Author's response to reviews

Title: HIV vaccine acceptability among high-risk drug users in Appalachia: A cross-sectional study

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Author's response to reviews: see over
We greatly appreciate the reviewers’ thorough review of our manuscript and believe that their suggestions led to substantial improvement of the manuscript. We provide a point-by-point response (in bold) to their suggestions below.

Reviewer: Peter A Newman

This is a clearly written manuscript focused on correlates of acceptability of a hypothetical HIV vaccine among drugs users located in Central Appalachia. As the authors indicate, this is an understudied population for HIV vaccine acceptability and one for which issues of acceptability and access might be expected to prove important. A few clarifications in the methods section would be helpful. Most importantly, the results need to be discussed and contextualized in light of past research on HIV vaccine acceptability; this would increase the usefulness of the study for the field.

Major Compulsory Revisions

How were the HIV vaccine characteristics tested identified? As previous studies have employed many of these, it would be helpful to so indicate.

We appreciate the reviewer bringing this omission to our attention. In fact, it was the Reviewer's research that informed the development of many of the measures used throughout the study. In response to the reviewer's suggestion, we have added a statement to the Vaccine Characteristics section that reads, "Participants were also asked about vaccine characteristics identified in previous research as factors that could affect acceptability (CITATIONS)...." We cite the review by Newman and Logie (2010), and Newman's articles in Vaccine (2010, vol 28; 2006, vol 24), and Health Services Research (2009).

Why were some characteristics that have been identified in previous research as correlated with HIV vaccine acceptability not included (e.g., side effects, duration of protection, route of administration, number of doses)? This should be noted as a further study limitation.

The reviewer makes an excellent point. Indeed, we overlooked two important vaccine-related characteristics (side effects and duration of protection) during questionnaire development that are potentially important to acceptability. We have now added this to our Limitations paragraph. Of note, we did include the other characteristics mentioned by the reviewer (route of administration and dosing) as well as those more rarely explored in quantitative research, including access to transportation, time to visit the clinic, and concerns about confidentiality. We mention these as well as dosing and route of administration in the paragraph in the Methods (e.g., Vaccine Characteristics), Table 3, the second paragraph under Attitudes.
toward HIV and HIV vaccination, and in Figure 1.

It would be helpful in the methods section to justify the different cut-offs used for dichotomization of the psychosocial attitudes included in the models of HIV vaccine acceptability.

A valid question. We used a consistent dichotomization approach across all Likert-style items. Each psychosocial question were dichotomized using an approach that we felt was most conceptually sound. Each question asked on a 4-point Likert scale used a forced choice method in which two values represented a positive response (e.g., agreement, likely, serious, sure) and two values represented a negative response (e.g., disagreement, unlikely, not serious, unsure). Each of these was dichotomized at the midpoint such that a value of 1 represented a positive response (e.g., strongly agree or agree) and 0 represented a negative response (e.g., strongly disagree or disagree). We dichotomized the variables because the skew in the response distribution (i.e. the most negative response was very rarely selected) made them difficult to treat as ordinal in the model. Moreover, the inclusion of the variables as ordinal in the model would have created too many variables in the model relative to our sample size (i.e. through the inclusion of an extra 3 dummy variables per one variable currently in the model).

Two psychosocial items were assessed not using a Likert scale. Experiential attitudes were assessed on three semantic differential scales, as has been done in previous research (e.g., Gagnon et al 2000). The semantic differential scales also used a forced choice design and were dichotomized using the same approach as was used for Likert items, such that 1 represented a positive response (e.g., relaxing, comforting, responsible) and 0 represented a negative response (e.g., stressful, frightening, irresponsible). We could not enter the variables separately into the model given the inter-item correlation. We also could not treat them as a scale, as composite variables representing sums and averages of these responses were very negatively skewed (i.e. peak in the response distribution corresponding with the most positive response options). Thus, we determined that the most conceptually defensible approach would be to classify respondents who gave a positive response on all three items as having positive experiential attitudes, as this coding represented the absence of negative experiential attitudes toward the vaccine.

Perceived barriers to vaccination were examined using a checklist style item (with an open-ended option) in which respondents selected/reported barriers that could affect their likelihood of accepting an HIV vaccine, or indicated that they had no barriers. We used this style item rather than embedding pre-selected barriers into Likert scale questions because we lacked formative research into what barriers may be most relevant in this population. We first attempted to create a scale score for each person by summing the number of barriers indicated. However, the distribution was
very negatively skewed and difficult to treat as ordinal in analysis (especially given that 5 dummy variables would have been created). More importantly, however, we did not examine the extent to which each factor would serve as a barrier and were not comfortable creating a variable in which a respondent who selected several barriers (all of which may present only minor difficulties) had a higher perceived barrier score than a respondent who selected only one barrier (although the barrier could have significant impeded their ability to get the vaccine).

