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Phylodynamic analysis of the dissemination of HIV-1 CRF01_AE in Vietnam

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ABSTRACT

To estimate the epidemic history of HIV-1 CRF01_AE in Vietnam and adjacent Guangxi, China, we determined near full-length nucleotide sequences of CRF01_AE from a total of 33 specimens collected in 1997–1998 from different geographic regions and risk populations in Vietnam. Phylogenetic and Bayesian molecular clock analyses were performed to estimate the date of origin of CRF01_AE lineages. Our study reconstructs the timescale of CRF01_AE expansion in Vietnam and neighboring regions and suggests that the series of CRF01_AE epidemics in Vietnam arose by the sequential introduction of founder strains into new locations and risk groups. CRF01_AE appears to have been present among heterosexuals in South-Vietnam for more than a decade prior to its epidemic spread in the early 1990s. In the late 1980s, the virus spread to IDUs in Southern Vietnam and subsequently in the mid-1990s to IDUs further north. Our results indicate the northward dissemination of CRF01_AE during this time.

Introduction

HIV-1 infection in Vietnam was first documented in a young woman who was presumably infected by her foreign partner in late 1990 in Ho Chi Minh City (Lindan et al., 1997). By the early 1990s, HIV-1 had spread slowly among female commercial sex workers (fCSWs) and their clients. However, in 1993, an HIV-1 epidemic broke out among injecting drug users (IDUs) in Khanh Hoa Province and Ho Chi Minh City in Southern Vietnam (Subcommittee, 1998). By the end of 2005 the epidemic had spread to Northern Vietnam (UNAIDS/WHO, 2006a). Between 2000 and 2007, the estimated number of people living with HIV in Vietnam more than doubled from 122,000 to 290,000, and approximately 40,000 Vietnamese are estimated to be infected with HIV each year (UNAIDS/WHO, 2008).

CRF01_AE is almost the sole HIV-1 strain circulating in Vietnam, in all geographical regions and risk populations (Lan et al., 2003; Osmanov et al., 2002; Weniger et al., 1994). Only a few cases of HIV-1 subtype B infection have been reported so far (including the first Vietnamese case reported in 1990) (Kato et al., 1999; Menu et al., 1996). Previous studies, including ours, have identified genetic differences among HIV-1 CRF01_AE strains sampled from different locations and risk populations (Beyrer et al., 2000; Kusagawa et al., 1999; Nerurkar et al., 1996; Yu et al., 1999), and the similarity of viruses circulating among IDUs in Northern Vietnam and the nearby Guangxi Province of China suggests the cross-border transmission of CRF01_AE (Kato et al., 2001, 1999; Piyasirisilp et al., 2000).

In this study, we investigated the timescale and epidemic history of CRF01_AE transmission in Vietnam and neighboring locations, using established phylogenetic and evolutionary analysis methods.

Results

Phylogenetic characteristics of CRF01_AE isolates from Vietnam

A total of 33 near full-length nucleotide sequences (HXB2: 790–8795) representing CRF01_AE infections from Vietnam were subjected to phylogenetic analysis together with available reference sequences. The similarity between Vietnamese isolates and each subtype was calculated by Simplot analysis. The Vietnamese isolate (97VNHD10) showed greatest similarly with CRF01_AE (CM240), and this was confirmed by bootscanning analysis. One representative result (for 97VNHD10, which belongs to cluster 3) is shown in Figs. 1B and C. The recombination analysis results of other Vietnamese isolates were similar to those shown in Figs. 1B and C (data not shown). These results indicate that Vietnamese isolates obtained in the present study are CRF01_AE without evidence of further recombination events. Maximum likelihood trees revealed that all of the Vietnamese and Guangxi CRF01_AE sequences (except three) grouped as a single monophyletic cluster within the Thai isolates (Fig. 1A). The Vietnamese sequence group is composed of three distinct clusters (Fig. 1A

