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Disease Progression in HIV-1 Infected Children and Adolescents – Results of a German-Austrian Cohort Study

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Abstract

Objective: The Paediatric Working Group AIDS (PAAD) initiated a prospective cohort study in order to investigate disease progression in HIV- infected children and adolescents and the effect of antiretroviral treatment regimes.

Patients and methods: Between 1998 and 2003, paediatric centres documented HIV-infected patients under clinical care using a questionnaire for basic data and annual follow up. Main outcome measures were: use of antiretroviral therapy, adverse events, disease progression and change of therapeutic regimes.

Results: 174 HIV- infected paediatric patients were followed up in 12 centres in Germany and Austria between 1998 and 2003. Initially 54 (31%) patients had no antiretroviral therapy, 35 (20%) received a two-drug regimen (ART) and 85 patients (49%) a highly active antiretroviral therapy (HAART ≥ 3 drugs). After an observation period of 5 years, 8 patients (4%) had no therapy, 17 (10%) were on ART and 134 patients on HAART (77%). The number of patients with salvage therapy (≥ 4 drugs) increased from 5 (3%) to 15 patients (9%). 72 of 166 treated patients (43%) had no change of their drug regimes, 68 patients (41%) had one change and 26 patients (16%) ≥ 2 changes. Main reasons for changes were increased viral load (49%), immunologic deterioration (21%) and adverse events (14%).

During the follow up period no patient died. According to the CDC classification, disease progression was seen in 48 of 174 patients (28%), of whom 20 had deteriorations of clinical categories (A, B, C) and 28 of immunologic categories. Using Kaplan-Meier curves, the mean time from study onset until change of clinical categories was 61 months for patients on HAART, 26 months for patients on ART and 14 months for patients without ART.

Conclusion: In paediatric patients with HIV infection, disease progression has declined substantially by introduction of HAART. Superiority of HAART compared with ART was demonstrated. Non-adherence as well as other reasons for treatment failure have to be studied more carefully.

Key words: HIV, children, cohort study, disease progression

Introduction

Antiretroviral therapy with three or four drugs, established for adults infected with HIV1 since 1996, has led to prolonged survival time and an improved quality of life [1, 2, 3]. For children, however, the lack of age specific pharmacokinetic data and appropriate formulations delayed the introduction of HAART. Until the end of the 1999 [4], German paediatric treatment guidelines recommended the use of dual as well as triple antiretroviral therapies. As treatment data were limited and the observation period of most clinical studies was short, the Paediatric Working Group AIDS (PAAD) initiated a prospective cohort study in order to investigate disease progression and adverse events in HIV- infected children and adolescents on different therapeutic regimes. Whereas published studies have focussed mainly on the effect of new drugs or new drug combinations, we were also encouraged to document the frequency of therapeutic changes, reasons for changes and the percentage of patients without antiretroviral therapy. These data should provide a comparison of therapeutic effects within the period 1998 to 2003 with those of later periods.

Patients and Methods

The paediatric cohort study was started in January 1998 and a total of 203 children and adolescents were enrolled. All patients were treated and prospectively followed up by 12 centres in Germany and Austria. 4 patients changed hospitals during the observation period, in 3 of whom the documentation could be continued; the remaining patient was lost to follow up. All children with an annual follow up over a 5-year period (1998 to 2003) were included in the analysis. Whereas data of 174 children fulfilled the required criteria, 29 patients had to be excluded because these patients had less than five follow up during the observation period. In each centre, a member of the medical staff completed the standardized questionnaires. After changes of therapeutic regime, a second documentation was requested within two months. The dataset included demographic information, data on clinical events, antiretroviral

therapy, adverse events, reasons for changes of therapeutic regimes, results of T-cell subset- and HIV RNA viral load tests. Clinical and immunologic categories were defined according to the CDC classification [6].

Patients received antiretroviral therapy according to the national guidelines of the PAAD [4, 5]. Treatment was started when patients (age >1 year) entered category B or 2 or when patients in category A1 had a plasma HIV-1 RNA >100.000 copies/ml. The national guidelines from 1998 allowed two- and three-drug-combination, whereas the guidelines from 2001 recommended HAART for all children.

Statistical Methods

Statistical evaluation of the data was performed by the Department of Biostatistics, Paul-Ehrlich-Institute. In order to estimate disease progression, immunological and clinical categories of all 174 patients were reported during the observation period. According to the CDC classification, mild symptoms of immunodeficiency were classified as category A, moderate symptoms as category B and severe symptoms as category C. CD4- cell counts >25% corresponded with category 1, ≤25% with category 2 and ≤15% with category 3.

