

Decreased Replication Capacity of HIV-1 Clinical Isolates Containing K65R or M184V RT Mutations

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Introduction

- Mutations in HIV-1 that encode drug resistance may decrease viral replication capacity (RC) *in vitro*
- Most protease inhibitor (PI)-associated resistance mutations have shown decreased RC
- Decreased RC *in vitro* has been associated with lower viral loads and higher CD4 counts in patients
- In clinical trials of tenofovir DF, 2-3% of tenofovir DF-treated patients developed the K65R mutation, but these patients maintained some degree of viral load suppression (mean 0.9 log₁₀ reduction from baseline)

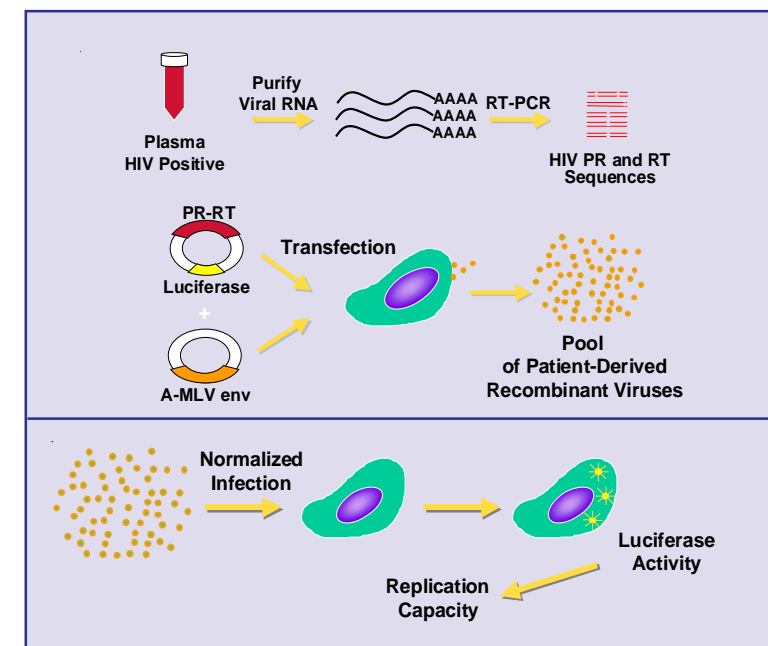
Objectives

- Characterize the replication capacity of a large panel of HIV-1 clinical isolates with defined nucleoside reverse transcriptase inhibitor (NRTI)-associated mutations with and without PI-associated mutations

Methods

- Patient isolates with defined resistance genotypes were selected from samples submitted to ViroLogic for routine genotypic, phenotypic and RC analysis
- Sample groups selected for analysis:
 - No NAMs or TAMs (no nucleoside- or thymidine analog-associated mutations as the control group)
 - TAMs = M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/H/R
 - NAMs = TAMs, E44D, K65R, T69D/S/N, L74X, V75X, Y115F, V118I, M184V/I, T69Ins, Q151M
 - M184V/I without other NAMs (= M184V/I alone)
 - K65R with or without M184V/I without other NAMs
 - TAMs with or without M184V/I + other NAMs
 - Q151M + M184V + other NAMs
 - T69Ins + M184V + other NAMs
- Sample groups were further stratified by number of TAMs, presence or absence of M184V, and presence or absence of PI-associated resistance mutations
 - PI-associated mutations were any substitution at positions 24, 30, 32, 46, 47, 48, 50, 54, 82, 84, 88 or 90 in protease (not including V82I)
- RC was determined for each sample (Fig. 1) and compared to the NL4-3 reference
 - Raw RC values were adjusted to account for the difference between the NL4-3 reference and average patient-derived wild-type reference
 - The mean adjusted RC of 700 samples without any known resistance mutations is 94% (See Poster #585, 10th CROI)
- Statistical analyses compared the mean RC of one sample group to that of the No NAM / No TAM control group from this study
 - p-values calculated with the unpaired t-test

