Title	A pharmacovigilance study to define the long-term safety profile of etravirine in HIV-1 infected children and adolescents
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Research question and objectives	Research question: What is the long-term safety profile of ETR in children and adolescents with HIV infection? The study objectives are to: 1) describe the clinical characteristics of patients at the start of ETR-based therapy 2) describe the incidence of DAIDS grade 3 and 4 adverse events (AEs) for key laboratory markers by duration of ETR use 3) provide the incidence and describe clinical serious adverse events which are considered to be causally related to ETR by duration of ETR use 4) report clinical non-serious adverse events which are considered to be causally related to ETR, where available 5) characterize reasons for discontinuation of ETR 6) provide information on any off-label use of ETR in children (excluding in utero exposure), including in treatment-naive children and those <6 years of age
Country(-ies) of study	Belgium, Germany, Italy, Poland, Portugal, Romania, Russia, Spain, Sweden, Switzerland, Thailand and the UK/Ireland
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1. Abstract

Title:	A pharmacovigilance study to define the long-term safety profile of etravirine in HIV-1 infected children and adolescents
Keywords:	Etravirine, safety, HIV, cohort study, paediatrics
Rationale and Background:	Etravirine (ETR) is licensed for use in treatment-experienced HIV-positive children ≥6 years of age. Little is known about its long-term safety in this group. The use and safety of ETR in children was assessed using data from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC).
Research Question and Objectives:	What is the long term safety profile of ETR use in children and adolescents with HIV-1 infection? The study objectives are to: 1) describe the clinical characteristics of patients at ETR start 2) describe the incidence of DAIDS grade ≥3 laboratory adverse events (AEs) 3) describe serious clinical AEs considered causally-related to ETR 4) report clinical non-serious AEs considered causally related to ETR 5) characterize reasons for discontinuation of ETR 6) provide information on off-label use of ETR
Study Design:	Longitudinal study: Pooled analysis of anonymised individual patient data for children who initiated ETR aged <18 years
Setting:	HIV-1 infected children in Europe, Russia and Thailand
Subjects and study size, including dropouts:	All children initiating ETR at <18 years of age and followed-up outside a Janssen-sponsored clinical trial
Variables and Data Sources	Data pooled from 17 cohorts across 13 countries in Europe, Russia and Thailand comprised: demographic factors, ART history, AIDS events, death, weight, CD4 cell counts, HIV viral loads, hepatitis B/C co-infection, laboratory test results, clinical AEs.
Results:	177 children received ETR outside of a company-sponsored clinical trial, 13 newly reported this year. 108 (61%) were aged 6-<18 years at ETR start and on a licensed dose, 23 (13%) were on ETR off-label (10 on unlicensed dose, seven not treatment-experienced and six were aged <6 years at ETR start), and 46 (26%) patients had missing weight and/or dose at ETR start. In the licensed dose group, 44% were still on ETR at last follow-up. Of 60 (56%) patients who stopped taking ETR, reasons for discontinuation were: lack of efficacy (6), safety (7), other reasons (43) and reason

unknown (4). Amongst those stopping for safety, (5/7, 71%) were due to hypersensitivity reactions. Overall rates of grade ≥3 DAIDS laboratory events were low for all markers (≤ 1[maximum 95%CI, 0-5] per 100 person-years of follow-up).

Eight clinical AEs were reported to be at least possibly causally related to ETR, all in the licensed dosage group (five rash/erythema, one generalised hypersensitivity reaction and two Stevens-Johnson syndrome (SJS)). Both cases of SJS were considered serious (one life threatening).Both patients were also exposed to darunavir at/just before the event and one case was reported as probably due to ETR or darunavir. Both patients recovered after discontinuation of ETR/darunavir. There were three deaths in the cohort during follow-up; two were on ETR at the time of death. Causes of death were: HIV-related metastatic adenocarcinoma (1) and an AIDS-defining event (2).

Discussion:

In general etravirine-containing regimens, both licensed and unlicensed, appear to be well tolerated in this population. Adverse laboratory and clinical events occurred infrequently. Serious skin/hypersensitivity reactions did sometimes occur, as has been previously reported in the adult population. Our results suggest that these reactions may occur slightly more frequently in children and adolescents than in adults. It should be noted however, the these adverse event may have occurred due to exposure to other ART drugs (including darunavir) at the time of the event.

Marketing authorisation holder:

Janssen-Cilag International NV

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2. List of abbreviations

3TC	Lamivudine
ABC	Abacavir
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral therapy
ATV	Atazanavir
cART	Combination ART
CD4	CD4 T-cell count
CI	Confidence Interval
DAIDS	Division of AIDS
d4T	Stavudine
ddC	Zalcitabine
ddI	Didanosine
DRV	Darunavir
EFV	Efavarenz
ETR	Etravirine
EPPICC	European Pregnancy and Paediatric HIV Cohort Collaboration
FTC	Emtricitabine
GI	Gastro-intestinal
HICDEP	HIV Cohorts Data Exchange Protocol
HBV	Hepatitis-B virus
HCV	Hepatitis-C virus
HIV	Human Immunodeficiency Virus
IDV	Indinavir
LPV	Lopinavir
LTFU	Lost to follow-up
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
PI	Protease Inhibitor
RAL	Raltegravir
RTVuns	Ritonavir (unspecified dose)
RTVl	Ritonavir (low dose)
SAE	Serious Adverse Event
TDF	Tenofovir
VL	Viral Load (HIV-1 RNA)
ZDV	Zidovudine

3. Investigators

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4. Other responsible parties

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Carlo Giaquinto:	President **(**PENTA Foundation)

5. Milestones

Milestone	Planned date	Actual date	Comments
Funding contract signed		March 2013	
Final protocol		October 2013	
Registration in the EU PAS register		March 2016	
1st year data merger	January 2014	January 2014	
1st year interim report submission	30 September 2014	15 September 2014	
2nd year data merger	January 2015	January 2015	
2nd year interim report submission	30 September 2015	21 September 2015	
3rd year data merger	January 2016	January 2016	
3rd interim report submission	30 September 2016	14 September 2016	
4th year data merger	January 2017	January 2017	
4th year interim report submission	30 September 2017	21 September 2017	
Final year (5th) data merger	January 2018	January 2018	
Final year (5th) report submission	30 July 2018	30 July 2018	Last-patient-visit date 30 January 2018

6. Rationale and Background

Etravirine (ETR, also known as Intelence®), manufactured by Janssen-Cilag International NV (formerly Tibotec), is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV. It was approved by the EMA in combination with a boosted protease inhibitor (PI) and other antiretroviral medicinal products for the treatment of HIV infection in antiretroviral therapy (ART) experienced paediatric patients aged ≥6 years in March 2013.

The recommended paediatric dose is based on body weight as follows:

- ≥16-<20kg 100mg twice daily
- ≥20-<25kg 125mg twice daily
- ≥25-<30kg 150mg twice daily
- ≥30kg 200mg twice daily (adult dose).

The indication in paediatric patients is based on 48-week analyses of a single-arm, Phase II trial in antiretroviral treatment-experienced paediatric patients (PIANO), evaluating the pharmacokinetics, safety, tolerability, and efficacy of INTELENCE in 101 antiretroviral

treatment-experienced HIV-1 infected paediatric patients from 6 years to less than 18 years of age and weighing at least 16 kg. The study enrolled patients on a stable but virologically failing antiretroviral therapy (ART) regimen, with a confirmed HIV-1 RNA plasma viral load ≥ 500 copies/ml. Sensitivity of the virus to INTELENCE at screening was required. The median baseline plasma HIV-1 RNA was 3.9 $\log_{10}$ copies/ml, and the median baseline CD4 cell count was 385cells/µL.

At week 48, 53.5% of all paediatric patients had a confirmed undetectable viral load <50 HIV-1 RNA copies/ml according to the TLOVR algorithm. The proportion of paediatric patients with <400 HIV-1 RNA copies/ml was 63.4%. The mean change in plasma HIV-1 RNA from baseline to Week 48 was -1.53 $\log_{10}$ copies/ml, and the mean CD4 cell count increase from baseline was 156 cells/µL.

In clinical trials in adult patients the most common (≥ 10%) adverse drug reactions (ADRs) in the ETR group were rash, diarrhoea, nausea, and headache, with rash occurring more frequently in females. The frequency, type and severity of adverse drug reactions in clinical trial paediatric patients were comparable to those observed in the adult trials.

Paediatric HIV infection is mainly acquired vertically, through mother-to-child transmission (MTCT). The European Centre for Disease Prevention and Control (ECDC) and the World Health Organization Regional Office for Europe (WHO/Europe) surveillance have estimated the cumulative number of HIV infected children in the European Union/European Economic Area, comprising of 30 countries, to be 7,032 by end of 2016 (1). The aim of ART in children is to achieve undetectable HIV RNA levels, to maintain viral suppression and thus to allow normal immune function, whilst minimising drug toxicities. Current paediatric and adolescent guidelines recommend the use of cART with at least three drugs, including a dual nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone with a boosted PI or an NNRTI (or an integrase inhibitor, an alternative particularly for treatment-experienced adolescents). Vertically infected children with access to cART have substantially improved health and life expectancy (2-5) and can expect to survive into adult life. Paediatric HIV infection is thus now recognised as a chronic disease, requiring life-long therapy.

The Current Risk Management Plan (RMP) for ETR mentions the following important identified risks for adult and paediatric patients: rash/severe cutaneous reactions, severe hypersensitivity including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), hepatotoxicity, pancreatitis, hyperlipidaemia, coronary artery disorders, development of drug resistance, and drug-drug interactions. Important potential risks include overdose due to medication errors and Immune Reconstitution Inflammatory Syndrome (IRIS).

The RMP identified the need for information on the long-term safety of ETR in children aged <18 years of age as little is known about the long-term and "real life" safety of ETR in HIV-infected children and adolescents. The Committee for Medicinal Products for Human Use (CHMP) has highlighted the need for a post-marketing surveillance study of ETR use in those <18 years of age. Janssen-Cilag International NV contracted the PENTA Foundation/European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) to conduct a pharmacovigilance study of the use and safety of ETR in HIV-infected children and adolescents.

7 Research question and Objectives

The overall aim of the study was to investigate the following research question, using data from the EPPICC network:

What is the long term safety profile of ETR use in children and adolescents with HIV infection?

The study objectives were to:

1) describe the clinical characteristics of patients at the start of ETR-based therapy

2) describe the incidence of DAIDS grade 3 and 4 adverse events for key laboratory markers by duration of ETR use

3) provide the incidence and describe clinical serious adverse events which were considered to be causally related to ETR by duration of ETR use

4) report clinical non-serious adverse events which were considered to be causally related to ETR, where available

5) characterize reasons for discontinuation of ETR

6) provide information on any off-label use of ETR in children (excluding in utero exposure), including in treatment-naive children and those <6 years of age.

8 Amendments and updates

None

9 Research Methods

9.1 Study design

This study pooled individual patient data from longitudinal observational cohorts participating in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC). EPPICC conducts epidemiological research on the prognosis and outcome of HIV-infected pregnant women and children as well as HIV-negative children exposed to HIV in utero. As the participating cohorts record the treatment and care of children with HIV in routine clinical practice, this study provides data on the effect of etravirine in a "real world" setting. The main outcomes of interest in this study were: characteristics of children receiving ETR, DAIDS grade ≥3 laboratory events, adverse clinical events and ETR discontinuations (both numbers and reasons).

9.2 Setting

Sixteen mother-child and/or paediatric cohorts and a single centre cohort of paediatric patients with both parenteral (non-recreational injecting drug use) and perinatal HIV transmission, who participate in EPPICC, provided data for this study (see Appendix 3 for key references for each cohort). [1] Cohorts collaborating in EPPICC who participated in the study and included in this final report are shown below:

- Hospital St Pierre Cohort, Brussels, Belgium
- Italian Register for HIV Infection in Children, Italy
- Polish paediatric cohort, Poland*
- Centro Hospitalar do Porto, Portugal*
- Hospital de Santa Maria/CHLN, Lisbon, Portugal*
- "Victor Babes" Hospital Cohort, Romania
- The City HIV Centre, St Petersburg, Russia*
- The Republican Hospital of Infectious Diseases, St Petersburg, Russia*
- CoRISPE-cat, Catalonia, Spain
- German Paediatric and Adolescent HIV cohort

[1] The Madrid Paediatric Cohort is now included within the Spanish cohort CoRISPE-S. Data from the two Spanish cohorts, CoRISPE-cat and CoRISPE-S, are presented together throughout this report. Data from the three Thai cohorts, two Portuguese cohorts and two Russian cohorts are also presented together by country throughout this report.

• CoRISPE-S, Spain (now including the Madrid Paediatric Cohort Study)

• Karolinska University Hospital, Stockholm, Sweden

• Swiss Mother and Child HIV Cohort Study (MoCHiV), Switzerland

• HIV-NAT, Bangkok, Thailand*

• Khon Kaen University, Thailand*

• Thailand Program for HIV Prevention and Treatment (PHPT) Study Group, Thailand*

• Collaborative HIV Paediatric Study (CHIPS) and National Study of HIV in Pregnancy and Childhood (NSHPC), UK/Ireland

Those with an asterisk (*) were not included in the original protocol, but participated subsequently.

The Rahima Moosa Mother and Child Hospital, South Africa was not in the original protocol, but contributed data on four patients in 2016. This cohort became no longer able to contribute data to this study in 2017 and is no longer participating in the EPPICC pharmacovigilance network. They have been removed from the list.

The European Collaborative Study and the Ukraine Paediatric Cohort Study were in the original protocol but had no eligible patients so were unable to contribute.

Individual participating cohorts were responsible for gaining their own ethics approval (if required for study participation) and complying with local regulatory requirements. All cohorts confirmed that the necessary ethics /regulatory approvals were in place.

9.3 Subjects

For this final report (year 5 of 5) cohorts submitted individual-patient-data to the EPPICC 2018 pharmacovigilance data merger in a similar manner to previous years of the study (2014-2017).
To be included in the study individuals must:

- be HIV-infected paediatric patients aged <18 years
- have been exposed to ETR (either currently or in the past)
- have follow-up outside of a company-sponsored clinical trial

There was no set date of enrolment in this study, therefore all patients who had ever been followed-up in the participating cohorts and who meet the above criteria were included, irrespective of their duration on ETR. Data were administratively censored at 30/01/2018. Safety data for patients participating in company-sponsored DRV trials (TMC114-C212, C228, C230, and C232) or etravirine (ETR) trials (TMC125-C213, C239) and taking ETR have been and will be reported to the EMA in the context of submission files. In this study, periods of time in these trials (where both the entry and exit date for that trial was known) were therefore excluded from the analysis in order to avoid duplicate reporting. In order to do this, the sponsor provided the EPPICC study team with dates of birth and dates of entry and exit into the trial for all trial participants, which were then matched to the EPPICC dataset. Only follow-up time on ETR after the end of the trial was included in this analysis.

9.4 Variables

Data collected on patients receiving ETR included: demographics (date of birth, sex, ethnicity, mode of infection), AIDS events and death during follow up, ART use (including start and stop dates, dosing and reasons for stopping), weight, viral load (HIV-1 RNA) and CD4 measurements at every visit, hepatitis B and C co-infection status, reasons for off-label use of ETR, laboratory test results (biochemistry and haematology), details of all clinical adverse events (AEs) and cohort context data.
Before data were sent to EPPICC, the data were pseudo-anonymised by the cohort.

9.5 Data sources and measurement

Each participating cohort provided data according to a predefined data specification. The data specification for the study followed the HIV Cohorts Data Exchange Protocol (HICDEP) (http://www.hicdep.org) and a Standard Operating Procedure (SOP) was developed (Appendix 4). The HICDEP format is based on a relational structure, and the data was collected in a series of tables, which are described in the SOP, together with the lookup tables for the codes used.
The study team, which includes a database manager with extensive experience of designing and maintaining HIV databases for clinical trials and cohort studies, obtained the data from the participating cohorts through an electronic data merger of datasets according to the SOP. Data were subjected to a battery of logical and consistency checks in order to assess accuracy and completeness. Any data queries arising were then discussed and resolved with the relevant cohort data managers, before data were pooled into a joint study database.

9.6 Bias

EPPICC cohorts vary widely with respect to national coverage. The CHIPS (UK/Ireland) cohort has near complete coverage of all children diagnosed with HIV in both countries. The Italian Register includes 80-90% of HIV-infected children in Italy. In contrast, some countries (e.g. Sweden and Russia) only contribute data on patients receiving care at tertiary specialist centres. The characteristics of these patients may differ from the HIV-positive population of that country as a whole. The ART regimens they receive may also not be representative. EPPICC cohorts include both children born in the country of care and those born abroad (commonly sub-Saharan Africa). Those born abroad tend to be older at first presentation to care. They are likely to include a higher proportion of long-term non progressors who have survived the high-mortality period of early childhood without ART. This could potentially lead to selection-bias.

The majority of children included in the ETR study came from Spain (40%) and Italy (20%), whose characteristics and outcomes may not be generalizable to all settings.

9.7 Study size

In total there were 182 individuals starting ETR when <18 years of age on whom EPPICC cohorts provided data (21 of whom were ever in a company-sponsored clinical trial). We excluded five individuals who had no follow-up time outside a company-sponsored clinical trial. Of the 177 included, 142 started in the pre-approval period (before the EMA ETR paediatric licensing date of March 2013). Of these 142 there were 16 with follow-up in a company-sponsored clinical trial (no patients who started post-approval had follow-up in a clinical trial).

9.8 Data transformation

The definitions and coding of variables included in the EPPICC database are described in the SOP (Appendix 3). The following variables were further categorised: age at ETR start (< 6, 6-8, 9-11, 12-14 and 15-<18 years), duration of ART before ETR start (<2, 2-4, 5-9 and ≥10 years) and viral load (≤400, >400 copies/ml).

For laboratory data (biochemistry and haemotology) test results were classified by their DAIDS grading (normal, grade 1, grade 2 and grade ≥3 (3 and 4 combined)).

9.9 Statistical methods

9.9.1 Main summary measures

Counts, unadjusted proportions and medians with interquartile ranges are presented. Where proportions were compared, p values are reported.

Person-years of follow-up are included in the laboratory data tables. Rates of each DAIDS grade (1, 2, ≥3) with 95% CI are reported for laboratory markers where sufficient data were available (n≥20).

9.9.2 Main statistical methods

Information on demographic characteristics, ART history, and adverse events occurring whilst on ETR were summarised separately for treatment-experienced patients who started ETR aged ≥6 years at a recommended dose for weight (on-label) and those who did not (off-label), as listed below. This classification was based on the patient's age, weight, dose, dosing frequency and prior ART treatment on the day of first reported ETR exposure.

'Treatment-experienced' patients were defined as those with previous exposure to a protease inhibitor (PI), nevirapine (NVP) or efavirenz (EFV). Treatment-experienced patients aged 6-<18 years were classified in the on-label group if they were taking a licensed dose or were within a window of ±20% of the licensed dose at the start of ETR (group i). Patients with off-label use were defined as: those aged 6-<18 years who started on an unlicensed dose for their weight (group ii), those who did not meet the above definition of treatment-experienced (group iii), and those aged <6 years at start of ETR (group iv). The final group of patients were aged 6-<18 years and treatment-experienced but with missing weight and/or dose data at start of ETR (group v). Children were considered to have a missing weight if there was no weight recorded within the three months prior to or following the start date of ETR. A dose was considered missing if no dose was recorded on the start date (+3 months) of ETR.

Characteristics of patients in the licensed dose group were compared to patients in the missing weight and/or dose group using Wilcoxon rank-sum tests for continuous variables and Pearson's chi-squared test for categorical variables.

- **On-label use group**

  (i) 6-<18 years, treatment-experienced and taking the licensed dose of ETR:

  - ≥16 - <20kg: 100mg ETR b.i.d.
  - ≥20 - <25kg: 125mg ETR b.i.d.
  - ≥25 - <30kg: 150mg ETR b.i.d.
  - ≥30kg: 200mg ETR b.i.d. (adult dose)

- **Off-label use groups**

  (ii) 6-<18 years, treatment-experienced and taking an unlicensed dose

  (iii) 6-<18 years, not treatment-experienced

  (iv) <6 years at start of ETR

- **Missing data group**

  (v) 6-<18 years, treatment-experienced with missing weight and/or dose at start of ETR

Data on the following laboratory tests were collected and analysed: absolute neutrophil counts (ANC); total cholesterol (CHOL); triglycerides (TRIG); alanine transaminase (ALT); alkaline phosphatase (APT); aspartate aminotransferase (AST); total bilirubin (BIL); fasting plasma glucose (FPG); non-fasting plasma glucose (non-FPG); pancreatic amylase (AMY); lipase (LIP); serum high-density lipoprotein cholesterol (HDL) and serum low-density lipoprotein cholesterol (LDL).

Division of AIDS (DAIDS 2014) gradings for paediatric adverse events were used to categorise the severity of results (6), apart from for HDL, where DAIDS gradings are not available and so guidelines from the US National Heart, Lung, and Blood Institute were used instead to categorise levels as 'acceptable' (>45 mg/dL), 'borderline' (40-45 mg/dL) or 'low' (<40 mg/dL) (7). As these categories are not DAIDS gradings, HDL results are presented in the text rather than in table 3 (where other laboratory results are presented by DAIDS grade). For each test type, results by severity are presented as numbers and rates.

In the first two annual reports (2014/2015), laboratory markers were categorised based on the DAIDS 2004 Classification (8). This year, like the last two years, all events (historical and more recent laboratory measures) have been classified using the revised DAIDS grades published in November 2014 (version 2) (6).

All children ever exposed to ETR with ≥3 month's follow-up after the start of ETR and with laboratory data available are included in the laboratory analysis. An episode on ETR was defined as a period of ETR exposure. If a child stopped ETR for less than 30 days then subsequently restarted ETR, this was considered to be part of the same episode. If a child stopped ETR for >30 days then subsequent ETR exposure was considered as a new episode. For each laboratory test the number of episodes are reported by DAIDS grade in four distinct time periods: (a) 12 months pre-ETR exposure, (b) 0-<12 months after start of ETR, (c) 12-24 months after start of ETR and (d) >24 months after start of ETR.

For each period after the start of ETR, incidence rates of DAIDS events per 100 person-years (PY) are provided if there are sufficient numbers of patients in follow-up (n=≥20) in each group to provide a meaningful estimate. As these estimates aim to reflect the incidence of adverse events whilst exposed to ETR, laboratory tests conducted >30 days after ETR discontinuation were excluded from all analyses. In summary, for each episode on ETR (if they had ≥3 months of follow-up after the start of ETR and laboratory test undertaken) patients contributed person-years of follow-up for the duration of ETR exposure and their data was censored at 30 days after discontinuation. This ensured all potentially relevant events were captured.

Amongst patients with multiple episodes on ETR, each episode was considered independently and patients became at risk of events at the start of each ETR episode (i.e. they re-entered at month 0). Follow-up time was censored at the highest grade event within each time period (with grades 3 and 4 counted together) in order to avoid an artificial overestimation of rates due to increased testing during an event. This was with the exception of overall rates, where total patient years of follow-up were censored at the first event in each time period on ETR (0-<12 months after start of ETR, 12-24 months after start of ETR and >24 months after start of ETR). A child with progressively more severe laboratory test results reported within one time period may therefore have contributed a maximum of one event in each of the mild (grade 1), moderate (grade 2) and severe/potentially life-threatening (grade 3/4) categories on ETR. In the first two annual reports (2014/2015) each episode on ETR were considered as a continuation from the previous episode, whilst in this final report, like the last two years, they are considered to be independent and therefore a patient with multiple episodes on ETR can contribute more than one DAIDS event in each time-period.

