point比較してみると、有意な差はみられなかった（図6）。

また、治療終了後約1年の時点で、CD4数が200以下に低下し、HAART再開が必要となった症例が1例あった。

●今後の予定

「B．研究方法」で述べたように、26症例すべてが治療を終了し2年間経過した時点で、最終的に評価するが、それには、HIV-RNAやCD4数、有害事象、日和見感染イベントの頻度、耐性変異の有無、免疫学的検索（細胞内サイトカイン発現量を用いたHIV-1特異的CD4細胞、MHCテトラマーを用いたHIV-1特異的CD8細胞（HIV-1特異的CTL））が含まれる予定である。

D．考察

このたび、免疫賦活を期待し、急性HIV感染者に対する計画的治療中断を含む早期治療介入を実施するにあたり、当院受診者に占める急性HIV感染者数を正確に把握するに至った。すると、本治験のエントリー期間である2年2ヶ月間に急性HIV感染と診断された者は、新患432名中32名（約7.5％）と、かなり高率であった。患者はすべて首都圏在住であり、この数字は、首都圏における深刻なHIV感染拡大が、「現在進行形」のかたちで存在することを示唆しており、今後一層の患者増加が予想される。HAART療法は、HIV感染者の予後を革命的に改善させたが、内服継続によるQOLの低下や莫大な医療コストは、今後より大きな問題となるであろう。

	前	1-6	7-12	13-18	19-24 months
n*	15	15	13*	13*	8*
平均HIV-RNA mean log c/ml (±SD)	4.99 (±0.80)	3.54 (±0.86)	3.74 (±0.73)	3.90 (±0.39)	3.72 (±0.89)
4log c/ml未満 (例)	2	9	9	6	2
(%)	13	60	69	46	25

（＊再治療例と受診中断のため検査できなかった例を除外）

6ヶ月毎　平均HIV-RNA<4logc/mlの割合

図5．6ヶ月毎 平均HIV- RNA(完遂例 n=15)

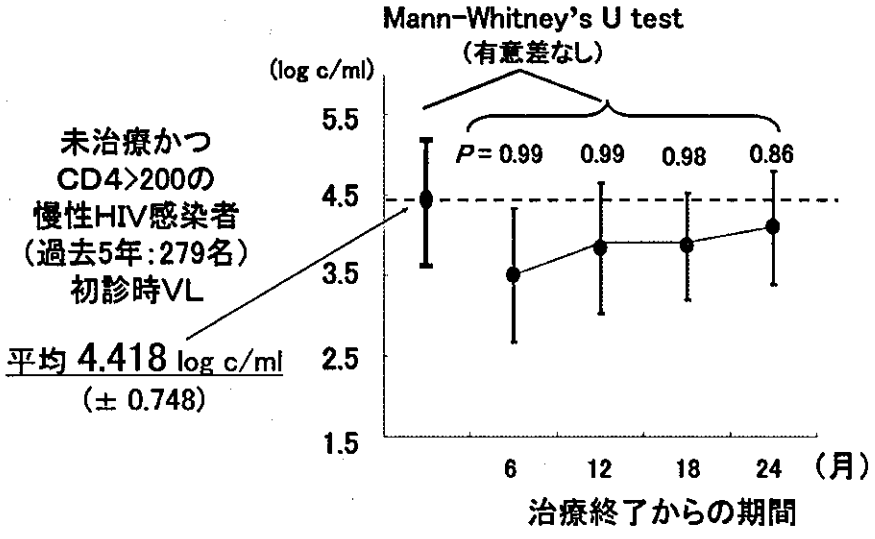

図6. 慢性期 set pointとの比較

免疫療法によるアプローチは、HIV特異免疫を惹起させることで、HIV-RNAを抑制させ、CD4数の減少をくいとめることを目標としている。すなわち、抗HIV療法の開始時期を遅らせて、結果的に内服期間を短縮させるのである。それは、個々の症例における副作用の軽減やQOLの改善という直接的な効果のみならず、医療費の削減につながり、経済上の効果も期待できると考えられる。

①休薬とHAARTの効果

これまでの抗HIV療法の一般的な考え方は、いったんHAARTを開始したら、特別な状況を除き、生涯治療を継続しなければならないというものであり、治療中断に関しては、一定の基準は定められていない。治療中断による耐性化が懸念されるからである。

しかし、本治験では、すべての症例において、休薬回数を重ねても一貫してHAARTに対する反応は良好であった。d4T/3TC/IDVをこの方法で用いた場合は、比較的安全にHAARTが中断できることが証明された。

②脱落例4例の背景

急性感染期に治療を導入しているにもかかわらず、CD4が低くてHAART休薬ができなかった脱落例が、15.4％みられた。それらの症例は、早くからCD4数が低い傾向にあったが、それ以外に、治療前の各データから脱落を予測することは困難であった。もし、脱落を予見する因子が解明されれば、STI療法の「適応群」をより明確に定めることができるかもしれない。今後、免疫学的な考察を加えて評価すべきと考えられる。

③5回のSTIを含むプロトコール完遂15例の経過

プロトコールを完遂した15例の治療終了後HIV-RNA量に関しては、これまでの海外の報告にあるような、著しいHIV-RNA量抑制効果は認められず、慢性感染例のset point比較してみても、有意な差はみられなかった。しかし、短期間、特に、治療終了後1年以内では、HIV-RNAが抑制されている症例が多く、期間を限定すれば、その効果が期待できるのではないかと考えられた。

この新しい治療法に関しては、不明な点が多く、適切なSTIの回数についても分かっていない。急性期に治療を導入せず観察されている例、急性期に治療を導入したがSTIを実施せずに治療が中断された例、STIを5回実施せずに本治験を中断した例、など、今後はそれらの症例群との比較も実施し、評価したいと考えている。

E. 結論

急性HIV感染者に対するSTIを含む早期治療介入の治験を行ったが、ウイルス量を持続的に抑制させる程の、劇的な効果は確認できなかった。しかし、治療終了後早期（約1年以内）においては、ウイルス量が低くおさえられている症例が多かった。これは、HIVの免疫療法の有用性を示唆する事実であり、一定期間、その効果が持続しうることを示していると考えられる。

F. 健康危険情報

特になし

G. 研究発表

1. 田沼順子、上田晃弘、吉田邦仁子、矢崎博久、本田美和子、潟永博之、源河いくみ、照屋勝治、立川夏夫、菊池　嘉、安岡　彰、岡　慎一、木村　哲。当院における急性HIV感染者に対するStructured Treatment Interruptions. 白馬シンポジウム。長野、8月。2002
2. 田沼順子、上田晃弘、吉田邦仁子、矢崎博久、本田美和子、潟永博之、源河いくみ、照屋勝治、立川夏夫、菊池　嘉、安岡　彰、岡　慎一、木村　哲。当院における急性HIV感染者に対するStructured Treatment Interruptions. 第77回日本感染症学会総会、福岡、4月、2003
3. 田沼順子、上田晃弘、吉田邦仁子、矢崎博久、本田美和子、潟永博之、源河いくみ、照屋勝治、立川夏夫、菊池　嘉、安岡　彰、岡　慎一、木村　哲。当院における急性HIV感染者に対するStructured Treatment Interruptions. 第17回日本エイズ学会、名古屋、11月、2003
4. 田沼順子、恩田順子、原田壮平、福島篤仁、阿部泰尚、横田恭子、上田晃弘、矢崎博久、本田美和子、潟永博之、源河いくみ、照屋勝治、立川夏夫、菊池　嘉、岡　慎一、木村　哲。当院における急性HIV感染者に対するStructured Treatment Interruptions. 第18回日本エイズ学会、静岡、12月、2004

研究成果の刊行物に関する一覧表

研究発表

主任研究者　岡　慎一　(含：立川夏夫、分担研究者)

1) Watanabe M, Nishimura K, Kimura S, and **Oka S** and the QoL Research Group of the AIDS Clinical Center and eight Regional AIDS Treatment Hospitals in Japan. A discriminative study of health-related quality of life assessment in HIV-1 infected persons living in Japan using the Multidimensional Quality of Life Questionnaire for Persons with HIV/AIDS. ***Int J STD AIDS*** 15: 107-115, 2004.

2) Tsuchiya K, Gatanaga H, **Tachikawa N**, Teruya K, Kikuchi Y, Yoshino M, Kuwahara T, Shirasaka T, Kimura S, and **Oka S**. Homozygous *CYP2B6 *6* (Q172H and K262R) correlates with high plasma efavirenz concentrations in HIV-1 patients treated with standard efavirenz-containing regimens. ***Biochem Biophys Res Commun*** 319: 1322-1326, 2004.

3) Hachiya A, Gatanaga H, Kodama E, Ikeuchi M, Matsuoka M, Harada S, Mitsuya H, Kimura S, and **Oka S**. Novel patterns of nevirapine-resistance-associated mutations of human immunodeficiency virus type-1 in treatment naïve patients. ***Virology*** 327: 215-224, 2004.

4) Bi X, Gatanaga H, Tanaka M, Honda M, Ida S, Kimura S, and **Oka S**. Modified Dynabeads method for enumerating CD4+ T cell count for widespread use in recourse-limited situations. ***JAIDS*** 38: 1-4, 2005.

