

Analytical Treatment Interruption in
HIV Cure Trials – Report of a
Consensus Workshop
July 9, 2018
Ragon Institute of MGH, MIT and
Harvard in Boston, MA

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Community Summary

Problems:

- There are **no robust markers or assays that could replace** analytical ART interruption (ATI) studies, nor are there **biomarkers** that are predictive of the effects of an ATI or **of control**
- **No “standards” regarding how these studies should be conducted** to maximize their utility and minimize their risk

• Goal:

- **To produce a set of recommendations** aimed at facilitating the conduct of ATIs in a manner that **maximizes the knowledge gained and minimizes the risk to participants** in clinical remission and viral eradication research.

• Key Consensus Outcome:

- Consensus on the **lack of alternatives for ATI studies**
- Consensus that there is **no “one size fits all” guideline for when ATIs are appropriate**
- Consensus on **many risk mitigation strategies , e.g. inclusion/exclusion criteria**
- Consensus that there is **no consensus on viral load based restart criteria** but some agreement that for certain study objectives longer and higher viremia needs to be tolerated
- **Some agreement that inclusion of a placebo group might be necessary** for the validity of a study and are therefore ethically sound.

Background

- ~23 studies that include an analytical ART interruption in clinicaltrials.gov (ongoing, planned or completed)
- **Eligibility criteria and ART restart criteria differ significantly** between studies
- **No “standards” regarding how these studies should be conducted to maximize their utility and minimize their risk**
- This creates many **challenges e.g. concerning the comparability of the studied interventions**

Goals of workshop

- **To bring together stakeholders** from all involved interest groups, including scientists, clinicians, people living with HIV, ethicists, social scientists, regulators, and advocacy groups
- **To produce a set of recommendations** aimed at facilitating the conduct of ATIs in a manner that **maximizes the knowledge gained and minimizes the risk to participants** in clinical remission and viral eradication research
- The workshop took place on July 9th 2018 at the Ragon Institute of MGH, MIT and Harvard in Boston, MA

Workshop participants

by alphabetical order: Jintanat Ananworanich¹, Katie Bar², Dan Barouch³, Marina Caskey⁴, Donn Colby⁵, Liza Dawson⁶, Lynda Dee⁷, Steven Deeks⁸, Krista Dong⁹, Karine Dube¹⁰, Joseph Eron¹¹, John Frater¹², Rajesh Gandhi¹³, Romas Geleziunas¹⁴, Maureen Goodenow¹⁵, Phillip Goulder¹⁶, George Hanna¹⁷, Richard Jeffreys¹⁸, Rowena Johnston¹⁹, Boris Julg⁴³, Daniel Kuritzkes²⁰, Jonathan Li²¹, Udom Likhitwonnawut²², Jan van Lunzen²³, Javier Martinez-Picado²⁴, John Mellors²⁵, Nelson Michael¹, Veronica Miller²⁶, Luis Montaner²⁷, Douglas Nixon²⁸, David Palm²⁹, Giuseppe Pantaleo³⁰, Holly Peay³¹, Deborah Persaud³², Merlin Robb¹, Jessica Salzwedel³³, Karl Salzwedel³⁴, Tim Schacker³⁵, Virginia Sheikh³⁶, Ole Sogaard³⁷, Serena Spudich³⁸, Kathryn Stephenson³, Jeremy Sugarman³⁹, Jeff Taylor¹⁹, Pablo Tebas⁴⁰, Caroline Tiemessen⁴¹, Randall Tressler⁴², Bruce Walker⁴³, Carol Weiss⁴⁴, Summer Zheng⁴⁵

Meeting Agenda and Format

- **Benefits & Risks of ATI Studies**
- **Risk Mitigation Strategies I: Eligibility Criteria**
- **Risk Mitigation Strategies II: Monitoring and ART Resumption Criteria**
- **Ethics of ATI Studies**

Each session consisted of a moderated Q&A section with a small group of panelists followed by open audience discussion and concluded with an electronic poll on major questions

Benefits & Risks of ATI Studies

- There was **agreement** that currently, there are **no robust markers or assays that could replace ATI studies**, nor are there **biomarkers that are predictive of the effects of an ATI or with control**
- The **onus is on investigators to demonstrate, prior to the ATI study**, e.g. in animal models or other diseases, that a strong scientific rationale exists for **why the intervention might conceivably affect time-to-rebound or post-interruption set-point**
- It was **agreed** that certain signals must be met to justify an ATI. It was suggested that **investigators should determine “go/no-go” criteria for when to incorporate ATIs in their development plans**

Benefits & Risks of ATI Studies

Which ATI readouts are best?

