Has suffered from: short-term memory loss, two hip replacements.

“A striking number of HIV patients are living longer, but getting older faster—showing early signs of dementia and bone weakness usually seen in the elderly...” *(David France, Published Nov 1, 2009)*



# New HIV Diagnostic Algorithm

A1: 4<sup>th</sup> generation HIV-1/2 immunoassay

(Architect)

A1+

A1(-)

Negative for HIV-1 and HIV-2 antibodies and p24 Ag

A2

HIV-1/HIV-2 differentiation immunoassay

(Multispot)

**HIV-1 +**

HIV-1 antibodies  
detected  
Initiate care  
(and viral load)

**HIV-2 +**

HIV-2 antibodies  
detected  
Initiate care

HIV-1&2 (-)

RNA

**RNA**

Acute HIV-1 infection  
Initiate care

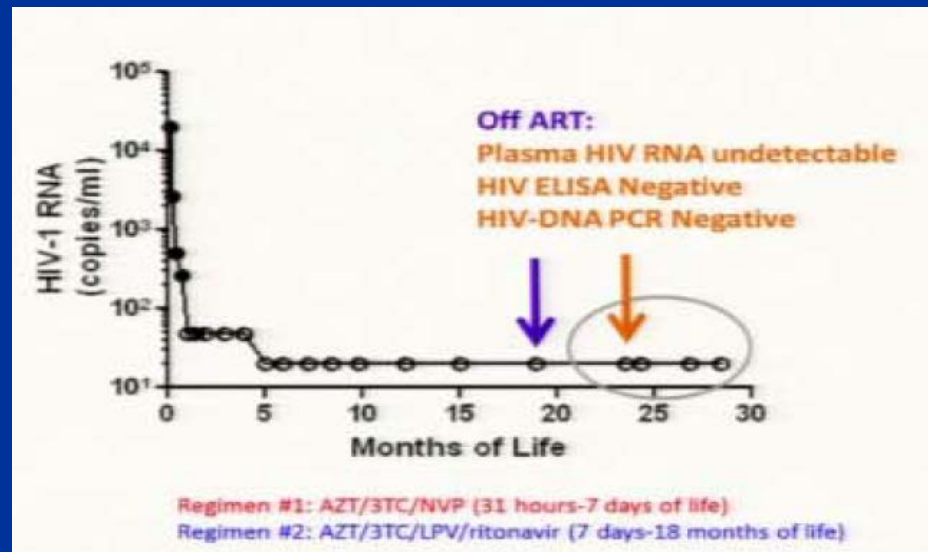
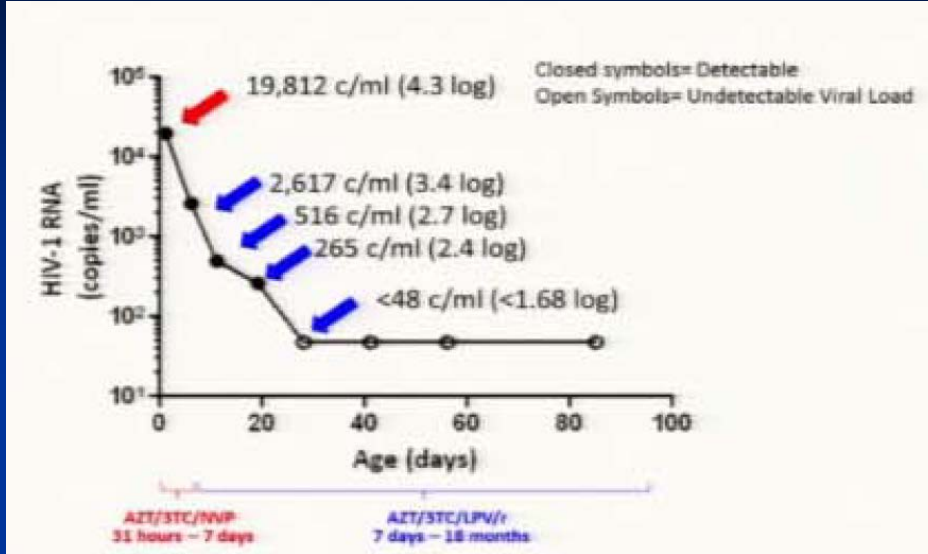
**RNA**

Negative for HIV-1

# Cured Baby?

## Hypotheses:

- Early treatment as PEP
- Early treatment and neonatal immune system prevented/limited reservoir and allowed for clearance
- Reservoir small and will take longer for rebound
- Child destined to be elite controller
- Other



**Why Start Antiretroviral Therapy in  
ALL Persons with HIV Infection?**

Deferred ART was associated with a 69% increase in risk of death versus early initiation in patients with CD4 351-500; 94% increase in risk of death for patients with CD4 >500

Risk of death associated with deferral of ART, according to CD4+ count at baseline, adjusted for HIV RNA level, age, and sex\*

Variable	351-to-500 CD4+ Count		More-Than-500 CD4+ Count	
	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Without inclusion of HIV RNA data				
Deferral of antiretroviral therapy	1.69 (1.26–2.26)	<0.001	1.94 (1.37–2.79)	<0.001
Female sex	1.21 (0.89–1.64)	0.24	1.85 (1.33–2.59)	<0.001
Older age (per 10-yr increment)	1.68 (1.48–1.91)	<0.001	1.83 (1.62–2.06)	<0.001
Baseline CD4+ count (per 100 cells/mm <sup>3</sup> )	1.13 (0.72–1.78)	0.59	0.93 (0.87–0.99)	0.03
With inclusion of HIV RNA data				
Deferral of antiretroviral therapy	1.63 (1.21–2.19)	0.002	1.85 (1.20–2.86)	0.006
Female sex	1.47 (1.02–2.12)	0.04	1.35 (0.85–2.15)	0.20
Older age (per 10-year increment)	1.89 (1.69–2.11)	<0.001	1.81 (1.58–2.07)	<0.001
Baseline CD4+ count (per 100 cells/mm <sup>3</sup> )	0.74 (0.55–1.00)	0.06	0.97 (0.89–1.05)	0.45
Baseline HIV RNA level (per log <sub>10</sub> copies/ml)	1.11 (0.96–1.28)	0.15	1.13 (0.96–1.33)	0.14

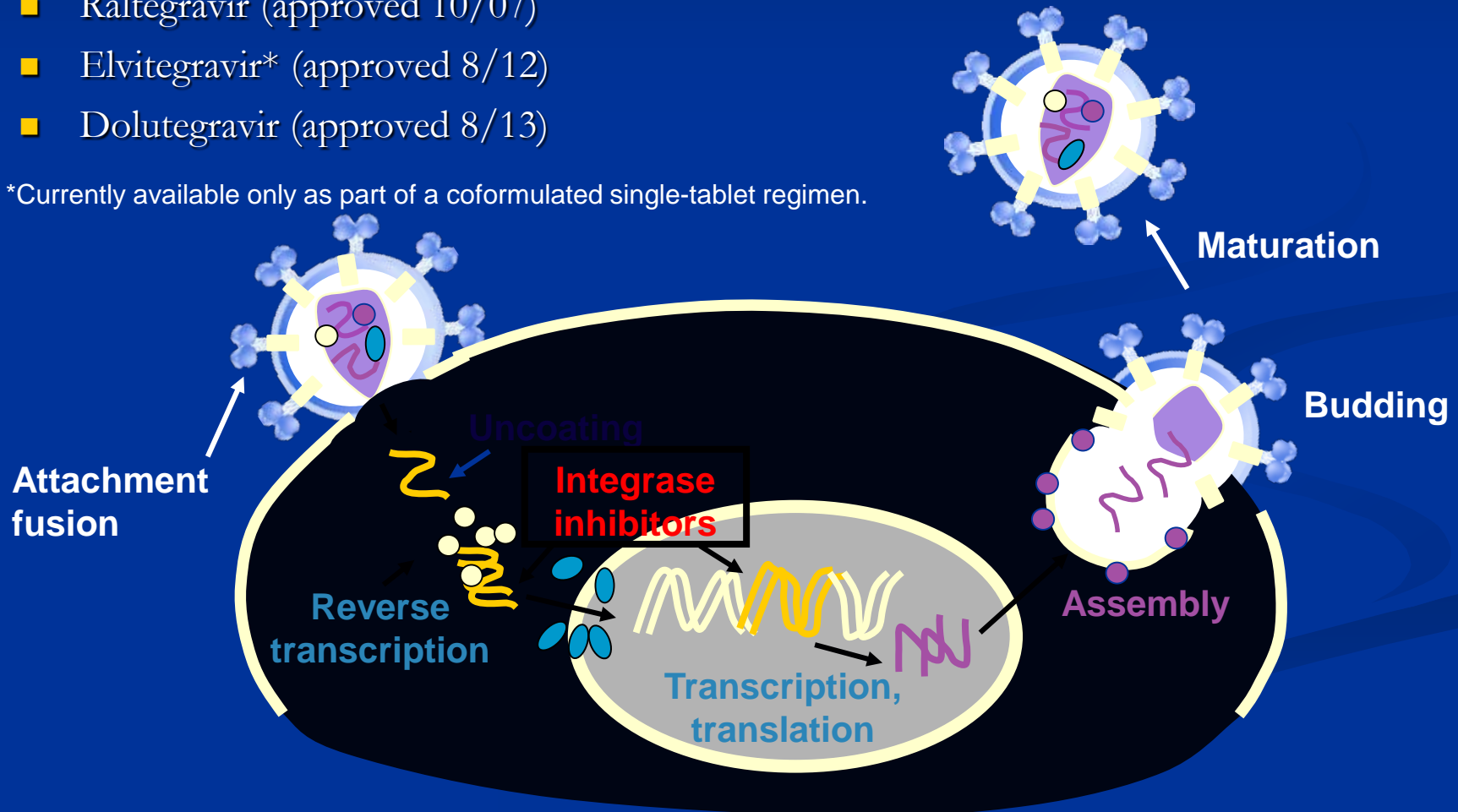
\* The CD4+ count was measured in cells per cubic millimeter. Results were calculated with the use of Cox regression analyses with inverse probability-of-censoring weights. HIV denotes human immunodeficiency virus.

# HIV Viral Life Cycle

Currently available integrase inhibitors

- Raltegravir (approved 10/07)
- Elvitegravir\* (approved 8/12)
- Dolutegravir (approved 8/13)

\*Currently available only as part of a coformulated single-tablet regimen.





# Integrase Inhibitors for Initial Therapy: Conclusions

- While there are many options for initial therapy, regimens that include an integrase inhibitor have many favorable characteristics
  - All are potent, well tolerated, favorable metabolic profile
  - Rates of transmitted (baseline) drug resistance to INSTIs presumed to be low
  - Few drug–drug interactions (RAL, DTG)
  - Resistance rarely reported with DTG
  - Available as single-pill regimen (EVG)

■ Integrase inhibitor based regimens may be

HIV/AIDS is the **world's** most deadly infectious disease. About 2 million people died of AIDS in 2007, including 270,000 children.

An estimated 33 million people were living with HIV at the end of 2007 and only one third of those eligible for ART receive it.

For every one person put on treatment, there are six new infections. 2.7 million people became newly infected with HIV in 2007.

TB = second most deadly infectious disease **worldwide**

TB kills > 1.7 million people /year

(almost as many as HIV/AIDS)

In 2007, estimated 9.3 million new TB cases

Many active TB cases go untreated each year.

Drug-resistant TB strains increasing.

About 5 % of TB cases (nearly 500,000) are multidrug-resistant (**MDR-TB**)

An estimated 40,000 cases of extensively-drug resistant TB, (**XDR-TB**) emerge yearly.

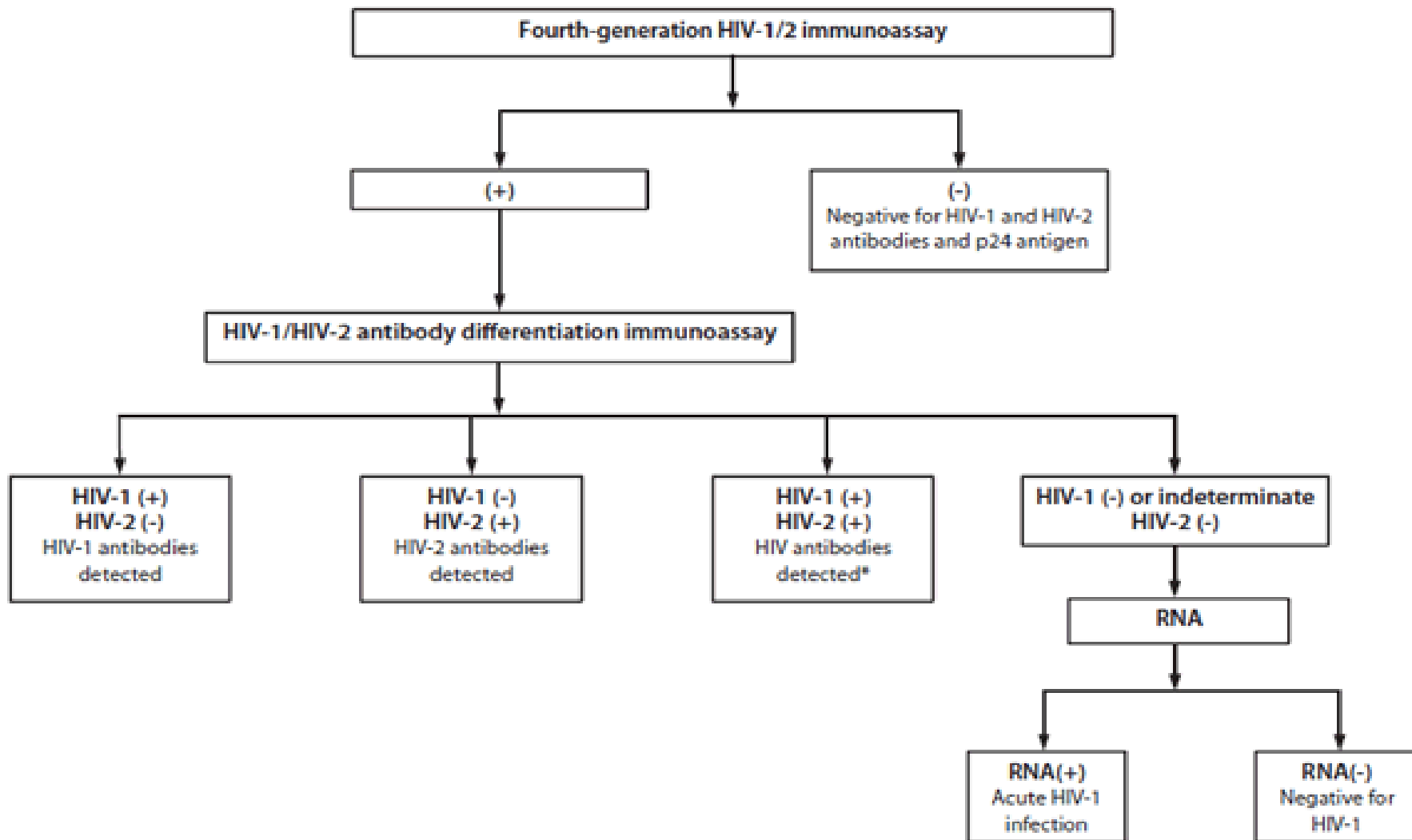
Both MDR & XDR-TB are extremely difficult to treat.

