



## SYSTEMATIC REVIEW

# Health risk behavior among perinatally HIV exposed uninfected adolescents: A systematic review [version 1; referees: awaiting peer review]

Derrick Ssewanyana <sup>1,2</sup>, Patrick N Mwangala <sup>2</sup>, Moses Kachama Nyongesa <sup>2</sup>, Anneloes van Baar <sup>1</sup>, Charles R Newton <sup>2-4</sup>, Amina Abubakar <sup>1-5</sup>

<sup>1</sup>Utrecht Centre for Child and Adolescent Studies, Utrecht University, Utrecht, The Netherlands

<sup>2</sup>Centre for Geographic Medicine Research Coast, Kenya Medical Research Institute (KEMRI), Kilifi, 230-80108, Kenya

<sup>3</sup>Department of Psychiatry, University of Oxford, Oxford, UK

<sup>4</sup>Department of Public Health, Pwani University, Kilifi, Kenya

<sup>5</sup>Institute for Human Development, Aga Khan University, Nairobi, Kenya

**v1** First published: 29 Oct 2018, 3:136 (<https://doi.org/10.12688/wellcomeopenres.14882.1>)

Latest published: 29 Oct 2018, 3:136 (<https://doi.org/10.12688/wellcomeopenres.14882.1>)

## Abstract

**Background:** Perinatally HIV exposed uninfected (PHEU) adolescents are an increasing sub-population, especially in high HIV epidemic settings. HIV exposure may have some lasting implications for adolescents' development, however, longer term health outcomes such as health risk behavior (HRB) are so far not well understood in this adolescent sub-population.

**Methods:** In this systematic review, we identify the prevalent forms, burden, and underlying risk factors for HRB of PHEU adolescents. We searched in PubMed, PsycINFO and Applied Social Sciences Index & Abstracts for peer reviewed empirical studies published between 1980 and August 2018 on HRB among PHEU adolescents aged 10 – 19 years.

**Results:** Eleven eligible studies, all conducted in North America were identified and they showed that sexual risk behavior such as lifetime unprotected sex increased drastically especially in mid-adolescence. PHEU adolescents' substance use (especially alcohol and marijuana) was high and increased over time. In a significant minority (10-18%) substance use disorder was screened. Some intra and interpersonal risk factors such as caregiver and PHEU adolescents' mental health problems, age and HIV status were shared across the two forms of HRB. However, other risk factors like race, gender and experience of traumatic life events were behavior specific.

**Conclusion:** Overall, there is need to conduct similar research in other settings especially those with high HIV burden where the PHEU adolescent sub-population is rising. Future research in this area could benefit from examining more forms of HRB and exploring the clustering of HRB among PHEU adolescents.

## Keywords

Adolescence, Behavior, Risk taking, HIV, Perinatal HIV exposure, Systematic review

## Open Peer Review

**Referee Status:** Awaiting Peer

Review

## Discuss this article

Comments (0)



This article is included in the [KEMRI | Wellcome Trust](#) gateway.

**Corresponding author:** Derrick Ssewanyana ([Dssewanyana@kemri-wellcome.org](mailto:Dssewanyana@kemri-wellcome.org))

**Author roles:** **Ssewanyana D:** Conceptualization, Data Curation, Formal Analysis, Methodology, Writing – Original Draft Preparation; **Mwangala PN:** Data Curation, Methodology, Writing – Review & Editing; **Kachama Nyongesa M:** Data Curation, Methodology, Writing – Review & Editing; **van Baar A:** Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Newton CR:** Conceptualization, Funding Acquisition, Methodology, Supervision, Writing – Review & Editing; **Abubakar A:** Conceptualization, Funding Acquisition, Methodology, Supervision, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

**Grant information:** This work was supported by the funding from the Initiative to Develop African Research Leaders (IDeAL) Wellcome Trust award [107769/Z/15/Z] to DS as a PhD fellowship and the Medical Research Council [MR/M025454/1] to AA. The MRC award to AA is jointly funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under MRC/DFID Concordant agreement and is also part of the EDCTP2 program supported by the European Union. The funding bodies do not have any role in the design of this study, collection, analysis, interpretation and writing of this manuscript.

