Implications of a perinatal HIV infection on adolescent health

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CHAPTER 1

THESIS INTRODUCTION AND OUTLINE

HIV: PAST AND PRESENT PERSPECTIVES

The human immunodeficiency virus-1 (HIV-1, hereafter: HIV) is one of two species of Lentivirus (blue box) causing an incurable infectious disease that – if untreated – evolves to a progressive state of immunologic failure leading to life-threatening opportunistic infections and malignancies: i.e. acquired immunodeficiency syndrome or AIDS [1].

HIV can be acquired either vertically (perinatally, abbreviated as PHIV) i.e. transmission from mother to child during pregnancy, birth or through breastfeeding, or horizontally (behaviorally) through unprotected sexual intercourse and exposure to infected blood, e.g. blood transfusions or injection drug use with shared needles [1,2].

BACKGROUND INFORMATION ON LENTIVIRUSES

HIV (a species of Lentivirus) is an enveloped RNA virus that can infect human's macrophages, monocytes and lymphocytes (CD4+). Lentiviruses – a genus of retroviruses – are hosted by other animals such as non-human primates (simian immunodeficiency virus or SIV) and cats (feline immunodeficiency virus or FIV). Retroviruses can incorporate their DNA into their host's DNA. All lentiviruses share similar clinical features: long incubation periods (hence its name, as "lenti" means slow), persistence despite robust immune response and invariably fatal outcome. Lentiviruses replicate in nondividing and terminally differentiated cells, a distinction from other retroviruses [64].

In forty years, HIV has changed from a fatal infection to a manageable chronic disease (blue box, next page) due to substantial advancements in diagnosis and treatment, including the limitation of drug related side effects [3]. Although older guidelines recommended treatment initiation dependent on CD4+ T-cell lymphocytes, currently the immediate initiation of treatment – i.e. combination antiretroviral therapy (cART) – is irrespective of CD4+ T-cell count and considered the standard recommendation [4]. Once diagnosed and treatment is initiated, persons living with HIV will require face life-long treatment.

Despite a decline in the incidence of HIV by 70% between 2000 and 2015 [5], HIV remains a significant global health burden. In 2021, UNAIDS reported an estimated 152,000 new vertical transmissions, which translates to a mother to child transmission every 3 to 4 minutes [6]. Almost 50% of these newly diagnosed children – who mainly live in rural areas in Sub-Saharan Africa – still do not have access to life saving treatment and will have died by the age of two years, underscoring the consequences of the rueful inaccessibility to treatment in predominantly high burden countries [7].

HISTORY OF HIV AND ITS TREATMENT

HIV emerged as a global health issue in the early 1980s. The first case series reported Kaposi sarcoma and Pneumocystis carinii (now: Pneumocystis jiroveci) pneumonia in previously healthy men who have sex with men were published in 1981 [65]. By 1983, there were case reports of children who had born from mothers with AIDS-related diseases. In the same year the causing pathogen was discovered [66]. In 1990, the Food and Drug Administration approved Zidovudine – a nucleoside reverse transcriptase inhibitor (NRTI) – as the first antiretroviral drug for children with HIV, three years after the approval for adults [68,69]. Protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) were introduced halfway the 1990s. In 2008 integrase strand transfer inhibitors (INSTIs) were approved [67]. Currently, the cornerstone of HIV treatment is referred to as combination antiretroviral therapy (cART) and consists of three drugs: two NRTIs and a potent third agent, such as an PI, INSTI or NNRTI [4].

In contrast to Sub-Saharan Africa, the absolute number of children and adolescents living with PHIV in the Netherlands is low. Between 1998 and 2020, there were 364 children and adolescents living with PHIV in the Netherlands, of which the majority (58%) was born in Sub-Saharan Africa. All were in care in either one of four Dutch pediatric HIV centers or in adult HIV centers. Since 2004, a national program has ensured standard HIV testing for all pregnant individuals and if necessary subsequent therapy to minimize the risk of transmission. Since then, new vertical transmissions are rarely seen in the Netherlands [8].

