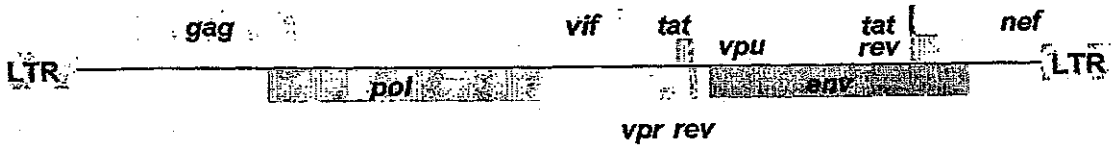
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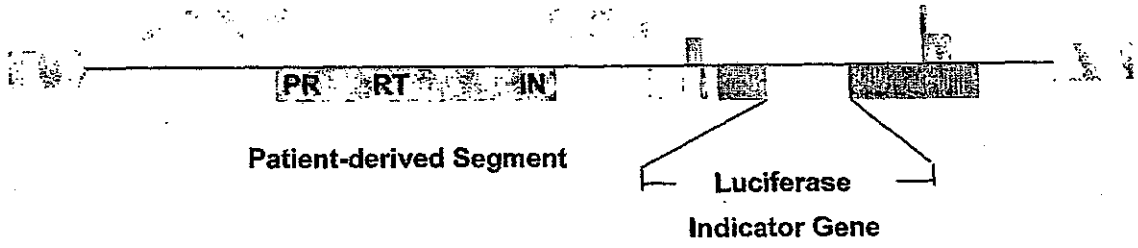
# FIGURE 1

## Resistance Test Vector

### HIV-1




## Resistance Test Vector



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# FIGURE 2

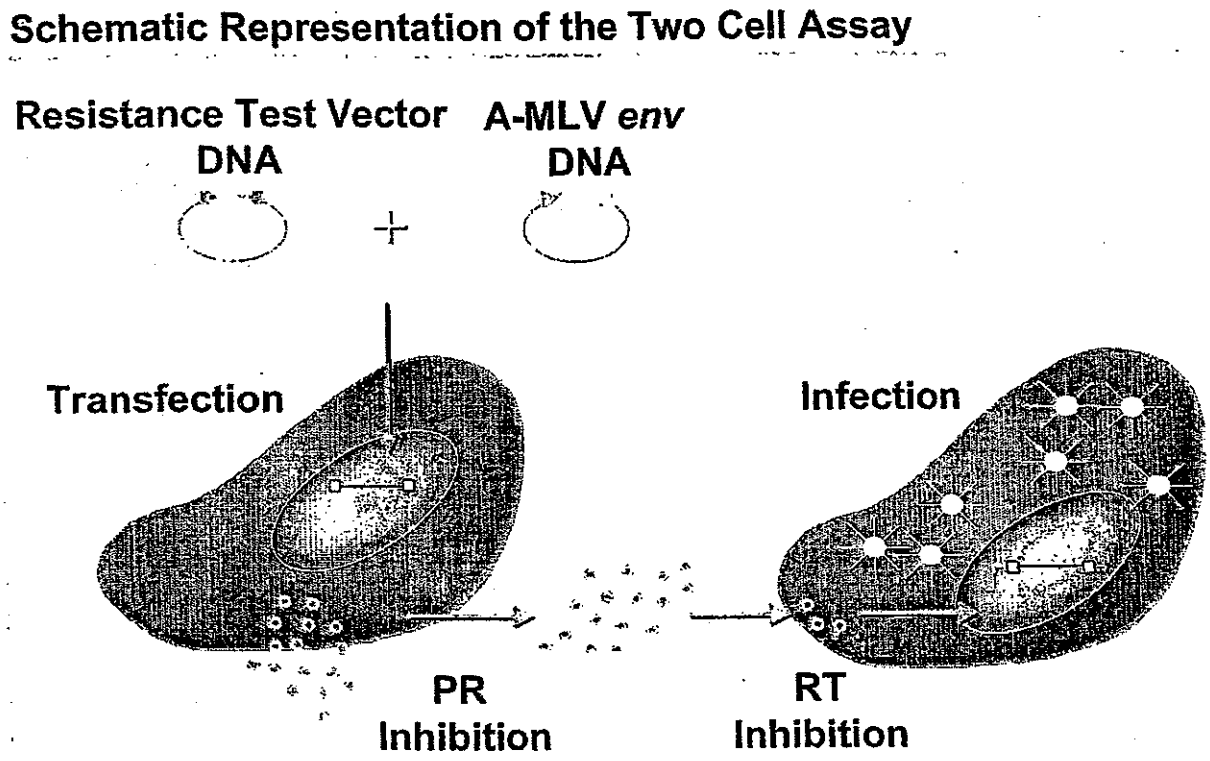
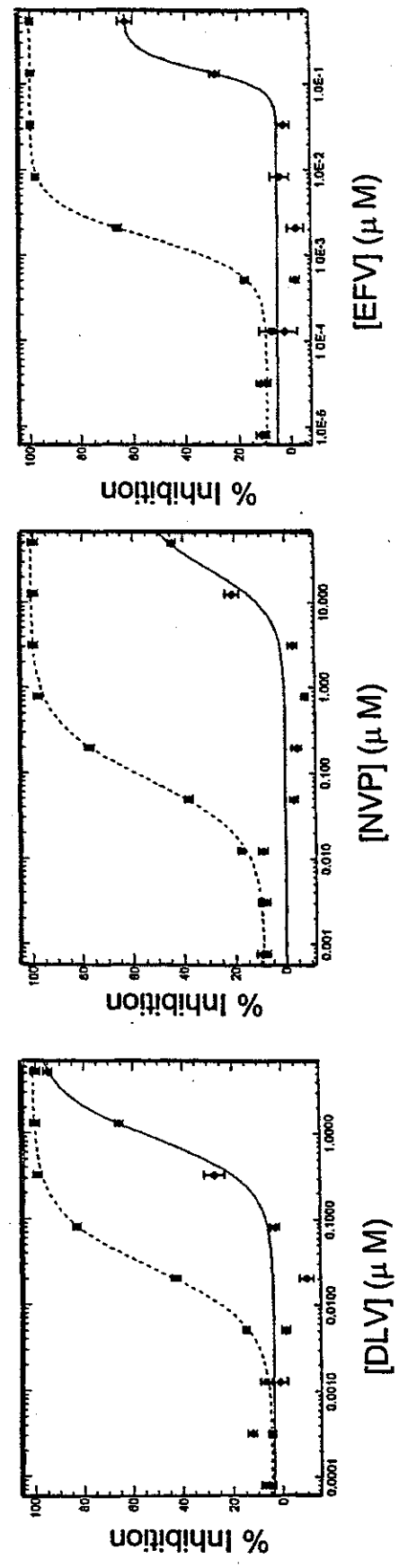


