



Impact of the removal of patient co-payments for antiretroviral therapy (ART) on out-of-pocket expenditure, adherence and virological failure among Australian adults living with HIV

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ABSTRACT

Background: : In 2015, New South Wales (Australia) removed patient co-payments for ART of HIV. We hypothesized the policy change would reduce overall out-of-pocket (OOP) healthcare expenditure, improve ART adherence, and better maintain HIV suppression. **Methods:** Using data from a national, 2-year prospective study of adults with HIV on ART (n=364) (2013–2017), we compared OOP healthcare expenditure, ART adherence, and virological failure (VF) in participants subject to the co-payment policy change with participants from other jurisdictions who never paid, and who always paid, co-payments. We used fixed effects regression models to compare outcomes, and incidence rates for VF.

Results: : Although ART co-payments declined, there was no significant change in total OOP healthcare expenditure in participants ceasing co-payments compared to those who continued (adjusted coefficient 0.09, 95% CI -0.31 to 0.48). Co-payment removal did not significantly reduce suboptimal ART adherence (from 17.5% to 16.3%) or VF (from 5.0 to 3.7 episodes per-100-person-years). Participants in the lowest income group but not receiving concessional government benefits incurred a non-significant increase in total OOP healthcare expenses; while concessional participants experienced a significant increase in non-ART HIV healthcare costs after the policy changed.

Conclusion: : In this population, ART co-payments represented a small proportion of OOP healthcare expenditure. Its removal did not materially impact ART adherence or VF, although the study was not powered to detect these.

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Introduction

Medication adherence is an important component of optimal therapy for chronic conditions. Sustained, high ($\geq 95\%$) levels of adherence to antiretroviral therapy (ART) for HIV infection is strongly recommended to maximise the likelihood of HIV suppression, to prevent HIV transmission, morbidity, AIDS, and death [1].

Despite the known benefits of ART, its interruption and discontinuation are common [2,3]. Across 84 studies, ART adherence was found to range from 59% to 83% [2], and socio-economically disadvantaged individuals had the lowest adherence rates in some studies [4]. Suboptimal ART adherence has also been associated with younger age, ART side effects, lack of a supportive patient-physician relationship, and lack of social support more generally [3,5,6]. There is also evidence, mainly from resource-limited countries, that high out-of-pocket (OOP) expenditure for patients can reduce ART adherence, resulting in higher hospitalisation rates and more medical expenses [7,8].

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Australia has a publicly funded universal health insurance scheme, Medicare, which is available to all Australian citizens and permanent residents. Medicare covers healthcare costs either in full or partially. The list of services covered, the schedule of fees for the service, and the portion of the fee that is covered by Medicare, are set out in the Medicare Benefits Schedule (MBS) [9]. Public hospital care is fully covered by Medicare, while other services (e.g. diagnostic imaging, radiotherapy) may be partially or fully covered dependent on the setting. Medical specialists and allied health professionals outside of a public hospital determine the amount they charge for a service, and if that amount is the same as the MBS fee, they bill Medicare directly and the service is free to the patient (known as 'bulk billing') [9]; however, if it exceeds the MBS fee, then patients pay the gap between the MBS fee and the cost charged [9,10].

Australians who are covered by Medicare also have access to subsidised medication through the Pharmaceutical Benefits Scheme (PBS) [11]. Medications listed on the PBS schedule are dispensed to patients, who also contribute a co-payment. A concessional benefit is available to pensioners, seniors, people receiving unemployment or low-income benefits, and veterans [11]. The concessional benefit entitles patients to a concession card that provides a reduction in the co-payment. In the period between 2013 and 2017, non-concessional patients paid a maximum co-payment for any single PBS-listed medication of A\$36.10 in 2013 to A\$38.80 in 2017. Patients with a concession card paid a reduced co-payment, ranging from A\$5.90 in 2013 to A\$6.30 in 2017, per prescription item. Jurisdictions can choose to waive the co-payment for some essential medicines, for example for chronic illness [12].

The PBS is underpinned by a safety net whereby once an individual or family reaches an expenditure threshold for their cumulative PBS co-payments in a calendar year, subsequent co-payments during that year are reduced for non-concessional patients and waived for people who hold a concession card [13]. There are two thresholds applied for patients with and without a concession card that, between 2013 and 2017 ranged from A\$354.00 to A\$378.00 and A\$1,390.60 to A\$1,494.90, respectively.

Medicare does not cover the indirect costs of commuting to access healthcare, taking time off from work for appointments, or non-prescription medications [14,15]. One previous study found a significant minority of HIV-positive outpatients at a large Sydney HIV clinic delayed or discontinued medication due to difficulty paying for co-payments and clinic travel costs [16]. A study examining pharmacy data on ART dispensed in a hospital and sexual health centre in Melbourne, Victoria, found patients who take multiple medications for comorbid conditions were especially vulnerable to high cumulative OOP expenses [15], and another study examining comorbidities in a cohort of Australian adults living with HIV found that 75% of participants took at least one concomitant medication, while 23% took five or more concomitant medications [17].

On 01 October 2015, the government of New South Wales (NSW), Australia's most populous state, removed the patient co-payment for ART to ease the financial burden for people living with HIV [18]. Western Australia and one sexual health clinic in the state of Victoria had never charged an ART co-payment, whilst other states and clinics charged the co-payment. Previous research on co-payment removal for patients with chronic conditions (e.g., diabetes, cardiovascular diseases, gout) yielded mixed results for treatment adherence [19–21]. Understanding the impact of the NSW initiative to remove ART co-payments could assist in positive policy development [22]. Our study utilises a natural experiment by using a before and after comparison in a prospective, national cohort study of adults living with HIV, and reports on the impact of the NSW initiative to remove the ART co-payment on

OOP healthcare expenditure, ART adherence, and risk of virological failure.