In an effort to keep the manuscript concise, we have not included details of our rationale presented above in the manuscript text (though we certainly will if the editor deems it important). However, we did add information to the Demographic, Behavioral, and Psychosocial Measures section that explains that we dichotomized the 4-point scales due to skew and used the mid-point of the forced choice style response options as the cut-point.

In general, the authors cite a number of publications on HIV vaccine acceptability in their introduction, including a systematic review. However beyond merely using these to indicate the novelty of the population they are studying, it would help to constructively build on existing evidence from these studies and the systematic review to address and contextualize their own findings.

We appreciate the reviewer bringing this to our attention. We have greatly expanded the Discussion section and included 17 additional references to better contextualize our results, with detailed information about our gender finding (paragraphs 1 and 2, see response to comment below), comparison of our cost finding to those of previous studies (paragraph 3), discussion of previous studies’ findings on logistical constraints and confidentiality concerns (paragraph 4), and elaboration on the findings related to perceived social norms (paragraph 5). In the latter paragraph, we also cite our newly published research (in press, AIDS and Behavior) that specifically explored individuals' willingness to encourage their peers to receive the HIV vaccine. We believe these additions greatly improved the quality of the manuscript.

Several findings from this study are similar to correlates of HIV vaccine acceptability identified in previous research (including the systematic review) and these should be identified and differences discussed. As it stands, only 3 studies are referenced in the discussion, with no reference to the 9 studies of HIV vaccine acceptability (2-10) cited in the introduction.

[see response to suggestion above]

As one of the main correlates of HIV vaccine acceptability identified is gender, it would be helpful to discuss this in reference to a previous study that identified different attitudinal correlates of acceptability by gender (Kakinami et al., 2008).

This suggestion was very valuable and post-hoc analyses that we
conducted in response to this suggestion revealed interesting patterns in the data. In the first paragraph of the Discussion, we have added information about previous studies which have assessed gender as a correlate to HIV vaccine acceptability. We also describe the study by Kakinami et al, specifically mentioning that the study revealed gender differences in concerns about and motivations for vaccine acceptability, but that the study identified no statistically significant association between gender and vaccine acceptability. Most importantly, we conducted post-hoc analysis to determine if there were gender differences in any of the psychosocial constructs that may be contributing to the gender-difference in vaccine acceptability. Interestingly, we found that men were significantly more likely to perceive barriers to vaccination (specifically, cost, time to visit the clinic, and requirement for multiple doses). We have updated Figure 1 in response to these findings to demonstrate gender differences and to indicate their statistical significance (marked by a *). We explored sociodemographic reasons (e.g., income, employment) for these differences in perceived barriers may exist and highlight the finding’s relevance to future dissemination strategies. We elaborate in detail on these findings in our Discussion paragraphs 1 and 2.

This same study, as well as several others cited by the authors (e.g., 4,5), also identifies the same implication stated in the first paragraph of the discussion re: "a one-size-fits-all approach to HIV vaccine promotion", a statement that should be referenced. Indeed this is part of the benefit of conjoint analysis techniques, that they help to specifically target social marketing approaches.

We appreciate the review of our manuscript by an expert in the field who is intimately familiar with the HIV vaccine acceptability literature. We apologize for the oversight in citing the "one size fits all" phrase. We have now cited the publication by Newman et al (2004) in AIDS Patient Care and STDs. We have also mentioned the advantage of conjoint analysis (compared to our approach) and its ability to better inform social marketing (see Limitations paragraph).

Additionally, it might be helpful to speculate on why gender might have emerged as a significant correlate of acceptability in this study, but not in Kakinami or the previously published meta-analysis.

[See response to revision suggested above]

The authors identify some of the important study limitations. They should also note limitations of asking respondents about individual characteristics of a hypothetical product, such as an HIV vaccine, in contrast to previous research that has employed approaches such as conjoint analysis (e.g., 4,5) and discrete choice experiments (Cameron et al. 2013--see below). The latter have many advantages in that they may more accurately estimate acceptability; and in that
end users evaluate trade-offs among different features of hypothetical vaccines, which enable estimation of relative valuations of different characteristics, including in terms of their cost (willingness to pay).

The reviewer makes an important suggestion. We have added mention of this limitation in the second to last paragraph of the Discussion and, in doing so, have cited other studies that have used conjoint analysis and Cameron et al (2013) when referring to discrete choice experiments.

