Renal impairment in children and young adults living with HIV in Europe and Thailand

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Background & Aim

- Renal impairment (RI) is a known complication in adults living with HIV [1].
- Data on RI in children and young adults living with HIV (CYALHIV) in the modern antiretroviral therapy (ART) era are limited.

We assessed prevalence and incidence of RI among CYALHIV who had ever initiated ART and were in routine care in Europe and Thailand.

1. Ekrikpo *et al.*, PLoS One 2018. doi: 10.1371/journal.pone.0195443.

Methods

Inclusion criteria for analysis:

- Aged <18 years and in follow-up in one of 12 cohorts in the Epidemiology of Pregnancy and Paediatric Infections International Cohort Collaboration (EPPICC) (Figure 1) at any point between 1st January 2015 and 31st December 2024 (study period),
- Ever initiated ART,
- Had ≥2 serum creatinine (SCr) laboratory measurements available from 1st January 2015 onwards.

Follow-up data after age 18 years were included where available.

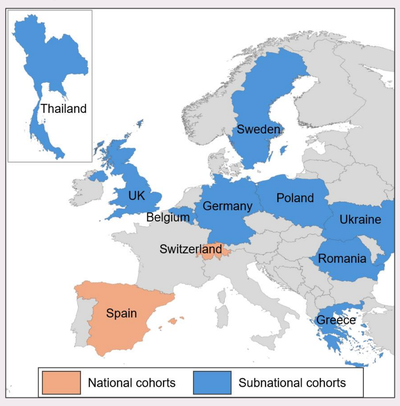


Figure 1. Location of EPPICC cohorts contributing to the analysis.

Definitions

RI: two consecutive grade ≥2 (DAIDS) SCr or estimated glomerular filtration rate (eGFR)* measurements.**

An episode of RI started on the date of the first grade ≥2 SCr/eGFR measurement. End date/censoring are described in Table 1.

Analyses

1. **Burden of RI** (follow-up data before and after ART initiation were included):
   a) Overall prevalence of RI: proportion (95% confidence interval (95% CI)) of CYALHIV ever experiencing a RI episode at any time during the study period.
   b) Duration of RI: median (95% CI) time (years) to resolution (confirmed) was estimated using Kaplan-Meier methods.
2. **Risk of RI** (follow-up data after ART initiation were included):
   a) Incidence of first RI: rate (95% CI) per 100 person-years (100 PY) of first RI was estimated overall and by time-updated characteristics.
   - Time at risk was from the latest of: ART initiation date, 1st January 2015, 1st SCr measurement.
   - CYALHIV with ongoing RI episodes at the start of the time at risk were excluded.
   - PY were censored at the start of the first RI or, if no RI, at the censoring date§ in Table 1.

   b) Characteristics at onset of first RI: demographic and clinical characteristics at onset, summarised as n (%) or median [IQR].

Table 1. Definitions of RI resolution/censoring.

Episode status	Criteria for episode end date	End date/censoring
Confirmed resolved	2 x normal SCr/eGFR	1st normal measurement
Unconfirmed resolved	1 x normal SCr/eGFR, no further data	1st normal measurement
Ongoing	SCr/eGFR never returned to normal	§ Censored at earliest of: 1 year after last SCr, administrative censoring date, or 31st December 2024

* Calculated using the Schwartz Pediatric Bedside equation for ages ≥1 and <18 years, and the CKD-EPI creatinine equation (2021) for ages ≥18 years. ** The definition of RI did not include change from baseline SCr or eGFR.

Results: Population characteristics

Table 2. Characteristics of 1618 CYALHIV included in the analysis.

Characteristic (N with data*)	n (%) or median [IQR]
Sex, male (N=1615)	797 (49%)
Region	
Western Europe	1011 (63%)
Central/Eastern Europe	343 (21%)
Thailand	264 (16%)
Born abroad (N=1521)	533 (35%)
Perinatally acquired HIV (N=1452)	1350 (93%)
Age (years) at HIV diagnosis (N=1309)	1.8 [0.4, 5.9]
Age (years) at ART initiation	3.1 [0.6, 9.5]
Year of ART initiation	2011 [2006, 2015]
Age (years) at censoring	17.8 [14.3, 19.6]
Age >21 years at censoring	239 (15%)
Duration (years) of follow-up in study period**	5.2 [3.0, 8.6]
N. of SCr measurements in study period	10 [6, 16]

* N includes all 1618 CYALHIV unless otherwise indicated. ** Time from latest of 1st January 2015 or 1st SCr measurement to censoring date. **Abbreviations**: ART, antiretroviral therapy; CYALHIV, children and young adults living with HIV; IQR, interquartile range; N, number

