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Authors

Bwakura Dangarembizi, Mutsa
Samson, Pearl
Capparelli, Edmund V
et al.

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Establishing dosing recommendations for Efavirenz in HIV/TB coinfected children less than three years of age.

Mutsa Bwakura Dangarembizi[a], **Pearl Samson**[b,i], **Edmund V. Capparelli**[c,d], **Carolyn Bolton Moore**[e,f], **Patrick Jean-Philippe**[g], **Stephen A. Spector**[c,d], **Nahida Chakhtoura**[h], **Alex Benns**[i], **Bonnie Zimmer**[i], **Lynette Purdue**[g], **Chivon Jackson**[j], **Carole Wallis**[k], **Jennifer L. Libous**[l], and **Ellen G. Chadwick**[m] **IMPAACT P1070 Study Team**

[a]University of Zimbabwe College of Health Sciences, Harare, Zimbabwe

[b]Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

[c]University of California, San Diego, La Jolla, California, USA

[d]Rady Children's Hospital, San Diego, California, USA

[e]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia

[f]University of Alabama at Birmingham, Birmingham, Alabama, USA

[g]National Institutes of Allergy and Infectious Diseases, Bethesda, Maryland, USA

[h]Eunice Kennedy Shriver National Institute for Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA

[i]Frontier Science and Technology Research Foundation, Amherst, New York, USA

[j]Department of Pediatrics, Texas Children's Hospital Baylor College of Medicine, Houston, Texas, US

[k]BARC-SA and Lancet Laboratories, Johannesburg, South Africa

[l]IMPAACT Operations Center, FHI360, Durham, North Carolina, USA

[m]Northwestern University's Feinberg School of Medicine, Chicago, Illinois, USA

Abstract

Background: CYP2B6 516 genotype-directed dosing improves efavirenz (EFV) exposures in HIV-infected children <36 months of age but such data are lacking in those with tuberculosis (TB) co-infection.

Methods: Phase I, 24-week safety and pharmacokinetic (PK) study of EFV in HIV-infected children 3-<36 months of age, with or without TB. CYP2B6516 genotype classified children into extensive [(EM), 516TT/GT] and poor metabolizers [(PM), 516TT]. EFV doses were 25–33% higher in children with HIV/TB co-infection targeting EFV area-under-the-curve (AUC) 35–180

Corresponding author: Dr Mutsa Bwakura Dangarembizi, University of Zimbabwe College of Health Sciences, Box A178, Avondale, Harare, Zimbabwe.

mcg*hr/mL, with individual dose adjustment as necessary. Safety and virologic evaluations were performed every 4–8 weeks.

Results: Fourteen children from 4 African countries and India with HIV/TB enrolled, 11 3-<24 months of age and 3, 24–36 months; 12 EM and 2 PM. Median (Q1,Q3) EFV AUC was 92.87 (40.95,160.81) mcg*h/mL in 8/9 evaluable children 3-<24 months and 319.05 (172.56, 360.48) mcg*h/mL in children 24–36 months. AUC targets were met in 6/8 and 2/5 of the younger and older age groups, respectively. EFV clearance was reduced in PM's and older children. Pharmacokinetic modelling predicted adequate EFV concentrations if children <24 months received TB-uninfected dosing. All nine completing 24 weeks achieved viral suppression. Five/14 discontinued treatment early: 1 neutropenia, 3 non-adherence and 1 with excessive EFV AUC.

Conclusion: Genotype-directed dosing safely achieved therapeutic EFV concentrations and virologic suppression in HIV/TB-co-infected children <24 months, but further study is needed to confirm appropriate dosing in those 24–36 months of age. This approach is most important for young children and currently a critical unmet need in TB-endemic countries.

Keywords

Children; HIV; tuberculosis; pharmacokinetics; efavirenz

Background

Childhood tuberculosis (TB) comprises more than 10% of total TB cases in high burden countries.[1,2] HIV/TB co-infection carries a higher mortality risk in younger children and in those with more advanced HIV-related immunosuppression.[3] The World Health Organisation (WHO) recommends a 4-drug TB treatment regimen (rifampicin, isoniazid, pyrazinamide and ethambutol) in TB/HIV co-infected children.[4] Antiretroviral therapy (ART) should be initiated within 2–8 weeks of starting anti-TB treatment (ATT) but is complicated by drug-drug interactions with rifampicin. Rifampicin, a potent inducer of the cytochrome P450 (CYP) enzyme system, [5] enhances CYP2B6-mediated efavirenz (EFV) clearance and reduces the maximum plasma concentration (C_{max}) and area under the curve (AUC) of EFV in healthy volunteers. [6] In adults, an EFV dose increase of 33% when given in combination with rifampicin has provided similar EFV levels to standard EFV dosing without rifampicin.[7,8] However, a recent study in children 3–14 years of age suggests a complex interaction in which rifampicin and isoniazid may counteract each other to neutralize the effect on EFV clearance such that no dose adjustment of EFV is required during ATT.[9]

