Benefits, Risk, and Uncertainty: Preferences of Antiretroviral-Naïve African Americans for HIV Treatments

A. Brett Hauber, Ph.D.,1 Ateesha F. Mohamed, M.A.,1 Maria E. Watson, Ph.D.,2 F. Reed Johnson, Ph.D.,1 and Jaime E. Hernandez, M.D.2

Abstract

While African Americans in the United States are disproportionately affected by HIV, they are less likely to take antiretroviral therapies. Different first-line antiretroviral therapies are associated with short-term and long-term adverse event (AE) risks. We estimated the willingness of antiretroviral-naïve, HIV-positive African Americans to accept risks of acute AEs with known outcomes and long-term AEs with uncertain outcomes in exchange for virologic suppression. We estimated the relative importance of short-term and long-term AE risks. Two hundred thirty-five subjects were recruited through eight clinics in the United States. One hundred fifty-eight subjects met study inclusion criteria. One hundred fifty-three subjects completed a series of choice-format conjoint trade-off tasks. In each task, subjects were asked to choose between two hypothetical treatments with varying levels of virologic failure, risks of hypersensitivity reaction, decreases in bone mineral density (BMD), and renal impairment, and outcome uncertainty associated with the risks of decreased BMD and renal impairment. Attributes were expressed as probabilities of occurrence. We calculated the relative importance of each AE and the level of risk subjects would accept to reduce the risk of virologic failure. Subjects indicated that short-term AEs with relatively certain outcomes are preferred to long-term AEs with uncertain outcomes. Subjects were strongly averse to the risk of decreased BMD that could not be treated successfully or when the outcome was uncertain and to the risk of renal impairment that could not be treated successfully. Subjects were willing to accept increased risks of AEs in exchange for lower risk of virologic failure.

Introduction

An estimated one million Americans have been diagnosed with HIV/AIDS.1 Racial and ethnic minorities in the United States are disproportionately affected by the epidemic. African Americans constituted 49% of all new cases of HIV/AIDS in the United States in 2005.2 However, African Americans are less likely to take antiretroviral treatments (ARTs) and are less likely to participate in clinical trials for new ARTs.3

Adverse events (AEs) have been reported with all antiretroviral drugs. While some common adverse effects were identified during clinical trials, some less frequent toxicities and some long-term complications were not recognized until after a drug had been used in a larger population for a longer duration. Some acute or more common adverse events that were first seen during clinical trials have been well studied and characterized. In contrast, the outcomes associated with long-term toxicities remain uncertain. Now that life expectancy for people with HIV/AIDS has increased and people with HIV/AIDS are taking ARTs for longer periods of time, long-term AEs are of increasing concern.

Recommended first-line dual nucleoside reverse transcriptase inhibitor (NRTI) treatment for antiretroviral-naïve adults and adolescents include coformulated abacavir plus lamivudine (Epzicom™, GlaxoSmithKline, Research Triangle Park, NC) and coformulated tenofovir plus emtricitabine (Truvada®, Gilead Sciences, Foster City, CA).4 Both abacavir and tenofovir are associated with potentially serious AE risks. Abacavir is associated with serious and sometimes fatal hypersensitivity reactions.5 Abacavir hypersensitivity is an acute reaction with known consequences and can be managed.6

2GlaxoSmithKline, Research Triangle Park, North Carolina.
Tenoforv is associated with decreases in bone mineral density (BMD) and impaired renal function. Both decreased BMD and impaired renal function can go undetected if not properly monitored and both the timing and outcomes of these adverse events are uncertain a priori.

While earlier studies have looked at HIV patient preferences, none have explicitly looked at the effect of outcome uncertainty on preferences. Therefore, we estimated the willingness of HIV-positive African American subjects who have chosen not to start ART to accept risks of acute AEs with known outcomes and long-term AEs with uncertain outcomes in exchange for virologic suppression as well as the relative importance of short-term and long-term AE risks. Specifically, we evaluated these preferences using well-established stated-choice (SC) methods. Researchers have applied SC, a systematic method for eliciting individual preferences through a structured set of trade-offs, to health care decision-making to quantify the relative levels of importance that people assign to various treatment attributes when making treatment decisions. It is based on the premise that medical interventions are characterized by a set of beneficial and potentially harmful attributes and that the attractiveness of a particular intervention to patients (or providers or health-plan managers) is a function of these attributes. Because SC yields quantitative estimates of the rate at which subjects are willing to trade off different treatment attributes, these methods can be used to estimate the relative importance subjects place on different treatment attributes and to quantify the maximum acceptable risk (MAR) of AEs that subjects are willing to accept in exchange for various levels of treatment benefit.

