Trends in virological and clinical outcomes in individuals with HIV-1 infection and virological failure of drugs from three antiretroviral drug classes: a cohort study

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Summary

Background Limited treatment options have been available for people with HIV who have had virological failure of the three original classes of HIV antiretroviral drugs—so-called triple-class virological failure (TCVF). However, introduction of new drugs and drug classes might have improved outcomes. We aimed to assess trends in virological and clinical outcomes for individuals with TCVF in 2000–09.

Methods In our cohort study, we analysed data for adults starting antiretroviral therapy from 1998 in cohorts participating in the PLATO II project, which is part of COHERE, a collaboration of European cohorts. TCVF was defined as virological failure to at least two nucleoside reverse transcriptase inhibitors, one non-nucleoside reverse-transcriptase inhibitor, and one ritonavir-boosted protease inhibitor, with virological failure of a drug defined as one viral-load measurement of greater than 500 copies per mL after at least 4 months of continuous use. We used multivariable generalised estimating equation logistic models and Poisson regression models to study trends in virological suppression and incidence of AIDS or death after TCVF. We adjusted for sex, transmission group, age, AIDS status, CD4 cell count, plasma viral loads at TCVF, achievement of virological response (<50 copies per mL), and number of drug failures before TCVF.

Findings 28 of 33 cohorts in COHERE contributed data to the PLATO II project, of which four had no participants eligible for inclusion in this study. 2476 (3%) of 91764 participants from the remaining 24 cohorts had TCVF and at least one viral load measurement in 2000–09. The proportion of patients with virological response after TCVF increased from 19·5% in 2000 to 57·9% in 2009 (adjusted p<0·0001). Incidence of AIDS decreased from 7·7 per 100 person-years in 2000–02 to 2·3 in 2008 and 1·2 in 2009 (adjusted p<0·0001). Mortality decreased from 4·0 per 100 person-years between 2000 and 2002 to 1·9 in 2007 and 1·4 in 2008 (unadjusted p=0·023), but the trend was not significant after adjustment (p=0·22).

Interpretation A substantial improvement in viral load suppression and accompanying decrease in the rates of AIDS in people after extensive failure to drugs from the three original antiretroviral classes during 2000–09 was probably mainly driven by availability of newer drugs with better tolerability and ease of use and small cross-resistance profiles, suggesting the public health benefit of the introduction of new drugs.

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Introduction

Investigations of immunological and clinical outcomes for patients after virological failure to all three original antiretroviral classes[1–4] have shown the effects of widespread antiviral resistance on prognosis,[4] the importance of maintaining CD4 cell counts of 200 cells per μL or higher,[2] and the need to continue antiretroviral therapy even when viral load is not controlled.[2,5,6] Improved clinical outcomes were reported in individuals with triple-class virological failure (TCVF) dependent on the number of new drugs started, probably owing to more favourable resistance profiles.[1,3] However, most people in these early studies started antiretroviral therapy with only one or two drugs, which conferred a high risk of resistance to nucleoside reverse-transcriptase inhibitors (NRTIs). Now, all patients starting antiretroviral therapy are recommended to do so with potent combination regimens of three or more drugs.

Although current regimens have led to sustained viral suppression in an increasing proportion of people,[7] some individuals do still have virological failure to drugs from the three original classes. As part of the Pursuing Later Treatment Option II (PLATO II) project, we reported a low rate of TCVF (3·4% by 5 years)[8] in participants in the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) database who started antiretroviral therapy including a non-NTRI (NNRTI) or a ritonavir-boosted protease inhibitor from 1998. Virological and clinical outcomes for people who had TCVF, and in particular how these outcomes changed with time, have not been widely studied.[9] We aimed to assess trends in virological and clinical outcomes over the past decade in people with TCVF.

Methods

Study design and procedures

We analysed data obtained from participants in the PLATO II project from the COHERE database[10] (a collaboration of 33 observational cohort studies of HIV in Europe). The PLATO II project contains data from 28 participating cohorts, which submit information in a standardised format[11] to one of two regional coordinating centres, where error checks are done before data are merged into cohort data and added to COHERE. Duplicate records from people in more than one cohort were removed. We analysed data added to the COHERE database as part of the PLATO II project in 2010 for previously untreated participants aged 16 or older who started antiretroviral therapy from 1998.

We defined virological failure of a drug as plasma HIV-1 RNA loads of more than 500 copies per mL despite 4 months or more of continuous use, irrespective of concomitant use of other drugs in this timeframe. Virological failure of drugs from all three classes was defined as virological failure of two NRTIs, one NNRTI, and one ritonavir-boosted protease inhibitor. We refer to this combination as TCVF, although other drugs within these classes might retain antiviral activity (eg, newer protease inhibitors, such as darunavir, and NNRTIs, such as etravirine, which were designed to be not cross-resistant to existing drugs in the class). We included patients with TCVF from 2000 onwards in the present analysis if they had at least one plasma viral-load measurement after TCVF between 2000 and 2009.