Figure 1 • Measuring Replication Capacity of HIV



Results

Figure 2 • Distribution of Nucleoside-Associated Mutations in Sample Set (n=1829)

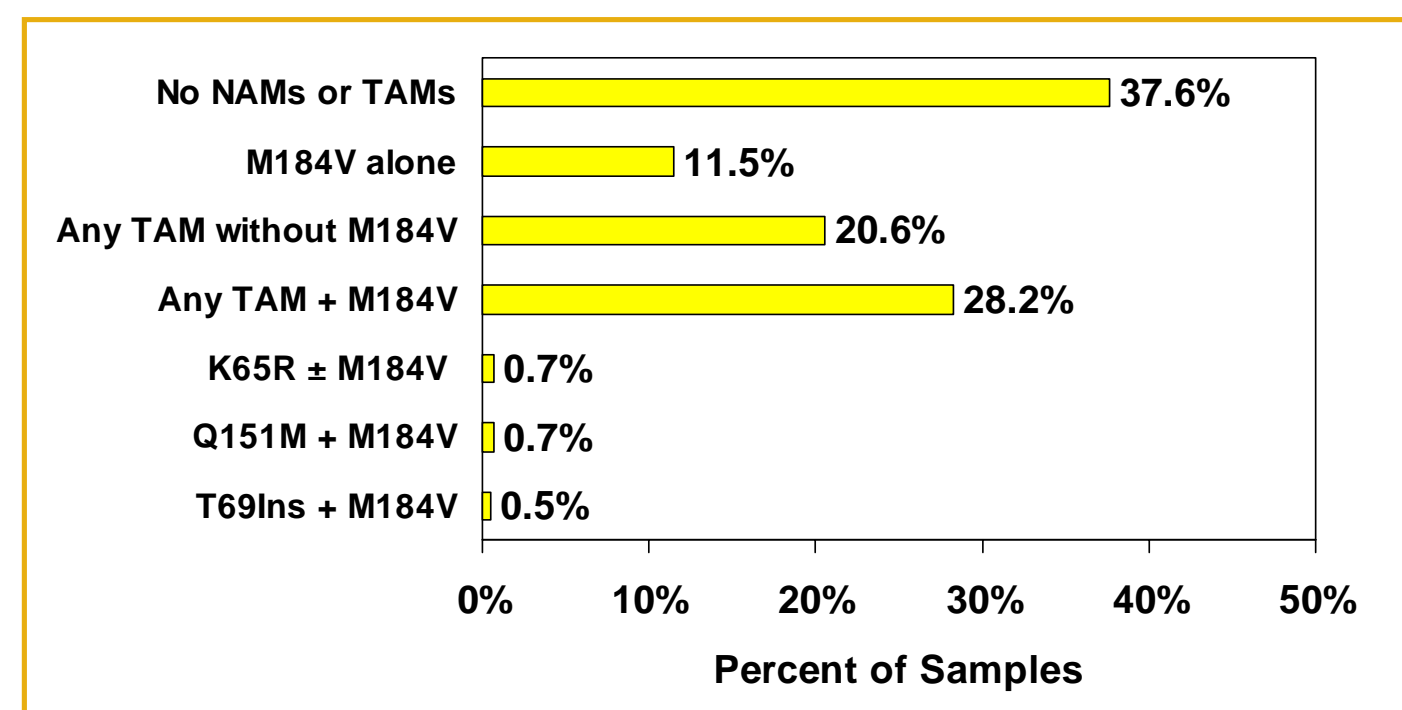


Figure 3 • Number of Samples with and without Protease Inhibitor-Associated Resistance Mutations

