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Lamivudine Monotherapy as a Holding Strategy in HIV-Infected Children in South Africa

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Abstract

Background: Treatment options for HIV-infected children failing combination antiretroviral therapy (ART) are limited. We describe lamivudine monotherapy (LM) as a holding strategy for ART-experienced virologically-failing children where a definitive suppressive regimen was not possible.

Methods: A retrospective review of data collected until the end of July 2010 from four sites in Johannesburg, South Africa was performed. Inclusion criteria were age ≤16 years with documented HIV-1 infection and use of LM for at least three months.

Results: Twenty three patients (52% female) were identified. Median age at LM was 8.02 years (IQR: 4.07–11.80). LM was initiated for intractable adherence issues in 20/23 children (87%) and for multi-drug resistance precluding construction of an active new regimen in 3/23 (13%). The median duration of LM was 6.13 months (IQR: 3.93–9.31). At six months post LM initiation, CD4 count decreased by 23% but did not reach pre-ART levels. Neither nadir CD4 (p=0.35) nor pre-LM ART regimen (p=0.50) predicted CD4 count decline. LM was stopped in nine children, seven of whom restarted combination ART. Reasons to restart ART were: immunological progression n=3, disease progression n=1 and adherence issues resolved n=3. The other 14 (60.9%) children were continuing LM at time of data collection. No deaths occurred during follow-up.

Conclusion: LM should be investigated through clinical trial as a short-term holding strategy in paediatric patients, where suppressive ART is challenging due to adherence or drug availability problems.

Keywords: Paediatric HIV; Lamivudine monotherapy; Holding strategy; Resource limited; South Africa; Children

Introduction

The burden of paediatric HIV is in Sub-Saharan Africa where more than 90% of the world's HIV-infected children reside and almost 400,000 children are receiving highly active antiretroviral therapy (ART) [1]. Despite high rates of favourable virological outcomes in HIV-infected paediatric cohorts, including those from resource limited settings, 4 - 20% of children fail therapy (viral loads >400 copies/ml after one year on ART) [2-4].

Paediatric patients are at higher risk than adults of developing virological failure [3]. Contributing factors include problems associated with caregiver-dependent medication measuring, psychosocial factors like stigma and non-disclosure [5,6], sub-adequate dosing due to failure to adjust doses for weight gain [3] and pill fatigue or resistance to taking medication particularly in older children and adolescents [7].

Limited drug options exist for HIV-infected children failing therapy. In the United States of America, eighteen drugs are registered for paediatric ART use compared to 25 drugs registered for adults [8], and in South Africa only 10 antiretroviral drugs are currently registered for use in children [9]. Many newer drugs lack paediatric formulations and dose finding studies are still ongoing; some are registered for use only in older children. Newer therapies are often prohibitively expensive or take time to be approved by local government medicine safety agencies. For example it took more than two years for the United States Food and Drug Administration (FDA) to approve darunavir, a new generation protease inhibitor, for use in children over 12 years of age and a further three years for approval for use in children over 3 years of age. Some resistance mutations, alone or in combination, result in cross resistance with other drugs within the same drug class, occasionally eliminating entire drug classes for use in future regimens [10].

Therefore for such cases, there exists a need for a holding strategy to delay deterioration of immune function without selecting for drug resistance mutations until a suitable second line/salvage regimen becomes available and appropriate.

Lamivudine is a well-tolerated nucleoside reverse transcriptase inhibitor (NRTI) and is one of the recommended first line drugs for the treatment of HIV in children in most paediatric guidelines including the World Health Organisation [11,12]. However, in the face of sub-adequate adherence to therapy, resistance to lamivudine occurs rapidly (within weeks) as a result of a single point mutation at codon 184 in the viral genome [13]. Whilst this mutation renders the drug ineffective, it

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also reduces viral replication capacity and makes the virus itself less fit [14,15]. A few adult studies have sought to exploit this reduction inviral fitness by using lamivudine or its structural relative, emtricitibine(FTC), as monotherapy in a so-called holding strategy, with bettermaintenance of clinical and immunological well-being compared to those who interrupted treatment completely [16-18].