Time to rebound (TTR) versus Rebound set point

- Safest and easiest endpoint in an ATI protocol might be the **time-to-rebound** e.g. as a “**test-of-cure**” or a **surrogate for the overall reservoir size**.
- Effects of immune-based therapeutics however might be best assessed by **determining rebound set point**. This would require a **longer period of high-level viremia to not miss post-treatment controller**.

Benefits & Risks of ATI Studies

Potential risks of ATIs

- **Acute retroviral syndrome (ARS)-flu type symptoms**
- **Increases in the reservoir size and viral diversity**
- **ART resistance and/or hindered viral re-suppression following ART re-initiation.**
- **Neurological, cardiovascular, cancer, hepato/renal risks**
- **Transmission risk during viral rebound**

Risk Mitigation Strategies I: Eligibility Criteria

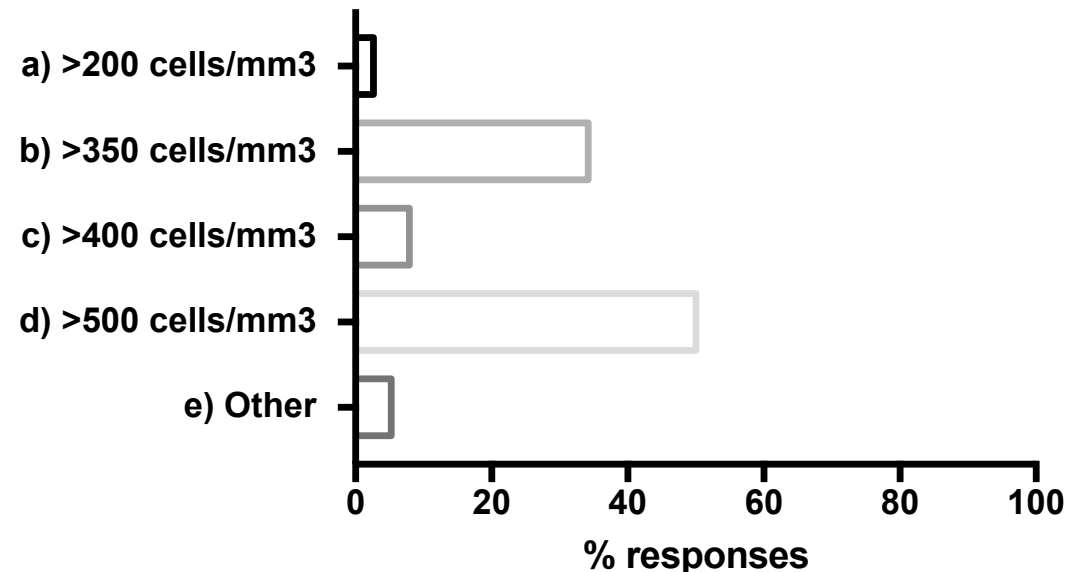
Who should be included in ATI studies?

General consideration: The FDA considers asymptomatic people with HIV infection who have many available treatment options to be “**healthy volunteers.**”

No single best population. There was no consensus regarding the ideal population for an ATI study. The population selected **will depend on the question being asked**