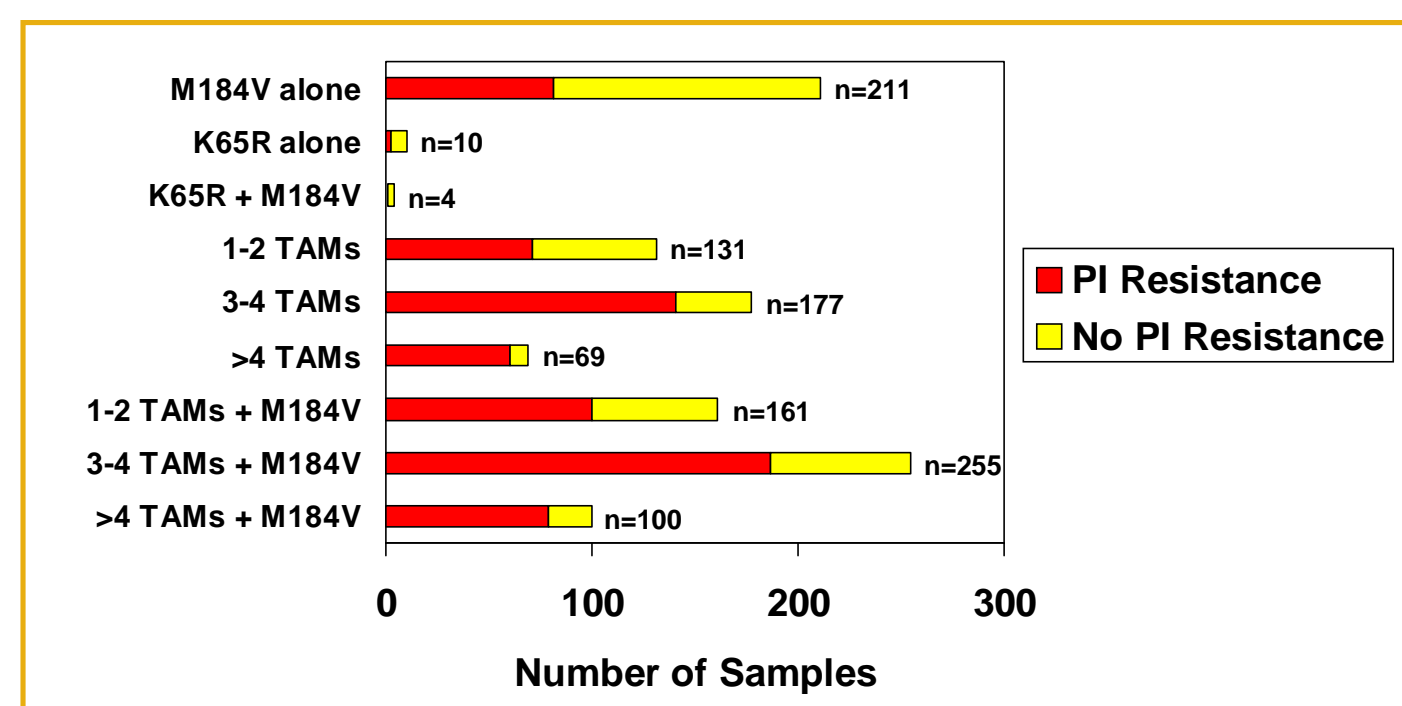


Figure 4 • Replication Capacity of HIV with and without Protease Inhibitor Resistance Mutations (n=1829)

