Improvements in transition times through the HIV cascade of care among gay and bisexual men with a new HIV diagnosis in New South Wales and Victoria, Australia (2012–19): a longitudinal cohort study

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Summary

Background Most studies assessing the HIV care cascade have typically been cross-sectional analyses, which do not capture the transition time to subsequent stages. We aimed to assess the longitudinal HIV cascade of care in Australia, and changes over time in transition times and associated factors.

Methods In this longitudinal cohort study, we included linked data for gay and bisexual men (GBM) with a new HIV diagnosis who attended clinics participating in the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance in New South Wales and Victoria between Jan 1, 2012, and Dec 31, 2019. We assessed three cascade transition periods: diagnosis to linkage to care (stage 1 transition); linkage to care to antiretroviral therapy (ART) initiation (stage 2 transition); and ART initiation to virological suppression (viral load ≤200 copies per mL; stage 3 transition). We also calculated the probability of remaining virologically suppressed after the first recorded viral load of less than 200 copies per mL. We used the Kaplan-Meier method to estimate transition times and cumulative probability of stage transition.

Findings We included 2196 GBM newly diagnosed with HIV between 2012 and 2019 contributing 6747 person-years of follow-up in our analysis. Median time from HIV diagnosis to linkage to care (stage 1 transition) was 2 days (IQR 1–3). Median time from linkage to care to ART initiation (stage 2 transition) was 33 days (30–35). Median time from ART initiation to first recorded virological suppression (stage 3 transition) was 49 days (47–52). The cumulative probability of ART initiation within 90 days of linkage to care increased from 36·9% (95% CI 32·9–40·6) in the 2012–13 calendar period to 94·1% (91·2–96·0) in the 2018–19 calendar period and cumulative probability of virological suppression within 90 days of ART initiation increased from 54·3% (48·8–59·3) in the 2012–13 calendar period to 82·9% (78·4–86·4) in the 2018–19 calendar period. 91·6% (90·1–93·1) of GBM remained virologically supressed up to 2 years after their first recorded virological suppression event.

Interpretation In countries with high cross-sectional cascade estimates such as Australia, the impact of treatment as prevention is better estimated using longitudinal cascade analyses.

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Introduction

HIV cascade of care indicators are widely used to establish benchmarks and monitor treatment as prevention strategies and improvements in the delivery of HIV care over time. Modelling by UNAIDS has projected progress towards ending the AIDS epidemic and associated HIV incidence reductions by 2030 based on the achievement of global HIV cascade of care targets.[1] By 2020, the aims of the targets were that 90% of people with HIV would be diagnosed, 90% of diagnosed individuals would be receiving antiretroviral therapy (ART), and 90% of individuals receiving ART would be virologically suppressed (90-90-90), increasing to 95-95-95 by 2030.[1]

Most studies assessing the HIV cascade of care provide cross-sectional estimates of the proportion of individuals in particular cascade stages at that time. On the basis of this approach, Australia has met the HIV cascade targets, with estimates of 90-92-97% in 2019.[2] These targets have been achieved as a result of government subsidised universal health care, which has supported high HIV service coverage for gay and bisexual men (GBM), among whom HIV incidence is highest in Australia (GBM account for approximately 74% of HIV notifications).[3] However, only modest improvements in the cascade have been observed between 2014 and 2019, with the estimated proportion of people with HIV receiving ART increasing from 85% in 2014 to 92% in 2019.[2] The relative magnitude of improvements in cross-sectional HIV cascades is not as obvious in settings of high service coverage,[4] thus measuring the HIV prevention impact

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Research in context

Evidence before this study

HIV cascade of care indicators are central components of prevention monitoring strategies. Modelling by UNAIDS has projected progress towards ending the AIDS epidemic by 2030, and associated HIV incidence reductions on the basis of achieving global HIV cascade of care targets, known as the 90-90-90 targets (and later updated to include 95-95-95 fast-track targets). Although these HIV cascade targets have been met in Australia, with estimates of 90-92-97% in 2019, on the basis of cross-sectional estimates, only modest improvements in cascade estimates have been observed between 2014 and 2019. However, in countries with high levels of HIV testing and engagement in treatment, using cross-sectional cascades to measure progress might lead to incorrect conclusions about the impact of preventive programmes and health system performance, partly because they are slow to respond to changes. Levels of community viraemia and infectiousness rely not only on the number of people with viraemia, but how long they remain able to transmit HIV. Therefore, an approach that accounts for the cumulative time individuals are viraemic after infection might offer a more sensitive indicator of HIV transmission risk at the population level. A longitudinal approach measuring time to transition through the HIV cascade of care is better suited to assessing temporal changes in health system performance, especially in countries with high coverage of testing and treatment, and might also offer a more sensitive indicator of HIV transmission risk at the population level. In early 2021, we searched PubMed for longitudinal and cross-sectional studies using a combination of the search terms "HIV" AND "cascade of care" AND "longitudinal" AND "HIV" AND "cascade of care" AND "(gay and bisexual men OR men who have sex with men)" AND "transitions" AND "cascade of care" AND "trends" without language restrictions. A small number of studies have assessed all clinical HIV cascade of care stages following diagnosis using a longitudinal approach, but these have been in the context of suboptimal health systems where structural, geographical, and resource constraints contribute to relatively low coverage of testing and treatment.

Added value of this study

This is the first study in Australia to assess all clinical HIV cascade of care stages following diagnosis using a longitudinal approach, and the first study globally to describe longitudinal changes in an HIV care cascade in the context of high baseline HIV testing and treatment coverage. We used linked data from 2196 gay and bisexual men (GBM) with a new HIV diagnosis attending clinics captured by the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance between 2012 and 2019. Contrasting relatively modest improvements in cross-sectional cascade indicators, considerable improvement was observed in cascade transition times. Our data provide the most up to date estimates on key HIV cascade indicators and progress toward HIV elimination, in addition to assessing the impact of ART initiation guidelines update in 2015. We provide an alternative approach to study the HIV cascade of care in Australia, enabling the estimation of changes in the time individuals remain viraemic and at risk of transmitting HIV.

