

## BEHAVIOR

## Sexual Development in Perinatally HIV-Infected Young People: A Systematic Review and Explorative Study



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### ABSTRACT

**Background:** Similar to other young people with a chronic health condition, perinatally HIV-infected (PHIV) adolescents may have an impacted sexual development.

**Objectives:** This paper aims to compare sexual milestones of PHIV to HIV uninfected peers, through a systematic review (SR) and explorative study.

**Methods:** We performed a systematic search in 4 electronic databases (Medline, Embase, Web of Science, and Scopus), according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Last search in all databases was performed in May 2021. We included studies that reported on quantitative data of any of the main outcomes and compared PHIV to HIV uninfected control groups. Main outcomes were defined as the occurrence and/or debut age of sexual milestones (falling in love, having been in a romantic relationship, masturbation, kissing, non-genital caressing (feeling or petting, touching), genital caressing (fingering, handjob), giving or receiving oral sex, and penetrative sex (vaginal or anal). We excluded case reports, audits, guidelines, editorials, abstracts, studies that reported on behaviorally infected HIV patients, studies that did not include an HIV uninfected control group and studies that could not be translated to English or Dutch. We used the Agency for Health Care Research and Quality (AHRQ) Checklist for quality assessment. We performed qualitative synthesis of the data. In the explorative study, we compared sexual milestones of PHIV and HIV uninfected controls matched for age, sex, ethnicity and educational level, using a subset of questions of a validated questionnaire.

**Results:** We included eighteen studies in the SR, describing outcomes of an estimated 1,963 participants. Seventeen studies compared the occurrence and/or debut age of intercourse in PHIV and HIV uninfected controls and 4 studies reported on any of the other sexual milestones. The majority of studies found no difference in occurrence (12 of 16 studies) or debut age (6 of 8 studies) of intercourse in PHIV compared to controls. Two of 4 studies reporting on any of the other milestones found no significant differences between PHIV and HIV uninfected controls. In the explorative study, we included ten PHIV participants and 16 HIV uninfected, matched controls. PHIV tended to report a later debut age of sexual milestones than controls (not significant).

**Strengths and Limitations:** The SR includes only a small number of studies and few studies report on non-penetrative milestones. The explorative study adds to this review by including non-penetrative milestones and comparing PHIV to HIV-uninfected, well-matched controls. However, the sample size was small.

**Conclusion:** PHIV seem to engage in sexual activities and achieve sexual milestones at a similar rate as their HIV uninfected peers, with a tendency of a later start in well treated PHIV. The review was registered in the PROSPERO database (CRD42021252103) and funded by AIDSfonds. AIDSfonds had no role in the study design or

Received November 4, 2021. Accepted September 13, 2022.

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<https://doi.org/10.1016/j.esxm.2022.100578>

interpretations of this study. **ter Haar AM, Fieten A, Van den Hof M, et al. Sexual Development in Perinatally HIV-Infected Young People: A Systematic Review and Explorative Study. Sex Med 2022;10:100578.**

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**Key Words:** Sexual Milestones; Perinatal HIV; Adolescents; Sexual Development

## INTRODUCTION

Adolescents perinatally infected with HIV (PHIV) are growing up with a chronic health condition, which may impact their sexual development. In the past decades, optimization of treatment has greatly declined the number of PHIV infections and has changed PHIV from a deadly disease to a chronic condition.<sup>1</sup> Still, an estimated 3.3 million young people (15-24 years) are living with HIV worldwide. In the Netherlands, an estimated 361 children and adolescents are living with PHIV, of which the majority has a background of immigration from regions in the world with a high HIV prevalence (eg, Sub-Saharan Africa).<sup>2</sup> With PHIV now being a chronic condition, the focus in high-income countries like the Netherlands has shifted from acute care to long-term well-being of children and adolescents with PHIV. Sexuality (and sexual development) can greatly impact well-being and should therefore be a point of focus in high quality care. However, little is known about the sexual development of adolescents growing up with PHIV.

Sexuality develops during the whole lifespan, but during adolescence, stimulated by the start of puberty and the accompanying hormonal changes, sexual development accelerates.<sup>3</sup> This development consists of a change in thinking on sexuality, sexual responsiveness, and sexual behavior. For most adolescents sexual behavior progresses in a stepwise matter, starting with masturbation, kissing, touching, followed by penetrative, and oral sex. The pace of this stepwise course of development is unique for everyone, but research suggests it is important to follow a stepwise sexual development to ascertain sexual wellbeing and healthy sexuality in adulthood.<sup>4-6</sup> Not only is healthy sexuality significant in its own right, but it also plays an important role in one's global self-esteem and quality of life.<sup>7,8</sup> For adolescents with a chronic health condition, developing healthy sexual behavior can be challenging due to disease-related, psychological, or relational factors.<sup>9</sup> Physical symptoms of pain and fatigue, as well as the need for hospital visits, medical treatments, and their side effects, can interfere with regular school attendance and maintaining peer relations.<sup>10</sup> Subsequent stress can lead to a diminished interest in sexual experimentation, while feelings of being different from others can cause social isolation and depressive symptoms which can further limit sexual experimentation. At the same time, wanting to be "like the others," being vulnerable to peer pressure due to a greater need to be accepted by their healthy peers, and high rates of emotional distress have been suggested to escalate the pace with which adolescents with chronic

health conditions become sexually active, which may have adverse sexual health outcomes.<sup>10-15</sup>

