	SAT/SMT Solverなど解析ツールの進化 ・関連鍵攻撃：AESへの攻撃など、鍵スケジュールを積極的に利用 ・不能差分攻撃 ・線形攻撃の一般化
実装に関する傾向	・より広い範囲の製品・サービス ・より安いコスト：消費電力など ・より安全に：進化する実装攻撃への防御が必要
注目すべき暗号	・HIGHT(2006) ：ブロック長 64ビット・鍵長128ビット、RFID向け、ハードウエア性能に優れ、約3Kgateで実装可能 ・CLEFIA(2007)：ブロック長128ビット・鍵長128/192/256ビット、ソフト・ハードともにバランス良く優位な性能 ・PRESENT(2008)：ブロック長64ビット・鍵長80/128ビット、速度は遅いが2Kgate以下（暗号回路のみ）の実装も可能

表 7　ブロック暗号の最新動向

項目	内容
暗号利用モード	ブロック暗号の欠点を補うパッチ
最近の動向	単なるパッチから安全な暗号プリミティブの手軽な構成方法へ ・多様化、様々なバリエーション ・証明可能安全性 ・(例) Tweakable Block Cipher ：ブロック暗号からブロック暗号へ（ディスクセクタ暗号化利用モードとしての応用あり）
評価方法に関する意見	・全般（公募カテゴリ）：用途、鍵長、ブロック長等毎に分類 ・セキュリティ要件（証明可能安全性）：証明の前提が崩れたときの耐性について、例えばHMAC 鍵回復攻撃など ・パフォーマンス要件：内部で用いるプリティ部はできる限り共通化して評価すべき ・標準化・利用実績・各種標準化をどこまで扱うのか

表 8　暗号利用モードの動向

項目	内容
最近の動向	・CMAC (OMAC)の NIST SP800-38B 公開⇒日本の貢献 - 偽装困難性を一個の鍵で実現した紹介可能安全な MAC ・Hash 関数ベースの MAC への攻撃 - 脆弱なハッシュ関数を用いた場合に鍵回復攻撃が可能 ・段数を削除したブロック暗号を利用した MAC (MT-MAC, PELICAN 等) - ただし証明可能安全性は精査の必要あり

表 9 MAC の動向

項目	内容
エンティティ認証	通信相手が意図した正しい通信相手であることを確認
最新動向	・フォーマルメソッドによる安全性証明がだんだん使えるようになってきた ・しかし、プリミティブが理想化できない場合に暗号学的メソッドの融合が必要
電子政府推奨暗号リストのエンティティ認証カテゴリの評価	・形式的な手法（フォーマルメソッド）を用いた評価⇒世界初 ・暗号プリミティブが既存の場合、これらを理想的安全として評価。新規の場合、理想化せずに安全性を検証 ・ただし、フォーマルメソッドツール自体の信頼性評価が重要

表 10 エンティティ認証の動向

項目	内容
動向と現状	・1995年、SHA-1 が FIPS 180-1 ・2002年、SHA-256/384/512 が FIPS 180-2 ・2004年、SHA-224がFIPS 280-2 ・2005年、SHA-1の Collision 攻撃 実はMD5が先に Collision発見され、後にMD5WithRSA1024Encriptionのデジタル証明書が解読される ・2007年、SHA-3 competition開始、SHA-3は 2012年に選定予定
SHA-3 competition	・SHA-3 は SHA-2 の replace でなく、FIPS 180-2 への追加を想定

	・最重要の評価基準は安全性 ・ハード性能は必須ではない ・応募総数64，第一ラウンド通過51，現在42
CRYPTRECへのコメント	・現在は汎用、特殊用途やハッシュ関数関連モードの検討の余地あり ・評価項目：SHA-3 と同じでよいが、ハードウエア性能も必要では

表 11　ハッシュ関数の動向

項目	内容
IBE　（　Identity Based Encryption）	自由なビット列を公開鍵暗号として設定可能な暗号で、色々な応用が知られている
最近の動向	・標準化が進んでいる： IEEE P1363.3，RFC5091 ・NISTも興味をもっている（NIST Workshop） ・世界で少なくとも600万人が使用
2008年度の暗号技術監視委員会の活動として、IDベース暗号WGが開設された	・報告書をまとめている最中 ・検討課題：運用（IDの信頼性、PKGの信頼性、ユーザ鍵管理、共通パラメータ管理）

表 12　IBE の動向

2.2.4本研究で採用する暗号アルゴリズムについて

本研究で採用する暗号アルゴリズムは、「AES(Advanced Encryption Standard)」を採用する。また、暗号化モードは「CBC(Cipher Block Chaining)」を利用する。

AESは、それまでの暗号規格「DES」がコンピューターの技術進歩により脆弱なものとなったため、NIST（アメリカ国立標準技術研究所）が次世代の暗号化標準（Advanced Encryption Standard）として選定したRIJNDAEL（ラインドール）という共通鍵方式の暗号化アルゴリズムで、FIPS PUB（米国連邦情報処理規格）197として規定、公開されている。ブロック長は128ビット、鍵長は128、192、256ビットから選べるようになっており、速度も「DES」に比べ非常に高速である。現在、強度、速度の両方において最も優れた暗号化アルゴリズムとして、米国政府機関における採用義務化はもとより、日本における電子政府推奨暗号やNESSIE（欧州連合の暗号規格）に公式認定されるなど、今後も世界中の多くで暗号標準への採用が進んでいくものと推測される。

よって本研究で試作する暗号化通信ツールでは、暗号化アルゴリズムとして「AES」を採用した。

2.3 漢字コード最新動向

2009年11月10日、文部科学省の「文化審議会国語分科会」において、常用漢字表の改正案が承認された。現行の常用漢字表にある1945字から「銑」「錘」「勺」「匁」「脹」の5字を削除し、新たに196字を追加する改正案で、2010年度の内閣告示を目指している。 新しい常用漢字表が告示されると、「シフトJIS」や「EUC-JP」といった従来からある文字コードを使用するシステムで大きな問題が生じる恐れがある。新しい常用漢字表2136字のなかに、シフトJISやEUC-JPでは書けない（扱えない）漢字が含まれている。

勺　錘　銑　脹　匁

図 6　新しい常用漢字表から削除される字種候補（5字）

挨　曖　宛　嵐　畏　萎　椅　彙　茨　咽　淫　唄　鬱
怨　媛　艶　旺　岡　臆　俺　苛　牙　瓦　楷　潰　諧
崖　蓋　骸　柿　顎　葛　釜　鎌　韓　玩　伎　亀　毀
畿　臼　嗅　巾　僅　錦　惧　串　窟　熊　詣　憬　稽
隙　桁　拳　鍵　舷　股　虎　錮　勾　梗　喉　乞　傲
駒　頃　痕　沙　挫　采　塞　埼　柵　刹　拶　斬　恣
摯　餌　鹿　叱　嫉　腫　呪　袖　羞　蹴　憧　拭　尻
芯　腎　須　裾　凄　醒　脊　戚　羨　煎　腺　詮　箋
膳　狙　遡　曽　爽　痩　踪　捉　遜　汰　唾　堆　戴
誰　旦　綻　緻　酎　貼　嘲　捗　椎　爪　鶴　諦　溺
塡　妬　賭　藤　瞳　栃　頓　貪　丼　那　奈　梨　謎
鍋　匂　虹　捻　罵　剝　箸　汎　汎　阪　斑　眉　膝
肘　訃　阜　蔽　餅　璧　蔑　哺　蜂　貌　頬　睦　勃
昧　枕　蜜　冥　麺　冶　弥　闇　喩　湧　妖　瘍　沃
拉　辣　藍　璃　慄　侶　瞭　瑠　呂　賂　弄　籠　麓
脇

図 7　新しい常用漢字表に追加される字種候補（196字）

表外漢字字体表には、印刷に用いるべき「印刷標準字体」として、「遡」「塡」「頬」など 1022 字が収録されている。ところが、シフト JIS や EUC-JP では、これら 1022 字をすべてはサポートできていない。そして、サポートできない文字のいくつかが、新しい常用漢字表に追加される見込みである。

