Triple-Class Virologic Failure in HIV-Infected Patients Undergoing Antiretroviral Therapy for Up to 10 Years

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Background: Life expectancy of people with human immunodeficiency virus (HIV) is now estimated to approach that of the general population in some successfully treated subgroups. However, to attain these life expectancies, viral suppression must be maintained for decades.

Methods: We studied the rate of triple-class virologic failure (TCVF) in patients within the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) who started antiretroviral therapy (ART) that included a nonnucleoside reverse-transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (PI/r) from 1998 onwards. We also focused on TCVF in patients who started a PI/r-containing regimen after a first-line NNRTI-containing regimen failed.

Results: Of 45 937 patients followed up for a median (interquartile range) of 3.0 (1.5-5.0) years, 980 developed TCVF (2.1%). By 5 and 9 years after starting ART, an estimated 3.4% (95% confidence interval [CI], 3.1%-3.6%) and 8.6% (95% CI, 7.5%-9.8%) of patients, respectively, had developed TCVF. The incidence of TCVF rose during the first 3 to 4 years on ART but plateaued thereafter. There was no significant difference in the risk of TCVF according to whether the initial regimen was NNRTI or PI/r based ($P=.11$). By 5 years after starting a PI/r regimen as second-line therapy, 46% of patients had developed TCVF.

Conclusions: The rate of virologic failure of the 3 original drug classes is low, but not negligible, and does not appear to diminish over time from starting ART. If this trend continues, many patients are likely to need newer drugs to maintain viral suppression. The rate of TCVF from the start of a PI/r regimen after NNRTI failure provides a comparator for studies of response to second-line regimens in resource-limited settings.

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LIFE EXPECTANCY AND, equivalently, age-specific death rates in people with HIV have been estimated to be approaching those of the uninfected general population in some successfully treated subgroups.[1,2] These promising life expectancies will only be realized, however, if death rates associated with HIV do not rise in the future. The main underlying mechanism by which rates have been reduced is complete suppression of viral replication by antiretroviral therapy (ART), and so low death rates are dependent on the duration of continued viral suppression. Most regimens used so far contain drugs from the original 3 ART classes: nucleos(t)ide reverse-transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs), and protease inhibitors (PIs). Current regimens tend to lead to sustained viral suppression in most patients, but rates of virologic failure (failure to [continue to] suppress viral load) remain appreciable. Virologic failure is thought to occur as the result of an uncertain mixture between suboptimal regimen adherence and the development of resistance. The fact that some patients are infected with resistant virus is probably an additional cause. So, while multiple drugs from several new classes are now available (integrase inhibitors, fusion inhibitors, and chemokine [C-C motif] receptor 5 [CCR5] antagonists), at least in high-income countries, lifelong viral suppression and consequential low death rates cannot be assured indefinitely. Virologic failure of the 3 original classes represents a key stage in a patient's drug failure history, and it is important to monitor the rate with which this is occurring to anticipate the continuing need for new drugs.[3-12] Such prediction of future need is important in the light of the lengthy drug development process.

In high-income countries, regimens containing a ritonavir-boosted PI (PI/r) with 2 NRTIs or an NNRTI with 2 NRTIs are recommended to be used as first-line treatment.[13-16] Short-term randomized trials have

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suggested that patients initiating ART with regimens based on the NNRTI efavirenz have at least as low rates of virologic failure as those starting with PI/r-containing regimens.[17] Long-term follow-up to compare rates of triple-class virologic failure (TCVF) according to the drug classes used in the starting regimen have been restricted to nonrandomized comparisons in cohort studies and have reported little marked difference between PI/r- and NNRTI-containing regimens, albeit with wide confidence intervals.[4] In resource-limited settings, NNRTI-containing regimens are the almost universal choice for initial regimens. Increasingly, second-line regimens containing a PI/r are being introduced in such settings for patients who appear, by whatever means of monitoring available, to be failing first-line regimens.[18] Viral load outcomes of first-line regimens in such settings have been reported, and increasingly, virologic responses to second-line PI/r-based regimens will also be reported. However, there is currently little robust data from high-income countries on response to PI/r-based regimens in patients who have previously failed a first-line NNRTI regimen that can be used as a benchmark for comparison.

