



Research into a functional cure for HIV in neonates: the need for ethical foresight

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In 2013, researchers announced that a newborn child from Mississippi, USA might have been functionally cured of HIV by being given combination antiretroviral therapy within hours of birth. Public and media attention has since been captured by the possibility of finding a cure for HIV transmitted from mother to child. Research into the strategy used for the Mississippi patient is crucially important to establish whether it can be replicated and shown to work in diverse populations. At the same time, any ethical issues likely to arise in such studies should be addressed and not ignored in the pursuit of a functional cure. In this Personal View we identify ethical issues that could arise in research towards achievement of a functional cure for HIV in neonates, including difficult trade-offs associated with choosing the study population and questions about the broader social implications of the research, and propose ways to resolve them.

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Introduction

A recent report suggests that an infant from Mississippi, USA, has been functionally cured of HIV or is at least in sustained viral remission without the need for further antiretroviral therapy (ART).¹ The importance of studies to assess whether the strategy used in Mississippi works in other infants² is clear, given the fact that around 260 000 infants worldwide were infected with HIV in 2012 alone,³ but in the excitement surrounding the Mississippi child, the ethical challenges raised by this line of investigation should not be neglected. Previous articles have surveyed the ethical concerns that arise in HIV cure research in general;⁴⁻⁶ however, this Personal View is the first to identify and propose solutions for the unique ethical challenges facing investigators on whether very early ART can functionally cure HIV in neonates (table). This analysis might also be relevant for other studies with neonates.

The Mississippi child

A woman in labour arrived at the hospital but was diagnosed with HIV too close to delivery to receive ART to reduce the risk of transmitting HIV to her child. Typically in these cases, infants receive two or three drugs for prophylaxis at lower doses than for treatment and following a different schedule. Although clinical trials have only recently shown the benefits of giving neonates combination drugs to prevent mother-to-child transmission of HIV,⁷ 2010 guidelines on prevention of HIV transmission allowed physicians to use up to three drugs for infants at high risk.⁸ The physician started the child on a three-drug regimen to prevent infection, with nevirapine given at a higher dose than typically used for treatment rather than prophylaxis.¹ When the child's HIV infection was confirmed by day 7 of life, she was maintained on ART as recommended by treatment guidelines.⁸ At some point between 15 months and 18 months of age, ART for the child was stopped by her caregiver for unknown reasons. When the child returned to care, she had no virus replicating in her bloodstream or detectable replication-competent viral reservoirs, which led the investigators to conclude that she was

probably functionally cured or in sustained viral remission;¹ plasma viral load and HIV-1 antibody titres remained undetectable at age 30 months.

Therefore, very early therapy might offer a unique opportunity to limit HIV replication and possibly functionally cure HIV in infants. On the basis of animal data, the window of opportunity to achieve a functional cure through very early therapy could close at some point between 48 h and 10 days after birth.⁹ This suggests that replication of the results in the Mississippi case might only be possible by treatment of infants before they are confirmed to be HIV infected, because up to 2 weeks are needed for this confirmation.

Without solid evidence that very early ART is an effective functional cure for HIV, or that it can lead to sustained viral remission, it would be premature for physicians to begin treating infants with the strategy used for the Mississippi baby. As a cautionary example, in the 1990s clinicians widely adopted high-dose chemotherapy with autologous bone marrow transplantation as a therapy for breast cancer, even though it was an expensive and toxic treatment that was later shown to offer no advantage over the existing standard of care.¹⁰ Therefore, research into the risks and benefits of very early therapy for HIV in neonates is clearly important, as is the need to identify and address the accompanying ethical challenges.

Choice of population and design

In view of the publicity surrounding the Mississippi child, some physicians might merely adopt the regimen used in that case. If the strategy of very early ART becomes widely adopted, one possibility would be to conduct observational research by identifying and studying these infants. Observational studies on infants started on combination therapy very soon after birth would need a widespread referral network and for providers to document their actions carefully and consistently. If practice is in fact changing, then this approach could help to answer the research question efficiently and diminish the burden of consent associated with research, because the only study-related procedures