Children with PHIV are not only entering adolescence with a chronic health condition, but face the extra challenge of living with a disease that is sexually transmittable and accompanied by social stigma.<sup>16,17</sup> In adult people living with HIV (PLWH), the diagnosis is known to affect sexual pleasure and intimacy due to fear of transmitting the virus and feelings of guilt, in some cases leading to sexual abstinence.<sup>18,19</sup> Studies in the adult population have suggested about half of PLWH experience sexual difficulties.<sup>20</sup> In contrast, very little is known about the sexuality of adolescents with PHIV. Qualitative studies have shown reluctance to start with sex or romantic behaviors among young HIV-infected patients.<sup>21-23</sup> HIV-infected adolescents can have concerns about jeopardizing their relationship when they disclose their HIV status to a boyfriend or girlfriend.<sup>23</sup> In one study, HIV-infected adolescents reported choosing to completely abstain from sexual relationships, to minimize the risk of any accusations of unethical behavior or of transferring HIV to others.<sup>21,22</sup> Studies comparing the sexual development of PHIV to that of healthy controls are scarce.

Therefore, this study aims to explore the occurrence (yes/no) and debut age (age at first occurrence) of sexual milestones of PHIV and compare these to their HIV uninfected controls. To this aim, we performed a systematic review to answer the following research question: do sexual milestones occur at a similar age in PHIV adolescents as in their HIV uninfected peers? Additionally, we performed an exploratory questionnaire study in which we compared sexual milestones in heterosexual PHIV adolescents with those of an heterosexual HIV uninfected control group matched for age, sex, ethnicity, participants' educational level, and educational level of parents, which are characteristics known to be associated with sexual activity.<sup>4,24,25</sup> Between PHIV and uninfected matched controls, we compared occurrence and debut age of sexual milestones (falling in love, kiss with tongue, masturbation, romantic relationship, non-genital caressing, genital caressing, and penile and/or vaginal penetration).

## MATERIALS AND METHODS

### Part I: Systematic Review

We included studies that reported quantitative data on percentages of the occurrence and/or the debut age of sexual

milestones in PHIV, in comparison to an HIV uninfected control group. Sexual milestones were defined as at least one of the following partnered sexual activities: kissing, non-genital caressing (feeling or petting, touching), non-penetrative sex, giving or receiving manual stimulation (fingering, handjob), giving or receiving oral sex, and penetrative sex or intercourse (vaginal or anal). We excluded case reports, audits, guidelines, editorials, and studies of which only abstracts are available. We also excluded studies that reported on behaviorally infected HIV patients and studies that did not include an HIV uninfected control group. Only studies that were written in English or Dutch or studies that could be translated to English or Dutch were included.

### Search Strategy

A systematic literature search was performed on May 4, 2021 in medical databases; Medline (Ovid), Embase (Ovid), Web of Science, and Scopus. Conference abstracts from Embase (Ovid) and Scopus were included to discover unpublished studies. Finally, manual citation and reference searching was performed on Google Scholar on May 19, 2021 on the included studies and 4 other relevant studies were manually included. A combination of Mesh and/or Emtree and free text words containing: HIV vertical transmission AND sexual behavior AND young adult. The full search strategy can be found in the supplement (S1).

### Data Extraction and Analysis

We imported all records into Rayyan<sup>26</sup> and removed the remaining duplicates. Two reviewers (A.M.t.H. and A.F.) independently screened titles and abstracts for eligibility and performed the full-text selection. Discrepancies were resolved by discussion and a third reviewer (D.P.) was consulted when necessary. Two reviewers (A.M.t.H. and A.F.) independently extracted the following data using a standardized form: administrative data (authors, year of publication, country of research, study design, study period, and description of population of cases and controls), study type, study location, study population, participant characteristics (age, sex, educational level, and ethnicity) and achievement (n%) and/or debut age (mean and/or median) of sexual milestones (adjusted p values and, if available, effect sizes). The authors of primary studies were contacted to provide missing or additional data when necessary.

### Quality Assessment

We registered the review protocol in the PROSPERO database (CRD42021252103) and can be accessed at [www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42011001752](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42011001752). Two reviewers (A.M.t.H. and A.F.) independently determined the quality of the individual studies, using the Agency for Healthcare Research and Quality (AHRQ) Checklist.<sup>27</sup> Disagreements between the reviewers were resolved by discussion, and a third reviewer (D.P.) was consulted when necessary.

