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Antiretroviral treatment in HIV-infected infants and young children: novel issues raised by the Mississippi baby

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Abstract

The recent case report of an HIV-infected child in Mississippi with viral control post-antiretroviral therapy (ART) interruption has sparked interest in the possibility of “functional cure” in infants if they initiate ART very soon after birth. The “Mississippi baby” also raises many new questions around clinical care of HIV-infected infants and young children, including when treatment should be initiated, why treatment should be initiated, what treatment should be initiated, and how to identify infants early enough to treat them adequately. Here, we review research conducted before the report of the “Mississippi baby” highlighting the important new issues that now need to be taken into consideration.

Keywords

HIV; antiretroviral treatment; functional cure; infants; viral reservoir

Introduction

The burden of pediatric HIV infection remains overwhelmingly a challenge for resource-limited settings, particularly sub-Saharan Africa. Despite the global scale up of prevention efforts, an estimated 230,000 children were newly-infected with HIV in sub-Saharan Africa in 2012 [1], adding to the existing pool of 2.9 million children estimated to be living with HIV in the region. These numbers stand in stark contrast to resource-rich regions, where new perinatal infections are rare and effective antiretroviral treatment (ART) is available. Driving this divide is the high prevalence of HIV among childbearing women and incomplete implementation of effective prevention of mother to child transmission (PMTCT) programs [1]. For HIV-infected children who are left without treatment, disease progression is rapid and mortality rates are high [2]. Though it is clear that early ART can

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prevent many deaths, prompt diagnosis of HIV infection in infants and early initiation of ART remain major unachieved public health goals in many resource-limited settings [3].

The Mississippi Baby

The recent case report of an HIV-infected child in Mississippi with viral control post-ART interruption has sparked interest in the possibility of “functional cure” in infants if they initiate ART soon after birth [4]. In brief (Table 1), the “Mississippi baby” was born at 35 weeks of gestation to an HIV-infected mother with no prenatal care. The child was initiated on a three-drug regimen of nevirapine, zidovudine, and lamivudine at approximately 30 hours of age, before HIV infection was confirmed. A subsequent positive result from a DNA PCR test performed on blood taken at 30 hours and a low HIV RNA quantity of 19,812 copies/mL (cpm) on a separate sample taken at 31 hours confirmed HIV infection and suggested that transmission likely occurred late in pregnancy or during delivery. The infant was switched from nevirapine to a ritonavir-boosted lopinavir (LPV/r) regimen at one week of age. Detectable HIV RNA quantities at three subsequent time points were 2,617 cpm (6 days), 516 cpm (11 days), and 265 cpm (19 days), consistent with declining viremia associated with response to ART, and fell below the limit of detection at 29 days. The child remained on ART until 18 months of age, at which point the mother missed several clinic appointments. When the mother returned, she reported that the child had been off ART for the past five months. When tested at this time (23 months of age), the child had no detectable HIV RNA. A repeat sample one month later (24 months) also had no detectable HIV RNA or HIV DNA by standard clinical assays. Using an ultrasensitive assay, an HIV RNA quantity of 1 cpm was detected at 24 months but, even with this assay, no HIV RNA was detectable at 26 months. No replication-competent HIV was detected in resting CD4+ T-cells at 24 months. HIV antibody tests at 24, 26, and 28 months of age were negative. At the time the case was reported, the child had been off therapy for 12 months (30 months of age) and had not experienced viral rebound. The authors hypothesize that the introduction of very early ART at 30 hours of life may have prevented the establishment of HIV reservoirs and hence resulted in “functional cure” [4].

The Mississippi baby raises many challenging and complex questions about HIV pathogenesis and the potential to achieve functional cure. The case equally raises many challenging and complex questions about *clinical* care of HIV-infected infants and young children. In this review, we focus on the clinical care aspects raised by this intriguing case highlighting some of the new issues that need to be considered. In particular, the Mississippi baby requires that we reassess several clinical approaches considered resolved in the field of pediatric HIV care and treatment prior to this case (Table 2), including 1) When should treatment be initiated – e.g. should we initiate ART at one year of age, six weeks of age, or at birth?; 2) Why should treatment be initiated – what outcomes are we trying to achieve?; 3) What treatment should be initiated – what options do we have available for early treatment?; and 4) How do we identify HIV-infected infants early enough to treat them adequately?

When should treatment be started?

