Antiretroviral Treatment Interruption and Loss to Follow-Up in Two HIV Cohorts in Australia and Asia: Implications for 'Test and Treat' Prevention Strategy

Rebecca Guy, MD,¹ Handan Wand,¹ Hamish McManus,¹ Saphonn Vonthanak, MD,² Ian Woolley, MD,³ Miwako Honda, MD,⁴ Tim Read,⁵ Thira Sirisanthana, MD,⁶ Julian Zhou,¹ and Andrew Carr, MD,⁷ on behalf of Australia HIV Observational Database (AHOD) and Treat Asia HIV Observation Database (TAHOD)

Abstract

Both antiretroviral treatment interruption (TI) and cessation have been strongly discouraged since 2006. We describe the incidence, duration, and risk factors for TI and loss-to-follow-up (LTFU) rates across 13 countries. All 4689 adults (76% men) in two large HIV cohorts in Australia and Asia commencing combination antiretroviral therapy (ART) to March 2010 were included. TI was defined by ART cessation >30 days, then recommencement, and loss to follow-up (LTFU) by no visit since 31 March 2009 and no record of death. Survival analysis and Poisson regression methods were used. With median follow-up of 4.4 years [interquartile range (IQR):2.1–6.5], TI incidence was 6.7 per 100 person years (PY) (95% CI:6.1–7.3) pre-2006, falling to 2.0 (95% CI:1.7–2.2) from 2006 ($p<0.01$). LTFU incidence was 3.5 per 100 PY (95% CI:3.1–3.9) pre-2006, and 4.1 (95% CI:3.5–4.9) from 2006 ($p=0.22$). TIs accounted for 6.4% of potential time on ART pre-2006 and 1.2% from 2006 ($p<0.01$), and LTFU 4.7% of potential time on ART pre-2006 and 6.6% from 2006 ($p<0.01$). Median TI duration was 163 (IQR: 75–391) days pre-2006 and 118 (IQR: 67–270) days from 2006 ($p<0.01$). Independent risk factors for the first TI were: Australia HIV Observational Database participation; ART initiation pre-2006; ART regimens including stavudine and didanosine; three nucleoside analogue reverse transcriptase inhibitors; ≥ 7 pills per day; and ART with food restrictions (fasting or with food). In conclusion, since 2006, 7.8% of patients had significant time off treatment, which has the potential to compromise any 'test and treat' policy as during the interruption viral load will rebound and increase the risk of transmission.

Introduction

BY IMPEDING HIV REPLICATION and suppressing viral load to undetectable levels, antiretroviral therapy (ART) is a key HIV transmission prevention strategy globally. Evidence supporting this effect includes a multinational, randomized trial (National Institutes of Health HPTN052) which found a 96% reduction in HIV transmission to an uninfected heterosexual partner,¹ as well as observational cohorts,^{2,3} and ecological population-level analyses.^{4,5}

Many countries are considering policies involving initiating ART upon diagnosis regardless of CD4 count ('test and treat'), or starting treatment at higher CD4 count than currently recommended. The Strategic Timing of Antiretroviral Treatment (START) trial⁶ is currently addressing the effects of early ART initiation on mortality, AIDS, and non-AIDS-related morbidity. The concept of using treatment as prevention (TasP) has been featured in recent guidelines, including the US Department of Health and Human Services (DHHS) guidelines.⁷

¹The Kirby Institute, University of New South Wales, Sydney, NSW, Australia.

²National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh, Cambodia.

³Monash Medical Centre and Monash University, Melbourne, VIC, Australia.

⁴National Center for Global Health and Medicine, Tokyo, Japan.

⁵Melbourne Sexual Health Centre, Melbourne, VIC, Australia.

⁶Research Institute for Health Sciences, Chiang Mai, Thailand.

⁷St Vincent's Hospital, Sydney, NSW, Australia.

One outcome that would compromise treatment policies, including 'test and treat,' is transient or permanent treatment interruption (TI), after which viral load will typically increase to pre-ART levels in 4 weeks, and so increase the risk of transmission. TI can also induce antiretroviral drug resistance,⁸ and have detrimental effects on CD4 count and clinical progression.^{9–14} The Strategies of Management of Antiretroviral Therapy (SMART) study was a two-armed treatment comparison between continuous therapy and CD4-guided interrupted therapy.⁹ The study was halted on January 11, 2006, due to safety concerns, as there was a 2.5 relative risk of clinical disease progression in the interrupted therapy arm.⁹ Since then, clinical guidelines have discouraged TI.

Despite the evidence now in favor of continuous ART from both therapeutic and public health perspectives, ART adherence is not straightforward for all people with HIV. Reasons that have been cited in studies of TI include drug toxicity, pill burden, financial constraints, lack of access to medication, and a range of other co-morbidities, including psychiatric or medical illnesses.^{15–19}

Of the few studies that have estimated the extent of TIs (including loss to follow-up; LTFU) since the SMART study; none compared pre-2006 to 2006 onwards, none measured the impact of the TI on HIV viral load or CD4 count, all defined TI using an interval of less than 4 weeks and thus included interruptions where viral load may not have been high enough to result in HIV transmission, and all were conducted in Africa or the United States.^{20–24}

The aim of this study was to investigate the incidence, frequency of TIs and LTFU pre and post 2006, risk factors for TI, and the impact of TI on plasma HIV viral load across 13 countries covering both high and low-income settings in Asia and the Pacific.

Methods

Study population

Patients with HIV infection who were consented and enrolled in the Australia HIV Observational Database (AHOD) cohort or the Treat Asia HIV Observation Database (TAHOD) cohort and who had initiated any combination of three or more antiretroviral drugs from 2000 onwards and had at least one subsequent clinical visit or result recorded in the database were included in the analysis. Both the cohorts have similar methodologies.

AHOD is an observational, clinical cohort study of patients with HIV infection in Australia, which has been described elsewhere in detail.²⁵ Prospective data collection for AHOD commenced in 1999, with retrospective data provided where available. Briefly, data are collected from 27 clinical sites in six of the eight states/territories of Australia, including hospitals, sexual health clinics, and general medical practices that offer specialist HIV care. Written, informed consent is obtained from all patients recruited to AHOD at the time of enrolment.

Prospective data collection for TAHOD commenced in 2003, with retrospective data provided where available. In TAHOD, data are collected from 17 participating clinical sites in the Asia-Pacific region including sites in Cambodia, China, India, Indonesia, Japan, Malaysia, Papua New Guinea, Singapore, South Korea, Taiwan, South Korea, and Thailand. Written consent was not a requirement of sites in TAHOD unless required by the site's local ethics com-

mittee because data are collected in an anonymous form. A detailed description of this collaboration has been published previously.²⁶

Data for both cohorts are transferred electronically to the Kirby Institute every March and September and include the same set of core variables, including:

1. Demographics: date of birth, sex, date of most recent visit, HIV exposure category, hepatitis B and C status and date of death.
2. Immunology and virology: CD4 and HIV viral load counts.
3. AIDS defining illness: Antiretroviral treatment uptake (including reasons for stopping therapy).
4. Opportunistic infection prophylaxis.