To our knowledge, there is no published literature on lamivudine monotherapy (LM) in children but, as a result of the few observational studies in adults, paediatric HIV clinicians have been utilizing LM as a holding strategy in children where a definitive suppressive regimen is difficult for various reasons. We present our experience with LM at four South African institutions.

Methods

Study design

This retrospective longitudinal study was conducted at four paediatric HIV treatment sites in Johannesburg, South Africa: Phatsima Khanya Clinic (PKC), Alexandra; Benoni Paediatric HIV Clinic (BPHC), Benoni; Perinatal HIV Research Unit (PHRU) and Harriet Shezi Clinic (WRHI), Soweto. In total these four clinics serviced around 5500 HIV-infected children at the time of study: PKC 674; BPHC 391, PHRU 1119 and WRHI 3328. Patients were followed up 3-6 monthly at all four sites.

The review was performed with data collected up until the end of July 2010.

Inclusion criteria were documented HIV-infection and use of LM for at least 3 months while below 16 years of age. Approval for the collection of data during time in care was obtained for each of the four sites from the Wits Human Research Ethics Committee.

Investigators at each site collected data on background characteristics, prior antiretroviral therapy, reasons for requiring a holding regimen, clinical and immunological condition at entry into care, at LM initiation and during LM from patient records. These were entered into standardised electronic spread sheets which were merged.

Statistical analysis

All analyses were done using SAS version 9.2 at a 5% significance level where applicable. Descriptive statistics (medians and inter-quartile ranges) were determined for age, immunological and anthropometric measures. The anthropometric measures of WAZ, HAZ, WHZ and BMIZ were determined using the CDC Growth Charts. Multiple linear regressions were done to determine whether nadir CD4 and pre-LM ART regimen were predictive of CD4 declines. The trajectory of immunological and anthropometric measures from enrolment up to 15 months is presented graphically. The graphical plots were generated by STATA 11.

Results

Demographics

Twenty three patients (52% female) were eligible for study inclusion. All patients were failing antiretroviral therapy at initiation of LM with median viral load 16,437 copies/ml (IQR 4,850 - 40,800 copies/ml).

In Table 1 the demographic, immunological and anthropometric characteristics of the patients at ART initiation and LM initiation respectively are shown. Children had received a median of 24.33 months (IQR: 19.49 - 32.03) of ART prior to LM initiation. Median duration of LM was 6.13 months (IQR: 3.93-9.31).

Variable	ART Initiation	LM Initiation
Median age in years (IQR)	6.20 (1.10–7.52)	8.02 (4.07–11.80)
Median CD4+ cells/mm^3 (IQR)	560 (214-1052)	671 (520-1239)
Median CD4+ % (IQR)	12.6 (7.0-15.0)	25.4 (18.0-32.1)
Weight-for-age z-score (IQR)	-0.92 (-1.9,0.16)	3.3 (-0.3,5.2)
Height-for-age z-score (IQR)	-1.5 (-2.2,-1.2)	-1.4 (-1.7,-0.8)
Weight-for-height z-score (IQR)	-0.3 (-1.3,0.7)	4.9 (0.9,8.5)

Table 1: Characteristics at ART and LM initiation respectively.

The failing antiretroviral regimen at initiation of LM was non-nucleoside reverse transcriptase inhibitor- (NNRTI) based in 13 (57%) children (efavirenz n=10; nevirapine n=3) and protease inhibitor- (PI) based in 10 (43%; all boosted lopinavir). Only five children had been receiving second line therapy at time of LM initiation. All second line regimens were PI-based. All patients had received lamivudine as part of the nucleoside backbone of their first line regimen.

Of seventeen children with genotyping results prior to LM, 15 (88%) had documented M184V mutation, ten (59%) had high level NNRTI resistance mutations; three (18%) had ≥3 thymidine analogue mutations (TAMs); one child had the 69 insertion complex and one had mutations conferring high level PI resistance. Seven children (41%) had high level resistance mutations to drugs from 2 or more classes, excluding lamivudine. Of the two patients who started LM without documented M184V, one was not on lamivudine at the time of testing but had failed a lamivudine-containing regimen previously. The other was started on LM more than six months after the genotyping result with ongoing non-adherence to a lamivudine containing regimen and insufficient funding to repeat genotyping.

