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Factors associated with delayed and late ART initiation among people living with HIV in BC: results from the engage study

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ABSTRACT

We examined correlates of late and delayed initiation of antiretroviral therapy (ART) in British Columbia, Canada. From December 2013 to December 2015 we recruited treatment-naïve people living with HIV who initiated ART within the previous year. 'Late initiation' was defined as CD4 cell count ≤500 cells/μL at ART initiation and 'delayed initiation' as ≥1 year between HIV diagnosis and initiation. Multivariable logistic regression assessed independent correlates of late and delayed initiation. Of 87 participants, 44 (51%) initiated late and 22 (26%) delayed initiation. Delayed initiation was positively associated with older age (adjusted odds ratio [AOR]: 1.06 per year, 95% confidence interval [95% CI]: 1.01–1.12) and inversely associated with wanting to start ART at diagnosis (AOR: 0.06, 95% CI: 0.02–0.21). Variables associated with late initiation were older age (AOR: 1.09 per year, 95% CI: 1.03–1.15) and medical reason(s) for initiation (AOR: 5.00, 95% CI: 1.41–17.86). Late initiation was less likely among those with greater perceived ART efficacy (AOR 0.94, 95% CI: 0.90–0.98) and history of incarceration (AOR: 0.12, 95% CI: 0.03–0.56). Disparities in timing of initiation were observed for age, perceived ART efficacy, and history of incarceration. Enhanced health services that address these factors may facilitate earlier treatment initiation.

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KEYWORDS
HIV; ART; treatment initiation; linkage to care

Background

Since the advent of combination antiretroviral therapy (ART), health outcomes of people living with HIV (PLHIV) have improved greatly (Lima, Eyawo, et al., 2015). ART has led to reductions in morbidity and mortality (Lima, Lourenco, et al., 2015; Lima, Reuter, et al., 2015) and decreased HIV transmission (Cohen et al., 2011). The benefits of immediate ART initiation have been demonstrated by the TEMPRANO (T.A.S. Group, 2015) and INSIGHT START (Insight Start Study Group et al., 2015) studies. Further, modern regimens have fewer adverse effects (Margolis, Heverling, Pham, & Stolbach, 2014) and decreased pill burden and dosing frequency (Hernandez Arroyo et al., 2016). Globally consensus has been reached; since 2015 guidelines uniformly recommend immediate initiation of ART regardless of CD4 cell count (Lundgren, Gatell, Rockstroh, & Furrer, 2015; Thompson et al., 2012; WHO, 2015). Despite known benefits (Boyd, 2009; Solomon & Sax, 2015), barriers to timely initiation persist (Cescon et al., 2015).

We examined factors associated with delayed ART initiation in British Columbia (BC), Canada. This study adds a unique perspective to the literature by including only individuals who recently initiated ART. Additionally, this study took place in a setting where ART is publicly funded and universally available, and implementation and expansion of the Seek and Treat to Optimize Prevention (STOP) HIV/AIDS program has promoted timely linkage of individuals to HIV treatment (BC Centre for Excellence in HIV/AIDS (BCCfE), April 4, 2013). Nonetheless, 20-30% of PLHIV in BC initiated ART with CD4 cell counts ≤200 cells/μL quarterly and only 39% began ART with a CD4 cell count >500 cells/μL in 2015 (BCCfE, 2016).

Methods

Cohort and study methods

The Engage Study is a prospective cohort of ART-naïve PLHIV who initiated treatment within one year of study

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enrollment. Eligible individuals were BC residents aged ≥19 years, with capacity to provide informed consent and complete surveys in English. From 9 December 2013 to 31 December 2015, 87 participants were recruited from 702 eligible individuals.

Participants completed a baseline and follow-up survey collecting sociodemographic data and information concerning participants' HIV care experiences. Surveys were completed with a Peer Research Associate, a person living with HIV who underwent research training. Simon Fraser University and the University of British Columbia's Research Ethics Boards granted ethical approval for this study.

Data linkage

Survey data were linked to the BCCfE's provincial Drug Treatment Program (DTP). The DTP dispenses the majority of ART in BC and houses comprehensive clinical information. This linkage enabled us to compare characteristics of study participants to eligible non-respondents, and to analyze factors associated with delayed ART initiation for all eligible individuals.

