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"Cure" versus "Clinical Remission": The impact of a medication description on the willingness of people living with HIV to take a medication.

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Abstract

Many people living with HIV (PLWHIV) state that they would be willing to take significant risks to be "cured" of the virus. However, how they interpret the word "cure" in this context is not clear. We used a randomized survey to examine whether PLWHIV had a different willingness to take a hypothetical HIV medication if it causes flu-like symptoms, but provides: a) cure, b) remission that was labeled "cure", or c) remission. PLWHIV (n=454) were more willing to take a medication that provided a "cure" versus a "remission" if the side effects lasted less than one year. PLWHIV were more willing to take a medication that provided a remission that was labeled "cure" versus a "remission" (p=0.01) if the side effects lasted two weeks. Clinicians and researchers should be aware of the impact of the word "cure" and ensure that PLWHIV fully understand the possible outcomes of their treatment options.

Abstract

Mucha gente que vive con el VIH dice que estaría dispuesta a tomar riesgos significativos para ser "curado(a)s" del virus. Sin embargo, no es claro cómo se interpreta la palabra "cura" en este contexto. Nosotros usamos una encuesta aleatoria para examinar que tanto la gente que vive con el VIH está dispuesta a tomar un medicamento hipotético para el VIH si causa síntomas como de la gripe, pero provee: a) cura, b) remisión que es etiquetada como "cura", o c) remisión. Las personas que vive con el VIH (n=454) estaban más dispuestas a tomar un medicamento que provee una "cura" en vez de una "remisión" si los efectos secundarios duraban menos que un año. Las personas que viven con el VIH estaban más dispuestas a tomar un medicamento que proveía una remisión que estaba etiquetada como "cura" envés de "remisión" (p=0.01) si los efectos secundarios duraban dos semanas. Los clínicos(a)s e investigadores deben tener en cuenta el impacto de la palabra "cura" y asegurarse que la gente que vive con el VIH entienda completamente los posibles resultados de sus opciones para tratamiento.

Keywords

Cure; Decision-making; Behavior; Remission; HIV; PLWHIV

INTRODUCTION

Many people living with HIV (PLWHIV) who take antiretroviral medication can now expect to have normal or near-normal life longevity (1–3). Yet some PLWHIV continue to experience substantial disability from their illness, dealing with physiological (4), psychological/stigma (5), time, monetary (6), and social costs (7). In fact, many PLWHIV say they are willing to expose themselves to major risks for the chance of a cure (8). But what exactly would it mean to be "cured" of HIV?

Biomedical researchers often speak about two types of HIV-cure: sterilizing and functional cure. "Sterilizing" cure refers to the complete eradication of the HIV-virus from the body (9–10). "Functional" cure, or "medicine-free remission", means that the virus does not replicate when a patient has no antiretroviral treatment. The virus can be still present in the body, but

it does not harm the body and the transmission does not occur (11–12). While the complete eradication of the virus, a "sterilizing cure," has so far been unattainable (13–14), researchers' efforts are directed toward discovering how to provide it in the future (10,15). For functional cure, several clinical trials are underway testing potential interventions (e.g. NCT03743376).

Since sterilizing and functional cure are both actively discussed in the scientific world, there is a critical need to understand whether PLWHIV accurately understand the difference between sterilizing and functional cure when consenting for a trial (16–18). We hypothesized that the presence of the word "cure" in the medication description, title, and/or informed consent of a clinical trial (e.g. NCT02961829, NCT03758625) may influence how PLWHIV weigh the pros and cons of taking a new HIV medication with the goal of "cure". In the experiment, we assessed PLWHIV interest in a hypothetical medication, depending on its outcome and the words used in its description.

METHODS

We used a randomized survey to examine whether PLWHIV's willingness to take a hypothetical new HIV medication vary if the word "cure" was present/absent in the medication description. We randomized participants into three groups: (a) the medication was described as a sterilizing cure and labeled "cure," (b); the medication was described as a clinical remission (functional cure) and labeled "cure," and (c) the medication was described as a clinical remission (functional cure) and labeled "medicine-free remission".

Procedure.

We recruited PLWHIV in HIV clinics located in two large cities, one on the East and one on the West coast of the United States. Each patient gave informed consent to participate and was given a $10 gift card for their time. Each institution obtained IRB approval for the study.

