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Triple class experience after initiation of combination antiretroviral treatment in Australia: survival and projections

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Abstract

Background—Patients who have become triple class experienced (TCE) are at a high risk of exhausting available treatment options. This study aims to investigate factors associated with becoming TCE and to explore the effect of becoming TCE on survival. We also project the prevalence of TCE in Australia to 2012.

Methods—Patients were defined as TCE when they stopped a combination antiretroviral treatment (cART) that introduced the third of the three major antiretroviral classes. Cox proportional hazards models were used to investigate factors associated with TCE and the effect of TCE on survival. To project TCE prevalence, we used predicted rates of TCE by fitting a Poisson regression model, together with the estimated number of patients who started cART in each year in Australia, assuming a mortality rate of 1.5 per 100 person-years.

Results—Of the 1498 eligible patients, 526 became TCE. Independent predictors of a higher risk of TCE included current CD4 counts below 200 cells μL^{-1} and earlier calendar periods. No significant difference in survival was observed between those who were TCE and those who were not yet TCE. An increasing number of patients are using cART in Australia and if current trends continue, the number of patients who are TCE is estimated to increase from 2800 in 2003 to 5000 in 2012.

Conclusion—Our results suggest that the prevalence of TCE in Australia is estimated to plateau after 2003. However, as an increasing number of patients are becoming TCE, it is necessary to develop new drugs that come from new classes or do not have overlapping resistance.

Additional keywords

antiretroviral therapy; cohort studies; HIV; prevalence; survival analysis; trends

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Conflicts of interest

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Introduction

The widespread availability of combination antiretroviral treatment (cART) for patients infected with HIV has lead to significant improvements in morbidity and mortality.[1–3] Although these benefits have been considerable, they have not been without cost; significant short- and long-term drug toxicities have emerged,[4] as has the issue of immune reconstitution.[5] In particular, toxicity and resistance have led to switching of therapy both within and between classes of antiretroviral treatment. As a result, increasing number of patients have become experienced to each of the three major classes of drugs available at the start of the cART era: nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI).[6] These patients, along with those who have experienced virological failure, have been identified as two groups who are at a high risk of facing lack of treatment options by ultimately exhausting all available classes of antiretroviral treatments.[7]

Managing treatment-experienced individuals where treatment options are limited by either prior drug toxicity or resistance is complex. In Australia, the estimated number of patients receiving treatment in 2007 was around 9900. This number is expected to increase as the rate of new infections continues to climb (with 983 new HIV diagnoses in 2007).[8] Therefore, the availability of new antiretrovirals and new classes is becoming increasingly pertinent.

The literature to date has focussed on virological failure to the three major classes. The Pursuing Later Treatment Options (PLATO) study was the first of several studies to define triple class failure (TCF) as failure of each of the three main classes of antiretroviral with a viral load of more than 1000 copies mL^{-1} for more than 4 months.[9] Using this definition, the rate of TCF ranged from 1.6–1.8 per 100 person-years[10,11] to as high as 3.9 per 100 person-years among individuals who were already treatment experienced at the time they commenced highly active antiretroviral treatment.[12] While a stricter definition using a viral load cut-off of < 400 copies mL^{-1} yielded a TCF rate as low as 0.6 per 100 person-years.[13] Factors commonly associated with TCF include lower CD4 T-cell count, higher baseline viral load, prior treatment experience, younger age and injecting drug use, among others.[10–13]

However, treatment failure encompasses more than virological failure, including toxicity and drug resistance. The aims of this study are to investigate factors associated with triple class experience (TCE) among patients from Australian HIV Observational Database (AHOD), and to investigate the effect of becoming TCE on survival. To gauge the likely need for new antiretroviral drug classes, we also project the prevalence of TCE in Australia to 2012.

Methods

Participants

AHOD is an observational cohort study of patients with HIV that was established in 1999. The study has been described elsewhere in detail,[6] but briefly, data are transferred electronically biannually to the National Centre in HIV Epidemiology and Clinical Research (NCHECR) from 27 clinical centres throughout Australia, including hospitals, sexual health clinics and general practitioners. All participants provide written informed consent at the time of enrolment. The following core data variables are collected: sex, date of birth, date of most recent visit, HIV exposure category, hepatitis B (HBV) and hepatitis C (HCV) status, CD4 counts, HIV viral load, antiretroviral treatment, AIDS-defining illness, and date and

cause of death (using CoDe methods (http://www.cphiv.dk/CoDe/tabid/55/Default.aspx; verified November 2010)).