In the discussion, the authors' comparison to previous research in terms of the impact of out-of-pocket cost in the present sample, while an important point, neglects to address that some of these other studies report the impact of cost relative to other vaccine characteristics. Furthermore, the systematic review (2) clearly identifies vaccine cost subsidies as a key intervention to promote uptake; this too should be cited here. The meta-analysis (2) also identifies the association of pragmatic obstacles, vaccine attitudes and perceived risk with acceptability, which should be discussed in the context of the present findings on attitudinal and other correlates of acceptability.

In response to this and the reviewer’s previous suggestions, we have greatly expanded the discussion section. We have dedicated an entire paragraph (paragraph 3) to discussing our finding about out-of-pocket costs and willingness to pay. In the revised version, logistical, or pragmatic, obstacles are also discussed in detail (paragraph 4). In these revisions, we have added citations to several previous studies. We also discuss the issue of cost and pragmatic obstacles in our expanded discussion of the gender findings in paragraph 1 of the Discussion. We also report that, in some situations, other vaccine-related characteristics may have a larger impact on vaccine acceptability than cost: “...some research has suggested that cost may not be as strongly associated with acceptability as are other vaccine characteristics [Newman et al 2006]...”

Finally, a recent publication (see below), while the outcome is not HIV vaccine acceptability but endorsement of mandatory HIV vaccination policy, would be relevant to address in that it identifies significantly lower endorsement among people who inject drugs (as well as the role of perceived risk and vaccine attitudes). This in part supports the importance of the present study in identifying correlates of acceptability among PWID.

We very much appreciate the reviewer bringing this publication (Newman et al 2014, Prevention Science) to our attention. We were previously unaware of this recent study and upon reading the manuscript, agreed with the reviewer that it is highly relevant to our rationale for conducting the presented research. We now discuss this study in the first paragraph of our Introduction.

Minor Essential Revisions
The word feasibility is used in the title, but I don't recall it being defined or discussed in the manuscript; consider changing the title. Additionally, "United States" in the title should be changed to something more apropos of the specific population and/or geography studied.

We appreciate this suggestion. We have revised the title from "Feasibility of HIV vaccination among rural, high-risk drug users in the United States: A cross-sectional study" to "HIV vaccine acceptability among high-risk drug users in Appalachia: A cross-sectional study."

Reviewer: Michele Andrasik

Reviewer's report:

Please find below my review of the manuscript entitled, "Feasibility of HIV vaccination among rural, high-risk drug users in the United States: A cross-sectional survey.

Overall this is an excellent manuscript which is well written and provides important information on acceptability and potential uptake of a preventive HIV vaccine among rural, high-risk drug users. The methods, statistical analyses and results are clear and the results are an important contribution to the field.

Major Compulsory Revisions

My overall enthusiasm for the paper is dampened by one major oversight that impacts the utility of the results. Initial vaccines to reduce HIV acquisition are likely to demonstrate very modest levels of protective efficacy likely ranging between 30% and at best 50%. Nowhere in the manuscript is this discussed and all questions in the analysis are based on a 90% efficacy level. As this level of protection is extremely unlikely, the fact that such a high number of rural drug users were likely or very likely to accept a 90% effective, preventive HIV vaccine really doesn't tell us much. This is not even listed as a limitation in the discussion section.

The reviewer raises a very important question that certainly warrants further explanation. We considered the issue of efficacy carefully during questionnaire design and recognized that the specification of a specific efficacy level (low or high) would present limitations in interpretation and generalizability regardless of our choice. Nonetheless, we chose to specify a level (rather than refer to only a ‘HIV vaccine’) as we were concerned that a vaguely worded item would create undue variance in responses, as interpretation of the item (conceptualization of efficacy) would likely vary from respondent to respondent. Ideally, questions could be repeated across a range of efficacy-levels, but this approach was time-prohibitive in
the current study given the inclusion of an extensive battery of behavioral questions and given the need to conduct some of the interviews in jails. We now state our inability to assess a range of efficacy levels as a limitation in the Limitations paragraph of the Discussion. In the current study, a 90% efficacy level was chosen for three reasons, (1) it presented one of the ‘best case scenarios’ for evaluation of acceptability, (2) allowed for the examination of the underlying psychosocial constructs that affect attitudes toward the vaccine while controlling, in a sense, for the impact of efficacy, and (3) was expected to precipitate a conservative (i.e. near to a ‘worst case scenario’), estimate of risk compensation (the focus of additional manuscripts). As the reviewer notes, the initial HIV vaccines approved for use will likely have lower efficacy levels. However, specifying the ‘most realistic scenario’ for HIV vaccination remains difficult and is subject to change. The development of a high-efficacy HIV vaccine is the ‘holy grail’ of HIV vaccine research and we are optimistic that this goal will ultimately be realized. To ensure the long-term relevance of our research as vaccine development progresses, we felt that specifying a high efficacy level was important. Our rationale for selecting the 90% measure and the limitations it imposed are now described in the Limitations paragraph.
Feasibility of HIV vaccination-vaccine acceptability among rural, high-risk drug users in Appalachia the United States: A cross-sectional study

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ABSTRACT

Background: A vaccine could substantially impact the HIV epidemic, but inadequate uptake is a serious concern. Unfortunately, people who use drugs, particularly those residing in rural communities, have been underrepresented in previous research on HIV vaccine acceptability. This study examined HIV vaccine acceptability among high-risk drug users in a rural community in the United States.