Materials and Methods

Data source

Data were drawn from the Predictors of Adherence to Antiretroviral Therapy (PAART) study, a national, 2-year cohort study of adults living with HIV on stable ART who had an undetectable plasma HIV viral load at study entry [3]. Between September 2013 and November 2015, 523 participants were recruited from 17 Australian general practice, sexual health, or hospital outpatient clinics. Of all participants, 159 (30.4%) were excluded from the present analysis as they were: not eligible for Medicare (n=25; 4.7%); did not complete a follow-up questionnaire (n=62; 11.8%); completed the study before the co-payment change or were included after the policy change was implemented (n=72, 13.8%).

To assess the impact of the NSW initiative to remove patient co-payments for ART (hereafter referred to as 'policy change'), our analysis compared three groups for whom data were available before and after the policy change: (1) participants in NSW who stopped paying the ART co-payment ('**stop-copay**' group); (2) participants from other states and territories who always incurred the ART co-payment ('**continued-copay**' group), and (3) participants from other states and territories who never incurred the ART co-payment ('**copay-exempt**' group).

As shown in Figure 1a, the study period was divided into two parts: 30 September 2013 to 30 September 2015 (i.e., before removal of the co-payment in NSW); and 01 October 2015 to 30 November 2017 (i.e., after co-payment removal). This pre-post and comparison-group design allows for a meaningful assessment of the impact of co-payment changes on OOP healthcare expenditure, ART adherence, and risk of virological failure.

Self-report questionnaire

All study participants were asked to complete the same questionnaire at Baseline, Month 12, and Month 24. The questionnaire captured data on social demographic characteristics; socioeconomic indicators; physical health; well-being, life stressors, and social supports; HIV disclosure, stigma, and discrimination; healthcare access; ART regimen, adherence, and side effects; healthcare and OOP expenditure; and treatment beliefs. The study methods are described in more detail elsewhere [3].

Out of pocket expenditure

The questionnaire asked participants to estimate their OOP expenditure over the previous 3 months on all HIV-related healthcare services (e.g., HIV specialist(s), general practitioner(s), counsellor(s), any HIV-related diagnostic expenses [e.g., diagnostic imaging, pathology]), and separately on non-HIV healthcare services (e.g., naturopath, herbalist, non-HIV specialists, treatment and diagnostic imaging).

To obtain ART-specific OOP expenditure in an objective manner, each participant's ART dispensing data, including the number of months for which ART was dispensed and OOP expenditure on ART, were obtained from all ART-dispensing pharmacies for the 12 months prior to baseline and at Months 12 and 24, thereby providing a 36-month objective record of ART expenditure data. For comparison before and after the policy change, the average quarterly OOP expenditure for ART was calculated by summing each participant's annual OOP expenditure associated with ART and dividing by four, which allowed for any safety net reductions to be accounted for.

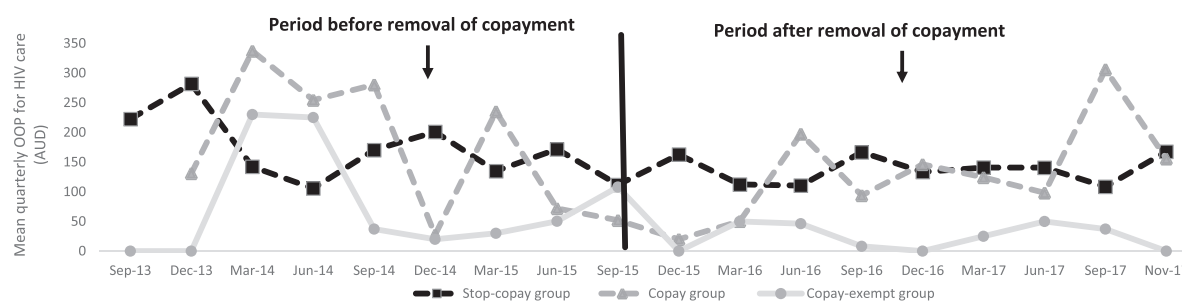


Figure 1a. Mean quarterly OOP HIV healthcare expenditure over the study period

Note: The study period was divided into two parts: 30 September 2013 to 30 September 2015 (i.e. period before removal of the co-payment in NSW); and 01 October 2015 to 30 November 2017 (i.e. after its removal). Study groups: **'Stop-copay'** group refers to participants in New South Wales who stopped paying the ART co-payment following the removal of patient co-payment for ART on 1 October 2015 (n=251 participants); **'Copay'** group refers to participants from other States and Territories that always incurred the ART co-payment (n=60 participants) and **'Copay-exempt'** group refers to participants from other States and Territories that never incurred the ART co-payment (n=53 participants).

Total OOP expenditure was estimated as the total amount of participant's own money spent to access any HIV-related healthcare (self-report), non-HIV related healthcare (self-report), or to obtain ART (pharmacy dispensing data extraction). Total OOP spending was divided by self-reported income and multiplied by 100 to obtain the percentage of income allocated to these expenditures. Of the study sample, 16 participants (4.3%) did not respond to all healthcare-related expenditure questions and were excluded from the analyses. The missing income data of the 28 participants (7.6%) who did not provide their income on the questionnaire were imputed using the median income of participants who provided this information if the participant was not a concession card holder. If participants reported only government payments as their income source without further specifying the amount, their income was imputed based on the government benefits (e.g., age pension payment or Disability Support Pension) they received. The OOP expenditure data were inflated to 2019 Australian dollars, using the Australian Institute of Health and Welfare inflation rate [23].

Outcomes

The outcomes of interest before and after the co-payment policy change were (a) OOP expenditure on healthcare, including on HIV and non-HIV related healthcare, and on ART; (b) suboptimal ART adherence, which was assessed in the self-report questionnaire and defined by self-reported missing ≥ 1 ART dose/month over the previous three months; and (c) risk of virological failure, measured by blood tests and defined as one instance of viral load >200 copies/mL plasma, two consecutive viral loads >50 copies/mL, or a single viral load >50 copies/mL followed by an ART switch. This definition of risk of virological failure represents a synthesis of the definitions used in current ART guidelines in the United States, Australia, and Europe [24,25].

