RESEARCH ARTICLE

Socioeconomic factors explain suboptimal adherence to antiretroviral therapy among HIV-infected Australian adults with viral suppression

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¶ Membership of the PAART Study Investigators is provided in the Acknowledgments.

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Abstract

Background

Missing more than one tablet of contemporary antiretroviral therapy (ART) per month increases the risk of virological failure. Recent studies evaluating a comprehensive range of potential risk factors for suboptimal adherence are not available for high-income settings.

Methods

Adults on ART with undetectable viral load (UDVL) were recruited into a national, multi-centre cohort, completing a comprehensive survey assessing demographics, socioeconomic indicators, physical health, well-being, life stressors, social supports, HIV disclosure, HIV-related stigma and discrimination, healthcare access, ART regimen, adherence, side effects, costs and treatment beliefs. Baseline data were assessed, and suboptimal adherence was defined as self-reported missing ≥1 ART dose/month over the previous 3-months; associated factors were identified using bivariate and multivariate binary logistic regression.

Results

We assessed 522 participants (494 [94.5%] men, mean age = 50.8 years, median duration UDVL = 3.3 years [IQR = 1.2–6.8]) at 17 sexual health, hospital, and general practice clinics across Australia. Seventy-eight participants (14.9%) reported missing ≥1 dose/month over the previous three months, which was independently associated with: being Australian-born (AOR [adjusted odds ratio] = 2.4 [95% CI = 1.2–4.9], p = 0.014), not being in a relationship (AOR = 3.3 [95% CI = 1.5–7.3], p = 0.004), reaching the “Medicare safety net” (capping annual medical/pharmaceutical costs) (AOR = 2.2 [95% CI = 1.1–4.5], p = 0.024), living in...
subsidised housing (AOR = 2.5 [95%CI = 1.0–6.2], p = 0.045), receiving home-care services (AOR = 4.4 [95%CI = 1.0–18.8], p = 0.046), HIV community/outreach services linkage (AOR = 2.4 [95%CI = 1.1–5.4], p = 0.033), and starting ART following self-request (AOR = 3.0 [95%CI = 1.3–7.0], p = 0.012).

Conclusions
In this population, 15% reported recent suboptimal ART adherence at levels associated in prospective studies with subsequent virological failure, despite all having an undetectable viral load. Associations were with social/economic/cultural/patient engagement factors, but not ART regimen/clinical factors. These associations may help identify those at higher risk of future virological failure and guide patient education and support.

Introduction
Antiretroviral therapy (ART) of HIV infection is effective at increasing quality of life and preventing HIV transmission, progression to AIDS, and death [1]. Suppression of HIV viral load to below detectable limits is the key predictor of efficacy [2, 3]. Once ART is initiated, it must be continued daily for life [4]. At least 95% adherence is recommended [5], including for contemporary, single-tablet, once-daily ART regimens [6]. One study comparing two single-tablet, initial ART regimens found that virological suppression at 48 weeks was 88–91% in those with ≥95% adherence, 75–79% with 90–95% adherence, but only 56–70% with <90% adherence [7]. Others have found virological response falls from 89–99% at >95% adherence to 62–75% with ≤95% adherence [6, 8].

Despite its benefits, not all patients fully adhere to ART. Non-adherence encompasses ART interruption as well as ongoing ART use with missed doses. A global meta-analysis estimated 90% ART adherence rates to be only 62% [9]. In Australia, which provides highly subsidised ART to all citizens and permanent residents, an estimated 92% of people on ART achieve viral suppression [10]. However, some patients who achieve virological suppression subsequently experience treatment failure (in Australia, about 3.5% per year [11]).

Australian permanent residents and citizens are able to access subsidised ART through the Pharmaceutical Benefits Scheme. Some patients contribute to the cost of their medicine (a copayment), with a safety net in place to reduce these costs following meeting the annually-determined threshold. In some circumstances, patients can qualify for a concession card to further reduce their contribution (e.g. social welfare recipients, pensioners, department of veterans’ affairs, etc.). Despite these subsidies, medicine costs in Australia have been noted to be moderate to high in comparison to other OECD countries [12], and even low co-payments have been identified as a potential barrier to accessing medications [13] [14]. Although narrowing, gaps remain in participation in paid employment and other social determinants of health (e.g. education) in HIV-positive adults in Australia [15].

Reasons for suboptimal ART adherence in resource-rich countries in a contemporary setting are not well understood [16]. Much of the literature on adherence pre-dates the era of single tablets regimens, or treatment as prevention [17, 18]. Factors individually associated with lower adherence include complex medication regimens (more than one tablet or dosing time per day) [19, 20], ART toxicity [21], ART costs and financial stress [22], attitudes and beliefs about ART necessity [23, 24], concerns about ART (e.g. side effects, reliance on ART)
[24], poor relationships with healthcare providers, sociocultural relationship factors (e.g. unsupportive social networks), substance abuse [25], and HIV-associated neurocognitive disorders [26].

Prior studies of covariates of suboptimal ART adherence have several limitations. Many were not performed in the current era of simple, once-daily ART. Also, to the best of our knowledge, no study has comprehensively assessed the wide range of factors that may influence ART adherence, so it is unknown to what extent various factors are independently associated with adherence, nor which might be most associated. Furthermore, some potentially critical covariates have been studied infrequently. For example, an EMBASE / OVID search of the literature published between 2010 and 2016, with keywords (exploded) “HIV”, “antiretroviral therapy”, and “adherence” limited to adults and available in English language returned 291 results; adding “finance/finances/financial”, returned two publications in the OECD context; including previous work completed by our group which did not evaluate an extensive range of variables [22]. We identified only one other study that reported the association between adherence and costs of ART to patients in a resource-rich setting [27]. Furthermore, most of the available literature in the OECD setting reports on findings from the United States, which may not be generalizable to the Australian demographic.

To increase our understanding of adherence behaviours, we conducted a cross-sectional analysis of the baseline sample, investigating a large number of patient, treatment, and socio-economic characteristics to determine the extent and predictors of suboptimal ART adherence in HIV-infected adults in Australia despite a suppressed viral load.

Methods
Study design and setting
We established a national, 2-year cohort study of HIV-infected adults on ART with an undetectable viral load. Participants were enrolled at 17 Australian general practice, sexual health, and hospital outpatient clinics between September 2013 and November 2015.

Ethical approval was obtained from the Human Research Ethics Committee at each study site. Written, informed consent was obtained from each participant prior to any study activity. Approving HREC names and approval reference numbers are: St Vincent’s Hospital HREC (HREC/12/SVH/186), ACT Health Canberra HREC (ETH.7.13.178), Government of Western Australia South Metropolitan Health Service HREC (ref 13/70), The Alfred Hospital HREC (444/14) and Monash Health HREC (15O28X).

To avoid selection bias (e.g. selecting only those patients who were compliant and would complete the questionnaire), site co-ordinators (usually a research nurse) were instructed to invite all eligible patients during routine clinics, until each site reached its predetermined sample size (proportional to its estimated eligible patient population and capacity to recruit). The aim was to recruit a representative sample of patients at each site and, to not exclude patients deemed at risk of ART failure for any reason. This allowed all patients seen at the study sites over the recruitment period an equal opportunity of participation in the cohort.

Participants
HIV-infected adults (≥18 years of age) were eligible if they were on ART, had an HIV viral load less than 50 copies/mL plasma (at enrolment or on most recent assessment), could complete the study questionnaire (with the assistance of an interpreter, if required), and had HIV viral load, CD4 T-lymphocyte count, full blood count and biochemistry results in the last 3 months.
Assessments

Questionnaire. Using a study-provided laptop computer, participants complete a 204-question questionnaire (divided between 124 items and 13 themes) at baseline, Month 12, and Month 24 (this report focuses on the baseline data only). Questionnaire feasibility had been tested in a pilot study, which found a mean completion time of 40 minutes with 99% data completion [28].