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

**Copyright:** © 2018 Ssewanyana D *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**How to cite this article:** Ssewanyana D, Mwangala PN, Kachama Nyongesa M *et al.* **Health risk behavior among perinatally HIV exposed uninfected adolescents: A systematic review [version 1; referees: awaiting peer review]** Wellcome Open Research 2018, 3:136 (<https://doi.org/10.12688/wellcomeopenres.14882.1>)

**First published:** 29 Oct 2018, 3:136 (<https://doi.org/10.12688/wellcomeopenres.14882.1>)

## Introduction

A high propensity for risk taking among adolescents is extensively documented<sup>1,2</sup>. In the past, most of the research on health risk behavior (HRB) among adolescents focused on the general population<sup>3,4</sup>, however, emerging evidence indicates that HRB such as aggressive behavior, multiple sexual partnerships, and early sexual debut, are common among HIV affected adolescents<sup>5–8</sup>. HRB are specific forms of behavior that are known to increase susceptibility to disease or ill health on the basis of social or epidemiological data<sup>9</sup>. The [Centres for Disease Control and Prevention](#) (CDC) and World Health Organization (WHO) prioritize alcohol, tobacco and drug use, unhealthy dietary habits, sexual behaviors contributing to unintended pregnancy and sexually transmitted diseases, behavior that contributes to unintentional injury or violence, poor hygiene, and inadequate physical activity as major forms of HRB<sup>10,11</sup>.

For most of the studies, the “HIV affected adolescents” comprise a diverse assortment of HIV infected, HIV orphaned, perinatally HIV exposed uninfected (PHEU) and uninfected adolescents living with a HIV infected household member or caregiver<sup>8,12</sup>. One shortcoming of combining HIV status groups in to one (i.e. HIV affected) is the potential variation in the magnitude and associated risk factors for HRB across HIV status sub-groups. For instance, some studies have found different levels of cumulative psychosocial risk and burden of HRB between perinatally and behaviorally HIV infected adolescents, which highlights the potential challenge of consolidating research outcomes of different HIV groups<sup>13</sup>.

Of specific interest in this review is the burden of HRB among PHEU adolescents. This sub-population is steadily growing as a result of better access to the prevention of mother to child transmission of HIV (PMTCT) services<sup>14</sup>. Although numerous health indicators such as morbidity, immunity and mortality are sub-optimal among PHEU adolescents, especially during early childhood<sup>15,16</sup>, presently not much is documented on PHEU adolescents’ longer-term health outcomes. HRB is an example of longer-term health outcomes that warrant more research in the PHEU group, since potentially predisposing factors like the poor EF and cumulative psychosocial risk are commonly documented in this group<sup>17,18</sup>. This stated, most of the time PHEU children and adolescents are not actively monitored through healthcare systems that attend to their siblings or caregivers and thus rarely screened for HRB or attended to for the various psychosocial risks they face<sup>19</sup>. Besides, HRB is a significant public health threat that could compromise health and other quality of life of outcomes of PHEU adolescents.

The current systematic review aims to document the burden of HRB among PHEU adolescents. Specifically, we set out to: 1) identify and summarize characteristics of studies quantifying HRB among PHEU adolescents globally; 2) summarize the major forms of HRB assessed among PHEU adolescents; 3) identify commonly documented risk factors for HRB among PHEU and 4) document the burden of HRB among this adolescent sub-population. We anticipate that the results from this study will highlight some of the relevant behavioral specific needs

of PHEU adolescents and consequently inform research and intervention programs in this field.

## Methods

### Search strategy

This study utilized Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)<sup>20</sup>. A comprehensive data base search in [PubMed](#), [PsycINFO](#) and [Applied Social Sciences Index & Abstracts](#) was conducted for peer reviewed articles published from January 1980 up to 31<sup>st</sup> August 2018. We utilized a stepwise approach to implement a database search criterion with search terms comprising of subject headings and Boolean operators in titles, abstracts, topics and keywords as follows: (HIV exposed uninfected OR HIV exposed-uninfected OR HIV exposed OR HIV affected) AND (Adolescent\* OR Peer\* OR Youth\* OR Teen\*) AND (Risk Taking OR Risk Behavior OR Risk Behaviour OR Life Style OR Health Behavior OR Health Behaviour).

The eligibility criteria of the studies was guided by the participants, intervention, comparison, outcome and study design (PICOS) criteria. Studies were eligible if: 1) they were empirical studies; 2) were conducted among adolescents aged 10–19 years who were perinatally exposed to HIV but were not infected; 3) they assessed and reported any form of HRB among the PHEU adolescents.