Proposals	
Choice of population and design	
If practice is changing, can the study include opportunistic data collection only?	To ensure enough participants, study will need to actively recruit before therapy is initiated
Chosen design should be able to answer important scientific questions, minimise risks, and maximise benefits	Initial proof-of-concept study could be achieved with a one-arm interventional study
Need to avoid potential exploitation of participants in LMICs	Results are relevant to LMICs; plan for expected needs after the study
Enrol more susceptible participants at higher risk or participants at lower risk of transmission?	Enrol more high-risk patients to improve risk-to-benefit ratio for participants
Risks and benefits for infants	
Risks of very early combination ART in many infants who will not be infected	Enrol population at high risk of HIV transmission to enhance benefits, carefully monitor safety, and test for HIV as soon as possible
Treatment discontinuation	Develop rigorous criteria for discontinuation and restarting if needed
Risks and benefits for mothers	
Risk of inadvertent disclosure of mothers' HIV status	Approach mothers alone
Burden of consent during labour	Use strategies to reduce burden; if available and appropriate, allow mothers to defer to fathers
Informed consent	
Ability to give valid consent during labour?	Develop stepwise, short form consent process to minimise burdens
Social effect	
Pressure to stop early	Devise careful stopping rules, safety monitoring plan
Need for follow-up research even if standard of care changes	Harness existing momentum to motivate needed future research
Possibility of negative results	Gather data in infants in whom cure strategy did not work
LMICs=low-income and middle-income countries. ART=antiretroviral therapy.	
Table: Ethical challenges in research into early antiretroviral therapy in neonates with HIV	

would be HIV testing, data collection, and discontinuation of therapy according to the protocol. Whether this strategy alone could recruit enough infants to answer the research question effectively is unknown, so initially investigators should plan to actively recruit women before therapy is initiated.

To the extent that the goal of the initial studies is to establish whether the Mississippi results can be replicated, it is not clear whether there is a scientific reason to do a randomised controlled trial. Moreover, careful testing could rule out potential confounders, such as the possibility that any infants identified as functionally cured were never actually infected or are elite controllers. Ethically, the most appropriate design is that most likely to answer the question while exposing participants to the least risk. To design the initial investigation as a one-arm interventional trial or even as an observational study, as opposed to a randomised controlled trial, might forfeit some certainty but minimises possible harm and maximises possible benefit for the infants.

Should the participants be first recruited from high-income countries (HICs) or from low-income and middle-income countries (LMICs)? Most infants with HIV are in LMICs; however, studies in LMICs might exploit participants if interventions tested will only benefit people in HICs.^{11,12} Such concerns can be allayed if research is relevant to local health priorities and resources, and the study results are likely to be put into practice in LMICs.¹³⁻¹⁵ Importantly, research into very

early treatment of neonates is clearly relevant to the health priorities of LMICs and is likely to include drugs that are licensed and available in LMICs with high burdens of HIV/AIDS. To address worries about the translation of the results into practice, researchers should engage with ministries of health, treatment programmes, and international organisations in advance to help stakeholders anticipate how to meet possible needs created by the research. Another worry is that, in LMICs, comorbidities could be more common and might increase the risks or make identification of safety concerns more difficult. Careful monitoring of participants and timely access to care will help minimise these risks and maintain scientific integrity.

One reason to do this research in LMICs is that infants in these countries will comprise most of the target population for a potential functional cure, and their enrolment could help ensure that the results are relevant. Inclusion of patients from both high-income and low-income settings will enable participants to be found more quickly, and faster enrolment will give earlier answers to the research questions and ensure that others benefit from the study results sooner.

Should the study enrol participants at high risk of HIV transmission or at lower risk? This choice brings up ethical trade-offs regarding the vulnerability of the mothers and the risks and benefits for the infants, because a functional cure study would include very early initiation of ART. Women at high risk of HIV transmission who have not previously had prenatal care

might be less well educated, less well integrated into the health-care system, and of lower socioeconomic status than women at low risk of HIV, and they might also be unaware of their HIV-positive status.¹⁶ Historically, vulnerable groups have sometimes been targeted for inclusion in research studies because they were less able to protect their own interests. Ethical guidelines therefore recommend that vulnerable groups are only enrolled when non-vulnerable groups cannot.¹³ To select participants to take advantage of their vulnerability would clearly be wrong. However, automatic exclusion of vulnerable populations from clinical studies is misguided when it does not address the source of their vulnerability and merely restricts their ability to choose substantial potential benefits.¹⁷

The reason for inclusion of women at high risk of transmission is to increase the chance of benefiting their vulnerable infants and to answer scientific questions—not to target them because they would have little time to consent or are probably unfamiliar with the medical system. If the investigation includes women not taking ART and presenting to hospitals during labour, the overall risk of transmission is around 8·5%. This risk varies somewhat on the basis of how many drugs are given to the infants to prevent infection.⁷ By contrast, a functional cure study that enrolls women who are well controlled on ART (at 1–2% risk of transmission)¹⁸ would have to enrol and expose many infants to the risks of very early combination therapy, most of whom would not ultimately be infected with HIV with routine prophylaxis.

This analysis suggests that proof-of-concept research should enrol infants at high risk of infection. Of course, the enrolment of a high-risk population also depends on ensuring that the risk-to-benefit ratio for that population is acceptable.

Risks and benefits

Infants

Children are vulnerable in that they cannot consent for themselves; therefore, ethical paediatric studies should ensure that either the risks are justified by the potential benefits in relation to the alternatives, or that any risks not justified by the benefits are low and justified by the social value.¹⁹ Would the research satisfy these conditions?

