Update from Toronto

Microbicides – a new priority in the fight against HIV/AIDS

A town hall meeting with Jim Pickett

AIDS Foundation of Chicago
International Rectal Microbicide Working Group

Nashville - September 20, 2006
Brought to you by

- Tennessee Association of People with AIDS in cooperation with...
- Southeast Tennessee Development District
- TN Department of Health - HIV/AIDS/STD Section
- Global Campaign for Microbicides
- Vanderbilt AIDS Clinical Trials Center
- Community Advisory Board
- Vanderbilt HIV Vaccine Program
- Community Advisory Board
- Planned Parenthood of Middle and East Tennessee
What we’re going to cover

- Prevention?
- What are microbicides?
- How do/will they work?
- Who will benefit?
- What’s going on with research?
- How can WE get involved?
The state of prevention
25 years into the epidemic...

- Fear/crisis fatigue
- Navel to knee syndrome
- Condom fatigue
- Different frames
- Complacency
- Not me
- I’m negative
- I don’t know
- HAART optimism
- Sex ed/or the lack thereof
- Power dynamics
- Social vulnerability
- Desire for natural sex, aka “raw”/”bareback”
Our prevention work has not adequately addressed...

- Intimacy
- Our relationships
- Value of fluid exchange
- Sero-sorting, nuanced sexual communications, e.g. “strategic positioning”
- Risk equations
- Substance ab/use ("tina", Viagra, alcohol)
- Internet
- Depression
- Mental health issues
- Partner violence
- Childhood sexual abuse
"A strategy driven by fear of infection cannot succeed…

…long term success can only come through an approach based on values – the values of human rights and human dignity. Let us not forget that the Universal Declaration of Human Rights starts by placing dignity first."

Irene Khan
Secretary General
Amnesty International
Bangkok 2004
HIV/AIDS today

- 4.1 million infections in 2005 worldwide
- About 2.8 million deaths worldwide - 8,000/day
- 38.6 million living with, 24 million in Africa
- 9% of MSM 2006 received any type of prev (global)
- Less than 20% IDU 2006 received any type of prev (global)
- 9% of pregnant women covered with services to prevent MTC
- Less than 50% of young people worldwide have any significant level of knowledge about HIV/AIDS
- Over a million living with HIV in United States
- 40-60,000 new U.S. infections
- 6 out of 10 new infections globally are women, 27% – U.S.
- 45% MSM – U.S.

(UNAIDS Global Report, 2006)
#1 Risk Factor for Women?
Why are we satisfied with this?
What if we had a complete HIV prevention toolkit?

<table>
<thead>
<tr>
<th>Prior to exposure</th>
<th>Point of transmission</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rights-focused behaviour change</td>
<td>• Male and female condoms and lube</td>
<td>• Improved antiretroviral therapy</td>
</tr>
<tr>
<td>• Voluntary counselling and testing</td>
<td>• ART to prevent perinatal transmission</td>
<td>• Treatment for opportunistic infections</td>
</tr>
<tr>
<td>• STI screening and treatment</td>
<td>• Clean injecting equipment</td>
<td>• Basic care/nutrition</td>
</tr>
<tr>
<td>• Preventative Vaccines</td>
<td>• Vaginal and rectal microbicides</td>
<td>• Prevention for positives</td>
</tr>
<tr>
<td>• Pre-exposure prophylaxis (PREP)</td>
<td>• Cervical barriers</td>
<td>• Education and behavior change</td>
</tr>
<tr>
<td>• Male circumcision</td>
<td>• Post-exposure prophylaxis (PEP)</td>
<td>• Therapeutic vaccines</td>
</tr>
</tbody>
</table>
“Microbicides will help overturn the fundamental imbalance that makes so many women vulnerable to HIV infection. Scientific momentum must go hand in hand with sustained political commitment to deliver on promises to give women this vital new prevention tool.”

Graca Machel, President, Foundation for Community Development in Mozambique and Hilde F. Johnson, former Norwegian Minister of International Development
Okay... so what are microbicides?

Something **NEW** for our prevention toolbox
A microbicide is a substance that can reduce the transmission of HIV and other STD pathogens when applied vaginally and or rectally.

They are not yet available.

- **Right now:**
  - Gels, lubes, creams

- **In the future:**
  - Sponges, vaginal rings
  - Gels with barrier devices
  - Douche, enema, suppository?
How will microbicides work?

