Title:

Incidence of switch to second-line antiretroviral therapy and associated factors in children with HIV: an international cohort collaboration

Authorship: The Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Global Cohort Collaboration

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RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed for studies published in English before November 16, 2017, which assessed the probability of switch to second-line ART in children across regions and under different monitoring strategies, using the search terms “child”, “children” or “adolescent”, “HIV”, “antiretroviral therapy”, “switch” and “second-line”. We identified clinical trials and several cohort studies reporting on the probability of switch that used various different definitions of switch. Very few studies have estimated the incidence of switch to second-line ART in children across multiple countries with varying treatment monitoring strategies. To our knowledge, there is no published global level analysis of switch to second-line ART using a uniform definition of switch.

Added value of this study

This study provides the first global estimates of incidence of switch to second-line ART, with individual patient level data on almost 100,000 children across 52 countries. We show a low cumulative incidence of switch of 3.1% by 3-years after ART start globally but with significant variations across geographic regions and treatment monitoring strategies. Compared to CD4 only monitoring, children in settings with routine or targeted viral load monitoring had double the probability of switch while those in settings with clinical only monitoring had a third lower probability of switch.

Implications of all the available evidence

As HIV treatment programmes mature, understanding trends in the use of second-line ART is critical in ensuring future paediatric treatment needs are met. The wide variations in the incidence of switch across regions and monitoring strategies highlights the need to assess the impact of delayed and lower rates of switch on clinical outcomes in children and the potential implications of expanding access to viral load testing on future use of second-line ART in resource-limited settings.

Abstract

Background: Estimates of incidence of HIV-infected children switching to second-line antiretroviral therapy (ART) over time are necessary to inform the need for paediatric second-line formulations. This study aims to quantify the cumulative incidence of switch to second-line ART in children through an international cohort collaboration.

Methods: Individual patient data on children aged <18 years initiating ART (≥2 nucleoside reverse-transcriptase inhibitors (NRTI) plus a non-NRTI (NNRTI) or boosted protease inhibitor (PI)) between 1993-2014 were pooled from 12 observational cohort networks in the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER). Switch to second-line was defined as: (i) change of ≥1 NRTI plus either change in drug class (NNRTI to PI or vice versa) or PI change, (ii) change from single to dual PI, or (iii) addition of a new drug class. Cumulative incidence curves assessed time to switch; proportional hazards models explored patient- and cohort-level factors associated with switch, with death and loss to follow-up (LTFU) as competing risks.

Findings: Of 93,351 eligible children, 90% were from sub-Saharan Africa. At ART initiation, median[IQR] age was 3.9 [1.6,6.9] years, 89% initiated NNRTI-based and 11% PI-based regimens. Median duration on ART was 26 [9,52] months. Overall, 3,883 (4.2%) switched to second-line after a median 35[20,57] months of ART. The global cumulative incidence of switch at 3-years was 3.1 (95% CI 3.0, 3.2), but varied widely across monitoring strategies, from 6.8% (6.5,7.2) in routine CD4 and viral load (VL) monitoring to 0.8% (95% CI 0.6,1.0) in clinical-only monitoring settings . Male sex, older age at ART initiation, NNRTI-based initial regimen, and higher-income country were associated with higher incidence of switch. Routine or targeted VL monitoring was associated with 166% increase in hazard of switch as compared to CD4-only monitoring.

Interpretation: This global paediatric analysis detected wide variations in the incidence of switch to second-line across monitoring strategies. These findings suggest the scale-up of VL monitoring will likely increase demand for paediatric second-line ART formulations.

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INTRODUCTION

Globally, an estimated 1.8 million children (<15 years) were living with HIV in 2017, of whom 52% had access to antiretroviral treatment (ART)(1). Achievement of the ambitious UNAIDS 90-90-90 goals to end AIDS by 2020 in children will take a concerted effort to ensure (i) 90% of children living with HIV are diagnosed, (ii) 90% of those diagnosed are on ART, and (iii) 90% of those on ART attain and maintain viral suppression(2). Children and adolescents have persistently lagged behind adults in their progress towards the first two 90% targets(3), leading to increased efforts to expand access to HIV diagnosis and ART for children across multiple settings(4). As more children receive ART and treatment programs mature, development of strategies to meet the third 90 of sustained viral suppression will be the long-term challenge. Achievement of this goal requires a comprehensive understanding of the durability of first-line ART regimens and patterns of switch to second-line ART across geographic regions and different country income settings to ensure future treatment needs are met (5).

The short-term effectiveness of ART in children is undisputed, with high survival rates, immune and growth recovery, and the proportion suppressing viral load at 12 months after ART initiation ranging from 70-95%(6-8). There are fewer data on the durability of first-line ART in children and the use of second-line treatment. The PENPACT trial, conducted predominately in high income countries, reported that 71% of children remained on their first-line regimen 5 years after ART start, compared to ≥95% in the CHER and ARROW trials conducted in Africa(7-9). Observational cohorts have reported wide variations in the probability of switch to second-line following different types of treatment failure. One large South African observational cohort reported that 19% of children experienced virological failure by 3 years of ART, with 38% of those failing switched to second-line within 1 year following failure(10). In a West African cohort, 12% of children had clinical-immunological failure after 24 months on ART, with 7% of those

failing switched to second-line(11). Other cohort studies in Asia and Europe reported 17-23% probability of switch to second-line by 5 years after ART start (12, 13). Comparison across these studies is difficult due to the heterogeneity of patient characteristics, initial regimens, monitoring strategies and the varying definitions of failure and switch.

The objectives of this study were to provide the first global estimates of the incidence of switch to second-line ART among children with HIV using a uniform definition of switch, and to assess associated factors. This analysis is a key step in understanding the use of second-line regimens globally, across programs operating under a spectrum of treatment monitoring strategies and guidelines for switch to second-line.

METHODS

STUDY DESIGN AND POPULATION

The Collaborative Initiative for Pediatric HIV Education and Research (CIPHER) is a global network of observational paediatric HIV cohorts. The collaboration includes 12 international networks: BIPAI (Baylor International Pediatric AIDS Initiative), EPPICC (European Pregnancy and Paediatric HIV Cohort Collaboration), the IeDEA Consortium (International Epidemiology Databases to Evaluate AIDS: Asia-Pacific, Caribbean, Central and South America network [CCASAnet], Central Africa, East Africa, West Africa and Southern Africa), IMPAACT 219C and P1074 (International Maternal Pediatric Adolescent AIDS Clinical Trials), MSF (Médecins Sans Frontières), Optimal Models (ICAP at Columbia University), and PHACS (Pediatric HIV/AIDS Cohort Study). Most networks comprised multiple cohorts and each cohort included data from one or more clinics (primary care clinic or hospital). Individual patient-level data were submitted to the University of Cape Town, South Africa data center in March 2015, using a standardized protocol based on the HIV Cohorts Data Exchange Protocol (www.hicdep.org).

The inclusion criteria for this analysis were: age <10 years at cohort enrolment (a proxy for perinatal HIV infection), age <18 years at initiation of a 'standard' combination ART regimen (at least three antiretroviral drugs, including at least two nucleoside reverse-transcriptase inhibitors (NRTIs) plus either a non-NRTI (NNRTI) or a ritonavir-boosted protease inhibitor (PI)), and ≥1 day of follow-up after ART initiation. Children documented as horizontally infected and those enrolled in clinical trials of treatment monitoring, switch or interruption strategies were excluded.

STATISTICAL ANALYSIS

The primary study outcome was cumulative incidence of "all cause" switch to second-line ART for any reason (henceforth referred to as "switch"). Switch was defined as: (i) change of ≥1 NRTI plus either change in drug class (NNRTI to PI or vice versa) or PI change; (ii) change from single to dual PI; or (iii) addition of a new drug class. This definition endeavored to capture major treatment changes due to treatment failure or major toxicity as well as allow for comparisons with previous analyses of switch in children that used similar approaches(12, 13)

We explored cohort and patient-level potential predictors of switch. Cohort-level factors were geographic region, treatment monitoring strategy and country income group. Geographical region was categorized as: Europe, USA, Asia, Latin America (Caribbean, Central and South America), Southern Africa (SA) or the rest of sub-Saharan Africa (R-SSA). SA was defined as South Africa and Botswana, and was considered separate from the rest of SSA due to the introduction of lopinavir-based regimens as first-line ART for children <3 years in 2010 and early roll-out of routine viral load (VL) monitoring(14, 15).

Treatment monitoring strategy was assigned at the cohort-level according to the presence and frequency of CD4 and VL measurements. Cohorts were classified as "routine" CD4 or VL monitoring if >60% of children had ≥1 CD4 or VL measurement after ART start and the median time between consecutive measurements was <60 weeks. Cohorts were classified as "targeted" CD4 or VL monitoring if 5%-60% of children had ≥1 CD4 or VL measured after ART start or >60% children had ≥1 measurement but consecutive measures were >60 weeks apart. Based on these definitions cohorts were classified into four groups: (i) routine CD4 and VL monitoring, (ii) routine CD4 and targeted VL monitoring, (iii) routine CD4 monitoring only (<5% of children with VL measurement), or (iv) clinical monitoring only (targeted CD4 only or <5% with CD4 and VL measurement). Country income group was assigned using the World Bank classification(16) (high/upper middle, lower middle, or low-income economies) at the median year of ART initiation in the cohort.

Patient-level independent variables measured at ART initiation were: sex (male or female), age at ART initiation (<3, 3-5, 6-9 and ≥10 years), known previous AIDS (WHO 3/4 or CDC C stage) diagnosis (yes or no), initial ART regimen (PI- or NNRTI-based) and calendar year (≤2004, 2005-2007, 2008-2010 and ≥2011). .

Children were followed from ART initiation until the earliest of: switch to second-line; death; last visit or 21st birthday. Time to switch was summarised using cumulative incidence, accounting for the competing risks of death and LTFU (17). Cumulative incidence of switch at 3 years after ART start was stratified by geographical region, initial ART regimen and cohort monitoring strategy.

