DETERMINANTS OF HIV DRUG RESISTANCE TESTING IN BRITISH COLUMBIA

by

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ABSTRACT

International therapeutic guidelines recommend HIV drug resistance testing as an important part of routine clinical practice in HIV/AIDS treatment and care. This study aims to examine the factors that determine who gets tested for HIV drug resistance in a setting where access to HIV care is free of charge. Clinical and socio-demographic data from a prospective cohort (LISA) of HIV-positive persons on HAART in British Columbia (BC) was collected at the BC Centre for Excellence in HIV/AIDS. Independent associations between key explanatory variables and the probability of having been tested before or after starting HAART were analyzed via logistic regression. The findings suggest that in BC, a setting with free access to HIV care, resistance testing is not consistently carried out. Furthermore, several explanatory variables were predictive of who is likely to be tested. The clinical community will benefit from a review of the implementation levels of resistance testing practice.

Keywords: Antiretroviral Therapy; Antiretroviral Therapy Guidelines & Recommendations; HAART, HIV Drug Resistance; HIV Drug Resistance Testing

Subject Terms: AIDS (Disease) – Diagnosis; AIDS (Disease) – Treatment; HIV infections – Diagnosis; HIV infections – Treatment

DEDICATION

This work is dedicated to my dear sister, Favour, for her unwavering determination and quest for higher education, and to my parents, for their belief in me.

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GLOSSARY

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
BC	British Columbia
Centre	BC Centre for Excellence in HIV/AIDS
CIHR	Canadian Institutes of Health Research
DTP	Drug Treatment Program
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
IAS	International AIDS Society
LISA	Longitudinal Investigations into Supportive and Ancillary health services (cohort study funded by CIHR)
pVL	Plasma Viral Load
RNA	Ribonucleic Acid
WHO	World Health Organization

1. INTRODUCTION

1.1. Introduction to the Public Health Problem

Contemporary pharmacotherapy for HIV/AIDS disease, otherwise known as highly active antiretroviral therapy (HAART), has led to a reduction in mortality and morbidity from HIV infection and has been shown to ultimately prolong the life of persons on treatment (Chan, Cheng, Chan, & Wong, 2005; Hogg et al., 1998; Jerene, Naess, & Lindtjorn, 2006; Murphy et al., 2001; Palella et al., 1998; Wood et al., 2003a). In high-income countries where HAART is widely available, HIV/AIDS is increasingly being viewed as a manageable chronic disease. In the resource limited settings, the chances of survival are increasing in part due to the up-scaling access to HAART. While the success of HAART has been applauded, its triumph remains threatened by the development of resistance to antiretroviral (ARV) drugs.

The introduction of HAART has changed the way HIV disease is managed and has led to some modifications in HIV clinical therapeutic guidelines. HIV drug resistance testing, a practice that has been recently promoted as part of routine clinical practice in HIV/AIDS care is one example of this overhaul in the clinical management of the disease. This procedure is fundamental to HIV/AIDS

management as antiretroviral resistance has been repeatedly implicated in incomplete viral suppression. Several studies which have examined the drivers and predictors of HIV drug resistance have shown that antiretroviral resistance is associated with incomplete viral suppression (Harrigan et al., 2005; Hirsch et al., 2008; Hogg et al., 2006; Lima et al., 2008; Lorenzi et al., 1999; Masuhr et al., 2002).

The development of antiretroviral resistance and ultimately virological failure has important implications for treatment success. To preserve and maximally employ potential therapeutic opportunities, timely identification of drug resistant mutations is essential (British Columbia Centre for Excellence in HIV/AIDS, 2006). Results of a resistance test can assist physicians in deciding on the best drug choices for patients failing therapy as well as initiating the most appropriate regimen for ARV naïve patients who may have HIV-1 RNA resistant strains. In this light, the importance of resistance testing cannot be overemphasised.

1.2. Purpose of the Paper

The purpose of this study is to assess the determinants of resistance testing and examine the factors that predict HIV drug resistance testing in a setting where access to HIV care is free of charge. Current therapeutic guidelines recommend that patients should be tested for HIV drug resistance before they initiate HAART treatment and subsequently tested routinely *after* the initiation of HAART. First, the paper will assess whether the guideline recommendations regarding resistance testing have been followed closely by the clinical community. Secondly, it aims to identify the explanatory factors that are associated with testing for drug resistance prior to start of HAART as well as after starting HAART. Since recommendations to test for drug resistance have not been around for very long, the study aims to follow the chronological changes in clinical guidelines, in terms of HIV drug resistance testing since the advent of HAART. The changes in guidelines will be matched against patient response to ascertain the impact of the practice on patient treatment success.

To achieve these goals, data from a prospective cohort of HIV-positive persons in British Columbia (BC) who started treatment on HAART will be collected. It is important to highlight that in BC, eligible HIV-positive patients have access to HAART and HIV care at no cost. We ask the question: is the recommendation of testing for resistance being effectively implemented? If not, what can public health do to ensure that this patient important practice is carried out consistently?

