

## Supplementary appendix

Supplement to: 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; published online Feb 12. [http://dx.doi.org/10.1016/S2352-3018\(18\)30329-1](http://dx.doi.org/10.1016/S2352-3018(18)30329-1).

## Supplementary Methods. Research into context panel – Search strategy and list of included papers

### Step 1 Database search

Database	Pubmed
Date	6-6-2018
Search terms	((Efavirenz[TW] OR "efavirenz"[Supplementary Concept] OR "HIV-1 reverse transcriptase inhibitor"[TW] OR "NNRTI"[TW] OR sustiva[TW] OR stocrin[TW] OR EFV[TW] OR EFZ[TW]) AND (children[TW] OR "adolescent"[TW] OR teenager[TW] OR teenagers[TW] OR baby[TW] OR babies[TW] OR adolescent[TW] OR adolescents[TW] OR adolescence[TW] OR toddler[TW] OR toddlers[TW] OR youngster[TW] OR youngsters[TW] OR "young people"[TW] OR youth[TW] OR youths[TW] OR juvenile[TW] OR juveniles[TW] OR newborn[TW] OR newborns[TW] OR "infant, newborn"[MeSH] OR "infant"[MeSH Terms] OR infant[TW] OR infants[TW] OR infantile[TW] OR "child"[TW] OR child[TW] OR neonate[TW] OR neonates[TW] OR pediatrics[TW] OR paediatric[TW] OR kid[TW] OR kids[TW] OR "pediatrics"[TW] OR paediatrics[TW]))
Yield	987 papers

### Step 2 Title/abstract screening

Excluded	No EFV (or no unspecified ART)
	No pediatric study
	No primary data or case report
	No clinical outcomes
Yield	158 papers

### Step 3 Full text screening

Excluded	No full text available
	No EFV treatment (or outcomes not specified for EFV)
	No data on CNS toxicity or adherence
Yield	39 papers + 5 relevant reviews/letters

## List of included papers

1. Weekends-off efavirenz-based antiretroviral therapy in HIV-infected children, adolescents, and young adults (BREATHER): a randomised, open-label, non-inferiority, phase 2/3 trial. *The lancet HIV* 2016; **3**(9): e421-e30.
2. Barro M, Some J, Foulongne V, et al. Short-term virological efficacy, immune reconstitution, tolerance, and adherence of once-daily dosing of didanosine, lamivudine, and efavirenz in HIV-1-infected African children: ANRS 12103 Burkina. *Journal of acquired immune deficiency syndromes (1999)* 2011; **57 Suppl 1**: S44-9.
3. Bienczak A, Denti P, Cook A, et al. Plasma Efavirenz Exposure, Sex, and Age Predict Virological Response in HIV-Infected African Children. *Journal of acquired immune deficiency syndromes (1999)* 2016; **73**(2): 161-8.
4. Coovadia A, Abrams EJ, Strehlau R, et al. Efavirenz-Based Antiretroviral Therapy Among Nevirapine-Exposed HIV-Infected Children in South Africa: A Randomized Clinical Trial. *Jama* 2015; **314**(17): 1808-17.
5. Dahourou DL, Amorissani-Folquet M, Malateste K, et al. Efavirenz-based simplification after successful early lopinavir-boosted-ritonavir-based therapy in HIV-infected children in Burkina Faso and Cote d'Ivoire: the MONOD ANRS 12206 non-inferiority randomised trial. *BMC medicine* 2017; **15**(1): 85.
6. Elise A, France AM, Louise WM, et al. Assessment of adherence to highly active antiretroviral therapy in a cohort of African HIV-infected children in Abidjan, Cote d'Ivoire. *Journal of acquired immune deficiency syndromes (1999)* 2005; **40**(4): 498-500.
7. Fortuin-de Smidt M, de Waal R, Cohen K, et al. First-line antiretroviral drug discontinuations in children. *PloS one* 2017; **12**(2): e0169762.
8. Fraaij PL, Neubert J, Bergshoeff AS, et al. Safety and efficacy of a NRTI-sparing HAART regimen of efavirenz and lopinavir/ritonavir in HIV-1-infected children. *Antiviral therapy* 2004; **9**(2): 297-9.
9. Funk MB, Notheis G, Schuster T, et al. Effect of first line therapy including efavirenz and two nucleoside reverse transcriptase inhibitors in HIV-infected children. *European journal of medical research* 2005; **10**(12): 503-8.
10. Hauptfleisch MP, Moore DP, Rodda JL. Efavirenz as a cause of ataxia in children. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde* 2015; **105**(10): 876.
11. Hien H, Meda N, Diabougba S, et al. 24-Month adherence, tolerance and efficacy of once-a-day antiretroviral therapy with didanosine, lamivudine, and efavirenz in African HIV-1 infected children: ANRS 12103/12167. *African health sciences* 2013; **13**(2): 287-94.
12. Lapphra K, Vanprapar N, Chearskul S, et al. Efficacy and tolerability of nevirapine- versus efavirenz-containing regimens in HIV-infected Thai children. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* 2008; **12**(6): e33-8.
13. Larru B, Eby J, Lowenthal ED. Antiretroviral treatment in HIV-1 infected pediatric patients: focus on efavirenz. *Pediatric health, medicine and therapeutics* 2014; **5**: 29-42.
14. Lowenhaupt EA, Matson K, Qureishi B, Saitoh A, Pugatch D. Psychosis in a 12-year-old HIV-positive girl with an increased serum concentration of efavirenz. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2007; **45**(10): e128-30.
15. McComsey G, Bhumbra N, Ma JF, Rathore M, Alvarez A. Impact of protease inhibitor substitution with efavirenz in HIV-infected children: results of the First Pediatric Switch Study. *Pediatrics* 2003; **111**(3): e275-81.
16. McKinney RE, Jr., 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): e416-23.
17. Murnane PM, Strehlau R, Shiao S, et al. Switching to Efavirenz Versus Remaining on Ritonavir-boosted Lopinavir in Human Immunodeficiency Virus-infected Children Exposed to Nevirapine: Long-term Outcomes of a Randomized Trial. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2017; **65**(3): 477-85.
18. Murnane PM, Strehlau R, Shiao S, et al. Reply to Van de Wijer et al. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2018; **66**(7): 1151-2.

