

**Treatment limitations imposed by
antiretroviral therapy: a comparison of
first line regimes containing boosted-protease inhibitors
and non-nucleoside reverse transcriptase inhibitors**

By

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ABSTRACT

NNRTI-based ART is mainly used as first-line treatment for HIV in resource-limited settings. Anecdotal evidence suggests a greater chance of resistance from failing NNRTI-based regimens compared to boosted-PI. Development of resistance mutations among individuals who initiated ART with boosted-PIs were compared with those who initiated ART with NNRTIs in a retrospective study of ART-naïve individuals in BC, Canada. A total of 1666 participants initiated ART with 818 (49.1%) on NNRTI-based regimen. Participants who initiated NNRTI-based regimens had more resistance mutation compared to those on boosted-PI (40.3% vs. 27.3%, $p < 0.001$). After switching therapy to second line, the odds of achieving two consecutive pVLs of < 50 copies/ml after switching was inversely associated with NNRTI use in the initial ART regimen (OR: 0.32; 95% CI: 0.11 - 0.97). The use of NNRTI-based first-line regimens was associated with more ART drug resistance patterns which limit the number of available second-line drug choices.

Key words: Highly Active Antiretroviral Therapy, Non Nucleoside Reverse Transcriptase Inhibitors, Boosted-Protease Inhibitors, Resource Limited Settings, Drug Resistance

DEDICATION

This work is dedicated to my wife Jenipher and my two boys Brian and Charles. Working through my MPH program has not been an easy path. It kept me so busy that I did not have enough time for you guys. I love you so much and thank you for always being there for in both difficult and good times. I would also like to dedicate this work to my late mother, Corina M. Njovu, who passed on in 2001 and the many Zambians infected or affected by the HIV/AIDS problem.

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List of abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ABC	Abacavir
ART	Antiretroviral Therapy
ARVs	Antiretrovirals
AZT	Zidovudine
BC CfE	British Columbia Center for Excellence in HIV/AIDS
D4T	Stavudine
DDI	Didanosine
EFV	Efavirenz
FTC	Emtricitabine
GSS	Genotypic Sensitivity Score
HAART	Highly Active Antiretroviral Therapy
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HOMER	HAART Observation, Medical Evaluation Research
IAS	International AIDS Society
LPV	Lopinavir
NFV	Nelfinavir
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
PI	Protease Inhibitor

TREATMENT LIMITATIONS IMPOSED BY ANTIRETROVIRAL THERAPY- BOOSTED PI VS NNRTI

pVL	Plasma Viral Load
RNA	Ribonucleic Acid
RTV	Ritonavir
3TC	Lamivudine
TAMs	Thymidine Analogue Mutations
TDF	Tenofovir
UNAIDS	Joint United Nations Program on HIV/AIDS
VL	Viral Load
WHO	World Health Organization

1.0 Introduction to the public health problem

More than 90% of the 33 million people living with Human Immunodeficiency Virus (HIV) worldwide live in resource-limited settings. The global AIDS epidemic has reduced life expectancy by more than 20 years, slowed economic growth, and deepened household poverty in the countries most heavily affected (UNAIDS, 2008). In 2008 however, the annual death rate due to HIV dropped to 2.0 million from 2.2 million in 2005. Part of this reduction has been attributed to increased access to antiretroviral treatment (UNAIDS, 2008).

Most resource-limited countries have embarked on national antiretroviral programs to treat as many HIV positive individuals as possible (Beck et al, 2006). The implementation of these programs, in resource-limited settings is based on a public health approach that delivers comprehensive HIV care. These strategies maximizes survival of HIV infected persons through standardized sequencing of available ARVs delivered to individuals through simplified approaches supported by clinical and basic laboratory monitoring (WHO, 2006). One recommended approach for standardized sequencing is the use of non-nucleoside reverse transcriptase inhibitors (NNRTIs) based regimens for first line and reserving protease inhibitor (PI) based regimens for second line antiretroviral therapy. With over 80% of individuals on antiretroviral therapy worldwide in low and middle income countries (WHO, 2008b), it is imperative that these recommendations are the very best. This

paper will discuss the effectiveness of this recommendation and its implications for individuals living in resource-limited settings.

2.0 Purpose of the paper

The purpose of this paper is to measure the effectiveness of two different antiretroviral therapy regimens used in first line treatment of HIV. The study compares individuals taking non-nucleoside reverse transcriptase inhibitor based regimens to those taking boosted protease inhibitor based regimens.