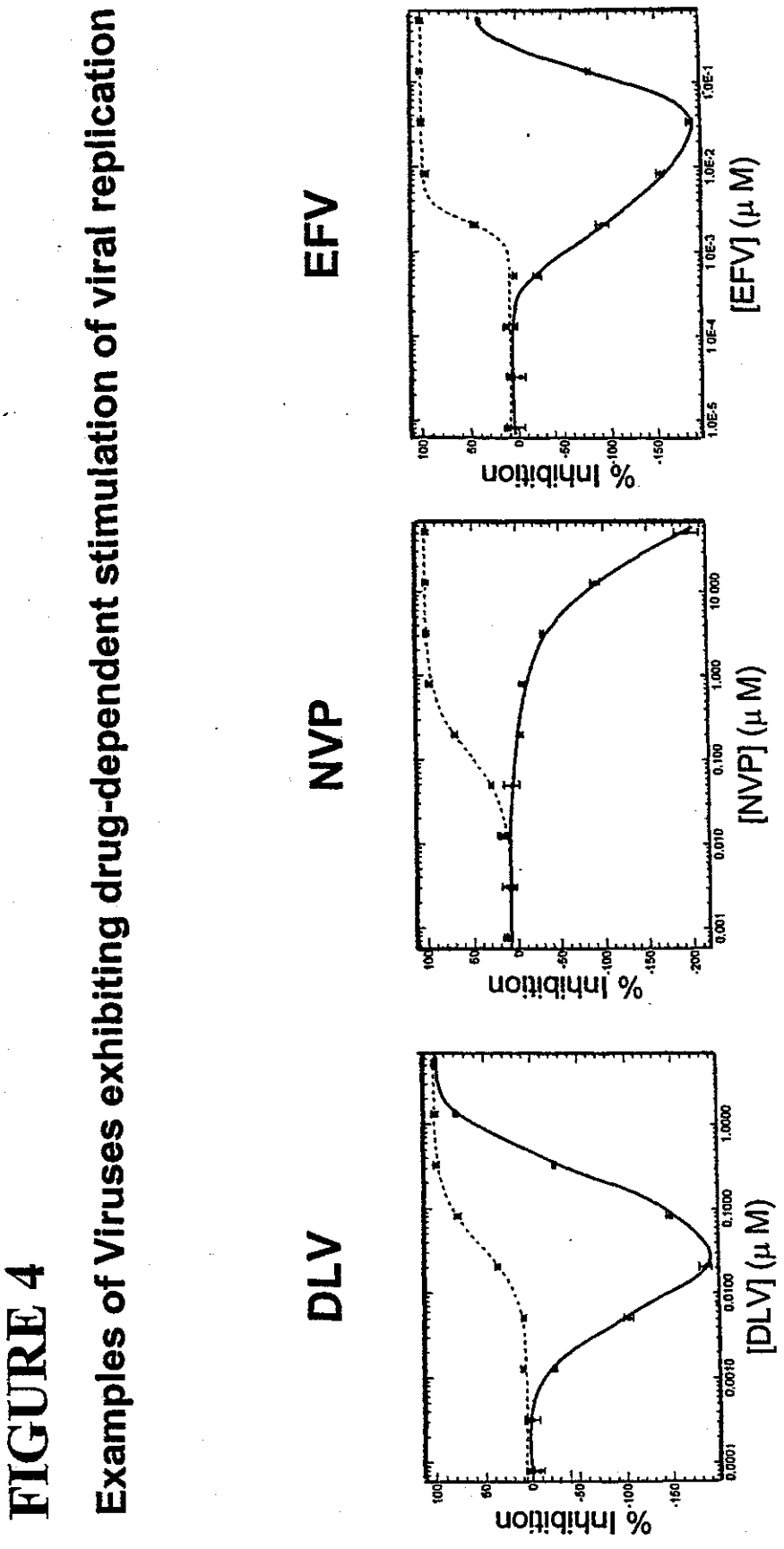
FIGURE 3

Examples of Phenotypic Drug Susceptibility Profiles



# FIGURE 4

**Examples of Viruses exhibiting drug-dependent stimulation of viral replication**



# FIGURE 5

**Table of patient viruses containing M230L mutations (example 3, 4, and 5)**

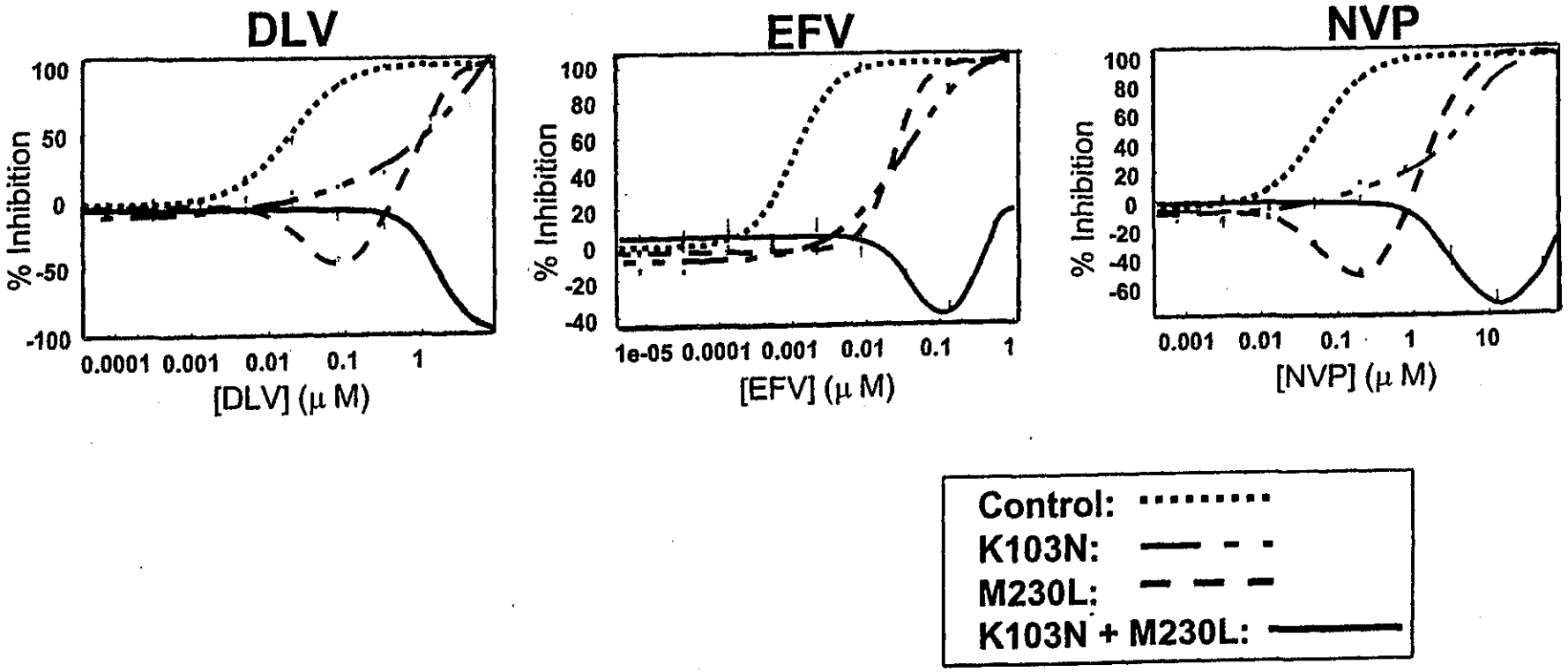
| ACCESSION # | Date of Draw | Mutations Observed in Reverse Transcriptase | DLV | EFV | NVP |
|---|---|---|---|---|---|
| **ARG-014 (Example 3)** | | | | | |
| 98-773 | 11/18/97 | M41L, L74I, M184V, L210W, R211K, T215Y, L228R, T296S | 0.3 | 0.3 | 0.4 |
| 98-1046 | 1/13/98 | M41L, L74I, Y181C, M184V, H198L, L210W, R211K, T215Y, L228R, M230L, T296S | >250 | 5.3 | >600 |
| 98-887 | 3/17/98 | M41L, L74I, Y181C, M184V, L210W, R211K, T215Y, L228R, M230L, T296S | 160.9 | 6.7 | >600 |
| **CCTG-2165 (Example 4)** | | | | | |
| 99-2-009089 | 11/10/99 | K49R, Q102K, K122E, E169D, I178M, M184V, I195T, T200A, R211K, V245M, D250E, K275Q, V276I, R277K, T286A, P294T | 0.9 | 0.2 | 1.1 |
| 00-2-010835 | 1/26/00 | K49R, Q102K, K103N, K122E, E169D, I178M, M184V, I195T, T200A, R211K, M230L, V245M, D250E, K275Q, V276I, R277K, T286A, P294T | >250 | 269.7 | >600 |
| **CCTG-1025 (Example 5)** | | | | | |
| AA2919 | 3/30/99 | D67D/N, D86E, Q102K, V118I, K122P, A158S, C162S, Q174H, D177E, R211K, F214L, T215Y, A272P, K275N, V276V/A/I/T, R277K, Q278H, K281R, T286A, V293I | 0.4 | 0.5 | 0.7 |
| 00-2-012090 | 2/29/00 | D67N, D86E, K101K/E, Q102K/R, K103K/N, V118I, K122P, A158S, C162S, Q174H/R, D177E, G190G/S, L210L/R/W, R211K, F214L, T215Y, H221H/Y, M230M/L, K238K/T, A272P/S, K275K/Q, V276V/A/I/T, R277K, Q278Q/H, K281K/R, T286A, V293I | 144.0 | >450 | >600 |