Children were considered as LTFU if they had no visit for ≥1 year before the cohort data closing date, except for cohorts in the EPPICC, PHACS and IMPAACT networks, where a cut off of ≥2 years was used due to annual data collection and time lags in reporting. Follow-up of children was administratively censored at the date of last clinic visit.

The independent associations between cumulative incidence of switch and patient characteristics at ART start and cohort characteristics were summarised by sub-distribution hazard ratios calculated using multivariable competing risks proportional hazards regression(18). Analyses were performed using Stata version 14.2.

Two sensitivity analyses were performed. Firstly, to assess the potential association of low weight and immunosuppression at ART start and switch, the regression models were repeated including weight-for-age z-score and immunodeficiency for age based on the WHO standard definition(19) in the subset of cohorts in which >60% of children had weight and CD4 measurements at ART initiation. Weight-for-age z-scores were calculated relative to the 1990 British Growth Reference values in Stata(20). Secondly, all analyses were repeated with switch

to second-line redefined by removing the requirement for a simultaneous change of ≥1 NRTI when changing across drug class (PI to NNRTI or vice versa) or within the PI drug class.

All participating networks received local ethics approvals to transfer anonymised data for this study. The pooling of data at the UCT data centre was approved by the University of Cape Town Health Research Ethics Committee [UCT HREC reference 264/2014].

ROLE OF FUNDING SOURCE

The study was sponsored by International AIDS Society-CIPHER. Funders of CIPHER had no role in the study design, the collection, analysis or interpretation of data, nor in the writing of the paper.

RESULTS

A total of 182,747 children living with HIV were included in the CIPHER data merger, of whom 93,351 (51%) met our inclusion criteria (Supplement Figure S1). The majority of children were in R-SSA (71%), with 19% in SA, 7% in Asia and <5% in other regions (Figure 1). The calendar year of ART initiation ranged across regions from 1993-2014, with >70% of children initiating in 2008 onwards. Half of the children were male, and median age [interquartile range (IQR)] at ART initiation was 3.9 [1.6, 6.9] years, with two-thirds (68%) aged ≤5 years at start of ART (Table 1). The median age at ART start was comparable at 3-4 years across all regions except for in the USA where the median age was <1 year. Forty-three per cent had a known AIDS diagnosis at ART initiation, and among those with CD4 data available (55% of all children), 75% had advanced or severe immunodeficiency, with the highest proportions with severe immunodeficiency among children in Asia and SA.

The large majority of children (89%) initiated an NNRTI-based regimen (two-thirds nevirapine), although there were regional variations: over 40% of children initiated PI-based regimens in the USA, Europe and SA as compared to ≤11% of children in Latin America, Asia and R-SSA (Supplement Figure S2a). Among children aged <3 years at ART initiation, 84% of those in SA initiated a ritonavir-boosted lopinavir-based regimen compared to 4.5% in R-SSA (Supplement Figure. S2b).

The treatment monitoring strategy also varied across regions: in the USA, Europe and SA, virtually all children were followed in cohorts with routine CD4 and VL monitoring, while in Asia 56% of children were in cohorts with routine CD4 and VL monitoring and 40% with routine CD4 and targeted VL monitoring. In R-SSA, 3% of children were in cohorts with routine CD4 and VL, 22% with routine CD4 and targeted VL monitoring; 54% with only CD4 monitoring and 21% with only clinical monitoring.

Median duration of follow-up after ART initiation was 26 [IQR 9, 52] months, with longer follow-up in regions outside of Africa (Table 2). . The follow-up status at data cut-off (without use of competing risks) was: 5.8% died, 14.8% LTFU and not known to have died, 21% transferred out and 58% were still in follow-up.

Over a total of 265,942 person-years of follow-up, 3,883 children (4.2%) met our definition of switch to second-line, 0.5% died, 20% LTFU and 20% transferred out before switch based on competing risks analysis. The crude rate of switch was 14.6 (95% confidence interval [CI] 14.1, 15.1) per 1,000 person years. Globally, the cumulative incidence (95% CI) of switch by 3 years after ART initiation was 3.1% (3.0, 3.2), with wide variations across regions, from 1.5% (1.4, 1.6) in R-SSA to 26.1% (20.0, 32.7) in the USA (Table 2, Figure 2a). The cumulative incidence of switch by 1, 2 and 3 years after ART initiation by region, initial regimen and monitoring strategy are presented in Supplement Table 1, and by monitoring strategy among those initiated ART in recent calendar years (≥2011) in Supplement Table 2. As R-SSA was the only region using all four different types of routine monitoring strategies, the cumulative incidence of switch was explored further within this region (Figure 2b), showing 6.1% (95% CI, 5.0, 7.4) switch at 3 years in cohorts with routine CD4 and VL monitoring compared to <2% in cohorts with no VL monitoring.

In multivariable analyses, individual-level factors associated with higher hazard of switch were male sex, older age, NNRTI-based initial regimen and earlier calendar years at ART initiation (Table 3). We investigated interactions between sex and age at ART start and there was a trend towards a stronger effect of sex in children aged<10 years and no effect in those aged≥10 years at ART start (p for interaction=0.0825).

Compared to CD4-only monitoring, routine CD4 and VL monitoring was associated with 166% increase in hazard of switch, while clinical-only monitoring was associated with a 32% reduction in hazard. High/upper middle-income countries was associated with a higher hazard of switch compared to low-income countries. All regions outside of Africa had higher hazards of switch compared to SA, while there was no difference between SA and R-SSA.

In the first sensitivity analysis restricted to children in cohorts with CD4 and weight data at ART initiation (n=39,724), the risk factors for switch remained consistent with the main analyses, except some differences in the region effect; children in R-SSA had a lower hazard of switch compared to SA (Table 3). Additionally, children with severe immunodeficiency had an increased hazard of switch as compared to those with advanced immunodeficiency (sHR 1.40, 95% CI, 1.21, 1.62, p<0.0001), but there was no association between switch and weight-for-age z-score at ART start. .

In the second sensitivity analysis broadening the definition of switch, the number of children meeting the definition increased from 3883 (4.2%) to 4035 (4.3%). The majority of additional switches were from an NNRTI to a PI. Factors associated with switch and hazard estimates were broadly similar (Supplement Table S3).

Among the 3,883 children who switched to second-line ART, the median time to switch was 35 [IQR 20, 57] months (Supplement Table S4). The median age at switch was 8.6 [IQR 5.5, 11.5] years, 86% of switches were from NNRTI- to PI, 11% from PI to NNRTI-based ART and 4% were other switches. Among children with CD4 measurements at time of switch (n=3,016), 42% had severe immunodeficiency and 12% advanced immunodeficiency. Among the 62% of children with VL measurements at switch, 83% had VL >1000 copies per mL. Five percent of children had a tuberculosis diagnosis at time of switch. Among the 57% with a reason for

188 switch reported , 51% were for treatment failure, 3% toxicity and 46% were reported as for
189 “other” (unspecified) reasons.

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DISCUSSION

To our knowledge, this study provides the first global estimates of the incidence of switch to second-line ART, of 14.6 per 1000 person-years with a cumulative incidence of switch of approximately 3% by 3 years after ART initiation. However, we identified large variations across individual patient characteristics as well as regions and by cohort monitoring strategy.

At 3 years of ART, the cumulative incidence of switch was lowest at ~1% among children in R-SSA with clinical-only monitoring, and was only marginally higher where CD4-only monitoring was available. These estimates are lower than the 6% switched after a median of 4 years of follow-up reported in the ARROW trial conducted in R-SSA, where all children initiated NNRTI-based regimens and were managed with clinical-only or CD4-only monitoring(7). However, the latter represents a clinical trial setting with close follow-up, rather than the routine care setting in our study, and the median duration of follow-up was shorter in our cohort. WHO forecasting models estimate that the proportion of children on ART globally receiving second-line regimens, irrespective of duration on ART, was 4.1% in 2013 increasing to 6.1% in 2015(21). However, these estimates are cross-sectional, based on extrapolations from historical trends in global antiretroviral procurement data and projections based on assumptions regarding ART coverage. Therefore they cannot be directly compared to our estimates of cumulative incidence of switch at 3 years after ART start.

Within our analysis, children managed in settings with VL monitoring were twice as likely to switch to second-line ART as children in settings with only access to CD4 and/or clinical monitoring. This is consistent with findings from adult HIV modelling work which estimated a two to three-fold increase in the number of patients receiving second-line ART in settings with rapid versus slow or no scale-up of viral load monitoring(22).

Recent studies have reported 20-40% of children with only clinical or CD4 monitoring had evidence of virological failure (VL ≥1000 copies/mL) at 3-4 years after ART start, highlighting the poor sensitivity of these monitoring strategies in detecting virological failure(23, 24). This is particularly critical in SSA where the vast majority of children initiate on NNRTI regimens with low genetic thresholds for resistance(25). While the PENPACT-1 trial reported no difference in clinical outcomes of children with rapid versus delayed switch to second-line after virologic failure on NNRTI-based regimens(9), adult studies in SSA have shown increased risks of morbidity and mortality in patients with delayed switch to second-line ART(26, 27). A comparison of the clinical outcomes of children managed under a variety of monitoring strategies and duration between treatment failure and switch is warranted to determine the best utilization of resources in order to obtain optimal outcomes in this population.

In our study, most regions had higher estimates of cumulative incidence of switch to second-line for children initiating an NNRTI-based as compared to a PI-based regimen. However, in the rest of SSA, the opposite was found, although this was based on small proportion of children starting PIs in that region (2.4%, all lopinavir/ritonavir). Review of the data indicates that this may be partly due to incident tuberculosis and the need to avoid PIs when initiating a rifampin-containing tuberculosis treatment regimen. As the tuberculosis data were incomplete, this hypothesis could not be completely explored. The finding that older age at ART start is associated with a higher hazard of switch has been previously reported and may be partly due to the lack of available paediatric formulations for young children, as well as poorer adherence in adolescents(11, 13).The higher switch rates observed among males has been previously reported in paediatric and adult cohorts (11, 12),(28), we observed a trend towards a stronger sex effect in younger children which warrants further exploration .

