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## Editorial

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# It's Time to Examine the Impact of Genetic Susceptibility on the Incidence of Diabetes among HIV-Infected Individuals

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The remarkable advances in application of anti-retroviral therapy (ART) to treat HIV-infection has had a profound impact on the HIV epidemic as well as improved the quality and longevity of life for those who receive such treatment. Nonetheless, as individuals receiving ART live longer, they may develop chronic non-communicable disease at an increased incidence and/or severity when compared to non-infected and/or untreated individuals. Prime examples of this include cardiovascular and neurological disease, as well as metabolic syndrome and diabetes mellitus. Whether these growing disease burdens are identical in origin and outcome to disease in uninfected individuals, and whether ART impacts disease incidence and severity in addition to limiting HIV infection is often poorly distinguished. The data on type 2 diabetes mellitus (T2DM) provides a welcome case in point for this discussion.

There is now a wealth of data documenting the increased incidence of T2DM in HIV-infected subjects under ART. While the range of this increase varies by study population, location, and drug therapy, the most comprehensive studies typically show an increase of 2.25- 4.7 fold in the incidence of T2DM in HIV positive subjects on ART at four years after diagnosis and treatment.<sup>1,2</sup> Related studies have more recently tied these effects to an increase in the prevalence of dyslipidemia and metabolic syndrome,<sup>3,4</sup> to elevated BMI and hypertension as opposed to the level of HIV or CD4 count,<sup>5</sup> and lastly to an increase in the rate of death from the complications of diabetes.<sup>6</sup>

While the impact of HIV infection on T2DM in the absence of ART remains in debate,<sup>7</sup> there is ample evidence that various protease inhibitors used for ART cause insulin resistance independent of increases in visceral adipose tissue or lipid and lipoprotein levels.<sup>8</sup> Thus, multiple factors likely bear on the increase in T2DM seen in HIV infected subjects, especially when undergoing ART. Diabetes mellitus is a complex disease, and risk factors such as family history, genetics, obesity, race/ethnicity, age, and dyslipidemia are all poorly understood in HIV-infected individuals. However, remarkable insights into the genetic factors that foster predisposition to T2DM are rapidly emerging.<sup>9</sup> These observations illustrate that risk of T2DM is mediated by hundreds of genetic factors, the majority of which commonly occur in the general population.

Although using genetic factors to predict individual risk of T2DM is a challenge, these findings have revealed new genes and processes involved in disease pathogenesis. For example, T2DM variants affect the activity of the melatonin receptor gene that functions in circadian regulation of glucose homeostasis.<sup>10</sup> Many T2DM genetic factors—such as *TCF7L2*—cause defects in insulin secretion and alter pancreatic islet function, other factors—such as *PPARG* and *FTO*—contribute to insulin resistance,<sup>11</sup> and additional factors influence BMI and dyslipidemia.<sup>12</sup> Collectively these genes have profoundly informed the underlying causes of T2DM.

One key insight from these studies is that genetic factors for T2DM do not typically alter the protein product of a gene, and instead predominantly lie in non-coding sequences.<sup>9,10</sup> Detailed maps of the epigenome in disease-relevant tissues such as pancreatic islets, adipose,

skeletal muscle and liver have helped uncover precise genetic elements affected by T2DM risk variants.<sup>9</sup> These data suggest that much of the genetic risk of T2DM is encoded in regulatory elements activated in these tissues that affect tissue-specific gene expression. These genetic elements are thus critical to target in at-risk individuals.

Whether HIV infected subjects display an enhanced disposition and/or altered pattern of origin in T2DM that is linked to these genetic components has not been studied. This warrants immediate investigation as the populations and samples are well defined, and the tools now in place to accomplish this goal in a cost-effective manner. As the relative effect of HIV infection and/or ART on the incidence of T2DM is not absolute, studies of genetic associations and gene expression in these populations might provide clues to help decipher the relative effects of various genetic elements in predisposition to T2DM. Under the best circumstances these results might also provide a means to enhanced monitoring of certain individuals with a predisposition to develop diabetes—the ultimate goal being better preparedness and improved management of long-term health in these patients.

#### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest related to this manuscript.

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## Editorial

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# Understanding Barriers to Linking High Risk Heterosexual African American Women to Care in the Upper South

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## BACKGROUND

As part of Centers for Disease Control and Prevention's (CDC's) HIV prevention strategic plan through 2010,<sup>1</sup> 4 national goals were identified to reduce by half the new HIV infections in the United States. One of the 4 goals is to strengthen the national capacity to monitor the human immunodeficiency virus (HIV) epidemic to better direct and evaluate prevention efforts. In response to these goals, the CDC awarded funds to state health departments to develop and implement a surveillance system to monitor behaviors that put people at risk for HIV infection in metropolitan statistical areas (MSA) with high incidence of human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS). Three target populations making up the majority of HIV/AIDS cases were selected for surveillance including: men who have sex with men, injection drug users and heterosexuals living in high risk areas (defined by poverty and HIV/AIDS incidence). Each year a different population was interviewed and analyzed in a 3 year rotating cycle.

HIV/AIDS cases acquired through heterosexual contact constitute 34% of all diagnosed adult and adolescent HIV/AIDS cases reported in 33 areas with confidential name reporting in 2010. Over the last 25 years of the epidemic, transmission category has shifted with more cases being acquired through heterosexual contact, less through injection drug use and an increase in females being diagnosed with HIV/AIDS. Most of the HIV/AIDS cases being diagnosed (79%) in 2010 were female adults and adolescents with primary transmission factor of heterosexual contact.<sup>1</sup> In response to the increase of female HIV/AIDS cases, CDC's National HIV Behavioral Surveillance (NHBS) project was awarded additional funds from the Minority AIDS Initiative (MAI) to conduct a one-time study of risk behaviors of male partners of minority women (African American and Hispanic). The supplement survey (referred to as partner supplement) was conducted with minority women who complete the National HIV Behavioral Surveillance-heterosexuals (NHBS-HET) survey and an HIV test during NHBS-HET cycle. Women were then asked to recruit up to 2 of their male sexual partners to take the survey.

The data collected on heterosexuals in high risk areas through NHBS will assist the CDC to monitor behaviors of heterosexuals in high risk areas that lead to HIV infection and individuals access to HIV prevention programs in high risk areas. Information on risk and testing behaviors and access to prevention programs will assist local health departments in funding allocations to increase prevention services and lower the risk of HIV infection.

## SPECIFIC AIMS OF HET CYCLE

The goal of NHBS is to “*enhance understanding of risk and testing behaviors and to develop and evaluate HIV prevention programs that provide services to these groups*” (CDC NHBS-HET Protocol, page 1-1). Specific aims include utilizing data collected during the heterosexuals in high risk areas cycle to:

- Assess the prevalence of and trends in risk behaviors, including:
  - Sexual risk behaviors;
  - Drug-use risk behaviors.
- Assess HIV Testing Behaviors
  - Assess the prevalence of and trends in HIV testing behaviors;
  - Assess prevention;
  - Assess the exposure to and use of prevention services;
  - Assess the impact of prevention services on behavior; and
  - Identify prevention-service gaps and missed opportunities for prevention.

The partner supplement for minority women and their partners will also aim to identify:

- Risk behaviors of male sex partners of minority women; and
- To what extent do minority women's perceptions of their male sex partners' risk behaviors match the partners reported behaviors.

#### VIRGINIA BACKGROUND ON HETEROSEXUALS

The Eastern Virginia health region ranks number one in the number of HIV infections and AIDS cases in Virginia. The Norfolk, VA eligible metropolitan area (EMAs) (defined by Ryan White and based on HIV/AIDS cases) consists of the Eastern health region and parts of North Carolina. Along with Arlington, Alexandria and Richmond, the Eastern region has a higher share of HIV and AIDS incidence in Virginia especially among African Americans with lower median incomes.<sup>2</sup> As of December 31, 2010, the Norfolk MSA had a total of 3,075 persons living with HIV infection and 2,227 persons living with AIDS. Approximately 30% of HIV and 26% of AIDS cases were female. Blacks are disproportionately represented with 72% of HIV and 69% of AIDS cases. According to the 2011 epidemiological profile released by the Virginia Department of Health, HIV will infect 4.9 black females to every 1 white female.<sup>2</sup>

According to CDC,<sup>1</sup> HIV/AIDS cases acquired through heterosexual contact constituted 34% of all adult and adolescent HIV/AIDS cases reported by 33 areas with confidential name based reporting in 2010. Through the HIV epidemic, transmission has shifted from homosexual contact to an increasing percent of heterosexual contact. For example, 79% of HIV/AIDS cases diagnosed among female adults and adolescents in 2010 was through heterosexual contact; and 17% of the males diagnosed were attributed to transmission through heterosexual contact. Minority women have also become more affected by HIV over the last half of the epidemic. "*African American and Hispanic women together accounted for 80% of all reported cases of HIV infection in 2010*".<sup>1</sup>

Heterosexual behavior is not the only indicator of risk. Studies have found that geographic clustering of the HIV epidemic within cities was identified as an important consideration. Correlations among poverty, increasing AIDS incidence, and higher proportions of single mother households have also been identified. Therefore, more information needs to be gathered to understand not only the role of heterosexual behavior in HIV transmission, but also to explore areas with higher rates of disease and poverty and their access to and utilization of HIV prevention programs.

