

ABSTRACT

Background: *In vitro* resistance studies have shown that HIV containing non-nucleoside reverse transcriptase (NNRTI) mutations other than K103N are sensitive to inhibition by efavirenz (EFV). Emivirine is a potent NNRTI that has a low incidence of K103N mutation when given in combination with lamivudine.

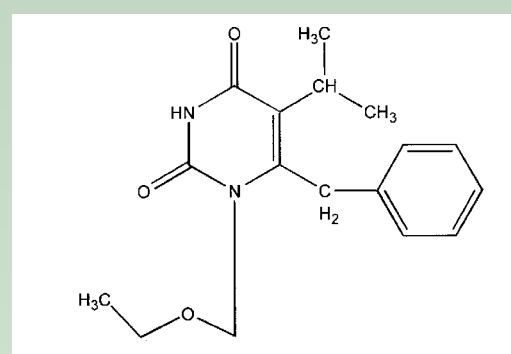
Methods: Therapy naïve subjects were enrolled in a randomized, open label study (MKC-401) to compare EMV vs abacavir (ABC) in the background of stavudine/emtricitabine (d4T/FTC). HIV RNA viral load was measured at baseline and every twelve weeks thereafter. Subjects who experienced virologic failure (VF) in the emivirine arm were allowed to switch to EFV and ABC + d4T. To determine if antiviral drug resistance was associated with therapy failure, genotypic analysis was performed at the time of a protocol-defined VF.

Results: To date, forty-five subjects in MKC-401 have switched to EFV + ABC + d4T. Genotypic analysis was available for 36 of the 45 subjects. NNRTI mutations were observed in 14/36 (39%) of these subjects, with 8/14 having single NNRTI mutations and 6/14 with multiple NNRTI mutations. The NNRTI mutations observed were; E138K (7/36), K103N (6/36), V108I (4/36), K101E/Q (2/36), K103T (2/36) and Y188C (1/36). Twenty-one of the 36 (58%) subjects remained wild type at time of failure, and one subject developed NRTI associated mutations only. VL analysis of the subjects by week 12 following switch to EFV indicated that 25/34 (74%) of the subjects were ≤ 400 copies/mL and fifty percent of these subjects were ≤ 50 copies/mL. Twenty of the twenty-one patients with wild type virus at failure had VL measurements post switch. Eighteen of the 20 subjects achieved a VL ≤ 400 copies/mL and 15/20 subjects (75%) achieved ≤ 50 copies/mL. For subjects who failed with a NNRTI mutation but did not have a K103N, 7/8 (87.5%) had VL ≤ 50 copies/mL following 4 to 84 weeks on efavirenz. Data available for 5 of the 6 subjects with the K103N showed that 40% were able to achieve a transient decrease in viral load ≤50 copies/mL prior to discontinuing therapy. Of the sixteen subjects who have discontinued alternate therapy, three discontinued due to virologic failure, four due to AE, two lost to follow-up, and seven due to other reasons (withdrew consent, pregnancy, etc.).

Conclusions: These results show that subjects who fail an EMV containing regimen subsequently achieved suppression of viral load to ≤ 50 copies/mL following rollover to an EFV containing regimen.

INTRODUCTION

Coactinon (Emivirine): Description
Structural Formula:



6-benzyl-1-(ethoxymethyl)-5-isopropyluracil

- A nucleoside analogue derivative that functions as a non-nucleoside reverse transcriptase inhibitor.
- Mechanism of action: Emivirine binds to an allosteric site on HIV-1 reverse transcriptase, resulting in noncompetitive inhibition.
- Potent activity against HIV-1 *in vitro* and *in vivo*.

Genotypic/Phenotypic Profile:

- Genotypic analysis of virus isolated from patients treated with emivirine occur at positions G190, Y181, K101, V106, K103, V108, Y188, and E138 either alone or in combination.
- Isolates that lack the K101E or K103N mutation remain phenotypically sensitive to at least one of the other approved NNRTIs.
- To date, the overall incidence of the K103N mutation in patients who have failed an emivirine containing regimen ranges between 0 and 45% (depending upon the background therapy) which is considerably less frequent than what has been reported for other NNRTIs, especially efavirenz.

