Case report

Transmission of integrase strand-transfer inhibitor multidrug-resistant HIV-1: case report and response to raltegravir-containing antiretroviral therapy

Benjamin Young[1,2], Signe Fransen[3], Kenneth S Greenberg[1], Amy Thomas[1], Sharon Martens[3], Marty St Clair[4], Christos J Petropoulos[3], Belinda Ha[4]*

[1]Rocky Mountain CARES/DIDC, Denver, CO, USA
[2]Health Connections International, Amsterdam, the Netherlands
[3]Monogram Biosciences, Inc., South San Francisco, CA, USA
[4]GlaxoSmithKline, Research Triangle Park, NC, USA

*Corresponding author e-mail: byoung@rockymountaincares.org

We report the case of an integrase strand-transfer inhibitor (INI)-resistant and four-drug-class-resistant HIV-1 variant infecting an antiretroviral therapy-naive man. The virus harboured INI drug resistance substitutions (Q148H and G140S) along with multiple reverse transcriptase and protease inhibitor resistance mutations. This case illustrates an emerging need to consider the possibility of acquired INI resistance among newly diagnosed treatment-naive individuals harbouring multidrug-resistant HIV-1.

Introduction

The transmission of HIV-1 strains that have acquired resistance to reverse transcriptase (RT) and protease (PR) inhibitors has been well-described [1–3]. Consequently, resistance testing is recommended in the United States prior to the initiation of antiretroviral therapy [4]. The first reports of acquired drug-resistant HIV-1 followed the introductions of non-nucleoside reverse transcriptase inhibitors (NNRTIs) and PR inhibitors by 2–3 years [5–8]. Raltegravir, a strand-transfer inhibitor and the first integrase (IN) strand-transfer inhibitor (INI) approved for use in the United States (2007) is rapidly gaining wide use in both treatment-experienced, and more recently, treatment-naive patient populations. To our knowledge, transmission of INI-resistant HIV-1 has not been observed. Here, we report the case of infection with an HIV-1 variant resistant to IN, RT and PR inhibitors.