#### SUMMARY OF FINDINGS

Initial findings from the analysis of the data reveals perceived barriers to accessing heterosexual women and their partners. This data set consisted of six key informant interviews and two focus groups. Participants were African American women. From this subset the following data is abstracted; barriers or challenges to accessing heterosexual women and their partners; suggestions for improving heterosexual women's participation and a summary of the overall formative assessment findings and the implications for the partner study.

#### Barriers to Accessing Heterosexual Women and their Partners

The barriers to accessing heterosexual women and their partners resulted in eight themes, specifically, *shame or fear; sex partners with multiple issues; pride; denial; lack of education; stigma; lack of trust; and ultimate responsibility/double standard.*

When comparing the results of this targeted subset of the larger group there is an overlap concerning specific themes, namely, lack of trust, stigma and denial. The new themes that arose were shame or fear of losing primary sex partner, sex partners

with multiple issues, pride, lack of education, and ultimate responsibility/double standard. The overlap of themes and the distinct differences between the two groups suggest a starting point for developing targeted campaigns that address barrier specific challenges. Lack of trust, stigma, and denial are overlapping themes that indicate that there are powerful structural forces inherent in the belief systems of both of these groups. With the exception of lack of education, the new themes that emerged from the groups comprised of heterosexual women are all issues that are gender specific. As such, they offer suggestions for improving heterosexual women's participation, these points will be discussed more fully in the next section.

### Suggestions for Improving Heterosexual Women's Participation

The pertinent question for this group of responses is *"How can the operation and participation for the partner study be improved based on these findings?"* Respondents overwhelmingly suggested that one of the most efficient motivators for heterosexual women's participation is monetary compensation for their time. Other points that were discussed were will significantly enhance participation by this group of targeted people included bring them to one place to assess them, provide 'real world' solutions to their complex lives that would benefit them beyond the completion of the study, keep everything anonymous, pass out health education materials that stresses self-preservation, choose office locations that are convenient to parks and community centers frequented by the target population, avoid making judgments or overarching stereotypes about individual's sex lives and to take time to build trusting relationships with the target community before asking for participants. These suggestions address some of the barriers previously mentioned. However, creative and gender specific strategies are needed to improve both partner participation and recruitment. After careful analysis a stumbling block arises concerning the following challenges; shame or fear of losing primary sex partner, sex partners with multiple issues and ultimate responsibility or double standard. These issues are all gender and perhaps culturally specific. One suggestion for mastering these would be to utilize African American women as interviewers, it would also be helpful to sensitize them to the reoccurring issues beforehand. One way that this could be done is to establish a training session for interviewers where they learn more about substance abuse, spousal abuse, alcohol abuse, battered women's issues and the implications of the current shortage of black men in the African American community. Furthermore, interviewers should not be judgmental when asking women about recruiting their sex partners, role playing how the interviewee will ask her partner to participate may provide one solution. Interviewers should also be prepared to give informants referrals to community resources that offer assistance with alcohol abuse, drug abuse, battered women's shelters and financial assistance.

### Overall Summary and Implications for the Partner Study

When comparing the barriers and challenges of the general population and the targeted population of heterosexual African American women, the largest issue that arises is that the majority of these theme (e.g. denial, lack of trust, stigma, lack of education) have been a long standing challenge or concern regarding health education (or lack thereof) around HIV/AIDS in the African American community. Perhaps, their continued presence here is an indication that a principle recommendation that comes out of this data set is the dire need for more efficient health education campaigns targeted at high risk African American populations.

The new themes (e.g. shame or fear of losing primary sex partner, sex partners with multiple issues, pride, and ultimate responsibility/double standard) are gender specific and a realistic example of the multi-vocality of African American populations. In this respect, it is wise to address these gender specific themes through education of both the interviewers and interviewees as they are the prime concerns that separate this subset of the population from the previous groups, specifically men who have sex with men and intravenous drug users. Developing culturally sensitive materials that address these matters will strengthen the recruitment process and the sustainability of the intervention.

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## Research

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# HIV/AIDS and Contraceptive Method Choice: Demographic and Socio-Economic Correlates of Contraceptive Method Choice among HIV-Positive Women Practising Family Planning In Kenya

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### ABSTRACT

**Introduction:** As the generalized HIV epidemic in specific settings of sub-Saharan Africa continues to evolve, there is need for evidence-based response to address emerging challenges, which include enabling the large number of women living with HIV make informed choices to achieve their reproductive goals.

**Objectives:** This paper seeks to (i) examine the effect of HIV/AIDS on contraceptive method choice among women using contraceptives in Kenya; and (ii) identify correlates of contraceptive method choice among HIV-positive women practising family planning.

**Material and Methods:** We apply multinomial Logistic regression models to a sample of 3190 sexually-active women of reproductive age using contraceptives from the 2003 and 2008 Kenya Demographic and Health Surveys to examine the effect of HIV/AIDS on contraceptive method choice. The analysis of correlates of method choice among HIV-positive women is based on a sample of 255 HIV-positive women using contraceptives and involves bivariate cross-tabulations with Chi-Square tests.

**Result:** Overall association between HIV status and contraceptive method choice is consistent with expected patterns, with women who are HIV-positive being more than twice as likely to use condoms rather than hormonal contraceptives, compared to their counterparts of similar characteristics who are HIV-negative ( $p < 0.05$ ). Among women infected with HIV, those who were previously tested for HIV were more likely to use condoms and less likely to use hormonal methods ( $p < 0.05$ ) than those who had never been tested. The higher use of condoms by HIV-positive women is only evident among those who had previously been tested for HIV. Significant correlates of contraceptive method choice among HIV-positive women include parity, marital status, age group, education and ethnicity. Overall trends suggest a notable shift from use of hormonal methods to condoms by HIV-positive women, but predominant use of hormonal methods (60%) and low use of condoms (23%) by HIV-positive young women aged 15-24 practising family planning is of potential concern.

**Conclusion:** The findings have important implications for family planning policies/programs targeting young women living with HIV and underscore the need to intensify efforts towards improved HIV testing coverage to enable HIV-positive women make informed reproductive choices.

**KEYWORDS:** HIV-positive women; Contraceptive method choice; Demographic and socio-economic correlates; Multinomial regression analysis; Demographic and health survey; Kenya.

### INTRODUCTION

Kenya has a generalized HIV epidemic, driven primarily by hetero sexual transmission. According to recent estimates, national HIV prevalence among adults aged 15-64 years was 5.6% in 2012, translating to an estimated 1.2 million adults living with HIV.<sup>1</sup> Women are

disproportionately affected (prevalence of 6.9% for females *versus* 4.4% for males in 2012) and wide regional variations exist in the country. Despite a recent overall national decline in HIV prevalence among adults aged 15-64 in Kenya from 7.2% in 2007 to 5.6% in 2012, the prevalence in the worst affected region of Nyanza Province remained unchanged at about 15% during the same period.<sup>1</sup> Prevailing trends for women of reproductive age (aged 15-49 years) mirror these national patterns—the prevalence declined from around 9% in 2003 to 7% in 2012, but remained unchanged at about 18% in the highest prevalence region of Nyanza province. An earlier study revealed unique reproductive experiences of women in the highest HIV prevalence setting of Nyanza province,<sup>2</sup> suggesting an intricate link between HIV and reproductive behaviour. Notwithstanding impressive strides in HIV testing and treatment coverage in the country during recent years,<sup>3</sup> the number of people living with HIV has remained high. It has been noted that as Kenya's HIV epidemic continues to evolve, there is need for continued evidence-based action to respond to emerging challenges,<sup>4</sup> which include addressing the reproductive needs of the large number of women living with HIV.

HIV-positive women have special family planning needs. Of particular concern is the apparent greater risk of unintended pregnancy among HIV-positive than HIV-negative women<sup>5,6</sup> which may be attributable to overall lower uptake of contraceptives<sup>7</sup> or use of less effective methods<sup>5</sup> by HIV-positive women. These patterns have implications for overall maternal and child health in settings of high HIV prevalence such as sub-Saharan Africa (SSA), including vertical transmission of HIV from mother to child. Furthermore, the apparent link of some hormonal contraceptives, especially injectables, to increased HIV transmission<sup>8,9</sup> has important implications for contraceptive method choice in high HIV prevalence SSA settings with wide spread use and rising popularity of injectables.

It is important to improve understanding of the extent to which HIV-positive women are using suitable family planning (FP) methods, consistent with their reproductive goals and desires. It has been noted that the risks of unprotected sex, sexually transmitted infections, infertility and unintended pregnancy are inextricably linked,<sup>10</sup> making the issue of using appropriate methods of protection a critical one. Condom use has been recognized as the mainstay of dual protection of HIV infection and unintended pregnancy,<sup>11</sup> but acceptability remains low in most settings of sub-Saharan Africa (SSA), especially in long-term relationships.<sup>12</sup> Furthermore, inconsistent condom use has been noted as a major cause of concern, leading to unplanned pregnancies among women living with HIV.<sup>5</sup>

Although all the available reversible methods of contraception can generally be used by women at risk of HIV infection and by HIV infected women, hormonal contraception, especially injectables, have been linked to increased risk of HIV infection and transmission.<sup>8,9,13</sup> Therefore, the increasing popularity and dominance of injectable contraceptives in most SSA

countries<sup>14-16</sup> have far-reaching repercussions for contraceptive method choice in settings of high HIV risk. Integrated services have been linked to increased use of condoms and reduced use of other modern contraceptives.<sup>17</sup> A better understanding of the link between HIV/AIDS and contraceptive method choice in settings adversely affected by HIV/AIDS will help inform effective integration of HIV/AIDS and FP services.