The inclusion criteria involved: age 18+, fluency in English, on HIV ART-medication, an undetectable viral load for at least one year, no current cancer or opportunistic infections, and willingness to participate in a 30-minute survey. We chose these criteria to mimic those used in current HIV cure trials (19–20). Research coordinators verified patients' current HIV viral load by reviewing their medical charts. We recruited participants through flyers and brochures in the clinics.

The survey was administered using iPads. Qualtrics software was used to perform the randomization. The survey and randomization procedures were identical between sites. Each site contributed an equal proportion of patients for each of the three conditions. This procedure helped us to ensure that the site differences do not interfere with the results. In each group, participants were informed that the hypothetical medication would require a hospital stay. The medication would be intravenous and would cause serious side effects for one month, such as problems with heart rhythms, feeling sick, throwing up, muscle aches, and weakness. In addition, to mirror the uncertainty of individualized responses to medications, we described that only 80 out of 100 people would benefit from the medication and achieve the described outcome. The remaining 20 people would need to go back on their

HIV ART-medication. Some of them would need to change their ART-medication, with a very small chance that no antiretroviral medicine would work. Finally, we informed participants in all groups that if they were cured, or achieved clinical remission, they could still be infected from another person. The details of the outcome that varied across three groups are summarized below.

In the *Cure* group, participants were instructed that the hypothetical medication might cure their HIV infection, and the virus would be gone from their body. In the *Remission labeled "cure"* group, participants were told that the hypothetical medication might cure their HIV infection, but the virus could still be hiding somewhere in their body. In the *Remission* group, participants were told that the hypothetical medication might result in a medicine-free remission, and the virus could still be hiding somewhere in their body. Table I highlights the main differences among the three groups. Participants were not informed of the content of the scenarios that they were not randomized to read.

Measures.

We assessed participants' intentions to take the medication with the following question: "Would you take the treatment?" (*1 = definitely no, 2 = no, 3 = probably no, 4 = probably yes, 5 = yes, 6 = definitely yes*). We also measured participants' attitudes toward the medication with the following questions: "Taking this treatment would be a bad idea for me (scoring reversed)," and "I feel good about this treatment" (response options are the same as above). These two items were averaged to form a composite measure of attitude towards the medication (Cronbach $\alpha = 0.72$).

To better understand participants' intention to take the medication, we asked whether they would be willing to take the same medication if the side effects instead lasted: (1) two weeks, (2) two months, and (3) one year. Participants provided their answers to these three questions on the same 6-point Likert scale. Finally, participants reported their demographics and experience with HIV medications.

Statistical analyses.

As planned, the data collected in two sites were combined in a large dataset. We used ANOVA and MANOVA analysis to assess for an overall effect of each measure and Bonferroni adjustment to compare groups pair-wise. While parametric tests were chosen as our primary analysis, we conducted non-parametric tests to assess the robustness of our results and reported the results in Appendix.

RESULTS

The descriptive statistics are included in Tables II and III. None of the among-group differences were statistically significant.

Intention to take medication.

There was an overall difference among groups in their intention to take the medication, $F(451, 2) = 6.23$, $p = 0.002$, $\eta^2 = 0.03$. Participants in the *Cure* group were more willing to

take the medication than those in the *Remission* group (mean difference = 0.54, p = 0.002, 95% CI [0.17, 0.92]). Twelve percent more participants said they would take the medication if it had the chance of providing a cure versus when the medication had a chance of providing a remission. The difference between the *Cure* group and *Remission labeled "cure"* group was not significant (mean difference = 0.20, $p = 0.63$). Only three percent more participants would take the medication if it had the chance of providing a cure versus a remission labeled "cure." The difference between the *Remission labeled "cure"* and the *Remission* group was not significant (mean difference = 0.35, p = 0.09, 95% CI [−0.04, 0.73]). Nine percent more participants would take the medication if it had the chance of providing a remission labeled "cure" versus a remission labeled a "medicine-free remission." Figure 1a illustrates the percentage of people who reported that they would take the medication (by choosing answers: "probably yes," "yes," and "definitely yes") across the groups.

Attitude toward medication.

