妊娠と授乳

未治療の結核は，結核の治療をすること以上に妊婦と胎児に危険を与える．未治療結核の妊婦から生まれた新生児は健康な妊婦から生まれた新生児に比べ低体重になることがあるし，まれに先天性結核を合併する可能性がある．

治療はINH，RFP，EBで開始すべきである．SMをEBの代用として用いてはいけない．WHO（世界保健機関）とIUATLD（国際結核肺疾患予防連合）はPZAのルーチンの使用を勧めているが，米国では安全性を示すデータが十分ではないということで，PZAのルーチンの使用を勧めていない．PZAを初期治療に含まない場合は最短の治療期間は9か月となる．INHの投与を受けている妊婦にはピリドキシン25 mg/日の併用が必要である．

INH，RFP，EBは胎盤を通過するが，いずれも催奇形性はない．SMは胎児に障害を与えることが証明されている唯一の抗結核薬であるが，耳の発達障害を生じ，先天性聴覚障害を引き起こす可能性がある．KM，AMK，CPMも同様の副作用を起こすと思われるが，重度の障害についての特別な報告はほとんどない．PASはかつてINHとともに使われたが，この2薬剤の投薬を受けた妊婦から生まれた胎児への催奇形性はなかった．CSとTHの危険性を決定するほど十分なデータはない．THによる非特異的な催奇形性についての報告が一つある．フルオロキノロンでは若い動物に関節病変を生じやすいというデータがあるので，できれば妊婦の投与は控えるべきである．

一般に抗結核薬の投与は，中絶の適応とはならない．しかし，二次薬の危険性については知られていないものがあるので，耐性結核菌の治療の場合は，十分なカウンセリングが必要である．

一次薬の投与を受けている女性の授乳は問題ない．母乳内に分泌される薬剤はわずかであり，新生児に影響を与えることはないからである．逆に，母乳内に抗結核薬が分泌されるからといって，新生児の活動性結核や潜在性結核に対して治療効果を期待してはいけない．ピリドキシンは授乳中の母親だけでなく，新生児にも与えられるべきである．フルオロキノロンは授乳中の母親に投与すべきでない．

免疫機能低下

免疫機能が低下したコンプロマイズド・ホストに合併した結核といえども，治療の遅れがなく耐性菌でなければ一般に治療には良好に反応する．多剤耐性結核菌では治療に難渋し，コンプロマイズド・ホストでは予後不良である．RFPは肝臓においてチトクロームP450を誘導し，各種薬剤（ステロイド，免疫抑制剤，抗HIV薬など）の代謝を促進する．その結果，併用薬剤の血中濃度の低下をもたらし，基礎疾患の悪化をきたすことがある．したがって，薬剤の組み合わせには十分注意し，可能であれば併用薬剤の血中濃度のモニタリングも考慮すべきである．その結果によっては併用薬剤の増量が必要な場合がある．

ここでは，免疫機能が低下する病態のうち最も結核発病のリスクの高いHIV感染症について詳しく述べる．

1. HIV感染症合併結核の治療上の問題点

HIV感染症合併結核の治療行う上で注意すべき点としては，おもに以下の3点がある．

a）薬剤の副反応が起こりやすい．

HIV感染症では薬剤の副反応が起こりやすく，特に，抗結核薬では皮疹と肝障害の副作用が多い．抗結核薬と抗HIV薬を同時に内服する場合は両者の副反応を生じる可能性が高く，原因薬剤の同定が困難となるだけでなく，

すべての治療を中断せざるを得ない状況に追い込まれることがある.

b) リファマイシン系薬剤と抗HIV薬との間に薬剤相互作用がある.

リファマイシン系薬剤（RFP, リファブチン, リファペンチン）は肝臓と腸管においてチトクローム P450（CYP3A4）の誘導作用が強い. CYP3A4により代謝されるプロテアーゼ阻害薬や非核酸系逆転写酵素阻害薬の血中濃度は, リファマイシン系薬剤と併用することにより著しく低下し, 抗HIV作用は低下する. また, 逆にプロテアーゼ阻害薬は強力なCYP3A4抑制作用をもつ.

結核の治療中に上記2系統の抗HIV薬を開始する場合は, RFPよりもCYP3A4の誘導が弱いリファブチン〔わが国では承認されておらず, エイズ治療薬研究班（東京医科大学臨床病理科）より譲り受ける〕を用いることが多かったが, CDC（米国疾病管理センター）[4]はRFPとリトナビル, リトナビル+サキナビル, エファビレンツとの併用を可能としたため選択肢が増えた. 当院ではRFPとエファビレンツの併用を行っているが, エファビレンツの血中濃度の測定を行い, 有効性を確認している.

c) 免疫再構築症候群が起こることがある

結核治療中に早期に抗HIV療法を開始した場合, 結核の一時的悪化をみることがある[5]. 症状・所見としては高熱, リンパ節腫脹, 胸部X線所見の悪化（肺野病変および胸水の増悪）などがみられる. この反応は細胞性免疫能が回復し, 生体側の反応が強くなったために引き起こされると考えられており, 免疫再構築症候群といわれている.

免疫再構築症候群と診断された場合は抗結核薬の変更は必要ないが, 症状が強い場合は抗炎症剤や短期の副腎皮質ステロイドの投与, 重症例では抗HIV薬の中止が必要になることがある.

2. HIV感染症合併結核の治療

感受性菌であれば, 非HIV感染者における結核と同様に抗結核薬によく反応する. 治療法としては, INH, RFP, PZA, EB（あるいはSM）の4剤を2か月間投与し, その後INH, RFPの2剤（あるいはEBを加えた3剤）を4か月継続して, 全治療期間を6か月とする, いわゆる短期療法でよいとされている[6]. しかし, 臨床的に効果の遅い症例や3か月以上結核菌の喀痰培養が陽性の症例では治療期間を延長すべきである.

INH・RFP両剤耐性を含む耐性結核菌を多剤耐性結核菌というが, HIV感染者に多剤耐性結核菌感染が生じた場合は極めて予後不良である. 感受性の残った薬剤とニューキノロン製剤などを用い, 長期の治療が必要となる.

