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The pharmacological treatment of acute HIV infections in neonates

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Abstract

Introduction: Recent goals of antiretroviral treatment of neonates have expanded from reducing morbidity and mortality to also aiming to facilitate HIV remission.

Areas Covered: In this review, we present and discuss the rationale and evidence-bases for each of these distinct goals. Next we discuss the challenges of how to identify HIV-infected. Finally, we discuss the specific antiretroviral drugs that are preferred for this group, the distinctions between the use of these agents in prevention and treatment.

Expert Commentary: The clinical and scientific challenges of pharmacological treatment of acute HIV infection in neonates are complicated by externalities beyond biology.

At the same time, these challenges are energized by the unique biological opportunities afforded by investigating this population, including a unique immune profile, ability to study both mother and neonate as well as transmitted and acquired virus, and time period spanning both the period soon after infection as well as the period of viral reservoir establishment and related damage.

Given the unique scientific opportunities afforded by study of pharmacologic treatment of acute HIV infection in neonates, we hypothesize that over the next five years breakthroughs may occur that may lead to new interventions effective at achieving HIV remission.

Keywords

Antiretroviral therapy; HIV; immunity; neonates; remission

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Declaration of Interest

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Introduction

The success of antiretroviral drugs for prevention of mother-to-child HIV transmission (PMTCT) has made new infections among neonates a relatively rare occurrence. Antiretroviral drug regimens given to HIV-infected women combined with prophylactic antiretroviral drug regimens given to HIV-exposed infants have generally been shown to achieve perinatal transmission rate of 1–2%.¹ The challenge, however, is that the number of HIV-exposed pregnancies is exceedingly high in some parts of the world, notably southern Africa where 20–40% of pregnant women are HIV-positive.² Even with excellent coverage, the large denominator means that sizable numbers of neonates newly acquire HIV infection despite PMTCT. Moreover the large denominator necessitates considerable resources to attain and sustain coverage of PMTCT.

In this review, we discuss some special issues in the pharmacological treatment of HIV-infected neonates. First, we discuss the goals of treatment of this population with antiretroviral therapy (ART). These goals have expanded beyond reduction of morbidity and mortality, which is conventionally associated with ART, to include aiming to facilitate HIV remission. We present and discuss the rationale and evidence-bases for each of these distinct goals. Next we discuss the challenges of how to identify HIV-infected neonates. These challenges are both technical and are affected by complexities of biology and are influenced by logistics and cost. Finally, we discuss the specific antiretroviral drugs that are preferred for this group, making distinctions between the use of these agents in prevention and treatment.

1. What is the intended purpose of ART for HIV-infected neonates?

In the conventional way, ART is prescribed with the intention of reducing HIV-associated morbidity and mortality achieved through viral control.^{3,4} A plasma HIV RNA level below the threshold of detection of approved assays (usually <20 copies/ml) is generally used as the primary indirect marker of the success of ART. But treatment of HIV-infected *neonates* has, in the past few years, accumulated a somewhat more ambitious agenda: namely to facilitate HIV remission. The size of the latent viral reservoir, usually measured as cell-associated HIV DNA in peripheral blood, is generally taken as the primary indirect marker of success in relation to this purpose.⁵ The only direct way to assess success along this dimension is to withdraw ART and follow-up to ascertain whether virologic and immunologic control can be maintained in the absence of ART.

These two inter-related objectives of early ART in neonates may seem at first glance to be synergistic: both seem to encourage initiation of ART as soon as is practically feasible in the newborn. However, confusion of purpose can be problematic in some circumstances. One of the challenges is that the evidence-base and reasoning to support the more conventional purpose of ART (reduction of morbidity and mortality) is distinct from the evidence-base and reasoning to support the more ambitious purpose of early ART (remission). In addition, close scrutiny of the evidence-base for either objective reveals gaps and limitations. These two purposes may also pull in opposite directions at times raising new clinical conundrums.