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# FIGURE 6

**Reduced Susceptibility and drug-dependent Stimulation of Viral Replication: Site Directed Mutants K103N and M230L**

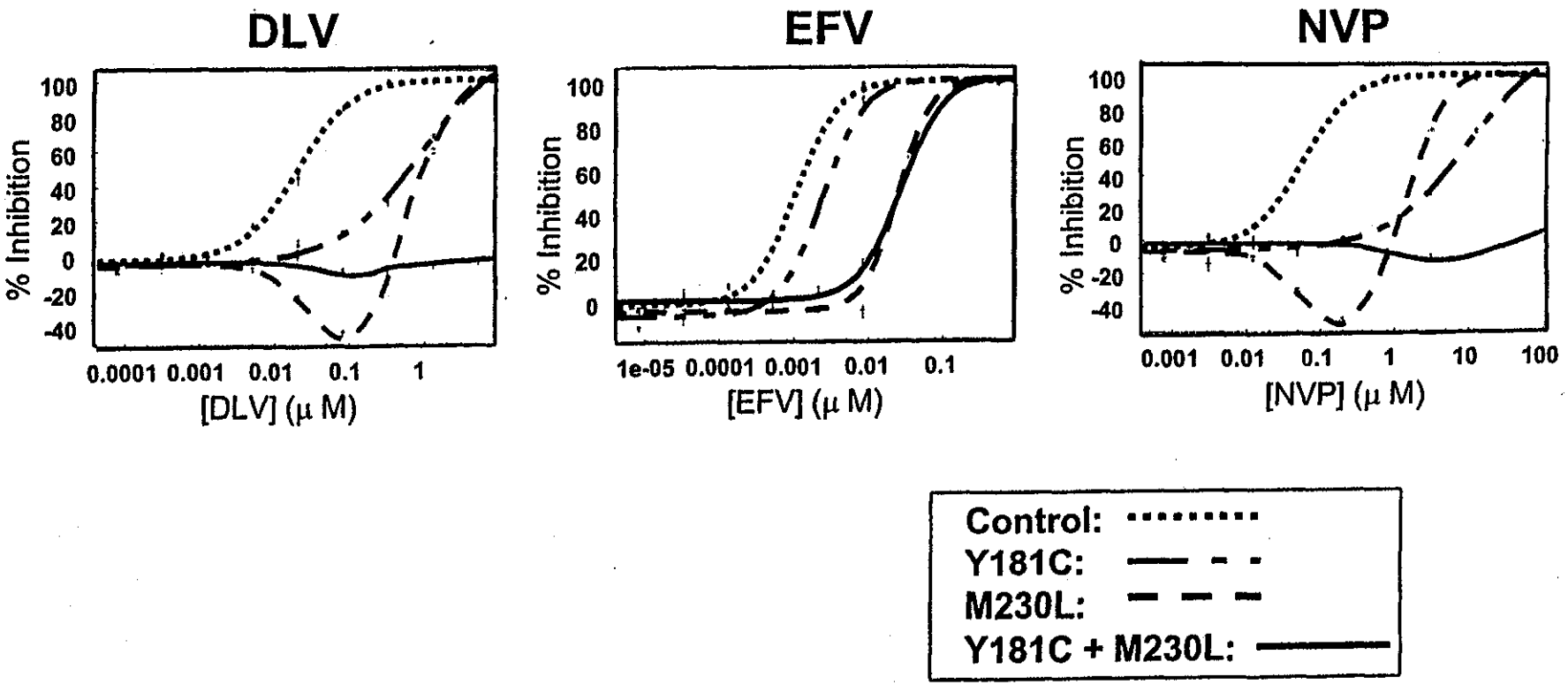





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# FIGURE 7

**Reduced Susceptibility and drug-dependent Stimulation of Viral Replication: Site Directed Mutants Y181C and M230L**

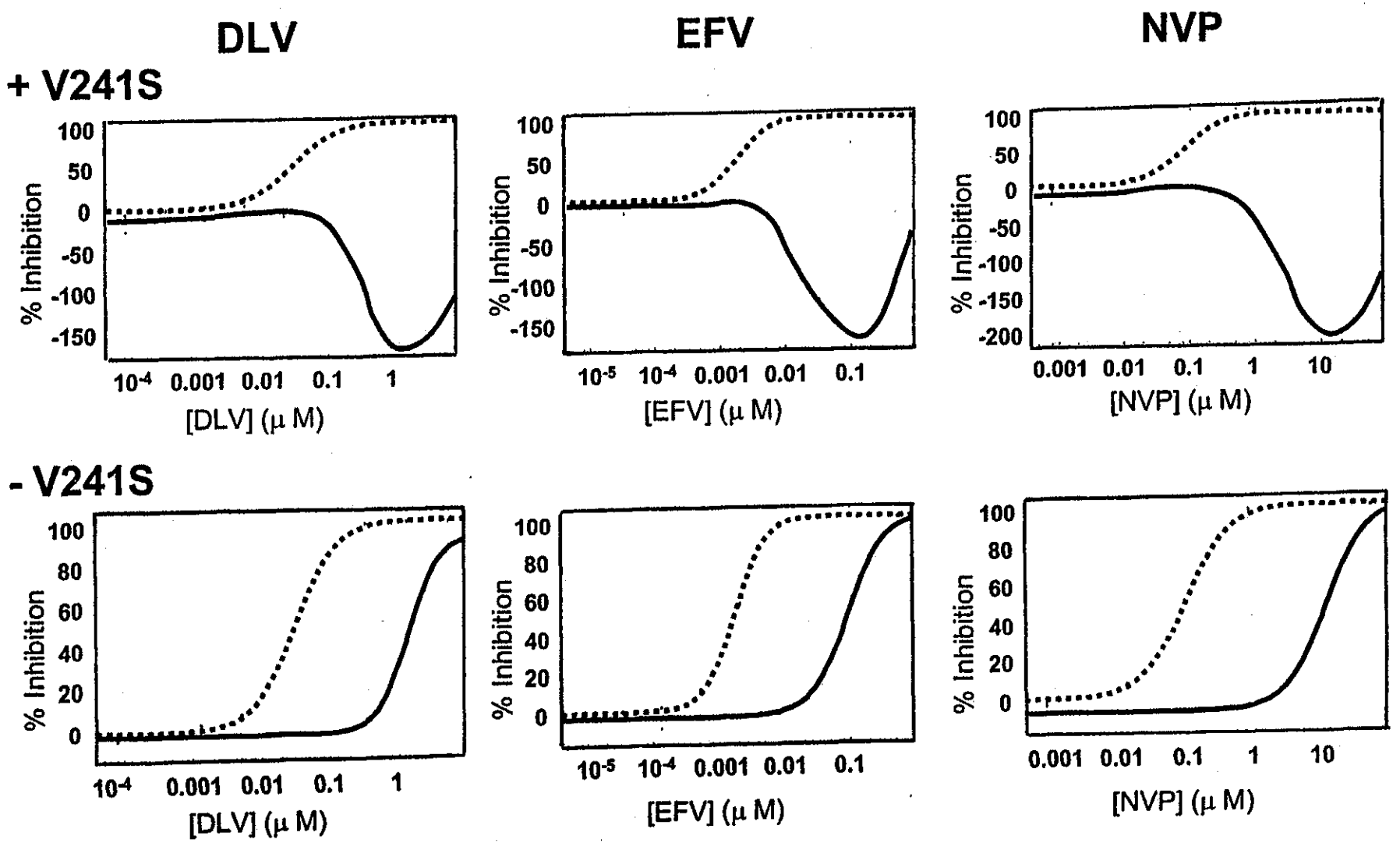





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# FIGURE 8

