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# EFAVIRENZ-THERAPY IN HIV-PATIENTS WITH UNDERLYING LIVER DISEASE: IMPORTANCE OF CONTINUOUS TDM OF EFV

A. Katsounas[1], A. Frank[2], H. Klinker[3], P. Langmann[4]

[1]Division of Gastroenterology, University of Essen, Germany
[2]Institute of Virology, University of Essen, Germany
[3]Division of Infectious Diseases, University of Wuerzburg, Germany
[4]Private Praxis, Karlstadt, Germany

**Abstract**
*Objective:* Many HIV-patients have a chonic liver disease due to HBV-/HCV-coinfections and/or consume of alcohol. In these patients therapy with EFV is often problematic because of NNRTI associated liver toxicity. Measurement of EFV plasmalevels and dose adjustment using TDM should be evaluated in this study.
*Methods:* EFV-plasmasamples were standardized drawn 12h after ingestion. Measurement of 576 EFV plasmalevels was performed by HPLC. EFV plasmalevels as well as ALT-, AST- and GGT-values of 64 patients treated with EFV (5206 weeks) were measured regularly. 16 patients had a HCV-coinfection, 3 had a HBV-coinfection and 5 had an concomitant alcoholic liver disease. Maximal changes of ALT-, AST- and GGT-values (ΔALT, ΔAST, ΔGGT), CD4-/CD8 cells and HIV-RNA were registered during therapy. Dose adjustment was performed for EFV plasmalevels out of target range 1000-4000 ng/ml
*Results:* EFV plasmalevels of 40 HIV-patients (2288 ± 1199 ng/ml) showed no significant differences compared to plasmalevels of HIV/HCV-patients (2391 ± 976ng/ml) or to plasmalevels of HIV/HBV-patients (1913 ± 288ng/ml) or to those of HIV-patients with alcoholic liver disease (1702 ± 506ng/ml). In 24 HIV-patients with underlying liver disease median ΔGGT was +25 IU/l, median ΔALT was +13 IU/l and median ΔAST was +8 IU/l. Dose adjustment was performed in 1 patient during study period. Increasing rates of ALT-, AST- and GGT-values showed no significant differences between liver healthy HIV-patients and those with a liver disease. 44 patients with continous EFV plasmalevels in target range reached a viral suppression <100 c/ml during therapy.
*Conclusions:* EFV-plasmalevels of HIV-infected patients showed no significant differences compared to EFV-plasmalevels of coinfected patients with concomitant liver disease. In those patients ΔALT, ΔAST and ΔGGT were not significantly different than in liver-healthy HIV-patients with normal EFV-plasmaconcentrations. EFV plasmalevels in target range of 1000-4000 ng/ml correlate to a good viral response. One patient after dose adjustment was able to continue therapy. Using TDM EFV therapy in patients with underlying liver disease is save.

*Key words:* efavirenz, therapeutic drug monitoring [TDM], HPLC, NNRTI plasmalevels, hepatotoxicity

## INTRODUCTION

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) recommended as first line drug in antiretroviral therapy of HIV-patients [1, 2, 3, 4]. Longterm efficacy was shown comparable to boosted protease- inhibitor based regimen in multiple clinical studies [4, 5]. Beside CNS adverse events liver toxicity is associated with EFV. Several clinical studies with EFV observed elevations of GGT levels [6] due to EFV induced liver enzyme activity as well as a sign of EFV induced liver toxicity [7, 8, 9, 10].

EFV is associated with intrinsic (dose dependent) liver toxicity reactions as well as idiosyncratic (dose independent) toxicities attributable to pharmacogenetic differences. Measurement of EFV plasmalevels and dose adjustment using therapeutic drug monitoring (TDM) should be evaluated in this study for HIV-patients with significant risk factors (like alcoholic liver disease, coinfections with Hepatitis B and C) for emerging EFV associated liver toxicity [7, 10, 13].

## MATERIALS AND METHODS

64 HIV-patients (13 without any-, 27 with one-, 11 with two-, 10 with three- an 3 with four former therapeutic courses) were recruited at the outpatient clinic at the University Hospital of Wuerzburg, Germany for four years.. The median age of these patients amounted 39,5 years. 46 patients were males and 18 were females. Median body weight was 68 kg.