Methods

Survey sample

Subjects were recruited through eight clinical sites in Pennsylvania, Illinois, Virginia, the District of Columbia, Maryland, and New York between October 2006 and February 2007. As an incentive to complete the survey, $25 gift cards were given to all subjects. All subjects were required to be United States residents at least 18 years of age, African American, HIV-positive, but ART-naïve, and able to read and understand English at the sixth-grade level. All subjects who participated in the study provided informed consent.

Survey

An SC survey instrument was developed to evaluate the importance of various treatment-related risks relative to ART efficacy. Treatment attributes included one measure of treatment efficacy (virologic failure), one measure of the risk of a short-term AE with a certain outcome (allergic reaction or hypersensitivity reaction [HSR]), two measures of the risks of long-term AEs with uncertain outcomes (decreased BMD and renal impairment), and one measure of outcome uncertainty associated with the two long-term AE risks (the degree to which the outcomes of decreased BMD or renal impairment could be treated successfully). In the survey, decreased BMD was described as bone damage and renal impairment was described as kidney damage. HSR and kidney damage are of particular importance in this population because African Americans appear to have a lower risk of HSR than other ethnic or racial groups. In addition, HIV-positive African Americans have a higher risk of kidney damage than HIV-negative African Americans and other ethnic or racial groups.

Table 1 lists the five treatment attributes and the levels associated with each choice-format question. Prior to the choice-format trade-off questions, the survey contained text describing each attribute. Attribute descriptions were developed using consultations with medical experts and input from potential subjects through focus groups and survey pretests. Attribute levels were chosen to encompass the range over which events might plausibly occur (based on published studies) and over which subjects will have preferences, even if the level is clinically implausible.

The levels for the risk of virologic failure within 1 year ranged from 7% to 21%. For the short-term AE (HSR), risk levels ranged from 0% to 12% for experiencing HSR in the first 6 weeks of treatment (this study did not consider HLA-B*5701 testing for risk of abacavir hypersensitivity). Testing reduces uncertainty around HSR risk and gives providers additional information to help guide treatment decisions. For bone damage and kidney damage (long-term AEs), risk levels ranged from 0% to 10% for experiencing the event within the next 5 years. Focus groups and pretests of the instrument confirmed that 5 years is a reasonable planning horizon for HIV subjects. The nature of HIV and its treatment are easily described in relation to a time horizon of several years.

Understanding and conceptualizing numerical probabilities often is cognitively challenging. Researchers have experimented with various graphical representations to assist subjects in understanding quantitative risks, but there is no general consensus about the most effective approach. We used methods evaluated in a previous study of effective risk-communication techniques that portray absolute risks using a risk grid in which each square of the grid represents one person. This method helps subjects visualize probabilities using shaded squares in a 100-square grid, where the shaded squares represent people who would experience the AE and...
the unshaded squares represent people who would avoid the AE.

In each choice task, subjects were asked to choose between two treatment options. Each treatment option was described according to the same attributes but the levels of these attributes were varied across options and across choice tasks. Subjects were told to assume that these were the only two choices available (Fig. 1). We used a variation of a commonly used algorithm to construct an experimental design resulting in 24 pairs of treatment options. The survey also collected demographic information (e.g., age, gender, education, and employment status) as well as the year in which each study subject learned he or she was HIV positive. The survey was approved by RTI International’s Office of Research Protection and Ethics.

Statistical analysis

We used multivariate, random-parameters, or mixed-logit regression to estimate the relative importance of each attribute. Random-parameters logit avoids potential estimation bias from unobserved preference heterogeneity in discrete-choice models by estimating a distribution of tastes for each preference parameter. Explanatory variables in the random-parameters logit model included the attribute levels listed in Table 1. All statistical analyses were conducted using Gauss version 7.0 (Aptech Systems, Inc., Black Diamond, WA).

Using the choice data, we estimated the relative importance of each attribute and MARs. MAR is defined as the maximum additional probability of experiencing an AE that subjects are, on average, willing to accept to obtain a given increase in treatment benefits (a decrease in the risk of virologic failure). We estimated MARs for HSR, bone damage, and kidney damage that correspond to a 1 percentage-point reduction in the risk of virologic failure. Details on the statistical methods used to estimate MAR are presented elsewhere.

