

Research

***Corresponding author**

Moreen Kamateeka, MBChB, MPH
Junior Investigator
Makerere University – Johns Hopkins
University Research Collaboration
P.O. Box 23491, Kampala, Uganda
Tel. (+256) 414 541044
Fax: (+256) 414 543002
E-mail: mkamateeka@mujhu.org

Volume 2 : Issue 1

Article Ref. #: 1000HARTOJ2104

Article History

Received: March 6th, 2015

Accepted: April 21st, 2015

Published: April 21st, 2015

Citation

Kamateeka M, Barlow-Mosha L, Mubiru M, Lutajumwa M, Mudioppe P, Musoke PM. Immunologic and virologic responses to nevirapine based antiretroviral therapy (ART) among HIV-Tuberculosis co-infected Ugandan children on rifampicin based anti-tubercular treatment. *HIV/AIDS Res Treat Open J.* 2015; 2(1): 27-36. doi: [10.17140/HARTOJ-2-104](https://doi.org/10.17140/HARTOJ-2-104)

Copyright

©2015 Kamateeka M. This is an open access article distributed under the Creative Commons Attribution 4.0 International License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Immunologic and Virologic Responses to Nevirapine Based Antiretroviral Therapy (ART) Among HIV-Tuberculosis Co-Infected Ugandan Children on Rifampicin Based Anti-Tubercular Treatment

Moreen Kamateeka^{1*}, L. Barlow-Mosha¹, M. Mubiru¹, M. Lutajumwa¹, P. Mudioppe² and P. M. Musoke^{1,3}

¹*Makerere University – Johns Hopkins University Research Collaboration, Upper Mulago Hill Road, P. O. Box 23491, Kampala, Uganda*

²*Uganda AIDS Commission, Plot 1-3 Salim Bay Road, P. O. Box 10779, Kampala, Uganda*

³*Department of Paediatrics and Child Health, Makerere University, Wandegaya, Kampala, Uganda*

ABSTRACT

Background: Children co-infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) require concurrent treatment with anti-tuberculosis drugs and Antiretroviral therapy (ART). Drug interaction between nevirapine and rifampicin leads to decreased nevirapine levels. The impact of this drug-drug interaction on virologic and immunologic outcomes in the treatment of HIV - TB co-infected children has not been fully studied. A retrospective analysis was conducted to compare the response to nevirapine-based ART regimen among HIV- infected Ugandan children on a rifampicin containing anti-TB regimen for TB disease *versus* those only on ART.

Methods: We analyzed data from HIV infected children aged 6 months to 12 years attending a Paediatric HIV clinic in Kampala, Uganda who between October 2004-June 2006 were enrolled into an ART program based on the 2002 World Health Organization (WHO) ART guidelines for Resource Limited Settings. In this retrospective analysis, children were divided into two groups; those on nevirapine based ART and rifampicin containing anti-TB treatment (TB group) and those on ART alone (no TB group). CD4 cell percent and viral load data obtained at baseline and thereafter 12 weekly until 48 weeks was compared using Wilcoxon rank sum test. Kaplan Meir plots were used to compare virologic success between the two groups over the 48 week follow up period.

Results: The analysis included a total of 127 children of whom 20% (26/127) were in the TB group. Median log₁₀ HIV RNA (Interquartile range-IQR) at baseline was 5.69 (5.19-6.19) in the TB group *versus* 5.59 (4.86-6.32) in the no TB group; $p=0.576$. Median viral load was undetectable for all children by 12 weeks post ART initiation and this was sustained through 48 weeks irrespective of receiving rifampicin. Baseline median CD4% was not significantly different between the two groups. The median CD4% (IQR) during follow-up for the TB group *versus* the no TB group was: 17.0 (8.0-26) *versus* 20.9 (8.0- 33.8), $p=0.147$ by 12 weeks; 26.0 (12.7-39.3) *versus* 22.9 (7.5-38.3), $p=0.472$ by 24 weeks; 26.6 (13.6-39.6) *versus* 26.4 (12.3-40.5), $p=0.927$ by 36 weeks and 29.0 (20.0-38) *versus* 28.9 (16.8-41), $p=0.931$ by 48 weeks respectively.

Conclusion: HIV/TB co-infected children receiving rifampicin demonstrated satisfactory immunologic and virologic responses to nevirapine based ART, similar to children not on anti- TB treatment. These findings provide evidence that nevirapine based ART may remain effective

among HIV positive children co-infected with TB who receive rifampicin-based anti-TB treatment.

KEYWORDS: Nevirapine and rifampicin co-administration; HIV-TB co-infected children; Immunologic and virologic outcomes.

INTRODUCTION

The global estimate of HIV infected children at the end of 2013 stood at 3.2 million with 91% in sub-Saharan Africa.¹ TB is among the most common opportunistic infections affecting HIV infected children. In 2013, the World Health Organization (WHO) estimated that there were 550,000 TB cases and 80,000 TB deaths among children.² WHO recommends initiating ART as soon as possible for any HIV infected child diagnosed with TB disease.³ In areas of high HIV/TB incidence such as sub-Saharan Africa, co-administration of ART and anti-TB treatment is very common.

Despite the general trend of increasing availability of ART in Sub-Saharan Africa over the past decade, paediatric ART in resource-limited settings still faces multiple challenges, particularly the availability of appropriate, affordable and simplified pediatric ARV formulations. Nevirapine (NVP) is widely used in sub-Saharan Africa because of its availability in fixed dose formulations which provides easy drug administration, reduced pill burden, convenient storage and low cost. In resource-limited settings, NVP is the most widely used Non-nucleoside reverse transcriptase inhibitor (NNRTI) in first line ART regimens for children unless contraindicated. WHO currently recommends a Lopinavir/ritonavir (LPV/r) based regimen for first line ART among all children under 3 years of age, however NVP is still recommended for this age group if a LPV/r regimen is not feasible.³ HIV/TB co-infected children under 3 years of age cannot use an Efavirenz (EFV) containing ART regimen, therefore NVP and LPV/r are commonly used with rifampicin (back bone for the short course anti-TB treatment regimen) resulting in drug-drug interactions.

