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研究報告の概要

○ドイツで同定された初のB/Gサブタイプ間組換え型ヒト免疫不全ウイルス1型(HIV-1)は市販のウイルス定量試験で検出不能または定量限界以下であった

HIV-1は遺伝的多様性が高く、また組換え型が頻繁に出現し、HIVの世界的な進展だけでなく診断、モニタリング、治療戦略にも重要な影響を与える。本研究では、ドイツにおけるHIV-1の初のB/Gサブタイプ間組換え株を報告する。この株は、抗体検査では検出可能なものの、NucliSens HIV-1 QT assay (Organon Teknika/bioMerieux)では検出不能で、Monitor v1.5 test (Roche Molecular Systems)ではLCx(R) HIV RNA Quantitative assay (Abbott Laboratories)と比較して有意に定量性が減少しており、臨床的観点から注目に値する。ウイルス定量試験のプライマー及びプローブ結合部位におけるグループ及びサブタイプ指定を確立し、遺伝的多様性の程度を評価するためにgag p24、pol IN、及びenv gp41免疫優勢領域(IDR)塩基配列の特性を明らかにした。系統発生解析から、このウイルスはサブタイプ間B/G組換え株であることが明らかになった。gag p24領域はサブタイプG、env gp41 IDRはサブタイプB、pol INはB/Gキメラである。プライマー及びプローブ結合部位におけるヌクレオチドの不整合から、ウイルス定量試験間で観察された差異について分子的根拠が得られた。HIV-1の遺伝的多様性から、検出の信頼性及びウイルス定量試験について問題が提起される。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
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血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
ドイツで同定された初のB/Gサブタイプ間組換え型ヒト免疫不全ウイルス1型(HIV-1)は市販のウイルス定量試験で検出不能または定量限界以下であったとの報告である。	これまで、本製剤によるHIV感染の報告はない。本製剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれている。また最終製品についてHIV-NAT陰性であることを確認していることから、本製剤の安全性は確保されており、念のため情報収集に努めるも、今後特別の対応を必要としない。

(5)

別紙2

Journal of Medical Virology 78:311–317 (2006)

The First B/G Intersubtype Recombinant Form of Human Immunodeficiency Virus Type 1 (HIV-1) Identified in Germany Was Undetected or Underquantitated by Some Commercial Viral Load Assays

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The high level of genetic diversity of human immunodeficiency virus type 1 (HIV-1) and the continual emergence of recombinant forms have important implications not only for the global evolution of HIV but also for diagnosis, monitoring, and treatment strategies. The present study reports the first intersubtype B/G recombinant strain of HIV-1 in Germany. This strain is notable from a clinical perspective, since it was undetectable in the NucliSens HIV-1 QT assay (Organon Teknika/bioMérieux) and was significantly underquantitated in the Monitor v1.5 test (Roche Molecular Systems) relative to the LCx® HIV RNA Quantitative assay (Abbott Laboratories). *Gag*-encoded p24 (*gag* p24), *pol*-encoded integrase (*pol* IN), and *env*-encoded gp41 (*env* gp41) immunodominant region (IDR) sequences were characterized to establish group and subtype designation and to evaluate the degree of genetic diversity at primer and probe binding sites of the viral load assays. Phylogenetic analysis revealed that this virus is an intersubtype B/G recombinant strain. The *gag* p24 region is subtype G, *env* gp41 IDR is subtype B, and *pol* IN is a B/G chimera. Nucleotide mismatches within primer and probe-binding sites provided the molecular basis for differences in quantitation observed between viral load assays. Genetic diversity of HIV-1 continues to challenge the reliability of detection and quantitation by viral load assays. ***J. Med. Virol. 78:311–317, 2006.*** © 2006 Wiley-Liss, Inc.

KEY WORDS: HIV-1; genetic diversity; quantitation; recombinant

INTRODUCTION

Human immunodeficiency virus type 1 (HIV-1) is characterized by a high degree of genetic variability that is reflected in the diversity of forms that constitute the global pandemic. This extraordinary genetic heterogeneity results from the introduction of mutations by an error-prone reverse transcriptase and from recombination of the two RNA genomes packaged in the virion during the synthesis of proviral DNA. It has been estimated that 10^8 or more virions are produced per day in untreated patients thus, virtually every position within the 9.4 kb genome is mutated multiple times daily [Coffin, 1995].

HIV-1 strains are classified into three phylogenetically distinct groups: M (major), O (outlier), and N (non-M and non-O) [Barin et al., 1997]. Based on the analyses of full-length nucleotide sequences, group M strains are further subdivided into nine different clades, designated as subtypes A–D, F–H, J, and K [Robertson et al., 2000]. The HIV-1 subtypes are genetically quite distinct, differing at the nucleotide level by up to 30% in *env* and 15% in the *gag* gene [Cornelissen et al., 1996]. In addition to "pure" subtypes, recombinant strains derived from more than one subtype or group have been identified. In a recent global analysis, mosaic strains represented more than 18% of new infections in the year 2000 [Osmanov et al., 2002]. Recombinant genomes of identical composition identified in several unlinked individuals are classified as circulating recombination forms (CRF). Of the 16 currently recognized CRFs, two are considered to have originated in Europe: CRF03_AB from Kalliningrad, Russia [Liitsola et al., 2000] and CRF14_BG from Galicia, Spain [Delgado et al., 2002].

