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Transmission of Integrase Strand-Transfer Inhibitor Multi-drug Resistant HIV: Case Report and Natural History of Response to Raltegravir-containing Antiretroviral Therapy

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Abstract

Background To our knowledge, there are no reported cases of HIV transmission with integrase strand-transfer inhibitor (INI)-resistance. We describe here the case of a person with acquired four-drug class resistance.

Methods Genotypic and phenotypic analyses were performed by Monogram Biosciences. Replication capacity (RC) was measured separately for the PRRT and IN coding regions.

Results A 53 year-old treatment naïve man initiated abacavir/lamivudine + raltegravir therapy. Baseline CD4 T-cell count was 340 cells/mm^3, plasma HIV RNA 77,600 copies/mL. HIV RNA declined to 82 copies/mL at Week 8 [W8]. By W48, viral load was 591 copies/mL, CD4 count 377 cells/mm^3. Retrospective baseline genotype identified multiple resistance mutations to RT inhibitors (K70K/R, K103N, V106A), protease inhibitors (L10I, V32I, M46I, A71V, V82A, L90M), and integrase inhibitors (G140S and Q148H). At W48, baseline PR, RT, and IN inhibitor resistance mutations persisted while RT mutations V75I and M184V emerged with other RT and IN substitutions.

Phenotypic susceptibility was determined at baseline and W48. At W48, non-nucleoside reverse transcriptase inhibitor and raltegravir resistance persisted and resistance to lamivudine emerged; abacavir susceptibility was reduced (FC = 3.74), but remained below the clinical cutoff (FC = 4.5). Replication capacity (RC) based on PRRT vs IN was discordant; baseline and W48 PRRT RC were 1% and 1.5%, respectively; baseline and W48 IN RC was 97% and 146%.

Conclusions We believe this is the first documented case of transmitted INI resistant HIV-1. Despite receiving ART with raltegravir, reduction in viral replication (-2 $\log_{10}$ copies/mL) persisted. Patients with high-level transmitted RT and PR inhibitor resistance should be considered for INI resistance testing.

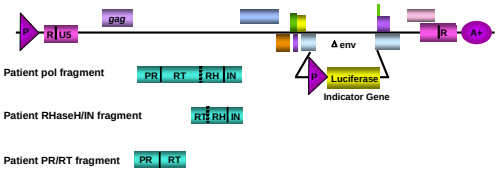
Background

- Transmission of protease (PR) and reverse transcriptase (RT) inhibitor resistant HIV-1 is well described.
- To our knowledge, there are no reported cases of transmission of integrase (IN) inhibitor resistant HIV-1.
- This report describes the first case of HIV-1 infection involving resistance to PR, RT and IN inhibitors.

Methods

- Genotypic and phenotypic analyses were performed at baseline and week 48 (W48) using the GeneSeq and PhenoSense PRRT and IN assays, respectively.
- Replication capacity (RC) was measured using resistance test vectors (RTVs) containing patient-derived PR/RT, RNaseH/IN or PR/RT/RNaseH/IN (pol) (Figure 1).

Figure 1. Resistance Test Vectors (RTVs) used to measure RC

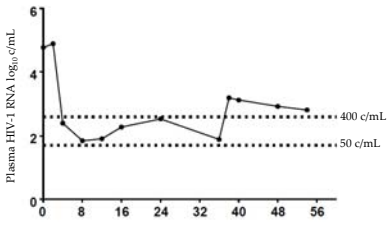


- A series of site-directed mutant virus (SDMs) containing combinations of RT and IN mutations observed in the patient virus were constructed and evaluated.

Results

- **Viral load history:** The subject is a 53-year-old, HIV-positive, treatment-naïve male who initiated therapy with abacavir (ABC), lamivudine (3TC) and raltegravir (RAL) with a baseline viral load of 77,600 copies/mL (c/mL), which declined to 82 c/mL by W8 and 591 c/mL by W48 (Figure 2).

Figure 1. Viral load history of a treatment-naïve male beginning treatment with abacavir, lamivudine, and raltegravir at baseline



Note: A specimen handling error at the laboratory led to the reporting of an erroneous drug resistance report that was considered in the selection of this regimen.

- **Resistance:** Retrospective genotypic analysis of the baseline virus identified mutations associated with resistance to PR inhibitors (L10I, V32I, M46I, A71V, V82A, L90M), RT inhibitors (K70K/R, K103N, V106A), and IN inhibitors (G140S and Q148H) (Table 1).
- PR, RT, and IN inhibitor resistance mutations observed at baseline persisted at W48. Additional RT resistance mutations, V75I and M184V, emerged along with other substitutions in RT and IN (Table 1).

