The epidemiology of adolescents living with perinatally-acquired HIV: a cross-region global cohort analysis

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Abstract:

Background: Globally, the population of adolescents living with perinatally-acquired HIV (APH) continues to expand. For the first time our knowledge, we pooled data from observational paediatric HIV cohorts and cohort networks, allowing comparisons of adolescents with perinatally acquired HIV in "real life" settings across multiple regions. We describe the geographic and temporal characteristics and mortality outcomes of APH across multiple regions including South America and Caribbean, North America, Europe, sub-Saharan Africa and South and Southeast Asia.

Methods and findings: Through the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER), individual retrospective longitudinal data from 12 cohort networks were pooled. All HIV-infected children who entered care before age 10 years, not known to have horizontally-acquired HIV, and followed-up beyond age 10 years were included in this analysis conducted from May 2016 to January 2017. Our primary analysis describes patient and treatment characteristics of APH at key time points including first HIV-associated clinic visit, ART start, age 10 years and last visit, and compares these characteristics by geographic region, country income group and birth period. Our secondary analysis describes mortality, transfers out and loss to follow-up (LTFU) as outcomes at age 15 years, using competing risk analysis. Among the 38,187 APH included, 51% were female, 79% were from sub-Saharan Africa (SSA) and 65% lived in low income countries. APH from 51 countries were included (Europe - 14 countries and 3,054 APH; North America - 1 country and 1,032 APH; South America & Caribbean - 4 countries and 903 APH; South & Southeast Asia - 7 countries and 2,902 APH; SSA - 25 countries and 30,296 APH). Observation started as early as 1982 in Europe and 1996 in sub-Saharan Africa and continued until at least 2014 in all regions. The Median [interquartile range IQR] duration of adolescent follow-up was 3.1 [1.5; 5.2] years for the total cohort and 6.4 [3.6; 8.0] years in Europe, 3.7 [2.0; 5.4] years in North America, 2.5 [1.2; 4.4] years in South & Southeast Asia, 5.0 [2.7; 7.5] years in South America & Caribbean and 2.1 [0.9; 3.8] years in SSA. Median [IQR] age at first visit differed substantially by region, ranging from 0.7 [0.3; 2.1] years in North America to 7.1 [5.3; 8.6] years in SSA. The median age at ART start varied from 0.9 [0.4; 2.6] years in North America to 7.9 [6.0; 9.3] years in SSA. The cumulative incidence estimates [95% CI] at age 15 years for mortality, transfers out and LTFU for all APH were 2.6% [2.4%; 2.8%], 15.6% [15.1%; 16.0%] and 11.3% [10.9%; 11.8%], respectively. Mortality was lowest in Europe (0.8% [0.5%; 1.1%]) and highest in South America & Caribbean (4.4% [3.1%; 6.1%]). However, LTFU was lowest in South
Comparison of mortality across regions was limited by the high LTFU in SSA, being the main study limitation.

Conclusion: To our knowledge, our study represents the largest multi-regional epidemiological analysis of APH. Despite probable under-ascertained mortality, mortality in APH remains substantially higher in SSA, South & Southeast Asia and South America & Caribbean than in Europe. Collaborations such as CIPHER enable us to monitor current global temporal trends in outcomes over time to inform appropriate policy responses.

Suggested Reviewers:

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Dr. Zanoni has extensive clinical and research experience with adolescents living with perinatally-acquired HIV. This work has been conducted in both the USA and South Africa and he has an in-depth understanding of the complexities of both high and low-middle income settings.

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Financial Disclosure

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Requests from Editors:

We ask you to add some additional details to the abstract. Thank you for these suggestions, please see responses below detailing additions made.

In the "background" subsection, we suggest adding a few words to state the practical value of studies of this type. A sentence was added: For the first time our knowledge, we pooled data from observational paediatric HIV cohorts and cohort networks, allowing comparisons of adolescents with perinatally acquired HIV in “real life” settings across multiples regions. (line 164-166)

You may wish to add the acronym "CIPHER"; Added (line 170).

Can you be more specific about the month or months in 2017 when the analysis was carried out? The months during which the analysis was conducted has been added to the abstract (line 172).

Please specify the total number of countries involved, the number of countries in each region, the number of APH in each region, and the length of follow-up in each region. Added (lines 178-180, 181-184).

The final sentence of the abstract and the final bullet point of the "author summary" section are very similar, and we ask you to trim and reword both of these sentences. The final sentence of the abstract has been revised: “Collaborations such as CIPHER enable us to monitor current global temporal trends in outcomes over time to inform appropriate policy responses.” (lines 195-196).
The final bullet point of the author summary has been revised: “Collaborations such as CIPHER are useful to monitor current global temporal trends in outcomes of adolescents living with perinatally-acquired HIV over time to inform and guide policy responses”. (Lines 229-230)

A full point needs to be removed at line 117. Thank you, this additional point has been removed.

You mention at line 130 that "all analyses were prespecified". We assume this does not apply to the Kaplan-Meier methodology requested by the statistical reviewers, and ask that you amend the text to identify this and any other analyses that were not prespecified. The Kaplan-Meier analysis as well as the competing risks analysis were both pre-specified, as indicated in the ‘Statistical Analysis’ section (pages 4 & 5) of the Project Concept Analysis Plan (Supplementary 1). We have therefore not added any additional wording.

Where the Kaplan-Meier analysis is mentioned (line 267), we ask you add an additional sentence, say, to quote key estimates, with CIs, to illustrate the similarity between the results of the two types of analysis. Key Kaplan-Meier estimates have been added (lines 430-432).

Please review the reference list to ensure that all citations match journal format--the journal names for references 15 and 16 appear to need abbreviating. Reference style checked and amended accordingly.

Please amend the STROBE checklist to remove the text from the manuscript itself, and refer to the relevant items in the manuscript by section and paragraph numbers. The STROBE list has been amended.
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4) Please ensure that your Ethics statement is available at the beginning of your Methods section in its entirety and that it matches the version in the submission form verbatim. The ethics statement has been moved from the end of the methods section to the beginning (lines 281-285).

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Marissa Vicari - "MVs work at CIPHER is funded through Unrestricted Educational grants received from ViiV Healthcare and Janssen to the International AIDS Society."

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Best wishes,

Rebecca Green
Full title: The epidemiology of adolescents living with perinatally-acquired HIV: a cross-region global cohort analysis

Short title: The epidemiology of adolescents living with perinatally-acquired HIV

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58. Regina Succi

59. Annette Sohn

60. Azar Kariminia

61. Andrew Edmonds

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69. Lorna Renner

70. Mariam Sylla

71. Mark J. Abzug

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Membership of the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Global Cohort Collaboration is provided in S2 Text.

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Abstract

Background: Globally, the population of adolescents living with perinatally-acquired HIV (APH) continues to expand. For the first time our knowledge, we pooled data from observational paediatric HIV cohorts and cohort networks, allowing comparisons of adolescents with perinatally acquired HIV in “real life” settings across multiple regions. We describe the geographic and temporal characteristics and mortality outcomes of APH across multiple regions including South America and Caribbean, North America, Europe, sub-Saharan Africa and South and Southeast Asia.

