What is "too much risk" in HIV cure clinical research in the United States?

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Background

HIV cure research strategies, such as latency-revering agents, autologous and allogeneic stem cell transplants, gene therapy and immune-based strategies, are associated with various degrees of risks. We assessed perceptions of what constitutes "too much risk" in HIV cure clinical research in the United States. Data inform possible risk thresholds and risky features that would make participants reluctant to join HIV cure studies or regulators to approve them.

Methods

We implemented a cross-sectional survey among 400 HIV-positive adults in the United States in September – October 2015. The sample was ethnically diverse (65% Caucasian, 17% African-American, 12% Hispanic, 4% mixed and 2% Asian) and 38 U.S. states were represented. We also conducted key informant interviews with 36 people living with HIV, clinician-researchers, bioethicists, members of Institutional Review Boards (IRBs) and regulatory agencies to assess perceptions of what is "too much risk" in HIV cure-related studies in the United States. Narratives cut across a number of topics that are summarized below. Each group of stakeholders contributed a unique perspective to the inquiry.

Results

Perceptions of "too much risks" among potential study participants

Survey results revealed a high degree of variability in perceptions of what constitutes "too much risk" in HIV cure-related research. Activation of genes that would cause cancer (49% [95% CI: 44, 54%]; n = 358) and development of resistance to antiretroviral drugs (ARVs) (37% [95% CI: 32, 42%]; n= 358) were the clinical factors most likely to discourage participation among HIV-positive volunteers. Perceptions of "too much risk" among potential study participants ranged from first-in-human studies without underlying proof of concept, painful procedures, significant increases in viral load and decreases in CD4, interventions that would cause viral rebound, irreversible long-term side effects, damage to vital organs, immune system shut down, anything that would cause HIV to become unmanageable, progression to AIDS, hospitalization, debilitation or risk of death. Other potential HIV cure research volunteers mentioned "too much cutting," major surgeries or "too much time" away from home. Unacceptable social risks included drastic changes in quality of life, transmission of HIV to others, and inability to work or care for family. Financial risks included loss of disability income or insurance coverage. A minority did not place an upper limit on acceptable risk.

Themes	Quotations
First-in-Human Studies	*"Trying an approach never tested on humans (…). That said, I must feel confident researchers care about my heath, first and foremost, not lab results."* *Any first in human study without an underlying proof of concept in an animal model."* – Patient-Participants
Becoming Detectable or Viral Load Increase	*"If I were to become detectable again with no recourse"* *"If my dormant virus multiplied in a vengeful way"* – Patient-Participants
HIV Becoming Untreatable	*"Anything that might cause my HIV to become untreatable"* *"If I could not go back on medication"* *"For HIV to mutate beyond known/pending treatment options"* – Patient-Participants
Significant Change in CD4+ Count	*"If my CD4 count (…) pushed me back into the category of having AIDS."* *"If the cure research put me back under 200 T cells and I was in danger for PCP pneumonia again, that would be too much risk for me."* – Patient-Participants
Pain	*"Well, I am really averse to pain. If you ask me to go through a bone marrow, I'll run the other way… There would need [to be] something to keep me from experiencing the pain."* – Patient-Participant
Cancer Risk	*"A cure-related case study that is known to cause various cancers of any kind."* *"Gene manipulations that result in cancers probably would be the most frightening and unbearable, but frankly if I was really sick, I would risk a lot more to get better."* – Patient-Participants
Developing Resistance to Antiretroviral Drugs	*"The chance of resistance for me is too much"* *"If I were to become resistant to the drugs that are saving my life at present"* *"I'm very treatment experienced and do not want to risk losing the drugs I take now to viral resistance"* *"As I already have resistance and am limited in my options for medication, I worry that any additional mutations may prohibit me from achieving viral suppression"* – Patient-Participants
Permanent, Irreversible Side Effects	*"A risk that would have me end up in irreversibly poorer health than I am now."* *"Anything that might become permanent or irrevocable."* – Patient-Participants
Hospitalization	*"Extended hospital stay"* – Patient-Participant
Debilitation	*"Too much risk would be an outcome that leaves me disabled without the resources to provide for myself. Anything that would cause functional disability such as loss of sight."* – Patient-Participant
Death	*"Certain death"* *"A study where there have been deaths due to the medications prescribed"* *"Greater than 1% risk of death"* *"Death… I'm a Mom to a 5 year old little boy""* *Anything that would kill me – been living with AIDS for twenty [years] and feel I still have left many good years"* – Patient-Participants

