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Supplementary appendix

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APPENDIX

The CIPHER Global Cohort Collaboration

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Hospital, Jenila Health Center, Jijiga Health Center, Jimma Hospital, Karamara Hospital, Kuyu Hospital, Leghare Health Center, Limmu-Genet Hospital, Mariam Work Hospital, Melka-Jebdu Health Center, Metehara Hospital, Metu Karl Hospital, Misrak Arbegnoch Hospital, Negele Hospital, Robe Dida, Sabian Health Center, Shashemene Hospital, Sher Ethiopia Private Hospital, St. Luke (Wolisso) Hospital, Tulu Bolo Hospital, Wonji Hospital, Yabelo, Yimaji Private Hospital. *Kenya* - Mark Hawken, ICAP Kenya; Maureen Kamene Kimenye, PASCO Central province; Irene N. Mukui, National AIDS and STIs Control Programme. Abidha Health Center, Ahero Sub District Hospital, Akala Health Center, Aluor Mission, Athi River Health Center, Awasi Mission, Bar Agulu Dispensary, Bar Olengo, Bondo District Hospital, Boro Dispensary, Daniel Comboni Dispensary-Ndithini, Dienya Health Center, Gobei Dispensary, Hawinga Dispensary, Kali Dispensary, Kathiani Sub District Hospital, Kibwezi Health Center, Kikoko Mission Hospital, Kitui District hospital, Madiant District Hospital, Mahaya Health Center, Malanga Health Center, Manyuanda Dispensary, Masogo Subdistrict Hospital, Matangwe mission Hospital, Mtito Andei Health Center, Muhoroni SDH, Mulaha Dispensary, Naya Dispensary, Ndere Health Center, Ndori Dispensary, Ngiya Mission, Nyakach AIC Dispensary, Nyangoma Kogelo, Ongiello Health Center, Rangala Mission, Rera Health Center, Siaya District Hospital, Sigomere Health Center, Sikalame Health Center, Tawa Health Center, Tingwangi Health Center, Ukwala Health Center, Usigu Health Center, Uyawi Health Center, Wagai Dispensary, Yala Sub District Hospital. *Mozambique* - Josue Lima, ICAP Mozambique; Antonio Mussa, ICAP Mozambique; Américo Rafi Assan, Ministry of Health Mozambique. 17 de Setembro Health Center, 25 de Setembro Health Center – Nampula, Akumi Health Center – Nacala, Anchilo Health Center, Angoche HR, Coalane Health Center, Gurue Rural Hospital Ilha de Mocambique, Liupo Health Center, Lumbo Health Center, Malema Health Center, Marrere General Hospital, Meconta Health Center, Memba Health Center, Milange Health Center, Military Hospital-Maputo, Mocuba Rural Hospital, Moma Health Center, Monapo HR, Monapo Health Center, Mossuril HR, Nacala-Porto District Hospital, Nacala-Porto Health Center, Nacuxa HR, Nametil Health Center, Namialo Health Center, Namitoria Health Center, Nampula Central Hospital, Namuinho Health Center, Nicoadala Health Center, Pediatric Central Hospital – Nampula, Ribaue Rural Hospital; *Rwanda* - Vincent Mutabazi, Treatment and Research AIDS Center; Ruben Sahabo, ICAP Rwanda. Avega Clinic, Bethsaida Health Center, Bigogwe Health Center, Busasamana Health Center, Butare Hospital, Carrefour Polyclinic, Central Hospital-Kigali, Congo Nil Health Center, Gisenyi District Hospital, Gisenyi Prison, Gisovu Health Center, Kabaya District Hospital, Kabusunzu Health Center, Kayove Health Center, Kibuye District Hospital, Kicukiro Health Center, Kigali Central Prison, Kigufi Health Center, Kinunu Health Center, Kirambo Health Center, Kirinda District Hospital, Kivumu Health Center, Mugonero District Hospital, Muhima District Hospital, Muhororo District Hospital, Mukungu Health Center, Munzanga Health Center, Murunda District Hospital, Mushubati Health Center, Mwendo Health Center, Ndera Neuropsychiatric Hospital, Nyabirasi Health Center, Nyakiriba Health Center, Nyange A health Center, Nyange B Health Center, Ramba Health Center, Rambura Health Center, Rubengera Health Center, Rugarama Health Center, Rususa health Center, Shyira District Hospital; *Tanzania* - Gretchen Antelman, ICAP Tanzania; Redempta Mbatia, ICAP Tanzania; Geoffrey Somi, National AIDS Control Program. Al-Rahma Hospital, Bagamoyo District Hospital, Baleni Dispensary, Biharamulo Designated District Hospital, Bunazi Health Center, Bwanga Health Center, Chake Chake Hospital, Chalinze Health Center, Chato District