Statistical analysis

We calculated the proportion of people with virological response (<50 copies per mL) after TCVF for the year 2000–09, using values recorded closest to July 1 for each patient. We assessed trends in viral suppression adjusted for characteristics of people at the time of TCVF that could affect the probability of virological response by fitting a multivariable logistic regression model. We adjusted for sex, transmission group, age, presence of AIDS, CD4 cell count, plasma viral load at TCVF, previous achievement of virological response, and number of drug failures before TCVF. For the adjusted analysis of virological response, we included all plasma HIV RNA

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Individuals in follow-up	41	192	368	594	848	1138	1415	1561	1609	795
Age (years)	37 (32–40)	39 (33–44)	39 (34–44)	39 (35–44)	40 (35–45)	41 (36–46)	41 (36–47)	42 (37–47)	43 (38–48)	43 (38–49)
Year of TCVF development	2000 (2000–2000)	2001 (2000–2001)	2001 (2001–2002)	2002 (2001–2003)	2003 (2002–2004)	2004 (2002–2004)	2004 (2003–2005)	2005 (2003–2006)	2005 (2004–2007)	2006 (2004–2007)
Years since start of antiretroviral therapy	2 (1–2)	3 (2–3)	3 (3–4)	4 (3–5)	5 (4–6)	6 (4–7)	7 (5–8)	8 (6–9)	8 (6–10)	9 (7–11)
Group										
Men who have sex with men	18 (44%)	79 (41%)	119 (32%)	188 (32%)	251 (30%)	356 (31%)	419 (30%)	466 (30%)	482 (30%)	233 (29%)
Heterosexual men	4 (10%)	24 (13%)	70 (19%)	121 (20%)	186 (22%)	241 (21%)	307 (22%)	331 (21%)	337 (21%)	165 (21%)
Heterosexual women	9 (22%)	40 (21%)	73 (20%)	116 (20%)	180 (21%)	257 (23%)	343 (24%)	407 (26%)	422 (26%)	180 (23%)
Injecting-drug users	5 (12%)	30 (16%)	67 (18%)	101 (17%)	135 (16%)	166 (15%)	201 (14%)	204 (13%)	208 (13%)	126 (16%)
Other or unknown	5 (12%)	19 (10%)	39 (11%)	68 (11%)	96 (11%)	118 (10%)	145 (10%)	153 (10%)	160 (10%)	91 (11%)
Individuals with AIDS before TCVF	19 (46%)	88 (46%)	156 (42%)	254 (43%)	352 (42%)	465 (41%)	540 (38%)	599 (38%)	605 (38%)	338 (43%)
Antiretroviral therapy received										
At least one PI/r	32 (78%)	145 (76%)	264 (72%)	444 (75%)	686 (81%)	913 (80%)	1182 (84%)	1320 (85%)	1322 (82%)	647 (81%)
At least one NNRTI	20 (49%)	65 (34%)	91 (25%)	131 (22%)	157 (19%)	181 (16%)	192 (14%)	205 (13%)	219 (14%)	130 (16%)
At least two NRTIs	33 (80%)	160 (83%)	301 (82%)	485 (82%)	676 (80%)	920 (81%)	1166 (82%)	1286 (82%)	1295 (81%)	634 (80%)
At least four drugs	21 (51%)	60 (31%)	94 (26%)	156 (26%)	206 (24%)	260 (23%)	315 (22%)	350 (22%)	345 (21%)	163 (21%)
At least one new drug*	0	4 (2%)	8 (2%)	40 (7%)	218 (26%)	408 (36%)	624 (44%)	661 (42%)	789 (49%)	415 (52%)
At least two new drugs*	0	0	1 (<1%)	3 (<1%)	18 (2%)	30 (3%)	46 (3%)	67 (4%)	133 (8%)	86 (11%)
Darunavir	0	0	0	0	0	5 (<1%)	38 (3%)	92 (6%)	182 (11%)	117 (15%)
Enfuvirtide	0	4 (2%)	5 (1%)	11 (2%)	43 (5%)	55 (5%)	70 (5%)	62 (4%)	31 (2%)	13 (2%)
Etravirine	0	0	0	0	1 (<1%)	1 (<1%)	1 (<1%)	11 (<1%)	43 (3%)	35 (4%)
Maraviroc	0	0	0	0	0	1 (<1%)	3 (<1%)	3 (<1%)	15 (<1%)	16 (2%)
Raltegravir	0	0	0	0	0	1 (<1%)	3 (<1%)	32 (2%)	151 (9%)	92 (12%)
Tipranavir	0	0	1 (<1%)	11 (2%)	13 (2%)	31 (3%)	38 (3%)	25 (2%)	15 (<1%)	2 (<1%)
Atazanavir	0	0	3 (<1%)	21 (4%)	179 (21%)	345 (30%)	518 (37%)	519 (33%)	528 (33%)	253 (32%)
None	3 (7%)	9 (5%)	19 (5%)	33 (6%)	42 (5%)	68 (6%)	65 (5%)	72 (5%)	71 (4%)	28 (4%)

