The role of compartment penetration in PI-Monotherapy: the Atazanavir-Ritonavir Monomaintenance (ATARITMO) Trial

Pietro Vernazza[a], Synøve Daneel[a], Véronique Schiffer[b], Laurent Decosterd[c], Walter Fierz[d], Thomas Klimkait[e], Matthias Hoffmann[a], Bernard Hirschel[b] and The Swiss HIV Cohort Study

Objectives: To limit exposure to anti-HIV drugs and minimize risk of long-term side effects, studies have looked at the possibility of simplified maintenance strategies. Ritonavir-boosted protease-inhibitor (PI)-monotherapies are an attractive alternative, but limited compartmental penetration of PI remains a concern.

Design: Non-comparative 24-week pilot study.

Method: Ritonavir-boosted atazanavir (ATV/r) monotherapy administered to fully suppressed patients (>3 month HIV RNA < 50 copies/ml). Plasma was obtained every 4 weeks and cerebrospinal fluid (CSF) and semen at W24.

Results: Two patients (7%) failed ATV/r monotherapy. One patient was subsequently identified as a protocol violator since he had a previous history of treatment failure under indinavir. The second patient deliberately decided to stop treatment after W20. Excluding failing patients, individual measurements of HIV RNA in patients having occasional viral 'blips' was found in five patients. At W24, 3/20 patients had elevated viral loads in CSF (HIV RNA > 100 copies/ml), and 2/15 in semen, despite viral suppression in plasma (< 50 copies/ml). Samples with elevated HIV RNA (> 500 copies/ml) in CSF were all wild type. The mean ATV drug concentration ratio (CSF/blood, n = 22) was 0.9%. Indicators of altered immune activation (CD8CD38 C-reactive protein) remained unchanged.

Conclusion: This study supports previous results indicating the potential use of PI-based mono-maintenance therapies. However, our results in CSF cautions against the uncontrolled use of PI-based monotherapies. © 2007 Lippincott Williams & Wilkins

AIDS 2007, **21**:1309–1315

Keywords: Protease inhibitor, monotherapy, HIV, atazanavir, cerebrospinal fluid, semen, HIV RNA

Introduction

Currently, HAART consists of at least three drugs including protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI; nucleoside analogues) or non-nucleoside reverse transcriptase inhibitors (NNRTI). Patients on long-term therapy develop side effects, particularly mitochondrial toxicity and metabolic disturbances [1]. Studies have looked at structured treatment interruption (STI) to limit exposure to HIV

From the [a]Division of Infectious Diseases, Department of Internal Medicine, Cantonal Hospital, St. Gallen, Switzerland, the [b]Division of Infectious Diseases, University Hospital, Geneva, Switzerland, the [c]Laboratory of Clinical Pharmacology, University Hospital, Lausanne, Switzerland, the [d]Logolab, Zurich, Switzerland, and the [e]Institute of medical Microbiology, University of Basel, Switzerland.

Correspondence to P. Vernazza, DIM, Infektiologie, Kantonsspital St. Gallen, 9007 St. Gallen, Switzerland.

Tel: +41 71 494 2631; fax: +41 71 494 6114; e-mail: Pietro.Vernazza@kssg.ch
Received: 14 January 2007; revised: 20 February 2007; accepted: 5 March 2007.

ISSN 0269-9370 © 2007 Lippincott Williams & Wilkins

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

drugs [2–5]. After the unexpected termination of the SMART study January 2006, due to an increased risk in disease progression and mortality of the STI arm, a temporary stop has been put to this treatment option [6]. The possibility of simplified maintenance strategies has thus gained both in importance and attractiveness, with HIV monotherapies reducing the risk of long-term side effects.

Lipodystrophy is mainly caused by the mitochondrial side effects of NRTI [7]. Although some NRTI are less toxic to the mitochondria, complete elimination of NRTI from HAART is likely to reduce the long-term risk of lipodystrophy associated with NRTI. In addition, mono-maintenance treatment results in reduced cost which is an important requirement for the treatment of infected individuals in resource limited countries.

Given the high trough levels and increased barrier for resistance of boosted PI these drugs are currently the most interesting candidates to be evaluated for the use in mono-maintenance regimens.

A prerequisite of efficient HIV drugs is their ability to reach blood levels far above inhibitory concentrations of wild-type HIV. Co-administration of ritonavir (RTV), a potent inhibition of cytochrome P450, greatly improves pharmacokinetics (AUC and plasma half life) of PI.

