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A Historical Note: "Confounding by Indication" in Early Perinatal HIV Treatment Trials

Anoji Seneviratne, Bart K Holland, Savita Naik*, George McSherry, Peter Wenger, Arry Dieudonne, Sachith Seneviratne, Dashefsky Barry and Oleske James

UMDNJ-New Jersey Medical School, Department of Pediatrics, Newark, NJ, USA

Abstract

Our study was done at a time when Perinatal HIV infection (PHI) treatment guidelines were not yet developed, which provided the opportunity to evaluate early developing antiretroviral treatment (ART) in the setting of clinical trials for naive pediatric populations. Medical records of 44 treatment- naïve PHI infected infants and children (1-16 yrs) who received ART therapy by participation in Clinical Trials from 1/1996 to 12/1998, were longitudinally followed over 3 years. This initial cohort was divided into PHI patients progressed to AIDS (CDC classification C or PAIDS), and patients who did not progress to AIDS (CDC classification N, A, B or non-PAIDS). The response to ART was measured and compared by HIV viral load, CD4 cell absolute count and percentage, any change in clinical status after 6 and 12 months. The PAIDS defined cohort had less viral clearance than the non PAIDS cohort (P values 0.01). When these two cohorts were compared by CDC immune status the difference of response was approaching significance (P value 0.06). This retrospective review of our early interventional trials resulted in an unintended but important "historical prospective" on effectiveness of ART therapy that demonstrated the epidemiological concept of "Confounding by Indication".

Keywords: HIV clinical trials; Pediatric AIDS; Perinatal HIV

Introduction

Statement of hypothesis

Early Anti-Retroviral Therapy (ART), through clinical trials programs if started at time of diagnosis or early in the course of Perinatal HIV Infection (PHI), increases the chance of positive treatment outcomes as demonstrated by stable clinical status, an improved or stabilized immune response (CD4+ T cell percentage, absolute count) and a decrease in HIV RNA viral load (VL). A delay in treatment of PHI until CDC defined AIDS is reached, markedly diminishes the chance of a positive response to ART treatment as manifested by persistence in HIV viral load. Any delay in diagnosis until CDC AIDS defining category being met also introduces the major bias of "confounding by indication", in which only the most ill patients are enrolled into investigational clinical trials which markedly diminishes the efficacy of a possible effective treatment.

Background

The rapid spread of HIV-1worldwide and high mortality, pressured the development of effective treatments initially with the discovery of AZT monotherapy, with rapid development of multiple ART of increasing complexity, enabled by the development of later 3 classes of ART medications defined by their separate mechanism of action: Nucleoside Reverse Transcriptase Inhibitors (NRTI), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) and Protease Inhibitors (PI). The decision to initiate ARV therapy in infants and children with PHI, prior to the development of treatment guidelines, was usually based on the severity of the illness as established in the 1987 [1] CDC classification of HIV infection and AIDS that were revised in 1994 [2], and were based on clinical criteria (categories N, A, B, and C) as well as laboratory studies of CD4+T- cell absolute count and percentage (categories 1, 2 and 3), and, as the technology developed, in the HIV RNA viral load (VL) assessment with the expectation that effective HIV treatment after 6 months would lower VL and stabilize the percentage and absolute count of CD4 cells. The technology to assess HIV VL was introduced just after this study was initiated and thus HIV VL was not consistently used in clinical practice although it was uniformly used in clinical trials. At the early stage of the epidemic, it was not known whether the outcome of ART in CDC class C3 children (AIDS defining illness), was any different to initiating ART in early stage HIV infection (CDC classification class N, A & B, and 1 & 2).

ART therapy evolved as a progression from single drug therapy to multiple ARV medications in differing formulations and dosing intervals and is now defined as HAART with the use of 3 ARV drugs from 3 different classes of ARV medications with one being a PI. At the onset of the our study in 1995, little was known about the effectiveness and outcome of treatment of PHI in infants or children with early, less advanced HIV infection versus those with progression to AIDS defining illness. In US urban centers, where the early HIV epidemic was concentrated, health care facility clinicians who had the experience to provide care to HIV infected children were usually the same clinical investigators at centers that offered initial access to investigational anti-HIV drug trials. The poor, frequently ill care taker of an HIV infected child may well have perceived that the only option to obtain good health for their child is to also participate in an investigational clinical trial. This placed an extra burden on the health care provider to ensure the provision of equal clinical care regardless of a particular child's participation, or not, in an investigational drug trial [3]. There was, however, also an advantage when clinical care and screening, selection, enrollment, and follow up in clinical trials are provided by the same program and clinicians. Thus, our study resulted in an unintended but important study of the effectiveness of early and developing ART in a