Hospital, ChemChem (Miburani) Dispensary, Heri Mission Hospital, Ikwiriri Health Center, Isingiro Hospital, Izimbya Hospital, Kabanga Mission Hospital, Kagera Sugar Hospital, Kagondo Hospital, Kahororo Dispensary, Kaigara Health Center, Kakonko Health Center, Kanazi Health Centre, Kasulu District Hospital, Katoro Health Centre, Kayanga Health Centre, Kibiti Health Center, Kibondo District Hospital, Kigarama Health Centre, Kigoma Dispensary, Kigoma Regional Hospital, Kilimahewa Mission Dispensary, Kirongwe Dispensary, Kisarawe District Hospital, Kishanje Health Centre, Kisiju Health Centre, Kivunge Hospital, Kongowe Dispensary, Lugoba Health Center, Mabamba Health Center, Mafia District Hospital, Maneromango Health Center, Masaki Health Centre, Mchukwi Hospital, Michiweni Hospital, Miono Health Centre, Mkamba Health Centre, Mkoani Health Centre, Mkomaindo Hospital, Mkuranga District Hospital, Mlandizi Health Center, Mnazi Mmoja Hospital, Mugana Designated District Hospital, Murgwanza Designated District Hospital, Murongo Health Center, Mwembeladu Maternity Hospital, Mzenga Health Centre, Ndanda Hospital, Ndolage Hospital, Newala Hospital, Nguruka Health Centre, Nkwenda Health Center, Nyakahanga Designated District Hospital, Nyamiaga Health Centre, Ocean Road Cancer Institute, Rubya Designated District Hospital, Rulenge Hospital, Rwamishenye Health Centre, St. Therese Bukoba Health Center, Tumbi Regional Hospital, Ujiji Health Center, Utende Dispensary, Utete District Hospital, Uvinza Dispensary, Wete Hospital, Zam Zam Health Centre. *ICAP Central* - Matthew Lamb, Denis Nash, Harriet Nuwagaba-Biribonwoha.

Table S1. Cumulative incidence (%) of switch to second-line ART by 1, 2, and 3 years after start of ART: by initial regimen and region