常用漢字表	S-JIS	EUC-JP	UCS-2	UTF-16	UTF-8
叱	-	-	-	D842DF9F	F0A0AE9F
塡	-	8FB8B4	5861	5861	E5A1A1
剝	-	-	525D	525D	E5899D
頬	-	8FE8A4	9830	9830	E9A0B0

図 8　新しい常用漢字表にあってシフト JIS にない 4 字

したがって「叱←口へんに七」「塡」「剝」「頬」の 4 字を含む新しい常用漢字表をサポートするためには、文字コードは、Unicode（UTF-16 か UTF-8）を使う必要性がでてくる。これまでの常用漢字と同じ構成要素の字体を、やはり許容字体として併記することを要望します。その上で、「付 情報機器に搭載されている印刷文字字体の関係で…当該の字体の使用を妨げるものではない。」という文言は、削除すべき等、改定常用漢字表試案への意見が多数出されている。文字コードは、将来的に Unicode で統一される方向であると思われるが、現状、一部の OS 等では、コードが振られていない異体字の存在や、標準収録されている漢字違い、拡張漢字未対応など、様々な課題がある。

このため、患者参加型ポータルサイト構築、治療データ蓄積、印刷という概念のない患者携帯端末等への情報発信等、漢字を使用する場面での検証・考慮が求められる。

2.3.1 本研究における対応について

事前調査の結果、上記のようなことが判明した為、今回試作した暗号化通信ツールで利用する文字コードは、UTF-8 としている。

・設定したOSの文字コード　→　UTF-8
・設定したミドルウェアの文字コード　→　UTF-8

刊行物一覧

菊池 嘉

Authors	title	Journal
INSIGHT-ESPRIT Study Group; SILCAAT Scientific Committee, Abrams D, Lévy Y, Losso MH, Babiker A, Collins G, Cooper DA, Darbyshire J, Emery S, Fox L, Gordin F, Lane HC, Lundgren JD, Mitsuyasu R, Neaton JD, Phillips A, Routy JP, Tambussi G, Wentworth D.	Interleukin-2 therapy in patients with HIV infection.	N Engl J Med. 2009 Oct 15;361(16):1548-59
Watanabe T, Yasuoka A, Tanuma J, Yazaki H, Honda H, Tsukada K, Honda M, Gatanaga H, Teruya K, Kikuchi Y, Oka S.	Serum (1-->3) beta-D-glucan as a noninvasive adjunct marker for the diagnosis of Pneumocystis pneumonia in patients with AIDS.	Clin Infect Dis. 2009 Oct 1;49(7):1128-31.
Kamimura M, Watanabe K, Kobayakawa M, Mihara F, Edamoto Y, Teruya K, Kikuchi Y, Oka S.	Successful absorption of antiretroviral drugs after gastrojejunal bypass surgery following failure of therapy through a jejunal tube.	Intern Med. 2009;48(12):1103-4.
Yotsuyanagi H, Kikuchi Y, Tsukada K, Nishida K, Kato M, Sakai H, Takamatsu J, Hige S, Chayama K, Moriya K, Koike K.	Chronic hepatitis C in patients co-infected with human immunodeficiency virus in Japan: a retrospective multicenter analysis.	Hepatol Res. 2009 Jul;39(7):657-63.
Honda H, Gatanaga H, Matsumura J, Kamimura M, Goto K, Tsukada K, Honda M, Teruya K, Kikuchi Y, Oka S.	Favourable use of non-boosted fosamprenavir in patients treated with warfarin.	Int J STD AIDS. 2009 Jun;20(6):441
Gatanaga H, Tsukada K, Honda H, Tanuma J, Yazaki H, Watanabe T, Honda M, Teruya K, Kikuchi Y, Oka S.	Detection of HIV type 1 load by the Roche Cobas TaqMan assay in patients with viral loads previously undetectable by the Roche Cobas Amplicor Monitor.	Clin Infect Dis. 2009 Jan 15;48(2):260-2

BRIEF REPORT

Serum (1→3) β-D-Glucan as a Noninvasive Adjunct Marker for the Diagnosis of *Pneumocystis* Pneumonia in Patients with AIDS

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High serum (1→3) β-D-glucan levels are described in patients with *Pneumocystis* pneumonia (PCP). We evaluated the diagnostic value of β-D-glucan in 111 patients with AIDS who had PCP and confirmed its usefulness. However, it does not correlate with disease severity and is not suitable for monitoring response to treatment.

Pneumocystis pneumonia (PCP) is associated with significant morbidity and mortality in patients with human immnuodeficiency virus type 1 (HIV-1) infection [1, 2]. PCP is usually diagnosed microscopically by identifying *Pneumocystis jirovecii* in bronchoalveolar lavage fluid (BALF) or bronchoscopically obtained lung tissue [3]. Bronchoscopy, however, is invasive, especially in patients with hypoxemia associated with PCP. Therefore, a minimally invasive method is desirable for diagnosis.

Serum (1→3) β-D-glucan (hereafter, β-D-glucan) is a common component of the cell wall of most fungi and is the major component of the cyst of *P. jirovecii*. Therefore, it is measured in patients who are suspected to have PCP, as well as in those with deep-seated mycotic infections [4]. Although β-D-glucan has been used as an adjunct test for the diagnosis of PCP [5], only a few reports have evaluated its level [5–7] and its correlation with other parameters (such as lactate dehydrogenase [LDH] level) in mixed populations that included a small number of HIV-infected patients [6]. For this purpose, we analyze the correlation between β-D-glucan levels and other parameters among patients with AIDS who have PCP.

Methods. We evaluated data from 111 consecutive HIV-1 infected patients with PCP at the International Medical Center of Japan, an 885-bed tertiary care hospital in Tokyo, from April 1997 through July 2007. This study was approved by the Ethics Review Committee of the hospital (IMCJ-H20-569). Patients who did not undergo diagnostic bronchoscopy were excluded from the study.

Medical records were reviewed, and the following data were collected: age; sex; mode of infection; $CD4^+$ cell count; serum levels of LDH, β-D-glucan, and C-reactive protein (CRP); and alveolar-arterial oxygen tension gradient ($AaDO_2$). Serum β-D-glucan levels were measured using the Fungitec G MK test (Seikagaku). Manipulation was performed described elsewhere [4, 5], in accordance with the manufacturer's instructions. Serum β-D-glucan levels in HIV-1–infected patients without PCP determined during the same period were used as a control. If serum β-D-glucan levels had been determined several times for the same patient, only the first measurement was included. Although oral and esophageal candidiasis are superficial infections, they were included as an independent factor and analyzed. In this report, the term *candidiasis* refers to oral and/or esophageal candidiasis.

The diagnosis of PCP was established by identification of *jirovecii* in BALF. Each BALF specimen (100 μL) was centrifuged at 900 *g* for 2 min by means of a Shandon Cytospin III device and a monolayer of deposited cells were stained using Diff Quik (Dade Behring) and examined microscopically for the presence of *P. jirovecii*.

Data were expressed as means ± standard deviations (SD) or as medians. Differences in categorical variables between patients with PCP and control patients were assessed using the Mann-Whitney *U* test. The Mann-Whitney *U* test (for comparison of 2 groups) and the Kruskal-Wallis test (for comparison of 3 groups) were used for analysis of differences in serum β-D-glucan levels. A receiver-operating-characteristic (ROC) curve was constructed to illustrate the cutoff value for β-D-glucan. The relationships were analyzed by linear regression analysis. Differences were considered significant at $P < .05$. Statistical analyses were performed using SPSS, version 17 (SPSS).

Results. A total of 111 patients had a definite diagnosis of PCP, and serum β-D-glucan level was measured in each. (

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these patients, 67 also had candidiasis at admission. Of the control group (425 patients who did not have PCP), 28 had candidiasis, 3 had cryptococcal infection, and 394 had neither.