Current treatment guidelines issued by the World Health Organization (WHO) recommend that treatment be started in all children under 5 years of age regardless of clinical signs and symptoms and regardless of CD4 status [5]. These most recent revisions to the WHO guidelines followed from earlier guidelines dating from 2008 that infants (i.e. children under 12 months), and then later updated to include all young children under 2 years of age (2010), initiate treatment irrespective of clinical and immunological status. The 2008 guidelines were largely informed by the Children with HIV Early Antiretroviral (CHER) trial conducted at two sites in South Africa [6,7]. In brief, 377 asymptomatic infants who met eligibility criteria (6-12 weeks of age, confirmed HIV infection, CD4 percentage $\geq 25\%$) were randomized to one of three strategies: immediate ART for 40 weeks (iART-40W), immediate ART for 96 weeks (iART-96W), or deferred ART (ART-Def). For children in the ART-Def arm, ART was only initiated if clinical or CD4 criteria (CD4% less than 20% before February 2007 or CD4% less than 25% after February 2007 or CD4 count less than 1000 cells/mm³) were met. The first-line regimen used in the trial was LPV/r, zidovudine, and lamivudine and the primary endpoints were time to death or failure of first-line ART. Interim findings published in 2008 showed that early mortality was reduced by 75% in the two immediate ART groups relative to the deferred group [6]. In the final study results, after a median follow-up of 4.8 years, the risk of death or failure of first-line ART was 41% lower in the iART-40W arm (hazard ratio (HR) 0.59, 95% CI: 0.38-0.93, $p=0.023$) and 53% lower in the iART-96W arm (HR 0.47, 95% CI: 0.29-0.76, $p=0.002$) compared to the ART-Def arm. The risk of a first severe CDC B or C event or death was 47% lower in the iART-40W arm (HR 0.53, 95% CI: 0.34 to 0.82, $p=0.005$) and 58% lower in the iART-96W arm (HR 0.42, 95% CI: 0.26 to 0.67, $p=0.0003$) compared to the ART-Def arm. Mortality was 18% for the ART-Def arm compared to approximately 9% in the iART-40W and iART-96W arms [7]. The CHER trial clearly demonstrated the superiority of starting ART promptly in young asymptomatic infants rather than waiting for CD4 T-cells to be depleted or clinical symptoms to develop.

The CHER study offered a paradigm shift for the field by simply allowing the diagnosis of HIV infection to be the reason for ART initiation in infants, irrespective of other signs and symptoms or laboratory tests. In adults, guidelines for when to start treatment have generally been based on clinical and CD4 criteria [8]. Prior to 2008, this was also the case in children. Criteria for starting treatment in children prior to 2008 included WHO stage 3 or 4 disease or CD4 percentage of less than 20% for children 12 months to 36 months of age or a CD4 percentage of less than 25% for children younger than 12 months of age [9]. During infancy lymphocyte numbers are high and variable [10,11]. Thus part of the need for immediate ART is the weaker prognostic significance of CD4 criteria in infancy relative to in older children and adults [12]. Furthermore, access to CD4 testing is a barrier to treatment in some resource-limited settings and starting ART on all young children circumvents this barrier.

Another important driving force supporting early initiation of ART in infants and young children is that disease progression in this group is more rapid than observed in older children and adults [13-15]. Early studies of perinatally-infected children suggested a bimodal distribution with one group of about 20-30% of children progressing rapidly to

AIDS and death in the first year of life and the rest progressing at a slower rate more similar to adults [13]. More recent evidence supports this view. In an analysis of 4000 perinatally-infected children, the risk of progression to AIDS and death for a one-year-old with an HIV RNA quantity of 100,000 cpm was 11% and 5%, respectively, compared to a ten-year-old (risk of 5.1% and 2%, respectively) [16]. In adults it is rare to observe HIV-related mortality within weeks or even months of infection. The dramatic reduction in mortality associated with early treatment in the CHER study was the impetus to recommend ART initiation as soon as possible after diagnosis.

It is tempting to interpret the CHER findings to imply that treatment should be started at birth if a child is identified at birth as in the case of the Mississippi baby; however, this is an awkward extrapolation. Children in the CHER trial were a median of 7.4 weeks (IQR 6.6-8.9) of age at enrollment. The usual practice in these settings at the time the study was conducted would have been to offer an HIV DNA PCR test at six weeks with the result returned at eight weeks and treatment initiated at some point hopefully “soon” thereafter. Thus the results from CHER are largely uninformative about whether or not treatment should be started at birth or what the relevant window of time would be after birth diagnosis to initiate treatment.

At the older end of the age spectrum, i.e. children 2 to 5 years, WHO guidelines now recommend immediate treatment despite the fact that both clinical trial and observational data suggest it is not necessary [5]. The PREDICT trial enrolled 300 children 1-12 years of age in Thailand and Cambodia (median age 6.4 years) and randomized them to immediate treatment at study entry or deferred treatment when CD4 percentage declined to less than 15% [17]. This study did not find differences in AIDS-free survival between the deferred and early treatment groups and mortality was exceptionally low. A modeling study conducted by the IeDEA-Southern Africa Network on 2,934 ART-naïve children 24-59 months old with CD4 counts above existing eligibility thresholds also did not show any difference in survival between ART initiation based on the current CD4 threshold (750 cells/mm^3 or less than 25%) or regardless of CD4 count [18]. In this population, an estimated 72.2% of the children with a CD4 count greater than 750 cells/mm^3 or greater than 25% would become eligible for treatment initiation by three years after enrollment. The rationale for the WHO guidelines appears to be largely programmatic, to simplify approaches to pediatric treatment with the goal of improving ART coverage for children.

