Acknowledgements

The authors would like to thank all the patients for their participation and all the members of the Unité de Soins Ambulatoires et de Conseils in Abidjan, Côte d’Ivoire. They also thank Fassyery Dembele, Edouard Djo-B Djo, Adou Aman, Isabelle Adou Tchimou, Justine Kounamé, Fatoumata Kone Koffi, Alex Ali, Jonas Seri Boga, and Habane Guéhi Calixte for their assistance in the data collection.

aUnité de Soins Ambulatoires et de Conseils, Abidjan, Côte d’Ivoire; bDépartement de Médecine Sociale et Preventive, Université Laval, Quebec, Quebec, Canada; cUnité de Recherche en Santé des Populations, Centre Hospitalier affilié Université de Québec, Quebec, Canada; and dInstitut National de Santé Publique du Québec, Quebec, Canada.

The study was approved by the research ethics committees of Université Laval, Quebec, Canada and of the Ministry of Health of Côte d’Ivoire. Informed written consent was obtained from all participants.

Sponsorship: M.A. is a national researcher of the Fonds de la Recherche en Santé du Québec, Canada (grant no. 8722).

Received: 24 May 2007; revised: 10 July 2007; accepted: 18 July 2007.

References


Chronology of the HIV-1 CRF07_BC expansion in East Asia

Kok Keng Tee, A.D., Oliver G. Pybus, C, Huanan Liao, C, Rie Uenishi, C, Saiki Hase, C, Adeeba Kamuruzaman, C, Xiao-Jie Li, C, and Yutaka Takebe, C

The HIV-1 epidemic among injecting drug users (IDU) in Taiwan is caused primarily by CRF07_BC infections. Evolutionary analyses, which utilize outgroup reference strains from northwestern China (Xinjiang), reveal that CRF07_BC was introduced into southern Taiwan in 1998–2001 and spread to central–northern Taiwan in 2001–2003, causing the largest HIV/AIDS epidemic in Taiwan. The separate introduction of CRF07_BC into Xinjiang occurred in 1992–1995. This study illustrates the temporal dynamics of CRF07_BC spread among IDU across east Asia.

The HIV-1 circulating recombinant form 07_BC (CRF07_BC) is a recombinant comprised of HIV-1 subtype B (Thailand genotype of subtype B) and subtype C. This strain accounts for most infections among injecting drug users (IDU) in northwestern China (Xinjiang province), where an outbreak was detected in 1996 [1], although the most plausible origin of CRF07_BC as a whole is probably Yunnan province [2,3]. Outside mainland China, CRF07_BC is associated with a dramatic increase in HIV/AIDS cases in Taiwan; it was detected among IDU in prisons in southern Taiwan (Tainan) in 2002 and later detected in 2003–2004 in central (Nantou) and northern (Taipei) Taiwan [4]. By
In the end of September 2007, 15,183 HIV cases have been reported in Taiwan since 1984 and the majority of infections occurred relatively recently among IDU [5]. CRF07_BC accounts for 98% of the infections among IDU in Taiwan [4].

To estimate the timescale of CRF07_BC spread in mainland China and Taiwan, we performed phylogenetic and Bayesian coalescent analyses on env sequences obtained from GenBank. The CRF07_BC env sequences used in this study are from Xinjiang province, China (n = 4; sampled in 1997–1998), and from three cities in Taiwan; in particular, Tainan (southern; n = 19), Nantou (central; n = 8) and Taipei (northern; n = 8), all sampled in 2004 (accession numbers EF078077–EF078079, EF078082–EF078105 and EF078107–EF078114). As shown in Fig. 1a, the CRF07_BC sequences group into three distinct phylogenetic clusters, denoted Xinjiang (China), Tainan (southern Taiwan) and Nantou–Taipei (central and northern Taiwan). Using the molecular clock approach implemented in BEAST v1.4 [6], we estimated the rate of evolution of the hypervariable region-stripped env gene (HXB2 7077–7665 nt) from an independent dataset of 41 HIV-1 subtype C strains with known sampling dates that ranged from 1989 to 2005. The