The annual patient self-completed questionnaire incorporates a series of measures [22, 29–39], assessing the following categories (themes) of variables: socio-demographic characteristics (18 items), financial and employment status (8 items), income (2 items), healthcare and treatment access (19 items), physical health (5 items), mental health (2 items), quality of life (1 item), drug and alcohol use (19 items), life stressors and social supports (3 items), HIV disclosure and perceived or experienced stigma (5 items), ART regimen, side effects, consistent use, and dose adherence (24 items), ART-related necessity beliefs and concerns (10 items), non-ART medication (8 items). Table 1 includes the detailed measures, the majority either existing (e.g. SMAQ [38], PHQ-9 [35] [36], CAGE [39], see Table 1) or pre-validated (e.g. the majority of those have been used among HIV-positive Australians, see Table 1). From the 43-item PROQOL-HIV scale [37]), 41 items were maintained, and two original items (general health and the impact of ART-related side-effects on treatment adherence items) were replaced by separate questions on general health (without the limitation of the past two-week timeframe) and a more detailed set of questions on ART side effects in our study.

Table 1. Questionnaire composition.

| Heading                                | Number of Items | Item clusters                                                                 | Embedded items / literature source                                                                 |
|----------------------------------------|-----------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Demographics                           | 18              | age, sex, sexual orientation, country of birth, citizenship status, English fluency, Medicare status, partner, household, education | Positive Health (ph) Cohort [29]                                                                   |
| Physical health                        | 5               | prior AIDS, hospitalizations, time in bed / off work due to illness            | Positive Health (ph) Cohort [29]                                                                   |
| Mental health / emotional wellbeing    | 22              | mood, alcohol and illicit drug use                                            | Positive Health Questionnaire (PHQ-9) [35, 36], Professional Quality of Life Scale (the PROQOL-HIV scale) [37], CAGE [39] questionnaire for alcohol dependence |
| Life stressors, social support         | 3               | Events, severity, social network                                             | Positive Health (ph) Cohort [29]                                                                   |
| HIV disclosure, stigma                 | 5               | Disclosure, stigma, discrimination                                           | National Association of People With HIV Australia (NAPWHA) HIV Stigma Audit’s Community Survey [34], Professional Quality of Life Scale (the PROQOL-HIV scale) [37] |
| Health and treatment perception        | 10              | Attitudes to ART and HIV, adverse events, mood                              | Chronic Illness Acceptance Questionnaire [33], Pleasure and Sexual Health (PASH) study [32], Beliefs About Medications Scales (BMQ-HAART) [31] |
| HIV healthcare access, treatment adherence, side effects | 51              | Current / prior ART and concomitant medications: doses and pills / day, dosing requirements, side effects, adherence to treatments doctors and allied health professional: frequency of attendance, changes to healthcare team, costs of care | Simplified Medication Adherence Questionnaire (SMAQ) [38],                                                                 |
| Financial and employment status        | 10              | Income, life costs, healthcare costs                                        | St Vincent’s Immunology B Ambulatory Care’s finance and adherence survey [22]                                                                             |
Participants were asked if they had met the Medicare Safety Net threshold, this threshold provides financial relief for medical services covered under the Medicare benefits system (e.g. a discounted patient co-payment for prescribed pharmaceuticals). In 2015, the Medicare safety net threshold was A$2,000 for a regular Medicare holder, and A$638.40 for a concessional status cardholder [40].

Neurocognitive assessment. For the present analysis, neurocognitive function was assessed at baseline using computerized screening (Cogstate brief battery [41]) (future analyses will include data from Months 12 and 24). The Cogstate brief battery includes four tasks (detection, identification, one back and the one-card learning tasks) examining: processing speed, sustained attention, divided attention, visual learning and working memory [41]; and has previously been validated as a reliable screening tool in HIV-positive adults similar to the currently enrolled cohort [42]. Z-scores for each of four domains were generated using Cogstate normative standards [42] and were used to calculate a global deficit score (GDS) [43, 44]. Adjustments were not made for depression or substance use because neither correlated with GDS in this sample (p = 0.122 and p = 0.63 respectively) [45]. The standard GDS of >0.5 (averaged over four tasks [43]) was used as the cut-off point for cognitive impairment, and was analysed using the dichotomous classification of impaired or unimpaired.

Antiretroviral dispensing records. ART dispensing data for the 12 months preceding the baseline assessment were collected from every ART-dispensing pharmacy serving each study participant. Data collected are: antiretroviral medications dispensed, months dispensed, total cost to patient (inclusive of any patient co-payment), and whether medication(s) were obtained via a clinical trial.

Clinical and laboratory data. The study coordinator collects clinical and laboratory data semi-annually for the duration of follow-up including: medical history; HIV history (date and mode of transmission, past AIDS-defining illnesses, opportunistic infections, serious non-AIDS events [46]); ART history (date of commencement, components and duration of current regimen, pill burden, dosing frequency and requirements, duration of undetectable HIV viral load); concomitant medications; comorbidities; sexually transmitted infections; and patient retention in care (number of attendances, missed appointments, clinical trial enrolment, directly-observed therapy). Laboratory data collected are: HIV viral load, CD4+ T-lymphocyte counts (current and nadir), haemoglobin, estimated glomerular filtration rate (eGFR) and alanine aminotransaminase (ALT).

Outcome variable
The main outcome variable for the present analysis of the baseline data was ART adherence over the previous three months as reported by participants at study entry. Given the cohort design, all participants included at baseline had an undetectable viral load within three months prior to enrolment. As the main study objective is to identify risk for adherence over time, the cohort data will be analysed in future (when data become available), for participants who experience ART failure. For the present analysis, we were interested in ascertaining the actual adherence of this virologically controlled sample. Given the requirement of >95% adherence to ART, even in contemporary regimens, missing greater than one dose per month places a patient at risk of virological failure. Therefore, suboptimal adherence was defined as an average of at least 1 missed ART dose per month over the previous three months [6, 7], based on participant self-report. This was ascertained by asking participants how many ART doses were missed/skipped in the previous 3-months.

Participants taking once-daily ART (by single tablet regimen or otherwise) who missed one ART dose per month or more were considered to have had suboptimal adherence. Those
participants who took twice-daily ART and missed doses at a threshold of >2 doses per month for three months were considered sub-optimally adherent. For the 23 participants taking twice-daily ART who missed less than two doses per month for three months (but missed more than one dose per month; e.g. missing 5 doses over the 3-month period), additional sensitivity analysis was conducted.

**Sample size**

The main study was powered based on a previous study conducted by our group that showed 9% of patients had ceased or interrupted medication, and 29% of those who had difficulty meeting pharmacy costs had ceased medication [22]. Assuming characteristics associated with non-adherence would be more prevalent in the non-adherent group, a sample size of 500 was sufficient to give 85% power to detect an odds ratio $\geq 3$ for associations with a covariate, with a prevalence of 29% in the sub-optimally adherent versus adherent participants, at a 2-sided significance level of 5%.

**Statistical methods**

For items that were part of a validated scale, results were used to generate a summary score as intended (e.g. PHQ9 for depression [35], PROQOL-HIV [37] and CAGE for alcohol abuse [39]). Categorical data were re-coded into binary responses (e.g. housing: subsidized or not). Continuous data were dichotomized based on clinical significance where supported (e.g. ALT, eGFR) or on sample median or mean values, depending on distribution (e.g., median/mean split). Those continuous data dichotomised by sample median/mean included: age, income, duration of care from primary HIV physician, cost of healthcare/alternative healthcare services over previous 12-months, money spent last time HIV medication was obtained, money spent in previous 3-months on non-HIV medications, cost of all healthcare needs, CD4 T-lymphocyte cell count, missed clinical appointments, number of life stressors, and concomitant medication pill burden. Data dichotomised by a reference point included: year HIV diagnosed (prior to 1996), nadir CD4 ($<200$), length of undetectable HIV viral load ($>12$ months), ART year commenced (prior to 2004), haemoglobin ($<130 g/L$ males, $<120 g/L$ females), ALT ($>40 U/L$ males, $>35 U/L$ females), eGFR ($<90$), hospitalisations/inpatient days ($>1$), bed days due to illness ($>1$), doctors’ visits due to illness ($>1$).

