

# Quality of Life, Risk Factors and Mortality in Children with HIV/AIDS on 2<sup>nd</sup> Line Treatment, Slow Progressors and Late Presenters in Cambodian Orphanage

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**Abstract:**

Purpose of this paper was to review group of Cambodian children with AIDS - late presenters, coming to our programme with low immunologic status (CD4<5%, and <100 CD4 cells) and opportunistic infections as well as children who started HAART too late according to the guidelines valid in 2003 – 2005 (<200 CD4 cells per cubic millimetre). Another aim of this study was to compare children with AIDS who are on 2<sup>nd</sup> line HAART for risk factors, failure and outcome in comparison to children on 1<sup>st</sup> line ARV. There was relatively low proportion of children on 2<sup>nd</sup> line treatment since beginning of ART (27 of 140, 19%). Mortality in late presenters is higher than in non-late presenters and also opportunistic infections were higher in the group of late presenters, including HZV and TB. Relatively high proportion of slow progressors was found among included children as well.

**Conflict of interest:**

The authors whose names are listed in the title of the article certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, or other equity interest), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

**Introduction**

HIV/AIDS is a deadly disease, with 100% mortality if untreated. In Europe, current guidelines (1) recommend to treat anybody who is HIV positive who and has absolute count of CD4 cells of 500 and less. In previous recommendations (2), for

patients with 350-500 cells, treatment is offered if severe co-infections occur, and therapy started at 200 cells per mm<sup>3</sup> obligatory. Therefore, proportion of HIV positive individuals who are not receiving any treatment is decreasing nowadays. Current guidelines in US recommend treating any infected

individual irrespective to CD4 count (1), however WHO guidelines reflects also situation in low income settings (2).

Purpose of this short communication is to review group of children with AIDS, who were diagnosed late (late presenters) coming to our programme with low immunologic status ( $CD4 < 5\%$ , and  $< 100$  CD4 cells) and opportunistic infections as well as children who started HAART too late according to the guidelines valid in 2003 – 2005 ( $< 200$  CD4 cells per cubic millimetre).

We have also analysed a cohort of children who were not receiving HAART (slow progressor) for 10-16 years due to stable CD4 count and stable viral load neither presenting with opportunistic infections and AIDS-related comorbidities.

Third aim of this study is to compare children with AIDS who are on 2<sup>nd</sup> line HAART for risk factors, failure and outcome in comparison to children on 1<sup>st</sup> line ARV.

## Patients and Methods

One hundred and thirteen (113) children with HIV on first line treatment (stavudin + lamivudine + efavirenz) were compared to 27 children on second line therapy (ritonavir/lopinavir, efavirenz + abacavir) with active antiretroviral therapy (HAART) within years 2002 – 2015. All but 3 children were treated as indoor children in House of Family and House of Hope from 2002, in Phnom Penh (12 years) and Sihanoukville from 2005 (10 years) Subgroup of children who did not need therapy at least 10 years (slow progressors, LPG or SPG) was compared with all other children. All children were orphans with mothers died due to AIDS. Subgroup of children who came to receive treatment, when their relative CD4 count was  $< 5\%$  and CD4 absolute count  $< 99$  we have indicated as late presenters (LPG). Indoor management of HIV positive children included daily check-up in symptomatic patients, weekly check-up when for asymptomatic patients,

directly observed HAART treatment (to achieve 100% compliance) and Anti TB therapy where applicable. Children received food 5x daily food including daily meat, 2x weekly fish, 2x daily fresh fruit, 1x daily vegetables, seed oil used for preparation of meals (modified Okinawa fish diet). Psycho-social support after – school activities daily, as a part of daily indoor orphanage require where performed. In all children supplementation with iron, folic acid, zinc and Albendazole plus Praziquantel deparasitisation every 6 months to prevent anaemia and malnutrition were used. For statistical analysis, univariate analysis  $\chi^2$  test and t test with open source package EPI, FO from CDC Atlanta 2004 was used.

## Results and discussion

### First line versus second line ARV treatment

Of 140 children on ART since 2003 – 2005, 113 are still on 1<sup>st</sup> line HAART and 27 on 2<sup>nd</sup> line, none of them receive 3<sup>rd</sup> line therapy. Lowest duration of 1<sup>st</sup> line is 12 years, of 2<sup>nd</sup> line 8 years. Three (3) children died, all were on 1<sup>st</sup> line, 1-4 weeks of the initiating of therapy (all three of them were late presenters with  $CD4 < 1\%$ , abs  $CD4 < 20$ ).

Comparing both Groups for risk factors and outcome, those on 2<sup>nd</sup> line HAART were less, likely to be slow progressors ( $P = 0.01$ ) and more likely to be late presenters (38,5% vs 19,4%;  $P = 0.015$ ). Mortality was 2,2% and was similar among both groups (similar mortality). Number of infectious episodes within last year was similar (1.8% vs 1.1%,  $P = 0.03$ ). Also TB and HZV as opportunistic infections occurred more frequently in those on 2<sup>nd</sup> line therapy. Mortality, was similar in both Groups (1<sup>st</sup> line vs. 2<sup>nd</sup> line) (3% vs. 0%,  $P > 0.05$ ).

