

Impact of universal coverage for antiretroviral therapy (ART) on health outcomes

Question

What are the benefits of universal antiretroviral therapy (ART) coverage on individual and population level health outcomes?

Key Take-Home Messages

- As of 2017, the annual cost of single-tablet antiretrovirals (ART) in Ontario was estimated to be CAD 15,552 according to the Ontario Drug Benefit Formulary (1, 2). Universal, no-cost ART for all people living with HIV in Ontario has the potential to improve access to ART among those lacking the means for deductibles and co-payments and could remove the need to join programs such as the Ontario Disability Support Program (ODSP) to obtain coverage (3).
- High-income countries with higher ART coverage have been more likely to achieve a greater proportion of individuals that are virally suppressed (4), and beginning ART at the time of HIV diagnosis regardless of CD4 cell count is associated with increased viral suppression (5).
- Expanded ART coverage in the U.S. is associated with reductions in HIV transmission (6), mortality (7), and comorbidities such as certain cancers (8).
- In terms of costs, the scale-up of ART was found to be highly cost-effective in British Columbia (9); in Australia, expanding ART to temporary residents was estimated to considerably reduce HIV transmission at little additional cost (10). In Italy, high costs for ART was compensated for by improvements in health outcomes and reductions in health care use (11).

Rapid Response: Evidence into Action

The OHTN Rapid Response Service offers quick access to research evidence to help inform decision making, service delivery, and advocacy. In response to a question, the Rapid Response Team reviews the scientific and grey literature, consults with experts if required, and prepares a review summarizing the current evidence and its implications for policy and practice.

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The Issue and Why it's Important

In recent years, there has been a global shift in guidelines for antiretrovirals from “treating the sickest” towards “treating all” individuals living with HIV (12). In 2016 guidelines, the World Health Organization broadly defined universal access to ART as “...a high level of treatment coverage (80% or more of the eligible population) that is accessible and affordable. It does not necessarily mean 100% coverage” (13). These guidelines also recommended that adults, pregnant women, breastfeeding women, and youth should have ART initiated regardless of their clinical staging and at any CD4 cell count (13). This approach has also been described as “test-and-treat” initiatives (4). Globally, rates of coverage for ART has increased from about 7% in 2005 to 62% in 2018 (12, 14). It is estimated that the introduction and scaleup of ART has averted about 9.5 million deaths from AIDS and 7.9 million HIV infections between 1995 to 2015 (15). Nevertheless, ART coverage has not been equitable across all populations and settings (12).

In Canada, coverage for medications including antiretrovirals is managed and delivered by each province or territory (1). As a result, individuals with the same prescription pay a different amount for their medications depending on the jurisdiction in which they reside, and may need to use a combination of private insurance, public funders, and out-of-pocket payments (1, 16). A 2017 publication found that the annual cost of single-tablet ART was CAD 15,552 in Ontario according to the Ontario Drug Benefit Formulary (1, 2). As of February 2021, the formulary estimates that a single table of abacavir/lamivudine/dolutegravir is CAD 45.53, which is estimated to cost approximately CAD 16,620.24 annually (17). In the U.S., the cost of ART is described as “disproportionately expensive” with limited variety in the drug market for ART (18). A 2020 study estimated that a year’s supply of ART had a median cost of USD 35,780, of which Medicare would cover approximately 53% to 67% (19). Unless patients qualify for other low-income subsidies, they often contribute USD 3,000 to 4,000 annually out-of-pocket for ART (19).

The costs of medications such as ART can compete with other demands, resulting in “cost-related non-adherence” situations where individuals skip their antiretrovirals to pay for other priorities (1). Even though Ontario offers coverage through various public programs, a 2019 study from the Ontario HIV Treatment Network Cohort Study (OCS) found that about 13% of cohort participants surveyed had trouble obtaining ART in the last year (20). In examining the barriers to accessing treatment in Ontario, a 2020 study found that health disparities such as poverty, housing, stigma, and immigration status can affect access to prescription medications (3). The study suggested that an initiative offering universal, no-cost antiretrovirals for all people living with HIV would improve access to antiretrovirals among individuals lacking the means for deductibles and co-payments, and could remove the need to join programs such

References

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as the Ontario Disability Support Program (ODSP) (3).