The 12-months pre-ETR period provides a summary of the frequency and severity of adverse events in this population prior to start of ETR. However, rates are not provided for this period due to the complex ART treatment histories of many patients starting ETR which would make them difficult to interpret. In addition, the number and proportion of patients with DAIDS events after start of ETR are presented for the missing weight and/or dose group, but rates are not presented as they would be difficult to interpret without the weight/dose information.

Clinical adverse events (AEs) which are considered potentially related to ETR are reported for all patients subsequent to ETR exposure, irrespective of duration on the drug or duration since discontinuation of ETR. Events are coded using an in-house coding system at the

Clinical Trials Unit, validated in international trials, which codes AEs according to the body system affected (similar to MedDRA).
In addition, information on all serious adverse events (SAE) is also captured. An event is classified as an SAE when it:

- results in death
- is life-threatening (defined as any event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event that may not be immediately life threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or require intervention (e.g. medical, surgical) to prevent one of the other serious outcomes listed in the definition above).

Clinical adverse events are presented according to whether they were considered causally related to ETR by the treating physician. All adverse events reported by the clinician as definitely, probably or possibly related to ETR are shown in Tables 5a-e (Appendix 1).

All serious adverse events not considered causally associated with ETR or where the probability of a causal association was reported as remote/unlikely are presented in Table 6a-e. Serious adverse events where the probability of a causal association with ETR was unknown or not available are presented in Tables 7a-e (Appendix 1).

The frequency of and reasons for treatment discontinuations are presented in Table 8, which includes only patients who permanently discontinued ETR (i.e. excludes patients who discontinued and then re-started ETR), irrespective of duration on ETR. For patients with multiple episodes on ETR, the reason and duration to discontinuation is based on their final episode on ETR. Reasons for discontinuation of ETR are categorised as follows: lack of efficacy, safety, other reasons such as patient's wish or treatment simplification, and unknown reasons. This final report provides further information on those patients who discontinued ETR for safety reasons (Table 8b, Appendix 1)

To assist in the interpretation of the results, a summary of key contextual characteristics of each cohort overall (for all paediatric patients regardless of ETR exposure) is provided in

Tables 9-10 (Appendix 1), including the number of paediatric patients followed in each cohort and their current ART treatment status.

Descriptive statistics, such as mean and medians were employed for each of the data tables.

Appendix 2 summarises data changes occurring over the course of the study including new data reported since last year and also provides a short narrative for all serious adverse events (Appendix 2, Table 6).

9.9.3 Missing values

No imputation of missing values was undertaken. During the data cleaning individual cohorts were contacted by the data manager and asked to provide missing data where available.

9.9.4 Sensitivity analyses

Not applicable.

9.9.5 Amendments to the statistical analysis plan

The statistical analysis plan was not amended during the course of the study.

9.9.6 Quality control

As stated above in section 9.5, data were subjected to a battery of logical and consistency checks in order to assess accuracy and completeness. Any data queries arising were discussed and resolved with the relevant cohort data manager, before data were pooled. Further data checks were also conducted by the study statistician prior to data analysis.

10 Results

10.1 Participants

Data are presented for all 177 EPPICC paediatric patients (to 30/01/2018) meeting the inclusion criteria. The earliest date of ETR initiation was 15th November 2006 and the latest date was 5th October 2017. Data were administratively censored at 30/01/2018. There were 13 new patients this year: four from Italy, five from Spain, three from the UK/Ireland and one from Portugal.

The 177 patients were subdivided into the following five mutually exclusive groups based on their age, weight, dose and ART history when they started taking ETR:

- **On label**

  (i) n=108 treatment-experienced patients aged 6-<18 years taking a licensed dose of ETR

- **Off label (unlicensed, treatment inexperienced and <6 years of age) (n=23)**

  Unlicensed
  (ii) n=10 treatment-experienced patients aged 6-<18 years, taking an unlicensed dose

  Treatment inexperienced (no record of prior PI, NVP or EFV)
  (iii) n=7 patients aged 6-<18 years who were not treatment-experienced

  (iv) n=6 patients aged <6 years at start of ETR

- **Missing weight and/or dose**

  (v) n=46 patients aged 6-<18 years and treatment-experienced, with missing weight and/or dose data

Of these 177 patients, 142 started ETR prior to March 2013 (the EMA paediatric approval date for ETR) and 35 started in the post-approval period. Of the 142 starting pre-approval: 91 (64%) started on a subsequently licensed dose, 5 (4%) on a subsequently unlicensed dose, 5 (4%) were treatment-inexperienced, 3 (2%) were <6 years of age and 38 (27%) had a missing weight and/or dose. Of the 35 starting post-approval: 17 (49%) started on a licensed dose, 5 (14%) on an unlicensed dose, 2 (6%) were treatment-inexperienced, 3 (9%) were <6 years of age and 8 (23%) had a missing weight and/or dose.

The quality of data submitted by the participating cohorts improved between 2015 and 2016, remaining stable thereafter. The percentage of patients with missing weight and/or dose data at the start of ETR is now 26% (46/177). Confirmation of weight/dose data has resulted in six patients who were in the missing weight/dose group last year being reclassified this year, five to the licensed dose group and one to the unlicensed group (see Appendix 2 Table 3). However, six new patients have this year entered the missing weight/dose group.

Overall, seven patients (4%) had insufficient follow-up data available (<3-months) after starting ETR to allow for inclusion in the analyses of laboratory adverse events (Figure 1),

but all are included in the cohort description and clinical adverse events analyses (Tables 1, 2, 5-10). Four of the seven patients had <3 months follow-up because they transferred to adult care soon after starting ETR. For the remaining three patients, one patient died within 3-months of starting ETR (HIV related metastatic adenocarcinoma, Appendix 1, Table 7a, patient #2, previously reported), one patient was still on ETR at last visit but had no further follow-up and one patient moved to another clinic. Of the 170 patients with ≥3-months of follow-up, 153 had laboratory data available (Figure 1).

10.2 Descriptive data

Tables and figures referred to in this section can be found in Appendix 1. Characteristics of the 177 patients who had ever taken a dose of ETR are presented in Table 1. Overall, 54% of patients were male, 36% were white, 12% were black African, 28% of other ethnicity and 24% of unknown ethnicity. Virtually all were infected with HIV through mother to child transmission (MTCT) (98%). Four patients (3%) were co-infected with hepatitis-C, and three (2%) with hepatitis-B. Just under half of the patients (n=78, 45%) had ever been diagnosed with AIDS, 77 (99%) of which occurred prior to the date of ETR start (data not shown). Overall, three patients died during the follow-up time, the same as reported in the last three reports with no new deaths (Table 1).

Of the 108 patients on the licensed dose, 40% were from the Spanish cohorts, 20% from Thailand and 19% from the UK/Ireland. Overall 37% were of white ethnicity and 42% had ever had an AIDS diagnosis during follow-up. Two of the three deaths were in this group (Table 6a #1/7a #2, both deaths previously reported).

Of the 10 patients who started ETR on an unlicensed dose (one new patient and one with improved data moved into this group this year), four were from the Swiss and four from the Spanish cohorts (36% of total each) with the UK/Ireland and Russian cohorts contributing one patient each (9% of total each). Seven patients had ever had an AIDS diagnosis and one patient died during follow-up (Table 6b #1, the death was previously reported). A summary of the reasons why patients were classified as on an unlicensed dose and why clinicians chose to use ETR in this way (where known) are shown in Table 1b (along with information for the other off-label categories).

Seven patients (one new this year) did not meet the definition of treatment-experienced at ETR start; five were from the Italian cohort and one each from the Thai and Spanish cohorts. Two of the patients in this group had ever been diagnosed with AIDS. Details of their prior treatment history are reported in Table 1b.

Six patients (one new this year) had started ETR aged <6 years, four were from Italy and two from Spain. Three children had ever had an AIDS diagnosis. Further details of their age and ETR dose are shown in Table 1b.

Of the 46 patients classified as missing weight and/or dose, 35 were missing weight, four were missing dose and seven were missing both weight and dose data (data not shown). Of these 46 patients, six were also missing dosing frequency. Two of those missing frequency were also missing weight and dose and four were missing only dose. Spanish cohorts contributed 46% of patients, 35% came from the Italian cohort, 7% from Portuguese cohorts with the remaining 12% coming from Thailand, the UK/Ireland, Russia and Switzerland (Table 1). 57% of patients were male and 51% ever had an AIDS diagnosis. A column for p-values is included in Table 1, comparing the characteristics of patients in the licensed dose group with those in the missing weight and/or dose group. There were some differences in the distribution of patients across the participating cohorts and ethnic groups, all other characteristics were similar. Those missing weight/dose patients were more likely to be from Italy (and less likely to be from Thailand or the UK/Ireland) and to be of unknown ethnicity.

A total of 13 new patients contributed data this year. The total person-years (PY) of follow-up occurring since the last report was 112 PY (Appendix 2, Table 1, please see the footnote regarding a data correction since last year). Additional information on annual changes in the number of patients included in the reports since the first interim report five years ago can be found in Appendix 2 Table 2 (please note that drop-out numbers including those lost to follow-up and transferring to adult care have been amended this year due to improved classification). Table 3 of Appendix 2 summarises the changes in the number of patients in each dosing category for each year of the report and reasons for those changes including movements between groups.

Table 2 (Appendix 1) presents ART-related characteristics of patients at ETR start, as well as during subsequent follow-up.

Within the licensed dose group, patients were heavily treatment-experienced at start of ETR. The median age at the start of any ART regimen was 2.2 years [IQR, 0.5-6.3] and the median age at start of an ETR-containing regimen was 14.6 years [IQR, 12.6-15.7]. The median duration of ART exposure prior to starting an ETR-containing regimen was 11.1years [IQR, 7.8-12.5].The majority of patients in the licensed group (53 %) had received ≥8 ART drugs before starting ETR. The median CD4 count at ETR start was 463 [IQR, 294-657] cells/µL. Amongst patients with a viral load sample available, the proportion with viral load suppressed ≤400 copies/mL increased from 50% (45/90) at start of ETR to 84% (69/82) at

12-months after start of ETR (although there were fewer patients in the latter group). The median time on an ETR-containing regimen was 40.4 months [IQR, 17.1-64.0] in the licensed dose group.

The 10 patients in the unlicensed dose group (two new to the group this year) had a median duration on ART before start of ETR of 13.3 years [IQR, 9.2-15.6] and median age at starting ETR of 14.9 years [IQR, 13.7-16.3]. Five of the ten (50%) had received ≥8 ART drugs before starting ETR. Median duration on ETR was 12.2 [IQR, 4.8-22.7] months.

Seven patients (one new this year) were not considered treatment-experienced at start of ETR (with previous exposure to NRTIs or low dose RTV only). The median duration on ART at start of ETR was 10.1 [IQR, 5.6-13.5] years, with no documented prior exposure to PIs, NVP or EFV. The median age at start of ETR was 12.9 [IQR, 11.8-15.6] years, and the median duration on ETR was 54.7 [IQR 35.2-73.2] months.

Six patients (one new this year) started ETR aged <6 years, the median age at start of any ART was 0.2 [IQR 0.1-1.1] years and the median age at start of ETR was 4.5 [IQR 2.2-5.0] years. Two of the six children (33%) had been exposed to ≥8 ART drugs before starting ETR. Patients in this group had been on ETR for a median of 28.4 months [IQR, 13.9-40.6] at last follow-up.

Data on the characteristics of the 46 patients with missing weight and/or dose were compared with those of the licensed dose group (last column of Table 2). Higher median CD4% at ETR start was seen in the missing group (23% vs. 18%). The missing group was also more treatment-experienced at ETR start (63% vs 53% had been exposed to ≥8 ART drugs).

The cohort as a whole accrued 608 patient-years of follow-up (PYFU) after ETR start (Table 2). A total of 504 PYFU were reported last year, but this has now been corrected to 496, because eight PYFU reported last year have been corrected (the cohort provided more accurate follow-up end dates this year). A summary of data contributed by new and existing patients are shown in Appendix 2, Table 1.

At ETR start, 90% of patients combined ETR with a PI, 32% with an integrase inhibitor, 5% with a fusion inhibitor, 5% with a C-C chemokine receptor type 5 (CCR5) inhibitor and 0.6% with another NNRTI (data not shown).
Tables 9 and 10 provide characteristics of the cohorts participating in this study (grouped by country), to aid interpretation of study findings. They provide information on all patients from contributing cohorts regardless of whether patients have been exposed to ETR or not. The UK/Ireland, Russia, Thailand and Italy have the greatest numbers of patients <18 years in current follow-up (with 713, 653, 312, 316 respectively) (Table 9). The hepatitis-C virus

(HCV) sero-status was available for 1888 patients. Of those tested 97 (5%) were HCV seropositive, of whom: 3 were from Thailand, 68 were from Russia (where 10% of patients with data available were seropositive), 19 were from the UK/Ireland and five were from Spain. The overall HCV sero-prevalence maybe over-estimated due to targeted testing of patients known to be exposed. Hepatitis-B virus (HBV) status was available for 2052 patients of which 44 (2%) were HBV positive. Of these 44 HBV-positive patients 25 were in the UK/Ireland cohort and six were from Russia.

Table 10 shows that approximately 28% of patients aged <18 years and in current follow-up were taking an NNRTI + NRTIs and 42% were taking a boosted PI + NRTIs with 25% of patients on a range of other regimens. The percentage of patients not currently on ART in each cohort varied from 0% in Poland and Romania to 21% in Switzerland.

10.3 Outcome data

10.4 Main results

The three main outcomes of interest were laboratory adverse events (AEs), clinical AEs and discontinuations (both number and reason).

10.4.1 Adverse Events (Laboratory)

Laboratory data for periods on ETR were available for 97 of the 108 patients aged 6-<18 years on the licensed dose who had ≥3 months of follow-up (Figure 1).

Table 3a provides information on laboratory tests undertaken on patients on a licensed dose of ETR. The table includes (for each laboratory test): the total number of episodes of ETR exposure, the number of test results available and the number of Division of AIDS 2014 gradings of each severity (9). The number of patients/episodes with ≥1 test result in each DAIDS grade are presented by duration of time prior to starting ETR and on ETR (12 months pre-ETR, <12 months on ETR, 12-24 months on ETR, >24 months on ETR). The rates of first abnormal test for episodes in each DAIDS category are shown per 100 patient-years. In addition, the number and proportion of tests which were grade ≥3 is also presented. In general the number and rate of grade ≥3 episodes was low.

Some cohorts sent data corrections for previously reported laboratory data this year. In previous reports some normal laboratory values had been incorrectly classified as abnormal, due to incorrect units. This has now been corrected and has led to a reduction in the numbers of DAIDS events for some laboratory markers. Where a previously reported grade 3 or 4 event has been confirmed as incorrect, it has been removed from the relevant Table 3 and 4 with a footnote explanation.

There were 1065 alanine transaminase (ALT) test results, reported for 96 patients with 98 episodes on ETR. There were three grade 2 events, all during the first 12 months of ETR (rate 4 per 100 PY [95% CI, 1-12] during that time period). There was one grade ≥3 episode which also occurred in the first 12 months episode.

A total of 294 pancreatic amylase (AMY) tests were performed for 38 patients each with a single episode on ETR. Eleven grade 2 events were distributed across the time periods, with an overall rate of 6 per 100PY [95% CI, 2-12]. There were two grade ≥3 events, one in the 12-24 months and one in the >24 months period (after ETR start), with an overall rate of 1 per 100PY [95% CI, 0-5].

There were 1049 absolute neutrophil count (ANC) test results during 97 episodes of ETR exposure in 95 patients. During follow-up, one grade 2 and two grade ≥3 events occurred, all within the 12-months of starting ETR.

A total of 580 alkaline phosphatase (APT) test results were reported during 64 episodes of ETR exposure in 63 patients. Eleven grade 2 events occurred distributed across the time periods (with seven first events across all three time periods counted in the total row). One grade ≥3 events occurred, in the first 12-months of ETR with an overall incidence rate across all time periods of 0.4 per 100 PY [95% CI, 0-2].

Aspartate aminotransferase (AST) tests totalled 694 during 82 episodes in 80 patients. Three grade 2 events occurred, one in the <12 months period and two in the >24 months category. There were no grade ≥3 events.

In 71 patients, 646 bilirubin (BIL) tests were recorded during 73 episodes on ETR. There were two grade 2 events both occurring in the >24 month period. There were also two grade ≥3 events, both in the <12 month time period with an overall incidence rate of 1 per 100 PY [(95%, CI 0-3].

There were 934 total cholesterol (CHOL) results for 96 patients during 98 episodes of exposure to ETR. As reported last year, rates of mild and moderate (grade 1 and 2) CHOL results were relatively high in the first and second year of ETR (especially for grade 2 events in the <12months and 12-24 month after ETR start period), with a decline thereafter. There were 83 grade 2 events with an incidence rate of 52 per 100 PY [95% CI, 35-74] in the first 12-months increasing slightly to 55 per 100 PY [95% CI, 36-80] after 12-24 months and decreasing to 21 per 100 PY [95% CI, 14-30] after 24 months on ETR. However, there were low rates of grade 3 and 4 CHOL events, with two events occurring within 12

months of starting ETR and one after 24 months giving an overall incidence rate of 1 per 100 PY [95% CI, 0-3].

During follow-up time there were six grade 2 results reported for fasting plasma glucose (FPG) (686 test results available for 74 patients during 76 episodes) giving an overall incidence rate of 2 per 100 PY [95% CI, 1-5]. There were no grade ≥3 events.

Amongst 569 low-density lipoprotein cholesterol (LDL) test results reported for 79 patients with 80 episodes on ETR, there were 53 grade 2 events and four grade ≥3 test results across the time-periods. Overall rates were 15 per 100 PY [95% CI, 10-21] for grade 2 events and 1 per 100 PY [95% CI, 0-4] for grade ≥3 events.

There were no grade 2 or grade ≥3 test results for lipase (LIP) (134 test results available for 20 patients/episodes). There were no grade ≥3 results for non-fasting plasma glucose (non-FPG) and only one grade 2 results after 131 tests in 17 patients/episodes.

Of the 920 triglyceride (TRIG) test results reported for 96 patients with 98 episodes on ETR, there were 28 grade 2 and four grade ≥3 test results across the time-periods, with an overall rate of 7 per 100 PY [95% CI, 4-11] and 1 per 100 PY [95% CI, 0-3], respectively.

In total 702 HDL test results were available for 85 patients during 87 episodes on ETR. For 49 patient during 50 episodes a borderline HDL result occurred (21 patient/episodes were within 12 months of ETR start). During 49 episodes in 47 patients a low HDL result was recorded (26 patients in 28 episodes were within 12 months of ETR start).

Table 3b presents laboratory data for the ten patients aged 6-<18 years on an unlicensed dose of ETR with laboratory data available and ≥3 months follow-up. Rates are not presented due to the small number of patients. There were five grade 2 and one grade ≥3 test results overall. A total of 42 ANC tests were undertaken for six patients/episodes and there was one grade 2 test result (17% of children tested). Of the 46 tests undertaken for APT in seven patients/episodes there was one grade ≥3 test result (14% of children tested). There were 53 cholesterol tests undertaken in ten patients/episodes, with two grade 2 test results (20% of children tested) and no grade ≥3 events. Of the 31 FPG tests undertaken in six patients/episodes, there was one grade 2 event (17% of children tested) and no grade ≥3 events. For TRIG, one grade 2 test result was reported (10% of the children tested) during 53 tests in 10 patients/episodes. HDL test results were available for ten patients/episodes), four patients/episodes had borderline HDL results and five patients/episodes had low HDL (47 test results were available).

Table 3c summarises the laboratory data for the seven children who were not treatment-experienced and who had laboratory data available and ≥3 months follow-up. There were nine grade 2 events and one grade ≥3 events. Of the 39 CHOL tests undertaken in six patients/episodes there were three grade 2 test results (50% of the children tested). There were 28 FPG tests undertaken in six patients/episodes, one test previously classified as grade ≥3 was corrected this year and so no abnormal results were observed. In total, 30 LDL test were undertaken in six patients/episodes, of which four tests were grade 2 (67% of children tested) and no tests were grade ≥3. There were 40 TRIG tests taken in six patients/episodes, one of which had a grade ≥3 event (17% of children tested). For HDL, 30 tests were undertaken in six patients/episodes; three patients/episodes had borderline HDL results and three had low HDL.

Table 3d presents data for the five children aged <6 years at ETR start with laboratory data available and ≥3 months follow-up. There were six grade 2 events and one grade ≥3 event. Grade 2 events occurred for: CHOL (34 tests, five patients/episodes with a grade 2 event in three (60%) of children tested), LDL (30 tests, five patients/episodes with a grade 2 event in two (40%) children tested) and APT (25 tests, four patients/episodes with a grade 2 event in one (25%) of the children tested). There was also a single grade ≥3 event for APT (25% of children tested). There were 33 HDL tests available for five patients/episodes, of which one had borderline HDL results and four had low HDL results.

Table 3e presents data from the 34 children missing dose and/or weight who had laboratory data available and ≥3 months follow-up. There were 46 grade 2 and ten grade ≥3 test results. A single grade 2 and/or grade ≥3 event occurred for the following parameters: AMY (37 tests, five patients/episodes, one grade 2 event (20% of children tested)), ANC (298 tests, 33 patients with 35 ETR episodes, with one grade 2 event (3% of children tested)), APT (158 tests, 19 patients with 21 ETR episodes with one grade 2 event (5% of children tested)). Two grade 2 events and two ≥3 events occurred for ALT (291 tests, 32 patients with 34 ETR episodes (both 6% of children tested)). Two grade 2 events occurred for both AST (215 tests, 25 ETR episodes in 23 patients (8% of children tested)) and BIL (184 tests, 24 ETR episodes in 22 patients (8% of children tested)), there were also three grade ≥3 episodes for BIL (13% of children tested). A relatively high level of grade 2 CHOL events occurred in those missing dose for weight with 16 grade 2 laboratory results (288 tests, 34 episodes in 32 patients (47% of children tested)), there was one grade ≥3 CHOL episode (3% of children tested). There were 13 grade 2 LDL test results (191 tests, 23 ETR episodes in 21 patients), accounting for 57% of children tested and two grade ≥3 test results (9% of children tested). Of the 283 TRIG tests undertaken in 32 patients with 34 ETR episodes there were eight grade 2 events (24% of patients tested) and two grade ≥3 events (6% of children tested). In total, 198 HDL test results were available for 25 patients during 27 episodes on ETR. Of

these 10 patients (12 episodes) had borderline HDL results and 14 patients/episodes had a low HDL result.

Tables 4a-e present further details of patients in each dosing group with DAIDS grade ≥3 results. Any changes to these tables since last year, as a result of data corrections by the cohorts, are included in the footnotes.

Table 4a provides details of treatment-experienced patients aged 6-<18 years starting ETR on the licensed dose. Of the 16 patients with a grade ≥3 event whilst on ETR included this year, 14 were previously reported last year (#1-14).

