Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study

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Summary

Background **The effect of transmitted drug resistance (TDR) on first-line combination antiretroviral therapy (cART) for HIV-1 needs further study to inform choice of optimum drug regimens. We investigated the effect of TDR on outcome in the first year of cART within a large European collaboration.**

Methods **HIV-infected patients of any age were included if they started cART (at least three antiretroviral drugs) for the first time after Jan 1, 1998, and were antiretroviral naive and had at least one sample for a genotypic test taken before the start of cART. We used the WHO drug resistance list and the Stanford algorithm to classify patients into three resistance categories: no TDR, at least one mutation and fully-active cART, or at least one mutation and resistant to at least one prescribed drug. Virological failure was defined as time to the first of two consecutive viral load measurements over 500 copies per mL after 6 months of therapy.**

Findings **Of 10 056 patients from 25 cohorts, 9102 (90·5%) had HIV without TDR, 475 (4·7%) had at least one mutation but received fully-active cART, and 479 (4·8%) had at least one mutation and resistance to at least one drug. Cumulative Kaplan-Meier estimates for virological failure at 12 months were 4·2% (95% CI 3·8–4·7) for patients in the no TDR group, 4·7% (2·9–7·5) for those in the TDR and fully-active cART group, and 15·1% (11·9–19·0) for those in the TDR and resistant group (log-rank p<0·0001). The hazard ratio for the difference in virological failure between patients with TDR and resistance to at least one drug and those without TDR was 3·13 (95% CI 2·33–4·20, p<0·0001). The hazard ratio for the difference between patients with TDR receiving fully-active cART and patients without TDR was 1·47 (95% CI 0·19–2·38, p=0·12). In stratified analysis, the hazard ratio for the risk of virological failure in patients with TDR who received fully-active cART that included a non-nucleoside reverse transcriptase inhibitor (NNRTI) compared with those without TDR was 2·0 (95% CI 0·9–4·7, p=0·093).**

Interpretation **These findings confirm present treatment guidelines for HIV, which state that the initial treatment choice should be based on resistance testing in treatment-naive patients.**

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Introduction

In Europe, widespread use of combination antiretroviral therapy (cART) has been associated with a substantial improvement in survival. However, this improvement is paralleled by increased transmission of antiretroviral drug resistance: an estimated 10–15% of antiretroviral-naive patients in Europe[1–5] and the USA[6] carry viruses with at least one drug resistance mutation.

Mutations in the HIV genome that confer drug resistance are a major reason for virological failure and can affect immunological response to ART. Treatment guidelines recommend genotypic testing in antiretroviral-naive patients to detect the presence of transmitted drug resistance (TDR) and to adapt their first-line treatment accordingly.[7,8] However, the effect of TDR on virological and immunological response remains controversial and has not been fully described. In particular, the effect of TDR on virological response in patients treated with a fully-active regimen has not been assessed in large datasets in the context of systematic genotypic testing before treatment initiation.

We assessed the effect of TDR on virological and immunological response in the first year of cART in adults and children within a large European collaboration of HIV observational cohorts (EuroCoord) and the European Collaborative HIV and Anti-HIV Drug Resistance Network (CHAIN).

Methods

Study population

The collaborative HIV cohorts CASCADE (Concerted Action on SeroConversion to AIDS and Death in Europe),

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See Online for webappendix

COHERE (Collaboration of Observational HIV Epidemiological Research Europe), EuroSIDA, and PENTA-EPPICC (Paediatric European Network for Treatment of AIDS—European Pregnancy and Paediatric HIV Cohort Collaboration) are the four founding networks of EuroCoord. CHAIN and EuroCoord joined their collaborative efforts for this project.

25 cohorts that participated through the EuroCoord network submitted a defined dataset (patient demographics, use of cART, CD4 cell counts, and HIV RNA measurements up to 16 months after the start of cART; clinical events [AIDS and death]; and genotypic resistance test results) to their network-specific coordination centre, by the HIV cohort data exchange protocol.[9]

HIV-infected patients of any age were included if they started cART (at least three antiretroviral drugs) for the first time after Jan 1, 1998, and were antiretroviral naive and had at least one sample for a genotypic test taken before the start of cART. We focused our analysis on response in patients with TDR who were receiving a fully-active treatment as well as regimens containing two nucleoside reverse transcriptase inhibitors (NRTIs) with either a ritonavir-boosted protease inhibitor or a non-NRTI (NNRTI), because these regimens are recommended as first-line treatments in high-income countries.[7,8]

Each coordinating centre ensured that their participating cohorts had documented evidence of ethics approval for such a project and that use of these data complied with local and national data protection requirements.

Procedures

Genotype test results were submitted as nucleotide sequences or as lists of mutations for protease and reverse transcriptase, in relation to an HXB2 consensus sequence. Mutation data were combined if more than one test result was available. Virus subtype was used as reported by the cohorts or as identified by the Rega subtyping tool (version 2).[10]

TDR was defined in two steps. First, we used the WHO drug resistance surveillance list[11] to distinguish between patients harbouring a virus with at least one TDR mutation and those with no TDR mutation from this list. Second, for patients harbouring a virus with at least one TDR mutation, we used the Stanford algorithm (version 6.0.5)[12] to classify patients into those receiving fully active cART (Stanford levels 1 [susceptible] or 2 [potential low-level resistance] for all prescribed drugs), or patients harbouring a resistant HIV strain (Stanford levels 3 [low-level resistance], 4 [intermediate resistance], or 5 [high-level resistance]) that affected at least one of their prescribed drugs. For robustness analyses, we further distinguished between patients with high-level resistance (level 5) and those with low-level or intermediate resistance (level 3 or 4) to at least one of their drugs. Virological failure was defined as two consecutive viral loads over 500 copies per mL after 6 months of treatment, with the date of first viral load over 500 copies per mL as the failure date. Patients were censored if they died, stopped cART, were lost to follow-up, or were censored at their last available viral load date in a 6–16-month window (patients with only one viral load after 6 months were censored at the date of viral load measurement).