---

**Fig. 1.** Phylogenetic and evolutionary analysis of HIV-1 sequences from injection drug users in mainland China and Taiwan. (a) Estimated phylogeny for the env gene of HIV-1 CRF07_BC (HXB2 7077–7665 nt). For visual clarity, sequences are labeled with symbols according to location of isolation. (b) Estimated dates of the most recent common ancestors (MRCA) of CRF07_BC sequences from China (Xinjiang), southern Taiwan (Tainan), and central–northern Taiwan (Nantou–Taipei). Vertical lines denote the 95% highest posterior density credible intervals. Dates were estimated under various nucleotide substitution and evolutionary models: HKY, Hasegawa–Kishino–Yano model; GTR, general time reversible model; G, gamma distributed among-site rate heterogeneity; Cons, constant population size; Expo, exponential population growth. ■ Central–northern (Nantou–Taipei) cluster; ● southern Taiwan (Tainan) cluster; ▲ China (Xinjiang) cluster; (c) Change in annual HIV/AIDS cases in Xinjiang, China (square) and Taiwan (triangle) between 1984 and 2005. The time to the MRCA of CRF07_BC clusters detected in the indicated locales are depicted with 95% highest posterior density credible intervals (in parentheses).
evolutionary rate estimate obtained (4.7–5.0 \times 10^{-3}
substitutions per site per year) was then incorporated as a
prior probability distribution in the analysis of the
CRF07_BC sequences [7]. A Bayesian Markov chain
Monte Carlo method was used to estimate the dates of the
most recent common ancestors (MRCA) of
CRF07_BC in Xinjiang and Taiwan under various
nucleotide substitution and evolutionary models. As
illustrated in Fig. 1b, the likely year of origin of
CRF07_BC from Xinjiang, China, was August 1993
[95% credible region (CR) March 1992–March 1995].
MRCA of CRF07_BC strains from southern and
central-northern Taiwan were dated to August 1999
(95% CR April 1998–January 2001) and February 2002
(95% CR March 2001–August 2002), respectively. The
evolutionary and statistical assumptions used have almost
no effect on the estimated dates (Fig. 1b).

This study indicates that CRF07_BC was introduced into
the IDU population in Xinjiang in the early to mid 1990s
(1992–1995). The strain also spread into IDU in
southern Taiwan in the late 1990s (1998–2001), and
subsequently disseminated northward to IDU in central–
northern Taiwan in the early 2000s (2001–2003),
resulting in the largest ever HIV/AIDS epidemic in
Taiwan. HIV/AIDS surveillance detected a dramatic
upsurge of HIV cases in Xinjiang in the mid-1990s
(1995–1996), and in 2003–2004 in Taiwan (Fig. 1c),
suggesting that CRF07_BC may have been present
among IDU for a year or two in each region before the
epidemic spread and subsequent detection of the
infection. It is most likely that both the Xinjiang and
Taiwan outbreaks trace their origins back to Yunnan
province, thought to be the geographical origin of
CRF07_BC [2,3]. We note, however, that MRCA dates
can also be more recent than the date of outbreak
discovery, either because extant virus diversity has been
incompletely sampled, or because the founding lineages
of the outbreak have since gone extinct [8,9]. These
results illustrate the history of the regional and
international spread of HIV-1 CRF07_BC in east Asia.

Acknowledgements

The authors would like to thank Andrew Rambaut for
advice, Naoti Yamamoto for support and Timothy
Mastro for critical reading of the manuscript.

\*Laboratory of Molecular Virology and Epidemiology,
AIDS Research Center, National Institute of
Infectious Diseases, Tokyo, Japan; \*Department
of Medicine, Faculty of Medicine, University of
Malaya, Kuala Lumpur, Malaysia; \*Department
of Zoology, University of Oxford, Oxford, UK; and
\*Department of Dermatology, The First People’s
Hospital, Shanghai Jiao Tong University, Shanghai,
China.

Sponsorship: This work was supported by grants
from the Ministry of Health, Labour and Welfare, the
Ministry of Education, Science and Technology,
the Japanese Foundation for AIDS Prevention and
the Royal Society International Project Fund.

Conflicts of interest: None.

Received: 14 June 2007; revised: 28 September 2007;
accepted: 2 October 2007.

References

Characterization of a virtually full-length human immuno-
deficiency virus type 1 genome of a prevalent intersubtype
11376.
Precise mapping of recombination breakpoints suggests a
common parent of two BC recombinant HIV type 1 strains
circulating in China. AIDS Res Hum Retroviruses 2002; 18:
1133–1140.
generation of multiple forms of HIV-1 intersubtype recombi-
nants in the Yunnan Province of China. AIDS 2002; 16:1401–
1407.
Molecular epidemiology of HIV-1 infection and full-length
genomic analysis of circulating recombinant form 07_BC strains
from injection drug users in Taiwan. \*J Infect Dis 2007; 195:1283–
1293.
6. Drummond AJ, Rambaut A. BEAST v1.4. 2006. Available at:
7. Pybus OG, Drummond AJ, Nakano T, Robertson BH, Rambaut A.
The epidemiology and iatrogenic transmission of hepatitis C
virus in Egypt: a Bayesian coalescent approach. Mol Biol Evol
evolutionary history of HIV-1: subtype G is a circulating
rapid spread of human immunodeficiency virus type 1 BF