Bivariate associations between adherence and all covariates were assessed. Where individual items were correlated, we selected the one showing the most significant relationship with the outcome variable to avoid multi-collinearity. After assessing all covariates for significance, all of those variables significantly (p $< 0.05$) associated with suboptimal adherence in bivariate analysis were included in a multivariable logistic regression analysis using the Enter method, whereby all variables are entered (forced) into the equation simultaneously.

The multivariable logistic regression methodology was chosen to help explore specific covariates that were associated with suboptimal adherence, rather than using data reduction to identify thematic associations, as a goal of the present analysis was to provide clinicians with specific variables to help identify less adherent patients.

Sensitivity analyses were performed using backward-stepwise and forward-stepwise approaches. Additional sensitivity analysis was conducted after reclassifying those on twice-daily ART dosing who potentially missed less than 2 doses of ART per month in the previous 3 months (e.g. missing 5 doses over the previous three months) from the non-adherent to the adherent group.

All statistical analyses were conducted in IBM SPSS Statistics for Windows, Version 22.0.
Results

Main demographic and clinical characteristics

Of the 523 participants enrolled, one (0.2%) did not respond to the primary outcome measure and was excluded from this analysis. Of the 522 participants analysed, 203 (38.9%) were enrolled at sexual health clinics, 174 (33.3%) at hospital clinics, and 145 (27.8%) at HIV high-caseload general practices (sample characteristics are outlined in Table 2). Four-hundred-ninety-four (94.6%) participants were male, and participants had a mean age of 50.8 (SD 12.3) years. Three-hundred twenty-two participants (61.6%) were Australian-born. Two-hundred twenty-six (43.3%) participants were in a relationship, of which 136 (26.1%) were with HIV serodiscordant partners.

Mean CD4+ T-lymphocyte count was 659 cells/mm$^3$ (SD 273), 122 (22.9%) had a prior AIDS-defining illness, and 70 (13.4%) had hepatitis B and/or C co-infection. Eighty-seven (16.7%) participants had symptoms consistent with a major depressive disorder and 148 (28.3%) were classified as neurocognitively impaired.

The median weekly after-tax income (including social welfare payments) was $580 Australian dollars (about US$422; €377), and median annualized healthcare expenditure was A$598. Nearly all participants (507 [97.1%]) had Medicare coverage (publically-funded hospital and medical services), and 94 (18.0%) had reached the "Medicare safety net" in the previous 12 months. One-hundred thirty-eight (26.4%) participants had relied upon financial assistance to obtain basic necessities (e.g. rent, groceries, utilities) over the previous 12 months, and 114 (21.8%) participants had insufficient financial means to meet basic necessities over the previous 12 months. One-hundred-four (19.9%) participants lived in subsidized housing and 212 (40.6%) were on social welfare.

Seventy-seven (14.8%) participants were linked with one or more HIV community organizations / peer support groups as part of their HIV care, and 14 (2.3%) were receiving home-care services.

ART regimen and adherence

The median duration of undetectable HIV viral load was 3.3 years (IQR 1.2–6.8 years), and the median ART duration was 11.0 years (IQR 5–19 years), with 137 (26.3%) participants on their current ART regimen for no more than 12 months. Three-hundred thirty-three participants (63.8%) were taking once-daily ART and 158 (30.3%) were taking a single-tablet ART regimen; 352 participants (67.4%) were on regimens with specific food / fasting requirements. Two-hundred eleven (40.4%) participants were on a non-nucleoside reverse-transcriptase inhibitor (NNRTI) and nucleoside / nucleotide reverse transcriptase inhibitor (NRTI/NtRTI) regimen, 99 (19.0%) were on an NRTI plus integrase strand transfer inhibitor (INSTI) regimen, 79 (15.1%) were on an NRTI plus protease inhibitor (PI) regimen, and 133 (25.5%) were on an alternative regimen (predominantly 3-class or NRTI-sparing). Three-hundred twenty-eight participants (62.8%) had started ART following advice from their treating doctor, while 64 participants (12.3%) had started ART following their own request; 195 participants (37.4%) had started treatment to prevent transmission to partners or their community.

Seventy-eight participants (14.9%) reported missing an average of at least one ART dose per month over the previous 3 months (Table 3). Associations with covariates in bivariate analyses are shown in Table 4. The multivariable logistic regression model was statistically significant ($x^2 = 123(45), p < 0.001$) and correctly classified 86.6% of cases. The final model contained 501 participants with 100% data collected on all included variables. Suboptimal ART adherence was independently associated with the following variables (Table 5): being born in
Table 2. Sample characteristics.

| Variables                                                                 | n (%) or mean (SD) |
|---------------------------------------------------------------------------|--------------------|
| **Demographic characteristics**                                           |                    |
| Age (years; mean, SD)                                                    | 50.8 (12.3)        |
| Gender (Male)                                                            | 494 (94.6)         |
| Men who have sex with men                                                | 410 (78.5)         |
| Australian born                                                          | 322 (61.6)         |
| Living alone                                                              | 212 (40.5)         |
| Speaks English at home                                                   | 493 (94.3)         |
| Ability to read, speak and understand English rated as ‘excellent’       | 427 (81.6)         |
| Australian citizen                                                       | 461 (88.1)         |
| Has Medicare access                                                      | 508 (97.1)         |
| Met the Medicare safety net\(^a\) in previous 12-months                   | 94 (18.0)          |
| Has private health insurance                                             | 221 (42.3)         |
| Lives in a major city                                                    | 452 (86.4)         |
| University educated                                                       | 197 (38.0)         |
| **Financial / employment status**                                         |                    |
| On social welfare                                                        | 212 (40.6)         |
| Required financial assistance in previous 12 months                       | 138 (26.4)         |
| No employment                                                            | 226 (43.2)         |
| Underemployment (would increase hours if available)                      | 220 (42.1)         |
| Current weekly income after tax (median, IQR)                            | 645 (580)          |
| Lives in public-subsidized accommodation                                 | 105 (20.1)         |
| Lives with someone who is financially dependent on them                  | 48 (9.2)           |
| Received financial assistance in previous 12 months from family           | 42 (21.8)          |
| from Centrelink\(^b\)                                                    | 97 (50.3)          |
| from partner                                                             | 18 (9.3)           |
| from non-governmental organization                                       | 80 (41.4)          |
| In previous 12 months, for financial reasons, had to forego food, groceries, rent, household bills, furniture, clothing, white goods | 114 (21.8)         |
| **HIV healthcare and treatment access**                                   |                    |
| Uses the following for HIV management:                                   |                    |
| hospital based HIV clinic                                                 | 254 (48.7)         |
| health center specialized in HIV treatment                               | 135 (25.9)         |
| community based general practice                                         | 174 (33.3)         |
| sexual health clinic / center                                            | 168 (32.2)         |
| naturopath                                                               | 26 (5.0)           |
| hospital pharmacy                                                        | 259 (49.6)         |
| home or community care                                                   | 14 (2.3)           |
| drug or alcohol services                                                 | 9 (1.7)            |
| HIV-related community organizations or support groups                     | 77 (14.8)          |
| **Primary HIV physician**                                                |                    |
| general practitioner                                                     | 181 (34.7)         |
| hospital physician                                                       | 223 (42.7)         |
| sexual health physician                                                  | 114 (21.8)         |
| **Study enrolment site**                                                 |                    |
| high-caseload general practice                                          | 145 (27.8)         |
| hospital located clinic                                                  | 174 (33.3)         |