2. Rationale for early ART on conventional grounds

Pediatrics has led the HIV treatment research field in the question of “when to start” ART. Largely on the basis of the results of one clinical trial (Children with HIV Early Antiretroviral Therapy [CHER] Study), treatment guidelines for infants i.e. children under one year of age, have advised immediate initiation of ART regardless of clinical or immunological criteria since 2009.^{6,7} It was only in more recent years that guidelines for treatment of HIV-infected adults have shifted to advising universal treatment regardless of CD4 count.⁸ The adult recommendations have been controversial, in part, because of the relatively low, although arguably not absent, increased risk of morbidity and mortality in individuals with higher CD4 counts.^{9,10} Hence the marginal benefit in terms of improved outcomes is small when treatment is started in chronic infection among adults with higher CD4 counts. The lower the CD4 count when ART is started, the more dramatic and clear-cut the life-saving benefits of ART.

Disease progression in infants is more rapid than in adults and this was one of the factors that was used to motivate for the more aggressive treatment recommendations for children at a time when treatment recommendations in adults were more conservative.¹¹ In perinatally-infected infants, the initial plasma HIV RNA peak is generally in the range of millions of copies/ml, and the viral set-point in the absence of treatment is established more slowly in children than in adults over about a 5 year period and stabilizes at a set-point generally above that observed in adults.^{12,13} Moreover, mortality is high – between 25–50% of perinatally HIV-infected infants and young children die in the first two years of life if ART is not initiated.^{14,15} This aggressive disease course makes an intuitive case for the need for rapid intervention with ART.

A more subtle reason why pediatric ART guidelines could be so ahead of their time is that CD4 count and CD4 percentage are less discriminating markers of the likelihood of progression in infants than in adults. Normal infants have 2–3 fold higher numbers of lymphocytes, and larger percentages of CD4+ lymphocytes, than adults or older children.^{16,17} These developmental differences explain the weaker predictive capacity of CD4 counts/percentage. In adults with chronic infection, although CD4 count is not the only factor related to likelihood of morbidity and mortality in the ensuing few years, it is a powerful one.^{18,19} Hence this immune marker was used as an effective way to identify those individuals at highest risk and at greatest need of ART; first setting a threshold at 200, then 350, then 500 cells/mm³ before ART was initiated. In infants, although a low CD4 count or percent indicates a poor prognosis, it is rare: most infants have CD4 counts and percentages in the normal range offering little discrimination in terms of who is likely to progress.

The clinical trial in infants that directly compared immediate initiation of ART versus deferred initiation of ART (deferred until clinical and CD4 count/percentage criteria in place at the time were met) definitively demonstrated benefits for morbidity and mortality of immediate initiation of ART.⁶ It is hard to argue with a randomized clinical trial, particularly when results are so unequivocal and have mortality as an outcome. The results also fit with knowledge of the natural history of HIV infection in children. However, there are significant limitations of this trial in terms of the inferences that can be drawn.

One of the key limitations of CHER was that for ethical reasons the trial was restricted to infants who did not already meet clinical criteria to initiate ART, i.e. those who were asymptomatic and had normal CD4 parameters.⁶ In other words, the study excluded those infected infants at highest risk of death. Thus the generalizability of the benefit of immediate ART initiation for sick HIV-infected infants is unclear. Co-morbidities and congenital infections, including cytomegalovirus infection, tuberculosis and other lower respiratory tract infections, are not uncommon in newly-diagnosed HIV-infected infants.²⁰ This raises thorny questions, which have been tackled in controversial adult studies, about delaying ART while co-infections are treated. The challenges of drug-drug interactions, immune reconstitution syndrome, exacerbation of coinfections, amongst other issues, involved in treating the full spectrum of infant HIV infection were not addressed by the CHER trial. Observational studies, likely to be more generalizable, have generally found worse outcomes (i.e. higher mortality) with ART than observed in CHER.^{21–23} While one conclusion is that these worse outcomes are attained because we have left ART for “too late,” another conclusion is that for some infants it is always too late. Their disease course is such that no matter how early we start ART we will not be able to save them. Or, perhaps, of greater concern is that if ART had been delayed and other conditions addressed first, outcomes could have been better.