19. Mutwa PR, Fillekes Q, Malgaz M, et al. Mid-dosing interval efavirenz plasma concentrations in HIV-1-infected children in Rwanda: treatment efficacy, tolerability, adherence, and the influence of CYP2B6 polymorphisms. *Journal of acquired immune deficiency syndromes (1999)* 2012; **60**(4): 400-4.
20. Nacro B, Zoure E, Hien H, et al. Pharmacology and immuno-virologic efficacy of once-a-day HAART in African HIV-infected children: ANRS 12103 phase II trial. *Bulletin of the World Health Organization* 2011; **89**(6): 451-8.
21. Natukunda HPM, Cluver LD, Toska E, Musiime V, Yakubovich AR. Beyond clinical trials: Cross-sectional associations of combination antiretroviral therapy with reports of multiple symptoms and non-adherence among adolescents in South Africa. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde* 2017; **107**(11): 965-75.
22. Nazziwa R, Sekadde M, Kanyike F, Wobudeya E, Nabukeera-Barungi N. Efavirenz poisoning in a 12 year old HIV negative African boy. *The Pan African medical journal* 2012; **12**: 86.
23. Pavia-Ruz N, Rossouw M, Saez-Llorens X, et al. Efavirenz Capsule Sprinkle and Liquid Formulations With Didanosine and Emtricitabine in HIV-1-infected Infants and Children 3 Months to 6 Years of Age: Study AI266-922. *The Pediatric infectious disease journal* 2015; **34**(12): 1355-60.
24. Pinillos F, Dandara C, Swart M, et al. Case report: Severe central nervous system manifestations associated with aberrant efavirenz metabolism in children: the role of CYP2B6 genetic variation. *BMC infectious diseases* 2016; **16**: 56.
25. Puthanakit T, Tanpaiboon P, Aурpibul L, Cressey TR, Sirisanthana V. Plasma efavirenz concentrations and the association with CYP2B6-516G >T polymorphism in HIV-infected Thai children. *Antiviral therapy* 2009; **14**(3): 315-20.
26. Rosso R, Di Biagio A, Maggiolo F, et al. Patient-reported outcomes and low-level residual HIV-RNA in adolescents perinatally infected with HIV-1 after switching to one-pill fixed-dose regimen. *AIDS care* 2012; **24**(1): 54-8.
27. Saitoh A, Fletcher CV, Brundage R, et al. Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. *Journal of acquired immune deficiency syndromes (1999)* 2007; **45**(3): 280-5.
28. Scherpbier HJ, Bekker V, Pajkrт D, Jurriaans S, Lange JM, Kuyjpers TW. Once-daily highly active antiretroviral therapy for HIV-infected children: safety and efficacy of an efavirenz-containing regimen. *Pediatrics* 2007; **119**(3): e705-15.
29. Shubber Z, Calmy A, Andrieux-Meyer I, et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. *AIDS (London, England)* 2013; **27**(9): 1403-12.
30. Soeria-Atmadja S, Osterberg E, Gustafsson LL, et al. Genetic variants in CYP2B6 and CYP2A6 explain interindividual variation in efavirenz plasma concentrations of HIV-infected children with diverse ethnic origin. *PloS one* 2017; **12**(9): e0181316.
31. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *The New England journal of medicine* 1999; **341**(25): 1874-81.
32. Strehlau R, Martens L, Coovadia A, et al. Absence seizures associated with efavirenz initiation. *The Pediatric infectious disease journal* 2011; **30**(11): 1001-3.
33. Sumari-de Boer M, Schellekens A, Duinmaijer A, et al. Efavirenz is related to neuropsychiatric symptoms among adults, but not among adolescents living with human immunodeficiency virus in Kilimanjaro, Tanzania. *Tropical medicine & international health : TM & IH* 2018; **23**(2): 164-72.
34. Teglas JP, Quartier P, Treluyer JM, Burgard M, Gregoire V, Blanche S. Tolerance of efavirenz in children. *AIDS (London, England)* 2001; **15**(2): 241-3.
35. Tukei VJ, Asimwe A, Maganda A, et al. Safety and tolerability of antiretroviral therapy among HIV-infected children and adolescents in Uganda. *Journal of acquired immune deficiency syndromes (1999)* 2012; **59**(3): 274-80.
36. Van de Wijer L, Kinabo GD, McHaile DN, de Mast Q, Schellekens AFA, van der Ven A. Safety Evaluation of Efavirenz in Children: Don't Forget the Central Nervous System. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2017.

37. Van de Wijer L, Schellekens AFA, Burger DM, Homberg JR, de Mast Q, van der Ven A. Rethinking the risk-benefit ratio of efavirenz in HIV-infected children. *The Lancet Infectious diseases* 2016; **16**(5): e76-e81.
38. Van den Hof M, Blokhuis C, Cohen S, et al. CNS penetration of ART in HIV-infected children. *The Journal of antimicrobial chemotherapy* 2018; **73**(2): 484-9.
39. van Dijk JH, Sutcliffe CG, Hamangaba F, Bositis C, Watson DC, Moss WJ. Effectiveness of efavirenz-based regimens in young HIV-infected children treated for tuberculosis: a treatment option for resource-limited settings. *PloS one* 2013; **8**(1): e55111.
40. van Rossum AM, Fraaij PL, de Groot R. Efficacy of highly active antiretroviral therapy in HIV-1 infected children. *The Lancet Infectious diseases* 2002; **2**(2): 93-102.
41. Vigano A, Aldrovandi GM, Giacomet V, et al. Improvement in dyslipidaemia after switching stavudine to tenofovir and replacing protease inhibitors with efavirenz in HIV-infected children. *Antiviral therapy* 2005; **10**(8): 917-24.
42. Viljoen M, Karlsson MO, Meyers TM, Gous H, Dandara C, Rheeders M. Influence of CYP2B6 516G>T polymorphism and interoccasion variability (IOV) on the population pharmacokinetics of efavirenz in HIV-infected South African children. *European journal of clinical pharmacology* 2012; **68**(4): 339-47.
43. Wintergerst U, Hoffmann F, Jansson A, et al. Antiviral efficacy, tolerability and pharmacokinetics of efavirenz in an unselected cohort of HIV-infected children. *The Journal of antimicrobial chemotherapy* 2008; **61**(6): 1336-9.
44. Wynberg E, Williams E, Tudor-Williams G, Lyall H, Foster C. Discontinuation of Efavirenz in Paediatric Patients: Why do Children Switch? *Clinical drug investigation* 2017.

