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Does short-term virologic failure translate to clinical events in antiretroviral-naïve patients initiating antiretroviral therapy in clinical practice?

Antiretroviral Therapy Cohort Collaboration, (ART-CC); Mugavero, M J; May, M; Harris, R; Saag, M S; Costagliola, D; Egger, M; Phillips, A; Günthard, H F; Dabis, F; Hogg, R; de Wolf, F; Fatkenheuer, G; Gill, M J; Justice, A; D'Arminio Monforte, A; Lampe, F; Miró, J M; Staszewski, S; Sterne, J A C

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Abstract

OBJECTIVE: To determine whether differences in short-term virologic failure among commonly used antiretroviral therapy (ART) regimens translate to differences in clinical events in antiretroviral-naïve patients initiating ART. DESIGN: Observational cohort study of patients initiating ART between January 2000 and December 2005. SETTING: The Antiretroviral Therapy Cohort Collaboration (ART-CC) is a collaboration of 15 HIV cohort studies from Canada, Europe, and the United States. STUDY PARTICIPANTS: A total of 13 546 antiretroviral-naïve HIV-positive patients initiating ART with efavirenz, nevirapine, lopinavir/ritonavir, nelfinavir, or abacavir as third drugs in combination with a zidovudine and lamivudine nucleoside reverse transcriptase inhibitor backbone. MAIN OUTCOME MEASURES: Short-term (24-week) virologic failure (>500 copies/ml) and clinical events within 2 years of ART initiation (incident AIDS-defining event, death, and a composite measure of these two outcomes). RESULTS: Compared with efavirenz as initial third drug, short-term virologic failure was more common with all other third drugs evaluated; nevirapine (adjusted odds ratio = 1.87, 95% confidence interval (CI) = 1.58-2.22), lopinavir/ritonavir (1.32, 95% CI = 1.12-1.57), nelfinavir (3.20, 95% CI = 2.74-3.74), and abacavir (2.13, 95% CI = 1.82-2.50). However, the rate of clinical events within 2 years of ART initiation appeared higher only with nevirapine (adjusted hazard ratio for composite outcome measure 1.27, 95% CI = 1.04-1.56) and abacavir (1.22, 95% CI = 1.00-1.48). CONCLUSION: Among antiretroviral-naïve patients initiating therapy, between-ART regimen, differences in short-term virologic failure do not necessarily translate to differences in clinical outcomes. Our results should be interpreted with caution because of the possibility of residual confounding by indication.

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The Antiretroviral Therapy Cohort Collaboration (ART-CC)*

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Design: Observational cohort study of patients initiating ART between January 2000 and December 2005.

Setting: The Antiretroviral Therapy Cohort Collaboration (ART-CC) is a collaboration of 15 HIV cohort studies from Canada, Europe, and the United States.

Study participants: A total of 13 546 antiretroviral-naïve HIV-positive patients initiating ART with efavirenz, nevirapine, lopinavir/ritonavir, nelfinavir, or abacavir as third drugs in combination with a zidovudine and lamivudine nucleoside reverse transcriptase inhibitor backbone.

Main outcome measures: Short-term (24-week) virologic failure (>500 copies/ml) and clinical events within 2 years of ART initiation (incident AIDS-defining event, death, and a composite measure of these two outcomes).

Results: Compared with efavirenz as initial third drug, short-term virologic failure was more common with all other third drugs evaluated; nevirapine (adjusted odds ratio = 1.87, 95% confidence interval (CI) = 1.58–2.22), lopinavir/ritonavir (1.32, 95% CI = 1.12–1.57), nelfinavir (3.20, 95% CI = 2.74–3.74), and abacavir (2.13, 95% CI = 1.82–2.50). However, the rate of clinical events within 2 years of ART initiation appeared higher only with nevirapine (adjusted hazard ratio for composite outcome measure 1.27, 95% CI = 1.04–1.56) and abacavir (1.22, 95% CI = 1.00–1.48).

Conclusion: Among antiretroviral-naïve patients initiating therapy, between-ART regimen, differences in short-term virologic failure do not necessarily translate to differences in clinical outcomes. Our results should be interpreted with caution because of the possibility of residual confounding by indication.

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Introduction

Combination antiretroviral therapy (ART) has resulted in dramatic reductions in HIV-associated morbidity and mortality for persons with access to treatment. Preferred initial ART regimens have changed over time largely on the basis of the evidence from randomized controlled clinical trials (RCTs). However, clinical trials are usually powered to detect between-regimen differences in short-term suppression of plasma HIV RNA. Due to the rarity, in recent years, of clinical events such as incident AIDS-defining events and death [1–3], clinical trials are

Correspondence to Michael J. Mugavero, MD, MHSc, CCB 178 1530, 3rd Avenue S., Birmingham, AL 35294-2050, USA.
E-mail: mmugavero@uab.edu

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typically underpowered to detect differences in these clinical outcome measures.

Collaborations of observational cohort studies, a complementary study design to RCTs, may have the statistical power to evaluate between-regimen differences in clinical outcomes. However, results from such studies are likely to be affected by confounding because of the nonrandomized selection of initial ART regimens in clinical practice [4], often referred to as 'confounding by indication' [5]. Statistical methods can adjust for measured imbalances between treatment groups, but unmeasured confounding can never be fully excluded [6]. Recognizing these limitations, observational HIV cohort studies can play an important role in providing evidence that is not available from RCTs [7,8].

Previous observational studies have evaluated between-regimen differences in short-term virologic failure in treatment-naïve patients initiating ART in clinical practice settings, often yielding findings consistent with RCT results [9–21]. However, these studies have largely been underpowered to evaluate between-regimen differences in clinical outcomes. Previously, the ART Cohort Collaboration (ART-CC) evaluated between-regimen differences in virologic and clinical outcomes in patients initiating ART between 1996 and 2002 [22]. However, several regimens evaluated in that study are no longer widely used in clinical practice. Furthermore, ritonavir-boosted (RTV) protease inhibitors (amprenavir, lopinavir, saquinavir, and indinavir) were evaluated together due to the low number of such regimens in the database at the time of the study. Heterogeneity of outcomes between boosted protease inhibitor regimens may have affected the overall findings for these regimens, which were found to be inferior for both virologic and clinical outcomes, relative to efavirenz (EFV). Here, we analyse the data from an updated ART-CC database to evaluate between-regimen differences in short-term virologic failure and rates of clinical events among treatment-naïve patients initiating ART between 2000 and 2005; all analyses were conducted at the level of the individual regimen. We hypothesized that between-ART regimen differences in short-term virologic failure would not fully predict the effects on clinical endpoints.

Methods

Cohorts

The Antiretroviral Therapy Cohort Collaboration (ART-CC) is a collaboration of 15 HIV cohort studies from Canada, Europe, and the United States that was established in 2001. The collaboration has been described in detail elsewhere [23–26]. Briefly, prospective cohort studies were eligible for participation if they had enrolled at least 100 HIV-1–infected patients aged 16 years or more who had not previously received antiretroviral treatment, started ART with a combination of at least three antiretroviral drugs after 1996, and been followed for a median duration of at least 1 year after ART initiation. The database was updated in 2007 to additionally include patients who had started ART up until 31 December 2005 with follow-up until 1 July 2006. All cohorts have been approved by their local ethics committees or institutional review boards, use standardized methods of data collection, and schedule follow-up visits at least once every 6 months.

The cohorts in the dataset for this analysis are French Hospital Database on HIV (FHDH) ANRS CO4 [27] and the Aquitaine Cohort ANRS CO3 (France) [28], the AIDS Therapy Evaluation project Netherlands (ATHENA) [29], Italian Cohort of Antiretroviral-Naive Patients (ICONA) [30], Swiss HIV Cohort Study (SHCS) [31], Frankfurt HIV Cohort [32] and Köln/Bonn Cohort (Germany) [33], the EuroSIDA study (20 countries in Europe and Argentina) [34], the Collaborations in HIV Outcomes Research US (CHORUS) [35], the University of Alabama at Birmingham 1917 Clinic Cohort [36] and the Veterans Aging Cohort Study (VACS) (USA) [37], the Royal Free Hospital Cohort (United Kingdom) [38], the British Columbia Centre for Excellence in HIV/AIDS [39] and the South Alberta Clinic (Canada) [40], and PISCIS, Catalonia and Balearic Islands (Spain) [41].

Data collection

Patient selection and data extraction were performed at the data centres of the participating cohorts. Anonymized data on a predefined set of demographic, laboratory, and clinical variables were pooled and analysed centrally. Cohort data managers from EuroSIDA were asked to provide a unique study identification for each record as EuroSIDA patients may also be members of other cohort studies.