Although other rifamycins like rifabutin are associated with less drug-drug interactions if used with these ARV regimens, they are more costly and not readily available in resource-limited settings. Rifampicin is thus the most frequently used and preferred primary drug in the treatment of TB in these settings. Studies in Uganda, Zambia and Thailand have shown decreased NVP levels in HIV-TB co infected children on a NVP based ART regimen and a rifampicin containing anti-TB regimen with about half of the children with sub therapeutic trough levels.⁴⁻⁶ Adult studies have demonstrated that the drug interaction between NVP and rifampicin results in decreased levels of NVP that may be suboptimal for complete viral suppression.^{7,8}

We conducted a retrospective analysis to compare the immunologic and virologic response to NVP based ART regimen among HIV-TB Co- infected Ugandan children on rifampi-

cin based anti-TB treatment compared to those on ART alone.

METHODS

Study Setting and Population

Between October 2004 and June 2006, HIV-infected children aged 6 months to 12 years attending the Mulago Hospital Paediatric HIV clinic and the Makerere University – Johns Hopkins University Research Collaboration (MUJHU) Research clinic in Kampala Uganda, were screened for initiation of ART based on the WHO antiretroviral therapy guidelines for Resource Limited Settings, 2002.⁹ Those children who were eligible for ART were initiated on treatment.

Screening evaluations for the ART program were performed over 3 weekly visits. Prior to ART initiation, all the children and their care givers were screened to assess clinical eligibility as well as psychosocial readiness to initiate ART and to provide counseling on adherence and HIV care. Clinical assessments included screening for Opportunistic Infections (OIs) and since TB is a common OI in this setting, all children underwent TB screening prior to initiation of ART. Screening laboratory assessments included CD4 cell count/percent, baseline liver and kidney function tests.

The criteria for ART initiation in the ART program was based on WHO antiretroviral therapy guidelines for Resource Limited Settings, 2002 and included; symptomatic HIV infected children (WHO stage III or IV); WHO clinical stage III (2003) and or CD4 cell percentage, 20% or, 15% in those younger than 1 year and older than 1 year, respectively; creatinine <1.2 mg/dL in children under 2 years, <1.7 mg/dL in children 2 years and older; Alanine transferase (ALT)/Aspartate transferase (AST) <5 x upper limit of normal and parent/care taker psychosocial readiness.⁹

Some of the children enrolled into the ART program were enrolled into an observational ART cohort study whose objective was to compare the response to NVP based ART regimens among Ugandan HIV infected children exposed and non-exposed to single dose nevirapine (sdNVP) at birth as described elsewhere.¹⁰ In addition to the criteria for ART initiation in the ART program indicated above, eligibility criteria for enrollment into the study included; confirmed HIV infection by HIV rapid tests (Determine and Unigold in series) or 2 positive HIV-1 DNA Polymerase Chain Reaction (PCR) tests (Roche Ampli-cor, Roche Diagnostics, Indianapolis, IN) for those children under 18 months of age, hemoglobin >7.0 g/dL, platelet count >49,000 /mm³, absolute neutrophil count >250 /mm³, Alanine transferase (ALT)/Aspartate transferase (AST) ≥5 x upper limit of normal, parent/care taker willing to provide informed consent for child's study participation, residing within 20 km radius of the study clinic and parent/care taker willing to be visited at home by study staff. Exclusion criteria for the study included

known hypersensitivity to Nevirepine (NVP), malignancy, or on current cytotoxic chemotherapy.^{10,11} Before enrollment into the study, children underwent the standard screening procedures for the ART program as earlier described. Specifically for the study, these included adherence counseling, clinical and psychosocial assessments, details on history of single dose nevirapine (sdNVP) exposure and a home visit. Parents/caretakers provided informed consent for enrollment of their children into the study. Children were assigned to cohort 1 if they had history of exposure to sdNVP at birth and to cohort 2 if they had no prior exposure to sdNVP.¹⁰

Antiretroviral Treatment Regimens

Following determination of eligibility for ART initiation, children were started on adult fixed dose Triomune tablet (30/40 mg d4T/150 mg 3TC/200 mg NVP) manufactured by CIPLA India or stavudine (d4T), lamivudine (3TC) and NVP syrups for those who weighed less than 10 kg. Dosage was based on the children's weight bands as shown in Table 1. These dosing weight bands were developed prior to the 2006 WHO dosing weight bands.¹²

Dosing of Triomune by weight		NVP dosing mg/kg
Weight of patient (kg)	Drug dose	mg/kg/dose
<10 kg	syrups	4mg/kg/dose for 14 days 7mg/kg/dose maintenance
10-12.9 kg	¼ tab Triomune 40 bd	3.9-5.0
13-15.5 kg	½ tab Triomune 30 bd	6.3-7.7
16-25.5 kg	½ tab Triomune 40 bd	3.9-6.25
26-59.5 kg	1 tab Triomune 30 bd	3.5-7.7
>60 kg	1 tab Triomune 40 bd	3.3

Table 1: Weight band dosing used for the study children on Fixed Dose Combination Triomune.

In summary, 127 eligible children aged 6 months to 12 years were initiated on ART according to the 2002 WHO ART guidelines.

After initiation of ART, the children in the program and study were reviewed at routine study visits, weekly for the first month, every 2 weeks for the second month and then every 4 weeks until 48 weeks. In the second year of follow up, routine visits were conducted every 3 months until week 96. Clinical monitoring was done at every routine study visit and laboratory monitoring was done at baseline, 12, 24, 36, 48, 72 and 96 weeks after initiating ART. Laboratory monitoring included; Complete Blood Count (CBC) and CD4 cell count (absolute and percent). Quantitative HIV-1 Ribonucleic acid (RNA) Polymerase Chain Reaction (PCR) was not routine standard of care at that time under the ART program and was performed for only children in the observational cohort study at 3 monthly intervals in year one of follow up and then every 6 months in year 2 of follow up. Children in the study also had plasma samples stored for future HIV resistance testing.¹³ Chemistries (ALT and AST) were done

at baseline, 2 weeks after ART initiation and then subsequently if clinically indicated for all children.