Methods: Interviewer-administered questionnaires included questions about risk behavior and attitudes toward HIV vaccination from 433 HIV-negative drug users (76% with history of injection) enrolled in a cohort study in Central Appalachia. HIV vaccine acceptability was measured on a 4-point Likert scale. Generalized linear mixed models were used to determine correlates to self-report of being "very likely" to receive a 90% effective HIV vaccine (i.e. "maximum vaccine acceptability", or MVA). Adjusted odds ratios (AORs) and corresponding 95% confidence intervals (CIs) are reported.

Results: Most (91%) reported that they would accept a preventive HIV vaccine, but concerns about cost, dosing, transportation constraints, vaccine-induced seropositivity, and confidentiality were expressed. Cash incentives, oral-administration, and peer/partner encouragement were anticipated facilitators of uptake. In multivariate analysis, men were significantly less likely to report MVA (AOR: 0.33, CI: 0.21 – 0.52). MVA was more common among participants who believed that they were susceptible to HIV (AOR: 2.31, CI: 1.28 – 4.07), that an HIV vaccine would benefit them (AOR: 2.80, CI: 1.70 – 4.64), and who had positive experiential attitudes toward HIV vaccination (AOR: 1.85, CI: 1.08 – 3.17). MVA was also more common among
participants who believed that others would encourage them to get vaccinated and anticipated that their behavior would be influenced by others' encouragement (AOR: 1.81, 95% 1.09 – 3.01).

Conclusions: To our knowledge, this study was among the first to explore and provide evidence for feasibility of HIV vaccination in a rural, high-risk population in the United States. This study provides preliminary evidence that gender-specific targeting in vaccine promotion may be necessary to promoting vaccine uptake in this setting, particularly among men. The data also underscore the importance of addressing perceived risks and benefits, social norms, and logistical constraints in efforts to achieve widespread vaccine coverage in this high-risk population.

Keywords: HIV; vaccination; AIDS vaccines; HIV vaccines; attitude; drug users; psychological theory; rural health
Introduction

Since 1987, the scientific community has been in pursuit of an effective HIV vaccine [1]. In response to the possibility that an HIV vaccine is on the horizon, researchers have mobilized to examine the feasibility of disseminating the vaccine. In high-risk populations around the world, numerous studies on HIV vaccine acceptability have been conducted, but people who use drugs have been underrepresented. Recent research investigating attitudes toward compulsory HIV vaccination among high-risk individuals in Los Angeles found that people who inject drugs (PWID) were significantly less likely to endorse universal vaccination or vaccination of all children or adults compared to their non-injecting counterparts [2]. The authors point out that the strong opposition to compulsory vaccination policies among PWID may be indicate future challenges in HIV vaccine acceptance and dissemination [2], thus reinforcing the need for additional research. Of the 15 quantitative studies from the US included in a recent review [3], only three included drug users [4-6]; none of which reported results stratified by drug use. Qualitative studies on HIV vaccine acceptability are equally limited, as nearly all of those involving people who use drugs have been conducted in one setting (i.e. Los Angeles) [6-11]. There are no studies to date evaluating HIV vaccine acceptability in a high-risk, rural drug-using population in the US. National surveillance data indicate that while the prevalence of AIDS has gradually declined in most urban areas since the mid 1980's, the number of cases continues to slowly increase in many rural communities, particularly in the South [12, 13]. Given the historically low prevalence of HIV in rural areas and the common misconception that HIV is an "urban problem", many rural communities are unequipped to deal with the social, economic, and healthcare burden posed by an increase in HIV.
Central Appalachia, which encompasses some of the most economically distressed counties in the US [14], would face many of the challenges posed by an increase in HIV and AIDS. The Appalachian region is characterized by marked health disparities [15], an under-resourced health infrastructure [15], and prevalent misuse of prescription drugs [16-18]. While HIV prevalence is currently low in this population [19], recent evidence from Eastern Kentucky, in Central Appalachia, suggested that many nonmedical prescription drug users were infected with hepatitis C [20], had engaged in injection drug use (IDU) [21] and frequent unprotected sex [22], and were embedded in a highly cohesive and centralized risk network that could facilitate HIV transmission [23]. Given these risk factors, stigma surrounding HIV [24], and myriad cultural and socioeconomic complexities, Central Appalachia is a setting in which greater knowledge of potential barriers and facilitators to HIV vaccine acceptability will be essential in achieving adequate coverage. The purpose of this study was to examine demographic, behavioral, and psychosocial correlates to HIV vaccine acceptability among a sample of HIV negative, high-risk drug users in Central Appalachia.

