Calendar Time Trends in the Incidence and Prevalence of Triple-Class Virologic Failure in Antiretroviral Drug-Experienced People With HIV in Europe

The Pursuing Later Treatment Options II (PLATO II) project team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Group**

Background: Despite the increasing success of antiretroviral therapy (ART), virologic failure of the 3 original classes [triple-class virologic failure, (TCVF)] still develops in a small minority of patients who started therapy in the triple combination ART era. Trends in the incidence and prevalence of TCVF over calendar time have not been fully characterised in recent years.

Methods: Calendar time trends in the incidence and prevalence of TCVF from 2000 to 2009 were assessed in patients who started ART from January 1, 1998, and were followed within the Collaboration of Observational HIV Epidemiological Research Europe (COHERE).

Results: Of 91,764 patients followed for a median (interquartile range) of 4.1 (2.0–7.1) years, 2722 (3.0%) developed TCVF. The incidence of TCVF increased from 3.9 per 1000 person-years of follow-up [95% confidence interval (CI): 3.7 to 4.1] in 2000 to 8.8 per 1000 person-years of follow-up (95% CI: 8.5 to 9.0) in 2005, but then declined to 5.8 per 1000 person-years of follow-up (95% CI: 5.6 to 6.1) by 2009. The prevalence of TCVF was 0.3% (95% CI: 0.27% to 0.42%) at December 31, 2000, and then increased to 2.4% (95% CI: 2.24% to 2.50%) by the end of 2005. However, since 2005, TCVF prevalence seems to have stabilized and has remained below 3%.

Conclusions: The prevalence of TCVF in people who started ART after 1998 has stabilized since around 2005, which most likely results from the decline in incidence of TCVF from this date. The introduction of improved regimens and better overall HIV care is likely to have contributed to these trends. Despite this progress, calendar trends should continue to be monitored in the long term.

Key Words: antiretroviral therapy, HIV, treatment experienced patients, triple class failure, virologic failure

(*J Acquir Immune Defic Syndr* 2012;59:294–299)

INTRODUCTION

The primary objective of antiretroviral therapy (ART) is to achieve and sustain viral load levels below the limit of detection of current assays (generally 50 copies/mL)[1,2] so that accumulation of resistance mutations can be prevented and immune reconstitution can occur. The success of ART means that suppression is established and maintained in most treated people.[3–6] However, virologic failure, which includes both failure to achieve viral suppression and confirmed viral rebounds, still develops in a small minority.[7–10] Virologic failure may be the consequence of the presence of resistance mutations or of insufficient drug levels due to reasons such as poor adherence, drug intolerance, insufficient drug dosages, or drug–drug interactions.[1,2] Thus, although virologic failure of a drug does not necessarily correspond to presence of resistance to that drug or mean that the drug is no longer an option for future use, it is clearly a negative outcome reflecting some problem with the course of treatment. Further, it is an outcome that can be reasonably completely ascertained due to regular viral load monitoring in all patients.

Recommended first-line regimens in resource-rich countries consist of 2 nucleos(t)ide reverse transcriptase inhibitors and either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (PI/r).[1,2,11] Despite the low

Received for publication June 21, 2011; accepted October 28, 2011.
The Pursuing Later Treatment Options II project is funded by Medical Research Council award G0700832. The Collaboration of Observational HIV Epidemiological Research Europe study group has received generic funding from the Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS), France; HIV Monitoring Foundation, the Netherlands; and the Augustinus Foundation, Denmark. Collaboration of Observational HIV Epidemiological Research Europe receives funding from the European Union Seventh Framework Programme (FP7/2007–2013) under EuroCoord grant agreement no: 260694. A list of the funders of the participating cohorts can be found on the Regional Coordinating Centre websites athttp://www.cphiv.dk/COHERE/tabid/295/Default.aspx and http://etudes.isped.u-bordeaux2.fr/cohere.
The funding sources had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the article, or in the decision to submit it for publication.
No member of the PLATO II analysis and writing committee has any financial or personal relationships with people or organizations that could inappropriately influence this work, although some members of the group have, at some stage in the past, received funding from a variety of pharmaceutical companies for research, travel grants, speaking engagements or consulting fees.
The members of the PLATO II Project Team for the COHERE group are listed in the Appendix I.
Correspondence to: Fumiyo Nakagawa, MSc, Research Department of Infection and Population Health, UCL, Royal Free Campus, Rowland Hill Street, London NW3 2PF, United Kingdom (e-mail: f.nakagawa@ucl.ac.uk).