To identify the risks, we have to first establish what participants would otherwise receive as standard of care. The standard of care for prevention of mother-to-child transmission of HIV is evolving, and clinicians might be changing their practices after the reporting of the Mississippi patient. In general, the current standard of care involves starting newborn babies at high risk of HIV transmission on one or more drugs proven to work for HIV prevention.²⁰ For infants later confirmed to be HIV positive, families will be educated about treatment and infants placed on lifelong ART.

By contrast, a functional cure study would treat infants earlier with more drugs, thereby exposing infants to the

risks associated with very early combination therapy and with stopping treatment in infected infants to see whether they are functionally cured. Because about 8·5% of high-risk infants would actually be HIV-infected at birth, 91·5% of the infants would be exposed unnecessarily to the risks of ART for at least 2 weeks (until the results of negative HIV DNA and RNA PCR tests from samples obtained during the first 2 days of life are available). Little is known about the toxic effects of short-term ART for neonates, but several have been described in infants exposed in utero for prevention of mother-to-child transmission of HIV. These risks include mitochondrial toxic effects, transient growth and haematological abnormalities, anaemia, and changes in liver function.^{21–24} The risk of mitochondrial toxic effects seems low^{21,22} and it is not clear what their long-term significance is, or the extent to which they might be affected by HIV infection itself.²² Investigators should carefully consider available evidence about the safety of specific drugs in neonates when selecting a combination ART regimen. To reduce the risk of exposure of uninfected infants to ART, as previously discussed, mothers at high risk of transmission should be enrolled, and uninfected infants should be taken off ART as soon as possible. The study team should also develop safety procedures to minimise known risks, such as inclusion of regular monitoring for anaemia and changes in liver function, and exclusion of premature infants.

Discontinuation of ART poses risks of viral rebound, development of resistance, and other unknown risks.²⁵ However, results from one study have shown that children having planned treatment interruptions could successfully be restarted on ART with viral suppression and improvement in CD4 cell counts.²⁶ The decision of when to discontinue ART in studies investigating a paediatric cure for HIV is an important and complex issue—experts need to come together to develop consistent standards across different studies. In general, ART should not be discontinued until ample time has been given for the strategy to work on the basis of existing data, and children should be carefully monitored after treatment discontinuation. Independent safety monitoring will be an essential component of risk minimisation in these studies, to ensure that the standards for discontinuation can be quickly modified if necessary. Counselling and other strategies to maintain adherence might be important to ensure parents do not discontinue ART prematurely. Additionally, rigorous criteria should be developed to ensure that children restart ART as soon as possible if they are not functionally cured.

One standard to determine whether the benefits justify the risks to individual infants is to ask whether a reasonable clinician would recommend that their patient enrol in the study.²⁶ Institutional review boards for the trials could assess the benefits and risks by consulting experts in paediatric HIV and prevention of mother-to-

child transmission. In theory, the strategy offers potentially large benefits and a moderate risk and is a reasonable alternative to lifelong ART (which carries significant long-term risks of toxic effects). Moreover, infants at risk of infection cannot have access to the potential benefit of a functional cure unless they are enrolled before confirmation of HIV infection. For these reasons, a clinician might be likely to recommend enrolment for infants, especially for those at high risk, which suggests that doing the initial study in infants at high risk of HIV transmission is ethically acceptable.

Mothers

Women in a study might be at risk of inadvertent disclosure of their HIV status. One study²⁷ reported that only 37% of HIV-positive women in prenatal care had disclosed their HIV status to their husbands. Disclosure of HIV positivity can be risky,²⁸ so women should be approached carefully for their consent with a description of the investigation in generic terms that does not reveal their HIV status when others are present, and investigators should find a way to discuss the details of the study with only the mother in the room. Clinicians who treat such patients might already face many similar challenges, so these issues might not be wholly unique to research, but investigators should nevertheless think of creative ways to minimise these risks.

Consent during labour

Mothers would have to decide whether to enrol their newborn babies into a trial during labour or immediately after, which could incur substantial burdens. Women in labour or who have just delivered might not be able to focus on a research consent process, and some mothers might not even be aware of their HIV diagnosis before arriving at the hospital. Clinicians associated with the study should be trained how to disclose HIV-positive status and provide any counselling needed in the context of labour and afterwards. Moreover, these women are at the highest risk of transmitting HIV to their infants and are likely to value the benefit of a potential functional cure. Development of a consent process that is too stringent to be used in the context of labour could make it impossible for many women to enrol in the study and obtain significant benefits, and therefore might not respect their autonomy.²⁹

