Growing up with HIV

Research into brain development and long-term health

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General Introduction

HIV: A THREAT TO ADULTS AND CHILDREN

Since the first cases were recognized in the early 1980s (1, 2), the human immunodeficiency virus type 1 (HIV-1) has emerged as a major global health threat to both adults and children. Although various prevention and treatment options are available, HIV continues to be a threat, being one of the leading causes of death in low-income countries (3). UNAIDS estimates that more than 37 million people are living with HIV worldwide; 1.7 million of them are children under the age of 15. New HIV infections occur in 1.7 million people every year, including 160 000 children (4).

By attacking specific cells of the host's immune system, HIV infiltrates and gradually weakens the body's defense against pathogens. Without treatment, this leads to progressive susceptibility to severe opportunistic infections and specific malignancies, a state also known as the acquired immunodeficiency syndrome (AIDS) (5). Young children progress to AIDS more rapidly than adults, as their immune system is still immature. When HIV-positive children do not receive treatment, they face a high mortality rate early in life, both in high and low/middle-income countries (6-8). In contrast, HIV-positive adults usually progress to AIDS considerably more slowly, with many years of clinical latency.

HIV transmission can occur in two different ways. In *horizontal transmission*, HIV transmission occurs between persons who are not in a parent-child relationship; this occurs by unprotected sexual intercourse, intravenous drug use or by the use of infected blood products. In *vertical transmission*, the predominant route of infection in children, HIV transmission occurs from an HIV-positive mother to her child. This takes place particularly around the time of delivery (perinatally), but may also happen earlier during pregnancy, or while breastfeeding. Without any preventive actions, 20 to 45 children out of 100 pregnancies in HIV positive women result in infection of the child (9).

Over the last decade, prevention programs have been widely implemented to prevent HIV transmission from mother to child (PMTCT). These have resulted in a significant decline in the incidence of perinatal HIV infection among children worldwide, from 490 000 new infections among children under 15 in 2000 to 160 000 in 2018 (4). Nowadays – with proper implementation of prevention programs – out of 100 pregnancies in HIV-positive women, less than two children become infected (10). Despite the success of these programs, each day more than 400 children still become infected with HIV; the vast majority in sub-Saharan Africa (4).

Change of perspective: from a fatal disease to a chronic manageable condition

During the early years of the HIV epidemic, no treatment was available. As a result, people living with HIV had a short life expectancy. In 1987, the first drug against HIV, zidovudine, became available, able to prevent HIV from inserting its viral genetic material into its host cell

(11). However, the inhibitory effect of zidovudine on viral replication did not last long, as HIV quickly became resistant after initiation (12). Over the following years, more antiretroviral drugs (ARVs) against HIV became available and physicians adopted the strategy to combine two drugs to improve HIV treatment (dual therapy). Indeed, dual therapy resulted in a more potent suppression of viral replication than using only one drug. Nevertheless, in the vast majority of treated patients, HIV still became resistant to dual therapy within a short period of time. In 1996, a landmark year in the history of treatment of HIV/AIDS, this insight resulted in the strategy to use a combination of three antiretroviral drugs acting on different stages of the HIV life cycle. Combination antiretroviral therapy (cART) proved to be sufficiently effective in achieving durable HIV suppression (13-16). With the development of many new potent ARVs over the following years, regimens became more effective and better tolerated with fewer and less severe side effects. This resulted in a gradual shift in treatment guidelines to initiate therapy at an earlier stage (17, 18). Ultimately, this has led to the current recommendations (2015) to initiate therapy immediately in everyone living with HIV, regardless of symptoms or the degree of immunodeficiency.

cART has resulted in a drastic reduction in mortality and morbidity among adults and children living with HIV worldwide (13-16). Life expectancy has increased significantly as a consequence, and HIV has been transformed from a fatal illness to a chronic, manageable condition (19, 20). Children living with HIV now have the perspective of growing up into adulthood. As a result of that, we are now able to expand the horizon; besides concentrating on short-term perspectives, we are now able to focus on long-term outcomes. This is important, as children living with perinatally acquired HIV (PHIV) are exposed to long-standing HIV infection and its treatment during their entire life. Furthermore, since childhood is a critical period for growth and development, it is essential to study the impact of HIV and its treatment on child development – particularly brain and cognitive development.