% switched to second-line	USA	Latin America	Europe	Asia	Southern Africa	Rest of sub-Saharan Africa	Total
Overall:							
1 year	9.9 (6.2, 14.7)	1.1 (0.6, 1.9)	4.8 (3.9, 5.8)	0.6 (0.5, 0.9)	0.9 (0.7, 1.0)	0.3 (0.3, 0.3)	0.6 (0.5, 0.6)
2 years	19.0 (13.8, 24.9)	3.1 (2.1, 4.4)	9.5 (8.2, 10.8)	3.2 (2.8, 3.7)	3.1 (2.8, 3.7)	0.8 (0.7, 0.8)	1.7 (1.6, 1.8)
3 years	26.1 (20.0, 32.7)	6.5 (4.9, 8.3)	12.2 (10.8, 13.7)	6.6 (5.9, 7.3)	5.4 (5.1, 5.9)	1.5 (1.4, 1.6)	3.1 (3.0, 3.2)
NNRTI-based ART:							
1 year	15.9 (9.9, 23.2)	1.2 (0.6, 2.2)	6.7 (5.3, 8.2)	0.6 (0.4, 0.8)	1.0 (0.8, 1.2)	0.3 (0.2, 0.3)	0.5 (0.5, 0.6)
2 years	28.5 (20.5, 37.0)	3.3 (2.2, 4.7)	12.5 (10.7, 14.5)	3.3 (2.8, 3.8)	4.0 (3.6, 4.4)	0.7 (0.6, 0.8)	1.6 (1.5, 1.7)
3 years	37.0 (28.1, 45.9)	6.6 (5.0, 8.5)	16.1 (14.0, 18.4)	6.6 (5.9, 7.4)	7.0 (6.4, 7.6)	1.4 (1.3, 1.5)	3.0 (2.9, 3.2)
PI-based ART:							
1 year	1.3 (0.1, 6.2)	-	2.4 (1.6, 3.6)	1.7 (0.6, 4.0)	0.7 (0.5, 0.9)	2.0 (1.3, 2.9)	1.0 (0.9, 1.3)
2 years	0.5 (0.2, 11.8)	1.1 (0.9, 5.4)	5.4 (4.1, 7.1)	2.2 (0.8, 4.8)	1.8 (1.5, 2.1)	3.8 (2.8, 5.1)	2.5 (2.1, 2.8)
3 years	10.1 (4.4, 18.5)	5.1 (1.6, 11.6)	7.0 (5.4, 8.8)	3.6 (1.6, 7.1)	3.2 (2.7, 3.7)	4.3 (3.2, 5.7)	3.9 (3.4, 4.3)
NNRTI-based ART, routine CD4/VL monitoring:	-	-	-	-	-		
1 year						1.2 (0.8, 1.9)	
2 years						3.4 (2.6, 4.4)	
3 years						5.9 (4.7, 7.2)	
NNRTI-based ART, routine CD4, targeted VL monitoring:	-	-	-	-	-		
1 year						0.3 (0.3, 0.5)	
2 years						1.0 (0.8, 1.1)	
3 years						2.1 (1.8, 2.4)	
NNRTI-based ART, routine CD4 monitoring only:	-	-	-	-	-		
1 year						0.2 (0.2, 0.5)	
2 years						0.5 (0.4, 0.6)	
3 years						1.1 (0.9, 1.2)	
NNRTI-based ART, clinical monitoring only:	-	-	-	-	-		

1 year						0.2 (0.1, 0.3)	
2 years						0.3 (0.2, 0.5)	
3 years						0.7 (0.6, 1.0)	
PI-based ART, routine CD4/VL monitoring:	-	-	-	-	-		
1 year						2.5 (0.7, 6.7)	
2 years						9.7 (4.4, 17.5)	
3 years						9.7 (4.4, 17.5)	
PI-based ART, other monitoring strategy:	-	-	-	-	-		
1 year						1.9 (1.3, 2.8)	
2 years						3.4 (2.4, 4.6)	
3 years						3.8 (2.7, 5.2)	

ART=antiretroviral therapy; PI=protease inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; VL=viral load.

Table S2. Cumulative incidence (%) of switch to second-line ART by 1, 2, and 3 years after start of ART among patients who initiated ART in 2011-2014: by monitoring strategy

Year after ART start	Percent (95% CI) switched to second-line		
	1 year	2 years	3 years
Monitoring strategy, among those starting ART ≥2011			
Routine VL, routine CD4	0.9 (0.7, 1.3)	2.8 (2.2, 3.5)	4.1 (3.3, 5.2)
Targeted VL, routine CD4	0.4 (0.2, 0.6)	0.9 (0.6, 1.3)	1.6 (1.1, 2.2)
Routine CD4 only	0.3 (0.2, 0.4)	0.6 (0.4, 0.8)	1.2 (0.8, 1.6)
Clinical monitoring	0.3 (0.1, 0.5)	0.3 (0.2, 0.6)	0.8 (0.4, 1.5)
Total	0.4 (0.3, 0.5)	1.0 (0.9, 1.2)	1.8 (1.5, 2.2)

Table S3: Sensitivity analyses with alternative definition of switch (without requirement for change in \geq NRTI)