1.3. Literature Review

The introduction of life-saving HAART in 1996 was a major turning point in HIV/AIDS clinical therapeutic efforts (Carpenter et al., 1996). However, to achieve desired treatment outcomes while on HAART, high levels of adherence to drug regimen are necessary. HIV management practices emphasize the need for routine clinical monitoring of patient plasma HIV RNA levels and CD4 counts. HIV drug resistance testing has been identified as a useful clinical tool in directing antiretroviral therapy (Dybul, Fauci, Bartlett, Kaplan, & Pau, 2002; Paul & Jorden, 2003; Yeni et al., 2004). Three major studies have demonstrated that therapy guided by resistance testing led to better virologic suppression than therapy guided by clinical judgment alone (Baxter et al., 1999; Cohen et al., 2000; Durant et al., 1999). In treatment-naïve patients with chronic HIV infection, the cost-effective nature of resistance testing practice was suggested in a study by Sax and colleagues (Sax et al., 2005).

There are two available types of assays for HIV drug resistance testing: genotypic, in which mutations in a patient's HIV genome is assessed and phenotypic assays, which quantifies the level of patient HIV virus under varying drug regimens. These assays are useful in predicting the emergence of resistance to a particular drug or drug type and help to identify drugs that may not be clinically active in achieving viral suppression (Geretti & Easterbrook, 2001; Paul & Jorden, 2003; Youree & D'Aquila, 2002). The most challenging feature of these assays is the accurate interpretation of the results.

Genotypic assays uses polymerase chain reaction, sequencing and other techniques to access specific gene regions and then compares the patient's genome with known mutation patterns associated with resistance to specific drug regimen (Paul & Jorden, 2003; Youree & D'Aquila, 2002). It is used to detect mutations associated with drug resistance. A genotypic assay typically cost about $400 per sample and the results are usually ready within two weeks or more. Genotypic assay is limited majorly by the interpretation of the results.

Phenotypic assays are usually cell culture-based replication assays or *in vitro* assays, and are aimed at determining the ability of the HIV virus to grow in the presence of specific drugs. In other words, it directly measures the sensitivity of a patient's HIV to specific drugs (Youree & D'Aquila, 2002). Phenotypic assays cost about $700 to $900 per sample and results are usually ready within an average time of 2-8 weeks. In general, genotypic tests are usually preferred over phenotypic tests because they are faster, cheaper and more readily accessible (Hammer et al., 2006; Youree & D'Aquila, 2002). Both genotypic and phenotypic assays require >500 – 1000 copies/ml of viral RNA to enable successful completion of the process (Geretti & Easterbrook, 2001).

Despite clearly-defined international standards, resource-limited settings lack the complex laboratory monitoring resources to guide the selection of antiretroviral drug options. Thus most HIV management options are not patient-based; rather they consist of a population-wide "standardized simplified therapy protocol, standardized management approaches and decentralized service delivery" (Gilks et al., 2006). In these settings, decision to start, substitute or

switch therapy are guided mostly by clinical observation and the World Health Organization (WHO) clinical staging, and when available, by CD4 count, haematology and biochemistry (Bertagnolio et al., 2008). Selection of second-line drugs is based mainly on availability and affordability.

1.3.1. International HIV Drug Resistance Testing Recommendations

A chronology of HIV drug resistance testing recommendations as prescribed by the governing committee of the International AIDS Society (IAS) was complied from 1996 till present i.e. since the HAART era (1996 – date). To identify IAS publications that presented guidelines regarding resistance testing practice, I searched major biomedical search engines using the following key words:

i. “HIV AND antiretroviral treatment AND recommendation”

ii. “Antiretroviral therapy for HIV infection”

iii. “HIV AND resistance testing AND recommendation”

The searches were conducted mainly through MEDLINE via PubMed. Supplemental searches were done through Google Scholar. Where full text was unavailable through the search engines, I used interlibrary loans to order full text articles. Following the searches, information regarding recommendations for HIV drug resistance testing was extracted from the obtained full text annual/biennial report publications of the IAS.

Table 1 shows the chronological progression and stages of the introduction of resistance testing practice into routine HIV/AIDS treatment guidelines as prescribed by the governing committee of the International AIDS Society (Carpenter et al., 1996; Carpenter et al., 1997; Carpenter et al., 1998; Carpenter et al., 2000; Hammer et al., 2006; Hammer et al., 2008; Hirsch et al., 2008; Yeni et al., 2002; Yeni et al., 2004). Although ideas about the potential usefulness of HIV drug resistance testing were identified early in the HAART era, concerns regarding the interpretation of the results as well as availability and affordability challenges did not permit the endorsement of the practice as a key part of the routine clinical management of HIV. As such, the practice was introduced into clinical practice in stages, based on evidence and consensus among the clinical community. Table 1 carefully describes this progression. In general, recommendation for resistance testing was determined by the setting in question and the clinical status of the population/individual.

Current international clinical guideline standards recommend HIV drug resistance testing (Hammer et al., 2008; Hirsch et al., 2008; Yeni et al., 2004) in the following settings:

- before therapy initiation for primary infection (acute or recent HIV infection cases),
- before initiating treatment in established HIV infection or chronic cases,
- in cases of treatment failure and
- for pregnant women before initiating therapy.