(Continued)
Table 2. (Continued)

| Variables                                      | n (%) or mean (SD) |
|-----------------------------------------------|--------------------|
| sexual health clinic / center                 | 203 (38.9)         |
| Feels actively involved in the management / treatment of HIV | 506 (96.9)         |
| Consults with primary HIV physician at least every six months | 512 (98.1)         |
| Duration of care from primary HIV physician (years: mean, SD) | 11.3 (8.0)         |
| Changed primary HIV physician in previous 12 months | 80 (15.3)          |
| No payment required from patient for HIV consultations | 288 (82.8)         |
| Has seen other medical specialists in the previous 12 months | 321 (61.5)         |
| Has other healthcare providers involved in HIV care | 324 (62.1)         |
| Cost of healthcare services over previous 12 months (dollars: mean, SD) | 281 (616)          |
| Cost of alternative healthcare services over previous 12 months (dollars: mean, SD) | 675 (1161)         |
| Cost a barrier to accessing medical services in the previous 12 months | 71 (13.6)          |
| ART pharmacy charges a patient co-payment | 292 (55.8)         |
| Money spent last time HIV medication obtained (dollars: mean, SD) | 106 (410)          |
| Money spent in previous three months on non-HIV medication (dollars: mean, SD) | 145 (434)          |
| Cost of all health needs (except medications) in previous 3 months (dollars: mean, SD) | 303 (1135)         |
| HIV history                                   |                    |
| HIV diagnosed prior to 1996                  | 213 (40.8)         |
| Male-to-male sexual transmission of HIV      | 406 (77.6)         |
| Nadir CD4 T-lymphocyte count <200 cells      | 202 (38.7)         |
| Previous AIDS                                 | 120 (22.9)         |
| Comorbidities                                 |                    |
| Heart disease                                 | 57 (10.9)          |
| Hypertension                                  | 94 (18.0)          |
| Stroke                                       | 9 (1.7)            |
| Peripheral vascular disease                  | 8 (1.50)           |
| Diabetes                                     | 31 (5.9)           |
| Chronic liver failure                        | 2 (0.4)            |
| Chronic kidney disease                       | 14 (2.7)           |
| Other diagnosed comorbidity                  | 102 (19.5)         |
| Current health                                |                    |
| CD4 T-lymphocyte count (mean, SD)            | 659 (273)          |
| Length of undetectable HIV viral load >1 year | 399 (76.4)         |
| Currently enrolled on a clinical trial       | 45 (8.6)           |
| Anaemia<sup>2</sup>                          | 33 (6.3)           |
| Elevated ALT<sup>3</sup> (>40 U/L males, >35 U/L females) | 130 (24.9)         |
| eGFR<sup>4</sup> <90 mls/min/1.73m2          | 290 (55.6)         |
| Hepatitis co-infection                       | 70 (13.4)          |
| Sexually transmitted infection in previous 12-months | 71 (13.6)         |
| Hospitalized for ≥1 night in previous 12 months | 108 (20.7)        |
| Missed ≥1 clinic appointment in previous 12 months | 71 (13.6)         |
| Physical health                              |                    |
| Self-reported good / very good overall health | 435 (83.3)         |
| One or more bed days due to illness in previous 12 months | 284 (54.4)         |
| One or more doctor visits due to illness in previous 12 months | 358 (68.6)         |
| Greater than one hospital inpatient day in previous 12 months | 100 (19.2)        |
Table 2. (Continued)

| Variables                                      | n (%) or mean (SD) |
|------------------------------------------------|--------------------|
| **Mental health**                              |                    |
| Major depressive disorder on PHQ-9[35, 36]      | 87 (16.7)          |
| Psychiatric illness—currently clinically active | 112 (24.3)         |
| **Cognitive function**                         |                    |
| Neurocognitive impairment                      | 148 (28.3)         |
| **Alcohol and drug use**                       |                    |
| Alcohol dependent (CAGE[39])                   | 106 (20.3)         |
| Use of following drugs monthly or more in previous 12 months: |     |
| cigarettes                                     | 143 (27.4)         |
| marijuana / hash                               | 94 (18.0)          |
| amyl / poppers                                 | 67 (12.8)          |
| benzodiazepines                                | 39 (7.5)           |
| ecstasy                                        | 1 (0.2)            |
| injected speed / amphetamines                  | 20 (3.8)           |
| snorted or smoked speed / amphetamines         | 17 (3.3)           |
| injected cocaine                               | 2 (0.4)            |
| snorted cocaine                                | 3 (0.6)            |
| crystal methamphetamine                       | 23 (4.4)           |
| GHB / GBH / liquid E / fantasy                 | 6 (1.1)            |
| LSD                                            | 2 (0.4)            |
| PDE5 inhibitor (“viagra” or ‘similar’)         | 67 (12.8)          |
| heroin                                         | 3 (0.6)            |
| methadone                                      | 9 (1.7)            |
| opiates                                        | 11 (2.1)           |
| **Life stressors**                             |                    |
| More than 2 major stress events in previous 12 months | 133 (25.5)       |
| **Social support**                             |                    |
| Married / de facto / in regular relationship   | 226 (43.2)         |
| In a serodiscordant sexual relationship        | 136 (26.0)         |
| Received less social support than wanted / needed | 302 (57.9)     |
| Not linked to an HIV support organization      | 388 (74.3)         |
| **HIV disclosure, stigma and discrimination**  |                    |
| Did not disclose HIV status                    | 25 (4.8)           |
| Has been made to feel ashamed of HIV diagnosis | 224 (43.0)         |
| Has felt blamed for having HIV                 | 173 (33.1)         |
| Has felt avoided, excluded or rejected for having HIV | 214 (41.0)   |
| Has had awkward interactions for having HIV    | 248 (47.5)         |
| **Antiretroviral therapy**                     |                    |
| ART as a single tablet regimen                 | 158 (30.3)         |
| Once-daily ART dosing                          | 333 (63.7)         |
| Twice-daily ART dosing                         | 186 (35.6)         |
| ART requires fasting / food conditions         | 351 (67.2)         |
| Commenced ART within one year of diagnosis     | 245 (46.8)         |
| Commenced ART prior to 2004                    | 247 (47.3)         |
| Receiving ART through a clinical trial         | 28 (5.4)           |
| Receiving ART through directly observed therapy (DOT) | 8 (1.5)        |
Table 2. (Continued)

| Variables                                                                 | n (%) or mean (SD) |
|---------------------------------------------------------------------------|-------------------|
| When started ART felt ‘not at all’ / ‘only somewhat’ informed about ART   |                   |
| side effects                                                              | 178 (34.1)        |
| benefits                                                                  | 115 (22.0)        |
| dosing requirements                                                       | 44 (8.4)          |
| lifestyle impacts                                                         | 151 (28.9)        |
| own ART regimen                                                           | 106 (20.3)        |
| Reason for starting ART:                                                  |                   |
| to prevent HIV disease progression to AIDS                                 | 325 (62.6)        |
| to reduce HIV symptoms                                                     | 167 (32.2)        |
| to prevent transmission to HIV-negative partners                          | 101 (19.5)        |
| to prevent transmission to the community                                  | 94 (18.1)         |
| due to high viral load                                                    | 233 (44.9)        |
| due to low CD4 t-lymphocyte cell count                                    | 263 (50.7)        |
| following doctor’s advice                                                 | 328 (63.2)        |
| following their own request                                               | 64 (12.3)         |
| Never speaks with HIV doctors or nurses about                             |                   |
| balancing ART regimen with overall health and lifestyle                   | 174 (33.5)        |
| side effects associated with ART                                          | 101 (19.5)        |
| delaying, interrupting or changing ART                                    | 250 (48.3)        |
| cost burden of ART                                                        | 425 (82.1)        |
| I forget to take ART medications                                          | 242 (46.4)        |
| I am careless at times about taking ART medications                       | 86 (16.5)         |
| Sometimes if I feel worse I stop taking ART medications                   | 48 (9.2)          |
| Skipped ART once or more in the previous weekend                          | 35 (6.7)          |
| Experienced ART side effects in the previous 12 months                    | 297 (56.9)        |
| Experienced difficulties accessing pharmacy for ART                       | 32 (6.1)          |
| Missed ART once or more in the previous week                              | 83 (15.9)         |
| Delayed / interrupted ART in the previous 12 months                       | 34 (6.5)          |
| Delayed / interrupted ART in the previous 12 months for ≥1 week           | 20 (4.0)          |
| Doctor unaware of ART interruption / delay in previous 12 months          | 7 (1.3)           |
| Delayed / interrupted ART prior to 12 months ago                          | 85 (17.5)         |
| Delayed / interrupted ART prior to 12 months ago for ≥1 week              | 66 (12.6)         |
| Doctor unaware of prior ART interruption / delay                          | 14 (2.7)          |
| ART necessity concerns                                                    |                   |
| Necessity concerns summary score² (mean, SD)                             | 62.0 (7.0)        |
| Concomitant medications                                                   |                   |
| Daily concomitant medication pill burden (mean, SD)                       | 3.6 (4.3)         |
| Delayed / interrupted in previous 12 months                               | 60 (14.0)         |
| Delayed / interrupted in previous 12 months for ≥1 week                   | 37 (7.1)          |
| Doctor unaware of interruption / delay in previous 12 months              | 27 (5.2)          |
| Delayed / interrupted prior to 12 months ago                              | 49 (12.3)         |
| Delayed / interrupted prior to 12 months ago for ≥1 week                  | 32 (6.1)          |
| Doctor unaware of prior ART interruption / delay                          | 19 (3.6)          |
| PRO-QOL HIV                                                               |                   |
Australia; not being in a relationship; having reached the Medicare safety net threshold; living in subsidized housing; receiving home-care services; linkage to HIV community organizations; and having started ART at the patient’s request. Those with more than three of these variables present had a particularly elevated rate of suboptimal ART adherence (Table 6).