OBJECTIVES

- Characterize the genotypic profile of HIV-1 from patients who experienced virological failure while on emivirine, emtricitabine and stavudine combination therapy
- To determine the success of sequencing the NNRTI, efavirenz, following virologic failure on an emivirine regimen.
- To determine the impact of the NNRTI mutations on virologic response upon sequencing with an efavirenz-containing regimen.

METHODS

Open Label 2:1 (EMV:ABC) Randomization:

Arm 1: emivirine (750 mg BID) + stavudine (40 mg BID) + emtricitabine (200 mg QD) or emivirine (500 mg BID) + emtricitabine (200 mg QD) + stavudine (40 mg BID)

Arm 2: abacavir (300 mg BID) + stavudine (40 mg BID) + emtricitabine (200 mg QD)

Patients from Arm 1 who experienced virological failure (without the K103N or K101E mutations) were given the option to receive an alternate treatment regimen [efavirenz (600 mg QD) + abacavir (300 mg BID) + stavudine (40 mg BID)].

Prior to virological failure, patients must have achieved a ≥ 1 log₁₀ decrease in HIV-1 RNA from baseline or HIV-1 RNA ≤400 copies/mL.

Genotypic analysis was performed on the patient plasma HIV at baseline and time of virologic failure. Dideoxy sequencing was performed by use of the ABI 377 sequencing system, in which all of the Protease (AA 1-99) and the Reverse Transcriptase (AA 1-400) were analyzed.

Genotype of the virus at time of virologic failure was provided to the investigators to facilitate subsequent choice of therapy and eligibility for sequencing with the alternate therapy provided for by the protocol.

RESULTS

Table 1. Disposition of Patients who have switched to the Efavirenz Regimen EFV+ABC+d4T

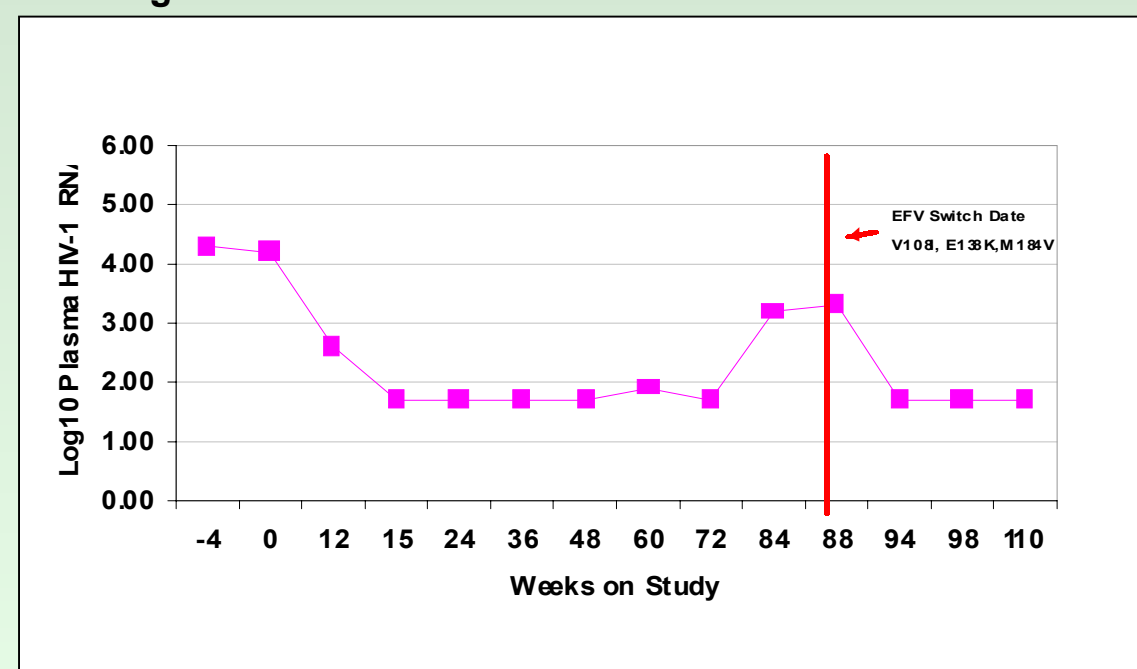
Number of Patients Switched to Efavirenz	54
Number of Patients Discontinued Efavirenz (Total)	25
Adverse Event	3
Virologic Failure	3
Lost to Followup	4
Withdrew Consent	2
Protocol Violation	4
Non Compliance	1
Disease Progression	1
Genotype (K103 or K101 mutation)	7

