

microbicides 2008

February 24 - 27, 2008
Hotel Ashok, New Delhi, India

Striving towards HIV Prevention



Highlights of Tuesday 26th February, 2008

Clinical

Update on efficacy trials

HPTN 035: Phase IIB – PRO2000 and Buffergel, MDP 301 -PRO 2000, CAPRISA 004 - 1% Tenofovir gel
All extraordinary trials, very difficult, committed researchers, being done on time with good retention and adherence

HPTN 035: Enrollment completed, results expected early next year

2 control arms: placebo gel and no gel [condom only], efficient use of control groups, proof of concept study
BG acid buffer and PRO2000 entry inhibitor

Update on efficacy trials

MDP301: Enrollment 9637 women, 0.5% and 2% PRO2000 gel

2% gel arm stopped following fertility analysis

At one year, >84 retention censored and not-censored by pregnancy

Adherence at last sex act >80%, use of gel high irrespective of condom use

0.5% PRO2000 gel might prove to be useful

CAPRISA401: 1% Tenofovir gel study 960 women, coitally dependent gel use 2 doses per sex act

Innovative mechanisms used to talk with communities about gel use

Enrollment by June 2008, data available by 2009

Proof of concept study of a topical Prep strategy

Clinical safety studies

What have we learnt? What do we need to know?

Safe: integrity of epithelium, microflora, no systemic absorption and not inflammatory

N-9 unsafe on frequent testing, microflora disruption, antiviral activity at cytotoxic effects and with inflammatory changes, risk of BV in high risk populations

C31G- Savvy stopped due to fertility, higher dose more irritating, more reproductive track events, HIV incidence similar in treatment and control arms

CS tendency to cause harm, erythema, higher rate of HIV acquisition in CS arm, no difference in AEs, CONRAD continues the investigation: N9 and CS related evaluation for inflammatory changes

Symptoms and colposcopy do not necessarily indicate safety

Markers for general toxicity at early stage

What have we learnt? What do we need to know?

Colposcopy widely used, but does not have predictive value for safety evaluation

Effect on buccal mucosa also has to be kept in mind: oral toxicity and absorption studies

Extension of the product in endocervix and uterus: should this be included as part of the safety evaluation: Is MRI the best and most cost-effective method? Cost of trial?

Statistical inference of toxicity data in Phase II trials needs to evolve

Long-term safety assessment is an issue

Lessons learned from cohort studies

Contraceptive provisions and choices [Baxter]

High pregnancy rates seen among various sub-populations in the CAPRISA 004 trial

Contraceptive counseling was stressed, 75% opted for injectables, 22% for pills and 2% for tubal ligation

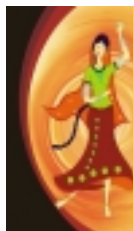
At the end of 6 months of follow-up, there was encouraging low pregnancy rate of 2.7% per year

Attitudes towards male and female condoms [Smit]

Predictors of positive attitudes towards use of male and female condoms were studied in female undergraduate students in Africa

Factors like experience with vaginal products, condoms efficacy beliefs and comfort in communicating with partners about condom use were studied

Perception of product efficacy was found to be important for acceptance of condoms



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Lessons learned from cohort studies

HSV-2 suppression: C Celum

There are reasons that can explain higher chances of HIV acquisition in presence of HSV-2 infection
Randomized placebo controlled HSV suppressive trial
No difference in HIV survival among those on suppressive therapy and the other group

When clinical trials end

Multi-country trials: Lut Van Damme

CS trial CONRAD trial in India, Uganda and South Africa
Another study in Nigeria, DSMB meeting at the completion of 50% endpoints
25/1333 sero-conversions after 12 months follow-up in 3 African sites
Trial stopped due to potential harm, Nigerian trial was also stopped
Informing trial sites, investigators, IRBs, regulatory agencies, advocacy groups
Press release that the trial is being stopped
Main issue for clinical team: safety of participants, retraction of gel [participants objected to return the gel]
Updating the database and freezing the data
Lessons learned
•Communication of information: researchers and the community, communicate the trial is not a failure
•Visiting the sites immediately
Final investigators meeting: How can one be emotionally and practically ready for a negative result