Table 1: Chronological progression of resistance testing guideline in the HAART era

Year	Resistance testing guideline	Consideration
1996	No guidelines regarding resistance testing at this time	Lack of data to support the practice
1997	HIV drug resistance testing was not recommended for patient management at this time. Despite it was not recommended, anticipation of its future usefulness was highlighted	Unavailability of accurate, affordable, and quick laboratory assays (genotypic and phenotypic)
1998	For initial therapy, the use of drug resistance testing should be considered in population with high resistance prevalence. Routine use for treatment-naïve persons was not recommended at this time	To prescribe the best drug regimen. It was not fully recommended because other factors like pVL, CD4+ counts and patients' clinical state, played a role in decision concerning treatment initiation
2000	Baseline drug resistance testing was suggested among the options to aid choice of initial therapy	Availability of HIV drug resistance testing methods. Continuing limitations include cost and insufficient knowledge about their optimal usage
2002	Recommended as standard of care in managing treatment failure and for guiding therapy in HIV-positive pregnant women. Resistance testing in treatment-naïve persons was suggested but not strongly recommended.	It helps to identify drugs to which there is resistance as well as deciding on the drug with optimal effectiveness
2004	Recommended in acute or recent HIV infection cases, before initiating treatment in established HIV infection, in cases of treatment failure and in therapy for HIV-positive pregnant women	Important for detection of transmission of resistant virus and for choosing the right drugs with optimal results
2006	Baseline resistance testing is recommended in settings with high drug resistance prevalence (>5%) and also in cases of treatment failure. It is not recommended if the pVL is below 500 to 1000 copies/mL	At low pVL, the assays may be difficult to carry out because of unsuccessful PCR amplification
2008	Recommended before therapy initiation for primary infection, chronic infection, in cases of treatment failure and for pregnant women before initiating therapy	

2. METHODS

2.1. Study Population

In British Columbia, Canada, the Drug Treatment Program (DTP) at the BC Centre for Excellence in HIV/AIDS (Centre) distributes antiretroviral drugs at no cost to clinically eligible HIV-positive individuals. The therapeutic guidelines of the Centre are consistent with other major international guidelines and are used to monitor and direct the prescription of antiretroviral therapy (British Columbia Centre for Excellence in HIV/AIDS, 2006). Details of the DTP have been described elsewhere (Hogg et al., 1998; Hogg et al., 2001).

Longitudinal Investigations into Supportive and Ancillary health services (LISA) study, a prospective population-based cohort of almost 800 people that have initiated HAART, is a study within the DTP. The study is funded by Canadian Institutes of Health Research (CIHR). In brief, the LISA study is designed to evaluate the effect of health services on patients' adherence and response to antiretroviral therapy. To be eligible for the LISA study, participants must be registered in the DTP, aged 18 years or older and must have been ARV-naïve prior to initiating HAART.

Our study sample is a subset within LISA and consists primarily of people who are currently on HAART therapy and have data measuring adherence over the past 12 months.

2.2. Data Collection

Data collection for the LISA study takes place by way of an interviewer-administered survey which obtains information about the socio-demographic attributes, quality of life, health status and behaviour of the participants. Clinical data are obtained through a confidential record linkage directly with the DTP. The therapeutic guidelines of the Centre recommend the monitoring of the patients' plasma HIV-1 RNA levels or plasma viral load (pVL) and CD4 cell counts at baseline, after one month of initiating HAART and subsequently at three months interval (British Columbia Centre for Excellence in HIV/AIDS, 2006). The HIV drug resistance testing procedure used by the Centre for the determination of HIV drug resistance mutations has been previously reported (Harrigan et al., 2005). To assess whether a patient was tested for HIV drug resistance *prior to* or *after* starting HAART, the Centre's monitoring and evaluation reporting system, was consulted and this was reported as "yes" versus "no". Extensive detail about the Centre's clinical data collection process has been described elsewhere (Hogg et al., 2006). Ethical approval for this study was obtained from the Providence

Health Care/ University of British Columbia Research Ethics Board as well as the Simon Fraser University Research Ethics Office.

2.2.1. Outcome Measures and Explanatory Variables

The primary outcome measure was HIV drug resistance testing, coded as 'yes' (patient has been tested) *versus* 'no' (patient has not been tested). Two time measures of resistance testing were assessed. The first measure assessed whether a patient was tested *before* initiating HAART and the second assessed whether testing was done *after* initiation of HAART. The following socio-demographic variables were examined: age, gender, ethnicity, sexual orientation, housing status, education level, number of years since diagnosed with HIV, year-period of HAART initiation, adherence within the last 12 months, history of injection drug use and incarceration history. The following clinical variables were also examined: baseline and current CD4 cell count, baseline and current pVL, viral suppression status and history of Hepatitis C infection.

For the assessment of injection drug use, incarceration history and housing status, we relied on self reporting by the participants. Adherence to therapy was assessed over a 12-month window preceding the study, and was measured through medication refills as previously described (Harrigan et al., 2005; Hogg et al., 2006). Complete viral suppression status (i.e. virologically suppressed? = yes) was conferred when the pVL was <50 copies/mL.

2.3. Statistical Methods

Bivariable and multivariable analyses were conducted to identify and assess any relationship between the explanatory variables and whether or not a person was tested for HIV drug resistance prior to or after initiating HAART. Bivariable analyses were carried out using Fisher's Exact Test and the Chi-squared for categorical explanatory variables and the Wilcoxon Rank Sum Test for continuous explanatory variables. Two exploratory models (clinical and a socio-demographic model) were created for each time measure of resistance testing (i.e. before or after HAART initiation). Due to the relatively small sample size, not all variables could be included in the multivariable models. Hence, a limited set of predictors were defined *a priori* for multivariable models based on the results of the bivariable analyses as well as the subject knowledge and interests of the researcher. Only participants who had complete data for these variables of interest were included in the logistic regressions analyses. Approximately 91% of the participants met this criterion. All of the analysis was carried out with the SAS statistical software version 9.1.3. Test of significance were 2-sided with p-values of ≤ 0.05 considered as statistically significant.