## PART II: EXPLORATIVE STUDY

### Participants

This explorative cross-sectional study is part of the second assessment of the Neurological, Visual and Cognitive performance in HIV-infected Children (NOVICE)-cohort.<sup>28-32</sup> NOVICE is a prospective, observational cohort study that investigates the potential effect of HIV infection and the use of combination antiretroviral therapy (cART) in children at the Amsterdam University Medical Centers (Amsterdam UMC), Academic Medical Center, the Netherlands. Participants in the NOVICE cohort were 23 PHIV patients from the outpatient clinic of the Amsterdam University Medical Centre (Amsterdam UMC), location Academic Medical Center (AMC), and 21 HIV uninfected (HIV-) controls. Eligibility criteria for the NOVICE cohort are described in more detail elsewhere.<sup>28-32</sup> Groups were frequency matched for age, sex, ethnicity, and socio-economic status (SES) to eliminate potential sources of bias. SES was defined as the level of parental education and parental occupational status. Parental education was scored according to the International Standard Classification of Education [ISCED].<sup>33</sup> Occupational status was defined as 0, 1, or 2 caregivers with a paid job.<sup>34</sup>

We approached all NOVICE participants who were over 12 years old during the period of recruitment and data collection (February 2017–July 2018) to participate in this explorative study. The number of participants who consented to participate decided the sample size. We obtained written informed consent from all participants and from parents or legal guardians of participants younger than 18 years old. The ethics committee of the Amsterdam University Medical Center approved the study protocol. This study was registered with the Netherlands Trial Register (ID NL6813).

### Demographic, HIV- and cART Related Variables

We collected the following sociodemographic data: age, gender, ethnicity, region of birth, substance use (alcohol, smoking, and drugs), education level of participant and education level of (adoptive) parents (as a proxy for SES), and pubertal development. Education level was scored according to the ISCED.<sup>33</sup> ISCED is scored from 0 to 9, ranging from less than primary education to a doctoral or equivalent level. We measured pubertal development by Tanner staging, using the standardized method proposed by Marshall and Tanner for the staging of sexual maturation.<sup>35-37</sup> For PHIV participants, we performed laboratory testing of HIV-1 RNA viral load (VL). In HIV uninfected controls, we performed HIV testing to confirm their HIV uninfected status. The Dutch HIV Monitoring Foundation provided historical data (age at HIV diagnosis, route of HIV transmission, age at cART initiation) and data since registration in the Netherlands (Centers for Disease Control and Prevention [CDC] clinical staging). CART was defined as the use of at least 3 antiretroviral drugs from 2 or more classes.

## Main Outcome: Sexual Milestones

In PHIV and controls, sexual development was measured by a relevant subset of questions of a national questionnaire; “*Seks onder je 25e*” (Sex under the age of 25 years), developed and validated by Rutgers and SOA AIDS Nederland.<sup>24</sup> This subset of questions can be found in the supplements (S2). Sexual milestones included in this questionnaire are falling in love, being in a romantic relationship, masturbation, kissing with tongue, non-genital caressing (“feeling and stroking”), manual genital caressing (“fingering, handjob”), and penile and/or vaginal penetration. For each milestone, individuals were asked about the occurrence (did they ever experienced it [yes/no]) and debut age (age [in years] at first occurrence).

## Statistical Analyses

We performed sensitivity analyses to test differences in demographic characteristics of NOVICE participants who did and those who did not fill in the sexual development questionnaire. We compared demographic characteristics between PHIV and HIV uninfected controls. For continuous data, we used a *t*-test for normally distributed variables, or a Mann-Whitney U test for not normally distributed variables. For categorical variables, Fisher’s exact test was used. We used Fisher’s exact test to compare the number of PHIV having achieved each sexual milestone with the HIV uninfected control group. For participants who achieved sexual milestones, we used Mann-Whitney U tests to compare median ages at debut between PHIV and HIV uninfected participants. To compare sexual milestones of PHIV and HIV uninfected participants with the general Dutch population, we included participants who reached the age at which 50% of Dutch adolescents have achieved each sexual milestone (median Dutch debut age). We then used Fisher’s exact test to compare the number of included participants having achieved each sexual milestone in the PHIV group with HIV uninfected controls. All statistical analyses were performed using SPSS Statistics, version 26. *P* values below .05 were considered statistically significant.

## RESULTS

### Part I: Systematic Review

**Selection Procedure.** The search provided 1275 titles and abstracts, of which 38 were selected for full-text screening (see supplement 2: Flow diagram). Based on the inclusion and exclusion criteria, we included fourteen studies. We included another 4 studies through snowballing (backward, forward, and related searches in Google Scholar). This resulted in the inclusion of eighteen studies.

**Study Characteristics.** Sixteen studies had a cross-sectional design and 2 studies reported on both longitudinal and cross-sectional data (Table 1). In the 18 included studies, we identified

nine study populations as many studies examined the same study participants concurrently but reported on different associations with sexual development outcomes. Seven studies sampled patients from the CASAH (Child and Adolescent Self-Awareness and Health Study) cohorts. The CASAH cohort included 6 time points over 10 years (baseline to follow-up 5); in this review, we grouped the results of the studies reporting on data from the same time points (Table 2). Two studies combined and reported on participants of the CASAH cohort and the R&R (Risk and Resilience in Youth with HIV+ Mothers) cohort and 2 studies reported on patients from the TAPHOD (TREAT Asia Pediatric HIV Observational Database) cohort. The studies from these cohorts are described separately. Studies were mainly conducted in the United States (*n* = 12)<sup>(38-49)</sup> 1 study additionally included Puerto Rico<sup>50</sup>, followed by Asia (*n* = 4),<sup>51-54</sup> Africa (South Africa, *n* = 1),<sup>55</sup> and Europe (*n* = 1).<sup>48</sup> The number of included PHIV adolescents ranged from 27 to 571, with a median of 192. Although it was not possible to track down exactly how many patients were reported in more than 1 paper, the total population of all studies comprised approximately 1963 unique participants. The age of study participants ranged from 9 to 42 years. Studies predominantly included PHIV exposed, uninfected (PHEU) participants as the control group (*n* = 10)<sup>38,40-46,50,56</sup> or HIV uninfected participants from the same communities. In thirteen studies, groups were matched for age and gender, and in 7 studies also for ethnicity.