Statistical analyses

Bivariate analyses were conducted using Pearson's chi-square tests for categorical variables and t-tests for continuous variables to compare the baseline socioeconomic characteristics of participants in the 'stop-copay' group with the 'continued-copay' group and the 'copay-exempt' group.

For all three groups ('stop-copay', 'continued copay', and 'copay exempt'), the mean quarterly OOP on HIV related healthcare, non-HIV related healthcare, and ART co-payments and their difference were calculated for the period before and after the policy change.

To assess changes in OOP expenditure for ART, we used a difference-in-differences (DiD) analysis. This approach entails com-

paring mean changes in OOP spending for ART before and after the policy change by co-payment status ('stop-copay' group versus 'continued-copay' group). The DiD method allows for the estimation of the effect of the policy change, as it accounts for time-invariant differences between the study groups and changes in OOP spending across time (i.e., a period before and after the policy change was in effect). The model structure is set out as follows:

$$y_{i,t} = \beta_0 + \beta_1 x_i + \beta_2 z_t + \beta_3 (x_i * z_t) + \beta_4 w_{it} + \epsilon_{i,t}$$

whereby $y_{i,t}$ is the natural log of OOP expenditure of group i at time t x_i is a dummy variable to indicate the 'stop-copay' group (i.e., $P_i = 1$) and the 'continued-copay' group (i.e. $P_i = 0$). z_t is a dummy variable indicating pre and post 'non-payment' periods (i.e. post-policy change period = 1). The coefficient β_3 , for the interaction term $x_i * z_t$, indicates the effect of the removal of the co-payment policy on the 'stop-copay' group (i.e., difference-in-differences). The vector w_{it} represents covariates that were significant at the $p < 0.05$ level in the bivariate analysis between the 'stop-copay' group and 'continued-copay' group, and other control variables (i.e., age, sexuality, income, tertiary education, living in a capital city, having private health insurance, number of co-morbidities, and self-assessed health status) that could potentially affect OOP expenditure.

Subsequently, fixed effects linear regression models were utilised to assess within-person changes in the total OOP expenditure in relation to change in co-payment status. This approach reduces potential biases where each individual acts as their own control and estimates are not confounded by time-invariant characteristics such as socio-demographic or environmental factors. We controlled for a number of relevant covariates (age, sexuality, income, tertiary education, living in a capital city, having private health insurance, number of co-morbidities, and self-assessed health status) in the fixed-effect models. Subgroup analyses were conducted to examine changes in outcome for concessional and non-concessional card holders. As the distribution of OOP expenditure is positively skewed, a natural logarithm transformation of the expenditure was applied to the expenditure included in the regression model. Individual-level standard error clustering was used to account for repeated measures. We assessed the validity of the parallel trend assumption by checking for any differential trends in OOP expenditure for ART between the 'continued-copay' group and 'stop-copay' group by graphing the pre-policy data (Figure 1b).

We assessed the OOP expenditure for HIV related services and ART expenses relative to income for the 'stop copay' group and the effect of the policy change on their spending difference (in percentage terms) after the policy change (as this was the only group directly impacted by the policy change). We further stratified the analysis by concession card holder status. For participants who did

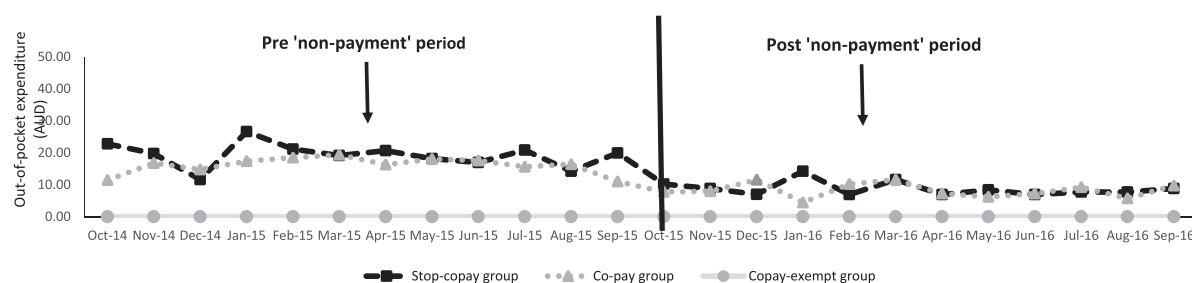


Figure 1b. Adjusted mean OOP spending on ART – ‘stop co-pay’ group, ‘copay’ group and ‘copay-exempt’ group

Note: Figure 1b shows the mean monthly out-of-pocket expenditure for ART in the twelve months before and after the removal of the patient co-payments in NSW on 1 October 2015 for the three study groups. About one in ten participants in the ‘stop-copay’ group continued to pay for ART despite the removal of patient co-payment for ART (i.e. post ‘non-payment’ policy1 period)

not have a concession card we further analysed by income, to elucidate the impact on the lower income, non-concessional participants.

For ART adherence and risk of virological failure, the within-subject difference in rates between pre- and post-policy change periods were tested using paired McNemar tests and t-tests, respectively. The incidence rate of virological failure was determined and expressed in person years of follow-up.

All statistical analyses were performed with STATA version 15.0 (STATACorp, College Station, TX, USA). For all tests, $p < 0.05$ was considered statistically significant.

Results

Participant characteristics

Baseline characteristics of the 364 included participants by co-payment status are shown in Table 1. Baseline characteristics of included and excluded participants were similar (data not shown). Participants’ mean age was 52.6 years ($SD=11.3$), and most were male ($n=348$, 95.6%) and had at least one diagnosed comorbidity ($n=208$, 57.1%). Participants’ median weekly after-tax income was A\$587; 156 (42.9%) held a concession card and were therefore eligible for the concessional co-payment rate for ART (verified by the ART-dispensing pharmacies).

In the 12 months prior to baseline, 93 participants (25.6%) reported a need for financial support for basic living expenses such as food/groceries and household bills, and 61 (16.8%) reported delaying or interrupting ART due to financial hardship. Just over 15% reported suboptimal ART adherence over the previous three months. The number of participants taking a single tablet regimen (STR) prior to the policy change was 110 (30.2%); after the policy change, 161 participants were taking an STR (44.4%).