rate with which people cumulatively experience virologic failure to each of these 3 original drug classes [triple-class virologic failure, (TCVF)] these rates are non-negligible and, furthermore, have not decreased over time.[12] Although patients in resource-rich countries with TCVF have access to newer classes of antiretrovirals (fusion and integrase inhibitors and CCR5 antagonists[13–16]) and partially or fully active drugs from within the original classes, eventual exhaustion of treatment options is a concern.

Previously, most patients with virologic failure were those who initiated ART with monotherapy or dualtherapy.[17,18] Trends in incidence and prevalence of TCVF over time have not been fully characterized in recent years, specifically in patients who started therapy in the triple combination ART era. The aim of this study was to describe calendar time trends in the incidence and prevalence of TCVF between 2000 and 2009 in routine clinical populations in Europe in patients who started ART from 1998 onwards.

METHODS

COHERE is a collaboration of most HIV observational cohorts in Europe.[19] Twenty-eight of these cohorts participate in the Pursuing Later Treatment Options II (PLATO II) project,[12,20] which is a follow-up study of the original PLATO collaboration reported in 2004.[17] This analysis (on data merged in 2010) was restricted to antiretroviral-naive patients 16 years or older who started ART from 1998 onwards. Patients were included only if they had at least 4 months (122 days) of follow-up.

Virologic failure of a drug was defined as 1 viral load measurement above 500 copies/mL despite 4 months of continuous drug use. TCVF was defined as virologic failure of at least 2 nucleos(t)ide reverse transcriptase inhibitors, 1 NNRTI and 1 PI/r. Triple-class exposure was defined as having experienced such drugs for at least 4 months with a viral load measurement available.

Patient follow-up was calculated from the date of starting ART until the date of TCVF or the last viral load measurement if they did not experience TCVF. The incidence of TCVF in a given year was the number of ART-experienced patients who developed TCVF within the year, divided by the total person-years of follow-up in that year. The prevalence was calculated at the end of each year, as the proportion of ART-experienced patients under follow-up in that year in whom TCVF had been attained at some point previously. To be included in any given calendar year, patients had to start ART before the end of that year and have at least 1 viral load measurement during that year. Patients were followed to the date of their last viral load measurement.

All *P* values are two-sided. Analyses were performed using SAS software, version 9.1 (SAS Inc, Cary, NC).

RESULTS

Data on 91,764 patients from 26 cohorts were included. Most (71%) were male and at ART initiation, median (interquartile range) age, CD4 cell count and viral load were 37 (31-44) years, 271 (134-430) cells/μL and 4.7 (3.7-5.2) $\log_{10}$copies/mL respectively. Patients were followed for a median of 4.1 (2.0-7.1) years from ART initiation, during which time 2722 (3.0%) developed TCVF. The total observed follow-up time was 428,391 person-years. The characteristics of patients under follow-up in each year (Table 1) remained fairly constant throughout the study period, except for initial regimen type where the proportion of patients starting with NNRTI or PI/r gradually increased over time, whereas the use of unboosted PI decreased. The prevalence of triple-class exposure increased steadily over time from 1.7% in 2000 to 17.0% in 2009. In addition to the number of people under follow-up in each year, we show the number for whom their last recorded viral load was in the year.

