Study Title	An Observational, Drug Utilization Study of Viread® in Children and Adolescents with HIV-1 Infection
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EU PAS Register No	ENCEPP/SDPP/7814
Active substance / Medicinal Product	ATC Code: J05AF07, Antiviral for systemic use: Nucleoside and nucleotide reverse transcriptase inhibitors Active substance: Tenofovir disoproxil (as fumarate) Product: Viread®
Indication	In combination with other antiretroviral medicinal products for the treatment of HIV-1 infected children and adolescents aged 2 to < 18 years with NRTI resistance or toxicities precluding the use of first line agents.
Product reference / Procedure number	EU/1/01/200/001-009
Joint PASS	No
Country (-ies) of study	EU countries that participate in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) pharmacovigilance programme.
Marketing authorization holder / Sponsor	Gilead Sciences International Limited Cambridge, United Kingdom, CB21 6GT
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TABLE OF CONTENTS

TABLE OF CONTENTS 2
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS 3
1. RESPONSIBLE PARTIES 4
2. PROTOCOL SYNOPSIS/ABSTRACT 5
3. AMENDMENTS AND UPDATES 10
4. MILESTONES 11
5. BACKGROUND 12
5.1. Rationale for the Current Study 12
6. OBJECTIVES / RESEARCH QUESTIONS 14
7. RESEARCH METHODS 15
7.1. Study Design 15
7.2. Setting / Study Population 15
7.3. Exposure / Outcomes and other Variables 15
7.4. Criteria for Discontinuation of Follow up 16
7.5. Data Sources 16
7.6. Study size 16
7.7. Data Management 16
7.8. Data Analysis 18
7.9. Quality Control 19
7.10. Limitations of the Study/Analysis 19
7.11. Statistical Power / Sample Size Considerations 20
8. PROTECTION OF HUMAN SUBJECTS 21
8.1. Good Pharmacoepidemiology Practices 21
8.2. Institutional Review Board (IRB) Review 21
8.3. Informed Consent 21
8.4. Confidentiality 21
9. MANAGEMENT AND REPORTING OF SAFETY INFORMATION 22
9.1. Adverse Events 22
10. RESPONSIBILITIES / PLANS FOR DISSEMINATING STUDY RESULTS 23
10.1. Investigator Responsibilities 23
10.1.1. Study Files and Retention of Records 23
10.1.2. Inspections 23
10.1.3. Protocol Compliance 23
10.2. Sponsor Responsibilities 23
10.2.1. Protocol Modifications 23
10.2.2. Study Report and Publications 23
10.3. Joint Investigator/Sponsor Responsibilities 24
10.3.1. Access to Information for Auditing or Inspections 24
10.3.2. Study Discontinuation 24
11. REFERENCES 25
12. APPENDICES 26

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ART	antiretroviral therapy
BMD	bone mineral density
CHB	chronic hepatitis B
CHIPS	Collaborative HIV Paediatric Study
DSPH	Drug Safety & Public Health
EPPICC	European Pregnancy and Paediatric HIV Cohort Collaboration
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GSI	Gilead Sciences, Inc.
GVP	Good Pharmacovigilance Practices
HICDEP	HIV Cohorts Data Exchange Protocol
HIV, HIV-1	Human Immunodeficiency Virus, Human Immunodeficiency Virus Type 1
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Affairs
NSHPC	National Study of HIV in Pregnancy and Childhood
SAE	serious adverse event
STROBE	Guidelines for Strengthening the Reporting of Observational Studies in Epidemiology
TDF	tenofovir disoproxil fumarate
US, USA	United States, United States of America

1. RESPONSIBLE PARTIES

Marketing Authorization Holder	Gilead Sciences International Limited
Study Director	PPD, Gilead Sciences, Inc.
Study Investigator / Author	PPD, MRC Clinical Trials Unit