OOP expenditure

The mean quarterly OOP spending on healthcare before and after the policy change is shown in Table 2. Although ART co-payments declined, total OOP expenditure did not decrease significantly in any group after the policy change.

The results from the adjusted regression models with estimates for the total OOP expenditure (HIV and non-HIV-related care and ART) between the ‘continued-copay’ group and the ‘stop-copay’ group are presented in Table 3. Although the policy change reduced the OOP for ART, the analysis showed no significant difference in the total OOP spending for HIV and non-HIV-related care in the ‘stop-copay’ group as compared to the ‘continued-copay’ group over the study period. When the analyses were stratified by concession card holder status, the model estimates showed a significant increase in OOP spending on HIV-related healthcare for participants with a concession card after the policy change. In both

groups there was a significant decrease in the percentage of after-tax income spent on ART following the introduction of the policy change.

The results of the analysis of OOP spending relative to income shows that for the ‘stop-copay’ group (that is, the people directly impacted by the policy change), there was a significant decrease in the percentage of after-tax income spent on ART following the introduction of the policy change (Table 4). The percentage of after-tax income spent on HIV-related clinical services remained unchanged at 2.0%. When the analysis was stratified by income quintiles for non-concession card holders, the results showed a significant decrease in the relative amount of spending among participants with a weekly income of more than A\$650. Although not significant, participants with bottom income quintile (i.e. weekly income \leq A\$650) experienced the highest financial burden in both time periods. The relative amount of OOP spending increased from 2.4% to 4.0% of their after-tax income on HIV-related clinical services ($p=0.23$).

It is noteworthy that 9.5% of participants in the ‘stop-copay’ group continued to pay an ART co-payment after the policy to remove co-payments for ART was introduced (Figure 1b).

ART adherence

We did not find a significant difference in self-reported ART adherence after the policy change in any of the three groups (Table 5). Suboptimal adherence did not improve significantly in any group, and there was no significant difference between groups in the magnitude of change.

Virological failure

Comparison of rates of virological failure before and after the policy change for all three groups (‘stop-copay’, ‘continued-copay’, ‘copay-exempt’) are presented in Table 5. Overall, 34 participants (9.3%) had an episode of virological failure during the study period. In the ‘stop-copay’ group, 22 participants (8.7%) experienced virological failure over a median of 277 days (IQR: 164 – 571), giving a failure rate of 4.5 cases per 100 person-years of follow-up; this did not vary significantly before and after the policy change.

Discussion

To the best of our knowledge, this is the first study in a resource-rich country to examine the financial and clinical impacts of a state-wide initiative to remove the patient co-payment for ART of HIV. We found that removing the ART co-payment reduced ART expenditure but did not significantly reduce overall OOP healthcare expenditure, improve ART adherence, or reduce the risk of virological failure. Participants in the lowest income group but above the

Table 1
Baseline characteristics.

Variable	All included participants (n=364)	Co-payment status 'Continued-Copay' group (Always paid) (n=60)	'Copoly-exempt' group (Never paid) (n= 53)	'Stop-copay' group (Stopped) (n=251)
<i>Demographic indicators</i>				
Age (years) mean \pm SD	52.6 \pm 11.3	50.7 \pm 14.4	50.7 \pm 13.6	53.4 \pm 9.9
Male, n (%)	348 (95.6)	56 (93.3)	45 (86.5)***	247 (98.0)
Self-identified as gay, n (%)	285 (78.3)	40 (66.7)**	35 (67.3)***	210 (83.3)
Lives in capital city, n (%)	313 (85.3)	49 (81.7)	47 (90.4)	217 (86.1)
Married/de facto, n (%)	125 (40.1)	31 (51.7)	22 (42.3)	92 (36.7)
<i>Socioeconomic indicators</i>				
Tertiary education, n (%)	136 (37.4)	19 (31.7)	23 (44.2)	94 (37.3)
Private health insurance, n (%)	160 (44.0)	26 (43.3)	27 (51.9)	107 (42.5)
Main source of personal income ¹ n (%)				
From wages	162 (44.5)	33 (55.0)	26 (50.0)	103 (40.9)
Non-wages (e.g. savings)	46 (12.6)	3 (5.0)	11 (21.1)*	32 (12.7)
Government (e.g. age pension)	156 (42.9)	24 (40.0)	15 (28.9)	117 (46.4)
Income per week after tax (AUD)				
Median (IQR) AUD per week	587 (749)	502 (805)	678 (788)	582 (673)
\leq A\$400, n (%)	69 (19.0)	16 (26.7)	8 (15.1)	45 (17.9)
A\$401 to A\$800, n (%)	147 (40.4)	20 (33.3)	21 (39.6)	106 (42.2)
\geq A\$801, n (%)	148 (40.6)	24 (40.0)	24 (45.3)	100 (39.8)
Concessional status ²				
Non-concession card holder	208 (57.1)	36 (60.0)	37 (71.1)	135 (45.4)
Concession card holder	156 (42.9)	24 (40.0)	15 (28.9)	117 (46.4)
Accommodation, n (%)				
Own property	162 (44.5)	29 (48.3)	28 (53.9)	105 (41.7)
Social/public housing	119 (32.7)	8 (13.3)	19 (36.5)	77 (30.6)
Other (e.g. private rental)	83 (22.8)	23 (38.4)	5 (9.6)***	70 (27.8)
Required financial assistance for basic living in last 12 months, n (%)	93 (25.6)	11 (18.3)	7 (13.5)*	75 (29.8)
<i>Health indicators</i>				
Self-assessed health status "good" or "very good", n (%)	305 (83.8)	55 (91.7)*	46 (88.5)	204 (80.9)
Diagnosed Comorbidity ³ , n (%)	208 (57.1)	35 (58.3)	20 (37.7)**	153 (61.0)
Delayed/interrupted ART in previous 12 months due to financial hardship, n (%)	61 (16.8)	12 (20.7)	9 (17.3)	54 (21.4)
Suboptimal ART adherence ⁴ n (%)	56 (15.4)	8 (13.3)	4 (7.7)	44 (17.5)
ART as a single tablet regimen	110 (30.2)	25 (41.7)	20 (37.7)	65 (25.9)

Note: 'Stop-copay' group refers to participants in New South Wales who stopped paying the ART co-payment following the removal of patient co-payments for ART on 01 October 2015; 'Continued-Copay' group refers to participants from other States and Territories that always incurred the ART co-payment; and 'Copoly-exempt' group refers to participants from other States and Territories that never incurred the ART co-payment.

