Rates and Factors Associated with Major Modifications to First-Line Combination Antiretroviral Therapy: Results from the Asia-Pacific Region

Stephen Wright1, Mark A. Boyd1,2, Evy Yunihastuti3, Matthew Law1, Thira Sirisanthana4, Jennifer Hoy5,6, Sanjay Pujari7, Man Po Lee8, Kathy Petoumenos1, on behalf of the International Epidemiologic Databases to Evaluate AIDS (IeDEA) Asia-Pacific HIV Observational Database (APHOD)

1 Kirby Institute, Sydney, Australia, 2 St. Vincent’s Hospital, Sydney, Australia, 3 Cipto Mangunkusumo General Hospital, Jakarta Pusat, Indonesia, 4 Chiang Mai University, Chiang Mai, Thailand, 5 The Alfred Hospital, Melbourne, Australia, 6 Monash University, Melbourne, Australia, 7 Institute of Infectious Diseases, Pune, India, 8 Queen Elizabeth Hospital, Kowloon, Hong Kong

Abstract

Background: In the Asia-Pacific region many countries have adopted the WHO’s public health approach to HIV care and treatment. We performed exploratory analyses of the factors associated with first major modification to first-line combination antiretroviral therapy (ART) in resource-rich and resource-limited countries in the region.

Methods: We selected treatment naive HIV-positive adults from the Australian HIV Observational Database (AHOD) and the TREAT Asia HIV Observational Database (TAHOD). We dichotomised each country’s per capita income into high/upper-middle (T-H) and lower-middle/low (T-L). Survival methods stratified by income were used to explore time to first major modification of first-line ART and associated factors. We defined a treatment modification as either initiation of a new class of antiretroviral (ARV) or a substitution of two or more ARV agents from within the same ARV class.

Results: A total of 4250 patients had 961 major modifications to first-line ART in the first five years of therapy. The cumulative incidence (95% CI) of treatment modification was 0.48 (0.44–0.52), 0.33 (0.30–0.36) and 0.21 (0.18–0.23) for AHOD, T-H and T-L respectively. We found no strong associations between typical patient characteristic factors and rates of treatment modification. In AHOD, relative to sites that monitor twice-yearly (both CD4 and HIV RNA-VL), quarterly monitoring corresponded with a doubling of the rate of treatment modifications. In T-H, relative to sites that monitor once-yearly (both CD4 and HIV RNA-VL), monitoring twice-yearly corresponded to a 1.8 factor increase in treatment modifications. In T-L, no sites on average monitored both CD4 & HIV RNA-VL concurrently once-yearly. We found no differences in rates of modifications for once- or twice-yearly CD4 count monitoring.

Conclusions: Low-income countries tended to have lower rates of major modifications made to first-line ART compared to higher-income countries. In higher-income countries, an increased rate of RNA-VL monitoring was associated with increased modifications to first-line ART.

Introduction

The introduction of combination antiretroviral therapy (ART) has dramatically changed the management of HIV infection. Combination ART can suppress plasma HIV replication to levels below the level of detection of highly sensitive contemporary assays, allowing reconstitution of the immune system and concomitant protection against AIDS diseases and mortality [1,2]. Since the introduction of zidovudine (AZT) in 1987, ART has evolved rapidly over time with multiple agents now licensed for use [3,4]. In high-income countries where access to ART is widely available, an effective regimen usually consists of a combination of antiretrovirals selected from five classes, where each class targets independent viral replication processes. The availability of five classes of ART gives prescribers a variety of potential initial as well as second- and third-line treatment options that afford full virological suppression [5]. In high-income
countries, initial ART regimens are individualized in order to minimize toxicity and adverse events, and maximize tolerability and efficacy of treatment. This is done to facilitate the chance of good adherence and thereby successful long-term HIV treatment outcomes.

In low- and middle-income countries the availability of ART is generally more restricted, limiting prescription to a narrower selection of ART combinations. Monitoring of disease, including HIV RNA viral load monitoring, is also restricted in many of these settings as is the widespread availability of expert medical care. In response, the World Health Organization (WHO) has recommended that access to HIV care including ART in such settings be facilitated by a public health based approach. This approach provides access to simple, affordable and well-studied ART regimens and disease monitoring schedules that allow for adequate care in the absence of sophisticated and expensive medical technologies [6].

The Asia-Pacific region has a large burden of HIV with estimates of around 4.9 million persons living with HIV/AIDS [7]. Over 85% of this burden is carried by India, China, Thailand, Indonesia and Vietnam [7]. The scale-up of ART in the Asia-Pacific region has increased substantially over recent years with most countries within the region now having widespread access to first-line ART, but only minimal second-line therapy options [8]. Most countries within the region have adopted a public health approach-based treatment strategy aligned with the WHO recommendations [6]. However, in this politically and economically diverse region, a number of approaches to the management of HIV exist. Different strategies have been adopted according to a range of considerations including HIV monitoring, ART dosing, and were formed partly on lack of evidence as to best practice [9].

In the absence of a cure, ART is considered to be a life-long means of achieving virological control. Numerous studies have shown that ART prolongs and improves the quality of life of a person living with HIV. In some settings, survival of people living with HIV may be similar to that observed in HIV-negative populations [10–12]. Poor adherence to the appropriate ART dosing schedule selects for drug resistance and can shorten the regimen’s durability [13]. Because of the critical importance of achieving and maintaining virological control, prescribers in collaboration with their patients may adapt and change ART regimens if individuals are experiencing barriers to adequate adherence. This decision to modify treatment is an important consideration as there are currently only a finite number of active ART combinations available for life-long treatment [14].

There are minimal data published on the rates of switching or modifying first-line ART for any reason in the Asia-Pacific region. The objective of this analysis was to explore the differences between resource rich and resource limited countries rates of major modifications made to first-line ART. Specifically we seek to further describe by income group, the first ART regimens initiated, frequency of HIV disease monitoring, and factors associated with major modifications to first-line ART regimens.

Methodology

Data Collection

The Asia-Pacific HIV Observational Database (APHOD) consists of two adult and one pediatric cohort and is part of the International Epidemiological Database Evaluating AIDS (eDEA) collaboration. This analysis utilizes data from the two adult cohorts in the Asia-Pacific region; the Australian HIV Observational Database (AHOD) and the TREAT Asia HIV Observational Database (TAHOD). APHOD data are collected twice annually (March & September) on a core set of demographic and clinical variables including information to assess and monitor patterns of ART, treatment efficacy, patterns of toxicity, markers of disease stage, and to monitor HIV-related and non-HIV-related causes of death. Data collection methodology for each cohort and baseline clinical characteristics have been described elsewhere [15,16]. Data are transferred electronically to The Kirby Institute, Sydney and all data are subjected to internal quality control and assurance procedures. This analysis is based on all data collated as of 31 March 2011 for AHOD and 30 September 2011 for TAHOD.