### Sensitivity analyses

Sensitivity analysis using backward-step and forward-step approaches yielded similar results (Table 7). In sensitivity analysis, we examined the 38 participants on twice-daily ART, and following removal of 23 participants receiving twice-daily ART who missed less than 2 doses per month within the previous three months from the suboptimal group (thereby reclassifying them to the adherent group, but maintaining the 15 participants on twice-daily ART with more than two-missed doses per month within the previous three months as non-adherent), three predictor variables remained statistically significant (reaching the Medicare safety net, receiving home care services, and self-requesting ART); the other four predictors in the primary model were no longer statistically significant (relationship status, country of birth, subsidized housing, and accessing HIV community organisations). One variable became of borderline significance: injecting crystal methamphetamine (AOR 23.8; 95%CI 1.1–524.4; \( p = 0.045 \)). Of these 23 participants, 11 were prescribed a once-daily ART co-formulated nucleoside backbone (either tenofovir with emtricitabine or abacavir with lamivudine).

Notable variables that were significant in bivariate, but not multivariate, analysis included ART-specific factors (non-single-tablet regimens, greater than once-daily ART dosing), injection drug use, and other markers of socioeconomic status (notably low income, unemployment, financial strain and cost barriers to ART access).
**Table 4. Variables associated with suboptimal ART adherence.**

| Variables                                                                 | Missed ART in last 3 months | OR[^1] | 95% CI[^2] | P-value |
|---------------------------------------------------------------------------|-----------------------------|--------|------------|---------|
|                                                                            | >3 (n = 78) n               | <3 (n = 444) n |           |         |
| Socio-demographic                                                         |                             |        |            |         |
| Not currently in a relationship                                          | No                          | 17     | 207        |         |
|                                                                            | Yes                         | 61     | 237        | 3.1     | 1.8–5.5 | <0.001 |
| Born in Australia                                                        | No                          | 15     | 186        |         |
|                                                                            | Yes                         | 63     | 258        | 3.0     | 1.7–5.5 | <0.001 |
| Living alone                                                             | No                          | 35     | 276        |         |
|                                                                            | Yes                         | 43     | 168        | 2.0     | 1.2–3.3 | 0.004  |
| Living in subsidized housing                                             | No                          | 56     | 362        |         |
|                                                                            | Yes                         | 22     | 82         | 1.7     | 1.0–3.0 | 0.047  |
| Living outside of an urban area                                          | No                          | 62     | 391        |         |
|                                                                            | Yes                         | 16     | 53         | 1.9     | 1.0–3.5 | 0.039  |
| HIV transmission route other than male-to-male sexual intercourse         | No                          | 57     | 370        |         |
|                                                                            | Yes                         | 21     | 74         | 1.9     | 1.1–3.2 | 0.030  |
| Finances and employment                                                  |                             |        |            |         |
| Medicare safety net[^*] reached in previous 12 months                    | No                          | 49     | 343        |         |
|                                                                            | Yes                         | 29     | 101        | 2.1     | 1.2–3.7 | 0.009  |
| Having no private health insurance                                       | No                          | 22     | 199        |         |
|                                                                            | Yes                         | 56     | 245        | 2.1     | 1.2–3.5 | 0.006  |
| Income <=$580 per week                                                   | No                          | 28     | 233        |         |
|                                                                            | Yes                         | 50     | 211        | 2.0     | 1.2–3.2 | 0.007  |
| Unemployed                                                                | No                          | 36     | 260        |         |
|                                                                            | Yes                         | 42     | 184        | 1.8     | 1.1–2.9 | 0.019  |
| Required financial assistance in the previous 12 months                   | No                          | 39     | 346        |         |
|                                                                            | Yes                         | 39     | 98         | 3.5     | 2.1–5.8 | <0.001 |
| Going without for financial reasons (food, rent, etc.)                   | No                          | 43     | 365        |         |
|                                                                            | Yes                         | 35     | 79         | 3.8     | 2.3–6.3 | <0.001 |
| Cost was a barrier to accessing HIV healthcare                            | No                          | 61     | 390        |         |
|                                                                            | Yes                         | 17     | 54         | 2.1     | 1.1–3.7 | 0.022  |
| ART pharmacy expenditure <= sample mean monthly ART expenditure           | No                          | 22     | 187        |         |
|                                                                            | Yes                         | 56     | 257        | 1.9     | 1.1–3.1 | 0.021  |
| HIV healthcare and treatment access                                       |                             |        |            |         |
| Primary HIV care provided by a general practitioner                       | No                          | 44     | 304        |         |
|                                                                            | Yes                         | 34     | 140        | 1.7     | 1.0–2.7 | 0.037  |
| Receives home care services                                              | No                          | 70     | 438        |         |
|                                                                            | Yes                         | 8      | 6          | 8.3     | 2.8–24.8| <0.001 |
| Receives drug and alcohol services                                       | No                          | 74     | 439        |         |
|                                                                            | Yes                         | 4      | 5          | 4.7     | 1.2–18.1| 0.012  |
| Linked to HIV community organisation(s)                                  | No                          | 56     | 389        |         |
|                                                                            | Yes                         | 22     | 55         | 2.8     | 1.6–4.9 | <0.001 |
| Required other healthcare specialists in previous 12 months              | No                          | 21     | 180        |         |
|                                                                            | Yes                         | 57     | 264        | 1.9     | 1.1–3.2 | 0.023  |
| Other healthcare providers were involved in HIV management               | No                          | 16     | 182        |         |
|                                                                            | Yes                         | 62     | 262        | 2.7     | 1.5–4.8 | 0.001  |
| Having difficulty with ART pharmacy access                                | No                          | 67     | 423        |         |
|                                                                            | Yes                         | 11     | 21         | 3.3     | 1.5–7.2 | 0.001  |