XDR-TB is often incurable.

# HIV in the World

- 40 M of 70 M are still alive with HIV in 2005
- mostly heterosexual transmission; 90% **unaware** of Dx
- For every one HIV Rx'd there are 6 **new** cases; (12,000/day)
- 56,000 **new cases**/year in the USA (2007)
- 6% prevalence in Africa. Life expectancy 65 → 35 (2006)
- Africa has 10% of the world's population;  
70% of the world's HIV
- 3% prevalence in Washington, DC (3/2009)
- Co-infection with TB, costs, prevention, detection, etc
- **No cure** (when was the last time you cured a diabetic?)

# New HIV diagnostic testing algorithm evaluated — United States, 2011–2013

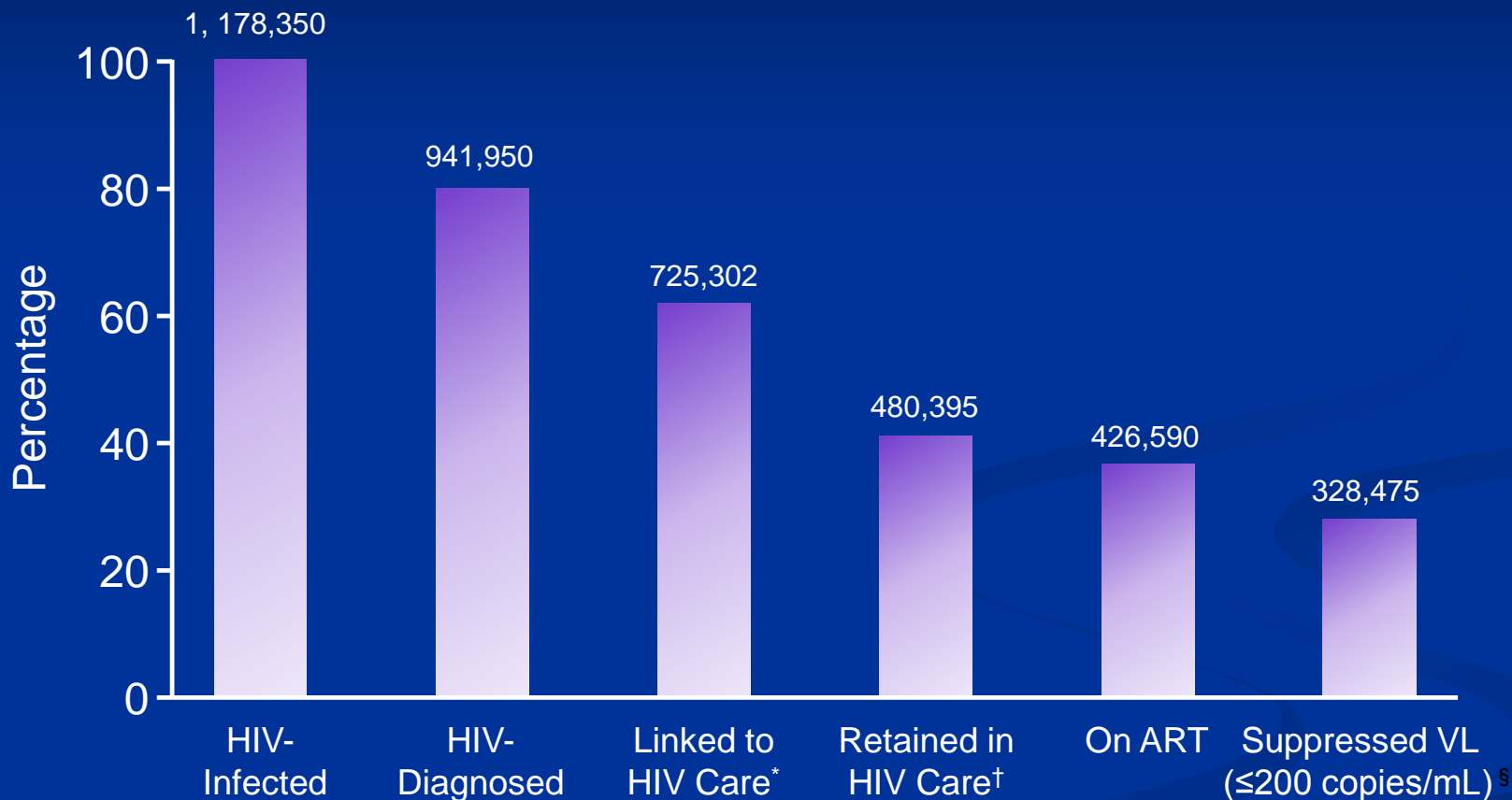




# Reasons why routine HIV testing is appropriate in 2009

- HIV is serious health disorder that can be detected before symptoms occur
- Reliable, inexpensive, non-invasive screening widely available
- Infected persons have years of life to gain if infection is detected early - early detection improves treatment responses
- Awareness of infection status can lead to behavior changes
- Costs of screening are reasonable relative to the anticipated benefits which include lower transmission risks – secondary prevention

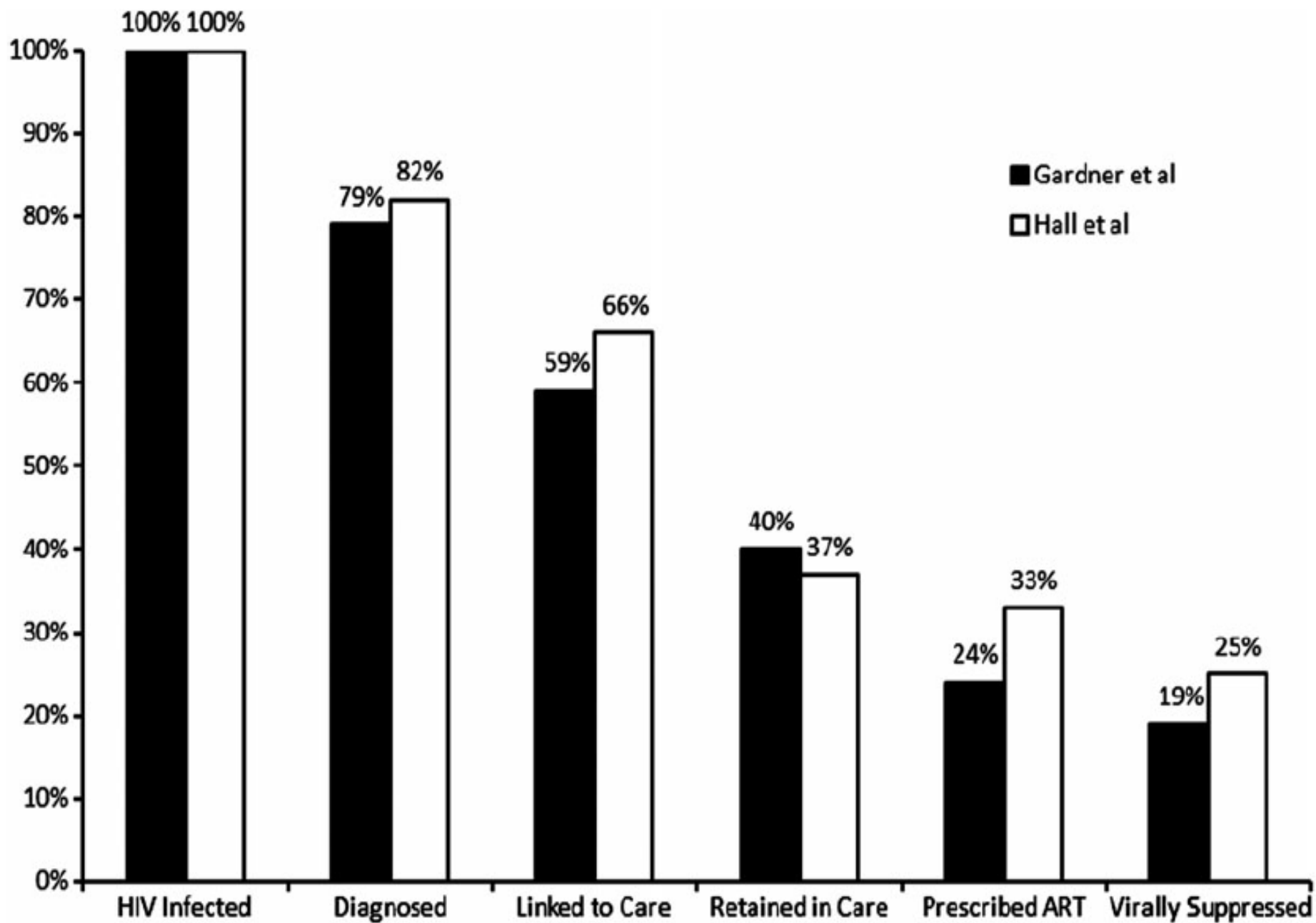
# Breakdown of HIV-Infected Individuals



\*Estimated number diagnosed x estimated percentage linked to care. † Estimated number diagnosed x estimated percentage retained in care. ‡ Estimated number on ART x percentage with suppressed VL.

VL = viral load.

CDC. *MMWR*. 2011;60(47):1618-1623.



# More reasons to do HIV testing

- In 2008, an estimated 252,000 to 312,000 (25-30%) of the more than 1 million persons living with HIV in the United States are *unaware* they are infected
- Even when HIV is diagnosed in a patient, it is often not until the CD4 count is quite low and clinical symptoms have emerged
- Therapy reduces risk of HIV spread

# Causes of increasing viral burden

- progressive disease
- a failing antiretroviral regimen
- lack of compliance
- immunizations
- opportunistic infections



# HIV in USA 2007

- 56,000 **new** cases/year in the USA (2007)
- 1 out of 11 HIV + is **older than 50 years**
- 7000 HIV + females were pregnant in 2007
- 14,000 AIDS patients die yearly in USA
- 1.2 million infected with HIV in USA
- 25% do **not** know that they are infected
- Every 9.5 minutes there is a newly HIV infected person in the USA
- Profound racial disparity exists with HIV
- Blacks made up 12% population aged  $\geq 13$  years but accounted for 46% of the number of persons estimated to be living with HIV\*

CID 2003: 36;212

Clin Geriatric Med 2007;23;567

\*[CDC. HIV prevalence estimates---USA, 2006. MMWR 2008;57:1073--6](#)

# Questions

- Initial evaluation of HIV patients
- Other health issues in HIV
- Basic HIV management
- When do you start?
- HIV is an outpatient disease, usually...
- Overlooked healthcare issues in HIV
- Physical examination – looking for what?
- Initial laboratory evaluation
- Tenets of HAART therapy

# Initial evaluation of HIV patients

- patient's understanding / perception of HIV
- support structures - family, friends, religion
- employment, financial, living condition
- goals of care
- emphasis on the **patient is in charge** of his/her future

# Health issues in HIV

- value of circumcision in prevention
- tuberculosis, toxoplasmosis, STDs
- tobacco use & other risk factors
- hepatitis
- immunizations: hepatitis A & B, pneumococcal, influenza, etc
- herpes simplex & zoster viruses
- chronic diarrhea

# Basic HIV management

- patient is in charge
- multidisciplinary / individualized care
- holistic
- psychosocial issues
- partners' notification of risk / safe sex
- needle exchange programs
- optimism
- resources: internet, HIV organizations



# Overlooked healthcare issues

- education in **written** form
- tobacco, alcohol, drug abuse issues
- seat belts, sunglasses, nutrition, exercise
- pets and travel risks
- birth control
- drug interactions
- psycho-social issues
- pain management

# HIV is an outpatient disease

- **Conditions that increase risk of hospitalization**
  - Undiagnosed HIV infection
  - Homelessness
  - Substance abuse
  - Mental health issues
  - Advanced immunosuppression
  - Polypharmacy

# Physical examination

- comprehensive
- skin
- lymph nodes
- oral cavity
- neurologic, fundoscopic
- psychologic
- cervical PAP smear  
(anal PAP in MSM)

Thrush

Genital & peri-anal lesions

Lymphadenopathy

Skin:

KS lesions

folliculitis

psoriasis

Neurologic:

peripheral neuropathy

neurosyphilis

# Initial laboratory evaluation

- HIV RNA quantitative viral load
- CD4 count, genotype resistance
- CBC, platelets, CMP, lipid profile
- RPR, toxo titer, HAV<sub>(IgG)</sub>, HBV, HCV
- Urinalysis, GC/chlamydia, pregnancy test
- chest xray
- PPD skin test (positive is > 5mm in HIV pt)

# HIV therapy

- patient's readiness for HAART
- when to start HAART
- combination therapy **always**
- **never** add one drug to a failing regimen
- lack of compliance = rapid viral resistance
- alternative therapies
- costs

# **HIV** Past, Present, & Future

Review some history of HIV

HIV in 2018 & what internists can do

Glimpse of the future

Interactive audience desired



# Human Retroviruses

HTLV-1      Adult T-cell Leukemia, HAM / TSP

HTLV-2      Possible association with HAM / TSP

HIV-1

HIV-2      Extremely slow progression to AIDS



→ HIV-1 Group M

→ HIV-1 Group N

→ HIV-1 Group O

SIV (Chimpanzee)



→ HIV-2

SIV (Sooty Mangabey)

# SIV in nonhuman primates

## Potential for new strains of HIV

- HIV-1 and -2 crossed species from nonhuman primates
- Assay of meat derived from butchered primates for SIV-type viruses
  - Meat from 17 species
  - 1096 samples assayed
- 14/17 species found to contain **SIV-like viruses** with range of positive samples 5–40%
- Significant potential for human exposure and resulting in HIV-3, HIV-4, HIV-5...