5) Yamanaka H, Teruya K, Kikuchi Y, Takahashi T, Kimura S, **Oka S,** and the HIV/Influenza Vaccine Study Team. Efficacy and immunologic responses to influenza vaccine in HIV-1-infected persons. ***JAIDS*** (in the press)

分担研究者

滝口　雅文

1) Yokomaku Y, Miura H, Tomiyama H, Kawana-Tachikawa A, **Takiguchi M,** Kojima A, Nagai Y, Iwamoto A, Matsuda Z, and Ariyoshi K. Impaired Processing and Presentation of Cytotoxic T-Lymphocyte (CTL) Epitope is a Major Escape Mechanism from CTL Immune Pressure in Human Immunodeficiency Virus Type 1 Infection. ***J Virol*** 78: 1324-1332, 2004.

2) Tomiyama H, Takata H, Matsuda T, and **Takiguchi M**. Phenotypic classification of human CD8+ T cells reflecting their function: An inverse correlation between quantitative expression of CD27 and cytotoxic effector function. ***Eur J Immunol*** 34: 999-1010, 2004.

3) Takata H, Tomiyama H, Fujiwara M, Kobayashi N, and **Takiguchi M**. Expression of Chemokine Receptor CXCR1 on Human Effector CD8+ T Cells. ***J Immunol (Cutting Edge)*** 173: 2231-2235, 2004.

4) Ueno T, Tomiyama H, Fukjiwara M, **Oka S**, and **Takiguchi M**. Functionally impaired HIV-specific CD8 T cells show high-affinity TCR-ligand interactions. ***J Immunol*** 173: 5451-5457, 2004.

5) Ueno T, Fujiwara M, Tomiyama H, Onodera M, and **Takiguchi M**. Reconstitution of anti-HIV effector functions of primary human CD8 T lymphocytes by transfer of HIV-specific αβ TCR genes. ***Eur J Immunol*** 34: 3379-3388, 2004.

6) Kobayashi N, Takata H, Yokota S, and **Takiguchi M**. Down-regulation of CXCR4 expression on human CD8+ T cells during peripheral differentiation. ***Eur J Immunol*** 34: 3370-3378, 2004.

7) Tomiyama H, Fujiwara M, **Oka S,** and **Takiguchi M**. Epitope-dependent effect of Nef-mediated HLA class I down-regulation on ability of HIV-1-specific CTL to suppress HIV-1 replication. ***J Immunol (Cutting Edge)*** 174: 36-40, 2005.

8) Satoh M, Takamiya Y, **Oka S**, Tokunaga K, and **Takiguchi M** *: Identification and characterization of HIV-1-specific CD8+ T cell epitopes presented by HLA-A*2601, **Vaccine** (in the press)

松下　修三

1) **Matsushita S**, Yoshimura K, Kimura T, Kamihira A, Takano M, Eto K, **Shirasaka T**, **Mitsuya H**, and **Oka S**. Spontaneous recovery of hemoglobin and neutrophil levels in Japanese patients on a long-term Combivir® containing regimen. ***J Clin Virol*** (in the press).

2) Sakaguchi N, Kimura T, **Matsushita S**, Fujimura S, Shibata J, Araki M, Sakamoto T, Minoda S, and Kuwahara K. Generation of high-affinity antibody against T cell-dependentantigen in *ganp* gene-transgenic mouse. ***J Immunol*** (in the press).

森内　浩幸

1) Moriuchi M, and **Moriuchi H**. Seminal fluid enhances replication of human T-cell leukemia virus type I: Implications for sexual transmission. ***J Virol*** 78:12709-12711, 2004.

2) Moriuchi M, and **Moriuchi H**. Cell-type-dependent effect of transforming growth factor-β, a major cytokine in breast milk, on human immunodeficiency virus type 1 infection of mammary epithelial MCF-7 cells or macrophages. ***J Virol*** 78:13046-13052, 2004.

満屋　裕明

1) Maeda K, Nakata H, Koh Y, Miyakawa T, Ogata H, Takaoka Y, Shibayama S, Sagawa K, Fukushima D, Moravek J, Koyanagi Y, and **Mitsuya H**. Spirodiketopiperazine-based CCR5 inhibitor which preserves CC-chemokine/CCR5 interactions and exerts potent activity against R5 human immunodeficiency virus type 1 in vitro. ***J Virol*** 78:8654-8662, 2004.

2) Maeda K, Nakata H, Ogata H, Koh Y, Miyakawa T, and **Mitsuya H**. The current status of, and challenges in, the development of CCR5 inhibitors as therapeutics for HIV-1 infection. ***Curr Opin Pharmacol*** 4:447-452, 2004.

3) Tamiya S, Mardy S, Kavlick MF, Yoshimura K, and **Mitsuya H**. Amino acid insertions near Gag cleavage sites restore the otherwise compromised replication of human immunodeficiency virus type 1 variants resistant to protease inhibitors. ***J Virol*** 78:12030-12040, 2004.

4) Kitano K, Kohgo S, Yamada K, Sakata S, Ashida N, Hayakawa H, Nameki D, Kodama E, Matsuoka M, **Mitsuya H**, and Ohrui H. Attempt to reduce cytotoxicity by synthesizing the L-enantiomer of 4'-C-ethynyl-2'-deoxypurine nucleosides as antiviral agents against HIV and HBV. ***Antivir Chem Chemother*** 15:161-167, 2004.

5) Kohgo S, Yamada K, Kitano K, Iwai Y, Sakata S, Ashida N, Hayakawa H, Nameki D, Kodama E, M. Matsuoka M, **Mitsuya H**, and Ohrui H. Design, efficient synthesis, and anti-HIV activity of 4'-C-cyano- and 4'-C-ethynyl-2'-deoxy purine nucleosides. ***Nucleosides Nucleotides Nucleic Acids*** 23:671-690, 2004.

6) Yanada R, Koh Y, Nishimori N, Matsumura A, Obika S, **Mitsuya H**, Fujii N, and Takemoto Y. Indium-mediated atom-transfer and reductive radical cyclizations of iodoalkynes: synthesis and biological evaluation of HIV-protease inhibitors. ***J Org Chem*** 69:2417-2422, 2004.

7) Hayakawa H, Kohgo S, Kitano K, Ashida N, Kodama E, **Mitsuya H**, and Ohrui H. Potential of 4'-C-substituted nucleosides for the treatment of HIV-1. ***Antivir Chem Chemother*** 15:169-187, 2004.

8) Yasunaga J, Taniguchi Y, Nosaka K, Yoshida M, Satou Y, Sakai T, **Mitsuya H**, and Matsuoka M. Identification of aberrantly methylated genes in association with adult T-cell leukemia. ***Cancer Res*** 64:6002-6009, 2004.

9) Matsuno N, Hoshino K, Nanri T, Kawakita T, **Mitsuya H**, and Asou N. Transcriptional repression of the p15 gene predicts the clinical outcome of acute myeloblastic leukemia with intermediate and adverse cytogenetics. ***Leukemia*** 18:1146-1148, 2004.

10) Siddiqui MA, Hughes SH, Boyer PL, **Mitsuya H**, Van QN, George C, Sarafinanos SG, and Marquez VE. A 4'-C-ethynyl-2',3'-dideoxynucleoside analogue highlights the role of the 3'-OH in anti-HIV active 4'-C-ethynyl-2'-deoxy nucleosides. ***J Med Chem*** 47:5041-5048, 2004.

11) Depboylu C, Reinhart TA, Takikawa O, Imai Y, Maeda H, **Mitsuya H**, Rausch D, Eiden LE, and Weihe E. Brain virus burden and indoleamine-2,3-dioxygenase expression during lentiviral infection of rhesus monkey are concomitantly lowered by 6-chloro-2',3'-dideoxyguanosine. ***Eur J Neurosci*** 19:2997-3005, 2004.

12) Nakata H, Maeda K, Miyakawa T, Shibayama S, Matsuo M, Takaoka Y, Ito M, Koyanagi Y, and **Mitsuya H**. Potent anti-R5-HIV-1 effects of a CCR5 antagonist AK602 in a novel hu-PBMC-non-obse diabetic-SCID, IL-2R-chain-knocked-out AIDS mouse model. ***J Virol*** 79: 2087-2096, 2005.

別紙５

研究成果の刊行に関する一覧表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Watanabe M, Nishimura K, Kimura S, and **Oka S** and the QoL Research Group of the AIDS Clinical Center and eight Regional AIDS Treatment Hospitals in Japan.	A discriminative study of health-related quality of life assessment in HIV-1 infected persons living in Japan using the Multidimensional Quality of Life Questionnaire for Persons with HIV/AIDS.	***Int J STD AIDS***	15	107-115	2004
Tsuchiya K, Gatanaga H, **Tachikawa N**, Teruya K, Kikuchi Y, Yoshino M, Kuwahara T, Shirasaka T, Kimura S, and **Oka S**.	Homozygous *CYP2B6* *6 (Q172H and K262R) correlates with high plasma efavirenz concentrations in HIV-1 patients treated with standard efavirenz-containing regimens.	***Biochem Biophys Res Commun***	319	1322-1326	2004
Hachiya A, Gatanaga H, Kodama E, Ikeuchi M, Matsuoka M, Harada S, Mitsuya H, Kimura S, and **Oka S**.	Novel patterns of nevirapine-resistance-associated mutations of human immunodeficiency virus type-1 in treatment naïve patients.	***Virology***	327	215-224	2004
Bi X, Gatanaga H, Tanaka M, Honda M, Ida S, Kimura S, and **Oka S**.	Modified Dynabeads method for enumerating CD4+ T cell count for widespread use in recourse-limited situations.	***JAIDS***	38	1-4	2005
Yamanaka H, Teruya K, Kikuchi Y, Takahashi T, Kimura S, **Oka S**, and the HIV/Influenza Vaccine Study Team.	Efficacy and immunologic responses to influenza vaccine in HIV-1-infected persons.	***JAIDS*** (in the press)			