3. 強力な抗HIV療法（highly active antiretroviral therapy: HAART）の開始時期

結核の診断がついたときにすでに以前よりHAARTを行っている患者では, HAARTが有効であれば抗HIV薬はそのまま継続し, 結核の治療を開始する.

結核の診断がついた時点でHAARTを行っていない症例については, 結核の治療を優先する. 結核の治療開始後に新たにHAARTを開始する場合は,【1. HIV感染症合併結核の治療上の問題点】で示した3点についての配慮が必要であり, いつからHAARTを開始すべきか悩む症例が多い. 現時点では, HAARTの開始時期についてevidenceの明確な推奨はなく, 以下のようにいくつかの指針が示されている.

CDC/ATS（米国胸部疾患学会）は結核治療とHAARTを同時に始めてはいけないとしており, HAARTを4～8週遅らせるように推奨している.

WHOの推奨[7]では, CD4数＜200/mm³では結核の治療が順調であれば早期にHAARTを開始する（2週～8週後）. CD4数200～

350/mm³ではHAART開始を考慮し，開始するのであれば，結核の初期治療を2か月間が終了後，HAARTを開始する．CD4＞350/mm³では結核の治療終了後，HAARTを開始する．

British HIV Associationの推奨[8]では，CD4＜100/mm³ではできるだけ早急にHAARTを開始する．しかし，医師により，2か月まで待つという医師もいる．CD4 100～200/mm³では2か月後にHAARTを開始する．CD4＞200/mm³では6か月の結核治療終了後にHAARTを開始する．

CD4の数値により種々の基準があるが，筆者らはおもにWHOの基準を用いている．しかし，抗結核薬の副作用やそのほかの合併症のために，予定通りHAARTを開始できない症例が多いのが実情である．基本的には症例毎に判断しなければならない．

小児

小児で一般にみられる一次結核症（肺門縦隔リンパ節炎，中・下葉病変，空洞がない）は，成人にみられる肺結核に比べ結核菌量が少なく，治療失敗・再発・耐性化の生じる可能性は低い．

INH，RFP，PZAの3剤治療が中心となる．この3剤の治療成功率は95%，副作用は2%以下である．この3剤治療が勧められる理由は，小児では菌量が少ない，小児は多量の薬剤を飲むのが困難である，EBを内服した場合の視力検査を行うのが困難であるなどである．しかし，耐性菌が疑われるときはEBを投与してもよく，その場合の投与量は15～20 mg/kg/日である．SM，KM，AMKの投与も可能である．週3回の間欠投与は勧められない．INHを内服中で，栄養状態不良例，症状のあるHIV感染者，授乳中の小児にはピリドキシンの併用が勧められる．

小児の場合，結核菌の検出が難しいので，治療効果を菌の検出で判定するのが難しい．臨床的所見や胸部X線写真所見で効果判定する場合もでてくる．しかし，肺門リンパ節腫脹や無気肺の改善に2～3年かかることもあり，胸部X線写真の異常所見が治療継続の判定材料にならない場合がある．治療失敗や再発の判断はしばしば困難である．薬剤の変更などを臨床所見だけで行わなければならないことがある．

一般に小児の肺外結核は，肺結核と同様の治療が行われる．例外は播種性結核と髄膜炎であり，両者は6か月間の治療では不十分であり，INH，RFP，SM，PZAの4剤治療を2か月，その後INH，RFP10か月，合計12か月行うことが勧められる．

HIV陽性小児の肺結核の適切な治療法は明確になっていない．米国小児科学会は初期治療として少なくともINH，RFP，PZAの3種類を2か月投与し，治療期間は少なくとも9か月間とすべきであるとしている．

高齢者

高齢者では糖尿病，悪性腫瘍など種々の合併症を有している場合が多く，そのため治療に難渋し，死亡率も高い．全身状態が不良のため抗結核薬の内服が困難で，注射剤しか投与できない症例もしばしば経験する．低栄養のため中心静脈栄養を入院時より行わなければならない症例もある．高齢者は肝，腎の機能低下を有している場合があり，それに応じた薬剤投与法を検討する必要がある．1日あたりの最大投与量の減量も考慮すべきであり[3]，治療開始後は副作用の出現を注意深く追う必要がある．一般に，80歳以上では薬剤性肝障害を生じやすいのでPZAを控え，65歳以上ではアミノグリコシドを避けるべきとされている．しかし，標準治療から著しく逸脱した治療を行ってはいけない．

高齢者は合併症の治療のために，種々の治

療薬を内服している場合がある．RFPは前述のようにCYP3A4を誘導し，他の薬剤の血中濃度を低下させてしまう．Ca拮抗薬，βブロッカー，ワーファリン，アゾール系抗真菌薬，副腎皮質ステロイド薬，免疫抑制剤，スルホニルウレア剤，テオフィリン，メキシチールなどの血中濃度が低下し，合併症が悪化する可能性があるので注意が必要である．逆に，フェニトイン，カルバマゼピンなどの抗けいれん薬はINHにより代謝が阻害され，血中濃度が上昇し中毒症状が生じる可能性がある．可能であれば，併用薬の血中濃度測定を行いながら，治療をすすめるべきである．

関節リウマチ薬投与時の治療

最近の関節リウマチ薬であるTNF α阻害薬には，インフリキシマブ（抗ヒトTNF αモノクローナル抗体製剤）とエタネルセプト（完全ヒト型可溶性TNF α / LT α レセプター製剤）がある．前者には関節リウマチだけでなく，Crohn病，Beçhet病による難治性網膜ぶどう膜炎にも適応がある．