The incidence and prevalence of TCVF for each calendar year are shown in (Fig. 1). The incidence of TCVF initially increased from 3.9 per 1000 person-years of follow-up (95% CI: 3.7 to 4.1) in 2000 to 8.8 per 1000 person-years of follow-up (95% CI: 8.5 to 9.0) in 2005, which was when the incidence was at its peak. By 2009, it had decreased to 5.8 per 1000 person-years of follow-up (95% CI: 5.6 to 6.1). The prevalence of TCVF was 0.3% (95% CI: 0.27% to 0.42%) at the end of 2000, which then increased to 2.4% (95% CI: 2.24% to 2.50%) by the end of 2005. Since 2005, the prevalence of TCVF appears to have stabilized and has remained below 3%, with prevalence (95% CI) of 2.6% (2.51% to 2.77%), 2.8% (2.65% to 2.92%), 2.9% (2.73% to 2.99%), and 2.5% (2.33% to 2.66%), respectively, at the end of 2006, 2007, 2008, and 2009.

DISCUSSION

In this large study based on 91,764 patients seen in clinics around Europe who started therapy after January 1, 1998, we found that 2722 (3.0%) developed TCVF by the end of 2009. Although the cumulative proportion of people exposed to all 3 classes has gradually increased since 2000, the prevalence of TCVF has reached a somewhat stable level at below 3%. This seems to be due in part to the decrease in incidence of TCVF since 2005, which dropped to 5.8 per 1000 person-years of follow-up by the end of 2009. These trends are most likely attributable to the use of potent antiretrovirals, in particular, improved first-line regimens and use of fixed-dose combinations providing greater regimen stability in recent years.[21] Other reasons for the improvements made in the last 5 years could be a mixture of earlier diagnosis, better quality care, enhanced knowledge of adherence, and a better understanding of ART (eg, timing of initiation, toxicities, drug–drug interactions). There has also been increased use and improved interpretation of drug resistance testing, allowing physicians to choose appropriate regimens for antiretroviral-naive patients infected with drug-resistant strains and patients with detectable viral load.[22]

We have previously described factors associated with the rate of development of TCVF after ART initiation in this patient group.[12] The main factors identified to predict a higher rate of TCVF were younger age, risk category other than MSM, and a lower CD4 cell count and higher viral load at start of ART. Interestingly, in that analysis, we did not identify a lower risk of TCVF for patients starting ART in more recent calendar years. However, this discrepancy is thought to

TABLE 1. Patient Characteristics in the PLATO II Study at the End of Each Calendar Year

	2000	2001	2002	2003	2004
Number under follow-up	24966	31087	37047	42950	48289
Number with last ever viral load measurement (%)*	1245 (5)	1572 (5)	1919 (5)	2964 (7)	2743 (6)
Male (%)	18225 (73)	22456 (72)	26612 (72)	30584 (71)	34245 (71)
Risk group (%)					
MSM	9193 (37)	11394 (37)	13610 (37)	15874 (37)	18145 (38)
Heterosexual male	4247 (17)	5404 (17)	6619 (18)	7796 (18)	8780 (18)
Heterosexual female	4859 (19)	6340 (20)	7845 (21)	9461 (22)	10839 (22)
IDU	4369 (18)	4988 (16)	5457 (15)	5767 (14)	5859 (12)
Other	2298 (9)	2961 (10)	3516 (9)	4052 (9)	4666 (10)
Initial regimen (%)					
2 NRTI + 1 NNRTI	7074 (28)	9653 (31)	11928 (32)	14717 (34)	17346 (36)
2 NRTI + 1 PI/r	1716 (7)	2998 (10)	4666 (13)	6555 (15)	9025 (19)
2 NRTI + 1 unboosted PI	10773 (43)	11424 (37)	11696 (31)	11665 (27)	11365 (23)
3 NRTI	1137 (5)	2057 (6)	2955 (8)	3622 (9)	3758 (8)
Other from original 3 classes†	4266 (17)	4952 (16)	5797 (16)	6376 (15)	6757 (14)
Other including 'new' classes‡	0 (0)	3 (0)	5 (0)	15 (0)	38 (0)
At start of ART, median (IQR)					
Age, yrs	36 (31–42)	36 (31–42)	36 (31–43)	36 (31–43)	37 (31–43)
CD4 cell count, cells/μL§	279 (124–454)	269 (120–443)	262 (117–434)	260 (119–427)	260 (120–420)
Viral load, $\log_{10}$ copies/mL	4.7 (3.9–5.3)	4.7 (3.9–5.3)	4.7 (3.9–5.3)	4.7 (3.9–5.3)	4.7 (3.9–5.3)
Years on ART, median (IQR)	0.6 (0–1.4)	1.1 (0.1–2.2)	1.6 (0.3–2.9)	2.1 (0.5–3.7)	2.5 (0.6–4.4)
Prevalence of TCE, %	1.7	3.7	5.5	7.3	9.6

