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Virological and Immunological Long-Term Outcome of Human Immunodeficiency Virus-1 Infected Children Treated before One Year and after Two Years of Age in a Resource-Limited Setting of South Africa

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Abstract

Introduction: Benefits of early Highly Active AntiRetroviral Therapy (HAART) to reduce infant mortality and morbidity have been demonstrated in resource-limited and rich settings. However, immunovirological data collected in Sub-Saharan Africa are scarce. This study describes the long-term outcome of South African children who started HAART before one year of age (Early Starters Cohort or ESC) and compare their immunovirological outcomes to children who started their therapy after two years of age (Late Starters Cohort or LSC). Immunovirological results will be compared in order to evaluate the long-term non-inferiority of early treatment initiation.

Methods: Fifty-five children were included in the ESC (mean follow-up period 7.9 years) and 96 children were included in the LSC (mean follow-up period 6.3 years). Children from the ESC and the LSC were subdivided into three subgroups according to CD4$^+$% at HAART initiation (<15%, between 15-24% and ≥ 25%).

Results: All children included in the ESC achieved normal CD4$^+$% at least once during the entire follow-up period, contrary to the LSC where 89.6% children achieved normal CD4$^+$% (p=0.014). Furthermore, mean CD4$^+$% became higher in the ESC six years after treatment initiation. Children with CD4$^+$% between 15 and 24% at HAART initiation reached higher CD4$^+$% in the ESC, three years after treatment initiation. The proportion of children who experienced virological failure (>1000 cp/ml) was comparable in both cohorts but persistent undetectable viral load (<50 cp/ml) after initial virological suppression was more frequent in the ESC (p=0.008). Finally, the proportion of children with detectable viral loads (50 to 1000 cp/ml) at least once after initial virological suppression was higher in the LSC (p=0.0022).

Conclusion: HAART appeared highly effective in terms of immunovirological outcomes both in children treated before one and after two years of age. The results of this study demonstrate that early treated children more often achieved normal CD4$^+$%, tended to have higher mean CD4$^+$% and more sustained virological suppression. These results encourage the current international recommendations to initiate HAART as soon as possible in RLS.

Keywords: HIV; Children; Resource-limited setting; Long-term; South Africa; Treatment

Introduction

In 2010 the World Health Organization (WHO) recommended an immediate start of Highly Active AntiRetroviral Therapy (HAART) in all patients diagnosed with HIV before 2 years of age [1]. This recommendation was extended to children younger than 5 years of age in 2013 [2] and to all children and adults in 2015 [3]. Benefits of early treatment initiation on infant mortality [4,5], neurodevelopmental outcome [5,6], growth recovery [7], immunologic restoration and virological suppression [8,9], have been demonstrated in short term follow-up studies implemented in resource-limited settings (RLS). A systematic review including 5 African studies, showed a 12 months HIV RNA suppression rate of 70% and a CD4$^+$ cell percentage (CD4$^+$%) increase of 13.7%, for children initiating HAART in RLS [10].

Between 2005 and 2014, children treated with HAART increased from 71.500 to 824.000 [11] but long-term (>3 years) virological and immunological data collected in Sub-Saharan Africa are scarce [12-16]. Children are at risk to develop treatment failure due to inappropriate antiretroviral formulations, adherence difficulties, drug toxicity or development of resistance [17].

The aim of this study is to describe the long-term outcome in a real life setting of children who started HAART before 1 year of age (early starters cohort or *ESC*) and after 2 years of age (late starters cohort or *LSC*) in the same RLS of KwaZulu-Natal, South Africa (SA). Immunovirological results will be compared in order to know if early treatment initiation, which is a major advantage in a short-term point of view, could lead to a poorer long-term evolution in terms of CD4$^+$% and viral load (VL).

Method

Study population and setting

This non-inferiority retrospective study was conducted in SA

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between September and December 2014 at Edendale Regional Hospital located in a peri-urban and RLS of KwaZulu-Natal. The overall prevalence of HIV is the highest of SA with 16.9% of people infected [18].