Our analysis suggested that even after adjusting for monitoring strategy and patient-level characteristics, being in R-SSA and in low-income countries remained independently associated

with lower hazard of switch. The comparatively less frequent use of second-line ART in such settings, even when VL monitoring was available, may be partly due to the higher VL thresholds for failure previously recommended by WHO for low and middle-income countries (29). It may also reflect the limited access to second-line drugs and clinician fears about availability of subsequent third-line therapy, although these factors were not measured in our study.

The low global cumulative incidence of switch to second-line reported in our analysis, which was dominated by large number of children in SSA, reflects standard practice during the study period within participating programs up to 2014. Since then there has been ongoing scale-up of VL monitoring which is likely to significantly increase the early detection of treatment failure and demand for second-line ART. However the extent of the increased demand of second line ART across settings remain unclear and will still be subject to the local resource environment and guidance. Though there is less guidance and data on it's optimal use in children, the roll-out of low-cost integrase inhibitor dolutegravir as first and/or second line ART in adults will likely lead to increased calls for its use in children(30). As our study spans a large age spectrum and calendar year period, it provides a critical insight into how clinicians have assessed and responded to first line failure in children on ART to date. These insights can be utilized both to forecast future paediatric ART needs and to identify places where the system may be failing children as well as potential intervention points. Future assessments of the durability of first line regimens as new drugs are rolled out will be critical to ensure sufficient availability of paediatric formulations in the mid- to long-term.

This analysis had several limitations. First, few cohorts reported data on the reasons for ART switch, and among those with reasons reported, almost half were unspecified "other" reasons. Few had data on VL at the time of switch to elucidate whether switch was due to treatment failure. However, because of our conservative definition of switch, we feel that the vast majority were true switches to second-line rather than minor treatment modifications or simplifications.

Since 2010, in South Africa there has been a recommendation a switch to a NNRTI-based regimen at age ≥3 years for children <3 years at initiation of lopinavir-based ART, if virally suppressed(14). We considered that this might lead to over-estimation of switch among this group, however, only 77 children were switched in this manner while suppressed, and thus their potential misclassification would not significantly impact our findings.

Second, this is an observational study with sources of potential bias such as the high proportion of children LTFU which has likely resulted in incomplete ascertainment of switch and death. This has been addressed in part by utilizing a competing risk analysis. Third, there may be under-reporting of AIDS diagnosis at ART start in some settings. There is also incomplete data on co-infections (e.g. tuberculosis) and the availability of alternative antiretroviral drugs constrained our ability to explore possible reasons for the geographic variations in switch patterns.

In conclusion, we found that the cumulative incidence of switch to second-line varied widely between both geographic regions and monitoring strategies. Given the maturing cohorts and expanding roll-out of VL testing and new drugs, we anticipate that the use of second-line regimens will increase although geographic variation will likely persist for the foreseeable future. The impact of delayed versus faster switch to second-line ART on longer term clinical outcomes and treatment options in children remain unclear and warrant further exploration.

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Tables and Figures

CONTRIBUTORS

Corresponding authors IJ Collins and K Wools-Kaloustian and statisticians R Goodall and C Smith wrote the first draft of the Article, which was reviewed by all members of the Project Team and the Writing Committee on behalf of The CIPHER Global Cohort Collaboration (see Appendix page 1-2 for the full list).

DECLARATION OF INTEREST

We declare no competing interests.

FUNDING

The study was sponsored by the International AIDS Society (IAS)-CIPHER (http://www.iasociety.org/CIPHER). CIPHER is made possible by support from founding sponsor ViiV Healthcare and Janssen. Funding details of the individual cohort networks are listed in the Appendix (page 2-3).
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

DATA ACCESS

Data are accessible in principle by applying to the CIPHER Cohort Collaboration Data Centres. The CIPHER Cohort Collaboration is a multi-network, multi-site collaboration and this analysis combined data from different sites. The data do not belong to the CIPHER Cohort Collaboration itself, but data ownership remains with the participating sites. Each site has approval from its own local Institutional Review Board to collect routine data on patients and to transfer those data anonymously to the CIPHER Cohort Collaboration Project data center. For some sites and networks, IRB approval for use of this data is restricted to the specific protocols approved in order to protect patient identities. Requests for access to data can be directed to the International AIDS Society CIPHER, Samantha Hodgetts,
email: samantha.hodgetts@iasociety.org.

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Table 1. Characteristics at time of ART initiation

	USA	Latin America	Europe	Asia	Southern Africa	Rest of sub-Saharan Africa	Total
N	192	926	2142	6107	17857	66127	93351
Sex, male	89 (46.4)	441 (47.6)	1016 (47.4)	3213 (52.6)	9070 (50.8)	33236 (50.3)	47065 (50.4)
Age, median [IQR]	0.7 [0.2, 3.4]	4.2 [1.6, 7.3]	3.2 [0.7, 7.0]	4.5 [2.3, 7.0]	3.6 [1.1, 6.8]	3.8 [1.7, 6.9]	3.9 [1.6, 6.9]
<3 years	138 (71.9)	362 (39.1)	1028 (48.0)	1927 (31.6)	8082 (45.3)	27856 (42.1)	39393 (42.2)
3-5 years	34 (17.7)	242 (26.1)	447 (20.9)	2068 (33.9)	4127 (23.1)	16876 (25.5)	23794 (25.5)
6-9 years	20 (10.4)	244 (26.4)	450 (21.0)	1910 (31.3)	4934 (27.6)	19042 (28.8)	26600 (28.5)
10+ years	-	78 (8.4)	217 (10.1)	202 (3.3)	714 (4.0)	2353 (3.6)	3564 (3.8)
CD4% (<5 yrs)*, N (%)	92 (57.1)	323 (61.5)	995 (75.0)	2208 (65.9)	7315 (67.6)	14643 (37.0)	25576 (45.9)
Median [IQR]	32 [24, 38]	19 [13, 28]	23 [16, 33]	15 [8, 21]	17 [11, 24]	16 [11, 21]	16 [11, 23]
CD4 count (≥5 yrs)*, N (%)	21 (67.7)	391 (97.5)	718 (88.1)	2381 (86.5)	4753 (67.5)	16262 (61.2)	24526 (65.2)
Median [IQR]	409 [218, 631]	335 [165, 568]	330 [204, 525]	195 [59, 332]	308 [147, 537]	306 [162, 522]	297 [148, 507]
WHO immunodeficiency for age**							
N (%)	113 (58.9)	714 (77.1)	1718 (80.2)	4693 (76.9)	12202 (68.3)	31452 (47.6)	50892 (54.5)
None	45 (39.8)	175 (24.5)	463 (27.0)	402 (8.6)	1944 (15.9)	5100 (16.2)	8129 (16.0)
Mild	26 (23.0)	76 (10.6)	238 (13.9)	375 (8.0)	1081 (8.9)	3005 (9.6)	4801 (9.4)

Advanced	16 (14.2)	126 (17.7)	280 (16.3)	803 (17.1)	1474 (12.1)	5303 (16.9)	8002 (15.7)
Severe	26 (23.0)	337 (47.2)	737 (42.9)	3113 (66.3)	7703 (63.1)	18044 (57.4)	29960 (58.9)
Known AIDS diagnosis	20 (10.4)	45 (4.9)	368 (17.2)	3526 (57.7)	9910 (55.5)	26392 (39.9)	40261 (43.1)
Weight-for-age z-score							
N (%)	95 (49.5)	841 (90.8)	1051 (49.1)	5575 (91.3)	11610 (65.0)	49090 (74.2)	68262 (73.1)
≤-2	19 (20.0)	368 (43.8)	168 (16.0)	3664 (65.7)	5498 (47.4)	27257 (55.5)	36974 (54.2)
-2 to <0	52 (54.7)	394 (46.9)	486 (46.2)	1644 (29.5)	4911 (42.3)	17785 (36.2)	25272 (37.0)
≥0	24 (25.3)	79 (9.4)	397 (37.8)	267 (4.8)	1201 (10.3)	4048 (8.3)	6016 (8.8)
Initial ART regimen							
NNRTI-based	114 (59.4)	827 (89.3)	1194 (55.7)	5850 (95.8)	10368 (58.1)	64532 (97.6)	82885 (88.8)
NVP	*85 (44.3)*	*277 (29.9)*	*680 (31.8)*	*4383 (71.8)*	*885 (5.0)*	*55354 (83.7)*	*61664 (66.1)*
EFV	*28 (14.6)*	*550 (59.4)*	*514 (24.0)*	*1467 (24.0)*	*9483 (53.1)*	*9178 (13.9)*	*21220 (22.7)*
Other NNRTI	*1 (0.5)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*1 (0.0)*
PI-based	78 (40.6)	99 (10.7)	948 (44.3)	257 (4.2)	7489 (41.9)	1595 (2.4)	10466 (11.2)
LPV/r	*66 (34.4)*	*94 (10.2)*	*895 (41.8)*	*253 (4.1)*	*7486 (41.9)*	*1595 (2.4)*	*10389 (11.1)*
Other PI	*12 (6.3)*	*5 (0.5)*	*53 (2.5)*	*4 (0.1)*	*3 (0.0)*	*0 (0.0)*	*77 (0.1)*
Calendar year							
≤2004	152 (79.2)	321 (34.7)	643 (30.0)	535 (8.8)	1600 (9.0)	1448 (2.2)	4699 (5.0)
2005-2007	28 (14.6)	207 (22.4)	529 (24.7)	1733 (28.4)	5071 (28.4)	15639 (23.7)	23207 (24.9)
2008-2010	8 (4.2)	218 (23.5)	630 (29.4)	1891 (31.0)	7440 (41.7)	26433 (40.0)	36620 (39.2)
≥2011	4 (2.1)	180 (19.4)	340 (15.9)	1948 (31.9)	3746 (21.0)	22607 (34.2)	28825 (30.9)
Monitoring strategy							
Routine CD4 & VL	192 (100.0)	402 (43.4)	2123 (99.1)	3404 (55.7)	17857 (100.0)	2005 (3.0)	25983 (27.8)
Routine CD4 & targeted VL	-	-	19 (0.9)	2442 (40.0)	-	14246 (21.5)	16707 (17.9)
Routine CD4 only	-	524 (56.6)	-	260 (4.3)	-	35748 (54.1)	36532 (39.1)
Clinical only	-	-	-	1 (0.0)	-	14128 (21.4)	14129 (15.1)
Country income group							