## Fruit bats for sale in Cameroon market





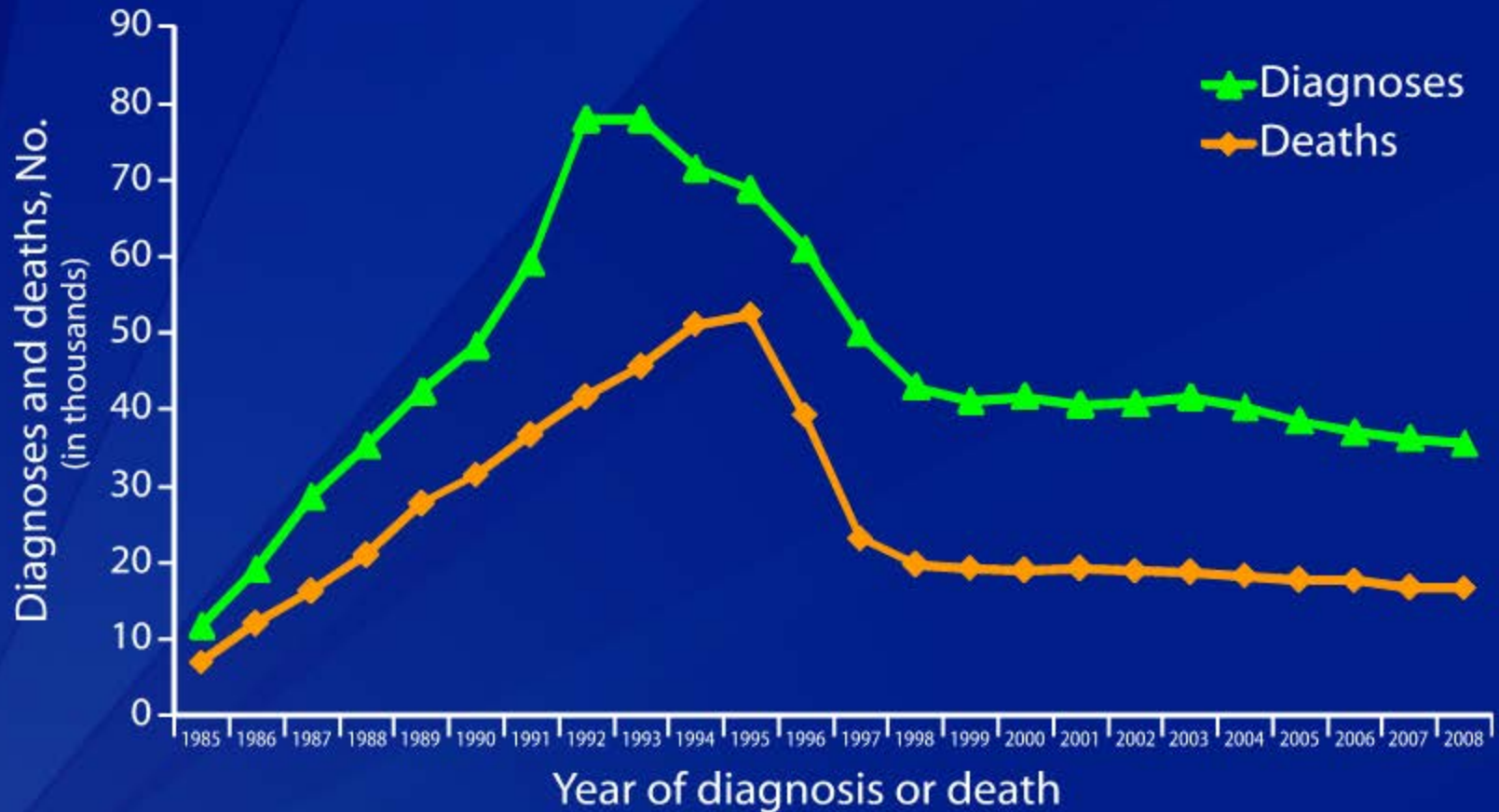
# Historical facts

- 1<sup>st</sup> HIV + on record ? In the USA ?
- Start of HIV epidemic in USA ?
- 1<sup>st</sup> identification of the virus ?
- 1<sup>st</sup> serologic test for HIV ?
- 1<sup>st</sup> anti retroviral therapy ?
- Why did HIV/AIDS numbers peak in 1996 ?
- How many different ARTs are on market ?

# Facts

- How many living with HIV in USA ?
- How many **new** cases of HIV yearly in USA ?
- How many HIV + do **NOT** know they are positive ?
- How many HIV + report no risk factors for HIV ?
- How many HIV + are engaged in therapy ?
- How many HIV + have **non** detectable viral loads ?
- **Why** is the above important & **what** can we do ?

# AIDS Diagnoses and Deaths of Adults and Adolescents with AIDS, 1985–2008—United States and Dependent Areas

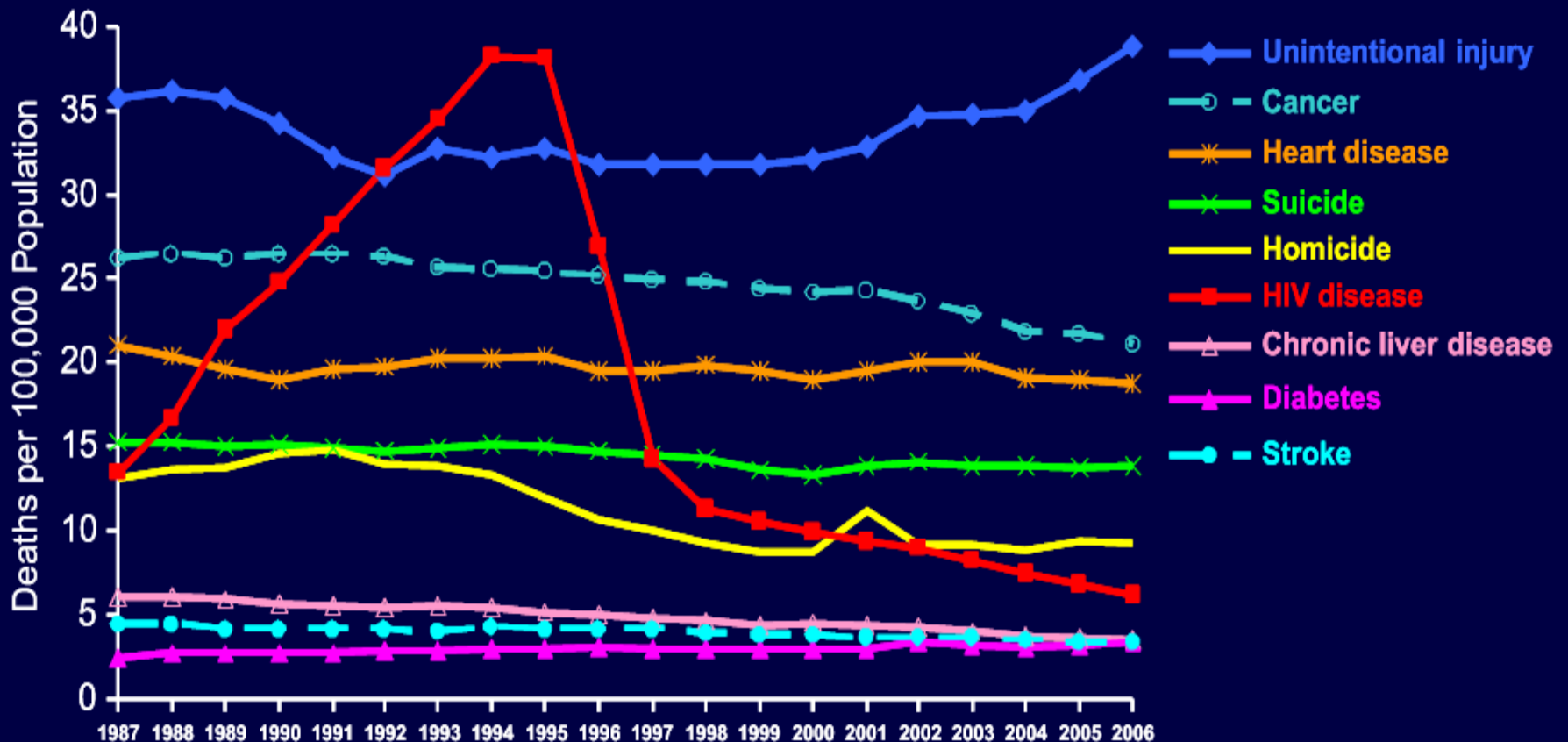


Note. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting. Deaths of persons with an AIDS diagnosis may be due to any cause.





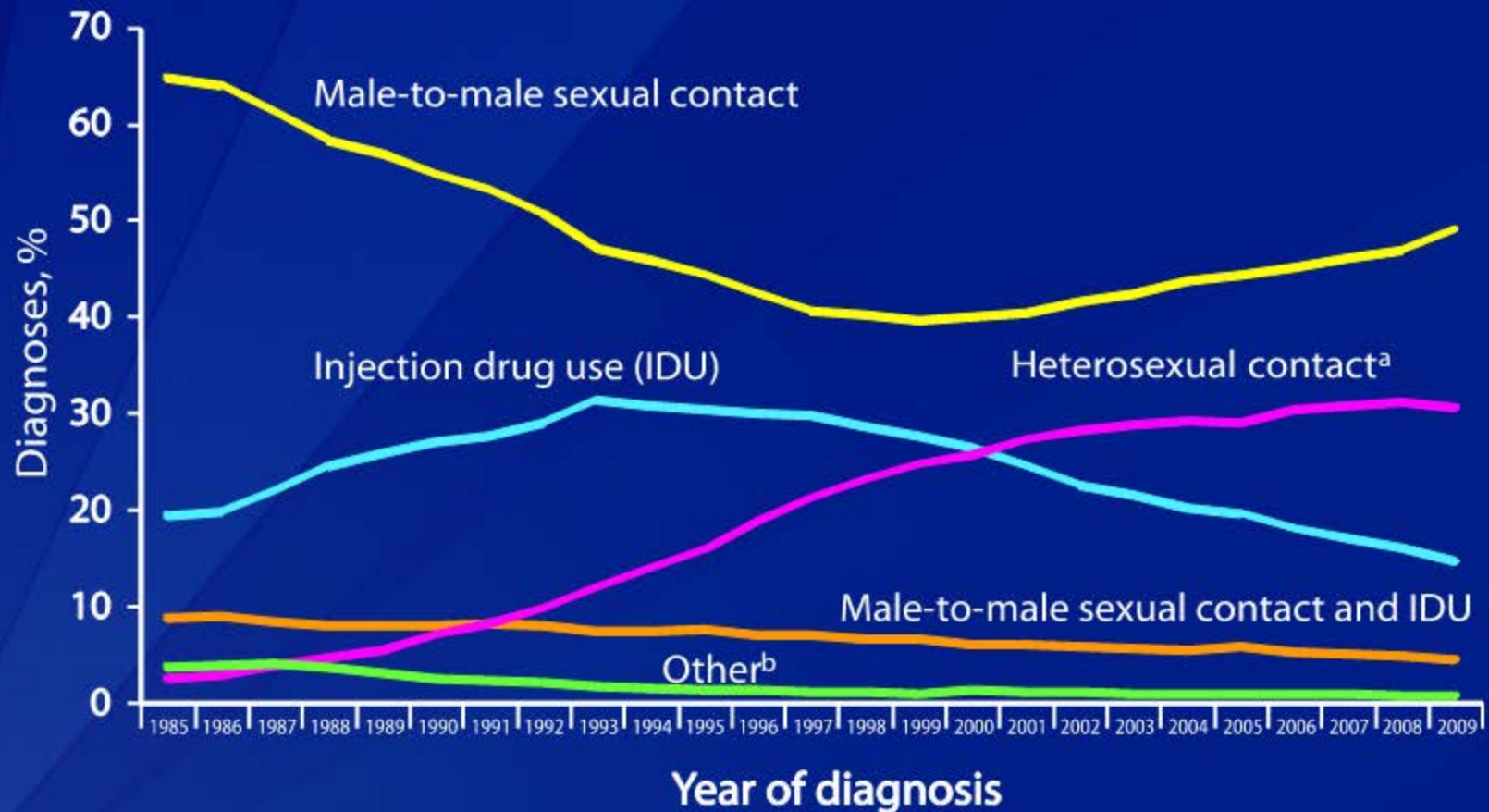
# Trends in Annual Rates of Death due to the 9 Leading Causes among Persons 25–44 Years Old, United States, 1987–2006



Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.



# AIDS Diagnoses among Adults and Adolescents, by Transmission Category and Year of Diagnosis, 1985–2009—United States and Dependent Areas



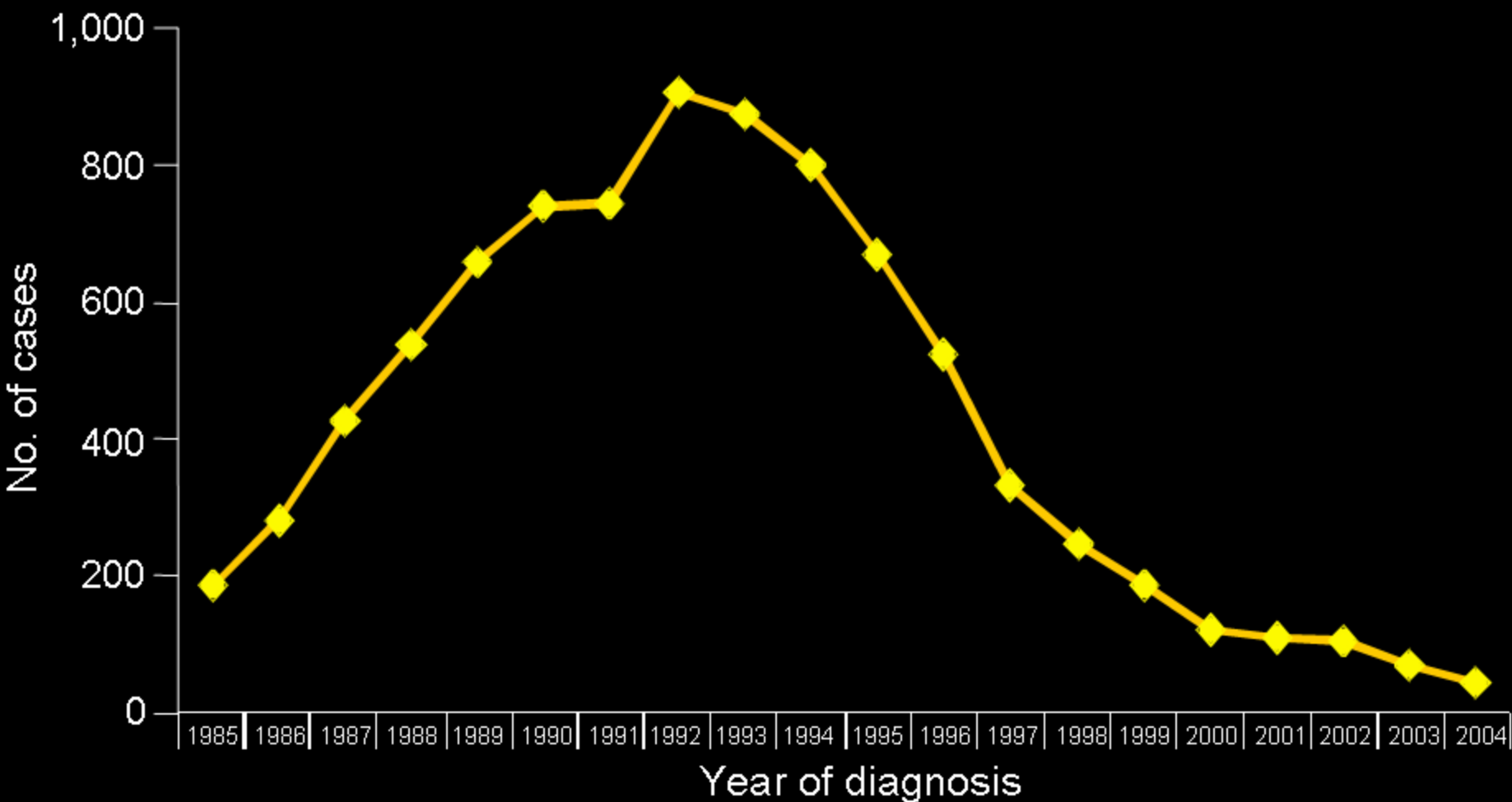
Note. All displayed data have been statistically adjusted to account for reporting delays and missing risk-factor information, but not for incomplete reporting.

