Long-term virological outcome and resistance mutations at virological rebound in HIV-infected adults on protease inhibitor-sparing highly active antiretroviral therapy

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Objective: To assess the durability of the undetectability of HIV plasma viraemia (pV) and to determine the factors associated with virological rebound (VR) in HIV-infected adults on protease inhibitor (PI)-sparing highly active antiretroviral therapy (HAART). The development of resistance mutations during virologically successful therapy and VR was also analysed.

Materials and methods: One hundred and twenty-six HIV-infected adults on PI-sparing HAART were prospectively followed from April 1998 to December 2002: Group 1, naive for antiretroviral drugs (n = 26); Group 2, previously PI-HAART-exposed patients (n = 19); Group 3, previously exposed to suboptimal therapy (n = 81). Genotypic resistance tests on peripheral blood mononuclear cells or on plasma RNA (when feasible) were carried out when undetectable HIV pV was demonstrated for at least 48 weeks. Additionally, patients showing a therapy adherence >95% developing VR were also tested at rebound, at simplification and during previous suboptimal therapy exposure.

Results: The median follow-up time was 630 [329–903] days. VR was considered as two consecutive pV levels >50 copies/mL. Twenty-two (17.5%) patients developed VR. Only therapy adherence <95% was independently associated with VR (adjusted hazard ratio: 8.42; 95% CI: 3.33–21.27). Twenty (40%) of the 50 patients with pV < 50 copies/mL for at least 48 weeks showed at least one thymidine-associated mutation (TAM) but none had NNRTI-resistance mutations. Ten (83.3%) of 12 available adherent patients showing VR harboured NNRTI-resistance-associated mutations; 50% of them were considered as wild-type strains at simplification time. However, the TAM number and resistance mutations profile found on suboptimal exposure were very similar to those found at VR on simplification therapy.

Conclusions: PI-sparing HAART allows maintenance of successful long-term control of HIV replication, adherence to therapy being the main factor associated with VR. However, a small proportion of patients on simplification regimen may develop VR regardless of therapy compliance. VR on PI-sparing HAART is characterized by the emergence of NNRTI cross-resistance mutations. Finally, TAMs ‘archived’ during previous suboptimal exposures are partially involved in subsequent VR on simplification HAART.

Keywords: PI-sparing HAART, simplification therapy, virological rebound, resistance mutations

Introduction

The introduction of highly active antiretroviral therapy (HAART) including protease inhibitor (PI) drugs and nucleoside reverse transcriptase inhibitors (NRTIs) has dramatically changed the course of human immunodeficiency virus (HIV) infection, reducing mortality and morbidity events associated with this disease.¹² These regimens have allowed successful control of HIV replication. However, the burden of toxicity resulting from the use of PI drugs is of concern as it constitutes a threat to the sustained success of HIV treatment.³ Thus,
PI drugs have been typically associated with the emergence of lipo-dystrophy syndrome, severe hepatic damage and other metabolic disturbances, such as dyslipidaemia and diabetes mellitus.

PI-sparing antiretroviral regimens based on non-nucleoside reverse transcriptase inhibitors (NNRTIs) or triple NRTI combinations have been proposed as an effective alternative to PI-HAART in terms of control of HIV replication in HIV patients, at least in the setting of patients naïve for previous antiretroviral treatment. Moreover, these therapeutic approaches have been related to inducing less-severe adverse events than PI-based therapy. In this way, switches from successful PI-based regimens to triple NRTI or NNRTI-based combinations have been proposed to avoid and even reverse the metabolic changes observed during long-term PI-including therapy, this strategy is known as treatment simplification. However, long-term studies assessing the virological outcome of these therapeutic approaches are lacking. Several factors have been potentially associated with virological rebound (VR) on simplification therapy, such as therapeutic adherence, previous antiretroviral regimen exposures and the presence of resistance-associated mutations. According to this, the appearance of resistance-associated mutations on PI-sparing HAART as a result of the low genetic barrier, even in virologically well-suppressed patients, might lead to a subsequent plasma viraemia rebound. In any case, the clinical implications of these factors on the long-term outcome of HIV-infected patients on simplification therapy are still unclear.