International Journal of STD & AIDS 2004; 15: 107–115

ORIGINAL RESEARCH ARTICLE

A discriminative study of health-related quality of life assessment in HIV-1- infected persons living in Japan using the Multidimensional Quality of Life Questionnaire for persons with HIV/AIDS

Megumi Watanabe RN[1], **Koichi Nishimura** MD[2], **Tomoko Inoue** RN[3], **Satoshi Kimura** MD[1], **Shinichi Oka** MD[1] and the **QoL Research Group of the AIDS Clinical Centre and eight regional AIDS treatment hospitals in Japan***

[1]*AIDS Clinical Centre, International Medical Centre of Japan, Tokyo;* [2]*Kyoto-Katsura Hospital, Kyoto;* [3]*Division of Comprehensive Health Nursing Sciences, Graduate School of Allied Health Sciences, Tokyo Medical Dental University, Tokyo, Japan.*

Summary: The aim of this study is to evaluate the discriminative properties of the Multidimensional Quality of Life Questionnaire for HIV infection (MQoL-HIV) and to determine those factors contributing to the health-related quality of life (HRQoL) of HIV-1 infected persons living in Japan. The MQoL-HIV, the Nottingham Health Profile (NHP) as a generic instrument, and the Center for Epidemiologic Studies–Depression Scale (CES–D) as a psychological measure were administered in 375 patients as a multiple-centre study. The score distribution of the MQoL-HIV showed a unimodal distribution. The Cronbach's α coefficient scored more than 0.7 in seven out of 10 domains, but was low in both the physical functioning and sexual functioning domains. There was a strong correlation between the CES–D and MQoL-HIV index scores (R−0.73). Relatively high coefficient values were found between psychiatric and nervous symptoms and the index score (R=−0.60). In total, the MQoL-HIV may possess discriminative properties.

Keywords: health-related quality of life, Multidimensional Quality of Life Questionnaire for HIV/AIDS, Nottingham Health Profile

Introduction

HIV/AIDS is an infectious disease that is also considered to be a chronic disorder. The health-related quality of life (HRQoL) or health status has become an important consideration in the treatment of patients with chronic disorders. The purpose of medical intervention for chronic disorders is defined as improvement in both the quantity and quality of life. The former corresponds to an improvement in mortality, whereas the latter indicates improvement in the HRQoL. The importance of HRQoL as a health index, especially in the evaluation of health care services for treatment of chronic disorders, has long been emphasized. However, there have been few reports examining the HRQoL of AIDS patients.

This disease is thought to be significantly influenced by social and cultural background. When compared with Western countries, the prevalence of HIV infection is low in Japan[1]. A rare disease in a closed society like Japan may easily lead to prejudice by the general public against AIDS patients and asymptomatic carriers (AC), resulting in the patients experiencing social isolation. Several disease-specific instruments to measure HRQoL for AIDS patients have been developed and validated in the literature[2–7]. Smith and colleagues developed the Multidimensional Quality of Life Questionnaire for HIV/AIDS (MQoL-HIV), which is one of the most comprehensive disease-specific measures currently available for evaluating HIV/AIDS[5]. We first initiated our study to establish a Japanese version of the MQoL-HIV. Ultimately, the goal was to investigate the contributions of symptoms, laboratory findings, and psychosocial status to the HRQoL of AIDS patients to highlight the characteristics of the

Correspondence to: Shinichi Oka MD, Director, AIDS Clinical Centre International Medical Centre of Japan, 1-21-1, Toyama, Shinjuku-ku, Tokyo 162-8655, Japan
E-mail: oka@imcj.hosp.go.jp

*Contributors to the QoL Research Group are listed in the Appendix

MQoL-HIV, and to identify its most influential factors.

Materials and methods

Translation of the MQoL-HIV

The MQoL-HIV was translated into Japanese in accordance with standardized methodology[8]. After obtaining from the author permission to translate the MQoL-HIV, the translation followed an established forward–backward translation procedure, with both independent and counter translations. Briefly, two researchers with clinical experience in treating AIDS patients independently translated the questionnaire into Japanese. These two translations were then proofread by a specialist (KN). A native English speaker who is fluent in Japanese but who has no medical experience translated the questionnaire back into English, and then this English translation was again translated into Japanese and carefully examined. Finally, 10 physicians who are routinely engaged in treating AIDS patients reviewed the questionnaire, and based on these reviews, the specialist finalized the Japanese translation.

The ethics committee of the International Medical Centre of Japan approved this study (IMCJ-H12-27).

Patients in a cross-sectional study

A total of 423 consecutive patients with HIV/AIDS from the AIDS Clinical Centre, International Medical Centre of Japan and eight other regional HIV treatment hospitals in Japan were recruited for this cross-sectional study from January to May 2000. All eligible patients completed all of the examinations described below, and an informed consent was obtained from each patient.

The patients were requested to complete a self-administered booklet. This booklet included the Japanese versions of the MQoL-HIV and the Nottingham Health Profile (NHP) for health status measurements[9], and the Japanese version of the Center for Epidemiologic Studies–Depression Scale (CES–D) for psychological evaluation[10]. In addition, the booklet included questions concerning personal issues such as disclosure of the HIV infection to others, employment status, and support from others, as an evaluation of their lifestyle and social background. Lastly, the booklet included questions concerning subjective symptoms.

For the subjective symptom analysis, 46 typical subjective symptoms of AIDS patients were selected from published reports. We used a five-point Lickert scale ranging from 'having no problem' to 'having serious problems' to obtain answers. We then classified the answers into two categories: '1, with symptoms' and '2, without symptoms'. Patients who answered 'having a problem' and 'having a serious problem' were grouped into the former category, whereas patients who chose any other answers were grouped into the latter. The results indicated that the patients with lower scores had more self-reported symptoms. In addition to the self-administered questionnaires, the following laboratory findings were recorded by coordinating nurses from individual medical records: age, gender, infectious route (blood product transfusion or sexual relationship), stage of disease (AC or AIDS), the presence or absence of treatment with anti-HIV drugs at the time of the examination, co-morbidity, CD4-positive lymphocyte count, and HIV-RNA levels. Furthermore, the attending nurses' opinions on the functional capacity of the patients were expressed by the Karnofsky Performance Status Scale (KPSS). The scale has a range of values from 0–100, where 0 means the patient is dead and 100 means the patient is healthy.

Assessment of HRQoL and psychological status

The HRQoL was measured by the MQoL-HIV[5], a disease-specific instrument, and the NHP[9], a generic instrument. The MQoL-HIV is a self-administered questionnaire consisting of the following 10 domains, totalling 40 items: mental health, physical health, physical functioning, social functioning, social support, cognitive functioning, financial status, partner intimacy, sexual functioning, and medical service (Table 1). Each domain consists of four items, and each item has seven response options. The score from each domain ranged from four to 28, and a lower score indicated a poorer HRQoL. In addition, we used a score range of 12 to 84 calculated from the equation, Mental health×2+Physical functioning, as the index score for the overall HRQoL.

The NHP is a self-administered questionnaire composed of two sections containing 45 items. In the present study, only the first section with 38 items was used to assess the following: energy (three items), pain (eight items), emotional reaction (nine items), sleep (five items), social isolation (five items), and physical mobility (eight items). All items have a yes/no answer format. The dimension scores ranged from 0–100. The higher the NHP score, the greater the health problems for that patient.

To assess the psychological status, a previously validated Japanese version of the CES–D was used for evaluating the patients' depression status[10]. The scores ranged from 0–60 with, 16 being the cut-off point. A score of 15 or less was regarded as normal, and a score of 16 or more as depression. Depression was classified into three categories according to the scores: mild (16–20), medium (21–30), and severe (over 31).

Table 1. Patient characteristics in 375 persons with HIV/AIDS

	Mean ± SD	Range
Age (years)	36.5 ± 10.3	20–74
CD4+ lymphocytes (/mL)	409 ± 227	2–1224
HIV-RNA (copies/mL)	11334 ± 52968	<400–680000
CES-D	16 ± 12	0–60
	Number (%)	
Female	31 (8)	
Stage		
Asymptomatic carrier	299 (80)	
AIDS	76 (20)	
Infection route		
Blood products	122 (33)	
MSM	175 (47)	
Heterosexual	68 (18)	
Disclosure of HIV infection	314 (84)	
Getting support	340 (91)	
Having a job	265 (71)	
Complications	200 (53)	
No ongoing HIV treatment	69 (18)	

CES-D = Center for Epidemiologic Studies–Depression Scale; MSM = men who have sex with men

Statistical analysis

All results are presented as means ± SD. Pearson's correlation test was used to analyse the relationship between two sets of data, and a P value of <0.05 was considered to be statistically significant. In addition, calculating the Cronbach's α coefficient enabled us to assess the internal consistency[11].

Factor analysis techniques were used to reduce or rearrange large sets of symptoms into smaller sets of factors of related symptoms[12]. All 46 symptoms were included in the analysis, and a maximum likelihood iterative solution was used. In this analysis, a matrix of correlation values between the variables was created, and then the data were transformed into linear combinations of variables that shared common variance between the measures. The correlation between the original variables and the linear combinations or factors is called factor loading. The factors were interpreted and defined based on which variables were highly loaded on each factor. The relationships between these factor scores and the index scores and the scores from the 10 domains of the MQoL-HIV were analysed, accordingly.