2. PROTOCOL SYNOPSIS/ABSTRACT

Gilead Sciences International Limited
Cambridge
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Study Title:	An Observational, Drug Utilization Study of Viread® in Children and Adolescents with HIV-1 Infection
Rationale and Background:	On 22 November 2012 the European Commission adopted a Decision on applications to extend the indications for Viread® to include children and adolescent patients with HIV-1 infection aged 2 to <18 years and adolescents with chronic hepatitis B (CHB) infection aged 12 to <18 years. The SmPCs updated in November 2012 for the different formulations of Viread® contain information relevant to pediatric patients, including the approved indications and appropriate doses of Viread®, and recommendations on monitoring of renal function and management of renal and bone abnormalities. In addition, educational brochures specific to the use of Viread® in children and adolescents with HIV-1 infection have been developed as a risk minimization tool and will be distributed to HIV-1 pediatric prescribers. In Europe, several established, prospective observational cohort studies of HIV-1 infected children and adolescents participate in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC). Gilead Sciences has initiated collaboration with EPPICC to conduct a Drug Utilization Study using these cohorts of HIV-1 infected children living in the EU. The rationale for this study is to assess characteristics of patients treated with Viread® prior to and following the approval of the pediatric indication on 22 November 2012, and to assess how physicians are prescribing Viread® to children and adolescents, including off-label use in the 0 to <2 years group, in order to determine the effectiveness of the risk minimization measures i.e. the SmPC and the educational brochures, which have been implemented subsequent to approval. In addition, the study will assess the characteristics of all children and adolescents receiving tenofovir disoproxil fumarate (TDF)-based regimens (including off-label use of TDF-containing FDC) at or after the Viread® approval date.

Research Question and Objectives:	Primary objectives: • To describe the characteristics of HIV-1 infected patients <18 years of age being treated with Viread® by collection of the following: — Appropriateness of dose of Viread® for the patients' age and weight — ART before starting Viread® therapy — Documented evaluation of renal function (serum creatinine and serum phosphate) prior to initiating Viread® and during Viread® therapy • To assess the outcome of any ≥ Grade 3 renal and bone biochemistry markers (serum creatinine, serum calcium and serum phosphate) and serious adverse drug reactions in patients receiving Viread® • In the post-approval group receiving Viread: — to assess the clinical management and outcome of any ≥ Grade 3 renal and bone biochemistry markers (serum creatinine and/or serum calcium); — to assess the clinical management and outcome of confirmed serum phosphate values of < 3.0mg/dl (0.96 mmol/l), in order to determine if they are being managed in accordance with the European SmPC. • To compare the characteristics of HIV-1 infected patients less than 18 years of age receiving Viread® at and each year after, the approval of the pediatric indication for Viread®. Secondary objectives: • To evaluate and describe the characteristics of HIV-1 infected patients < 18 years of age being treated with tenofovir disoproxil fumarate (TDF)-based regimens (including off-label use of TDF-containing FDC) at or after the approval of the pediatric indication for Viread® by collection of the following variables: — Dose of TDF for the patients' age and weight — ART before starting TDF-FDC therapy — First TDF-based regimen — Documented evaluation of renal function (serum creatinine and serum phosphate) prior to initiating TDF-FDC and during TDF-FDC-based therapy • To assess the outcome of any ≥ Grade 3 renal and bone biochemistry markers and serious adverse drug reactions in patients receiving TDF-FDC.

Study Design:	Pooled analysis of individual patient data for cohorts participating in the EPPICC pharmacovigilance programme will be conducted for all children treated with Viread® or TDF-FDC. The analysis will include children treated with Viread® or TDF-FDC at or after Viread® approval date (22 November 2012).
Population / Setting:	HIV-1 infected children and adolescents aged 2 to <18 years taking Viread® or TDF-FDC in the EU. The data will be collected by annual pooling of anonymised individual patient data in cohorts participating in EPPICC. Patients in cohorts are followed up until they transfer to adult care, the median age of which varies by country.
Eligibility Criteria:	All HIV-1 infected patients at age <18 years are eligible for inclusion including any patient treated with Viread® or TDF-FDC at or after Viread® approval date (22 November 2012).
Duration of Study:	The duration of the study from the first data cohort to final report is October 2014-December 2017, broken down as follows: Finalisation of study SOP for data merger: October-December 2014 First year data merger: January-March 2015 First year analysis: April-June 2015 First year resolution of outcome of grade 3/4 AEs: June-September 2015 First year report: 31 December 2015 Second year (2016) and third year (2017) timelines to follow first year timelines. Final report: 31 December 2017
Data Sources:	Pooled analyses of anonymised individual patient data on children treated with Viread® or TDF-FDC from European cohort studies participating in the EPPICC relative to the approval of Viread® for the treatment of HIV-1 infected patients aged 2 to < 18 years of age.
Study Procedures:	Three data mergers will take place for this study, in January 2015, 2016 and 2017. The first data merger in 2015 included all children and adolescents receiving Viread® at or after Viread® approval date. In the second and third years, follow-up data will be reported on all of these patients continuing Viread®, as well as data on any new patients commencing Viread® in the intervening period which would give an indication of physicians' practice since approval.