P value: * <0.05, ** <0.01 *** <0.001 AUD: Australian dollars

¹ Income refers to after-tax income adjusted; non-wage income e.g. superannuation and private savings; government support e.g. age pension and disability support pension. Missing income data was imputed using participants with income data for participants with missing data, or where participants report only government payments as their income source, their missing income data were imputed based on the type of government benefits they received.

² Concessional status are individuals with a 'concession' card (e.g. pensioners, unemployed) and therefore, paid a reduced co-payment for medication.

³ Diagnosed comorbidities include cardiovascular diseases, liver disease, kidney disease, diabetes and psychiatric conditions.

⁴ Suboptimal adherence is defined as missing an average of at least one ART dose per month over the last three months prior to survey.

threshold income to be eligible for a concession card did not experience a significant financial benefit from the co-payment policy change and incurred a non-significant increase in total OOP healthcare expenses; while participants who had a concession card experienced a significant increase in non-ART HIV healthcare costs following the policy change.

If the policy was intended to decrease OOP for ART, the policy can be said to have been effective. However, considering the co-payment for ART alone, overlooks the significance of other OOP healthcare expenditures. There were also no positive flow-on effects from this policy change to HIV outcomes related to ART i.e. improved adherence or reduced virological failure; although the study was not powered to detect these outcomes. One likely reason for the absence of a significant policy effect could be the relatively small ART co-payment cost compared to total OOP cost (e.g., concomitant medication co-payments, medical consultations, diagnostic imaging and pathology). This is consistent with previous Australian studies that found medical services such as therapeutic procedures and pathology tests accounted for a greater proportion of OOP expenditure than prescription drugs amongst people with cancer [26,27].

Although the Australian government subsidises the cost of a wide range of medical services and pharmaceuticals for almost all residents, many medical services such as diagnostic imaging and pathology tests incur significant patient co-payments [28]. Regular OOP spending on these services can pose a substantial burden, especially for low-income, non-concession card holders (the "working poor") and those with substantial medical needs. In our study, despite safety nets, OOP costs for HIV care as a percentage of total income were highest in the (non-concessional) lowest-income group. Although the policy change aimed to reduce OOP expenditure for HIV, the incremental differences between concession card holders and lower-income non-concession card holders to reach the safety net threshold may become substantial, especially for the 'working poor'. This suggests that even after removing the co-payment, the burden of OOP expenses may disproportionately impact those who can least afford it.

The current MBS and PBS schemes assist people living below the low-income threshold through safety nets and concession status. However, there is increasing evidence that having concession status does not prevent HIV care from being a financial burden [29]. In a longitudinal survey of people with HIV in Australia, one-

Table 2
Mean quarterly out-of-pocket expenditure (unadjusted).

OOP	Pre-policy mean (95%CI) (AUD)	Post-policy mean (95%CI) (AUD)	Mean difference (95%CI) (AUD)
'Stop-copay' group (stopped, n=251)			
Total OOP¹	319 (271 – 367)	270 (224 – 317)	49 (-17 – 115)
HIV related OOP	125 (96 – 154)	127 (98 – 157)	-2 (-43 – 39)
Non-HIV related OOP	145 (117 – 174)	129 (102 – 157)	16 (-23 – 55)
ART co-payment	48 (41 – 54)	13 (10 – 17)	35 (27 – 42)***
'Continued-Copay' group (always paid, n=60)			
Total OOP	330 (227 – 433)	257 (147 – 367)	73 (-76 – 223)
HIV related OOP	155 (82 – 229)	115 (51 – 178)	40 (-55 – 137)
Non-HIV related OOP	134 (82 – 187)	112 (59 – 165)	22 (-51 – 96)
ART co-payment	40 (30 – 50)	30 (23 – 37)	10 (-2 – 22)
'Copay-exempt' group (never paid, n=53)			
Total OOP	219 (110 – 328)	106 (59 – 152)	113 (-4 – 231)
HIV related OOP	102 (50 – 153)	35 (18 – 52)	66 (12 – 120)**
Non-HIV related OOP	116 (18 – 214)	70 (29 – 111)	46 (-59 – 151)
ART co-payment	0	0	0

Note: 'Stop-copay' group refers to participants in New South Wales who stopped paying the ART co-payment following the removal of patient co-payments for ART on 01 October 2015; 'Continued-Copay' group refers to participants from other States and Territories that always incurred the ART co-payment; and 'Copay-exempt' group refers to participants from other States and Territories that never incurred the ART co-payment.

OOP expenditure for HIV includes 18 participants (7.1%) who reported zero OOP healthcare expenditure in the period before the 'policy change' and 68 participants (27.0%) who reported zero OOP healthcare expenditure after 'policy change'.

OOP: Out of pocket; **AUD:** Australian dollars. All figures are rounded to nearest integers. P value: * <0.05, ** <0.01 *** <0.001

¹ Mean (unadjusted) OOP healthcare expenditure and their differences before and after the removal of patient co-payments for ART in NSW (i.e. 'policy change') for three HIV healthcare spending categories (i) HIV-related (self-reported questionnaire) (ii) non-HIV related (self-reported questionnaire) and (iii) ART (objective pharmacy dispensing data).

Table 3
Quarterly out-of-pocket healthcare expenditure before and after policy change and by concessional status.