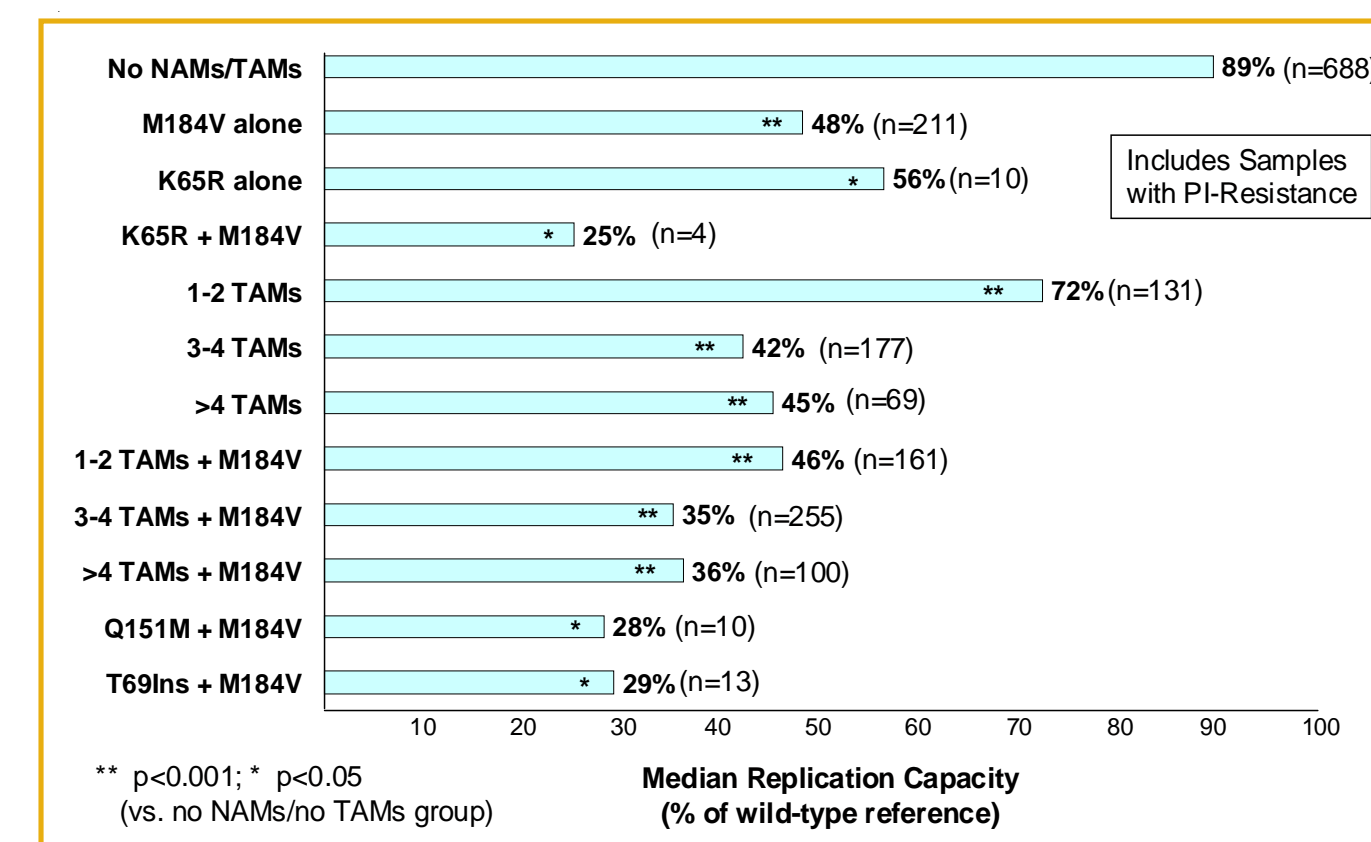
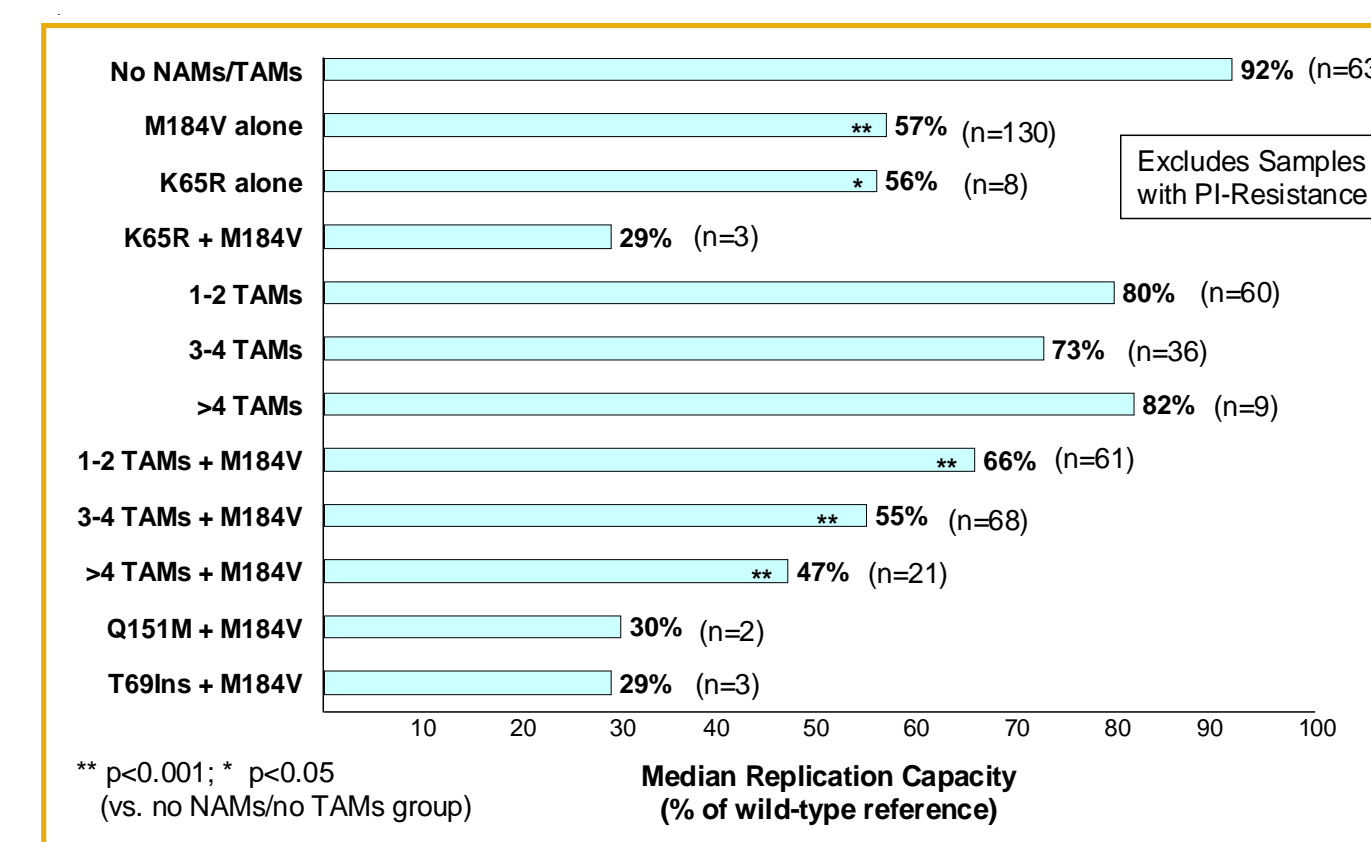


Figure 5 • Replication Capacity of HIV without Protease Inhibitor Resistance Mutations (n=1040)



Conclusions

- Among patient samples sent for routine resistance testing, thymidine analog-associated mutations (TAMs) show a higher prevalence (49%) than K65R (<1%) or the multinucleoside resistance mutations Q151M or T69Ins (each <1%)
- Patient-derived viruses with both nucleoside- and PI-associated mutations showed reduced replication capacity (RC) as compared to those without resistance mutations
- When excluding samples with PI-resistance, viruses with the K65R or M184V mutations in RT exhibited significantly decreased RC
 - Addition of M184V decreased RC to a level comparable to M184V alone
- Effects of resistance mutations on RC appear additive with one another
 - Effects of PI-resistance mutations
 - Effects of M184V
 - Effects of K65R

Discussion

- Decreased replication capacity of the K65R mutant virus may contribute to the HIV viral load suppression observed in tenofovir DF-treated patients who developed K65R
- Although therapeutic strategies should attempt to avoid development of resistance, the clinical consequences of certain resistance mutations may be moderated by the reduced replication capacity of the mutant virus