TNFは肺胞マクロファージの活性化や肉芽腫形成といった結核菌に対する免疫防御に不可欠なサイトカインであり，これを抑えるTNF α阻害薬は結核発病のリスクをもっている．報告では播種性結核（粟粒結核）および肺外結核（髄膜，胸膜，リンパ節等）を含む結核が発症し，死亡例も認められている．結核の既感染者ではこれらの薬剤を用いると，症状の顕在化および悪化のおそれがあるため，本剤投与に先立って結核に関する十分な問診，胸部X線検査およびツベルクリン反応検査を行い，適宜胸部CT検査等を行うことにより，結核感染の有無を確認することが重要である．そして活動性結核や結核感染が疑われる患者には，結核治療経験のある医師に相談して，結核治療・予防内服を考慮するよう求められている．しかし，BCG接種が行われている日本では，ツベルクリン反応がどの程度であれば潜在性結核感染とするかは，決められない．近年，リンパ球のインターフェロンγ産生能を測定することによって結核感染の診断を行う方法（QuantiFERON-TB 第2世代）が普及しつつあり，これを用いて結核感染の有無を判断することは有意義である．

RFPはTNF α阻害薬の代謝に影響を及ぼさないので，両者の併用は特に問題ない．

糖尿病

糖尿病に結核を合併するリスクは高く，当院の入院結核患者の10～15%は糖尿病合併例である．糖尿病については未治療でコントロール不良例が多い．したがって，しばしば結核の治療と同時にインスリンを用いた糖尿病の治療を開始することになる．

抗結核薬が糖尿病に及ぼす影響として，INH多量投与での炭水化物代謝阻害による血糖値上昇，PASによる耐糖能障害などが知られている．また，前述したようにRFPは肝臓のチトクローム P450を誘導し，薬剤の代謝を亢進するが，スルホニルウレア剤の代謝にも影響があり，血中濃度を低下させ，効果を減弱させる可能性があるので，注意が必要である．

結核の標準治療期間を延長する場合として糖尿病があげられており，3か月（90日）間延長することができる[9]．これは糖尿病合併例では，排菌量の多い症例が多く，菌陰性化が遅れる症例が少なからず存在するためである．

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Successful Efavirenz Dose Reduction in HIV Type 1–Infected Individuals with Cytochrome P450 2B6 *6 and *26

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Background. Efavirenz (EFV) is metabolized primarily by cytochrome P450 2B6 (CYP2B6), and high plasma concentrations of the drug are associated with a G→T polymorphism at position 516 (516G→T) of *CYP2B6* and frequent central nervous system (CNS)–related side effects. Here, we tested the feasibility of genotype-based dose reduction of EFV.

Methods. *CYP2B6* genotypes were determined in 456 human immunodeficiency virus type 1 (HIV-1)–infected patients who were receiving EFV treatment or were scheduled to receive EFV-containing treatment. EFV dose was reduced in *CYP2B6* 516G→T carriers who had high plasma EFV concentrations while receiving the standard dosage (600 mg). EFV-naive homozygous *CYP2B6* 516G→T carriers were treated with low-dose EFV. In both groups, the dose was further reduced when plasma EFV concentration remained high.

Results. *CYP2B6* 516G→T was identified in the **6* allele (found in 17.9% of our subjects) and a novel allele, **26* (found in 1.3% of our patients). All EFV-treated *CYP2B6* **6/*6* and **6/*26* carriers had extremely high plasma EFV concentrations (>6000 ng/mL) while receiving the standard dosage. EFV dose was reduced to 400 mg for 11 patients and to 200 mg for 7 patients with persistently suppressed HIV-1 loads. EFV-containing treatment was initiated at 400 mg in 4 *CYP2B6* **6/*6* carriers and one **6/*26* carrier. Two of them still had a high plasma EFV concentration while receiving that dose, and the dose was further reduced to 200 mg, with successful HIV-1 suppression. CNS-related symptoms improved with dose reduction in 10 of the 14 patients, although some had not been aware of the symptoms at initial dosage.

Conclusions. Genotype-based EFV dose reduction is feasible in *CYP2B6* **6/*6* and **6/*26* carriers, which can reduce EFV-associated CNS symptoms.

Efavirenz (EFV) is an important anti–HIV-1 agent in current combination treatment and is usually prescribed at a fixed dosage of 600 mg once daily [1, 2]. The plasma concentration of EFV varies widely in individuals, and the prevalence of CNS symptoms is higher in those with high concentrations [3]. EFV is metabolized mainly by cytochrome P450 2B6 (CYP2B6), and its concentration was reported to be associated with the *CYP2B6* 516G→T genetic polymorphism [4–8]. Previously, we reported that all Japanese patients with the 516TT genotype had extremely high EFV concentrations (>6000 ng/mL), without exception [4]. However, other studies reported some exceptional cases of subjects with the 516TT genotype with normal concentrations, although most of the

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516TT carriers had high concentrations [5–8]. The difference between our data and those of others may reflect polymorphisms other than 516G→T in *CYP2B6*. If this is the case, analysis of other polymorphisms and determination of the *CYP2B6* haplotype may be helpful in predicting EFV plasma levels. In the present study, we determined the *CYP2B6* haplotype of 456 HIV-1–infected patients and analyzed its relationship with EFV concentration in 111 of them. Furthermore, we reduced the EFV dose in 12 patients whose EFV concentrations had been high while receiving the standard dosage. We also used reduced doses of EFV in 5 EFV-naive patients in whom EFV concentration was predicted to become extremely high while receiving the standard dosage, on the basis of *CYP2B6* haplotype determination.

SUBJECTS, MATERIALS, AND METHODS

Patients. This analysis included 60 previously reported HIV-1–infected individuals at the International Medical Center of Japan (IMCJ) [4] and another group of 396 HIV-1–infected patients who were receiving treatment of the standard dosage (600 mg once daily) of EFV or were scheduled to begin receiving EFV-containing treatment at the following 11 hospitals in Japan: Hokkaido University (Sapporo), Sendai Medical Center (Sendai), Niigata University (Niigata), Higashi Saitama Hospital (Hasuda), IMCJ (Tokyo), Ishikawa Prefecture Central Hospital (Kanazawa), Nagoya Medical Center (Nagoya), Osaka National Hospital (Osaka), Hiroshima University (Hiroshima), Kyushu Medical Center (Fukuoka), and Kumamoto University (Kumamoto). The ethics committee of each hospital approved this study, and each participant gave written informed consent.

