Lopinavir/ritonavir single agent therapy as a universal combination antiretroviral therapy stopping strategy: results from the STOP 1 and STOP 2 studies

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Objectives: We designed two different studies to evaluate two different combination antiretroviral therapy (cART) stopping strategies namely a ‘staggered stop’ approach (STOP 1 study) and a ‘protected stop’ approach (STOP 2 study) to find the best ‘universal stop’ strategy.

Patients and methods: Patients who stopped cART for any reason were recruited. In STOP 1, 10 patients on efavirenz continued dual nucleos(t)ide reverse transcriptase inhibitors (NRTIs) for 1 week after discontinuing efavirenz. Efavirenz concentrations were measured weekly for up to 3 weeks. In STOP 2, 20 patients stopped their cART and replaced it with two tablets of lopinavir/ritonavir (Kaletra) (100/50 mg) twice daily for 4 weeks. Lopinavir, efavirenz, nevirapine and tenofovir concentrations were measured weekly for up to 4 weeks. Virological and resistance testing were performed.

Results: In STOP 1 five patients still had efavirenz present (median \( t_{1/2} \approx 148.4 \text{ h} \) 3 weeks after stopping. In STOP 2, 15/20 patients had a viral load (VL) of \(<40 \text{ copies/mL} \) and 3/20 patients had a reduction in VL by 4 weeks. Six patients opted not to stop lopinavir/ritonavir and still had \(<40 \text{ copies/mL} \) at week 8. Week 1–4 median trough lopinavir concentrations were well above the EC\(_{95}\). Six patients still had detectable concentrations of original cART persisting for >1 week after stopping. No patients developed new resistance mutations.

Conclusions: Plasma efavirenz concentrations can persist up to 3 weeks after patients stop efavirenz-containing regimens. This suggests a strategy of stopping efavirenz only 1 week before NRTIs may not be long enough for some individuals. The use of lopinavir/ritonavir monotherapy for a 4 week period may be an alternative pharmacologically and virologically effective universal stopping strategy which warrants further investigation.

Keywords: HIV, stopping therapy, lopinavir/ritonavir monotherapy, efavirenz, pharmacokinetics

Introduction

HIV-1-infected patients might stop their combination antiretroviral therapy (cART) for various reasons, such as patient choice, drug toxicity, drug interactions, therapeutic failure or following completion of a mother-to-child transmission prevention regimen. In developing countries the most common reason for patients to stop their therapy is the inability to access a continual supply of their medication. One of the risks of stopping cART is drug resistance, particularly when patients are taking pharmacologically unbalanced regimens that may lead to ‘functional monotherapy’ when all components are stopped simultaneously. This is particularly true if low drug concentrations persist for a considerable time, when a drug with a low genetic barrier to resistance is used and viral rebound occurs. This can have significant implications if the same regimen is restarted when the drug supply is resumed.

The aim of controlled cART stopping is to postpone viral rebound, which occurs normally around week 2, and thus to prevent drug resistance.
resistance from developing. Studies have, however, shown that nevirapine and efavirenz can be present at sub-therapeutic concentrations beyond 1 week after stopping therapy.\(^6,7\)

Currently there are limited data on effective strategies to stop therapy which can minimize the risk of developing resistance and thus preserve future treatment options.\(^8\) Antiretroviral drugs differ in their relative plasma elimination half-lives (\(t_{1/2}\)). The \(t_{1/2}\) of efavirenz, a recommended first-line non-nucleoside reverse transcriptase inhibitor (NNRTI), is stated to be 40–55 h after multiple doses.\(^9\)

Furthermore, studies have reported that differences in gender, ethnicity and CYP2B6 genotype lead to marked inter-patient variability in plasma efavirenz concentrations.\(^10,11\) It follows that there may also be significant variability in the plasma \(t_{1/2}\). This may have major clinical implications when it comes to safely stopping efavirenz, which may remain at therapeutic and sub-therapeutic concentrations for a longer period than other drugs in the regimen, effectively resulting in efavirenz monotherapy.