3. RESULTS

3.1. Study Participants

There are currently about 750 participants in the LISA cohort. As at the time this data was collected (July 2008), there were about 492 participants in the LISA cohort. Our analyses included 363 of them who were currently being prescribed HAART and also had data for adherence in the past 12-month period. 288 (79.3%) of them were men. The median CD4 and IQR of the participants who were tested *before* starting HAART was 185 (120-340) cells/mm^3, and for those tested *after* starting HAART, it was 350 (210-520) cells/mm^3. Less than one-half of participants (47.9%) were tested for resistance *before* starting HAART. Of those who were not tested *before* starting HAART, 79% had a baseline CD4 cell count of <350 cells/mm^3. Since starting therapy, about two-thirds (68%) of participants had been tested. Of those who had not been tested *after* starting therapy, 36% had a CD4 cell count of <350 cells/mm^3. For those persons with viral loads in amounts considered as unsuppressed, 54% were not tested *before* starting HAART and 14% had not been tested *after* starting HAART.

Cases of missing data were due to unavailability of the data from the DTP or in instances where the participants did not provide answers to certain questions. Further details of the baseline characteristics of the study population are provided in Table 2.

Table 2: Characteristics of population under study, stratified by whether resistance testing was done *before* or *after* starting HAART

	Tested for resistance *before ARV start*				Tested for resistance *after ARV start*			
Variables	**NO n (%)**	**YES n (%)**	**Total N (%)**	**P-value**	**NO n (%)**	**YES n (%)**	**Total N (%)**	**P-value**
‡Age	N= 189	N= 174	363 (100)	0.13	N= 116	N= 247	363 (100)	0.01
Median	46.1	47.5			48.8	45.9		
Interquartile range	41.2-51.0	41.5-55.6			43.1-56.5	40.9-51.8		
Gender			363 (100)	0.01			363 (100)	0.13
Female	50 (66.7)	25 (33.3)	75 (20.7)		18 (24)	57 (76)	75 (20.7)	
Male	139 (48.3)	149 (51.7)	288 (79.3)		98 (34)	190 (66)	288 (79.3)	
Ethnicity			363 (100)	<0.01			363 (100)	0.33
Aboriginal	75 (65.8)	39 (34.2)	114 (31.4)		32 (28.1)	82 (71.9)	114 (31.4)	
Not Aboriginal	114 (45.8)	135 (54.2)	249 (68.6)		84 (33.7)	165 (66.3)	249 (68.6)	
Sexual orientation			363 (100)	0.67			363 (100)	0.03
Bisexual	14 (53.8)	12 (46.2)	26 (7.2)		4 (15.4)	22 (84.6)	26 (7.2)	
Gay/lesbian/transgender/other	62 (55.4)	50 (44.6)	112 (30.9)		45 (40.2)	67 (59.8)	112 (30.9)	
Straight	113 (50.2)	112 (49.8)	225 (61.9)		67 (29.8)	158 (70.2)	225 ()	
MSM transmission?			363 (100)	0.50			363 (100)	0.06
No	122 (50.6)	119 (49.4)	241 (66.4)		69 (28.6)	172 (71.4)	241 (66.4)	
Yes	67 (54.9)	55 (45.1)	122 (33.6)		47 (38.5)	75 (61.5)	122 (33.6)	
Heterosexual transmission			363 (100)	0.43			363 (100)	0.03
No	62 (55.4)	50 (44.6)	112 (30.9)		45 (40.2)	67 (59.8)	112 (30.9)	
Yes	127 (50.6)	124 (49.4)	251 (69.1)		71 (28.3)	180 (71.7)	251 (69.1)	
† Currently in stable housing?			361 (99.4)	0.58			361 (99.4)	0.01
No	59 (49.6)	60 (50.4)	119 (33)		26 (21.8)	93 (78.2)	119 (33)	
Yes	129 (53.3)	113 (46.7)	242 (67)		88 (36.4)	154 (63.6)	242 (67)	
High school education or greater?			363 (100)	0.05			363 (100)	0.01
No	86 (58.5)	61 (41.5)	147 (40.5)		35 (23.8)	112 (76.2)	147 (40.5)	
Yes	103 (47.7)	113 (52.3)	216 (59.5)		81 (37.5)	135 (62.5)	216 (59.5)	
Year-period of HAART initiation			363 (100)	< 0.01			363 (100)	< 0.01
1996 - 2003	138 (58.2)	99 (41.8)	237 (65.3)		48 (20.3)	189 (79.7)	237 (65.3)	
2004 or after	51 (40.5)	75 (59.5)	126 (34.7)		68 (54)	58 (46)	126 (34.7)	
† Number of years since diagnosed with HIV			357 (98.3)	0.01			357 (98.3)	< 0.01
< 10 years	80 (45.2)	97 (54.8)	177 (49.6)		80 (45.2)	97 (54.8)	177 (49.6)	
≥ 10 years	105 (58.3)	75 (41.7)	180 (50.4)		33 (18.3)	147 (81.7)	180 (50.4)	

