

Efavirenz versus boosted atazanavir-containing regimens and immunologic, virologic, and clinical outcomes

A prospective study of HIV-positive individuals

Lauren E. Cain, PhD*, Ellen C. Caniglia, Andrew Phillips, Ashley Olson, Roberto Muga, Santiago Pérez-Hoyos, Sophie Abgrall, Dominique Costagliola, Rafael Rubio, Inma Jarrín, Heiner Bucher, Jan Fehr, Ard van Sighem, Peter Reiss, François Dabis, Marie-Anne Vandenhende, Roger Logan, James Robins, Jonathan A. C. Sterne, Amy Justice, Janet Tate, Giota Touloumi, Vasilis Pappas, Anna Esteve, Jordi Casabona, Rémonie Seng, Laurence Meyer, Sophie Jose, Caroline Sabin, Miguel A. Hernán, on behalf of the HIV-CAUSAL Collaboration

Abstract

Objective: To compare regimens consisting of either ritonavir-boosted atazanavir or efavirenz and a nucleoside reverse transcriptase inhibitor (NRTI) backbone with respect to clinical, immunologic, and virologic outcomes.

Design: Prospective studies of human immunodeficiency virus (HIV)-infected individuals in Europe and the United States included in the HIV-CAUSAL Collaboration.

Methods: HIV-positive, antiretroviral therapy-naïve, and acquired immune deficiency syndrome (AIDS)-free individuals were followed from the time they started an atazanavir or efavirenz regimen. We estimated an analog of the “intention-to-treat” effect for efavirenz versus atazanavir regimens on clinical, immunologic, and virologic outcomes with adjustment via inverse probability weighting for time-varying covariates.

Editor: Kersten Koelsch.

The contributors to the HIV-CAUSAL Collaboration are listed at the end of the article.*

Funding/support: This research was supported by NIH grants R01-AI073127, U10-AA013566, and MRC grant G0700820.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Andrew Phillips received fees for speaking from Gilead Sciences, consulting from GSK Biologicals, and advisory board membership from AbbVie.

Sophie Abgrall is a member of Janssen-Cilag board, received travel/accommodations for meeting from Gilead, Janssen-Cilag, Viiv.

Dominique Costagliola was a member of the French Gilead HIV board up to 2015. In the past 3 years, she gave lectures for Janssen-Cilag, Merck-Sharp & Dohme-Chibret, Viiv and received travel/accommodations/meeting expenses from Gilead, Viiv, Janssen-Cilag. She conducted post-marketing studies for Janssen-Cilag, Merck-Sharp & Dohme-Chibret and Viiv. She is currently a consultant of Innovaviv.

Rafael Rubio has acted as a consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Janssen and has received payment for talks from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Roche, and Viiv Healthcare.

Heiner Bucher has received honoraria from BMS and Gilead Sciences in the past 6 months. His institution has received grants from BMS and Gilead Sciences and funds for travel reimbursement from Gilead Sciences and Viiv Healthcare.

Jan Fehr was a member of the advisory boards for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Viiv-Healthcare and has also received travel grants, educational grants and research grants from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Pfizer, Roche, Viiv-Healthcare. He is a member of the Swiss Federal Commission for Sexual Health.

Ard van Sighem received grants, paid to his institution, from the European Centre for Disease Prevention and Control (ECDC), and honoraria, paid to his institution, from Janssen Cilag, Gilead Sciences, and Viiv Healthcare.

Peter Reiss through his institution has received independent scientific grant support from Gilead Sciences, Janssen Pharmaceuticals Inc, Merck & Co, Bristol-Myers Squibb and Viiv Healthcare; he has served on scientific advisory board for Gilead Sciences; he has served on data safety monitoring committee for Janssen Pharmaceuticals Inc; chaired a scientific symposium by Viiv Healthcare, for which his institution has received remuneration.

Caroline Sabin is a member of the speakers' bureau for Gilead Sciences. She provides educational training materials for Gilead Sciences, Viiv Healthcare and Janssen-Cilag. She is a member of Data Safety and Advisory Boards for Janssen-Cilag and Viiv Healthcare and has given talks for Bristol Myers Squibb.

Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA.

* Correspondence: Lauren E. Cain, Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Ave. Boston, MA 02115 (e-mail: lcain@hsph.harvard.edu).

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Medicine (2016) 95:41(e5133)

Received: 11 March 2016 / Received in final form: 26 July 2016 / Accepted: 27 July 2016

<http://dx.doi.org/10.1097/MD.0000000000005133>

Results: A total of 4301 individuals started an atazanavir regimen (83 deaths, 157 AIDS-defining illnesses or deaths) and 18,786 individuals started an efavirenz regimen (389 deaths, 825 AIDS-defining illnesses or deaths). During a median follow-up of 31 months, the hazard ratios (95% confidence intervals) were 0.98 (0.77, 1.24) for death and 1.09 (0.91, 1.30) for AIDS-defining illness or death comparing efavirenz with atazanavir regimens. The 5-year survival difference was 0.1% (95% confidence interval: -0.7%, 0.8%) and the AIDS-free survival difference was -0.3% (-1.2%, 0.6%). After 12 months, the mean change in CD4 cell count was 20.8 (95% confidence interval: 13.9, 27.8) cells/mm³ lower and the risk of virologic failure was 20% (14%, 26%) lower in the efavirenz regimens.

Conclusion: Our estimates are consistent with a smaller 12-month increase in CD4 cell count, and a smaller risk of virologic failure at 12 months for efavirenz compared with atazanavir regimens. No overall differences could be detected with respect to 5-year survival or AIDS-free survival.

Abbreviations: AIDS = acquired immune deficiency syndrome, ANRS = Agence Nationale de Recherches sur le SIDA, INSTI = integrase strand transfer inhibitor, NNRTI = nonnucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor.

Keywords: atazanavir, efavirenz, HIV, mortality, observational studies

1. Introduction

Until recently, most clinical guidelines for human immunodeficiency virus (HIV)-positive individuals recommended 1st-line regimens consisting of either a ritonavir-boosted protease inhibitor (PI) or a nonnucleoside reverse transcriptase inhibitor (NNRTI) in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs). One of the most commonly prescribed boosted PIs was atazanavir and one of the most commonly prescribed NNRTIs was efavirenz. The European acquired immune deficiency syndrome (AIDS) Clinical Society, the Department of Health and Human Services, and the International AIDS Society USA Panel all currently recommend atazanavir and efavirenz equally while the British HIV Association recommends atazanavir over efavirenz.^[1-4] However, in the most recent Department of Health and Human Services guidelines, both atazanavir and efavirenz were moved from recommended to alternative in favor of integrase strand transfer inhibitors (INSTIs) and darunavir. The World Health Organization recommends efavirenz as part of 1st-line therapy and atazanavir as part of 2nd-line therapy.^[5] In resource-limited settings, efavirenz and atazanavir remain cornerstones of antiretroviral therapy.

The comparative effectiveness of regimens based on ritonavir-boosted atazanavir and efavirenz is, however, incomplete. Two randomized clinical trials^[6,7] and 3 observational studies^[8-10] studied short-term virologic and immunologic outcomes with inconclusive results. All these studies were relatively small and few had follow-up times sufficient for the assessment of clinical outcomes such as death and AIDS-defining illness.

Here we examine clinical, immunologic, and virologic outcomes among AIDS-free individuals who started a 1st-line regimen consisting of either efavirenz or ritonavir-boosted atazanavir with different types of NRTI-backbones in a large collaboration of prospective cohort studies from the United States and Europe.