The objective of this study was to assess the durability of the undetectability of plasma HIV viraemia achieved on PI-sparing HAART and to determine the factors associated with VR in a cohort of HIV-infected adults on PI-sparing HAART. Moreover, the development of resistance-associated mutations on simplification antiretroviral therapy was also assessed to determine whether they might predict a subsequent VR. Additionally, the genotypic characteristics of viral strains at VR have also been analysed.

Materials and methods

Population

In April 1998, our tertiary care AIDS unit started a programme aimed to reduce and prevent adverse events related to PI-based HAART, along with increasing the rate of therapeutic adherence in an HIV-infected cohort. All HIV-1-infected patients between 1 April 1998 and 31 December 2002 who fulfilled one of the following therapeutic profiles were proposed to participate in this study: Group 1, patients naïve for antiretroviral therapy who started a PI-sparing regimen as initial treatment at entry in our therapeutic cohort (n = 26). Patients from Group 1 were included in the study cohort at starting HAART if HIV plasma viral load levels <50 copies/mL were demonstrated in two consecutive determinations; Group 2, patients who previously received PI-HAART as initial therapy and were switched to PI-sparing HAART (n = 19); Group 3, patients who were previously exposed to suboptimal therapy (mono or dual NRTI therapy) before PI-HAART and who were later simplified to PI-sparing HAART (n = 81). Patients from Groups 2 and 3 were included when changed to PI-sparing HAART. Switch to PI-sparing HAART was carried out (Group 2 and Group 3) when HIV plasma viral load levels were below the detection threshold (<50 copies/mL) for at least the last 6 months on PI-HAART. For the purpose of this study, HAART was considered to be the combination of two NRTIs and either, at least one PI (PI-HAART), or plus one NNRTI or abacavir (PI-sparing HAART). One hundred and twenty-six patients were included in this study.

All patients were prospectively followed, and haematological, biochemical, immunological and virological determinations were carried out at entry in the study cohort, and every 12 weeks thereafter in fresh blood samples. Peripheral blood mononuclear cells (PBMC) were isolated and kept frozen until genotypic resistance tests were carried out. For the purpose of this study, two consecutive HIV plasma viraemia levels >50 copies/mL demonstrated at any time during the follow-up were considered VR.

Self-reported adherence data, obtained by means of a direct interview carried out by the physician in charge, was expressed as the proportion of pills taken out of the total pills prescribed. Patients receiving zidovudine were considered non-adherent, regardless of the data they reported, when an increase in the mean corpuscular volume that was ≥10% of the baseline values was not found.

Virological and immunological measures

Plasma HIV viral load levels were determined using a commercial test (Amplicor HIV Monitor Test, Roche, Basle, Switzerland) according to the manufacturer’s instructions. This method has a detection threshold of 50 HIV RNA copies/mL. CD4 cell counts were determined using a conventional flow cytometry procedure.

HIV genotyping test

PBMC were isolated from heparinized blood by density-gradient centrifugation on Ficoll (Pharmacia Biotech, Uppsala, Sweden) and cryopreserved on liquid nitrogen until DNA extraction. Cellular DNA was prepared by DNA extraction kit (Qiagen) following the manufacturer’s instructions. A 1820 bp fragment encompassing the RT gene was generated by nested PCR. PCR amplification was carried out by adding 5 µL of purified DNA to 40 µL of the master mix reaction (1× PCR buffer, 200 µM dNTP, 2.5 U Taq polymerase) including 20 pmol of primers pol 11 (3′ GGC TGT TGG AAA TGT GGC 5′) and pol 13 (3′ TTT GCT ACT ACA GGT GGC 5′). Cycling parameters were: 94 °C for 5 min followed by 35 cycles of 94 °C for 30 s, 55 °C for 30 s and 72 °C for 90 s, followed by a 7 min hold at 72 °C. For the second round PCR product, 2 µL was transferred to a second PCR reaction containing 48 µL of master mix (1× PCR buffer, 200 µM dNTP, 2.5 U Taq polymerase), and 20 pmol of each of the following primers: pol 15 (3′ GTA GGA CCT ACA CCT GTC 5′) and pol 12 (3′ CAC TAG CCA TTG CTC TCC 5′). Cycling parameters were: 94 °C for 5 min followed by 30 cycles of 94 °C for 30 s, 55 °C for 30 s and 72 °C for 60 s, followed by a 10 min hold at 72 °C. Nested PCR products were sequenced with dRhodamine dye-labelled dideoxynucleotides (Applied Biosystems, Fosters City, CA, USA) with 5 pmol of each of following primers: two sense: pol 15 and pol 16 (3′ CAG AAA GAA CCT TTC C 5′), and one antisense, pol 17 (3′ GTC CAT TTA TCA GGA TGG 5′). The sequencing reactions were then analysed on an ABI Model 310 instrument (Applied Biosystems). Isolated sequences were compared with a consensus B sequence.