	In addition, the mergers will continue to accept data on children and adolescents treated with TDF-based regimens, including off-label use of TDF-FDC. An EPPICC standard operating procedure has been developed and the data merger will follow the HIV Cohorts Data Exchange Protocol (HICDEP).
Variables:	Variables to be collected on all children taking Viread® or TDF-FDC will include: basic demographic details (date of birth, sex, mode of infection, ethnicity, hepatitis B co-infection status); patient weights and heights at every clinic visit; ART dosing history, including reasons for stopping a drug; dosing of TDF for Viread and TDF-FDC patients; renal and bone serum chemistries (actual values), commencing 12 months prior to Viread® or TDF-FDC initiation and serious clinical adverse events (coded using MedDRA). Variables will also be collected on children taking Viread® or TDF-FDC who experience a ≥ grade 3 renal or bone event including the outcome of the event (resolved versus continuing) and whether Viread® or TDF-FDC was discontinued. For the children newly starting Viread® post-approval who experience a ≥ grade 3 renal or bone event or confirmed serum phosphate of < 3.0 mg/dl (0.96 mmol/l) the analysis will include: the outcome of the event (resolved versus continuing); whether Viread® was discontinued; consultation with endocrinologist/nephrologist; and concomitant medication at the time of the event, including dietary supplementation.
Sample Size:	118 patients who were taking Viread® at or after Viread® approval were included in the first year data merger. During the first merger 326 patients were also reported as taking TDF-FDC and were analysed and presented in a supplemental report. It is anticipated that 130 additional patients taking Viread® will be included in the subsequent mergers. In addition, this study will continue to accept data on children receiving TDF-FDC and it is expected that this number will increase to approximately 500 patients in the next mergers.
Matching / Statistical Methods:	Data from EPPICC will be summarized using descriptive statistics (proportions, means, medians, inter-quartile ranges).
Milestones:	Interim report 1: 31 December 2015 Interim report 2: 31 December 2016 Final report: 31 December 2017

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs) and Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

3. AMENDMENTS AND UPDATES

Amendment or update number	Date	Section of study protocol	Amendment or update	Reason
1	30 July 2014	Cover page Sections 1.0, 2.0, 6.1 and 13.0	Update	Administrative revision of EU QPPV, updates to glossary terms used within the protocol, addition of the Marketing Authorization Holder designee responsible for study coordination and reporting, clarify data capture period and change to reflect accountable parties signing the Investigator Statement; inclusion of questionnaire and updated SOP
		Sections 8.7, 8.8, 10.1,8.7,and 10.1	Amendment	Change status on the standard operating procedure; roles in data management and reporting, clarification on adverse event criteria, change status on the follow-up questionnaire; clarification on data sources and revision to reflect minor site variations in completing the follow-up adverse event questionnaire
2	03 December 2015	Cover page and Protocol Signature Page	Update	Change to reflect new protocol version
		Cover page Sections 3.0, 8.1 and 8.5	Amendment	Addition of Portugal
3	24 May 2016	Cover page and Protocol signature page	Update	Change to reflect new protocol version, update of the EU PASS register reference
		Section 2, 3, 4, 5.1, 6, 7.1, 7.2, 7.3, 7.5, 7.6, 7.7, 7.8, 7.10, 7.11, 9.1, 10.2.2, 12 and cover page	Amendment	Adding secondary objective to collect variables on children treated with a TDF-based regimen including off label use of TDF-based fixed dose combination treatments, adding DAIDS criteria for classifying low serum phosphate values of children treated with Viread® in the pre-approval group, update to the study population size based on revised projections, remove the listing of countries to focus on EU countries only participating in the EPPICC programme, adding timepoint for conduct of renal function tests prior to initiation of Viread®
4	10 April 2017	Cover page and Protocol signature page	Update	Change to reflect new protocol version
		Section 2, 6 and 7.8	Amendment	Clarification and re-wording of study objectives to align with the PRAC Rapporteur's recommendations and data that are effectively being collected, analysed and presented in the study reports; adding of TDF dosing for Viread and TDF-FDC patients as a variable; clarification to the renal and bone monitoring timing relative to Viread/TDF-FDC initiation.