Statistical analysis

Time to virological failure was assessed with Kaplan-Meier curves and analysed by Cox proportional hazards model stratified by cohort. Baseline is defined as date of cART initiation.

We modelled the difference in CD4 cell counts between treatment and follow-up. All CD4 cell counts measured after start of cART and before 12 months were used, and CD4 cell counts taken after treatment stops or changes were excluded. Children younger than 5 years were excluded from this analysis because of substantial differences in the variation of absolute CD4 cell count in this group.[13] We used a piecewise linear mixed model with two slopes to model the difference in CD4 cell counts before treatment and during follow-up. The first slope was defined up to 1 month and the second slope after 1 month up to 12 months on the basis of graphically identified slope change at 1 month.

Multivariable models were adjusted for sex, age, viral load and CD4 cell count before treatment ($\log_{10}$ transformed), HIV subtype (B, non B, unknown), ethnic origin (African, European, other and unknown), previous AIDS diagnosis (yes, no, unknown), HIV transmission risk group (homosexual or bisexual, heterosexual, injecting drug user, perinatal, or other or unknown), and year of treatment start (1998–99, 2000–02, 2003–04, 2005–06, and 2007–08 for virological response main analysis; and 1998–99, 2000–05, and 2006–08 for sensitivity analyses, stratified analysis, and immunological response). Analyses were done with SAS (version 9.1). p values are double sided. Several sensitivity analyses were done and are described in webappendix pp 7–11.

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. LW had full access to all the data in the study. LW, DP, and GC had final responsibility for the decision to submit for publication.

Results

Of 12 016 eligible patients, 10 056 had sufficient follow-up data and were included in the main analysis (table 1); 6126 (60·9%) of 10 056 patients had at least one nucleotide sequence available and for 3930 (39%) the result of the resistance test was reported as a list of mutations. The plasma sample for genotypic testing was taken before ART initiation in all patients but the date of testing was after initiation in some patients: 37% of patients were tested before initiation (median 2 months, IQR 1–9), 25%

after initiation (34 months, 2–76), and 38% had an unknown test date (table 1). Median time between diagnosis of HIV and the start of treatment was 11 months (IQR 2–42).

Of 10 056 patients included, 4845 (48·2%) received two NRTIs and one NNRTI, 3117 (31·0%) two NRTIs and one ritonavir-boosted protease inhibitor, 1220 (12·1%) two NRTIs and one unboosted protease inhibitor, 282 (2·8%) NRTIs only (three or four), and 592 (5·9%) other combinations (webappendix pp 1–2). Cumulative Kaplan-Meier estimates for complete cART interruption were 9·8% (95% CI 9·2–10·4) at 6 months and 13·6% (12·9–14·3) at 12 months. Of 1479 patients who interrupted treatment up to 16 months the reason for interruption was treatment failure in 53 (3·6%), toxicity and tolerance issues in 352 (23·8%), and other or unknown reasons in 1074 (72·6%). Cumulative Kaplan-Meier estimates for changing at least one drug were 25·4% (95% CI 24·5–26·2) at 6 months and 37·7% (38·7–36·7) at 12 months. Reasons for the change were treatment failure in 157 (4·3%) patients, tolerance or toxicity in 1138 (30·9%), and other or unknown reasons in 2382 (64·8%). Of 10 056 patients, 440 had virological failure up to 16 months, 66 were censored because they died, 142 were censored because they were lost to follow-up, and 1437 were censored because they interrupted cART; 7971 were censored at their last available viral load measurement at 6–16 months, 1289 of whom had only one viral load assessment after 6 months. Median follow-up was 13·3 months (IQR 9·5–14·7) for all patients.

At least one TDR mutation was identified in 954 of 10 056 patients (9·5%, 95% CI 8·9–10·0), of whom 475 (49·8%) received fully-active cART and 479 (50·2%) were resistant to at least one prescribed drug (webappendix pp 3–5). Of these 479 patients, 157 (32·8%) had Stanford level 5 for at least one prescribed drug, 136 (28·4%) had Stanford level 4, and 186 (38·8%) had Stanford level 3. Median number of active drugs for patients with TDR and at least low-level resistance was 2·5 (IQR 2·0–2·5; range 0·0–4·5).