- Kill/inactivate/immobilize the virus
- Boost the body’s natural defenses
- Create a physical barrier between pathogen and vulnerable tissue
- Interfere with entry of virus into target cell
- Inhibit viral replication once virus has entered the cell
  - Or some combination of these approaches
Other features may include

- Contraceptive or non-contraceptive
- May reduce risk of other STDs
- Must be inexpensive and available over the counter
- Could be used without partner’s cooperation or even awareness
Microbicides MUST BE

- SAFE
- EFFECTIVE
- EASY TO USE
Who might use microbicides?

- Anyone, HIV+ and HIV-, who engages in vaginal and/or anal sex.
  - Women who have sex with men
  - Gay men
  - Males who have sex with males
  - Men who have sex with women
How would they benefit HIV+ people?

- Reduce risk of re-infection with other HIV strains
- Help protect both partners – bi-directional
- Reduce risk of other STIs, yeast and bladder infections
- Allow conception while protecting partner
“A microbicide would be extraordinarily important in the fight against HIV/AIDS. Empowering women on the prevention front is an incredibly important effort.”

Mark Dybul, MD
US Global AIDS Coordinator
US Department of State
## Vaginal microbicide pipeline – Phase 3

<table>
<thead>
<tr>
<th>Product</th>
<th>Sponsor/Developer</th>
<th>Women</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buffer Gel</td>
<td>ReProtect LLC (acid buffer)</td>
<td>Feb 2005 - 3,220 women</td>
<td>South Africa, Malawi, Tanzania, Zambia, and Philadelphia</td>
</tr>
<tr>
<td>Carraguard</td>
<td>Population Council (entry inhibitor)</td>
<td>Mar 2004 - 6,639 women</td>
<td>South Africa – 3 locations</td>
</tr>
<tr>
<td>Savvy</td>
<td>Biosyn, Inc (surfactant)</td>
<td>Sept 2004 – 2,140 women</td>
<td>CLOSED August 28, 2006, Nigeria</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Candidate</td>
<td>Developer</td>
<td>Phase*</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Vaginal defense enhancers (N=2)</td>
<td>ACIDFORM™/Amphora™</td>
<td>CONRAD; Instead, Inc.</td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>BufferGel®</td>
<td>ReProtect, Inc.</td>
<td>Phase 2/2B</td>
</tr>
<tr>
<td>Entry/fusion inhibitors (N=5)</td>
<td>VivaGel™/SPL7013</td>
<td>Starpharma Ltd.</td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>Invisible Condom™</td>
<td>Laval University</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td></td>
<td>Carraguard®</td>
<td>Population Council</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>Cellulose sulfate/CS (Ushercell)</td>
<td>CONRAD</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>PRO 2000</td>
<td>Indevus Pharmaceuticals, Inc.</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Replication inhibitors</td>
<td>UC-781</td>
<td>CONRAD</td>
<td>Phase 1</td>
</tr>
<tr>
<td>(N=3)</td>
<td>TMC120</td>
<td>International Partnership for Microbicides</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td></td>
<td>Tenofvir/PMPA gel</td>
<td>Gilead Sciences, Inc.</td>
<td>Phase 2/2B</td>
</tr>
<tr>
<td>Uncharacterized mechanism (N=1)</td>
<td>Praneem polyherbal vaginal tablet</td>
<td>Talwar Research Foundation</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Combinations (N=1)</td>
<td>PC 815 (Carraguard and MIV-150)</td>
<td>Population Council</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

*Some candidates are in more than one phase of clinical testing. The phase listed in this table represents the most advanced clinical trial currently planned or underway for each candidate. This table does not include trials of contraceptive efficacy.

For modifications, please contact Carolyn Plescia, email cplescia@microbicide.org, tel. 301-587-3302.
"HIV is progressively taking on the face of a woman. It is absolutely essential we address the special concerns of women in protecting themselves."

Anthony Fauci, MD, Director, National Institute of Allergy and Infectious Diseases
Clinical Trial Sites 2006