Statistical analyses

Analyses were restricted to HIV-1-positive patients aged 16 years or older, who first started antiretroviral therapy in the period 1 January 2000 to 31 December 2005 and had at least 6 months of potential follow-up before the cohort-specific database close date. Because of the focus on more recent ART regimens, study inclusion criteria required initiation of efavirenz (EFV), nevirapine (NVP), lopinavir/ritonavir (LPV/r), nelfinavir (NFV), or abacavir (ABC) as 'third drugs'. We evaluated short-term (24-week) virologic failure (HIV RNA >500 copies/ml) and longer-term clinical outcomes (incident AIDS-defining event, death from any cause, and a composite measure of these two outcomes) by third drug, in patients who were taking zidovudine and lamivudine (ZDV and 3TC) as the nucleoside reverse transcriptase inhibitor (NRTI) backbone. This approach was taken to focus on differences in virologic failure and clinical outcomes

between third drugs given in combination with the same NRTI pair, such that potential differences in prescribing patterns for NRTI backbones across third drugs was not a factor. ZDV and 3TC were chosen as the NRTI backbone as this combination represented the most commonly prescribed NRTI pair (68% of regimens). All centres used the 1993 US Centers for Disease Control and Prevention criteria and guidelines for the definitive or presumptive diagnosis of AIDS-defining events [42]. Only new AIDS diagnosis, defined as the first occurrence of each AIDS-defining condition was considered to be an incident event; recurrences of conditions were not considered. Change in regimen at 6 months after initiating ART was a secondary outcome.

To evaluate short-term virologic failure, logistic regression models were used to estimate crude and adjusted odds ratios (ORs) of detectable 24-week plasma HIV-1 RNA, that is more than 500 copies/ml, among patients with an available measurement at that time (±3-month window). For this analysis, patients who died prior to 24 weeks and those with missing 24-week plasma HIV-1 RNA values were excluded. Logistic regression models were also used to estimate the crude and adjusted OR of not being on the initial regimen at 24 weeks; 24-week regimen change was evaluated as a secondary outcome measure. Sensitivity analyses were conducted evaluating 24-week virologic failure and initial ART regimen change for all patients, including those with missing 24-week measurements. For these analyses, patients with missing 24-week plasma HIV RNA measures (±3 months), including those who died, were considered treatment failures ('missing equals failure').

To evaluate clinical outcomes, we measured time from the date of initiating ART to earlier of the date that clinical endpoints occurred and the date of censoring (end of follow-up). In patients free of events, follow-up was censored on the date of the most recent visit plus half the usual visit interval (usually 3 months) for AIDS and the combined endpoint (incident AIDS event or death from any cause). For mortality, the censoring date was extended to the date the patient was last known to be alive in cohorts that could assert complete vital registration; otherwise, as above. Because the proportion of patients remaining on their initial regimen decreases over time, effects of initial regimen become increasingly diluted by regimen changes with increasing time since initiation of ART. Follow-up was therefore censored at 2 years after starting ART or at the cohort-specific close of database date, if either of these occurred sooner. Additional analyses, removing the 2-year censoring, were conducted to evaluate longer-term differences in clinical events according to initial ART regimen.

Weibull proportional hazards regression models were used to model the association of initial treatment regimen and other prognostic factors with disease progression as measured by clinical outcome measures. We estimated crude and adjusted hazard ratios comparing other third drugs with EFV when taken in combination with ZDV and 3TC. Analyses followed an 'intent to continue initial therapy' principle, in that eligible participants were analysed according to initial regimen, regardless of whether they later discontinued or modified their therapeutic regimen.

All multivariable models were adjusted for age at initiation of therapy (16–29, 30–39, 40–49, and >50 years), sex, transmission risk group [injection drug user (IDU), non-IDU], clinical stage (A/B, C), baseline CD4 cell count (<25, 25–49, 50–99, 100–199, 200–349, and ≥350 cells/μl), baseline plasma HIV-1 RNA (<1000, 1000–9999 10 000–99 999, and ≥100 000 copies/ml), year of starting ART and cohort. Sensitivity analyses were restricted to patients who started ART with a CD4 cell count 200 cells/μl or less and to those whose reported transmission risk group was non-IDU.

AIDS-free survival up to 2 years after initiation of therapy by third drug was plotted using the estimated probability of a survival free of an incident AIDS-defining event or death from the adjusted Weibull model with covariates set at their average value across the population of patients and for the cohort with median survival.

Results

Overall, 13 546 patients in the ART-CC initiated ART with the third drugs of interest (EFV, NVP, LPV/r, NFV, ABC) paired with ZDV and 3TC during the study period. Among study participants, 69% were men, 13% reported a history of IDU, and 20% had CDC clinical stage C disease (Table 1). Overall, the median age (interquartile range) was 38 years (31–45) and the median CD4 cell count and plasma log10 HIV RNA levels were 218 cells/μl (104–329) and 4.9 (4.4–5.3), respectively, at the time of ART initiation. During the study period, EFV was the most commonly prescribed third drug (28%), followed by LPV/r (21%), ABC (19%), NFV (16%), and NVP (16%). Temporal trends in prescribing patterns measured as the proportion of overall ART prescriptions in a given year represented by each antiretroviral drug indicated increased use of LPV/r and decreased use of all other third drugs over the course of the observation period (Fig. 1). Compared with other third drugs, LPV/r was more commonly prescribed to patients with lower CD4 cell counts (median 150 cells/μl) and higher plasma HIV RNA levels (5.1 log10 copies/ml), whereas the opposite was observed for ABC (median 251 cells/μl and 4.7 log10 copies/ml) and NVP (median 260 cells/μl and 4.7 log10 copies/ml) (Table 1).

Table 1. Patient characteristics of 13 546 antiretroviral naïve HIV-infected patients in the Antiretroviral Therapy Cohort Collaboration initiating ART with zidovudine and lamivudine stratified by third drug, 2000–2005.

	Overall	EFV	NVP	LPV/r	NFV	ABC
Frequency third drug [*N* (row %)]	13 546 (100)	3788 (28)	2151 (16)	2875 (21)	2217 (16)	2515 (19)
Characteristic by third drug						
N (column %)						
Male	9368 (69)	2967 (78)	1306 (61)	2088 (73)	1229 (55)	1778 (71)
IDU	1740 (13)	492 (13)	261 (12)	232 (8)	321 (14)	434 (17)
Clinical CDC stage C	2674 (20)	848 (22)	255 (12)	766 (27)	443 (20)	362 (14)
Median (IQR)						
Age (years)	38 (31–45)	39 (33–47)	36 (30–43)	38 (32–46)	36 (29–44)	38 (32–46)
CD4 cell count (cells/μl)	218 (104 –329)	207 (94–320)	260 (171–366)	150 (55–264)	214 (92–351)	251 (163–354)
HIV RNA (log copies/ml)	4.9 (4.4–5.3)	4.9 (4.5–5.4)	4.7 (4.2–5.1)	5.1 (4.7–5.5)	4.8 (4.2–5.3)	4.7 (4.2–5.1)

3TC, lamivudine; ABC, abacavir; EFV, efavirenz; IQR, interquartile range; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NVP, nevirapine; ZDV, zidovudine.

In multivariable logistic regression analyses among patients who had 24-week plasma HIV RNA measures ($n = 11\,194$, 83%), detectable 24-week plasma HIV RNA (>500 copies/ml) was more common with all other third drugs than with EFV (Table 2). Findings were most pronounced for NFV (adjusted OR = 3.20, 95% CI = 2.74–3.74), whereas patients treated with NVP (1.87, 95% CI = 1.58–2.22) and ABC (2.13, 95% CI = 1.82–2.50) had roughly twice the odds of short-term virologic failure. There was a modest increase in the odds of 24-week virologic failure for LPV/r (adjusted OR = 1.32, 95% CI = 1.12–1.57). Among those with available 24-week data ($n = 11\,338$, 84% of cohort), patients receiving NVP (adjusted OR = 1.30, 95% CI = 1.13–1.51) and NFV (1.39, 95% CI = 1.20–1.60) were less likely to be treated with their initial regimen at 24 weeks than those receiving EFV (Table 2).

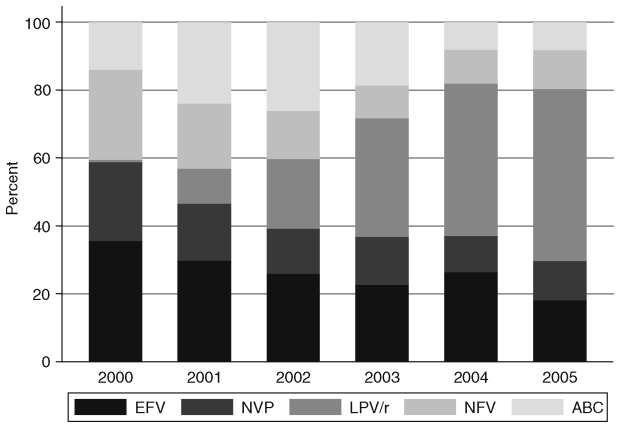

Fig. 1. Temporal trends in antiretroviral prescribing patterns among 13 546 antiretroviral naïve HIV-infected patients in the Antiretroviral Therapy Cohort Collaboration initiating antiretroviral therapy with ZDV/3TC and stratified by third drug, 2000–2005. ABC, abacavir; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NVP, nevirapine. Shaded bars represent the proportion of Antiretroviral Therapy Cohort Collaboration (ART-CC) patients initiating HAART with each of the listed third drugs during each of the calendar years from 2000 to 2005.

In general, sensitivity analyses including all patients ($n = 13\,546$) and utilizing a 'missing equals failure' approach gave similar results to those observed in primary analyses, but with ORs that were attenuated towards one (Table 3). In these analyses, the odds of virologic failure were similar for LPV/r relative to EFV (adjusted OR = 1.03, 95% CI = 0.91–1.16). This is in contrast to the primary analyses in which the odds of 24-week virologic failure were higher with LPV/r compared with that in EFV. Sensitivity analyses of 24-week change of initial ART regimen yielded similar results to primary analyses, and parameter estimates were of comparable magnitude (Table 3).