Cumulative Kaplan-Meier estimates for virological failure at 12 months were 4·2% (95% CI 3·8–4·7) for patients in the no TDR group, 4·7% (2·9–7·5) for those in the TDR and fully-active cART group, and 15·1% (11·9–19·0) for those in the TDR and resistant group (figure 1; log-rank p<0·0001). In adjusted analyses, virological response differed significantly according to the TDR groups (p<0·0001; table 2). Patients in the TDR and resistant group had a 3·13-times higher risk of virological failure (p<0·0001) than did those with no TDR (table 2). By contrast, the risk of virological failure was not significantly different between patients in the TDR and fully-active cART group and those in the no TDR group (p=0·12; table 2). In patients predicted to have resistance to at least one prescribed drug, we assessed the difference in virological failure between patients with at least low-level or intermediate resistance and those fully resistant to at least one prescribed drug (figure 1; log-rank p<0·0001). Compared with patients in the no

	All (n=10 056)	Two NRTIs and one NNRTI (n=4845)	Two NRTIs and one ritonavir-boosted protease inhibitor (n=3117)
Female*	2404 (23·9%)	976 (20·1%)	782 (25·1%)
Age (years)	38 (32–44)	38 (32–45)	38 (32–44)
<2	63 (0·6%)	8 (0·2%)	9 (0·3%)
3–5	60 (0·6%)	11 (0·2%)	3 (0·1%)
6–12	90 (0·9%)	39 (0·8%)	5 (0·2%)
13–17	46 (0·5%)	22 (0·5%)	12 (0·4%)
18–29	1702 (16·9%)	767 (15·8%)	552 (17·7%)
30–39	4099 (40·8%)	1922 (39·7%)	1263 (40·5%)
40–49	2710 (26·9%)	1408 (29·1%)	873 (28·0%)
50–59	952 (9·5%)	496 (10·2%)	298 (9·6%)
≥60	334 (3·3%)	172 (3·6%)	102 (3·3%)
Year of treatment start			
2007–08	2001 (19·9%)	1116 (23·0%)	754 (24·2%)
2005–06	3349 (33·3%)	1781 (36·8%)	1322 (42·4%)
2003–04	2087 (20·8%)	1136 (23·4%)	663 (21·3%)
2000–02	1578 (15·7%)	633 (13·1%)	282 (9·0%)
1998–99	1041 (10·4%)	179 (3·7%)	96 (3·1%)
Transmission risk group			
Homosexual or bisexual men	5025 (50·0%)	2693 (55·6%)	1525 (48·9%)
Injecting drug user	754 (7·5%)	254 (5·2%)	242 (7·8%)
Heterosexual	3259 (32·4%)	1481 (30·6%)	1060 (34·0%)
Perinatal	214 (2·1%)	62 (1·3%)	19 (0·6%)
Other or unknown	804 (8·0%)	355 (7·3%)	271 (8·7%)
Ethnic origin			
African	1002 (10·0%)	448 (9·2%)	283 (9·1%)
European	5653 (56·2%)	2375 (49·0%)	1829 (58·7%)
Other or unknown	3401 (33·8%)	2022 (41·7%)	1005 (32·2%)
Previous AIDS diagnosis			
Yes	1451 (14·4%)	596 (12·3%)	520 (16·7%)
No	7679 (76·4%)	3877 (80·0%)	2248 (72·1%)
Unknown	926 (9·2%)	372 (7·7%)	349 (11·2%)
Subtype			
Non B	2676 (26·6%)	1293 (26·7%)	843 (27·0%)
B	6906 (68·7%)	3345 (69·0%)	2141 (68·7%)
Unknown	474 (4·7%)	207 (4·3%)	133 (4·3%)
Pretreatment viral load (log_{10} copies per mL)†	5 (4·4–5·4)	4·9 (4·4–5·3)	5 (4·5–5·5)
Pretreatment CD4 cell count (cells per μL)‡	218 (124–310)	216 (137–289)	207 (101–313)
Time of genotypic testing§			
Before treatment start	3722 (37·0%)	2114 (46·6%)	1275 (40·9%)
After treatment start	2536 (25·2%)	893 (18·4%)	777 (24·9%)
Unknown	3798 (37·8%)	1838 (40·0%)	1065 (34·2%)

Data are number (%) or median (IQR). Only data from the two most common treatment regimens are shown. Percentages do not add up to 100 in some cases because of rounding. NRTI=nucleotide reverse transcriptase inhibitor. NNRTI=non-nucleotide reverse transcriptase inhibitor. *All n=10 053, two NRTIs and one NNRTI n=4845, and two NRTIs and one ritonavir-boosted protease inhibitor n=3114. †All n=9601, two NRTIs and one NNRTI n=4609, and two NRTIs and one ritonavir-boosted protease inhibitor n=2983. ‡All n=9425, two NRTIs and one NNRTI n=4566, two NRTIs and one ritonavir-boosted protease inhibitor n=2941. §All samples taken before treatment start.

Table 1: **Characteristics of patients at the time of starting combination antiretroviral therapy**

