AIDS

DOI: 10.1097/QAD.0000000000001666

Abacavir use and risk of recurrent myocardial infarction: the D:A:D Study

Short title: Abacavir and recurrent MI

Caroline A SABIN[1], Lene RYOM[2], Antonella d'ARMINIO MONFORTE[3], Camilla I HATLEBERG[2], Christian PRADIER[4], Wafaa EL-SADR[5], Ole KIRK[1], Rainer WEBER[6], Andrew N PHILLIPS[1], Amanda MOCROFT[1], Fabrice BONNET[7], Matthew LAW[8], Stephane DE WIT[9], Peter REISS[10], Jens D LUNDGREN[2], for the D:A:D Study Group

1. Research Department of Infection and Population Health, Royal Free Campus, University College London, London, UK
2. CHIP, Department of Infectious Diseases Section 2100, Finsencentret, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
3. Dipartimento di Scienze della Salute, Clinica di Malattie Infettive e Tropicali, Azienda Ospedaliera-Polo Universitario San Paolo, Milan, Italy
4. Department of Public Health, Nice University Hospital, Nice, France
5. ICAP-Columbia University and Harlem Hospital, New York, USA
6. Division of infectious diseases and hospital epidemiology, University hospital Zurich, University of Zurich, Switzerland
7. CHU de Bordeaux and INSERM U897, Université de Bordeaux, Talence, France
8. Kirby Institute, UNSW Sydney, Sydney, Australia

9. Division of Infectious Diseases, Saint Pierre University Hospital, Université Libre de Bruxelles, Brussels, Belgium

10. Academic Medical Center, Dept. of Global Health and Div. of Infectious Diseases, University of Amsterdam, and HIV Monitoring Foundation, Amsterdam, The Netherlands.

Address for correspondence:

Professor Caroline A Sabin

Research Department of Infection and Population Health

University College London (UCL)

Royal Free campus,

Rowland Hill Street,

London NW3 2PF

Tel: 0044 207 794 0500 ext. 34752

E-mail: c.sabin@ucl.ac.uk

Word count: 1797 words

Abstract

Objective: To investigate the association between abacavir (ABC) use and recurrent myocardial infarction (MI) among HIV-positive people with a prior MI.

Design: International multi-cohort collaboration with follow-up from 1999-2016.

Methods: The rate of recurrent MI was described among D:A:D participants who experienced an index MI whilst in the study, and who remained under follow-up beyond 28 days after this MI. Follow-up was considered to the date of next MI, death, 01/Feb/2016 or 6 months after last clinic visit. Poisson regression models considered associations between recurrent MI and exposure to ABC (use at index MI, current post-MI exposure and cumulative exposure), before and after adjusting for calendar year.

Results: The 984 individuals who experienced an index MI during the study (91.3% male, median age 51 at index MI) were followed for 5312 person-years (PY) over which time there were 136 recurrent MIs (rate 2.56/100 PY, 95% Confidence Interval 2.13-2.99). Rates were 2.40 (1.71-3.09) and 2.65 (2.10-3.21)/100 PY in those who were and were not on ABC, respectively, at the index MI, and 2.90 (2.01-3.78) and 2.44 (1.95-2.93)/100 PY in those who were and were not currently receiving ABC, respectively, post-MI. No association was seen with recurrent MI and either cumulative exposure to ABC (RR=0.86 [0.68-1.10]/5 years), receipt of ABC at index MI (0.90 [0.63-1.29]) nor recent post-MI exposure to ABC (1.19 [0.82-1.71]).

Conclusions: Among people with a previous MI, there was no evidence for an association between use of ABC post-MI and an elevated risk of a recurrent MI.

Key words: Abacavir; cardiovascular disease; myocardial infarction; risk;

INTRODUCTION

Since the initial presentation of findings from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study in early 2008 demonstrating a 90% increase in the risk of myocardial infarction (MI) in HIV-positive individuals receiving antiretroviral therapy (ART) regimens that included abacavir (ABC) [1], other studies have reported inconsistent findings [2-5]. A recent updated analysis from the D:A:D study, that included follow-up and events from 2008 onwards, reported that the relative hazard (RR) for MI associated with recent ABC use in the post-2008 period was unchanged from that previously reported [6]. These findings, in the context of demonstrated changes in the characteristics of those receiving ABC-based regimens, suggested that the association was unlikely to be explained by a higher underlying risk of MI in ABC-treated individuals prior to starting the drug.

Most of the studies that have considered the association between ABC exposure and MI risk, including the D:A:D analyses, have focussed on populations of HIV-positive people in which few individuals have already experienced a prior MI. However, such individuals represent a very high-risk subgroup that will likely be exposed to multiple lifestyle and clinical interventions for secondary prevention. We investigated the association between ABC use and subsequent MI risk among the patients who had already experienced an MI during prospective D:A:D follow-up.

METHODS

Study design

The D:A:D Study was an observational study of >49,000 HIV-1-positive patients from 11 cohorts from Europe, Australia, and the United States [7]. The primary study aim was to investigate associations between the use of ART and the risk of cardiovascular disease (CVD) and other major disease events. The standardised dataset, collected prospectively during routine clinic visits, includes information on socio-demographic factors, AIDS events and deaths, risk factors for CVD, laboratory markers for monitoring HIV (including CD4 count and HIV RNA) and CVD, ART and treatments that influence CVD risk.

Information on incident MI events was reported to the study co-ordinating centre via a study event form which captured detailed information about the event and related circumstances. Each reported event was validated and coded using criteria applied in the WHO MONICA Study [8], with this process being performed blind to information about the patient's ART status. Reported MIs were classified as definite, possible or unclassifiable using standardised criteria for classification including relevant symptoms, relevant increase and decline in cardiac enzymes, ischemic changes in electrocardiographic readings and, in cases of death, autopsy results if available. Fatal MI events were additionally validated using information collected on the Coding of Causes of Death (CoDe) form [9], and all complex and/or fatal MI cases were additionally validated with the input of an independent cardiologist.

Statistical methods

We considered the rate of recurrent MI among D:A:D participants who experienced an MI during study follow-up (the 'index' MI) and who remained alive and under follow-up at 28 days post-MI (to exclude any index MIs resulting in death). Follow-up was considered from 28 days post-MI to the first date of next MI, death, 01/Feb/2016 or 6 months after last clinic visit. Sixty-four of the individuals (6.5%) had experienced an MI prior to D:A:D entry (and prior to the index MI); to be consistent with the main D:A:D analyses, we did not exclude this subgroup but sensitivity analyses (which excluded the subgroup) suggested that our findings were robust to their inclusion.