Low	-	524 (56.6)	-	2947 (48.3)	-	36780 (55.6)	40251 (43.1)
Lower middle	-	169 (18.3)	390 (18.2)	507 (8.3)	-	29347 (44.4)	30413 (32.6)
High/upper middle	192 (100.0)	233 (25.2)	1752 (81.8)	2653 (43.4)	17857 (100.0)	0 (0.0)	22687 (24.3)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

ART=antiretroviral therapy; NNRTI=non-nucleoside reverse-transcriptase inhibitor; PI=protease inhibitor; NVP=nevirapine; EFV=efavirenz; LPV/r=ritonavir-boosted lopinavir; VL=viral load.

*CD4% is reported in children aged<5 years and CD4 count in children aged ≥5 years. The denominators for calculations of the percentages with a measurement are therefore in the subgroups aged <5 and ≥5 years, respectively

** WHO immunodeficiency for age classification (19): None: CD4%>35% for <12months; >30% for 12-35 months, >25% for 36-59 months and CD4>500 cells per µL for >5 years. Mild: CD4% 30-35% for <12months; 25-30% for 12-35 months, 20-25% for 36-59 months and CD4 350-499 cells per µL for >5 years. Advanced: CD4% 25-29% for <12months; 20-24% for 12-35 months, 15-19% for 36-59 months and CD4 200-349 cells per µL for >5 years. Severe: CD4<25% for age <12 months; <20% for 12-35 months; <15% for 35-59 months and CD4 <200 cells per µL for ≥5 years.

Table 2. Follow-up status and cumulative incidence of switch by 3 years after start of ART by region

	Region						Total
	USA	**Latin America**	**Europe**	**Asia**	**Southern Africa**	**Rest of sub-Saharan Africa**	
N	192	926	2142	6107	17857	66127	93351
Median duration of follow-up [IQR], months*	41 [23, 79]	52 [24, 93]	49 [23, 81]	38 [17, 69]	29 [12, 58]	24 [8, 47]	26 [9, 52]
Follow-up status using competing risks, n (%)							
Switch*	72 (37.5)	123 (13.3)	464 (21.7)	587 (9.6)	1255 (7.0)	1382 (2.1)	3883 (4.2)
Died*	0	4 (0.4)	3 (0.1)	31 (0.5)	17 (0.1)	394 (0.6)	449 (0.5)
LTFU*	15 (7.8)	214 (23.1)	235 (11.0)	674 (11.0)	3446 (19.3)	13688 (20.7)	18272 (19.6)
Administrative censoring*	105 (54.7)	585 (63.2)	1440 (67.2)	4815 (78.8)	13139 (73.6)	50663 (76.6)	70747 (75.8)
Cumulative incidence (95% CI) switched by 3 years after start of ART, n (%)							
Overall	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)
Age at start of ART							
<3 years	25.7 (18.5, 33.4)	4.9 (2.9, 7.6)	11.7 (9.8, 13.9)	7.0 (5.8, 8.3)	3.7 (3.2, 4.2)	1.1 (0.9, 1.2)	2.5 (2.3, 2.7)
3-5 years	27.6 (13.7, 43.3)	5.0 (2.7, 8.5)	8.9 (6.4, 12.0)	7.0 (5.8, 8.4)	6.5 (5.7, 7.4)	1.4 (1.2, 1.6)	3.1 (2.9, 3.4)
6-9 years	27.1 (9.8, 48.0)	8.3 (5.1, 12.4)	14.8 (11.5, 18.4)	5.6 (4.5, 6.9)	7.2 (6.3, 8.1)	2.0 (1.8, 2.3)	3.7 (3.4, 4.0)
≥10 years	-	12.3 (5.7, 21.6)	16.6 (11.5, 22.5)	6.7 (2.7, 13.5)	6.7 (4.5, 9.5)	2.4 (1.7, 3.4)	4.9 (4.0, 5.9)
Initial ART regimen							
PI-based	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	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)
Monitoring strategy							
Routine CD4 & VL	26.1 (20.0, 32.7)	7.7 (5.3, 10.7)	12.3 (10.8, 13.8)	8.7 (7.8, 9.8)	5.4 (5.1, 5.9)	6.1 (5.0, 7.4)	6.8 (6.5, 7.2)
Routine CD4 & targeted VL	-	-	5.9 (0.4, 23.5)	2.8 (2.0, 3.7)	-	2.1 (1.8, 2.4)	2.2 (1.9, 2.4)
Routine CD4 & no VL	-	5.5 (3.6, 7.9)	-	3.5 (1.1, 8.3)	-	1.1 (1.0, 1.3)	1.2 (1.1, 1.4)
Clinical only	-	-	-	-	-	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)

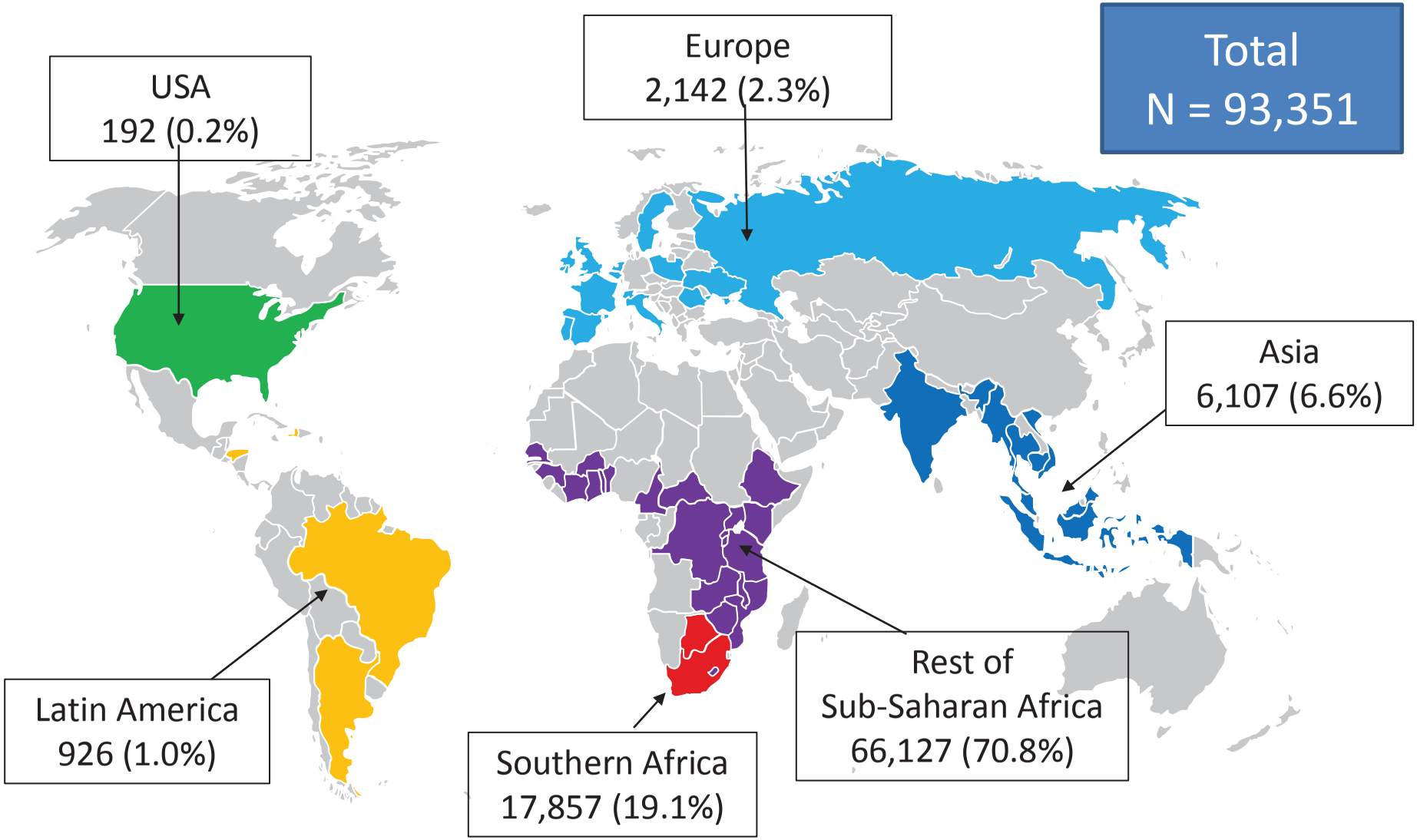
NOTE. Data are no. (%) of patients, unless otherwise indicated. *Competing risk analysis, censored at the first of the following events: switched to second-line, death, loss to follow-up (LTFU) or date of last clinic visit (before transfer out or close of data). NNRTI=non-nucleoside reverse-transcriptase inhibitor; PI=protease inhibitor; VL=viral load.