Ethics and study governance approval for AHOD was granted by the University of New South Wales Human Research Ethics Committee, and site-specific study governance granted by their nominated institutional review boards. Patient’s written and informed consent was obtained at time of enrolment. Ethics approval was granted for TAHOD by the University of New South Wales Human Research Ethics Committee. Sites specific study governance was granted by site-relevant institutional review boards. Written informed consent was not sought in TAHOD unless required by a site’s local institutional review board. Informed consent was waived at some sites as information is collected via an anonymous case report form. All study procedures were developed in accordance with the revised 1975 Helsinki Declaration.

We included all patients with a known starting date of combination ART who had not previously received mono/duo ART (treatment naive). We defined initial ART as two nucleos(tide) reverse transcriptase inhibitor (N(t)RTI) anchored with one of the following; non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or integrase inhibitor (II). To reduce the reliance on treatment records captured prior to patient enrolment and to ensure our analysis was based largely on treatment records captured after enrolment, we further restricted our analysis population to patients who initiated ART after or ≤ two years prior to cohort enrolment. We excluded patients who reported an undetectable plasma HIV RNA viral load (RNA-VL) measurement (defined as <400 copies/ml) prior to the reported ART initiation date.

Statistical Analysis

For comparative purposes we classified countries participating in TAHOD into a dichotomous income variable based on the World Bank’s per capita 2009 gross national income (GNI) estimates [17]. We defined high- to upper middle-income as per capita GNI>$3945 and lower middle- to low-income as per capita GNI<$3946. We summarised typical patient characteristics by income grouping and evaluated the frequency of HIV disease monitoring.

The primary endpoint for this analysis was time until first major first-line treatment modification, defined as either initiating a new class of antiretroviral or a substitution of two or more of the original antiretroviral agents with different agents from within the same ART class. Patients were censored at five years of follow-up after initiating ART. We defined a patient as lost to follow-up if they had not presented to care for at least one year prior to the last site’s data transfer date. Patients who died were considered to have completed follow-up and were censored at their date of death. We recorded the primary reason for ART modification as identified by the treating nurse or physician. Reasons for modifying an ART regimen were aggregated into four broad categories: treatment failure (clinical, immunological, virological), adverse event or toxicity, patient or physician decision (including drug-drug interaction switches) and unknown/not reported.
Table 1. Crude rate of first major modification to ART and average per patient per year HIV monitoring (CD4 cell count and HIV RNA-VL) by country.

| Income grouping | Country      | Start of cohort | No. Patients (switches) | Rate of switch (95% CI) | 1:CD4 (%) | 1:RNA (%) | 2:CD4 (%) | 2:RNA (%) |
|-----------------|--------------|-----------------|-------------------------|-------------------------|-----------|-----------|-----------|-----------|
| AHOD            | Australia    | 1999            | 945 (350)               | 14.7 (13.3–16.4)        | 93        | 91        | 79        | 78        |
| High/Upper      | Singapore    | 2003            | 87 (36)                 | 15.7 (11.3–21.8)        | 96        | 49        | 82        | 15        |
| Middle          | Taiwan       | 2003            | 175 (67)                | 12.8 (9.9–16)           | 89        | 87        | 65        | 65        |
|                 | Malaysia     | 2003            | 155 (46)                | 9.3 (6.9–12.4)          | 92        | 86        | 56        | 48        |
|                 | South Korea  | 2007            | 113 (24)                | 9.1 (6.1–13.5)          | 99        | 98        | 79        | 79        |
|                 | Japan        | 2005            | 180 (48)                | 8.1 (6.1–10.7)          | 95        | 95        | 73        | 73        |
|                 | Thailand     | 2003            | 471 (114)               | 7.1 (5.9–8.5)           | 92        | 71        | 55        | 18        |
|                 | Hong Kong SAR| 2003            | 79 (17)                 | 5.7 (3.5–9.2)           | 100       | 98        | 95        | 62        |
| Lower middle/   | India        | 2003            | 523 (104)               | 6.7 (5.5–8.1)           | 85        | 28        | 46        | 15        |
| Low             | China        | 2003            | 257 (35)                | 5.5 (4–7.7)             | 87        | 45        | 46        | 16        |
|                 | Philippines  | 2003            | 175 (31)                | 5.4 (3.8–7.7)           | 71        | 6         | 23        | 0         |
|                 | Cambodia     | 2005            | 208 (36)                | 4.9 (3.6–6.8)           | 100       | 12        | 72        | 1         |
|                 | Indonesia    | 2004            | 392 (38)                | 4 (2.9–5.5)             | 87        | 18        | 41        | 2         |
|                 | Vietnam      | 2010            | 490 (15)                | 3.3 (2–5.5)             | 99        | 18        | 45        | 6         |

doi:10.1371/journal.pone.0064902.t001
# Table 2. Patient demographics by country income grouping.