Methods and findings: Through the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER), individual retrospective longitudinal data from 12 cohort networks were pooled. All HIV-infected children who entered care before age 10 years, not known to have horizontally-acquired HIV, and followed-up beyond age 10 years were included in this analysis conducted from May 2016 to January 2017. Our primary analysis describes patient and treatment characteristics of APH at key time points including first HIV-associated clinic visit, ART start, age 10 years and last visit, and compares these characteristics by geographic region, country income group and birth period. Our secondary analysis describes mortality, transfers out and loss to follow-up (LTFU) as outcomes at age 15 years, using competing risk analysis. Among the 38,187 APH included, 51% were female, 79% were from sub-Saharan Africa (SSA) and 65% lived in low income countries. APH from 51 countries were included (Europe – 14 countries and 3,054 APH; North America – 1 country and 1,032 APH; South America & Caribbean – 4 countries and 903 APH; South & Southeast Asia – 7 countries and 2,902 APH; SSA – 25 countries and 30,296 APH). Observation started as early as 1982 in Europe and 1996 in sub-Saharan Africa and continued until at least 2014 in all regions. The Median [interquartile range IQR] duration of adolescent follow-up was 3.1 [1.5; 5.2] years for the total cohort and 6.4 [3.6; 8.0] years in Europe, 3.7 [2.0; 5.4] years in North America, 2.5 [1.2; 4.4] years in South & Southeast Asia, 5.0 [2.7; 7.5] years in South America & Caribbean and 2.1 [0.9; 3.8] years in SSA. Median [IQR] age at first visit differed substantially by region, ranging from 0.7 [0.3; 2.1] years in North America to 7.1 [5.3; 8.6] years in SSA. The median age at ART start varied from 0.9 [0.4; 2.6] years in North America to 7.9 [6.0; 9.3] years in SSA. The cumulative incidence estimates [95% CI] at age 15 years for mortality, transfers out and LTFU for all APH were 2.6% [2.4%; 2.8%], 15.6% [15.1%; 16.0%] and 11.3% [10.9%; 11.8%], respectively. Mortality was lowest in Europe...
(0.8% [0.5%; 1.1%]) and highest in South America & Caribbean (4.4% [3.1%; 6.1%]). However, LTFU was lowest in South America & Caribbean (4.8% [3.4%; 6.7%]) and highest in SSA (13.2% [12.6%; 13.7%]).

Comparison of mortality across regions was limited by the high LTFU in SSA, being the main study limitation.

Conclusion: To our knowledge, our study represents the largest multi-regional epidemiological analysis of APH. Despite probable under-ascertained mortality, mortality in APH remains substantially higher in SSA, South & Southeast Asia and South America & Caribbean than in Europe. Collaborations such as CIPHER enable us to monitor current global temporal trends in outcomes over time to inform appropriate policy responses.
Author summary

Why was this study done?

- With increasing access to antiretroviral therapy across the globe, children with HIV acquired around the time of birth or through breastfeeding (perinatally-acquired HIV) are surviving into adolescence. However, globally, adolescents living with perinatally-acquired HIV experience poorer HIV-related outcomes compared to younger children and adults with HIV, dying more often and experiencing greater challenges in terms of treatment adherence and staying in care.
- A direct comparison of outcomes for adolescents living with perinatally-acquired HIV across multiple regions of the world has not previously been conducted, yet such an understanding is required to inform the appropriate policy responses to meet the needs of this dynamic and complex population of adolescents.
- The Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) global project describes for the first time as far as we are aware, the global epidemiology of adolescents living with perinatally-acquired HIV in terms of geographic and temporal trends and compares mortality, transfer and loss to follow-up between 10 and 15 years of age across geographic regions, country income groups and birth cohorts.

What did the researchers find?

- Among 38,000 adolescents living with perinatally-acquired HIV, 79% of whom were living in sub-Saharan Africa, adolescents in North America and Europe, as well as high income group countries, generally presented to care and started antiretroviral therapy at a younger age with higher CD4 counts and less impaired height growth compared to other regions or country income groups.
- Analysis by country income group suggested that patients in high income countries had younger age, higher CD4 percent and less impaired height when starting antiretroviral therapy compared to middle or low income countries.
- Similarly HIV-associated mortality during adolescence was substantially higher in sub-Saharan Africa, South & Southeast Asia and South America & Caribbean than in Europe.
What do these findings mean?

- Although the population of adolescents living with perinatally-acquired HIV is likely to decline in the future, due to declining new perinatally-acquired HIV infections, there is still a lot of work to be done to achieve equality in health and survival for all adolescents living with perinatally-acquired HIV irrespective of geographic location.

- Collaborations such as CIPHER are useful to monitor current global temporal trends in outcomes of adolescents living with perinatally-acquired HIV over time to inform and guide policy responses.

**Key words:** HIV, adolescents, children, youth, perinatal, survival, retention, cohort, surveillance
**Abbreviations**

- **aHR** – adjusted hazard ratio
- **APH** – adolescents living with perinatally-acquired HIV
- **ART** – antiretroviral therapy
- **CD** – clusters of differentiation
- **CI** – confidence interval
- **CIG** – country income group
- **CIPHER** – Collaborative Initiative for Paediatric HIV Education and Research
- **HAZ** – height-for-age-Z-score
- **HIV** – Human Immunodeficiency Virus
- **HR** – hazard ratio
- **IPW** – inverse probability weighting
- **IQR** – interquartile range
- **LTFU** – lost to follow-up
- **MI** – multiple imputation
- **SSA** – sub-Saharan Africa
- **S&SE Asia** – South & Southeast Asia
- **uHR** – unadjusted hazard ratio
- **WHO** – World Health Organization
Introduction

It is estimated that almost 2.1 million (uncertainty bounds 1.4 million – 2.7 million) adolescents aged 10 to 19 years are living with either perinatally- or horizontally-acquired HIV [1,2]. Prior to 2005, perinatally HIV-infected children in most of the world had poor access to antiretroviral therapy (ART), with high mortality during infancy and poor survival beyond childhood [3]. With expansion of effective ART initially in Europe and North America, subsequently in South America and Asia and now in Africa, the population of children living with perinatally-acquired HIV surviving into adolescence and early adulthood is growing [1,4,5].

By the time perinatally HIV-infected children reach the developmental transition period of adolescence, they have been living for a decade with a chronic disease that even with ART treatment can still result in substantial morbidity [6]. Globally, it is recognized that adolescents living with perinatally-acquired HIV (APH) experience poorer HIV-related outcomes compared to younger children and adults, including higher mortality and virologic treatment failure rates and poorer retention in care [1,7-15]. Studies assessing the outcomes of APH over time and across geographic and economic settings are limited [16]. Based on studies in adults, after two years on ART, HIV-associated mortality in South Africa approached that in the United States, and the differential between South Africa and Europe was substantially reduced [17]. As the global community pursues attainment of the Sustainable Development Goals by 2030, particularly to ensure healthy lives and promote wellbeing for all at all ages (Goal 3) as well as to achieve gender equality (Goal 5), and reduce inequality within and among countries (Goal 10), multiregional direct comparisons of APH outcomes can inform the appropriate policy responses to meet the needs of this dynamic and complex population of adolescents living with HIV [18].

