Antiretroviral therapy initiation in an Australian cohort: implications for increased use of antiretroviral therapy

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ARTICLE

Antiretroviral therapy initiation in an Australian cohort: implications for increased use of antiretroviral therapy

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Abstract Human immunodeficiency virus (HIV) management is entering a "universal test and treat" phase, although the benefits from this approach in developed world scenarios are uncertain. We analyzed 79 combination anti-retroviral therapy (cART)-naïve HIV-positive individuals who were intensively prospectively followed from 2004 to 2013. We studied HIV-related illnesses, potential HIV transmissions, impact on sexual behavior, and factors impeding earlier cART initiation. Sixty-eight (86 %) subjects commenced cART at a mean of 6.0 years after diagnosis: 71 % with a CD4 T-cell count <350 cells/μl. A significant minority of subjects (29 %) resisted initiation of cART despite physician recommendation for a mean of 18 months. Only one HIV-related illness occurred in a patient who had not previously recorded a CD4 T-cell count <500 cell/μl, totaling 195 person-years of observation. A 40 % increase in sexually transmitted infections (STIs) occurred after commencing cART. We detected six HIV transmissions in our cohort, all of which were before initiating cART and 5 of them had a prior CD4 T-cell count <500 cells/μl. Illnesses related to cART deferral were rare and most HIV transmissions we detected occurred in people with a prior CD4 T-cell count <500 cells/μl. Our study raises concerns about increasing STI rates after cART initiation. Focusing resources on cART initiation among patients with CD4 T-cell counts <500 cells/μl and enhancing safe sexual practices should remain a priority.

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Introduction

Recommendations for commencing combination anti-retroviral therapy (cART) in asymptomatic human immunodeficiency virus (HIV)-positive subjects have evolved over the last decade [1, 2]. Successive guidelines generally raised the CD4 T-cell count at which cART should be initiated, based on incremental individual benefits of the order of one to two HIV-related events prevented for every 100 person-years of cART [1, 3].

Government-subsidized cART has long been available to Australian residents with CD4 T-cell counts <500 cells/μl, although, since 2005, the Australian HIV expert panel has endorsed U.S. Department of Health and Human Services (DHHS) guidelines [4]. These guidelines now include people with CD4 T-cell counts >500 cells/μl, although international bodies differ in the strength of their recommendations [5, 6]. Recommending universal cART is based, in part, on HPTN052 trial data [7]: "…showing that viral suppression with cART reduces HIV transmission" [5]. Therein, early initiation of cART (CD4 T-cell count of 350–550/μl) in HIV-discordant heterosexual couples residing in developing countries reduced HIV-related illnesses and prevented one HIV transmission per 62 patient-years, compared to delayed cART initiation (CD4 T-cell count <250/μl)[7]. It is unclear to what extent HPTN052 data can be extrapolated to epidemics primarily among men-who-have-sex-with-men (MSM) cohorts in developed country scenarios with CD4 T-cell counts >500 cells/μl. Furthermore, issues of behavioral disinhibition have been raised as a consequence of biological interventions to reduce HIV transmissions [8–10].

To examine these issues, we reviewed a prospectively enrolled cohort of HIV-positive cART-naïve individuals initially recruited and followed as part of another study [11]. We focused on when subjects met Australian criteria for government-subsidized cART (CD4 T-cell count <500 cells/μl) and when they actually started cART. We examined the impact of cART initiation on patient health, behavioral disinhibition, and possible relation to HIV transmission.