Herein, we report the rates of TCVF of the 3 original drug classes in over 45 000 patients within the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) group[19] who started ART with an NNRTI- or PI/r-containing regimen. We further present the rate of TCVF in the subgroup of patients for whom an NNRTI-containing regimen virologically failed before they started a PI/r-containing regimen. This study forms part of the PLATO II project. The original PLATO collaboration reported in 2004 on outcomes in patients for whom viral suppression treatment with an NRTI, an NNRTI, and a PI virologically failed.[11]

METHODS

PATIENTS

COHERE is a collaboration of most HIV observational cohorts in Europe.[19] The 28 cohorts participating in the PLATO II project submitted data in a standardized format[20] to 1 of 2 regional coordinating centers where error checks were performed prior to the cohort data being merged to form the COHERE database. Patients appearing in more than 1 cohort were identified, and duplicate records removed. This analysis (on data merged in 2008) was restricted to antiretroviral-naïve patients 16 years or older who started ART from 1998 onwards with an initial regimen of 2 NRTIs and either an NNRTI or a PI/r. Patients were followed up from the start of ART to their last viral load measurement. Because the definition of virologic failure used in this study requires 4 months of use of a drug, patients were only included if they had at least 4 months (122 days) of follow-up.

STATISTICAL METHODS

Virologic failure of a drug was defined as 1 viral load found to be above 500 copies/mL following at least 4 months of continuous drug use. The main end point in this study was TCVF, defined as virologic failure of 2 NRTIs, 1 NNRTI, and 1 PI/r. Modifications to the definition of virologic failure were considered in several sensitivity analyses: (1) virologic failures were excluded if they were followed by the finding of a viral load below 50 copies/mL without any change in treatment; (2) 3 months of continuous drug use was required instead of 4 months; (3) 6 months of continuous drug use was required; (4) virologic failure was defined as a viral load above 1000 copies/mL instead of 500 copies/mL. A further sensitivity analysis considered a combined virologic failure and drug cessation end point defined as follows: (1) virologic failure of 2 NRTIs or the use and cessation of 5 NRTIs; and (2) virologic failure of a PI/r or the use and cessation of 3 PIs; and (3) virologic failure of an NNRTI or the use and cessation of both nevirapine and efavirenz.

Kaplan-Meier and Cox regression methods were used to investigate the risk of TCVF after starting ART. Potential predictors of TCVF at the time of starting ART were risk group (incorporating sex), year of starting ART, age, initial regimen, pre-ART AIDS diagnosis, CD4 lymphocyte count, and viral load.

In further analyses we focused on a subgroup of patients who had followed a common currently recommended treatment strategy of an NNRTI-based regimen followed, after virologic failure, by a PI/r-based regimen. Patients included in these analyses started ART with an NNRTI-based regimen, experienced virologic failure of an NNRTI regimen (not necessarily their original NNRTI) while PI-naïve, and later started a PI/r regimen while still PI naïve. Follow-up from NNRTI failure to the start of the PI/r therapy was retrospectively broken down by ART use and viral load. These patients were also followed up from the start of the PI/r to TCVF: Kaplan-Meier and Cox regression methods were used to investigate the risk of TCVF after starting the PI/r. Potential predictors of TCVF at the start of the PI/r treatment were risk group, age, AIDS diagnosis between the start of ART and the start of the PI/r regimen, CD4 lymphocyte count, viral load, year of starting the PI/r regimen, number of new NRTIs in the regimen at the start of the PI/r regimen, and cumulative time spent on ART with a viral load above 500 copies/mL (after an NNRTI had virologically failed and before the PI/r regimen was first begun).

The continuous variables (age, CD4 lymphocyte count, and viral load) were fitted as categorical variables to allow us to investigate the shape of the relationship between these variables and the risk of TCVF. The Cox regression models were stratified by cohort. All *P* values are 2 sided. Analyses were performed using SAS software, version 9.1 (SAS Inc, Cary, North Carolina).

RESULTS

DEVELOPMENT OF TCVF IN PATIENTS STARTING ART

The pre-ART characteristics of the 45 937 patients included in the analysis are summarized in **Table 1**. Patients were followed up for a median (interquartile range [IQR]) of 3.0 (1.5-5.0) years (maximum follow-up, 10.2 years), and 980 developed TCVF (2.1%). The incidence of TCVF after ART initiation rose in the first 3 to 4 years but appeared to plateau at around 1.0 to 1.5 per 100 person-years thereafter, up to year 9 (**Figure**). By 5 and 9 years from the start of ART, the estimated cumulative proportions of patients who had developed TCVF were 3.4% (95% confidence interval [CI], 3.1%-3.6%) and 8.6% (95% CI, 7.5%-9.8%), respectively. Of the included patients, 1238 died without developing TCVF (2.7%).

