ORIGINAL PAPER

Prevalence of Clinical, Immunological and Virological Failure among Children on Haart at the University Teaching Hospital, Lusaka, Zambia

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ABSTRACT

Background: There is increasing evidence that the current clinical and immunological monitoring tools are not sufficient to identify early enough patients who are failing on treatment. Development of resistance to the limited treatment options for children and premature switching are the dangers. The objective of this study was to review patient records to see how well WHO staging, CD4 profiles and viral load estimations relate in children on treatment at the University Teaching Hospital (UTH).

Methods: A retrospective chart review of all children aged between 0-19 years that started treatment between January 2004 and Dec 2010 was carried out at the UTH. Systematic sampling was done of every second child who received HAART for more than 24 weeks, with at least one viral load (VL) reading beyond 24 weeks of treatment. Six-monthly clinical (WHO staging) immunological (age- related CD4 count/%) and virological data were collected until last follow-up review or five years on treatment. The 2010 Zambian Pediatric Guidelines were used to gauge age-related clinical, immunological and virological failure (VL> 1,000).

Results: A total of 517 patient records were reviewed (table 1). Mean age at ART initiation was 7 years ((SD 4.7yrs). Mean time after ART initiation when first viral load test was done was 2.7 years (SD 1.5yrs). Of all the viral loads done, 64% (328) had a routine indication for patients on treatment nearing the 3 year mark (mean 2.7 years). In 40% of children the first viral load test result was above 1,000 after 24 weeks or more of treatment. A total of 482 patients had WHO staging done at the time first VL test was done. Of the 359 patients (table 2) with a clinical stage I/II (not severely immunosuppressed), 41% were failing virologically. On the other hand, 63% of the patients with clinical stage III/IV had a VL below 1,000. Table 3 shows that there were 509 patients who had an immunological staging done at the time first VL was done. Of the 106 patients who were failing immunologically, 28% were virologically well suppressed. On the other hand of the 403 who were immunologically doing fine, 32% were failing virologically.

Conclusions: Clinical staging and Immunological monitoring in children on ART does not accurately identify those that are failing. A push for routine, affordable virological testing is needed to identify treatment failures early to prevent development of ART resistance and to avoid premature switches to second line in those who are actually well suppressed.

INTRODUCTION

Regular plasma HIV viral load testing is part of the standard of care for the follow-up of HIV-infected children in the developed world. However, in most resource-limited settings, including Zambia, the decision to initiate and monitor ART in children and adolescents relies on clinical and/or immunological assessment. As the scale up of ART programs continues to reach the needy and children stay on treatment for a longer period of time, more information is needed to define the optimal treatment monitoring modality in both adults and children.

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The Pediatric ART program in Zambia was launched in 2004 and has rapidly scaled up since. Routine monitoring is done using clinical and immunological parameters and viral load testing in Zambia is limited to very select patients failing on first or second line therapy and patients under study conditions.

The Department of Paediatrics and Child Health at the University Teaching Hospital (UTH) was among the first sites in Zambia to provide treatment to children.Implementation of routine provider initiated counseling and testing at the UTH, contributes to over 95% of children testing and large numbers referred to care and treatment program. At initiation of the program, clinical outcomes and CD4 counts were used as the mainstay of monitoring patient progress. To date close to 4,000 children have been initiated on treatment from the UTH program. Most of these children were perinatally infected and with early intervention, many have survived into adolescence and adulthood. Routine clinical and immunological monitoring is carried out at least once every six months.

Since September 2007, the laboratory capacity has improved and viral load testing is performed more frequently especially for patients who have been on HAART for 3 years or more. To date (July 2011) just over 1,000 patient samples have been tested, yet no analysis has been done on the levels of viral suppression, or the relationshipbetween the viral load and routine clinical and immunological criteria used to monitor the children. There is increasing evidence that the routine clinical and CD4 monitoring, may not be sufficient to identify early enough patients who are failing on first line treatment. The development of viral resistance to a number of drugs poses a great danger and limits treatment options for the future[1]. On the other hand, using clinical and CD4 monitoring to determine failure may not be predictable and could result in premature switching to expensive second line treatment. Cost is cited as the main reason for not using routine viral load testing, however the cost of resistance and second line treatment is a much higher price to pay[2]. Recent developments, with cheaper point-of-care viral load tests that are on the horizon need to be explored for routine use in resource limited settings[3].

The study was carried out to review clinical (WHO stage), immunological (age-related CD4 profile) and virological outcomes among the pediatric and adolescent population at UTH.