Implications of all the available evidence

Among newly HIV diagnosed GBM in Australia, HIV cascade transitions occur rapidly and considerable improvements in transition times were observed between 2012 and 2019. The observed reductions in time from diagnosis to ART initiation and virological suppression among newly diagnosed GBM are likely to have contributed to published estimates showing a substantial decline in HIV incidence among GBM in Australia between 2012 and 2018. To end the AIDS epidemic by 2030, and ultimately eliminate HIV in Australia, continued efforts to increase early diagnosis and immediate ART initiation at HIV diagnosis are warranted. In countries with high rates of virological suppression such as Australia, longitudinal cascade analysis can improve measurement of the impact of treatment as prevention.

of enhancements to the HIV cascade might require alternative measures.

A longitudinal approach that measures time to transition through the cascade of care is better suited to assessing temporal changes in health system performance,[5,6] and has been used to demonstrate the effectiveness of targeted public health and clinical interventions aimed to shorten periods of HIV viraemia.[7] Cross-sectional cascades might lead to incorrect inference when used to evaluate the performance of health systems.[8] For example, a simulation study[8] showed that in the calendar year following a change in ART initiation guidelines, a lower proportion of individuals was estimated to be virologically supressed. Due to an increase in the number of new individuals on ART, it took some time for this new group of ART initiators (ie, the numerator) to reach viral supression, rather than a change in the probability of achieving viral supression.[8] Moreover, an approach that accounts for the cumulative time individuals remain viraemic after infection might offer a more sensitive indicator of population-level HIV transmission risk than simply the estimated number of people who are viraemic. For these reasons it has been suggested that a time component should be included in the UNAIDS targets[8]—eg, 90% of individuals who initiate ART should be virologically supressed within 90 days.

Using data between 2012 and 2019 among newly diagnosed GBM in the states of New South Wales and Victoria, Australia, we aimed to assess the probability of transitioning through the HIV cascade of care stages, differences in the longitudinal cascade by calendar period and associated clinical and sociodemographic factors,

and sustained virological suppression following the first recorded undetectable viral load after ART initiation.

Methods

Study population and participants

For this longitudinal cohort study, we included data that were collected as part of the Treatment with Antiretrovirals and their Impact on Positive And Negative Men (TAIPAN) study.[9] Briefly, TAIPAN established a surveillance platform to monitor temporal changes in HIV incidence and the cascade of care among GBM who live in the Australian states of New South Wales and Victoria using data from the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS) system.[10] ACCESS extracts de-identified data from clinic patient management and laboratory data systems, capturing 48–60% of new HIV notifications in New South Wales and Victoria. Around 56% of the total population of Australia reside in these states and an estimated 67% of the total GBM population.[11] Longitudinal HIV data (patient demographics and all pathology results and prescriptions) from GBM are extracted from clinic patient management systems and linked across the ACCESS network using an encrypted linkage algorithm that uniquely identifies patients.[12] For the present study, we included individual-level data from all identified GBM presenting to 21 primary health clinics, 19 sexual health clinics, and one hospital who were diagnosed with HIV or presented for care between Jan 1, 2012, and Dec 31, 2019, in our analysis. Patients were classified as GBM if they were identified as such in the clinic patient management system or via a previously validated method based on being male and ever having a rectal swab for chlamydia or gonorrhoea recorded in ACCESS.[13] These settings are typical of those where GBM receive HIV care in Australia, with shared care delivered by HIV specialist primary care clinicians.[14] Approximately 70% of HIV treatment is delivered through primary and sexual health clinics in Australia and this remained unchanged during the observation period.[15] All settings provided free or government subsidised HIV treatment and care services during the observation period, with patients typically incurring small out-of-pocket expenses for clinical services at primary care clinics.

Participants were included if they had evidence of a new HIV diagnosis in the observation period based on a recorded HIV seroconversion during follow-up (HIV-positive test result preceded by an HIV-antibody-negative test result), laboratory evidence of an acute infection, or laboratory evidence of a new diagnosis (eg, two repeated reactive results for HIV antibody or an HIV antibody-positive test) without evidence of when they became infected.[16] Among individuals with evidence of HIV diagnosis, date of diagnosis was taken as the date of first recorded HIV positive test. The ACCESS study protocol was approved by the ethics committees of St Vincent's Hospital (Sydney, NSW, Australia), the Alfred Hospital (Melbourne, VIC, Australia), and the University of New South Wales (Sydney, NSW, Australia). The requirement for written informed consent was waived due to the nature of the study.

Cascade stage definitions and follow-up

We assessed three cascade transition periods. Stage 1 transition was defined as transition from HIV diagnosis to the first CD4 cell count or viral load measurement (ie, linkage to care).[17] Stage 2 transition was defined as transition from linkage to care to ART initiation indicated by date of the first recorded ART prescription. Stage 3 transition was defined as transition from ART initiation to first viral load measurement of 200 copies per mL or less. Individuals were followed up until the date that the stage event was reached, or at the last recorded date of an HIV-associated clinic visit for individuals who did not transition to a subsequent stage. We also assessed time to transition from HIV diagnosis to each subsequent cascade stage event.

Eligibility for a stage event was conditional on reaching a previous stage. However, individuals who transitioned from HIV diagnosis to ART initiation without a linkage to care record were included in the ART initiation stage