With currently available potent cART, the global adage says “U=U” which means that undetectable equals untransmissible. It emphasizes the importance of HIV testing and initiation of cART to prevent new cases [9]. The majority of children and adolescents living with PHIV worldwide receive cART [10] and as a consequence, the mortality and morbidity of children and adolescents living with PHIV have substantially decreased and their life expectancy is similar to that of the general population [3]. In recent years, research has therefore shifted towards understanding the health implications of living with HIV as a chronic disease and requiring long-life therapy.

KEY POINTS

- HIV remains a significant global health problem
- cART reduces mortality and morbidity and increases life expectancy
- Research focuses on long-term effects of HIV and its treatment

HIV: NEUROTROPIC PROPERTIES

In the pre-cART era, the incidence of severe HIV-associated neurocognitive disease (HAND) – e.fg. HIV-encephalopathy in children and HIV-associated dementia in adults – was about 25% [11,12]. The occurrence of HAND demonstrates the neurotropic properties of HIV and its ability to cross the blood-brain barrier (BBB) which might occur as early as eight days after infection [13]. A proposed hypothesis is that HIV enters the brain while residing in cells that usually pass the BBB, i.e. the Trojan horse hypothesis. This phenomenon is observed in another lentivirus [14]. Subsequently, HIV proteins (e.g. Tat) activate human brain microvascular endothelial cells to release inflammatory mediators that expedite the migration of infected cells pass the BBB [15]. Autopsies of patients who had HIV encephalitis revealed evidence of HIV replication in macrophages and microglial cells i.e. mononuclear phagocytes [16]. These brain cells respond to various types of injury: from vascular problems to protein accumulation as for example is seen in Alzheimer's disease [17]. There are several hypotheses underlying the neuropathogenesis associated with HIV. Infected and uninfected cells fuse into multinucleated giant cells (MNGCs) which indicates HIV-associated neuropathology [15,18]. Besides direct viral damage, brain injury is also secondary through inflammation, indicated by elevated immunological markers such as tumor necrosis factor alfa and interleukins 1B and 6 [19]. However, it is likely that more pathophysiological mechanisms underlying HIV-associated brain injury are yet to be elucidated.

KEY POINTS

- HIV invades the brain rapidly after infection
- Neurological and cognitive complications are present despite cART
- Underlying pathophysiological mechanisms are largely unknown

HIV: NEUROLOGICAL COMPLICATIONS

Although severe manifestations of HAND have substantially declined with the introduction of cART, HAND remains the largest HIV-associated comorbidity with a reported incidence of up to 50% [20]. Despite effective treatment, there is accumulating evidence that children and adolescents living with PHIV still experience neurological complications [21,22]. Magnetic resonance imaging (MRI) or, to a lesser extent, computed tomography (CT) studies are used to non-invasively visualize the brain and possible brain injury [23]. These studies have indicated structural brain changes which include lower brain volume, lower white matter (WM) integrity, and higher WM hyperintensities (WMH) volume in children and adolescents living with PHIV compared to controls [24–29]. There is also evidence of impaired cognitive function, such as lower intelligence quotient (IQ) and executive function in adolescents living

with PHIV compared to controls [11,30]. As MRIs can visualize the brain in vivo, affected brain areas could be detected and may in turn contribute to the understanding of the underlying pathogenesis of HAND.

HIV: COMPLICATIONS IN VIEW

WHITE MATTER HYPERINTENSITIES (WMH)

WMH are macroscopic hyperintense lesions – of presumably vascular origin – which are usually visualized with MRI or, to a lesser extent, with CT imaging [23]. In the general population, the presence of WMH is associated with higher rates of cognitive impairment, a three times higher risk of stroke, and a higher risk of developing dementia [31]. There is contrasting evidence as to whether WMH are more prevalent in children and adolescents living with PHIV compared to HIV-negative controls. One cross-sectional study found that HIV-positive individuals had a higher WMH prevalence and volume compared to non-infected controls [24]. Another cross-sectional study in Zambia found comparable WMH prevalence between children living with PHIV and controls [32]. A previous longitudinal study found comparable WMH volume over time between adolescents living with PHIV and HIV-negative controls [33]. Although WMH in adults living with HIV were more frequently studied than in children, the conclusions were similarly contrasting. One cross-sectional study reported that men living with HIV had a higher WMH volume, which in turn was associated with cognitive impairment compared to HIV-negative controls [34]. Another case-control study found that HIV was an independent risk factor for having WMH [35]. However, a longitudinal study did not detect differences in WMH volume between adults living with HIV and controls after a follow-up of two years [36]. Thus, evidence regarding WMH prevalence in both children and adults living with HIV compared to their peers not living with HIV appear to have a similar contrasting pattern. A direct comparison between children and adults living with HIV would increase pathophysiological understanding of WMH in people living with HIV, as these groups differ in both age and mode of HIV acquisition.