When clinical trials end

Translating trial closure, advocates: Manju Chatani

African Microbicide Advocacy Group
Who are advocates? Community advocates: country-wide differences
Many trials have ended and there have been disappointments
Responding to N9 closure in 2000: few advocates, no trust, confusing messaging. Reaction: worried, upset, public release of information
Communication is the key, advocates involved in planning
Scenario involved in Carraguard: participants, Govt, advocates and researchers to be involved
Preparation of communication plan
Coordination, collaboration and communication before, during and after the trial

When clinical trials end

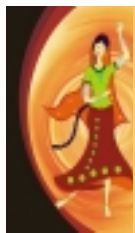
Trial closures in South Africa: Gita Ramjee

Lot of Phase III trials ongoing in sub-Saharan Africa
In terms of endpoints, intervention can have no added advantage, a distinct advantage and risk.
Trial end: Natural completion or premature closure
Inform the sites, track the participants, inform various agencies before press release
Meeting with Minister of Health and Parliamentary committee
Investigation and audit of clinical trials
Impact on other clinical trials: Issues and concerns raised were discussed, answer community uproar, decide the action taken
Meetings with local councilors, political councilors
Communication with regulatory bodies before the press release
Developing community partners = correct language

Moving microbicides into vulnerable populations

R Beigi: Pregnant women

Why consider pregnancy? Effect on study design, safety, analysis, ethics
Safety is the first challenge
Detection problems in case of early pregnancy
2 study groups having differential pregnancy rates
Women in trials should be using contraception, they have side effects
Ethics: Non-maleficence, autonomy, inappropriate to exclude pregnant women



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MTN approach: test microbicides in pregnancy, pregnancy registry, PK safety and tolerability study

I McGowan: People who practice anal intercourse

Significance of development of rectal microbicides: unicellular columnar epithelium

US: Increase incidence among MSM

N9 and hyper-osmolar products would cause extensive rectal damage

Some data available on macaque models

Phase I rectal safety study designing rapidly, Reasonable pipeline of products

Rectal specific applicators under development

Move from safety to efficacy??

Moving microbicides into vulnerable populations

K Slack: Adolescent

Need to focus on adolescents: Half of new infections, biological and behavioral differences than adults, vulnerable

Previous consultations: WHO/ UNAIDS 2004, 2006, Global Campaign 2005

Limited haring between MTN and adolescents

Adolescents in trials: Vaccine: South Africa HVTN 503, US PAVE 100, Microbicides: South Africa, Tanzania and Uganda

Relative vulnerabilities: Funding, history of trial closures, evaluations of safety

Concerns: efficacy can not be addressed directly in adolescents, informed consent, confidentiality and privacy requirements, enrollment rationale not clear, data on adolescent sexual behavior needed, reporting requirements:

abuse, crimes, sexual offenses, regulatory reviews, social harms, health services

Need to train staff and investigators

Jointly develop common platform of issues and maximize responses

Socio-behavioural

Plenary-Male sexuality and HIV risk

- Male sexuality is important in the acceptance of microbicides among women
- Research shows that men also experience gender violence and are at risk of HIV/AIDS. For example, societal expectations on men about masculinity put men at a particularly high risk
- Current interventions on women perceive men as dominators and women as vulnerable.
- Men who are at risk in India do not perceive themselves to be so.

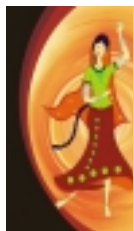
Microbicides formulations and delivery systems: behavioural perspectives

- Gel behaviour user perspectives determined by: rheological properties, physical properties, applied forces, characteristics of the vaginal environment.
- Different properties of the gel may bring about the different perceptions of the acceptability e.g. leakage, sexual pleasure

Community engagement in trials

- It is Important to recognise that communities have values, perspectives and rights on health issues and hence their perspectives should be taken on board.
- Strategies developed by interventions to improve retention include education to participants, reward system at set time period of the trial, use of community advisory boards, use of peer educators and involvement of male partners (e.g. provided for education and treatment for STIs) and free transport.
- It is important to closely monitor participants to ensure higher retention-Proper understanding of trial procedures and informed consent is important
- Education is not all for preventing or resolving conflict as this may not work in already informed communities

