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 t1/2 = 148.4 h) 3 weeks after stopping. In STOP 2, 15/20 patients had a viral load (VL) of <40 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 copies/mL at week 8. Week 1–4 median trough lopinavir concentrations were well above the EC95. 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 (t1/2). The t1/2 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 t1/2. 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.12

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 t1/2 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(ide) reverse transcriptase inhibitor (NNRTI) cover and to see whether this stopping 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 nevirapine 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 of 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 African women. The median age was 37 years (range 28–64 years) and six patients had a viral load of <50 copies/mL (range <50–15,000 copies/mL) prior to stopping efavirenz. Median CD4 count on stopping efavirenz was 374 cells/mm³ (range 247–845 cells/mm³). The median efavirenz t1/2 was 114.6 h (range 36–286 h) and five individuals had t1/2 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 EC95 and three patients had concentrations >1000 ng/mL. Two weeks after stopping, five patients had plasma efavirenz concentrations above the EC95 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 EC95 [median 445.5 ng/mL (range 84–762 ng/mL)]. No patients developed new resistance mutations from baseline to week 3. However,
universal cART stopping strategy

Table 1. Results from the STOP 1 study

<table>
<thead>
<tr>
<th>Patient Ethnicity Gender</th>
<th>Weight (kg)</th>
<th>CYP2B6</th>
<th>Reason for stopping</th>
<th>Drugs continued</th>
<th>3 week EFV (ng/mL)</th>
<th>6/10 weeks EFV (ng/mL)</th>
<th>t1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>white male</td>
<td>66</td>
<td>GT</td>
<td>high lipids</td>
<td>changed to NVP</td>
<td>6796</td>
<td>3996</td>
<td>&gt;100 h</td>
</tr>
<tr>
<td>white male</td>
<td>72</td>
<td>GG</td>
<td>NNRTI</td>
<td>stopped</td>
<td>6996</td>
<td>3996</td>
<td>&gt;100 h</td>
</tr>
<tr>
<td>white male</td>
<td>63</td>
<td>GT</td>
<td>virological failure</td>
<td>EFV stopped 1st</td>
<td>6996</td>
<td>3996</td>
<td>&gt;100 h</td>
</tr>
<tr>
<td>white male</td>
<td>78</td>
<td>GG</td>
<td>primary HIV</td>
<td>EFV stopped 1st</td>
<td>6996</td>
<td>3996</td>
<td>&gt;100 h</td>
</tr>
<tr>
<td>white male</td>
<td>62</td>
<td>GT</td>
<td>toxicity</td>
<td>EFV stopped 1st</td>
<td>6996</td>
<td>3996</td>
<td>&gt;100 h</td>
</tr>
<tr>
<td>white male</td>
<td>53</td>
<td>S3</td>
<td>toxicity</td>
<td>EFV stopped 1st</td>
<td>6996</td>
<td>3996</td>
<td>&gt;100 h</td>
</tr>
<tr>
<td>black female</td>
<td>65</td>
<td>GT</td>
<td>toxicity</td>
<td>EFV stopped 1st</td>
<td>6996</td>
<td>3996</td>
<td>&gt;100 h</td>
</tr>
<tr>
<td>black female</td>
<td>115</td>
<td>GT</td>
<td>toxicity</td>
<td>EFV stopped 1st</td>
<td>6996</td>
<td>3996</td>
<td>&gt;100 h</td>
</tr>
<tr>
<td>black female</td>
<td>55</td>
<td>GT</td>
<td>toxicity</td>
<td>EFV stopped 1st</td>
<td>6996</td>
<td>3996</td>
<td>&gt;100 h</td>
</tr>
</tbody>
</table>