The distribution of subtypes and CRFs is unequal and dynamic in nature. Although subtype B strains

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represent the majority of infections in Western Europe and North America, 84% and 95%, respectively, only 12% of global HIV-1 cases are subtype B [Osmanov et al., 2002]. With the continued evolution of the HIV-1 pandemic, increasing numbers of non-subtype B infections are being identified in Europe and United States. In Lisbon, Portugal, subtype G is already the second most prevalent HIV-1 subtype, accounting for approximately 21% of all infections [Esteves et al., 2003]. In France, a study of blood donors from 1985 to 1995 revealed an increase of non-subtype-B infections from 4% to more than 20% [Barin et al., 1997]. In the United Kingdom, ~27% of HIV infections are estimated to be non-subtype B [Parry et al., 2001]. Moreover, nearly 20% of non-B subtype strains from United Kingdom harbor genetic material from two or more different subtypes [Barlow et al., 2001; Parry et al., 2001]. These findings suggest the spread of non-B subtype infections to heterosexuals born in the United Kingdom from individuals previously infected in regions of high prevalence. Subtype B is also decidedly predominant in the German population, but other subtypes have been detected. In a retrospective study of newly diagnosed HIV infections from the Robert Koch Institute in Berlin, an increase of non-subtype-B infections from 9.5% in 1985 to 19.8% in 1995 was observed [Brunn et al., 1998].

Genetic diversity of HIV-1 has important implications not only for the global evolution of HIV but also from the perspective of diagnostics, patient monitoring assays (e.g., quantitation of HIV-1 RNA in plasma), and therapeutic strategies [Tatt et al., 2001]. Because most commercially available assays for monitoring viral load were developed in the U.S. or Western Europe, performance was optimized using primarily subtype B specimens. In fact, most of these assays are calibrated against an HIV-1 subtype B standard prepared by the Viral Quality Assurance Laboratory of the AIDS Clinical Trials Group. Nucleotide polymorphisms occurring within primer and/or probe binding sites have the potential to reduce hybridization efficiency. Therefore, strains of non-B subtypes and intersubtype recombinants may be undetectable or significantly underquantitated.

In the present study, the first identification of infection with a B/G intersubtype recombinant strain in Germany, found in an injecting drug user, is reported. In addition, the performance of three commercial viral load assays on this strain is compared and demonstrates the impact of genetic diversity on reliability of viral load measurement.

MATERIALS AND METHODS

Subject

The index case is a 23-year-old female German citizen with a history of injecting drug use. According to her own specifications, she became infected with HIV-1 and Hepatitis-C virus (subtype 1b) in Portugal 10 months prior to the first blood draw of the present study. The first HIV-Antibody-Test (Dade Behring, Germany) and the HIV-1 Western blot confirmation test were positive in July 2001. She had no history of antiretroviral therapy.

Virus Load Determination

Three commercial HIV-1 RNA quantitative test kits were used to measure viral load in plasma samples (EDTA) stored at −70°C. Assays were performed in accordance with the manufacturers' guidelines.

(i) NucliSens HIV-1 QT assay (NucliSens; Organon Teknika/bioMérieux Boxtel, The Netherlands). HIV-1 RNA was extracted from 0.5 ml plasma by a guanidine thiocyanate-silica-based extraction method. The *gag* p24 target region of the wild-type virus (WT) was co-amplified (isothermal at 41°C) with three internal calibrators (Qa, Qb, and Qc) of known RNA concentrations. Amplification products were detected individually by using electrochemiluminescence (ECL)-labeled probes. The amount of initial WT HIV-1 RNA was calculated from the ratio of WT signal to the Qa, Qb, and Qc signals. The lower limit of detection is 80 RNA copies/ml.

(ii) COBAS AMPLICOR HIV-1 MONITOR v1.5 test (Monitor v1.5; Roche Molecular Systems, Branchburg, NJ). HIV-1 RNA was extracted from 0.5 ml of plasma. A 155-bp target region of *gag* p24 was amplified using reverse transcriptase (RT)-PCR. An RNA quantitation standard (QS) with primer binding sites identical to those on the HIV-1 target was incorporated into each reaction mixture to monitor efficiency of sample preparation and amplification. The lower limit of quantitation (LLQ) is 50 RNA copies/ml.