Poisson regression models were used to evaluate associations between recurrent MI and exposure to ABC. As in previous analyses of the dataset [5], each individual's follow-up was split into a series of consecutive one-month periods and his/her clinical, immunologic and virologic status at the start of each period was established. Three different exposures to ABC were considered: i) use of ABC at the time of initial MI (time-fixed); ii) current, post-MI exposure (time-updated, defined as currently receiving ABC or having received the drug at any time in the six months leading up to the start of each month); and iii) cumulative exposure (time-updated, including exposure both pre- and post-MI and scaled to reflect a 5-year increment). Fixed confounders considered were gender, ethnic group, and mode of HIV acquisition. Time-updated covariates considered were calendar year, age (continuous covariate), smoking status, body mass index (BMI), cumulative exposure to the protease inhibitors lopinavir, indinavir and darunavir, and the development of dyslipidaemia, diabetes mellitus or hypertension (Table 1).

All analyses were performed using SAS version 9.3.

RESULTS

Of the 1191 participants who developed an index MI during the study, 984 remained under follow-up for at least 28 days and were included in the study. These individuals were largely male (91.3%) and infected with HIV through sex between men (58.8%). At the time of the index MI, the participants had a median age of 51 years (inter-quartile range [IQR] 45-59), the majority were current (55.5%) or ex- (24.3%) smokers, 14.3% had a family history of MI, and most had either a moderate (10-20%, 33.0%) or high (>20%, 27.1%) 10-year predicted Framingham risk for CVD. The index MI had occurred in 1999-2001, 2002-2004, 2005-2007, 2008-2010, 2011-2013 and from 2014-2016 in 95 (9.7%), 209 (21.2%), 207 (21.0%), 196 (19.9%), 184 (18.7%) and 93 (9.5%) of participants, respectively.

The median CD4 count at index MI was 511 (IQR 348-740) cells/mm^3. At the time of index MI, the majority of participants (959, 97.5%) had ever received ART, with 860 (87.4%) of patients currently receiving ART. Two-thirds (691, 70.3%) had an HIV RNA <50 copies/ml. Of the 584 people who were not already receiving lipid-lowering drugs at the time of the index MI, 306 (52.4%) started them within the first 28 days after MI. Similarly, 245/763 (32.1%) of those not already receiving angiotensin converting enzyme (ACE) inhibitors and 330/699 (47.2%) of those not already receiving anti-hypertensives started these within the first 28 days post index MI. Two-thirds of participants (63.2%) received an angioplasty and 44 (4.5%) received coronary artery bypass surgery in the first 28 days post MI

Five hundred and three (51.2%) people had received ABC prior to their index MI for a median of 3.1 years (range 0-13.9) of whom 327 were still on ABC at the time of the index MI. Two hundred and thirty-nine of the 327 (73.1%) stopped the drug at a median of 323 (range 0-5252) days after MI, with 71 of them subsequently re-starting the drug. Eighty of the 481 participants who had not previously received ABC prior to the index MI (16.6%), started the drug for the first time at a median of 1089 (range 3-4384) days after the index MI. Of the 151 people who either started ABC for the first time or who restarted ABC after previous use, the majority (116/151) did so prior to the publication of the initial D:A:D study findings in 2008 [1].

The 984 included participants were followed for a median of 4.7 (range 0.1-15.3) years after the index MI (total person-years (PY): 5312). Over this time, 136 people (13.8%) had at least one recurrent MI (rate: 2.56/100 PY (95% confidence interval [CI] 2.13-2.99). Rates of recurrent MI were 2.40 (1.71-3.09, 47 events over 1959 PY) and 2.65 (2.10-3.21, 89 events over 3353 PY)/100 PY in those who were and were not on ABC at the time of their index MI; rates were 2.90 (2.01-3.78, 41 events over 1415 PY) and 2.44 (1.95-2.93, 95 events over 3897 PY)/100 PY in those who were and were not currently receiving ABC post-MI, respectively. There was no significant association between recurrent MI and either cumulative exposure to ABC (RR 0.86 [0.68-1.10]/5 years), receipt of ABC at index MI (0.90 [0.63-1.29]) or current post-MI exposure (1.19 [0.82-1.71], Table 1). Whilst earlier calendar year, a non-sexual or injection drug use route of HIV acquisition and a prior diagnosis of diabetes were each associated with an increased risk of recurrent MI in univariate analyses (Table 1), adjustment for these factors did not reveal any significant associations with exposure to ABC.

CONCLUSIONS

Whilst previous study findings have suggested that current use of ABC in HIV-positive people is associated with an almost doubling in MI risk [1], we found no evidence that use of ABC was associated with an elevated risk of recurrent MI in those with a previous MI. Although most of the continued/new ABC use in those with an MI was in the earlier years of the study, when the risk of recurrent MI was higher than it is currently [10-12], adjustment for calendar year did not modify our findings.

Whilst these results appear to contradict with previous findings, there are two main reasons why we might expect the association with ABC exposure to differ in those with a prior MI. Firstly, recurrent MIs in those with an index MI are more likely to reflect the uptake and success of post-MI interventions to manage CVD and prevent subsequent cardiovascular events in this group than differences in established risk factors for a primary MI. Our finding that few of the established CVD risk factors are associated with recurrent MI, other than diabetes, supports the existence of a different set of risk factors for recurrent MI, a notion which is consistent with the limited literature from the general population [13-15]. Secondly, one of the reasons for the continued debate about the potential association between ABC and MI is that there is no confirmed biological mechanism for the association. Arguably, the most promising potential mechanism to date relates to the association reported between ABC and platelet reactivity [16-18], a mechanism that would be consistent with the apparent reversible nature of the ABC association with MI; a similar association has also recently been described with protease inhibitors [19]. We would, however, expect the majority of those with an MI to be

receiving anti-platelet therapy, more recently with the dual combination of aspirin and clopidogrel, which could plausibly modify any effects of ABC on platelet reactivity. Unfortunately, we do not collect detailed information on the clinical presentation of each MI or on subsequent management and are therefore unable to assess the numbers treated in this way to test this hypothesis.

We note that our aim in the present study was to exclude the possibility that any of the established CVD risk factors may have confounded (and possibly obscured) an association with ABC rather than to identify risk factors for recurrent MI *per se*. For this reason, we have not investigated above factors in more depth, or a the potential role of chronic kidney disease, a factor previously demonstrated to be associated with CVD risk in the study [20] – information on the latter was often unavailable in the earlier years of the study although in more recent years, ABC may have been a treatment of choice in people with chronic kidney disease. Furthermore, we do not capture information on lifestyle/behavioural modifications, and so cannot investigate whether any changes in these may have modified the subsequent risk of recurrent MI and/or its association with continued or new ABC use. We cannot, therefore, rule out the possibility that our findings may result from residual confounding due to different post-MI management among those who are and are not receiving ABC.

In summary, among people with a previous MI, there was no evidence for an association between use of ABC post-MI and an elevated risk of a recurrent MI.

REFERENCES

1. The D:A:D Study Group. **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* 2008; **371**:1417-26;

2. Mallon PW. **Impact of nucleoside reverse transcriptase inhibitors on coronary heart disease.** *Rev Cardiovasc Med* 2014; **15 Suppl 1**:S21-S29.