In total, hundred fifty-one children were included in the present study in the ESC and the LSC.

Children in the ESC were included in a previous study about feasibility and effectiveness of early HAART initiation in RLS, which took place between 2005 and 2008 [19]. First condition to be included in this previous study was to be younger than 1 year of age at HAART initiation (median 8.6 months, range 2.1–11.9 months). Other criteria to initiate HAART included positive HIV-1 DNA PCR, WHO stage 2-4 and/or $CD4^+$% <30% [19].

Children included in the LSC were invited to participate to the present study during a planned appointment in the HIV clinic. Inclusion criteria were to have initiated HAART after 2 years of age in the HIV clinic and to be vertically infected according to HIV status of the mothers. Age at HAART initiation had to be mentioned in the patient's file. These children were not included in the previous study between 2005 and 2008 because they were older than 1 year during this period or because they started HAART after 2008. They initiated HAART in function of their WHO clinical stage, $CD4^+$% or comorbidities following the successive South African guidelines between 2005 and 2012.

Children from both cohorts came from the same region with the same socio-economical environment. They were followed-up by the local staff between 2008 and 2014 and were treated following the national recommendations.

Study procedures

Parents or caregivers gave a written informed consent prior any procedure. Data were collected from the medical files (before 2010 records on paper and later on computer). The study was approved by the South African ethical committee «Umgungundlovu Health District Review Board (UHERB)» and the Belgian Ethical committee «Comité d'Ethique Hospitalo-Facultaire Saint Luc – UCL».

Definitions

Children with $CD4^+$% <15%, between 15-24% and ≥ 25% at treatment initiation were described as low (LIS), intermediate (IIS) and high (HIS) immunological subgroups.

Virological failure was defined as a VL above 1000 copies/mL based on the annual blood check.

Viral suppression was obtained when VL was less than 50 copies/mL.

Laboratory procedures

Blood samples were analyzed during routine consultation at the Edendale Hospital laboratory. $CD4^+$ count was analyzed by flow cytometer FC 500 series® from Beckman Coulter (Paris France) and expressed as % of leucocytes and absolute value. VL was measured by real time PCR with the "COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0 (Roche Diagnostics)". The lower limit of quantification (LLOQ) was 20 copies/mL.

Current South African antiretroviral treatment guidelines

All infants and children under 3 years of age (or <10 kg) are treated with Abacavir (ABC), Lamivudine (3TC) and Lopinavir boosted ritonavir (LPV/r) when they initiate their treatment. Children over 3 years of age are treated with ABC, 3TC and Efavirenz (EFV) [20]. Before 2010, guidelines recommended to start treatment with Stavudine (d4T) instead of ABC [21].

Statistical analysis

Immunological and virological mean values were compared with the Student t test. Proportions between the ESC and the LSC were compared with the exact Fisher test. Differences in CD4 means were also tested with the non-parametric Wilcoxon test, which resulted in p-values similar to the ones obtained with the t-test.

Results

Study population

From the 94 subjects described in the 2005-2008 study [19], 55 were included in the present research (23 females and 32 males). The remaining 36 patients were transferred to other centers and lost to follow-up (33/36) or died (3/36). Mean age at inclusion was 9.6 years (range 7.1-10.5 years) with a mean follow-up period of 7.9 years (range 6.8-9.8 years).

The control group (LSC) included 96 subjects (42 females and 54 males) who initiated HAART after 2 years of age (median 4.3 years range 2.0-7.6 years) between 2005 and 2012. Mean age was 10.6 years (range 6.6-14.8 years) and the mean follow-up period was 6.3 years (range 2.5-9.8 years).

Initial therapies

In the ESC, 98% of children were initiated on HAART with a regimen including one protease inhibitor (PI) and two nucleoside reverse transcriptase inhibitors (NRTIs) and 2% with one non-nucleoside reverse transcriptase inhibitor (NNRTI) and two NRTIs.