In Weibull proportional hazards analysis of clinical outcomes, rates of incident AIDS events (adjusted hazard ratio = 1.28, 95% CI = 1.02–1.60), death (1.54, 95% CI = 1.09–2.19), and combined clinical outcome (1.27, 95% CI = 1.04–1.56) appeared higher for NVP than for EFV (Table 4). Because baseline CD4 cell counts tended to be higher for patients initiating NVP (median baseline CD4 cell count 260 cells/μl) than those starting EFV (median 207 cells/μl), adjusted hazard ratios for this comparison were markedly greater than crude hazard ratios. In contrast, for the comparison of LPV/r (median baseline CD4 cell count 150 cells/μl) with EFV adjusted hazards were attenuated towards one after controlling for patient characteristics at baseline. In adjusted analyses, there was little evidence that rates of clinical events in patients on LPV/r differed from those in patients receiving EFV (AIDS-event adjusted hazard ratio = 1.14, 1.14, 95% CI = 0.93–1.39, death 1.12, 95% CI = 0.80–1.57, combined outcome measure 1.13, 95% CI = 0.94–1.36) (Table 4). Figure 2 shows that by 2 years after starting ART, there was an estimated difference of about 2% in the cumulative probability of AIDS-free survival, between patients initiating ART on NFV and those initiating NVP.

Relative to EFV, hazards of AIDS events (adjusted hazard ratio = 0.98, 95% CI = 0.79–1.21), death (0.89, 95% CI = 0.63–1.28), and the combined clinical endpoint

Table 2. Short-term (24-week) regimen durability and virologic failure among 11 338 antiretroviral naïve HIV-infected patients in the Antiretroviral Therapy Cohort Collaboration (plasma HIV RNA >500 copies/ml) initiating ART with zidovudine and lamivudine stratified by third drug, 2000–2005.

		Odds ratio (95% CI)						
		No longer on initial regimen at 24 weeks			24-week virologic failure ART-CC (plasma HIV RNA >500 copies/ml)			
Third drug	Observed	*N* (%)	Crude	Adjusted[a]	Observed	*N* (%)	Crude	Adjusted[a]
EFV	3258	679 (21)	1	1	3087	383 (12)	1	1
NVP	1759	448 (25)	1.30 (1.13–1.49)	1.30 (1.13–1.51)	1776	348 (20)	1.72 (1.47–2.02)	1.87 (1.58–2.22)
LPV/r	2518	622 (25)	1.25 (1.10–1.41)	1.04 (0.91–1.19)	2457	365 (15)	1.23 (1.06–1.44)	1.32 (1.12–1.57)
NFV	1715	490 (29)	1.52 (1.33–1.74)	1.39 (1.20–1.60)	1829	593 (32)	3.39 (2.93–3.92)	3.20 (2.74–3.74)
ABC	2088	432 (21)	0.99 (0.87–1.13)	0.94 (0.81–1.08)	2045	486 (24)	2.20 (1.90–2.55)	2.13 (1.82–2.50)

ABC, abacavir; ART-CC, Antiretroviral Therapy Cohort Collaboration; CI, confidence interval; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NVP, nevirapine.
[a]Multivariable logistic regression models adjusted for age, sex, injection drug user (IDU), entry CD4, entry HIV RNA, year starting ART, and cohort.

(0.92, 95% CI = 0.76–1.11) were slightly lower for NFV (Table 4). In adjusted analyses, hazards of death (adjusted hazard ratio = 1.41, 95% CI = 1.01–1.99) and the combined clinical endpoint (1.22, 95% CI = 1.00–1.48) appeared higher for ABC than for EFV. Such differences were not apparent in unadjusted analyses, in part because the median baseline CD4 cell count was higher for patients on ABC (median 251 cells/μl) than for those on EFV (median 207 cells/μl).

In general, sensitivity analyses of the combined clinical outcome measure (incident AIDS event or death) restricted to patients with baseline CD4 cell counts 200 cells/μl or less when initiating ART yielded parameter estimates of similar magnitude for each third drug relative to the primary analyses, although CIs were wider (Table 5). However, larger shifts in hazards ratios relative to primary analyses were observed when AIDS events and death were modelled separately, relative to models of the composite clinical outcome measure. On the whole, sensitivity analyses of clinical outcomes restricted to non-IDU patients yielded similar findings to primary analyses (Table 6). Evaluation of longer-term clinical events by initial ART regimen removing 2-year censoring yielded similar results to primary analyses, although, as expected, hazard ratios were attenuated towards one (Table 7).

Discussion

Among antiretroviral-naïve patients initiating ART in clinical practice settings, short-term (24-week) virologic failure was more common for all third drugs evaluated (NVP, LPV/r, NFV, and ABC) relative to EFV when given in combination with ZDV and 3TC. However, compared with EFV, estimated rates of AIDS and death appeared higher only with NVP and ABC. For LPV/r and NFV, we found little evidence that rates of AIDS and death differed from those on EFV. Taken together, these findings suggest that, between ART regimen, differences in short-term virologic failure do not necessarily translate to differences in clinical outcomes.

Although suppression of plasma HIV RNA is an important goal of treatment to avoid the emergence of viral resistance among other reasons, the ultimate aim of

Table 3. Sensitivity analysis of short-term (24-week) regimen durability and virologic failure among 13 546 antiretroviral naïve HIV-infected patients in the Antiretroviral Therapy Cohort Collaboration (plasma HIV RNA >500 copies/ml) initiating ART with zidovudine and lamivudine stratified by third drug (missing data = failure), 2000–2005.

		Odds ratio (95% CI)					
		No longer on initial regimen at 24 weeks			24-week virologic failure ART-CC (plasma HIV RNA >500 copies/ml)		
Third drug	Observed	*N* (%)	Crude	Adjusted[a]	*N* (%)	Crude	Adjusted[a]
EFV	3788	1209 (32)	1	1	1084 (29)	1	1
NVP	2151	840 (39)	1.37 (1.22–1.53)	1.29 (1.14–1.45)	723 (34)	1.26 (1.13–1.42)	1.44 (1.27–1.63)
LPV/r	2875	979 (34)	1.10 (0.99–1.22)	1.04 (0.92–1.16)	783 (27)	0.93 (0.84–1.04)	1.03 (0.91–1.16)
NFV	2217	992 (45)	1.73 (1.55–1.92)	1.54 (1.37–1.72)	981 (44)	1.98 (1.77–2.21)	1.98 (1.76–2.22)
ABC	2515	859 (34)	1.11 (0.99–1.23)	1.01 (0.90–1.14)	956 (38)	1.53 (1.37–1.70)	1.53 (1.36–1.72)

ABC, abacavir; ART-CC, Antiretroviral Therapy Cohort Collaboration; CI, confidence interval; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NVP, nevirapine.
[a]Multivariable logistic regression models adjusted for age, sex, injection drug user (IDU), entry CD4, entry HIV RNA, year starting ART, and cohort.

Table 4. Clinical outcomes (incident AIDS-defining event, death, and composite measure of these two outcomes) within 2 years of ART initiation among 13 546 antiretroviral naïve HIV-infected patients in the Antiretroviral Therapy Cohort Collaboration initiating ART with zidovudine and lamivudine stratified by third drug, 2000–2005.

		Hazard ratio (95% CI)								
		Incident AIDS event			Death			Incident AIDS event or Death		
Third drug	Observed	*N*	Crude	Adjusted[a]	*N*	Crude	Adjusted[a]	*N*	Crude	Adjusted[a]
EFV	3788	259	1	1	98	1	1	320	1	1
NVP	2151	117	0.90 (0.72–1.12)	1.28 (1.02–1.60)	54	1.16 (0.82–1.64)	1.54 (1.09–2.19)	147	0.91 (0.74–1.11)	1.27 (1.04–1.56)
LPV/r	2875	208	1.39 (1.15–1.68)	1.14 (0.93–1.39)	72	1.46 (1.06–2.02)	1.12 (0.80–1.57)	249	1.39 (1.16–1.65)	1.13 (0.94–1.36)
NFV	2217	146	1.02 (0.83–1.26)	0.98 (0.79–1.21)	47	0.88 (0.62–1.25)	0.89 (0.63–1.28)	167	0.95 (0.79–1.15)	0.92 (0.76–1.11)
ABC	2515	130	0.85 (0.69–1.06)	1.12 (0.89–1.40)	62	1.21 (0.87–1.68)	1.41 (1.01–1.99)	175	0.95 (0.79–1.15)	1.22 (1.00–1.48)

ABC, abacavir; CI, confidence interval; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NVP, nevirapine.
[a]Multivariable Weibull regression models adjusted for age, sex, injection drug user (IDU), entry CD4, entry HIV RNA, and year starting ART and stratified on cohort.
Follow-up restricted to 2 years.

Table 5. Sensitivity analysis restricted to 6235 patients with baseline CD4 cell counts 200 cells/μl or less at antiretroviral therapy initiation.