	'Continued-Copay' group (Always paid) (n=60) Mean (post-pre) Differences (AUD)	'Stop-copay' group (Stopped) (n=251) Mean (post-pre) Differences (AUD)	Adjusted ¹ coefficient (95%CI)	p-value
Total OOP	-73	-49	0.09 (-0.31 to 0.48)	0.65
HIV related OOP	-40	2	0.32 (-0.34 to 1.00)	0.34
Non-HIV related OOP	-22	-16	0.25 (-0.15 to 0.66)	0.22
ART co-payment	-10	-35	-0.88 (-1.15 to -0.61)	<.001
'Continued-Copay' group (n=36) 'Stop-copay' group (n=134)				
Non-concession card holders				
Total OOP	-109	-105	-0.15 (-0.67 to 0.36)	0.55
HIV related OOP	-73	-25	-0.05 (-0.73 to 0.84)	0.89
Non-HIV related OOP	-18	-22	-0.04 (-0.55 to 0.48)	0.89
ART co-payment	-18	-57	-0.96 (-1.28 to -0.63)	<.001
'Continued-Copay' group (n=24) 'Stop-copay' group (n=117)				
Concession card holders				
Total OOP	-23	15	0.32 (-0.38 to 1.01)	0.37
HIV related OOP	5	33	1.53 (0.53 to 2.53)	<0.01
Non-HIV related OOP	-30	-9	0.62 (-0.05 to 1.31)	0.07
ART co-payment	1	-9	-1.00 (-1.41 to -0.57)	<.001

Note: Concession card holders pay a reduced co-payment for ART. There is also a safety net so that when a patient reaches the cumulative spending threshold their PBS patient contribution for medication is reduced (non-concession card holders) or removed (concession card holders).

PBS: Pharmaceutical Benefits Scheme **AUD:** Australian dollars

¹ Model is adjusted for age, sexuality (self-identified as gay), income, tertiary education completion, capital city residence, private health insurance, number of co-morbidities, and self-assessed health status. Individual-level standard error clustering was used in model calculation.

quarter of respondents living below the poverty line rated co-payment(s) for prescribed medication as 'very difficult' to pay [30]. Furthermore, for people with incomes above the threshold, there is little government subsidy until they have incurred high OOP expenses and reach the medical expenditure threshold. In our analysis, this group of patients remains vulnerable to the relatively high burden of the cost of HIV care, which could undermine the affordability of care.

Our findings may also reflect issues in how government policies are implemented and how they might unintentionally affect vulnerable patients. In our study, based on expenditure data extracted from ART-dispensing pharmacies, almost one in ten participants were still paying the patient co-payment for ART after the policy changed for its removal. It is possible that some pharmacies were operating on a paper-based system, and pharmacists were not aware of the policy change and continued to impose co-payment(s) on ART. This is further compounded by structural bar-

Table 4

The 'Stop-copay' group (n=251): mean percentages of after-tax income spent as out-of-pocket healthcare expenditure.

	Pre-policy Mean % (95%CI)	Post-policy Mean % (95%CI)	Difference ¹ Mean % (95%CI)	p-value
Total OOP expenditure	1.9 (1.4 – 2.3)	2.1 (1.5 – 2.7)	-0.2 (-1.0 – 0.5)	0.52
ART	0.5 (0.4 – 0.5)	0.2 (0.1 – 0.2)	0.3 (0.2 – 0.4)	<.001
HIV related OOP	1.4 (0.9 – 1.9)	2.0 (1.4 – 2.6)	-0.5 (-1.3 – 0.2)	0.15
Concessional status² (ART and HIV related OOP)				
Concession card holder	1.8 (1.0 – 2.7)	2.3 (1.3 – 3.4)	- 0.5 (-1.9 – 0.8)	0.41
Non-concession card holder	1.9 (1.5 – 2.4)	1.9 (1.2 – 2.6)	0.0 (-0.8 – 0.8)	0.96
Weekly Income ≤ A\$650	2.4 (1.1 – 3.7)	4.0 (1.7 – 6.3)	- 1.5 (-4.2 – 1.0)	0.23
Weekly Income A\$651 to A\$1600	2.0 (1.4 to 2.6)	1.3 (0.8 to 1.7)	-0.8 (0.1 to 1.5)	0.03
Weekly Income >A\$1600	1.2 (0.8 to 1.5)	0.6 (0.2 to 1.0)	0.6 (0.0 to 1.1)	0.03

Note:

Percentage of weekly income expended on HIV-related services and ART by income categories were based on first and third quintile of reported weekly income of non-concession card holding participants

¹ Difference in the percentages of after-tax income spent on HIV-related services before and after the removal of the patient co-payment for ART in NSW. Missing values were excluded from the analysis.² Concessional status refers to if a person had a concession card (e.g. pensioners, unemployment benefit recipients) and paid a reduced co-payment for healthcare expenditure. There is also a safety net so that when a patient reaches the cumulative spending threshold their PBS patient contribution for medication is reduced (non-concession card holder) or removed (concession card holder).**Table 5**

ART adherence and virological failure.

Suboptimal adherence rate ¹	Pre-policy n (%)	Post-policy n (%)	p-value
'Stop-copay' group (n=251)	44 (17.5)	41 (16.3)	0.06
'Continued-copay' group (n=60)	8 (13.3)	4 (6.7)	0.15
'Copay-exempt' group (n=53)	4 (7.8)	5 (9.6)	0.70
Incidence rate of virological failure	Pre-policy per 100 PYs (95% CI)	Post-policy per 100 PYs (95% CI)	Overall per 100 PYs (95% CI)
'Stop-copay' group (n=251)	5.0 (2.9 – 8.4)	3.7 (1.8 – 7.4)	4.5 (2.9 – 6.8)
'Continued-copay' group (n=60)	2.0 (0.3 – 14.3)	4.5 (1.5 – 14.0)	3.5 (1.3 – 9.2)
'Copay-exempt' group (n=53)	5.6 (1.4 – 22.4)	9.0 (4.0 – 20.1)	7.8 (3.9 – 15.7)

100 PYs: 100 Person Years of follow-up¹ Suboptimal adherence is defined as missing an average of at least one ART dose per month over the last three months prior to survey.

riers, as most pharmacies dispensing ART were hospital-based, and changes to the ART co-payment policy may not have been communicated effectively to rotating or new staff [31]. Participants who were unaware of the changes to co-payments may be unable to duly self-advocate. This is supported by a single-site study, which reported that only about 5% of people living with HIV reported ever being asked about ART affordability [16]. This finding underscores the importance to equip healthcare providers with effective screening strategies to engage patients in a routine discussion about treatment affordability to ensure that OOP is not a barrier to accessing treatment. All points of healthcare interaction are opportunities to inform patients of any policy changes related to their healthcare, and all members of the multi-disciplinary team can contribute to keeping patients aware of changes that may impact them.