Two patients had grade ≥3 hyperbilirubinemia (#1 and #4) both reported last year. One of the two children (#1) was also taking atazanavir at the time of the event, which is known to raise plasma concentrations of unconjugated bilirubin (10). Both patients had normal test results following these events, both of whom later discontinued ETR. Patient #1 discontinued all drugs about 5.5 months later due to lipodystrophy, and patient #4 discontinued ETR eight months after the elevated BIL result due to virological failure. Grade ≥3 AMY test results were reported for one patient from the UK/Ireland (#2). For this patient four grade 3 and one grade 4 results were reported, with the first abnormal result occurring seven months after starting ETR; amylase levels were not reported to have normalised (no further data available), but this patient also had grade 3 hypercholesterolemia which did resolve and this patient remained on ETR. Two additional patients had grade ≥3 hypercholesterolemia. One patient from the Belgian cohort (#5) had a grade 3 hypercholesterolemia nearly three years after starting ETR and did not have a subsequent normal value, but continued on ETR. An Italian patient (#13), had two grade 3 CHOL test results seven and eight months after starting ETR and four grade 3 LDL test results; this patient had no normal result subsequently for both CHOL and LDL and ETR was stopped over two years after starting at the physician's decision.

Two patients (#3 and #8), both reported last year, had grade ≥3 neutropenia and both had a subsequent normal ANC result and continued on their ETR-containing regimen (one is still on ETR, the other stopped four years later to simplify treatment). One patient (#7) had a single grade 3 APT test result, with a subsequently normal value and remained on ETR. Three additional patients (#6, #9 and new patient #16) had grade ≥3 LDL test results. Patient #6 had no further tests reported and transferred to adult care. Patient #9 had no subsequently normal tests reported and stopped ETR over 3.5 years later due to treatment simplification. Patient #16 had no subsequently normal tests, but is still on ETR.

Grade ≥3 TRIG test results occurred in four patients (#10, #11, #14 and #15), including one new event (#15) this year. Two of these patients had subsequently normal values (#11 and

#15), one of whom went on to stop ETR due to treatment failure and one who remains on ETR. Two patients did not have subsequent normal values (#10 and #14), one patient was lost to follow-up and one stopped ETR to simplify treatment. One patient from UK/Ireland (#12) had six grade ≥3 ALT test results (one grade 3 and five grade 4, all within the first month of ETR); a subsequently normal value was reported but ETR was discontinued one month after the event due to a hypersensitivity reaction.

In the unlicensed group, one grade 3 test result was reported for APT in a patient from Russia (#1, Table 4b). Normal values were subsequently reported. The patient remained on ETR for over two years following the APT event before discontinuing ETR due to treatment failure.

There was one grade ≥3 test results in one patient in the treatment inexperienced group (Table 4c, #1). This patient experienced a grade 3 TRIG test result, had a subsequently normal value and stopped ETR for reasons unrelated to the drug more than four years after the event.

One Italian patient in the age <6 years at start of ETR group was reported to have had a grade 3 APT result and the patient discontinued ETR four months after the abnormal APT result due to toxicity (Table 4d, #1).

In the missing weight and/or dose group (Table 4e) there were eight events, including one new event reported this year (#8). Italian patient #1 had one grade 3 ALT test result ten days after starting ETR, with the value subsequently returning to normal. This patient discontinued ETR 26 months later for unknown reasons. A Spanish patient (#2) experienced hyperbilirubinemia with nine (updated from the seven reported last year) tests being grade 3. The first grade 3 test results occurred about 19 months after starting ETR, a subsequently normal test was reported and the patient remains on ETR. Patient #7 also had a (single) grade 3 test result for BIL with a subsequent normal value and the patient remains on ETR.

Grade 3 LDL test results are reported for two patients (#3 and #6). One of these patients (#3) had no subsequently normal result and stayed on ETR until transfer to adult care about three years later. No further test results for LDL were reported for patient #6 who is still on ETR. This patient also had one grade 3 CHOL test result on the same day as the LDL result, with no subsequently normal CHOL results. Abnormal TRIG results were reported for two patients (#4 and #5) who both had a single grade 3 test result more than a year after starting ETR. Neither patient had a subsequent normal result and both patients stopped the drug (one due to virological failure and the other for reasons unrelated to treatment).

10.4.2 Adverse Events (Clinical)

All clinical adverse events which were considered by the clinician to be at least possibly causally related to ETR are included in the Table 5a-e. All serious clinical adverse events not thought to be causally related to ETR or where the association with ETR was undesignated or unknown are described in Table 6a-e and Table 7a-e, respectively. A detailed narrative of all serious adverse events is provided in Appendix 2.

Table 5a presents eight clinical adverse events which were considered to be at least possibly causally related to ETR in the licensed dose group. All of the events were previously reported last year. The first event, from Italy (#1) was a rash which resolved and the patient remained on ETR. It was not reported whether the rash was considered to be serious or not and it was thought to be possibly linked to ETR. The second patient from Spain (#2) had a generalised hypersensitive reaction/urticaria, which was not considered to be serious, diagnosed 24 days after ETR start; ETR was discontinued and the event resolved. A third case in a female patient from Spain (#3) has been confirmed by the cohort to have been Stevens-Johnson syndrome. The event was considered serious but not life-threatening and was diagnosed six days after starting ETR when the drug was discontinued and the condition resolved after about six weeks. The patient was also taking darunavir at the time which has also been linked to Stevens-Johnson syndrome. In the two latter cases, the events were considered by the clinician to be probably linked to ETR. A patient (#4) from the UK/Ireland was confirmed to have experienced Stevens-Johnson syndrome one month after starting ETR and the event was considered to be life threatening and possibly associated with ETR. This event resolved five days after it was first reported which was six days after ETR was stopped due to a hypersensitivity reaction. This patient had also been taking darunavir until the day before the event. A Spanish female patient (#5) experienced a rash and erythema four days after starting ETR. The event was not considered to be serious, but was thought to be probably due to ETR administration and the event resolved within four weeks when ETR was stopped by the clinician due to hypersensitivity. Three other clinical events reported were all from Spain (#6, #7 and #8) and all were rash/erythema. Two of these (#6 and #7) were not considered serious and one (#8) was of unknown seriousness. All three events were reported as definitively causally linked to ETR. Two of the events were reported to have resolved (#6 and #7) and none of these patients discontinued ETR due to the event. Two of these three patients subsequently discontinued ETR (one for “other” causes not related to the drug and one for virological failure) whilst one is still taking ETR.

No clinical adverse events considered at least possibly causally related to ETR were reported this year amongst the other groups (Table 5b-e): the unlicensed dose group (clinical data available in 10/11), the treatment inexperienced group (clinical data available in 2/7), those

with missing weight and/or dose (clinical data available in 29/46) and patients <6 years of age (clinical data available in 2/6).

Tables 6a-e presents serious AEs by dosing group which were reported by the clinician as unlikely to be or not causally related to ETR. Overall seven patients had SAEs reported as unlikely to be/not causally related to ETR. Five of these patients were in the licensed dose group (Table 6a) one event was newly reported this year (Table 6a #5 from Thailand). One patient was in the unlicensed dose group (Table 6b) and one in the missing weight and/or dose group (Table 6e).

Table 6a provides details of the five serious adverse events in the licenced group not thought to be causally associated with ETR. The first patient (#1), reported last year, was a 13 year old female Spanish individual who died. The cause of death was stated as an AIDS-defining event diagnosed on the date of death. This patient had been diagnosed with two other AIDS-defining events prior to this (HIV wasting syndrome three years before death, and leishmaniasis 2 years before death). Etravirine was initiated 8.9 months prior to death and was discontinued 2.5 weeks before death, upon physician's decision. A detailed narrative is provided in Appendix 2. The second patient (#2), a female Thai patient, experienced anaemia which was thought to be life threatening, but it resolved and the patient remained on ETR. A third male patient from Germany (#3) had a number of adverse events all considered serious but none thought to be life-threatening. An episode of nausea and vomiting occurred after nine months on ETR, two weeks later the child experienced pyrexia and gastro-intestinal disease, with a further episode of indigestion/oesophageal reflux/gastritis more than two years later. All these adverse events resolved and the patient remained on ETR. The fourth was a Thai female patient (#4) with abdominal/epigastric pain. The event occurred more than a year after starting ETR and resolved five days later. The event was thought to be serious but not life threatening and the patient remains on ETR. The new event this year was a cardiovascular event caused by ergotism (not related to ETR) that occurred in a Thai patient (#5*). This event was diagnosed more than 4.5 years after starting ETR, it resolved and the patients is still on ETR.

The second death was in the unlicensed group (Table 6b) and was in a male patient from Spain who died from an AIDS-defining event following shock/heart failure four days earlier. This patient was on ETR at the time of death, and the treating clinician designated the death as not causally related to ETR (Table 6b, #1, and Appendix 2, Table 6). This patient started ETR 9 months before death.

There were no serious clinical adverse events considered not to be causally related to ETR in either the treatment inexperienced group or the group who started ETR aged <6 years.

In the missing weight and/or dose group there was one patient from Russia who experienced serious adverse events not thought to be causally related to ETR, previously reported last year (Table 6e, #1). The patient experienced multiple events, including chronic otitis media/conductive deafness (which required hospitalisation) and bacterial pneumonia more than 3.5 years after starting ETR. The otitis media/conductive deafness did not resolve but the bacterial pneumonia resolved two months later. The patient experienced two episodes of pneumococcal pneumonia, one episode of which occurred after the patient had stopped ETR. This patient also experienced exfoliative dermatitis/Stevens-Johnson syndrome/TEN whilst not taking ETR (occurred 4 months after discontinuation of ETR), the cause of which was attributed to Atazanavir (ATZ). The exfoliative dermatitis/Stevens Johnson/TEN was considered to be life-threatening.

Tables 7a-e present serious adverse events by dosing group where the causal link with ETR exposure was unknown or not reported. There were three patients with events reported, all in the licensed dose group, all were previously reported. A case of lipodystrophy in a patient from the UK/Ireland (Table 7a, #1 and Appendix 2, Table 6, #9) was reported over six months after starting ETR; the event was thought to be serious (as it required hospitalisation) but not life threatening. This patient discontinued ETR due to other causes not specified 16 days after the event and it is not known whether the lipodystrophy resolved. Another patient from the UK/Ireland cohort died of an HIV-related metastatic adenocarcinoma (Table 7a, #2 and Appendix 2, Table 6, #10), the third and final death reported. The patient was on ETR at the time of death; the patient was first diagnosed with AIDS at the time of death, three months after starting ETR. A Thai patient experienced four events: anaemia, hypokalaemia, shock/heart failure/CCF/pulmonary oedema and meningitis. The first three events were diagnosed over eight months after starting ETR and all were considered to be life-threatening; all these events resolved within two weeks. The patient stopped ETR at the clinician's request eight months after these events. The meningitis occurred more than four years after stopping ETR, it was considered serious, but not life-threating and it resolved about 2 months later.

No events of unknown causality (with respect to ETR) occurred in the unlicensed, treatment inexperienced group or amongst those who started ETR aged<6 years (Tables 7b-e).

The overall percentage of those on ETR who reported a skin/hypersensitivity reaction in this study was 5.8% [95%CI, 2.7-10.7%]. The percentage who experienced Stevens-Johnson syndrome was 1.4% [95%CI, 0.2-4.7%] (n=2 events).

10.4.3 Discontinuations

A total of 98 out of 177 (55%) patients were not on ETR at their last follow-up visit (compared to 82 of the 164 (50%) patients last year) (Table 8a). Three patients classified as discontinued last year restarted ETR and were on ETR at last follow-up this year. Therefore, 19 patients have newly discontinued this year (98-82+3).

Reasons for discontinuation are presented in Table 8a by dosing group and overall (for patients who discontinued ETR more than once, reasons for discontinuation are given for the final episode only). The largest cause of discontinuation was due to 'other' reasons (58% of discontinuations (57/98)). "Other" reasons included: transfer to adult care, loss to follow-up, simplified treatment, non-compliance and patient's wishes/physician's decision. A total of 13 (13%) patients discontinued due to lack of efficacy, 11 (11%) due to safety and 17 (17%) for reasons unknown. Table 8b provides further details of the reasons for discontinuation due to safety.

Of the 108 patients in the licensed group, 60 (56 %) discontinued ETR, 14 within the first year, and 46 (77%) after ≥12 months of treatment with an ETR-containing regimen. Amongst the 60 patients who discontinued ETR, the reasons for stopping were: lack of efficacy (10%), safety (12%), other reasons (72%) and reasons unknown (7%). Of the seven stopping for safety, one patient died (Appendix 1, Table 7a, #2, cause of death HIV-related metastatic adenocarcinoma), five patients had hypersensitivity reactions and one patient stopped due to gastrointestinal (GI) tract toxicity (Table 8b).

Of the 10 patients on an unlicensed dose, eight (80%) had discontinued ETR by last follow-up due to: lack of efficacy (1), safety (1), other reasons (4) and reasons unknown (2). The patient who stopped for safety died (Appendix 1, Table 6b #1, not related to ETR). Of the seven patients who had started ETR when not treatment-experienced, four (57%) had discontinued ETR by last follow-up: three for other reasons and one for reasons unknown. Amongst the six patients who started ETR aged <6 years, three (50%) discontinued ETR, all after ≥12 months of treatment, two for lack of efficacy and one due to GI toxicity.

In the missing dose or weight group, 50% (23/46) had discontinued ETR by last follow-up, due to: lack of efficacy (4), safety (2), other (7) and reasons unknown (10). Seventeen of the discontinuations occurred after ≥12 months of ETR treatment. Of those stopping for safety, one was due to a hypersensitivity reaction and one due to a GI toxicity.

10.5 Other analyses

None

10.6 Adverse events/adverse reactions

Laboratory and clinical adverse events are outcomes of interest in this study and are described above in 10.3.1 and 10.3.2. A narrative of all serious clinical AEs is provided in Appendix 2, Table 6.

It should be noted that individual patient AEs/reactions attributed to ETR are also reported by treating physicians in accordance with country specific and European law.

11 Discussion

11.1 Key results

In this analysis 17 cohorts from 13 countries reported 177 patients who had ever taken ETR outside a company-sponsored clinical trial. Thirteen new patients were reported this year. In total 108 patients were aged 6-<18 years at start of ETR on the licensed dose and 24 took ETR off-label: ten patients were aged 6-<18 years and on an unlicensed dose, seven patients did not meet the definition of 'treatment-experienced' and six were aged <6 years. The remaining 46 patients were aged 6-<18 years, treatment-experienced and had missing data for weight and/or dose. The percentage of patients in the missing weight/dose group has decreased slightly since last year (26% vs. 28%). Amongst the 170 patients with ≥3 months follow-up (across all groups) laboratory data were available for 90% (153/170) a slight improvement since last year.

In the licensed dose group (n=108), the median age at the start of any ART regimen was 2.2 [IQR, 0.5-6.3] years. The median age at the start of an ETR-containing regimen was 14.6 [IQR 12.6-15.7] years, comparable to last year and 53% of patients had taken ≥8 ART drugs before starting ETR. The licensed group had accrued a total of 378 PY on ETR with a median follow-up of 40.4 [IQR, 17.1-64.0] months. In this group 44% were still on ETR at last follow-up (down from 49% last year). There were 60 (56%) patients on the licensed dose who stopped taking ETR by the end of follow-up. Reasons for discontinuation were: lack of efficacy (6/60, 10%), safety (7/60, 12%), other reasons (43/60, 72%) and reason unknown (4/60, 7%). Amongst those stopping ETR for safety reasons, the most common reason was due to hypersensitivity reactions (4/7, 57%) including skin eruptions. Of these patients who stopped the majority (46/60, 77%) did so after 12 months of more on ETR.

The 10 patients who initiated ETR on an unlicensed dose had a median duration on ETR of 12.2 [IQR 4.8-22.7] months. Eight (80%) of these patients had discontinued ETR at the time of last follow up due to: lack of treatment efficacy (1), safety (1), other reasons (4) and reasons unknown (2). The one patient discontinuing for safety did so due to death, which the clinician reported as not associated with ETR exposure.

The seven patients aged 6-<18 years who were not treatment-experienced at the time of ETR start had a median duration on ETR of 54.7 [IQR, 35.2-73.2] months. Four (57%) of these patients had discontinued ETR at the time of last follow-up, three due to other reasons and one for unknown reasons.

There were six patients who started on ETR aged <6 years, with a median duration on ETR of 28.4 [IQR, 13.9-40.6] months, three (50%) discontinued ETR ≥12 months after start of ETR, two due to a lack of efficacy and one for gastro-intestinal toxicity.

The group with missing weight and/or dose (n=46) had similar characteristics to the licensed dose group. Median age at ETR start was 14.4 [IQR, 11.8-16.1] years and median duration on ETR 33.1 [IQR, 17.6-69.6] months. In this group 50% (23/46) were still on ETR at last follow-up. For the 23 patients in this group who discontinued ETR, reasons given were: lack of efficacy (4, 17%), safety (2, 9%), other (7, 30%) and unknown (10, 44%). One of those stopping for safety did so due to a hypersensitivity reaction and the other due to gastro-intestinal toxicity.

The overall numbers and rates (where numbers were sufficient to calculate) of grade ≥3 DAIDS laboratory events across all laboratory markers and dosing groups have been consistently low in this final report and in all interim reports for this study.

Within the licensed dose group, the overall rate of grade ≥3 episodes per 100 person-years were as follows: 1 [95% CI, 0-2] for ANC, 1 [95% CI, 0-3] for CHOL, 1 [95% CI, 0-4] for LDL, 0.4 [95% CI, 0-2] for APT, 1 [95% CI, 0-3] for BIL, 1 [95% CI, 0-5] for AMY, 1 [95%CI, 0-2] ALT and 1 [95% CI, 0-3] for TRIG. No grade 3 and 4 results were reported for AST, LIP, FPG and NonFPG. Within the licensed dose group, moderate (grade 2) hypercholesterolemia was reported amongst 40 episodes on ETR during 236 PY of follow-up giving an incidence rate of 17 per 100 person-years [95%CI, 12-23], with the highest rates seen in the 12-24 month period. For grade 2 LDL, there was an overall incidence of 15 [95% CI, 10-21] per 100 patient years with declining incidence over time on ETR. HDL test results were available for 85 patients within 87 episodes on ETR in the licensed group and 49 ETR episodes had at least one low HDL test result reported. Some of these laboratory rates are lower than those reported last year due to subsequent data corrections.

Eight clinical adverse events were reported to be definitively/probably/possibly causally related to ETR in the licensed dose group. All of these were reported in last year's annual report, with no new events this year. They comprised five rash/erythema, one generalised hypersensitivity reaction and two confirmed cases confirmed of Stevens-Johnson syndrome. Both cases of Stevens-Johnson syndrome were considered to be serious and one was life threatening. Both children with Steven-Johnson syndrome discontinued ETR following the event and both events resolved. The events were reported as probably or possibly related to ETR (in the clinician's opinion). Both patients were also exposed to darunavir at the time of (or just before) the event however, and for one patient the event was reported as probably due to ETR or darunavir. Of the five rash/erythema events three were not considered to be serious (all these resolved, only one of which stopped ETR due to the reaction) and two were of unknown seriousness (one of which was known to have resolved, neither patients stopped ETR due to the event). The generalised hypersensitivity (urticarial) reaction was not considered serious, but ETR was stopped and the condition resolved. The overall percentage of those on ETR (with clinical data available) who reported a skin/hypersensitivity reaction in this study was 5.8% [95%CI, 2.7-10.7%] and the percentage who experienced Steven-Johnson syndrome was 1.4% [95%CI, 0.2-4.7%] (n=2 events).

Of the 24 patients who took ETR off-label (at an unlicensed dose, when not treatment-experienced or when aged <6 years), three reported grade ≥3 laboratory events. One patient from Russia taking a dose under the licensed range for their weight reported one grade 3 APT test result. There were subsequent normal values. One patient from Thailand who was not treatment-experienced at start of ETR had a grade ≥3 TRIG result. The abnormal result resolved and the patient remained on ETR for more than 5.5 years after the event. One patient from Italy who started ETR aged <6 years also reported one grade ≥3 APT laboratory event. There was no subsequent normal value and the patient discontinued ETR due to toxicity. In the off-label groups, there were no clinical adverse events considered to be causally related to ETR.

In the group with missing weight and/or dose, eight patients experiencing grade ≥3 laboratory events, three were from Spain, four from Italy and one from Thailand. Eight events (in seven patients) were previously reported last year: one raised ALT, two raised BIL, one raised LDL, one raised CHOL and LDL and two raised TRIG. There was one newly reported laboratory event this year, a grade 4 ALT in an Italian patient which occurred four years after starting ETR. The abnormality resolved and the patient remained on ETR for more than 3.5 years after the event

There were three deaths in the cohort during follow-up, all previously reported with no new deaths reported this year. Two patients were in the licensed dose group, one died due to HIV-related metastatic adenocarcinoma (they were on ETR at the time of death) and one

due to an AIDS-defining event (they discontinued ETR over 2 weeks before death and the event was not thought to be causally related to ETR). The third patient was in the unlicensed dose group and died of an AIDS-defining event (shock or heart failure) which was not thought to be causally related to ETR. Two of these patients had advanced HIV disease and the third was diagnosed with AIDS for the first time at the time of death.

There were 2600 paediatric patients from participating EPPICC cohorts (excluding Germany for which data are unavailable) in current follow-up aged <18 years (Table 10) reported this year. The same cohorts submitted data on just 177 patients aged <18 years who had ever taken ETR as part of routine care, suggesting that ETR remains infrequently used in paediatric patients. Most patients (90%) took ETR in combination with a PI (data not shown).

This study found that less than half of paediatric patients (n=79) were on an ETR-containing regimen at last follow-up (Table 8a).

11.2 Limitations

This study used observational data pooled from seventeen cohorts. There are differences in data collection methods as well as clinical practices across countries, cohorts and sites. All EPPICC cohorts, however, follow the same standard operating procedure when providing data. This minimizes the risk of differences and biases arising from different interpretations of data items across cohorts.

This is a descriptive study.

All individuals included in the study had been exposed to ETR, many of whom were heavily treatment-experienced and may not be comparable to the broader paediatric HIV-positive population of the countries included.

Causality was based solely on the clinician's assessment.

This study used observational data from routine care. Data were missing for some variables in some patients. Cohorts worked hard to improve data quality and completeness over the course of the study. No imputation of missing values was undertaken.

Patients were assigned to a dosing group (licensed, unlicensed, treatment inexperienced, <6 years of age, missing weight and/or dose) based on the dose given at ETR initiation (baseline) and the analysis did not account for changes in dosing group over time.

11.3 Interpretation

ETR was prescribed infrequently in this study with few new patients this year. There has been an increase in the number of paediatric ART formulations becoming available recently, which may explain this (11, 12).

In line with findings from adult patients, hypersensitivity reactions were sometimes reported and these were occasionally serious and in one case life-threatening. The overall percentage of those on ETR who reported a skin/hypersensitivity reaction in this study was 5.8% [95% CI, 2.7-10.7%] which is lower than that reported in adults (13, 14). The percentage who experienced Steven-Johnson syndrome was 1.4% [95% CI, 0.2-4.7%] (n=2 events).

It is important to note that the two patients who had Steven-Johnson syndrome were also exposed to darunavir at the time of event. Darunavir or etravirine exposure could have been the cause of these reactions and the attending clinician of one case reported the event was possibly related to either ETR or DRV. The percentage of ETR exposed patients experiencing Steven-Johnson syndrome is higher than that reported in the adult population (<0.1, Etravirine SmPc).

11.4 Generalisability

The data in this study represent 'real world' prescribing of ETR and are likely to be more generalizable than results from clinical trials with selective inclusion criteria.

It is not possible to reliably estimate the coverage of the EPPICC paediatric cohorts, in terms of the number of children included in these cohorts compared with the number infected as a whole in the countries represented. This is due to a wide variation in the quality of the surveillance systems used in these countries, making national estimates, and comparison of estimates between countries, unreliable. Several participating cohorts do however have complete or near complete national coverage. The UK and Ireland cohort (CHIPS) which contributed 13% of all patients has in recent years included all children receiving HIV-related care in both countries. The Italian Register contributed 20% of patients and includes 80-90% of HIV-infected children in Italy.