- Houston, USA
- Pittsburgh, USA
- Providence, USA
- Norfolk, USA
- New York, USA
- New Brunswick, USA
- Baltimore, USA
- Santo Domingo, Dominican Republic
- Los Angeles, USA
- Seattle, USA
- Chicago, USA
- Cincinnati, USA
- New Brunswick, USA
- Pittsburgh, USA
- London, UK
- New York, USA
- Antwerp, Belgium
- Quebec, Canada
- Durban, South Africa
- Blantyre, Malawi
- Prague, Czech Republic
- Harare, Zimbabwe
- Lusaka, Zambia
- Johannesburg, South Africa
- Pune, India
- Chandigarh, India
- Accra, Ghana
- Lagos, Nigeria
- Cameroon
- Kenya
- Kampala, Uganda
- Moshi, Tanzania
- Blantyre, Malawi
- Harare, Zimbabwe
- Johannesburg, South Africa
- Durban, South Africa
- Osaka, Japan
- Tokyo, Japan
- Sydney, Australia
- Adelaide, Australia
- Chiang Mai, Thailand
- Vienna, Austria
- Lombardy, Italy
- Antwerp, Belgium
- London, UK
- New York, USA
- Chicago, USA
- Birmingham, USA
- Florida, USA
- Santo Domingo, Dominican Republic
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- Durban, South Africa
- Osaka, Japan
- Tokyo, Japan
- Sydney, Australia
- Adelaide, Australia
- Chiang Mai, Thailand
- Vienna, Austria
Alright… what about the BOOTY?

Rectal microbicides anyone?
Who needs rectal microbicides?

- **Women**
  - U.S. – 35% report at least one episode of anal intercourse (AI) in lifetime
  - U.S. – 6.7% het couples practice AI at least once/mo.
  - 30% of het pop in many cultures practice AI (virginity, contraception)
  - Volume unprotected AI (UAI) 5x higher in het compared to gay/MSM

- **Men**
  - Among U.S. gay and MSM, most report practicing AI: 76-90%.
  - U.K.: 48.8% UAI (Gay Men’s Sex Survey 2002)
  - U.S.: 30% UAI HIV – men (EXPLORE Study 2003)
  - STD rates confirm high prevalence of UAI
  - Higher prevalence of AI, UAI compared to heterosexual population = more risk per act
Anal sex and HIV transmission

- HIV transmission is 10- to 100-fold more efficient through unprotected anal rather than unprotected vaginal sex
- Women engaging in AI seldom use condoms
- Condom use is challenging for many of us
- South African het men – 2x as likely as male counterparts reporting only vaginal sex to be HIV+
Anatomy 101

Transverse colon
Ascending colon
Stomach
Descending colon
Sigmoid colon
Rectum
Cecum
Appendix
Small intestine
Anus
Physiological differences = R&D challenges

<table>
<thead>
<tr>
<th>Vagina</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most of the epithelium is 40 cell layers thick</td>
<td>Very fragile epithelium, 1 cell layer thick.</td>
</tr>
<tr>
<td>Fewer CD4 cells than rectum</td>
<td>More inflammatory cells under surface</td>
</tr>
<tr>
<td></td>
<td>(CD4 receptors)</td>
</tr>
<tr>
<td>Acidic pH</td>
<td>Alkaline, rather than acidic pH</td>
</tr>
<tr>
<td>Enclosed pouch</td>
<td>Open-ended tube</td>
</tr>
</tbody>
</table>
There are significant socio-cultural and political challenges to developing a safe and effective rectal microbicide for the men and women who need them:

- Homophobia
- Stigma
- Taboo
- Denial

Civil society and policy makers have an unwillingness to acknowledge AI, incomplete data around prevalence, mechanics, where infection occurs, researchers scrub their abstracts.
"At any given moment, more heterosexual women than gay men are engaging in anal intercourse. A receptive sex partner is a receptive sex partner. We need rectal microbicides, just as we need vaginal microbicides, to help receptive sex partners save their own lives."

– Anna Forbes
Global North Programs Coordinator
Global Campaign for Microbicides
Rectal research questions

- Infection – more to learn about anal intercourse and HIV infection
- Testing - what assays (tests) to measure impact?
- Distribution – how would it spread?
- Application methods?
- Dosing – how much, what is acceptable?
- How does rectal shedding of HIV impact risk?
In the laboratory

To learn more about:
- How HIV infection occurs in the rectum – what cells are most vulnerable
- The impact of intercourse on rectal tissue (trauma, inflammation, speed of healing)
- What markers can we look at to determine impact of a product on the rectum?
What’s up with rectal microbicide research?

- Phase 0 trials, or baseline studies measure the baseline levels of injury and inflammation that occur in the rectum during typical AI.
- Distribution studies look at how a microbicide might travel and be distributed during and after sex.
- A Phase 1 clinical trial tests the safety and applicability of UC-781 for rectal use, using the vaginal microbicide gel formulation.
  - Set to begin in fall 2006 at UCLA!
- "Male Tolerance" trials are studying whether potential microbicides may cause irritation to the penis or within the male urethra.
- Acceptability or behavioral studies to learn what kinds of products people might be willing and able to use.
  - How much is too much? Study AI/sexual behaviors, associated behaviors such as enema use...
We won’t know if the first vaginal microbicides are **effective** for rectal use. Likely they won’t be…

But we MUST know if they are **safe** to put in the rectum or not.