Of the 29 282 patients starting ART with an NNRTI regimen, 4836 had a pre-ART AIDS diagnosis (16.5%), compared with 4140 of the 16 655 starting ART with a PI/r regi-

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Table 1. Patient Characteristics at the Time of Starting ART

Characteristic	Value[a] (n=45 937)
Combined sex/risk group	
Homosexual men	16 649 (36.2)
Heterosexual men	9122 (19.9)
Heterosexual women	10 523 (22.9)
IDU	5586 (12.2)
Other or unknown	4057 (8.8)
Age, y	
16-24	2570 (5.6)
25-34	15 467 (33.7)
35-44	17 814 (38.8)
45-59	8516 (18.5)
≥60	1570 (3.4)
Year of starting ART	
1998-2001	16 509 (35.9)
2002-2003	11 474 (25.0)
2004-2008	17 954 (39.1)
Initial regimen	
2 NRTIs + 1 NNRTI	29 282 (63.7)
Efavirenz	16 978 (58.0)
Nevirapine	12 304 (42.0)
2 NRTIs + 1 PI/r	16 655 (36.3)
Lopinavir/r	9638 (57.9)
Indinavir/r	2731 (16.4)
Saquinavir/r	1804 (10.8)
Atazanavir/r	1279 (7.7)
Fosamprenavir/r	1016 (6.1)
Amprenavir/r	129 (0.8)
Tipranavir/r	47 (0.3)
Darunavir/r	11 (0.1)
Positive AIDS diagnosis prior to starting ART	8976 (19.5)
CD4 lymphocyte count, cells/μL	
0-49	5937 (12.9)
50-199	13 310 (29.0)
200-349	13 478 (29.3)
350-499	5014 (10.9)
≥500	3708 (8.1)
Unknown	4490 (9.8)
Viral load, $\log_{10}$ copies/mL	
0.00-3.99	7431 (16.2)
4.00-4.49	5300 (11.5)
4.50-4.99	9406 (20.5)
5.00-5.49	10 455 (22.8)
5.50-5.99	6473 (14.1)
≥6.00	1528 (3.3)
Unknown	5344 (11.6)
Age, median (IQR), y	37 (32-44)
CD4 lymphocyte count, median (IQR), cells/μL	211 (100-321)
Viral load, median (IQR), $\log_{10}$ copies/mL	4.9 (4.3-5.4)

Abbreviations: ART, antiretroviral therapy; IDU, injection drug users; IQR, interquartile range; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; /r, ritonavir-boosted drug.

[a] Unless otherwise indicated, data are reported as number (percentage) of patients.

men (24.9%). The respective median (IQR) CD4 lymphocyte counts and viral loads were 228 (129-335) cells/μL and 4.8 (4.1-5.3) $\log_{10}$ copies/mL in patients starting an NNRTI regimen and 178 (66-297) cells/μL and 5.0 (4.5-5.5) $\log_{10}$ copies/mL in patients starting a PI/r regimen.

A lower risk of TCVF was observed in homosexual men than in the other combined sex and risk groups (**Table 2**). Older age at the time of starting ART was found to be associated with a lower risk of TCVF (age ≥60 years vs age 35-44 years, adjusted hazard ratio [HR], 0.56; 95% CI, 0.35-0.92; age 16-24 years vs age 35-44 years, adjusted HR, 1.73; 95% CI, 1.35-2.22). Lower pre-ART CD4 lymphocyte count and higher pre-ART viral load were associated with an increased risk of TCVF (CD4, 350-499 cells/μL vs 200-349 cells/μL adjusted HR, 0.63; 95% CI, 0.49-0.82; viral load ≥6.0 $\log_{10}$ copies/mL vs <4.0 $\log_{10}$ copies/mL adjusted HR, 1.86; 95% CI, 1.30-2.67). There was no significant difference in the risk of TCVF according to whether an NNRTI or a PI/r was used in the initial ART regimen (adjusted HR for initial PI/r vs initial NNRTI, 0.88; 95% CI, 0.75-1.03) (P=.11).

