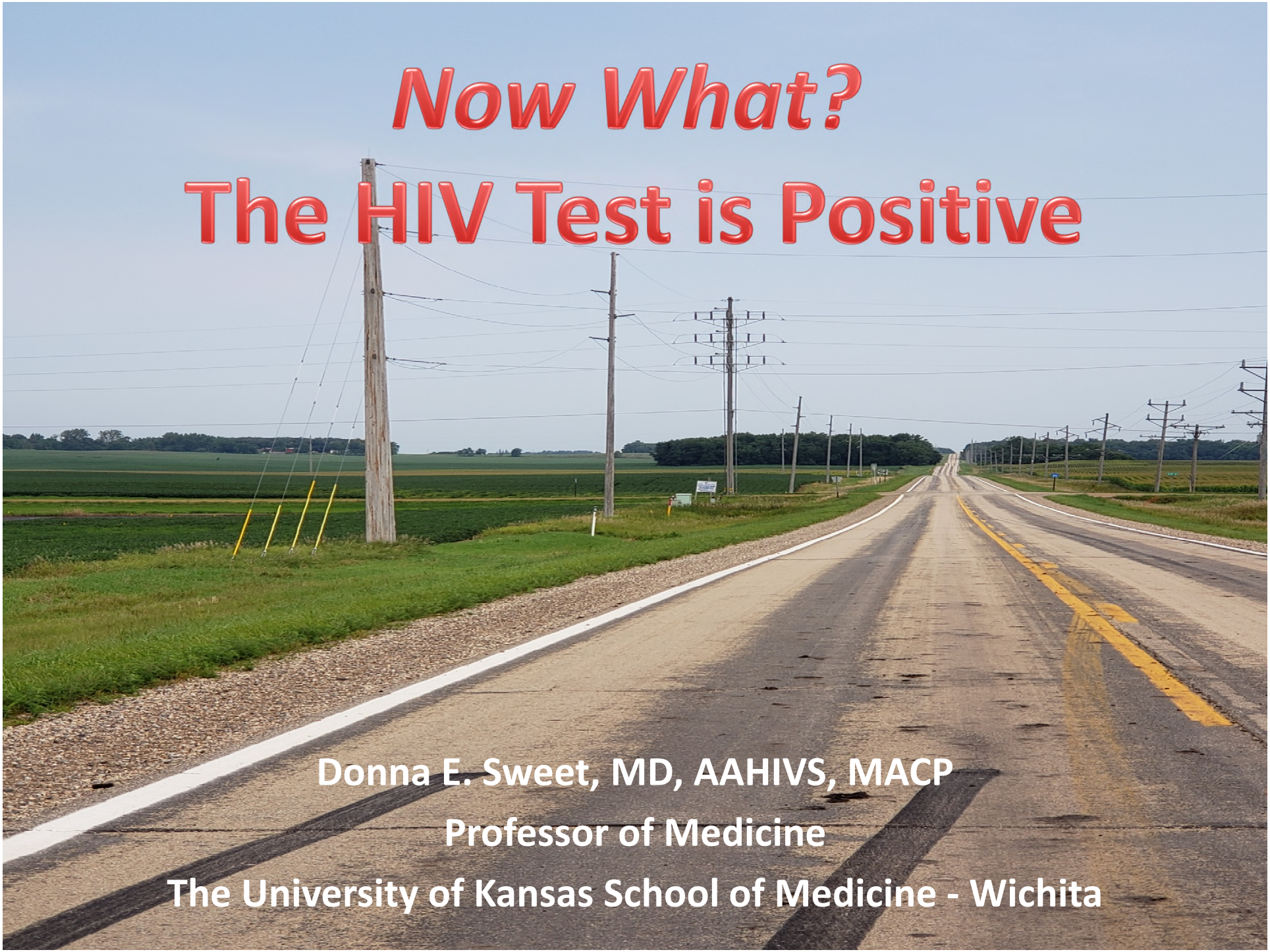

Now What?
The HIV Test is Positive
Donna E. Sweet, MD, AAHIVS, MACP
Professor of Medicine
The University of Kansas School of Medicine - Wichita

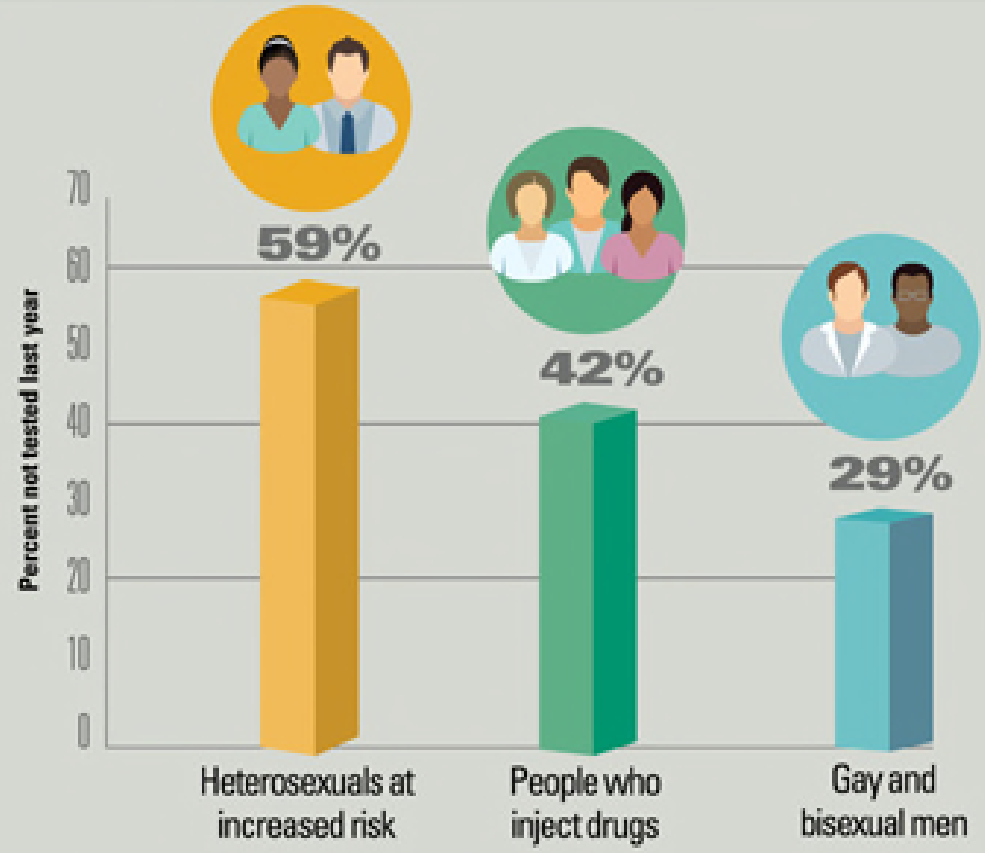
Many people have HIV for years before they know it.

In 2015, **nearly 40,000** people in the US received an HIV diagnosis

1 in **2** had been living with HIV 3 years or more

1 in **4** had been living with HIV 7 years or more

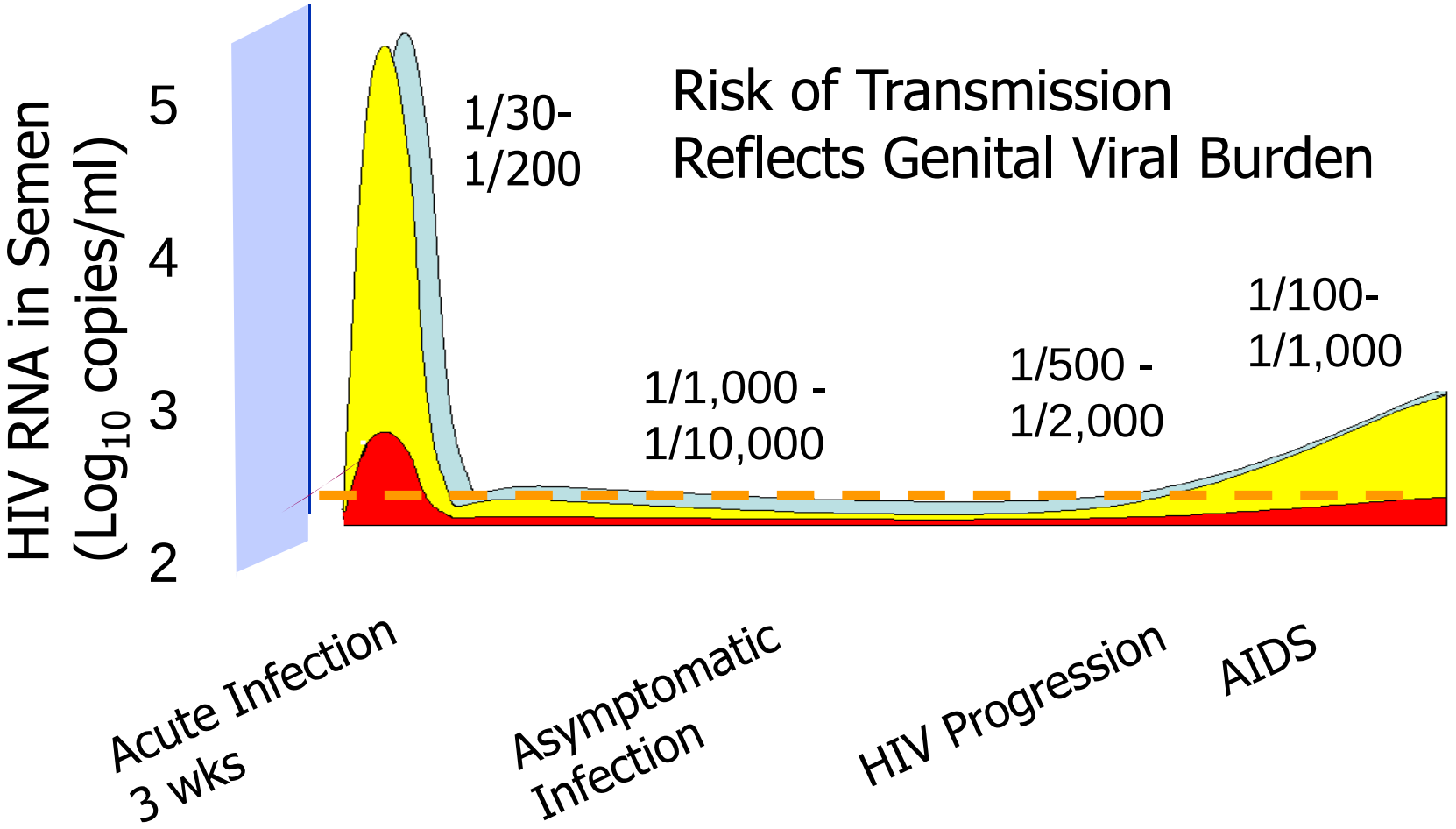
1 in **5** already had the most advanced stage of HIV (AIDS)



Many people at high risk* for HIV aren't getting tested every year

*People at high risk for HIV include: 1) sexually active gay and bisexual men, 2) people who inject drugs, and 3) heterosexuals who have sex with someone who is at risk for or has HIV.

Risk of Sexual Transmission of HIV



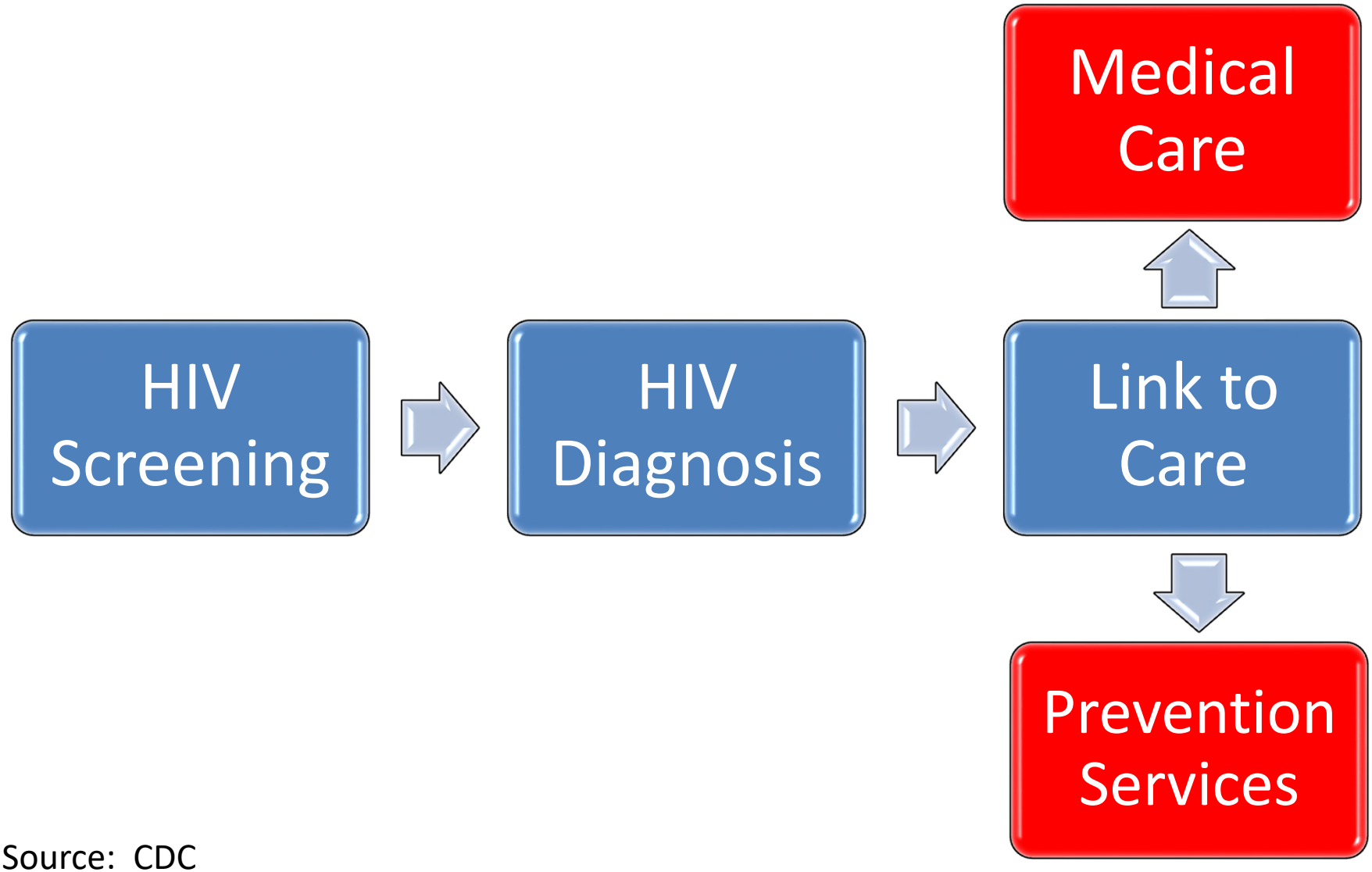
Cohen MS, et al. *J Infect Dis*. 2005; 191:1391-3.