Legend: ‡ = Statistics presented as median and IQR (interquartile range) and NOT in the "n (%)" format, † = includes variables where data are missing due to one or more reasons identified in the text, * = statistically significant

Table 2: Characteristics of population under study, stratified by whether resistance testing was done *before* or *after* starting HAART (continued)

	Tested for resistance *before ARV start*				Tested for resistance *after ARV start*			
Variables	**NO n (%)**	**YES n (%)**	**Total N (%)**	**P-value**	**NO n (%)**	**YES n (%)**	**Total N (%)**	**P-value**
† Ever incarcerated?			362 (99.7)	1.00			362 (99.7)	< 0.01
No	84 (52.2)	77 (47.8)	161 (44.5)		67 (41.6)	94 (58.4)	161 (44.5)	
Yes	104 (51.7)	97 (48.3)	201 (55.5)		49 (24.4)	152 (75.6)	201 (55.5)	
Drug use			363 (100)	0.38			363 (100)	0.01
Never used drugs	23 (43.4)	30 (56.6)	53 (14.6)		25 (47.2)	28 (52.8)	53 (14.6)	
Used drugs but not currently	76 (54.3)	64 (45.7)	140 (38.6)		47 (33.6)	93 (66.4)	140 (38.6)	
Currently using drugs	90 (52.9)	80 (47.1)	170 (46.8)		44 (25.9)	126 (74.1)	170 (46.8)	
Adherence within the last 12 months			363 (100)	0.33			363 (100)	< 0.01
< 95%	73 (55.7)	58 (44.3)	131 (36.1)		27 (20.6)	104 (79.4)	131 (36.1)	
≥ 95%	116 (50)	116 (50)	232 (63.9)		89 (38.4)	143 (61.6)	232 (63.9)	
† Baseline CD4 (at start of therapy)			359 (98.9)	0.17			359 (98.9)	< 0.01
< 200	86 (48.9)	90 (51.1)	176 (49)		67 (38.1)	109 (61.9)	176 (49)	
200-350	60 (59.4)	41 (40.6)	101 (28.1)		34 (33.7)	67 (66.3)	101 (28.1)	
≥ 350	39 (47.6)	43 (52.4)	82 (22.8)		14 (17.1)	68 (82.9)	82 (22.8)	
† Current CD4 (at time of interview)			346 (95.3)	0.14			346 (95.3)	0.02
< 200	41 (61.2)	26 (38.8)	67 (19.4)		13 (19.4)	54 (80.6)	67 (19.4)	
200-350	47 (53.4)	41 (46.6)	88 (25.4)		28 (31.8)	60 (68.2)	88 (25.4)	
≥ 350	90 (47.1)	101 (52.9)	191 (55.2)		72 (37.7)	119 (62.3)	191 (55.2)	
† Baseline viral load (at start of therapy)			329 (90.6)	0.01			329 (90.6)	0.07
< 10, 000 copies/mL	23 (71.9)	9 (28.1)	32 (9.7)		15 (46.9)	17 (53.1)	32 (9.7)	
10, 000-100,000	67 (47.2)	75 (52.8)	142 (43.2)		39 (27.5)	103 (72.5)	142 (43.2)	
≥ 100, 000	65 (41.9)	90 (58.1)	155 (47.1)		56 (36.1)	99 (63.9)	155 (47.1)	
† Current viral load (at time of interview)			356 (98.1)	0.78			356 (98.1)	0.13
< 10, 000 copies/mL	175 (52.1)	161 (47.9)	336 (94.4)		113 (33.6)	223 (66.4)	336 (94.4)	
10, 000-100,000	7 (63.6)	4 (36.4)	11 (3.1)		1 (9.1)	10 (90.9)	11 (3.1)	
≥ 100, 000	5 (55.6)	4 (44.4)	9 (2.5)		1 (11.1)	8 (88.9)	9 (2.5)	
† Virologically suppressed?			356 (98.1)	0.82			356 (98.1)	< 0.01
No	56 (53.8)	48 (46.2)	104 (29.2)		15 (14.4)	89 (85.6)	104 (29.2)	
Yes	131 (52)	121 (48)	252 (70.8)		100 (39.7)	152 (60.3)	252 (70.8)	
† Hepatitis-C co-infection?			360 (99.2)	0.28			360 (99.2)	0.01
No	67 (48.6)	71 (51.4)	138 (38.3)		55 (39.9)	83 (60.1)	138 (38.3)	
Yes	121 (54.5)	101 (45.5)	222 (61.7)		60 (27)	162 (73)	222 (61.7)	

Legend: ‡ = Statistics presented as median and IQR (interquartile range) and NOT in the "n (%)" format, † = includes variables where data are missing due to one or more reasons identified in the text, * = statistically significant

3.2. Bivariable Analyses

In the bivariable analyses (Table 2), baseline viral load measure was the only clinical variable showing a statistically significant relationship (p-value ≤ 0.05) with whether a patient was tested for drug resistance *prior to* HAART initiation. Socio-demographic variables such as gender, ethnicity, education level, year-period of HAART initiation and number of years since diagnosed with HIV, all showed a statistically significant relationship with testing prior to HAART initiation.