The WHO-preferred ART regimen in children starting ART while receiving rifampicin-based ATT includes triple nucleoside reverse transcriptase inhibitors (NRTI) in all children and EFV plus 2 NRTIs in children aged 3 years or older, highlighting the dearth of data to inform ART choice and dosing, particularly in children younger than 3 years.[10] High inter-subject pharmacokinetic variability has impeded the establishment of EFV dosing recommendations in children <3 years of age. In a previously published report, we found a strong influence of CYP2B6 G516T genotype on EFV exposures in children with HIV aged 3–36 months. [11] Based on these data, we recommended genotype-directed dosing and found

that using that approach, children <3 years of age with the CYP2B6 516TT genotype (poor metabolizers, PM) required only 25% of the EFV dose given to participants with GG and GT genotypes (extensive metabolizers, EM) to achieve therapeutic EFV exposures. We now present 24-week safety, pharmacokinetics and virologic response of EFV-based ART using genotype-directed dosing in children 3–36 months of age with HIV/TB co-infection receiving concomitant ATT.

Methods

Study design

IMPAACT Protocol P1070 was a prospective, Phase I open-label trial of EFV in children with HIV in two age groups (3-<24 months and 24–36 months) without (Cohort I) or with TB co-infection (Cohort II), implemented in four tuberculosis-endemic countries in Sub-Saharan Africa and India between 2010 and 2015. Cohort I results and the overall study design of the trial have been previously reported.[11] This paper reports findings from Cohort II children, and children who developed TB while enrolled in Cohort I and moved to Cohort I, Step 2 after starting ATT. EFV capsules were supplied as part of the study, while background NRTIs and ATT were obtained locally. Children were treated with once-daily EFV as opened capsules mixed with breast milk, formula or food and two NRTIs selected by the site clinicians.

Dosing Approach

CYP2B6 516 genotype and an intensive pharmacokinetic (PK) study was performed at week 2 with subsequent individual dose adjustments based on the PK results. The dose adjustment criteria based on a target AUC of 35 −180 mcg*h/mL was similar to that used in Pediatric AIDS Clinical Trials Group protocol P1021[12]. The first eight PM participants in protocol version (V)1.0 had excessive EFV exposures which were not amendable to the study-directed dose adjustment, so the study was amended to V2.0, to require that the CYP2B6 genotyping be performed at screening before initiating EFV therapy.[11] Based on adult data reporting increased EFV metabolism with rifampicin-based therapy, the starting EFV dose for TB co-infected participants (Cohort II) was designed to be approximately 25–33% greater than doses in the TB-uninfected cohort.[7,8] Using weight band dosing, the V1.0 EFV dose was approximately 2000mg x (Weight in kgs/70)$^{0.7}$QD. In V2.0 of the protocol, a genotype-directed dose reduction of ~75% was initiated in PMs resulting in a dose of ~500mg x (Weight in kgs/70)$^{0.7}$QD. (Table 1)

Genotyping methods

Genomic DNA to investigate CYP2B6 G516T (rs3745274) was extracted from dried blood spots (DBS) and processed using standard methods and performed real-time during the study. [13] CYP2B6 T983C (rs28399499) was assessed from stored DBS after study closure.

Pharmacokinetic Assessments

Intensive PK sampling was performed two weeks after initiation of study treatment: prior to the observed EFV dose and 2, 4, 8, 12 and 24 hours post-dose. DBS and plasma samples were prepared from each PK sample. DBS samples were shipped and analyzed real time and

individual dose adjustments made if the AUC was outside the established target range of 35–180mcg*h/mL.[12] Plasma samples were batched for determination of PK parameters in the final analysis. Efavirenz AUC was determined by non-compartmental methods. A modified intensive PK study with samples collected pre-dose, 4, 8, and 24 hours post-dose was performed in participants who required dose adjustments based on the week 2 intensive PK evaluation. Participants assessed to be adherent to therapy who did not achieve an AUC of 35–180 mcg*h/mL even after a dose adjustment were taken off study treatment and treated with non-study ART.

Safety and virologic assessments

Adverse events were assessed at all participant visits using Division of AIDS Toxicity Grading Tables (https://rsc.niaid.nih.gov/sites/default/files/table-for-grading-severity-of-adult-pediatric-adverse-events.pdf). Virologic response was assessed using plasma HIV-RNA at weeks 4,8,16 and 24. Virologic success was defined as at least 1-log drop from study entry HIV RNA or HIV RNA level <400 copies/mL at week 8. A safety endpoint was defined as any treatment-related Grade 3 or Grade 4 toxicity requiring permanent discontinuation of EFV.

Dose Finding Guidelines

To establish a dose for each age group, the first 8 EM participants were evaluated based on their week 2 AUC plasma PK results and safety data through week 4. The dose was considered safe for the age group if no participants experienced a Grade 4 life-threatening toxicity or a Grade 4 toxicity accompanying any serious adverse event (SAE) or death judged to be at least possibly related to EFV. At least 6 of 8 participants were required to achieve a plasma AUC within the target range to deem the dose acceptable.