A 2020 study in Vancouver examined levels of material security and ART adherence among people who use drugs (n=623) (21). Material security was described as access to necessities such as housing and food (21). Results found no significant associations between level of material security and achieving ART adherence which suggested that the negative impact of poverty on ART adherence can be mitigated in a setting that provided universal, no-cost HIV treatment (21).

This review aims to provide a general overview of ART coverage in high income countries and the benefits of universal ART on various individual and population level health outcomes.

What We Found

Coverage for antiretrovirals

In Canada, in 2017, five federal programs and six of 13 jurisdictions offered universal coverage (1). In 2018, Saskatchewan became the seventh jurisdiction to offer universal coverage under the Saskatchewan Drug Plan (22, 23). Other jurisdictions that provide universal coverage for antiretrovirals at no cost include: Alberta under the Alberta Health Care Insurance Plan (24), British Columbia under the HIV Drug Treatment Program through the BC Centre for Excellence in HIV/AIDS (25) since 1996 (9), the Northwest Territories under the Extended Health Benefits for Specified Disease Conditions Program (26), Nunavut under the Extended Health Benefits program (27), and Prince Edward Island under their HIV Drug Program (28). New Brunswick provides ART coverage under their HIV/AIDS plan for individuals who do not have private insurance coverage (1).

In Ontario, individuals living with HIV who do not have employer coverage for ART can apply for government-sponsored programs, with any remaining costs paid for out-of-pocket (20). These government-sponsored programs include:

- **Ontario Drug Benefit (ODB) Program:** This program covers costs of certain prescription drugs including ART for certain individuals living in Ontario. This includes coverage for those aged 65 and older, with coverage amounts depending on their income and marital status. The ODB also covers the cost of prescriptions for individuals aged 24 or younger without a private insurance plan (29).
- **Ontario Works (OW) or Ontario Disability Support Program (ODSP):** Individuals receiving benefits from either of these programs are automatically covered by the ODB and pay up to CAD 2 for each drug filled and do not pay a deductible (29).

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- **Trillium Drug Program:** Individuals who do not qualify for ODB under any of the aforementioned programs and do not have an insurance plan that pays for 100% of their medication costs can qualify for this program. Individuals pay a deductible that is usually about 4% of their income after taxes and then pay about CAD 2 per prescription filled (29, 30).

A 2018 study developed hypothetical cases to estimate approximate out-of-pocket costs for ART prescriptions across Canada as of December 2017 (1). In the first scenario, a man with no dependants with an annual income of CAD 39,000 was estimated to have an annual out-of-pocket expense for ART of CAD 45 to 1,944 depending on where he lived in Canada, with an estimated annual expense of CAD 1,352 if he lived in Ontario (1). In the second scenario, a woman with two dependents and an annual income of about CAD 80,000 would have to pay CAD 2,720 to 7,993 out-of-pocket depending on where she lived in Canada, with an estimated annual expense of CAD 3,000 if she lived in Ontario (1). Neither hypothetical case would have had any out-of-pocket expenses in jurisdictions that provided universal ART coverage (1).

In 2010, the U.S. passed the Patient Protection and Affordable Care Act (ACA) (31) which increased access to insurance coverage for millions of individuals living in the U.S., including those living with HIV (18). The ACA improved access to insurance coverage by: authorizing all states to expand Medicaid coverage, removing exclusions for individuals with pre-existing conditions, and including protections against discrimination in health care (18). Individuals with HIV receive insurance coverage for prescription drugs such as antiretrovirals from various sources including:

- **Medicaid:** This is the largest public insurance program in the U.S. which provides coverage for low-income individuals, with approximately 40% of individuals living with HIV relying on it for benefits such as antiretrovirals (18).
- **Private insurance:** This includes plans often provided through an employer which can vary in terms of included benefits and cost-sharing (18). About 35% of individuals living with HIV rely on private insurance coverage which is much lower than private insurance coverage in the general population at 56% (32).
- **Medicare:** This program provides insurance coverage for individuals aged 65 and older as well as for younger individuals living with long-term disabilities (18). About 8% of individuals living with HIV solely rely on Medicare for insurance coverage, with about 28% of individuals living with HIV using Medicare in combination with other types of coverage (18).