3. Bavinger C, Bendavid E, Niehaus K, Olshen RA, Olkin I, Sundaram V, et al. **Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review.** *PLoS ONE* 2013; **8**:e59551.

4. Ding X, Andraca-Carrera E, Cooper C, Miele P, Kornegay C, Soukup M, et al. **No association of abacavir use with myocardial infarction: findings of an FDA meta-analysis.** *J Aquir Imm Defic Syndr* 2012; **61**:441-447.

5. Cruciani M, Zanichelli V, Serpelloni G, Bosco O, Malena M, Mazzi R, et al. **Abacavir use and cardiovascular disease events: a meta-analysis of published and unpublished data.** *AIDS* 2011; **25**:1993-2004.

6. Sabin CA, Reiss P, Ryom L, Phillips AN, Weber R, Law M, et al. **Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration.** *BMC Med* 2016; **14**:61.

7. The DAD Study Group. **Class of antiretroviral drugs and the risk of myocardial infarction.** *N Engl J Med* 2007; **356**:1723-1735.

8. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pamak A. **Myocardial infarction and coronary deaths in the World Health Organization MONICA Project registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents.** *Circulation* 1994; **90**:583-612.

9. Kowalska JD, Smith C, Lundgren JD. **System to classify cause of deaths in HIV-positive persons: time to harmonize.** *AIDS* 2012; **26:**1835-1836.

10. Smedegaard L, Charlot MG, Gislason GH, Hansen PR. **Temporal trends in acute myocardial infarction presentation and association with use of cardioprotective drugs: A nationwide registry-based study.** *Eur Heart J Cardiovasc Pharmacother* 2017 [in press].

11. Rahimi K, Duncan M, Pitcher A, Emdin CA, Goldacre MJ. **Mortality from heart failure, acute myocarcial infarction and other ischaemic heart disease in England and Oxford: a trend study of multiple-cause-coded death certification.** *J Epidemio Comm Health* 2015; **69**:1000-1005.

12. Chaudhry SI, Khan RF, Chen J, Dharmarajan K, Dodson JA, Masoudi FA, et al. **National trends in recurrent AMI hospitalizations 1 year after acute myocardial infarction in Medicare beneficiaries: 1999-2010.** *J Am Heart Assoc* 2014; **3**:e001197 doi: 10.1161/JAHA.114.001197.

13. Cao C-F,Li S-F, Chen H, Song J-X. **Predictors and in-hospital prognosis of recurrent acute myocardial infarction.** *J Geriatric Cardiol* 2016; **13**:836-839.

14. Gao M, Zheng Y, Zhang W, Cheng Y, Wang L, Qin L**. Non-high-density lipoprotein cholesterol predicts nonfatal recurrent myocardial infarction in patients with ST segment elevation myocardial infarction.** *Lipids Heath Dis* 2017; **16**:20.

15. Nakashima H, Mashimo Y, Kurobe M, Muto S, Furudono S, Maemura K. **Impact of morning onset on the incidence of recurrent acute coronary syndrome and progression of coronary atherosclerosis in acute myocardial infarction.** *Circ J* 2017; **81**:361-367.

16. Satchell CS, O'Halloran JA, Cotter AG, Peace AJ, O'Connor EF, Tedesco AF, et al**. Increased platelet reactivity in HIV-1-infected patients receiving abacavir-containing antiretroviral therapy.** *J Infect Dis* 2011; **204**:1202-1210.

17. Baum PD, Sullam PM, Stoddart CA, McCune JM. **Abacavir increases platelet reactivity via competitive inhibition of soluble guanylyl cyclase.** *AIDS* 2011; **25**:2243-2248.

18. Espluges JV, De Pablo C, Collado-Diaz V, Hernandez C, Orden S, Alvarez A**. Interference with purinergic signalling: an explanation for the cardiovascular effect of abacavir?** *AIDS* 2016; **30**:1341-1351.

19. Hauguel-Moreau M, Boccara F, Boyd A, Salem J-E, Brugier D, Curjol A, et al. Platelet reactivity in human immunodeficiency virus infected patients on dual

antiplatelet therapy for an acute coronary syndrome: the EVERE$_2$ST-HIV study. *Eur Heart J* 2017; **38:** 1676-1686.

20. Ryom L, Lundgren JD, Ross M, Kirk O, Law M, Morlat P, et al. **Renal impairment and cardiovascular disease in HIV-positive individuals: The D:A:D Study.** *J Infect Dis* 2016; 214: 1212-1220.

ROLE OF AUTHORS

CS, CIH, LR, ANP and JDL developed the initial analysis protocol. LR and CIH performed study co-ordination and prepared the datasets for analysis. CS performed all statistical analysis, and prepared the initial draft of the manuscript. All authors provided input at all stages of the project and have seen and approved the final manuscript.

CONFLICTS OF INTEREST

CS has received honoraria for the membership of Data Safety and Monitoring Boards, Advisory Boards and Speaker Panels from Gilead Sciences, ViiV Healthcare and Janssen-Cilag; she has received funding to support the development of educational materials from Gilead Sciences and ViiV Healthcare. Ad'AM has received grants for advisory boards or lectures by Abbve, BMS, Gilead, Janssen, MSD and ViiV. CP reports non-financial support from Janssen, personal fees from Gilead Sciences, non-financial support from ViiV Healthcare, and non-financial support from MSD. AM has received travel support, honoraria, speaker fees and/or lecture fees from BMS, Gilead, ViiV, Pfizer, Merck, BI and Wragge LLC. ML has received unrestricted grants from Boehringer Ingelhiem, Gilead Sciences, Merck Sharp & Dohme, Bristol-Myers Squibb, Janssen-Cilag and ViiV HealthCare; he has also received consultancy payments from Gilead Sciences, and DSMB sitting fees from Sirtex Pty Ltd. PR has through his institution received independent scientific grant support from Gilead Sciences, Janssen Pharmaceuticals Inc, Merck & Co, Bristol-Myers Squibb and ViiV Healthcare; he has served on a scientific advisory board for Gilead Sciences and a data safety monitoring committee for Janssen Pharmaceuticals Inc; he chaired a scientific symposium by ViiV

Healthcare, for which his institution has received remuneration. LR, CIR, WE-S, FB, SdW, OK, RW, ANP and JL have no disclosures to declare.

