BRITISH COLUMBIA
CENTRE *for* EXCELLENCE
in HIV/AIDS
EDUCATION & TRAINING

Module 1:
Background to HIV Prevention

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MD

Faculty Disclosure

- **Faculty:** Dr. Silvia Guillemi

- **Relationships with commercial interests:**
  - **Grants/Research Support:** none to disclose
  - **Speakers Bureau/Honoraria:** participation in advisory board meetings with honoraria for Gilead Sciences, ViiV Healthcare
  - **Consulting Fees:** none to disclose
  - **Other:** none to disclose

- Antiretroviral medications are not approved by Health Canada as post-exposure prophylaxis (PEP) for the prevention of HIV. Recommendations for HIV PEP are considered "off-label" use of medications.

Disclosure of Commercial Support

- **This program has not received any financial or in-kind commercial support.**

- **<u>Potential for conflict(s) of interest</u>:**
  - No commercial organization has supported this program.

Mitigating Potential Bias

- The content of the presentation is consistent with guidelines developed by the BC-CfE Post-Exposure Prophylaxis (PEP) Committee, a sub-committee of the Committee for Drug Evaluation and Therapy (CDET)

- Generic names of medications are used in place of brand names

Learning Objectives

On completion of this module, participants will develop an understanding of:

- Treatment as Prevention® (TasP®) & the HIV epidemic in BC
- HIV testing in BC
- HIV transmission and acute infection
- Chemoprophylaxis terminology

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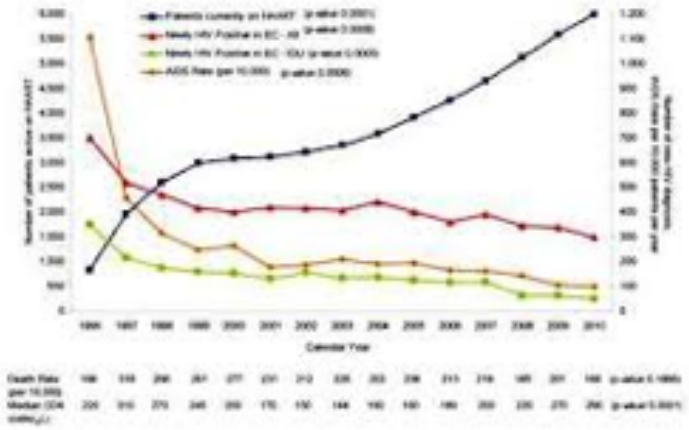
The British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) is commited to improving the health of British Columbians living with HIV through the development, ongoing monitoring, and dissemination of comprehensive research and treatment programs for HIV and related diseases. It also provides guidelines and educational resources for the community and health care providers in issues related to HIV testing, care, and prevention.



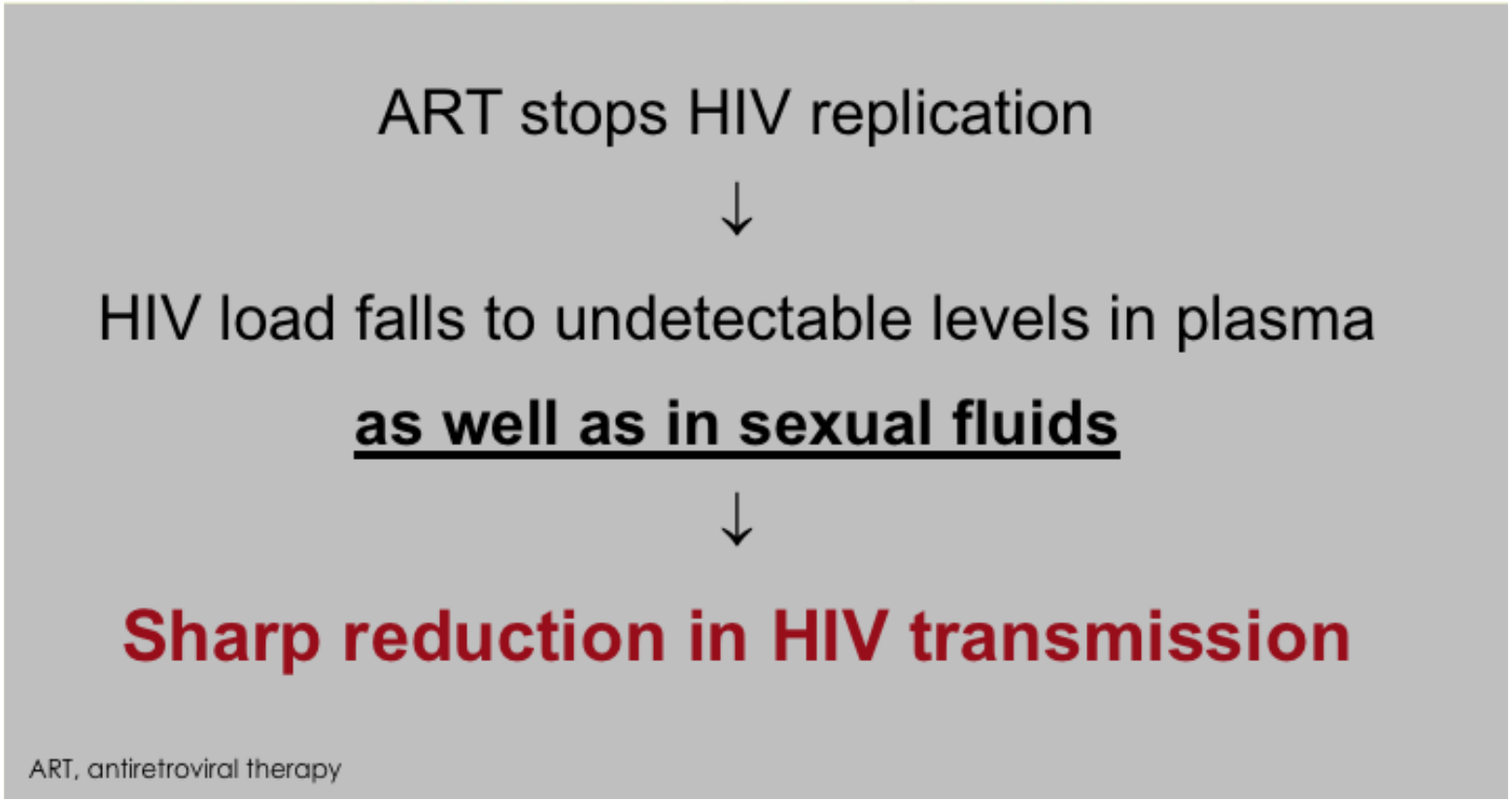
UBC

Providence HEALTH CARE
How you want to be treated.

Lancet 2006; 368: 531–36

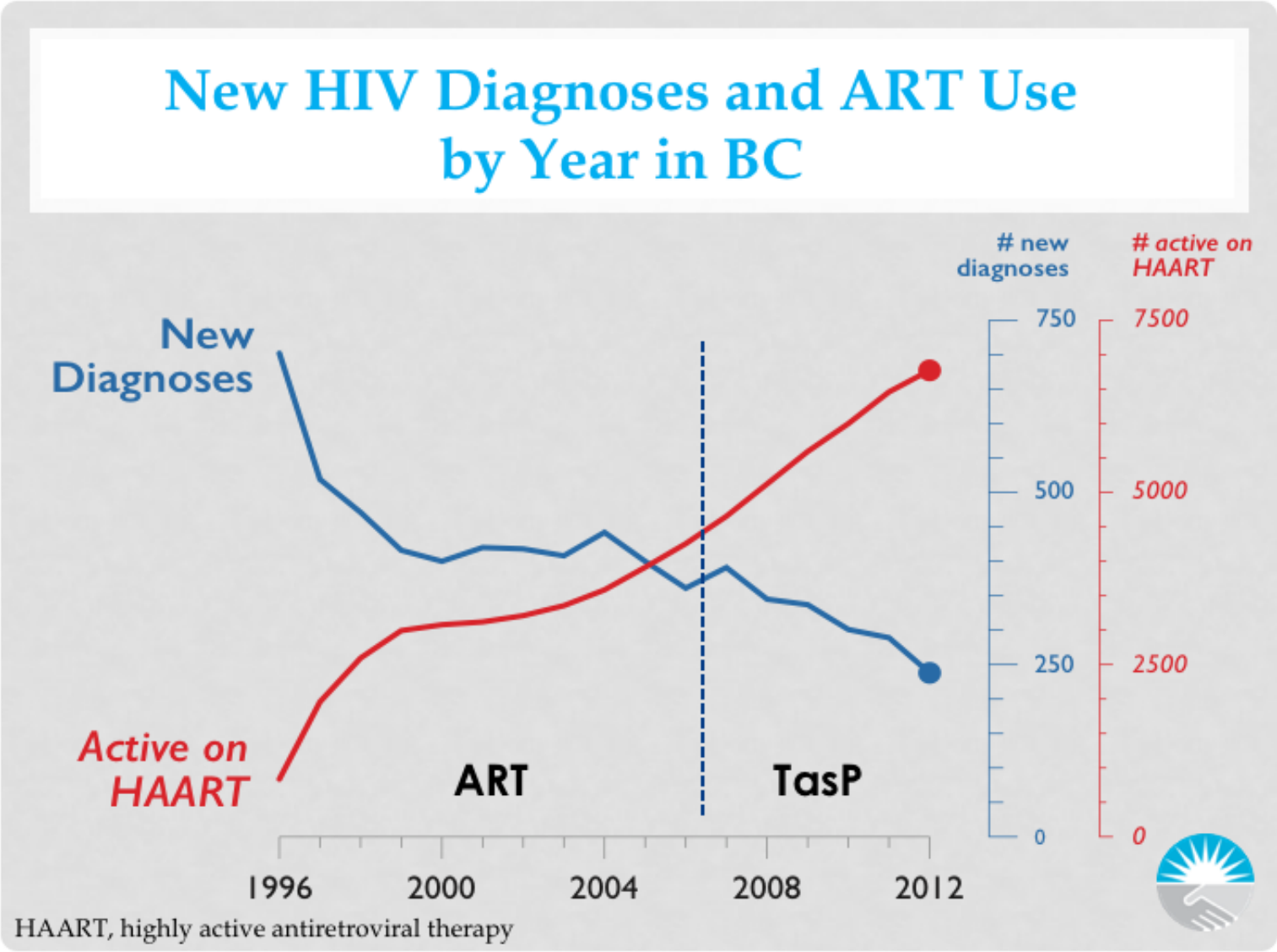
The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic

Julio S G Montaner, Robert Hogg, Evan Wood, Thomas Kerr, Mark Tyndall, Adrian R Levy, P Richard Harrigan



The concept that antiretroviral therapy (ART) can impact HIV transmission has been under consideration since ART first emerged in the 1980's.

In brief, ART rapidly and effectively decreases HIV virus levels to undetectable in blood and sexual fluids in the vast majority of patients receiving treatment. Among people living with HIV (PLWH), ART-induced sustained HIV undetectability allows for immune reconstitution, thereby preventing the emergence of AIDS-related diseases and premature death. At the prevention level, ART-induced sustained HIV undetectability markedly reduces the likelihood of HIV transmission.



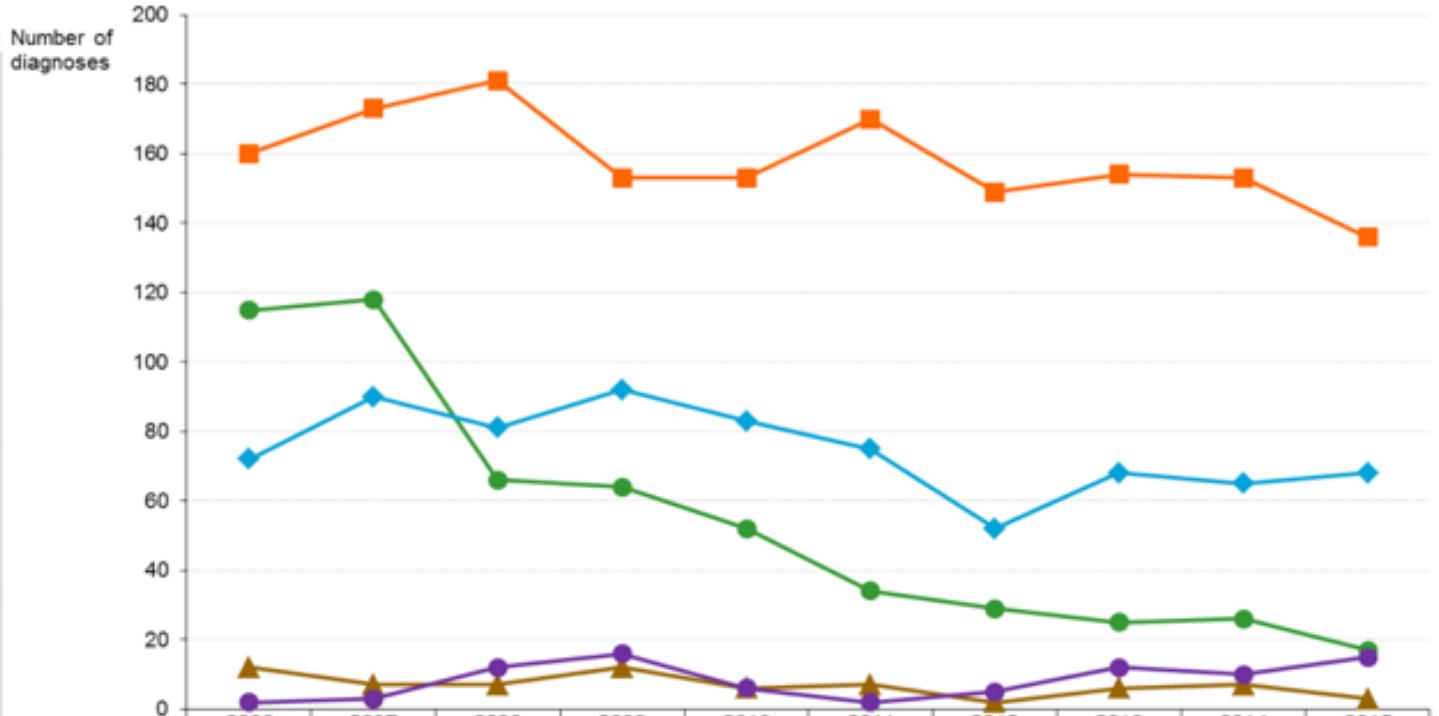
In British Columbia (BC), the effect of ART on new cases of HIV was apparent (note the reduction of new diagnoses from 1996 to 2000 and 2004 onward) despite a steady rise in syphilis rate during the same period (not shown). These data suggested that ART could be much more effective in reducing HIV transmission at the population level than had previously been suspected.

BC has experienced a marked decrease in HIV/AIDS morbidity and mortality since the implementation of ART in 1996. This has been associated with a nearly 60% decrease in new HIV diagnoses, to the current level of 255 cases diagnosed in 2016.

Source:

Modified from Montaner JS, et al. PLoS One. 2014;9(2):e87872.

New Diagnoses in BC by Exposure Category, 2006 to 2015



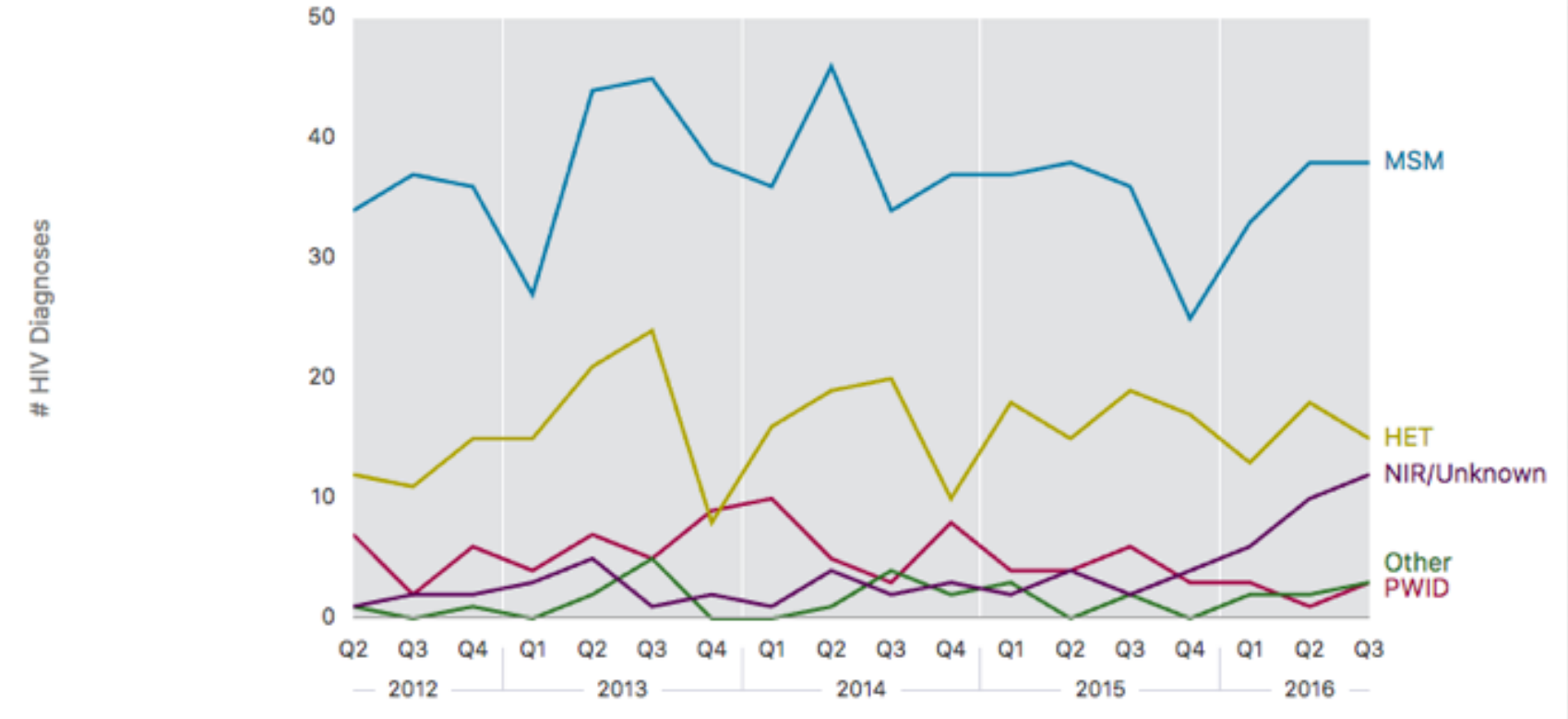
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
MSM	160	173	181	153	153	170	149	154	153	136
PWID	115	118	66	64	52	34	29	25	26	17
HET	72	90	81	92	83	75	52	68	65	68
Other	12	7	7	12	6	7	2	6	7	3
NIR/UNK	2	3	12	16	6	2	5	12	10	15