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- **The Ryan White HIV/AIDS Program (RWHAP):** This program provides coverage for individuals who are uninsured or underinsured with funding provided to states and organizations in the form of grants from the federal government (18). In 2018, 82% of uninsured individuals living with HIV received assistance from the RWHAP program and the program also provided cost assistance to 38% of individuals living with HIV with private insurance coverage (32).

Other sources of coverage for HIV treatment in the U.S. includes the Veterans Health Administration, community health centers, and the Indian Health Service (18).

In Australia, ART is provided to citizens and permanent residents through sexual health clinics, general practitioner clinics, and hospitals, and is funded through the country's universal health care system, known as Medicare (33), with low direct costs to patients (34). The Pharmaceutical Benefits Scheme (PBS) provides a subsidy which covers the cost of ART for eligible individuals under the universal health care system (35). As of January 2020, individuals pay a co-payment of up to AUD 41.30 for most PBS prescriptions, with the government paying the remaining cost (36). As of January 2021, under the PBS Safety Net, general patients that reach a payment threshold of AUD 1,497.20 for their prescriptions are eligible to receive a higher Medicare benefit for their medications to reduce their out-of-pocket costs (36).

Health outcomes

Viral suppression

A study from 37 European and Central Asian countries found that countries with higher ART coverage were more likely to achieve a greater proportion of virally suppressed individuals (4). Furthermore, countries that did not have CD4 limits for ART were statistically significantly more likely to have more viral suppression among patients than countries that restricted treatment to only individuals with a low CD4 cell count (4). In Ontario, one study found that once eligible individuals successfully enroll into Trillium coverage they are able to achieve viral suppression, suggesting that timely access and coverage can result in better health outcomes (20).

A 2016 study examined health outcomes including viral suppression among 58 inmates living with HIV in a major Canadian remand centre between 2007 to 2011 (37). The province in which the study was conducted (Alberta) mandated the provision of ART regardless of incarceration (37). Results found that ART adherence was higher one-year post-incarceration with 70.7% adhering to ART compared 55.2% adhering to ART pre-incarceration (37). The highest level of adherence was found during incarceration at 88.7% (37). The

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proportion of participants virally suppressed increased from 44.4% at one-year pre-incarceration to 77.8% at exit from incarceration, with 70.4% maintaining viral suppression at one-year post-release (37). The authors concluded that it is possible to improve HIV-related health outcomes among a remand population in a universal health care coverage setting (37).

In the U.S., Massachusetts became the first state to have “nearly universal health insurance coverage” with early adoption of expanded Medicaid in 2006 (38, 39). In 2014, the state had viral suppression levels higher than the national average; additionally, about 89% of individuals retained in care were experiencing viral suppression (40). Medicaid expansion in the U.S. following the implementation of the ACA has led to increased progress towards viral suppression (38). From 2010 to 2015, viral suppression rates increased 2.8% annually among people living with HIV in the U.S (38, 41). A systematic review identified 12 articles on the early impacts of the ACA on people living with HIV (42), eight of which reported positive health related outcomes (43–50). Results of the systematic review found that implementing the ACA had been positively associated with health outcomes, including viral suppression (42).

In the years following the implementation of the ACA, some states provided uninsured individuals with coverage for medications such as antiretrovirals through Qualified Health Plans (QHPs) under AIDS Drug Assistance Programs (ADAPs) (51). A 2020 study examined QHP enrollment and viral suppression among individuals living with HIV who were eligible for ADAP-funded QHPs in Nebraska, South Carolina, and Virginia (n=7,776) (51). Results found that 52% of eligible participants enrolled in a QHP and stayed enrolled over the study period (51). Enrollment was associated with viral suppression across all states and demographic groups (51). Among the total number of participants engaged in care (n=4,597), those enrolled in a QHP had a higher viral suppression rate of 86.0% than those who were not enrolled in a QHP, who had a viral suppression rate of 80.2% (51). The study concluded that if enrollment in QHPs led to improved viral suppression, another 2.4% of ADAP patients could achieve viral suppression nationally (51).

In Australia, access to ART and treatment in community settings led to rapid initiation of ART and decreased periods of infectivity (34). From the period between 2004 to 2015, treatment coverage for ART had increased (52). This led to an increase in the proportion of individuals that were virally suppressed, which decreased the chance of HIV transmission (52, 53). The estimated proportion of virally suppressed gay and bisexual men increased from about 30.2% in 2004 to 73.7% in 2015 (52). A 2018 study in Australia estimated that 79.3% of people living with HIV in New South Wales were virally suppressed in 2016 (35). Factors attributed to this high rate of viral suppression included promoting the benefits of early treatment as well as the removal of co-payments for specialized drugs such as ART in New South Wales in 2015 (35, 54).