Eligibility criteria and endpoints

All patients recruited to AHOD by 31 March 2008 who commenced their first cART after 1 January 1997 for more than 14 days and who had at least 3 months of follow-up were included in these analyses. cART was defined as a combination of at least three antiretroviral drugs.

The following endpoints were considered: mortality and TCE. Patients were defined as TCE at the time they stopped (for any reason) a cART regimen that introduced the third of the three major ARV classes (NRTI, PI or NNRTI).

Statistical analyses

Follow-up began at the date of starting cART to the time the outcome occurred, the last follow-up date or the end of study period (31 March 2008), whichever occurred first. Cox proportional hazards models were used to determine factors associated with TCE and mortality. Factors included in univariate analyses as time-dependent covariates were CD4 count, viral load, prior AIDS and calendar year. Age, sex, exposure category, HBV and HCV co-infection status, prior antiretroviral use, first cART regimen, number of drugs in first cART regimen and year of initiating cART were included as fixed variables at start of cART. The survival of patients who were TCE was compared with those who were not TCE, considering TCE status as a time-dependent covariate in the survival analyses. Baseline CD4 count and HIV viral load were based on the most recent measure within 6 months before commencing cART. Among patients who became TCE, the most recent measures of CD4 count and HIV viral load within 3 months before becoming TCE were also summarised.

Multivariate models were built using forward stepwise methods. Variables were considered for inclusion in the multivariate model if they had a P-value ≤ 0.10 in the univariate analysis. Statistical significance was considered as a two-sided P-value <0.05. The analyses were checked for multicolinearity, using tolerance and the variance inflation factor. A tolerance of 0.1 or less or, equivalently, a variance inflation factor of 10 or greater may indicate multicolinearity. No signs of multicolinearity were present.

Projecting TCE prevalence in Australia

The total number of patients on cART in each year in Australia was estimated from the Australian Government's Highly Specialised Drugs (s100) program, together with data on antiretroviral use from AHOD using previously described methods.[14] The total number of patients who started cART in each year was then obtained by subtracting the number of patients on cART in the previous year from number on cART in that year, assuming a mortality rate of 1.5 per 100 person-years.[15] We assumed all patients on cART in 1996 started cART in that year, reflecting the year cART was first widely available in Australia.

Predicted rates of TCE by year of starting cART and by number of years since starting cART were estimated from AHOD using a Poisson regression model. The number of patients in Australia who were TCE was then estimated by applying these AHOD-predicted rates of TCE to the total number of patients starting cART derived from the s100 data. Mortality rates before and after TCE were derived based on the estimated survival hazard ratio of the time-dependent TCE status.

Using the χ^2 goodness of fit test, little evidence of over-dispersion was observed. We refitted the Poisson model using negative binomial regression; the coefficients and standard errors were virtually identical to those obtained from the corresponding Poisson model.

Projections through to 2012 were made using Poisson regression methods assuming that the pattern of starting treatment over the last few years and the rates of developing TCE remained consistent. The prevalence of TCE in each calendar year was then calculated as the estimated total number of patients with TCE up to that year divided by the estimated total number of patients on cART during that year. More details of the methods used to project TCE prevalence are given in the Appendix. All analyses were performed using STATA version 10 (Stata Corporation, College Station, TX, USA).

Results

Patient characteristics

By March 2008, 2667 patients were recruited to AHOD from 26 of 27 sites. Of these, 1536 patients commenced their first cART after 1 January 1997, and 1498 patients had at least 3 months of follow-up and satisfied the inclusion criteria (Table 1). The majority of patients were male (93%), had three drugs in their first cART regimen (94%) and did not have a prior AIDS-defining illness (88%). The main mode of transmission was homosexual contact (71%).

Triple class experience

During a median follow-up time of 4.7 years, 526 patients became TCE, yielding an overall crude incidence rate of 6.7 per 100 person-years (95% confidence interval (CI): 6.2–7.3). Of these, 419 patients had a viral load measure available at the time of becoming TCE, with 68% having an undetectable viral load (≤400 copies mL^{-1}), and the mean CD4 was 514 cells μL^{-1} among 426 individuals with a CD4 measure available at the time of TCE. Patients who became TCE during follow-up had lower CD4 count at the start of cART (median: 297 (interquartile range (IQR): 150–443) *v.* 312 (IQR: 180–480) cells μL^{-1}), higher viral loads (median: 70 794 (IQR: 9700–290 000) *v.* 53 000 (IQR: 10 000–171 500) copies mL^{-1}) and were more likely to have experienced an AIDS-defining illness before baseline (16% *v.* 9%). Patients who were TCE and those who were not TCE were similar with regard to age, gender and coinfection with HBV and HCV (Table 1).