12 Other information

Not Applicable.

13 Conclusion

Results from this five year pharmaco-epidemiology study which included data from 17 cohorts in 13 mainly European countries suggest that ETR is prescribed infrequently in patients ≤18 years of age. There were just 13 patients newly reported as starting ETR this year.

In general etravirine-containing regimens, both licensed and unlicensed, appear to be well tolerated in this population, with discontinuations for adverse events occurring

infrequently. Serious skin/hypersensitivity reactions did sometimes occur, as has been previously reported in the adult population. Our results suggest that these reactions may occur slightly more frequently in children and adolescents than in adults. It should be noted however, the these adverse event may have occurred due to exposure to other ART drugs (including darunavir) at the time of the event.

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Appendices
Appendix 1: Figures and Tables

Figure 1: Flowchart of patients and first episodes on ETR

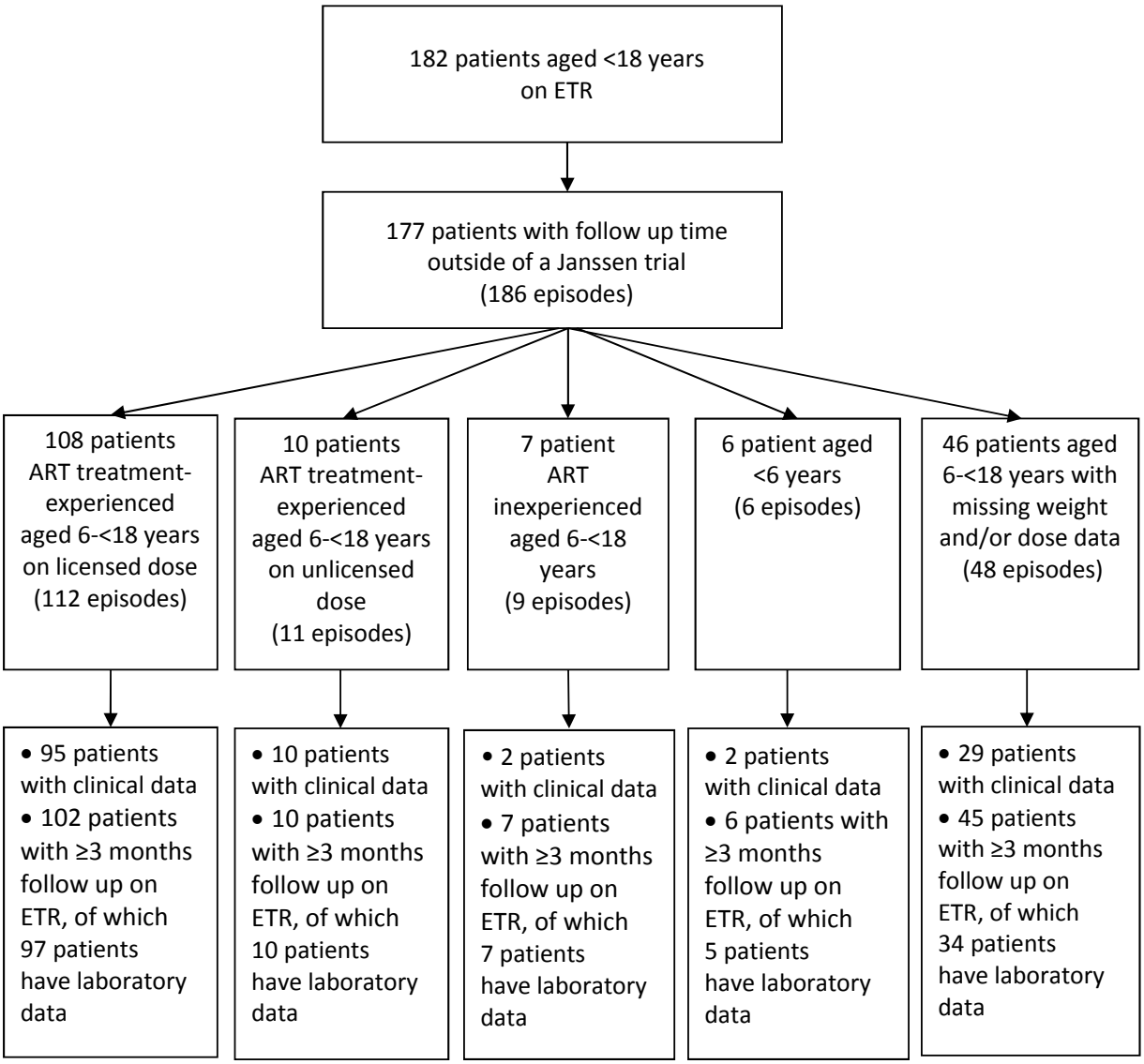

Table 1: Characteristics of all patients taking ETR (n=177) (continues on next page)

	Treatment status (n (%))						
	Aged 6-<18 years on licensed dose (n=108)	Aged 6-<18 years on unlicensed dose (n=10)	Aged 6-<18 years treatment inexperienced (n=7)	Age <6 years (n=6)	Missing weight and/or dose (n=46)	Total (n=177)	P value (licensed dose v missing weight/dose)*
Country	*107*	*11*	*7*	*6*	*46*	*177*	
Belgium	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)	
Germany	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	
Italy	10 (9)	0 (0)	5 (71)	4 (67)	16 (35)	35 (20)	
Poland	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	
Portugal	1 (1)	0 (0)	0 (0)	0 (0)	3 (7)	4 (2)	
Romania	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	
Russia	3 (3)	1 (9)	0 (0)	0 (0)	1 (2)	5 (3)	
Spain	43 (40)	4 (36)	1 (14)	2 (33)	21 (46)	71 (40)	
Sweden	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	
Switzerland	2 (2)	4 (36)	0 (0)	0 (0)	1 (2)	7 (4)	
Thailand	21 (20)	0 (0)	1 (14)	0 (0)	2[1] (4)	24 (14)	
UK/Ireland	20 (19)	1 (9)	0 (0)	0 (0)	2 (4)	23 (13)	0.001
Gender							
Male	58 (53)	6 (64)	3 (43)	3 (50)	26 (57)	96 (54)	0.7
Ethnic group							
White	40 (37)	5 (45)	0 (0)	0 (0)	18 (39)	63 (36)	
Black African	18 (17)	1 (9)	0 (0)	1 (17)	2[1] (4)	22 (12)	
Other	34 (32)	4 (36)	2 (29)	1 (17)	8[1] (17)	49 (28)	
Unknown	16 (15)	0 (0)	5 (71)	4 (67)	18 (39)	43 (24)	0.001

Mode of infection							
MTCT	107 (99)	10 (100)	7 (100)	6 (100)	43 (93)	173 (98)	
Other	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	2 (1)	
Unknown	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0.2
HCV positive (antibody or PCR)							
Value present	93	6	7	6	43[1]	155	
Yes	2 (2)	1 (14)	0 (0)	0 (0)	1 (2)	4 (3)	1.0
HBV positive (surface antigen)							
Value present	98	6	7	6	44	161	
Yes	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)	0.2
Ever AIDS event during follow-up							
Value present	106	10	7	6	43	172	
Yes	44 (42)	7 (64)	2 (29)	3 (50)	22 (51)	78 (45)	0.3
Died during follow-up							
Yes	2 (2)	1 (9)	0 (0)	0 (0)	0 (0)	3 (2)	0.4

Notes

*Compares proportion of patients in the licensed dose and missing weight/dose groups using Pearson's Chi-squared test

The denominator is different for HCV/HBV/AIDS and for each the denominator is shown in the Value present row

[1]Decreased since last year, because even though the number of patients with missing weight/dose is the same they are not the same 46 patients

Table 1b: Description of off-label ETR use (n=23)

Group	Cohort	Dose[1]	Reason for dose being off-label	Reason for off-label use	Age at ETR start
Age 6-<18 years on unlicensed dose	Spain	350	dose too high for weight	Unknown	13.7
	Spain	400	dose too high for weight	Unknown	14.8
	Spain*	400	dose too high for weight	Unknown	9.5
	Spain*	400	dose too high for weight	Unknown	16.3
	Switzerland	400	once daily dosing	Adherence issues	15.8
	Switzerland	400	once daily dosing	Adherence issues	14.9
	Switzerland	400	once daily dosing	Adherence issues	17.7
	Switzerland	400	once daily dosing	Adherence issues	18.0
	UK/Ireland*	400	once daily dosing	Poor adherence and many resistance mutations	14.8
	Russia	200	dose too low for weight	Unknown	11.9
Age 6-<18 years not treatment-experienced	Spain	400	(RTVl+ZDV+d4T+ddI)[3]	Unknown	10.8
	Italy	400	(3TC+ZDV+d4T+ddC+ddI)[3]	Patient's parents refused other ART	16.2
	Italy*	400	(3TC + RTVuns + ZDV)[3]	Multiple resistance mutations	12.6
	Italy	500	(completely ART naïve)[3]	Unknown	11.8
	Italy	500	(3TC+ABC+ZDV+d4T+ddI)[3]	Started in a trial	15.6
	Italy	U[2]	(3TC+ABC+ZDV)[3]	Started in a trial	15.5
	Thailand	400	(ddI+ZDV)[3]	Multiple resistance mutations	12.9
Age <6 years	Spain	300	age < 6 years	Multiple resistance mutations	5.0
	Spain	400	age < 6 years	Multiple resistance mutations	4.6
	Italy	320	age < 6 years	Multiple resistance mutations	4.4
	Italy*	200	age < 6 years	Multiple resistance mutations	2.2
	Italy	200	age < 6 years	Started ETR 2 weeks before 6th birthday	5.9
	Italy	U[2]	age < 6 years	Multiple resistance mutations	2.0

Notes

*New this year

[1]Dose is total dose received per day

[2]U- ART dose unknown

[3] Treatment-experienced is defined as prior exposure to a protease inhibitor, nevirapine or efavirenz. All prior ART drugs to which the patient has been exposed are shown in brackets

Table 2: Antiretroviral therapy profile of all paediatric patients taking ETR (n=177) (continued on next page)

	Treatment status (n (%)/ Median[IQR])						
	Aged 6-<18 years on licensed dose (n=108)	Aged 6-<18 years on unlicensed dose (n=10)	Aged 6-<18 years treatment inexperienced (n=7)	Age <6 years (n=6)	Missing weight and/or dose (n=46)	Total (n=177)	P value (licensed dose v missing weight/dose)*
Age at ART start	*107*	*11*	*7*	*6*	*46*	*177*	
Median (years)	2.2 [0.5,6.3]	1.1 [0.4,3.0]	2.1 [0.9,5.5]	0.2 [0.1,1.1]	1.6 [0.5,3.1]	1.7 [0.5,4.5]	0.3
Age at ETR start (years)							
<6 years	0 (0)	0 (0)	0 (0)	6 (100)	0 (0)	6 (3)	
6-8 years	6 (6)	0 (0)	0 (0)	0 (0)	2 (4)	8 (5)	
9-11 years	13 (12)	2 (18)	2 (29)	0 (0)	10[1] (22)	27 (15)	
12-14 years	40 (37)	4 (36)	2 (29)	0 (0)	14 (30)	60 (34)	
15-<18 years	49 (45)	4 (40)	3 (43)	0 (0)	20 (43)	76 (43)	
Median age at ETR start	14.6 [12.6,15.7]	14.9 [13.7,16.3]	12.9 [11.8,15.6]	4.5 [2.2,5.0]	14.4 [11.8,16.1]	14.5 [12.3,15.8]	0.5
Duration on ART before ETR (years)							
<2 years	5 (5)	0 (0)	0 (0)	2 (33)	1 (2)	8 (5)	
2-4 years	7 (7)	1 (9)	0 (0)	4 (67)	1 (2)	13 (7)	
5-9 years	32 (30)	2 (18)	2 (29)	0 (0)	11 (24)	47 (27)	
≥10 years	64 (59)	7 (70)	4 (57)	0 (0)	31 (67)	106 (60)	
Unknown	0	0	0	0	1	1	
Median duration	11.1 [7.8,12.5]	13.3 [9.2,15.6]	10.1 [5.6,13.5]	3.0 [2.0,4.3]	12.2 [9.1,14.3]	11.2 [7.7,13.3]	0.2
ART history before ETR							
Naïve	0 (0)	0 (0)	1 (14)	0 (0)	2 (4)	3 (2)	
1-7 ART drugs	49 (46)	5 (45)	5 (71)	4 (67)	15[1] (33)	78 (44)	
8+ ART drugs	57 (53)	5 (50)	0 (0)	2 (33)	29 (63)	93 (53)	
Unknown	2 (2)	0 (0)	1 (14)	0 (0)	0 (0)	3 (2)	0.06
VL at ETR start							

Value present	90	(84)	10	(91)	3	(43)	4	(67)	36	(78)	143	(81)	
<=400	45	(50)	6	(60)	2	(67)	1	(25)	21	(58)	75	(52)	
>400	45[2]	(50)	4	(40)	1	(33)	3	(75)	15	(42)	68	(48)	
Median VL (log_{10}c/ml)	2.6	[1.7,4.1]	2	[1.7,4.7]	2.4	[2.4,5.5]	3.6	[2.1,4.6]	2.0	[1.6,3.9]	2.6	[1.7,4.1]	0.2
VL at 12 months after ETR start													
Not on ETR at 12 months	21[2]	(19)	4	(40)	1	(14)	0	(0)	10[1]	(22)	36	(20)	
On ETR at 12 months and value present	82	(77)	6	(55)	5	(71)	3	(50)	28	(61)	124	(70)	
<=400	69	(84)	3	(50)	5	(100)	0	(0)	22	(79)	99	(80)	
>400	13	(16)	3	(50)	0	(0)	3	(100)	8	(29)	17	(14)	
Median VL (log_{10}c/ml)	1.7	[1.3,1.9]	3.3	[1.6,4.9]	1.6	[1.3,1.6]	4.4	[3.6,5.0]	1.6	[1.6,1.7]	1.7	[1.4,1.9]	0.6
CD4 at ETR start													
Value present	92	(86)	10	(91)	4	(57)	4	(67)	30	(65)	140	(79)	
Median CD4 count (c/mm^3)	463	[294,657]	378	[238,567]	513	[221,950]	1025	[601,1111]	552	[316,790]	480	[287,713]	0.2
CD4% at ETR start													
Value present	85	(79)	9	(82)	4	(57)	4	(67)	29	(63)	131	(74)	
Median CD4%	18	[14,26]	21	[20, 25]	23	[10,38]	29	[17,34]	23	[18 ,28]	20	[16 ,28]	0.05
Time on ETR													
Total patient years on ETR	378	(62)	14	(2)	33	(5)	21	(3)	162	(27)	608	(100)	
ETR duration:													
<12mths	19	(18)	5	(50)	0	(0)	0	(0)	6	(13)	30	(17)	
12-24mths	17	(16)	3	(27)	0	(0)	3	(50)	10	(22)	33	(19)	
>24 mths	70	(65)	2	(18)	7	(100)	3	(50)	29	(63)	111	(63)	
Median time on ETR (months)	40.4	[17.1, 64.0]	12.2	[4.8, 22.7]	54.7	[35.2, 73.2]	28.4	[13.9, 40.6]	33.1	[17.6, 69.6]	37.1	[16.0, 64.6]	0.9

Notes

* Compares patients in the licensed dose and missing weight/dose groups. Continuous variables have been compared using a Wilcoxon rank-sum test, and categorical variables (ART history before ETR start) using Pearson's chi-squared test.

[1]Decreased since last year, because even though the number of patients with missing weight/dose is the same they are not the same 46 patients

[2]Data has been corrected since last year

Table 3a: Laboratory data for paediatric patients aged 6-<18 years on licensed dose of ETR (n=97 with laboratory data & ≥3 months follow-up) (continued on next 2 pages)

Test	Time since start of ETR	No. of tests	No. of ETR episodes	No. of patients	DAIDS grading of test results on ETR: no. episodes with ≥1 test results in each grade[2] (rates of first events per 100 patient years) [95% CI]												No. tests grade ≥3 (% of tests)	
					Mild (grade 1)				Moderate (grade 2)				Severe or potentially life-threatening[3] (grade 3 or 4)					
					n	PY	Rate	CI	n	PY	Rate	CI	n	PY	Rate	CI	n	%
ALT	12 months preETR	271		86													0	(0)
	<12 months	334	82	80	8	69	12	[5,23]	3	74	4	[1,12]	1	75	1	[0,7]	6	(2)
	12-24 months	228	74	73	8	64	12	[5,24]	0	68	0	[0,0]	0	68	0	[0,0]	0	(0)
	>24 months	503	67	67	5	190	3	[1,6]	0	197	0	[0,0]	0	197	0	[0,0]	0	(0)
	Total [1]	1065	98	96	16	324	5	[3,8]	3	338	1	[0,3]	1	339	0	[0,2]	6	(1)
AMY	12 months preETR	81		28													0	(0)
	<12 months	101	30	30	6	24	25	[9,54]	3	28	11	[2,32]	0	30	0	[0,0]	0	(0)
	12-24 months	69	26	26	5	21	23	[8,54]	4	22	18	[5,46]	1	24	4	[0,23]	2	(3)
	>24 months	124	23	23	0	68	0	[0,0]	4	59	7	[2,17]	1	63	2	[0,9]	3	(2)
	Total [1]	294	38	38	8	114	7	[3,14]	6	109	6	[2,12]	1	117	1	[0,5]	5	(2)
ANC	12 months preETR	258		79													4	(2)
	<12 months	304	79	77	8	66	12	[5,24]	1	72	1	[0,8]	2	71	3	[0,10]	4	(1)
	12-24 months	236	75	74	8	63	13	[5,25]	0	68	0	[0,0]	0	68	0	[0,0]	0	(0)
	>24 months	509	67	67	6	197	3	[1,7]	0	203	0	[0,0]	0	203	0	[0,0]	0	(0)
	Total [1]	1049	97	95	12	326	4	[2,6]	1	343	0	[0,2]	2	342	1	[0,2]	4	(0)
APT	12 months preETR	126		48													2	(2)
	<12 months	152	49	48	10	40	25	[12,46]	5[1]	43	12	[4,27]	1	46	2	[0,12]	1	(1)
	12-24 months	116	43	42	9	35	26	[12,49]	2	40	5	[1,18]	0	41	0	[0,0]	0	(0)
	>24 months	312	45	45	13	107	12	[6,21]	4	132	3	[1,8]	0	140	0	[0,0]	0	(0)
	Total [1]	580	64	63	17	183	9	[5,15]	7[1]	215	3	[1,7]	1	227	0	[0,2]	1	(0)
AST	12 months preETR	148		58													0	(0)
	<12 months	211	65	63	8	56	14	[6,28]	1	62	2	[0,9]	0	63	0	[0,0]	0	(0)
	12-24 months	151	56	56	3	49	6	[1,18]	0	51	0	[0,0]	0	51	0	[0,0]	0	(0)

	>24 months	332	54	54	2	161	1	[0,4]	2	158	1	[0,5]	0	163	0	[0,0]	0	(0)
	Total [1]	694	82	80	11	267	4	[2,7]	3	270	1	[0,3]	0	276	0	[0,0]	0	(0)
BIL	12 months preETR	153		53													2	(1)
	<12 months	197	59	57	2	54	4	[0,13]	0	55	0	[0,0]	2	54	4	[0,13]	2	(1)
	12-24 months	145	49	49	1	45	2	[0,12]	0	46	0	[0,0]	0	46	0	[0,0]	0	(0)
	>24 months	304	45	45	1	124	1	[0,5]	2	124	2	[0,6]	0	125	0	[0,0]	0	(0)
	Total [1]	646	73	71	3	223	1	[0,4]	2	224	1	[0,3]	2	225	1	[0,3]	2	(0)
CHOL	12 months preETR	208		82													1	(0)
	<12 months	260	80	78	33	55	60	[41,84]	29	56	52	[35,74]	2	73	3	[0,10]	3	(1)
	12-24 months	200	74	73	31	54	57	[39,81]	27	49	55	[36,80]	0	68	0	[0,0]	0	(0)
	>24 months	474	67	67	39	88	44	[31,61]	27	131	21	[14,30]	1[1]	201	0	[0,3]	1	(0)
	Total [1]	934	98	96	59	197	30	[23,39]	40	236	17	[12,23]	3[1]	342	1	[0,3]	4	(0)
FPG	12 months preETR	132		55													0	(0)
	<12 months	166	58	56	3	54	6	[1,16]	1	55	2	[0,10]	0	56	0	[0,0]	0	(0)
	12-24 months	136	53	52	2	49	4	[0,15]	1	49	2	[0,11]	0	49	0	[0,0]	0	(0)
	>24 months	384	55	55	8	160	5	[2,10]	4	166	2	[1,6]	0[1]	173	0	[0,0]	0	(0)
	Total [1]	686	76	74	11	263	4	[2,7]	6	270	2	[1,5]	0	278	0	[0,0]	0	(0)
LDL	12 months preETR	96		47													0	(0)
	<12 months	156	61	60	19	49	39	[23,61]	18	50	36	[21,57]	2	58	3	[0,13]	5	(3)
	12-24 months	127	50	49	17	38	45	[26,72]	14	39	36	[20,61]	1[1]	46	2	[0,12]	1	(1)
	>24 months	286	53	53	21	107	20	[12,30]	21	129	16	[10,25]	1[1]	165	1	[0,3]	1	(0)
	Total [1]	569	80	79	38	194	20	[14,27]	32	218	15	[10,21]	4[1]	269	1	[0,4]	7	(1)
LIP	12 months preETR	42		15													0	(0)
	<12 months	48	18	18	0	18	0	[0,0]	0	18	0	[0,0]	0	18	0	[0,0]	0	(0)
	12-24 months	36	15	15	0	14	0	[0,0]	0	14	0	[0,0]	0	14	0	[0,0]	0	(0)
	>24 months	50	8	8	1	20	5	[0,27]	0	23	0	[0,0]	0	23	0	[0,0]	0	(0)
	Total [1]	134	20	20	1	52	2	[0,11]	0	55	0	[0,0]	0	55	0	[0,0]	0	(0)
NonFPG	12 months preETR	51		17													0	(0)
	<12 months	51	16	16	0	14	-	-	0	14	-	-	0	14	-	-	0	(0)
	12-24 months	32	12	12	1	11	-	-	0	11	-	-	0	11	-	-	0	(0)
	>24 months	48	11	11	1	28	-	-	1	28	-	-	0	28	-	-	0	(0)

	Total [1]	131	17	17	2	54	-	-	1	54	-	-	0	54	-	-	0	(0)
TRIG	12 months preETR	204		80													3	(1)
	<12 months	254	79	77	45	44	102	[75,137]	7	69	10	[4,21]	1	73	1	[0,8]	1	(0)
	12-24 months	198	74	73	32	51	63	[43,89]	7	65	11	[4,22]	1	67	1	[0,8]	1	(1)
	>24 months	468	67	67	40	93	43	[31,58]	14	167	8	[5,14]	2	198	1	[0,4]	2	(0)
	Total [5]	920	98	96	66	188	35	[27,45]	21	301	7	[4,11]	4	338	1	[0,3]	4	(0)

Notes

702 HDL test results were available for 85 patients with 87 episodes on ETR. 49 patients with 50 episodes had borderline HDL results (21 patients within 12 months of ETR start) and 47 patients with 49 episodes had low HDL results (26 patients in 28 episodes within 12 months of ETR start). Rates are not given if there were fewer than 20 patients tested for that laboratory biomarker.