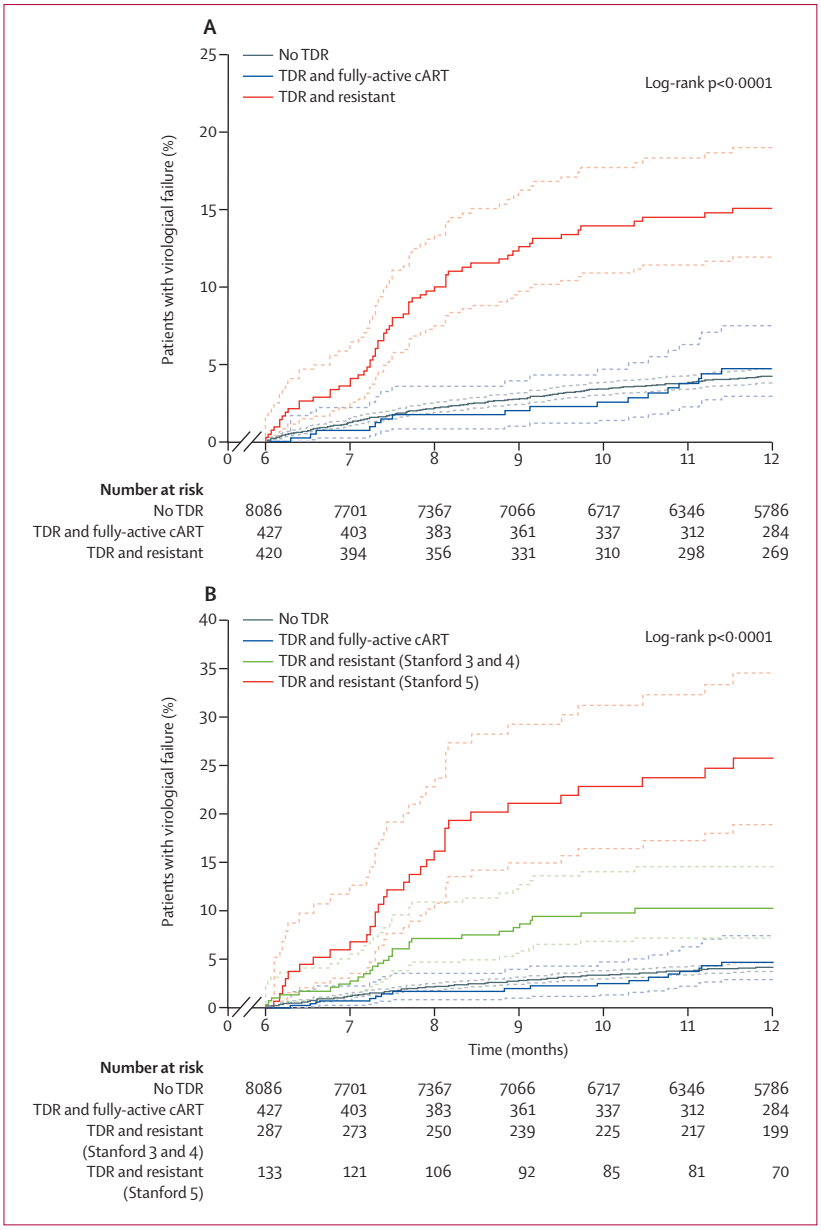

Figure 1: **Kaplan-Meier estimates of the proportion of patients with virological failure**
(A) Risk of virological failure according to patient groups. (B) Risk of virological failure in patients with intermediate and high-level resistance. cART=combination antiretroviral therapy. TDR=transmitted drug resistance. Dotted lines=95% CI.

TDR group, a significantly higher risk of virological failure was reported in those with low-level or intermediate resistance to at least one drug (adjusted HR 2·2, 95% CI 1·5–3·3; p=0·0001); patients with high-level resistance to at least one drug had a 6·3 times higher risk for virological failure (95% CI 4·2–9·4, p<0·0001; webappendix p 9).

Patients who received two NRTIs and a ritonavir-boosted protease inhibitor were more likely to be women (p<0·0001), to have initiated cART in 2006 or later (p<0·0001), to be of European origin (p<0·0001), and to have higher viral loads before treatment (p<0·0001), and were less likely to be homosexual (p<0·0001) than were patients who received two NRTIs and one NNRTI (table 1).

The cumulative Kaplan-Meier estimates for virological failure for patients receiving two NRTIs plus one NNRTI at 12 months were 2·8% for the no TDR group, 4·3% for the TDR and fully-active cART group, and 10·6% for the TDR and resistant group. The risk of virological failure for patients receiving two NRTIs and a ritonavir-boosted protease inhibitor were 2·7% for the no TDR group, 2·7% for the TDR and fully-active cART group, and 10·9% for the TDR and resistant group.

There was weak evidence of higher risk of virological failure in patients with TDR who received fully-active cART consisting of two NRTIs and one NNRTI (HR 2·0, 95% CI 0·9–4·7, p=0·093) compared with those in the no TDR group. By contrast, the risk for virological failure for patients in the TDR and fully-active treatment group who received a treatment regimen containing a ritonavir-boosted protease inhibitor was similar to the group with no TDR (HR 0·9, 95% CI 0·4–2·0, p=0·73; figure 2; webappendix p 10). The interaction was not significant between TDR and the two treatment strata of two NRTIs plus either NNRTI or a ritonavir-boosted protease inhibitor (global p=0·34) or TDR and fully-active cART only (p=0·17). For patients who received other treatments with a low genetic barrier (ie, two NRTIs and an un-boosted protease inhibitor and three or four NRTIs), there was weak evidence of a higher risk for virological failure for patients with TDR but who were predicted to have received a fully-active treatment (two NRTIs and an unboosted protease inhibitor p=0·0823; three or four NRTIs group p=0·0381; webappendix p 11). The interaction between TDR and these four treatment strata was significant in an unadjusted analysis (p=0·0105).