USPSTF Recommends an "A" grade for Routine HIV Screening: April 2013

- The USPSTF statement recommends clinicians screen for HIV in all adolescents and adults aged 15-65 years.
- It also recommends…
  - Repeat HIV screenings for those who are at increased risk for HIV infection, including men who have sex with men and people who inject drugs.
  - Younger adolescents and older adults who are at increased risk for HIV infection should also be screened.
- These updated USPSTF recommendations align with CDC's 2006 guidelines which state that HIV testing should be a routine part of medical care for all American adults and adolescents.

http://www.cdc.gov/hiv/dhap/ehap/fyi/050113.html

Goal of Routine HIV Screening



Source: CDC

Risk of HIV Transmission Highest Early On

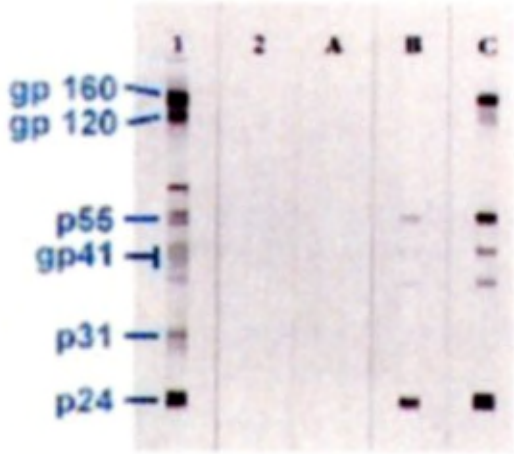
- Montreal, Canada
  - Newly infected patients were 8 times as likely to transmit the virus as individuals who had been infected for several years.
  - Overall, early infection accounted for about one half of all HIV transmissions
  - Because the early state of infection can be asymptomatic, newly infected people may not be aware of their status and will likely test negative on conventional antibody screening

Therapy at early stages of the disease was cited as a way to prevent HIV transmission.

Source: *Journal of Infectious Diseases* (2007;195:951-959)

Testing for HIV: Old Algorithm

- HIV enzyme immunoassay (EIA). If positive, confirmatory western blot (WB)
- Problem with old algorithm:
  - Western blot doesn't turn positive until well after patient acquires infection (6-8 wks): "window period"
  - Reactive EIA & negative WB may be erroneously interpreted as negative test
  - Western blot no longer recommended

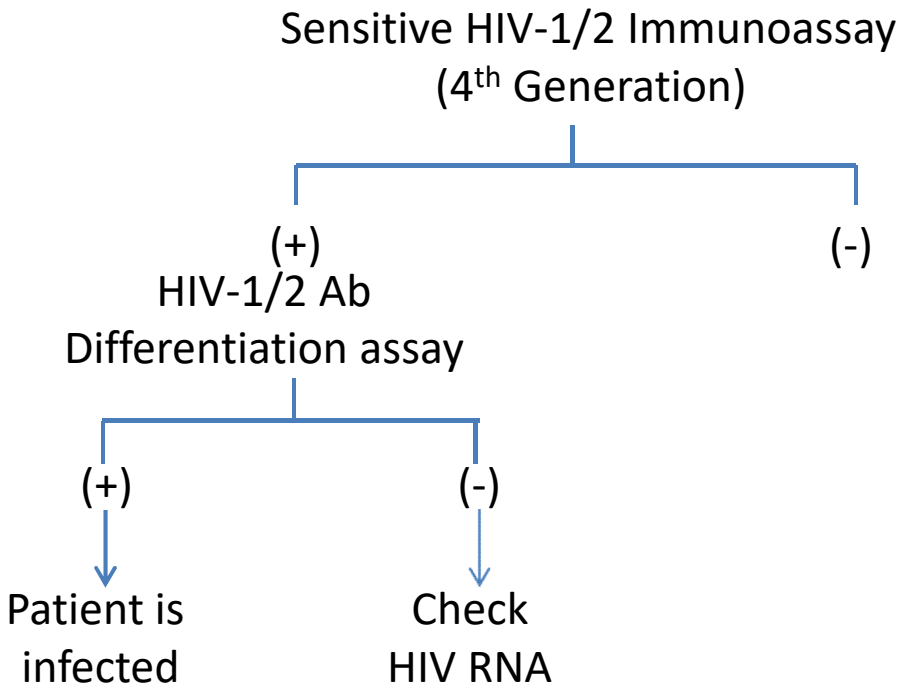


Immunoassay generations:

- 1st: viral lysate Ags (detects IgG; includes WB, IFA)
- 2nd: peptide/recombinant protein Ags (detects IgG)
- 3rd: peptide/recombinant protein Ags (detects IgM, IgG)
- 4th: peptide/recombinant protein Ags, p24 antibody (detects IgM, IgG, p24 antigen)

HIV Testing: Current Algorithm

To "close the window", current testing algorithm:



Advantages:

- RNA testing identifies patients with acute HIV
  - Averted missed diagnoses in 8 – 32% of HIV patients
  - All antibody-positive speciments tested for HIV-2
  - Same day turnaround

4th gen. immunoassay: HIV-1/HIV-2 antibodies and p24 antigen

Branson B, Stekler J. JID. 2012; MMWR June 21, 2013
Laboratory Testing for the Diagnosis of HIV Infection, Updated CDC Recommendations, June 27, 2014.

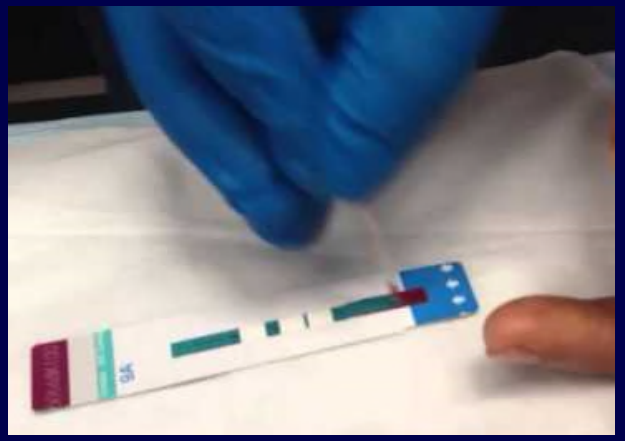
Caveat emptor!

- Although current algorithm more likely to detect HIV during routine screening, if acute HIV suspected, check immunoassay (IA) and HIV RNA
- If IA negative and HIV RNA low (<10,000), repeat RNA testing to r/o false positive result.
- If very recent exposure(<10-15 d), repeat testing 1-2 wks later, particularly if symptoms develop

Point-of-Contact (Rapid) 4th Generation HIV Testing

Alere Determine HIV-1/2 Ag/Ab Combo

- 4th generation for fingerstick or venous whole blood, serum or plasma
- Can be used to detect acute (early) HIV infection before antibody detection
- Distinguish between the detection of p24 antigen and HIV antibodies
- Results in about 20 minutes



http://www.alere.com/ww/en/brands/determine.html


We offer HIV testing
to all patients.
If we fail to ask, ask us.

Routine Testing: The Benefits

Reduces HIV transmission

- HIV+ people who know their status reduce high-risk sex by about 50%
- Lower viral loads from ARVs also reduce transmission

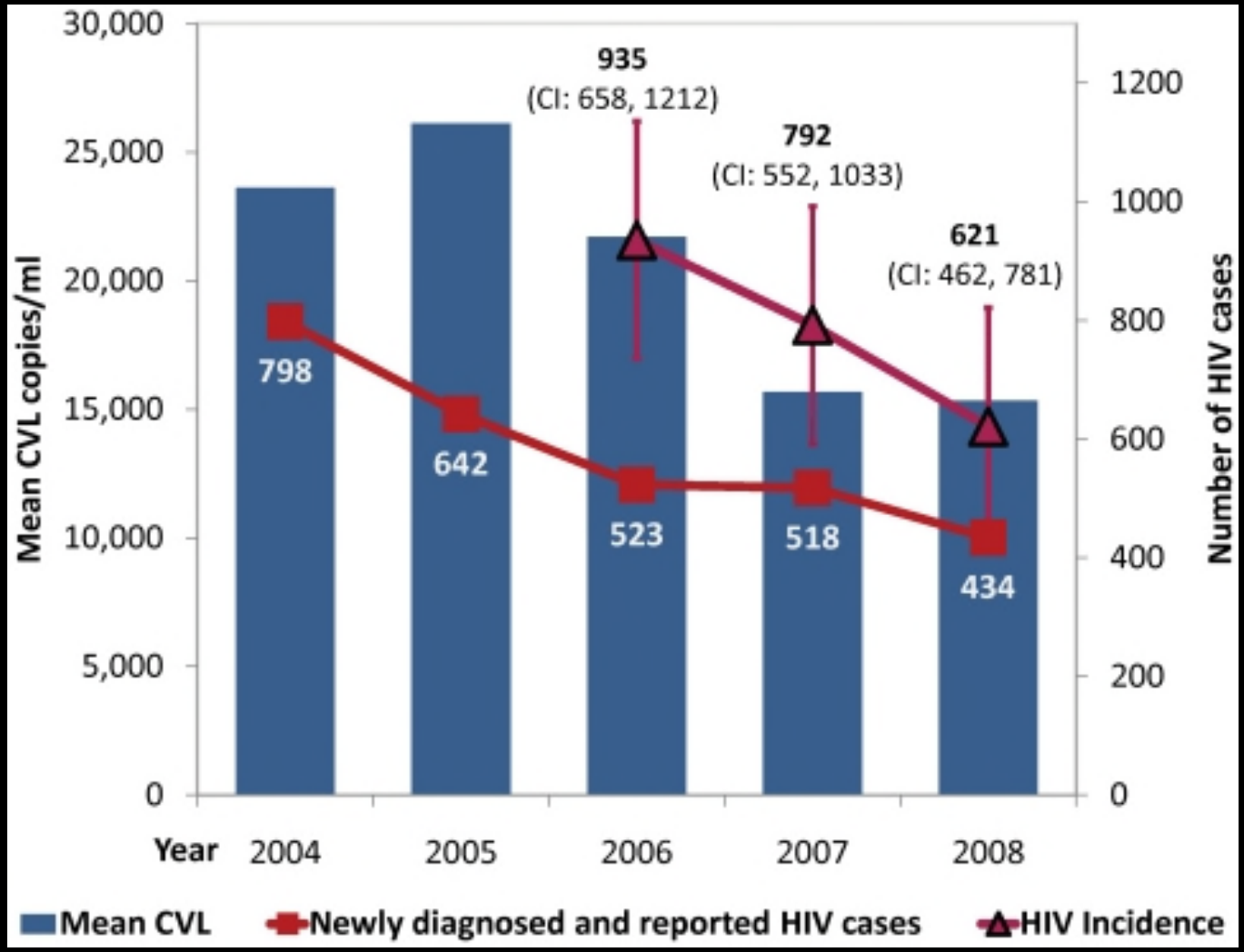
Prolongs Life

- HIV treatment can increase survival by many years and improve quality of life

Preserves Resources

- Successful ART reduces overall care costs for HIV+ patients from $36,532 to $13,865 (U. of Alabama)

Reduced Community Viral Load (CVL) and New HIV Infections, San Francisco



Das M, et al. *PLoS One.* 2010;5:e11068.

