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Evaluating immunologic response and clinical deterioration in treatment-naïve patients initiating first-line therapies infected with HIV-1 CRF01_AE and subtype B

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Abstract

Background—HIV-1 group M viruses diverge 25%–35% in envelope, important for viral attachment during infection, and 10–15% in the *pol* region, under selection pressure from common antiretrovirals. In Asia, subtypes B and CRF01_AE are common genotypes. Our objectives were to determine whether clinical, immunologic or virologic treatment responses differed by genotype in treatment-naïve patients initiating first-line therapy.

Methods—Prospectively collected, longitudinal data from patients in Thailand, Hong Kong, Malaysia, Japan, Taiwan and South Korea were provided for analysis. Covariates included demographics, hepatitis B and C coinfections, baseline CD4 T lymphocyte count and plasma HIV-1 RNA levels. Clinical deterioration (a new diagnosis of CDC category B/AIDS-defining illness or death) was assessed by proportional hazards models. Surrogate endpoints were 12-month change in CD4 cell count and virologic suppression post-therapy, evaluated by linear and logistic regression, respectively.

Results—Of 1105 patients, 1036 (93.8%) infected with CRF01_AE or subtype B were eligible for inclusion in clinical deterioration analyses and contributed 1546.7 person-years of follow-up

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(median:413 days, IQR:169–672 days). Patients >40 years demonstrated smaller immunological increases (p=0.002) and higher risk of clinical deterioration (HR=2.17; p=0.008). Patients with baseline CD4 cell counts >200 cells/μL had lower risk of clinical deterioration (HR=0.373; p=0.003). A total of 532 patients (48.1% of eligible) had CD4 counts available at baseline and 12 months post-therapy for inclusion in immunolgic analyses. Patients infected with subtype B had larger increases in CD4 counts at 12 months (p=0.024). A total of 530 patients (48.0% of eligible) were included in virologic analyses with no differences in response found between genotypes.

Conclusions—Results suggest that patients infected with CRF01_AE have reduced immunologic response to therapy at 12 months, compared to subtype-B-infected counterparts. Clinical deterioration was associated with low baseline CD4 counts and older age. The lack of differences in virologic outcomes suggests that all patients have opportunities for virologic suppression.

Keywords

HIV-1; Asia; genotype; CRF01_AE; subtype B

Introduction

HIV-1 group M viruses account for most infections internationally [1] and, based on genetic similarity, are classified into nine different subtypes (A–D, F–H, J, K). Variants, however, diverge 25%–35% in envelope (*env*), important for viral attachment to target cells during infection, and 10–15% in the *pol* region, under selection pressure from common antiretrovirals (ARVs) [1–3]. Subtypes A and F are further divided into sub-subtypes A1, A2 and F1, F2, respectively. Although subtypes B and D are as similar as sub-subtypes, for historical reasons they maintain separate subtype classification [1]. Formerly, HIV-1 genotype assignments were based on gene fragments. Later, when *gag* and *pol* regions were genotyped, subtype E *env* viruses were found to include subtype A sections in the other regions of the viral genome, resulting in subtype E's reclassification as an A/E recombinant, CRF01_AE [4]. Circulating recombinant forms (CRFs) result from recombination between HIV-1 genotypes within a dually infected person [1] but no complete subtype E genome has been found, leaving CRF01_AE's recombinant status inconclusive.

Subtype B is the genotype historically common in developed countries and nucleotide substitutions (mutations or naturally occurring polymorphisms), insertions and deletions in the HIV-1 genome are made in reference to the earliest characterised subtype B wild-type strain, HXB2 [5,6]. ARVs, commonly designed on subtype B, are classified based on where the HIV-1 life cycle is interrupted. Synergistic combinations of ARVs, known as highly active antiretroviral therapy (HAART), suppress viral load (VL) thereby reducing the risk of opportunistic infections and death [7,8]. However, natural drug-resistant polymorphisms may exist in patients pre-therapy with higher frequencies being found in non-B subtypes [9].

In vitro studies suggest differences in viral transmission characteristics between genotypes and viral heterogeneity may have implications for disease progression. HIV-1 infection depends on the interaction of *env* gp120 with the target cell CD4 receptor [10] and this interaction promotes binding to a coreceptor, viral tropism being determined by the *env* amino acid sequence and structure. Most genotypes use R5 coreceptors during transmission and in early stages of infection with X4-using syncytium inducing variants emerging later [11,12]. Subtype C studies generally report a lack of coreceptor switching from R5 to X4, possibly affecting transmission [11], and dual tropic virus (X4/R5) found in other genotypes have not been reported in subtype D viruses [13]. Where subtypes A and D co-circulate, more rapid disease progression has been found for subtype D compared with subtype A [14] although the literature suggests that subtype A infections are outpacing subtype D [15]. A

retrospective analysis found faster rates of CD4 decline and virologic failure in subtype D infection compared to subtypes A, B or C suggesting differences in HIV-1 genotypes with respect to patient response to therapy [16].

