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# TITLE PAGE

**Division:** ViiV Healthcare
**Information Type:** ViiV Healthcare Epidemiology Final Study Report
**Control: Non-Interventional.**

| | |
|---|---|
| **Title:** | Abacavir Use and Risk of Myocardial Infarction and Coronary Artery Disease: Meta-analysis of Data from Clinical Trials |
| **Phase:** | IV |
| **Compound Number:** | GI265235 |
| **Effective Date:** | 06-JUL-2017 |

**Subject:** HIV, abacavir, safety, meta-analysis, myocardial infarction

**Author(s):** PPD

This study was performed in compliance with Good Clinical Practices and GlaxoSmithKline Standard Operating Procedures for all processes involved, including the archiving of essential documents.

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# 1 ABSTRACT

## Title

Abacavir Use and Risk for Myocardial Infarction and Coronary Artery Disease: Meta-analysis of Data from Clinical Trials

## Keywords

Safety, Abacavir, HIV, myocardial infarction

**Background:** Several observational studies and randomized controlled trials (RCTs) have suggested an association between abacavir (ABC) use and myocardial infarction (MI) but others, including meta-analyses of clinical trial data, have not.

**Methods:** This updated meta-analysis estimates exposure-adjusted incidence rate (IR) and relative rate (RR) of MI and coronary artery disease (CAD) in subjects receiving ABC and non ABC-containing combination antiretroviral therapy (cART). Summary data from 52 Phase II-IV RCTs from a previous meta-analysis were combined with aggregate data from 14 new RCTs. Subjects were either randomized to ABC cART vs other cARTs, or ABC was prescribed as a background medication. Primary analyses included ABC-randomized trials with a follow-up of ≥48 weeks and focused on MI. Secondary analyses included shorter duration trials and non-ABC-randomized trials and estimated IR and RR for both MI and CAD.

**Results:** In 66 clinical trials (75% male, aged 18-85 years), 13,119 adults were on ABC-containing cART and 7,350 were not. Exposure-adjusted IR for MI was 1.5 per 1,000 person-years (PY) [95% Confidence Interval (CI) 0.67 – 3.34] in the ABC-exposed group, and 2.18 per 1,000 PY (95% CI 1.09 – 4.40) in the unexposed group with a RR of 0.69 (95% CI 0.24 – 1.98). RR for MI was 0.69 (95% CI 0.24 – 1.99) with inclusion of shorter duration studies, and 0.83 (95% CI 0.44 – 1.60) with inclusion of ABC non-randomized studies.

The IR for CAD was 2.9 per 1,000 PY (95% CI 2.09- 4.02) in the ABC-exposed group and 4.69 per 1,000 PY (95% CI 3.4- 6.47) in the unexposed group with studies of ≥48 weeks of follow-up, with a RR of 0.62 (95% CI 0.39 -0.98). With inclusion of studies of <48 weeks, IR for CAD in the ABC-exposed group was 2.96 per 1,000 PY (95% CI 2.14-4.08) and 4.65 per 1,000 PY (95% CI 3.37 – 6.42) in the unexposed group with a RR of 0.64 (95% CI 0.4 – 1.0).

**Conclusion:** This expanded meta-analysis found comparable IRs for MI and CAD among ABC-exposed and unexposed subjects, suggesting no increased risk for MI or CAD following ABC exposure. These findings provide further evidence against an association between MI and CAD and ABC exposure in this clinical trial population. Modifiable risk factors for MI and CAD should be addressed when prescribing ART for treatment of HIV.

# 2 LIST OF ABBREVIATIONS

| | |
|---|---|
| 3TC | Lamivudine |
| ABC | Abacavir |
| AE | Adverse Event |
| ARV | Antiretroviral |
| ATV | Atazanavir |
| CAD | Coronary Artery Disease |
| cART | Combination Antiretroviral Therapy |
| CI | Confidence Interval |
| CVD | Cardiovascular Disease |
| DTG | Dolutegravir |
| FDA | Food and Drug Administration |
| FDC | Fixed Dose Combination |
| FTC | Emtricitabine |
| GSK | GlaxoSmithKline |
| HIV | Human Immunodeficiency Virus |
| LPV | Lopinavir |
| MI | Myocardial Infarction |
| RCT | Randomized Controlled Trial |
| RTV | Ritonavir |
| SAS | Statistical Analysis Software |
| TDF | Tenofovir Disoproxil Fumarate |
| US | United States |

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# 3 INVESTIGATORS

**GlaxoSmithKline, UK**
Cassandra Nan, RWE & Epidemiology
Rimgaile Urbaityte, Clinical Statistics
James Oyee, Clinical Statistics
Judy Hopking, Clinical Statistics

**ViiV Healthcare**
Leigh Ragone, Epidemiology & RWE
Mark Shaefer, Global Medical Lead
Vani Vannappagari, Epidemiology & RWE

# 4 MILESTONES

| Milestone | Planned date | Actual date | Comments |
|---|---|---|---|
| Start of data collection | 01 DEC 2016 | 01 DEC 2016 | Data was already collected as part of clinical trials. Data consolidation started on 1 DEC |
| Registration in the EU PAS register | 30 NOV 2016 | 24 NOV 2016 | |
| Final report of study results | 30 APR 2017 | | |

# 5 RATIONAL AND BACKGROUND

## 5.1 Background

Cardiovascular disease (CVD) is a leading cause of death in HIV-positive individuals, accounting for approximately 11% of total deaths in this population (Smith et al. 2014). The proportionate mortality due to CVD in HIV-positive individuals in the United States (US) has significantly increased between 1999 and 2013 (Feinstein et al. 2016). The risk of CVD is higher in HIV-positive individuals compared with HIV-negative individuals (Bedimo et al. 2011; Hemkens and Bucher 2014; Triant et al. 2007). The reported incidence of myocardial infarction (MI) in cohort studies ranges from 3–11 cases per 1,000 patient-years in HIV-positive individuals compared with 2–7 cases per 1,000 patient-years in HIV-negative individuals (Durand et al. 2011; Klein et al. 2002; Triant et al. 2007; Worm et al. 2010). Additionally, the prevalence of many CVD risk factors tends to be higher among HIV-positive individuals than among HIV-negative individuals, and these must be accounted for in any assessment of the relative incidence of CVD (Bedimo et al. 2011; Durand et al. 2011; Triant 2013; Triant et al. 2007).

Several studies have suggested an association between abacavir (ABC) use and increased risk of MI (Choi et al. 2011; Durand et al. 2011; Lundgren et al. 2008; Obel et al. 2010;

Sabin et al. 2016; Sabin et al. 2008; Worm et al. 2010; Martin et al. 2009). However, other studies do not confirm this (Daar et al. 2011; Martinez et al. 2010; Moyle et al. 2013; Sax et al. 2011; Smith et al. 2009; Squires et al. 2012; Bedimo et al. 2011; Lang et al. 2010), including meta-analyses conducted on clinical trial data by GSK (Brothers et al. 2009), the US Food and Drug Administration (FDA) (Ding et al. 2012) and independent researchers (Cruciani et al. 2011; Ribaudo et al. 2011).

While the published evidence remains conflicting, and a plausible biological mechanism for this potential association has not yet been identified, this study aims to update a previous meta-analysis that was conducted by GSK. The current meta-analysis included aggregate data on ABC exposure from ViiV Healthcare-sponsored clinical trials, conducted since the last such meta-analysis (Brothers et al. 2009).

### 5.2 Rationale

Since the last analysis of GSK clinical trial data in 2009, several new studies have been conducted, generating additional data on ABC use and risk for MI and coronary artery disease (CAD). The current meta-analysis was part of ViiV Healthcare's continued pharmacovigilance efforts to monitor this risk.

## 6 RESEARCH QUESTION AND OBJECTIVES

The objective was to estimate the exposure adjusted incidence rate and relative rate of MI and CAD events reported in subjects treated with ABC-containing cART regimens and in subjects treated with non-ABC-containing cART regimens.

## 7 RESEARCH METHODS

### 7.1 Study design

This meta-analysis was based on all GSK/ViiV Healthcare-sponsored clinical trials in which subjects were exposed to ABC, with at least 24 weeks of exposure to cART and for which at least the primary objective had been completed by Dec 2016. Summary data from the 52 studies from the previous GSK meta-analysis (Brothers et al. 2009) were combined with aggregate data from 14 studies that were conducted since 2009. Subjects were either randomized to ABC vs other ARTs, or ABC was prescribed as a background medication by investigator.

The included studies ranged from Phase II-IV, and were originally designed to investigate safety, efficacy and tolerability or to demonstrate non-inferior antiviral activity of one regimen compared to another (Table 1).