2. Methods

2.1. Study population

The HIV-CAUSAL Collaboration has been described elsewhere.^[11] Briefly, the collaboration includes several prospective cohort studies from 6 European countries and the United States: UK CHIC (United Kingdom Collaborative HIV Cohort), ATHENA (AIDS Therapy Evaluation in the Netherlands),

FHDH-ANRS CO4 (French Hospital Database on HIV-Agence Nationale de Recherches sur le SIDA), Aquitaine (France), SHCS (Swiss HIV Cohort Study), PISCIS (Proyecto para la Informa-tización del Seguimiento Clínicoepidemiológico de la Infección por HIV y SIDA [Spain]), CoRIS (Cohorte de la Red de Investigación en SIDA [Spain]), VACS-VC (Veterans Aging Cohort Study-Virtual Cohort [United States]), AMACS (Athens Multicenter AIDS Cohort Study [Greece]), UK Register of HIV Seroconverters, ANRS PRIMO and ANRS SEROCO (Agence Nationale de Recherches sur le SIDA [France]), and GEMES (Grupo Espanol Multicéntrico para el Estudio de Seroconver-tores-Haemophilia [Spain]). All cohorts included in the HIV-CAUSAL Collaboration were assembled prospectively and are based on data collected for clinical purposes within national healthcare systems with universal access to care. Each cohort in the collaboration collects all CD4 cell counts, HIV-1 RNAs, treatment initiations, AIDS-defining illnesses, and deaths.

For each individual, follow-up started at the initiation of a 1st-line antiretroviral regimen containing either efavirenz or atazanavir (baseline). Our analysis was restricted to HIV-positive individuals who met the following eligibility criteria at baseline dates between January 2004 and January 2013: age 18 years or older, previously antiretroviral therapy-naive, no history of an AIDS-defining illness,^[12] not pregnant (when information was available), and CD4 cell count and HIV-1 RNA measurements within 6 months prior to baseline. For the analysis of clinical outcomes, follow-up ended at the occurrence of the outcome, 12 months after the most recent laboratory measurement (i.e., we considered an individual to be lost to follow-up if and when he had no new CD4 or HIV-1 RNA measurements for 12 months), pregnancy (if known), or the cohort-specific administrative end of follow-up (ranging from September 2010 to March 2013), whichever occurred first. For the analysis of immunologic and virologic outcomes, follow-up ended on average at 12 months after baseline.

2.2. Outcomes

We considered clinical, immunologic, and virologic outcomes. The clinical outcomes of interest were death from any cause and clinical AIDS-defining illness^[12] or death. Dates of death were identified using a combination of national and local mortality registries and clinical records as described elsewhere,^[11] and AIDS-defining illnesses were ascertained by the treating physicians.

The main immunologic and virologic outcomes of interest were the 12-month change in CD4 cell count after baseline and virologic failure defined as HIV-RNA > 50 copies/mL at 12 months, respectively. Our definition of virologic failure was chosen to allow for comparison with the results from the trials. Although a single measurement of HIV-RNA > 50 copies/mL could be a viral blip as opposed to a failure, our results would only be affected if the frequency of blips varies by antiretroviral regimen. If CD4 cell count or HIV-RNA was not measured exactly 12 months after baseline, we used the closest measurement within 2 months. In secondary analyses, we also studied the CD4 cell count and virologic failure at 24 months.

2.3. Antiretroviral regimens

We considered 2 types of 1st-line regimens: efavirenz and atazanavir regimens. The analysis was restricted to individuals who started an NRTI backbone and either efavirenz or ritonavir-boosted atazanavir at baseline. Individuals were excluded if they started an ineligible drug (i.e., an INSTI, a fusion inhibitor, an NNRTI other than efavirenz, or a PI other than ritonavir/atazanavir) or both efavirenz and atazanavir at baseline.

In our main analysis, we allowed efavirenz or ritonavir-boosted atazanavir to be paired with any NRTI backbone. In subgroup analyses, we included those backbones that appear in the most recent guidelines^[1-4] or that were used in the randomized trials.^[6,7] Specifically, we focused on the backbones abacavir/lamivudine and tenofovir/emtricitabine.

2.4. Statistical methods

We fit pooled logistic models to estimate the hazard ratio of each clinical outcome for efavirenz versus atazanavir regimens. Both models included a regimen indicator (1: efavirenz, 0: atazanavir), cohort, month of follow-up (modeled as a restricted cubic spline with 4 knots at 1, 6, 24, and 60 months), and the following baseline covariates: sex, age (<35, 35-49, ≥50 years), race (white, black, other or unknown), geographic origin (Western countries, sub-Saharan Africa, other, or unknown), mode of HIV acquisition (heterosexual, homosexual/bisexual, injection drug use, other or unknown), CD4 cell count (<200, 200-299, 300-399, 400-499, and ≥500 cells/mm³), HIV-1 RNA (<10,000, 10,000-100,000, and >100,000 copies/mL), calendar year (2004-2007, ≥2008), and years since HIV diagnosis (<1, 1-4, ≥5 years or unknown). For the immunologic outcome, we fit a linear regression model with the same covariates to estimate the 12-month change in CD4 cell count for efavirenz versus atazanavir regimens among those with measurements at 12 ± 2 months. For the virologic outcome, we fit a modified Poisson regression model^[13] with the same covariates to estimate the risk ratio of virologic failure at 12 months for efavirenz versus atazanavir regimens among those with measurements at 12 ± 2 months.

In the analyses of the immunologic and virologic outcomes, some individuals did not have a measurement during the interval 12 ± 2 months after baseline. To adjust for potential selection bias, we estimated stabilized inverse probability weights^[14] of having a measurement via pooled logistic models for artificial censoring that included the time-fixed covariates and time-varying CD4 cell count (<200, 200-299, 300-399, 400-499, and ≥500 cells/mm³), HIV-1 RNA (<10,000, 10,000-100,000, and >100,000 copies/mL), and month of last laboratory measurement (continuous).

Under the assumption that we measured and successfully adjusted for all confounders, the estimated coefficient for the regimen indicator in the adjusted models is analogous to the “intention-to-treat” effect that would have been estimated from an open-label randomized trial with similar adherence and follow-up. Because we defined the clinical regimens of interest in terms of the 1st-line regimen only, it was unnecessary to adjust for joint determinants of switching and death.

For the 2 clinical outcomes, we also estimated absolute risks by fitting adjusted models like the one described above that also included product (“interaction”) terms between the regimen indicator and month of follow-up with spline terms. The predicted values from the models were then used to estimate the 5-year survival and 5-year AIDS-free survival curves from baseline.

2.5. Subgroup and sensitivity analyses

For all outcomes, we compared efavirenz and atazanavir in subgroups defined by baseline calendar year, sex, age, mode of HIV acquisition, baseline CD4 cell count, and baseline HIV-1 RNA.

Because the lower limit of detection was unknown in <5% of observations with HIV-1 RNA between 50 and 400 copies/mL, we conducted a sensitivity analysis in which we defined virologic failure as HIV-1 RNA > 400 copies/mL.

In another sensitivity analysis, we allowed a 6-month grace period for individuals to complete one of the regimens of interest as opposed to requiring individuals to start all of the drugs in their regimen simultaneously. Follow-up on individuals was artificially censored if and when they started an ineligible drug before completing a regimen or at 6 months from baseline if their regimen was not yet complete. As previously described, to adjust for potential selection bias due to the artificial censoring, we estimated unstabilized inverse probability weights^[14] via pooled logistic models for artificial censoring that included the time-fixed covariates and time-varying CD4 cell count (restricted cubic spline with 5 knots at 10, 200, 350, 500, and 1000 cells/mm³), HIV-1 RNA (<10,000, 10,000-100,000, and >100,000 copies/mL), AIDS-defining illness (when the outcome was death alone), and time since last laboratory measurement (0, 1-2, 3-4, 5-6, and ≥7 months).

Several other sensitivity analyses were also performed. For all 4 outcomes, we used continuous as opposed to categorical baseline covariates and investigated the effect of including chronic hepatitis C infection^[15] as a baseline covariate. For the clinical outcomes, we weighted individuals' contributions to the models by the inverse of their probability of remaining uncensored due to infrequent laboratory measurements. For the immunologic and virologic outcomes, we also weighted by the inverse probability of remaining alive at 12 ± 2 months after baseline as a form of competing risks analysis.

All 95% CIs were estimated via a nonparametric bootstrap with 500 samples. All analyses were conducted with SAS 9.3 (SAS Institute, Cary, NC). The institutional review board at Harvard T.H. Chan School of Public Health approved our research.