Statistical analysis

Continuous variables are expressed as median [interquartile (IQR) range] and categorical ones are expressed as number of cases (percentage). A χ² test was carried out to compare proportions. The relationship between VR and the following potential baseline risk factors was assessed: age, sex, intravenous drug use, AIDS diagnosis, CD4 cell count, previous suboptimal antiretroviral therapy (i.e. either mono or dual NRTI combination or triple therapy including two NRTIs plus saquinavir), therapy adherence and previous transient plasma HIV viral load increases (blips). A survival analysis was carried out to study the relationship between VR during the follow-up and these variables. In such study, the event was to show the first of two consecutive plasma HIV viraemia >50 copies/mL during the follow-up. Event-free subjects were right censored as of 31 December 2002. Participants were not followed
TABLE 1. Baseline characteristics of the population studied

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>37 (33-41)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>90 (71.4%)</td>
</tr>
<tr>
<td>Previous therapy: Group 1 (%)</td>
<td>26 (20.6)</td>
</tr>
<tr>
<td>Group 2 (%)</td>
<td>19 (15.1)</td>
</tr>
<tr>
<td>Group 3 (%)</td>
<td>81 (64.3)</td>
</tr>
<tr>
<td>AIDS* (%)</td>
<td>42 (33.3)</td>
</tr>
</tbody>
</table>

*Median [IQR range].
Antiretroviral treatment based on mono or dual NRTI therapy.
AIDS defined as C clinical category or/and baseline CD4 cell count <200 cells/mμm².
Infecting drug user.
Only one transient plasma HIV RNA determination >50 copies/mL.

Results

Characteristics of the population

The main characteristics of the study population at baseline are summarized in Table 1. The median time of follow-up was 630 days [329–903 days]. During the period of study, eight patients (6.3%) were lost to follow-up. One hundred and seven (84.9%) and 9 (7.1%) patients received NNRTI-based HAART or triple NRTI combination therapy, respectively. All factors showing a univariate association level <0.1 with VR were entered into the multivariate analysis. All statistical procedures were carried out by means of the Statistical Package for Social Studies (Chicago, IL, USA).

Virological outcome

Twenty-two (17.5%) patients showed a confirmed VR during the period of study. The median value of viral load level at rebound was 582 [166–1657] copies/mL. Thirty (10.3%) of them reported a therapy adherence >95%. The median time to viral load rebound was 416 [160–706] days. Figure 1(a) shows the probability of VR for the whole study cohort during the follow-up period.

Risk factors associated with VR

On the univariate analysis, male gender (P = 0.04), showing a therapy adherence <95% (P = 0.001) (Figure 1b), previous suboptimal treatment (Figure 1c) and including either mono or dual NRTI combination therapy (P = 0.01) were statistically associated with VR on PI-sparing HAART on the univariate test (Table 2). Showing at least one blip during the follow-up was almost significant (P = 0.09) and was included in the multivariate analysis as described in Materials and methods.

On the Cox proportional hazard model, only having a therapy adherence <95% (Hazard Ratio [HR]: 8.42; 95% CI: 3.33–21.27) was found to be a baseline predictor of VR during the follow-up (Table 2). Thus, patients reporting therapy adherence lower than 95% were eight times more likely to show a plasma viral load rebound on PI-sparing regimens than those who reported therapy compliance >95%. Although previous suboptimal therapy exposure was not found to be independently associated with VR on the multivariate analysis, statistical significance was almost reached (Table 2).