For testing done *after* HAART initiation, clinical variables like CD4 cell counts, viral suppression status (yes *versus* no), and hepatitis C co-infection history, showed a statistically significant relationship with whether a patient had been tested. Socio-demographic variables such as age, sexual orientation, heterosexual transmission, housing status, education level, year-period of HAART initiation, number of years since diagnosed with HIV, incarceration history, drug use history, and adherence measure, showed a statistically significant relationship with whether testing was done at this stage.

3.3. Multivariable Analyses

Table 3 presents the multivariable analyses results for the clinical model as shown by the adjusted odds ratio (AOR) and confidence intervals (CI). In terms of whether testing was done before the initiation of HAART, several variables were strongly predictive of whether an individual was tested. Baseline CD4 (AOR: 0.98-1.26) was only marginally predictive of whether an individual had been tested. Being female (AOR: 0.50, CI: 0.29-0.89) was associated with a decreased likelihood of having been tested. An increasing gradient of resistance testing prior to therapy initiation was observed with year-period of HAART initiation. Persons who initiated HAART in 2004 or after (AOR: 2.03, CI: 1.23-3.32), were more likely to be tested. Increases in the baseline viral load (AOR: 1.66, CI: 1.20-2.28) was associated with an increased likelihood of having been tested.

In terms of whether testing was done after the initiation of HAART, several variables were strongly predictive of whether an individual was tested. Current CD4 count (AOR: 0.91, CI: 0.81-1.01) was only marginally predictive of whether someone had been tested. Persons who had been diagnosed with HIV for a period of 10 years or longer (AOR: 2.33, CI: 1.31-4.13), were more likely to have been tested. Persons who initiated HAART in 2004 or more recently (AOR: 0.22, CI: 0.13-0.40) had a decreased likelihood of having been tested. This observation is in contrast to what we observed when we considered testing prior to HAART initiation. Those in a virologically suppressed state (AOR: 0.20, CI:

0.10-0.41) were less likely to have been tested after initiating HAART. Although the association was not as strong as for the other variables, every 100 cell increase in the current CD4 count (AOR: 0.91, CI: 0.81-1.01) was associated with a decreased likelihood of having been tested.

Table 4 presents the multivariable analyses results for the socio-demographic model. The analysis shows that gender, ethnicity, MSM transmission and education levels were strongly predictive of whether someone was tested for HIV drug resistance *prior to* start of HAART. Being female (AOR: 0.51, CI: 0.28-0.95) was associated with a decreased likelihood of having been tested. Aboriginal ethnicity (AOR: 0.42, CI: 0.25-0.70) was also associated with a decreased likelihood of having been tested. In terms of sexual habits, MSM transmission (AOR: 0.48, CI: 0.28-0.84) was associated with a decreased likelihood of having been tested. Persons with high school education or better (AOR: 1.70, CI: 1.02-2.82), were more likely to have been tested. Those who initiated HAART in 2004 or more recently (AOR: 1.50, CI: 0.93-2.42) had a higher likelihood of having been tested. This variable however, was only marginally predictive of whether someone had been tested.

In terms of whether testing was done *after* initiating HAART, some variables were strongly predictive of who had been tested. Persons with adherence level ≥ 95% (AOR: 0.54, CI: 0.32-0.93) also had a decreased likelihood of having been tested. People who had ever been incarcerated (AOR: 2.17, CI: 1.30-3.62) were more likely to have been tested for resistance. Persons who initiated HAART in 2004 or more recently (AOR: 0.24, CI: 0.14-0.39) had a

decreased likelihood of having been tested. Generally, with regards to the year-period of HAART initiation (2004 or after), the results present a trend showing an increasing gradient of resistance testing prior to therapy initiation, and a decreasing gradient of testing after initiation of HAART.

Table 3: Multivariable clinical explanatory model testing the probability of getting tested for HIV drug resistance

Variable	Tested for resistance *before* starting HAART OR (95% CI)		Tested for resistance *after* starting HAART OR (95% CI)	
	Unadjusted N= 330	**Adjusted N= 330**	**Unadjusted N= 330**	**Adjusted N= 330**
Age (per year increase)	1.02 (1.00-1.05)§	- -	0.98 (0.96 – 1.01)§	--
Gender? (female *versus* male)	0.50 (0.29 – 0.87)*	0.50 (0.29 – 0.89)*	1.12 (0.63 – 2.01)	--
Number of years since diagnosed with HIV (≥ 10 years *versus* < 10 years)	0.68 (0.44 – 1.06)	- -	3.63 (2.19 – 6.02)*	2.33 (1.31 – 4.13)*
Year-period of HAART initiation (2004 or after *versus* 1996-2003)	1.64 (1.04 – 2.57)*	2.03 (1.23 – 3.32)*	0.22 (0.14 – 0.37)*	0.22 (0.13 – 0.40)*
Baseline CD4 at start of therapy (per 100 cell increase)	1.01 (0.90 – 1.13)	1.11 (0.98 – 1.26)§	N/A	N/A
Current CD4 (per 100 cell increase)	N/A	N/A	0.89 (0.81 – 0.97)*	0.91 (0.81 – 1.01) §
Baseline viral load (at start of therapy) (per Log_{10} copies/mL increase)	1.55 (1.14 – 2.12)*	1.66 (1.20 – 2.28)*	N/A	N/A
Virologically suppressed? (Yes *versus* No)	N/A	N/A	0.23 (0.13 – 0.41)*	0.20 (0.10 – 0.41)*
Overall Adherence ≥ 95%? (Yes *versus* No)	N/A	N/A	0.48 (0.29 – 0.79)*	--
Hepatitis C co-infection? (Yes *versus* No)	1.34 (0.85 – 2.10)	--	1.65 (1.03 – 2.66)*	--