Growing up with hiv poses a threat to normal brain development

HIV is a virus that is able to enter the brain. Although one of the functions of the blood-brain barrier (BBB) is to prevent pathogens from entering, HIV can cross this barrier, and it does so shortly after infection. Researchers have demonstrated the presence of HIV on the other side of the BBB as soon as eight days after infection (21, 22). This can even take place before birth; post-mortem neuropathology studies have found HIV in the brains of aborted foetuses (23, 24). After passing the BBB, HIV enters and replicates in specific cells, in particular in macrophages and microglia cells. These types of cells serve as scavengers and play an important role in the immune response. Viral replication continues within these cells, which results in a cascade of inflammation, leading to the release of a variety of inflammatory mediators, such as tumour necrosis factor alpha (TNF-α), Interleukin (IL) 1β, IL-6, IL-8 and interferon alpha (IFN-α). These mediators further lead to immune activation and cerebral injury (25).

What do we know about brain development in children with hiv

HIV has a potentially devastating effect on children's brains (26, 27). Before cART was available, 20 to 50 out of 100 infected children showed severe and progressive neurological impairment, or arrested neurodevelopment (28). After the introduction of cART, the prevalence of these neurological complications has been significantly reduced to fewer than two children out of 100 HIV-positive children (29). With the current focus on long-term outcomes, researchers have studied the impact of growing up with HIV and its treatment on brain development using different perspectives.

Looking at brain development from a cognitive perspective, researchers have found that children living with PHIV perform on cognitive tests generally poorer, but not consistently so (30, 31), compared to that of healthy peers. This finding involved the comparison between PHIV-positive children and different control groups: HIV-negative peers who had been exposed to HIV perinatally, HIV-negative peers who had been unexposed to HIV, and applicable norm groups; it also involved studies from high-income (32-35) as well as from low/middle-income countries (36-43). A meta-analysis showed that the cognitive domains of memory and executive function appear to be most often affected (44, 45); however, as this analysis also included studies from before the era of cART, it may not be fully generalisable to the era of cART availability. Evidence suggests that children with prior AIDS and have recovered are particularly vulnerable for cognitive difficulties. Infected children without prior AIDS show similar cognitive functioning to uninfected controls (46-50). Only a handful of studies have investigated actual cognitive development, i.e. cogntive performance in the same children over time (39, 50-54). Those studies have suggested that cognitive development in children living with PHIV and its treatment, as opposed to studies that measured cognitive performance once, is similar to that of healthy peers.

The availability of imaging techniques, such as magnetic resonance imaging (MRI), has given researchers the opportunity to visualize the human brain. This provides us with insights in how structure and even the function of the brain changes during development. Although the most dramatic developmental changes in the brain take place before birth and during the first few years of life (55), the brain continues to undergo substantial structural remodelling throughout childhood and adolescence, and into adulthood (56). Available evidence in the field of perinatally acquired HIV has reported that the brains of children living with PHIV and having treatment are different from the brains of healthy peers. Children living with PHIV had lower brain volume, of both grey and white matter, poorer quality of white matter, and had more structural abnormalities of white matter (57-68), although not consistently (69, 70). Lower brain volume, more white matter abnormalities and poorer quality of white matter have been associated with correlates of HIV disease severity (57, 59). Only two pediatric studies looked into the development of brain structure, i.e. assessing brain structure in the same children over time (71, 72). Although

both had a short time of follow-up, these studies suggest normal brain structure development in children living with PHIV and its treatment.