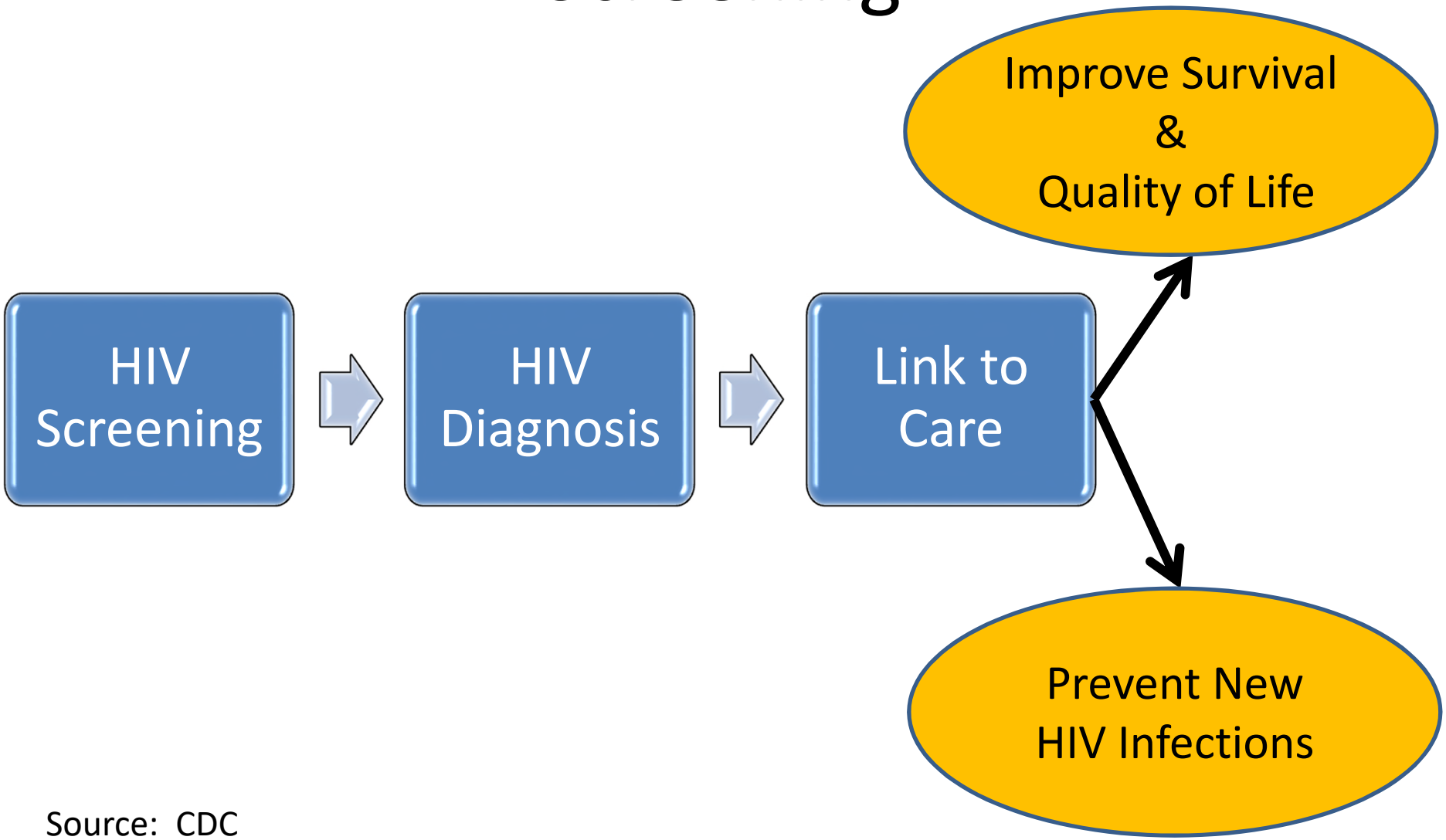
Routine Testing: The Challenges

- **Stigma and discrimination (jobs)**
  Normalizing testing could decrease stigma
- **Patient awareness**
  Provider responsibility to inform, educate
- **Lose possible benefit of counseling**
- **Perceived coercion, privacy, civil liberties**
- **Legal issues (state laws)**
- **Resources to pay for more testing and care**
- **Insurers' disincentive to know**

Approach to Barriers to Routinization of HIV Testing

- Provider should strongly recommend testing as “Standard of Care”.
- Utilize existing indigenous staffing
  - “Empower Them”
- Get your EHR to help
  - “Pop-up reminders
- Offer as Opt-out
  - No informal consent required
  - No required prevention counseling
- Written/Visual information in lobby and exam rooms.
  - “CDC materials”

Desired Outcome of Routine HIV Screening

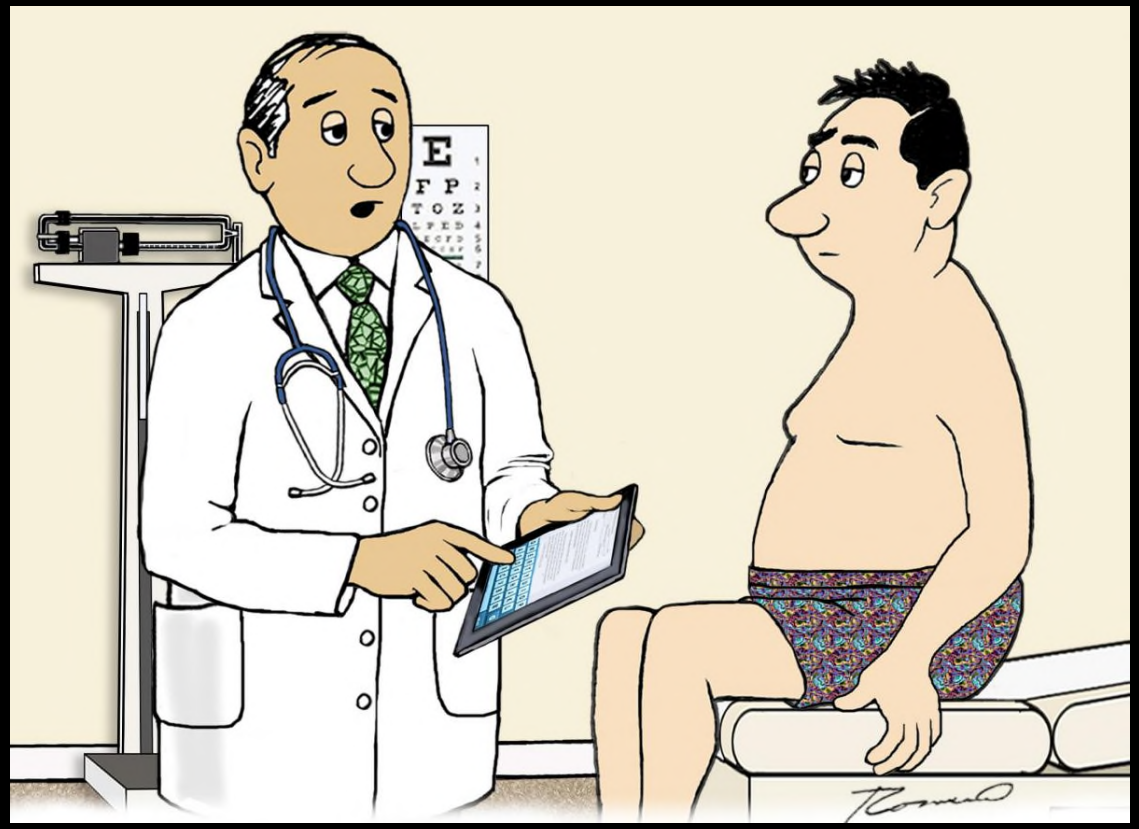


Source: CDC

KEY POINTS!

- Test everyone aged 15-65 at least once
- Test at least annually for those at risk
- Confirm that your patient is linked to care

“Doc, how long do I have…?”



…”Many decades”


IF they get the
right care!

General Lab Orders For New HIV Patient

Laboratory
CBC
CMP
Lipids
Triglycerides
HDL
Cholesterol
LDL

Laboratory
Hepatitis A Ab
Hepatitis B S Ag + Ab
Hepatitis C Ab
Quantiferon

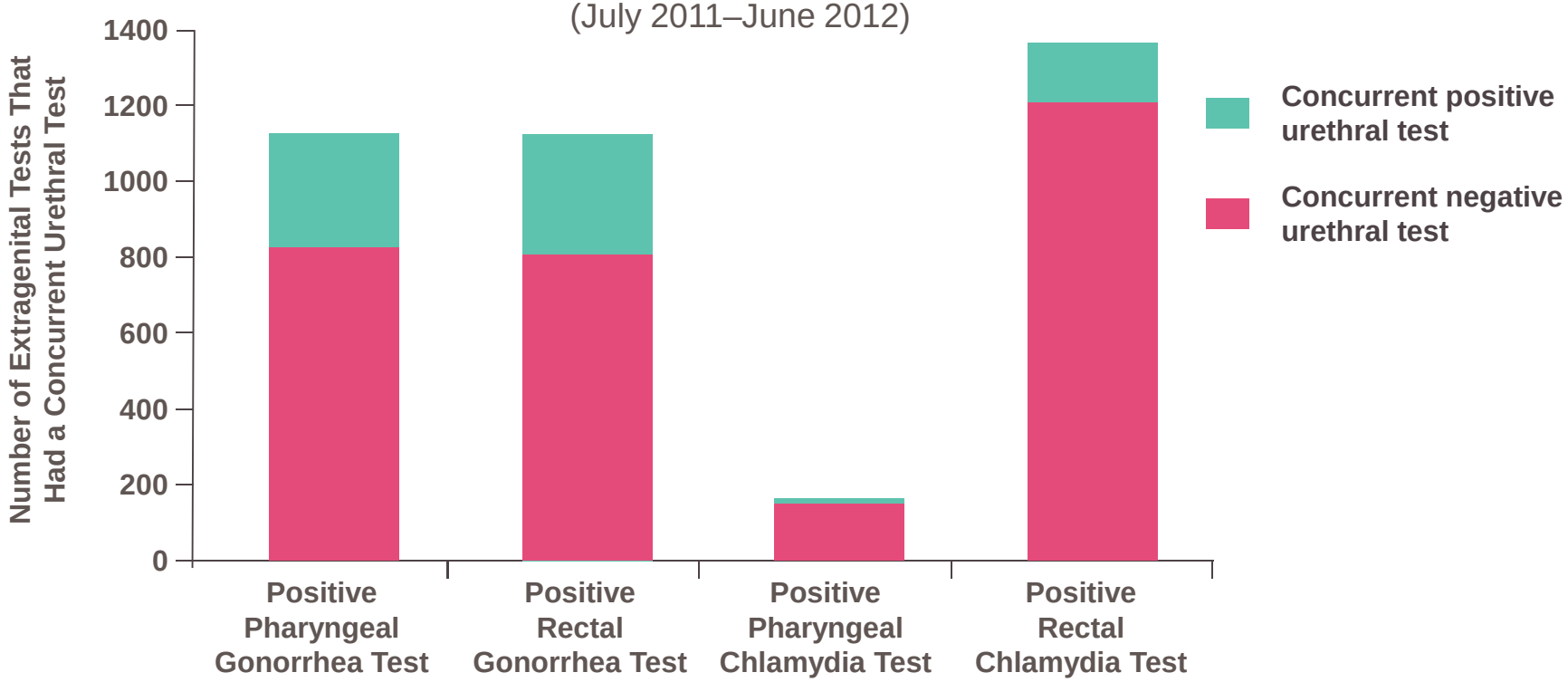
STI Evaluation

- Chlamydia
- Gonorrhea
- Syphilis
- PAP, females (HPV)

The Importance of Extragenital STI Screening

Proportion of Extragenital Gonorrhea And Chlamydia Infections Associated With Concurrent Negative Urethral Tests

Data from 21,994 MSM who had 44,105 visits to STD clinics in the STD Surveillance Network (July 2011–June 2012)



- Most patients with extragenital gonorrhea/chlamydia infections in this study did not have concurrent urethral infections
- 73.8% of pharyngeal gonorrhea infections, 71.8% of rectal gonorrhea, 92.2% of pharyngeal chlamydia infections and 88.3% of rectal chlamydia infections would not have been detected, and presumably would have remained untreated, if only urethral screening had been performed

Patton ME, et al. *Clin Infect Dis*. 2014;58:1564-1570.

- Physicians are faced with the challenge of diagnosing the disease and its most unusual sequelae
- Many manifestations
- Acute onset of nephrotic syndrome, specifically membranous glomerulonephritis, is rare

Syphilis Treatment Update

- HIV patients, follow regimens for non-HIV patients
- PCN should be used, when possible, in HIV patients
- Suggest PCN desensitization if patient is allergic

MMWR Dec. 2010

Syphilis Follow Up

In HIV patients, follow up is the same *EXCEPT*:

- Latent syphilis repeat titers @ 6, 12, 18, 24 mos

Pregnant women

- Titers repeated @ 28-32 wks gestation
- AND at time of delivery
- May need monthly titers in women @ high risk
- Inadequate therapy possible if deliver within less than 30 days of tx

MMWR Dec. 2010

Syphilis In the U.S.