All patients were treated for at least 3 weeks with EFV 600mg once daily in combination with other antiretroviral agents. The combination with EFV consisted in all 64 patients in 2 NRTI and additional in 16 patients in amprenavir plus ritonavir (3 patients) or indinavir plus ritonavir (2 patients) or indinavir alone (1 patient) or saquinavir plus nelfinavir (3 patients) or saquinavir plus ritonavir (2 patients) or ritonavir alone (2 patients) or lopinavir (3 patients).

Measurement of 576 EFV plasmalevels was performed by high performance liquid chromatography (HPLC) as described elsewere [14, 15]. Plasmasamples for the determination of EFV- and PI levels were performed before oral intake of morning dose. This procedure, conducted already in former studies, results in

8 – 20 h post-dosing EFV plasmalevels and PI trough levels. Blood samples were collected, centrifugated and stored at -20 °C until analysis [14, 16].

ALT-, AST- and GGT- values of 64 patients treated with EFV (5206 EFV-weeks) were measured regularly. Continuos TDM of EFV plasmalevels was performed monthly over maximal 188 Weeks. 16 patients had a HCV-coinfection, 3 patients had a HBV-coinfection and 5 patients had an alcohol associated liver disease. Maximal changes of ALT-, AST- and GGT-values (ΔALT, ΔAST, ΔGGT), number of CD4- and CD8-positive cells and quantitative HIV-RNA levels were analyzed every three months during therapy. Plasmalevels of EFV between 1000 and 4000 ng/ml were assumed to be in the attempeted therapeutic range [16] and dose adjustment was performed if EFV plasmalevel was out of the target range of 1000-4000 ng/ml. PI trough levels were assumed to be in optimal therapeutic range if the plasma concentration was above the lower 95% interval of confidence of the mean of all samples measured at therapeutic drug monitoring unit in our institute [17]. The assumed therapeutic levels of the various PIs were the folowing: amprenavir (APV) 750 ng/ml, indinavir (IDV) 1.000 ng/ml, nelfinavir (NLF) 1.000 ng/ml, saquinavir (SQV) 750 ng/ml, and ritonavir (RTV) 3.500 ng/ml. [17]

## RESULTS

64 patients were recruited for this study. 24 patients suffered from chronic liver disease. During application of an EFV containing therapy over a median observation time of 70,5 weeks [min.-max.: 3-192 weeks], 79,5% of all samples were measured in the target range of 1000 - 4000 ng/ml, 9,25% of all samples amounted over 4000 ng/ml, and 11,25% of all samples were below 1000 ng/ml.

EFV plasmalevels (MW ± SD: 2288 ± 1199ng/ml) in HIV-infected patients showed no significant differences compared to EFV plasmalevels (MW ± SD: 2177 ± 790ng/ml) in HIV-patients with underlying liver disease [Table 1]. EFV-plasmalevels in HIV/HCV-coinfected patients (MW ± SD: 2391 ± 976ng/ml) compared to EFV-plasmalevels in HIV/HBV-coinfected patients (MW ± SD: 1913 ± 288ng/ml) and to those in HIV-patients with alcoholic liver disease (MW ± SD: 1702 ± 506 ng/ml) (Fig. 1) are also not significantly different.

Maximal changes of ALT-, AST- and GGT-values (ΔALT, ΔAST, ΔGGT) were measured monthly during therapy.

50 patients had increased GGT-values under ongoing therapy with EFV. Here 31 patients had a ΔGGT below 50 U/l, 15 patients had a ΔGGT between 50 and 100 U/l and 4 patients had a ΔGGT over 100 U/l. 2 of those patients had a chronic liver disease due to HCV-coinfection and alcohol consume. 45 patients had increased ALT levels under ongoing therapy with EFV. Here 43 patients had a ΔGGT below 50 U/l and 2 patients with chronic liver disease had a ΔGGT between 50 and 100 U/l due to a HCV-coinfection. 44 patients had increased AST-values (with only slight inflammatory activity in the liver: ALT>AST) under ongoing therapy with EFV. 42 of those patients had a ΔAST below 50 U/l and 2 patients (one of those with a chronic liver disease due to a HCV-coinfection) had a ΔAST between 50 and 100 U/l.