|                          | AHOD (n = 945) | TAHOD High Income (n = 1260) | TAHOD Low Income (n = 2045) |
|--------------------------|----------------|-----------------------------|-----------------------------|
| **Sex**                  |                |                             |                             |
| Male                     | 891 (94)       | 951 (75)                    | 1434 (70)                   |
| Female                   | 54 (4)         | 309 (25)                    | 611 (30)                    |
| **Age at ART initiation (Years)** |                |                             |                             |
| less than 30             | 121 (13)       | 273 (22)                    | 590 (29)                    |
| 30 to 50                 | 646 (68)       | 829 (66)                    | 1313 (64)                   |
| greater than 50          | 178 (19)       | 158 (13)                    | 142 (7)                     |
| mean                     | 41.1           | 38.1                        | 35.1                        |
| median (interquartile range) | 40.3 (33.4–47.5) | 36.2 (30.9–43.4)            | 33.8 (29.1–39.5)           |
| **AIDS**                 |                |                             |                             |
| None                     | 793 (84)       | 511 (41)                    | 709 (35)                    |
| Yes                      | 152 (16)       | 749 (59)                    | 1336 (65)                   |
| AIDS illness pre-ART     | 50 (33)        | 173 (23)                    | 343 (26)                    |
| AIDS illness post-ART    | 102 (67)       | 576 (77)                    | 993 (74)                    |
| **Exposure**             |                |                             |                             |
| Homosexual               | 644 (68)       | 392 (31)                    | 151 (7)                     |
| Heterosexual             | 120 (13)       | 736 (58)                    | 1345 (66)                   |
| IDU                      | 50 (5)         | 34 (3)                      | 319 (16)                    |
| Other                    | 131 (14)       | 98 (8)                      | 230 (11)                    |
| **HBV**                  |                |                             |                             |
| Negative                 | 721 (76)       | 884 (70)                    | 1202 (59)                   |
| Positive                 | 36 (4)         | 175 (14)                    | 134 (7)                     |
| Not Tested               | 188 (20)       | 201 (16)                    | 709 (35)                    |
| **HCV**                  |                |                             |                             |
| Negative                 | 737 (78)       | 887 (70)                    | 769 (38)                    |
| Positive                 | 80 (8)         | 78 (6)                      | 384 (19)                    |
| Not Tested               | 128 (14)       | 295 (23)                    | 892 (44)                    |
| **CD4 cell count at ART initiation*** |                |                             |                             |
| mean (cells/µL)          | 305            | 150                         | 128                         |
| median (interquartile range) | 271 (159–400)  | 125 (34–227)                | 110 (38–199)                |
| **Log RNA at ART initiation*** |                |                             |                             |
| mean (copies/ml)         | 4.85           | 4.7                         | 4.96                        |
| median (interquartile range) | 4.96 (4.44–5.35) | 4.73 (4.15–5.30)           | 5.0 (4.56–5.57)            |
| **Year ART Initiation**  |                |                             |                             |
| 1996 to 2004             | 499 (53)       | 728 (58)                    | 507 (25)                    |
| 2005 to 2011             | 446 (47)       | 532 (42)                    | 1538 (75)                   |
| **Time followed on ART** |                |                             |                             |
| mean (years)             | 5.3            | 5.1                         | 3.1                         |
| median (interquartile range) | 5.3 (2.9–7.5)  | 5.5 (2.9–7.5)               | 2.4 (0.9–5.1)              |
| **CD4 measurements (per year per person)** |                |                             |                             |
| mean                     | 3.4            | 1.9                         | 1.7                         |
| median (interquartile range) | 3 (2–4)        | 2 (1–2)                     | 1 (1–2)                     |
| **RNA measurements (per year per person)** |                |                             |                             |
| Mean                     | 3.3            | 1.4                         | 0.6                         |
| median (interquartile range) | 3 (2–4)        | 1 (1–2)                     | 0 (0–1)                     |

*Closest record to ART initiation within a window of 6 month prior to ART and 1 week following ART initiation.

doi:10.1371/journal.pone.0064902.t002
We tabulated by income grouping (AHOD, TAHOD-High, TAHOD-Low) the number of individual antiretroviral agents used at ART initiation, class of anchor agent used in the first-line ART regimen, reported reason for ART modification, and ART regimen switched-to. We used competing risk methods [as described by Fine and Gray (18)] to estimate the cumulative incidence of patients that made a major modification to their first-line ART regimen. We used multivariable Cox proportional hazards methods to evaluate any association between patient characteristics and rates of major modification to ART. Factors evaluated included sex, age at ART initiation, HIV exposure category (men who have sex with men, injecting drug user, heterosexual contact and other), hepatitis B virus (HBV) and hepatitis C virus (HCV) seropositivity, year of ART initiation (1996–2004 or 2005–2011), pre-ART AIDS-defining illness, pre-ART CD4 count (0–199, 200–349, 350–500, >500 cells/μL or unknown), pre-ART HIV RNA-VL (1–10^4, 10^4–10^6, >10^6 copies/ml and unknown) and an indicator for site resourcing (see below). Multivariable models were run separately on subsets of data split by income grouping. For comparative purposes we applied the same a priori defined covariate models and used the same reference level for each categorical factor across each model. Each country within its respective income grouping has different levels of resources allocated to manage HIV. Furthermore, within each country, individual treating sites can have differing capacities to provide HIV care and treatment (e.g. urban vs rural). To evaluate associations between site resourcing and rates of major modifications to ART, we used a proxy indicator variable for site resourcing. We defined site resourcing as a function of the average proportion of patients having “x” yearly, routine HIV monitoring laboratory measurements (RNA-VL and CD4 cell counts). To assign this indicator we first calculated for each site the proportion of patients that had on average in a year: one, two, three or four CD4 cell counts measured along with zero, one, two, three or four RNA-VL measurements. Using a median cutoff, we assigned for each site the highest number of measurements for which the average proportion of patients was greater than 50%. For example, if a site on average had 78% of its patients having three or more CD4 cell count measurement per year, but only 45% for four or more CD4 cell count measurements per year, then it would be assigned an average of three CD4 cell count measurements per year. Similarly, for RNA-VL, if the same site on average had 89% of its patients having two RNA-VL measurement per year, but only 36% for three RNA-VL measurements per year, then it would be assigned an average of two RNA-VL measurements per year. The two monitoring schedules were then concatenated to form the resourcing variable – i.e. 3CD4::2RNA-VL. Using a 50% cutoff point for the classification of site resourcing has the interpretation- more than half of the patients at the site had 3 or more CD4 cell counts measurements and 2 or more HIV RNA-VL measurements per year. It was not a requirement that CD4 cell counts and RNA-VL had to be measured on the same date.

Results

Of the 3378 AHOD patients enrolled by 31 March 2011, 945 (28%) satisfied the analysis eligibility criteria. Of the AHOD patients excluded from the analysis, 2111 (62%) were not included due to timing of ART initiation (ART initiation date >2 years prior to enrolment) and 158 (5%) were excluded as they received mono/duo therapy prior to first-line ART. Similarly for TAHOD, of the 5988 TAHOD patients enrolled by 30 September 2011, 3305 (55%) satisfied the analysis eligibility criteria. Of the TAHOD patients excluded from the analysis, 2444 (41%) were not included due to the timing of ART initiation and 115 (2%) were excluded for prior mono/duo therapy exposure. The mean time followed on ART for AHOD and TAHOD-High was five years compared to approximately three years for TAHOD-Low. Similar rates (95% confidence intervals) of patients lost to follow up are reported for AHOD: 4.9 (4.3–5.6) per 100 patient years and TAHOD-High: 4.6 (4.1–5.1) per 100 patient-years. TAHOD-

| Number At Risk | AHOD | TAHOD-High | TAHOD-Low |
|----------------|------|------------|-----------|
| AHOD           | 945  | 1260       | 2045      |
| TAHOD-High     | 686  | 1053       | 1360      |
| TAHOD-Low      | 498  | 852        | 1008      |
|                | 365  | 705        | 782       |
|                | 262  | 578        | 574       |
|                | 207  | 451        | 429       |
Low had a slightly higher rate, 7 (6.4–7.7) per 100 patient-years. The crude mortality rate for AHOD was 0.82 (0.61–1.12) per 100 patient years, for TAHOD-High: 0.92 (0.71–1.19) per 100 patient years and for TAHOD-Low: 1.64 (1.34–2.00) per 100 patient years.