Our group has evaluated the efficacy of simpler treatment regimens in two pilot studies. The first of these used ritonavir-boosted indinavir (IDV/r) [8]. Patients on monotherapy were able to maintain HIV RNA suppression (50 copies/ml) during a median follow-up time of 78 weeks. Subsequently, other groups investigated monotherapies using ritonavir-boosted PI [9,10]. Most have used the coformulation of lopinavir with ritonavir (LPV/r, Kaletra) because of ease of administration and high potency. Three randomized studies comparing LPV/r with standard triple HAART in patients as maintenance therapy found no significant difference in the two treatment arms [11–13]. A fourth study comparing LPV/r with standard triple HAART in naive patients, found LPV/r monotherapy to be inferior to standard triple HAART [14]. All four studies found an increase in low level viral rebound during treatment but the significance of this finding is unknown.

PI don't penetrate well into the central nervous system or the genital tract [15], raising concerns about the local selection for drug resistance, with eventual re-entry into the circulation of resistant virus [16]. In our first monotherapy study we deliberately selected IDV/r for its lower protein binding, and therefore superior compartment penetration [7]. The limitation of that treatment was the frequency of renal and dermatological side effects. When this study was terminated, fosamprenavir was not available to us. We therefore selected ritonavir-boosted atazanavir (ATV/r) as a continuation of our monotherapy-study based on the relatively low level of protein binding of this drug. The purpose of this study was to test the feasibility of ATV/r mono-maintenance and its effect on HIV RNA levels in the spinal fluid and seminal plasma.

Materials and methods

Study design

Patients having followed a conventional HAART for at least 6 months (stable HAART during last 3 months), or patients who previously participated in the IDV/r monotherapy study [8] were eligible for the study.

At baseline, all combination therapies or IDV/r monotherapy were stopped and only ritonavir boosted atazanavir (300 mg/100 mg q.d.) was administered for up to 24 weeks. Patients were supplied with study medications and instructed to always take their drug at the same time, together with a meal. Based on drug monitoring at week 4, ATV/r dosage was adjusted to 400 mg/100 mg. In order to evaluate viral replication and drug penetration into cerebrospinal fluid (CSF) and genital compartment, patients were asked to provide a CSF sample at week 24 and a semen sample at baseline and at week 24. This additional sampling was not mandatory for the participation in this pilot study. In addition, patients entering the study from IDV/r monotherapy were also asked to provide an additional CSF sample at baseline. Drug concentration in CSF was evaluated based on ATV drug monitoring and comparison between CSF and plasma. Primary study endpoint was defined as two consecutive HIV RNA values >400 copies/ml, three consecutive HIV HIV RNA values >200 copies/ml, or four consecutive HIV RNA values >100 copies/ml. The additional endpoints (200 or 100 copies/ml) were planned to avoid continued monotherapy in patients with prolonged phases of low-level replication. Any patient reaching a pre-defined study endpoint was switched back to HAART. Local ethical committees approved the study. Written informed consent was obtained from all patients.

Patients

Patients were recruited and followed at the Department of Infectious Diseases at the Cantonal Hospital in St Gallen or the University Hospital in Geneva, Switzerland. Only patients with suppressed viral loads during the last 3 months prior to study initiation were included (two recent RNA measurements and screening RNA <50 copies/ml). Major exclusion criteria were any history of treatment failure. Patients with lipid lowering drugs during the last 28 days prior to study start, or concomitant intake of medications likely to influence ATV pharmacokinetics were excluded. Additional

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

exclusion criteria were active opportunistic infections, insulin dependent diabetes, ECG abnormalities or presence of cardiovascular disease, serum alanine aminotransferase (ALT) (or aspartate aminotransferase, AST) $> 5 \times$ upper limit of normal (ULN), serum bilirubin $> 2 \times$ ULN, serum creatinine $> 1.5 \times$ ULN. A negative pregnancy test was required for female participants.

Follow-up

Upon screening, patients were included at baseline and followed every 4 weeks until study termination at week 24. Each follow-up visit included HIV RNA determination, CD4/CD8 cells (total, %), haematology, blood chemistry, and lactate assessments. At week 4, therapeutic drug monitoring (TDM) was performed, and drug dose adjustments were carried out if necessary. Fasting cholesterol [total, triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL)] and urine parameters were determined at baseline, week 8, 16, and 24. A glucose tolerance test was carried out at baseline and at week 24.

In one centre, CD8 activation markers were measured in all patients at week 0, 4, 8 (12) and 24 and blood from these four time points was analysed batchwise to detect C-reactive protein (CRP; highly sensitive method) as a surrogate for altered immune-activation during monotherapy.