In 24 HIV-patients with underlying liver disease median ΔGGT was +25 U/l (MW ± SD: 44 ± 190 U/l), median ΔALT was +13 U/l (MW ± SD: (-4) ± 65 U/l) and median ΔAST was +8 U/l (MW ± SD: (-2) ± 64 U/l) over a median time of 83,5 EFV-weeks (MW ± SD: 85 ± 62) [Table 1]. In 40 HIV-patients without liver disease median ΔGGT was +25 U/l (MV ± SD: 44 ± 190 U/l), median ΔALT was +10 U/l (MW ± SD: 5 ± 25 U/l) and median ΔAST was +6 U/l (MW ± SD: 1 ± 29 U/l) over a median time of 67,5 EFV-weeks (MW ± SD: 79 ± 51) [Table 1].

In the individual time course of TDM in patient number 63, high EFV trough plasmaconcetrations [max. 13016 ng/ml] and high RTV plasmalevels [max. 13127 ng/ml] were measured during therapy with AZT, 3TC, RTV: 1,2 mg/d and EFV: 600mg/d. This patient had a chronic liver disease due to a HIV-/HCV-coninfection and suffered from malaise and vomiting within 2 weeks after initiation of EFV/RTV therapy, while acute on chronic elevation of liver enzymes (ALT, AST, GGT, GLDH) and bilirubin values as well as slight decreased function parameters (INR) revealed begining hepatotoxicity. Figures 2a and 2b show the course of daily dose (Fig. 2a) as well as of

*Table 1.* In 64 patients treated with an EFV containing regime: maximal change of GGT, ALT and AST along the median observation time of 67.5 weeks for 40 HIV-monoinfected patients and 83.5 weeks for 24 HIV-patients with underlying liver diseases.

| patients | value | ΔGGT [U/l] | ΔALT [U/l] | ΔAST [U/l] | therapy [weeks] | EFV [ng/ml] |
|---|---|---|---|---|---|---|
| **HIV without liver disease** | **MW ± SD(1)** | 31 ± 104 | 5 ± 25 | 1 ± 29 | 79 ± 51 | 2288 ± 1199 |
| **n = 40** | Median | 25 | 10 | 6 | 67.5 | 1910 |
| **HIV+HBV HIV+HCV HIV+alcohol** | **MW ± SD(1)** | 44 ± 190 | (-4) ± 65 | (-2) ± 64 | 85 ± 62 | 2177 ± 790 |
| **n = 24** | Median | 25 | 13 | 8 | 83.5 | 1948 |

(1)MW ± SD: Mean Value ± Standard Deviation

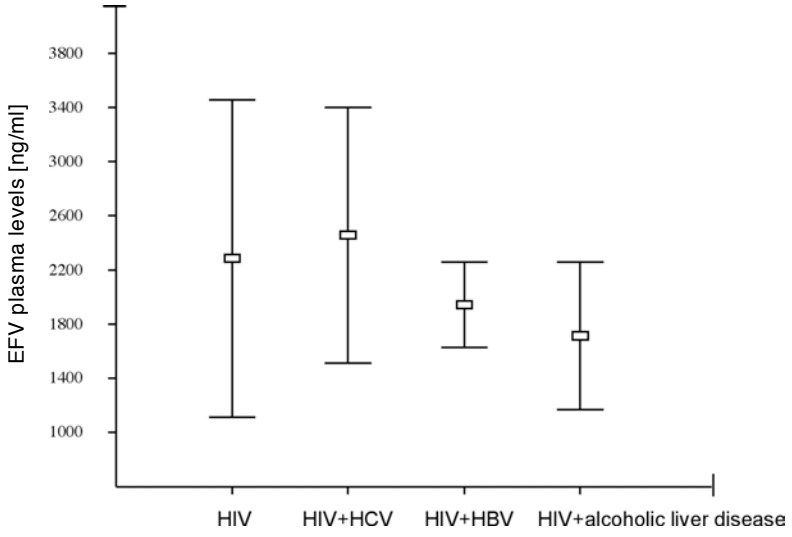


*Fig. 1*. EFV-plasmalevels of liver healthy HIV-patients (2288 ± 1199ng/ml) 1) showed no significant differences compared to EFV-plasmalevels of HIV/HCV-infected patients (2391 ± 976ng/ml) or to EFV-plasmalevels of HIV/HBV-infected patients (1913 ± 288ng/ml) or to those of HIV-patients with underlying alcoholic liver disease (1702 ± 506 ng/ml) (1) MW ± SD: Mean Value ± Standard Deviation