Predictive Efavirenz PK Modeling

It was recognized that a unified approach to EFV dosing in infants regardless of TB treatment status could simplify EFV use. Predicted EFV AUC and trough (C24) exposures in HIV/TB co-infected participants with the lower Cohort I dosing were estimated, assuming linear EFV PK. The observed AUCs and C24 from Cohort II and Cohort I, Step 2 participants were multiplied by the ratio of the Cohort I dose/actual received doses in Cohort II to generate predicted AUC and C24. The frequency of AUC and C24 in the target ranges of 35–180 mcg*h/mL and 1–4 mcg/mL, respectively, between these strategies were compared.

Statistical Methods

Pharmacokinetic analyses included participants enrolled in Cohort II and the two Cohort I participants who developed TB while on study. Safety and efficacy analyses included only participants enrolled in Cohort II and are presented in aggregate; other analyses are further stratified by age and/or CYP2B6 516 genotype. Descriptive statistics were used to summarize study entry demographic data. The proportion of participants experiencing adverse events deemed to be at least possibly treatment-related was bounded by 95% exact confidence interval (CI). Median and interquartile ranges (IQR) were calculated for AUC,

C24, apparent clearance (CL/F), Cmax and the time taken to reach the maximum drug concentrations (Tmax). Virologic response was analyzed using an 'as-treated' analysis such that only participants who remained on study drug and with evaluable data were included in this analysis. Proportion of participants achieveing virologic success and median and IQR $\log_{10}$ HIV-RNA changes from study entry were calculated.

Ethical Review

The protocol, amendments, informed consent forms and relevant study documents were approved by local ethics committees of all participating sites. Written informed consent was obtained from the participants' parents/legal guardians. The Clinical Trials.gov identifier is NCT00802802.

Results

Study Participants

Fourteen participants with HIV/TB co-infection were enrolled in P1070 Cohort II and spent a median duration of 24 weeks on study (Supplemental Figure 1); baseline characteristics by CYP2B6516 genotype are presented in Table 2. In addition to the Cohort II participants, two participants (both EM's in the 24- <36 month age group) who initially enrolled in Cohort I without TB developed TB while on study and entered Cohort I, Step 2. Their EFV dose was adjusted to the Cohort II dosage and the pharmacokinetic evaluations repeated.

Pharmacokinetic Results

Eight of nine EM 3 to <24 month old participants had evaluable PK; one was unevaluable because the mother was taking EFV while breastfeeding. Median EFV AUC for this age group was 92.87 mcg*h/mL and met protocol criteria for dose acceptance, with one participant above and one below the target exposure (Table 3). The participant below target experienced adherence difficulties and the one over target achieved the target range after dose reduction. The median trough in this age group was 1.42 mcg/mL, also within target exposure with trough concentrations highly correlated with AUC (r^2>0.95). EFV Tmax concentration occurred approximately 2 hours and 4 hours post dose for the younger age group and the older age group, respectively. The overall median EFV concentration versus time profile for all HIV/TB co-infected participants was comparable to that previously seen in HIV-infected/TB-uninfected receiving a 20–30% lower dose (Figure 1).

Due to slow accrual in the 24 to <36 months age group, the study closed before the EFV dose could be established for this age; a total of five were included in PK analyses, three in Cohort II and two in Cohort I Step 2. All were EMs and CL/F for this age group was lower than in the younger EM participants. (Supplemental Figure 2) Two met the AUC PK target but three had AUC >180mcg*h/mL and trough concentrations significantly higher than the younger age group (median 9.18 mcg/mL). (Supplemental Figure 3A) These PK results suggest a lower dose might be preferable to achieve the desired EFV concentrations in this age range.

The predicted EFV AUC for the lower HIV-infected/TB-uninfected EFV dose is shown in Supplemental Figure 3B. The median daily EFV dosage for these predictions was 400mg compared to 500mg for the observed dosage. While in two participants in the 3 to <24 month age group the predicted AUCs dropped just below the target range with modelling, the median in this age group remained more than 50% above the lower boundary of the target range. In the older age group, although the lower dose brought the AUCs down somewhat, three of five still had EFV exposures above the target range.

Of the two PM's enrolled in Cohort II, both were in the 3 to <24 month age group. The first PM received the version 1.0 EFV dose and exhibited a low CL/F (0.047 L/h/kg) resulting in excessive EFV concentrations with a very high AUC (1381 mcg*h/mL). The second PM was enrolled under version 2.0 with a genotype-directed reduced dose and also had a low CL/F (0.246 L/h/kg), but the AUC (56 mcg*h/mL) was in the target range.