## Table 1 Characteristics of included studies conducted since 2009[1].

| Study name (Study identifier) | Study period [primary objective completed] | Phase | Primary objective | Countries |
|---|---|---|---|---|
| ARIA[2] (ING117172) | AUG 2013 - DEC 2020 [SEP 2015] | IIIb | To demonstrate the non-inferior antiviral activity, safety and tolerability of DTG/ABC/3TC FDC compared to ATV+RTV and TDF/FTC FDC in HIV-1 infected, ART-naïve women. | **North-America:** Canada, United States **LATAM:** Argentina, Mexico, Puerto Rico **Europe:** Italy, France, Portugal, Russia, Spain, United Kingdom **Africa:** South Africa **Australasia:** Thailand |
| ARIES (EPZ108859) | MAR 2007 - JUL 2010 | IIIb | To compare the safety and efficacy of ATV/r administered once daily (QD) followed by randomization (1:1) to a simplification regimen of ATV QD or continuation of ATV/r QD, each in combination with ABC/3TC FDC QD in ART-naïve, HIV-1 infected, HLA-B*5701 negative subjects. | **North-America:** Canada, United States **LATAM:** Puerto Rico |
| ASSERT[2] (CNA109586) | JUN 2007 – DEC 2009 | IV | To demonstrate a superior renal safety profile in subjects who received ABC/3TC FDC compared to TDF/FTC FDC, both administered with efavirenz. | **Europe:** Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Latvia, Netherlands, Portugal, Spain, Switzerland, United Kingdom |
| ASSURE[2] (EPZ113734) | APR 2010 – DEC 2012 | IV | To evaluate the efficacy, safety, and tolerability of the antiviral response betwee<br><br>n ATV/RTV+ TDF/FTC and ATV + ABC/3TC without ritonavir in HIV-1 infected, HLA-B*5701 negative subjects previously suppressed on ATV/RTV + TDF/FTC. | **North-America:** United States **LATAM:** Puerto Rico |
| FLAMINGO (ING114915) | OCT 2011 – DEC 2016 | IIIb | To demonstrate the non-inferior antiviral activity of DTG 50mg administered once daily compared to DRV+RTV 800mg + 100mg once daily both administered with either ABC/3TC or TDF/FTC in HIV-1 infected therapy-naïve subjects. | **North-America:** United States **LATAM:** Puerto Rico **Europe:** France, Germany, Italy, Romania, Russia, Spain, Switzerland |
| HEAT[2] (EPZ104057) | JUL 2005 – APR 2008 | IV | To establish that ABC/3TC is virologically non-inferior to TDF/FTC when administered in combination with LPV/r in ART-naïve, HIV-1 infected subjects and to compare the safety and tolerability of ABC/3TC versus TDF/FTC when administered in combination with LPV/r. | **North-America:** United States **LATAM:** Puerto Rico |
| LATTE (LAI116482) | AUG 2012 – DEC 2020 [OCT 2013] | IIb | To select a dose of Cabotegravir for further evaluation as part of a two drug combination ART regimen with rilpivirine, following a 24 week induction period of Cabotegravir with two NRTIs (either ABC/3TC or TDF/FTC, in | **North-America:** Canada, United States |

| | | | | |
|---|---|---|---|---|
| | | | HIV-1 infected, antiretroviral naïve subjects. | |
| LATTE-2 (200056) | APR 2014 – DEC 2020 [AUG 2015] | IIb | To evaluate a Long-Acting Intramuscular Regimen of GSK1265744 plus TMC278 For The Maintenance of Virologic Suppression Following an Induction of Virologic Suppression on an Oral regimen of GSK1265744 plus Abacavir/Lamivudine in HIV-1 Infected, Antiretroviral Therapy-Naive Adult Subjects | **North-America:** Canada, United States<br>**Europe:** Germany, France, Spain |
| MERIT (APV109141) | MAR 2007 – AUG 2008 | IIIb | To demonstrate non-inferior antiviral activity of FPV/RTV 1400 mg/100 mg once daily compared to FPV/RTV 700 mg/100 mg BID, both administered with abacavir/lamivudine fixed dose combination (ABC/3TC FDC) once daily. | **Europe:** Belgium, France, Germany, Italy, Romania, Russia, Spain, Switzerland, United Kingdom |
| SINGLE[2] (ING114467) | FEB 2011 – DEC 2015 | III | To demonstrate the non-inferior antiviral activity of DTG + ABC/3TC once daily therapy compared to EFV/TDF/FTC in HIV-1 infected ART-naïve subjects. | **North-America:** Canada, United States<br>**Europe:** Belgium, Denmark, Italy, France, Germany, Netherlands, Poland, Romania, Spain, United Kingdom<br>**Australasia:** Australia |
| SPRING-1 (ING112276) | JUL 2009 – DEC 2016 | II | To select a DTG once daily dose for further evaluation in Phase III based on a comparison of the antiviral activity and tolerability of a range of oral doses of DTG taken in combination with either ABC/3TC or TDF/FTC in HIV-1 infected therapy-naïve adult subjects. | **North-America:** United States<br>**Europe:** France, Germany, Italy, Russia, Spain |
| SPRING-2 (ING113086) | OCT 2010 – JUN 2016 | III | To demonstrate the antiviral activity of DTG 50 mg administered once daily compared to RAL 400 mg twice daily, both administered with either ABC/3TC or TDF/FTC in HIV-1 infected therapy-naive subjects. | **North-America:** Canada, United States<br>**Europe:** France, Germany, Italy, Russia, Spain, United Kingdom<br>**Australasia:** Australia |
| STRIIVING[2] (201147) | APR 2014 – DEC 2015 | IIIb | To compare switching from current antiretroviral regimen to ABC/DTG/3TC administered once daily in the treatment of human immunodeficiency virus type 1 (HIV-1) infected adults who are virologically suppressed. | **North-America:** United States<br>**LATAM:** Puerto Rico |
| - (ING116070) | JAN 2012 – MAY 2014 | III | A single-arm study of the safety, efficacy and central nervous system and plasma PK of GSK1349572 (dolutegravir, DTG) 50 mg once daily in combination with the abacavir/lamivudine fixed dose combination tablet over 96 | **North-America:** United States |

| | | | | |
|---|---|---|---|---|
| | | | weeks in HIV-1 infected antiretroviral naïve adult subjects. | |

[1]For details on studies conducted before 2009, refer to Brothers et al.(2009)
[2]Randomized with respect to ABC therapy.

## 7.2 Subjects

For the current meta-analysis, studies were identified through the GSK clinical trial repository. Studies that have been conducted since the 2009 meta-analysis, and for which at least the primary objective had been completed by Dec 2016 were eligible. Similar to the previous meta-analysis, only studies that included at least 24 weeks exposure to cART, with ABC in the active treatment or comparator arm, were selected for inclusion in the meta-analysis.

All included subjects were at least 18 years of age, and women of child-bearing potential were only included if on contraception to prevent pregnancy. Subjects in all included trials had been on cART for less than 14 days after their HIV diagnosis – except in ASSURE (EPZ113734) and STRIVING (201147), in which patients were required to have been on at least 6 months of treatment or switched regimens. Three studies (ARIES, ASSERT and HEAT) did not allow patients to have previously taken any nucleoside analog reverse-transcriptase inhibitors (NRTI) and/or non-nucleoside reverse-transcriptase inhibitors (NNRTI) and/or protease inhibitors (PI). ARTs taken by subjects prior to entering a GSK/ViiV Healthcare-sponsored study were ignored in this meta-analysis, and cardiac events were not necessarily an exclusion criteria for the clinical trials.

## 7.3 Variables

### 7.3.1 Exposure definitions

The exposed group included patients who were exposed to ABC as part of cART. The unexposed comparator group included patients who were not exposed to an ABC-containing cART regimen. Antiretroviral (ARV) drugs taken before subjects entered a clinical trial were not taken into account. Each subject contributed to only one of the exposure categories.

For studies where ABC was administered as one of two possible dual NRTI therapies in addition to the 3rd agent, the total exposure was obtained by taking the mean exposure in days and multiplying it with the total number of subjects for each exposure group in each trial. If the background regimen was chosen by principal investigator, the exposure was calculated by grouping the subject level data according to the background therapy (ABC vs. non-ABC) and calculating exposure time using the same calculation as in studies where ABC was administered as one of two possible dual NRTI therapies in addition to the 3rd agent. If all subjects in the trial were administered an ABC-containing therapy,

this study would just contribute exposure for ABC category and none for the non-ABC exposed.

To obtain the total exposure in person-years, the total number of days in each trial was divided by 365.25.

### 7.3.2 Outcome definitions

The same definitions as in the initial meta-analysis by Brothers et al. (2009) were used to select the events of interest based on MedDRA High-Level Terms of *coronary artery disorders not elsewhere classified* and *ischemic coronary artery disease*. MedDRA terms for angina were also included as CADs, as these were included in the 2009 meta-analysis. The following specific preferred terms were used for MI:

- Acute myocardial infarction,
- Myocardial infarction,
- Myocardial ischemia.

The following specific preferred terms were used for CAD:

- Arteriosclerosis coronary artery,
- Coronary artery disease,
- Coronary artery occlusion,
- Angina pectoris,
- Angina unstable.

Any pre-existing events were not collected as part of the clinical trials, unless there was a change in severity during the trial. Therefore, any pre-trial MIs and CADs were not collected and not included in the database.

### 7.3.3 Confounders and effect modifiers

Concurrent ARTs, baseline demographics, HIV disease characteristics, established cardiovascular risk factors, presence or absence of preexisting CVD before enrolment could have potential confounding effects in the analysis. Due to the relatively small number of events, a full statistical analysis exploring the impact of other covariates was not considered viable.

## 7.4 Study size

From the current 14 GSK/ViiV Healthcare-sponsored clinical trials since 2009, a total of 6,051 individual subjects contributed to the analysis, of which 244 switched to an ABC-containing regimen during STRIVING (Table 2). In these trials, over 3,617 were exposed to regimens that included ABC, and 2,678 were in comparator groups with regimens that did not include ABC. Including data from the previous meta-analysis (Brothers et al. 2009), the current analysis was based on a total of 20,469 subjects, with adults who

received ABC (n= 13,119) or not (n= 7,350), that provided a cumulative summary of the clinical trial evidence on the relationship between ABC and MI risk.

