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Virologic and immunologic response to highly active antiretroviral therapy among HIV-1-infected children in Côte d'Ivoire

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ABSTRACT

BACKGROUND: Little information is available about the long-term therapeutic response to highly active antiretroviral therapy (HAART) of children living in Africa. In this analysis, we describe changes in plasma viral loads (VL) and CD4 counts and occurrence of adverse laboratory events among children in Côte d'Ivoire, who initiated HAART during 1998-2002.

METHODS: We analyzed data from an observational cohort of HIV-1-infected children (< 13 years), who were screened and followed in the Drug Access Initiative in Abidjan. For antiretroviral-naïve children who initiated HAART, we estimated changes from baseline VL and CD4 counts, using pre-treatment linear regression, and estimated the probability of developing a severe (grade 3) or life-threatening (grade 4) adverse laboratory event, using modified Kaplan-Meier methodology for interval-censored data.

RESULTS: Of 605 children who were screened, 193 (32%) initiated HAART. Of these initiating HAART, 51% had an AIDS-defining condition, 70% had severe immunosuppression (immune category 3), 22% had previously taken antiretroviral drugs, and 43% returned to the clinic for at least 1 follow-up visit. For children who initiated HAART and had VL and CD4 counts at both baseline and follow-up, VL was an estimated 2.6 log₁₀ copies/mL lower and CD4 count >300 cells/μL higher than baseline values, after 1 year of follow-up. For children, who were free from grade 3 or 4 abnormal laboratory values at baseline and had subsequent laboratory measurements, the cumulative probability of an adverse event was 0.07, 0.11, and 0.14 within 1, 6, and 12 months, respectively, after initiating HAART.

CONCLUSION: After initiating HAART, these HIV-infected children had similar virologic and immunologic outcomes and probability of adverse laboratory events as patients enrolled in clinical trials in the USA and Europe. These results suggest that providing HAART for children can be an effective strategy for reducing the burden of HIV disease in Africa.

INTRODUCTION

Highly active antiretroviral therapy (HAART) is associated with increased CD4 T-lymphocyte count, a key index of disease progression, and reduced HIV-1 RNA among children living in industrialized countries. Immunologic and virologic response to antiretroviral therapy in sub-Saharan Africa, where the majority of HIV-infected persons reside, is less well-defined.

OBJECTIVES:

- To assess short-term (one year) CD4+ T-lymphocyte and HIV-1 RNA response to HAART in African children who remain in care.
- To describe the distribution of significant laboratory abnormalities in the study population before and after HAART.

METHODS

DESIGN: Observational cohort.

PATIENTS: Children presenting for evaluation at seven study sites (hospitals and clinics) in Abidjan who met the following criteria:

- Screened between August 1998 and January 2003
- Age less than 13 years
- Clinical symptoms of HIV infection or CD4 count less than 15% or HIV RNA greater than 3 log₁₀ copies/mL.

DATA COLLECTION: Children were scheduled for visits at baseline, after one month of HAART, and every three months thereafter. At each visit, physicians performed a clinical evaluation, recorded the type of antiretroviral regimen prescribed, and took blood samples to measure HIV RNA, CD4 T-lymphocytes, hemoglobin, neutrophils, platelets, alanine transaminase, separate transaminase, bilirubin, creatinine, and amyase. Children were followed until death, loss to follow-up, or January 2003.

OUTCOMES:

- Immunologic response to HAART as measured by change from baseline in CD4+ T-lymphocyte count and percent.
- Virologic response as measured by change from baseline in HIV RNA, stratified by type of response (maximal, partial, or no response).
- Severe or life-threatening laboratory abnormalities at screening (prevalent abnormalities) during follow-up (incident abnormalities).

DEFINITIONS:

- Maximal virologic response to HAART: Undetectable HIV RNA at any time during follow-up.
- Partial response: < 0.5 log₁₀ HIV RNA copies/mL, decrease from baseline.
- No response: < 0.5 log₁₀ HIV RNA copies/mL, decrease from baseline.
- Laboratory abnormality: Any blood count or serum chemistry value that is classified as severe (grade three) or life-threatening (grade four) following the criteria established by the Pediatric AIDS Clinical Trials Group.

STATISTICAL ANALYSES:

• GEE linear spline regression to estimate changes from baseline in CD4+ count and percent, and HIV RNA, after initiation of HAART.

• Restricted to drug-naïve patients initiating HAART who had CD4+ count and HIV RNA data at baseline and at least one follow-up visit (< 12 and < 47, respectively).

• Intero-visit attrition: All follow-up visits after the initiation of HAART were analyzed irrespective of changes or discontinuation in treatment.

• Virologic response was stratified by maximal, partial, or no response.

• Chi-square tests for categorical variables and non-parametric tests (Wilcoxon-Mann-Whitney) for continuous variables to compare baseline characteristics between sub-groups.