Time to progression was defined as the time until the first aggravation of CDC category starting from the CDC category at first visit. The Kaplan-Meier product-limit method was used to calculate time to progression for all patients in each CDC category and to compare the effect of ART and HAART. Data of patients who had no disease progression (changes of CDC categories) during the observation period were censored. Because of the large percentage of patients without disease progression, the calculated time to progression has to be assumed as underestimated.

Whereas disease progression was described, any improvement due to antiretroviral treatment was not covered by the CDC classification and an upgrade of the immunologic categories due to an increased CD4 cell count was not allowed. The increase in CD4 cell count and the decrease of viral load after an initial antiretroviral therapy are given as tables and the difference between ART and HAART was calculated using Fisher's Exact Test.

The frequency of prescribed antiretroviral drugs was related to the number of all prescribed drugs during the 5-year period. The frequency of the chosen drug combination was related to the number of all chosen drug combination during the observation period.

We defined any drug replacement as a change of treatment, thus the frequency of treatment changes was related to the number of patients on antiretroviral therapy during the 5-year period.

Concerning the cause of treatment changes, the questionnaire offered six options: deterioration in of clinical category, deterioration of immunologic category, increase of viral load, adverse events, drug resistance and non-adherence.

The documentation of drug-related adverse events was restricted to already known severe adverse effects. Unknown effects could not be documented and therefore were not evaluated.

Results

Patients

Between 1998 and 2003, a total of 203 patients (91 female and 112 male) were enrolled. 29 patients were not included in the final analysis because of incomplete data. Evaluation was done on the basis of 174 completely documented patients, 81 female and 93 male. Mean age at study onset was 6.5 years (median: 5.9 years, range: 0.2 – 16.4 years). 149 patients (85.6%) were vertically infected, 25 (14.4%) horizontally by blood products. 10 of the 149 vertically infected patients (6.7%) had a zidovudine prophylaxis during the last trimester of pregnancy and/ or postpartum.

Primary and Secondary Prophylaxis

Of 174 patients, 30 (17%) received a primary prophylaxis with intravenous immunoglobulin mainly at a dose of 0.4g/kg bodyweight every 4 to 6 weeks. Prophylactic treatment was given to category B or category C patients who repeatedly had severe bacterial infections due to B- cell deficiency.

31 of 174 patients (17%) received a trimethoprim and sulfamethoxazole prophylaxis at a dose of 5 mg/ 25 mg per kilogram bodyweight daily or three times per week. PCP prophylaxis was given to all infants and two children with low CD4 cell counts (category 3). By the second year of life or when the CD4 cell count was > 15%, PCP- prophylaxis was discontinued in most of the children [7].

10 patients (6%) of category 2 or 3 needed limited prophylaxis with isoniazid because of tuberculosis exposure. Isoniazid was given as mono-therapy (5 mg/kg bodyweight daily) over a period of 6 – 12 months.

9 infants (age <36 months) received an antimycotic treatment (usually fluconazole suspension, 3-5mg/kg bodyweight daily) as a secondary prophylaxis for mucosal mycosis.

Antiretroviral Therapy

The follow up of 174 patients during a mean period of 5 years resulted in 873 years of treatment. During 762 of these 873 years, patients received antiretroviral therapy and during 111 years no treatment was given. Summing up the different treatment regimes the following distribution was found:

• Period without antiretroviral treatment	111 years	(13%)
• Period of treatment with two antiretroviral drugs	119 years	(14%)
• Period of treatment with three antiretroviral drugs	568 years	(65%)
• Period of treatment with four antiretroviral drugs	72 years	(8%)

Table 1. Number and frequency of prescribed drug registered during five annual follow ups.

	Number of treatment-years	**Frequency** (related to 2311 drug prescriptions in 5 years)
Nucleoside reverse transcriptase inhibitors		
Lamivudine (3TC)	451	19.5 %
Stavudine (D4T)	323	14.0 %
Zidovudine (AZT)	315	13.6 %
Didanosine (DDI)	272	11.8 %
Abacavir (ABC)	198	8.6 %
Protease inhibitor		
Nelfinavir (NFV)	334	14.5 %
Ritonavir (RTV)	93	4.0 %
Saquinavir (SQV)	35	1.5 %
Indinavir (IDV)	5	0.2 %
Boosted protease inhibitors		
Lopinavir / Ritonavir (LPV/r)	13	0.6 %
Nonnucleoside reverse transcriptase inhibitors		
Efavirenz (EFV)	186	8.0 %
Nevirapin (NVP)	86	3.7 %

During the 873 years of treatment an average of 2.65 antiretroviral drugs were prescribed per patients resulting in 2311 drug prescriptions. The number of all prescribed single drugs and frequency of prescriptions are given in Table 1.