**Table 1:** Risk factors and mortality in those on 1<sup>st</sup> line and 2<sup>nd</sup> line therapy

<b>Table 1: First line vs. Second Line:</b>				
<b>Tab.1</b>	<b>2nd. line (27)</b>	<b>1st. line (113)</b>	<b>total (140)</b>	<b>D</b>
(LPS) Late presenters	2 (7,9)	25 (23,2)	28	0,01
(SPG) slow progressor	10 (38,5)	22 (19,4)	32	0,015
Death n AIDS	0 (0)	3 (2,8%)	3 (2,2)	NS
Ovell no of Inf.Episodes	42 (1,8)	120 (1,1)	162 (2)	0,03
Zoster (HZV)	17 (48%)	51 (46%)	68 (43%)	NS
TBC (TB)	19 (71%)	47 (42%)	66 (41%)	0,001

### Slow progressors (SPG)

32 children of 140 (23%) did not present any sign of AIDS (clinically or immunologically or virologically) for 10 years from the year they have been diagnosed to be HIV positive. They were fully asymptomatic, therefore due to the guidelines valid in that time, they did not received HAART. The oldest patients (adolescent) in the program was 22 years, and was receiving HAART from his 16 years and was asymptomatic, first 15 years of his life. There are 6 children older than 20 years, less than 6 years on HAART in this cohort.

the guidelines). Comparing this Group of 32 children infected perinatally or during breastfeeding (mothers of all children died on HIV/AIDS), to the group of slow progressors, average age, when received 1st HAART was 12 years in LPG and 9,2 years in the Non-SPG Group. (Tab. 2)

### Late presenters (LPS)

Table 3 present risk factors and mortality in the Group of Late presenters (LPS) and non-Late presenters of those who received first line therapy. Average number of opportunistic infections (1,3 vs. 0,7 per year) was

**Table 2:** Risk factors for SPG vs. NON SPG

<b>Tab.2</b>	<b>SPG (32)</b>	<b>NON SPG 108</b>	<b>140</b>	<b>P</b>
Mortality	3(11,1%)	0	3 (2,2)	0,04
1st.line	25 (87%)	89 (85%)	14	NS
2nd.line	2 (7,5%)	24 (22%)	26	0,01
HZV	17 (66%)	51 (39)	68	0,01
TBC	9 (33%)	57 (45%)	66	0,01
Average number of inf. episodes	0,7	1,3	162	0,01
LPS (all)	4 (18%)	24 (27%)	28	0,04

In those children at the day of the diagnosis of HIV/AIDS and also of the day they had more than 20% of relative and more than 350 of absolute CD4 cells, undetectable viremia and no opportunistic infections, therapy has started (due to the change of

lower in non-Late presenters, as well as the incidence of TBC (0.01) and HZV (0.01). First line therapy was significantly more common among LPG, mortality (LPG vs. non- LPS) was 11,1 vs. 0%; P<0.05.

Table 3 also shows comparison between the Group of Children who came late to our program (defined as Total Number of CD4 <99 and Relative count of CD4<5% at admission), versus those who came for therapy earliest (with CD4 >5%, abs CD4≥100). Occurrence herpes zoster (HZV) or/and TB (as 2 commonest opportunistic infections (OI)) was significantly lower (39,4 vs 75%) in non-Late presenters and that in LPS.

No statistically significance was observed between Late presenters and non-Late presenters in the proportion of slow progressors (47% vs 20%, NS) and between the children receiving 1<sup>st</sup> vs 2<sup>nd</sup> line therapy, who were equally distributed in both Groups. However, mortality (annual death rate) was higher in LPS (9,9% vs. 0,0%, P<0.45).

with relatively and absolutely high cell count, to prevent mortality and achieving better secondary outcomes, such as lower percentage of opportunistic infections. Our study confirms that opportunistic infections were higher in the group of late presenters, including HZV and TB.

Third finding was relatively high proportion of slow progressors among included children. At least one study (6) has already been focused on proportion of slow progressors in South East Asia. However, staying 15-20 years without therapy and major changes in clinical status, is still difficult to explain. Virulence of particular virus genotypes, social status and nutrition of perinatally infected children, may play a significant role in the explanation.

**Table 3: Late presenters LPS vs. non-Late presenters**

	Late Presenters (28)	non-Late presenters (112)	Total (140)	
SPG	8 (29%)	24 (20%)	32	NS
Death	3 (9,9%)	0 (0)	3	0,045
HZV	24 (75%)	44 (39%)	68	0,01
TBC	26 (83%)	40 (31%)	66	0,01
Average of infect Episodes	1,2	0,9	162	0,015
1st.line	220(75%)	90 (85%)	112	NS
2nd.line	68 (25%)	22 (15%)	28	

## Discussion

There are few points to be addressed in discussion. There is relatively low proportion of children on 2<sup>nd</sup> line treatment since beginning of ART (27 of 140, 19%), especially in comparison to Africa or US (4). Most probable explanation could be DOTS (directly observed treatment strategy) used in program for ensuring compliance of children. Good adherence to treatment is always assumption for optimal clinical response.

Mortality in late presenters is higher than in non-late presenters. This confirms hypothesis of early start of ART in patients

## Conclusion

There is relatively low proportion of children on 2<sup>nd</sup> line treatment since beginning of ART, mainly due to the good adherence to the treatment. Mortality and infectious events in late presenters is higher than in non-late presenters which supports early start of ART in patients. Relatively high proportion of slow progressors in South East Asia should be addressed in new studies.

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