The median increase in CD4 cell count between the start of cART and 12 months was 183 cells per μL (IQR 105–282). Figure 3 shows the unadjusted changes according to the three groups. There was no significant difference in the increase in CD4 cell count in the first month after the start of treatment (global p=0·40) regardless of the presence of TDR and predicted susceptibility to cART. There was weak evidence of a lower CD4 cell increase after the first month for the TDR and resistant group compared with the no TDR group (global p=0·069). Compared with patients in the no TDR group, the estimated difference in increase in CD4 count after 1 month of therapy was eight cells per μL per 12 months (95% CI –11 to 27; p=0·43) for patients with TDR and fully-active cART group and –25 cells per μL per 12 months (–48 to –2; p=0·0326) for patients in the TDR and resistant group.

Compared with the no TDR group, patients who received two NRTIs and one ritonavir-boosted protease inhibitor had an estimated difference of 16 cells per μL

per 12 months (95% CI –10 to 42; p=0·22) in the TDR and fully-active cART group and –18 cells per µL per 12 months (–60 to 23; p=0·39) in the TDR and resistant group. For patients who received two NRTIs plus one NNRTI, the estimated difference was minus seven cells per µL per 12 months (95% CI –37 to 22, p=0·63) in the TDR and fully-active cART group and –34 cells per µL per 12 months (–68 to 0; p=0·0514) in the TDR and resistant group compared with the no TDR group.

Discussion

In this large assessment, TDR was associated with virological failure in patients who received at least one drug to which the virus had lost susceptibility, which confirms results from previous studies (panel).[14–16] We reported that the prescription of a drug classified even with low-level resistance is associated with a significantly higher risk for virological failure, which underscores the need for at least three fully-active antiretroviral drugs to optimise the virological response to a first-line regimen. A stratified analysis showed weak evidence of a higher risk of virological failure in patients who started on a regimen that contained two NRTIs plus one NNRTI if the patient harboured a virus with TDR even when the prescribed treatment was predicted to be fully active. Patients with TDR who started a regimen containing two NRTIs plus one ritonavir-boosted protease inhibitor and who received fully-active treatment had a similar risk of virological failure to that in patients with a virus with no TDR mutations.

The findings for patients receiving two NRTIs plus one NNRTI might be partly explained by the presence of minority NNRTI resistant strains, which would support previous findings that the presence of minority NNRTI resistance mutations might be associated with virological failure if patients start a NNRTI-based regimen.[23–27] In all sensitivity analyses we noted weak evidence for a higher risk of virological failure for patients receiving two NRTIs plus one NNRTI in presence of TDR even when the regimen was predicted to be fully active. The proportion of patients with NRTI mutations in this treatment stratum was higher than that in patients who received two NRTIs plus a boosted protease inhibitor. Thus, the higher rate of virological failure in patients with TDR starting two NRTIs plus one NNRTI when receiving a fully active treatment might not be linked to minority NNRTI mutations but could be caused by minority NRTI mutations affecting the efficiency of the NRTI in the regimen.[28] Furthermore, unmeasured confounding, such as adherence, cannot be ruled out.

The interaction between TDR and treatment strata was not significant, suggesting that the effect of TDR mutations in patients receiving a fully active treatment is not different between the strata two NRTIs plus one NNRTI or a boosted protease inhibitor. However, for other treatment combinations with a low genetic barrier, patients with TDR who received fully active cART had weak evidence of a higher risk for virological failure compared with those harbouring a virus with no TDR. This finding supports the hypothesis that detection of TDR at a population sequencing level might be a sign of hidden resistant minority species. This theory could have clinical implications, especially in resource-limited settings where resistance tests are not routinely available but TDR is expected to rise to equal that in developed countries.

	Univariable (n=10 056)		Multivariable (n=9326)*	
	HR (95% CI)	p	HR (95% CI)	p
TDR	..	<0·0001‡	..	<0·0001‡
No TDR†	1·00	..	1·00	..
TDR and fully-active cART§	1·15 (0·72–1·83)	0·56	1·47 (0·91–2·38)	0·12
TDR and resistant¶	3·30 (2·52–4·32)	<0·0001	3·13 (2·33–4·20)	<0·0001
Sex	..	..	..	..
Female	1·00	..	1·00	..
Male	0·83 (0·67–1·03)	0·09	1·04 (0·80–1·36)	0·76
Risk per additional year of age	0·98 (0·97–0·99)	<0·0001	0·99 (0·98–1·00)	0·15
Year of treatment start	..	<0·0001‡	..	<0·0001‡
2007–08	1·00	..	1·00	..
2005–06	1·95 (1·23–3·10)	0·0047	1·92 (1·14–3·21)	0·0135
2002–04	2·37 (1·47–3·84)	0·0004	2·25 (1·32–3·83)	0·0029
2000–02	4·75 (2·98–7·56)	<0·0001	4·40 (2·61–7·40)	<0·0001
1998–99	6·39 (3·97–10·3)	<0·0001	6·85 (4·03–11·66)	<0·0001
Transmission risk group	..	<0·0001‡	..	<0·0001‡
Heterosexual	1·00	..	1·00	..
Injecting drug user	1·16 (0·82–1·63)	0·41	1·08 (0·74–1·58)	0·69
Homosexual men	0·65 (0·52–0·83)	0·0004	0·67 (0·49–0·91)	0·0113
Perinatal	8·46 (4·07–17·62)	<0·0001	6·56 (2·86–15·03)	<0·0001
Other or unknown	0·93 (0·63–1·37)	0·71	0·92 (0·60–1·41)	0·72
Ethnic origin	..	0·0062‡	..	0·0497‡
European	1·00	..	1·00	..
African	1·63 (1·20–2·22)	0·0019	1·60 (1·10–2·34)	0·0151
Other or unknown	1·28 (0·91–1·78)	0·15	1·17 (0·81–1·68)	0·41
Previous AIDS diagnosis	..	0·0102‡	..	0·12‡
No	1·00	..	1·00	..
Yes	1·41 (1·10–1·81)	0·0067	1·29 (0·98–1·70)	0·066
Unknown	0·73 (0·31–1·76)	0·49	0·79 (0·29–2·11)	0·63
Subtype	..	0·19‡	..	0·034‡
B	1·00	..	1·00	..
Non B	1·10 (0·87–1·38)	0·42	0·87 (0·65–1·18)	0·38
Unknown	0·71 (0·46–1·10)	0·13	0·50 (0·30–0·86)	0·0111
Pretreatment viral load per additional $\log_{10}$ copies per mL	1·02 (0·91–1·14)	0·74	1·03 (0·92–1·16)	0·61
Pretreatment CD4 cell count per additional 100 cells per µL	0·99 (0·95–1·03)	0·55	0·96 (0·92–1·00)	0·064