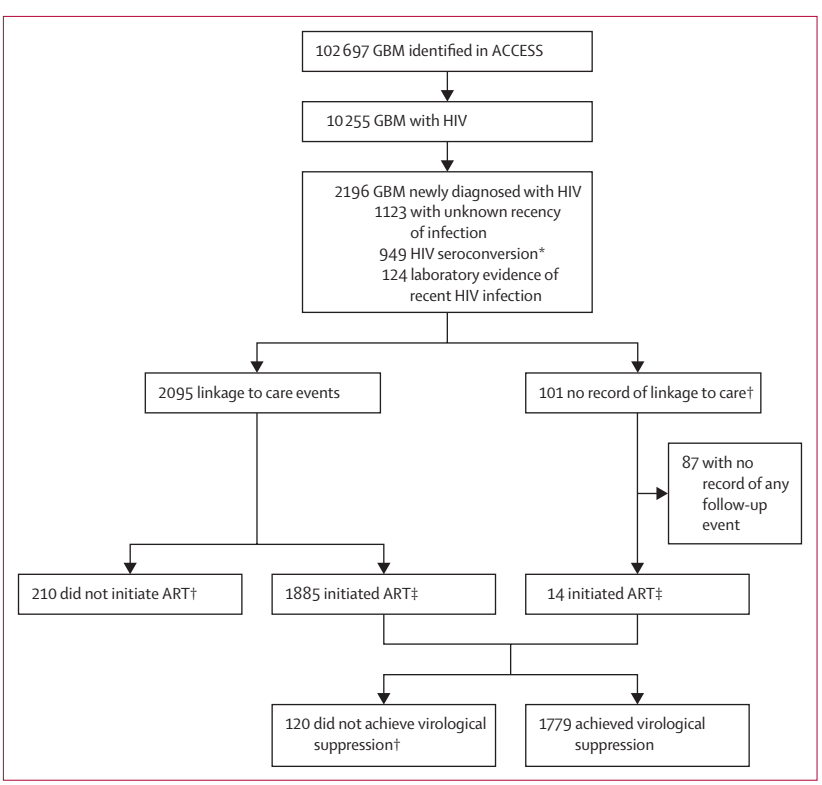

Figure 1: **Study flowchart**
GBM=gay and bisexual men. ACCESS=Australian Collaboration for Coordinated Enhanced Sentinel Surveillance. ART=antiretroviral therapy. *607 (64·0%) of 949 GBM had a maximum seroconversion interval of 12 months. †GBM who were censored during each transition period. ‡Overall, 1899 GBM initiated ART, of whom 1885 GBM had a recorded linkage to care and 14 had no recorded linkage to care.

transition period (figure 1). Individuals could also have simultaneous transitions and were included in the denominator of all the stages reached on the same date.[8]

Statistical analysis

We used Kaplan-Meier curves to estimate cumulative transition probabilities within 90 days and 1 year of stage eligibility and HIV diagnosis, as previously described.[6,8] The Kaplan-Meier method assumes that censoring is independent of the likelihood of stage transition. We assessed whether the cascade transition period probabilities differed by calendar period at the start of each stage (2-year calendar periods starting from 2012 until 2019), age group at HIV diagnosis, type of clinic at HIV diagnosis, and first CD4 cell count at or after HIV diagnosis.

To investigate sustained virological suppression, we estimated the proportion of individuals who were virologically supressed at their last visit and used the Kaplan-Meier method to assess the cumulative probability of remaining virologically supressed. For the cumulative probability of remaining virologically supressed, individuals entered the risk-set at the first

	2012–13 (n=642)	2014–15 (n=670)	2016–17 (n=485)	2018–19 (n=399)
Age, years				
15–29	216 (33·6%)	237 (35·4%)	191 (39·4%)	165 (41·4%)
30–39	213 (33·2%)	230 (34·3%)	164 (33·8%)	135 (33·8%)
≥40	213 (33·2%)	203 (30·3%)	130 (26·8%)	99 (24·8%)
State				
New South Wales	320 (49·8%)	341 (50·9%)	200 (41·2%)	161 (40·4%)
Victoria	322 (50·2%)	329 (49·1%)	285 (58·8%)	238 (59·6%)
Standard Australian Classification of Countries*				
Oceania and Antarctica	293 (62·2%)	292 (57·1%)	178 (44·0%)	149 (43·2%)
North-West Europe	34 (7·2%)	39 (7·6%)	20 (4·9%)	14 (4·1%)
Southern and Eastern Europe	10 (2·1%)	10 (2·0%)	6 (1·5%)	6 (1·7%)
North Africa and the Middle East	5 (1·1%)	7 (1·4%)	11 (2·7%)	3 (0·9%)
South-East Asia	57 (12·1%)	71 (13·9%)	87 (21·5%)	85 (24·6%)
North-East Asia	36 (7·6%)	51 (10·0%)	54 (13·3%)	33 (9·6%)
Southern and Central Asia	6 (1·3%)	9 (1·8%)	12 (3·0%)	19 (5·5%)
Americas	25 (5·3%)	24 (4·7%)	35 (8·6%)	32 (9·3%)
Sub-Saharan Africa	5 (1·1%)	8 (1·6%)	2 (0·5%)	4 (1·2%)
Health facility				
Sexual health	368 (57·3%)	402 (60·0%)	325 (67·0%)	311 (77·9%)
Primary health or general practice	274 (42·7%)	268 (40·0%)	160 (33·0%)	88 (22·1%)
Known recency of HIV infection at diagnosis				
Recent diagnosis	411 (64·0%)	399 (59·6%)	360 (74·2%)	295 (73·9%)
Recent HIV infection	231 (36·0%)	271 (40·4%)	125 (25·8%)	104 (26·1%)
Median CD4 count at diagnosis, cells per µL (IQR)†	480 (335–683)	465 (347–642)	440 (322–609)	390 (229–545)
Median HIV viral load at diagnosis, copies per mL (IQR)‡	41 085 (12 825–177 988)	52 354 (12 944–130 999)	42 200 (10 273–115 500)	45 700 (10 248–171 851)
Linked to care				
No	18 (2·8%)	41 (6·1%)	23 (4·7%)	19 (4·8%)
Yes	624 (97·2%)	629 (93·9%)	462 (95·3%)	380 (95·2%)
Initiated ART				
No	106 (16·5%)	108 (16·1%)	50 (10·3%)	33 (8·3%)
Yes	536 (83·5%)	562 (83·9%)	435 (89·7%)	366 (91·7%)
Achieved viral suppression				
No	125 (19·5%)	135 (20·1%)	79 (16·3%)	78 (19·5%)
Yes	517 (80·5%)	535 (79·9%)	406 (83·7%)	321 (80·5%)

Recency of known HIV diagnosis was based on the Australian national notifiable diseases case definitions. *Data missing for 171 participants in the 2012–13 calendar period, 159 participants in the 2014–15 calendar period, 80 participants in the 2016–17 calendar period, and 54 participants in the 2018–19 calendar period. †Data missing for 198 participants in the 2012–13 calendar period, 185 participants in the 2014–15 calendar period, 144 participants in the 2016–17 calendar period, and 117 participants in the 2018–19 calendar period. ‡Data missing for 220 participants in the 2012–13 calendar period, 230 participants in the 2014–15 calendar period, 147 participants in the 2016–17 calendar period, and 124 participants in the 2018–19 calendar period.

