Overview of the Genotypic Findings from Emtricitabine-Treated HIV+ Patients

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Introduction

- Emtricitabine (FTC) is a potent nucleoside reverse transcriptase inhibitor (NRTI) with long plasma and intracellular half-lives, approximately 10 and 39 hours, respectively, which supports once-daily (QD) dosing[1]
- Short-term monotherapy studies have demonstrated that FTC 200 mg QD reduces human immunodeficiency virus (HIV) RNA levels by 1.7 - 1.9 $\log_{10}$ copies/mL[2]
- *In vitro*, reduced susceptibility to FTC was associated with a mutation in the HIV-1 reverse transcriptase (RT) gene at codon 184, which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I)[3]
- Mechanistic studies of fluorinated nucleosides indicate differences in the binding of these analogues to RT may have important implications for drug resistance[4]

Objective

- To summarize the incidence of virologic failure (VF) in antiretroviral therapy-naïve HIV-infected subjects treated with FTC within triple combination HAART regimen
- To assess the HIV-1 RT genotypic profile of subjects failing a triple combination HAART regimen including FTC

Methods

- The analyses are based on the Virologic Evaluable population (subjects with a valid plasma HIV-1 RNA measurement on or after Week 12) from three multicenter, randomized, controlled, 48-week clinical trials (FTC-301A, FTC-302, and MKC-401)
- In these studies, ART naïve, HIV-infected subjects were treated with FTC 200mg QD within triple-drug regimens including either two NRTIs or a NRTI plus a non-nucleoside reverse transcriptase inhibitor (NNRTI):
  - FTC 200mg QD + didanosine (ddI) 400mg QD + efavirenz (EFV) 600mg QD (FTC-301A)
  - FTC 200mg QD + stavudine (d4T) 40mg BID + nevirapine (NVP) 200mg BID/EFV 600mg QD (FTC-302)
  - FTC 200mg QD + d4T 40mg BID + abacavir (ABC) 300mg BID (MKC-401)
- VF was defined as lack of response (failure to achieve plasma HIV-1 RNA < 400 copies/mL) or loss of response (plasma HIV-1 RNA > 400 copies/mL on two consecutive measurements after achieving < 400 copies/mL)

Methods (cont'd)

- Genotypic analysis was performed on plasma samples (baseline and time of failure) from 72 of the 73 subjects who experienced a protocol defined VF
- HIV-1 RNA isolated from plasma served as the template for RT-PCR amplification of the protease and RT gene. Dideoxy sequencing was performed by use of the ABI 377® sequencing system, in which the Protease (amino acids 1-99) and the Reverse Transcriptase (amino acids 1-400) were analyzed
- The incidence of NRTI and NNRTI new mutations relevant to study medications at time of failure were summarized to depict the genotypic profile of the VFs
- Comparisons were analyzed using 95% confidence intervals and associated p-values for the difference between groups

Table 1. Baseline Demographics by Study Regimen

	FTC + ddI+EFV	FTC + d4T+NVP/EFV	FTC + d4T+ABC	Overall
Subjects Treated (n)	286	234	188	708
Gender (n, %)				
Male	239 (84)	99 (42)	81 (43)	419 (59)
Female	47 (16)	135 (58)	107 (57)	289 (41)
Race (n, %)				
White	136 (48)	24 (10)	23 (12)	183 (26)
Black	52 (18)	186 (80)	143 (76)	381 (54)
Hispanic	77 (27)	0	1 (<1)	78 (11)
Other	21 (7)	24 (10)	21 (11)	66 (9)
Age (years)				
Mean	36	33	34	34
Min–Max	18-67	18-59	20-54	18-59
Plasma HIV RNA ($\log_{10}$ copies/mL)				
Mean	4.8	4.5	4.2	4.5
Min–Max	2.6-7.0	2.4-5.9	2.6-5.5	2.4-5.9
CD4+ Cell Count (cells/mm^3)				
Mean	312	392	416	373
Min–Max	5-1156	106-1348	152-983	5-1348

Table 2. Summary of Subject Disposition by Study Regimen

	FTC + ddI+EFV	FTC + d4T+NVP/EFV	FTC + d4T+ABC	Overall
Subjects Treated (n)	286	234	188	708
Completed Week 48 (n, %)	237 (83)	167 (71)	101 (54)	505 (71)
Premature Discontinuations (n, %)	49 (17)	67 (29)	87 (46)	203 (29)
Median Time on Study (weeks)	60	61	60	60
Min–Max	1-110	2-73	1-133	1-133
Virologic Evaluable (n)	265	208	174	647
Virologic Failures (n, %)	17 (6)	33 (16)	23 (13)	73 (11)
Virologic Failures Genotyped (n)	16	33	23	72