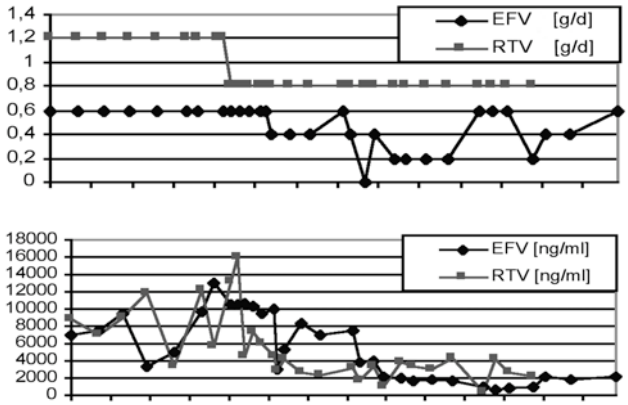


*Fig. 2a and 2b*. Course of efavirenz (EFV) plasmalevels and daily dose and ritonavir (RTV) plasmalevels and daily dose in patient number 63 with a HIV-/HCV-coinfection. Due to high EFV and RTV plasma concentrations a dose reduction of EFV and RTV was performed. After dose adjustment NNRTI and PI plasmalevels were in target range and the patient was able to continue therapy.

plasmalevels (Fig. 2b) of EFV and RTV. Dose reduction of EFV down to 400mg/d (intermediately even down to 200mg/d) and dose reduction of RTV to 800mg/d resulted in a decrease of EFV- and RTV-plasmalevels followed by a reversibel course of liver enzymes (ΔGGT:-323 IU/l, ΔALT: -138 IU/l, ΔAST: -61 IU/l) and liver function parameters. There was an effective viral suppression in the same range as before (HIV-RNA: <100 copies/ml).

44 patients with continuous normal EFV plasmalevels (MV ± SD) 2449 ± 1286 ng/ml had an effective viral suppression (HIV-RNA: <100 copies/ml) during therapy, 9 patients showed only a partial virological response (HIV-RNA: 100-1000 copies/ml) having EFV plasmaconcentrations (MV ± SD) 2201 ± 1172 ng/ml and 11 patients developed a virological failure having EFV plasmalevels (MV ± SD) 1930 ± 964 ng/ml [Table 2] (Fig. 3). 12 of the 44 responding patients had one routinely measured EFV plasma level below 1.000 ng/ml, and 8 of the 11 patients with viral failure had ≥1 (1 - 8) repeated EFV levels below 1.000 ng/ml. Positive likelihood ratios (LPR) for EFV plas-

*Table 2*. Basic characteristics of 64 patients treated with an EFV containing regimen according to their virologic response.

| **Virologic response** (copies/ml) | **Patients (n)** | | | **median duration** (weeks) [MV±SD](1) | **median time** (weeks) **to VL -nadir** | **median CD4** (/µl) [MW ± SD](1) | | **median baseline HIV-RNA** (copies/ml) [MW ± SD](1) |
|---|---|---|---|---|---|---|---|---|
| | **(I)+(II)** | **HIV (I)** | **HIV + liver disease (II)** | | | **baseline** | **end** | |
| < 100 | 44 | (27) | (17) | 94.5 [93.3 ± 58.9] | 12 | 257 [285 ± 247] | 377 [434 ± 297] | 7000 [62.532 ± 132.400] |
| 100 -1000 | 9 | (8) | (1) | 40 [50,5 ± 33,6] | 18 | 323 [320 ± 238] | 373 [370 ± 321] | 3000 [34.563 ± 68.471] |
| > 1000 | 11 | (5) | (6) | 54 [58,6 ± 37,3] | – | 206 [228 ± 190] | 203 [193 ± 134] | 50000 [334.046 ± 887.482] |
| ∑ 64 | (40) | (24) | | | | | | |