There was an overall difference between groups in attitudes toward the medication F(451, 2) = 8.33, p = 0.00, $\eta^2 = 0.04$. Participants had more positive attitudes toward it when the medication provided the chance of a cure versus remission (mean difference = 0.55, p = 0.00, 95% CI [0.22, 0.88]). There was no difference in attitudes between the *Cure* and *Remission labeled "cure"* groups (mean difference = 0.31, p = 0.10, 95% CI [−0.33, 0.62]). There was also no difference in attitudes towards the medication between the *Remission labeled "cure"* and *Remission* groups (mean difference = 0.26, p = 0.19). Figure 1b illustrates an average score for each group.

Intention to take medication by the duration of side effects.

We excluded participants (n = 34) who had internal inconsistency in their answers, defined as participants who agreed to take a medication that was associated with a longer duration of side effects but rejected the same medication when it was associated with a shorter duration of side effects. Thus, the sample size for this analysis was n = 420. The analysis with the full sample is in Appendix.

The MANOVA test indicated a significant difference overall, F(415, 3) = 4.00, p = 0.001, $\eta 2 = 0.03$; thus, we looked at the effect of conditions within each length of side effect. There was a significant difference in participants' willingness to take the medication between Cure and Remission groups when the side effects lasted 2 weeks (mean difference = 0.68, p = 0.00, 95% CI [0.31, 1.06]) and 2 months (mean difference = 0.71. p = 0.00, 95% CI [0.28, 1.14]) but not one year (mean difference = 0.46, p = 0.056, CI [−0.01, 0.92]). In addition, there was a significant difference in participants' willingness to take the medication between Remission labeled "cure" and Remission groups at 2 weeks (mean difference = 0.50, p = 0.01 95% CI [0.11, 0.88]) but not 2 months (mean difference = 0.33, p = 0.21, 95% CI [−0.11, 0.76]) or 1 year, (mean difference = 0.23, p = 0.74, 95% CI [−0.24, 0.70]). Mean differences and statistics for each item is reported in Table IV. The columns illustrate the mean difference in participants' willingness to take the medication between each pair of groups. In all cases, the mean of the second group listed was subtracted from the mean of the first group listed. Higher numbers indicated a stronger intent to take the medication.

Participants' willingness to take the medication was not significantly different between *Cure* and *Remission labeled "cure"* groups regardless of the duration of side effects. Figure 2 illustrates the percentage of people who said: "probably yes," "yes," and "definitely yes" to taking the medication if side effects lasted: 2 weeks, 2 months, and 1 year.

DISCUSSION

In a survey of 454 PLWHIV, we found that their willingness to take a hypothetical HIV medication was influenced by the specific description of its outcome. PLWHIV were more willing to take a hypothetical HIV medication when the outcome was described as providing the possibility of achieving a cure with eradication of the virus (sterilizing cure) versus a medicine-free remission (functional cure). This could have substantive implications for HIV "cure" trials, whereby studies that aim to eradicate HIV from the body (or describe their aim as such) might expect greater enrollment than studies that aim for clinical remission.

The effect of the label "cure" itself varied depending on the length of the medication side effects. When PLWHIV considered taking the medication with side effects lasting 2 weeks, they were significantly more motivated to take a medication that was described as a remission but had the label "cure" than a medication with the same outcome without the label "cure". This difference disappeared, however, when the side effects lasted one or two months, although the trend persisted across all levels. It is possible that if patients perceive the risks of a medication to be relatively low, they pay less attention to the description of the outcome. Instead, they make decisions based on optimistic promises incorporated into the name of a medication or a trial. Further, there was no difference between any groups when side effects lasted one year, suggesting there is likely some point at which the cost in terms of side effects is so great that these variations may not matter. Future research could fully assess this possibility.

Our findings are consistent with the research suggesting that PLWHIV predicted having different attitudes toward medications that aim to eradicate the virus versus to provide a remission (21–22) and the research suggesting that the choice of words in the description of treatment can influence patients' behavior (23–26). Our results raise an important question, whether and when, if at all, the word "cure" should be used in discussions about novel HIV clinical trials. Some researchers suggest, that the word "cure" could be appropriate for communication with a broader public (e.g. politicians) with the goal to raise awareness about HIV (19, 27). With patients, in some situations, avoiding the word "cure" may have unexpected negative consequences. When a new medication for a sterilizing cure will be ready for clinical trials, not using the word "cure" while introducing a clinical trial might result in lowering PLWHIV's willingness to join the research. In this case, avoiding the word "cure" might undermine patients' autonomy as it reduces their enthusiasm toward an option that possibly supports their true preferences.