A plan for a robust consent process during labour could include an assessment of whether the women are capable of providing consent. This assessment would include checking factors such as fatigue, severe pain, and degree of inward focus. Some precedents already exist for women being asked to consent during labour to some interventions—women routinely give or withhold consent for oxytocin, epidurals, caesarean sections, and forceps, during labour. The results of some studies show that women are capable of giving valid consent during labour,^{30–33} although others have questioned their ability

to recall information received during consent processes about emergency interventions.³⁴ It might be preferable to obtain consent from both the mother and father when possible, because infants in the study could face substantial risks and the study might be controversial and high profile. Although consent from both parents is not required by regulation in the USA,³⁵ it might be required by other countries' regulations. However, some fathers might not be present, and their absence should not be a reason to exclude otherwise eligible infants. As mentioned, serious risks are associated with inadvertent disclosure of a woman's HIV diagnosis. Therefore when fathers are present, assuming that regulations allow for only one parent to give consent, the mother could be asked if she has any concerns about the father being approached to give consent. In some cases, the mother might prefer the father to make the decision in her place, to relieve the burden of providing consent. If, however, the mother is in a very advanced stage of labour and the father is absent, the infant should not be enrolled without any parental consent.

The burden of decision making might be minimised by delaying consent until after delivery for at least some women, or with a shortened consent form that would cover the first few days of participation. The functional cure strategy being tested, however, relies on initiation of therapy as soon as possible, and delaying consent until after labour could delay therapy initiation. Blood samples might need to be drawn during labour or soon after birth for research purposes, so consent for these samples could not be delayed. There are also many demands on women in the period immediately after labour, including initiation of breastfeeding in some cases, learning to care for a new infant, receiving visitors, and recuperation.

A shortened consent form administered during labour could therefore be a more useful solution. Results from studies have shown that concise consent forms can lessen burden without decreasing comprehension or satisfaction,^{36,37} and a more comprehensive informed consent process could happen after delivery. As has been done with other studies,³⁸ ongoing consent should be obtained with different consent forms (or reminders of the previous consent) used at key points in the investigation.³⁹

Community consultation, which is required for emergency research and often done in international research,⁴⁰ could further alleviate the burdens associated with consent. Women with HIV who have previously given birth might have insight on when and how to obtain consent. With efforts to maintain scientific accuracy and communicate clearly in lay language, engagement with host communities and local media networks might be able to help disseminate information widely in advance. Careful dissemination could be a valuable source of information for some potential participants before enrolment.

Social implications of research

To avoid incurring unintended and adverse consequences, the broader implications of the investigations should be thought through. With intense scrutiny of the research, pressure might be applied to stop enrolment early and publicise positive results—particularly after the first infant seems to be functionally cured or in remission. Even if early results are positive, because participants would not be randomly assigned to treatment groups in a proof-of-concept study, there is no ethical imperative to stop the studies, and plenty of good reason to continue to gather longer-term and more complete data. Nevertheless, the investigators should plan when to publicise positive interim results. On one hand, favourable results should not be released without high confidence in their validity because they are highly likely to change practice. On the other hand, waiting longer than necessary could miss opportunities to protect many infants from HIV infection.

Even if an initial study is successful, future research will be very important to establish how applicable results are to different populations and to refine a strategy towards neonatal functional cure of HIV. For instance, if results are positive but very early ART causes significant toxic effects, the possibility of a cure with fewer drugs or a shorter duration of therapy should be explored. Follow-up studies could be challenging, because if the functional cure strategy becomes standard of care for infants at high risk of HIV infection, it could be regarded as unethical not to offer participants the best proven treatment.

Negative results (or viral reactivation with potential drug resistance) are possible with this study, and therefore consultations with local health authorities in advance will be important to ensure access to second-line ART drugs for infants who need them after the study is finished.^{41–43} If the study is unsuccessful, establishing why the cure strategy did not work in some infants will be essential. The tremendous amount of attention and energy generated from the publicity that surrounded the Mississippi child has galvanised support for future research. To maintain progress towards a functional cure for HIV in neonates, this momentum should be kept going with a clear communication strategy, irrespective of whether the results are positive or negative.

Conclusion

The apparent functional cure of the Mississippi child should be followed by research to find a cure for HIV in all infants. This goal is of substantial importance, in terms of potential lives saved, the symbolic value in the battle against HIV, and the possibility of elimination of paediatric HIV infection.⁴⁴ In this endeavour, as with other medical breakthroughs that capture the public imagination, sponsors and investigators need to move forward with this research while considering carefully the choice of study population and how to minimise the risks and burdens for participants, plan for negative

results, and address the important ethical implications that could arise even if the study achieves the full measure of its promise.

Contributors

SKS and CG helped with the conception of this Personal View. SKS did the literature search, wrote the first draft, and managed all subsequent revisions. CG, DP, DSW, HAT, HG, and MK provided comments on the draft, information, and editing of the manuscript.

Declaration of interests

We declare no competing interests.

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