(iii) LCx® HIV RNA Quantitative assay (LCx HIV; Abbott Laboratories, Abbott Park, IL). HIV-1 RNA was extracted from 1.0 ml plasma using a modified Qiagen sample preparation kit. Internal control transcript was added prior to extraction to monitor sample preparation and amplification efficiency. The *pol* Integrase (*pol IN*) target region was amplified using competitive RT-PCR. Amplification products were hybridized to differentially labeled probes specific for HIV-1 and the internal control. The automated LCx Analyzer detected the HIV-1 and internal standard amplicons and calculated the concentration of HIV-1 RNA per ml of plasma. The LLQ is 50 RNA copies/ml.

Molecular Characterization

Three regions of the HIV-1 genome were targeted for sequence analysis, *gag* p24, *pol* IN, and *env* gp41 immunodominant region (IDR). Total nucleic acid was extracted from 200 µl plasma using a QIAamp Blood Kit (Qiagen, Inc., Valencia, CA) according to the manufacturer's instructions. Nested RT-PCR and sequence analysis were performed using primers and

conditions described previously [Swanson et al., 2003]. GenBank accession numbers for *gag* p24, *pol* IN, and IDR are AY816212, AY816213, and AY816214, respectively.

Phylogenetic Analysis

Nucleic acid sequences were aligned with HIV-1 group M subtype reference sequences (http://www.hiv.lanl.gov/content/hiv-db/SUBTYPE_REF/Table1.html) sing the CLUSTAL method (MegAlign, Lasergene, DNASTAR, Inc., Madison, WI) and manually edited. Alignments were converted into the desired format (PHYLIP or FASTA) using ForCon (version 1.0 for Windows; J. Raes, University of Antwerp, Belgium). Phylogenetic analysis was done using the PHYLIP software package (version 3.5c; J. Felsenstein, University of Washington, Seattle, WA). Evolutionary distances were estimated with Dnadist (Kimura two-parameter method) and phylogenetic relationships determined by Neighbor (neighbor-joining method). Drawtree was used to generate phylogenetic trees; Seqboot (100 replicates) and Consense were used to determine branch reproducibility. Programs were run with default parameters. CPZGAB was used as the outgroup. Sequences were examined for potential recombination using SimPlot (version 2.5; S. Ray, Johns Hopkins University, Baltimore, MD; http://sray.med.som.jhmi.edu/SCRoftware/SimPlot).

RESULTS

In July 2001, a blood sample was drawn from a patient with a reported risk of primary HIV-1 infection 10 months previously and found positive for anti-HIV antibodies in ELISA and Western blot. As part of the patient's assessment, HIV-1 viral load was measured using the NucliSens assay. Remarkably, although the patient had no history of treatment with antiretroviral drugs, there was no detectable viral load (Table I). The lower limit of detection for the NucliSens assay was 80 copies/ml. HIV-1 remained undetectable by the NucliSens assay in subsequent draws in October 2001 and January 2002. Although CD4 counts remained within the normal range, the unexpectedly undetectable level of plasma viremia prompted further analyses. Utilizing archived plasma specimens, viral load assessments were then performed using two additional commercial assays, Monitor v1.5 and LCx HIV. In contrast to results obtained with the NucliSens assay, significant levels of HIV-1 RNA were detected in both assays, although varying considerably in quantity (Table I). In the July 2001 sample, Monitor v1.5 and LCx HIV measured the viral load at 70,000 and 260,000 copies/ml, respectively. In the subsequent bleeds, viral loads of 600,000 and 680,000 copies/ml were obtained in LCx HIV as compared to 28,000 and 27,000 copies/ml, respectively, estimated in Monitor v1.5. Thus, although virus was detectable in both assays, Monitor v1.5 underquantitated two of the three specimens by >1 $\log_{10}$ copies/ml relative to the LCx HIV assay.

The magnitude of the differences in viral load values obtained between the three commercial viral load assays prompted further characterization of the HIV-1 strain (designated herein as 9196/01) harbored by this patient. To determine subtype, three independent regions of the genome, *gag* p24, *pol* IN, and *env* gp41 IDR were amplified and sequenced. Phylogenetic analysis revealed differences in the subtype derivation between the regions examined (Fig. 1). The *gag* p24 region from 9196/01 clustered with high confidence (bootstrap value of 99%) with subtype G reference strains, whereas the IDR region clustered with subtype B reference strains. Phylogeny of the *pol* IN gene was slightly more ambiguous. Although a significant association with subtype G reference strains was observed for this gene (bootstrap value of 81%), the 9196/01 branch originates near the base of the subtype G branch, with a bootstrap value of 85% segregating it from the reference G sequences.

One potential explanation for the phylogeny of the *pol* IN from 9196/01 was that it is a mosaic gene derived from more than one subtype. Bootscanning was performed using SimPlot software to interrogate the *pol* IN sequence for evidence of recombination breakpoints. Results of this analysis are shown in Figure 2. The first 300–350 nt of the 5′ end and 200–250 nt at the 3′ end of *pol* IN are subtype G-derived, whereas ~250 nt fragment in the central part of the gene clusters with subtype B. Based on this analysis, two recombination breakpoints were evident within *pol* IN, one at 331–372 nt and the other at 602–615 nt.