To identify those variables which influenced the index score and the scores from the 10 domains of the MQoL-HIV, a backward stepwise multiple logistic regression analysis was conducted, as previously described elsewhere[13]. The dependent variables included scores from each domain and the index score of the MQoL-HIV. The independent variables were selected from those variables that were significantly correlated with the MQoL-HIV scores, but were not strongly correlated with each other. The independent variables were as follows: age (years), gender (1: male, 2: female), infectious route (1: blood product transfusion, 2: sexual transmission), stage of disease (1:AC, 2: AIDS), HIV treatment (1: currently under treatment, 2: currently not under treatment), complications (1: present, 2: absent), CES-D (0–60), CD4-positive lymphocyte count, HIV-RNA quantity in actual numbers, disclosure of HIV infection to others (1: disclosed, 2: not disclosed), employment status (1: working 2: not working), support from others (1: supported, 2: not supported), eight symptoms determined by the factor analysis (1: present, 2: absent), and the KPSS (0–100). The dependent variables for this statistical model were the index score and the scores from the 10 domains of the MQoL-HIV. P values of <0.05 were considered to be statistically significant. These analyses were performed by a Statistical Package for the Social Sciences (SPSS).

Results

The booklets from a total of 375 of 423 patients (88.7%) were valid, and were used for further analysis. The clinical backgrounds of all the patients are summarized in Table 1. The average

Table 2. Score distribution* and internal consistency of the MQoL-HIV in 375 persons with HIV/AIDS

	Score			No. of persons with		Cronbach's
	Median	Mean	SD	Minimum score	Maximum score	α coefficient
Mental health	19	17.9	5.2	5	5	0.76
Physical health	23	21.6	4.9	0	26	0.76
Physical functioning	20	19.0	5.5	5	27	0.61
Social functioning	20	19.5	5.7	1	29	0.74
Social support	16	16.7	7.4	19	45	0.85
Cognitive functioning	24	23.1	4.6	1	84	0.84
Financial status	23	22.5	4.9	4	57	0.73
Partner intimacy	19	18.4	7.2	6	44	0.82
Sexual functioning	21	18.5	5.1	6	5	0.47
Medical service	23	22.4	4.8	1	52	0.67

MQoL-HIV = Multidimensional Quality of Life Questionnaire for HIV/AIDS

* The score can range from 4 (the minimum score) to 28 (the maximum score)

Table 3. Results of factor analysis used to reduce or rearrange large sets of symptoms into smaller sets of factors of related symptoms

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7	Factor 8	Factor 9
Factor 1: Psychiatric and nervous symptoms									
Depression	0.78	0.12	0.19	0.08	0.09	0.06	0.09	0.29	0.12
Anxiety	0.71	0.08	0.20	0.13	0.07	0.13	0.11	0.19	0.18
Fatigue	0.70	0.27	0.09	0.15	0.21	0.19	0.13	0.04	−0.00
Feeling sluggish	0.70	0.28	0.22	0.12	0.18	0.06	0.09	0.14	−0.03
Easily fatigued	0.69	0.22	0.17	0.13	0.21	0.17	0.15	0.00	0.01
Irritability	0.65	0.14	0.22	0.13	0.09	0.17	0.06	0.11	0.21
Insomania	0.52	0.28	0.12	0.20	0.02	0.09	0.10	0.26	0.13
Factor 2: Upper digestive symptoms									
Nausea	0.20	0.76	0.15	0.11	0.19	0.11	0.14	0.07	−0.05
Upset stomach	0.28	0.66	0.08	0.09	0.21	0.15	0.18	0.12	0.36
Vomiting	0.20	0.66	0.21	0.25	0.06	0.06	0.19	0.16	−0.04
Heartburn	0.23	0.63	0.13	0.13	0.19	0.19	0.19	0.07	0.33
Factor 3: Respiratory and circulatory symptoms									
Short of breath	0.31	0.19	0.76	0.14	0.19	0.17	0.11	0.09	0.10
Choking	0.31	0.20	0.71	0.18	0.20	0.13	0.13	0.14	0.08
Palpitation	0.26	0.21	0.71	0.20	0.19	0.10	0.10	0.19	0.10
Factor 4: Inflammatory and haemorrhagic symptoms									
Haematuria	0.06	0.11	0.08	0.60	0.17	0.09	−0.02	0.09	0.01
Blood in stool	0.12	0.13	0.11	0.59	0.01	0.14	0.11	0.13	0.09
Pain on urination	0.03	−0.01	0.30	0.51	0.28	0.04	0.13	0.21	0.14
Factor 5: Sensory symptoms									
Change in taste	0.15	0.29	0.15	0.20	0.63	0.21	0.09	0.08	−0.02
Change in sensation around mouth	0.18	0.37	0.16	0.22	0.58	0.19	0.08	0.16	−0.05
Factor 6: Dermatological symptoms									
Itching	0.15	0.15	0.15	0.18	0.14	0.82	0.15	0.08	0.07
Dry skin	0.17	0.16	0.10	0.13	0.21	0.66	0.05	0.10	0.13
Rash	0.26	0.09	0.13	0.37	0.08	0.55	0.17	0.16	−0.13
Factor 7: Lower digestive symptoms									
Soft stool	0.11	0.19	0.08	0.09	0.13	0.13	0.82	0.14	0.02
Diarrhoea	0.15	0.17	0.10	0.13	0.07	0.07	0.80	0.05	0.05
Factor 8: Appearance									
Change in weight	0.27	0.17	0.06	0.09	0.21	0.17	0.12	0.52	0.14
Change in body shape	0.29	0.14	0.20	0.10	0.32	0.15	0.15	0.50	0.03
Other factors									
Headache	0.35	0.38	0.18	0.21	0.12	0.10	0.03	0.20	0.08
Dizziness	0.33	0.36	0.36	0.11	0.11	0.03	0.08	0.22	0.15
Hallucination	0.16	0.24	0.20	0.33	0.01	0.00	0.08	0.37	−0.02
Nightmare	0.39	0.17	0.31	0.23	0.01	0.05	0.01	0.39	0.02
Feverish	0.35	0.23	0.25	0.42	0.02	0.15	0.23	0.05	−0.03
Feeling a chill	0.31	0.30	0.39	0.43	0.14	0.12	0.11	0.10	−0.05
Cough	0.25	0.22	0.30	0.29	0.18	0.16	0.10	0.10	0.19
Change in appetite	0.31	0.49	0.13	0.14	0.22	0.14	0.19	0.21	0.07
Abdominal pain	0.22	0.28	0.20	0.25	0.07	0.20	0.41	0.07	0.29
Constipation	0.28	0.13	0.20	0.22	0.03	0.01	0.04	0.15	0.38
Gas	0.19	0.20	0.18	0.10	0.10	0.13	0.30	0.28	0.33
Swelling	0.26	0.14	0.18	0.21	0.36	0.20	0.16	0.40	0.20
Changing urine volume/time	0.14	0.22	0.18	0.27	0.45	0.11	0.09	0.26	0.20
Numbness	0.23	0.18	0.26	0.17	0.35	0.09	0.07	0.19	0.22
Changing eyesight	0.27	−0.04	0.36	0.29	0.36	0.17	0.14	0.13	0.18
Oral thrush	0.25	0.16	0.14	0.32	0.11	0.19	0.15	0.13	0.07
Increase in sweating	0.35	0.10	0.31	0.29	0.11	0.28	0.24	0.04	0.11
Muscle pain	0.29	0.09	0.34	0.31	0.36	0.15	0.17	−0.00	0.35
Bleeding tendency	0.13	0.11	0.02	0.46	0.18	0.13	0.09	−0.06	0.12

Table 4. Pearson's correlation coefficient between the score of the MQoL-HIV and Center for Epidemiologic Studies–Depression Scale (CES–D), the Karnofsky Performance Status Scale (KPSS) and self-reported symptoms

MQoL-HIV appearance	CES–D	KPSS	Psychiatric and nervous symptoms	Upper and digestive symptoms	Respiratory and circulatory symptoms	Inflammatory and haemorrhagic symptoms	Sensory symptoms	Dermatological symptoms		Lower digestive symptoms
Index score	−0.73	0.33	−0.60	−0.38	−0.43	−0.33	−0.34	−0.31	−0.30	−0.34
Mental health	−0.73	0.20	−0.60	−0.34	−0.38	−0.28	−0.29	−0.29	−0.30	−0.31
Physical health	−0.57	0.33	−0.60	−0.58	−0.52	−0.46	−0.48	−0.32	−0.40	−0.38
Physical functioning	−0.34	0.41	−0.28	−0.24	−0.29	−0.22	−0.23	−0.17	−0.13	−0.20
Social functioning	−0.61	0.18	−0.49	−0.29	−0.33	−0.29	−0.31	−0.22	−0.23	−0.26
Social support	−0.30		−0.16	−0.06	−0.11	−0.11	−0.18	−0.12	−0.11	
Cognitive functioning	−0.50	0.11	−0.49	−0.35	−0.38	−0.30	−0.41	−0.17	−0.26	−0.31
Financial status	−0.44		−0.36	−0.21	−0.26	−0.19	−0.22	−0.24	−0.25	−0.27
Partner intimacy	−0.33		−0.14	−0.07	−0.06	−0.08				
Sexual functioning	−0.23		−0.23	−0.19	−0.14	−0.11	−0.15	−0.12	−0.18	−0.14
Medical care	−0.41		−0.43	−0.24	−0.34	−0.28	−0.29	−0.18	−0.29	−0.35

MQoL-HIV = Multidimensional Quality of Life Questionnaire for HIV/AIDS
All values listed represent statistically significant relationship ($P<0.05$); missing values indicate no significant relationship

age was 37 years, and males, haemophilia patients infected through blood products, and patients with jobs accounted for 92, 33, and 71% of the total, respectively.

