

Quadruple Nucleoside Reverse Transcriptase Inhibitor (NRTI) Therapy with Trizivir (TZV) and Viread (TDF) in Naive and Experienced HIV/AIDS Patients: A 30-Month Follow-up

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BACKGROUND

- Triple NRTI regimens may be class-sparing, but ACTG 5095 demonstrated TZV (ABC/3TC/AZT) alone inferior to EFV-containing regimens¹.
- Use of once-daily, non-thymidine analog, triple NRTI regimens, e.g. ABC/3TC/TDF²⁻⁴ and ddI/3TC/TDF⁵, resulted in high rates of early virologic failure, possibly due to the low genetic barriers of the components used in these regimens.
- Quadruple-NRTI regimens preserve other classes for future sequencing options, while lowering the risk of drug-drug interactions.
- TDF is a potent and well-tolerated NRTI and may improve the efficacy of TZV alone.
- Several clinical trials have evaluated the use of TZV/TDF in treatment-naïve and -experienced individuals through 24-48 weeks:
 - Moyle et al.⁶ compared TZV/TDF with CBV/EFV and showed equivalent viral load and CD4+ changes at week 48 in treatment-naïve individuals.
 - ESS300005 (ZIP)⁷ demonstrated successful viral suppression through week 24 using TZV/TDF after first failure with AZT/(or D4T)/3TC with a PI or nNRTI.
 - COL402838⁸ evaluated TZV/TDF in ARV-naïve individuals and showed good virologic responses, especially with baseline PCR <100,000 c/ml, at week 24.
 - We previously demonstrated that TZV/TDF provided potent and durable viral suppression for >12 months in ARV-naïve and -experienced patients, whether intensifying with TDF or simplifying HAART⁹.
- We present the longest follow-up to-date on patients taking TZV/TDF with our original 75 patient cohort having been followed for up to 46 months (mean 30 months).

METHODS

- Prospective safety/efficacy follow-up of our 75 patients taking TZV/TDF from 3 different clinics:
 - Mt. Vernon Hospital HIV/AIDS Clinic, Mt. Vernon, NY; inner city clinic
 - CIRCLE Medical LLC, Norwalk, CT; private practice setting
 - New York Hospital, Queens HIV/AIDS Clinic, Flushing, NY; private practice and public hospital clinic settings
- Patients were stratified into two GROUPS and the treatment-experienced group was stratified into two ARMS:
 - Group A: HAART-naïve (n=25)
 - Group B: HAART-experienced (n=50)
 - Arm 1: TZV intensification with TDF (n=21)
 - Arm 2: HAART simplification to TZV/TDF (n=29)
- Patients were selected for analysis as follows:
 - Group A: if they had taken at least 4 weeks of TZV/TDF
 - Group B:
 - Arm 1: if they were taking TZV alone, were intensified with TDF regardless of PCR, and took at least 4 weeks of TZV/TDF
 - Arm 2: if they simplified HAART, began TZV/TDF for any reason (choice, AE, rebound viremia, etc.), and took at least 4 weeks of TZV/TDF
- Virologic Failure was defined as:
 - Failure to attain a viral load <400 copies/ml by study end
 - Viral Rebound by ≥0.5 log (i.e. to ≥1265 copies/ml) after achieving a viral load <400 copies/ml
- Data was updated and analyzed through October, 2005 following submission of the abstract in July, 2005.

RESULTS

Demographics

TABLE 1: Baseline Demographics: Age, Gender, Race, Risk, Time HIV+, % AIDS, % HCV

	Group A (Naïve, n=25)	Group B (Experienced, n=50)
Age: median, yrs (range)	42 (31-57)	42 (23-65)
Gender: Male, %	72	76
Race:		
Caucasian, n (%)	15 (60)	18 (36)
Black/AA, n (%)	8 (32)	18 (36)
Hispanic, n (%)	2 (8)	14 (28)
Risk Factor, HIV:		
MSM, n (%)	12 (48)	27 (54)
heterosexual contact, n (%)	10 (40)	15 (30)
Injection drug use, n (%)	1 (4)	10 (20)
Other/Unknown, n (%)	0	1 (2)
Time HIV+: mean, mos. (range)	33 (18-59)	74 (14-188)
AIDS, n (%)	6 (24)	30 (60)
HIV/HCV, n (%)	5 (20)	10 (20)

In Group B, Arm 1 (intensity) had more Caucasian, MSM, males than Arm 2 (simplify), which had more Black/AA, heterosexual, females.