3. Results

The dataset included 23,087 individuals of which 4301 followed an atazanavir regimen and 18,786 followed an efavirenz regimen. Table 1 shows the characteristics of the study population by regimen type at baseline. A higher proportion of women, those

Table 1**Characteristics of 23,087 therapy-naive HIV-positive individuals at baseline, HIV-CAUSAL Collaboration 2004 to 2013.**

Characteristic		No. of individuals, %					
		Atazanavir (n = 4301)		Efavirenz (n = 18,786)		Total (n = 23,087)	
Sex	Men	3372	(78.4)	16,021	(85.3)	19,393	(84)
	Women	929	(21.6)	2765	(14.7)	3694	(16)
Age, years	<35	1435	(33.4)	6436	(34.3)	7871	(34.1)
	35–50	2035	(47.3)	8883	(47.3)	10,918	(47.3)
	>50	831	(19.3)	3467	(18.5)	4298	(18.6)
Geographic origin	Western countries	3215	(74.8)	13,589	(72.3)	16,804	(72.8)
	Sub-Saharan Africa	601	(14)	2423	(12.9)	3024	(13.1)
	Other	348	(8.1)	1755	(9.3)	2103	(9.1)
	Unknown	137	(3.2)	1019	(5.4)	1156	(5)
Acquisition group	Heterosexual	1444	(33.6)	5118	(27.2)	6562	(28.4)
	Homosexual	1892	(44)	9597	(51.1)	11,489	(49.8)
	Injection drug use	187	(4.3)	492	(2.6)	679	(2.9)
	Other/unknown*	778	(18.1)	3579	(19.1)	4357	(18.9)
CD4 cell count, per mm ³	<200	1226	(28.5)	5246	(27.9)	6472	(28)
	200–299	1245	(28.9)	6124	(32.6)	7369	(31.9)
	300–399	1030	(23.9)	4513	(24)	5543	(24)
	400–499	427	(9.9)	1587	(8.4)	2014	(8.7)
	≥500	373	(8.7)	1316	(7)	1689	(7.3)
HIV-1 RNA, copies/mL	<10,000	827	(19.2)	3473	(18.5)	4300	(18.6)
	10,000–100,000	1958	(45.5)	8805	(46.9)	10,763	(46.6)
	>100,000	1516	(35.2)	6508	(34.6)	8024	(34.8)
Calendar year	2004–2007	1296	(30.1)	6799	(36.2)	8195	(35.5)
	≥2008	3005	(69.9)	11,987	(63.8)	14,892	(64.5)
Cohort	UK CHIC	704	(16.4)	5174	(27.5)	5878	(25.5)
	ATHENA	380	(8.8)	2749	(14.6)	3129	(13.6)
	FHDH-ANRS CO4	1491	(34.7)	2778	(14.8)	4269	(18.5)
	Aquitaine	322	(7.5)	916	(4.9)	1238	(5.4)
	SHCS	421	(9.8)	2094	(11.1)	2515	(10.9)
	PISCIS/AMACS	182	(4.2)	1609	(8.6)	1791	(7.8)
	CoRIS	152	(3.5)	658	(3.5)	810	(3.5)
	Seroconverters†	553	(12.9)	2646	(14.1)	3199	(13.9)
	VACS-VC	96	(2.2)	162	(0.9)	258	(1.1)
	Hepatitis C infection	Definite/Probable	116	(2.7)	557	(3)	673
Possible	139	(3.2)	467	(2.5)	606	(2.6)	
None	4046	(94.1)	17,762	(94.5)	21,808	(94.5)	

AMACS= Athens Multicenter AIDS Cohort Study, ANRS= Agence Nationale de Recherches sur le SIDA, ATHENA= AIDS Therapy Evaluation in the Netherlands, CoRIS= Cohorte de la Red de Investigación en SIDA, FHDH= French Hospital Database on HIV, GEMES= Grupo Español Multicéntrico para el Estudio de Seroconvertidores-Hemofilia, HIV= human immunodeficiency virus, PISCIS= Proyecto para la Informatización del Seguimiento Clínicoepidemiológico de la Infección por HIV y SIDA, SHCS= Swiss HIV Cohort Study, UK CHIC= United Kingdom Collaborative HIV Cohort, VACS-VC= Veterans Aging Cohort Study-Virtual Cohort.

* Other/Unknown acquisition group included all VACS-VC participants.

† Includes the UK Register of HIV Seroconverters, ANRS PRIMO, ANRS SEROCO, and GEMES cohorts.

Table 2**Clinical and virologic outcomes by recommended nucleoside reverse transcriptase inhibitor backbone for regimens based on efavirenz versus atazanavir, HIV-CAUSAL Collaboration 2004 to 2013.**

Backbone	No. of individuals/ No. deaths/No. of AIDS or deaths		Death Hazard ratio ^{*,†} (95% CI)	AIDS or death Hazard ratio ^{*,†} (95% CI)	Virologic failure Risk ratio ^{*,‡} (95% CI)
	Atazanavir	Efavirenz			
All backbones	4301/83/157	18,786/389/825	0.98 (0.77, 1.24)	1.09 (0.91, 1.30)	0.80 (0.74, 0.86)
Abacavir/lamivudine	658/9/23	1629/38/85	2.52 (1.04, 6.10)	1.71 (0.99, 2.94)	0.76 (0.58, 0.98)
Tenofovir/emtricitabine	3286/43/96	14,247/218/479	1.16 (0.82, 1.63)	1.15 (0.91, 1.45)	0.77 (0.70, 0.85)
Abacavir/lamivudine and tenofovir/emtricitabine	3944/52/119	15,876/256/564	1.23 (0.90, 1.67)	1.17 (0.96, 1.42)	0.77 (0.70, 0.83)

AIDS= acquired immune deficiency syndrome, CI= confidence interval, HIV= human immunodeficiency virus, No.= number.

* Adjusted for the baseline covariates (sex, age, race, geographic origin, mode of transmission, CD4 cell count, HIV-1 RNA, calendar year, and years since HIV diagnosis).

† Hazard ratio of efavirenz versus atazanavir.

‡ Risk ratio of efavirenz versus atazanavir based on 2878 and 13,643 individuals with HIV-1 RNA measurements at 12 ± 2 months in the atazanavir and efavirenz groups, respectively.

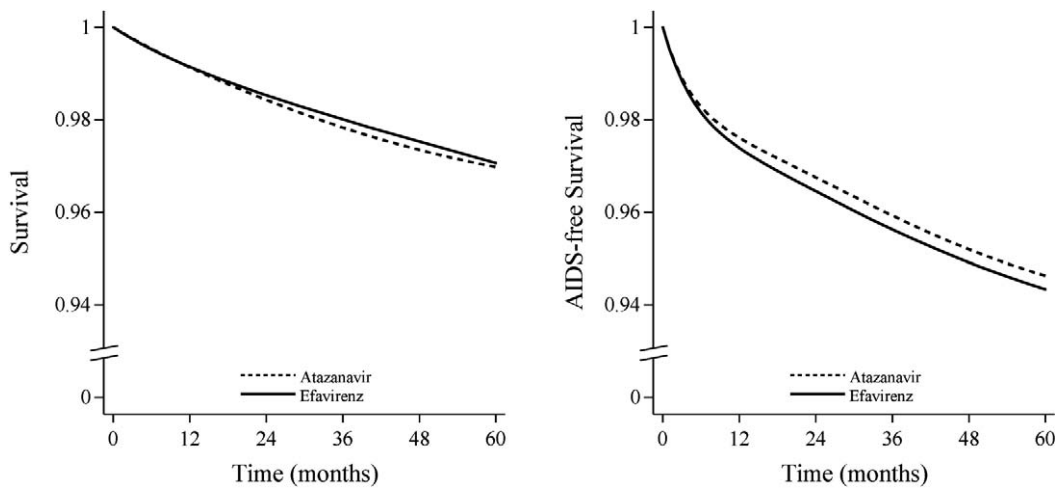


Figure 1. Survival (left) and AIDS-free survival (right) for efavirenz versus atazanavir, HIV-CAUSAL Collaboration 2004 to 2013. The curves are standardized by the baseline covariates listed under Table 2.

who acquired HIV through heterosexual transmission, and those starting treatment in 2008 or later, initiated atazanavir than efavirenz.