[1]These rates have all gone down since last year due to data corrections (see Table 4a for details).

ANC, absolute neutrophil count; CHOL, total cholesterol; TRIG, triglycerides; ALT, alanine transaminase; BIL, total bilirubin; FPG, fasting plasma glucose; NonFPG, non-fasting plasma glucose, AMY, pancreatic amylase; LIP, lipase; APT, aspartate aminotransferase; APT, alkaline phosphatase; LDL, low-density lipoprotein cholesterol.

1 It is not possible to add the number of patients in each time period to equal the total as the same child can contribute follow-up time to >1 time period.

2 Each child/episode can be counted only once in each grade (with grades 3 and 4 counted together) in each time period, to prevent an artificial overestimation of rates due to increased testing during an event. For the calculation of rates, follow-up time is censored at the first event within each grade and time period with the exception of overall rates where total patient years of follow-up are censored at the first event across the three time periods on ETR.

3 For grade 3 and 4 events follow-up time is censored at the first grade 3 event, and if there is no grade 3 event then at the first grade 4 event.

All totals shown are for periods on ETR only.

Table 3b: Laboratory data for paediatric patients aged 6-<18 years on an unlicensed dose (n=10 with laboratory data and ≥3 months follow-up)

Test	No. of tests	No. of ETR episodes	No. of patients	DAIDS grading of test results on ETR: no. episodes with ≥1 test results in each grade						No. tests grade ≥3 (% of tests)	
				Mild (grade 1)		Moderate (grade 2)		Severe or potentially life-threatening (grade 3 or 4)			
				n	%	n	%	n	%	n	%
ALT	54	9	9	1	(11)	0	(0)	0	(0)	0	(0)
AMY	20	3	3	0	(0)	0	(0)	0	(0)	0	(0)
ANC	42	6	6	1	(17)	1	(17)	0	(0)	0	(0)
APT	46	7	7	1	(14)	0	(0)	1	(14)	1	(2)
AST	32	6	6	3	(50)	0	(0)	0	(0)	0	(0)
BIL	27	5	5	0	(0)	0	(0)	0	(0)	0	(0)
CHOL	53	10	10	4	(40)	2	(20)	0	(0)	0	(0)
FPG	31	6	6	1	(17)	1	(17)	0	(0)	0	(0)
LDL	28	5	5	2	(40)	0	(0)	0	(0)	0	(0)
LIP	4	2	2	0	(0)	0	(0)	0	(0)	0	(0)
NonFPG	21	4	4	0	(0)	0	(0)	0	(0)	0	(0)
TRIG	53	10	10	3	(30)	1	(10)	0	(0)	0	(0)

Notes

47 HDL test results were available for 10 patients with 10 episodes on ETR. 4 patients with 4 episodes had borderline HDL results and 5 patients with 5 episodes had low HDL results. Rates and breakdowns by time period on ETR are not presented due to small number of patients and events in most categories.

Table 3c: Laboratory data for treatment inexperienced patients aged 6-<18 years (n=7 with laboratory data & ≥3 months follow-up)

Test	No. of tests	No. of ETR episodes	No. of patients	DAIDS grading of test results on ETR: no. episodes with ≥1 test results in each grade						No. tests grade ≥3 (% of tests)	
				Mild (grade 1)		Moderate (grade 2)		Severe or potentially life-threatening (grade 3 or 4)			
				n	%	n	%	n	%	n	%
ALT	56	7	7	0	(0)	0	(0)	0	(0)	0	(0)
AMY	2	2	2	1	(50)	0	(0)	0	(0)	0	(0)
ANC	57	7	7	0	(0)	0	(0)	0	(0)	0	(0)
APT	14	3	3	2	(67)	1	(33)	0	(0)	0	(0)
AST	50	7	7	0	(0)	0	(0)	0	(0)	0	(0)
BIL	27	5	5	0	(0)	1	(20)	0	(0)	0	(0)
CHOL	39	6	6	4	(67)	3	(50)	0	(0)	0	(0)
FPG	28	6	6	0	(0)	0	(0)	0	(0)	0	(0)
LDL	30	6	6	3	(50)	4	(67)	0	(0)	0	(0)
LIP	2		1	0	(0)	0	(0)	0	(0)	0	(0)
NonFPG	18	1	1	0	(0)	0	(0)	0	(0)	0	(0)
TRIG	40	6	6	3	(50)	0	(0)	1	(17)	1	(17)

Notes

30 HDL test results were available for 6 patients with 6 episodes on ETR. Three patients with 3 episodes had borderline HDL results and 3 patients with 3 episodes had low HDL results.

Table 3d: Laboratory data for patients aged <6 taking ETR (n=5 with laboratory data & ≥3 months follow-up)

Test	No. of tests	No. of ETR episodes	No. of patients	DAIDS grading of test results on ETR: no. episodes with ≥1 test results in each grade						No. tests grade ≥3 (% of tests)	
				Mild (grade 1)		Moderate (grade 2)		Severe or potentially life-threatening (grade 3 or 4)			
				n	%	n	%	n	%	n	%
ALT	35	5	5	0	(0)	0	(0)	0	(0)	0	(0)
AMY	5	1	1	1	(100)	0	(0)	0	(0)	0	(0)
ANC	38	5	5	0	(0)	0	(0)	0	(0)	0	(0)
APT	25	4	4	2	(50)	1	(25)	1	(25)	1	(4)
AST	34	5	5	1	(20)	0	(0)	0	(0)	0	(0)
BIL	25	4	4	0	(0)	0	(0)	0	(0)	0	(0)
CHOL	34	5	5	4	(80)	3	(60)	0	(0)	0	(0)
FPG	29	5	5	2	(40)	0	(0)	0	(0)	0	(0)
LDL	30	5	5	4	(80)	2	(40)	0	(0)	0	(0)
LIP	5	1	1	0	(0)	0	(0)	0	(0)	0	(0)
Non-FPG	0	0	0	0	(0)	0	(0)	0	(0)	0	(0)
TRIG	34	5	5	2	(40)	0	(0)	0	(0)	0	(0)

Notes: 33 HDL test results were available for 5 patients with 5 episodes on ETR. 1 patient with 1 episode had borderline HDL results and 4 patients with 4 episodes had low HDL results.

Table 3e: Laboratory data for patients with missing weight and/or dose (n=34 with laboratory data & ≥3 months follow-up)

Test	No. of tests	No. of ETR episodes	No. of patients	DAIDS grading of test results on ETR: no. episodes with ≥1 test results in each grade						No. tests grade ≥3 (% of tests)	
				Mild (grade 1)		Moderate (grade 2)		Severe or potentially life-threatening (grade 3 or 4)			
				n	%	n	%	n	%	n	%
ALT	291	34	32	4	(12)	2	(6)	2	(6)	2	(1)
AMY	37	5	5	1	(20)	1	(20)	0	(0)	0	(0)
ANC	298	35	33	0	(0)	1	(3)	0	(0)	0	(0)
APT	158	21	19	5	(24)	1	(5)	0	(0)	0	(0)
AST	215	25	23	6	(24)	2	(8)	0	(0)	0	(0)
BIL	184	24	22	2	(8)	2	(8)	3[1]	(13)	11[1]	(6)
CHOL	288	34	32	20	(59)	16	(47)	1	(3)	1	(0)
FPG	219	26	24	2	(8)	0	(0)	0	(0)	0	(0)
LDL	191	23	21	14	(61)	13	(57)	2[1]	(9)	2[1]	(1)
LIP	4	3	3	0	(0)	0	(0)	0	(0)	0	(0)
NonFPG	8	2	2	0	(0)	0	(0)	0	(0)	0	(0)
TRIG	283	34	32	22	(65)	8	(24)	2	(6)	2	(1)

Notes

198 HDL test results were available for 25 patients with 27 episodes on ETR. 10 patients with 12 episodes had borderline HDL results and 14 patients with 14 episodes had low HDL results

[1]These numbers have gone down due to lab data corrections (see Table 4e for details)

Table 4a: Characteristics of patients aged 6-<18 years on a licensed ETR dose with grade ≥3 laboratory test results whilst on ETR *(continues over)*

Patient	Country	ETR start date	ETR end date (reason for stopping)	Test	Number grade ≥3 tests	Test dates/range	Number grade 3 tests	Number grade 4 tests	Other ART drugs at test(s)	ETR dose	Age at first grade ≥3 test	"Normal" value following last grade ≥3 result	Last test date (any grade) on ETR†
1	UK/Ireland	19/07/2007	21/03/2008 (SAE)[1]	BIL	1	03/10/2007	1	0	ATZ+RTVl	400	15.5	Y	21/02/2008
2	UK/Ireland	14/02/2008	Still on drug	CHOL	1	18/09/2008	1	0	3TC+ABC+DRV+RAL+RTVl+TDF	350	14.2	Y	16/09/2014
				AMY	5	17/09/2009 - 16/06/2011	4	1	3TC+ABC+DRV+RAL+RTVl+TDF	400	15.2	No further tests	16/06/2011
3	UK/Ireland	18/06/2008	Still on drug	ANC	3	06/08/2008 - 03/02/2009	3	0	3TC+DRV+RAL+RTVl+ZDV	400	12.7	Y	12/10/2011
4	Spain	24/11/2008	29/01/2010 (Virological failure)[2]	BIL	1	20/05/2009	1	0	DRV+MRV+RAL+RTVl[3]	400	15.9	Y	20/01/2010
5	Belgium	28/12/2009	Still on drug	CHOL	1	16/11/2012	1	0	DRV+FTC+RAL+RTVl+TDF	400	20.1	N	06/12/2012
6	Spain	15/07/2008	19/05/2010 (Transfer to adult care)	LDL	1	19/05/2010	1	0	DRV+RAL+RTVl	400	17.7	No further tests	19/05/2010
7	UK/Ireland	01/12/2010	Still on drug	APT	1	25/10/2011	1	0	DRV+RAL+RTVl	400	15.1	Y	15/07/2015
8	UK/Ireland	03/09/2012	18/09/2016 (Simplified treatment available)	ANC	1	10/09/2012	1	0	DRV+MRV+RTVl	400	13.4	Y	08/08/2016
9	Spain	15/03/2012	21/07/2016 (Simplified treatment available)	LDL	1	18/12/2012	1	0	DRV+RTVl	200	7.6	N	07/06/2016
10	Spain	14/07/2008	21/12/2010 (Lost to follow up)	TRIG	1	25/06/2009	1	0	DRV+RAL+RTVl	400	16.4	N	01/10/2010
11	Spain	18/03/2008	28/06/2013[4] (Treatment failure (i.e. virological,/immunological/clinical failure)	TRIG	1	15/10/2009	1	0	DRV+ddI+RTVl	400	10.4	Y	16/01/2013
12	UK/Ireland	20/08/2011[5]	19/10/2011 (Hypersensitivity reaction (skin eruption etc.))	ALT	6	20/09/2011 - 25/09/2011	1	5	DRV+RAL+RTVl		14.8	Y	17/10/2011

13	Italy	04/06/2012	14/10/2015 (Physician's decision, not specified above)	CHOL	2	03/01/2013 -02/04/2013	2	0	DRV+RTVl	500	16.8	N	13/10/2015
				LDL	4	03/01/2013 -13/05/2013	4	0	DRV+TTVl	500	16.8	N	13/10/2015
14	Spain	29/01/2013	18/07/2017 (Simplified treatment available)	TRIG	1	25/04/2017	1	0	DRV+RTVl	400	14.0	N	18/07/2017
15*	Spain	22/03/2007	Still on drug	TRIG	1	12/03/2012	1	0	DRV+RTVl	400	22.5	Y	19/12/2014
16*	Italy	16/06/2009	Still on drug	LDL	1	10/08/2015	1	0	DRV+RAL+RTVl	400	21.8	N	12/09/2017

Notes

† Last reported test of the same marker as reported grade ≥3 test (for example, last reported BIL test if reported grade ≥3 BIL test)

*New this year

Patients #14, 15 and 17 from the 2017 report are no longer in the table due to a data correction (units were wrong) and their values were in fact normal

Patient 16 in last year's report is now patient #14 this year and the LDL lab value relating to the grade ≥3 event reported last year has been corrected due to an issue with the units

The following corrections have been made to the data since last year

[1] ETR end date was 20/02/2008 last year, now corrected

[2] ETR end date was 30/12/2009 last year, now corrected

[3] Other ART drugs at time of test were DRV+FTC+RAL+RTVl+TDF, now corrected

[4] ETR end date was 29/05/2013, now corrected

[5] ETR start date was 19/08/2011, now corrected

Table 4b: Characteristics of patients aged 6-<18 years on unlicensed ETR dose with grade ≥3 laboratory test results whilst on ETR

Patient	Cohort	ETR start date	ETR end date (reason for stopping)	Test	Number grade ≥3 tests	Test dates/ range	Number grade 3 tests	Number grade 4 tests	Other ART at test(s)	ETR dose	Age at first grade ≥3 test	"Normal" value following last grade ≥3 result	Last test date (any grade) on ETR†
1	Russia	16/10/2010	12/02/2014[1] (Treatment failure (Virological/ immunological/ clinical failure)	APT	1	07/06/2012	1	0	ABC+DRV+ RTVl	200	13.5	Y	11/02/2014[2]

Notes

†last reported test of the same marker as reported grade ≥3 test (for example, last reported BIL test if reported grade ≥3 BIL test)
The following data corrections have taken place
[1]ETR end date was 13/01/2014
[2]Last test date was 13/01/2014

Table 4c: Characteristics of treatment inexperienced patients aged 6-<18 years with grade ≥3 laboratory test results whilst on ETR

Patient	Cohort	ETR start date (in trial)	ETR start date	ETR end date (reason for stopping)	Test	No. grade ≥3 tests	Test dates/range	No. grade 3 tests	No. grade 4 tests	Other ART drugs at test(s)	ETR dose	Age at 1st grade ≥3 test	"Normal" value following last grade ≥3 result	Last test date (any grade) on ETR†
1	Thailand	23/08/2010	27/07/2011	20/04/2017 (Other[1])	TRIG	1	19/12/2012	1	0	ATZ+RTVuns+TDF	400	15.3	Y	26/07/2016

Notes

† Last reported test of the same marker as reported grade ≥3 test (for example, last reported BIL test if reported grade ≥3 BIL test)

[1] Change in treatment not due to side-effects, failure, poor adherence or contra-indication

The FPG lab value relating to the grade ≥3 event reported last year has been corrected due to an issue with the units

Table 4d: Characteristics of patients aged <6 years taking ETR with grade ≥3 laboratory test results whilst on ETR

Patient	Cohort	ETR start date	ETR end date (reason for stopping)	Test	No. grade ≥3 tests	Test dates/range	No. grade 3 tests	No. grade 4 tests	Other ART drugs at test(s)	ETR dose	Age at first grade ≥3 test	"Normal" value following last grade ≥3 result	Last test date (any grade) on ETR[1]
1	Italy	03/11/2012	27/11/2013 (Toxicity, predominately from abdomen/GI tract)	APT	1	26/07/2013	1	0	3TC+ABC+TDF	180	5.1	N	27/11/2013

Notes

† Last reported test of the same marker as reported grade ≥3 test (for example, last reported BIL test if reported grade ≥3 BIL test)

Table 4e: Characteristics of patients with missing weight and/or dose taking ETR with grade ≥3 laboratory test results whilst on ETR

Patient	Cohort	ETR start date	ETR end date (reason for stopping)	Test	Number grade ≥3 tests	Test dates/range	No. grade 3 tests	No. grade 4 tests	Other ART drugs at test(s)	ETR dose	Age at first grade ≥3 test	"Normal" value following last grade ≥result	Last test date (any grade) on ETR†
1	Italy	20/09/2010	25/11/2012 (Unknown)	ALT	1	30/09/2010	1	0	DRV+RTVl		17.2	Y	13/09/2012
2	Spain	21/12/2010	Still on drug	BIL	9	13/07/2012 -18/01/2017	9	0	ATZ+RTVl	400	13.4	Y	10/07/2017
3	Spain	08/04/2009	26/09/2014 (Transfer to adult care)	LDL	1	29/12/2011	1	0	DRV+MRV+RTVuns	400	15.7	N	24/04/2014
4	Italy	19/04/2007	19/10/2008 (Virological failure)	TRIG	1	22/04/2008	1	0	3TC+ABC+DRV+RTVl		17.5	N	19/09/2008
5	Italy	13/02/2008	19/01/2010 (Other causes)	TRIG	1	03/06/2009	1	0	3TC+ABC+DRV+RTVl	500	16.4	N	20/01/2010
6	Thailand	25/04/2012	Still on drug	CHOL	1	06/11/2013	1	0	3TC+DRV+RTVuns	400	14.7	N	01/04/2015
				LDL	1	06/11/2013	1	0	3TC+DRV+RTVuns	400	14.7	No further tests	06/11/2013
7	Spain	08/09/2009	Still on drug	BIL	1	16/08/2016	1	0	DRV+RTVl+TDF		16.2	Y	28/09/2016
8*	Italy	19/03/2010	21/01/2018 (Simplified treatment)	ALT	1	09/05/2014	0	1	DRV+RAL	200	19.2	Y	17/11/2017

Notes

† Last reported test of the same marker as reported grade ≥3 test (for example, last reported BIL test if reported grade ≥3 BIL test)

*New this year

Patient #1 no longer has a BIL event, the data were corrected (a decimal place error)

Patients #4 and 8 from last year's table are no longer in the table due to a data correction (lab values are no longer abnormal due to use of the correct unit conversion factor)

Patients #5, #6 & #7 from last year's table are now patients #4, #5, and #6. Patient #10 last year is now patient #7

Patient #9 from last year's table has moved to the licensed group and in addition has corrected lab data which is normal, so the patient is not reported in Table 4a

Table 5a: Clinical adverse events for patients aged 6-<18 years on licensed ETR dose which were considered to be causally related to ETR (n=95 with clinical data)

Patient	Cohort	ETR start date	ETR end date (reason for stopping)	Adverse event	Date event diagnosed	Adverse event resolved (Date if known)	Causal link to ETR	Whether adverse event considered serious	If serious, whether life threatening	Other ART drugs at time of diagnosis	Age at clinical event (years)	Gender	ETR dose	Concomitant medication
1	Italy	12/03/2012	Still on drug	Rash, erythema	23/03/2012	Yes (Unknown)	Possible	U	N	3TC+DRV+ EFV+RTVl+ZDV	12.9	M	400	N
2	Spain	07/08/2008	08/09/2008 (Generalised hypersensitive reaction-urticaria)	Generalised hypersensitive reaction, urticaria	01/09/2008	Yes (08/09/2008)	Probable	N	N	DRV+FTC+RTVl+ TDF	13.8	F	400	N
3	Spain	14/04/2010	20/04/2010 (Hypersensitivity reaction (skin eruption etc.))	Stevens-Johnson	20/04/2010	Yes (01/06/2010)	Probable	Y	N	DRV+MRV+ RTVuns	9.9	F	400	N
4	UK/Ireland	20/08/2011	19/09/2011 (Hypersensitivity reaction (skin eruption etc.))	Stevens-Johnson	20/09/2011	Yes (25/09/2011)	Possible	Y	Y	(DRV+RAL+ RTV)*	14.8	M	(400)*	N
5	Spain	26/05/2015	23/06/2015 (Hypersensitivity reaction (skin eruption etc.))	Rash, erythema	30/05/2015	Yes (23/06/2015)	Probable	N	N	RAL + DRV	16.9	F	400	N
6	Spain	06/03/2009	22/05/2012 Other causes, not specified	Rash, erythema	16/03/2009	Yes (21/03/2009)	Definitive	N	N	DRV+ETR+RTVl+TDF	14.2	M	400	N
7	Spain	22/03/2007	Still on drug	Rash, erythema	22/03/2007	Yes (29/03/2007)	Definitive	N	N	-	17.5	M	-	N
8	Spain	18/10/2013	08/11/2013 Virological failure	Rash, erythema	28/10/2013	U	Definitive	U	U	DRV+RAL+ RTVuns+TDF	17.6	F	400	N

Notes: U – Unknown * This patient stopped ETR/DRV and all other ART the day before the event.

Table 5b: Clinical adverse events for patients aged 6-<18 years on unlicensed ETR dose which were considered to be causally related to ETR

(n=10 with clinical data)

No observations

Table 5c: Clinical adverse events for treatment inexperienced patients aged 6-<18 years which were considered to be causally related to ETR

(n=2 with clinical data)

No observations

Table 5d: Clinical adverse events for patients aged <6 years which were considered to be causally related to ETR

(n=2 with clinical data)

No observations

Table 5e: Clinical adverse events for patients with missing weight and/or dose which were considered to be causally related to ETR

(n=29 with clinical data)

No observations

Table 6a: Serious clinical AEs in patients aged 6-<18 years on a licensed dose of ETR which the clinician considered not causally related to ETR

Patient	Cohort	ETR start date	ETR end date (reason for stopping)	Adverse event	Date event diagnosed	Adverse event resolved (Date if known)	Causal link to ETR	Whether adverse event considered serious	If serious, whether life threatening	All ART drugs at time of diagnosis	Age at clinical event (years)	Sex	ETR dose	Concomitant medication
1	Spain	03/05/ 2010	10/01/ 2011 (Physician's decision)	Death	28/01/ 2011		Not related	Y	Y		13.1	F	200	N
2	Thailand	14/07/ 2010	Still on drug	Anaemia	13/03/ 2013	Yes (17/10/2014)	Remote/ unlikely	Y	Y	3TC+DRV+ ETR+ RTVuns	12.5	F	400	N
3	Germany	28/02/ 2010	Still on drug	Nausea	01/12/ 2010	Yes (14/04/ 2011)	Remote/ unlikely	Y	N	3TC+ABC+ ETR	8.7	M	200	Anti-psychotics
				Vomiting	01/12/ 2010	Yes (15/01/ 2014)	Remote/ unlikely	Y	N	3TC+ABC+ ETR	8.7		200	Anti-psychotics
				Chills or fever/ rigor (pyrexia)	13/12/ 2010	Yes (20/12/ 2010)	Remote/ unlikely	Y	N	3TC+ABC+ETR	8.7		200	Anti-psychotics
				Other gastro-intestinal disease	13/12/ 2010	Yes (20/12/ 2013)	Remote/ unlikely	Y	N	3TC+ABC+ETR	8.7		200	Anti-psychotics
				Indigestion, oesophageal reflux, gastritis	21/03/ 2013	Yes (21/03/ 2013)	Not related	Y	N	3TC+ABC+ETR	11.0		300	Anti-psychotics+ Unknown
4	Thailand	11/09/ 2012	Still on drug	Abdominal pain	20/11/ 2013	Yes (25/11/ 2013)	Not related	Y	N	DRV+ETR+RAL+ RTVuns	17.0	F	400	N
5*	Thailand	07/08/2012	Still on drug	Cardiovascular (Ergotism)	25/02/2017	Yes (10/03/2017)	Not related	Y	N	DRV+ETR+RTVuns+TDF	19.2	F	400	N

Notes: *New event since last year. Patient #1, cause of death: non-AIDS defining event

Table 6b: Serious clinical adverse events in patients aged 6-<18 years on an unlicensed dose which the clinician considered not causally related to ETR

Patient	Cohort	ETR start date	ETR end date (reason for stopping)	Adverse event	Date event diagnosed	Causal link to ETR	Whether adverse event considered serious	If serious, whether life threatening	All ART drugs at time of diagnosis	Age at clinical event (years)	Sex	ETR dose	Concomitant medication
1	Spain	15/02/ 2007	18/11/2007 (Death)	Shock or heart failure, CCF, pulmonary oedema	14/11/ 2007	Not related	Y	Y	3TC+DRV+ETR+ RTVl	14.4	M	350	Cotrimoxazole
				Death	18/11 /2007	Not related	Y	Y	3TC+DRV+ETR+ RTVl	14.4	M	350	Cotrimoxazole

Notes: Patient #1- Cause of death: non-AIDS-defining event

Table 6c: Serious clinical adverse events in treatment inexperienced patients aged 6-<18 years the clinician considered not causally related to ETR

No observations

Table 6d: Serious clinical adverse events in patients aged <6 years which the clinician considered not causally related to ETR

No observations

Table 6e: Serious clinical adverse events in patients with missing ETR weight/dose which the clinician considered not causally related to ETR

Patient	Cohort	ETR start date	ETR end date (reason for stopping)	Adverse event	Date event diagnosed	Adverse event resolved (Date if known)	Causal link to ETR	Whether adverse event considered serious	If serious, whether life threatening	All ART drugs at time of diagnosis	Age at clinical event (years)	Sex	ETR dose	Concomitant medication
1	Russia	25/ 03/ 2011	15/06/ 2015 (Virological failure)	Chronic otitis media or conductive deafness	15/10/ 2014	No	Not related	Y	N	3TC+ABC+ ETR	13.5	M	200	N
				Pneumonia - other bacterial	15/10/ 2014	Yes (15/12/2014)	Not related	Y	N	3TC+ABC+ ETR	13.5	M	200	N
				Lobar pneumonia - pneumococcal	15/03/ 2015	Yes (15/05/2015)	Not related	Y	N	3TC+ABC+ ETR	13.9	M	200	Sulfamethoxazole/ trimethoprim
				Lobar pneumonia - pneumococcal	31/08/ 2015	Yes (15/11/2015)	Not related	Y	N	3TC+ABC+ DRV+RTVl	14.4	M		Sulfamethoxazole/ trimethoprim
				Exfoliative dermatitis, SJS, TEN	22/09/ 2015	Yes (15/10/2015)	Not related	Y	N	3TC+ABC+ ATZ+RTVl	14.4	M		Sulfamethoxazole/ trimethoprim

Notes

The patient was on ATZ at the time of the exfoliative dermatitis/Stevens-Johnson/TEN and this was event was thought to be related to ATZ.

