

Failures of 1 week on, 1 week off antiretroviral therapies in a randomized trial

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Background: Scheduled treatment interruptions are being evaluated in an effort to decrease costs and side effects of highly active antiretroviral therapy (HAART). A schedule of 1 week on and 1 week off therapy offers the promise of 50% less drug exposure with continuously undetectable HIV RNA concentration.

Methods: In the Staccato study 600 patients on successful HAART were to be randomized to either continued therapy, CD4-guided therapy, or one week on, one week off therapy. A scheduled preliminary analysis evaluated effectiveness in the 1-week-on–1-week-off arm.

Results: Of 36 evaluable patients, 19 (53%) had two successive HIV RNA concentrations > 500 copies/ml at the end of the week off therapy, and were classified as virological failure. Most of those who failed took didanosine, stavudine, saquinavir, and ritonavir (11 patients). In these patients, there was no evidence of mutations suggestive of drug resistance, and plasma saquinavir levels were within the expected range. Two of three patients failing on triple nucleotides had drug resistance mutations, but nonetheless responded to reintroduction of triple nucleotide therapy. One of two patients taking nevirapine, and one of eight taking efavirenz, also failed. Both had resistance mutations at the time of failure, but not at baseline.

Conclusions: The 1-week-on–1-week-off schedule, as tested in the Staccato study, showed an unacceptably high failure rate and was therefore terminated.

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Introduction

Highly active antiretroviral therapies (HAART) decrease complications of HIV infections and prolong life expectancy [1–3]. Nonetheless, concerns remain re-

garding complications and costs of HAART. Scheduled treatment interruptions (STI) have the potential to decrease side effects and expense, but still need to be properly evaluated in comparison to conventional (continuous) therapies.

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Several types of STI are being explored. Long STI may have a fixed schedule (e.g., 2 months on, 2 months off therapy), or may be guided by the CD4 cell count: stop treatment once the CD4 cell count has risen, start it again after a fall. During long STI, HIV RNA concentrations rebound, with a probable increase in contagiousness and a decrease in CD4 cell counts [4].

In contrast, short STI only last a few days. Because viral rebound is not immediate, patients remain aviraemic, and CD4 cell counts are not expected to fall. Dybul *et al.* [5] have published a small case series, using a 1-week-on–1-week-off schedule with the combination of stavudine, lamivudine, and ritonavir-boosted indinavir at a dosage of 800/100 mg twice daily. In eight patients more than 90% of measured HIV RNA concentrations were < 50 HIV RNA copies per ml, during a follow-up of 32–68 weeks.

Based on these preliminary data, the protocol of Staccato was devised, in order to compare long and short treatment interruptions of continuous therapy. From the start, an intermediary analysis was planned after randomization of the first 150 patients, in order to determine if viral load breakthroughs in the 1-week-on–1-week-off arm were more frequent than the expected acceptable limit of 10%.

Methods

STACCATO is a randomized trial of intermittent versus continuous anti-retroviral treatment. Six-hundred patients on HAART, with viral load < 50 copies/ml and CD4 cell count > $350 \times 10^6/l$, are to be recruited in Thailand (400 patients), Switzerland (100), Australia, Argentina, and Canada. They will be randomized into three groups and will receive different treatment during 96 weeks: arm 1, continuation (control) arm. Drugs will be continued or changed according to current guidelines and good clinical practice; arm 2, CD4-guided arm. Drugs discontinued and reintroduced according to CD4 cell counts, with HAART being administered only if CD4 cell count is < $350 \times 10^6/l$; arm 3, 1-week-on–1-week-off arm. Treatment for 1 week, pause for 1 week. From weeks 96 to 108, all three groups will receive HAART.