Analytical methods

CSF samples were collected in portions (4×2 ml), with plasma collected at the same time. Semen samples were collected at the beginning and at the end of the study. Seminal plasma and CSF samples were kept frozen at -70°C until analysis. HIV-1 RNA was quantified in cell-free plasma, CSF, and semen using ultra sensitive PCR with a detection limit of 50 copies/ml (Amplicor, Roche Diagnostics, Rotkreuz, Switzerland). ATV concentration in plasma was determined by HPLC with UV-photodiode array detection at 201 nm using a validated method [17,18]. The LC-MS/MS method was calibrated using matrix-matched samples prepared in artificial CSF (glucose 0.8 g/l, albumin 0.2 g/l, NaCl 7.3 g/l, KCl 0.3 g/l, $NaHCO_3$ 1.9 g/l, (pH adjusted to 7.5 with $NaHPO_4$ buffer), as previously reported [19]. The lower limit of quantification of ATV by LC-MS/MS is 0.2 ng/ml. Blood and CSF were collected at median 12 (2–26) h after the last intake of ATV/r. Lumbar puncture was timed within 30 min of concurrent blood sampling. Genotypic resistance tests (ViroSeq, Abbott Diagnostocs, Rotkreuz, Switzerland) were performed if HIV RNA was > 400 copies/ml.

Statistical analysis

Comparison of outcome variables between baseline and week 24 was performed using paired sample t test. For non-parametric data the Wilcoxon's signed rank test was used.

Results

Thirty patients were included in the study (nine patients had previously been treated by IDV/r monotherapy). Baseline characteristics are shown in Table 1.

According to endpoint criteria two (7%) patients failed the ATV/r monotherapy (two consecutive HIV RNA > 400 copies/ml). One patient failed at week 8, but was subsequently identified as a protocol violator having previously failed IDV based HAART. The second patient deliberately decided to stop treatment after week 20. One patient had persistant low-level replication above

Table 1. Patient baseline characteristics.

Characteristic	Value
Male [n (%)]	26 (87)
Age (years) [mean ± SD)]	44 ± 6.6
Weight (kg) [mean ± SD]	72.9 ± 10.9
Transmission mode [n (%)]	
Heterosexual	3 female/6 male (30)
Men who have sex with men	14 (47)
Injecting drug user	1 female/6 male (23)
CDC classifications (n)	
CDC A–A3	17
CDC B2–B3	7
CDC C3	6
Prior HIV therapy (n)	
1 PI (IDV/r monotherapy)	9
Trizivir	6
Efavirenz	10
1 PI/r + 2 NRTI	5
Duration of Previous HAART (months) (mean ± SD)	61 ± 33.2
CD4 cell count (cells/μl) (mean ± SD)	618 ± 347
CD4% (mean ± SD)	30 ± 9.2
CD8 cell count (cells/μl) (mean ± SD)[a]	980 ± 675
CD8% (mean ± SD)[a]	43 ± 12
CD8/CD38% (mean ± SD) (n = 20)[a]	8.3 ± 8.0
Lipid profile (mmol/l) (mean ± SD)	
Cholesterol	6.2 ± 1.4
LDL-cholesterol	3.8 ± 1.2
HDL-cholesterol	1.2 ± 0.4
Triglycerides [median (range)]	1.6 (0.6–16.1)
Glucose profile (mmol/l)	
Patients with fasting glucose > 7 (n)	None
Patients with fasting glucose > 5 (n)	13
Fasting glucose at baseline (mean ± SD)	5.0 ± 0.8
Change in glucose upon challenge (mean ± SD)	0.2 ± 1.5
C-peptide (pmol/l) [median (range)]	699 (4–1699)
Lactate (mmol/l) [median (range)]	1.4 (0.6–3.2)
Haemoglobin (g/l) (mean ± SD)	149 ± 12
Leukocytes ($\times 10^9$/ml) (mean ± SD)	6.2 ± 1.7
Thrombocytes ($\times 10^9$/l) [median (range)]	217 (119–386)
ALT (U/l) [median (range)]	24 (9–127)
AST (U/l) [median (range)]	25 (13–101)
Bilirubin (μmol/l) [mean ± SD]	21 ± 19.6
Creatinine (μmol/l) [mean (range)]	78 (13.4)
hsCRP (mg/l) [median (range)][a]	1.2 (0.2–25.8)

[a]Indicators of altered immune activation (CD8+ CD38+; and hsCR: highly sensitive C-reactive protein), were only determined at one site (n = 20). PI, Protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; LDL, low density lipoprotein; HDL, high density lipoprotein; ALT, alanine aminotransferase; AST, aminotransferase; hsCRP, highly sensitive C-reactive protein.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

