



CATIE/PAN Pacific Educational Conference
September 14-15, 2011

Presentation: The Biology of HIV Sexual Transmission and
Prevention – Part 2

On Wednesday September 14, 2011

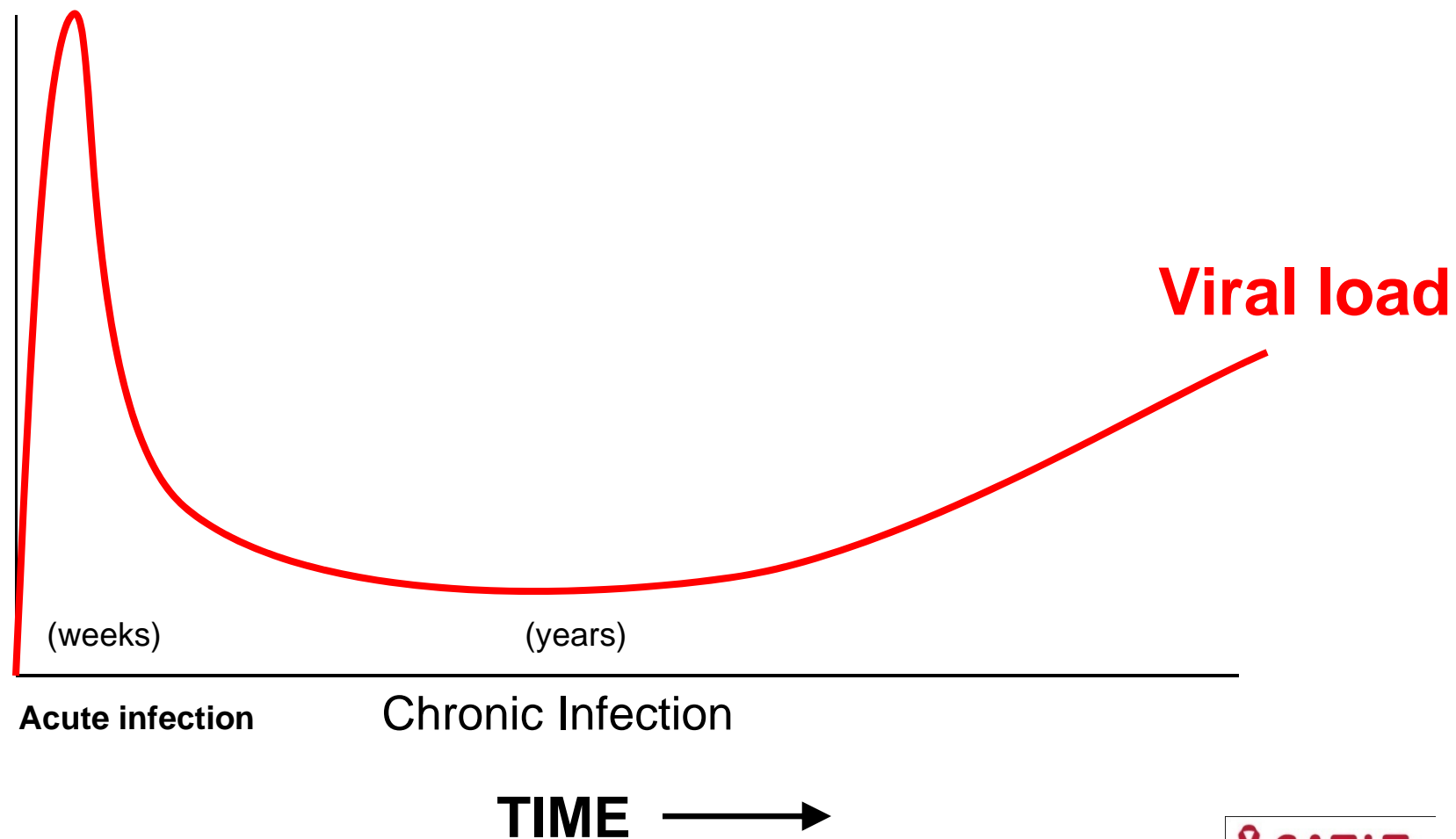
Vancouver Airport Marriott Hotel

Recent HIV infection

What's happening in the body after infection?

1. Virus replicates very quickly and amount of virus in body fluids rises rapidly
2. Some, but not all, develop symptoms including fever, fatigue, night sweats, headache, diarrhea, sore throat, and/or rash
3. Body's immune system produces antibodies against HIV, about 3 weeks after infection (on average)
4. Amount of virus in the body fluids gradually decreases and stabilises at lower level after 4-6 months

Viral load during untreated HIV infection



How many transmissions originate from recently infected individuals?