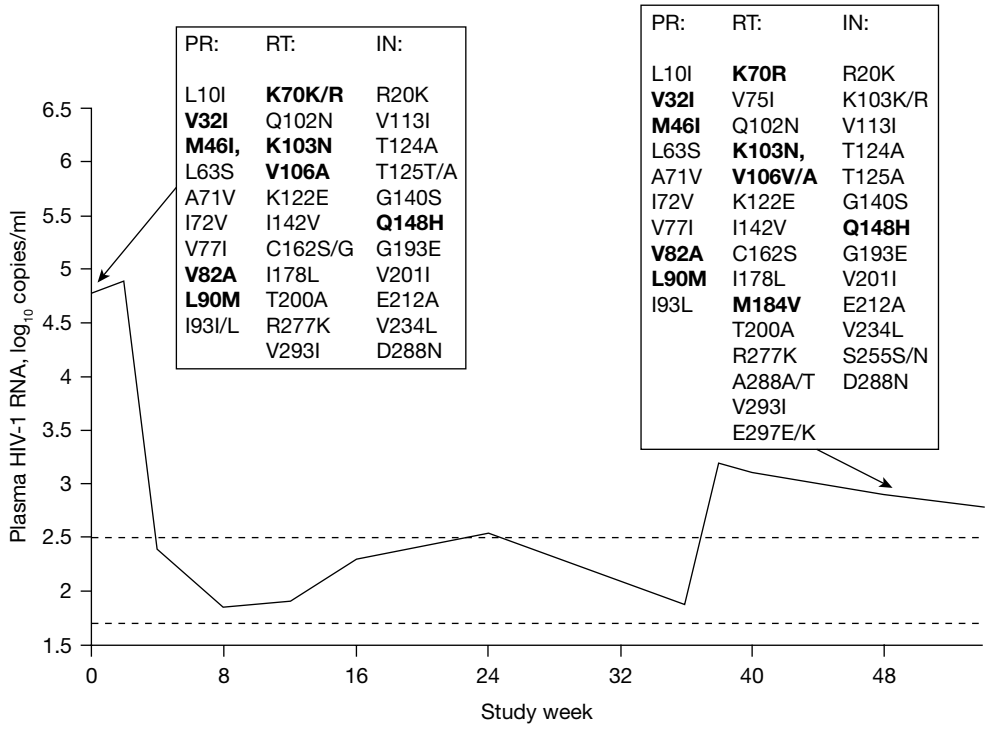
Methods

Retrospective population-based genotypic and phenotypic analyses were performed by Monogram Biosciences (South San Francisco, CA, USA) using PhenoSense GT for PR and RT inhibitors [8] and PhenoSense and GeneSeq Integrase for INI [8]. Replication capacity was measured separately for the PR–RT and IN coding regions, as previously described [9]. Susceptibility measures were expressed as the fold change (FC) in 50% inhibitory concentration relative to the wild-type reference strain. Replication capacity was determined and expressed as a percentage of viral infectivity (luciferase activity) in the absence of drug relative to the wild-type reference strain (NL4-3).

Results

The patient is a 53-year-old treatment-naive, chronically HIV-1-infected man who was diagnosed HIV-1-positive in May 2008. At the time of diagnosis, he was asymptomatic, $CD4^+$ T-cell count was 207 cells/mm^3 and plasma HIV-1 RNA was 14,600 copies/ml. He reported having multiple male sexual partners in the past and was unable to provide specific information about the source of his HIV-1 infection. The patient denied seeking out HIV-1-infected sexual partners, diagnosis of other sexually transmitted infections, history of injection drug use or any recent international travel. Previous HIV-1 testing history was not available. The patient enrolled in a clinical trial in August 2008; baseline $CD4^+$ T-cell count was 340 cells/mm^3

Figure 1. Viral load and genotypic history



Bold font indicates International AIDS Society major mutations [16]. The dotted lines represent the conventional limits of HIV viral RNA detection (50 and 400 copies/ml). IN, integrase; PR, protease; RT, reverse transcriptase.

and plasma HIV-1 RNA was 77,600 copies/ml. A specimen handling error at a contract laboratory led to the reporting of an erroneous drug resistance report. The interpretation of this report ('no evidence of resistance' in PR or RT drug classes) led to the initiation of antiretroviral therapy with a regimen of abacavir 600 mg/lamivudine 300 mg once-daily and raltegravir 400 mg twice daily. After 8 weeks of therapy, HIV-1 RNA levels decreased to 82 copies/ml (Figure 1). By week 16, the patient experienced virological rebound with plasma viral RNA rising to 344 copies/ml. At week 48, viral RNA was 591 copies/ml and $CD4^+$ T-cell count was 377 cells/mm^3.

Retrospective analyses were performed on stored specimens. Genotypic tests on a baseline sample identified multiple mutations associated with resistance to RT inhibitors (K70K/R, K103N and V106A), PR inhibitors (L10I, V32I, M46I, A71V, V82A and L90M) and INI (G140S and Q148H). Genotypic testing at week 48 revealed that the PR, RT and INI resistance mutations observed at baseline persisted along with the emergence of additional mutations in RT (including V75I and M184V) and IN (Figure 1).

Phenotypic drug susceptibility was determined at baseline and week 48 (Table 1). At baseline, large reductions in susceptibility (resistance) to NNRTIs (efavirenz FC>700 and nevirapine FC>400) and raltegravir (FC>150) were observed. At week 48, NNRTI and raltegravir resistance persisted (efavirenz FC=27, nevirapine FC>400 and raltegravir FC>150) and resistance to lamivudine emerged (FC>200); abacavir susceptibility was reduced relative to baseline (FC=3.74 versus FC=0.58, respectively) but remained below the clinical cutoff (FC=4.5). Replication capacities of recombinant pseudoviruses derived from patient PR–RT sequences versus patient IN sequences were discordant; however, no changes were observed at week 48 relative to baseline for the specific patient sequence measured. The PR–RT replication capacities of the baseline and week 48 viral isolates were both low (1% and 1.5%, respectively), whereas the IN replication capacities of the baseline and week 48 viruses were both high (97% and 146%, respectively).

After the discovery of virological failure and multidrug resistance, the patient's antiretroviral treatment was switched to tenofovir/emtricitabine, etravirine,

Table 1. Phenotypic susceptibility testing at baseline and week 48

	Integrase inhibitor:	Reverse transcriptase inhibitors				Protease inhibitors	
Time point	raltegravir	Abacavir	Lamivudine	Efavirenz	Nevirapine	Indinavir	Ritonavir
Resistant FC cutoff	–	4.5	3.5	2.5	2.5	2.1	2.5
Baseline	>150	0.58	0.50	>700	>400	10.2	14.0
Week 48	>150	3.74	>200	27.2	>400	5.78	20.3

Results expressed as a fold change (FC) in the 50% inhibitory concentration relative to the wild-type reference virus.

ritonavir and darunavir. His subsequent plasma HIV-1 RNA levels were <50 copies/ml and have remained below the level of detection through October 2010.

