New HIV Prevention Technologies

The Basics and the State of Research

July 12, 2011
Marc-André LeBlanc and San Patten
33 million people now live with HIV/AIDS

Only half of the 33 million know their HIV status

2.6 million new infections annually

Among newly infected people:
- 50% are women (higher in some areas)
- 95% live in developing countries

80–90% of all HIV+ people in southern Africa do not know they have HIV
HIV/AIDS in Canada (in 2008)

- 65,000 Canadians living with HIV
- 2300 – 4300 new infections
  - 44% MSM
  - 20% heterosexual/non-endemic
  - 16% heterosexual/endemic
  - 17% IDUs

- 26% of HIV-positive Canadians are unaware of their status
National Policy

HIV prevention (including NPTs) is a core component of the following national policy frameworks:

- Leading Together: Canada Takes Action on HIV/AIDS
- Federal Initiative to Address HIV/AIDS in Canada
- Canadian HIV Vaccines Initiative
- Canadian HIV Vaccines Plan
- Canadian Microbicides Action Plan
Imagine a full spectrum of interventions

<table>
<thead>
<tr>
<th>Prior to exposure</th>
<th>Point of transmission</th>
<th>After infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rights-focused behaviour change</td>
<td>• Male &amp; female condoms and lubricant</td>
<td>• Antiretroviral treatment</td>
</tr>
<tr>
<td>• Voluntary counselling &amp; testing</td>
<td>• Treatment to prevent vertical transmission</td>
<td>• Treatment for opportunistic infections</td>
</tr>
<tr>
<td>• Sexually transmitted infection screening and treatment</td>
<td>• Clean injecting equipment</td>
<td>• Basic care/nutrition</td>
</tr>
<tr>
<td>• Male medical circumcision</td>
<td>• Post-exposure prophylaxis (PEP)</td>
<td>• Prevention for positives</td>
</tr>
<tr>
<td>• Pre-exposure prophylaxis (PrEP)</td>
<td>• Vaginal &amp; rectal microbicides</td>
<td>• Education and rights-focused behaviour change</td>
</tr>
<tr>
<td>• Preventative vaccines</td>
<td>• Cervical barriers</td>
<td>• Treatment as prevention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Therapeutic vaccines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Functional cure</td>
</tr>
</tbody>
</table>
Clean injecting equipment

Vaccins

Microbicides

Cervical barriers: vaginal diaphragms

HIV Prevention

Treatment as Prevention

PEP

PMTCT

Male and female condoms

Male circumcision

Voluntary counselling and testing
Percentage of at-risk people with access to HIV prevention

- <20% Sex workers with access to behaviour change programmes
- 11% HIV+ pregnant women with access to PMTCT
- 10–12% Adults in Africa accessing HIV testing
- 9% Men who have sex with men with access to appropriate behaviour change programmes
- 9% Sexually active people with access to male condoms
- 8% Injection drug users with access to harm reduction programmes

Protection in Primary Partnerships: Difficult to Achieve

- People generally are willing to use condoms with new partners, or during casual or commercial sex
  - But once “trust” enters the equation the condom comes off
  - Sex with a primary partner is the biggest source of HIV infection among women globally
Why condoms are not enough
And in Canada…

**Motivation Regarding Safer Sex**

"Why didn’t you use a condom?"

- Married/only one partner/monogamous: 76%
- No risk of getting an infectious disease: 7%
- Birth control pill: 6%
- Trying to get pregnant: 5%
- Partners have been recently tested for HIV: 4%
- Assume that partner(s) do not have HIV/AIDS: 3%
- I don’t like using condoms: 2%
- Not prepared for it: 1%
- No sexual intercourse: 1%
- DK/NR: 7%

n=1106  
HIV/AIDS Awareness Survey, February 2006
Efficacy vs. effectiveness

- Efficacy = how well a product works under ideal conditions
- Effectiveness = how well a product works in practice
- For example, condom efficacy is 80-95% when used consistently and correctly. Their effectiveness is 69% because some people don’t always use them correctly or consistently.
Partial efficacy
Condoms and NPTs

Prevention Equation

Correct. In this case, the microbicide would offer the woman more protection.

Amount of protection provided

100%

microbicides more protective

0%

Consistency of Use

Never used 0%

Always used 100%

20%

Condoms

Never used 0%

Always used 100%

30% 66%

Microbicides

In fact, she would only need to use the microbicide 30% of the time to get as much protection as a condom used 20% of the time.

Move the green slider above to 30% to see a demonstration of this.