Genetic characterization of 9196/01 included analysis of *gag* p24, the target region of the NucliSens and Monitor v1.5 assay, and *pol* IN targeted by the LCx HIV assay. Nucleotide conservation within the primer and probe binding sites was assessed. A summary of the mismatches relative to all three assays is presented in Table II. Seventeen mismatches were identified relative to the primer and probe binding sites in the NucliSens assay. Ten mismatches were observed relative to the Monitor v1.5 assay target sequences. In contrast, only one nucleotide mismatch was observed relative to the

TABLE I. Diagnostic Testing Results

				Plasma viral load (HIV-1 RNA copies/ml)		
Test date	CD4 T+ (cells/μl)	CD8 T+(cells/μl)	Ratio	NucliSens	Monitor v1.5	LCx HIV
July 2001	609	974	0.62	<80	70,000	260,000
October 2001	640	870	0.73	<80	28,000	600,000
January 2002	774	1,785	0.43	<80	27,000	680,000

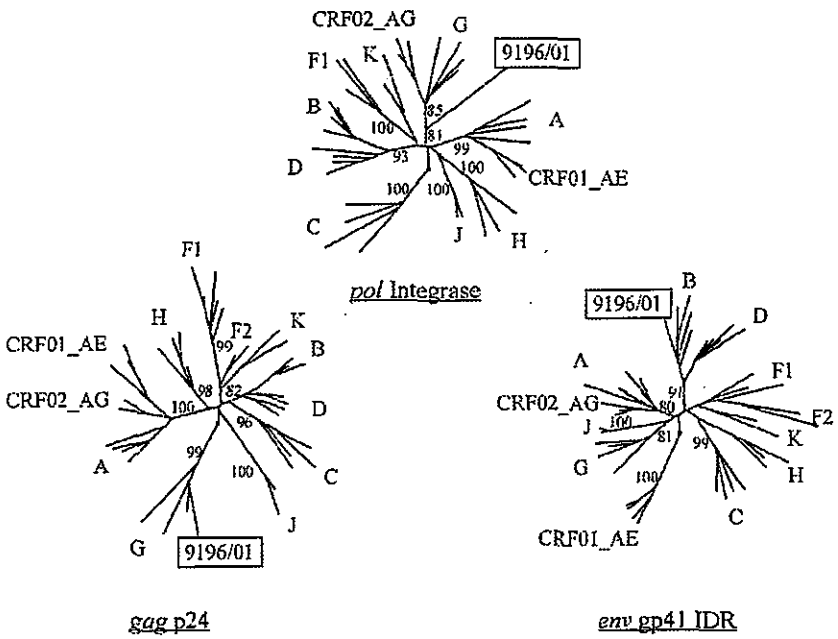

Fig. 1. Neighbor-joining trees generated for *gag* p24, *pol* IN, and *env* gp41 IDR. Selected bootstrap values greater than 80 are shown at each node.

primers and probe of the LCx assay. This polymorphism was located within the 5′ half of the reverse primer.

An alignment depicting nature and position of nucleotide mismatches within the NucliSens and Monitor v1.5 assay primer and probe regions relative to 9196/01 *gag* p24 is shown in Figure 3A,B. In the NucliSens assay, internal mismatches were identified in the forward and reverse primers (2 and 3, respectively). One reverse primer mismatch was in the penultimate position at the 3′ end. The majority of mismatches relative to 9196/01 were present within the probe sites; five in the capture probe and seven in wild-type (target) probe. In both cases, mismatches were distributed across the binding sites. The Monitor v1.5 assay had three internal mismatches in the forward primer and two in the reverse primer. None were near the critical 3′ end of the primers. Notably, five mismatches distributed across the probe region were identified.

DISCUSSION

In Western Europe, the majority of individuals with non-subtype B infections are immigrants from sub-Saharan Africa, or persons with a known history of unprotected heterosexual exposure to non-European individuals. This report documents the first case of HIV-1 infection with an intersubtype B/G recombinant virus in Germany. The infected patient had no epidemiological link to African countries. However, she had resided in Portugal for several months and had a history of injecting drug use during this time, resulting in HCV infection. The presence of subtype G and B/G mosaic strains within injecting drug users in Portugal and the Galicia region of Spain has been well documented [Thomson et al., 2001; Delgado et al., 2002; Esteves et al., 2003]. Thus, it seems quite probable that this individual was infected in Portugal.