<sup>a</sup> Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

<sup>b</sup> Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.



# Perinatally Acquired AIDS Cases, 1985-2004, United States

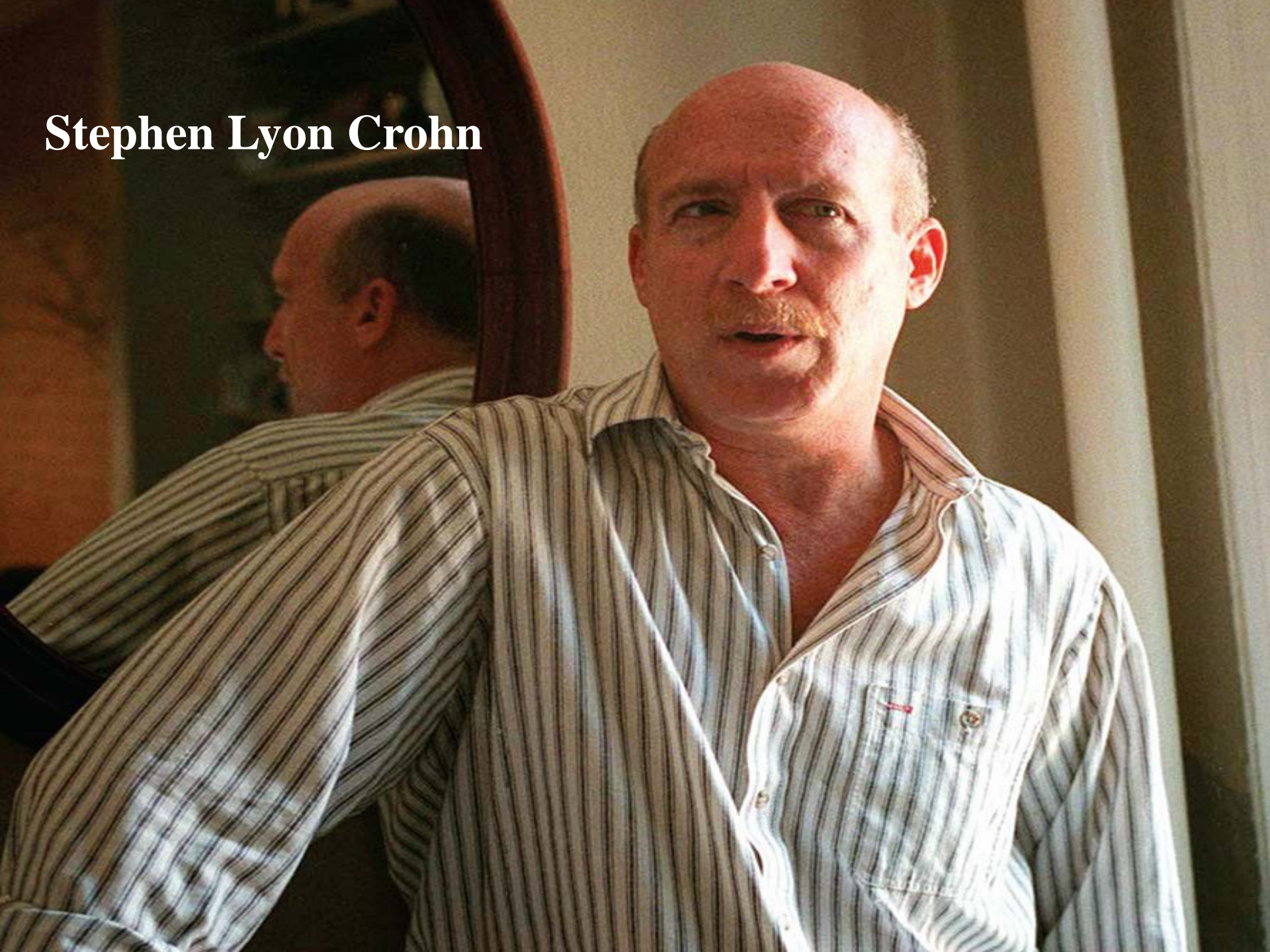


Note. Data have been adjusted for reporting delays and cases without risk factor information were proportionally redistributed.

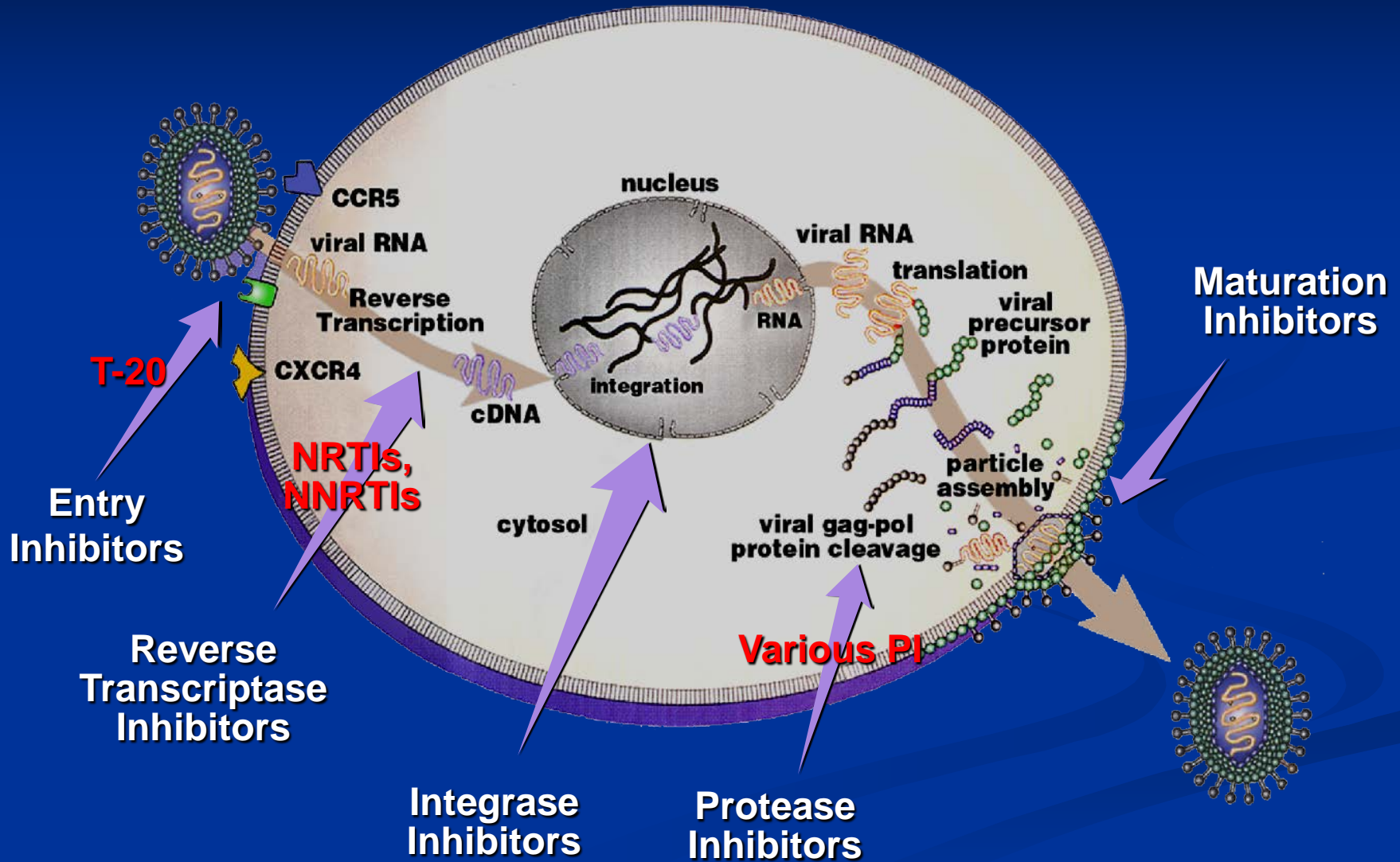




**Stephen Lyon Crohn**



# Integrated Approaches to HIV Treatment





# Work Towards a Cure

The New York Times

SCIENCE TIMES

TUESDAY, NOVEMBER 29, 2011

## New Hope of a Cure for H.I.V.

BY ANDREW POLLACK  
NOVEMBER 29, 2011



**VIRUS-FREE** Timothy Brown of San Francisco had two bone-marrow transplants to treat leukemia, and H.I.V. can no longer be detected in his body. (Heidi Schumann for The New York Times)

### Procedure and Events

- Ablative chemotherapy
- Total body XRT
- Graft vs. host
- Transplant with CCR5 $\Delta$ 32 homozygous donor



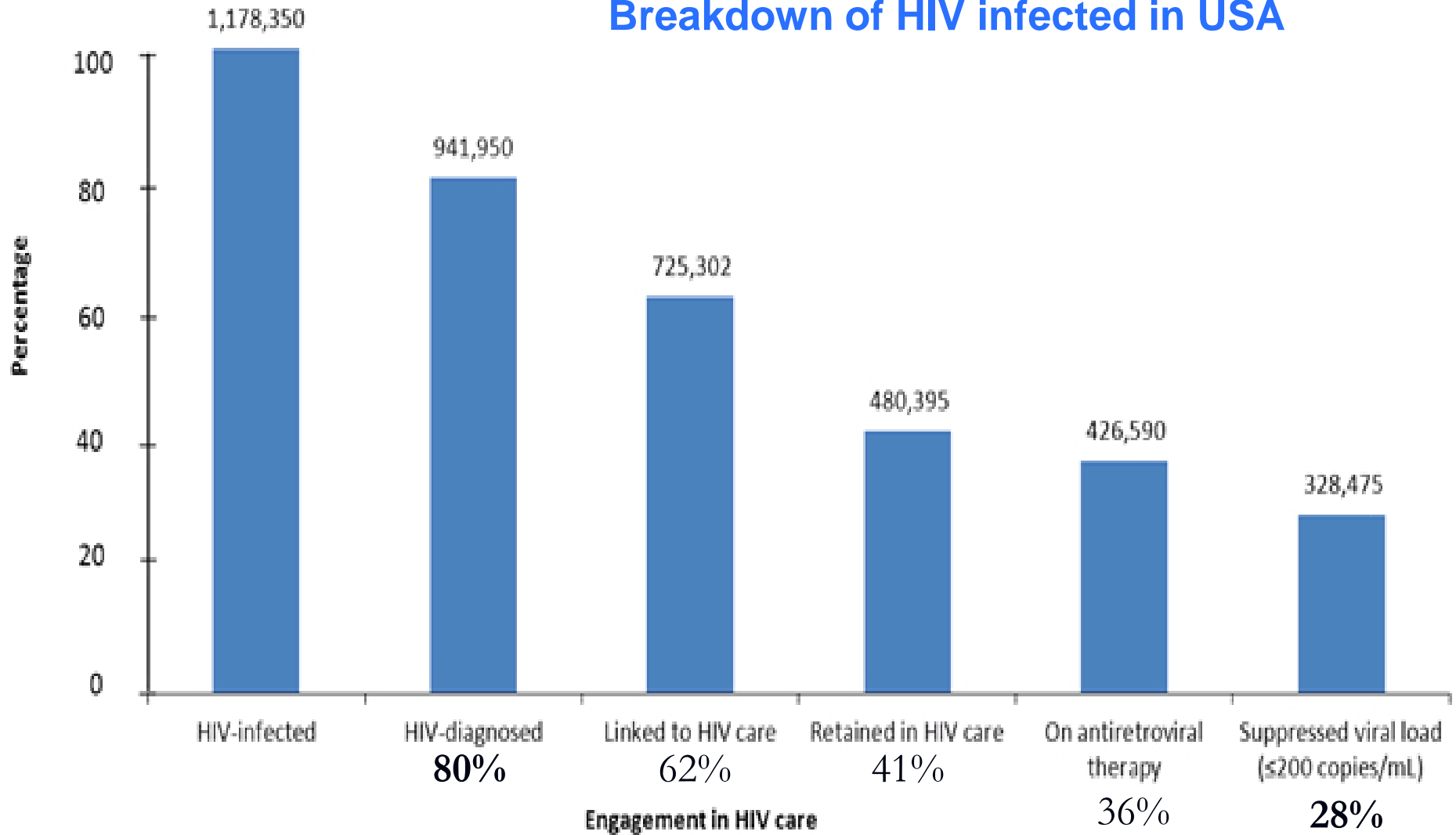
# Facts

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- How many HIV + are engaged in therapy ?
- How many HIV + have **non** detectable viral loads ?
- **Why** is the above important & **what** can we do ?

# Testing for HIV



## Breakdown of HIV infected in USA



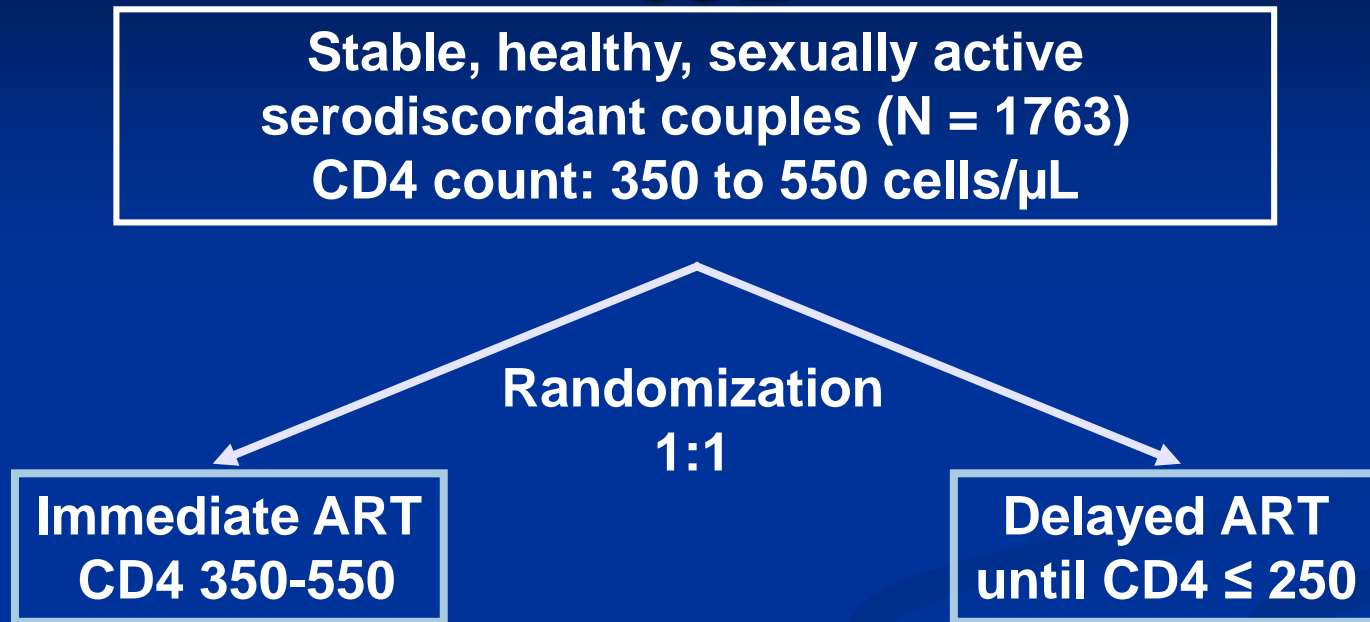
Source: Centers for Disease Control and Prevention. Vital Signs: HIV prevention through care and treatment—United States. *MMWR* 2011;60(47):1621.