**Patient 11073, reverse mutagenesis of positions 241 and 277 (example 6)**

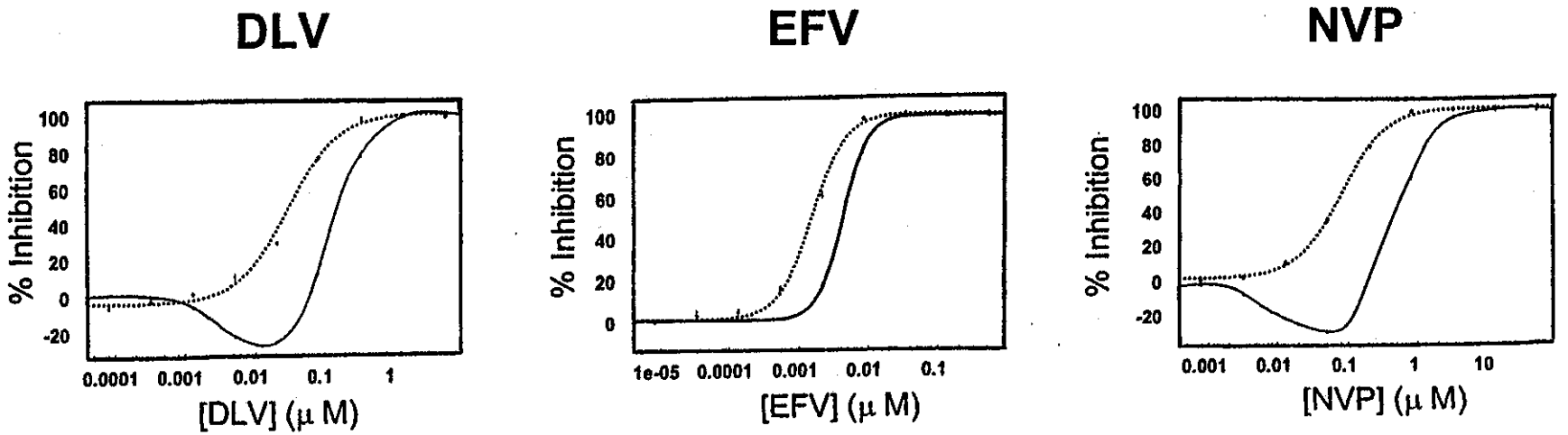





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# FIGURE 9

**Reduced Susceptibility and drug-dependent Stimulation of Viral Replication: Site Directed Mutant V241S**



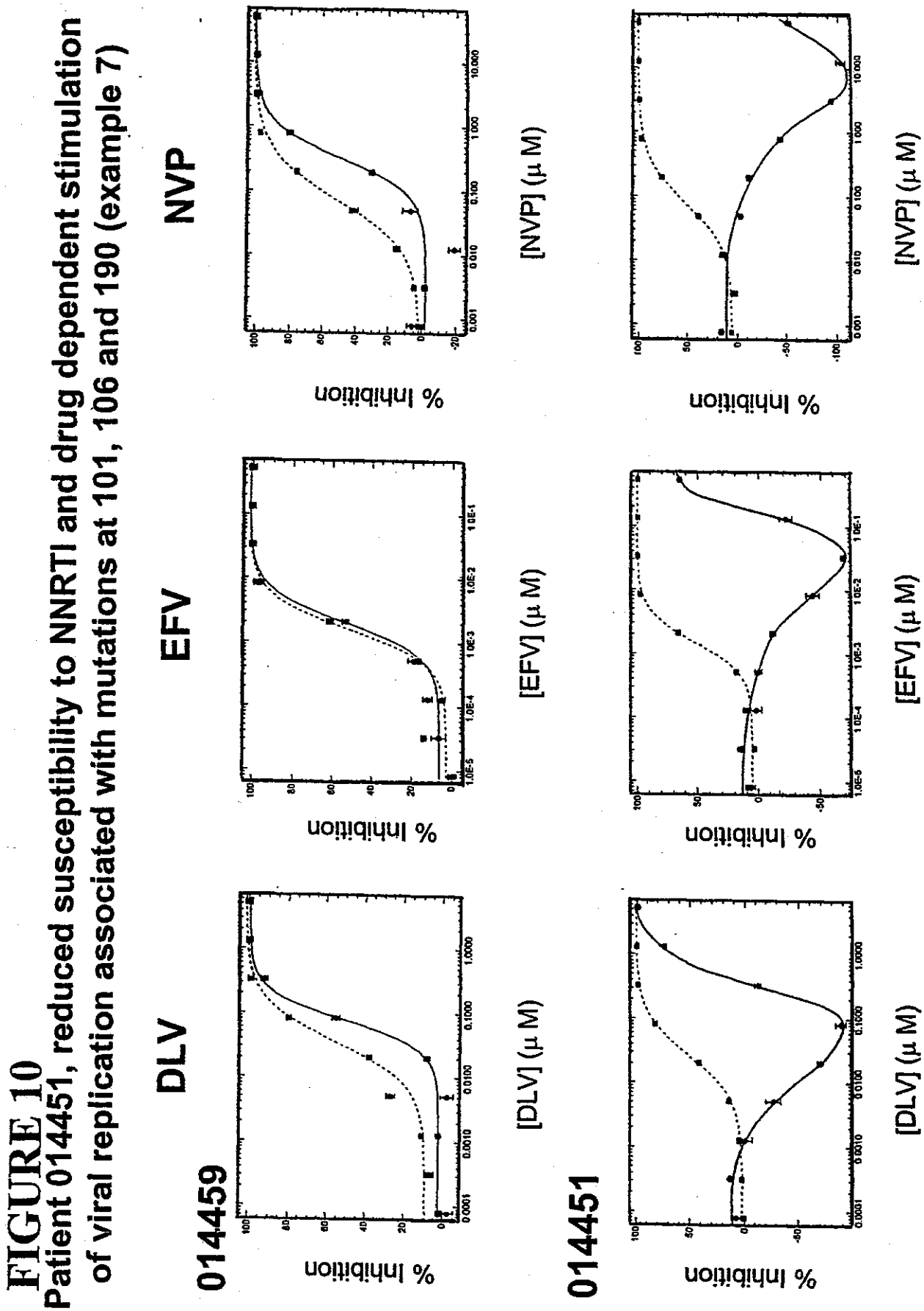



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**FIGURE 10**
**Patient 014451, reduced susceptibility to NNRTI and drug dependent stimulation of viral replication associated with mutations at 101, 106 and 190 (example 7)**