	Global p-value sHR (95% CI)			
	Complete case (n=93,351)		Sub-group of cohorts with routine CD4 monitoring and children with immune/WAZ ascertainment (n=32,989)	
	Univariate	Multivariate	Univariate	Multivariate
Characteristics at start of ART				
Sex	P<0.0001	P<0.0001	P<0.0001	P<0.0001
Female vs male	0.80 (0.75, 0.85)	0.79 (0.74, 0.84)	0.81 (0.76, 0.87)	0.82 (0.76, 0.89)
Age (years)	p<0.0001	p<0.0001	p<0.0001	p<0.0001
<3	0.62 (0.57, 0.67)	0.64 (0.59, 0.69)	0.59 (0.55, 0.64)	0.63 (0.57, 0.71)
3-5	0.77 (0.71, 0.84)	0.72 (0.67, 0.78)	0.78 (0.71, 0.84)	0.71 (0.64, 0.79)
6-9	1.00	1.00	1.00	1.00
\geq 10	1.29 (1.11, 1.50)	1.14 (0.97, 1.33)	1.16 (1.00, 1.36)	1.25 (1.04, 1.50)
Known AIDS diagnosis	p=0.028	p=0.029	p=0.60	p=0.64
Yes vs no	0.93 (0.88, 0.99)	0.93 (0.87, 0.99)	1.02 (0.95, 1.09)	0.98 (0.90, 1.07)
WHO immunodeficiency for age			p<0.0001	p<0.0001
None			1.08 (0.91, 1.28)	0.92 (0.77, 1.11)
Mild			1.24 (1.03, 1.49)	1.19 (0.97, 1.45)
Advanced			1.00	1.00
Severe			1.38 (1.22, 1.57)	1.41 (1.22, 1.63)
Weight for age z-score			p=0.16	p=0.26
<-2			0.93 (0.86, 1.01)	1.06 (0.97, 1.16)
-2 to <0			1.00	1.00
\geq 0			1.02 (0.89, 1.18)	0.94 (0.81, 1.10)
Regimen	p=0.0017	p<0.0001	p<0.0001	p<0.0001
PI vs NNRTI	1.15 (1.05, 1.26)	0.70 (0.63, 0.78)	0.69 (0.62, 0.76)	0.58 (0.50, 0.68)
Calendar year	p<0.0001	p<0.0001	p<0.0001	p<0.0001
\leq 2004	2.98 (2.72, 3.25)	1.33 (1.21, 1.47)	2.30 (2.10, 2.52)	1.35 (1.18, 1.53)
2005-2007	1.45 (1.35, 1.56)	1.25 (1.16, 1.35)	1.27 (1.17, 1.37)	1.18 (1.07, 1.30)
2008-2010	1.00	1.00	1.00	1.00
\geq 2011	0.54 (0.47, 0.62)	0.61 (0.53, 0.70)	0.48 (0.41, 0.57)	0.59 (0.48, 0.72)

CI, 95% confidence interval; sHR, standardized hazard ratio; ART, antiretroviral therapy; WAZ, weight-for-age z-score. See also Supplementary Tables S1 and S2 and Figures 1 and 2 (Lancet HIV).

Cohort level factors				
Monitoring strategy	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Routine CD4 & VL	4.79 (4.38, 5.23)	2.69 (2.25, 3.21)	2.95 (2.67, 3.25)	2.33 (1.91, 2.84)
Routine CD4 & targeted VL	2.16 (1.94, 2.40)	1.94 (1.74, 2.17)	1.27 (1.13, 1.43)	1.42 (1.23, 1.64)
Routine CD4 only	1.00	1.00	1.00	1.00
Clinical only	0.74 (0.61, 0.89)	0.67 (0.55, 0.82)	-	-
Country income group	p<0.0001	p<0.0001	p<0.0001	P=0.70
Low	1.00	1.00	1.00	1.00
Lower middle	1.02 (0.93, 1.12)	1.08 (0.97, 1.20)	0.99 (0.89, 1.11)	1.00 (0.87, 1.14)
High/upper middle	3.38 (3.13, 3.64)	1.57 (1.35, 1.84)	2.39 (2.20, 2.59)	1.09 (0.89, 1.33)
Region	p<0.0001	p<0.0001	p<0.0001	p<0.0001
USA	4.15 (3.19, 5.39)	4.05 (3.09, 5.32)	3.05 (1.87, 4.97)	4.40 (2.30, 8.40)
Europe	2.46 (2.22, 2.74)	2.41 (2.15, 2.70)	2.18 (1.96, 2.44)	2.46 (2.09, 2.91)
Latin America	1.36 (1.14, 1.63)	2.14 (1.74, 2.62)	1.43 (1.19, 1.73)	2.35 (1.85, 2.99)
Asia	1.47 (1.34, 1.61)	1.70 (1.53, 1.90)	1.38 (1.25, 1.52)	1.11 (0.96, 1.28)
Southern Africa	1.00	1.00	1.00	1.00
Rest of SSA	0.35 (0.32, 0.38)	1.05 (0.88, 1.26)	0.47 (0.43, 0.51)	0.81 (0.65, 1.02)