Why should treatment be initiated?

Rapid disease progression is a distinctive feature of early life HIV infection. In the absence of ART, about 20% of perinatally HIV-infected children progress to AIDS or death in the first year of life [2,19]. Substantial mortality is exhibited even in infants who receive HIV care by 5 months of age [20]. The traditional goal of early ART initiation for children is to reduce mortality and morbidity, as well as to achieve normal growth and development and improve quality of life.

Mortality

Evidence from the CHER clinical trial and observational studies have demonstrated early initiation of ART reduces mortality. The CHER trial demonstrated that immediate initiation of ART in infants, rather than deferred treatment until clinical criteria are met, reduces early mortality by 75% [6]. Prospective follow up of infants in European cohorts provided an opportunity to evaluate the clinical benefit of early initiation of ART. This collaborative study found that those initiating treatment before three months of age relative to those deferring treatment had reduced risk of mortality and disease progression to AIDS (1.6% versus 11.7% at 1 year and 4.6% versus 21.5% at 5 years, $p<0.001$) [21].

Growth

Treatment clearly improves growth of HIV-infected children. In the United States, HIV-infected children aged 4 months to 17 years can achieve normal weight (weight-for-age z-score = 0) by one year and near normal height (height-for-age z-score = 0) by two years after ART initiation [22]. Studies of young children in sub-Saharan Africa also indicate significant improvements in growth after initiation of ART (children started on ART at a median age of five and three years, respectively) at varied rates of improvement [23,24]. Data emphasize the importance of early ART initiation to ensure adequate growth [17,25]. An observational study in Kenya (median age 4.7 years) saw more rapid reconstitution in children starting treatment before three years of age compared to those starting treatment at 6-10 years of age [25]. In the PREDICT trial (median age 6.4 years), the mean height gain per year was greater for those in the immediate treatment arm compared to those in the deferred treatment arm (5.4 cm versus 4.9 cm, $p=0.001$) [17]. We have shown that even at the younger end of the age spectrum earlier initiation of ART i.e. before six months of age is also associated with more rapid growth recovery than initiation between 6 and 12 months or between 12 and 24 months [26].

Morbidity

Several observational studies have suggested that initiation of ART before 6 months of age reduces the occurrence of early onset severe disease. In a study of HIV-infected infants born in the French Perinatal Cohort, six of 43 infants receiving ART after six months of age developed AIDS-associated events and encephalopathy during the first 24 months of life compared to none of 40 infants receiving ART before 6 months of age [27]. A multicenter study in Italy noted that no infants treated before six months of age experienced a CDC category A, B or C clinical event over the follow-up period while 44 of 103 (42.7%) infants receiving deferred treatment after six months of age moved to a more severe category (e.g. CDC category A to B) [28]. An even earlier age at ART initiation may have greater benefits. Initiation of mono/dual ART before two months of age is associated with delayed and decreased progression to category C conditions by three years of age, compared to initiation at 3-4 months [29]. In addition, in the CHER trial, more children in the deferred arm than the immediate treatment arms required hospitalization (70 versus 50 in each of the immediate ART arms, $p<0.0001$) and the total hospital duration for those admitted was 1018 days for the ART-Def arm versus 533 days for the iART-40W arm and 414 days for the iART-96W arm ($p=0.004$) [7].

Neurodevelopment

Infancy is a critical period for neurodevelopment, and data show neurodevelopmental delay in HIV-infected versus HIV-uninfected children [30-32]. In CHER, HIV-infected infants who started treatment early exhibited better neurodevelopment outcomes on the General and Locomotor subscales of the Griffiths Mental Development Scales [33]. Results in older children were slightly different; in the PREDICT trial, HIV-infected children surviving beyond one year of age without ART had similar neurodevelopmental outcomes whether randomized to initiate ART immediately or to defer treatment until meeting CD4 criteria, but both had poorer scores than HIV-uninfected children on intelligence quotient, Beery visual motor integration, and Binet memory tests [34].

Immunologic response

Early treatment is also associated with improved immunological response. In an Italian multicenter study, no infants treated before 6 months of age showed a CD4 T-lymphocyte percentage of less than 15% at any time point during follow-up compared to 20 of 103 infants receiving ART after 6 months of age ($p=0.02$) [28]. The European Collaborative Study found that initiation of ART at less than five months of age was associated with a more rapid improvement in CD4 count [35]. A recent modeling study characterizing patterns of long term CD4 recovery predicted higher long-term CD4 counts for children starting ART at younger ages [36].