# FIGURE 11

## Table of patient viruses containing mutations at amino acid 245 (examples 8 - 11)

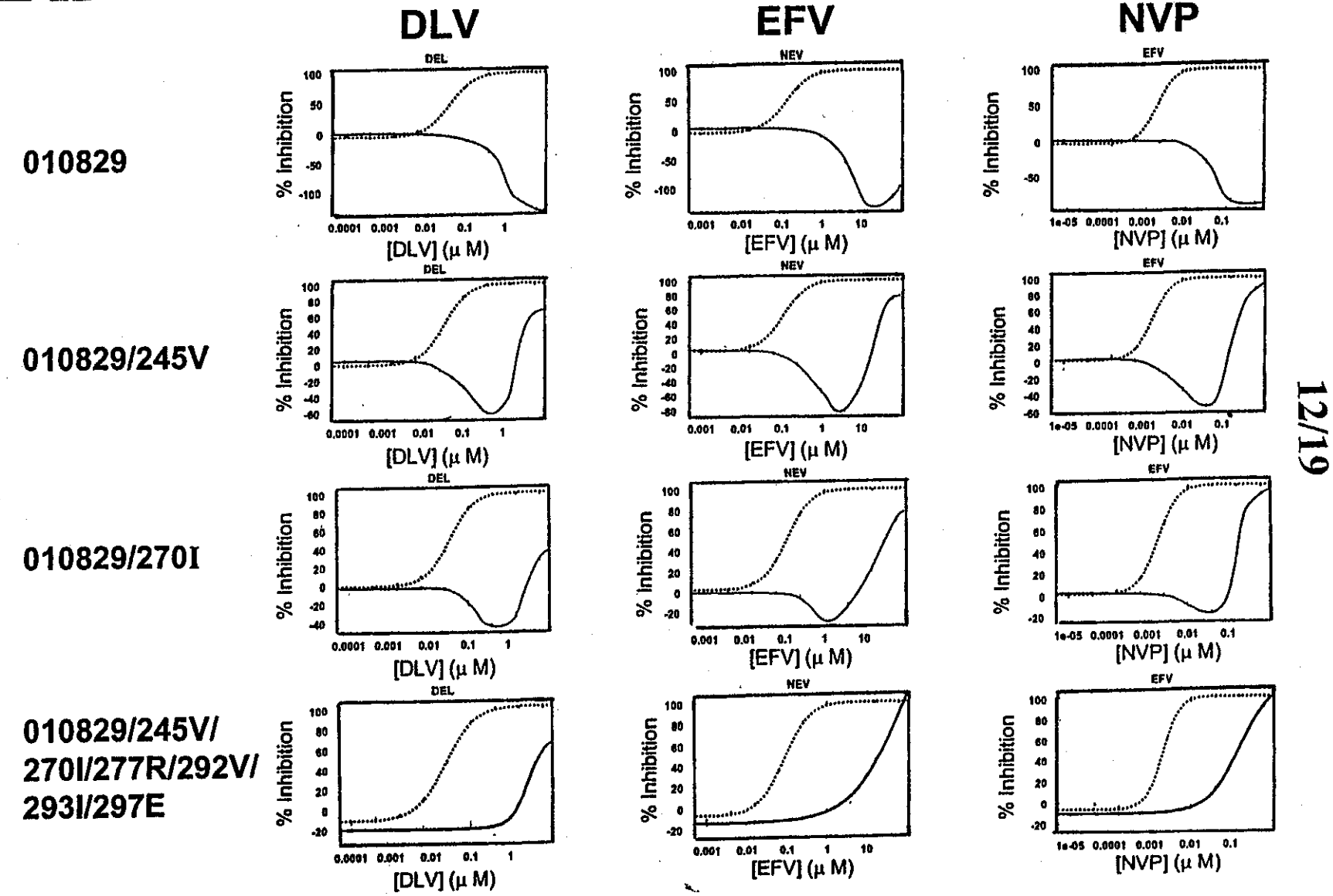
| Accession # | Mutations in Reverse Transcriptase | DLV Fold Change | DLV Stimulation | EFV Fold Change | EFV Stimulation | NVP Fold Change | NVP Stimulation |
|---|---|---|---|---|---|---|---|
| 00-2-005738 | D67N, K70R, R83K, A98G, Q102K, K122P, I135T, I142V, C162S, K173Q, I178L, Y181C, G196E, I202V, T215F, D218E, K219Q, V245E, A272P, R277K, V293I, E297Q | 63.2 | 40%, | 17.5 | 20% | >600 | 20% |
| 00-2-011311 | K43K/E, D67N, K70R, Q102K, K103N, K122E, I135I/M, C162S, Q174A/E, I178I/R, M184V, G190G/A, Q207E, H221H/Y, E224E/G, V245E, A272P, R277K, L283I, K287K/Q, V293I | >250 | 40% | >450 | 40% | >600 | 30% |
| 00-2-10829 | I31L, V35I, V90V/I, Q102K, K103N, K122E, C162S, G196E, R211K, F214F/L, T215Y, L228H, V245E, I270M, V276V/I, R277K, V292I, V293I, E297K | >250 | 100% | >450 | 80% | >600 | 100% |
| 00-2-006782 | Q102K, D123E, I135T, E138A, C162S, G196E, I202V, V245T, R277K, T286A, V293I, P294T, E297K | 18.5 | 70% | 5.2 | 25% | 7.8 | 60% |
| 00-1-012123 | K20R, T39E, M41L, E44D, V60I, D67N, A98G, Q102K, K103N, V118I, K122E, I135T, I142V, C162S, K173Q, Y181C, G190A, G196E, I202V, L210Y, T215Y, H221Y, V245T, A272P, R277K, V293I, E297K | >250 | 80% | >450 | 70% | >600 | 0 |
| 00-1-014397-01 | I31L, Q102K, K103N, D123E, C162S, K166R, D177E, R211K, T215F, L228R, V245T, A272G, R277K | >250 | 100% | >450 | 70% | >600 | 100% |
| 00-1-013415 | V35T, Q102K, K103N, K122E, D123N, I135T, C162S, D177E, T200A, Q207E, R211K, P225H, V245M, L264F, R277K, T290S | >250 | 30% | >450 | 20% | >600 | 20% |