Internal consistency and score distributions

The mean index score was 55.1 ± 12.7 in a score range of 12–84 with unimodal distribution. Table 2 shows the score distribution from each of the 10 domains and the values for the Cronbach's α coefficient. The score from some domains tended to be skewed towards the lower end of the quality of life scale. The best possible score (ceiling effect) for the cognitive functioning domain was noted in 84% of the patients. The values for Cronbach's α coefficient were more than 0.7 in 7 domains out of 10. Low values of 0.61, 0.47 and 0.67 were observed in the remaining three domains: physical functioning, sexual functioning and medical service, respectively.

Factor analysis of self-reported symptoms

The factor analysis yielded eight factors, which accounted for 76.9% of the total variance of the data. Table 3 provides a summary of the varimax rotation of the factor analysis. Depression, anxiety, fatigue, feeling sluggish, easily fatigued, irritability and insomnia loaded predominantly on factor one, which appeared to be the factor for psychiatric and nervous symptoms. Factor two appeared to be related to upper digestive symptoms. Variables with high loading on this factor included nausea, upset stomach, vomiting and heartburn. Factor three appeared to represent respiratory and circulatory symptoms, including shortness of breath, choking and palpitation. Factor four included haematuria, blood in the stool and pain during urination, and appeared to be related to inflammatory and haaemorrhagic symptoms. Sensory symptoms were found in factor five. Changes in taste and in sensation around the mouth loaded predominantly on this factor. Factor six appeared to represent dermatological symptoms. Factor seven was related to lower digestive symptoms where soft stool and diarrhoea loaded predominantly. Factor eight appeared to represent changes in appearance, including changes in weight and in body shape. The other 19 symptoms could not be grouped with any of the above factors, and we decided to focus on these eight different symptoms to further investigate their contribution to the MQoL-HIV score.

Relationship between symptoms, psychological status, functional capacity and the NHP

Table 4 shows the correlation coefficients between the following: the CES–D score as a psychological measure, the eight symptoms determined by the factor analysis, the KPSS as an index of functional capacity, and the index scores and the scores from each of the 10 domains. A strong correlation was observed between the CES–D score and the index score, with a coefficient of −0.73. With respect to the CES–D score, the same strong coefficient of 0.73 was found with the mental health domain, which was the strongest among the 10 domains. The correlation coefficients between the psychiatric and nervous symptoms and the index score, and between mental health and physical health showed the same value of −0.60, whereas the coefficients between the upper digestive symptoms and physical health and between the respiratory and circulatory symptoms and physical health showed values of −0.58 and −0.52, respectively. These relatively high values indicate that these symptoms are related to physical health. On the other hand, there was no significant correlation between the

Table 5. Pearson's correlation coefficient between MQoL-HIV and subscale of the Nottingham Health Profile (NHP)

	Subscale of the NHP					
MQoL-HIV	Energy	Pain	Emotional reaction	Sleep	Social isolation	Physical mobility
Index score	−0.51	−0.34	−0.69	−0.37	−0.62	−0.39
Mental health	−0.45	−0.24	−0.70	−0.37	−0.60	−0.23
Physical health	−0.56	−0.52	−0.52	−0.39	−0.45	−0.42
Physical functioning	−0.32	−0.35	−0.31	−0.18	−0.35	−0.48
Social functioning	−0.45	−0.21	−0.60	−0.32	−0.65	−0.21
Social support	−0.13		−0.25		−0.36	
Cognitive functioning	−0.51	−0.35	−0.47	−0.42	−0.41	−0.26
Financial status	−0.30	−0.20	−0.45	−0.28	−0.41	−0.10
Partner intimacy	−0.15		−0.25		−0.29	
Sexual functioning	−0.23		−0.30	−0.16	−0.23	
Medical care	−0.38	−0.21	−0.43	−0.31	−0.42	−0.16

MQoL-HIV = Multidimensional Quality of Life Questionnaire for HIV/AIDS
All values listed represent statistically significant relationship ($P<0.05$); missing values indicate no significant relationship

KPSS and social support, financial status, partner intimacy, sexual functioning, or medical care. The KPSS was not closely correlated to indices measured by the MQoL-HIV.

Table 5 summarizes the correlation coefficients between the index scores and the scores from the six sub-scales of the NHP, a generic instrument. The index score correlated strongly with the emotional reaction, showing the highest coefficient of −0.69 whereas its correlation to pain was the weakest, showing a coefficient of −0.34.

Stepwise multiple regression analyses for the identification of the best variables to predict the MQoL-HIV

To identify the factors contributing to the index scores and the scores from each of the 10 domains, we conducted stepwise multiple regression analyses using the seven background parameters of the patients as shown in Table 1, the CES–D scores, and the eight different symptoms determined by the factor analysis (Table 6). The CED–S was identified as the contributing factor for all 10 domains. In the mental health domain, age, CES–D, and psychiatric and nervous symptoms accounted for 60% of the variance. On the other hand, in the sexual functioning domain, the presence of numerous unknown factors was suggested because only 14% of the variance could be explained by variables used in this analysis.

Discussion

The results from the stepwise multiple regression analyses of all 10 domains suggested the CES–D as the most significant contributing factor to determine the scores of the MQoL-HIV. This is a predictable conclusion based on the concept that the HRQoL should be comprehensively evaluated on the basis of symptoms, functional capacity, psychosocial status and social interactions. The KPSS, an index of functional capacity, has been suggested to be a significant determinant of the MQoL-HIV index score in addition to the scores from two domains (physical health and physical functioning), although the correlation coefficient was extremely low. Employment status, which is thought to be related to the concept of social interaction, contributed as a significant factor only in the financial status and sexual functioning domains. Therefore, psychosocial status appears to be the most important factor contributing to the scores of the MQoL-HIV.

The statistical method of factor analysis can be considered to be a data reduction technique, and has been utilized previously to clarify the relationships between various parameters[12]. Grouping of symptoms by factor analysis facilitated the selection of individual symptoms that most closely represent the conceptual meaning of a composite variable. In the present study, it is reasonable to presume that depression, anxiety, fatigue, feeling sluggish, easy fatiguibility, irritability and insomnia, which comprised factor one, have a common conceptual meaning. Likewise, we were able to group 46 separated self-reported symptoms of AIDS patients into eight categories. As a consequence, we were able to determine that the psychiatric and nervous symptoms contributed significantly to the MQoL-HIV index score, as did the scores from five domains, and the former were the most important determinant of self-reported symptoms for the MQoL-HIV.

Age has been reported to be one independent determinant of HRQoL in the general population and in patients with chronic diseases[14,15]. When we examined each domain and the patient's age as contributing factors, we found that older age was associated with a favourable HRQoL in the mental health, financial status and partner intimacy domains. In contrast, younger age was correlated with a better HRQoL in the physical functioning, social functioning, and social support domains. We were therefore unable to confirm the widely

Table 6. Results of backward stepwise multiple logistic regression analysis to identify those variables which influenced the index score and the scores from the 10 domains of the MQoL-HIV

	Index score	Mental health	Physical health	Physical functioning	Social functioning	Social support	Cognitive functioning	Financial status	Partner intimacy	Sexual functioning	Medical care
R^2	0.59	0.60	0.52	0.27	0.45	0.27	0.36	0.29	0.21	0.14	0.25
Age		0.11		−0.17	−0.09	−0.16		0.13	0.11		
Gender						0.11					
Disease duration				−0.11						0.12	
Infection route				0.14	−0.11			−0.12			−0.13
With or without treatment					0.09						
No. of CD4-positive lymphocytes								−0.11			
With or without complications					0.11		0.12			−0.13	0.12
Disclosure of HIV infection			0.09			−0.24		0.10	−0.24		0.10
With or without support					−0.12	−0.20			−0.13		
Employed or not					−0.12		0.11	−0.16		0.15	
CES-D	−0.58	−0.60	−0.28	−0.20	−0.48	−0.29	−0.33	−0.38	−0.34	−0.21	−0.26
KPSS	0.16		0.11	0.22							
Psychiatric and nervous symptoms	−0.19	−0.32	−0.17		−0.18		−0.25				−0.17
Upper digestive symptoms			−0.24			0.13		0.15			0.14
Respiratory and circulatory symptoms				−0.12							
Inflammatory and haemorrhagic symptoms											
Sensory symptoms			−0.12				−0.26				
Dermatological symptoms							0.14				
Lower digestive symptoms							0.12			−0.12	
Appearance	0.93	1.15	1.01	0.96	1.30	1.13	1.33	1.15	0.81	0.73	0.92

MQoL-HIV = Multidimensional Quality of Life Questionnaire for HIV/AIDS; CES-D: Center for Epidemiologic Studies-Depression Scale; KPSS = the Karnofsky Performance Status Scale

known phenomenon of a poorer HRQoL with advanced age. One possible explanation is that our multidimensional approach cancelled the positive and negative influences, rendering age an insignificant contributing factor to the MQoL-HIV index score in the present study.