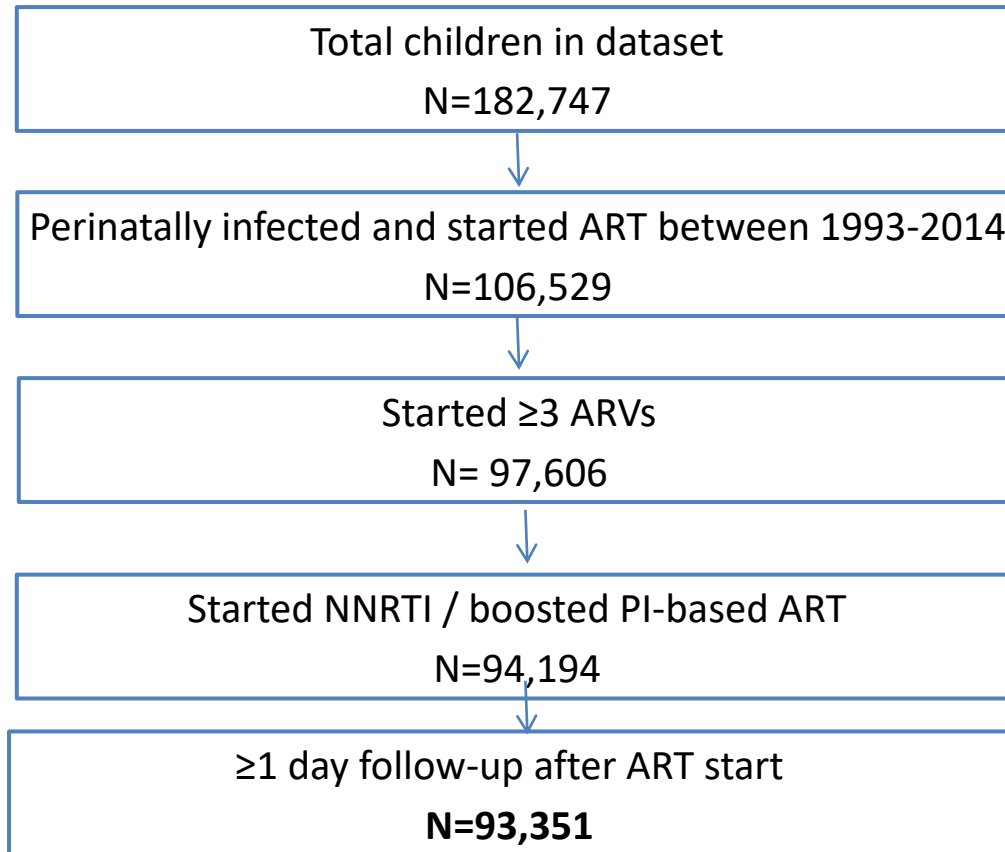
ART=antiretroviral therapy; sHR=Sub-distribution hazard ratio; CI=confidence interval; PI=protease inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI= nucleoside reverse transcriptase inhibitor; WAZ=weight-for-age z-score; VL=viral load; SSA=sub-Saharan Africa.