In the LSC, 12% of children were initiated on HAART with a regimen including one PI and two NRTIs (children between two and three years of age at treatment initiation) and 88% with one NNRTI and two NRTIs (children older than three years at treatment initiation) (Table 1). Only 5 children were followed-up after 8 years in each cohort; therefore the results are not shown for any longer period of time.

PI/NNRTIs	NRTIs	ESC	LSC
Lopinavir/ritonavir	Stavudine/Lamivudine	50/55 (91%)	12/96 (12%)
Lopinavir/ritonavir	Zidovudine/Lamivudine	4/55 (7%)	/
Nevirapine	Stavudine/Lamivudine	1/55 (2%)	/
Efavirenz	Stavudine/Lamivudine	/	55/96 (58%)
Efavirenz	Abacavir/Lamivudine	/	28/96 (29%)
Efavirenz	Zidovudine/Lamivudine	/	1/96 (1%)

PI: Protease Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitors; NRTI: Nucleoside Reverse Transcriptase Inhibitor; ESC: Early Starters Cohort; LSC: Late Starters Cohort

Table 1: HAART regimen at treatment initiation in early and late starters cohorts.

Switch of therapy

A large proportion of children have changed treatment in both cohorts mainly due to revisions of the national recommendations. ESC and LSC replaced d4T by another NRTI (ABC, AZT or TDF) in 78% and 52% of patients respectively regardless of virological failure.

Switch to a second line of HAART due to virological failure was not significantly different between the ESC (11%) and the LSC (14%) (p =

0.624). Successive lines of treatment after virological failure are detailed in Table 2.

Among the ESC, one patient replaced AZT for d4T due to anemia and one patient changed from LPV/r to EFV (reason not specified). Among the LSC, one child changed from EFV to LPV/r due to drowsiness (data not shown).

Immunological outcome

Mean CD4⁺% at HAART initiation was not significantly different and increased in the same proportions, in the ESC and the LSC during the first five years after treatment initiation (+18.3% vs. +16.2%). The largest increase occurred during the first year of therapy in cohorts (+13.8% vs. +11.9%). Six years after treatment initiation, mean CD4⁺% stayed significantly higher in the ESC (Figure 1 and Table 3).

All children included in the ESC (55/55) achieved normal CD4⁺% at least once during the entire follow-up period, contrary to the LSC where 86/96 (89.6%) children achieved normal CD4⁺% (p=0.014).

In a second analysis, results were subdivided in three subgroups in function of the CD4⁺% at HAART initiation (as explained in the definitions paragraph). First subgroup is the LIS (47% of the ESC vs. 56% of the LSC), second is the IIS (37% of the ESC vs. 32% of the LSC) and third is the HIS (16% of the ESC vs. 12% of the LSC). The proportion of children included in each subgroup was not significantly different in both cohorts (p=0.56, 0.47 and 0.74, respectively).

LIS from both cohorts had comparable mean CD4⁺% at HAART initiation and during the entire follow-up period (p>0.05). Mean CD4⁺% became higher than 25% in both cohorts after two years of treatment (Figure 2 and Table 4). In the ESC, 26/26 children achieved normal CD4⁺% at least once during the entire follow-up period and 47/54 (87%) children achieved normal CD4⁺% in the LSC (p=0.089).

IIS from both cohorts had comparable mean CD4⁺% at HAART initiation but in children from the ESC it became and stayed significantly higher than in the LSC, three years after HAART initiation. Mean CD4⁺% became higher than 25% in both cohorts after two year of treatment (Figure 2 and Table 4). In the ESC, 20/20 children achieved normal CD4⁺% at least once during the entire follow-up period, and 27/30 (90%) children achieved normal CD4⁺% in the LSC (p=0.27).

HIS from both cohorts had comparable mean CD4⁺% at HAART initiation and during the entire follow-up period (p>0.05) except at six months of treatment (27.1% vs. 42.7%, respectively). Mean CD4⁺% stayed higher than 25% in both cohorts during the entire follow-up period (Figure 2 and Table 4).