Data are n (%) or median (IQR). TCVF=triple-class virological failure. NNRTI=non-nucleoside reverse transcriptase inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. PI/r=ritonavir-boosted protease inhibitor. *Darunavir, enfuvirtide, etravirine, maraviroc, raltegravir, tipranavir, or atazanavir.

Table 1: **Characteristics of individuals with TCVF in follow-up in the specified year**

measurements obtained for all people after TCVF. Because viral load was a repeated measurement, we used generalised estimating equation models with an exchangeable covariance matrix. Notably, because our objective was mainly descriptive, we did not attempt to further adjust for time-dependent variables such as access to new drugs or improvements in adherence.

We estimated trends in incidence per person-year of new AIDS-defining events (first new diagnosis of AIDS since diagnosis of TCVF, which might or might not be the first AIDS disease) between 2000 and 2009 and in death rates between 2000 and 2008. We used the European definition of AIDS,[12] corresponding to the clinical part of the US Centers for Disease Control and Prevention definition. Person-years of follow-up were censored 6 months after the last measurement of CD4 cell count or viral load, the end of the year used in the analysis, or on Dec 31, 2009, whichever occurred first. For incidence of AIDS, follow-up was censored at death. For death, follow-up was censored on Jan 1, 2009, because otherwise records might have been incomplete for some cohorts. Thus, we only report death rates to 2008. We used multivariable Poisson regression models to assess the trends in the risk of AIDS or death in people with TCVF, with the same covariates as we used for the analysis of viral load. Patient-years with missing CD4 counts were excluded from the analyses.

All tests of significance were two-sided, and $p<0·05$ was regarded as significant. Analyses were done with SAS software version 9.1 and Stata software version 11.0.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Dominique Costagliola, Rebecca Lodwick, Bruno Ledergerber, and Andrew Phillips had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Two of 28 cohorts in the PLATO II project were paediatric cohorts not included in this analysis. We also excluded two cohorts that had few data for patients aged 16 years or older starting combined antiretroviral therapy and no data for patients with TCVF. By 2010, the PLATO II project contained data for 91764 individuals, of whom 2722 (3%) had TCVF. Overall, 2709 (>99%) of 2722 people with TCVF in included cohorts had failure in 2000–09, and 2476 (91%) had at least one viral-load measurement after TCVF in this time. 1665 (67%) patients were men, 703 (28%) were men who have sex with men, 528 (21%) were heterosexual men, 637 (26%) were heterosexual women, and 354 (14%) were injecting drug users. At time of TCVF, the median age was 39·5 years (IQR 34·4–45·2), median viral load was 4·0 $\log_{10}$ copies per mL (3·2–4·8), and median CD4 cell count was 270 cells per µL (147–430). 936 (38%) of 2476 people had had an AIDS defining event.

