CHILDREN, HIV, TB, INFECTIONS, TRIALS AND A FEW OTHER THINGS ALONG THE WAY

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October 2015
WELCOME

I thank all for attending this special event. I am grateful for this opportunity to reflect on my work in the presence of loved ones (my family), friends, colleagues and guests. I am thrilled that my wife Reena, and two of my children (Jonny and Zanny) are here, as is Reena’s father (who will celebrate his 90th birthday in eight days’ time). Our youngest daughter Sonya is at the Zhejiang Normal University in Jinhua, China. I wish she could be here.
I thought I would look back at early career influences, motivations and seemingly random events that were pivotal in my life. I often reflect on how meeting and working with many colleagues with similar and different backgrounds sometimes allowed exciting and innovative projects to develop and advance the field. First and foremost, I acknowledge and thank my wife Reena, whose love, presence, support and direction has made many things possible, and who, in no uncertain terms, lets me know right from wrong and guides decision-making from wrong to right. Reena has a BSc in nursing. We graduated in the same year at UCT and when Reena decided to become a veterinarian in 1981, we relocated to Pretoria. There I completed my compulsory military service in 1 Military Hospital’s Department of Paediatrics, headed by Dr (Commandant) Celia Marais, an inspiring and pragmatic mentor. I was already committed to becoming a paediatrician, won over since my paediatric rotation in the Old Somerset Hospital in my fourth year of study, and by the excellent training we received from outstanding paediatricians at the Red Cross Children’s Hospital. I had already completed a senior house officer rotation at Red Cross Children’s Hospital. At 1 Military Hospital in Voortrekkerhoogte, in Pretoria, Dr Andre Venter (now Head of Paediatrics, University of the Free State) had established a learning disability clinic. Dr Andrew Argent (now a professor and Head of Intensive Care at Red Cross Children’s Hospital) continued the clinic. When he left, I continued caring for children with learning disabilities of permanent force Army members. This experience led to my first clinical trial a few years later. Had Reena not decided to become a veterinarian, I am sure I would have stayed in Cape Town, but I cannot imagine how my career would have unfolded.

When my military service was completed, I did my residency in Paediatrics at the University of the Witwatersrand. The new Head of Department, Prof Alan Rothberg, in an informal conversation, asked if any of the registrars were interested in learning disabilities. I certainly was. So we devised a double-blind, randomised, crossover study to evaluate children with attention deficit disorder already on, and considered responsive to, methylphenidate (Ritalin®) at the New Hope School in Pretoria. I had conducted rounds with Dr I Gelderblom, a child psychiatrist, attached to the learning disability clinic at 1 Military Hospital. The idea to use Connors charts for measuring responses to active drug or placebo came from Dr Joan Cartwright, a specialist paediatrician in learning disabilities and now affiliated to the Department of Paediatrics and Child Health at Stellenbosch University. I was eager to use a non-validated measuring instrument which I had designed but had not piloted. The study would however have failed, should I not have used a validated measuring instrument. Our data showed that children did better on placebo than Ritalin, suggesting that the original decision to treat the children may have been faulty. One of my difficulties...
with studying learning disabilities was my inability to understand the literature coming from the USA and UK. I longed for something more defined.

While in the second year of my residency (1985) and at Baragwanath Hospital (now Chris Hani Baragwanath (CHB)), I met Dr Frank Berkowitz, the first South African paediatric infectious diseases specialist, who had just returned from a two-year fellowship in paediatric infectious diseases in Denver, Colorado, USA. (Formal training in this new sub-specialty became a reality in South Africa only in 2005). I became intrigued by his approach of combining empathy for his patients and their families with incisive enquiries about home circumstances. He combined skilled clinical examination, awareness of natural history of diseases and the application of scientific reasoning to developing a rational approach, and thus solving many vexing clinical problems. During this year, I encountered my first patient with HIV. This young boy had haemophilia, and acquired HIV through contaminated Factor VIII replacement therapy. The nurses surrounded his bed with mobile screens as they were fearful of HIV. From Frank, I learned that one can conduct highly relevant research using one's daily work. I also learned the importance of a case report, to extend one's knowledge and become a better doctor. For example, while working in the ICU at Coronation Hospital, a premature infant developed inflammation at a “drip site”. Frank suggested an aspirate, gram stain and culture. In this way we documented for the first time that yeast (candida) could infect a ‘drip site’ in a premature infant [1]. He suggested the need to document hospital-acquired infections in the children’s wards at CHB. There was no data from Africa, so I developed a protocol after reading a publication by Welliver et al. [2]. I found that, while in hospital, almost 15% of children developed a new infection, 70% were resistant to first-line antibiotics and just under a third developed the infection while either waiting for a procedure or to go home. At the time, measles was prevalent, with 28 children hospitalized after acquiring measles in the outpatient department [3]. Acquiring a new infection in hospital remains a perplexing problem today and is a constant theme in work in our Department of Paediatrics and Child Health.