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

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

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 <100 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 in VL by 4 weeks (to 131, 1263 and 238 copies/mL respectively). Six patients with 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 64 523 copies/mL (range 405–386 874 copies/mL). Median [lopinavir]12 at week 1 was 7368 ng/mL (range 227–14152 ng/mL), at week 2 it was 7324 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 6334 ng/mL (range 1231–13202 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,1–2 an observation now confirmed in other studies.11,13 In the STOP 1 study we demonstrated a prolonged t½ 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 t½, 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 t½ (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>
<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>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 40 100000</td>
<td>WT</td>
<td>WT</td>
<td>no</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 40 40</td>
<td>WT</td>
<td>NA</td>
<td>yes</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>male</td>
<td>simplification</td>
<td>ABC/3TC/LPV/r</td>
<td>40 40 40</td>
<td>WT</td>
<td>NA</td>
<td>yes</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>male</td>
<td>toxicity</td>
<td>ABC/DDI/LPV/r</td>
<td>40 40 40</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>yes</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 1263 4923</td>
<td>K103N</td>
<td>WT</td>
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</tr>
<tr>
<td>7</td>
<td>C</td>
<td>male</td>
<td>patient choice</td>
<td>TDF/ABC/NVP</td>
<td>40 40 16769</td>
<td>WT</td>
<td>WT</td>
<td>no</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>male</td>
<td>simplification</td>
<td>ABC/NVP/ATV/r</td>
<td>40 40 40</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NA</td>
<td>yes</td>
</tr>
<tr>
<td>9</td>
<td>C</td>
<td>male</td>
<td>virological failure</td>
<td>ABC/DDI/NVP/LPV/r</td>
<td>40 40 40</td>
<td>K103N</td>
<td>NA</td>
<td>yes</td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>male</td>
<td>took wrong doses; attempt to rationalize treatment</td>
<td>TDF/FTC/NVP</td>
<td>128789 238 8328 184V, 101E, 181C</td>
<td>WT</td>
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<td>no</td>
</tr>
<tr>
<td>11</td>
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<td>female</td>
<td>overdose</td>
<td>ABC/3TC/NVP</td>
<td>353 131 386874</td>
<td>K103N, Y181C, M36I, D60E, I93L</td>
<td>M36I, D60E, I93L</td>
<td>no</td>
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<tr>
<td>12</td>
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<td>overdose</td>
<td>ZDV/3TC/EFV</td>
<td>40 40 40</td>
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<td>NA</td>
<td>started ZDV/3TC/EFV</td>
</tr>
<tr>
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<td>C</td>
<td>male</td>
<td>seroconversion&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>183 40 165276</td>
<td>WT</td>
<td>WT</td>
<td>no</td>
</tr>
<tr>
<td>14</td>
<td>BC</td>
<td>female</td>
<td>SJ syndrome</td>
<td>ABC/3TC/NVP</td>
<td>40 40 198623</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>WT</td>
<td>no</td>
</tr>
<tr>
<td>15</td>
<td>C</td>
<td>male</td>
<td>seroconversion&lt;sup&gt;a&lt;/sup&gt;</td>
<td>TDF/FTC/EFV</td>
<td>40 40 7461</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>WT</td>
<td>no</td>
</tr>
<tr>
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<td>male</td>
<td>seroconversion&lt;sup&gt;a&lt;/sup&gt;</td>
<td>TDF/FTC/EFV</td>
<td>40 40 61041</td>
<td>WT</td>
<td>WT</td>
<td>no</td>
</tr>
<tr>
<td>17</td>
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<td>male</td>
<td>seroconversion&lt;sup&gt;a&lt;/sup&gt;</td>
<td>TDF/FTC/EFV</td>
<td>40 40 40</td>
<td>WT</td>
<td>no</td>
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</tr>
<tr>
<td>18</td>
<td>BA</td>
<td>female</td>
<td>acute renal failure</td>
<td>TDF/FTC/NVP</td>
<td>76 40 68004</td>
<td>WT</td>
<td>WT</td>
<td>no</td>
</tr>
<tr>
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<td>acute renal failure</td>
<td>TDF/FTC/EFV</td>
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<td>WT</td>
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<tr>
<td>20</td>
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<td>male</td>
<td>ARV toxicity</td>
<td>TDF/FTC/DRV/r</td>
<td>40 135 1780</td>
<td>WT</td>
<td>WT</td>
<td>no</td>
</tr>
</tbody>
</table>

<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. Another stag-

re-suppression after treatment interruption than a strategy in

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-

STOP 1 study does not support a staggered stop strategy of con-

et al

individuals. A case of an extremely long half-life of plasma efa-

centrations revealed a much longer half-life in some 

netic approach was utilized following efavirenz discontinuation,

is supported by other studies in which a population pharmacoki-

etic approach was used following efavirenz discontinuation, 

with estimated $t_{1/2}$ of 23, 27 and 48 h for patients with the 

GG, GT and TT genotypes for the CYP2B6 516G>T polymor-

However, determination of plasma efavirenz concentra-

tions revealed a much longer half-life in some individuals. A case of an extremely long half-life of plasma efa-

virenz was also reported by Sadiq et al. 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 

supported by other studies in which a population pharmacoki-

netic approach was utilized following efavirenz discontinuation, 

with estimated $t_{1/2}$ of 23, 27 and 48 h for patients with the 

GG, GT and TT genotypes for the CYP2B6 516G>T polymor-

pharmacological and virological rationale to recommend a 

simple, easily understandable and universally applicable 

approach to stopping any drug regimen irrespective of the $t_{1/2}$ 

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, 

predominantly 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-

ported 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 
routine (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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References