MSM - men who have sex with men
PWID - people who inject drugs
HET - heterosexual contact
NIR - no identified risk
UNK - exposure unknown
Other - blood/blood products and occupational/perinatal/other exposures

Although there has been a significant decrease in the number of new HIV diagnoses in BC since the early 2000's in most exposure categories, the biggest impact has been observed among individuals who inject drugs (IDU). In contrast, there has been no significant change during the same period in the number of new HIV diagnoses among men who have sex with men (MSM) or the heterosexual population.

Source:
BCCDC, 2017.

New HIV Diagnoses in BC by Exposure Category: Data from STOP HIV/AIDS® Quarterly Report



MSM (men who have sex with men)	34	37	36	27	44	45	38	36	46	34	37	37	38	36	25	33	38	38
PWID (people who inject drugs)	7	2	6	4	7	5	9	10	5	3	8	4	4	6	3	3	1	3
HET (heterosexual)	12	11	15	15	21	24	8	16	19	20	10	18	15	19	17	13	18	15
Other (other exposure identified)	1	0	1	0	2	5	0	0	1	4	2	3	0	2	0	2	2	3
NIR/Unknown (no identified exposure)	1	2	2	3	5	1	2	1	4	2	3	2	4	2	4	6	10	12

The STOP HIV/AIDS® Quarterly Monitoring Report: British Columbia, Q1 2017, continues to show that the number of new diagnoses in the MSM population has not decreased significantly over time.

Source:

STOP HIV/AIDS® Quarterly Monitoring Report, British Columbia, Q1 2017, http://stophivaids.ca/data-monitoring/

Mother to Child Transmission (MTCT)

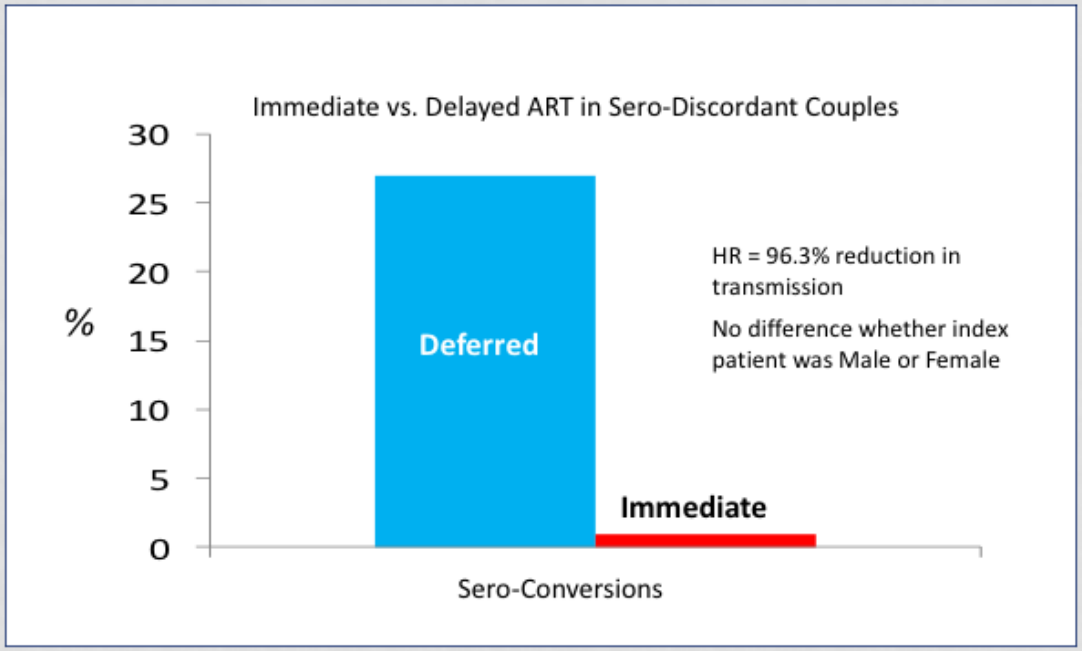
ART is virtually **100% effective** at preventing MTCT

Over the last 15 years, with the widespread use of ART, MTCT has been virtually eliminated in BC

- **2** HIV+ newborns in **300** HIV+ pregnancies
- Both cases failed to use ART (**diagnosed at labour**)
- Expected number of new cases in the absence of ART **>30 cases**

The use of ART has significantly reduced the transmission of HIV from mother to child, virtually eliminating this mode of HIV transmission in BC. This is another model that clearly illustrates the impact of ART on HIV transmission.

