

CAUSES AND CLINICAL DISCRIMINATORS OF FEBRILE ILLNESS IN TROPICAL ASIAN SCHOOLCHILDREN

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Background: Undifferentiated febrile illnesses are a major cause of morbidity in children who reside in or travel to tropical countries. We sought to describe the causes and clinical discriminators of febrile illness in schoolchildren in 2 areas of rural Thailand.

Methods: Patients 7-18 years of age presenting with documented fever $>38^{\circ}\text{C}$ without focal infection provided sera for testing at reference laboratories in Atlanta and Bangkok using Leptospirosis MAT, Dengue EIA, and *S. typhi* dot-ELISA.

Results: Of 342 schoolchildren enrolled, 339 (99%) provided convalescent sera. Testing to date has identified dengue in 112/328 (34%), typhoid fever in 60/315 (19%), and leptospirosis in 10/208 (5%). Schoolchildren with dengue were more likely to have a rash (28% vs. 14%, $p<0.01$), as well as leukopenia (50% vs. 15%, $p<0.01$), thrombocytopenia (29% vs. 10%, $p<0.01$), and elevated SGOT (26% vs 7%, $p<0.01$). Those with typhoid fever more often had vomiting (56% vs 41%, $p=0.04$) and lymphadenopathy (28% vs. 17%, $p=0.05$) than those with other causes of fever; bloody diarrhea, rose spots and hepatosplenomegally were infrequent (0-2%) in all patients. Schoolchildren with leptospirosis more commonly had elevated alkaline phosphatase (72% vs. 33%, $p<0.01$), bilirubin (45% vs. 6%, $p<0.01$), and creatinine (27% vs. 6%, $p<0.01$).

Conclusion: Dengue was the most important cause of fever among this group of school-children in Thailand; typhoid may be important, but further microbiologic investigations are indicated. Basic clinical and laboratory findings can help to discriminate between major pathogens. Severe headache and cytopenias indicate dengue infection, vomiting and lymphadenopathy point to typhoid fever, and elevated alkaline phosphatase, bilirubin and creatinine are seen in leptospirosis.

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BIOLOGIC CHARACTERIZATION OF HIV-1 AE/B RECOMBINANTS: IMPLICATIONS FOR HIV VACCINE DEVELOPMENT

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Background: Several HIV-1 recombinants have become prevalent circulating forms, such as CRF 01_AE and the recently identified CRF 15_01/B. The goal of this study was to characterize the neutralizing antibody (NAb) profiles and biotypes of HIV-1 recombinant isolates from Thailand to assess the potential impact of these recombinants on vaccine development.

Methods: One unique NSI AE/B recombinant (NP1623), and two SI CRF 15_01/B isolates (99.Mu.2079 and OUR1332) were recovered by co-culture. Neutralization was assessed using an extracellular p24 assay and an intracellular (IC) p24 flow cytometry endpoint in which PBMC are stained for both CD4 and p24. Coreceptor usage was measured in GHOST cells and in a PBMC assay using coreceptor inhibitors.

Results: NP1623 has an E gp120 and a B gp41 and was neutralized by both B and E sera. In contrast, the CRF 15 isolates have a predominantly B envelope and were neutralized most potently by B sera. In the IC p24 assay, the neutralization of CRF 15 isolates was evident in the ability of the NAb to block CD4 down-regulation, not p24 production. Using a CD4 monoclonal Ab (CD4-v4) that binds outside of the CD4/gp120 domain, the apparent CD4 down-regulation was not due to free envelope binding to CD4. While NP1623 used CCR5 and was inhibited by RANTES, the CRF 15_01/B isolates used CXCR4 (X4), but were not blocked by AMD3100 (an X4 receptor agonist). In contrast to other SI/X4 isolates, infection of CD4+ PBMC by X4 CRF 15 viruses appears to be enhanced more than one log by AMD3100.

Conclusions: The neutralization profiles of AE/B recombinants are complex and may be influenced by determinants in both gp120 and gp41. The enhancement of CRF 15_01/B isolates by AMD3100 implies a novel env-CD4-coreceptor interaction that may be influenced by their ability to down-regulate CD4. Characterization of the biology of HIV-1 recombinants with mosaic envelopes will provide important information for developing vaccine and therapeutic strategies for Southeast Asia and other regions where multiple subtypes co-circulate.

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THE CHANGING MOLECULAR EPIDEMIOLOGY OF HIV TYPE 1 AMONG NORTHERN THAI DRUG USERS, 1999 TO 2002

Tovanabutra S, Beyrer C, Sakkhachornphop S, Razak MH, Ramos GL, Vongchak T, Rungruengthanakit K, Saokhieo P, Tejafong K, Kim B, de Souza M, Robb ML, Birx DL, Jittiwutikarn J, Suriyanon V, Celentano DD and McCutchan FE

CRF01_AE and subtype B have dominated the HIV-1 epidemic in Thailand since 1989. We reported a new circulating recombinant form of HIV-1, CRF15_01B, as well as other unique CRF01_AE/B recombinants among prevalent HIV infections in Thailand. We sought to study this challenging molecular picture through assessment of subtypes among recent HIV-1 seroconverters in northern Thai drug users. A total of 847 HIV-1 seronegative drug users (342 IDU and 505 non-IDU) were enrolled, from 1999 to 2002, in a prospective study; 39 HIV-1 incident cases were identified and characteristics were collected. The overall HIV-1 incidence rate was 2.54/100PY, but it was 10.0/100PY among male IDU. HIV was strongly associated with injection history; 38 of 39 seroconverters gave a history of IDU. A near full-length genome of HIV-1 was recovered by PCR amplification and sequenced from peripheral mononuclear cell extracted DNA of 38 seroconverters. Phylogenetic analysis revealed that 33 (86.8%) were CRF01_AE and 5 (13.2%) were CRF01_AE/B recombinants. These recombinants had different structure but shared some common breakpoints, indicating an ongoing recombination process. Recombinant infection increased with year of sampling (0 to 57.1%). The molecular epidemiology of HIV-1 among drug users in northern Thailand has thus entered a new era. CRF01_AE remains predominant while pure subtype B is becoming rare, and now a substantial component of the epidemic. These findings support the need for CRF01_AE and subtype B components in clade-matched vaccine strategies for Thai phase III trials. Ongoing molecular surveillance of circulating HIV-1 strains is imperative for the evaluation of HIV vaccine efficacy.

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