Methods

Characteristics of HIV-infected subjects

Between 2004 and 2008, 79 HIV-positive cART-naïve ambulatory adults were recruited through Alfred Health (Alfred Health Ethics approval numbers 248/06 and 337/12). The patient characteristics are shown in Table 1. Bias in HIV management was addressed by recruiting subjects at two sites managed by a broad range of physicians (n=14). Subjects were enrolled an average of 3.7 (0.1–19) years after the diagnosis of HIV and followed until data were censored on 31 July 2013, totaling 793.9 person-years of follow-up, including 514.4 person-years (mean 6.5 years) prior to the initiation of cART and 279.5 patient-years of follow-up after cART initiation (mean 4.1 years). We studied the clinical and laboratory parameters of HIV infection before and after the initiation of cART. Subjects remained familiar to clinicians and researchers throughout the study; other clinical services were contacted as needed. When clinical and/or laboratory parameters did not coincide exactly, proximate data were utilized. The date of HIV diagnosis was taken from the first positive Western blot (WB), except in one instance where WB was indeterminate but the subject had detectable HIV plasma RNA. HIV plasma RNA levels (viral loads) of $>10^5$ copies/ml were annotated as 100,001 copies/ml; undetectable viral loads were annotated at the level of assay detection. HIV-related illnesses were based on clinician evaluation, whilst adverse drug events were considered significant if cART was changed. The term "last follow-up" refers to the last clinical or laboratory evaluation of the subject up to 31 July 2013 or until the patient was lost to follow-up.

HIV transmissions

Probable HIV transmissions were based on interviews with the patients and/or their treating physicians and an acknowledgment by the source or recipient, or by comparison of shared mutations detected during drug resistance genotyping and not by whole genome sequencing.

Sexually transmitted infections

We searched electronic and paper records of the 75 subjects attending the Melbourne Sexual Health Centre (MSHC), focusing on attendances for STIs: gonorrhea, chlamydia, non-gonococcal urethritis, proctitis, and early syphilis. Rates were expressed as STIs acquired per year and divided into three periods: (1) prior to HIV diagnosis, (2) after HIV diagnosis but prior to commencing cART, and (3) after cART initiation.

Statistics

Linear regression analyses were performed using Prism® software. Differences in STI rates were based on crude incidence rate ratios.

Results

Summary of cohort

Overall, 79 cART-naïve subjects were recruited between 2004 to 2008, at an average of 3.7 years (range 0–19 years) after being diagnosed with HIV, and followed prospectively until 31 July 2013. The total time (including evaluation of histories) was 793.9 person-years (Table 1). Subjects were evaluated for 514.4 person-years prior to commencing cART and a further 279.5 person-years after commencing cART. Table 2 details the clinical and laboratory parameters of the cohort with respect to the commencement of cART. Only two subjects were lost to follow-up prior to the conclusion of the observation period: one moved interstate and one could not be located.

CD4 T-cell count at the initiation of cART

The mean CD4 T-cell count at cART initiation was 318 cells/μl: 48 (71 %) had a CD4 T-cell count <350 cells/μl (including ten with a CD4 T-cell count <200 cells/μl), while 14 (21 %) commenced cART in the range 350–500 cells/μl. The main reason for delayed initiation of cART (i.e., CD4 T-cell count <350 cells/μl where there is consensus that the risks for HIV-related illness is high) could broadly be described as psychosocial factors resulting in poor engagement with medical services (including psychiatric illness and illicit drug use; n=13; 27 %) and patient resistance (n=11; 23 %). Other factors included a rapid decline in CD4 T-cell count between outpatient visits (n=11; 23 %), clinician preference (n=4; 9 %), late presentation (n=3), and ineligibility for subsidized cART in Australia (lack of residency visa, n=3).

The delay in cART uptake is predicated upon numerous factors. For the 74 subjects in our group who met long-term

Table 1 Demographics of the human immunodeficiency virus (HIV) cohort

All subjects	79
Follow-up (patient-years)	479.0
Mean age at enrolment (years, range)	38 (20–64)
Risk group: men who have sex with men	65[a]
Risk group: heterosexual male	4
Risk group: heterosexual female	5
Risk group: bisexual male	2
Risk group: intravenous drug user	3
Mean CD4 T-cell count (cell/μl) at diagnosis	653 (range 189–1,800; median 571)
Mean plasma viral load (copies/ml) at diagnosis	35,546 (range 49–100,001)

