Comparison of Viral Load Suppression among HIV-1 Infected Children Aged 5 to 12 Years on Once Daily Versus Twice Daily Abacavir-Containing Regimens at University Teaching Hospitals - Children's Hospital, Lusaka, Zambia

Mukumbi Mutenda,[1] Derrick Munkombwe,[2] Patrick Kaonga[3], Mukuka Mwamba[4]

1. University Teaching Hospitals, Children's Hospital, P/B RW1X, Lusaka, Zambia
2. University of Zambia, School of Health Sciences, Department of Pharmacy, Lusaka, Zambia
3. University of Zambia, School of Public Health
4. University Teaching Hospitals, HIV AIDS Program – Adult Infectious Diseases Centre

Address of Correspondence:
Mukumbi Mutenda; University Teaching Hospitals – Children's Hospital, P/B RW1X, Lusaka, Zambia; Mobile phone: +260977193702; Email: mukumbi.kabesha@gmail.com
DOI 10.53974/unza.jabs.6.3.1000

ABSTRACT

Abacavir is one of the first-line drugs used to treat HIV infection in paediatric patients in Zambia, whose use in children has not been widely published. This study compared the virologic response of abacavir given as part of a once-daily regimen with the response when given as part of a twice-daily regimen. A total of eighty-two children aged two to twelve years currently receiving antiretroviral therapy at the Paediatric Centre of Excellence, University Teaching Hospitals, Lusaka, Zambia, were observed in the study. This was a prospective cohort study. All the children were initially on twice daily abacavir containing regimen with lamivudine twice daily and efavirenz once daily, with 40 maintained on this regimen by the attending clinician and 42 switched to once-daily abacavir, lamivudine and efavirenz by the attending clinician. Profiles were obtained for each child to compare viral load at baseline and week 24. Data was analysed using Stata Version 16.

The proportion of children with undetectable viral load in the once-daily group at twenty-four weeks was 64.3 per cent compared to 72.5 per cent in the twice-daily group. Twice-daily dosing reduced the odds of achieving an undetectable viral load by about 59 per cent, while being male reduced the odds of achieving an undetectable HIV viral load by 19.6 per cent. Baseline haemoglobin, creatinine, or alanine transferase levels were not predictors of viral load suppression.

The study suggests that once-daily dosing of an abacavir-containing regimen achieved a lower viral suppression rate when compared to twice-daily dosing. It is recommended that once-daily dosing of abacavir containing regimen should be considered as a dosing option for Zambian children living with HIV.

Key Words: Abacavir, Viral Suppression, Once-daily dosing, Twice-daily dosing

INTRODUCTION

Zambian children have been severely affected by the Human Immunodeficiency Virus (HIV), which leads to Acquired Immunodeficiency Syndrome (AIDS), with an estimate of more than 250,000 children and adolescents being orphaned by AIDS since the pandemic began. In Zambia, the prevalence of HIV in children 14 years and below was estimated at 1.1 per cent in 2016, with only 33.4 per cent of children receiving antiretroviral therapy (ART) achieving viral load suppression [1-2].

Strict adherence to antiretroviral drugs is a requirement for achieving viral suppression. Subjects with an adherence rate of at least 95 per cent or more were 1.66 times less likely to experience virologic failure than those with less than 95 per cent adherence. The adherence rate was based on perception and not verified. The consequences of not adhering well to antiretroviral therapy are disease progression and, ultimately, death as a result of unsuppressed viral load. Disease progression is more rapid in HIV-infected children below two years of age. Factors associated with antiretroviral therapy regimens, such as frequency of administration and pill burden, have a bearing on adherence and, consequently, the success of treatment. A Zambian study revealed that 29% of children missed their doses prior to their clinic appointment, citing forgetfulness as one of the barriers to adherence. Adherence challenges are dependent on the caregiver's commitment to and understanding of the importance of adherence as well as that of the child. Once-daily dosing significantly improves drug adherence and is highly acceptable in children and their caregivers [3-6].

Several studies comparing once-daily abacavir-containing regimens have reported virologic control being achieved or maintained after switching to once-daily administration. The PENTA 13 study of children aged 2 to 12 years old reported 89 per cent (n=19) viral suppression at week 24, defined as an HIV RNA level of below 100 copies/ml [7].