(Continued)
Table 4. (Continued)

| Variables                                      | Missed ART in last 3 months | OR1 | 95% CI | P-value |
|------------------------------------------------|-----------------------------|-----|--------|---------|
| Self-rated health status as poor/very poor     | No 56 378                  |     |        |         |
|                                                | Yes 22 66                   | 2.3 | 1.3–3.9 | 0.004   |
| >1 bed days for illness in previous 12 months  | No 23 215                  |     |        |         |
|                                                | Yes 55 229                 | 2.5 | 1.5–4.4 | 0.001   |
| ≥1 unscheduled doctor visits                  | No 17 147                  |     |        |         |
|                                                | Yes 61 297                 | 1.8 | 1.0–3.3 | 0.045   |
| ≥1 overnight hospitalization in previous 12 months | No 54 360             |     |        |         |
|                                                | Yes 24 84                  | 1.9 | 1.1–3.3 | 0.017   |
| Hepatitis co-infection                         | No 61 393                  |     |        |         |
|                                                | Yes 17 51                  | 2.1 | 1.2–4.0 | 0.013   |
| HIV diagnosis prior to 1996                    | No 38 271                  |     |        |         |
|                                                | Yes 40 173                 | 1.7 | 1.0–2.7 | 0.034   |
| Mental Health                                  |                             |     |        |         |
| Major depressive disorder                      | No 49 386                  |     |        | <0.001  |
|                                                | Yes 29 58                  | 3.9 | 2.3–6.7 |         |
| Alcohol and drug use (at least monthly)        |                             |     |        |         |
| Cigarette smoking                              | No 42 337                  |     |        | <0.001  |
|                                                | Yes 36 107                 | 2.7 | 1.6–4.4 |         |
| Marijuana                                      | No 52 376                  |     |        |         |
|                                                | Yes 26 68                  | 2.8 | 1.6–4.7 | <0.001  |
| Benzodiazepine                                 | No 63 420                  |     |        |         |
|                                                | Yes 15 24                  | 4.2 | 2.1–8.4 | <0.001  |
| Injected speed                                 | No 70 432                  |     |        |         |
|                                                | Yes 8 12                   | 4.1 | 1.6–10.4 |0.001    |
| Injected methamphetamines                      | No 71 428                  |     |        |         |
|                                                | Yes 7 16                   | 2.6 | 1.0–6.6 | 0.033   |
| Opiate use                                     | No 74 437                  |     |        |         |
|                                                | Yes 4 7                    | 3.4 | 1.0–11.8 |0.044    |
| Life stressors                                  |                             |     |        |         |
| Major stressful event in the previous 12 months | No 20 211                 |     |        | <0.001  |
|                                                | Yes 58 233                 | 2.6 | 1.5–4.5 |         |
| HIV disclosure and stigma                      |                             |     |        |         |
| Have felt shamed/excluded /having awkward interactions since HIV diagnosis | No 21 197 |     |        | <0.001  |
|                                                | Yes 57 247                 | 2.2 | 1.3–3.7 |         |
| ART regimen, side effects, consistent use and dose adherence |             |     |        |         |
| ART initiation prior to 2004                    | No 30 245                  |     |        | 0.004   |
|                                                | Yes 48 199                 | 2.1 | 1.3–3.4 |         |
| ART side effects                                | No 25 200                  |     |        | 0.033   |
|                                                | Yes 53 244                 | 1.7 | 1.0–2.9 |         |
| On a multiple-tablet ART regimen                | No 15 143                  |     |        | 0.021   |
|                                                | Yes 63 301                 | 2.0 | 1.1–3.6 |         |
| Greater than once-daily ART dosing             | No 40 295                  |     |        | 0.010   |
|                                                | Yes 38 149                 | 1.8 | 1.2–3.1 |         |
| Feeling uninformed about ART when starting      | No 65 414                  |     |        | 0.004   |
|                                                | Yes 13 30                   | 2.7 | 1.4–5.5 |         |
In our cohort of adults with HIV in Australia, with a median of three years of sustained viral suppression, 15% self-reported suboptimal ART adherence over the previous three months at a level that is likely to place them at increased risk of ART failure.

Other studies of self-reported ART adherence found similar or higher findings of suboptimal adherence. The average rate of reporting ≥90% adherence is estimated to be 62% [9]. One anonymous, community-based online survey (HIV Futures 7) found that about 20% of 1,058 HIV-positive, Australian adults reported <90% adherence [48]. While viral suppression in

### Table 4. (Continued)

| Variables                                      | Missed ART in last 3 months | OR¹ | 95% CI² | P-value |
|------------------------------------------------|----------------------------|-----|---------|---------|
| Starting ART following patient request         | No  | 61  | 397     | 2.3     | 1.3–4.3 | 0.006  |
|                                                | Yes | 17  | 47      |         |         |        |
| ART-related necessity concerns                 | No  | 30  | 247     |         |         |        |
| Necessity concerns score > sample mean         | No  | 31  | 249     |         |         |        |
| Non-ART medication consistent use and adherence| No  | 31  | 249     |         |         |        |
| Concomitant medication pill burden >2 pills per day | No  | 31  | 249     |         |         |        |
| Quantity of Life                               | No  | 27  | 271     | 1.9     | 1.2–3.2 | 0.008  |
| PRO-QOL HIV score > sample mean                | Yes | 51  | 173     | 3       | 1.8–4.9 | <0.001 |

¹Odds Ratio
²95% Confidence Interval
*whereby medical costs—including pharmaceutical co-payments, are capped after reaching an annual threshold

https://doi.org/10.1371/journal.pone.0174613.t004

### Table 5. Variables independently associated with suboptimal adherence.

| Covariate                                      | Adjusted odds ratio | 95% CI   | P-value |
|------------------------------------------------|---------------------|----------|---------|
| Born in Australia                              | No                  |          |         |
|                                                | Yes                 | 2.4      | 1.2–4.9 | 0.014  |
| Not in a relationship                          | No                  |          |         |
|                                                | Yes                 | 3.3      | 1.5–7.3 | 0.004  |
| Medicare Safety Net* reached in previous 12 months | No          |          |         |
|                                                | Yes                 | 2.2      | 1.1–4.5 | 0.024  |
| Living in subsidized housing                   | No                  |          |         |
|                                                | Yes                 | 2.5      | 1.0–6.2 | 0.045  |
| Receiving home care services                   | No                  |          |         |
|                                                | Yes                 | 4.4      | 1.0–18.8| 0.046  |
| Linked to HIV community organisation(s)        | No                  |          |         |
|                                                | Yes                 | 2.4      | 1.1–5.4 | 0.033  |
| Starting ART following patient request         | No                  |          |         |
|                                                | Yes                 | 3.0      | 1.3–7.0 | 0.012  |

*whereby medical costs—including pharmaceutical co-payments, are capped after reaching an annual threshold

https://doi.org/10.1371/journal.pone.0174613.t005

### Discussion

In our cohort of adults with HIV in Australia, with a median of three years of sustained viral suppression, 15% self-reported suboptimal ART adherence over the previous three months at a level that is likely to place them at increased risk of ART failure.

Other studies of self-reported ART adherence found similar or higher findings of suboptimal adherence. The average rate of reporting ≥90% adherence is estimated to be 62% [9]. One anonymous, community-based online survey (HIV Futures 7) found that about 20% of 1,058 HIV-positive, Australian adults reported <90% adherence [48]. While viral suppression in
Australia is estimated to be 92% of those engaged in care; this represents only 68% of those diagnosed [10], it is unknown how much of that gap is represented by non-adherence.

We found several factors to be independently associated with suboptimal ART adherence, including socioeconomic, cultural, social, relationship, and patient engagement factors, but not clinical or ART regimen-related factors. Of these, 3 variables were common to all analyses: reaching the Medicare safety net, receiving home care services, and self-requesting ART. Being born in Australia was associated with less adherence in our sample, which is supported by a higher rate of loss to follow-up in Australian-born individuals within another Australian cohort [49]; adherence data is not collected in that cohort. Mills et al [50] showed significantly higher adherence to ART in sub-Saharan Africa (77%) compared to North America (55%). Ortego et al [9] in meta-analysis found that participants in countries with high Human Development Index (HDI) had lower adherence rates than those with low HDI. However, in our sample, of those not born in Australia, the country of birth was most likely to be in the United Kingdom or New Zealand, where national healthcare is similarly available. In our cohort, there was a higher proportion of low-income earners in those who were Australian born, and a higher proportion of women in those born overseas; while other characteristics between the groups were similar.

Not being in a relationship was also independently associated with lower ART adherence. Other research has found adherence levels to increase with perceived quality of the relationship, and also with a partner’s support of ART [51].