This paper focuses on the association between HIV/AIDS factors and contraceptive method choice among women currently using contraceptives in Kenya. An earlier qualitative study in a low contraceptive prevalence setting in Kenya had noted that for some HIV-positive women, their HIV status dictated their contraceptive decisions.<sup>18</sup> Besides HIV status, other HIV/AIDS-related factors, including: HIV risk perception, HIV/AIDS stigma, HIV/AIDS awareness and previous HIV testing are considered of interest as they may also influence individual's contraceptive choice. For instance, it is possible that in settings where most individuals do not know their HIV status, perceived HIV risk may be a more important determinant of contraceptive behaviour than actual HIV status. The specific objectives are to:

- (i) examine the effect of HIV/AIDS on contraceptive method choice among women in Kenya; and
- (ii) identify demographic and socio-economic correlates of contraceptive method choice among HIV-positive women using family planning.

## MATERIAL AND METHODS

### The Data

This study is based on secondary analysis of data from the Kenya Demographic and Health Surveys (KDHS) conducted in 2003 and 2008.<sup>16,19</sup> These two surveys included HIV testing for nationally-representative samples, providing a unique opportunity to anonymously link HIV test results to the full survey record at individual level. From an overall sample of 16,639 women of reproductive age (aged 15-49 years) included in the two surveys (8195 in 2003 and 8444 in 2008), a total of 9132 women (i.e survey respondents residing in every other household) were eligible for HIV testing. The protocol for HIV testing in the two KDHS surveys was as follows:

*'... all eligible women and men who were interviewed were asked to voluntarily provide some drops of blood for HIV testing. ...tested with a Vironostika Anti-HIV-1/2 Plus enzyme-linked immunosorbent assay (ELISA) test kit (DADE Behring HIV-1/2) for verification purposes. All positive samples and 5 percent of negative samples were then tested with a Murex HIV-1/2 Micro ELISA System. For quality assurance, all positive samples and a 10 percent random sample of the negative samples were retested at the KEMRI HIV laboratory using the same testing algorithm of both Vironostika and Murex Micro ELISA systems. Finally, 30 discrepant samples were tested by polymerase chain reaction (PCR) DNA at KEMRI laboratory'.<sup>16</sup>(pp. 9-10)*

Our study sample included all women tested for HIV who were using contraceptive methods at the time of the survey (27% in 2003 and 39% in 2008), making a total of 3190 respondents (for Objective i analysis). About eight percent of this sample was HIV-positive, representing a sample of 255 HIV-positive women (for Objective ii analysis). The comparative nature of DHS data allows for pooling of data across surveys to achieve sufficient samples and monitor trends. Pooling data across the two surveys is deemed necessary due to the limited size of HIV-positive sample of women using contraceptives in each of the two surveys.

Contraceptive method choice is the outcome variable of interest while HIV/AIDS-related factors (i.e. whether previously tested for HIV, HIV/AIDS awareness, HIV/AIDS stigma, HIV risk perception and sero-status) constitute the key explanatory variables. The study takes into consideration a number of other key explanatory variables, recognizing that the association between HIV/AIDS and contraceptive method choice is likely to be influenced by a range of background demographic and socio-economic moderating factors or confounders associated with both HIV/AIDS and contraceptive method choice. A summary description of study variables is presented in Table 1.

**METHODS OF ANALYSIS**

The analysis involved both descriptive bivariate analysis and multivariate modelling. Chi-Square tests were used to assess significance of bivariate associations in cross-tabulations, while multivariate analysis was based on multinomial logistic regression analysis of factors associated with contraceptive method choice. The response (dependent) variable in our analysis-contraceptive method choice – was classified into four mutually exclusive categories: hormonal method (pills and injectables), condoms, periodic abstinence, and other methods (mainly sterilization and other long-term methods). Although dual use of condoms with other contraceptives was considered of particular interest, this was not used as a distinct category because of very small numbers. Dual contraceptive methods, combining condoms with other methods were classified as ‘condoms’, since use of condoms was of particular interest.

Preliminary analysis assessed potential clustering of contraceptive method choice within communities or clusters, but there was no evidence of significant intra-cluster correlations. Hence, the analysis was based on single-level rather than multi-level models. The general equation for the multinomial logistic

VARIABLE	Description
<b>Dependent variable</b>	
Contraceptive method choice	Current contraceptive method used, classified as: hormonal (pill/injectable); condom; abstinence; and other. 'Other' comprised mainly sterilization and long-term methods.
<b>HIV/AIDS-related factors</b>	
HIV status	Binary variable, coded as 1=if respondent is HIV-positive; 0=negative.
Previously tested for HIV	Binary variable, coded as 1 if responded was previously tested for HIV; 0=has never been tested
Knows someone with or died of HIV/AIDS	Binary variable, coded as 1 if respondent knows someone with or who died of HIV/AIDS; and 0=otherwise.
HIV/AIDS comprehensive knowledge	A composite awareness index derived from a series of questions on misconceptions about HIV/AIDS, knowledge of how HIV is transmitted and ways to avoid infection. The resulting score classified into quintiles (1-4), with lowest awareness coded as 1.
HIV/AIDS Stigma	A composite index derived from a set of four DHS questions on HIV/AIDS stigma. The resulting score is classified as 0 for 'low' stigma or 1 for 'high' stigma.
Perceived risk of HIV/AIDS	Classified as: 0= no/low risk; or 1= moderate/high perceived risk
<b>Demographic and background socio-economic factors</b>	
Respondent's age	Three age-group categories: 15-24, 25-34 and 35+.
Respondent's parity	The total number of children ever born, classified into four categories: 0, 1-2, 3-4 and 5+
Respondent's marital status	Marital or union status at time of survey, classified as: never married, currently married (monogamous/polygamous), widowed, divorced/separated
Fertility intention	Future fertility intention, coded as 1 if respondent wants no more children; 0=otherwise
Recent sexual activity	Period since last sex, classified as: within one week, 1-4 weeks, 1-6 months; and more than 6 months
Respondent's education	Highest educational attainment classified into: no formal education; primary level, and secondary and above.
Household wealth index	DHS composite wealth index <sup>20</sup> based on household possessions and amenities, classified into quintiles: poorest, poorer, middle; richer and richest
Respondent's religion	Religious affiliation, classified into: Catholic, Protestant/other Christian, and Muslim and other
Respondent's ethnicity	Classified into four categories: Kikuyu, Luo, Luhya and other
Region of residence	Seven provinces: Central, Coast, Eastern/North Eastern, Nairobi, Nyanza, Rift Valley and Western
Urban/rural residence	Binary variable, coded as 1=urban or; 0=rural residence.

Table 1: A summary description of variables included in the study.

regression used in the analysis takes the form:

$$\text{Log} [\pi^{(s)}/\pi^{(r)}] = b^{(s)}_0 + b^{(s)}_1 X^{(s)}_1 + b^{(s)}_2 X^{(s)}_2 + \dots + b^{(s)}_k X^{(s)}_k;$$

S=2, 3, 4.

Where:

$\pi^{(s)}$  is the probability of using a particular contraceptive method (s);

$\pi^{(r)}$  is the probability of using reference-category contraceptive method - r=hormonal (1);

$b^{(s)}_0$  is the regression intercept/constant for contraceptive method (s);

$X^{(s)}_{1-k}$  are covariates for k explanatory variables for contraceptive method (s); and

$b^{(s)}_{1-k}$  are the associated usual regression parameter estimates.

The second part of the analysis focused on HIV-positive women (Objective ii) and examined factors associated with contraceptive method choice among HIV-positive women. Due to sample size limitations, this part of the analysis was confined to bivariate associations. It was necessary to merge some of the

categories of explanatory variables with relatively few HIV-positive women using contraceptives at the time of the survey to achieve sufficient samples for valid Chi-Square tests.

**RESULTS**

**Associations between HIV/AIDS and Contraceptive Method Choice**

The bivariate associations between HIV/AIDS-related factors and contraceptive method choice among current users are resented in Table 2.