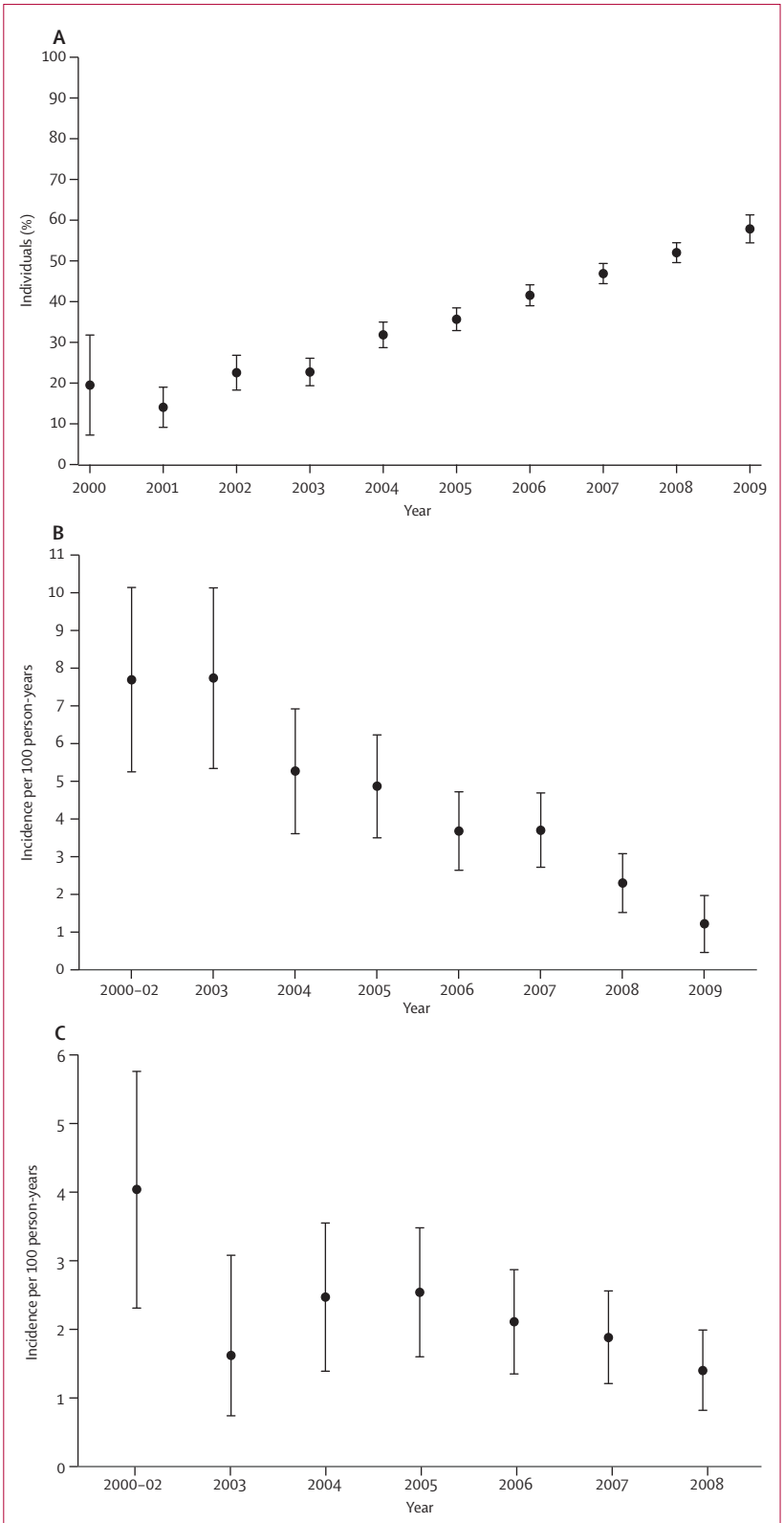

Figure: **2000–09 trends in virological and clinical outcomes in people with triple-class virological failure**
(A) Individuals with plasma HIV-1 RNA <50 copies per mL. (B) Incidence of new AIDS event. (C) Death rate.

	n	Univariable analysis		Multivariable analysis	
		Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Year			<0·0001		<0·0001
2000–02	1792 (7%)	0·29 (0·22–0·38)	..	0·27 (0·20–0·36)	..
2003	1882 (7%)	0·41 (0·33–0·51)	..	0·40 (0·32–0·50)	..
2004	2746 (11%)	0·65 (0·56–0·74)	..	0·63 (0·55–0·73)	..
2005	3524 (14%)	1 (reference)	..	1 (reference)	..
2006	4435 (17%)	1·18 (1·06–1·32)	..	1·18 (1·06–1·33)	..
2007	4695 (18%)	1·65 (1·46–1·87)	..	1·65 (1·46–1·88)	..
2008	4756 (19%)	2·28 (2·00–2·60)	..	2·29 (2·00–2·62)	..
2009	1855 (7%)	2·82 (2·39–3·33)	..	2·79 (2·35–3·32)	..
Group			<0·0001		<0·0001
Men who have sex with men	7911 (31%)	1 (reference)	..	1 (reference)	..
Heterosexual men	5266 (20%)	0·77 (0·66–0·91)	..	0·77 (0·64–0·93)	..
Heterosexual women	6337 (25%)	0·67 (0·57–0·78)	..	0·63 (0·52–0·75)	..
Injecting-drug users	3473 (14%)	0·71 (0·59–0·86)	..	0·81 (0·65–1·01)	..
Other or unknown	2698 (10%)	0·90 (0·73–1·11)	..	0·95 (0·75–1·20)	..
Age at TCVF (years)			0·013		0·59
16–29	2940 (12%)	0·83 (0·67–1·01)	..	0·95 (0·74–1·23)	..
30–39	11307 (44%)	1 (reference)	..	1 (reference)	..
40–49	8255 (32%)	1·12 (0·98–1·27)	..	1·02 (0·88–1·18)	..
≥50	3183 (12%)	1·16 (0·97–1·39)	..	1·15 (0·92–1·42)	..
Drugs failed by date of TCVF			0·28		0·31
≤4	4059 (16%)	1·17 (0·98–1·41)	..	1·23 (0·98–1·53)	..
5	6185 (24%)	1·13 (0·96–1·33)	..	1·03 (0·85–1·24)	..
6	8222 (32%)	1·11 (0·96–1·29)	..	1·07 (0·89–1·27)	..
≥7	7219 (28%)	1 (reference)	..	1 (reference)	..
AIDS present before TCVF (yes *vs* no)	Yes 10800 (42%); no 14885 (58%)	0·99 (0·88–1·12)	0·90	1·15 (0·99–1·32)	0·061
Never achieving viral load <50 copies per mL before TCVF (yes *vs* no)	Yes 9813 (38%); no 15872 (62%)	0·42 (0·37–0·48)	<0·0001	0·62 (0·53–0·73)	<0·0001
Median viral load at TCVF (per log_{10} copies per mL increase)	4·0 (3·2–4·8)	0·75 (0·70–0·80)	<0·0001	0·90 (0·83–0·98)	0·013
Median CD4 cell count at TCVF* (per 100 cells per μL increase)	269 (140–416)	1·13 (1·10–1·16)	<0·0001	1·06 (1·03–1·10)	0·0002