A critical limitation of inferring from the CHER trial to the question at hand of neonatal ART is that few of the infants in the trial, even in the immediate treatment arm, were initiated on ART during the neonatal period i.e. the first 28 days of life. Recruitment for the trial, which took place at two sites in South Africa (Johannesburg and Cape Town), was largely reliant on routine systems for infant diagnosis. At that time, it was recommended that HIV-exposed infants be tested for HIV by PCR at 6 weeks of age. While the study teams working at major tertiary hospitals were able to intervene and initiate ART promptly after diagnosis, the median age of ART initiation in the immediate group was 7.4 weeks.⁶ While the more general point that “earlier is better” can be safely inferred from the trial – pushing the interpretation to as early as possible when early is measured in hours or days is more tenuous.

3. Remission Rationale for early ART

The addition to this already complex field of expanding the objectives of ART initiation in infancy to include striving for remission came from a somewhat separate stream of research. Interest was piqued by the Mississippi baby who, in the first report, appeared to offer the intriguing possibility that ART within the first two days of life could lead to functional cure i.e. undetectable virus after ART cessation.²⁴ That HIV RNA rebound eventually occur months after ART was withdrawn somewhat dampened enthusiasm but drew the attention of the pediatric HIV research community to research underway in adults with acute or primary infection.²⁵

In adults, identifying primary or acute infection entails its own set of logistic problems. First a cohort of individuals at high enough risk of acquiring infection needs to be identified and then engaged in follow-up with repeat testing to identify new infections. Several such cohorts were established, generally evaluating viral response to immediate ART, including

effects on the size of the viral reservoir. Studies in adults have been consistent in demonstrating excellent viral control, and importantly smaller HIV viral reservoirs, with ART initiated during acute infection compared to ART initiated during chronic infection.^{26–28} Many of these studies also evaluated ART withdrawal. Almost all studies of ART started during acute infection in adults have observed that some individuals can control HIV, at low although not necessarily undetectable levels, and maintain good immune parameters when ART is withdrawn. This phenotype is reasonably rare occurring among 5–20% of those who stop ART depending on the cohort and the definitions.^{29–33}

Since initiation of ART in first few weeks and months of life in perinatally-infected infants is essentially equivalent to treatment of acute infection, this quite distinct field of adult studies was extrapolated to the pediatric world. Several retrospective analyses of the size of the viral reservoir in treated HIV-infected children were done. Although each of these studies has limitations in terms of comparison groups, small numbers and shifting definitions, results have been remarkably consistent in demonstrating that initiation of ART “earlier” leads to smaller viral reservoirs over the subsequent years when children are retained on ART.^{34–41}

4. How to identify HIV infection in neonates

Vertically-infected children acquire HIV intrauterine, intrapartum or via breastfeeding. The precise timing of intrauterine infection cannot be directly observed but has been presumed for some time on the basis of testing HIV PCR positive on a blood sample collected within 48 hours of birth.⁴² It is presumed that an intrapartum infection, i.e. one acquired during delivery, will need more than 48 hours to become detectable by PCR. Intrapartum infections are presumed if the sample taken within 48 hours of life yields a negative result but a subsequent positive result; and breastfeeding-associated infections are those detectable beyond about 4–6 weeks.⁴² Limited, of course, by the frequency of testing, interpretation is also likely limited by variability between infections of how rapidly they become detectable. While the model of early treatment of perinatal infection as treatment of acute infection seems initially straight-forward, it is rather fuzzy and is further constrained by several logistical challenges.

Despite these imperfections, existing health services and infant HIV diagnosis programs when functioning well will identify HIV-infected infants roughly within the period usually deemed to be “soon after infection”. Testing infants at birth is likely to be the best starting point as it provides the first sweep to detect intrauterine as well as rapidly detectable intrapartum infections.

It is also a practical time since mothers and infants are captive in the health system, at least for a little. Modeling studies have suggested, moreover, that intrauterine infection is generally late in the pregnancy,⁴³ thus theoretically allowing initiation of ART within hours or days of infection. However, infections may have occurred earlier during pregnancy making this a very rough approximation.

For intrapartum acquired infections where time after birth is exactly the time of infection, it appears as if existing diagnostic technologies can only detect all of these infections within 4–6 weeks

of life. This limitation of our infant diagnostic tests was demonstrated on older tests than are currently in usage.^{44,45} Whether 4–6 weeks is still necessary to detect an infection with currently approved PCR tests is unknown. Postnatal acquired infections have the same constraint plus the added challenge of potentially occurring at any time during the duration of breastfeeding. In addition, these infections are rare when maternal ART is onboard, making it very expensive to find these infections later.