- 6,013 cases in 2001
- 19,999 cases in 2014

- Rates of primary and secondary syphilis increased by 15.1% in the US from 2013 to 2014
- Deaths dropped by 44.1% between 1990 and 2010 world wide

HIV Specific Laboratory Evaluation

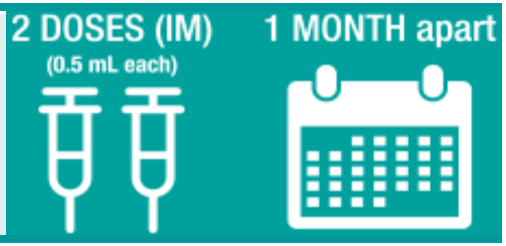
Laboratory Studies
Genotype
HLA B5701
CD4/CD8 lymphocyte panel
HIV RNA quantitative

Immunizations: New HIV Patient

Hepatitis A/B
Pneumococcal 1st: pneumococcal 13-valent conjugate (PCV13, Prevnar) 2nd: 23-valent pneumococcal poly-saccharide vaccine (PPSV23, Pneumovax) after one year.
Tdap
Herpes Zoster
Human Papilloma Virus (HPV)

https://www.infectiousdiseaseadvisor.com/clinical-charts/2018-vaccination-schedule-adults/article/419055/

FDA Approves Heplisav-B for Adults



- Recombinant hepatitis B vaccine – first new in 25 years.
- For all known subtypes of the virus
- Adults aged 18 or older
- Adults who haven't been vaccinated as children
- Two doses with the second dose provided at one month.
- Combination of HBV surface antigen with Dynavax's proprietary Toll-like receptor 9 (TLR9) agonist, designed to enhance immune response.
- Two doses provide higher and earlier seroprotection rates than three doses of the other approved vaccines

Shingrix: Routine Vaccination of People 50 Years Old and Older

- Shingrix® is preferred over Zostavax® (zoster vaccine live) for the prevention of herpes zoster (shingles) and related complications.
- 2 doses of Shingrix separated by 2 to 6 months for immunocompetent adults age 50 years and older:
  - Whether or not they report a prior episode of herpes zoster
  - Whether or not they report a prior dose of Zostavax
- Who have chronic medical conditions unless a contraindication or precaution exists.
- Zostavax remains a recommended vaccine for prevention of herpes zoster in healthy adults 60 years and older and may be used in certain cases, such as when a patient prefers Zostavax or is allergic to Shingrix.
- Efficacy 91% > 70 yo.

https://www.cdc.gov/vaccines/vpd/shingles/hcp/shingrix/recommendations.html

Timing Considerations for Giving Shingrix

For patients who previously had herpes zoster

- There is no specific amount of time you need to wait before administering Shingrix to patients who have had herpes zoster.
- However, you should not give Shingrix to patients who are experiencing an acute episode of herpes zoster.

https://www.cdc.gov/vaccines/vpd/shingles/hcp/shingrix/recommendations.html

RZV (Shingrix) in Immunocompromised Patients

- ***ACIP has not made recommendations regarding the use of RZV in Immunocompromised patients***;
  - this topic is anticipated to be discussed at upcoming ACIP meetings in October 2018 as additional data become available. [1]

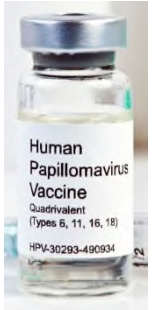
- HIV Recommendations from the Immunization Action Coalition recommend that if the patient is 50 or older and have no symptoms of HIV, you should get the 2-dose series of Shingrex brand of shingles vaccine, even if you were already vaccinated with Zostavax. [2]

1. https://www.cdc.gov/mmwr/volumes/67/wr/mm6703a5.htm?s_cid=mm6703a5_w
2. www.immunize.org/catg.d/p4041.pdf. Item #P4041 (6/18)

RZV (Shingrix) - Study in Immunocompromised Patients

- A phase 1/2a, randomized, placebo-controlled study (N = 123) evaluated the immunogenicity and safety of Shingrix compared to placebo (saline) administered on a 3-dose schedule (0, 2 and 6 months) in adults $\geq$ 18 yrs of age with HIV.
- The results showed:
  - Superiority of the *Shingrix* group over the saline group with respect to cell-mediated response in the sub-population of those with high $CD4^+$ T-cell counts (ART-receiving plus ART naive) was demonstrated since the lower limit of CI for the GMR vaccine: saline at month 7 was >3 (46.22 [90% CI, 33.63.53]; P<0.0001).

Berkowitz EM, Moyle G, Stellbrink HJ, et al. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized placebo-controlled study. JID 2015; 211:1279-1286.



Human papilloma virus (HPV) vaccination

- Females through age 26yrs and males through age 21yrs should receive HPV vaccine.
- Males 22–26yrs may be vaccinated based on individual clinical decision.
- Give a 3-dose series at 0, 1–2, and 6mos to persons with no previous dose of HPV. The minimum interval should be 4wks between doses 1 and 2, 12wks between doses 2 and 3, and 5mos between doses 1 and 3; repeat doses if given too soon.
- If initiated vaccination at 9–14yrs and received 1 dose or 2 doses <5mos apart, give 1 dose. No additional dose is needed if initiated vaccination at 9–14yrs and received 2 doses at least 5mos apart.
- HPV vaccination is recommended for men who have sex with men (MSM) and for immunocompromised persons (including those with HIV infection) through age 26yrs who have not received any HPV vaccine.
- Not recommended for use in pregnant women. However, pregnancy testing is not needed before vaccination. If a woman is found to be pregnant after initiating the vaccination series, no intervention is needed; the remainder of the 3 dose series should be delayed until completion of or termination of pregnancy.

HIV & Smoking: Deadly Combo

- The study also estimated the total potential years of life gained if some of the 248,000 people with HIV in the United States who smoke were to stop smoking.
  - They found that among people with HIV who entered care when they were age 40 (with a mean $CD4^+$ T-cell count of 360 cells/mm^3) and who continued to smoke, men lost 6.7 years of life expectancy and women lost 6.3 years compared with people with HIV who never smoked.
  - Men with HIV who quit smoking got back 5.7 years of life, while women got back 4.6 years.
- People with HIV in this study received a greater benefit from smoking cessation if they were younger, had higher baseline $CD4^+$ T-cell counts, and were adherent to their ART.
- The study estimated that smoking cessation by 10% to 25% of people with HIV who smoke could save approximately 106,000 to 256,000 years of life.

http://www.medpagetoday.com/resource-center/Contemporary-HIV-Management/ART-and-Smoking/a/62814?eun=g6511588d19r&xid=NL_MPT_HIVMANAGEMENT_2017-02-09

Take Note!

People with HIV who smoke may now face a risk to their life expectancy from smoking <u>equal to or greater than that from HIV itself</u>

Stated by:
Krishna P. Reddy, MD, attending pulmonologist and critical care physician at Massachusetts General Hospital and an instructor in medicine at Harvard Medical School.

Dr. Reddy is also the lead author of a new study on the impact of cigarette smoking and smoking cessation on life expectancy among people with HIV in the United States.[2]

http://www.medpagetoday.com/resource-center/Contemporary-HIV-Management/ART-and-Smoking/a/62814?eun=g6511588d19r&xid=NL_MPT_HIVMANAGEMENT_2017-02-09

HIV & Smoking: Deadly Combo

- Among people with HIV in the United States who are in care, more than 40% are smokers, and an additional 20% are former smokers.
- Smoking makes people living with HIV more vulnerable than smokers in the general population in a number of ways.
  - the risk of death for people with HIV who currently smoked was 2.8 times that of people with HIV who never smoked.
  - The risk of death for people with HIV who were former smokers was 1.0 to 1.8 times that of people with HIV who never smoked, depending on how old the former smoker was when he or she stopped smoking.

http://www.medpagetoday.com/resource-center/Contemporary-HIV-Management/ART-and-Smoking/a/62814?eun=g6511588d19r&xid=NL_MPT_HIVMANAGEMENT_2017-02-09

When to Treat

Note…

"Antiretroviral therapy (ART) is recommended for all HIV-infected individuals. . . . Individualizing treatment with involvement of the patient in decision making is the cornerstone of any treatment plan."

Panel on Antiretroviral Guidelines for Adults and Adolescents.
www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Changing Criteria for Antiretroviral Therapy Initiation in DHHS Guidelines

CD4+ Count, cells/mm^3	1998	2001	2006	2008	2009	2012
> 500	Offer if VL > 20K	Offer if VL > 20K	Consider if VL ≥ 100K	Consider in certain groups*	Consider†	Treat
350-500	**Offer if VL > 20K**	**Consider if VL > 55K**	**Consider if VL ≥ 100K**	**Consider in certain groups***	**Treat**	**Treat**
200-350	Offer if VL > 20K	Offer, but controversy exists	Offer after discussion with patient	Treat	Treat	Treat
< 200 or symptomatic	**Treat**	**Treat**	**Treat**	**Treat**	**Treat**	**Treat**

*Pregnant women, patients with HIV-associated nephropathy, and patients with HBV that requires treatment.

†50% of panel members recommended starting antiretroviral therapy; 50% of members viewed treatment as optional.

"As a triad of critical clinical trials, SMART, HPTN 052, and START settle the debate concerning early initiation of ART. Clinicians and patients can now be assured that ART's benefits outweigh the risks for the infected person, regardless of CD4+ T-CELL Count."

- Dr. Anthony S. Fauci, MD

Source: N ENGL J MED 373:23 NEJM.org December 3, 2015

What is the START Study

- The START ("Strategic Timing of AntiRetroviral Treatment") study is a randomized, controlled clinical trial designed to more clearly define the optimal time for HIV- infected individuals to begin antiretroviral therapy.
- The trial enrolled healthy, asymptomatic, HIV-infected people whose level of CD4+ T cells—a measure of immune system health—exceeded 500 cells per cubic millimeter (mm3).
- The primary objective was to determine whether taking antiretroviral therapy immediately would lead to a lower risk of AIDS, other serious illnesses or death compared to waiting until a person's CD4+ T-cell count fell to 350 cells/mm3.

Key Findings From START Study

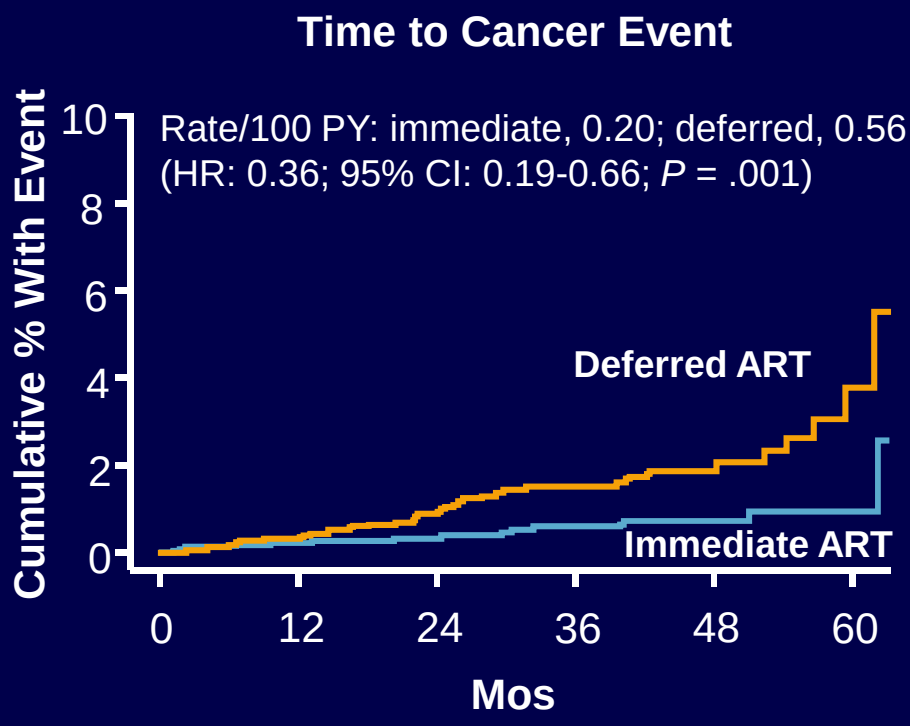
Types of Events	No. of Persons With an Event		Hazard Ratio in Early vs Deferred Group, 95% CI and *P* Value
	Early ART Group, n=2,326	Deferred ART Group, n=2,359	
Opportunistic diseases	14	50	0.28 (0.15-0.50; *P*<0.001)
Serious non-AIDS events (cardiovascular, liver, and kidney disease + non-AIDS-defining cancers) and death not attributable to AIDS	29	47	0.61 (0.38-0.97; *P*=0.04)
Cancer[a]	14	39	0.36 (0.19-0.66; *P*=0.001)

[a] Of the 53 cancer events, 26 (5 vs 21 in the early and deferred groups, respectively) were affected by immunodeficiency, whereas the remaining 27 (9 vs 18, respectively) were not.