**Quality of Studies.** In the majority of studies (*n* = 16), the authors did not describe any assessments undertaken for quality assurance purposes (supplementary table 2). Most studies (*n* = 11) did not describe how confounding was assessed and/or controlled. In 17 studies, PHIV participants differed from controls on important demographic variables.

**Sexual Milestones Outcomes.** Fifteen distinct cross-sectional studies and 2 longitudinal studies compared the occurrence (*n* = 16) and/or debut age (*n* = 8) of intercourse in PHIV and HIV uninfected controls<sup>38-40,42-46,48-56</sup> (Table 1). Intercourse was defined as either vaginal and/or anal penetration in nine of the cross-sectional studies and in both longitudinal studies.<sup>38,40,41,43-46,48-50,55-57</sup> Three studies additionally included oral sex in this definition.<sup>38,39,50,55</sup> Three studies reported on intercourse without further specification.<sup>51-54</sup> Four distinct studies reported on any of the other sexual milestones.<sup>40,41,47-49</sup>

**Occurrence of Intercourse.** Eleven of 15 cross-sectional studies reporting on the occurrence of intercourse concluded that it was comparable between groups,<sup>38,42,43,45,46,48-50,52-54,56</sup> whereas 3 studies found a lower occurrence in PHIV compared to HIV uninfected controls.<sup>39,44,55</sup> One study reported no difference in the occurrence of intercourse between PHIV and controls when they looked at intercourse separately but did find a lower

**Table 1.** Characteristics of the included studies (n = 18)

Author	Year	Country	study design	PHIV-infected patients (n); origin of patients; age	HIV-negative controls (n); origin of controls; matched for	Milestones reported on (definition of intercourse used in paper)
Abrams	2018	USA	cross-sectional	N = 151; from CASAH cohort; mean age 22.4 y	N = 97; PHEU from same medical centers; NA	Intercourse (oral, vaginal and/or anal penetration)
Aepfelbacher	2020	USA	cross-sectional	N = 35; NA; mean age 29 y	N = 20; NA; HIV-uninfected; age-, race, sex-matched	Intercourse (not further specified)
Ananworanich	2015	Thailand	cross-sectional	N = 40; pediatric HIV clinic; median age 18 y	N = 10; HIV-uninfected and behaviorally HIV-infected from same testing clinic; NA	Intercourse (not further specified)
Bauermeister	2009	USA	cross-sectional	N = 191; from CASAH cohort; mean age 12.0 y	N = 125; PHEU from same medical centers; NA	Kissing, genital touching, oral sex, Intercourse (oral, vaginal and/or anal)
Bauermeister	2012	USA	longitudinal	N = 113; from CASAH + R&R cohort; mean age 12 y	N = 114; PHEU from same medical centers; NA	Oral, Intercourse (vaginal and/or anal)
Benson	2018	USA	cross-sectional	N = 178; from CASAH cohort; mean age 18 y	N = 105; PHEU from same medical centers; NA	Intercourse (vaginal and/or anal)
Brittain	2019	South-Africa	cross-sectional	N = 506; from CTAAC cohort; median age 11.9	N = 110; youth center; matched for age and gender	Intercourse (oral, vaginal and/or anal)
Elkington	2009	USA	cross-sectional	N = 206; from CASAH cohort; mean age 12.3 y	N = 134; PHEU from same medical centers; NA	Intercourse (vaginal and/or anal)
Elkington	2012	USA	cross-sectional	N = 163; from CASAH + R&R cohort; mean age 12.1 y	N = 257; PHEU from same medical centers; NA	Intercourse (vaginal and/or anal)
Elkington	2015	USA	longitudinal + cross- sectional	N = 195; from CASAH cohort; mean age 12.7 y	N = 129; PHEU from same medical centers; NA	Intercourse (vaginal and/or anal)
Gromadzka	2015	USA	cross-sectional	N = 191; from CASAH cohort; mean age 12.8 y	N = 125; PHEU from same medical centers; NA	Intercourse (vaginal and/or anal)
Judd	2018	UK	cross-sectional	N = 296; from AALPHI cohort; median age 16 y	N = 96; HUU with a HIV infected parent, sibling, friend, or partner; NA	Anal sex, Intercourse (vaginal and/ or anal)
Kaushik	2016	USA	cross-sectional	N = 27; PHIV in pediatric HIV-clinic; mean age 17	N = 100; HUU from the same children's Hospital; NA	Intercourse (vaginal and/or anal)
Mellins	2009	USA	cross-sectional	N = 193; from CASAH cohort; mean age 12.15 y	N = 127; PHEU from same medical centers; NA	Genital touching, oral sex, intercourse (vaginal and/or anal)
Mellins	2011	USA, Puerto Rico	cross-sectional	N = 238; from PHACS cohort; mean age 13.7 y	N = 111; PHEU from same medical centers; NA	Intercourse (vaginal and/or anal)
Prasitsuebsai	2018	Malaysia, Thailand, Vietnam	cross-sectional	N = 250; from TApHOD cohort; median age 14.5 y	N = 59; other clinics and outreach services; age- and sex matched	Intercourse (not further specified)
Rolland-Guillard	2019	Thailand	cross-sectional	N = 571; from TEEWA cohort; age range 12-19 y	N = 571; general population; age- , sex and place of residence matched	Intercourse (not further specified)
Ross	2019	Malaysia, Thailand, Vietnam	cross-sectional	N = 250; from TApHOD cohort; median age 14 and 17 y	N = 59; other clinics and outreach services; age- and sex matched	Intercourse (not further specified)