Methods

Sample

The data used for this analysis were collected during the 24-month assessment of the longitudinal Social Networks among Appalachian People (SNAP) study. Recruitment and assessment are described in detail elsewhere [20, 23, 25]. To be eligible, participants were required to be age 18 or older, reside in Appalachian Kentucky, and to have used prescription opioids, heroin, crack/cocaine, or methamphetamine to get high in the prior 30 days. Participants (n=503) were recruited from rural Appalachian Kentucky using respondent-driven sampling and
data were collected using questionnaires administered by trained community-based staff. Participants completed follow-up interviews and HIV testing at 6-month intervals. The 24-month interview was completed by 435 participants between March 2012 and May 2013.

**Measures**

Following their 24-month interview, participants (n=433) were invited to complete an interviewer-administered questionnaire on their attitudes toward HIV vaccination (two who were interviewed in jail were not invited due to time-constraints). All invited participants consented and were compensated $35 for participation. Before the questionnaire, interviewers read a script reminding them that HIV can be transmitted through sharing drug equipment and having unprotected sex, that HIV is the cause of AIDS, and that there is currently no cure. The script informed participants that the vaccine referred to throughout the questionnaire would not cure HIV, but would prevent acquisition. A 90% efficacy level was specified for the questions presented in these analyses. The University's Institutional Review Board approved the protocol.

**HIV Vaccine Acceptability.** HIV vaccine acceptability was assessed with: “Imagine that an affordable HIV vaccine was approved and made available to you in the next 12 months. This vaccine would prevent you from getting HIV almost all of the time (90% effective). How likely would you be to get this vaccine?” followed by a 4-point Likert scale ranging from 'very unlikely' to 'very likely'. Due to skewness, the responses were dichotomized for analysis (0=Very unlikely/Unlikely/Likely; 1=Very likely). Given the debatable association between these intentions and actual behavior [26], this conservative dichotomization may provide a better indication of future uptake. Hereafter, those who were 'very likely' to accept the vaccine are referred to as reporting “maximum vaccine acceptability” (MVA).
Vaccine Characteristics. Participants were also asked about vaccine characteristics that identified in previous research as factors relevant to could affect acceptability [3, 5, 6, 27, 28]. Items assessed willingness to pay (continuous), minimum acceptable vaccine efficacy (ordinal in increments of 10%), and whether cash incentives, dosing (multiple vs. single), administration (oral vs. injected), and/or vaccine-induced positive results on future HIV tests would affect vaccine acceptability.

Demographic, Behavioral, and Psychosocial Measures. Basic demographic and behavioral data were also collected (listed in Table 2). The psychosocial measures were based on a modified version [29] of the Integrative Model (IM) [30], which posits that behavior is directly affected by intention. Intention is influenced by attitudes, perceived norms, and personal agency, which are in turn influenced by background factors (e.g., demographic, behavioral, and other contextual characteristics). Table 1 describes the items and coding scheme used to assess the following: attitudes (instrumental and experiential), subjective norms (descriptive and injunctive), and personal agency (perceived behavioral control and self-efficacy). Due to skew in the response distribution of the four-point Likert-scale and semantic differential scale measures, items were dichotomized at the mid-point of the ‘forced choice’ style response options such that a value of 1 indicated a positive response and a value of 0 indicated a negative response.

Experiential and instrumental attitudes refers to emotional and cognitive responses, respectively, to performing a behavior [31]. Experiential attitudes were examined with semantic differential scale items used in a similar study [32]. The instrumental attitude measures were adapted from the Health Belief Model [33]; these include perceived severity of and susceptibility to HIV, and perceived benefits of and barriers to HIV vaccination.
Injunctive norms are a person's beliefs about and motivation to comply with what others think he/she should do. Descriptive norms refer to a person's perceptions about others' behavior and his/her motivation to comply with (i.e. imitate) their actions [34, 35]. Descriptive and injunctive norms are each comprised of two sub-constructs: normative beliefs and motivation to comply. Self-efficacy and perceived behavioral control were also examined. Self-efficacy is the belief in one's general capabilities to exercise control over his/her behavior [36], while perceived behavioral control focuses on one's abilities to perform a behavior in light of various barriers [37].