Figure 1. Incidence of Virologic Failure by Genotypic Mutation

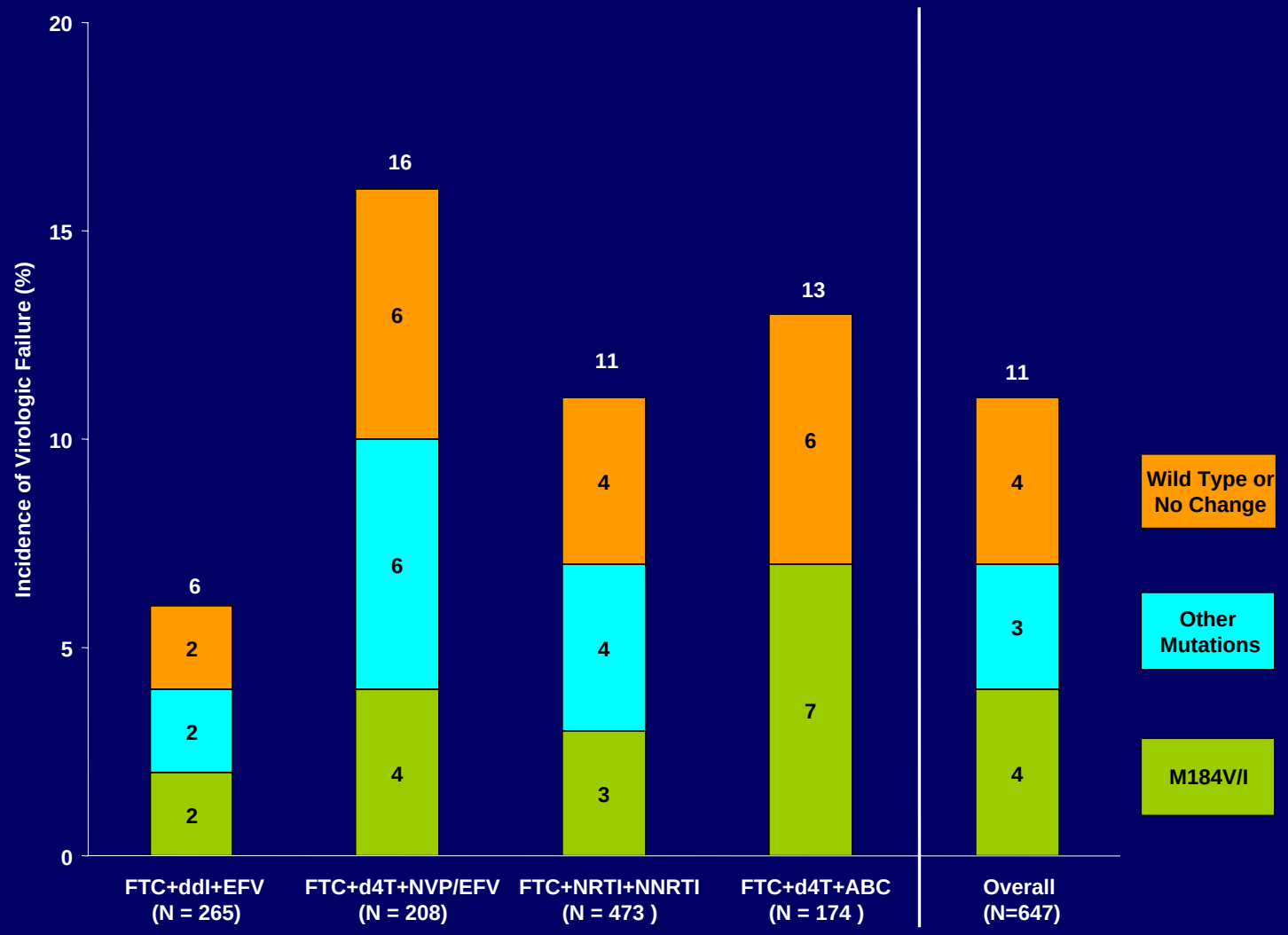
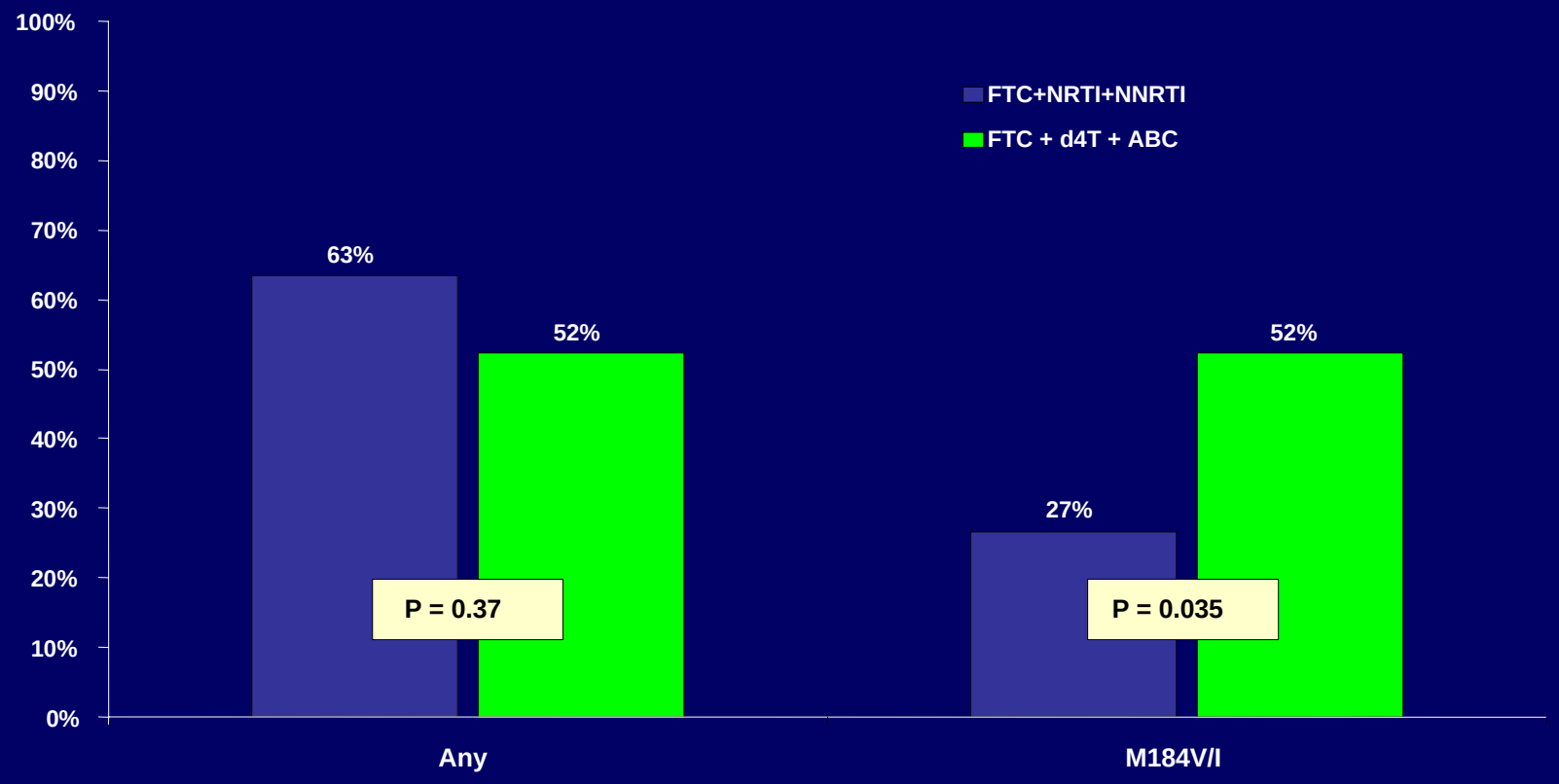