Study Design

We conducted a retrospective analysis of the data collected from Ugandan HIV infected children on NVP based ART regimen who were grouped according to whether they were on a rifampicin containing regimen for TB treatment or not on treatment for TB disease. In this analysis we compared two groups, 101 HIV infected children without TB disease initiated on a NVP based ART regimen (no TB group) and 26 HIV infected children co-infected with TB, receiving rifampicin containing anti-TB treatment and NVP based ART (TB group) (Figure 1). Children who were already on a rifampicin anti-TB treatment regimen for TB disease at the time of ART initiation were also included in the latter group.

For this analysis data over 48 weeks of follow up was included. Immunologic and virologic outcome data over the second year of follow up was incomplete and was excluded from the analysis.

TB Diagnosis and Treatment

As part of the routine screening evaluations for ART initiation and clinical monitoring while on ART, all children were screened for TB disease at enrollment and during study follow up when clinically indicated. Clinical symptoms/signs, history of PTB contact, tuberculin (PPD) skin testing and Chest X-ray (CXR) were used for TB screening. A PPD of ≥ 5 mm skin induration was considered positive. The diagnosis of tuberculosis infection was based on the WHO criteria and categorized as probable TB or confirmed TB.¹⁴

All children with tuberculosis disease were treated with a 6 month short course anti-TB regimen of rifampicin/isoniazid/pyrazinamide in the 2 months intensive phase followed by 4 months of rifampicin/isoniazid. Clinical monitoring was done monthly at scheduled anti-TB drug refill visits. At each follow up study visit a history and examination was done including assessment of TB signs and symptoms, adherence to medication, and measurement of weight and height. A CXR was done at completion of the TB treatment.

Immunologic and Virologic Monitoring

Immunologic and virologic outcomes of children in the two groups were assessed by absolute CD4 cell count/percent and plasma HIV-1 RNA PCR, respectively. Tests were performed at baseline, every 12 weeks until 48 weeks of follow-up and then 6 monthly until 96 weeks of follow up. Viral load testing was not routine standard of care at that time and was performed for children in the observational cohort study. In the present analysis, we included immunologic and virologic outcome data up to 48 weeks of follow up because a large percentage of children in

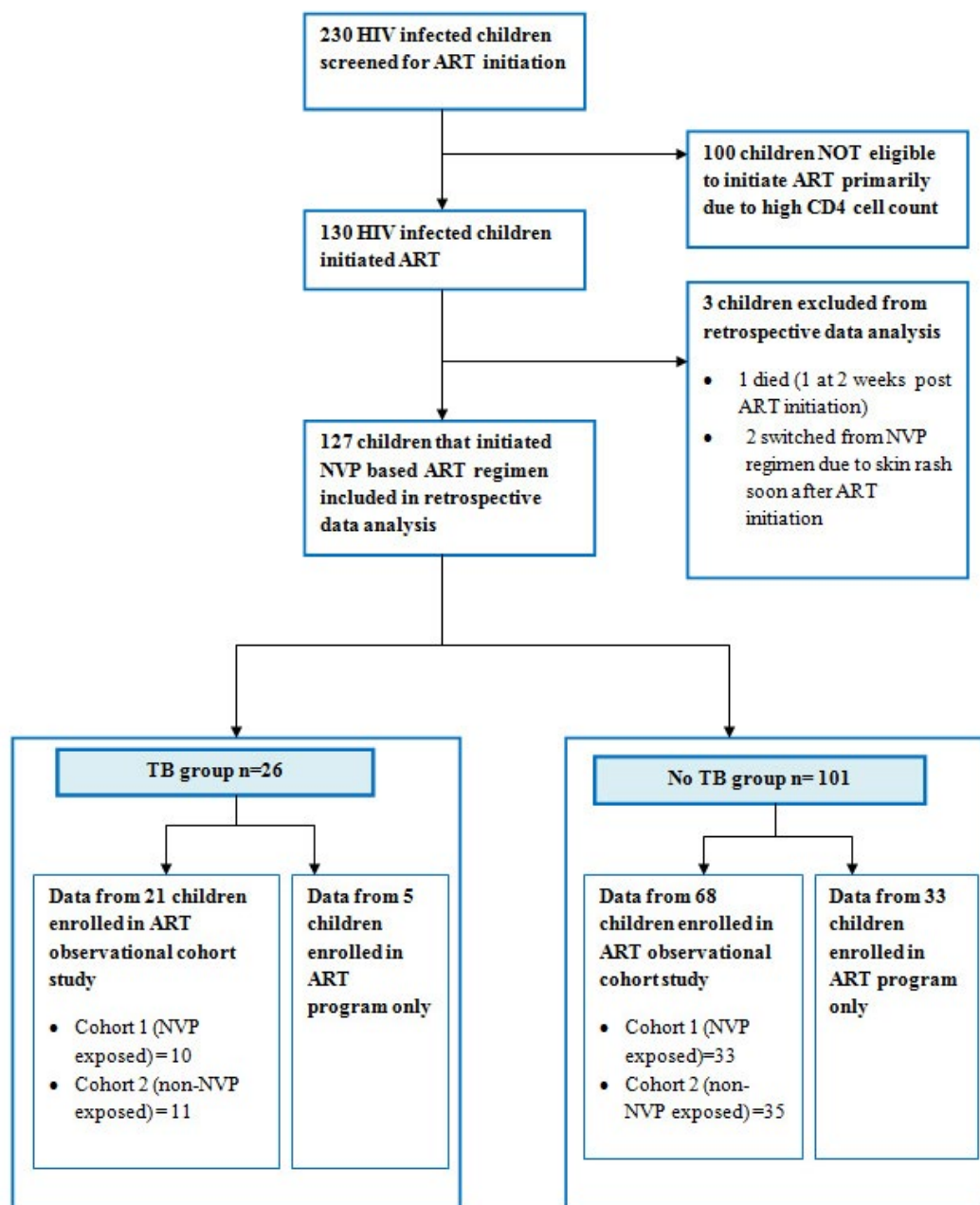


Figure 1: Study Profile

both groups did not have CD4 cell count and viral load data at week 72 and week 96.