Current US, European and WHO guidelines advocate covering the slow elimination of drugs with a long half-life, such as nevirapine and efavirenz, with dual nucleoside cover for at least 1 week.\(^12\)–\(^14\) The guidelines also acknowledge disagreement amongst experts on the length of coverage and also whether other approaches, such as exchange stops, are more appropriate.

In this study we first describe a ‘staggered stop’ strategy (STOP 1), which is one of the first studies to describe a profoundly prolonged \(t_{1/2}\) of efavirenz in patients stopping efavirenz-containing regimens. The aim of this study was to look at the efavirenz concentration at the end of 1 week of dual nucleoside reverse transcriptase inhibitor (NRTI) cover and to see whether this stoppering strategy provides long enough cover for persisting low plasma efavirenz concentrations. We then describe a separate subsequent proof-of-concept study investigating a ‘protected stop’ approach of using lopinavir/ritonavir as a single-agent therapy with a view to developing a universal cART stopping strategy (STOP 2). This is in contrast to an ‘exchange stop’ approach, which replaces the NNRTI with a protease inhibitor (PI) whilst maintaining the NRTI backbone. STOP 2 therefore represents a proof-of-concept study with the aim of providing a pharmacological and virological rationale for the proposed strategy. Again, the study endpoint was the number of patients who still had detectable efavirenz or nevirapine drug levels when lopinavir/ritonavir was stopped after 4 weeks of monotherapy. This strategy was developed with consideration for ease of understanding by both medical staff and patients and lack of a requirement for in-depth pharmacological knowledge. We report here the first validation of the strategy in terms of safety and preservation of the component agents in the stopped regimen. This would allow patients to resume their original (or new) cART regimen with the confidence that the original regimen should have retained full antiretroviral activity.

**Patients and methods**

Ethics committee approval for both the STOP 1 and STOP 2 studies was granted by Birmingham Heartlands Hospital Ethics committee and written informed consent was obtained from participants.

In the STOP 1 study, HIV-1-positive individuals who were about to stop or change efavirenz-containing regimens were enrolled into an extended pharmacokinetic study. The reasons for discontinuation were stated by the patient and their clinician prior to entry to the study (Table 1). A staggered stopping strategy in which efavirenz was discontinued 1 week prior to other components in the regimen was employed. The majority of patients were on a zidovudine and lamivudine nucleoside backbone. Plasma efavirenz was assayed by validated HPLC methodology at baseline (day 0) and at days 4, 7, 14 and 21 after discontinuation. Efavirenz plasma \(t_{1/2}\) was determined by regression analysis as previously described.\(^12\) HIV viral DNA determinations were made using the Roche Cobas Taqman assay at each visit. Population-based genotypic resistance testing of the protease and first 347 amino acids of the reverse transcriptase using established Applied Biosystems sequencing protocols was performed when viral load exceeded 500 copies/mL. The CYP2B6 516 G>T single-nucleotide polymorphism was detected as previously described.\(^11\) Efavirenz concentrations >1000 ng/mL were considered therapeutic.\(^16\) and concentrations between the protein-binding corrected EC\(_{95}\) of 46.7 ng/mL for wild-type virus and 1000 ng/mL were considered sufficient to impart a selective pressure on replicating virus.

In the STOP 2 study, HIV-1-positive patients stopping cART for any reason were enrolled into a multicentre, single-arm, pharmacokinetic and virological study to investigate the strategy of using single replacement therapy with lopinavir/ritonavir (two tablets of Kaletra (100 mg of lopinavir/50 mg of/ritonavir) twice daily) for 4 weeks as a ‘universal cART stopping strategy’. Patients stopped all components of their original cART regimen on day 0 and lopinavir/ritonavir was started on day 0 and continued for 4 weeks. Patients were reviewed at baseline and weeks 1, 2, 3, 4 and 8 after stopping their original cART. Plasma samples were analysed for lopinavir trough concentrations (\([\text{lopinavir}]_{12}\)) each week from week 1 to week 4. Plasma concentrations of individual cART components with long half-lives (nevirapine, efavirenz and tenofovir) were measured weekly until undetectable using methods previously described.\(^17,18\) Viral load analysis was performed at all timepoints as described above. Genotypic resistance tests were performed on all samples with a viral load of >500 copies/mL and if virological rebound at week 8 of the study was observed. When resistance-associated mutations were detected at any timepoint, stored samples from before initiation of the study were analysed retrospectively.