All data are subject to standardized quality control procedures.

Definitions

TI was defined by ART cessation for at least 30 days for any reason and subsequent recommencement. TIs of <30 days duration were excluded as short interruptions are common, sometimes unavoidable (for example, after side-effects), less likely to be accurately recorded in databases, and less likely to result in increased plasma HIV viral load and so to HIV transmission.²⁷ LTFU was defined by any participant starting ART in the study period with last recorded site visit prior to March 31, 2009 and no record of death. For pre-2006 LTFU rates, LTFU included any participant starting ART in the study period prior to December 31, 2005 with last recorded site visit prior to December 31, 2005 and no record of death. For post-2006 LTFU rates, LTFU included any participant starting ART after December 31, 2005 with last recorded site visit prior to March 31, 2009 and no record of death.

Time on ART was defined by the difference between the date ART commenced and the patient's last visit date. Chronic infection with hepatitis B and C were determined by the presence of hepatitis B surface antigen and hepatitis C antibody, respectively. Patients were assumed to be co-infected for the duration of follow-up.

Combination ART generally includes two nucleoside analogue reverse transcriptase inhibitors (NRTIs) and one non-nucleoside analogue RTI (NNRTI), or one protease inhibitor, an integrase inhibitor or, rarely, a third NRTI. We grouped antiretroviral drugs by the type of dual-NRTI backbone, and by the type of third drug. ART complexity was described using three factors: number of pills per days; number of doses per day; and, food intake requirements (any drug required to be taken with food or when fasting or no such requirement). ART information was sourced from pharmaceutical product label inserts, and related to the current ART recommendations.

Analysis

All adults commencing ART from January 1, 2000 to March 31, 2010 with at least one clinical visit post-ART initiation were included. Frequency tables were produced for all categorical baseline characteristics. For continuous baseline characteristics, the median and interquartile ranges (IQRs) were reported. We assessed the proportion of patients on ART experiencing none, one, two, or more TIs during 2000–2010,

and the duration of all TIs. Two major comparisons were made; AHOD versus TAHOD, and before 2006 versus 2006–2010. Unless stated, results represent combined data from both cohorts.

The CD4+ lymphocyte count and viral load of participants during the first TI (after stopping ART, within 360 days of re-starting, and >24 weeks after commencing ART) were compared to the CD4+ lymphocyte counts and viral loads prior to the first TI (<360 days prior to interruption, and >24 weeks after commencing ART) and before commencing ART (within 360 days before commencing ART).

We used viral load categories of <400, 400–10,000 and >10,000 copies/mL, with <400 copies/mL reflecting undetectable levels,²⁸ and >10,000 copies/mL a high level of infectiousness.²⁹ Several studies have suggested that each 1.0 log₁₀ increment in viral load corresponds to a near twofold or greater risk of viral transmission through heterosexual contact.²⁹ CD4+ lymphocyte counts were categorized into: <200, 200–499, and 500+ cells/ μ L.²⁸

We also estimated the proportion of potential time on ART during which any patient was LTFU by dividing the numerator (last possible study date minus the date of censoring or loss to follow up) by the observed follow-up time in the study plus the numerator.

Standard survival analysis methods including Kaplan-Meier estimates and random effects were used. Poisson regression models were used to analyze the rates of TI and LTFU, and determinants of the first TI in 2000–2010 and also from 2006. The following factors were included in the model: cohort (AHOD, TAHOD), follow-up period (from 2006, pre-2006), demographics, HIV exposure category, CD4+ count, viral load, ART (duration, NRTI backbone category, third drug, pills per day, doses per day, dosing relative to food), and co-infection (hepatitis B surface antigen, hepatitis C antibody status). Chronic hepatitis indicators were included in the model as HIV TIs in co-infected patients may potentially result in liver disease flares and rapid liver disease progression.^{30,31}

For the estimation of TI incidence before 2006, we censored follow-up at December 31, 2005, and in the period from 2006 we censored at March 31, 2010. Risk factors for LTFU were not calculated as they had been already been determined recently using TAHOD data.³²

For comparison between <2006 and from 2006, we used a rank-sum test for continuous variables, *t*-test for proportions, and Mantel-Cox rate ratio for TI and LTFU rates.

All analyses were carried out using Stata version 10.0 (Stata Corp LP, College Station, TX, United States).

Results

Patient characteristics

There were 4689 patients in the two cohorts combined who commenced ART for the first time and subsequently followed for a median 4.4 years [interquartile range (IQR): 2.1–6.5]; 75.5% were men (Table 1). In AHOD, 961 patients (94.1% men) were included with median follow-up of 3.8 years (IQR 1.6–6.6). In TAHOD, 3728 patients (70.7% men) were included with median follow-up of 4.4 years (2.1–6.4).

The most common dual-NRTI backbones in AHOD participants were ZDV-3TC and TDF-FTC, with 33% and 29% commencing ART with these drugs, respectively. In TAHOD, the most common dual-NRTI backbones were ZDV-3TC

(40%) and d4T-3TC/FTC (44%). The most common third class drugs in AHOD were NNRTI (60%) and boosted PI (22%) and in TAHOD were NNRTI (81%) and boosted PI (11%). The least commonly used third class drugs when commencing ART was NRTI (1.5%), NNRTI+PI +NRTI (1.2%), and Integrase (0.4%), with higher use by AHOD than TAHOD participants (Table 1). NRTI use as a third drug use declined over time; 9% pre 2006 to 4% from 2006 (AHOD), and 1.0% pre 2006 to 0% from 2006 (TAHOD).

Frequency and duration of TIs

Overall, 566 patients (12.1%) had 770 TIs: 434 (9.3%) had 1 TI, and 132 (2.8%) had ≥ 2 TIs, and the median time to the first TI was 0.9 years (IQR 0.3–2.2) and 2.6 years (1.4–4.2) to the second TI. The median TI duration was 163 days pre-2006 (IQR 75–391) and 118 days (IQR 67–270) from 2006 ($p < 0.01$; Table 2).

Incidence of TIs

The incidence of any TI was 3.7 per 100 person years (PY) (95% CI 3.5–4.0) over the entire study period: 6.7 per 100 person years (PY) (95% CI 6.1–7.3) pre-2006, falling to 2.0 per 100 PY (95% CI 1.7–2.2) from 2006 ($p < 0.01$; Table 3). In AHOD, the TI incidence was 11.7 per 100 PY (95% CI 10.2–13.5) pre-2006, falling to 3.5 per 100 PY (95% CI 2.8–4.4) from 2006 ($p < 0.01$). In TAHOD, the TI incidence was 5.3 per 100 PY (95% CI 4.7–5.9) in pre-2006, decreasing to 1.6 per 100 PY (95% CI 1.4–1.9) from 2006 ($p < 0.01$).