Table 2. Incidence and Percent of Genotypic Mutations in Patients with Virologic Failures

Mutation Position	EMV (N = 72)		EFV Rollover (N = 53)	
	N	%	N	%
Any NNRTI	27	37.5	22	41.5
Single NNRTI	17	23.6	12	22.6
Multiple NNRTI	10	13.9	10	18.9
E138K	10	13.9	10	18.9
K103N	10	13.9	9	17
V108I	8	11.1	8	15.1
K101E	3	4.2	2	3.8
Y188C/H	2	2.8	1	1.9
Y181C	1	1.4	1	1.9
G190A	1	1.4	0	0
Other*	3	4.2	2	3.8
Wild Type	41	56.9	30	56.6

*V106A, K103T/R

Figure 1. Example of a Virologic Profile for a Patient who has Switched to Efavirenz following Virologic Failure on an Emivirine Regimen



RESULTS (continued)

Table 3. Mutational Patterns at the time of Virologic Failure on an EMV containing regimen

Mutation pattern	Number of Patients
Wild Type*	29 (59.2%)
K103N*	8 (16.3%)
103N, 184V	3
103K/N, 108V/I, 138K, 184V	1
103N/T/K, 138K/E, 184V	1
103K/N, 184V/C	1
103N/K, 138K/E, 184V	1
103K/N, 108V/I, 184V	1
K101E*	2 (4.1%)
101E, 184V	1
101K/E, 108V/I, 184V	1
Other NNRTI*	10 (20.4%)
108I, 138K, 184V	1
108V/I, 138E/K, 184M/V	1
108I/V, 138K/E, 184V	1
108V/I, 184V	1
138K, 184V	1
138E/K, 184V	1
138K, 184V	1
108V/A, 184V	1
181C, 184V	1
103T/K, 184V	1
Other (NRTI Only)*	1
41M/I, 184V	1
Unable to Genotype	1
Patients without viral load data post switch to efavirenz	
103N, 184V	1
Wild Type	1
108V/I, 138K, 184V	1

Figure 2. Percentage of Patients with Viral Load ≤ 50 copies/mL and < 400 copies/mL Post Switch to an Efavirenz Regimen