Resistance-associated mutation profiles

PBMC DNA samples were extracted from all the first 50 consecutive patients showing HIV RNA levels <50 copies/mL for at least 48 weeks on PI-sparing HAART. Genotypic resistance tests were carried out at that time. Five (10%), 12 (24%) and 33 (66%) patients belonged to Group 1, Group 2 and Group 3, respectively. Twenty (40%) individuals showed at least one resistance-associated mutation. These were thymidine-associated mutations (TAMs). No patient showed mutations associated with resistance to NNRTIs. The median number of resistance-associated mutations was two [range 1–6]. K70R (55%) and M41L (25%) were the resistance mutations most frequently found. When previous antiretroviral exposure was considered, the proportion of patients showing TAMs was significantly higher in patients from Group 3 (17 out of 31 patients) than in patients from Group 2 (three out of 18) (χ² test, P < 0.05). No patient starting PI-sparing regimen as initial therapy (Group 1) showed resistance-associated mutations.

Additionally, samples were analysed from 12 patients who developed a VR despite self-reported adherence >95% (Table 3). All belonged to Group 3. Determinations were carried out on PBMC DNA because of the low number of HIV RNA copies at rebound. Three of them (patients 2, 8 and 10) harboured wild-type viral sequences. Patient 2 showed higher plasma HIV viraemia levels at rebound, so a resistance test could be carried out on plasma HIV RNA. In this case, a mutation conferring cross-resistance to NNRTI (K103N) was demonstrated. Thus, 10 (83.3%) of 12 patients studied harboured NNRTI resistance-associated mutations. Patients 4 and 7 only harboured resistance mutations to drugs included in the current regimen, such as 3TC and NVP, but no TAMs (Table 3). None had been previously exposed to these drugs. The remaining seven patients showed at least one TAM along with the NNRTI-associated mutations described (Table 3).

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In order to assess if these TAMs were already present at therapy simplification, frozen samples obtained before PI-HAART switching were also analysed (Table 3). Strikingly, the number of TAMs found was significantly lower than those found at rebound. Thus, six (50%) patients harboured wild-type virus at baseline. To clarify this surprising finding, samples obtained on suboptimal therapy were also analysed. This analysis could be carried out on plasma HIV RNA because HIV viraemia levels were sufficiently high. Amplification did not occur in four cases (patients 7, 9, 10, 11). All patients showing either non-mutant virus or no TAM mutations at rebound time (patients 2, 4 and 8) harboured wild-type HIV strains. The number of TAMs and the resistance mutation profile found on suboptimal therapy were very similar to those found at plasma HIV rebound on simplification therapy.

Discussion

Several main conclusions can be extracted from this study. First, PI-sparing HAART allows successful long-term control of HIV replication despite the genetic ‘fragility’ classically associated with these therapeutic approaches. Second, adherence to therapy is the main factor associated with VR, a compliance ≥95% being necessary to guarantee long-term efficacy. Third, despite this effectiveness, a small proportion of patients on simplification regimen may develop plasma HIV viraemia rebound regardless of therapy compliance. Accordingly, this study demonstrates for the first time that archived TAMs, emerging during previous suboptimal therapy routines, are at least partially involved in subsequent VR on PI-sparing HAART. Finally, VR on PI-sparing HAART is characterized by the emergence of NNRTI cross-resistance mutations.