The patients with PCP were older than the control patients (mean ± SD, 42.3 ± 11.9 vs 38.7 ± 11.7 years; $P < .01$), and $CD4^+$ cell counts were significantly higher in the control patients than in the patients with PCP (mean ± SD, 178.6 ± 155.6 vs 49.1 ± 63.1 cells/μL; $P < .001$). Sex and mode of transmission of HIV were similar in both groups ($P = .81$ and $P = .53$, respectively). All patients with PCP received treatment, and 6 patients died of PCP.

Of the patients with PCP, 67 had candidiasis and 44 did not; of the control patients, 28 had candidiasis, 3 had cryptococcal infection, and 394 did not have any fungal infection. The median (range) serum β-D-glucan level in each group was 171.2 (14.9–2966), 209.6 (2.4–2469), 7.40 (1.0–73.0), 22.7 (9.3–69.7), and 8.25 (1.0–310) pg/mL, respectively (Figure 1). The median serum level of β-D-glucan among all patients with PCP (174.8 [2.4–2966] pg/mL) was significantly higher than that among the control patients (8.2 [1.0–310.1] pg/mL) ($P < .001$). The presence of candidiasis in both the PCP group and the control group and of cryptococcal infection in the control group did not significantly influence serum levels of β-D-glucan ($P = .53$, $P = .83$, and $P = .08$, respectively).

With respect to the diagnostic value of β-D-glucan, the area under the ROC curve for β-D-glucan level was 0.964 (95% confidence interval, 0.945–0.984) (Figure 2). A β-D-glucan cutoff value of 23.2 pg/mL (which represented the technique's threshold of detection) had a sensitivity of 96.4% and a specificity of 87.8%.

There was no correlation between serum levels of β-D-glucan and $AaDO_2$ at room air ($r = 0.125$; $P = .30$), LDH ($r = .030$; $P = .76$), or CRP ($r = .002$; $P = .62$). In 42 instances, serum β-D-glucan levels were measured before and after treatment. On the basis of a cutoff value of 23.2 pg/mL, normalization of serum β-D-glucan levels was noted in 7 patients. In contrast, serum β-D-glucan levels slightly increased in 9 patients despite clinical improvement being noted at week 3. This finding indicates that β-D-glucan levels reflected the clinical course in only 16.7% of patients (7 of 42) within 3 weeks of treatment.

Discussion. The present study has reported 3 major findings. The first major finding is the usefulness of quantitative measurement of serum β-D-glucan levels for the diagnosis of PCP. With a cutoff value of 23.2 pg/mL, β-D-glucan level had

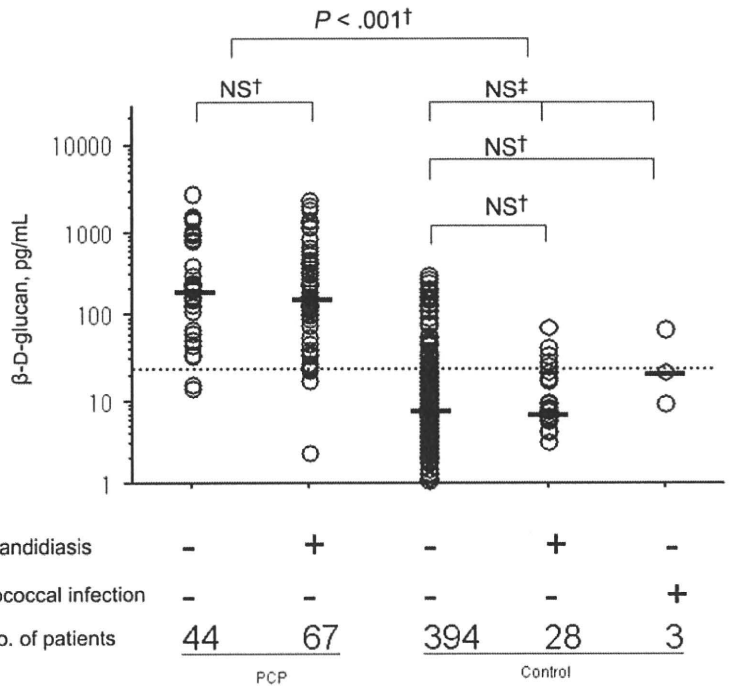

Figure 1. Serum levels of (1→3) β-D-glucan. Levels of β-D-glucan in serum were examined before treatment of *Pneumocystis* pneumonia (PCP), candidiasis, and cryptococcal infection. The Mann-Whitney *U* test (†) and the Kruskal-Wallis test (‡) were used for comparison of serum β-D-glucan levels. Individual values are plotted, and horizontal bars represents medians. The presence of candidiasis in both the PCP group and the control group and of cryptococcal infection in the control group did not significantly influence serum β-D-glucan levels ($P = .53$, $P = .83$, and $P = .08$, respectively). Serum β-D-glucan levels were significantly higher in patients with PCP than in those without PCP, despite the presence of candidiasis and cryptococcal infection ($P < .001$). NS, not significant.

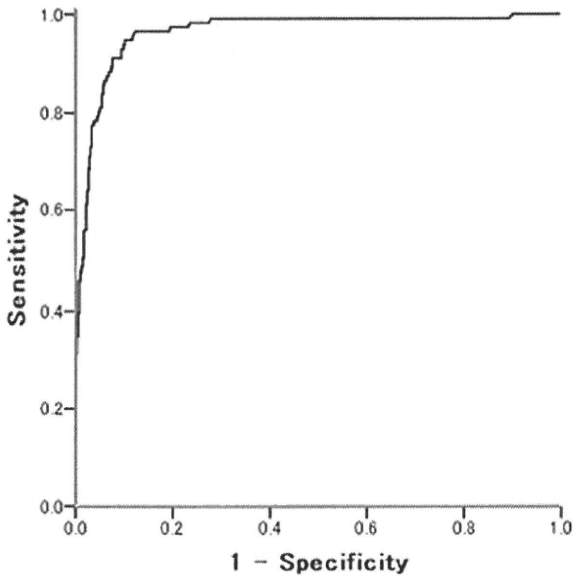

Figure 2. Receiver-operating-characteristic (ROC) curve for the (1→3) β-D-glucan cutoff. The area under the ROC curve for β-D-glucan was 0.964 (95% confidence interval, 0.945–0.984). A β-D-glucan cutoff value of 23.2 pg/mL (which represented the technique's threshold of detection) had a sensitivity of 96.4% and a specificity of 87.8%.

a high sensitivity (96.4%) and specificity (87.8%) for the diagnosis of PCP. Interestingly, serum β-D-glucan levels among those with PCP were not affected by the presence of superficial fungal infection (ie, oral and/or esophageal candidiasis). Deep-seated mycosis other than PCP and cryptococcal infection are quite rare in Japan, and no patients were suspected to have aspergillosis in this study. Hence, we could not analyze the effect of aspergillosis. According to our data and those of others [4], β-D-glucan level increases during cryptococcal infection, but the level is significantly lower than that observed during PCP. The number of *P. jirovecii* organisms in the lungs of patients with AIDS may be significantly higher than that in patients without AIDS [8]. In a meta-analysis of 7 reports in which PCP was diagnosed by staining, the average sensitivity of induced sputum was 56%, whereas that of BALF was >95% [9]. To eliminate false-positive and false-negative results, we analyzed data obtained only from patients who underwent BALF analysis and had a definite diagnosis of PCP.

The second major finding was that the serum level of β-D-glucan does not reflect the severity of PCP in patients with AIDS. Although Shimizu et al [10] reported that β-D-glucan is a negative prognostic marker for PCP in patients with connective tissue diseases, there was no significant difference in β-D-glucan level between survivors and nonsurvivors in our study. Furthermore, Tasaka et al [6] reported that serum levels of LDH correlated with those of β-D-glucan in patients with PCP, whereas our data showed no such relationship. These differences are probably the result of differences in the patient populations studied, especially regarding whether the patients have HIV-1 infection. Considered collectively, these results emphasize the need for further studies to define the exact relationship between β-D-glucan and prognosis as well as LDH.