- Recently infected individuals may account for a disproportionate number of HIV transmissions
 - Research suggests up to of HIV transmissions may originate from recently infected individuals

Why are recently infected people more likely to transmit HIV?

- **Higher biological infectiousness**
 - High viral load
 - STIs
- **Higher risk behavior**
 - Engaging in behavior that lead to infection
 - Unaware of HIV status

Why do most recently infected people not know their HIV status?

- **Low levels of testing**
 - Perceived risk of infection
 - Non-specific symptoms
 - Barriers to HIV testing
- **Limitations of HIV tests**
 - Window period
 - Length of time to provide results

Types of HIV tests and their window periods

Antibody tests

- Cannot detect someone with acute HIV infection
- Point of care (POC) rapid tests available
- Window period: 34 days

Combined p24/antibody tests

- Detects p24 antigen and antibodies
- Window period: 10-14 days

HIV nucleic acid amplification test (NAAT)

- Detects HIV RNA
- Window period: 7-14 days

How can we do a better job of reducing transmissions from recently infected individuals?

- Increase levels of HIV testing
 - Educate on benefits of testing
 - Increase perception of risk and awareness of symptoms of recent infection
 - Remove barriers to testing
- Increase awareness of window period and elevated risk of transmission during early infection
- Educate on risks of using serosorting as a risk-reduction strategy
- Advocate for improved access to rapid antibody tests and tests that can detect acute HIV infection

Anti-HIV treatment as prevention

What is antiretroviral treatment?

- The daily use of a combination of at least three antiretroviral drugs by people living with HIV
- Over 25 antiretrovirals drugs currently available
- Goals of treatment
 - Limit viral replication
 - Raise levels of CD4 cells
 - Slow progression of HIV disease



When is antiretroviral treatment started?

Summary of when to start treatment

CD4 count and physical condition	Recommendation
CD4 count below 200 cells or any significant symptoms or conditions related to HIV infection	Start treatment immediately
CD4 count below 350 cells	Start treatment
CD4 count above 350 cells	Consider starting treatment
Women who are pregnant or considering becoming pregnant (with any CD4 count)	Start treatment immediately if pregnant; consider starting treatment before pregnancy

CATIE's Practical Guide to HIV Drug Treatment

Antiretroviral treatment and HIV transmission

- We know that...
 1. Blood viral load is associated with the risk of HIV transmission
 2. Successful treatment reduces the blood viral load to undetectable levels
- Opens the possibility of using treatment to prevent HIV transmission
- Also known as “treatment as prevention”

The use of treatment as prevention

- **Individual level**

- The use of treatment as a risk-reduction strategy
- Individual risk-taking behavior

- **Population level**

- The use of treatment as an intervention to reduce HIV infections in a population
- Public health perspective

What does the research say about treatment as prevention?

1. Heterosexual serodiscordant couples
 - Is transmission less likely if HIV-positive partner is on treatment?
2. Population-based
 - Does increasing the number of people on treatment in a population reduce HIV transmissions?

What does the research say about treatment as prevention?

- **Observational studies**
 1. Heterosexual serodiscordant couples
 - Is transmission less likely if HIV-positive partner is on treatment?
 - **What does the research say?**
 - Recent review of seven observational studies
 - » 71 transmissions among treated couples
 - » 365 transmissions among untreated couples
 - Treatment reduced HIV transmission by up to 86%

Why does undetectable \neq sexually non-infectious?

- Undetectable does not mean there is no virus
 - It means that the virus is below the limit of detection
- Undetectable in the blood does not always mean the virus is undetectable in other fluids
 - Antiretroviral drug levels (blood vs. mucous membranes)
 - Sexually transmitted infections
- Viral load may have increased since last measurement
 - Poor adherence
 - Drug resistance
 - Unexplained “blips”

What does the research say about treatment as prevention?

- **Observational studies**

1. Heterosexual serodiscordant couples

2. Population-based

- Does increasing the number of people on treatment in a population reduce HIV transmissions?

- **What does the research say?**

- The research is mixed
 - » Reduced number of HIV transmissions → British Columbia, San Francisco, Taiwan
 - » No effect in other locations. Why?

What is a “test and treat” strategy?

- Improving access to HIV testing, care, support, and treatment
- Objectives
 1. Increase the number of people living with HIV who know their HIV status.
 2. Ensure that those who test positive are linked to care.
 3. Increase the number of people living with HIV who are on treatment (if **ready** to start).
 4. Support people who are on treatment with regular clinical monitoring, management of side-effects, adherence counseling, diagnosis and treatment of STIs, and risk-reduction counseling.