[a] Some subjects had multiple risk factors

eligibility criteria for government-subsidized cART (i.e., CD4 T-cell count <500 cells/μl), the delay between becoming eligible and actually commencing cART (or study conclusion) was 318.2 person-years (average 4.3 years; range 0–16 years). Only 11 (15 %) of these 74 subjects commenced cART within 12 months of first recording a CD4 T-cell count <500 cells/μl, while 21 (28 %) commenced cART within 2 years. Excluding two patients who were lost to follow-up, 21 (29 %) resisted commencing cART despite clinician recommendation for a mean of 18 months (range 2 months to 10 years), although 17 (81 %) eventually commenced cART at a mean CD4 T-cell count of 321 cells/μl. Six (35 %) of these 17 subjects developed HIV-related illnesses: two prior to cART recommendation (herpes zoster, cutaneous Kaposi's sarcoma) and four after cART recommendation (neuralgic arm pain, oral hairy leukoplakia, esophageal candida, and herpes zoster). The four subjects who remained cART-naïve had a mean final CD4 T-cell count of 441 cells/μl; one developed troublesome oral candida which resolved with anti-fungal therapy.

"Universal test and treat" advocates initiating cART soon after HIV diagnosis. Across our cohort, 27 (34 %) of subjects had an initial CD4 T-cell count <500 cells/μl, including 8 (10 %) with CD4 T-cell count <350 cells/μl. However, the earliest initiation of cART occurred on day 73 after diagnosis and only 3 (4 %) subjects commenced cART within 1 year of diagnosis, indicating that early initiation of cART is not common. Across our subjects, the cumulative time between HIV diagnosis and recording a CD4 T-cell count above the previous government-subsidized cART initiation threshold of 500 cells/μl was 196.2 person-years.

Correlation between the initiation of cART and year

Between 19 January 2005 and 19 June 2013, 68 subjects commenced cART, including 15 for symptomatic HIV infection (Table 1), four who entered clinical trials, one subject due to high risk of transmission, and one after the diagnosis of melanoma. The remaining 48 subjects commenced cART whilst asymptomatic. Linear regression showed that, over these 8.4 years, there was a non-significant increase in the CD4 T-cell count at which asymptomatic HIV-positive subjects commenced cART (243 to 335 cells/μl; $p=0.16$).

HIV-related and other significant illnesses

Fifteen (19 %) subjects developed an HIV-related illness (Table 3) at a mean CD4 T-cell count of 338 cells/μl (range 100–571 cells/μl), all of which were mild. Only one subject had not recorded a CD4 T-cell count <500 cells/μl prior to his illness. All other symptomatic subjects had recorded a CD4 T-cell count <500 cells/μl a mean of 4.4 years prior to their illness. One patient presented with submandibular

Table 2 Comparison of subjects who did and did not commence combination anti-retroviral therapy (cART)

	Commencing cART	Not commencing cART
n	68 (86 %)	11 (14 %)
Observation (person-years)	685.3[a]	108.6
Mean time prior to commencing cART (range)	6.0 years (0.2–20.1)	9.9 years (5.1–19.2)
Mean CD4 T-cell count at diagnosis (range)	609 cells/μl (189–1,392)	924 cells/μl (486–1,800)
Mean CD4 T-cell count at initiation of cART/end study	318 cells/μl (100–831[b])	677 cells/μl (357–1,965)
Median viral load at diagnosis (range)	38,189 copies/ml (49–100,001)	19,207 copies/ml (399–100,001)
Median viral load at cART initiation/end study (range)	58,692 copies/ml[c] (100–100,001)	22,977 copies/ml (19–72,900)
Suppressed viral load (<200 copies/ml)	66 (97 %)	2 (18 %)

[a] Includes 405.8 person-years prior to commencing cART and 279.5 person-years after commencing cART

[b] One subject commenced cART at CD4 T-cell count 831 cells/μl due to entering a clinical trial