In Thailand, treatment was standardized, comprising stavudine (30 or 40 mg twice daily depending on weight), didanosine (250 or 400 mg once daily depending on weight), plus saquinavir-hard gel capsule 1600 mg once daily and ritonavir 100 mg once daily. In Switzerland, the HAART used was at the physicians' discretion. HIV RNA concentrations were measured using reverse transcription (RT)-PCR (Roche HIV Monitor Version 1.5; Roche Diagnostics, Basel,

Switzerland). In the 1-week-on–1-week-off arm, we measured HIV RNA concentrations at the end of the 'off' week, after 2, 4, 8, and 12 weeks, and every 12 weeks thereafter. Patients with two consecutive HIV RNA concentrations > 500 HIV RNA copies/ml were scored as 'viral load failures'. Drug plasma concentrations of saquinavir were measured with validated HPLC methods [6]. Reverse transcriptase and protease sequences were performed on proviral DNA at baseline (patients with undetectable HIV-RNA concentration) and in the first available plasma following virological failure with viral load > 1000 HIV-1 RNA copies/ml [7].

Final outcome of Staccato will be assessed by the amount of drugs used, side effects, viral load and CD4 cell counts, and number of clinical events, after 96 and 108 weeks. Numbers are given as mean (standard deviation) when normally distributed, otherwise as median (interquartile range). Statistical analysis were done with SPSS, version 9 (SPSS Inc., Chicago, USA).

Results

Recruitment for the Staccato study started during 2002, in Switzerland and Thailand. By January 2003, 150 patients had been randomized. The present data is based on patients who had at least an 8-week follow-up, in order to allow a preliminary assessment. There were 37 such patients (mean follow-up, 24.1 weeks) in the continued treatment arm, 39 (mean follow-up 24.9 weeks) in the CD4-guided arm, and 36 patients in the 1-week-on–1-week-off arm (mean follow-up, 27.8 weeks).

Fig. 1 shows the results in these 36 patients. Each line represents one patient: solid line for those who have not failed, dashed line for those who failed. The regimens used are indicated.

Overall, 19/36 (53%) patients have failed the 1-week-on–1-week-off arm regimen. These failures occurred within the first 12 weeks in patients on triple nucleotides in Switzerland (three of four patients), and in patients on didanosine/stavudine/saquinavir/ritonavir in Thailand (11 of 17 patients). In Switzerland, there were two late (> 12 weeks) failures on nelfinavir, lamivudine, and zidovudine, one on saquinavir/ritonavir/stavudine twice daily, and one late failure on nevirapine, lamivudine and zidovudine. Of eight patients on efavirenz, lamivudine and zidovudine, one has failed. Univariate and bivariate analyses of pre-treatment HIV RNA concentrations and types of HAART, and time on HAART before treatment interruption, show no statistically significant differences between those who failed and those who did not (P , 0.34–0.74).

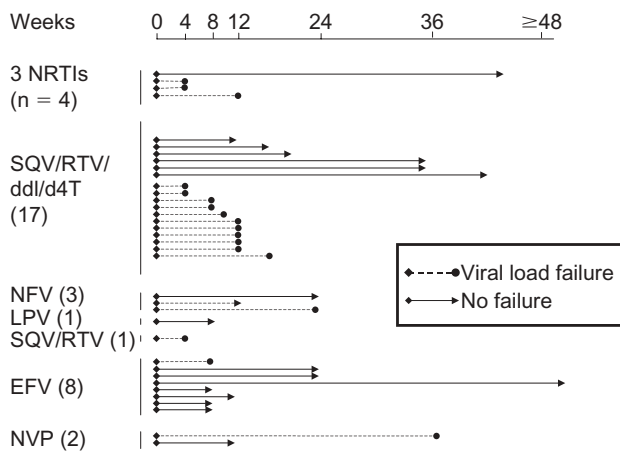


Fig. 1. Treatment experience on a regimen of 1-week-on-1-week-off therapy. Each line represents one patient; broken lines, patients who failed; uninterrupted lines, patients who did not fail. NRTI, Nucleoside reverse transcriptase inhibitor; SQV, saquinavir; RTV, ritonavir; ddI, didanosine; d4T, stavudine; NFV, nelfinavir; LPV, lopinavir; EFV, efavirenz; NVP, nevirapine.

In the continuous treatment arm of Staccato, two failures have occurred so far in 37 patients ($P < 0.001$, compared to the 1-week-on-1-week-off arm by χ^2 test). In the CD4-guided arm, no failures have occurred yet in 39 patients.