What we do not yet know about brain development in children with hiv
As discussed above, evidence suggests poorer cognitive performance, more abnormalities in brain structure, and delayed attainment of developmental milestones in children living with PHIV. The word *development* in itself implicates a change over time, thus requiring more than one measurement, yet most of the studies in the field of brain and cognitive development in this population have been cross-sectional, i.e. using data measured at only one point in time (73, 74). Such data provide only a snapshot, and does not reveal whether a difference found at one point in time remains static or might be subject to change. Rather than researching brain and cognitive development – such cross-sectional studies can be said to research brain and cognitive *performance*. In order to study actual brain development in children living with PHIV and its treatment, longitudinal studies are essential.

The research of this thesis seeks to address the following central question:
In children living with PHIV and on proper treatment, are long-term outcomes – in particular long-term brain development – similar to those in healthy peers?

Studying the relationship between hiv and brain development is a challenge
To investigate the impact of HIV (and antiretroviral treatment) on brain development, we have to compare brain development of children living with PHIV with that of a control group of HIV-negative peers. To provide a meaningful comparison, it is important that HIV-negative peers resemble PHIV-positive children in characteristics that are on itself associated with brain development, such as age, gender and socioeconomic status (75). The Achilles heel of studies on cognitive development, however, is that a large number of factors may affect brain development, which need to be taken into account.

As already mentioned, over the years, researchers have increasingly included children who were exposed to maternal HIV but did not become infected as controls. These children are highly similar to HIV-positive children in environmental factors, which limits potential confounding. Exposure to HIV and cART *in utero* may itself have a negative impact on the brain. Studies have reported poorer cognitive performance and differences in brain morphology among children who were exposed to HIV but did not become infected, compared to children who were not exposed to HIV and therefore uninfected (76-79). However, this is not consistent, with some of them reporting no detrimental effects inperinatally HIV-exposed children (80-83).

The study of brain and cognitive development in children living with PHIV in high-income countries with well-working PMTCT programs is complicated by other challenges. An increas-

ing proportion of the children living with PHIV originates from sub-Sahara Africa, and has a background of international adoption. As adopted children are prone to exposure to childhood adversities, including poor health, economic hardship and compromised rearing environment in their family of origin or within institutions, this may introduce confounding in studies investigating the relationship between HIV and brain development and has to be further addressed (84, 85).

Cardiovascular disease, another long-term concern in people living with HIV

Compared with the general population, adults who acquired HIV at an older age (through horizontal transmission) are at elevated risk of cardiovascular disease (86, 87). Proposed underlying mechanisms are multifactorial and include ongoing inflammation despite effective ART, toxicity of cART and lifestyle-related risk factors, such as smoking. In children living with PHIV, clinical manifestations are not yet apparent, due to the still young age of the population. However, similar to adults, researchers have observed increased inflammatory markers as well as abnormal lipid profiles, along with structural vascular changes (88-90). These findings may suggest elevated risk of cardiovascular disease in children, but is still an underdeveloped field in pediatric HIV research.

Observational cohort studies

To study long-term outcomes, in particular in brain development in children living with PHIV, we made use of a cohort, called NOVICE. The research presented in this thesis is mainly based on the results of this cohort. We set up this cohort at the Amsterdam University Medical Centers, location Academic Medical Center, between 2012 and 2014, to study the Neurological Visual and Cognitive performance in children living with PHIV who were on long-term treatment, growing up into adulthood. This cohort initially served as a cross-sectional cohort study. All children living with PHIV from the outpatient department of the hospital, between 8 and 18 years old, were eligible. At enrolment, it included thirty-five children living with perinatally acquired HIV, between 8 and 18 years old. The cohort also recruited 37 HIV-negative controls. In order to include a proper control group, HIV-negative controls were frequency matched to HIV-positive children with regard to age, sex, ethnicity and socioeconomic status. After four to five years, we performed follow-up assessments, which changed the design from a cross-sectional cohort to an observational cohort study, which we used to assess brain *development*.