Factors associated with TCE

Table 2 shows factors associated with TCE in univariate and multivariate analyses. Of the factors assessed, current CD4 count ($P < 0.001$), current viral load ($P = 0.002$), having had an AIDS-defining illness ($P < 0.001$), calendar year ($P < 0.001$), year of starting cART ($P < 0.001$), number and class of drugs in first cART regimen ($P < 0.001$), and prior exposure to mono or dual therapy ($P < 0.001$) were associated with becoming TCE in the univariate analyses.

In the final model, the following factors were significantly associated with higher risk of TCE: current CD4 counts below 200 cells μL^{-1}, a prior AIDS-defining illness diagnosis, earlier calendar periods, receiving more than three drugs in first cART regimen, regimens that included both an NNRTI and a PI as the first cART regimen, and being antiretroviral-experienced. Of note, patients with CD4 counts <200 cells μL^{-1} had a two-fold higher risk of TCE compared with those with CD4 count ≥500 cells μL^{-1} ($P < 0.001$). At any time point, having prior AIDS was associated with a 28% increased risk of TCE (hazard ratio (HR): 1.28; 95% CI: 1.04–1.59; $P = 0.022$). There was a 56% decrease in TCE risk after 2003 compared with before 2000 (HR: 0.44; 95% CI: 0.31–0.61; $P < 0.001$).

Effect of TCE on survival

Over a median of 7.5 years of follow-up, 88 deaths were reported, yielding a crude mortality rate of 0.8 per 100 person-years (95% CI: 0.7–1.1). More than half (57%) were non-AIDS related deaths. Forty-one (46%) deaths were among those who became TCE during the study period.

In the multivariate model, independent risk factors for mortality were: the most recent measurement of CD4 count ($P < 0.001$) and viral load ($P = 0.019$), as well as age at initiation of cART ($P = 0.001$) and co-infection with HBV ($P < 0.001$). In crude analyses, at any time point, the hazard for a patient who was TCE was double the hazard for a patient who was not yet TCE (HR 2.1: 95% CI: 1.34–3.3; $P = 0.001$). However, after adjusting for the final model, the difference in the risk of death between those who were TCE and those who were not yet TCE was reduced and not significant (Table 3).

Projecting TCE prevalence in Australia

If the overall crude death rate among patients with HIV is 1.5 per 100 person-years,[16] then this unadjusted hazard ratio of 2.1-fold greater mortality for patients who were TCE corresponds to a mortality rate of 2.3 after TCE and 1.1 before TCE.

Table 4 shows the predicted rates of TCE using Poisson regression. The estimated prevalence of TCE and the estimated number of patients receiving cART in Australia are shown in Fig. 1. The total number on cART is estimated to have increased from 5900 in 1998 to 9900 in 2007. If current trends continue, the number receiving cART will increase to 13 600 in 2012. While the prevalence of TCE is estimated to plateau at around 38% after 2003, this reflects an increasing number of individuals who are TCE, from 2800 in 2003 to 5000 in 2012.

Discussion

In AHOD, more than one-third of patients who commenced cART on or after 1 January 1997 have been exposed to and stopped a drug from the three major antiretroviral treatment classes during follow-up, with an overall TCE incidence rate of 6.7 per 100 person-years. Commencing cART with more than three drugs or with a PI, being antiretroviral-experienced, most recent CD4 count, prior AIDS diagnosis and calendar year were all associated with TCE. TCE was associated with a two-fold increased risk of death in univariate analyses, although this effect was reduced and not significant once adjusted for lower CD4 count, higher HIV viral load, older age and co-infection with HBV. The number of HIV-infected people in Australia receiving cART in 2012 was estimated to increase to 13 600 from 9900 in 2007.[16] Of these, ~38% are projected to be TCE by our definition.