4. MILESTONES

Milestone	Planned date
First data merger for study	January-March 2015
Second data merger for study	January-March 2016
Third data merger for study	January-March 2017
Registration in the EU PASS register	14 January 2013
Final report of study results	31 December 2017

5. BACKGROUND

5.1. Rationale for the Current Study

On 22 November 2012 the European Commission adopted a Decision on applications to extend the indications for Viread® to include children and adolescent patients with HIV-1 infection aged 2 to <18 years and adolescents with CHB infection aged 12 to <18 years.

The HIV-1 pediatric indication for Viread® is used in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected pediatric patients 2 to < 18 years of age with NRTI resistance or toxicities precluding the use of first line agents. The following formulations of Viread® are available for use in HIV-1 infected children and adolescents:

- Viread® 33 mg/g granules for children from 2 to < 6 years of age, and patients above 6 years of age for whom a solid dosage form is not appropriate.
- Viread® 123 mg, 163 mg, 204 mg film-coated tablets for children aged 6 to < 12 years who weigh from 17 kg to < 22 kg, 22 kg to < 28 kg, and 28 kg to < 35 kg, respectively.
- Viread® 245 mg film-coated tablets for adolescents aged 12 to < 18 years who weigh ≥ 35 kg.

Tenofovir is principally eliminated via the kidney. Renal failure, renal impairment, elevated creatinine, hypophosphatemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of Viread® in clinical practice. Reductions in bone mineral density (BMD) Z-score have also been reported in adult and pediatric patients.

The SmPCs updated in November 2012 for the different formulations of Viread® contain information relevant to pediatric patients, including on the approved indications and appropriate doses of Viread®, and recommendations on monitoring of renal function and management of renal and bone abnormalities.

In addition, educational brochures specific to the use of Viread® in children and adolescents with HIV-1 infection have been developed as a risk minimization tool and will be distributed to HIV-1 pediatric prescribers. The brochures include information on the approved pediatric indications, the appropriate dosing of Viread®, monitoring of renal function, and management of renal and bone effects in pediatric patients in accordance with the recommendations in the Viread® SmPC.

In Europe, several prospective observational cohort studies of HIV-1 infected children and adolescents have been established which participate in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC). Gilead Sciences has initiated a collaboration with EPPICC to conduct a Drug Utilization Study using these cohorts of HIV-1 infected children living in the EU. Several participating cohorts in the EPPICC network have complete or near complete national coverage. For example, the UK and Ireland cohort (CHIPS) has in recent years included

all children receiving HIV-related care in these countries {Judd et al 2007} and the Italian Register covers 80-90% of HIV infected children in Italy {Chiappini et al 2007}. Further, EPPICC cohorts tend to include the largest clinical sites caring for and treating HIV-1 infected children. Therefore, utilization of the EPPICC cohorts is considered to provide a robust data source with a wide coverage of HIV-1 infected children across several EU countries.

The study will address if physicians are following the recommendations in the Viread® Summary of Product Characteristics (SmPC) and educational brochures with respect to information relevant to pediatric patients on the approved indications and appropriate doses of Viread®, and complying with the recommendations with respect to monitoring of renal function and management of renal and bone abnormalities in these patient populations.

The rationale for this study is to assess characteristics of patients treated with Viread® at or after 22 November 2012, and to assess how physicians are prescribing Viread® to children and adolescents, including off-label use in the 0 to < 2 years group, in order to determine the effectiveness of the risk minimization measures i.e. the SmPC and the educational brochures, which have been implemented subsequent to approval of the pediatric indication on 22 November 2012.

The 2015 EPPICC data merger conducted in support of the GS-EU-104-0433 first interim report included data from HIV-infected pediatric patients (age < 18 yrs) in the EU who received tenofovir disoproxil fumarate (TDF) as a single agent (i.e. Viread®) *and* as part of fixed dose combinations (FDC). The TDF-containing FDC are currently not approved for use in a paediatric population and the data in the first merger were received in error. A supplemental SAP and report was prepared to reflect the data received. These findings provide important insights into the real-life clinical use of TDF in children and the safety of these children when exposed to such treatments. Therefore and to fulfill Gilead's pharmacovigilance obligations, this study will continue to accept data on children receiving any TDF-containing regimens (including off-label use of FDC) as a secondary objective and the data will be presented in the next interim and final study report.

