

# No evidence for a poor immunologic response in patients treated with antiretroviral therapy containing tenofovir and didanosine at a weight adjusted dose

Abstract # N-176

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## Summary

**Objective:** To analyse whether antiretroviral therapy (ART) containing tenofovir (TDF) and didanosine (ddl) is associated with a poor CD4-cell recovery or maintenance compared to regimens containing TDF without ddl and whether such an effect is ddl-dose dependent.

**Design:** Retrospective longitudinal analysis of the immunologic outcome of 614 patients of the Swiss HIV Cohort Study (SHCS) treated with ART containing TDF with ddl (n=221), or TDF without ddl (n=393).

**Methods:** Univariable and multivariable linear regression analyses were performed to identify factors influencing the immunologic performance of different ART regimens measured by the CD4 slope after start of a TDF-containing ART.

**Results:** CD4 cell slopes were comparable between patients treated with TDF and a weight-adjusted ddl-dose of <4.1 mg/kg per day (n=143) vs. TDF without ddl (n=393). In the multivariable model the slopes differed by -13 cells/μl per year [95% confidence interval (CI) -42 to 17], p=0.40]. In contrast, patients treated with TDF and a higher ddl-dose (>4.1 mg/kg/day, n=78) experienced a significantly impaired immunologic response (-45 CD4-cells/μl per year, CI -80 to -11, p=0.01).

**Conclusions:** Our results suggest that ART containing TDF and ddl does not lead to an increased risk for a poor immunologic response, if the ddl-dose is adjusted to less than 4.1 mg/kg/day.

## Background

ART-regimens with the potential for once daily (OD) dosing are becoming increasingly popular since simple treatment regimens increase the patient's quality of life and improve adherence. TDF and ddl can both be administered OD but controlled, prospective trials of this combination are lacking. However, early virologic failure has been reported in small studies, if TDF and ddl were combined with either efavirenz or nevirapine, possibly due to a low resistance barrier (1-3).

In addition, Negrodo et al. have demonstrated a substantial loss of CD4-cells despite viral suppression, if patients received TDF and ddl at 400 mg per day concomitantly (4). Since TDF increases ddI-exposure substantially, the dose of ddl should be reduced to 250 mg/day in TDF-treated patients weighing more than 60 kg and even further in patients <60 kg (5).

In this study, we addressed the question, whether ART regimens containing TDF and ddl at an adjusted dose have a negative impact on the immunologic response measured by the CD4-cell slope.

## Patients and Methods

Retrospective analysis of 614 patients of the SHCS treated with ART newly containing TDF (n=393) or TDF+ddl (n=221). A minimal follow up of at least 6 months with ≥ 2 CD4-determinations to calculate a subsequent CD4-slope and exact ddl-dose information were required.

Patients with concurrent immuno-suppressive or -modulating treatment were excluded (n=38).

Patients were stratified according to tertiles of the daily administered weight adjusted ddl-dose leading to four different treatment groups: no ddl (comparator, n=303), low ddl-dose (ddl-LD, <3.3 mg/kg, n=73), intermediate ddl-dose (ddl-ID, 3.3-4.1 mg/kg, n=70) and high ddl-dose (ddl-HD, >4.1 mg/kg, n=78).

Baseline predictors of the subsequent CD4-slope were calculated using univariable and multivariable weighted linear regression analyses. Individual weights were given according to the number of CD4-determinations for each patient. Median with 95% CI or mean with interquartile ranges are presented.

Figure 1

Univariable analyses of CD4-slopes in different ddl-dose groups. Bars indicate the median gain in CD4-cells/μl per year. Error bars indicate the standard error of the mean. Significant differences are highlighted.

Abbreviations: ns, not significant; LD, low dose; ID, intermediate dose; HD, high dose.