The third major finding of the present study was that β-D-glucan level did not reflect the effectiveness of therapy. In nearly 85% patients, serum β-D-glucan levels did not decrease to normal despite clinical improvement. Furthermore, 20% of patients had increased levels of β-D-glucan during the early phase of treatment. However, β-D-glucan levels normalized several months or years after treatment in all patients. These results mean that β-D-glucan levels increase transiently early during treatment and decrease thereafter but do not always return to normal during treatment. The transient increase in β-D-glucan level is probably due to lysis of *P. jirovecii* shortly after treatment.

PCP is usually suspected on the basis of chest radiographic findings, clinical symptoms, and low $CD4^+$ cell counts in HIV-infected patients. In the present study, a high serum level of β-D-glucan (especially >23.2 pg/mL by the MK test) was found to be highly indicative of PCP in practically all patients with AIDS. Therefore, the β-D-glucan test is useful for the diagnosis of PCP, especially in HIV-infected patients who are unable to undergo bronchoscopy owing to severe hypoxemia. In conclusion, the present study has demonstrated that β-D-glucan is a useful, noninvasive adjunct marker for the diagnosis of PCP in patients with AIDS. However, its serum levels do not reflect the severity of the disease, and it is not suitable for monitoring response to treatment.

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Potential conflicts of interest. All authors: no conflicts.

References

1. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus–associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. Clin Infect Dis **2000**; 30(Suppl 1):S5–14.
2. Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994–98: the EuroSIDA study. Lancet **2000**; 356:291–6.
3. Cushion MT, Beck JM. Summary of *Pneumocystis* research presented at the 7th International Workshop on Opportunistic Protists. J Eukaryot Microbiol **2001**; 48(Suppl):101S–5S.
4. Obayashi T, Yoshida M, Mori T, et al. Plasma (1→3)-beta-D-glucan measurement in diagnosis of invasive deep mycosis and fungal febrile episodes. Lancet **1995**; 345:17–20.
5. Yasuoka A, Tachikawa N, Shimada K, Kimura S, Oka S. (1→3) beta-D-glucan as a quantitative serological marker for *Pneumocystis carinii* pneumonia. Clin Diagn Lab Immunol **1996**; 3:197–9.

6. Tasaka S, Hasegawa N, Kobayashi S, et al. Serum indicators for the diagnosis of pneumocystis pneumonia. Chest **2007**; 131:1173–80.
7. Marty FM, Koo S, Bryar J, Baden LR. (1→3) beta-D-glucan assay positivity in patients with *Pneumocystis (carinii) jiroveci* pneumonia. Ann Intern Med **2007**; 147:70–2.
8. Thomas CF Jr, Limper AH. *Pneumocystis pneumonia.* N Engl J Med **2004**; 350:2487–98.
9. Cruciani M, Marcati P, Malena M, Bosco O, Serpelloni G, Mengoli C. Meta-analysis of diagnostic procedures for *Pneumocystis carinii* pneumonia in HIV-1-infected patients. Eur Respir J **2002**; 20:982–9.
10. Shimizu A, Oka H, Matsuda T, Ozaki S. (1→3)-beta-D glucan is a diagnostic and negative prognostic marker for *Pneumocystis carinii* pneumonia in patients with connective tissue disease. Clin Exp Rheumatol **2005**; 23:678–80.

INTERNAL MEDICINE

□ CASE REPORT □

Successful Absorption of Antiretroviral Drugs after Gastrojejunal Bypass Surgery following Failure of Therapy through a Jejunal Tube

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Abstract

Lopinavir, an antiretroviral drug against human immunodeficiency virus (HIV), was administered through various routes to an HIV-infected patient with duodenal malignant lymphoma. Antiretroviral drugs were first administered through a jejunal tube, and then through bypass route between the stomach and jejunum that was 20 cm distal from the ligament of Treitz after surgery. Oral administration through the bypass achieved sufficient serum concentrations of lopinavir, whereas administration through the jejunal tube did not.

Key words: lopinavir, serum concentration, absorption, viral suppression, jejunal tube

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Introduction

Patients infected with the human immunodeficiency virus (HIV) can now survive longer thanks to recent advances in antiretroviral therapy (ART). Although the present case is a patient with acquired immunodeficiency diseases syndrome (AIDS)-related malignant lymphoma of the duodenum, non-AIDS-related carcinoma has been increasing among HIV-infected patients in the ART era (1). For a variety of reasons, such as metastasis in the brain and upper gastrointestinal tract, the need for enteral feeding has been increasing. The site of absorption of ART within the alimentary tract remains poorly defined in humans (2).

Case Report

A 28-year-old man was admitted to our hospital diagnosed with AIDS-related malignant lymphoma of the duodenum, of the diffuse large B cell type, stage IV. He had not received antiretroviral therapy on admission. The CD4 cell count was 113/mm^3 and plasma HIV-RNA was 7.1×10^4 copies/mL, indicating severe immunosuppression. Further examination showed Candida esophagitis, an AIDS-defining disease. Due to duodenal stenosis caused by the lymphoma, the patient was unable to take any food orally except for liquids. Furthermore, bile had to be drained by percutaneous transhepatic cholangiole drainage (PTCD) tube. Two weeks after admission, he received systemic chemotherapy including cyclophosphamide 750 mg/m^2 (day 1), doxorubicin 50 mg/m^2 (day 1), vincristine 1.4 mg/m^2 (day 1), and prednisolone 100 mg/day (days 1-5) with intrathecal injection of prednisolone 20 mg and methotrexate 15 mg. Completion of six cycles of the above systemic chemotherapy induced complete remission.

ART was started with a combination of two nucleotide reverse transcriptase inhibitors (NRTIs), lamivudine 300 mg/day and abacavir 600 mg/day (powder forms), and a protease inhibitor, lopinavir 800 mg/day with ritonavir 200 mg/day (LPV/r) (liquid forms). Although the patient achieved complete remission, the duodenum remained stenosed due to fibrosis. He was able to take powdered ART orally and HIV-RNA decreased from 2.4×10^4 copies/mL to < 400 copies/mL within two weeks. Frequent vomiting was noted probably due to food-induced duodenal obstruction, and drained material through the PTCD tube contained food residues and

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Table 1. Serum Lopinavir Concentration 12 Hours after Administration

Administration route	Orally without food	By jejunal tube with fat food		Orally through bypass with fat food
After ART (Weeks)*	2	7	11	18
Serum LPV concentration (mg/mL)	0.79	2.04	<0.20	20.83
HIV-RNA (copies/mL)	<400 **	<400**	2.2×10^4	52
CD4 (/mm^3)	19	61	106	215

*: weeks after initiating ART by each route

**: undetectable limit of viral load by standard *Amplicor*

ART: antiretroviral therapy, LPV: lopinavir

Other medications that were occasionally co-administered were cefoperazone/sulbactam, linezolid, micafungin, respectively for sepsis, and aciclovir for Herpes zoster.

powered antiretroviral drugs. Accordingly, ART was stopped at week 7.

For stable enteral drug delivery and nutrition, jejunostomy was performed two weeks after stopping oral ART. Three days later, ART with fat-containing food was started through the percutaneous jejunal tube, which was placed at ≧ 35 cm distal to the ligament of Treitz in the jejunum. The combination of ART was not changed. Serum lopinavir concentrations measured at weeks 7 and 11 were 2.04 and < 0.20 μg/mL, respectively. Although HIV-RNA decreased to 210 copies/mL at 7 weeks, it increased again to 11,000 copies/mL at 11 weeks with M184V mutation.