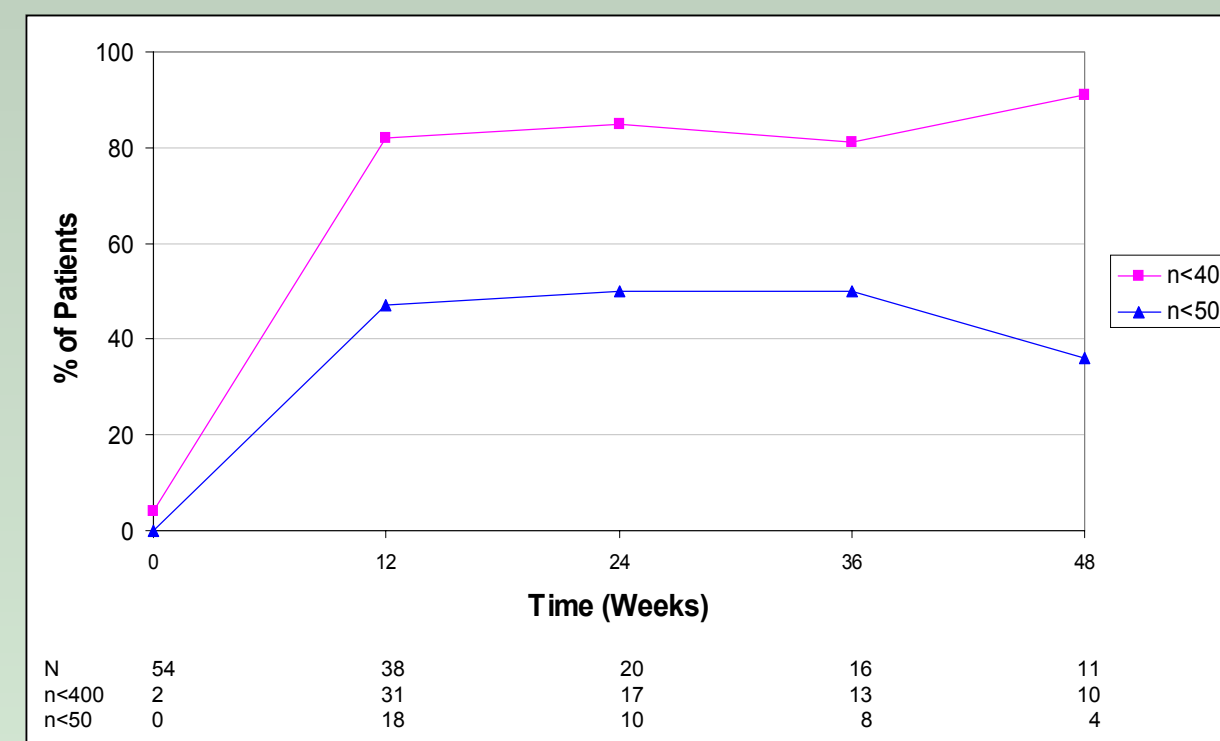
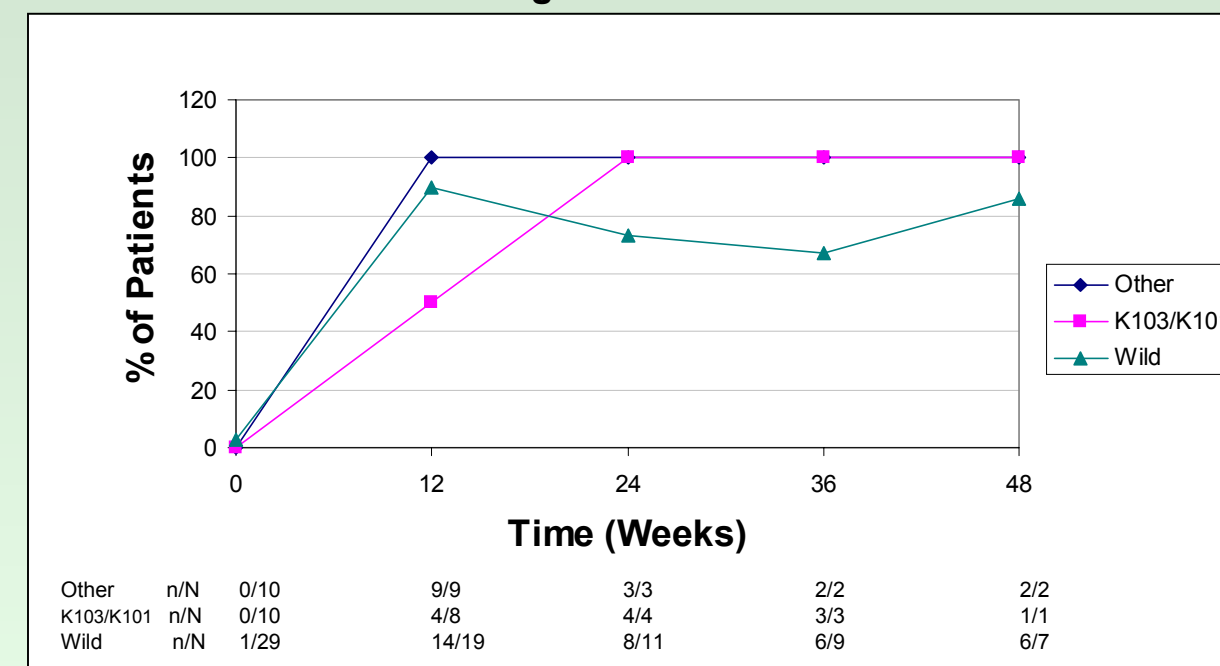
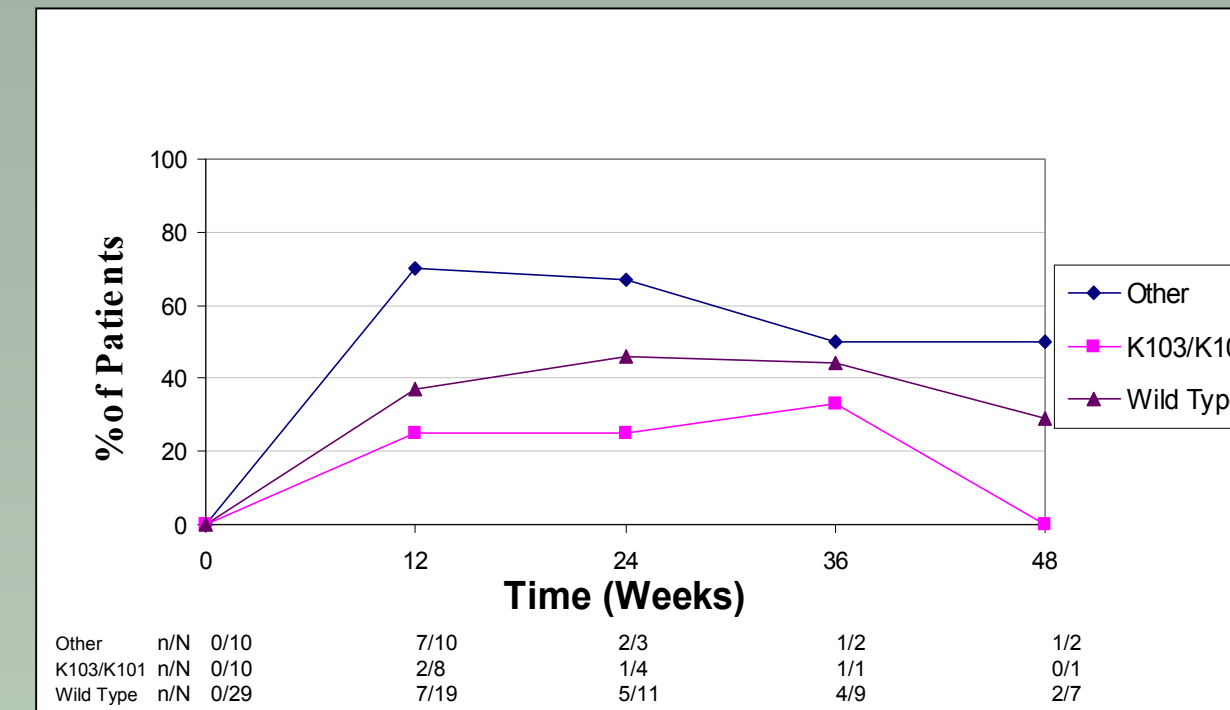