RESULTS (continued)

TABLE 2: Baseline Demographics: CD4, Viral Load at 1st HAART and TZV/TDF Start, ARV History

	Group A (Naïve, n=25)	Group B (Experienced, n=50)	
		Arm 1: (Intensity, n=21)	Arm 2: (Simplify, n=29)
Mean Prior ARVs, # (range)	N/A	4 (3-6)	6 (3-11)
Mean Time Prior ARVs, mos (range)	N/A	4 (2-6)	4 (3-11)
% Prior ARV (TZV, TDF) use			
AZT	N/A	100	59
3TC		100	90
ABC		100	41
TDF		0	14
1 st HAART:			
Median CD4+, cells/mm ³ (range)	N/A	207 (0-445)	218 (16-518)
Median CD4% (range)		15 (0-38)	13 (1-29)
Mean HIV-1 RNA, log ₁₀ (range)		5.1 (3.3-5.7)	5.3 (3-6)
TZV/TDF Start:			
Median CD4+, cells/mm ³ (range)	340 (128-625)	471 (204-840)	435 (5-1334)
Median CD4% (range)	22 (4-35)	27 (13-45)	21 (1-37)
Mean HIV-1 RNA, log ₁₀ (range)	4.7 (2-5)	2.9 (1.7-5.2)	3.1 (1.7-5.5)
% <400, #	0	48	45

Adverse Events and Discontinuations

TABLE 3: Time on TZV/TDF, % Discontinuations, Serious Adverse Events

	Group A (Naïve, n=25)	Group B (Experienced, n=50)	
		Arm 1: (Intensity, n=21)	Arm 2: (Simplify, n=29)
Mean Time TZV/TDF, mos. (range)	33 (25-46)	27 (6-42)	29 (10-43)
Mean Discontinuations, n (%)	3 (10)	4 (19)	6 (21)
% Time on TZV/TDF at discontinuation, mos. (range)	26 (20-27)	20 (11-32)	20 (10-31)
Reasons for discontinuation:			
Adverse event, n (events)	1 (GI)	2 (3 GI, 1 lactic acidosis/PCR)	0
Noncompliance, n (%)	2	0	3 (7)
Virologic Failure, n (%)	0	1 (5)	2 (7)
Other, n (reason)	0	0	1 (31)
Serious Adverse Events:			
%HSR	0	0	0
Grade III/IV Scr, n (%)	0	1 (5)	0
Grade III/IV AEs, n (%), type	0	1 (5, lactic acidosis)	0

Immunologic and Virologic Responses

TABLE 4: Immunologic (median CD4) and Virologic (mean PCR) Responses

	BASELINE			ON-TREATMENT		
	CD4%	CD4#	PCR (log ₁₀)	CD4%	CD4#	PCR (log ₁₀)
Group A: (Naïve, n=25)	22 (9-36)	340 (108-625)	4.7 (3-5.7)	33 (26-43)	612 (301-1334)	2.1 (1.7-2.5)
Overall	25 (14-35)	398 (194-840)	3.0 (1.7-5.2)	28 (14-44)	515 (210-1334)	2.2 (1.7-2.5)
Group B: (Experienced, n=50)						
Arm 1: (Intensity, n=21)	27 (13-40)	471 (204-840)	2.9 (1.7-5.2)	30 (19-44)	599 (20-1334)	2.0 (1.7-2.5)
Arm 2: (Simplify, n=29)	21 (1-37)	376 (5-1334)	3.1 (1.7-5.5)	26 (14-32)	507 (0-1334)	2.3 (1.7-2.5)

- Median % Change in CD4 cell count from Baseline:
 - Group A: +73%
 - Group B (Arm 1, Intensity): +27%
 - Group B (Arm 2, Simplify): +39%
- Median % Change in CD4% from Baseline:
 - Group A: +55%
 - Group B (Arm 1, Intensity): +23%
 - Group B (Arm 2, Simplify): +24%