Based on the viral failure, ART was completely stopped through the jejunal tube at week 13 of ART. The patient underwent gastrojejunal bypass surgery two weeks before stopping ART. This bypass route was from the gastric corpus to the jejunum about 20 cm distal from the ligament of Treitz. The bypass site was more proximal than the tip of the jejunal tube. Three days after surgery, he started oral intake including fat-containing food. ART was restarted orally with LPV/r liquid monotherapy after a 10-day suspension. At 6 weeks after re-initiating liquid LPV/r, HIV-RNA decreased from 2.2×10^4 copies/mL to 280 copies/mL. Two NRTIs, abacavir and tenofovir were added subsequently. The serum concentration of lopinavir was 20.83 μg/mL at 18 weeks (Table 1). HIV-RNA finally decreased and remained below the detection level (50 copies/mL).

Discussion

Successful HIV suppression requires sufficient serum concentration of several antiretroviral drugs. To our knowledge, this case was the first report that showed that the administration site may be important to achieve a clinically sufficient serum concentration of LPV. The absolute bioavailability of LPV co-formulated with ritonavir in humans has not been established (3). Although HIV-RNA decreased to less than 400 copies/mL, the concentration of LPV/r was low. After administration by jejunal tube, the concentration of LPV was unstable and could not reach clinically effective concentrations. However, oral administration with high fat meal through gastrojejunal bypass finally achieved a sufficient concentration of LPV. Another case report showed that good absorption of LPV was obtained in a patient with gastrectomy (4). These two case reports suggest that absorption of LPV does not need gastric acid. Furthermore, in the present case, LPV was well absorbed without bile and pancreatic juice since the PTCD tube was still in place after bypass surgery.

Taken together, with regard to the site of absorption of LPV, the jejunum must be the most important; at least within 35 cm from the ligament of Treitz. We should pay more attention to the site of absorption to maintain effective drug concentrations when antiretroviral drugs are administered through an unusual route, such as a jejunal tube.

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References

1. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med 148: 728-736, 2008.
2. Kumar GN, Jayanti VK, Johnson MK, et al. Metabolism and disposition of the HIV-1 protease inhibitor lopinavir (ABT-378) given in combination with ritonavir in rats, dogs, and humans. Pharm Res 21: 1622-1630, 2004.
3. Abbott Laboratories. Kaletra (lopinavir/ritonavir) package insert. May, 2008.
4. Boffito M, Lucchini A, Maiello A, et al. Lopinavir/ritonavir absorption in a gastrectomized patient. AIDS 17: 136-137, 2003.

OR, 6.2; 95% CI, 2.5–15.4). There was no increase in the risk of *T. vaginalis* infection among women who were infected with *T. vaginalis* during the immediately preceding interval (4.4%), compared with women who were not (3.9%). However, 13 (62%) of 21 new infections occurred in women who had been previously infected with *T. vaginalis*, and 11 (85%) of 13 had negative test results during the immediately preceding interval (figure 1).

Some of the women might have acquired infections during sexual contact that they did not report, and some might have had infections that were not detected at the baseline visit. However, many women were treated for infection, had negative test results, and then had positive test results again, which suggests that *T. vaginalis* was undetected by testing but still present for months after treatment. The possibility of long-term asymptomatic carriage is consistent with the age distribution of infected women; *T. vaginalis* is found more often in older women [8, 9]. This pattern is different from the pattern for bacterial sexually transmitted diseases but similar to that for incurable viral infections, such as herpes simplex virus type 2 [10]. Trials have suggested cure rates of >90%, but most have tested women once within a few weeks after treatment [11]. When women were tested again a few months after treatment, some of the previously cured women had infection detected again [11], and none of the studies continued testing women beyond a few months. Cultures might not detect infections if the concentration of *T. vaginalis* is low, which would be expected in asymptomatic infections [6, 12, 13]. Nucleic acid amplification tests may be better, but reports are inconsistent and the tests are not commercially available in the United States [14]. Similarly, self-obtained vaginal swab specimens occasionally miss infections, but the sensitivity of tests performed with self-obtained specimens has compared favorably with that of tests performed with clinician-obtained specimens [15].

Treatment failure could explain many of our findings, because 13 women had a documented preceding infection. However, our results were not simply attributable to treatment failure. Most of the women ($n = 11$) had an intervening negative test result before having a positive result during an interval when they reported not having sex. This suggests that, after treatment, *T. vaginalis* infection can become nondetectable for months and then reappear. Because these findings were unexpected and obtained with a small number of participants, additional studies are needed to confirm or refute these observations.

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References

1. Metcalf CA, Douglas JM Jr, Malotte CK, et al.; RESPECT-2 Study Group. Relative efficacy of prevention counseling with rapid and standard HIV testing: a randomized controlled trial (RESPECT-2). Sex Transm Dis **2005**; 32: 130–8.
2. Johnson RE, Newhall WJ, Papp JR, et al. Screening tests to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections—2002. MMWR Recomm Rep **2002**; 51:1–38.
3. Weinhardt LS, Forsyth AD, Carey MP, Jaworski BC, Durant LE. Reliability and validity of self-report measures of HIV-related sexual behavior: progress since 1990 and recommendations for research and practice. Arch Sex Behav **1998**; 27:155–80.
4. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. MMWR Recomm Rep **2002**; 51: 1–78.
5. Levi MH, Torres J, Pina C, Klein RS. Comparison of the InPouch TV culture system and Diamond's modified medium for detection of *Trichomonas vaginalis*. J Clin Microbiol **1997**; 35:3308–10.
6. Caliendo AM, Jordan JA, Green AM, Ingersoll J, DiClemente RJ, Wingood GM. Real-time PCR improves detection of *Trichomonas vaginalis* infection compared with culture using self-collected vaginal swabs. Infect Dis Obstet Gynecol **2005**; 13:145–50.
7. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika **1986**; 73:13–22.
8. Torok MR, Miller WC, Hobbs MM, et al. The association between *Trichomonas vaginalis* infection and level of vaginal lactobacilli, in nonpregnant women. J Infect Dis **2007**; 196: 1102–7.
9. Helms DJ, Mosure DJ, Metcalf CA, et al. Risk factors for prevalent and incident *Trichomonas vaginalis* among women participating in a randomized, controlled trial. Sex Transm Dis **2008**; 35:484–8.
10. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance, 2005. Atlanta, GA: US Department of Health and Human Services, **2006**.
11. Forna F, Gulmezoglu AM. Interventions for treating trichomoniasis in women. Cochrane Database Syst Rev **2003**; 2:CD000218.
12. Garber GE, Sibau L, Ma R, Procter EM, Shaw CE, Bowie WR. Cell culture compared with broth for detection of *Trichomonas vaginalis*. J Clin Microbiol **1987**; 25:1275–9.
13. Radonjic IV, Dzamic AM, Mitrovic SM, et al. Diagnosis of *Trichomonas vaginalis* infection: the sensitivities and specificities of microscopy, culture and PCR assay. Eur J Obstet Gynecol Reprod Biol **2006**; 126:116–20.
14. Schwebke JR, Burgess D. Trichomoniasis. Clin Microbiol Rev **2004**; 17:794–803.
15. Schwebke JR, Morgan SC, Pinson GB. Validity of self-obtained vaginal specimens for diagnosis of trichomoniasis. J Clin Microbiol **1997**; 35:1618–9.

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Detection of HIV Type 1 Load by the Roche Cobas TaqMan Assay in Patients with Viral Loads Previously Undetectable by the Roche Cobas Amplicor Monitor

To the Editor—In March 2008, the Roche Cobas TaqMan assay replaced the Roche Cobas Amplicor Monitor, version 1.5, for measuring plasma HIV type 1 (HIV-1) load in Japan. This has resulted

in the detection of an HIV-1 load >50 copies/mL in some of the patients whose HIV-1 load had been undetectable (<50 copies/mL) by the Amplicor Monitor over several years and for whom antiretroviral treatment regimens had not been changed [1, 2].