In every SC survey, some subjects tend to focus on one attribute and always or almost always select the option with the better value of that single attribute. For example, a subject who has a strong aversion to kidney damage may almost always choose the treatment alternative that has the lowest level of kidney damage, regardless of how unattractive other attributes of that alternative might be. This pattern of responses indicates that subjects are unwilling to accept any trade-offs within the ranges offered in the survey.

At least two possible explanations can account for such dominated preferences. One explanation is that some subjects made their choices according to one attribute as a way of simplifying the trade-off task, thus providing little or no information about their actual preferences. Another explanation is that some subjects do have strong preferences for one attribute over the others; therefore, their responses are an accurate reflection of their preferences and the survey never offers a combination that is sufficiently attractive to induce them to trade away from the dominant attribute. These subjects presumably would make similar choices in selecting real treatment alternatives. While we can identify subjects with dominated preferences, we cannot determine what motive led to the observed pattern of responses. We defined subjects as having dominated preferences if they chose the alternative with the better levels of an attribute in at least 9 of the 10 choice tasks. These subjects were deleted from the final analysis because including subjects who dominate on a single attribute may potentially bias parameter estimates upward for the dominant attribute (We tested whether excluding subjects with dominated preferences had a statistically significant impact on the results of the study).
Of the 235 subjects recruited, 158 met the inclusion criteria for the study. Of these, 5 (3%) subjects did not answer any of the choice questions, which is a very low non-response rate. Four (2.6%) subjects had no variation in their answers to the ten choice questions; that is, they always selected the same answer in each question (either Medicine A or Medicine B). Two subjects (1.3%) dominated on kidney damage (including these 2 subjects increased the mean relative importance of kidney damage but the difference is not statistically significant compared with the results reported below). In total, the final model included responses from 147 subjects. Subject demographic characteristics are summarized in Table 2.

**Importance ratings**

Without considering the different possible outcomes associated with the long-term AEs, bone damage was the most important attribute, and virologic failure was the least important attribute in determining subjects’ preferred treatments. When considering the outcomes of the long-term AEs, bone damage that cannot be treated successfully was the most important attribute and bone damage that can be treated successfully was the least important (Fig. 2). Results indicate that subjects were not concerned about bone damage if it could be treated successfully. Subjects were only marginally concerned with kidney damage when it could be treated successfully or the outcome was uncertain. Subjects were strongly averse to the risk of bone damage when it could not be treated successfully \( (p < 0.01) \) or when the outcome was uncertain \( (p < 0.01) \) and to the risk of kidney damage when the problem could not be treated successfully \( (p < 0.01) \) therefore confirming the hypothesis that subjects had preferences over not only the level of risk, but the uncertainty of the outcome.

**Maximum acceptable risk**

The survey results revealed a willingness of subjects to trade off higher risks of AEs against the benefits of treatment (reduction in the risk of virologic failure). The MARs for HSR, kidney damage, and bone damage were calculated for a 1% point reduction in the risk of virologic failure (Fig. 3).
The MAR for HSR was higher than that for bone damage if the damage could not be treated successfully or if the outcome was uncertain indicating that subjects are willing to accept higher levels of HSR risk than bone damage risk if the bone damage cannot be treated successfully or if the outcome is uncertain (we did not estimate a MAR for bone damage that could be treated successfully because the estimated coefficient in the mixed-logit model was not statistically different from zero). Similarly, the MAR for HSR was higher than the MAR for kidney damage that could not be treated successfully or kidney damage with an uncertain outcome. When kidney damage could be successfully treated, the MAR was higher than that for HSR.

**Discussion**

HIV has been transformed from a rapidly progressing disease with low survival to a chronic condition with which patients can live for many years. People with HIV may be taking active treatment for several years and thus are exposed to both acute and long-term treatment-related risks. Acute AEs with well-known and relatively certain outcomes are fundamentally different from long-term AEs for which outcomes are uncertain and we expect that patients will view these two types of AEs differently. In this study, HIV-positive, ART-naïve African Americans indicated that they are willing to accept some level of risk in order to achieve the benefits of ART; however, the level of acceptable AE risk differs between short-term and long-term AEs and among long-term AEs with different levels of outcome uncertainty.

This is the first SC study of which we are aware that elicits treatment preferences specifically from the ART-naïve, African American, HIV-positive population. By eliciting preferences of this targeted subgroup of the HIV-positive population, we are able to understand how HIV treatment risks are perceived by this subpopulation. Understanding the HIV treatment preferences of this population may help physicians and policy makers understand why this group of patients is underrepresented among those patients being treated with ART. In addition, this is the first study to include AE outcome uncertainty in addition to AE risk. Including AE outcome uncertainty in this study allowed us to elicit preferences in a decision context that explicitly addresses the range of risk and uncertainty surrounding treatment choices.