Data are number of viral load measurements (%) or median (IQR), unless otherwise stated. TCVF=triple-class virological failure. *Missing for 82 (0·3%) of 25 685 included viral load measurements.

***Table 2*: Predictors of virological response (viral load <50 copies per mL) in individuals with TCVF**

The median year of start of antiretroviral therapy was 2000 (1998–2001) and the median year of TCVF was 2005 (2003–2006), which was a median of 4·3 years (2·7–6·2) after the start of antiretroviral therapy. 892 (36%) of 2476 patients started on two NRTIs and one NNRTI, 679 (27%) received two NRTIs and one protease inhibitor, 295 (12%) received two NRTIs and one ritonavir-boosted protease inhibitor, 123 (5%) received three NRTIs, and 487 (20%) received other combinations. Table 1 lists characteristics of individuals in follow-up in 2000–09. Notably, the proportion of people receiving at least one new drug (ie, atazanavir, darunavir, enfuvirtide, etravirine, maraviroc, raltegravir, or tipranavir) rose from 0% in 2000 to 52% in 2009. Few individuals received at least two of these drugs (<1% in 2003 to 11% in 2009). In 2009, 253 (32%) of 2476 individuals were receiving atazanavir, 117 (15%) were receiving darunavir, 92 (12%) were receiving raltegravir, and 35 (4%) were receiving etravirine. The proportion of people not on antiretroviral therapy remained low for all years, but decreased from three (7%) of 41 people in 2000 to 28 (4%) of 795 in 2009.

We obtained data for 25685 measurements of plasma viral load after TCVF, with a median of eight measurements (IQR four to 15) per person, of which 9564 (37%) were fewer than 50 copies per mL. The proportion of patients with virological response after TCVF increased from 19·5% for people followed up in 2000 to 57·9% in 2009 (p<0·0001; figure).

1 year after TCVF, the estimated proportion of participants with virological response was 17·1% in those who had TCVF in 2000 and 49·2% in those who had TCVF in 2008. Irrespective of the year of TCVF (see webappendix), people followed up to the most recent calendar years had the best outcomes.

See Online for webappendix

	Univariable analysis		Multivariable analysis	
	Incidence rate ratio (95% CI)	p value	Incidence rate ratio (95% CI)	p value
Year		<0·0001		<0·0001
2000–02	1·58 (1·03–2·41)	..	1·30 (0·85–2·00)	..
2003	1·59 (1·05–2·41)	..	1·47 (0·97–2·24)	..
2004	1·08 (0·71–1·65)	..	1·04 (0·68–1·58)	..
2005	1 (reference)	..	1 (reference)	..
2006	0·76 (0·51–1·12)	..	0·81 (0·55–1·21)	..
2007	0·76 (0·52–1·12)	..	0·86 (0·58–1·27)	..
2008	0·47 (0·30–0·73)	..	0·56 (0·36–0·87)	..
2009	0·25 (0·13–0·49)	..	0·31 (0·16–0·62)	..
Group		0·54		0·98
Men who have sex with men	1 (reference)	..	1 (reference)	..
Heterosexual men	1·14 (0·83–1·58)	..	0·91 (0·65–1·26)	..
Heterosexual women	1·08 (0·79–1·48)	..	0·98 (0·71–1·35)	..
Injecting-drug users	1·32 (0·93–1·86)	..	1·00 (0·71–1·43)	..
Other or unknown	1·27 (0·86–1·87)	..	0·96 (0·65–1·42)	..
Age at TCVF (years)		0·45		0·80
16–29	0·99 (0·69–1·42)	..	1·00 (0·69–1·44)	..
30–39	1 (reference)	..	1 (reference)	..
40–49	0·84 (0·65–1·08)	..	0·90 (0·69–1·17)	..
≥50	0·81 (0·56–1·17)	..	0·86 (0·59–1·27)	..
Drugs failed by date of TCVF		0·68		0·30
≤4	1·10 (0·78–1·55)	..	1·19 (0·84–1·68)	..
5	0·89 (0·65–1·23)	..	0·89 (0·65–1·23)	..
6	1·04 (0·78–1·39)	..	1·16 (0·86–1·54)	..
≥7	1 (reference)	..	1 (reference)	..
AIDS present before TCVF (yes *vs* no)	2·00 (1·60–2·50)	<0·0001	1·64 (1·30–2·06)	<0·0001
Never achieving viral load <50 copies per mL before TCVF (yes *vs* no)	2·22 (1·78–2·78)	<0·0001	1·46 (1·16–1·85)	0·0016
Median viral load at TCVF (per $\log_{10}$ copies per mL increase)	1·79 (1·59–2·01)	<0·0001	1·35 (1·19–1·54)	<0·0001
Median CD4 cell count at TCVF* (per 100 cells per μL increase)	0·65 (0·60–0·70)	<0·0001	0·74 (0·68–0·80)	<0·0001