Legend: * = statistically significant association, §= marginally statistically significant association, OR = odds ratio, CI = confidence intervals, N/A= not included in the model selection

Table 4: Multivariable socio-demographic explanatory model testing the probability of getting tested for HIV drug resistance

Variable	Tested for resistance *before* starting HAART OR (95% CI)		Tested for resistance *after* starting HAART OR (95% CI)	
	Unadjusted N= 330	**Adjusted N= 330**	**Unadjusted N= 330**	**Adjusted N= 330**
Age (per year increase)	1.02 (1.00 – 1.05)§	--	0.98 (0.96 – 1.01)§	--
Gender? (female *versus* male)	0.50 (0.29 – 0.87)*	0.51 (0.28 – 0.95)*	1.12 (0.63 – 2.01)	--
Aboriginal? (Yes *versus* No)	0.36 (0.23 – 0.58)*	0.42 (0.25 – 0.70)*	1.27 (0.77 – 2.09)	- -
Year-period of HAART initiation (2004 or after *versus* 1996-2003)	1.64 (1.04 – 2.57)*	1.50 (0.93 – 2.42)§	0.22 (0.14 – 0.37)*	0.24 (0.14 –0.39)*
Heterosexual transmission? (Yes *versus* No)	1.11 (0.69 – 1.79)	--	1.70 (1.04 – 2.79)*	--
MSM transmission? (Yes *versus* No)	0.87 (0.55 – 1.38)	0.48 (0.28 – 0.84)*	0.68 (0.41 – 1.10)	--
Adherence ≥ 95%? (Yes *versus* No)	N/A	N/A	0.48 (0.29 – 0.79)*	0.54 (0.32 – 0.93)*
Stable Housing? (Yes *versus* No)	0.94 (0.59 – 1.47)	--	0.48 (0.28 – 0.81)*	--
High school education or better? (Yes *versus* No)	1.72 (1.11 – 2.68)*	1.70 (1.02 – 2.82)*	0.50 (0.31 – 0.81)*	--
Drug use				
Used drugs previously but not currently *versus* Never used	0.58 (0.28 – 1.21)	--	1.84 (0.90 – 3.76)	--
Currently using drugs *versus* Never used drugs	0.56 (0.58 – 1.13)	--	2.47 (1.23 – 4.94)*	--
Ever been incarcerated? (Yes *versus* No)	0.92 (0.59 – 1.42)	--	2.67 (1.66 – 4.29)*	2.17 (1.30 – 3.62)*

Legend: * = statistically significant association, §= marginally statistically significant association, OR = odds ratio, CI = confidence intervals, N/A= not included in the model selection

4. DISCUSSION

4.1. Discussion

The findings suggest that in a prospective cohort of HIV-positive British Columbians on HAART, HIV drug resistance testing practice is not being consistently carried out. Furthermore, our analyses demonstrate the association that exist between certain socio-demographic and clinical variables and the likelihood of having been tested for HIV drug resistance *prior* to or *after* starting HAART.

In both socio-demographic and clinical models (Tables 3 & 4), women showed a lower tendency of undergoing HIV resistance testing prior to starting HAART. This finding is disturbing. It suggest that prior to HAART initiation, women access treatment options less than men, hence were not tested before starting therapy. This finding is supported by a study from Mocroft and colleagues which reported gender differences in the likelihood of starting HAART therapy (Mocroft, Gill, Davidson, & Phillips, 2000). After starting therapy, however, no association was observed between gender and the likelihood of getting tested.

Persons of Aboriginal ethnicity were less likely to have been tested *prior* to start of therapy. This relationship is reflected in previous reports that have shown

that Aboriginals have a lower access rate to available HIV treatment services than their non-Aboriginal counterparts (Wood et al., 2003b). Aboriginal ethnicity did not play a role in who gets tested after the initiation of therapy.

In both models, we observed that persons, who initiated HAART in 2004 or after 2004, were more likely to have been tested *prior to* starting therapy. This observation does not come as a surprise since recommendations requiring resistance testing prior to therapy initiation, have not been around for very long. We however noticed a dissimilar relationship when we looked at resistance testing *after* initiation of therapy (Table 3 & 4). People, who started therapy in 2004 or after, were less likely to have been tested after therapy initiation. While this observation does not quite follow what was observed earlier in terms of testing done prior to HAART initiation, we can only suggest that because of improved treatment methods, those who started in 2004 or after may have suppressed viral loads and therefore may have been less likely to have been tested.