**Table 2 Study duration and number of abacavir- (ABC) exposed vs unexposed subjects for each included study conducted since 2009**

| Study name | Study identifier | Study duration included in meta-analysis (weeks) | ABC exposed | ABC unexposed |
|---|---|---|---|---|
| ARIA | ING117172 | 48 | 248 | 247 |
| ARIES | EPZ108859 | 144 | 515 | 0 |
| ASSERT | CNA109586 | 96 | 192 | 193 |
| ASSURE | EPZ113734 | 48 | 199 | 97 |
| FLAMINGO | ING114915 | 96 | 159 | 325 |
| HEAT | EPZ104057 | 96 | 343 | 345 |
| LATTE | LAI116482 | 24 | 94 | 149 |
| LATTE-2 | 200056 | 48[1] | 309 | 0 |
| MERIT | APV109141 | 48 | 212 | 0 |
| SINGLE | ING114467 | 144 | 414 | 419 |
| SPRING-1 | ING112276 | 96 | 67 | 138 |
| SPRING-2 | ING113086 | 96 | 333 | 489 |
| STRIIVING | 201147 | 48 | 519 | 276[2] |
| | ING116070 | 96 | 13 | 0 |

[1]All subjects (n=309) took CAB+ABC/3TC in the induction phase for 20 weeks and 56 subjects continued taking ABC for additional 48 weeks.
[2]At Week 24, individuals originally randomly assigned to CAB switched to ABC/DTG/3TC FDC and were followed for an additional 24 weeks (n=244).

## 7.5 Statistical methods

### 7.5.1 Main summary measures

The number of subjects, exposure to ABC- or non-ABC-containing regimens in person-years and number of events were calculated for all studies and summarized according to the exposure category (ABC vs. non-ABC). Proportions of events, exposure-adjusted incidence rates per 1,000 person-years and relative rates were provided with 95% confidence intervals (CIs). The same summary measures are reported for the main and all sensitivity analyses.

### 7.5.2 Main statistical methods

All statistical analyses were performed using SAS software version 9.3. CIs for the estimates of proportions of MI and CAD events were based on exact binomial 2-sided CIs. A Poisson regression model was fitted to estimate incidence rates of MI and CAD events, which were expressed as rates per 1,000 person-years with 95% CIs. The log link was used with an offset, because rates rather than number of events were being modelled. There was no adjustment for confounders.

### 7.5.3 Essential analysis

The main analysis included data from studies that were randomized to ABC or non-ABC-containing regiments and included follow-up of ≥48 weeks – 12 studies were included in the previous meta-analysis (Brothers et al. 2009) and 5 were GSK/ViiV Healthcare-sponsored studies identified post-2009. This analysis was only conducted for MI events.

### 7.5.4 Sensitivity analyses

Comparable to the previous meta-analysis, the following sensitivity analyses were performed to assess the impact of including studies with shorter follow-up periods, and studies where patients were not necessarily randomized to an ABC-containing regimen:

1. Randomized to ABC or control studies with follow-up of <48 weeks duration conducted for MI.
2. Randomized or non-randomized to ABC or control studies with follow-up of ≥48 weeks duration conducted for MIs and CADs
3. Randomized or non-randomized studies with follow-up of <48 or ≥48 weeks duration conducted for MIs and CADs

## 7.6 Study Management

### 7.6.1 Ethical approval and subject consent

N/A, ethical approval was obtained for primary data collection as part of the clinical trials. This meta-analysis used previously collected, anonymized clinical trial data.

### 7.6.2 Subject confidentiality

This meta-analysis used previously collected, anonymized clinical trial data and no identifying information was provided.

### 7.6.3 Study milestones

| Milestone | Planned date |
|---|---|
| Start of data analysis | 01 DEC 2106 |
| Draft report | 31 MAR 2017 |
| Final report of study results | 30 APR 2017 |

# 8 RESULTS

## 8.1 Participants

Only studies in which subjects were exposed to ABC-containing cART were eligible for inclusion. A total of 14 studies conducted since the last meta-analysis (Brothers et al. 2009) were included along with the previous 52 studies, comprising 20,469 subjects in the current meta-analysis. 5,959 subjects with at least 48 weeks of follow-up data contributed to the main analysis, of which 2,966 received ABC (3999 person-years) and 2,993 did not (3670 person-years).

## 8.2 Descriptive data

The age range of subjects across studies was 18 – 85 years (Table 3). The majority of study subjects were male across studies, except for ARIA where all subjects were female. Subjects in all included trials had been on cART for less than 14 days after their HIV diagnosis – except in ASSURE (EPZ113734) and STRIIVING (201147), in which patients were required to have been on at least 6 months of treatment or even switched regimens.

**Table 3 Description of subjects for each included study conducted since 2009 and the previous meta-analysis**

| Study name | Study identifier | % male subjects | Age range in years (min-max) |
|---|---|---|---|
| ARIA | ING117172 | 0 | 19 - 79 |
| ARIES | EPZ108859 | 85.4 | 19 – 72 |
| ASSERT | CNA109586 | 82.6 | 18 – 70 |
| ASSURE | EPZ113734 | 79.1 | 20 – 68 |
| FLAMINGO | ING114915 | 85 | 18 – 67 |
| HEAT | EPZ104057 | 81.8 | 18 – 74 |
| LATTE | LAI116482 | 95.9 | 18 - 70 |
| LATTE-2 | 200056 | 91.3 | 19 – 64 |
| MERIT | APV109141 | 73.6 | 18 – 70 |
| SINGLE | ING114467 | 84.2 | 18 – 85 |
| SPRING-1 | ING112276 | 86.5 | 20 – 79 |
| SPRING-2 | ING113086 | 85.6 | 18 – 75 |
| STRIIVING | 201147 | 86.4 | 22 - 80 |
| | ING116070 | 100 | 28 – 52 |
| Brothers et al.(2009) | | 81.5 | 18 – 78 |

## 8.3 Main results

Table 4 outlines the results from the primary analysis. The exposure-adjusted incidence rate of MI in the ABC-exposed group was 1.5 per 1,000 person-years (95% confidence interval (CI) 0.67 – 3.34), compared with an incidence rate of 2.18 per 1,000 person-years (95% CI 1.09 – 4.40) in the unexposed group. The relative rate was estimated at 0.69 (95% 0.24 – 1.98), but was not statistically significant.

**Table 4 Association between myocardial infarctions (MI) and ABC exposure, based on clinical trials with ABC randomization and with ≥48 weeks of post-exposure follow-up.**

| ABC exposure category | N | ART exposure (person-years) | # Events | Proportion of events (95% CI) | Exposure-adjusted incidence rate (95% CI) | Relative rate (95% CI) |
|---|---|---|---|---|---|---|
| Exposed | 2966 | 3999 | 6 | 0.27 (0.12, 0.53) | 1.50 (0.67, 3.34) | 0.69 (0.24, 1.98) |
| Unexposed | 2993 | 3670 | 8 | 0.20 (0.07, 0.44) | 2.18 (1.09,4.4) | |

## 8.4 Other analyses

The sensitivity analyses that included MI data from trials that were not randomized to ABC or had <48 weeks of follow-up (Table 5) resulted in exposure-adjusted incidence rates of 1.46 per 1,000 person-years (95% CI 0.66 – 3.25) to 1.68 per 1,000 person-years (95% CI 1.09 – 2.57) in the ABC-exposed group, and 2.01 per 1,000 person-years (95% CI 1.23 – 3.28) to 2.11 per 1,000 person-years (95% CI 1.06 – 4.22) in the unexposed group. The relative rate ranged between 0.69 (95% CI 0.24 – 1.99) to 0.83 (95% CI 0.44 – 1.60) for MI.

The exposure-adjusted incidence rate of CAD (Table 6) in the ABC-exposed group was 2.96 per 1,000 person-years (95% CI 2.14-4.08), compared with an exposure adjusted incidence rate of 4.65 per 1,000 person-years (95% CI 3.37 – 6.42) in the ABC-unexposed group. The relative rate was 0.64 (95% CI 0.40 – 1.00). The relative rate for coronary artery disease was 0.62 (95% CI 0.39 – 0.98) per 1,000 person-years if only studies with ≥48 weeks of follow-up were included. The inclusion of studies with <48 weeks follow-up had very limited impact on the estimates. If studies with <48 weeks of follow-up were also included, the relative rate was 0.64 (95% CI 0.40 – 1.00).

**Table 5 Association between myocardial infarctions and ABC exposure when all studies were included.**

| Sensitivity analysis | ABC exposure category | N | ART exposure (person-years) | # Events | Proportion of events (95% CI) | Exposure-adjusted incidence rate (95% CI) | Relative rate (95% CI) |
|---|---|---|---|---|---|---|---|
| #1 Randomized to ABC, <48 or ≥48 weeks follow-up | Exposed | 3241 | 4115 | 6 | 0.19 (0.07, 0.40) | 1.46 (0.66,3.25) | 0.69 (0.24,1.99) |
| | Unexposed | 3269 | 3790 | 8 | 0.25 (0.11, 0.48) | 2.11 (1.06, 4.22) | |
| #2 Randomized or non-randomized to ABC, ≥48 weeks follow-up | Exposed | 12796 | 12426 | 20 | 0.16 (0.10, 0.24) | 1.61 (1.04, 2.50) | 0.79 (0.41, 1.53) |
| | Unexposed | 6963 | 7897 | 16 | 0.23 (0.13, 0.37) | 2.03 (1.24, 3.31) | |
| #3 Randomized or non-randomized to ABC, <48 or ≥48 weeks follow-up | Exposed | 13119 | 12520 | 21 | 0.16 (0.10, 0.25) | 1.68 (1.09, 2.57) | 0.83 (0.44, 1.60) |
| | Unexposed | 7074 | 7956 | 16 | 0.23 (0.13, 0.37) | 2.01 (1.23, 3.28) | |

**Table 6 Association between coronary artery disease and ABC exposure when all studies were included.**

| Follow-up | ABC exposure category | N | ART exposure (person-years) | # Events | Proportion of events (95% CI) | Exposure-adjusted incidence rate (95% CI) | Relative rate (95% CI) |
|---|---|---|---|---|---|---|---|
| Randomized or non-randomized to ABC, ≥48 weeks | Exposed | 12796 | 12426 | 36 | 0.28 (0.20, 0.39) | 2.90 (2.09, 4.02) | 0.62 (0.39, 0.98) |
| | Unexposed | 6963 | 7897 | 37 | 0.53 (0.37, 0.73) | 4.69 (3.40, 6.47) | |
| Randomized or non-randomized to ABC, <48 or ≥48 weeks | Exposed | 13119 | 12520 | 37 | 0.28 (0.20, 0.39) | 2.96 (2.14, 4.08) | 0.64 (0.40, 1.00) |
| | Unexposed | 7074 | 7956 | 37 | 0.52 (0.37, 0.72) | 4.65 (3.37, 6.42) | |

# 9 DISCUSSION

Overall, for ABC-exposed and ABC-unexposed subjects, the exposure-adjusted incidence rates of MI and CAD events ranged between 1.46 and 4.65 per 1,000 person-years, which is largely in line with – although slightly lower than – previously reported rates in HIV-positive individuals. Although the MI incidence rates were slightly higher among ABC-unexposed subjects, the differences with incidence rates in ABC-exposed subjects were not statistically significant. This result is similar to what was reported in previous meta-analyses.