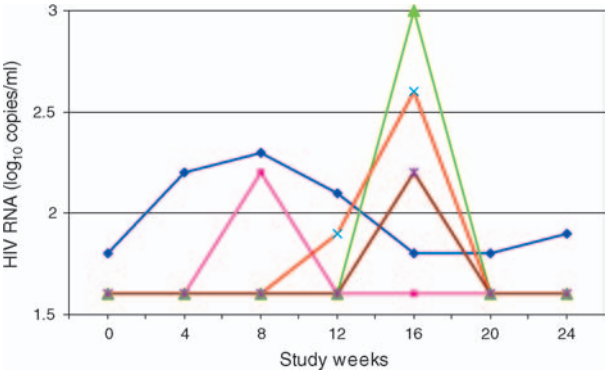

Fig. 1. Sequence of HIV-RNA in five patients with occasional copy numbers > 50 (1.7 $\log_{10}$)copies/ml. Five patients suppressed at week 24, experienced occasional increase in HIV RNA > 50 copies/ml during the study. Of those, four had a single viral load measurement > 50 copies/ml, with only two having single blips > 200 copies/ml. The blue line represents one patient with poor adherence and who had < 50 copies/ml at screening but 1.8 $\log_{10}$ copies/ml at baseline. HIV-RNA values remained at low level during the study, and the patient was switched to HAART after the study.

50 copies/ml but never reached the failure criteria (Fig. 1). All other patients (n = 27; 90%) were virologically suppressed in plasma at week 24 (HIV RNA < 50 copies/ml). Excluding the two failing patients, short term viral blips greater than 10^2 copies/ml were found in five patients (18%, Fig. 1). Among those, four had a single viral load measurement > 50 copies/ml with only two patients (7%) having a single blip > 200 copies/ml. One patient who admitted poor adherence had a viral load < 50 copies/ml at screening but 1.8 $\log_{10}$ at baseline. HIV RNA values remained at low levels during the study, and the patient was switched to an efavirenz based HAART after the study was terminated.

At week 24, spinal fluid was obtained from 20 patients with fully suppressed HIV RNA. Three patients (15%) had elevated viral loads in CSF (HIV RNA in CSF: 2.8, 2.2, 3.8 $\log_{10}$ copies/ml) despite viral suppression in plasma (< 50 copies/ml). Resistance testing on CSF-RNA failed in the patient with the low viral load (2.2 $\log_{10}$ copies/ml) and showed wild type in the two other patients. The two patients with HIV RNA > 400 copies/ml in CSF were switched to conventional HAART. The high CSF-RNA (3.8 $\log_{10}$ copies/ml) was reconfirmed (3.2 $\log_{10}$ copies/ml) upon retesting. The patient with the lowest CSF viral load (2.2 $\log_{10}$) decided to remain on ATV/r monotherapy, and CSF viral load was 1.9 $\log_{10}$ upon retesting after 1 year.

For those patients switching from IDV/r monotherapy (n = 9), five provided a CSF sample at the beginning of the study; two refused an additional lumbar puncture at week 24. The analysis was done batch-wise when all these patients reached week 24. The patient with the highest CSF viral load at week 24 was subsequently found to have detectable HIV RNA in CSF at baseline (3.2 $\log_{10}$ copies/ml) prior to starting ATV/r monotherapy. A second IDV/r patient was found to have detectable HIV RNA in CSF (2.7 $\log_{10}$ copies/ml) at baseline. Resistance testing on CSF-RNA showed wild type virus. As the patient refused an additional lumbar puncture at week 24, he was switched back to conventional HAART.

A total of 22 (85%) men provided at least one semen sample for virological determination (18 at baseline, 15 at week 24). Eleven men gave a semen sample both at baseline and at week 24. At week 24, despite viral suppression in plasma, two (13%) men had semen samples with HIV RNA values > 10^2 copies/ml (HIV RNA in semen: 2.23, 2.24 $\log_{10}$ copies/ml). Of the two patients with HIV RNA above 10^2 copies/ml at week 24, one patient already had detectable HIV RNA at baseline (2.05 $\log_{10}$ copies/ml).

A drug comparison between plasma and CSF was available in 22 patients. ATV concentration in plasma and CSF was significantly different, with a median drug concentration in plasma of 1250 ng/ml (range, 205–3555 ng/ml) compared to 8.3 ng/mL (range, 0.6–40 ng/ml) in CSF ($P < 0.001$). Mean ratio of CSF/plasma drug concentration was 0.9% (± 0.8, range, 0.1–2.7%). These levels were similar to other published results and slightly above the EC_{50} (1 ng/ml) for wild type virus [20].

CD8 activation markers were measured in 20 patients with no significant change detected between baseline and week 24. Still, there seemed to be a tendency towards a slight decrease in percent-activated cells between baseline (8.4 ± 8.3%) and week 24 (4.8 ± 7.0%), but these differences were not statistically significant. At week 4, percent-activated cells were comparable to baseline (9.0 ± 10.7%). The same was true for CRP, used as an additional indicator of altered immune activation, with no changes between baseline and week 24. Even though not significant, CD4 cells showed an increase during 24 weeks of PI-monotherapy by a mean of 15 cells/μl. Table 2 presents mean changes in metabolic parameters between baseline and week 24. The protocol violator who failed at week 8 is excluded from the comparison.