PENTA 15 was a pharmacokinetic study of once-daily versus twice-daily abacavir and lamivudine in HIV-type-1 infected children aged 3-<36 months to explore the pharmacokinetics of abacavir in infants and younger children. Virologic control was maintained throughout the study at 94 per cent, 100 per cent and 89 per cent at weeks 12, 24 and 48, respectively. Viral suppression was, however, defined as an HIV RNA level below 400 copies/ml (8). This study used a higher limit to define viral load suppression and therefore doesn't serve as an appropriate reference point for the study. With the availability of newer machines, viral load can be detected at less than 20 or 50 copies/ml.

The United Nations estimated that 1.7 million children live with HIV globally, with about 90 per cent in Sub-Saharan Africa (9). Strict adherence to antiretroviral therapy is a prerequisite for achieving viral Ribonucleic Acid (RNA) suppression. One of the universal barriers to successful antiretroviral therapy is failure to adhere to treatment. Barriers to adherence in children reported in a multicentre observational study conducted in the United States include an unpleasant taste of the medication, forgetting to take the medication and the child feeling 'well' (10)55 per cent were African American, 54 per cent were boys, and the average age was 12.8 years. The most frequently reported barrier by either the caregiver or youth was \"forgot.\" There were varying degrees of agreement between child and caregiver on the following barriers: \"forgot,\" \"taste,\"

\"child was away from home,\"\"child refused,\" and \"child felt good.\" Children who knew their HIV status were more likely to report logistical barriers, such as scheduling issues. Children with a biological parent as their caregiver were more likely to report regimen or fear of disclosure as a barrier. Lack of agreement was observed for more than half of the studied barriers, indicating discrepancies between children's and caregivers' perceptions of factors that influence medication-taking. The findings suggest a need for the interventions that involve both the child and caregiver in the tasks of remembering when to administer the child's medications, sustaining adherence, and appropriately transitioning medication responsibility to the youth. Copyright © 2012 by the American Academy of Pediatrics.","author":[{"dropping-particle":"","family":"Buchanan","given":"Ashley L.","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Montepiedra","given":"Grace","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Sirois","given":"Patricia A.","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Kammerer","given":"Betsy","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Garvie","given":"Patricia A.","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Storm","given":"Deborah S.","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Nichols","given":"Sharon L.","non-dropping-particle":"","parse-names":false,"suffix":""}],"container-title":"Pediatrics","id":"ITEM-1","issue":"5","issued":{"date-parts":[["2012"]]},"title":"Barriers to medication adherence in HIV-infected children and youth based on self- and caregiver report","type":"article-journal","volume":"129"},"uris":["http://www.mendeley.com/documents/?uuid=a3fb4dc6-3710-4e84-a817-0b8b6d7449af"]}],"mendeley":{"formattedCitation":"(Buchanan et al., 2012. Forgetfulness was also stated as a barrier to adherence in a study undertaken in a Sub-Saharan African setting (11). The study further identified side effects and lack of food to take along with the medication as other barriers.

One of the factors associated with treatment success is reduced dosing frequency (4). School-going children report difficulties adhering to the twice-daily regimen, especially during the school holidays when they find it difficult to wake up in time for their morning dose.

The prevalence of HIV-infected children below fourteen years of age receiving ART in Zambia with unsuppressed viral loads was 33.4 per cent [2]. In a study aimed at improving viral suppression in Zambian children, Munthali *et al.* identified non-adherence as one of the barriers to achieving viral suppression in children. Viral suppression rates in children, particularly those under four years of age, are lower than that of adults. Approximately 29 per cent of children between the age of five and nine years had missed doses of their antiretroviral drugs since their previous clinic visit. Forgetting doses was one of the reasons stated for non-adherence [5]. A once-daily regimen would be ideal for children as their caregivers would have less chance of forgetting to administer a dose within 24 hours, increasing the likelihood of them maintaining their first-line regimen and ultimately delaying treatment failure.

It is not known whether the once-daily administration of an abacavir-containing regimen in HIV-infected Zambian children achieves similar viral load suppression when compared to twice-daily administration.

