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Virological response to nucleos(t)ide analogues backbones initiated after virological failure on thymidine analogues-containing treatments

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BACKGROUND

The World Health Organisation (WHO) recommends that in resource limited settings (RLS), initial treatment includes a thymidine analougue (e.g. zidovudine or stavudine) and lamivudine. In patients experiencing immunological/clinical failure to these regimens, which subsequent nucleos(t)ide analogue is associated with the best virological response remains poorly defined. This question cannot be answered in populations receiving treatment in RLS because currently there is no virological monitoring in place. In HIV-infected people in industrialized countries, in the face of virological failure on lamivudine and detection of mutation 184V, it has been argued that the NRTI-pair tenofovir/didanosine should be avoided as, when used in PI-spared regimens, it is associated with several adverse outcomes including increased rates of virological failure, reduced CD4 count responses and occurrence of drug-specific toxicities (i.e. pancreatitis and renal insufficiency) [Negredo E et al, Maitland D et al, van Lunzen J et al].

PATIENTS

We considered patients in EuroSIDA who had documented virological failure on thymidine analogues (defined as having a viral load>400 copies/mL while on these drugs ≥4 months after starting them). We included in the analysis nucleos(t)ide treatment episodes (NTE) that occurred after this date of failure on thymidine analogues. NTE had to include ≥3 antiretrovirals and one of the following nucleoside-backbones currently considered by WHO as candidates for second-line regimens as newly started drugs:

- abacavir/didanosine (ABC/ddI)
- tenofovir/lamivudine (TDF/3TC)
- tenofovir/didanosine (TDF/ddI)
- zidovudine/tenofovir (AZT/TDF)
- didanosine/lamivudine (ddI/3TC)
- tenofovir/abacavir (TDF/ABC)
- abacavir/lamivudine (ABC/3TC)
- zidovudine/lamivudine/tenofovir (AZT/3TC/TDF)

METHODS

After the inclusion of one NTE, a patient could re-enter the analysis if he/she started the same or another of the above WHO candidate nucleos(t)ide backbones.

Two main outcomes were considered:

i) the short term virological response estimated by calculating the odds of achieving a viral load (VL) ≤400 copies/mL at 4 months; the 4 months viral load was defined as the closest measure to 4 months among those falling in the 3-8 month windows from the date of the NTE; logistic regression was used, excluding patients with a missing month-4 VL and ignoring treatment switches.

ii) the longer term virological response, by calculating the hazards of experiencing virological failure; the time to virological failure was defined as the time to the first of 2 consecutive VL>400 copies/mL after >6 months of the date of the NTE; Cox proportional hazards regression was used, censoring patients at the date of last viral load and ignoring treatment switches.

The most frequently used WHO backbone (ABC/ddI) was used as the comparator. Estimates were adjusted for a similar set of potential confounders in the two analyses as described at the bottom of Tables 4/5. The analyses accounted for non independence of NTE coming from the same patient.

RESULTS

1,228 patients contributed 1,441 NTE. Patients basic characteristics are described in Table 1 and are similar to those of EuroSIDA patients as a whole.

As expected, the patients tended to be extensively pre-treated, 87% having experienced virological failure on lamivudine, 76% on a PI and 47% on a NNRTI before the date of NTE (Table 2). In 714 NTE (50%) ≥1 genotypic test was available before the date of NTE and the prevalence of TAMs ranged between 24% (219EQ) to 48% (41L); 184V was detected in 64% of NTE (Table 2).

Table 3 shows the distribution of the drugs used in the NTE. The third drug most frequently used was lopinavir/r (28%).

Overall, 1,182 patients (84%) who had a 4-month viral load measure were included in the analysis of percentage with suppressed viral load at 4 months. Of these, 646 (53%) had a VL≤400 copies/mL. This percentage was not significantly different between backbones and ranged between 48% (TDF/ABC) to 63% (TDF/ddI) (p=0.07). Table 4 shows crude and adjusted ORs from fitting a logistic regression.

The estimated median KM time to virological failure was 25 months (95% CI:19-32). Table 5 shows crude and adjusted RH of failure from fitting the Cox regression model; again, there was little difference in the hazard of long term virological failure when comparing backbones.

Sensitivity analyses

Because patients in RLS are likely to have experienced virological failure on lamivudine when due to start their 2nd line regimen, we repeated the analysis in n=1,056 with previous lamivudine-failure and we obtained similar results (data not shown).

Similarly, because these patients are likely to remain on their first regimen with high viral load for a long period of time we repeated the analysis in n=694 who had previously exposed to zdv/d4t with a VL>400 for longer than 2 years. In this analysis, patients who started tenofovir/lamivudine had significantly lower chance of achieving a 4-month viral load ≤400 copies/mL than those who started abacavir/didanosine (adjusted OR=0.45, 95% CI:0.25-0.82, p=0.009). The time to virological failure analysis carried consistent results (adjusted RH=1.46 TDF/3TC vs. ABC/ddI, 95% CI:0.99-2.19, p=0.06).