LTFU rate

The LTFU rate was 3.5 per 100 PY (95% CI 3.1–3.9) pre-2006 and 4.1 per 100 PY (95% CI 3.5–4.9) from 2006 ($p = 0.22$). In AHOD, the LTFU rate was 3.8 per 100 PY (95% CI 2.9–4.8) pre-2006 and 3.9 per 100 PY (95% CI 2.7–5.6) from 2006 ($p = 0.77$). In TAHOD, the LTFU rate was 3.4 per 100 PY (95% CI 2.9–3.9) in pre-2006 and 4.2 per 100 PY (95% CI 3.4–5.1) from 2006 ($p = 0.21$).

Follow-up time associated with any TIs and LTFU

TIs comprised 3.1% of total PY of follow-up (6.4% of follow up time pre-2006, and 1.2% from 2006, $p < 0.01$). In AHOD, TIs comprised 7.1% of total PY of follow-up (14.9% pre-2006 and 2.0% from 2006, $p < 0.01$). In TAHOD, TIs comprised 2.1% of total PY of follow-up (4.1% pre-2006 and 1.0% from 2006, $p < 0.01$).

LTFU comprised 4.7% of potential follow-up on ART pre-2006, and 6.6% from 2006. In AHOD, LTFU comprised 5.4% potential follow-up on ART pre-2006 and 5.7% from 2006. In TAHOD, LTFU comprised 4.6% of potential follow-up on ART pre-2006 and 6.9% from 2006.

CD4+ lymphocyte count and viral load during the first TI, prior to the first TI and before commencing ART

Among those experiencing their first TI, viral load and CD4 count measurements were available for a subset of patients at the three time periods of interest (before ART commencement, prior to the first TI, and during the first TI); in AHOD (viral load: 87%, 51%, 76%, CD4 count: 88%, 53%, 77%) and TAHOD (viral load: 35%, 31%, 30%, CD4 count: 74%, 45%, 57%), respectively.

TABLE 1. PATIENT CHARACTERISTICS

Characteristics	All N = 4689 n (%)	AHOD N = 961 n (%)	TAHOD N = 3,728 n (%)	Chi-2 p value ^c
<i>Patient</i>				
Age ^a				
Median (IQR)	37 (32,44)	41 (35,48)	36 (31,43)	<0.01
Sex				
Male ^b	3538 (75.5)	904 (94.1)	2634 (70.7)	<0.01
Female	1151 (24.5)	57 (5.9)	1094 (29.4)	
HIV exposure				
Heterosexual	2645 (56.4)	132 (13.7)	2513 (67.4)	<0.01
MSM	1307 (27.9)	661 (68.8)	646 (17.3)	
MSM + IDU	35 (0.8)	31 (3.2)	4 (0.1)	
IDU	276 (5.9)	15 (1.6)	261 (7.0)	
Other/unknown	426 (9.1)	122 (12.7)	304 (8.2)	
AIDS during cohort period				
Yes	2534 (54.0)	156 (16.2)	2378 (63.8)	<0.01
No	2155 (46.0)	805 (83.77)	1350 (36.2)	
CD4 count ^a (cells/ul) (n = 3886)				
Median (IQR)	149 (50–255)	290 (179–448)	116 (40–217)	<0.01
HIV viral load ¹ copies/mL (n = 2288)				
Median (IQR)	64,706 (366–231,000)	48,000 (1990–126,000)	70,000 (5490–283,000)	<0.01
HBV surface antigen positive				
Yes	283 (6.0)	33 (3.4)	250 (6.7)	<0.01
No/not tested	4406 (94.0)	928 (96.6)	3478 (93.3)	
HCV antibody positive				
Ever positive	404 (8.6)	77 (8.0)	327 (8.8)	<0.01
No/not tested	4285 (91.4)	884 (92.0)	3401 (91.2)	
<i>Antiretroviral therapy</i>				
NRTI backbone ^a				
ZDV-3TC	1789 (38.2)	314 (32.7)	1475 (39.6)	<0.01
d4T-3TC/FTC	1703 (36.3)	61 (6.4)	1642 (44.1)	<0.01
TDF-FTC	356 (7.6)	274 (28.5)	82 (2.2)	<0.01
d4T-ddl	262 (5.6)	47 (4.9)	215 (5.8)	0.29
ABC-3TC	227 (4.8)	146 (15.2)	81 (2.2)	<0.01
Other + ddl	191 (4.1)	42 (4.4)	149 (4.0)	0.60
TDF-3TC	139 (3.0)	66 (6.9)	73 (2.0)	<0.01
Third class drug ^a				
NNRTI	3600 (76.8)	572 (59.5)	328 (81.2)	<0.01
Boosted PI	633 (13.5)	210 (21.9)	423 (11.3)	
Unboosted PI	296 (6.3)	60 (6.2)	236 (6.3)	
NRTI	71 (1.5)	57 (5.9)	14 (0.4)	
NNRTI + PI + NRTI	57 (1.2)	36 (3.8)	21 (0.6)	
Integrase	19 (0.4)	15 (1.6)	4 (0.1)	
Other – HAART	13 (0.3)	11 (1.1)	2 (0.05)	
ARV pills per day ^a				
Mean, SD	4.8 (2)	4.5 (3)	4.9 (2)	<0.01
ARV doses per day ^a				
Mean, SD	4.3 (1)	3.6 (1)	4.4 (1)	<0.01
ARV food restriction ^a				
Fasting or with food only	1788 (38.1)	494 (51.4)	1294 (34.7)	<0.01
No restriction	2901 (61.9)	467 (48.6)	2434 (65.3)	
Time on ART (years)				
<2	1054 (22.5)	262 (27.3)	792 (21.2)	<0.01
2–3	1062 (22.6)	220 (22.9)	842 (22.6)	
4–5	1105 (23.6)	174 (18.1)	931 (25.0)	
≥6	1468 (31.3)	305 (31.7)	1163 (31.2)	

(continued)

TABLE 1. (CONTINUED)

Characteristics	All N = 4689 n (%)	AHOD N = 961 n (%)	TAHOD N = 3,728 n (%)	Chi-2 p value ^c
Year commenced ART				
2000–2001	681 (14.5)	224 (23.3)	457 (12.3)	<0.01
2002–2003	1321 (28.2)	178 (18.5)	1143 (30.7)	
2004–2005	1158 (24.7)	161 (16.8)	997 (26.7)	
2006–2007	825 (17.6)	184 (19.2)	641 (17.2)	
2008–2010	704 (15.0)	214 (22.3)	490 (13.1)	
Treatment interruption frequency				
0	4123 (87.9)	781 (81.3)	3342 (89.7)	<0.01
1	434 (9.3)	124 (12.9)	310 (8.3)	
2	89 (1.9)	33 (3.4)	56 (1.5)	
≥3	43 (0.9)	23 (2.4)	20 (0.5)	

^aWhen commenced ART, ^bincludes 7 reported as transgender, ^cAHOD versus TAHOD.