HR=hazard ratio. TDR=transmitted drug resistance. cART=combination antiretroviral therapy. *Patients were excluded if there were values missing for pretreatment viral load, pretreatment CD4 cell count, or sex. †No mutation from WHO 2009 list of mutations for surveillance of transmitted drug resistant HIV strains. ‡Global p value of the variable. §At least one mutation of the WHO list and Stanford levels 1 or 2 to all prescribed drugs. ¶At least one mutation of the WHO list and resistant to at least one drug in the prescribed regimen (Stanford levels 3, 4, or 5).

Table 2: **Univariable and multivariable analysis of risk factors for time to virological failure**

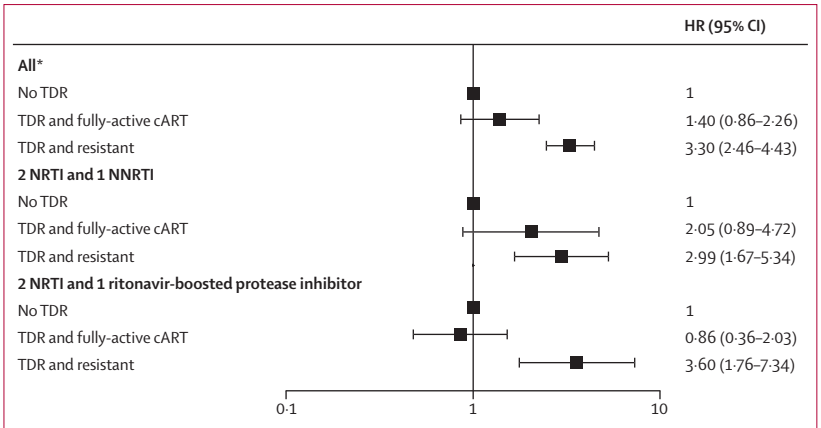

Figure 2: **Adjusted HRs in all patients and patients starting a regimen containing two NRTIs plus either one NNRTI or one ritonavir-boosted protease inhibitor**
HR=hazard ratio. NRTI=nucleotide reverse transcriptase inhibitor. NNRTI=non-nucleotide reverse transcriptase inhibitor. TDR=transmitted drug resistance. cART=combination antiretroviral therapy. *With the following categories for year of treatment start: 1998–99, 2000–05, and 2006–08 in the multivariable model.

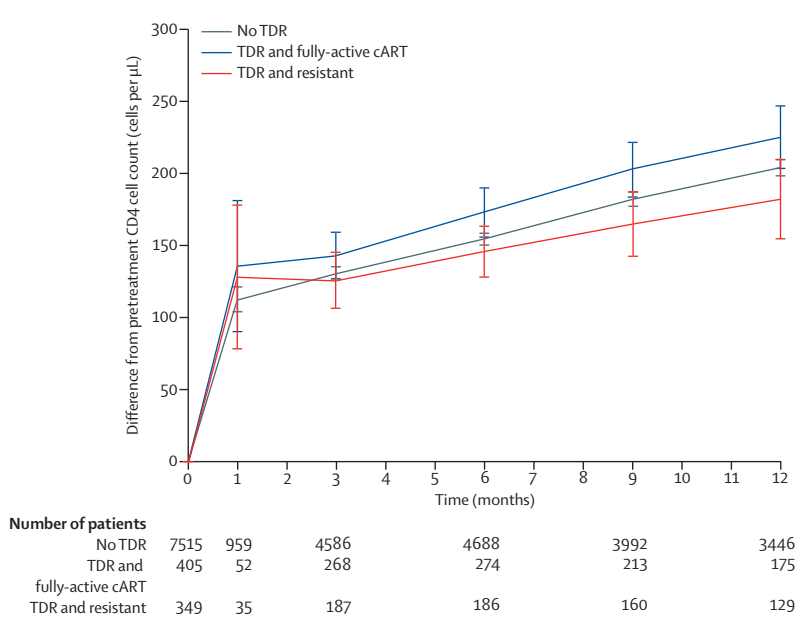

Figure 3: **Change in CD4 cell count**
Vertical bars=95% CI. TDR=transmitted drug resistance.