CONCLUSIONS

Although subject to bias due to confounding and limited statistical power, these results suggest that patients who previously had virological failure on thymidine analogues, experienced a virological response to a number of nucleos(t)ide-backbones that was comparable to that achieved with ABC/ddI. We have no evidence to confirm that particularly undesirable virological outcomes may be observed if the pair tenofovir/didanosine is used. Ideally, a world-wide collaboration including several cohort studies in Europe and USA should be set up in order to increase the power of this analysis.

Table 1

Characteristics of the 1,434 patients at starting of NTE

Gender, n(%)	
Female	352 (24%)
Mode of HIV exposure, n(%)	
Homosexual contacts	650 (45%)
IDU	303 (21%)
Heterosexual contacts	393 (27%)
Age, median (range)	
Years	41 (21-80)
CD4 count, median (IQR)	
Cells/µl	240 (128-378)
Viral load, median (IQR)	
Log_{10} copies/mL	4.50 (3.77-5.11)
Calendar year of NTE, median (range)	2003 (1997-2006)
Contributing NTEs, n(%)	
1	1054 (86%)
2	147 (12%)
≥3	27 (2%)
Time from NTE to month 4-VL, median (range)	
Months	4 (3-8)

Table 2

Treatment history and drug resistance before starting the NTE

Time on zdv/d4T with a VL>400, median (IQR)	
Months	28 (15-47)
No. Drugs in WHO-regimen, median (range)	3 (3-8)
Previous use / failure while on, n(%)	
TDF	16% / 7%
3TC	95% / 87%
ABC	39% / 23%
ddI	75% / 45%
PI	89% / 76%
NNRTI	71% / 47%
Detection of mutations (n=714 tested), n(%)	
41L	345 (48%)
67N	271 (39%)
70R	204 (29%)
184IV	458 (64%)
210W	224 (32%)
215Y	330 (46%)
219EQ	169 (24%)

Table 3

Description of NTEs and 3rd drugs started

WHO-backbone, n(% of NTEs)	
ABC/ddI	282 (20%)
TDF/3TC	272 (19%)
TDF/ddI	232 (16%)
AZT/TDF	46 (3%)
ddI/3TC	204 (14%)
TDF/ABC	133 (9%)
ABC/3TC	225 (16%)
AZT/3TC/TDF	47 (3%)
Third drugs, n(% of NTEs)	
Efavirenz	254 (21%)
Lopinavir/r	334 (28%)
Atazanavir/r	106 (9%)
Saquinavir/r	53 (4%)
Indinavir/r	35 (3%)
(Fos)amprenavir/r	52 (4%)
Nevirapine	136 (11%)
Other	244 (20%)

Table 4

Odds ratios of 4-month virological response (≤400 copies/mL) from fitting a logistic regression model

	Crude	Adjusted
ABC/ddI	1.00	1.00
TDF/3TC	0.88 (0.61-1.27) p=0.49	0.70 (0.44-1.12) p=0.14
TDF/ddI	1.65 (1.10-2.46) p=0.01	1.35 (0.84-2.19) p=0.22
AZT/TDF	1.34 (0.68-2.66) p=0.40	1.05 (0.47-2.35) p=0.89
ddI/3TC	0.92 (0.61-1.38) p=0.68	1.17 (0.73-1.87) p=0.51
TDF/ABC	1.30 (0.82-2.08) p=0.27	0.82 (0.46-1.44) p=0.48
ABC/3TC	1.01 (0.68-1.49) p=0.96	1.10 (0.70-1.72) p=0.69
AZT/3TC/TDF	1.12 (0.57-2.19) p=0.88	1.39 (0.62-3.09) p=0.42

Adjusted for: age, gender, mode of HIV transmission, viral load and CD4 count at initiation of NTE, total number of drugs in regimen, previous duration of exposure to thymidine analogues with a VL>400, previous failure of TDF, 3TC, ABC, ddI PI or NNRTI, third drug in NTE, exact time between initiation of NTE and date of 4-month VL and calendar year of NTE

Table 5

Relative Hazards of virological failure (>400 copies/mL) from fitting a Cox regression model

	Crude	Adjusted
ABC/ddI	1.00	1.00
TDF/3TC	0.82 (0.64-1.07) p=0.14	1.16 (0.84-1.60) p=0.38
TDF/ddI	0.66 (0.51-0.87) p=0.003	0.92 (0.66-1.28) p=0.62
AZT/TDF	0.88 (0.52-1.47) p=0.64	1.15 (0.65-2.01) p=0.64
ddI/3TC	1.04 (0.81-1.34) p=0.76	0.95 (0.72-1.25) p=0.70
TDF/ABC	0.70 (0.50-0.99) p=0.05	0.92 (0.61-1.41) p=0.71
ABC/3TC	1.02 (0.80-1.30) p=0.89	1.00 (0.76-1.31) p=0.99
AZT/3TC/TDF	0.79 (0.45-1.39) p=0.41	1.14 (0.62-2.11) p=0.67

Adjusted for: age, gender, mode of HIV transmission, viral load and CD4 count at initiation of NTE, total number of drugs in regimen, previous duration of exposure to thymidine analogues with a VL>400, previous failure of TDF, 3TC, ABC, ddI PI or NNRTI, third drug in NTE and calendar year of NTE

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