**Results**

**STOP 1 study**

Ten patients were enrolled, comprising six Caucasian men and four black women. The median age was 37 years (range 28–64 years) and six patients had a viral load of <50 copies/mL (range <50–15000 copies/mL) prior to stopping efavirenz. Median CD4 count on stopping efavirenz was 374 cells/mm\(^3\) (range 247–845 cells/mm\(^3\)). The median efavirenz \(t_{1/2}\) was 114.6 h (range 36–286 h) and five individuals had \(t_{1/2}\) values >100 h (see Table 1).

Median plasma efavirenz concentrations were 3069 ng/mL (range 2071–9733 ng/mL), 311 ng/mL (<40–4478 ng/mL), 149 ng/mL (<40–1845 ng/mL) and 62 ng/mL (<40–762 ng/mL) at days 0, 7, 14 and 21 respectively. One week after stopping efavirenz, seven patients still had efavirenz concentrations above the efavirenz EC\(_{95}\) and three patients had concentrations >1000 ng/mL. Two weeks after stopping, five patients had plasma efavirenz concentrations above the EC\(_{95}\) and three patients had efavirenz concentrations >1000 ng/mL. Three weeks after stopping efavirenz, five patients (three black African females) had plasma efavirenz above the EC\(_{95}\) (median 445.5 ng/mL (range 84–762 ng/mL)). No patients developed new resistance mutations from baseline to week 3. However,
## Table 1. Results from the STOP 1 study

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ethnicity</th>
<th>Gender</th>
<th>CYP2B6</th>
<th>Gender</th>
<th>Reason for stopping</th>
<th>Drugs continued</th>
<th>Co-medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>white</td>
<td>male</td>
<td>GT</td>
<td>516G</td>
<td>high lipids</td>
<td>EFV stopped</td>
<td>warfarin</td>
</tr>
<tr>
<td>2</td>
<td>white</td>
<td>male</td>
<td>GG</td>
<td>516G</td>
<td>virological failure</td>
<td>EFV stopped</td>
<td>interferon</td>
</tr>
<tr>
<td>3</td>
<td>white</td>
<td>female</td>
<td>GT</td>
<td>516G</td>
<td>patient choice</td>
<td>EFV stopped</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>white</td>
<td>female</td>
<td>GT</td>
<td>516G</td>
<td>toxicity</td>
<td>EFV stopped</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>white</td>
<td>female</td>
<td>GT</td>
<td>516G</td>
<td>toxicity</td>
<td>EFV stopped</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>black</td>
<td>male</td>
<td>GT</td>
<td>516G</td>
<td>toxicity</td>
<td>EFV stopped</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>black</td>
<td>female</td>
<td>GT</td>
<td>516G</td>
<td>toxicity</td>
<td>EFV stopped</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>black</td>
<td>female</td>
<td>GT</td>
<td>516G</td>
<td>toxicity</td>
<td>EFV stopped</td>
<td>—</td>
</tr>
</tbody>
</table>

- ZDV, zidovudine; 3TC, lamivudine; NVP, nevirapine; EFV, efavirenz; TDF, tenofovir; ABC, abacavir.

## Discussion

The STOP 1 study findings were presented previously and this was one of the first studies to draw attention to the fact that plasma efavirenz is frequently detected beyond the 1 week staggered stop period,\(^1\) an observation now confirmed in other studies.\(^2\) In the STOP 1 study we demonstrated a prolonged \(t_{1/2}\) of efavirenz, which was >100 h in five patients. This finding five patients continued cART after discontinuation of efavirenz and retained an undetectable viral load (VL) throughout the study.