HPTN 052: Effectiveness of Treatment as Prevention®

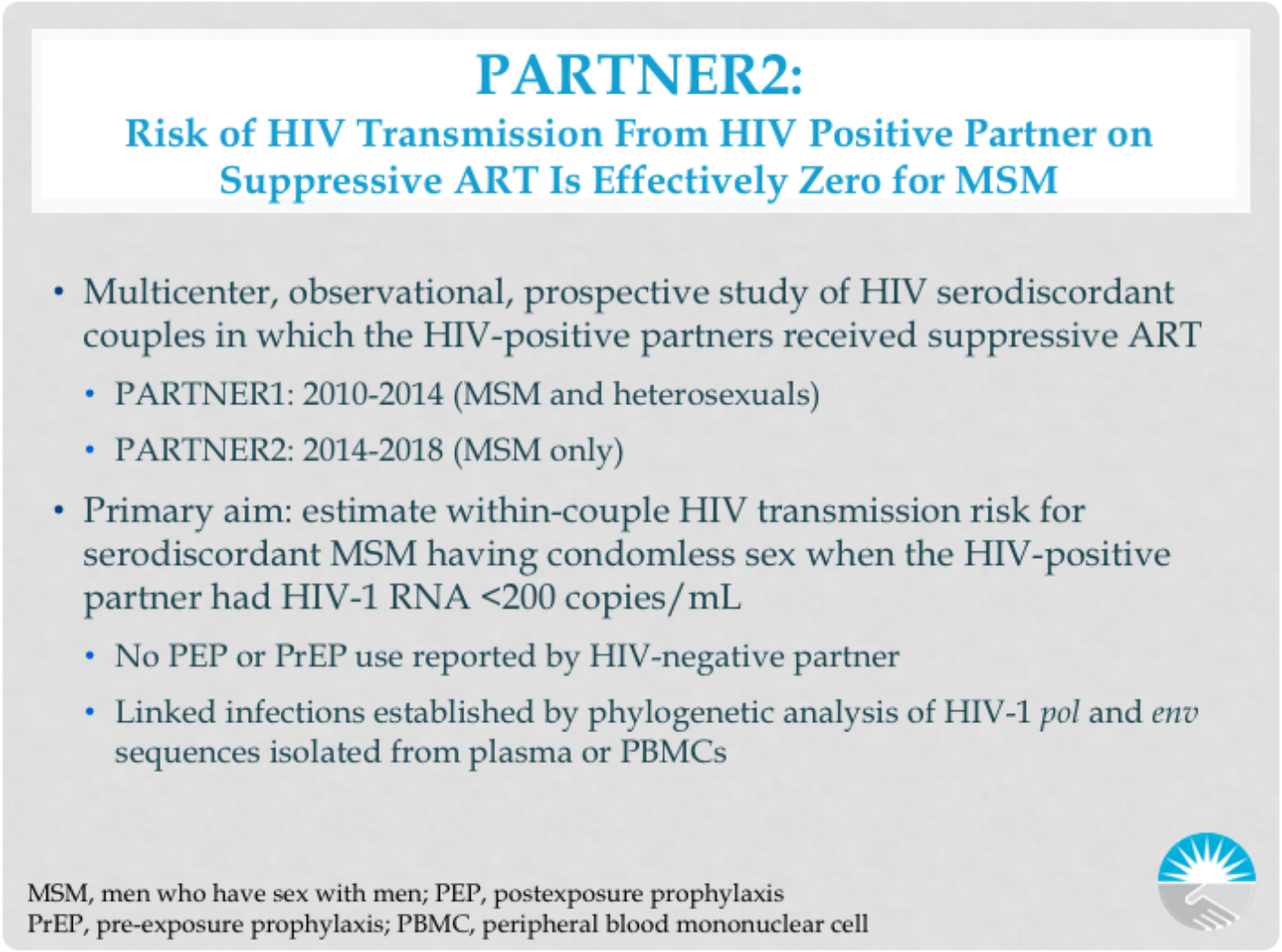


The HPTN 052 trial assessed HIV transmission in serodiscordant couples. They enrolled 1763 serodiscordant couples at 13 sites in nine countries; couples were randomly assigned to two study groups, an early-ART group and a delayed-ART group. In the early-ART group, index participants initiated ART at the time of enrollment. In the delayed-ART group, index participants initiated ART when CD4+ counts fell below 250 cells per cubic millimeter or they had an illness indicative of acquired immunodeficiency syndrome (i.e., an AIDS-defining illness).

After a median follow-up of 1.7 years, investigators found that early ART use was associated with a 96% lower risk of index-to-partner, genetically linked HIV-1 infections than delayed ART. They also showed that early ART provided health benefits to the index participants. The final results of the HPTN 052 study showed that successful treatment of HIV-1 is a highly effective tool for the prevention of sexual transmission of the virus.

Sources:

Cohen MS, et al. IAS 2011. Abst MOAX0102.
Cohen MS, et al. N Engl J Med. 2016;375(9):830-9.



The PARTNER1 study contributed to our understanding of Treatment as Prevention®, with the limitation that the number of MSM participants was relatively small. Even though there were no linked transmission events identified in any population in PARTNER1, the confidence intervals around that estimate were relatively wide for MSM. The PARTNER2 study, implemented between 2014 and 2018, was exclusively MSM to improve the precision of the estimate. They focused on the same population of virally suppressed, discordant couples who were primarily having condomless sex without PEP or PrEP, and they did a very detailed analysis of any transmission events to demonstrate whether the virus acquired was phylogenetically linked to the partner's virus.

Sources:

Rodger A, et al. AIDS 2018. Abstract WEAX0104LB.

Clinical Care Options: www.clinicaloptions.com

PARTNER2: HIV Transmission

- No linked transmissions documented in ~77,000 condomless sex acts when the HIV-positive MSM partner had suppressed HIV-1 RNA <200 copies/mL

Sexual Behavior Reported by HIV-Negative Partner	Linked Transmissions, n	Upper 95% CL*	Condomless Sex Acts, n	CYFU
Any sex	0	0.23†	76991	1596
Anal sex	0	0.24	70743	1546
Insertive anal sex	0	0.27	52572	1345
Receptive anal sex without ejaculation	0	0.43	23153	867
Receptive anal sex with ejaculation	0	0.57	20770	652
Any sex with an STI	0	2.74	6301	135

- Unlinked transmissions occurred in 15 initially HIV-negative MSM partners

MSM, men who have sex with men; CL, confidence limit
CYFU, couple-years follow-up; STI, sexually transmitted infection

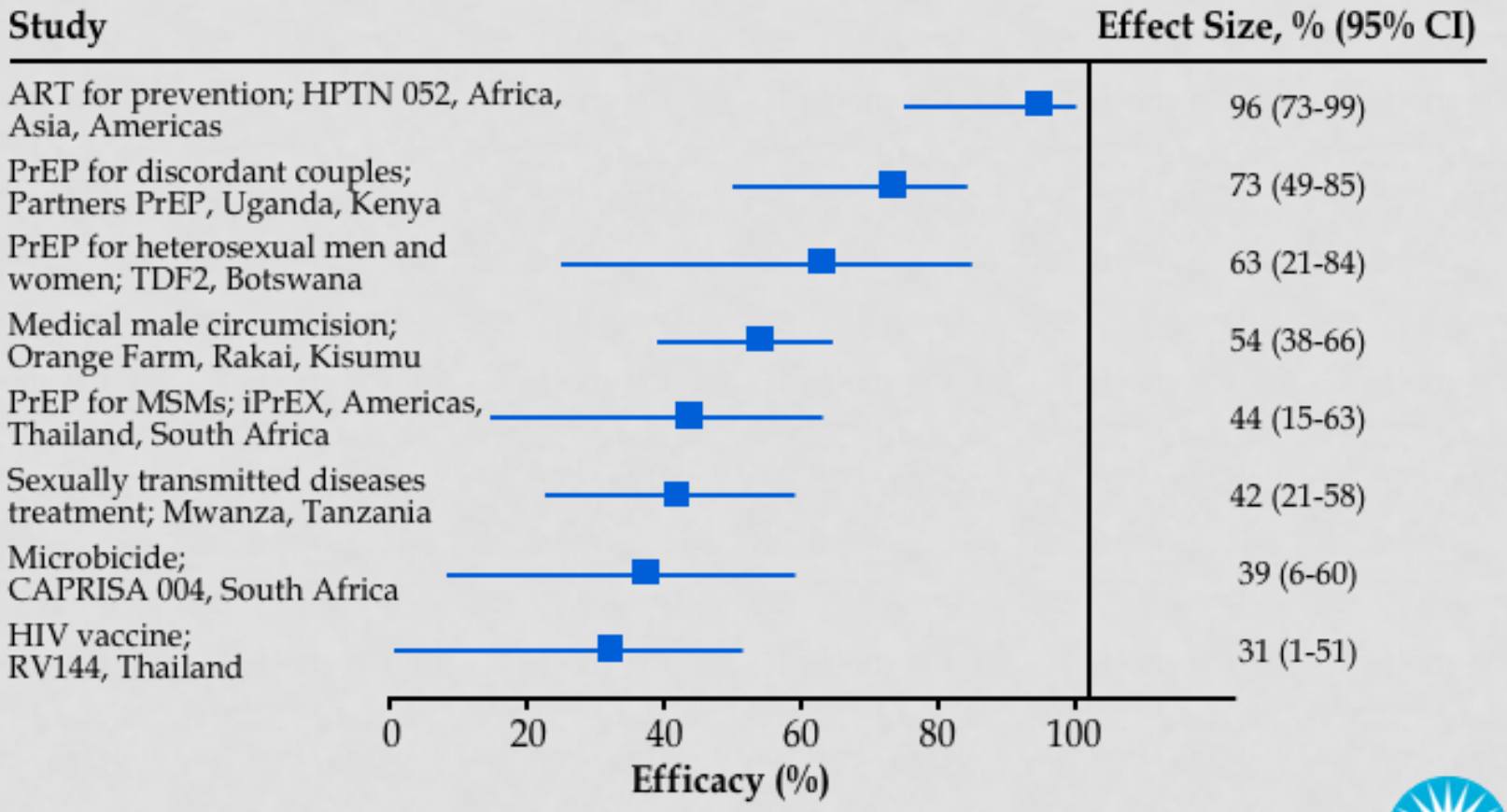
The key result: there were no linked transmissions among over 77,000 condomless sex acts. There were, as is seen in every trial, some unlinked transmission that occurred (n=17), but the table above shows the number of linked transmissions is 0 across all exposure types, with very tight confidence limits because of the increased numbers. The upper 95% confidence limit for any sex was 0.23, and even for receptive anal sex it was only 0.43.

This data provides further evidence to support the concept that U=U: Undetectable equals Untransmittable across all populations.

Sources:

Rodger A, et al. AIDS 2018. Abstract WEAX0104LB.
Clinical Care Options: www.clinicaloptions.com

Efficacy of HIV Prevention Strategies: Randomized Clinical Trials



PrEP, pre-exposure prophylaxis; CI, confidence interval

This analysis of key randomized clinical trials for preventing HIV infection illustrates that TasP® (HPTN 052 trial) was the most effective method of preventing HIV acquisition. Other studies, such as early pre-exposure prophylaxis (PrEP) randomized trials, have also shown significant reduction in HIV transmission.

Source:

Karim SS & Karim QA. Lancet. 2011;378(9809):e23-5.

HIV Testing Recommendations

We recommend that health care providers know the HIV status of all patients under their care.