ART, antiretroviral therapy

START: Cancer Events With Immediate vs Deferred ART

Cancer Event, n	Immediate ART (n = 2326)	Deferred ART (n = 2359)
Total	**14**	**39**
Kaposi's sarcoma	1	11
Lymphoma, NHL + HL	3	10
Prostate cancer	2	3
Lung cancer	2	2
Anal cancer	1	2
Cervical or testis cancer	1	2
Other types*	4	9



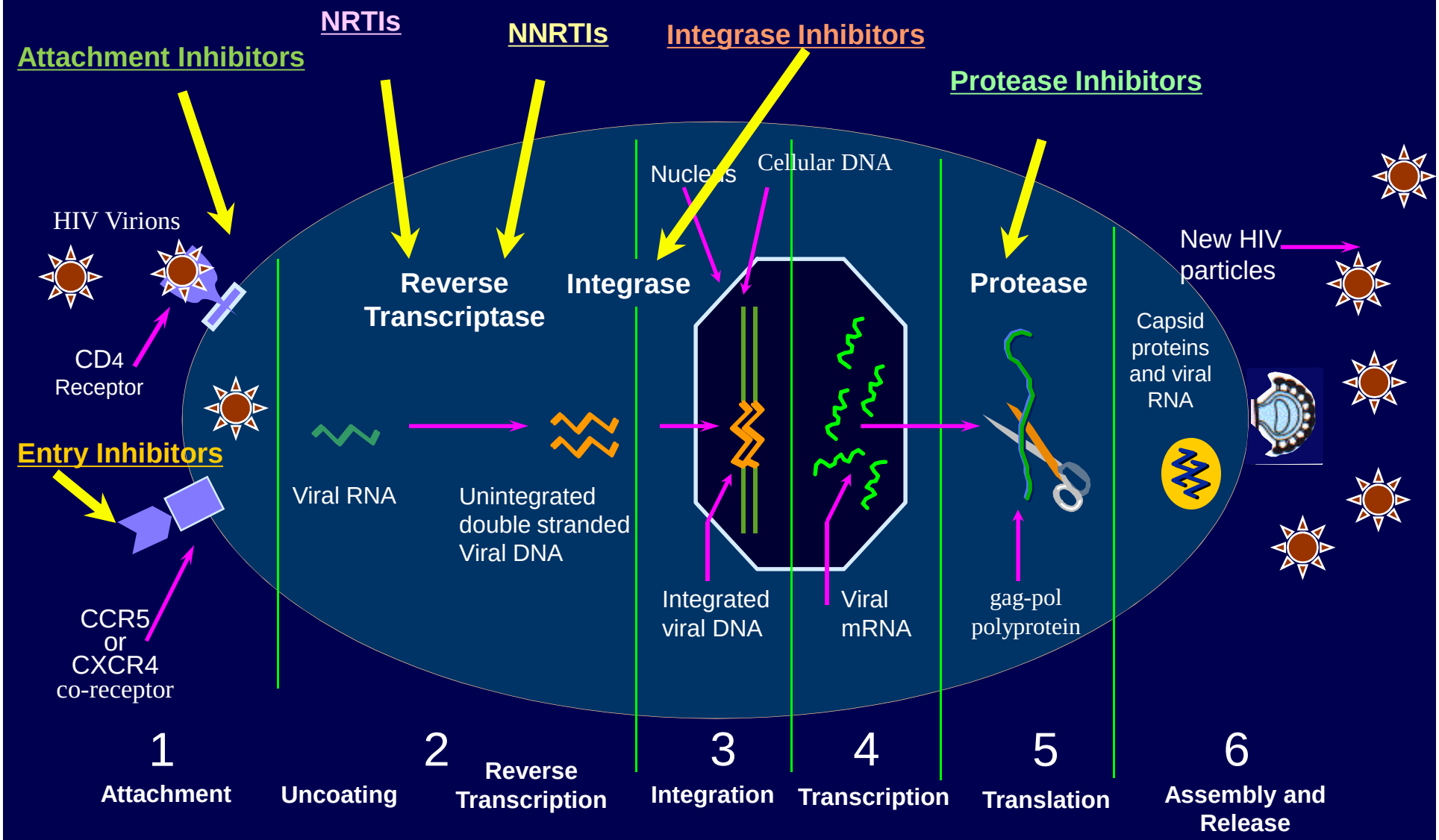
*Immediate ART: squamous cell carcinoma, plasma cell myeloma, bladder cancer, fibrosarcoma. Deferred ART: gastric adenocarcinoma, breast cancer, ureteric cancer, malignant melanoma, myeloid leukemia, thyroid cancer, leiomyosarcoma, liver cancer, squamous cell carcinoma of head and neck.

Lundgren JD, et al. N Engl J Med. 2015;373:795-807.
Lundgren J, et al. IAS 2015. Abstract MOSY0302.

Slide credit: clinicaloptions.com

What to Use

HIV Replication Cycle and Sites of Drug Activity



Adapted:Levy JA. HIV and the Pathogenesis of AIDS. 2nd ed. Washington, DC: American Society for Microbiology; 1998:9-11

Licensure of Antiretroviral Agents by Year

Updated: 7/17/2018

1987:	zidovudine (Retrovir)
1991:	didanosine (Videx)
1992:	zalcitabine (Hivid)
1994:	stavudine (Zerit)
1995:	lamivudine (Epivir) saquinavir (Invirase)
1996:	ritonavir (Norvir) indinavir (Crixivan) nevirapine (Viramune)
1997:	nelfinavir (Viracept) delavirdine (Rescriptor)
1998:	efavirenz (Sustiva) abacavir (Ziagen)
1999:	amprenavir (Agenerase)
2000:	lopinavir/ritonavir (Kaletra)
2001:	tenofovir (Viread)
2003:	enfuvirtide (Fuzeon)
6/03:	atazanavir (Reyataz)
7/03:	emtricitabine (Emtriva)
8/04:	lamivudine/abacavir sulfate (Epzicom)
6/05:	tipranavir (Aptivus)
6/06:	darunavir (Prezista)
7/06:	efavirenz/emtricitabine, tenofovir DF (Atripla)
8/07	maraviroc (Selzentry)
10/07	raltegravir (Isentress)
1/08	etravirine (Intelence)
5/20/11	rilpivirine (Edurant)
8/11/11	rilpivirine/ tenofovir/ emtricitabine(Complera)
7/16/12	emtricitabine/tenofovir disoproxil fumarate (Truvada)
8/28/12	emtricitabine/ tenofovir/elvitegravir/ cobicistat. (Stribild)
8/12/13	dolutegravir (Tivicay)
8/30/14	abacavir/dolutegravir/lamivudine (Triumeq)
1/29/15	atazanavir 300 mg and cobicistat /150 mg (Evotaz)
11/5/15	elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide.(Genvoya)
3/1/16	rilpivirine+emtricitabine+tenofovir alafenamide (Odefsey)
4/6/16	emtircitabine+tenofovir alafenamide (Descovy)
11/21/2017	dolutegravir sodium / rilpivirine hydrochloride (Juluca)
2/7/2018	bictegravir 50 mg /emtricitabine 200 mg/tenofovir alafenamide 25 mg (Biktarvy)
3/6/2018	Trogarzo (ibalizumab-uiyk) IV 2,000mg/800mg
7/17/2018	Symtuza (darunavir 800 mg/cobicistat 150 mg/ emtricitabine 200 mg/tenofovir alafenamide 10 mg)

Blue: Fixed dose combinations of existing drugs

Then…and now…

- 1996
  - Typical ART regimens: 18-24 pills, divided 3-4 times per day

- 2018
  - 1 pill once a day

Treatment Is Effective, Safe, Simple, and Tolerable

Once-daily, single-tablet regimens

- EFV/TDF/FTC (Atripla®)[a]
- RPV/TDF/FTC (Complera®)[b]
- RPV/TAF/FTC (Odefsey®)[c]
- **EVG/Cobi/TDF/FTC (Stribild®)[d]**
- **EVG/Cobi/TAF/FTC (Genvoya®)[e]**
- **DTG/ABC/3TC (Triumeq®)[f]**
- DTG/RPV (Juluca®)[g]
- **BIC/TAF/FTC (Biktarvy®)[h]**

a. Atripla PI; b. Complera PI; c. Odefsy PI; d. Stribild PI; e. Genvoya PI; f. Triumeq PI, g. Juluca PI, h. Biktarvy PI.

So What ART is *REALLY* New?

Two Drugs/One Pill - Juluca

Antiretroviral Treatment: New TAF Drugs

Non-TAF	TAF Drug
(Stribild) emtricitabine/ tenofovir/ elvitegravir/ cobicistat	(Genvoya) FTC/TAF + EVG/COBI
(Complera) rilpivirine/ tenofovir/emtricitabine	(Odefsey) FTC/TAF + RPV
(Truvada) emtricitabine/tenofovir disoproxil fumarate	(Descovy) FTC/TAF

BIKTARVY®
(bictegravir 50 mg/emtricitabine 200 mg/ tenofovir alafenamide 25 mg)

- A single-tablet regimen (STR)
- Combines the FTC/TAF backbone with bictegravir, a novel and unboosted integrase strand transfer inhibitor.
- Bictegravir is an integrase inhibitor with a 50 mg dose that does not need to be boosted or taken with food.
- It is co-formulated with 200 mg emtricitabine and a 25 mg dose of TAF.

BIKTARVY®
(bictegravir 50 mg/emtricitabine 200 mg/ tenofovir alafenamide 25 mg)

- Bictegravir has a plasma half-life of 18 hours, which suggests some flexibility for adherence and
- a resistance profile that might retain sensitivity to resistance mutations associated with raltegravir and elvitegravir but that is similar to dolutegravir.

Approved 7/17/2018

SYMTUZA™

(darunavir 800 mg/cobicistat 150 mg/ emtricitabine 200 mg/tenofovir alafenamide 10 mg)

- One pill daily with food
- A complete regimen (1 pill daily) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults:
  - who have no prior antiretroviral treatment history or
  - who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir.

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=210455

Approved 7/17/2018

SYMTUZA™

(darunavir 800 mg/cobicistat 150 mg/ emtricitabine 200 mg/tenofovir alafenamide 10 mg)

- Prior to Initiation:
  - Prior to or when initiating, test patients for HBV infection
  - Prior to or when initiating, and druing treatmet on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients.
    - In patients with chronic kidney disease, also assess serum phosphorus

Breakthrough!
First Biologic!

FDA approved March 6, 2018

TROGARZO (ibalizumab-uiyk)

- Treatment of human immunodeficiency virus type 1 (HIV-1) infection
- Injection for intravenous use in heavily treatment-experienced adults with multidrug resistant (MDR) HIV-1 infection failing their current antiretroviral regimen.
- A recombinant humanized monoclonal antibody, blocks HIV-1 from infecting CD4+ T cells by binding to domain 2 of CD4 and interfering with post-attachment steps required for the entry of HIV-1 virus particles into host cells and preventing the viral transmission that occurs via cell-cell fusion

Breakthrough!
First Biologic!

FDA approved March 6, 2018

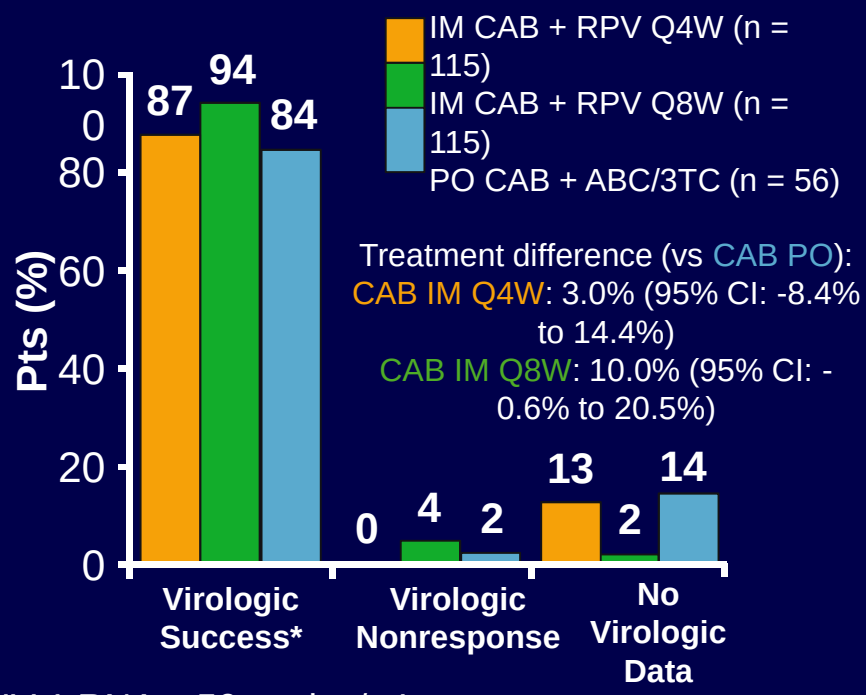
TROGARZO (ibalizumab-uiyk)

- TROGARZO is administered intravenously once every 14 days and used in combination with other antiretroviral medications.
- Patients should receive a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks.
- The most common adverse reactions to TROGARZO were
  - diarrhea,
  - dizziness,
  - nausea and
  - rash.
- Severe side effects included rash and changes in the immune system (immune reconstitution syndrome).