We relocated to Cape Town at the end of 1987. Reena’s mother seemed in remission from ovarian cancer, diagnosed in May 1986, a compelling reason to return to Cape Town (although I would have preferred to stay in Johannesburg because of the many opportunities in the field of Infectious Diseases (ID)). There were two alternatives available to me in Cape Town: (1) Working as registrar in community paediatrics at Red Cross Children’s Hospital or (2) as junior consultant in the Department of Paediatrics and Child Health at Tygerberg Hospital and Stellenbosch University, supporting the outpatient service in C3A.

As Peter Donald was at Tygerberg, already undertaking clinically relevant research in paediatric meningitis and childhood tuberculosis, there was no debate. I started by establishing an infectious disease service, using the experience gained from Frank Berkowitz. Mentored by Peter Donald, I undertook research into hyponatraemia (low serum sodium) in children with Tuberculous Meningitis (TBM). We found that low serum sodium due to inappropriate secretion of antidiuretic hormone occurred frequently (17 of 24 [71%]) in children. We found that mean arterial pressure was correlated with plasma antidiuretic hormone levels. As intracranial pressure is raised in Tuberculous Meningitis, we hypothesised that the antidiuretic hormone was secreted to increase arterial pressure and allow brain perfusion. Giving excess fluids, especially with low sodium concentrations (as was common at the time), would cause dangerously low levels of sodium and lead to seizures [4, 5].

SOME BACKGROUND ON HIV

In June 1981, a case series of Pneumocystis pneumonia in four young homosexual men was reported in Los Angeles, USA. This type of pneumonia had previously been seen in patients whose immune systems had been compromised by cancer treatment or after organ transplant. All had evidence of cytomegalovirus (CMV) infection and oral candidiasis, suggesting immunocompromise [6]. Three months later, the first peer-reviewed article appeared on the subject, reporting on eight young homosexuals with Kaposi Sarcoma, an rare malignancy seen only previously in the elderly. Some had CMV and some had hepatitis B infection [7]. The term “GRID”, or Gay-related Immunodeficiency Disease, was adopted and was found offensive by members of the gay community, who had already begun mobilising in Western counties. Dr. Bruce Voeller, an activist scientist, suggested the term, the Acquired Immunodeficiency Syndrome (AIDS), then formally adopted by the CDC. Eighteen months after the first description, AIDS was described in infants born to mothers with known risk factors: commercial sex work and IV drug use. Therefore AIDS could be transmitted vertically from mother to child [8]. HIV was identified in 1983 and its target, the CD4 marker on CD4 (Helper)
lymphocytes, in 1984 [9, 10]. A specific antibody test, essential for diagnosis, also appeared in 1984 [11]. Early studies using the new antibody test in Kinshasa revealed a high prevalence and heterosexual spread. Also, multi-use of needles was implicated.

FELLOWSHIP IN PAEDIATRIC INFECTIOUS DISEASE IN USA, PREPARING FOR UNFOLDING HIV PANDEMIC IN SOUTH AFRICA

In 1991, we relocated to Denver, CO, where I followed in Frank Berkowitz’s footsteps to undertake a three-year fellowship in Paediatric ID. The main reason was to prepare for the HIV pandemic which I knew would reach South Africa, by learning clinical skills and undertaking laboratory research on HIV pathogenesis (how HIV causes disease). I joined a team superb and thoughtful clinicians, many of whom also undertook laboratory research. The Division of Pediatric ID in Denver already belonged to the PACTG (Pediatric AIDS Clinical Trial Group), a multi-center trial network for conducting trials and other research in Children who had HIV. During the fellowship, the first year is almost entirely clinical, with two months spent in Virology and Microbiology service laboratories and interviewing faculty for the best place to undertake laboratory studies in the second and third years. I chose to work in Dr Terri Finkel’s laboratory at the National Jewish Center for Immunology and Respiratory Medicine. At this stage, apoptosis, a new form of physiological cell death had been described. At that time, people wondered how HIV actually caused disease. It was well known that a surface glycoprotein on HIV, gp120, bound to the target CD4 on CD4 lymphocytes to enter the cell, and that the hallmark of HIV infection is a decline in these CD4 helper cells which causes immune collapse. Terri and Nirmal Banda showed that gp120 could cause CD4 cells from people without HIV to die by apoptosis, suggesting that loss of uninfected ‘bystander cells’ caused immunodeficiency. This was the first time an understandable molecular mechanism had been proposed to explain HIV pathogenesis. This idea was extended to lymph nodes in HIV+ adults and also rhesus macaques infected with Simian Immunodeficiency Virus (SIV) [12].