# Reasons why routine HIV testing is appropriate in 2015

- HIV = serious infection that can be detected early
- Reliable, inexpensive, non-invasive screening tests exist
- Infected persons can lead “normal” life span if viral load non detectable on Rx; early detection → better responses
- Awareness of HIV status can lead to behavior changes
- 20% to 26% of HIV + patients report no risk factors
- Infected people with **non detectable viral loads** are **not contagious, ergo, therapy is preventative**

# Treatment as Prevention: HPTN

## 052

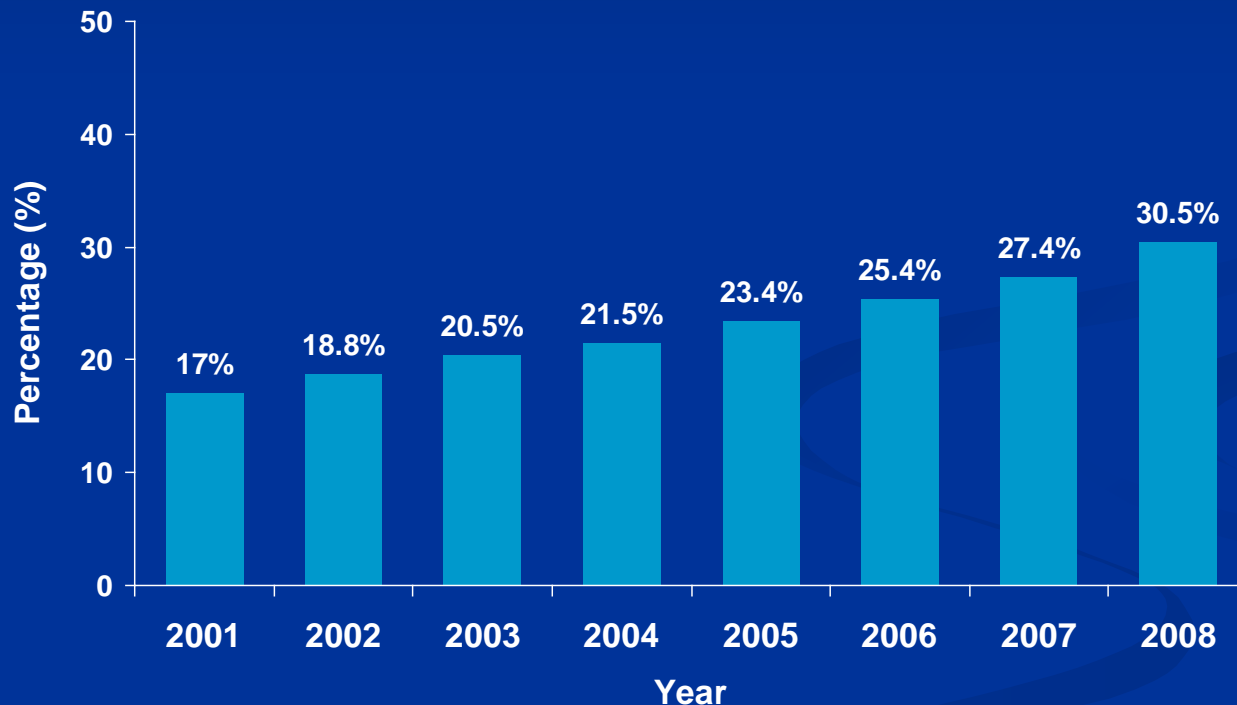


- **Primary transmission end point:** virally linked transmission events
- **Results:** 39 total HIV transmission events (28 linked events)
  - Immediate ART: 1 linked transmission
  - Delayed ART: 27 linked transmissions
  - **96% reduction in risk of HIV transmission** ( $P < .001$ )



# An Increasing Proportion of the HIV Population Is Older

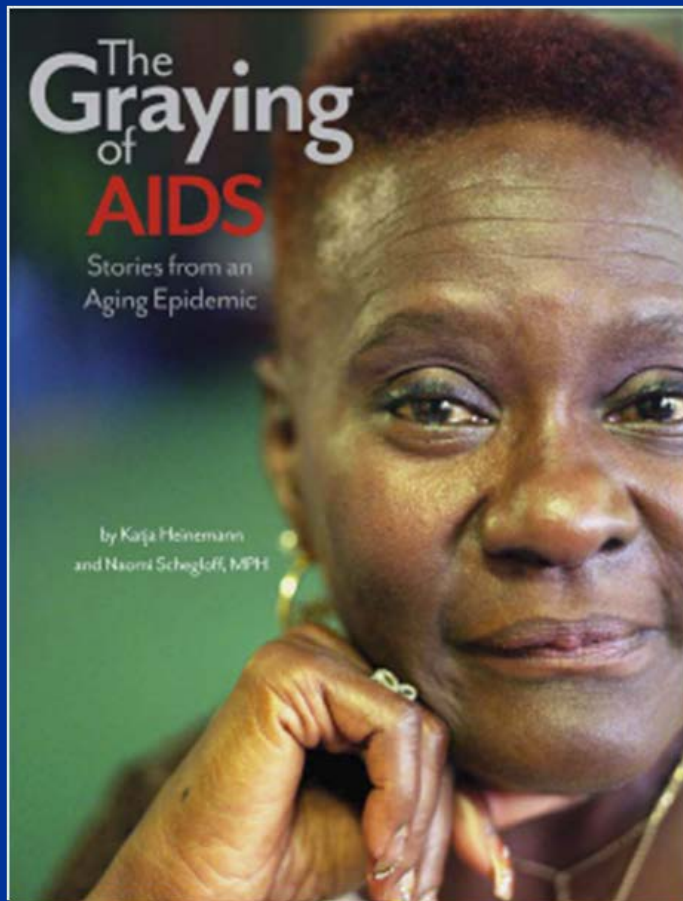
Percentage of Persons in the US Living With Diagnosed HIV Infection  
Age 50 Years or Older, by Year (Estimated)<sup>1</sup>



By 2015, 50% of people in USA with HIV will be 50 years or older<sup>2</sup>

# Older patients account for 17% of new HIV diagnoses

- Up from 13% in 2001



**I didn't know...**

**I could be at risk**

**was clueless**

**only met her once**

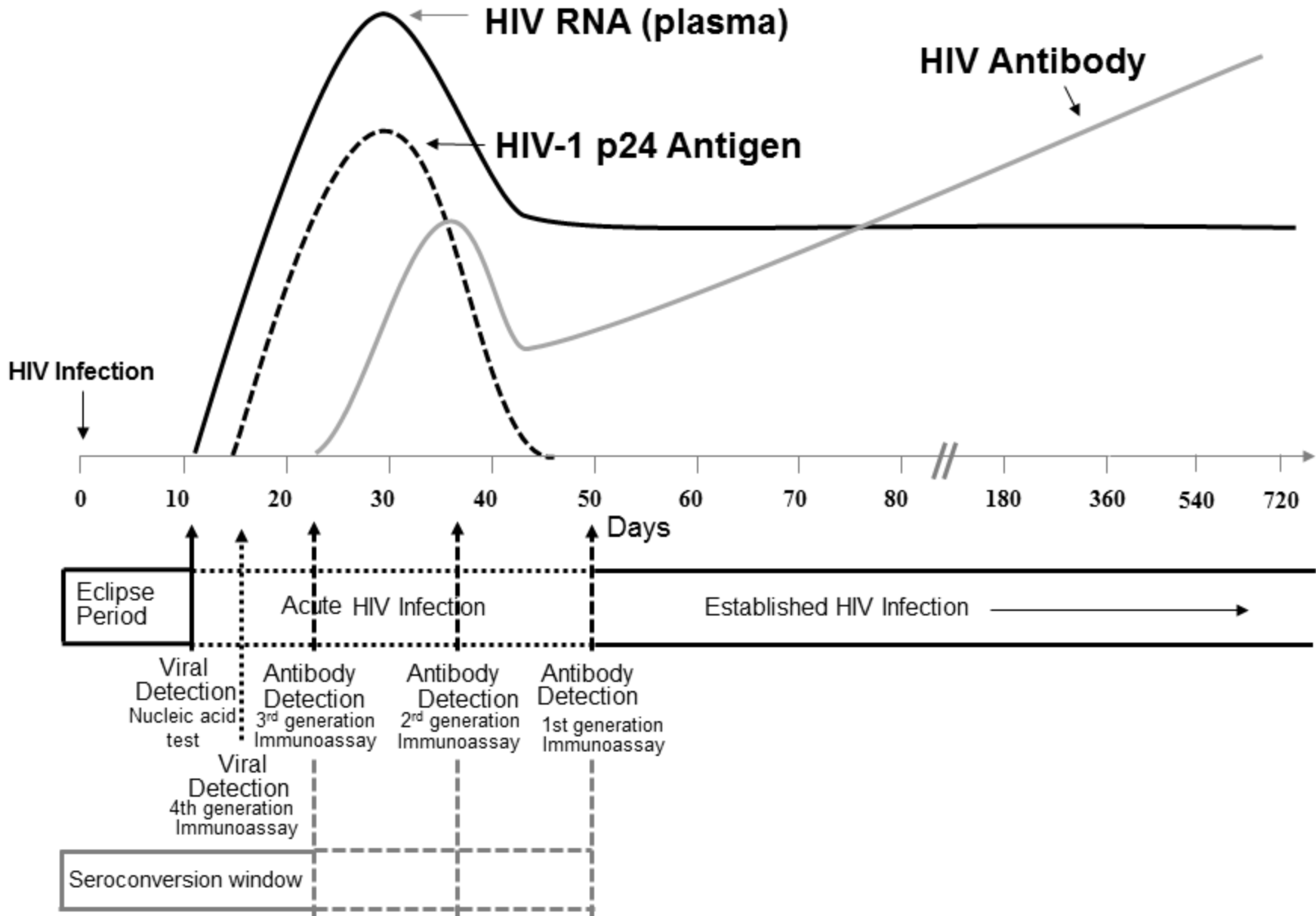
Carlos, 59/Bronx, NY

**AgeisnotaCondom.org**

Get informed. Be safe. Get tested for HIV.

NYS 800-541-AIDS    NYC 800-TALK-HIV  
800-541-2437    800-825-5448

20 YEARS    NYC



HIV Infection

HIV RNA (plasma)

HIV-1 p24 Antigen

HIV Antibody

0 10 20 30 40 50 60 70 80 180 360 540 720

Days

Eclipse Period

Acute HIV Infection

Established HIV Infection

Viral Detection Nucleic acid test

Antibody Detection 3<sup>rd</sup> generation Immunoassay

Antibody Detection 2<sup>nd</sup> generation Immunoassay

Antibody Detection 1<sup>st</sup> generation Immunoassay

Viral Detection 4<sup>th</sup> generation Immunoassay

Seroconversion window

# Acute HIV presents how ?

How many acute HIV /year & significance ?

## Acute HIV presentation

Fever, night sweats, fatigue, rash

Headache, viral meningitis

Nausea, vomiting, diarrhea

Sore throat, lymphadenopathy

Myalgia or arthralgia

Oral ulcers, genital ulcers

Thrombocytopenia

Just like EBV, CMV, Parvovirus, et al

How many acute HIV /year & significance ?



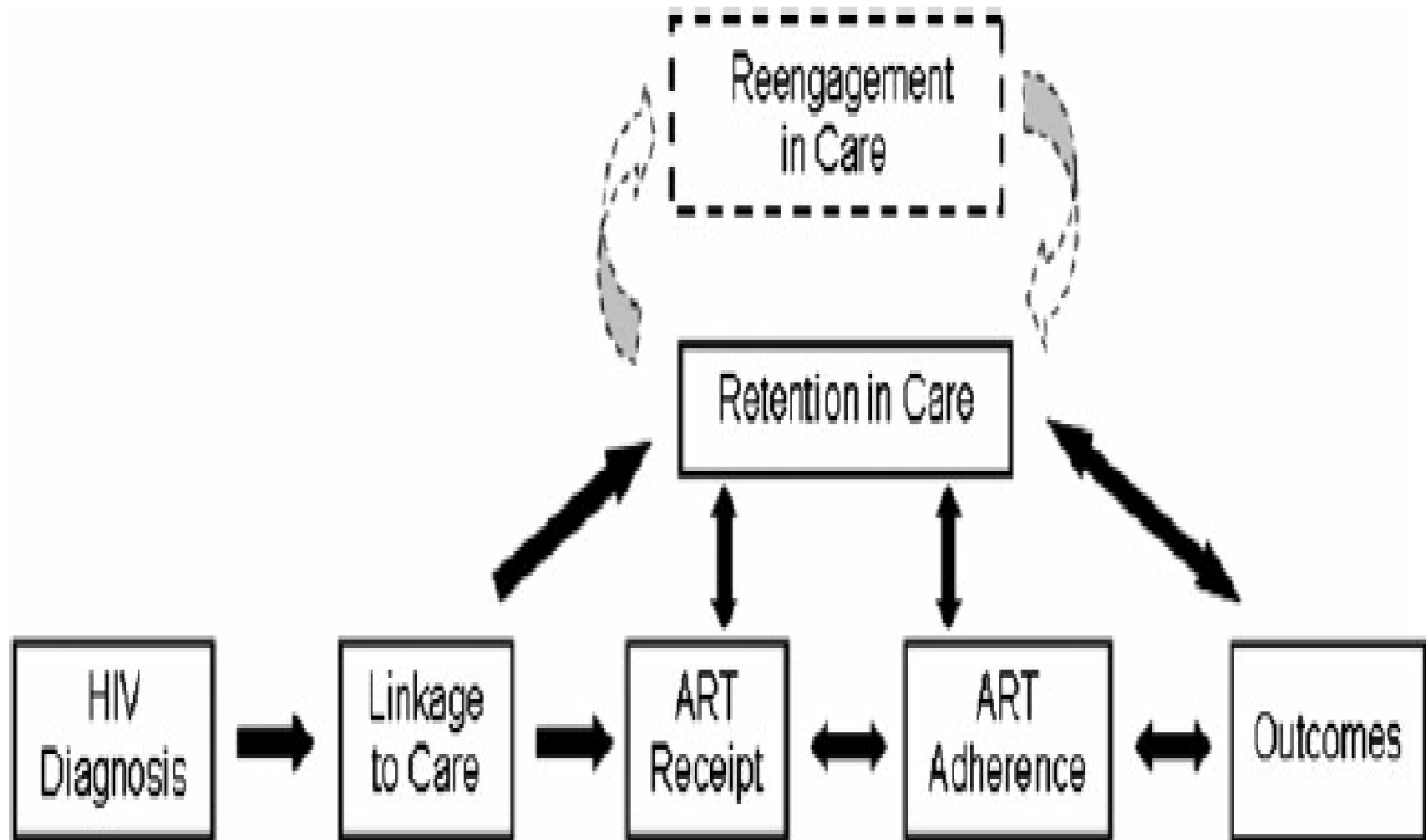


# Inflammation Predicts Disease & Mortality in Treated HIV Infection

- Cardiovascular Disease
- Lymphoma
- Venous Thromboembolism
- Type II Diabetes
- Cognitive Dysfunction
- Frailty

Kuller, *PLoS Med.* 2008; Duprez, *Atherosclerosis.* 2009; Breen, *Cancer Epi Bio Prev.* 2010; Musselwhite, *AIDS.* 2011; Brown, *Diabetes Care.* 2010; CROI 2012: Burdo, Abs#81; Letendre Abs#82; Erlandson, *IAS,* 2011, Abstract #TULBPE029.