The estimated rate of a major modification in AHOD was 14.7 (13.3–16.4) per 100 person-years (Table 1). The highest major modification rate for TAHOD-High was in Singapore, 15.7 (11.3–21.8) per 100 person-years and the lowest in Hong Kong, 5.7 (3.5–9.2) per 100 person-years. Similarly for TAHOD-Low, the highest rate was in India, 6.7 (5.5–8.1) per 100 person-years and lowest in Vietnam, 3.3 (2.0–5.5) per 100 person-years. The average patient age at ART initiation in AHOD was 41 years compared to 38 years for TAHOD-High and 35 years old for TAHOD-Low (Table 2). AHOD HIV exposure is predominately through homosexual contact as opposed to TAHOD in which the majority reported transmission is through heterosexual contact. The proportion of HIV exposure through injecting drug use (IDU) was highest in TAHOD-Low (16%) vs. TAHOD-High (3%) or AHOD (5%). There were differences for HBV surface antigen positivity across AHOD (5%) and TAHOD (7–14%). TAHOD-High/Low reported more AIDS-defining illnesses, 59–65% of patients, compared to AHOD- 16%. Of those AIDS-defining illnesses, timing of the event, pre-ART or post-ART, were similar. Mean pre-ART CD4 cell count was approximately 2-fold higher in AHOD compared to TAHOD-High/Low (300 vs. 150 cells/μL). Pre-ART RNA-VL was similar across the income groups. The proportion of patients initiating ART in more recent periods, 2005–2011, was highest in TAHOD-Low (75%) compared to AHOD (43%) and TAHOD-High (42%). The estimated median (q1–q3 quartiles) number of CD4 cell measurements per year per patient are AHOD: 3 (2–4), TAHOD-High: 2 (1–2), TAHOD-Low: 1 (1–2). The estimated median number of RNA-VL measurements were as follows: AHOD: 3 (2–4), TAHOD-High: 2 (1–2), TAHOD-Low: 0 (0–1).

Table 3 presents by income group the distribution of anchor agent used in first-line ART initiated and the regimen switch-to following modification. The proportions of reasons given for

| Number of different ARV agents used for initial ART regimen* | AHOD | TAHOD | TAHOD |
|-------------------------------------------------------------|-------|-------|-------|
| N(t)RTI                                                      | 9     | 7     | 7     |
| NNRTI                                                       | 2     | 2     | 2     |
| PI                                                          | 8     | 9     | 5     |
| II                                                          | 1     | 1     | 0     |
| Initial ART regimen                                         |       |       |       |
| 2 N(t)RTI+NNRTI                                             | 574 (61) | 852 (68) | 1976 (97) |
| 2 N(t)RTI+PI                                                | 279 (30) | 364 (29) | 67 (3) |
| 2 N(t)RTI+II                                                | 25 (3) | 6 (0) | 0 (0) |
| Other (non-standard, e.g. 3 N(t)RTI)                        | 67 (7) | 38 (3) | <5 (0) |
| Number of switches from initial ART regimen                  | 350   | 352   | 259   |
| Reported reason for modification                             |       |       |       |
| Treatment failure                                           | 47 (19) | 45 (13) | 73 (29) |
| Adverse event/toxicity                                      | 97 (38) | 141 (41) | 107 (42) |
| Patient decision/Physician decision                        | 110 (43) | 162 (47) | 76 (30) |
| Not reported                                                | 96    | <5    | <5    |
| Modified ART regimen                                        |       |       |       |
| Initial ART: 2 N(t)RTI+NNRTI                                |       |       |       |
| 2 N(t)RTI+NNRTI                                             | 48 (30) | 67 (34) | 85 (35) |
| 2 N(t)RTI+PI                                                | 75 (47) | 69 (35) | 66 (27) |
| 2 N(t)RTI+II                                                | 6 (4) | 0 (0) | 0 (0) |
| Other (non-standard)                                        | 29 (18) | 63 (32) | 93 (38) |
| Initial ART: 2 N(t)RTI+PI                                   |       |       |       |
| 2 N(t)RTI+PI                                                | 42 (27) | 80 (65) | <5 (10) |
| 2 N(t)RTI+NNRTI                                             | 64 (41) | 30 (24) | 9 (65) |
| 2 N(t)RTI+II                                                | 9 (6) | <5 (5) | 0 (0) |
| Other (non-standard)                                        | 41 (26) | 8 (6) | <5 (25) |

*Individual ARV agents with each class where less than 5 people initiated where excluded from the total count.
N(t)RTI = Nucleoside Reverse Transcriptase Inhibitor, NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor, PI = Protease Inhibitors, II = Integrase Inhibitor.

Table 3. Antiretroviral agents available for first-line ART, ART anchor agent, reported reason for major modification and selected switched-to ART regimen by country income grouping.
Figure 2. Time to first major modification of ART by country income grouping stratified by reported reason for modification. Panel (a) - reported treatment failure, Panel - (b) adverse event/toxicity, Panel (c) - patient/physician decision. Cumulative Incidence are adjusted for competing risk of death and competing reasons for modification. Shaded bands are mean 95% confidence bands. doi:10.1371/journal.pone.0064902.g002
treatment modification by income group are also presented in Table 3. The rate of major modification made to first-line ART by income group adjusted for competing risk of death (dashed line - competing risk of death and lost to follow-up) are presented, along with an at-risk population table in Figure 1. After five years of ART, adjusting for the competing risk of death, the cumulative incidence (95% CI) of first-line treatment modifications was 0.48 (0.44–0.52) for AHOD, 0.33 (0.30–0.36) for TAHOD-High and 0.21 (0.18–0.23) for TAHOD-Low.

The cumulative incidence for treatment modification adjusted for competing risk of death and competing reason for modification are presented in Figure 2. Table 4 outlines clinical factors and associations of rates of major modifications to first-line ART by income grouping. Multivariable estimated hazard ratios by income grouping were similar in relative magnitude and direction for most covariates. The majority of covariates including sex, age at ART initiation, HIV exposure, HBV serostatus, pre-ART AIDS-defining Illness, pre-ART CD4 and pre-ART RNA-VL, were not significantly associated with major treatment modifications. HCV positive serostatus and more recent periods of ART initiation were indicative of reduced rates of treatment modification across all income grouping models.