Standards of Care Cross-Track



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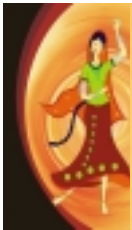


- GCM found a range of specific services offered in trial, from whether or not cervical screening provided, how sites Cared for HIV seroconverters or those screened out of trial. All trials offered comprehensive risk reduction services. Most trials offered contraception and some ancillary services. Carraguard trial said they would provide this from the beginning now. Most of HIV treatment provision or referral differed by site. Carraguard said it would find ways to fast track referral for HIV in future. Only a few trial sites extended ancillary services or HIV services to family.
- Only one trial provided HIV support group.
- No trials specifically consulted community when deciding SOC – prior to trial. NARI engaged in a national consultation about ethical committee roles, how long to monitor and support participants for the IAVI trials. They also conducted a SOC study using qualitative methods.

Policy Advocacy and Community

Session: Modelling the impact of microbicide introduction

- moderately effective rectal microbicides (50% efficacy) with moderate use (30% use) can have substantial impact on HIV prevention in 'bathhouses'
- Men benefit more than women in terms of HIV prevention if:
 - o Microbicide adherence is moderate to low
 - o Microbicide efficacy is moderate to low
 - o Microbicide advocacy involves male partners
 - o Systemic absorption of ARV-based microbicides occurs
- *Microbicides are important empowerment tools for women but **paradoxically** microbicides could benefit men more than women in terms of both: infection prevented and infections prevented/resistant cases*
- Condom migration/ replacement after microbicide introduction is unlikely to increase anymore
- Condom migration is unlikely to be a concern with microbicide introduction in communities with low consistent condom use
- A comprehensive advocacy approach, spanning science, policy and the community, is needed to bring safe, acceptable and effective rectal microbicides to market.
- Data consistently reveal that men and women around the world engage in receptive anal intercourse, often without the use of a condom.
- The development of a rectal microbicide, which could provide some protection from HIV transmission during anal intercourse, is hampered by biological and scientific challenges, socio-cultural and political barriers such as stigma, denial and homophobia, and a lack of adequate resources necessary for the development of a robust pipeline of rectal microbicide candidates.
- Rectal safety studies should be conducted on all viable vaginal microbicides
- Testing of additional commercial lubricants for rectal safety be encouraged and regulatory bodies and policies should be supportive too
- There is a gap in policy and programmes to build the social and health platform for the adolescents (10-19 years), youth (15-24 years), especially young girls.
- Conventional "youth programs" and "adolescent sexual reproductive health" programs do not reach the majority of vulnerable adolescent girls, who remain overlooked and underserved.
- Any effort to reach adolescents girls and young women with a microbicide product would need to address the heterogeneity of this potential user group: they have diverse needs and situations they deal with, for



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- example: some live outside the protective structure of family and school (school drop-outs); some are under pressure to exchange sex for food, money, shelter, school fees; many are married
- Targeted messages and a range of protection strategies and services for a diverse group of girls will be needed.
 - Adolescent and young people are unaware (and often remain *out of the reach*) of the existing services like VCT, family planning, peer programmes, social marketing, pharmacies etc
 - There is little understanding of reproductive health products the girls currently use (*emergency contraceptive, female condom, contraceptive etc*)
 - Poverty and social isolation are associated with higher chances of girls engaging in transactional and non-consensual sex and of having multiple sexual partners.

 - As microbicides are being developed, HIV-positive women are raising numerous issues related to safety, trial design and ethics, which require consideration and implementation in current trials and future research.
 - From mid-2006 to mid-2007 teleconferences were held between HIV positive women and research community members, and a final report published in June 2007 summarized the results
 - A clear research protocol was developed to study the potential emergence of resistant strains with population subsets who become HIV positive during trials;
 - Safety of microbicides-under-test in pregnancy for trial participants and the foetus, should be evaluated
 - Community engagement in informed consent processes including potential risks and standard of care and treatment for those who test positive during trials is a key
 - Communication channels to keep HIV positive women's groups apprised of new developments on microbicides research should be developed