Limitations of the many opportunities for mother-to-child HIV transmission aside, HIV PCR tests, while having excellent sensitivity and specificity under optimal conditions, do not have perfect sensitivity and specificity under real world conditions. Specimen mix-ups, laboratory errors, and test inaccuracies occur, albeit rarely, depending on quality control processes in place.^{46,47} Nevertheless both false positive and false negative results have serious import. This has led to various approaches to deal with confirmation of diagnosis.

Given the accuracy of PCR methodology, generally a repeat test on an independent sample is considered adequate confirmation of a positive result. But since turn-around time from the laboratory also has to be taken into account, often initiation of ART on the basis of a presumptive, i.e. unconfirmed, positive result may be advisable. This is reasonable when the confirmatory test result conforms with expectations, but poses conundrums when it contradicts the initial result. The lack of confirmation of a positive diagnosis does not necessarily rule out infection. It will be more likely to rule out infection if the confirmatory test is conducted on a sample collected prior to the initiation of ART and also not too close in time to the previous test. The case for delaying initiation of ART until diagnosis is confirmed can also be reasonably made. Once on ART, negative diagnostic tests can no longer be considered definitive indicators of an uninfected status as effective treatment can lead to negative results in confirmed infected children. If ART initiation was not delayed to confirm diagnosis, ART interruption may now be justified and even necessary to confirm true infection status. If infection is confirmed, we may have done wrong by taking the child off ART. If infection is not confirmed, we may have done wrong by starting the child on ART in the first place on the basis of an erroneous laboratory result. Or, we may have cured/prevented infection in the child. We will just never know.

5. Prevention vs. treatment: which is it?

Antiretroviral *therapy* for neonates occurs in a context where antiretroviral drugs are being widely used for *prophylaxis*. PMTCT with antiretroviral drugs is widely lauded as one of the major success in counteracting the HIV epidemic. Currently ART is recommended for all pregnant women as soon as diagnosed, continued indefinitely without interruption, for the purpose of maternal therapy and acting as prophylaxis against vertical transmission occurring intrauterine, intrapartum and through breastfeeding.⁸ Most antiretroviral drugs cross the placenta and penetrate breast milk. Antiretroviral drugs are also given directly to HIV-exposed neonates as prophylaxis.

While true HIV infections in neonates will be concentrated in those born to mothers with absent or imperfect ART histories, most settings have devoted considerable resources to roll-out PMTCT programs. Thankfully, this means that new infections are uncommon but also that most new HIV-infected neonates have been exposed to intrauterine antiretroviral drug.

Moreover, antiretroviral drugs are still recommended as prophylaxis even with perfect maternal ART histories. And patchy maternal histories prompt longer regimens with more drugs. In fact, several programs recommend regimens as prophylaxis essentially indistinguishable from treatment regimens.

Using therapy as prophylaxis or prophylaxis as therapy may seem a perfect solution for the problem of when to start. Whether the intervention was therapy or prophylaxis can simply be defined retrospectively by whether the neonate is infected (therapy) or uninfected (prophylaxis). But this approach raises the new problem of when to stop. For the confirmed infected, the case is relatively uncomplicated – continue therapy. For all others, new complications are introduced. For non-breastfed infants, prophylaxis would need to continue to at least 6 weeks to rule out intrapartum infections (if we are to rely on data from the pre-ART era). For breast-fed infants, a longer timeline may be necessary depending on other calculations about risk.⁴⁸ But does a negative PCR result, in this context so saturated with antiretrovirals, rule out infection? There is considerably more concern and speculation on this point than actual data. Theoretically, antiretrovirals may suppress viral nucleic acids below the detection threshold of diagnostic assays but this has not yet been convincingly demonstrated to occur other than after several months on treatment.³⁴ Nevertheless, even if it does occur it would be very difficult to quantify as most infants with negative tests are not systematically followed-up. Moreover ruling out infections that occur later during breastfeeding is close to impossible. Given the rates of transmission that are generally observed when good follow-up is in place, it seems unlikely PMTCT-masking of infections is a common event.