**Table 2.** Cross-sectional studies reporting on occurrence and/or age at debut of sexual milestones

Author	Group	Subgroup	Age	Occurrence of sexual milestones						Age at debut
				Kissing	Touching	Oral	Anal	Intercourse	Overall	
Gromadzka (2015), Elkington (2009+2015), Bauermeister (2009), Mellins (2009)	CASAH	Baseline	11.95 (2.35) - 12.76 (2.18)	=	=/↑ <sup>§</sup>	=	=	=/↓ <sup>§</sup>	↓	↓ <sup>  </sup>
Elkington (2012)	CASAH + R&R	Baseline	12.1 (2.16)					=		
		FU1	±14.5					↓		
Elkington (2015)	CASAH	FU1	± 14.3 y					=		
Elkington (2015), Benson (2018)		FU2	16.73 (2.74) - 17.98 (2.76)					=		
Benson (2018)	CASAH	FU4	19, r 15-26					=		
Abrams (2018)	CASAH	FU5	22.38 (2.68)					=*		
Aepfelbacher (2020)	-		29 (5.0)					↓ <sup>†</sup>		=   ,†
Brittain (2019)	CTAAC		11.9 [10.7, 13.3]					↓ <sup>*</sup>		
Mellins (2011)	PHACS		13.7 (1.8)					=		=
Prasitsuebsai (2018)	TApHOD		14.5 (13.3–15.7)					= <sup>†</sup>		= ¶
Ross (2019)	TApHOD		13-18					= <sup>†</sup>		↑ ¶,†
Rolland-Guillard (2019)	TEEWA		12-19					= <sup>†</sup>		
Kaushik (2016)	-		17 (1.7)			=	↑ <sup>‡</sup>	=		=
Judd (2018)	AALPHI		16 [15- 18]				=	=		= ¶
Ananworanich (2015)	-		18 (17-19)							=   ,†

Differences are shown as higher (↑) and lower (↓) engagement or age at debut in PHIV+ compared to controls. “=” indicates no significant differences.

Intercourse is defined as vaginal and/or anal penetration.

Overall indicates any kissing, touching, or oral or penetrative sex.

\*Definition of intercourse also includes oral sex.

†Definition of intercourse is unclear.

‡Receptive anal sex in males.

§After accounting for the likelihood of engaging in all other sexual milestones.

|| Defined as mean of median age at debut.

¶ Defined as <14 or <15 years at debut.

**Table 3.** Longitudinal studies reporting on occurrence in sexual milestones

Author	Year	Group	Moment	Intercourse		Oral sex	
				OR*	<i>p</i>	OR	<i>p</i>
Bauermeister	2012	CASAH + R&R	B + FU1	1.06 [0.77-1.47]	>0.05	1.22 [0.84-1.76]	>0.05
Elkington	2015	CASAH	Baseline + FU 1 + FU2	1.40 [0.91–2.14]	>0.05	...	...

\*The odds of engaging in sex over time, HIV uninfected controls serving as the reference group.

occurrence in PHIV, after accounting for the likelihood of the occurrence of all other sexual milestones.<sup>40</sup>

Two studies longitudinally compared the occurrence of intercourse over time between PHIV and HIV uninfected controls and found no differences between groups<sup>41,45</sup> (Table 3).

**Occurrence of Other Milestones.** Three distinct cross-sectional studies<sup>40,41,47-49</sup> (Table 3) and 1 longitudinal study<sup>41</sup> (Table 2) reported on any of the other sexual milestones. No studies found a difference in the occurrence of kissing ( $n = 1$ ),<sup>40</sup> touching a partner's genitals ( $n = 1$ ),<sup>40,47</sup> oral sex ( $n = 3$ ),<sup>40,41,49,56</sup> or anal penetration ( $n = 2$ ),<sup>40,48</sup> yet 1 study reported a higher number of PHIV males compared to HIV uninfected males to engage in receptive anal penetration.<sup>49</sup> One study reported that PHIV were less likely to be sexually active (as defined by reporting any kissing, genital touching, oral or penetrative sex) than HIV uninfected controls.<sup>40</sup> This study also showed that sexually active PHIV were more likely to engage in touching behaviors than sexually active HIV uninfected controls.

**Age at Debut.** Seven distinct studies compared age of debut between PHIV and HIV uninfected controls<sup>39,40,48,49,51,52,54,56</sup> (Table 2). Sexual debut was defined as vaginal and/or anal penetration in 2 studies,<sup>48,49</sup> as oral sex, vaginal or anal penetration in 2 studies<sup>40,56</sup> and as sexual intercourse without further specification in 4 studies.<sup>39,51,52,54</sup> Three of 4 studies comparing the mean or median age at debut concluded that it was comparable between groups,<sup>39,49,51</sup> whereas 1 study found an earlier age of debut in PHIV compared to HIV uninfected controls.<sup>40</sup> Two of 3 studies comparing the rate of “early starters” (defined as debut age <14 or <15 years old) found no differences between groups,<sup>48,52</sup> whereas 1 study found fewer early starters among PHIV compared to HIV uninfected controls.<sup>54</sup> No studies reported on the age of debut of any of the other sexual milestones.