Number of patients ESC	First Line	Second Line	Third Line	Fourth line	Reason to change
1	AZT/3TC/NVP	AZT/3TC/LPV	ABC/3TC/EFV		//NVP+VF
1	d4T/3TC/LPV	ABC/3TC/EFV	AZT/3TC/LPV	TDF/3TC/LPV	//d4T+VF+anemia
1	d4T/3TC/LPV	d4T/3TC/EFV			VF
1	d4T/3TC/LPV	ABC/AZT/EFV			VF
1	d4T/3TC/LPV	ABC/3TC/EFV			VF
1	d4T/3TC/LPV	AZT/ABC/LPV/EFV			VF
Number of patients LSC	**First Line**	**Second Line**	**Third Line**	**Fourth line**	
3	ABC/3TC/EFV	AZT/3TC/LPV			VF
1	ABC/3TC/EFV	ddI/AZT/LPV			VF
3	d4T/3TC/EFV	AZT/3TC/LPV			VF
1	d4T/3TC/EFV	ABC/AZT/LPV			VF
3	d4T/3TC/EFV	ddI/AZT/LPV	AZT/3TC/LPV		VF+//ddI
2	d4T/3TC/EFV	ddI/AZT/LPV	ABC/AZT/LPV		VF+//ddI
1	d4T/3TC/LPV	ddI/AZT/EFV	TDF/3TC/LPV		VF+//ddI

//: No More Used Following National Recommendations; VF: Virological Failure; ESC: Early Starters Cohort; LSC: Late Starters Cohort; AZT: Zidovudine; 3TC: Lamivudine; NVP: Nevirapine; ABC: Abacavir; LPV: Lopiniavir/Ritonavir; TDF: Tenofovir; d4T: Stavudine; ddI: Didanosine; EFV: Efavirenz

Table 2: Successive treatments after virological failure in the ESC and the LSC.

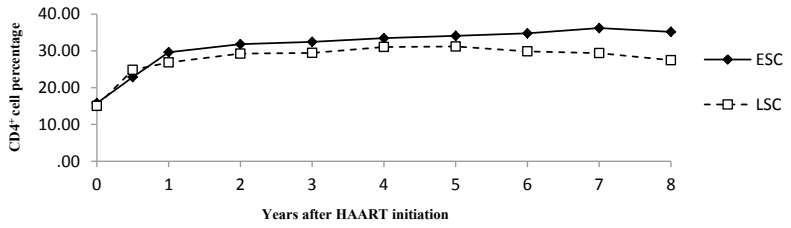

Figure 1: Mean CD4 in the ESC and the LSC.

	0 year	0.5 year	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years
ESC mean CD4⁺%	**15.8** (55/55)	**22.9** (52/55)	**29.6** (47/55)	**31.8** (47/55)	**32.4** (47/55)	**33.5** (49/55)	**34.1** (47/55)	**34.8** (52/55)	**36.2** (33/55)	**35.2** (17/55)
LSC mean CD4⁺%	**15.0** (96/96)	**24.8** (75/96)	**26.9** (72/96)	**29.3** (77/96)	**29.5** (79/96)	**31.1** (66/96)	**31.2** (51/96)	**29.9** (51/96)	**29.4** (32/96)	**27.5** (17/96)
p value	0.59	0.26	0.088	0.13	0.064	0.13	0.067	0.042	<0.001	0.013

Numbers in brackets represent the number of data available for that year

Table 3: Mean CD4⁺% in the ESC and the LSC during the entire follow-up period.

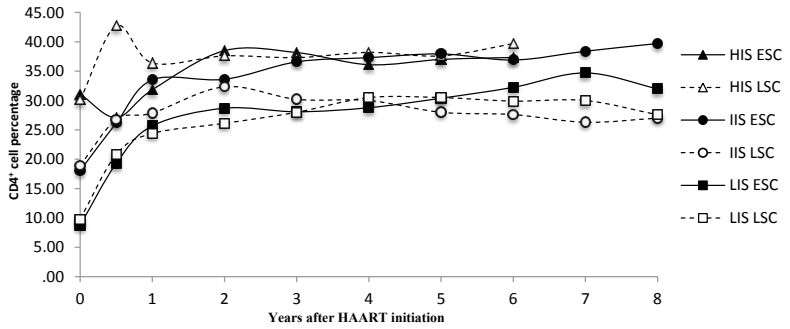

Figure 2: Mean CD4⁺% of the LIS, IIS and HIS in the ESC and the LSC.