The first follow up documented 54 of 174 patients (31%) who had not received any antiretroviral treatment. In 46 of these 54 patients (85%), treatment was started, whereas 8 patients had no treatment during the entire follow up period. 18 of 35 patients on an initial two drug- regime were changed to a three drug regimen. At the end of the observation period, 17 of 174 patients (10%) were still treated with two drugs, 134 patients (77%) with three drugs and 15 patients (9%) with four or more drugs in parallel. 72 of 166 treated patients (43%) had no change of treatment, 68 patients (41%) had one change, 22 patients (13%) had two changes and 4 patients (3%) had three changes. A total of 94 changes of antiretroviral regime were reported in 166 patients during the observation period.

Documented reasons for changes in therapeutic regime were an increase of viral load (49%), decrease of CD4 cell count (21%) and disease progression (2%). Adverse events were registered as the main reason in 14% of all changes, drug resistance and non-adherence each with 7%.

Changes of Antiretroviral Regimes

During the follow up period (1998 – 2003), the frequency of regimes with three NRTI decreased from 20% to 8%, whereas the frequency of regimes with NRTI and PI increased from 35% to 40% and of regimes with NRTI and NNRTI increased from 11% to 30% (Fig. 1). At the end of the documented period, antiretroviral combinations containing boosted PI were given to 9 % of treated patients as well as salvage therapy with ≥ 4 drugs.

Adverse Events

Documentation of adverse events was restricted to the 12 items of the follow up- questionnaire. In total, 63 of 166 treated patients (38%) had transient or persisting treatment associated adverse events. The frequency of adverse events was given as percentage of all treated patients during the full observation period (mean value) and also as range describing the variation during the five years of follow up.

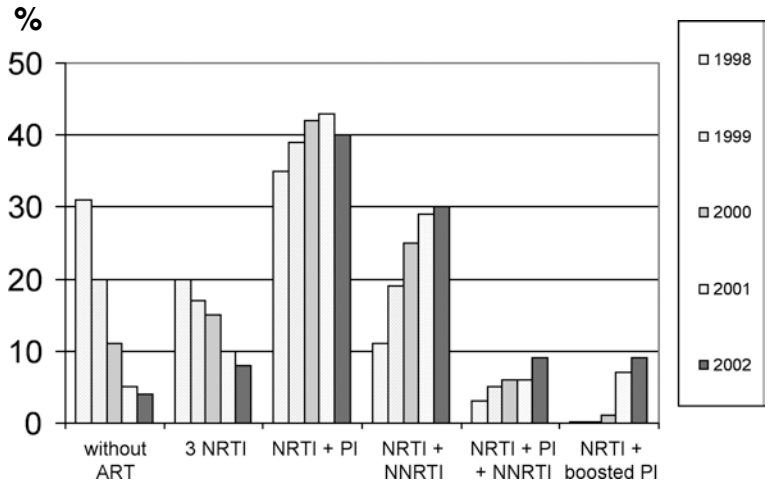

Fig. 1. Changes of antiretroviral regimes during a follow up period of 5 years.

Table 2a. Data of 46 patients of category 1, 2 and 3 two months after the onset of a first-line treatment. Viral load related to immunologic category and antiretroviral regime.

Category	ART (2 drugs) Reduction of viral load to cop./ml			HAART (≥ 3 drugs) Reduction of viral load to cop./ml			Sum
	≤ 50	51-500	> 500	≤ 50	51-500	> 500	
1	1	0	1	4	2	1	9
2	1	0	4	5	1	7	18
3	0	2	4	7	1	5	19
Sum (1-3)	**4**		**9**	**20**		**13**	**46**

Table 2b. Data of 37 patients of category 2 and 3 two months after the onset of a first-line treatment. Increase of CD4- cell count related to immunologic category and antiretroviral regime.