The incidence rates of CAD events only differed significantly between both exposure categories when studies with ≥48 weeks follow-up were included, whereby the incidence rate was higher in ABC-unexposed subjects. However, the confidence interval was very wide, which was likely do to with large variations between individual studies, rather than being a clinically significant finding.

## 9.1 Limitations

Only a review of the GSK/ViiV Healthcare clinical trial database was performed to identify studies for inclusion. It is possible that more data has been published from non-GSK/ViiV Healthcare-sponsored clinical trials that were not included in this analysis.

As the clinical trials were not specifically designed to evaluate cardiovascular outcomes, the collection of baseline risk factors for cardiovascular events may not have been incorporated in the original study protocols. Cardiac events were also likely a stopping criterion in the clinical trials, and therefore none of the trial subjects had multiple cardiac events. Additionally, there was no additional adjudication for MI and CAD events for the

current meta-analysis. Furthermore, pre-treatment events were not recorded, making it impossible to determine whether the event reported during the clinical trials was a recurrence or a new event. Although most trials only included treatment naïve patients, the definition of treatment naïve varied from not having been on any ARV for more than several weeks since diagnosis to not having been on specific ARV classes before. It is possible that these other ARV exposures may been linked to an increased risk of CVD, but it was not possible to include this into the analysis.

Based on these limitations of the available data, the current meta-analysis is mainly descriptive in nature. Considering the precautions in ABC-related product leaflets, it is likely that the number of cardiac events outside of clinical trials will be limited due to lifestyle advice to patients and potentially fewer prescriptions to patients at high risk for CVD.

This analysis used summary data rather than patient level data to calculate exposure time. The included studies were generally designed as efficacy studies, and the primary endpoint was not cardiovascular outcomes, thus the total drug exposure in person-years was defined as an average time exposed to the treatment rather than calculated until time to event or end of study, whichever occurred first. Thus, the fact that once the event occurred the subject was no longer at risk of having an outcome of interest was not taken into account. However, due to the small number of events, the post-MI/CAD follow-up time would have a very limited effect on the exposure.

Another limitation due to the relatively small number of events is that it was not possible to perform a full statistical analysis exploring the impact of potential confounders.

## 9.2 Interpretation

This meta-analysis found largely comparable incidence rates of MI and CAD among ABC-exposed and unexposed subjects, suggesting that there is no increased risk of MI or CAD following ABC exposure among clinical trial subjects. These findings provide further evidence against an association between MI and CAD and ABC exposure in this clinical trial population.

## 9.3 Generalisability

According to the Centers for Disease Control and Prevention, 76% of all HIV-positive adults and adolescents in the US in 2010 were male (Centers for Disease Control and Prevention 2017), which is comparable to the proportion of male subjects in the current study. Additionally, this meta-analysis included several studies where ABC was not the drug under investigation, but was prescribed to subjects at the discretion of their physician, which would resemble a real world setting more. The results from this meta-analysis can be considered mainly representative for HIV-positive clinical trial subjects

in high and middle income countries, but may not necessarily be representative of low resource countries.

# 10 CONCLUSIONS

MI and CAD were uncommon in GSK/ViiV Healthcare-sponsored clinical trials in which subjects were exposed to ABC-containing cART. This expanded meta-analysis found comparable IRs for MI and CAD among ABC-exposed and unexposed subjects, suggesting no increased risk for MI or CAD following ABC exposure. These findings provide further evidence against an association between MI and CAD and ABC exposure in this clinical trial population. However, modifiable risk factors for MI and CAD should be addressed when prescribing ART for treatment of HIV.

# 11 REFERENCES

Bedimo, R. J., A. O. Westfall, H. Drechsler, G. Vidiella, and P. Tebas. 2011. 'Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era', *Clin Infect Dis*, 53: 84-91.

Brothers, C. H., J. E. Hernandez, A. G. Cutrell, L. Curtis, M. Ait-Khaled, S. J. Bowlin, S. H. Hughes, J. M. Yeo, and D. H. Lapierre. 2009. 'Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects', *J Acquir Immune Defic Syndr*, 51: 20-8.

Centers for Disease Control and Prevention. 2017. 'HIV Among Men in the United States', Accessed 21 APR 2017. https://www.cdc.gov/hiv/group/gender/men/.

Choi, A. I., E. Vittinghoff, S. G. Deeks, C. C. Weekley, Y. Li, and M. G. Shlipak. 2011. 'Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons', *AIDS*, 25: 1289-98.

Cruciani, M., V. Zanichelli, G. Serpelloni, O. Bosco, M. Malena, R. Mazzi, C. Mengoli, S. G. Parisi, and G. Moyle. 2011. 'Abacavir use and cardiovascular disease events: a meta-analysis of published and unpublished data', *AIDS*, 25: 1993-2004.

Daar, E. S., C. Tierney, M. A. Fischl, P. E. Sax, K. Mollan, C. Budhathoki, C. Godfrey, N. C. Jahed, L. Myers, D. Katzenstein, A. Farajallah, J. F. Rooney, K. A. Pappa, W. C. Woodward, K. Patterson, H. Bolivar, C. A. Benson, A. C. Collier, and Aids Clinical Trials Group Study A Team. 2011. 'Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1', *Ann Intern Med*, 154: 445-56.

Ding, X., E. Andraca-Carrera, C. Cooper, P. Miele, C. Kornegay, M. Soukup, and K. A. Marcus. 2012. 'No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis', *J Acquir Immune Defic Syndr*, 61: 441-7.

Durand, M., O. Sheehy, J. G. Baril, J. Lelorier, and C. L. Tremblay. 2011. 'Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Quebec's public health insurance database', *J Acquir Immune Defic Syndr*, 57: 245-53.

Feinstein, M. J., E. Bahiru, C. Achenbach, C. T. Longenecker, P. Hsue, K. So-Armah, M. S. Freiberg, and D. M. Lloyd-Jones. 2016. 'Patterns of Cardiovascular Mortality for HIV-Infected Adults in the United States: 1999 to 2013', *Am J Cardiol*, 117: 214-20.

Hemkens, L. G., and H. C. Bucher. 2014. 'HIV infection and cardiovascular disease', *Eur Heart J*, 35: 1373-81.

Klein, D., L. B. Hurley, C. P. Quesenberry, Jr., and S. Sidney. 2002. 'Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection?', *J Acquir Immune Defic Syndr*, 30: 471-7.

Lang, S., M. Mary-Krause, L. Cotte, J. Gilquin, M. Partisani, A. Simon, F. Boccara, D. Costagliola, and H. I. V. Clinical Epidemiology Group of the French Hospital Database on. 2010. 'Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4', *Arch Intern Med*, 170: 1228-38.

Lundgren, J. D., A. Babiker, W. El-Sadr, S. Emery, B. Grund, J. D. Neaton, J. Neuhaus, and A. N. Phillips. 2008. 'Inferior clinical outcome of the CD4+ cell count-guided antiretroviral treatment interruption strategy in the SMART study: role of CD4+ Cell counts and HIV RNA levels during follow-up', *J Infect Dis*, 197: 1145-55.

Martin, A., M. Bloch, J. Amin, D. Baker, D. A. Cooper, S. Emery, and A. Carr. 2009. 'Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-Lamivudine: a randomized, 96-week trial', *Clin Infect Dis*, 49: 1591-601.

Martinez, E., M. Larrousse, D. Podzamczer, I. Perez, F. Gutierrez, M. Lonca, P. Barragan, R. Deulofeu, R. Casamitjana, J. Mallolas, J. Pich, J. M. Gatell, and Bicombo Study Team. 2010. 'Abacavir-based therapy does not affect biological mechanisms associated with cardiovascular dysfunction', *AIDS*, 24: F1-9.

Moyle, G. J., H. J. Stellbrink, J. Compston, C. Orkin, J. R. Arribas, P. Domingo, C. Granier, H. Pearce, S. Sedani, M. Gartland, and Assert Team. 2013. '96-Week results of abacavir/lamivudine versus tenofovir/emtricitabine, plus efavirenz, in antiretroviral-naive, HIV-1-infected adults: ASSERT study', *Antivir Ther*, 18: 905-13.

Obel, N., D. K. Farkas, G. Kronborg, C. S. Larsen, G. Pedersen, A. Riis, C. Pedersen, J. Gerstoft, and H. T. Sorensen. 2010. 'Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study', *HIV Med*, 11: 130-6.