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, combination antiretroviral therapy; d4T, stavudine; ddI, didanosine; FTC, emtricitabine; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, injecting drug use; IQR, inter-quartile range; MSM, men who have sex with men; NNRTI, non-nucleoside analogue reverse transcriptase inhibitor; NRTI, nucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation; TDF, tenofovir; ZDV, zidovudine.

Among those who had a TI and for whom viral load measurements were available, 74.1% had a viral load of >10,000 copies/mL during the TI, higher than the 13.6% before the first TI ($p < 0.01$), and comparable to the 76.6% before ART commencement ($p = 0.36$). A similar pattern was observed in both AHOD and TAHOD (Fig. 1). Among those who had a TI and for whom CD4 count measurements were available, 45.5% had a CD4 count of <200 cells/ μ L during the TI, significantly higher than the 21.4% before the first TI ($p < 0.01$), and significantly lower than the 62.7% before ART commencement ($p < 0.01$). A similar pattern was observed in both AHOD and TAHOD, although in TAHOD a higher percent (71.6%) had a CD4 count of <200 cells/ μ L before ART commencement, compared with 30.2% in AHOD (Fig. 2).

Predictors of TIs

Factors associated with increased risk of a first TI in univariate analysis were: initiating ART pre-2006; male sex; participants in the AHOD cohort; HIV risk category being recorded as men who have sex with men or other/unknown exposure; ART including stavudine-didanosine (d4T-ddI), or any regimen containing didanosine; ART not including an NNRTI as the third agent; taking 7 or more pills per day compared with 1–2; ART with food restrictions (fasting or with food); the CD4 count before ART commencement being >200 cells/ μ L; and hepatitis C co-infection (Table 4). Factors associated with a decreased risk of first TI were: co-infection with HBV; and commencing ART with tenofovir/emtricitabine (TDF-FTC).

TABLE 2. DURATION OF TREATMENT INTERRUPTIONS BY TIME PERIOD AND COHORT

Time period	Time period (days)	Both cohorts		AHOD cohort		TAHOD cohort		Chi-2 p value ^c
		n	%	n	%	n	%	
2000–2010	30–179	425	55.2	144	51.3	281	57.5	0.24
	180–364	146	19.0	57	20.3	89	18.2	
	≥365	199	25.8	80	28.5	119	24.3	
	Any	770	100.0	281	100.0	489	100.0	
	Median, IQR	152 (73–367)		169 (78–419)		146 (67–358)		0.02 ^b
pre-2006	30–179	315	52.4	100	46.5	215	55.7	0.07
	180–364	118	19.6	44	20.6	74	19.2	
	≥365	168	28.0	71	33.0	97	25.1	
	Any	601	100.0	215	100.0	386	100.0	
	Median, IQR	163 (75–391)		197 (84–599)		153 (66–365)		$p < 0.01^b$
from 2006	30–179	110	65.1	44	66.7	66	64.1	0.37
	180–364	28	16.6	13	19.7	15	14.6	
	≥365	31	18.3	9	13.6	22	21.4	
	Any	169	100.0	66	100.0	103	100.0	
	Median, IQR	118 (67–270)		119 (67–223)		112 (67–328)		0.90 ^b
p Value ^a		<0.01 ^b		<0.01 ^b		<0.01 ^b		

^apre-2006 versus 2006; ^brank sum test; ^cAHOD versus TAHOD.
IQR, inter-quartile range.

TABLE 3. TREATMENT INTERRUPTION AND LOSS TO FOLLOW-UP RATES BY TIME PERIOD AND COHORT

Outcome	Time-frame	Person-years at risk	Both cohorts		AHOD cohort		TAHOD cohort	
			n	Incidence per 100 PY (95% CI)	n	Incidence per 100 PY (95% CI)	n	Incidence per 100 PY (95% CI)
TI	2000–2010	20594	770	3.7 (3.5–4.0)	281	6.9 (6.2–7.8)	489	3.0 (2.7–3.2)
	pre-2006	7793	519	6.7 (6.1–7.3)	197	11.7 (10.2–13.5)	322	5.3 (4.7–5.9)
	from 2006	12793	251	2.0 (1.7–2.2)	84	3.5 (2.8–4.4)	167	1.6 (1.4–1.9)
	<i>p</i> value ^a			<0.01		<0.01		<0.01
LTFU	2000–2010	20594	910	4.4 (4.1–4.7)	186	4.6 (4.0–5.3)	724	4.4 (4.1–4.7)
	pre-2006	7793	272	3.5 (3.1–3.9)	63	3.8 (2.9–4.8)	209	3.4 (2.9–3.9)
	from 2006	3033	125	4.1 (3.5–4.9)	28	3.9 (2.7–5.6)	97	4.2 (3.4–5.1)
	<i>p</i> value ^a			0.22		0.77		0.21

^apre-2006 versus from 2006 rates compared using Mantel-Cox rate ratio significance test.
LTFU, loss to follow-up; PY, person years; TI, treatment interruption.

In the multivariate model, independent predictors of increased risk of a first TI were: participant in AHOD; ART initiation before 2006; d4T-ddl as the dual-NRTI backbone; taking 7 or more pills per day; ART with food restrictions (fasting or with food); and ART with a NRTI as the third agent. Factors associated with a decreased risk of first TI were the HIV risk category recorded as men who have sex with men.

When restricted to the period from 2006, independent predictors of the first TI were: participants in AHOD [adjusted hazard ratio (AHR) 3.60, 95% CI 1.88–6.73]; commencing ART with d4T-ddl (AHR 77.75, 95% CI 9.74–620.13); taking 3–6 pills per day (AHR 3.12, 95% CI 1.14–8.55), or 7 or more pills per day (AHR 4.21, 95% CI 1.20–14.80); taking ART with food restrictions (AHR 2.77, 95% CI 1.52–5.09); and commencing ART with a NRTI as the third agent (AHR 84.58, 95% CI 36.72–194.82).

Discussion

Our analysis represents the first estimates comparing the TI and LTFU rates in the eras before and after recommendations resulting from the SMART study. Post 2006 LTFU was more

common than TI (4.1% vs. 2.0% per year, respectively) and more importantly affected a far greater possible duration of ART than TI (6.6% and 1.2%, respectively). During the TIs (and presumably during LTFU), HIV viral load rebounded to a level comparable to that before commencing ART.

An outcome that would compromise the ‘test and treat’ policy is transient or permanent treatment interruption (TI). Since 2006, the LTFU rate was 4.1% per year (3.9% in AHOD and 4.2% in TAHOD). The LTFU rate is of concern as since 2006 LTFU has equated to 6.6% of potential follow-up on ART. A recent analysis of TAHOD data demonstrated that patients with shorter HIV infection history, poorer response to antiretroviral treatment, and infrequent or no clinical monitoring were at higher risk of LTFU,³² and thus are a group that warrant additional support to prevent LTFU.