Category	ART (2 drugs) Increase of CD4- cell count			HAART (≥ 3 drugs) Increase of CD4- cell count			Sum
	> 15%	> 25%	unchanged	> 15%	> 25%	unchanged	
2		2	3		11	2	18
3	2		4	11	1	1	19
Sum (2-3)	**4**		**7**	**23**		**3**	**37**

Transient diarrhoea was reported annually in a mean of 10% of all patients and was the most common adverse event in children, ranging from 12% to 9 % within the 5-year period.

Transient or persisting hyperlipidaemia was the second common adverse event, reported in 6% of all treated patients (range: 7% - 4.5%). Single parameters of lipid profiles and the course of blood values were not documented.

5% of our patients had unspecific gastrointestinal complaints (range: 5.8% - 4.2%), transient bone marrow depletions such as anaemia, neutropenia and thrombocytopenia were seen in 4% (range: 5.8% - 3.1%). Skin rash and allergic exanthema were reported in 3.5% (range: 3.6% - 2.5%), but were usually a temporary reaction. Abacavir hypersensitivity occurred only in one patient during the observation period.

Nephrolithiasis and episodes of unspecific weakness were rare adverse events, documented in 2% (range: 2.4% - 1.8%) and 1.5% (range 1.8% - 1.2%) of patients on antiretroviral therapy respectively.

Lipodystrophy was also a rare event (mean: 1.8%), but the frequency increased slightly from 1.2% to 2.4% during the study period.

Onset of Antiretroviral Therapy

46 patients started with antiretroviral therapy during the observation period. CD4 cell count was documented before onset and within 2 months after onset of treatment. 9 patients of category 1 started with their treatment because of increased viral load (HIV-1 RNA > 100.000 copies/ ml). Antiretroviral therapy was started in 18 patients of category 2 and in 19 patients of category 3. 13 children received a regime with 2 drugs and 33 patients with three drugs (Table 2a).

Within 2 months after the onset of therapy, 24 of 46 patients had a reduction of viral load < 500 copies/ml, representing a sufficient antiretroviral effect. In 22 of 46 patients, values < 500 copies/ml were not attained. Comparing patients with ART and HAART, 4 of 13 patients (31%) on a two-drug regime had a sufficient viral load reduction and 20 of 33 patients (61%) on three-drug regime. The difference was distinct but not significant (p-value: 0.103; Fisher's Exact Test).

For a complete viral load reduction a significant difference could be demonstrated. 2 of 13 patients (15%) on a two-drug regime and 16 of 33 patients (48%) on three-drug regime had a viral load < 50 copies/ml (p-value: 0.049; Fisher's Exact Test).

Statistical analysis was also done comparing 37 patients, who were in category 2 or 3 at treatment onset. After 2 months, 27 of these 37 patients had an increased CD4 cell count, which would represent an improvement of their immunologic category (Table 2b). 10 patients had no increase of their CD4 cell count. Comparing the effect of ART and HAART, 4 of 11 patients (36%) with a 2-drug regime showed a relevant increase of CD4 cell count and 23 of 26 patients (88%) with a 3-drug regime (p: 0.0026; Fisher's Exact Test).

The median increase of CD4 cell count in 9 patients of category 1 was 4% (absolute CD4 cell count: 288/µl) with a range of 1% to 4% (absolute: 47 – 740/µl).

Disease Progression

During the first and fifth follow ups, 20 of 174 (11.5%) patients showed a worsening in clinical category (A to B, B to C). All patients had a progression of one category (Table 3a). No case of AIDS related death was reported between 1998 and 2003.

28 of 174 patients (16.1%) changed immunologic category. 27 patients had progression of one category; one patient of two categories (Table 3b). A sustained

Table 3a. Disease progression of 174 HIV- infected paediatric patients. Change of clinical categories between the first and fifth follow up.

Disease progression	**Category A**	**Category B**	**Category C**	**Sum (5. follow up)**
Unchanged	108 (62%)	30 (17%)	16 (9%)	154 (88.5%)
Degrade (one category)	11 (6%)	9 (5%)	-	20 (11.5%)
Sum (1. follow up)	119 (68%)	39 (22%)	16 (9%)	174 (100%)

Table 3b. Disease progression of 174 HIV- infected paediatric patients. Change of immunologic categories between the first and fifth follow up.

Disease progression	**Category 1**	**Category 2**	**Category 3**	**Sum (5. follow up)**
Unchanged or improved	68 (39%)	47 (27%)	31 (18%)	146 (83.9%)
Degrade (one category)	20 (11%)	7 (4%)	-	27 (15.5%)
Degrade (two categories)	1 (1%)	-	-	1 (0.6%)
Sum (1. follow up)	89 (51%)	54 (31%)	31 (18%)	174 (100%)

Table 4. Analysis of time to progression of 174 paediatric patients during the period 1998 - 2003.