HPTN 052 – First randomized controlled trial

- Study participants
 - 1,800 heterosexual serodiscordant couples
 - CD4 count between 350-550 cells/mm
 - Willing to start treatment earlier than guidelines
- HIV-positive partner randomized to either
 1. Start treatment immediately (CD4 count higher than 350)
 2. Delay treatment until CD4 count drops below 250 cells/mm

Earlier initiation of treatment by HIV-positive partner reduced the risk of transmission to HIV-negative partner by 96%

What do we know about treatment as prevention?

- Antiretroviral treatment significantly reduces – but not eliminate - the risk of sexual HIV transmission
- Although rare, it is still possible for a person with an undetectable viral load to transmit HIV
- Earlier initiation of treatment by the HIV-positive partner in a *heterosexual serodiscordant relationship* reduces the risk of HIV transmission to the HIV-negative partner
- A “test and treat” strategy may be an effective way of reducing the number of HIV transmissions in a population

Unanswered questions...

- What is the risk of HIV transmission when the blood viral load is undetectable?
- How effective is treatment at reducing the risk of HIV transmission through anal sex? Injecting drug use?
- Is a “test and treat” strategy feasible?
- Does starting treatment earlier provide a benefit to the person living with HIV?

Other biological factors

Other biological factors

- Vaginal infections that are not STIs
 - Bacterial vaginosis
 - Yeast infection (candidiasis)
- Hormone-related vulnerability
 - Progesterone-based birth control
 - Pregnancy
 - Menopause
- Cervix-related vulnerability
 - Cervical ectopy/erosion
- Genetics, immune system, characteristics of the virus, and other unknown factors

Part III

HIV Prevention Technologies

Objectives

1. To explore the research on new HIV prevention technologies
2. To understand how these prevention technologies may be able to reduce the risk of infection from an exposure
3. To discuss the challenges in implementing new HIV prevention technologies

What do we mean by new prevention technologies?

“Old” prevention technologies

- Barrier methods (male and female/internal condoms)
- New needles
- Testing technologies
- Lubricants

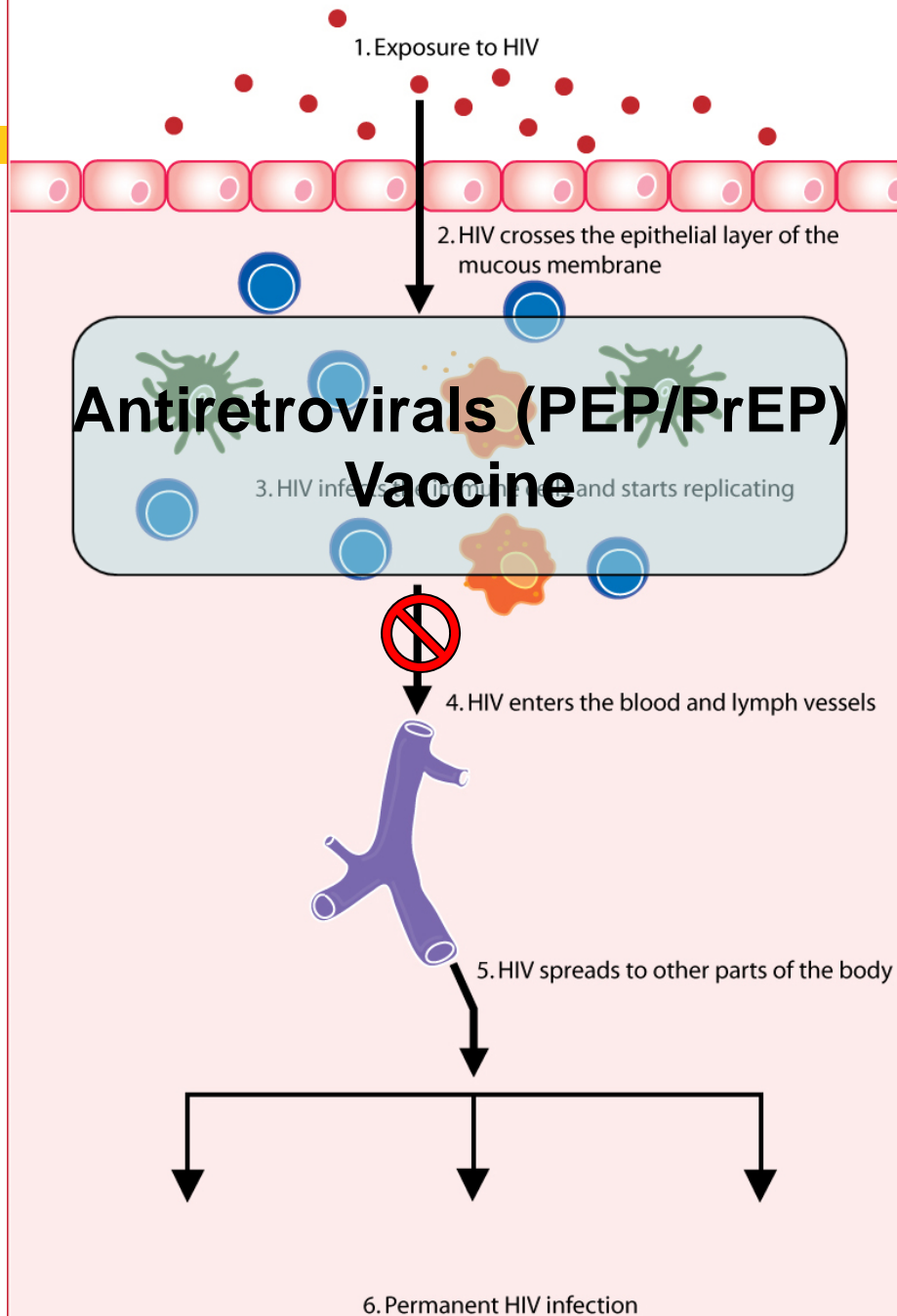
“New” types of prevention technologies (NPTs)