Although short- or medium-term efficacy of non-PI HAART regimens has previously been stated either in the setting of initial PI-sparing HAART or PI switch regimens, their impact on long-term treated HIV-infected adults is still unclear. We report herein a long-term simplification therapy cohort followed for a long period of time (median time almost 2 years). Thus, these results confirm and extend previously reported results, since the PI-sparing regimen is as effective as PI-based HAART in terms of HIV viraemia control even in the long-term. An issue that must be highlighted is that a very strict virological failure criterion was considered in this study: two consec-
Long-term virological outcome on PI-sparing regimens

Table 2. Results of the statistical analysis (univariate and multivariate)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>No. of VR</th>
<th>P value</th>
<th>Hazard ratio</th>
<th>95% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;37 years</td>
<td>9</td>
<td>0.44</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Male gender</td>
<td>7</td>
<td>0.04</td>
<td>0.10</td>
<td>–</td>
</tr>
<tr>
<td>Injecting drug use</td>
<td>8</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Previous suboptimal therapy use</td>
<td>15</td>
<td>0.01</td>
<td>0.06</td>
<td>–</td>
</tr>
<tr>
<td>Suboptimal therapy &gt;1365 days</td>
<td>6</td>
<td>0.85</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>NVP in current therapy</td>
<td>14</td>
<td>0.41</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>AIDS at baseline</td>
<td>6</td>
<td>0.95</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Baseline CD4 &gt;493 cells/mm³</td>
<td>9</td>
<td>0.65</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Therapy adherence &lt;95%</td>
<td>8</td>
<td>0.001</td>
<td>0.0001</td>
<td>8.42</td>
</tr>
<tr>
<td>Blip during PI-sparing HAART⁰</td>
<td>9</td>
<td>0.09</td>
<td>0.26</td>
<td>–</td>
</tr>
</tbody>
</table>

Hazard ratios and 95% confidence intervals are shown only for independent predictive variables in the stepwise multivariate analysis.

¹Eight out of nine patients reporting therapy adherence <95% showed VR during the follow-up; the remaining one was lost before VR was confirmed by a second plasma viraemia measurement.

²Only one transient plasma HIV RNA determination >50 copies/mL.

Table 3. Resistance-associated mutations at VR on PI-sparing HAART, at PI-sparing starting time (baseline) and previous suboptimal therapy in 12 out of 14 patients who developed VR despite a therapy adherence >95%.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Suboptimal therapy⁰</th>
<th>Baseline⁰</th>
<th>VR⁰</th>
<th>Current HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D67N, K70R, I178M</td>
<td>K70R</td>
<td>K70R, Y181C, M184V</td>
<td>D4T + 3TC + NVP</td>
</tr>
<tr>
<td>2</td>
<td>wild</td>
<td>wild</td>
<td>K103N⁴</td>
<td>D4T + 3TC + NVP</td>
</tr>
<tr>
<td>3</td>
<td>M41L, K70R</td>
<td>M41L</td>
<td>M41L, D67N, A98G, M184V, L210W</td>
<td>D4T + 3TC + NVP</td>
</tr>
<tr>
<td>4</td>
<td>wild</td>
<td>wild</td>
<td>K103N, M184V</td>
<td>D4T + 3TC + NVP</td>
</tr>
<tr>
<td>6</td>
<td>M41L, D67N, T69D, K70R, L210W</td>
<td>N.A.</td>
<td>M41L, D67N, T69D, K70R</td>
<td>D4T + 3TC + NVP</td>
</tr>
<tr>
<td>7</td>
<td>N.A.</td>
<td>wild</td>
<td>G190A</td>
<td>D4T + 3TC + NVP</td>
</tr>
<tr>
<td>8</td>
<td>wild</td>
<td>wild</td>
<td>D67N, Y181C, M184V</td>
<td>D4T + 3TC + NVP</td>
</tr>
<tr>
<td>9</td>
<td>N.A.</td>
<td>wild</td>
<td>wild</td>
<td>D4T + 3TC + NVP</td>
</tr>
<tr>
<td>10</td>
<td>N.A.</td>
<td>wild</td>
<td>D67N, K70R</td>
<td>AZT + 3TC + NVP</td>
</tr>
<tr>
<td>11</td>
<td>N.A.</td>
<td>D67N, K70R</td>
<td>D67N, K70R, K103N</td>
<td>AZT + 3TC + NVP</td>
</tr>
</tbody>
</table>

N.A. denotes no amplification. All mutations shown are described as associated with antiretroviral resistance according to Stanford guides. Current HAART at VR: D4T ( stavudine), 3TC (lamivudine), AZT (zidovudine), NVP (nevirapine).