***Corresponding author:** Savita Naik, UMDNJ-New Jersey Medical School, Department of Pediatrics, Newark, NJ, 185 South Orange Avenue, PO Box 1709, Newark, NJ 07103-1709, USA, Tel: 973-972-1504; Fax: 973-972-6443; E-mail: savitanaik2000@gmail.com

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diverse pediatric population of early stage HIV infection through those who progressed to AIDS. This diverse population posed additional challenges that included a bias in evaluation of best combination therapy (soon to be called HAART) due to "confounding by Indication" (the most ill children often given priority for enrollment to the clinical trial which would impact efficacy evaluations). HIV infected infants who were enrolled in early clinical trials (pre 2000) with combination ARV medications were more likely to have had advanced to AIDS defining illness, therefore introduced this bias when compared to infants with less advanced perinatal HIV infection based on CDC clinical and laboratory definitions for stage of disease.

Materials and Methods

This study was, by standard epidemiological definition, a retrospective cohort study, but we prefer to use the alternative term a "historical prospective study" to indicate that all children were longitudinally followed and evaluated by the first author (A.S.), with the supervision of other authors at the Children's Hospital AIDS Program (CHAP) of the then United Children's Hospital of New Jersey, Newark, NJ. Medical records of 44 perinatal HIV infected, treatment-naïve children between 1-16 years of age, who subsequently received developing ART from January 1996 to December 1998, were reviewed. The trial was conducted for 3 years but the data of each cohort was studied for a period of 12 months after the initiation of developing ART. All the patients treated had a viral load over 400.

The former PID fellow (A.S.) was responsible with one of the division attending (G.M.) for both clinical care, enrollment and eligibility for clinical trials for approximately 1/3 of all perinatal HIV infected patients followed in our CHAP clinical care program and PACTG clinical trials program. All patients were randomly assigned one of the 3 clinical care teams with a balance of HIV clinical stage maintained across the clinical teams. All PID fellows and attending physicians frequently met to discuss all cases and standard clinical treatment protocols were followed. At a clinic visit the patient was seen by one of the PID fellow with an attending physician, a nurse case manager, social worker and a nutritionist. The patients were seen and followed at monthly intervals. At each clinic visit vital signs were recorded, clinical assessment was performed and parameters of growth recorded, blood was drawn as required, social problems were addressed and most importantly, adherence to the medications prescribed was reviewed and emphasized.

The infants enrolled in this early ART clinical trials program had determination of HIV viral load at 6 months had CD4 levels measured at 12 months after starting ART. Most children had multiple VL and CD4+ levels measured with more laboratory studies done in the later years of the study. The CD4+ T lymphocyte levels were measured as absolute number and percentage of total lymphocyte count. The percentage was used to correct for the age related CD4 variability of the population and was used in analysis of this study. Both Viral load and CD4 levels were utilized to categorize patients prior to the initiation of ARV therapy using the modified CDC criteria [4-6]. All patients studied had blood assays for HIV RNA levels (VL) and CD4 counts at least twice before the initiation of ART. HIV RNA levels were measured quantitatively using the Roche Application. Blood was drawn at monthly intervals. The minimum viral load recorded was 400 copies/ml and maximum observed was 750,000 copies. Any viral load that was <400 was recorded as undetectable and any more than 750,000 was reported as >750,000 copies/ ml.

In the evaluation and classification of ART outcomes, a good response was defined as undetectable RNA viral load on two consecutive measurements (<400 copies/ml) at the end of 6 month study period. In addition a CD+ T lymphocyte percentage was also compared between the two groups at 12 months of ART. A good response for those who had AIDS defining illness at study onset was defined as a CD4+ lymphocyte percent >15%. Because the group of HIV infected children who did not meet the CDC criteria for AIDS usually had CD4+ T cells percentage already over 15%, CD4+ lymphocyte percent were analyzed instead to ensure that there was no deterioration in this group.

The compliance to medications was closely monitored by the social worker and the nurse case manager. The compliance was also confirmed by study pharmacist working in the CHAP program with reminder calls to assure that medications were taken and refilled on an appropriate schedule. In some cases, where poor adherence was suspected, the social worker and the nurse case manager would visit the patient's home to encourage compliance with ART medications and determine the factors associated with poor compliance.