As shown in Table 2, 83 individuals died and 157 developed an AIDS-defining illness or died among those initiating an atazanavir regimen, and 389 individuals died and 825 developed an AIDS-defining illness or died among those initiating an efavirenz regimen. In the mortality analysis, the median (interquartile range) follow-up time was 27 (14, 45) months for the atazanavir regimens and 32 (17, 52) months for the efavirenz regimens. A total of 956 (22%) individuals following an atazanavir regimen and 4617 (25%) following an efavirenz regimen were lost to follow-up. The numbers were similar in the AIDS or death analysis. Compared with atazanavir, the hazard ratio (95% CI) for efavirenz was 0.98 (0.77, 1.24) for death and 1.09 (0.91, 1.30) for AIDS or death.

Figure 1 plots the estimated 5-year survival and 5-year AIDS-free survival with all backbones. The 5-year survival was 96.9% (96.3%, 97.6%) for the atazanavir regimens and 97.0% (96.7%, 97.4%) for the efavirenz regimens. The survival difference was 0.1% (−0.7%, 0.8%) at 5 years. The 5-year AIDS-free survival

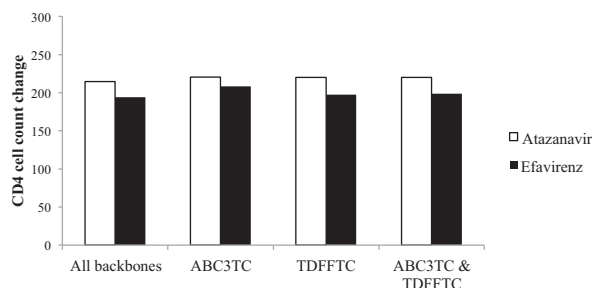
proportion was 94.6% (93.7%, 95.5%) for the atazanavir regimens and 94.3% (93.9%, 94.7%) for the efavirenz regimens. The AIDS-free survival difference was −0.3% (−1.2%, 0.6%) at 5 years.

Table 2 also provides the risk ratios of virologic failure at 12 ± 2 months comparing efavirenz with atazanavir. Among those initiating atazanavir and efavirenz regimens, 683/2878 (24%) and 2644/13,643 (19%) had HIV-1 RNA >50 copies/mL at 12 months, respectively. Compared with atazanavir, the risk ratio of virologic failure at 12 months for efavirenz was 0.80 (0.74, 0.86). Results were similar in subgroups defined by backbone. Among those initiating atazanavir and efavirenz regimens, 19% and 15% had HIV-1 RNA >50 copies/mL at 24 months, respectively. Compared with atazanavir, the risk ratio of virologic failure at 24 months for efavirenz was 0.81 (0.74, 0.89).

Figure 2 shows the 12-month adjusted mean change in CD4 cell count by backbone. Compared with atazanavir, the estimated mean change in CD4 cell count (95% CI) for efavirenz was −20.8 (−27.8, −13.9) for all backbones. The mean CD4 cell count would have increased from 280 to 495 cells/mm³ over 12 months had all individuals taken an atazanavir regimen, and from 280 to 474 cells/mm³ had all individuals taken an efavirenz regimen. Results were similar in subgroups defined by backbone. Compared with atazanavir, the estimated mean change in CD4 cell count over 24 months (95% CI) for efavirenz was −15.6 (−25.3, −5.9).

Most individuals initiated a backbone of either abacavir/lamivudine (10%) or tenofovir/emtricitabine (76%). Abacavir/lamivudine was used more frequently with atazanavir, while tenofovir/emtricitabine were used equally with atazanavir and efavirenz. In the subgroup of individuals using 1 of these 2 backbones, the hazard ratio for efavirenz was 1.23 (0.90, 1.67) for death and 1.17 (0.96, 1.42) for AIDS or death (Table 2).

None of the sensitivity analyses yielded appreciably different results (data not shown). In subgroup analyses, estimates for all 4 outcomes were similar when we restricted to baseline years 2008 and beyond, men, those aged less than 50 years, noninjection drug users, those with baseline CD4 cell counts below 350 cells/mm³, those with baseline viral loads above 100,000 copies/mL, and those from Western countries. When we defined virologic



ABC = abacavir, 3TC = lamivudine, TDF = tenofovir, FTC = emtricitabine

Figure 2. Immunologic outcomes by recommended NRTI backbone for regimens based on efavirenz versus atazanavir, HIV-CAUSAL Collaboration 2004 to 2013. 3TC=lamivudine, ABC=abacavir, FTC=emtricitabine, HIV=human immunodeficiency virus, NRTI=nucleoside reverse transcriptase inhibitor, TDF=tenofovir.

failure as HIV-1 RNA >400 copies/mL, the percentage with virologic failure decreased, but the risk ratio comparing efavirenz with atazanavir remained similar. Finally, allowing a 6-month grace period for individuals to complete one of the regimens of interest had little effect on the estimates.

4. Discussion

The clinical effectiveness of efavirenz versus ritonavir-boosted atazanavir has not been directly studied in randomized trials, which have focused on short-term immunologic and virologic outcomes. Our study compared efavirenz versus atazanavir regimens with respect to clinical outcomes among antiretroviral-naïve, AIDS-free individuals in Europe and the United States. We did not detect any differences in mortality or AIDS-defining illness.

We also found that individuals on efavirenz regimens were 20% less likely to have virologic failure at 12 months as those on atazanavir regimens and experienced a smaller 12-month increase in CD4 cell count by 20.8 cells/mm³. This absolute difference in CD4 cell count was small and of questionable clinical relevance, especially for greater than 450 cells/mm³ CD4 cell counts that are expected in our study at 12 months.

Our virologic and immunologic findings were consistent with those of the 2 previous trials.^{16,71} The Altair Study found that the mean change in CD4 cell count was 5 cells/mm³ higher in the atazanavir arm than in the efavirenz arm over 48 weeks. The A5202 study estimated the median change in CD4 cell count and found a 10 cells/mm³ greater increase in the efavirenz arm when a backbone of abacavir/lamivudine was used and a 12 cells/mm³ smaller increase in the efavirenz arm when a backbone of tenofovir/emtricitabine was used compared with the atazanavir arm. Like in our study, these differences were small and of little clinical relevance. The A5202 study found advantages of efavirenz over atazanavir with respect to virologic failure at 48 weeks, but little association was found in the Altair study.

Our estimates are based on less restrictive inclusion criteria, and therefore are potentially more relevant to the general population of HIV-infected individuals than those of the trials. Specifically, both trials restricted to individuals with baseline HIV-1 RNA ≥ 5000 copies/mL and included some individuals who were not AIDS-free at baseline. The trials also excluded those with low CD4 cell counts (Altair study: 50 cells/mm³, A5202 study: 100 cells/mm³ if prior AIDS, 75 cells/mm³ if not prior AIDS). When we restrict to individuals with baseline HIV-1 RNA ≥ 5000 copies/mL, CD4 ≥ 50 cells/mm³, and to one of the backbones used in the trials, the 12-month adjusted mean change in CD4 cell count for efavirenz versus atazanavir was -22.8 ($-30.5, -15.1$) and the risk ratio of virologic failure at 12 months for efavirenz versus atazanavir was 0.77 (0.71, 0.85). We compared these estimates to those from a meta-analysis we conducted with the published information in the 2 trials. This virologic result was not as strong as the result of the meta-analysis: 0.65 (0.49, 0.85). Unfortunately, we were unable to conduct a meta-analysis using the available information for CD4 cell count change.

In the Altair study, both arms had a backbone of tenofovir/emtricitabine. In the A5202 study, both arms had a backbone of either tenofovir/emtricitabine or abacavir/lamivudine. In our main analysis, any backbone could be used. We also conducted analyses restricted to the backbones used in the trials. Results in subgroups defined by backbone were similar to those for all backbones with the exception of the clinical outcomes when

abacavir/lamivudine was used. However, these results were based on few events and confidence intervals were wide.

Like all observational estimates, ours rely on the untestable assumption that we have successfully measured and adjusted for all confounders. In this analysis, we measured and adjusted for sex, age, race, geographic origin, mode of HIV acquisition, CD4 cell count, HIV-1 RNA, calendar year, and years since HIV diagnosis. If further adjustment is necessary to account for confounding factors responsible for large prognostic differences between patients initiating efavirenz versus atazanavir, the assumption would not hold.