6. How early is early, how soon is acute?

The neonatal period will be more than 28 days after intrauterine infection if the infection occurred at any time other than the immediate period before delivery. The neonatal period may be over by the time an infection acquired intrapartum or through breastfeeding is even detected. For infections detectable soon after birth, this lack of certainty may seem to be grounds for haste. For the intrapartum and postnatal infections, the option of confounding prevention and treatment may seem like the only way. But is there a strong basis to justify the rush?

Turning to the field of treatment of primary infection in adults, clarifying with any precision the day of infection will depend on the frequency of testing and the particular behavioral profile. In general the field has relied on a combination of viral nucleic acids and antibody tests to classify acute HIV infections along the staging system described by Fiebig et al.⁴⁹ Briefly, detectable HIV RNA without other markers is considered Fiebig I, development of p24 antigen indicates Fiebig II, IgM antibody indicates Fiebig III, an indeterminate Western blot indicates Fiebig IV, a positive Western blot without the p31 band indicates Fiebig V, and Fiebig VI has a positive Western blot including a p31 band.

This system is not directly applicable to the infant situation as infant antibody detection is complicated by passive transfer of maternal antibody, making routine methods for HIV antibody detection all but useless. But it is interesting to note that Fiebig stages I-IV last on average 3–5 days, whereas stage V is estimated to last 69.5 days on average⁴⁹. Many studies

include in their definitions of treatment during primary infection, treatment that occurred as long as 6 months after the presumed date of infection.

Time pressure to speed up introduction of ART may come from externalities as well. Engaging directly with the mother at the time of diagnosis before she is discharged after delivery may offer the best opportunity to provide the impetus and support for the subsequent challenges of providing infant ART. Introducing delays and barriers with extra tests and prevarications may suggest to her lack of commitment to what is likely to be a highly challenging undertaking and may leave her feeling quite unsupported. Alternatively, springing on a new mother an overload of emotionally-charged and complicated information at a time when she is already exhausted may also not be advisable. ART initiation has often been considered a slower and multi-step process with time for discussion and reflection with the goal focused on long-term sustainability rather than on haste towards initiation. But whether a more leisurely approach favors the patient or the clinician is debatable.

7. Reliance on nevirapine as a starting regimen

The non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine, may seem like an unlikely candidate to be favored for ART in neonates given the ambitious goals applied to treatment of this vulnerable population. Clinical trials comparing nevirapine-based vs lopinavir/ritonavir-based treatment in infants and young children found nevirapine-based therapy to be inferior.^{50,51} Yet nevirapine-based regimens are the regimens currently being used in the major NIH-supported clinical trials of neonates. Nevirapine is a highly effective drug for PMTCT even when used as a single-dose and, in comparative evaluations, leads to increased efficacy when combined with other agents such as zidovudine. The downside of nevirapine as PMTCT is that it almost invariably selects resistance mutations in infected infants who acquire infection despite prophylaxis.^{52,53} This raises concern about use of nevirapine-based regimens as treatment for these infants since single-point mutations confer resistance to NNRTIs.

Despite these concerns, nevirapine-based initial ART is still favored at least in the short term. One of the reasons for this is safety and experience. With the massive roll-out of PMTCT, the global experience with nevirapine in neonates is vast. Hundreds of thousands of neonates have been prophylaxed with this antiretroviral drug. Although not without some risks, some rare neutropenia, its safety profile is good. This is a crucial consideration in this age group especially in the light of the blurry boundaries between prevention and treatment.

Since treatment and prevention are all but indistinguishable in terms of the antiretroviral drugs being used, one question is whether treatment necessitates a higher dose than prophylaxis. On the basis of small pharmacokinetic studies in neonates and pharmacological modeling, the field settled on a treatment dose several fold higher than the prophylaxis dose in the first few weeks and becoming almost identical to the prophylaxis dose at later time points.^{54–57} That these are “off-label” dosing guidelines dampens enthusiasm for the regimen and more research on this point would be advantageous.

But concern about drug resistance has generally led to recommendations for quite short periods of use of nevirapine for therapy – in contrast to its use for months as prophylaxis.