In the TB group, 15/26 (58%) and 16/26 (62%) of the children did not have viral load and CD4 cell count data at week 72 and 96 respectively. In the no TB group, 24/100 (26%) and 35/100 (35%) of the children did not have both CD4 cell count and viral load data at week 72 and week 96 respectively.

Adverse Drug Reaction Monitoring

An assessment of clinical signs and symptoms was conducted at each study visit to monitor adverse drug reactions.

ALT and AST were assessed at baseline, 2 weeks after ART initiation and thereafter when clinically indicated, to monitor NVP toxicity.

Laboratory Methods

The CD4 cell counts/ percent, HIV-1 RNA and Liver Function Tests (LFTs) were done at the College of American Pathologists (CAP) certified MUJHU core Research Laboratory in Kampala, Uganda. CD4 cell testing was performed using a fluorescence-activated cell sorting instrument (Becton-Dickinson, San Jose CA, USA). Quantitative HIV-1 RNA PCR was performed using the Roche HIV-1 Amplicor MONITOR assay

v1.5 kit (Roche Diagnostics, Indianapolis IN, USA) on plasma separated from whole blood and frozen at -70 °C within 24 hours of collection.

Data Collection and Statistical analysis

Data of ART eligible children enrolled in the ART program and ART observational cohort at MUJHU were obtained from the study database and through chart review of participant source files.

Baseline characteristics (sex, age, WHO clinical staging, weight for age and height for age Z scores with respect to the WHO-based reference population of children of similar age and gender) of the children in the TB group and those in the no TB group were compared using Chi square (χ^2) and Wilcoxon rank sum test. Statistical comparisons of CD4 cell percent and HIV-1 RNA PCR at baseline, every 12 weeks until 48 weeks are based on the student's t-test and Wilcoxon rank sum test. Graphs of mean and 95% Confidence Interval (CI) bars are used to illustrate virologic and immunologic trends during 48 weeks of follow up. Differences in virologic outcome of the two groups over the follow up period by Kaplan Meir plots were assessed for statistical significance using the log rank test. The *p*-values are evaluated for statistical significance at the 0.05 two sided alpha significance level. All data analysis was performed with STATA Version 10 (StataCorp.2007. Statistical Software: Release 10, College Station, TX, StataCorp LP).

Ethical Approvals

Institutional Review Board (IRB) approval was obtained from Makerere University, Faculty of Medicine Research and Ethics Committee and the Uganda National Counsel of Science and Technology (UNCST) for the primary observational cohort study. Written informed consent was obtained from parents/

legal guardians of the children enrolled in the ART observational cohort study before study specific procedures were performed; however written assent was not obtained from the children because it was not an IRB requirement at that time.

RESULTS

Baseline Characteristics

A total of 127 HIV infected Ugandan children on a NVP containing ART regimen were included in the retrospective analysis. Twenty-six (20.5%) of these 127 children were also treated with a rifampicin containing regimen for TB disease (TB group) and 101 (79.5%) received ART alone (no TB group). Three of the 26 (11%) children in the TB group were diagnosed with TB disease and started anti-TB treatment from other care centers prior to initiating ART at the MUJHU clinic. The rest, 23/26 (89%) were diagnosed during follow up in the ART program and were classified as probable TB. There were no cases of culture confirmed tuberculosis. The baseline characteristics of the children in both groups are shown in Table 2. Children in the TB group were significantly younger than those in the no TB group with median age of 2.7 years (IQR 1.2-4.4) *versus* 5.2 years (IQR 2.4-7.0) (*p*=0.034). There was no significant difference in the WHO clinical stage of the two groups with about 1/3 of the children in each group in WHO clinical stage 3 & 4 (*p*=0.085). There were no significant differences in sex, median weight for age and height for age Z scores between the two groups at baseline.

Immunologic Outcomes

Children in both the TB group and no TB group were severely immunosuppressed at enrollment with a median baseline CD4 cell percent (IQR) of 9.2 (0.5-17.5) *versus* 12.9 (2.1-23.7) respectively. There was a robust increase in median CD4

Variable	TB group (n=26)	No TB group (n=101)	<i>p</i> value
Sex Male (%)	15 (58%)	48 (48%)	0.355
Primary Caregiver mother (%)	18 (69%)	68 (67%)	0.648
Caregiver level of education (%)	04 (15.4%)	11 (10.9%)	0.507
No education			
Primary, Higher & Tertiary level	22 (84.6%)	90 (89.1%)	
Median age in years (IQR)	2.7 (1.2-4.4)	5.2 (2.4-7.0)	0.034
WHO clinical stage 3 & 4	10 (38%)	29 (29%)	0.085
Median weight for age Z score (IQR)	-2.41 ((-3.17)-(-0.87))	-1.76(-2.66-0.914)	0.129
Median height for age Z score (IQR)	-0.42 (-1.31-0.36)	-0.34 (0.98-0.57)	0.369

Table 2: Baseline characteristics of HIV infected Ugandan children on a nevirapine based ART regimen grouped by treatment with or without rifampicin.

cell percent by 12 weeks and a sustained 3 fold increase with a median increase of 19.8% in the TB group *versus* 16% in the no TB group by 48 weeks of follow-up. The median CD4% (IQR) during follow-up for the TB group *versus* the no TB group was: 17.0 (8.0-26) *versus* 20.9 (8.0-33.8), $p=0.147$ by 12 weeks; 26.0 (12.7-39.3) *versus* 22.9 (7.5-38.3), $p=0.472$ by 24 weeks; 26.6 (13.6-39.6) *versus* 26.4 (12.3-40.5), $p=0.927$ by 36 weeks and 29.0 (20.0-38) *versus* 28.9 (16.8-41), $p=0.931$ by 48 weeks respectively.