Much of the evidence for the benefits of early treatment is from non-randomized observational studies, which present several methodological challenges. A strong selection bias may be present in many of the observational studies, as children who survive to an age to be included in these studies may represent an elite group who are less likely to die or be lost to follow up in the future. Selection bias may also affect clinical trials hampering generalizability. Confounding by indication is another issue present in many of the observational studies, as decisions to treat earlier or later may be dependent on disease severity and other indicators of prognosis.

Shifting goal posts: Should the goal of ART be “cure”?

The well-publicized “Berlin patient” is generally thought to be the one example of an “HIV cure.” The Berlin patient was treated for acute myeloid leukemia with total ablative chemotherapy, radiation therapy and stem cell transplantation with donor cells homozygous for chemokine receptor 5 (CCR5) delta 32 [37,38]. Thus the Mississippi baby who appears to have achieved this same endpoint simply with the early initiation of ART has ignited the hope that the goals of ART could be more ambitious i.e. to achieve “functional cure” rather than simply achieving its traditional objectives of reducing morbidity and mortality. Obviously, the goal of “functional cure” cannot be at the expense of compromising on the usual desirable attributes of ART. Determining whether early ART truly has this potential requires careful consideration of what endpoints might be considered evidence of steps along the way to “functional cure” justifying withdrawal of ART. “Functional cure” is generally defined as the lack of detectable viral replication in the absence of ongoing ART but in the case of the Mississippi baby, the mother made the decision to stop ART, not the

clinicians responsible for the child's care. Some studies have examined viral rebound after stopping ART but other parameters have been considered important in adding plausibility to the claim of functional cure, including the size of the viral reservoir, the extent and nature of residual viremia while on treatment, and the detection of HIV-specific immune responses.

Viral rebound

The Mississippi baby had an undetectable plasma level of HIV RNA more than 12 months after stopping ART [4]. This is unusual as in most studies of ART interruption in children, viral rebound above 50 cpm is common [39,40]. Viral rebound after ART cessation has also been shown in treatment interruption trials in children, although the focus of these studies has been on clinical endpoints, and several studies have found that interruption of treatment can be safe in some circumstances [7,41-43]. The key distinction is that the Mississippi baby was started on ART very soon after birth and presumably close to the time of HIV transmission. Thus the only studies of relevance as a comparison is in adult cohorts treated soon after primary HIV acquisition. The French Viro-Immunological Sustained CONtrol after Treatment Interruption (VISCONTI) study identified 14 post-treatment controllers who started ART within two months after presumed infection [44]. The Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) study also identified 11 post-treatment controllers at 24 months after treatment interruption out of 259 adults (4.2%) who initiated ART within three months after seroconversion [45]. However, these cases are rare, and viral rebound is reported in many adults starting ART close to HIV acquisition. In a study of participants in protocol-indicated ART interruption trials (SPARTAC and SMART), stopping ART initiated in primary HIV infection and chronic HIV infection was associated with viral rebound in similar proportions of participants four weeks after stopping treatment (78% versus 79%), but the level of rebound was significantly lower among those initiating in primary HIV infection compared to chronic HIV infection [46]. An additional study of viral rebound dynamics in adults undergoing a single treatment interruption found that all 46 chronic HIV infection patients had viral rebound over 48 weeks post-treatment cessation as well as 22 of 24 primary HIV infection patients but time to rebound was slower in the primary HIV infection patients (8 weeks versus 4 weeks, $p<0.001$) [47].

Size of the viral reservoir

The latent viral reservoir for HIV in resting memory CD4+ T-cells remains one of the greatest barriers to eradicating HIV in both adults and children [48-52]. Within the reservoir, the virus remains latent i.e. present but not actively replicating to produce new viruses and cannot be eliminated by ART, which can only target active forms of the virus [52]. The establishment of the latent reservoir occurs early in primary infection [53] and evidence supports that early initiation of ART may reduce the size of this reservoir [54,55]. A study of 47 Thai adults with recently-acquired infection reported that those started on ART in the earliest stages had the least amount of integrated virus in PBMC and in the sigmoid colon, restricting the "seeding" of long-lived central memory T-cells [55]. In a study of viral dynamics in 17 HIV-infected infants starting treatment in the first six months of life, the size of the viral reservoir declined over time and was found to be associated with time to first undetectable viral load [56]. Thus, early treatment of the Mississippi baby soon after birth may have reduced the size of the viral reservoir.