Applying our definition of TCE yielded a rate of 6.7 per 100 person-years in the AHOD data, at least two-fold higher than the rate of TCF reported by other cohorts that applied the PLATO definition of failure, ranging from 0.6 to 3.9.[11–13] Our definition includes people who have changed treatment for reasons other than virological failure and can be seen to provide an upper estimate of the rate of treatment experience. Despite the difference in definition, we have shown a decline in the rate of TCE over the study period similar to the decline in TCF demonstrated in the literature.[11] The rate of TCE decreased from 8.4 (95% CI: 7.1–9.9) per 100 person-years between 1997 and 1999, to 5.5 (95% CI: 4.8–6.3) after 2003, and was also greatest for patients with antiretroviral exposure before commencing cART. Similar findings were also reported by other studies when assessing TCF.[11,12] The decreasing rate of TCE over the calendar periods that we observed may largely be explained by less toxic regimens being available in later time periods such as new generation NRTIs and PIs, including tenofovir and atazanavir, which became available in Australia in 2001

and 2004 respectively. Although it may be argued that the higher rate in the earlier periods may be due in part to constantly evolving new treatments, and also to patients changing to simpler combinations, including changes to fixed dose combinations, to reduce pill burden and dosing frequency or to enhance tolerability as specified in the Australian antiretroviral treatment guidelines (http://www.ashm.org.au/default2.asp?active_page_id=252#; verified November 2010); this change in cART may equally reflect changes due to toxicity, particularly PI use.[17] Although we were unable to assess specific reasons for stopping or changing treatment in AHOD, we found 68% of patients with an available viral load measure at the time of becoming TCE had an undetectable viral load (<400 copiesmL^{-1}), demonstrating that a significant proportion stopped due to toxicity or adherence difficulties, or were changing to more effective drugs.

In AHOD, most recent CD4 count, prior AIDS, number of antiretrovirals in first cART regimen, having received mono or dual therapy before commencing cART, commencing their first cART regimen with a PI and calendar year were predictive of TCE, reflecting more advanced disease among the TCE group. The rate of death after becoming TCE in AHOD was estimated at 2.3 per 100 person-years, which was much lower than the reported rate of death following TCF: 5.0 and 5.5 per 100 person-years for the EuroSIDA and PLATO studies respectively.[12] TCE was also associated with a two-fold increased risk of death in univariate analyses, and although this effect was reduced and not significant once adjusted for the independent risk factors (lower CD4 count, higher HIV viral load, older age and co-infection with HBV), TCE patients remained at an increased risk of death. Overall, our findings suggests a slightly poorer prognosis in the TCE group, emphasising the need for ongoing resistance testing, and the development of new and improved antiretroviral treatments to optimise treatment outcomes within this growing population.

Our finding that co-infection with HBV is associated with mortality is consistent with other studies;[18,19] however, this is the first time this association has been observed in AHOD. Previously, hepatitis was not reported as a significant predictor of either AIDS related or non-AIDS related death in AHOD,[15,20] nor with poorer immune response at 24 months following cART.[21] We attribute this new finding in our current study to the increase in the number of participants co-infected with HBV.

There are several limitations to our study. First, we chose the definition of TCE rather than TCF as defined by the PLATO study and commonly used in the literature. Our decision to consider TCE was partly to reflect the broader definition of treatment failure to include not only virological failure, but also toxicity and resistance. We also used this definition because AHOD is a relatively small cohort, despite including more than 10% of people living with HIV in Australia and therefore underpowered to assess an endpoint applying the PLATO definition for TCF. Second, we were unable to assess reasons for stopping regimens, as these reasons were not reported in a standard approach across all AHOD sites. We also do not collect resistance data. Australian guidelines recommend resistance testing to be conducted when individuals change antiretroviral treatments in cases of virological failure (>1000 copiesmL^{-1}) (http://www.ashm.org.au; verified November 2010). As a result, we were unable to assess accurately whether patients were changing drugs due to toxicity, resistance or simplification. Third, our projections of the number of TCE patients were based on several assumptions. These include that the number of patients starting cART, the rate of becoming TCE, and the mortality rates before and after TCE all remain at currently observed rates into the future; and that rates observed in AHOD apply across the whole Australian population. Since patients generally receive three or more antiretroviral drugs in combination, we also assumed all patients receiving antiretrovirals in each year in Australia were on cART. These assumptions are difficult to verify, and projections made should be viewed as indicative and interpreted cautiously.