Concurrent to the ART co-payment policy change in NSW, many new co-formulated ART regimens arrived on the market. Whereas previously, a patient would be charged three co-payments for a three-drug ART regimen, the same three drugs, when co-formulated in a single-tablet regimen, would only incur a single co-payment (i.e., the co-payments decreased by two-thirds). In other analyses of our cohort, we found that between Baseline and Month-12, forty-eight (9.2%) participants changed their ART to a single-tablet regimen for no other reason than treatment simplification (i.e., there was no medical indication) [32]. To this end, these participants in our study may have already experienced a significant reduction in OOP expenses independent of the NSW policy change.

Adherence to medication is complex, and many factors have been found to act as barriers or enablers of optimal adherence [33]. We examined whether waiving the co-payment for ART would be associated with a change in ART adherence. We found no statistically significant association between co-payment removal and adherence. Furthermore, as a direct consequence of adherence, we assessed the objective outcome of virological failure, as achieving and maintaining HIV viral suppression relies on taking almost all ART [34]. We found no impact of the co-payment removal on the risk of subsequent virological failure. However, our study was not powered to reliably detect changes in virological failure associated with this policy change.

A strength of the present analysis is the use of a natural experiment to compare participants who have or have not been subject to the policy change during the study period. This allowed us to compare the periods before and after the policy came into effect and to compare the 'stop-copay' group and the 'continued-copay' group. Also, analysing OOP expenditure on ART relative to total OOP healthcare expenditure and total income provides a valuable context for assessing the implication of the change in the co-payment structure for ART.

Our study has limitations. Income, OOP spending, and ART adherence were mostly self-reported, and therefore subject to recall bias but recall bias is, unlikely to differ between the groups. The study used an indicator of personal income as questions on total household income were not asked in the questionnaire. Although it is possible that people living with HIV have access to resources from other household members, analysis using personal income

represents a person's access to their socio-economic resources. Moreover, one third of the participants in the current study lived alone. Our study enrolled a predominantly gay male sample in a high-income setting with universal healthcare entitling all citizens and permanent residents to a range of subsidised healthcare services, so our results may not be generalizable to other populations or settings. Also, as participants had achieved viral suppression before enrolment, our results could be biased towards more motivated patients. Our study was not specifically designed to assess the impact of the policy change on virological failure or adherence. Due to the small sample, our analyses of adherence and virological failure was limited. It is noteworthy that our analysis stratified by concessional status was based on smaller numbers and should be interpreted with extra caution. For example, there were 24 concession card holder participants in the 'co-pay' group compared to 117 participants in the 'stop-copay' group.

Our cohort had a high degree of comorbidity, with 75% taking concomitant medication(s) and nearly 25% having polypharmacy of concomitant medications [15]. Further research examining the cost impact of concomitant medication and co-payments is warranted.

Conclusion

Our study found that removal of the patient ART co-payment had a limited impact on total OOP healthcare expenditure and was not associated with significantly greater ART adherence or less virological failure. This highlights that factors contributing to successful ART are myriad, and a multipronged approach to adherence and prevention of virological failure is required. Our research found that participants with moderate and lower incomes paid a higher percentage of their income for HIV-related services than those with higher incomes. This suggests that existing safety-nets such as Medicare safety-nets have not effectively addressed the problems associated with OOP, particularly for those with a modest income and significant medical requirements. This could potentially undermine their access to care and the affordability of continual care.

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Conflicts of Interest

EL, LM, JdW and JR have no conflicts to declare; AC has received research funding from Bristol-Myers Squibb, Gilead Sciences, and ViiV Healthcare; lecture and travel sponsorships from Gilead Sciences and ViiV Healthcare; and has served on advisory boards for Gilead Sciences, MSD and ViiV Healthcare; KJS has received travel sponsorship from Gilead Sciences.