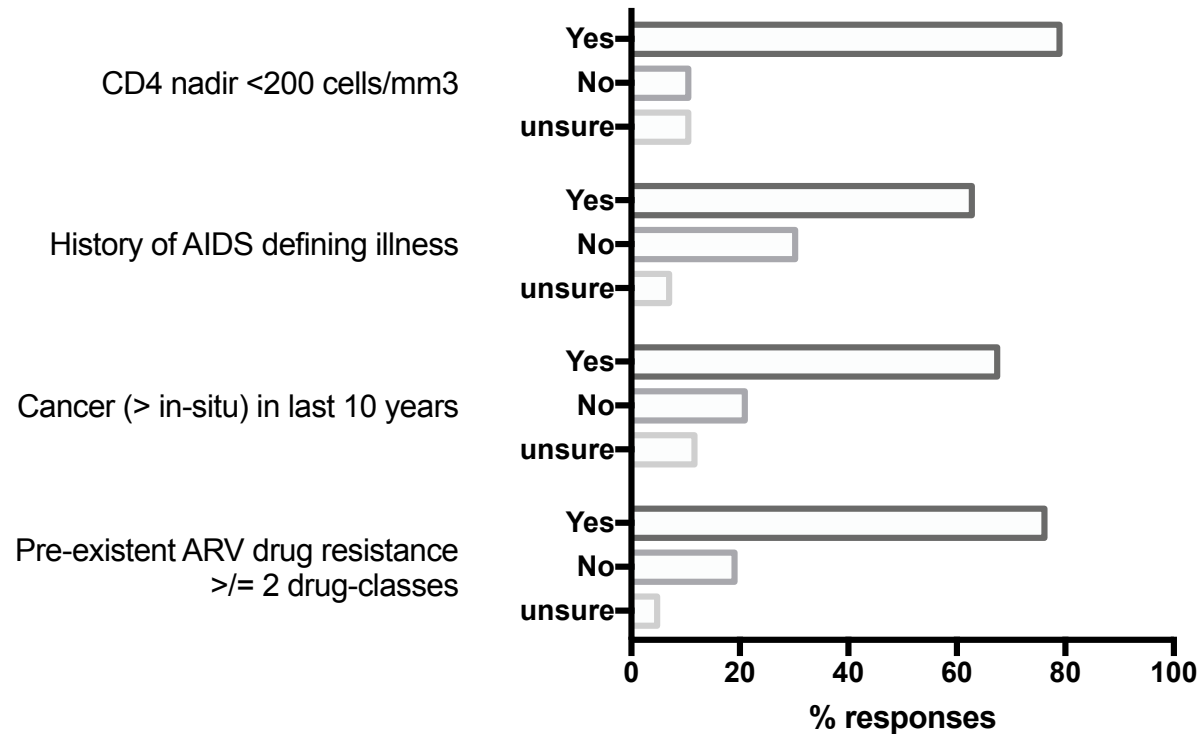
The healthiest individuals first. There was consensus that current ATI studies, which are largely experimental, **should focus on relatively healthy individuals.**

CD4 T-cell count threshold for inclusion.



Risk Mitigation Strategies I: Eligibility Criteria

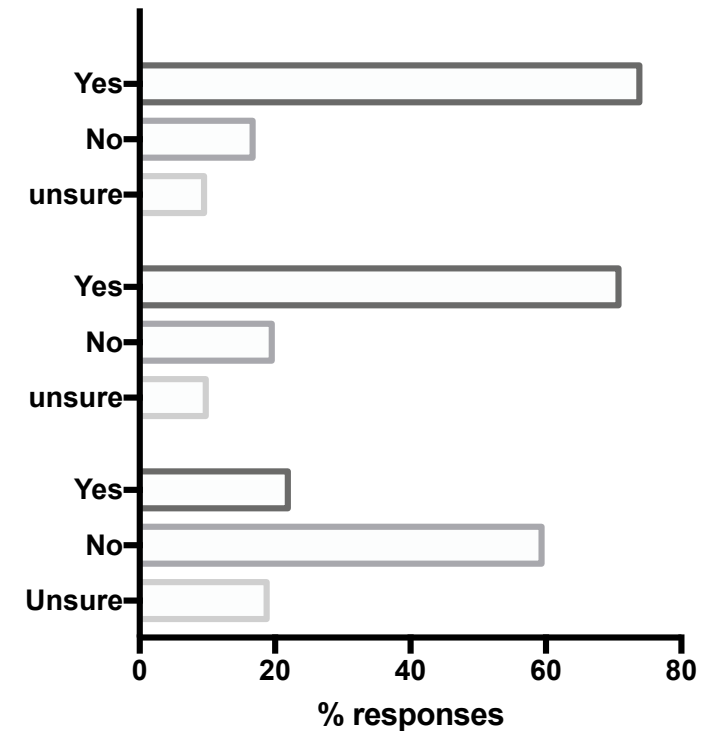
What should be considered strict exclusion criteria?