Outcome variables

Late ART initiation is defined as CD4 cell count ≤500 cells/μL based on therapeutic guidelines for ART initiation in BC that recommend initiation at any CD4 cell count, and ≤500 cells/μL for long-term non-progressors (BCCfE's Committee for Drug Evaluation and Therapy, 2013). Late initiation is often defined by CD4 cell count, a clinical variable that indicates HIV disease progression, and is readily available for studies using clinical or administrative data. CD4 cell count at initiation was obtained from the most recent test result on or before the person's first ART prescription date.

Delayed initiation provided an alternate measure of timely ART initiation based on self-reported HIV diagnosis date, and is defined as ≥1 year between HIV diagnosis date and ART initiation. There is no standard definition of delayed initiation in the literature; this definition was chosen to ensure a sufficient time period to identify those who opted to delay treatment.

Explanatory variables

Key explanatory variables, established by previous research to impact timing of initiation (Cescon et al., 2015; Joseph et al., 2016; Lourenco et al., 2015; Palmer et al., 2014), included: sex at birth, age, ethnicity, HCV seropositivity, history of IDU, history of homelessness, and income. Additional variables included in this analysis were: physician advice regarding ART initiation, medical reasons for initiating ART, concerns about ART, and participant scores on the Antiretroviral Medication Attitude Scale (AMAS) (Viswanathan, Aanderson, & Thomas, 2005), the HIV Treatment Adherence Self-Efficacy Scale (HIV-ASES) (Johnson et al., 2007), and the Continuity of Care Scale (Uijen et al., 2012).

Statistical analysis

Univariable and multivariable logistic regression identified independent predictors of late and delayed ART initiation. Significant variables in univariable analysis (p-value < 0.05) were considered in the final multivariable model. In instances of collinear covariates, the variable with the higher effect size was used. The Akaike information criterion method determined the final model selection.

Results

Of 87 participants, 15 (17%) were female and 56% were from Vancouver Coastal Health Authority. The median age was 39 years (Q1–Q3: 29–46 years), 28% had a history of IDU, 20% were HCV-seropositive and 56% identified as men who have sex with men.

The median CD4 cell count at ART initiation was 510 (Q1–Q3: 280–660) cells/μL and 43 (49%) participants initiated late, with CD4 cell count ≤500 cells/μL, and 22 (26%) delayed initiation. Median time between HIV diagnosis and ART initiation was three months (Q1–Q3: 1–14 months).

Table 1 compares participants to the 615 eligible non-respondents. Median CD4 cell count was significantly higher among participants, while median age was significantly lower among study participants.

Table 1 presents factors associated with late initiation among all eligible individuals. In multivariable logistic regression, factors positively associated with late initiation were: older age (AOR: 1.03 per year, 95% CI: 1.02–1.05 per year) and residence in the Island, Interior or Northern Health Authorities compared to Vancouver Costal Health Authority (AOR: 2.19, 95% CI: 1.42–3.37).

Table 2 depicts participant characteristics dichotomized by CD4 cell count at ART initiation and results of univariable and multivariable analysis of factors associated with late initiation. In multivariable analysis, individuals of older age (AOR: 1.09, 95% CI: 1.03–1.15) and those who reported initiating ART due to medical reasons (AOR: 5.00, 95% CI: 1.14–17.86) were more likely to initiate ART late. History of incarceration (AOR: 0.12. 95% CI: 0.03–0.56) and higher HIV-ASES

Table 1. Descriptive statistics and multivariable factors associated with late initiation for all eligible individuals ($n = 702$).