Discussion

We believe this report is the first documented case of transmitted INI resistant HIV-1. In this case, in the absence of accurate baseline resistance testing, the degree of PR and RT inhibitor resistance was underappreciated and there was little reason to suspect INI resistance. Consequently, the patient initiated a treatment regimen that included raltegravir. Despite initiation of antiretroviral treatment with a raltegravir-containing treatment, plasma HIV-1 RNA levels dropped to nearly undetectable levels and remained approximately 2 $\log_{10}$ copies/ml below baseline at week 48. Incomplete viral suppression in this individual was accompanied by further emergence of nucleoside reverse transcriptase inhibitor resistance mutations and minimal change in $CD4^+$ T-cell counts.

It is noteworthy that the K103N NNRTI resistance mutation was detected in this patient's viral isolates at baseline and at 48 weeks of follow-up despite the absence of NNRTI drug pressure. These data are consistent with previous observations describing the ability of NNRTI resistance mutations to persist after primary infection [3]. By analogy, the presence of G140S and Q148H INI resistance mutations at baseline is suggestive not of genetic polymorphism but rather of treatment selection [10]. Although common among chronically infected patients failing raltegravir-based treatments [11,12], this mutational pattern suggests that like NNRTI-resistance mutations, INI resistance mutations may persist after primary infection in the absence of selective pressure from INI treatment.

Replication capacity was determined for recombinant viruses containing either PR and RT or IN sequences derived from the baseline and week 48 viruses. The replication capacity of viruses containing baseline and week 48 PR–RT sequences was severely impaired relative to the reference virus. By contrast, the replication capacity of viruses containing baseline and week 48 IN sequences was comparable to the reference virus. This contrasts reports from patients experiencing failure of INI-based treatments that exhibited ongoing genotypic evolution and an overall decrease in replicative capacity over time [11] but is consistent with reports of high IN replicative capacity for viruses containing G140S and Q148H and displaying phenotypic resistance [13,14]. A possible explanation for this observation is that the G140S mutation in HIV-1 IN from raltegravir-resistant patients rescues a catalytic defect due to the Q148H resistance mutation [15].

Our analysis is subject to several limitations. First, we have limited information about the patient's HIV-1 testing history, limiting our ability to characterize social aspects and the temporal behaviour of the case and resistance mutations. Nevertheless, the clinical and laboratory characteristics of the patient at time of HIV-1 diagnosis suggest that he was chronically infected at that time. The patient's laboratory history provides 4 months of monitoring from time of initial diagnosis to first HIV-1 genotype, a minimum estimate of the time from primary infection. We are also limited in that we only report a single case from one city. The frequency of INI resistance and association with other drug resistance mutations may differ in different geographical regions as a function of the clinical setting of raltegravir use. Lastly, we acknowledge the interest in characterizing the source and social setting around the transmission of this viral isolate. Unfortunately, the patient was unable to provide any significant details of the event.

This case is the first documented demonstration of raltegravir resistant HIV-1 transmission and persistence in chronic infection. Despite viral suppression, the accumulation of additional drug resistance mutations during the initial course of antiretroviral therapy in this patient reinforces the need to construct regimens with as many active agents as possible and underscores the need to counsel patients living with drug-resistant HIV-1 about additional risks of transmitting drug-resistant virus. Because it is likely that the source in this case was someone failing multiple previous regimens, including at least one raltegravir-containing regimen, the detection of multi-antiretroviral class resistance at baseline should prompt the consideration of additional testing for INI resistance.

Disclosure statement

BY has received recent research grants from Bristol–Myers Squibb, Cerner Corporation, Gilead Sciences, Merck, Roche and GlaxoSmithKline and/or is a member of advisory boards for Bristol–Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck and Viiv Healthcare. KSG has received recent research grants from Bristol–Myers Squibb, Cerner Corporation, Gilead Sciences, Merck, Roche, Boehringer Ingelheim and GlaxoSmithKline and/or is a member of advisory boards for Gilead Sciences, GlaxoSmithKline, Merck and Viiv Healthcare. SF, SM and CJP are employees of Monogram Biosciences. MSC and BH are employees of GlaxoSmithKline. AT declares no competing interests.

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