		Hazard ratio (95% CI)								
		Incident AIDS event			Death			Incident AIDS event or death		
Third drug	Observed	*N*	Crude	Adjusted	*N*	Crude	Adjusted	*N*	Crude	Adjusted
EFV	1837	206	1	1	69	1	1	244	1	1
NVP	697	66	0.96 (0.73–1.28)	1.13 (0.85–1.50)	37	1.70 (1.12–2.58)	1.99 (1.31–3.03)	86	1.05 (0.82–1.36)	1.24 (0.96–1.59)
LPV/r	1771	178	1.13 (0.91–1.39)	1.08 (0.86–1.36)	57	1.23 (0.85–1.79)	1.02 (0.69–1.51)	207	1.13 (0.93–1.38)	1.06 (0.86–1.30)
NFV	1059	118	1.03 (0.81–1.29)	0.94 (0.74–1.19)	28	0.73 (0.47–1.15)	0.72 (0.46–1.14)	133	0.98 (0.79–1.22)	0.91 (0.73–1.14)
ABC	871	87	1.03 (0.79–1.33)	1.14 (0.87–1.49)	40	1.59 (1.06–2.39)	1.63 (1.07–2.47)	115	1.18 (0.94–1.49)	1.29 (1.01–1.63)

ABC, abacavir; CI, confidence interval; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NVP, nevirapine.
[a]Multivariable Weibull regression models adjusted for age, sex, injection drug user (IDU), entry CD4, entry HIV RNA, and year starting ART and stratified on cohort.
Follow-up restricted to 2 years.

Table 6. Sensitivity analysis restricted to 11 806 patients with mode of HIV acquisition recorded as non-injection drug user.

		Hazard ratio (95% CI)									
		Incident AIDS event			Death			Incident AIDS event or death			
Third drug	Observed	*N*	Crude	Adjusted[a]	*N*	Crude	Adjusted[a]	*N*	Crude	Adjusted[a]
EFV	3247	224	1	1	74	1	1	270	1	1
NVP	1807	94	0.84 (0.65–1.07)	1.18 (0.92–1.52)	41	1.13 (0.76–1.67)	1.55 (1.04–2.33)	117	0.86 (0.68–1.07)	1.20 (0.95–1.50)
LPV/r	2211	188	1.36 (1.11–1.66)	1.09 (0.88–1.35)	62	1.57 (1.10–2.25)	1.14 (0.78–1.66)	221	1.36 (1.13–1.64)	1.08 (0.89–1.32)
NFV	1754	129	1.09 (0.87–1.36)	1.02 (0.81–1.28)	32	0.83 (0.55–1.27)	0.88 (0.57–1.34)	142	1.00 (0.81–1.23)	0.95 (0.77–1.18)
ABC	1870	96	0.77 (0.60–0.98)	0.99 (0.77–1.28)	45	1.24 (0.85–1.82)	1.62 (1.09–2.42)	130	0.89 (0.72–1.11)	1.16 (0.92–1.45)

ABC, abacavir; CI, confidence interval; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NVP, nevirapine.
[a]Multivariable Weibull regression models adjusted for age, sex, injection drug user (IDU), entry CD4, entry HIV RNA, and year starting ART and stratified on cohort. Follow-up restricted to 2 years.

Fig. 2. Estimated AIDS free survival among 13 546 antiretroviral naïve HIV-infected patients in the Antiretroviral Therapy Cohort Collaboration initiating antiretroviral therapy with ZDV/3TC stratified by third drug, 2000–2005. Survival curves shown are estimated from a Weibull model with follow-up censored at 2 years, with covariates set at the average value across the population of patients and for the cohort with median survival. Corresponding adjusted hazard ratios are shown in Table 4.

antiretroviral therapy is to prevent clinical progression and death. Preferred initial ART regimens change frequently, based on differential rates of virologic suppression observed in clinical trials. Our study suggests that such differences in virologic suppression between ART regimens may not translate to differences in clinical events among patients receiving treatment in a clinical practice setting. This observation may relate, in part, to the many available antiretroviral treatment options: patients failing treatment at 24-weeks may subsequently switch to other effective ART regimens. A recent study recognized the association of longitudinal CD4 cell count and plasma HIV RNA responses in contributing to long-term clinical outcomes in patients initiating modern ART, regardless of specific initial regimen [43].

Most previous observational studies (like RCTs) have lacked statistical power to analyse between-regimen differences in clinical events among patients initiating ART [9–20]. The ART-CC makes such comparisons possible through the collaborative efforts of multiple observational HIV cohort studies. The current study advances the findings of an earlier report from the ART-CC [22], by focusing on more recent ART regimens at the level of the third drug among patients receiving the same NRTI backbone (ZDV and 3TC). Importantly, the current study allowed for the evaluation of LPV/r individually, and not grouped with other RTV-boosted protease inhibitors (amprenavir, saquinavir, and indinavir) as done in the earlier analysis due to the relatively small frequency of LPV/r use during the earlier evaluation period (1996–2002).

Table 7. Longer-term clinical outcomes removing the 2-year censoring with follow-up through 1 July 2006 or cohort-specific database close date.

		Hazard ratio (95% CI)									
		Incident AIDS event			Death			Incident AIDS event or death			
Third drug	Observed	*N*	Crude	Adjusted[a]	*N*	Crude	Adjusted[a]	*N*	Crude	Adjusted[a]
EFV	3788	312	1	1	152	1	1	399	1	1
NVP	2151	143	0.91 (0.74–1.12)	1.24 (1.01–1.52)	74	1.02 (0.77–1.36)	1.29 (0.96–1.72)	185	0.92 (0.77–1.10)	1.22 (1.02–1.47)
LPV/r	2875	223	1.43 (1.20–1.72)	1.18 (0.97–1.43)	85	1.39 (1.05–1.85)	1.06 (0.79–1.43)	268	1.40 (1.19–1.64)	1.15 (0.97–1.37)
NFV	2217	193	1.10 (0.92–1.32)	1.05 (0.87–1.26)	83	0.95 (0.73–1.25)	0.93 (0.70–1.22)	231	1.03 (0.87–1.21)	0.98 (0.83–1.16)
ABC	2515	155	0.87 (0.72–1.07)	1.11 (0.91–1.37)	86	1.14 (0.87–1.50)	1.32 (1.00–1.75)	214	0.97 (0.82–1.16)	1.21 (1.02–1.45)

ABC, abacavir; CI, confidence interval; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NFV, nelfinavir; NVP, nevirapine.
[a]Multivariable Weibull regression models adjusted for age, sex, injection drug user (IDU), entry CD4, entry HIV RNA, and year starting ART and stratified on cohort.

In contrast with our earlier study, in which RTV-boosted protease inhibitors were associated with increased rates of both short-term virologic failure and clinical outcomes compared with EFV [22], LPV/r was associated only with 24-week virologic failure in the current study. The AIDS Clinical Trial Group (ACTG) 5142 study found a higher frequency of virologic failure among ARV-naïve patients treated with two NRTIs and LPV/r compared with those treated with two NRTIs and EFV [44]. Although EFV outperformed LPV/r in achieving plasma HIV RNA levels of less than 50 copies/ml and showed a trend for superiority at less than 200 copies/ml, increases in CD4 cell counts were greater for patients receiving LPV/r than for those receiving EFV in that randomized clinical trial. In the current study, similar 24-week CD4 responses were observed for patients treated with LPV/r and EFV (median CD4 cell count increase 110 vs. 100 cells/μl, respectively). These similar CD4 responses among ART-CC patients treated with LPV/r and EFV may have contributed to comparable hazards of clinical outcomes, despite a higher frequency of 24-week virologic failure in patients treated with LPV/r.

Another possible explanation for the apparent lack of difference in clinical endpoints between EFV and LPV/r may relate to varying resistance patterns emerging upon treatment failure between different initial ART regimens. Recently, it was shown that patients failing a first-line nonnucleoside reverse transcriptase inhibitor (NNRTI) containing regimen harboured viruses with higher numbers of IAS-USA drug resistance mutations and resistance to more antiretroviral drug classes when compared with patients initiating therapy with ritonavir-boosted protease inhibitor containing regimens [45]. Thus, EFV-based regimens, although more virologically effective as shown in this study, may result in more HIV resistance upon failure making it more difficult to generate potent successive ART regimens. In contrast, it might be easier to find effective salvage regimens for patients failing an initial boosted protease inhibitor regimen due to the lower number of drug resistance mutations observed. Furthermore, another study found the emergence of resistance to NNRTIs was associated with a greater risk of subsequent death than was the emergence of protease inhibitor resistance [46].

This updated analysis of the ART-CC found higher odds of 24-week virologic failure and hazards of clinical endpoints with NVP compared with EFV in analyses adjusted for covariates (Table 4). The findings regarding virologic failure are in contrast to the 2NN clinical trial [47], but consistent with other observational studies comparing these NNRTIs [18–20]. Although we are not able to determine the reasons for the observed inferior virologic and clinical outcomes associated with NVP use in the current study, it is possible that EFV outperformed NVP in a clinical practice setting. It is also possible that unmeasured confounders associated with NVP selection

in clinical practice, confounding by indication, contributed to the inferior outcomes for NVP in the current study. Notably, shifts in parameter estimates for both NVP (increased) and LPV/r (decreased) for clinical outcome measures were observed between unadjusted and adjusted analyses attributable to differential patient profiles (e.g., baseline CD4 cell count and plasma HIV viral load) among patients stratified by third drug receipt (Table 1).