Residual viremia

In most HIV-infected individuals receiving ART, residual viremia (i.e. below the limit of detection of the standard clinical assay) can be detected using ultrasensitive assays and replication-competent virus can be isolated from CD4+ T-cells. The well-documented Berlin patient has had no trace of replication competent HIV and is deemed to be cured of HIV infection [38]. In the Mississippi baby, no HIV RNA was detected at 26 months using ultrasensitive virologic tests and a culture of CD4+ T-cells obtained at 24 months of age did not produce any replication-competent HIV [4]. It is unknown if the Mississippi baby is “cured” of HIV infection and longer follow up is needed, but there is other evidence in children that early ART initiation may result in decreased production of replication-competent HIV. In a recent report, replication-competent virus was detected in zero of five and residual plasma viremia in one of five children who initiated ART early at a median two months of age compared to all children who did not initiate ART until late childhood [57]. Several studies have shown better initial virological control when treatment is started early in children [28,58,59].

HIV-specific immunity

The Mississippi baby did not have detectable HIV antibody when tested post-ART cessation at 24, 26, and 28 months of age [4]. In an early U.S. report, 16 out of 17 infants initiating ART at 15 days to three months of age became antibody negative by 16 months [60]. Further updates have reported similar findings; at a median age of 16 years having remained on ART, HIV-specific antibodies were present in only one of five children who initiated ART early (median two months of age) compared to four of four children who did not initiate ART until late childhood [57]. Five of 12 children in Belgium started on ART within 66 days of age and four of six in Italy started on ART within 3 months of age have also been reported to be persistently antibody negative once suppressed [61,62]. The age at which ART should be initiated for HIV antibody negativity to be achieved is unclear. HIV-specific cellular immune responses generally are no longer detectable soon after initiation of ART [60] but the clinical significance of this is unclear.

What treatment should be initiated?

Pediatric HIV infection presents unique therapeutic challenges. First, the choice of first-line ART regimen is complex. There are few appropriate formulations available for infants and limited data on dosage. Drug resistance is another major issue. Children exposed to non-nucleoside reverse transcriptase inhibitors (NNRTIs) for PMTCT, commonly have viral resistance [63]; children who failed single-dose nevirapine have a high rate of virologic failure when nevirapine is used for treatment in the first year of life [64]. Drug resistance may even be detectable among children who missed PMTCT [65,66]. There are additional concerns about long-term toxicities, including effects on growth and lipid metabolism [67,68]. Thus, treatment options are highly limited.

Current treatment recommendations for children in resource-limited settings have been informed by randomized clinical trials. A summary of the main trials is provided in Table 3. The P1060 trial, which randomized children six months to three years of age in six African

countries to first-line nevirapine-based or LPV/r-based ART [69,70], found that more children in the nevirapine group reached the primary endpoint of failure by 24 weeks than the LPV/r group (39.6% versus 21.7%, $p=0.02$) among children previously exposed to single dose-nevirapine (Cohort 1). A similar result was observed among children two months to three years of age not previously exposed to single-dose nevirapine (Cohort 2) (40.1% versus 18.6%, $p<0.001$), suggesting that LPV/r is superior to nevirapine regardless of prior NNRTI exposure due to PMTCT. The CHER trial also supported this finding, with successful viral suppression on a LPV/r based first-line ART regimen for the majority of infants.

Results from P1060 differ from data from the Combined Paediatric European Network for Treatment of AIDS (PENTA) 9/Pediatric AIDS Clinical Trials Group (PACTG) 390 (PENPACT-1) multinational trial of older children in North and South America and Europe (only 25% were less than three years old), which assessed what first-line regimen to start with and when to switch to second-line ART [71]. In PENPACT-1, 266 ART naïve children (median age 6.5 years, IQR 2.8-12.9) were randomized in a factorial design to first-line protease inhibitor (PI)- or NNRTI-based ART at thresholds for switching at 1,000 cpm or 30,000 cpm. Over four years of follow up, no significant difference was found between children starting PI- or NNRTI-based regimens in primary (change in log₁₀ HIV RNA copies between baseline and 4 years) or secondary endpoints (regimen switch, change in CD4% from baseline, HIV RNA <400 cpm at week 24 on first-line ART, HIV RNA <400 cpm at 4 years, continued viral load suppression on first-line ART, failure of second-line ART, grade 3/4 adverse events, new CDC stage C events and resistance) [71]. This finding differs from that observed in the P1060 trial, which found LPV/r-based therapy to be superior to nevirapine-based therapy in both single-dose nevirapine exposed (Cohort 1) and unexposed (Cohort 2) children [69,70]. However, the trials were conducted in different settings, with P1060 having greater relevance for sub-Saharan Africa. In addition, while P1060 focused specifically on younger children, PENPACT-1 included a mix of ages complicating inference for younger children only. Finally, clinicians could choose the initial regimen in PENPACT-1, and at that time zidovudine was given as the PI of choice to almost half of the children on PIs rather than LPV/r, potentially leading to suboptimal outcomes in the PI group.

Although LPV/r is recommended as part of first line regimens in children, it is an expensive drug that requires a cold-chain and has poor palatability. Hence many programs in sub-Saharan Africa have opted to utilize nevirapine-based regimens instead, even among the youngest and PMTCT-exposed children. At least two of such programs have obtained outstanding clinical outcomes even with nevirapine-based therapy [72,73].