Patients who received a boosted protease inhibitor plus two NRTIs had the same risk for virological failure in the presence of TDR if the treatment was predicted to be fully active, which might be because of the higher genetic barrier of boosted protease inhibitors compared with NNRTIs.[29] Our finding is in agreement with previous studies that reported that, even when minority protease inhibitor resistant variants were detected by ultra-deep sequencing or when NRTI mutations were detected by allele-specific PCR during primary infection, the virological response was not affected if patients received a boosted protease inhibitor.[28,30] From a clinical point of view, if drug resistance mutations are detected before treatment initiation, a ritonavir-boosted protease inhibitor can be included in the first treatment regimen, which, because of its higher genetic barrier, could better protect from the risk of virological failure than could NNRTI.

Patients infected with TDR who were resistant to at least one prescribed drug had a similar increase in CD4 cell count up to 1 month and showed weak evidence of a lower CD4 cell increase after 1 month compared with patients with no TDR. This finding might be a result of the higher virological failure rate in these patients because we only adjusted for viral loads before treatment and is thus probably not a direct effect of TDR on CD4 cell count. However, this finding is important because it suggests that a poor virological response in patients with TDR who are started on a suboptimum regimen will result in a poorer CD4 response and ultimately higher

Panel: Research in context

Systematic review

We searched PubMed (between 2006 and January, 2011) for studies that investigated the effects of TDR on response to first-line treatment. We identified eight cohort studies from Europe and two from the USA (webappendix pp 12–13). Some studies reported no significant association between presence of TDR and either time to HIV RNA suppression or proportions of patients with suppressed HIV RNA[1,17,18] or with immunological response.[1,17–19] Other studies reported poorer virological response in patients with TDR than in those without,[14–16,20,21] or a significantly shorter time to HIV RNA suppression among patients with susceptible strains than in those without.[19,22]

Interpretation

This European observational multicohort study confirms present treatment guidelines that state that the initial treatment choice should be based on resistance testing in treatment-naive patients.[7,8] This is the first study we know of to distinguish between patients who present with drug resistance and who are receiving a fully active cART and those who received at least one drug predicted to have low-level drug resistance on the basis of the WHO list for TDR and a recent version of the Stanford algorithm. Overall, the risk of virological failure of patients with TDR who received a fully-active cART was not significantly different to that in patients with no TDR. Patients who received a treatment regimen with a low genetic barrier had weak evidence of higher risk of virological failure in the presence of TDR and when they have received a treatment predicted to be fully active compared with those in the no TDR group. However, this finding did not occur for patients who received two NRTIs plus a boosted protease inhibitor, which suggests that in regions where genotypic testing is not routinely available but TDR exists, first-line regimens containing boosted protease inhibitor should probably be considered.

risk of disease progression. Conversely, for patients infected with TDR but who received fully active cART, there was no significant difference in the increase in CD4 cell count, before or after 1 month, compared with patients with no TDR. This finding is in accordance with previous studies that reported no effect of TDR on immunological outcome.[1,17,19,22]

Results from genotypic testing were known after the start of treatment for some patients. Thus, treatment was not necessarily guided by resistance testing and this could be one explanation for why some suboptimum cART regimens were used. However, this study design did allow the prospective investigation of the effect of TDR on treatment outcome, and a randomised trial would not have been ethical.

The time of genotypic testing was not included as a covariate in the main multivariable model because we had about 40% missing data for the exact date of sequencing. Furthermore, interpretation algorithms change over time and even patients predicted to be susceptible to a specific drug at the start of treatment could now be classified as resistant if the algorithm for this drug has changed. Clinicians could also have used an interpretation algorithm different from the Stanford algorithm we used. When we adjusted for time of testing in additional analyses we noted no effect (data not shown).

Furthermore, because routine resistance testing before the start of treatment has increased over time in response to guidelines, the patients, particularly those who started treatment in the earlier years, might not be representative of the diagnosed HIV-infected population. However, we minimised selection of patients as the only inclusion criterion was to have had a sample for genotypic testing available before treatment initiation.

Contributors

All members of the EuroCoord-CHAIN project team participated in the study design, statistical analyses, and interpretation, and were involved in the preparation and review of the final manuscript. LW and GC did all analyses and drafted the Article. LW was guarantor for the analyses. Data was acquired by HFG, FdW, DD, AC-L, AdL, CK, NO, VvW, BM, CS, CT, AA, FG, AJ, KP, RT, HC, AIvS, CC, JK, JDL, AP, BC, AP, DP, GC, and the EuroCoord-CHAIN study group. LW, DD, AC-L, AJ, RT, VvW, HC, AP, and GC did the statistical analysis. LW, HFG, FdW, DD, AC-L, AdL, CK, VvW, BM, AJ, KP, RT, HC, JDL, RP, BC, AP, DP, and GC interpreted the data. HFG, FdW, DD, AC-L, AdL, CK, VvW, BM, AJ, KP, RT, HC, RP, BC, AP, and DP critically revised the manuscript. All members of the EuroCoord-CHAIN writing group and study group were involved in the review of the final manuscript.