CYP2B6 *genotype.* DNA samples were extracted from peripheral blood specimens obtained from participants, and genotyping of *CYP2B6* 64C→T (*rs8192709*), 415A→G (*rs12721655*), 499C→G (*rs3826711*), 516G→T (*rs3745274*), 777C→A (*rs* number not available), 785A→G (*rs2279343*), 1375A→G (*rs* number not available), and 1459C→T (*rs3211371*) was performed by allele-specific fluorogenic 5′ nuclease chain reaction assay with predesigned primers and TaqMan MGB probes (TaqMan SNP Genotyping Assay; Applied Biosystems) or previously published primers and MGB probes [4]. In subjects confirmed to carry 499C→G, all 9 exons of the *CYP2B6* gene were amplified with previously published primers [9], and their DNA sequences were directly determined. For haplotype analysis of the *CYP2B6* allele, PCR amplification of the genomic region (3130 bp) containing exons 4 and 5 was performed using sense primer 5′-AACTGTACTCACTCCCAGAGT-3′ and antisense primer 5′-CTCCCTCTGTCTTTCATTCTGT-3′. The amplified PCR product was subjected to subcloning, and the DNA sequence of each clone was determined. For genotyping of *CYP2B6* 983T→C (*rs28399499*), new primers and probes were designed as follows: forward primer, 5′-GCCTGAAATGCCTCTTTAAAATGAGATTC-3′; reverse primer, 5′-GCGATGTGGGCCAATCAC-3′; VIC probe for 983T, 5′-CTGTTCAATCTCCC-3′; and FAM probe for 983C, 5′-CTGTTCAGTCTCCC-3′. The obtained genotyping results of *CYP2B6* 983T→C for >10 patients were confirmed by direct sequencing of exons 7 and 8 with use of primers published elsewhere [9].

Plasma EFV concentration. Samples of peripheral blood were collected during a daytime office visit (9–16 h after the patient took EFV) from the patients who had received EFV treatment at 600-mg dose at bedtime for >4 weeks. EFV concentration was measured by the reverse-phase high-performance liquid chromatography (HPLC) method [10]. For cases of EFV-dose reduction, plasma concentration was measured >2 weeks after the change in EFV dose. Differences in EFV concentrations between groups were examined for statistical significance with Student's t test. A P value <.05 denoted the presence of a statistically significant difference.

RESULTS

Novel* CYP2B6 *allele. The *CYP2B6* genotype was analyzed in 456 HIV-1–infected patients, including 442 Japanese, 8 other Asians, and 6 others. During the analysis, we noticed that some patients had the *CYP2B6* 499C→G polymorphism, substituting Ala for Pro at the 167th amino acid, which is already registered in the SNP Database, although the *CYP2B6* allele containing 499G had not been determined yet. TaqMan Genotyping Assay indicated that *CYP2B6* 449G was heterozygous with 499C in 12 individuals (2.6%), who were all Japanese (table 1). Direct sequencing of all the exons confirmed the results of TaqMan Genotyping Assay and showed that 8 subjects had 516GT, 785AG, and 1375AA genotypes; 3 had 516TT, 785GG, and 1375AA genotypes; and 1 had 516GT, 785AG, and 1375AG genotypes without any other mutation. Subcloning analysis of the PCR products confirmed that 499G always coexisted in the same allele with 516T and 785G (figure 1). Therefore, it was concluded that the novel haplotype containing 499C→G had 2 other single-nucleotide polymorphisms (SNPs): 516G→T and 785A→G. We formally registered this novel allele with the Human Cytochrome P450 Allele Nomenclature Committee, and it was designated "*CYP2B6 *26*" (http://www.cypalleles.ki.se/). With use of this nomenclature, the *CYP2B6* haplotype of the twelve 499C→G carriers were identified as eight **1/*26* heterozygotes, three **6/*26* heterozygotes, and one **23/*26* heterozygote (table 1). The allelic frequency of **26* was 1.3% in our study participants.

CYP2B6 *haplotype determination.* In 456 HIV-1–infected individuals, we determined the genotypes of 9 SNP positions (64C→T, 415A→G, 499C→G, 516G→T, 777C→A, 785A→G, 983T→C, 1375A→G, and 1459C→T) in *CYP2B6* (table 1). No *CYP2B6* genetic polymorphism was detected in 211 patients, and their haplotype was determined to be **1/*1*. The haplotypes

Table 1. *CYP2B6* haplotype and allele frequencies in study participants.

CYP2B6 status	*CYP2B6* genotype at nucleotide position								No. (%) of subjects	
	415	499	516	777	785	983	1375	1459	All[a]	Japanese
Haplotype:										
**1/*1*	AA	CC	GG	CC	AA	TT	AA	CC	211 (46.3)	205 (46.4)
**1/*2*	AA	CC	GG	CC	AA	TT	AA	CC	30 (6.6)	30 (6.8)
**1/*4*	AA	CC	GG	CC	AG	TT	AA	CC	43 (9.4)	42 (9.5)
**1/*5*	AA	CC	GG	CC	AA	TT	AA	CT	4 (0.9)	3 (0.7)
**1/*6*	AA	CC	GT	CC	AG	TT	AA	CC	104 (22.8)	101 (22.9)
**1/*23*	AA	CC	GG	CC	AA	TT	AG	CC	2 (0.4)	2 (0.5)
**1/*26*	AA	CG	GT	CC	AG	TT	AA	CC	8 (1.8)	8 (1.8)
**2/*4*	AA	CC	GG	CC	AG	TT	AA	CC	6 (1.3)	5 (1.1)
**2/*5*	AA	CC	GG	CC	AA	TT	AA	CT	1 (0.2)	1 (0.2)
**2/*6*	AA	CC	GT	CC	AG	TT	AA	CC	5 (1.1)	5 (1.1)
**4/*4*	AA	CC	GG	CC	GG	TT	AA	CC	5 (1.1)	5 (1.1)
**4/*6*	AA	CC	GT	CC	GG	TT	AA	CC	12 (2.6)	12 (2.7)
**5/*5*	AA	CC	GG	CC	AA	TT	AA	TT	1 (0.2)	1 (0.2)
**5/*6*	AA	CC	GT	CC	AG	TT	AA	CT	1 (0.2)	1 (0.2)
**6/*6*	AA	CC	TT	CC	GG	TT	AA	CC	19 (4.2)	17 (3.8)
**6/*26*	AA	CG	TT	CC	GG	TT	AA	CC	3 (0.7)	3 (0.7)
**23/*26*	AA	CG	GT	CC	AG	TT	AG	CC	1 (0.2)	1 (0.2)
Total									456	442
Allele:										
**1*	A	C	G	C	A	T	A	C	613 (67.2)	596 (67.4)
**2*	A	C	G	C	A	T	A	C	42 (4.6)	41 (4.6)
**4*	A	C	G	C	G	T	A	C	71 (7.8)	69 (7.8)
**5*	A	C	G	C	A	T	A	T	8 (0.9)	7 (0.8)
**6*	A	C	T	C	G	T	A	C	163 (17.9)	156 (17.6)
**23*	A	C	G	C	A	T	G	C	3 (0.3)	3 (0.3)
**26*	A	G	T	C	G	T	A	C	12 (1.3)	12 (1.4)
Total									912	884