About 20% of our cohort initiated ART with the aim of preventing transmission to others, and 12% at his/her own request. Therefore, it is noteworthy that suboptimal ART adherence was more common if the primary reason for having started ART was the patient’s own request. This is important, as the purpose of initiating ART, for personal or public health benefit, may influence a patient’s likelihood for adherence. Recently, in a study of HIV serodiscordant couples investigating ART as prevention of HIV (HPTN 052), high levels of ART adherence by pill count and self-report were reported in those initiating ART as prevention [52]. Good mental health was the only factor significantly associated with optimal ART adherence. HPTN 052 provides the only prospective adherence data regarding predictors of ART adherence in a population who initiated ART treatment as a means for prevention of HIV transmission. The participants were under clinical trial conditions, and actively received adherence counselling throughout the study visits, whether the same high levels of adherence will be achieved in the real world is unknown. Moreover, the investigators defined high-level adherence as ≥80% of prescribed doses, which is a lower threshold than we examined. Assessment of adherence over time in those who started ART at their own request will be important to follow-up in our

| Number of independent variables* present | n (%) | ART non-adherent | ART adherent | Odds Ratio (95%CI) P-value ** |
|-----------------------------------------|-------|------------------|--------------|-------------------------------|
| 0                                       | 47 (9.0) | 4 (8.5) | 43 (91.5) | 1.0 | - |
| 1                                       | 163 (31.2) | 14 (8.6) | 149 (91.4) | 1.0 (0.3–3.2) | 0.987 |
| 2                                       | 194 (37.2) | 25 (12.9) | 169 (87.1) | 1.6 (0.5–4.8) | 0.408 |
| 3                                       | 91 (17.4) | 26 (28.6) | 65 (71.4) | 4.3 (1.4–13.2) | 0.007 |
| 4–7                                     | 27 (5.2) | 9 (33.3) | 18 (66.7) | 5.4 (1.5–19.7) | 0.007 |

*As listed in Table 5
** P-trend <0.0001

https://doi.org/10.1371/journal.pone.0174613.t006
We are unable to explain why those participants who self-requested ART (seemingly motivated therefore to initiate ART) would be less adherent. It may be that patients self-requesting ART may be doing so for reasons such as onward transmission (e.g. pressure from sexual partners or media), or lack of education around ART requirements or side effects once started. Also, given that our sample is highly treatment-experienced, it is possible that some of the patients self-requesting ART did so after an ART break [4].

| Risk Factor                                      | ≥3 (n = 78) | <3 (n = 444) | n = Total | % | Univariate | Regression—Forward Step Wald | Regression—Enter Method | Regression—Backward Wald |
|--------------------------------------------------|-------------|--------------|-----------|---|------------|-----------------------------|-------------------------|-------------------------|
| Currently not in a relationship                  |             |              |           |   |            | OR | 95% CI | p | AOR | 95% CI | p | AOR | 95% CI | p |
| No                                               | 17          | 207          | 224       | 7.6 | 20.5       | 3.1 | 1.8–5.5 | <0.001 | 2.6 | 1.4–5.0 | 0.002 | 3.3 | 1.5–7.3 | 0.004 |
| Yes                                              | 61          | 237          | 298       |     |            |    |         |       |     |         |       |     |         |     |
| Born in Australia                                |             |              |           |   |            | OR | 95% CI | p | AOR | 95% CI | p | AOR | 95% CI | p |
| No                                               | 15          | 186          | 201       | 7.5 | 20.5       | 3.1 | 1.8–5.5 | <0.001 | 2.7 | 1.4–5.1 | 0.003 | 2.4 | 1.2–4.9 | 0.014 |
| Yes                                              | 63          | 258          | 321       |     |            |    |         |       |     |         |       |     |         |     |
| Medicare Safety Net reached in previous 12 months |             |              |           |   |            | OR | 95% CI | p | AOR | 95% CI | p | AOR | 95% CI | p |
| No                                               | 49          | 343          | 392       | 12.5| 33.3       | 3.9 | 2.3–6.7 | <0.001 | 2.1 | 1.1–3.9 | 0.025 |     |         |     |
| Yes                                              | 29          | 101          | 130       |     |            |    |         |       |     |         |       |     |         |     |
| Major Depressive Disorder (PHQ-9)                |             |              |           |   |            | OR | 95% CI | p | AOR | 95% CI | p | AOR | 95% CI | p |
| No                                               | 49          | 386          | 435       | 11.3| 33.3       | 3.9 | 2.3–6.7 | <0.001 | 2.1 | 1.1–3.9 | 0.025 |     |         |     |
| Yes                                              | 29          | 58           | 87        |     |            |    |         |       |     |         |       |     |         |     |
| Marijuana use ≥ monthly                          |             |              |           |   |            | OR | 95% CI | p | AOR | 95% CI | p | AOR | 95% CI | p |
| No                                               | 52          | 376          | 428       | 12.1| 20.5       | 3.1 | 1.8–5.5 | <0.001 | 2.1 | 1.1–3.9 | 0.025 |     |         |     |
| Yes                                              | 26          | 68           | 94        |     |            |    |         |       |     |         |       |     |         |     |
| Receives home care services                      |             |              |           |   |            | OR | 95% CI | p | AOR | 95% CI | p | AOR | 95% CI | p |
| No                                               | 70          | 438          | 508       | 13.8| 20.5       | 3.1 | 1.8–5.5 | <0.001 | 2.1 | 1.1–3.9 | 0.025 |     |         |     |
| Yes                                              | 8           | 6            | 14        |     |            |    |         |       |     |         |       |     |         |     |
| Participates in HIV Community Organisations      |             |              |           |   |            | OR | 95% CI | p | AOR | 95% CI | p | AOR | 95% CI | p |
| No                                               | 56          | 389          | 445       | 12.6| 20.5       | 3.1 | 1.8–5.5 | <0.001 | 2.1 | 1.1–3.9 | 0.025 |     |         |     |
| Yes                                              | 22          | 55           | 77        |     |            |    |         |       |     |         |       |     |         |     |
| Necessity Concerns score > sample mean           |             |              |           |   |            | OR | 95% CI | p | AOR | 95% CI | p | AOR | 95% CI | p |
| No                                               | 30          | 247          | 277       | 10.8| 20.5       | 3.1 | 1.8–5.5 | <0.001 | 2.1 | 1.1–3.9 | 0.025 |     |         |     |
| Yes                                              | 48          | 197          | 245       |     |            |    |         |       |     |         |       |     |         |     |
| Starting ART following patient request           |             |              |           |   |            | OR | 95% CI | p | AOR | 95% CI | p | AOR | 95% CI | p |
| No                                               | 61          | 397          | 458       | 13.3| 20.5       | 3.1 | 1.8–5.5 | <0.001 | 2.1 | 1.1–3.9 | 0.025 |     |         |     |
| Yes                                              | 17          | 47           | 64        |     |            |    |         |       |     |         |       |     |         |     |
| Living in subsidized housing                     |             |              |           |   |            | OR | 95% CI | p | AOR | 95% CI | p | AOR | 95% CI | p |
| No                                               | 56          | 362          | 418       | 13.4| 20.5       | 3.1 | 1.8–5.5 | <0.001 | 2.1 | 1.1–3.9 | 0.025 |     |         |     |
| Yes                                              | 22          | 82           | 104       |     |            |    |         |       |     |         |       |     |         |     |
| Having difficulty with ART pharmacy access       |             |              |           |   |            | OR | 95% CI | p | AOR | 95% CI | p | AOR | 95% CI | p |
| No                                               | 67          | 423          | 490       | 13.7| 34.4       | 3.3 | 1.5–7.2 | 0.001 | 2.8 | 1.0–7.6 | 0.050 |     |         |     |
| Yes                                              | 11          | 21           | 32        |     |            |    |         |       |     |         |       |     |         |     |

https://doi.org/10.1371/journal.pone.0174613.t007

cohort. We are unable to explain why those participants who self-requested ART (seemingly motivated therefore to initiate ART) would be less adherent. It may be that patients self-requesting ART may be doing so for reasons such as onward transmission (e.g. pressure from sexual partners or media), or lack of education around ART requirements or side effects once started. Also, given that our sample is highly treatment-experienced, it is possible that some of the patients self-requesting ART did so after an ART break [4].