The greatest concern about treatment interruption or cessation in relation to the ‘test and treat’ policy is that during the break viral load will typically increase to pre-ART levels in 4 weeks, and so increase the risk of transmission. Since 2006, about three-quarters of participants had an HIV viral load >10,000 copies/mL during the TI after being off ART for an average duration of 4 months. Many studies have

FIG. 1. Viral load results when commencing ART, pre TI, and during TI, 2000–2010 (among those who had at least one interruption), by cohort.

FIG. 2. CD4 count when commencing ART, pre TI, and during TI, 2000–2010 (among those who had at least one interruption), by cohort.

demonstrated a direct correlation between HIV viral load and probability of transmission.^{33,34} Thus, if unprotected sex occurred during the TI (or LTFU period), the risk of HIV transmission would be greatly increased. Non-adherence has been associated with greater number of sex partners and engaging in unprotected anal intercourse in some but not all studies.^{35,36} In addition to the increasing viral load, just under 50% patient had a CD4 count <200 cells/ μ L during the TI, placing these patients at increased risk of AIDS-defining illness. The drop in CD4 count and rebound in viral load seen here are consistent with other studies.³⁷

We found people in Australia participating in AHOD were more likely to have a TI than people participating in Asia in TAHOD. A possible reason for this is that in many TAHOD countries, patients often start ART with a CD4 count of <200 cells/ μ L, and thus are more likely to be unwell and so perhaps more inclined to remain on ART. This is supported in our analysis by a lower median CD4 count at baseline in TAHOD than AHOD (116 vs. 290 cells/ μ L), and in the univariate analysis a CD4 count of >200 cells/ μ L was a significant predictor of the first TI, or conversely a CD4 count of $\leq$ 200 cells/ μ L was associated with a decreased risk of first TI. It may also reflect differences in patient autonomy in different cultures. Further research is needed to investigate these differences observed.

When rolling out of the 'test and treat' policy, there will need to be a detailed understanding of the extent of the interruptions and cessations, but also the underlying reasons for these outcomes. In our analysis we found many of the factors associated with TI are related to ART side-effect profile and complexity (pills per day, doses per day, food requirements). The multivariate analysis also showed triple-NRTI ART was a significant predictor of TI, most likely due to these regimens being less virologically potent, toxicity, or tolerance issues.^{38–40} However, only a small proportion of people in AHOD and TAHOD were started on this regime before 2006, and less so from 2006, and many would have switched to a different regimen,⁴¹ so this finding may be less relevant now. The multivariate analysis also showed regimens involving 3–6, or 7+ pills per days and ART recommended to be taken either with food or fasting were

associated with TI. These findings are consistent with self-reported data from surveys in Australian gay men⁴² and a recent systematic review including 70 studies from low, middle, and high income countries.³⁷ Collectively, these studies emphasise that prescribing regimens that are simple to take, have a low pill burden and frequency of dosing, have no food requirements, and have low incidence and severity of adverse effects will facilitate adherence.

Other reasons for TIs identified in studies include poor/current health, mental health, alcohol/party drug use, attitudes to treatment, health service injecting drug use, CD4 count, socioeconomic variables, pharmacy stock outs, and treatment costs.^{37,42} Also qualitative studies among marginalized patient population in the Bronx, New York found multiple determinants influenced retention in HIV care such as acceptance of diagnosis, stigma, HIV cognitive/physical impairments, and global constructs of self-care.⁴³

There is a growing menu of possible interventions that have demonstrated adherence efficacy such as adherence support groups, peer adherence counselors, behavioral interventions, cognitive-behavioral and reminder strategies, and use of community-based case managers and peer educators.^{44–46} Also, as HIV testing coverage is scaled up in response to 'test and treat', programs have been established to ensure strong linkages with HIV care services. In the US, emergency department clinicians incorporated HIV diagnostic testing into their routine work and dedicated staff linked 90% of newly diagnosed cases and out-of-care HIV-infected patients into HIV care services.⁴⁷

The strengths of this study are that the overall large sample size, follow-up time, and multiple countries. There are also possible limitations. First, patients in the cohorts may not be representative of all patients with HIV infection on ART and patients perceived likely to be adherent could be selectively recruited to ART in some settings. Second, we did not obtain the patient or physician reported reasons for interrupting ART to confirm if the TI was CD4-count guided (structured) or not. Third, HIV viral loads were missing from a large proportion of TAHOD participants as it was not routinely conducted in many participating TAHOD sites. Also some participants did not have CD4 counts and viral loads at all the