Ribaudo, H. J., C. A. Benson, Y. Zheng, S. L. Koletar, A. C. Collier, J. J. Lok, M. Smurzynski, R. J. Bosch, B. Bastow, J. T. Schouten, and Actg A. Allrt Protocol Team. 2011. 'No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT', *Clin Infect Dis*, 52: 929-40.

Sabin, C. A., P. Reiss, L. Ryom, A. N. Phillips, R. Weber, M. Law, E. Fontas, A. Mocroft, S. de Wit, C. Smith, F. Dabis, A. d'Arminio Monforte, W. El-Sadr, J. D. Lundgren, and D. A. D. Study Group. 2016. 'Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration', *BMC Med*, 14: 61.

Sabin, C. A., S. W. Worm, R. Weber, P. Reiss, W. El-Sadr, F. Dabis, S. De Wit, M. Law, A. D'Arminio Monforte, N. Friis-Moller, O. Kirk, C. Pradier, I. Weller, A. N. Phillips, and J. D. Lundgren. 2008. 'Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration', *Lancet*, 371: 1417-26.

Sax, P. E., C. Tierney, A. C. Collier, E. S. Daar, K. Mollan, C. Budhathoki, C. Godfrey, N. C. Jahed, L. Myers, D. Katzenstein, A. Farajallah, J. F. Rooney, B. Ha, W. C. Woodward, J. Feinberg, K. Tashima, R. L. Murphy, M. A. Fischl, and Aids Clinical Trials Group Study A Team. 2011. 'Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results', *J Infect Dis*, 204: 1191-201.

Smith, C. J., L. Ryom, R. Weber, P. Morlat, C. Pradier, P. Reiss, J. D. Kowalska, S. de Wit, M. Law, W. el Sadr, O. Kirk, N. Friis-Moller, Ad Monforte, A. N. Phillips, C. A. Sabin, J. D. Lundgren, and D. A. D. Study Group. 2014. 'Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration', *Lancet*, 384: 241-8.

Smith, K. Y., P. Patel, D. Fine, N. Bellos, L. Sloan, P. Lackey, P. N. Kumar, D. H. Sutherland-Phillips, C. Vavro, L. Yau, P. Wannamaker, M. S. Shaefer, and Heat Study Team. 2009. 'Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment', *AIDS*, 23: 1547-56.

Squires, K. E., B. Young, E. DeJesus, N. Bellos, D. Murphy, D. Ward, H. H. Zhao, L. L. Ross, M. S. Shaefer, and Aries Study Team. 2012. 'ARIES 144 week results: durable virologic suppression in HIV-infected patients simplified to unboosted atazanavir/abacavir/lamivudine', *HIV Clin Trials*, 13: 233-44.

Triant, V. A. 2013. 'Cardiovascular disease and HIV infection', *Curr HIV/AIDS Rep*, 10: 199-206.

Triant, V. A., H. Lee, C. Hadigan, and S. K. Grinspoon. 2007. 'Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease', *J Clin Endocrinol Metab*, 92: 2506-12.

Worm, S. W., C. Sabin, R. Weber, P. Reiss, W. El-Sadr, F. Dabis, S. De Wit, M. Law, A. D. Monforte, N. Friis-Moller, O. Kirk, E. Fontas, I. Weller, A. Phillips, and J. Lundgren. 2010. 'Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study', *J Infect Dis*, 201: 318-30.

# SPONSOR SIGNATORY SIGNATURE PAGE

*I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of the study PRJ2815: Abacavir Use and Risk for Myocardial Infarction and Coronary Artery Disease: Meta-analysis of Data from Clinical Trials (eTrack Project # 207263).*

Name of Project Officer: Vani Vannappagari

Title of Project Officer: Global Head, Epidemiology and Real World Evidence

Signature: PPD

Date: 6/28/2017

Name: Harmony Garges

Title: VP, Global Medical Sciences

Signature: PPD

Date: 28 June 17

Name: Nassrin Payvandi

Title: VP, Safety and Pharmacovigilance

Signature: PPD

Date: 6 July 2017

# TITLE PAGE

**Information Type:** ViiV Healthcare Epidemiology Study Protocol

| | |
|---|---|
| **Title:** | Abacavir Use and Risk for Myocardial Infarction and Coronary Artery Disease: Meta-analysis of Data from Clinical Trials |

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| **Compound Number:** | GI265235 |
| **Development Phase** | IV |
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| **Subject:** | Safety, Abacavir, HIV |
| **Author(s):** | PPD |

## TABLE OF CONTENTS

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# 1. LIST OF ABBREVIATIONS

| | |
|---|---|
| 3TC | Lamivudine |
| ABC | Abacavir |
| AE | Adverse Event |
| ATV | Atazanavir |
| CAD | Coronary Artery Disease |
| cART | Combination Antiretroviral Therapy |
| CI | Confidence Interval |
| CVD | Cardiovascular Disease |
| D:A:D | Data Collection on Adverse Events of Anti-HIV Drugs |
| DTG | Dolutegravir |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| FDA | Food and Drug Administration |
| FDC | Fixed Dose Combination |
| FTC | Emtricitabine |
| GSK | GlaxoSmithKline |
| HIV | Human Immunodeficiency Virus |
| LPV | Lopinavir |
| MI | Myocardial Infarction |
| RCT | Randomized Controlled Trial |
| RTV | Ritonavir |
| TDF | Tenofovir Disoproxil Fumarate |
| US | United States |
| VH | ViiV Healthcare |

## 2. **RESPONSIBLE PARTIES:** SPONSOR INFORMATION PAGE

**MARKETING AUTHORISATION HOLDER**

ViiV Healthcare UK Limited

**Sponsor Legal Registered Address:**

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

# 3. ABSTRACT

**Title:** Abacavir Use and Risk for Myocardial Infarction and Coronary Artery Disease: Meta-analysis of Data from Clinical Trials

**Rationale and background:** While some observational studies and randomized controlled trials (RCTs) suggest an association between abacavir (ABC) use and myocardial infarction (MI), other observational studies and RCTs do not confirm this, including meta-analyses conducted on clinical trial data by GlaxoSmithKline (GSK), the United States (US) Food and Drug Administration (FDA) and independent researchers. Although the published evidence remains conflicting, and a plausible biological mechanism for this potential association has not yet been identified, ViiV Healthcare (VH) continues to monitor data as it becomes available. The proposed meta-analysis will include summary data from the previous meta-analysis performed by GSK (Brothers et al. 2009) and aggregate data on ABC exposure from GSK/VH-sponsored clinical trials conducted since then.

**Research question and objectives:**

The primary objective is to estimate the exposure adjusted incidence rate and relative rate of MI and coronary artery disease (CAD) events reported in subjects treated with ABC-containing combination antiretroviral therapy (cART) regimens and in subjects treated with non-ABC-containing cART regimens.

**Study design:** This meta-analysis will include data that were previously collected for GSK/VH-sponsored clinical trials from Phase II–IV of drug development. Subjects were either randomized to ABC vs other ARTs, or ABC was prescribed as a background medication by investigator.

**Study size:** The previous GSK meta-analysis (Brothers et al. 2009) and 14 GSK/VH-sponsored clinical trials completed since then comprise a total of approximately 20,000 subjects contributed to the analysis. Nearly 14,000 patients were exposed to regimens that included ABC, and 7,500 were in comparator groups with regimens that did not include ABC.

**Data analysis:** The incidence of MIs and CADs will be calculated from frequencies of reported adverse events (AEs) in the included clinical trials; 95% CIs will be based on exact binomial 2-sided CIs. To assess the exposure adjusted incidence rate and relative rate of MI and CAD in human immunodeficiency virus (HIV) patients treated with ABC-containing cART regimens compared with subjects treated with non-ABC containing cART regimens Poisson regression models will be used. 95% CIs will be calculated for rates and relative rates. The main analysis will include ABC-randomized trials with a duration of 48 weeks or longer. Sensitivity analyses will be performed to investigate the impact of including trials with follow-up shorter than 48 weeks and non-ABC-randomized trials.

# 4. AMENDMENTS AND UPDATES

N/A

# 5. MILESTONES

| Milestone | Planned date |
|---|---|
| Start of data analysis | 01 DEC 2106 |
| Draft report | 31 MAR 2017 |
| Final report of study results | 30 APR 2017 |

# 6. BACKGROUND AND RATIONALE

## 6.1. Background

Cardiovascular disease (CVD) is a leading cause of death in HIV-infected individuals, accounting for approximately 11% of total deaths in this population (Smith et al. 2014). The risk of CVD is higher in HIV-infected individuals compared with uninfected individuals (Bedimo et al. 2011; Hemkens and Bucher 2014; Triant et al. 2007). The reported incidence of MI in cohort studies ranges from 3–11 cases per 1000 patient-years in HIV-infected individuals compared with 2–7 cases per 1000 patient-years in HIV uninfected individuals (Durand et al. 2011; Klein et al. 2002; Triant et al. 2007; Worm et al. 2010).

Mechanisms for increased CVD risk in HIV remain incompletely defined and probably include both direct effects of HIV infection, including HIV-associated inflammation and immune activation, and exacerbation of risk factors by HIV infection and/or cART (Triant 2013; Triant et al. 2010). The prevalence of many CVD risk factors tends to be higher among HIV-infected individuals than among uninfected individuals, and these must be accounted for in any assessment of the relative incidence of CVD (Bedimo et al. 2011; Durand et al. 2011; Triant 2013; Triant et al. 2007). For example, data collected in two large US hospitals between 1996 and 2004 found a significantly higher prevalence between HIV-infected and uninfected individuals of smoking (38 vs. 18%), hypertension (21 vs. 16%) diabetes (12 vs. 7%) and dyslipidaemia (23 vs. 18%) (Triant et al. 2007).