	2005	2006	2007	2008	2009
Number under follow-up	54104	58663	60578	59731	33640
Number with last ever viral load measurement (%)*	4191 (8)	6378 (11)	8160 (13)	—	—
Male (%)	38361 (71)	41611 (71)	43178 (71)	43012 (72)	25221 (75)
Risk group (%)					
MSM	20699 (38)	22954 (39)	24328 (40)	24624 (41)	14750 (44)
Heterosexual male	9804 (18)	10500 (18)	10673 (18)	10320 (17)	5455 (16)
Heterosexual female	12265 (23)	13297 (23)	13589 (22)	12920 (22)	6107 (18)
IDU	6126 (11)	6280 (11)	6240 (10)	5900 (10)	3756 (11)
Other	5210 (10)	5632 (10)	5748 (10)	5967 (10)	3572 (11)
Initial regimen (%)					
2 NRTI + 1 NNRTI	20040 (37)	22432 (38)	24175 (40)	24828 (42)	14598 (43)
2 NRTI + 1 PI/r	11750 (22)	14497 (25)	16207 (27)	16455 (27)	9336 (28)
2 NRTI + 1 unboosted PI	11255 (21)	10663 (18)	9736 (16)	8792 (15)	5031 (15)
3 NRTI	3836 (7)	3771 (7)	3388 (6)	3005 (5)	1151 (3)
Other from original 3 classes†	7112 (13)	7153 (12)	6861 (11)	6328 (11)	3261 (10)
Other including 'new' classes‡	111 (0)	147 (0)	211 (0)	323 (0)	263 (1)
At start of ART, median (IQR)					
Age, yrs	37 (31–43)	37 (31–44)	37 (32–44)	37 (32–44)	38 (32–44)
CD4 cell count, cells/μL§	261 (122–420)	264 (128–420)	270 (132–424)	274 (137–430)	284 (138–453)
Viral load, $\log_{10}$ copies/mL	4.7 (3.9–5.3)	4.7 (3.8–5.3)	4.7 (3.8–5.3)	4.7 (3.8–5.2)	4.7 (3.9–5.3)
Years on ART, median (IQR)	2.9 (0.8–5.1)	3.2 (0.9–5.7)	3.5 (1.1–6.4)	3.9 (1.4–7.1)	4.8 (2.0–8.0)
Prevalence of TCE, %	11.7	13.2	14.7	15.9	17.0

*The number of people who had their last viral load measurement taken in that calendar year, whether the reason for this was loss to follow-up or death.
†Any combination of NRTIs, NNRTIs, and PIs not listed above.
‡Any combination of drugs including those from the "new" classes (which are CCR5 antagonists, integrase inhibitors, and fusion inhibitors).
§461 of 91,764 (0.5%) patients from the whole study period did not have an initial CD4 cell count recorded.
MSM, men who have sex with men; IDU, injecting drug user; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PI/r, ritonavir-boosted PI; ART, antiretroviral therapy; IQR, interquartile range; TCE, triple-class exposure.