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# FIGURE 12

**Patient 010829: Efect of reversion of mutations at 245, 270, 277, 292, 293 and 297**

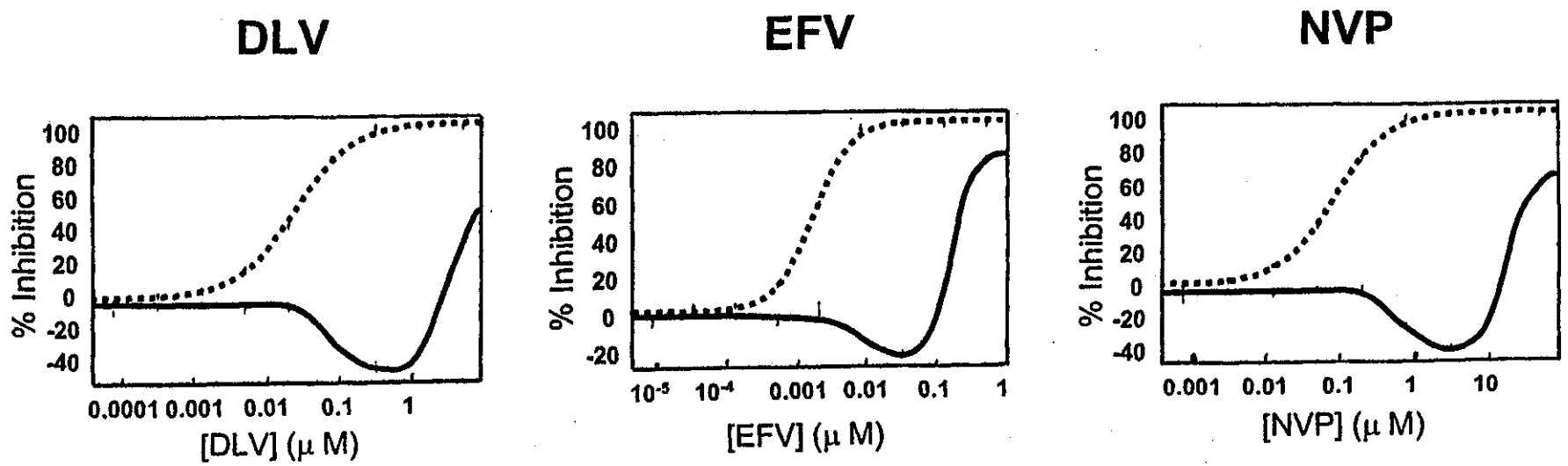





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# FIGURE 13

**Reduced Susceptibility and drug-dependent Stimulation of Viral Replication: Site Directed Mutants K103N, I135T AND V245T**