METHODS

This study was a retrospective chart review of routinely collected patient data from a cohort of HIV positive children and adolescents between 0 to 19 years that started treatment between January 2004 and Dec 2010 in the Department of Pediatrics, at the University Teaching Hospital. Systematic sampling was done of every second child who received HAART for more than 24 weeks, with at least one viral load reading beyond 24 weeks of treatment. A total of 517 patient records were reviewed. Six-monthly WHO staging, immunological and virological data were collected until last follow-up review or up to five year time point on treatment. The 2010 Zambian Pediatric Guidelines were used to gauge clinical stage, age-related immunological status and virological failure (viral load > 1,000). For the majority of patients there was a one off viral load test done during the course of treatment, majority around 3 years of treatment.

Data was entered using Microsoft Access and analyzed using SPSS version 18.0. Initial univariate analysis to describe frequencies was run, followed by bivariate analysis of clinical WHO staging and CD4 against viral load (dependent variable).

RESULTS

Baseline characteristics of the patients

A total of 517 patients were included in the study. Highlights of baseline characteristics are presented in **Table 1** below**.** Females accounted for 48% of all the children. At first contact/enrollment into ART program, 77% were eligible for treatment based on either CD4 count or clinical staging. Clinical staging at initiation of ART was documented in 95% (n=471) of the patients. The majority (78%) were in WHO stage III and IV.

Of all 517 patients, the initial VL results after 24 weeks of treatment (indication of the VL was for routine purpose in 64%) showed that 40% had a VL above 1,000, indicating failure after at least 24 weeks of therapy. A total of 168 (32%) were switched to second line treatment in the follow up period (beyond 24 weeks and up to five years). The decision to switch was based mainly on viral load criteria (73%) with clinical and/or immunological criteria supporting this switch in 26% of patients. Self-reported adherence data though captured in the data collection form, were not taken into account in this analysis. Outcome data shows that 91% of patients were with the UTH PCOE program by 31st July 2011.

Table 1: Baseline characteristics of Children on HAART at the UTH PCOE

Baseline Characteristic	Value
Demographics/Social	
All patients	517
Female	48%
Median Age at ART initiation	7 years (1mth – 17 yrs)
Orphaned (n=233)	45%
Clinical/immunological at initiation	
Clinical Stage done at initiation (n=491)	95%
III and IV	78%
Initial BMI Z -score -2 or less	30%
Initial hemoglobin (mean)	10 (4 – 21)g/dl
CD4% (children Less than 2 years at initiation (n=112)	
CD4 count children above 5 years (n=307)	
CPT prophylaxis at or before initiation	84%
TB treatment at enrollment/initiation	13.5%
Eligible for ART initiation at enrollment	77%
Viral Load	
Initial Viral Load test - mean time after initiation	33 months (2.7 yrs)
Initial VL test result above 1,000	40%
Antiretroviral treatment : Initial ART drug choice	
AZT/3TC/NVP or EFV	44%
D4T/3TC/NVP or EFV	52%
Switch to second -line (n=168)	32%
Reason for switch based on VL	73%
Outcome n (%)	
Active on treatment (up to July 2011)	91%
Outcome of those not active (n=47)	
Transferred Out	19%
Lost to follow up	70%
Died	11%

Prevalence of clinical failure

Table 2: WHO Staging at the time first viral load was done

		Viral Load (copies/mL)		TOTAL
		< 1000	> 1000	
WHO Staging at first VL	I and II	210 (58.5%)	149 (48.5%)	359
	III and IV	78 (63.4%)	45 (36.6%)	123
TOTAL		288 (59.8%)	194 (40.25%)	482

Table 2 shows that a total of 482 patients had WHO staging done at the time first VL test was done. Of the 359 patients with a clinical stage I or II (not severely immunosuppressed), 41% were failing virologically. On the other hand, 63% of the patients with poor clinical picture (clinically severely immunosuppressed); had a viral load below 1,000.

Prevalence of Immunological Failure

Table 3: Immunological Failure at the time first viral load test done

		Viral Load (copies/mL)		TOTAL
		<1000	>1000	
Immunological Status	Immunological failure	30 (28.3%)	76 (71.7%)	106
	Immunologically stable	273 (67.7%)	130 (32.3%)	403
TOTAL		303 (59.5%)	206 (40.5%)	509

Table 3 shows that there were 509 patients who had an immunological staging done at the time first VL was done. Of the 106 patients who were failing immunologically, 28% were virologically well suppressed. On the other hand of the 403 who were immunologically doing fine, 32% were failing virologically.