6. OBJECTIVES / RESEARCH QUESTIONS

The primary objectives of this Drug Utilization Study are:

- To describe the characteristics of HIV-1 infected patients <18 years of age being treated with Viread® by collection of the following:

  — Appropriateness of dose of Viread® for the patients' age and weight
  — Prior antiretroviral therapy (ART) before starting Viread® therapy
  — Documented evaluation of renal function (serum creatinine and serum phosphate) prior to initiating Viread® and during Viread® therapy

- To assess the outcome of any ≥ Grade 3 renal and bone biochemistry markers (serum creatinine, serum calcium and serum phosphate) and serious adverse drug reactions in patients receiving Viread®

- In the post-approval group receiving Viread:

  — to assess the clinical management and outcome of any ≥ Grade 3 renal and bone biochemistry markers (serum creatinine and/or serum calcium)
  — to assess the clinical management and outcome of confirmed serum phosphate values of < 3.0mg/dl (0.96 mmol/l); in order to determine if they are being managed in accordance with the European SmPC.

- To compare the characteristics of HIV-1 infected patients less than 18 years of age receiving Viread® at and each year after, the approval of the pediatric indication for Viread®.

Secondary objectives:

- To evaluate and describe the characteristics of HIV-1 infected patients < 18 years of age being treated with tenofovir disoproxil fumarate (TDF)-based regimens (including off-label use of TDF-containing FDC) at or after the approval of the pediatric indication for Viread® by collection of the following variables:

  — Dose of TDF for the patients' age and weight
  — ART before starting TDF-FDC therapy
  — First TDF-based regimen
  — Documented evaluation of renal function (serum creatinine and serum phosphate) prior to initiating TDF-FDC and during TDF-FDC-based therapy

- To assess the outcome of any ≥ Grade 3 renal and bone biochemistry markers and serious adverse drug reactions in patients receiving TDF-FDC.

7. RESEARCH METHODS

7.1. Study Design

This is an observational study involving the pooled analysis of anonymised individual patient data from prospective cohort studies in the European Union, 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, children and children exposed to HIV in utero. Data on children treated with Viread® pre-approval and continuing post-approval as well as data on children newly treated with Viread® post-approval will be collected by pooled analysis of anonymised individual patient data for prospective cohorts participating in the EPPICC pharmacovigilance programme. Three data mergers will take place for this study, in January 2015, 2016 and 2017. The first data merger in 2015 included all children and adolescents ever treated with Viread® pre-approval and continuing on Viread® post-approval, as well as new patients commencing Viread® post-approval. In the second and third years, follow-up data will be reported on all of these patients continuing Viread®, as well as data on any new patients commencing Viread® in the intervening period.

In addition, the three mergers will include anonymised individual patient data conducted for all children aged <18 years treated with TDF-FDC at or after 22 November 2012.

7.2. Setting / Study Population

All HIV-infected children and adolescents aged <18 years treated with Viread® or TDF-FDC at or after 22 November 2012 will be included in the study, regardless of clinical stage. Patients in cohorts are followed up until they transfer to adult care, the median age of which varies by country.

7.3. Exposure / Outcomes and other Variables

Exposure is defined as the amount of time the subject is treated with Viread® or TDF-FDC. Variables to be collected on all children taking Viread® or TDF- FDC will include: basic demographic details (date of birth, sex, mode of infection, ethnicity, hepatitis B co-infection status); patient weights and heights at every clinic visit; ART dosing history, including reasons for stopping a drug; renal and bone serum chemistries (actual values), commencing 12 months prior to Viread® or TDF- FDC initiation; serious clinical adverse events (coded using MedDRA, and including renal and bone adverse events).

Variables will also be collected on children taking Viread® or TDF-FDC who experience a ≥ grade 3 renal or bone event including the outcome of the event (resolved versus continuing) and whether Viread® or TDF-FDC was discontinued. For the children newly starting Viread® post-approval who experience a ≥ grade 3 renal or bone event or confirmed serum phosphate of < 3.0 mg/dl (0.96 mmol/l) the analysis will include: the outcome of the event (resolved versus continuing); whether Viread® was discontinued; consultation with endocrinologist/nephrologist; and concomitant medication at the time of the event, including dietary supplementation.