Pharmacokinetics of saquinavir 1600 mg combined with ritonavir 100 mg once daily was evaluated. In six of seven patients who failed the 1-week-on-1-week-off arm and resumed continuous therapy with this same regimen, saquinavir trough level was above a threshold of 0.1 mg/l (the 50% inhibitory concentration for wild-type virus is 0.05 mg/l). Twenty-three of 25 additional patients treated with this regimen also had trough levels above 0.1 mg/l.

Before starting Staccato, the 11 patients on stavudine, didanosine, saquinavir and ritonavir, 1-week-on-1-week-off, were among 73 antiretroviral-naïve patients treated continuously with this regimen. Of these 73, 72 [98.6%; 95% confidence interval (CI), 95.9–99.9] had an HIV RNA viral load < 400 copies/ml after 24 weeks, and the proportion with viral load < 50 copies/ml was 94.5% (95% CI, 85.3–98.2).

The genotypes of the reverse transcriptase and protease genes were determined in 18 of 19 failing patients (see Table 1). New 184V mutations appeared in two of seven patients on lamivudine, a new 103N mutation in the patient on efavirenz, and a new 181C mutation in the patient on nevirapine. None of the 14 protease inhibitor-treated patients, had major mutations [8] suggestive of protease inhibitor [or nucleoside reverse

transcriptase inhibitor (NRTI)] resistance. Follow-up data after at least 4 weeks of re-initiation of continuous treatment is available on 14 patients; all except two have viral load < 400 (see Table 1).

Discussion

Staccato is a comparative study of antiretroviral treatment strategies, enrolling patients whose HAART had been successful in that the CD4 cell count had increased to $> 350 \times 10^6/l$, with an HIV RNA viral load < 50 copies/ml. When such patients are treated continuously with established HAART, future viral load failure is rare, occurring in less than 5% of patients per year [9]. As noted in Results, there were only two failures in the continuous treatment arm of Staccato.

In contrast, the failure rate observed in the 1-week-on-1-week-off arm is clearly higher and reached 53% after an extremely short period of follow-up. Projected over the planned trial duration of 108 weeks, failure might be almost universal. In accordance with pre-established criteria, 1-week-on-1-week-off was therefore terminated.

Our experience also offers hints that patients may fail some treatment regimens more frequently than others. In the 1-week-on-1-week-off arm, there was only one failure in eight patients on efavirenz, lamivudine and zidovudine. Efavirenz-based HAART has also been successful in seven patients treated for longer than 1 year in the USA (M. Dybul, personal communication). The long half-life of efavirenz (17–40 h [10]) and its high plasma levels relative to inhibitory concentrations may maintain effective drug levels during most of the week off drugs; this could explain its relative success using the 1-week-on-1-week-off schedule.

The failure of ritonavir-boosted saquinavir compared to the success of ritonavir-boosted indinavir [5] is puzzling. Patient characteristics may have been different, although relevant differences are not obvious, as judged from published data [5]. The terminal half-life of ritonavir-boosted indinavir is similar to the half-life of ritonavir boosted saquinavir (reviewed in [11]). It should be noted that the NRTI backbone also varied, with successful combinations [5] using lamivudine, whereas Thai patients in Staccato received stavudine and didanosine. However, the use of lamivudine cannot have been the decisive factor, because three out of four patients receiving abacavir, lamivudine, and zidovudine or stavudine also failed. In addition, the active metabolites of didanosine and stavudine persist at least as long as those of lamivudine [12–14].

There were only isolated patients on ritonavir-boosted

Table 1. Results of genotyping and of re-treatment in patients failing on 1-week on–1 week off regimens.