ACKNOWLEDGEMENTS

D:A:D participating cohorts: AHOD (Australia), Aquitaine (France), Athena (The Netherlands), BASS (Spain), CPCRA (USA), EuroSIDA (multi-national), **HivBivus** (Sweden), ICONA (Italy), Nice (France), SHCS (Switzerland) and St. Pierre (Belgium)

D:A:D Steering Committee: Names marked with *, Chair with ¢

Cohort PIs: W El-Sadr* (CPCRA), G Calvo* (BASS), F Bonnet and F Dabis* (Aquitaine), O Kirk* and A Mocroft* (EuroSIDA), M Law* (AHOD), A d'Arminio Monforte* (ICONA), L Morfeldt* (HivBIVUS), C Pradier* (Nice), P Reiss* (ATHENA), R Weber* (SHCS), S De Wit* (St. Pierre)

Cohort coordinators and data managers: A Lind-Thomsen (coordinator), R Salbøl Brandt, M Hillebreght, S Zaheri, FWNM Wit (ATHENA), A Scherrer, F Schöni-Affolter, M Rickenbach (SHCS), A Tavelli, I Fanti (ICONA), O Leleux, J Mourali, F Le Marec, E Boerg (Aquitaine), E Thulin, A Sundström (HIVBIVUS), G Bartsch, G Thompsen (CPCRA), C Necsoi, M Delforge (St. Pierre), E Fontas, C Caissotti, K Dollet (Nice), S Mateu, F Torres (BASS), K Petoumenos, A Blance, R Huang, R Puhr (AHOD), K Grønborg Laut, D Kristensen (EuroSIDA)

Statisticians: CA Sabin*, AN Phillips*, DA Kamara, CJ Smith, A Mocroft*

D:A:D coordinating office: CI Hatleberg, L Ryom*, A Lind-Thomsen, RS Brandt, D Raben, C Matthews, A Bojesen, AL Grevsen, JD Lundgren*¢

Member of the D:A:D Oversight Committee: B Powderly*, N Shortman*, C Moecklinghoff*, G Reilly*, X Franquet*

D:A:D working group experts:

Kidney: L Ryom*, A Mocroft*, O Kirk*, P Reiss*, C Smit, M Ross, CA Fux, P Morlat, E Fontas, DA Kamara, CJ Smith, JD Lundgren*¢

Mortality: CJ Smith, L Ryom*, CI Hatleberg, AN Phillips*, R Weber*, P Morlat, C Pradier*, P Reiss*, FWNM Wit, N Friis-Møller, J Kowalska, JD Lundgren*¢

Cancer: CA Sabin*, L Ryom*, CI Hatleberg, M Law*, A d'Arminio Monforte*, F Dabis*, F Bonnet*, P Reiss*, FWNM Wit, CJ Smith, DA Kamara, J Bohlius, M Bower, G Fätkenheuer, A Grulich, JD Lundgren*¢

External endpoint reviewers: A Sjøl (CVD), P Meidahl (oncology), JS Iversen (nephrology)

Funding: 'Oversight Committee for The Evaluation of Metabolic Complications of HAART' with representatives from academia, patient community, FDA, EMA and a consortium of AbbVie, Bristol-Myers Squibb, Gilead Sciences, ViiV Healthcare, Merck and Janssen Pharmaceuticals.

The current members of the 11 Cohorts are as follows:

ATHENA (AIDS Therapy Evaluation Project Netherlands):

Central coordination: P. Reiss*, S. Zaheri, M Hillebregt, F.W.N.M. Wit;

CLINICAL CENTRES (¤ denotes site coordinating physician) Academic Medical Centre of the University of Amsterdam: J.M. Prins¤, T.W. Kuijpers, H.J. Scherpbier, J.T.M. van der Meer, F.W.N.M. Wit, M.H. Godfried, P. Reiss*, T. van der Poll, F.J.B. Nellen, S.E. Geerlings, M. van Vugt, D. Pajkrt, J.C. Bos, W.J. Wiersinga, M. van der Valk, A. Goorhuis, J.W. Hovius, J. van Eden, A. Henderiks, A.M.H. van Hes, M. Mutschelknauss, H.E. Nobel, F.J.J. Pijnappel, S. Jurriaans, N.K.T. Back, H.L. Zaaijer, B. Berkhout, M.T.E. Cornelissen, C.J. Schinkel, X.V. Thomas. Admiraal De Ruyter Ziekenhuis, Goes: M. van den Berge, A. Stegeman, S. Baas, L. Hage de Looff, D. Versteeg. Catharina Ziekenhuis, Eindhoven: M.J.H. Pronk¤, H.S.M. Ammerlaan, E.S. de Munnik. A.R. Jansz, J. Tjhie, M.C.A. Wegdam, B. Deiman, V. Scharnhorst. Emma Kinderziekenhuis: A. van der Plas, A.M. Weijsenfeld. Erasmus MC, Rotterdam: M.E. van der Ende¤, T.E.M.S. de Vries-Sluijs, E.C.M. van Gorp, C.A.M. Schurink, J.L. Nouwen, A. Verbon, B.J.A. Rijnders, H.I. Bax, M. van der Feltz. N. Bassant, J.E.A. van Beek, M. Vriesde, L.M. van Zonneveld. A. de Oude-Lubbers, H.J. van den Berg-Cameron, F.B. Bruinsma-Broekman, J. de Groot, M. de Zeeuw- de Man, C.A.B. Boucher, M.P.G Koopmans, J.J.A van Kampen, S.D. Pas. Erasmus MC–Sophia, Rotterdam: G.J.A. Driessen, A.M.C. van Rossum, L.C. van der Knaap, E. Visser. Flevoziekenhuis, Almere: J. Branger¤, A. Rijkeboer-Mes, C.J.H.M. Duijf-van de Ven. HagaZiekenhuis, Den Haag: E.F. Schippers¤, C. van Nieuwkoop. J.M. van IJperen, J. Geilings. G. van der Hut. P.F.H. Franck. HIV Focus Centrum (DC Klinieken): A. van Eeden¤. W. Brokking, M. Groot, L.J.M. Elsenburg, M. Damen, I.S. Kwa. Isala, Zwolle: P.H.P. Groeneveld¤, J.W. Bouwhuis, J.F. van den Berg, A.G.W. van Hulzen, G.L. van der Bliek, P.C.J. Bor, P. Bloembergen, M.J.H.M. Wolfhagen, G.J.H.M. Ruijs. Leids Universitair Medisch

