



The Pediatric AIDS
Clinical Trials Group

Phase I/II Randomized Trial of the Safety and Immunogenicity of Live Attenuated Influenza Vaccine (LAIV) vs. Inactivated Influenza Vaccine (TIV) in HIV infected (HIV+) Children; PACTG 1057



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678 (R-106)

Abstract

Background: ACIP recommendations are for HIV+ children to be given a yearly influenza vaccine. Standard practice has been to use TIV annually. Little data is available with regard to safety and immunogenicity of the recently licensed LAIV (FluMist®) in this population.

Methods: Three groups of HIV+ children 5-18 years of age (stratified by prior and current CD4%) who had received prior priming with TIV were enrolled in the fall of 2004, prior to the onset of the 2004-5 influenza season. Only children with current viral load <60,000 and CD4>15% were enrolled. Subjects were randomized (1:1) to receive either TIV or LAIV. Safety and nasal surveillance for viral shedding (LAIV recipients only) occurred at days 14, 28 and 42. Subjects with a history of reactive airway disease were enrolled if there was no recent exacerbation of disease. Adverse events occurring up to day 28 were reviewed for causality.

Results: 243 HIV+ children were enrolled. Comparing LAIV vs. TIV: 53% in each group were male; the majority were Black (59% and 68%) and Hispanic (22% and 21%), mean age was 11.4 and 11.9, mean CD4% was 33% and 34% and mean Log10 viral load was 2.9 in both groups. There were no changes in CD4% or viral load related to study vaccine administration. Among LAIV recipients, influenza shedding was detected in 31 (27%) of 115 subjects at day 3 (N=1 A Type A, 6 Type B, and 6 both A&B), in 3 (2.5%) of 119 subjects at day 14 (N=1 A and 2 B), and in 1 (0.9%) of 115 subjects at day 28 (Type A). A follow-up culture in this subject at day 56 was negative. There were 73 grade ≥2 signs and symptoms events and 32 diagnoses that occurred within 28 days from the vaccination (LAIV: 61, TIV: 44) but only 6 grade ≥3 signs and symptoms occurring within 28 days of vaccination. Of all these 105 events, 15 were possibly treatment related; 6 to TIV and 9 to LAIV. Events related to LAIV included: fever and malaise, conjunctivitis (2), AOM, sinusitis, pharyngitis and LRT illness (2, one of whom was hospitalized). The 6 events related to TIV were AOM (2), pharyngitis (2), conjunctivitis (1) and injection site swelling (1). One patient receiving LAIV had two events (fever and malaise).

Conclusions: There were no unexpected toxicities or serious adverse events associated with administration of either LAIV or TIV in HIV+ children in this study. Prolonged shedding of vaccine virus was not observed. LAIV appears to be safe and well tolerated in HIV+ children with CD4%>15%.

Introduction

Background: Influenza has a greater potential to cause bacterial complications in some HIV-infected children, and is more likely to complicate their routine care during epidemic periods than in normal children. There is also the theoretical possibility that this viral illness will enhance HIV replication by activating CD4+ cells (especially in children with incomplete drug suppression) and thereby will stimulate more rapid HIV disease progression.

ACIP recommendations are for HIV+ children to be given a yearly influenza vaccine. Standard practice has been to use TIV annually. Little data is available with regard to safety and immunogenicity of the recently licensed LAIV (FluMist®) in this population.

Are they safe?
Are they immunogenic?

This PACTG multicenter study was designed to evaluate the safety and immunogenicity in HIV-infected children on antiretrovirals, of LAIV (FluMist®) compared with TIV.

Entry Criteria

- Age 5-18 years at entry
- HIV RNA <60,000 copies/ml within 60 days prior to screening
- Stable antiretroviral therapy for ≥16 weeks
 - 3 different antiretrovirals from at least 2 different therapeutic classes
- Received TIV in at least one of the prior two years

Results:

Baseline characteristics

- 53% Male, 47% Female
- Ethnicity
 - White, non-Hispanic: 13%
 - Black, non-Hispanic: 63%
 - Hispanic: 22%
- No differences across vaccinated groups for age, gender or ethnicity

- 4 subjects (1.6%, 3 to LAIV and 1 to TIV) experienced at least one grade ≥3 AE
 - 6 events, 5 to LAIV and 1 to TIV) within 28 days of vaccination
- Of these 6 grade ≥ 3 signs & symptoms events, only injection site swelling was related to TIV
- Fever and Malaise from one subject receiving LAIV are possibly related to LAIV

Comparison between two vaccines

- No significant differences were found for the proportion of number subjects who had ≥ Grade 2 signs & symptoms events between LAIV and TIV (19% vs. 17%)
- No significant differences were found for the proportion of number subjects who had ≥ Grade 3 signs & symptoms events between LAIV and TIV (2.5% vs. 0.8%)
- No significant differences were found for the proportion of number subjects who had vaccine related or possibly related events between LAIV and TIV (6.6% vs. 5%)

Lab or ART Changes Over Time:

- HIV RNA viral load
 - No clinically significant change over study
- CD4%
 - No clinically significant change over study
 - No changes in ART due to vaccination