Table 1. Baseline Characteristics of included patients

	all patients	TDF without ddl	TDF with ddl	p-value*
No of patients	614	393 (64%)	221 (36%)	
Male sex	448 (73%)	286 (72.8%)	162 (73.3%)	0.89
Age (years)	43 (38-49)	43 (38-49)	42 (38-48)	0.53
Mode of transmission				0.43
MSM	266 (43.9%)	169 (43%)	97 (43.9%)	
IVDU	126 (20.5%)	86 (21.9%)	40 (18.1%)	
heterosexual	221 (34%)	133 (33.8%)	78 (35.3%)	
other	11 (1.8%)	5 (1.3%)	6 (2.7%)	
Bodyweight (kg)	68 (61-77)	68 (61-77)	69 (61-78)	0.35
CD4-count (cells/μl)	317 (204-484)	330 (205-508)	303 (199-464)	0.26
HIV-RNA (log <sub>10</sub> copies/ml)	2.2 (1.0-4.3)	1.8 (0.8-4.2)	2.7 (1.2-4.5)	0.02
HCV-seropositive	139 (22.6%)	90 (23%)	49 (22.2%)	0.96
Treatment naïve	24 (3.9%)	19 (4.8%)	5 (2.3%)	0.08
No of previous ARVs	6.3 (0-14)#	6.2 (0-14)#	6.6 (0-14)#	0.10

Numbers indicate the median value and the interquartile range of the number of patients (percentage) in the different treatment groups, respectively. (# Exception: # mean and total range). \*p-values comparing treatment groups (TDF without ddl versus TDF+ddl) are derived from chi-square or Wilcoxon rank sum tests. Abbreviations: No, number; MSM, men having sex with men; IVDU, intravenous drug user; HCV, hepatitis C virus; ARVs, antiretroviral drugs.

### Baseline characteristics (Table 1)

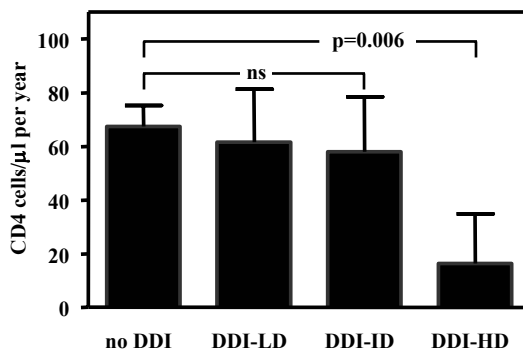
Baseline characteristics of included patients were comparable across treatment groups with the important exception of HIV-RNA, which was significantly higher in patients treated with TDF+ddl than in patients treated with TDF without ddl (2.7 vs. 1.8, p=0.02). This most probably reflects differences in the reason for changing ART. TDF+ddl was more often used in treatment failure, whereas TDF without ddl was preferentially used to replace another nucleoside analog (for convenience or management of side effects).

### Univariable models (Table 2 and Figure 1)

Overall, the median gain in CD4-cells/μl and year was 60 (95% CI 48-72). Several baseline parameters were significant predictors of the subsequent CD4-slope. The following parameters had a positive influence on the CD4-slope: younger age, higher body weight, higher baseline viral load (VL), lower baseline CD4-count and percentage and less previous ART experience.

**ddl-dose:** Receiving a high dose of ddl (>4.1mg/kg) was clearly associated with a reduced gain of CD4-cells (slope difference -51 cells/μl per year, 95%CI -15 to -87, p=0.006) compared to patients receiving TDF without ddl, confirming the results of Negrodo et al (4). Importantly, the CD4-slope of patients receiving a low or intermediate dose of ddl (<4.1 mg/kg) was comparable to the patients treated without ddl (slope difference 1.5 cells/μl and year, -31 to 28, p=0.924).