The impact of confounding by indication in the selection of third drugs was more apparent in the evaluation of clinical outcomes than observed in analyses of short-term virologic failure; more marked shifts in parameter estimates between crude and adjusted analyses were observed for the clinical outcomes models (Tables 2 and 4). Prior studies have shown the importance of baseline CD4 cell counts at the time of ART initiation on subsequent clinical events [24,48]. Taking into account the drastically different median CD4 cell counts among patients initiating ART observed in this study (e.g., LPV/r 150 cells/μl, NVP 260 cells/μl, and ABC 251 cells/μl), it would be expected that multivariable models controlling for these differences would lead to shifts in estimates observed for crude analyses, as was seen. Although the impact of confounding by indication is observed across analyses in this study, it is notable that sensitivity analyses of adjusted models largely yielded consistent findings to those observed in primary analyses.

The findings of our study must be interpreted with regard to the study limitations. The potential for confounding is inherent to all observational studies. The impact of confounding by indication is demonstrated and discussed in this study, but it is possible that other unmeasured confounders not included in adjusted statistical models may have contributed to observed study findings. As with prior studies of the ART-CC, we have adjusted for factors associated with clinical events (e.g., baseline CD4 cell count), but cannot rule out the possibility of unmeasured confounding. For example, it is possible that a provider's selection of initial ART regimen was influenced by their expectations of a patient's adherence to their antiretroviral medications. Such prescribing bias may represent unmeasured confounding that contributed to the between-regimen differences in outcomes observed in this study. Furthermore, between-provider differences (e.g., experience) may also have contributed to differential outcomes. Finally, although the ART-CC has broad geographic representation from Europe and North America, findings of this study may not apply to other geographic settings.

In summary, among patients initiating ART from 2000 to 2005 in clinical practice settings with a ZDV and 3TC backbone, those receiving third drugs other than EFV (NVP, LPV/r, NFV, and ABC) were more likely to experience short-term (24-week) virologic failure. However, such differences were not as prominent in the evaluation of clinical events, which were more common (relative to EFV) in patients receiving NVP and ABC as the third drug of their initial ART regimen, but with little evidence of such differences for those receiving NFV and LPV/r. This study clearly demonstrates the impact of confounding by indication: such confounding, as well as the potential for unmeasured confounding should be taken into account when conducting, evaluating, and reviewing studies utilizing this methodology [6,49]. Because of the limited available evidence from randomized trials on the impact of initial ART regimens on rates of clinical events, findings from well designed observational cohort studies may serve a complementary role to findings from clinical trials in informing clinical practice.

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Author contributions: *Study conception and design*: Robert Hogg, Michael J. Mugavero, Margaret May, Michael S. Saag, Matthias Egger, Jonathan A.C. Sterne.

Data analysis: Margaret May, Ross Harris.

Acquisition of data and/or interpretation of data: Dominique Costagliola, Frank de Wolf, Amy Justice, Matthias Egger, Huldrych F. Günthard, Antonella D'Arminio Monforte, Jose M. Miró, Schlomo Staszewski, Andrew Phillips, Robert Hogg, Francois Dabis, Fiona Lampe, Gerd

Fatkenheuer, M. John Gill, Michael J. Mugavero, Michael S. Saag, Margaret May, Ross Harris, Jonathan A.C. Sterne.

Drafting the manuscript: Michael J. Mugavero, Margaret May, Michael S. Saag, Jonathan A. C. Sterne.

Critical revision of the manuscript for important intellectual content: Ross Harris, Dominique Costagliola, Matthias Egger, Andrew Phillips, Huldrych F. Günthard, Francois Dabis, Robert Hogg, Frank de Wolf, Gerd Fatkenheuer, M. John Gill, Amy Justice, Antonella D'Arminio Monforte, Fiona Lampe, Jose M. Miró, Schlomo Staszewski.

Final manuscript approval: Michael J. Mugavero, Margaret May, Ross Harris, Michael S. Saag, Dominique Costagliola, Matthias Egger, Andrew Phillips, Huldrych F. Günthard, Francois Dabis, Robert Hogg, Frank de Wolf, Gerd Fatkenheuer, M. John Gill, Amy Justice, Antonella D'Arminio Monforte, Fiona Lampe, Jose M. Miró, Schlomo Staszewski, Jonathan A.C. Sterne.

The antiretroviral therapy cohort collaboration (ART-CC) study group.

Steering committee: Jordi Casabona (PISCIS), Geneviève Chêne (Aquitaine), Dominique Costagliola (FHDH), François Dabis (Aquitaine), Antonella D'Arminio Monforte (ICONA), Julia del Amo (CoRIS-MD), Frank de Wolf (ATHENA), Matthias Egger (SHCS), Gerd Fätkenheuer (Koln/Bonn), John Gill (South Alberta Clinic), Jodie Guest (HAVACS), Robert Hogg (BCCfE-HIV), Amy Justice (VACS), Mari Kitahata (Washington), Fiona Lampe (Royal Free), Bruno Ledergerber (SHCS), Amanda Mocroft (EuroSIDA), Peter Reiss (ATHENA), Michael Saag (Alabama), Schlomo Staszewski (Frankfurt).

Coordinating team: Matthias Egger, Margaret May, Ross Harris, Jonathan Sterne (Principal Investigator).

Writing committee: Michael J. Mugavero, Division of Infectious Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, USA; Margaret May, Department of Social Medicine, University of Bristol, Bristol, UK; Ross Harris, Department of Social Medicine, University of Bristol, Bristol, UK; Michael S. Saag, Division of Infectious Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, USA; Dominique Costagliola, INSERM U720, UPMC Paris 06, Paris, France; Matthias Egger, Department of Social and Preventive Medicine, University of Bern, Bern, Switzerland; Andrew Phillips, Department of Primary Care and Population Sciences Royal Free and University College Medical School, London, UK; Huldrych F. Günthard, Divison of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland; Francois Dabis, INSERM U593, Université Victor Segalen Bordeaux, France; Robert Hogg, Division of Epidemiology and Population Health, British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada; Frank de Wolf, Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. The Netherlands; Gerd Fatkenheuer, Department of Internal Medicine, University of Cologne, Germany; M. John Gill, Division of Infectious Diseases, University of Calgary, Calgary, Canada; Amy Justice, Yale University School of Medicine, New Haven, CT, USA and VA Connecticut Healthcare System, West Haven, CT, USA; Antonella D'Arminio Monforte, Clinic of Infectious Diseases & Tropical Medicine, 'San Paolo' Hospital, University of Milan, Italy; Fiona Lampe, Department of Primary Care and Population Sciences Royal Free and University College Medical School, London, UK; Jose M. Miró, Hospital Clinic – IDIBAPS. University of Barcelona, Barcelona, Spain; Schlomo Staszewski, Zentrum der Inneren Medizin, J.W. Goethe Universität, Frankfurt, Germany; Jonathan A.C. Sterne, Department of Social Medicine, University of Bristol, Bristol, UK.

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Antiretroviral Therapy Cohort Collaboration (ART-CC) Contributing Cohorts

French Hospital Database on HIV (FHDH)

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.

DMI2 coordinating center: French Ministry of Health (A Pariente-Khayat, Valérie Salomon), Technical Hospitalisation Information Agency, ATIH (N Jacquemet, A Rivet).

Statistical analysis center: INSERM U720 (S Abgrall, D Costagliola, S Grabar, M Guiguet, I Kousignian, E Lanoy, L Lièvre, M Mary-Krause, V Potard, H Selinger-Leneman) ·

CISIH Paris area: CISIH de Bichat-Claude Bernard (Hôpital Bichat-Claude Bernard: E Bouvet, B Crickx, JL Ecobichon, C Leport, S Matheron, C Picard-Dahan, P Yeni), CISIH de Paris-Centre Ouest (Hôpital Européen Georges Pompidou: D Tisne-Dessus, L Weiss; GH Tarnier-Cochin: D Salmon, D Sicard; Hôpital Saint-Joseph: I Auperin, J Gilquin; Hôpital Necker adultes: L Roudière, JP Viard), CISIH de Paris-Sud (Hôpital Antoine Béclère: F Boué, R Fior; Hôpital de Bicêtre: JF Delfraissy, C Goujard; Hôpital Henri Mondor: C Jung, Ph Lesprit; Hôpital Paul Brousse), CISIH de Paris-Est (Hôpital Saint-Antoine: N Desplanque, JL Meynard, MC Meyohas, O Picard; Hôpital Tenon: J Cadranel, C Mayaud, G Pialoux), CISIH de Pitié-Salpétrière (GH Pitié Salpétrière: F Bricaire, S Herson, C Katlama, A Simon), CISIH de Saint-Louis (Hôpital Saint-Louis: JP Clauvel, JM Decazes, L Gerard, JM Molina; GH Lariboisière-Fernand Widal: M Diemer, P Sellier), CISIH 92 (Hôpital Ambroise Paré: H Berthé, C Dupont; Hôpital Louis Mourier: C Chandemerle, E Mortier; Hôpital Raymond Poincaré: P de Truchis), CISIH 93 (Hôpital Avicenne: M Bentata, P Honoré; Hôpital Jean Verdier: V Jeantils, S Tassi; Hôpital Delafontaine: D Mechali, B Taverne).