⁰Performed on HIV RNA.

³Performed on DNA extracted from PBMC.
PI-sparing regimen as initial therapy showed resistance-associated mutations. Thus, simplification therapy seems to be effective enough when prescribed in previously antiretroviral non-exposed HIV-infected adults, despite its low genetic barrier. Several potential factors involved in VR on simplification therapy have been reported previously. Therapy adherence has been well documented as the main factor for virological success among HIV-infected patients on antiretroviral therapy. The present results show that an adherence <95% of total dose should be considered as suboptimal in the setting of simplification antiretroviral regimens. This issue might be explained by the low genetic barrier associated with these antiretroviral regimens. Thus, mutant virus harbouring NNRTI cross-resistance mutations were found at VR. Previous suboptimal therapy has also been proposed as a potential risk factor for VR on PI-sparing HAART. In this study, an independent association between previous suboptimal therapy exposure and subsequent VR was almost reached (95%). All patients who developed HIV viraemia rebound on PI-sparing HAART despite adherence ≥95%, except two, were previously exposed to suboptimal therapy. One of these two naïve patients harboured a primary PI-resistant mutant, which was acquired through a sexual contact. The second patient started PI-HAART including two NRTI plus saquinavir, a PI drug, which has been demonstrated to have a low intestinal absorption rate. Thus, both patients might be considered to have been previously exposed to a sequential or 'hidden' suboptimal therapy.

The emergence of resistance mutations on PI-sparing HAART, which has been classically considered a genetically 'fragile' regimen, has been hypothesized to explain subsequent VR. To clarify this issue, genotypic profiles at rebound were determined in those patients with a therapy adherence ≥95%. Only three patients harboured non-resistant mutant virus. However, one of them harboured a mutation conferring cross-resistance to NNRTIs when HIV RNA was analysed. According to this, we could hypothesize that the remaining two patients might harbour it as well as a 'hidden' RNA mutation, which would explain the subsequent rebound. Another alternative explanation would be that the method of assessing therapy adherence might have overestimated the real compliance rates in these individuals. Moreover, all patients harbouring mutant viruses carried NNRTI cross-resistant viral strains. This might be expected owing to the low genetic barrier of these regimens. This finding has important implications, since in this setting, the whole NNRTI drug family is included.

The presence of TAMs at VR might be explained by two alternative hypotheses. First, the emergence of 'new' TAMs occurred during simplification therapy, or second, the elucidation of 'archived' mutations acquired during previous suboptimal exposures. Strikingly, when samples obtained at the start of PI-sparing HAART were analysed, the number of TAMs was significantly lower than that obtained at time of rebound. According to this, the performance of a genotypic resistance test at PI-switching time would not allow the identification of patients at risk of developing subsequent VR during later follow-up. When we tried to demonstrate the second hypothesis, two interesting findings were made. As expected, patients harbouring wild-type strains at rebound were also infected with non-mutant virus at suboptimal therapy time. Moreover, patients having a high number of TAMs at rebound showed similar genotypic resistance profiles on suboptimal therapy. This is the first time that a molecular study has demonstrated that TAMs appearing at VR on simplification therapy had emerged and were 'archived' during previous suboptimal exposures. This issue might, at least partially, explain the higher rate of VR among previously NRTI mono or dual therapy-exposed individuals when compared with individuals who started PI or non-PI HAART as initial therapy. Thus, physicians treating HIV patients should take into account previous antiretroviral backbones before switching from PI-based HAART to a simplification therapy including NNRTI or abacavir. On the other hand, using more accurate molecular methods such as cloning or single genome sequencing probably might allow detection of minority mutant populations on DNA samples at PI switching in order to predict VR.

In conclusion, PI-sparing regimens are as effective as PI-based HAART for long-term treatment periods. However, the antiretroviral backbone must be carefully reviewed in HIV-infected patients before switching from PI to NNRTI or abacavir as part of simplification therapy, since patients previously exposed to suboptimal therapy have a higher probability of subsequent VR. Moreover, these regimens should be preferentially prescribed to highly adherent patients since minimal reductions in therapy adherence are associated with VR.

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