The primary objective of this Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) global project was to describe the global epidemiology of APH in terms of geographic and temporal trends of patient and treatment characteristics at entry into care, ART start, entry into adolescence (age 10 years) and last visit. Our secondary objective was to compare the outcomes of mortality, transfer and loss to follow-up between 10 and 15 years of age across regions, country income groups (CIG) and birth cohorts.
Methods

Primary data collection by all participating networks was approved by their respective research ethics boards of authority and consent or assent for study participation provided by participants as required. The pooling of data and analysis at the UCT data centre was approved by the University of Cape Town Health Research Ethics Committee (UCT HREC reference 264/2014). The study concept and *a priori* analysis plan are available in supplementary material (S1 Analysis Plan). All analyses were pre-specified.

Study methods:

The CIPHER Cohort Collaboration is a global network of observational paediatric HIV cohorts or cohort networks convened by CIPHER of the International AIDS Society. The following 12 cohort networks contributed data to this collaborative project: Baylor International Pediatric AIDS Initiative at *Texas Children’s Hospital* (BIPAI); European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC); International Epidemiology Database to Evaluate AIDS (IeDEA) – Asia Pacific; IeDEA – Central Africa; IeDEA – East Africa; IeDEA – Southern Africa; IeDEA – West Africa; Caribbean, Central and South America Network for HIV Research (CCASAnet); Pediatric Late Outcomes Protocol (PACTG/IMPAACT 219/219c); Prospective Surveillance Study of Long-term Outcomes in HIV-infected Infants, Children and Adolescents (IMPAACT P1074); Médecins Sans Frontières (MSF) Pediatric Cohorts; Pediatric HIV/AIDS Cohort Study Adolescent Master Protocol (PHACS AMP); Identifying Optimal Models for Care in Africa (Optimal Models-ICAP). The data contributed by the networks were drawn from a range of care settings including dedicated research cohorts, routine care cohorts and programmatic services. Using a standardized data transfer protocol based on the HIV Cohorts Data Exchange Protocol [19], and following quality checks and queries at the central University of Cape Town data centre, individual level data on 183,119 HIV-infected children were merged in May 2016. Participants contributed data to only a single network and there was no duplication of participants amongst networks.

Analytic methods:
We conducted a retrospective cohort analysis. APH were defined as HIV-infected children with at least one documented HIV care visit prior to age 10 years, as a proxy for perinatally-acquired HIV, and at least one additional HIV care visit after 10 years of age. Children with known non-vertical routes of HIV-infection e.g. horizontal transmission from blood products, unsafe injections or sexual abuse, were excluded. Our primary analysis described patient and treatment characteristics of APH at key time points including first HIV-associated clinic visit, ART start, age 10 years and last visit, and compared these characteristics by geographic region, CIG and birth cohort. Observation time was censored at 19 years of age in adolescents with follow-up beyond this age.

The first visit was defined as the first recorded date in the database of any contact with a health care facility for HIV-related care, and first visit measurements (height, CD4 T-lymphocyte counts and percentages, and HIV viral load) were taken as the closest measurement to the first visit date, but could be no later than 182 days after the first visit. If ART was started within 182 days of the first visit, only measurements up to 14 days after ART start were considered. The date of ART start was defined as the earliest date in the network database of initiation of any two antiretroviral drugs prior to the year 2000 or three or more antiretroviral drugs from the year 2000 or later. Measurements at ART start were taken as those closest to the ART start date but limited to a window of 182 days prior to or 14 days after ART start. Measurements at age 10 years were taken as those closest to the child’s 10th birthday limited to a window of 182 days either side of the 10th birthday. The last visit was defined as the last date of any recorded visit, laboratory test or ART record. Measurements at the last visit were taken as those closest to the last visit date within a window of 18 months prior to the last visit date, to allow for only annual monitoring in stable patients on ART. It is possible for there to be overlap with individual measurements classified as occurring at more than one time point e.g. a measurement classified as a first visit measurement can also be classified as an ART start measurement and similarly for measurements at age 10 years and last visit. World Health Organization (WHO) height-for-age Z-scores (HAZ) were calculated for APH in all regions from the measured heights using the WHO ‘igrowup_restricted’ Stata macro for HAZ up to 5 years of age [20] and the ‘who2007’ Stata macro for HAZ from 5 to 19 years of age [21]. Stunting was defined as HAZ < -2 standard deviations from the mean. Viral suppression was considered as an HIV viral load...
measurement of less than 400 copies/ml, or less than the level of detection of the test at the time if greater than 400 copies/ml. Geographic regions were categorized as Europe, North America, South America & Caribbean, South & Southeast Asia and sub-Saharan Africa. CIG were assigned according to World Bank country income group classification for the median year of first visit for each country [22]. Birth cohorts were categorized as born prior to 1995, born between 1995 and 1999 and born between 2000 and 2005.

Our secondary analysis focused on patient outcomes between 10 and 15 years of age, classified as mortality, transferred out, lost to follow-up (LTFU) or alive and retained in care. Mortality included all-cause mortality as reported in the database. Transfer out included documented transfer to a different HIV care site for any reason. LTFU was defined as no observed visit for more than 365 days before the last observed visit for the cohort. APH classified as LTFU were censored 365 days after their last observed visit. APH considered to be alive and in care at database closure were those not known to have died or transferred and with an observed visit within 365 days prior to the last visit for the cohort. Cumulative incidence functions for the outcomes mortality, transfer out and LTFU at 15 years of age were calculated using competing risks analysis for the whole cohort as well as by region, CIG and birth period with person-time accruing from age 10 years [23]. Cumulative incidence functions for birth cohorts stratified separately by region or by CIG were calculated for the outcomes at 13 years of age due to few APH in the most recent birth cohort having reached age 15 years. Transfer out and LTFU were both considered to be competing risks for mortality rather than censoring events. This approach was chosen as the survival distribution of adolescents transferred out or LTFU is likely to be different to those retained in care, with better survival in stable transferred patients and poorer survival in patients LTFU and possibly no longer on ART [23]. For comparison, cumulative mortality estimates at 15 years of age were also calculated using the Kaplan-Meier product limit estimator.