Even though LDL-cholesterol was high at baseline (mean, 3.8 ± 1.2 mmol/l), with borderline cholesterol (mean, 6.2 ± 1.4 mmol/l) and TG values (median, 1.6 mmol/l; range, 0.6–16 mmol/l), lipid profile had not changed significantly by the end of the study. Still, an indication towards an improvement in lipid profile was suggested. Response to glucose challenge was comparable between baseline and week 24, with no increase in percentage of patients having a fasting glucose levels above 5 or 7 mmol/l. As expected, bilirubin levels increased

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Table 2. Changes in metabolic parameters between baseline and week 24.

Metabolic parameter	Mean (±) change from baseline
Weight (kg)	2.1 ± 2.6
CD4 cell count (cells/μl)	15.0 ± 222
CD4%	1.6 ± 7.4
CD8 cell count (cells/μl)	−52.5 ± 472.8
CD8%	3.1 ± 16.8
CD8/CD38% (n = 21)	−3.4 ± 8.3
Lipid profile (mmol/l)	
Cholesterol	−0.3 ± 1.4
LDL-cholesterol	−0.2 ± 0.8
HDL-cholesterol	0.1 ± 0.3
Triglycerides	−0.7 ± 4.1
Glucose profile (mmol/l) (n = 27)	
Patients with fasting glucose > 7 at week 24	No change
Patients with fasting glucose > 5 at week 24	+ 1 patient
Change in plasma glucose upon glucose challenge	−0.6 ± 0.3
C-peptide (pmol/l)	107 ± 471
Lactate (mmol/l)	0.1 ± 0.5
Haemoglobin (g/l)	−0.5 ± 8.8
Leucocytes ($\times 10^9$/ml)	−0.2 ± 1.6
Thrombocytes ($\times 10^9$/l)	−15.4 ± 37.0
ALT (U/l)	16.4 ± 75.7
AST (U/l)	1.5 ± 29.0
Bilirubin (μmol/l)	52.4 ± 74.9*
Creatinine (μmol/l)	0.1 ± 6.4
hsCRP (mg/l)	0.8 ± 5.6

Except for the one failing patient stopping ritonavir-boosted atazanavir monotherapy at week 8, all patients (n = 29) are included in the comparison. Statistical significance is set at $P < 0.05$. LDL, low density lipoprotein; HDL, high density lipoprotein; ALT, alanine aminotransferase; AST, aminotransferase; hsCRP, highly sensitive C-reactive protein.
*$P < 0.001$.

significantly between baseline and week 24, from a mean of 21.0 ± 19.3 μmol/l to a mean of 73.7 ± 74.2 μmol/l. All other parameters were comparable between baseline and week 24 (Table 2).

Upon study completion, patients had the option to remain on ATV/r monotherapy. Of the two study failures (plasma HIV RNA $> 10^2$ copies/ml), the protocol violator switched back to conventional HAART and the non-compliant patient remained off drugs. Of the two patients with elevated CSF one switched to HAART, while one patient stayed on PI monotherapy. Some time after study completion, an additional three patients were switched back to HAART (one hyperbilirubinemia, two adherence failures).

Thus, 23 patients (77%) originally recruited for the PI monotherapy studies (IDV/r and ATV/r), continue this treatment regimen. For the seven patients originally recruited for the IDV/r trial, mean current PI monotherapy treatment duration amounts to 56.0 ± 1.7 months. The median duration of follow-up of all patients who remained on monotherapy (n = 23; IDV/r and ATV/r) is 27.1 (range, 13.6–57.4) months. Fig. 2 summarizes all longitudinal data in ATV/r monotherapy patients.

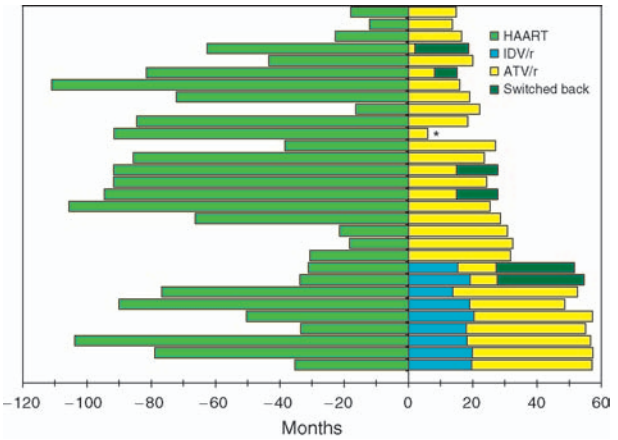

Fig. 2. Duration of PI monotherapy in study patients. Of the 30 patients originally recruited for the PI monotherapy studies (IDV/r and ATV/r) 23 (77%) patients currently still follow the ATV/r treatment regimen. For the seven patients originally recruited for the IDV/r trial, mean current PI monotherapy treatment duration amounts to 56.0 ± 1.7 months. The median duration of follow-up in patients remaining on PI monotherapy (n = 23; IDV/r and ATV/r) is 27.1 (range, 13.6–57.4) months. *The one failing patient stopping monotherapy treatment after week 20, did not whish to restart HAART but preferred to remain off therapy.