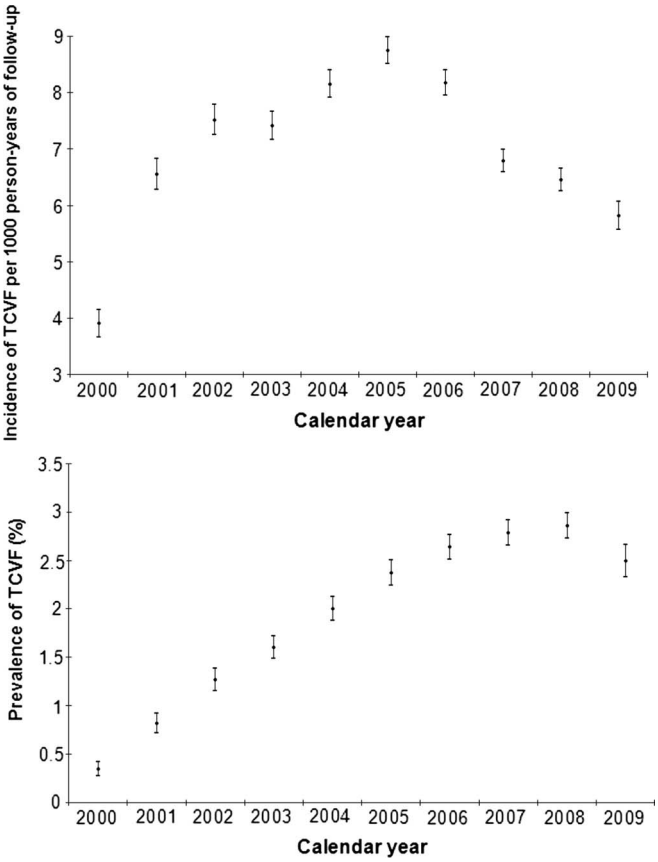

FIGURE 1. Incidence per 1000 person-years of follow-up of triple-class virologic failure (TCVF) over calendar time among patients who started ART since 1998 (Top). Prevalence of TCVF (%) over calendar time among patients who started ART since 1998 (Bottom). For both graphs, vertical lines represent 95% CIs, the two horizontal dashes on either side represent 95% confidence limits and the circles represent the point estimates.

be due to the different initial regimens used by the 2 studies and because our analysis includes 2 extra years of follow-up.

Estimates for both prevalence and incidence vary across previous studies due to differences in definition of TCVF, ART regimen, and study setting. Here, we adopted the same definition as in previous PLATO II analyses.[12] Alternative definitions include the following: viral load measurement above 1000 copies/μL required for virologic failure,[17,23–25] at least 6 months continuous use of a drug required for virologic failure,[3,26] and inclusion of patients who had been on monotherapy or dualtherapy before combination ART.[17,26] The results of our current analysis are largely applicable to current practice as our inclusion criteria require that patients started therapy after the time that triple combination ART was in widespread use. In the EuroSIDA study, the prevalence of TCVF rose from 0% in 2000 to 5.6% in 2005 in patients who started ART after 1999, and there was some evidence that the incidence of TCVF decreased with increasing calendar year of follow-up.[24] In the UK CHIC study, the proportion of patients who had experienced TCVF grew from 0.9% in 2000 to 3.9% in 2007, and using a mathematical model, it was predicted that this increase would continue until 2012, although the number with TCVF and without viral suppression was projected to remain stable.[26] In the Danish HIV Cohort,[25] the risk of TCVF decreased from 1997 to 2003, and the prevalence of TCVF stabilized after 2000 and did not rise above 7%.

Development of TCVF is associated with a greater likelihood of experiencing a CD4 cell count less than 200 cells/μL[3] and increased clinical progression.[17,23] Other implications of TCVF include potential for transmission of multidrug-resistant HIV strains,[27] higher costs to health systems owing to increased prices of newer drugs, and the need for more frequent contact with healthcare providers. As the duration on therapy increases for patients with TCVF, further virologic failure of the remaining available drugs in the original 3 classes, as well as the newer drug classes, may well continue. Although we have shown here that the prevalence of TCVF has not been increasing over the last 5 years, it is important to continue monitoring these trends over extended periods of time.