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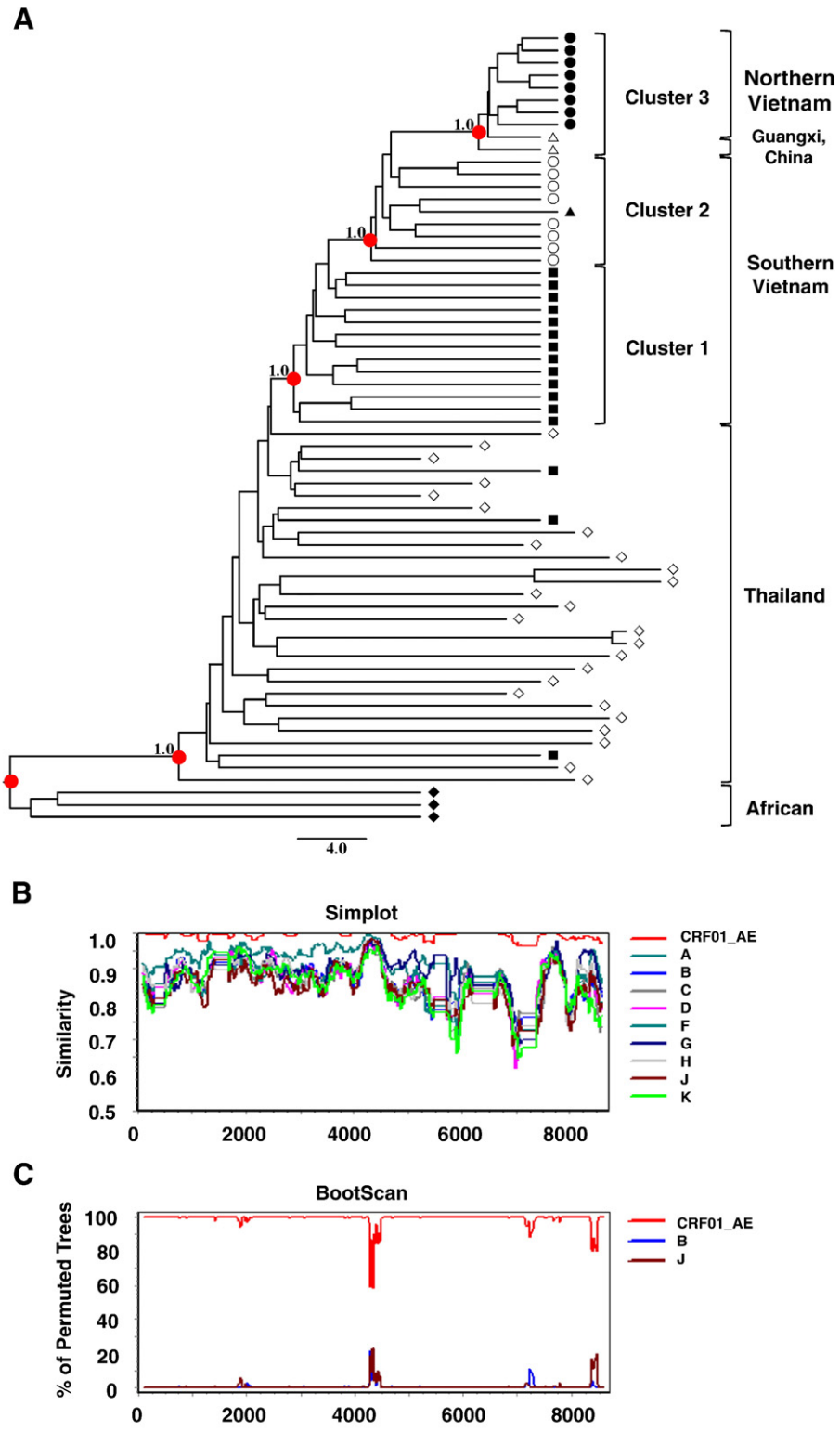