TCVF=triple-class virological failure. *Missing for 28 (0·4%) person-years of follow-up.

Table 3: **Predictors of new AIDS event[12] after TCVF**

Table 2 shows the results of the univariable and multivariable models for prediction of virological response. In the multivariable model, male and female heterosexuals and injecting drug users were less likely to achieve virological response than were men who have sex with men. Individuals with a lower viral load and a higher CD4 cell count at time of TCVF were more likely to achieve virological response, whereas people who had never achieved virological response before TCVF were less likely to achieve it. Finally, patients who were followed later (ie, closer to 2009) were more likely to achieve viral suppression. Notably, there was no overlap between the CI of the odds ratios for 2008–09 and those for 2006–07. Results were robust when we used an autoregressive covariance matrix instead of an exchangeable one (webappendix).

In 7777 patient-years of follow-up 311 people had a new AIDS event. The crude incidence of AIDS-defining event decreased from 7·7 per 100 patient-years between 2000 and 2002 to 2·3 in 2008 and 1·2 in 2009 (p<0·0001; figure). This significant trend was strongest in 2008 and 2009 in univariable and multivariable analyses (table 3). People with a higher viral load, a lower CD4 cell count, or a previous AIDS event at time of TCVF, or without virological response before TCVF were more likely to have a new AIDS event.

160 people died in 7568 patient-years of follow-up. The crude rate of death decreased from 4·0 per 100 patient-years between 2000 and 2002 to 1·9 in 2007 and 1·4 in 2008 (p=0·023; figure). Injecting drug users, young people (<30 years old), older people (≥50 years old), and those who had had an AIDS event were more likely to die (table 4). People with a higher CD4 cell count at time of TCVF were less likely to die than were those with a low CD4 cell count. After accounting for these variables, the trend noted over time (p=0·023) was no longer significant (p=0·22). To account for the fact that injecting drug users are more likely to die from causes not influenced by HIV infection and its treatment, we did a post-hoc sensitivity analysis excluding this group. In this analysis, 120 people

	Univariable analysis		Multivariable analysis	
	Incidence rate ratio (95% CI)	p value	Incidence rate ratio (95% CI)	p value
Year*		0·023		0·22
2000–02	1·59 (0·90–2·80)	..	1·40 (0·79–2·51)	..
2003	0·64 (0·30–1·35)	..	0·61 (0·29–1·30)	..
2004	0·97 (0·55–1·73)	..	0·93 (0·52–1·65)	..
2005	1 (reference)	..	1 (reference)	..
2006	0·83 (0·50–1·39)	..	0·88 (0·53–1·47)	..
2007	0·74 (0·44–1·24)	..	0·83 (0·50–1·39)	..
2008	0·55 (0·32–0·97)	..	0·63 (0·36–1·11))	..
Group		0·0005		0·0008
Men who have sex with men	1 (reference)	..	1 (reference)	..
Heterosexual men	1·04 (0·64–1·68)	..	0·78 (0·47–1·27)	..
Heterosexual women	0·93 (0·57–1·50)	..	0·91 (0·56–1·49)	..
Injecting-drug users	2·15 (1·39–3·33)	..	2·03 (1·29–3·19)	..
Other or unknown	1·80 (1·08–2·98)	..	1·33 (0·80–2·23)	..
Age at TCVF (years)		0·012		0·0021
16–29	1·59 (0·97–2·61)	..	1·80 (1·09–2·97)	..
30–39	1 (reference)	..	1 (reference)	..
40–49	1·31 (0·90–1·92)	..	1·37 (0·93–2·01)	..
≥50	2·05 (1·32–3·19)	..	2·34 (1·48–3·70)	..
Drugs failed by date of TCVF		0·91		0·68
≤4	0·84 (0·51–1·39)	..	0·86 (0·52–1·43)	..
5	0·93 (0·60–1·43)	..	0·90 (0·59–1·40)	..
6	0·98 (0·66–1·46)	..	1·12 (0·75–1·67)	..
≥7	1 (reference)	..	1 (reference)	..
AIDS present before TCVF (yes *vs* no)	2·41 (1·75–3·31)	<0·0001	1·90 (1·37–2·65)	0·0001
Never achieving viral load <50 copies per mL before TCVF (yes *vs* no)	1·68 (1·23–2·30)	0·0010	1·18 (0·85–1·64)	0·32
Median viral load at TCVF (per $\log_{10}$ copies per mL increase)	1·42 (1·21–1·67)	<0·0001	1·07 (0·90–1·28)	0·46
Median CD4 cell count at TCVF† (per 100 cells per μL increase)	0·66 (0·59–0·74)	<0·0001	0·71 (0·63–0·80)	<0·0001