It should be noted that there are some limitations to this study. Patients were only included if they started ART post-1998, which makes our cohort somewhat artificial in that clinic populations will also include some people who started ART before 1998, often with mononucleoside or dual-nucleoside regimens. Since there is inevitably a time lag between initiation of ART and the first time that TCVF can occur (because TCVF nearly always requires at least two separate regimen failures and at least one switch in regimen), the restriction to patients starting ART after 1998 is the likely explanation for the observed increase in incidence from 2000 to 2005. Another limitation as mentioned by the PLATO II project team[12] is that patients included in COHERE may not be representative of the population of European patients on ART because they are likely to have increased access to care and treatment due to cohort participation in various research studies. Further, it should be noted that TCVF does not in all cases mean that resistance to the 3 classes is present; TCVF will also occur as a result of poor adherence without resistance and without complete and regular genotypic data and data on adherence, it is difficult to establish the cause of TCVF. On the other hand, some people who do not experience virologic failure of a drug by our definition may nevertheless have developed resistance. This may occur, for example, if drugs were switched before the viral load had reached 500 copies/μL. We are separately investigating to what extent we can document the presence of triple class resistance in people with TCVF.

In summary, the prevalence of TCVF among people starting ART since 1998 has stabilized since around 2005 to a relatively low level of below 3%, which most likely results from the decline in incidence of TCVF from 2005. The introduction of improved regimens and better HIV care is likely to have contributed to these trends. Despite the improvements seen in the last decade, the serious implications of TCVF call for further long-term research. New antiretroviral drugs may be necessary to sustain current low levels of incidence and prevalence.

REFERENCES

1. BG Gazzard on behalf of the BHIVA Treatment Guidelines Writing Group. British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. *HIV Med*. 2008;9: 563–608.
2. Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection. 2010 recommendations of the international AIDS society-USA panel. *JAMA*. 2010;304:321–333.
3. Sabin CA, Hill T, Lampe F, et al. Treatment exhaustion of highly active antiretroviral therapy (HAART) among individuals infected with HIV in the United Kingdom: multicentre cohort study. *BMJ*. 2005;330:695.
4. Lampe FC, Smith CJ, Madge S, et al. Success of clinical care for human immunodeficiency virus infection according to demographic group among sexually infected patients in a routine clinic population, 1999 to 2004. *Arch Intern Med*. 2007;167:692–700.
5. Ledergerber B, Egger M, Opravil M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. *Lancet*. 1999;353:863–868.
6. Chaix ML, Descamps D, Wirden M, et al. Stable frequency of HIV-1 transmitted drug resistance in patients at the time of primary infection over 1996-2006 in France. *AIDS*. 2009;23:717–724.
7. Mocroft A, Ruiz L, Reiss P, et al. Virological rebound after suppression on highly active antiretroviral therapy. *AIDS*. 2003;17:1741–1751.
8. Martin-Carbonero L, Gil P, Garcia-Benayas T, et al. Rate of virologic failure and selection of drug resistance mutations using different triple nucleos(t)ide analogue combinations in HIV-infected patients. *AIDS Res Hum Retroviruses*. 2006;22:1231–1235.