- Male circumcision
- Treatment as prevention
- **Post-exposure prophylaxis (PEP)**
- **Pre-exposure prophylaxis (PrEP)**
- **Microbicides**
- **Vaccines**

The “window of opportunity”

- The brief time period after HIV has crossed the epithelial barrier **but** before it has spread throughout the body
- During this time HIV is vulnerable
 - Number of virus is small
 - Virus needs to replicate for one to three days
 - Virus is fighting a battle against the immune system
- An opportunity for a vaccine, PEP, or PrEP to help the immune system clear the virus

From exposure to infection: sexual transmission of HIV



HIV/AIDS Vaccines

What is a vaccine and how do they work?



- Vaccines teach our immune system how to recognize and fight a germ before we are exposed to it
 - Vaccines contain a dead germ or part of a dead germ which cause a “fake infection”
- A vaccine-prepared immune system is able to react more quickly when an actual exposure occurs
- An HIV/AIDS vaccine would give our immune system a better chance of clearing the virus during the “window of opportunity”

Why is it challenging to create a vaccine against HIV?

- HIV mutates quickly
- HIV weakens the immune system
- HIV can hide in our immune cells

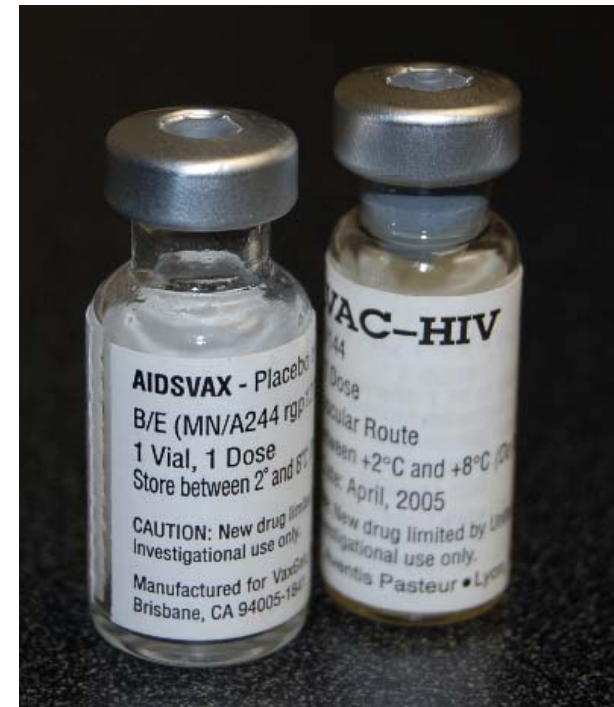
- We don't know...
 - what "part" to put into the vaccine
 - what immune response we have to prepare (antibodies or killer cells?)
 - **how to prepare the immune cells at the mucous membranes**

Why do we think its possible to create an HIV/AIDS vaccine?

- HPV vaccine
- Early control of HIV by our immune system
- Highly exposed seronegative individuals
- Thailand HIV/AIDS Vaccine Trial

Thai Vaccine Trial

- Enrolled over 16,000 heterosexual men and women
- Contained two vaccines
 - ALVAC – stimulated killer T cells
 - AIDSVAX – stimulated antibodies
- Reduced risk of HIV infection by 26-32%
 - Vaccine provided 60% protection at one year
 - Protection decreased over time
- Researchers are trying to figure out how it worked!



How good is good enough?

