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Early Initiation of ARV Therapy in Perinatally Infected Infants Decreases Mortality

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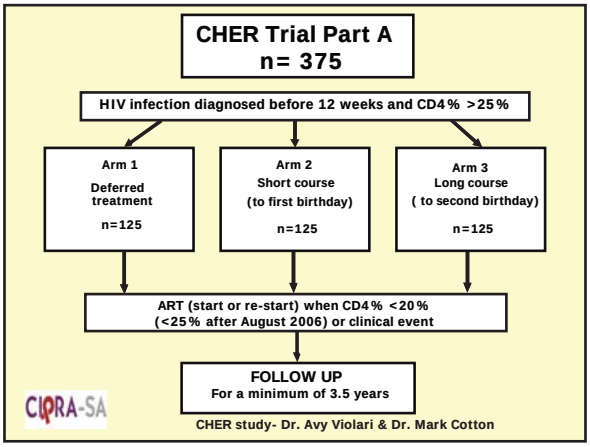
On July 25, 2007, National Institute of Health (NIH) released data from the "Children with HIV Early Antiretroviral Therapy" (CHER) study, a phase III, randomized clinical trial being conducted in South Africa. The data were presented at the International AIDS Society Conference in Sydney Australia on 7/25/07 by Dr. Violari. The CHER study began in July of 2005. It was designed and initiated to evaluate whether giving antiretroviral (ARV) medications over a limited period of time would delay disease progression. It is the first randomized clinical trial, which shows that infants who received ARV therapy before three months of age did better than infants whose ARV therapy was delayed.

Study Design

- HIV infected infants between 6 and 12 weeks of age, without immune suppression (CD4% > 25%) or severe symptoms of clinical disease were enrolled.
- By early 2007, 377 infants had been enrolled in one of the three arms of the study:
  - 1: ARV therapy started only after clinical signs of illness or immunological deterioration towards AIDS.
  - 2: ARV therapy starting immediately and continued for 40 weeks or until 1st birthday.
  - 3: ARV therapy starting immediately and continued for 96 weeks or until 2nd birthday.
- For all arms, ARV therapy was started (or re-started) when CD4% <20% (or < 25% after August 2006) or clinical event.



Arm 1 was the control group and received the current standard of care in South Africa. The trial was designed to continue through 2011.

Routine review of the early trial data, on June 20, 2007, by the trial Data and Safety Monitoring Board (DSMB) noted striking results:

- Infants who received early initiation of ARV therapy (between 6 and 12 weeks of age) had a higher survival rate.

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- 96% of infants who received early ARV therapy were alive compared to 84% of the control infants.
- The table below summarizes the mortality rates.

Mortality Rates

Variable	Died or Deceased (% of group)	Person Years of Follow-up	Rates per 100 Person-Years (95% CI)
Arm 1 (control group) n=125	**20 (16%)**	**79**	**25.3 (15.5;39)**
Arms 2 & 3 (early treatment groups) n=252	**10 (4%)**	**167**	**6 (2.9;10)**
Total n=377	**30 (8%)**	**246**	**12.2 (8.2;17.4)**

- The hazard ratio for dying in groups 2 and 3 was 0.24 (95% CI: 0.11; 0.51), with a calculated p value of 0.0002.

DSMB Conclusion

Early ARV therapy for perinatally infected infants was more effective in preventing early death than delaying treatment until clinical symptoms and/or immunological deterioration were observed.

Recommendations

- There should be no further enrollment into the control group.
- Infants previously in the control group should be evaluated for potential initiation of ARV therapy.
- All infants enrolled in this study should be followed for approximately 3.5 years, the proposed end of the trial.
- Those infants in the other two arms of immediate ARV therapy (40 and 96-week groups) should continue with the study.

The recommendations of the DSMB are appropriate:

- given the available data at the time of the review
- recognizing the established ethical mandates
- considering the need to ensure the safety of the participants in this trial and
- understanding that the continuation of the other two treatment arms is essential to identify potential side effects and toxicities of early ARV therapy for large numbers of children in resource poor settings.