No patients were homozygous for CYP2B6 516G>T whilst 6/10 were heterozygous (see Table 1). In a univariate analysis of efavirenz \(t_{1/2}\), heterozygosity for CYP2B6 516G>T was significantly associated (\(P=0.048\)) and trends were observed for ethnicity (\(P=0.057\)), sex (\(P=0.057\)) and body weight (\(P=0.101\)). In multivariate analysis a trend was observed for heterozygosity for CYP2B6 516G>T genotypes (\(P=0.098\)) and ethnicity (\(P=0.099\)), but body weight was the only independent predictor of efavirenz \(t_{1/2}\) (\(P=0.016\)). A trend in association of CYP2B6 516G>T heterozygosity with baseline (\(P=0.11\)) but not week 3 (\(P=0.43\)) plasma efavirenz concentrations was observed. The pharmacogenetic data should be interpreted with caution because of the small sample size, which also precluded analysis of other CYP2B6 polymorphisms that have been reported to exert functional effects on efavirenz clearance.\(^{19-21}\)

### STOP 2 study

Twenty patients were enrolled, of whom the majority (15/20) were Caucasian men. The median age was 46 years (range 23–74 years). The reasons for discontinuing the original cART are described in Table 2.

In 12 of the 20 patients the cART regimens stopped were classified as pharmacologically ‘unbalanced’: 8 with the potential for NNRTI monotherapy and 4 with the potential for tenofovir or emtricitabine monotherapy. All of the 17 patients who had a VL <200 copies/mL upon stopping had a VL <40 copies/mL following 4 weeks of lopinavir/ritonavir monotherapy. The three patients with detectable VL at baseline (353, 90288 and 128789 copies/mL) had a reduction to <200 copies/mL upon stopping had a VL <40 copies/mL at week 4 opted not to stop lopinavir/ritonavir monotherapy and still had <40 copies/mL at week 8. Two were immediately swapped to alternative cART regimens and also retained undetectable VL at week 8. The HIV viral load rebounded in all 12 patients who stopped lopinavir/ritonavir after 4 weeks of monotherapy, with a median week 8 VL of 64523 copies/mL (range 405–386874 copies/mL). Median [lopinavir]\(_{12}\) at week 1 was 7368 ng/mL (range 227–14152 ng/mL), at week 2 it was 6334 ng/mL (range 733–14049 ng/mL), at week 3 it was 6996 ng/mL (range 2080–11989 ng/mL) and at week 4 it was 7324 ng/mL (range 733–14049 ng/mL). Lopinavir concentrations were >1000 ng/mL in all but two samples (in which the patients were suspected of being poorly adherent to their medication prior to sampling). The pharmacokinetics of the original cART stopped drugs (nevirapine, efavirenz, tenofovir) were consistent with known data; six patients on unbalanced regimens had sub-therapeutic concentrations of longer half-life drugs present >1 week after stopping (see Figure 1).

### Discussion

The STOP 1 study findings were presented previously and this was one of the first studies to draw attention to the fact that plasma efavirenz is frequently detected beyond the 1 week staggered stop period,\(^1\) an observation now confirmed in other studies.\(^2\) In the STOP 1 study we demonstrated a prolonged \(t_{1/2}\) of efavirenz, which was >100 h in five patients. This finding five patients continued cART after discontinuation of efavirenz and retained an undetectable viral load (VL) throughout the study.