*Data censored on Jan 1, 2009, to avoid potential incomplete data reporting for some cohorts. †Missing for 27 (0·4%) person-years of follow-up. TCVF=triple-class virological failure.

Table 4: **Predictors of death after TCVF**

died during 6477 years of follow-up. In these analyses, the decrease in the risk of death between 2000 and 2008 was significant in the univariable analysis (p=0·0045) and neared significance in the multivariable analysis (p=0·064).

Discussion

Between 2000 and 2009, the proportion of people who had virological response after TCVF improved substantially, and there was a concomitant decrease in AIDS incidence. However, we did not note an overall decrease in mortality.

Our aim was to assess whether there was an improvement in outcomes for people who had TCVF in the past decade, and we adjusted our models only for variables measured at the time of TCVF because such characteristics might change with time and affect outcomes. With this type of analysis we were able to show if there was, or not, a true trend in time. We chose not to analyse the extent to which the measures of improvements in antiretroviral therapy could statistically explain (ie, remove) the positive trends. This choice was made because we did not have measures of drug adherence or good measures of the presence of viral drug resistance. However, we intend in the future to merge data for viral resistance in our study population to assess trends in detected resistance. Because of our objective, we do not think any other independent variables available at TCVF should have been added in the models. For example, CD4 cell count at treatment initiation, which might have changed dependent on the year and might be associated with any one of the three outcomes, would be strongly correlated with CD4 cell counts at TCVF, so would not be an independent factor.

The positive trends that we noted probably relate to improvements in adherence and management of resistance, increasing availability of new drugs within existing classes (such as the protease inhibitor darunavir and the NNRTI etravirine), and increasing availability of drugs from new classes, making new regimens with minimal cross-resistance possible.[13] The trend for an

improved virological outcome was strongest in 2008 and 2009, shortly after four new drugs were approved in Europe (darunavir in February, 2007, maraviroc in September, 2007, raltegravir in December, 2007, and etravirine in August, 2008).

Our results suggest effectiveness at a routine clinical population scale of new antiretroviral drugs in terms of morbidity and rates of virological suppression (panel). In particular, because the risk of death did not seem to increase and was perhaps decreasing in individuals who do not use injecting drugs, this study supports the notion that any adverse effects of these new drugs on mortality are outweighed by the benefits. The positive trends we reported between 2000 and 2009 in this study probably result from improvements in tolerability and ease of use of drug regimens,[14,15] and in the availability of drugs with non-overlapping resistance profiles. Our results are consistent with recent studies indicating that the proportion of overall clinic populations with suppressed viral load has increased with time.[16–18]

Although we suggest there was a trend towards a decline in mortality, this finding was not significant in multivariable analyses; however, there was a substantial decrease in the rate of new cases of AIDS. The reason for this difference might be the small sample size (160 endpoints for death *vs* 311 for AIDS). In the analysis excluding injecting drug users, the time trend for a decline in death rate approached significance in the multivariable analysis even though its power was smaller than in the overall analysis (120 endpoints instead of 160). Another reason for the absence of a significant response in death rate might be because, between 2000 and 2009, a comparatively small and diminishing proportion of deaths in those with TCVF was caused by AIDS.[19,20] Thus, there is less room for improvement through increased virological control. Nevertheless, there is evidence that HIV increases the risk of several serious non-AIDS conditions[21] so some decrease with time in death rates from non-AIDS causes would be expected. Such disorders might relate to HIV-induced immune activation and inflammation, which generally persist in the first few years after virological control, and could partly explain the lesser trend that we noted for risk of death.[22,23] Furthermore, long-term adverse events might have contributed to the weak trend. We are aware that not all cohorts link their data with national death registries, which might result in an underestimation of mortality. A long delay in ascertainment of deaths could lead to overestimation of any positive trends in mortality. By contrast, ascertainment of AIDS should be high because this outcome is chiefly diagnosed at the clinics themselves. This reasoning is why we censored data on Jan 1, 2009, for death and report results about death to 2008. Nevertheless, this issue cannot explain weakness of the trend for death.