In the context of recruiting patients for clinical trials today, the word "cure" might be misleading. Even if the word "cure" is formally defined as a functional cure or medicine-free remission, patients might be sensitive to the word itself and experience false hope for virus eradication. This could influence how patients weigh the characteristics of a new

medication. PLWHIV might agree to discontinue ART and tolerate substantial health risks in a clinical trial expecting to receive a sterilizing cure while having a chance only for a medicine-free remission. Subsequently disappointed, patients might distrust the medical system, as well as experience physical and emotional discomfort.

If clinicians or researchers intend to use the term “cure” and “functional cure” (e.g. NCT03758625), they should ensure that PLWHIV truly understand the meaning of the word in the circumstances of a specific clinical trial and do not downplay the risks of the medication. This can be accomplished with pilot studies and validated surveys.

Our study has several limitations. First, we used hypothetical scenarios to evaluate patients’ attitudes toward hypothetical HIV medication. People’s actual choices in a clinical setting might differ from hypothetical settings. However, this hypothetical scenario allowed us to assess variations in patients’ attitudes that would not be feasible or ethical to test in actual clinical settings. In addition, our hypothetical scenarios do not fully reflect the current state of the available treatments. There is currently no medication that could completely remove the virus from the body or provide forever-lasting remission (28, 29). This discrepancy, however, underwrites the deeper point that “cure” language may create false impressions compared to what is currently testable in clinical trials.

Second, our sample may not be fully generalizable. While our study included two centers, the population was relatively homogeneous, in that, they all were on stable regimens with an undetectable viral load. Future studies could address this limitation by exploring the influence of “cure” language among PLWHIV who have different viral loads.

Another limitation is that participants were recruited via flyers and brochures. This approach added an element of self-selection to the study. Because participants chose to approach our researcher by their own initiative, they might be more open towards new medications and research related to HIV than other PLWHIV.

Finally, in this experiment, we could not disentangle whether people were downplaying risks when they read the label “cure” or overreacting to risks when they read the label “medicine-free remission.” Future research would be needed to make more normative conclusions regarding the appropriateness of the word “cure” in these settings.

CONCLUSION

PLWHIV’s willingness to take a hypothetical HIV medication was influenced by variations in the definition and labeling of its outcome. Specifically, PLWHIV were more willing to take a medication that provided a cure versus a remission. In addition, when the duration of side effects was shorter, PLWHIV were more willing to take a medication that provided a clinical remission if it was labeled as a “cure” versus a “remission.” Clinicians and researchers should be aware of the effects of these words and ensure that people fully understand the likely outcomes of their research prior to making decisions about participation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

Intention to take medication.

Due to skewness in the data, we also ran a non-parametric test, which indicated similar results (Kruskal-Wallis Test, $\chi 2 = 13.60$, $p = 0.001$); *Cure* group vs. *Remission* group (Mann-Whitney U = 9,182.00, p <.001); *Cure* group vs *Remission labeled "Cure"* group (Mann-Whitney U = 10,169.00, p = 0.10); *Remission labeled "Cure"* group vs. *Remission* group (Mann-Whitney U = 9,535.50, p = 0.04).

Attitude toward medication.

We ran a non-parametric test, that indicated similar results: *Cure* group provided the highest rating, *Remission* group provided the lowest rating, and *Remission labeled "Cure"* group was in between of them (Kruskal-Wallis Test, $\chi 2 = 16.99$, $p = 0.00$). *Cure* group vs. *Remission* group (Mann-Whitney U = 8,785.50, p = 0.00). *Cure* group vs *Remission labeled "Cure"* group (Mann-Whitney U = 9,579.50, p = 0.02); *Remission labeled "Cure"* group vs. *Remission* group (Mann-Whitney U = 9,730.50, p = 0.08).

Intention to take medication by the duration of side effects.