One of the largest and most comprehensive data sets on CVD risk in HIV-infected individuals is the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, an international multi-cohort collaboration set up to prospectively assess the incidence of MI among HIV-infected individuals receiving cART (Friis-Moller, Sabin, et al. 2003; Friis-Moller, Weber, et al. 2003). The primary objective of the study was to determine whether exposure to cART is independently associated with risk of MI (Friis-Moller, Sabin, et al. 2003). Among the findings of the D:A:D study was an association between recent use of ABC and an increased rate of MI (Sabin et al. 2008). This was unexpected since ABC is not known to adversely affect lipids and glucose metabolism, factors that are normally considered to be pro-atherogenic.

Following the initial publication of MI results from the D:A:D study (Sabin et al. 2008), an increased risk of MI was also reported among patients who received ABC in three observational studies and a retrospective analysis of one randomised clinical trial (RCT). In consideration of these data, VH proposed a safety update to the SmPC for ABC/3TC (lamivudine):

*"Observational studies have shown an association between myocardial infarction and the use of abacavir. Those studied were mainly antiretroviral experienced patients. Data from clinical trials showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date there is no established biological mechanism to explain a potential increase in risk. When prescribing Kivexa, action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia)."*

The current Global Datasheet (GDS) includes the following on MI

*Some observational, epidemiological studies have reported an association with abacavir use and the risk of myocardial infarction. Meta-analyses of randomised controlled trials have demonstrated no excess risk of myocardial infarction with abacavir use. To date, there is no established biological mechanism to explain a potential increase in risk. In totality the available data from observational studies and from controlled clinical trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction.*

*As a precaution the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking).*

While some observational studies (Choi et al. 2011; Durand et al. 2011; Lundgren et al. 2008; Obel et al. 2010; Sabin et al. 2016; Sabin et al. 2008; Worm et al. 2010) and RCTs (Martin et al. 2009) suggest an association between ABC use and MI, other observational studies (Bedimo et al. 2011; Lang et al. 2010; Lichtenstein et al. 2010; Triant et al. 2010) and RCTs (Daar et al. 2011; Martinez et al. 2010; Moyle et al. 2013; Sax et al. 2011; Smith et al. 2009; Squires et al. 2012) do not confirm this, including meta-analyses conducted on clinical trial data by GSK (Brothers et al. 2009), the US Food and Drug Administration (FDA) (Ding et al. 2012) and independent researchers (Cruciani et al. 2011; Ribaudo et al. 2011). Although strict inclusion/exclusion criteria make RCTs less prone to selection and classification bias and confounding, they may also limit comparability with HIV patients in clinical practice as clinical trial subjects are generally healthier and have a lower cardiovascular risk. On the other hand, observational studies are subject to channelling bias; a difference in baseline characteristics of patients resulting from the way that they are assigned to a particular treatment. Channelling bias could not be ruled out in previous observational studies, e.g. D:A:D or SMART study (Lundgren et al. 2008; Sabin et al. 2008). Neither study excluded patients with chronic kidney disease (an important cardiovascular risk factor) and patients had cART

experience prior to receiving ABC. In both studies, the investigators acknowledged the potential for high-risk individuals to be channelled towards ABC (Lundgren et al. 2008; Post and Campbell 2008; Sabin et al. 2008).

Overall, the available data from observational cohorts and RCTs are inconclusive regarding the relationship between ABC treatment and the risk of MI or cardiovascular events. However, the differences in effect size seen between the observational and the RCT evidence cannot be attributed to differences in cardiovascular risk among the study populations. In the D:A:D study, the association between ABC use and MI incidence was strongest, in relative terms, in individuals with low cardiovascular risk. This would predict that an association between ABC use and MI incidence should be visible in the lower-risk populations included in RCTs.

While the published evidence remains conflicting, and a plausible biological mechanism for this potential association has not yet been identified, VH continues to monitor data as it becomes available. The proposed meta-analysis will include aggregate data on ABC exposure from VH-sponsored clinical trials, conducted since the last such meta-analysis (Brothers et al. 2009).

### 6.2. Rationale

Since the last analysis of GSK clinical trial data in 2009, several new studies have been conducted, generating additional data on ABC use and risk for MI and CAD. The proposed meta-analysis is part of VH's continued pharmacovigilance efforts to monitor this risk.

## 7. RESEARCH QUESTION AND OBJECTIVE(S)

The primary objective is to estimate the exposure adjusted incidence rate and relative rate of MI and CAD events reported in subjects treated with ABC-containing cART regimens and in subjects treated with non-ABC-containing cART regimens.

## 8. RESEARCH METHODS

### 8.1. Study Design

This study is formed to update the previously established Brothers et al. (2009) meta-analysis results of 52 GSK-sponsored clinical trials in adult subjects. In addition to summary data from the previous meta-analysis, the current analysis will include data that were collected as part of GSK/VH-sponsored clinical trials from Phase II–IV of drug development since 2009. Subjects were either randomized to ABC vs other ARTs, or ABC was prescribed as a background medication by the investigator. ARTs taken by subjects prior to entering a VH-sponsored study will be ignored in this meta-analysis.

Data for nearly 6,000 HIV-infected adult subjects from the 14 post-2009 GSK/VH-sponsored clinical trials will be investigated with the aim of evaluating the association between ABC and the risk of MI and CAD as outcomes in addition to the 14,174 HIV-infected individuals which were included in the previous meta-analysis (Brothers et al. 2009).

## 8.2. Study Population and Setting

In addition to data from the previous GSK meta-analysis (Brothers et al. 2009), data from 14 GSK/VH-sponsored clinical trials conducted since the 2009 meta-analysis, with at least 24 weeks of cART exposure will be included in this analysis (see Table 1). Only studies that were completed or for which the primary objective was completed, will be included. Overall, this analysis will be based on 66 studies, in which a total of approximately 20,000 subjects were randomized to various treatment regimen, some ABC containing and others non-ABC regimen, but in many studies randomization was not based on ABC.

**Table 1. Overview of post-2009 GSK/VH-sponsored clinical trials included in the meta-analysis.**

| Study name | Study identifier | Study duration included in meta-analysis | Primary objective | ABC exposed | ABC unexposed |
|---|---|---|---|---|---|
| ARIA[1] | ING117172 | 48 | A Phase IIIb study to demonstrate the non-inferior antiviral activity, safety and tolerability of DTG/ABC/3TC FDC compared to ATV+RTV and TDF/FTC FDC in HIV-1 infected, ART-naïve women. | 248 | 247 |
| ARIES | EPZ108859 | 144 | A Phase IIIb study to compare the safety and efficacy of ATV/r administered once daily (QD) followed by randomization (1:1) to a simplification regimen of ATV QD or continuation of ATV/r QD, each in combination with ABC/3TC FDC QD in ART-naïve, HIV-1 infected, HLA-B*5701 negative subjects. | 369 | 0 |
| ASSERT[1] | CNA109586 | 96 | A Phase IV study to demonstrate a superior renal safety profile in subjects who received ABC/3TC FDC compared to TDF/FTC FDC, both administered with efavirenz. | 192 | 193 |
| ASSURE[1] | EPZ113734 | 48 | A Phase IV study to evaluate the efficacy, safety, and tolerability of the antiviral response between ATV/RTV+ TDF/FTC and ATV + ABC/3TC without ritonavir in HIV-1 infected, HLA-B*5701 negative subjects previously suppressed on ATV/RTV + TDF/FTC. | 199 | 97 |
| FLAMINGO | ING114915 | 96 | A Phase IIIb study to demonstrate the non-inferior antiviral activity of DTG 50mg administered once daily compared to DRV+RTV 800mg + 100mg once daily both administered with either ABC/3TC or TDF/FTC in HIV-1 infected therapy-naïve subjects. | 159 | 325 |

| | | | | | |
|---|---|---|---|---|---|
| HEAT[1] | EPZ104057 | 96 | A Phase IV study to establish that ABC/3TC is virologically non-inferior to TDF/FTC when administered in combination with LPV/r in ART-naïve, HIV-1 infected subjects and to compare the safety and tolerability of ABC/3TC versus TDF/FTC when administered in combination with LPV/r. | 343 | 345 |
| LATTE | LAI116482 | 24 | A Phase IIb study to select a dose of Cabotegravir for further evaluation as part of a two drug combination ART regimen with rilpivirine, following a 24 week induction period of Cabotegravir with two NRTIs (either ABC/3TC or TDF/FTC, in HIV-1 infected, antiretroviral naïve subjects. | 94 | 149 |
| LATTE-2[1] | 200056 | 32[2] | A Phase IIb Study Evaluating a Long-Acting Intramuscular Regimen of GSK1265744 plus TMC278 For The Maintenance of Virologic Suppression Following an Induction of Virologic Suppression on an Oral regimen of GSK1265744 plus Abacavir/Lamivudine in HIV-1 Infected, Antiretroviral Therapy-Naive Adult Subjects | 56 | 230 |
| MERIT | APV109141 | 48 | A Phase IIIb study To demonstrate non-inferior antiviral activity of FPV/RTV 1400 mg/100 mg once daily compared to FPV/RTV 700 mg/100 mg BID, both administered with abacavir/lamivudine fixed dose combination (ABC/3TC FDC) once daily. | 212 | 0 |
| SINGLE[1] | ING114467 | 144 | A Phase III study to demonstrate the non-inferior antiviral activity of DTG + ABC/3TC once daily therapy compared to EFV/TDF/FTC in HIV-1 infected ART-naïve subjects. | 414 | 419 |
| SPRING-1 | ING112276 | 96 | A Phase II study to select a DTG once daily dose for further evaluation in Phase III based on a comparison of the antiviral activity and tolerability of a range of oral doses of DTG taken in combination with either ABC/3TC or TDF/FTC in HIV-1 infected therapy-naïve adult subjects. | 67 | 138 |
| SPRING-2 | ING113086 | 96 | A Phase III study to demonstrate the antiviral activity of DTG 50 mg administered once daily compared to RAL 400 mg twice daily, both administered | 333 | 489 |

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|---|---|---|---|---|---|
| | | | with either ABC/3TC or TDF/FTC in HIV-1 infected therapy-naive subjects. | | |
| STRIIVING[1] | 201147 | 48 | A Phase IIIb study to compare switching from current antiretroviral regimen to ABC/DTG/3TC administered once daily in the treatment of human immunodeficiency virus type 1 (HIV-1) infected adults who are virologically suppressed. | 275 | 276[3] |
| | ING116070 | 96 | A single-arm study of the safety, efficacy and central nervous system and plasma PK of GSK1349572 (dolutegravir, DTG) 50 mg once daily in combination with the abacavir/lamivudine fixed dose combination tablet over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects. | 13 | 0 |

[1]Randomized with respect to ABC therapy (i.e. an experimental control for ABC).
[2]Additional 20 weeks of the induction phase where all subjects (n=309) took CAB+ABC/3TC will be included in the analysis
[3]At Week 24, individuals originally randomly assigned to CAR switched to ABC/DTG/3TC FDC and were followed for an additional 24 weeks (n=244).