	Descriptive statistics at ART initiation			Multivariable factors associated with late initiation			
				Late initiation			
Variable	Engage study participants ($n = 87$)	Eligible individuals ($n = 615$)	*P*-value	No (>500) ($n = 260$)	Yes (≤500) ($n = 442$)	*P*-value	Multivariable logistic regression
CD4 cell count (cells/μL)	510 (280–660)	380 (190–580)	**0.010**	650 (570–780)	260 (110–370)	(Outcome variable)	(Outcome variable)
Age	39 (29–46)	40 (32–51)	**0.020**	35 (28–48)	42 (34–52)	**<.001**	**1.03 (1.02–1.05)**
Sex at birth			0.636			0.388	Not selected
Male	72 (83)	521 (85)		224 (86)	369 (84)		
Female	15 (17)	94 (15)		36 (14)	73 (17)		
Ethnicity			0.240			0.174	Not selected
Indigenous	17 (20)	50 (13)		20 (12)	47 (16)		
White	49 (57)	226 (59)		108 (64)	167 (55)		
Other	20 (23)	108 (28)		40 (24)	88 (29)		
HCV-seropositive			0.887			0.270	Not selected
No	70 (80)	454 (74)		195 (75)	329 (74)		
Yes	17 (20)	119 (19)		43 (17)	93 (21)		
Unknown	0	42 (7)		22 (9)	20 (5)		
IDU history			0.266			0.833	Not selected
No	63 (72)	355 (58)		158 (61)	260 (59)		
Yes	24 (27)	100 (16)		45 (17)	79 (18)		
Unknown	0	160 (26)		57 (22)	103 (23)		
Health authority of residence			0.074			**0.001**	
Vancouver coastal	48 (56)	297 (49)		77 (30)	118 (27)		Ref
Fraser	27 (31)	168 (28)		38 (15)	115 (26)		1.08 (0.75–1.56)
Other	11 (13)	142 (23)		143 (55)	202 (46)		**2.19 (1.42–3.37)**

Notes: Results are *n* (%), median (Q1–Q3) and adjusted odds ratio (95% confidence interval). Bold *P*-values indicate statistical significance. ART: antiretroviral therapy; HCV: Hepatitis C virus; IDU: injection drug use.

Table 2. Descriptive characteristics and univariate and multivariate factors associated with late initiation ($n = 87$).

Variable	Late ART initiation (CD4 cell count < 500 cells/μL)			Univariable logistic regression	Multivariable logistic regression
	No (>500) ($n = 44$)	Yes (≤500) ($n = 43$)	*P*-value		
Median CD4 cell count (cells/μL)	650 (545–800)	280 (140–380)	n/a	(Outcome variable)	(Outcome variable)
Time from HIV diagnosis to ART initiation (months)	3 (1–14)	2 (1–24)	0.626	1.00 (0.99–1.01)	Not included
Sex at birth					Not included
Male	37 (84)	35 (81)	0.783	Reference	
Female	7 (16)	8 (19)		1.21 (0.40–3.68)	
Age (years)	32 (28–44)	41 (34–49)	**0.010**	**1.06 (1.01–1.10)**	**1.09 (1.03–1.15)**
Ethnicity			0.322		Not included
Indigenous	9 (21)	8 (19)		Reference	
White	25 (58)	24 (56)		1.08 (0.36–3.26)	
Other	9 (21)	11 (25)		1.38 (0.38–5.03)	
Sexual orientation			0.606		Not included
Heterosexual	11 (25)	14 (33)		Reference	
LGBTQ	33 (75)	29 (68)		0.69 (0.27–1.76)	
HCV-seropositive			0.280		Not included
No	33 (75)	37 (86)		Reference	
Yes	11 (25)	6 (14)		0.49 (0.16–1.46)	
Injection drug use (ever)			0.231		Not included
No	29 (66)	34 (79)		Reference	
Yes	15 (34)	9 (21)		0.51 (0.20–1.34)	
Health authority			0.621		Not included
Fraser	15 (35)	12 (28)		Reference	
Vancouver costal	24 (56)	24 (56)		1.25 (0.49–3.22)	
Other	4 (9)	7 (16)		2.19 (0.52–9.27)	
Median personal monthly income ($CAD)	1175 (675–3000)	1100 (610–2200)	0.220	1.00 (1.00–1.00)	Not included
Sexual partners (in year prior to interview)	5 (1–11)	2 (1–6)	**0.026**	0.95 (0.90–1.00)	Not selected
Relationship status			0.644		Not included
In a relationship+	12 (27)	14 (33)		Reference	
Not in a relationship~	32 (73)	29 (67)		0.78 (0.31–1.95)	
History of incarceration			0.062		**0.12 (0.03–0.56)**
No	31 (70)	38 (88)		Reference	
Yes	13 (30)	5 (12)		**0.31 (0.10–0.98)**	
History of homelessness			**0.029**		Not selected
No	21 (48)	31 (72)		Reference	
Yes	23 (52)	12 (28)		**0.35 (0.15–0.86)**	
Ever tested for HIV before diagnosis			0.352		Not included
No	4 (9)	7 (16)		Reference	
Yes	40 (91)	36 (84)		0.51 (0.14–1.90)	
Motivation for testing: feeling sick†					
No	33 (75)	24 (56)		Reference	
Yes	11 (25)	19 (44)	0.073	2.38 (0.96–5.90)	Not included
Who gave HIV diagnosis			0.188		Not included
Regular care provider (physician)	7 (16)	8 (19)		Reference	
Other physician (ER doctor/ doctor at clinic/infectious disease specialist)	16 (36)	25 (58)		1.27 (0.42–4.51)	
Nurse	2 (5)	10 (23)		0.42 (0.12–1.47)	
Had heard of ART before HIV diagnosis			0.618		Not included
No	9 (20)	11 (26)		Reference	
Yes	35 (80)	32 (74)		0.75 (0.27–2.04)	
Advice doctor gave about starting ART			0.114		Not included
Told to start immediately	6 (14)	14 (33)		Reference	
Told it was up to me	32 (73)	24 (59)		**0.32 (0.11–0.96)**	
Other[&]	6 (14)	5 (12)		0.36 (0.08–1.64)	
Motivation for ART initiation: medical reason^			**0.006**		**5.00 (1.41–17.86)**
No	39 (89)	27 (63)		Reference	
Yes	5 (11)	16 (37)		**4.63 (1.51–14.08)**	
Wanted to start ART when diagnosed with HIV			0.646		Not included
No	15 (34)	12 (28)		Reference	
Yes	29 (66)	30 (70)		1.29 (0.52–3.23)	
Don't know	0	1 (2)		(cell count too small)	
Concern about ART initiation: medication*			**0.039**		Not selected
No	11 (25)	3 (7)		Reference	
Yes	33 (75)	40 (93)		**4.44 (1.14–17.27)**	
AMAS score	49 (47–54)	49 (46–55)	0.731	0.98 (0.92–1.04)	Not included
HIV ASES score	97 (91–104)	92 (77–101)	**0.049**	0.97 (0.94–1.00)	**0.94 (0.90–0.98)**