Safety Outcomes

Overall, 5 of 14 participants (36%, 95% CI [13,65]), 4 EM and 1 PM, had events deemed to be at least possibly treatment related (Table 4). One EM who was receiving rifampicin/isoniazid and cotrimoxazole had grade 4 ALT/AST at week 24 which resolved when EFV was held and other drugs were discontinued. The liver enzymes remained normal when EFV was reinitiated. Two EM participants experienced neutropenia; one had grade 2 absolute neutrophil count (ANC) which resolved spontaneously, and the other had a grade 4 ANC at week 12. All ARVs were discontinued and restarted 4 days later with nevirapine substituted for EFV and the ANC improved to grade 0.

One EM had a grade 2 rash which resolved after 5 days and one PM in V1.0 receiving non-genotype-directed dose experienced Grade 1 and 2 irritability and sleepiness, respectively, which resolved after treatment discontinuation. There were no deaths, life-threatening toxicities, Grade 4 toxicities accompanying a serious adverse event (i.e., hospitalizations) or seizures judged to be as at least possibly related to treatment.

Virologic Outcomes and Study Discontinuations

At week 8, 11 EM and 1PM Cohort II participants met the criteria for virologic success. All nine (8 EM/1 PM) of the 14 participants who completed 24 weeks of treatment met virologic success criteria at week 24. (Supplemental Fig 4). Five of 14 (36%) participants discontinued study treatment before 24 weeks. (Supplemental Figure 1) Reasons for discontinuation were non-virologic and included: non-adherence to treatment and study visits in three EMs; protocol-defined toxicity (grade 4 neutropenia at week 12) in one PM with a high AUC (319 mcg*hr/mL); and one PM from Version 1.0 with an excessive AUC (1381 mcg*hr/mL) who also had symptomatic neurologic toxicity.

Discussion

Dosing recommendations for a potent antiretroviral regimen that can be co-administered with ATT in HIV/TB co-infected children <3 years of age have been elusive. We studied EFV as opened capsules in this highly vulnerable age group and found that genotype-directed weight band dosing provides EFV exposure in the range shown to be effective in

older children and adults. EFV is one of the few highly active ARVs with limited drug-drug interactions with ATT, and is the WHO preferred treatment option in children >3 years of age. [10] Given the limited ART options for children <3 years receiving ATT in resource-constrained countries, the 2016 WHO guidelines endorse either a triple-NRTI regimen or "super-boosting" of lopinavir/ritonavir (LPV/r). [10] Triple NRTIs have no interactions with ATT but have reduced virologic efficacy, unless suppression has already been achieved. [14] Super-boosting is performed by adding ritonavir to lopinavir/ritonavir to achieve equal doses of each drug [10], but this approach has not been widely adopted due to poor palatability, gastrointestinal upset, short shelf life and the refrigeration requirement for ritonavir syrup, which is challenging in resource-constrained settings.[15-19] Doubling the dose of LPV/r has demonstrated efficacy in adults,[20] but the same approach has resulted in low trough concentrations in young children.[17]

Efavirenz pharmacokinetics are known to be complicated by variable absorption and metabolism and higher mg/kg EFV doses are needed in children to achieve similar troughs to those seen in adults. This higher dose requirement is pronounced in infants and toddlers and likely due to more rapid elimination and reduced absorption. An EFV suspension was developed and demonstrated adequate absorption in older children, but exhibited administration difficulties and low concentration in young children leading to discontinued clinical development in favour of other dosage forms. [21] In the current study, we used opened capsules, a pediatric-friendly approach with demonstrated bioequivalency with intact capsules in adults.[22]

As seen in Cohort I of this study, we demonstrated a high EFV dosage requirement to achieve target EFV concentrations in young EMs being treated for HIV/TB co-infection. The median 500mg EFV dose for a 10kg EM HIV/TB co-infected participant is approximately two fold higher than the FDA recommended pediatric dose for this age group and several fold higher than the adult mg/kg dose recommended for HIV/TB co-infection. [21]

The critical role of CYP2B6 in EFV metabolism has been well documented.[23] The CYP2B6 516TT genotype has been shown to reduce EFV apparent clearance in adults and children. [24,25] The difference in EFV metabolism based on this polymorphism was exaggerated in children <3 years from Cohort I of this study and the potential induction of EFV by ATT did not alter the impact of this polymorphism on EFV metabolism. Among the two PM participants, the one in protocol V1.0 who was treated with EM EFV dosing resulted in excessive concentrations while the other was able to achieve target concentration when given 25% of the EM dosage in V2.0. When examining another less frequent pharmacogenomic polymorphism that can affect EFV metabolism, CYP2B6 983 (rs28399499), it is interesting to note that the one EM participant who was heterozygous at both CYP2B6 516 and 983 had by far the highest EFV AUC (662 mcg*h/mL) of EM participants and thus likely had impaired CYP2B6 activity from both alleles. This synergistic interaction has been observed in a study modelling EFV PK in the presence of multiple genetic polymorphisms in African children.[26]

Rifampicin has been shown to induce CYP2B6 expression, increasing EFV metabolism and altering its metabolite profile in adults, [7,8,27] supporting the rationale for use of a higher

dosage in this study. However, a recent trial has observed higher EFV concentrations when given with ATT suggesting that isoniazid, through inhibition of CYP2A6, can potentially counter rifampicin's drug metabolism induction effects on EFV.[9] In the current study, Cohort II EMs EFV CL/F was in the range seen in Cohort I, slightly higher in the younger age strata (median 0.62vs 0.42 L/h/kg) and lower in the older age strata (median 0.14 vs 0.36 L/h/kg).