Coronary artery disease and/or heart failure greater than NYHA class 1/AHA stage A

Chronic kidney disease >= stage 3

HIV negative sexual partner not using or able to access PrEP

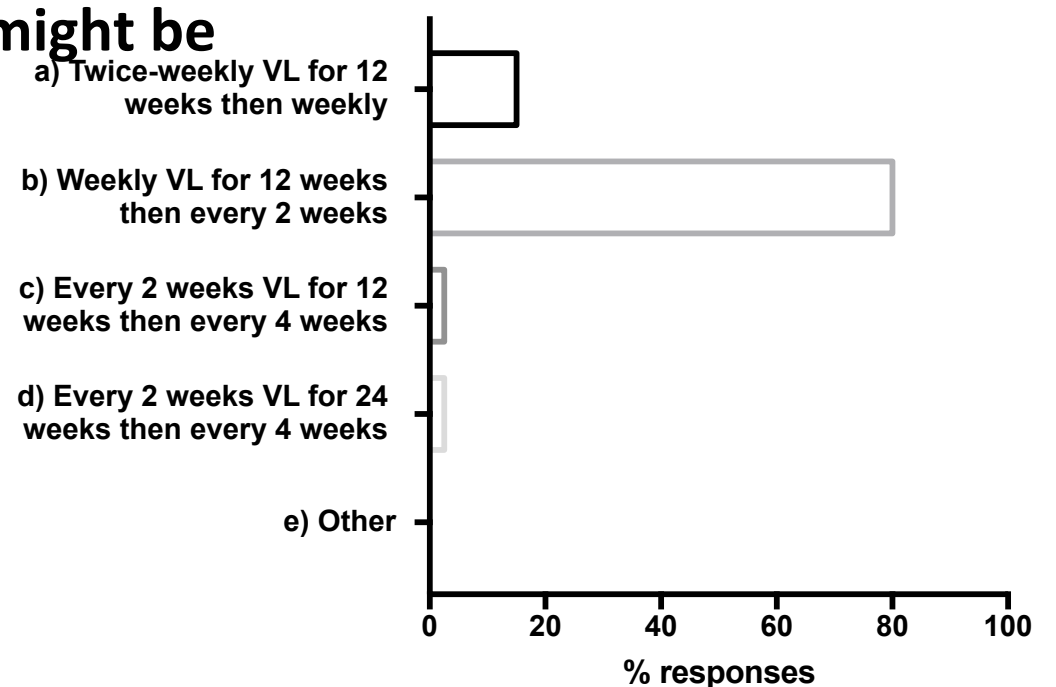


- There was consensus that **all children who are younger than 2 years of age should be excluded.**

Risk Mitigation Strategies II: Monitoring and ART Resumption Criteria

What is adequate monitoring during ATIs?

- Viremia, clinical symptoms and CD4 counts as critical measures
- Weekly monitoring is a realistic maximum.
- Switching to every other week monitoring might be considered after 12 weeks
- Home testing considerations



Risk Mitigation Strategies II: Monitoring and ART Resumption Criteria

When should ART be re-initiated: Safe ART restart criteria?

There was **consensus that ART should in general be restarted if requested** by the participant, if a **participant becomes pregnant** or if ART deemed **medically necessary** for non-HIV related causes.

Symptomatic HIV disease.

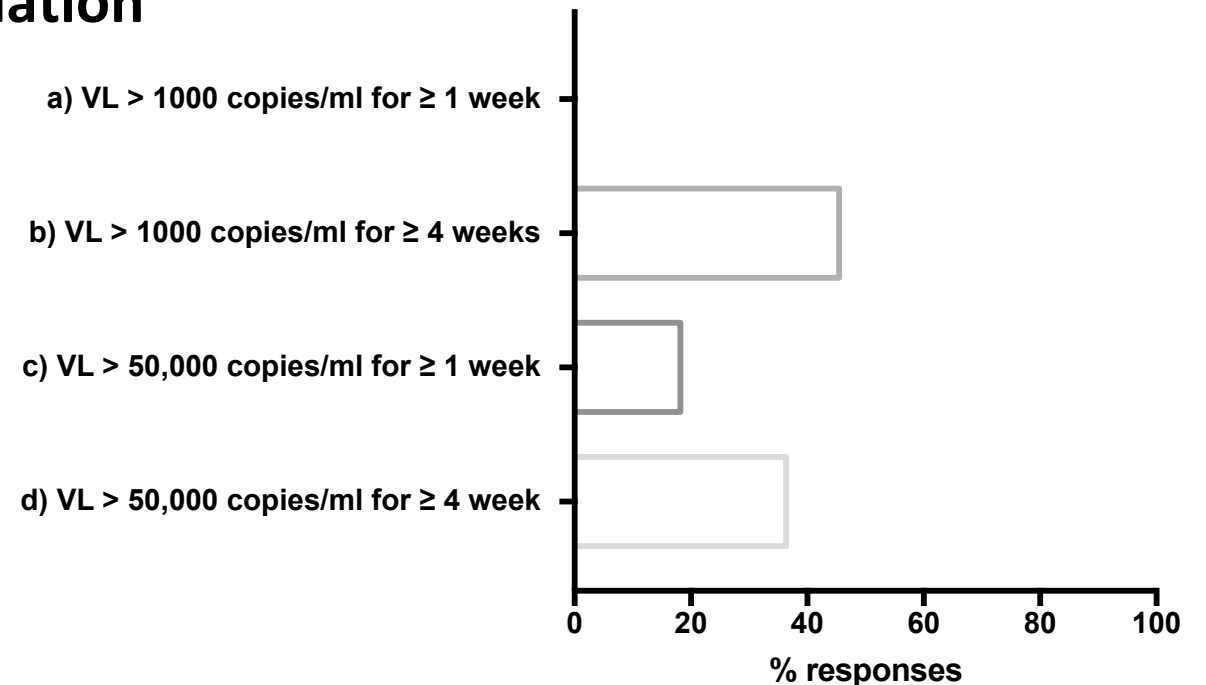
CD4 levels. It was proposed to use an absolute CD4 value (i.e. **CD4 <350 cells/mm³** or **CD4% <15**) versus a % decrease (e.g. **how relevant is a decline of 30% in someone with 1000 cells/mm³**)