# Our task to end the HIV pandemic



# An AIDS free generation

- Scientifically, we can end the HIV/AIDS pandemic
- Eliminate vertical & neonatal transmission
- “15 X 15” by Dec 2015 have 15 million HIV + in the world on ARTs
- Interventions = **Rx as prevention**, condoms, male circumcision, microbicide rings, pre-exposure prophylaxis, mother to child prevention
- Focus on MSM, IVDA, prisons, & the marginalized
- Cure will likely require drugs that draw the virus from memory reservoirs in T cells & other tissues.
- An effective vaccine would be of enormous value.



## *The* NEW ENGLAND JOURNAL *of* MEDICINE

### **The Quest for an HIV-1 Vaccine — Moving Forward**

Dan H. Barouch, M.D., Ph.D.

Related article, p. 2083

**V**accines have historically been the most effective biomedical interventions for controlling global infectious diseases. The development of a safe and effective vaccine against human immuno-

cise types of immune responses that need to be induced by a vaccine are not well understood. Fourth, although a series of broad and potent neutralizing mono-

There are clear reasons for optimism in the quest to develop an HIV-1 vaccine. The modest protection achieved in the RV144 study provides the proof of concept that an HIV-1 vaccine is in fact possible.

November 28, 2013



# ART Pipeline – new classes

**1. Binding and fusion:** free HIV virus binds to a CD4 molecule and one of two coreceptors (either CCR5 or CXCR4). The virus then fuses with the host cell

**2. Infection:** virus penetrates cell. Contents emptied into cell

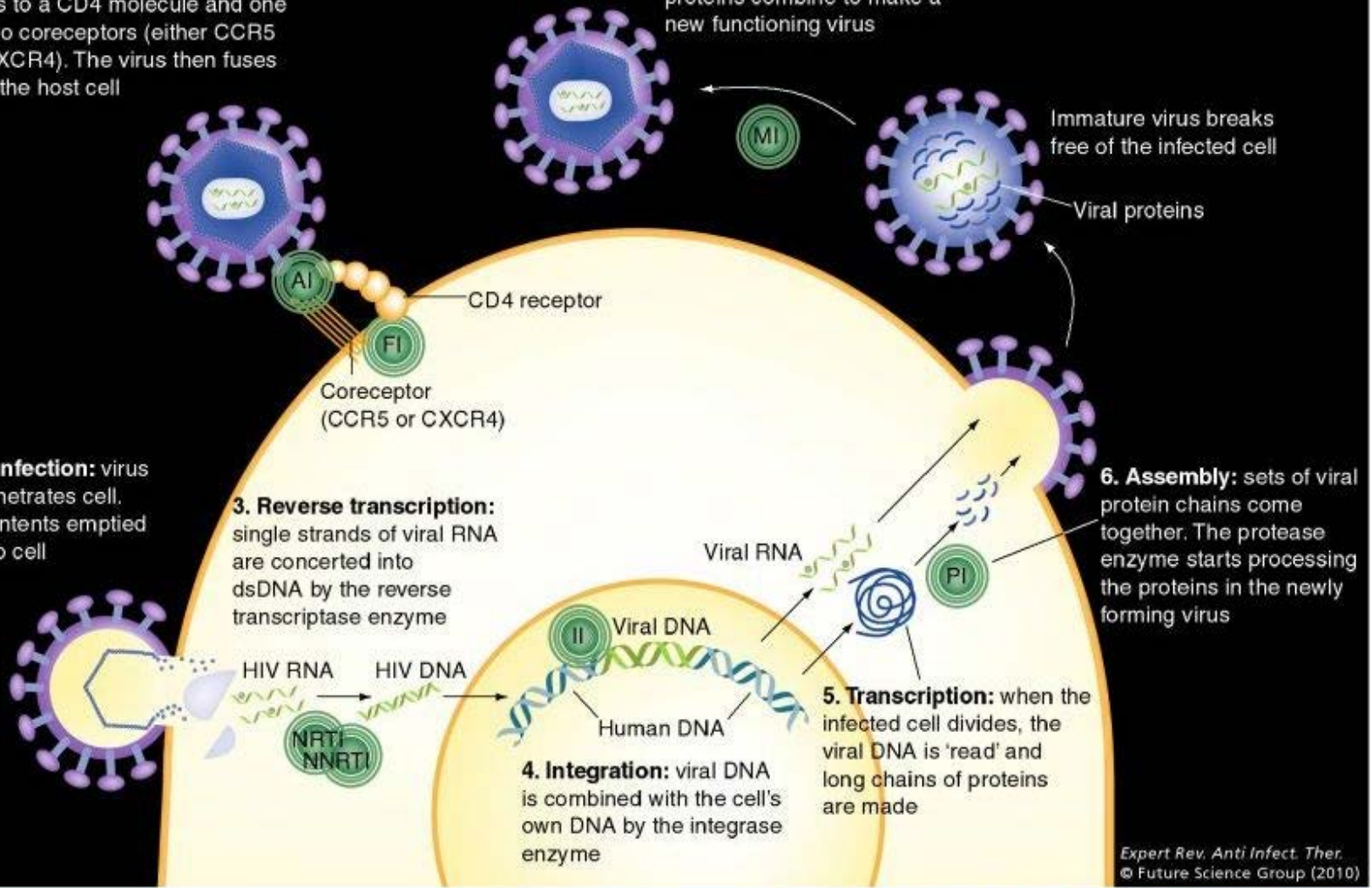
**3. Reverse transcription:** single strands of viral RNA are converted into dsDNA by the reverse transcriptase enzyme

**4. Integration:** viral DNA is combined with the cell's own DNA by the integrase enzyme

**7. Maturation:** the individual proteins combine to make a new functioning virus

**6. Assembly:** sets of viral protein chains come together. The protease enzyme starts processing the proteins in the newly forming virus

**5. Transcription:** when the infected cell divides, the viral DNA is 'read' and long chains of proteins are made



Expert Rev. Anti Infect. Ther. © Future Science Group (2010)

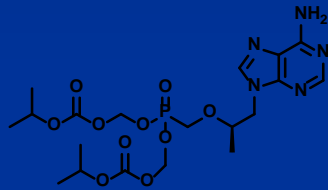


# What is TAF? What is a pro-drug?

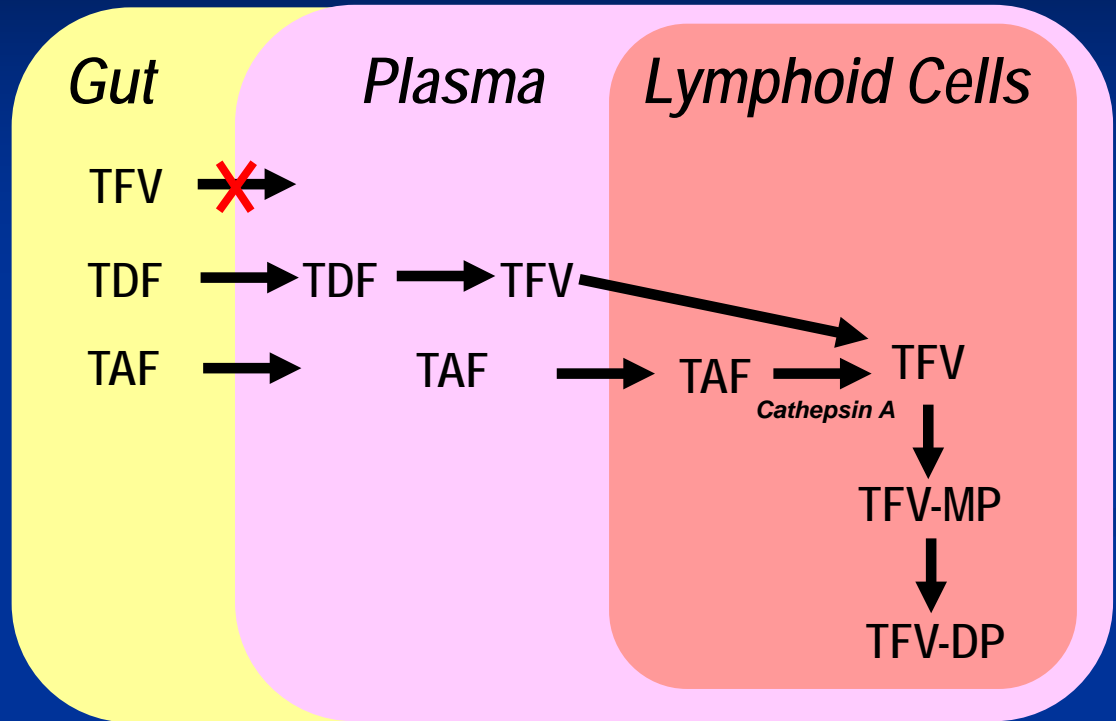
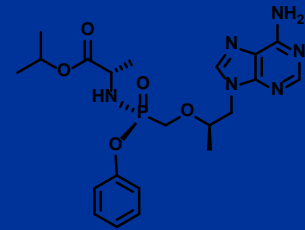
Tenofovir  
(TFV)



Tenofovir  
disoproxil  
fumarate  
(TDF)



Tenofovir  
alafenamide  
(TAF)



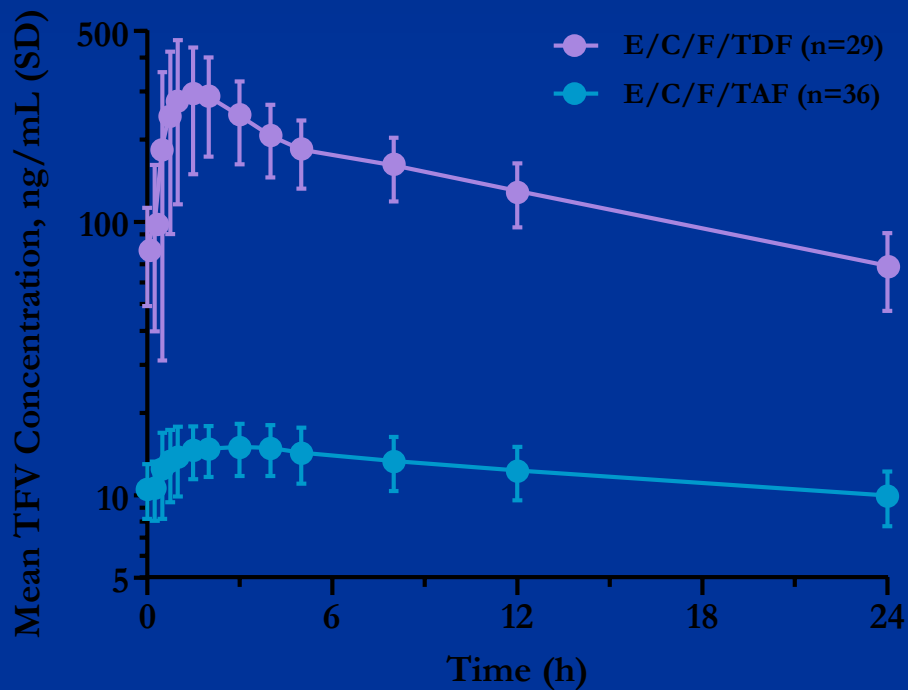
- TAF is more stable in plasma compared with TDF.<sup>1</sup>
- Intact TAF transits directly into target cells where it is intracellularly activated to tenofovir diphosphate (TFV-DP).<sup>1-3</sup>
- TAF at an equivalent dose of 25mg (10mg in boosted regimens) has ~90% lower circulating plasma TFV levels compared to TDF 300mg.<sup>4-6</sup>

1. Lee W et. Antimicrob Agents Chemo 2005;49(5):1898-1906.  
 2. Birkus G et al. Antimicrob Agents Chemo 2007;51(2):543-550.  
 3. Babusis D, et al. Mol Pharm 2013;10(2):459-66.