Fig. 1. HIV-1 CRF01_AE strains from Vietnam grouped into three distinct clusters. (A) Maximum clade credibility (MCC) tree of near full-length HIV-1 CRF01_AE isolates obtained by Bayesian MCMC analysis (see Materials and methods for details). Symbols represent different locations and risk groups: ♦ = African CRF01_AE; ◊ = Thailand CRF01_AE; ■ = heterosexuals in Southern Vietnam; ○ = IDU in Southern Vietnam; ● = IDU in Northern Vietnam; ▲ = heterosexuals in Northern Vietnam; △ = IDU in Guangxi Province of China. Posterior probabilities are indicated for each cluster. Scale bar is years. (B) The similarity between the Vietnam isolates and the references were plotted using Simplot program. (C) The recombination analysis of each Vietnamese isolate was performed by BootScan within SimPlot program. The reference subtypes are indicated in the box.

and Supplemental Fig. S1). Cluster 1 ($n = 13$) is paraphyletic and exclusively contains sequences from heterosexuals in Southern Vietnam. Cluster 2 ($n = 9$) is paraphyletic and contains sequences from IDUs in Southern Vietnam ($n = 8$) plus one sequence from a Northern Vietnamese STD patient (98VNND15). Cluster 3 ($n = 10$) is monophyletic and contains sequences from IDUs in Northern Vietnam ($n = 8$) and the nearby Chinese province of Guangxi ($n = 2$). The only exceptions that did not belong to these clusters are 3 specimens from

Table 1
Distribution of Vietnamese CRF01_AE isolates (clusters 1 to 3) in different locations and risk groups.

Location	Risk factor	Thai cluster	Cluster 1	Cluster 2	Cluster 3	*n*
Southern Vietnam	Sexual	3[a]	13[b]	0	0	16
	IDU	0	0	8	0	8
Northern Vietnam	Sexual	0	0	1	0	1
	IDU	0	0	0	8	8
Total		3	13	9	8	33

[a] Specimens from An Giang.
[b] 5 specimens from Ho Chi Minh City; 8 specimens from An Giang.

heterosexuals in Southern Vietnam, which were placed within the Thai CRF01_AE group (Fig. 1A; Table 1).

Evolutionary history of CRF01_AE in Vietnam

To estimate the timescale of CRF01_AE expansion in Vietnam, we estimated the date of origin of each CRF01_AE cluster using a Bayesian approach under both strict and relaxed molecular clock models, as implemented in BEAST v1.4. Rates of evolution (in units of nucleotide substitutions per site per year) were estimated by analysis of the same dataset sampled between 1990 and 2004. The estimated evolutionary rates and dates of origin for each cluster are listed in Table 2. The estimated date of the most recent common ancestor of the African CRF01_AE isolates was the late 1960s, and the corresponding date for the Thai CRF01_AE isolates was the late 1970s. The estimated dates of origin of each Vietnamese cluster were as follows: the early 1980s for cluster 1, the late 1980s for cluster 2, and the mid 1990s for cluster 3. The dates estimated using different molecular clock models and different substitution models were highly consistent (Fig. 2, Table 2 and Supplemental Table S2).

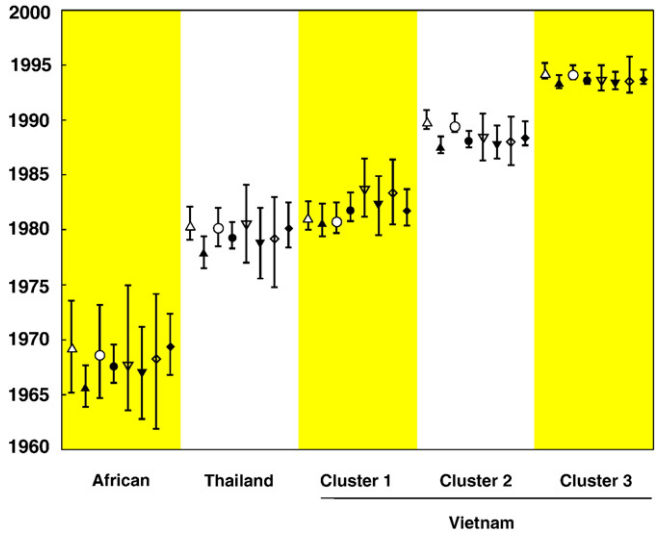

Fig. 2. Estimated dates of origin of CRF01_AE strains. Molecular clock analyses were performed using BEAST v1.4 (see Materials and methods for details). Horizontal bars represent the 95% credible region (confidence limits) for each estimate. For each cluster, estimates were obtained under four different evolutionary models: △ = GTR with Relaxed clock, constant; ▲ = GTR with Strict clock, constant; ○ = HKY with Relaxed clock, constant; ● = HKY with Strict clock; ▽ = GTR with Relaxed clock, skyline; ▼ = GTR with Strict clock, skyline; ◊ = HKY with Relaxed clock, skyline; ◆ = HKY with Strict clock, skyline.