1. Do you think that the Thai vaccine should be made widely available? Why or why not?
2. What is the minimum level of protection a technology should provide in order for it to be made widely available? Why?

Microbicides

Microbicides

- A gel, suppository, ring, or film applied vaginally or rectally to reduce HIV transmission
- The first microbicides to be developed were vaginal gels that contained inexpensive substances
- These all failed to prevent HIV transmission when used by humans (some may have *increased* the risk of infection)



Antiretroviral-based strategies

Turning to antiretrovirals for prevention

The use of antiretrovirals for prevention by

1. HIV-positive individuals to reduce their risk of transmitting HIV
 - Treatment as prevention

2. HIV-negative individuals to reduce their risk of infection
 - Post-exposure prophylaxis (PEP)
 - Pre-exposure prophylaxis (PrEP)
 - » Oral PrEP (pills)
 - » Topical PrEP (ARV-based microbicides)

What are advantages/disadvantages of using antiretrovirals for prevention?

Advantages	Disadvantages

What are advantages/disadvantages of using antiretrovirals for prevention?

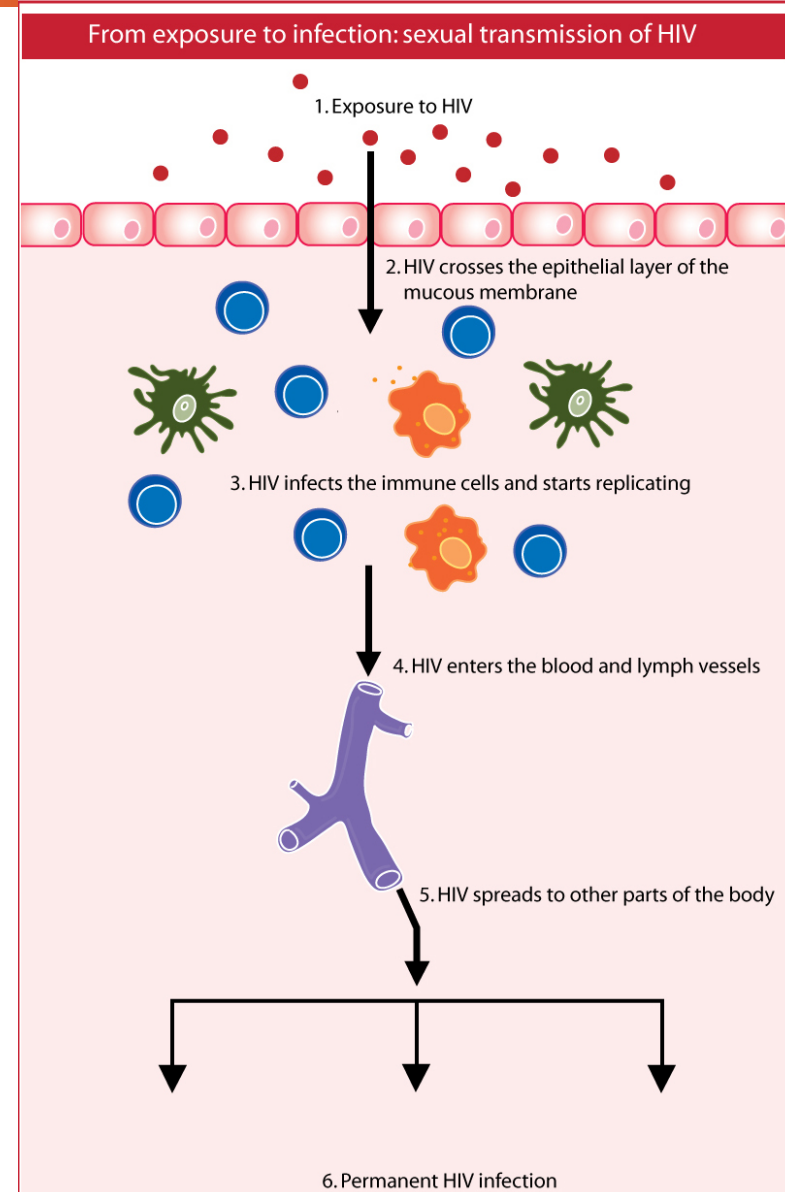
Advantages	Disadvantages
Already available	
Specific and potent	
Knowledge from use as treatment	
Successfully used to prevent HIV transmission (PMTCT)	

What are advantages/disadvantages of using antiretrovirals for prevention?

Advantages	Disadvantages
Already available	Toxicity and side-effects
Knowledge from use as treatment	Drug resistance
Specific and potent	Adherence
Successfully used to prevent transmission (PMTCT)	Partial protection <ul style="list-style-type: none"><li data-bbox="1087 929 1590 982">• Risk compensation<li data-bbox="1087 1008 1663 1061">• Messaging/counseling
	No protection against other STIs
	Cost and access issues

How would PEP/PrEP reduce the risk of infection?