**Supplementary table 1. Demographic and socioeconomic characteristics**

Characteristic	Non-efavirenz (n = 69)	Efavirenz (n = 72)	P-value
Caretaker's age, mean (SD) years	44 (12)	44 (13)	0.98
Number of siblings, median (IQR)	2 (2)	2 (2)	0.90
Ethnicity			
Chagga	39/69 (56.5)	34/71 (47.9)	0.53
Pare	4/69 (5.8)	10/71 (14.1)	
Masai	1/69 (1.4)	2/71 (2.8)	
Meru	2/69 (2.9)	2/71 (2.8)	
Other	23/69 (33.3)	23/71 (32.4)	
Religion			
Christianity	56/69 (81.2)	59/72 (81.9)	1.00
Islam	13/69 (18.8)	13/72 (18.1)	
Caretaker's education			
No education	2/69 (2.9)	3/72 (4.2)	0.35
Primary education	53/69 (76.8)	48/72 (66.7)	
Secondary education	8/69 (11.6)	16/72 (22.2)	
Tertiary education	6/69 (8.7)	5/72 (6.9)	
Highest qualified profession caretaker			
Agriculture	22/69 (31.9)	19/72 (26.4)	0.26
Labourer	21/69 (30.4)	23/72 (31.9)	
House/home maker	0/69 (0.0)	4/72 (5.6)	
Self-employed	22/69 (31.9)	22/72 (30.6)	
Unemployed	4/69 (5.8)	2/72 (2.8)	
Student	0/69 (0.0)	2/72 (2.8)	
Highest food source			
Purchase	50/67 (74.6)	50/70 (71.4)	0.88
Own source	15/67 (22.4)	18/70 (25.7)	
Support relatives	2/67 (3.0)	2/70 (2.9)	
Monthly income caretaker (Tshs)*			
<100,000	34/67 (50.7)	35/69 (50.7)	0.85
100,000-500,000	22/67 (32.8)	20/69 (29.0)	
>500,000	2/67 (3.0)	2/69 (2.9)	
Refuses to answer or unknown	9/67 (13.4)	12/69 (17.4)	
Place of residence			
Town	23/69 (33.3)	32/72 (44.4)	0.23
Water availability			
Infrequent	3/67 (4.5)	3/71 (4.2)	0.38
Weekly	0/67 (0.0)	1/71 (1.4)	
Daily	1/67 (1.5)	5/71 (6.9)	
Always	63/67 (94.0)	63/71 (87.5)	
House type			
Stone house	59/67 (88.1)	62/72 (86.1)	0.23
Mud house	6/67 (9.0)	10/72 (13.9)	
Wooden house	2/67 (3.0)	0/72 (0.0)	
House status			
Dilapidated	1/67 (1.5)	3/72 (4.2)	0.53
Major repairs needed	19/67 (28.4)	15/72 (20.8)	
Incompletely built	16/67 (23.9)	22/72 (30.6)	
Minor or no repairs needed	31/67 (46.3)	32/72 (44.4)	
Toilet type			
Bush or none	0/67 (0.0)	1/72 (1.4)	0.58
Traditional pit	24/67 (35.8)	21/72 (29.6)	
Modern pit	16/67 (23.9)	15/72 (20.8)	
Flush	27/67 (40.3)	35/72 (48.6)	
Livestock owned			
None	27/67 (40.3)	28/72 (38.9)	0.47
<5	18/67 (26.9)	14/72 (19.7)	
≥5	22/67 (32.8)	30/72 (42.3)	

Data are depicted as n/N (%) unless stated otherwise. Data analysed using student's T-test (or Mann Whitney-U) for continuous variables and Pearson's chi-square (or Fisher's exact) for categorical variables.

\* Tshs 100,000 was equal to 45 USD at the time the study was conducted.

Tshs=Tanzanian Shilling.

**Supplementary table 2. Child Behaviour Checklist T scores and prevalence of psychopathology**

Characteristic	Non-efavirenz		Efavirenz	
	T scores mean (SD)	Children in borderline-clinical range n/N (%)	T scores mean (SD)	Children in borderline-clinical range n/N (%)
<b>CBCL competence scales*</b>				
CBCL Total competence	47.0 (9.6)	15/69 (21.7)	46.7 (9.9)	21/71 (29.6)
Activities	46.7 (11.1)	9/69 (13.0)	46.4 (9.3)	5/71 (7.0)
Social	49.6 (6.8)	1/69 (1.4)	50.7 (7.3)	1/71 (1.4)
School	45.2 (6.7)	7/69 (10.1)	41.2 (9.0)	19/71 (26.7)
<b>CBCL syndrome scales</b>				
CBCL Total problems	52.4 (6.8)	8/69 (11.6)	53.2 (8.0)	9/72 (12.5)
CBCL Internalizing problems	56.1 (6.3)	17/69 (24.6)	57.8 (7.1)	22/72 (30.6)
Anxious or depressed	54.1 (3.9)	1/69 (1.4)	55.2 (4.6)	3/72 (4.2)
Withdrawn	57.8 (6.3)	8/69 (11.6)	60.0 (8.9)	16/72 (22.2)
Somatic complaints	57.4 (6.7)	10/69 (14.5)	58.4 (7.5)	11/72 (15.3)
CBCL Externalizing problems	50.2 (8.0)	6/69 (8.7)	49.4 (8.9)	7/72 (9.7)
Rule-breaking behaviour	54.5 (5.2)	4/69 (5.8)	54.4 (6.5)	8/72 (11.1)
Aggressive behaviour	53.3 (4.9)	3/69 (4.3)	53.0 (4.7)	3/72 (4.2)
CBCL Other problems				
Social problems	55.4 (5.4)	3/69 (4.3)	55.8 (6.5)	9/72 (12.5)
Thought problems	53.7 (5.4)	4/69 (5.8)	54.2 (6.4)	9/72 (12.5)
Attention problems	54.1 (5.3)	3/69 (4.3)	54.6 (6.8)	5/72 (6.9)

*Children within the borderline-clinical range are defined as total, internalizing or externalizing CBCL T scores above the 84<sup>th</sup> percentile, syndrome CBCL T scores above the 93<sup>th</sup> percentile, total competence CBCL T score below the 16<sup>th</sup> percentile, and activities, social and school performance CBCL T scores below the 7<sup>th</sup> percentile. CBCL T scores=Child Behaviour Checklist age, sex and (Kenyan) population specific scores.*

*\*One child of the efavirenz group was excluded from the CBCL competence analyses due to missing data.*

**Supplementary table 3. Raven's Coloured Progressive matrices normative scores**

	<b>Non-efavirenz n/N (%)</b>	<b>Efavirenz n/N (%)</b>
Children below the normal South African cut-off scores	4/69 (5.8)	2/72 (2.8)
Children below the normal Kenyan cut-off scores	0/43 (0.0)	0/34 (0.0)

*Children scoring below the 10th percentile of the age-adjusted South African<sup>1</sup> and Kenyan<sup>2</sup> normative scores. Kenyan normative scores were only available until the age of 10 years and 3 months.*