[a] Including 442 Japanese, 8 other Asians (5 Thai, 2 Koreans, and 1 Filipino), 4 Hispanics, and 2 non-Hispanic whites.

of single-SNP carriers with 64CT, 785AG, 1375AG, and 1459CT were determined to be **1/*2*, **1/*4*, **1/*23*, and **1/*5*, respectively. Those of homozygous polymorphism carriers with 785GG only, 1459TT only, and both 516TT and 785GG were determined to be **4/*4*, **5/*5*, and **6/*6*, respectively. When the fact that **2* is the only allele harboring 64C→T is considered, patients with 64CT and 785AG; 64CT and 1459CT; and 64CT, 516GT, and 785AG were identified as **2/*4*, **2/*5*, and **2/*6* heterozygotes, respectively. Patients with both 516GT and 785GG genotypes but without other polymorphisms were determined to have **4/*6* heterozygotes. There were 104 patients (22.8%), including 101 Japanese, who held both 516GT and 785AG genotypes without other polymorphisms. There were 2 possible haplotypes, **1/*6* and **4/*9*, in this genotypic pattern. When the fact that **9* had not been reported in Japanese subjects was considered [11], we found that all 101 Japanese were **1/*6* heterozygotes. Haplotype analysis by subcloning of PCR products described above was performed in the 3 others, and their haplotype was determined as **1/*6*. One Japanese patient had 516GT, 785AG, and 1459CT genotypes without other polymorphisms, and there were 2 possible haplotypes, **1/*7* and **5/*6*, in this genotypic pattern. Because **7* had not been reported in Japanese subjects [11], the haplotype in this patient was determined to be **5/*6*. Overall, the allelic frequency of **6* was 17.9% in our study participants. The 415A→G, 777C→A, and 983T→C polymorphisms, which are the determinants of **8*, **3*, and **18*, respectively, were not observed in our subjects.

CYP2B6 *and EFV concentration.* We determined the *CYP2B6* haplotype in 251 patients at IMCJ and in 205 patients at the other 10 hospitals. Of the 251 genotype-analyzed patients at IMCJ, 101 were being treated or were beginning treatment with a standard dose of EFV during this study period (figure 2). Plasma EFV concentrations were measured in all 101 patients, including sixty-seven 516GG holders, twenty-eight 516GT holders, and six 516TT holders. To clarify the effect of the 516TT genotype, EFV concentration was also measured in ten 516TT holders undergoing treatment with the standard dose of EFV at other hospitals. The mean concentration (± SD)

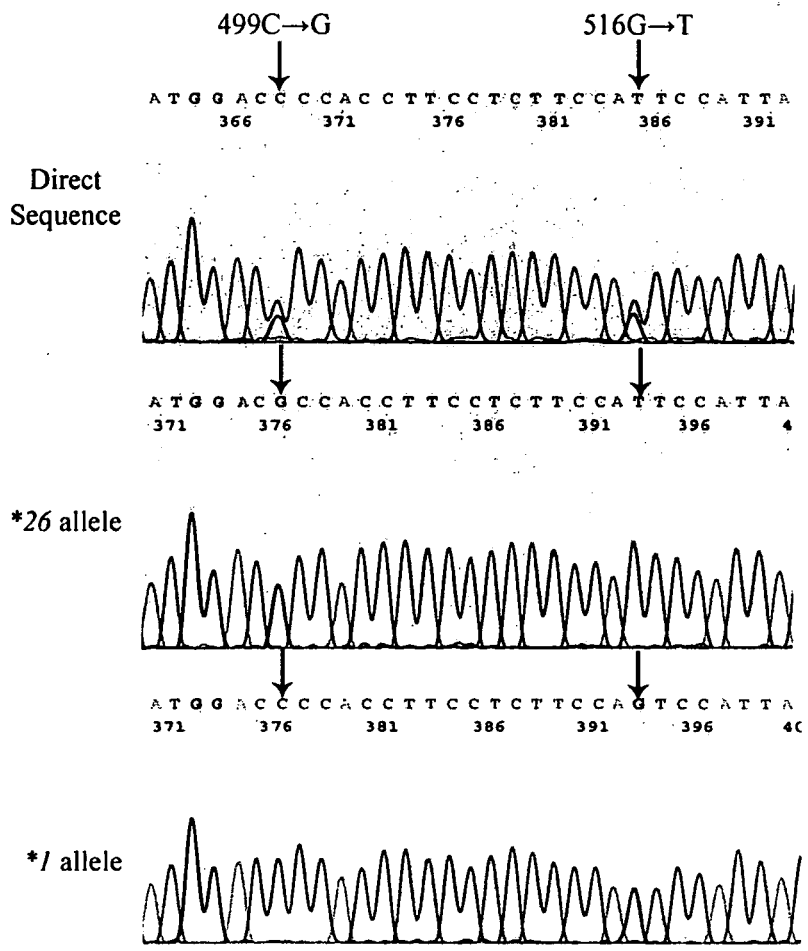

Figure 1. Direct *(top panel)* and subclonal *(middle and bottom panels)* sequences of *CYP2B6* in 499C→G carriers. The genotypes 499G, 516T, and 785G (not shown) exist in the same allele, newly designated as "*CYP2B6 *26*." The same results were obtained in all 9 patients with the 499CG, 516GT, and 785AG genotypes, and the patients were identified as eight **1/*26* carriers and one **23/*26* carrier. Although shown are the sense-strand sequences only, both strands were sequenced. Arrows indicate the variant nucleotide positions 499 and 516.