- Antiretrovirals prevent HIV from replicating in immune cells
- The goal of PEP/PrEP is to reduce the replication of HIV at the mucous membranes during the “window of opportunity”
- This may help the immune system win the battle against HIV and prevent the virus from spreading throughout the body



Post-exposure prophylaxis (PEP)

What is post-exposure prophylaxis (PEP)?

- The use of a combination of antiretrovirals by HIV-negative individuals for a **short period** of time **after** a *suspected* or *known* exposure to HIV
 - Must be started as soon as possible but within 72 hours after the exposure
 - Must be taken everyday for 28 days
 - Must avoid additional exposures while taking PEP
- Only meant to be used in case of emergencies
- Types of exposures
 - Occupational
 - Non-occupational (nPEP)

How well does PEP work?

- We don't know how protective PEP is
- We know it is not 100% protective
 - People have become infected despite using PEP
- Protection likely depends on:
 - Starting PEP quickly
 - Being adherent
 - The risk of transmission from the exposure
 - Avoiding additional exposures
 - The number and type of antiretrovirals used

What's involved in taking PEP?

1. Assessment
2. Counseling
3. Prescription
4. Follow-up

Why do so few people use nPEP in Canada?

- People may not think they are at risk
- Lack of national and provincial guidelines
- Use of nPEP is not promoted
- Only available in some emergency departments and urgent care clinics
- Cost is only covered by some provincial and private insurance plans
- Side-effects, adherence, monitoring, counseling

Discussion

1. Why is there a reluctance to make PEP for non-occupational exposures more widely available?
2. Do you think PEP for non-occupational exposures should be made more widely available and promoted?

Pre-exposure prophylaxis (PrEP)

What is PrEP to prevent HIV infection?

- The **ongoing** use of one or two antiretrovirals by HIV-negative individuals starting **before** an exposure and continuing **afterwards**
 - A potential option to prevent infection from ongoing exposures to HIV during periods of risk
- A recently proven strategy still being studied
- PrEP is currently unapproved by Health Canada

What's being researched?

Large studies

- Viread or Truvada pill taken daily
 - Viread → tenofovir
 - Truvada → tenofovir + emtricitabine
- Tenofovir vaginal gel used before/after sex or daily

Small Studies

- Gels used rectally
- Pills used intermittently or before/after sex
- Slow-release intravaginal rings
- Long-lasting injections
- Antiretrovirals other than tenofovir and emtricitabine

How is the research conducted?

- Biomedical prevention trials
 - Enrollment criteria
 - Randomized
 - Placebo-controlled
 - Blinded
- Comprehensive package of prevention services
 - Risk-reduction counseling
 - Access to male and female condoms
 - Adherence counseling
 - HIV testing
 - STI diagnosis and treatment

What does the research say about PrEP?

Study participants				
PrEP strategy				
Reduced risk of HIV infection				
Overall				
Consistent users				
Safety concerns				

What does the research say about PrEP?

	CAPRISA 004			
Study participants	Heterosexual women			
Type of PrEP	Coital tenofovir gel (vaginal)			
Reduced risk of HIV infection				
Overall	39%			
Consistent users	54%			
Safety concerns	<ul style="list-style-type: none"> • Diarrhea 			

What does the research say about PrEP?

	CAPRISA 004	iPrEx		
Study participants	Heterosexual women	Men who have sex with men (MSM) and trans women		
Type of PrEP	Coital tenofovir gel (vaginal)	Daily Truvada pill		
Reduced risk of HIV infection				
Overall	39%	44%		
Consistent users	54%	73%		
Safety concerns	<ul style="list-style-type: none"> • Diarrhea 	<ul style="list-style-type: none"> • Nausea • Headache • Decrease in kidney function and bone density • Drug resistance 		

What does the research say about PrEP?

	CAPRISA 004	iPrEx	FEM-PrEP	
Study participants	Heterosexual women	Men who have sex with men (MSM) and trans women	Heterosexual women	
Type of PrEP	Coital tenofovir gel (vaginal)	Daily Truvada pill	Daily Truvada pill	
Reduced risk of HIV infection				
Overall	39%	44%	0%	
Consistent users	54%	73%	-	
Safety concerns	<ul style="list-style-type: none"> • Diarrhea 	<ul style="list-style-type: none"> • Nausea • Headache • Decrease in kidney function and bone density • Drug resistance 	<ul style="list-style-type: none"> • No major safety concerns 	

What does the research say about PrEP?