Figure 3 plots multivariable model estimate hazard ratios for the site resourcing covariate by income group (adjusted for factors listed above). In AHOD, the relative base was two CD4 counts and two RNA-VLs per year (e.g. monitored twice-yearly). In

| Table 4. Predictors of major first-line modification by income grouping. |
|---------------------------------------------------------------|
| **AHOD** | **TAHOD-High** | **TAHOD-Low** |
| **Sex** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** |
| Male | 1.00 | 1.00 | 0.76 (0.56–1.03) | 0.08 |
| Female | 0.92 (0.55–1.55) | 0.75 | 0.93 (0.7–1.25) | 0.64 |
| **Age at ART initiation (years)** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** |
| <30 | 1.00 | 1.00 | 1.00 |
| 30–50 | 1.07 (0.76–1.49) | 0.71 | 0.79 (0.61–1.03) | 0.08 | 1.04 (0.77–1.4) | 0.81 |
| >50 | 1.14 (0.76–1.71) | 0.52 | 0.87 (0.6–1.25) | 0.45 | 0.81 (0.46–1.44) | 0.47 |
| **Exposure** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** |
| Homosexual | 1.00 | 1.00 | 1.00 |
| Heterosexual | 0.92 (0.63–1.34) | 0.67 | 1.34 (0.97–1.86) | 0.08 | 1.17 (0.69–1.98) | 0.56 |
| IDU | 1.29 (0.81–2.07) | 0.28 | 1.57 (0.81–3.05) | 0.18 | 1.16 (0.58–2.33) | 0.67 |
| Other | 0.93 (0.67–1.27) | 0.63 | 1.08 (0.66–1.75) | 0.77 | 0.98 (0.52–1.86) | 0.96 |
| **Hepatitis B** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** |
| Neg/Not Tested | 1.00 | 1.00 | 1.00 |
| Positive | 1.05 (0.59–1.84) | 0.88 | 1.21 (0.88–1.66) | 0.24 | 1.14 (0.68–1.9) | 0.62 |
| **Hepatitis C** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** |
| Neg/Not Tested | 1.00 | 1.00 | 1.00 |
| Positive | 0.63 (0.4–0.97) | 0.04 | 0.87 (0.53–1.41) | 0.56 | 0.65 (0.39–1.11) | 0.12 |
| **Year of ART Initiation** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** |
| 1996–2004 | 1.00 | 1.00 | 1.00 |
| 2005–2011 | 0.81 (0.64–1.02) | 0.08 | 0.7 (0.54–0.91) | 0.01 | 0.62 (0.48–0.81) | <0.001 |
| No | 1.00 | 1.00 | 1.00 |
| Yes | 1.43 (1.02–2.01) | 0.04 | 0.97 (0.77–1.21) | 0.77 | 1.15 (0.88–1.5) | 0.32 |
| **CD4 cell count at ART initiation (cells/µL)** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** |
| 0–199 | 1.00 | 1.00 | 1.00 |
| 200–350 | 1.00 | 1.00 | 1.00 |
| 350–500 | 1.1 (0.75–1.35) | 0.99 | 1.28 (0.92–1.76) | 0.14 | 1.19 (0.86–1.64) | 0.29 |
| >500 | 1.1 (0.78–1.55) | 0.60 | 1.45 (0.93–2.25) | 0.10 | 0.61 (0.19–1.93) | 0.40 |
| Unknown | 1.12 (0.63–2.01) | 0.69 | 1.1 (0.79–1.54) | 0.58 | 1.24 (0.83–1.85) | 0.29 |
| **RNA–VL at ART initiation (copies/ml)** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** | **Hazard Ratio** | **p** |
| 1–10 | 1.00 | 1.00 | 1.00 |
| 10–10⁵ | 0.76 (0.52–1.11) | 0.15 | 0.71 (0.44–1.17) | 0.18 | 1.59 (0.54–4.72) | 0.40 |
| >10⁶ | 0.81 (0.55–1.17) | 0.26 | 0.78 (0.49–1.25) | 0.31 | 2.24 (0.8–6.27) | 0.13 |
| Unknown | 0.79 (0.43–1.44) | 0.44 | 1.01 (0.62–1.64) | 0.96 | 1.46 (0.54–3.99) | 0.46 |

Hazard ratios calculated from multivariable model including adjustment for site resourcing.

*Closest record to ART initiation within a window of 6 month prior to ART and 1 week following ART initiation.

doi:10.1371/journal.pone.0064902.t004
AHOD, sites that monitored on average four-times per year corresponded with an 2-fold increase in the rate of major first-line modification. Similarly for TAHOD-High, relative to once-yearly monitoring (both CD4 counts and RNA-VL), sites that monitor twice-yearly demonstrated an increase in rate of first-line modifications by a factor of 1.8. No sites in TAHOD-Low monitored one-yearly CD4 count and RNA-VL concurrently. There were no differences in modifications to first-line ART for patients who had one or two CD4 count measurements per year.

Discussion

In the Asia-Pacific region, the overall rate of major modification to first-line ART was associated with country income and HIV monitoring levels, particularly RNA-VL. Low- to lower middle-income countries typically had lower rates of major modification to first-line ART by a factor of 0.36 (0.31–0.41) relative to Australia. We found little evidence of significant associations between treatment modification and standard patient characteristics. By evaluating rates of major modifications and associations with a proxy indicator for site resourcing, we showed that there is a relationship between the number of RNA-VL tests and major modification to first-line ART. In AHOD, relative to sites that monitor twice-yearly, quarterly monitoring corresponded with an approximate doubling of the rate of major modification. We saw a similar pattern in TAHOD-High, where relative to sites that monitored once-yearly, a doubling of monitoring to twice-yearly corresponded to just below a doubling of major modifications. We were unable to evaluate this association in TAHOD-Low as no sites performed at least once-yearly concurrent monitoring of CD4 count and RNA-VL. Within the lower income sites, an increase of CD4 monitoring from once- to twice-yearly monitoring did not result in an increase in major modification made to first-line ART.