The careful follow-up and management of these children in such a setting will determine:

- if continuous ARV therapy might be stopped at a future time in those children who begin ARVs before 3 months of age and develop “adequate immune responses”
- if early initiation of ARV therapy is in fact feasible, efficacious and safe and
- the ongoing risks and benefits of starting ARV therapy as early as 3 months of age in such a setting.

Children with HIV: Improved Mortality and Morbidity with Combination Antiretroviral Therapy[3]

Facts about perinatally acquired HIV infection:

- There is a rapid progression of perinatally acquired HIV infection in infants and young children, because they have an immature immune system at the time of their HIV infection which makes them more susceptible to progression of the infection.
- Approximately 20% of children with perinatally acquired HIV infection, without treatment, progress to AIDS or death in the first year of life.
- By 6 years of age, approximately 40% of HIV-infected children, without treatment, will progress to AIDS or death in the US or Europe.
- Various factors have been reported to influence the morbidity and mortality rates in the HIV-infected child including:
  - severity of maternal illness
  - timing of vertical transmission (intrauterine, intrapartum, postnatal)
  - occurrence of opportunistic infections.
- In the United States or Europe, HIV-infected children, who receive good supportive care and are readily treated with ARV therapy in the early stages of disease, rarely progress to AIDS or death.[3]
- A number of studies from the US and Europe document that the early initiation of ARV therapy before 3 months of age and even before 6 months of age improves survival, limits the progression of HIV disease and improves the immune function of HIV-infected children.[3]

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Other studies:

- Newell ML et al[4] and the Ghent International AIDS Society working group on HIV infection in women and children performed a meta-analysis of 7 randomized mother-to-child transmission (MTCT) intervention trials. The results showed mortality rates of 35.2% in HIV-infected children compared to 4.9% in uninfected children at 1 year of age and 52.5% in HIV-infected children compared to 7.6% in uninfected children at 2 years of age. In this analysis, mortality was significantly lower in children infected later (after 4 weeks of age) than those infected earlier (before 4 weeks of age).
- Marinda et al[5] and the ZVITAMBO Study Group from Harare, Zimbabwe reported 2-year mortality rates of 2.9% in non-HIV exposed infants; 9.2% in not infected, HIV exposed infants; 67.5% in HIV-infected infants with intrauterine infection; 65.1% in infants infected with HIV intrapartum; and 33.2% in infants infected postnatally.

Current Recommendations for the Initiation of ARV Therapy in HIV-infected Infants in the United States[6]

- Initiation of ARV therapy *is recommended* for infants < 12 months of age who have clinical symptoms of HIV disease regardless of CD4% or viral load.
- Initiation of ARV therapy *is recommended* for asymptomatic infants < 12 months of age with CD4% < 25%.
- Initiation of ARV therapy *should be considered* for asymptomatic infants < 12 months with CD4% ≥ 25%.
- For children, > 1 year and < 4 years of age, ARV therapy *is recommended* if the child has AIDS or significant HIV-related symptoms or is asymptomatic/has mild symptoms and CD4% < 20%.
- For children, > 1 year and < 4 years of age, ARV therapy *should be considered* if the child is asymptomatic/has mild symptoms and a CD4% of 20-24% or HIV RNA > 100,000 copies/mL.
- For children, > 1 year and < than 4 years of age, ARV therapy *should be deferred* if the child is asymptomatic and CD4% is ≥ 25% and HIV RNA < 100,000 copies/mL.

The early results of the CHER study underscore the importance:

- of continued efforts for the prevention of perinatal HIV infection
- early and accurate diagnosis of HIV in children
- improving the availability and acceptability of ARV therapy for children in these settings.

The results do not justify a change in the current guidelines for the initiation of ARV therapy in infants and children in the United States.

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