In this part, we repeated analysis for the intention to take the medication with the full sample (n = 454). We evaluated the participants' willingness to tolerate side effects for each item using a MANOVA procedure with Bonferroni adjustment to account for multiple comparisons. The MANOVA test indicated a significant difference overall, MANOVA results, $F(449, 3) = 4.23$, $p = .00$, $\eta 2 = .03$. Mean differences and statistics for each item is reported in Table IV. The columns illustrate the mean difference in participants' willingness to take the medication between each pair of groups. In all cases, the mean of the second group listed was subtracted from the mean of the first group listed. Higher numbers indicated a stronger intend to take the medication.

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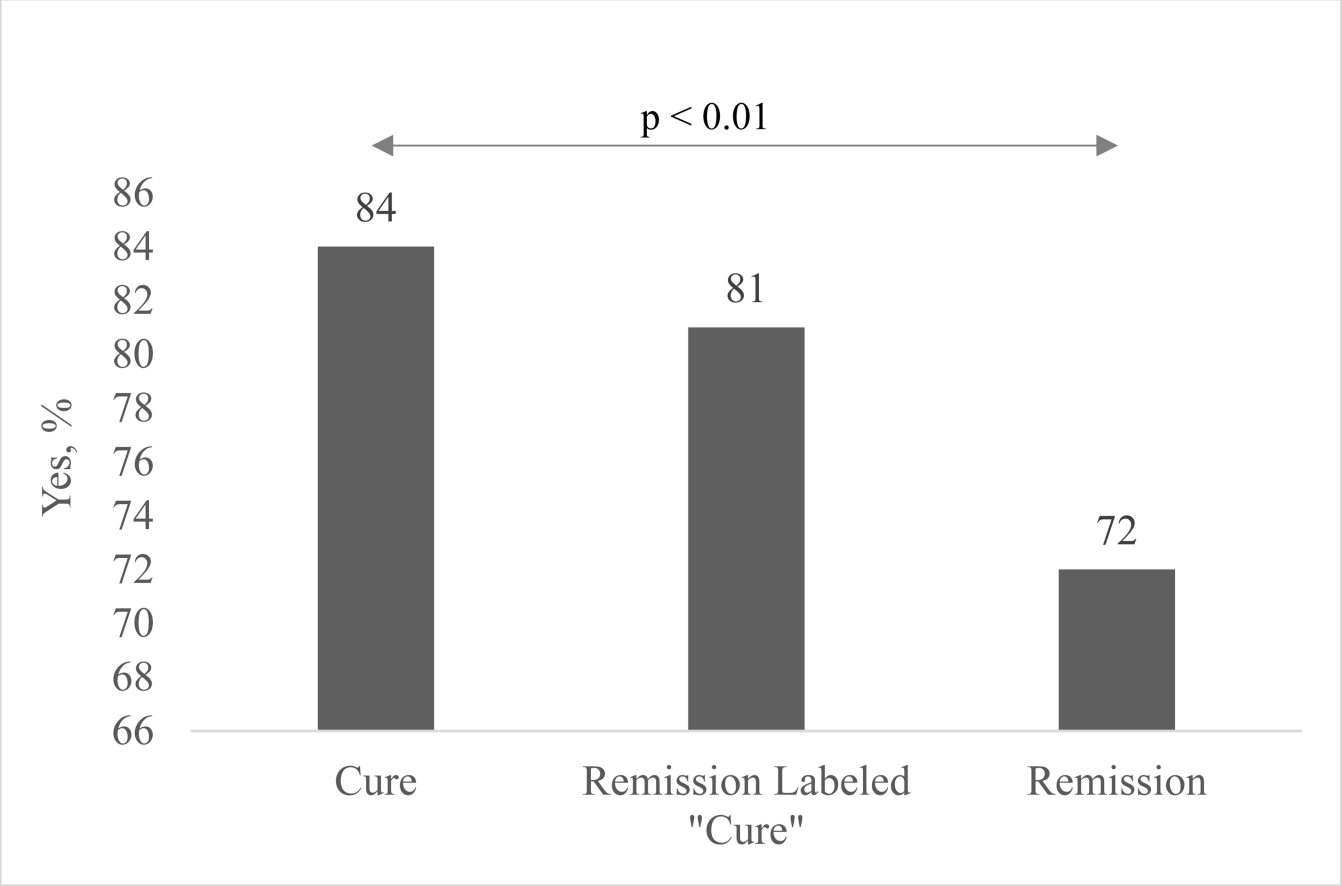

Figure 1a:
Bars illustrate the percent of patients who answered: “probably yes,” “yes,” and “definitely yes.” The significance is based on the ANOVA test results with a continuous variable.