Japan is considered to be a relatively homogenous and closed society, and hence the prevalence of prejudice towards AIDS patients can easily become widespread. We speculate that such prejudice influences the psychosocial status of the AIDS patients, leading to a poor HRQoL. The scores from the domains of physical health, financial status and medical care were better for those patients who kept their HIV infection a secret from others. However, the interpretation of this observation is complicated by the fact that more support from others is generally needed for those patients who require intensive medical treatments. It is also confounded by the receipt of special governmental medical aid as a result of handicapped status. Another possible reason is that in circumstances where only professional medical staffs are aware of the patient's HIV infection status, the patient generally receives consistent and favourable mental care. In contrast, the HRQoL tends to be better in the domains of social support and partner intimacy in those patients who disclosed their HIV infection to others. This suggests the possibility of the patient maintaining a good relationship with those to whom they have chose to disclose, thus receiving aid and support. There were no statistically significant differences in the MQoL-HIV index score between those patients who have disclosed and those who have not. Therefore, the present study could not demonstrate a correlation between HRQoL and the disclosure of HIV infection to others.

There were no significant differences in the MQoL-HIV index score attributable to route of infection (sexual relations or blood product transfusion). HIV/AIDS patients with haemophilia have problems with physical functioning due to hepatitis C and joint defects caused by repeated haemorrhage. We believe that this is the reason why those patients who were infected through sexual relations showed generally better scores in the domains of physical functioning, social functioning, and medical care. With respect to the presence or absence of ongoing HIV treatment, those patients who were not currently under treatment showed a better score in the physical health domain, whereas those who were currently under treatment showed a better score in the social functioning domain.

There are some limitations in the present study. First, the Cronbach's α coefficient, which indicates internal consistency was found to be low in both the physical functioning and sexual functioning domains. A low value for this coefficient in the sexual functioning domain has also been observed in studies using the original version of the MQoL-HIV in the USA. These results may indicate difficulty in obtaining accurate answers regarding sexual behaviour from the examinees. This is probably not a problem specific to the design of the questionnaire, but rather an issue that should be recognized as a general phenomenon. Second, the responsiveness, which is important to measure outcome of intervention, was not examined in the present study. Therefore, further examination along this line is a subject for future studies.

In conclusion, the MQoL-HIV is reliable, and may possess discriminative properties. However, there were particularly low values in the physical functioning and sexual functioning domains, leaving these domains with uncertain reliability. Among the factors that determined the score on the MQoL-HIV, psychological factors clearly contributed to the largest degree, and the contribution of factors related to functional capacity and social interaction was relatively minor. With 10 domains, this instrument interacts with various contributing factors in a complicated manner. These factors could not predict the whole spectrum of the HRQoL, and the contribution of these particular factors to the HRQoL was limited. Therefore, the HRQoL should be measured directly and results should be based on the score of the instrument rather than by estimating it from individual factors.

Acknowledgements: The authors thank Mrs Fraser for her comments and Dr Bi for her assistance. We also would like to thank NE Avis, PhD (Principal Research Scientist, New England Research Institutes) for giving us permission to use the Japanese version of the MQoL-HIV. Requests for the Japanese versions of the MQoL-HIV and NHP should be addressed to Koichi Nishimura, MD (koichi-nishimura@nifty.ne.jp). This study was supported by a Research Grant (H12-AIDS-001) from the Ministry of Health, Labour, and Welfare of Japan.

Appendix

The QoL Research Group of the AIDS Clinical Centre and eight regional AIDS treatment hospitals in Japan

Ms Ishihara, Ms Ikeda, Ms Ogane, Ms Ohashi, and Mrs Koyanagi (the AIDS Clinical Centre, International Medical Centre of Japan), Professor Koike and Ms Ono (the Hokkaido University Medical Hospital), Dr Sato and Ms Sugawara (the National Sendai Hospital), Dr Igarashi and Ms Uchiyama (the Niigata University Medical Hospital), Dr Utsumi and Mrs Hashiguchi (the National Nagoya Hospital), Dr Kawamura and Ms Yamashita (the Ishikawa Prefectural Central Hospital), Dr Shirasaka and Ms Oda (the Osaka National Hospital), Dr Takata and Ms Iwasaki (the Hiroshima University Medical Hospital) and Dr Yamamoto and Ms Jyouzaki (the National Kyushu Medical Centre Hospital).

References

1 Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report, 1997–2000; 9–12 (No. 2). [Online] www.cdc.gov/hiv/dhap.htm

2 Lubeck DP, Fries JF. Assessment of quality of life in early stage HIV-infected persons: data from the AIDS time-oriented health outcome study (ATHOS). *Qual Life Res* 1997;6:494–506

3 Lenderking WR, Testa MA, Katzenstein D, *et al.* Measuring quality of life in early HIV disease: the modular approach. *Qual Life Res* 1997;6:515–30

4 Wu AW, Revicki DA, Jacobson D, *et al.* Evidence for reliability, validity and usefulness of the Medical Outcomes Study HIV Health Survey (MOS-HIV). *Qual Life Res* 1997;6: 531–54

5. Smith KW, Avis NE, Mayer KH, *et al.* Use of the MQoL-HIV with asymptomatic HIV-positive patients. *Qual Life Res* 1997; 6:555–60

6 Holmes WC, Shea JA. Performance of a new, HIV/AIDS-targeted quality of life (HAT-QoL) instrument in asymptomatic seropositive individuals. *Qual Life Res* 1997;6:561–71

7 Peterman AH, Cella D, Mo F, *et al.* Psychometric validation of the revised functional assessment of human immunodeficiency virus infection (FAHI) quality of life instrument. *Qual Life Res* 1997;6:572–84

8 Bullinger M, Alonso J, Apolone G, *et al.* Translating health status questionnaires and evaluating their quality: the IQOLA Project approach. *J Clin Epidemiol* 1998;51:913–23

9 Hunt SM, McEwem J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. *J Roy Coll Gen Pract* 1985;35:185–8

10 Radolff LS. The CES–D scale: a self-reported depression scale for research in the general population. *Appl Psychol Meas* 1977;1:385–401

11 Cronbach L. Coefficient alpha and the internal structure of tests. *Psychometrika* 1951;16:297–334

12 Ries AL, Kaplan RM, Blumberg E. Use of factor analysis to consolidate multiple outcome measures in chronic obstructive pulmonary disease. *J Clin Epidemiol* 1991;6:497–503

13 Hosmer DW, Lemeshow S. In: *Applied logistic regression.* John Wiley & Sons, New York, 1989:1–173

14 Fukuhara S, Ware JE Jr, Kosinski M, *et al.* Psychometric and clinical tests of validity of the Japanese SF-36 health survey. *J Clin Epidemiol* 1998;51:1045–53

15 Tsukino M, Nishimura K, Ikeda A, *et al.* Physiologic factors that determine the health-related quality of life in patients with COPD. *Chest* 1996;110:896–903

(Accepted 21 January 2003)

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Biochemical and Biophysical Research Communications 319 (2004) 1322–1326
BBRC
www.elsevier.com/locate/ybbrc

Homozygous *CYP2B6* *6 (Q172H and K262R) correlates with high plasma efavirenz concentrations in HIV-1 patients treated with standard efavirenz-containing regimens

Kiyoto Tsuchiya,[a] Hiroyuki Gatanaga,[a] Natsuo Tachikawa,[a] Katsuji Teruya,[a] Yoshimi Kikuchi,[a] Munehiro Yoshino,[b] Takeshi Kuwahara,[b] Takuma Shirasaka,[c] Satoshi Kimura,[a] and Shinichi Oka[a,*]

[a] *AIDS Clinical Center, International Medical Center of Japan, Tokyo 162-8655, Japan*
[b] *Department of Pharmacy, Osaka National Hospital, Osaka 540-0006, Japan*
[c] *Department of Immunological and Infectious Diseases, Osaka National Hospital, Osaka 540-0006, Japan*

Received 21 April 2004
Available online 4 June 2004

Abstract

Efavirenz (EFV) is metabolized by cytochrome P450 2B6 (*CYP2B6*) in the liver. We analyzed the genotypes of *CYP2B6* and their contribution to plasma EFV concentrations in 35 EFV-treated patients in International Medical Center of Japan. The mean plasma EFV concentration of patients with *CYP2B6* *6/*6 (Q172H and K262R) ($25.4 \pm 7.5\,\mu M$, $\pm$ SD, $n = 2$) was significantly higher than that of patients with genotypes *6 heterozygote ($9.9 \pm 3.3\,\mu M$, $n = 10$) or without alleles *6 ($8.0 \pm 2.6\,\mu M$, $n = 23$) ($p < 0.0001$). To confirm our result, we further analyzed nine patients (three with high EFV concentrations and arbitrarily selected six with normal EFV concentrations) treated in Osaka National Hospital, and it resulted that the only three patients with the high concentrations were the *6/*6 holder. EFV dose could be decreased in those patients harboring the genotype to reduce toxicity with compromising potency, representing the first step of the Tailor-Made therapy of HIV-1 infection.