To a lesser extent, this thesis made use of data of children enrolled in the AIDS Therapy Evaluation in the NetherlAnds (ATHENA) cohort. This is a unique population-based observational cohort that follows up on the clinical outcomes of all consenting HIV-positive people in HIV care in the Netherlands, since the introduction of cART in 1996. The Dutch HIV Monitoring Foundation (Stichting HIV Monitoring) manages the ATHENA Cohort and collects data from medical records. The Netherlands has centralized pediatric HIV care in the following five ac-

credited hospitals: Amsterdam University Medical Centers, location Academic Medical Center / Emma Children's Hospital, University Medical Center Utrecht / Wilhelmina Children's Hospital; Erasmus Medical Center, Rotterdam / Sophia Children's Hospital; Radboud University Medical Center, Nijmegen / Amalia Children's Hospital, and University Medical Center, Groningen / Beatrix Children's Hospital) (91).

Significance and limitations of the studies described in this thesis

With this thesis, I intend to contribute to the improvement of health of children living with PHIV worldwide. The studies presented aim to advance our knowledge on long-term outcomes in children living with PHIV, with a special focus on brain development. This thesis aims to answer the question whether current HIV care, including the use of potent antiretroviral treatment, ensures normal brain development. If this is demonstrated not to be the case, this thesis could provide a starting point for improvement.

A key strength of this thesis is that it investigates brain development with a long follow-up of almost five years, during an important time in growing up. Another important strength is the inclusion of a well-matched control group. Previous studies carried out before the establishment of this cohort, either lacked an HIV-negative control group or included controls that were unmatched for previously described important confounding variables. Last, this thesis includes a study that investigates the impact of (factors related to) adoption on brain development, which is unique in this field of research.

The reader should bear in mind that the research presented in this thesis is not able to disentangle the effect of HIV and cART on brain development directly, as cART is standard treatment for everybody living with HIV worldwide. Therefore, no group of untreated children with PHIV was available for this study.

The content of this thesis

This thesis consists of ten chapters, including this introductory chapter, **chapter 1**. This thesis starts with the focus on the long-term outcome of brain development. First, **Chapter 2** gives an overview of the current evidence on differences in brain structure and structural brain development between PHIV-positive children and HIV-negative peers, using advanced brain imaging techniques. **Chapter 3** presents a longitudinal study from the NOVICE cohort, in which we compare structural brain development in children living with PHIV to that of HIV-negative peers. The final chapter on brain development is **Chapter 4**, which presents a similar longitudinal study in which we investigate cognitive development. The following chapters, chapters 5, 6 and 7, examine potential determinants of brain development and hiv-related outcomes. **Chapter 5** presents a population-based cohort study, which investigates whether long-term immunological and virological outcomes differ by adoption status. Additionally, it provides an overview of the

demographics and treatment characteristics of children living with PHIV in the Netherlands. **Chapter 6** investigates whether having a background of international adoption serves as a potential confounder in the relationship between HIV and cognitive performance. For this purpose, we included a control group of HIV-negative children, who were adopted from similar regions as children living with PHIV. **Chapter 7** investigates the role of antiretroviral drugs in cognitive performance, by assessing the penetration of individual drugs across the blood-brain barrier, as well as viral replication in the brain (by assessing viral load in CSF). The last section of this thesis investigates cardiovascular disease risk in children living with PHIV. C**hapter 8** presents the findings of a cross-sectional study evaluating a specific cardiovascular disease marker, lipoprotein(a). The concluding chapters, **Chapters 9** and **10**, draw upon the work of this entire thesis. In these chapters, we address the lessons learned with respect to the overarching research question and discuss the implications of our findings for the clinical field as well as for future research.

Throughout this thesis, I use the term 'HIV-positive children' to refer to children who acquired HIV perinatally. I use the term 'HIV' to refer to HIV type 1 infection.

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