TABLE 4. PREDICTORS OF FIRST TREATMENT INTERRUPTION, 2000–2010

		PY at risk	TI (n)	TI incidence / 100 PY (95% CI)	Univariate		Multivariate	
Breakdown					Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
General Cohort								
	TAHOD	14966	386	2.6 (2.3,2.8)	1			
	AHOD	3156	180	5.7 (5.0,6.6)	2.53 (2.05,3.11)	<0.01	2.75 (2.08–3.64)	<0.01
Follow-up period		2006+	6008	90	1.5 (1.2,1.8)	1		
	pre-2006	12114	476	3.9 (3.6,4.2)	2.33 (1.93,2.81)	<0.01	1.88 (1.54–2.30)	<0.01
Patient								
Age (years)		<30	2822	96	3.4 (2.8,4.2)	1		
	30–39	8006	269	3.4 (3.0,3.8)	1.03 (0.79,1.35)	0.82		
	40+	7294	201	2.8 (2.4,3.2)	0.80 (0.61,1.06)	0.12		
Sex		Female	4623	112	2.4 (2.0,3.0)	1		
	Male	13499	454	3.4 (3.1,3.7)	1.52 (1.19,1.92)	<0.01		
HIV exposure category		Heterosexual	11185	304	2.7 (2.4,3.0)	1		
	MSM + IDU	89	9	10.1 (5.2,19.4)	5.81 (2.56,13.19)	<0.01	1.48 (0.64–3.38)	0.36
	IDU	634	28	4.4 (3.0,6.4)	1.32 (0.85,2.08)	0.22	1.32 (0.81–2.15)	0.26
	MSM	4818	184	3.8 (3.3,–4.4)	1.44 (1.16,1.79)	<0.01	0.59 (0.44–0.78)	<0.01
	Other/ unknown	1396	41	2.9 (2.2,4.0)	1.41 (1.00,1.99)	0.05	0.83 (0.57–1.19)	0.31
CD4 count cells/ μ L) ^a		≤200	9656	250	2.6 (2.3,2.9)	1		
	>200	5033	209	4.1 (3.6,4.7)	1.49 (1.20,1.86)	<0.01	1.23 (0.97–1.55)	0.09
	Missing	3412	107	3.1 (2.6,3.8)	1.19 (0.91,1.54)	0.20	1.04 (0.80–1.36)	0.78
Viral load copies/mL plasma ^a		<400	1486	43	2.9 (2.1,3.9)	1		
	400–10,000	1129	48	4.2 (3.2,5.6)	1.54 (0.93,2.55)	0.09		
	>10,000	6250	224	3.6 (3.1,4.1)	1.37 (0.94,2.02)	0.11		
	missing	9256	251	2.7 (2.4,3.1)	1.01 (0.70,1.49)	0.92		
HBV surface antigen		No/not tested	16862	543	3.2 (3.0,3.5)	1		
	Ever positive	1260	23	1.8 (1.2,2.7)	0.63 (0.41,0.98)	0.04		
Hepatitis C antibody		No/not tested	16971	518	3.1 (2.8,3.3)	1		
	Ever positive	1150	48	4.2 (3.1,5.5)	1.49 (1.06–2.1)	0.02		
Antiretroviral therapy								
Duration (years)		≤2	1028	38	3.7 (2.7,5.1)	1		
	3	2924	95	3.2 (2.7,4.0)	0.98 (0.66,1.5)	0.91		
	4+	14170	433	3.1 (2.8,3.4)	0.98 (0.69,1.4)	0.89		
NRTI backbone category ^a		TDF-FTC	1502	19	1.3 (1.0,2.0)	0.44 (0.31,0.64)	<0.01	
	ZDV-3TC	7635	231	3.0 (2.7,3.4)	1.06 (0.89,1.30)	0.49		
	d4T-3TC/FTC	5023	140	2.8 (2.4,3.3)	0.85 (0.69–1.03)	0.10		
	d4T-ddl	614	52	8.5 (6.4,0.11)	2.7 (2.00–3.80)	<0.01	1.56 (1.11,2.19)	0.01
	TDF-3TC	676	25	3.7 (2.5,5.5)	1.11 (0.78,1.57)	0.56		
	ABC-3TC	1088	26	2.4 (1.6,3.5)	0.76 (0.54,1.1)	0.11		
	Other ddl	1126	51	4.5 (3.4,6.0)	1.57 (1.20–2.10)	<0.01		
Third drug ^a		NNRTI	13404	321	2.4 (2.1,2.7)	1		
	Boosted PI	2769	112	4.0 (3.4,4.9)	1.80 (1.45,2.22)	<0.01	0.92 (0.68,1.22)	0.56
	Unboosted PI	935	46	5.0 (3.7,6.6)	1.94 (1.38,2.75)	<0.01	0.86 (0.57,1.28)	0.45
	NRTI	358	49	13.7 (10.3,18.1)	9.84 (6.80,14.26)	<0.01	5.96 (3.96,8.98)	<0.01
	NNRTI + PI	224	10	4.5 (2.4,8.3)	1.37 (0.70,2.71)		0.50 (0.24,1.01)	0.06
	Other/integrase	431	28	6.5 (4.5,9.4)	2.29 (1.60,3.27)		1.30 (0.88,1.92)	0.19
Pills per day ^a		1–3	915	29	3.2 (2.2,4.6)	1		
	3–6	11458	327	2.9 (2.6,3.2)	0.84 (0.59,1.21)	0.35	1.54 (0.97,2.43)	0.07
	7+	1970	116	5.9 (4.9,7.1)	1.70 (1.15,2.52)	<0.01	2.18 (1.27,3.75)	0.01
Doses per day ^a		1	2413	49	2.0 (1.5,2.7)	1		
	2+	15697	517	3.3 (3.0,3.6)	1.45 (1.13,1.86)	0.03	1.25 (0.93,1.70)	0.15
Dosing relative to food ^a		No restriction	10756	184	1.7 (1.5,2.0)	1		
	Fasting/with food	7366	382	5.2 (4.7,5.7)	3.53 (2.91,4.29)	<0.01	3.18 (2.49,4.07)	<0.01

^aWhen commenced ART.

3TC, lamivudine; ABC, abacavir; AHR, adjusted hazard ratio; ART, combination antiretroviral therapy; CI, confidence interval; d4T, stavudine; ddI, didanosine; FTC, emtricitabine; HR, hazard ratio; IDU, injecting drug use; MSM, men who have sex with men; NNRTI, non-nucleoside analogue reverse transcriptase inhibitor; NRTI, nucleoside analogue reverse transcriptase inhibitor; PI, protease inhibitor; PY, person years; TDF, tenofovir; ZDV, zidovudine.

three intervals of interest (commencement of ART, prior to TI, and during TI, or when re-starting), which may have biased the findings in ways we cannot ascertain. We included viral load or CD4 counts anytime during the TI or when re-starting, thus if the viral load was in the first few weeks of the TI, this would not reflect the peak viral load during the TI. Fourteen percent of those interrupting ART had viral loads >10,000 copies/mL prior to stopping, suggesting that some patients had already stopped or were non-adherent to medication when their treatment officially ceased, thus viral loads prior to TI may be over-estimated. Finally, people who inject drugs are under-recruited in TAHOD. Assuming these patients are less likely to be in regular care, this may have underestimated the TI and LTFU rates in this population.

In conclusion, despite strong recommendations that ART be continuous, TIs have occurred in 2% of patients per year since 2006, and last 4 months on average, with an additional 4.1% of patient per year LTFU, such that an additional 7.8% of ART exposure is lost. If the test and treat prevention strategy rolls out, adherence and retention strategies will need to be strengthened.