RETURN TO SOUTH AFRICA – AS RESPONSE TO HIV; NOT WITHOUT PRACTICAL OBSTACLES AND UNEXPECTED DIVERSIONS

Shortly after my return to the Department of Paediatrics and Child Health at Stellenbosch University and Tygerberg Hospital, I became involved in a seminal experience that changed my outlook on what my role could be. Between May and June 1996, the neonatal wards had experienced an unexpected increase in mortality from 12 to 20%. At the time funding had been reduced, personnel were demoralised because of voluntary retrenchment packages for experienced nursing personnel. The neonatal wards had become infested with cockroaches. Most infants had sepsis due to extended spectrum B-lactamase-producing *Klebsiella pneumoniae* and had developed a devastating condition associated with prematurity, namely necrotizing enterocolitis (NEC). A few months earlier, I had written a letter to the chief medical superintendent outlining the appalling state of the neonatal wards and the risk of hospital-acquired infection. Somehow, the letter found its way to the press and, with the media attention and its own stresses, the hospital authorities reacted well, prioritising renovation, cleaning and cockroach control.
We established a team and collected isolates from blood, stool colonisation and from the cockroaches themselves. Having just returned from Denver, I contacted a colleague (emails had just arrived), Mary-Anne De Groot, who suggested typing the organisms through pulsed field gel electrophoresis, which could be done in her supervisor Dr Ferric Fang’s laboratory. This was ably accomplished by Dr Elizabeth Wasserman, who transported the isolates in her suitcase to Denver [13]. Moreover, we could link NEC to breaches in infection control practice, thus giving some guidance for prevention [14].

An important lesson from this experience in the midst of an unchecked HIV assault on an unsuspecting population, was my realisation that research on HIV immunopathogenesis was less important than treating children. My focus needed to be on clinical care and how to use research as a tool to expand care.

HIV had increased logarithmically in South Africa between 1990 and 2002. In Denver, children were being treated with first one and then two antiretrovirals (ARVs) combined, with some efficacy. In 1994, the landmark PACTG 076 trial results were released showing that zidovudine (ZDV) given antenatally and during labour to the mother and thereafter to the baby reduced vertical transmission by 68% [15]. Prior to this study, all ARV studies for treatment and prevention were unsuccessful or showed limited, temporary benefit. In 1995, the first data on triple antiretroviral therapy (ART) outcomes were released. Patients were recovering and viral replication could not be detected in blood tests by viral load assays. Between 1995 and 2004, there was no ARV programme for public patients in South Africa, however.

HIV is spread through sexual contact, but infants acquire the virus vertically through the placenta before birth, through contact with secretions during birth and then through breast-feeding. Without intervention, approximately a third of infants acquire HIV in this way. In 1998, Wade et al published experience from New York City that even just giving post-natal ZDV to babies whose mothers had missed antenatal intervention, was effective [16]. Dr. Helena Rabie, supported by Dr. Clarissa Pieper and I, gave ZDV to all HIV+ mothers in the post-natal wards. Most mothers had been identified, as they were either ill or a doctor had sustained a needle-stick injury. Four of 26 babies were infected. Possibly we prevented infection in approximately 8 more infants [17]. The first structured programme to prevent vertical transmission took place in Khayelitsha in January 1999, led by Dr Fareed Abdullah [18], using a simpler ZDV regimen and, amid much controversy, pilot programmes using nevirapine began in the nine provinces from approximately 2002. In the Western Cape, steady progress was made with coverage of the entire province by 2003/4.

Although there were few data in published studies, we were seeing with our own eyes just how devastating this infection could be. The most effective treatment was triple therapy, but we knew that in the short term a single ARV such as zidovudine might still have benefit. We had no idea that triple therapy would ever be available for our patients, since it seemed to be too expensive at the time.