Table 1: **Baseline characteristics of gay and bisexual men with a new HIV diagnosis between 2012 and 2019 in New South Wales and Victoria, Australia**

	Overall	2012–13	2014–15	2016–17	2018–19
HIV diagnosis to linkage to care					
90 days	94·3 (93·3–95·2)	95·4 (93·4–96·7)	91·8 (89·4–93·6)	95·4 (93·0–96·9)	95·6 (93·0–97·2)
1 year	95·5 (94·6–96·3)	96·3 (94·5–97·5)	93·8 (91·6–95·3)	96·2 (94·0–97·6)	96·5 (94·1–98·0)
Median, days (IQR)	2 (1–3)	3 (1–5)	1 (0–3)	3 (0–4)	0 (0–3)
Linkage to care to ART initiation					
90 days	68·8 (66·8–70·8)	36·9 (32·9–40·6)	70·4 (66·5–73·8)	87·1 (83·7–89·8)	94·1 (91·2–96·0)
1 year	83·5 (81·8–85·1)	66·4 (62·3–70·0)	85·9 (82·7–88·4)	92·3 (89·5–94·4)	95·9 (93·2–97·5)
Median, days (IQR)	33 (30–35)	179 (148–214)	38 (34–43)	21 (21–25)	15 (14–18)
ART initiation to viral suppression					
90 days	70·5 (68·3–72·5)	54·3 (48·8–59·3)	70·0 (66·2–73·3)	73·6 (69·3–77·3)	82·9 (78·4–86·4)
1 year	92·7 (91·4–93·8)	93·4 (90·2–95·6)	91·8 (89·3–93·6)	91·2 (88·2–93·4)	95·5 (92·2–97·4)
Median, days (IQR)	49 (47–52)	84 (78–91)	50 (46–56)	42 (40–46)	38 (36–41)

Data are cumulative probability (95% CI), unless stated otherwise. ART=antiretroviral therapy.

Table 2: **Cumulative probability of cascade transitions and median time to transition between each cascade stage**

recorded undetectable viral load and follow-up continued until the first viral load with more than 200 copies per mL or the last visit among individuals who remained virologically supressed. Analyses were done using the longitudinalcascade package version 0.3.2.1 in R (version 3.6.2).

Some treatment prescriptions might not have been captured in the dataset when paper-based prescriptions were not entered or when individuals received treatment from a clinic not captured by ACCESS. Therefore, we made some assumptions to impute the date of ART initiation. For individuals who reached virological suppression on the same day or before of their first recorded ART prescription date (n=177) or individuals who reached virological suppression without a previous ART prescription recorded (n=79), we assumed ART initiation at the midpoint between HIV diagnosis and first virological suppression dates. For individuals who only had detectable viral loads, but were missing a viral load measurement at their last visit (n=53), we assumed they did not achieve virological suppression. In sensitivity analysis, we excluded individuals for whom we made assumptions on ART initiation date or having a detectable viral load. We did an additional sensitivity analysis including only individuals with a recorded HIV seroconversion in ACCESS (ie, individuals who had a negative HIV-antibody test followed by an HIV positive test) and we compared these transition times with the main analyses.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

102 697 GBM had at least one visit to a primary health clinic, sexual health clinic, or hospital recorded in ACCESS during the observation period, of whom 10 255 (10·0%) had at least one recorded positive HIV test result (inclusive of HIV monitoring tests). 2196 had a new HIV diagnosis recorded between 2012 and 2019, and thus were included in this analysis. Median age at HIV diagnosis was 32 years (IQR 27–41) and median CD4 count at HIV diagnosis was 450 cells per µL (IQR 321–621). 949 (43·2%) of 2196 GBM had a recorded HIV seroconversion. Among the 949 GBM with a recorded HIV seroconversion, median time from last HIV-antibody-negative test date to HIV diagnosis date was 271 days (IQR 117–673).

Median time from HIV diagnosis to last HIV-associated clinic visit was 2·8 years (IQR 0·8–5·2). From 6747 person-years of follow-up among 2196 GBM with newly diagnosed HIV, 2095 (95·4%) transitions to linkage to care, 1899 (86·4%) transitions to ART initiation, and 1779 (81·0%) transitions to virological suppression were observed (figure 1). 101 (4·6%) of 2196 GBM with newly diagnosed HIV had no record of linkage to care after diagnosis (of whom 27 had at least one recorded clinic visit after diagnosis), 210 (10·0%) of 2095 GBM who were linked to care had no record of ART initiation after being linked to care (of whom 114 had at least one recorded clinic visit after linkage to care), and 120 (6·3%) of 1899 GBM who initiated ART had no record of virological suppression after initiating ART (of whom 65 had at least one visit after ART initiation). 87 (4·0%) of 2196 newly diagnosed GBM had no record of any follow-up event.

When comparing individuals diagnosed across 2-year calendar periods, diagnoses among younger GBM slightly increased over time (table 1). Most individuals were diagnosed at sexual health clinics, with the highest proportion observed in the 2018–19 calendar period. The proportion of new diagnoses among GBM born in South-East Asia increased between the 2012–13 calendar period (57 [12%; 95% CI 9·5–15·4] of 471 GBM with available data) and the 2018–19 calendar period (85 [25%;

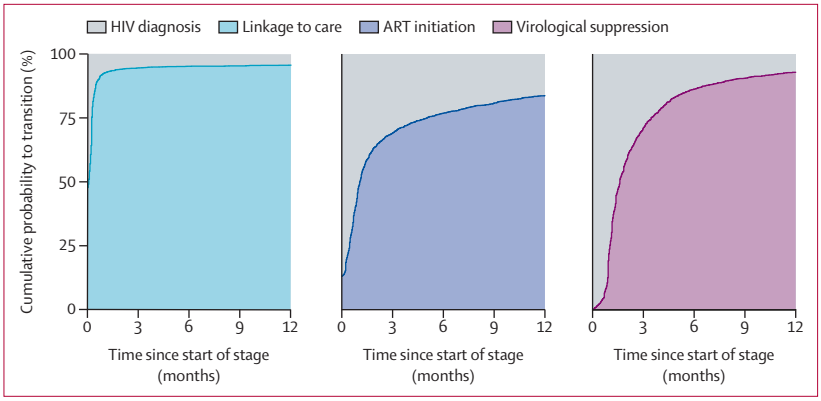

Figure 2: **Cumulative probabilities of transition through the HIV cascade of care between 2012 and 2019**
ART=antiretroviral therapy.