of EFV in all patients was 3740 ± 2800 ng/mL. When divided by the genotype of position 516, striking discreteness was observed (figure 3). All (95% CI 91.1%–100%) of the 16 carriers of 516TT genotype, including fourteen **6/*6* carriers and two **6/*26* carriers, had extremely high EFV concentrations (>6000 ng/mL). Their mean concentrations (9500 ± 2580 ng/mL) were many orders of magnitude higher than those of the other genotype carriers ($P < 10^{-4}$). There was no significant difference in EFV concentration between **6/*6* carriers and **6/*26* carriers. On the other hand, there were only 2 patients who had such high EFV concentrations among the other genotype carriers. One was a **1/*6* carrier (7140 ng/mL), and the other was a **1/*26* carrier (9710 ng/mL). Direct sequencing of all *CYP2B6* exons showed no polymorphism other than 499C→G, 516G→T, and 785A→G in these individuals. The mean concentrations of EFV of the twenty-eight 516GT carriers, including twenty-five **6*-heterozygotes (3320 ± 1240 ng/mL; $P < 10^{-4}$) and three **26*-heterozygotes (5470 ± 3840 ng/mL; $P < 10^{-4}$), were significantly higher than those of the sixty-seven 516GG genotype carriers (2450 ± 770 ng/mL). None (95% CI 0%–0.1%) of the 516GG carriers had a high EFV concentration (>6000 ng/mL). Considered together, it was concluded that high plasma EFV concentrations were associated with *CYP2B6 *6* and **26* and that *CYP2B6 *6/*6* and **6/*26* carriers had extremely high plasma EFV concentrations at standard dosage, without exception.

EFV dose reduction from 600 mg. To determine whether the EFV dose can be reduced in patients who have a high concentration while receiving the standard dose, a dose-reduction protocol was applied in 12 patients with high plasma concentrations (>6000 ng/mL [range, 6170–14,690 ng/mL]), including one **1/*26* heterozygote, nine **6/*6* homozygotes, and two **6/*26* heterozygotes. Before the dose reduction, plasma HIV-1 load was undetectable (<50 copies/mL) in all patients for >1 month with treatment of a standard antiretroviral regimen containing 600 mg of EFV. In these 12 patients,

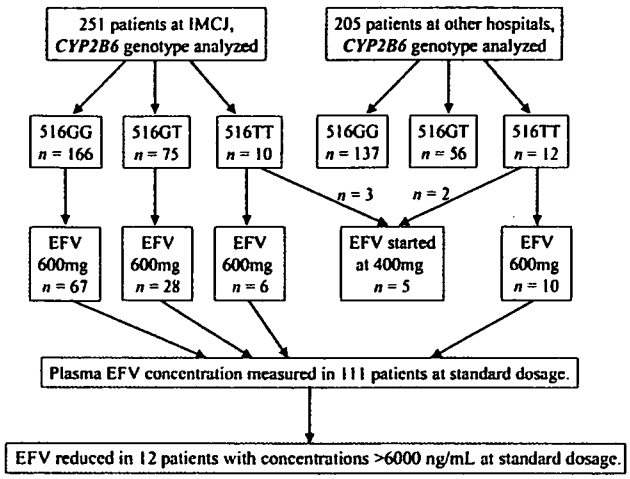

Figure 2. Flow diagram of study participants. The *CYP2B6* genotype was analyzed in 251 patients at the International Medical Center of Japan (IMCJ) and in 205 patients at other hospitals. Standard dosage of EFV was administered in 101 patients at IMCJ, including sixty-seven *CYP2B6* 516GG, twenty-eight 516GT, and six 516TT holders, whose EFV concentrations were measured. Ten 516TT holders at the other hospitals were administered standard dosages of EFV, and their EFV concentrations were also measured. A reduced-dose (400 mg) regimen of EFV was initiated in 5 other 516TT holders.

the EFV dose was reduced from 600 to 400 mg in 11 subjects and was further reduced to 200 mg in 7 of them who consented to further reduction. The plasma EFV concentrations decreased by approximately one-third (36%–46%), to 3720–6160 ng/mL, with dose reduction from 600 to 400 mg in 10 of 11 subjects, and further decreased by approximately one-half (51%–59%), to 1620–2960 ng/mL, with reduction from 400 to 200 mg in 6 of 7 subjects (figure 4). In one patient who had a markedly high EFV concentration (14,690 ng/mL) at the standard 600-mg dose, however, the concentration decreased unexpectedly by 69%, to 4500 ng/mL, with the reduction to 400 mg and further decreased by 82%, to 790 ng/mL, lower than the recommended range (>1000 ng/mL) [1], with the reduction from 400 to 200 mg. Therefore, the dose was increased in this patient back to 400 mg. In another patient who had reported severe dizziness during treatment with the standard dose (600 mg), the dose was reduced immediately to 200 mg at the patient's request. The plasma EFV concentration was also markedly high in this patient (14,360 ng/mL) during treatment with the standard dosage. However, it decreased by 83%, to 2410 ng/mL, with the dose reduction to 200 mg. Consequently, the final EFV dose was 400 mg in 5 subjects and 200 mg in 7 subjects. The determined dosage for each patient was continued for >6 months (the longest was 26 months for a patient who received the 200-mg dose), and the plasma HIV-1 load was continuously undetectable in all patients.