In order to compare the effectiveness of these two regimens, the study will examine the development of resistance mutations among individuals on highly active antiretroviral therapy (HAART). Individuals receiving boosted-PI based first line regimens will be compared to those receiving NNRTI-based first line regimens in order to determine the remaining available active drugs from the putative list of typically used antiretroviral drugs in resource-limited settings. Clinical outcomes for patients who switch from first line to second line treatment regimens will also be compared. From the author's knowledge, there has not been any study published to date that has compared the use of these two antiretroviral treatment regimens. These findings will add to the body of knowledge on the effectiveness of NNRTI and PI-based antiretroviral therapy (ART) regimens and help further structure future recommendations on ART policy and guidelines especially in resource-limited settings. This is also important considering that more than 97% of individuals on treatment in resource limited settings may be at risk of developing resistance that will reduce the number of future treatment options.

3.0 Literature review

The World Health Organization's guidelines development group has recommended the use of two nucleoside reverse transcriptase inhibitors (NRTIs) and one no nucleoside reverse transcriptase inhibitor as first line antiretroviral therapy for individuals with HIV-1 in resource limited countries. It further advises reserving protease inhibitor-based regimens for second line therapy (WHO, 2006). These recommendations have been standardized and simplified to allow for easy expansion of antiretroviral therapy (WHO, 2006). These guidelines have been widely adopted by resource limited countries (Beck et al, 2006; Akileswaran et al, 2005) and recent data shows that more than 97% of both adults and children on therapy in these settings are on first line antiretroviral therapy (WHO, 2008b).

The primary goal of antiretroviral therapy is to increase disease free survival through maximal suppression of viral replication and preservation of immunological function (Hammer et al, 2008). HAART has been recommended for the treatment of HIV since 1996. The key feature of HAART is that at least three antiretroviral drugs are used in combination for the treatment of HIV. Most treatment guidelines recommend the use of two NRTIs with either an NNRTI or a PI (WHO, 2008b; IAS-USA, 2000). The initial selection of these drugs depend on the drug susceptibility of the individual patient's HIV, the pill burden, frequency of dosing, anticipated tolerability, co-morbid conditions, and short and long term adverse event profiles in addition to potential for emergence of resistance during therapy (Hammer et al, 2008). In most developed countries the choices of first

line antiretroviral therapy are individual based (Hammer et al, 2008) where as in the resource limited they are population based. The western model of specialist physician management and advanced laboratory monitoring is not feasible in most resource-limited settings (Calmy et al, 2007). Drug selection in these countries depends on simplified tools and approaches to clinical decision-making centred on when to start drug treatment, when to substitute for toxicity, when to switch after treatment failure, and when to stop (Gilks et al, 2006). These features enable lower level health-care workers to deliver care. The population based approach has played an important role in the types of choices made, on what therapy to start with and has been key in the quick expansion of antiretroviral therapy in resource limited settings (WHO, 2008a).

About 95% of adults on first line ART in resource-limited settings are on non nucleoside reverse transcriptase inhibitor based treatment regimens (WHO, 2008b). The individuals on non nucleoside reverse transcriptase inhibitors versus those on boosted protease inhibitors, in developed countries, are almost equal (BC CfE, 2008).

The International AIDS Society -USA recommends that baseline genotypic testing for resistance be performed in treatment-naïve patients regardless of duration of infection (Hammer et al, 2008). Additional testing includes measurements of plasma HIV-1 RNA levels, CD4 count, viral tropisms, and therapeutic drug monitoring (Hammer et al, 2008). These recommendations were developed for all patients preparing to start antiretroviral therapy. However, technical constraints and the high costs associated with most of these tests do

not make them feasible in resource-limited settings (Petti et al, 2006). Most patients in these settings do not have access to viral load testing and use alternative measures to assess HIV progression (Ekong et al, 2004). Consequently, some individuals may remain on incompletely suppressive regimens for long periods of time, which predispose them to drug resistant mutations (Gandhi et al, 2007), before they are diagnosed with treatment failure and switched to a second-line regimen. Most patients on NNRTI-based first line ART treatment can be expected to have NNRTI resistance and many will have NRTI resistance mutations by the time they are switched to a second-line regimen (Akileswaran et al, 2005; Harrigan et al, 2005). These mutations are not expected to affect their chances of successful treatment on the second-line regimens which are based on a protease inhibitor coupled with two novel NRTIs to which patients have not been previously exposed (WHO, 2006). Studies, however, have found that NNRTI resistance mutations have been associated with a higher rate of mortality (Hogg et al, 2006). The development of thymidine analogue mutations (TAMs) or other major NRTI mutations while on a failing first-line regimen also has the potential to render these second-line regimens ineffective because of the widespread cross-resistance that occurs with other NRTIs (Whitcomb et al, 2004). There is anecdotal evidence suggesting that failing NNRTI-based regimens result in a greater susceptibility to developing non-lamivudine NRTI resistance mutations, than do PI-based regimens (Lima et al, 2008). Similar results have been suggested by a recent clinical trial comparing efavirenz-based HAART with lopinavir/ ritonavir-based HAART (Riddler et al,

2008). Riddler and her colleagues found that NNRTI based regimens with efavirenz were slightly more likely to develop drug resistance mutations than lopinavir/ritonavir (boosted-PI) based regimen (9% vs. 6%).