20·3–29·5] of 345 GBM with available data) and the proportion of GBM born in Oceania and Antarctica, including Australia, decreased between the 2012–13 calendar period (293 [62%; 57·7–66·5] of 471 GBM with available data) and 2018–19 calendar period (149 [43%; 38·1–48·5] of 345 GBM with available data). Median first CD4 count at HIV diagnosis was lowest in the 2018–19 calendar period, decreasing from 480 cells per µL (IQR 335–683) in the 2012–13 calendar period to 390 cells per µL (229–545) in the 2018–19 calendar period (table 1).

See Online for appendix

Among 2196 newly diagnosed GBM, the median transition time from HIV diagnosis to linkage to care (stage 1 transition) was 2 days (IQR 1–3; table 2, figure 2), with 967 (44·0%) receiving their HIV diagnosis and CD4 cell count or viral load assessment on the same day. When simultaneous transitions were excluded, the median transition time to linkage to care was 7 days (IQR 7–8). 94·3% (95% CI 93·3–95·2) of GBM were linked to care within 90 days of HIV diagnosis, and 95·5% (94·6–96·3) of GBM were linked to care within 1 year of HIV diagnosis (figure 2).

Among 2109 GBM (including 2095 with a recorded linkage to care event and 14 without a recorded linkage to care event), median transition time from linkage to care to ART initiation (stage 2 transition) was 33 days (95% CI 30–35; figure 2). Among the 1483 individuals who had a CD4 count result within 3 months of the ART initiation, median CD4 count at ART initiation was 445 cells per µL (IQR 312–600).

181 (9·5%) of 1899 GBM initiated ART at HIV diagnosis and 126 (6·6%) initiated ART on the same day they were linked to care. 101 GBM initiated ART and were linked to care on the same day as their HIV diagnosis. Within 90 days of linkage to care, 68·8% (95% CI 66·8–70·8) of GBM had initiated ART and within 1 year of linkage to care, 83·5% (81·8–85·1) of GBM had initiated ART (table 2). Median time from HIV diagnosis to ART initiation was 42 days (IQR 40–46).

Among 1899 GBM who initiated ART, median transition time from ART initiation to first recorded virological suppression (stage 3 transition) was 49 days (IQR 47–52; figure 2). After 90 days of ART initiation, 70·5% (95% CI 68·3–72·5) of GBM had achieved virological suppression and after 1 year of ART initiation 92·7% (91·4–93·8) of GBM had achieved virological suppression (table 2). Median time from HIV diagnosis to virological suppression was 128 days (IQR 119–139).

In sensitivity analyses, median transition times and cumulative probabilities for all stages were similar to the main analysis.

Of 1779 GBM who achieved virological suppression, 1635 (91·9%) GBM had a subsequent viral load test that allowed assessment of sustained virological suppression. During 5029 person-years of follow-up, 170 GBM had a test on which viral load was higher than 200 copies per mL. Among these 170 individuals, median viral load at the first detectable test was 1344 copies per mL (IQR 426–18 162), and 55 (32%) had a viral load of less than 500 copies per mL. 91·6% (95% CI 90·1–93·1) of GBM remained virologically supressed up to 2 years after first recorded virological suppression event, and 85·8% (83·6–88·1) of GBM remained virologically supressed up to 5 years after their first recorded virological suppression event (appendix p 1). At the last viral load test, 1597 (97·7%) of 1635 GBM had an undetectable viral load.

Transition from HIV diagnosis to linkage to care was quick and stable between 2012 and 2019 (figure 3, table 2). Transition times from linkage to care to ART initiation decreased between 2012 and 2019 (median 179 days [IQR 148–214] in 2012–13 calendar period *vs* 15 days [14–18] in the 2018–19 calendar period). The cumulative probability of ART initiation by 90 days of linkage to care increased from 36·9% (95% CI 32·9–94·1) in the 2012–13 calendar period to 94·1% (91·2–96·0) in the 2018–19 calendar period, and cumulative probability by 1 year increased from 66·4% (62·3–70·0) in 2012–13 to 95·9% (93·2–97·5) in the 2018–19 calendar period. The proportion of individuals who initiated ART at HIV diagnosis (181 of 2196 GBM) increased, from 3·1% (20 of 642 GBM with a new diagnosis) in the 2012–13 calendar period to 18·3% (73 of 399 GBM with a new diagnosis) in the 2018–19 calendar period.

Transition times from ART initiation to virological suppression decreased between 2012 and 2019. 82·9% (95% CI 78·4–86·4) of GBM had reached virological suppression within 90 days of ART initiation in the 2018–19 calendar period compared with 54·3% (48·8–59·3) of GBM in the 2012–13 calendar period. The median time to virological suppression since ART initiation decreased from 84 days (IQR 78–91) in the 2012–13 calendar period to 38 days (36–41) in the 2018–19 calendar period. The most substantial decrease in transition times from linkage to care to ART initiation

and ART initiation to virological suppression occurred between the 2012–13 and 2014–15 calendar periods (table 2).

Transition probabilities for all transition stages were similar across age groups at HIV diagnosis (appendix p 2). Individuals diagnosed at sexual health clinics initiated ART slightly faster and reached virological suppression earlier than those diagnosed in primary health-care clinics (appendix p 3). Individuals with higher CD4 cell counts at HIV diagnosis had a lower cumulative probability of ART initiation at 1 year after linkage to care (appendix p 4). When transition probabilities were stratified by diagnoses that occurred before or after 2015, small differences were observed in time to ART initiation by CD4 count group among those diagnosed at or after 2015 (appendix p 5).

Discussion

Using data from a sentinel surveillance system in Australia with high coverage of HIV testing and treatment among GBM, we showed that HIV cascade transitions occur rapidly among this group. During the total observation period (2012–19), we found that 94% of GBM were linked to care within 90 days of diagnosis, 69% initiated ART within 90 days of linkage to care, and 71% were virologically suppressed within 90 days of ART initiation. Considerable improvement was observed in time from linkage to care to ART initiation and ART initiation to virological suppression between 2012 and 2019. For the 2018–19 calendar period, the cumulative probability of reaching each stage within 90 days was 96% for linkage to care, 94% for initiation of ART, and 83% for achievement of virological suppression.