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In Denmark, where access to HIV treatment is free, a 2016 study examined the impact of treatment as prevention (TasP) among men who have sex with men from 1996 to 2013 using data from the Danish HIV Cohort Study (5). Authors found a strong correlation between a decrease in HIV incidence and an increase in treatment coverage since 1996 (5). As of 2011, all people living with HIV could begin immediate ART regardless of their CD4 cell count, which increased the rate of viral suppression (5). TasP did not significantly reduce the HIV incidence rate until treatment coverage reached about 35% of those infected (5). Denmark has since achieved a high rate of treatment coverage with about 92% of men who have sex with men on treatment, 98% of whom were virally suppressed (5).

Another 2016 study examined the impacts of a community-wide TasP intervention in British Columbia among 819 people living with HIV who used drugs (55). Study participants were recruited from 2006 to 2014 and contributed at least one viral load observation (55). The intervention included changes to clinical guidelines to increase ART initiation and providing ART adherence supports (55). The study found a sharp increase in ART coverage, and the proportion of participants that had an undetectable viral load increased from 28.1% to 62.9% over the course of the study (55). There was also a decrease in the rate of drug resistance among participants (55). The authors concluded that the results support the need to scale up ART among those living with HIV who use drugs (55).

Recent studies have found the costs of antiretrovirals to be associated with a lack of viral suppression (56, 57). Participants in a Quebec study (n=8 female patients; 8 providers) noted that the lack of complete coverage of ART was a major barrier to achieving the benefits of a suppressed viral load, as individuals living with HIV and experiencing poverty would forego ART in order to pay for other necessities (57). Participants suggested complete financial coverage of ART due to the societal benefits of an undetectable viral load (57). A 2018 study in Ontario among 1,247 participants from 2008 to 2013 found that those with coverage through the ODB program were significantly less likely to be virally suppressed than those with employer coverage for ART (20). Possible explanations for the limited effect of ODB coverage included the fact that the study only examined participants' last viral load for each year of the study period (20). Other factors included the fact that co-pays for those on the ODB can act as a financial barrier to receiving ART, certain ART medication doses may not be covered by the ODB which can lead to pill burden, and those on disability likely face barriers such as comorbid conditions that can act as a barrier to achieving viral suppression (20).

HIV transmission

A 2017 study in British Columbia used health administrative and registry data from 1996 to 2013 to estimate the effects of ART and harm reduction services on reducing HIV incidence through needle

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sharing (58). Based on the models developed, results indicated that 3,204 HIV cases and 461 deaths were averted due to the combined effects of ART coverage and expansion of harm reduction services (58). In a proposed scenario, if harm reduction services stayed constant at 1996 levels, ART alone would have had a substantial independent effect by averting 1,409 HIV cases from needle-sharing (58).

A 2017 review article references a study from British Columbia, stating that population viral load has decreased in recent years due to an increase in the number of patients with a suppressed viral load, which reflects improved ART coverage in the province (59, 60). This 2010 study found that from 1996 to 2009, the number of individuals living with HIV that received ART increased by 547% (from 837 to 5,413), and the number of new HIV diagnoses decreased by 52% (from 702 to 338 per year) (60). These results indicated “a strong population-level association between increasing HAART coverage, decreased viral load, and decreased number of new HIV diagnoses per year” (60).

A 2018 retrospective cohort study among youth living with HIV in Philadelphia (n=240) used data from 2002 to 2015 to examine their insurance coverage and HIV transmission potential (6). The youth were followed for approximately 22 months upon initiation of ART (6). Authors found that the odds of high HIV transmission potential was reduced by more than half among those with insurance coverage compared to those without, after adjusting for various factors such as race and age at time of ART initiation (6). Insurance coverage was protective against HIV transmission risk, although this association was not significant (6). Authors conclude these results may indicate a “pivotal role for universal ART coverage in treatment as prevention” (6).