MATERIALS AND METHODS

This was a prospective observational cohort study, conducted at the Paediatric Centre of Excellence, University Teaching Hospitals - Children's Hospital, Lusaka, Zambia. The children were initiated on twice-daily abacavir and lamivudine with once-daily efavirenz according to body weight according to national guidelines. After a minimum of twelve weeks, the attending clinician reviewed the patients routinely and either switched to once-daily or maintained on twice-daily abacavir with lamivudine and efavirenz as the second and third drugs, respectively. The total daily dose of both abacavir and lamivudine were the same for each weight band, with the dose for those receiving twice daily being divided into two equal doses. The average doses given for children weighing 19 kg were Abacavir 300mg, lamivudine 150mg and Efavirenz 300mg. Each child was weighed, and blood samples were collected for baseline biochemical tests, haemoglobin, CD4 cell profile and RNA viral load. The profiles were repeated for each child at week twenty-four as per routine practice. Viral load suppression was defined as an undetectable viral load of below twenty copies per millilitre for the purposes of this study. The viral load tests and CD4 counts were performed at the Kaposi's Sarcoma Laboratory, Children's Hospital - University Teaching Hospitals, Lusaka, using Cobas Ampliprep Taqman@96 manufactured by Roche Molecular Systems and the BD FACSCalibur manufactured by Becton, Dickinson and Company respectively.

A data collection form was developed to record age, sex, weight, haemoglobin levels, creatinine and alanine transferase levels.

Intention to treat was applied. Data analysed using STATA v 16. manufactured by StataCorp. Shapiro-Wilk test was used to test for normality. Creatinine levels were analysed using an unpaired t-test, and Mann Whitney was used to analyse CD 4 count, haemoglobin, alanine transferase and weight at a 95 per cent confidence level. A binomial logistic regression model was used to identify determinants of viral load suppression. Confounders were identified using stepwise backward algorithms with a probability of removal set at 0.2. P-values for removals were calculated using the likelihood ratio test.

RESULTS

Demographic and Baseline Clinical Characteristics of HIV-infected Children

The majority of participants were male, accounting for 56.1 per cent, and the mean weight was 19.5kg with a median age of seven years. The age and weight of the participants were evenly distributed among the groups. The median haemoglobin was on the lower limit of the normal range (11.5 – 15.5 grams/decilitre) for children, whereas the mean creatinine and median alanine transferase were within normal ranges for children (23 – 68 micromoles/litre and 0 – 34 units/litre respectively).

Clinical Characteristics and Viral Load Status of HIV-infected Children at Children's Hospital at 24 Weeks

At twenty-four weeks of treatment, 56 (68.3%) children achieved undetectable viral loads, with 51.8 per cent of the children on twice-daily dosing and

48.2 per cent on once-daily dosing. An increase in haemoglobin was observed in all children.

The odds of achieving undetectable viral load on twice-daily dosing relative to once-daily dosing was 0.408, i.e. twice-daily dosing reduced the odds of achieving undetectable viral load by about 59 per cent = (1-0.408) *100 (95% confidence interval: 0.341, 0.489).

DISCUSSION

Abacavir is the nucleoside reverse transcriptase inhibitor drug of choice for first-line ART in children infected with HIV in Zambia [12]. The safety and tolerability of abacavir in Zambian children have been demonstrated, as reported in the CHAPAS 3 trial conducted in Zambian and Ugandan children [13 -14]. Similarly, during the follow-up of the participants, no adverse events were reported. This study observed a reduction in viral load and increased CD4 count in both the once-daily and twice-daily groups. This is expected in a child adhering to antiretroviral therapy regardless of the regimen. All laboratory values remained within the normal range after twenty-four weeks on ART.