Given that one goal of HIV monitoring is to provide guidance on the optimal time to switch ART, it is unsurprising that increasing the frequency of RNA-VL monitoring also increases the rate of major modifications made to first-line ART. We speculate that regular and frequent point-of-care visits lead to continual dialogue and discussion of patient experiences and concerns about their wellbeing including review and discussion of all test results. Modification of ART may also be on the basis of reporting of adverse events, barriers to adherence, observed toxicity on routine test results (e.g. reduced estimated glomerular filtration rate, subclinical but biochemical hepatitis, anemia, etc.) leading to more treatment modifications aimed at maximising benefit and minimising adverse events. Figure 2 collectively outlines this point. The rate of treatment modification due to treatment failure is relatively low and similar across all income groups. However the rate of treatment modification reported due to adverse events/toxicity (or patient/physician decisions) is much higher in higher income countries compared to lower income countries. It is unlikely that the ART regimens distributed in lower income countries are less toxic or better tolerated than their higher income counterparts. Therefore we believe this data indicates that higher income countries have additional flexibility to make treatment modifications on varying levels of reported adverse events/toxicity or by choice of the patient or at the discretion of the treating physician.

It still remains unclear if access to all available ARVs and quarterly RNA-VL monitoring actually increases or decreases the number of unnecessary treatment modifications. An analysis by the EuroSIDA group found that the risk of virological failure following one year of well-tolerated fully suppressive ART is low [19]. Patients in that analysis were monitored quarterly and the authors concluded that twice-yearly monitoring could be an effective monitoring schedule for stable patients. To date there are few randomised clinical trial or cohort data evaluating the optimal timing of HIV disease monitoring that minimises cost and maximises treatment outcomes in high resource settings [20]. A cost-effectiveness analysis based on mathematical modelling assessed multiple HIV monitoring strategies in Southern Africa. The authors concluded that monitoring RNA-VL and CD4 count quarterly over twice-yearly has only a modest effect on additional costs.

![Figure 3. Multivariable adjusted associations for site resourcing and time to major first-line ART modification.](image-url)
life expectancy and contributes to a small reduction in opportunistic diseases [21].

Our study does not report mortality or treatment outcomes (clinical, immunological and virological) between the different income groups. Although not directly comparable due to differing analysis populations, treatment outcome differences in the Asia-Pacific have been reported elsewhere [22–25]. Briefly, Egger et al reported a lower absolute mean difference of in mean CD4 cell counts (7 to 7 cell/mcL) in TAHOD compared to AHOD [26]. A follow-up study by Achhra et al concluded that this mean CD4 cell count difference translated to minimal clinical significance in terms of mortality and new AIDS-defining illness [22]. A comprehensive analysis of AIDS-related and non-AIDS-related mortality in AHOD and TAHOD also reported little evidence of differing hazard ratios of mortality in TAHOD-High and TAHOD-Low relative to AHOD [24]. However, in a TAHOD-specific study, Oyomopito et al reported less favorable treatment outcomes for sites that reported less than once-yearly RNA-VL testing compared to those sites that monitored RNA-VL at least once-yearly [25]. In aggregate these finding suggest that there are minimal population differences in treatment outcomes between AHOD and TAHOD. Collectively these results are consistent with a study conducted by the Swiss HIV Cohort Study (SHCS) and the International Epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA) group that directly compared HIV treatment outcomes between a high-income country (Switzerland) and a low-income country (South Africa) [26]. The investigators concluded that although patients switched treatment much more often in Switzerland, there were minimal differences between longer-term treatment outcomes.

Our results are consistent with studies that have previously evaluated factors associated with switching from first-line ART to second-line regimens in both resource-rich and resource-limited settings. Although we cannot compare our results directly due to differing analysis designs—including reasons for switching algorithms and importantly, regional differences in antiretroviral treatment guidelines. These studies have found few factors associated with switching from first-line ART. Of the large observational cohorts evaluating switching in resource-limited settings, a large multi-country cohort analysis from the ART-LINC group showed an increasing risk association between switching to second-line ART (for any reason) and low pre-ART CD4 cell count (<150 cells/ml) and earlier time periods of ART initiation [27]. Similar associations, low pre-ART CD4 and earlier time-periods of ART initiation were also found in Sub-Saharan Africa [28].

There are limitations to our analysis. First, although we have designed an analysis based largely on prospective treatment records from a population of patients receiving routine care at multiple sites throughout the Asia-Pacific region, we are unable to quantify selection bias due to the observational nature of the data. Second, in our analysis we have used World Bank-defined criteria to categorise countries into high/middle/low-income groupings based on gross national income. Clearly, economic prosperity or disparity change over time, and we note that our income groupings and the associated results are specific to the observed time period. Furthermore, we note that the ART treatment guidelines have changed overtime. Although we have attempted to address these differences through adjusting for year of ART initiation, we are unable to quantify any remaining impact on our result for these treatment guideline changes. Third, our association analysis endpoint (Table 4, Figure 3) is composite and captures all major modifications to first-line ART regardless of reason. Although we have recorded reasons for modification, we are hesitant to differentiate the analysis (e.g using a competing risk framework) based on this variable. Reasons for treatment modification are complex due to co-dependence, where adverse events influence adherence, which in turn leads to treatment failure. Furthermore, there are a large number of unreported reasons for modification in AHOD and exclusion of these events would likely introduce bias due-to missing information. Finally, we are unable to evaluate any site-specific bias in our included variable for site resourcing. A given resourcing level (e.g. 2CD4::1RNA-VL) may actually correspond to only a single site within the income group, thus limiting interpretation of site resourcing categories with infrequent events or observed years.

In summary, we found that low-income countries tended to have lower rates of major modifications made to first-line ART compared to higher-income countries, where increased HIV monitoring led to increased modifications of first-line ART. The clinical significance of this finding at an individual patient level is unknown. Given the current need for life-long therapy in the management of HIV, further research evaluating the optimal monitoring schedule which balances overall cost and favorable treatment outcomes would be of value to both resource-rich and resource-limited countries.

Acknowledgments

We would like to acknowledge all of the patients and collaborators (Appendix 1) of the Asia-Pacific HIV Observational Database cohort study, without whom this work would not have been possible.