Condom use is higher among HIV-positive women (30%) than those who were negative (20%), but hormonal contraceptives (pill and injectables) is the predominant method among both HIV-infected (42%) and uninfected (49%) women currently using contraceptives. Current users who were previously tested for HIV, had personal acquaintance with HIV/AIDS victims or had higher HIV/AIDS awareness are generally more likely to use hormonal contraceptives, but less likely to use pe-

HIV/AIDS factor	Method currently used (percent)				Cases
	Hormonal	condoms	abstain	other	
HIV sero status**					
- Negative	48.9	20.0	14.5	16.7	2935
- Positive	41.5	29.5	14.1	14.9	255
Previously tested for HIV***					
- No	44.6	19.4	18.2	17.8	1543
- Yes	51.7	22.0	10.9	15.4	1637
Knows someone who has or died of HIV/AIDS**					
- No	47.8	22.8	17.9	11.5	430
- Yes	48.5	20.4	13.8	17.3	2746
HIV/AIDS awareness***					
- Lowest	42.2	23.3	19.5	14.9	463
- Lower	47.9	18.7	16.4	16.9	877
- Higher	50.2	20.0	14.2	15.7	948
- Highest	50.1	22.0	10.1	17.9	902
HIV/AIDS Stigma*					
- Low	46.3	21.4	15.9	15.9	1519
- high	50.1	20.0	13.1	16.8	1671
Perceived HIV/AIDS risk***					
- Mod-high or has AIDS	46.4	24.8	13.6	15.1	1902
- No-low risk	51.3	14.1	15.7	18.9	1288
All	48.3	20.7	14.4	16.6	3190

\*Chi-Square p<0.05; \*\*p<0.01; \*\*\*p<0.001

**Table 2:** Contraceptive method choice among current users by HIV/AIDS-related factors.

riodic abstinence compared to counterparts who never tested, knew no one living with or died of HIV/AIDS, or had lower HIV/AIDS awareness. Those who perceive themselves to be at a moderate or high risk of HIV infection are more likely to use condoms (25%) than those who perceive themselves to be at no or low risk (14%).

Multivariate results based on multinomial regression analysis (Table 3) reveals independent associations between HIV/AIDS-related factors and contraceptive method choice, once background socio-economic and demographic factors are controlled for. The parameter estimates from multinomial Logistic regression are presented in the form of relative risk (RR)

factors, with 95% confidence intervals, to ease interpretation. A relative risk factor greater than 1.00 implies that the factor is associated with higher use of a particular contraceptive method than the reference category (i.e. hormonal method), while a value less than 1.00 implies lower use.

The results suggest that HIV status is a significant determinant of method choice, with HIV-positive women being more likely to use condoms or periodic abstinence rather than hormonal contraceptives (pills or injectables). Women who are HIV-positive are more than twice as likely to use condoms rather than hormonal contraceptives compared to their counterparts of similar characteristics who are HIV-negative (RR=2.41). There

Parameter (reference categories in brackets)	Condom		Periodic abstinence		Sterilization/other	
	RR (95% CI of RR)		RR (95% CI of RR)		RR (95% CI of RR)	
2008 survey (2003)	3.45 (2.29, 5.21)	*	0.91 (0.68, 1.21)		0.75 (0.58, 0.96)	*
HIV positive (negative)	2.41 (1.58, 3.67)	*	1.58 (1.02, 2.46)		1.17 (0.78, 1.77)	
Previously tested (no)	1.12 (0.84, 1.49)		0.71 (0.55, 0.91)		1.07 (0.85, 1.35)	*
HIV awareness (lowest)						
- lower	0.88 (0.58, 1.34)		0.78 (0.55, 1.11)		0.97 (0.68, 1.38)	
- higher	1.01 (0.66, 1.52)		0.87 (0.61, 1.24)		1.05 (0.73, 1.50)	
- highest	0.76 (0.50, 1.15)		0.60 (0.42, 0.87)		1.02 (0.72, 1.46)	*
Perceived HIV /AIDS mod-high risk (no-low)	1.02 (0.76, 1.35)		0.98 (0.77, 1.26)		0.96 (0.76, 1.20)	
Age group (15-24)						
- 25-34	1.23 (0.85, 1.77)		1.19 (0.83, 1.72)		2.22 (1.41, 3.48)	*
- 35+	2.58 (1.61, 4.16)	*	2.59 (1.66, 4.03)	*	5.30 (3.23, 8.69)	*
Parity (0)						
- 1-2	0.06 (0.03, 0.10)	*	0.13 (0.07, 0.24)	*	0.24 (0.10, 0.55)	*
- 3-4	0.02 (0.01, 0.05)	*	0.10 (0.05, 0.20)	*	0.23 (0.10, 0.56)	*
- 5+	0.02 (0.01, 0.04)	*	0.17 (0.08, 0.35)	*	0.34 (0.14, 0.85)	*
Education (none)						
- Primary	1.16 (0.51, 2.63)		1.44 (0.75, 2.76)		0.70 (0.41, 1.20)	
- Sec+	1.31 (0.56, 3.06)		1.64 (0.83, 3.23)		0.97 (0.55, 1.70)	
Wealth index (poorest)						
- Poorer	0.93 (0.54, 1.59)		0.91 (0.57, 1.45)		0.77 (0.48, 1.22)	
- Middle	0.68 (0.39, 1.18)		0.77 (0.48, 1.23)		0.66 (0.42, 1.05)	
- Richer	0.90 (0.52, 1.54)		0.77 (0.48, 1.22)		1.06 (0.68, 1.67)	
- Richest	0.72 (0.39, 1.34)		0.65 (0.37, 1.12)		0.99 (0.59, 1.66)	
Religion (Catholic)						
- Protestant	0.83 (0.62, 1.13)		0.83 (0.63, 1.08)		1.20 (0.93, 1.54)	
- Muslim/ Other	1.66 (0.97, 2.85)		1.52 (0.93, 2.50)		1.78 (1.07, 2.96)	*
Ethnic group (Kikuyu)						
- Luhya	2.23 (1.21, 4.45)	*	1.16 (0.65, 2.09)		0.49 (0.29, 0.83)	*
- Luo	4.42 (2.46, 8.30)	*	1.64 (0.91, 2.97)		0.60 (0.36, 1.02)	
- Other	2.19 (1.33, 3.60)	*	1.57 (1.03, 2.40)		0.74 (0.52, 1.07)	

Region (Central)				
- Nairobi	1.58 (0.83, 3.04)		1.10 (0.61, 1.98)	1.38 (0.85, 2.25)
- Coast	1.26 (0.63, 2.50)		0.87 (0.48, 1.58)	0.92 (0.54, 1.55)
- Eastern/North Eastern	0.92 (0.46, 1.83)		0.66 (0.38, 1.16)	0.61 (0.37, 1.00)
- Nyanza	1.27 (0.64, 2.54)		0.67 (0.37, 1.24)	1.58 (0.95, 2.62)
- R.Valley	1.82 (0.97, 3.42)		1.99 (1.22, 3.27)	* 1.18 (0.76, 1.82)
- Western	2.02 (0.93, 4.39)		0.72 (0.35, 1.45)	1.79 (0.98, 3.25)
Urban residence (rural)	1.08 (0.70, 1.66)		1.12 (0.75, 1.67)	0.88 (0.62, 1.25)
Want another child (no)	0.86 (0.64, 1.17)		1.64 (1.24, 2.16)	* 0.61 (0.46, 0.81)
Marital status				
- married-monogamous	0.15 (0.09, 0.26)	*	0.82 (0.46, 1.44)	1.98 (0.89, 4.42)
- married-polygamous	0.21 (0.11, 0.42)	*	0.54 (0.27, 1.09)	2.35 (1.00, 5.55)
- div./sep./widowed	0.54 (0.30, 0.95)	*	0.45 (0.22, 0.92)	* 1.45 (0.62, 3.43)
Last sexual activity (within one week)				
- within one month	1.21 (0.87, 1.70)		1.32 (0.98, 1.78)	1.37 (1.05, 1.78)
- 1-6 months	1.33 (0.87, 2.04)		1.67 (1.10, 2.52)	1.20 (0.79, 1.83)
- > 6 month	0.52 (0.28, 0.95)	*	1.52 (0.85, 2.72)	* 1.58 (0.92, 2.73)

\* - sig at 5% level ( $p < 0.05$ )

**Table 3:** HIV/AIDS and other determinants of contraceptive method choice.

is little evidence that the other HIV/AIDS factors relating to HIV/AIDS awareness, previous testing for HIV or HIV/AIDS risk perception have a significant association with choice of condoms or other contraceptive methods (i.e. sterilization and other) *versus* hormonal contraceptives. However, those with higher HIV/AIDS awareness (RR=0.60) or previously tested for HIV (RR=0.71) are less likely to use periodic abstinence *versus* hormonal methods, compared to their counterparts of similar characteristics who have lower HIV/AIDS awareness or never been previously tested for HIV.

The results show little evidence of significant variations in contraceptive method choice by background socio-economic factors controlled for in the analysis such as urban/rural residence, educational attainment or household wealth, once the effects of other important factors are controlled for. However, there is some evidence of method choice being affected by ethnicity, religion and region of residence. Women of all ethnic groups are significantly more likely to use condoms rather than hormonal contraceptives, compared to Kikuyu women of similar characteristics.

Although age and parity are expected to be positively correlated, they show opposite patterns on method choice. Higher parity is associated with lower use of condoms, periodic abstinence and sterilization/other methods *versus* hormonal contraceptives, while the opposite is the case for older age. Those who want more children in future are more likely to use periodic abstinence (RR=1.64) and less likely to use sterilization/other (RR=0.61) *versus* hormonal contraceptives. Those who are cur-

rently married are less likely to use condoms *versus* hormonal than never married women of similar characteristics (RR=0.15 for monogamous married; RR=0.21 for polygamous married). Also, the previously married (i.e. divorced/separated and widowed) are less likely to use condoms (RR=0.54) or abstinence (RR=0.45) than the never married counterparts of similar characteristics.