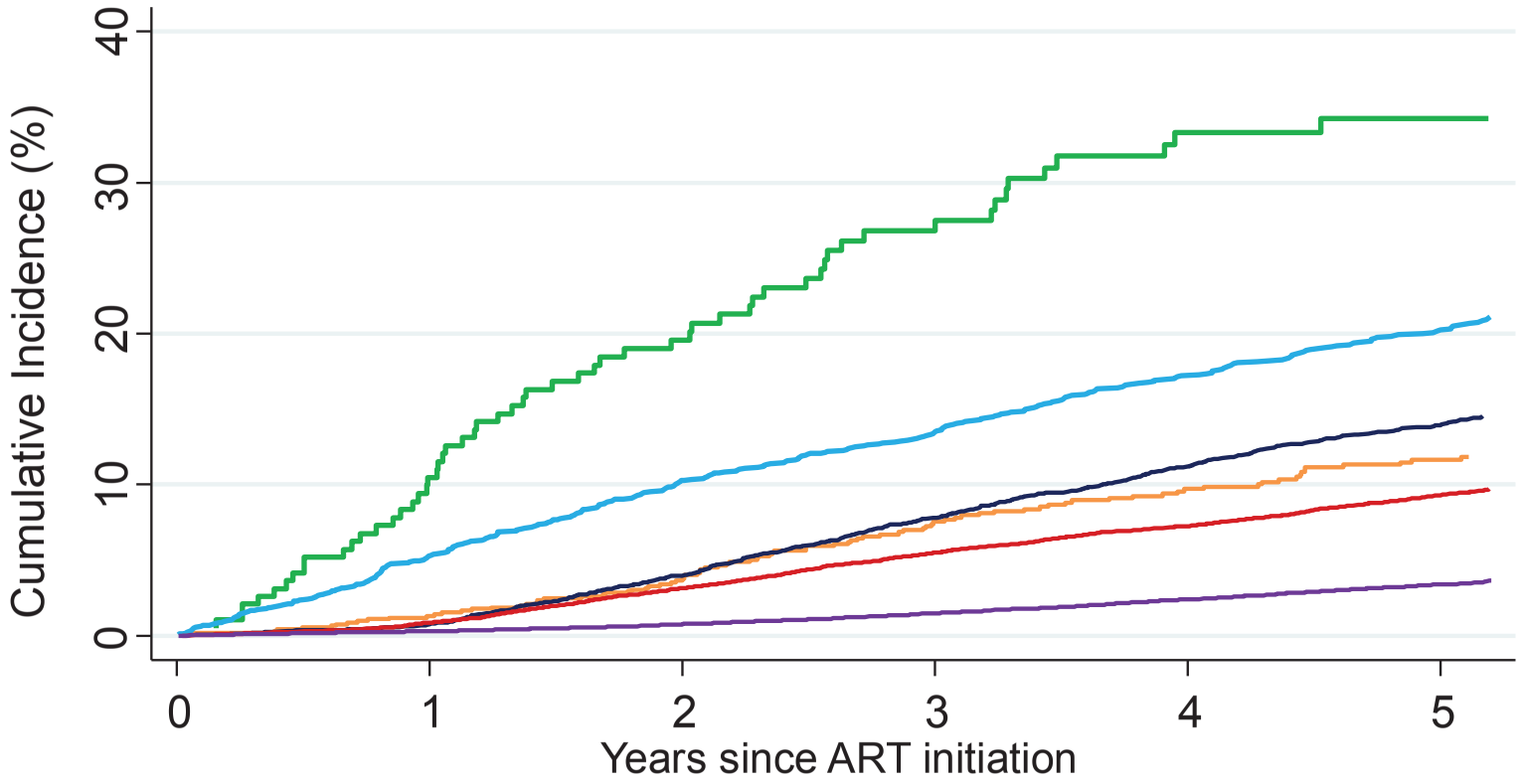
Table 3. Factors associated with higher hazard of switch to second-line ART

	Global p-value sHR (95% CI)				
	All children (n=93,351)		Sub-group of cohorts with routine CD4 monitoring and children with immune/WAZ ascertainment (n=39,724)		
	Univariable	Multivariable	Univariable	Multivariable not including CD4 and WAZ	Multivariable
Characteristics at start of ART					
Sex	P=<0.0001	P=<0.0001	P=<0.0001	P=<0.0001	P=<0.0001
Female vs male	0.79 (0.74, 0.84)	0.78 (0.73, 0.83)	0.80 (0.75, 0.86)	0.79 (0.74, 0.84)	0.81 (0.74, 0.88)
Age (years)	P=<0.0001	P=<0.0001	P=<0.0001	P=<0.0001	P=<0.0001
<3	0.61 (0.56, 0.66)	0.63 (0.58, 0.68)	0.58 (0.54, 0.63)	0.68 (0.62, 0.74)	0.62 (0.54, 0.70)
3-5	0.77 (0.71, 0.84)	0.73 (0.67, 0.79)	0.78 (0.71, 0.85)	0.75 (0.69, 0.82)	0.71 (0.64, 0.79)
6-9	1.00	1.00	1.00	1.00	1.00
≥10	1.24 (1.11, 1.51)	1.15 (0.98, 1.35)	1.17 (1.00, 1.37)	1.17 (0.99, 1.38)	1.26 (1.05, 1.51)
Known AIDS diagnosis	P=0.16	P=0.10	P=0.16	P=0.87	P=0.96
Yes vs no	0.96 (0.90, 1.02)	0.95 (0.88, 1.01)	1.05 (0.98, 1.12)	1.01 (0.94, 1.08)	1.00 (0.88, 1.16)
WHO immunodeficiency for age	-	-	P=<0.0001	-	P=<0.0001
None			1.07 (0.90, 1.27)		0.91 (0.75, 1.10)
Mild	-	-	1.21 (1.00, 1.46)	-	1.16 (0.85, 1.43)
Advanced	-	-	1.00	-	1.00
Severe	-	-	1.39 (1.21, 1.58)	-	1.40 (1.21, 1.62)
Weight-for-age z-score	-	-	P=0.38	-	P=0.17
<-2	-	-	0.95 (0.87, 1.03)	-	1.07 (0.97, 1.17)
-2 to <0	-	-	1.00	-	1.00
≥0	-	-	1.00 (0.87, 1.16)	-	0.93 (0.80, 1.09)
Initial ART regimen	P=0.004	P=<0.0001	P=<0.0001	P=<0.0001	p=<0.0001
PI- vs NNRTI-based	1.15 (1.05, 1.26)	0.70 (0.63, 0.79)	0.68 (0.61, 0.76)	0.51 (0.45, 0.58)	0.58 (0.49, 0.68)