A low CD4 cell count at TCVF was associated with low probability of virological success and high risk of new AIDS events and death. This result, once again, emphasises the importance of maintenance of a healthy CD4 cell count and of an early identification and treatment of HIV infection.

Despite improvements, viral loads cannot be suppressed for some people with TCVF. This effect is probably caused by insufficient adherence to drug regimens rather than presence of a virus resistant to all drugs.[24] However, some people do have viruses with resistance to all drugs available in 2009.[25,26]

Whether the improving trend, or even the current rate of viral suppression in 2009, can be sustained in the future is unclear. Continued improvement will likely need continued development of new drugs, which are active against virus with resistance to existing drugs.

COHERE accumulates data from cohorts in most countries in western Europe, and includes data for more than 70% of the patients in care in France, the Netherlands, and Switzerland, and 50% of such patients in the UK. Individuals from these four countries make up two-thirds of our dataset and thus we believe that our results are representative of the trends for these countries, and probably for western Europe as a whole. However, we cannot exclude the possibility that, in these countries, clinics contributing to the cohorts have a higher standard of care and perhaps a greater level of viral suppression than do non-participating clinics.

***Panel:* Research in context**

Systematic review

Previous studies that investigated virological or clinical outcomes in people who had virological failure on the original three classes of antiretroviral drugs dealt mainly with people who had started antiretroviral therapy with one or two drugs;[1–4] however, this group is now of decreased relevance. We searched PubMed for articles published in any language between January, 2004, and June, 2011, that investigated virological or clinical outcomes (see webappendix) in people with triple-class virological failure who started treatment when combined therapy with three or more drugs had become the norm (1998); we identified only one such study.[9] Because of its small size (167 people with triple-class virological failure), this study had a little power to assess trends of virological and clinical outcomes after triple-class virological failure.

Interpretation

In western Europe, there has been a striking improvement of virological status of people with triple-class virological failure between 2000 and 2009 in routine clinical practice, especially since 2008, and an accompanying decrease in the rate of AIDS. This effect is probably largely due to the fact that, in the same period, several drugs have become available that are easier to use and better tolerated than were existing drugs, and tend to be active against virus resistant to typical first-line and second-line drugs.

Overall, we showed substantial improvements between 2000 and 2009 in virological suppression in people who had virological failure to drugs from the three original classes of antiretrovirals, and accompanying decreases in rates of AIDS. We suggest that the set of available drugs is sufficient to enable construction of active regimens for most infected people. However, because previously untreated patients who start antiretroviral therapy from 2011 will do so with drugs that are different from those used in 1998–2001, drug resistance profiles will differ in the future and thus there will be a continuing need for new drugs with non-overlapping resistance profiles.

Contributors

All members of the PLATO II analysis and writing committee participated in discussions about the design of the study, choice of statistical analyses, and interpretation of the findings, and critically reviewed the manuscript. Dominique Costagliola, Bruno Ledergerber, Carlo Torti, Ard van Sighem, Daniel Podzamczer, Amanda Mocroft, Maria Dorrucci, Bernard Masquelier, Andrea de Luca, Klaus Jansen, Stephane De Wit, Niels Obel, Gerd Fätkenheuer, Giota Touloumi, Cristina Mussini, Antonella Castagna, Cristoph Stephan, Federico García, Robert Zangerle, Xavier Duval, Santiago Pérez-Hoyos, Laurence Meyer, Jade Ghosn, Céline Fabre-Colin, Jesper Kjaer, and Genevieve Chene contributed to data acquisition and management. Céline Fabre-Colin, Jesper Kjaer, and Jesper Grarup provided administrative, technical, and material support. Dominique Costagliola, Rebecca Lodwick, Bruno Ledergerber and Andrew Phillips were responsible for the study concept and design, had full access to the dataset, did all analyses, interpreted the data, and drafted the report.

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For **participating cohorts** see http://www.cphiv.dk/COHERE/tabid/295/Default.aspx and http://etudes.isped.u-bordeaux2.fr/cohere

Conflicts of interest

No member of the PLATO II analysis and writing committee has any financial or personal relationships with people or organisations that could inappropriately influence this work, although most 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 consultancy fees.

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