Table 7a: Serious clinical adverse events diagnosed in patients aged 6-<18 years on licensed dose where the causal association to ETR was not designated or was reported as unknown

Patient	Cohort	ETR start date	ETR end date (reason for stopping)	Adverse event	Date event diagnosed	Adverse event resolved (Date if known)	Causal link to ETR	Whether adverse event considered serious	If serious, whether life threatening	All ART drugs at time of diagnosis	Age at clinical event (years)	Sex	ETR dose	Concomitant medication
1	UK/ Ireland	19/07/ 2007	20/02/2008 (Other causes, not specified)	Lipodystrophy, unspecified	04/02/ 2008	Unknown	Unknown	Y	N	ATZ+ETR+ RTVl	15.8	M	400	N
2	UK /Ireland	23/02/ 2009	22/05/2009 (Death)	Death	22/05/ 2009	No	Unknown	Y	Y	DRV+ETR+ RAL+RTVl	15.4	M	400	N
3	Thailand	05/03/ 2010	08/08/ 2011 (Physician's decision)	Anaemia	29/11/ 2010	Yes (10/12/2010)	Unknown	Y	Y	3TC+DRV+ ETR+RAL+ RTVuns+ TDF	13.9	M	250	Azithomycine + Cotrimoxazole + Fluconazole
				Hypokalaemia	29/11/ 2010	Yes (01/12/2010)	Unknown	Y	Y	3TC+DRV+ETR+ RAL+ RTVuns+ TDF	13.9	M	250	Azithomycine + Cotrimoxazole + Fluconazole
				Shock or heart failure, CCF, pulmonary oedema	30/11/ 2010	Yes (10/12/2010)	Unknown	Y	Y	3TC+DRV+ETR+ RAL+ RTVuns+ TDF	13.9	M	250	Azithomycine + Cotrimoxazole + Fluconazole
				Meningitis, Unspecified	06/10/ 2015	Yes (12/12/2015)	Unknown	Y	N	3TC+DRV+MRV+ RAL+ RTVuns+TDF	18.8	M		N

Notes

Patient #2- Cause of death: HIV-related metastatic adenocarcinoma

Table 7b: Serious clinical adverse events diagnosed in patients aged 6-<18 years on unlicensed dose where the causal association to ETR was not designated or reported as unknown

No observations

Table 7c: Serious clinical adverse events diagnosed in treatment inexperienced patients aged 6-<18 years where the causal association to ETR was not designated or reported as unknown

No observations

Table 7d: Serious clinical adverse events diagnosed in patients aged <6 years where the causal association to ETR was not designated or reported as unknown

No observations

Table 7e: Serious clinical adverse events diagnosed in patients with missing weight and/or dose where the causal association to ETR was not designated or reported as unknown

No observations

Table 8a: Reasons for ETR discontinuations

	Treatment status (n (%))					
	Aged 6-<18 years on licensed dose (n=108)	Aged 6-<18 years on unlicensed dose (n=10)	Age 6-<18 years not treatment-experienced (n=7)	Age <6 years (n=6)	Missing weight and/or dose (n=46)	Total (n=177)
Total not on ETR at last follow-up	**60 (56)**	**8 (80)**	**4 (57)**	**3 (50)**	**23 (50)**	**98 (55)**
Time to discontinuation:						
<1 month	6 (10)	0 (0)	1 (25)	0 (0)	3 (14)	10 (10)
1 - <6 months	4 (7)	3 (33)	0 (0)	0 (0)	1 (5)	8 (8)
6 - <12 months	4 (7)	2 (22)	0 (0)	0 (0)	2 (9)	8 (8)
>=12 months	46 (78)	3 (33)	3 (75)	3 (100)	17 (74)	72 (74)
Reasons for stopping ETR:						
Lack of efficacy	6 (10)	1 (13)	0 (0)	2 (67)	4 (17)	13 (13)
Other	43 (72)	4 (50)	3 (75)	0 (0)	7 (30)	57 (58)
Safety	7[1] (12)	1 (13)	0 (0)	1 (33)	2 (9)	11[1] (11)
Unknown	4 (7)	2 (25)	1 (25)	0 (0)	10 (43)	17 (17)

"Other" reasons for stopping ETR include: Non-compliance, patients wish, simplified treatment, physicians decision (not otherwise specified), drug not available, study treatment ended and other causes

[1]There is one less patient stopping for safety this year when compared to last year's interim report (year 4, 2017).

Table 8b: Further information on patients discontinuing ETR for safety reasons

Total stopping for safety	Aged 6-<18 years on licensed dose (n=7[1])	Aged 6-<18 years on unlicensed dose (n=1)	Age 6-<18 years not treatment-experienced (n=0)	Age <6 years (n=1)	Missing weight and/or dose (n=2)	Total (n=11)
Death	1 (14)	1 (100)	0 (0)	0 (0)	0 (0)	2 (18)
Hypersensitivity reaction (skin eruption etc.)	5 (71)	0 (0)	0 (0)	0 (0)	1 (50)	6 (55)
Toxicity-GI tract/abdomen	1 (14)	0 (0)	0 (0)	1 (100)	1 (50)	3 (27)

These tables only include patients who permanently discontinued ETR. For patients with multiple episodes on ETR, the time to discontinuation is based on their last episode.

Table 9: Enrolment and HCV infection status by cohort

Cohort	Cohort size		HCV positive/known HCV status (n (%))		HBV positive/known HBV status (n (%))	
	Ever in cohort	Aged <18 yrs in current follow-up				
Belgium	175	45	0/29	(0)	4/15	(27)
Germany			-	-	-	-
Italy	1852	316	-	-	-	-
Poland	137	49	1/49	(2)	0/49	(0)
Portugal	163	81	0/81	(0)	1/81	(1)
Romania	588	33	1/33	(3)	1/33	(3)
Russia	1443	653	68/653	(10)	6/653	(1)
Spain	1238	287	5/287	(2)	2/287	(1)
Sweden	134	68	0/67	(0)	2/67	(3)
Switzerland	284	43	0/3	(0)	1/3	(33)
Thailand	1503	312	3/107	(3)	2/233	(1)
UK/Ireland	2098	713	19/579	(3)	25/631	(4)
Total	9615	2600	97/1888	(5)	44/2052	(2)

Notes

There are 2 cohorts who contribute data from Portugal, Spain and Russia and 3 cohorts from Thailand.

Table 10: ART regimens for patients aged <18 years in current follow-up by cohort, n (row %) (n=2600)

Country	In current follow-up	ART regimen (n (%))											
		NNRTI + NRTIs		Boosted PI + NRTIs		Unboosted PI + NRTIs		Boosted PI + NNRTI + NRTIs		Unboosted PI + NNRTI + NRTIs		Other ART regimen		Not on ART	
Belgium	45	7	(16)	7	(16)	1	(2)	0	(0)	0	(0)	23	(51)	7	(16)
Germany	-	-		-		-		-		-		-		-	
Italy	316	84	(27)	160	(51)	4	(1)	2	(1)	0	(0)	29	(9)	37	(12)
Poland	49	16	(33)	11	(22)	0	(0)	0	(0)	0	(0)	22	(45)	0	(0)
Portugal	81	18	(22)	32	(40)	0	(0)	6	(7)	0	(0)	20	(25)	5	(6)
Romania	33	12	(36)	15	(45)	0	(0)	1	(3)	0	(0)	5	(15)	0	(0)
Russia	653	101	(15)	380	(58)	2	(0)	1	(0)	0	(0)	157	(24)	12	(2)
Spain	287	100	(35)	112	(39)	5	(2)	6	(2)	0	(0)	55	(19)	9	(3)
Sweden	68	12	(18)	13	(19)	0	(0)	0	(0)	0	(0)	42	(62)	1	(1)
Switzerland	43	10	(23)	10	(23)	12	(28)	1	(2)	1	(2)	0	(0)	9	(21)
Thailand	312	137	(44)	139	(45)	0	(0)	2	(1)	0	(0)	28	(9)	6	(2)
UK/Ireland	713	238	(33)	201	(28)	4	(1)	3	(0)	1	(0)	223	(31)	43	(6)
Total	2600	735	(28)	1080	(42)	28	(1)	22	(1)	2	(0)	604	(23)	129	(5)

Notes

There are 2 cohorts who contribute data from Portugal, Spain and Russia and 3 cohorts who contribute data from Thailand

Summary data is unavailable for Germany

Totals corrected since last year

Appendix 2: Summary of new data since the Last Interim Report and Narratives For All Serious Adverse Events

Table 1: Summary of numbers of new and existing patients who contributed new data since the 2017 report and their person-years of follow-up

	Number contributing new follow-up data since last report	Total person-years of new follow-up since last report
New patients	**13**	**35**
Existing patients	**57***	**77[#]**

Note: *This excludes existing patients with no new follow-up data since last year, for example those dropped out of the cohort (loss to follow up, move out of the cohort/clinic or transferred to adult care) and those reported as in active follow-up but with no new follow-up data which may be due to reporting delays or gaps in care. [#] Eight years of follow-up reported last year has now found to be incorrect (due to the cohort providing updated information on follow-up end dates). 504 PYFU was reported last year, but the correct number was in fact 496 (the 608 total PYFU reported this year in Table 2 therefore comprises 496 from last year and 112 from this year).

Table 2: Changes in the number of patients reported each year since study inception

	2014	2015	2016	2017	2018
Cumulative total included in ETR report	100	106	155	164	177
Total included from previous year	N/A	98*	106	150†	164
Newly entered ETR report this year	N/A	8	49	14	13
Total discontinued ETR[1]	26	35	51	82	98
Total dropout (no longer in FU) [2]	20	43	57	68	80
Drop out summary‡: LTFU	15	33	20¥	30	36
Moved out of cohort	1	1	1	1	1
Transferred to adult care	4	9	36	37	43

Notes:

Please note that the number of patients no longer in active follow-up each year (i.e. total drop out and drop out summary highlighted in grey) is higher this year than previously reported due to improvements in identification of those no longer in active follow-up.

*A Swiss patient (lost to follow-up in 2014) and a Russian patient (discontinued in 2014) are not included in the 2015 report

†From 2017 the South African cohort are no longer participating in the EPPICC Network PV studies (n=4) and in 2017 a Swiss patient was confirmed as not eligible (after a data correction showing no ETR exposure)

‡Updated since last year due to new data received from cohorts

¥There are 24 patients who in 2015 were reported as LTFU but in 2016 (and thereafter) they have been reported as transferred to adult care

Note some patients who discontinued ETR and those dropped out are not mutually exclusive.

[1] All patients who have an ETR end date and are known to have discontinued (which may have been prior to subsequently being no longer in follow-up)

[2] All patients who we know dropped out either due to LTFU, moving out of cohort or transferring to adult care. This includes patients who we know discontinued prior to dropping out

Table 3: Changes in patients' treatment status by year

Treatment status	2014	2015	2016	2017	2018
Total	100	106*	155	164†	177
New since previous year		8	49	14	13
Excluded since previous year		2	0	5	0
Licensed dose	47	60 (+2 new patients, +12 corrected dose/weight data, -1 patient no longer eligible)	91 (+30 new patients, +1 corrected dose/weight data)	99 (+6 new patients, +4 corrected weight/dose, -2 no longer eligible	108 (+4 new patients, +5 with improved data)
Unlicensed dose	5	6 (+2 new patients, -1 no longer eligible)	12 (+6 new patients)	8 (+1 new patient, -3 corrected weight/dose data, -2 no longer eligible)	10 (+1 new patient, +1 with improved data)
ART inexperienced	1	1	4 (+2 new patients, +1 corrected dose/weight data)	6 (+2 new patients)	7 (+1 new patient)
Aged <6 years	1	4 (+1 new, +2 corrected dose/weight data)	5 (+1 new patient)	5 (1 new patient, -1 no longer eligible)	6 (+1 new patient)
Missing dose/weight	46	35 (+3 new patients, -14 with improved data)	43 (+10 new patients, -2 with improved data)	46 (+4 new patients, -1 with improved data)	46 (+6 new patients, -6 with improved data)

Notes: Changes in the number of patients in each group as compared to the previous year and the reasons for the change are shown in brackets

*Excludes 1 patient in 2015 who was lost to follow-up and 1 patient who discontinued ETR.

†Excludes 4 patients from the South African cohort who, in 2017, were no longer contributing data to the EPPICC PV network and 1 patient who had no evidence of ETR exposure in 2017.

Table 4: Summary of patients on ETR with new DAIDS grade 3 or 4 laboratory test results since the 2017 report

Table/Patient & Country[2]	ETR start date	ETR end date (stopping reason)	Test	Number grade ≥3 tests	Test dates /range	Number grade 3 tests	Number grade 4 tests	Other ART drugs at test(s)	Age at 1st grade ≥3 test	"Normal" value following last grade ≥3 result	Last test date (any grade) on ETR[1]
4a #19 Spain	22/03/2007	Still on drug	TRIG	1	12/03/ 2012	1	0	DRV+RTVl	22.5	Y	19/12/2014
4a #20 Italy	16/06/2009	Still on drug	LDL	1	10/08/ 2015	1	0	DRV+RAL+RTVl	21.8		12/09/2017
4e #11 Italy	19/03/2010	21/01/2018 (Simplified treatment)	ALT	1	09/05/ 2014	0	1	DRV+RAL	19.2	Y	17/11/2017

Notes:

[1] **-** Last reported test of the same marker as reported grade ≥3 test (for example, last reported BIL test if reported grade ≥3 BIL test)

[2] -Patient number and table number in which patient is reported in main body of the report

Table 5: Clinical adverse events experienced by patients on ETR which were newly reported since the 2017 report

Table/ Patient & Country[1]	ETR start date	ETR end date (reason for stopping)	Adverse event	Date event diagnosed	AE resolved (Date if known)	Causal linked to ETR	Serious AE	If serious whether life threatening	Other ART drugs at diagnosis	Age at event (years)	Gender	ETR dose	Concomitant medication
6a #5 Thailand	07/08/2012	Still on drug	Cardiovascular (Ergotism)	25/02/2017	Yes (10/03/2017)	Not related	Y	N	DRV+ETR+ RTVuns+TDF	19.2	F	400	N

Note: [1]Patient number and table number in which patient is reported in the main body of the report

Table 6: Narratives of all serious clinical adverse events in those with prior exposure to ETR

	Summary
1	Table 5a #3: A 9 year old female patient from a Spanish cohort infected with HIV through mother-to-child transmission (MTCT) experienced Stevens -Johnson syndrome six days after starting ETR. The patient started ART aged four months with no CD4 cell count or HIV viral load recorded prior to ART initiation; ETR was initiated when the patient was nine years old when the CD4 cell count was 794 cells/µL, HIV viral load was undetectable and the child had no previous history of an AIDS or CDC stage C events. The patient was on ART at the time of the event comprising: DRV; MRV; RTVuns and 400mg of ETR per day. ETR was thought to be probably the cause of the event and the patient was not on any concomitant medication. ETR and DRV were discontinued on the day of the event and the condition resolved six weeks later. The event was considered to be serious.
2	Table 5a #4: A fourteen year old male patient from UK/Ireland with perinatal HIV infection experienced Stevens-Johnson syndrome. The subject started ART aged 10 years; no information is available about CD4 cell count, HIV viral load or CDC stage at ART initiation. ETR was initiated when the subject was aged 14 years with a CD4 cell count of 4 cells/µL and HIV viral load of 64141 copies/mL. The patient's ART regimen up until the day before the event was: DRV+RAL+RTV and ETR at dose of 400mg per day. All ART including ETR was stopped one day before the event (one month after starting ETR), due to a hypersensitivity reaction, when the CD4 cell count was 112 cells/µL and the HIV viral load was 11,232 copies/mL. The event was considered potentially life-threatening and possibly causally associated with ETR; this event was reported to the UK government under the Yellow Card Scheme for suspected adverse drug reactions. The condition resolved five days after the event. The patient was not on any concomitant medication at the time of the event.
3	Table 6a #1: A 13 year old female patient from Spain died. The patient entered HIV care and started ART aged two months with a CD4 cell count of 3035 cells/µL and a HIV viral load of 120000 copies/mL. The cause of death was stated as an AIDS-defining event; the patient was diagnosed with candidiasis on the date of death, and had been diagnosed with two other AIDS-defining events prior to this (HIV wasting syndrome three years before death, and leishmaniasis two years before death). ETR was initiated 8.9 months prior to death, with an HIV viral load of 757 copies/mL and CD4 of 53 cells/mm^3. ETR was discontinued 2.5 weeks before death, upon physician's decision. The patient was not on any ARV at time of death and the death was considered to be not related to ETR.
4	Table 6a #2: A 12 year old female Thai patient, experienced anaemia. The patient had entered HIV care aged 2.0 years, following perinatal HIV infection and started ART two weeks later with a CD4 cell count of 214 cells/µL and no HIV viral load measurement. ETR was started when the girl was 9.8 years with a CD4 cell count of 534 cells/µL and an HIV viral load of 4698 copies/mL. At the time of the event, the patient was taking 400mg of ETR daily and the following: 3TC; DRV and RTVuns, but no concomitant medication. The patient had no history of other adverse events. The

	event was thought to be life threatening, but it resolved and the patient remained on ETR. It was thought that the event was unlikely to be related to ETR.
5	Table 6a #3: An 8 year old male patient from Germany with perinatal HIV infection experienced a number of serious adverse events whilst on ETR. The subject started ART aged one month. ETR was initiated when the subject was seven years old with an undetectable viral load and CD cell count of 1206 cells/µL. The individual was on 3TC and ABC as well as 200mg of ETR at the time of the first event, when the patient's viral load was undetectable and the CD4 cell count was 1042 cells/µL. The patient was also taking antipsychotic medication. An episode of nausea and vomiting thought to be serious, occurred a little over nine months after starting ETR, both resolved whilst the patient remained on ETR. An episode of pyrexia and gastro-intestinal disease occurred just under two weeks later and resolved within a week. The patient had an episode of indigestion, oesophageal reflux and gastritis aged 11 years, when viral load was undetectable and CD4 cell count was 1304 cells/µL, which resolved the same day; the patient remained on ETR and the initial regimen. All these events were thought to be serious, but not life-threatening. It was thought that all these events were unlikely to be related to ETR.
6	Table 6a #4: A 17 year old Thai female patient with perinatal HIV infection experience abdominal/epigastric pain. The individual started ART with initial regimen DRV, RAL and RTV aged 15 years and received ETR at a dose of 400mg daily. Their CD4 cell count was 117 cells/µL and they had a viral load of 24,1138 copies/mL. The episode of abdominal/epigastric pain was thought to be serious but not life threatening and resolved five days later. The event was not thought to be related to ETR exposure. The patient did not stop ETR during the episode, is still on the drug and was not taking any concomitant medication. The patient had experienced one AIDS defining event (Cytomegalovirus).
7*	Table 6a #5: A 19 year old female peri-natally infected Thai patient developed ergotism. They had started ART aged 8 years and started etravirine at 14 years when their CD4 cell count was 132 cells/µL and their HIV viral load was 282 860 copies/mL. The ergotism was not thought to be life threatening and resolved about 2 weeks later. The event was not considered by the clinician to be related to ETR. The patient did not stop the ETR (400mg daily) containing regimen (which also included DRV+RTVuns+TDF) and is still on the drug without concomitant medication.
8	Table 6b #1: In the unlicensed group a 14 year old male patient with perinatal HIV infection from Spain died from an AIDS-defining event following shock/heart failure four days earlier. The patient entered started ART aged 4.5 years with no available CD4 cell count and no HIV viral load measurement. This patient had a CD4 count of 20 cells/mm^3 and an HIV viral load of 50,000copies/mL at ETR start, nine months before death. The patient was taking 350mg of ETR daily at the time of death as well as the following ART: 3TC; DRV and RTVI. The patient was also taking cotrimoxazole. Previous AIDS-defining events experienced by the child comprised: serious recurrent bacterial infections, wasting syndrome; candidiasis and cytomegalovirus. The treating clinician designated the death as not causally associated with ETR.