As children typically have high viral loads, researchers hypothesized that treating early with four drugs rather than three drugs may result in more rapid virologic control and immunologic recovery as well as more efficacious long-term treatment. The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) observational study of 437 European infants starting either PI- or NNRTI-based ART before 12 months of age and followed for a median of 5.9 years found better virological and immunological response in children initiating four-drug NNRTI-based regimens compared to three-drug NNRTI-based

and LPV/r-based regimens [74]. The AntiRetroviral Research for Watoto (ARROW) trial conducted in children and adolescents aged three months to 17 years in Uganda and Zimbabwe, assessed whether starting children on four drugs for a short period of time before continuing with three drugs would be superior in the long term than starting on the standard three drugs [75]. Children were randomized to treatment groups A) NNRTI, lamivudine, and abacavir; B) NNRTI, lamivudine, abacavir, and zidovudine for 36 weeks followed by NNRTI, lamivudine, and abacavir; or C) NNRTI, lamivudine, abacavir, and zidovudine for 36 weeks followed by lamivudine, abacavir, and zidovudine. Though the four drug-groups (B, C) were superior to the three drug group (A) in the short term at 36 weeks (mean CD4 percentage change for A, B, C: 12.4% versus 14.1% versus 14.6%, $p<0.0001$), they did not have an advantage over the long term and mean CD4 percentage change did not differ between ART groups at 72 weeks (16.5% versus 17.1% versus 17.3%, $p=0.33$) or 144 weeks ($p=0.69$). In addition, there were excess grade 3 or 4 events in groups B (HR 1.32, 95% CI: 1.07-1.63) and C (HR 1.58, 95% CI 1.29-1.94) compared to A.

Current guidelines for initiation of ART in infants and younger children less than three years of age are based upon a model where infants are diagnosed at the earliest at six weeks of age and ideally initiated on ART soon thereafter. The Mississippi baby, however, was initiated at 30 hours of life, raising unique challenges about the appropriate starting regimen. The Mississippi baby was started on a three-drug regimen of nevirapine (2 mg/kg twice daily), zidovudine (2 mg/kg every six hours), and lamivudine (4 mg/kg twice daily). This regimen is similar to regimens routinely given as *prophylaxis* for PMTCT except doses were somewhat higher. At seven days, the child was shifted to a more standard *therapeutic* regimen of LPV/r (dosing) with zidovudine and lamivudine.

Antiretroviral drugs have been extensively used during the newborn period as *prophylaxis* as part of PMTCT regimens [76-79]. Nevirapine, lamivudine, and zidovudine have been the drugs most widely used as post-exposure prophylaxis or as “peri”-exposure prophylaxis in the case of breastfeeding infants [76-79]. However, in resource-limited settings, antiretrovirals given as *therapy* have generally not been used within days of birth given the logistic challenges of diagnosing HIV at this early stage. Limited pharmacokinetic data are available for infants in the first two weeks of life and optimal dosing to achieve therapeutic (rather than prophylactic) levels in the neonate is not well established. LPV/r (300/75 mg/m² twice daily) is considered safe and effective in HIV-infected infants initiating ART between two and six weeks of age [80], but the Mississippi baby was switched to an LPV/r-based regimen even earlier at seven days of life. In addition, newborns initiating LPV/r may be at risk for complications, as evidenced by reports of transient adrenal dysfunction and cardiac toxicity [81,82]. Since the Mississippi baby report, the Food and Drug Administration issued a warning against the use of LPV/r in infants younger than 14 days of age due to high ethanol and propylene glycol content in its liquid formulation, which may place infants, especially preterm neonates, at high risk of propylene glycol-associated adverse events [83]. In addition, the long-term risk of metabolic complications among children who initiate LPV/r early in life is unknown.

The bottom line is that more drug choices and formulations are needed for children in general and for newborns in particular who require liquid formulations. Although studies of

alternative options are ongoing, there are currently limited data available for this age group. As with any treatment decision, benefits of early initiation of ART in children need to be carefully balanced against the potential drawbacks and costs of such a strategy, including the development of resistance in a context where there are limited therapeutic options, the management of adverse effects, and the potential short and long-term toxicities. The potential significant benefit of “functional cure”, if it is confirmed, may require modification of usual risk-benefit calculations if treatment can eventually be stopped.

How do we identify HIV-infected infants in order to initiate treatment?

Early initiation of ART depends on early diagnosis of HIV-infected infants. Identifying HIV-exposed infants for testing and diagnosis of HIV infection remains a challenge in sub-Saharan Africa. In part this is due to the costs of PCR testing and the requirements for a relatively sophisticated laboratory infrastructure to support this testing, but is also due to the logistic challenges of ensuring adequate follow-up of HIV-exposed infants after delivery. Guidelines generally encourage testing at 6 weeks of age and not at birth. This age was selected to maximize detection of perinatally HIV-infected children since it is only by this age that close to all HIV infections acquired during pregnancy (*in utero*) or during labor and delivery (intrapartum) can be detected with current technology. Test results are then generally communicated to mothers some two to four weeks later. It is not until this point that an infant may be initiated on ART if found to be HIV-infected.