In Asia, predominant genotypes are subtypes B and C, CRF01_AE and their recombinants, with country-specific epidemics featuring different group M genotypes. During 2000–2007, in India, approximately 97% of infections were from subtype C while four Mekong River countries (Cambodia, Myanmar, Thailand and Viet Nam) reported almost 80% of infections were from CRF01_AE [17]. Subtype B infections are primarily reported in Japan and the Republic of Korea (South Korea) [17–20]. In China's Special Administrative Region of Hong Kong and in Malaysia, subtype B and CRF01_AE co-circulate [17,21,22] while in Taiwan, subtype B, CRF01_AE and CRF07_BC have been found [23,24]. Epidemic distributions differ depending on the sub-populations at risk with subtype B frequently found in injecting drug users and men-who-have-sex-with-men (MSM), whereas CRF01_AE is more commonly found in heterosexual populations [25].

Previously we reported that mainly CRF01_AE and subtype B were infecting patients from Thailand, Hong Kong and Malaysia [26]. The objectives were to determine whether treatment responses (clinical deterioration, immunologic response or virologic suppression) differed between these genotypes in treatment-naïve patients initiating a first-line HAART regimen.

Methods

Patient data

Patients providing data were enrolled in either the TREAT Asia Studies to Evaluate Resistance monitoring protocol (TASER-M) [26] or the TREAT Asia HIV Observational Database (TAHOD) [27]. Data for these longitudinal, cohort studies are collected prospectively. Most TASER-M sites are selected from TAHOD sites which consist of government- or university-based clinics and hospitals or private clinics, situated in major cities and other urban areas. Pre-treatment drug resistance prevalence for the TASER-M cohort has been published elsewhere [28]. Clinical interventions and testing procedures were implemented according to local practices, excepting HIV-1 genotyping in TASER-M which was collected under the protocol.

Treatment-naive patients were eligible for inclusion if they were initiating first-line HAART regimens and had HIV-1 genotype available. Eligible patients enrolled at March 2010 from 11 clinic locations in Thailand (4), Hong Kong (China) (2), Malaysia (2), Japan (1), Taiwan (1) and South Korea (1) provided prospective and retrospective data (TAHOD) for analysis. Patient covariates included demographics (age at entry to cohort, gender, HIV source exposure), hepatitis B (HBV) and hepatitis C (HCV) coinfections and baseline indices of illness severity (CD4 lymphocyte count, HIV-1 RNA and CDC classification [29]). The most severe pre-therapy CDC category recorded was used as the baseline clinical status. HBV (HCV) positive status was defined as having any HBsAg (HCV-Ab) positive result prior to enrolment. HIV-1 genotypes were determined by Virco BVBA, Belgium. For assessing associations between patient covariates and genotype, patients were restricted to those infected with subtype B or CRF01_AE whose sequences passed Virco's quality control procedures. Due to small numbers, patients reporting injecting drug use exposure, receipt of blood products, perinatal transmission or unknown exposure were collapsed into an "Other" transmission category.

Analysis endpoints

Patients were required to have at least one clinic visit or test procedure recorded post-therapy initiation for inclusion. Clinical deterioration was determined as a new diagnosis of

a CDC B or C (AIDS-defining) illness or death from any cause. Patient follow-up commenced at HAART initiation and ended at earliest clinical deterioration endpoint or censored at the most recent contact. Surrogate endpoints were plasma HIV-1 RNA viral suppression (< 400 copies/mL) and change in CD4 cell count from baseline at 12 months post-HAART. For calculating the 12-month immunologic change, the surrogate marker value closest to the 12-month target date was chosen from windows of 9–15 months and the CD4 count sampled within the 91 days prior, and closest to therapy initiation, was selected as the baseline value.

Statistical analysis

For eligible patients, baseline comparisons by country ($\chi 2$, Fisher's exact or Cochrane-Armitage test for trend) were performed, as appropriate. Determinants of change in CD4 cell count and 12-month HIV-1 RNA suppression were assessed via linear regression and logistic regression, respectively. Proportional hazards models were used to evaluate predictors of time to progression to a new clinical deterioration endpoint. Analyses were based on an intention-to-continue treatment approach in that we did not take into account regimen changes or interruptions post-therapy. Forward stepwise techniques were used to determine the best fitting models. Binary covariate p-values and multi-categorical parameter p-values (from tests for trend/heterogeneity) of <0.1, in univariate analyses, were considered for inclusion in multivariate patient covariate models. Final models consisted of patient covariates remaining significant at the 0.05 level. Then, because of our *a priori* interest in the effect of HIV-1 genotype on outcomes, we assessed the effect of HIV-1 genotype, adjusting for any significant patient covariates, and tested for interactions between genotype and cohort. Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and STATA version 10 (STATA Corp., College Station, TX, USA).

Results

A total of 1105 ARV-naïve patients had HIV-1 genotype information available [TASER-M: n=922 (83.4%); Thailand: n=675 (73.2%); Hong Kong: n=160 (17.4%); Malaysia: n=87 (9.4%); TAHOD: n=183 (16.6%); Japan: n=65 (35.5%); Hong Kong: n=49 (26.8%); Taiwan: n=43 (23.5%); South Korea: n=15 (8.2%)]. Differences in ethnicity reflected population distributions within countries contributing data [TASER-M; Thai: n=675 (73.2%), Chinese: n=177 (19.2%), Malay: n=37 (4.0%), Indian: n=11 (1.2%), Caucasian: n=5 (0.5%); TAHOD; Thai: n=14 (7.7%), Chinese: n=88 (48.1%), Japanese: n=65 (35.5%), Korean: n=15 (8.2%), Caucasian: n=1 (0.5%)].