9	Table 6e #1: A male patient from Russia experienced adverse events not thought to be causally related to ETR; this patient is newly reported this year and none of the events were thought to be life threatening, but all were considered serious. The patient with perinatal HIV infection started ART aged three years with an HIV viral load of 393,960 copies/mL and a had a subsequent CD4 cell count of 490 cells/µL, eight months later. ETR was started aged nine years. The patient experienced an AIDS diagnosis and CDC stage C event, 1 year 6 months after starting ETR. The patient had their first serious adverse event aged 13 years when they presented with chronic otitis media/conductive deafness and bacterial pneumonia. At the time of all events the patient was taking the following ART: 3TC; ABC as well as 200mg of ETR daily and no other concomitant medication. The otitis media/conductive deafness did not resolve but the bacterial pneumonia resolved two months later. The patient experienced two episodes of pneumococcal pneumonia, one episode of which occurred whilst the patient was on the same regimen but was also receiving sulfamethoxazole and trimethoprim and one episode after the patient had stopped ETR and was taking: 3TC; ABC; DRV and RTVI and was continuing on the antibiotics. This patient also experienced exfoliative dermatitis/Stevens-Johnson/TEN after the discontinuation of ETR, the cause of which was attributed to ATZ: all ART was stopped due to this adverse event. All events were considered to be serious because they required hospitalization.
10	Table 7a #1: A case of lipodystrophy in a 15 year old male patient from the UK/Ireland was reported over six months after starting ETR. The patient started ART in December 1996 aged four years with a CD4% of 13 and a HIV viral load of 110,500 copies/mL. ETR was started when the individual was 15.3 years when the CD4 cell count was 550 cells/µL and an HIV viral load of 400 copies/mL. No AIDS diagnoses were reported. The event was thought to be serious (as it required hospitalization) but not life threatening and the causal relationship with ETR was unknown. The CD4 cell count at the time of the event was 558 cells/µL and the HIV viral load was undetectable. The regimen the patient was on at the time of the event comprised the following ART: ATZ; RTVI and 400mg of ETR daily. The patient discontinued ETR due to other causes not specified 16 days after the event and it is not known whether the lipodystrophy resolved.
11	Table 7a #2: A 15 year old male patient from the UK/Ireland cohort, reported last year, died of an HIV-related metastatic adenocarcinoma. This patient with perinatal HIV infection started ART aged four years with no HIV viral load or CD4 cell count at the time of ART initiation. ETR was started aged 15 years with a CD4 cell count of 470cells/µL and a HIV viral load of 6606 copies/mL. At the time of death two months later the patient was taking a regimen which comprised: DRV; RAL; RTVI and 400mg of ETR per day with no concomitant medication. At the time of death the patient had a CD4 cell count of 670 cell/µL. The causal relationship with ETR was unknown.
12	Table 7a #3: A 13 year old, male Thai patient experienced three events at the same time: autoimmune haemolytic anaemia; hypokalaemia and shock/heart failure/CCF/ pulmonary oedema. The patient with perinatal HIV infection started ART aged six years with no prior HIV viral load or CD4 cell count. ETR was started aged 13 years

	with a CD4 cell count of 18 cells/µL and a viral load of 460,756 copies/mL. These events were diagnosed over eight months after starting ETR when the patient was taking the following regimen: 3TC; DRV; RAL; RTVuns; TDF and 250mg of ETR daily. The patient was also taking fluconazole, azithomycine and cotrimoxazole at the time of the event. All events were considered to be life-threatening; all events resolved within 2 weeks. The causal relationship with ETR was unknown. The patient stopped ETR upon the physician's decision eight months after these events. This patient was also diagnosed with meningitis newly reported this year; the event occurred more than four years after stopping ETR when the patient was 18 years of age. The regimen being taken at the time of the event comprised: 3TC; DRV; MRV; RAL; RTVuns and TDF. The causal relationship with ETR was recorded as unknown.

*-New event since last year

Appendix 3: Cohort Key References for Further Reading

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Appendix 4: EPPICC Standard Operating Procedure, 2018 Version 1.0

(Highlights in the document indicate changes from the previous data maerger)

European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

Pharmacovigilance studies on the use of ART
in HIV-infected children and young people in Europe

Standard Operating Procedure
Version 1.0
2018 data merger

Table of Contents

1. Introduction

This document provides guidance on the preparation of data files for the EPPICC pharmacovigilance data merger 2018.

Please refer to section 4 for details on the specific drug under pharmacovigilance this year.

By participating in this merger, each cohort agrees to submit data in accordance with the study protocol, GCP and national ethics and regulatory requirements.

Cohorts agree to report serious adverse events if required under national requirements.

2. Participating cohort studies:

If your details are not listed here and you are interested in joining a PV study (pharmacovigilance study) , please contact Laura Mangiarini at PENTA and Jeannie Collins at EPPICC (Laura.Mangiarini@pentafoundation.org; jeannie.collins@ucl.ac.uk) to check if the study is open to new cohorts and to ensure all ethics and regulatory requirements are met before proceeding with the data merger. Also, please report any changes to the key contact person for your cohort to the EPPICC data Manager (c.duff@ucl.ac.uk).

Belgium: Hospital St Pierre Cohort, Brussels
Contact: Dr Tessa Goetghebuer

Copenhagen Cohort, Denmark
Contact: Niels Valerius

French Perinatal Cohort Study / Enquête Périnatale Français
Contact: Dr Josiane Warszawski, Dr Jêrome Le Chenadec

German Pediatric and Adolescent HIV cohort
Contact: Dr Chris Koenigs

Greece Cohort
Contact: Vana Spoulou

HIV-NAT, Bangkok
Contact: Dr Wasana Prasitsuebsai

Holland: ATHENA national observational HIV cohort
Contact: Dr Colette Smit, Henriette Scherpbier

Italian Register for HIV infection in children
Contact: Dr Maurizio de Martino, Dr Luisa Galli

Khon Kaen University, Thailand
Contact: Dr Pope Kosalaraksa and Dr Pagakrong Lumbiganon

Latvia: Latvian Cohort
Contact: Dr Santa Ansone

Polish Paediatric Cohort
Contact: Magda Marczynska

Portugal: Centro Hospitalar do Porto
Contact: Laura Marques

Portugal: HSM/CHLN Lisbon Cohort
Contact: Filipa Prata

Romania: "Victor Babes" Hospital Cohort, Bucharest
Contact: Dr Luminita Ene

Russia: Republican Hospital of Infectious Diseases, St Petersburg
Contact: Evgeny Voronin, Liubov Okhonskaia

Russia: The City HIV Centre, St Petersburg
Contact: Anna Samarina

Russia: Irkutsk AIDS Centre
Contact: Yulia Plotnikova, Vladimir Rozenberg

Spain: Catalonia Cohort of HIV-infected Children (CoRISPE-cat)
Contact: Dr Ton Noguera

Spain: Rest of Spain Cohort of HIV-infected Children (CoRISPE-S)
Contact: Dr Maribel Gonzalez

Swedish Cohort Study
Contact: Lars Naver

Swiss Mother and Child HIV Cohort Study (MoCHiV)
Contact: Dr Christoph Rudin

Thailand Program for HIV Prevention and Treatment (PHPT) Study Group (PHPT)
Contact: Gonzague Jourdain

UK / Ireland National Study of HIV in Pregnancy and Childhood (NSHPC) and Collaborative HIV Paediatric Study (CHIPS)
Contact: Dr Claire Thorne (NSHPC), Dr Ali Judd (CHIPS)

Ukraine Paediatric HIV Cohort Study, Odessa
Contact : Dr Ruslan Malyuta

Rahima Moosa Mother and Child Hospital South Africa
Contact: Dr Karl Technau

EPPICC Data Manager:
Charlotte Duff
email c.duff@ucl.ac.uk

3. Timing

Each cohort will be responsible for gathering, computerizing and submitting its own data, which will be sent to the EPPICC Data Manager to be electronically merged.

The deadline for data submission for this merger is Monday 29th January 2018. Data received after this date will not be guaranteed inclusion. Cohorts are welcome to send data in advance of this date.

During the 2 months after the submission of data, up to Friday 30th March 2018, we will work closely with cohorts to clean their data. This will involve:

- sending out data consistency checks in the form of a discrepancy report
- processing responses and sending further checks where necessary.

The cleaning of the data should be finally completed by Friday 30th March 2018.

4. Information specific to this year's merger

For this 2018 data merger, there is only one drug under pharmacovigilance.

- Etravirine (ETR)

The eligibility criteria for patients are as follows:

- Ever (current or previous) use of ETR
- Age under 18 years when started ETR

5. General data considerations

Formats based on the HIV Cohorts Data Exchange Protocol (HICDEP) will be used for all data submissions for this study. The HICDEP format is based on a relational structure, and the data for this study will be collected in a series of tables, which are described in the next section. All lookup tables for the codes to be used can be found in the Excel worksheet supplied with this SOP (with the exception of the very simple codings e.g yes/no , which specified within the data specificaction).

The data requested will generally refer to the entire period of follow-up for each patient - i.e. before, during, and after taking ETR - unless otherwise indicated. Please provide as complete information as possible. Particularly important are the following variables during the time the patient was on ETR:

- ART doses
- weights
- viral loads
- reason for stopping ART if applicable
- laboratory toxicity data for periods immediately before and while on the drugs
- adverse events possibly related to the drugs

Please provide us with your raw data for numeric values, such as weight, and please do not round these values up or down. If data are missing, please ensure that the field contains a NULL, unless otherwise indicated; note also that missing data coded as a zero could be misinterpreted as valid coded data.

Please also note that if any patients were included in our analyses last year then you must send last year's data again, and add any new follow-up data, even if they have subsequently stopped taking the drugs or have moved on to another clinic. If you have no new information additional to what was sent last year, please just resend last year's data (see section 3.2 for notes on payments).

Please refer to the latest published HICDEP specification for further clarification of variable definitions and formats:

http://www.hicdep.org/wiki/Hicdep_1.100

Please contact the EPPICC Data Manager if you have any queries.

6. Data transfer procedure

6.1 Extraction

We are happy to accept files in either Access or Excel. However, if it makes no difference to you, our preferred format is Access as it is significantly quicker and easier to import.

If you would like to send data in another format, please pre-arrange this with the EPPICC Data Manager.

6.2 Transfer Process

Files should all be sent together. Please do not send incomplete files or different files on different dates. Files may be sent via email.

The initial data files should be zipped and password-protected (preferably using WinZIP AES encryption) and emailed to the EPPICC Data Manager, Charlotte Duff: c.duff@ucl.ac.uk

Each cohort will be sent their individually allocated password when they confirm participation in the study. In compliance with UK Data Protection Laws, the password will be sent to cohorts by another member of the EPPICC team in London (ie not the data manager).

For all data submissions, the data manager will email the cohort to confirm that the data have been successfully received and opened. If you do not receive confirmation of data receipt within a day, contact the data manager.

7. Details of variables needed

7.0 CONTEXT table – aggregated data on key contextual characteristics (1 row per cohort)
Please complete this table for **all children in your cohort** (not just for those for whom you are submitting data in this merger).

Field name	Format	Description
COHORT	Text	Cohort code
SAMPSI_EVER	Numeric	Total number of children that have ever been in the cohort (including lost to follow-up, deaths, transfers to adult care etc)
SAMPSI_NOW	Numeric	Number of children aged <18 in current follow-up
FREQ_1	Numeric	No. of patients aged <18 currently on NNRTI+NRTIs
FREQ_2	Numeric	No. of patients aged <18 currently on boosted PI+NRTIs
FREQ_4	Numeric	No. of patients aged <18 currently on unboosted PI+NRTIs
FREQ_5	Numeric	No. of patients aged <18 currently on boosted PI+NNRTI+NRTI
FREQ_6	Numeric	No. of patients aged <18 currently on unboosted PI+NNRTI+NRTI
FREQ_7	Numeric	No. of patients aged <18 currently on other ART regimen
FREQ_8	Numeric	No. of patients aged <18 currently not taking ART **Note that the sum of Freq1-Freq8 should equal SAMPSI_NOW** **FREQ1 - FREQ8 are mutually exclusive** **Note that "currently" for these fields means "at the last patient visit". So include a patient if at their last visit they were under18 and on that drug regimen.**
HCV_STAT	Numeric	Number of patients aged <18 in current follow-up for whom HCV antibody status is known
HCV_POS	Numeric	Number of patients aged <18 in current follow-up known to be anti-HCV seropositive
HBV_STAT	Numeric	Number of patients aged <18 in current follow-up for whom HBV infection status is known
HBV_POS	Numeric	Number of patients aged <18 in current follow-up known to be HBV surface antigen positive

AE_NONSER	Numeric 0=No 1=Yes, non-serious AEs collected for ETR 9=unknown	Does your cohort collect non-serious AEs considered causally related to ETR? If yes, these should be reported in table AE
AE_NONSER_TEXT	Free text	Details if AE_NONSER=2

7.1 BAS table - basic clinical and demographic data (1 row per patient)

Field name	**Format**	**Description**
COHORT	Text	Cohort code
PATIENT	Character or numeric	Cohort patient ID (unique and anonymous)
CENTER	Character	Clinic/centre/hospital where patient is seen
BIRTH_D	dd/mm/yyyy	Birth date
ENROL_D	dd/mm/yyyy	Enrolment date
GENDER	1=Male 2=Female 9=Unknown	Sex
MODE	Coding list in associated Excel workbook	Mode of acquisition of HIV infection
MODE_OTH	Free text	Details if MODE=90 (other)
ETHNIC	Coding list in associated Excel workbook	Ethnic group
HIVDIAG_D	dd/mm/yyyy	Date of HIV diagnosis
AIDS_Y	0=No 1=Yes 9=Unknown	Has patient been given an AIDS diagnosis?
AIDS_D	dd/mm/yyyy	If yes, date of AIDS diagnosis
HCVANTI_Y	0=No 1=Yes 9=Unknown	Is patient anti-HCV seropositive (excluding tests before age 18 months)
HBSAG_Y	0=No 1=Yes 9=Unknown	Is the patient HBV surface antigen positive?
HBACTIVE_Y	0=No 1=Yes 9=Unknown	Does the patient have active hepatitis B (i.e. detectable HBV DNA and/or HBeAg positive?)
PMTCT	0=No 1=Yes 9=Unknown	Did the patient receive ART for PMTCT when they were a baby?

7.2 STUDY table - basic data about inclusion in the ETR study (1 row per patient)

In 2018 we have only one study drug (ETR), so please enter one row for each patient in this table

Field name	Format	Description
COHORT	Text	Cohort code
PATIENT	Character or numeric	Cohort patient ID (unique and anonymous)
AE_Y	0=no 1=yes 9=unknown	Has the patient had a clinical (serious or non serious) adverse event since starting ETR?

7.3 LTFU table – death, transfer and drop-out data (1 row per patient)

Field name	Format	Description
COHORT	Text	Cohort code
PATIENT	Character or numeric	Cohort patient ID
DROP_Y	0=No 1=Yes	Has the patient dropped out? (i.e. been lost to follow-up or transferred away /to adult care)
DROP_D	dd/mm/yyyy	If YES, date of last visit
DROP_RS	Coding list in associated Excel workbook	If YES, reason for DROP
DEATH_Y	0=No 1=Yes	Has the patient died? Please note that all deaths must also be reported in AE table
DEATH_D	dd/mm/yyyy	If YES, date of death
DEATH_R1	Coding list in associated Excel workbook	Cause of death
DEATH_RC1	I=immediate cause U=underlying cause/condition C=contributing cause N=not available	Coding of causal relation of the code given in DEATH_R1 to the death
DEATH_R2	Coding list in associated Excel workbook	Cause of death
DEATH_RC2	I=immediate cause U=underlying cause/condition C=contributing cause N=not available	Coding of causal relation of the code given in DEATH_R2 to the death
DEATH_R3	Coding list in associated Excel workbook	Cause of death
DEATH_RC3	I=immediate cause U=underlying cause/condition C=contributing cause N=not available	Coding of causal relation of the code given in DEATH_R3 to the death

DEATH_R# and DEATH_RC# should be continued for as many reasons as are recorded.

7.4 OVERLAP table – patients overlapping with other cohorts (1 row per overlap)

If a patient has no overlaps, please do not put any rows in this table. Only complete a row in this table if you think this patient will also be reported to the merger by another cohort mentioned in this SOP

Field name	**Format**	**Description**
COHORT	Text	Cohort code
PATIENT	Character or numeric	Cohort patient ID (unique and anonymous)
COH_OTH	Character	Other cohort who this patient is part of
PAT_OTH	Character	Unique patient ID in the other cohort

7.5 VIS table - basic follow-up/ visit related data (1 row per measurement)

Please report every weight, preferably from first presentation.

Field name	Format	Description
COHORT	Text	Cohort code
PATIENT	Character or numeric	Cohort patient ID
VIS_D	dd/mm/yyyy	Date of patient visit
WEIGH	Numeric or 999=unknown	Weight at patient visit (kg)

7.6 ART table - antiretroviral treatment data (1 row per date per drug)

Please complete this table for all ART being taken, not just ETR.

DOSE:
For drug under pharmacovigilance (ETR), please report **doses, including all dose changes.**

We have brought this specification in line with HICDEP so, now ART_DO should be dose per intake, unless only the total daily dose is known, in which case ART_DO = total daily dose and ART_FR = -1.

STOP REASON and END DATE:
If a child was still receiving a drug at last follow-up, please code reason for stopping as "0". If a child had stopped taking a drug but the stop date is unknown, please enter the stop date as "11/11/1911".
Where a child stops taking ETR, if the main reason for stopping is because of toxicity related to ETR please ensure this toxicity is also documented in the AE table.

GENERIC DRUGS:
For generic drugs, please code using the HICDEP drug code for the active component, but complete the codes GENERIC_CODE and GENERIC _DESCRIPTION at the end of this table. For non-generic drugs, you may leave these fields blank. If you have any problems with this specification, please contact the EPPICC Data Manager.

Field name	Format	Description
COHORT	Text	Cohort code
PATIENT	Character or numeric	Cohort patient ID
ART_ID	Coding list in associated Excel workbook	Code representing the antiretroviral treatment
ART_FORM	1 = tablet 2 = granules	Drug formulation Please note – this only needs to be completed for the study drug (ETR)
ART_SD	dd/mm/yyyy	Start date

ART_SD_P	< = before this date D = exact to the date M = exact to the month Y = exact to the year > = after this date U = unknown	Precision of ART_SD.
ART_ED	dd/mm/yyyy	Stop date
ART_ED_P	< = before this date D = exact to the date M = exact to the month Y = exact to the year > = after this date U = unknown	Precision of ART_ED.
ART_DO	Numeric Missing =999	Dose per intake. If the dose per intake is unknown and only the total daily dose is known, then please enter the total daily dose here and ensure you state this in the dose frequency (ART_FR=-1, see beneath).
ART_FR	-1 = Frequency not known. ART_DO contains total daily dosage per day 0.33 = 1 dose every third day 0.5 = 1 dose every second day 1 = 1 daily dose/qd 2 = 2 daily doses/bid 3 = 3 daily doses/tid 4... = code gives number of daily doses	Frequency of dosing (now using same convention as HICDEP)
ART_RS	Coding list in associated Excel workbook	Main reason for stopping Note that if there is more than one main reason, please code as 98=Other and put the reason codes into ART_RS_OTH text field.
ART_RS_OTH	Character (free text)	Other reason for stopping (if ART_RS = 98 (“Other causes”)
GENERIC_CODE	Character	Your own cohort code for this generic drug
GENERIC_DESCRIPTION	Character	Name (sold as)

7.7 MED table - other non-ART medication (1 row per measurement)

If a child had stopped taking a drug but the stop date is unknown, please enter the stop date as "11/11/1911".

Field name	Format	Description
COHORT	Text	Cohort code
PATIENT	Character or numeric	Cohort patient ID
MED_ID	Coding list in associated Excel workbook	Code representing other medication
MED_ONG	0=No, stopped drug 1=Yes, patient still on drug 9=Unknown	Is the patient still on the drug?
MED_SD	dd/mm/yyyy	Date of initiation
MED_ED	dd/mm/yyyy	Date of stopping

7.8 DIS table - CDC B and AIDS-defining events (1 row per event diagnosed)

Please note that we are collecting CDC clinical category B and C events for this project.

Field name	Format	Description
COHORT	Text	Cohort code
PATIENT	Character or numeric	Cohort patient ID
DIS_ID	Coding list in associated Excel workbook	Code to identify event
DIS_D	dd/mm/yyyy	Date of event
DIS_WD	1=definitive 2=presumptive 3=diagnosis from autopsy 4=diagnosis from registry 9=unknown	Means of diagnosis

7.9 LAB table - laboratory data (1 row per measurement)

Please provide **all available data** on laboratory test results and normal as well as abnormal results, for the 12 months prior to starting ETR up to the present.

This is the full list of lab markers that we will be investigating in 2018:

Marker	LAB_ID	Unit	Code (LAB_U)
Absolute neutrophil count	ANC	10^9/L	8
Total colesterol	CHOL	mmol/L	1
Triglycerides	TRIG	mmol/L	1
Alanine aminotransferase	ALT	u/L	5
Total bilirubin	TBIL	µmol/L	6
Blood glucose fasting	FPG	mmol/L	1
Blood glucose non-fasting	Non-FPG	mmol/L	1
Pancreatic amylase	P-AMY	u/L	5
Lipase	LIP	u/L	5

Serum HDL	HDL	mmol/L	1
Serum LDL	LDL	mmol/L	1
Alkaline phosphatase	APT	u/L	5
Aspartate aminotransferase	AST	u/L	5

Please do not report CD4 and HIV-1 RNA values here – see separate tables LAB_CD4 and LAB_RNA

Field name	**Format**	**Description**
COHORT	Text	Cohort code
PATIENT	Character or numeric	Cohort patient ID
LAB_ID	Coding list in associated Excel workbook	Laboratory test type
LAB_D	dd/mm/yyyy	Date of lab measurement
LAB_V	Numeric If value is undetectable, please record as -1	Value of measurement
LAB_U	Coding list in associated Excel workbook	Unit of measurement used – SI units only
LAB_LLN	Numeric	Lower limit normal for lab conducting test. Note – this MUST be when LAB_V=-1
LAB_ULN	Numeric	Upper limit normal for lab conducting the test Note – this MUST be completed for bilirubin, pancreatic amylase, lipase, ALT, AST, alkaline phosphatase and creatinine
LAB_FA	0=No 1=Yes 9=unknown	Was the blood sample taken whilst fasting?
LAB_ST	WB = whole blood P=plasma S=serum	Specimen type

7.11 LAB_CD4 table - CD4 data (1 row per measurement)

If both CD4 count and CD4 percentage are recorded, please provide both in separate records.

Field name	**Format**	**Description**
COHORT	Text	Cohort code
PATIENT	Character or numeric	Cohort patient ID
CD4_D	dd/mm/yyyy	Date of CD4 measurement
CD4_V	Numeric If undetectable, please record -1	Value of CD4 measurement
CD4_U	Numeric with codes 1=cells/mm^3 2=% 3=total lymphocytes/µl	CD4 cell count or CD4 %

7.12 LAB_RNA table – HIV-1 RNA data (1 row per measurement)

Field name	Format	Description
COHORT	Text	Cohort code
PATIENT	Character or numeric	Cohort patient ID
RNA_D	dd/mm/yyyy	Date of HIV-1 RNA measurement
RNA_V	Put the value here OR -1 if below level of detection or 1 if above upper limit	HIV-1 RNA measurement value (copies/ml)
RNA_L	Numeric	Lower limit of HIV-1 RNA assay
RNA_U	Numeric	Upper limit of HIV-1 RNA assay

For any VL result obtained from a diluted sample, please report the VL and LOD taking the dilution factor into account. For example, if a Roche US assay was used (LOD 50) on a 1:2 diluted sample, a VL reading of undetectable this would be reported as RNA_V=-1 & RNA_L=100, a VL reading of 245 would be reported as RNA_V=490 & RNA_L=100.

7.13 AE table – CLINICAL adverse events (1 row per measurement)

Please note that this table is different from the HICDEP AE table, and is more relevant to pharmacovigilance. It should contain all serious* non-HIV-related adverse events and non-AIDS-defining malignancies. It must also include all deaths, which should be reported in BOTH the LTFU table and this AE table. For deaths use code D1 for AE_ID.

Please also report all non-serious AEs related to the study drug, where available. Cohorts which collect data on non-serious AEs related to the study drug should indicate this in the AE_NONSER field in the CONTEXT table.

For any AE, which becomes an SAE, a new record should be entered with the onset date specifically for the SAE.