In this review, we considered HRB that have been considered as priority based on epidemiological and social data according to CDC and WHO for example behavior that results to injury or violence; any form of risky sexual behavior; alcohol, tobacco and drug use; unhealthy dietary habits; and inadequate physical activity<sup>10,11</sup>. We excluded all studies: 1) that did not verify the perinatal HIV exposure status of the adolescent; 2) were non empirical; 3) whose participants’ age range, mean or median did not fall within 10 – 19 years<sup>21</sup>; 4) were published in languages other than English; and iv) did not assess or document HRB of the PHEU adolescents. In order to identify other potentially eligible articles that had not been retrieved in the database search, we further searched the reference lists of identified articles and also searched in [Google Scholar](#) using the following search terms: ‘perinatally HIV exposed uninfected’ OR ‘seroreverters’ AND ‘risk behavior’. Three authors (DS, PNM, MKN) independently screened the titles, abstracts and full articles for eligibility and reached consensus on the data extracted.

### Data extraction

From all the eligible studies data on: the author and date of publication; country where the study was conducted; year the study was conducted; study characteristics (including sample size); participant characteristics; and forms of HRB assessed were extracted into a Microsoft Excel 2013 data sheet ([Table 1](#)). Details of each form of HRB and associated risk factors were then extracted into a separate Excel data sheet. The detailed summary is presented in the results section. Data extraction was independently conducted by two authors (DS and PNM) who thereafter compared their results and reached consensus

**Table 1. A summary of the characteristics of eligible studies.**

Author	Country	Study recruitment period	Study characteristics	Participant characteristics	HRBs assessed	Study quality assessment
Elkington <sup>22</sup>	USA	2003 – 2008	Baseline, follow-up 1 & 2 of a cohort study (CASA project)	134 PHEU and 206 PHIV adolescents Mean age 12.4 years and 16.7 at follow-up 2	Marijuana use	satisfactory
Mutumba <sup>23</sup>	USA	2003 – 2008	Baseline, follow-up 1 & 2 of a cohort study (CASA project)	129 PHEU and 196 PHIV adolescents Mean age for PHEU adolescents at baseline was 11.9 years and 16.7 at follow-up 2	Substance use (excluding nicotine)	satisfactory
Elkington <sup>24</sup>	USA	2003 – 2008	Baseline, follow-up 1 & 2 of a cohort study (CASA project)	129 PHEU and 195 PHIV adolescents Mean age for PHEU adolescents was 12.4 years at baseline and 16.7 at follow-up 2	Risky sexual behavior, Alcohol use, Marijuana use	satisfactory
Alperen <sup>25</sup>	USA	2007 – 2009	Baseline of a cohort study (AMP)	157 PHEU and 354 PHIV adolescents Mean age for PHEU adolescents was 12.3 years	Alcohol use, Cigarette use, Marijuana use	satisfactory
Dolezal <sup>26</sup>	USA	2009	Follow-up 2 of a cohort study (CASA project)	47 PHEU and 88 PHIV sexually active adolescents Mean age for PHEU sexually active adolescents was 18.7 years	Risky sexual behavior	satisfactory
Mellins <sup>19</sup>	USA	2007 – 2010	Baseline and follow-up 1 of a cohort study (AMP)	111 PHEU and 238 PHIV adolescents Mean age for PHEU adolescents was 12.7 years	Risky sexual behavior, Alcohol use, Marijuana use	satisfactory
Bauermeister <sup>27</sup>	USA	2003 – 2007	Baseline of a cohort study (CASA project)	127 PHEU and 195 PHIV adolescents Mean age for PHEU adolescents was 11.9 years	Risky sexual behavior	satisfactory
Elkington <sup>28</sup>	USA	2003 – 2008	Baseline of a cohort study (CASA project)	134 PHEU and 206 PHIV adolescents Mean age for PHEU adolescents was 11.9 years	Risky sexual behavior, Alcohol use, Cigarette use, Marijuana use	satisfactory
Mellins <sup>29</sup>	USA	2003 – 2008	Baseline of a cohort study (CASA project)	134 PHEU and 206 PHIV adolescents Mean age for PHEU adolescents was 11.9 years	Substance use (marijuana & alcohol)	satisfactory
Mellins <sup>30</sup>	USA	2003 – 2008	Baseline of a cohort study (CASA project)	127 PHEU and 193 PHIV adolescents Mean age for PHEU adolescents was 11.9 years	Risky sexual behavior, Alcohol use, Cigarette use, Marijuana use	satisfactory
Benson <sup>31</sup>	USA	2003–2008	Follow-up 2 and follow-up 4 of a cohort study (CASA project)	105 PHEU and 178 PHIV adolescents Mean age 17 years at follow-up 2 and 19 years at follow-up 4	Substance use (marijuana, alcohol and other drugs) Risky sexual behavior	satisfactory