4.0 Methods

4.1 Study population

The HAART Observational Monitoring Evaluation and Research (HOMER) study is a prospective observational cohort of all antiretroviral-naïve patients aged 18 years and older initiating HAART in British Columbia, Canada. It has been described in more detail elsewhere (Wood et al, 2003, Hogg et al, 2001). All antiretroviral naïve patients initiating HAART in the province of British Columbia (BC) are automatically enrolled into the study. The British Columbia Center for Excellence in HIV/AIDS (BC CfE) through the drug treatment program distributes antiretroviral drugs based on specific guidelines generated by the center's therapeutic guidelines committee (BC CfE, 2006). The 2006 guidelines recommend triple combination therapy for all HIV infected individuals with CD4 cell count less than $200/\text{mm}^3$ and between $200/\text{mm}^3$ and $350/\text{mm}^3$ when viral load is more than 50,000 copies/mL (BC CfE, 2006). The BC CfE recommends that plasma HIV-1 RNA levels and CD4 count be monitored at baseline, at four weeks after starting antiretroviral therapy and every three months thereafter (BC CfE, 2006). Ethics approval for the study was obtained from the Simon Fraser University Ethics Review Board.

4.2 Inclusion criteria

The inclusion criteria included (I) being ART naïve at the time of initiating ART, (II) 18 years and older, (III) receiving HAART consisting 2 NRTIs and either an

NNRTI or a boosted PI for longer than or equal to 90 days. Using individuals in the HOMER cohort, a retrospective cohort study was conducted among those who started HAART between January 2000 and June 2006 with follow-up to June 2007. Individuals included in the study were only those participants who were on medications on the putative list of antiretroviral medications. This list was obtained from the drug access initiative in Uganda (UNAIDS, 2006) and Ministry of health in Zambia (Zambia MoH, 2007) and is used in most resource limited settings. The antiretroviral drugs contained include: NRTIs [Zidovudine (AZT), Stavudine (D4T), Lamivudine (3TC), Tenofovir (TDF), Emtricitabine (FTC), Didanosine (DDI) and Abacavir (ABC)], NNRTIs [Efavirenz (EFV) and Nevirapine (NVP)] and Lopinavir boosted with ritonavir (LPV/r) as the boosted-PI.

4.3 Measures

The main outcome measures were: antiretroviral drug resistance mutations measured in terms of genotypic sensitivity scores, viral load measurements in follow-up, CD4 cell counts in follow-up and ART prescription refills. The explanatory variables of interest included: age, sex, baseline CD4 and viral load, CD4 cell count and viral load at time of last visit prior to switch to second line, AIDS diagnosis at baseline; adherence to therapy in first year of ART, intravenous drug use status, Hepatitis C status, initial NRTI combination in regimen, initial 3rd drug in regimen (PI or NNRTI) and 3rd drug in regimen after switch.

The genotypic sensitivity score (GSS) was calculated as the number of drugs in the study regimen to which the patient's virus was likely to be sensitive as described by DeGruttola et al (2000). For each drug in the regimen a value of 0 was assigned if there was genotypic evidence of resistance to that drug in the patient's baseline virus, and a value of 1 if there was no genotypic evidence of resistance to that drug. The drugs in the study regimen were those in the putative list of antiretroviral drugs explained above. The list gave 30 possible triple antiretroviral drug combinations as shown in Table 1 (see page 13).

Table 1: Thirty possible active antiretroviral drug combinations obtained from a lists from Uganda¹ and Zambia²

PI Based		NNRTI based³	NRTI based
Kaletra (LPV/r)	Nelfinavir ⁴ (NFV)	Efavirenz/ Nevirapine	
AZT/3TC (or FTC) + LPV / r	AZT/3TC (or FTC) + NFV	AZT/3TC (or FTC) +NVP	ABC/3TC/AZT
D4T/3TC (or FTC) + LPV/r	D4T/3TC(or FTC) + NFV	D4T/3TC(or FTC)+NVP	TDF/3TC/AZT
TDF/3TC (or FTC) + LPV/r	TDF/3TC (or FTC) + NFV	TDF/3TC (or FTC)+NVP	ABC/3TC/D4T
ABC/3TC (or FTC) + LPV/r	ABC/3TC (or FTC) + NFV	ABC/3TC (or FTC)+NVP	TDF/3TC/D4T
DDI/ 3TC (or FTC) + LPV/r	DDI/3TC (or FTC) + NFV	DDI/3TC (or FTC)+NVP	
AZT/ABC+ LPV/r	AZT/ABC +NFV	AZT/ABC+ NVP	
AZT/TDF + LPV/r	AZT/TDF +NFV	AZT/TDF + NVP	
DDI/ABC+ LPV/r	DDI/ABC +NFV	DDI/ABC+ NVP	
DDI/TNF + LPV/r	DDI/TNF +NFV		

¹Drug Access Initiative Uganda (UNAIDS, 2006), ²Ministry of Health Zambia (2007), Antiretroviral therapy for chronic HIV infection in adults and adolescents document ³All NNRTI based combinations can be either with EFV or NVP and due to cross resistance between EFV and NVP only gives 8 combinations. ⁴ Individuals on Nelfinavir were not included in the study.