One financial indicator independently associated with suboptimal ART adherence in our sample was living in subsidized housing. In comparison, one systematic review of five studies found that medication adherence was positively associated with housing stability in HIV-infected adults [53]. However, living in subsidized housing, as assessed in our study, does not
necessarily imply that the housing is unstable (e.g. transient). The implication that subsidised housing may not represent housing stability is important; as one study found that residents in long-term public housing had better ART adherence than those in short-term or transient housing situations (e.g. hostels or shelters) [54].

In our sample, reaching the Medicare safety net was positively associated with suboptimal adherence. Housing status and meeting Medicare safety net thresholds may reflect broader differences in socioeconomic status (SES). Lower SES has been associated with poorer treatment outcomes in HIV, although this has predominantly been investigated in the United States where subsidised healthcare was not universally available [16], while our sample overwhelmingly has access to subsidized healthcare, as in western Europe and Canada for example. Those patients who meet the Medicare safety net threshold are more likely to have multiple comorbidities, given that the threshold is met by service utilisation. It may be that exceeding the Medicare safety net thresholds places participants at such a high level of financial strain that ART delay or interruption follows. This would suggest that lowering the Medicare safety net threshold may improve ART adherence. While the ART co-payment costs to participants were not associated with suboptimal adherence, this is just one component of the financial burden that contributes to meeting the Medicare safety net threshold (thereby reduced once the threshold is met). Recently (01 October 2015), the ART co-payment was removed in the state of New South Wales. Other jurisdictions in Australia still apply a co-payment, while some do not (or never have). The influence this has on ART adherence in different jurisdictions and over time is yet to be determined.

Suboptimal adherence also associated with home-care services and linkage to HIV-community organisations / outreach. These covariates may also be indicative of other factors that exacerbate non-adherence, as they may be the result of a higher dependency on medical care, or self-identified requirements to engage in outreach, for example, patients with chronic or more complex needs. These variables are unlikely to be the cause of low adherence per se, but rather may be a result of complex sets of factors that predispose to low adherence, such as low income, higher healthcare costs, low education, drug use, and mental ill-health.

Sensitivity analysis was conducted, fitting the model after reclassifying 23 participants from the “sub-optimally adherent” group as they were on twice-daily ART dosing. The two analyses overlapped in that statistically significant variables in the reduced sample were reaching the Medicare safety net, receiving home care services, and self-requesting ART; and of borderline statistical significance was injecting crystal methamphetamine. Importantly, 11 of these 23 participants were on a once-daily backbone therapy. It is unknown from our data which / what ART dose was missed.

Our study looked at a comprehensive set of factors that may influence adherence. In multivariate analysis, ART medications and regimens (e.g. STRs) were not as important as socioeconomic, cultural, social indicators or participant preference to start ART. Other factors, such as injection drug use and depression, were also no longer significant following regression analysis. Also contrary to previous work in the US which concentrated on more advanced HIV-positive cases with a higher prevalence of HIV-associated dementia [26], we did not find an association with neurocognitive impairment.

Our data suggest that improvements in ART dosing and tolerability may have less effect on improving adherence than will addressing the modifiable variables we found to be associated with suboptimal adherence. The findings of the current study arguably suggest that interventions designed specifically for this vulnerable part of the Australian population are further needed as, despite current supports, it is possible that complex and combined life stresses associated with lower socio-economic status in high-income countries lead to non-optimal adherence and so the risk of disease progression.
Our study has limitations. Adherence was based solely on participant self-report; which may overestimate true adherence [55]. Hence it is possible that suboptimal adherence is underestimated in this sample. It should be noted, however, that all participants had achieved sustained viral suppression. Our study did not collect refusal rates during recruitment due to the nature of establishing a multi-site clinical cohort, relying on divergent local site management. This limitation is of particular importance to the risk of selection bias, if there are a subset of patients who were considered ineligible by the sites or themselves unwilling to complete the questionnaire (e.g. given the length of time involved).

Findings may not generalise to other population groups, such as women and heterosexual men, to patients who are experiencing virological failure, or to other settings, such as one without access to free or highly subsidized ART, community supports or social housing. The sample and setting of this study nevertheless captures the community most affected by HIV in Australia [56] and it is reassuring that our cohort’s demographics are very similar to the national demographic data [57].

There is a risk that in such a comprehensive data-set, there will be co-linearity between some variables. We chose to use a multivariable regression model, as the aim was to identify variables that could be easily identified in a clinical consult, to enable healthcare workers to determine allocation of adherence-improving resources in a clinically meaningful way; and for this reason using multivariable regression modelling and conducting sensitivity analyses was the approach chosen. Other studies investigating correlates of adherence have used similar approaches [58].

In the current era of early and lifelong ART, it is imperative that a patient’s likelihood for suboptimal adherence be assessed at regular intervals, and that those who would benefit from adherence interventions are identified and offered appropriate supports. From a broadly scoped, multi-dimensional assessment we identified a limited number of variables independently associated with suboptimal adherence. These variables are not routinely monitored in clinical care, cohort studies or clinical trials; but could be incorporated into these settings. These variables provide information that could be readily assessed prior to ART initiation and periodically whilst receiving ART as indicators of an elevated risk of suboptimal adherence. It will be important to undertake a longitudinal assessment of associations between covariates and suboptimal adherence, drawing on the data prospectively collected in the current study, to gauge if the predictors of incident and sustained low adherence are similar to covariates identified in the current report.

Supporting information
S1 File. Minimal data set.
(SAV)

Acknowledgments
The authors would like to thank all participants and to acknowledge all site lead investigators and study coordinators: The Albion Centre, Sydney (Prof Don Smith, Ms Denise Smith); The Alfred Hospital, Melbourne (Dr James McMahon, Ms Cath Downs, Ms Jess Costa); Brookong Sexual Health Clinic, Wagga Wagga (Dr Kym Collins, Ms Sally-Anne Brennan, Ms Jennifer Macleod); Cairns Sexual Health Service (Dr Darren Russell, Ms Faith Bassett, Ms Colette Cashman); Canberra Sexual Health Centre (Dr Sarah Martin, Mr Rendry Del Rosario, Ms Ruth Evans, Ms Anne Baynes); The Centre Clinic, Melbourne (Dr BK Tee, Ms Helen Lau); East Sydney Doctors (Dr David Baker, Ms Vicki Ieroklis, Ms Elizabeth Odgers, Ms Katherine
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Ognenovska); Fremantle Health and Hospital Services / Fiona Stanley Hospital (Dr John Dyer, Ms Annamaria Palermo); Holdsworth House Medical Practice, Sydney (Dr Mark Bloch, Mr Avindra Jayawardene, Ms Lily Alldridge, Ms Toni Gaunson); Melbourne Sexual Health Centre (Dr Tim Read, Ms Julie Silvers, Ms Helen Kent); Monash Health (A/Prof Michelle Giles, Ms Mellissa Bryant); Royal North Shore Hospital Clinic 16, Sydney (Prof Suran Fernando, Ms Anisa Cheshire); SHAIDS Sexual Health Service, Lismore (Dr David Smith, Ms Kate Allardice, Ms Arian Minc, Ms Amber Tarver); St Vincent’s Hospital, Sydney (Ms Nicola MacKenzie, Ms Kate Sinn, Ms Dianne Morris); Sydney Sexual Health Clinic (A/Prof Anna McNulty, Ms Ruthy McIver); Taylor Square Private Clinic, Sydney (Dr Robert Finlayson, Ms Sophie Din- ning, Mr David Ninham, Ms Shruti Gupta); Western Sydney Sexual Health Centre (Dr Catriona Ooi, Ms Karen Biggs, Ms Melissa Power); and administrative assistance by Ms Stephanie Riches.

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