One of these confounding factors might be adherence. Atazanavir was independently associated with suboptimal adherence in a study of individuals from the SMART study.¹¹⁶ Atazanavir also has a higher genetic barrier to resistance than efavirenz.¹⁷ These facts may suggest that atazanavir was more often prescribed to individuals whose future adherence was questionable (e.g., because of markers of poor health such as cardiovascular disease). However, we measured and adjusted for several proxies for adherence, including HIV-1 RNA, calendar year, intravenous drug use, years since HIV diagnosis, and time since last laboratory measurement.

In addition, during the course of this study, both drugs may have been used in a way that is no longer considered optimal. Efavirenz is contraindicated for patients with psychiatric illness and pregnant women, while ritonavir-boosted atazanavir is not recommended for use with antacids and other drugs that raise gastric pH.¹²¹ Although our data did not allow us to investigate psychiatric illness or the use of nonantiretroviral drugs, we excluded women known to be pregnant in all analyses. The magnitude of the reported association makes it unlikely that our immunologic and virologic estimates can be fully explained by the use of antacids, anti-psychotics, or other drugs.

In summary, our findings extend those of randomized trials from immunologic and virologic outcomes to clinical outcomes. Our findings do not support changes to the current clinical guidelines for HIV-positive individuals, but the new evidence presented here may be informative to those drafting the next set of guidelines. Future studies need to consider the effects of efavirenz and atazanavir on other clinical outcomes including non-AIDS-defining illnesses, when paired with specific backbones and over longer periods. This is particularly true in resource-limited settings and other areas where efavirenz and atazanavir are needed as antiretroviral therapy alternatives.

Acknowledgments

Contributors to the HIV-CAUSAL Collaboration: UK CHIC: Steering Committee: Jonathan Ainsworth, Jane Anderson, Abdel Babiker, Valerie Delpech, David Dunn, Martin Fisher, Brian Gazzard, Richard Gilson, Mark Gompels, Teresa Hill, Margaret Johnson, Clifford Leen, Chloe Orkin, Andrew Phillips, Deenan Pillay, Caroline Sabin (PI), Memory Sachikonye, Achim Schwenk, John Walsh. Central co-ordination: Research Department of Infection & Population Health, UCL, London (T Hill, S Huntington, S Jose, A Phillips, C Sabin, A Thornton); Medical Research Council Clinical Trials Unit (MRC CTU), London (D Dunn, A Glabay). Participating centres: Bart's and The London NHS Trust, London (C Orkin, J Lynch, J Hand, C de Souza); Brighton and Sussex University Hospitals NHS Trust (M Fisher, N Perry, S Tilbury, D Churchill); Chelsea and Westminster NHS Trust, London (B Gazzard, M Nelson, M Waxman, D Asboe, S Mandalia); Health Protection Agency Centre for Infections London (V Delpech); Homerton University Hospital NHS Trust,

London (J Anderson, S Munshi, D Awosika); King's College Hospital, London (F Post, H Korat, C Taylor, Z Gleisner, F Ibrahim, L Campbell); UCL Medical School and The Mortimer Market Centre, London (R Gilson, N Brima, I Williams); North Bristol NHS Trust (M Gompels, S Allen); North Middlesex University Hospital NHS Trust, London (A Schwenk, J Ainsworth, C Wood, S Miller); Royal Free NHS Trust and Department of Infection & Population Health, UCL, London (M Johnson, M Youle, F Lampe, C Smith, H Grabowska, C Chaloner, D Puradiredja); Imperial College Healthcare NHS Trust, London (J Walsh, N Mackie, A Winston, J Weber, F Ramzan); The Lothian University Hospitals NHS Trust, Edinburgh (C Leen, A Wilson); University of Leicester NHS Trust (A Palfreeman, A Moore, L Fox); South Tees Hospitals NHS Foundation Trust (D Chadwick, K Baillie); Woolwich NHS Trust (S Kegg, P Main); Coventry NHS Trust (S Allan); St George's NHS Trust (P Hay, M Dhillon); York (F Martin, S Douglas).

ATHENA: The ATHENA database is maintained by Stichting HIV Monitoring and supported by a grant from the Dutch Ministry of Health, Welfare and Sport through the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment. CLINICAL CENTRES * denotes site coordinating physician Academic Medical Centre of the University of Amsterdam: HIV treating physicians: JM Prins*, TW Kuijpers, HJ Scherpbier, JTM van der Meer, FWMN Wit, MH Godfried, P Reiss, T van der Poll, FJB Nellen, SE Geerlings, M van Vugt, D Pajkrt, JC Bos, WJ Wiersinga, M van der Valk, A Goorhuis, JW Hovius, AM Weijnsfeld. HIV nurse consultants: J van Eden, A Henderiks, AMH van Hes, M Mutschelknauss, HE Nobel, FJJ Pijnappel. HIV clinical virologists/chemists: S Jurriaans, NKT Back, HL Zaaijer, B Berkhout, MTE Cornelissen, CJ Schinkel, XV Thomas. Admiraal De Ruyter Ziekenhuis, Goes: HIV treating physicians: M van den Berge, A Stegeman. HIV nurse consultants: S Baas, L Hage de Loeff. HIV clinical virologists/chemists: D Versteeg. Catharina Ziekenhuis, Eindhoven: HIV treating physicians: MJH Pronk*, HSM Ammerlaan. HIV nurse consultants: ES de Munnik. HIV clinical virologists/chemists: AR Jansz, J Tjhie, MCA Wegdam, B Deiman, V Scharnhorst. Emma Kinderziekenhuis: HIV nurse consultants: A van der Plas, AM Weijnsfeld. Erasmus Medisch Centrum, Rotterdam: HIV treating physicians: ME van der Ende*, TEMS de Vries-Sluijs, ECM van Gorp, CAM Schurink, JL Nouwen, A Verbon, BJA Rijnders, HI Bax, M van der Feltz. HIV nurse consultants: N Bassant, JEA van Beek, M Vriesde, LM van Zonneveld. Data collection: A de Oude-Lubbers, HJ van den Berg-Cameron, FB Bruinsma-Broekman, J de Groot, M de Zeeuw- de Man. HIV clinical virologists/chemists: CAB Boucher, MPG Koopmans, JJA van Kampen. Erasmus Medisch Centrum—Sophia, Rotterdam: HIV treating physicians: GJA Driessen, AMC van Rossum. HIV nurse consultants: LC van der Knaap, E Visser. Flevoziekenhuis, Almere: HIV treating physicians: J Branger*, A Rijkeboer-Mes. HIV nurse consultant and data collection: CJHM Duijff-van de Ven. HagaZiekenhuis, Den Haag: HIV treating physicians: EF Schippers*, C van Nieuwkoop. HIV nurse consultants: JM van Ijperen, J Geilings. Data collection: G van der Hut. HIV clinical virologist/chemist: PFH Franck. HIV Focus Centrum (DC Klinieken): HIV treating physicians: A van Eeden*. HIV nurse consultants: W Brokking, M Groot, LJM Elsenburg. HIV clinical virologists/chemists: M Damen, IS Kwa. Isala, Zwolle: HIV treating physicians: PHP Groeneveld*, JW Bouwhuis. HIV nurse consultants: JF van den Berg, AGW van Hulzen. Data collection: GL van der Blik, PCJ Bor. HIV clinical virologists/chemists: P Bloembergen, MJHM Wolfhagen, GJHM Ruijs. Leids Universitair Medisch Centrum, Leiden: HIV treating physicians: FP Kroon*, MGJ de Boer, MP Bauer, H Jolink, AM