4.4 Statistical analyses

Numbers of individuals who initiated HAART during the study period and those who met the inclusion criteria were described. Individuals who met the study inclusion criteria and had drug resistance testing performed, stratified by the 3rd drug class in their initial regimen were also described. The proportion of individuals with any resistance mutations and the effect of the mutations on drug susceptibility for the putative list of available drugs (termed genotypic sensitivity scores) were compared for those who initiated HAART with boosted PI-based regimens and those who initiated with NNRTI based regimens. Variables were included in the multivariate analysis if they had p-values ≤ 0.05 based on the bivariable Fisher's Exact test, Chi-squared test, or Wilcoxon rank-sum test. A backward-selection procedure based on the Akaike Information Criterion (AIC) was used to select the variables to be included in the final multivariable models. The Hosmer-Lemeshow test was used to examine the goodness-of-fit. Patients were classified as having between 0 and 11 remaining active drugs based on their drug resistance patterns. Multivariate logistic regression analysis was used to examine factors associated with having thirty possible combinations of ART regimens versus less. The class of 3rd drug (PI or NNRTI) was included in models as a covariate including other potential variables thought to affect the development of resistance. The proportion of individuals who achieved virologic suppression after a switch in their 3rd drugs were compared for those who initiated HAART with boosted-PI based regimens to those who initiated with NNRTI based regimens. Logistic regression was used to analyze factors

associated with achieving virologic suppression (plasma viral load < 50 copies/mL) after switching therapy from boosted-PI to NNRTI and vice versa. The Kaplan-Meier survival analysis was also conducted for time to development of less than 30 antiretroviral drug combinations for all individuals in the cohort.

5.0 Results

A total of 1,666 participants' data was analyzed with overall median follow up of 36.85 months (IQR: 20.53, 56.15). Eighty percent of the participants were males and 51% of the individuals in the cohort started with boosted-PI based regimens.

Table 2 (on page 16) shows the baseline demographic characteristics and clinical outcomes of the participants in the cohort. More individuals diagnosed with AIDS started with boosted-PI based regimen as compared to those who started with NNRTI based regimen (21.5% vs. 9.5%, $p < 0.001$). Individuals with greater than 95% adherence to ART were on boosted-PI based regimens than the NNRTI based (68.3% vs. 56.8%, $p < 0.001$). Forty-seven percent of participants had drug resistance tests done during therapy. Among those tested for drug resistance during the course of treatment, 34.6% had at least one drug resistance mutation and the proportion of individuals with drug resistance mutations was lower for the boosted-PI group as compared to the NNRTI group (27.3% vs. 40.3%, $p < 0.001$). There was no significant difference in the proportion of individuals who achieved virologic suppression in the two groups after one year of therapy with 67.2% of boosted-PI group and 65.5% of NNRTI group. Almost one in five participants (18.5%) switched therapy from boosted-PI to NNRTI or vice versa. In both groups, those who switched had plasma viral loads greater than or equal to 50 copies /mL (98.4% of PI group and 98.9% of NNRTI group, $p = 0.99$).

Table 2: Baseline Characteristics and clinical outcomes of participants in the cohort during therapy

Characteristics	Category	NNRTI % (n)	Boosted-PI % (n)	P-value (2 sided)
<i>Baseline Characteristics</i>				
Gender	Female	190(23.2)	132(15.6)	<0.001
	Male	628(76.8)	716(84.4)	
History of Injection drug use		245(30)	189(22.3)	<0.001
AIDS at baseline		78(9.5)	182(21.5)	<0.001
HCV Positive	No	264(32.3)	358(42.2)	<0.001
	Yes	301(36.8)	194(22.9)	
	Unknown	253(30.9)	296(34.9)	
Aboriginal ethnicity	No	242(29.6)	339(40)	<0.001
	Yes	53(6.5)	47(5.5)	
	Unknown	523(63.9)	462(54.5)	
Baseline CD4 count, Median (IQR) cells/ µL		190 (120,270)	120 (40, 200)	<0.001
Baseline viral load (Log ₁₀), Median (IQR)		4.9 (4.5, 5.0)	5.0 (4.9, 5.0)	<0.001