There was no significant difference in immunologic response to treatment between the children on NVPART alone and those on NVPART and rifampicin (see Figure 2).

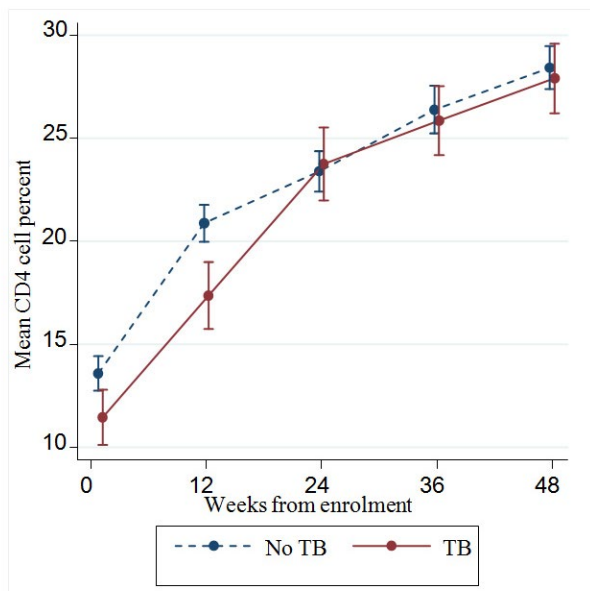


Figure 2: Immunologic response of HIV infected Ugandan children on a nevirapine based ART regimen with or without concurrent rifampicin anti-TB treatment.

Virologic Outcomes

There was no significant difference in the median $\log_{10}$ RNA copies (IQR) between the TB group and the no TB group at baseline with values of 5.69 (5.19-6.19) *versus* 5.59 (4.86-6.32); $p=0.576$. By 12 weeks and through 48 weeks, children in both groups had median $\log_{10}$ RNA copies of 2.60 (undetectable viral load). Median $\log_{10}$ RNA copies (IQR) during follow up for the TB group *versus* the no TB group was as follows: 2.60 (2.60-3.06) *versus* 2.60 (2.48-2.72); $p=0.86$ by 12 weeks; 2.60 (2.60-2.99) *versus* 2.60 (2.60-2.60); $p=0.358$ by 24 weeks; 2.60 (2.60-2.89) *versus* 2.60 (2.60-2.60); $p=0.706$ by 36 weeks and 2.60 (2.60-2.99) *versus* 2.60 (2.60-2.60); $p=0.327$ by 48 weeks respectively. All children attained a 3 fold drop ($0.5 \log_{10}$) in mean viral load by 12 weeks which was sustained through 48 weeks irrespective of receiving rifampicin (Figure 3). Kaplan-Meier plot for achieving virologic success (viral load <400 copies/ml) demonstrates success in about 60% of the children in both groups by 12 weeks on ART (Figure 4). By 24 weeks, at least 80% of all children attained virologic success, with no significant difference between the two groups $p=0.637$.

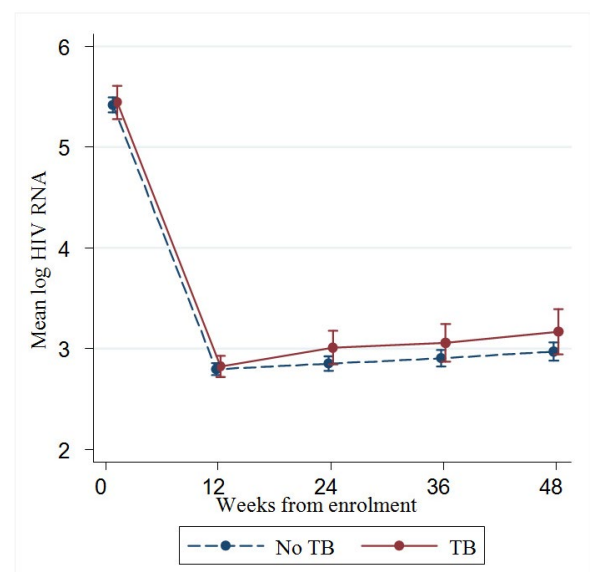


Figure 3: Virologic response of HIV infected Ugandan children on a nevirapine based ART regimen with or without concurrent rifampicin anti-TB treatment.

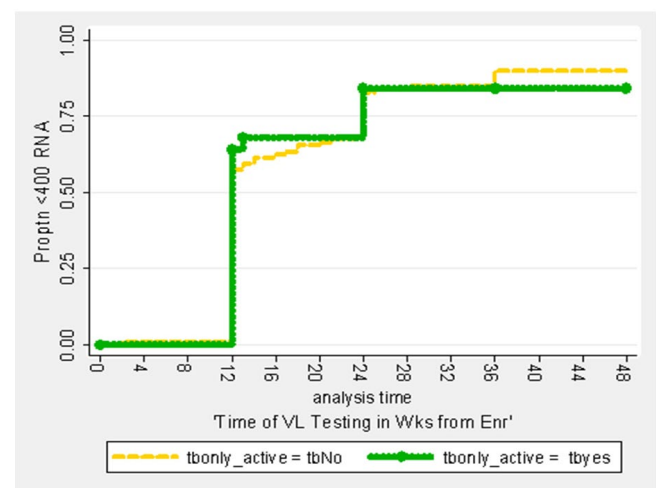


Figure 4: Kaplan Meier analysis for virologic success (<400copies/ml) over time in HIV infected Ugandan children on nevirapine based ART regimen alone or with a rifampicin anti-TB regimen for TB disease treatment, baseline to 48 weeks after ART initiation.

Adverse drug reactions

Overall there were few (seven) adverse events classified as suspected adverse drug reactions. Skin rash occurred in 3 of the 127 children, with 2 in the TB group and 1 in no TB group. Raised ALT/AST was observed in 3/127 (2.4%) of the children with one in the TB group and two in the no TB group. All the events were of mild to moderate severity and none warranted stopping either the anti-TB treatment or ART. All suspected adverse drug reactions resolved spontaneously during follow-up. There was one death due to HIV nephropathy in the no TB group at 44 weeks of follow-up.