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References

- [1] Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011;365:493–505.
- [2] Ortego C, Huedo-Medina TB, Llorca J, Sevilla L, Santos P, Rodriguez E, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. *AIDS Behav* 2011;15(7):1381–96.
- [3] Siefried KJ, Mao L, Kerr S, Cysique LA, Gates TM, McAllister J, et al. Socioeconomic factors explain suboptimal adherence to antiretroviral therapy among HIV-infected Australian adults with viral suppression. *PLoS One* 2017;12(4):e0174613.
- [4] Gari S, Doig-Acuña C, Smail T, Malungo JR, Martin-Hilber A, Merten S. Access to HIV/AIDS care: a systematic review of socio-cultural determinants in low and high income countries. *BMC Health Serv Res* 2013;13(1):198.
- [5] Jiamsakul A, Kumarasamy N, Ditangco R, Li PCK, Phanuphak P, Sirisanthana T, et al. Factors associated with suboptimal adherence to antiretroviral therapy in Asia. *J Int AIDS Soc* 2014;17(1):18911.
- [6] Kelly JD, Hartman C, Graham J, Kallen MA, Giordano TP. Social support as a predictor of early diagnosis, linkage, retention, and adherence to HIV care: results from the steps study. *J Assoc Nurses AIDS Care* 2014;25(5):405–13.
- [7] Barennes H, Frichittavong A, Gripenberg M, Koffi P. Evidence of high out of pocket spending for HIV care leading to catastrophic expenditure for affected patients in Lao People's Democratic Republic. *PLoS One* 2015;10(9):e0136664.
- [8] Bisson GP, Frank I, Gross R, Lo Re V, Strom JB, Wang X, et al. Out-of-pocket costs of HAART limit HIV treatment responses in Botswana's private sector. *AIDS* 2006;20(9):1333–6.
- [9] Australian Government, Services Australia. About Medicare. 2019. Available from: <https://www.servicesaustralia.gov.au/individuals/subjects/whats-covered-medicare/about-medicare>. Accessed 04 June 2021.
- [10] Essue B, Kelly P, Roberts M, Leeder S, Jan S. We can't afford my chronic illness! The out-of-pocket burden associated with managing chronic obstructive pulmonary disease in western Sydney, Australia. *J Health Serv Res Policy* 2011;16(4):226–31.
- [11] Australian Government Department of Health. The Pharmaceutical Benefits Scheme. 2021. Available from: <https://www.pbs.gov.au/info/about-the-pbs>. Accessed 04 June 2021.
- [12] New South Wales Government. Co-payments for section 100. 2019. Available from: <https://www.health.nsw.gov.au/pharmaceutical/s100copay/Pages/default.aspx>. Accessed 04 June 2021.
- [13] Medicare Australia. Medicare Benefit Scheme (MBS) Medicare Australia. 2019. Available from: <https://www.humanservices.gov.au/individuals/enablers/who-medicare-safety-net>. Accessed 04 June 2021.
- [14] Newman CE, Mao L, Persson A, Holt M, Slavin S, Kidd MR, et al. Not until I'm absolutely half-dead and have to: Accounting for non-use of antiretroviral therapy in semi-structured interviews with people living with HIV in Australia. *AIDS Patient Care STDS* 2015;29(5):267–78.

- [15] Wilkinson AL, McMahon J, Cheah YS, Bradshaw CS, El-Hayek C, Stoové M. Paying the price in an era of HIV treatment as prevention: A retrospective study of the cost burden of HIV treatment for people living with HIV in Victoria, Australia. *Sex Heal*. 2015;12(1):34–8.
- [16] McAllister J, Beardsworth G, Lavie E, Macrae K, Carr A. Financial stress is associated with reduced treatment adherence in HIV-infected adults in a resource-rich setting. *HIV Med* 2013;14(2):120–4.
- [17] Siefried KJ, Mao L, Cysique LA, Rule J, Giles ML, Smith DE, et al. Concomitant medication polypharmacy, interactions and imperfect adherence are common in Australian adults on suppressive ART. *AIDS* 2018;32(1):35.
- [18] New South Wales Health. Co-payments for Section 100, 2015. Accessed 20 Oct 2019. available at: <https://www.health.nsw.gov.au/pharmaceutical/s100copay/Pages/default.aspx>.
- [19] Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M, et al. Full coverage for preventive medications after myocardial infarction. *N Engl J Med* 2011;365(22):2088–97.
- [20] Gibson TB, Mahoney J, Ranghell K, Cherney BJ, McElwee N. Value-based insurance plus disease management increased medication use and produced savings. *Health Affairs* 2011;30(1):100–8.
- [21] Knott RJ, Petrie DJ, Heeley EL, Chalmers JP, Clarke PM. The effects of reduced copayments on discontinuation and adherence failure to statin medication in Australia. *Heal Pol* 2015;119(5):620–7.
- [22] Wong CY, Greene J, Dolja-Gore X, van Gool K. The Rise and fall in out-of-pocket costs in Australia: An analysis of the strengthening Medicare reforms. *Health Econ* 2017;26(8):962–79.
- [23] Australian Institute of Health and Welfare (AIHW). Health expenditure Australia 2014–2015. Canberra, Australia: AIHW, 2015.
- [24] US Department of Health and Human Services, Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Washington, DC 2017.
- [25] Clumeck N, Pozniak A, Raffi F. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of HIV-infected adults. *HIV Med* 2008;9(2):65–71.
- [26] Gordon LG, Elliott TM, Olsen CM, Pandeya N, Whiteman DC. Patient out-of-pocket medical expenses over 2 years among Queenslanders with and without a major cancer. *Aust J Prim Health* 2018;24(6):530–6.
- [27] Newton JC, Johnson CE, Hohnen H, Bulsara M, Ives A, McKiernan S, et al. Out-of-pocket expenses experienced by rural Western Australians diagnosed with cancer. *Support Care Cancer* 2018;26(10):3543–52.
- [28] Carpenter A, Islam MM, Yen L, McRae I. Affordability of out-of-pocket health care expenses among older Australians. *Heal Pol* 2015;119(7):907–14.
- [29] Kemp A, Roughhead E, Preen D, Glover J, Semmens J. Determinants of self-reported medicine underuse due to cost: a comparison of seven countries. *J Health Serv Res Policy* 2010;15(2):106–14.
- [30] Grierson J, Pitts M, Koelmeyer R. HIV Futures Seven: the health and wellbeing of HIV positive people in Australia. The Australian Research Centre in Sex. Melbourne, Australia: Health and Society La Trobe University; 2013.
- [31] Mak VS, Clark A, Poulsen JH, Udengaard KU, Gilbert AL. Pharmacists' awareness of Australia's health care reforms and their beliefs and attitudes about their current and future roles. *Int J Pharm Pract* 2012;20(1):33–40.
- [32] Siefried KJ, Mao L, Riches S, Kerr S, Rule J, McAllister J, et al. Failure of antiretroviral therapy (ART) in Australian adults is mainly due to ART toxicity The Australasian HIV and AIDS Conference. AUS: Canberra; 2017.
- [33] Osterberg L, Blaschke T. Adherence to medication. *New England J Med* 2005;487–97.
- [34] Garcia F, de Lazzari E, Plana M, Castro P, Mestre G, Nomdedeu M, Fumero E, Martinez E, Mallolas J, Blanco JL, Miro JM, Pumarola T, Gallart T, Gatell JM. Long-term CD4+ T-cell response to highly active antiretroviral therapy according to baseline CD4+ T-cell count. *J Acquir Immune Defic Syndr* 2004;36(2):702–13.