Years of enrolment differed as a function of cohort recruitment and 80% of TAHOD patients were enrolled prior to opening of the TASER-M cohort. Patients initiated therapy from 2003–2010 (TASER-M: 2007–2010; TAHOD: 2003–2010) and significant differences between cohorts were noted for covariates as shown in Table 1. All Table 1 covariates were evaluated for significance in endpoint analyses.

Most first-line regimens included lamivudine (3TC) as a nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone component [n=1013 (91.7%)]. Regimens for the cohorts differed in the second NRTI component [TASER-M; stavudine (d4T): n=479 (52.0%); zidovudine (AZT): n=221 (24.0%); abacavir (ABC): n=67 (7.3%); TAHOD; d4T: n=37 (20.2%); AZT: n=84 (45.9%); ABC: n=26 (14.2%), p<0.001]. Most regimens were based on non-nucleoside reverse transcriptase inhibitors (NNRTIs) with more TAHOD patients being prescribed efavirenz (EFV) and TASER-M patients' regimens including higher proportions of nevirapine (NVP) [TASER; NVP: n=484 (58.9%), EFV: n=338 (41.1%); TAHOD; EFV: n=77 (82.8%), NVP: n=16 (17.2%); p<0.001]. Of protease inhibitor (PI) regimens, most included ritonavir-boosted atazanavir (ATZ) or lopinavir

(LPV), proportions of which marginally differed between cohorts [TASER-M; ATZ/r: n=28 (38.9%), LPV/r: n=44 (61.1%); TAHOD; ATZ/r: n=17 (22.7%), LPV/r: n=58 (77.3%); p=0.048].

In East Asia, there is a higher odds of CRF01_AE infecting heterosexual populations and subtype B is more frequently found in MSM. We found differences in genotype proportions consistent with patient-reported HIV source exposures (Table 1) [TASER-M; CRF01_AE: n=740 (86.8%), subtype B: n=113 (13.2%); TAHOD; CRF01_AE: n=38 (20.8%); subtype B: n=145 (79.2)%; p<0.001]. In TASER-M, both HIV-1 *pol* protease (PR) and reverse transcriptase (RT) genotypes are recorded and 59 (6.4%) of TASER-M patients were infected with discordant PR and RT genotypes, reflecting possible dual infection and/or recombination. Of discordant genotypes, 28 (47.5%) included subtype B components (assessed as including subtype B, CRF08_BC, CRF08_BC or CRF15_01B) and 23 (39.0%) were CRF01_AE recombinants (assessed including CRF01_AE or CRF15_01B). The remaining discordant genomes [n=8 (13.6%)] included both B and AE components. Discordant genotypes and subtypes CRF02_AG (n=1), CRF 07_BC (n=3), C (n=5), subtype D (n=1) were excluded from further evaluation.

Progression to CDC B or CDC C (AIDS-defining) illness or death

A total of 1036 patients (93.8%) infected with CRF01_AE or subtype B were eligible for inclusion in clinical deterioration analyses (Table 2) and contributed 1546.7 person-years of retrospective and prospective follow-up (median: 413 days, IQR: 169–672 days). During this time, there were a total of 104 events (22 CDC B diagnoses, 63 AIDS diagnoses and 19 deaths) giving an event rate of 6.7 per 100 person-years [95% CI: 5.5–8.1]. Clinical deterioration endpoints were recorded between 2003 and 2010 (TASER: n=76, range: 2007–2010; TAHOD: n=28, range: 2003–2009). Significant univariate associations were found with age group, baseline CD4 count and HIV-1 RNA viral load. After adjustment for Table 1 covariates, patients older than 40 years had higher risk of clinical deterioration (HR=2.17; p=0.008) while patients having baseline CD4 cell counts greater than 200 cells/μL had lower risk of clinical deterioration (HR= 0.373; p<0.003). A total of 450 (43.4%) patients contributing to the clinical deterioration analyses were also included in immunologic and virologic analyses.

Change in CD4 cell count at 12 months following HAART

For immunologic analyses, 532 patients (48.1% of eligible) had CD4 counts available at baseline and at 12 months, with a median increase of 187.2 cells/μL over the period (Table 3). To calculate the change in CD4 over the period, baseline CD4 was subtracted from the 12-month result. In unadjusted analyses, smaller increases in CD4 counts were associated with age older than 40 years while larger improvements were associated with being infected with subtype B. Excluding patients with unknown baseline VL, compared to patients with less than 10,000 copies/mL, patients with higher VLs evidenced larger increases. These associations were maintained after adjustment for other covariates (Age>40 years; p=0.002; Subtype B; p=0.024, HIV-1 RNA >=10,000 copies/mL; p=0.024). There was no interaction between HIV-1 genotype and cohort membership (Change in CD4: TASER-M; median: 168 cells/μL, IQR: 100 – 252 cells/μL, TAHOD: median: 166 cells/μL, IQR: 101 – 250 cells/μL; Interaction; p<0.402). As shown in Table 3, 459 (86.3%) patients had greater than 10,000 copies/mL at study entry. Median CD4 count increases for these patients, in all age categories, were higher for subtype B-infected patients (Age<30 years; Subtype B: median: 185 cells/μL, IQR: 138–289, CRF01_AE: median: 178.5 cells/μL, IQR: 120–276; Age 30–40 years; Subtype B: median: 251 cells/μL, IQR: 165–299, CRF01_AE: median: 176 cells/μL, IQR: 99–250; Age>40 years; Subtype B: median: 157.5 cells/μL, IQR: 101.5–217, CRF01_AE: median: 152.5 cells/μL, IQR: 76–218). Most patients infected with CRF01_AE