Table 2 Continued

Characteristics	NNRTI % (n)	Boosted-PI % (n)	P-value (2 sided)
<i>Clinical outcomes during treatment</i>			
Adherence to therapy > 95% (12 months)	465(56.8)	579(68.3)	<0.001
Tested for Drug Resistance	444(54.3)	341(40.2)	<0.001
At least one drug resistance mutation	179(40.3)	93(27.3)	<0.001
With 2 class drug resistance mutation	71(16)	22(6.5)	<0.001
VL <50 x 2 in first year of therapy	536(65.5)	570(67.2)	0.47
Switched 3rd drug in regimen to other class	185(22.6)	123(14.5)	<0.001
VL≥50 during 6 months prior to drug switch	183(98.9)	121(98.4)	0.99
Median genotypic sensitivity score	9.8	11.0	<0.001

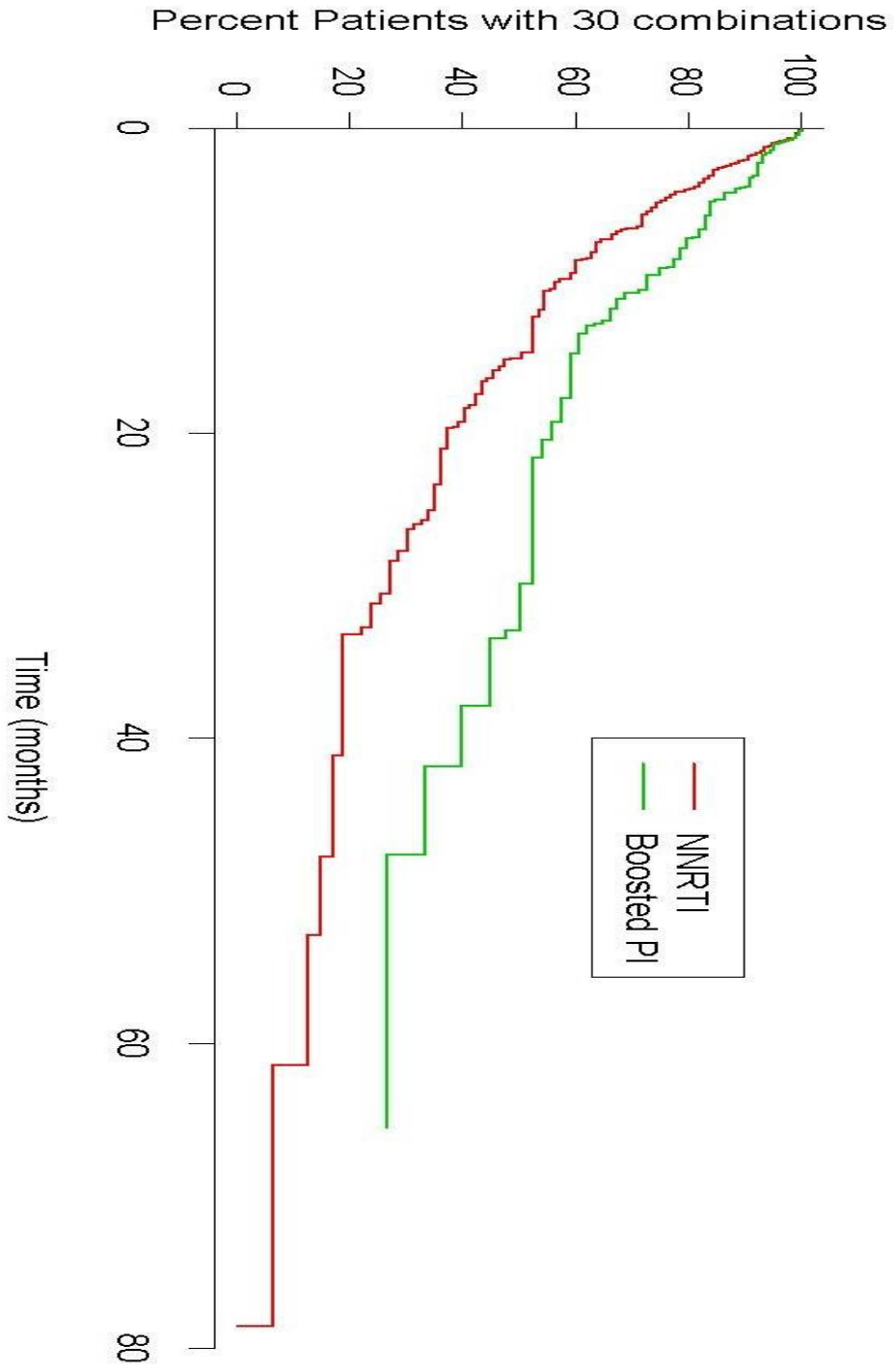
Genotypic sensitivity scores: The bivariate and multivariate analysis shown in Table 3 (page 19) shows factors associated with having 30 possible active combinations of antiretroviral drugs versus less than 30. The median time to testing for drug resistance was 47.18 months (IQR: 27.86, 64.53). Individuals who were on boosted-PI based regimens were more than three times more likely to have 30 possible active combinations as compared to those on NNRTI based regimens (OR: 3.68; 95% CI: 2.25, 6.01). Greater than 95% adherence to ART (OR: 1.84; 95% CI: 1.16, 2.92) and having a baseline CD4 count higher than 200 cells/ μ L (OR: 3.44; 95% CI: 1.73, 6.84) was also associated with having 30 possible combinations. Participants who initiated boosted-PI based regimens had higher median GSS (11.0 vs. 9.8; $p < 0.001$) than those in the PI-group (Table 1, page 18).