7.4. Criteria for Discontinuation of Follow up

There are no criteria for discontinuation of follow up in this study

7.5. Data Sources

Data on children treated with Viread® or TDF-FDC will be collected from pooled analyses of anonymised individual patient data from European prospective cohort studies participating in EPPICC pharmacoepidemiology programme.

7.6. Study size

118 patients who were taking Viread® at or after Viread® approval were included in the first year data merger. During the first merger 326 patients were also reported as taking TDF-FDC and were analysed and presented in a supplemental report.

It is anticipated that 130 additional patients taking Viread® will be included in the subsequent mergers. In addition, this study will continue to accept data on children receiving TDF-FDC and it is expected that this number will increase to approximately 500 patients in the next mergers.

7.7. Data Management

Each year the data merger will take place in January. A bespoke relational database in Microsoft Access software will be used. The database is owned and managed by the PENTA Foundation and will not be accessible by the MAH. The MRC analytic team will summarize data derived from the database in the form of tabulations and listings and will provide these to the MAH for incorporation into annual reports. Data checking and query resolution will take place in February and March, and data management in April to June. Data analyses will take place in July to September.

Variables will also be collected on children taking Viread® or TDF-FDC who experience a ≥ grade 3 renal or bone event including the outcome of the event (resolved versus continuing) and whether Viread® or TDF-FDC was discontinued.

Sites with paediatric patients newly starting Viread® post-approval with confirmed serum phosphate of < 3.0 mg/dl (0.96 mmol/l) or with clinical events or laboratory tests meeting the DAIDS definition of a grade 3 or 4 renal and bone adverse event will complete a questionnaire (see Appendix 1) requesting further details of the management and outcomes in these patients. The questionnaire will be completed by the attending physician or study nurse. The EPPICC study coordination team at the MRC CTU will manage and track the completion of the questionnaires. Some cohorts have incorporated the questionnaire variables into the database for patients with eligible events, therefore it will not be necessary for them to complete the questionnaire. If the forms or additional data have not been completed/received within 2 weeks of a request then a reminder email will be sent as well as a follow up telephone call as needed.

Draft tables and listing will be provided to the MAH between September and November, with a study report drafted by the MAH and jointly approved by PENTA and the MAH.
The report will be available to participating cohorts in November. The MAH will submit the report to the EMA/CHMP at the end of December. The same timetable will be followed in subsequent years of the study.

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. A detailed standard operating procedure (SOP) for data collection processes for the study includes the data specification (see Appendix 1), 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.

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 1, together with the lookup tables for the codes to be used. All available data on laboratory test results (in particular, calcium, phosphate, creatinine, absolute neutrophil count, fasting total cholesterol, fasting triglycerides, alanine aminotransferase, total bilirubin, blood glucose fasting, pancreatic amylase and lipase) are to be collected for the 12 months prior to starting Viread® or TDF-FDC up to the most recent follow-up visit, with normal as well as abnormal results to be reported. Baseline data will include ART history, classified as ART-naïve prior to initiation on Viread® or TDF-FDC, ART-experienced (one to three previous ART regimens) and highly pretreated (four or more previous ART regimens). For children stopping Viread® or TDF-FDC data collection will continue for all follow-up visits available. 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 1). Complete CD4, viral load, weight and height data will be collected.

Additional variables collected on children taking TDF-FDCs who experience a DAIDS ≥ grade 3 renal or bone event include: the outcome of the event (resolved versus continuing); whether TDF-FDC was discontinued.

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.

7.8. Data 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). Analyses will be presented for all patients treated with Viread® or TDF- FDC, and also for the following three groups: patients aged 2-<18 years treated with Viread® prior to the approval of the indication for Viread® and who continue Viread® post-approval; patients aged 2-<18 years newly starting Viread® post-approval; and patients aged <2 years.

Standard descriptive statistics will be used to summarise the data. Patients will be categorized according to whether they took a licensed or unlicensed dose at the start of Viread® therapy. Demographic characteristics (eg sex, ethnic group, mode of infection, ever AIDS diagnosis) of participants taking Viread® will be described, by licensed v unlicensed dose and age. Formulation will be described for patients newly starting Viread® post-approval.
The antiretroviral therapy profile of children on licensed and unlicensed Viread® doses will also be described, and will include: age starting any ART; age starting Viread®; ART duration before Viread® (including previous NRTI exposure); viral load and CD4 at Viread® start; other drug classes prescribed with Viread®; and median estimated months and total patient years on Viread®. Where NRTIs have been prescribed prior to Viread®, reasons for stopping NRTIs will be described.