Slow enrolment precluded full accrual into the 24–36 month age group, limiting formal comparisons between age groups. Still it is noteworthy that the highest EFV AUCs occurred in the older age stratum. Since all but 2 EMs (both in the younger age stratum) received 500mg, the heavier older age stratum participants actually received lower mg/kg doses than the younger age group, approximately 44 vs 63 mg/kg, yet still had higher EFV concentrations. This potential age difference in EFV pharmacokinetics is in contrast to our prior results from Cohort I which demonstrated similar EFV AUC and CL/F between the two age groups.[11] It is possible that the relative impact of rifampicin CYP2B6 induction or isoniazid CYP2A6 inhibition may be age-dependent or the relative contribution of each pathway may change over time with age. Low EFV concentrations in infants and young children have been attributed to low bioavailability which improves with age, resulting in lower weight adjusted clearance and much lower mg/kg dosing in older children and adults. The pattern of transition from "infant-like" to "mature child" absorption has yet to be fully characterized. It is also possible that ATT or TB infection itself may hasten this transition. The developmental characteristics of EFV pharmacokinetics in the setting of concomitant ATT require further study.

EFV safety profile was acceptable in this cohort with only one participant, an EM, permanently discontinuing EFV for a grade 4 ANC. One participant experienced a possibly related grade 4 liver enzyme elevation while also taking ATT. Only one participant, a PM with extremely elevated EFV levels, experienced neurologic toxicity consisting of grade 1 irritability and grade 2 sleepiness. Neurologic toxicity including long term neuropsychiatric symptoms continue to be a concern in young children receiving EFV particularly at high exposures [28,29] suggesting a potential mitigating role for genotype-directed EFV dosing in young children.

Virologic efficacy was excellent for all children who completed 24 weeks of treatment, with a median decrease of >3.5 $\log_{10}$ RNA level from study entry. These findings are similar to an observational study assessing the effectiveness of EFV-based ART in 48 HIV/TB co-infected Zambian children <3 years of age weighing 4 to 20 kg given a 300 mg EFV dose. Among the 79% of the participants who survived, 92% and 78% were able to achieve and maintain HIV RNA <400 copies/mL after 12 and 24 months on EFV treatment, when their ATT was complete.[30] They observed 10 deaths (22%) and 5 (11%) seizures in this very ill population. We observed no deaths or seizures in this cohort, or in the larger P1070 Cohort I study.[11] The majority of toxicities observed in this trial occurred in children with high EFV concentrations, suggesting the need to use the lowest doses that can consistently achieve therapeutic EFV concentrations.

To evaluate a more implementable unified dosing approach for all children <3 years of age with or without ATT, we used pharmacokinetic modelling to predict target EFV concentrations when the same dosing for the TB-uninfected (Cohort I) participants is used. Model simulations showed adequate EFV exposure with median predicted AUCs in the younger age group solidly within the target range. Although EFV AUCs were brought closer to the target range, they remained elevated in the majority of children in the 24-<36 month age group.

Conclusion

EFV was found to be safe and effective in treatment of HIV/TB co-infected children <3 years of age. Pharmacokinetic modeling suggests that appropriate EFV exposures can be achieved without need for dose increase while receiving concurrent anti-TB therapy in children 3-<24 months of age but more study is needed to confirm appropriate EFV dosing for children 24–36 months of age. Pharmacogenomic testing to direct EFV dosing is especially important for this young age group at high risk of mortality and is currently a critical unmet need in TB-endemic countries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. World Health Organisation. Global Tuberculosis Report 2018. Geneva2018.
2. World Health Organisation. Roadmap towards ending TB in children and adolescents. Geneva: World Health Organisation;2018.
3. Dodd PJ, Prendergast AJ, Beecroft C, Kampmann B. The impact of HIV and antiretroviral therapy on TB risk in children: a systematic review and meta-analysis. Thorax. 2017;72(6):559–575. [PubMed: 28115682]
4. World Health Organisation. Rapid Advice Treatment of tuberculosis in children. Geneva, Switzerland: World Health Organisation;2010.