Discussion

To our knowledge, this is the first study evaluating the effect of PI monotherapy in the central nervous system and seminal plasma. Given the open non-comparative design of this study, we cannot compare the overall treatment results with standard HAART. However, similar to most other recently presented studies of PI-monotherapy, we found few treatment failures in the 30 patients observed during 24 months. In fact, only two patients (7%) had a treatment failure according to our failure criteria. One patient decided to stop treatment after week 20 for reasons not related to the study. The second patient failed treatment at week 8. Subsequent evaluation of his previous treatment history revealed that the patient had previously failed on a PI-based HAART (IDV), he should therefore be considered a protocol violator. Thus, all 28 patients who fulfilled the entry criteria and who remained on the assigned treatment maintained their HIV RNA level below 50 copies/ml.

These results confirm the results of other short-term studies of the effect of PI-monotherapy in the blood. Most other monotherapy studies have been conducted on

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

LPV/r and a recently published, non-comparative ACTG pilot study demonstrated similar results in 30 patients treated with ATV/r for 24 weeks [21].

While these studies indicate a potential value of monotherapies for HIV-maintenance therapy, no definitive conclusions can be drawn due to the limited power of all of them. Cameron [11] demonstrated an increased frequency of short-term, low-level viraemia ('viral blips') in patients on monotherapy compared with the comparison arm on continued HAART. While increased viral blips might indicate reduced antiviral potency of monotherapy, it could also be a result of differences in adherence or laboratory errors.

In our previous pilot study we did not find a higher frequency of viral blips in study patients compared with historical controls on standard HAART [7].

Another method to detect low level replication could be the determination of immune activation. HIV replication itself stimulates the activation of CD8 cells [22,23]. In fact, persistent immune activation *per se* enhances HIV replication, reduces the naive T-cell pool, accelerates depletion of CD4 T cells, and impedes both cellular and humoural immunity [24,25]. Highly sensitive CRP (hsCRP) is a marker for immune activation and is associated with diseases progression in HIV-infection [26]. However, we found no increase in markers of immune activation after initiation of monotherapy, either by measurement of CD8CD38HLADR cells or hsCRP.

The main focus of this study was on the effect of monotherapy in the genital tract and central nervous system. Indeed, our finding of increased HIV RNA in 3/20 patients after 24 weeks on monotherapy must be considered relevant. When the study was designed, no clinical data on ATV drug penetration in the CSF was available. The low drug level found in CSF in this study is supported by a recent presentation [27], where ATV concentrations in CSF ($n = 26$) were found to be highly variable with concentrations 100-fold lower than plasma, even with ritonavir boosting. Observed CSF concentrations were lower than estimated free plasma concentrations (~ 140 ng/ml) and a CSF : plasma ratio of 0.0098 ($n = 24$). In addition, reference values for the CSF : plasma ratio range between 0.0021 and 0.0226 (AIDSinfo, FDA approved drugs/Reyataz).

The authors hypothesize that an active efflux pump is responsible for the low ATV levels in spinal fluid. Interestingly, two of five individuals on IDV/r monotherapy who consented to a lumbar puncture at ATV/r baseline also had increased HIV RNA levels. Such high levels of HIV RNA are rarely reported in patients under HAART but the data on HIV RNA levels in CSF under HAART is limited. Hull [28] presented a case report of a patient who had fully suppressed HIV RNA in blood and who developed HIV encephalopathy. He was subsequently found to have detectable levels of HIV RNA in CSF despite fully suppressed HIV RNA in blood over several years. The HIV RNA level in CSF in that case was in the range of our two patients with high RNA levels in CSF. We would therefore caution against the uncontrolled administration of PI-based monotherapies until complete suppression of viral load in the central nervous system is documented.

Compartmentalized HIV RNA replication in the genital tract could also be a source of concern. In addition to the risk of development of resistance, it could increase the risk of HIV transmission from treated individuals. The relatively low level of HIV RNA in semen of two men (among 15 who gave a semen sample at week 24) is reassuring but further studies should investigate a potential compartment effect in semen before monotherapies can be implemented outside of clinical studies.