(1)MW ± SD: Mean Value ± Standard Deviation

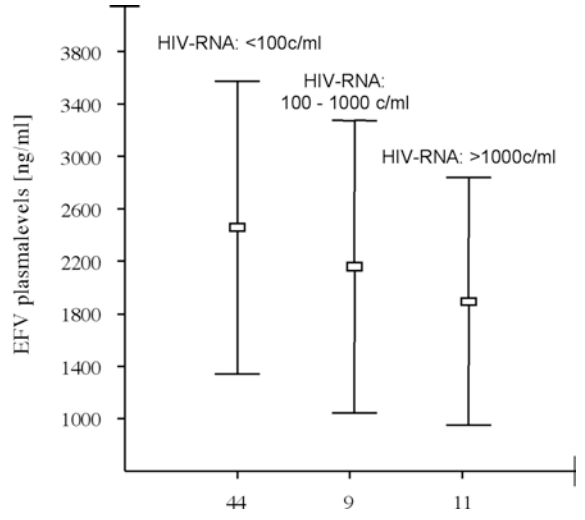


*Fig. 3.* 44 patients with EFV plasmalevels (2449 ± 1286 ng/ml) had a maximal viral suppression (HIV-RNA <100 c/ml). 9 patients had a partial response (HIV-RNA: 100-1000 c/ml) with EFV-plasmalevels (2201 ± 1172 ng/ml). 11 patients had a virological failure with EFV-plasmalevels (1930 ± 964 ng/ml)

malevels below 1.000 ng/ml and virologic failure were calculated as sensitivity/(1 - specifity) results 0.98 (n.s.) [14].

Genotypic resistance testing revealed NNRTI specific mutations in 8 of 11 nonresponders, whereas 6 of these patients had two or more EFV plasmalevel below 1.000 ng/ml. [Table 3]. In particurarly, two mutations (M184V and K103N) occured in all 8 of 11 nonresponding patients with at least one measured EFV plasmalevel below 1.000 ng/ml. Time to viral failure, current ART-combinationstherapy, median EFV plasma concentration, number of samples with an EFV plasmalevel below 1.000 ng/ml during the observation period and subsequent genotypic resistance mutations for 8 patients with virologic failure are described in Table 3. A significant correlation between number of EFV plasmalevels below 1.000 ng/ml and time to viral failure could not be found. Surprisingly, we observed a linear correlation between heights of median EFV plasmavalues and time to viral failure in these 8 nonresponding patients with ≥1 plasmalevel below 1.000 ng/ml.

## Discussion

Continuous TDM showed 79,5% of all EFV plasmalevels beeing in target range. Further results of our investigation showed 12h post dosing no significant differences in EFV plasmalevels between liver healthy HIV-patients and those with chronic liver disease [19]. No significantly differences in increasing rates of ALT-, AST- and GGT-values (median Δ-GGT/GPT/GOT) between liver-healthy HIV-patients and those with underlying liver disease were observed during continuous TDM of EFV-plasmalevels. These results are similar to already published data for HIV-patients with no severe chronic liver disease [7, 10, 13, 21]. Interestingly, none of the patients with maximal increase of

*Table 3.* Number of patients, antiretroviral regimen, number of plasma samples with an EFV level below of 1000 ng/ml, and the pattern of genotypic resistance mutations in 8 patients with virologic failure during combination therapy with EFV.

| Pat.Nr | Time to viral failure [weeks] | ART-Combination | EFV-Median (ng/ml) | number of samples with plasmalevel <100 ng/m (n) | genotypic Resistance (mutation) |
|---|---|---|---|---|---|
| 1 | 62 | AZT/3TC/APV/RTV/EFV | 3317 | 3 | A62V, M184V, **K103N**, **Y188L**, L10I |
| 2 | 33 | D4T/DDI/ABC/EFV | 1634 | 1 | M41L, M184V, L210W, T215Y, A98G, **K103N**, D30N, L63P, V77I, N88D |
| 3 | 21 | AZT/3TC/ EFV | 930 | 4 | M41L, D67N, L210W, T215Y, L10F, L33F, M36I, I54V, L63P, A71V, G73S, M184V, L90M, **K103N**, **Y181C**, I84V |
| 4 | 18 | AZT/3TC/IDV/EFV | 1101 | 1 | **K103N**, M184V, T69SCG, L63P, A71V, G73S, V82A, L90M |
| 5 | 28 | AZT/3TC/ EFV | 1196 | 2 | L63P, L33F, **G190A**, **K103N**, M184V, **Y188L** |
| 6 | 16 | D4T/3TC/ABC/EFV | 724 | 3 | E44D, A98G, **K103N**, V118I, M184V, L210W, T215Y, L63P, A71V, V77I |
| 7 | 54 | AZT/3TC/ EFV | 1476 | 1 | M41L, D67N, K70R, M184V, V118I, L210W, T215Y, K219E, **K103N**, **G190A**, L10I, K20M, M46I, I84V, L90M, E44D |
| 8 | 15 | AZT/3TC/APV/RTV/EFV | 417 | 8 | M36 I, M184 V, **Y188L**, G73S, **K103N**, L90M, V77I |