Centrum, Leiden: , F.P. Kroon¤, M.G.J. de Boer, M.P. Bauer, H. Jolink, A.M. Vollaard, W. Dorama, N. van Holten, E.C.J. Claas, E. Wessels. Maasstad Ziekenhuis, Rotterdam: J.G. den Hollander¤, K. Pogany, A. Roukens, M. Kastelijns, J.V. Smit, E. Smit, D. Struik-Kalkman, C. Tearno, M. Bezemer, T. van Niekerk, O. Pontesilli. Maastricht UMC+, Maastricht: S.H. Lowe¤, A.M.L. Oude Lashof, D. Posthouwer, R.P. Ackens, J. Schippers, R. Vergoossen, B. Weijenberg-Maes, I.H.M. van Loo, T.R.A. Havenith. MCH-Bronovo, Den Haag: E.M.S. Leyten¤, L.B.S. Gelinck, A. van Hartingsveld, C. Meerkerk, G.S. Wildenbeest, J.A.E.M. Mutsaers, C.L. Jansen. MC Slotervaart, Amsterdam: J.W. Mulder, S.M.E. Vrouenraets, F.N. Lauw, M.C. van Broekhuizen, H. Paap, D.J. Vlasblom, P.H.M. Smits. MC Zuiderzee, Lelystad: S. Weijer¤, R. El Moussaoui, A.S. Bosma. Medisch Centrum Leeuwarden, Leeuwarden: M.G.A.van Vonderen¤, D.P.F. van Houte, L.M. Kampschreur, K. Dijkstra, S. Faber, J Weel. Medisch Spectrum Twente, Enschede: G.J. Kootstra¤, C.E. Delsing, M. van der Burg-van de Plas, H. Heins, E. Lucas. Noorwest Ziekenhuisgroep, Alkmaar: W. Kortmann¤, G. van Twillert¤, J.W.T. Cohen Stuart, B.M.W. Diederen, D. Pronk, F.A. van Truijen-Oud, W. A. van der Reijden, R. Jansen. OLVG, Amsterdam: K. Brinkman¤, G.E.L. van den Berk, W.L. Blok, P.H.J. Frissen, K.D. Lettinga W.E.M. Schouten, J. Veenstra, C.J. Brouwer, G.F. Geerders, K. Hoeksema, M.J. Kleene, I.B. van der Meché, M. Spelbrink, H. Sulman, A.J.M. Toonen, S. Wijnands, M. Damen, D. Kwa, E. Witte. Radboudumc, Nijmegen: P.P. Koopmans, M. Keuter, A.J.A.M. van der Ven, H.J.M. ter Hofstede, A.S.M. Dofferhoff, R. van Crevel, M. Albers, M.E.W. Bosch, K.J.T. Grintjes-Huisman, B.J. Zomer, F.F. Stelma, J. Rahamat-Langendoen,D. Burger. Rijnstate, Arnhem: C. Richter¤, E.H. Gisolf, R.J. Hassing, G. ter Beest, P.H.M. van Bentum, N. Langebeek, R.

Tiemessen, C.M.A. Swanink. Spaarne Gasthuis, Haarlem: S.F.L. van Lelyveld¤, R. Soetekouw, N. Hulshoff, L.M.M. van der Prijt, J. van der Swaluw, N. Bermon, W.A. van der Reijden, R. Jansen, B.L. Herpers, D.Veenendaal. Medisch Centrum Jan van Goyen, Amsterdam: D.W.M. Verhagen, M. van Wijk. St Elisabeth Ziekenhuis, Tilburg: M.E.E. van Kasteren¤, A.E. Brouwer, B.A.F.M. de Kruijf-van de Wiel, M. Kuipers, R.M.W.J. Santegoets, B. van der Ven, J.H. Marcelis, A.G.M. Buiting, P.J. Kabel. Universitair Medisch Centrum Groningen, Groningen: W.F.W. Bierman¤, H. Scholvinck, K.R. Wilting, Y. Stienstra, H. de Groot-de Jonge, P.A. van der Meulen, D.A. de Weerd, J. Ludwig-Roukema, H.G.M. Niesters, A. Riezebos-Brilman, C.C. van Leer-Buter, M. Knoester. Universitair Medisch Centrum Utrecht, Utrecht: A.I.M. Hoepelman¤, T. Mudrikova, P.M. Ellerbroek, J.J. Oosterheert, J.E. Arends, R.E. Barth, M.W.M. Wassenberg, E.M. Schadd, D.H.M. van Elst-Laurijssen, E.E.B. van Oers-Hazelzet, S. Vervoort, M. van Berkel, R. Schuurman, F. Verduyn-Lunel, A.M.J. Wensing. VUmc, Amsterdam: E.J.G. Peters¤, M.A. van Agtmael, M. Bomers, J. de Vocht, M. Heitmuller, L.M. Laan, A.M. Pettersson, C.M.J.E. Vandenbroucke-Grauls, C.W. Ang. Wilhelmina Kinderziekenhuis, UMCU, Utrecht: S.P.M. Geelen, T.F.W. Wolfs, L.J. Bont, N. Nauta. COORDINATING CENTRE P. Reiss, D.O. Bezemer, A.I. van Sighem, C. Smit, F.W.N.M. Wit., T.S. Boender, S. Zaheri, M. Hillebregt, A. de Jong, D. Bergsma, P. Hoekstra, A. de Lang, S. Grivell, A. Jansen, M.J. Rademaker, M. Raethke, R. Meijering, S. Schnörr, L. de Groot, M. van den Akker, Y. Bakker, E. Claessen, A. El Berkaoui, J. Koops, E. Kruijne, C. Lodewijk, L. Munjishvili, B. Peeck, C. Ree, R. Regtop, Y. Ruijs, T. Rutkens, L. van de Sande, M. Schoorl, A. Timmerman, E. Tuijn, L. Veenenberg, S. van der Vliet, A. Wisse, T. Woudstra, B. Tuk.

Aquitaine Cohort (France)

Composition du Conseil scientifique :

Coordination: F. Bonnet*, F. Dabis*

Scientific committee: M. Dupon, V. Gaborieau, D. Lacoste, D. Malvy, P. Mercié, P. Morlat, D. Neau, JL. Pellegrin, S. Tchamgoué, E. Lazaro, C. Cazanave, M. Vandenhende, M.O. Vareil, Y. Gérard, P. Blanco, S. Bouchet, D. Breilh, H. Fleury, I. Pellegrin, G. Chêne, R. Thiébaut, L. Wittkop, L. Wittkop, O. Leleux, S. Lawson-Ayayi, A. Gimbert, S. Desjardin, L. Lacaze-Buzy, V. Petrov-Sanchez

Epidemiology and Methodology: F. Bonnet*, G. Chêne, F. Dabis*, R. Thiébaut, L. Wittkop

Infectious Diseases and Internal Medicine: K. André, N. Bernard, F. Bonne*t, O. Caubet, L. Caunegre, C. Cazanave, I. Chossat, C. Courtault, FA. Dauchy, S. De Witte, D. Dondia, M. Dupon, P. Duffau, H. Dutronc, S. Farbos, I. Faure, H. Ferrand, V. Gaborieau, Y. Gerard, C. Greib, M. Hessamfar, Y. Imbert, D. Lacoste , P. Lataste, E. Lazaro, D. Malvy, J. Marie, M. Mechain, P. Mercié, E.Monlun, P. Morlat, D. Neau, A. Ochoa, JL. Pellegrin, T. Pistone, I. Raymond,MC. Receveur, P. Rispal, L. Sorin, S. Tchamgoué, C. Valette, MA. Vandenhende, MO. Vareil, JF. Viallard, H. Wille, G. Wirth.