Discussion

Full-length genomic sequencing helps to understand HIV-1 genetic diversity and contributes to the fields of HIV epidemiology, diagnosis, pathogenesis, and vaccine development. Our phylogenetic and evolutionary analysis of near full-length CRF01_AE sequences from Vietnam indicates that HIV-1 CRF01_AE was introduced from Africa to Thailand in the late 1970s (Figs. 2 and 3; Table 2). This lineage is likely the ancestor of all CRF01_AE strains in Asia. Our CRF01_AE sequences from Vietnam and Guangxi (China) clustered within the Thai sequences and could be classified into three distinct phylogenetic clusters (clusters 1 through 3) (Fig. 1A and Supplemental Fig. S1). Each cluster was associated almost exclusively with a specific risk population in a particular geographic location (Table 1; Fig. 1A). The pattern of monophyly and paraphyly suggests that CRF01_AE in Vietnam originated from Thailand and points towards the transmission of CRF01_AE between heterosexuals and IDUs in Southern Vietnam. WHO has reported that the use of non-sterile injecting equipment is widespread in Vietnam, and significant percentages of fCSW inject drugs, many of whom had clients who were IDUs (UNAIDS/WHO, 2006b). Our results show that CRF01_AE was transmitted from heterosexuals (Cluster 1) to IDUs (Cluster 2) among risk populations in Southern Vietnam in the late 1980s. A more recent cluster (cluster 3) that contains strains from IDUs in Northern Vietnam and Guangxi, China is located within cluster 2 (Table 1; Fig. 1A), indicating the northward dissemination of CRF01_AE among IDUs in Vietnam (Fig. 3). This result is in agreement with our previous study, in suggesting that cross-border transmission of CRF01_AE between Vietnam and China occurs (Kato et al., 2001, 1999). However, current sampling prevents us from pinpointing the exact route between these two regions.

Only 3 isolates, sampled from heterosexuals in Southern Vietnam, belonged to the Thai CRF01_AE group. These specimens were collected from a sexual risk population in An Giang, a city in Southern Vietnam near the Cambodian border. Other heterosexual specimens collected from Ho Chi Minh City ($n = 5$) and An Giang ($n = 8$) grouped together in cluster 1 (Fig. 1A). This suggests that CRF01_AE strains

Table 2
Estimated substitution rates and dates of origin for each cluster[a].

Cluster	Value (HPD) of the evolutionary parameter according to the indicated model							
	GTR + γ4 constant size				HKY + γ4 constant size			
	Strict		Relaxed		Strict		Relaxed	
	μ[b] = 3.45 (2.81–4.08)		μ = 4.33 (3.46–5.15)		μ = 3.71(3.24–4.19)		μ = 4.24 (3.32–5.30)	
	tMRCA[c]	ESS	tMRCA	ESS	tMRCA	ESS	tMRCA	ESS
African	1965.9 (1963.9–1967.7)	296.442	1969.7 (1965.2–1973.6)	184.848	1967.8 (1966.1–1969.6)	515.348	1968.9 (1964.7–1973.2)	349.256
Thailand	1978.1 (1976.5–1979.4)	287.177	1980.7 (1979.1–1982.1)	158.868	1979.5 (1978.3–1980.7)	275.732	1980.4 (1978.5–1982.0)	234.105
Cluster 1	1980.8 (1979.4–1982.4)	175.926	1981.4 (1980.0–1982.6)	128.040	1982.0 (1980.8–1983.4)	277.077	1981.0 (1979.7–1982.5)	222.471
Cluster 2	1987.7 (1987.0–1988.5)	358.300	1990.0 (1989.2–1990.9)	140.653	1988.3 (1987.5–1989.0)	677.595	1989.8 (1988.9–1990.6)	328.843
Cluster 3	1993.6 (1992.9–1994.1)	704.553	1994.5 (1993.8–1995.2)	428.838	1993.8 (1993.3–1994.3)	1182.570	1994.4 (1993.7–1995.0)	659.016