RESULTS

1. COMPARISON: RETURNED AFTER SCREENING VERSUS FAILED TO RETURN

Characteristic	RETURNED AFTER SCREENING (n=403)	FAILED TO RETURN AFTER SCREENING (n=176)	COMPARISON IN CHI-SQUARE OR RISK RATIO
	n (%)	n (%)	p-value
DEMOGRAPHIC:			
Age, years	4 (2-8)	4 (2-8)	ns
% female	15%	17%	ns
In residence in Abidjan	82%	83%	ns
BACKGROUND (PAST):			
Untreated	17%	16%	< 0.05
No previous school	34%	37%	< 0.05
Unemployed	12%	45%	< 0.05
DEMOGRAPHIC AT SCREENING:			
Severe immune suppression	82%	68%	< 0.05
CD4+ COUNT:			
NR, inter-quartile range, vs. non-treatment	0 (0-33)	10 (0-29)	

2. CHARACTERISTICS OF STUDY COHORT (N=122)

Characteristic	Value n (%) or median (IQR)
DEMOGRAPHIC:	
Age, years	5.2 (3.1-8.7)
% female	7.2 (57.8%)
DEMOGRAPHIC (AT BASELINE):	
Severe immune suppression	102 (82.9%)
CD4+ percent	10 (2-13)
VIREMIA (AT BASELINE):	
HIV RNA, log ₁₀ copies/mL	5.7 (5.1-6.3)
INITIAL RESPONSE:	
Maximal	81 (66.4%)
Partial	36 (29.5%)
None	5 (4.1%)
Unknown	1 (0.8%)

NR, inter-quartile range

IQR, inter-quartile range

% based on 122 children with laboratory values

* based on 94 children with non-zero viral loads

3. DISTRIBUTION OF SEVERE OR LIFE-THREATENING, PREVALENT AND INCIDENT LABORATORY ABNORMALITIES

Laboratory parameter	Criterion for severe abnormalities	Prevalent abnormalities (n=226)	Incident abnormalities (n=126)
Hemoglobin	< 7 g/dL	31 (13%)	2 (2%)
Neutrophils	< 400 cells/μL	2 (2%)	1 (2%)
Platelets	< 50,000 cells/μL	1 (0%)	---
Liver function (one or more)			
Alanine transaminase	> 400 U for boys > 200 U for girls	---	---
Amylase (transaminase)	> 140 U for boys > 100 U for girls	3 (0%)	2 (2%)
Bilirubin	> 3 mg/dL	---	---
Amylase	> 200 U	33 (15%)	1 (1%)
Multiple systems		6 (3%)	---

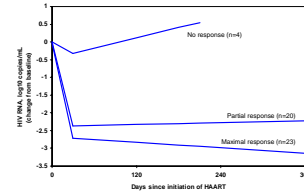
PREVALENCE OF LABORATORY ABNORMALITIES: 8%

• 85 events were observed in 87 drug-naïve children at screening.

INCIDENCE OF LABORATORY ABNORMALITIES: 9/100 PERSON-YEARS

• 9 events were observed in 94 drug-naïve, at-risk children during follow-up after initiation of HAART.

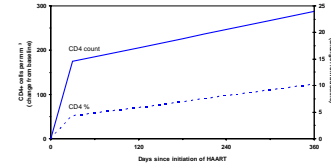
4. HIV RNA RESPONSE TO HAART (N=47)



Estimated change from baseline one year after initiation of HAART for children who responded (n=43)

• HIV RNA: Approximately 2.6 log₁₀ copies/mL lower at one year

5. CD4+ T-LYMPHOCYTE RESPONSE TO HAART (N=122)



Estimated change from baseline one year after initiation of HAART

• CD4 COUNT: ~250 cells/mm³ higher at one year

• CD4 PERCENT: ~3% higher at one year

DISCUSSION

CONCLUSIONS:

• Virologic and immunologic response to HAART in West African children is similar to the response observed in North American and European children despite probable differences in viral subtypes.

• Although clinical endpoints were not assessed, these results suggest that HAART will be an effective public health intervention for the treatment of pediatric HIV/AIDS in Côte d'Ivoire and similar populations.

• The prevalence of severe or life-threatening laboratory abnormalities, particularly depressed hemoglobin and elevated amyase, among untreated children is high.

• Pre-treatment screening programs to identify prevalent laboratory abnormalities and address their underlying causes will be a necessary component of programs aimed at delivering antiretroviral therapies.

• Many children who are eligible for, and in need of, HAART fail to return for treatment. Lower socioeconomic status and less advanced disease are associated with the failure to return for treatment.

• Strategies to improve retention are called for, and additional efforts are needed to identify and remove barriers to available treatment.

LIMITATIONS:

• **Selective attrition:** Children who remain in follow-up tend to have better outcomes than those who drop out because of toxicity, treatment failure, loss to follow-up or death. Thus, our results may overestimate the true virologic and immunologic response and underestimate the incidence of laboratory abnormalities.

• **Participation bias:** Many children who were eligible for treatment did not receive treatment. Results will be biased to the extent that these children differ from those who did receive treatment.

• **Fewl events:** Because of the variability in frequency and timing of laboratory measurements, the small size of the study population, and the high loss to follow-up, our findings should be interpreted with caution. These data describe the public health impact of HAART, and should not be taken as an assessment of the biologic efficacy of HAART. For this reason, confidence limits are not given.

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