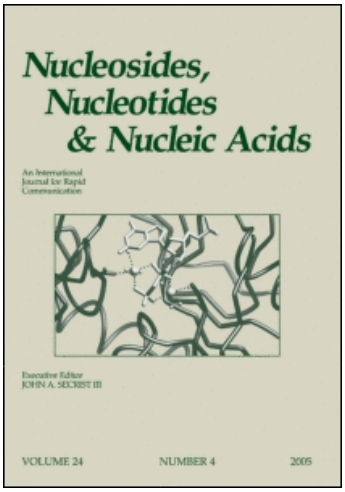

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ANTIVIRAL ACTIVITY OF TENOFOVIR (PMPA) AGAINST NUCLEOSIDE-RESISTANT CLINICAL HIV SAMPLES

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ABSTRACT

The presence of the lamivudine-associated M184V RT mutation increases tenofovir susceptibility in multiple HIV genotypes. Tenofovir is uniquely active against multinucleoside-resistant HIV expressing the Q151M mutation, but shows reduced susceptibility to the T69S insertion mutations. HIV with common forms of zidovudine and lamivudine resistance are susceptible to tenofovir, corroborating phase II clinical results demonstrating the activity of tenofovir DF in treatment-experienced patients.

Resistance to anti-HIV drugs limits the effectiveness of current HIV treatments and new anti-HIV drugs with activity against drug-resistant HIV are needed. Tenofovir (formerly PMPA) is a nucleotide analogue with activity against retroviruses and hepadnaviruses (1,2). An oral prodrug of tenofovir, tenofovir disoproxil fumarate (tenofovir DF), has shown efficacy against HIV-1 infection in phase I and II clinical trials (3,4) and is currently in phase III clinical trials for the treatment

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of HIV-1 infection. *In vitro*, a K65R reverse transcriptase (RT) mutation in HIV-1 has been selected by tenofovir resulting in 3 to 4-fold reduced susceptibility to tenofovir (5). The K65R RT mutation is rarely observed *in vivo* (6), although it can be selected by didanosine, zalcitabine and abacavir (7–9). HIV expressing the lamivudine-associated M184V RT mutation has shown increased susceptibility to tenofovir *in vitro* (5,10). The objective of the current study was to characterize the tenofovir susceptibility of clinical HIV samples expressing a variety of nucleoside-associated resistance mutations.

METHODS

Phenotypic susceptibility of 63 outpatient HIV samples was assessed with the Antivirogram™ assay by Virco Central Virological Laboratories (Mechelen, Belgium). Clinical HIV samples expressing the lamivudine-associated resistance mutation M184V (n = 10), high-level zidovudine-associated resistance mutations (T215Y + others ± M184V, n = 20), multinucleoside resistance mutations (Q151M complex and T69S double amino acid insertions ±M184V, n = 25) or the K65R resistance mutation (±M184V, n = 8) in RT were selected for analysis. Phenotypic classification is based upon IC_{50} changes relative to wild-type where sensitive is <4-fold, intermediate susceptibility is 4 to 10-fold, and resistant is >10-fold.

RESULTS

Mean tenofovir fold changes and the range of tenofovir fold changes for each genotypic group are presented in Table 1. Fold changes to other nucleoside analogues are provided for comparison. HIV expressing M184V alone showed mild (0.7 fold) hypersensitivity to tenofovir as previously reported (5,10). High-level zidovudine-resistant HIV (ZDV-HI, 47-fold resistance to ZDV) remained sensitive to tenofovir (3.7-fold), with 3 samples having an intermediate phenotype of 4 to 10-fold reduced susceptibility. With M184V, high-level ZDV mutations showed increased sensitivity to tenofovir (2.4-fold), but still maintained 15-fold resistance to ZDV. Multinucleoside-resistant HIV with the Q151M RT mutation complex showed full sensitivity to tenofovir (1.7-fold) regardless of the presence of M184V. These same viruses were >10-fold resistant to ZDV, stavudine and all other nucleoside analogues. HIV with the currently rare multinucleoside-resistant T69S double amino acid insertions were resistant to tenofovir (23-fold), but, with M184V, intermediate susceptibility was observed (6-fold). These viruses also showed >30-fold resistance to ZDV and varying degrees of resistance to all other nucleoside analogues. HIV expressing the K65R mutation showed 3.4-fold reduced sensitivity to tenofovir, but only 1.5-fold when present with M184V.

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Table 1. Summary of Tenofovir and Nucleoside Susceptibilities

Resistance Group	N	Mean Fold Change in Susceptibility from Wild-Type (*range*)					
		Tenofovir	Zidovudine	Lamivudine	Didanosine	Stavudine	Abacavir
M184V	10	0.7 (0.3−1.3)	0.9 (0.2−1.5)	>50 (>50)	1.0 (0.3−2.4)	1.4 (0.4−2.8)	1.3 (0.9−2.4)
ZDV-HI[1]	10	3.7 (0.8−8.4)	47 (9.3−82)	4.3 (0.4−12)	1.6 (0.3−3.4)	2.5 (0.5−6.7)	2.6 (0.5−5.6)
ZDV-HI[1] + M184V	10	2.4 (0.9−3.8)	15 (2.1−34)	>50 (>50)	1.8 (0.7−4.5)	1.7 (0.7−4.3)	4.6 (1.8−9.5)
Q151M Complex	5	1.8 (1.1−3.0)	43 (9.6−85)	2.1 (1.3−2.6)	13 (6.4−31)	20 (6.1−57)	11 (3.0−24)
Q151M + M184V	5	1.6 (0.8−3.3)	46 (19−70)	>50 (>50)	19 (4.8−38)	11 (3.7−20)	16 (3.9−24)
T69 Insertions	5	23 (14−35)	101 (60−149)	28 (8.3−53)	4.1 (1.4−6.4)	9.3 (2.4−20)	20 (10−29)
T69 Ins + M184V	10	6.0 (2.1−15)	31 (2.1−54)	>50 (>50)	1.8 (0.4−3.3)	4.2 (1.3−15)	8.1 (2.1−28)
K65R[2]	4	3.4 (2.0−6.7)	17 (0.7−64)	20 (1.1−61)	4.7 (0.9−8.3)	8.4 (1.2−27)	7.8 (1.3−24)
K65R[2] + M184V	4	1.5 (0.4−2.8)	20 (0.4−70)	>50 (>50)	12 (2.7−35)	8.7 (0.9−26)	13 (2.3−34)

1 All ZDV-HI samples contained the T215Y or F mutation plus other ZDV-associated mutations at codons 41, 67, 70, 210 or 219 (mean of 3.3 ZDV-associated mutations).
2 Two samples from each K65R resistance group also contained the Q151M mutation complex.

CONCLUSIONS

The presence of the lamivudine-associated M184V RT mutation increases tenofovir susceptibility in multiple HIV genotypes. Tenofovir is uniquely active against multinucleoside-resistant HIV expressing the Q151M complex of resistance mutations, but shows reduced susceptibility to the currently rare T69S double amino acid insertion mutations. HIV with common forms of ZDV and lamivudine resistance are susceptible to tenofovir, corroborating phase II clinical results demonstrating the potent and durable activity of tenofovir DF in treatment-experienced patients with a high prevalence of resistance mutations at baseline (4).

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