The idea that nevirapine can be given initially and then changed to a drug without resistance concerns rests, optimistically, on the assumption that initial viral decline may not be adversely influenced by pre-existing resistance. Rather resistance may influence the longer-term sustainability of suppression. Good penetrance of nevirapine into tissue compartments and rapid action further support its use. Despite this optimism, the prime reason why nevirapine is included as part of the initial neonatal regimen is that there simply is no other choice.

8. Why not ritonavir/lopinavir?

The black box warning on ritonavir/lopinavir that advises against its use in the first two weeks of life, and most especially advises against its use in preterm infants, is the main reason why nevirapine is preferred initially.⁵⁸ Serious adverse events, strongly associated with prematurity, including cardiac abnormalities and fatalities, were reported with ritonavir/lopinavir used for prophylaxis during the neonatal period. This led to the black box warning against the use of this agent before 42 weeks adjusted post-menstrual age. Prior to this concern, ritonavir/lopinavir would have been the prime contender to be part of the first-line treatment for neonates.

Due to concerns about drug resistance selected by PMTCT, a randomized clinical trial was conducted comparing nevirapine- vs. ritonavir/lopinavir-based regimens in PMTCT-exposed and unexposed infants and young children.^{50,51} The trial had unequivocal results supporting better outcomes with ritonavir/lopinavir. The wrinkle, however, was the better outcomes were observed in both the PMTCT-exposed and unexposed groups, suggesting that drug resistance may not be the major reason for favoring this regimen.^{50,51} Given cost, logistics (cold-chain), and adherence (bad taste) challenges of using ritonavir/lopinavir, many programs in low resource settings were slow or unwilling to shift to it. Excellent outcomes using nevirapine-based regimens have been reported when used in infants and young children even in settings with well-established PMTCT programs.⁵⁹

9. Nucleoside reverse transcriptase (NRTI) backbone choices

For the nucleoside backbone drugs, again options are limited for antiretrovirals available in formulations suitable for neonates and with dosing established for this age group. The only three drugs that fit the bill are zidovudine, lamivudine and stavudine.⁸ With stavudine rejected for toxicities frequent with long-term use, for practical purposes, we are essentially left with zidovudine and lamivudine as the only options. Abacavir can be introduced by 3 months of age when a dose is available. Four-drug treatment intensification studies have also been tried.⁶⁰

10. Integrase inhibitors

From the discussion above it is clear that the pharmacological treatment of acute HIV infection in neonates is reliant on old drugs, generally out of favor for the treatment of adult HIV infections, most with known toxicities and limitations. This highly limited armamentarium is due the lack of pediatric ART options. Noticeable for their absence is mention of integrase inhibitors which are rapidly emerging as superior in many respects for the treatment of HIV infection in adults.

Raltegravir, as one of the first integrase inhibitors to become available, has been tested and had a suitable dose for infants as young as 4 weeks of age.^{61–63} Were it not for this age constraint, theoretically, raltegravir would be an attractive candidate to use in primary treatment of neonates. The concept would be ensuring rapid and effective viral suppression, along the lines of treatment intensification strategies used in adults, with the goal of impacting the viral reservoir.⁶⁴ Somewhat equivocal and disappointing results have been obtained from some of the studies of treatment intensification in adults with little to no reduction in markers of the size of the viral reservoir.⁶⁵

Recently, the large multi-site National Institutes of Health-supported study of very early treatment in HIV-infected neonates has revised its protocol to include the option of using raltegravir.⁶⁶ The study has also revised its protocol to make provision for the use of an anti-HIV monoclonal antibody (VCR01) that has had good success when used in prevention.⁶⁷ We eagerly await the results of this innovative new approach to facilitating remission in early-treated infants.

Dolutegravir is currently under investigation in children but no studies are currently planned, to our knowledge, to evaluate its use in neonates.