Our first task was to collect data to document what was happening to children who had HIV. We collected information on children who had been hospitalised between 1991 and 1996. Of 91 children identified, 40% had died. Over the two years after publication of the successful PACTG 076 on preventing vertical HIV transmission, more than R1 million had been spent providing palliative care for a preventable condition in Tygerberg Children’s Hospital [19].

In early 1996, shortly after my return to South Africa, an infant aged nine months was hospitalised with severe upper airway obstruction causing breathing difficulty. According to the mother the infant often stopped breathing when asleep. The infant was profoundly immunosuppressed and both infant and mother were seropositive for HIV. Symptomatic treatment was prescribed for the infant and very enlarged tonsils and adenoids were removed, once confirmed on endoscopy. The infant recovered and went home. Four days later, the infant came back, this time even more severely distressed and with severe heart failure. The only intervention possible was a tracheostomy with post-operative care in the ICU. However, the nursing personnel were justifiably worried about the risks of blood exposure to themselves. We reasoned that if we gave ZDV to the infant, it would reduce any risk from exposure. Remarkably, the infant recovered very quickly and began gaining weight, removing the need for the tracheostomy. Using stored plasma, we found that the upper airway obstruction was likely precipitated by Epstein-Barr virus co-infection [20]. We had a number of similar experiences with using a single ARV for children with extremely complicated disease symptoms, on the grounds that by reducing hospitalisation treatment would be cost-effective [21]. Using a single agent can however lead to resistance whereas three ARVs together give a durable response. We felt that, given our experience, there was a rationale for ‘sub-optimal’ therapy to meet defined goals.
OPENING AN HIV CLINIC FOR CHILDREN, THE SECOND IN AFRICA

There was no space for a paediatric HIV clinic in the Department, but the Infectious Diseases Clinic for Adults was under-utilised, and Drs Mark Beale and Michelle Zeier were welcoming. Thus, the Family Clinic for HIV was established in January 1997, the second such a clinic (to our knowledge) in Africa. We could share resources with our colleagues and could communicate easily about children and their parents. We shared a social worker (Nocawe Frans) and benefitted from the able leadership of the facility manager, Sr Vivienne O’Brian (a true woman of worth).

For HIV, the major question was not scientific, but rather how antiretroviral therapy (ART) could be accessed for sick children and adults (what we saw every day) and how vertical transmission of HIV from mother to child (PMTCT) could be reduced or prevented. An option for patients requiring ART was to participate in clinical trials, though this was clearly inequitable. Access would be determined by patients being lucky enough to live nearby and by funders considering us as a worthwhile study site. In 1999 we initiated our first ART trial where a new ARV was being developed and two additional drugs were provided by the sponsors. The trial took place at Tygerberg and the Perinatal HIV Research Unit (PHRU) at Chris Hani Baragwanath Hospital – led by Glenda Gray and Avy Violari). Through a combination of pharmaceutical trials, voluntary donations, a funded ARV study through Secure the Future (Bristol Myers-Squibb Foundation), and the HIV Outreach Prevention & Education (HOPE-Cape Town), established by Stefan Hippler and Monika Esser, we started more than 100 children on ART before the public roll-out began and had then had sufficient resources and experience to rapidly start 300 children on ART in 2004.

FULL FOCUS ON AFRICA, THE EPICENTRE OF AIDS

The year 2000 was pivotal for HIV. For the first time a World AIDS Congress took place in Africa, the epicentre of the AIDS pandemic. The XIII World AIDS Congress was hosted in Durban, South Africa. Cost of medication and access to treatment became a human rights issue and entered the public domain.

In the space of a year, we found ourselves in a situation where opportunities became available to link research to clinical care and ART and, above all, to expand infrastructure. We witnessed a terrible shortage of ART that was easily available in well-resourced countries and in South Africa, if one could afford it. The clinical load was immense, but there was no alternative but to engage. We began a number of processes more or less simultaneously. One of the most important outputs was that we established the Children’s Infectious Diseases Clinical Research Unit (KID-CRU) in ward J8 of Tygerberg Hospital. This was an abandoned children’s ward which became vacant when the Tygerberg Children’s Hospital was established in the “G” Block of the hospital in 2000.

INCREASING OPPORTUNITIES TO JOIN GLOBAL RESEARCH EFFORTS TO ADDRESS HIV IN CHILDREN

I became involved in several research projects and will briefly comment on some.