Analysis 1: Burden of RI

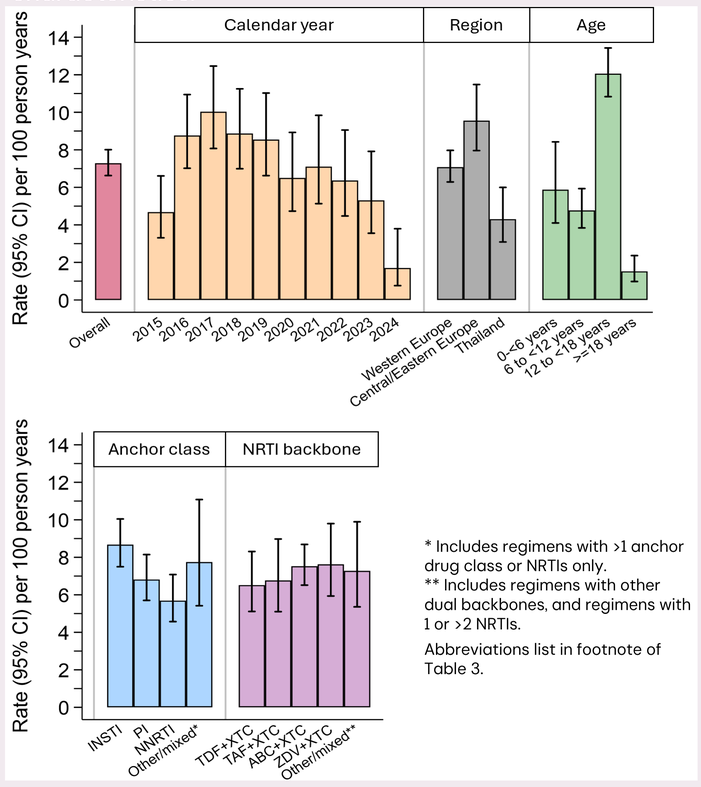
617/1618 CYALHIV experienced a total of 725 RI episodes, before or after ART initiation.

Overall prevalence of RI (95% CI) was 38% (36%, 41%). Maximum SCr/eGFR **DAIDS grade** during an episode was **moderate (Grade 2) for 634 (87%) episodes**, severe (Grade 3) for 87 (12%) and life threatening (Grade 4) for 4 (1%).

382 (53%) episodes were confirmed resolved, 108 (15%) unconfirmed resolved and 235 (32%) were ongoing. **The median (95% CI) time to confirmed resolution was 3.0 (2.7, 3.4) years**.

Analysis 2a: Incidence of first RI

Figure 2. Incidence of first RI overall and by time-updated characteristics.



* Includes regimens with >1 anchor drug class or NRTIs only.
** Includes regimens with other dual backbones, and regimens with 1 or >2 NRTIs.
Abbreviations list in footnote of Table 3.

Of 1490 CYALHIV included in the incidence analysis, 454 had a RI episode over 6232 PY (from the start of the time at risk to censoring date, as defined in the methods). Median [IQR] time at risk was 3.6 [1.9, 5.9] years.

Overall rate of first RI (95% CI) was **7.3 (6.6, 8.0) episodes per 100 PY**, which generally declined from 2017 (Figure 2).

By time-updated subgroup, **incidence was highest** in:

- **Age 12-<18 years:** 12.1 (10.8, 13.4) per 100 PY
- **Central/Eastern Europe:** 9.6 (8.0, 11.5) per 100 PY
- **On integrase inhibitors (INSTI):** 8.7 (7.5, 10.0) per 100 PY
- Limited difference by nucleoside reverse transcriptase inhibitor (NRTI)-backbone

Analysis 2b: Characteristics at onset of first RI

At first RI onset (N=454):

- Median [IQR] **time since ART initiation was 9.0 [4.9, 13.4] years** (Table 3).
- **44% were on INSTI-based** regimens and **42% were on a NRTI backbone of ABC+XTC**.
- **Most (92%) had no/mild immunosuppression-for-age.**
- Half (53%) had prior advanced/severe immunosuppression and 24% had prior AIDS diagnosis.

Table 3. Characteristics at onset of first RI among 454 children and young adults living with HIV.

Characteristics at RI onset (N with data*)	n (%) or median [IQR]
Year RI episode started	
2015-2017	192 (42.3)
2018-2020	165 (36.3)
2021-2024	97 (21.4)
Time since ART start, years	9.0 [4.9, 13.4]
Anchor drug	
INSTI	199 (43.8)
PI	125 (27.5)
NNRTI	82 (18.1)
Other/mixed†	35 (7.7)
Off ART	13 (2.9)
NRTI backbone	
TDF+XTC	69 (15.2)
TAF+XTC	51 (11.2)
ABC+XTC	192 (42.3)
ZDV+XTC	66 (14.5)
Other/mixed‡	44 (9.7)
No NRTI/unknown	19 (4.2)
Off ART	13 (2.9)
Immunosuppression-for-age (closest measurement ±12 weeks (N=394)§	
None/mild	364 (92.4)
Advanced/severe	30 (7.6)
Nadir immunosuppression-for-age (N=393)	
None/Mild	184 (46.8)
Advanced/severe	209 (53.2)
Prior diagnosis with AIDS-defining illness (N=409)	100 (24.4)

* N includes all 454 CYALHIV who experienced a RI episode unless otherwise indicated. † Includes regimens with >1 anchor drug class or NRTIs only. ‡ Includes regimens with other dual backbones and regimens with 1 or >2 NRTIs. § Immunosuppression-for-age was categorised using WHO 2007 criteria, using CD4% for ages <5 years, and CD4 count for ages ≥5 years (for ages ≥5 years, severe immunosuppression was defined as <200 cells/μL).

Abbreviations: ABC, abacavir; ART, antiretroviral therapy; CI, confidence interval; INSTI, integrase inhibitor; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RI, renal impairment; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; XTC, lamivudine or emtricitabine; ZDV, zidovudine.

Conclusions

- In this cohort of mostly early treated children and young adults with perinatally acquired HIV, **RI was common** with over one-third experiencing an RI episode during the study period, which persisted for a median of 3 years; most episodes were of moderate severity.
- RI incidence was **highest in adolescents and occurred largely in those with good immune health.**
- The higher incidence observed among those on INSTI-based regimens may reflect reduced tubular creatinine secretion rather than pathological RI and should be interpreted with caution.
- These results highlight the **need to monitor renal health across the life course** to ensure healthy ageing in this population and to better understand the long-term clinical implications of these results.
- Factors associated with RI warrant further investigation to aid the development of RI prevention strategies.

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