Table 3: Multivariate and bivariate analysis of factors associated with having 30 ART combinations compared to less than 30 combinations after resistance testing

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Boosted-PI vs. NNRTI	3.04 (1.95, 4.76)	3.68 (2.25, 6.01)
Male vs. female	1.13 (0.68, 1.86)	-
Age	1.02 (1.00, 1.04)	-
Injection drug use vs. not	0.72 (0.46, 1.13)	-
AIDS diagnosis at baseline vs. no	0.91 (0.52, 1.59)	-
> 95% adherence vs. < 95%	2.09 (1.35, 3.23)	1.84 (1.16, 2.92)
Baseline CD4>200 cells/ μ L	2.06 (1.11, 3.79)	3.44 (1.73, 6.84)
Baseline VL (per log10 increase)	1.42 (0.86, 2.34)	-
Adherence (per10%)	1.08 (0.99, 1.19)	-

Figure 1(on page 21) is the Kaplan-Meier curve showing the proportion of individuals with 30 possible active combinations of ART at different times of follow-up in boosted-PI and NNRTI groups. At 60 months of follow up more than 35% of individuals in boosted-PI group had 30 possible combinations as compared to less than 20% for NNRTI group.

Figure 1: Kaplan-Meier Curve for percentage of participants with 30 combinations versus time on treatment



Factors associated with virologic suppression after switching therapy: The bivariate and multivariate analysis in Table 4 (page 23) shows the factors associated with achieving virologic suppression (pVL<50) after switching therapy from NNRTI to boosted-PI or vice versa. The median time to switching therapy among individuals who switched (n= 156) was 7.61 months (IQR: 2.87, 17.41). Being on NNRTI based first line was inversely associated with achieving virologic suppression in the second line therapy (OR: 0.322; 95% CI: 0.107, 0.972). Male participants were more than three times more likely to achieve virologic suppression after switching OR: 3.593 (95% CI: 1.474, 8.757) than females and individuals with baseline CD4 counts of greater than or equal to 200 cells/ μ L were more than four times more likely to achieve virologic suppression after switching therapy (OR: 4.623; 95% CI: 1.472, 14.52) than those with lower CD4 counts.

Table 4: Logistic regression analysis of factors associated with achieving two consecutive viral load measurements < 50 copies/ mL after drug switch from primary regimen (n=156)

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Initial drug regimen:		
Boosted PI	1.00	1.00
NNRTI	0.29 (0.11, 0.82)	0.32 (0.11, 0.97)
Male vs. female	3.23 (1.488, 7.00)	3.59 (1.47, 8.76)
Increased Age in years	1.03 (0.99, 1.07)	
History of IDU	0.32 (0.15, 0.65)	
AIDS diagnosis at baseline	2.61 (0.56, 12.15)	2.461 (0.46, 13.05)
HIV RNA (log₁₀ increase copies/ml) at switching	0.44 (0.24, 0.81)	0.442 (0.22, 0.88)
CD4 count at time of switching:		
<50 cells / μ L	1.00	1.00
50 –199 cells/ μ L	1.50 (0.58, 3.91)	1.83 (0.62, 5.43)
\geq 200 cells/ μ L	4.16 (1.51, 11.48)	4.62 (1.47, 14.52)

6.0 Discussion

This study found that individuals on NNRTI-based first line regimens were more prone to develop antiretroviral drug resistance mutations as compared to those on boosted-PI first line regimens. The study found that the proportion of individuals on NNRTI regimens with more than one resistance mutation was 16% as compared to those on boosted-PI regimens which was 6.5%. This high frequency of resistance mutations in the initial drug regimen has the potential to reduce the number of future options of second line drug regimens. This was demonstrated in the mean genotypic sensitivity scores for which first line NNRTI regimens scored 9.8 against 11.0 for boosted-PI based first line regimens and the odds of having 30 active combinations which was more than three times higher in individuals who used boosted-PIs as first line after 47 months of follow up. These findings support earlier work done by other researchers. Lima et al (2008) found significant differences in development of resistance between NNRTI based regimens against boosted-PI based (OR, 0.42 [95% CI, 0.28–0.62]) and Riddler et al (2006) found that efavirenz based ART was more prone to drug resistant mutations as compared to Lopinavir-ritonavir (9% vs. 6%).