Mortality hazard ratios (HR) and 95% confidence intervals (CI) were calculated for geographic regions using Cox proportional hazard models with Europe as the reference group. Continuous variables, including age, CD4 count and CD4 percent were included in the Cox models as continuous variables after confirming a linear relationship with mortality. Proportionality assumptions were evaluated using the Schoenfeld test. Adjusted
HRs were calculated adjusting for baseline differences between regions. Missing CD4 and height measurements were imputed for the multivariable models using multiple imputation by chained equations [24]. The imputation model contained all measured variables and used predictive mean matching for CD4 counts. Imputation of missing CD4 measurements was performed for all countries and subsequently also restricted only to countries with at least 50 CD4 measurements at first visit or for countries with less than 50 APH, at least 50% of APH with CD4 measurements at first visit. Sensitivity analyses were conducted to better understand how LTFU may have biased mortality estimates. Firstly, inverse probability weighting (IPW) was applied to the multivariable model giving greater weight to APH not LTFU but with characteristics similar to APH who were LTFU. Secondly, under varying assumptions about the proportion of LTFU that could be due to mortality, mortality was randomly assigned to a proportion of APH that were originally classified as LTFU [25]. Unadjusted HRs as well as cumulative incidence functions were recalculated under these assumptions. All analyses were conducted using Stata version 13.0 (StataCorp, College Station, Texas, USA) and the ‘stcompet’ package was used to calculate the cumulative incidence functions from the competing risks analysis. Figures were plotted using the ggplot2 package in R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

Of the 183,119 children included in the CIPHER multi-regional dataset a total of 38,187 APH were included (Fig 1), from 51 countries across five regions of the world, with 79% from sub-Saharan Africa (Table 1). Observation started as early as 1982 in Europe and 1996 in sub-Saharan Africa and continued until at least 2014 in all regions. The median (interquartile range (IQR)) year of birth was earliest in North America (1994 (1992; 1996)) and latest in South & Southeast Asia, (2001 (1999; 2002)). A total of 112,976 person-years were observed between 10 and 19 years of age and the median (IQR) duration of adolescent follow-up was longest in Europe (6.4 (3.6; 8.0) years) and shortest in sub-Saharan Africa (2.1 (0.9; 3.8) years) (Table 1). Overall 44% (46/104) of included cohorts provided data only on APH that had ever received ART.
**Table 1: Profile of geographic regions included in the CIPHER Global Cohort adolescent analysis (N=38,187 adolescents)**

<table>
<thead>
<tr>
<th>Region</th>
<th>Countries included</th>
<th>Number of study centres</th>
<th>Number of adolescents (%)</th>
<th>Observation period</th>
<th>Year of birth median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Europe</strong></td>
<td>Belgium, France, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Russian Federation, Spain, Sweden, Switzerland, Ukraine, United Kingdom</td>
<td>153</td>
<td>3054 (8.0)</td>
<td>1982-2015</td>
<td>1995 (1991; 1999)</td>
</tr>
<tr>
<td><strong>South &amp; Southeast Asia</strong></td>
<td>Cambodia, India, Indonesia, Malaysia, Myanmar, Thailand, Vietnam</td>
<td>73</td>
<td>2902 (7.6)</td>
<td>1994-2014</td>
<td>2001 (1999; 2002)</td>
</tr>
<tr>
<td><strong>South America &amp; Caribbean</strong></td>
<td>Argentina, Brazil, Haiti, Honduras</td>
<td>6</td>
<td>903 (2.4)</td>
<td>1990-2015</td>
<td>1998 (1995; 2000)</td>
</tr>
</tbody>
</table>

IQR – interquartile range
Comparison by geographic region

More than two thirds of APH living in sub-Saharan Africa and South and Southeast Asia were born between 2000 and 2005, compared to only 7% of APH in North America (Table 2). In all regions, approximately half of the APH were female. Median (IQR) age at first visit differed substantially by region, ranging from 0.7 (0.3; 2.1) years in North America to 7.1 (5.3; 8.6) years in sub-Saharan Africa. Similarly, APH in North America started ART at a median (IQR) age of 0.9 (0.4; 2.6) years, compared to 7.9 (6.0; 9.3) years in sub-Saharan Africa (Table 2, Fig 2 Panel A). In the 61% of APH with a CD4 count or percent measurement recorded at ART start, the median (IQR) CD4 count was 321 (165; 575), with substantial variation by region (Table 2). Similarly, median (IQR) CD4% at ART start varied by region, and was highest in North America (28% (20%; 36%)) and lowest in South & Southeast Asia (10% (4%; 16%)). By age 10 years and last visit there was less variation in CD4% by region (Fig 2 Panel B). Median (IQR) HAZ at first visit and ART start was well below WHO normative data in all regions and lowest in South & Southeast Asia, at -2.36 (-3.26; -1.42) at first visit and -2.41 (-3.31; -1.51) at ART start (Fig 2 Panel C). In APH in Europe and North America, HAZ improved by age 10 years and last visit, but at least 25% of APH in South & Southeast Asia, South America & Caribbean and sub-Saharan Africa remained stunted at their last visit (Table 2). Eighty eight percent of APH received ART at some stage, of whom 12% started ART after age 10 years, and 80% remained on ART at their last visit. Of the 7,401 (19%) APH not known to be on ART at their last visit, 62% were ART naïve. Only 38% of all APH had an HIV viral load recorded at some stage, and this proportion was lowest in sub-Saharan Africa at 25% (Table 2). Of those with an HIV viral load and on ART at their last visit, 72% (9,388/13,114) were virologically suppressed.
Table 2: Adolescent characteristics at first visit, ART start, age 10 years and last visit and cumulative incidence of outcomes (mortality, transferred out, lost-to-follow-up) compared by region