» RESEARCH QUESTION

Is there a different pattern of WMH between children and adults living with HIV?

WHITE MATTER INTEGRITY (WM INTEGRITY)

Besides macroscopic WMH, microstructural brain WM can be investigated in vivo as well. A particular MRI sequence – diffusion tensor imaging (DTI) – is used to measure the diffusion of water molecules in WM [37]. This is of interest, as it detects microscopic changes and therefore can hint at underlying pathology – e.g. ischemia – before conventional MRI sequences can

visualize potential macroscopic WM changes. It is usually reported by means of WM integrity which is defined as a parameter that gives information about relations of various WM networks and their connectivity [38]. In children and adolescents living with PHIV, there is growing evidence that suggests that this population has lower WM integrity compared to HIV-negative controls [24,28]. One explorative longitudinal study found persistently lower WM integrity in effectively treated adolescents living with PHIV compared to HIV-negative controls with a follow-up of almost five years [33]. Interestingly, a growing subpopulation of adolescents living with PHIV in predominantly high resource settings have been adopted. The previous studies did not control for early life adversities or adoption status. It is unknown to what extent international adoption status may have (indirectly) confounded the results depicted in previous studies, as adoption usually occurs in early life, thus coinciding with important periods of brain WM development [39]. Moreover, adoption is associated with early life adversities, such as malnutrition and social deprivation [40]. In turn, these factors are associated with WM maldevelopment [41,42]. To further understand the etiology of brain WM injury in PHIV subpopulation, WM integrity and other MRI parameters were compared with an adoption status matched control group.

» RESEARCH QUESTION

Do adolescents living with PHIV have more brain injury compared to adoption status matched controls?

CEREBRAL BLOOD FLOW (CBF)

Apart from structural brain parameters, present-day MRI techniques can also measure cerebral perfusion [43]. In children and adolescents living with PHIV, it is of interest to investigate cerebral blood flow (CBF) for several reasons. First, WMH – which may be more prevalent in adolescents living with PHIV than in HIV-negative controls – are of presumed vascular origin [21,31]. Second, HIV is known to have vasculopathological properties [44].

It is well established that adolescents living with PHIV are prone to cognitive complications, such as decreased executive function as compared to HIV-negative controls, suggesting deterioration in brain function over time [45]. In the general population, CBF alterations are associated with cognitive function [46]. A previous cross-sectional study found higher CBF in WM, subcortical regions and the thalami of adolescents living with PHIV compared to HIV-negative controls [47]. By investigating CBF over time, additional clinical evidence on the development of CBF – as proxy of brain function – and its associations with cognitive profiles in adolescents living with PHIV will be gained.

» RESEARCH QUESTION

Is there a difference in CBF between adolescents living with PHIV and matched controls over time?

NEUROAXONAL DAMAGE

Although the incidence of severe neurological complications, such as HIV-associated encephalopathy, have substantially decreased with the early initiation of cART, HAND still manifests in people living with HIV with an incidence of up to 50% [20]. The pathophysiological mechanisms underlying HAND are most likely multifactorial. It is hypothesized to include direct viral damage prior to treatment initiation, neurotoxicity associated with cART, as well as low grade ongoing inflammation and/or damage associated with HIV [19]. To assess ongoing, low grade damage and its possible association with change in cognitive function, various biomarkers have been identified, including neurofilament light (NfL), which is associated with immune activation and damage in the PHIV population [48,49]. NfL is a sensitive diagnostic and prognostic biomarker reflecting neuroaxonal damage and could serve as a proxy of the observed brain WM injury in adolescents living with PHIV. Moreover, NfL can be measured in plasma, with plasma values correlating with values in cerebral spinal fluid (CSF) [50], which can therefore bypass the need of a lumbar puncture. To investigate possible neuroaxonal damage progression in adolescents living with PHIV, we measured plasma NfL values longitudinally.