To our knowledge, this is the first study to compare the survival of patients who became TCE during follow-up with those who were not yet TCE by the end of study period. Considering TCE status as a time-dependent covariate enabled us to eliminate survival treatment selection bias by continual comparison of TCE patients who survived to the same point in time with those who were not yet TCE.[22]

In summary, our results suggest that although the rate of TCE is declining, the need for new antiretroviral options remains. This is particularly pertinent as the number of patients who are expected to be treated with cART in Australia will increase to more than 13 000 in 2012. Of these, an estimated 38% will become TCE, illustrating the need to develop appropriate treatment regimens, and the challenges faced in the long-term management of HIV-positive patients. In recent years, new antiretroviral classes like entry and integrase inhibitors have become available, and have been approved in some jurisdictions for first-line therapy. These new classes should improve treatment for the growing number of treatment-experienced patients.

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Appendix

Let $I_{TCE}(i, j)$ = predicted number of new TCE cases in Australia among patients who started cART in year i and have $j-1$ to j years follow up since starting cART.

It is calculated as:

$$I_{TCE}(i,j)=N_{start}(i) \times r_{TCE}(i,j) \times 1/2(j=1)$$
$$I_{TCE}(i,j)=N_{risk}(i,j) \times r_{TCE}(i,j)(j>1)$$
$$N_{risk}(i,j)=N_{risk}(i,j-1)-I_{TCE}(i,j-1)-0.011 \times (N_{risk}(i,j-1)-I_{TCE}(i,j-1))(j>1)$$
$$N_{start}(i)=N_{cART}(i)-N_{cART}(i-1)+0.015 \times N_{cART}(i-1)(i>1996)$$
$$N_{start}(i)=N_{cART}(i)(i=1996)$$

where:

- $N_{start}(i)$ = number of patients who started cART in year i in Australia
- $r_{TCE}(i, j)$ = predicted rate of TCE from fitted Poisson regression in AHOD by year of staring cART and number of years since starting cART
- $N_{risk}(i, j)$ = number of patients at risk of TCE in Australia among patients who started cART in year i and have $j-1$ to j years follow up since starting cART
- $N_{cART}(i)$ = Total number of patients on cART in year i
- 0.011 is the death rate among patients who are not yet TCE
- 0.015 is the assumed average annual death rate among patients with HIV.

The new TCE cases in each year ($I_{TCE}(i)$) were calculated as:

$$I_{TCE}(i)=I_{TCE}(i,1)+I_{TCE}(i-1,2)+I_{TCE}(i-2,3)+\ldots+I_{TCE}(1996,i-1996+1)$$

The total number of TCE patients in each calendar year was then estimated as follows:

$$N_{\mathrm{TCE}}(i) = I_{\mathrm{TCE}}(i) + (N_{\mathrm{TCE}}(i-1) - N_{\mathrm{TCE}}(i-1) \times 0.023)$$

where 0.023 is the death rate following TCE.

In order to smooth out number of patients receiving cART before 2000 and prevent getting negative numbers for people starting cART in these years, predicted numbers were estimated by fitting a linear regression model on the number of patients on cART before 2000.