CAPRISA 004	iPrEx	FEM-PrEP	TDF2	Partners PrEP
Heterosexual women	Men who have sex with men (MSM) and trans women	Heterosexual women	Heterosexual men and women	Serodiscordant heterosexual couples
Coital tenofovir gel (vaginal)	Daily Truvada pill	Daily Truvada pill	Daily Truvada pill	Daily Viread pill Daily Truvada pill
39%	44%	0%	63%	62% (Viread) 73% (Truvada)
54%	73%	-	78%	-
<ul style="list-style-type: none"> • Diarrhea 	<ul style="list-style-type: none"> • Nausea • Headache • Decrease in kidney function and bone density • Drug resistance 	<ul style="list-style-type: none"> • No major safety concerns 	<ul style="list-style-type: none"> • Nausea • Vomiting • Dizziness 	<ul style="list-style-type: none"> • Nausea • Diarrhea

What do we know about PrEP?

- In combination with a comprehensive package of prevention services...
 1. Daily Truvada reduced the risk of infection when used by
 - MSM and trans women
 - Heterosexual men and women
 2. Daily Viread reduced the risk of infection when used by heterosexual men and women
 3. A vaginal tenofovir gel used before and after sex reduced the risk of infection when used by women.
- It needs to be used consistently for it to work.
- The risk of side effects, toxicity, and drug resistance are low.

What don't we know about PrEP?

- Safety/effectiveness of...
 - A pill taken occasionally
 - A gel used in the rectum
 - Long-lasting options (intravaginal ring or injection)
 - Other antiretrovirals
- Safety/effectiveness of Viread, Truvada and tenofovir gel...
 - In populations not included in trials
 - Over a longer period of time
 - **In the “real world”**

What's next for oral and topical PrEP?

1. Ongoing research
2. Regulatory Approval
3. Roll out

Ongoing PrEP research

Study	Location	Population	Intervention	Completion
CDC 4370	Thailand	2,400 people who use injection drugs	<ul style="list-style-type: none">• Daily Viread pill	2012
VOICE	East/South Africa	5,000 heterosexual women	<ul style="list-style-type: none">• Daily Viread pill• Daily Truvada pill• Daily tenofovir gel	2013

Go to www.avac.org for latest trial information

Rolling out PrEP

- **Clinical services**
 - Eligibility assessment and prescription
 - HIV testing
 - Drug resistance testing
 - Medical and clinical monitoring
 - STI treatment and diagnosis
- **Non-clinical services**
 - Outreach and education
 - Risk-reduction counseling
 - Adherence support
 - Advocacy

- In 2011, CDC released interim guidance for healthcare providers on the prescription of PrEP
- “PrEP has the potential to contribute to effective and safe HIV prevention for MSM if
 1. Targeted to MSM at high risk for infection
 2. Delivered as part of a comprehensive set of prevention services (risk-reduction and adherence counseling, condom access, diagnosis and treatment of STIs)
 3. Accompanied by monitoring of HIV status, side-effects, adherence, and risk behaviors at regular intervals”
- Why were these guidelines released before the regulatory approval of PrEP?

BOX. CDC interim guidance for health-care providers electing to provide preexposure prophylaxis (PrEP) for the prevention of HIV infection in adult men who have sex with men and who are at high risk for sexual acquisition of HIV

Before initiating PrEP

Determine eligibility

- Document negative HIV antibody test(s) immediately before starting PrEP medication.
- Test for acute HIV infection if patient has symptoms consistent with acute HIV infection.
- Confirm that patient is at substantial, ongoing, high risk for acquiring HIV infection.
- Confirm that calculated creatinine clearance is ≥ 60 mL per minute (via Cockcroft-Gault formula).

Other recommended actions

- Screen for hepatitis B infection; vaccinate against hepatitis B if susceptible, or treat if active infection exists, regardless of decision about prescribing PrEP.
- Screen and treat as needed for STIs.

Beginning PrEP medication regimen

- Prescribe 1 tablet of Truvada* (TDF [300 mg] plus FTC [200 mg]) daily.
- In general, prescribe no more than a 90-day supply, renewable only after HIV testing confirms that patient remains HIV-uninfected.
- If active hepatitis B infection is diagnosed, consider using TDF/FTC for both treatment of active hepatitis B infection and HIV prevention.
- Provide risk-reduction and PrEP medication adherence counseling and condoms.

Follow-up while PrEP medication is being taken

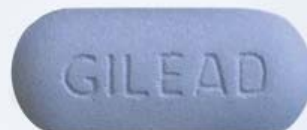
- Every 2–3 months, perform an HIV antibody test; document negative result.
- Evaluate and support PrEP medication adherence at each follow-up visit, more often if inconsistent adherence is identified.
- Every 2–3 months, assess risk behaviors and provide risk-reduction counseling and condoms. Assess STI symptoms and, if present, test and treat for STI as needed.
- Every 6 months, test for STI even if patient is asymptomatic, and treat as needed.
- 3 months after initiation, then yearly while on PrEP medication, check blood urea nitrogen and serum creatinine.