**PHEU- Perinatally HIV Exposed Uninfected**  
**Mean age is for the PHEU**

## Statistical analysis

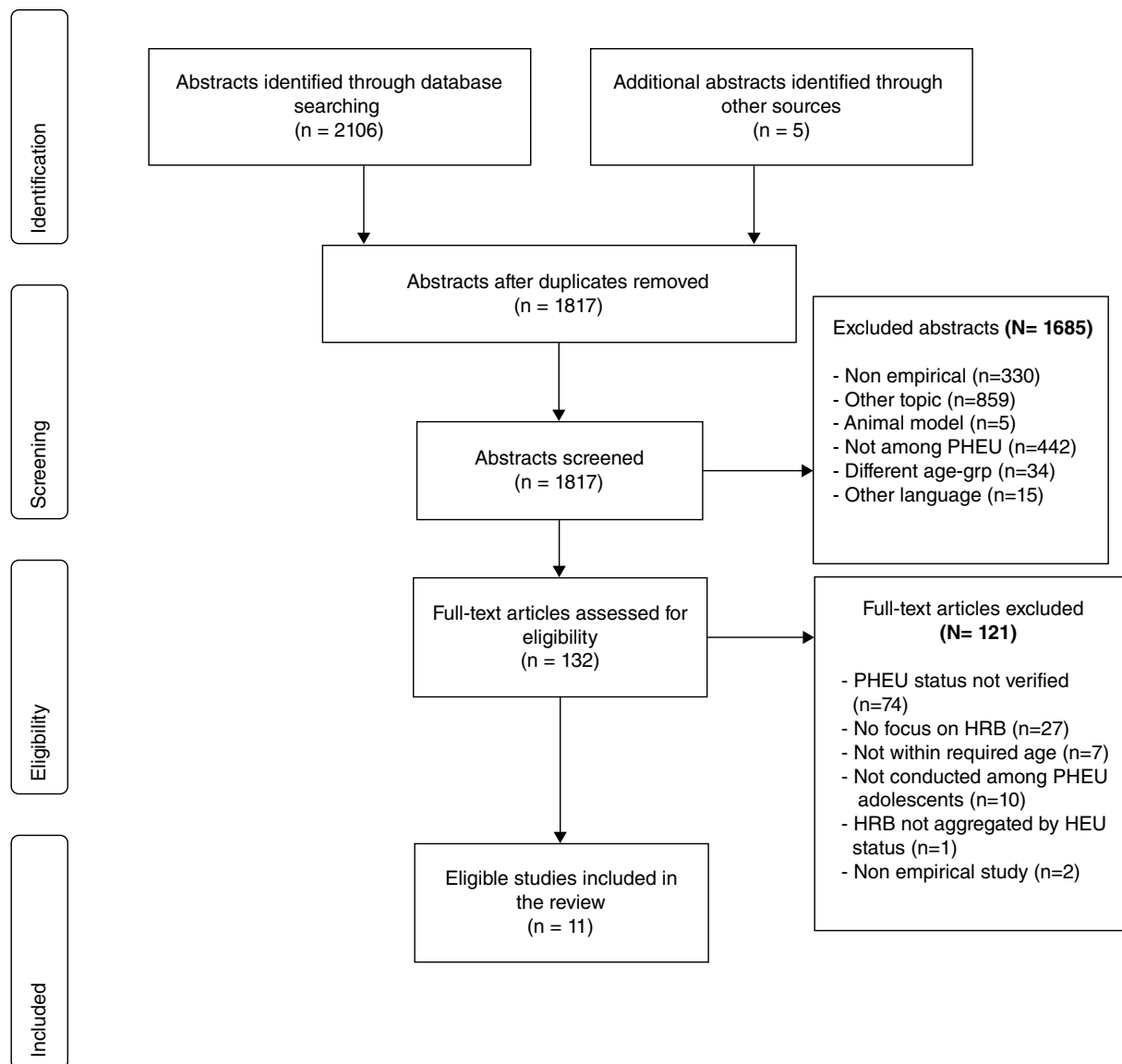
We narratively synthesized the findings from all the eligible studies in this review. We report the various forms of HRB and furthermore, specific details in terms of percentages (prevalence), means, frequencies and dates that were used to summarize the findings and to draw interpretations of the data. We utilized a Socio-Ecological model<sup>32</sup> to scrutinize the underlying risk factors for HRB. This model posits that there are 5 levels of interaction which determine human behavior. These are: intrapersonal factors that comprise personal history and biological factors; interpersonal factors which involves support systems like family, and friendships, and formal or informal social networks; institutional factors such as social institutions with organizational characteristics; community factors like relationships among informal networks, organization, and institutions; and

public policy factors which entails local, state and national laws or policies.