No patients were homozygous for CYP2B6 516G>T whilst 6/10 were heterozygous (see Table 1). In a univariate analysis of efavirenz \(t_{1/2}\), heterozygosity for CYP2B6 516G>T was significantly associated (\(P=0.048\)) and trends were observed for ethnicity (\(P=0.057\)), sex (\(P=0.057\)) and body weight (\(P=0.101\)). In multivariate analysis a trend was observed for heterozygosity for CYP2B6 516G>T genotypes (\(P=0.098\)) and ethnicity (\(P=0.099\)), but body weight was the only independent predictor of efavirenz \(t_{1/2}\) (\(P=0.016\)). A trend in association of CYP2B6 516G>T heterozygosity with baseline (\(P=0.11\)) but not week 3 (\(P=0.43\)) plasma efavirenz concentrations was observed. The pharmacogenetic data should be interpreted with caution because of the small sample size, which also precluded analysis of other CYP2B6 polymorphisms that have been reported to exert functional effects on efavirenz clearance.\(^{19-21}\)
Table 2. Results from the STOP 2 study

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ethnicity</th>
<th>Gender</th>
<th>Reason for stopping</th>
<th>Combination discontinued</th>
<th>Viral load (copies/mL)</th>
<th>Resistance at baseline</th>
<th>Resistance weeks 1-8</th>
<th>LPV/r continued</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>week 4</td>
<td>week 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>C</td>
<td>male</td>
<td>seroconversion&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZDV/3TC/EFV</td>
<td>40</td>
<td>100000</td>
<td>WT</td>
<td>WT</td>
</tr>
<tr>
<td>2</td>
<td>BA</td>
<td>male</td>
<td>took wrong doses; attempt to rationalize treatment</td>
<td>ZDV/3TC/NVP</td>
<td>107</td>
<td>40</td>
<td>WT</td>
<td>NA</td>
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<tr>
<td>3</td>
<td>C</td>
<td>male</td>
<td>simplification</td>
<td>ABC/3TC/LPV/r</td>
<td>40</td>
<td>40</td>
<td>40 WT</td>
<td>NA</td>
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<tr>
<td>4</td>
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<td>male</td>
<td>toxicity</td>
<td>ABC/DDI/LPV/r</td>
<td>40</td>
<td>40</td>
<td>40 NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
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<td>male</td>
<td>virological failure, poor adherence</td>
<td>ABC/3TC/EFV</td>
<td>90288</td>
<td>1263</td>
<td>4923 K103N</td>
<td>WT</td>
</tr>
<tr>
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<td>C</td>
<td>male</td>
<td>patient choice</td>
<td>TDF/ABC/NVP</td>
<td>40</td>
<td>40</td>
<td>16769 WT</td>
<td>WT</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>male</td>
<td>simplification</td>
<td>ABC/NVP/ATV/r</td>
<td>40</td>
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<td>40 NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NA</td>
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<tr>
<td>9</td>
<td>C</td>
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<td>virological failure</td>
<td>TDF/FTC/ABC/3TC/NVP</td>
<td>128789</td>
<td>238</td>
<td>8328 184V, 101E, 181C</td>
<td>WT</td>
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<tr>
<td>10</td>
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<td>female</td>
<td>took wrong doses; attempt to rationalize treatment</td>
<td>ABC/3TC/NVP</td>
<td>353</td>
<td>131</td>
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<td>M36I, D60E, I93L</td>
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<td>overdose</td>
<td>ZDV/3TC/EFV</td>
<td>40</td>
<td>40</td>
<td>40 NA&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<td>female</td>
<td>seroconversion&lt;sup&gt;a&lt;/sup&gt;</td>
<td>TDF/FTC/LPV/r</td>
<td>183</td>
<td>40</td>
<td>165276 WT</td>
<td>WT</td>
</tr>
<tr>
<td>13</td>
<td>C</td>
<td>male</td>
<td>SJ syndrome</td>
<td>ABC/3TC/EFV</td>
<td>40</td>
<td>40</td>
<td>198623 NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>WT</td>
</tr>
<tr>
<td>14</td>
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<td>female</td>
<td>acute renal failure</td>
<td>TDF/FTC/ABC/3TC/NVP</td>
<td>40</td>
<td>40</td>
<td>7461 NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>WT</td>
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<tr>
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<td>acute renal failure</td>
<td>TDF/FTC/ABC/3TC/NVP</td>
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<td>40</td>
<td>61041 WT</td>
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<tr>
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<td>40</td>
<td>405 WT</td>
<td>NA</td>
</tr>
<tr>
<td>17</td>
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<td>male</td>
<td>acute renal failure</td>
<td>TDF/FTC/ABC/3TC/NVP</td>
<td>76</td>
<td>40</td>
<td>68004 WT</td>
<td>WT</td>
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<tr>
<td>18</td>
<td>BA</td>
<td>female</td>
<td>acute renal failure</td>
<td>TDF/FTC/ABC/3TC/NVP</td>
<td>40</td>
<td>NA</td>
<td>163000 WT</td>
<td>WT</td>
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<tr>
<td>19</td>
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<td>male</td>
<td>acute renal failure</td>
<td>TDF/FTC/ABC/3TC/NVP</td>
<td>40</td>
<td>135</td>
<td>1780 WT</td>
<td>WT</td>
</tr>
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</table>