DISCUSSION

Nevirapine is still widely used as part of the first line ART regimen in sub-Saharan Africa and HIV-TB co-infection

presents a treatment dilemma especially in children where ARV drug options are limited. Currently, WHO recommends initiation of ART for all HIV infected children ≤ 5 years of age, regardless of WHO clinical stage or CD4 count. For HIV-TB co-infected children, both ART and anti-TB treatment should be initiated as soon as the diagnosis of either is made.³ If TB diagnosis is made prior to initiation of ART, TB treatment should be initiated first and then ART started as soon as possible thereafter (preferably within 2-8 weeks of initiation of TB treatment).³ Despite the current WHO recommendations on using a LPV/r based regimen as first line ART for all HIV infected infants under 3 years of age, the need for NVP based ART regimens in this age group has not been eliminated because many countries in Africa have limited access to Protease Inhibitor (PI) - based regimens due to cost implications and the need to maintain a cold chain. Although a triple nucleoside ART regimen provides a suitable option in the treatment of HIV-TB co-infection in children under 3 years of age, currently "there is limited data on the efficacy of this regimen in the context of TB".³ It is thus very important to study the potential effect of concomitant use of rifampicin with a NVP based ART regimen in children.

Our study demonstrated that concomitant use of a rifampicin anti-TB regimen for treatment of TB in HIV infected children on a NVP based ART regimen does not significantly alter their early immunologic and virologic response over 48 weeks of treatment. All children on NVP based ART including those who were severely immunosuppressed at baseline with CD4% < 15 , were able to attain a significant immune response by 48 weeks of follow up, irrespective of receiving rifampicin. These children were also able to achieve virologic suppression which was sustained through 48 weeks. Our findings are similar to those reported by Manosuthi et al where there was no difference in long term virologic and immunologic outcomes on NVP based ART (at a dose of 400 mg/day) among HIV/TB co-infected adults receiving rifampicin compared to adults without TB co-infection.¹⁵ In this prospective observational study, 70 HIV-TB co-infected adults on rifampicin and 70 HIV infected adults on NVP based ART, were followed for 4 years of ART and their immunologic and virologic outcomes evaluated 12 weekly until 96 weeks and then every 24 weeks thereafter. The percentage of patients who achieved HIV-1 RNA < 50 copies/ml was 52.9% in the TB group and 50% in the control group ($p=0.866$).¹⁵ A retrospective study done in Botswana ($n=310$) also found no difference in the immunologic and virologic outcomes of HIV positive adults on NVP based ART as compared to EFV based ART irrespective of rifampicin co-administration for TB treatment over the first 12 months on ART.¹⁶

A recent open label randomized trial conducted in Mozambique involving over 500 HIV-TB co-infected adults randomized to receive either a NVP based ART regimen or EFV based ART regimen demonstrated no significant difference in virologic outcomes between the two groups at 48 weeks.¹⁷ In the paediatric population, published data in this area is limited

and mainly focused on pharmacokinetics of NVP. There are limited published studies directly evaluating the effect of rifampicin on immunologic and virologic outcomes in HIV-TB co-infected children on NVP based ART regimens and it is important to study this because unlike adults, children tend to have higher viral loads and are thus less likely to be adequately suppressed with lower plasma NVP drug levels.¹⁸

Rifampicin is a known strong inducer of cytochrome P450 and as such results in reduced plasma concentrations of NNRTIs and PIs if used concurrently with these drugs.¹⁹ Both adult and paediatric studies done in Africa, Thailand and India have shown varying levels of the effect on NVP plasma levels as a result of the drug-drug interaction during concomitant use of a rifampicin containing anti-TB regimen and a NVP based ART regimen.^{4-6,8,20-23} An intensive pharmacokinetic study of standard-dose NVP with and without rifampicin in South African adults found sub-therapeutic NVP levels in 6 of 16 patients during rifampicin dosing.⁸ A pharmacokinetic sub analysis conducted on 20 of the children in this study as reported by Barlow Mosha et al. also found that NVP trough concentration was significantly reduced in children who received rifampicin and NVP concurrently.⁵ This is consistent with findings from another pharmacokinetic study in 37 Zambian HIV infected children aged < 3 years which reported reductions in NVP plasma levels among 41% of children on a NVP based ART regimen and concomitant tuberculosis therapy with rifampicin compared to those on NVP alone ($p<0.001$).⁶ These findings raise concerns about increased risk of resistance in these circumstances of suboptimal NVP plasma concentrations and this has been documented in a sub population of children included in this analysis.¹³ Resistance testing was performed on samples from 74 children who were enrolled in our primary observational ART cohort study and pre-ART samples from 2 children (2.7%) were found to have resistance to NNRTIs and Nucleoside Reverse Transcriptase Inhibitors (NRTIs).¹³ In addition, 5 (9.8%) pre-ART samples from 51 of children with HIV sub-type A and D among the 74 children were found to have selected NVP resistance mutations (K103N, Y181C, and G190A), with majority (68%) of these children having had prior exposure to single dose NVP (sdNVP) for Prevention of Mother To Child HIV Transmission (PMTCT). Resistance testing was performed on 12 samples from the 74 children who had pre-ART samples analysed for resistance and were not virologically suppressed at 48 weeks. All the 12 samples had resistance to NNRTIs including NVP ($n=12$), EFV ($n=2$) and delavirdine ($n=10$).¹³ Five of the 12 children who had NVP resistance mutations had history of sdNVP exposure at birth and 1 of these children initiated ART at 12 months of age while the rest initiated ART between 14 and 16 months of age. However, in this drug resistance analysis, the effect of concomitant administration of rifampicin among HIV-TB co-infected children was not specifically evaluated.