## PART II: EXPLORATIVE STUDY

### Characteristics of PHIV Adolescents and HIV Uninfected Matched Controls

Of 22 PHIV and 26 HIV uninfected controls of the NOV-ICE cohort who were over 12 years of age, 14 PHIV (64%) and 20 controls (77%) responded to our questionnaire. In both groups, 4 eligible participants declined consent to participate. Finally, 10 PHIV (46%) and 16 HIV uninfected controls (62%) filled in the questionnaire about sexual development ( $P = .384$ ).

Data of all participants was analyzed and there was no missing data. Sensitivity analyses showed no differences between participants who did and those who did not fill in the sexual development questionnaire.

Table 4 shows relevant characteristics of the PHIV and HIV uninfected controls, who have completed the questionnaire about sexual development. PHIV and HIV uninfected controls did not differ significantly in gender, age, ethnicity, ISCED score, and parents' ISCED score (all  $P$  values > .05). PHIV adolescents were more often born outside of the Netherlands (80% vs 19%;  $P = .004$ ) and living with non-biological family (40% vs 0%;  $P = .014$ ) compared to HIV uninfected controls.

**Sexual Milestones.** Table 5 shows the number of participants for whom romantic and sexual milestones had occurred.

For fewer PHIV than HIV uninfected adolescents most sexual milestones had occurred at the time of assessment, although the difference was not statistically significant. Significantly fewer PHIV reported having been in a relationship compared to HIV uninfected adolescents (2/10 vs 12/16;  $P = .014$ ). For all sexual milestones, PHIV reported a higher debut age as compared to the HIV uninfected controls, although the difference was not statistically significant (Table 6). Figure 1 shows the debut ages of PHIV and HIV uninfected controls, with the median debut age of Dutch adolescents as a reference.<sup>24</sup> Table 7 and Figure 1 show the number and percentage of participants who achieved sexual milestones at the median age of debut of Dutch adolescents. Fewer PHIV (33%) than HIV uninfected controls (64%) had engaged in genital caressing, yet the difference was not significant.

## DISCUSSION

In the systematic review, we summarized the available evidence on differences in sexual development between PHIV and healthy controls. Very few studies report on any other milestones than sexual intercourse. Most studies suggest that PHIV are as likely as healthy controls to engage in sexual intercourse, while a smaller number of studies suggest PHIV to be less likely to engage in sexual intercourse than their healthy peers. PHIV that do engage in sexual intercourse tend to report a similar age of debut as healthy controls. Very few studies report on any of the other sexual milestones.

Our explorative study adds to this review by reporting on the occurrence and debut age of sexual intercourse as well as

**Table 4.** Characteristics of PHIV+ and HIV-uninfected participants in the pilot study

Characteristics	n	PHIV+ (n = 10)	n	HIV- (n = 16)	p*
Female gender	10	6 (60%)	16	10 (63%)	1.000
Age in years, mean (SD)	10	17.2 (3.7)	16	18.5 (2.5)	.307
Ethnicity	10	8 (80)	16	11 (68.8)	.506
Black		0		2 (12.5)	
Caucasian		2 (20)		3 (18.8)	
Mixed/Other					
Born outside of the Netherlands	10	8 (80%)	16	3 (19%)	.004
Living with non-biological family (adoptive or foster care)	10	4 (40%)	16	0 (0%)	.014
Age arrived in the Netherlands, years, median (IQR)	10	3.5 (0.0-6.5)	16	0 (0.0-0.0)	.014
ISCED level of participant, median (IQR)	10	3.0 (1.8-3.0)	15	3.0 (3.0-3.0)	.317
ISCED level of parent <sup>†</sup> , median (IQR)	10	5.5 (3.0-6.0)	16	5.5 (4.3-6.0)	.835
Tanner stage					
Genitals (males only, median)	2	4.5	4	5	.333
Breasts (females only, median)	6	5	9	5	.604
Pubic hair (median)	8	5	13	5	.882
Cis gender	10	10 (100%)	16	16 (100%)	1.000
Heterosexual	10	10 (100%)	16	15 (93.8%)	1.000
Lifestyle					
Ever smoked	10	1 (10%)	16	5 (31%)	.352
Ever used alcohol	10	4 (40%)	16	11 (69%)	.228
Ever used drugs	10	1 (10%)	16	6 (38%)	.190
<i>HIV- and cART-related characteristics</i>					
Age at HIV diagnosis, years, median (IQR)	10	1.83 (0.77-6.19)			
CDC category N or A	10	3 (30%)			
Undetectable HIV viral load	10	9 (90%)			
Participants on cART	10	10 (100%)			
Age at cART initiation, years, median (IQR)	9	3.52 (1.14-9.60)			

\*Comparison between PHIV and HIV-uninfected participants.