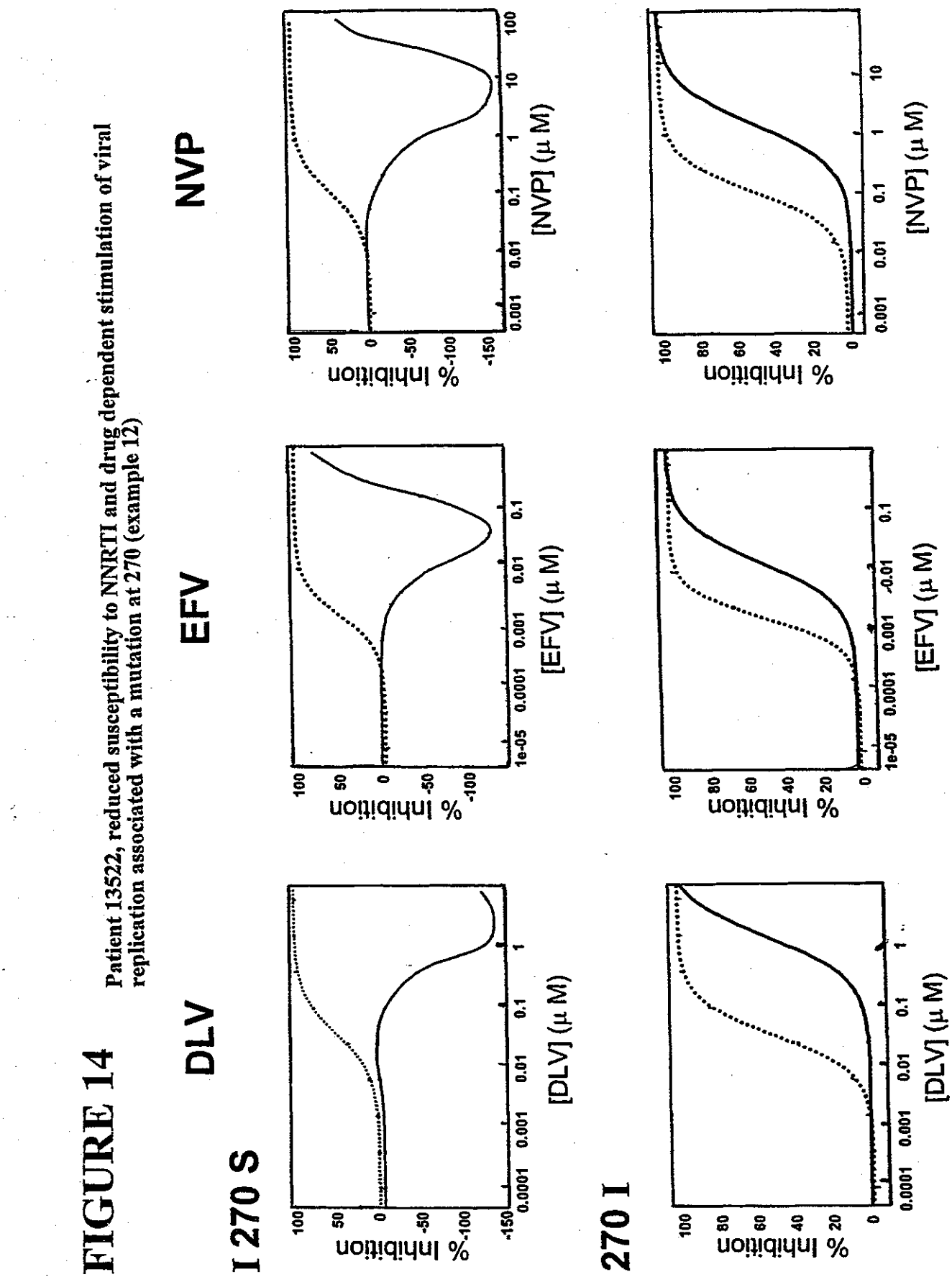





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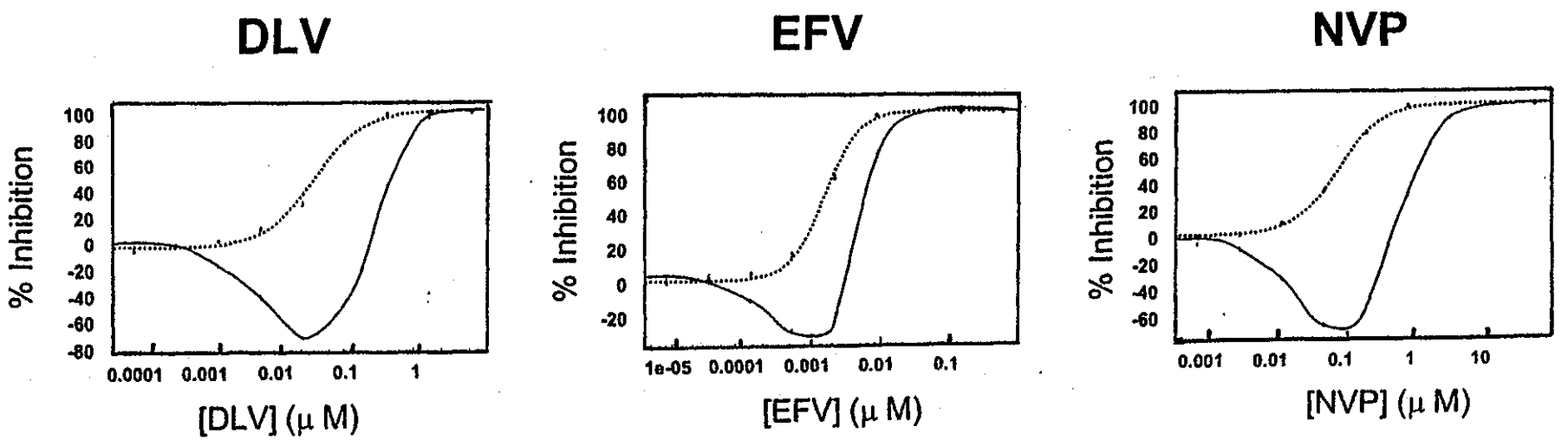
FIGURE 14

Patient 13522, reduced susceptibility to NNRTI and drug dependent stimulation of viral replication associated with a mutation at 270 (example 12)



# FIGURE 15

## Reduced Susceptibility and drug-dependent Stimulation of Viral Replication: Site Directed Mutant I270S






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# FIGURE 16

**Clinical History of Patient 1033**

| Sample ID | Date of Draw | Drug treatment | Duration | Viral load | NVP | DLV | EFV |
|---|---|---|---|---|---|---|---|
| 97-309 | 09/17/97 | AZT, 3TC, IDV | 2 yrs. | 545000 | 1.78 | 0.97 | 1.03 |
| 98-754 | 09/22/97 | " | 2 yrs. | 801000 | 1.19 | 1.16 | |
| | 10/03/97 | ABC, d4T, NFV, SQV | start | 900000 | | | |
| 98-1032 | 10/10/97 | NVP, d4T, NFV, SQV | start | 1160000 | 1.37 | 0.79 | 0.93 |
| | 10/15/97 | | | 2120000 | | | |
| 00-2-011658 | 11/12/97 | " | | 13300 | 2.6 | 1.1 | 1.4 |
| 00-2-011659 | 11/19/97 | " | | 84500 | 272 | 3.1 | 4.5 |
| | 12/03/97 | | | 329000 | | | |
| 98-1033 | 12/29/97 | d4T, NFV, SQV | start | 1220000 | *, dip-250% | 13.2, dip--180% | 214, dip-170% |
| 99-2-8973 | 01/28/98 | " | 12wks | 277000 | *, dip-180% | 18.4, dip-100% | 300, dip-150% |
| 98-757 | 02/26/98 | " | 16 wks | 488000 | *, dip-80% | 5.2, dip-20%? | 16.1, dip-80% |
| | 03/25/98 | | | 831000 | | | |
| 99-2-8980 | 04/22/98 | " | 24 wks | 607000 | *, dip-40% | 9.3, dip-25% | 28, dip-30% |
| | 05/20/98 | | | 572000 | | | |
| | 06/17/98 | | | 397000 | | | |
| 98-1080 | 07/15/98 | AZT, 3TC, IDV | start | 354000 | *, dip-45% | 2.77, dip-20% | 21.86, dip-50% |
| | 08/24/98 | | | 100000 | | | |
| AA1264 | 12/17/98 | " | | | 8.7 | 0.4 | 2.5 |
| 99-2-6174 | 05/20/99 | " | | | 9.87 | 0.07 | 1.59 |



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# FIGURE 17

## Sequences of Reverse Transcriptase of Patient 1033 Virus Samples

| Sample ID | RT Sequence |
|---|---|
| 97-309 (9/17/97) | V35I, D67N, T69D, K70R, L109I, M184V, V189L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, L228H, L283I, R284K, V293I, E297K |
| 98-754 (9/22/97) | V35I, D67N, T69D, K70R, L109I, M184V, V189L, T200A, I202T, H208Y, R211K,T215F, D218E, K219Q, H221Y, L228H, L283I, R284K, V293I, E297K |
| 98-1032 (10/10/97) | V35I, D67N, T69D, K70R, L109I, M184V, V189L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, L228H, L283I, R284K, V293I, E297K |
| 00-2-011658 (11/12/97) | V35I, D67N, T69D, K70R, L109L/I/MI, M184V, V189V/L, T200A, I202T, H208H/Y, R211K, T215F, D218E, K219Q, H221H/Y, L228H, L283I, R284K, T286T/A, V293I, E297K |
| 00-2-011659 (11/19/97) | V35I, D67N, T69D, K70R, L109L/I/MI, V179V/I, Y181Y/C, M184M/V, V189V/L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, F227F/L, L228H, L283I, R284K, T286T/A, V293I, E297K |
| 98-1033 (12/29/97) | V35I, D67N, T69D, K70R, V106A, V189L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, F227L L228H, L283I, R284K, T286A, V293I, E297K |
| 99-2-008973 (1/28/98) | V35I, D67N, T69D, K70R, V106A, Y181Y/C, V189L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, F227L L228H, L283I, R284K, T286A, V293I, E297K |
| 98-757 (2/26/98) | V35I, D67N, T69D, K70R, V106V/A , V108V/I, L109L/V, Y181C, V189L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, F227L, L228H, L283I, R284K, T286A, V293I, E297K |
| 99-2-8980 (4/22/98) | V35I, D67N, T69D, K70R , V108I, L109V, Y181C, D121D/Y, Y181C, V189L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, F227L, L228H, L283I, R284K, T286T/A, V293I, E297K |
| 98-1080 (7/15/98) | (V35I), D67N, T69D, K70R , V108I, L109V, Y181C, V189L, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, F227L, L228H, L283I, R284K, T286T/A, V293I, E297K |
| AA1264 (12/17/98) | V35M/I, D67N, T69D, K70R, V108V/I, L109?, D121D/Y, M184V, V189L, T200A, I202T, H208Y, R211K,T215Y, D218E, K219Q, H221Y, F227F/L, L228H, L283I, H284K, T286A, V293V/I, E297K |
| 99-2-006174 (5/20/99) | V35M, D67N, T69D, K70R, L109I, D121Y, M184V, V189X, T200A, I202T, H208Y, R211K,T215F, D218E, K219Q, H221Y, F227L, L228H, L283I, R284K, T286A, E297K |
| 00-2-011720 (2/14/00) | V35M, D67N, T69D, K70R , V108I, L109V, D121Y, Y181C, V189L, G190A, T200A, I202T, H208Y, R211K, T215F, D218E, K219Q, H221Y, F227L, L228H, L283I, R284K, T286A, V293V/I, E297K |



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# FIGURE 18

Patient 014451, reduced susceptibility to NNRTI and drug dependent stimulation of viral replication associated with a mutations at 101, 106 and 190 (example 7)