On discontinuing PrEP (at patient request, for safety concerns, or if HIV infection is acquired)

- Perform HIV test(s) to confirm whether HIV infection has occurred.
- If HIV positive, order and document results of resistance testing and establish linkage to HIV care.
- If HIV negative, establish linkage to risk-reduction support services as indicated.
- If active hepatitis B is diagnosed at initiation of PrEP, consider appropriate medication for continued treatment of hepatitis B.

Does PrEP have a role to play in Canada?





There is no magic pill.

An Open Letter to Gilead on PrEP:

As the nation's largest AIDS organization, AIDS Healthcare Foundation (AHF) takes the matter of HIV prevention very seriously. We are concerned about the implications of a recent study of pre-exposure prophylaxis (PrEP) using Gilead Sciences, Inc.'s drug Truvada using 2,500 gay men and showing a 44% effectiveness rate in preventing HIV transmission.

Such modest results are insufficient to support U.S. Food and Drug Administration approval of Truvada as an HIV prevention tool for gay men because:

- *PrEP lacks effectiveness* - 44% effectiveness is much too low to merit FDA approval as a prevention tool. If we were talking about protecting the general population with a treatment that was only 44% effective, would we be celebrating?
- *Real world information is lacking* - The 44% who received a benefit from Truvada were intensively counseled monthly and tested frequently for sexual infections. This is in no way representative of the real world.
- *Increased risk* - How likely are uninfected men to take pills every day for the rest of their lives to prevent a possible HIV infection? The consequences of patients who take Truvada haphazardly are that they will become infected, develop drug resistance, and spread drug-resistant virus to others.
- *Condoms work* - HIV prevention with Truvada has not been shown to be as effective as condom-use. Using medication to prevent infection is based on the premise that we cannot succeed in getting gay men to use condoms. Are we really ready to give up on gay men protecting themselves and their partners?

AHF supports continued research on HIV prevention, but opposes quick fixes that run the risk of contributing to the spread of HIV and drug-resistant viruses. We must consider these issues if we are going to offer up hundreds of thousands of gay men for this experiment.

For more information or to send a letter to Gilead CEO John C. Martin,
Please visit nomagicpills.org.





There is no magic pill.

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Key Points on NPTs

- An HIV/AIDS vaccine is a long way away but we have finally had some success.
- PEP is already available but underused for non-occupational exposures. It is only meant to be used in case of emergencies.
- PrEP is a recently proven but unapproved strategy. Some types of PrEP are already available. It could be used as a regular method of prevention but would need to be provided as one part of a comprehensive approach.

Part 4

Summary

Overcoming the barriers

1. Crossing the epithelial layer
 - Number of virus / Amount of fluid
 - Integrity of layer
 - Surface area
 - Duration of contact
2. Battling the immune cells
 - Number of target cells
 - “Window of Opportunity” technologies



Risk of transmission is a balancing act

Increases risk

- Higher viral load
 - Acute HIV infection
 - STIs
 - Poor adherence/resistance
- Higher risk types of sex
- STIs/bacterial vaginosis
- Foreskin
- Tearing
- Inflammation
- Cervical ectopy
- Progesterone-based birth control?
- Sexual lubricants?



Decreases risk

(non-condom risk-reduction strategies)

- Lower viral load
 - Successful treatment
 - Undetectable viral load
- Engaging in less risky types of sex
 - Strategic positioning
 - Oral sex
- Treatment of STIs/bacterial vaginosis
- Male circumcision
- PEP or PrEP
- Withdrawal
- Sexual lubricants?
- Vaccine?

What's the risk of HIV infection? I want a number!

Key Points

- The risk of transmission from a **single exposure** is unique and impossible to quantify.
- The risk of HIV transmission **over time** depends on the number of exposures and unique risk of transmission from each exposure
- The protection provided by **non-condom risk reduction strategies** may be reduced by factors that increase risk of HIV transmission from an exposure
- If an exposure occurs, there is no way of reducing the risk of transmission to zero.

Messaging activity: What would you say to

- A person or couple
 1. who are not using condoms because they are using _____ as a risk-reduction strategy
 2. want to know how effective _____ is at reducing the risk of transmission
 - Treatment
 - Undetectable blood viral load
 - PEP
 - PrEP
 - Male circumcision
 - Serosorting
 - Strategic positioning
 - Only engaging in oral sex
 - Lots of lube
 - Withdrawal