Notes: Results are n (%), median (Q1–Q3) or odds ratio (95% confidence interval). Bold values indicate statistical significance. ART: Antiretroviral Therapy; LGBTQ: lesbian, gay, bisexual, transgender, or queer; HCV: Hepatitis C virus; CAD: Canadian Dollar; AMAS: Antiretroviral Medication Attitude Scale; HIV ASES: HIV Treatment Adherence Self-Efficacy Scale. Not included indicates that variables were not considered for inclusion in multivariable analysis. Not selected indicates that variables were not significant in the model. + Includes response options: married, common-law or steady relationship. ~ Includes response options: single, dating, widowed, separated or divorced. † Motivation for testing of feeling sick includes response options: felt sick, had infection/condition doctor said may be caused by HIV, tested while in medical care (ER/surgery). & Other advice a doctor gave regarding when to initiate ART includes response options: being told to delay initiation; not discussing ART with a health care provider, just being given a prescription; and, "'other, please specify"' free text responses. ^ Motivation for ART initiation of medical reason includes response options: being in hospital and having to start ART, having another condition/infection, feeling sick. * Concern about ART initiation of medication includes response options: side effects, perceived financial cost, not wanting to rely on ART for life, unnecessary to survive, other treatments would help, would do more harm than good.

Table 3. Descriptive characteristics and univariate and multivariate factors associated with delayed initiation ($n = 86$).