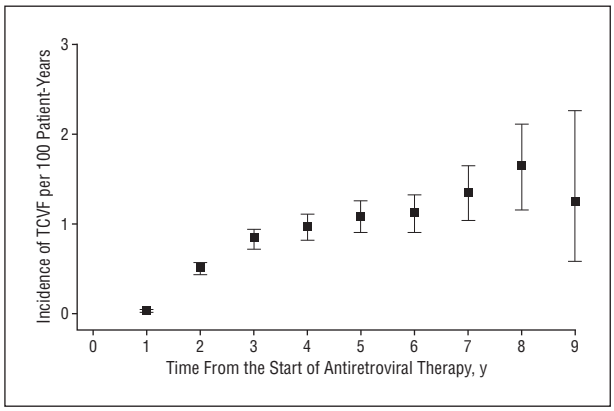

Figure. Incidence with 95% confidence intervals (vertical brackets) of triple-class virologic failure (TCVF) during each year after the start of antiretroviral therapy.

DEVELOPMENT OF TCVF IN PATIENTS STARTING A PI/r REGIMEN AS SECOND-LINE ART

Of the 29 282 patients who started ART with an NNRTI, 6568 experienced virologic failure of an NNRTI (22.4%). Of those for whom an NNRTI virologically failed, 6334 were PI-naïve (96.4%). Among these 6334 people, 2429 later started a PI regimen, of whom 2042 (84.1%) started a PI/r regimen. The characteristics of these patients at the time of starting the PI/r treatment are summarized in **Table 3**. The median (IQR) time from starting ART to the NNRTI failure was 0.9 (0.5-1.9) years, and the median (IQR) time from the NNRTI failure to starting a PI/r regimen was 0.8 (0.3-2.2) years. Of a total of 2945 person-years of follow-up between failure of the NNRTI and initiation of the PI/r regimens, 353 person-years were spent off ART (12%); 1928 person-years were spent on ART with viral loads higher than 500 copies/mL (65%); and 664 person-years were spent on ART with viral loads of 500 copies/mL or lower (23%).

Of the 2042 patients in this analysis, 575 developed TCVF (28.2%), in all cases on the date of virologic failure of a PI/r. The estimated cumulative proportions (95% CIs) of patients with TCVF 1 and 5 years after starting a PI/r regimen were 20.4% (18.4%-22.3%) and 46.3% (42.8%-49.7%), respectively. In the heterosexual risk groups, 56.3% (95% CI, 49.3%-60.0%) developed TCVF after 5 years. Predictors of TCVF after the start of the PI/r regimen in this group of patients are listed in **Table 4**. Higher viral loads

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Table 2. Selected Findings of Statistical Analysis for Risk of TCVF

Characteristic	TCVF by 5 y, % (95% CI)[a]	Univariable Analysis[b] HR (95% CI)	Univariable Analysis[b] *P* Value	Multivariable Analysis[c] HR (95% CI)	Multivariable Analysis[c] *P* Value
Risk group					
Homosexual men	2.3 (1.9-2.6)	1 [Reference]	<.001	1 [Reference]	<.001
Heterosexual men	4.3 (3.6-4.9)	1.86 (1.55-2.23)		1.70 (1.41-2.05)	
Heterosexual women	4.2 (3.6-4.8)	1.73 (1.45-2.06)		1.53 (1.28-1.83)	
IDU	3.7 (3.0-4.5)	1.96 (1.58-2.42)		1.86 (1.49-2.30)	
Other or unknown	3.5 (2.6-4.4)	1.62 (1.26-2.08)		1.47 (1.14-1.90)	
Age, y					
16-24	5.7 (4.2-7.1)	1.53 (1.20-1.95)	<.001	1.73 (1.35-2.22)	<.001
25-34	3.6 (3.1-4.0)	1.16 (1.01-1.34)		1.26 (1.09-1.46)	
35-44	3.3 (2.9-3.7)	1 [Reference]		1 [Reference]	
45-59	2.5 (2.0-3.0)	0.78 (0.64-0.96)		0.79 (0.64-0.97)	
≥60	1.8 (0.8-2.8)	0.59 (0.36-0.96)		0.56 (0.35-0.92)	
Year of starting ART					
1998-2001	3.4 (3.1-3.7)	1 [Reference]	.58	1 [Reference]	.93
2002-2003	3.4 (2.9-3.9)	1.09 (0.92-1.28)		1.01 (0.85-1.20)	
2004-2008		0.98 (0.75-1.29)		0.96 (0.73-1.27)	
Initial regimen					
2 NRTIs + 1 NNRTI	3.3 (3.0-3.6)	1 [Reference]	.21	1 [Reference]	.11
2 NRTIs + 1 PI/r	3.5 (3.0-4.0)	1.10 (0.95-1.27)		0.88 (0.75-1.03)	
Pre-ART AIDS					
No	3.0 (2.8-3.3)	1 [Reference]	<.001	1 [Reference]	.02
Yes	4.7 (4.1-5.4)	1.63 (1.41-1.87)		1.21 (1.03-1.41)	
CD4 lymphocyte count, cells/μL					
0-49	5.8 (4.9-6.7)	2.08 (1.73-2.51)	<.001	1.70 (1.38-2.11)	<.001
50-199	4.0 (3.5-4.5)	1.31 (1.10-1.56)		1.22 (1.02-1.46)	
200-349	2.9 (2.4-3.3)	1 [Reference]		1 [Reference]	
350-499	1.8 (1.2-2.3)	0.61 (0.47-0.80)		0.63 (0.49-0.82)	
≥500	1.7 (1.1-2.2)	0.52 (0.38-0.71)		0.55 (0.40-0.74)	
Unknown	3.4 (2.6-4.2)	1.32 (1.05-1.66)		1.22 (0.90-1.65)	
Viral load, $\log_{10}$ copies/mL					
0.00-3.99	2.9 (2.3-3.5)	1 [Reference]	<.001	1 [Reference]	<.001
4.00-4.49	2.6 (2.0-3.2)	1.03 (0.79-1.34)		0.96 (0.74-1.26)	
4.50-4.99	3.0 (2.4-3.5)	1.17 (0.93-1.46)		1.03 (0.82-1.29)	
5.00-5.49	3.5 (3.0-4.1)	1.51 (1.22-1.88)		1.24 (0.99-1.55)	
5.50-5.99	4.2 (3.5-5.0)	1.88 (1.50-2.37)		1.44 (1.13-1.84)	
≥6.00	5.0 (3.2-6.7)	2.41 (1.70-3.42)		1.86 (1.30-2.67)	
Unknown	3.7 (2.9-4.4)	1.54 (1.21-1.97)		1.15 (0.85-1.56)	