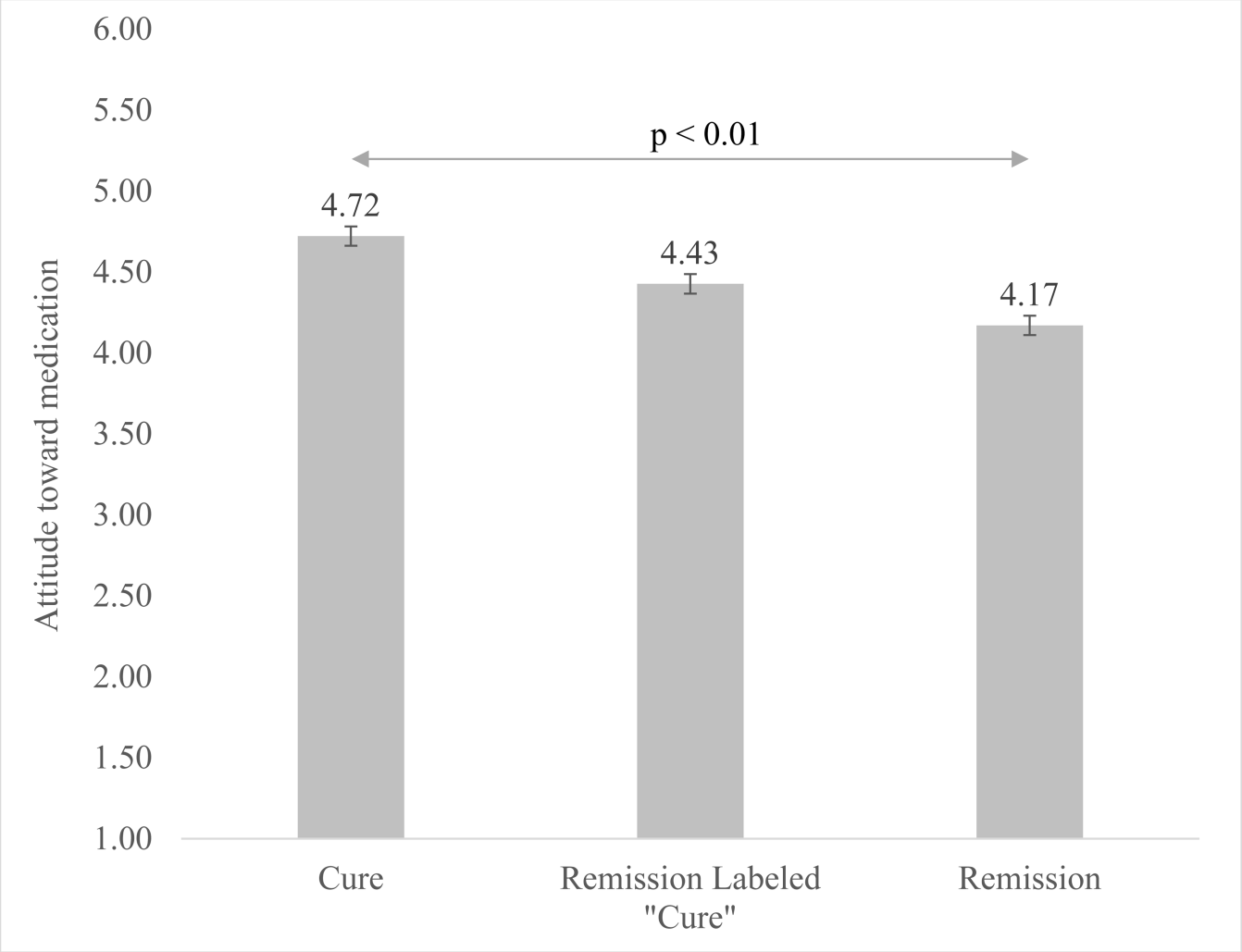

Figure 1b.

