

Successful Rescue Therapy in Patients Developing K65R on Tenofovir Containing Regimens: Long Term Follow-up

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Background

- Few data are available regarding future treatment options in patients who developed the K65R mutation in HIV-1 RT. High rates of K65R have been observed in once-daily triple nucleoside regimens like tenofovir DF, abacavir and lamivudine. In contrast, development of K65R was infrequent in the regimen containing tenofovir DF, lamivudine and efavirenz. In either case, success of rescue therapy after potential development of K65R needs to be assessed.

Methods

- 22 patients who developed K65R were followed after a 2nd line rescue regimen. Treatment and virological outcome were evaluated.
- 14 patients (#1-14) were from the Tonus trial, a pilot, open-label, multicenter trial in ART-naïve patients: TDF 300 mg + ABC 600 mg + 3TC 300 mg as a QD regimen.
- Eight patients (#15-22) were from the GS 903 trial, a randomized, blinded study which compared in ART-naïve patients TDF + 3TC + EFV to d4T + 3TC + EFV.
- Phenotypic analyses from stored plasma samples were performed by ViroLogic (South San Francisco, California, USA) using the standard PhenoSense HIV assay which included a single-cycle assay for viral replication capacity (RC). All baseline and K65R samples with HIV RNA >1000 copies/mL were attempted for analysis.

Results

At Baseline before Treatment Modification

- 14 patients developed K65R + M184V, 5 patients K65R + M184V + NNRTI-R, and 3 patients K65R + NNRTI-R.
- Median viral load (VL) and CD4 cell count were 6336 copies/mL [80-229 511] and 268 cells/mm³ [15-453], respectively, prior to new therapy.
- For NRTIs in the 2nd line regimens:
 - TDF and 3TC were not changed in 5 and 9 patients, respectively.
 - AZT and ddl were used in 13 and 11 patients, respectively.
- For 3rd drug modification, a PI was used in 16 patients (10/16 lopinavir/r) and NNRTIs in 6 patients previously treated with TDF+3TC+ABC.

Results (cont'd)

Virological Outcome after Rescue Therapy

- 19/22 (86%) patients have VL <50 copies/mL after a median follow-up of 48 weeks (range: [14-177]).
- One patient (#20) on AZT/ddI/NFV responded with >2 log₁₀ VL reduction to 423 copies/mL but was then lost to F/U at Week 68.
- One patient (#21) on AZT/3TC/APV was considered non adherent with VL of 1905 copies/mL at Week 32 and subsequent development of M184V.
- One patient (#22) was lost to follow-up prior to new therapy.
- Interestingly, 2 patients (#10 and #11) remained on their previous failing triple nucleoside regimen and only added EFV and became undetectable despite failure VL of 92,400 and 14,100 copies/mL. These patients have 24 and 47 weeks of undetectable F/U, respectively.

Table 1. Rescue Treatment in 22 Patients with K65R

Patient ID	HIV-1 RNA at failure before changing therapy (copies/ml)	CD4 cell count (cells/mm ³) at failure	Ongoing treatment	Follow-up HIV-RNA (copies/ml)	Follow-up (weeks)
1	25700	106	AZT/DDI/LPV	< 50	64
2	4790	408	AZT/DDI/LPV	< 50	60
3	209	453	AZT/DDI/LPV	< 50	38
4	80	247	AZT/DDI/LPV	< 50	49
5	2540	354	AZT/3TC/ABC/EFV	< 50	47
6	885	368	ABC/DDI/LPV	< 50	48
7	3170	132	ABC/DDI/LPV	< 50	52
8	3300	176	AZT/3TC/EFV	< 50	45
9	21600	351	AZT/DDI/EFV	< 50	45
10	92400	300	ABC/3TC/TDF/EFV	< 50	24
11	14100	359	ABC/3TC/TDF/EFV	< 50	47
12	1000	325	ABC/3TC/TDF/EFV	< 50	48
13	1300	274	LPV/SQV	< 50	14
14	21100	277	AZT/EFV/NFV	< 50	52
15	18332	262	AZT/TDF/LPV	< 50	177
16	2945	94	DDI/3TC/TDF/LPV	< 50	155
17	5623	159	DDI/D4T/IDV	< 50	151
18	34295	31	DDI/IDV	< 50	163
19	229511	15	AZT/3TC/SQV	< 50	48
20	7047	93	AZT/DDI/NFV	423	68 and LFU
21	40903	446	AZT/3TC/APV	1905	32 non-adherence
22	80600	88	AZT/3TC/LPV	NA	LFU prior to new therapy
Median (Range)	6336 (80 - 229000)	268 (15 - 453)		< 50	48 (14 - 177)

Table 2. Phenotypic Susceptibility and Replication Capacity For Patients with K65R (n = 15)

Patient ID (NRTI-R)	AZT (2.5)	d4T (1.7)	TDF (1.4/4.0)	ddl (1.7)	ABC (4.5/6.5)	3TC (2.5)	EFV (2.5)	NVP (2.5)	RC (% of Wild-Type)
2 (+M184V)	0.4	1.1	1.2	2.6	8.9	>>	0.2	0.2	99%
8 (+S68G M184I)	0.4	1.3	1.4	3.1	5.3	>>	0.4	0.2	12%
9 (+S68S/N Y115F M184V)	0.5	1.0	1.8	2.4	32	>>	0.3	0.9	31%
11*(+M184V)	0.3	0.6	0.5	1.5	3.5	>>	0.7	0.4	51%
12 (+S68G M184V)	0.4	0.9	1.2	2.7	7.7	>>	0.2	0.3	63%
13*(+M184V)	0.5	1.1	0.9	2.0	6.4	>>	0.4	0.6	97%
14 (+M184V)	0.4	1.2	1.3	3.2	9.4	>>	0.4	0.3	79%
15 (+S68G M184V)	0.3	0.9	1.2	3.7	6.2	>>	>>	73	NA
16 (+S68G M184V)	0.5	1.0	1.3	3.0	7.0	>>	76	>>	72%
17 (+M184V)	0.3	0.8	1.1	1.9	4.6	>>	>>	40	50%
18	0.2	0.6	1.0	0.7	1.2	11	>>	>>	2%
19	0.4	1.1	1.4	1.6	1.5	8.7	>>	>>	16%
20* (+S68G M184V)	0.9	0.8	0.9	1.2	1.3	>>	>>	>>	60%
21 (+S68G)	0.5	1.2	2.2	1.9	4.2	13	>>	>>	82%
22	0.5	0.9	1.0	1.6	2.4	13	175	>>	36%

* Mixture of K65R/K

- Mean Viral Replication Capacity: 54% of Wild-Type

Conclusions

- Development of K65R and M184V did not appear to have a negative effect on long-term rescue therapy with a variety of regimens, even if plasma HIV RNA was high before regimen change.
- The phenotypic data indicate full susceptibility of the double mutant virus to either AZT or d4T, and partial susceptibility to TDF.
- The level of activity of ddl in these regimens is uncertain given the reduction in susceptibility observed phenotypically (2.2-fold).
- The K65R+M184V mutant showed hypersusceptibility to EFV, NVP and AZT of approximately 0.4-fold, and this may have contributed to the virologic success in patients who began using EFV and/or AZT.
- Reduced replication capacity of the K65R+M184V mutant virus (54% of wild-type) may have also contributed to the subsequent virologic success.