Prompt linkage to HIV care is defined by the US Centers for Disease Control and Prevention and European expert consensus statement[17] as linkage within 3 months of diagnosis. The observed rapid transition from diagnosis to linkage to care (median 2 days) is likely to reflect streamlined HIV care services and shared care clinical models for people living with HIV in Australia, whereby most patients are managed in primary care settings, often in the same clinics they are diagnosed. In contrast, other high-income countries often deliver HIV care through tertiary care settings.[17] However, although considerable improvements have been observed in the proportion of people who started treatment on the same day as HIV diagnosis, around 80% of treatments were not initiated on the day of diagnosis in the 2018–19 calendar period. Although the prevention benefits of same-day treatment commencement are widely acknowledged in Australia, the adoption of such an approach is influenced by considerations of clinician and patient autonomy and patient-centred care. Current Australian treatment guidelines[18] include recommendations for baseline clinical investigations to guide treatment and also emphasise consideration of a patient's capacity to adjust to the implications of an HIV diagnosis and adhere to treatment

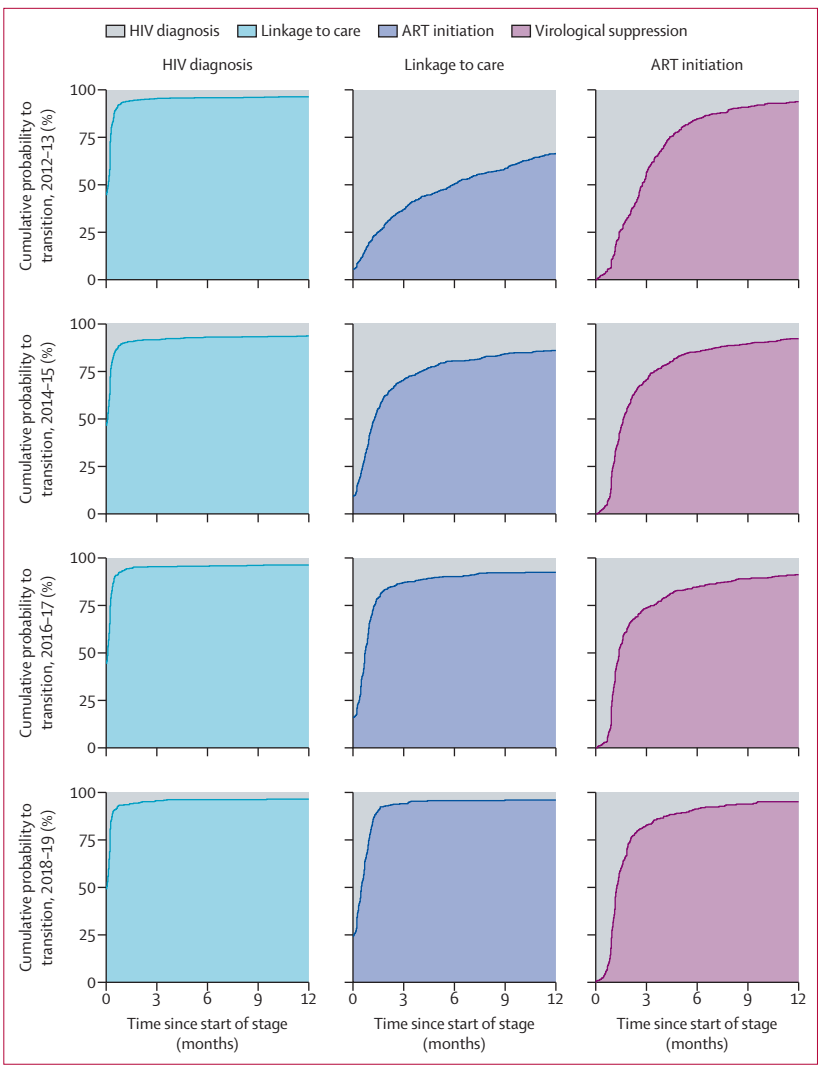

Figure 3: **Cumulative probabilities of transition through the HIV cascade of care between 2012 and 2019 by calendar period**

ART=antiretroviral therapy.

regimens, and the availability of interpersonal support to do so. Although several studies (mostly done in African countries) have assessed time to transition to ART initiation and virological suppression,[19,20] data on linkage to care transition following diagnosis are scarce. Between-country comparison with variation in models of care could provide further insights into the associations between health systems, health-care practice, and linkage to care transitions and inform responses to enhance health and HIV prevention outcomes.

Consistent with other high-income countries and single site analyses in Australia, time from diagnosis to ART initiation and virological suppression significantly declined between 2012–13 and 2018–19 calendar periods.[21–23] The decline in time between linkage to care and ART initiation was largest between the 2012–13 and 2014–15 calendar periods. Although Australian HIV

guidelines recommended immediate ART commencement irrespective of clinical stage, viral load, or CD4 count in 2015,[24] the earlier declines observed are likely due to changes in discretionary prescribing practice in response to emerging evidence of treatment as prevention and in anticipation of guideline changes.[25] Ongoing declines in time to ART initiation might have also been influenced by extensive media campaigns targeting the gay community, which promoted the health and benefits of early treatment commencement.[26] The observed reductions in time from diagnosis to ART initiation and virological suppression among newly diagnosed GBM are likely to have contributed to the decrease in HIV incidence observed in Australia between 2012 and 2018.[27] The introduction of universal pre-exposure prophylaxis (PrEP) access in March, 2016, in Australia and the implementation of large PrEP demonstration studies before this date[28] have also likely influenced the continued decrease in HIV incidence, although the effect of PrEP and treatment as prevention is difficult to disentangle.

The decreased transition time to virological suppression might be partly explained by the widespread uptake of integrase strand-transfer inhibitor-containing regimens known to lead to more rapid virological suppression than other classes of antiretrovirals.[29] The first integrase inhibitor was made available in Australia in 2011, proportional increases in integrase inhibitor use was observed from 2013 onwards,[30] and widespread use coincided with 2015 Australian guidelines recommending three integrase inhibitors as initial ART. Identified time to virological suppression is also likely to have been affected by clinical practice and patient health-seeking behaviours, as the transition time in this study was measured as the first recorded viral load test of 200 copies per mL or less after ART initiation. More rapid detection of virological suppression following ART initiation was potentially also influenced by an increasing proportion of people treated at diagnosis, reducing the number of clinic visits thereafter and shortening transition to the virological suppression stage. A study of GBM in Amsterdam (2008–17) reported the median time from diagnosis to virological suppression within a universal ART initiation approach (ie, irrespective of CD4 cell count) was 95 days,[7] which is comparable to the median (128 days) in this study during the observation period. After implementing a strategy for increasing detection of acute HIV infection (targeted online promotion to self-identify acute HIV infection symptoms with an online risk score) and immediate ART initiation on the basis of point-of-care HIV RNA testing and same-visit delivery of results, median time to virological suppression decreased to 55 days and more than 90% of individuals reached this stage within 90 days of diagnosis.[7] Although transition times are short in Australia, additional changes to diagnostic practice and accompanying health promotion could reduce transition times even further.