A total of 1387 HIV-1–infected patients visited our outpatient clinic from March through June 2008, and their HIV-1 load was measured by the TaqMan assay. Among these patients, 876 regularly visited the clinic (once every 1–3 months) and had an undetectable HIV-1 load by the Amplicor Monitor at the last visit. Surprisingly, the TaqMan assay detected an HIV-1 load >50 copies/mL in 253 (28.9%) of the 876 patients, although antiretroviral treatment had not been modified for these patients. Furthermore, another 22 patients (2.5%) were found to have an HIV-1 load >40 copies/mL with use of the TaqMan assay. The same assay also detected HIV-1 RNA at levels lower than the linear range of the assay (<40 copies/mL) in 128 (14.6%) of the 876 patients.

We analyzed the relationship between TaqMan detectability and time during which the HIV-1 load was undetectable by the Amplicor Monitor. This time was defined as the period from the first HIV-1 load undetectable by the Amplicor Monitor to the viral load first measured by the TaqMan assay, without any HIV-1 load rebound or blip detected during the period. Interestingly, among the patients who had a viral load undetectable by the Amplicor Monitor for <1 year, 43.7% had an HIV-1 load >50 copies/mL detected by the TaqMan assay; among the patients who had a viral load undetectable by the Amplicor Monitor for >4 years, 18.5% had an HIV-1 load >50 copies/mL detected by the TaqMan assay (figure 1). Conversely, 37.3% of patients who had a viral load undetectable by the Amplicor Monitor for <1 year had HIV-1 RNA undetectable by the TaqMan assay, and 70.2% of patients who had a viral load undetectable by Amplicor Monitor for >4 years had an HIV-1 load undetectable by the TaqMan assay. Thus, the proportion of patients who had an HIV-1 load >50 copies/mL was inversely correlated with the duration that the viral load was undetectable ($R^2 = 0.895$), and the proportion of patients with undetectable viral load was positively correlated with the duration that the viral load was undetectable ($R^2 = 0.979$). These findings indicate that the longer the effective treatment, the greater the number of patients with HIV-1 RNA undetectable by the TaqMan assay.

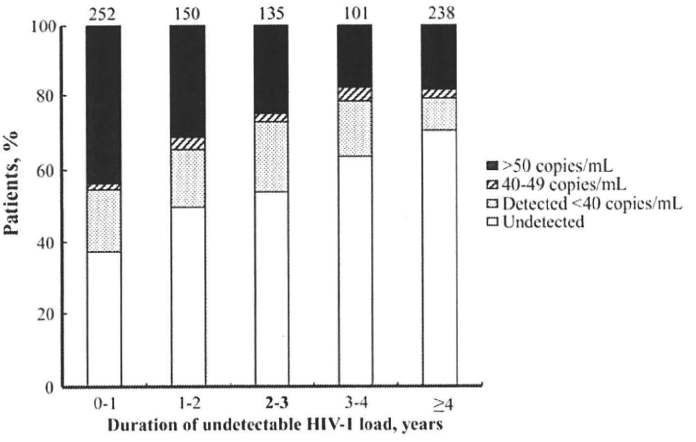

Figure 1. Results of the TaqMan assay and duration of undetectable HIV-1 load in 876 patients whose HIV-1 load was undetectable (<50 copies/mL) when the last Amplicor Monitor was performed. The number of patients is shown above each bar.

We observed significant discrepancy of HIV-1 detectability between the TaqMan assay and the Amplicor Monitor [3–5]. The TaqMan assay detected HIV-1 RNA in a significant percentage of treated patients with HIV-1 loads previously undetectable by the Amplicor Monitor; this is confusing to clinicians and patients and may be a critical problem in ongoing clinical trials of antiretroviral treatment. To determine the permissible range of detectable HIV-1 load during successful antiretroviral treatment, year-long clinical follow-up of treated patients is necessary. Our observation revealed that the detection rate of HIV-1 RNA with use of the TaqMan assay was inversely correlated with the previous duration of undetectable HIV-1 load, suggesting that long-term antiretroviral treatment can further suppress HIV-1 load even after it has decreased to below the detection limit of the Amplicor Monitor.

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References

1. Erali M, Hillyard DR. Evaluation of the ultrasensitive Roche Amplicor HIV-1 Monitor assay for quantitation of human immunodeficiency virus type 1 RNA. J Clin Microbiol **1999**; 37: 792–5.
2. Perrin L, Pawlotsky JM, Bouvier-Alias M, Sarrazin C, Zeuzem S, Colucci G. Multicenter performance evaluation of a new TaqMan PCR assay for monitoring human immunodeficiency virus RNA load. J Clin Microbiol **2006**; 44:4371–5.

3. Katsoulidou A, Petrodaskalaki M, Sypsa V, et al. Evaluation of the clinical sensitivity for the quantitation of human immunodeficiency virus type 1 RNA in plasma: comparison of the new Cobas TaqMan HIV-1 with three current HIV-RNA assays–LCx HIV RNA quantitative, Versant HIV-1 RNA 3.0 (bDNA) and Cobas Amplicor HIV-1 Monitor v1.5. J Virol Methods **2006**; 131:168–74.
4. Damond F, Roquebert B, Benard A, et al. Human immunodeficiency virus type 1 (HIV-1) plasma load discrepancies between the Roche Cobas Amplicor HIV-1 Monitor version 1.5 and the Roche Cobas AmpliPrep/Cobas TaqMan HIV-1 assays. J Clin Microbiol **2007**; 45:3436–8.
5. Oliver AR, Pereira SF, Clark DA. Comparative evaluation of the automated Roche TaqMan real-time quantitative human immunodeficiency virus type 1 RNA PCR assay and the Roche Amplicor version 1.5 conventional PCR assay. J Clin Microbiol **2007**; 45:3616–9.

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Use of Active Surveillance Cultures in Intensive Care Units

To the Editor—I appreciated the systematic review by McGinigle et al. [1] of active surveillance cultures (ASCs) for methicillin-resistant *Staphylococcus aureus* (MRSA) in the intensive care unit (ICU) but question their conclusions about the lack of enough robust evidence to provide definitive recommendations for the use of ASCs in the control of MRSA infection. The authors included 20 studies, but only 13 of these studies seem to be original intervention studies that assess the effect of ASCs on the rate of MRSA infection. In addition, as the authors indicate, the methodology and/or robustness of many of these studies are not optimal.

Because I have been interested in this subject for many years, I have collected the literature on another 7 published nonpediatric and nonneonatal ICU studies that merit inclusion in the systematic review by McGinigle et al. [1–8], as well as another 6 neonatal and/or pediatric ICU studies (not referenced). It would be interesting to understand why these adult ICU studies were not included in the systematic review by McGinigle et al. [1]. Three of these studies were interrupted-time series, and 1 was a controlled before-and-after study; both of these methodologies are fairly robust. It is true that not all of the studies included weekly ASCs, but this seems to be a questionable exclusion criteria if a reduction in the rate of MRSA infection was still reported. However, the consistency of positive findings in the adult ICU studies is worth emphasizing (i.e., ASCs can aid in the control of MRSA infection in the ICU, particularly when ASCs are combined with at least 1 of the following: patient and environmental decontamination and hand-hygiene initiatives).

It is noteworthy that, of the 20 studies (13 in the systematic review and the 7 aforementioned adult ICU studies), only 3 do not mention use of additional hygiene and/or decontamination procedures (4 of 26 studies, if the neonatal and/or pediatric ICU studies are also considered). Moreover, although all but 1 study reported a reduction in the rate of MRSA infection after introduction of ASCs, this 1 study was notable for its poor hand-hygiene compliance, late isolation of MRSA-positive patients, and absence of any decontamination or disinfection.

Finally, the rating of high-quality interrupted-time series as only "fair" evidence by McGinigle et al. [1] is debatable. The most important difference between my interpretation of the data and that of McGinigle and colleagues is my observation of the consistency, strength, temporal relationship, and plausibility of the evidence; this insight led me to conclude that ASCs should be recommended as standard practice, particularly in high-risk areas, such as ICUs, where there is a high rate of hospital-acquired MRSA infection and a great risk of MRSA infection.