Figure 3. Percentage of Patients with Viral Load ≤ 400 copies/mL by Mutation Post Virologic Failure



RESULTS (continued)

Figure 4. Percentage of Patients with Viral Load ≤ 50 copies/mL by Mutation Post Virologic Failure



CONCLUSION

- Overall, the incidence of the K103N mutation at failure with EMV+FTC+d4T was 13.9% (10/72). This was comparable to the subset of patients (18.9% 10/53) who chose to switch to an efavirenz containing regimen. The second most frequent mutation was E138K (18.9%; 10/53).
- Most patients did not express any mutations upon failure with EMV (56.9% were wild type at failure). This suggests that patients were not adherent to the study regimen.
- The switch to an efavirenz regimen was well tolerated. Three (3) patients discontinued due to an adverse event (peripheral neuropathy, rash and psychotic episode).
- Overall, 91% of patients who failed EMV therapy and then switched to EFV+ABC+d4T were <400 copies/mL at Week 48. Thirty-six percent (36%) of the patients were <50 copies/mL at Week 48.
- The mutational pattern was predictive of response to a viral load of <50 copies/mL. At Week 48, patients with a mutational pattern excluding K103 or K101 achieved a 50% frequency of <50 copies/mL; with K103/K101 0% were <50 copies/mL, and 29% of patients with WT genotype were <50 copies/mL suggesting poor adherence in this subset.

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MKC-401 Participating Investigators (EFV Substudy)

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