Evidence of unprotected sex. It was suggested that **participants that are unable to adhere to transmission precautions, i.e. as documented by new diagnosed sexual transmitted disease, should be excluded from the trial or restarted on ARTs immediately.**

Risk Mitigation Strategies II: Monitoring and ART Resumption Criteria

When should ART be re-initiated-safe ART restart criteria?

- Restart ART after two tests confirm predefined viremia threshold
- No consensus on generally applicable VL threshold for ART restart
- **>100.000 cp/ml should result in ART reinitiation**
- **Concerns:**
 - If the VL ART restart criteria are too restrictive, will we miss post-treatment controllers?
 - If rebound set point is the objective, it might be reasonable to tolerate longer periods of viremia



Ethics of ATI Studies

Should we avoid “cure” in protocol titles and informed consent forms? What terminology should we use?

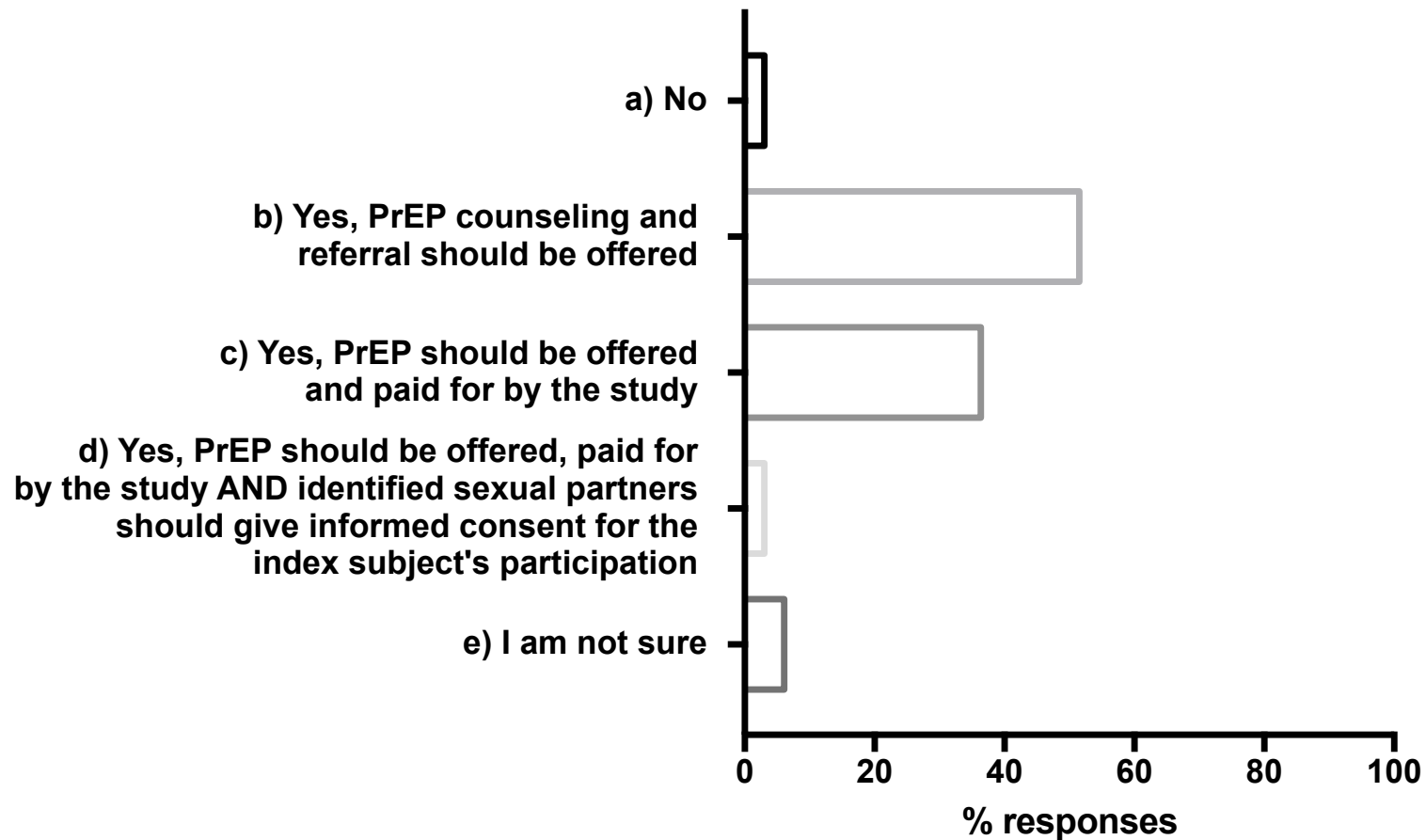
- There was **some agreement** that “**cure**” should *not* be used in titles and consent forms for studies.
- **Alternatives** suggested included “**drug free long-term control**”, “**undetectable off treatment**”, “**remission**”, “**viral suppression off treatment**”, “**ART free viral remission.**”