Australian HIV Observational Database collaborators (asterisks indicate steering committee members in 2012)

New South Wales: D Ellis, General Medical Practice, Cooffs Harbour; M Bloch, T Frain*, S Agrawal, L McCann, N Cunningham, T Vincent, Holdsworth House General Practice, Darlinghurst; D Allen, J Little, Holden Street Clinic, Gosford; D Smith, C Gray, Lismore Sexual Health & AIDS Services, Lismore; D Baker*, R Vale, East Sydney Doctors, Surry Hills; DJ Templeton*, CC O’Connor, C Dijanosie, RPA Sexual Health Clinic, Camperdown; E Jackson, K McCallum, Blue Mountains Sexual Health and HIV Clinic, Katoomba; M Grotowski, S Taylor, Tamworth Sexual Health Service, Tamworth; D Cooper, A Carr, F Lee, K Hesse, K Sinu, St Vincent’s Hospital, Darlinghurst; R Finlayson, I Pron, Taylor Square Private Clinic; Nanninga, J Shanks, Nepean Sexual Health and HIV Clinic, Penrith; K Brown, C McGrath, V McGrath, S Halligan, Illawarra Sexual Health Service, Warranong; L Wray, P Read, H Lu, Sydney Sexual Health Centre, Sydney; D Couldwell, Parramatta Sexual Health Clinic; D Smith, V Turner, Albion Street Centre; Dubbo Sexual Health Centre, Dubbo; J Watson*, National Association of People living with HIV/AIDS; C Lawrence*, National Aboriginal Community Controlled Health Organisation; B Mullard*, Department of Public Health and Community Medicine, University of Sydney; M Law*, K Petoumenos*, S Wright*, H McManus*, C Kendall*, M Boydt*, The Kirby Institute, University of NSW.

Northern Territory: A Kulatunga, P Knibbs, Communicable Disease Centre, Royal Darwin Hospital, Darwin.

Queensland: J Chua*, M Ngie, B Dickson, Gold Coast Sexual Health Clinic, Miami; D Russell, S Downing, Cairns Sexual Health Service, Cairns; D Sowden, J Broom, K Taing, C Johnston, K McGill, Clinic 87, Sunshine Coast-Wide Bay Health Service District, Nambour; D Orth, D Youts, Gladstone Road Medical Centre, Highgate Hill; M Kelly, A Gibson, H Magon, Brisbane Sexual Health and HIV Service, Brisbane.

South Australia: W Donohue, O’Brien Street General Practice, Adelaide.

Victoria: R Moore, S Edwards, R Lidde, P Locke, Northside Clinic, North Fitzroy; NJ Roth*, J Nicolson*, H Lau, Prahran Medical Clinic, South Yarra; T Read, J Silvers*, W Zeng, Melbourne Sexual Health Centre, Melbourne; J Hoy*, K Watson*, M Bryant, S Price, The Alfred Hospital, Melbourne; I Woolley, M Giles, T Korman, J Williams, Monash Medical Centre, Clayton.
Western Australia: D Nolan, J Skett, J Robinson, Department of Clinical Immunology, Royal Perth Hospital, Perth.

TREAT Asia HIV Observational Database collaborators (asterisks indicate steering committee member in 2012; † Steering Committee Chair; ‡ co-Chair)

Cambodia: CV Mean, V Saphorn* and K Voith, National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh, Cambodia;

China: FJ Zhang*, HX Zhao and N Han, Beijing Ditan Hospital, Capital Medical University, Beijing, China; PCK Li* and MP Lee, Queen Elizabeth Hospital, Hong Kong, China;

India: N Kumarasamy*, S Saghayam and C Eziharisare, YRG Centre for AIDS Research and Education, Chennai, India; S Pujari*, K Joshi, and A Makane, Institute of Infectious Diseases, Pune, India;

Indonesia: TP Merati*, DN Wirawan and F Yuliana, Faculty of Medicine Udayana University & Sanglah Hospital, Bali, Indonesia; E Yunibastuti* ‡, D Imran, A Widhani, Working Group on AIDS Faculty of Medicine, University of Indonesia/Ciptomangunkusumo Hospital, Jakarta, Indonesia;

Japan: S Okas*, J Tanuma and T Nichijima, National Center for Global Health and Disease, Tokyo, Japan;

South Korea: JY Choi*, Na S, and JM Kim, Division of Infectious Diseases, Dept. of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea;

Malaysia: CK Lee*, B HL Sim and R David, Hospital Sungai Buloh, Kuala Lumpur, Malaysia; A Kamarulzaman* and A Kajidur, University of Malaysia Medical Centre, Kuala Lumpur, Malaysia;

Philippines: R Dimang*, E Uy and R Rantique, Research Institute for Tropical Medicine, Manila, Philippines;

Taiwan: YMA Chen*, WW Wong and LH Kuo, Taipei Veterans General Hospital and AIDS Prevention and Research Centre, National Yang-Ming University, Taipei, Taiwan;

Singapore: OT Ng*, A Chua, LS Lee and A Loh, Tan Tock Seng Hospital, Singapore;

Thailand: P Phanuphak*, K Ruxrungtham, A Avihingsanon, and M Mongkhonbattrayothin, HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand; S Kiertubunarakul †, ‡, S Sunkanumarp, and N Sammeera, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; R Chaivari*, T Sirisaithana and W Kotaratthithit, Research Institute for Health Sciences, Chiang Mai, Thailand; P Kantipong and P Kambua, Chiang Rai Prachanukroh Hospital, Chiang Rai, Thailand;

Vietnam: VK Nguyen*, VH Bui and TT Cao, National Hospital for Tropical Diseases, Hanoi, Vietnam; TT Pham*, DD Cuong and HL Ha, Bach Mai Hospital, Hanoi, Vietnam;

Coordinating office: AH Sohn*, Nicolas Durier* and B Petersen, TREAT Asia, amfAR - The Foundation for AIDS Research, Bangkok, Thailand; DA Cooper, MG Law*, A Jamasak* and DC Boettiger, The Kirby Institute, The University of New South Wales, Sydney, Australia.

Independent reviewers: F Drummond, M Boyd.

Author Contributions
Conceived and designed the experiments: STW MAB EY ML TS JH SP.

References
1. Mocroft A, Ledegerber B, Katlama C, Kirk O, Reiss P, et al. (2005) Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet 362: 22–29. doi:10.1016/S0140-6736(05)13092-0.

2. May MT, Sterne JAC, Costagliola D, Sabin CA, Phillips AN, et al. (2006) HIV treatment response and prognosis in Europe and North America in the first decade of highly active antiretroviral therapy: a collaborative analysis. Lancet 368: 451–458. doi:10.1016/S0140-6736(06)69152-6.

3. Fischl MA, Richman DD, Gottlieb MS, Volberding PA, et al. (1987) The efficacy of azidothymidine (AZT) in the treatment of patients with the AIDS-related complex. A double-blind, placebo-controlled trial. N Engl J Med 317: 185–191. doi:10.1056/NEJM198707233170401.