Specifically, we recommend that providers offer an HIV test:

- **Routinely,** every five years, to all patients aged 18-70 years
- **Routinely,** every year, to all patients aged 18-70 years who belong to populations with a higher burden of HIV infection
- **Once** for patients older than 70 years of age, if HIV status is not known

AND offer an HIV test to patients, including adults 18-70, youth and the elderly, whenever:

- Ordering diagnostic blood work for a new or worsening medical condition
- They present with symptoms of HIV infection or advanced HIV disease
- They or their providers identify a risk for HIV acquisition
- They request an HIV test
- They are pregnant
- They are tested for or diagnosed with a sexually transmitted infection (STI), hepatitis C, hepatitis B, or tuberculosis

In 2014, the HIV Testing Guidelines were released in BC. Their recommendations are summarized on this slide. Universal testing is recommended regardless of the patient's perceived HIV risk.

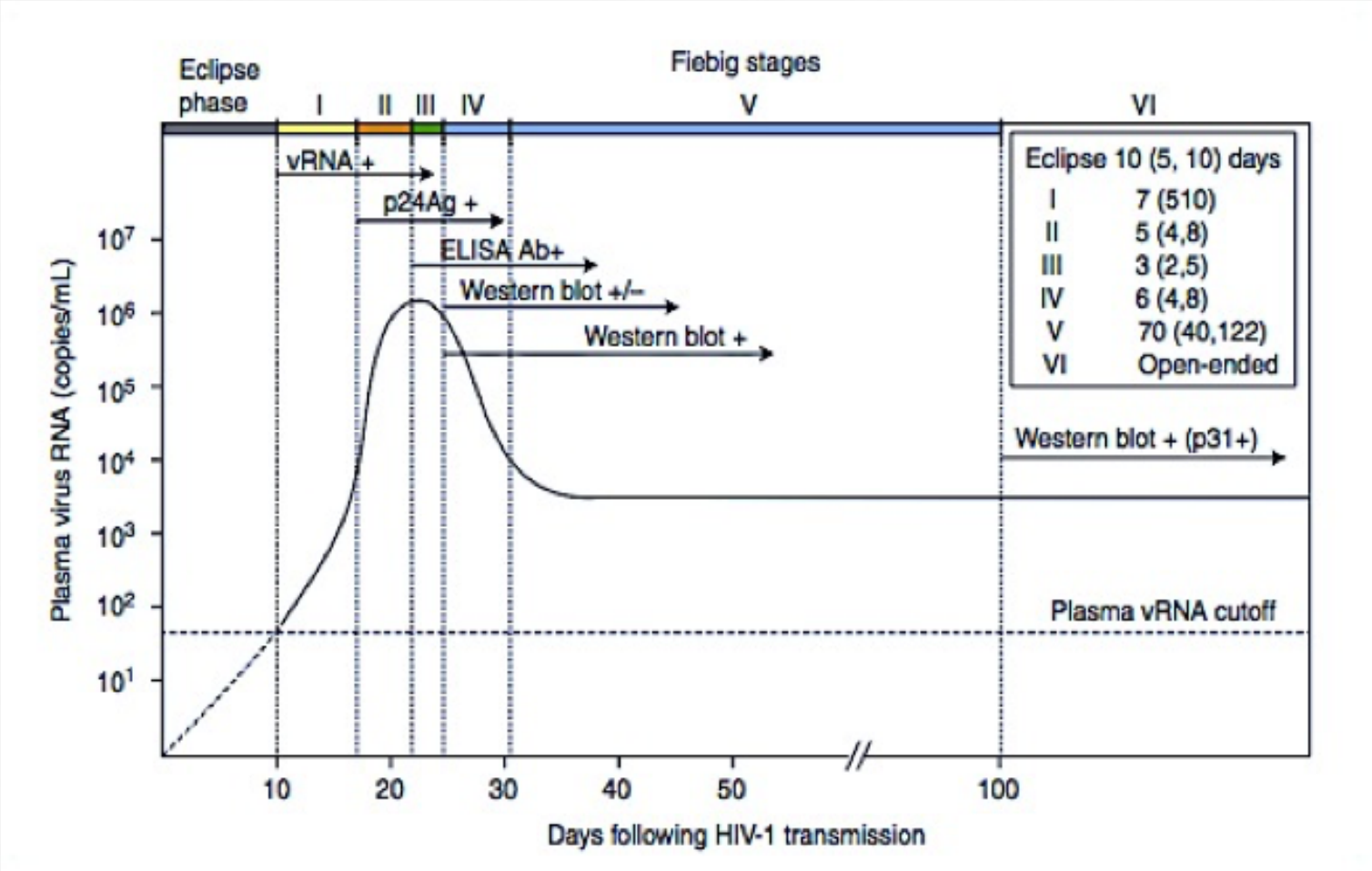
In regards to testing after a possible HIV exposure, the guidelines state:

"It is important to understand HIV testing window periods when considering an HIV test after a possible exposure. Traditionally, waiting 3 months after exposure was recommended; however, newer 4th generation HIV tests have shortened the window period. The average window period for 4th generation enzyme immunoassays (EIA) tests (which detect p24 antigen and HIV antibodies) is 16-18 days. Most patients can be tested at **4 weeks following exposure** (>95% of infected individuals will have detectable antibodies at this time). If negative, **repeat testing at 3 months** is recommended (>99% of infected individuals will have a positive EIA at this time)."

Source:

BCCDC. HIV Testing Guidelines for the Province of BC, 2014.

Laboratory Staging And Natural History Of Acute And Early HIV Infection



HIV tests are based on three different markers of HIV infection in the blood: viral RNA, p24 Antigen, and antibody. The first marker to present is **viral RNA**, which is the presence of the virus in the blood. The second to appear is the **P24 Antigen**, which is a protein component of the HIV virus. The p24 antigen is transient. The last to appear in the blood are the **antibodies**.

Sources:

Shaw GM, & Hunter E. Cold Spring Harb Perspect Med. 2012;2(11).
Fiebig, et al. AIDS. 2003;17(13):1871-9.

Fiebig Laboratory Staging

Eclipse phase: the initial period between the moment when the first cell is infected and when virus is first detectable in the blood. Duration of this period: estimated to be approximately 7 – 21 days.

Fiebig stage I: appearance in the plasma of HIV-1 viral RNA.

Fiebig stage II: appearance of viral p24 antigen.

Fiebig stage III: appearance of virus-specific antibodies detectable by recombinant protein based enzyme-linked immunosorbant assay.

Fiebig stage IV: virus-specific antibodies detectable by Western immunoblotting, with indeterminate banding pattern.

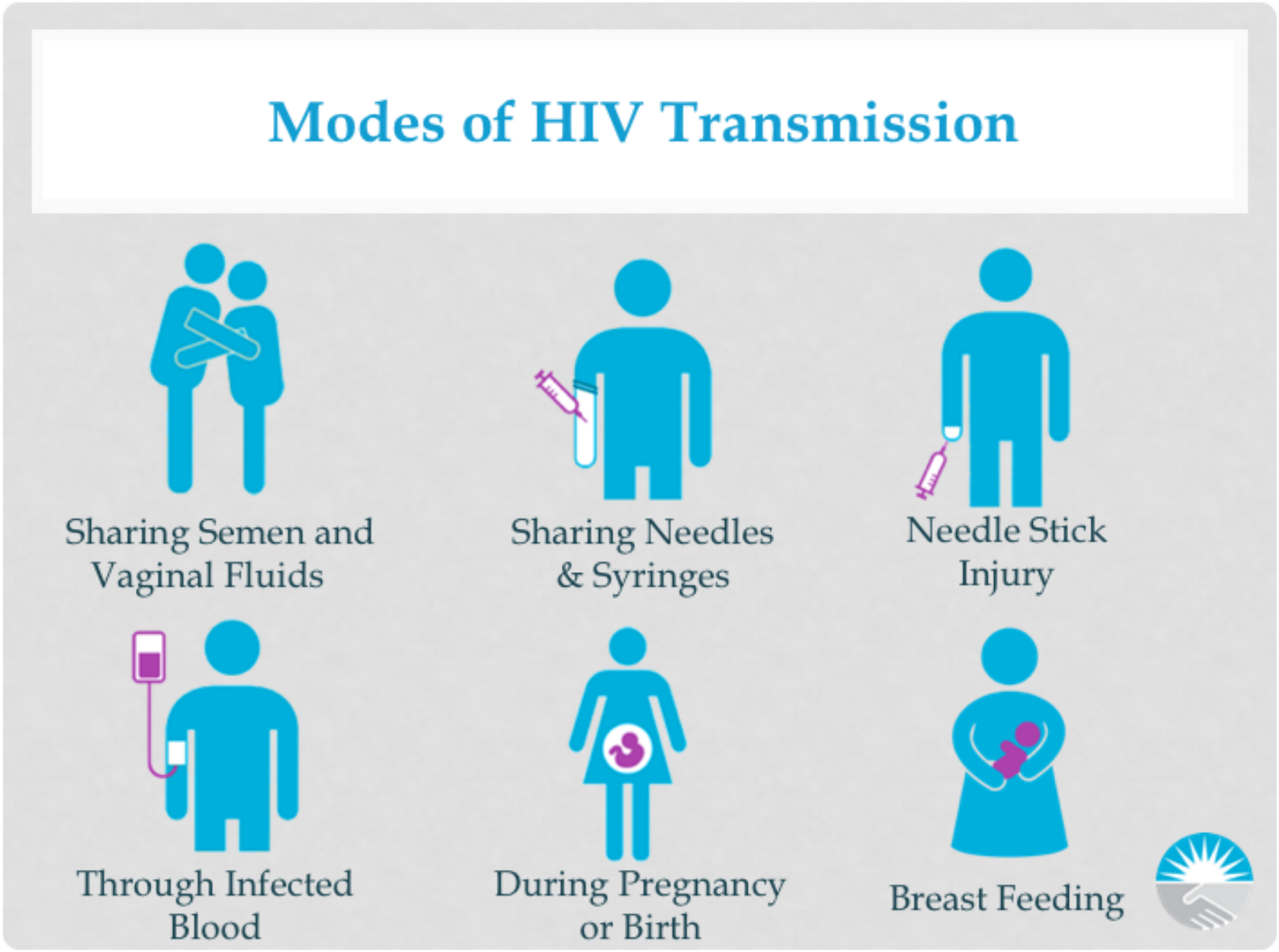
Fiebig stage V: virus-specific antibodies detectable by Western immunoblotting, with a diagnostic banding pattern but missing p31 reactivity.