In this exercise, we assume that condoms reduce the risk of infection by 90% per sex act and a microbicide could reduce the risk of infection by 60% per sex act.
ARV-BASED PREVENTION METHODS
ARV-based prevention options

Prior to exposure

Point of transmission

After exposure

Preventing vertical transmission (PMTCT+)

PrEP

Treatment of HIV+ partner

Vaginal microbicides (rings)

Vaginal microbicides (gels) and rectal microbicides

PEP
HIV prevention

Not ARV-based
- Male & female condoms
- Circumcision
- Clean injecting equipment
- Vaccines
- VCT

ARV based
- Vaginal and rectal microbicides
- Preventing vertical transmission
- PEP
- PrEP
- Treatment for HIV+ partner
TREATMENT AS PREVENTION
Treatment as prevention

HIV+ people taking ARVs regularly

- Does it work at individual level?
  - Treatment = less virus = less transmission

- Can it work at population level?
  - Increased testing = more knowledge of status = less risk-taking
  - Increased testing = more HIV+ people on treatment = less virus
  - Less risk-taking + less virus = less transmission?
Steps needed for “Treatment as prevention”

ARVs for prevention

Access to treatment

Knowledge of status
MICROBICIDES
What is a microbicide?

A suppository or a gel applied with an applicator before sex

A vaginal ring that stays in place for up to a month

A lube used before and during sex

A douche or enema used before and/or after sex
## Comparing ARV-based and non-ARV-based microbicides

<table>
<thead>
<tr>
<th></th>
<th>ARV</th>
<th>Not ARV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>□ More potent against HIV</td>
<td>□ Could work against HIV and other sexually transmitted infections</td>
</tr>
<tr>
<td></td>
<td>□ May be long lasting</td>
<td>□ Could be contraceptive</td>
</tr>
<tr>
<td></td>
<td>□ Not contraceptive</td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>□ May be more toxic</td>
<td>□ May be less potent against HIV</td>
</tr>
<tr>
<td></td>
<td>□ May cause resistance</td>
<td>□ Must be used at time of sex</td>
</tr>
<tr>
<td></td>
<td>□ Unlikely to protect against other sexually transmitted infections</td>
<td></td>
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</tbody>
</table>
PRE-EXPOSURE PROPHYLAXIS
Pre-exposure prophylaxis (PrEP)

HIV prevention strategy that uses ARVs to protect HIV-negative people from HIV infection

Taking medicine to **prevent** rather than to **treat** a disease or condition.

For example:
- Taking pills to prevent malaria when you travel.
- Using hormonal contraceptives (injections or pills) to prevent pregnancy.
- Taking pills to avoid pneumonia, if you are at risk.
Next steps for science

- Gather more data on how PrEP works across populations
- Address safety concerns through current trials and further research
- Learn how to monitor widespread resistance
- Study intermittent use: for example, taking it only when you expect to have sex
- Find out about impact on pregnancy and breast feeding
- Test other ARVs to see if they might also work as PrEP
VACCINES
Vaccines

- A vaccine is a substance that teaches the body to recognize and defend itself against bacteria and viruses that cause disease.

- A vaccine causes a response from the immune system—the body's defense system—preparing it to fight, and also to remember how to fight, if exposed to a specific infection.

- A vaccine is not a cure, but prevents infection or slows disease progression.
Challenges in HIV Vaccine Research

- **Viral Genetic Diversity:** HIV is not just one specific virus.
- **Immune Protection:** We don’t know what immune responses are needed, or how strong they need to be.
- **Vaccine Testing:** Slow process, very expensive.
...but on the bright side...

- **Precedent from other systems:** Success against other viral infections
- **Precedent from animal studies:** Long-term control of infection in vaccinated monkeys
- **Neutralizing antibody:** Recent discovery of broadly neutralizing antibodies.
- **Immune control of HIV-1:** Infected individuals control infection
- **Vaccine Trials:** In progress
UNDERSTANDING HIV PREVENTION RESEARCH
Clinical Trials Process

**For Vaccines**

- **Preclinical**
  - **Phase I**
    - Smallest group of volunteers
    - Lasts 12 – 18 months
    - Studies Safety
  - **Phase II**
    - Larger group of volunteers
    - Lasts up to 2 years
    - Studies Safety & Immunogenicity
  - **Phase IIIB**
    - "Test of Concept"
    - Bigger than Phase II but smaller than Phase III
    - Used to determine what products to move to Phase III
  - **Phase III**
    - Largest group of volunteers
    - Lasts 3 – 4 years
    - Studies Safety & Efficacy

**For Microbicides**

- Lasts up to 2 years
- Studies Safety & Acceptability

Sometimes simultaneous studies (HIV+ and penile)

Licensure, Manufacturing & Distribution
The product pipeline

Source: Alliance for Microbicide Development
Scenario #1: Benefit (It Works!)