Variable	Delayed ART initiation (longer than 1 year after diagnosis)				
	No (<1 year) ($n = 64$)	Yes (≥1year) ($n = 22$)	*P*-value	Univariate logistic regression	Multivariable logistic regression
Median CD4 cell count (cells/μL)	500 (285–640)	490 (171–660)	0.628	0.96 (0.80–1.15) per 100 cell increase	Not included
Time from HIV diagnosis to ART initiation (months)	2 (1–3)	88 (31–185)	0.000	(Outcome variable)	(Outcome variable)
Sex at birth			0.336		Not included
Male	55 (86)	17 (77)		Reference	
Female	9 (14)	5 (23)		1.80 (0.53–6.10)	
Age (years)	34 (28–44)	45 (38–48)	**0.022**	1.04 (1.00–1.09)	**1.06 (1.01–1.12)**
Ethnicity			0.119		Not included
Indigenous	10 (16)	7 (32)		Reference	
White	41 (64)	8 (36)		**0.28 (0.08–0.95)**	
Other	13 (20)	7 (32)		0.77 (0.20–2.92)	
Sexual orientation			**0.037**		Not selected
Heterosexual	14 (22)	11 (50)		Reference	
LGBTQ	50 (78)	11 (50)		**0.28 (0.10–0.78)**	
HCV-seropositive			0.356		Not included
No	53 (83)	16 (73)		Reference	
Yes	11 (17)	6 (27)		1.81 (0.58–5.66)	
Injection drug use (ever)			0.783		Not included
No	47 (73)	15 (68)		Reference	
Yes	17 (27)	7 (32)		1.29 (0.45–3.71)	
Health authority			0.139		Not included
Fraser	18 (29)	8 (36)		Reference	
Vancouver Costal	39 (62)	9 (41)		1.88 (0.44–7.99)	
Other	6 (9)	5 (23)		0.52 (0.17–1.57)	
Median personal monthly income ($CAD)	1175 (610–2500)	1100 (926–2000)	0.951	1.00 (1.00–1.00)	Not included
Sexual partners (in year prior to interview)	5 (1–10)	1 (1–5)	**0.033**	0.95 (0.87–1.03)	Not selected
Relationship status			**0.030**		Not selected
In a relationship+	15 (23)	11 (50)		Reference	
Not in a relationship~	49 (77)	11 (50)		**0.31 (0.11–0.85)**	
History of incarceration			0.124		Not included
No	54 (84)	15 (68)		Reference	
Yes	10 (16)	7 (32)		2.52 (0.82–7.74)	
History of homelessness			0.314		Not included
No	41 (64)	11 (50)		Reference	
Yes	23 (36)	11 (50)		1.78 (0.67–4.75)	
Ever tested for HIV before diagnosis			**0.016**		Not selected
No	4 (6)	6 (27)		Reference	
Yes	60 (94)	16 (73)		**0.18 (0.05–0.71)**	
Motivation for testing: Feeling sick†			0.800		Not included
No	41 (64)	15 (68)		Reference	
Yes	23 (36)	7 (32)		0.83 (0.30–2.34)	
Who gave HIV diagnosis			**0.037**		Not included
Regular care provider (physician)	10 (16)	5 (23)		Reference	
Other physician (ER doctor/doctor at clinic/infectious disease specialist)	26 (41)	14 (64)		1.08 (0.31–3.78)	
Nurse	28 (44)	3 (14)		0.21 (0.04–1.07)	
Had heard of ART before HIV diagnosis			0.141		Not included
No	12 (19)	8 (36)		Reference	
Yes	52 (81)	14 (64)		0.40 (0.14–1.18)	
Advice doctor gave about starting ART			**0.005**		Not selected
Told to start immediately	15 (23)	5 (23)		Reference	
Told it was up to me	46 (72)	10 (46)		0.65 (0.19–2.21)	
Other[&]	3 (5)	7 (32)		**7.00 (1.29–37.89)**	
Decision to initiate ART: medical reason^			0.776		Not included
No	49 (77)	16 (73)		Reference	
Yes	15 (23)	6 (27)		1.23 (0.41–3.69)	
Wanted to start ART when diagnosed with HIV			**0.000**		**0.06 (0.02–0.21)**
No	10 (16)	16 (73)		Reference	
Yes	53 (83)	6 (27)		**0.07 (0.02–0.23)**	
Don't know	1 (2)	0		(cell count too small)	
Concern about ART initiation: medication*			1.000		Not included
No	10 (16)	3 (14)		Reference	
Yes	54 (84)	19 (86)		1.17 (0.29–4.72)	
AMAS score	51 (47–55)	47 (44–50)	**0.019**	0.93 (0.87–1.00)	Not selected
HIV ASES score	97 (85–104)	87 (71–95)	**0.007**	**0.96 (0.93–0.99)**	Not selected