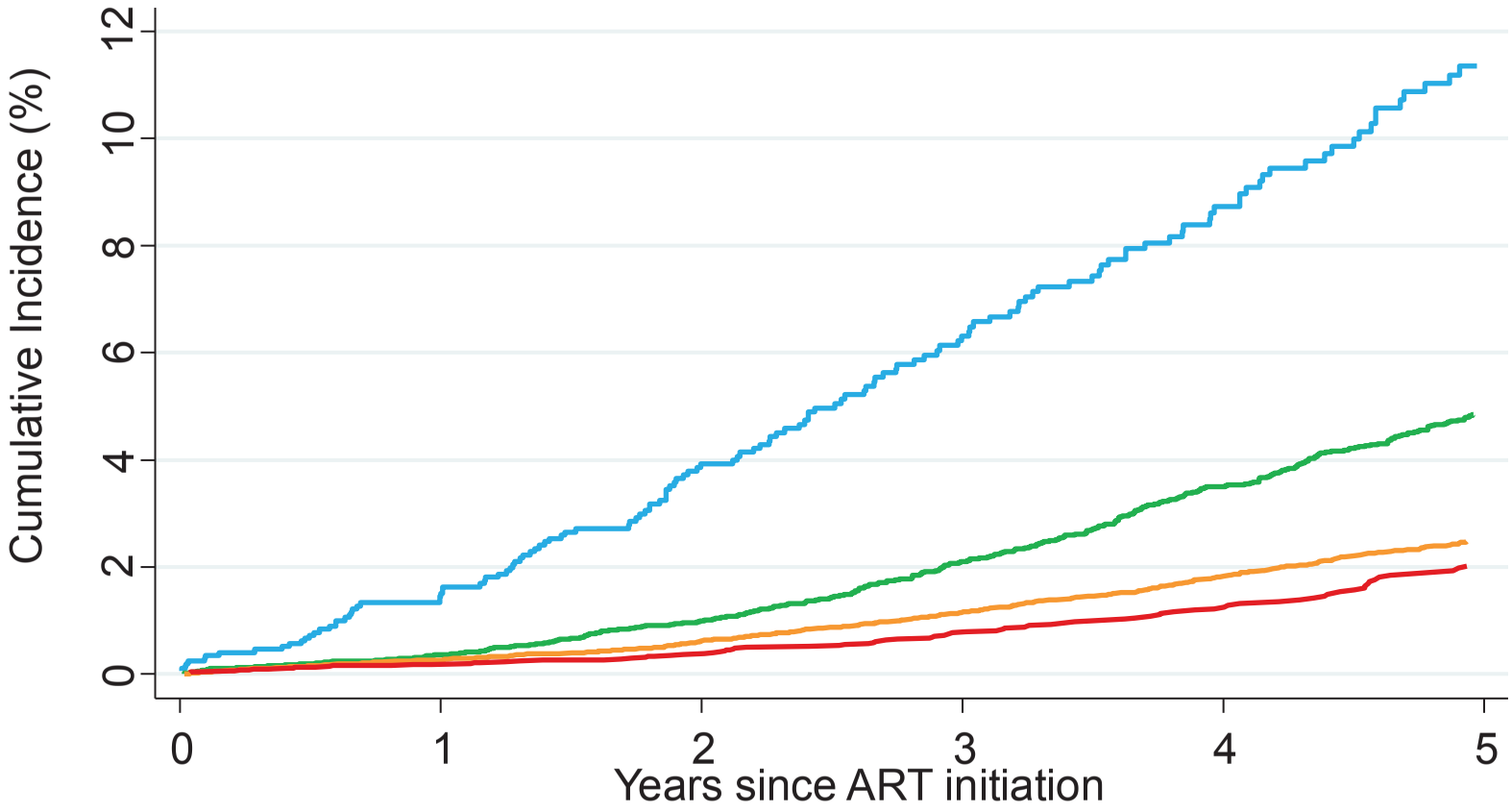
Calendar year	P=<0.0001	P=<0.0001	P=<0.0001	P=<0.0001	P=<0.0001
≤2004	2.96 (2.70, 3.24)	1.39 (1.26, 1.53)	2.28 (2.08, 2.51)	1.41 (1.27, 1.56)	1.41 (1.24, 1.61)
2005-2007	1.45 (1.35, 1.57)	1.26 (1.17, 1.36)	1.27 (1.17, 1.38)	1.18 (1.08, 1.28)	1.18 (1.07, 1.30)
2008-2010	1.00	1.00	1.00	1.00	1.00
≥2011	0.55 (0.47, 0.63)	0.61 (0.53, 0.71)	0.49 (0.41, 0.58)	0.53 (0.44, 0.62)	0.59 (0.48, 0.73)
Cohort level factors					
Cohort Monitoring strategy	P=<0.0001	P=<0.0001	P=<0.0001	P=<0.0001	P=<0.0001
Routine CD4 & VL	4.57 (4.18, 5.00)	2.66 (2.22, 3.19)	2.81 (2.55, 3.10)	1.90 (1.60, 2.26)	2.37 (1.94, 2.89)
Routine CD4 & targeted VL	2.18 (1.95, 2.43)	1.95 (1.75, 2.18)	1.29 (1.15, 1.45)	1.29 (1.13, 1.46)	1.43 (1.24, 1.66)
Routine CD4 only	1.00	1.00	1.00	1.00	1.00
Clinical only	0.75 (0.62, 0.91)	0.68 (0.56, 0.83)	-	-	-
Country income group	P=<0.0001	P=0.0017	P=<0.0001	P=0.22	P=0.44
Low	1.00	1.00	1.00	1.00	1.00
Lower middle	1.04 (0.94, 1.14)	1.09 (0.98, 1.21)	1.01 (0.90, 1.12)	1.09 (0.96, 1.20)	1.01 (0.88, 1.16)
High/upper middle	3.21 (2.98, 3.47)	1.33 (1.13, 1.56)	2.26 (2.09, 2.46)	1.14 (0.97, 1.33)	0.87 (0.71, 1.08)
Region	P=<0.0001	P=<0.0001	P=<0.0001	P=<0.0001	P=<0.0001
USA	4.16 (3.20, 5.42)	4.04 (3.07, 5.32)	3.01 (1.84, 4.93)	2.73 (1.63, 4.58)	4.39 (2.28, 8.46)
Europe	2.30 (2.07, 2.56)	2.22 (1.97, 2.49)	2.05 (1.83, 2.29)	1.84 (1.63, 2.09)	2.22 (1.87, 2.63)
Latin America	1.23 (1.03, 1.49)	1.73 (1.40, 2.15)	1.28 (1.05, 1.55)	1.59 (1.27, 2.00)	1.88 (1.46, 2.42)
Asia	1.27 (1.15, 1.40)	1.38 (1.23, 1.54)	1.18 (1.07, 1.31)	1.06 (0.94, 1.18)	0.86 (0.74, 1.01)
Southern Africa	1.00	1.00	1.00	1.00	1.00
Rest of SSA	0.35 (0.33, 0.38)	0.89 (0.74, 1.07)	0.47 (0.44, 0.52)	0.69 (0.57, 0.83)	0.66 (0.52, 0.84)

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

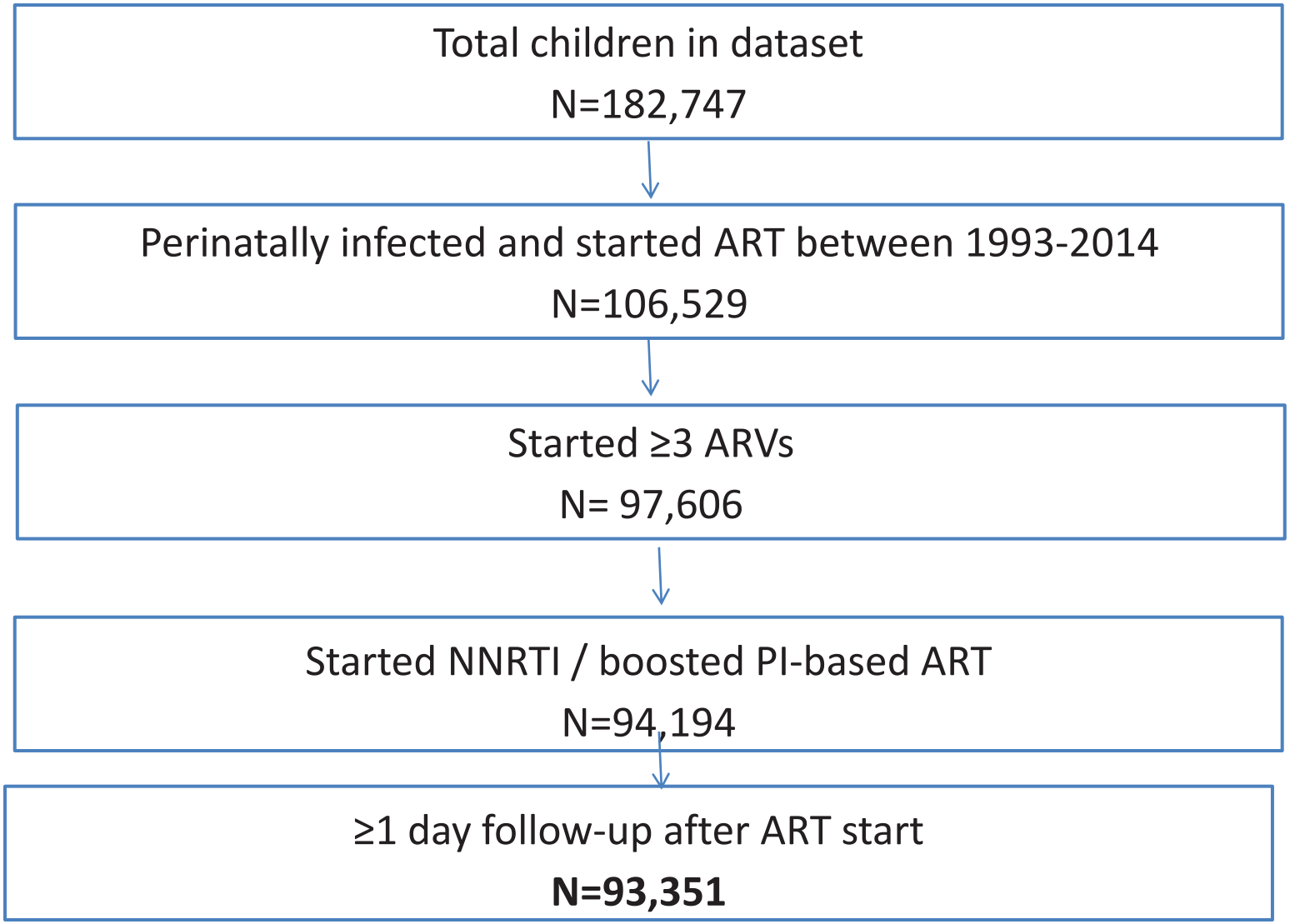

USA
192 (0.2%)
Europe
2,142 (2.3%)
Total
N = 93,351
Asia
6,107 (6.6%)
Latin America
926 (1.0%)
Southern Africa
17,857 (19.1%)
Rest of
Sub-Saharan Africa
66,127 (70.8%)



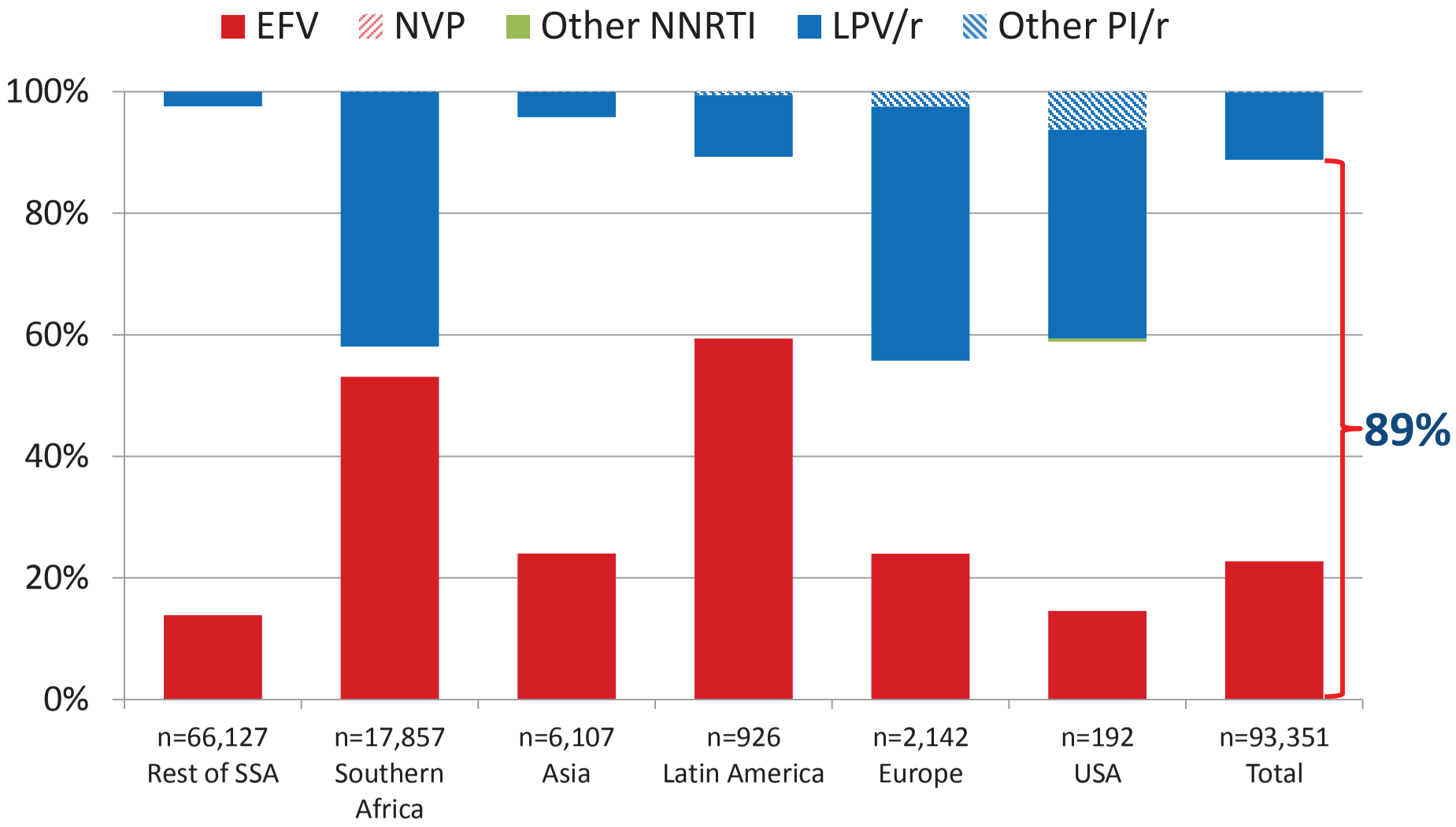
North America	192	167	142	108	84	68
Latin America	926	802	699	574	491	410
Europe	2142	1873	1571	1345	1086	855
Asia	6107	4950	3988	3174	2474	1914
Southern Africa	17857	13347	10171	7604	5740	4222
Rest of Sub-Saharan Africa	66127	44225	32659	23535	16160	10707