LATTE-2: 96-Wk Results for Cabotegravir IM + Rilpivirine IM as Long-Acting Maintenance ART

- **Cabotegravir:** INSTI formulated as PO tablet and for long-acting IM injection
- LATTE-2: phase IIb study in which pts randomized to CAB 400 mg + RPV 600 mg IM Q4W, CAB 600 mg + RPV 900 mg IM Q8W, or CAB 30 mg + ABC/3TC 600/300 mg PO QD after induction/virologic suppression with oral CAB + ABC/3TC (N = 309)

Wk 96 Virologic Efficacy



*HIV-1 RNA < 50 copies/mL.

- At 96 wks, ~ 30% pts receiving IM injection experienced ISR
  - 99% of ISRs mild/moderate
- AEs leading to withdrawal
  - Pooled Q4W/Q8W IM arms, 4%; PO arm, 2%
- Withdrawals between Wks 48 and 96: CAB IM arms, n = 4 (n = 1 for AE, n = 3 withdrew consent); CAB PO arm, n = 3 (all withdrew consent)
- No additional PDVFs after Wk 48 in any arm
- ~ 88% of pts receiving IM CAB very satisfied to continue present treatment vs 43% receiving PO CAB

Eron J, et al. IAS 2017. Abstract MOAX0205LB. Margolis DA, et al. Lancet. 2017;[Epub ahead of print].

Dual-Therapy Regimens for Initial ART

- **ANDES:** randomized phase IV study of DRV/RTV + 3TC vs DRV/RTV + TDF/3TC in ART-naive pts (N = 145)[1]
  - Baseline: 24% HIV-1 RNA > 100,000 c/mL

HIV-1 RNA < 400 c/mL (ITT) at Wk 24, n/N (%)	DRV/RTV + 3TC	DRV/RTV + TDF/3TC
Overall	71/75 (95)	68/70 (97)
BL HIV-1 RNA > 100,000 c/mL	20/20 (100)	15/15 (100)

- 1 virologic failure with DRV/RTV + TDF/3TC

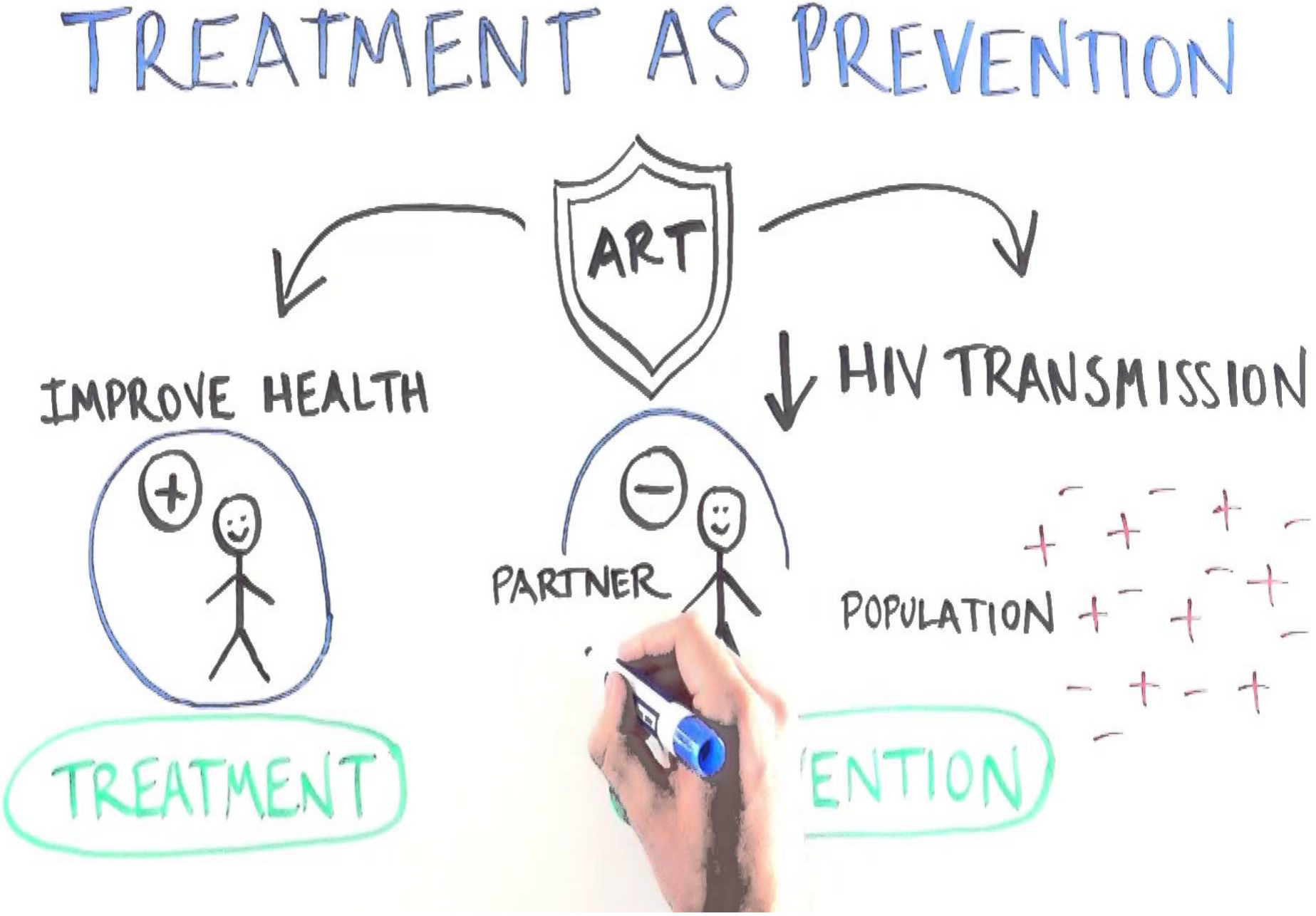
- **ACTG A5353:** single-arm phase II study of DTG + 3TC in ART-naive pts (N = 120)[2]
  - Baseline: 31% HIV-1 RNA > 100,000 c/mL

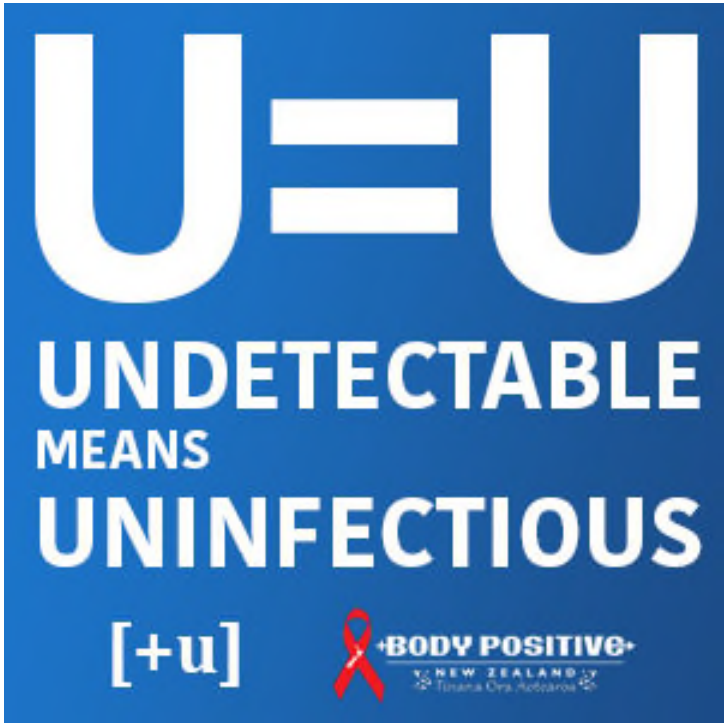
Virologic Outcome at Wk 24, n (%)	Baseline HIV-1 RNA, c/mL		Total (N = 120)
	> 100,000 (n = 37)	≤ 100,000 (n = 83)	
Success*	33 (89)	75 (90)	108 (90)
Nonsuccess	3 (8)	2 (2)	5 (4)
No data	1 (3)	6 (7)	7 (6)

*HIV-1 RNA < 50 copies/mL.

- n = 3 with PDVF; n = 1 with emergent M184V and R263R/K mixture
- GEMINI 1/2 randomized phase III trials of DTG + 3TC ongoing[3,4]

1. Sued O, et al. IAS 2017. Abstract MOAB0106LB. 2. Taiwo BO, et al. IAS 2017. Abstract MOAB0107LB. 3. ClinicalTrials.gov. NCT02831673. 4. ClinicalTrials.gov. NCT02831764.


TREATMENT AS PREVENTION
ART
IMPROVE HEALTH
HIV TRANSMISSION
PARTNER
POPULATION
TREATMENT
ENTION



- There is now evidence-based confirmation that the risk of HIV transmission from a person living with HIV (PLHIV), who is on Antiretroviral Therapy (ART) and has achieved an undetectable viral load in their blood for at least 6 months is negligible to non-existent.

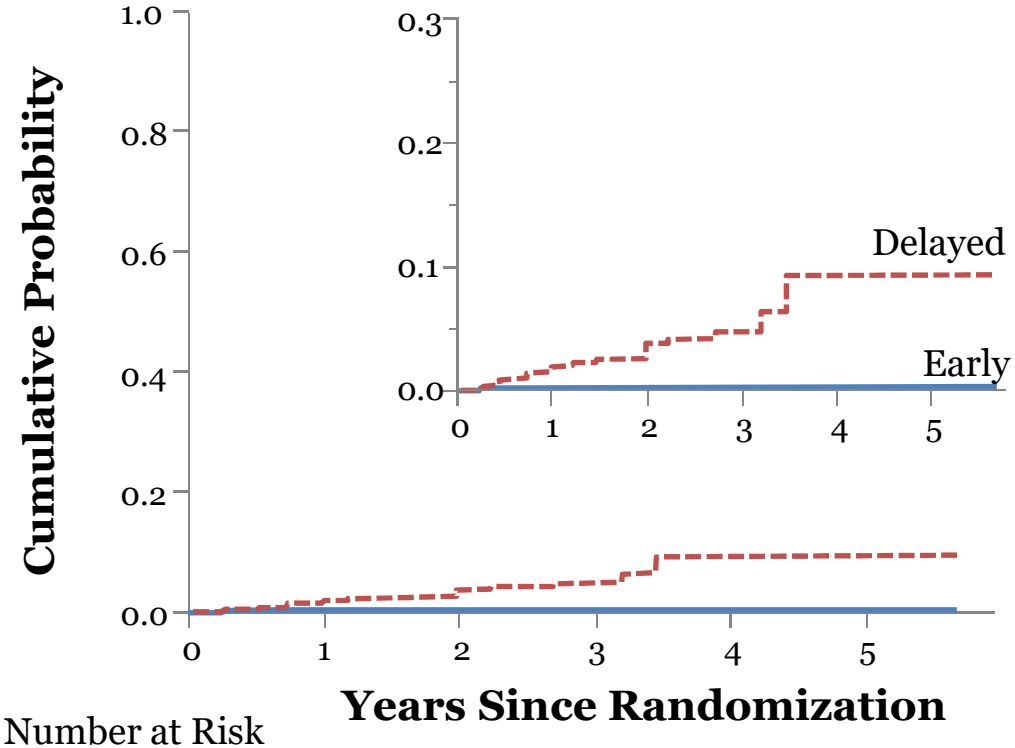
- While HIV is not always transmitted even with a detectable viral load, when the partner with HIV has an undetectable viral load this both protects their own health and prevents new HIV infections.

https://www.preventionaccess.org/consensus

Treatment as Prevention: HPTN 052–96% Reduction in HIV Transmission

- HIV serodiscordant couples randomized to receive either early or delayed ART
- Early ART was initiated in the HIV-infected partner at enrollment
- Delayed ART was initiated after 2 consecutive CD4 cell counts ≤250 cells/mm^3 or the development of an AIDS-related illness

Kaplan-Meier estimate for cumulative probabilities of linked HIV-1 transmission between partners among those in the early-therapy and delayed-therapy groups



Number at Risk

Early	893	658	298	79	31	24
Delayed	882	655	297	80	26	22

Cohen MS, et al. *N Engl J Med.* 2011;365:493-505.