CISIH Outside Paris area: CISIH Auvergne-Loire (CHU de Clermont-Ferrand: F Gourdon, H Laurichesse; CHRU de Saint-Etienne: A Fresard, F Lucht); CISIH de Bourgogne-Franche Comté (CHRU de Besançon; CHRU de Dijon; CH de Belfort: P Eglinger, JP Faller; CHRU de Reims); CISIH de Caen (CHRU de Caen: C Bazin, R Verdon), CISIH de Grenoble (CHU de Grenoble), CISIH de Lyon (Hôpital de la Croix-Rousse: A Boibieux, D Peyramond; Hôpital Edouard Herriot: JM Livrozet, JL Touraine; Hôtel-Dieu: L Cotte, C Trepo), CISIH de Marseille (Hôpital de la Conception: I Ravaux, H Tissot-Dupont; Hôpital Nord: JP Delmont, J Moreau; Institut Paoli Calmettes: JA Gastaut; Hôpital Sainte-Marguerite: I Poizot-Martin, F Retornaz, J Soubeyrand; CHG d'Aix-En-Provence: T Allegre, PA Blanc; Centre pénitentiaire des Baumettes: A Galinier, JM Ruiz; CH d'Arles; 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), CISIH de Montpellier (CHU de Montpellier: J Reynes; CHG de Nîmes), CISIH de Nancy (Hôpital de Brabois: T May, C Rabaud), CISIH de Nantes (CHRU de Nantes: E Billaud, F Raffi), CISIH de Nice (Hôpital Archet 1: P Pugliese, C Pradier; CHG Antibes Juan les Pins), CISIH de Rennes (CHU de Rennes: C Arvieux, C Michelet), CISIH de Rouen (CHRU de Rouen: F Borsa-Lebas, F Caron), CISIH de Strasbourg (CHRU de Strasbourg: P Fraisse, JM Lang, D Rey; CH de Mulhouse), CISIH de Toulouse (CHU Purpan: E Arlet-Suau, L Cuzin, P Massip, MF Thiercelin Legrand; Hôpital la Grave; CHU Rangueil), CISIH de Tourcoing-Lille (CH Gustave Dron; CH de Tourcoing: Y Yasdanpanah), CISIH de Tours (CHRU de Tours; CHU Trousseau).

Overseas: CISIH de Guadeloupe (CHRU de Pointe-à-Pitre), CISIH de Guyane (CHG de Cayenne: R Pradinaud, M Sobesky), CISIH de Martinique (CHRU de Fort-de-France), CISIH de La Réunion (CHD Félix Guyon: C Gaud, M Contant).

Italian Cohort of Antiretroviral-Naive Patients (ICONA)

M. Italy: Ancona: M Montroni, G Scalise, MC Braschi, A Riva. Aviano (PN): U Tirelli, R Cinelli. Bari: G Pastore, N Ladisa, Bergamo: F Suter, C Arici.

Bologna: F Chiodo, V Colangeli, C Fiorini. Brescia: G Carosi, G Cristini, C Torti, C Minardi, D Bertelli. Busto Arsizio: T Quirino. Cagliari: PE Manconi, P Piano. Catanzaro: L Cosco, A Scerbo. Chieti: J Vecchiet, M D'Alessandro.

Como: D Santoro, L Pusterla. Cremona: G Carnevale, A Zoncada. Cuggiono: P Viganò, M Mena. Ferrara: F Ghinelli, L Sighinolfi. Firenze: F Leoncini, F Mazzotta, M Pozzi, S Lo Caputo. Foggia: G Angarano, B Grisorio, A Saracino, S Ferrara. Galatina (LE): P Grima, F Grima. Genova: G Pagano, G Cassola, A Alessandrini, R Piscopo. Grosseto: M Toti, M Trezzi. Latina: F Soscia, L Tacconi. Lecco: A Orani, P Perini. Lucca: A Scasso, A Vincenti. Macerata: F Chiodera, P Castelli. Mantova: A Scalzini, L Palvarini. Milano: M Moroni, A Lazzarin, G Rizzardini,

A d'Arminio Monforte, A Galli, S Merli, C Pastecchia, MC Moioli. Modena: R Esposito, C Mussini. Napoli: N Abrescia, A Chirianni, CM Izzo, M Piazza, M De Marco, R Viglietti, E Manzillo, S Nappa.

Palermo: A Colomba, V Abbadessa, T Prestileo, S Mancuso. Parma: C Ferrari, P Pizzaferri. Pavia: G Filice, L Minoli, R Bruno, S Novati. Perugia: F Baldelli, M Tinca. Pesaro: E Petrelli, A Cioppi. Piacenza: F Alberici, A Ruggieri. Pisa: F Menichetti, C Martinelli. Potenza: C De Stefano, A La Gala. Ravenna: G Ballardini, E Rizzo. Reggio Emilia: G Magnani, MA Ursitti.

Rimini: M Arlotti, P Ortolani. Roma: R Cauda, F Dianzani, G Ippolito, A Antinori, G Antonucci, M Ciardi, P Narciso, N Petrosillo, V Vullo, A De Luca, M Zaccarelli, R Acinapura, P De Longis, A Brandi, MP Trotta, P Noto, M Lichtner, MR Capobianchi, F Carletti, E Girardi, P Pezzotti, G Rezza.

Sassari: MS Mura, M Mannazzu. Torino: P Caramello, G Di Perri, M Sciandra, GC Orofino. Varese: PA Grossi, C Basilico. Verbania: A Poggio, G Bottari.

Venezia: E Raise, F Ebo. Vicenza: G Pellizzer, D Buonfrate. Taranto: F Resta, K Loso. London, UK: A Cozzi Lepri.

Swiss HIV Cohort Study (SHCS)

M. Battegay, E. Bernasconi, J. Böni, HC Bucher, Ph. Bürgisser, A. Calmy, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, M. Fischer, M. Flepp, A. Fontana, P. Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, CH-1011- Lausanne), H. Furrer (Chairman of the Clinical and Laboratory Committee), C. Fux, M. Gorgievski, H. Günthard (Chairman of the Scientific Board), H. Hirsch, B. Hirschel, I. Hösli, Ch. Kahlert, L. Kaiser, U. Karrer, C. Kind, Th. Klimkait, B. Ledergerber, G. Martinetti, B. Martinez, N. Müller, D. Nadal, M. Opravil, F. Paccaud, G. Pantaleo, A. Rauch, S. Regenass, M. Rickenbach (Head of Data Center), C. Rudin (Chairman of the Mother & Child Substudy), P. Schmid, D. Schultze, J. Schüpbach, R. Speck, P. Taffé, A. Telenti, A. Trkola, P. Vernazza, R. Weber, S. Yerly.

AIDS Therapy Evaluation project Netherlands (ATHENA)

L.A. Gras (bio-statistician), A.I. van Sighem (senior researcher), C. Smit (epidemiologist), F. de Wolf (director).

Treating physicians (∗Site coordinating physicians)

W. Bronsveld, M.E. Hillebrand-Haverkort, Medisch Centrum Alkmaar; J.M. Prins, J. Branger, J.K.M. Eeftinck Schattenkerk, J. Gisolf, M.H. Godfried, J.M.A. Lange, K.D. Lettinga, J.T.M. van der Meer, F.J.B. Nellen, T. van der Poll, P. Reiss, Th.A. Ruys, R. Steingrover, J.N. Vermeulen, S.M.E. Vrouenraets, M. van Vugt, F.W.M.N. Wit, Academisch Medisch Centrum bij de Universiteit van Amsterdam; T.W. Kuijpers, D. Pajkrt, H.J. Scherpbier, Emma Kinderziekenhuis- AMC, Amsterdam; A. van Eeden, St. Medisch Centrum Jan van Goyen, Amsterdam; K. Brinkman, G.E.L. van den Berk, W.L. Blok, P.H.J. Frissen, J.C. Roos, W.E.M. Schouten, Onze Lieve Vrouwe Gasthuis, Amsterdam; J.W. Mulder, E.C.M. van Gorp, J. Wagenaar, Slotervaart Ziekenhuis, Amsterdam; J. Veenstra, St. Lucas Andreas Ziekenhuis, Amsterdam; S.A. Danner, M.A. Van Agtmael, F.A.P. Claessen, R.M. Perenboom, A. Rijkeboer, M.G.A. van Vonderen, VU Medisch Centrum, Amsterdam; C. Richter, J. van der Berg, Ziekenhuis Rijnstate, Arnhem; R. Vriesendorp, F.J.F. Jeurissen, Medisch Centrum Haaglanden, locatie Westeinde, Den Haag; R.H. Kauffmann, K. Pogány, Haga Ziekenhuis, locatie Leyenburg, Den Haag; B. Bravenboer, Catharina Ziekenhuis, Eindhoven; C.H.H. ten Napel, G.J. Kootstra Medisch Spectrum Twente, Enschede; H.G. Sprenger, S. van Assen, J.T.M. van Leeuwen, Universitair Medisch Centrum, Groningen; R. Doedens, E.H. Scholvinck, Universitair Medisch Centrum, Beatrix kliniek, Groningen; R.W. ten Kate, R. Soetekouw, Kennemer Gasthuis, Haarlem; D. van Houte, M.B. Polée, Medisch Centrum Leeuwarden; F.P. Kroon, P.J. van den Broek, J.T. van Dissel, E.F. Schippers, Leids Universitair Medisch Centrum, Leiden; G. Schreij, S. van der Geest, S. Lowe, A. Verbon, Academisch Ziekenhuis Maastricht; P.P. Koopmans, R. Van Crevel, R. de Groot, M. Keuter, F. Post, A.J.A.M. van der Ven, A. Warris, Universitair Medisch Centrum St. Radboud, Nijmegen; M.E. van der Ende, I.C. Gyssens, M. van der Feltz, J.L Nouwen, B.J.A. Rijnders, T.E.M.S. de Vries, Erasmus Medisch Centrum, Rotterdam; G. Driessen, M. van der Flier, N.G. Hartwig, Erasmus Medisch Centrum, Sophia, Rotterdam; J.R. Juttman, M.E.E. van Kasteren, C. Van de Heul, St. Elisabeth Ziekenhuis, Tilburg; I.M. Hoepelman, M.M.E. Schneider, M.J.M. Bonten, J.C.C. Borleffs, P.M. Ellerbroek, C.A.J.J. Jaspers, T. Mudrikove, C.A.M. Schurink, E.H. Gisolf, Universitair Medisch Centrum Utrecht; S.P.M. Geelen, T.F.W. Wolfs, T. Faber, Wilhelmina Kinderziekenhuis-UMC, Utrecht; A.A. Tanis, Ziekenhuis Walcheren, Vlissingen; P.H.P. Groeneveld, Isala Klinieken, Zwolle; J.G. den Hollander, Medisch Centrum Rijnmond Zuid, locatie Clara, Rotterdam; A. J. Duits, K. Winkel, St. Elisabeth Hospitaal/Stichting Rode Kruis Bloedbank, Willemstad, Curaçao.