Acknowledgments

The writing committee would like to acknowledge several thousands of patients, the TAHOD Steering Committee [The TREAT Asia HIV Observational Database: CV Mean, V Saphonn,* and K Vohith, National Center for HIV/AIDS, Dermatology & STDs, Phnom Penh, Cambodia; 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; N Kumarasamy,* S Saghayam, and C Ezhilarasi, YRG Centre for AIDS Research and Education, Chennai, India; S Pujari,* K Joshi, and A Makane, Institute of Infectious Diseases, Pune, India; TP Merati*, DN Wirawan, and F Yuliana, Faculty of Medicine Udayana University and Sanglah Hospital, Bali, Indonesia; E Yuniastuti,* D Imran, and A Widhani, Working Group on AIDS Faculty of Medicine, University of Indonesia/ Ciptomangunkusumo Hospital, Jakarta, Indonesia; S Oka,* J Tanuma, and T Nishijima, National Center for Global Health and Medicine, Tokyo, Japan; JY Choi,* SH Han, and JM Kim, Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; CKC Lee,* BHL Sim, and R David, Hospital Sungai Buloh, Kuala Lumpur, Malaysia; A Kamarulzaman,*† and A Kajindran, University of Malaya Medical Centre, Kuala Lumpur, Malaysia; R Ditangco,* E Uy, and R Bantique, Research Institute for Tropical Medicine, Manila, Philippines; YMA Chen,* WW Wong, and LH Kuo, Taipei Veterans General Hospital and AIDS Prevention and Research Centre, National Yang-Ming University, Taipei, Taiwan; OT Ng,* A Chua, LS Lee, and A Loh, Tan Tock Seng Hospital, Singapore; P Phanuphak,* K Ruxrungtham, and M Khongphattananayothin, HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand; S Kiertiburanakul,*‡ S Sungkanuparph, and N Sanmeema, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; T Sirisanthana,* R Chaiwarith, and W Kotarathitum, Research Institute for Health Sciences, Chiang Mai, Thailand; 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; AH Sohn,* N Durier,* and B Petersen, TREAT Asia, amfAR–The Foundation for AIDS Research, Bangkok, Thailand; DA Cooper,* MG Law,* and A Jiamsakul, The Kirby Institute, The University of New South Wales, Sydney, Australia. *TAHOD Steering Committee member; †Steering Committee Chair; ‡co-Chair. TAHOD reviewers: PCK Li, MP Lee, S Vanar, S Faridah, A Kamarulzaman, JY Choi, B Vannary, R Ditangco, K Tsukada, SH Han, FJ Zhang, YMA Chen, N Kumarasamy, A Dravid, OT Ng, C Duncombe, S Sungkanuparph, T Sirisanthana. Independent reviewer: M Boyd] and the AHOD Steering Committee [The Australian HIV Observational Database: D Ellis, General Medical Practice, Coffs Harbour, NSW; M Bloch, T Franic,* S Agrawal, T Vincent, Holdsworth House General Practice, Darlinghurst, NSW; R Moore, S Edwards, R Liddle, Northside Clinic, North Fitzroy, VIC; D Nolan, J Robinson, J Skett, Department of Clinical Immunology, Royal Perth Hospital, Perth, WA; NJ Roth,*† J Nicolson,* Pahrnan Market Clinic, South Yarra, VIC; D Allen, JL Little Holden Street Clinic, Gosford, NSW; D Smith, C Gray Lismore Sexual Health & AIDS Services, Lismore, NSW; D Baker,* R Vale, East Sydney Doctors, Darlinghurst, NSW; D Russell, S Downing, Cairns Sexual Health Service, Cairns, QLD; D Templeton,* C O'Connor, C Dijanosic, Royal Prince Alfred Hospital Sexual Health, Camperdown, NSW; D Sowden, K McGill, Clinic 87, Sunshine Coast and Cooloola HIV Sexual Health Service, Nambour, QLD; D Orth; D Youds, Gladstone Road Medical Centre, Highgate Hill, QLD; E Jackson, K McCallum, Blue Mountains Sexual Health and HIV Clinic, Katoomba, NSW; T Read, J Silvers,* Melbourne Sexual Health Centre, Melbourne, VIC; A Kulatunga, P Knibbs, Communicable Disease Centre, Royal Darwin Hospital, Darwin, NT; J Hoy,* K Watson,* M Bryant, S Price, The Alfred Hospital, Melbourne, VIC; M Grotowski, S Taylor, Tamworth Sexual Health Service, Tamworth, NSW; D Cooper, A Carr, K Hesse, K Sinn, R Norris, St Vincent's Hospital, Darlinghurst, NSW; R Finlayson, I Prone, Taylor Square Private Clinic, Darlinghurst, NSW; E Jackson, J Shakeshaft, Nepean Sexual Health and HIV Clinic, Penrith, NSW; M Kelly, A Gibson, H Magon, Sexual Health & HIV Service, Brisbane, QLD; K Brown, V McGrath, Illawarra Sexual Health Clinic, Warrawong, NSW; L Wray, P Read, H Lu, Sydney Sexual Health Centre, Sydney, NSW; W Donohue, The Care and Prevention Programme, Adelaide University, Adelaide, SA; I Woolley, M Giles, A Gillies, T Korman, Monash Medical Centre, Clayton, VIC; J Watson,* National Association of People Living with HIV/AIDS; C Lawrence,* National Aboriginal Community Controlled Health Organisation; B Mulhall,* School of Public Health, University of Sydney, Sydney, NSW; J Chuah,* Holdsworth House Medical Practice–Bryon Bay, NSW; M Law,* K Petoumenos,* H McManus,* S Wright,* C Bendall,* M Boyd,* The Kirby Institute, University of NSW, Sydney, NSW. *Steering Committee member 2011, †Current Steering Committee chair. Cause of Death (CoDE) reviewers AHOD reviewers: D Sowden, D Templeton, J Hoy, L Wray, J Chuah, K Morwood, T Read, N Roth, I Woolley, M Kelly, J Broom].

Author Disclosure Statement

No competing financial interests exist.

Funding: The TREAT Asia HIV Observational Database and the Australian HIV Observational Database are initiatives

of TREAT Asia, a program of amfAR, The Foundation for AIDS Research, with support from the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, Eunice Kennedy Shriver National Institute of Child Health and Human Development, and National Cancer Institute, as part of the International Epidemiologic Databases to Evaluate AIDS (IeDEA; U01AI069907), and the Dutch Ministry of Foreign Affairs through a partnership with Stichting Aids Fonds. The Kirby Institute is funded by the Australian Government Department of Health and Ageing, and is affiliated with the Faculty of Medicine, The University of New South Wales. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