transaminases (ΔGGT / ΔALT / ΔAST) between 50 and 100 U/l) with or without underlying liver disease developed acute or late onset CNS- or skin-associated adverse effects or liver failure. In generally, GGT is a liver enzyme, which expression and function can be induced by increased metabolic activity in the liver due to hepatic elimination of various drugs, also NNRTIs and PIs [20]. In this context, a slide increase of GGT-values with ALT, AST and liver function parameters (INR, Albumin) in the near normal range is not a sufficient criterium for emerge of hepatic toxicity. Moreover, TDM could help to screen and prevent intrinsic liver toxicity due to EFV. Dose individualization within a range in plasmalevel of 1.000 – 4.000 ng/ml was recommended in a former study [16]. On this background, dose adjustment of EFV and RTV had to be performed in a patient with a HIV-/HCV-coninfection but no severe liver disease - beeing on treatment with AZT+3TC+EFV+RTV - because of high EFV and RTV plasmaconcetrations [max. >13000ng/ml] and increased transaminases. A reduction of EFV and RTV dose resulted in a decrease of EFV and RTV plasmalevels within the target range, followed by a normalisation of transaminases. This patient was able to continue therapy after dose adjustment and to keep obtaining a effective viral suppression (HIV-RNA: <100 copies/ml) [14, 15]. This reveals two major points in practicing safe and effective HAART nowadays: 1) Impaired liver function requires continuous TDM and 2) TDM facilitates dose adjustment and continuation of therapy. Plasmalevels of NNRTI (and PI) correlate not only with adverse events but of course with viral suppression as well [22]. In a former study with highly pretreated patients could be shown, viral efficacy of EFV containing regimen is higher in patients without any single sample below 1.000 ng/ml [23]. In this context, 44 patients (69%) having continous normal EFV-plasma-concentrations had a maximal viral suppression (HIV-RNA <100 copies/ml) during therapy. This outcome is comparable to response rates of large controlled and randomized clinical trials [24]. A significant correlation between number of EFV plasmalevels below 1.000 ng/ml and time to viral failure could not be found, while a linear correlation between heights of median EFV plasmavalues and time to viral failure has been shown in 8 nonresponders with ≥1 plasmalevel below 1.000 ng/ml. In conclusion, virologic failure was seen more often than in patients with one or more EFV level below 1.000 ng/ml, but no statistical significance was reached. In our study, 71% of the HIV-patients with liver disease and 68% of the HIV-patients without liver disease were complete responders. According to these results, no significant influence of liver disease on virological response rates was observed in HIV-patients treated with EFV. In the group of responding patients no significant correlation between EFV plasmalevels and therapy time (EFV-weeks) until reaching maximal viral suppression (VL <100 copies/ml) or between EFV plasmalevels and heights of virologic (ΔVL: copies/ml) or immunologic (ΔCD4: cells/µl) response were observed for continuous EFV plasmalevels ≥1000ng/ml. The two single mutations known to confer clinically significant EFV resistance, a: RT K103N and b: RT Y188L, were observed at a frequency of only a: 25% and b: 12,5% early (16 weeks) as well as a: 50% and b: 25% late (48 weeks) in the nonresponding group during treatment [22]. In our prospective study EFV key mutations (including Y181C and G190A) occured in 8/11 nonresponding patients (73%) [total incidence: 10/64 patients (15,5%)] after 4 to 16 months with correlation to patients with EFV plasmalevels below of 1.000 ng/ml.

## Conclusion

EFV plasmalevels in patients with chronic liver disease no significant difference to patients without liver-disease in efficacy and toxicity could be found over a long observation period. From the results of this investigation we conclude that an EFV plasmalevel of at least 1.000 ng/ml is a sensitive marker for longterm efficacy in heavily pretreated patients. So continuous measurement will be usefull in clinical practise for long term efficacy of the therapeutic regimen. In patients with impaired liver function TDM is recommended. Therapeutic drug monitoring facilitates dose adjustment and continuation of therapy.

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*Address for correspondence:*
Peter Langmann
Private Praxis
Am Tiefen Weg 2
97753 Karlstadt
Germany
Phone: +49 93-53 42 42