Reasons for LM

Twenty of the 23 patients had been switched to LM due to ongoing adherence problems. These were mostly related to poor social circumstances where caregivers were unable or unwilling to give medication correctly, or to increased pill burden due to concomitant treatment for tuberculosis (TB).

The remaining three patients were apparently adherent to their ART regimen at the time of LM initiation but prior adherence history was questionable. LM was initiated as the clinicians were unable to construct a new regimen containing more than one active drug due to extensive nucleoside reverse transcriptase inhibitor (NRTI) and NNRTI resistance mutations following an extended period of time on failing NNRTI based therapy.

Clinical outcomes

During 279 patient-months of follow up, one child defaulted follow up; one was transferred out; seven (30.4%) had LM stopped by their treating clinician in order to restart ART (immunological progression n=3, clinical disease progression [suspected disseminated tuberculosis] n=1; underlying adherence issue resolved n=3). The median time to stop LM was 5.75 months (IQR: 3.95 - 7.40).The other 14 (60.9%) children were continuing LM at the time of data collection having experienced no indication to restart ART according to clinician assessment; that is, no immunological or clinical disease progression and no improvement in adherence challenges or access to active drugs for construction of a new regimen. Of these children continuing LM, 6/14 had been receiving LM for more than 12 months and one child had been on LM for 30 months at time of data collection.

There were no deaths during time of follow up, though the outcome of the child who defaulted care is unknown.

Figure 1 illustrates median weight-for-age z-scores (WAZ), height-for-age z-scores (HAZ) and weight-for-height z –scores (WHZ) at ART initiation and during LM. WAZ remained stable during LM. None of the changes were statistically significant.

Immunological outcomes

The CD4 counts and percentages (CD4%) of all 23 children during the first 6 months of LM are shown in Table 2. Figure 2A and 2B represent the trajectory of median CD4% and CD4 cell count respectively during LM, and in comparison to levels at ART initiation. CD4% was maintained during LM at statistically higher levels compared to levels at ART initiation, however, there was a decline in both CD4 % and CD4 cell count 6 months after LM initiation.

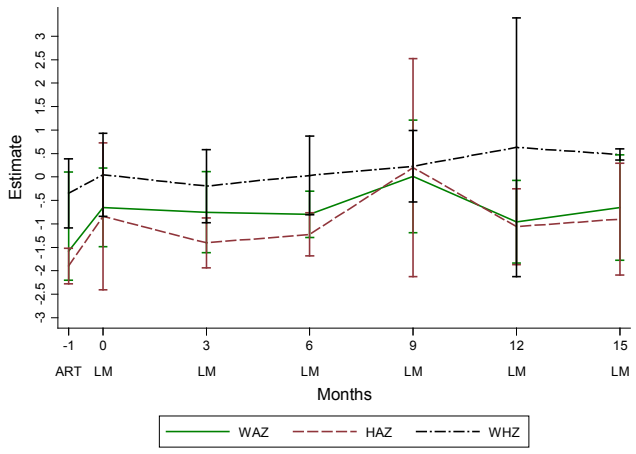
Compared to LM initiation, CD4 count decreased by a fifth at 3 and 6 months respectively (22% (p=0.13) and 23% (p=0.29)). CD4% declined by around one tenth at 3 and 6 months respectively (11% (p=0.52) and 13% (p=0.55)).

Nadir CD4 did not predict CD4 count nor CD4% decline at 6 months (CD4 count p=0.35/CD4% p=0.72). Similarly ART regimen at the time of LM initiation did not predict CD4 count or CD4 % decline at 6 months (p=0.5/ p=0.49).

Discussion

To our knowledge, this is the first description of LM in children. This is a small group of patients with limited follow up time, and as there is no comparison group, we do not know whether these children would have done better on a non-suppressive ART regimen or a brief treatment interruption period.

Holding regimens are by definition "last resort" options and as such are not intended to provide all the benefits of suppressive ART, but rather to slow the inevitable clinical and immunological deterioration when triple therapy cannot be used. Without triple therapy, virological suppression is highly unlikely. In our resource constrained setting, viral load monitoring is not recommended in guidelines for children not on ART [9]. Hence viral loads were not monitored in our cohort. On LM, the children in this study did not deteriorate to their pre-ART immunological condition. Our results suggest that children's



WAZ: Weight-for-age z-score
HAZ: Height-for-age z-score
WHZ: Weight-for-height z-score

Figure 1: Growth parameters at antiretroviral therapy (ART) initiation and during lamivudine monotherapy (LM): medians with 95% confidence interval.