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; IDU, injection drug users; IQR, interquartile range; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; /r, ritonavir-boosted drug; TCVF, triple-class virologic failure.

[a] Kaplan-Meier estimates of the cumulative proportions with TCVF by 5 years from the start of ART.

[b] Hazard ratios for the risk of TCVF after starting ART from univariable Cox regression models.

[c] Hazard ratios from a multivariable Cox regression model.

and lower CD4 lymphocyte counts at the time of starting a PI/r regimen were associated with a higher risk of TCVF, and the risk of TCVF was lower in homosexual men than in the other risk groups. Patients who, between NNRTI failure and PI/r regimen initiation, spent less time on ART with a viral load above 500 copies/mL had a lower risk of TCVF after starting the PI/r regimen (3-6 months vs 0-3 months adjusted HR, 1.43; 95% CI, 1.11-1.84). Inclusion of new NRTIs in the regimen at the time of starting the PI/r treatment was not statistically significant for predicting TCVF (at least 1 new NRTI vs no new NRTIs adjusted HR, 0.85; 95% CI, 0.70-1.03).

SENSITIVITY ANALYSES

In an analysis that excluded those virologic failures that were followed by a viral load below 50 copies/mL without any change in treatment, 880 patients developed TCVF (1.9%). The estimated cumulative proportions (95% CIs) of patients with TCVF by 5 and 9 years after starting ART were 3.0% (2.8%-3.3%) and 7.8% (6.7%-9.0%), respectively. The results from the multivariable Cox regression model were consistent with those from the model obtained for the main analysis.

When the definition of virologic failure was modified to require 3 months of continuous use of a drug before failure, the estimated cumulative proportion (95% CI) with TCVF by 9 years from the start of ART was 9.5% (8.3%-10.6%). For 6 months of continuous use, the same estimate was 7.5% (6.3%-8.6%). Where the definition was modified to require 4 months of continuous use and a viral load above 1000 copies/mL, the estimate was 7.6% (6.6%-8.6%).