*A Serious AE is defined as any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as any event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or require intervention (eg medical, surgical) to prevent one of the other serious outcomes listed in the definition above)

Please refer to DAIDS toxicity tables when completing AE_WORST:

http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf

Field name	Format	Description
COHORT	Text	Cohort code
PATIENT	Character or numeric	Cohort patient ID
AE_D	dd/mm/yyyy	Date of event

AE_ID	Coding list in associated Excel workbook	Code for event. If this is blank, full details must be completed in field AE_DESCRIP
EVENT_ID	Numeric	Unique numeric identifier for the event – used to link to table AE_NADM where necessary
AE_RES	0=no 1=yes 9=unknown	Whether adverse event has resolved
AE_RES_D	dd/mm/yyyy	Date resolved. Please code 11/11/1911 if adverse event known to have resolved but date resolved not known.
AE_WORST	1 = Mild 2 = Moderate 3 = Severe 4 = Life threatening 9 = unknown	Worst grade (please refer to and code from DAIDS toxicity tables)
AE_SAE	0=no 1=yes 9=unknown	Whether AE was considered serious. If YES AE_SAE_C must be completed
AE_SAE_C	1=death 2=life threatening 3= hospitalization 4=disability 5=birth defect 6=medical event 9=unknown	Criteria for seriousness (Leave blank if AE_SAE =0)
AE_ART	0=no 1=yes 9=unknown	ART stopped or modified
AE_DESCRIP	Character (free text)	Full description of the event (this field replaces AE_TEXT)
AE_R_Y	0 = not related 1 = definitive 2 = remote/unlikely 3 = possible 4 = probable 9 = unknown	Relation to treatment with DRUG in AE_DRUG – note if coded 1,3 or 4 then AE_DRUG must be completed
AE_DRUG	Character with codes	Code representing the antiretroviral treatment (see coding list for ART_ID in associated Excel) MUST be filled in if AE_R_Y, 3 or 4=1
AE_R_Y1	0 = not related 1 = definitive 2 = remote/unlikely 3 = possible 4 = probable 9 = unknown	Relation to treatment with DRUG in AE_DRUG1 – note if coded 1,3 or 4 then AE_DRUG must be completed
AE_DRUG1	Character with codes	Code representing the second antiretroviral treatment if there are more than one

Continue AE_R_Yx and AE_DRUGx for as many are necessary. i.e. AE_DRUG, AE_DRUG1, AE_DRUG2, AE_DRUG3 etc

7.14 AE_NADM – non-AIDS defining malignancies

Field name	Format	Description
COHORT	Text	Cohort code
PATIENT	Character or numeric	Cohort patient ID
EVENT_ID	Numeric	Unique numeric identifier for the event – used to link to table AE where necessary
CANTYP_T	Character	Type of cancer
CANLOC_T	Character	Primary location of cancer (if known)
CANLOC_Y	1=Unknown	Primary location of cancer unknown
ICD10	Character	ICD-10 code for cancer disease
ICD9	Character	ICD-9 code for cancer disease
SPREAD_V	1=Localized 2=Disseminated 9=Unknown	Stage (spread) at diagnosis
PATREP_Y	0=No 1=Yes, full report 2=Summary of report 9=Unknown	Is the pathology report (or summary report) available?
PATREP_S	Character	Summary of pathology report
DIARAD_Y	1=Yes 0=No 9=Unknown	Diagnosis based on radiology
DIABIO_Y	1=Yes 0=No 9=Unknown	Diagnosis based on biochemistry
DIAVIS_Y	1=Yes 0=No 9=Unknown	Diagnosis based on visual inspection
DIAOTH_Y	1=Yes 0=No 9=Unknown	Diagnosis based on other
DIA_S	Free text	Specify what the diagnosis is based on

7.15 PREV_STUDY table – reasons why a patient has not been included this year when they were included previously for the ETR study

There is no need to fill in this table except for any patients for whom you have sent data in previous years, but who you have been unable to include this year.

Note – this table may also be used to give details of any patients who have changed their patient ID for some reason.

Field name	Format	Description
COHORT	Text	Cohort code
PATIENT	Character or numeric	Cohort patient ID (unique and anonymous)
WHY_NOT_INCLUDED	Character	Please explain very briefly why you are unable to submit data on this patient

SOP Appendix 1 – Overlaps between tables:

Deaths should be reported in both LTFU and AE tables.

If an adverse event causes a drug to be stopped, this information should appear in both the AE and ART tables

Information on non-AIDS defining malignancies should be recorded in both AE and AE_NADM

Any HIV-related adverse events (i.e. CDC B and C events) should be reported in the DIS table and not the AE table

SOP Appendix 2 – Answers to frequently asked questions and clarifications

This section explains some of the data specification in more detail and provides clarification about issues often causing a problem.

Look-up tables

These are now all documented in the Excel spreadsheet supplied with this SOP entitled EPPICC_PV _CODES_2018_v1.0.xlsx

Simple look-up lists (0=no, 1=yes, 9=unknown) are documented within the data specification above.

ART Dose reporting

When the PV studies began, we used to ask you to record ART_DO as the total daily dose. However, to be consistent with HICDEP, we now ask for ART_DO the dose per intake. The additional field ART_FR shows how many times per day this dose is taken.

ART_FR x ART_DO = total daily dose

If the dose of study drug is reported incorrectly by you, this can cause major problems as it can put your patient into a different category for analysis and therefore cause errors in our reporting tables.
ART_DO should always be the dose per intake and ART_FR the frequency of doses per day.
If the frequency is unknown, put ART_FR=-1 and ART_DO = total daily dose

Viral load

If the value is lower than the lower limit of detection, please record RNA_V as -1 and ensure that you have recorded the lower limit of detection in RNA_L

If the value is higher than the upper limit of detection, please record RNA_V as 1 and ensure that you have recorded the upper limit of detection in RNA_U

If there is no value detected, please code as -1.

If you feel your data needs any additional codings, please do not use them without checking with the data manager first.

Lab Units

All lab markers should be reported in SI units as specified in this document. It causes enormous problems and confusions if not.

Event Reporting

Two problems seem to be occurring regularly in cohort data:

1) An event previously reported does not get reported in a subsequent year. Please ensure that you report all events.

2) If an adverse event is a lab marker abnormality, that event should be in the data in 2 places, as a low/high result in the LAB table and also in the AE table.

Changes made to this document

Version	Date	Author	Reason
1.0	1st December 2017	Charlotte Duff	First version sent to cohorts

Appendix 5: PENTA Protocol

Pharmacovigilance study to define the long-term safety profile of etravirine in HIV-infected children and adolescents in Europe: Study protocol

European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

Final protocol, version 11 October 2013

Authors: Ali Judd, Jeannie Collins, Carlo Giaquinto

1. Introduction

Paediatric HIV infection is mainly acquired vertically, through mother-to-child transmission (MTCT). There were an estimated 3.3 million children aged less than 15 years living with HIV worldwide at the end of 2011, with 330,000 new infections in 2011 alone[1]. The number of HIV-infected children <15 years of age living in Western and Central Europe, was estimated by the WHO to be 1600 (range 1300-2000) for 2011, with data not reported for most countries, and is likely to be an underestimate (see Discussion) [2]. In the European Union, the rate of newly diagnosed HIV infections was estimated at 5.75 per 100,000 in 2010 [3]. MTCT rates in Western Europe are at an all time low (<1-2%) due to a combination of interventions, particularly the widespread use of combination antiretroviral therapy (cART) both for treatment of maternal HIV disease and as prophylaxis for prevention of MTCT[4-6]. However, immigration of HIV-infected children born abroad also contributes to the population of infected children living in Europe.

The aim of antiretroviral therapy in children is to achieve undetectable HIV RNA levels, to maintain viral suppression and thus to allow normal immune function, whilst minimising drug toxicities. Current guidelines recommend the use of cART with at least three drugs, including a dual nucleoside analogue reverse transcriptase inhibitor (NRTI) backbone with either a boosted protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Vertically infected children with access to cART have substantially improved health and life expectancy[7-11] and can expect to survive into adult life. Paediatric HIV infection is thus now recognised as a chronic disease, requiring life-long therapy.

Etravirine (ETR, Intelence®), a non-nucleoside reverse transcriptase inhibitor, is indicated in Europe for use in antiretroviral treatment-experienced patients aged ≥6 years[11]. The paediatric dose is based on body weight as follows:

- ≥16-<20kg 100mg twice daily
- ≥20-<25kg 125mg twice daily
- ≥25-<30kg 150mg twice daily
- ≥30kg 200mg twice daily (adult dose).

In clinical trials in adults patients the most common (≥ 10%) adverse drug reactions (ADRs) in the ETR group were rash, diarrhoea, nausea, and headache, with rash occurring more

frequently in females. The frequency, type and severity of adverse drug reactions in clinical trial paediatric patients were comparable to those observed in the adult trials.

The Risk Management Plan (RMP) for ETR mentions the following risks for adult and paediatric patients: severe cutaneous reactions, severe hypersensitivity including DRESS, hepatotoxicity, pancreatitis, hyperlipidaemia, coronary artery disorders, and development of drug resistance. Overdose due to medication errors is identified as a potential risk. The RMP identified a lack of information on long-term safety in children aged 6 to <18 years of age. Indeed, little is known about the “real life” use and safety of ETR in the European population of HIV-infected children and adolescents. The Committee for Medicinal Products for Human Use (CHMP) has highlighted the need for a post-marketing surveillance study of ETR use in the paediatric population. Janssen-Cilag International NV has approached the PENTA Foundation/ European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) about establishing such a study in HIV-infected children and adolescents living in Europe.

2. Aim and objectives

The aim of this study is to collect long-term safety data on ETR use in children and adolescents with HIV infection in a "real world" setting in Europe.

The objectives are:

1) to describe the clinical characteristics of patients at start of ETR-based therapy
2) to describe the incidence of grade 3 and 4 adverse events for key laboratory markers by duration of ETR use
3) to provide the incidence and describe clinical serious adverse events which are considered to be causally related to ETR by duration of ETR use
4) to report clinical non-serious adverse events which are considered to be causally related to ETR, where available
5) to characterise reasons for discontinuation of ETR
6) to provide information on any off-label use of ETR in children (excluding in utero exposure), including in treatment-naive children and those <6 years.

3. Study design

This is an observational study involving the pooled analysis of individual patient data from prospective cohort studies participating in the EPPICC pharmacovigilance programme. EPPICC conducts epidemiological research on the prognosis and outcome of HIV-infected pregnant women, children and children exposed to HIV in utero and currently consists of the following paediatric studies:

Belgium: Hospital St Pierre Cohort, Brussels
Contact: Dr Tessa Goetghebuer

Europe-wide: European Collaborative Study
Contact: Dr Claire Thorne

Germany: Competence Network on HIV infected children
Contact: Dr Chris Koenigs

Italy: Italian Register for HIV infection in children

Contact: Dr Maurizio de Martino, Dr Luisa Galli

Romania: "Victor Babes" Hospital Cohort, Bucharest

Contact: Dr Dan Duiculescu, Dr Luminita Ene

Spain: Madrid Paediatric HIV Cohort Study

Contact: Dr Jose Thomas Ramos Amador

Spain: CoRISPE-cat study, Catalonia

Contact: Dr Ton Noguera

Spain: CoRISPE-1 study, rest of Spain

Contact: Dr Pablo Rojo Conejo

Sweden: Swedish Cohort Study
Contact: Lars Naver

Ukraine: Ukraine Paediatric Cohort Study

Contact: Ruslan Malutya

UK/Ireland: Collaborative HIV Paediatric Study (CHIPS) and National Study of HIV in Pregnancy and Childhood (NSHPC)

Contact: Dr Ali Judd (CHIPS)/ Dr Pat Tookey (NSHPC)

Inclusion criteria:

All HIV-infected children and adolescents with current or previous use of ETR treatment (excluding in utero exposure), regardless of clinical stage, and who were aged < 18 years at commencement of ETR treatment will be included in the study.

Study size:

At the time of the first data merger for the study in early 2014, it is expected that approximately 80 patients will be eligible for inclusion in the study. In the second year of the study, follow-up data on these 80 ETR-exposed children will be collected as well as new data on

any children newly reported to have started an ETR-containing regimen over the previous 12 months. This process will be repeated in subsequent years, and it is envisaged that this study will run for five years, with the number of exposed subjects expected to increase to approximately 100 and the total cumulative duration of exposure similarly increasing over time.

Each year the data merger itself will take place in January. Data checking, query resolution and data analyses will take place over the next 5 months, with a draft study report available to Janssen-Cilag International NV in July, and a final study report at the end of September. The same timetable will be followed in subsequent years of the study.

Coverage:

It is not possible to reliably estimate the coverage of the EPPICC paediatric cohorts, in terms of the number of children included in these cohorts compared with the number infected as a whole in the countries represented. This is due to a wide variation in the quality of the surveillance systems used in these countries, making national estimates, and comparison of estimates between countries, unreliable. However, several participating cohorts do have complete or near complete national coverage: for example, the UK and Ireland cohort (CHIPS) which has in recent years included all children receiving HIV-related care in these countries[6] and the Italian Register, which covers 80-90% of HIV-infected children in Italy[9]. As the EPPICC cohorts tend to include the largest clinical sites caring for and treating HIV-infected children it is unlikely that many ETR-treated children will be missed in this study. Thus, the relatively small number of children and adolescents expected to be included in the first year is largely a reflection of the currently relatively low levels of ETR use in the European paediatric population.

4. Methods

Data collection:

Data captured by cohorts through their routine study data collection include information on demographics, growth, use of antiretroviral drugs (including start and stop dates), HIV clinical status, HIV RNA levels, CD4 counts and percentages and medical history. Although the EPPICC cohorts have similar protocols, there are some differences with regard to specific data items that are routinely collected, including dosing, non-ART medications, adverse events (AEs) and

biochemistry/haematology. For example, although CHIPS and CoRISPE-cat routinely collect information on AEs through study data collection forms, for the other participating cohorts this is not the case, and additional data will be requested from reporting clinics as necessary.

A detailed standard operating procedure (SOP) for data collection processes for the study will be developed and reviewed by all participating cohorts. The SOP will include the data specification (see Appendix), together with instructions on the data extraction and transfer procedures. An electronic data collection form will be provided for circulation by participating cohorts to the relevant treatment physicians to aid data extraction from patient records on variables not included in the cohort database (where applicable). Data formats based on the HIV Cohorts Data Exchange Protocol (HICDEP) will be used for this study (Appendix 1).

The HICDEP format is based on a relational structure, and the data for this study will be collected in a series of tables, which are described in the Appendix, together with the lookup tables for the codes to be used. All available data on laboratory test results (in particular, absolute neutrophil count, total, HDL and LDL cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, blood glucose, pancreatic amylase and lipase) are to be collected for the 12 months prior to starting ETR up to the most recent follow-up visit, with normal as well as abnormal results to be reported. Fasting values will be requested but it is likely that most values reported will be non-fasting. Baseline data will include ART history, classified as ART-naïve prior to initiation on ETR-containing regimen, ART-experienced (one to three previous ART drugs) and highly pretreated (four or more previous ART drugs). For children stopping ETR use, data collection will continue for all follow-up visits up to 12 months after ETR cessation. Data collected on serious adverse events will include type of AE, date of event, date of resolution, severity, seriousness category and causality assessment by the original reporter (see Variable definitions and Appendix). Where possible, data will also be collected on non-serious adverse events related to ETR. Complete CD4, viral load, weight and height data from first visit will also be collected.

The PENTA Foundation-appointed study team, which includes a database manager with extensive experience of designing and maintaining HIV databases for clinical trials and cohort studies, will obtain data from the participating cohorts through annual electronic data mergers of datasets according to the SOP. The database manager will remove any patient identifiers to

ensure patient confidentiality. Data will then be subject to a battery of logical and consistency checks in order to assess accuracy and completeness; any data queries arising will be discussed and resolved with the relevant cohort data manager, before data are pooled into a joint study database.

Variable definitions

Variables to be collected on all children taking ETR will include: basic demographic details (date of birth, sex, mode of infection, ethnicity, hepatitis B co-infection status); patient weights and heights from all clinic visits including prior to start of first ART regimen; ART dosing history, including reasons for stopping a drug; commencing 12 months prior to ETR initiation.

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product (International Conference on Harmonisation).

Severity of the AE will be defined using the Division of AIDS (DAIDS) toxicity tables. A Serious AE is defined as any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as any event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or require intervention (eg medical, surgical) to prevent one of the other serious outcomes listed in the definition above)

Causality assessment will be performed by the original reporter for all causes of death and all (S)AEs not classified as HIV-related (CDC B and C) events.

Statistical analysis

Statistical analysis of the pooled dataset will be carried out at the Medical Research Council Clinical Trials Unit, London, using STATA software (StataCorp, College Station, Texas). If relevant, participant follow-up time whilst in a Janssen-Cilag International NV ETR trial will be excluded from analysis as adverse events occurring during this time will have already been reported to the EMA. Children will be characterised by previous ART treatment (naive v previous ART) and viral load (<400 v ≥400c/ml). Standard descriptive statistics will be used to summarise the data. Demographic and baseline disease characteristics (eg sex; ethnic group; mode of infection; ever AIDS diagnosis) as well as antiretroviral therapy exposure (eg age starting any ART; age starting ETR; ART duration before ETR; viral load and CD4 at ETR start; other drug classes prescribed with ETR; and median estimated months and total patient years on ETR) of children taking ETR will be described, by the following groups:

- ART treatment-experienced children aged 6-<18 years taking the licensed dose
- ART treatment-experienced children aged 6-<18 years taking an unlicensed dose
- ART naive children aged 6-<18 years
- children <6 years of age.

Additionally immunological and virological response at 12 months for ART naïve children, and virological response at 12 months for ART experienced children, will be presented. Also further breakdowns by 6-<12 years and 12-<18 years will be presented if the sample size allows.

Laboratory toxicity data for periods on ETR will be summarised by duration of time on ETR (for example, <12 months, 12-24 months, >24 months). Rates of events for children on the licensed dose will be presented along with 95% confidence intervals, by DAIDS grade. Additional descriptive analyses will be presented on an individual patient basis for all patients with a grade ≥3 test result whilst on ETR.

Medical Dictionary for Regulatory Affairs (MedDRA) will be used for coding all AEs which are reported as free text in the datasets (Appendix). Characteristics of serious adverse events occurring whilst on ETR and which were considered by the reporting physician to be causally related to ETR will be presented, and will include the type of adverse event, severity using the DAIDS toxicity table, the date it was diagnosed and resolved (if relevant) other ART drug and concomitant medications taken at the time of the event, the sex and age of the participant at

the time of the event, and the ETR dose taken. Similarly serious adverse events which were not considered to be causally related to ETR and non-serious AEs which were considered causally related to ETR will also be presented. If appropriate, additional descriptive analyses will be performed for the identified and potential risks mentioned in the Risk Management Plan (RMP) and for any newly identified potential signals. Relevant cases for the analyses for identified and potential risk will be retrieved using predefined MedDRA queries, as specified in the RMP. Three or more similar SAEs, accumulated in separate individuals, will be considered a potential signal.

The number of children who discontinue ETR-containing treatment will be tabulated and the reasons for drug discontinuation summarised.

It will not be possible to determine whether a potential control group is appropriate and available until after the first year of data collection and the initial characterisation of the group of children and adolescents receiving ETR. The control group would be drawn from the EPPICC studies and thus would be from the same 'real-life' population.

Ongoing data collection in the participating cohorts

All participating studies' protocols require follow-up of enrolled HIV-infected children and adolescents to continue up to age 18 years or up to the time that they transfer into adult care, if this is earlier. In some EPPICC cohorts, follow-up continues into early adulthood. EPPICC is part of a research programme funded by the European Union (EU) FP7 for a 5-year Network of Excellence - the European Coordinating Committee for the Integration of Ongoing Coordination Actions Related to Clinical, Virological and Epidemiological HIV Research (EuroCoord) network. The EuroCoord network formally started on 1st January 2011; funding from EuroCoord underpins EPPICC activities from 2011 to 2016, and together with individual cohort studies' own country-specific funding ensures that these studies will continue beyond the duration of this study.

Study strengths and limitations

The strength of this study is the large number of prospective paediatric HIV cohorts included in EPPICC which participate in the current post-marketing safety surveillance program. These cohorts routinely collect clinical, laboratory, and treatment data in HIV-infected children across

Europe and thus the results derived from this study have good generalisability to most European countries. As the participating cohorts assess the treatment and care of children with HIV served in routine clinical practice, this study provides data on use and safety of ETR in a "real world" setting.

With regard to limitations of the study, the participating cohorts were not specifically designed for pharmacovigilance purposes, and in some cases data may be missing, for example on serious AEs. Cohorts will make every effort to obtain any missing information via treating physicians' review of patient notes. Non-serious clinical related AEs may not have been collected in a systematic manner across the individual cohort studies, and so may be considered a minimum estimate. Also, non-serious not related AEs are not being collected in the context of this study. However laboratory reporting is expected to be much more complete and so rates of grade 1 and 2 laboratory events will be presented. Of note, most participants are likely to be non-fasting at blood sampling.

5. Study conduct

Ethics approval

The individual cohorts will be responsible to adhere to their appropriate local ethics approval procedures for this surveillance program (i.e. to contact their local ethics committee to determine whether additional protocol approval and additional informed consent form is required or an amendment to the existing protocol approval). Data received by the PENTA Foundation appointed team will be anonymised, and patient identifiers will be removed to ensure patient confidentiality.

Roles and responsibilities

A PENTA Foundation appointed team will provide overall study coordination with the individual cohorts, perform the study data management and analysis, draft the annual reports and liaise with Janssen-Cilag International NV. Participating studies will be responsible for extracting available data on eligible children from their study databases, coordinating the extraction of missing values for core variables from medical notes via treating physicians, formatting all available data according to the standard operating procedure, transferring the dataset, liaising with the study data manager with respect to data queries and providing input into the report writing process.

Reports and publication

Results will be written up as a draft report presenting only aggregated data. The draft report will be circulated and reviewed among the participating cohorts as well as with Janssen-Cilag International NV for input and comments prior to finalisation and submission to Janssen-Cilag International NV/ EMA.

Data archiving

Documentation and archiving of the datasets will be implemented at the end of the study period.

6. Expedited reporting of Serious Related Adverse Events

As the design of this study involves analysis of secondary data, identification of any serious adverse events by the PENTA study team would take place a considerable time after the event. In addition, the specific protocols of cohorts and studies participating in EPPICC vary, with some collecting prospective data regularly over the year, whilst others having a system of annual collection of prospectively collected data within participating sites, leading to considerable reporting delay. National systems for reporting of serious related adverse events vary across Europe, with some countries having mandatory reporting systems, while most have voluntary systems in place. For those studies in countries where reporting is voluntary, the responsible cohort coordinator will remind participating clinicians of their obligations towards their local / national Health Authorities regarding expedited reporting of safety data (serious adverse events); this may be done via a number of means including email, cohort newsletters, web-pages and study meetings.

7. Timelines

The study will start in October 2013 and end in September 2018, and comprises of the following periods:

- Oct – Dec 2013: Finalisation of study SOP for data merger
- Jan – Mar 2014: First year data merger and data cleaning/ checking
- Apr – Jun 2014: First year analysis and report writing
- Jul 2014: Draft report circulated
- Sep 2014: Final report circulated.

Subsequent years will follow the same January to September timeline, and report delivery dates are shown in the table below. The final report will be prepared by 30 September 2018.

	Report delivery date to EMA
1st year data	September 30 2014
2nd year data	September 30 2015
3rd year data	September 30 2016
4th year data	September 30 2017
5th year data	September 30 2018

Annex 1: List of stand-alone documents

None