Statistical Analyses

Given potential autocorrelation among responses, generalized linear mixed models were used. Models were estimated using the PROC GLIMMIX [38] procedure (SAS software, version 9.3) with a random effect for subject and Laplace approximation [39]. To adjust for potential biases presented by respondent-driven sampling [40, 41], individualized weights computed in RDSAT 7.1 (Ithaca, NY) [42] were used in all analyses. The weights were based on individual network size and partition analysis on the dependent variable using enhanced data smoothing and 25,000 bootstrap iterations. Odds ratios (ORs), adjusted odds ratios (AORs), and 95% confidence intervals (CIs) were reported. Each demographic and behavioral variable was assessed independently for its association with the outcome, and those reaching significance (p<0.05) were entered into multivariate analyses. Due to the a priori nature of the IM, all psychosocial variables were entered into multivariate analyses regardless of bivariate significance, as suggested in previous research [43].

Results
Descriptive demographic and behavioral data are presented in Table 2. Briefly, the median age was 34 years (range: 21–68), 55% were male, and most respondents were White (94%); the latter is reflective of the demographic profile of Central Appalachia [44]. Most (76%) reported a lifetime history of IDU and 34% reported recent IDU (past 6 months). Receptive and distributive needle sharing were uncommon, but 13% had shared other injection paraphernalia. Approximately 24% reported multiple sex partners in the past 6 months and 71% had unprotected sex, including 20% who had done so with PWID.

Attitudes toward HIV and HIV vaccination

Psychosocial attitudes are shown in Table 1 and anticipated barriers are displayed in Figure 1. Most reported that they would be very likely (59%) or likely (32%) to receive an HIV vaccine. Psychosocial attitudes are shown in Table 1 and anticipated barriers, stratified by gender, are displayed in Figure 1. Of note, men were significantly more likely to report cost, requirement for multiple doses, and time as barriers to vaccine acceptability; women were more likely to report that there were no barriers to vaccine acceptability. Overall, Nearly 76% were unsure or only somewhat sure that they could get vaccinated if they had to pay out-of-pocket, travel out of town to get it (58%), or if their friends/partner were unsupportive (39%). Most (83%) reported that most people they knew would accept the vaccine, but only 51% would be more likely to accept the vaccine if most people did so. Similarly, 94% believed that most people would be supportive of their vaccination and 60% would be more likely to be vaccinated if most people encouraged them.

Table 3 describes attitudes toward specific vaccine characteristics. Most reported that requirement for multiple doses would not influence vaccine acceptability; however, 44% reported that they would be more likely to accept an orally-administered vaccine. Most (62%)
reported that they would be more likely to get vaccinated if there was a cash incentive to do so; the median incentive amount necessary to motivate vaccination was $50. The majority (56%) reported that the vaccine would need to be 90% effective before they would agree to be vaccinated and 18% reported that the vaccine would need to provide complete protection. Nearly all (93%) were willing to pay for a 90% effective vaccine; the median price participants were willing to pay was $100.

**Bivariate and Multivariate Results**

Bivariate results are presented in Table 4. Men and older participants were significantly less likely to report MVA. Injection drug use, use of an unclean needle, and unprotected sex with PWID in the past 6 months was positively associated with MVA. Perceived susceptibility to HIV, perceived benefit of the vaccine, positive experiential attitudes, and perceived behavioral control were also positively associated with MVA. Respondents reporting that people important to them would accept an HIV vaccine and that they would be more likely to accept the vaccine if others did so were more likely to report MVA. Similarly, those who believed that people would encourage them to receive the vaccine and who reported being more likely to accept the vaccine if others encouraged them were nearly twice as likely to report MVA.

Multivariate results are described in Table 5. Controlling for other variables in the model, men were less likely to report MVA (AOR: 0.33, CI: 0.21 - 0.52). Participants who believed they were susceptible to HIV (AOR: 2.31, CI: 1.28 - 4.17), perceived that the vaccine would benefit them (AOR: 2.80, CI: 1.70 - 4.64), and reported positive experiential attitudes (AOR: 1.85, CI: 1.09 - 3.01) were significantly more likely to report MVA. Injunctive norms were also positively associated with vaccine acceptability (AOR: 1.81, CI: 1.09 – 3.01).