Keywords: Cytochrome P450; Genetic polymorphism; HIV-1; Efavirenz; Plasma concentration

Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor that shows potent inhibitory activity against HIV-1 and is stated as a key drug of the first line regimens in the HIV-1 treatment Guideline [1]. However, a number of patients treated with EFV develop central nervous system symptoms including headache, dizziness, insomnia, and fatigue. These side effects are more frequent in patients with high plasma concentration of EFV [2,3] as well as worsen with long-term therapy, and are the main reason for poor adherence or interruption of therapy. EFV is reported to be metabolized by cytochrome P450 (CYP) 3A4 (*CYP3A4*) and 2B6 (*CYP2B6*) to hydroxylated metabolites in the liver [4]. The recent HIV-1 treatment Guideline stated that EFV is metabolized by *CYP3A* [1], whereas an in vitro study indicated that EFV is mainly metabolized by *CYP2B6* [5]. Furthermore, a pharmacogenetic study demonstrated the association of the homozygous variant of multidrug-resistance transporter (*MDR1*; gene product P-glycoprotein) C3435T and good immune recovery in patients treated with EFV-containing regimens [6]. In order to clarify the contribution of polymorphisms to plasma EFV concentration in vivo, we analyzed genotypes of *CYP2B6*, *CYP3A4*, and *MDR1*, and their correlation with plasma EFV concentrations.

Materials and methods

Patients. A total of 60 HIV-1 patients who were treated with EFV-containing regimens at the AIDS Clinical Center, International

* Corresponding author. Fax: +81-3-5273-5193.
E-mail address: oka@imcj.hosp.go.jp (S. Oka).

0006-291X/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2004.05.116

Medical Center of Japan (IMCJ), were examined for their allelic variants of *CYP2B6*, *CYP3A4*, and *MDR1*. Among them, 35 patients were on standard therapy of EFV-containing regimens (600 mg EFV once daily dosing with two nucleotide reverse transcriptase inhibitors) and fully adhered to the regimens based on self-reports. Their plasma EFV concentrations were measured and the correlation between variants and EFV concentrations was analyzed. We excluded those patients who were taking other agents that could potentially interact with plasma EFV concentration such as protease inhibitors and those taking EFV twice daily from the analysis of the correlation. The mean age and body weight of these 35 patients (34 males and 1 female) were 41.6 ± 11.5 years and 63.4 ± 10.9 kg, respectively. The median latency between commencement of treatment and analysis of EFV concentration was 76.9 weeks (range, 4–200). The means ± SD alanine aminotransferase level was 33.1 ± 18.4 U/L. Blood samples were taken between 10 and 14 h (mean, 12.0 h) after dosing. To confirm the results of patients treated at the IMCJ, we further analyzed the allelic variants of nine patients who were treated at the Osaka National Hospital (ONH) [three patients with high plasma EFV concentrations (one patient was taking only 200 mg EFV once daily due to severe side effects) and six patients with normal EFV concentrations]. The Ethics Committee for the Study of Human Genome in each hospital approved this study (IMCJ-H14-36, ONH-23) and all patients gave a written informed consent.

Genotyping. Genomic DNA was isolated from peripheral blood using a QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). Genotyping of allelic variants of *CYP2B6* [7] [**1* (wild type), **2* (C64T), **3* (C777A), **4* (A785G), **5* (C1459T), **6* (G516T and A785G), **7* (G516T, A785G, and C1459T), and **8* (A415G)], CYP3A4 [**11* (C1088T; unstable form [8]), **12* (C1117T; has an altered testosterone hydroxylase activity [8]), **13* (C1247T; lack of expression [8]), **17* (T566C; exhibits lower turnover numbers for testosterone and chlorpyrifos [9]), and **18* (T878C; exhibits higher turnover numbers for testosterone and chlorpyrifos) [9] and *MDR1* C3435T was carried out using the allelic-specific fluorogenic 5′ nuclease chain reaction assay by the ABI PRISM 7700 sequence detection system (Applied Biosystems, Foster City, CA). Each 25 μl PCR mixture contained 20 ng genomic DNA, 900 nM primers, 200 nM TaqMan minor groove binder (MGB) probes, and 12.5 μl TaqMan universal PCR master mix (Applied Biosystems). The primers and TaqMan MGB probes used in this study are summarized in Table 1. The thermal cycler program was set up at 50 °C for 2 min and 95 °C for 10 min, and then repeated 40 cycles with 95 °C for 15 s and 60 °C for 1 min.

Plasma efavirenz concentration. Plasma was isolated by centrifugation (10 min at 1800*g*) on the same day as blood sampling and stored at −80 °C until analysis. EFV concentration was measured by reverse-phase high performance liquid chromatography (HPLC) method [10] at BioMedical Laboratory (Saitama, Japan). HPLC was performed on an Inertsil ODS-3 column (5 μm, 250 × 4.6 mm; GL Sciences, Tokyo, Japan) at a flow rate of 1.2 ml/min with ultraviolet-detection at 247 nm. The mobile phase consisted of acetonitrile and water (65:35, v/v).

Statistical analysis. StatView version 5.0 software (SAS Institute, Cary, NC) was used for the comparison of different genotype groups. If one-way analysis of variance (ANOVA) was significant ($p < 0.05$), post hoc Scheffe's F test was applied.

Table 1
Primers and TaqMan MGB probes used in this study

	Forward primer	Reverse primer	VIC probe (wild-type)	6-FAM probe (mutant)
CYP2B6				
C64T	CCTCACAGGACTCTTGCTACTC	AGGCGGTCATGGGTGTTAG	TGGTTCAGCGCCACC	CTGGTTCAGTGCCACC
A415G	CTGTGACCACTATGAGGGACTTC	CTGAGCCTCCTCCTGAATCC	ACACTCCGCTTTCCCAT	CACTCCGCTCTCCCAT
G516T	TCATGGACCCCACCTTCCT	GACGATGGAGCAGATGATGTTG	TTCCAGTCCATTACC	CTTCCATTCCATTACC
C777A	TGGAGAAGCACCGTGAAACC	GAGCAGGTAGGTGTCGATGAG	CCCAGCGCCCCCA	CCCCAGAGCCCCCA
A785G	TGGAGAAGCACCGTGAAACC	TGGAGCAGGTAGGTGTCGAT	CCCCCAAGGACCTC	CCCCAGGGACCTC
C1459T	CCCAGAAGACATCGATCTGACA	GAATGACCCTGGAATCCTTTGAC	AGATCCGCTTCCTG	AGATCTGCTTCCTGC
CYP3A4				
T566C	GGCCTACAGCATGGATGTGAT	TGGATTGTTGAGAGAGTCGATGTT	AGCACATCATTTGGA	AGCACATCATCTGGA
T878C	TCTTTCCTCTCCTTTCAGCTCTGT	GGTTTCATAGCCAGCAAAAATAAAG	CGATCTGGAGCTCG	CGATCCGGAGCTC
C1088T	TGTGCTACAGATGGAGTATCTTGACA	CATCCCATTGATCTCAACATCTTTT	TCTGAGCGTTTCATT	CTGAGCATTTCATTCA
C1117T	TCTTGACATGGTGGTGAATGAAA	CATCCCATTGATCTCAACATCTTTT	CCCTCTCAAGTCTC	CCTCTCAAATCTC
C1247T	AAAGTACTGGACAGAGCCTGAGAAG	GGAGGGCTCCCCTTCCCA	TTCCTCCCTGAAAGG	CCTCCTTGAAAGGTA
MDR1				
C3435T	AACAGCCGGGTGGTGTCA	ATGTATGTTGGCCTCCTTTGCT	CTCACGATCTCTTC	CCTCACAATCTCTT

MGB, minor groove binder; VIC, vasoactive intestinal contractor; 6-FAM: 6-carboxyfluorescein.
Bold indicates the site of substitution.

Results and discussion

Frequency of genotypic variants of CYP2B6, CYP3A4, and MDR1

We first analyzed the frequency of genotypic variants of the 60 patients seen at IMCJ. The *CYP2B6* genotypes were **1/*1* in 28 patients, **1/*2* in 4, **1/*4* in 5, **1/*6* in

Table 2
Frequency of CYP2B6 alleles and genotypes in 60 HIV-1 patients at IMCJ[a]

	Frequency (%)	95% CI
CYP2B6 allele		
**1*	78 (65)	56.5–73.5
**2*	9 (7.5)	3.8–14.2
**4*	10 (8.3)	4.4–15.3
**5*	2 (1.7)	0.3–6.0
**6*	21 (17.5)	10.7–24.3
CYP2B6 genotype		
**1/*1*	28 (46.7)	33.7–60.0
**1/*2*	4 (6.7)	1.8–16.2
**1/*4*	5 (8.3)	2.7–18.4
**1/*6*	13 (21.7)	12.1–34.2
**2/*4*	2 (3.3)	0.4–11.5
**2/*6*	3 (5.0)	1.0–13.9
**4/*4*	1 (1.7)	0.02–8.9
**4/*6*	1 (1.7)	0.02–8.9
**5/*5*	1 (1.7)	0.02–8.9
**6/*6*	2 (3.3)	0.4–11.5

95% CI, 95% confidence intervals.
[a] IMCJ, International Medical Center of Japan.

13, **2/*4* in 2, **2/*6* in 3, **4/*4* in 1, **4/*6* in 1, **5/*5* in 1, and **6/*6* in 2 (Table 2). The *CYP3A4* polymorphisms were only shown in T878C T/C heterozygote in three patients and other alleles were not found. *MDR1* C3435T polymorphisms were C/C in 19 patients, C/T in 31, and T/T in 10.