Prevalence of Virological Failure at 3 years and 5 years of treatment

Table 4: below shows the number of VL tests done at 36 and 60 months of treatment

VL after ART initiation	# still on follow -up	Total # VL tests	VL Failure (above 1000)	Routine Indication	Clinical / immunological Indication	VL done while on second line
VLat 36 months	399	141	57 (40%)	87 (62%)	37 (26%)	17 (12%)
VLat 60 Months	172	88	33 (37.5)	47 (53%)	16 (18%)	25 (28%)

Of note is that at **3 years (36 months)** of treatment, there were still 399 patients being followed up. 141 patients had a VL test done and 40% were failing (either on first or second line of therapy). The majority had a routine indication for VL test (62%). A more detailed look at this time point showed 124 (88%) of the patients were still on first line treatment with 40% (50/124) failing on their first regime. Of the 17 on second line treatment, 7 patients were still failing virologically.

A further analysis at the 5 year (60 month) time point showed that there were 172 patients still on treatment 88 patients (51%) had a VL test done with nearly half (53%) having a routine indication for the test. From the 88 with VL done, 63 (72%) were still on first line drugs with 59% (37/63) well suppressed and 41%

(26/63) failing on first line at 60 months of treatment. Of the remaining 25 (25/88) who were on second line by 60 months of treatment, a further 6 were failing on their second line drugs.

DISCUSSION

In Zambia CD4 testing is available in all ART sites (onsite or remotely) therefore immunological criteria are widely used to determine treatment failure. Many studies in adults have shown that clinical and immunological criteria do not correlate well with virological failure[4,5,6].

In this study WHO clinical staging did not relate well with the viral load test results. Table 2 shows that 41% of patients who seem to be doing fine on WHO clinical staging, are failing virologically. On the other hand, 63 percent of the patients are clinically doing poorly (stage III and IV), but when the corresponding viral loads are taken they are actually well suppressed.

Studies in children in resource limited settings have been limited to clinical and CD4 outcomes as illustrated by studies in South African[7](Janssen et al) and Zambia[8](Bolton-Moore et al). Both these studies document "good" clinical/immunological outcomes, but they were limited in their ability to measure corresponding viral load outcomes.

Relationship between Immunological criteria and viral load in this study showed some worrying trends (table 3). The CD4 criteria wrongly identified those that are failing in 28% (30/106) of the patients who, without VL testing would have been switched to second line treatment. This would have resulted in a significant number being switched to second line therapy prematurely. Conversely 32% (130/403) were failing virologically but not detected by CD4 estimations and these would have been continued on a failing regime, breeding multiple resistance to current drugs. In a closely monitored cohort of 300 HIV infected children in Uganda [9] viral suppression rates were high (83%) beyond 24 weeks of therapy, however, 19 out of 20 children with sustained viremia were not detected using age related CD4 criteria for treatment failure. Similarly a study in Tanzania [10] that followed up a much smaller number of children who had been on treatment for a longer period (median three years three months) found that 11 out of 19 children were virologically failing. In spite of this widespread failure, only one child was failing clinically and none had CD4 criteria to suspect treatment failure.

The virological failure rates in children in our study are high (40%) beyond 24 weeks of therapy (40% at 36 months and 41% by 60 months for those still on first line). Similar reports in children with long term follow-up have been made by others. Song[11], 2007, in a study in Kenya showed that 45% of children were not suppressed virologically after 9 months of treatment. Bratholm followed up 19 children in a Tanzanian study with VL results for a median for 40 months and found that 58% were failing on treatment. The numbers with VL results in this particular Tanzanian study were small, but few studies have assessed long term follow up. Other studies showed better outcomes; at up to 4 years follow up of 250 children who had VL 80% were well suppressed[12]. Davies et al (2009)[13] reported excellent treatment outcomes in a large pediatric multicenter cohort in South Africa with 82.4% of the children well suppressed after 3 years on ART.

Adult virological failure rates after long term therapy in many studies are much lower than this: 6% in a Ugandan study[14] with median three year follow-upand 12 % in a study that followed up patients for four years in rural Tanzania[15]and 16% failure in a South African study[16] (2-4 yrs. follow up).

Our study looked at a number of variables, and further analysis will be carried out on the prediction of viralogical failure using immunologic criteria; relationship between reported adherence rates and VL failure as well as stratification by adolescent age group and indication for VL testing - routine versus clinical or immunological indication. Finally, the role of malnutrition in determining virological failure needs to be explored. These subsequent findings may shed more light on the outcomes reported so far.

CONCLUSIONS

This study shows that clinical staging and immunological monitoring in children on ART does not accurately identify those that are failing. A push for routine, affordable virological testing is needed to identify treatment failures early to prevent development of ART resistance and to avoid premature switches to second line in those who are actually well suppressed.

RECOMMENDATIONS

1. There is need to advocate the use of routine viral load testing in Zambia for an efficacious monitoring of ART program.
2. A further study is required to determine the long term outcomes of HAART in children in whom the viral load is used as a gold standard for follow up beyond 36 months.

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