Table S4. Characteristics at time of switch among children switched to second-line ART

	USA	Latin America	Europe	Asia	Southern Africa	Rest of sub-Saharan Africa	Total
N	72	123	464	587	1255	1382	3883
Median time from ART start to switch, months [IQR]	24 [12, 42]	42 [26, 72]	35 [14, 66]	35 [22, 52]	33 [19, 55]	38 [23, 57]	35 [20, 57]
Male sex	33 (45.8)	61 (49.6)	223 (48.1)	359 (61.2)	702 (55.9)	816 (59.1)	2194 (56.5)
Median age, years [IQR]	4.1 [1.9, 7.5]	10.3 [6.7, 13.8]	8.2 [4.2, 12.0]	7.7 [5.5, 10.0]	8.3 [5.3, 11.2]	9.4 [6.3, 12.0]	8.6 [5.5, 11.5]
Drug class of switch							
NNRTI to PI	56 (77.8)	117 (95.1)	330 (71.1)	573 (97.6)	940 (74.9)	1313 (95.0)	3329 (85.7)
PI to NNRTI	8 (11.1)	4 (3.3)	78 (16.8)	5 (0.1)	277 (22.1)	47 (3.4)	419 (10.8)
Other	8 (11.1)	2 (1.6)	56 (12.1)	9 (1.5)	38 (3.0)	22 (1.6)	135 (3.5)
WHO immunodeficiency for age							
N with measurement available	56 (77.8*)	106 (86.2*)	394 (84.9*)	525 (89.4*)	984 (78.4*)	951 (68.8*)	3016 (77.7*)
None	25 (44.6)	31 (29.3)	183 (46.5)	129 (24.6)	496 (50.4)	174 (18.3)	1038 (34.4)
Mild	18 (32.1)	9 (8.5)	55 (14.0)	58 (11.1)	137 (13.9)	77 (8.1)	354 (11.7)
Advanced	6 (10.7)	8 (7.6)	50 (12.7)	68 (13.0)	95 (9.7)	132 (13.9)	359 (11.9)
Severe	7 (12.5)	58 (54.7)	106 (26.9)	270 (51.4)	256 (26.0)	568 (59.7)	1265 (41.9)
Viral load							
N with measurement available	53 (73.6*)	56 (45.5*)	414 (89.2*)	433 (73.8*)	1034 (82.4*)	429 (31.0*)	2419 (62.3*)
≤1000 copies/mL	9 (17.0)	9 (16.1)	124 (30.0)	28 (6.5)	226 (21.9)	10 (2.3)	406 (16.8)
>1000 copies/mL	44 (83.0)	47 (83.9)	290 (70.1)	405 (93.5)	808 (78.1)	419 (97.7)	2013 (83.2)
Tuberculosis diagnosis	0 (0.0)	0 (0.0)	1 (0.2)	38 (6.5)	49 (3.9)	115 (8.3)	203 (5%)

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR: interquartile range; ART=antiretroviral therapy; PI=protease inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI= nucleoside reverse transcriptase inhibitor; WAZ=weight-for-age z-score; VL=viral load

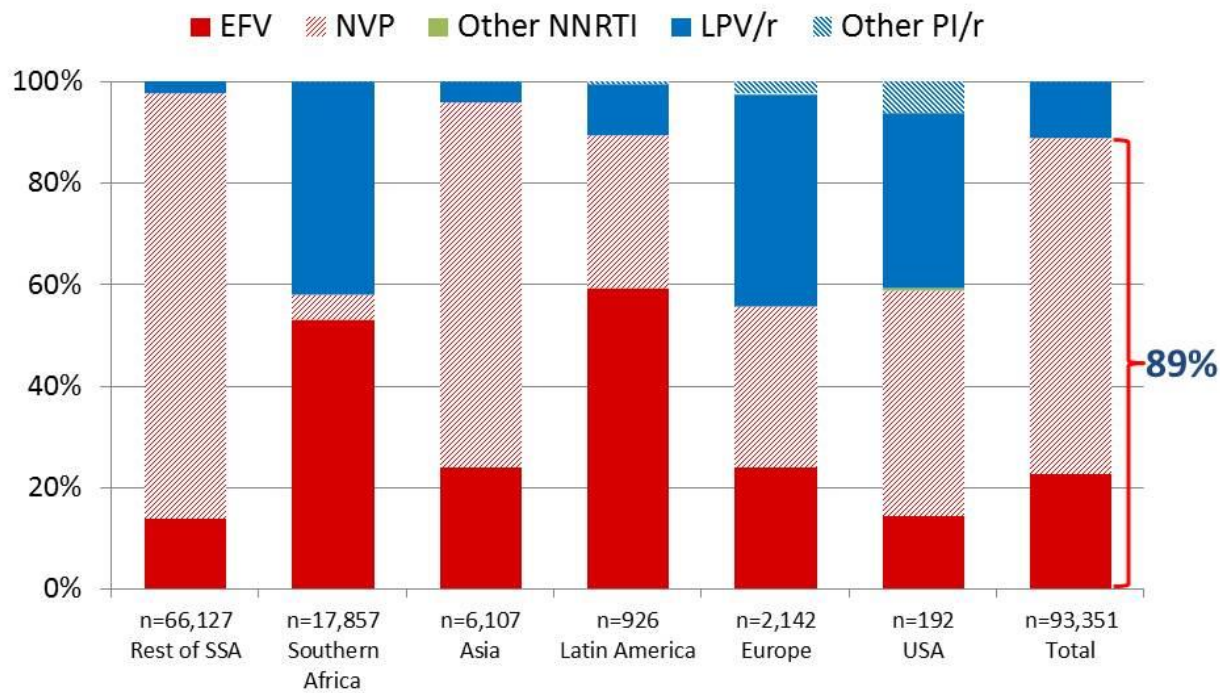
Figure S1. Flowchart of children included in the analysis