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Table 3. Patient Characteristics at the Time of Starting a PI/r Regimen as Second-Line Antiretroviral Therapy[a]

Characteristic	Subjects, No. (%) (n=2042)
Combined sex/risk group	
Homosexual men	631 (30.9)
Heterosexual men	465 (22.8)
Heterosexual women	484 (23.7)
IDU	303 (14.8)
Other or unknown	159 (7.8)
Age, y	
16-24	62 (3.0)
25-34	587 (28.8)
35-44	947 (46.4)
45-59	382 (18.7)
≥60	64 (3.1)
Year of first starting a PI/r regimen	
1998-2003	750 (36.7)
2004-2005	851 (41.7)
2006-2008	441 (21.6)
Positive AIDS diagnosis between start of ART and starting a PI/r regimen	258 (12.6)
CD4 lymphocyte count, cells/μL	
0-49	200 (9.8)
50-199	579 (28.4)
200-349	650 (31.8)
350-499	351 (17.2)
≥500	256 (12.5)
Unknown	6 (0.3)
Viral load, $\log_{10}$ copies/mL	
0.00-2.99	353 (17.3)
3.00-3.99	495 (24.2)
4.00-4.99	703 (34.4)
≥5.00	426 (20.9)
Unknown	65 (3.2)
New NRTIs in regimen	1501 (73.5)
Cumulative time undergoing ART with viral load >500 copies/mL after virologic failure of NNRTI and before first starting a PI/r regimen, mo	
0-3	536 (26.3)
3-6	429 (21.0)
6-18	601 (29.4)
≥18	476 (23.3)
Initial PI (or PI pair)	
Lopinavir/r	1081 (52.9)
Atazanavir/r	509 (24.9)
Other single PI/r	368 (18.0)
Double PI/r	84 (4.1)
Age, median (IQR), y	38 (33-44)
CD4 lymphocyte count, median (IQR), cells/μL	244 (140-380)
Viral load, median (IQR), $\log_{10}$ copies/mL	4.2 (3.3-4.9)

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; IDU, injection drug users; IQR, interquartile range; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; /r, ritonavir-boosted drug; TCVF, triple-class virologic failure.

[a]Unless otherwise indicated, data are reported as number (percentage) of patients.

An end point intended to capture exhaustion of the original 3 antiretroviral classes through use and cessation of drug regimens as well as through virologic failure was experienced by 1177 patients (2.6%): the estimated cumulative proportions by 5 and 9 years were 3.8% (3.5%-4.1%) and 12.7% (11.2%-14.2%), respectively.

COMMENT

In this large collaborative analysis we found that the rate with which patients experienced virologic failure of the original 3 drug classes rose over the first 3 to 4 years from start of ART to around 1% per year and then stayed around this level thereafter. By 9 years from the start of ART, an estimated 8.6% of patients had developed TCVF. While this confirms the low rate with which the virologic benefits of these classes are lost,[3-5,10] from the perspective of lifelong maintenance of viral suppression it suggests that many patients are likely to eventually require newer drugs within the coming decades.

It is worth noting that development of TCVF may not necessarily mean that all 3 classes have been exhausted, particularly given the availability of newer PIs and NNRTIs such as darunavir and etravirine, which have been shown to be effective in treatment-experienced patients.[21] Drugs from new classes are now available in high-income countries,[22-24] and encouraging results have been obtained in clinical trials. However, they all have limitations in routine clinical practice: integrase inhibitors are somewhat prone to lose efficacy due to resistance development[25]; enfuvirtide requires injection; and CCR5 antagonists are only active against R5 strains of virus. Thus, in patients who have experienced virologic failure of the 3 original classes, it is uncertain whether these new classes will then be able to ensure lifelong viral suppression. Some patients will eventually require further options, and given the length of the drug development process, it is important that new compounds continue to be developed.

The rates of development of TCVF were very similar whether ART was started with NNRTI-containing regimens or PI/r-containing regimens, consistent with previous observations from cohort studies.[4,10] This finding supports current guidelines that recommend that specific drugs within either class be used in first-line regimens.[13-16] Factors in our analysis associated with slower development of TCVF included being in the homosexual male risk group and older age. While the improved outcome in older people, identified in previous studies,[4] is likely to be explained by a tendency for better adherence in older people,[26,27] the reasons for the better outcomes observed in homosexual men are less clear, although factors such as adherence, socioeconomic status, migration status, and health-seeking behavior could also play a role.

We also found that those with lower pre-ART viral load and those with higher pre-ART CD4 lymphocyte count tended to develop TCVF more slowly, as noted in previous observations.[4,5] This could partly be explained by differences in health-seeking behavior, and hence adherence, between those who present early for therapy and therefore start ART at a higher CD4 lymphocyte count.