Cross-sectional cascade estimates were first formally reported in Australia for 2013 and reported thereafter annually using a combination of modelled estimates (proportion of people with HIV who are undiagnosed) and health service datasets (in care, treated, virologically suppressed).[31] In New South Wales and Victoria in 2013, the cascades showed 89% of people living with HIV were diagnosed with HIV, 85% were receiving treatment, and 89% were virologically suppressed and, as a result, relatively modest improvements were observed thereafter (increasing to 90%, 94%, and 98% in 2017, respectively; Gray R, Kirby Institute, Sydney, NSW, Australia, personal communication).[32,33] Our data, however, show that greater decreases in time taken to transition through the HIV cascade of care have occurred in these states; the 1-year cumulative probability of ART initiation was 39% higher in individuals linked to care during the 2016–17 calendar period than those linked to care during the 2012–13 calendar period. Longitudinal cascades offer a more sensitive approach to investigate cascade trends in places such as Australia with high baseline HIV service coverage and provide key treatment as prevention indicators, which are not included in the current UNAIDS 90-90-90 targets.

Our study has several limitations. First, some individuals might have transferred their care to clinics outside of our surveillance system, although the proportion of eligible individuals not reaching subsequent cascade stages was small. Anyone lost to follow-up in our dataset was assumed to not have transitioned until the point of censorship, meaning our estimated transition times are conservative. Second, simultaneous transition from HIV diagnosis to linkage to care might have resulted from transferring care into a specialist service from low case load clinics not captured by the surveillance system. In those instances, individuals would likely have had HIV confirmatory antibody tests and CD4 cell count or viral load tests on the same day. Third, we do not systematically capture mortality data that could represent a competing event. However, we do not expect mortality to be common in the study period among GBM with a new HIV diagnosis.[34] Fourth, although ACCESS covers a large proportion of all new HIV diagnosis among GBM (48–60%), most included clinics were located in inner-urban areas with high HIV caseloads and thus, transition periods might be longer for GBM living in rural areas or those diagnosed and presenting for HIV care in non-specialist clinical services.

Our study has several strengths. Using longitudinal data increases internal consistency compared with cross-sectional estimates by using the same denominator population throughout all stages. We have data to 2019 providing the most up to date estimates on progress toward HIV elimination and we were able to monitor changes following the ART initiation guidelines update in 2015. Moreover, we were able to include individuals with a recorded HIV seroconversion during follow-up,

and transition times and probabilities were similar in this group when compared with the total study population. We provide a different approach to study the HIV cascade of care in Australia, allowing us to estimate the time individuals remain viraemic and at risk of transmitting HIV. Unlike most studies assessing time to ART initiation and virological suppression, this method allowed the inclusion of skipped and simultaneous transitions, thus portraying a more realistic scenario of HIV care trajectories of GBM.

In conclusion, among newly HIV diagnosed GBM in New South Wales and Victoria, HIV cascade transitions occurred rapidly, with considerable improvement observed in time to ART initiation and virological suppression between 2012 and 2019. In countries such as Australia with high cross-sectional cascade estimates, the impact of treatment as prevention is better estimated using longitudinal cascade analyses. To end the AIDS epidemic by 2030 and ultimately eliminate HIV in Australia, continued efforts to increase early diagnosis and immediate ART initiation at HIV diagnosis are warranted, including expanded coverage of accessible and convenient testing models (eg, HIV self-testing) that promote high frequency testing and referral to care, and health promotion to enhance awareness of the benefits of early diagnosis and treatment among people at risk of HIV.

Contributors

DKvS conceived the study. DKvS, MS, RG, JA, and MWT contributed substantially to study conception and study design and the acquisition, analysis, and interpretation of data. NAH provided methodological support. DKvS, JA, and MWT had full access to all the data in the study and verified the data. All authors revised the manuscript critically for important intellectual content and approved the final version for publication.

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Declaration of interests

MWT has received honoraria for scientific meetings from Gilead Sciences. JHM and JFH have received grants via their institutions from Gilead Sciences, ViiV Health Care, and Merck Sharpe Dohme for the conduct of clinical trials and participation on advisory boards. MH has received funding for investigator-initiated research from Gilead Sciences and AbbVie, unrelated to this work. RG has received research support funding from Gilead Sciences. MS has received funding for investigator-initiated research from Gilead Sciences and AbbVie unrelated to this work; and consultancy fees from Gilead Sciences for activities unrelated to this work. All other authors declare no competing interests.

Data sharing

De-identified individual participant data included in this study are not available. Study protocols (TAIPAN and ACCESS) have been published previously.

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References

1 Joint United Nations Programme on HIV/AIDS (UNAIDS). Ending AIDS. Progress towards the 90-90-90 targets, 2017. https://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf (accessed Aug 2, 2021).

2 Kirby Institute. HIV. https://data.kirby.unsw.edu.au/hiv (accessed Feb 8, 2021).

3 Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia. Annual surveillance report 2018. https://kirby.unsw.edu.au/sites/default/files/kirby/report/KI_Annual-Surveillance-Report-2018.pdf (accessed Aug 2, 2021).

4 Scott N, Stoové M, Kelly SL, Wilson DP, Hellard ME. Achieving 90-90-90 Human Immunodeficiency Virus (HIV) targets will not be enough to achieve the HIV incidence reduction target in Australia. *Clin Infect Dis* 2018; **66:** 1019–23.

5 Haber N, Pillay D, Porter K, Bärnighausen T. Constructing the cascade of HIV care: methods for measurement. *Curr Opin HIV AIDS* 2016; **11:** 102–08.

6 Haber N, Tanser F, Bor J, et al. From HIV infection to therapeutic response: a population-based longitudinal HIV cascade-of-care study in KwaZulu-Natal, South Africa. *Lancet HIV* 2017; **4:** e223–30.

7 Dijkstra M, van Rooijen MS, Hillebregt MM, et al. Decreased time to viral suppression after implementation of targeted testing and immediate initiation of treatment of acute HIV infection among men who have sex with men in Amsterdam. *Clin Infect Dis* 2020; **72:** 1952–60.