Vollaard. HIV nurse consultants: W Dorama, N van Holten. HIV clinical virologists/chemists: ECJ Claas, E Wessels. Maasstad Ziekenhuis, Rotterdam: HIV treating physicians: JG den Hollander*, K Pogany, A Roukens. HIV nurse consultants: M Kastelijns, JV Smit, E Smit, D Struik-Kalkman, C Tearnno. Data collection: M Bezemer, T van Niekerk. HIV clinical virologists/chemists: O Pontesilli. Maastricht UMC+, Maastricht: HIV treating physicians: SH Lowe*, AML Oude Lashof, D Posthouwer. HIV nurse consultants: RP Ackens, J Schippers, R Vergoossen. Data collection: B Weijenberg-Maes. HIV clinical virologists/chemists: IHM van Loo, TRA Havenith. MC Slotervaart, Amsterdam: HIV treating physicians: JW Mulder, SME Vrouwenraets, FN Lauw. HIV nurse consultants: MC van Broekhuizen, H Paap, DJ Vlasblom. HIV clinical virologists/chemists: PHM Smits. MC Zuiderzee, Lelystad: HIV treating physicians: S Weijer*, R El Moussaoui. HIV nurse consultant: AS Bosma. Medisch Centrum Alkmaar: HIV treating physicians: W Kortmann*, G van Twillert*, JWT Cohen Stuart, BMW Diederer. HIV nurse consultant and data collection: D Pronk, FA van Truijen-Oud. HIV clinical virologists/chemists: WA van der Reijden, R Jansen. Medisch Centrum Haaglanden, Den Haag: HIV treating physicians: EMS Leyten*, LBS Gelinck. HIV nurse consultants: A van Hartingsveld, C Meerkerk, GS Wildenbeest. HIV clinical virologists/chemists: JAEM Mutsaers, CL Jansen. Medisch Centrum Leeuwarden, Leeuwarden: HIV treating physicians: MGA van Vonderen*, DPF van Houte, LM Kampschreur. HIV nurse consultants: K Dijkstra, S Faber. HIV clinical virologists/chemists: J Weel. Medisch Spectrum Twente, Enschede: HIV treating physicians: GJ Kootstra*, CE Delsing. HIV nurse consultants: M van der Burg-van de Plas, H Heins. Data collection: E Lucas. OLVG Amsterdam: HIV treating physicians: K Brinkman*, GEL van den Berk, WL Blok, PHJ Frissen, KD Lettinga, WEM Schouten, J Veenstra. HIV nurse consultants: CJ Brouwer, GF Geerders, K Hoeksema, MJ Kleene, IB van der Meché, M Spelbrink, H Sulman, AJM Toonen, S Wijnands. HIV clinical virologists: M Damen, D Kwa. Data collection: E Witte. Radboudumc, Nijmegen: HIV treating physicians: PP Koopmans, M Keuter, AJAM van der Ven, HJM ter Hofstede, ASM Dofferhoff, R van Crevel. HIV nurse consultants: M Albers, MEW Bosch, KJT Grintjes-Huisman, BJ Zomer. HIV clinical virologists/chemists: FF Stelma, J Rahamat-Langendoen. HIV clinical pharmacology consultant: D Burger. Rijnstate, Arnhem: HIV treating physicians: C Richter*, EH Gisolf, RJ Hassing. HIV nurse consultants: G ter Beest, PHM van Bentum, N Langebeek. HIV clinical virologists/chemists: R Tiemessen, CMA Swanink. Spaarne Gasthuis, Haarlem: HIV treating physicians: SFL van Lelyveld*, R Soetekouw. HIV nurse consultants: N Hulshoff, LMM van der Pijnt, J van der Swaluw. Data collection: N Bermon. HIV clinical virologists/chemists: WA van der Reijden, R Jansen, BL Herpers, D Veenendaal. Stichting Medisch Centrum Jan van Goyen, Amsterdam: HIV treating physicians: DWM Verhagen. HIV nurse consultants: M van Wijk. St Elisabeth Ziekenhuis, Tilburg: HIV treating physicians: MEE van Kasteren*, AE Brouwer. HIV nurse consultants and data collection: BAFM de Kruijff-van de Wiel, M Kuipers, RMWJ Santegoets, B van der Ven. HIV clinical virologists/chemists: JH Marcelis, AGM Buiting, PJ Kabel. Universitair Medisch Centrum Groningen, Groningen: HIV treating physicians: WFW Bierman*, H Scholvinck, KR Wiltling, Y Stienstra. HIV nurse consultants: H de Groot-de Jonge, PA van der Meulen, DA de Weerd, J Ludwig-Roukema. HIV clinical virologists/chemists: HGM Niesters, A Riezebos-Brilman, CC van Leer-Buter, M Knoester. Universitair Medisch Centrum Utrecht, Utrecht: HIV treating physicians: AIM Hoepelman*, T Mudrikova, PM Ellerbroek, JJ Oosterheert, JE Arends, RE Barth, MWM Wassenberg, EM Schadd. HIV nurse consultants: DHM

van Elst-Laurijssen, EEB van Oers-Hazelzet, S Vervoort, Data collection: M van Berkel. HIV clinical virologists/chemists: R Schuurman, F Verduyn-Lunel, AMJ Wensing. VU medisch centrum, Amsterdam: HIV treating physicians: EJJ Peters*, MA van Agtmael, M Bomers, J de Vocht. HIV nurse consultants: M Heitmuller, LM Laan. HIV clinical virologists/chemists: AM Pettersson, CMJE Vandenbroucke-Grauls, CW Ang. Wilhelmina Kinderziekenhuis, UMCU, Utrecht: HIV treating physicians: SPM Geelen, TFW Wolfs, LJ Bont. HIV nurse consultants: N Nauta. COORDINATING CENTRE Director: P Reiss. Data analysis: DO Bezemer, AI van Sighem, C Smit, FWMN Wit. Data management and quality control: S Zaheri, M Hillebregt, A de Jong. Data monitoring: D Bergsma, P Hoekstra, A de Lang, S Grivell, A Jansen, MJ Rademaker, M Raethke. Data collection: L de Groot, M van den Akker, Y Bakker, M Broekhoven, E Claessen, A El Berkaoui, J Koops, E Kruijine, C Lodewijk, R Meijering, L Munjshvili, B Peeck, C Ree, R Regtop, Y Ruijs, T Rutkens, L van de Sande, M Schoorl, S Schnörr, E Tuijn, L Veenenberg, S van der Vliet, T Woudstra. Patient registration: B Tuk.

FHDH-ANRS CO4: Scientific committee: S Abgrall, F Barin, M Bentata, E Billaud, F Boué, C Burty, A Cabié, D Costagliola, L Cotte, P De Truchis, X Duval, C Duvivier, P Enel, L Fredouille-Heripret, J Gasnault, C Gaud, J Gilquin, S Grabar, C Katlama, MA Khuong, JM Lang, AS Lascaux, O Launay, A Mahamat, M Mary-Krause, S Matheron, JL Meynard, J Pavie, G Pialoux, F Pilorgé, I Poizot-Martin, C Pradier, J Reynes, E Rouveix, A Simon, P Tattevin, H Tissot-Dupont, JP Viard, N Viget DM2 coordinating center: French Ministry of Health (Valérie Salomon), Technical Hospitalization Information Agency, ATIH (N Jacquemet). Statistical analysis center: U943 INSERM et UPMC (S Abgrall, D Costagliola, S Grabar, M Guiguet, E Lanoy, L Lièvre, M Mary-Krause, H Selinger-Leneman), INSERM Transfert (JM Lacombe, V Potard). COREVIH: Paris area: Corevih Ile de France Centre (GH Pitié-Salpêtrière: F Bricaire, S Herson, C Katlama, A Simon; Hôpital Saint-Antoine: N Desplanque, PM Girard, JL Meynard, MC Meyohas, O Picard; Hôpital Tenon: J Cadranel, C Mayaud, G Pialoux), Corevih Ile de France Est (Hôpital Saint-Louis: JP Clauvel, JM Decazes, L Gerard, JM Molina; GH Lariboisière-Fernand Widal: M Diemer, P Sellier; Hôpital Avicenne: M Bentata, P Honoré; Hôpital Jean Verdier: V Jeantils, S Tassi; Hôpital Delafontaine: D Mechali, B Taverne), Corevih Ile de France Nord (Hôpital Bichat-Claude Bernard: E Bouvet, B Crickx, JL Ecobichon, S Matheron, C Picard-Dahan, P Yeni), Corevih Ile de France Ouest (Hôpital Ambroise Paré: H Berthé, C Dupont; Hôpital Louis Mourier: C Chandemerle, E Mortier; Hôpital Raymond Poincaré: P de Truchis), Corevih Ile de France Sud (Hôpital Européen Georges Pompidou: D Tisne-Dessus, L Weiss; GH Tarnier-Cochin: D Salmon; Hôpital Saint-Joseph: I Auperin, J Gilquin; Hôpital Necker adultes: L Roudière, JP Viard; Hôpital Antoine Bécère: F Boué, R Fior; Hôpital de Bicêtre: JF Delfraissy, C Goujard; Hôpital Henri Mondor: C Jung, Ph Lesprit; Hôpital Paul Brousse: D Vittecoq). Outside Paris area: Corevih Alsace (CHRU de Strasbourg: P Fraisse, JM Lang, D Rey; CH de Mulhouse: G Beck-Wirth), Corevih de l'Arc Alpin (CHU de Grenoble: JP Stahl, P Lecercq), Corevih Auvergne-Loire (CHU de Clermont-Ferrand: F Gourdon, H Laurichesse; CHRU de Saint-Etienne: A Fresard, F Lucht); Corevih Basse-Normandie (CHRU de Caen: C Bazin, R Verdon), Corevih Bourgogne (CHRU de Dijon: P Chavanet), Corevih Bretagne (CHU de Rennes: C Arvieux, C Michelet), Corevih Centre (CHRU de Tours: P Choutet, A Goudeau, MF Maître), Corevih Franche-Comté (CHRU de Besançon: B Hoen; CH de Belfort: P Eglinger, JP Faller); Corevih Haute-Normandie (CHRU de Rouen: F Borsa-Lebas, F Caron), Corevih Languedoc-Roussillon (CHU de Montpellier: J Reynes; CHG de Nîmes: JP