The figure illustrates the average participants' agreement with two statements:" Taking this treatment would be a bad idea for me" (reversed) and "I feel good about this treatment" on a 6-point Likert Scale, such that higher numbers indicate more positive attitudes. Error bars illustrate standard error.

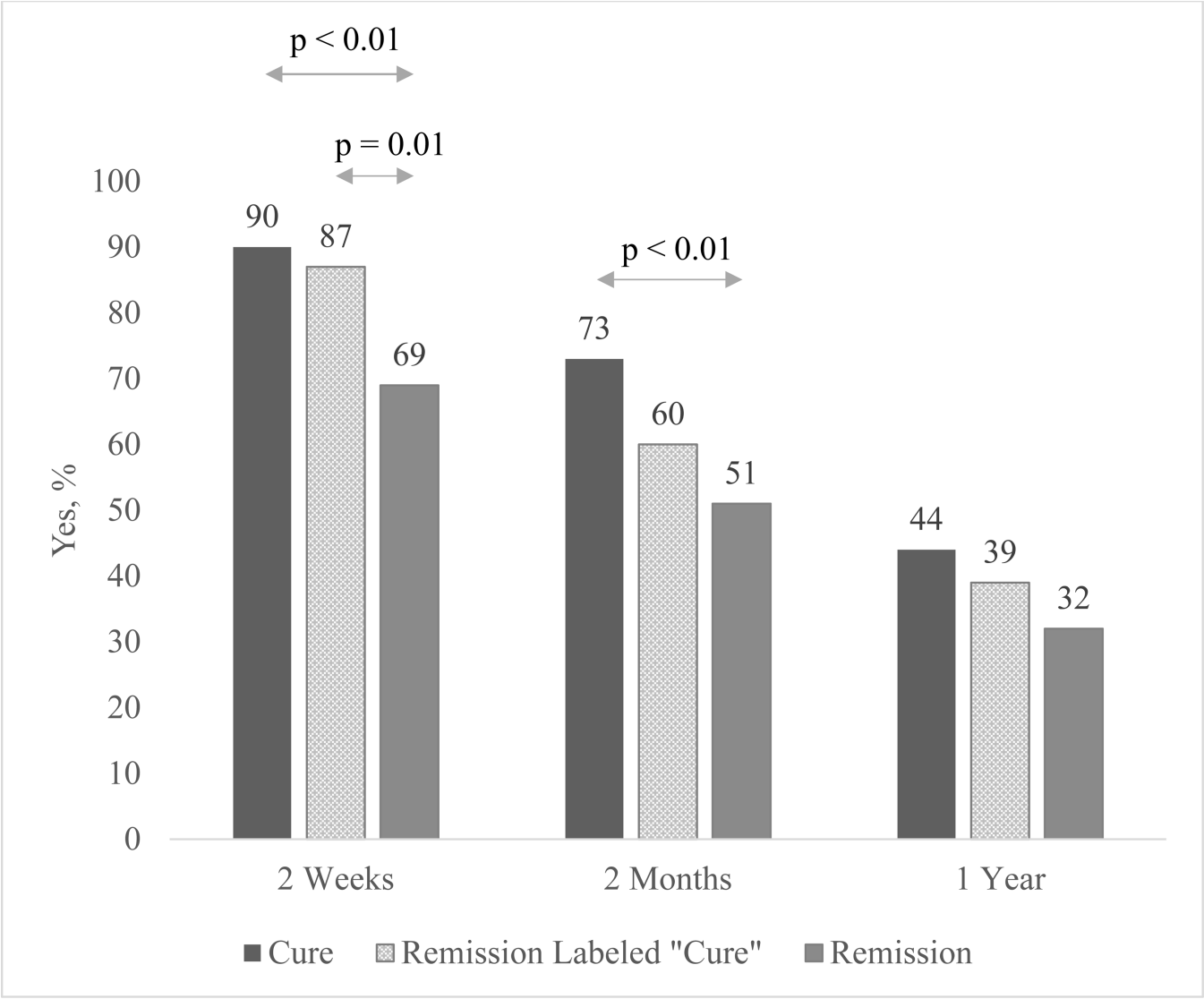

Figure 2:
Bars illustrate the percent of patients who answered: probably “yes,” “yes,” and “definitely yes.” The significance is based on the MANOVA test results with a continuous variables that illustrate the average participants’ agreement with the statements “Would you take the treatment”, if side effects last 2 weeks, 2 months, 1 year?