[c] 25 (37 %) subjects had viral load >100,000 copies/ml when cART was commenced

Table 3 HIV-associated illnesses and proximate CD4 T-cell count

HIV-related illness	Proximate CD4 T-cell count (cells/μl)	Time (years) from CD4 T-cell count <500 cells/μl to illness
Cytomegalovirus colitis	100	2.2
Thrombocytopenia	182	3.6
Cutaneous Kaposi's sarcoma	223	7.7
Oral hairy leukoplakia	256	3.3
Pneumocystis pneumonia	303	3.4
Neuropathic arm pain[a]	304	15.9
Esophageal candidiasis	306	5.3
Diarrhea	331	1.4
Cutaneous Kaposi's sarcoma	349	3.9
Shingles	353	5.6
Diarrhea; weight loss[b]	371	0.0
Shingles	380	2.8
Shingles	451	3.6
Persistent oral candidiasis[c]	526[d]	3.4
Pneumonia; shingles	571[d]	4.3

[a] Subsequently developed immune reconstitution inflammatory syndrome (IRIS) progressive multifocal leukoencephalopathy (PML)

[b] Had not previously recorded a CD4 T-cell count below 500 cells/μl

[c] Subject continued to decline cART; nadir CD4 T-cell count 377 cells/μl

[d] Two subjects had proximate CD4 T-cell counts >500 cells/μl but had had CD4 T-cell counts below 500 cells/μl in the preceding years

lymphadenopathy—biopsy showed metastatic melanoma, which proved fatal. He was diagnosed with HIV 8 years previously—nadir CD4 T-cell count (at the time of presentation) was 418 cells/μl. All of the remaining 78 subjects were alive at the last follow up. Two other subjects had successful excision of melanomas (one prior to HIV acquisition). There were no instances of stroke, ischemic heart disease, or significant renal or hepatic impairment.

Table 4 Significant adverse events (AEs) related to cART

Adverse event	Outcome
Severe IRIS PML[a]	Major neurological deficits
Efavirenz rash[a]	Changed efavirenz to atazanavir
Darunavir rash[a]	Changed darunavir to atazanavir
Severe CNS SEs	Changed efavirenz to rilpivirine
Diarrhea	Changed lopinavir to atazanavir
Hepatitis	Changed atazanavir to rilpivirine
Lipodystrophy	Changed zidovudine to raltegravir
Icterus	Changed atazanavir to efavirenz
Nausea	Changed zidovudine to abacavir
Renal impairment	Changed tenofovir to abacavir
Cardiac arrhythmia[b]	Changed atazanavir to tenofovir
Depression; dreams[b]	Changed efavirenz to rilpivirine
Diarrhea[c]	Changed lopinavir to efavirenz
Proteinuria[c]	Changed tenofovir to rilpivirine
Diarrhea	Changed lopinavir to efavirenz
Anxiety	Changed efavirenz to rilpivirine
Rash	Changed efavirenz to atazanavir
Renal impairment	Changed tenofovir to raltegravir

[a] Same patient with three AEs

[b] Same patient with two AEs

[c] Same patient with two AEs

Adverse events associated with cART

Fourteen (21 %) subjects initiating cART developed 18 significant adverse events (AEs) (Table 4), including three subjects who had multiple AEs. One subject developed severe immune reconstitution inflammatory syndrome (IRIS) from progressive multifocal leukoencephalopathy (PML). He had resisted cART for at least 18 months, whilst his first CD4 T-cell count <500 cells/μl was measured 16 years previously. He agreed to start cART after presenting with troublesome upper limb pain, thought to be HIV-related neuropathic pain (CD4 T-cell count 304 cells/μl), but then developed debilitating paresis persisting until study conclusion (3 years later). A second patient commenced efavirenz (CD4 T-cell count 282 cells/μl) 3.1 years after first recording a CD4 T-cell count <500 cells/μl. He developed severe vertigo, ceased work, and remained

Table 5 Rate of sexually transmitted infection (STI) diagnoses in 75 subjects followed at the Melbourne Sexual Health Centre (MSHC)

Totals	Overall	Pre-diagnosis	Pre-cART	Post-cART
Patient-years	695.6	106.0	382.4	207.8
STI cases	166	28	78	60
Annual case rate	0.24	0.26	0.20	0.29

unemployed at study conclusion (16 months later), although symptoms abated with a change of cART.