Daures), Corevih Lorraine (Nancy Hôpital de Brabois: T May, C Rabaud; CHRU de Reims: JL Berger, G Rémy), Corevih de Midi-Pyrénées (Toulouse CHU Purpan: E Arlet-Suau, L Cuzin, P Massip, MF Thiercelin Legrand; Toulouse Hôpital la Grave: G Pontonnier; Toulouse CHU Rangueil), Corevih Nord-Pas de Calais (CH de Tourcoing: N Viget, Y Yasdanpanah), Corevih PACA Est (Nice Hôpital Archet 1: P Dellamonica, C Pradier, P Pugliese; CHG Antibes-Juan les Pins: K Aleksandrowicz, D Quinsat), Corevih PACA Ouest (Marseille Hôpital de la Conception: I Ravaux, H Tissot-Dupont; Marseille Hôpital Nord: JP Delmont, J Moreau; Marseille Institut Paoli Calmettes: JA Gastaut; Marseille Hôpital Sainte-Marguerite: I Poizot-Martin, F Retornaz, J Soubeyrand; Marseille Centre pénitentiaire des Baumettes: A Galinier, JM Ruiz; CHG d'Aix-En-Provence: T Allegre, PA Blanc; CH d'Arles: D Bonnet-Montchardon; CH d'Avignon: G Lepeu; CH de Digne Les Bains: P Granet-Brunello; CH de Gap: JP Esterni, L Pelissier; CH de Martigues: R Cohen-Valensi, M Nezri; CHI de Toulon: S Chadapaud, A Laffeuillade), Corevih Pays de la Loire (CHRU de Nantes: E Billaud, F Raffi), Corevih de la Vallée du Rhône (Lyon Hôpital de la Croix-Rousse: A Boibieux, D Peyramond; Lyon Hôpital Edouard Herriot: JM Livrozet, JL Touraine; Lyon Hôtel-Dieu: L Cotte, C Trepo). Overseas: Corevih Guadeloupe (CHRU de Pointe-à-Pitre: M Strobel; CH Saint-Martin: F Bissuel), Corevih Guyane (CHG de Cayenne: R Pradinaud, M Sobesky), Corevih Martinique (CHRU de Fort-de-France: A Cabié), Corevih de La Réunion (CHD Félix Guyon: C Gaud, M Contant).

Swiss HIV Cohort Study (SHCS): Aubert V, Barth J, Bategay M, Bernasconi E, Böni J, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Gorgievski M, Günthard H (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kovari H, Kouyos R, Ledergerber B, Martinetti G, Martinez de Tejada B, Metzner K, Müller N, Nadal D, Pantaleo G, Rauch A (Chairman of the Scientific Board), Regenass S, Rickenbach M (Head of Data Center), Rudin C (Chairman of the Mother & Child Substudy), Schmid P, Schultze D, Schöni-Affolter F, Schüpbach J, Speck R, Staehelin C, Tarr P, Telenti A, Trkola A, Vernazza P, Weber R, Yerly S.

PISCIS: Coordinators: J Casabona, Centre d'Estudis Epidemiològics les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT), Jose M Miró (Hospital Clínic de Barcelona-Idibaps, Universitat de Barcelona, Barcelona, Spain). Field coordinator: A Gallois (CEEISCAT). Steering committee: J Casabona, A Gallois, A Esteve (CEEISCAT), Jose M Miró (Hospital Clínic de Barcelona-Idibaps, Universitat de Barcelona), D Podzamczar (Hospital de Bellvitge de Barcelona), J Murillas (Hospital Son Espases). Scientific committee: JM Gatell, C Manzano (Hospital Clínic-Idibaps, Universitat de Barcelona), C Tural, B Clotet (Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona), E Ferrer (Hospital de Bellvitge), M Riera (Hospital Son Espases), F Segura, G Navarro (Corporación Sanitaria Universitaria Parc Taulí, Universitat Autònoma de Barcelona), L Force (Hospital de Mataró), J Vilaró (Hospital General de Vic), A Masabeu (Hospital de Palamós), I García (Hospital General d'Hospitalet), M Guadarrama (Hospital Alt Penedès de Vilafranca), C Cifuentes (Hospital Son Llàtzer), D Dalmau, À Jaen (Hospital Universitari Mútua de Terrassa), C Agustí (CEEISCAT). Data Management and statistical analysis: A Esteve, A Montoliu (CEEISCAT), I Pérez (Hospital Clínic-Idibaps, Universitat de Barcelona). Technical support: I Pérez (Hospital Clínic de Barcelona-Idibaps, Universitat de Barcelona), Freyra Gargoulas (Hospital Son Espases and Hospital Son Llàtzer). Clinicians involved: JL Blanco, F Garcia-Alcaide,