<sup>†</sup>Most educated parent.cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; HIV-, HIV-uninfected; IQR, interquartile range; ISCED, International Standard Classification of Education; PHIV, perinatally HIV infected; SD, standard deviation. Undetectable values are defined as <40c/mL, including viral blips. Values are reported as n (%), unless otherwise stated. Tanner stage indicates pubertal development, higher staging indicates further development into puberty.

non-penetrative milestones (kissing, non-genital caressing, and genital caressing) in PHIV compared to HIV uninfected, well-matched controls. Due to low statistical power, no differences

between groups were found in this study, although PHIV seem to report a later debut of sexual milestones than their uninfected peers.

A later debut age of sexual milestones could indicate fear of transmission or disclosure in PHIV.<sup>16,22,48,58</sup> It is suggested that

**Table 5.** Achievement of sexual milestones in PHIV+ and HIV-uninfected, matched controls

	PHIV+ (n=10)	HIV-uninfected (n=16)	p
Being in Love	5 (50.0)	13 (81.3)	.189
Romantic relationship	2 (20.0)	12 (75.0)	.014
Kissing with tongue	4 (40.0)	10 (62.5)	.422
Masturbation	4 (40.0)	8 (50.0)	.701
Non-genital caressing	4 (40.0)	9 (56.3)	.688
Genital caressing	2 (20.0)	8 (50.0)	.218
Penetrative sex	3 (30.0)	7 (43.8)	.683

HIV-, HIV uninfected; PHIV+, perinatally HIV infected. Values are reported as n (%).

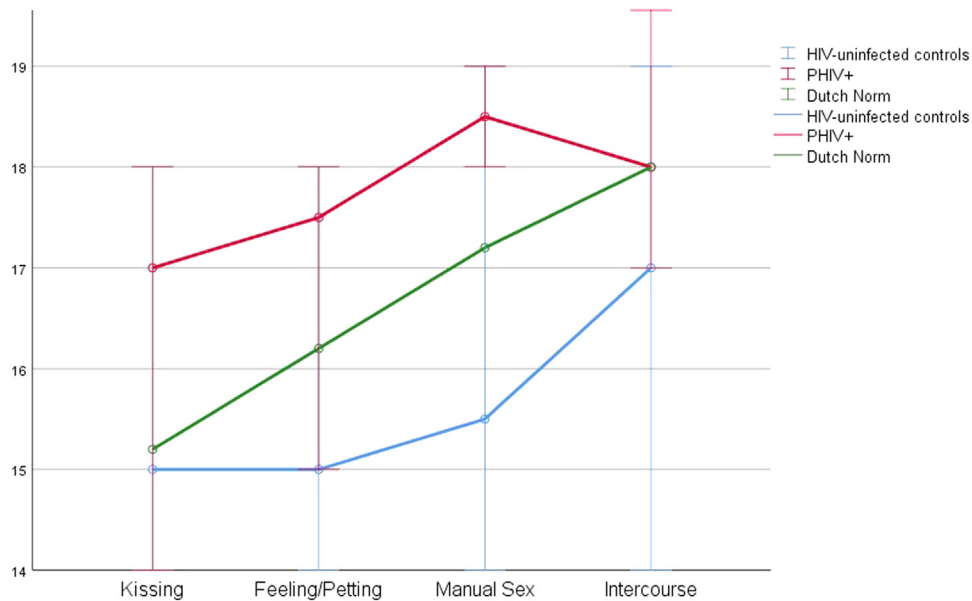
**Table 6.** Sexual milestones and median age at debut in PHIV+ and HIV-uninfected, matched controls

	PHIV+	HIV-uninfected	p
Kissing with tongue	17.0 (14.5-18.0)	15.0 (12.8-17.3)	.304
Masturbation	16.5 (13.8-17.0)	14.0 (11.5-14.8)	.109
Non-genital caressing	17.5 (15.5-18.0)	15.0 (14.0-16.5)	.199
Genital caressing	18.5 (18.0-19.0)	15.5 (14.0-17.8)	.178
Penetrative sex	18.0 (17.0-20.0)	17.0 (14.0-18.0)	.183

IQR, interquartile range; PHIV+, perinatally HIV infected.

Age (in years) is reported as median (IQR). Where n≤3, age is reported as median (range).





**Figure 1.** Median debut age of sexual milestones in PHIV+ and HIV-uninfected, matched controls. Values plotted are the median age (in years) and error bars represent 95% confidence interval. The green line represents the Dutch norm age at which 50% of Dutch adolescents have reached the milestone. Abbreviations: PHIV+, perinatally HIV infected. (Color version of figure is available online.)

PHIV therefore tend to engage more in touching behaviors than penetrative sex to reduce these risks.<sup>40</sup> However, in our explorative study the occurrence of touching behaviors as well as penetrative sex appeared lower (and debut ages appeared higher) in PHIV compared to healthy peers (all findings non-significant). This could indicate that better social-sexual skills instead might be a reason for their later sexual debut (eg, partner selection, negotiation of wishes and boundaries.<sup>59,60</sup> While a later sexual start is associated with more sexual problems (ie, arousal and orgasm) and lower subjective well-being,<sup>6,61</sup> better social-sexual skills increase the chances for a more positive sexual experience.<sup>59,60</sup> Consequently, to understand the implications of

these findings in PHIV we need more information on their sexual wellbeing and social-sexual skills.