The results of this study are best interpreted with several issues and qualifications in mind. First, when discussing MAR it is important to keep in mind that MAR estimates represent the maximum acceptable risk of a specific AE that subjects are willing to accept in exchange for a given level of benefits. Therefore, the interpretation of MAR is in part a function of the specified benefit. In this case, the benefit measure is a reduction in the risk of virologic failure—a surrogate marker for HIV disease. If we had chosen instead to specify the benefit of ART as a reduction in the likelihood of death or a specific opportunistic infection, the MAR estimate for each AE would be different; however, the relative importance rankings of the other attributes would remain unchanged.

While SC methods are widely used in health economics to elicit preferences and assess health-related quality of life, they have limitations. One inherent limitation is that SC trade off tasks ask subjects to evaluate hypothetical treatments. These trade offs are intended to simulate possible clinical decisions but do not have the same clinical, financial, and emotional consequences as actual decisions. Thus differences can arise between stated and actual choices. We have attempted to minimize such potential differences by offering alternatives that mimic real-world trade-offs as closely as possible. In addition, our subjects include ART-naïve individuals who would presumably make treatment decisions without prior experience with the outcomes included in this study.

Some health professionals are skeptical that people have sufficient understanding of efficacy and risk information to competently evaluate treatment alternatives. The survey instrument, which was reviewed by experienced clinicians, provided balanced information on treatment attributes, but some subjects might have had difficulty assimilating and applying the information provided. In particular, although we provided numeric and graphical representations of serious AE risks, numeracy skills in the general population are poorly developed. Subjects may have applied simplifying heuristics that are inconsistent with actual numeric magnitudes in comparing probabilities.

SC surveys often include attributes that describe disease outcomes and treatment features as certain outcomes. Rarely do studies describe attributes in probabilistic terms. Understanding and conceptualizing numerical probabilities often is cognitively challenging. In this study we included four risk grid quiz questions before the subjects answered the SC questions to test their understanding of the probabilities presented. Subjects performed well on these four questions with the percent of correct responses increasing from 74% on the first question to 89% on the fourth. Our risk-grid approach, which included both a numerical and graphical representation of absolute risk levels, is an appropriate method for including probabilistic attribute levels in SC surveys. Furthermore, the rates of trade-off nonresponse (3.2%) and dominance (1.3%) are low.

The AEs included in this study were chosen because they are potentially serious and are associated with the two first-line dual-NRTI regimens recommended for use in treatment-naïve adults and adolescents. In addition, these
AEs provide a clear contrast between short-term AEs with known consequences and long-term AEs, the outcomes of which are uncertain. However, there are other features of ART that are likely to influence treatment preferences including development of resistance, regimen convenience, and treatment-related sleep disturbance and sexual dysfunction. While the inclusion of any or all of these or other AEs may result in different estimates of relative importance among attributes, we believe it is unlikely that excluding these attributes influenced the relative impact of outcome uncertainty on the importance of the long-term AEs.

With so many ART options available, HIV providers are able to tailor treatment regimens to individual patients. In addition, physicians can evaluate the risks associated with different ART alternatives based on the characteristics of each patient. For example, because kidney disease is more common among African Americans, physicians may lean toward prescribing ART regimens that pose a lower risk of kidney damage in this population. In addition, HLA-B*5701 testing for risk of abacavir-related hypersensitivity reaction can identify patients for whom abacavir is not a viable treatment option. Despite advances in tailoring medicine to individual patients, assessments of AE risks by regulatory authorities, decision makers, and providers do not routinely account for the preferences of people for whom these drugs are prescribed. The results of this analysis indicate that, in addition to the growing number of tools physicians have available to help them choose the best treatment option for each patient, physicians should also consider individual risk preferences with regard to both short-term and long-term adverse events when discussing alternative ART options with their patients.

**Author Disclosure Statement**

This study was funded by GlaxoSmithKline, Research Triangle Park, North Carolina. The views expressed here do not necessarily reflect those of GlaxoSmithKline. As the supervisor for the study, A. Brett Hauber had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**References**


Address reprint requests to:
A. Brett Hauber
RTI Health Solutions
RTI International
200 Park Offices Drive
PO Box 12194
Research Triangle Park, NC 27709-2194
E-mail: abhauber@rti.org