Immunology: I. Pellegrin, P. Blanco

Virology: H. Fleury, Me. Lafon, P. Trimoulet, P. Bellecave, C. Tumiotto

Pharmacology: S. Bouchet, D. Breilh, F. Haramburu, G. Miremeont-Salamé

Data collection, Project Management and Statistical Analyses: MJ. Blaizeau, M. Decoin, C. Hannapier, E. Lenaud et A. Pougetoux; S. Delveaux, C. D'Ivernois, F. Diarra B. Uwamaliya-Nziyumvira, O. Leleux; F. Le Marec, Eloïse Boerg, S. Lawson-Ayayi;

IT department and eCRF development: G. Palmer, V. Conte, V. Sapparrart

AHOD (Australian HIV Observational Database, Australia):

Central coordination: M. Law*, K. Petoumenos, R Puhr, R Huang (Sydney, New South Wales). Participating physicians (city, state): R. Moore, S. Edwards, J. Hoy, K. Watson, N. Roth, H Lau (Melbourne, Victoria); M Bloch, D. Baker, A. Carr, D. Cooper, (Sydney, New South Wales);M O'Sullivan (Gold Coast, Queensland), D. Nolan, G Guelfi (Perth, Western Australia).

BASS (Spain):

Central coordination: G. Calvo, F. Torres, S. Mateu (Barcelona);

Participating physicians (city): P. Domingo, M.A. Sambeat, J. Gatell, E. Del Cacho, J. Cadafalch, M. Fuster (Barcelona); C. Codina, G. Sirera, A. Vaqué (Badalona).

The Brussels St Pierre Cohort (Belgium):

Coordination: S. De Wit*, N. Clumeck, M. Delforge, C. Necsoi.

Participating physicians: N. Clumeck, S. De Wit*, AF Gennotte, M. Gerard, K. Kabeya, D. Konopnicki, A. Libois, C. Martin, M.C. Payen, P. Semaille, Y. Van Laethem.

CPCRA (USA):

Central coordination: J. Neaton, G. Bartsch, W.M. El-Sadr*, E. Krum, G. Thompson, D. Wentworth;

Participating physicians (city, state): R. Luskin-Hawk (Chicago, Illinois); E. Telzak (Bronx, New York); W.M. El-Sadr* (Harlem, New York); D.I. Abrams (San Francisco, California); D. Cohn (Denver, Colorado); N. Markowitz (Detroit, Michigan); R. Arduino (Houston, Texas); D. Mushatt (New Orleans, Louisiana); G. Friedland (New Haven, Connecticut); G. Perez (Newark, New Jersey); E. Tedaldi (Philadelphia, Pennsylvania); E. Fisher (Richmond, Virginia); F. Gordin (Washington, DC); L.R. Crane (Detroit, Michigan); J. Sampson (Portland, Oregon); J. Baxter (Camden, New Jersey).

EuroSIDA (multinational)

Steering Committee: J Gatell, B Gazzard, A Horban, I Karpov, M Losso, A d'Arminio Monforte*, C Pedersen, M Ristola, A Phillips*, P Reiss*, JD Lundgren*, J Rockstroh

Chair: J Rockstroh

Study Co-leads: A Mocroft*, O Kirk*

Coordinating Centre Staff: O Kirk*, L Peters, C Matthews, AH Fischer, A Bojesen, D Raben, D Kristensen, K Grønborg Laut, JF Larsen, D Podlekareva

Statistical Staff: A Mocroft*, A Phillips*, A Cozzi-Lepri, L Shepherd, A Schultze, S Amele

The multi-centre study group, EuroSIDA (national coordinators in parenthesis).

Argentina: (M Losso), M Kundro, Hospital JM Ramos Mejia, Buenos Aires.

Austria: (B Schmied), Pulmologisches Zentrum der Stadt Wien, Vienna; R Zangerle, Medical University Innsbruck, Innsbruck.

Belarus: (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; D Paduto, Regional AIDS Centre, Svetlogorsk.

Belgium: (N Clumeck), S De Wit*, M Delforge, Saint-Pierre Hospital, Brussels; E Florence, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Gent, Gent.

Bosnia-Herzegovina: (V Hadziosmanovic), Klinicki Centar Univerziteta Sarajevo, Sarajevo.

Croatia: (J Begovac), University Hospital of Infectious Diseases, Zagreb.

Czech Republic: (L Machala), D Jilich, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen.

Denmark: G Kronborg, T Benfield, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, Rigshospitalet, Copenhagen; NF Møller, C Pedersen, Odense University Hospital, Odense; L Ostergaard, Skejby Hospital, Aarhus, L Wiese, Roskilde Hospital, Roskilde; L N Nielsen, Hillerod Hospital, Hillerod.

Estonia: (K Zilmer), West-Tallinn Central Hospital, Tallinn; Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve.

Finland: (M Ristola), I Aho, Helsinki University Central Hospital, Helsinki.

France: (JP Viard), Hôtel-Dieu, Paris; P-M Girard, Hospital Saint-Antoine, Paris; C Pradier*, E Fontas, Hôpital de l'Archet, Nice; C Duvivier, Hôpital Necker-Enfants Malades, Paris.

Germany: (J Rockstroh), Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover; O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; C Stefan, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne.

Georgia: (N Chkhartishvili) Infectious Diseases, AIDS & Clinical Immunology Research Center, Tbilisi

Greece: (P Gargalianos), G Xylomenos, K Armenis, Athens General Hospital "G Gennimatas"; H Sambatakou, Ippokration General Hospital, Athens.

Hungary: (J Szlávik), Szent Lásló Hospital, Budapest.

Iceland: (M Gottfredsson), Landspitali University Hospital, Reykjavik.

Ireland: (F Mulcahy), St. James's Hospital, Dublin.

Israel: (I Yust), D Turner, M Burke, Ichilov Hospital, Tel Aviv; E Shahar, G Hassoun, Rambam Medical Center, Haifa; H Elinav, M Haouzi, Hadassah University Hospital, Jerusalem; D Elbirt, ZM Sthoeger, AIDS Center (Neve Or), Jerusalem.

Italy: (A D'Arminio Monforte*), Istituto Di Clinica Malattie Infettive e Tropicale, Milan; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la

Sapienza, Rome; M Zaccarelli, A Antinori, R Acinapura, M Plazzi, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, A Castagna, N Gianotti, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan.

Latvia: (B Rozentale), Infectology Centre of Latvia, Riga.

Lithuania: (V Uzdaviniene) Vilnius University Hospital Santariskiu Klinikos, Vilnius; R Matulionyte, Center of Infectious Diseases, Vilnius University Hospital Santariskiu Klinikos, Vilnius.

Luxembourg: (T Staub), R Hemmer, Centre Hospitalier, Luxembourg.

Netherlands: (P Reiss*), Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam.

Norway: (V Ormaasen), A Maeland, J Bruun, Ullevål Hospital, Oslo.

Poland: (B Knysz), J Gasiorowski, M Inglot, Medical University, Wroclaw; A Horban, E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; R Flisiak, A Grzeszczuk, Medical University, Bialystok; M Parczewski, K Maciejewska, B Aksak-Was, Medical Univesity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; T Smiatacz, M Gensing, Medical University, Gdansk; E Jablonowska, E Malolepsza, K Wojcik, Wojewodzki Szpital Specjalistyczny, Lodz; I Mozer-Lisewska, Poznan University of Medical Sciences, Poznan.

Portugal: (L Caldeira), Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon.