Data from 2014 in the Netherlands indicated that 84% of pregnant women had a suppressed viral load during delivery which increased to 97% in 2015 (61). This increase was believed to be attributable to the implementation of universal ART in 2015 (61). As a result, no HIV infections were reported in 2015 among children born in the country (61).

Life expectancy and mortality

A 2015 study examined life expectancy among adults living with HIV across eight sites in British Columbia, Ontario, and Quebec (62). Results found that life expectancy at age 20 increased over time from 30.8 years, to 38.6 years, and to 54.2 years in the time-periods from 2000 to 2003, 2004 to 2007, and 2008 to 2012, respectively (62). Increased life expectancy was likely due to improved ART coverage, ART regimes, and HIV care (62, 63). A 2016 study in British Columbia examined the expansion of combination ART from 1996 to 2012 in the province and found that it was associated with a decrease in morbidity, mortality, and HIV transmission at the population

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level (64). The study “...estimated that for every 1% increase in the number of individuals suppressed on ART, the HIV/AIDS morbidity and mortality decreased by 2%, and HIV incidence rate decreased by 1%” (64). A cohort study in California used data from 2000–2016 to examine life-expectancy among 39,000 adults living with HIV in comparison to about 388,000 uninfected adults (65). Results found that life expectancy at age 21 was 37.6 years for those living with HIV and 57.9 years for those without HIV in 2000 to 2003. Life expectancy at age 21 increased to 59.4 years among those living with HIV in 2014 to 2016, indicating an improvement over time with earlier ART initiation (65). Another U.S. study examined data from 2010 to 2014 and found that U.S. states with slightly higher health care coverage under the RWHAP had 4% to 11% lower mortality rates among older age groups (7). Generally, mortality rates were lower in states with anti-discrimination laws related to sexual orientation and gender identity as well as in states with viral suppression among RWHAP participants (7).

Comorbidities

A 2017 study in the U.S. examined HIV registries from 1996 to 2012 and found that expanded ART use has likely contributed to decreased virus-related cancer and lung cancer risks among people living with HIV (8). A 2017 study in Switzerland used data of 6,411 men who had sex with men from the Swiss HIV Cohort Study between 1983 to 2015 to model the impact of anal cancer screening and ART coverage on anal cancer incidence (66). Results of the model found that cancer incidence peaked in 2009 at 81.7 per 100,000 person-years and will decrease to 58.7 per 100,000 person-years by 2030 with consistent ART coverage (66). If universal ART coverage was initiated from 2016 onwards, the incidence of anal cancers was estimated to reduce to about 50 per 100,000 person-years by 2030 (66).

A 2016 retrospective study examined the incidence of pneumococcal infections among 80 cases (individuals with HIV and pneumococcal infection) and 160 controls (individuals with HIV without pneumococcal infection) across two hospitals in France (67). Results found that from 2000 to 2014, the number of patients with an undetectable viral load increased as the incidence of those infected with pneumococcal infection decreased (67). The study estimated that the incidence of pneumococcal infection among those virally suppressed and without comorbidities was about 7.6 per 100,000 patients, while the incidence of pneumococcal infection among those without viral suppression was 107 per 100,000 patients (67). The authors concluded that with an increased proportion of virally suppressed individuals, HIV infection is no longer in itself a significant risk factor for pneumococcal infections (67).

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Cost and cost-effectiveness

A 2015 study compared the costs of observed access to ART in British Columbia from 1997 to 2010 to hypothetical scenarios of less comprehensive access to ART at 75% and 50% of observed access (9). These hypothetical scenarios were meant to represent “expected levels of treatment uptake in the absence of a range of province-wide initiatives to inform and engage physicians in HIV treatment” (9). From a payer perspective, the cost of ART from 1997 to 2010 was comparable across the observed and hypothetical scenarios (9). From 1997–2010, ART access was estimated to cost about CAD 646 million, 75% of observed ART access costing about CAD 598 million, and 50% of observed ART access costing about CAD 520 million (9). Observed ART access was estimated to cost CAD 23,679 per Quality Adjusted Life-Year (QALY) gained when compared to the 75% access scenario, and CAD 24,250 per QALY gained when compared to the 50% access scenario (9). This indicated that the scale-up of ART in British Columbia was highly cost-effective in the examined study period (9). Furthermore, observed ART access averted 263 or 676 incident HIV cases when compared to the 75% and 50% access scenarios, respectively (9). When extending the hypothetical model to 2035, the current observed ART access had savings of over CAD 25 million and CAD 65.5 million when compared to the 75% and 50% access scenarios, respectively (9).