## 8.3. Variables

### 8.3.1. Exposure definitions

The exposed group was treated with ABC as part of cART. The comparator group was treated with non-ABC-containing cART regimen. A single subject may only contribute to one of the exposure categories (except in STRIIVING where some subjects switched from cART to ABC/DTG/3TC after 24 weeks, and LATTE-2 where all subjects received CAB+ABC/3TC during the induction phase).

The mean exposure in days will be collected from published trial results from exposure summary tabulations information for each trial for each treatment. Exposure categories will be constructed according to exposure to ABC or not in the cART. The total exposure time in person-years to the cART regimen, will be obtained by taking the mean exposure in days and multiplying it with the total number of subjects for each treatment group in each trial, and dividing it by 365.25.

### 8.3.2. Outcome definitions

For the additional 14 GSK/VH-sponsored clinical trials, outcomes were identified on the basis of reported AEs listed in an aggregated clinical trials database maintained by GSK/VH. Any pre-existing AEs were not collected unless there was a change in severity during treatment, therefore any pre-treatment MIs and CADs were not collected and therefore not included in the database.

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The same definitions as in the initial meta-analysis Brothers et al. (2009) will be used to select the events of interest based on MedDRA High-Level Terms of Coronary artery disorders not elsewhere classified and Ischemic coronary Aartery disease. The following specific preferred terms will be used:

- Arteriosclerosis coronary artery,
- Coronary artery disease,
- Coronary artery occlusion,
- Acute myocardial infarction
- Myocardial infarction
- 
- Myocardial ischemia.

MedDRA terms for angina (angina pectoris and angina unstable) will also be included as CADs, as these were included in the 2009 meta-analysis.
In addition, MedDRA terms for the outcome of MI will include acute MIs and MIs.

### 8.3.3. Confounders and effect modifiers

Concurrent ARTs, baseline demographics, HIV disease characteristics, established cardiovascular risk factors, presence or absence of preexisting CVD before enrolment could have potential confounding effects in the analysis. Due to the relatively small

number of events, a full statistical analysis exploring the impact of other covariates is not viable.

## 8.4. Data sources

The studies that will be included in the meta-analysis were initially identified in the GSK/VH clinical-trial repository that includes prospectively collected data from GSK/VH-sponsored trials and contains clinical studies from phases II–IV of drug development.

## 8.5. Study size

From the current 14 GSK/VH-sponsored clinical trials since 2009, nearly 6,000 subjects contributed to the analysis. In these trials, over 3,500 were exposed to regimens that included ABC, and nearly 3,000 were in comparator groups with regimens that did not include ABC (as noted in Section 8.3.1 some subjects in STRIIVING and LATTE-2 received both regimens). Including data from the previous meta-analysis (Brothers et al. 2009), the current analysis will be based on a total of approximately 20,000 subjects, with adults who received ABC (n= ~14,000) or not (n= ~7,500), that will provide a cumulative summary of the clinical trial evidence on the relationship between ABC and MI risk.

## 8.6. Data management

### 8.6.1. Timings of Assessment during follow-up

The timing of follow-up in the original clinical trials varied from 24 weeks up to 144 weeks post-treatment initiation. A sensitivity analysis will be performed to identify potential differences in signal detection between follow-up periods of at least 48 weeks and follow-up periods that are shorter than 48 weeks.

## 8.7. Data analysis

The main analysis will combine data from studies that were randomized to ABC or control, from studies included in the previous meta-analysis (Brothers et al. 2009) as well as from GSK/VH-sponsored studies identified post-2009. This analysis will look at studies with a follow-up of ≥48 weeks. This analysis will be conducted for MI.

The following sensitivity analyses will be performed:

- Randomized to ABC or control studies including studies of <48 weeks duration conducted for MI.
- Randomized and non-randomized to ABC or control studies of ≥48 weeks duration conducted for MIs and CADs
- Randomized and non-randomized studies including studies of <48 weeks duration conducted for MIs and CADs

### 8.7.1. Essential analysis

*Incidence of MI and CAD*

Percentages will be based on the frequency of AEs collected during the conduct of clinical trials. 95% CIs will be based on exact binomial 2-sided confidence intervals (CIs).

*Relationship between exposure to ABC and development of outcome*

Exposure adjusted incidence rates per 1,000 person-years will be calculated, and Poisson regression models will used to calculate unadjusted relative rates, no adjustment for confounders will be performed. 95% CIs will be calculated for rates and relative rates.

*Sensitivity analyses*

Table 1 includes several trials that included relatively short periods of follow-up. Sensitivity analyses will be performed including trials in which subjects were randomized to ABC or control, and the follow-up time was shorter than 48 weeks.
Additional analyses will be performed including all studies which were randomized with respect to ABC or not. This will be conducted excluding studies of <48 weeks duration, and also including these studies
.

### 8.7.2. General considerations for data analyses

None of the patients had multiple cardiac events, but it is possible that patients who had a cardiac event were excluded from the remainder of the study, or were lost to follow-up. This will be further investigated as part of the data analysis. The possibility of multiple events in one patient may not need to be taken into account. The clinical trials from which the data is derived were designed to investigate the safety and efficacy of various antiretroviral agents, including ABC, and the primary endpoint was not cardiovascular outcomes.

## 8.8. Quality control and Quality Assurance

Quality control and quality assurance processes have been performed as part of the clinical trial protocols. Two statisticians will independently program for this analysis to ensure quality control of highest level.

Additionally, the analyses will be performed per European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (2010).

## 8.9. Limitations of the research methods

Only a review of the GSK/VH clinical trial database was performed to identify studies for inclusion. It is possible that more data has been published from non-GSK/VH-sponsored clinical trials that were not included in this analysis.

As the clinical trials were not specifically designed to evaluate cardiovascular outcomes, the collection of baseline risk factors for cardiovascular events may not have been incorporated in the original study protocols. Additionally, there will be no additional adjudication for MI and CAD events for the current meta-analysis. Furthermore, pre-treatment events were not recorded, making it impossible to determine whether the event reported during the clinical trials were a recurrence or a new event. Based on these limitations of the available data, the current meta-analysis will mainly be descriptive in nature.

This analysis used summary data rather than patient level data to calculate exposure time. The included studies were generally designed as efficacy studies, and the primary endpoint was not cardiovascular outcomes, thus the total drug exposure in person-years will be defined as an average time exposed to the treatment rather than calculated until time to event or end of study, whichever occurred first. Thus, the fact that once the event occurred the subject was no longer at risk of having an outcome of interest will not be taken into account. Due to the small number of events, the post-MI/CAD follow-up time will have a very limited effect on the exposure.

Finally, due to the relatively small number of events, it is not possible to perform a full statistical analysis exploring the impact of potential confounders.

### 8.9.1. Study closure/uninterpretability of results

N/A

# 9. PROTECTION OF HUMAN SUBJECTS

## 9.1. Ethical approval and subject consent

N/A, ethical approval was obtained for primary data collection as part of the clinical trials. This meta-analysis will use previously collected, anonymized clinical trial data.

## 9.2. Subject confidentiality

This meta-analysis will use previously collected, anonymized clinical trial data. No identifying information will be provided.

# 10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves secondary use of anonymized data from RCTs. All serious and non-serious AEs, pregnancy exposures and incidents related to any VH product during the conduct of the RCTs have already been reported to the case management and regulatory authorities per the RCT protocols. There is no potential for identification of any additional AEs or SAEs. Hence there will not be a study specific pharmacovigilance plan developed.

# 11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

## 11.1. Target Audience

The target audience includes healthcare providers, regulatory and health authorities. The study results will be made available externally through peer reviewed manuscript and conference presentation.

## 11.2. Study reporting and publications

Study results will be included in safety and regulatory reports as appropriate. Results will also be submitted for publication in a peer reviewed journal, and for consideration to be presented at relevant conference.

## 12. REFERENCES

Bedimo, R. J., A. O. Westfall, H. Drechsler, G. Vidiella, and P. Tebas. 2011. 'Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era', *Clin Infect Dis*, 53: 84-91.

Brothers, C. H., J. E. Hernandez, A. G. Cutrell, L. Curtis, M. Ait-Khaled, S. J. Bowlin, S. H. Hughes, J. M. Yeo, and D. H. Lapierre. 2009. 'Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects', *J Acquir Immune Defic Syndr*, 51: 20-8.