came from Thailand [Thailand: n=288 (75.0%), Hong Kong: n=68 (17.7%), Malaysia: n=27 (7.0%), Taiwan: n=1 (0.3%)] whereas the majority of subtype B patients came from high-income economies [Hong Kong: n=74 (50.0%), Taiwan: n=32 (21.6%), Japan: n=13 (8.8%) South Korea: n=11(7.4%) vs. Thailand: n=15 (10.1%), Malaysia: n=3 (2.0%)]. TAHOD patients from Japan and South Korea were only infected with subtype B but excluding these patients from analyses did not impact upon interpretations.

HIV RNA at 12 months following HAART

Due to the heterogeneity of virology assays and associated dynamic ranges across sites, we defined the lower limit of detection (LLD) as 400 copies/mL. Analyses included 530 patients (48.0% of eligible) who had an HIV-1 RNA result available at 12 months and 92.6% of patients were virologically suppressed below the LLD (TASER: n=383 (94.3%), TAHOD n=108 (87.1%). Multivariate analyses showed no associations between the patient characteristics shown in Table 1 and the virologic outcome.

Discussion

Subtype B and CRF01_AE have been circulating in Asia for more than 10 years [30] and we report on the first evaluation of treatment responses in these genotypes in ARV-naïve patients. Patients initiated therapy from 2003–2010 and findings from adjusted analyses demonstrated that patients infected with subtype B had increased immunological response to therapy, compared to CRF01_AE. A retrospective, cross-sectional study of mainly treated patients also found lower immunologic response in CRF01_AE patients compared to subtype B [9]. However, our finding in treatment-naive patients is uncomplicated by genomic variation attributable to drug selection pressures. A study from Singapore found increased CD4+ T-cell loss in predominantly Chinese males infected with CRF01_AE [31] and, as mentioned previously, studies in other cohorts have reported differences in HIV-1 transmission and disease progression. Several *in vitro* studies have suggested structural reasons for these differences.

Patients older than 40 years had reduced immunologic response at 12-months while baseline HIV-1 RNA greater than 10,000 copies/mL at study entry was predictive of larger CD4 counts increases, compared patients with lower viral burdens. Older patients with low CD4 counts pre-therapy had increased risk of clinical deterioration, consistent with the literature [32]. Comparisons of virologic suppression in other genotypes have yielded mixed results [16,33] but we found no differences in virologic suppression post-HAART and approximately 90% of patients achieved virologic suppression at 12-months post-therapy.

Patients being followed under protocol at funded study sites or with HIV-1 genotype recorded in observational data suggest that site clinicians have diagnostic technologies available to guide patient treatment. Consequently, treatment outcomes for our patients may be better than those experienced in general clinic populations. Adherence information was not available and limited follow-up for TASER-M patients may have contributed to our nonsignificant finding in relation to clinical deterioration. Country differences were not specifically controlled for although cohort membership may serve as a surrogate for these effects. Separate PR and RT genotypes are not reported in TAHOD and we noted 6.4% of discordant genotypes among the TASER-M patients. Therefore, a small proportion of TAHOD patients with discordant genotypes may have been misclassified.

ARVs are commonly designed on subtype B. If immunologic response in the year following HAART affects patient prognosis, our findings of a reduced response for patients infected with CRF01_AE may possibly translate to a higher burden on country health systems, for these patients than for their subtype-B infected counterparts. Studies of longer duration in

representative patient populations, including socio-economic information and *in vitro* studies are required to investigate this hypothesis. Patients starting therapy with low CD4 counts have been infected for some time and are commencing therapy later than recommended by international guidelines [34,35]. Late therapy initiation for patients from developing economies generally reflects resourcing issues. However, for patients from high-income Asian economies, this may be due to ignorance of HIV-positive status. Increased testing to alert of HIV infection, before CD4 counts decrease substantially, should be encouraged, particularly in high-risk groups.

Our finding of no differences in virologic response to treatment suggests that with appropriate diagnostic testing, all patients have opportunities to suppress circulating virus to non-detectable levels, thereby potentially increasing disease-free-survival. In addition to being a welcome outcome for individual patients, levels of onward transmission are reduced in virologically suppressed individuals [36].

The HIV pandemic is of increasing complexity and where genotypes co-circulate, individuals coinfected with multiple variants provide HIV-1 opportunities for recombination, augmenting viral diversity [37]. We found discordant PR and RT genotypes in 6.4% of our patients, reflecting possible dual infection and/or recombination. Strategies such as serosorting, where same HIV-status partners are sought for unprotected sex, have been reported in MSM, as have higher frequencies of multi-variant transmission [38]. Serosorting is not supported as a risk reduction strategy and increases opportunities for recombination [39], further complicating vaccine initiatives which seek to target transmitted virus.