If ART is to be initiated at birth, as seems to be advisable based on the Mississippi baby, then routine diagnosis will also need to shift to birth. However, even if blood drawing can be performed soon after birth, it is unlikely that turnaround of results from central laboratories could be achieved before the usually rapid discharge of parturient women and their newborns soon after delivery. Thus to achieve early initiation of ART, point-of-care HIV diagnosis is a practical necessity. Point-of-care HIV diagnosis systems have been developed and tested and appear to have excellent performance characteristics, e.g. the Simple Amplification Based Assay (SAMBA) system [84]. A robust point-of-care test would allow for immediate diagnosis of HIV in newborns and ART could then be initiated before they are discharged after delivery. An added advantage of this approach is eliminating the often protracted period between birth, returning for the follow-up HIV diagnostic test, returning for the result of that test, and initiation of ART that may result in loss to follow-up between all the steps along the way [85].

One downside to moving diagnosis to birth is that it will only detect infections that occurred *in utero* and cannot be a replacement for later tests. Further testing will still be required to detect intrapartum and early postnatal infections that would have been only detectable by 6 weeks. Given the high costs of PCR testing, this is a major consideration for programs since it necessitates more tests. In addition, testing still needs to continue for breastfed infants who have ongoing postnatal exposure to HIV until all breastfeeding ends.

Expert Commentary and Five-Year View

As children have a high risk of death and disease progression in infancy, early initiation of ART can prolong survival and reduce morbidity. The Mississippi baby raises challenging new questions for the care and treatment of perinatally HIV-infected children (Table 2) that the scientific community must take into consideration. Moving the window of time for initiation of treatment to birth may open the door to the possibility of “functional cure” or other potentially beneficial outcomes, including better virologic control on treatment. However, diagnostic challenges at birth remain formidable, requiring the implementation of new services. Furthermore, acting on early test results requires availability of safe and effective treatment options for use in newborns.

Lifelong HIV treatment is not an ideal option for anyone, and especially not for children. Additional proof of concept studies are crucial to leverage the exciting new scientific breakthrough provided by the Mississippi baby [4] to develop better treatment options for children. Starting more infants on treatment immediately at birth will also require infrastructure for continued care and adherence on medication. Despite the promise the Mississippi baby approach may hold for HIV-infected newborns, prevention of mother-to-child transmission should remain a central priority and treatment should continue to be scaled up for children who are already infected and not receiving ART.

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Key Issues

- The recent case report of an HIV-infected infant with viral control post-antiretroviral therapy (ART) interruption has sparked interest in the possibility of “functional cure” in infants with ART initiated soon after birth.
- The Mississippi baby raises challenging new questions for the care and treatment of perinatally HIV-infected children.
- 1) When should treatment be initiated – e.g. should we initiate ART at one year of age, six weeks of age, or at birth? Results from CHER are largely uninformative about whether or not treatment should be started at birth or what the relevant window of time would be after birth diagnosis to initiate treatment.
- 2) Why should treatment be initiated – what outcomes are we trying to achieve? The traditional goal of early ART initiation for children is to reduce mortality and morbidity, as well as to achieve normal growth and development and improve quality of life. We need to carefully consider what endpoints might be considered evidence of steps along the way to “functional cure” justifying withdrawal of ART.
- 3) What treatment should be initiated – what options do we have available for early treatment? The Mississippi baby was initiated at 30 hours of life, raising unique challenges about the appropriate starting regimen, as limited options are available in this early window.
- 4) How do we identify HIV-infected infants early enough to treat them adequately? If ART is to be initiated at birth, as seems to be advisable based on the Mississippi baby, then routine diagnosis will also need to shift to birth with point-of-care diagnostic tests being the only practical approach.

Table 1

Timeline of the Mississippi baby case [4]