Conclusion

In conclusion, our study supports previous studies indicating the potential use of PI-based monotherapies for simplified long-term maintenance treatment. The long-term observation of our group of patients on monotherapy is reassuring. PI-based monotherapy might be a topic of interest for some selected patients. However, our results on the effect of monotherapy in CSF cautions against the uncontrolled use of such monotherapies. In addition, long-term efficacy of monotherapies remains to be shown. We suggest that future monotherapy studies should include an evaluation of compartment effects, at least in a subset of patients.

Acknowledgement

The members of the Swiss HIV Cohort Study are: M. Battegay, E. Bernasconi, J. Böni, H. Bucher, Ph. Bürgisser, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, P. Erb, M. Fischer, M. Flepp, A. Fontana, P. Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, CH-1011- Lausanne), H. Furrer (Chairman of the Clinical and Laboratory Committee), M. Gorgievski, H. Günthard, H. Hirsch, B. Hirschel, I. Hösli, Ch. Kahlert, L. Kaiser, U. Karrer, C. Kind, Th. Klimkait, B. Ledergerber, G. Martinetti, B. Martinez, N. Müller, D. Nadal, M. Opravil, F. Paccaud, G. Pantaleo, M. Rickenbach (Head of Data Center), C. Rudin (Chairman of the Mother & Child Substudy), P. Schmid, D. Schultze, J. Schüpbach, R. Speck, P. Taffé, P. Tarr, A. Telenti, A. Trkola, P. Vernazza (Chairman of the Scientific Board), R. Weber, S. Yerly.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Sponsorship: This study was financed in the spframework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation.