Fiebig stage VI: diagnostic banding pattern with Western immunoblotting and p31 reactivity.

The sequential appearance of laboratory markers of acute and early HIV-1 infection was systematically evaluated by Fiebig and colleagues (2003).

Source:

Fiebig, et al. AIDS. 2003;17(13):1871-9.



How HIV is transmitted?

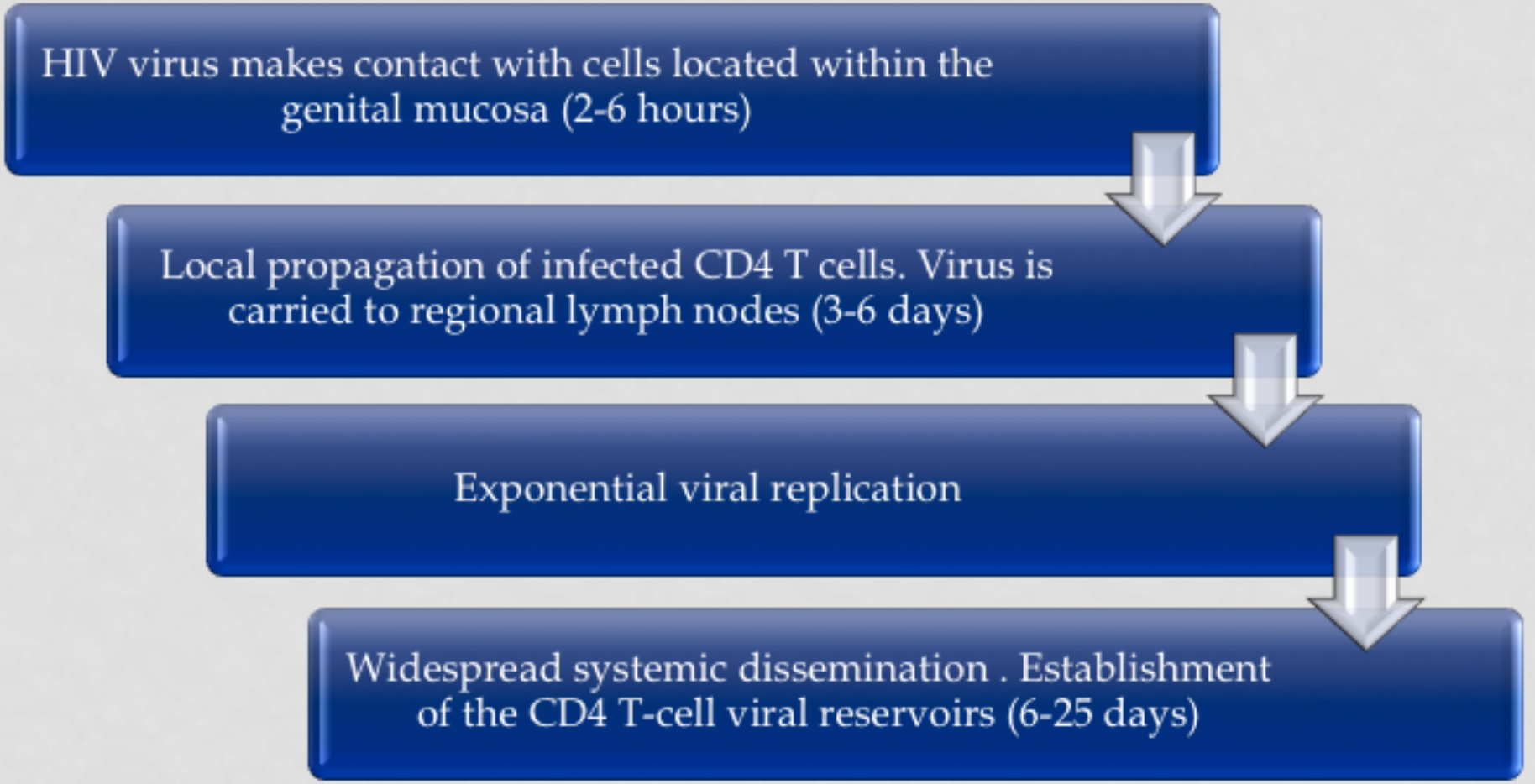
- HIV is transmitted from one person to another through the exchange of blood as well as certain body fluids, including vaginal secretions and semen. Sexual intercourse (vaginal and anal) is one way in which HIV can be transmitted.
- Blood transfusion; deep needlestick; or sharing needles, syringes, and other paraphernalia are ways transmission can occur via exposure to blood.
- HIV can be transmitted vertically from mother to child during pregnancy, delivery, or during breast feeding. If the mother is not receiving ART, the likelihood of mother-to-child transmission is up to 30%.

How HIV Infects the Body
(Sexual Transmission)

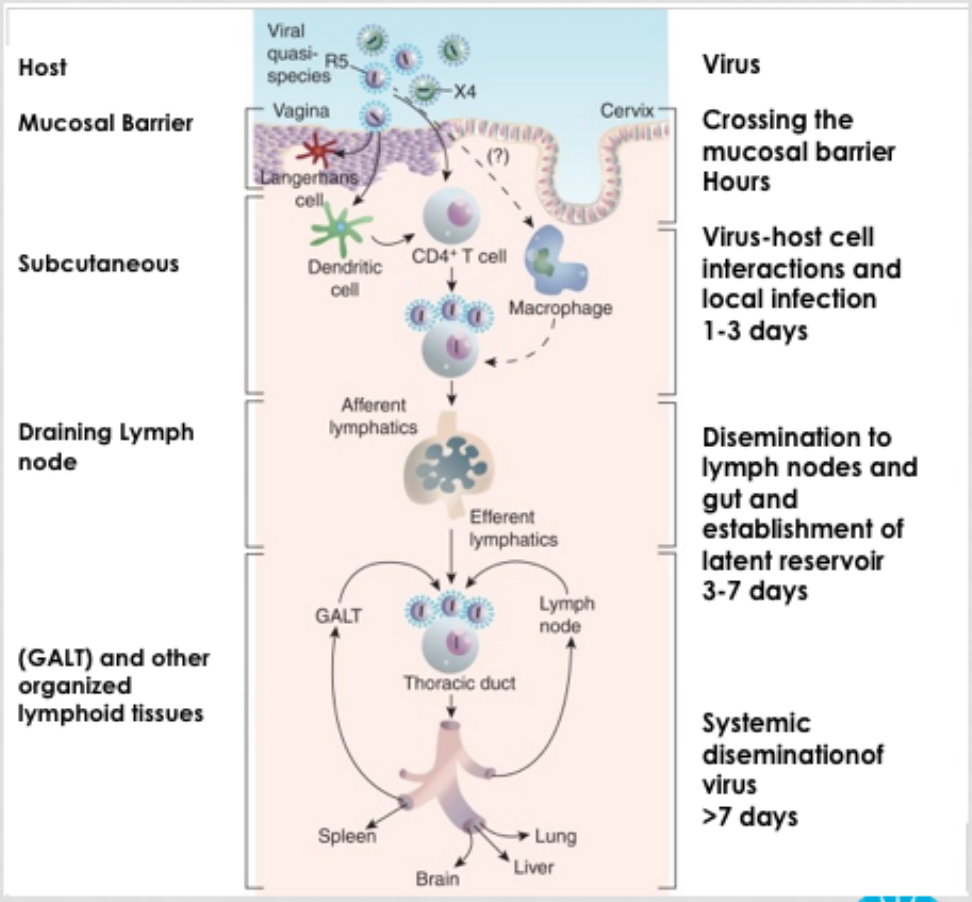
- HIV enters the bloodstream via mucous membranes lining the vagina, rectum, and mouth (note: oral transmission can only occur if there is a wound, such as an ulcer or a cut, in the oral cavity).
- Immediately after exposure and transmission, as HIV-1 is replicating in the mucosa, submucosa, and draining lymphoreticular tissues, the virus cannot be detected in plasma (eclipse phase; 7 - 21 days).
- Once HIV-1 RNA reaches a concentration of 1 to 5 copies per milliliter in plasma, the virus can be detected with the use of sensitive qualitative methods of nucleic acid amplification; at concentrations of 50 copies per milliliter, HIV-1 can be detected by means of quantitative clinical assays used to monitor viral load.
- Regardless of the route of HIV transmission and the initial cells infected, within a few days, viral replication converges on the lymphoreticular system of the gastrointestinal tract (i.e., gut-associated lymphoid tissue).