4. Vella SS, Schoenlander BB, Sew SPS, Eholie SPS, Murphy KLR (2012) The history of antiretroviral therapy and of its implementation in resource-limited areas of the world. AIDS 26: 1251–1241. doi:10.1097/QAD.0b013e2825521a3.

5. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services, August 27, 2012. Available at: http://aidsinfo.nih.gov/guidelines/adult/2012/PanelonAntiretroviralGuidelinesforAdultsandAdolescents2012.pdf.

6. World Health Organization (2011) Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 revision. Geneva: World Health Organization. 2010. Available from http://whqlibdocwhoint/publications/2010/9789241599764_eng.pdf. Accessed 9 November 2011: 1–359.

7. Joint United Nations Programme on HIV/AIDS (2011) HIV in Asia and the Pacific: Getting to Zero. 1–144. Bangkok, 2011. Available at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20110826_APGettingToZero_en.pdf.

8. Srikrithan P, Giddimelli M, Bachani D, Chasombat S, Daoni E, et al. (2010) Scale-up of national antiretroviral therapy programs: progress and challenges in the Asia Pacific region. AIDS 24: S62.

9. Boyd MA, Cooper DA (2012) Optimization of HIV care and service delivery: doing more with less. Lancet. doi:10.1016/S0140-6736(12)61534-4.

10. The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord, Leveden C, Bouteiloup V, De Wit S, C Sab, et al. (2012) All-cause mortality in treated HIV-infected adults with CD4+ < 300/ mm3 compared with the general population: evidence from a large European observational cohort collaboration. International Journal of Epidemiology 41: 433–445. doi:10.1093/ije/dyr164.

11. The Antiretroviral Therapy Cohort Collaboration (2009) Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries. International Journal of Epidemiology 38: 1624–1633. doi:10.1093/ije/dyp306.

12. McManus H, O’Connor CC, Boyd M, Broom J, Russell D, et al. (2012) Long-Term Survival in HIV Positive Patients with up to 15 Years of Antiretroviral Therapy. PLoS ONE 7: e48839. doi:10.1371/journal.pone.0048839.

13. Parsons J, Massari V, Decamps D, Vabret A, Bouvet A, Bovey E, et al. (2004) Predictors of virological failure and resistance in HIV-infected patients treated with nevirapine-or efavirenz-based antiretroviral therapy. Clinical Infectious Diseases 38: 1511.

14. Costagliola DD, Lodwick RR, Ledegerber BB, Torri CC, van Sighem AA, et al. (2012) Trends in virological and clinical outcomes in individuals with HIV-1 infection and virological failure of drugs from three antiretroviral drug classes: a cohort study. The Lancet Infectious Diseases 12: 119–127. doi:10.1016/S1473-3099(11)70248-1.

15. Australian HIV Observational Database (2002) Rates of combination antiretroviral treatment change in Australia, 1997–2000. HIV Med 3: 28–36.

16. Zhou J, Kumarasamy N, Ditangco R, Kamarulzaman A, Lee CKC, et al. (2005) The TREAT Asia HIV Observational Database: baseline and retrospective data. J Acquir Immune Defic Syndr 38: 174–179.

17. World Bank, editor (n.d.) World Bank GNI per capita Operational. Available: http://siteresources.worldbank.org/DATASTATISTICS/Resources/OGHISTR.xls. Accessed 2012 August 29.

18. Fine JP, Gray RJ (1999) A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association 94: 437–442.

19. Reekie J, Mocroft A, Sambatakou H, Machala L, Chiesi A, et al. (2008) Does less frequent routine monitoring of patients on a stable, fully suppressed cART regimen lead to an increased risk of treatment failure? AIDS 22: 2381–2390. doi:10.1097/QAD.0b013e3282f7a6e7.

20. Walker AS, Gibb DM (2011) Monitoring of highly active antiretroviral therapy in HIV infection. Curr Opin Infect Dis 24: 27–33. doi:10.1097/QCO.0b013e328329f4e4.
21. Bendavid E, Young SD, Katzenstein DA, Bayoumi AM, Sanders GD, et al. (2008) Cost-effectiveness of HIV monitoring strategies in resource-limited settings: a southern African analysis. Arch Intern Med 168: 1910–1918. doi:10.1001/archinternmed.2008.1.

22. Ashgra ACA, Zhou JJ, Choi JYJ, Hoy JJ, Zhang FF, et al. (2011) The Clinical Significance of CD4 Counts in Asian and Caucasian HIV-Infected Populations: Results from TAHOD and AHOD. J Int Assoc Physicians AIDS Care (Chic) 10: 160–170. doi:10.1177/1545109711402213.

23. Egger S, Petersenos K, Kamarulasaman A, Hoy J, Sungkanuparp S, et al. (2009) Long-term patterns in CD4 response are determined by an interaction between baseline CD4 cell count, viral load, and time: The Asia Pacific HIV Observational Database (APHOD). J Acquir Immune Defic Syndr 50: 513–520.

24. Falster K, Choi JY, Donovan B, Duncombe C, Mulhall B, et al. (2009) AIDS-related and non-AIDS-related mortality in the Asia-Pacific region in the era of combination antiretroviral treatment. AIDS 23: 2323–2336. doi:10.1097/QAD.0b013e32832e05b2.

25. Oyomopito R, Lee MP, Database TAHO, 21 (2010) Measures of site resourcing predict virologic suppression, immunologic response and HIV disease progression following highly active antiretroviral therapy (HAART) in the TREAT Asia HIV Observational Database (TAHOD). HIV Med 11: 319–329. doi:10.1111/j.1468-1293.2010.00822.x.

26. Keiser O, Orrell C, Egger M, Wood R, Brinkhof MWG, et al. (2008) Public-health and individual approaches to antiretroviral therapy: township South Africa and Switzerland compared. PLoS Med 5: e148–e1111. doi:10.1371/journal.pmed.0050148.

27. ART-LINC of IeDEA Study Group, Keiser O, Tweya H, Boulle A, Bratstein P, et al. (2009) Switching to second-line antiretroviral therapy in resource-limited settings: comparison of programmes with and without viral load monitoring. AIDS 23: 1867–1874. doi:10.1097/QAD.0b013e328352d3f2.

28. Palomba L, Marazzi MC, Guidotti G, Germano P, Buonomo E, et al. (2009) Incidence and Predictors of Death, Retention, and Switch to Second-Line Regimens in Antiretroviral-Treated Patients in Sub-Saharan African Sites with Comprehensive Monitoring Availability. Clinical Infectious Diseases 48: 115–122. doi:10.1086/593312.