Though the suggestion of boosted-PI based regimens can be viewed as premature due to insufficient data, this change can lead to fewer antiretroviral drug resistance mutations and hence a higher number of available second line options especially in resource-limited settings. The substitution can be essential because most of the people living with HIV are in resource limited settings where

drug resistance tests are rarely done. The switch may have an impact on the reduction of HIV related mortality which continues to be higher in these settings despite the fact that individuals are accessing HAART (Brinkhof et al, 2009). Much of the mortality in resource-limited settings has also been related to late commencement of ART, and from the above findings individuals who were much sicker (diagnosed with AIDS, low CD4 counts and higher viral loads) were prescribed boosted-PI regimens and they did better. It may also lead to a reduction in the mortality associated with difficulties in decision making on when to switch from first line to second line due to lack of specificity of the new WHO guidelines on when to switch to second line (Rewari et al, 2009; Keiser, 2009; Iwe et al, 2009). The impact of higher drug resistance rates associated with NNRTI use poses a great danger in the near future with the rising numbers of children on antiretroviral therapy (Lockman et al, 2009) and women being given single dose Nevirapine for the prevention of mother to child transmission of HIV (Lockman and the A5208 / OCTANE study team, 2009).

The two drug regimens were equally efficacious as evidenced by percentages of individuals who achieved virologic suppression in the first year of therapy (65.5% for NNRTI and 67.2% for boosted-PI group). However, when individuals on failed first line regimens were switched to the opposite regimen, those who started on boosted-PI regimen had higher odds of achieving virologic suppression as compared to those on NNRTI based regimens. This further strengthens the idea that starting with boosted-PI regimens will increase the likelihood of successful treatment after a failed first line regimen.

The generalization of these findings to resource limited settings may be limited by the fact that this study was done in a developed country where most of the social demographic features are different from resource limited settings. Furthermore, the study focuses on antiretroviral drug resistance among those infected by HIV-1 subtype B which accounts for only 10% of HIV infections worldwide (Soares, 2008) and recent evidence suggests that different HIV genetic variants have different biological properties, including susceptibility and response to antiretroviral drugs. In addition, the way that antiretroviral therapy is managed in the face of drug resistance is much different in British Columbia from most resource-limited settings.

With an increasing concern of resistance to available antiretroviral drugs (Perno.et al, 2008), the judicious use of antiretroviral drugs becomes highly critical. Resource limited settings need standardized, simple ART regimens to allow for easy expansion but it is important to be wary of remaining available options of further treatment as the people living with HIV are living longer. The decisions on which drugs to recommend should be based on more than just the ease of expansion of the service, but thinking of the future implications of the recommended treatments as much as the cost is considered.

7.0 Implications for public health practice and policy

The Impact of HIV/AIDS in low-income countries cannot be underestimated. The availability of HAART has reduced some problems associated with HIV/AIDS. The reduction in the annual number of AIDS deaths from 2.2 million in 2005 to 2.0 million in 2007, has been attributed in part to increase in access to HIV treatment (UNAIDS, 2008).

Though HIV mortality rate has been reduced by the use of HAART in resource-limited settings, there is room to do better. Mortality among individuals on HAART remains higher in resource-limited settings than developed countries due to late commencement of ART. Starting ART early and use of boosted-PI based regimens for those starting late may reduce mortality in these settings. Reduction of mortality will further help reduce household poverty by reducing the number of households without parents or orphaned children. Individuals will also live longer and hence increase the economic productivity of these countries.

Morbidity associated with chronic HIV/AIDS has also been reduced using current HAART recommendations in resource-limited settings. Since drug resistance tests are rarely done in these settings, individuals on failing HAART regimens will not be easily identified. Continuing treatment in these individuals though might be beneficial, will not be as effective due to resistance developed against the drugs by their viruses. It might worsen their conditions because most of these antiretroviral drugs are associated with toxic side effects. This will increase morbidity in the end because these individuals will not only suffer from HIV/AIDS but also the effects of the drugs. Use of boosted-PI based regimes in

place of NNRTI based first line may help reduce the number of individuals developing drug resistance HIV strains and reduce the morbidity rates. The reduction in morbidity can increase the economic productivity of individuals in these settings and reduce household poverty.

The cost of antiretroviral therapy is one of the most important determinants of policy decisions in resource-limited settings. On average, the cost of treating one patient on NNRTI based treatment regimes in resource-limited settings for one year is \$221.84. This cost is seven fold cheaper than the cost on boosted-PI which is \$1,625 (UNAIDS, 2007). The higher cost of boosted-PI based regimes may limit the adoption of these regimes in resource limited settings as these countries are likely to have many other competing costs including struggles against poverty and other infectious diseases. The decision making, however, should also take into consideration the morbidity that may be associated with drug resistant HIV and the possibility that a lot of individuals will have fewer options of second line treatment regimens if boosted-PI regimes are not used in place of NNRTI ones.