References

1. Umeh OC, Currier JS. **Lipids, metabolic syndrome, and risk factors for future cardiovascular disease among HIV-infected patients.** *Curr HIV/AIDS Rep* 2005; **2**:132–139.
2. Fagard C, Oxenius A, Gunthard H, Garcia F, Le Braz M, Mestre G, *et al*. **A prospective trial of structured treatment interruptions in human immunodeficiency virus infection.** *Arch Intern Med* 2003; **163**:1220–1226.
3. Dybul M, Nies-Kraske E, Dewar R, Maldarelli F, Hallahan CW, Daucher M, *et al*. **A proof-of-concept study of short-cycle intermittent antiretroviral therapy with a once-daily regimen of didanosine, lamivudine, and efavirenz for the treatment of chronic HIV infection.** *J Infect Dis* 2004; **189**: 1974–1982.
4. Ananworanich J, Nuesch R, Le Braz M, Chetchotisakd P, Vibhagool A, Wicharuk S, *et al*. **Failures of 1 week on, 1 week off antiretroviral therapies in a randomized trial.** *AIDS* 2003; **17**:F33–F37.
5. Ananworanich J, Gayet-Ageron A, Le Braz M, Prasithsirikul W, Chetchotisakd P, Kiertiburanakul S, *et al*. **CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: results of the Staccato randomised trial.** *Lancet* 2006; **368**:459–465.
6. El Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, *et al*. **CD4+ count-guided interruption of antiretroviral treatment.** *N Engl J Med* 2006; **355**:2283–2296.
7. Shikuma CM, Hu N, Milne C, Yost F, Waslien C, Shimizu S, *et al*. **Mitochondrial DNA decrease in subcutaneous adipose tissue of HIV-infected individuals with peripheral lipoatrophy.** *AIDS* 2001; **15**:1801–1809.
8. Kahlert C, Hupfer M, Wagels T, Bueche D, Fierz W, Walker UA, *et al*. **Ritonavir boosted indinavir treatment as a simplified maintenance 'mono'-therapy for HIV infection.** *AIDS* 2004; **18**:955–957.
9. Arribas JR, Pulido F, Delgado R, Lorenzo A, Miralles P, Arranz A, *et al*. **Lopinavir/ritonavir as single-drug therapy for maintenance of HIV-1 viral suppression: 48-week results of a randomized, controlled, open-label, proof-of-concept pilot clinical trial (OK Study).** *J Acquir Immune Defic Syndr* 2005; **40**:280–287.
10. Campo RE, Lalanne R, Tanner TJ, Jayaweera DT, Rodriguez AE, Fontaine L, *et al*. **Lopinavir/ritonavir maintenance monotherapy after successful viral suppression with standard highly active antiretroviral therapy in HIV-1-infected patients.** *AIDS* 2005; **19**:447–449.
11. Arribas JM, Pulido F, Delgado R, Cabrero E, Cepeda CS, Gonzalez-Garcia G, *et al*. **Lopinavir/ritonavir as single-drug maintenance therapy in patients with HIV-1 viral suppression: forty eight week results of a randomized, controlled, open label, clinical trial (OK04 study)**. *XVI International Conference on AIDS*. Toronto, August 2006 [abstract THLB0203].
12. Cameron W, da Silva B, Arribas JM, Myers R, Bellos N, Gilmore N, *et al*. **A two-year randomized controlled clinical trial in antiretroviral-naive subjects using agent lopinavir/ritonavir (LPV/r) monotherapy after initial induction treatment compared to an efavirenz (EFV) 3-drug regimen (Study M03-613)**. *XVI International Conference on AIDS*. Toronto, August 2006 [abstract THLB0201].
13. Nunes EP. **48-weeks efficacy and safety results of simplification to single agent lopinavir/ritonavir (LPV/r) regimen in patients suppressed below 80 copies/mL on HAART – the KalMo Study**. *XVI International Conference on AIDS*. Toronto, August 2006 [abstract TUAB0103].
14. Delfraissy JF, Flandre P, Delaugerre C, Horban A, Girard PM, Rouzioux C, *et al*. **MONARK Trial (MONotherapy AntiRetroviral Kaletra): 48-weeks analysis of lopinavir/ritonavir (LPV/r) monotherapy compared to LPV/r + zidovudine/lamivudine (AZT/3TC) in antiretroviral-naive patients**. *XVI International Conference on AIDS*. Toronto, August 2006 [abstract THLB0202].
15. Vernazza PL, Eron JJ, Fiscus SA, Cohen MS. **Sexual transmission of HIV: infectiousness and prevention.** *AIDS* 1999; **13**:155–166.
16. Kepler TB, Perelson AS. **Drug concentration heterogeneity facilitates the evolution of drug resistance.** *Proc Natl Acad Sci USA* 1998; **95**:11514–11519.
17. Colombo S, Beguin A, Telenti A, Biollaz J, Buclin T, Rochat B, *et al*. **Intracellular measurements of anti-HIV drugs indinavir, amprenavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, efavirenz and nevirapine in peripheral blood mononuclear cells by liquid chromatography coupled to tandem mass spectrometry.** *J Chromatogr B Analyt Technol Biomed Life Sci* 2005; **819**:259–276.
18. Colombo S, Guignard N, Marzolini C, Telenti A, Biollaz J, Decosterd LA. **Determination of the new HIV-protease inhibitor atazanavir by liquid chromatography after solid-phase extraction.** *J Chromatogr B Analyt Technol Biomed Life Sci* 2004; **810**:25–34.
19. Ostermann S, Csajka C, Buclin T, Leyvraz S, Lejeune F, Decosterd LA, *et al*. **Plasma and cerebrospinal fluid population pharmacokinetics of temozolomide in malignant glioma patients.** *Clin Cancer Res* 2004; **10**:3728–3736.
20. Busti AJ, Hall RG, Margolis DM. **Atazanavir for the treatment of human immunodeficiency virus infection.** *Pharmacotherapy* 2004; **24**:1732–1747.
21. Swindells S, DiRienzo AG, Wilkin T, Fletcher CV, Margolis DM, Thal GD, *et al*. **Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression.** *JAMA* 2006; **296**:806–814.
22. Kestens L, Vanham G, Gigase P, Young G, Hannet I, Vanlangendonck F, *et al*. **Expression of activation antigens, HLA-DR and CD38, on CD8 lymphocytes during HIV-1 infection.** *AIDS* 1992; **6**:793–797.
23. Bouscarat F, LevacherClergeot M, Dazza MC, Strauss KW, Girard PM, Ruggeri C, *et al*. **Correlation of CD8 lymphocyte activation with cellular viremia and plasma HIV RNA levels in asymptomatic patients infected by human immunodeficiency virus type 1.** *AIDS Res Hum Retroviruses* 1996; **12**:17–24.
24. Douek DC. **Disrupting T-cell homeostasis: how HIV-1 infection causes disease.** *AIDS Rev* 2003; **5**:172–177.
25. Hazenberg MD, Otto SA, Hamann D, Roos MT, Schuitemaker H, de Boer RJ, *et al*. **Depletion of naive CD4 T cells by CXCR4-using HIV-1 variants occurs mainly through increased T-cell death and activation.** *AIDS* 2003; **17**:1419–1424.
26. Lau B, Sharrett AR, Kingsley LA, Post W, Palella FJ, Visscher B, *et al*. **C-reactive protein is a marker for human immunodeficiency virus disease progression.** *Arch Intern Med* 2006; **166**:64–70.
27. Best B. **Low atazanavir concentrations in cerebrospinal fluid**. *Thirteenth Conference on Retroviruses and Opportunistic Infections*. Denver, CO, February 2006 [abstract 576].
28. Hull M, Johnston D, Sherlock C. **Evidence of neurological deterioration due to compartmentalized HIV-1 with discordant viral load and resistance evolution in cerebrospinal fluid in a treatment-expreienced patient with undetectable plasma viral load: a case report**. *XVI International Conference on AIDS*. Toronto, August 2006 [abstract THPE0071].

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.