In 2018, temporary residents in Australia were not eligible for a Medicare card, and therefore could not access subsidized ART (10). A 2018 study used a mathematical model to determine the reduction in HIV infections if temporary residents in Australia were provided subsidized ART (10). Results found that expanding ART to 450 temporary residents living with HIV for 5 years would prevent 80 infections (10). The estimated median discounted cost for treatment was approximately AUD 36 million, and the median discounted savings in lifetime care and ART costs was about AUD 22 million (10). The authors concluded that expanding ART coverage to temporary residents would considerably reduce transmission at little additional cost to the Australian government (10).

A 2018 study in Italy examined the economic and clinical burden of HIV management after starting systematic use of ART prescription in recent years (11). The study compared hospital costs and patient data from 2009 in comparison to 2015 (11). Results found that the mean CD4 cell count and viral suppression increased significantly among participants from 2009 to 2015 (11). The costs for ambulatory care, exams, and drugs increased while the cost for hospitalizations decreased in this time period (11). The increase in costs for combination ART from EUR 9.08 million in 2009 to EUR 9.10 million in 2015 was offset by decreases in costs such as hospitalizations (11). The average cost per-patient hospitalization decreased from EUR 10,107 in 2009 to EUR 9,063 in 2015, partially due to reductions in the rate of hospitalizations (11). The study concluded that the high costs for combination ART was compensated for by improvements in health outcomes and reductions in health care use (11).

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Beyond universal coverage

Inequities in ART coverage still exists despite policies for universal ART (12) as universal coverage does not always equal universal availability and access to care (68, 69). For example, even though British Columbia provides universal ART coverage, in 2014 Indigenous people account for 5% of the provincial population, yet represented about 11% to 17% of new HIV cases, and men who have sex with men still represent about 58% of new cases (68, 70). France provides universal access to ART to all individuals living with HIV regardless of their socioeconomic status, yet a 2018 study found that migrants to France from sub-Saharan Africa had a 46% lower likelihood of initiating ART and a 48% lower likelihood of having a virological response than migrants from Western Europe (71). Hypothesized reasons in delaying ART included fear of stigmatization and other priorities to meet basic needs (71). Authors recommended targeted social and educational interventions that are culturally tailored to provide adherence support for migrants (71). A 2018 study in Italy found that social determinants such as unemployment and low education significantly impacted access to ART and related health outcomes despite having universal ART coverage in the country (72). Similarly, a 2018 study in Montreal found that participants who did not have paid employment delayed ART initiation despite a maximum co-payment of CAD 87.16 per month for those not on social welfare and covered by provincial insurance (73). A 2016 study in the UK, which provides free health care including HIV treatment, found that the negative effects of socioeconomic disadvantage go beyond the ability to access and pay for ART (74). Four markers of socioeconomic disadvantage including financial hardship, unemployment, unstable housing, and non-university education were strongly associated with non-adherence to ART among study participants (74).

Factors That May Impact Local Applicability

Types of ART treatment, ART coverage, and associated costs varied across examined jurisdictions which may not be entirely applicable to the local context. There is limited evidence on the impact of universal ART coverage on health outcomes in a Canadian context, with the majority of identified Canadian studies taking place in British Columbia which may not be generalizable to Ontario. Also, while ART coverage has likely led to reductions in HIV incidence, it is important to note that these reductions are likely to be not only due increases in ART coverage alone (75).

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What We Did

We searched Medline (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) using a combination of (terms [HIV or anti-retroviral] in titles or abstracts] or text terms [antiretroviral or antiretroviral therapy or anti retroviral agents or antiretroviral therapy highly active] or MeSH terms [Agents, Antiretroviral or Antiretroviral Agents or Antiretroviral Therapy, Highly Active or Highly Active Antiretroviral Therapy]) AND (MeSH term Insurance Coverage or terms [coverage or universal access or universal treatment] in titles or abstracts). Searches were conducted on March 8, 2021 and results limited to English articles from high-income countries published since 2016. Reference lists of identified articles were also searched. Google (grey literature) searches using different combinations of these terms were also conducted. The searches yielded 1,877 references from which 75 were included.

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