» RESEARCH QUESTION

Is there evidence of ongoing neuroaxonal damage in adolescents living with PHIV who receive cART?

OPHTHALMOLOGICAL OUTCOMES

The second cranial nerve – i.e. optic nerve – spurs bilaterally into the retina and contains more than one million axons [51]. The optic nerve is technically part of the central nervous system as it is ensheathed in all three meningeal layers and derived from the diencephalon [52]. In the cART era, evidence suggests the presence of retinal abnormalities in children living with PHIV. Previous cross-sectional studies reported contrasting results: one found a thinner fovea, whereas two other studies reported thicker fovea in the study population living with HIV compared to HIV-negative controls [53–55]. As retinal complications might be associated with visual impairment in adolescents living with PHIV, the development of their retina should be investigated to shed light

on the risk of this association. To gain further insight in the extent of brain injury, it is essential to determine potential damage to the retina, for it is technically part of the central nervous system and thus can be viewed as a "window to the brain" [56].

» RESEARCH QUESTION

Do adolescents living with PHIV have an altered development of the retina?

CARDIOVASCULAR COMPLICATIONS

HIV is an independent risk factor to develop cardiovascular disease (CVD), which is more frequent and occurring at younger age in adults living with HIV compared to the general population [57]. The non-communicable manifestations of HIV may become more apparent, as the life expectancy of people living with HIV increases. While a small number of adolescents living with PHIV exhibit CVD manifestations already at a relatively young age [58], the majority do not, as CVD usually manifests at an older age. HIV-associated CVD manifestations include myocardial and endothelial dysfunction, and increased carotid intima-media thickness [59]. Possible pathological mechanisms contributing to HIV-associated CVD risk include use of certain antiretroviral drugs, dyslipidemia, and vascular inflammation [60,61]. It is hypothesized that vascular inflammation may additionally contribute to the pathogenesis of brain injury [31], thus the potential that HIV-associated CVD risk and brain injury might share a pathological interaction. Lipoprotein(a) is a biomarker that is an established and independent risk factor for CVD [62]. A previous cross-sectional study found higher Lp(a) levels in adolescents living with PHIV compared to controls [63]. Longitudinal studies can help to further determine the potential CVD risk of adolescents living with PHIV. This is necessary as the majority of adolescents living with PHIV have a normal life expectancy but are not old enough to exhibit CVD complications. Results from longitudinal research could fill in the current knowledge gap for clinicians. More importantly, it may give rise to the development of strategies that lower Lp(a), thus concurrent CVD risk.

» RESEARCH QUESTION

Do adolescents living with PHIV have an increased CVD risk?

OUTLINE OF THIS THESIS

This thesis aims to identify the implications of a perinatal HIV infection on adolescent health. This thesis is divided into five sections. **Chapter 1** is the general introduction and the first section. The second section contains studies that investigated the characteristics of brain injury in adolescents living with PHIV. **Chapter 2** identifies differences in incidence and location of WMH between children and adults living with HIV. Chapter 3 up to and including 7 contain studies that compared adolescents living with PHIV to matched HIV-negative controls. The potential role of international adoption status on lower WM integrity and other MRI parameters is determined in **Chapter 3**, whilst **Chapter 4** zooms in on change in CBF over time and its association with cognitive function. **Chapter 5** explores the presence of ongoing neuroaxonal damage in the context of plasma NfL levels.

Section three sheds light on ophthalmological outcomes. It is comprised of one longitudinal and one cross-sectional sub-study integrated into **Chapter 6** which addresses the development of the retina and its association with MRI parameters.

Section four is composed of two longitudinal substudies combined into **Chapter 7**. This study investigated plasma Lp(a) levels over time and explored the subsequent CVD risk.

Section five encompasses of **Chapter 8 and 9** which contain the general discussion in which the implications of PHIV on adolescent health is put into perspectives with current literature. Moreover, I aim to propose potential future areas of research and health perspectives. This section ends with a summary in both English and Dutch (Nederlandse samenvatting).

» AIM OF THESIS

To identify implications of PHIV on adolescent health.

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EDITORIAL COMMENT

The terminology used to describe adolescents living with perinatally acquired HIV is not always the most recent. It is also not always in line with widely used terms as indicated by the International AIDS Society. This applies to Chapters 2 to 7.