Results

Table 1 provides information about population characteristics of 44 patients who were enrolled in to this study in order to evaluate response to developing ARV treatment. As expected due to the demographic characteristics of Newark, NJ, the majority were African American. About half of the PHI children were considered to be HIV infected but not had progressed to AIDS according to CDC clinical or laboratory definitions. There was no difference of the mean age among children who met the clinical classification of AIDS (7.5yrs) compared to HIV infected children who had not progressed to AIDS (7.3yrs). There was a preponderance of females compared to males enrolled in the study: 29/44 (66%) females and 15/44 (34%) males. Of interest, 10 of the males (2/3), met CDC clinically defined AIDS diagnosis, whereas in the females they were equally divided in CDC defined clinical definitions.

Table 2 which provide the response to ARV therapy after 6 months, based on CDC clinical criteria. It demonstrated a concordance of low VL in 13/20 (65%) patients starting ART when they had not yet developed AIDS defining CDC clinical definitions, while only 6/24 (25%) of those initiating ARV treatment with CDC clinical defined AIDS demonstrated a positive response by VL <400cop/ml. Similarly, when CDC laboratory levels of CD4+ lymphocyte were used to define

Patient Demographics		CDC Clinical Class		CD4 Percentage	
Total number of patients (44)		PHI not progressed to AIDS (CDC AIDS clinical class N, A or B)	PHI progressed to AIDS(CDC AIDS clinical class C)	CD4% >15	CD4% <15
		20/44 (45.5%)	24/44 (54.5%)	21/44 (47.7%)	23/44 (52.2%)
Age		Mean 7.3 (range 1.5-14)	Mean 7.5 (range 1 -16)		
Gender		Males 5/44 (11.3%)	Males 10/44 (22.7%)		
		Females 15/44 (34%)	Females 14/44 (31.8%)		
Race/ ethnicity	**Black 39/44 (88.6%)**	18/44 (40.9%)	21/44 (47.7%)		
	Hispanic 2/44 (4.5%)	0	2/44 (4.5%)		
	White 3/44 (6.8%)	2/44 (4.5%)	1/44 (2.2%)		

Table 1: Population Characteristics of Perinatal HIV infected infants and Children enrolled by CDC Clinical Class.

how HIV infected children responded to 6 months of ART, those meeting CDC laboratory class 1, 2 (non AIDS defining), 12/21 (57%) demonstrated a positive response to ART with a concordance of VL <400 copies when starting with a CD4+ T cell percentage of >15%. On the other hand, there was a lack of concordance of low VL and CD4+ cell <15% that meet the CDC criteria of AIDS defining illness with only 6/23 (26%) of children who began ART with AIDS defined levels having a positive response to ART Table 3 examined the changes in mean CD4+ cell percentage before and after one year of ARV therapy for children who had either met CDC classification for AIDS defining illness, Class C (24) or were HIV infected but had not met CDC criteria for AIDS, class N,A and B (20). Children with AIDS defining illness before treatment, demonstrated an increase from 8.5% to 16.1% in mean CD4+ percentage which by two tail P value showed significant improvement (P=0.0001). Children who did not have AIDS defining illness before treatment showed an improvement from 32% to 35% which was not significant due to the already normal CD4+ cell% in most of our non-AIDS cohort before starting ART. The data from this Table 3 demonstrated that, despite meeting CDC criteria for an AIDS diagnosis, ARV treatment for 12 months can improve the levels of CD4+Cell % from CDC AIDS defining levels category to CDC non-AIDS defining levels.

Discussion

Significance of research

PHI has been a topic of interest since it was discovered in early 1980s [7,8]. The FDA approved use of ARV therapy in Pediatrics has always lagged behind adult experience and as a result treatment trails in PHI had not advanced as rapidly as in adults, despite the fact that PHI infants and children have a more rapid progression to opportunistic morbidities and mortality compared to adult acquired HIV infection. Therapeutic options and adverse drug reactions have become more complicated with the advent of the Highly Active Antiretroviral Therapy (HAART), while disease monitoring has become more accurate with the ability to measure the HIV RNA copies, as a marker of disease activity with ARV treatments. Our study population was categorized as those PHI children who meet the CDC criteria for AIDS defined infection (C3) and children with HIV infection but had not progressed to CDC defined AIDS (N, A, and B) and the response to ARV therapy as measured by HIV VL by these two cohorts after 6 months. The AIDS defined cohort had less virological clearance in 6 months than the non AIDS cohort (P values 0.0138). When the Pediatric AIDS defined cohort was defined by immunological status (CDC class 1, 2 and 3), the difference of response, were approaching significance (P value 0.065).