Romania: (R Radoi), C Oprea, Spitalul de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucarest.

Russia: (A Panteleev), O Panteleev, St Petersburg AIDS Centre, St Peterburg; A Yakovlev, Medical Academy Botkin Hospital, St Petersburg; T Trofimora, Novgorod Centre for AIDS, Novgorod, I Khromova, Centre for HIV/AIDS & and Infectious Diseases, Kaliningrad; E Kuzovatova, Nizhny Novgorod Scientific and Research Institute of Epidemiology and Microbiology named after Academician I.N. Blokhina, Nizhny Novogrod; E Borodulina, E Vdoushkina, Samara State Medical University, Samara.

Serbia: (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade.

Slovenia: (J Tomazic), University Clinical Centre Ljubljana, Ljubljana.

Spain: (JM Gatell), JM Miró, Hospital Clinic Universitari de Barcelona, Barcelona; S Moreno, J. M. Rodriguez, Hospital Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, C Tural, J Puig, I Bravo, Hospital Germans Trias i Pujol, Badalona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona; JM Laporte, Hospital Universitario de Alava, Vitoria-Gasteiz.

Sweden: (K Falconer), A Thalme, A Sonnerborg, Karolinska University Hospital, Stockholm; A Blaxhult, Venhälsan-Sodersjukhuset, Stockholm; L Flamholc, Malmö University Hospital, Malmö.

Switzerland: (A Scherrer), R Weber*, University Hospital Zurich; M Cavassini, University Hospital Lausanne; A Calmy, University Hospital Geneva; H Furrer, University Hospital Bern; M Battegay, University Hospital Basel; P Schmid, Cantonal Hospital St. Gallen.

Ukraine: A Kuznetsova, Kharkov State Medical University, Kharkov; G Kyselyova, Crimean Republican AIDS centre, Simferopol; M Sluzhynska, Lviv Regional HIV/AIDS Prevention and Control CTR, Lviv.

United Kingdom: (B Gazzard), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, E Simons, S Edwards, Mortimer Market Centre, London; A Phillips*, MA Johnson, A Mocroft*, Royal Free and University College Medical School, London (Royal Free Campus); C Orkin, Royal London Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; A Clarke, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh.

The following centers have previously contributed data to EuroSIDA:

Infectious Diseases Hospital, Sofia, Bulgaria

Hôpital de la Croix Rousse, Lyon, France

Hôpital de la Pitié-Salpétière, Paris, France

Unité INSERM, Bordeaux, France

Hôpital Edouard Herriot, Lyon, France

Bernhard Nocht Institut für Tropenmedizin, Hamburg, Germany

1st I.K.A Hospital of Athens, Athens, Greece

Ospedale Riuniti, Divisione Malattie Infettive, Bergamo, Italy

Ospedale di Bolzano, Divisione Malattie Infettive, Bolzano, Italy

Ospedale Cotugno, III Divisione Malattie Infettive, Napoli, Italy

Dérer Hospital, Bratislava, Slovakia

Hospital Carlos III, Departamento de Enfermedades Infecciosas, Madrid, Spain

Kiev Centre for AIDS, Kiev, Ukraine

Luhansk State Medical University, Luhansk, Ukraine

Odessa Region AIDS Center, Odessa, Ukraine

HivBivus (Sweden):

Central coordination: L. Morfeldt, G. Thulin, A. Sundström.

Participating physicians (city): B. Åkerlund (Huddinge); K. Koppel, A. Karlsson (Stockholm); L. Flamholc, C. Håkangård (Malmö).

The ICONA Foundation (Italy):

BOARD OF DIRECTORS

A d'Arminio Monforte* (President), A Antinori, A Castagna, F Castelli, R Cauda, G Di Perri, M Galli, R Iardino, G Ippolito, GC Marchetti, CF Perno, F von Schloesser, P Viale

SCIENTIFIC SECRETARY

A d'Arminio Monforte*, A Antinori, A Castagna, F Ceccherini-Silberstein, A Cozzi-Lepri, E Girardi, S Lo Caputo, C Mussini, M Puoti

STEERING COMMITTEE

M Andreoni, A Ammassari, A Antinori, C Balotta, A Bandera, P Bonfanti, S Bonora, M Borderi, A Calcagno, L Calza, MR Capobianchi, A Castagna, F Ceccherini-Silberstein, A

Cingolani, P Cinque, A Cozzi-Lepri, A d'Arminio Monforte, A De Luca, A Di Biagio, E Girardi, N Gianotti, A Gori, G Guaraldi, G Lapadula, M Lichtner, S Lo Caputo, G Madeddu, F Maggiolo, G Marchetti, S Marcotullio, L Monno, C Mussini, S Nozza, M Puoti, E Quiros Roldan, R Rossotti, S Rusconi, MM Santoro, A Saracino, M Zaccarelli.

STATISTICAL AND MONITORING TEAM

A Cozzi-Lepri, I Fanti, L Galli, P Lorenzini, A Rodano, M Shanyinde, A Tavelli

BIOLOGICAL BANK INMI

F Carletti, S Carrara, A Di Caro, S Graziano, F Petrone, G Prota, S Quartu, S Truffa

PARTICIPATING PHYSICIANS AND CENTERS

Italy A Giacometti, A Costantini, V Barocci (Ancona); G Angarano, L Monno, C Santoro (Bari); F Maggiolo, C Suardi (Bergamo); P Viale, V Donati, G Verucchi (Bologna); F Castelli, C Minardi, E Quiros Roldan (Brescia); T Quirino, C Abeli (Busto Arsizio); PE Manconi, P Piano (Cagliari); B Cacopardo, B Celesia (Catania); J Vecchiet, K Falasca (Chieti); A Pan, S Lorenzotti (Cremona); L Sighinolfi, D Segala (Ferrara); F Mazzotta, F Vichi (Firenze); G Cassola, C Viscoli, A Alessandrini, N Bobbio, G Mazzarello (Genova); C Mastroianni, V Belvisi (Latina); P Bonfanti, I Caramma (Lecco); A Chiodera, P Milini (Macerata); A d'Arminio Monforte, M Galli, A Lazzarin, G Rizzardini, M Puoti, A Castagna, G Marchetti, MC Moioli, R Piolini, AL Ridolfo, S Salpietro, C Tincati, (Milano); C Mussini, C Puzzolante (Modena); A Gori, G Lapadula (Monza); N Abrescia, A Chirianni, G Borgia, R Orlando, G Bonadies, F Di Martino, I Gentile, L Maddaloni (Napoli); AM Cattelan, S Marinello (Padova); A Cascio, C Colomba (Palermo); F Baldelli, E Schiaroli (Perugia); G Parruti, F Sozio (Pescara); G

Magnani, MA Ursitti (Reggio Emilia); M Andreoni, A Antinori, R Cauda, A Cristaudo, V Vullo, R Acinapura, G Baldin, M Capozzi, S Cicalini, A Cingolani, L Fontanelli Sulekova, G Iaiani, A Latini, I Mastrorosa, MM Plazzi, S Savinelli, A Vergori (Roma); M Cecchetto, F Viviani (Rovigo); G Madeddu, P Bagella (Sassari); A De Luca, B Rossetti (Siena); A Franco, R Fontana Del Vecchio (Siracusa); D Francisci, C Di Giuli (Terni); P Caramello, G Di Perri, S Bonora, GC Orofino, M Sciandra (Torino); M Bassetti, A Londero (Udine); G Pellizzer, V Manfrin (Vicenza) G Starnini, A Ialungo(Viterbo).