9. Deeks SG, Gange SJ, Kitahata MM, et al. Trends in multidrug treatment failure and subsequent mortality among antiretroviral therapy-experienced patients with HIV infection in North America. *Clin Infect Dis*. 2009;49: 1582–1590.
10. Geretti AM, Smith C, Haberl A, et al. Determinants of virological failure after successful viral load suppression in first-line highly active antiretroviral therapy. *Antivir Ther*. 2008;13:927–936.
11. Clumeck N, Pozniak A, Raffi F, et al. and the EACS Executive Committee. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of HIV-infected adults. *HIV Med*. 2008;9:65–71.
12. The Pursuing Later Treatment Options II (PLATO II) Project Team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE). Triple-class virologic failure in HIV-infected patients undergoing antiretroviral therapy for up to 10 years. *Arch Intern Med*. 2010;170:410–419.
13. Gatell JM, Katlama C, Grinsztejn B, et al. Long-term efficacy and safety of the HIV integrase inhibitor raltegravir in patients with limited treatment options in a phase II study. *J Acquir Immune Defic Syndr*. 2010;53: 456–463.
14. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med*. 2003;348:2186–2195.
15. Dorr P, Westby M, Dobbs S, et al. Maraviroc (UK-427,857), a potent, orally bioavailable, and selective small-molecule inhibitor of chemokine receptor CCR5 with broad-spectrum anti-human immunodeficiency virus type 1 activity. *Antimicrob Agents Chemother*. 2005;49:4721–4732.
16. Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Department of Health and Human Services. January 10, 2011:1–166. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed October 14, 2011.
17. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet*. 2004;364:51–62.
18. Costagliola D, Potard V, Duvivier C, et al. Impact of newly available drugs on clinical progression in patients with virological failure after exposure to three classes of antiretrovirals. *Antivir Ther*. 2005;10: 563–573.
19. The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group. Response to combination antiretroviral therapy: variation by age. *AIDS*. 2008;22:1463–1473.
20. The Pursuing Later Treatment Options II (PLATO II) Project Team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE). Risk of triple-class virological failure in children with HIV: a retrospective cohort study. *Lancet*. 2011;377:1580–1587.
21. Lodwick RK, Smith CJ, Youle M, et al. Stability of antiretroviral regimens in patients with viral suppression. *AIDS*. 2008;22:1039–1046.
22. Hirsch MS, Günthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an international AIDS society-USA Panel. *Clin Infect Dis*. 2008;47: 266–285.
23. Mocroft A, Ledergerber B, Viard JP, et al. Time to virological failure of 3 classes of antiretrovirals after initiation of highly active antiretroviral therapy: Results from the EuroSIDA study group. *J Infect Dis*. 2004; 190:1947–1956.
24. Mocroft A, Horban A, Clotet B, et al. Regional differences in the risk of triple class failure in European patients starting combination antiretroviral therapy after 1 January 1999. *HIV Med*. 2008;9:41–46.
25. Lohse N, Obel N, Kronborg G, et al. Declining risk of triple-class antiretroviral drug failure in Danish HIV-infected individuals. *AIDS*. 2005; 19:815–822.
26. Bansi L, Sabin C, Delpech V, et al. Trends over calendar time in antiretroviral treatment success and failure in HIV clinic populations. *HIV Med*. 2010;11:432–438.
27. Brenner BG, Routy JP, Petrella M, et al. Persistence and fitness of multidrug-resistant human immunodeficiency virus type 1 acquired in primary infection. *J Virol*. 2002;76:1753–1761.