Table 3. Genotypic Mutations at Time of Failure within VFs

	FTC + NRTI + NNRTI			FTC + 2 NRTIs	Overall
	FTC + ddI+EFV (N = 16)	FTC + d4T+NVP/EFV (N = 33)	Combined (N = 49)	FTC + d4T+ABC (N = 23)	(N = 72)
Any	69%	61%	63%	52%	60%
M184V/I	37%	21%	27%	52%	35%
NRTI[a]	6%	3%	4%	4%	4%
NNRTI[b]	62%	61%	61%	NA	42%
K103N	50%	27%	35%	NA	24%
No change	31%	39%	37%	48%	40%

[a] K65, V75
[b] A98, L100, K103, V106, Y181, Y188, G190, P225

Figure 2. Frequency of Treatment-Emergent Mutations within VFs



Conclusions

- Antiretroviral-naïve subjects treated with FTC-containing HAART regimens resulted in:
  - Low incidence of virologic failures overall (11%), with lowest failure rate observed when FTC was used in entirely once-daily regimen
  - Low incidence of virologic failure with mutations (7%)
  - Low incidence of M184V/I (4%)

- Subjects who experienced virologic failure had a statistically significant lower incidence of M184V/I in NNRTI regimens compared to the FTC + d4T + ABC regimen ($p=0.035$)

References

[1] Wang LH, et al., XIV International AIDS Conference, poster #4546, Barcelona (2002)

[2] Rousseau FS, et. al., J Antimicrobial Chemotherapy 48: 507-514 (2001)

[3] Tisdale M, et al., Proc Natl Acad Sci Jun 15; 90 (12): 5653-5656 (1993)

[4] Ray AS, et al., Antiviral Chemistry and Chemotherapy, In Press (2003)