Virologists

N.K.T. Back, M.E.G. Bakker, B. Berkhout, S. Jurriaans, H.L. Zaaijer, Academisch Medisch Centrum,

Amsterdam; Th. Cuijpers, CLB Stichting Sanquin Bloedvoorziening, Amsterdam; P.J.G.M. Rietra, K.J. Roozendaal, Onze Lieve Vrouwe Gasthuis, Amsterdam; W. Pauw, A.P. van Zanten, P.H.M. Smits, Slotervaart Ziekenhuis, Amsterdam; B.M.E. von Blomberg, P. Savelkoul, A. Pettersson, VU Medisch Centrum, Amsterdam; C.M.A. Swanink, Ziekenhuis Rijnstate, Arnhem; P.F.H. Franck, A.S. Lampe, HAGA ziekenhuis, locatie Leyenburg, Den Haag; C.L. Jansen, Medisch Centrum Haaglanden, locatie Westeinde, Den Haag; R. Hendriks, Streeklaboratorium Twente, Enschede; C.A. Benne, J. Schirm Laboratorium voor Infectieziekten, Groningen; D. Veenendaal,, Streeklaboratorium Volksgezondheid Kennemerland, Haarlem; H. Storm, J. Weel, J.H. van Zeijl, Laboratorium voor de Volksgezondheid in Friesland, Leeuwarden; A.C.M. Kroes, H.C.J. Claas, Leids Universitair Medisch Centrum, Leiden; C.A.M.V.A. Bruggeman, V.J. Goossens, Academisch Ziekenhuis Maastricht; J.M.D. Galama, W.J.G. Melchers, Y.A.G. Poort, Universitair Medisch Centrum St. Radboud, Nijmegen; G.J.J. Doornum, M.G. Niesters, A.D.M.E. Osterhaus, M. Schutten, Erasmus Medisch Centrum, Rotterdam; A.G.M. Buiting, C.A.M. Swaans, St. Elisabeth Ziekenhuis, Tilburg; C.A.B. Boucher, R. Schuurman, Universitair Medisch Centrum Utrecht; E. Boel, A.F. Jansz, Catharina Ziekenhuis, Veldhoven.

Pharmacologists

A. Veldkamp, Medisch Centrum Alkmaar; J.H. Beijnen, A.D.R. Huitema, Slotervaart Ziekenhuis, Amsterdam; D.M. Burger, P.W.H. Hugen, Universitair Medisch Centrum St. Radboud, Nijmegen; H.J.M. van Kan, Academisch Medisch Centrum (UvA), Amsterdam.

The Multicenter Study Group on EuroSIDA

Argentina (M Losso), A Duran, Hospital JM Ramos Mejia, Buenos Aires. Austria (N Vetter) Pulmologisches Zentrum der Stadt Wien, Vienna. Belarus (I Karpov), A Vassilenko, Belarus State Medical University, Minsk. Belgium (N Clumeck) S De Wit, B Poll, Saint-Pierre Hospital, Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp Czech Republic (L Machala) H Rozsypal, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. Denmark (J Nielsen) J Lundgren, T Benfield, O Kirk, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, A-B E Hansen, P Skinhøj, Rigshospitalet, Copenhagen; C Pedersen, Odense University Hospital, Odense. Estonia (K Zilmer) West-Tallinn Central Hospital, Tallinn. France (C Katlama) Hôpital de la Pitié-Salpétière, Paris; J-P Viard, Hôpital Necker-Enfants Malades, Paris; P-M Girard, Hospital Saint-Antoine, Paris; T Saint-Marc, Hôpital Edouard Herriot, Lyon; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Archet, Nice; F Dabis, Unité INSERM, Bordeaux. Germany M Dietrich, C Manegold, Bernhard-Nocht-Institut for Tropical Medicine, Hamburg; J van Lunzen, H-J Stellbrink, Eppendorf Medizinische Kernklinik, Hamburg; S Staszewski, M Bickel, JW Goethe University Hospital, Frankfurt; F-D Goebel, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne; J Rockstroh, Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover. Greece (J Kosmidis) P Gargalianos, H Sambatakou, J Perdios, Athens General Hospital, Athens; G Panos, A Filandras, E Karabatsaki, 1st IKA Hospital, Athens. Hungary (D Banhegyi) Szent László Hospital, Budapest. Ireland (F Mulcahy) St. James's Hospital, Dublin. Israel (I Yust) D Turner, M Burke, Ichilov Hospital, Tel Aviv; S Pollack, G Hassoun, Rambam Medical Center, Haifa: Z Sthoeger, Kaplan Hospital, Rehovot; S Maayan, Hadassah University Hospital, Jerusalem. Italy (A Chiesi) Istituto Superiore di Sanità, Rome; R Esposito, R Borghi, Università Modena, Modena; C Arici, Ospedale Riuniti, Bergamo; R Pristera, Ospedale Generale Regionale, Bolzano; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; Vullo, M Lichtner, University di Roma la Sapienza, Rome; A Chirianni, E Montesarchio, Presidio Ospedaliero AD. Cotugno, Monaldi Hospital, Napoli; G Antonucci, F Iacomi, P Narciso, M Zaccarelli, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, R Finazzi, Ospedale San Raffaele, Milan; A D'Arminio Monforte, Osp. L. Sacco, Milan. Latvia (L Viksna) Infectology Centre of Latvia, Riga. Lithuania (S Chaplinskas) Lithuanian AIDS Centre, Vilnius. Luxembourg (R Hemmer), T Staub, Centre Hospitalier, Luxembourg. Netherlands (P Reiss) Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. Norway (J Bruun) A Maeland, V Ormaasen, Ullevål Hospital, Oslo. Poland (B Knysz) J Gasiorowski, Medical University, Wroclaw; A Horban, Centrum Diagnostyki i Terapii AIDS, Warsaw; D Prokopowicz, A Wiercinska-Drapalo, Medical University, Bialystok; A Boron-Kaczmarska, M Pynka, Medical Univesity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; H Trocha, Medical University, Gdansk. Portugal (F Antunes) E Valadas, Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Matez, Hospital Curry Cabral, Lisbon. Romania (D Duiculescu) Spitalul de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucarest; A Streinu-Cercel, Institute of Infectious Diseases, Bucarest. Russia E Vinogradova, St Petersburg AIDS Centre; A Rakhmanova, Medical Academy Botkin Hospital, St Petersburg. Serbia & Montenegro (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. Slovakia (M Mokráš) D Staneková, Dérer Hospital, Bratislava. Spain (J González-Lahoz) M Sánchez-Conde, T García-Benayas, L Martin-Carbonero, V Soriano, Hospital Carlos III, Madrid; B Clotet, A Jou, J Conejero, C Tural, Hospital Germans Trias i Pujol, Badalona; JM Gatell, JM Miró, Hospital Clinic i Provincial, Barcelona. Sweden (A Blaxhult) Karolinska University Hospital, Solna; A

Karlsson, Karolinska University Hospital, Stockholm; P Pehrson, Karolinska University Hospital, Huddinge. Switzerland (B Ledergerber) R Weber, University Hospital, Zürich; P Francioli, A Telenti, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, V Soravia-Dunand, Hospital Cantonal Universitaire de Geneve, Geneve; H Furrer, Inselspital Bern, Bern. Ukraine (E Kravchenko) N Chentsova, Kyiv Centre for AIDS, Kyiv. United Kingdom (S Barton) St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, D Mercey, Royal Free and University College London Medical School, London (University College Campus); A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); M Murphy, Medical College of Saint Bartholomew's Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; M Fisher, Royal Sussex County Hospital, Brighton; R Brettle, Western General Hospital, Edinburgh. Virology group C Loveday, B Clotet (Central Coordinators) plus ad hoc virologists from participating sites in the EuroSIDA Study. Steering Committee Francisco Antunes; Anders Blaxhult; Nathan Clumeck; Jose Gatell; Andrzej Horban; Anne Johnson; Christine Katlama; Bruno Ledergerber (chair); Clive Loveday; Andrew Phillips; Peter Reiss; Stefano Vella. Coordinating centre staff J Lundgren (project leader), I Gjørup, O Kirk, N Friis-Moeller, A Mocroft, A Cozzi-Lepri, W Bannister, D Mollerup, D Podlevkareva, C Holkmann Olsen, J Kjær.