APPENDIX 1: The Members of the PLATO II Project Team For the COHERE Group

Analysis and Writing Committee

Fumiyo Nakagawa, Rebecca Lodwick, Dominique Costagliola, Ard van Sighem, Carlo Torti, Daniel Podzamczer, Amanda Mocroft, Bruno Ledergerber, Maria Dorrucci, Alessandro Cozzi-Lepri, Klaus Jansen, Bernard Masquelier, Federico García, Stephane De Wit, Christoph Stephan, Niels Obel, Gerd Fätkenheuer, Antonella Castagna, Helen Sambatakou, Cristina Mussini, Jade Ghosn, Robert Zangerle, Xavier Duval, Laurence Meyer, Santiago Perez-Hoyos, Céline Fabre Colin, Jesper Kjaer, Genevieve Chene, Jesper Grarup, Andrew Phillips.

PLATO II Project Team

Antonella Castagna (San Raffaele), Dominique Costagliola (ANRS CO4 FHDH), Alessandro Cozzi-Lepri (ICONA), Andrea De Luca (ICONA), Stephane De Wit (St Pierre Cohort), Frank de Wolf (ATHENA), Maria Dorrucci (CASCADE), Xavier Duval (ANRS CO8 COPILOTE), Gerd Fätkenheuer (Cologne Bonn), Federico García (CoRIS), Jade Ghosn (ANRS CO6 PRIMO), Huldrych Günthard (SHCS), Klaus Jansen (KOMPNET), Louise Jørgensen (Danish HIV Cohort), Ali Judd (CHIPS), Bruno Ledergerber (SHCS), Sergio Lo Caputo (Italian Master Cohort), Rebecca Lodwick (statistician), Bernard Masquelier (ANRS CO3 AQUITAINE), Laurence Meyer (ANRS CO2 SEROCO), Amanda Mocroft (EuroSIDA), Cristina Mussini (Modena Cohort), Antoni Noguera-Julian (CORISPE-cat), Niels Obel (Danish HIV Cohort), Dimitrios Paraskevis (AMACS), Roger Paredes (EuroSIDA), Santiago Pérez-Hoyos (GEMES-Haemo), Andrew Phillips (PLATO II project leader; UK HIV Drug Resistance Database / UK CHIC), Deenan Pillay (UK HIV Drug Resistance Database / UK CHIC), Daniel Podzamczer (PISCIS), José T. Ramos (Madrid Cohort), Christoph Stephan (Frankfurt HIV Cohort), Pat A. Tookey (NSHPC), Carlo Torti (Italian Master Cohort), Giota Touloumi (AMACS), Ard van Sighem (ATHENA), Josiane Warsawski (ANRS CO1 EPF), Robert Zangerle (AHIVCOS).

COHERE Steering Committee

Contributing cohorts: Robert Zangerle (AHIVCOS), Giota Touloumi (AMACS), Josiane Warszawski (ANRS CO1 EPF/ANRS CO11

OBSERVATOIRE EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE), Murielle Mary Krause (ANRS CO4 FHDH), Jade Ghosn (ANRS CO6 PRIMO), Catherine Leport (ANRS CO8 COPILOTE), Frank de Wolf (ATHENA), Peter Reiss (ATHENA), Maria Prins (CASCADE), Heiner Bücher (CASCADE), Caroline Sabin (CHIC), Diana Gibb (CHIPS), Gerd Fätkenheuer (Cologne Bonn), Julia Del Amo (CoRIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Christoph Stephan (Frankfurt), Santiago Pérez-Hoyos (GEMES-Haemo), Antoni Noguera-Julian (NENEXP and CORISPE-cat), Andrea Antinori (ICC), Antonella d'Arminio Monforte (ICONA), Norbert Brockmeyer (KOMPNET), José Ramos (Madrid Cohort), Manuel Battegay (MoCHIV), Andri Rauch (SHCS), Cristina Mussini (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M. Miró (PISCIS), Antonella Castagna (San Raffaele), Stephane de Wit (St. Pierre Cohort), Tessa Goetghebuer (St Pierre Paediatric Cohort), Carlo Torti (Italian Master Cohort), Ramon Teira (VACH), Myriam Garrido (VACH). European AIDS Treatment Group: David Haerry.

Executive committee: Ian Weller (Chair, University College London), Jordi Casabona (PISCIS), Dominique Costagliola (FHDH), Antonella d'Arminio-Monforte (ICONA), Manuel Battegay (MoCHIV), Maria Prins (CASCADE), Frank de Wolf (ATHENA), Jesper Grarup (Head of Copenhagen Regional Coordinating Centre), Genevieve Chene (Head, Bordeaux Regional Co-ordinating Centre).

Regional co-ordinating centres: Bordeaux RCC cohorts: Céline Colin, Christine Schwimmer, Guillaume Touzeau; Copenhagen RCC cohorts: Jesper Kjaer, Maria Paulsen.

Project leaders and statistical analysis: Julia Bohlius, Vincent Bouteloup, Heiner Bucher, Alessandro Cozzi-Lepri, François Dabis, Antonella d'Arminio Monforte, Frank de Wolf, Maria Dorrucci, Matthias Egger, Frederik Engsig, Hansjakob Furrer, Ole Kirk, Olivier Lambotte, Charlotte Lewden, Rebecca Lodwick, Sophie Matheron, Laurence Meyer, Jose Miro, Amanda Mocroft, Niels Obel, Roger Paredes, Andrew Phillips, Massimo Puoti, Joanne Reekie, Caroline Sabin, Alexandra Scherrer, Colette Smit, Jonathan Sterne, Rodolphe Thiebaut, Claire Thorne, Carlo Torti, Viktor von Wyl, Linda Wittkop, Jim Young.