8 Haber NA, Lesko CR, Fox MP, et al. Limitations of the UNAIDS 90-90-90 metrics: a simulation-based comparison of cross-sectional and longitudinal metrics for the HIV care continuum. *AIDS* 2020; **34:** 1047–55.

For the **TAIPAN and ACCESS protocols** see https://pubmed.ncbi.nlm.nih.gov/27955627/ and https://pubmed.ncbi.nlm.nih.gov/30459142/

9 Callander D, Stoové M, Carr A, et al. A longitudinal cohort study of HIV 'treatment as prevention' in gay, bisexual and other men who have sex with men: the Treatment with Antiretrovirals and their Impact on Positive And Negative men (TAIPAN) study protocol. *BMC Infect Dis* 2016; **16:** 752.

10 Callander D, Moreira C, El-Hayek C, et al. Monitoring the control of sexually transmissible infections and blood-borne viruses: protocol for the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS). *JMIR Res Protoc* 2018; **7:** e11028.

11 Callander D, Mooney-Somers J, Keen P, et al. Australian 'gayborhoods' and 'lesborhoods': a new method for estimating the number and prevalence of adult gay men and lesbian women living in each Australian postcode. *Int J Geogr Inf Sci* 2020; **34:** 1–17.

12 Nguyen L, Stoové M, Boyle D, et al. Privacy-preserving record linkage of deidentified records within a public health surveillance system: evaluation study. *J Med Internet Res* 2020; **22:** e16757.

13 Ampt FH, El Hayek C, Agius PA, et al. Anorectal swabs as a marker of male-to-male sexual exposure in STI surveillance systems. *Epidemiol Infect* 2017; **145:** 2530–35.

14 Australasian Society for HIV Medicine. HIV shared care. GP management plan (GPMP) guide 2015. Sydney, Australia: Australasian Society for HIV Medicine, 2015.

15 Grierson J, Pitts M, Koelmeyer R. HIV futures seven: the health and wellbeing of HIV positive people in Australia. Melbourne, VIC, Australia: Australian Research Centre in Sex, Health and Society, LaTrobe University, 2013. https://www.acon.org.au/wp-content/uploads/2015/04/HIV-Futures-7-report-2013.pdf (accessed Aug 2, 2021).

16 Australian Goverment Department of Health. Human immunodeficiency virus (HIV) (newly acquired) case definition. https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_hivnew.htm (accessed July 1, 2019).

17 Croxford S, Raben D, Jakobsen SF, et al. Defining linkage to care following human immunodeficiency virus (HIV) diagnosis for public health monitoring in Europe. *Euro Surveill* 2018; **23:** 1700858.

18 Australasian Society for HIV Medicine. Antiretroviral guidelines. https://arv.ashm.org.au/ (accessed May 13, 2021).

19 Esber AL, Coakley P, Ake JA, et al. Decreasing time to antiretroviral therapy initiation after HIV diagnosis in a clinic-based observational cohort study in four African countries. *J Int AIDS Soc* 2020; **23:** e25446.

20 Teasdale CA, Wang C, Francois U, et al. Time to initiation of antiretroviral therapy among patients who are ART eligible in Rwanda: improvement over time. *J Acquir Immune Defic Syndr* 2015; **68:** 314–21.

21 Robertson MM, Braunstein SL, Hoover DR, Li S, Nash D. Timeliness of human immunodeficiency virus diagnosis and antiretroviral treatment initiation in the era of universal testing and treatment. *J Infect Dis* 2019; **220:** 648–56.

22 Le Guillou A, Pugliese P, Raffi F, et al. Reaching the second and third joint United Nations programme on HIV/AIDS 90-90-90 targets is accompanied by a dramatic reduction in primary human immunodeficiency virus (HIV) infection and in recent HIV infections in a large French nationwide HIV cohort. *Clin Infect Dis* 2020; **71:** 293–300.

23 Medland NA, Nicholson S, Chow EPF, et al. Time from HIV infection to virological suppression: dramatic fall from 2007 to 2016. *AIDS* 2017; **31:** 2377–85.

24 Australasian Society for HIV Medicine. Antiretroviral drugs and other therapies in HIV patients. https://hivmanagement.ashm.org.au/antiretroviral-drugs/ (accessed May 13, 2021).

25 McManus H, Callander D, Donovan B, et al. Early initiation of antiretroviral therapy for people newly diagnosed with HIV infection in Australia: trends and predictors, 2004–2015. *Med J Aust* 2019; **210:** 269–75.

26 Victorian AIDS Council. Media release: VAC and Living Positive Victoria launch groundbreaking campaign to encourage early treatment for HIV. https://cdn.thorneharbour.org/media/documents/397a26b7-20160412_vac_lpv_treat-hiv-now-launch.pdf (accessed May 13, 2021).

27 McManus H, Callander D, Asselin J, et al. A new method for estimating the incidence of infectious diseases. *Am J Epidemiol* 2021; **190:** 1386–95.

28 Ryan KE, Asselin J, Fairley CK, et al. Trends in human immunodeficiency virus and sexually transmitted infection testing among gay, bisexual, and other men who have sex with men after rapid scale-up of preexposure prophylaxis in Victoria, Australia. *Sex Transm Dis* 2020; **47:** 516–24.

29 Girometti N, Lander F, McOwan A, et al. Rapid ART start in early HIV infection: time to viral load suppression and retention in care in a London cohort. *HIV Med* 2020; **21:** 613–15.

30 Huang R, Petoumenos K, Gray RT, et al. National characteristics and trends in antiretroviral treatment in Australia can be accurately estimated using a large clinical cohort. *J Clin Epidemiol* 2018; **100:** 82–91.

31 Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia: annual surveillance report 2016. NSW, Australia: UNSW, 2016.

32 Keen P, Gray RT, Telfer B, et al. The 2016 HIV diagnosis and care cascade in New South Wales, Australia: meeting the UNAIDS 90-90-90 targets. *J Int AIDS Soc* 2018; **21:** e25109.

33 Gray RT, Bretana N. leftygray/Cascade_calculations. https://github.com/leftygray/Cascade_calculations (accessed Sept 1, 2021).

34 Bhaskaran K, Hamouda O, Sannes M, et al. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA* 2008; **300:** 51–59.