The rapid expansion of HIV-1, first in gut-associated lymphoid tissue and then systemically, along with a sharp rise in plasma levels of viral RNA, is clinically important because of the coincident irreversible destruction of reservoirs of helper T cells and the establishment of viral latency.

How HIV Infects the Body
(Sexual Transmission)



Model of HIV Mucosal Transmission



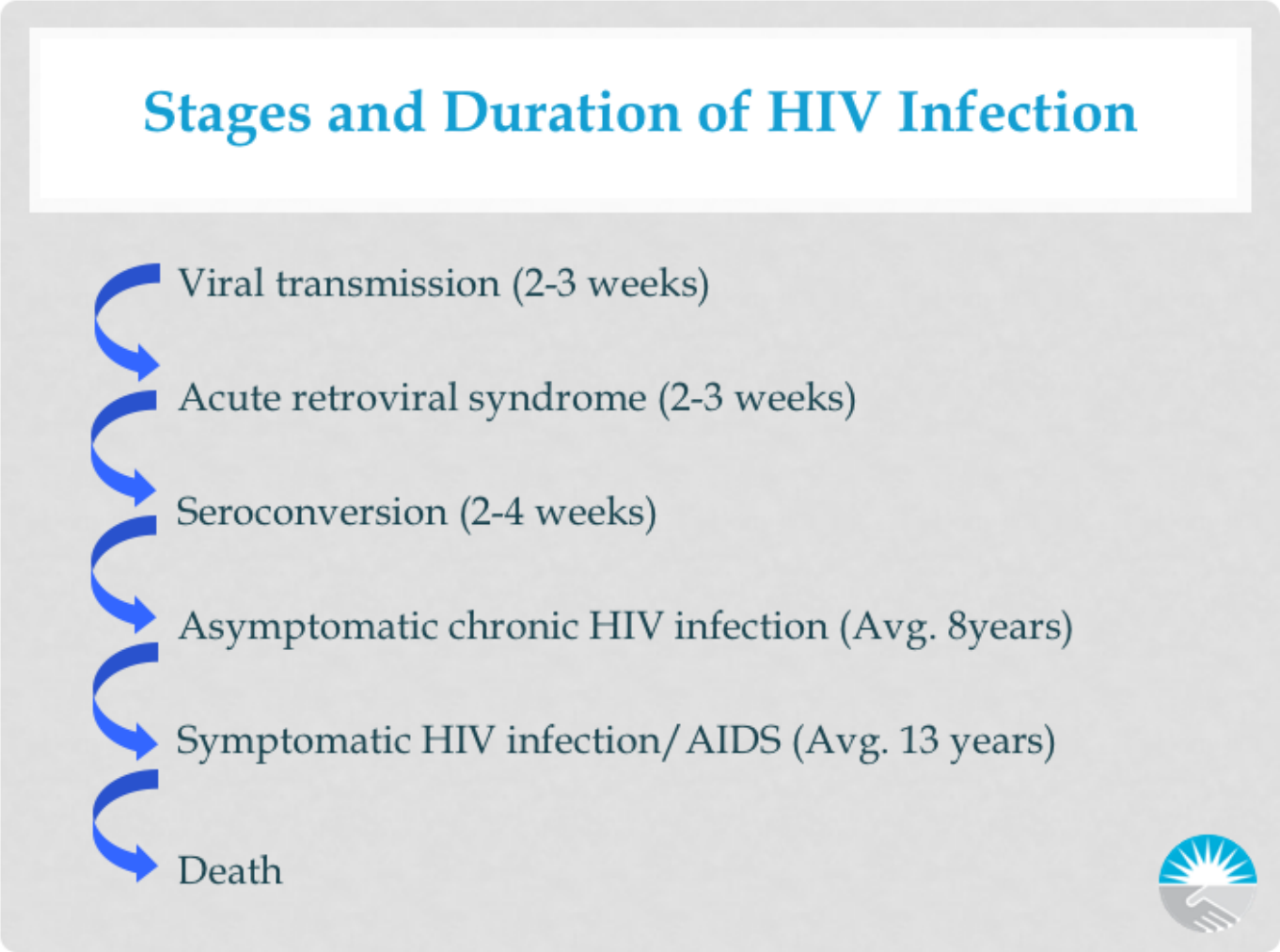
GALT, gastrointestinal tract

This model illustrates the primate SIV infection model, capturing many of the essential elements of virus-host interaction discussed in the previous slides.

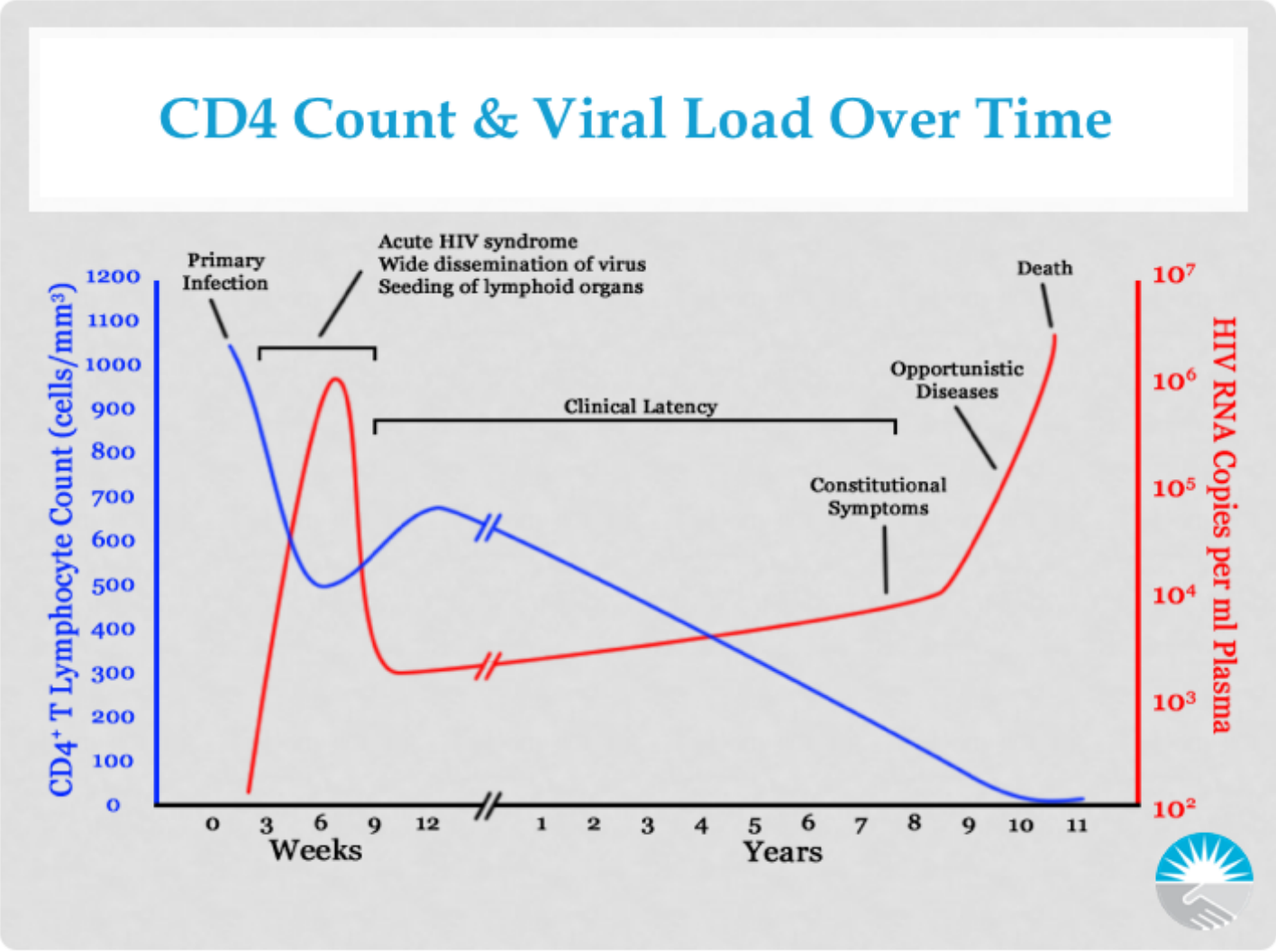
HIV transmission results from virus exposure at mucosal surfaces or from percutaneous inoculation. Because such exposures in humans are inaccessible to direct analysis, our understanding of the transmission event must necessarily come from insights gleaned from studies of HIV-1 epidemiology, viral and host genetics, risk factor and behaviour analyses, animal models, human explant tissues, and in vitro studies of virus-target cell interactions.