5. Kwara A, Ramachandran G, Swaminathan S. Dose Adjustment of the Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs) during Concurrent Rifampicin-Containing Tuberculosis Therapy: One Size does not Fit All. Expert Opinion in Drug Metabolism Toxicology. 2010;61(5):55–68.
6. Cho Doo-Yeoun, Shen JHQ, Lemler SM, et al. Rifampin enhances cytochrome P450 (CYP) 2B6-mediated efavirenz 8-hydroxylation in healthy volunteers. Drug metabolism and pharmacokinetics. 2016;31(2):107–116. [PubMed: 27053325]
7. Manosuthia W, Kiertiburanakulb S, Sungkanuparphb S, et al. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. AIDS. 2006;20(1):131–132. [PubMed: 16327334]
8. López-Cortés LF, Ruiz-Valderas R, Viciana P, et al. Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. Clinical Pharmacokinetics. 2002;41(9): 681–690. [PubMed: 12126459]
9. Kwara A, Yang H, Antwi S, et al. Effect of rifampin/isoniazid-containing antituberculosis therapy on efavirenz pharmacokinetics in HIV-infected children aged 3 to 14 years old. Antimicrobial agents and chemotherapy. 2019;63(1):e01657–01618. [PubMed: 30397066]
10. World Health Organisation G. Consolidated guidleines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. 2016.
11. Bolton Moore C, Capparelli EV, Samson P, et al. CYP2B6 Genotype-directed dosing is required for optimal efavirenz exposure in children 3–36 months with HIv infection. AIDS. 2017(31): 1129–1136. [PubMed: 28323755]
12. McKinney RE, Rodman J, Hu C, et al. Long-term Safety and Efficacy of a Once-Daily Regimen of Emtricitabine, Didanosine, and Efavirenz in HIV-Infected, Therapy-Naive Children and Adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. Pediatrics. 2007;120(2):e416–e423. [PubMed: 17646352]
13. Saitoh A, Sarles E, Capparelli E, et al. CYP2B6 genetic variants are associated with nevirapine pharmacokinetics and clinical response in HIV-1-infected children. AIDS. 2007;21:2191–2199. [PubMed: 18090046]
14. ARROW Trial team. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. Lancet. 2013;381(9875):1391–1403. [PubMed: 23473847]
15. Habtewold A, Makonnen E, Amogne W, et al. Is there a need to increase the dose of efavirenz during concomitant rifampicin-based antituberculosis therapy in sub-Saharan Africa? The HIV-TB pharmagene study. Pharmacogenomics. 2015;16(10):1047–1064. [PubMed: 25831219]
16. Zhang C, Mcllleron H, Ren Y, et al. Population pharmacokinetics of lopinavir and ritonavir in combination with rifampicin-based antitubercular treatment in HIV-infected children. Antiviral Therapy. 2012;17(1):25–33. [PubMed: 22267466]
17. Mcllleron H, Ren Y, Nuttal J, et al. Lopinavir exposure is insufficient in children given double doses of lopinavir/ritonavir during rifampicin-based treatment for tuberculosis. Antiviral therapy. 2011;16(3):417–421. [PubMed: 21555825]
18. Frohoff C, Moodley M, Fairlee L, et al. Antiretroviral Therapy Outcomes in HIV-infected Children after adjusting Protease Inhibitor Dosing during Tuberculosis Treatment. Plos One. 2011;6(2).
19. Sulis G, Amadasi S, Odone A, Penazzato M, A. M. Antiretroviral Therapy in HIV Infected Children with Tuberculosis: A Systematic Review. Pediatric Infectious Disease Journal. 2017;37(5):e117–e125.
20. Decloedt EH, Maartens G, Smith P, Merry C, Bango F, H. M. The Safety, Effectiveness and Concentrations of Adjusted Lopinavir/Ritonavir in HIV-Infected Adults on Rifampicin-Based Antitubercular Therapy. Plos One. Vol 72012:e32173. [PubMed: 22412856]
21. Bristol-Myers Squibb, Inventor. Sustiva (Efavirenz capsule). 1998.
22. Kaul S, Ji P, Lu M, Nguyen KL, Shangguan T, Grasela D. Bioavailability in healthy adults of efavirenz capsule contents mixed with a small amount of food. American Journal of Health-System Pharmacy. 2010;67(3):217–222. [PubMed: 20101064]
23. Ward BA, Borski JC, Jones DR, Hall SD, Flockhart DA, Desta Z. The Cytochrome P450 2B6 (CYP2B6) Is the Main Catalyst of Efavirenz Primary and Secondary Metabolism: Implication for HIV/AIDS Therapy and Utility of Efavirenz as a Substrate Marker of CYP2B6 Catalytic Activity.

Journal of Pharmacology and Experimental Therapeutics 2003;306(1):287–300. [PubMed: 12676886]