CDC Clinical Class↓	Response to ARV Treatment		
	Good response to ARV therapy with viral load <400 copies/ ml	Poor response to ARV therapy with viral load >400 copies/ ml	Total
(Non PAIDS)CDC class N, A and B[a]	13/20 (65%)	7 /20 (35%)	20
CDC class C(PAIDS)[a]	6/24 (25%)	18 /24 (75%)	24
Total	19	25	44
Base line CD4+%↓	<400 copies/ ml	>400 copies/ ml	
CD4 + % cell >15%[b]	12/21 (57%)	9/21(42%)	21
CD4+ % cell <15%[b]	6/23(26%)	17/23(73%)	23
Total	18	26	44

Table 2: Qualitative Virological Response to 6 months of ARV therapy by CDC HIV Clinical Category (N, A, B or C) and CDC HIV Laboratory levels of CD4+cell % (Level 1, 2 or 3) at onset of ARV treatment.

CDC clinical class	Mean CD4+ percentage	
	Mean CD4+ percentage at baseline	Mean CD4+ at 12 months of ARV therapy
CDC class N, A and B(Non PAIDS)	32%	35%
CDC class C(PAIDS)	8.5%	16.1%

Paired T test results: Two tailed P value of the CDC class C category before and after therapy P=.0001, Mean improvement =7.68% 95% CI- 4.25-11.11 %

Table 3: Change of mean CD4+ percentage after 12 months of ARV treatment based on CDC clinical class.

The analysis of the Pediatric AIDS defined cohort showed a significant rise in CD4 cell count with ARV therapy at the end of 12 months (P value 0.0001). Similar analysis of the non AIDS HIV infected cohort could not be practically performed as pre- treatment CD4+ cell % were already in the normal range prior to treatment. Our study had limitations; perinatal acquired HIV is now relatively unusual in US and there are few patients available for interventional drug trials due to the success of prevention of Perinatal HIV transmission by treatment of HIV pregnant women at the end of the first trimester with ARV medication(s). Our initial study population of 44 patients, who were ARV naïve, although relatively small in number, was still able to demonstrate clinical response to ARV therapy in both cohorts of PHI infants and children.

The findings in Table 2 demonstrate the principle of "confounding by indication". Investigational drug trials, especially in situations where the use of a placebo is ethically not appropriate, can be very biased if either a disproportionate number of very ill or relatively well subjects are enrolled; when there is a preponderance of very ill patients enrolled in a treatment trial, the efficacy of a treatment will be markedly blunted and a potentially useful medication for an illness may not be developed for clinical use. Likewise, if a clinical drug trial enrolls mostly asymptomatic effected patients, the efficacy of a treatment may be exaggerated over the usual short clinical period of a clinical trial, to prevent disease progression. In the case of PHI there is greater risk for the first scenario of the sickest infants and children being enrolled into a clinical trial rather than the second scenario due to the more rapid progression of untreated PHI and the unlikely confounder of having lack of progression. Thus Table 2 documents what was a priori the expectation of the investigations during the course of clinical trials treatment and confirmed at the time of chart review and analysis of outcome: early ARV treatment was more effective and appropriately should be initiated as soon as perinatal infection is diagnosed in an infant or child. While there was not enough cases of non-African Americans in our study to demonstrate this for Hispanic and white races, nonetheless any perinatal infected infant or child should begin ARV therapy as soon as HIV infection is confirmed.

These results in PHI children reflected the benefit of therapy as seen in earlier adult treatment trials of HIV infected patients. Our study was done at a time when PHI treatment guidelines were not yet developed and follow up studies of pediatric cohorts of HIV infants and children was undergoing rapid changes. This study provided the opportunity to study ARV treatment in naive pediatric population and allowed us to review this early clinical trials experience to present a "historical prospective" study that demonstrated an underappreciated epidemiological principle that should be always considered in clinical trials of high mortality epidemic infectious diseases, such as HIV/AIDS.

Conclusion

Our hypothesis that the response to 12 months of ARV therapy, based on measurement of HIV VL, would be more significant in PHI that had not progressed to AIDS defining clinical status population compared to the cohort of PHI with AIDS defining illness is true. The response at the end of 12 month period of ART given in the context of clinical trials even in the PHI cases that had progressed to CDC AIDS defining illness was significant as measured by improvement in CD4+ cell %. Similar response could not be assessed in the non-AIDS cohort using the CD4+ cell % alone, as it seem to be a poorer marker to detect significant improvement in this population, as the CD4+ cell % were too close to normal levels even before the treatment was initiated. This is relevant in more recent cohorts of PHI, as the ARV therapy response in early HIV infection is markedly better than when they are diagnosed and treated later in the disease [9]. Measurement of CD4+ cell%, although more accurate for age related correction of absolute numbers, may have its limitations in the assessment of response to treatment in this population of PHI children.

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