CD4 and routine VL	2005	1415	1078	769	547	339
CD4 and targeted VL	14246	10387	8141	6144	4435	3277
CD4 monitoring	35748	23915	17300	12304	8261	5250
Clinical only	14128	8508	6140	4318	2917	1841



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


EFV
NVP
Other NNRTI
LPV/r
Other PI/r
100%
80%
60%
40%
20%
0%
89%
n=66,127
Rest of SSA
n=17,857
Southern Africa
n=6,107
Asia
n=926
Latin America
n=2,142
Europe
n=192
USA
n=93,351
Total

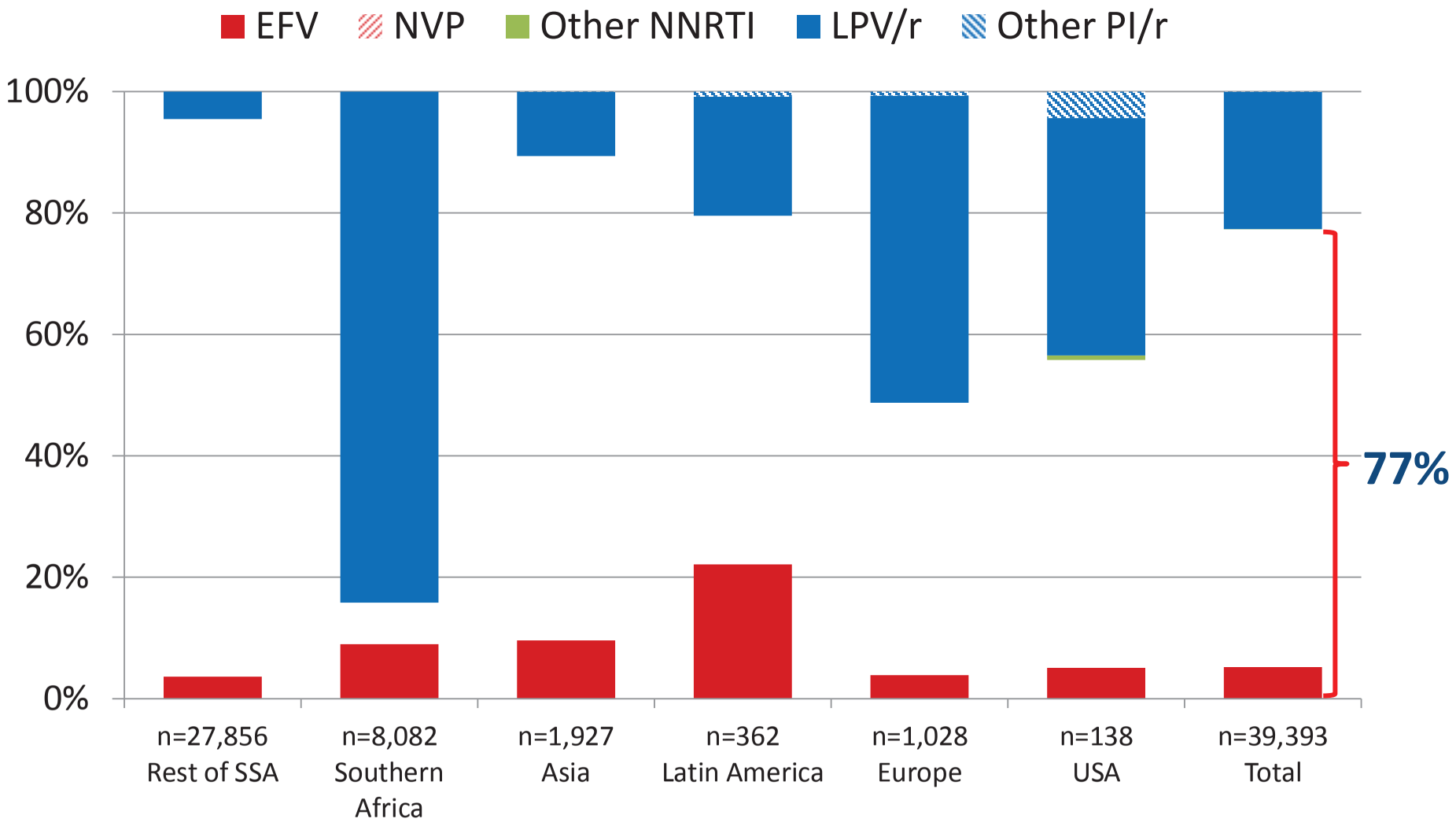

EFV
NVP
Other NNRTI
LPV/r
Other PI/r
100%
80%
60%
40%
20%
0%
77%
n=27,856
Rest of SSA
n=8,082
Southern Africa
n=1,927
Asia
n=362
Latin America
n=1,028
Europe
n=138
USA
n=39,393
Total

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

	Percent (95% CI) switched to second-line		
Year after ART start	**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 ≥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
≥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
≥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
≤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
≥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)

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)

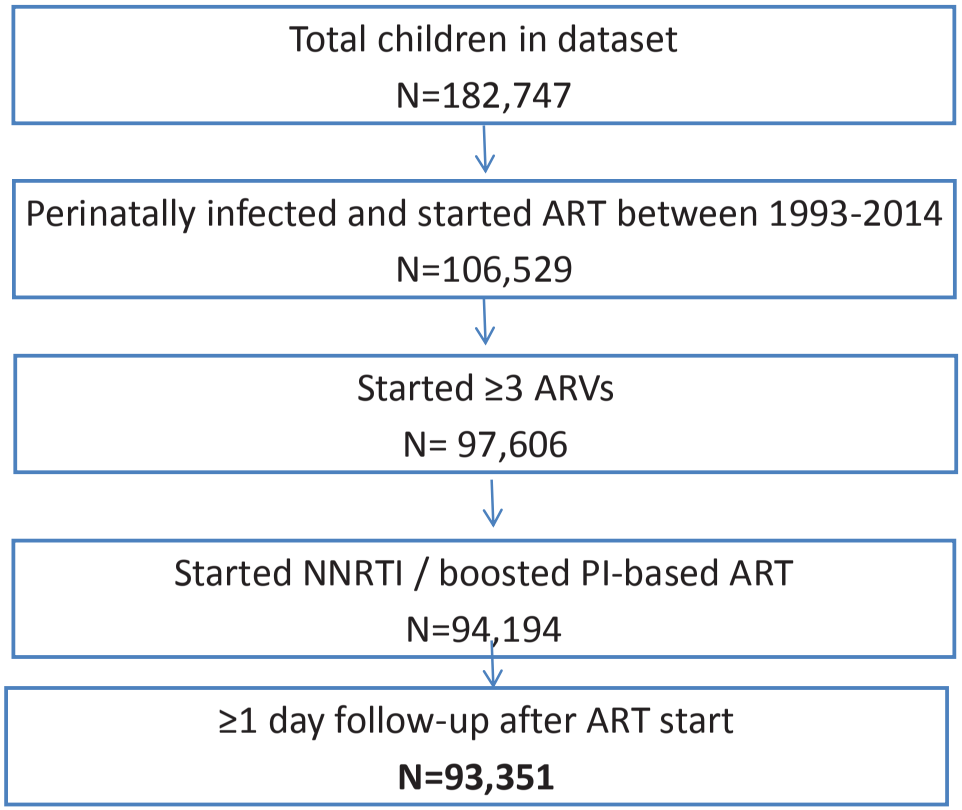
ART=antiretroviral therapy; sHR=Sub-distribution hazard ratio; CI=confidence interval; PI=protease inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI= nucleoside reverse transcriptase inhibitor; WAZ=weight-for-age z-score; VL=viral load; SSA=sub-Saharan Africa.

