Overview

- Burden of severe influenza illness in South Africa.
- Efficacy of trivalent influenza vaccine in HIV-infected adults.
- Efficacy of trivalent influenza vaccine in HIV-infected children.
- Studies on efficacy of trivalent influenza vaccine in HIV-infected and HIV-uninfected pregnant women for protection of mothers and young infants.

Meta-analysis of Effectiveness of Influenza Vaccine in HIV-infected Adults (N=646).

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAOCT: Military Recruits; USA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observational residential facility outbreak, USA</td>
<td>2002</td>
<td></td>
</tr>
<tr>
<td>Prospective observational cohort, Japan</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>PPV = TIV, observational study, Italy</td>
<td>2008</td>
<td></td>
</tr>
</tbody>
</table>

Immunogenicity of TIV in HIV-infected South African Adults, 2008

<table>
<thead>
<tr>
<th>Immunogenicity measure</th>
<th>N</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu HA assay</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>Pre-vaccine (GMT 95% CI)</td>
<td>11.3 (7.7, 17.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Post-vaccine (GMT 95% CI)</td>
<td>61.4 (39.6, 95.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean GMT fold increase (95% CI)</td>
<td>5.6 (4.2, 7.4)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Adhili J et al; BMC Infect Dis 2006; 6:136: 1-6
Madhi S.A et al; C/infect Dis 2011; 52: 138
Efficacy of TIV Against Influenza-Confirmed Illness in HIV-infected Adults (N=506), South Africa 2008

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TIV</th>
<th>Placebo</th>
<th>Rate reduction</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza Virus A or B</td>
<td>3.00a(2)</td>
<td>12.00(2)</td>
<td>0.18</td>
<td>0.018</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>11.02(2)</td>
<td>10.00(2)</td>
<td>-0.02</td>
<td>0.887</td>
</tr>
<tr>
<td>Acute respiratory illness</td>
<td>4.00(6)</td>
<td>47.00(6)</td>
<td>0.16</td>
<td>0.402</td>
</tr>
</tbody>
</table>

* Figures in parentheses are incidence per 100 person-weeks unless otherwise indicated.
* Rate reduction per 100 person-weeks.

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H3N2 HAI Responses Pre-Vaccination and One-Month Post 2nd Dose TIV in HIV-infected Children

Amino Acid Mismatches of Seasonal H3N2 Wild-type Strains compared to Vaccine H3N2 Strain, 2009

Overview

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GRANT: Bill and Melinda Gates Foundation

Safety, immunogenicity and efficacy of trivalent inactivated influenza vaccination (TIV) of pregnant women against early-infant and maternal influenza virus associated illness in an area with a high prevalence of HIV.

Program Objectives

- Objective 1: Immunogenicity of TIV in HIV+ women and kinetics of transplacental TIV antibody transfer.
- Objective 2: Efficacy of TIV in pregnant women against influenza illness in their infants <24 weeks age (Independently in HIV-infected and HIV-uninfected women).
- Objective 3: Safety and efficacy of TIV in pregnant women against influenza confirmed illness in the women during and until 24 weeks after birth (Independently in HIV-infected and HIV-uninfected women).
- Objective 4: Immunogenicity of TIV in HIV-uninfected women and kinetics of transplacental HAI antibody transfer.
- Objective 5: Interaction of maternal TIV vaccination against pneumococcal acquisition rate in the infants.

Trial design: HIV-uninfected, pregnant women

- Prospective, double-blind, randomized, placebo controlled trial evaluating efficacy of TIV.
- Initially independently powered for efficacy in each of two consecutive cohorts (2011 and 2012). Subsequently changed to composite of two consecutive-year cohort using the same vaccine formulation.

Primary Objectives

- Determine the efficacy of TIV vaccination of pregnant women against vaccine-strain matched laboratory-confirmed influenza illness in infants up to 24 weeks of chronological age.
- Evaluate the immunogenicity of TIV in pregnant women vaccinated between 20-34 weeks of gestational age.

Secondary Objectives (Fetus and Infant)

Fetus:
- Compare obstetrical outcomes: low birth weight (<2500g), premature delivery (<37 GA), emergency CS and early onset sepsis (<3 days).

Infant:
- Determine the efficacy of TIV vaccination of pregnant women against ALL laboratory-confirmed influenza illness in infants up to 24 weeks of chronological age.
- Define the efficacy of TIV-vaccination of pregnant women against protocol defined clinical ILI in their infants up to 24 weeks of chronological age.

Secondary Objectives (Mother)

Mother:
- Evaluate the efficacy of TIV against laboratory-confirmed influenza illness during pregnancy and until 24 weeks post-partum.
- Evaluate the efficacy of TIV against vaccine-strain matched laboratory-confirmed influenza illness during pregnancy and until 24 weeks post-partum.
- Define the efficacy of TIV against protocol defined clinical ILI during pregnancy and until 24 weeks post-partum.
Secondary Objectives

Immunogenicity:
- Determine the kinetics of transplacentally transferred maternal Hemagglutinin (HA) antibodies to the newborns until 24 weeks post-partum.
- Evaluate cell mediated immune responses to TIV.

Pneumococcal colonization:
- Define efficacy of TIV against acquisition of pneumococcal carriage in infants up to 24 weeks of chronological age.

HIV-infected Pregnant Women: Initial Immunogenicity and Safety Study

- Data reviewed by SSC & DSMB, November 2011
- Consensus that based on the inferior immune response observed in HIV-infected women and in particular the lower GMTs post-vaccination, that the project does not proceed to undertaking an efficacy trial in HIV-infected mother-infant dyads in 2012.
- Plan to 2012: alternate dosing schedule study in HIV-infected women

Dosing Schedule Study in HIV-infected Women

1. Single dose (N=275)
   - visit 1: 1 dose vaccine, 1 dose placebo
   - Visit 2: 1 dose placebo

2. Double-strength dose (same day) (N=275)
   - visit 1: 2 doses vaccine
   - Visit 2: 1 dose placebo

3. Two separate doses (1 month apart) (N=275)
   - visit 1: 1 dose vaccine, 1 dose placebo
   - Visit 2: 1 dose vaccine

4. High-dose (60ug) single dose (N=275)
   - visit 1: 1 HD vaccine, 1 dose placebo
   - Visit 2: 1 dose placebo

Conclusion

- Established efficacy in HIV-infected adults with CD4+ >100 cells per µl and on ART.
- Need to study in HIV-infected (and –uninfected adults) with underlying PTB and HIV+ with CD4+ <100 cells/ul.
- Efficacy not established in HIV-infected children on ART. Consider different dosing schedule or vaccine formulation (adjuvant) in young HIV+ children (6 to <36 mo.).
- Relatively poor/modest immunogenicity in HIV-infected pregnant women. Studying alternate dosing schedules and consider adjuvant vaccine.
- Safety and efficacy data from HIV-uninfected mother-infant dyads in African setting pending last quarter of 2013.