Figure 1: CD4-slopes of different ddl-treatment groups



## Results

Table 2. Predictors of CD4-slope in univariable and multivariable regression analyses

independent variable	Univariable models			Multivariable model			
	coeff. y	95% CI	p-value	coeff.	95% CI	p-value	
CD4-slope (cells/μl/year)	60	48 to 72		125*	10 to 238	0.032	
ddl dose (in mg/kg)	no ddl	67	52 to 83				
	ddl-LD (< 3.3)	6	-33 to 45	0.77	-16	-57 to 25	0.44
	ddl-ID (3.3-4.1)	-9	-50 to 31	0.65	-9	-47 to 30	0.66
	ddl-HD (> 4.1)	-51	-87 to -15	0.006	-47	-82 to -12	0.009
Gender	male	60	46 to 75				
	female	-1	-28 to 27	0.97	18	-17 to 53	0.32
Increasing age	per 10 years	-20	-34 to -7	0.004	-24	-37 to -10	0.001
Increasing weight	per 10 kg	12	2 to 21	0.018	1.4	0.30 to 3	0.013
Transmission categories	all others	57	41 to 74				
	MSM	7	-18 to 31	0.60	20	-11 to 50	0.22
	all others	64	51 to 78				
	IVDU	-21	-52 to 9	0.17	-20	-70 to 29	0.42
HIV RNA - at baseline (BL)	per log <sub>10</sub> reduction	-28	-21 to -34	<0.001			
	>50 copies/ml	88	73 to 103				
HIV RNA: - during follow up#	<50 copies/ml	-72	-96 to -47	<0.001	-47	-76 to -18	0.001
	>50 copies/ml	15	3 to 26	0.013			
CD4-cells/μl at BL	per 100 cell increase	-17	-22 to -13	<0.001	-19	-25 to -12	<0.001
	per 1% increase	-3	-4 to -2	<0.001	1.0	-1.0 to 2.7	0.28
ART experience	ART-experienced	57	44 to 69				
	naïve	97	33 to 161	0.003	45	-23 to 112	0.20
Number of previous antiretrovirals (ARVs)	< 4 ARVs	87	58 to 117				
	4-5 ARVs	-7	-46 to 32	0.74	32	-9 to 73	0.12
	6-8 ARVs	-32	-68 to 3	0.08	10	-28 to 49	0.60
	> 9 ARVs	-56	-94 to -19	0.003	-29	-71 to 13	0.18
Number of new drugs added	One new drug	35	16 to 53				
	Two new drugs	38	8 to 68	0.012	10	-20 to 39	0.53
	> two new drugs	53	24 to 81	<0.001	-0.2	-3.4 to 3.4	0.99
HCV coinfection	HCV negative	62	48 to 76				
	HCV-Ab positive	25	-24 to 74	0.31	37	-21 to 94	0.21
	HCV-RNA positive	-22	-56 to 11	0.19	-8.4	-56 to 39	0.73

\* constant term or fixed comparator from individual univariable models  
# effect modifier by independent variable in relation to the constant term or comparator  
\* constant term for the multivariate model  
# not a baseline parameter, therefore not included into the multivariate analysis

### Multivariable model (Table 2)

In the multivariable model increasing age, lower body weight, low HIV-RNA and high absolute CD4-counts at baseline remained predictors of a reduced gain in CD4-cells. Treatment experience was not a significant predictor of the CD4-slope in the multivariable model.

**ddl-dose:** Receiving a high dose of ddl (>4.1mg/kg) was a strong predictor of a reduced CD4-slope [-47 (95%CI -82 to -12), p=0.009] and was thus associated with a poor immunologic response. Patients receiving low (<3.33 mg/kg) or intermediate (3.33-4.1 mg/kg) doses of ddl had a similar CD4-slope as patients receiving no ddl, with slope differences of -16 (p=0.44) and -9 (p=0.66), respectively. Virologic success (HIV-RNA <50 copies/ml) during follow up was similar in patients receiving different doses of ddl (80-82%).

## Conclusions

Combined use of TDF and ddl at a dose of >4.1 mg/kg is associated with poor immunologic responses.

Treatment with TDF and an adjusted ddl-dose (i.e. <4.1 mg/kg) showed a similar immunologic response as treatment with TDF and no ddl.

Therefore, ART containing TDF and ddl appears immunologically safe as long as the ddl-dose is below 4.1 mg/kg.

## References

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