Clinical category (A, B, C)	**Number of patients**	**time to progression Mean [months]**	**Standard deviation**	**Log-Rank-Test**
Total number of patients	174	58.8*	1.22	
Patients without therapy	14	13.6*	1.31	
Patients with 2 drugs	27	26.0*	1.16	**0.0491**
Patients with ≥ 3 drugs	133	61.0*	1.12	
Immunologic category (1, 2, 3)				
Total number of patients	174	46.5*	1.21	
Patients without therapy	24	24.2*	3.25	
Patients with 2 drugs	23	20.2*	0.75	**0.1514**
Patients with ≥ 3 drugs	127	50.5*	1.06	

* The mean time to progression and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

increase of CD4 cell count which is not categorised by the CDC classification was registered in 25 patients (14.4%), 4 category 3 patients had an increase of CD4 cell count equivalent to an improvement of two categories.

Analysis of Time to Progression

Time to progression was defined as the time until the first aggravation of CDC category starting from the CDC category at first visit.

Analysis of all 174 patients revealed a mean time of 58.8 months for a change in clinical category and of 46.5 months for a change in immunologic category (Table 4, Fig. 2).

Comparing the time to the first aggravation of clinical category, a significant difference (p-value: 0.0491 Log-Rank test) was seen between patients with a two-drug combination (mean time to progression: 26.0 months) and patients with three- drug combination (mean time to progression: 61.0 months).

Also analysis of the times from first observation to the first aggravation of immunological category revealed a strong advantage of the three-drug combination (50.5 versus 20.2 months), without demonstrating a statistical significance (p-value: 0.1514).

Discussion

Progression

The introduction and increased use of a highly active antiretroviral therapy (≥ 3 drugs) can reduce disease progression in HIV-infected patients as demonstrated by cohort studies with both adult [8, 9] and paediatric patients [10, 11, 12]. The investigations published until now have focused on the progression to AIDS (from category B to category C) or to death and the effect of treatment was mainly expressed by the evaluation of the specific „hazard ratio".

In our cohort, only 9 of 174 patients (5.2%) changed from category B to category C and no HIV-associated

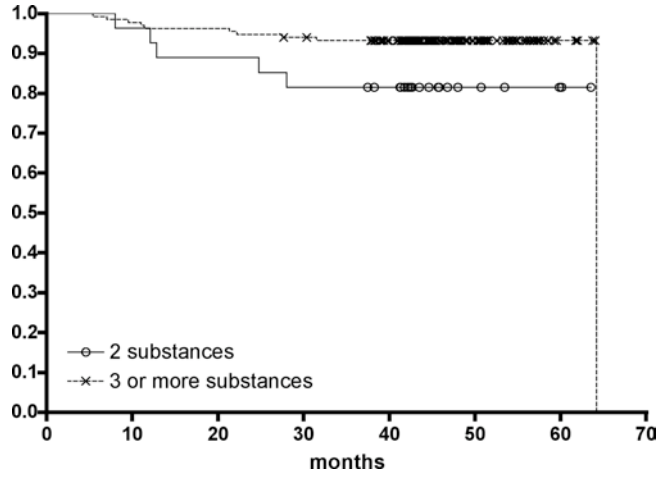

Fig. 2. Time to progression curves (Kaplan-Meier-Plots). Time (months) from first observation to first aggravation of clinical category (A, B, C) for all patients stratified for medication before aggravation (2 substances, solid line: 27 patients, 5 aggravations, 22 censored; 3–4 substances, dashed line: 133 patients, 10 aggravations, 123 censored).

death was reported within a period of 5 years. In order to describe disease progression of our patients, we evaluated any deterioration of clinical and immunologic categories. As only the first aggravation of CDC categories was calculated, the Kaplan-Meier method could be used. According to the national guidelines, antiretroviral treatment was started in category B or category 2 patients or when viral load in category A- patients increased distinctly (>100.000 copies/ml). In so far published studies, antiretroviral treatment was started when paediatric patients entered category B [10, 11, 13], whereas many of our patients received treatment when the viral load increased and before entering category B. Therefore comparison of disease progression of former studies and our cohort is difficult and of limited value [12]. We estimate a time to progression of 61 months for paediatric patients on HAART to change clinical categories and an interval of 50 months to change immunological categories. Although these intervals certainly underestimate the real time course of disease progression, it will help us to compare the effect of future antiretroviral regimes.