In the present study, the phylogeny of this isolate was determined based on sequence analysis of three independent regions of the genome. The discordant phylogeny observed for strain 9196/01 between *gag* p24 (subtype G) and *env* gp41 IDR (subtype B), although consistent with a mosaic virus, could also have reflected dual infection with subtype B and G viruses. Formal demonstration of an intersubtype recombinant genome requires identification of a recombination breakpoint. Although the *pol* IN gene of 9196/01 segregated with subtype G, it radiated from a point near the base of the subtype G branch. Thus, the phylogeny was somewhat less definitive than that of the other regions. The explanation for this ambiguity in phylogeny became evident when results of the bootscan analysis were considered. Two recombination breakpoints were identified within *pol* IN; the central section of the gene was derived from subtype B whereas it was flanked by subtype G segments. The majority of this chimeric gene was subtype G, but a readily identifiable portion was subtype B-derived. This is consistent with the phylogenetic results obtained from analysis of the entire gene segment. Identification of the crossovers within *pol* IN unequivocally demonstrated that 9196/01 is a B/G intersubtype recombinant virus. Moreover, subsequent analysis of the subtype G-derived segments of 9196/01 revealed that they are more closely related to CRF14_BG than to the subtype G reference sequences. For example, when all available subtype G and five CRF14_BG reference strains from the Los Alamos database were added to the *gag* p24 analysis, the

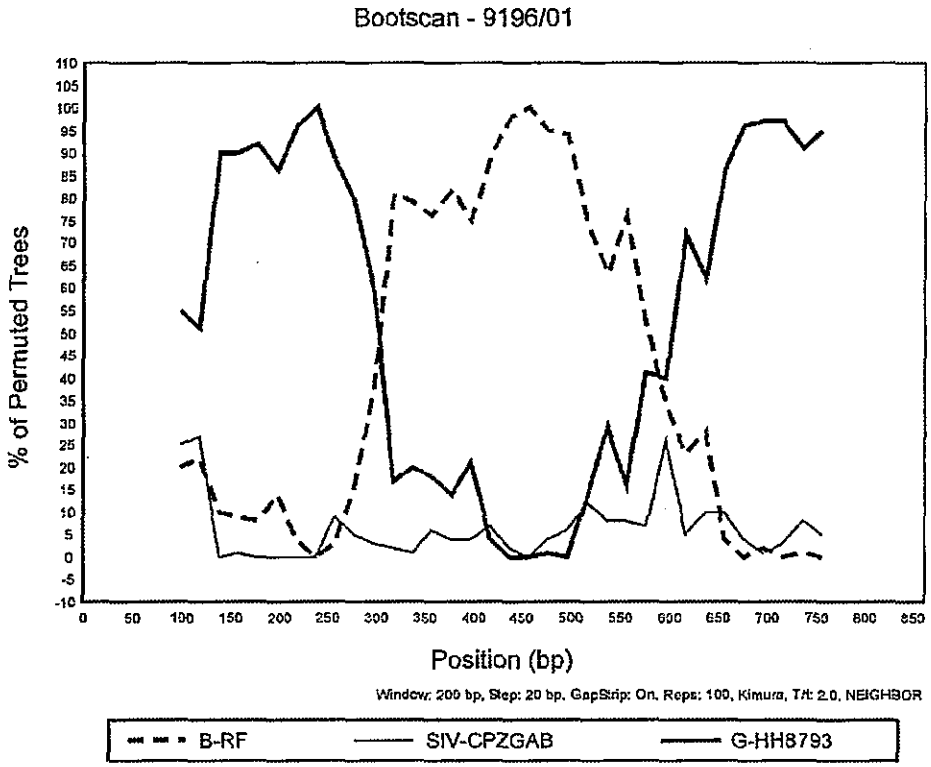

Fig. 2. Bootscan analysis of *pol* IN from 9196/01. Strain 9196/01 compared with subtype reference strains RF (B) and HH8793-1.1 (G) using SIV-CPZGAB as the outgroup (Accession numbers M17451, AF061640, and X52154, respectively). Bootscanning analysis was performed using a window of 200 nucleotides and a step of 20 nucleotides. The thick solid line represents subtype G, the dashed line subtype B, and the thin solid line SIV-CPZGAB.

bootstrap value of 9196/01 with CRF14_BG was 96%. The average genetic distance between 9196/01 and CRF14_BG reference strains, 0.0235, is less than half of the average distance between 9196/01 and the standard G reference strains, 0.0582. Although 9196/01 has a B/G recombinant composition and contains some regions closely related to CRF14_BG, it is clearly distinguishable from this CRF due to the subtype B-derived region within *pol* IN [Delgado et al., 2002]. This has since been confirmed based on full length genome analysis [Harris et al., 2005]. The phylogenetic relatedness between 9196/01 and CRF14_BG reference strains supports the contention that this patient was infected in Portugal.