Abacavir, whether, given once-daily or twice-daily as part of a combination antiretroviral therapy, is potent enough to cause a rise in viral load suppression. Our study found that 64.2 per cent of the participants on once daily and 72.5 per cent on twice daily dosing recorded undetectable viral loads. The suppression rate for children taking twice daily dosing is comparable to what was recorded in Ugandan children, where 72 per cent of children on once-daily dosing and 73 per cent on twice daily achieved viral loads below 80 copies per millilitre (p=0.65) (15)but no randomized trial has compared virological outcomes. Methods: Children taking abacavir + lamivudine-containing first-line regimens twice daily for more than thirty-six weeks in the ARROW trial (NCT02028676, ISRCTN24791884. Other studies conducted in various countries that compared once and twice-daily regimens either as crossover studies or parallel reported higher viral load suppression rates than this local study. Children aged 2 to 12 years old enrolled in the PENTA 13 trial recorded a viral load suppression rate of 80 per cent at baseline and 89 per cent twenty-four weeks after children were switched from twice daily to once daily abacavir-containing regimen (7). A study done in Europe, with children below three years demonstrated maintained viral suppression of 89 per cent at baseline and 100 per cent at twenty-four weeks of therapy in all children taking once and twice-daily abacavir-containing regimens (8). However, the study only had eighteen participants, and viral load suppression was defined as below 400 copies per millilitre. A similar study of Thai children with median age of 8.8 (6.6–11.3) years and bodyweight 21.9 (19.2—30.6) kg found that most children on both once-daily and twice-daily abacavir-containing regimen maintained their viral suppression after ninety-six weeks of antiretroviral treatment (16). While the overall viral load suppression rate was lower than that reported in other countries, the overall suppression rate of 68 per cent is also lower than Zambia's overall suppression rate in children, which stands at 72 per cent (2). The cause of the lower viral load suppression rates, regardless of dosing frequency, can be partly explained by the more stringent definition of viral load suppression, which was at below 50 copies per millilitre compared to below 80 and, in some cases, below 400 copies

set by some other studies.

A meta-analysis of 11 randomised controlled trials, whose main objective was to compare adherence between once-daily and twice-daily dosing frequencies, revealed that adherence rate was better with once-daily regimens (+2.9%; 95% confidence interval, 1.0%–4.8%; P < .003) than with twice-daily regimens [17]. Given that once-daily dosing improves adherence and that good adherence is the bedrock of successful antiretroviral therapy, it follows that if children on once-daily dosing an abacavir-containing regimen are able to achieve viral load suppression, it should be recommended.

Very few studies have been done in children comparing viral load suppression with once-daily compared to a twice-daily regimen. The majority of studies compare different regimens in children. Viral load suppression in children is generally lower than in adults, regardless of the regimen used.

Plasma drug levels were not done because local laboratories did not have the capacity to perform the tests. This would have given a better picture of the performance of the drug as well as the implications of dosing frequency on drug levels. Adherence was based on perception of caregivers as reported by the number of doses missed. It was not measured by more accurate methods such as therapeutic drug monitoring or electronic devices.

CONCLUSIONS

The study suggests that abacavir when given as part of a once-daily regimen, is a suitable alternative to twice-daily dosing in achieving HIV viral load suppression. However, further detailed studies are required to provide more evidence.

REFERENCES

1. Joint United Nations Programme on HIV/AIDS (UNAIDS), Global Report (2018)
2. Ministry of Health, Zambia. Zambia Population-based HIV Impact Assesment (ZAMPHIA) 2016:
3. Gross, R., Yip, B., Lo Re, V., Wood, E., Alexander, C. S., Harrigan, P. R., Bangsberg, D. R., Montaner, J. S. G., & Hogg, R. S. (2006). A simple, dynamic measure of antiretroviral therapy adherence predicts failure to maintain HIV-1 suppression. *Journal of Infectious Diseases*, *194*(8), 1108–1114.
4. Stone, V. E., Jordan, J., Tolson, J., Miller, R., & Pilon, T. (2004). Perspectives on Adherence and Simplicity for HIV-Infected Patients on Antiretroviral Therapy. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *36*(3), 808–816.
5. Munthali, B. T., Hachizovu, S., & Washington, M. (2020). *Perspective*. 6–9.
6. Maitland, D., Jackson, A., Osorio, J., Mandalia, S., Gazzard, B. G., & Moyle, G. J. (2008). Switching from twice-daily abacavir and lamivudine to the once-daily fixed-dose combination tablet of abacavir and lamivudine improves patient adherence and satisfaction with therapy. *HIV Medicine*, *9*(8), 667–672.
7. Bergshoeff, A., Burger, D., Verweij, C., Farrelly, L., Flynn, J., Le Prevost, M., Walker, S., Novelli, V., Lyall, H., Khoo, S., & Gibb, D. (1359). *Plasma pharmacokinetics of once- versus twice-daily lamivudine and abacavir: simplification of combination treatment in HIV-1-infected children (PENTA-13)*.