HPTN 052: HIV Transmission Reduced by 96% in Serodiscordant Couples

Total HIV-1 Transmission Events: 39
(4 in immediate arm and 35 in delayed arm; $P < .0001$)

Linked Transmissions: 28

Unlinked or TBD Transmissions: 11

Delayed Arm: 27

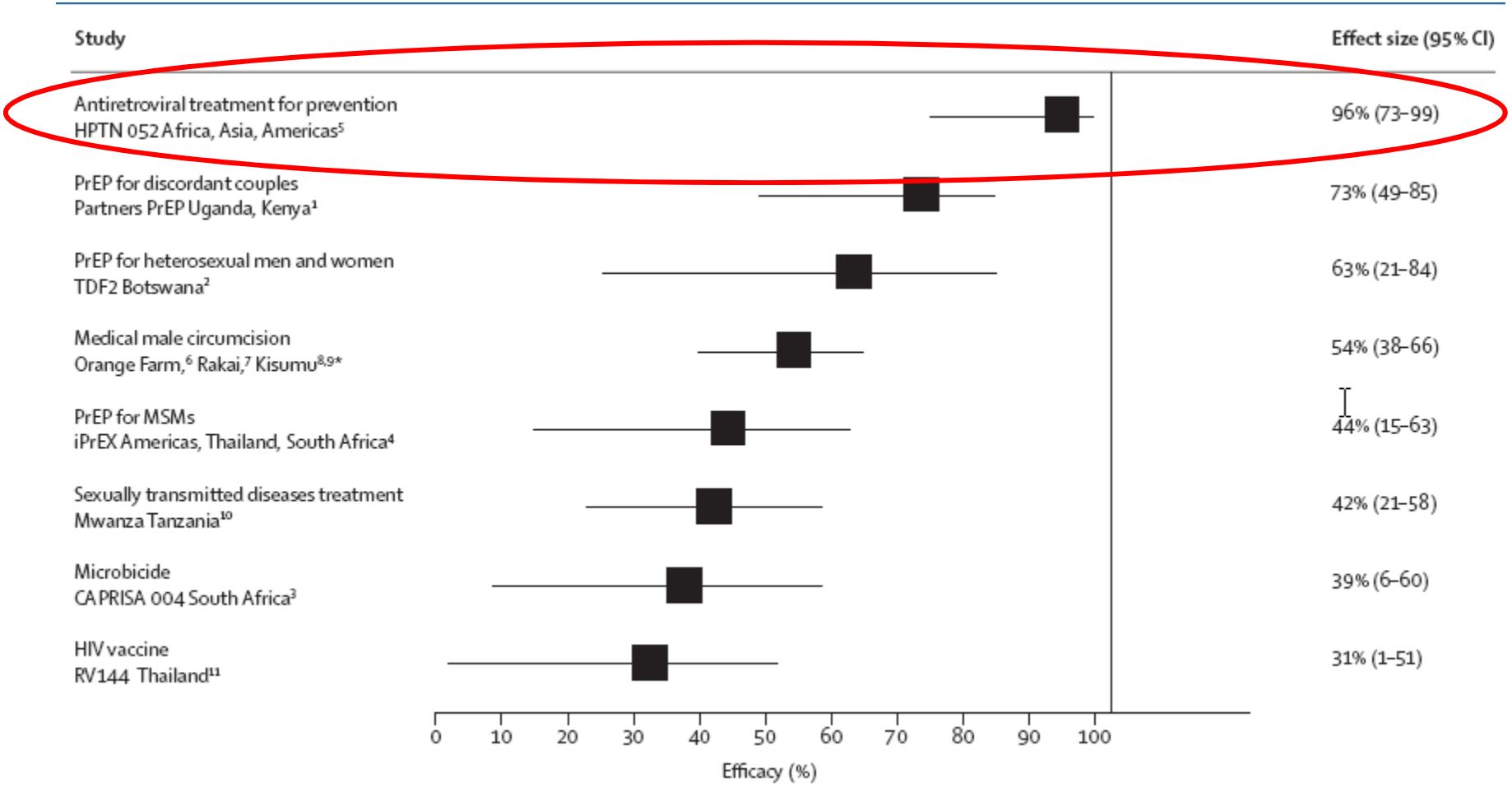
Immediate Arm: 1

***P* < .001**

Single transmission in patient in immediate ART arm believed to have occurred close to time therapy began and prior to suppression of VL

Cohen MS, et al. IAS 2011. Abstract MOAX0102.
Cohen MS, et al. *N Engl J Med* 2011

Efficacy of HIV Prevention Strategies From Randomized Clinical Trials



The difference is in the denominators • All people living with HIV (includes persons with diagnosed and undiagnosed infection) is used as the denominator for the prevalence-based continuum. People living with ***diagnosed*** HIV is the denominator used for the diagnosis-based continuum.

Figure 1: Prevalence-based HIV Care Continuum, 2015

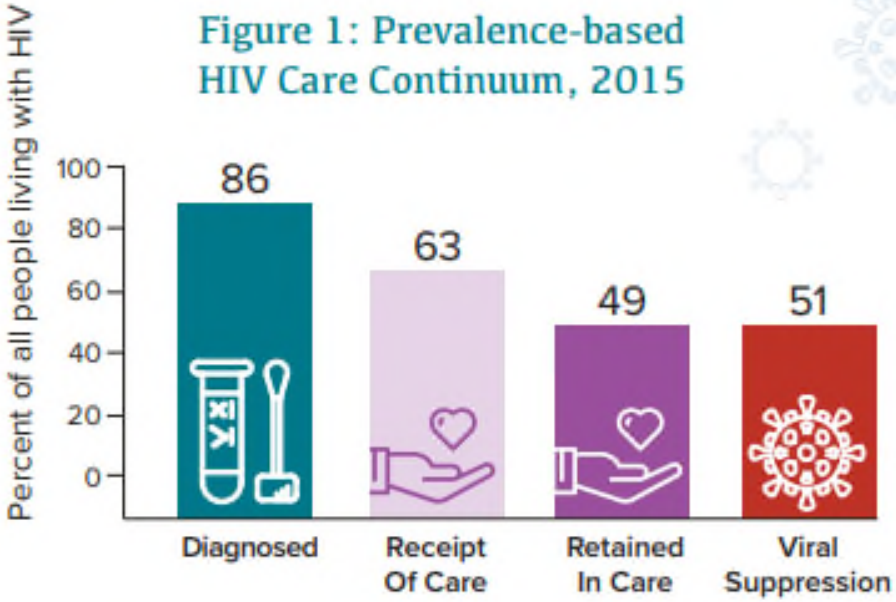
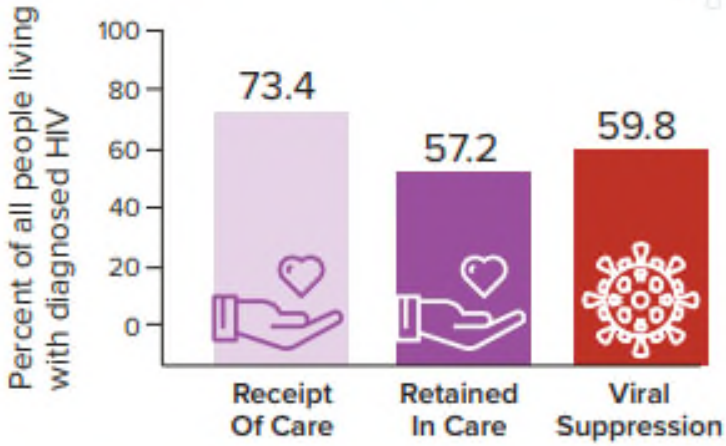
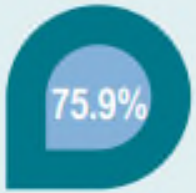


Figure 2: Diagnosis-based HIV Care Continuum, 2015



Linked to Care

- In 2016, 75.9% of persons receiving a diagnosis of HIV were linked to care within 1 month.
- Defined as linked to care within 1 month of HIV diagnosis.



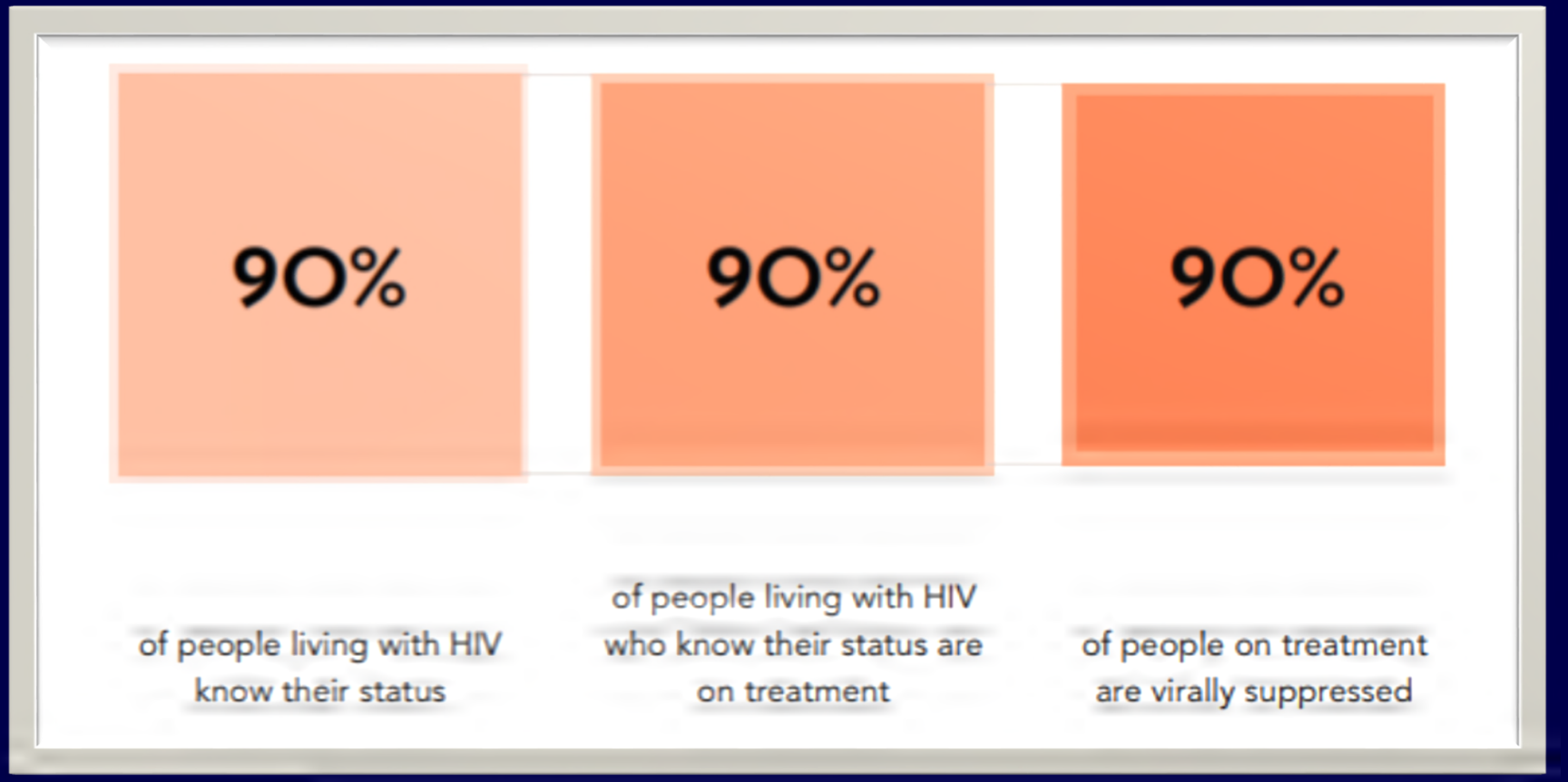
- Denominator is persons receiving a diagnosis of HIV in a measurement year; numerator is the number of persons who were linked to care within 1 month of HIV diagnosis.
- Because it has a different denominator, it cannot be directly compared to other steps.

See Table 1 on page 4 for additional details

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of HIV/AIDS Prevention

https://www.cdc.gov/hiv/pdf/library/factsheets/cdc-hiv-care-continuum.pdf

The 90 – 90 – 90 Targets for 2020



http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf

Most Women Diagnosed with HIV Not Linked to Care

- More than half of women surveyed in the US and its territories who tested positive for HIV in 2015 had received a diagnosis in the past; however, most were not linked to care.

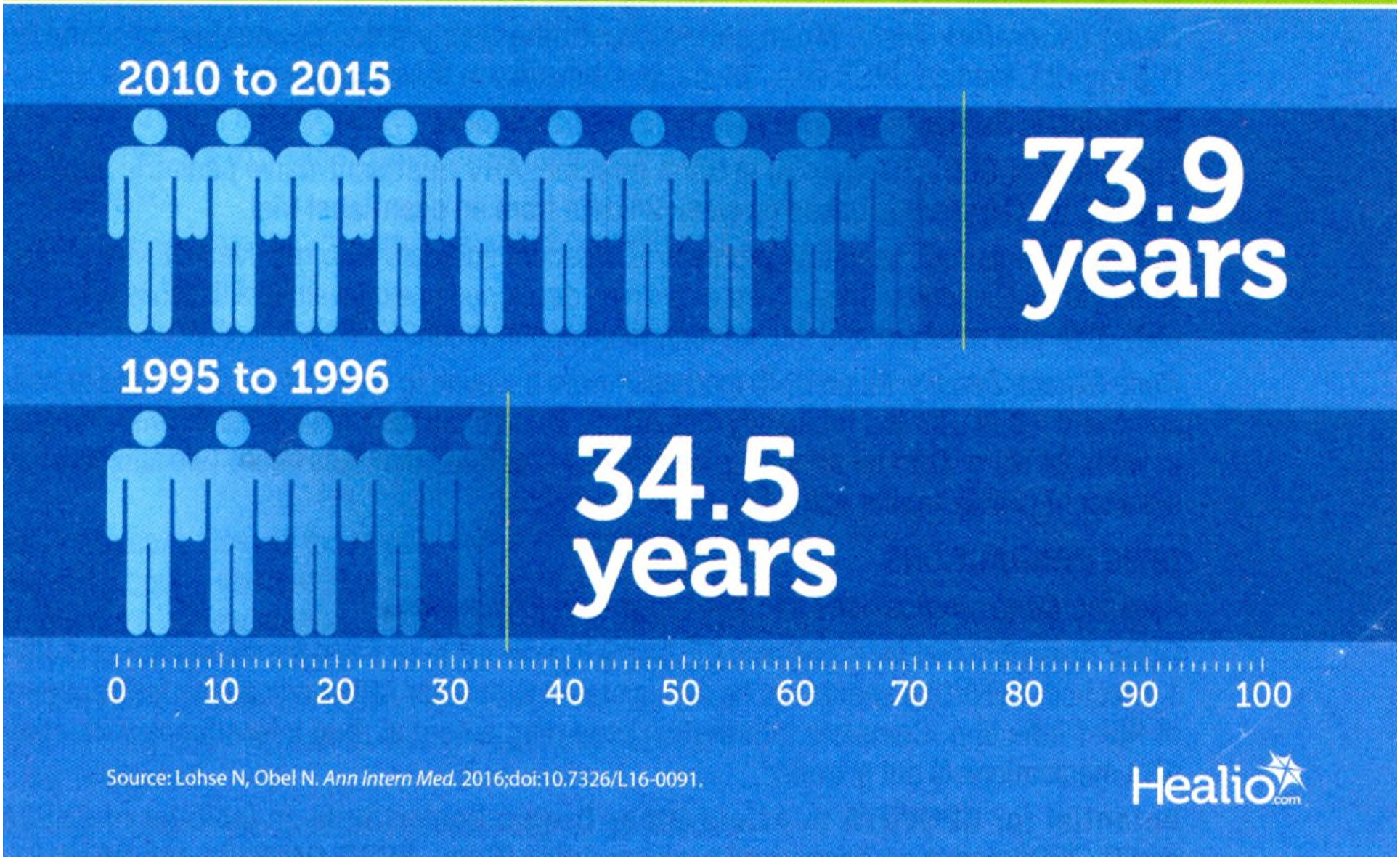
Stein R, et al. MMWR Morb Mortal Wkly Rep. 2017.doi;10.15585/mmwr.mm6641a2