Renal and bone laboratory monitoring will be summarised by timing relative to Viread/TDF-FDC initiation (for example, proportion of patients receiving test within the one month prior to initiation of Viread/TDF-FDC; median time to first test; and proportion receiving a test within ≤ 3 months, following Viread®/TDF-FDC start). Rates of renal and bone laboratory events will also be presented along with 95% confidence intervals, by DAIDS grade and time period relative to Viread/TDF start (<12 months/12-24 months/>24 months).

Medical Dictionary for Regulatory Affairs (MedDRA) will be used for coding all AEs which are reported as free text in the datasets (Appendix 1). Characteristics of serious adverse events reactions occurring whilst on Viread® and which were considered by the reporting physician to be causally related to Viread® will be presented, and will include the type of severity using the DAIDS toxicity table, and the date it was diagnosed.

Further patient-level data will be presented for grade 3 and 4 renal and bone events or confirmed serum phosphate <3.0 mg/dL whilst on Viread® or within 30 days after discontinuation of Viread® in patients newly starting Viread® post-approval. Data will be collected on resolution of the event (if relevant), other ART drug and concomitant medications (including dietary supplements) taken at the time of the event, whether an endocrinologist or nephrologist was consulted, and whether Viread® was stopped or continued. The number of children who discontinue Viread® will be tabulated and the reasons for drug discontinuation summarised.

Variables will also be collected on all children taking TDF-FDC. Basic demographic details will include date of birth, sex, mode of infection, ethnicity, hepatitis B co-infection status. The study will also collect patient weights and heights at every clinic visit; antiretroviral treatment (ART) dosing history including age at starting any ART, ART duration before initiating TDF-FDC

and reasons for stopping a drug; age starting TDF-FDC; viral load and CD4 at TDF-FDC start; other drug classes prescribed with TDF-FDC; renal and bone serum chemistries (actual values), commencing 12 months prior to TDF-FDC initiation and serious clinical adverse events.

Additional variables will be collected on children taking TDF-FDC who experience a ≥ grade 3 renal or bone including the outcome of the event (resolved versus continuing) and whether TDF-FDC was discontinued.

7.9. Quality Control

As stated above, data will be subjected 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. Further data checks will be conducted by the study statistician prior to data analysis.

7.10. Limitations of the Study/Analysis

The strength of this study is the geographically diverse 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 of Viread® and TDF-FDC in a "real world" setting.

With regard to limitations of the study, the new Viread® formulations (123 mg, 163 mg, 204 mg film-coated tablets and 33 mg/g granules) will not be commercially available in all EU countries. In countries where Viread® formulations will not be commercially available, they will be available on a compassionate use basis or as part of a medical need programme; this includes Poland and Belgium, which have participating cohorts in the study. In addition, the timelines to launch and the availability of the educational brochures in the remaining countries where there are participating cohorts will vary depending on national Regulatory procedures and timelines for approval.

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.

Also, the tendency for treating patients with TDF-FDC revealed by the first data merger may contribute to the limited number of patients newly starting Viread® therapy post approval.

7.11. Statistical Power / Sample Size Considerations

The sample size has been generated based on the estimated amount of EU data that will be included by the cohorts into the EPPICC database.

118 patients who were taking Viread® at or after Viread® approval were included in the first year data merger. During the first merger 326 patients were also reported as taking TDF-FDC and as such were included in the analysis.

It is anticipated that 130 additional patients taking Viread® will be included in the subsequent mergers. In addition, this study will continue to accept data on children receiving TDF-FDC and it is expected that this number will increase to approximately 500 patients.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Good Pharmacoepidemiology Practices

The investigator will ensure that this study is conducted in accordance with the principles of the International Conference on Harmonization (ICH) guidelines, the guidelines of Good Pharmacoepidemiology Practices (GPPs), Heads of Medicines Agencies (HMA), Good Pharmacovigilance Practices (GVP) and with the laws and regulations of the country in which the research is conducted.