The effect of suboptimal NVP concentrations on immunologic and virologic response has not been fully explored in

children. Studies evaluating immunologic, virologic responses and ARV drug resistance in HIV-TB co-infected children in relation to concomitant rifampicin and NVP ART regimen administration are crucial. Adult studies have demonstrated that the decreased bioavailability of NVP due to rifampicin co-administration could be overcome by increasing the dose of NVP.²⁴ Findings from a study done in India indicate that concomitant administration of a NVP ART regimen and rifampicin in HIV-TB co-infected children does not alter NVP blood levels if the NVP dose is increased by 50-90 mg/m²/day.²⁵ This however was a cross-sectional study involving only 7 HIV-TB co-infected children and was not powered enough to draw generalizable conclusions. WHO currently recommends an increased dose of NVP of 200 mg/m² when co-administered with rifampicin among children under 3 years of age.³ Further research is therefore needed to document pharmacokinetic responses as well as efficacy of higher dose NVP when co-administered with rifampicin among children.

The virologic and immunologic treatment success in both groups of children in this retrospective analysis could probably be attributed to possible high adherence rates to ART in this study setting with intensive participant follow up, frequent adherence counseling/support, the use of a Fixed Dose Combination (FDC), and close clinical monitoring. Although a study done in Zambia and Malawi demonstrated that children who received half or quarter tablet of Triomune FDC were more likely to be under dosed with NVP as compared to those who received a full tablet findings from this observational cohort of Ugandan children showed sustained clinical, immunologic and virologic response in children who received the divided adult Triomune tablet.¹¹ Other studies in Sub Saharan Africa have demonstrated similar immunologic and virologic outcomes among children on Triomune FDC followed for 6-12 months as well as other newer NVP based pediatric FDCs.^{26,27}

The strengths of this study include the longitudinal laboratory and clinical monitoring as well as high rates of follow up in the parent study. The TB and No TB groups were immunologically and virologically comparable at baseline.

One limitation of this study is the variation in duration of TB treatment in relation to time of ART initiation. The follow up period of 48 weeks and a relatively small sample size of HIV/TB co-infected children may not be used to generalize long term immunologic and virologic outcomes of HIV-TB co-infected children. Longer duration study with larger sample size could confirm the findings of this study.

CONCLUSION

The results of this study are encouraging and suggest that NVP based ART may remain effective among children co-infected with TB who received rifampicin-based treatment for TB disease. The TB-group demonstrated satisfactory immuno-

logic and virologic responses to nevirapine - based ART similar to those children without TB disease. These findings should be confirmed through larger prospective studies and would be helpful in countries with high HIV/TB burden and limited antiretroviral options. Since NVP is a convenient and relatively affordable antiretroviral drug because of its availability in generic fixed-dose combinations, large robust studies to evaluate the efficacy of the currently recommended higher dose of NVP with concurrent use of rifampicin in paediatric HIV-TB co-infection, particularly among children under 3 years of age, will further inform the current WHO recommendations.³

ACKNOWLEDGEMENTS

The authors would like to thank the families and children who participated in the International Leadership Award (ILA) study and the ILA ART Program. We would also like to acknowledge the staff (P. Ajuna, M. Owor, I. Kimuli, M. Luttajumwa, B. Musoke, G. Nalubega, R. Namwanjje, R. Kayondo and P. Buyondo) based at Makerere University – Johns Hopkins University Research Collaboration under the leadership of Associate Professor. Philippa Musoke (ILA recipient) without whose dedication this study could not have been done. We sincerely appreciate the support of the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) through the ILA grant for the study.

CONFLICTS OF INTEREST: None.

REFERENCES

1. WHO. Global update on the health sector response to HIV 2014, World Health Organization. Website: <http://www.who.int/hiv/en/>. 2015; Accessed 2015.
2. WHO. Global tuberculosis report 2013; , World Health Organization. Website: <http://apps.who.int/iris/handle/10665/91355>. 2013; Accessed 2015.
3. WHO. Consolidated guidelines for use of antiretroviral drugs for treating and preventing HIV infection; recommendations for a public health approach. Website: <http://www.who.int/hiv/pub/guidelines/arv2013/en/>. 2013; Accessed 15 Feb 2014.
4. Prasitsuebsai W, Cressey T, Capparelli E, et al. Pharmacokinetics of nevirapine when co administered with rifampicin in HIV infected Thai children with tuberculosis in 16th Conference on Retroviruses and Opportunistic Infections. Montreal, Canada. 2009.
5. Barlow-Mosha L, Musoke P, Ajuna P, et al. Early effectiveness of Triomune in HIV infected Ugandan children. in 3rd IAS Conference on HIV Pathogenesis and Treatment. Rio de Janeiro, Brazil. 2005.
6. Oudijk JM, McIlleron H, Mulenga V, et al. Pharmacokinetics