24. Saitoh A, Fletcher CV, Brundage R, et al. Efavirenz Pharmacokinetics in HIV-1-Infected Children Are Associated with CYP2B6-G516T Polymorphism. J Acquir Immune Defic Syndr. 2007;45:280–285. [PubMed: 17356468]
25. Gounden V, van Niekerk C, Snyman T, JA G. Presence of the CYP2B6 516G> T polymorphism, increased plasma Efavirenz concentrations and early neuropsychiatric side effects in South African HIV-infected patients. AIDS Research and Therapy. 2010;7(32).
26. Bienczak A, Cook A, Wiesner L, et al. The impact of genetic polymorphisms on the pharmacokinetics of efavirenz in African children. British Journal of Clinical Pharmacology. 2016;82:158–198.
27. Choa DY, Shen JHQ, Lemler SM, et al. Rifampin enhances cytochrome P450 (CYP) 2B6-mediated efavirenz 8-hydroxylation in healthy volunteers. . Drug Metab Pharmacokinetics. 2016;31(2):107–116.
28. Pressiat C, Amorissani-Folquet M, Yonaba C, et al. Pharmacokinetics of Efavirenz at a High Dose of 25 Milligrams per Kilogram per Day in Children 2 to 3 Years Old. Antimicrobial agents and chemotherapy. 2017;61(7): e00297–00217. . [PubMed: 28483965]
29. Van de Wijer L, Mchaile DN, de Mast Q, et al. Neuropsychiatric symptoms in Tanzanian HIV-infected children receiving long-term efavirenz treatment: a multicentre, cross-sectional, observational study. Lancet HIV. 2019.
30. van Dijk JH, Sutcliffe CG, Hamangaba F, Bositis C, Watson DC, WJ M. Effectiveness of Efavirenz-Based Regimens in Young HIV-Infected Children TReated for Tuberculosis: A Treament Option for Resource-Limited Settings. Plos One. 2013;8(1).

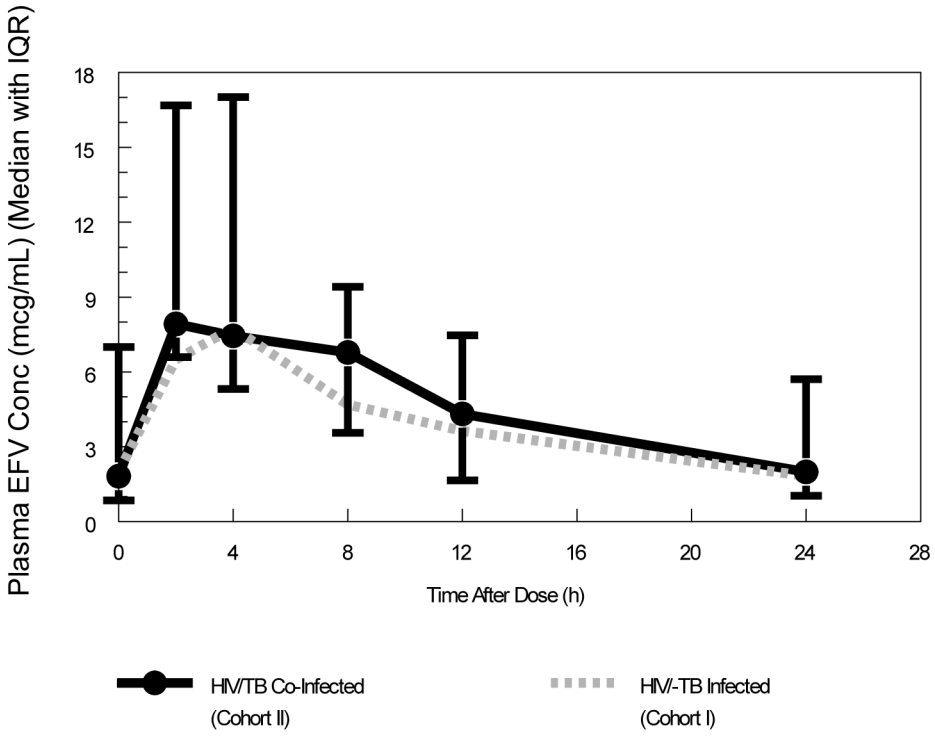

Figure 1. 24-hour plasma PK at week 2:

Efavirenz median (+/− SE) concentrations in HIV / TB co-infected EM participants receiving concomitant rifampin containing TB therapy – Cohort II (black closed circles – solid line). Efavirenz concentrations were similar to those previously reported for HIV-infected, TB-uninfected participants in Cohort I who were not on TB therapy and received lower EFV doses (grey open circles - dashed line).

Table 1:

P1070 Version 2.0 Efavirenz Dosing by Weight Band and Genotype

	CYP 2B6 516 GG and GT genotypes			CYP 2B6 516 TT genotype	
Weight (kg)	Cohort I, Step 1	Cohort I, Step 2 and Cohort II		Cohort I, Step 1	Cohort I, Step 2 and Cohort II
3-4.99	200 mg	300 mg		50 mg	50 mg
5-6.99	300 mg	400 mg		50 mg	100 mg
7-9.99	400 mg	500 mg		100 mg	100 mg
10-13.99	400 mg	500 mg		100 mg	150 mg
14-16.99	500 mg	600 mg		150 mg	150 mg
≥ 17	600 mg	800 mg		150 mg	200 mg

Table 2.

Baseline Participant Characteristics by CYP2B6516 Genotype. Median (IQR) or frequency (percentage) are presented. Table includes participants that initiated EFV while receiving TB therapy, Cohort II. Two participants on EFV prior to TB therapy, Cohort I- Step 2, are not included.