In our study we find that adolescent PHIV may experience fewer sexual (developmental) hesitance as compared to most studies in adults.<sup>19,20</sup> In comparison to adolescents with PHIV, behaviorally infected adults may be more aware of the severity of their disease and may be more apprehensive of the risk of transmission with unprotected sexual intercourse. Both these 2 aspects have been downsized and therefore have little impact on young people, due to treatment optimization in the past decades and the finding of the fact that HIV cannot be transmitted through sex when the viral load is undetectable (Undetectable = Untransmittable (U = U) concept).<sup>62</sup>

**Table 7.** Achievement of sexual milestone at median Dutch debut age in PHIV+ and HIV-uninfected, matched controls

	PHIV+	HIV-uninfected	p
Kissing with tongue, n/N (%)	4/7 (57%)	9/15 (60%)	.628
Non-genital caressing, n/N (%)	4/6 (67%)	7/11 (64%)	.661
Genital caressing, n/N (%)	2/6 (33%)	7/11 (64%)	.247
Intercourse, n/N (%)	3/4 (75%)	6/9 (67%)	1.000

PHIV+, perinatally HIV infected.

Presented are the number (N) of participants older than the median Dutch debut age for each separate milestone, and the number (n) and percentage (%) within that group having reached the sexual milestone.

The median Dutch debut age is the age at which 50% of Dutch adolescents have reached a sexual milestone. These are 15.4 years for kissing with tongue, 16.2 years for non-genital caressing, 17.2 years for genital caressing and 18.0 years for intercourse.

This review is the first to provide an overview of the existing literature on the occurrence and age of debut of sexual milestones in PHIV compared to healthy controls. A strength of this review is its thorough systematic search. Regardless, we identified only few eligible studies and the included studies had some important limitations. First, half of the studies reported on participants from the same cohorts.<sup>38,40-46,56</sup> Secondly, PHIV participants often differed from healthy controls in terms of age,<sup>38,50,51,57</sup> ethnicity,<sup>44,48,50,55</sup> socioeconomic status<sup>38-40,44,45,50,53,55</sup> and whether they were living with a biological parent.<sup>38,44,45,50,52-55</sup> Most studies did not control for these important confounders. Thirdly, between studies we found great variation in how sexual milestones were defined, while some papers did not specify their terminology at all (eg, “first time sex” without further specification). Moreover, most of the studies only partially addressed the review questions by solely reporting on sexual intercourse and

not including other sexual milestones. These limitations make it difficult to compare studies and draw firm conclusions.

With our explorative study we tried to address these limitations, by including a well-matched control group, clearly specifying the terminology and addressing sexual milestones that typically precede penetrative sexual activities. It is one of the first to report on non-penetrative sexual milestones while there is growing evidence that these experiences are of equal importance for a healthy sexual development.<sup>60</sup> However, there are some important limitations. Results should be interpreted as a first attempt to gain insight into sexual milestones in PHIV and should not be generalized beyond this small sample. The NOVICE cohort includes a reasonable number of PHIV and matched controls, yet the response rate for this study is low (46% vs 62%). Also, since the PHIV group was generally young (17.2y, vs 18.5y in controls), many had not yet reached the norm age at which the debut of sexual milestones usually takes place. It is therefore not possible to reliably interpret the difference in the occurrence of sexual milestones between groups. It is, however, still possible to compare median age at debut between groups, but since this can only be reported once a milestone has been achieved, these medians are based on small sample sizes. This explorative study thus needs to be extended to a larger study sample with a broader age range (12-30) to further elucidate the occurrence and debut age of sexual milestones in PHIV.

The findings of this review and explorative study should prompt further research into the sexual milestones of PHIV. Future studies should include all sexual milestones and compare PHIV to well-matched controls. If findings of lower occurrence and later debut age in PHIV start are replicated in extended samples, the scope should be extended to motivations and consequences to better interpret these results. Furthermore, many other aspects of sexuality that are known to impact adults (eg, quality of the sexual response, sexual quality of life), were not the focus of this review and should be studied further in adolescents.<sup>20,63</sup>

Although there is still much to learn about sexual development in PHIV, we want to emphasize the importance for health care professionals to talk about sex with their adolescent and young adult PHIV patients. Concerns about infecting a potential partner can be addressed by talking about the U = U concept (4). Although adverse outcomes of sexual activity and prevention strategies are commonly discussed, other topics are similarly important.<sup>64,65</sup> These topics include, but are not limited to, their past and current engagement in sexual activities, their motivations to engage in or refrain from sexual activities, and the quality of their experience (eg, was there mutual consent, was the experience pleasurable).

## CONCLUSION

In conclusion, young people growing up with PHIV appear to engage in sex quite like their uninfected peers, with a tendency of a later start in well treated PHIV. While the number of studies

in the review and participants in the explorative study were both small, these results must be interpreted carefully.

## ACKNOWLEDGMENTS

The authors thank all study participants and their parents for participating, and HIV pediatric nurses for their support with the recruitment of patients at the outpatient department. This work was supported by AIDSfonds (grant number 2015009).

## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.esxm.2022.100578](https://doi.org/10.1016/j.esxm.2022.100578).

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*Conflict of Interest:* The authors report no conflicts of interest.

*Funding:* This work was supported by AIDSfonds (grant number 2015009).

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