We also investigated the rate of development of TCVF in people for whom an NNRTI regimen virologically failed and who then started a PI/r-containing regimen as their first PI treatment. Owing to their failure history, this group generally had poorer adherence than patients who had not previously experienced virologic failure. There are relatively few robust data on virologic responses in pa-

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Table 4. Selected Findings of Statistical Analysis for Risk of TCVF for Patients Who Started a PI/r Regimen as Second-Line Antiretroviral Therapy

Characteristic[a]	TCVF by 1 y, % (95% CI)[b]	Univariable Analysis[c] HR (95% CI)	Univariable Analysis[c] *P* Value	Multivariable Analysis[d] HR (95% CI)	Multivariable Analysis[d] *P* Value
Risk group					
Homosexual men	13.4 (8.8-18.0)	1 [Reference]	<.001	1 [Reference]	<.001
Heterosexual men	25.5 (21.0-29.9)	1.86 (1.46-2.37)		1.64 (1.27-2.10)	
Heterosexual women	22.3 (18.1-26.5)	1.84 (1.46-2.34)		1.70 (1.33-2.18)	
IDU	22.9 (17.6-28.2)	1.74 (1.30-2.33)		1.56 (1.16-2.11)	
Other or unknown	22.2 (14.9-29.5)	1.58 (1.12-2.23)		1.36 (0.96-1.93)	
Age, y					
16-24	29.8 (17.5-42.2)	1.60 (1.06-2.41)	.27	1.41 (0.93-2.15)	.51
25-34	19.9 (16.3-23.4)	1.03 (0.84-1.25)		1.05 (0.86-1.28)	
35-44	19.1 (16.3-21.9)	1 [Reference]		1 [Reference]	
45-59	21.8 (16.8-26.8)	1.03 (0.81-1.31)		1.04 (0.82-1.33)	
≥60	26.4 (14.5-38.3)	1.12 (0.70-1.80)		1.25 (0.77-2.03)	
Year of first starting a PI/r regimen					
1998-2003	20.4 (17.4-23.3)	1 [Reference]	.003	1 [Reference]	<.001
2004-2005	18.8 (15.9-21.7)	1.24 (1.03-1.50)		1.30 (1.07-1.57)	
2006-2008	26.6 (19.8-33.3)	1.71 (1.23-2.37)		1.82 (1.30-2.54)	
AIDS diagnosis between start of ART and first starting a PI/r regimen					
No	19.2 (17.2-21.3)	1 [Reference]	.003	1 [Reference]	.24
Yes	28.1 (21.9-34.2)	1.40 (1.12-1.76)		1.15 (0.91-1.45)	
CD4 lymphocyte count, cells/μL					
0-49	40.6 (33.1-48.2)	2.39 (1.86-3.08)	<.001	1.93 (1.47-2.53)	<.001
50-199	25.0 (21.0-28.9)	1.38 (1.12-1.69)		1.25 (1.00-1.54)	
200-349	18.5 (15.1-21.8)	1 [Reference]		1 [Reference]	
350-499	12.5 (8.6-16.5)	0.72 (0.54-0.96)		0.83 (0.62-1.11)	
≥500	9.0 (5.0-13.0)	0.70 (0.51-0.96)		0.83 (0.60-1.16)	
Unknown		1.66 (0.39-7.00)		1.82 (0.43-7.77)	
Viral load, $\log_{10}$ copies/mL					
0.00-2.99	9.8 (6.1-13.4)	1 [Reference]	<.001	1 [Reference]	<.001
3.00-3.99	16.1 (12.5-19.7)	1.32 (0.96-1.82)		1.34 (0.96-1.85)	
4.00-4.99	22.1 (18.6-25.5)	1.78 (1.33-2.40)		1.60 (1.17-2.19)	
≥5.00	31.6 (26.7-36.6)	2.52 (0.86-3.42)		2.07 (1.48-2.89)	
Unknown	12.8 (3.9-21.7)	1.52 (0.88-2.62)		1.30 (0.74-2.27)	
New NRTIs in regimen, No.					
0	24.2 (20.1-28.4)	1 [Reference]	.06	1 [Reference]	.10
≥1	19.1 (16.8-21.3)	0.84 (0.69-1.01)		0.85 (0.70-1.03)	
Cumulative time undergoing ART with viral load >500 copies/mL after virologic failure of an NNRTI and before first starting a PI/r regimen, mo					
0-3	16.1 (12.8-19.5)	1 [Reference]	.02	1 [Reference]	.004
3-6	18.4 (14.2-22.6)	1.31 (1.02-1.70)		1.43 (1.11-1.84)	
6-18	24.8 (20.9-28.6)	1.44 (1.14-1.82)		1.51 (1.20-1.90)	
≥18	21.6 (17.2-26.0)	1.37 (1.06-1.78)		1.28 (0.99-1.66)	

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio; IDU, intravenous drug user; IQR, interquartile range; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; /r, ritonavir-boosted drug; TCVF, triple-class virologic failure.