Table I:

Key differences between hypothetical scenarios for the three groups.

Cure	Remission labeled "Cure"	Remission
Imagine you are considering taking a **treatment that might CURE** your HIV infection. But, it would have some serious side effects.	Imagine you are considering taking a **treatment that might CURE** your HIV infection. But it would have some serious side effects.	Imagine you are considering taking a **treatment that might put** your HIV infection into **medicine-free remission**. But it would have some serious side effects.
80 out of 100 people who take the treatment will be cured of their HIV virus forever.	80 out of 100 people who take the treatment will most likely have their HIV virus cured. We cannot know for sure that they will stay cured.	80 out of 100 people who take the treatment will most likely have their HIV virus put into medicine-free remission. We cannot know for sure that they will stay in medicine-free remission.
There will be no HIV virus in your blood.	***The virus is no longer detectable on any blood tests***	***The virus is no longer detectable on any blood tests***
The virus would be **totally gone** from your body—it won't be hiding anywhere else in your body.	We **won't know if the virus is completely gone** from your body. The HIV virus might still be hiding somewhere in your body.	We **won't know if the virus is completely gone** from your body. The HIV virus might still be hiding somewhere in your body.
You would ***NOT need to take any HIV medicines*** if you are cured.	You might ***NOT need to take any HIV medicines*** if you are cured. But, if the HIV virus is still hiding in your body, and shows up again in your blood, you would have to go **back on HIV medicines.**	You might ***NOT need to take any HIV medicines*** if you are put into medicine-free remission. But, if the HIV virus is still hiding in your body, and shows up again in your blood, you would have to **go back on HIV medicines.**
	You will need to get your blood checked every 3 months to see if the virus is back in your blood.	You will need to get your blood checked every 3 months to see if the virus is back in your blood.

Table II:

Demographics

Characteristic	Cure	Remission labeled “cure”	Remission	Overall
Number of participants	157	145	152	454
Age, mean(SD)	50 (13)	49(13)	51 (10)	50 (12)
Sex, male/female,%	64/36	67/33	64/36	65/35
Race,				
African American,%	60	61	66	62
White,%	22	19	19	20
Hispanic,%	7	6	5al	6
Asian,%	2	3	3	3
Other, %	10	11	7	10
Education, some college and less, %	70	70	72	70
Sexual Orientation, Heterosexual, %	45	45	44	45
Homosexual, %	40	44	40	41
Not in a relationship, %	66	71	66	68
Live in a city, %	72	78	80	77
Year of diagnosis (median)	1999	2001	2002	2001
Contracted HIV via sexual encounter, %	79	77	76	77

Table III:

Participants' past experience with HIV medications

Question	Experience with HIV medications	Cure	Remission labeled "cure"	Remission	Overall
When did you start taking your current HIV medicines?	Medication started more than 5 years ago, %	63	69	59	63
How many individual pills do you take each day to treat your HIV?	No more than 1 HIV pill, %	52	51	51	51
How many times have you had to change your HIV medicines?	Medication was changed 1 time or less, %	51	59	52	54
How hard would it be for you to change to different HIV medicines?	6-point Likert-Scale (1 = very hard, 6 = very easy), Mean	4.4	4.3	4.1	4.3
How worried would you be to change to different HIV medicines?	6-point Likert-Scale (1 = very worried, 6 = Not worried at all), Mean	4.0	3.9	3.7	3.9

Table IV:

ANOVA test results indicating the pairwise-mean difference between groups in willingness to take treatment, by the duration of side effects:

Side effect duration	Cure vs Remission	Cure vs. Remission labeled “cure”	Remission labeled “cure” vs. Remission
2 weeks	0.68 **	0.19	0.50 **
2 months	0.71 **	0.38	0.33
1 year	0.46	0.23	0.23

** $p < 0.01$