**Supplementary table 4. Adherence**

Test	Non-efavirenz (n = 69)	Efavirenz (n = 72)	P-value
Non-adherence*	24/69 (34.8)	20/72 (27.8)	0.47
Non-adherence excl. low-dose efavirenz†	24/69 (34.8)	10/43 (23.3)	0.21
Medication reminder	39/69 (56.5)	39/72 (54.2)	0.87
Person reminding			
Parent	28/39 (71.8)	18/39 (46.2)	0.013
Relative	6/39 (15.4)	16/39 (41.0)	
Orphanage caretaker	0/39 (0.0)	1/39 (2.6)	
Other	3/39 (7.7)	1/39 (2.6)	
Not specified	2/39 (5.1)	3/39 (7.7)	
Interference medication with daily life			
A lot	0/69 (0.0)	1/72 (1.4)	0.39
Quite a lot	6/69 (8.7)	3/72 (4.2)	
Not much	12/69 (17.4)	9/72 (12.5)	
Not at all	51/69 (73.9)	59/72 (81.9)	
Way of interference with daily life‡			
Time restrictions	0/18 (0.0)	1/13 (7.7)	0.46
Fatigue	4/18 (22.2)	6/13 (46.2)	
Other physical complaints	4/18 (22.2)	2/13 (15.4)	
Other	1/18 (5.6)	0/13 (0.0)	
Not reported	9/18 (50.0)	4/13 (30.8)	
Reason missed doses past 2 weeks			
Run out of medication	3/69 (4.3)	1/72 (1.4)	0.63
Forgotten	4/69 (5.8)	6/72 (8.3)	
Medication expired	0/69 (0.0)	1/72 (1.4)	
Interference school hours, meals, sleep	1/69 (1.4)	0/72 (0.0)	
Different routine from normal	0/69 (0.0)	1/72 (1.4)	
Other	0/69 (0.0)	1/72 (1.4)	
No missed doses past 2 weeks	61/69 (88.4)	62/72 (86.1)	

Data depicted as n/N (%). Data analysed using Pearson's chi-square (or Fisher's exact).

\* Defined as  $\geq 1$  missed doses over the previous three days or marking  $< 100\%$  adherence since the last clinical visit on a visual analogue scale (VAS).<sup>3</sup>

† Non-adherence after exclusion children who received low doses of efavirenz

‡ Percentage of children and caretakers who reported interference of medication with daily life.

**Supplementary table 5. Age, sex, and HIV-RNA load low dose efavirenz vs. recommended-high efavirenz**

<b>Characteristic</b>	<b>Efavirenz low-dose (n = 28)</b>	<b>Efavirenz Recommended- high dose (n = 43)</b>	<b>P-value</b>
Age, years	10.1 (1.7)	9.9 (2.1)	0.69
Sex, male	15/28 (53.6)	16/43 (37.2)	0.22
HIV-RNA <40 copies per mL	21/28 (75.0)	32/43 (74.4)	1.00

*Data are depicted as n/N (%) or mean (SD). Data analyzes using Student's t test for continuous variables and Pearson's chi-square for categorical variables.*

**Supplementary table 6. Behavioural and neurocognitive test scores after exclusion children who received low doses of efavirenz**

Item	Control (n=69) Mean (SD)	Efavirenz (n=43) Mean (SD)	Crude model Mean difference (95% CI)	P-value	Adjusted model Mean difference (95% CI)	P-value
<b>CBCL competence scores</b>						
Total Competence	23.6 (4.1)	23.2 (4.1)	-0.39 (-1.97 to 1.19)	0.62	-2.55 (-4.56 to -0.55)	0.013
Activities	10.4 (2.7)	10.3 (2.1)	-0.07 (-1.03 to 0.89)	0.89	-1.02 (-2.32 to 0.27)	0.12
Social	8.5 (1.8)	8.9 (2.1)	0.40 (-0.34 to 1.14)	0.29	-0.47 (-1.40 to 0.46)	0.32
School	4.7 (0.9)	4.0 (1.3)	-0.74 (-1.15 to -0.33)	0.00055	-1.06 (-1.61 to -0.5)	0.00027
<b>CBCL problem scores</b>						
Total problems	25.3 (13.0)	28.7 (18.0)	3.34 (-2.48 to 9.16)	0.26	8.92 (1.24 to 16.60)	0.023
Internalizing problems	8.0 (3.9)	9.9 (6.1)	1.88 (0.01 to 3.74)	0.049	3.11 (0.60 to 5.63)	0.016
Anxious/depressed	3.4 (1.7)	4.0 (2.0)	0.61 (-0.09 to 1.31)	0.087	0.84 (-0.12 to 1.80)	0.087
Withdrawn	2.3 (1.9)	3.1 (3.0)	0.82 (-0.10 to 1.74)	0.080	1.17 (-0.11 to 2.44)	0.073
Somatic complaints	2.3 (2.2)	2.7 (2.4)	0.45 (-0.42 to 1.31)	0.31	1.11 (-0.03 to 2.25)	0.057
Externalizing problems	5.8 (4.7)	5.6 (5.2)	-0.21 (-2.09 to 1.67)	0.82	0.82 (-1.70 to 3.34)	0.52
Other problems						
Social problems	3.0 (2.4)	3.1 (2.9)	0.11 (-0.89 to 1.10)	0.83	1.00 (-0.33 to 2.33)	0.14
Thought problems	1.5 (1.9)	2.1 (2.4)	0.51 (-0.3 to 1.32)	0.22	1.25 (0.16 to 2.34)	0.025
Attention problems	3.4 (2.7)	3.8 (3.7)	0.42 (-0.78 to 1.61)	0.49	1.60 (0.03 to 3.17)	0.046
<b>Neurocognitive scores</b>						
RCPM score	19.8 (5.5)	22.2 (6.9)	2.42 (0.08 to 4.76)	0.043	1.98 (-0.95 to 4.91)	0.18
Digit Forwards	6.8 (2.1)	7.2 (2.7)	0.45 (-0.45 to 1.35)	0.33	0.58 (-0.51 to 1.68)	0.29
Digit Backwards	3.2 (1.6)	3.6 (2.2)	0.45 (-0.27 to 1.16)	0.22	0.55 (-0.30 to 1.39)	0.20

*Data depicted as mean (SD) test scores. Data analysed using ANCOVA with age, sex, parental loss, HIV disclosure, prior treatment failure, cART duration, history of tuberculosis treatment, and prior hospital admission entered as covariates in the adjusted models.*