### Correlates of Contraceptive Method Choice among HIV-Positive Women

An examination of contraceptive method choice among HIV positive women by HIV/AIDS related factors (Table 4) provides no evidence of significant variations by HIV/AIDS knowledge or knowing someone who has died of or living with HIV. However, HIV risk perception in marginally significant ( $p < 0.1$ ), suggesting that those who perceived themselves to be at moderate or high risk of HIV infection were more likely to use condoms and less likely to use hormonal contraceptives than those who perceived themselves to be at no or low risk. More conclusive patterns were observed with respect to previous HIV testing, with HIV-positive women who were previously tested for HIV being more likely to use condoms and less likely to use hormonal contraceptives than those who have never been tested ( $p < 0.05$ ). The importance of previous HIV testing is further highlighted in Figure 1, comparing contraceptive method choice of HIV-positive and HIV-negative women by previous HIV testing.

Figure 1 reveals that there is no difference in method

HIV/AIDS factor	Method currently used (percent)				Cases
	Hormonal	condoms	abstain	other	
Previously tested for HIV*					
- No	46.0	19.0	16.0	19.0	107
- Yes	37.9	37.1	12.9	12.1	148
Knows someone who has or died of HIV/AIDS (ns)					
- No	45.9	27.0	16.2	10.8	37
- Yes	41.2	30.7	12.1	16.1	216
HIV/AIDS awareness(ns)					
- Lowest	30.6	36.1	22.2	11.1	35
- Lower	49.0	27.5	7.8	15.7	55
- Higher	40.3	30.6	15.3	13.9	76
- Highest	43.2	27.2	12.3	17.3	89
Perceived HIV/AIDS risk (†)					
- Mod-high or has AIDS	37.2	34.6	14.7	13.5	157
- No-low risk	49.4	20.0	12.9	17.6	98
All	41.5	29.5	14.1	14.9	255

\*Chi-Square  $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ ; †  $p < 0.10$ .

Table 4: Method choice among HIV-positive current users by HIV/AIDS-related factors.

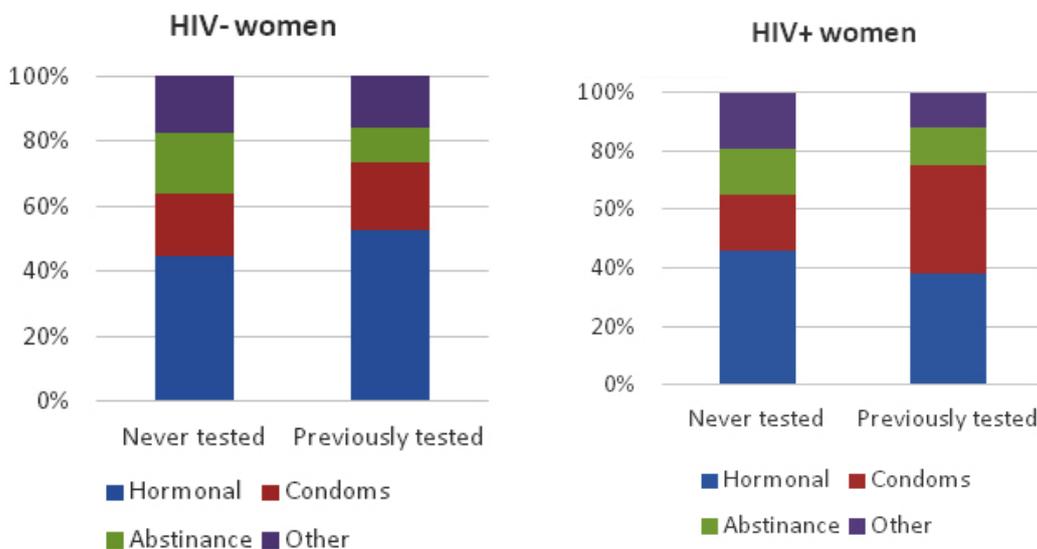


Figure 1: Comparing contraceptive method choice of HIV-positive and HIV-negative women by previous HIV testing.

choice between HIV-positive and HIV-negative women who never previously tested for HIV, but notably higher use of condoms (37% vs 19%) accompanied with lower use of hormonal methods (38% vs 46%) among HIV-positive than HIV-negative women previously tested for HIV. These patterns suggest that the observed higher use of condoms rather than hormonal contraceptives by HIV-positive compared to HIV-negative women (Tables 2 and 3) only applies to those previously tested for HIV. A further examination of contraceptive method choice among HIV-positive women by background characteristics (Table 5) reveal important patterns by a number of factors. Highly significant associations ( $p < 0.001$ ) are observed with respect to parity, marital status and year of survey, with condom use being notably higher than use of hormonal methods among those of parity

zero (90.5% condoms vs 9.5% hormonal), never married women (66.7% vs 23.3%) and in 2008 (40.9% vs 29.9%). Observed trends suggest a notable shift from use of hormonal methods to condoms by HIV-positive women. In 2003, a large majority of HIV-positive women using contraceptives were using hormonal methods (61%), with only a small minority (9%) using condoms. By 2008, these patterns had reversed, with condom use increasing from 9% to 41%, while use of hormonal methods declined from 61% to 30%.

Evidence of significant associations ( $p < 0.05$ ) are also observed with respect to age group, educational attainment and ethnic group. Higher use of condoms than hormonal methods is observed among women with at least secondary education (con-

Background characteristic	Contraceptive method currently used (%)				Unweighted Cases
	Hormonal	Condoms	Abstinence	Other	
Survey year ***					
- 2003	61.1	9.3	12.8	16.3	84
- 2008	29.9	40.9	14.9	14.3	171
Age group *					
- 15-24	60.0	22.5	15.0	2.5	41
- 25-34	41.2	33.3	9.6	15.8	118
- 35+	33.3	27.6	19.5	19.5	96
Parity ***					
- 0	9.5	90.5	0.0	0.0	22
- 1-2	48.1	28.6	11.7	11.7	80
- 3-4	52.0	22.7	12.0	13.3	83
- 5+	33.3	19.7	22.7	24.2	70
Education *					
- none / Primary	45.6	24.4	16.8	13.4	160
- Sec+	34.4	38.8	10.0	16.7	95
Wealth index (ns)					
- poorest / Poorer	32.6	30.2	14.0	23.3	47
- Middle	37.1	25.7	17.1	20.3	37
- Richer	41.7	31.7	13.3	13.3	60
- Richest	46.6	29.1	13.6	10.7	111
Religious affiliation (ns)					
- Catholic	41.5	33.8	7.7	16.9	72
- Protestant/Muslim/ Other	41.5	27.8	16.5	14.2	183
Ethnic group **					
- Kikuyu	40.0	22.5	10.0	27.5	46
- Luhya	25.0	28.1	21.9	25.0	38
- Luo	37.9	39.8	13.6	8.7	100
- Other	56.2	18.8	14.1	10.9	71
Region of residence (ns)					
- Nairobi	43.9	29.3	9.8	17.1	43
- Central	42.9	21.4	10.7	25.0	30
- Coast/ Eastern/N. Eastern	50.0	23.3	16.7	10.0	38
- Nyanza	36.7	40.5	12.7	10.1	84
- R.Valley	41.0	23.1	25.6	10.3	27
- Western	39.1	21.7	13.0	26.1	33
Residence					
- rural	36.6	31.4	16.3	15.7	143
- urban	50.0	26.1	10.2	13.6	112
Want another child †					
- no /later	39.6	31.5	10.7	18.1	159
- yes	44.6	26.1	19.6	9.8	96

Marital status ***					
- never married	23.3	66.7	6.7	3.3	34
- married	43.6	20.1	18.8	17.4	162
- div./sep./widowed	45.9	34.4	4.9	14.8	59
Last sexual activity					
- within one week	47.0	26.6	14.5	12.0	130
- within one month	37.1	30.6	16.1	16.1	60
- 1-12 months	34.4	34.4	11.5	19.7	65
Total	41.5	29.5	14.1	14.9	255

\*Chi-Square  $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ ; †  $p < 0.10$ .

**Table 5:** Contraceptive method choice among HIV-positive women by background characteristics.

doms -38%; hormonal -34%) and among the Luo ethnic group (condoms -40%; hormonal -38%). With respect to age group, contraceptive method choice among the youth is potentially of concern. A large majority of HIV-positive young women aged 15-24 using contraceptives are using hormonal methods (60%) while only 23% are using condoms.

## DISCUSSION AND CONCLUSIONS

The main objectives of the research reported in this paper were to: (i) examine the effect of HIV/AIDS on contraceptive method choice in Kenya; and (ii) Identify correlates of contraceptive method choice among HIV-positive women using contraceptives. The analysis of contraceptive method choice among current contraceptive users mainly aimed at ascertaining the extent to which HIV-positive women are using appropriate methods, commensurate with their reproductive goals and needs. Although dual use of condoms and other contraceptive methods would be of primary interest, inclusion of this classification was not possible, given the very small numbers using dual methods. Overall patterns of method choice are consistent with expected patterns, with women who are HIV-positive being more than twice as likely to use condoms rather than hormonal contraceptives compared to their counterparts who are HIV-negative. The observed higher use of condoms by HIV-positive women, especially those who know their HIV status, is consistent with findings elsewhere in Africa.<sup>17,21</sup> For example, Lopez et al<sup>17</sup> observed that HIV-positive women were more likely to discontinue their hormonal contraceptives, and more likely to use condoms.