TABLE II. Summary of Mismatches for Isolate 9196/01

NucliSens	
P2 primer 2 (forward)	3
P1 primer 1 (reverse)	2
Capture probe	5
WT probe (target probe)	7
Total	17
Monitor v1.5	
SK 145 (forward primer)	3
SKCC1B (reverse primer)	2
SK 102 (target probe)	5
Total	10
LCx HIV	
Forward primer	0
Reverse primer	1
Target probe	0
Total	1

Epidemiological evidence for spread of B/G recombinant strains to new regions within Europe is of considerable interest. However, the clinical implications related to accurate and reliable quantitation of these strains may be of even greater significance. The level of discordance in performance between the commercial tests used is noteworthy. NucliSens completely failed to detect 9196/01, while Monitor v1.5 detected but significantly underquantitated this strain relative to the LCx HIV assay. Analysis of the target regions revealed that performance reflected the level of conservation within the respective primer and probe sites (Table II). Seventeen natural polymorphisms were identified within the subtype G-derived target region of the NucliSens assay. Seven polymorphisms distributed across the wild-type (target) probe-binding site likely explain the inability to quantitate this strain. This is consistent with a previous study where NucliSens failed to detect most subtype G and B/G recombinant specimens [Antunes et al., 2003]. Reduced hybridization efficiency of the probe appears also to be the basis for underquantitation of 9196/01 in the Monitor v1.5 assay. Five internal mismatches were observed within the

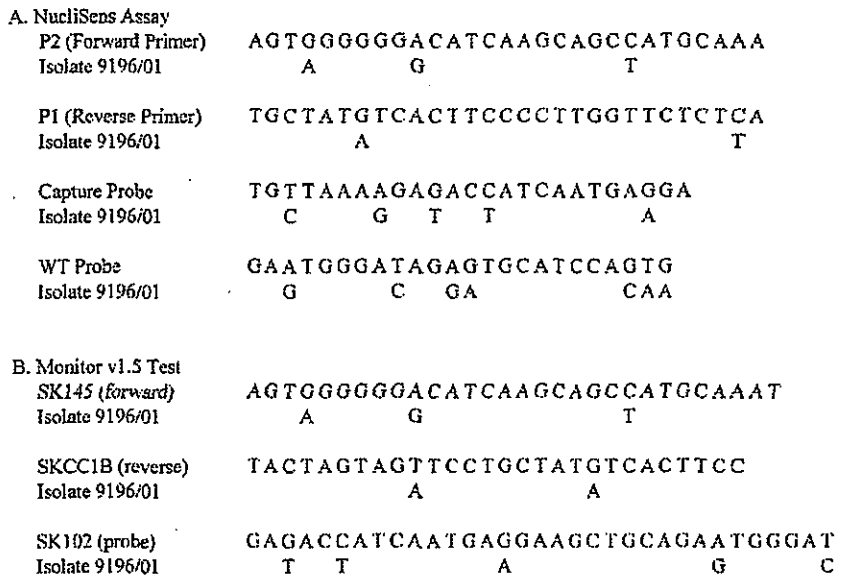

Fig. 3. Alignment of the *gag* p24 nucleotide sequence of strain 9196/01 against primer and probe sequences (oriented 5′-3′) of the NucliSens assay (A) and the Monitor v1.5 test (B). Only mismatches relative to the target sequences are shown. Primer and probe sequences for NucliSens were kindly provided by Organon Teknika/bioMérieux, Inc.; Monitor v1.5 sequences are from Pasquier et al., 1999.

probe-binding site of this subtype G-derived target region. Thus, although the Monitor v1.5 has improved efficiency of detection of non-subtype B viruses relative to earlier versions of the assay, quantitation of some divergent strains may still be unreliable. Underquantitation of other non-subtype B strains by Monitor v1.5 has been reported previously [Troonen et al., 2002; Geelen et al., 2003], although this is not the case for all subtype G and B/G recombinant strains [Antunes et al., 2003]. Consistent with the previous reports of a high level of conservation within the LCx target region [Swanson et al., 2000], 9196/01 had only one nucleotide polymorphism within the primer and probe binding sites. The significantly higher viral loads as measured in the LCx HIV assay relative to NucliSens and Monitor v1.5 reflected the level of conservation within the target region.

Genetic heterogeneity of HIV-1 has significant public health implications. HIV-1 diversity has the potential to affect accuracy and sensitivity of diagnostic and screening assays. This is illustrated by differences in antibody and antigen sensitivity for non-subtype B strains observed in a recent evaluation of fourth-generation combination assays [Ly et al., 2001]. As demonstrated in our study, reliability of molecular technologies used in screening, confirmatory algorithms, and for patient monitoring can also be compromised by genetic variability. Viral load determinations are routinely used in clinical practice to guide therapeutic intervention, monitor progression, and to assess risk of vertical transmission. Inaccurate results can have severe consequences [Geelen et al., 2003]. Moreover, relatively little is known concerning the impact of viral diversity on natural susceptibility to therapeutic agents and evolution of resistance. Clearly, the efficacy of antiretroviral treatment can be influenced by viral genetics [Descamps et al., 1997, 1998; Vergne et al., 2000]. In view of the presence and increasing prevalence of non-B variants in Germany and other European countries, it is important to monitor the ongoing diversification and redistribution of HIV-1 strains. Recombinant forms of HIV-1 add considerable complexity to surveillance and tracking of strains, and may contribute to increased unpredictability associated with pathogenesis and spread of the virus. Early detection of newly emerging variants and recombinant strains is critical to optimal management and control of HIV-1.