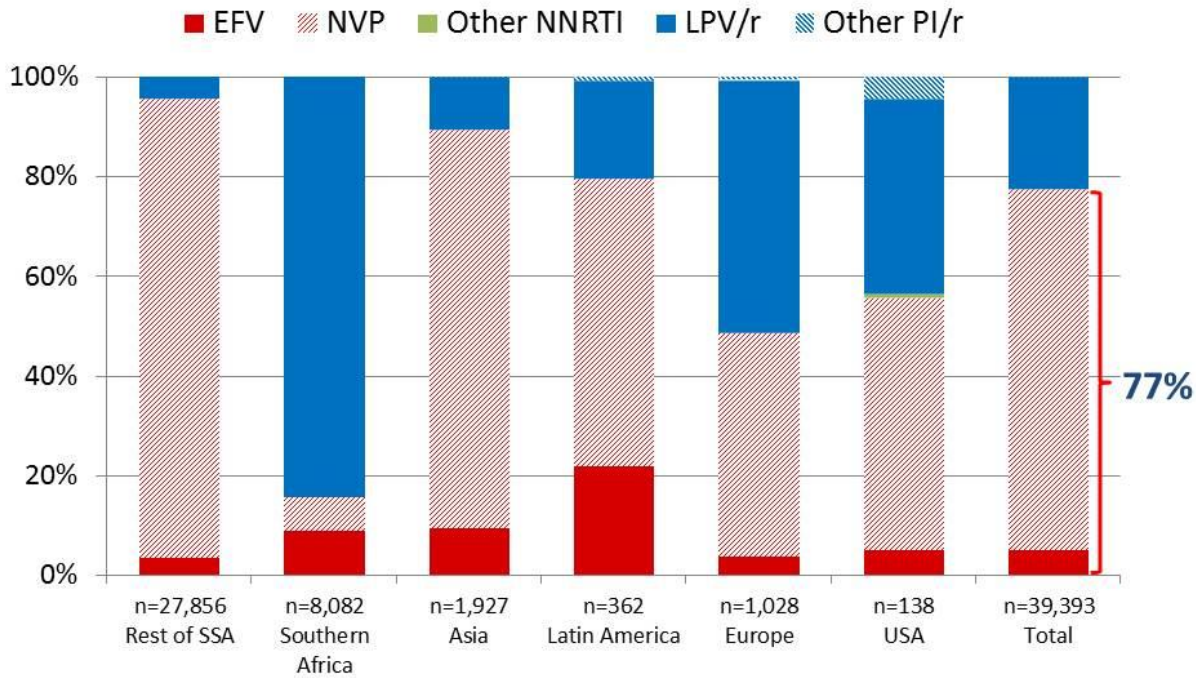
ART: antiretroviral therapy; ARVs=antiretroviral drugs; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.

Figure S2. Drug class used in first-line ART regimen, by region

(a) Amongst all children initiating ART



(b) Amongst children aged <3 years at ART initiation



ART: antiretroviral therapy; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; NVP=nevirapine; EFV=efavirenz; LPV=lopinavir; SSA=sub-Saharan Africa.

