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

Seema K Shah, Deborah Persaud, David S Wendler, Holly A Taylor, Hannah Gay, Mariana Kruger, Christine Grady

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 achievment 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.

Lancet Infect Dis 2014; 14: 893–98

This online publication has been corrected. The corrected version first appeared at thelancet.com on August 25, 2014

Published Online June 4, 2014 http://dx.doi.org/10.1016/S1473-3099(14)70766-2

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Clinical Center Department of Bioethics, National Institutes of Health, Bethesda, MD, USA (S K Shah JD, D S Wendler PhD, C Grady PhD); **Johns Hopkins University School of Medicine and Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, MD, USA** (D Persaud MD); **Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health and Johns Hopkins Berman Institute of Bioethics, Baltimore, MD, USA** (H A Taylor PhD); **Department of Pediatrics, University of Mississippi Medical Center, Jackson, MS, USA** (H Gay MD); **and Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa** (M Kruger PhD)

Correspondence to: Ms Seema Shah, Clinical Center Department of Bioethics, Division of AIDS, National Institutes of Health, Bethesda, MD 20892, USA **shahse@mail.nih.gov**

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 infants[2] 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 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