11. Clinical experience with neonatal treatment

There is surprisingly little published clinical experience with the treatment of HIV infection specifically in neonates. Part of the reason for this is that in the settings where pediatric HIV infection is common, i.e. sub-Saharan Africa, HIV infection is seldom detected this early. Early infant diagnosis programs, where they exist, tended to focus on routine testing at 4–6 weeks of age among infants born to mothers in PMTCT programs and in treatment centers as work-up for symptomatic admissions. At several sites in Johannesburg, a well-resourced urban center with excellent PMTCT coverage, a surveillance study in 2011 found that almost 80% of the new pediatric HIV infections identified were found as part of work up in in-patient facilities and not as part of routine testing.²³ Programs in South Africa have shifted, as of 2015, to testing HIV-exposed newborns before discharge after birth.⁶⁸ However, since recall is required to return results, these programs are only likely to mitigate this problem if adequate follow-up can be attained.

In North America and Europe where the resources are in place to initiate neonatal infant infections are uncommon. Case reports tend to be selective reporting not on the full experience of treatment but on children with specific outcomes. For instance in a report on the experience at several sites in Canada, 72 infants were reported as starting ART in the neonatal period but only four were described in detail.⁶⁹ These four were the ones with good outcomes. Several other case reports have focused on the failure of early treatment to prevent viral rebound when ART is withdrawn.^{70,71} In each of these cases, children were generally selected for consideration of ART withdrawal because of excellent viral control on ART. Two unselected cases from the United States have been described.⁷²

Effective PMTCT programs were put into place in North America soon after the results of the first demonstration of the benefits of antiretrovirals to prevent vertical transmission in the mid-1990s.⁷³ This corresponded in time with a decline in the numbers of HIV-exposed

pregnancies and combined with effective prophylaxis led to a massive decline in the number of new pediatric HIV infections. This has been widely lauded as one of the major successes in the fight against HIV. Prior to the mid-1990s, although HIV-infected neonates were mostly promptly identified, effective regimens were not yet in widespread clinical usage. Many vertically-infected children were started on single drug regimens, were exposed to regimens later found to be less effective, and reflect the challenges of the early years of HIV treatment where knowledge of the most effective approach was still accumulating and options for treatment were few. After the mid-1990s, strategies to treat infants and young children expanded and clarified. However, scientific interest in outcomes among optimally-treated neonates waned. Descriptions of virologic and clinical outcomes of treated neonates are mostly hidden in larger reports of treatment of infants and young children in general.^{60,69,74}

12. Is there any evidence of HIV remission with early treatment?

The first report of the Mississippi baby raised the tantalizing possibility that early treatment could lead to remission.²⁴ The enthusiasm about this approach was dampened when HIV RNA rebound eventually occurred in this child.²⁵ And was further dampened when rebound occurred in other early-treated children, handpicked to stop ART.^{70,71} Nevertheless, more recently, three new cases of early-treated perinatally-infected children with apparent remission have hit the headlines.^{75–77} Each have slightly different profiles in terms of when ART was started and stopped but share a common feature of years off ART with minor or no detectable HIV RNA. Further detailed study of these children will be invaluable to better understand the processes that led to these outcomes.

13. Conclusion

In the past few years, the goals of antiretroviral treatment of neonates have expanded from simply aiming to control viremia, and thereby reduce morbidity and mortality, to also aiming to facilitate HIV remission. The evidence-bases and rationales for each of these objectives is distinct. The evidence-base to support the benefits of early treatment to reduce morbidity and mortality comes largely from the CHER trial that randomized HIV-infected infants to either immediate or deferred treatment.⁶ This trial showed a clear benefit of immediate compared to deferred treatment on mortality and morbidity. However, limitations of this trial in terms of inclusion criteria make it largely uninformative about whether or not very early initiation of ART i.e. within hours or days of birth is more beneficial than early initiation of ART i.e. within the first few weeks of life or even within the neonatal period. The rationale to support the benefits of early treatment on facilitating HIV remission was jump-started with the initial report of the Mississippi baby who initially appeared to be in remission.^{24,25} This allowed the evidence-bases from studies of acute infection in adults to be brought into discussion in the pediatric arena.

Studies in adults have been consistent in demonstrating smaller HIV viral reservoirs with ART initiated during acute compared to chronic infection.^{26–28} These studies have also reported cases of apparent HIV remission on ART withdrawal.^{29–33}

With these combined motivators spurring early treatment in neonates, the field has had to face the challenges of how to identify HIV infection in neonates. These challenges are largely ones of logistics and cost. Repeat virological testing is necessary since infections acquired intrapartum can only be identified after some uncertain duration of time after birth and only intrauterine infections can be detected through testing at birth.