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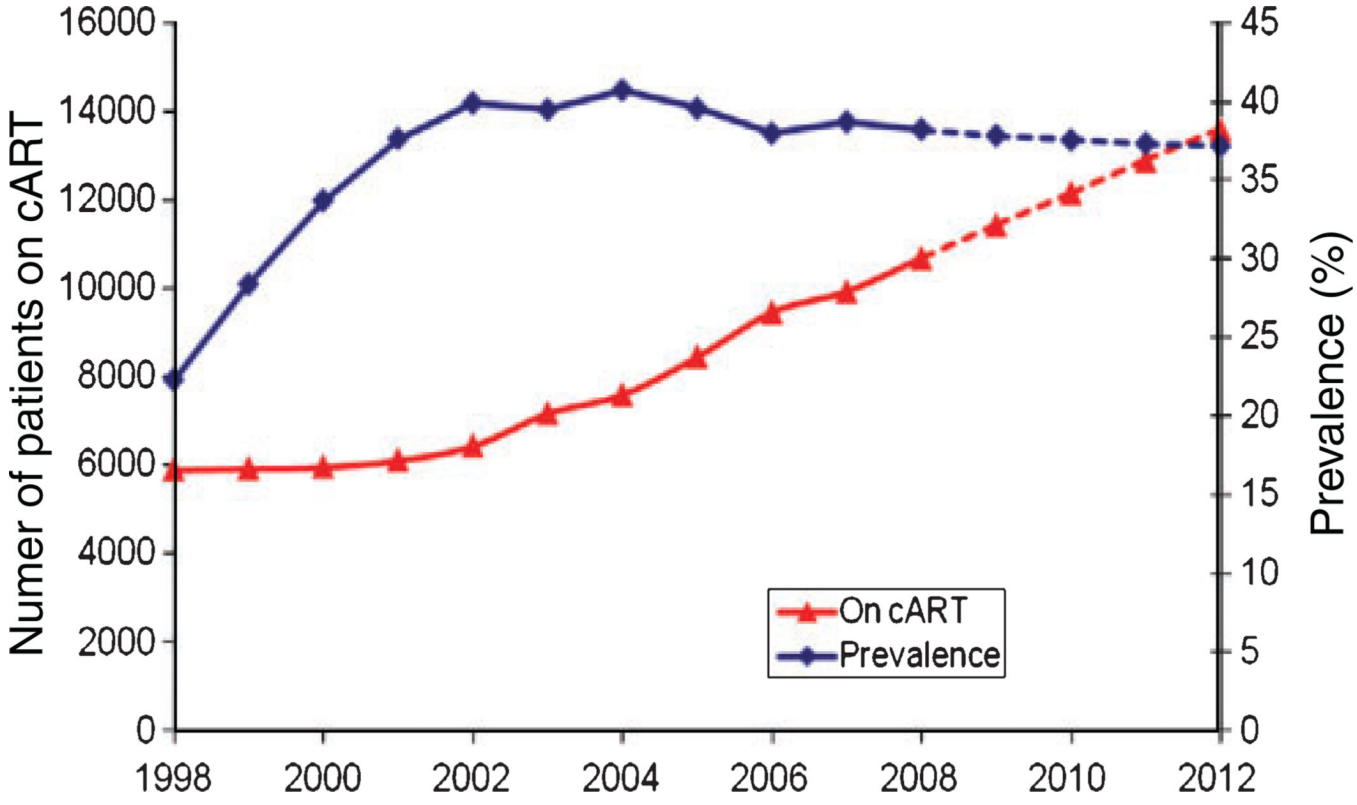

Fig. 1.
Prevalence of TCE and number of patients on cART in Australia.

Table 1

Baseline characteristics of patients

TCE, triple class experienced; s.d., standard deviation; ARV, antiretroviral; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; cART, combination antiretroviral treatment

	TCE *n* (%)	Not TCE *n* (%)
Total	526 (100)	972 (100)
Age (years)		
Mean (s.d.)	40 (10)	39 (10)
<30	70 (13)	133 (14)
30–39	212 (40)	395 (40)
40–49	156 (30)	279 (29)
50+	88 (17)	165 (17)
Gender		
Male	492 (93)	909 (93)
Female	33 (6)	59 (6)
Transgender	1 (<1)	4 (<1)
Exposure		
Homosexual	389 (74)	679 (70)
Other	134 (25)	281 (29)
Missing	3 (<1)	12 (1)
Prior AIDS		
No	441 (84)	884 (91)
Yes	85 (16)	88 (9)
Hepatitis B		
Negative or not tested	494 (94)	924 (95)
Positive	32 (6)	48 (5)
Hepatitis C		
Negative or not tested	460 (87)	874 (90)
Positive	66 (13)	98 (10)
Prior ARV		
No	313 (60)	744 (77)
Yes	213 (40)	228 (23)
First cART regimen		
NRTI ± PI, no NNRTI	321 (61)	377 (39)
NNRTI + PI, ±NRTI	52 (10)	6 (<1)
NRTI + NNRTI, no PI	153 (29)	589 (61)
No. of drugs in first cART regimen		
3	475 (90)	942 (97)
4+	51 (10)	30 (3)

	TCE ***n*** **(%)**	**Not TCE** ***n*** **(%)**
CD4 (cells μL^{-1})[A]		
Median (IQR)	297 (150–443)	312 (180–480)
<200	134 (25)	211 (22)
200–299	55 (10)	148 (15)
300–499	119 (23)	226 (23)
500+	69 (13)	183 (19)
Missing	149 (28)	204 (21)
Viral load (copies mL^{-1})[A]		
Median (IQR)	70 794 (9700–290 000)	53 000 (10 000–171 500)
≤400	25 (5)	89 (9)
401–10 000	72 (14)	100 (10)
10 000+	276 (52)	566 (58)
Missing	153 (29)	217 (22)
Year started cART		
1997	260 (49)	215 (22)
1998–99	174 (33)	281 (29)
2000–03	76 (14)	268 (28)
2004+	16 (3)	208 (21)

[A]The closest measure within 6 months before baseline.