Important demographic and socio-economic correlates of contraceptive method choice among HIV-positive women include parity, marital status, age group, education and ethnicity. Condom use is notably higher than use of hormonal methods among those of parity zero (condoms -90.5% vs hormonal -9.5%), never married women (66.7% vs 23.3%), those with at least secondary education (38% vs 34%) and among the Luo ethnic group (40% vs 38%). Overall prevailing trends in contraceptive method choice among HIV-positive women in Kenya which suggest a notable shift from use of hormonal methods to condoms, and the observed lower use of hormonal methods by HIV-positive compared to HIV-negative women are encouraging,

especially given the possible link of hormonal contraception to increased risk of HIV infection in previous research<sup>8,9,13</sup> and increasing popularity and dominance of injectable contraceptives in most SSA countries, including Kenya.<sup>14-16</sup> Recent research evidence has been inconclusive, calling for further research to establish safety of hormonal contraceptives for HIV-positive women.<sup>22,23</sup>

However, observed patterns also identify some sub-groups of HIV-positive women in Kenya for whom contraceptive method choice is potentially of concern. First, the fact that a large majority (60%) of HIV-positive young women aged 15-24 using contraceptives are using hormonal methods and only 23% using condoms suggests that contraceptive method choice among HIV-positive youth is potentially of concern. It raises an issue on the extent to which HIV-positive youth in Kenya are able to access suitable contraceptive methods, commensurate with their reproductive needs and desires. Although Condom use is recognized as one of the main strategies for combating the spread of HIV, promoting condom use among the youth in Kenya can be controversial, especially as some believe it encourages early sexual experimentation.<sup>16</sup> Nevertheless, our findings provide credence to an earlier recommendation on the need for particular attention to reproductive health information and services for HIV-positive adolescents.<sup>24</sup> Second, the relatively low condom use among sub-groups that are known to have particularly high HIV prevalence such as previously married women<sup>25</sup> is also of concern and warrants attention.

It is important to recognize that although use of condoms is recommended for HIV-positive individuals for prevention of HIV transmission, it is one of the least effective contraceptive methods. In a study in South Africa, Schwartz et al<sup>26</sup> observed that women who reported condom use were just as likely to have an unplanned pregnancy as women who reported using no contraception at all. Use of dual methods, combining condoms with other contraceptive methods, is preferred to improve contraceptive effectiveness.<sup>27</sup> However, dual method use in most sub-Saharan settings is low.<sup>21,28</sup> A recent study in Namibia, Kenya and Tanzania observed low dual method use and low use of highly effective contraception among people living with HIV for whom contraceptive protection was predominantly

through condom-only use.<sup>28</sup> Dual contraceptive use in Kenya is very low as some couples believe it is unnecessary.<sup>29</sup> Ralph et al<sup>9</sup> highlighted the need for future priorities to include expanding contraceptive choice and identifying effective ways of promoting use of dual methods. Besides condoms, use of other contraceptive methods, especially long-term methods, have been promoted for women living with HIV. For instance, Kimani et al<sup>6</sup> recommended greater use of long-term reversible contraceptives to reduce the risk of both vertical transmission of HIV as well as unintended pregnancy, while Siveregi et al<sup>7</sup> recommended promoting long-term permanent methods in family planning counselling for both HIV-positive and HIV-negative women to improve overall contraceptive uptake and reduce unintended pregnancies. Kimani et al<sup>6</sup> underscored the need to strengthen family planning services for women living with HIV to improve access to wide-ranging appropriate family planning services.

The observed patterns with respect to previous HIV testing underscore the importance of HIV testing in enabling HIV-positive women choose suitable contraceptive methods. The higher use of condoms and lower use of hormonal methods among HIV-positive than HIV-negative women previously tested for HIV, while there is no difference in method choice between HIV-positive and HIV-negative women who never previously tested for HIV, suggests that the observed higher use of condoms rather than hormonal contraceptives by HIV-positive women is only applicable to those previously tested for HIV. This is consistent with finding from a recent study of the effects of the HIV treatment on contraceptive choice in South Africa, where an increase in contraceptive use (especially condoms) across the cascade, from lowest level among HIV-positive women who did not know their status to highest levels among women who had been on HIV treatment for a long period of time was observed.<sup>27</sup> Similar findings have been observed in Malawi where women's knowledge of their HIV-positive status was found to be a significant predictor of their family planning practice.<sup>30</sup> Knowledge of HIV status is a prerequisite for appropriate action to address HIV-positive status. Despite a rising trend in HIV testing in Kenya and almost everyone previously tested having received their test results,<sup>16</sup> a significant proportion of women of reproductive age (e.g. more than 40% in 2008) has never been tested for HIV, highlighting the need to intensify efforts to improve coverage in HIV counselling and testing in the country to enable women make informed choices to achieve their reproductive needs and desires.

Finally, some key data limitations which may have potential implications on our interpretation of some of the study findings are worth noting. First, the KDHS data used in this study are based on a cross-sectional design which limits our ability to establish temporal ordering of events of interest. We recognize that HIV/AIDS factors and contraceptive behaviour are intrinsically linked and while in this paper our focus is on the role of HIV/AIDS-related factors in influencing contraceptive method choice, we recognize that contraceptive behaviour (especially condom use) may indeed influence the risk of HIV infection.

Therefore, we are unable to infer precise causal relationships from the patterns observed. It is important to recognize that the relationships observed provide evidence of simple associations rather than causal relationships. A second limitation relates to inadequate sample size which limits our statistical power to detect some important patterns in contraceptive method choice, especially among HIV-positive women. Even after pooling data across the two surveys, the sample of 255 HIV-positive women using contraceptives at the time of surveys is limited for meaningful multivariate analysis that would simultaneously take into consideration the effects of potential confounding factors in the relationships observed. Nevertheless, the bivariate associations provide useful patterns to enable identification of specific sub-groups that should be targeted by specific family planning and HIV/AIDS policies and programmes in Kenya and similar settings in SSA.

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## Short Communication

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# Natural Killer (NK) Cells and Human Immunodeficiency Virus (HIV) Infection

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### ABSTRACT

Human Immunodeficiency Virus (HIV) infection has become a serious problem of public health. Recently, it is observed cellular immunity is involved in HIV infection and disease progression, especially the Natural Killer (NK) cells, which are important part of innate immunity. In order to clearly understand the mechanism of HIV infection, we try to figure out the function of NK cells during HIV infection. The article reviews the function of NK cells and the effect of NK cells in HIV infection.

**KEYWORDS:** Natural Killer (NK); Human Immunodeficiency Virus (HIV) infection; Virus.

The human immunodeficiency virus (HIV) directly targets and devastates the host's immune system, leading to serious infection. Recently, research found innate immunity played very important role in the host's response against viruses, and increasing data indicate that innate immune responses play a key role in the development of effective vaccine-induced immune responses. In particular, Natural Killer (NK) cells represent important early effector cells of the antiviral innate immune defense, which was discovered from 1975 by Herberman.<sup>1</sup> NK cells, which account for up to 15% of Peripheral Blood Lymphocytes (PBL), are classified into three subsets, CD3<sup>neg</sup>CD16<sup>pos</sup>CD56<sup>dim</sup>, which is composed of 80%~90% NK cells; CD3<sup>neg</sup>CD56<sup>bright</sup>, which is composed of 2~10% NK cells; and CD3<sup>neg</sup>CD16<sup>pos</sup>CD56<sup>neg</sup>, which is composed of 5~10% NK cells.<sup>2</sup> NK cells can lyse virally infected cells without prior sensitization and participate in the regulation of innate and adaptive immune responses. The ability of NK cells mediating protection against viral infection depends on the relative abundance of each subset. Data from our laboratory and others have demonstrated that the clinical progression of HIV is correlated with changes in the distribution of NK cell sub-populations, namely a decrease in CD16<sup>pos</sup>CD56<sup>dim</sup> subsets and an increase in CD16<sup>pos</sup>CD56<sup>neg</sup> subsets.