Assays which evaluate patient circulating viral sequence for the presence of drug resistant mutations also determine the circulating viral genotype. Although phylogenetic investigations cannot determine the direction of HIV evolution, and, consequently the direction of transmission in humans [40], mechanisms to capture genotypes resulting from HIVDR testing at country-level may contribute to monitoring and quantification of HIV-1 diversity and genotypic proliferation in at-risk population networks [41]. Genotyping sequencing is expensive but there have been recent improvements in dried blood spot methodologies, a less expensive alternative for specimen collection [42]. Increased availability of lower cost genotyping may contribute to local surveillance efforts.

In summary, our finding of reduced immunologic response in CRF01_AE-infected patients, compared to subtype B, suggests that genotypic diversity impacts upon patient response to treatment. Evidence of dual infection and recombination in our patients may suggest a need for regional epidemic surveillance. Tracking of local variants may help to identify increasing incidence of HIV-1 genotypes in at-risk groups and contribute to monitoring HIV-1 diversity and proliferation in the region.

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References

1. Robertson DL, Anderson JP, Bradac JA, et al. HIV-1 nomenclature proposal. Science. Apr 7; 2000 288(5463):55–56. [PubMed: 10766634]
2. Korber B, Gaschen B, Yusim K, Thakallapally R, Kesmir C, Detours V. Evolutionary and immunological implications of contemporary HIV-1 variation. Br Med Bull. 2001; 58:19–42. [PubMed: 11714622]
3. Kantor R, Katzenstein D. Polymorphism in HIV-1 non-subtype B protease and reverse transcriptase and its potential impact on drug susceptibility and drug resistance evolution. AIDS reviews. Jan-Mar;2003 5(1):25–35. [PubMed: 12875105]
4. Carr JK, Salminen MO, Koch C, et al. Full-length sequence and mosaic structure of a human immunodeficiency virus type 1 isolate from Thailand. J Virol. Sep; 1996 70(9):5935–5943. [PubMed: 8709215]
5. Barre-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science. May 20; 1983 220(4599):868–871. [PubMed: 6189183]
6. Korber, B.; Foley, BT.; Kuiken, C.; Pillai, SK.; Sodroski, JG. Numbering Positions in HIV Relative to HXB2CG: Theoretical Biology and Biophysics Group. Los Alamos National Laboratory; Los Alamos, NM: 1998.
7. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. N Engl J Med. Dec 11; 2003 349(24):2293–2303. [PubMed: 14668455]
8. Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. N Engl J Med. Dec 11; 2003 349(24):2304–2315. [PubMed: 14668456]
9. Ariyoshi K, Matsuda M, Miura H, Tateishi S, Yamada K, Sugiura W. Patterns of point mutations associated with antiretroviral drug treatment failure in CRF01_AE (subtype E) infection differ from subtype B infection. Journal of acquired immune deficiency syndromes (1999). Jul 1; 2003 33(3): 336–342. [PubMed: 12843744]
10. Dalgleish AG, Beverley PC, Clapham PR, Crawford DH, Greaves MF, Weiss RA. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature Dec 20-1985. Jan 2; 1984 312(5996):763–767.
11. Ping LH, Nelson JA, Hoffman IF, et al. Characterization of V3 sequence heterogeneity in subtype C human immunodeficiency virus type 1 isolates from Malawi: underrepresentation of X4 variants. J Virol. Aug; 1999 73(8):6271–6281. [PubMed: 10400718]
12. Connor RI, Sheridan KE, Ceradini D, Choe S, Landau NR. Change in coreceptor use correlates with disease progression in HIV-1--infected individuals. J Exp Med. Feb 17; 1997 185(4):621–628. [PubMed: 9034141]
13. Tscherning C, Alaeus A, Fredriksson R, et al. Differences in chemokine coreceptor usage between genetic subtypes of HIV-1. Virology. Feb 15; 1998 241(2):181–188. [PubMed: 9499793]
14. Kaleebu P, French N, Mahe C, et al. Effect of human immunodeficiency virus (HIV) type 1 envelope subtypes A and D on disease progression in a large cohort of HIV-1-positive persons in Uganda. J Infect Dis. May 1; 2002 185(9):1244–1250. [PubMed: 12001041]
15. Kiwanuka N, Laeyendecker O, Quinn TC, et al. HIV-1 subtypes and differences in heterosexual HIV transmission among HIV-discordant couples in Rakai, Uganda. AIDS (London, England). Nov 27; 2009 23(18):2479–2484.
16. Easterbrook PJ, Smith M, Mullen J, et al. Impact of HIV-1 viral subtype on disease progression and response to antiretroviral therapy. J Int AIDS Soc. 2010; 13:4. [PubMed: 20205896]
17. Hemelaar J, Gouws E, Ghys PD, Osmanov S. Global trends in molecular epidemiology of HIV-1 during 2000–2007. AIDS (London, England). Mar 13; 2011 25(5):679–689.
18. Kato S, Saito R, Hiraishi Y, et al. Differential prevalence of HIV type 1 subtype B and CRF01_AE among different sexual transmission groups in Tokyo, Japan, as revealed by subtype-specific PCR. AIDS Res Hum Retroviruses. Nov; 2003 19(11):1057–1063. [PubMed: 14686327]