Table 2

Factors associated with becoming triple class experienced using Cox proportional hazards model

HR, hazard ratio; CI, confidence interval; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; HBV, hepatitis B; HCV, hepatitis C; cART, combination antiretroviral treatment. Bold type indicates significant covariates

	Univariate			Multivariate		
	HR (95% CI)	***P***	***p*^A**	**HR (95% CI)**	***P***	***p*^A**
Time-dependent covariates						
Current CD4 (cells μL^{-1})[B]						
<200	1.00			1.00		
200–300	**0.61 (0.44–0.85)**	**0.004**		**0.67 (0.48–0.93)**	**0.019**	
300–500	**0.42 (0.32–0.56)**	**<0.001**		**0.51 (0.38–0.68)**	**<0.001**	
500+	**0.39 (0.31–0.51)**	**<0.001**	**<0.001**	**0.47 (0.36–0.61)**	**<0.001**	**<0.001**
Current viral load (copies mL^{-1})[C]						
≤400	1.00			1.00		
400–10 000	**1.05 (0.80–1.38)**	**0.713**		0.85 (0.64–1.12)	0.243	
10 000+	**1.43 (1.15–1.78)**	**0.001**	**0.002**	1.19 (0.94–1.50)	0.140	0.246
Prior AIDS[B]						
No	1.00			1.00		
Yes	**1.84 (1.51–2.25)**	**<0.001**	**<0.001**	**1.28 (1.04–1.59)**	**0.022**	**0.022**
Calendar year[B]						
1997–99	1.00			1.00		
2000–02	**0.69 (0.52–0.91)**	**0.008**		**0.76 (0.57–1.01)**	**0.054**	
2003+	**0.36 (0.26–0.51)**	**<0.001**	**<0.001**	**0.44 (0.31–0.61)**	**<0.001**	**<0.001**
Fixed covariates						
Year started cART[C]						
1997	1.00			1.00		
1998–99	**0.67 (0.56–0.82)**	**<0.001**		0.78 (0.63–0.97)	0.027	
2000–03	**0.51 (0.40–0.67)**	**<0.001**		0.82 (0.56–1.21)	0.320	
2004+	**0.36 (0.22–0.60)**	**<0.001**	**<0.001**	0.94 (0.46–1.92)	0.876	0.128
No. of drugs in first cART regimen[B]						

	Univariate			Multivariate		
	HR (95% CI)	***P***	***P*^A**	**HR (95% CI)**	***P***	***P*^A**
3	1.00			1.00		
≥4	**3.10 (2.32–4.15)**	**<0.001**	**<0.001**	**1.92 (1.40–2.63)**	**<0.001**	**<0.001**
First cART regimen[B]						
NRTI ± PI, no NNRTI	1.00			1.00		
NNRTI + PI, ±NRTI	**4.56 (3.39–6.12)**	**<0.001**		**3.69 (2.69–5.07)**	**<0.001**	
NRTI + NNRTI, no PI	**0.43 (0.35–0.52)**	**<0.001**	**<0.001**	**0.50 (0.41–0.60)**	**<0.001**	**<0.001**
Exposure						
Homosexual	1.00					
Other	0.96 (0.79–1.17)	0.689	0.802			
Age						
<30	1.00					
30–39	0.99 (0.76–1.31)	0.999				
40–49	1.08 (0.82–1.44)	0.568				
50+	1.09 (0.79–1.49)	0.602	0.409			
Gender						
Male	1.00					
Female	1.06 (0.75–1.51)	0.741	0.741			
Prior regimens[B]						
None	1.00			1.00		
Mono	**1.57 (1.15–2.13)**	**<0.001**		**1.18 (0.86–1.61)**	**0.303**	
Dual	**1.64 (1.27–2.11)**	**<0.001**		**1.60 (1.23–2.07)**	**<0.001**	
Mono and dual	**2.00 (1.59–2.52)**	**<0.001**	**<0.001**	**1.50 (1.18–1.91)**	**0.001**	**<0.001**
HBV status						
Negative or not tested	1.00					
Positive	1.24 (0.87–1.78)	0.235	0.235			
HCV status						
Negative or not tested	1.00					
Positive	1.15 (0.89–1.49)	0.291	0.291			

[A] *P* overall, *P*-values reported for test of homogeneity in nominal covariates and test for trend in ordinal covariates. Patients with missing data were not included for testing trends.

[B] Variables included in the final model.

[C] Covariates adjusted for the final model.