	LM initiation		3 months† N=23		6 months‡ N=20	
	CD4 count	CD4%	CD4 count	CD4 %	CD4 count	CD4 %
1	520	18	347	14.2		
2	1512	35.4	1540	36.8	1355	30.4
3	627	19.65	610	22.3		
4	534	26.2	476	19.3	358	15.6
5	1984	32.1	1648	31.3	1462	33.6
6	527	25.4	569	24.6	549	22.5
7	578	29.4	380	24	447	23.2
8	500	30.6	546	29.7	755	30.4
9	84	3.4	8	0.58	Stopped LM after 5 months	
10	475	11.2	244	10	123	3.8
11	994	41.5	759	30.2	761	30.4
12	341	10.8	316	13.6	Stopped LM after 4 months	
13	547	16.3	425	14.7	478	15.3
14	895	21.53	1188	13.09	748	17.43
15	1745	14.69			1066	16.35
16	1730	25.36	1101	30	1166	29.94
17	1005	34.35	371	28.54	186	13.52
18	752	28.96	752	28.9	540	23.89
19	1239	19.8			Defaulted follow-up after 3 months	
20	982	17.9			872	19.41
21	285	18.4			285	19.8
22	1632	33.7	478	16.6	1136	22.7
23	715	34.8	477	29.2	649	31.6

* LM = Lamivudine monotherapy
† 4/23 did not have a CD4 measure performed at 3 months of follow-up.
‡ 2/20 who remained on LM at 6 months did not have a CD4 measure performed.

Table 2: CD4 count and CD4 percentage at LM* initiation and at 3 and 6 months of LM.

CD4 counts and CD4 percentages, as well as their growth parameters, may not decrease significantly when initiated on LM. LM maintained clinical and immunological status in the majority of these children who were unable to take suppressive ART due to non-adherence or drug option limitations. Since current antiretroviral drug options in children are limited, to preserve the available second and third line options, a holding strategy may be a useful bridge whilst addressing adherence problems.

Adherence issues in children can be particularly difficult to resolve. For example concomitant ART and TB therapy has been shown to be linked with poor virological outcomes [19]. In our study, three of the patients' adherence problems stemmed from their concomitant TB therapy. All three were receiving PI-based ART at the time of TB diagnosis. This necessitated them to take four antiretroviral medications, including poorly palatable boosted lopinavir and additional ritonavir, to counteract rifampicin enzyme induction, as well as four anti-tuberculosis medications, routine multivitamin and vitamin B6 supplementation [9,20].

Furthermore, this paper is in keeping with preliminary findings of viral resistance in the South African context in children [21,22], which may be related to non-adherence, nevirapine use in prevention of mother to child transmission (PMTCT) strategies, or drug-drug interactions affecting therapeutic levels. The finding of high level resistance patterns in these children may indicate a need for paediatric