Age of baby	Event
Prenatal	• Child's mother was HIV-infected and received no prenatal care • Child was born at 35 weeks of gestation
30 hours	• Initiated on a three-drug regimen of nevirapine, zidovudine, and lamivudine before confirmation of HIV infection • Positive HIV DNA PCR test
31 hours	• HIV RNA quantity of 19,812 copies/mL
6 days	• HIV RNA quantity of 2,617 copies/mL
7 days	• Switched from nevirapine to a ritonavir-boosted lopinavir (LPV/r) regimen
11 days	• HIV RNA quantity of 516 copies/mL
19 days	• HIV RNA quantity of 265 copies/mL
29 days	• HIV RNA quantity <48 copies/mL
29 days – 18 months	• Remained on ART
18-23 months	• Lost to follow up, missed clinic appointments • Off ART
23 months	• Returned to clinic, remained off ART • No detectable HIV RNA quantity by standard clinical assay
24 months	• No detectable HIV RNA quantity by standard clinical assay • HIV RNA quantity of 1 copy/mL using ultrasensitive assay • Negative HIV DNA PCR test • HIV proviral DNA detected near limit of detection but not in resting CD4+ T-cells • No replication competent HIV detected in resting CD4+ T-cells • Negative antibody test
26 months	• No detectable HIV RNA quantity using ultrasensitive assay • HIV proviral DNA detected near limit of detection but not in resting CD4+ T-cells • Negative antibody test
28 months	• Negative antibody test
30 months	• Case reported • No viral rebound

Table 2

Novel issues relating to care and treatment for HIV-infected infants and young children raised by the Mississippi baby

Issue	Status Quo	Implications of the Mississippi baby
<u>When</u> should treatment be started?	Window: 6-12 weeks	Window: birth-30 hours
<u>Why</u> should treatment be initiated?	To reduce mortality and morbidity	To achieve functional "cure"
<u>What</u> treatment should be initiated?	LPV/r plus 2 NRTIs If LPV/r not available, nevirapine plus NRTI backbone: zidovudine or abacavir + lamivudine	Limited treatment options at birth Mississippi baby was initiated on nevirapine + zidovudine + lamivudine at 30 hours of life and switched to LPV/r + zidovudine lamivudine + at 7 days
<u>How</u> do we identify HIV-infected early enough to treat them adequately?	Test at 6-12 weeks and then initiate on treatment when children return for results	Point-of-care diagnostic testing at birth

Abbreviations: LPV/r = ritonavir-boosted lopinavir; NRTI = nucleoside reverse transcriptase inhibitor

Table 3
Randomized trials evaluating first-line regimens for HIV-infected infants and young children

Study	Location	Cohort	Randomization	Endpoints	Main Results
P1060 [69,70]	South Africa, Zimbabwe, Zambia, Malawi, Uganda, Tanzania, India	Cohort 1: N=164, previously exposed to sd-NVP	Randomized to A) nevirapine, zidovudine, lamivudine or B) LPV/r, zidovudine, lamivudine	Primary endpoint: treatment failure (permanent discontinuation of treatment, death, toxic effects, virological failure)	Cohort 1: more children in the nevirapine group reached the primary endpoint of treatment failure at 24 weeks than the LPV/r group (39.6% versus 21.7%, p=0.02)
		Cohort 2: N=288, not previously exposed to sd-NVP Age: 6-36 months in Cohort 1; 2-36 months in Cohort 2			Cohort 2: more children in the NVP group reached the primary endpoint of treatment failure at 24 weeks than the LPV/r group (40.1% versus 18.6% p<0.001)
PENPACT-1 [71]	North and South America and Europe	N=266 Age: 0.1 to 17.8 years, median 6.5 years	Factorial design, randomized to A) PI-based regimen or B) NNRTI-based regimen as well as to a viral load threshold to switch regimen at 1,000 or 30,000 cpm	Primary endpoint: change in log10 HIV-1 RNA viral load between baseline and 4 years Secondary endpoints: regimen switch, change in CD4% from baseline, viral load <400 cpm at week 24 on first-line ART, viral load <400 cpm at 4 years, continued viral load suppression on first-line ART, failure of second-line ART, grade 3/4 adverse events, new CDC stage C events and resistance	No significant difference was found between children starting NNRTI- or PI-based regimens in primary or secondary endpoints
ARROW [75]	Uganda, Zimbabwe	N=1206 Age: 3 months to 17 years	Factorial design, randomized to A) three drugs - NNRTI, lamivudine, abacavir; B) four drugs - NNRTI, lamivudine, abacavir, zidovudine for 36 weeks then NNRTI, lamivudine, abacavir; or C) four drugs - NNRTI, lamivudine, abacavir, zidovudine for 36 weeks then lamivudine, abacavir, zidovudine, as well as to different monitoring strategies	Primary endpoint: new WHO stage 4 events or death for monitoring and change in CD4% at 72 and 144 weeks Co-primary toxicity endpoint: grade 3 or 4 adverse events	Mean CD4% change did not differ between ART groups at 72 weeks (16.5% vs. 17.1% vs. 17.3%, p=0.33) or 144 weeks (p=0.69). Four-drug groups (B, C) were superior to three-drug group A at 36 weeks (12.4% vs. 14.1% vs. 14.6%, p<0.0001). There were excess grade 3 or 4 events in groups B (hazard ratio 1.32, 95% CI: 1.07-1.63) and C (hazard ratio 1.58, 95% CI: 1.29-1.94) compared to A.

Abbreviations: PI = protease inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; LPV/r = ritonavir-boosted lopinavir