- of nevirapine in HIV-infected children under 3 years on rifampicin-based antituberculosis treatment. *AIDS*. 2012; 26(12): 1523-1528. doi: [10.1097/QAD.0b013e3283550e20](https://doi.org/10.1097/QAD.0b013e3283550e20)
7. Manosuthi W, Sungkanuparph S, Tantanathip P, et al. A randomized trial comparing plasma drug concentrations and efficacies between 2 nonnucleoside reverse-transcriptase inhibitor-based regimens in HIV-infected patients receiving rifampicin: the N2R Study. *Clinical Infectious Diseases*. 2009; 48(12): 1752-1759. doi: [10.1086/599114](https://doi.org/10.1086/599114)
8. Cohen, K, van Cutsem G, Boule A, et al. Effect of rifampicin-based antitubercular therapy on nevirapine plasma concentrations in South African adults with HIV-associated tuberculosis. *Journal of antimicrobial chemotherapy*. 2008; 61(2): 389-393. doi: [10.1093/jac/dkm484](https://doi.org/10.1093/jac/dkm484)
9. WHO. Scaling up antiretroviral therapy in resource-limited settings: guidelines for a public health approach: executive summary. Website: http://www.who.int/hiv/pub/prev_care/ScalingUp_E.pdf. 2002; Accessed 2015.
10. Musoke PM, Barlow-Mosha L, Bagenda D, et al. Response to antiretroviral therapy in HIV-infected Ugandan children exposed and not exposed to single-dose nevirapine at birth. *JAIDS*. 2009; 52(5): 560-568. doi: [10.1097/QAI.0b013e3181b93a5a](https://doi.org/10.1097/QAI.0b013e3181b93a5a)
11. Barlow-Mosha L, Bagenda D, Mudiope P, et al. The long-term effectiveness of generic adult fixed-dose combination antiretroviral therapy for HIV-infected Ugandan children. *African health sciences*. 2013; 12(3): 249-258.
12. WHO. Antiretroviral therapy of HIV infection in infants and children: towards universal access: recommendations for a public health approach. Website: <http://www.who.int/hiv/pub/guidelines/art/en/>. 2006; Accessed 2015.
13. Towler WI, Barlow-Mosha L, Church JD, et al. Analysis of drug resistance in children receiving antiretroviral therapy for treatment of HIV-1 infection in Uganda. *AIDS research and human retroviruses*. 2010; 26(5): 563-568. doi: [10.1089/aid.2009.0164](https://doi.org/10.1089/aid.2009.0164)
14. Harries AD, Maher D, Graham S. TB/HIV: a clinical manual. 2004: World Health Organization. Website: http://www.who.int/maternal_child_adolescent/documents/9241546344/en/. 2004; Accessed 2015.
15. Manosuthi W, Tantanathip P, Chimsuntorn S, et al. Treatment outcomes of patients co-infected with HIV and tuberculosis who received a nevirapine-based antiretroviral regimen: a four-year prospective study. *International Journal of Infectious Diseases*. 2010; 14(11): e1013-e1017. doi: [10.1016/j.ijid.2010.06.016](https://doi.org/10.1016/j.ijid.2010.06.016)
16. Shipton L, Wester C, Stock S, et al. Safety and efficacy of nevirapine-and efavirenz-based antiretroviral treatment in adults treated for TB-HIV co-infection in Botswana. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease*. 2009; 13(3): 360.
17. Bonnet M, Bhatt N, Baudin E, et al. Nevirapine versus efavirenz for patients co-infected with HIV and tuberculosis: a randomised non-inferiority trial. *The Lancet infectious diseases*. 2013; 13(4): 303-312. doi: [10.1016/S1473-3099\(13\)70007-0](https://doi.org/10.1016/S1473-3099(13)70007-0)
18. Venturini E, Turkova A, Chiappini E, et al. Tuberculosis and HIV co-infection in children. *BMC infectious diseases*. 2014. 14(Suppl 1): S5. doi: [10.1186/1471-2334-14-S1-S](https://doi.org/10.1186/1471-2334-14-S1-S)
19. Niemi M, Backman JT, Fromm MF, et al. Pharmacokinetic interactions with rifampicin. *Clinical pharmacokinetics*. 2003; 42(9): 819-850. doi: [10.2165/00003088-200342090-00003](https://doi.org/10.2165/00003088-200342090-00003)
20. Manosuthi W, Sungkanuparph S, Thakkinstian A, et al. Plasma nevirapine levels and 24-week efficacy in HIV-infected patients receiving nevirapine-based highly active antiretroviral therapy with or without rifampicin. *Clinical infectious diseases*. 2006; 43(2): 253-255. doi: [10.1086/505210](https://doi.org/10.1086/505210)
21. Sinha S, Dhooria S, Kumar S, et al. The antiretroviral efficacy of highly active antiretroviral therapy and plasma nevirapine concentrations in HIV-TB co-infected Indian patients receiving rifampicin based antituberculosis treatment. *AIDS Res Ther*. 2011; 8(1): 41. doi: [10.1186/1742-6405-8-41](https://doi.org/10.1186/1742-6405-8-41)
22. Ribera E, Pou L, Lopez RM, et al. Pharmacokinetic interaction between nevirapine and rifampicin in HIV-infected patients with tuberculosis. *Journal of acquired immune deficiency syndromes* (1999). 2001; 28(5): 450-453. doi: [10.1097/00126334-200112150-00007](https://doi.org/10.1097/00126334-200112150-00007)
23. Matteelli A, Saleri N, Villani P, et al. Reversible reduction of nevirapine plasma concentrations during rifampicin treatment in patients coinfecting with HIV-1 and tuberculosis. *JAIDS*. 2009; 52(1): 64-69. doi: [10.1097/QAI.0b013e3181b0328f](https://doi.org/10.1097/QAI.0b013e3181b0328f)
24. Ramachandran G, Hemanthkumar AK, Rajasekaran S, et al. Increasing nevirapine dose can overcome reduced bioavailability due to rifampicin coadministration. *JAIDS*. 2006; 42(1): 36-41. doi: [10.1097/01.qai.0000214808.75594.73](https://doi.org/10.1097/01.qai.0000214808.75594.73)
25. Ira S, Soumya S, Geetha R, et al. Serum nevirapine and efavirenz concentrations and effect of concomitant rifampicin in HIV infected children on antiretroviral therapy. *Indian Pediatrics*. 2011; 48(12): 943-947. doi: [10.1007/s13312-011-0153-3](https://doi.org/10.1007/s13312-011-0153-3)
26. O'Brien DP, Sauvageot D, Zachariah R, et al. In resource-limited settings good early outcomes can be achieved in children using adult fixed-dose combination antiretrovi-

ral therapy. *AIDS*. 2006; 20(15): 1955-1960. doi: [10.1097/01.aids.0000247117.66585.ce](https://doi.org/10.1097/01.aids.0000247117.66585.ce)

27. Wamalwa DC, Farquhar C, Obimbo EM, et al. Early response to highly active antiretroviral therapy in HIV-1-infected Kenyan children. *Journal of acquired immune deficiency syndromes* (1999). 2007;. 45(3): 311. doi: [10.1097/QAI.0b013e318042d613](https://doi.org/10.1097/QAI.0b013e318042d613)