CD4% at entry, patient groups:

| | Arm* | Target N | Nadir | Screening |
|---------|------|----------|--------------------|-----------|
| Group 1 | A | 50 | <15 | >=15 |
| | B | 50 | | |
| Group 2 | A | 50 | 15- <u><</u> 25 | >=15 |
| | B | 50 | | |
| Group 3 | A | 50 | >=25 | >=25 |
| | B | 50 | | |

*Arm A receiving LAIV, Arm B receiving TIV

Baseline Demographics

| All groups | LAIV | TIV | P-value |
|--------------------|-------|-------|---------|
| Number of patients | 122 | 121 | |
| Age (Yrs.) | 11.4 | 11.9 | 0.2 |
| Mean | 11.0 | 12 | |
| Standard deviation | 1.0 | 1.1 | |
| N | 122 | 121 | |
| CD4 Percent | 32.0 | 34.1 | 0.4 |
| Mean | 32.4 | 31.1 | |
| Standard deviation | 4.4 | 4.1 | |
| N | 122 | 121 | |
| CD4 Count | 841.5 | 896.2 | 0.54 |
| Mean | 825.9 | 876.1 | |
| Standard deviation | 819 | 814 | |
| N | 122 | 121 | |
| Viral Load (log10) | 2.9 | 2.9 | |
| Mean | 2.6 | 2.6 | |
| Standard deviation | 0.5 | 0.5 | 0.97 |
| N | 122 | 120 | |

Vaccine Schedule and Follow-up

- Live Attenuated Influenza Vaccine (LAIV) (Arm A) or inactivated Influenza Vaccine (TIV) (Arm B) were given at Entry
- The further contact to collect safety information were obtained on Days 3, 7, 14, and 21, 28, 42 and at 6 months.
- Laboratory evaluations:
 - Plasma HIV-1 RNA concentration, CD4+ count and CD4%
 - Serum HAI anti-influenza antibody against the vaccine strains and to selected drifted influenza strains (ongoing)
 - Serum neutralizing antibody using a microneutralization assay against the vaccine strain and to selected drifted influenza strains (ongoing)
 - Salivary IgG and IgA anti-influenza antibody to the vaccine strains and to selected drifted influenza strains (ongoing)
 - ELISPOT determination of CM1 to the vaccine antigens and a non-vaccine influenza antigen (ongoing)
 - Influenza Viral shedding for LAIV from nasal swabs at 3, 14, and 28 days after the vaccination

Results: Adverse Events

- 243 subjects were enrolled and included in safety analysis
- No deaths or life-threatening adverse events (AE) occurred
- There were 73 grade ≥ 2 signs & symptom events and 32 diagnoses that occurred within 28 days from the vaccination date
 - LAIV: 61
 - TIV: 44
 - only 6 grade ≥ 3 signs & symptoms events
- Of all these 105 events, 15 were treatment related or possibly treatment related; 6 to TIV and 9 to LAIV

Treatment related Toxicity events

- All Events (signs & symptoms, diagnoses) related or possibly related to LAIV:
 - Fever and Malaise,
 - Conjunctivitis: 2
 - AOM: 1
 - Sinusitis: 1
 - Pharyngitis: 1
 - LRT illness: 2, one of whom was hospitalized
- 8 subjects had events related or possibly related to LAIV (6.6%)

Treatment related Toxicity events

- Events (signs & symptoms, diagnoses) related or possibly related to TIV:
 - AOM (2),
 - Pharyngitis (2),
 - Conjunctivitis (1)
 - injection site swelling (1)
- 6 subjects had events related or possibly related to TIV (5%)

Events attributed to Vaccine

| CD4% Nadir / entry | Arm | N | Proportion of subjects with vaccine-attributable toxicities events (no. of subjects) |
|----------------------------|-----|----|--|
| <15% / ≥15% | A | 45 | .09 (4) |
| | B | 43 | .09 (4) |
| 15- <u><</u> 25% / ≥15% | A | 50 | .04 (2) |
| | B | 49 | .02 (1) |
| ≥25% / ≥25% | A | 27 | .07 (2) |
| | B | 29 | .03 (1) |

Conclusions: Vaccine Safety

- There were no unexpected toxicities or serious adverse events associated with administration of either LAIV or TIV in HIV+ children in this study
 - Slightly more AEs in lower CD4% groups
- Prolonged shedding of vaccine virus was not observed
- Vaccinations did not appear to result in either immunologic or virologic changes.

Influenza viral Shedding

| Frequency (%) | Days post Vaccination | | | |
|------------------|-----------------------|-----------|-----------|---------|
| | 3 | 14 | 28 | 56 |
| FLU A | 19 (.17) | 1 (.01) | 1 (.01) | 0 (0) |
| FLU A&B | 6 (.05) | 0 (0) | 0 (0) | 0 (0) |
| FLU B | 6 (.05) | 2 (.02) | 0 (0) | 0 (0) |
| Overall Positive | 31 (.27) | 3 (.03) | 1 (.01) | 0 (0) |
| Overall Negative | 84 (.73) | 116 (.97) | 114 (.99) | 3 (1.0) |
| Total # | 115 | 119 | 115 | 3 |

- Administration of LAIV and TIV is safe in HIV infected children ages 5-18 years with CD4%>15%. No significant differences between LAIV and TIV were found for toxicities events
- Immunogenicity studies of LAIV and TIV are ongoing.
- The genotyping of strain-specific isolates of influenza viral shedding is ongoing