19. Choi JY, Kim EJ, Park YK, Lee JS, Kim SS. National survey for drug-resistant variants in newly diagnosed antiretroviral drug-naive patients with HIV/AIDS in South Korea: 1999–2005. Journal of acquired immune deficiency syndromes (1999). Nov 1; 2008 49(3):237–242. [PubMed: 18845957]
20. Kim JY, Kim EJ, Choi JY, et al. Genetic variation of the HIV-1 integrase region in newly diagnosed anti-retroviral drug-naive patients with HIV/AIDS in Korea. Clin Microbiol Infect. Oct 14.2010
21. Chen JH, Wong KH, Chen Z, et al. Increased genetic diversity of HIV-1 circulating in Hong Kong. PLoS One. 2010; 5(8):e12198. [PubMed: 20808942]
22. Tee KK, Li XJ, Nohtomi K, Ng KP, Kamarulzaman A, Takebe Y. Identification of a novel circulating recombinant form (CRF33_01B) disseminating widely among various risk populations in Kuala Lumpur, Malaysia. Journal of acquired immune deficiency syndromes (1999). Dec 15; 2006 43(5):523–529. [PubMed: 17031320]
23. Chen YJ, Huang YH, Chuang SY, et al. Molecular epidemiology of HIV-1 subtype B, CRF01_AE, and CRF07_BC infection among injection drug users in Taiwan. Journal of acquired immune deficiency syndromes (1999). Apr 1; 2010 53(4):425–439. [PubMed: 20130472]
24. Kao CF, Chang SY, Hsia KT, et al. Surveillance of HIV Type 1 Recent Infection and Molecular Epidemiology Among Different Risk Behaviors Between 2007 and 2009 After the HIV Type 1 CRF07_BC Outbreak in Taiwan. AIDS Res Hum Retroviruses. Jan 15.2011
25. Oyomopito, R. Monitoring HIV-1 Group M in the Asia-Pacific: PhD Thesis. Faculty of Medicine, The University of New South Wales (UNSW); Sydney: 2011. Epidemiology and phylogenetic analysis of HIV-1 infection in Asia; p. 170-181.Available at: http://handle.unsw.edu.au/1959.4/51620
26. Hamers RL, Oyomopito R, Kityo C, et al. Cohort profile: The PharmAccess African (PASER-M) and the TREAT Asia (TASER-M) monitoring studies to evaluate resistance--HIV drug resistance in sub-Saharan Africa and the Asia-Pacific. International journal of epidemiology. Feb; 2012 41(1):43–54. [PubMed: 21071386]
27. Zhou J, Kumarasamy N, Ditangco R, et al. The TREAT Asia HIV Observational Database: baseline and retrospective data. Journal of acquired immune deficiency syndromes (1999). Feb 1; 2005 38(2):174–179. [PubMed: 15671802]
28. Sungkanuparph S, Oyomopito R, Sirivichayakul S, et al. HIV-1 Drug Resistance Mutations among Antiretroviral-naïve HIV-1-infected Patients in Asia: Results from the TREAT Asia Studies to Evaluate Resistance- Monitoring Study (TASER-M). Clin Infect Dis. 2011 In press.
29. CDC. Revised Surveillance Case Definitions for HIV Infection Among Adults, Adolescents, and Children Aged <18 Months and for HIV Infection and AIDS Among Children Aged 18 Months to <13 Years — United States, 2008. MMWR Recomm Rep. 2008; 57:1–16.
30. Tovanabutra S, Watanaveeradej V, Viputtikul K, et al. A new circulating recombinant form, CRF15_01B, reinforces the linkage between IDU and heterosexual epidemics in Thailand. AIDS Res Hum Retroviruses. Jul; 2003 19(7):561–567. [PubMed: 12908933]
31. Ng OT, Lin L, Laeyendecker O, et al. Increased Rate of CD4+ T-Cell Decline and Faster Time to Antiretroviral Therapy in HIV-1 Subtype CRF01_AE Infected Seroconverters in Singapore. PLoS One. 2011; 6(1):e15738. [PubMed: 21298051]
32. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet. Jul 13; 2002 360(9327):119–129. [PubMed: 12126821]
33. Geretti AM, Harrison L, Green H, et al. Effect of HIV-1 subtype on virologic and immunologic response to starting highly active antiretroviral therapy. Clin Infect Dis. May 1; 2009 48(9):1296–1305. [PubMed: 19331585]
34. DHHS. [Accessed 12 January 2011] Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 2011. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
35. EACS. Guidelines for the Clinical Management and Treatment of HIV Infected Adults in Europe Version 5-2. European AIDS Clinical Society. 2010:1–10.

36. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med. Mar 30; 2000 342(13): 921–929. [PubMed: 10738050]

37. Oyomopito, R. The HIV-1 group M epidemic in the Asia-Pacific. In: Murray, JE., editor. Exposure Therapy: New Developments. Nova Science Publishers, Inc; Hauppauge New York: 2012. p. 295-299.Available (Open Access) at: https://www.novapublishers.com/catalog/product_info.php?products_id=34906

38. Li H, Bar KJ, Wang S, et al. High Multiplicity Infection by HIV-1 in Men Who Have Sex with Men. PLoS Pathog. May.2010 6(5):e1000890. [PubMed: 20485520]

39. Heymer KJ, Wilson DP. Available evidence does not support serosorting as an HIV risk reduction strategy. AIDS (London, England). 2010; 24(6)

40. Kaye M, Chibo D, Birch C. Comparison of Bayesian and maximum-likelihood phylogenetic approaches in two legal cases involving accusations of transmission of HIV. AIDS Res Hum Retroviruses. Aug; 2009 25(8):741–748. [PubMed: 19619011]

41. Zhang M, Foley B, Schultz AK, et al. The role of recombination in the emergence of a complex and dynamic HIV epidemic. Retrovirology. 2010; 7:25. [PubMed: 20331894]

42. Charpentier C, Gody JC, Tisserand P, et al. Usefulness of a genotypic resistance test using dried blood spot specimens in African HIV-infected children with virological failure according to the 2010-revised WHO criteria. Arch Virol. Apr 11.2011

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Table 1

Patient characteristics at first-line therapy initiation by cohort

	TAHOD n (%)	TASER n (%)	P
Age at entry (years)			
<30	46 (25.1)	172 (18.7)	0.2741
30–40	67 (36.6)	395 (42.8)	
>40	70 (38.3)	355 (38.5)	
Gender			
Male	160 (87.4)	595 (64.5)	<0.0001
Female	23 (12.6)	327 (35.5)	
Exposure			
Heterosexual	59 (32.2)	688 (74.6)	<0.0001
Same sex contact	113 (61.7)	176 (19.1)	
Other	11 (6.0)	58 (6.3)	
CDC classification			
Category A	102 (55.7)	434 (47.1)	0.0574
Category B	17 (9.3)	110 (11.9)	
Category C	64 (35.0)	378 (41.0)	
Hepatitis B			
Negative	123 (67.2)	606 (65.7)	0.8893
Positive	14 (7.7)	68 (7.4)	
Not tested	46 (25.1)	248 (26.9)	
Hepatitis C			
Negative	142 (77.6)	548 (59.4)	<0.0001
Positive	4 (2.2)	55 (6.0)	
Not tested	37 (20.2)	319 (34.6)	
First-line regimen			
NNRTI	93 (50.8)	838 (90.9)	<0.0001
PI	90 (49.2)	84 (9.1)	
Baseline HIV-1 viral load (copies/mL) [a]			
< 10,000	9 (4.9)	59 (6.4)	0.6890
>= 10,000	94 (51.4)	760 (82.4)	
Unknown	80 (43.7)	103 (11.2)	
Baseline CD4 count (cells/μL) [a]			
<= 100	37 (20.2)	444 (48.2)	<0.0001
100–200	40 (21.9)	201 (21.8)	
>200	49 (26.8)	191 (20.7)	
Unknown	57 (31.1)	86 (9.3)	
HIV-1 genotype [b]			
01_AE	38 (20.8)	740 (80.3)	<0.0001
02_AG	0 (0.0)	1 (0.1)	

	TAHOD	TASER	P
	n (%)	n (%)	
07_BC	0 (0.0)	3 (0.3)	
B	145 (79.2)	113 (12.3)	
C	0 (0.0)	5 (0.5)	
D	0 (0.0)	1 (0.1)	
Discordant	0 (0.0)	59 (6.4)	
Total	**183 (16.6)**	**922 (83.4)**	

[a] Test performed on non-missing values.

[b] Test performed on subtype B and CRF01_AE.

Abbreviations: CDC, Centers for Disease Control and Prevention NNRTI, non-nucleoside reverse transcriptase, PI, protease inhibitor.

Table 2

Factors associated with clinical deterioration after initiating first-line therapy

	n	Follow-up (years)	No of events	Rate per 100 person-years	Univariate Analysis		Multivariate Analysis	
					HR	P	HR (95% CI)	P
Age at entry (years)								
<30	204	336.1	15	4.5		*0.000*		*0.000*
30–40	434	653.5	29	4.4	0.94	0.839	0.91 (0.5–1.7)	0.767
>40	398	557.1	60	10.8	2.21	0.006	2.17 (1.2–3.8)	0.008
Gender								
Male	705	1142.1	80	7.0				
Female	331	404.7	24	5.9	0.69	0.107	0.69 (0.4–1.1)	0.119
Exposure								
Heterosexual contact	708	884.8	65	7.3				*0.261*
Homosexual contact	270	601.6	33	5.5	1.09	0.689	1.45 (0.9–2.3)	0.105
Other	58	60.5	6	9.9	1.15	0.746	1.24 (0.5–2.9)	0.612
CDC classification								
Category A	499	730.6	44	6.0		*0.053*		*0.648*
Category B	119	205.7	6	2.9	0.52	0.132	0.48 (0.2–1.1)	0.096
Category C	418	610.5	54	8.8	1.48	0.054	1.11 (0.7–1.7)	0.623
Hepatitis B								
Negative	676	1006.6	67	6.7				
Positive	74	113.7	9	7.9	1.22	0.570	1.19 (0.6–2.4)	0.633
Not tested	286	426.4	28	6.6	1.01	0.968	1.06 (0.7–1.7)	0.799
Hepatitis C								
Negative	644	1037.8	64	6.2				
Positive	47	46.9	7	14.9	1.74	0.164	1.8 (0.8–4.0)	0.141
Not tested	345	462.1	33	7.1	1.03	0.905	1.07 (0.7–1.6)	0.760
First-line regimen								
NNRTI	872	1138.9	78	6.8				
PI	164	407.9	26	6.4	1.39	0.149	1.45 (0.9–2.3)	0.118
Baseline HIV-1 viral load (copies/mL)								