Antiretroviral Therapy

By 2003 the majority of our patients had received a highly active antiretroviral therapy whereas the percentage of patients on a two drug- regime had fallen to 10%. The statistical evaluation of the short-term effect as well as the long-term effect demonstrated a clear advantage of HAART. Decrease of viral load and increase of CD4 cell counts as well as reduction of disease progression were improved in patients on HAART. Only a third of all patients on a first line two-drug- regime demonstrated a sufficient reduction in viral load (< 500 copies/ ml) compared with two-thirds of patients on a three-drug regime. Former clinical trials have demonstrated a sufficient reduction of viral load (< 500 copies/ ml) in 44% to 61% of the initially treated patients 12 months after the onset of a two-drug- regime or an early three-drug regime [14, 15, 16]. A recently published study has demonstrated sufficient reduction of viral load (< 400 copies/ ml) in 85% and complete viral suppression (< 50 copies) in 72% of paediatric patients for at least two years of antiretroviral treatment [17], emphasising the potency of the actual three or four drug combinations.

Change of Regimes

Regarding change of antiretroviral regime, we recorded 94 changes in 166 treated patients during the 5-year observation period. The main reason for these changes was an increasing viral load on an initially successful regime. To improve the long-term effect, a higher percentage of our patients were put on combination with a reduced number of tablets. These regimes are easier to manage and may therefore improve adherence. Initially, combinations with boosted PI were only used as a third line therapy in order to obtain a sustained suppression of viral replication in drug experienced patients. At the end of our observation period, an increasing percentage of patients were switched to regimes including boosted PI. These combinations are now accepted as first line regimes. Finally an increasing number of our treated patients received salvage therapy including four and more drugs after a period of 5 years. Because of repeated treatment failure in these patients, salvage therapy seemed the only option to control viral replication.

In order to minimise the appearance of drug resistance and treatment failure, since 2001 our national guidelines recommend antiretroviral regimes which are able to suppress viral load < 50 copies/ml [5]. Furthermore, it is recommended to change the treatment regime quickly when the viral load is persistently > 500 copies/ml in patients with an initial successful treatment.

Adherence

More than a half of our patients had one or more changes of their antiretroviral regime during a 5-year period which seems relatively high. Besides increase of viral load and decrease of CD4 cell countdisease progression, adverse effects and non-adherence were reported as the most important reasons for change. According to published data, incomplete or non-adherence was found in up to 30% of children and adolescents on antiretroviral therapy [18, 19]. Both studies emphasised the complexity of the problem because

adherence is influenced by multiple factors, including medication characteristics, and psychosocial characteristics of both patients and their families.

In order to improve adherence, the family background of the child has to be considered and the capacity of the medical staff has to be improved. In our experience, adherence is an issue which should be regularly discussed with the patients by paediatricians and other professions such as social workers or nurses. This issue also has to be considered more carefully in our ongoing cohort study.

Adverse Effects

Reported reasons for changes in therapeutic regime focused on an increase of viral load and a decrease of CD4 cell count, whereas adverse events and non-adherence were registered only in 14% and 7%, respectively, of all changes. Compared with prospective studies the reported incidences of adverse events and non-adherence in our cohort study are quite low. This could be explained by the tendency to report rather the effect than the reason of treatment complication. Therefore future questionnaire should clearly distinguish between reasons and effects.

Among the reported complication transient diarrhoea was the most common adverse event, although the symptoms were normally mild and transient. Therefore educating both parents and children will help to overcome this problem. In contrast, hyperlipidaemia, the second common adverse of our cohort is of greater importance. Several studies have demonstrated transient or lasting elevated values of cholesterol and triglycerides in up to 65% of paediatric patients [20, 21], especially in those on protease inhibitor-containing regimes. At present it is too soon to assess the persisting dyslipidaemia and therefore difficult to estimate the long-term complications in children. The benefit of interventions such as exercise, diet or a lipid-lowering drug therapy has not been demonstrated. Therefore, lipid levels should be measured regularly in children on antiretroviral therapy and clinical manifestations need to be reported carefully.

Summarising our data we conclude that disease progression could be significantly reduced and the quality of life increased dramatically when sufficient three drug regimes are used in paediatric HIV- infected patients. Cohort studies are of great value to investigate the long-term benefit and complications and can help to improve therapeutic strategies.

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