8. Jacqz-Aigrain *et al*., (2010). Pharmacokinetic study of once-daily versus twice-daily abacavir and lamivudine in HIV type-1-infected children aged 3-<36 months. *Antiviral therapy*, *15*(3), 297–305. doi.org/10.3851/IMP1532
9. Joint United Nations Programme on HIV/AIDS (UNAIDS), Global Report (2019)
10. Buchanan, A. L., Montepiedra, G., Sirois, P. A., Kammerer, B., Garvie, P. A., Storm, D. S., & Nichols, S. L. (2012). Barriers to medication adherence in HIV-infected children and youth based on self- and caregiver report. *Pediatrics*, *129*(5).
11. Fetzer, B. C., Mupenda, B., Lusiama, J., Kitetele, F., Golin, C., & Behets, F. (2011). Barriers to and facilitators of adherence to pediatric antiretroviral therapy in a sub-Saharan setting: Insights from a qualitative study. *AIDS Patient Care and STDs*, *25*(10), 611–621.
12. Ministry of Health. (2020). *Zambia Guidelines for Treatment and Prevention of HIV Infection*. *February*, 138.
13. Mulenga,V.,Musiime,V.,Kekitiinwa, A., Cook, A. D., Abongomera, G., Kenny, J., Chabala, C., Mirembe, G., Asiimwe, A., Owen-Powell, E., Burger, D., McIlleron, H., Klein, N., Chintu, C., Thomason, M. J., Kityo, C., Walker, A. S., Gibb, D. M., Kabamba, D., … Lyall, H. (2016). Abacavir, zidovudine, or stavudine as paediatric tablets for African HIV-infected children (CHAPAS-3): An open-label, parallel-group, randomised controlled trial. In *The Lancet Infectious Diseases* (Vol. 16, Issue 2, pp. 169–179).
14. Musiime V, Kendall L. Bakeera-Kitaka S, Snowden WB, Odongo F, Thomason M, Musoke P, Adkison K, Burger D, Mugyeni P, Kekitiinwa A, Gibb D, Walker AS 2010. Pharmacokinetics and acceptability of once-versus twice-daily lamivudine and abacavir in HIV type-1-infected Ugandan children in the ARROW Trial. Antivir Ther.2010;15(8):1115-24. doi: 10.3851/IMP1695. PMID: 2114991
15. Musiime V, Kasirye P, Naidoo-James B, Nahirya-Ntege P, Mhute T, Cook A, Mugurura L, Munjoma M, Thoofer NK, Ndashimye E, Nankya I, Spyer MJ, Thomason MJ, Snowden W, Gibb DM, Walker AS, (2016). Once versus twice-daily abacavir and lamivudine in African children. AIDS, 30(11), 1761-1770. doi 10.97/QAD.0000000000001116
16. Bunupuradah T, Punyahotra P, Cressey TR, Srimuan A, Thammajaruk N, Sophonphan J, Sriheara C, Burger DM, Puthanakit T, Ananworanich J (2015). Plasma pharmacokinetics od once-daily abacavir-and-lamivudine-containing regimens and week 96 efficacy in HIV-infected Thai children. J Virus Erad. Jul 1;1(3):185-91. PMID: 27482411; PMCID: PMC4946738
17. Parienti JJ, Bangsberg DR, Verdon R, Gardner EM (2009). Better adherence with once-daily antiretroviral regimens: a meta-analysis. Clin Infect Dis. Doi:10.1086/596482. PMID: 19140758; PMCID: PMC2708315

TABLES AND FIGURES

Table 1: Demographic and Baseline Clinical Characteristics of HIV-infected children at Children's Hospital