Nice HIV Cohort (France):

Central coordination: C. Pradier*, E. Fontas, K. Dollet, C. Caissotti.

Participating physicians: P. Dellamonica, E. Bernard, J. Courjon, E. Cua, F. De Salvador-Guillouet, J.Durant, C. Etienne, S. Ferrando, V. Mondain-Miton, A. Naqvi, I. Perbost,S. Pillet , B. Prouvost-Keller, P. Pugliese, V. Rio, K. Risso, P.M. Roger.

SHCS (Swiss HIV Cohort Study, Switzerland):

The data are gathered by the Five Swiss University Hospitals, two Cantonal Hospitals,15 affiliated hospitals and 36 private physicians (listed in http://www.shcs.ch/180-health-care-providers).

Members of the Swiss HIV Cohort Study :

Aubert V, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the

Clinical and Laboratory Committee), Fux CA, Günthard HF (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Pantaleo G, Paioni P, Rauch A (Chairman of the Scientific Board), Rudin C (Chairman of the Mother & Child Substudy), Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R*, Yerly S.

Funding

Data on Adverse Events (D:A:D) Study: The D:A:D study was supported by the Highly Active Antiretroviral Therapy Oversight Committee (HAARTOC), a collaborative committee with representation from academic institutions, the European Agency for the Evaluation of Medicinal Products, the United States Food and Drug Administration, the patient community, and pharmaceutical companies with licensed anti-HIV drugs in the European Union: AbbVie, Bristol-Myers Squibb, Gilead Sciences Inc., ViiV Healthcare, Merck & Co Inc. and Janssen Pharmaceuticals. Supported also by a grant [grant number DNRF126] from the Danish National Research Foundation (CHIP & PERSIMUNE); by a grant from the Dutch Ministry of Health, Welfare and Sport through the Center for Infectious Disease Control of the National Institute for Public Health and the Environment to Stiching HIV Monitoring (ATHENA); by a grant from the Agence nationale de recherches sur le sida et les hépatites virales [ANRS, Action Coordonnée no.7, Cohortes] to the Aquitaine Cohort; The Australian HIV Observational Database (AHOD) is funded as part of the Asia Pacific HIV Observational Database, a program of

The Foundation for AIDS Research, amfAR, and is supported in part by a grant from the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) [grant number U01-AI069907] and by unconditional grants from Merck Sharp & Dohme; Gilead Sciences; Bristol-Myers Squibb; Boehringer Ingelheim; Janssen-Cilag; ViiV Healthcare. The Kirby Institute is funded by The Australian Government Department of Health and Ageing, and is affiliated with the Faculty of Medicine, The University of New South Wales; by grants from the Fondo de Investigación Sanitaria [grant number FIS 99/0887] and Fundación para la Investigación y la Prevención del SIDA en Espanã [grant number FIPSE 3171/00], to the Barcelona Antiretroviral Surveillance Study (BASS); by the National Institute of Allergy and Infectious Diseases, National Institutes of Health [grants number 5U01AI042170-10, 5U01AI046362-03], to the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA); by primary funding provided by the European Union's Seventh Framework Programme for research, technological development and demonstration under EuroCoord grant agreement n˚ 60694 and unrestricted grants by Bristol-Myers Squibb, Janssen R&D, Merck and Co. Inc., Pfizer Inc., GlaxoSmithKline LLC, (the participation of centres from Switzerland is supported by The Swiss National Science Foundation (Grant 108787)) to the EuroSIDA study; by unrestricted educational grants of AbbVie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Pfizer, Janssen Pharmaceuticals to the Italian Cohort Naive to Antiretrovirals (The ICONA Foundation); and financed within the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (grant #148522) and by the SHCS research foundation.

Table 1: Univariate associations between ABC exposure and established CVD risk factors and subsequent myocardial infarction

Factor		RR	95% CI	p-value
Cumulative exposure to ABC (/5 years)		0.86	(0.68, 1.10)	0.23
On ABC at time of MI		0.90	(0.63, 1.29)	0.58
Recent use of ABC		1.19	(0.82, 1.71)	0.36
Calendar year (time-updated)	1999-2001	7.73	(3.36, 17.79)	0.0001
	2002-2004	3.28	(1.79, 6.02)	0.0001
	2005-2007	2.25	(1.25, 4.04)	0.0001
	2008-2010	1.54	(0.86, 2.76)	0.15
	2011-2013	1.01	(0.55, 1.85)	0.97
	2014-2016	1	-	-
Gender	Male	0.85	(0.47, 1.54)	0.59
	Female	1	-	-
Age (/5 years older)		1.01	(0.99, 1.03)	0.19
Smoking status	Current	1.07	(0.59, 1.95)	0.82
	Ex-	1.25	(0.69, 2.29)	0.47
	Never	1	-	-
	Unknown	1.04	(0.42, 2.61)	0.93
Ethnic group	White	1	-	-

	Non-white	0.86	(0.62, 1.21)	0.40
Mode of acquisition	MSM	1	-	-
	IDU	0.66	(0.36, 1.20)	0.17
	Heterosexual	1.03	(0.68, 1.56)	0.89
	Other/unknown	2.25	(1.25, 4.04)	0.007
Dyslipidaemia[1]		0.68	(0.40, 1.16)	0.16
BMI	<18	1.14	(0.50, 2.60)	0.76
	≥18, ≤26	1	-	-
	>26, ≤30	0.90	(0.57, 1.44)	0.67
	>30	1.01	(0.49, 2.09)	0.97
	Not known	2.29	(1.19, 4.40)	0.01
Diabetes		1.70	(1.15, 2.51)	0.008
Hypertension[2]		0.74	(0.48, 1.16)	0.19
Cumulative exposure to lopinavir (/5 years)		0.84	(0.58, 1.21)	0.35
Cumulative exposure to indinavir (/5 years)		1.21	(0.81, 1.80)	0.35
Cumulative exposure to darunavir (/5 years)		0.61	(0.29, 1.29)	0.20

[1]Total cholesterol ≥6.2 mmol/l, HDL cholesterol ≤0.9 mmol/l, triglyceride ≥2.3 mmol/l or receipt of lipid-lowering medication; [2]Systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg or receipt of anti-hypertensive or ACE inhibitor medication; MI: myocardial infarction; ABC: abacavir; RR: relative rate; CI: confidence interval; MSM: men who have sex with men; IDU: injection drug users; BMI: body mass index.