Table 3

Factors associated with mortality using Cox proportional hazards model

HR, hazard ratio; CI, confidence interval; HBV, hepatitis B; HCV, hepatitis C; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; cART, combination antiretroviral treatment. Bold type indicates significant covariates

	Univariate			Multivariate		
	HR (95% CI)	***P***	***p*[A]**	**HR (95% CI)**	***P***	***p*[A]**
Time dependent covariates						
Current TCE status[B]						
No	1.00			1.00		
Yes	**2.10 (1.34–3.30)**	**0.001**	**0.001**	1.19 (0.75–1.88)	0.454	0.454
Current CD4 (cells μL^{-1})[C]						
<200	1.00			1.00		
200–300	**0.35 (0.18–0.68)**	**0.002**		**0.37 (0.19–0.73)**	**0.004**	
300–500	**0.16 (0.09–0.29)**	**<0.001**		**0.19 (0.1–0.35)**	**<0.001**	
500+	**0.09 (0.05–0.16)**	**<0.001**	**<0.001**	**0.11 (0.06–0.2)**	**<0.001**	**<0.001**
Current viral load (copies mL^{-1})[C]						
≤400	1.00			1.00		
400–10 000	**1.34 (0.62–2.87)**	**0.452**		**1.09 (0.50–2.39)**	**0.819**	
10 000+	**3.15 (1.97–5.03)**	**<0.001**	**<0.001**	**1.84 (1.09–3.10)**	**0.022**	**0.019**
Prior AIDS[B]						
No	1.00			1.00		
Yes	**2.53 (1.64–3.9)**	**<0.001**	**<0.001**	1.52 (0.95–2.43)	0.079	0.079
Calendar year						
1997–2003	1.00					
2004+	0.92 (0.5–1.67)	0.775	0.775			
Fixed covariates						
Year started cART[C]						
1997	1.00			1.00		
1998–99	0.91 (0.55–1.52)	0.733		0.96 (0.58–1.62)	0.895	
2000+	1.62 (0.92–2.86)	0.096	0.174	1.85 (1.03–3.33)	0.039	0.079

	Univariate			Multivariate		
	HR (95% CI)	***P***	***P*^A**	**HR (95% CI)**	***P***	***P*^A**
No. of drugs in first cART regimen						
3	1.00					
≥4	1.08 (0.44–2.68)	0.859	0.859			
First cART regimen						
NRTI ± PI, no NNRTI	1.00					
NNRTI + PI, ± NRTI	1.50 (0.59–3.79)	0.391				
NRTI + NNRTI, no PI	1.13 (0.74–1.74)	0.568	0.642			
Exposure						
Homosexual	1.00					
Other	1.39 (0.88–2.18)	0.154	0.324			
Age[C]						
<30	1.00			1.00		
30–39	**1.35 (0.63–2.93)**	**0.441**		**1.53 (0.70–3.32)**	**0.284**	
40–49	**1.29 (0.57–2.89)**	**0.540**		**1.65 (0.72–3.75)**	**0.229**	
50+	**2.59 (1.17–5.75)**	**0.019**	**0.012**	**3.73 (1.64–8.47)**	**0.002**	**0.001**
Gender						
Male	1.00					
Female	0.72 (0.26–1.97)	0.528	0.528			
Prior antiretroviral therapy						
No	1.00					
Yes	1.24 (0.81–1.91)	0.324	0.324			
HBV status[C]						
Negative or not tested	1.00			1.00		
Positive	**2.82 (1.50–5.31)**	**0.001**	**0.001**	**3.38 (1.76–6.50)**	**<0.001**	**<0.001**
HCV status[B]						
Negative or not tested	1.00			1.00		
Positive	**1.9 (1.16–3.26)**	**0.012**	**0.012**	1.54 (0.89–2.65)	0.120	0.120

[A] *P* overall, *P*-values reported for test of homogeneity in nominal covariates and test for trend in ordinal covariates. Patients with missing data were not included for testing trend.

[B] Variables included in the final model.

[C] Covariates adjusted for the final model.

Table 4
Predicted rates of TCE using Poisson regression

cART, combination antiretroviral treatment

Year started cART	Years since starting cART	Rate[A]
1997	≤1	0.075
1997	1–3	0.105
1997	3+	0.086
1998–99	≤1	0.052
1998–99	1–3	0.072
1998–99	3+	0.059
2000–03	≤1	0.039
2000–03	1–3	0.055
2000–03	3+	0.045
2004+	≤1	0.027
2004+	1–3	0.038
2004+	3+	0.031

[A] per person-year.