<table>
<thead>
<tr>
<th>Total</th>
<th>Europe</th>
<th>North America</th>
<th>South &amp; Southeast Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (row %)</td>
<td>38187 (100)</td>
<td>3054 (8.0)</td>
<td>1032 (2.7)</td>
</tr>
<tr>
<td>Birth Cohort - N (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pre-1995</td>
<td>2660 (7.0)</td>
<td>1399 (45.8)</td>
<td>640 (62.0)</td>
</tr>
<tr>
<td>1995-1999</td>
<td>13267 (34.7)</td>
<td>989 (32.4)</td>
<td>318 (30.8)</td>
</tr>
<tr>
<td>2000-2005</td>
<td>22260 (58.3)</td>
<td>666 (21.8)</td>
<td>74 (7.2)</td>
</tr>
<tr>
<td>Male – N (%)</td>
<td>18863 (49.4)</td>
<td>1475 (48.3)</td>
<td>515 (49.9)</td>
</tr>
<tr>
<td>Age in years – median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First visit</td>
<td>6.7 (4.4; 8.4)</td>
<td>1.9 (0.2; 5.5)</td>
<td>0.7 (0.3; 2.1)</td>
</tr>
<tr>
<td>ART start</td>
<td>7.5 (5.2; 9.2)</td>
<td>4.4 (1.2; 8.2)</td>
<td>0.9 (0.4; 2.6)</td>
</tr>
<tr>
<td>Last visit</td>
<td>12.4 (11.1; 14.4)</td>
<td>16.4 (13.6; 18.0)</td>
<td>13.7 (12.0; 15.4)</td>
</tr>
<tr>
<td>CD4 count in cells/mm³ – median (IQR)</td>
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<td></td>
</tr>
<tr>
<td>First visit all ages [N=19979]</td>
<td>427 (200; 757)</td>
<td>768 (375; 1580)</td>
<td>1263 (775; 2207)</td>
</tr>
<tr>
<td>First visit if age ≥ 5 years [N=14585]</td>
<td>358 (165; 632)</td>
<td>415 (202; 629)</td>
<td>504 (298; 598)</td>
</tr>
<tr>
<td>ART start all ages [N=20608]</td>
<td>321 (165; 575)</td>
<td>464 (241; 1029)</td>
<td>1129 (702; 1921)</td>
</tr>
<tr>
<td>ART start if age ≥ 5 years [N=16612]</td>
<td>292 (161; 469)</td>
<td>298 (161; 469)</td>
<td>590 (384; 767)</td>
</tr>
<tr>
<td>Age 10 years [N=26953]</td>
<td>685 (445; 972)</td>
<td>697 (468; 970)</td>
<td>796 (575; 1049)</td>
</tr>
<tr>
<td>Last visit [N=31951]</td>
<td>687 (464; 946)</td>
<td>628 (434; 868)</td>
<td>700 (494; 930)</td>
</tr>
<tr>
<td>CD4 % - median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First visit [N=13674]</td>
<td>16 (9; 25)</td>
<td>23 (15; 35)</td>
<td>30 (20; 39)</td>
</tr>
<tr>
<td>ART start [N=14740]</td>
<td>14 (8 ; 20)</td>
<td>18 (12; 28)</td>
<td>28 (20; 36)</td>
</tr>
<tr>
<td>Age 10 years [N=17974]</td>
<td>28 (20; 34)</td>
<td>29 (21; 35)</td>
<td>33 (26; 39)</td>
</tr>
<tr>
<td>Last visit [N=23292]</td>
<td>29 (21; 35)</td>
<td>30 (22; 37)</td>
<td>32 (25; 38)</td>
</tr>
<tr>
<td>HAZ – median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First visit [N=20269]</td>
<td>-1.92 (-2.91; -0.97)</td>
<td>-0.75 (-1.60; 0.15)</td>
<td>-1.15 (-2.22; -0.15)</td>
</tr>
<tr>
<td>ART start [N=20372]</td>
<td>-1.95 (-2.91; -1.02)</td>
<td>-0.77 (-1.61; 0.09)</td>
<td>-1.19 (-2.21; -0.16)</td>
</tr>
<tr>
<td>Age 10 years [N=26883]</td>
<td>-1.53 (-2.35; -0.72)</td>
<td>-0.32 (-1.08; 0.43)</td>
<td>-0.35 (-1.11; 0.47)</td>
</tr>
<tr>
<td>Last visit [N=32752]</td>
<td>-1.59 (-2.45; -0.72)</td>
<td>-0.40 (-1.14; 0.29)</td>
<td>-0.33 (-1.09; 0.42)</td>
</tr>
<tr>
<td>ART – N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever received</td>
<td>33514 (87.8)</td>
<td>2889 (94.6)</td>
<td>1016 (98.5)</td>
</tr>
<tr>
<td>Started &gt; age 10 years</td>
<td>4037 (12.0)</td>
<td>371 (12.8)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>On ART at age 10 years</td>
<td>25713 (67.3)</td>
<td>2021 (66.2)</td>
<td>866 (83.9)</td>
</tr>
<tr>
<td>On ART at last visit</td>
<td>30072(80.3)</td>
<td>2540 (84.1)</td>
<td>878 (86.1)</td>
</tr>
<tr>
<td>Virologic suppression – n/N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 10 years</td>
<td>6919/10209 (67.8)</td>
<td>1442/2500 (57.7)</td>
<td>576/1012 (56.9)</td>
</tr>
<tr>
<td>Last visit</td>
<td>9741/14200 (68.6)</td>
<td>2149/2994 (71.8)</td>
<td>617/1020 (60.5)</td>
</tr>
</tbody>
</table>

Cumulative incidence (95% CI) at age 15 years
<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Europe</th>
<th>North America</th>
<th>South &amp; Southeast Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (%)</td>
<td>2.6 (2.4; 2.8)</td>
<td>0.8 (0.5; 1.2)</td>
<td>1.1 (0.5; 2.1)</td>
<td>2.7 (1.9; 3.8)</td>
</tr>
<tr>
<td>Transferred out (%)</td>
<td>15.6 (15.1; 16.0)</td>
<td>3.5 (2.9; 4.3)</td>
<td>1.9 (1.1; 3.1)</td>
<td>6.7 (5.5; 8.0)</td>
</tr>
<tr>
<td>Lost to follow-up (%)</td>
<td>11.3 (10.9; 11.8)</td>
<td>6.1 (5.2; 7.0)</td>
<td>8.9 (6.7; 11.3)</td>
<td>7.1 (5.6; 8.7)</td>
</tr>
</tbody>
</table>

ART – antiretroviral therapy; CI – confidence interval; HAZ – WHO height-for-age Z-score; IQR – interquartile range

Note: 48.5%, 47.7% and 26.9% of first visit CD4 count, CD4 percent and HAZ measurements respectively overlapped with ART start measurements and 14.9%, 15.5% and 7.3% of age 10 year CD4 count, CD4 percent and HAZ measurements respectively overlapped with last visit measurements.

Fig 2: Comparison by geographic region of characteristics at first visit, ART start, age 10 years and last visit of adolescents living with perinatally-acquired HIV (ART – antiretroviral therapy; IQR – interquartile range; S&SE Asia – South and Southeast Asia; WHO – World Health Organization)

By competing risks analysis, the cumulative incidence estimates (95% CI) at 15 years of age for mortality, transfers out and LTFU for all APH were 2.6% (2.4%; 2.8%), 15.6% (15.1%; 16.0%) and 11.3% (10.9%; 11.8%) respectively (Table 2). Cumulative incidence of mortality before any other competing event occurred was estimated to be lowest in Europe (0.8% (0.5%; 1.1%)) and highest in South America & Caribbean (4.4% (3.1%; 6.1%)) (Table 2). However LTFU before mortality or transfer out was lowest in South American & Caribbean (4.8% (3.4%; 6.7%)) and highest in sub-Saharan Africa (13.2% (12.6%; 13.7%)). Transfers out before mortality or LTFU were also highest in sub-Saharan Africa (19.3% (18.7%; 20.0%)). Cumulative mortality [95% CI] when estimated by the Kaplan-Meier product limit estimator, was similar at 3.0% (2.8%; 3.3%) for the total cohort, ranging from 0.8% (0.5%; 1.2%) in Europe to 4.7% (3.3%; 6.6%) in South America & Caribbean (S1 Table).
Comparison by country income group

Sixty five percent of all APH in this cohort lived in low income countries, 7.9% in lower-middle income, 17.5% upper-middle income and 9.7% in high income countries. Variation in characteristics by CIG followed the geographic region trends, with younger age, higher CD4% and less impaired HAZ at first visit and ART start in APH in high income countries compared to upper-middle, lower-middle or low income countries (Table 3, Fig 3). Mortality before transfer out or LTFU was lowest in high income countries (0.9% (0.6%; 1.3%)) and highest in low income countries (3.5% (3.1%; 3.8%)) (Table 3). However LTFU before mortality or transfer out was highest in upper-middle income countries (12.8% (11.8%; 13.9%)).
### Table 3: Adolescent characteristics at first visit, ART start, age 10 years and last visit and cumulative incidence of outcomes (mortality, transferred out, lost-to-follow-up) compared by country income group