| Patient | Regimen; week of failure | Genotype ^a | HIV-RNA concentration after re-treatment ^b |
|---------|-----------------------------|--|---|
| 41503 | ZDV, 3TC, ABC; week 4 | Week 0: M184V Week 2 and 4: M184V, T215Y, L210W | Viral load < 50 copies/ml after 8 weeks |
| 41837 | ZDV, 3TC, ABC; week 4 | Week 0: K103N, M184V Week 4: K103N | Viral load < 50 copies/ml after 4 weeks |
| 60324 | ZDV, 3TC, ABC; week 12 | Week 0: No mutations Week 12: No mutations | VL < 50 copies/ml after 4 weeks |
| 99950 | ZDV, 3TC, EFV; week 8 | Week 0: No mutations Week 8: K103N | No follow-up yet |
| 25180 | ZDV, 3TC, NVP; week 36 | Week 0: No mutations Wk 36: M184V, Y181C | No follow-up yet |
| 30809 | d4T, RTV, SQV; week 4 | Week 0: No mutations Week 4: No mutations | 152 copies/ml after 4 weeks |
| 16823 | ZDV, 3TC, NFV; week 24 | Week 0: No mutations ^c Week 24: M184V | No follow-up yet |
| 31156 | ZDV, 3TC, NFV; week 12 | Week 0: N/A ^d Week 12: No mutations | No follow-up yet |
| 71003 | d4T, ddl, SQV, RTV; week 16 | Week 16: no mutation | < 50 copies/ml after 8 weeks |
| 71009 | d4T, ddl, SQV, RTV; week 12 | Week 12: no mutation | 204 copies/ml after 8 weeks |
| 71021 | d4T, ddl, SQV, RTV; week 12 | Week 12: no major mutation | < 50 copies/ml after 8 weeks |
| 71030 | d4T, ddl, SQV, RTV; week 12 | Week 12: no major mutation | No follow-up yet |
| 71035 | d4T, ddl, SQV, RTV; week 4 | Week 4: no major mutation | < 50 copies/ml after 8 weeks |
| 71092 | d4T, ddl, SQV, RTV; week 12 | Week 12: no major mutation | 75 copies/ml after 8 weeks |
| 71096 | d4T, ddl, SQV, RTV; week 8 | Week 8: no major mutation | 13 300 copies/ml after 8 weeks |
| 73001 | d4T, ddl, SQV, RTV; week 8 | Week 8: no major mutation | < 50 copies/ml after 8 weeks |
| 73003 | d4T, ddl, SQV, RTV; week 10 | Week 10 Reverse transcriptase: L210M Protease: no major mutation | 1100 copies/ml after 8 weeks |
| 72025 | d4T, ddl, SQV, RTV; week 8 | Week 8: no major mutation | < 50 copies/ml after 8 weeks |
| 72011 | d4T, ddl, SQV, RTV; week 4 | Week 4: no major mutation | < 50 copies/ml after 8 weeks |

^aMutations at week 0 were determined using DNA from blood lymphocytes. Mutations at time of failure were determined after reverse transcription and amplification of plasma virus. ^bThe same treatment regimen as before failure was used. Results are expressed as copies HIV1 RNA/ml plasma. ^cBaseline resistance data were obtained by using DNA from peripheral blood mononuclear cells, whereas resistance data at the time of failure were obtained from plasma. 'No mutations' means no mutations associated with drug resistance. ^dNot available due to failure of amplification. ZDV, Zidovudine; 3TC, Lamivudine; ABC, abacavir; EFV, efavirenz; NVP, nevirapine; d4T, stavudine; RTV, ritonavir; SQV, saquinavir; NFV, nelfinavir; ddl, didanosine.

lopinavir and nelfinavir (with two failures), and only two patients on nevirapine-containing combinations (with one failure), so that nothing can be inferred about their effectiveness in the 1-week-on–1-week-off arm. Experience from the SITT trial indicates that unboosted indinavir or nelfinavir would probably fail in the 1-week-on–1-week-off arm [15].

In a further search for explanations, we asked whether there was any evidence that the saquinavir/ritonavir/stavudine/didanosine combination might be less effective than other types of HAART, when used continuously. However, efficacy within antiretroviral-naïve patients in Thailand was above the range described for more standard regimens, with 72/73 patients reaching a viral load of < 400 copies/ml after 24 weeks. Low drug levels, and drug resistance mutations were not found in Thai patients. Prompt response to reinstitution of continuous therapy in 10 of 12 evaluable patients also indicates that drug resistance was not a major factor, although the follow-up is short and late relapses are still possible.

In conclusion, failures in the 1-week-on–1-week-off arm of Staccato occurred with different treatment regi-

mens; these findings prompted termination of this arm in Staccato, and, together with other findings [15] raise doubts about the feasibility of this approach to treatment interruption.

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Appendix

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