Categorical Variable	Dosing frequency			
	Once daily n = 42		Twice daily n = 40	
	Frequency	Column %	Frequency	Column %
Sex				
Female	21	50.0	15	37.5
Male	21	50.0	25	62.5
Numerical Variable	**Once daily**		**Twice daily**	
Age in years				
Mean (Standard Deviation)	7.0	(1.8)	7.3	(2.2)
Median (Inter-quartile Range)	7.0	(2.0)	7.0	(4.0)
Baseline viral load				
Mean (Standard Deviation)	36,345	(125,442)	55,905	(143,582)
Median (Inter-quartile Range)	21	(2,770)	96	(12,077)
Baseline CD4 count				
Mean (Standard Deviation)	855.5	(784)	740	(547)
Median (Inter-quartile Range)	695	(518)	684	(610)
Baseline haemoglobin level				
Mean (Standard Deviation)	10.9	(2.5)	10.6	(1.8)
Median (Inter-quartile Range)	11.4	(3.2)	11.0	(1.4)
Baseline creatinine level				
Mean (Standard Deviation)	40.9	(12.1)	37.4	(12.9)
Median (Inter-quartile Range)	43.7	(21.2)	38.7	(17.0)
Baseline alanine transaminase (ALT) levels				
Mean (Standard Deviation)	20.1	(10.8)	20.9	(9.9)
Median (Inter-quartile Range)	17.3	(6.7)	19.2	(15.8)
Baseline weight				
Mean (Standard Deviation)	19.7	(6.3)	19.4	(5.1)
Median (Inter-quartile Range)	20.1	(6.8)	19	(6.6)

SD = Standard Deviation, Viral load expressed as copies/millilitre, CD4 Count expressed as cells per microliter, IQR = Interquartile Range, Hb = Haemoglobin expressed as grams per decilitre; Creatinine expressed as micromoles per litre, ALT = Alanine transferase expressed as units per litre, weight expressed as kilograms

Table 2: Clinical Characteristics and Viral Load Status of HIV-infected Children at Children's Hospital at 24 Weeks

Variable	HIV Viral Load Status at End of Follow-up			
	Detectable VL (n=26)		Undetectable VL (n=56)	
	Freq.	Col %	Freq.	Col %
Sex				
Female	13	(50)	23	(41.07)
Male	13	(50)	33	(58.93)
Dosing Frequency				
Once daily	15	(57.69)	27	(48.21)
Twice daily	11	(42.31)	29	(51.79)
	Detectable VL (n=26)		**Undetectable VL (n=56)**	
Age in years				
Mean (Standard Deviation)	7.08	(1.67)	7.20	(2.14)
Median (Inter-quartile Range)	7.0	(2.0)	7.5	(3.0)
CD4 count				
Mean (Standard Deviation)	664.56	(343.58)	931.91	(602.9)
Median (Inter-quartile Range)	714	(533)	769	(496)
Haemoglobin level				
Mean (Standard Deviation)	12.2	(4.65)	12.6	(4.20)
Median (Inter-quartile Range)	11.35	(2.3)	11.95	(1.8)
Creatinine level				
Mean (Standard Deviation)	37.72	(11.47)	39.72	(14.13)
Median (Inter-quartile Range)	37.2	(15.95)	39.1	(12.2)
ALT levels				
Mean (Standard Deviation)	19.12	(8.23)	25.77	(30.61)
Median (Inter-quartile Range)	17.0	(11.9)	19.6	(14.0)
Weight				
Mean (Standard Deviation)	19.81	(5.48)	21.57	(5.69)
Median (Inter-quartile Range)	19.5	(7.5)	21.0	(5.5)

SD = Standard Deviation, Viral load expressed as copies/millilitre, CD4 Count expressed as cells per microliter, IQR = Interquartile Range, Hb = Haemoglobin expressed as grams per decilitre; Creatinine expressed as micromoles per litre, ALT = Alanine transferase expressed as units per litre, weight expressed as kilograms

Table 3: Viral Load Status by Dosing Frequency at 24 Weeks

Categorical Variable	HIV viral load status			
	Detectable		Undetectable	
	Frequency	Column %	Frequency	Column %
Sex				
Female	13	50.0	23	41.07
Male	13	50.0	33	58.93
Dosing Frequency				
Once daily	15	57.69	27	48.21
Twice daily	11	42.31	29	51.79
Numerical Variable	**Detectable**		**Undetectable**	