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Low Income</th>
<th>Lower-Middle Income</th>
<th>Upper-Middle Income</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total N (row %)</strong></td>
<td>38187 (100)</td>
<td>24794 (64.9)</td>
<td>3015 (7.9)</td>
<td>6669 (17.5)</td>
</tr>
<tr>
<td><strong>Male – N (%)</strong></td>
<td>18863 (49.4)</td>
<td>12191 (49.2)</td>
<td>1503 (49.9)</td>
<td>3372 (50.6)</td>
</tr>
<tr>
<td><strong>Age in years – median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First visit</td>
<td>6.7 (4.4; 8.4)</td>
<td>7.1 (5.4; 8.6)</td>
<td>6.3 (3.8; 8.1)</td>
<td>6.3 (3.7; 8.3)</td>
</tr>
<tr>
<td>ART start</td>
<td>7.5 (5.2; 9.2)</td>
<td>8.0 (6.2; 9.4)</td>
<td>7.2 (4.7; 9.0)</td>
<td>7.0 (4.7; 8.8)</td>
</tr>
<tr>
<td>Last visit</td>
<td>12.4 (11.1; 14.4)</td>
<td>12.1 (10.9; 13.7)</td>
<td>13.2 (11.4; 15.3)</td>
<td>12.6 (11.1; 14.6)</td>
</tr>
<tr>
<td><strong>CD4 count in cells/mm³ – median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First visit [N=19979]</td>
<td>427 (200; 757)</td>
<td>405 (194; 707)</td>
<td>348 (142; 610)</td>
<td>393 (183; 709)</td>
</tr>
<tr>
<td>First visit if age &gt; 5 years [N=14585]</td>
<td>358 (165; 632)</td>
<td>377 (176; 664)</td>
<td>302 (116; 540)</td>
<td>298 (132; 527)</td>
</tr>
<tr>
<td>ART start [N=20608]</td>
<td>321 (165; 575)</td>
<td>302 (155; 504)</td>
<td>277 (108; 455)</td>
<td>336 (171; 602)</td>
</tr>
<tr>
<td>ART start if age &gt; 5 years [N=16612]</td>
<td>292 (161; 469)</td>
<td>300 (154; 504)</td>
<td>245 (91; 360)</td>
<td>283 (139; 478)</td>
</tr>
<tr>
<td>Age 10 years [N=26953]</td>
<td>685 (445; 972)</td>
<td>661 (421; 955)</td>
<td>702 (463; 953)</td>
<td>719 (472; 1004)</td>
</tr>
<tr>
<td>Last visit [N=31951]</td>
<td>687 (464; 946)</td>
<td>679 (443; 956)</td>
<td>692 (492; 917)</td>
<td>727 (511; 968)</td>
</tr>
<tr>
<td><strong>CD4 % - median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First visit [N=13674]</td>
<td>16 (9; 25)</td>
<td>16 (9; 24)</td>
<td>13 (7; 20)</td>
<td>14 (8; 21)</td>
</tr>
<tr>
<td>ART start [N=14740]</td>
<td>14 (8; 20)</td>
<td>13 (8; 18)</td>
<td>11 (6; 17)</td>
<td>13 (8; 19)</td>
</tr>
<tr>
<td>Age 10 years [N=17974]</td>
<td>28 (20; 34)</td>
<td>27 (19; 34)</td>
<td>27 (21; 33)</td>
<td>28 (20; 35)</td>
</tr>
<tr>
<td>Last visit [N=23292]</td>
<td>29 (21; 35)</td>
<td>28 (20; 35)</td>
<td>29 (22; 35)</td>
<td>29 (22; 35)</td>
</tr>
<tr>
<td><strong>HAZ – median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First visit [N=20269]</td>
<td>-1.92 (-2.91; -0.97)</td>
<td>-2.02 (-3.00; -1.07)</td>
<td>-1.98 (-2.87; -1.09)</td>
<td>-1.89 (-2.80; -1.00)</td>
</tr>
<tr>
<td>ART start [N=20372]</td>
<td>-1.95 (-2.91; -1.02)</td>
<td>-2.05 (-3.01; -1.13)</td>
<td>-2.13 (-3.05; -1.29)</td>
<td>-1.93 (-2.79; -1.10)</td>
</tr>
<tr>
<td>Age 10 years [N=26883]</td>
<td>-1.53 (-2.35; -0.72)</td>
<td>-1.69 (-2.48; -0.92)</td>
<td>-1.83 (-2.55; -1.08)</td>
<td>-1.46 (-2.20; -0.77)</td>
</tr>
<tr>
<td>Last visit [N=32752]</td>
<td>-1.59 (-2.45; -0.72)</td>
<td>-1.79 (-2.62; -0.97)</td>
<td>-1.65 (-2.44; -0.87)</td>
<td>-1.46 (-2.24; -0.67)</td>
</tr>
<tr>
<td><strong>ART – N (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever received</td>
<td>33514 (87.8)</td>
<td>20851 (84.1)</td>
<td>2776 (92.1)</td>
<td>6351 (95.2)</td>
</tr>
<tr>
<td>Started &gt; age 10 years</td>
<td>4037 (12.0)</td>
<td>3028 (14.5)</td>
<td>305 (11.0)</td>
<td>423 (6.7)</td>
</tr>
<tr>
<td>On ART at age 10 years</td>
<td>25713 (67.3)</td>
<td>15444 (62.3)</td>
<td>2279 (75.6)</td>
<td>5323 (79.8)</td>
</tr>
<tr>
<td>On ART at last visit</td>
<td>30072 (80.3)</td>
<td>18408 (75.9)</td>
<td>2589 (87.8)</td>
<td>6002 (91.1)</td>
</tr>
<tr>
<td><strong>Virologic suppression – n/N (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 10 years</td>
<td>6919/10209 (67.8)</td>
<td>467/932 (50.2)</td>
<td>885/1039 (85.2)</td>
<td>3637/4843 (75.1)</td>
</tr>
<tr>
<td>Last visit</td>
<td>9741/14200 (68.6)</td>
<td>1342/2777 (48.3)</td>
<td>1210/1486 (81.4)</td>
<td>4684/6274 (74.7)</td>
</tr>
<tr>
<td><strong>Cumulative incidence (95% CI) at age 15 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>2.6 (2.4; 2.8)</td>
<td>3.5 (3.1; 3.8)</td>
<td>2.7 (2.1; 3.5)</td>
<td>1.4 (1.1; 1.9)</td>
</tr>
<tr>
<td>Transferred out (%)</td>
<td>15.6 (15.1; 16.0)</td>
<td>16.7 (16.1; 17.4)</td>
<td>14.3 (12.8; 15.8)</td>
<td>2.1 (2.0; 2.3)</td>
</tr>
<tr>
<td>Lost to follow-up (%)</td>
<td>11.3 (10.9; 11.8)</td>
<td>12.6 (12.0; 13.2)</td>
<td>7.5 (6.3; 8.8)</td>
<td>12.8 (11.8; 13.9)</td>
</tr>
</tbody>
</table>