C, Caucasian; BA, black African; BC, black Caribbean; LPV/r, lopinavir/ritonavir; TDF, tenofovir; FTC, emtricitabine; ZDV, zidovudine; 3TC, lamivudine; DRV/r, darunavir/ritonavir; NVP, nevirapine; ABC, abacavir; DDI, didanosine; ARV, antiretroviral; WT, wild-type; NA, not available.

<sup>a</sup>Patients went on combination antiretroviral therapy for a limited period following seroconversion according to the SPARtAC (Short Pulse Antiretroviral Therapy at HIV Seroconversion) trial protocol.

<sup>b</sup>Patient fully suppressed at start of study and baseline resistance assay pre-antiretroviral therapy not available.
which all drugs were stopped simultaneously. 2 Another stag-
re-suppression after treatment interruption than a strategy in
rates [adjusted odds ratio of 1.94 (95% CI 1.02–3.69)] of viral
study this staggered stop approach was associated with higher
enz concentration was still above the EC 95 at 3 weeks for 5/10
14 days after discontinuing efavirenz because the plasma efavir-
tinued use of zidovudine and lamivudine for 7 days or even
STOP 1 study does not support a staggered stop strategy of con-
et al
virenz was also reported by Sadiq
was supported by other studies in which a population pharmacoki-
etic approach was utilized following efavirenz discontinuation,
with estimated t1/2 of 23, 27 and 48 h for patients with the
GG, GT and TT genotypes for the CYP2B6 516G>T polymor-
phism.7 However, determination of plasma efavirenz con-
centrations revealed a much longer half-life in some indi-
siduals. A case of an extremely long half-life of plasma efaf-
irenz was also reported by Sadiq et al.,24 in a female African
patient with detectable plasma efavirenz 8 weeks after discon-
tinuation and subsequent development of NNRTI resistance.
There is evidence that a staggered stop strategy could be
successfully employed, as shown in a study of 24 Caucasian
men who stopped cART after primary infection.25 In a differ-
ent staggered stop approach was associated with higher
rates [adjusted odds ratio of 1.94 (95% CI 1.02–3.69)] of viral
re-suppression after treatment interruption than a strategy in
which all drugs were stopped simultaneously.2 Another stag-
gered stop study showed that covering the slow tail of drug elim-
ination with a 2 week NRTI regimen is adequate, but was only
performed on nine Caucasian men.26 In principle, therefore, the
STOP 1 study does not support a staggered stop strategy of con-
tinued use of zidovudine and lamivudine for 7 days or even
14 days after discontinuing efavirenz because the plasma efavir-
enz concentration was still above the EC95 at 3 weeks for 5/10
patients. This strategy is therefore unlikely to be appropriate for
all patients, especially in the case of some African females.