Source:

Shaw GM, & Hunter E. Cold Spring Harb Perspect Med. 2012;2(11).



The viral transmission stage is the onset of primary infection, marked by the virus rapidly making copies of itself and an initial drop in CD4+ T cells. Some individuals experience acute retroviral syndrome during this period.
Acute retroviral syndrome occurs when the virus is disseminated. It is characterized by fever, rash, lymphadenopathy, and sore throat (like other viral infections). If acute HIV infection is suspected, contact the medical microbiologist on call at BCCDC (**604-661-7033**) to discuss if HIV RNA testing is an option. Although 4th generation screening identifies most acute HIV cases, the NAAT has slightly higher sensitivity and will become positive a few days earlier.
After seroconversion, the patient will have HIV antibodies that can be detected by tests like ELISA and Western Blot.
The patient can remain symptomless for many years, eventually developing symptomatic HIV or AIDS (approximately 5 to 10 years after initial infection). The duration of the asymptomatic period, as well as the length of time between the development of AIDS and death, is highly variable.



This is a generalised graph of the relationship between HIV copies (viral load) and CD4 counts over the average course of untreated HIV infection.

- The blue line in the graph represents CD4+ T cell count (cells per µL)
- The red line represents HIV RNA copies per mL of plasma
- There are two times HIV viral load peaks. It becomes high shortly after initial infection, and again during the end stage of infection when CD4 count becomes low.
- HIV Infection is characterized by steady decline in the number of CD4 cells until complete immunosuppression occurs. At that point, constitutional symptoms and AIDS-related conditions appear.

Source:

Fauci, et al. Annals of Internal Medicine. 1996;124(7):654-63.

Primary HIV Infection
(Seroconversion Illness)

Early detection of HIV infection (Primary HIV Infection; PHI) is critical for:

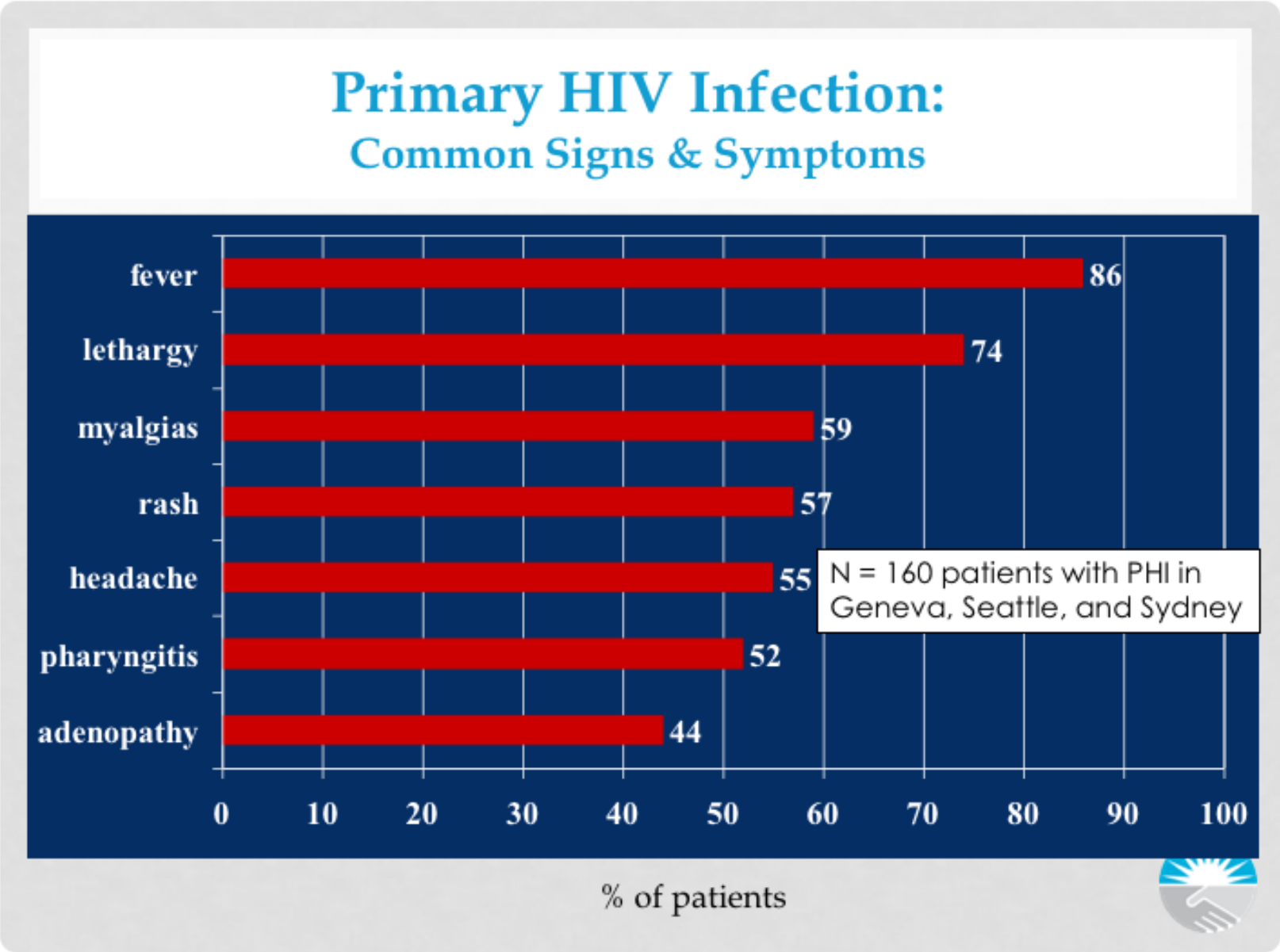
- Public health reasons:
  - Patients with PHI are likely to be highly infectious
  - Diagnosis of HIV infection may lead to safer sex
- Personal health reasons:
  - 40% of patients with HIV are not diagnosed until they have AIDS
  - ART during PHI may alter the natural course of HIV

The per-person probability of transmitting HIV-1 is most closely correlated with the viral burden in blood; each time the viral burden in an HIV-1–infected person increases by a factor of 10, the risk of transmission is expected to increase by a factor of 2.5. The risk of contagion from patients with acute, early infection appears to be much higher than that from patients with established infection, at least in part because of the high viral load and the homogeneity of viral variants clearly capable of causing infection.

In the literature it has been reported that 40% of patients with HIV are not diagnosed until they have AIDS; this number is closer to 20% in BC (BCCDC 2017).

Source:

Cohen M, et al. N Engl J Med. 2011; 364(20): 1943–1954.



The symptoms associated with acute HIV-1 infection are often too vague or nonspecific to lead to a diagnosis. Clinicians should have a high level of suspicion for acute HIV infection, particularly in regards to patients with a high risk for acquiring HIV.

This slide provides a list of the most common signs and symptoms found in multiple cohorts of patients presenting with acute HIV infection.

Source:

Vanhems, et al. AIDS. 2000;14(4):375-81.

HIV Chemoprophylaxis: Definitions

PEP:

- Post-exposure prophylaxis is a short-term antiretroviral treatment (28 days) taken after a single high-risk event in an occupational environment or an accidental exposure to reduce the likelihood of HIV infection.

nPEP:

- Non-occupational post-exposure prophylaxis is a short-term antiretroviral treatment (28 days) after an isolated high-risk sexual, injection drug use, or other non-occupational HIV exposure. nPEP will be included in and referred to as PEP in this course.

PrEP

- Pre-exposure prophylaxis is the use antiretroviral treatment, taken daily by individuals who do not have HIV, but who are at substantial risk of getting it, to *prevent* HIV infection.

The most effective methods for preventing HIV infection are those that protect against exposure. Antiretroviral therapy cannot replace behaviours that help avoid HIV exposure (i.e., sexual behaviour modification and harm reduction techniques for injection drug use).

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End of Module 1