Incidentally, my colleagues and I conducted a study [9] (which was incorrectly referenced in the systematic review) that demonstrated a two-thirds reduction in the rate of MRSA infection (a decrease from >15% to ~5% of ICU admissions, not the 11% reduction stated in the systematic review by McGinigle et al. [1]). Moreover, this reduction was entirely attributable to a reduction in the number of MRSA isolates from clinical specimens, not screening specimens. Although the number of MRSA isolates is only a surrogate for infection, it is more closely indicative of infection than colonization; that the number of MRSA isolates is a surrogate marker of colonization was wrongly implied by Milstone and Perl [10] in their accompanying editorial commentary. In support of the number of MRSA isolates being a surrogate marker of infection, there was a significant reduction in both length of stay and glycopeptide use associated with the introduction of ASCs.

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References

1. McGingle KL, Gourley ML, Buchanan IB. The use of active surveillance cultures in adult intensive care units to reduce methicillin-resistant *Staphylococcus aureus*—related morbidity, mortality and costs: a systemic review. Clin Infect Dis **2008**; 46:1717–25.
2. Blumberg LH, Klugman KP. Control of methicillin-resistant *Staphylococcus aureus* bacteraemia in high-risk areas. Eur J Clin Microbiol Infect Dis **1994**; 13:82–5.
3. Girou E, Pujade G, Legrand P, Cizeau F, Brun-Buisson C. Selective screening of carriers for control of methicillin-resistant *Staphylococcus aureus* (MRSA) in high-risk hospital areas with a high level of endemic MRSA. Clin Infect Dis **1998**; 27:543–50.
4. de la Cal MA, Cerdá E, van Saene HKF, et al. Effectiveness and safety of enteral vancomycin to control endemicity of methicillin-resistant *Staphylococcus aureus* in a medical/surgical intensive care unit. J Hosp Infect **2004**; 56: 175–83.
5. Cepeda JA, Whitehouse T, Cooper B, et al. Isolation of patients in single rooms or cohorts to reduce spread of MRSA in intensive-care

研究分担者　渡辺　大

吉野宗宏、矢倉裕輝、桑原健、坂東裕基、小川吉彦、矢嶋敬史郎、谷口智宏、大谷成人、富成伸次郎、渡邊大、上平朝子、白阪琢磨。	硫酸アタザナビルの血中濃度が高値の患者を対象とした、ATV/rからATV400へのスイッチ臨床試験結果。	日本エイズ学会誌	11(1)	50-3	2009
吉野宗宏、矢倉裕輝、桑原健、坂東裕基、小川吉彦、矢嶋敬史郎、谷口智宏、大谷成人、富成伸次郎、渡邊大、西田恭治、上平朝子、白阪琢磨。	ロピナビル・リトナビル配合剤（LPV/r）の1日2回から1日1回投与へのスイッチ臨床試験結果。	日本エイズ学会誌	11(3)	250-4	2009

 The Journal of AIDS Research

研究ノート

ロピナビル・リトナビル配合剤（LPV/r）の1日2回から1日1回投与へのスイッチ臨床試験結果

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目的：LPV/rをBIDで治療を開始し，LPVのトラフ濃度が6.00μg/mL以上であった患者を対象に，服薬方法をQDに変更した後の有効性と安全性について検討することを目的に臨床試験を実施した。

対象および方法：当院でLPV/rをBIDで服薬し，LPVのトラフ血中濃度が6.00μg/mL以上の患者8例を対象とした。QD変更後4，8，12，16，20，24週目に有害事象，トラフ濃度，HIV-RNA量，CD4細胞数，T-Cho，HDL-Cho，TGを確認し，BID服用時と比較検討した。

結果：対象患者8例のLPVのトラフ濃度（mean±S.D.）は，10.99±2.75μg/mL（range：7.46-14.94）であった。QDスイッチ4週後，LPVトラフ濃度の平均値は2.28±1.72μg/mL（range：0.41-5.85）に低下したが，HIV-RNA量は臨床試験を実施した24週間を通じて，全例感度未満を持続した。CD4細胞数，T-Cho，HDL-Cho，TGの変動は認められなかった。新たな有害事象として，便秘，嘔気等の消化器症状が出現したが，下痢の増加は軽微であった。

考察：LPVの血中濃度が比較的高く，臨床経過が安定している患者をQDに変更した場合の24週間における安全性と有効性を確認することができた。今回の試験結果が，本邦におけるQD投与の有用性確認の第一歩となったものと考える。

キーワード：HAART，LPV，RTV，血中濃度，QD

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序　文

ロピナビル・リトナビル配合剤（LPV/r）は，米国で2000年9月にHIV感染症の治療薬として承認されたプロテアーゼ阻害薬（PI）である。米国において承認されたLPV/rの用法・用量は，1回2錠の1日2回投与（BID）に加え，未治療患者または初回治療のLPV/r服薬患者に限り，1回4錠の1日1回投与（QD）が認められている[1)]。2008年11月3日付で改訂された米国DHHS（Department of Health and Human Services）ガイドラインは，LPV/rのQD投与を代替処方から推奨処方に変更した[2)]。

QD承認の基礎となった試験では，BID群とQD群を投与期間48週で比較し，HIV-RNA量が感度未満となった割合に有意な差を認めず，QD群では下痢の頻度が高かったとしている[3)]。この臨床試験における薬物動態では，BID群のトラフにおけるLPVの血中濃度（トラフ濃度）は約6μg/mLで，QD群では約3μg/mLに減少したものの[3,4)]，米国DHHSガイドラインが推奨するLPVの目標トラフ濃度1.00μg/mLを上回っていた[2)]。

我々はLPV/rをBIDで治療を開始し，治療効果が安定し，LPVのトラフ濃度が6.00μg/mL以上であった患者を対象に，服薬方法をQDに変更した後の，有効性と安全性について検討するための臨床試験を実施した。なお本試験は，国立病院機構大阪医療センターの倫理委員会に相当する受託研究審査委員会の承認を得た（承認番号：0724）。

対象および方法

国立病院機構大阪医療センター免疫感染症科に通院し，LPV/rを含むHAARTで治療を開始し，HIV-RNA量が12週以上感度未満を維持し，LPVのトラフ濃度が6.00μg/mL以上で，問診により血中濃度測定前1週間の服薬率が100%と見込まれた患者に対して，本試験の趣旨説明を行い，試験参加の同意を文書で得た。同意取得後，LPV/rをBIDからQDに変更した。LPVの血中濃度に影響を及ぼ

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すと考えられる高脂血症治療剤等の投与を受けた患者は本試験の対象外とした。調査期間は2008年3月1日から2009年2月28日までとした。

血中濃度測定は以下の方法で行った。ヘパリンナトリウムを添加した試験管に，1回5mLの血液を採取し，10℃以下3000回転10分間遠心分離し，ポリプロピレン製のスクリューキャップ付きチューブに血漿を2mL分注し，分析開始まで−80℃で凍結保存した。測定はHPLC法を用い，株式会社BMLにて実施した。また，血中濃度測定は，厚生労働科学研究費補助金「抗HIV薬の血中濃度に関する臨床研究」により実施した。

LPV/rをQDへ変更後4，8，12，16，20，24週目に採血を実施し，LPVのトラフ濃度，HIV-RNA量，CD4細胞数，T-Cho，HDL-Cho，TGを測定し，有害事象発現の有無を問診にて確認した。QD変更前後の24週間について比較し，T-Cho，HDL-Cho，TGについては，一元配置分散分析法を用いて解析した。

結　果

LPVのトラフ濃度が6.00μg/mL以上の患者は18例であった。そのうち，選択基準を満たし同意が得られた8例をBIDからQDに変更した。平均年齢（mean±S.D.）は43±12歳（range：27-60）で，男性7例，女性1例であった。併用した核酸系逆転写酵素阻害薬（NRTI）は，テノホビル/エムトリシタビン合剤（TVD）4例，アバカビル/ラミブジン合剤（EZC）3例，ジドブジン/ラミブジン合剤（COM）1例であった。試験期間を通じて中止例は認められなかった。