Sexually transmitted infections

Sexual disinhibition may occur when people undertake interventions designed to decrease their HIV infectivity [8–10]. We studied STIs in 75 of the 79 subjects in our cohort that were followed at one of the clinics (MSHC), since this service provides free treatment of STIs. An advantage of this analysis is that 25 (33 %) subjects had been managed at the MSHC for at least one month prior to their HIV diagnosis (mean 4.2 years, range 50 days to 14.9 years), allowing the analysis of STI rates prior to HIV infection, after HIV infection but prior to cART, and after cART initiation. Over 683 person-years of follow-up, 162 STIs were diagnosed and managed at the MSHC (Table 5). The rate of STIs post-diagnosis (but before commencing cART) fell non-significantly compared to pre-HIV diagnosis (relative incidence 0.77, 95 % confidence interval [CI] 0.50–1.24; p=0.25). The STI rate after commencing cART increased compared to before commencing cART (relative incidence 1.4, 95 % CI 1.0–2.0; p=0.043).

Transmission of HIV

We identified five subjects in our cohort causing six probable HIV transmissions to their sexual partners. In five cases, the transmitter/recipient acknowledged the likely link; in one instance, genotyping showed 11 of 11 shared polymorphisms in pol. All transmissions occurred prior to commencing cART (Table 6). Notably, 5 of the 6 identified transmissions were male to female, despite the cohort being primarily MSM. Three HIV transmissions were from non-Australian resident subjects who were ineligible for government-subsidized cART, even though their CD4 T-cell counts were <500 cells/μl. Only 1 of the 5 subjects had never recorded a CD4 T-cell count <500 cells/μl prior to the probable transmission event. This subject continued to refuse cART despite symptomatic persistent oral candidiasis and a CD4 T-cell count now below 500 cells/μl.

Discussion

We studied an Australian cohort of predominantly MSM HIV-positive cART-naïve individuals for 514 patient-years to examine the potential impact of universal immediate cART. In Australia, since 2002, the use of cART among our predominant MSM epidemic has increased from 52 % to 78 %, and viral suppression rates have increased from 50 % to 85 %. However, annual new acquisitions of HIV have actually increased by 65 % since that time period [12, 13]. Analyzing such a cohort may be more representative of European and USA conditions rather than those studied in the HPTN052 trial. The mean and median CD4 T-cell counts at diagnosis were 653 and 571 cells/μl, respectively, representing a population who would generally not receive cART under guidelines prevalent at the time. Overall, 71 % of subjects commenced cART with a CD4 T-cell count <350 cells/μl. This relatively late initiation of cART related mainly to poor engagement with medical services (27 % of subjects) and patient resistance (23 % of subjects).

The HPTN052 study (1,567 patient-years of follow-up, median final CD4 T-cell count 400 cells/μl) indicated individual patient benefit from early cART (CD4 T-cell 350–550 cells/μl), driven largely by 14 fewer cases of extrapulmonary tuberculosis (TB) or ~1 case prevented per 100 patient-years of cART [7]. In our cohort (514 person-years of follow up, final median CD4 T-cell count of 322 cells/μl prior to commencing cART), there were no cases of TB, highlighting differences between studies conducted in developed and developing world settings. In our cohort, only one HIV-related illness (persistent diarrhea and weight loss) occurred in a subject who had not previously recorded a CD4 T-cell count <500 cells/μl, covering 196 patient-years of observation. This is consistent with the low burden of HIV-related illnesses at high CD4 T-cells. The SMART study [3] indicated that early cART (CD4 T-cell count >350 cells/μl versus <250 cells/μl) prevented one major cardiovascular, renal, or hepatic event