**Discussion**
In this sample of rural drug users, 91% were likely or very likely to accept a 90% effective, preventive HIV vaccine. This percentage is comparable to that found in other urban and suburban populations in the US [45-47]. Men were significantly less likely to indicate that they were very likely to receive an HIV vaccine, after adjustment for behavioral characteristics and psychosocial constructs. Previous research on the association between gender and HIV vaccine acceptability is mixed, with one study finding that acceptability was higher among women [27] and another finding that it was higher among men [48]. Research conducted among high-risk adults in Los Angeles identified gender differences in concerns and motivations surrounding HIV vaccination (e.g., women were more likely to be influenced by factors related to their intimate relationships and experiences with healthcare providers, while men were more influenced by peer perceptions and risk of vaccine-induced seropositivity), but no significant association between gender and vaccine acceptability [49]. In the present study, differences in vaccination concerns, specifically those related to perceived barriers, may play an important role in the observed gender difference in vaccine acceptability. Men were significantly more likely to report cost, requirement for multiple doses (vs. a single dose), and time to visit the clinic would be barriers to vaccine acceptability. Post-hoc analysis to investigate these patterns revealed no significant gender differences in unemployment or total monthly income; however, men reported significantly more monthly income from employment and women reported significantly more income from partners, peers, family, and child support. Men were also more likely to report being uninsured. Interestingly, there was no gender difference in the amount participants were willing to pay for the vaccine. These patterns may indicate that while men and women have similar total gross incomes and willingness to pay, men have less net income to use for purchasing an HIV vaccine and the insurance coverage to reduce out-of-pocket costs.
Findings regarding the association between gender and barriers posed by dosing and time constraints would seem to indicate that men anticipate experiencing other logistical obstacles to accessing vaccination. Unavailability of time to visit the clinic for one or multiple doses may be related to a number of factors, including employment. Post-hoc analyses revealed no association between gender and past 6-month unemployment or full-time employment, but men were more likely to report part-time, irregular day work. The location, hours, and nature of this work is largely unknown, as are details about additional obligations that could compete with time available to seek vaccination. Although gender differences in psychosocial constructs aside from perceived barriers (e.g., perceived susceptibility to HIV, perceived severity of HIV) were not observed, it is important to note that perceived and/or actual barriers to vaccination are likely only part of the confluence of factors that could contribute to gender differences in HIV vaccine acceptability in this and other settings. In this setting, a "one-size-fits-all" approach to mitigating barriers to HIV vaccination may not be appropriate. Strategies that consider possible gender differences in constraints on HIV vaccine acceptance and, in turn, “meet men and women where they are” psychologically, socially, and geographically should be developed. These approaches may include strategic location of vaccine dissemination sites (e.g., at worksites, clinics, mobile units), varied hours of availability, and payment structures that limit out-of-pocket costs to those with and without insurance should be developed to address possible gender differences in vaccine uptake.

Given their low income and high rate of unemployment, it is unsurprising that most participants reported that cost would be a barrier to vaccine acceptability. Cost has been identified as an important influence in HIV vaccine acceptability in many [3, 27, 28], but not all [5, 51] previous studies. Interestingly, participants in one study believed that the vaccine should
be given at some cost, as free services were often perceived as inferior to those that were purchased [52]. Nearly all participants in the present study were willing to pay for a 90% effective HIV vaccine, but only one-third would be able to afford out-of-pocket costs exceeding $100. Though some research has suggested that cost may not be as strongly associated with acceptability as are other vaccine characteristics [5], in this setting, minimization of out-of-pocket costs would be critical to achieving adequate coverage.

The majority (60%) reported that a modest cash incentive (less than $50) would improve their likelihood of accepting the vaccine. Previous research among people who inject drugs PWID demonstrated that monetary incentives can improve compliance with a three-dose hepatitis B vaccine regimen [47]; the cost-effectiveness of a similar approach to HIV vaccination should be considered. Monetary incentives may assist in offsetting logistical costs, such as pragmatic barriers such as dosing and transportation, which were reported as a barrier to acceptability by a sizable minority of participants. This finding underscores the importance of minimizing logistical constraints on accessing vaccination logistical inconveniences to facilitate uptake. While nearly all were willing to pay for a 90% effective HIV vaccine, only one-third would be able to afford out-of-pocket costs exceeding $100. Though some research has suggested that cost may not be as strongly associated with acceptability as are other vaccine characteristics [5], in this setting, minimization of out-of-pocket costs would be critical to achieving adequate coverage. However, this must be coupled with interventions which address concerns regarding confidentiality; Also notable, nearly one in eight were concerned that providers would disclose their vaccination status to others. Participants in several previous studies have reported concern about peers’ negative social reactions to HIV vaccination [7, 49, 52-55], though less is known about participants’ confidentiality concerns.
related to healthcare providers administering the vaccine. Participants in a qualitative study in Los Angeles reported concern about being seen at vaccine dissemination sites [7] and one study in Thailand found that PWID were concerned about being seen at vaccine dissemination locations due to fear of legal consequences (e.g., arrest) [55]. In this and other settings, appropriate selection of vaccine dissemination sites as well as intensive training of providers about confidentiality and public assurance of privacy will be critical to ensuring adequate vaccine coverage among high-risk populations.