		0 year	0.5 year	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years
LIS mean CD4⁺%	**ESC**	**8.8** (26/26)	**19.3** (26/26)	**25.7** (22/26)	**28.7** (23/26)	**28.1** (25/26)	**28.8** (22/26)	**30.4** (23/26)	**32.2** (25/26)	**34.7** (17/26)	**32.0** (10/26)
	LSC	**9.8** (54/54)	**20.8** (43/54)	**24.4** (41/54)	**26.1** (44/54)	**28.0** (46/54)	**30.5** (38/54)	**30.5** (32/54)	**29.9** (35/54)	**30.0** (23/54)	**27.6** (14/54)
	p value	0.27	0.43	0.90	0.24	0.96	0.38	0.50	0.30	0.059	0.23
IIS mean CD4⁺%	**ESC**	**18.1** (20/20)	**26.2** (18/20)	**33.5** (19/20)	**33.6** (18/20)	**36.6** (17/20)	**37.3** (18/20)	**37.9** (16/20)	**36.9** (18/20)	**38.4** (13/20)	**39.7** (7/20)
	LSC	**18.9** (30/30)	**26.8** (25/30)	**27.9** (23/30)	**32.3** (26/30)	**30.2** (26/30)	**30.0** (23/30)	**28.0** (14/30)	**27.6** (14/30)	**26.3** (9/30)	**27.0** (3/30)
	p value	0.245	0.847	0.038	0.636	0.031	0.008	0.0007	0.014	0.002	0.001
HIS mean CD4⁺%	**ESC**	**31.1** (9/9)	**27.1** (8/9)	**31.8** (6/9)	**38.5** (6/9)	**38.2** (6/9)	**36.1** (8/9)	**37.0** (8/9)	**37.3** (9/9)	/	/
	LSC	**30.1** (11/11)	**42.7** (7/11)	**36.4** (8/11)	**37.6** (7/11)	**37.3** (7/11)	**38.2** (6/11)	**37.6** (5/11)	**39.7** (3/11)	/	/
	p value	0.63	<0.001	0.33	0.82	0.79	0.60	0.89	0.38	/	/

Numbers in brackets represent the number of data available for that year

Table 4: Variation of the CD4⁺% in the LIS, the IIS and the HIS in function of the age at initiation.

		0 year	0.5 year	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years
Viral loads log 10 (cp/mL)	**ESC**	**6.5**	**4.2**	**3.4**	**2.9**	**4.8**	**3.9**	**3.5**	**4.6**	**1.6**	**1.6**
	LSC	**5.7**	**4.4**	**4.4**	**3.8**	**4.1**	**3.7**	**3.8**	**4.1**	**3.3**	**3.8**
	p value	<0.001	0.72	0.21	0.047	0.31	0.79	0.41	0.39	0.054	0.11
Virological failure (%)	**ESC**	**97.6**	**16.0**	**15.6**	**15.9**	**14.0**	**11.1**	**13.7**	**9.4**	**0.0**	**0.0**
	LSC	**97.4**	**14.0**	**19.1**	**18.5**	**17.5**	**16.4**	**17.6**	**26.0**	**11.4**	**30.0**
	p value	1	0.085	0.66	0.066	0.63	0.43	1	0.038	0.078	0.014
Number of data/ year	**ESC**	43	50	51	51	50	54	51	52	36	17
	LSC	77	89	89	83	80	65	51	50	28	15

Table 5: Viral loads and proportion of virological failure in the ESC and the LSC.