[a] Based on BEAST analysis under the Constant size demographic model.
[b] Estimates of the mean evolutionary rate ($\mu \times 10^{-3}$ nucleotide substitutions/site/year) for the CRF01_AE.
[c] Mean time of the most recent common ancestor (tMRCA: year) for the CRF01_AE dataset (95% HPD in parentheses).

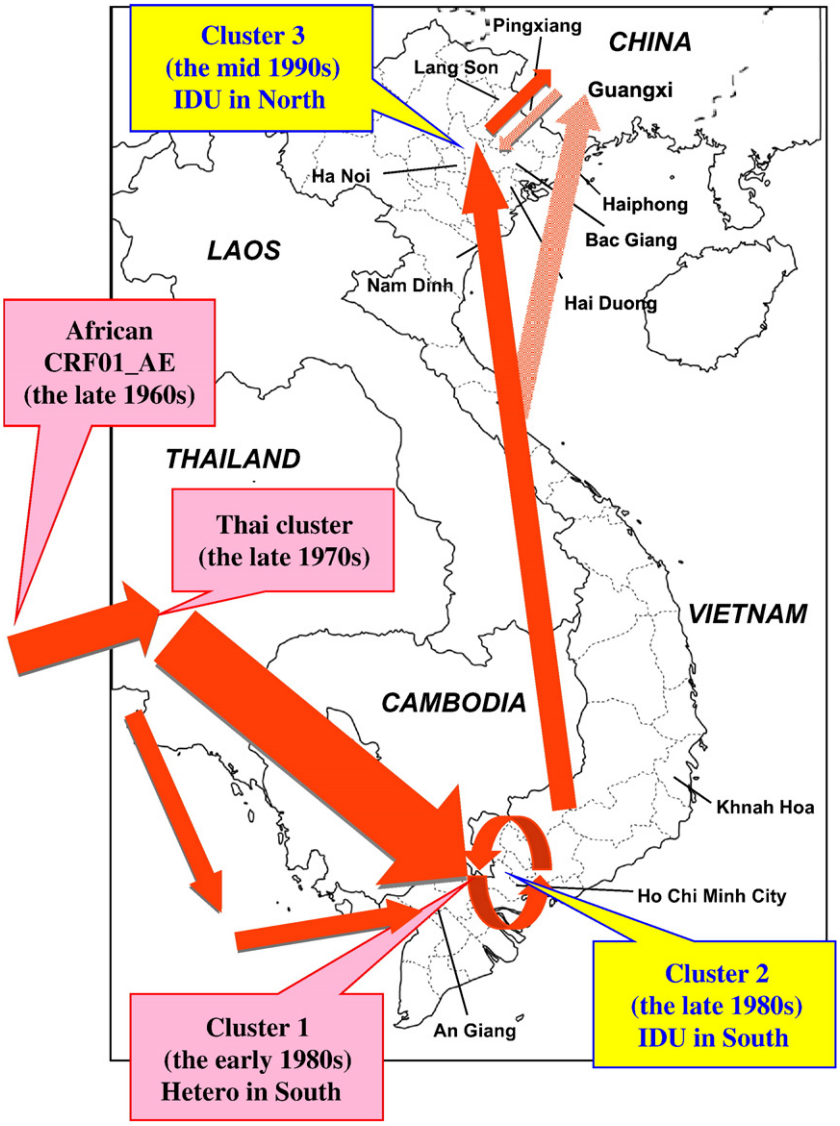

Fig. 3. Illustration of the hypothesized overland spread of CRF01_AE in Vietnam. Southern provinces of Vietnam and An Giang, near Cambodia, are likely portals of CRF01_AE of Thai origin. Cluster 1 predominated among heterosexuals (fCSW and their clients) in An Giang and Ho Chi Ming City in the early 1980s. A subset of cluster 1 (i.e. cluster 2) started to disseminate in IDUs in same area in the late 1980s. A subsequent secondary CRF01_AE variant (cluster 3) appears to have spread to IDUs in Northern Vietnam in the mid-1990s, and is also responsible for the outbreak among IDUs in near Guangxi Province of China. Two possible pathways of virus spread from the south to the north are depicted as solid and dotted arrows. The estimated time to the most recent common ancestor of African CRF01_AE is shown for reference (see Table 2).