Collaborations in HIV Outcomes Research US (CHORUS)

Stephen Raffanti, Douglas Dieterch, Amy Justice, Stephen Becker, Anthony Scarsella, Gregory Fusco, Bernard Most, Rukmini Balu, Rashida Rana, Robin Beckerman, Theodore Ising, Jennifer Fusco, Renae Irek, Bernadette Johnson, Ashwin Hirani, Edwin DeJesus, Gerald Pierone, Philip Lackey, Chip Irek, Alison Johnson, John Burdick, Saul Leon, Joseph Arch.

Frankfurt HIV Cohort, Germany

Schlomo Staszewski, Eilke B. Helm, Amina Carlebach, Axel Müller, Annette Haberl, Gabi Nisius, Tessa Lennemann, Christoph Stephan, Markus Bickel, Manfred Mösch, Peter Gute, Leo Locher, Thomas Lutz, Stephan Klauke, Gabi Knecht, Pavel Khaykin (Clinical Group); Hans W. Doerr, Martin Stürmer (Virology Group); Errol Babacan (Scientific Advisor and Data Management); Nils von Hentig (Pharmacology Group).

Aquitaine Cohort, France

Scientific committee: J. Beylot, G. Chêne, F. Dabis, M. Dupon, M. Longy-Boursier, JL. Pellegrin, JM. Ragnaud and R. Salamon. Methodological coordination: F. Dabis, G. Chêne, R. Thiébaut, C. Lewden and S. Lawson-Ayayi. Medical coordination: M. Dupon, P. Mercié, JF. Moreau, P. Morlat, JL. Pellegrin, JM. Ragnaud, N. Bernard, D. Lacoste, D. Malvy and D. Neau. Data Management and Analysis: MJ. Blaizeau, M. Decoin, S. Delveaux, C. Hannapier, S. Labarrère, V. Lavignolle-Aurillac, B. Uwamaliya-Nziyumvira, G. Palmer, D. Touchard, E. Balestre, A. Alioum, H. Jacqmin-Gadda and R. Thiébaut. Participating physicians: Bordeaux University Hospital: J. Beylot, P. Morlat, N. Bernard, M. Bonarek, F. Bonnet, B. Coadou, P. Gellie, D. Lacoste, C. Nouts; M. Dupon, F. Bocquentin, H. Dutronc, S. Lafarie; M. Longy-Boursier, P. Mercié, A. Aslan, D. Malvy, T. Pistonne, P. Thibaut, R. Vatan; JM.Ragnaud, D. Chambon, C. De La Taille, C. Cazorla, D. Neau, A. Ocho; JL.Pellegrin, JF. Viallard, O. Caubet, C. Cipriano E. Lazaro; P.Couzigou, L. Castera; H. Fleury, ME. Lafon, B. Masquelier, I. Pellegrin; D. Breilh; JF. Moreau, P. Blanco. Dax Hospital: P. Loste, L. Caunègre. Bayonne Hospital: F. Bonnal, S. Farbos, M. Ferrand. Libourne Hospital: J.Ceccaldi, S. Tchamgoué. Mont de Marsan Hospital: S. De Witte Villeneuve sur Lot Hospital: E. Buy

British Columbia Centre for Excellence in HIV (BCCfE-HIV), Canada

Linda Akagi, Eirikka Brandson, Eric Druyts, Kim Fernandes Nada Gataric, P Richard Harrigan, Marrianne Harris, Anna Hayden, Robert Hogg, Viviane Lima, Julio Montaner, David Moore, Evan Wood, Benita Yip, and Wen Zhang.

Royal Free Hospital Cohort, London UK

Clinical: S Bhagani, P Byrne, A Carroll, Z Cuthbertson, A Dunleavy, AM Geretti, B. Heelan, M Johnson, S Kinloch-de Loes, M Lipman, S Madge, N Marshall, D Nair, G Nebbia, B Prinz, L Swaden, M Tyrer, M Youle. Data management: C Chaloner, H Grabowska, J Holloway, J Puradiredja, D Ransom, R Tsintas. Biostatistics/ Epidemiology: W Bannister, L Bansi, A Cozzi-Lepri, Z Fox, E Harris, T Hill, F Lampe, R Lodwick, A Mocroft, A Phillips, J Reekie, C Sabin, C Smith. Laboratory: E Amoah, C. Booth, G Clewley, A Garcia Diaz, B Gregory, W Labbett, F Tahami, M Thomas.

South Alberta Cohort, Canada

M John Gill, Ron Read, Hartmut Krentz, Brenda Beckthold

Köln / Bonn Cohort, Germany

Gerd Faetkenheuer, Juergen Rockstroh

PISCIS, Catalonia and Balearic islands, Spain

Coordinators: J. Casabona (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain) y JM. Miró (Hospital Clínic-IDIBAPS, University of Barcelona, Spain).

Field coordinator: A. Alquézar (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain).

Steering committee: J. Casabona, A. Esteve, A.Alquézar (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain); JM. Miró (Hospital Clínic-Idibaps, Universitat de Barcelona); D. Podzamczer (Hospital de Bellvitge de Barcelona); J. Murillas (Hospital Son Dureta de Mallorca).

Scientific committee: A. Romero y C. Agustí (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain); JM Gatell, F. Agüero (Hospital Clínic-Idibaps, Universitat de Barcelona); C. Tural, B. Clotet (Hospital Universitari Germans Trias i Pujol, Universitat Autónoma de Barcelona); E. Ferrer (Hospital de Bellvitge de Barcelona); M. Riera (Hospital Son Dureta de Mallorca) F. Segura G. Navarro (Corporació Parc Taulí de Sabadell); L. Force (Hospital de Mataró); J. Vilaró (Hospital de Vic); A. Masabeu (Hospital de Palamós); I García (Hospital General d?Hospitalet); M.Guadarrama (Hospital Alt Penedès de Vilafranca).

Data Management and statistical analysis: A. Esteve, A. Montoliu y N. Ortega (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain), E. Lazzari (Hospital Clínic- Idibaps, Universitat de Barcelona).

Technical support: E. Puchol (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain); M. Sanchez (Hospital Clínic- Idibaps, Universitatde Barcelona).

Clinicians involved: JL Blanco, F. Garcia-Alcaide, E. Martinez, J. Mallolas, M. López-Dieguez, JF García-Goez, (Hospital Clínic- Idibaps, Universitat de Barcelona); G. Sirera, J. Romeu,, A. Jou. E. Negredo, C. Miranda, MC Capitan (Hospital Universitari Germans Trias i Pujol, Universitat Autónoma de Barcelona); M. Olmo, P. Barragan, M. Saumoy, F. Bolao, C. Cabellos, C. Peña. (Hospital Universitari de Bellvitge, L'Hospitalet, Barcelona), M. Sala, M. Cervantes, Mª Jose Amengual, M. Navarro y E Penelo (Corporació Sanitària Parc Taulí), P. Barrufet (Hospital de Mataró); M. Guadarrama (Hospital Alt Penedès de Vilafranca)".

1917 Clinic Cohort, University of Alabama, Birmingham US

Steering Committee: Michael S. Saag, Michael J. Mugavero, James H. Willig, James L. Raper, Jeroan J. Allison, Mirjam-Colette Kempf, Joseph E. Schumacher, Andrew O. Westfall

Faculty Investigators: Hui-Yi Lin, Maria Pisu, Linda Moneyham, David Vance, Laura Bachmann, Susan L Davies, Eta Berner, Edward Acosta, Jennifer King, Richard A. Kaslow

Research Support Team: Karen Savage, Christa Nevin, Frances B. Walton, Malcolm L. Marler, Sarah Lawrence, Barbara Files-Kennedy, D. Scott Batey

Informatics Team: Manoj A. Patil, Ujavala Patil, Mohit Varshney, Eugene Gibson, Alfredo Guzman, Dustin Rinehart

Veterans Aging Cohort Study (VACS), Connecticut, US

PI and Co-PI: AC Justice, DA Fiellin.

Scientific Officer (NIAAA): K Bryant

Participating VA Medical Centers: Atlanta (D. Rimland, C Jones-Taylor), Baltimore (KA Oursler, R Titanji), Bronx (S Brown, S Garrison), Houston (M Rodriguez-Barradas, N Masozera), Los Angeles (M Goetz, D Leaf), Manhattan-Brooklyn (M Simberkoff, D Blumenthal, J Leung), Pittsburgh (A Butt, E Hoffman), and Washington DC (C Gibert, R Peck)

Core Faculty: K Mattocks (Deputy Director), S Braithwaite, C Brandt, R Cook, J Conigliaro, K Crothers, J Chang, S Crystal, N Day, J Erdos, M Freiberg, M Kozal, M Gaziano, M Gerschenson, B Good, A Gordon, J Goulet, K Kraemer, J Lim, S Maisto, P Miller, P O'Connor, R Papas, C Rinaldo, M Roberts, J Samet

Staff: D Cohen, A Consorte, K Gordon, F Kidwai, F Levin, K McGinnis, M Rambo, J Rogers, M Skanderson, F Whitsett

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