People will try to use them rectally. “In about 10 minutes…”

If deemed harmful for the rectum, labels warning against rectal use are **imperative**. We will have our work cut out for us… who reads the labels?
Lube safety

- Tested 5 OTC lubes in mice to see if they caused damage to rectal cells
- KY-Plus (no longer on market) and DeLube caused the most damage
- Viamore, Vagisil and Astroglide caused some damage
- More research is underway, with findings expected soon. Preliminary findings in poster at M2006.
- Need more/ongoing research to see if these products cause damage to human rectal cells

Drs. Sudol & Phillips at Population Council, New York
Significant funds are needed

Why aren’t the big pharmaceutical companies investing?
  • Perceived low profitability
    • Liability concerns
  • Lack of in-house expertise
  • Uncertain regulatory environment

For the last 20 years, almost all funding for contraceptive development and related research has come from governments and foundations.

Microbicide Trials Network – NEW!
“We should use social justice criteria to decide HIV prevention funding priorities. Populations at gravest risk for HIV infection should have the highest priorities for HIV prevention and scientific resources.”

Dr. Ron Stall, University of Pittsburgh
Annual funding needs

- Policy and Advocacy: need $10M
- Trial sites: need $20M
- Clinical testing: need $120M
- Basic Scientific Research: need $130M
- All combined: Need $280M

Annual funding needs to double!

Actual 2004 funding levels vs. Additional annual funding needed

Rectal investments

- Total 2000 – 2006 = $34M
  - 2000 = $2M
  - 2006 = $7.2M (estimated)
Estimate of rectal needs

- Conservatively, rectal field probably needs 5 candidates over 10 – 15 year period
- Will require minimum $350M, or at least $35M/year for 10 years
- Annual rectal spending needs to increase 5-fold
How do we make safe, effective vaginal and rectal microbicides a reality for the men and women who need them?
Public awareness

Public demand

Political support

Increased resources for R&D ($$$)

Safe and effective microbicides on the market

All people know about and have access to affordable microbicides
Global Campaign for Microbicides

A worldwide effort co-sponsored by groups working on
- HIV/AIDS
- Reproductive health
- Gay health
- Women’s empowerment
- Prevention

Working to educate, raise awareness and generate collective advocacy for increased political and public investment in microbicide development in the states and the global north and south. Visit the website, endorse the campaign, sign up for their newsletter, host a talk…get involved!

www.global-campaign.org
Formed June 2005
Over 260 advocates, scientists and policy makers from 29 countries
Global listserv
Conference calls featuring scientific presentations
Advocacy agenda supporting the research and development of safe, effective rectal microbicides
Published “Rectal Microbicides: Investments and Advocacy” in April 2006, M2006 in Cape Town.

www.lifelube.org – more info
jpickett@aidschicago.org – sign up
U.S. Microbicide Development Act
H.R. 3854 and S. 550

• Will authorize funding increases as needed

• Will require the National Institutes of Health to:
  • establish a branch dedicated to microbicide research.
  • expand and coordinate the research efforts of all 3 federal branches (NIH, CDC and USAID).

• Bipartisan group of 47 Representatives and 19 Senators have signed on so far, but we need more support!
Please contact your legislators to urge them to support the new Microbicides Development Act by signing onto the MDA. Give them a fact sheet from the GCM site.

E-mail your legislators automatically on this issue, by visiting http://www.global-campaign.org/get_involved.htm and clicking on “write your Congressperson”

Call your legislators and leave a message. It could be as simple as: "I am calling to ask Representative/Senator _____________ to cosponsor the Microbicide Development Act. This bill can really make a difference in addressing the global AIDS epidemic…”
Potential public health impact

If a 60% effective product offered to 73 lower income countries is used by 20% people reached by health care during 1/2 of unprotected sex acts = 2.5 million HIV infections averted in 3 years including women, men and children
“We need to start addressing the drivers of this epidemic and these drivers are general inequality, the position of women, stigma, discrimination, homophobia and so on.”

Dr. Peter Piot,
Executive Director
Joint United Nations Program on HIV/AIDS
Thank you

Jim Pickett
jpickett@aidschicago.org

Global Campaign for Microbicides
www.global-campaign.org

Intl Rectal Microbicide Working Group
www.lifelube.org
What do you plan to do with this information?