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

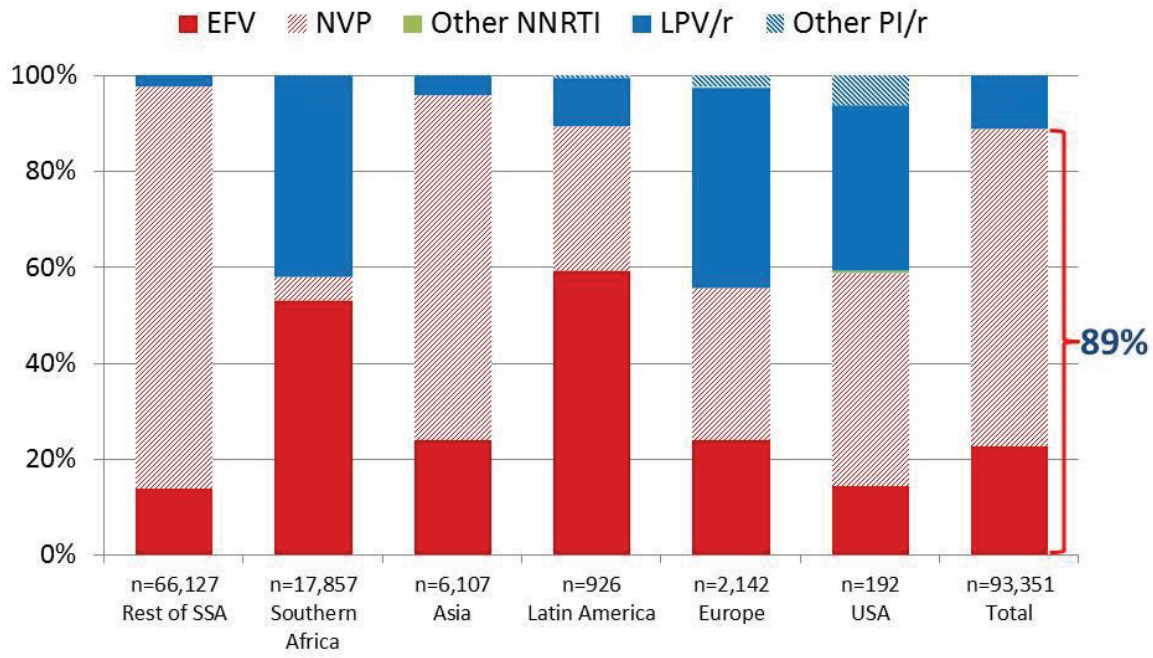
Figure S1. Flowchart of children included in the analysis



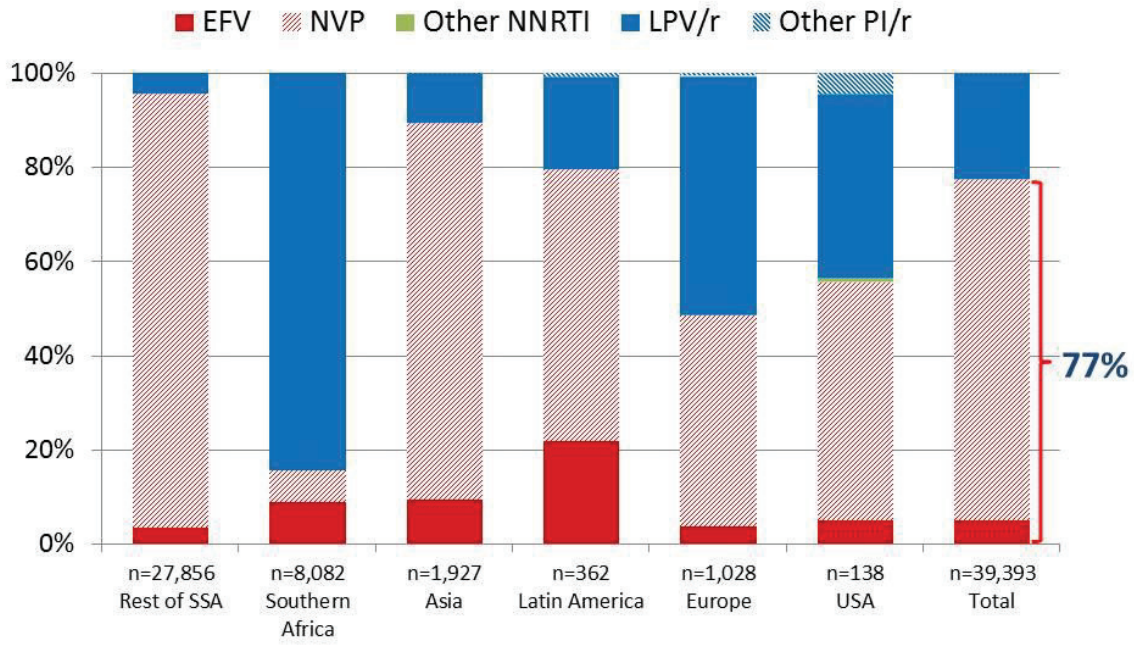
ART: antiretroviral therapy; ARVs=antiretroviral drugs; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.

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.

APPENDIX

The CIPHER Global Cohort Collaboration

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IMPAACT: The following sites participated in PACTG 219/219C: University of New Jersey Medical and Dental School, Boston Medical Center, Children's Hospital LA, Long Beach Memorial Medical Center, Miller Children's Hospital, Harbor/UCLA Medical Center, Johns Hopkins Hospital & Health System, University of Maryland Medical Center, Texas Children's Hospital, Cook County Hospital, Children's Hospital of Columbus Ohio, University of Miami Miller School of Medicine, University of California San Francisco School of Medicine, Children's Hospital & Research Center Oakland, University of California San Diego, Duke University School of Medicine, University of North Carolina at Chapel Hill School of Medicine, Schneider Children's Hospital, Harlem Hospital Center, New York University School of Medicine, Children's National Medical Center, University of Washington School of Medicine, University of Illinois College of Medicine at Chicago, Yale University School of Medicine, SUNY at Stony Brook School of Medicine, Howard University Hospital, LA County/University of Southern California Medical Center, University of Florida Health Science Center Jacksonville, North Broward Hospital District, Children's Diagnostic & Treatment Center, University of Rochester Medical Center, Golisano Children's Hospital, Medical College of Virginia, St. Jude Children's Research Hospital, University of Puerto Rico, U. Children's Hospital AIDS, Children's Hospital of Philadelphia, St. Christopher's Hospital for Children/Drexel University College of Medicine, Bronx-Lebanon Hospital Center, New York Medical College/Metropolitan Hospital Center, University of Massachusetts Memorial Children's Medical School, Baystate Medical Center, Connecticut Children's Medical Center, Medical College of Georgia School of Medicine, University of South Alabama College of Medicine, LSU Health Sciences Center, Tulane University Health Sciences Center, St. Josephs Hospital and Medical Center, Cooper University Hospital, Children's Hospital Boston, David Geffen School of Medicine at UCLA, Children's Hospital of Orange County, Children's Memorial Hospital University of Chicago, Mt. Sinai Hospital Medical Center Chicago, Columbia University Medical Center, Incarnation Children's Center, Cornell University, Bellevue Hospital, San Francisco General, Phoenix Children's Hospital,

Metropolitan Hospital Center New York, University of Cincinnati, SUNY Downstate Medical Center, Children's Hospital at Downstate, North Shore University Hospital, University of South Florida, Cornell University, Oregon Health & Science University, Children's Hospital of the King's Daughters, Lincoln Medical & Mental Health Center, Mt. Sinai School of Medicine, Emory University Hospital, San Juan City Hospital, UMDNJ - Robert Wood Johnson, Ramon Ruiz Arnau University Hospital, Medical University of South Carolina, SUNY Upstate Medical University, Wayne State University School of Medicine, Children's Hospital of Michigan, Children's Hospital at Albany Medical Center, Children's Medical Center of Dallas, University of Colorado at Denver and Health Sciences, Columbus Children's Hospital, University of Florida College of Medicine, University of Mississippi Medical Center, Palm Beach County Health Department, Children's Hospital LA, Vanderbilt University Medical Center, Washington University School of Medicine at St. Louis, St. Louis Children's Hospital, Children's Hospital & Medical Center Seattle, St. Luke's-Roosevelt Hospital Center, Montefiore Medical Center/Albert Einstein College of Medicine, Children's Hospital Washington DC, Children's Hospital of the King's Daughters, University of Alabama at Birmingham, Columbus Regional HealthCare System, The Medical Center, Sacred Heart Children's Hospital/CMS of Florida, Bronx Municipal Hospital Center/Jacobi Medical Center. The following sites participated in P1074: New Jersey Medical School, UCLA–Los Angeles/Brazil AIDS Consortium, Texas Children's Hospital, Lurie Children's Hospital of Chicago, Columbia University Medical Center, University of Miami Pediatric Perinatal HIV/AIDS, University of California San Diego, Mother-Child-Adolescent Program, Duke University Medical Center, Children's Hospital of Boston, Boston Medical Center Pediatric HIV Program, New York University, Jacobi Medical Center Bronx, Children's National Medical Center Washington, DC, Seattle Children's Hospital, University of South Florida Tampa, San Juan City Hospital, SUNY Stony Brook, Children's Hospital of Michigan, Howard University Washington DC, Harbor UCLA Medical Center, University of Southern California School of Medicine, University of Florida Health Science Center, University of Colorado Denver, South Florida Children's Diagnostic and Treatment Center Fort Lauderdale, Strong Memorial Hospital University of Rochester Medical Center, Rush University Cook County Hospital Chicago, Children's Hospital of Los Angeles, University of California San Francisco, Johns Hopkins University Baltimore, Miller Children's Hospital, University of Maryland Baltimore, Tulane University New Orleans, University of Alabama Birmingham, The Children's Hospital of Philadelphia, Bronx-Lebanon Hospital, St Jude's Children's Hospital, University of Puerto Rico Pediatric HIV/AIDS Research Program, Western New England Maternal Pediatric Adolescent AIDS.

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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.