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No. 2

医薬品 研究報告 調査報告書

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研究報告の概要

○諮問委員会がインフルエンザ大流行時の血液供給への影響に言及
米国保健省の血液安全・安定供給諮問委員会が2006年1月5日～6日に開かれ、インフルエンザ大流行と血液の安全性や安定供給への影響について話し合われた。議題は、大流行のサーベイランスと行政の対応、ワクチンなどの対策、リスクコミュニケーション、輸血や臓器提供における不明点の解消、血液事業団体の対応、供血者のインフルエンザ血症と輸血や臓器提供を通じた感染の可能性、準備のモデルなどだった。
大流行時には、血液製剤の安定供給、特に有効期限が短く高い需要が見込まれる血小板の供給が脅かされることが強調された。委員会は、血液供給に対する大流行の影響を推定するには追加のデータが必要であると指摘し、供血者のウイルス血症の可能性に関する調査を含め、血液安全への潜在的な影響に関してさらなる研究を求めた。また、以下の勧議を全会一致で採択し、保健省がこれらの課題について対応策を取るよう勧告した。
1. 血液・血漿のシステム(採血、製造、供給、使用)について、特に医療機関スタッフや血液・血漿ドナーが、保健省の計画における重要なインフラであるという共通認識を形成
2. 新型インフルエンザの研究に予算を配分(対象は、無症候ウイルス血症の可能性、病態・血液感染性・治療法やドナースクリーニング検査の研究、通常のインフルエンザのウイルス血症の研究、大流行時の血液供給と活用に関する量的モデルの開発とバリデーション・血液不足予防のための予備介入の効果についての研究)
3. 国内及び海外のサーベイランスをインフルエンザ対策に反映させるための連邦政府の支援
4. 政策決定、行政や関係団体との連絡など、AABBタスクフォースの役割を認識
5. 血液が不足している間、血液や血液製剤の供給・使用の割り当てを適正化し、格差を最小限に抑えるよう、政府の方針を形成

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
米国保健省の血液安全・安定供給諮問委員会で、インフルエンザ大流行と血液安全や安定供給への影響について話し合われ、対応策について勧議が採択されたとの報告である。	インフルエンザウイルスは脂質膜を持つRNAウイルスである。これまで、本製剤によるインフルエンザウイルス感染の報告はない。本製剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれている。本製剤の安全性は確保されていると考えるが、インフルエンザが大流行した場合、献血者減少につながることも予想されるので、今後も引き続き情報の収集に努める。

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Advisory Panel Addresses Impact of Flu Pandemic on Blood Supply

The Advisory Committee on Blood Safety and Availability (ACBSA) met Jan. 5-6, 2006, to discuss the issue of pandemic influenza and its impact on blood safety and availability. Topics discussed included pandemic surveillance and response at the national, state and local levels; vaccine preparation in an influenza pandemic; state and local preparedness; risk communication during an influenza pandemic; identifying the gaps of knowledge in transfusion and transplantation medicine in the event of a pandemic; blood community preparedness; influenza viremia in blood donors and potential transmission through transfusions and transplantations; and models for preparedness.

Mississippi Valley Regional Blood Center's Louis Katz, MD, chair of the AABB Interorganizational Task Force on Pandemic Influenza and the Blood Supply, represented AABB at the ACBSA meeting. He outlined the mission of the flu task force, which includes identifying issues that blood collection facilities and transfusion services will likely need to consider; identifying options for response to those issues; and providing guidance for planning to collection facilities and transfusion services. The flu task force will communicate with the AABB Interorganizational Task Force on Domestic Disasters and Acts of Terrorism to help facilitate its response regarding blood needs during a pandemic.

Inside *Weekly* ...

There was general agreement among committee members and presenters that the availability of blood products is likely to be highly compromised in the event of a pandemic. Katz and others highlighted particular threats to the supply of short-lived platelets, which will continue to be in high demand in the event of a pandemic. The committee noted that additional data are needed to appreciate the actual impact a pandemic would have on the blood supply. In addition, the committee called for more research regarding possible blood safety implications, including studies of potential viremia in blood donors.

The committee passed the following resolution unanimously, recommending that HHS take action on these issues. (Note: the final text of the resolutions may be modified before being sent to the secretary of HHS.)