entered the Southern Vietnamese heterosexual population several times from Thailand, probably through Cambodia, and that An Giang is a likely portal of entry of CRF01_AE.

The results presented in Fig. 1A and Table 2 imply that CRF01_AE spread to sexual risk populations in Southern Vietnam very shortly after its introduction to Thailand, suggesting a frequent exchange of infected individuals within this region. The transmission of CRF01_AE from heterosexuals to IDUs in Southern Vietnam took nearly 10 years, however, the spread of this strain, once in IDUs, from Southern to Northern Vietnam took less time, about 5 years (Table 2 and Supplemental Table S2; Fig. 2). These results suggest a greater degree of mixing of IDUs from different regions in Vietnam than among heterosexual risk populations from different regions.

The estimated date of the most recent common ancestor of Thai CRF01_AE appears predate the discovery, in 1989, of an increase in HIV-1 seropositivity in Northern Thailand (McCutchan et al., 1992; Menu et al., 1996). In addition, the origin of cluster 1 occurred 10 years or more before the detection of an outbreak among heterosexuals in Southern Vietnam, believed to have taken place in the early 1990s (Menu et al., 1996; Ou et al., 1993). These observations may reflect the initially slow process of virus spread among risk populations during the earliest phases of exponential epidemic spread.

Through back-calculation, AIDS case reporting can provide information on transmission patterns and levels of infection approximately 5–10 years in the past (Gilbert et al., 2007; UNAIDS/WHO, 2006a). Gilbert et al. (2007) have suggested that HIV-1 was circulating in the United States – one of the world's most medically-sophisticated regions – for more than a decade before AIDS was recognized. This conclusion was based on evolutionary analysis of HIV-1 subtype B in the United States (Gilbert et al., 2007). The apparent lag time between the introduction of the virus into a new area/population and the first recognition of symptomatic patients that we observed in Vietnam is, perhaps surprisingly, similar to the observation by Gilbert et al. (2007). Among individuals enrolled in large epidemiologic studies in Western countries, the mean time from infection with HIV to the development of AIDS-related symptoms has been approximately 10 to 12 years in the absence of antiretroviral therapy (NIAID, 2004). HIV testing was started in Vietnam in 1988 and the first case was reported in 1990. There were no reported cases the following year, but 11 cases were found in Southern Vietnam in 1992. In 1993 there was an

outbreak in IDUs in central and Southern Vietnam. 57 individuals had AIDS and 18 of these died (Nguyen and Wolffers, 1994). We might therefore conclude that CRF01_AE was introduced into Southern Vietnam more than a decade before 1993, in good agreement with our evolutionary analysis results (Fig. 3). Similarly, in Thailand, we would expect CRF01_AE to be present for 10 or more years before it was first detected in the year 1989 (McCutchan et al., 1992; Ou et al., 1992). Furthermore, the estimated dates of divergence of clusters 2 and 3 (Table 2; Fig. 2) also correspond with previously published reports (Cheng et al., 1994; Menu et al., 1996; Nerurkar et al., 1996; Piyasirisilp et al., 2000).

The epidemic history of HIV-1 we report here constitutes a series of bottleneck or founder events. There appear to be surprisingly few "successful" migration events, compared to the number of times that we might expect the virus to move from one place to the next. A similar phenomenon has been observed in the global migration of subtype B, from central Africa to the United State, via Haiti (Gilbert et al., 2007) and in the overland spread of CRF07_BC and CRF08_BC in East Asia (Tee et al., 2008a, 2008b).