E Martínez, J Mallolas, M López-Diequez, JF García-Goez, (Hospital Clínic- Idibaps, Universitat de Barcelona), G Sirera, J Romeu, A Jou, E Negro, C Miranda, MC Capitan (Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona), M Saumoy, A Imaz, JM Tiraboschi, O Murillo, F Bolao, C Peña, C Cabellos, M Masó, A Vila (Hospital Universitari de Bellvitge), M Sala, M Cervantes, M Jose Amengual, M Navarro, E Penelo (Corporación Sanitaria Universitaria Parc Taulí, Universidad Autónoma de Barcelona), P Barrufet, G Bejarano (Hospital de Mataró, Barcelona), J Molina, M Guadarrama, M Alvaro, J Mercadal (Hospital Alt Penedès de Vilafranca). Civil society representatives: Juanes Fernández (Comité 1er de Deseembre), Jesús E Ospina (RedVII). CoRIS/CoRIS-MD: Steering committee: J Berenguer, J del Amo, F García, F Gutiérrez, P Labarga, S Moreno, MA Muñoz. Field work, data management, and statistical analyses: AM Caromurillo, P Sobrino, I Jarrín, B Alejos, V Hernando, D Alvarez, S Monge, Y Rivero, C González. Participating centres: Hospital General Universitario de Alicante, Alicante: J Portilla, E Merino, S Reus, V Boix, L Giner, C Gadea, I Portilla, P Arcaina, Hospital Universitario de Canarias, Santa Cruz de Tenerife (JL Gómez Sirvent, P Rodríguez, MR Alemán, MM Alonso, AM López, MI Hernández, F Díaz-Flores), Hospital Carlos III, Madrid (V Soriano, P Labarga, P Barreiro, P Rivas, F Blanco, ME Vispo, L Martín, C Solera), Hospital Universitario Central de Asturias, Oviedo: V Asensi, E Valle, JA Cartón, Hospital Doce de Octubre, Madrid (R Rubio, F Pulido S Fiorante, J Llenas, V Rodríguez, M Matarranz), Hospital Donostia, San Sebastián (JA Iribarren, J Arrizabalaga, MJ Aramburu, X Camino, F Rodríguez-Arondo, MA von Wichmann, L Pascual, MA Goenaga, MJ Bustinduy, HA Galparsoro), Hospital General Universitario de Elche (F Gutiérrez, M Masiá, C López, S Padilla, A Navarro, F Montolio, C Robledano, JG Colomé), Hospital Gregorio Marañón, Madrid (J Berenguer, JC López, P Miralles, J Cosín, I Gutiérrez, M Ramírez, B Padilla, P Gijón, A Carrero, T Aldamiz-Echevarría, F Tejerina), Hospital Universitari de Tarragona Joan XXIII (F Vidal, J Peraire, S Veloso, C Viladés, M López-Dupla, M Olona, M Vargas, A Aguilar, JJ Sirvent, V Alba, O Calavia), Hospital La Fe, Valencia (JL Aldeguer, M Blanes, J Lacruz, M Salavert, M Montero, E Calabuig, S Cuéllar), Hospital Universitario La Paz, Madrid: J González, I Bernardino, JR Arribas, ML Montes, JM Peña, B Arribas, JM Castro, FJ Zamora, I Pérez, M Estébanez, S García, M Díaz, Hospital de la Princesa, Madrid (I de los Santos, J Sanz, A Salas, C Sarriá), Hospital San Pedro, Logroño (JA Oteo, JR Blanco, V Ibarra, L Metola, M Sanz, L Pérez-Martínez, J Pinilla), Hospital Universitario Mutua de Terrassa, Terrassa: D Dalmau, A Jaén, M Cairó, D Irigoyen, L Ibáñez, Q Jordano, M Xercavins, J Martínez-Lacasa, P Velli, R Font, Hospital de Navarra, Pamplona (M Rivero, MI Casado, JA Díaz, J Uriz, J Reparaz, MJ Arriaza, C Irigoyen), Hospital Ramón y Cajal, Madrid (S Moreno, JL Casado, F Drona, A Moreno, MJ Pérez, D López, C Gutiérrez, B Hernández, M Pumares, P Martí), Hospital Reina Sofía, Murcia: A Cano, E Bernal, A Muñoz, Hospital San Cecilio, Granada (F García, J Hernández, A Peña, L Muñoz, J Parra), Centro Sanitario Sandoval, Madrid: J Del Romero, C Rodríguez, T Puerta, JC Carrió, C González, M Vera, Hospital Universitario Santiago de Compostela, Santiago de Compostela: A Antela, A Prieto, E Losada, Hospital Universitario de Valme, Sevilla: JA Pineda, E Recio, F Lozano, J Macías, J del Valle, J Gómez-Mateos, Hospital Virgen de la Victoria, Málaga: J Santos, M Márquez, I Viciano, R Palacios, Hospital Universitario Virgen del Rocío, Sevilla (P Viciano, M Leal, LF López-Cortés, M Trastoy). 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GEMES: Principal Investigator: R Muga/S Pérez-Hoyos. Data analysis center: S Pérez-Hoyos, A Schiaffino Centro Nacional de Epidemiología: J del Amo, D Alvarez, S Monge. Participating centres: Cohorte del Hospital Germans Trias I Pujol, Badalona (R Muga, A Sanvisens, B Clotet, J Tor, F Bolao, I Rivas, D Fuster), Cohorte de Madrid-Sandoval (J del Romero, P Raposo, C Rodríguez, M Vera), Cohorte de los CIPS de la Comunidad Valenciana (I Hurtado, J Belda, E Fernandez, I Alastrue, C Santos, T Tasa, A Juan, J Trullen), Cohortes de los CAS, de las Prisiones de Cataluña y de hemofílicos del Hospital Vall d'Hebron, Barcelona (P Garcia de Olalla, J Cayla, E Masdeu, H Knobel, JM Miró, MA Sabeat, R Guerrero, E Rivera), Cohorte de hemofílicos del Hospital La Paz, Madrid (M Quintana, C Gonzalez), Cohorte de Navarra (J Castilla, M Guevara). Laboratory: C de Mendoza, N Zahonero, M Ortíz.

AMACS: Steering Committee: Antoniadou A, Chrysos G, Daikos G, Gargalianos-Kakolyris P, Gogos HA, Katsarou O, Kordossis T, Lazanas M, Nikolaidis P, Panos G, Paparizos V, Paraskevis D, Sambatakou H, Skoutelis A, Touloumi G (Chair). Coordinating Center: Department of Hygiene, Epidemiology and Medical Statistics, Athens University Medical School, Greece (Touloumi G, Pantazis N, Vourli G, Gountas I, Gioukari V.) Participating Centers: 4th Dept of Internal Medicine, Athens Medical School, Attikon University Hospital (Antoniadou A, Papadopoulou A, Petrikos G); Infectious Disease Unit, "Tzaneio" General Hospital of Pireaus (Chrysos G, Paraskeva D, Hatziastrous P); 1st Dept of Propedeutic Medicine, Athens University, Medical School "Laikon" General Hospital (Daikos G, Psychogiou M); 1st Dept of Medicine, Infectious Diseases Unit, "G Gennimatas" Athens General Hospital (Gargalianos-Kakolyris P, Xylomenos G); 1st Dept of Internal Medicine, Infectious Diseases Section, Patras University Hospital (Gogos HA, Marangos MN, Panos G); Haemophilia Centre, 2nd Blood Transfusion Centre, "Laikon" Athens General Hospital (Katsarou O, Kouramba A, Ioannidou P); AIDS Unit, Dept of Pathophysiology, "Laikon" Athens General Hospital and Athens University, Medical School (Kordossis T, Kontos A); Infectious Diseases Unit, Red Cross General Hospital of Athens (Lazanas M, Chini M, Tsogas N); 1st Dept of Internal Medicine, Infectious Diseases Division, AHEPA University Hospital, Aristotle University HIV Unit (Nikolaidis P, Kolaras P, Metallidis S); 2nd Internal Medicine Clinic, 1st IKA (Panos G, Haratsis G); AIDS Unit, Clinic of Venereologic & Dermatologic Diseases, Athens University, Medical School, Syngros Hospital (Paparizos V, Leuow K, Kourkounti S); HIV Unit, 2nd Dpt of Internal Medicine, Athens University, Medical School, Hippokraton General Hospital (Sambatakou H, Mariolis I); Infectious Diseases & HIV Division, Dept of Internal Medicine, Evaggelismos Athens General Hospital (Skoutelis A, Papastamopoulos V, Baraboutis I)

AQUITAINE: Principal investigator: Pr F Dabis. Scientific committee: Prs F Bonnet, D Breilh, F Dabis, M Dupon, G Chêne, H Fleury, D Malvy, P Mercié, I Pellegrin, P Morlat, D Neau, JL Pellegrin, R Thiébaud; Drs S Bouchet, V Gaborieau, D Lacoste, S Tchamgoué. Epidemiology and biostatistics: Prs G Chêne, F Dabis, R Thiébaud, Drs M Bruyand, S Lawson-Ayayi, L Wittkop. Clinical and biological hospital units: Bordeaux University Hospital: Pr P Morlat (Pr F Bonnet, Drs N Bernard, M Hessamfar, D Lacoste, MA Vandenhende); Pr M Dupon (Drs FA Dauchy, H Dutronc), Pr M Longy-Boursier (Pr P Mercié, Drs P Duffau, J Roger Schmeltz), Pr D Malvy (Drs T Pistone, MC Receveur), Pr D Neau (Drs C Cazanave, A Ochoa, MO Vareil), Pr JL Pellegrin (Pr JF Viillard, Drs C Greib, E Lazaro); Pr H Fleury (Pr ME Lafon, Drs S Reigadas, P Trimoulet); Pr D Breilh; Pr M

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