The effects of NK subsets rely on the composition of receptors on the NK cell surface, including inhibitory NK receptors (iNKR) and activating receptors.<sup>3</sup> These receptors recognize relative ligands of target cells, and induce activating or inhibitory signal. During infections, the binding of NK cell receptors to ligands on the target cell can cause it to overcome inhibitory signals and become activated, culminating in the killing of the target cell. NK cells can be activated by the binding of its receptors (such as CD16) to the Fc portion of antibodies attached to the surface of target cells. We also found increased expression of the activating receptor NKG2C, NKG2C and inhibitory receptor NKG2A in patients with deteriorating clinical status. The ratio of NKG2A to NKG2C receptors decreased with advanced clinical progression of disease. Therefore, increased activation of NK cells (through modulated expression of NKG2A compared to NKG2C) may be a marker for identifying the clinical course of HIV-1 infection. Epidemiological studies have shown that particular NK Killer cell immunoglobulin-like receptor (KIR) genes expressed in conjunction with their HLA ligands are associated with significantly slower HIV-1 disease progression and lower viral set-point.<sup>4,5</sup> NK cells expressing protective KIR genotypes are associated with protection from infection, can significantly inhibit HIV-1 replication *in vitro*.<sup>6-9</sup> We observed the inhibitory killer immunoglobulin-like receptor CD158a (KIR2DL1) to be up-regulated in HIV-positive individuals.<sup>6</sup>

More recently, scientists showed that NK cells are involved in several other pathways to combat HIV infection, such as through secreting degranulated perforin and granzyme B to kill target cells; the Fas-FasL pathway to induce lysis of infected cells; production of cytokines to regulate immunity; and antibody-dependent cell-mediated cytotoxicity (ADCC) to lysis infected cells.<sup>6</sup> NK cells could kill target cells and inhibit HIV-1 replication, at least partly due to antibody-dependent cell-mediated cytotoxicity (ADCC). The mechanism of ADCC against HIV-infected cells is: Fc receptor-positive effector cells bind to gp120 or gp41-expressing HIV-infected target cells *via* gp120 or gp41 specific antibodies of certain Immunoglobulin G (IgG) isotypes and mediate their killing. NK cell is the important effector cell inducing ADCC. However, the roles of NK cells against infection are still under debate, and mechanisms are needed intensive research. Consistent with some other studies, our study also showed that ADCC responses were associated with slower progression of HIV infection. In addition, NK cells are protective against HIV disease progression through combinations of killer cell immunoglobulin-like receptors (KIR) and specific human leucocyte antigen class I (HLA-1) ligands; the studies have shown that particular HLA alleles appear to be associated with stemming the progression of HIV-1 infection.<sup>10</sup> We also demonstrated that ADCC responses are associated negatively with the clinical progression of HIV-1 infection and correlated positively with infected time and specific HLA alleles (HLA-A\*30/B\*13/Cw\*06) in long-term survivors in a uniformly infected cohort.<sup>6</sup> Taken together, these studies suggest that NK cells might play an important role in controlling HIV-1 replication, and that the virus can evade NK cell mediated immune pressure by selecting for sequence polymorphisms in areas targeted by KIR<sup>+</sup> NK cells.

This review briefly summarized the function of NK cells immunity against HIV infection and disease progression, which may provide helpful data into understanding of HIV-1 pathogenesis and immune mechanisms, facilitating anti-virus drugs development and vaccine evaluation.

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## Opinion

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# Test and Start for People Living With HIV and Who Use Drugs in Low and Middle Income Countries

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**ABSTRACT**

“Test and Start” implements the World Health Organization (WHO) recommendation of “treat all” by providing anti-retroviral treatment to persons newly diagnosed with HIV infection, at the time of their diagnosis. This HIV treatment algorithm is derived from recent international clinical trials and the recent international HIV treatment guidelines by WHO, recommending all people living with HIV be provided anti-retroviral treatment. This “treat all” recommendation removes any and all limitations for receiving anti-retroviral treatment for all people living with HIV, including people who use drugs. However, there are a limited number of “Test and Start” programs that have focused on the barriers to anti-retroviral treatment for people who use drugs. With an increasing number of low and middle income countries developing guidance for “Test and Start” programs, this articles identified four elements that support access to and successful initiation of the early initiation of anti-retroviral treatment for people living with HIV, who use drugs. The elemental services are: outreach with social services, screening for and management of substance use disorders, comprehensive primary care and differentiated care in anti-retroviral treatment. Together these services can provide a supportive foundation for “Test and Start” programs for people living with HIV, who use drugs.

**KEYWORDS:** ART for all; Drug use; Substance use disorder treatment; HIV infection; Alcohol use; Test and Start.

**WHEN TO START ANTIRETROVIRAL TREATMENT AND INTERNATIONAL TREATMENT GUIDELINES**

Clinical trials and studies assessing the efficacy and uptake of antiretroviral treatment have formed the basis for both international and national HIV treatment guidelines on the use of drugs for treating and preventing HIV infection.<sup>1-4</sup> The most recent international treatment guidelines by the WHO recommend, for the first time, that all people living with HIV be provided anti-retroviral treatment.<sup>1</sup> This “treat all” recommendation removes any and all limitations for receiving anti-retroviral treatment for all people living with HIV, including people who use drugs. Past treatment guidelines on when to start anti-retroviral treatment, relied on findings from early clinical trials of treatment naive people living with HIV, by comparing the initiation of anti-retroviral treatment during chronic infection at CD4 levels at or between 200-350 cells/mm<sup>3</sup>.<sup>4,5</sup> The findings of these studies showed a statistically significant reduction in death when starting anti-retroviral treatment at higher CD4 counts. There was also a reduction of the risk of death and co-morbidities, such as tuberculosis, when starting anti-retroviral treatment at times earlier in infection at higher CD4 counts. Studies also showed that starting anti-retroviral

treatment at the initiation of care at higher CD4 counts, rather than deferring to start at a CD4 count of 250 cells/mm<sup>3</sup>, reduced the risk of disease progression. Based on these findings, the CD4 threshold to start anti-retroviral treatment in most national guidelines was raised to 350 cells/mm<sup>3</sup> by 2012 and later 500/mm<sup>3</sup> around 2009-2013.<sup>4,6,7</sup>

International guidelines have gone further and recommended treating all HIV-infected adults regardless of their CD4 count.<sup>1</sup> This most recent step has been justified by the results of three clinical trials, HPTN 052, Temprano ANRS 12136 and START. The HPTN 052 study was a Phase III randomized clinical trial at 13 international sites that evaluated both whether antiretroviral treatment can prevent the sexual transmission of HIV in serodiscordant couples, as well as, the optimal time to begin anti-retroviral therapy in order to reduce illness and death among people living with HIV. The study showed that starting anti-retroviral therapy early reduced HIV transmission by 93% over the course of the entire study.<sup>8</sup> The TEMPRANOANRS 12136 study showed, with a 2×2 factorial design of four treatment strategies, patients who started early anti-retroviral treatment with CD4 counts of ≤800 cells/mm<sup>3</sup> in a resource limited setting had a substantially lower risk of death and HIV related disease or co-morbidities, such as tuberculosis.<sup>9</sup> The Strategic Timing of Antiretroviral Treatment (START) study was a global clinical trial in six geographic regions that randomized patients with CD4 counts of >500 cells/mm<sup>3</sup> to either immediate or delayed initiation of anti-retroviral treatment. The immediate treatment groups showed a greater than 50% decrease in death or AIDS related event/co-infection compared to the delayed treatment group.<sup>10</sup> Taken together, these hallmark studies recruited over 8,000 patients in 37 countries and showed a roughly 50% reduction in severe morbidity in the early treatment groups. The trials outcomes were comparable and complementary in demonstrating that earlier initiation of treatment with anti-retroviral treatment is most beneficial to promote excellent clinical outcomes, i.e. reduced morbidity and co-infections, as well as, promoting retention in long term care. As a result of the latter trial, the “treat all” recommendation is now commonly called “Test and START”, an approach that begins the initiation of anti-retroviral treatment immediately after a diagnosis of HIV infection in an effort to improve health outcomes for people living with HIV.<sup>11</sup>

#### PEOPLE WHO USE DRUGS, LIVING WITH HIV AND ANTI-RETROVIRAL TREATMENT

People who use drugs are at high risk for HIV infection and are frequently disengaged from the healthcare system, thereby limiting their access to HIV services.<sup>12</sup> Screening for drug use, including alcohol consumption, is an important recommendation in international guidelines to promote the management of clinical issues that are barriers to HIV diagnosis and treatment.<sup>13</sup> Screening people living with HIV, who use drugs and inject illicit drugs, allows health care providers to address harmful alcohol use and stimulant use which can enhance the risk of sexual transmission of HIV or injection risk of HIV transmission, through injection opioid use and stimulant injection of amphetamine-type

stimulants.<sup>14-17</sup> Thus, alcohol, opioid and stimulant-use disorders are important co-morbidities for people living with HIV in the era of “treat all” as part of the medical management of HIV infection.<sup>17-22</sup> However, substance use disorders are not routinely screened for in HIV care settings although highly prevalent in people who use drugs and seeking care. Opioid use disorders, in particular, are recognized as a significant HIV risk factor for people who inject drugs and has been shown to be the largest contributor to disability-adjusted life years (DALYs) for people living with HIV who use drugs.<sup>16,17,23-25</sup>