*CBCL= Child Behaviour Checklist. RCPM=Raven's Coloured Progressive Matrices.*

**Supplementary table 7. Behavioural and neurocognitive test scores in children receiving correct efavirenz doses**

Item	Control (n=69) Mean (SD)	Efavirenz (n=40) Mean (SD)	Crude model Mean difference (95% CI)	P-value	Adjusted model Mean difference (95% CI)	P-value
<b>CBCL competence scores</b>						
Total Competence	23.6 (4.1)	23.3 (4.2)	-0.24 (-1.87 to 1.39)	0.77	-2.48 (-4.51 to -0.45)	0.017
Activities	10.3 (2.7)	10.3 (2.2)	-0.06 (-1.05 to 0.93)	0.90	-1.06 (-2.39 to 0.26)	0.11
Social	8.5 (1.8)	9.0 (2.1)	0.54 (-0.21 to 1.29)	0.16	-0.35 (-1.27 to 0.57)	0.45
School	4.7 (0.9)	4.0 (1.4)	-0.74 (-1.16 to -0.32)	0.00076	-1.06 (-1.63 to -0.49)	0.00035
<b>CBCL problem scores</b>						
Total problems	25.3 (13)	27.7 (17.9)	2.39 (-3.51 to 8.29)	0.42	8.74 (1.02 to 16.46)	0.027
Internalizing problems	8 (3.9)	9.3 (5.1)	1.31 (-0.40 to 3.03)	0.13	3.01 (0.68 to 5.34)	0.012
Anxious/depressed	3.4 (1.7)	3.9 (1.9)	0.48 (-0.21 to 1.17)	0.17	0.75 (-0.20 to 1.70)	0.12
Withdrawn	2.3 (1.9)	2.9 (2.6)	0.56 (-0.30 to 1.41)	0.20	1.13 (-0.05 to 2.31)	0.060
Somatic complaints	2.3 (2.2)	2.6 (2.1)	0.27 (-0.58 to 1.13)	0.52	1.13 (0.01 to 2.25)	0.048
Externalizing problems	5.8 (4.7)	5.6 (5.4)	-0.29 (-2.24 to 1.66)	0.77	0.78 (-1.80 to 3.36)	0.55
Other problems						
Social problems	3.0 (2.4)	3.1 (3)	0.06 (-0.96 to 1.09)	0.90	0.91 (-0.44 to 2.25)	0.18
Thought problems	1.5 (1.9)	1.9 (2.3)	0.39 (-0.42 to 1.19)	0.34	1.29 (0.22 to 2.35)	0.018
Attention problems	3.4 (2.7)	3.7 (3.7)	0.28 (-0.93 to 1.49)	0.65	1.63 (0.06 to 3.21)	0.043
<b>Neurocognitive scores</b>						
RCPM score	19.8 (5.5)	22.4 (7)	2.63 (0.24 to 5.02)	0.031	2.15 (-0.83 to 5.13)	0.16
Digit Forwards	6.8 (2.1)	7.3 (2.6)	0.49 (-0.41 to 1.39)	0.28	0.62 (-0.46 to 1.71)	0.26
Digit Backwards	3.2 (1.6)	3.7 (2.2)	0.54 (-0.19 to 1.27)	0.14	0.55 (-0.31 to 1.41)	0.20

*Data depicted as mean (SD) test scores. Data analysed using ANCOVA with age, sex, parental loss, HIV disclosure, prior treatment failure, cART duration, history of tuberculosis treatment, and prior hospital admission entered as covariates in the adjusted models.*

*CBCL= Child Behaviour Checklist. RCPM=Raven's Coloured Progressive Matrices.*

**Supplementary table 8. Characteristics of study outcome variables and covariates**

<b>Variable</b>	<b>Variable</b>	<b>Analysis</b>	<b>Type</b>	<b>Details</b>	<b>Presented in</b>
CBCL Total Competence	Outcome (prim)	Behaviour	Continuous	Normal	Table 2
Activities	Outcome (prim)	Behaviour	Continuous	Normal	Table 2
Social	Outcome (prim)	Behaviour	Continuous	Normal	Table 2
School	Outcome (prim)	Behaviour	Continuous	Near-normal	Table 2
CBCL Total problems	Outcome (prim)	Behaviour	Continuous	Near-normal	Table 2
Internalizing problems	Outcome (prim)	Behaviour	Continuous	Near-normal	Table 2
Externalizing problems	Outcome (prim)	Behaviour	Continuous	Near-normal	Table 2
Social problems	Outcome (prim)	Behaviour	Continuous	Near-normal	Table 2
Thought problems	Outcome (prim)	Behaviour	Continuous	Near-normal	Table 2
Attention problems	Outcome (prim)	Behaviour	Continuous	Normal	Table 2
RCPM score	Outcome (sec)	Cognition	Continuous	Normal	Table 2
Digit Forwards	Outcome (sec)	Cognition	Continuous	Normal	Table 2
Digit Backwards	Outcome (sec)	Cognition	Continuous	Normal	Table 2
Non-adherence	Outcome (sec)	Adherence	Dichotomous	Yes/no	Text
Abnormal dreaming	Outcome (expl)	CNS symptoms	Dichotomous	Yes/no	Table 3
Difficulty going to sleep	Outcome (expl)	CNS symptoms	Dichotomous	Yes/no	Table 3
Difficulty staying asleep	Outcome (expl)	CNS symptoms	Dichotomous	Yes/no	Table 3
Dizziness/balance problems	Outcome (expl)	CNS symptoms	Dichotomous	Yes/no	Table 3
Feeling of uneasiness	Outcome (expl)	CNS symptoms	Dichotomous	Yes/no	Table 3
Lack of vivacity	Outcome (expl)	CNS symptoms	Dichotomous	Yes/no	Table 3
Depressed or anxious	Outcome (expl)	CNS symptoms	Dichotomous	Yes/no	Table 3
Attention problems at school	Outcome (expl)	CNS symptoms	Dichotomous	Yes/no	Table 3
Age	Covariate	Adjusted models	Continuous	Normal	Suppl table 8
Sex	Covariate	Adjusted models	Dichotomous	Male/Female	Suppl table 8
Prior treatment discontinuation	Covariate	Adjusted models	Dichotomous	Yes/no	Suppl table 8
cART duration	Covariate	Adjusted models	Continuous	Near normal	Suppl table 8
Parental loss single	Covariate	Adjusted models	Dichotomous	Yes/no	Suppl table 8
Parental loss double	Covariate	Adjusted models	Dichotomous	Yes/no	Suppl table 8
HIV disclosure	Covariate	Adjusted models	Dichotomous	Yes/no	Suppl table 8
History of tuberculosis treatment	Covariate	Adjusted models	Dichotomous	Yes/no	Suppl table 8

*Prim= primary. Sec=secondary. Expl=exploratory. CNS= central nervous system*

**Supplementary table 9. Crude and adjusted models of the Child Behaviour Checklist items and the neurocognitive scores.**

