Randomized Trials of STD Control for HIV Prevention in Adults, Pregnant Women and Infants, Rakai, 1994-98

Results and Supplementary Analyses

Maria Wawer and Ron Gray on behalf of the RHSP
Objective: to assess whether STD control at the population level would be effective for HIV prevention

• STD Control for HIV Prevention
  • All non-pregnant adults

• Maternal Infant Supplementary Study (MISS)
  • Pregnant women and infants
Trial of STD Control in Adults

• 10 community clusters (each with 3-5 villages) randomized to Intervention (n=5) and Control (n=5) arms. (Genesis of the RCCS)

• **Intervention arm** received intensive presumptive mass-treatment of STDs via directly observed oral antibiotics and IM penicillin for serologic syphilis.

• **Control arm** received placebo and syndromic STD management.

• Follow-up at 10 month intervals over 20 months via RCCS surveys

Wawer et al. AIDS 1998
Wawer et al. Lancet 1999
Trial of STD Control in Adults: participant compliance

Annual participation rate: 94%

Provided

blood: 91%
urine: 94%
vag swabs: 93%

Accepted treatment: 95%
STD Trial Main Results

• 6602 intervention and 6124 control arm participants

• Significant reductions in vaginal STDs and syphilis

• HIV incidence 1.5/100 py in both arms
  \((RR=0.97, CI 0.81-1.16)\)

• Conclusion: STD mass treatment had no effect on HIV incidence at the community level

Wawer et al, Lancet, 1999
Rakai Program Tour of 1999

Geneva audience takes in the Rakai STD results
Mother Infant Supplementary Study (MISS)

• Nested in the adult STD Control Trial

• Pregnant women: 
  n=2070 intervention arm 
  n=1963 control arm

• Intervention arm received mass presumptive STD treatment with oral antibiotics once during pregnancy.

• Control arm received standard of care

• All pregnant women with positive syphilis serology received IM Benzathine penicillin in both arms

Gray et al. Amer J Obstet Gynecol 2001
## Maternal Infections Postpartum

<table>
<thead>
<tr>
<th>Infections</th>
<th>Intervention</th>
<th>Control</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis</td>
<td>3.4%</td>
<td>3.3%</td>
<td>1.18 (0.94-1.47)</td>
</tr>
<tr>
<td>Trichomonas</td>
<td>4.7%</td>
<td>15.9%</td>
<td>0.28 (0.18-0.49)</td>
</tr>
<tr>
<td>BV</td>
<td>36.3%</td>
<td>48.5%</td>
<td>0.78 (0.69-0.87)</td>
</tr>
<tr>
<td>Gonorrhea/Chlamydia</td>
<td>1.9%</td>
<td>4.3%</td>
<td>0.43 (0.27-0.68)</td>
</tr>
<tr>
<td>HIV Incidence</td>
<td>3.4/100 py</td>
<td>2.3/100 py</td>
<td>1.44 (0.64-3.25)</td>
</tr>
</tbody>
</table>
## Infant Infections and Birth Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention</th>
<th>Control</th>
<th>IRR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular Gonorrhea</td>
<td>0.6%</td>
<td>1.7%</td>
<td>0.35 (0.18-0.67)</td>
</tr>
<tr>
<td>Ocular Chlamydia</td>
<td>0.6%</td>
<td>1.1%</td>
<td>0.44 (0.19-0.98)</td>
</tr>
<tr>
<td>Low Birth Weight</td>
<td>9.1%</td>
<td>11.0%</td>
<td>0.70 (0.51-0.96)</td>
</tr>
<tr>
<td>Preterm Birth</td>
<td>9.8%</td>
<td>11.8%</td>
<td>0.73 (0.54-0.99)</td>
</tr>
<tr>
<td>Neonatal Death</td>
<td>25.4/1000</td>
<td>29.1/1000</td>
<td>0.83 (0.71-0.97)</td>
</tr>
<tr>
<td>MTCT of HIV</td>
<td>18.9%</td>
<td>22.3%</td>
<td>0.92 (0.29-2.91)</td>
</tr>
</tbody>
</table>
MISS Trial, Conclusion

Bacterial STD control during pregnancy
- reduced maternal and infant STD infections
- improved pregnancy outcomes

However, no effect on
- maternal HIV incidence
- mother-to-child transmission
HIV Incidence in Trials of Bacterial STD Control for HIV Prevention

Mwanza, Grosskurth, Lancet, 1997
Rakai, Wawer, Lancet 1999
MISS, Gray, AJ Obs Gyn 2001
Masaka: Kamali, Lancet, 2003
CSW: Kaul, JAMA 2005
Manicaland, Gregson, 2007
Trials of STD Control for HIV Prevention

- **WHY** did STD control not have the hypothesized effect?

- To explain the largely negative trials we analyzed Rakai trial data to assess factors associated with HIV acquisition.
Population attributable risk of HIV acquisition associated with STDs in Rakai

Population Attributable Fraction (PAF) of HIV Acquisition due to Treatable STDs

- Syphilis: 4.4%
- Gonorrhea: 4.2%
- Chlamydia: 1.4%
- Trichomonas: 7.5%
- All Treatable STDs: 17.5%

Even if all bacterial STDs could be eliminated, this would reduce HIV incidence by only \(~17\%\)

Gray et al. AIDS 2005
HIV viral load and infectivity in HIV discordant couples nested in the trial population cohort

HIV viral load is the main determinant of HIV transmission.

This led to Treatment as Prevention (TASP)

Quinn et al. NEJM 2000
HIV transmission per coital act by stage of infection. Retrospective analysis, Rakai HIV discordant couples nested in STD trial cohort.

Infectivity is highest in early and late stage HIV infection.

Wawer et al, JID 2005
Viral Load and Heterosexual Transmission of Human Immunodeficiency Virus Type 1

Thomas C. Quinn, M.D., Maria J. Wawer, M.D., Nelson Sewankambo, M.B., David Serwadda, M.B., Chuanjun Li, M.D., Fred Wabwire-Mangen, Ph.D., Mary O. Meehan, B.S., Thomas Lutalo, M.A., and Ronald H. Gray, M.D., for the Rakai Project Study Group


Combined, over 6,000 citations to date
Male Circumcision and HIV Transmission in HIV Discordant Couples Nested in STD Trial Cohort
Gray et al, AIDS 2000

Findings led to the Rakai trials of voluntary male circumcision for HIV prevention in men and women.
Conclusion

• Rakai STD control trials had negative outcomes with respect to HIV control

• However, they informed multiple future studies on determinants of HIV transmission and HIV prevention strategies