EuroCoord-CHAIN joint project

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Conflicts of interest

LW has received a PhD scholarship from Sidaction. Her institution received or is receiving study grants for the work under consideration from the French Agency for AIDS and hepatitis research (ANRS), Gilead, and EU FP7 grant (CHAIN); and travel support from EU FP7 (CHAIN). HFG's institution has received or is receiving study grants for the work under consideration from FP7/2007-2013 grant 22313, Swiss National Science Foundation (grant numbers 33CSC0-108787, 3247B0-112594, and 324730-130865), SHCS projects (numbers 470, 528, 569), the SHCS research Foundation, by a research grant of the Union Bank of Switzerland, in the name of a donor, and an unrestricted research grant from Tibotec, Switzerland, and from ViiV Healthcare. He has been an adviser and/or consultant for GlaxoSmithKline, Abbott, Novartis, Boehringer Ingelheim, Roche, Tibotec, and Bristol-Myers Squibb; and has received unrestricted research and educational grants from Roche, Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Tibotec, and Merck Sharp & Dohme. All these funds went to his institution. DD's institution has received study support from Bristol-Myers Squibb, Gilead Sciences, Pfizer, and Tibotec; and has received or is receiving study grants from EU FP7 grant (CHAIN). AC-L has received consultancy fees from GlaxoSmithKline; fees for development of educational presentations from GlaxoSmithKline; EU FP6 grant (NEAT); and travel grants from EuroSIDA, ICONA Foundation, INSIGHT, and EU FP7 grant (CHAIN). His institution has received employment fees from EuroSIDA, ICONA Foundation, and INSIGHT; and has received or is receiving study grants for the work under consideration from EU FP7 grant (CHAIN). AdL has received consultancy fees from ViiV Healthcare, Janssen, Abbott Virology, Monogram Biosciences, Gilead, GlaxoSmithKline, and Siemens Diagnostics; fees for development of educational presentation from GlaxoSmithKline and Abbott; and travel grants from Abbott and Janssen.

CK's institution was or is partly funded by the federal Ministry of Health (BMG) and by the EU FP7 grant (CHAIN). NO has received research funding from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, Abbott, Boehringer Ingelheim, Janssen-Cilag, and Swedish Orphan Drugs. BM has received speaking fees from Merck Sharp & Dohme, Pfizer, Gilead Sciences, Janssen-Cilag, and ViiV Healthcare; travel grants from GlaxoSmithKline, Gilead Sciences, and Janssen-Cilag; and his institution receives or will receive study grants from Pfizer and Janssen-Cilag. AA has received consultancy fees from Bristol-Myers Squibb, Gilead Sciences, and Abbott; speaking fees from Bristol-Myers Squibb, Janssen-Cilag, ViiV Healthcare, Abbott, Merck, and Boehringer-Ingelheim; fees for development of educational presentation from Bristol-Myers Squibb and Abbott; and travel grants from Abbott. His institution receives or will receive study grants from Bristol-Myers Squibb and ViiV Healthcare. FG has received consultancy fees from Merck, ViiV Healthcare, and GlaxoSmithKline; speaking fees from Merck, ViiV Healthcare, GlaxoSmithKline, Abbott, and MBS; and his institution receives or will receive study grants from Merck and ViiV Healthcare. AJ's institution received or is receiving study grants from EU FP7 grant (CHAIN). KP has received an honorarium from Tibotec and her institution has received or is receiving study grants from EU FP7 grant (CHAIN). RT's institution has received or is receiving study grants for the work under consideration from the French Agency for AIDS and hepatitis research (ANRS), Gilead, and EU FP7 grant (CHAIN); and his institution has received money for board membership from Gilead Sciences, Bristol-Myers Squibb, and Tibotec. HC's institution received or is receiving study grants from EU FP7 grant (CHAIN). CC's institution received or is receiving study grants for the work under consideration from the French Agency for AIDS and hepatitis research (ANRS), Gilead, and EU FP7 grant (CHAIN). RP has received consulting fees from Pfizer and grant support from Pfizer, Roche Diagnostics, Siemens, Merck, and Boehringer-Ingelheim. His institution has received or is receiving study grants from EU FP7 grant (CHAIN) and the Spanish AIDS network Red Temática Cooperativa de Investigación en SIDA (RD06/0006). APo has received money for board membership or advisory board activity from ViiV Healthcare, Gilead, Tibotec, Boehringer-Ingelheim, Abbott, Merck, Bristol-Myers Squibb, Virco, and Roche; consultancy fees from Roche and Bristol-Myers Squibb; fess for expert testimony as part of a legal review work and speaking fees from ViiV Healthcare, Gilead, Tibotec, Boehringer-Ingelheim, Abbott, Merck, Bristol-Myers Squibb, Virco, Roche; and fees for development of educational presentations from Gilead and Bristol-Myers Squibb. BC has been a consultant on advisory boards or participated in speakers' bureaus or conducted clinical trials with Boehringer-Ingelheim, Abbott, GlaxoSmithKline, Gilead, Janssen, Merck, Shionogi, and ViiV; and his institution has received or is receiving study grants from EU FP7 grant (CHAIN) and the Spanish AIDS network Red Temática Cooperativa de Investigación en SIDA (RD06/0006). APh has received fees for consultancy, speaking, or advisory board membership from Gilead, GlaxoSmithKline, and Janssen-Cilag. He has also received funds for research from Bristol-Myers Squibb. DP's institution has received consultancy fees for the advisory board from Pfizer, travel grants from Bristol-Myers Squibb, and study grants from EU FP7 grant (CHAIN). GC has received consultancy fees from Roche and fees for development of educational presentation from Boehringer-Ingelheim. Her institution has received or is receiving study grants for the work under consideration from the French Agency for AIDS and hepatitis research (ANRS), Gilead, and EU FP7 grant (CHAIN).

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