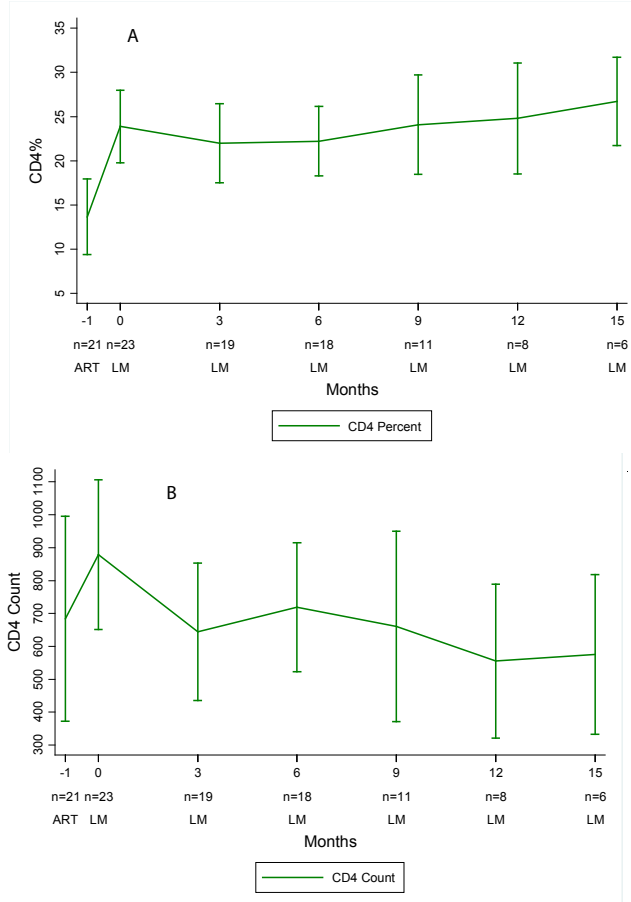


Figure 2: CD4 percentage (Figure 2A) and CD4 cells/mm^3 count (Figure 2B) from antiretroviral therapy (ART) initiation and during lamivudine monotherapy (LM): medians with 95% confidence intervals.

dosing and formulations of newer drug classes for third line regimens. To date, newer class antiretrovirals (ARVs) – second generation protease inhibitors and intergrase inhibitors – remain unregistered for paediatric use in South Africa and, even once registered, cannot be accessed in the public sector due to financial constraints. For children where currently approved and accessible ARVs were no longer options for suppressive treatment due to resistance, LM proved useful as a holding strategy until active drugs become available.

Because resistance to lamivudine by M184V mutation occurs within weeks in the context of monotherapy [23], the use of LM without confirmation of the mutation is not recommended. Resistance testing is not the standard of care in South Africa but can be requested and accessed at certain sites at the discretion of the senior clinician when funding is available. However, proving lamivudine resistance is not always possible: withdrawal of drug pressure at the time of specimen sampling, failure to amplify the virus (laboratory infrastructure) or lack of funding for testing may be possible contributors. Although one cannot always demonstrate M184V, where long-term poor adherence and virological non-suppression on a lamivudine-containing regimen is confirmed, LM may be considered under expert guidance and with close clinical and immunological monitoring.

In our study, time to LM initiation was relatively short: 2 – 3 years indicating fairly rapid development of resistance mutations particularly in children on NNRTI-based regimens. Whilst NNRTI mutations tend to be fairly predictable, children who are failing regimens containing thymidine analogues or protease inhibitors would benefit from greater access to genotyping in order to plan a future suppressive regimen.

There have been at least three previous studies describing LM in adults. In the original pilot study of LM, Castagna et al reported a slight but significantly better outcome for adults on LM versus treatment interruption with nadir CD4 counts >200cells/mm [3,16]. In our study, however, neither nadir CD4 count nor percentage predicted rate of CD4 decline. Opravil et al aimed at characterizing virological and immunological changes in adults on LM. The authors noted that patients on PI-based ART prior to LM experienced more rapid CD4 decline than those without PIs in their pre-LM regimens [18]. In contrast, our study showed no correlation of pre-LM ART regimen on CD4 count or percentage decline. This is in keeping with the Soria et al. study which compared LM to daily or weekly FTC [17].

The main limitation of this study is the lack of control group. We are thus unable to assess how LM would compare to continuing non-suppressive ART or treatment interruption in children. Adult studies have shown good immunological outcomes in patients continuing failing PI regimens [24] and, although adult studies have shown poor outcomes with structured treatment interruption [25], both the PENTA 11 study and the CHER study have shown that interruption of ART appears to be safe in older and younger children respectively in a controlled trial environment [26,27]. Another limitation was an obvious selection bias – not all non-adherent patients failing virologically were started on LM, and this limits our ability to generalize these findings. Lastly as there is no data from randomised control or large observational cohort studies in either children or adults, the use of LM is restricted to the limited experts in the field and thus the sample size of this study is small.

Whilst we do not know whether those who continue on failing ART or those who interrupt treatment fare better in terms of a successful next regimen, more data is needed on the use of LM in children. These preliminary findings demonstrate that LM could be used as a holding strategy in paediatric clinical trials assessing options available when suppressive ART is challenging to achieve. As holding strategies by definition are for short-term use only, there is an urgent need for new drugs and formulations for paediatric patients.

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Conflicts of Interest and Source of Funding

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For the remaining authors no conflicts of interest/ sources of funding were declared.

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