- Trial shows compelling evidence of benefit
Scenario #2: Flat Result

- The trial shows no benefit
- The product caused no harm
Scenario #3: Evidence of Harm

- Trial shows product has no protection
- Product causes harm
- Usually, these trials will be closed early...
All Clinical Trial Results Are Valuable

- They can tell us **which products are not worth pursuing**
- They can point to the kinds of modifications that could be made to **improve trial design**
- They may yield beneficial information about **behavioral and cultural practices** that influence HIV transmission and clinical trial outcomes; and
- They provide valuable information about **how prevention trials can be better managed**.
### HIV Prevention Trials Differ From Treatment Trials

<table>
<thead>
<tr>
<th>Treatment Trials:</th>
<th>HIV Prevention Trials:</th>
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<tbody>
<tr>
<td>□ Enroll those needing treatment – individual urgency.</td>
<td>□ Enrolling healthy people – no immediate benefit to individual</td>
</tr>
<tr>
<td>□ May help prevent disease progression.</td>
<td>□ May help prevent disease transmission.</td>
</tr>
<tr>
<td>□ Only benefits those with the disease.</td>
<td>□ Benefits society; everyone at risk of HIV.</td>
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</table>
Special Challenges of HIV Prevention Trials

- Complex clinical trial design: multi-site, multi-country, 2,000-10,000 participants, transnational research collaborations
- Healthy individuals -- yet at “high risk”: 3-5% annual incidence minimum
- Often involved marginalised or stigmatised populations (sex workers, IDU, MSM); stigma associated with HIV, sexual activity, drug use
- All new intervention likely to reduce, not eliminate risk = require large trials to detect partial efficacy
- No clear surrogate endpoints (“correlates of protection”); only new infections tell us whether a product works or not
- Results affected by user behaviour, in many cases
PAST TRIAL RESULTS
# Outcomes of past studies

<table>
<thead>
<tr>
<th>Safe</th>
<th>Signs of efficacy</th>
<th>No efficacy</th>
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<tbody>
<tr>
<td></td>
<td>Circumcision</td>
<td>Carraguard</td>
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<td></td>
<td>AIDSVAX/ALVAC</td>
<td>BufferGel</td>
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<tr>
<td></td>
<td>CAPRISA 004 (tenofovir gel)</td>
<td>AIDSVAX</td>
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<tr>
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<td>PrEP (3 trials)</td>
<td>MIRA (diaphragm)</td>
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<tr>
<td></td>
<td>Treatment as prevention</td>
<td>PrEP (1 trial)</td>
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| Tend towards harm | |
|-------------------| | |
| Tend towards harm | | |
|                    | | |
Medical male circumcision

- 3 studies conducted: South Africa, Uganda, Kenya
- Trials showed: circumcised men about 60% less likely to acquire HIV through unprotected vaginal intercourse
- WHO published recommendation based on study results
Medical male circumcision

- 60% risk reduction for HIV-negative circumcised men during unprotected vaginal intercourse with HIV+ woman
- Trials did not show reduction in transmission risk from circumcised HIV+ man to HIV-negative woman
  - In fact, one trial showed opposite trend: increased risk for wives of circumcised HIV+ husband; probably due to resuming sex too soon after circumcision
- Trials did not provide information on effect of circumcision on HIV transmission during anal sex—for either women or men
RV144: Thai vaccine trial

- 16,000 men and women in Thailand
- 6 vaccinations (prime/boost) over 6 months
- 74 (on placebo) vs 51 (on product) new infections

- Efficacy: 31.2%
- CI = 1.2-52.1%
- p = 0.04
CAPRISA 004: Tenofovir gel

- 889 South African women
  - 445 on product
  - 444 on placebo

- HIV
  - Effectiveness = 39%
  - CI = 6-60%
  - p = 0.017

- HSV-2
  - Effectiveness = 51%
  - p = 0.003

Adherence → Effectiveness

- <50% = 20%
- 50-80% = 38%
- >80% = 54%
iPrEx: Truvada

- 2,499 gay men and transgender women
- Peru, Ecuador, Brazil, US, South Africa, Thailand
- Effectiveness: 43.8% (CI=15.4-62.6, p=0.005)
- Poor adherence rates
  - Sub-analysis:
    - 9% of those who became HIV-positive had detectable levels of drug in their blood, versus
    - 51% among those who remained HIV-negative
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 estimated 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.

Abbreviations: HIV = human immunodeficiency virus; STI = sexually transmitted infection; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine.