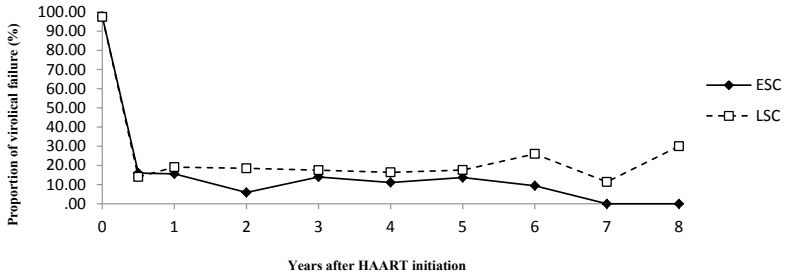

Figure 3: Proportion of virological failure in the ESC and the LSC.

Virological outcome

Pre-HAART VL was significantly higher in the ESC but the difference in VL waned 6 months after treatment initiation (Table 5).

In the ESC, 17/55 (30.9%) children experienced virological failure at least once after treatment initiation, 25/55 (45.5%) never experienced virological failure and 13/55 (23.6%) had detectable viral loads between 50 and 1000 cp/ml at least one time during the entire follow-up period.

In the LSC, 36/96 (37.5%) children experienced virological failure at least once after treatment initiation, 19/96 (19.8%) never experienced virological failure and 41/96 (42.7%) had detectable viral loads between 50 and 1000 cp/ml at least one time during the entire follow-up period.

The proportion of children who experienced virological failure at least once after the first year of HAART was comparable in both cohorts when the entire follow-up period was considered (p=0.48). However, when every year of follow-up was analyzed separately, proportion of

virological failure was higher in the LSC (p=0.038 and 0.014) at six and eight years of HAART, respectively (Figure 3 and Table 5).

The proportion of children with persistent undetectable VL after initial virological suppression was higher in the ESC than in the LSC (p=0.008).

Finally, the proportion of children with detectable viral loads between 50 and 1000 cp/ml at least one time during the entire follow-up period was higher in the LSC (p=0.0022).

Discussion

In 2012, only 34% of the HIV-infected children were treated with HAART in the world [2]. The 2013 and 2015 WHO guidelines successively revised and simplified their recommendations to expand treatment in children and increase accessibility to HAART in RLS [2,3]. The present study evaluated the long-term impact and application of these recommendations in the field.

Both cohorts initiated treatment with three antiretroviral drugs as recommended by the WHO and the South African guidelines [2,20]. Children included in the ESC and the LSC initiated HAART with 2 NRTI and 1 PI or 2 NRTI and 1 NNRTI according to age, which means that the guidelines for the first line therapies are clear and correctly applied.

Second line therapies were more heterogeneous in both cohorts probably because different recommended options are available in the WHO [2] (e.g. LPV/r replaced by EFV, d4T+3TC replaced by ABC/TDF+3TC) and the South African guidelines [20] (e.g. LPV/r replaced by LPV/r+EFV or a 3rd line, d4T+3TC replaced by ABC+AZT). ddI is no more recommended in both guidelines but is still used in RLS. Finally, expert advice is recommended after first line failure with a LPV/r based treatment. Experts are not always available and the choice of treatment depends more often on the habits of the local staff.

Immunological outcomes were favorable for both cohorts (ESC and LSC) and for the three subgroups (LIS, IIS, HIS), which underlines the importance of initiating HAART regardless of age. Children included in the ESC had at least comparable (or even better) immunological outcomes than children included in the LSC supporting the non-inferiority of early treatment initiation, as recommended by the WHO and the South African guidelines.

Some favorable outcomes can be underscored. Before treatment, the ESC and the LSC both had a high proportion (47% vs. 56%) (p=0.56) of children with severe immunosuppression (<15% CD4$^+$%). This is consistent with a review from Koller et al. who reported 70% of severe immunosuppression in children <2 years of age who started treatment in low and middle-income countries in 2010 [22]. Surprisingly, patients included in the present study had comparable mean CD4$^+$% independently of age at HAART initiation. It was not the case in European and West African studies [14,23] who showed more severe immunosuppression when treatment was started later in life (-0.82% of mean CD4$^+$% per year of HAART initiation delay) [14]. This difference could be explained in our study by the exclusion of rapid progressors [24] who possibly died before 2 years (before HAART initiation) in the LSC.