Results (continued)

Perceptions of "too much risks" among clinician-researchers

Clinician-researchers provided examples of risky modalities that would constitute "too much risk." Most of the key informants in this category said that stem cell transplants in otherwise healthy, cancer-free participants who are stable and suppressed on antiretroviral therapy would be too risky. Other clinician-researchers mentioned anti-programmed cell death protein 1 (PD-1) that have shown significant toxicities in non-human primates would be inadmissible in humans. Further, testing latency-reversing agents with treatment interruptions would be unwarranted since compounds have not yet been associated with a substantial reduction in the size of the replication-competent HIV DNA reservoir up to this point. A clinician-researcher commented that anything suggesting an irreversible and systemic side effect would be unacceptable; however, it may not be possible to know this until interventions are tested in humans.

Themes	Quotations
Stem-Cell Transplants	*"I mean the riskiest studies that I am aware of are the stem cell transplants that are happening. People have chemotherapy to make space for the transplant and those are being done on healthy people on HIV therapy. To me that's really pushing it"* – Clinician-Researcher
Anti-PD1 Studies	*"Some of the studies of PD-1 blockade are also sort of pushing it"* – Clinician-Researcher
Analytical Treatment Interruptions	*"Latency-reversing agents with treatment interruption"* – Clinician-Researcher

Perceptions of "too much risks" among regulators and policy-makers

Policy-makers/regulators confirmed that the evaluation of first-in-human studies or investigational new drug (IND) protocols is their primary responsibility. There is a category of "too much risk" in HIV cure clinical studies and some protocols have been put on clinical hold. The assessment is usually based on the available evidence or the strong biological plausibility of possible severe adverse drug reactions, even though this is more a judgement than a clear science. Policy-makers/regulators referred back to regulations. There are two possible scenarios that would constitute "too much risk:" 1) insufficient information to assess risk or 2) insufficient potential benefits to outweigh the risks. Risks would be deemed unacceptable if the procedure or drug was known to be significantly toxic and there was no counter-balancing procedure to reduce risk. Regulators were concerned if the proposed study failed to have a well thought-of study design, insightful endpoints or with prospect of interpretable results to advance the field forward. HIV cure research strategies associated with a high risk of viral rebound were also perceived as being unacceptable.

Themes	Quotations
Regulations and Clinical Holds	*"I would consider "too much" risk if the study drug or procedure is known to be significantly toxic. It is particularly concerning if there are limited data to support or indicate that the drug have the desired effect such as reducing the reservoir. Another concern would be if the study failed to include a well thought-of design such as well-defined endpoints. (..) If [we]'re going to subject people to risky interventions, [we] need at least interpretable results to be able to advance the field"* – Policy-Maker/Regulator
HIV Cure Research Strategies with High Risk of Viral Rebound	*"Viral rebound is unpredictable. Related risk is that the drug develops [a] new kind of resistance. [There is a [t]hreat to the host but to the broader public; particularly if the change is not immediately caught or recognized somehow."* – Policy-Maker/Regulator

Conclusions

Despite challenges of making risk determinations in HIV cure-related studies at this juncture, knowing what risks are unacceptable is important to inform study design and accrual as well as informed consent. We should strive to maintain public confidence in the HIV cure research enterprise and appreciate perceptions of what risks are perceived to be unacceptable.

Recommendations

- ✓ Perceptions of what constitutes "too much risk" or unacceptable risks should be taken into account when designing and approving studies as they influence the ethical development and implementation of HIV cure-related research.
- ✓ Because it is difficult to determine whether a study participant displays "too much altruism," there should be safeguards in place to protect them from taking "too much risk."
- ✓ More empirical research is needed on what represents "too much risk" in HIV cure-related research as the field is evolving quickly and there is scientific uncertainty associated with the various modalities under investigation.

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