A. Rockefeller Projects

With Prof Heather Zar (then Dr Zar) from Red Cross Children’s Hospital, I joined a work group planning for one of the first initiatives to combat HIV in Africa, the International Conference on AIDS Care in Africa, sponsored in part by the Rockefeller Foundation, in Kampala, Uganda, in April 2001. The meeting was divided into themes, each with facilitators. Ours, addressing immunization and preventing opportunistic infections, was led by Wafaa El-Sadr from Columbia University and Jon Kaplan from the Centers for Disease Control (CDC) TB programme. We prepared inputs on immunisation and cotrimoxazole to prevent Pneumocystis pneumonia (PCP), a preventable but severe, opportunistic infection, extremely common in young infants with undiagnosed HIV. The Foundation then set aside $100 000 for one project from each of the five working groups to conduct a research project. The projects were selected through a competitive process. Our project was funded. I wanted to compare daily and three times weekly cotrimoxazole for prevention (as both were being used) and Heather, with input from Greg Hussey, felt that TB prevention was equally or more important. We combined the two questions using a factorial design (we only discovered this term once we had devised our plan) to compare daily versus three times weekly cotrimoxazole for preventing opportunistic infections and isoniazid (INH) versus a placebo (dummy drug) given at the same frequencies (INH is an anti-TB medication, also used to prevent TB developing after contact with a patient who has active TB). Carl Lombard, from the Medical Research Council, South Africa, helped us to formulate the design. (Prior
to my fellowship in Denver, Carl analysed data from my tuberculosis meningitis project, investigating why sodium levels in blood became low and also its implications.)

Our study commenced at the end of 2002 and by early 2004 our Data Safety Monitoring Board (an independent group monitoring safety in the study) (DSMB) advised us to stop the placebo arm because of a large survival benefit for INH. Between 2012 and 2015, 12 manuscripts (= scientific contributions) were published This was the second major trial for children with HIV from Africa and the first to address TB prevention (and TB). (Di Gibb and her team published a randomised large trial showing that cotrimoxazole was far superior to placebo to prevent opportunistic infections [22].)

Some of the advances included:

1. INH significantly reduced mortality as well as new TB disease in young children [23].
2. The risk for TB in HIV+ children not yet on ART was established – 24 out of 100 children will develop TB each year [23].
3. Most children have highly antibiotic-resistant organisms in the nasopharynx, which may translate into bloodstream infections [24].
4. INH and ART together are more effective than each alone to prevent TB [25].
5. Most HIV+ children in our study (84%) had abnormal chest X-rays and 51% had severe abnormalities [26]
6. Chest X-rays improve on ART [27]

B. Pediatric AIDS Clinical Trial Group (PACTG) (2001-2005) and International Maternal Pediatric Adolescent Clinical Trial (IMPAACT) group – Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), USA

The ACTG was established in 1987, and in 1991 separated into adult and paediatric groups. In 2000, both the ACTG and PACTG expanded to high-prevalence countries. We established a combined Stellenbosch University and UCT initiative and successfully joined the PACTG. For MTCT studies, Mitch Besser (founder of Mothers to Mothers to 2B), represented UCT, and Prof Gerhard Theron, Stellenbosch University. I represented Stellenbosch University for Paediatrics. Greg Hussey from UCT led the initiative. We later became two independent units. As other South African research sites also joined the PACTG, we became a ‘virtual’ South African network. Members included the University of the Witwatersrand (Avy Violari [Perinatal HIV Research Unit] and Tammy Meyers [Harriet Shezi Clinic]) and the University of KwaZulu-Natal (Raziya Bobat). We joined an international group of experts who gained expertise in the USA and participated in many studies that advanced the HIV treatment and prevention of mother-to-child transmission of HIV agenda for children and in pregnancy. I have listed a few completed studies below indicating benefits and how treatment has been influenced.

1. HIV in pregnancy (Prof Gerhard Theron)
   a. Acceptability of undertaking HIV counselling and testing in labour [28].
   b. Most effective prevention for infants born to HIV+ mothers who have had no antenatal prevention and showed that two or three ARVs were more effective than a single ARV [29].
2. Antiretroviral strategies for children:
   Lopinavir/ritonavir is more durable than nevirapine as third ARV for African children (with two standard ARVs) [30, 31].
3. INH given as pre-exposure prophylaxis does not prevent TB in HIV-exposed infants [32].

The PACTG reformulated as a new network in 2007, the International Maternal Pediatric Adolescent AIDS Clinical Trial (IMPAACT) group actively engaged in new treatment strategies, including attempts to cure HIV. We are still involved and are involved in many projects. These include using broadly neutralising antibodies for treatment and prevention and also the correct dosages of medications in pregnancy and low birth-weight premature infants.