References

- Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011;365:493–505.
- Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: A prospective cohort analysis. *Lancet* 2010;375:2092–2098.
- Wood E, Kerr T, Marshall BD, et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: Prospective cohort study. *BMJ* 2009;338:b1649.
- Das M, Chu PL, Santos G-M, et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. *PLoS One* 2010;5:e11068.
- Montaner JSG, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: A population-based study. *Lancet* 2010;376:532–539.
- INSIGHT's START trial. Available from: <http://insight.cabr.unm.edu/start/>. (Last accessed August 30, 2013).
- 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 2011;1-161. Available from: <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf> (Last accessed August 30, 2013).
- Wang D, Hicks CB, Goswami N, et al. Evolution of drug-resistant viral populations during interruption of antiretroviral therapy. *J Virol* 2011;85:6403–6415.
- El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006;355:2283–2296.
- Lawrence J, Hullsiek KH, Thackeray LM, et al. Disadvantages of structured treatment interruption persist in patients with multidrug-resistant HIV-1: Final results of the CPCRA 064 study. *J Acquir Immune Defic Syndr* 2006;43:169–178.
- Pai NP, Lawrence J, Reingold AL, Tulskey JP. Structured treatment interruptions (STI) in chronic unsuppressed HIV infection in adults. *Cochrane Database Syst Rev* 2006;3:CD006148.
- Seminari E, De Silvestri A, Boschi A, Tinelli C. CD4+ guided antiretroviral treatment interruption in HIV infection: A meta-analysis. *AIDS Rev* 2008;10:236–244.
- Taffe P, Rickenbach M, Hirschel B, et al. Impact of occasional short interruptions of HAART on the progression of HIV infection: Results from a cohort study. *AIDS* 2002;16:747–755.
- Touloumi G, Pantazis N, Antoniou A, et al. Highly active antiretroviral therapy interruption: Predictors and virological and immunologic consequences. *J Acquir Immune Defic Syndr* 2006;42:554–561.
- d'Arminio Monforte A, Lepri AC, Rezza G, et al. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. *AIDS* 2000;14:499–507.
- Kiguba R, Byakika-Tusiime J, Karamagi C, et al. Discontinuation and modification of highly active antiretroviral therapy in HIV-infected Ugandans: Prevalence and associated factors. *J Acquir Immune Defic Syndr* 2007;45:218–223.
- Kim TW, Palepu A, Cheng DM, et al. Factors associated with discontinuation of antiretroviral therapy in HIV-infected patients with alcohol problems. *AIDS Care* 2007;19:1039–1047.
- Mocroft A, Phillips AN, Soriano V, et al. Reasons for stopping antiretrovirals used in an initial highly active antiretroviral regimen: Increased incidence of stopping due to toxicity or patient/physician choice in patients with hepatitis C coinfection. *AIDS Res Hum Retroviruses* 2005;21:743–752.
- Pasquet A, Messou E, Gabillard D, et al. Impact of drug stock-outs on death and retention to care among HIV-infected patients on combination antiretroviral therapy in Abidjan, Cote d'Ivoire. *PLoS One* 2010;5:e13414.
- Boyer S, Clerc I, Bonono CR, et al. Non-adherence to antiretroviral treatment and unplanned treatment interruption among people living with HIV/AIDS in Cameroon: Individual and healthcare supply-related factors. *Soc Sci Med* 2011;72:1383–1392.
- Clark RA, Mirabelli R, Shafe J, et al. The New Orleans HIV outpatient program patient experience with Hurricane Katrina. *J La State Med Soc* 2007;159:276, 278–279, 2281.
- Das-Douglas M, Riley ED, Ragland K, et al. Implementation of the Medicare Part D prescription drug benefit is associated with antiretroviral therapy interruptions. *AIDS Behav* 2009;13:1–9.
- Pyne-Mercier LD, John-Stewart GC, Richardson BA, et al. The consequences of post-election violence on antiretroviral HIV therapy in Kenya. *AIDS Care* 2011;23:562–568.
- Rougemont M, Stoll BE, Elia N, Ngang P. Antiretroviral treatment adherence and its determinants in Sub-Saharan Africa: A prospective study at Yaounde Central Hospital, Cameroon. *AIDS Res Ther* 2009;6:21.
- Australian HIV Observational Database. Rates of combination antiretroviral treatment change in Australia, 1997–2000. *HIV Med* 2002;3:28–36.
- Zhou J, Kumarasamy N, Ditangco R, et al. The TREAT Asia HIV observational database: Baseline and retrospective data. *J Acquir Immune Defic Syndr* 2005;38:174–179.
- Steingrover R, Pogany K, Fernandez Garcia E, et al. HIV-1 viral rebound dynamics after a single treatment interruption depends on time of initiation of highly active antiretroviral therapy. *AIDS* 2008;22:1583–1588.
- Law MG, Woolley I, Templeton DJ, et al. Trends in detectable viral load by calendar year in the Australian HIV observational database. *J Int AIDS Soc* 2011;14:10.
- Modjarrad K, Chamot E, Vermund SH. Impact of small reductions in plasma HIV RNA levels on the risk of heterosexual transmission and disease progression. *AIDS* 2008;22:2179–2185.
- Liaw Y-F, Chien R-N, Yeh C-T, et al. Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif

- mutation during lamivudine therapy. *Hepatology* 1999;30: 567–572.
31. Thabut D, Thibault V, Benhamou Y, et al. Successful control of subfulminant hepatitis related to lamivudine-resistant hepatitis B virus in an HIV-infected patient. *AIDS* 2001;15: 2463–2464.
 32. Zhou J, Tanuma J, Chaiwarith R, et al. Loss to followup in HIV-infected patients from Asia-Pacific region: Results from TAHOD. *AIDS Res Treat* 2012;2012.
 33. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000;342:921–929.
 34. Sheth PM, Kovacs C, Kemal KS, et al. Persistent HIV RNA shedding in semen despite effective antiretroviral therapy. *AIDS* 2009;23:2050–2054.
 35. Burman W, Grund B, Neuhaus J, et al. Episodic antiretroviral therapy increases HIV transmission risk compared with continuous therapy: Results of a randomized controlled trial. *J Acquir Immune Defic Syndr* 2008;49:142–150.
 36. Kalichman SC, Cherry C, Amaral CM, et al. Adherence to antiretroviral therapy and HIV transmission risks: Implications for test-and-treat approaches to HIV prevention. *AIDS Patient Care STDS* 2010;24:271–277.
 37. Kranzer K, Ford N. Unstructured treatment interruption of antiretroviral therapy in clinical practice: A systematic review. *Trop Med Int Health* 2011;16:1297–1313.
 38. Barnas D, Koontz D, Bazmi H, et al. Clonal resistance analyses of HIV type-1 after failure of therapy with didanosine, lamivudine and tenofovir. *Antivir Ther* 2010;15: 437–441.
 39. Bartlett JA, Johnson J, Herrera G, et al. Long-term results of initial therapy with abacavir and lamivudine combined with efavirenz, amprenavir/ritonavir, or stavudine. *J Acquir Immune Defic Syndr* 2006;43:284–292.
 40. Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naïve subjects. *J Infect Dis* 2005;192:1921–1930.
 41. Srasuebkul P, Calmy A, Zhou J, et al. Impact of drug classes and treatment availability on the rate of antiretroviral treatment change in the TREAT Asia HIV Observational Database (TAHOD). *AIDS Res Ther* 2007;4:18.
 42. Grierson J, Koelmeyer R, Smith A, Pitts M. Independent factors associated with difficulty taking antiretroviral medication in an Australian sample of people living with HIV. 6th IAS conference on HIV Pathogenesis, Treatment And Prevention. Rome, Italy; 2011. Abstract MOPE185.
 43. Smith LR, Fisher JD, Cunningham CO, Amico KR. Understanding the behavioral determinants of retention in HIV care: A qualitative evaluation of a situated information, motivation, behavioral skills model of care initiation and maintenance. *AIDS Patient Care STDS* 2012;26:344–355.
 44. Simoni JM, Amico KR, Smith L, Nelson K. Antiretroviral adherence interventions: Translating research findings to the real world clinic. *Curr HIV/AIDS Rep* 2010;7:44–51.
 45. Pop-Eleches C, Thirumurthy H, Habyarimana JP, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: A randomized controlled trial of text message reminders. *AIDS* 2011;25:825–834.
 46. Seruma N. The role of home based care in ensuring adherence on ART among people living with HIV/AIDS in resource limited settings. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention. Rome, Italy; 2011. Abstract CDB298.
 47. Christopoulos KA, Kaplan B, Dowdy D, et al. Testing and linkage to care outcomes for a clinician-initiated rapid HIV testing program in an urban emergency department. *AIDS Patient Care STDS* 2011;25:439–444.

Address correspondence to:

Rebecca Guy

The Kirby Institute

University of New South Wales

Sydney, NSW, 2052

Australia

E-mail: Rguy@kirby.unsw.edu.au