Item	Model	Variable	B (95% CI)	P-value
Total Competence	Crude model	Study group	-0.12 (-1.49 to 1.25)	0.86
	Adjusted model	Study group	-2.43 (-4.19 to -0.67)	0.0071
		Age	0.54 (0.15 to 0.93)	0.0071
		Sex	-0.91 (-2.22 to 0.41)	0.17
		HIV disclosure	1.36 (-0.19 to 2.91)	0.084
		Lost one parent	0.92 (-0.53 to 2.38)	0.21
		Lost both parents	-1.77 (-3.74 to 0.19)	0.076
		Prior treatment failure	-1.78 (-3.80 to 0.24)	0.084
		Prior hospital admission	0.24 (-1.21 to 1.69)	0.74
		History of TB	-0.91 (-2.46 to 0.63)	0.24
		Time (years) on cART	-0.52 (-0.83 to -0.2)	0.0015
		Activities	Crude model	Study group
Adjusted model	Study group		-0.90 (-2.01 to 0.21)	0.11
	Age		0.29 (0.04 to 0.54)	0.021
	Sex		-0.33 (-1.16 to 0.50)	0.43
	HIV disclosure		0.83 (-0.15 to 1.81)	0.096
	Lost one parent		0.34 (-0.58 to 1.26)	0.47
	Lost both parents		-0.75 (-2.00 to 0.49)	0.23
	Prior treatment failure		-0.81 (-2.09 to 0.48)	0.22
	Prior hospital admission		0.14 (-0.78 to 1.05)	0.77
	History of TB		-0.56 (-1.54 to 0.42)	0.26
	Time (years) on cART		-0.2 (-0.40 to 0.00)	0.048
	Social		Crude model	Study group
Adjusted model		Study group	-0.61 (-1.46 to 0.23)	0.15
		Age	0.17 (-0.02 to 0.36)	0.074
		Sex	-0.64 (-1.27 to -0.01)	0.048
		HIV disclosure	0.33 (-0.41 to 1.07)	0.38
		Lost one parent	0.56 (-0.14 to 1.27)	0.11
		Lost both parents	-0.19 (-1.14 to 0.75)	0.69
		Prior treatment failure	-0.95 (-1.92 to 0.02)	0.056
		Prior hospital admission	0.42 (-0.28 to 1.12)	0.24
		History of TB	-0.43 (-1.17 to 0.32)	0.26
		Time (years) on cART	-0.24 (-0.39 to -0.09)	0.0020
		School	Crude model	Study group
Adjusted model	Study group		-0.91 (-1.42 to -0.40)	0.00055
	Age		0.07 (-0.04 to 0.18)	0.24
	Sex		0.05 (-0.33 to 0.43)	0.78
	HIV disclosure		0.25 (-0.20 to 0.70)	0.27
	Lost one parent		0.04 (-0.38 to 0.47)	0.84
	Lost both parents		-0.84 (-1.41 to -0.27)	0.0043
	Prior treatment failure		-0.01 (-0.59 to 0.58)	0.98
	Prior hospital admission		-0.31 (-0.73 to 0.11)	0.15
	History of TB		0.05 (-0.40 to 0.50)	0.83
	Time (years) on cART		-0.07 (-0.16 to 0.02)	0.12
	Total problems		Crude model	Study group
Adjusted model		Study group	5.96 (-1.12 to 13.04)	0.098
		Age	-2.01 (-3.58 to -0.44)	0.013
		Sex	0.87 (-4.40 to 6.13)	0.74
		HIV disclosure	-1.66 (-7.89 to 4.57)	0.60
		Lost one parent	-0.33 (-6.19 to 5.52)	0.91
		Lost both parents	10.89 (2.99 to 18.80)	0.0073
		Prior treatment failure	4.22 (-3.93 to 12.37)	0.31
		Prior hospital admission	2.83 (-2.99 to 8.64)	0.34
		History of TB	-0.39 (-6.62 to 5.85)	0.90
		Time (years) on cART	0.45 (-0.81 to 1.72)	0.48

*cART=combination antiretroviral therapy. TB=tuberculosis.*

Item	Model	Variable	B (95% CI)	P-value
Internalizing problems	Crude model	Study group	1.60 (-0.06 to 3.25)	0.058
	Adjusted model	Study group	2.00 (-0.29 to 4.29)	0.086
		Age	0.04 (-0.46 to 0.55)	0.86
		Sex	0.06 (-1.64 to 1.76)	0.95
		HIV disclosure	-1.52 (-3.54 to 0.49)	0.14
		Lost one parent	0.24 (-1.66 to 2.13)	0.80
		Lost both parents	2.66 (0.11 to 5.22)	0.041
		Prior treatment failure	2.09 (-0.55 to 4.72)	0.12
		Prior hospital admission	1.7 (-0.18 to 3.58)	0.075
		History of TB	0.21 (-1.8 to 2.23)	0.83
		Time (years) on cART	-0.22 (-0.63 to 0.19)	0.28
Externalizing problems	Crude model	Study group	-0.15 (-1.85 to 1.56)	0.87
	Adjusted model	Study group	0.78 (-1.55 to 3.11)	0.51
		Age	-0.79 (-1.31 to -0.28)	0.0029
		Sex	-0.22 (-1.95 to 1.51)	0.80
		HIV disclosure	0.37 (-1.68 to 2.42)	0.72
		Lost one parent	-0.74 (-2.67 to 1.18)	0.45
		Lost both parents	2.37 (-0.23 to 4.97)	0.074
		Prior treatment failure	1.03 (-1.66 to 3.71)	0.45
		Prior hospital admission	-0.7 (-2.61 to 1.22)	0.47
		History of TB	1.05 (-1.00 to 3.10)	0.31
		Time (years) on cART	0.25 (-0.16 to 0.67)	0.23
Social problems	Crude model	Study group	0.08 (-0.79 to 0.96)	0.85
	Adjusted model	Study group	0.61 (-0.61 to 1.83)	0.32
		Age	-0.27 (-0.54 to 0.00)	0.053
		Sex	0.20 (-0.71 to 1.11)	0.66
		HIV disclosure	0.15 (-0.93 to 1.22)	0.79
		Lost one parent	-0.50 (-1.51 to 0.51)	0.33
		Lost both parents	0.70 (-0.66 to 2.06)	0.31
		Prior treatment failure	-0.66 (-2.07 to 0.74)	0.35
		Prior hospital admission	0.25 (-0.76 to 1.25)	0.63
		History of TB	-0.62 (-1.70 to 0.45)	0.25
		Time (years) on cART	0.16 (-0.06 to 0.38)	0.15
Thought problems	Crude model	Study group	0.19 (-0.51 to 0.88)	0.60
	Adjusted model	Study group	0.81 (-0.16 to 1.78)	0.10
		Age	-0.16 (-0.37 to 0.06)	0.16
		Sex	0.31 (-0.42 to 1.03)	0.40
		HIV disclosure	-0.25 (-1.11 to 0.60)	0.56
		Lost one parent	0.34 (-0.46 to 1.14)	0.40
		Lost both parents	1.35 (0.27 to 2.44)	0.015
		Prior treatment failure	0.51 (-0.60 to 1.63)	0.36
		Prior hospital admission	0.17 (-0.62 to 0.97)	0.67
		History of TB	-0.54 (-1.39 to 0.32)	0.22
		Time (years) on cART	0.12 (-0.05 to 0.29)	0.17
Attention problems	Crude model	Study group	0.11 (-0.93 to 1.14)	0.84
	Adjusted model	Study group	1.19 (-0.21 to 2.59)	0.096
		Age	-0.31 (-0.63 to 0.00)	0.048
		Sex	0.16 (-0.89 to 1.20)	0.77
		HIV disclosure	-0.26 (-1.49 to 0.98)	0.68
		Lost one parent	-0.07 (-1.23 to 1.09)	0.91
		Lost both parents	2.52 (0.96 to 4.09)	0.0018
		Prior treatment failure	0.79 (-0.82 to 2.41)	0.33
		Prior hospital admission	0.78 (-0.37 to 1.93)	0.18
		History of TB	-0.69 (-1.92 to 0.55)	0.27
		Time (years) on cART	0.17 (-0.08 to 0.42)	0.17