The other approach that has been utilized (in the SMART
study) was an exchange stop. In this approach the drug with
the longer half-life was exchanged for a drug with a higher
genetic barrier and shorter half-life. All three drugs were then
stopped simultaneously. This strategy was associated with a
higher chance [adjusted odds ratio of 3.64 (1.37–9.64)] of viro-
logical re-suppression than either the simultaneous or staggered
stopping strategy.2

Neither the staggered stop nor the exchange stop may be
appropriate when efavirenz is combined with drugs that have
similar extended half-lives, such as tenofovir and emtricitabine.
In this situation, tenofovir or emtricitabine may replace the
efavirenz as the agent(s) giving rise to functional monotherapy.
This is supported by findings in our STOP 2 study, in which
plasma tenofovir concentrations were still detectable 2 weeks
after stopping the drug in three patients (Figure 1). Unfortunately,
our study did not measure emtricitabine plasma concentrations.
Also, we did not assess intracellular drug concentrations, which
is important because the t1/2 of the phosphorylated metabo-
listes is considerably longer than that in plasma.27

The STOP 2 study was designed to solve the problem of func-
tional monotherapy with drugs that only need one mutation for
HIV to become fully resistant. The aim was to provide the
pharmacological and virological rationale to recommend a
simple, easily understandable and universally applicable
approach to stopping any drug regimen irrespective of the t1/2
of the component agents. We do not advocate stopping cART
but accept that it does happen frequently. In our clinical practice
we have witnessed a growing number of patients who have had
unexpected and unplanned interruptions in their therapy,
primarily due to interruptions in drug supplies in the devel-
oping world. Furthermore, with the use of fixed-dose combina-
tion tablets comprising pharmacologically unbalanced agents
this is likely to be the case for some time. The results obtained
in the STOP 2 study showed that the strategy of using 4 weeks
of lopinavir/ritonavir monotherapy when stopping cART is sup-
pported by the virological suppression maintained by therapeutic
lopinavir concentrations. In this small study no additional drug
resistance mutations were seen. This is supported by the knowl-
edge that pharmacological protection provided by a drug with a
high genetic barrier to resistance should prevent the develop-
ment of resistant viruses at times when the stopped drug con-
centrations fall through the zone of resistance selection.

One potential criticism of our protected stop strategy is that
there may be an interaction between the residual NNRTI and the
PI used to replace it, leading to lower PI exposure. However, the
NNRTI concentrations will drop over time and consequently
the induction effect will be short lived. No major effect was seen
on the lopinavir plasma concentration in our study. In addition,
any strategy to counteract lopinavir induction (e.g. by starting
with a higher PI dose) is likely to lead to an increased risk of side
effects or other drug interactions and would make this strategy
more complicated and less acceptable to the patient.

Although STOP 2 is a small study, it is the first study to
examine whether the protected stop strategy using lopinavir/
ritonavir monotherapy is a pharmacologically and virologically
safe and effective approach. Given that cART regimens will
always be pharmacologically unbalanced, we propose that this
protected stop strategy may be more effective than either a
staggered stop or exchange stop in terms of preserving future
treatment options. Also, providing patients with a 1 month
supply of lopinavir/ritonavir to be taken should treatment inter-
ruption occur, such as may be the case when patients relocate
back to resource-limited countries, may preserve treatment
options when drug supplies can be resumed.

In conclusion, it may be necessary to cover the tail of
long-half-life drugs upon stopping cART for at least 4 weeks to
prevent monotherapy with low genetic barrier drugs. The STOP
2 study provides some data to support the pharmacological
and virological rationale for recommending a universal protected

Figure 1. STOP 2 study: concentrations of lopinavir (lines) and stopped
cART agents (symbols) up to 4 weeks after stopping original cART
regimen (baseline) and commencement of lopinavir/ritonavir
single-agent therapy. Drug concentrations below the level of detection
are splayed for display purposes. Black circles, efavirenz; grey squares,
nevirapine; grey triangles, plasma tenofovir.
stop strategy using 4 weeks of lopinavir/ritonavir monotherapy irrespective of the half-lives of the original CART. Further studies to validate this approach are now warranted.

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