Time From HIV Infection to Diagnosis is Cut 17% in US

The average time between HIV infection and diagnosis decreased 17% in the United States from 3 years and 7 months in 2011 to 3 years in 2015, according to data released by the CDC.

Life expectancy for HIV patients approaches that of general population

Median age of death for patients with HIV aged 25 years



So…The Test is Negative
But a High Risk Testee

“The top doesn’t come off. It’s preventative medicine.”

Missed PrEP Opportunities

66% of patients newly diagnosed with HIV in South Carolina had, on average,

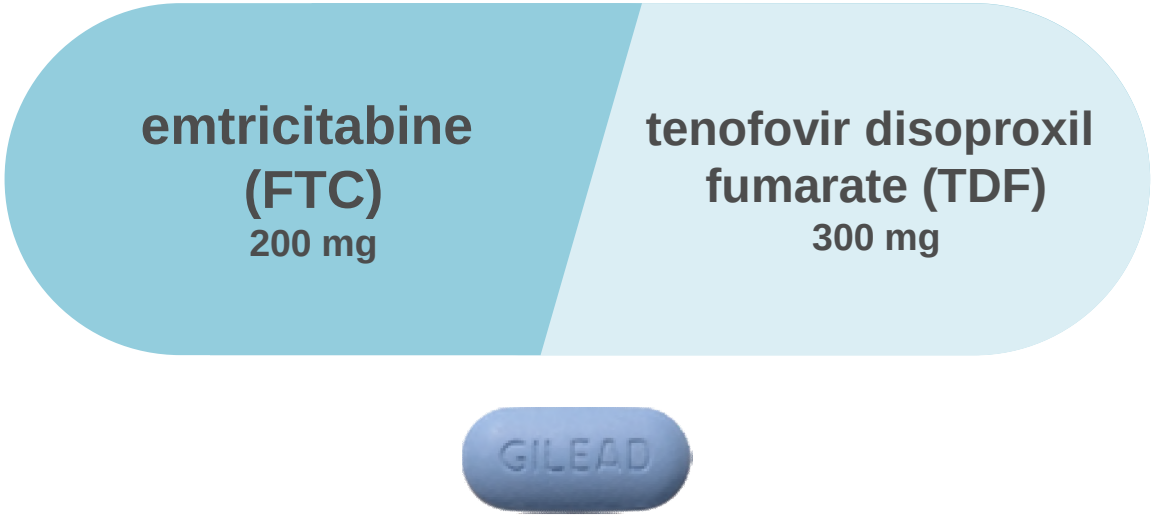
6.9 health care visits before their diagnosis

Source: *Infectious Disease News*. July 2019. Healio.com/ID
https://www.healio.com/infectious-disease/hiv-aids/news/in-the-journals/%7b8a567340-b2c1-4ee5-9750-400d08548dc9%7d/two-thirds-of-patients-with-hiv-had-missed-opportunities-for-prep

PrEP: A New Era in HIV Prevention

FTC/TDF (TRUVADA) FOR PrEP INDICATION

- FTC/TDF is indicated in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk
- This indication is based on clinical trials in MSM at high risk for HIV-1 infection and in heterosexual serodiscordant couples

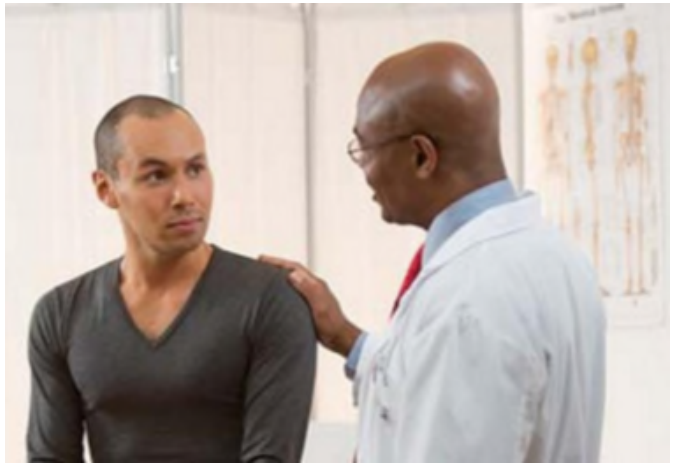


Pill image is for illustration only.

MSM, men who have sex with men.

TRUVADA Prescribing Information. Gilead Sciences, Inc. 2016.

PrEP Facts



Daily PrEP can reduce the risk of getting HIV from sex by more than **90%**.

Daily PrEP can reduce the risk of getting HIV among people who inject drugs by more than **70%**.

1 in 3 primary care doctors and nurses haven't heard about PrEP.

http://www.cdc.gov/vitalsigns/hivprep/index.html

CDC PrEP Guidance: Who is recommended for PrEP?

- Daily oral PrEP is recommended for adults at substantial risk of acquiring HIV infection:
  - Sexually active MSM
  - Heterosexually active men and women
  - Injection drug users

	MSM	Heterosexual Women and Men	Injection Drug Users
Detecting substantial risk of acquiring HIV infection	▪ HIV-positive sexual partner ▪ Recent bacterial STI ▪ High number of sex partners ▪ History of inconsistent or no condom use ▪ Commercial sex work	▪ HIV-positive sexual partner ▪ Recent bacterial STI ▪ High number of sex partners ▪ History of inconsistent or no condom use ▪ Commercial sex work ▪ In high-prevalence area or network	▪ HIV-positive injecting partner ▪ Sharing injection equipment ▪ Recent drug treatment (but currently injecting)

MSM=men who have sex with men; STI=sexually transmitted infection.

CDC. Preexposure Prophylaxis for the Prevention Of HIV Infection in the United States -- 2014: A Clinical Practice Guideline. Section: Summary of Guidance for PrEP Use. May 2014. www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf. Accessed 1/19/15.

TRUVADA FOR PrEP SHOULD BE USED AS PART OF A COMPREHENSIVE PREVENTION STRATEGY

Safer sex practices, including consistent and correct use of condoms, and reducing sexual risk behavior

- Knowledge of their own HIV-1 status and that of their partner(s)

- Regular testing for HIV-1 and other STIs
- Counsel uninfected individuals to strictly adhere to their dosing schedule

- TRUVADA for PrEP is not always effective in preventing the acquisition of HIV-1
- The effectiveness of TRUVADA for PrEP in reducing the risk of acquiring HIV-1 is strongly correlated with adherence

TRUVADA Prescribing Information. Gilead Sciences, Inc. 2016.

TRUVADA FOR PrEP: REQUIREMENTS FOR INITIATION AND MONITORING FOR HIV-1 INFECTION

Confirm HIV-1 status prior to TRUVADA for PrEP initiation

- Confirm negative HIV-1 status immediately prior to initiation
- If signs or symptoms of acute HIV-1 infection (eg, fever, fatigue, myalgia, skin rash) are present and recent exposures (<1 month) are suspected, delay initiation for ≥1 month, then reconfirm HIV-1 status
- Alternatively, confirm negative HIV-1 status with a test approved by the FDA to aid diagnosis of acute or primary HIV-1 infection

Discontinue if an HIV-1 infection is suspected

- Screen uninfected individuals for HIV-1 infection at least every 3 months while they are taking TRUVADA for PrEP
- If symptoms of acute HIV-1 infection develop following a potential exposure event, discontinue TRUVADA for PrEP until negative HIV-1 status is confirmed using a test approved by the FDA to aid diagnosis of acute or primary HIV-1 infection

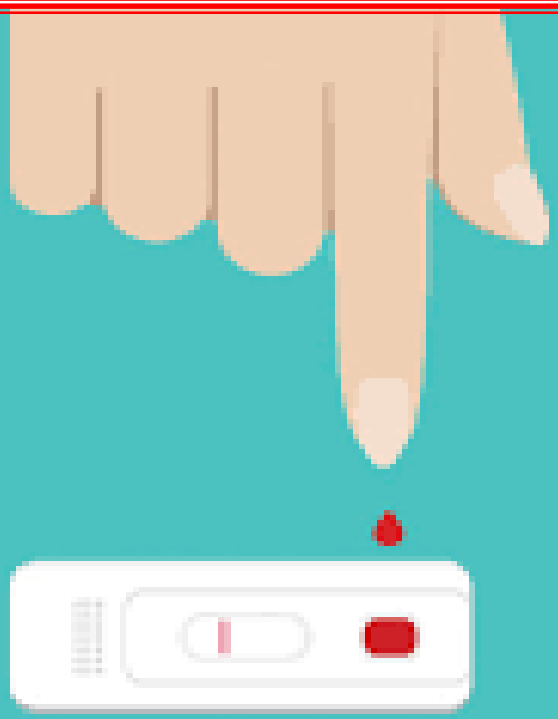
HIV-1 resistance may emerge in individuals with undetected HIV-1 infection who are taking only TRUVADA because this does not constitute a complete ART regimen for HIV-1 treatment.

ART, antiretroviral therapy.

TRUVADA Prescribing Information. Gilead Sciences, Inc. 2016.

PCPs Often Prescribe PrEP Before Ordering HIV Testing

Only 77% of patients were tested for HIV…



and 81% were tested for STIs before initiating PrEP

Source: *Infectious Disease News*. July 2018. Healio.com/ID

Follow-up Visits

- ☑ Screen for HIV-1 to confirm HIV-negative status every 3 months[1]
  - Use an FDA-approved test to confirm HIV-negative status
  - Drug-resistant HIV-1 variants have been identified with use of TRUVADA for PrEP following **undetected** acute HIV-1 infection
- ☑ Screen for STIs routinely (3-site testing)[2]
  - Not all STIs are symptomatic so test all sites of exposure including urethra, pharynx and rectum, regardless of condom use
- ☑ Counsel on importance of adherence and using TRUVADA for PrEP as part of a comprehensive HIV prevention plan[1]
  - Re-assess HIV risk at each visit
- ☑ Monitor renal function to ensure CrCl ≥60 mL/min[1]
  - Reassess potential risks and benefits of using TRUVADA for PrEP if a decrease in CrCl is observed during use
  - In patients at risk for renal dysfunction, periodically monitor serum phosphorus, urine glucose, and urine protein
- ☑ If appropriate, consider continuing TRUVADA (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg) for PrEP, 1 tablet PO daily, max 90-day supply[1]

1. TRUVADA Prescribing Information. Gilead Sciences, Inc. 2017; 2. Marcus JL, et al. *Sex Transm Dis*. 2011;38:922-924.

CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION, AND HBV TESTING

Contraindications:

- Do not use TRUVADA for PrEP in individuals with unknown or positive HIV-1 status

Dosage and Administration:

- TRUVADA for PrEP in HIV-1 uninfected adults: one tablet once daily with or without food

HBV Testing

- It is recommended that all individuals be tested for the presence of chronic HBV before initiating TRUVADA

TRUVADA Prescribing Information. Gilead Sciences, Inc. 2016.

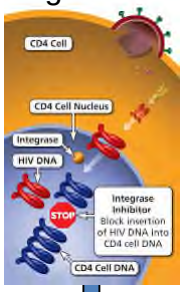
Drug for PrEP

HIV Therapy
Past, Present, Future

Cure?
Vaccine?

Long Acting Injectable?

Integrase Era



Single Tablet Regimen

Triple Drug Therapy

ZDV/3TC

HIV Monotherapy

HIV-1 discovered

1983 1987 1995 1986 2006 2012-13 2017 2020