When is there sufficient justification for including a placebo control? Are ATI studies valid without placebo controls?

- There was **consensus** that the **scientific validity** of a study—which may depend on the **presence of a placebo**—can have a **direct influence** on whether or not the study is also **ethically sound**.
- If a placebo group is necessary for the findings of a study to be properly interpreted, **it could be considered unethical *not* to include a placebo.**

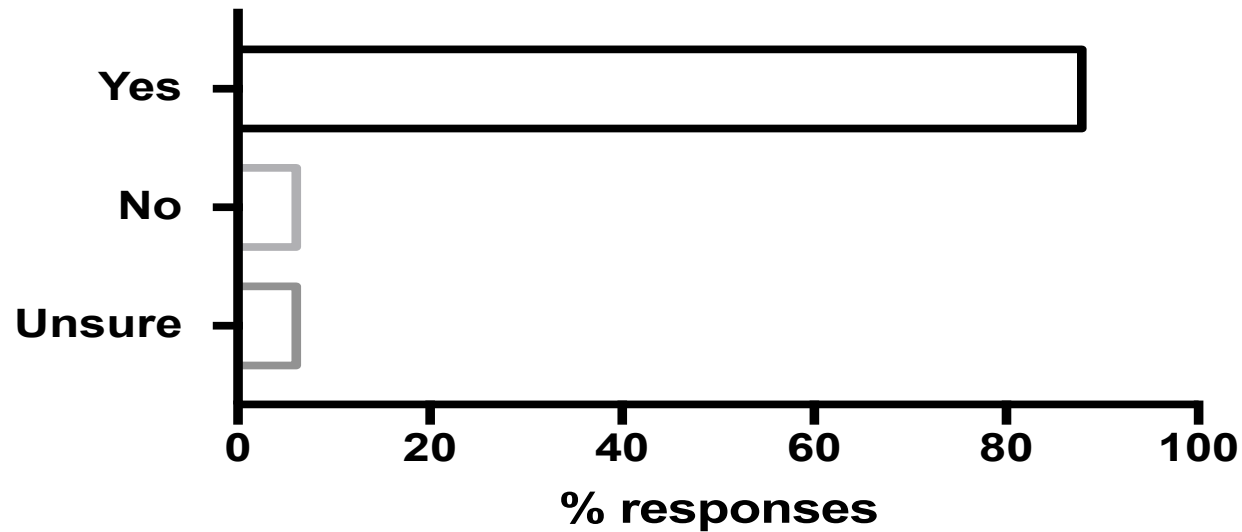
Ethics of ATI Studies

Responsibility towards sexual partners of ATI study participants: Should PrEP be offered to sexual partners of ATI study participants?



Ethics of ATI Studies

A set of socio-behavioral/ethics questions adapted to the protocol should be systematically examined during clinical research involving ATIs?



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