Choi, A. I., E. Vittinghoff, S. G. Deeks, C. C. Weekley, Y. Li, and M. G. Shlipak. 2011. 'Cardiovascular risks associated with abacavir and tenofovir exposure in HIV-infected persons', *AIDS*, 25: 1289-98.

Cruciani, M., V. Zanichelli, G. Serpelloni, O. Bosco, M. Malena, R. Mazzi, C. Mengoli, S. G. Parisi, and G. Moyle. 2011. 'Abacavir use and cardiovascular disease events: a meta-analysis of published and unpublished data', *AIDS*, 25: 1993-2004.

Daar, E. S., C. Tierney, M. A. Fischl, P. E. Sax, K. Mollan, C. Budhathoki, C. Godfrey, N. C. Jahed, L. Myers, D. Katzenstein, A. Farajallah, J. F. Rooney, K. A. Pappa, W. C. Woodward, K. Patterson, H. Bolivar, C. A. Benson, A. C. Collier, and Aids Clinical Trials Group Study A Team. 2011. 'Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1', *Ann Intern Med*, 154: 445-56.

Ding, X., E. Andraca-Carrera, C. Cooper, P. Miele, C. Kornegay, M. Soukup, and K. A. Marcus. 2012. 'No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis', *J Acquir Immune Defic Syndr*, 61: 441-7.

Durand, M., O. Sheehy, J. G. Baril, J. Lelorier, and C. L. Tremblay. 2011. 'Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Quebec's public health insurance database', *J Acquir Immune Defic Syndr*, 57: 245-53.

Friis-Moller, N., C. A. Sabin, R. Weber, A. d'Arminio Monforte, W. M. El-Sadr, P. Reiss, R. Thiebaut, L. Morfeldt, S. De Wit, C. Pradier, G. Calvo, M. G. Law, O. Kirk, A. N. Phillips, J. D. Lundgren, and H. I. V. Drugs Study Group Data Collection on Adverse Events of Anti. 2003. 'Combination antiretroviral therapy and the risk of myocardial infarction', *N Engl J Med*, 349: 1993-2003.

Friis-Moller, N., R. Weber, P. Reiss, R. Thiebaut, O. Kirk, A. d'Arminio Monforte, C. Pradier, L. Morfeldt, S. Mateu, M. Law, W. El-Sadr, S. De Wit, C. A. Sabin, A. N. Phillips, J. D. Lundgren, and D. A. D. study group. 2003. 'Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study', *AIDS*, 17: 1179-93.

Hemkens, L. G., and H. C. Bucher. 2014. 'HIV infection and cardiovascular disease', *Eur Heart J*, 35: 1373-81.

Klein, D., L. B. Hurley, C. P. Quesenberry, Jr., and S. Sidney. 2002. 'Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection?', *J Acquir Immune Defic Syndr*, 30: 471-7.

Lang, S., M. Mary-Krause, L. Cotte, J. Gilquin, M. Partisani, A. Simon, F. Boccara, D. Costagliola, and H. I. V. Clinical Epidemiology Group of the French Hospital Database on. 2010. 'Impact of individual antiretroviral drugs on the risk of

myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4', *Arch Intern Med*, 170: 1228-38.

Lichtenstein, K. A., C. Armon, K. Buchacz, J. S. Chmiel, K. Buckner, E. M. Tedaldi, K. Wood, S. D. Holmberg, J. T. Brooks, and H. I. V. Outpatient Study Investigators. 2010. 'Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study', *Clin Infect Dis*, 51: 435-47.

Lundgren, J. D., A. Babiker, W. El-Sadr, S. Emery, B. Grund, J. D. Neaton, J. Neuhaus, and A. N. Phillips. 2008. 'Inferior clinical outcome of the CD4+ cell count-guided antiretroviral treatment interruption strategy in the SMART study: role of CD4+ Cell counts and HIV RNA levels during follow-up', *J Infect Dis*, 197: 1145-55.

Martin, A., M. Bloch, J. Amin, D. Baker, D. A. Cooper, S. Emery, and A. Carr. 2009. 'Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-Lamivudine: a randomized, 96-week trial', *Clin Infect Dis*, 49: 1591-601.

Martinez, E., M. Larrousse, D. Podzamczer, I. Perez, F. Gutierrez, M. Lonca, P. Barragan, R. Deulofeu, R. Casamitjana, J. Mallolas, J. Pich, J. M. Gatell, and Bicombo Study Team. 2010. 'Abacavir-based therapy does not affect biological mechanisms associated with cardiovascular dysfunction', *AIDS*, 24: F1-9.

Moyle, G. J., H. J. Stellbrink, J. Compston, C. Orkin, J. R. Arribas, P. Domingo, C. Granier, H. Pearce, S. Sedani, M. Gartland, and Assert Team. 2013. '96-Week results of abacavir/lamivudine versus tenofovir/emtricitabine, plus efavirenz, in antiretroviral-naive, HIV-1-infected adults: ASSERT study', *Antivir Ther*, 18: 905-13.

Obel, N., D. K. Farkas, G. Kronborg, C. S. Larsen, G. Pedersen, A. Riis, C. Pedersen, J. Gerstoft, and H. T. Sorensen. 2010. 'Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study', *HIV Med*, 11: 130-6.

Post, F. A., and L. J. Campbell. 2008. 'Abacavir and increased risk of myocardial infarction', *Lancet*, 372: 803; author reply 04-5.

Ribaudo, H. J., C. A. Benson, Y. Zheng, S. L. Koletar, A. C. Collier, J. J. Lok, M. Smurzynski, R. J. Bosch, B. Bastow, J. T. Schouten, and Actg A. Allrt Protocol Team. 2011. 'No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT', *Clin Infect Dis*, 52: 929-40.

Sabin, C. A., P. Reiss, L. Ryom, A. N. Phillips, R. Weber, M. Law, E. Fontas, A. Mocroft, S. de Wit, C. Smith, F. Dabis, A. d'Arminio Monforte, W. El-Sadr, J. D. Lundgren, and D. A. D. Study Group. 2016. 'Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration', *BMC Med*, 14: 61.

Sabin, C. A., S. W. Worm, R. Weber, P. Reiss, W. El-Sadr, F. Dabis, S. De Wit, M. Law, A. D'Arminio Monforte, N. Friis-Moller, O. Kirk, C. Pradier, I. Weller, A. N. Phillips, and J. D. Lundgren. 2008. 'Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration', *Lancet*, 371: 1417-26.

Sax, P. E., C. Tierney, A. C. Collier, E. S. Daar, K. Mollan, C. Budhathoki, C. Godfrey, N. C. Jahed, L. Myers, D. Katzenstein, A. Farajallah, J. F. Rooney, B. Ha, W. C. Woodward, J. Feinberg, K. Tashima, R. L. Murphy, M. A. Fischl, and Aids Clinical Trials Group Study A Team. 2011. 'Abacavir/lamivudine versus tenofovir

DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results', *J Infect Dis*, 204: 1191-201.

Smith, C. J., L. Ryom, R. Weber, P. Morlat, C. Pradier, P. Reiss, J. D. Kowalska, S. de Wit, M. Law, W. el Sadr, O. Kirk, N. Friis-Moller, Ad Monforte, A. N. Phillips, C. A. Sabin, J. D. Lundgren, and D. A. D. Study Group. 2014. 'Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration', *Lancet*, 384: 241-8.

Smith, K. Y., P. Patel, D. Fine, N. Bellos, L. Sloan, P. Lackey, P. N. Kumar, D. H. Sutherland-Phillips, C. Vavro, L. Yau, P. Wannamaker, M. S. Shaefer, and Heat Study Team. 2009. 'Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment', *AIDS*, 23: 1547-56.

Squires, K. E., B. Young, E. DeJesus, N. Bellos, D. Murphy, D. Ward, H. H. Zhao, L. L. Ross, M. S. Shaefer, and Aries Study Team. 2012. 'ARIES 144 week results: durable virologic suppression in HIV-infected patients simplified to unboosted atazanavir/abacavir/lamivudine', *HIV Clin Trials*, 13: 233-44.

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). 2010. "Guide on methodological standards in Pharmacoepidemiology (Revision 5)." In.

Triant, V. A. 2013. 'Cardiovascular disease and HIV infection', *Curr HIV/AIDS Rep*, 10: 199-206.

Triant, V. A., H. Lee, C. Hadigan, and S. K. Grinspoon. 2007. 'Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease', *J Clin Endocrinol Metab*, 92: 2506-12.

Triant, V. A., S. Regan, H. Lee, P. E. Sax, J. B. Meigs, and S. K. Grinspoon. 2010. 'Association of immunologic and virologic factors with myocardial infarction rates in a US healthcare system', *J Acquir Immune Defic Syndr*, 55: 615-9.

Worm, S. W., C. Sabin, R. Weber, P. Reiss, W. El-Sadr, F. Dabis, S. De Wit, M. Law, A. D. Monforte, N. Friis-Moller, O. Kirk, E. Fontas, I. Weller, A. Phillips, and J. Lundgren. 2010. 'Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study', *J Infect Dis*, 201: 318-30.

**SPONSOR SIGNATORY:**

Cassandra Nan
Primary Author/ Project officer

**Date**

PPD

Harmony Garg PPD
VP, Global Medical Sciences

10 Nov 2016

**Date**

Nassrin Payvandi
VP, Safety and Pharmacovigilance

**Date**

**SPONSOR SIGNATORY:**

| | |
|---|---|
| Cassandra Nan<br>Primary Author/ Project officer | **Date** |
| Harmony Garges<br>VP, Global Medical Sciences | **Date** |
| PPD<br>Nassrin Payvandi<br>VP, Safety and Pharmacovigilance | 10 Nov 2016<br>**Date** |