[a] At the time of first starting a PI/r regimen.

[b] Kaplan-Meier estimate of the cumulative proportions with TCVF by 1 y from first starting a PI/r regimen.

[c] Hazard ratios for the risk of TCVF after first starting a PI/r regimen as second-line ART from univariable Cox regression models.

[d] Hazard ratios from a multivariable Cox regression model.

tients using PI/r-containing second-line regimens, and our estimate of 46% with TCVF by 5 years (55% in the heterosexual risk groups) provides a benchmark against which comparisons can be made, including studies of second-line regimens in resource-limited settings. Those comparisons will have to consider the factors associated with a slower time to TCVF in our analysis. Again, homosexual men experienced a slower rate of TCVF, as did those with lower viral load and those with higher CD4 lymphocyte count, possibly partially owing to these markers reflecting patient adherence. The observed increased risk of TCVF in patients starting the PI/r regimen in later calendar years is difficult to interpret. A possible explanation is that, as avoidance of initial virologic failure has improved in more recent calendar years, patients with more serious adherence issues may be overrepresented in later years of starting a PI/r regimen after NNRTI failure.

For those patients for whom an NNRTI-based first-line regimen virologically failed and who subsequently

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started a PI/r regimen as second-line ART, the time to the start of the PI/r regimen was long (median, 0.8 years) but in line with previous data.[28] Lower CD4 lymphocyte count and higher viral load at the time of first virologic failure were associated with shorter time to starting the third antiretroviral class (data not shown). In the present study, we observed that TCVF developed more slowly in patients who, between the failure of an NNRTI regimen and the starting of a PI/r regimen, had spent less than 3 months on ART with a viral load above 500 copies/mL. This finding is consistent with the view that earlier detection of failure of NNRTI-containing drug regimens and switch to a PI/r regimens without delay could potentially significantly reduce the rate of TCVF.

We considered the effect of modifications in our definition of TCVF, but none of these resulted in sizeable changes to our estimates.

There are several limitations to our analysis. First, we only studied virologic failure of drugs and did not directly factor in data on resistance mutations detected. In some cases, virologic failure occurs in the absence of resistance mutations, perhaps largely owing to poor adherence. If adherence issues can be overcome, then the drugs should remain active, and options have not been lost.

Second, in our comparison of NNRTI- and PI/r-containing regimens, patients were not randomized to receive one regimen or the other, so there were differences at ART initiation between these 2 patient groups. While we adjusted for factors measured at the start of ART that were associated with the rate of TCVF, bias in the comparison due to unmeasured confounding may well remain.

Third, although the maximum follow-up after starting ART was in excess of 10 years, the available follow-up for many patients was substantially less. It may be that, with longer follow-up, the incidence of TCVF would eventually begin to decrease with time from starting ART, both as patients most susceptible to periods of poor adherence are selected out and as the long-term impact on adherence of the more recent easy-to-take combination pills is realized.[29,30]

A further limitation is that patients included in COHERE tend to be treated in large clinics with strong research links, and so may not be representative of the population of patients on ART in Europe.

The rates of TCVF that we observed may at first sight seem inconsistent with results from randomized trials in which relatively high proportions of people have been observed to exhibit the signs of drug failure within 1 to 2 years of the start of therapy. However, most trials have used composite definitions of failure so that, for example, stopping treatment with some drugs and a missing viral load value are considered criteria for defining failure equal to the finding of an elevated viral load itself.[31] Therefore, it is not possible to directly compare those findings with those of the present study. Furthermore, most trials consider the failure of only 1 regimen, typically containing 2 drug classes, while we are considering the failure of 3 classes over at least 2 separate regimen failure episodes.

In conclusion, the rate of virologic failure of the 3 original drug classes is low, but not negligible, and does not appear to diminish with time from start of ART. If this trend continues, many patients are likely to eventually need newer drugs, possibly other than those currently available, to maintain viral suppression for their lifetime. It is important to continue to monitor the development of TCVF over longer periods of follow-up and to study the incidence of multiple class failure following exposure to the newer antiretroviral classes. The rate of TCVF from start of a PI/r regimen after previous NNRTI failure is relatively high at around 46% by 5 years and

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provides a relevant comparator for future studies in resource-limited settings.

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