ART – antiretroviral therapy; CI – confidence interval; HAZ – height-for-age-Z-score; IQR – interquartile range
Fig 3: Comparison by country income group of characteristics at first visit, ART start, age 10 years and last visit of adolescents living with perinatally-acquired HIV (ART – antiretroviral therapy; IQR – interquartile range; S&SE Asia – South and Southeast Asia; WHO – World Health Organization)
Comparison by birth cohort

Fifty eight percent of all APH were born in the year 2000 or later, ranging from 0.3% living in North America and 2.8% in high income countries to 86.9% living in sub-Saharan Africa and 73.6% in low income countries (S2 Table). Three-quarters (76.7%) of APH born prior to 1995 lived in Europe and North America, and age at first visit and ART start appear to be younger and CD4 count, CD4 percent and HAZ at first visit and ART start appear to be better in this group compared to those born in later calendar periods (S2 Table, S1 Fig). However for the two more recent birth cohorts, the majority of APH were from sub-Saharan Africa, and age at first visit and ART start was younger and CD4 count higher in APH born during 2000 to 2005 than 1995 to 1999. HAZ, however, did not show any improvement over time at ART start or at last visit for APH born between 2000 and 2005 compared to APH born between 1995 and 1999. Mortality before transfer or LTFU was lowest in APH born between 2000 and 2005 (1.84% (95% CI 1.50%; 2.23%)), although LTFU in this group was also more than double that of the previous two birth periods (23.34% (95% CI 19.96%; 26.88%)). When looking at birth cohort trends by region, mortality declined in every region for APH born between 2000 and 2005 compared to those born in the earlier birth cohorts, and no mortality was observed in the most recent APH birth cohort in Europe, North America and South America & Caribbean (S3 Table). However, LTFU increased for APH born between 2000 and 2005 in all regions except South America & Caribbean.

Mortality hazards compared by region

Relative to Europe, the unadjusted mortality HR (95% CI) was significantly higher in South & Southeast Asia (3.21 (2.03; 5.07)), South America & Caribbean (6.07 (3.87; 9.50)) and sub-Saharan Africa (4.35 (3.02; 6.28)), but not in North America (1.70 (0.87; 3.31)) (Table 4, model 1). After controlling for baseline characteristics including sex, birth cohort, age at first visit and any ART received, the adjusted mortality HR (aHR) increased slightly for North America and decreased for sub-Saharan Africa (Table 4, model 2). Inclusion of IPW in the model marginally reduced the HR further for all regions except North America (Table 4, model 3). Adjustment for CD4 measures, either as CD4 count or CD4%, at first visit only or time-updated and with or without multiple imputation for missing CD4 measures, also altered the individual region aHRs relative to Europe, but the
general pattern remained of elevated mortality in all regions relative to Europe and substantially elevated mortality in sub-Saharan Africa and South America & Caribbean (Table 4 and S4 Table).

Table 4: Mortality hazard ratios (95% confidence intervals) by region with reference to Europe

<table>
<thead>
<tr>
<th>Region</th>
<th>Crude mortality hazard ratio compared to Europe [N=38,187]</th>
<th>Adjusted for complete baseline characteristics* [N=38,187]</th>
<th>Adjusted for complete baseline characteristics* with IPW [N=38,187]</th>
<th>Adjusted for baseline characteristics* including CD4%, using complete cases only [N=13,699]</th>
<th>Adjusted for baseline characteristics* including CD4%, with imputation for missing CD4 [N=38,187]</th>
<th>Adjusted for baseline characteristics* including CD4%, with restricted imputationb [N=33,126]</th>
<th>Adjusted for baseline characteristics* including CD4 count, using complete cases only [N=19,979]</th>
<th>Adjusted for baseline characteristics* including CD4 count, with imputation [N=38,187]</th>
<th>Adjusted for baseline characteristics* including CD4 count, with restricted imputationb [N=33,126]</th>
<th>Adjusted for baseline characteristics* and time-updated CD4 count, with imputation [N=38,187]</th>
<th>Adjusted for baseline characteristics* including CD4 count and HAZ, with imputation [N=38,187]</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>1.70 (0.87; 3.31)</td>
<td>2.03 (1.02; 4.02)</td>
<td>2.52 (1.24; 5.11)</td>
<td>1.84 (0.58; 5.81)</td>
<td>2.34 (1.19; 4.71)</td>
<td>1.97 (0.97; 4.02)</td>
<td>2.18 (0.71; 6.66)</td>
<td>2.37 (1.19; 4.71)</td>
<td>2.02 (0.99; 4.11)</td>
<td>2.07 (1.05; 4.10)</td>
<td>2.31 (1.16; 4.60)</td>
</tr>
<tr>
<td>South &amp; Southeast Asia</td>
<td>3.21 (2.03; 5.07)</td>
<td>2.96 (1.79; 4.88)</td>
<td>2.78 (1.75; 4.42)</td>
<td>1.90 (0.73; 4.91)</td>
<td>1.87 (1.12; 3.13)</td>
<td>1.56 (0.91; 2.67)</td>
<td>3.16 (1.44; 6.96)</td>
<td>2.40 (1.45; 3.96)</td>
<td>1.56 (0.91; 2.67)</td>
<td>4.06 (2.45; 6.73)</td>
<td>2.21 (1.33; 3.67)</td>
</tr>
<tr>
<td>South America &amp; Caribbean</td>
<td>6.07 (3.87; 9.50)</td>
<td>5.94 (3.77; 9.38)</td>
<td>5.61 (3.58; 8.77)</td>
<td>4.20 (1.72; 10.29)</td>
<td>5.00 (3.17; 7.90)</td>
<td>4.16 (2.54; 6.80)</td>
<td>5.52 (2.62; 11.67)</td>
<td>5.49 (3.48; 8.65)</td>
<td>4.16 (2.54; 6.80)</td>
<td>5.49 (3.48; 8.65)</td>
<td>5.21 (3.29; 8.23)</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>4.35 (3.02; 6.28)</td>
<td>3.37 (2.17; 5.23)</td>
<td>3.23 (2.21; 4.73)</td>
<td>4.09 (1.84; 9.13)</td>
<td>2.70 (1.75; 4.19)</td>
<td>2.42 (1.51; 3.87)</td>
<td>4.57 (2.23; 9.35)</td>
<td>3.01 (1.95; 4.67)</td>
<td>2.70 (1.68; 4.33)</td>
<td>3.58 (2.28; 5.64)</td>
<td>2.85 (1.83; 4.43)</td>
</tr>
</tbody>
</table>

*Sex, birth period (pre-1995; 1995-1999; 2000-2005), age at first visit, antiretroviral therapy (never started, started on dual therapy before 2000, started on triple therapy); b Multiple imputation for missing CD4 restricted to countries with at least 50 CD4 observations at first visit, or <50% missing CD4 if total country N <50; HAZ – height-for-age-Z-score; IPW – inverse probability weights
Sensitivity analyses