*cART=combination antiretroviral therapy. TB=tuberculosis.*

Item	Model	Variable	B (95% CI)	P-value
Raven's Coloured Progressive Matrices	Crude model	Study group	2.33 (0.28 to 4.38)	0.026
	Adjusted model	Study group	1.29 (-1.36 to 3.93)	0.34
		Age	1.33 (0.74 to 1.92)	<0.0001
		Sex	-1.83 (-3.79 to 0.14)	0.068
		HIV disclosure	-0.57 (-2.9 to 1.75)	0.63
		Lost one parent	0.47 (-1.71 to 2.66)	0.67
		Lost both parents	-0.45 (-3.40 to 2.50)	0.76
		Prior treatment failure	0.09 (-2.95 to 3.13)	0.95
		Prior hospital admission	-0.51 (-2.68 to 1.66)	0.64
		History of TB	2.10 (-0.23 to 4.42)	0.077
		Time (years) on cART	-0.02 (-0.49 to 0.45)	0.93
		Digit Forwards	Crude model	Study group
Adjusted model	Study group		0.57 (-0.43 to 1.56)	0.26
	Age		0.42 (0.20 to 0.64)	0.00023
	Sex		0.51 (-0.23 to 1.25)	0.18
	HIV disclosure		0.55 (-0.32 to 1.43)	0.21
	Lost one parent		-0.21 (-1.04 to 0.61)	0.61
	Lost both parents		-0.62 (-1.73 to 0.49)	0.27
	Prior treatment failure		-0.15 (-1.3 to 0.99)	0.80
	Prior hospital admission		0.1 (-0.72 to 0.91)	0.82
	History of TB		0.26 (-0.61 to 1.14)	0.55
	Time (years) on cART		0.13 (-0.04 to 0.31)	0.14
	Digit Backwards		Crude model	Study group
Adjusted model		Study group	0.46 (-0.34 to 1.26)	0.25
		Age	0.43 (0.25 to 0.61)	<0.0001
		Sex	0.50 (-0.09 to 1.09)	0.098
		HIV disclosure	-0.08 (-0.79 to 0.62)	0.82
		Lost one parent	-0.16 (-0.82 to 0.5)	0.63
		Lost both parents	-0.86 (-1.75 to 0.03)	0.059
		Prior treatment failure	0.25 (-0.67 to 1.17)	0.59
		Prior hospital admission	-0.27 (-0.93 to 0.38)	0.41
		History of TB	0.43 (-0.27 to 1.13)	0.23
		Time (years) on cART	0.07 (-0.07 to 0.21)	0.35

*Depicted are crude models (incl. study group) and the final models (incl. study group and all covariates: age, sex, cART duration, prior treatment failure, prior admission, history of tuberculosis treatment, parental loss and HIV disclosure). P-values represent the p-values for the study group or the respective covariate. cART=combination antiretroviral therapy. TB=tuberculosis.*



**Supplementary table 10. Crude, final and intermediate models for large mean differences**

Dependent variable	Model	B (95% CI)	P-value
Total competence	Crude model	-0.12 (-1.49 to 1.25)	0.86
	Final model	-2.43 (-4.19 to -0.67)	0.0071
	<u>excl. cART duration</u>	<u>-1.01 (-2.60 to 0.57)</u>	<u>0.21</u>
	excl. age	-1.67 (-3.39 to 0.04)	0.055
	excl. prior treatment failure	-1.95 (-3.63 to -0.27)	0.023
	excl. lost one parent	-2.24 (-3.98 to -0.51)	0.012
	excl. sex	-2.40 (-4.16 to -0.64)	0.0080
	excl. prior admission	-2.45 (-4.20 to -0.71)	0.0062
	excl. HIV disclosure	-2.47 (-4.24 to -0.70)	0.0067
	excl. lost both parents	-2.64 (-4.40 to -0.89)	0.0034
School performance	Crude model	-0.59 (-0.97 to -0.22)	0.0022
	Final model	-0.91 (-1.42 to -0.40)	0.00055
	<u>excl. cART duration</u>	<u>-0.71 (-1.16 to -0.26)</u>	<u>0.0020</u>
	excl. age	-0.82 (-1.30 to -0.33)	0.0011
	excl. prior admission	-0.88 (-1.39 to -0.37)	0.00082
	excl. history of tuberculosis	-0.90 (-1.39 to -0.41)	0.00041
	excl. lost one parent	-0.90 (-1.40 to -0.40)	0.00050
	excl. prior treatment failure	-0.91 (-1.39 to -0.43)	0.00028
	excl. sex	-0.91 (-1.42 to -0.41)	0.00051
	excl. HIV disclosure	-0.92 (-1.43 to -0.41)	0.00051
Total problems	Crude model	2.07 (-3.11 to 7.25)	0.43
	Final model	5.96 (-1.12 to 13.04)	0.098
	<u>excl. age</u>	<u>3.15 (-3.72 to 10.02)</u>	<u>0.37</u>
	excl. cART duration	4.70 (-1.43 to 10.82)	0.13
	excl. prior treatment failure	4.83 (-1.91 to 11.56)	0.16
	excl. prior admission	5.67 (-1.38 to 12.72)	0.11
	excl. history of tuberculosis	5.84 (-0.97 to 12.66)	0.092
	excl. lost one parent	5.89 (-1.07 to 12.85)	0.096
	excl. sex	5.92 (-1.13 to 12.97)	0.099
	excl. HIV disclosure	6.01 (-1.05 to 13.06)	0.095
Attention problems	Crude model	0.11 (-0.93 to 1.14)	0.84
	Final model	1.19 (-0.21 to 2.59)	0.096
	<u>excl. cART duration</u>	<u>0.71 (-0.51 to 1.93)</u>	<u>0.25</u>
	excl. age	0.75 (-0.60 to 2.10)	0.27
	excl. prior treatment failure	0.98 (-0.36 to 2.31)	0.15
	excl. history of tuberculosis	0.99 (-0.37 to 2.34)	0.15
	excl. prior admission	1.11 (-0.29 to 2.51)	0.12
	excl. lost one parent	1.18 (-0.20 to 2.55)	0.093
	excl. sex	1.18 (-0.21 to 2.58)	0.096
	excl. HIV disclosure	1.20 (-0.20 to 2.59)	0.092
excl. lost both parents	1.49 (0.05 to 2.92)	0.043	