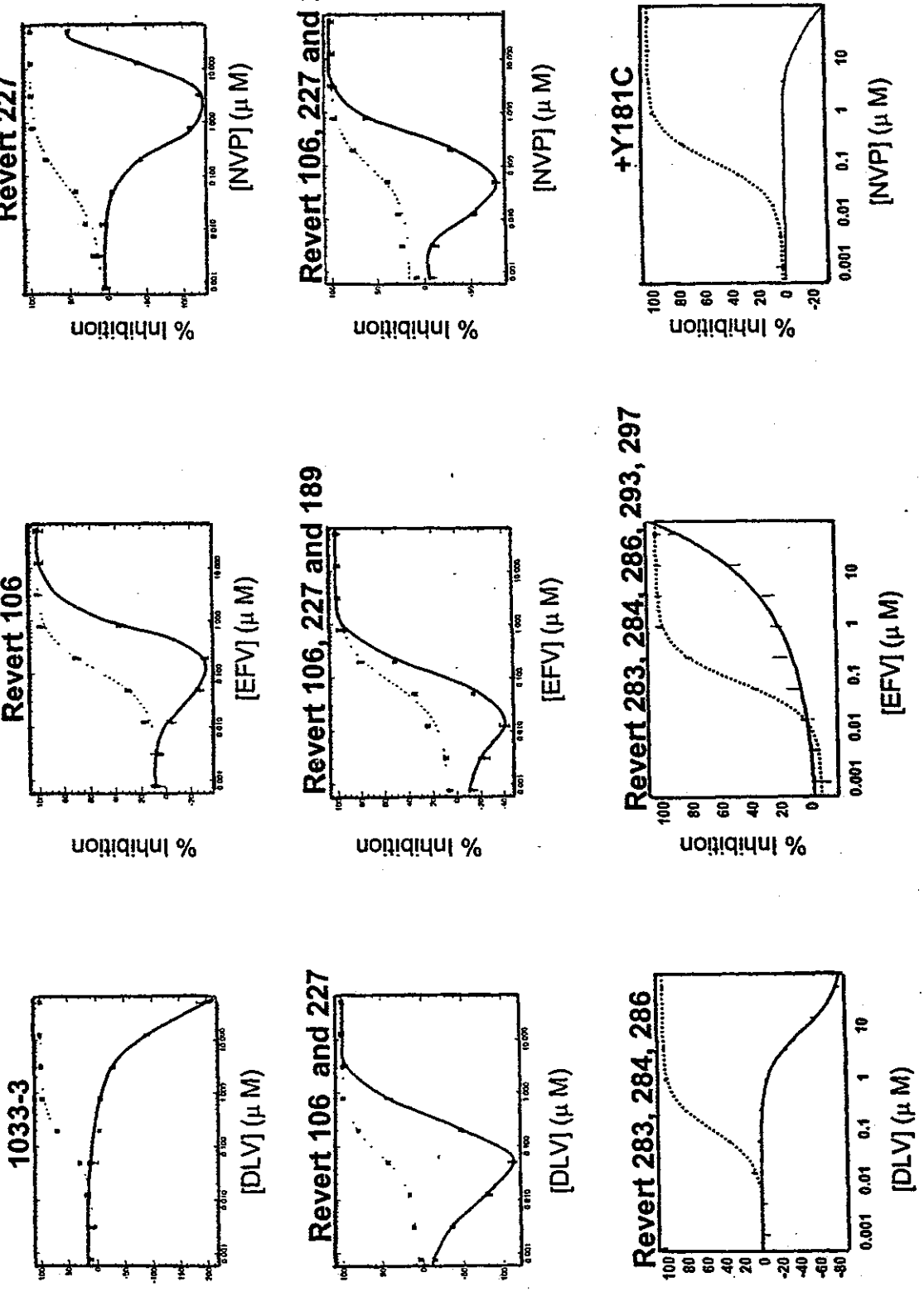
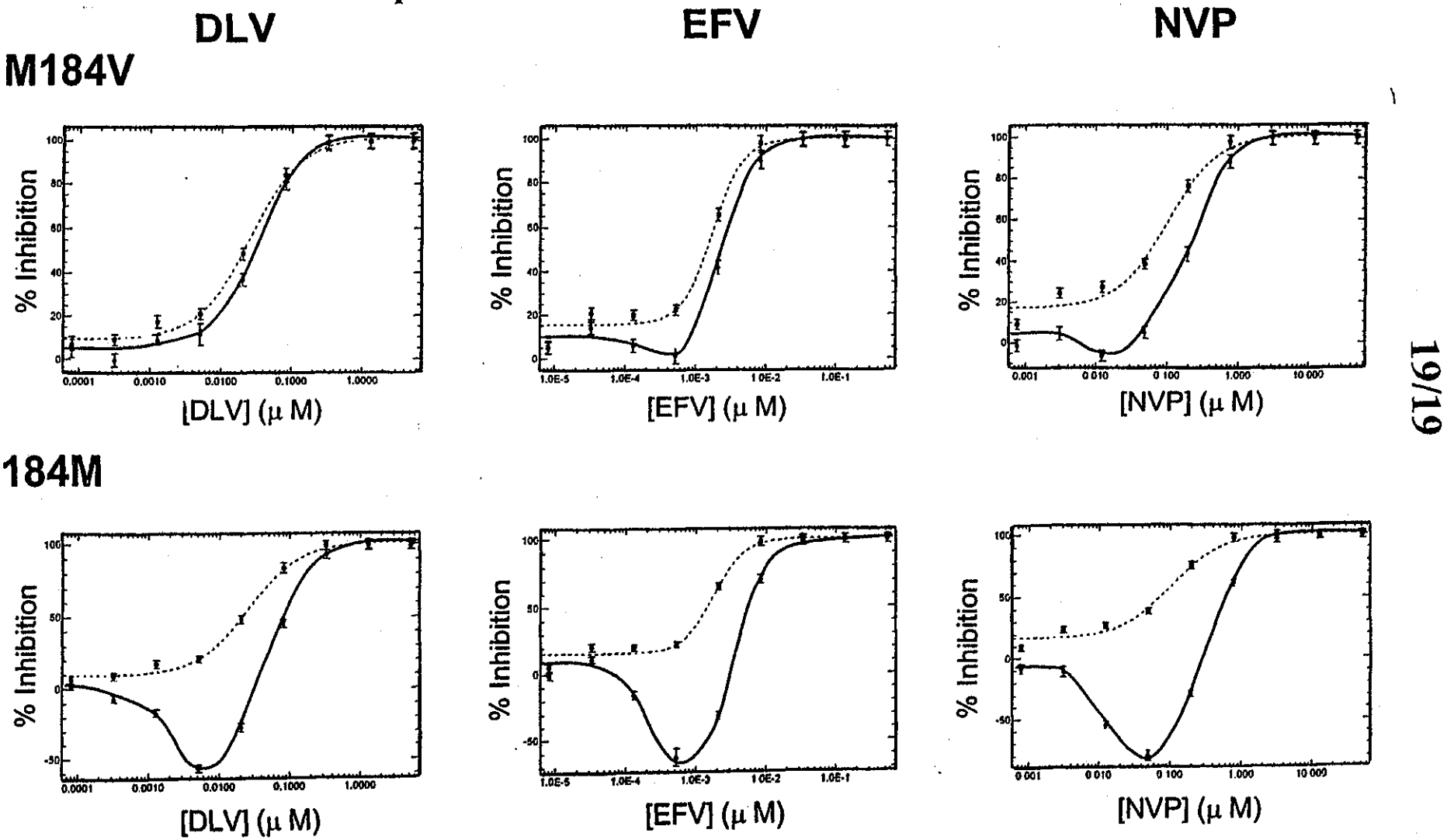



FIGURE 18

# FIGURE 19

**Effect of M184V mutation on drug-dependent stimulation of viral replication: RTV-309**






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