In sensitivity analyses, under varying assumptions of the proportion of APH classified as LTFU who may be unascertained mortality, the cumulative incidence for mortality before transfer out or LTFU in sub-Saharan Africa could be as high as 14.9% [95% CI 14.3%; 15.5%] if 100% of APH LTFU was truly mortality (S5 Table). Under the assumption that 100% of LTFU is due to mortality in all regions, the relative difference in mortality is attenuated in all regions in comparison to Europe, with the highest unadjusted HR (uHR) in sub-Saharan Africa at 1.46 (95% CI 1.33; 1.61) (S6 Table). If it is differentially assumed that in sub-Saharan Africa 50% of LTFU is unascertained mortality, but only 5% in all other regions, the uHR for mortality in sub-Saharan Africa may be as high as 7.09 (95% CI 5.45; 9.23) relative to Europe.
Discussion

To our knowledge, this is the largest analysis of APH to date, describing the characteristics and outcomes of more than 38,000 APH, across more than 100,000 person years of follow-up during adolescence, from five regions of the world, including 14 of the 15 highest adolescent HIV burden countries [1], and across low, middle and high income countries. This analysis essentially describes younger adolescents (10 to 14 years of age), 79% of whom were living in sub-Saharan Africa. Our findings show that APH in North America and Europe, as well as high income group countries, generally presented to care and started ART at a younger age with higher CD4 counts and less impaired height compared to other regions or CIG. Conversely, age at presentation to care and ART start was highest in sub-Saharan Africa. Despite probable under-ascertained mortality in some regions, the hazard of HIV-associated mortality during adolescence was substantially higher in sub-Saharan Africa, South & Southeast Asia and South America & Caribbean than in Europe. Results suggested that mortality may also have been higher in North America than Europe. Analysis by country income group followed these geographic trends, with results suggesting younger age, higher CD4 percent and less impaired height at first visit and ART start in high income countries compared to middle or low income countries.

Results also suggested a marked difference in regional and income group distributions across birth cohort groups. APH from North America and Europe, and likewise high income countries, predominated in the earliest birth cohort, with minimal representation from Asia and Africa, while the most recent birth cohort was dominated by APH living in sub-Saharan Africa. Younger age, higher CD4 and less impaired growth in the earliest birth cohort reflected this region and CIG distribution. These vastly different characteristics of APH across regions and over time require careful adjustment and interpretation due to different effects of variables across time. Nevertheless, some improvements for all APH born after 2000 compared to those born during 1995-1999 are evident, including younger age and higher CD4 count at first presentation and ART start. This trend is expected as criteria for initiating ART have progressively become less restrictive, with higher or no
CD4 thresholds, and access to ART has expanded across the globe [3,26-29]. Despite this, height was still severely impacted in APH in the most recent birth cohort. This may reflect that although APH born during 2000-2005 started ART earlier than APH born during 1995-1999, they still only started at a median of 7 years of age, having missed the benefits of early ART on growth, and probably also cognition and other morbidities, although the latter two outcomes were not evaluated in this analysis [30-32].

Comparing mortality across the regions is limited by high LTFU in sub-Saharan Africa relative to the other regions. Furthermore, LTFU rates in Europe may be overestimated due to reporting delay for some cohorts. Higher LTFU has been described in cohorts with shorter durations of follow-up where people may not yet have had the opportunity to return to care, while in cohorts of longer durations, people previously considered LTFU subsequently return to care [33]. This could affect patients born in the most recent birth cohorts in our analysis, particularly in sub-Saharan Africa. Methods have advanced in adult HIV cohort research to informatively adjust mortality estimates for under-ascertainment in those LTFU, informed by studies that actively traced patients LTFU to determine their vital status [34-37]. However, a recent systematic review identified few such tracing studies in children or adolescents living with HIV [25]. One study from Malawi traced 201 children who were LTFU, and of the 79% who were successfully traced, 11% had died, 26% had transferred to another clinic and 25% were alive but no longer on ART [38]. A better understanding of how program LTFU can bias mortality estimates specifically in adolescents is needed to truly understand and impact on mortality in adolescents living with HIV [1].

This study has limitations. As mode of transmission is generally poorly captured in routine care cohorts, we used a pragmatic definition of APH and included only HIV-infected children that had entered care before age 10 years. This was done to ensure exclusion of adolescents with horizontally-acquired HIV, who have a very different disease profile during adolescence to APH [39]. As a result of this approach, we may have excluded a relatively small but important group of APH diagnosed and entering care after age 10 years [40,41]. Our analysis does not include Nigeria, a country with the second largest burden of adolescents living with HIV and
the only country in which mortality in younger adolescents (10 to 14 years of age) is estimated to be rising [1].

Furthermore, the North American region is represented only by the United States in this analysis, and findings may not necessarily be generalizable to other North American countries. Our analysis may over-represent APH treated in healthcare settings with higher standards of care compared to the general population of adolescents, thus underestimating true mortality in APH. Additionally, approximately 44% of included cohorts collect data only on children started on ART, thus the proportion on ART observed in this analysis is likely overestimated for some regions. HIV viral load measurements were sparsely available and possibly selectively performed in the lower CIGs, with likely targeting of HIV viral load measurements to children with clinical or immunological failure where HIV viral load testing is not part of routine monitoring. This would result in overestimation of the proportion of patients with an unsuppressed HIV viral load and these HIV viral load data should be interpreted with care in this analysis.

The current generation of APH, and those represented in this CIPHER analysis, largely reflect HIV-infected children who survived early childhood without ART but at the same time experienced substantial growth morbidity, and possibly other morbidities not measured in this analysis. This current generation may be substantially different to future cohorts of APH who will have been more likely to have started ART in infancy and may be affected by different issues. It is expected that APH survival will continue to improve with greater access to early infant diagnosis and universal ART for all people living with HIV [42]. Although the population of APH is likely to decline in the future, due to declining new perinatally-acquired HIV infections, there is still a lot of work to be done to achieve equality in health and survival for all APH irrespective of geographic location. Collaborations such as CIPHER enable us to monitor current global temporal trends in APH outcomes over time to ensure that this and future generations of APH across the globe have the potential to thrive and contribute to society, outcomes that were denied to previous generations of HIV-infected children.

In summary, our analysis of a large cohort of APH between 1982 and 2014 across several regions of the globe suggests that APH generally entered HIV care at an earlier age in high income countries compared to other
CIG. Despite probable under-ascertainment, mortality continued to be substantially higher in sub-Saharan Africa, South & Southeast Asia and South America & Caribbean than in Europe, and warrants further monitoring and understanding.

Acknowledgements
We thank all contributing networks, their study teams and participants. Please see full list of acknowledgments in supplementary material (S1 Text)

References
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- S5 Table Cumulative incidence 10to15 Sensitivity - S3 Table
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<table>
<thead>
<tr>
<th>HIV-infected children in the CIPHER Global Cohort</th>
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<td>N=183,119</td>
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Excluded:
- Known non-perinatal HIV-infection N=222
- Unresolvable date discrepancies N=13
- First observation at age > 10 years N=1,989
- Last observation at age < 10 years N=142,701
- Missing gender N=7
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