Findings regarding the importance of perceived social norms may also inform appropriate and effective strategies for HIV vaccine promotion. Descriptive data revealed that nearly 40% were not sure or only somewhat sure that they would be able to get the HIV vaccine if a friend/partner was unsupportive. Several previous studies have indicated that peer support and positive social norms will be important for facilitating vaccine acceptability. Participants in previous studies have reported fear of negative reactions by family members [7, 49] and intimate partners [7, 9, 49, 56] and concern that others will perceive their vaccination as an indication of ‘promiscuous’ behavior [9, 52, 55]. In the present study, participants who believed that most people would encourage them to receive an HIV vaccine and who reported they would be motivated to comply with those recommendations were significantly more likely to report MVA. Interestingly, additional research in this sample has indicated that the overwhelming majority of respondents (94%) would be willing to encourage someone to get vaccinated, particularly in circumstances in which the partner was perceived to be at risk or pose a risk for HIV [57]. This finding may serve as preliminary evidence that peer-promotion of HIV vaccination could be a successful strategy for reaching those most at risk for HIV in this population. In this context, the lack of a multivariate association between descriptive norms and vaccine acceptability deserves
comment. These data suggest that passive diffusion of vaccine uptake through the social network (i.e. via imitation of others’ behavior) is unlikely, and underscore the importance of an active approach to peer-based promotion.

The findings from this study have several theoretical and methodological implications. This study demonstrates the importance of assessing both the injunctive and descriptive dimensions of social norms and of coupling measures of normative beliefs with assessments of individuals' motivation to comply. Most participants reported that other people would accept an HIV vaccine, but far fewer reported that they would be influenced by others' behavior. Although individuals may underestimate their susceptibility to peer influence, data on compliance with norms may provide preliminary insight into who may be most responsive to strategies such as social marketing.

The research focused on *intent* to receive an HIV vaccine and, until an HIV vaccine is approved, the correspondence between intentions and *actual* vaccine uptake remains unknown. Furthermore, there are limitations of querying respondents about the specific characteristics of a hypothetical vaccine; research employing conjoint analysis [5, 6, 49, 51, 58, 59] and discrete choice experiments [60] may yield better insight into relative valuations of various vaccine characteristics, project their impact on future acceptability, and inform targeted social marketing campaigns. Though the survey included assessment of several relevant vaccine-related characteristics (e.g., route of administration, dosing, vaccine-induced seropositivity) and included an open-ended item that allowed free-listing of additional barriers to vaccination, the survey did not include direct measures of two vaccine characteristics determined in previous research to be important to acceptability: duration of protection and side effects. Also, while one item measures of theoretical constructs can be problematic to establishing psychometric validity
and reliability, the use of scales was not feasible given respondent burden and time constraints for conducting interviews. Similarly, time constraints limited our ability to assess psychosocial correlates to vaccine acceptability by varying levels of vaccine efficacy. The efficacy of future HIV vaccines is currently unknown; however, it is important to specify an efficacy level in measures of vaccine acceptability in order to standardize the context of participants' responses. In the current study, a 90% efficacy level was chosen as it presented a near ‘best case scenario’ for evaluating on of acceptability given that the 'most realistic scenario' is difficult to determine at this stage of vaccine development and subject to change. Nevertheless, more research is needed to explore the generalizability of the findings to vaccines of lower efficacy. Finally, generalization of findings from this study to other regions of Appalachia and other rural areas in the US also should be made with caution, as sociocultural influences across settings are likely to vary.

In this rural community, despite low perceived vulnerability to HIV, most drug users were readily willing to accept an HIV vaccine. Minimization of out-of-pocket costs will be essential. Social norms could play a major role in influencing HIV vaccine uptake in this community, and leveraged appropriately, could present an effective mechanism for promoting the vaccine. To plan for effective promotion and dissemination strategies among populations at high risk for HIV, continued research is needed to explore influences on HIV vaccine acceptability among people who use drugs.
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Competing Interests

The authors declare that they have no competing interests.
Authors’ contributions

A.M.Y and J.R.H designed the study and wrote the protocol. A.M.Y conducted the statistical analyses and drafted the complete manuscript. D.S.H, R.J.D, and C.E.S provided feedback throughout the conduct of the study and assisted with editing the final manuscript. All authors contributed to and approved the final manuscript.
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Figure Legend

Figure 1. Anticipated barriers to HIV vaccine acceptability among men and women (n=433)

An asterisk (*) indicates a statistically significant difference (p<0.05) between men and women based on chi-square analysis.
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