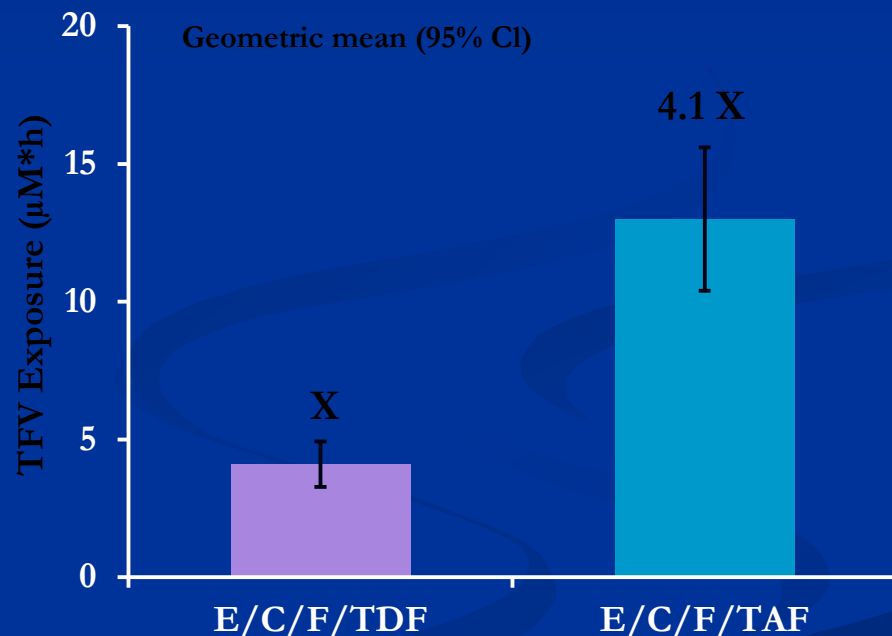
4. Ruane P, et al. J Acquir Immune Defic Syndr 2013; 63:449-5.  
 5. Sax P, et al. JAIDS 2014. 2014 Sep 1;67(1):52-8.  
 6. Sax P, et al. CROI 2015. Seattle, WA. #143LB

# Tenofovir Alafenamide (TAF): Plasma & Cell pK

Plasma TFV



Intracellular TFV-DP



# What to Start?

## ■ Nucleoside RTI:

AZT / Zidovudine (Retrovir)

3TC / Lamivudine (Epivir)

FTC / Emtricitaine (Emtriva)

d4T / Stavudine (Zerit)

ddI / Didanosine (Videx)

Abacavir (Ziagen)

Tenofovir (Viread)

## ■ Non-Nucleoside RTI:

Efavirenz (Sustiva)

Nevirapine (Viramune)

## ■ Protease Inhibitors:

Ritonavir (Norvir)

Fosamprenavir (Lexiva)

Lopinavir/Ritonavir (Kaletra)

Atazanavir (Reyataz)

Nelfinavir (Viracept)

Inidinavir (Crixivan)

Darunavir (Prezista)

## ■ Combinations:

Combivir (AZT + 3TC)

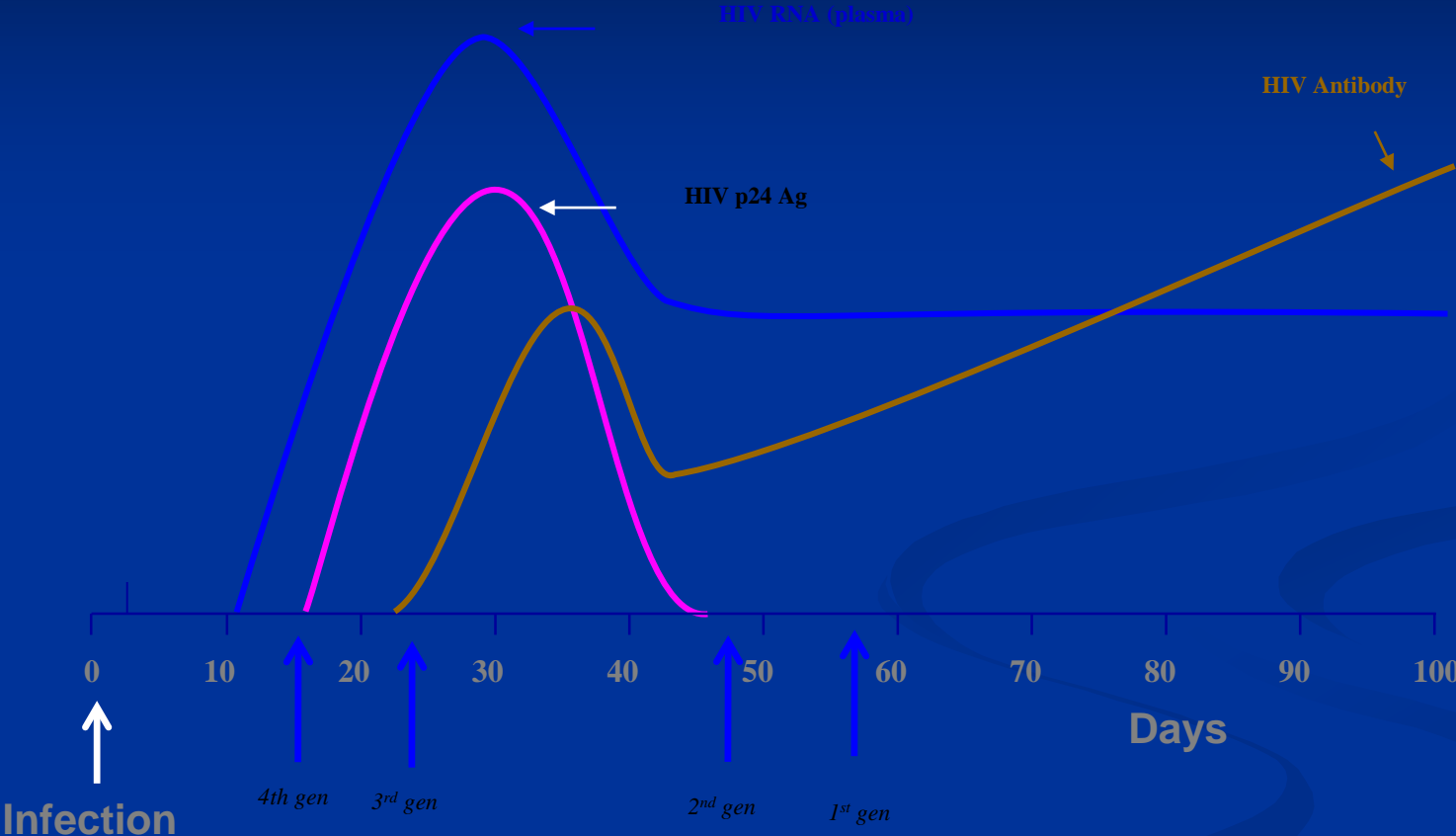
Truvada (Tenofovir + FTC)

Atripla (Tenofovir + FTC + Sustiva)

# Suggested Wholesale Price (SWP) of ART

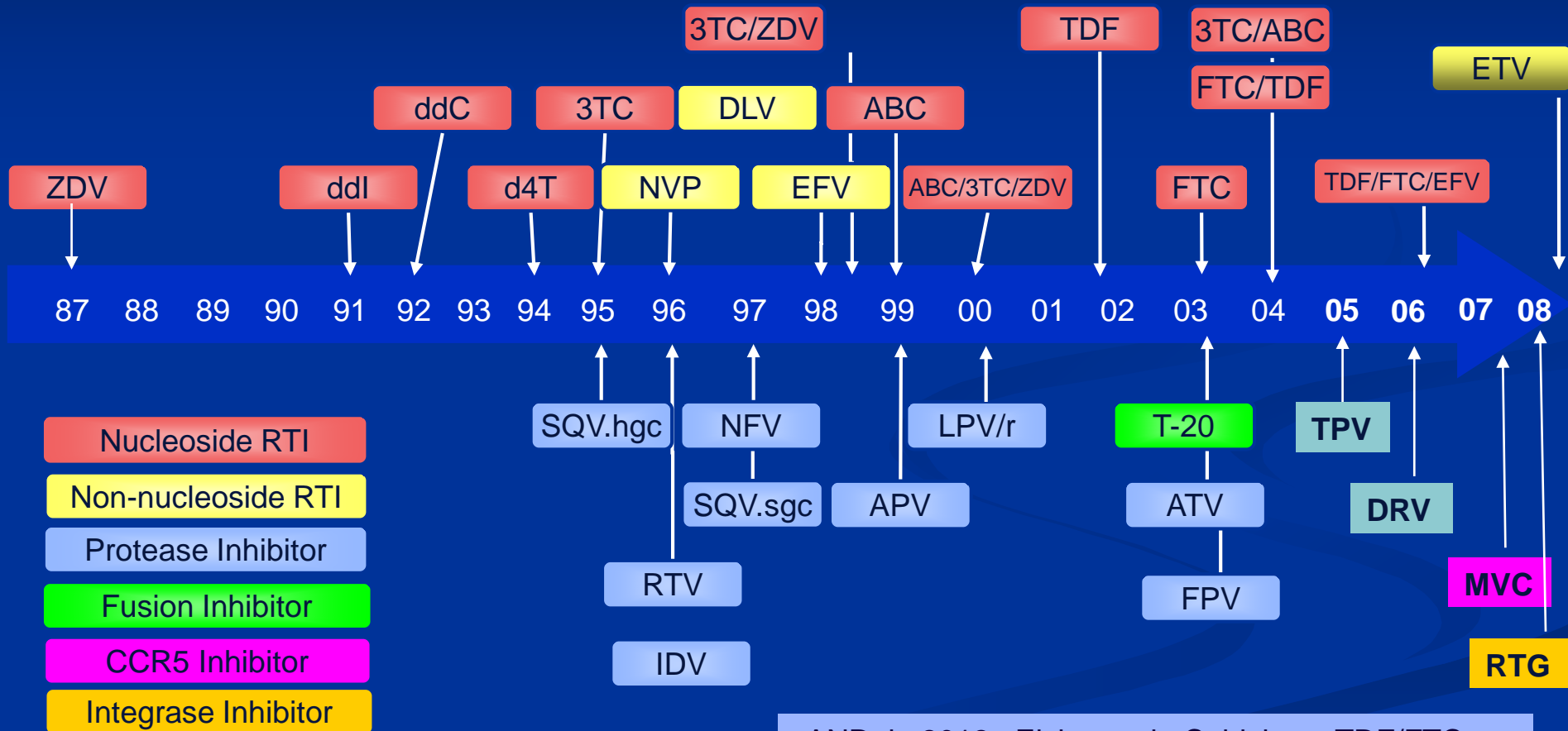
Drug or Combination	SWP of 30-day supply
ABC/3TC (Epzicom)	\$1118.90
TDF/FTC (Truvada)	\$1467.97
ATV/r	\$1519.16
DRV/r	\$1538.80
RAL	\$1228.69
DTG	\$1175.00 (estimated)
Atripla (TDF/FTC/EFV)	\$2253.88
Complera (TDF/FTC/RLP)	\$2195.83
Stribild (ELV/Cobi/TDF/FTC)	\$2810.96
ABC/3TC + DTG	\$2293.90
TDF/FTC +DTG	\$2642.97
TDF/FTC + DRV/r	\$3006.77

# HIV Infection and Laboratory Markers





# Approved Antiretroviral Agents 1987-2013

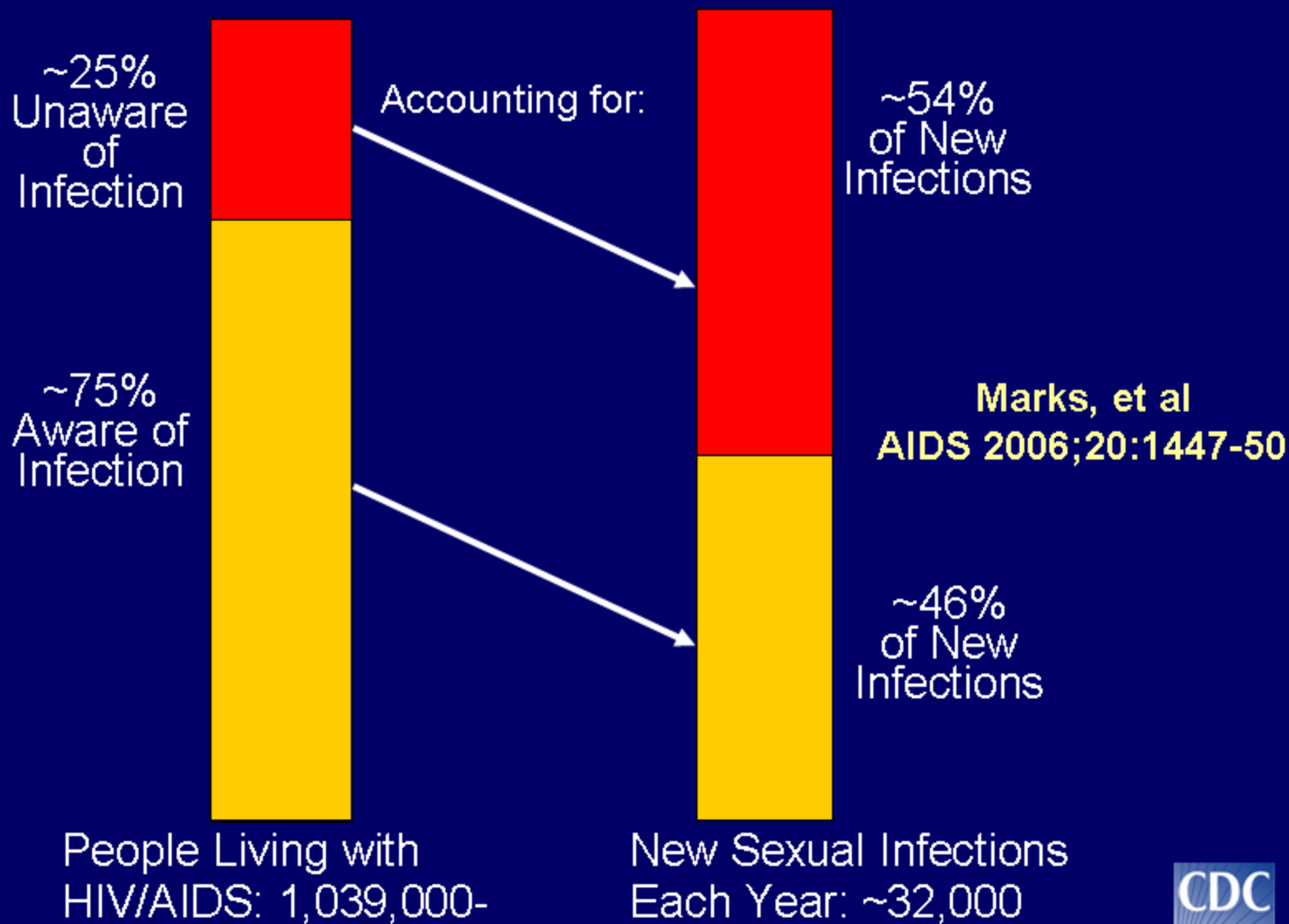


AND, in 2012: Elvitegravir, Cobicistat, TDF/FTC as a Single Tablet Regimen (STRIBILD)

AND, in 2011: rilpivirine (RPV) and TDF/FTC/RPV fixed dose (Complera)