		CYP2B6 516 Genotype		
Characteristic		**Extensive metabolizers (N=12)****	**Poor metabolizers (N=2)***	**Total (N=14)**
Gender	M	8 (67%)	2 (100%)	10 (71%)
	F	4 (33%)	0 (0%)	4 (29%)
Race	Asian	1 (8%)	0 (0%)	1 (7%)
	Black	7 (58%)	2 (100%)	9 (64%)
	Unknown	4 (33%)	0 (0%)	4 (29%)
CYP2B6 516 Genotype	GG	7 (58%)	0 (0%)	7 (50%)
	GT	5 (42%)	0 (0%)	5 (36%)
	TT	0 (0%)	2 (100%)	2 (14%)
Age in months	Median (Q1,Q3)	16.5 (11.5, 25.5)	10.0 (6,14)	14.5 (11, 23)
Log_{10} Baseline RNA	Median (Q1,Q3)	5.86 (5.33, 5.99)	6.24 (5.88, 6.60)	5.88 (5.43, 6.00)
Baseline CD4+ cell Count	Median (Q1,Q3)	1,069 (774, 1,898)	1,120 (950, 1,291)	1,069 (858, 1,291)
Baseline CD4+ cell Percentage	Median (Q1,Q3)	21.3 (15.6, 26.5)	13.8 (9.6, 18.0)	18.7, (14.8, 24.0)

* 3-24mos,

** (9) from 3-24mos and (3) from 24-36mos.

Table 3.

Week 2 Pharmacokinetic Parameters by Age in Extensive Metabolizers (EM) and Target Achievement. PK parameter values represent the median (IQR). The number and percent within, above and below the target AUC and trough are presented. The 24-36 mos (N=5) column includes the 2 Cohort I-Step 2 participants.

		Age Group			
Characteristic		**3-<24 mos (N=8)**	**24-36 mos (N=5)**	**Total (N=13)**	**p-value**
AUC (mcg*h/mL) Classification	AUC < 35	1 (13%)	0 (0%)	1 (8%)	0.21[a]
	AUC [35,180]	6 (75%)	2 (40%)	8 (62%)	
	AUC > 180	1 (13%)	3 (60%)	4 (31%)	
Trough (mcg/mL) Classification	Trough < 1	4 (50%)	0 (0%)	4 (31%)	0.09[a]
	Trough [1,4]	2 (25%)	1 (20%)	3 (23%)	
	Trough > 4	2 (25%)	4 (80%)	6 (46%)	
Dose amount (mg)	Median (Q1,Q3)	500 (450, 500)	500 (500, 500)	500 (500, 500)	
AUC (mcg*h/mL)	Median (Q1,Q3)	92.87 (40.95, 160.81)	319.05 (172.56, 360.48)	160.10 (72.79, 238.99)	0.028[b]
Trough (mcg/mL)	Median (Q1,Q3)	1.42 (0.55, 3.47)	9.18 (4.99, 11.02)	2.00 (0.99, 6.46)	0.028[b]
CL/F (L/h/kg)	Median (Q1,Q3)	0.62 (0.45, 1.65)	0.14 (0.12, 0.25)	0.51 (0.24, 0.66)	0.012[b]
Cmax (mcg/mL)	Median (Q1,Q3)	7.99 (5.29,12.84)	19.62 (13.85, 22.55)	8.63 (7.36, 17.56)	0.079[b]
Tmax (h)	Median (Q1,Q3)	2.0 (2.0, 4.0)	4.1 (2.1, 7.1)	2.1 (2.0, 4.0)	0.1128[b]

P-values:

[a]Fisher's Exact Test and

[b]Wilcoxon Test.

Table 4:

Toxicities Assessed to be at Least ‘Possibly Related’ to EFV.

Non-neurologic Toxicity: n=4 participants					
Type	**N**	**CYP2B6 516 Genotype**	**Grade**	**Comments**	**Week 2 AUC > 180 (mcg*hr/mL)**
Low Absolute Neutrophil Count (ANC)	1	GG	2	Week 11	NO
	1	GG	4	Week 12	YES[#]
Rash	1	GT	2	Week 1, diffuse maculopapular rash	YES
ALT/AST	1	GG	4	Week 24	YES[#]
Neurologic Toxicity: n=1 participant					
Type		**CYP 2B6 516 Genotype**	**Grade**	**Comments**	**Week 2 AUC > 180 (mcg*h/mL)**
Irritability/Sleepiness	1	TT	1	Week 2, Grade 1 irritability	YES[*]
			2	Week 3, Grade 2 Sleepiness	

[#]This participant’s EFV AUC was elevated at Week 2 of study, but subsequently achieved the target AUC following a dose reduction.

[*]This participant was dosed under Version 1.0 with AUC=1381 (mcg*h/mL), and permanently discontinued from treatment at week 4, as dose adjustment within protocol limits would not reduce EFV levels to acceptable levels.