8.2. Institutional Review Board (IRB) Review

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 anonymized, and patient identifiers will be removed to ensure patient confidentiality.

8.3. Informed Consent

No informed consent will be obtained to participate in this secondary analysis of existing data. However informed consent may have been granted when original study data were collected, depending on the ethics approval procedures of each country.

8.4. Confidentiality

The patient identifiers in all data sources have been removed and the data will contain no patient identifiable fields.

9. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

9.1. Adverse Events

This retrospective, observational study collects anonymised data which are extracted as part of existing EPPICC data mergers. As the study results will be comprised of aggregated data and derived from secondary use of existing datasets, collecting individual case safety reports on adverse events or adverse drug reactions related to bone and renal outcomes is not within the scope of the study. Adverse events will have been previously reported through national reporting systems.

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 drug reactions); this may be done via a number of means including email, cohort newsletters, web-pages and study meetings.

Also, as part of this study, the clinical management and outcome of any grade ≥3 renal and bone adverse event or confirmed serum phosphate <3.0 mg/dL whilst on Viread® or within 30 days after discontinuation of Viread® in patients newly starting Viread® post-approval will be assessed by means of a questionnaire requesting further details on the management and outcomes in these patients, or to provide the additional data using the EPPICC SOP variables. This will include questions regarding nephrologist and endocrinologist input, reversibility of toxicity, and concomitant medications. The questionnaire will be completed by the attending physician or study nurse. Some cohorts have incorporated the questionnaire variables into the database for patients with eligible events, therefore it will not be necessary for them to complete the questionnaire. If the forms or additional data have not been completed/received within 2 weeks of a request then a reminder email will be sent as well as a follow up telephone call as needed.

10. RESPONSIBILITIES / PLANS FOR DISSEMINATING STUDY RESULTS

10.1. Investigator Responsibilities

10.1.1. Study Files and Retention of Records

Suppliers of data must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) Common data model tables, and (2) Primary source subject data (database).

10.1.2. Inspections

Suppliers of data should understand that source documents for this study should be made available to appropriately qualified personnel from Gilead Sciences or its representatives, or to regulatory authority or health authority inspectors.

10.1.3. Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead Sciences. Approval must be obtained before changes can be implemented.

10.2.2. Study Report and Publications

A study report will be prepared and provided to the PRAC every 12 months with the final report due by 31 December 2017. Gilead Sciences will ensure that the report meets the standards set out in the STROBE Guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) {Vandenbroucke et al 2007}.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead Sciences may conduct inspections or audits of the study. If the MRC is notified of an inspection by a regulatory authority then they agree to notify Gilead Sciences immediately and to provide to representatives of a regulatory agency or Gilead Sciences access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.2. Study Discontinuation

The sponsor reserves the right to terminate the study at any time. Should this be necessary, the sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies).

11. REFERENCES

Chiappini E, Galli L, Tovo PA, Gabiano C, Lisi C, Gattinara GC, et al. Changing patterns of clinical events in perinatally HIV-1-infected children during the era of HAART. AIDS 2007;21 (12):1607-15.

Judd A, Doerholt K, Tookey PA, Sharland M, Riordan A, Menson E, et al. Morbidity, mortality, and response to treatment by children in the United Kingdom and Ireland with perinatally acquired HIV infection during 1996-2006: planning for teenage and adult care. Clin Infect Dis 2007;45 (7):918-24.

Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology 2007;18 (6):805-35.

12. APPENDICES

Appendix 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	Version 1.0	18 February 2013	Feasibility assessment of collecting routine safety data on all children on Viread® as well as management of renal toxicity in those experiencing grade 3 or 4 events
2	EPPICC Standard Operating Procedure	Updated yearly for each merger	European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) Pharmacovigilance studies on the use of Tenofovir in HIV-infected children and young people in Europe Standard Operating Procedure
3	TDF Pharmacovigilance Form (Questionnaire) Version 1.0	4 August 2014	European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) Tenofovir use in children in Europe

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An Observational, Drug Utilization Study of Viread® in Children and Adolescents with HIV-1 Infection

Final – Amendment #4: 10 April 2017

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval

PPD
Study Director (Printed)

PPD

19 April 2017
Date

PPD
Gilead EU QPPV (Printed) PPD

PPD
Signature PPD

18 Apr 2017
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the study.

Study Investigator Name (Printed)	Signature
Date	Site Number