	n	Follow-up (years)	No of events	Rate per 100 person-years	Univariate Analysis		Multivariate Analysis	
					HR	P	HR (95% CI)	P
< 10,000	60	70.7	1	1.4				
>= 10,000	804	1073.3	80	7.5	5.96	0.076	4.42 (0.6–32.0)	0.141
Unknown	172	402.8	23	5.7	6.91	0.059	4.93 (0.7–37.6)	0.124
Baseline CD4 count (cells/μL)								
<= 100	450	550.3	55	10.0		*0.002*		*0.001*
100–200	228	340.9	21	6.2	0.65	0.162	0.65 (0.4–1.1)	0.099
>200	222	344.0	11	3.2	0.37	0.003	0.37 (0.2–0.7)	0.003
Unknown	136	311.6	17	5.5	0.76	0.465	0.76 (0.4–1.3)	0.337
HIV-1 genotype								
CRF01_AE	778	891.1	69	7.7				
Subtype B	258	655.7	35	5.3	1.17	0.470	1.33 (0.9–2.1)	0.190
Total	*1036*	*1546.8*	*104*	6.7				

P values in italics are test for trend (Age at entry, CDC classification, Baseline CD4 count) evaluated by excluding categories representing unavailable information or test for homogeneity (Exposure).

Abbreviations: CDC, Centers for Disease Control and Prevention; NNRTI, non-nucleoside reverse transcriptase; PI, protease inhibitor.

Table 3

Factors associated with 12-month change in CD4 cell counts after initiating first-line therapy

	n	Change in CD4 (cells/μL)	Univariate analysis		Multivariate analysis	
			Coefficient	P	Coefficient (95% CI)	P
Age at entry (years)						
<30	105	209.6		*0.003*		*0.002*
30–40	222	195.9	−13.74	0.370	−13.14 (−43.1, 16.8)	0.389
>40	205	166.4	−43.20	0.006	−44.3 (−74.6, −14.0)	0.004
Gender						
Male	370	184.3				
Female	162	194.0	9.68	0.430	23.57 (−2.2, 49.4)	*0.073*
Exposure						
Heterosexual	356	183.5		*0.611*		0.749
Same sex contact	147	196.2	12.67	0.322	−10.98 (−40.2, 18.2)	0.461
Other	29	186.7	3.11	0.902	−7.81 (−57.1, 41.5)	0.756
CDC classification						
Category A	247	185.5		*0.277*		*0.281*
Category B	89	163.7	−21.75	0.176	−22.13 (−53.3, 9.0)	0.163
Category C	196	200.1	14.65	0.238	14.53 (−9.7, 38.8)	0.240
Hepatitis B						
Negative	346	193.3				
Positive	43	184.8	−8.49	0.687	−12.24 (−53.2, 28.7)	0.557
Not tested	143	173.2	−20.17	0.119	−22.78 (−47.9, 2.3)	0.075
Hepatitis C						
Negative	338	194.4				
Positive	20	188.6	−5.82	0.846	−6.27 (−65.3, 52.8)	0.835
Not tested	174	173.2	−21.21	0.081	−20.35 (−44.2, 3.5)	0.094
First-line regimen						
NNRTI	426	187.9				
PI	106	184.6	−3.23	0.819	−16.29 (−45.9, 13.3)	0.280
Baseline HIV-1 viral load (copies/mL)						

	n	Change in CD4 (cells/μL)	Univariate analysis		Multivariate analysis	
			Coefficient	P	Coefficient (95% CI)	P
< 10,000	33	143.6				
>= 10,000	459	190.7	47.10	0.045	52.54 (7.0, 98.1)	0.024
Unknown	40	182.8	39.16	0.200	45.91 (−13.5, 105.3)	0.130
Baseline CD4 count (cells/μL)						
<= 100	251	183.6		*0.328*		*0.308*
100–200	144	182.8	−0.86	0.949	3.01 (−23.7, 29.7)	0.825
>200	137	198.4	14.77	0.286	14.73 (−12.6, 42.1)	0.290
HIV-1 genotype						
CRF01_AE	384	179.3				
Subtype B	148	207.7	28.31	0.024	28.17 (3.75, 52.6)	0.024
Total	532	187.2				

P values in italics are test for trend (Age at entry, CDC classification, Baseline CD4 count) evaluated by excluding categories representing unavailable information or test for homogeneity (Exposure).

Abbreviations: CDC, Centers for Disease Control and Prevention; NNRTI, non-nucleoside reverse transcriptase; PI, protease inhibitor.