Table 1. Genotypic comparison of baseline and Week 48 results for protease (PR), reverse transcriptase (RT) and integrase (IN) sequences

Baseline Genotype	
PR	L10I, V32I, M46I, L63S, A71V, I72V, V77I, V82A, L90M, I93I/L
RT	K70K/R, Q102N, K103N, V106A, K122E, I142V, C162S/G, I178L, T200A, R277K, V293I
IN	R20K, V113I, T124A, T125T/A, G140S, Q148H, G193E, V201I, E212A, V234L, D288N
Week 48 Genotype	
PR	L10I, V32I, M46I, L63S, A71V, I72V, V77I, V82A, L90M, I93L
RT	K70R, V75I, Q102N, K103N, V106V/A, K122E, I142V,C162S, I178L, M184V, T200A, R277K, **A288A/T,** V293I, **E297E/K**
IN	R20K, **K103K/R,** V113I, T124A, T125A, G140S, Q148H, G193E, V201I, E212A, V234L, **S255S/N**, D288N

Red mutations are associated with resistance;
Underlined mutations were not present at baseline but are associated with resistance;
Bold mutations were not present at baseline but are not known to be associated with resistance

Results, continued

- **Changes in susceptibility:** At W48, reductions in susceptibility to PR inhibitors, non-nucleoside reverse transcriptase inhibitors, and raltegravir persisted, and reductions in susceptibility to 3TC and ABC were observed (Table 2).

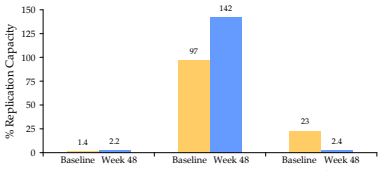
Table 2. Summary of susceptibility to representative drugs for each class of antiretroviral medication

Reverse Transcriptase Inhibitors				
Time Point	Abacavir	Lamivudine	Efavirenz	Nevirapine
Baseline	0.58	0.5	>700	>400
Week 48	3.74	>200	27.2	>400
Protease Inhibitors				
Time Point	Indinavir	Ritonavir	Atazanavir	Darunavir
Baseline	10.2	14	2.6	1.0
Week 48	5.8	20.3	3.7	0.8
Integrase Inhibitor				
Time Point	Raltegravir			
Baseline	>150			
Week 48	>150			

Results expressed as a fold change in IC50 relative to the wild type reference virus (FC)
Abacavir FC increased relative to baseline but remained under the clinical cutoff (FC = 4.5)

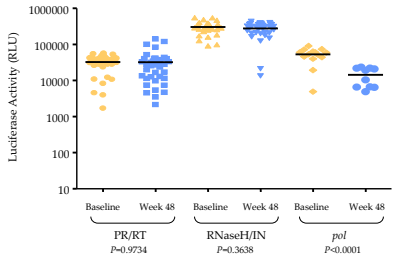
- **Resistance Test Vectors (RTVs):** PR/RT and RNaseH/IN RTVs did not differ in replication capacity (RC) at W48 compared to baseline. However *pol* RTVs displayed a 10-fold reduction in RC at W48 compared to baseline (Figure 3).

Figure 3. Replication capacity of viral populations at baseline and Week 48



- **Molecular clones:** Molecular clones isolated from viral populations confirmed no significant difference in infectivity when comparing PR/RT and RNaseH/IN RTVs at baseline and W48. However a significant difference was observed between baseline and W48 *pol* RTVs (Figure 4).

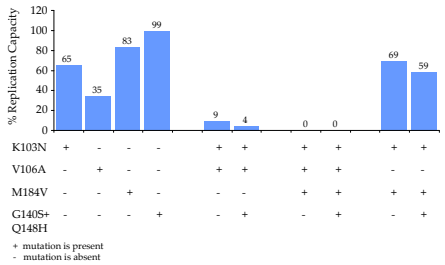
Figure 4. Infectivity of molecular clones isolated from viral populations



Note: the majority of viruses isolated from the Week 48 *pol* population were non functional; virus lacking V106A at Week 48 had higher RC, but was only present at <12%.

- **Site-directed mutant viruses (SDMs):** A panel of SDMs was constructed that contained combinations of mutations observed in the baseline and W48 patient virus. RC was severely compromised in mutants containing multiple resistance mutations. The addition of M184V to K103N/V106A with or without IN mutations resulted in virus that was unable to replicate, confirming the low replication capacity exhibited by the patient derived virus in the presence of multiple resistance mutations throughout *pol* (Figure 5).

Figure 5. Viruses containing site-directed mutants confirm low replication capacity observed in patient virus exhibiting resistance to RT and IN inhibitors



Conclusions

- This is the first documented case of transmitted IN inhibitor resistant HIV-1.
- The sustained reduction in viral replication observed in this patient is associated with the low replication capacity of virus exhibiting resistance to four drug classes.

Acknowledgements

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