EFV initiation at 400-mg dose. Our analysis showed that *CYP2B6* **6/*6* and **6/*26* carriers had extremely high EFV concentrations, without exception (figure 3), and that dose reduction was possible in patients with high EFV concentration with retention of therapeutically effective anti–HIV-1 activity (figure 4). In the next phase of our study, we used an antiretroviral regimen containing a reduced dose (400 mg) of EFV in 5 EFV-naive patients (four **6/*6* homozygotes and one **6/*26* heterozygote). Before the introduction of low-dose EFV-containing regimen, the plasma HIV-1 loads had been undetectable during receipt of the previous protease inhibitor–containing regimen in all 5 patients. Their EFV concentrations were 4080–9450 ng/mL, and all such concentrations (95% CI, 99.5%–100%) were therapeutically adequate (>1000 ng/mL) at the 400-mg dose (figure 5). One **6/*6* homozygote developed severe dizziness, necessitating discontinuation of EFV-treatment at day 16. His EFV concentration was 5430 ng/mL. In one **6/*26* heterozygote, severe thrombocytopenia emerged, probably because of overdosage of rifabutin prescribed for the treatment of coinfection with *Mycobacterium intracellulare*, and EFV treatment was stopped at day 15. The EFV concentration was 5770 ng/mL. Two of the remaining 3 patients still had extremely high EFV concentrations (6760 and 9450 ng/mL) at the 400-mg dose, and their dose was subsequently reduced to 200 mg. The plasma EFV concentrations decreased to 2690 and 3660 ng/mL (i.e., by 60% and 61%, respectively). Consequently, 2 subjects

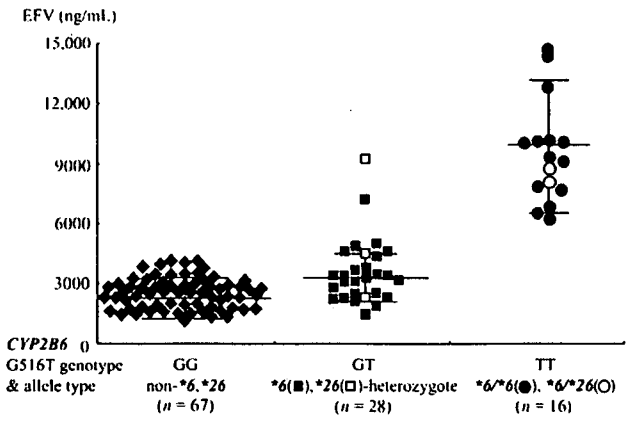

Figure 3. Plasma efavirenz (EFV) concentrations measured during EFV treatment with standard dose (600 mg). A total of 111 HIV-1–infected patients treated with EFV-containing regimens were divided into 3 groups on the basis of nucleotide genotype at *CYP2B6* position 516 (GG, GT, or TT), and their plasma EFV concentrations were compared. Blackened squares, **6* heterozygote with allele other than **26*; unblackened squares, *CYP2B6* 499C→G carriers (**26* heterozygote with allele other than **6*); blackened circles, **6* homozygote (**6/*6*); unblackened circles, *CYP2B6* 499C→G carriers (**6/*26* heterozygotes); blackened diamonds, other genotype carriers. Horizontal lines represent the mean (± SD) plasma EFV concentrations for each group.

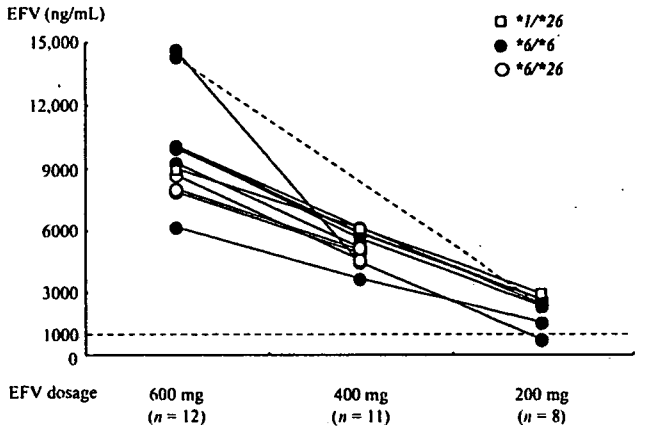

Figure 4. Dose reduction of efavirenz (EFV) in 12 patients whose concentrations were extremely high while receiving treatment with standard dose (600 mg). EFV dose was reduced from 600 to 400 mg in 11 patients and was further reduced, to 200 mg, in 7 patients. In one patient who had severe CNS symptoms while receiving treatment with standard dose, EFV dose was directly reduced to 200 mg (concentrations connected with a dotted line). The suggested minimum target concentration (1000 ng/mL) is indicated by the thin line.

discontinued the EFV-containing regimen, and 3 subjects continued low-dose EFV-containing regimen (400 mg for 1 patient and 200 mg for 2 patients). The low-dose regimen was continued for >6 months, and the plasma HIV-1 load was persistently undetectable in all 3 patients.

Improvement of CNS symptoms. As described above, the EFV dose was reduced from 600 to 400 and 200 mg as the final dose in 5 and 7 subjects, respectively (figure 4), and it was decreased from 400 mg as the initial dose to 200 mg for 2 other subjects (figure 5). To delineate the changes in CNS symptoms associated with the decrease in EFV concentration, a questionnaire survey of these 14 patients was conducted regarding 6 items: dizziness, strange dreams, depression, irritability, concentration problems, and sleep difficulty. More than 1 month after the dose had been reduced to the lowest dose, the patients were asked to judge the 6 CNS symptoms above at initial and final doses, with use of a 5-grade system ("none," "slight," "sometimes," "often," and "always"). Ten (71%) of the 14 patients had some of the aforementioned CNS symptoms during treatment with the initial dose (table 2). The most common symptom was dizziness (57%), followed by strange dreams (50%). Interestingly, all the symptoms improved after dose reduction in the 10 patients. Furthermore, dizziness and concentration problems disappeared during treatment with the final dose in one-half of the patients, although strange dreams and sleep difficulty were still reported by all the patients who had those difficulties at the initial dose. Finally, when the patients were asked whether they wanted to reincrease EFV to the previous dose, all 10 patients with CNS symptoms at the initial dose answered "no" (9 answered "absolutely no").