Whereas,

a) *Evidence suggests the possibility in the near term for a global pandemic of influenza A based on recent, highly virulent, human infections with an avian H5N1 virus,*
b) *The HHS plan for pandemic influenza recognizes the priority to preserve critical infrastructure in our society,*
c) *Ensuring the safety and availability of blood and blood products, including plasma products, is a critical public health need,*
d) *Although the scope and impact of the potential pandemic are uncertain, the availability of blood products is likely to be highly compromised during an influenza pandemic,*
e) *Data have suggested the possibility that influenza viruses may be present in the blood, organs and tissues of asymptomatic donors,*
f) *Influenza surveillance data, which come from diverse sources, are limited in scope, timeliness and integration,*
g) *Risk education and communication to the public, delivered by scientific and medical experts, are essential components of preparedness for pandemic influenza,*
h) *Preparedness of the blood and plasma system for pandemic influenza would contribute to the general disaster preparedness.*

The committee recommends that the secretary take immediate steps to:

1. *Establish national recognition of the blood and plasma systems (collection, processing, distribution and use) as key elements of the critical infrastructure under the HHS plan, specifically including facility staff and committed blood and plasma donors;*
2. *Assure full funding of research to resolve critical scientific questions regarding the potential impact of pandemic influenza on blood, organ and tissue safety and availability:*
    a. *Foster collaborations with investigators in countries affected by the current H5N1 influenza outbreak to promote studies of possible viremia in asymptomatic persons, including recent case contacts,*
    b. *Support studies of H5N1 and other potential pandemic strains in suitable animal models, including non-human primates, to investigate viremia and organ localization of infectivity in preclinical, clinical, and convalescent stages of disease; transfusion transmissibility of virus if present in blood; and impact of infection and/or drug treatment on the accuracy of donor screening tests,*
    c. *Support studies of influenza viremia during annual outbreaks of non-pandemic strains, including studies on blood and plasma donors, and product recipient,*
    d. *Support development and validation of quantitative models for blood availability and utilization in an influenza pandemic and the potential value of candidate interventions to prevent shortages,*
3. *Provide targeted federal support to enhance global and domestic surveillance for seasonal and pandemic influenza,*
4. *Recognize the central role of the AABB Interorganizational Task Force on Domestic Disasters and Acts of Terrorism in the development and implementation of a national strategy to address potentially massive blood and blood product shortages during a pandemic of influenza by*
    a. Assuring blood and plasma systems' input into key federal policy making and communication,
    b. Promoting communication and cooperation amongst state and local public health authorities and appropriate blood collection organizations, hospitals, medical professional organizations and patient advocacy organizations,
5. *Develop national principles under which state and local public health authorities and health care*

providers can prioritize allocation of and minimize disparities in blood and blood products availability and use during critical shortages.

Further detailed information on this and other topics discussed at ACBSA can be found in an upcoming issue of *Regulatory Update*. The next ACBSA meeting will take place in Spring 2006.

AABB Looks Back at 2005 Legislative Year

Congress recently concluded its first session of the 109th Congress by passing appropriation bills that provide only limited increases in funding for vital health care programs and cuts for other programs. In addition to these last-minute measures to fund the programs of the U.S. Department of Health and Human Services (HHS), Congress also worked in 2005 to adopt legislation related to patient safety, cord blood and Medicare.

Appropriations

Congress passed, in late December, the Labor, Health and Human Services, and Education (Labor-HHS) FY 2006 appropriations bill (H.R. 3010), which included a total of $142.5 billion in discretionary funding. However, this amount excludes a 1 percent across-the-board cut in discretionary funding as approved in the Department of Defense (DoD) FY06 appropriations bill. All amounts in the HHS appropriations below are prior to the 1 percent cut. The National Institutes of Health (NIH) received $28.62 billion, a 0.9 percent increase over last year before the 1 percent cut, which means NIH and its facilities are operating at a level $30 million below the FY05 level. The National Heart, Lung, and Blood Institute has been appropriated $2.95 billion for FY06, which is a $10.1 million (less than 0.5 percent) increase over FY05. The Centers for Disease Control and Prevention received $5.88 billion for FY06, a notable $713 million decrease from FY05, including $530 million for the Strategic National Stockpile and $1.70 billion for infectious diseases. Also included in the appropriations bill was $500 million for hospital emergency preparedness, $107.4 million for health information technology, and $4 million for a National Cord Blood Stem Cell Bank.

In the FY06 appropriations legislation, Congress also slashed $153 million in funding, or 51 percent, from the Title VII Allied Health Professions Programs. Included in the cut are the allied health and other related programs that fund the establishment and expansion of laboratory-based medical technology programs.

The U.S. Department of Agriculture FY06 appropriations legislation included $1.5 billion for the Food and Drug Administration (FDA), a 2.7 percent increase over FY05 funding. This appropriations bill also included $30 million to study mad cow disease and $28 million to agriculture agencies to control and manage avian influenza.

Faced with ongoing budgetary restraints, health care advocates will have an uphill battle once again this coming year, as they argue for increased funding for important public health and research programs. The first step in the battle will be responding to President George W. Bush's FY07 budget, which will be released in February and is expected to include, at the most, only very limited increases (likely below inflationary rates) for most health-related discretionary programs.

Patient Safety Legislation

Earlier this year, Congress passed S.544, the Patient Safety and Quality Improvement Act of 2005, which aims to reduce the number of fatalities due to medical errors. The law was signed six years after the Institute of Medicine's 1999 report, *To Err is Human*, which indicated that as many as 98,000