As can be seen from the clinical model (Table 3), the primacy of baseline viral load over baseline CD4 cell counts as a determinant of resistance testing prior to starting therapy, is apparent. It helps to reinforce the fact that CD4 count has been shown to be less strongly correlated with resistance development compared to pVL (Harrigan et al., 2005). Individuals with a virologically suppressed status (pVL < 50 copies/mL) showed a decreased likelihood of getting tested compared to those with unsuppressed viral loads. This outcome was expected. The same was expected for adherence. The fact that persons with

high adherence levels (≥ 95%) seemed less likely to have been tested for resistance is consistent with the literature that relates low adherence levels with high probability of resistance development (Bangsberg et al., 2001; Harrigan et al., 2005; Hogg et al., 2006). However, the strength of the association between adherence and the probability of having been tested was observed to weaken in the presence of clinical variables (Table 3). The reduced strength of the association of adherence may be due to the masking effect from clinically more important variables like virologically suppression status.

The level of education of patients was positively associated with whether testing was done prior to initiating therapy. This result suggests that education might be a useful tool in HIV/AIDS patient care. No association was observed with the level of patient education when we considered whether resistance testing was done after initiation of therapy. Reasons for this relationship are unclear at this time, but we suggest that after initiation of therapy, other factors (e.g. viral loads) may have influenced testing more than the patients' education level. Preliminary results from an ongoing study by my colleagues at the Centre, investigating patient comprehension of antiretroviral drug resistance, shows that knowledge of HIV drug resistance is low among patients (Racey et al., unpublished). Building health literacy capacity through patient targeted programs aimed at increasing knowledge of resistance may help close the gap in adherence and help to improve treatment success.

A novel finding was the observation that a history of incarceration was independently associated with an increased probability of having been tested for

HIV drug resistance after initiation of HAART. This observation may be due to continuity in care and access to treatment that is observed in British Columbia's jails. Previous studies have reported about the exemplary nature of British Columbia's correctional facilities in terms of HIV response efforts (Lines, 2002; Palepu et al., 2004). Our finding helps to support initiatives that ensure a continuity of care for those in jail. It also goes further to support calls for a model that would ensure continuity in care after HIV-positive inmates leave prisons (Palepu et al., 2004).

Readers should be cautious when interpreting these results as there may be some elements of the study that may have directly or indirectly affected the findings. First, the small sample size may have limited our ability to rigorously analyze a broader array of explanatory factors. Thus the analysis was limited to those factors that were considered to be relevantly linked to the research question. Second, since this study was carried out with a cohort from British Columbia, we wonder if the results may be different in some other provincial cohort of HIV-positive persons. Third, this study relied on self reporting from participants to obtain some of the data. The correctness of the participants' response cannot be totally determined. Finally, it should be noted that this was an observational study and does not represent a cause and effect.

Despite these limitations, this study has been able to highlight the inconsistency in HIV drug resistance testing practice even in settings where the services are free of charge. Socio-demographic indicators seem to be important predictors of whether a person is tested prior to initiating HAART. As expected,

after the initiation of HAART, resistance testing was mostly guided by clinical variables like pVL. The lack of proper monitoring can limit treatment success as antiretroviral resistance has been linked to incomplete viral suppression.

4.2. Implications and Recommendations for Public Health Practice and Policy

The significance of HIV drug resistance testing in the management of HIV/AIDS has been repeatedly stressed in the literature. This study has shown that the practice is not consistently carried out among British Columbia's HIV positive persons who are on treatment. This study is important for various reasons which include:

i. The study points to this gap in the management of HIV disease and urges the medical community to re-examine the implementation levels of HIV drug resistance practice.

ii. Special attention should be given to women and aboriginal HIV positive persons who seem less likely to be tested before they begin HAART therapy.

iii. The level of patient school education was noted to be associated with whether testing was done prior to initiation of therapy. This suggest that public health practice should encourage policy makers to invest in initiatives that would support the education of British Columbians since increased education levels might be a useful tool in HIV/AIDS patient care. Physician-patient relationship will be critical in such initiatives as a positive relationship can enhance patient health literacy and build capacity for increased adherence and ultimately better treatment outcomes.

iv. The finding that a history of incarceration was associated with an increased probability of having been tested for HIV drug resistance after initiation of HAART, goes to support policies that ensure adequate continuity of care for HIV-positive persons in prison. It goes further to support calls for a model that would ensure continuity in care after HIV-positive inmates leave prisons (Palepu et al., 2004).

In terms of recommendation, this study should inspire further research to investigate why HIV drug resistance testing practice is not optimally practised in HIV management efforts in British Columbia.

4.3. Personal Critical Reflection of Issue

HIV-positive persons in British Columbia and in most of the developed world are at an advantage point in terms of access to available HIV/AIDS treatment and management options. In BC, antiviral therapy is available free of charge to all HIV-positive persons requiring treatment. Despite this free access to HIV management services and treatment, it is a surprise to observe that optimal use of these services is lacking especially among people who are currently receiving HAART medicines.

Coming from sub-Saharan Africa, a society still struggling to provide universal access to these essential medicines, I cannot help but wonder why sub-optimal use of available HIV management options is the case in British Columbia where access to treatment is free. Resource-limited settings like sub-Saharan Africa do not feasibly implement resistance testing recommendations because of limitations related to high costs and technical constraints. Thus persons in this region face the risk of incomplete viral suppression as they may remain on drugs to which the virus is resistant. This ultimately reduces response to antiviral therapy and general patient success. While up-scaling access to HIV medicines is a good step in the right direction, alone it will not solve the problem of AIDS. At this point, I can only hope that the African continent advances to the point of not only achieving universal treatment access to medicines and HIV management options, but also be able to address other systemic fractures in our health care system.

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