DISCUSSION

In this study, we identified a novel *CYP2B6* allele, **26*, which includes 499C→G, 516G→T, and 785A→G in 12 Japanese patients, and we showed that, without exception, all **6/*6* and **6/*26* carriers, all holding 516TT, had extremely high plasma EFV concentrations while receiving the standard dose (600 mg) [4]. In other reports, however, there were some exceptional subjects with 516TT who had normal concentrations of EFV, and the discreteness of the EFV concentration with the position 516 genotype was not as clear as it was in our patients [5–8]. This difference may be because some of the 516TT carriers had other *CYP2B6* alleles, such as **7* (containing 516G→T, 785A→G, and 1459C→T), **9* (containing 516G→T only), and **13* (containing 415A→G, 516G→T, and 785A→G). Those alleles could not be found in our subjects, and their effects on EFV concentration were not well described. Because numerous additional *CYP2B6* variants with impact on expression and/or function were recently reported [12–18], correct determination of *CYP2B6* haplotype seems indispensable for prediction of EFV plasma levels.

We reduced the EFV dose in 12 patients whose plasma EFV concentrations were extremely high while receiving the standard dose, and we initiated EFV treatment at a 400-mg dose in 5 EFV-naive **6/*6* and **6/*26* carriers. In most patients, the plasma EFV concentration decreased proportionally with the dose-reduction ratio. In 2 subjects, however, the concentrations decreased much more than expected, given the dose reduction

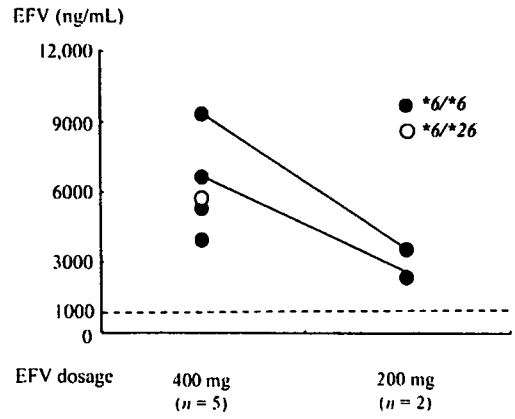

Figure 5. Introduction of low-dose efavirenz (EFV)-containing antiretroviral regimen to *CYP2B6 *6/*6* and **6/*26* carriers. Treatment was started in 4 EFV-naive carriers *CYP2B6 *6/*6* and one **6/*26* carrier, with 400-mg EFV-containing regimens. EFV dose was further reduced, to 200 mg, in 2 patients whose EFV concentrations were >6000 ng/mL while receiving treatment with the 400-mg dose.

Table 2. Changes in CNS-related symptoms after reduction of efavirenz dosage.

Symptom	No. (%) of subjects who reported symptom status during efavirenz treatment		
	Present[a] ($n=14$)	Improved[b]	Disappeared[b]
Dizziness	8 (57)	8 (100)	4 (50)
Strange dreams	7 (50)[c]	7 (100)[c]	0 (0)
Depression	5 (36)	5 (100)	1 (20)
Irritability	5 (36)	5 (100)	1 (20)
Concentration problem	4 (29)	4 (100)	2 (50)
Sleep difficulty	3 (21)	3 (100)	0 (0)
Any of the above	10 (71)[c]	10 (100)[c]	4 (40)

[a] Including the 4 grades "slight," "sometimes," "often," and "always" at the initial dosage. Includes 2 patients whose efavirenz treatment was originally 400 mg and was reduced to 200 mg.

[b] Percentage of those who initially reported "present."

[c] Including 1 patient whose efavirenz dose was originally 400 mg and was reduced to 200 mg.

ratio. Both of these patients had markedly high concentrations at standard dosage. Hasse et al. [19] reported a patient with excessively high plasma EFV concentration at standard dose, which decreased to one-thirtieth following dose reduction from 600 to 200 mg. Long-term exposure to such excessively high concentrations may induce CYP2B6 enzymatic expression in the liver, which could result in an unexpectedly large decrease in plasma EFV concentration by dose reduction if deinduction of the enzyme takes several weeks. At the 400-mg dose, the plasma concentrations of EFV were therapeutically adequate in all the treated **6/*6* and **6/*26* carriers in this study. Regarding the reduced dose, it is noteworthy that a phase II study during EFV development supported the use of a lower dose [20]. The same study indicated that the 600-mg dose of EFV is associated with a high rate of adverse events that could lead to discontinuation, which suggests that the lower dose of 400 mg may be almost as effective without the high discontinuation rate. In the present study, associated with the dose-reduction regimen, a significant number of patients experienced improvement of CNS symptoms, which was unexpected on the basis of previous reports [5, 21, 22]. Interestingly, some of these patients did not appreciate their clinical state and considered themselves to have no CNS-related symptoms during the standard-dose treatment. However, after the dose reduction, they reassessed the status and evaluated symptoms during the treatment with the standard dose as associated with CNS symptoms and indicated that the reduced dose of EFV relieved them of such symptoms. Because EFV-treated patients often stick to the regimen, previous reports of symptom questionnaires conducted during the standard treatment might have underestimated the EFV-associated CNS symptoms [5, 21, 22]. However, this finding might be confounded by placebo effect, because the patients were told that their EFV levels were high while receiving the initial dose and decreased throughout the dose-reduction protocol. Because of this possible placebo effect, a double-blind, placebo-controlled study would best address this question.

EFV dose reduction and initiation of EFV treatment at reduced dose is possible with therapeutic anti–HIV-1 potency retained in *CYP2B6 *6/*6* homozygotes and **6/*26* heterozygotes, which could relieve the patients of the EFV-associated CNS symptoms. It may also decrease the risk of development of EFV-resistant HIV-1 after mandatory treatment discontinuation, such as abdominal surgery [23], and reduce the treatment cost, an important issue in developing countries [24]. After dose reduction, however, careful monitoring is necessary until larger studies confirm the safety of reduced dose in such specific genotype carriers.

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