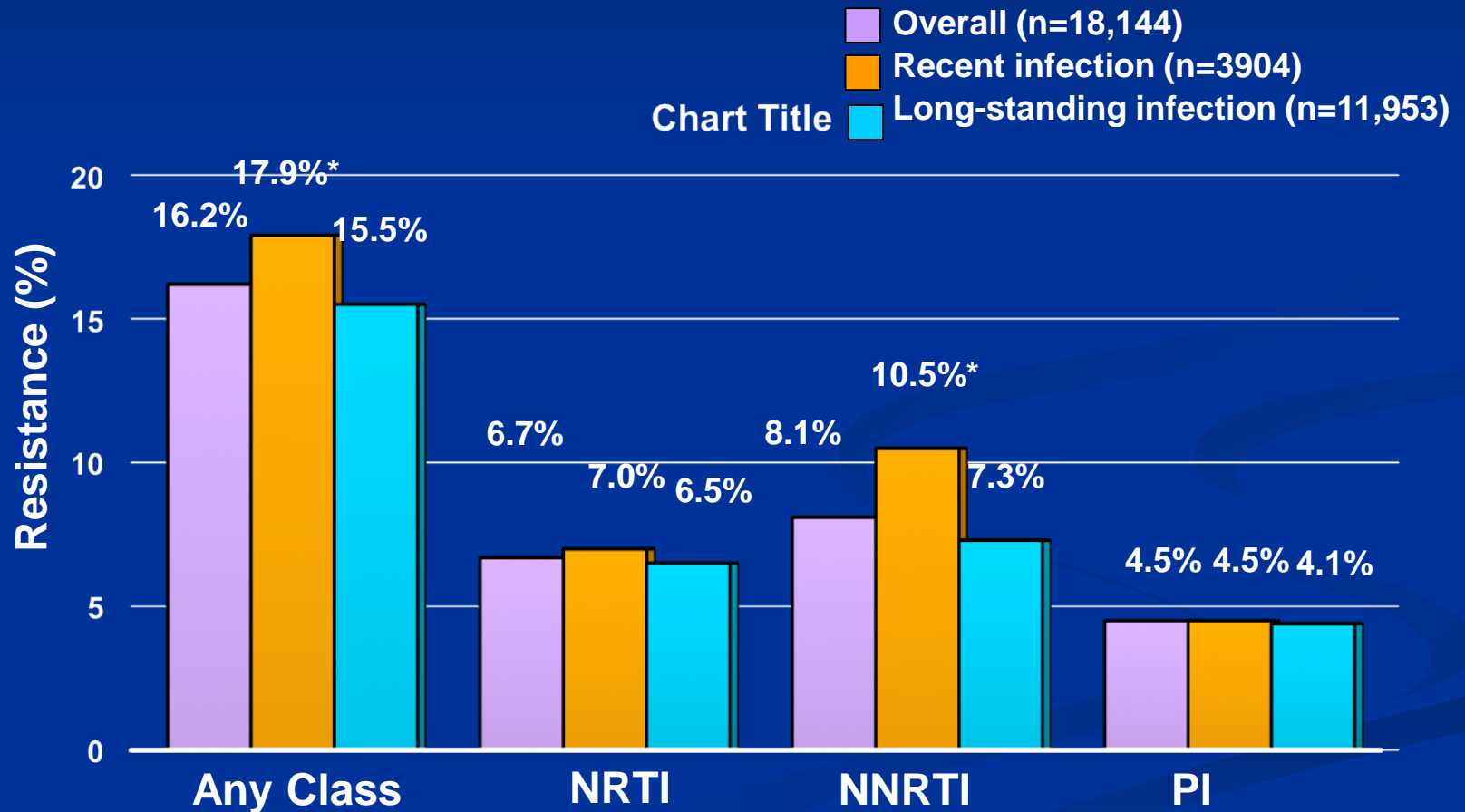
AND, in 2013: dolutegravir (DTG)

# Awareness of Serostatus Among People with HIV and Estimates of Transmission

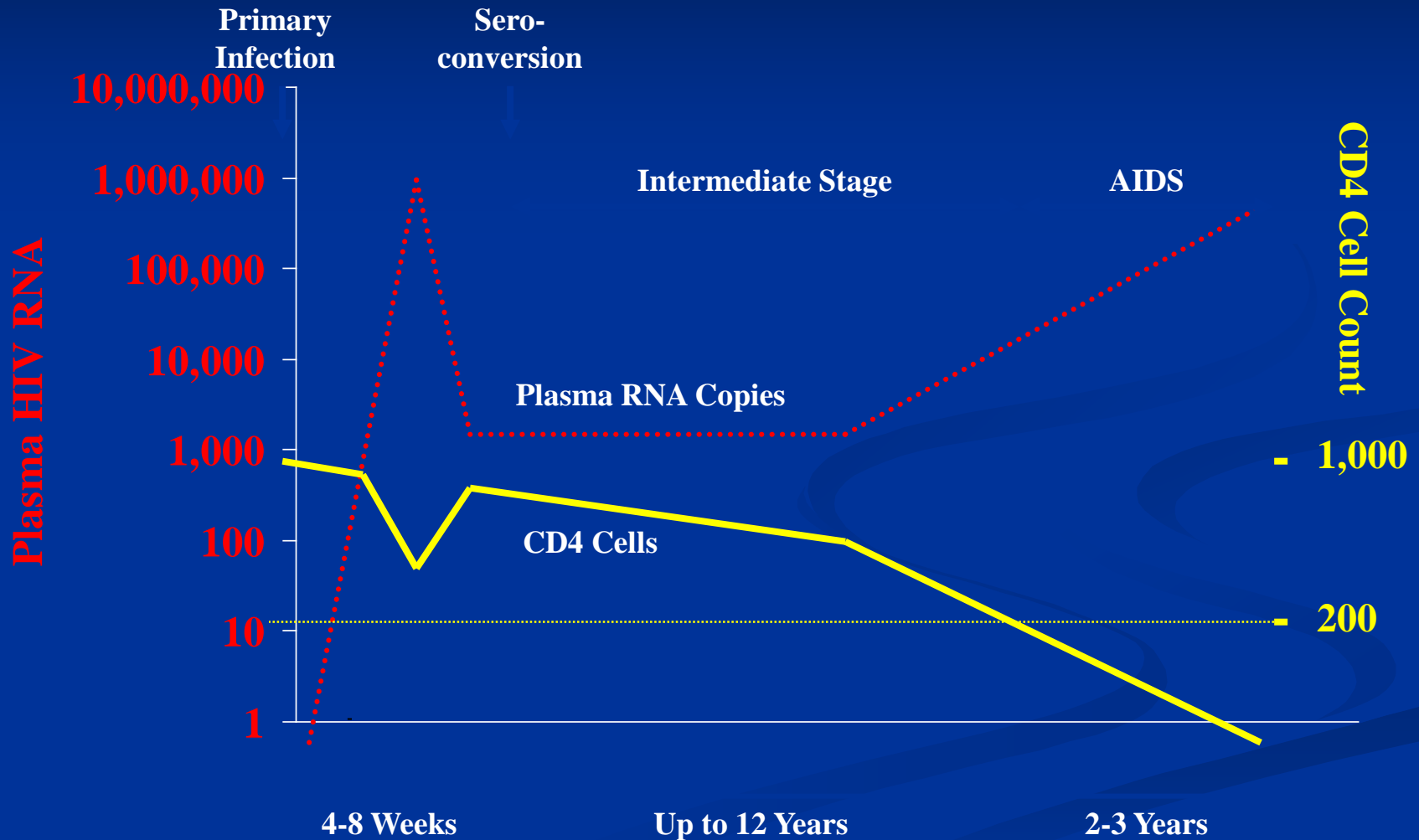


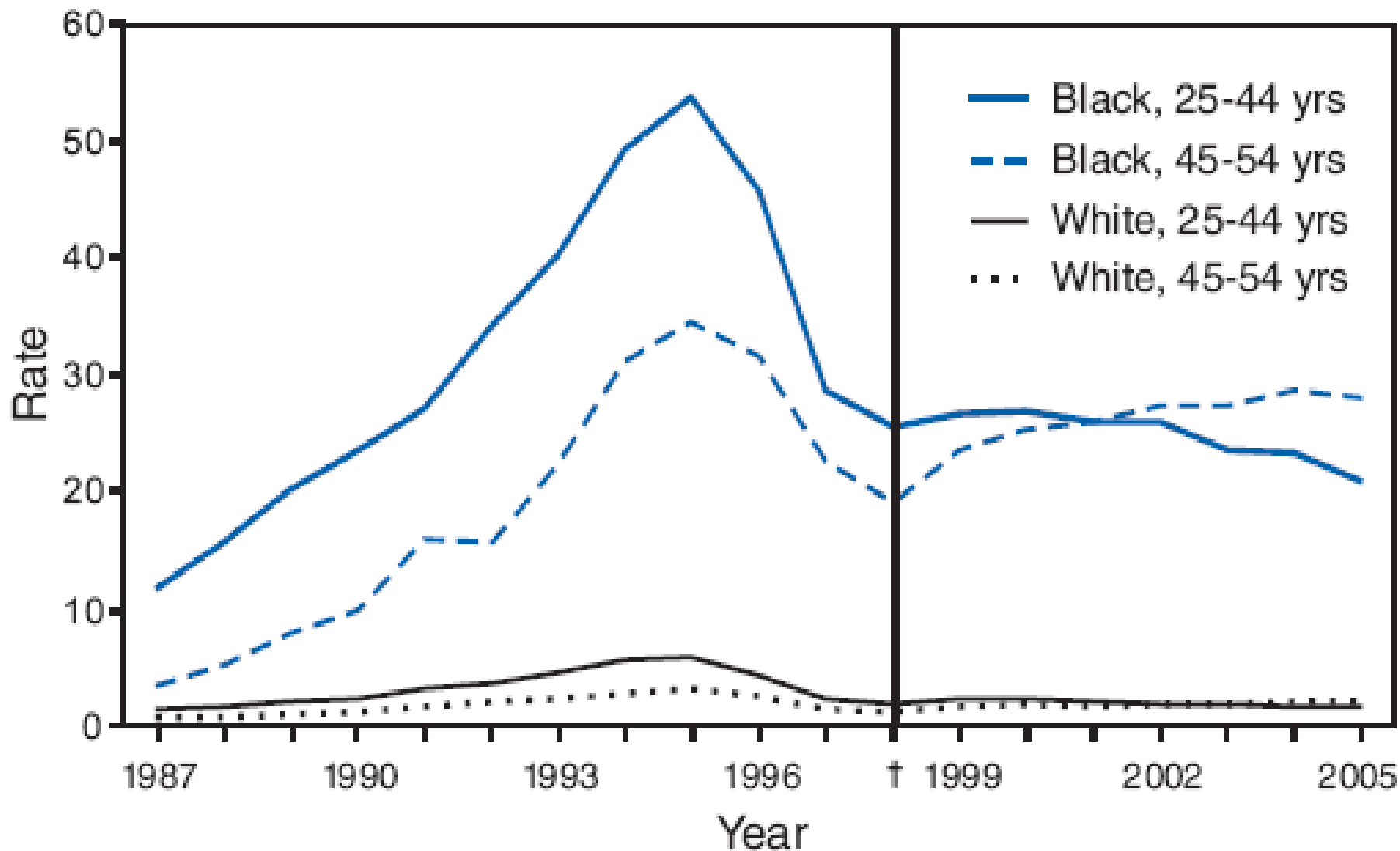
# Transmitted HIV Antiretroviral Drug Resistance (2007-2010)

10 HIV Surveillance Areas in US



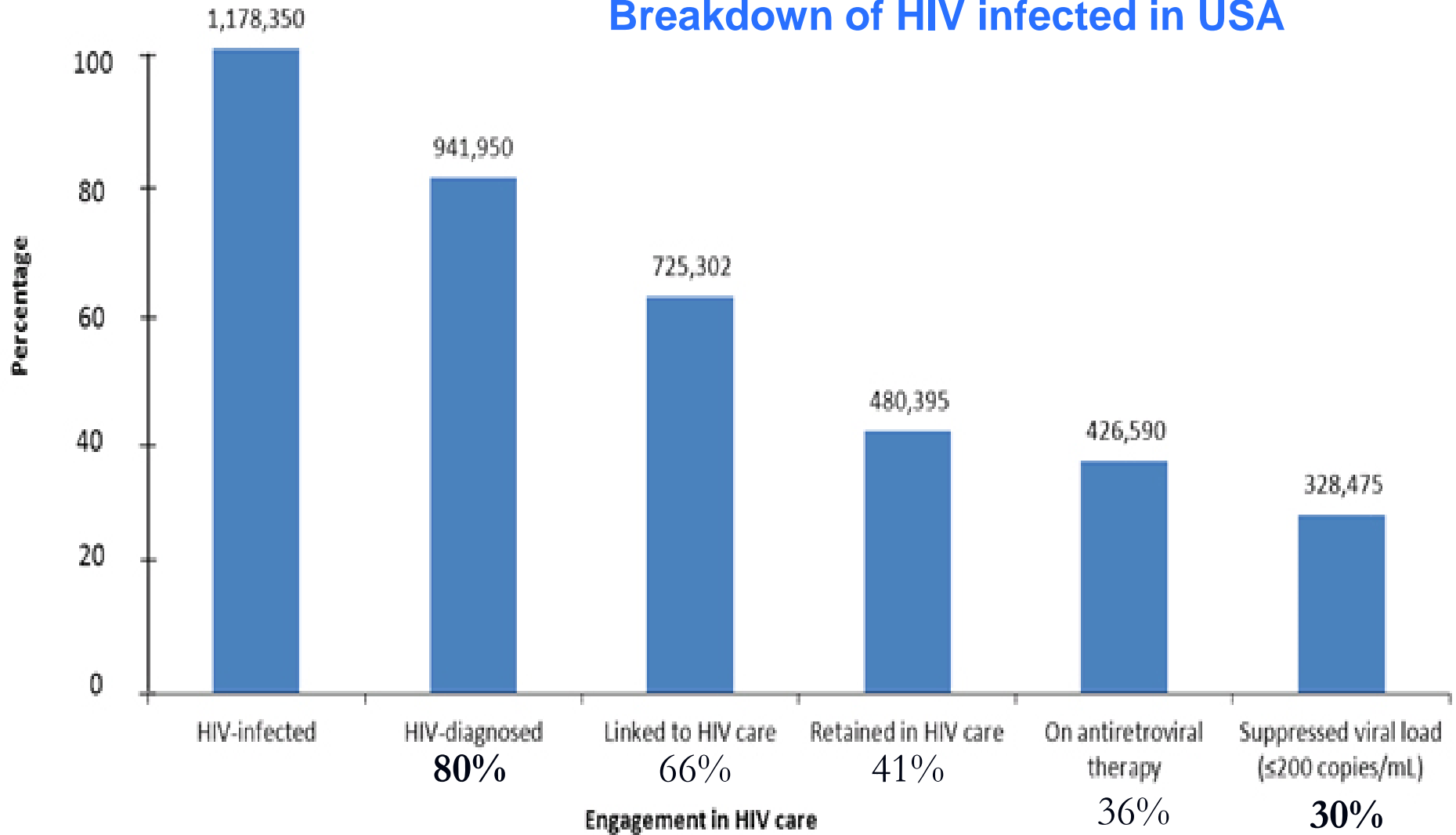
# Natural Course of HIV Infection





Rate per 100,000 population for HIV disease as **underlying cause of death**.  
 For **women** by **Race and Age Group** USA 1987--2005

## Breakdown of HIV infected in USA



Source: Centers for Disease Control and Prevention. Vital Signs: HIV prevention through care and treatment—United States. *MMWR* 2011;60(47):1621.



## Percentage of U.S. Adults Identifying as LGBT by Birth Cohort, 2012-2016

	<b>2012</b>	<b>2013</b>	<b>2014</b>	<b>2015</b>	<b>2016</b>
	%	%	%	%	%
Millennials (1980-1998)	5.8	6.0	6.3	6.7	7.3
Generation X (1965-1979)	3.2	3.3	3.4	3.3	3.2
Baby boomers (1946-1964)	2.7	2.7	2.7	2.6	2.4
Traditionalists (1913-1945)	1.8	1.8	1.9	1.5	1.4