Notes: Results are *n* (%), median (Q1–Q3) or odds ratio (95% confidence interval). Bold values indicate statistical significance. ART: Antiretroviral Therapy; LGBTQ: lesbian, gay, bisexual, transgender, or queer; HCV: Hepatitis C virus; CAD: Canadian Dollar; AMAS: Antiretroviral Medication Attitude Scale; HIV ASES: HIV Treatment Adherence Self-Efficacy Scale. Not included indicates that variables were not considered for inclusion in multivariable analysis. Not selected indicates that variables were not significant in the model. + Includes response options: married, common-law or steady relationship. ~ Includes response options: single, dating, widowed, separated or divorced. † Motivation for testing of feeling sick includes response options: felt sick, had infection/condition doctor said may be caused by HIV, tested while in medical care (ER/surgery) & Other advice a doctor gave regarding when to initiate ART includes response options: being told to delay initiation; not discussing ART with a health care provider, just being given a prescription; and, "other, please specify" free text responses. ^ ART initiation due to medical reason includes response options: being in hospital and having to start ART, having another condition/infection, feeling sick. * Concern about ART initiation of medication includes response options: side effects, perceived financial cost, not wanting to rely on ART for life, unnecessary to survive, other treatments would help, would do more harm than good.

scores (AOR: 0.94, 95% CI: 0.90–0.98) decreased the likelihood of late initiation.

Table 3 shows factors associated with delayed ART initiation. In multivariable analysis, older age was associated with delayed initiation (AOR: 1.06, 95% CI: 1.01–1.12), while those reporting wanting to start ART when diagnosed were less likely to delay initiation (AOR: 0.06, 95% CI 0.02–0.21).

Discussion

Consistent with prior results from BC, older age was associated with late and delayed ART initiation (Lourenco et al., 2015; Palmer et al., 2014). Notably, other research has found younger age to be associated with attrition in HIV care over time (Lourenco et al., 2014), suggesting a missed opportunity to retain younger people. History of incarceration was negatively associated with delayed initiation. This is contrary to existing literature, which finds that incarceration makes timely ART initiation and adherence more difficult (Joseph et al., 2016; Milloy et al., 2011). Extensive support programs for PLHIV experiencing incarceration in BC may explain these results (British Columbia Ministry of Justice, 2002; Correctional Service Canada, 2015).

Participants with higher HIV-ASES scores or who reported wanting to start ART upon diagnosis were less likely to initiate late or delay initiation, respectively. Moreover, our finding that participants' selection of "medical reasons" for initiating ART contributed to late initiation suggests that some individuals are waiting until their health is compromised to start treatment. This is supported by the literature that indicates better health or lack of physical HIV symptoms is associated with delayed linkage to care (Hanna et al., 2013; Takah et al., 2016), delayed diagnosis (Lee et al., 2010; Ndiaye et al., 2011) and treatment breaks (Begley, McLaws, Ross, & Gold, 2008; Newman et al., 2015). Counseling on the benefits and costs of ART, including peer support programs or peer-developed information resources, may help address individual-level barriers to initiating and remaining on ART.

Based on prior studies in BC, variables we expected to predict late initiation included the history of IDU, HCV seropositivity, and lower income (Joseph et al., 2016; Lourenco et al., 2015; Palmer et al., 2014). Our findings may reflect changing characteristics of new initiators in BC, or may be due to limited sample size and a high percentage of participants with a history of IDU and HCV seropositivity, which left little room to examine variability. Potential lack of generalizability due to significant clinical differences (i.e. CD4 cell counts at ART initiation) between participants and non-participants is another important limitation. Furthermore, this analysis does not include health providers' experiences of prescribing ART. Previous research has found that the lack of physician familiarity with the patient and patient depression were reasons for waiting to prescribe ART (Fehr et al., 2016). Finally, our study may not have captured longer-term non-initiators of ART since individuals who delayed initiation for longer than the study period were unable to participate.

In conclusion, our results show that late ART initiation is less likely among individuals with a history of incarceration or higher HIV-ASES score, and more likely among older individuals or those who initiate ART due to medical reasons. Older age also predicted delayed ART initiation, and wanting to start ART when diagnosed with HIV reduced the likelihood of delay. While trends in BC show that fewer people are waiting after diagnosis to initiate ART, efforts are warranted to increase the number of people initiating ART early, for individual and population health benefits.

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