C. The Children with HIV Early Antiretroviral (CHER) Trial – Part of CIPRA-SA (The Comprehensive International Program for Research in AIDS) – Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), USA

I recall receiving a telephone call from Glenda Gray in 2001. Would I be interested in joining the CIPRA-SA collaboration? The proposal was led by Prof. James McIntyre and included colleagues from UCT and Wits. I would be developing an early ART project together with Dr Avy Violari at the Perinatal HIV Research Unit (PHRU) at the Chris Hani Baragwanath Hospital. There
would also be a linked project with Dr Shabir Madhi, asking whether early ART would influence responses to pneumococcal immunization.

Of course there was no time, as there just seemed to be too much to deal with, but I accepted, anyway. The aim of the CIPRA programme was to develop ‘within country’ capacity to undertake clinical research and develop capacity for relevant clinical trials that might influence how we treat HIV. Dr Violari had already met Di Gibb at HIV meetings and Di worked closely with Prof Ab Babiker at the United Kingdom Medical Research Council in London (now affiliated with University College of London). Both were already deeply involved in trials that would profoundly influence HIV clinical practice in children as well as adults. We were very mindful of the cost of ARVs, rapid loss of efficacy due to resistance, concerns of cumulative toxicity that might occur if the infants survived into adulthood and heavy reliance on mothers to give the medication to their children twice daily continuously. In 2002, we learned that our proposals would be funded. We developed the Children with HIV Early Antiretroviral (CHER) trial, which after three years of preparation, opened in 2005. We planned to recruit HIV+ infants who were relatively asymptomatic and with CD4% above accepted thresholds at the time (20%, later changed to 25% in the first year of life). Infants would be randomised to a deferred arm (ART-Def) according to current standards or to two early arms to receive immediate therapy; ART-40W (first birthday) and ART-96W (second birthday). Thereafter, in these two arms, ART would be discontinued until the CD4% dropped to a threshold or the child became ill. By this time, PMTCT programs were established and ART was available in the public sector. Infant diagnosis through a PCR test at six weeks was established. The first hints of the severe outcome for children in Africa had appeared in October 2004. The data from seven MTCT studies were combined to show that 35% of HIV+ infants had died in the first year of life and just over half were dead by the end of the second year [33]. We were convinced that this would not happen in our study as the children would be intensively followed up and would receive treatment as soon as necessary. In June 2007, the study’s DSMB advised us to stop enrolling into ART-Def, as risk death was 75% higher in the ART-Def arm. When we looked at our screening data, we noted that by six weeks of age, 20% of infants had already had severe immunosuppression, suggesting very rapid disease progression. (Two years later, a team led by David Bourne, from the school of public health at UCT, using birth and death registrations, showed that most mortality was between one to four months of age and rose year by year as HIV prevalence increased in pregnancy [34].) Our findings simplified treatment guidelines: (1) treat all HIV+ infants as soon as the diagnosis is confirmed; and (2) Infant diagnosis cannot be delayed. We also showed that starting ART immediately halved new TB cases and improved neurodevelopment [35-37]. The USA and World Health Organization adopted these recommendations in 2008 and South Africa adopted them by the end of 2010. Our study continued and showed that temporary stopping ART seemed safe and that two years appeared better than one year for primary treatment [38]. The data was not strong enough to be incorporated into guidelines, but suggest that treatment interruption might be safe.

There were already hints that starting ART at six to seven weeks of age was too late for many infants, as our screening information had shown. The narrative of the Mississippi Baby and the data showing that much HIV cases could be detected at birth have shifted focus to even earlier initiation of ART. The Mississippi Baby started therapy on day two of life. The mother stopped giving medication from 15 months of age and did not bring the infant for clinic visits. Six months later, when back in care, there were minimal traces of HIV, which remained virtually undetectable for almost two years. [39]

HIV control after early treatment is now actively studied, with success in adults also. Under these circumstances, ART could probably be discontinued carefully. We are actively studying this possibility through the IMPAACT network.
CONCLUSION

HIV prevention and treatment continue to evolve. There is now an active ‘Cure’ agenda. Highly effective monoclonal antibodies that can neutralise 90% of clinical isolates across the world are in clinical trials and vaccine development to prevent or to control after early therapy is progressing. We look forward to participating in these exciting developments.
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