Table 6 Probable HIV transmissions and proximate CD4 T-cell counts

Mode of transmission	Proximate CD4 T-cell count prior to transmission	Nadir CD4 T-cell count	Time to transmission after CD4 T-cell count <500 cells/μl	Comments
BS-M to HS-F	622 cells/μl	580	Nil	Resisted cART
HS-M to HS-F	270 cells/μl	223	25 months	Non-resident
HS-M to HS-F	270 cells/μl	223	25 months	Non-resident
MSM to MSM	506 cells/μl	422	8 months	Non-resident
HS-M to HS-F	758 cells/μl	487	9 months	Resisted cART
BS-M to HS-F	574 cells/μl	197	10 months	Resisted cART

BS bisexual, *HS* heterosexual, *MSM* homosexual male, *M* male, *F* female

per 140 person-years of treatment. We might have anticipated three or four such serious non-acquired immunodeficiency syndrome (AIDS) events in our cohort; however, none were observed.

In asymptomatic individuals, it is unclear how best to balance morbidity from early AEs following early cART against a primary benefit of reduced HIV transmission to a third party. Overall, 21 % of subjects experienced AEs to cART requiring a change in therapy; two (3 %) had significant sequelae, although for the subject with IRIS PML, it is likely that his condition would not have eventuated had he initiated cART earlier. The HPTN052 trial [7] reported that, in preventing 23 clinical events, early cART initiation resulted in 26 additional severe or life-threatening clinical AEs, including a three-fold increase in non-fatal injuries, poisonings, central nervous system, and psychiatric disorders; there were also three (versus zero) suicides. Our 3 % rate of severe AEs is consistent with previous reports [14].

Our data showed a 40 % increase in STI rates after commencing cART. This is consistent with sexual disinhibition associated with biological interventions reported by other authors [9, 15]. Although increased rates of bacterial STIs would not be expected to offset reduced HIV transmission, morbidity from increased STIs following cART (e.g., syphilis) do have health implications. Our data likely underestimate the problem of increased STIs after cART, as we did not analyze human papillomavirus, hepatitis B, or hepatitis C virus infections. Increasing epidemics of sexually transmitted hepatitis C virus infection associated with significant morbidity and mortality are occurring among HIV-positive MSM since the advent of expanded cART [16–18].

Transmission benefits of cART in MSM cohorts in developed countries are not clear in the absence of controlled trials. Some previous HIV prevention interventions have been less effective in MSM than in heterosexual cohorts [9, 19–21]. We detected six probable HIV transmissions; however, we recognize that our findings are a likely underestimate. Five of six probable transmissions were male to female, yet, in Australia, the ratio of MSM to female heterosexual diagnoses is about 20:1. Five of the six probable transmissions occurred in people who had recorded a CD4 T-cell count <500 cells/μl a mean of 15.4 months prior to the detection of the transmission. Assuming cART is fully effective at preventing HIV transmission, the majority of probable transmissions we observed may have been prevented had subjects with a CD4 T-cell count <500 cells/μl commenced cART promptly. Three of the six transmissions we detected were from non-permanent Australian residents, making them ineligible for government-subsidized cART, highlighting a potential public health benefit from broader access to cART.

The balance of allocating resources for the HIV epidemic is difficult. An analysis modeled on HPTN052 conditions [22] indicated that the cost-effectiveness of early cART was not driven by benefits gained from transmissions prevented. Rather, benefit was attained via life-years saved in infected individuals, which may not be replicated in many developed world scenarios. Our data suggest that resources to care for HIV-infected subjects may be better channeled into factors we identified, including removing restrictions on providing government-subsidized cART to non-residents, improving engagement with HIV services, addressing resistance by patients to commence cART, and mitigating AEs. Furthermore, our data suggest that earlier cART initiation may be associated with an unwanted increase in the rates of STIs. In our conditions, focusing attention on improving the initiation of cART in people with lower CD4 T-cell counts and improving safer sexual practices would be beneficial.

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Conflict of interest The authors have nothing to disclose.

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