Addressing substance use disorders are fundamental components of personal health and well-being as defined by the WHO.<sup>26</sup> Substance use disorders can be addressed in a health care setting with interventions, such as screening and brief interventions with recovery management to reduce harmful use, as well as, by therapies such as cognitive-behavioral therapy (CBT)/ Motivational Enhancement Therapy (MET), or through pharmacotherapy and medical management.<sup>27-32</sup> For people living with HIV with opioid dependence, treatment with Medication Assisted Treatment (MAT) in HIV primary care improves the HIV-related outcomes of mortality, quality of life, retention in care, and anti-retroviral treatment adherence.<sup>33</sup> WHO notes that substance-use disorders are highly prevalent, globally, and burdensome to society; but the gap between providing needed treatment and that which is locally available to reduce the burden of disease remains very wide.<sup>34</sup> WHO guidelines underscore the importance of HIV care settings that can provide the opportunity to screen for and manage common substance-use disorders through a range of care and treatment options that include counseling and pharmacotherapy (MAT). The guidelines additionally urge that these services are part of national HIV/AIDS programs and integrated into primary care programs for people living with HIV.<sup>23,34</sup> Implementation and integration of HIV primary care to address substance-use disorders, including screening, diagnosis and treatment of substance use disorders, particularly the use of MAT for opioid dependence, can substantially impact public health and the HIV epidemic.<sup>35,36</sup>

People who use drugs face barriers to accessing anti-retroviral treatment for HIV infection resulting in not only less receipt of anti-retroviral treatment but also poorer clinical outcomes when provided anti-retroviral treatment late in care.<sup>37-39</sup> For people who inject drugs, access to anti-retroviral treatment is very low with only one in three reported to receive treatment.<sup>38</sup> For those being released from incarceration back into the community, only one in ten may be receiving anti-retroviral treatment.<sup>40</sup> However, the integration of substance abuse treatment and HIV primary care can enhance the access to anti-retroviral treatment for people who use drugs, as well as, enhance the efficacy of anti-retroviral treatment for people who inject drugs.<sup>41,42</sup> Medication assisted treatment has been shown to increase recruitment in anti-retroviral treatment programs, increase treatment coverage, increase retention in care and adherence to anti-retroviral treatment regimens and increase viral suppression.<sup>42</sup> Together, medication assisted treatment and anti-retroviral treatment have been shown to reduce all

cause mortality for people living with HIV who inject drugs.<sup>43</sup> When integrated into incarceration settings, medicated assisted treatment and anti-retroviral treatment improves HIV treatment outcomes for those being released into the community, can provide a bridge to community-based services post release, and promote better clinical outcomes during the post release period.<sup>44-46</sup>

#### TEST AND START FOR PEOPLE WHO USE DRUGS

Test and Start implements the WHO recommendation of “treat all” by providing anti-retroviral treatment to person newly diagnosed with HIV infection, at the time of their diagnosis. HIV policy watch reports that globally nine countries recommend the “Test and Start” strategy while a lower number of low and middle income countries, including Thailand, Malawi and Botswana, have a national policy that recommends anti-retroviral viral treatment regardless of CD4 count, including key populations.<sup>47</sup> Most recently, Tanzania has been added to the growing list.<sup>48</sup> This policy is important for people who use drugs since studies have shown that key populations, people who inject drugs, sex workers, men having sex with men, transgendered people and prisoners, are at high-risk for use and abuse of illicit drugs and alcohol and HIV infection.<sup>49</sup> A national policy supportive of “Test and Start” is an important first step in the implementation of “Test and Start” national programs. What can then follow are initial projects for feasibility and the development of standard operating procedures. The landmark clinical trials could help with standard operating procedures.<sup>50-52</sup> However, a closer look at the clinical protocols show that for the HPTN 052 study a history of drug use was an exclusion criteria; for the TEMPRANO study only psychiatric illness, anxiety and depression, were addressed; and while the START trial included injection drug users, it only randomized 64 participants, 1.4% of the study enrollment. This limited enrollment precluded a sub-analysis of the people who used drugs in this study.<sup>10</sup> These study designs show both the challenges to recruiting people who use drugs into HIV clinical trials, as well as, the limited information that can be utilized from clinical trials in developing standards of practice for people living with HIV, who use drugs.<sup>53</sup>

However, the Present’s Emergency Plan for AIDS Relief Scientific Advisory Board has provided recommendations regarding “Test and Start” and women’s treatment programs have begun to implement “Test and Start”.<sup>54-56</sup> The recommendations support the implementation of “Test and Start” initially in high volume clinics in urban areas in concert with clinical protocols that prioritize the sickest patients, as well as, provide continued access and retention for those receiving anti-retroviral treatment. Other recommendations include the importance of health care worker training and education and a public health education program for people living with HIV, peer educators, community health workers and differentiated care as part of anti-retroviral treatment.<sup>54</sup> Patient education about the health benefits of early initiation of anti-retroviral treatment is important, with a pilot “Test and Start” program in Uganda showing that asymptomatic patients questioning the need for medication.<sup>55</sup> Health service barriers to receiving anti-retroviral treatment

should be reduced with community initiated differentiated anti-retroviral treatment at point of HIV testing/diagnostic sites with patient access to comprehensive care. Thus, people living with HIV are met with care and treatment based on where they are in the course of infection and with a full array of services to meet their needs. The recommendations also support evidence-based guidelines for rapid start of anti-retroviral treatment for persons with opportunistic infection, tuberculosis and those who are pregnant.<sup>54,56</sup> Clear approaches and management of comorbidities and non-communicable diseases, such as substance use disorders is necessary. In the Uganda program, harmful alcohol consumption was perceived to be a barrier to early anti-retroviral treatment due to poor adherence.<sup>55,57</sup> In a high resource setting, a “Test and Start” program has shown that patients who inject drugs are less likely to obtain viral suppression.<sup>58</sup> In a resource limited setting, barriers to early initiation of anti-retroviral treatment for people living with HIV who inject drugs were identified as delays in receiving testing and clinical test results, off-site HIV clinics (non-integrated services and sites), stigma, lack of knowledge of the benefits of early treatment, initiation of treatment only when feeling ill, and dysfunctional care and treatment setting due to limited staff turnover.<sup>59</sup> Thus, there is a clear need to manage substance use disorders and the barriers to early initiation of anti-retroviral treatment in “Test and Treat” programs for people living with HIV, who use drugs.

Treatment of substance use disorders, particularly opioid use disorders, as part of HIV primary care promotes good clinical outcomes.<sup>21,22,60</sup> Medication assisted treatment for opioid dependence increases access to anti-retroviral treatment, anti-retroviral coverage, adherence to anti-retroviral treatment and retention in care, viral suppression, reduces viral transmission and mortality.<sup>21,60</sup> Screening for and management of alcohol use disorders in HIV care or anti-retroviral clinics results in an increase medication adherence and retention in care and treatment, a reduction of HIV transmission and morbidity and mortality, as well as, enhanced quality of life.<sup>22</sup> Thus, incorporating screening for and management of substance use disorders in “Test and Start” programs that target people who use drugs would promote the attainment of good clinical outcomes. Screening for and management of substance use disorders in people who use drugs allows for the development of patient stability from which further treatment of comorbidities, such as HIV infection, can result with improved clinical outcomes. Thus, “Test and Start” for people who use drugs would benefit from screening and management of drug and alcohol use/dependence as an early step in initiation of services.

For people living with HIV, who use drugs, a “Test and Start” program with the following services support the needs of people who use drugs: outreach with social services, screening for and management of substance use disorders, comprehensive primary care and differentiated care in anti-retroviral treatment (Table 1). Peer based outreach is critical to meet people who use drugs where they are in the community.<sup>61-63</sup> These peer groups can comprise community counselling teams, who are people who use drugs in recovery, family members affected by drug use and health care staff. These groups have drug scene credibility, local

Element	Activities that "Support Test and Start"
Outreach with Social Services	peer education of people who use drugs, provision of HIV prevention interventions, social support; screening for drug use and brief interventions, point of care for HIV rapid testing; prevention of overdose mortality
Substance Use Disorder Treatment	screening for and management of substance use disorders, medication assisted treatment for opioid dependence and alcohol dependence, point of care for HIV rapid testing; recovery support
Comprehensive Primary Care	Patient centered screening and management of co-infections and co-morbidities, confirmatory HIV testing
Anti-Retroviral Treatment	Differentiated care and tailored anti-retroviral treatment that allows for an enabling environment for people who use drugs

Table 1: Elements of "Test and Start" for people who use drugs.

knowledge and connectivity, and a level of medical competence to perform screening and brief interventions to reduce harmful substance use. With basic training in addiction counselling these groups can organize self-help groups, recovery communities and provide an alternative to law enforcement.<sup>62</sup> These individuals can also act as peer navigators promoting access to screening for substance use disorders and entry into treatment for substance use disorders and primary care.<sup>64</sup> An enabling, non-discriminatory environment in primary care for people who use drugs can be enhanced utilizing peer and community-based health care workers.<sup>65</sup> Community based care delivery models that are patient-centered models of care can facilitate people living with HIV, who use drugs to access and be retained on anti-retroviral treatment, promote adherence to medications and improve survival rates.<sup>66,67</sup> Differentiated care in anti-retroviral treatment provides tailored care so that people who use drugs with suppressed viral load visit the HIV clinic less frequently and focus on their treatment for substance use disorders; HIV clinic staff then focus attention on people who use drugs with unsuppressed viral load and the barriers these individuals face to achieve adherence and good clinical HIV outcomes.<sup>68</sup> Together outreach with social services, screening for and management of substance use disorders, comprehensive primary differentiated care and anti-retroviral treatment comprise a package of services that can comprise a "Test and Start" program for people living with HIV, who use drugs.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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