*Depicted are crude models (incl. study group), the final models (incl. study group and all covariates: age, sex, cART duration, prior treatment failure, prior admission, history of tuberculosis treatment, parental loss and HIV disclosure), and intermediate models (incl. study group and all covariates minus the covariate of interest). P-values represent the p-values for study group in the different models.*

**Supplementary table 11. Crude, final and intermediate OR models for large ORs**

Dependent variable	Model	OR (95% CI)	P-value
Abnormal dreaming	Crude model	0.54 (0.27 to 1.05)	0.071
	Final model	0.32 (0.11 to 0.90)	0.031
	<u>excl. age</u>	<u>0.55 (0.22 to 1.38)</u>	<u>0.20</u>
	excl. cART duration	0.39 (0.16 to 0.94)	0.036
	excl. history of tuberculosis	0.38 (0.14 to 1.04)	0.059
	excl. sex	0.34 (0.12 to 0.95)	0.040
	excl. prior admission	0.33 (0.12 to 0.93)	0.036
	excl. HIV disclosure	0.32 (0.11 to 0.91)	0.032
	excl. prior treatment failure	0.31 (0.11 to 0.86)	0.024
	excl. lost one parent	0.31 (0.11 to 0.89)	0.029
excl. lost both parents	0.29 (0.10 to 0.84)	0.022	
Feelings of uneasiness	Crude model	1.83 (0.81 to 4.10)	0.14
	Final model	3.45 (1.02 to 11.63)	0.046
	<u>excl. cART duration</u>	<u>2.38 (0.84 to 6.76)</u>	<u>0.10</u>
	excl. lost both parents	2.94 (0.92 to 9.47)	0.070
	excl. lost one parent	3.04 (0.93 to 9.93)	0.065
	excl. history of tuberculosis	3.23 (0.99 to 10.52)	0.051
	excl. prior admission	3.26 (0.98 to 10.84)	0.054
	excl. HIV disclosure	3.30 (1.00 to 10.90)	0.050
	excl. prior treatment failure	3.34 (1.06 to 10.52)	0.039
	excl. age	3.40 (1.07 to 10.84)	0.039
excl. sex	3.48 (1.04 to 11.68)	0.043	
Depressed or anxious	Crude model	3.25 (1.20 to 8.81)	0.021
	Final model	6.98 (1.43 to 34.03)	0.016
	<u>excl. prior treatment failure</u>	<u>4.39 (1.15 to 16.70)</u>	<u>0.030</u>
	excl. prior admission	5.51 (1.16 to 26.29)	0.032
	excl. lost one parent	5.70 (1.24 to 26.31)	0.026
	excl. HIV disclosure	6.51 (1.36 to 31.10)	0.019
	excl. sex	6.92 (1.44 to 33.25)	0.016
	excl. age	7.00 (1.49 to 32.85)	0.014
	excl. history of tuberculosis	7.27 (1.55 to 34.04)	0.012
	excl. lost both parents	7.31 (1.52 to 35.17)	0.013
excl. cART duration	7.82 (1.79 to 34.10)	0.0062	
Attention problems at school	Crude model	2.73 (1.11 to 6.75)	0.029
	Final model	6.92 (1.81 to 26.48)	0.0047
	<u>excl. cART duration</u>	<u>4.31 (1.31 to 14.24)</u>	<u>0.017</u>
	excl. prior admission	6.14 (1.66 to 22.73)	0.0066
	excl. history of tuberculosis	6.31 (1.74 to 22.93)	0.0051
	excl. age	6.34 (1.72 to 23.28)	0.0054
	excl. prior treatment failure	6.79 (1.92 to 24.03)	0.0030
	excl. sex	6.92 (1.81 to 26.45)	0.0047
	excl. lost one parent	7.12 (1.89 to 26.77)	0.0037
	excl. HIV disclosure	7.21 (1.90 to 27.40)	0.0037
excl. lost both parents	8.27 (2.19 to 31.24)	0.0018	

*Depicted are crude models (incl. study group), the final models (incl. study group and all covariates: age, sex, cART duration, prior treatment failure, prior admission, history of tuberculosis treatment, parental loss and HIV disclosure), and intermediate models (incl. study group and all covariates minus the covariate of interest). P-values represent the p-values for study group in the different models.*

### **Supplementary appendix reference list**

1. Knoetze J, Bass N, Steele G. The raven's coloured progressive matrices: Pilot norms for isiXhosa-speaking primary school learners in peri-urban Eastern Cape. *S Afr J Psychol* 2005; 35(2): 175-94.
2. Costenbader V, Ngari SM. A Kenya standardization of the Raven's Coloured Progressive Matrices. *School Psychol Int* 2001; 22(3): 258-68.
3. Harrison L, Ananworanich J, Hamadache D, et al. Adherence to antiretroviral therapy and acceptability of planned treatment interruptions in HIV-infected children. *AIDS and behavior* 2013; 17(1): 193-202.

## Study Participants

## Domain

## Instrument

141 children living in Kilimanjaro region, Tanzania

### Inclusion criteria

- Age 6-12 years
- HIV-1 positive
- cART ≥ 6 months
- HIV-RNA <1000 cps/ml
- Presence caretaker

### Exclusion criteria

- cART switch ≤6 months
- Acute illnesses
- Pre-existing mental health or developmental problems

## Behaviour and emotions

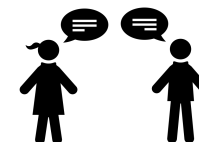
### Psychopathology

Internalizing problems (anxiety, withdrawn)  
Externalizing problems (rule-breaking, conflict)

### Competence

School  
Activities  
Social

### Child Behaviour Checklist



EFV n=72\*



WHO recommended-high dose n=43

Non-EFV n=69



NVP n=43

## Cognitive performance

### Intelligence

### Memory

Short-term and working memory

### RCPM



### Digit Span



Below WHO recommended dose n=28



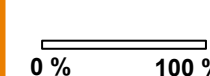
LPV/r n=26

## Adherence

### Non-adherence

<100% since last visit  
OR missed dose in past 3 days

### PENTA



## Central nervous system symptoms

E.g. dizziness or balance problems

### CNS checklist



**Supplementary figure 1. Study overview**

*\*Due to missing of body weight, the efavirenz dose (mg/kg) could not be determined for one of the participants.*

*cART=combination antiretroviral therapy. EFV =efavirenz. WHO=World Health Organization. NVP=nevirapine. LPV/r=ritonavir-boosted lopinavir. RCPM=Raven's Coloured Progressive Matrices. PENTA=Pediatric European Network for the Treatment of AIDS. CNS=central nervous system.*

*Adapted versions of the following icons were used in this figure: "Dizzy" by Gan Khoon Lay, "Checkbox" by Roman Shvets, "Woman" by TukTuk Design, "Man" by TukTuk Design, "chat" by TukTuk Design, all from thenounproject.com.*