The transmission of HIV drug resistance strains is another emerging problem associated with treatment of HIV/AIDS. Few countries in resource-limited settings have studies indicating tracking transmission of HIV resistant strains in ART naïve individuals (AIDS map, 2009). The transmission of resistant strains will lead to unsatisfactory treatment outcomes in ART naïve individuals who are started on NNRTI based regimens to which the viruses are expected to be resistant. Changing first line treatment to boosted-PI based regimen may lead to

a reduction in drug resistant HIV transmitted. It may also lead to improved treatment outcomes in terms of virologic suppression in ART naïve individuals initiating therapy as shown in this study.

The implementation of boosted-PI based first line regimen can be done using the public health approach, which is already widely used in resource-limited settings. Standardised sequences of available boosted-PI based regimen delivered to individuals by means of simplified approaches and supported by clinical and basic laboratory monitoring. Standardized therapies containing boosted-PIs that do not need maintenance of the cold chain can easily replace the NNRTI regimens as first line.

8.0 Recommendations

There is need for more research on the effectiveness of NNRTI based first line treatment regimens as compared to boosted-PI. This study was based on a study population with different socio-demographic characteristics from individuals in resource-limited settings. Studies in resource-limited settings will allow for generalization of results to these settings.

Conducting research in these settings will also help study the development of resistance in the HIV strains present in resource-limited settings. Since different HIV subtypes possess different characteristics affecting their development of resistance, studies in resource limited settings will provide information on the behavior of the HIV strains in resource limited settings. The studies could preferably be multi-center randomized controlled trials in order to be more informative and possibly inform recommendations for new treatment guidelines which can be generalized to these settings.

9.0 Conclusion

The use of NNRTI based first-line regimens was associated with a higher rate of HIV drug resistance mutations than boosted-PI based regimens. These mutations limited the number of available second-line drug choices. The findings of this study are consistent with results from previous research, and may have policy implications for resource limited settings.

There is need for more research in resource limited settings to evaluate the effectiveness of NNRTI based first line regimes against PI based ones. Much of the knowledge regarding antiretroviral drug resistance has been done on HIV-1 subtype B which accounts for only 10% of worldwide HIV infections and more recently, an increasing body of evidence suggests that distinct HIV genetic variants possess different biological properties, including susceptibility and response to ARVs.

10. Personal Critical reflection

This topic is very important to me especially having come from a country that is heavily affected by HIV (Zambia, Africa). I have friends and relatives who have suffered from HIV/AIDS, which makes my involvement in HIV research very important. I plan to present these findings at the Canadian Association in HIV/AIDS Research (CAHR) conference in April (Vancouver, BC) and the International AIDS Society Conference in July, 2009 (South Africa) so that I can share my findings. I would also like to have this paper published in the AIDS Care journal so that a wide population can have access to this valuable information. As a public health practitioner, I would like to advocate for more data to be collected on this subject. As outlined above, there is need for more research in resource limited settings to confirm or disapprove these findings as they are cardinal to the future of HIV management. I have almost completed working on the proposal for conducting a multicenter randomised controlled trial in to be done in resource limited setting. I hope to have it submitted for possible funding. I plan also to do a critical review of literature on antiretroviral therapy in resource limited settings so that more data is collected, compared with my findings and known before advocating for any change in therapy. The critical review will include all the data that favours the selection of NNRTI based regimens as opposed to boosted-PI based such as pricing, adverse effects profile, tolerability of medication, needs for therapeutic monitoring of individuals on these drugs and the need for maintenance of cold chain for some PI based regimens.

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APPENDIX A: ETHICS APPROVAL

FOR CONTACT IN REFERENCE TO THIS REVIEW

Application Number: 39620

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Reference Ethics Policy 20.01: <http://www.sfu.ca/policies/research/r20-01revised.htm>

Notification of Application Status

APPROVED

By Hal Weinberg at 2:51 pm, Mar 13, 2009

Investigator Surname	Mtambo
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Investigator Department	Faculty of Health Sciences
Investigator SFU Email	ama65@sfu.ca
Investigator Position	Graduate Student
Title Of Research	Treatment limitations imposed by antiretroviral drug resistance mutations: a comparison of initial regimens containing boosted protease inhibitors with those containing non nucleoside reverse transcriptase inhibitors
Supervisor Surname	Hogg
Supervisor First Name	Robert
Supervisor SFU Email	robert_hogg@sfu.ca
Co-Investigators	
Risk	Minimal
Approval Status	Pending REB (Blue)
Approval Date	March 13, 2009
Approval Start Date	March 13, 2009
Approval End Date	March 13, 2012
REB Date	00/00/00

Grant Information

Submitted To Agency For Review	No
Approved Subject To Ethics Approval	No
Reviewed By Any Other Agency	No
Title Of Grant	
Date Granting Agency Approval Began	00/00/00
Date Grant Ends	00/00/00