FIGURE 1: Interval Median Change in Absolute CD4+ Cell Count from Baseline

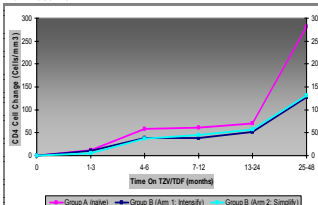
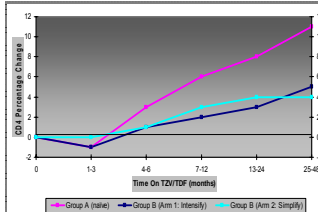


FIGURE 2: Interval Median Change in CD4% from Baseline



RESULTS (continued)

TABLE 5: Virologic Responses (ITT, MNC=F: intention-to-treat, missing=non-completed-failure)

	Group A (Naïve, n=25)	Group B (Experienced, n=50)	
		Arm 1: (Intensity, n=21)	Arm 2: (Simplify, n=29)
PCR <400 copies/ml (%):			
At Baseline	0	48	45
On TZV/TDF, At least once	100	95	97
On TZV/TDF, Mo 12, ITT, MNC=F*	88	76	86
On TZV/TDF, Study end, ITT, MNC=F*	80	81	72
PCR <50 copies/ml (%):			
At Baseline	0	14	14
On TZV/TDF, At least once	92	76	72
On TZV/TDF, Mo 12, ITT, MNC=F*	60	48	55
On TZV/TDF, Study end, ITT, MNC=F*	60	62	48
PCR Change from Baseline:			
Baseline PCR, copies/ml (4.7) (log ₁₀)	54,953	12,156	24,815
Mean copies/ml, log ₁₀ (2.6)	-2.6	-0.9	-0.74
Virologic Failure, n (%):			
As Treated	12	5	17
ITT, MNC=F*	12	19	21

Resistance Data

- One patient developed a K65R with virologic failure.
- Group A: Of the 3 patients meeting protocol-defined virologic failure, only 1 continued on HAART, was salvaged with ABC/TVD/ATZr without genotypic data, and resuppressed to PCR<400 within four months of the new regimen.
- Group B, Arm 1:
 - 1 pt. experienced virologic rebound (As Treated) with PCR 1421 and was successfully treated with ABC/TVD/FPVr with genotypic mutations at 41, K65R, 67, 184, 210, and 215. The possibility of superinfection exists from patient history.
 - 3 patients experiencing AEs, 1 with PCR 825 and 2 with PCR <50, were successfully salvaged with ABC/3TC/ATZr, TVD/EFV, and ddI/TVD/ATZr, respectively.
- Group B, Arm 2:
 - Of 5 pts. with virologic failure, 1 remains on TZV/TDF, 1 is lost-to-follow-up, and 3 were resuppressed to PCR<400 after a mean 4.5 months:
 - TVD/ATZr (PCR 1100, no GT),
 - ddI/TVD/ATZr (PCR log₁₀ 5.13, GT: RT: 41, 67, 74, 103, 118, 184, 210, 215; PI: 54, 63, 71, 82),
 - ABC/TVD/ATZr (PCR 3280, GT: 41, 67, 184, 210).

CONCLUSIONS

- The quadruple-NRTI regimen of TZV/TDF safely provides adequate and durable viral suppression without evidence of significant virological failure for up to 46 months with impressive immunological improvements in both HAART-naïve and HAART-experienced patients, whether intensifying TZV with TDF or simplifying HAART with TZV/TDF.
- The improved outcome seen in this study compared to that seen with triple NRTI combinations, such as AZT/ABC/3TC¹ and ABC/TDF/3TC²⁻⁴, suggests that ABC and TDF can be combined effectively as part of an appropriately configured regimen.
- The improved outcome may be attributable to the alternate pathway to resistance imposed by inclusion of AZT (i.e., TAM-mediated nucleotide excision) and the relative incompatibility of the K65R pathway, selected for by both ABC and TDF, with the TAM pathway.
- Future studies are needed to determine if this quadruple-NRTI approach is superior to TZV alone or comparable to multi-class regimens employing an NRTI backbone consisting of only 2 of the 4 NRTIs (ABC/3TC, TDF/3TC or FTC) used in this study.

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