治療変更前後の血中濃度を表1，臨床検査値を表2に示す。LPV平均トラフ濃度（mean±S.D.）は10.99±2.75μg/mL（range：7.46-14.94）であった。QDへの変更後4週目に，患者のLPV血中濃度は2.28±1.72μg/mL（range：0.41-5.85）に低下し，その後24週までほぼ一定の値を示した。HIV-RNA量は，臨床試験を実施した24週間を通じて，全例感度未満を持続し，CD4細胞数は，24週までほぼ一定の値を示した。変更後のT-Cho，HDL-Cho，TGの変動には有意差を認めなかった（p＝0.933，p＝0.607，p＝0.954）。

QD変更後の新たな有害事象として，嘔気，胃部不快感，便秘などの消化器症状が認められた。下痢の回数の変化について確認したところ，軽微な増加は認めたが，グレード2以上の症状は認められなかった（表3）。

表1　LPV trough plasma concentration (μg/mL)

patient	Baseline	week 4	week 8	week 12	week 16	week 20	week 24
#1	9.23	2.10	1.73	0.80	1.34	1.68	1.43
#2	14.94	2.43	3.94	1.65	2.78	2.62	2.49
#3	14.86	0.80	1.09	1.09	1.67	1.07	1.18
#4	9.63	1.10	0.41	0.40	0.40	0.41	0.40
#5	11.19	5.85	4.63	3.17	4.24	3.04	5.47
#6	7.46	2.32	2.89	2.71	3.46	3.41	3.36
#7	11.75	0.41	0.70	0.49	0.33	1.37	1.14
#8	8.89	3.24	6.58	6.22	7.08	6.02	6.28
Mean (S.D.)	10.99 (2.75)	2.28 (1.72)	2.75 (2.17)	2.07 (1.96)	2.66 (2.27)	2.45 (1.77)	2.72 (2.16)

表2　Laboratory parameters

Parameter	n	Baseline	week 4	week 8	week 12	week 16	week 20	week 24
T-Cho (mg/dL)	8	197.3 (33.5)	185.6 (26.6)	191.1 (15.6)	186.5 (15.3)	189.0 (21.8)	190.6 (20.9)	193.6 (24.7)
HDL-Cho (mg/dL)	8	56.2 (9.9)	50.0 (6.7)	54.8 (7.7)	53.8 (7.8)	55.3 (8.1)	59.3 (11.5)	60.4 (9.8)
TG (mg/dL)	8	207.5 (115.0)	174.6 (50.6)	206.4 (110.8)	201.1 (105.6)	230.8 (139.6)	201.1 (114.9)	170.1 (63.6)
CD4 (cells/mm^3)	8	360 (156.4)	340 (140.9)	340 (132.3)	382 (157.1)	375 (163.5)	348 (164.5)	358 (165.7)
HIV-RNA (copies/mL)	8	<50	<50	<50	<50	<50	<50	<50

Data expressed as Mean (S.D.)

考　　察

LPV/r は，大きな IQ (C_{min}/IC_{50} : Inhibitory Quotient) 値を示すことで強力な抗ウイルス作用を示し[5]，高い認容性，持続的なウイルス抑制作用[6]を併せ持つ PI である。PI のウイルス学的効果は血中濃度と相関することから[7,8]，ウイルス学的有効性を考えれば，より高く血中濃度を維持することは有用であると考えられる。しかし，血中濃度が高いと副作用の発現率が増加することから[9]，すべての PI の血中濃度を高く保つことは不可能である。また，有効な抗 HIV 薬も服薬アドヒアランスが低下すれば，服薬の中断あるいは耐性獲得による治療失敗となる[10]。近年，抗 HIV 薬の改良が重ねられ，QD が可能な抗 HIV 薬が複数承認されたことにより，QD は HAART の主流となりつつある。患者は，服薬方法を QD にすることで，BID に比べ服薬回数や服薬時間等の制約が軽減され，服薬アドヒアランスや QOL の向上が期待できる[11]。従って，LPV/r の QD と BID が同等の安全性と有効性を持つことを示すことができれば，臨床的な意義は大きいものと考える。

今回我々は，国内で承認されていない用法用量である QD による臨床試験を行うにあたり，臨床試験の安全性を担保するために，初回治療から LPV/r を BID で服用患者において，HIV-RNA 量が 12 週以上感度未満を維持し，さらに LPV のトラフ濃度が 6.00 μg/mL 以上を示す患者を QD 変更の対象とした。対象患者のトラフ濃度を 6.00 μg/mL 以上にした設定根拠は，海外臨床試験において，BID のトラフ濃度が 6.56±3.71 μg/mL であり，QD では 3.22±2.07 μg/mL とした報告に基づき[3]，DHHS のガイドラインが推奨する[2] LPV 目標トラフ濃度 1.00 μg/mL を維持するためには，トラフ濃度が 6.00 μg/mL 以上が必要であると仮定した。また，当院で LPV/r を BID で服用した患者 36 例の平均トラフ濃度が 6.85±4.13 μg/mL であったことから，日本人におけるトラフ濃度は先の海外報告と同様であると考え，今回の臨床試験の設定根拠とした（図 1）。

LPV/r を BID から QD へ変更 4 週後の平均トラフ濃度は 2.28±1.72 μg/mL であった。トラフ濃度の平均値は今回の試験期間 24 週間を通じて 1.00 μg/mL 以上を維持したことから，対象患者のトラフ濃度を 6.00 μg/mL 以上に設定したことは適切であったと考えられた。しかし，本臨床試験における QD の平均トラフ濃度は，海外報告[3]よりも低値であり，表 1 に示したように，測定した患者の血中濃度には目標トラフ濃度を下回ったデータもあった。臨床試験を実施した 24 週間における患者の HIV-RNA 量は，全例検出限界未満を維持していたものの，QD へ変更するための LPV トラフ濃度の設定に関しては，今後さらに検討が必要と考える。また目標トラフ濃度を複数回，下回った症

表 3　下痢回数の変化/日

患者	変更前 (BID)	変更後 (QD)
#1	5 回	3 回
#2	2-3 回	3-4 回
#3	無	2-3 回
#4	4-5 回	4-5 回
#5	無	無
#6	3 回	1-2 回
#7	無	無
#8	2-3 回	2-3 回

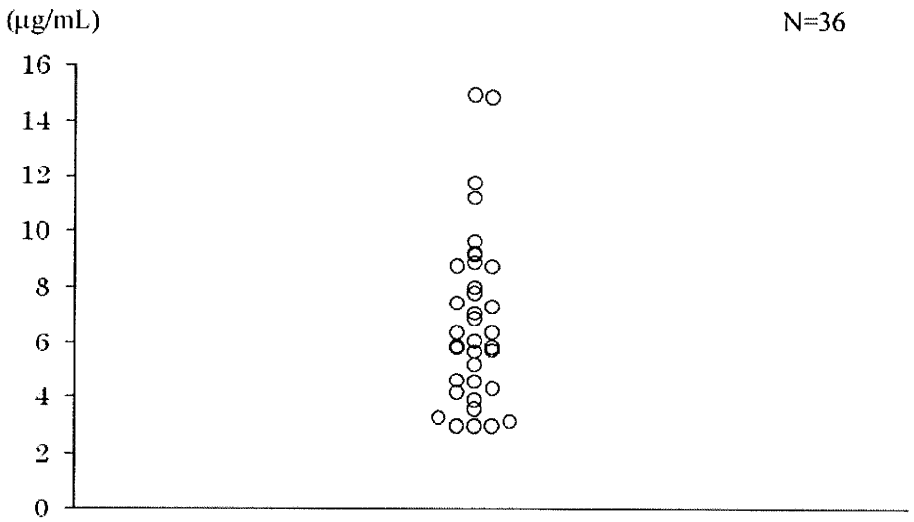

図 1　LPV BID trough plasma concentration (μg/mL)