Sources: CDC. Sexually transmitted diseases treatment guidelines, 2010. MMWR 2010;59(No. RR-12).
* These recommendations do not reflect current Food and Drug Administration-approved labeling for TDF/FTC.
FEM-PrEP: Truvada

- April 2011: Trial releases results early
- Nearly 1,800 out of the planned 3,900 women had been recruited. (Kenya, South Africa, Tanzania)
- 56 seroconversions: 28 among women on product; 28 among those on placebo
- Futile to continue: will be unable to demonstrate efficacy
- Why???
  - Adherence?
  - Delivery method: pill vs gel?
  - Drug distribution levels: blood vs vaginal vs rectal?
  - Exposure route: vaginal vs rectal?
  - Risk levels?
Partners PrEP: Truvada and Tenofovir

- July 2011: Data Safety Monitoring Board stops the trial
- 4758 serodiscordant couples in Kenya and Uganda
- 3 groups: Truvada, Tenofovir, placebo
- 78 seroconversions: 18 among those receiving the product; 47 among those on placebo

- Tenofovir: 62% fewer infections than those on placebo
  - CI = 34 – 78%; p = 0.0003

- Truvada: 73% fewer infections than those on placebo
  - CI = 49 – 85%; p < 0.0001
TDF2: Truvada

- July 2011: Results announced
- 1219 heterosexual men and women in Botswana
- 30 seroconversions: 9 among those receiving the product; 24 among those receiving the placebo

- Truvada: 62.6% fewer infections than those on placebo
  - IC = 21.5 – 83.4 %; p = 0.0133
HPTN052: Treatment as prevention

- Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, the United States and Zimbabwe
- 1,763 serodiscordant couples (97% M-F) were randomized into treatment when clinically needed (delayed) or early treatment (immediate) for HIV+ partner
- Prevention benefit:
  - 96% reduction in the risk of transmitting HIV among those who received early treatment (1 versus 28 infections)
- Treatment benefit:
  - fewer OIs among those provided with treatment immediately
UPCOMING TRIAL RESULTS
NPT late-stage trials: When will we know?

<table>
<thead>
<tr>
<th>2012+</th>
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<tbody>
<tr>
<td><strong>PrEP</strong></td>
<td>Injection drug users</td>
</tr>
<tr>
<td><strong>PrEP/Microbicides</strong></td>
<td>Women</td>
</tr>
<tr>
<td><strong>Vaccine</strong></td>
<td>Men who have sex with men</td>
</tr>
</tbody>
</table>

* Only in Phase 2 but most advanced trial
### PrEP: When will we know?

<table>
<thead>
<tr>
<th>Where</th>
<th>Who</th>
<th>What</th>
<th>When</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand (CDC)</td>
<td>Injection drug users</td>
<td>tenofovir</td>
<td>2012</td>
</tr>
</tbody>
</table>
## Microbicides: When will we know?

<table>
<thead>
<tr>
<th>Product</th>
<th>Phase</th>
<th>Location(s)</th>
<th>Results expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir gel</td>
<td>2b</td>
<td>South Africa, Uganda, Zambia, Zimbabwe</td>
<td>2013</td>
</tr>
<tr>
<td>MTN (VOICE)</td>
<td></td>
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</tr>
</tbody>
</table>

**Rectal microbicides…**
2 phase 1 trials completed  
1 phase 1 trial finishing  
1 phase 2 trial planned (US, Peru, South Africa, Thailand)
# Vaccines: When will we know?

## Phase 2

<table>
<thead>
<tr>
<th>Where</th>
<th>Who</th>
<th>What</th>
<th>When</th>
</tr>
</thead>
<tbody>
<tr>
<td>US (HVTN/NIH)</td>
<td>Men who have sex with men</td>
<td>Prime/boost (DNA/Ad5)</td>
<td>2012</td>
</tr>
</tbody>
</table>
NPT IMPLEMENTATION
Who will have access? Who decides?

The general public?

Most « at-risk » groups? Who is that in the national context?

How will decisions be made?

What factors will influence this?
How will it be available?

- Is it available now?
- Will it require a prescription?
- Will testing be a condition?
- Who will pay?
What practical questions are raised?

- Will receptive partners (male or female) who use a partially effective NPT find it harder to get their partner to use a condom?
- What if I use this differently than how it was tested in trials?
- How will our healthcare system deal with the increase in testing?
What ethical questions are raised?

What are the implications of limiting access to prevention options only to certain groups?

How do we deal with access inequality within our country? Between countries?

How do we deal with the stigma of associating some prevention tools with high-risk populations?
How does it fit in the HIV prevention landscape?

What evidence exists for this? How relevant is it for our context?

Do I know enough about these new tools to explain them to others?

Is our HIV 101 info up to date?

Will our agency take a position on whether or not this should be made available in our community?

How can we convey information on multiple prevention options without confusing people?
To learn more...

www.catie.ca  
www.cdnaids.ca  
www.cpha.ca  
www.icad-cisd.com

Marc-André LeBlanc: maleblanc27@yahoo.ca  
San Patten: san.patten@gmail.com

Join the MAG-Net listserv! Email bachirs@cdnaids.ca

Register for our other webinars!  
http://www.catie.ca/eng/GetInvolved/webinarseries.shtml