The same antiretroviral drugs are used for prophylaxis and for treatment albeit in slightly different doses. Some programs deliberately use prophylaxis as treatment and stop prophylaxis in those confirmed to be uninfected. Other programs initiate presumptive treatment for those with diagnostic results suggesting infection and await confirmation of diagnosis. In practice these two approaches are almost indistinguishable and either can result in serious challenges to the certainty of diagnosis.

Current clinical studies of neonatal treatment have preferred an initial regimen of nevirapine, lamivudine and zidovudine largely as a holding pattern until lopinavir/ritonavir can be introduced at two weeks and in preterm infants by 42 weeks post-menstrual age.^{66,78} Reluctance to use lopinavir/ritonavir earlier than the black-box warning has largely driven this regimen choice. Nevirapine might be presumed to be inadvisable given drug resistance selected by PMTCT.^{52,53} Nevirapine-based regimens have also been demonstrated to be inferior to ritonavir/lopinavir-based regimens in both PMTCT-exposed and unexposed infants and young children.^{50,51} Integrase inhibitors, now favored for adult treatment, are likely to supplant this approach if and when doses and formulations become available.⁸

14. Expert Commentary

The clinical and scientific challenges of pharmacological treatment of acute HIV infection in neonates are complicated by externalities beyond biology. The success of PMTCT has led to shrinking numbers of new infections in neonates. While this remarkable global achievement is highly acclaimed, the shrinking market for antiretroviral drugs for this age group has not gone unnoticed. While ethical imperatives exist for ensuring access to new drugs for all, including neonates, regulatory hurdles are many. With fewer neonates acquiring infection, clinical studies of this population are more costly and difficult. The need to sustain large prevention and treatment programs in high burden countries raise cost-effectiveness questions of the benefits of programs to optimally identify and treat this small albeit vulnerable population. Moreover, with increasing coverage of populations with effective PMTCT, these new infections occur in families with overlapping social and biological risk factors.

But the clinical and scientific challenges of pharmacological treatment of acute HIV infection in neonates are also energized by the unique biological opportunities afforded by investigating this population.^{16,79} The immune profile of neonates is an exquisite balance between tolerance of their mothers and harnessing of their mothers' immunity to protect against postnatal pathogens as their own (neonatal) immune system matures and develops.^{16,79} Both mother and neonate are available for study. Both transmitted and acquired virus is potentially available for study. The neonatal period covers the time period soon after infection as well as the period of viral reservoir establishment and related damage. We can ask for no more in terms of a window into viewing these initial processes so critical to

shaping the future course of HIV infection. Moreover the recent reports of three early-treated perinatally-infected infants who after stopping ART have controlled viremia for many years offers renewed hope about the potential of this strategy.^{75–77}

15. Five Year View

Over the past decades of HIV research, systematic, careful observation of the immune and viral parameters that create the clinical pathologies of HIV infection have steadily produced a richer account of how HIV does its damage. Some of these observations have led to beneficial interventions, including to the antiretroviral interventions that can now almost entirely prevent new infections in neonates. Given the unique scientific opportunities afforded by study of pharmacologic treatment of acute HIV infection in neonates, we hypothesize that over the next five years breakthroughs may occur that may lead to new interventions effective at achieving HIV remission.

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16.**Key issues**

- Recent goals of antiretroviral treatment of neonates have expanded from reducing morbidity and mortality to also aiming to facilitate HIV remission.
- Clinical and scientific challenges include identification of HIV-infected neonates, issues surrounding timing of treatment, as well as antiretroviral drug options available for this group. These challenges are complicated by externalities beyond biology.
- Investigating this population offers unique biological opportunities, including a specific immune profile, ability to study both mother and neonate as well as transmitted and acquired virus, and time period spanning both the period soon after infection as well as the period of viral reservoir establishment and related damage.
- Given the unique scientific opportunities afforded by study of pharmacologic treatment of acute HIV infection in neonates, we hypothesize that over the next five years breakthroughs may occur that may lead to new interventions effective at achieving HIV remission.