Our results provide molecular epidemiological evidence that CRF01_AE was introduced into Vietnam in the early 1980s and transferred from sexual risk populations to IDUs in Southern Vietnam in the late 1980s. The strain subsequently spread in IDUs from Southern to Northern Vietnam (and Guangxi, China) in the early or mid-1990s (Fig. 3).

Materials and methods

Study subjects and specimens

33 whole blood specimens in acid-citrate-dextrose (ACD) solution were collected between April 1997 and June 1998, from HIV-positive individuals in various risk groups in Southern Vietnam (Ho Chi Minh City, An Giang Province; $n=24$) and Northern Vietnam (3 northern provinces near Hanoi; $n=9$), including 16 IDUs, 8 sexually transmitted disease (STD) patients, 3 heterosexuals and 6 CSW (Table 1). Each specimen was named as follows: following the country code, VN, the two or three subsequent characters denote the sampling sites: Ho Chi Minh (HCM) and An Giang (AG) in Southern Vietnam; Bac Giang (BG), Hai Duong (HD) and Nam Dinh (ND) in Northern Vietnam. Reference nucleotide sequences belonging to CRF01_AE with known sampling dates were retrieved from the Los Alamos HIV Sequence Database (http://www.hiv.lanl.gov/content/index).

PCR amplification and nucleotide sequencing

Near full-length nucleotide sequences of HIV-1 were determined from either provirus DNA from peripheral blood mononuclear cells (PBMCs) (2 specimens) or from plasma virus RNA (31 specimens), as previously described (Brooks et al., 2006; Salminen et al., 1995).

Phylogenetic and recombinant analysis

Near full-length CRF01_AE nucleotide sequences (HXB2: 790–8795) obtained from Vietnam were aligned with reference sequences using the ClustalX 1.83 program, and further adjusted manually. The recombination analysis of each Vietnamese isolate was performed by SimPlot program using an algorithm of neighbor-joining with a sliding window of 200 nucleotides, overlapping by 50 nucleotides, and a transition–transversion ratio of 2.0, as previously described (Carr et al., 1996). Reference sequences for subtype A (92UG037), subtype B' (RL42), subtype B (RF), subtype C (95N21068), subtype D (NDK), CRF01_AE (CM240), subtype F (VI850), subtype G (SE6165), subtype H (V1991), subtype J (SE7022) and K (MP535) were used in the Simplot analysis and subtype B' (RL42), CRF01_AE (CM240) and subtype J (SE7022) were used in the BootScanning analysis. A posterior distribution of phylogenies was obtained using a Bayesian Markov chain Monte Carlo (MCMC) approach, as implemented in BEAST v1.4 (Drummond and Rambaut, 2007). To summarize this distribution, a maximum clade credibility (MCC) tree was calculated using the program TreeAnnotator (available from http://beast.bio.ed.ac.uk).

Divergence time estimation

Investigation of the evolutionary history of the CRF01_AE strains was carried out using BEAST v1.4 (Drummond and Rambaut, 2007), in order to estimate the date of the most recent common ancestor of each phylogenetic cluster (Fig. 1A) (Drummond et al., 2002; Pybus et al., 2003). Dates were estimated using Bayesian MCMC inference under both the GTR and HKY nucleotide substitution models, with a gamma-distribution model of among site rate heterogeneity (with four rate categories) (Hasegawa et al., 1985; Rodriguez et al., 1990; Yang, 1994). Divergence times were estimated using two different molecular clock models: a strict clock and an uncorrelated lognormal relaxed clock (Drummond et al., 2006). Coalescent population growths were estimated using constant size model and using the Bayesian skyline plot model. The analysis was computed for 10 million states sampled every 10,000 states. The MCMC output was tested for convergence and effective sample size using Tracer v1.4 (available from http://beast.bio.ed.ac.uk). The evolutionary rates were estimated from the same CRF01_AE dataset. The rates of evolution were then incorporated as a prior probability distribution in the analysis of these CRF01_AE sequences (Tee et al., 2008b).

Nucleotide sequence accession numbers

The GenBank accession numbers for the 33 nucleotide sequences obtained here are FJ185228 to FJ185260.

Conflict of interest
No conflict.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.virol.2009.05.023.

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