Influence of age at baseline, independently of immunological status, was studied in European [23,25-29] and a few African cohorts (1-8.7 years follow-up) [14,30]. Results were unconclusive. Four studies [25-28] concluded the absence of influence of age at baseline and five studies [14,23,29-31] described poorer immunological outcomes for late starters. The follow-up study of CHER [16] compared early time-limited HAART with deferred HAART in 377 South African infants with a median follow-up of 4.8 years. Early treated children (median age 7.4 weeks, CD4$^+$% of 35%) had better clinical and immunological outcomes than children treated later (median age 20 weeks, CD4$^+$% of 35%) even after planned treatment interruption at 40 or 70 weeks [16]. In our study, mean CD4$^+$% was normal in both cohorts. However, there were statistically less children who achieved normal CD4$^+$% in the LSC.

The European-American PENPACT-1 study [31], analyzed combined effects of CD4$^+$% and age at baseline. They found a significant interaction between CD4$^+$% and age on the probability of ever recovering a normal CD4$^+$% within 4 years. With increasing age, baseline CD4$^+$% had a stronger effect on the capacity to recover a normal CD4$^+$%. Children included in our three subgroups achieved normal mean CD4$^+$% independently of their immunological status at baseline. There was no statistical difference in the number of children who achieved normal CD4$^+$% in the LIS and the IIS, probably due to the small effectives in these subgroups.

In terms of virological outcome, VL was higher in the ESC at treatment initiation. This could be explained by their younger age and was already described in untreated perinatally infected infants, who had the highest HIV-1 RNA levels at 2 months of age followed by a slow decline during the first two years of life. These high VL and slow decline reflect the lower efficiency of the immature immune system, which cannot contain the viral replication and has possibly a greater number of HIV-susceptible cells [32].

The proportion of children, who experienced virological failure at least once after initial suppression, was not significantly different in both cohorts; with 30.9% and 37.5% in the ESC and LSC respectively. A recent retrospective study implemented in another rural area of South Africa found similar rates (38%) of virological failure (median duration since beginning HAART of 31 months) [13].

During the entire follow-up period, the proportion of children who sustained undetectable viral loads was significantly higher in the ESC and the proportion of children who experienced low-level viremia was higher in the LSC. Knowing that persistent low-level viremia is a risk factor of viral drug resistance [33,34], maintenance of an undetectable viral load decreases the risk to develop viral drug resistances in the ESC.

Limitations

This research has some limitations. It is a retrospective study that only includes a limited number of children who survived from 2005 until now and a number of children were lost to follow-up. Data collected at baseline could not be representative of all the infants from this region. Furthermore over the years some data were missing in the patients' files, which decrease the power of the study. However this is an operational study representing the real life on the field. Children included in the ESC and the LSC had, for most of them, different HAART regimens (PI vs NNRTI) at treatment initiation. A PI-based regimen initiation was described to be an advantage in terms of virological outcome in comparison with a Nevirapine-based regimen [35]. Our conclusions could be different if PI or NNRTI-based regimen were used in both cohorts.

Conclusion

HAART appeared highly effective in terms of immunological and virological long-term outcomes both in children treated before one year of age and after two years of age. The long-term results of this study

demonstrate that early HAART initiation was certainly not inferior to late treatment. Children from the ESC, treated with a PI-based regimen, more often achieved normal $CD4^+$% and sustained virological suppression than children from the LSC. These results encourage the current international recommendations to initiate HAART as soon as possible in RLS.

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Authors Contributions

JCB and DVDL participated in the redaction of the questionnaires, interpretation of the results and redaction of the article. JCB, MK and LH recruited the patients in the HIV family clinic. JCB, PG and JR participated to the redaction of the questionnaires, interpretation of the results and redaction of the article. All authors have read and approved the final manuscript.

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