Correlation between the genotypic variants and EFV concentrations

Among the 35 patients who were on standard therapy of EFV-containing regimens, two had significantly higher plasma EFV concentrations (30.7 and 20.0 μM) than the other patients. *CYP2B6* genotype of the two patients was **6/*6* homozygote. The mean plasma EFV concentrations of patients with *CYP2B6 *6/*6* genotype (25.4 ± 7.5 μM, $n = 2$) were significantly higher than those of patients with **6* heterozygous genotypes (9.9 ± 3.3 μM, $n = 10$) and non-**6* alleles (8.0 ± 2.6 μM, $n = 23$) [one-way ANOVA ($p < 0.0001$) and post hoc Scheffe's F test showed statistically significant difference in plasma EFV concentration between **6/*6* genotype and **6* heterozygous genotypes ($p < 0.0001$), and non-**6* alleles ($p < 0.0001$)]. As shown in Table 3, the differences of patients' characteristics in each *CYP2B6* genotype were not significant, indicating that these characteristics did not influence the difference of EFV concentrations among the three genotypes. Then, we analyzed the additional nine samples (three with high EFV concentrations) obtained from the ONH and found that *CYP2B6* genotypes of the three patients with high EFV concentration were also **6/*6* genotype. Consequently, only five patients whose EFV concentrations were >20 μM had *CYP2B6 *6/*6* genotype (Fig. 1A). There was a significant correlation between *CYP2B6 *6/*6* genotype and high plasma EFV concentrations. In contrast, there was no correlation between *CYP2B6 *5*, *CYP3A4*, *MDR1* genotypes, and plasma EFV concentrations (Figs. 1B–D) in our small number of patients examined in this study.

Homozygous variant of *MDR1* C3435T has been shown to associate with responsiveness to EFV therapy [6]. However, no correlation was found between the C3435T polymorphisms and plasma EFV concentration in our study. Then, the plasma EFV concentration could not explain the favorable clinical result. EFV is a non-nucleoside reverse transcriptase inhibitor and, therefore, plays an anti-HIV-1 activity within HIV-1 infected cells but not in plasma. It remains to be elucidated whether or not the C3435T polymorphisms correlate with high intracellular EFV concentration.

Genetic polymorphism is known to be associated with variable level of *CYP2B6* expression in the liver. Especially, the expression levels of *CYP2B6 *6/*6* genotype are significantly lower than those of wild and other genotypes [7,11]. The high plasma EFV concentration may be explained by the low expression level of this genotype. Based on our new finding, extremely high plasma EFV concentration can be predicted by determining the genotype before commencement of EFV-containing therapy. In such patients, the EFV dose could be decreased to reduce the cost and more importantly the associated toxicity, without compromising its potency. In fact, one patient was treated with 200 mg EFV once daily due to severe side effects but had higher EFV concentrations than other patients with other genotypes. The frequency of the *CYP2B6 *6/*6* genotype in IMCJ patients was 3.3% (2 in 60 patients), whereas

Table 3
Patients' characteristics in each CYP2B6 genotype in 35 patients who were treated with standard EFV-containing therapy at IMCJ[a]

	Non-**6* genotypes	**6* heterozygote genotypes	**6/*6* genotype	*p*
n	23	10	2	
Male:female	23:0	9:1	2:0	n.s.
Age (years) (mean ± SD)	38.8 ± 8.2	45.3 ± 14.8	55.5 ± 19.1	n.s.
Weight (kg) (mean ± SD)	64.3 ± 11.5	58.6 ± 7.5	77.0 ± 5.1	n.s.
Alanine aminotransferase level (U/L) (mean ± SD)	31.0 ± 20.4	35.3 ± 14.0	46.5 ± 3.5	n.s.

n.s., not significant.
[a] IMCJ, International Medical Center of Japan.

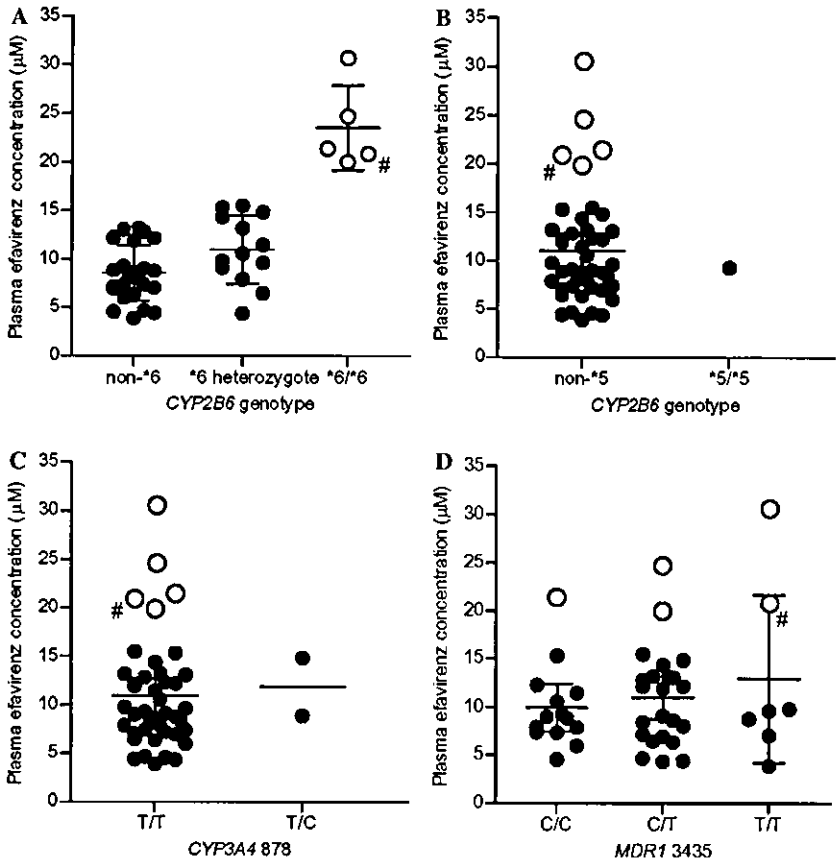

Fig. 1. Correlation between *CYP2B6 *6* genotypes (A), *CYP2B6 *5/*5* genotype (B), *CYP3A4* T878C genotype (C), *MDR1* 3435 genotypes (D), and plasma efavirenz concentrations. A total of 44 HIV-1 patients treated with standard EFV-containing regimens (35 from IMCJ and 9 from ONH) are depicted. Only homozygous genotypes of *CYP2B6* are represented in this figure [A (**6* genotypes) and B (**5/*5* genotype)]. Non-**6* genotypes ($n = 26$) include **1/*1* ($n = 18$), **1/*2* ($n = 2$), **1/*4* ($n = 3$), **2/*4* ($n = 2$), and **5/*5* ($n = 1$). **6* heterozygote genotypes ($n = 13$) include **1/*6* ($n = 9$), **2/*6* ($n = 3$), and **4/*6* ($n = 1$). Numbers of patients of *MDR1* 3435 C/C, C/T, and T/T genotypes are 14, 23, and 7 patients, respectively. Open circles: *CYP2B6 *6/*6* genotype holders, closed circles: other *CYP2B6* genotypes holders. Middle bar indicates mean, and upper and lower bars SD. (#) Patient on 200 mg EFV once daily.

the frequency was 6% in Caucasian population [7]. If these patients could be treated with low dose EFV based on genetic data of *CYP2B6 *6/*6* genotype, it could represent the first step of the Tailor-Made therapy of HIV-1 infection.

Acknowledgments

This study was supported by a Grant-in-Aid for AIDS Research from the Ministry of Health, Labour and Welfare of Japan (AIDS-H15-001), the Organization of Pharmaceutical Safety and Research (01-4), and the Japanese Foundation for AIDS Prevention (K.T.).

References

[1] Department of Health and Human Services, Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents, March 23, 2004.

[2] C. Marzolini, A. Telenti, L.A. Decosterd, G. Greub, J. Biollaz, T. Buclin, Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients, AIDS 15 (2001) 71–75.

[3] C. Csajka, C. Marzolini, K. Fattinger, L.A. Decosterd, J. Fellay, A. Telenti, J. Biollaz, T. Buclin, Population pharmacokinetics and effects of efavirenz in patients with human immunodeficiency virus infection, Clin. Pharmacol. Ther. 73 (2003) 20–30.

[4] J.C. Adkins, S. Noble, Efavirenz, Drugs 56 (1998) 1055–1064.

[5] B.A. Ward, J.C. Gorski, D.R. Jones, S.D. Hall, D.A. Flockhart, Z. Desta, The cytochrome P450 2B6 (CYP2B6) is main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate maker of CYP2B6 catalytic activity, J. Pharmacol. Exp. Ther. 306 (2003) 287–300.

[6] J. Fellay, C. Marzolini, E.R. Meaden, D.J. Back, T. Buclin, J.P. Chave, L.A. Decosterd, H. Furrer, M. Opravil, G. Pantaleo, D. Retelska, L. Ruiz, A.H. Schinkel, P. Vernazza, C.B. Eap, A. Telenti, Swiss HIV Cohort Study, Response to antiretroviral treatment in HIV-1-infected individuals with allelic variants of the multidrug resistance transporter 1: a pharmacogenetics study, Lancet 359 (2002) 30–36.

[7] T. Lang, K. Klein, J. Fischer, A.K. Nussler, P. Neuhaus, U. Hofmann, M. Eichelbaum, M. Schwab, U.M. Zanger, Extensive genetic polymorphism in the human CYP2B6 gene with impact on expression and function in human liver, Pharmacogenetics 11 (2001) 399–415.

[8] R. Eiselt, T.L. Domanski, A. Zibat, R. Mueller, E. Presecan-Siedel, E. Hustert, U.M. Zanger, J. Brockmoller, H.P. Klenk, U.A. Meyer, K.K. Khan, Y.A. He, J.R. Halpert, L. Wojnowski,