We also assessed the methodological quality of eligible studies using the [Newcastle-Ottawa Quality Assessment Scale](#)<sup>33</sup>. This tool is developed to assess the quality of non-randomized studies and utilizes a star rating system for which a study is judged based on three broad areas: the selection of study groups; the comparability of these groups; and the ascertainment of exposure or outcome of interest<sup>33</sup>. We considered a study to be of satisfactory methodological quality if six or more stars were scored out of a maximum of eight.

## Results

We identified 11 eligible studies from the 2,111 retrieved citations.



**Figure 1.** PRISMA flow diagram illustrating the screening process for all the manuscripts obtained during the literature review process.

These studies were conducted between 2003 and 2010 (original recruitment), and they all took place in the United States of America (USA). All the 11 studies were from 2 longitudinal studies with the majority (82%) from Child and Adolescent Self-Awareness and Health Study (CASA) and the rest from the Adolescent Master Protocol (AMP).

CASA is a multi-centre longitudinal study of perinatally HIV infected (PHIV) infected and PHEU adolescents designed to examine differences in mental health and behavioral health outcomes. Recruitment was conducted between 2003 and 2008 for adolescents aged 9 – 16 years from 4 primary and tertiary healthcare centres in New York. The first follow-up was conducted 18 months after the baseline and, when additional funding was found, re-recruitment from the original cohort was done, and 3 more follow-ups (CASA-2) conducted each a year apart. The first phase of this second follow-up (CASA-2) was conducted 3 years after the first follow-up<sup>23,24</sup>.

AMP is an ongoing cohort study comprising PHIV infected and PHEU children and adolescents (aged 7–15 years at inception) recruited from 15 medical centres (mainly based at academic medical centres in urban settings) across USA and Puerto Rico<sup>19</sup>.

The sample size of the PHEU adolescents among these studies included in our review ranged from 47 to 157. More details on study characteristics are presented in [Table 1](#).

### Risky sexual behavior

Sexual risk behavior of PHEU adolescents was documented in 7 of the 11 eligible studies (see [Table 1](#)). The specific forms of sexual risk behavior documented were early sexual debut<sup>19,27,31</sup>, lifetime unprotected sex<sup>24,28,30</sup>, recent (past 3 months) unprotected sex<sup>26,31</sup>, unprotected first time sex<sup>26</sup>, and multiple sexual partnerships<sup>28</sup>.

In one study, the sexual debut of PHEU adolescents was 12 years, and did not statistically differ from that of PHIV peers<sup>19</sup>. However, another study found a significantly higher age (13.4 years) of sexual debut among PHEU than that of PHIV adolescents (11.9 years)<sup>27</sup>. Although Benson and colleagues did not report the age of sexual onset, they noted that substance use and behavioral disorders were associated with earlier onset of sexual behavior among PHEU adolescents<sup>31</sup>.

Overall, prevalence of lifetime unprotected sex increased with time among PHEU adolescents and no significant differences were found across HIV groups (i.e. PHEU vs PHIV). For instance, in the CASA cohort, occurrence of lifetime unprotected sex increased from 33% at baseline (participant mean age of 11.9 years) to 50% after 18 months (first follow-up), and to 62.5% during the second follow-up period when participants were 16.7 years old on average<sup>24</sup>. However, during the second follow-up, PHEU adolescents reported significantly higher occurrence of lifetime unprotected sex than their PHIV peers (62.5% compared to 48.8%)<sup>24</sup>. Results from a different cohort study of PHEU adolescents (AMP) reported a 50% lifetime prevalence of unprotected sex (vaginal or anal) among the

sexually active PHEU adolescents (compared to 65% among PHIV) with a mean age of 12.7 years<sup>19</sup>.

Unlike lifetime unprotected sex, one study from CASA cohort that reported the prevalence of recent (past 3 months) unprotected sex (both anal and vaginal sex) of PHEU at second and fourth follow-up periods found a reduction from 43.1% at follow-up 2 to 29.2% at follow-up 4<sup>31</sup>. Although the trend of recent unprotected sex was different for the PHIV group (a rise from 22.7% to 31.5%), the authors did not find any statistical differences in prevalence of most recent unprotected sex by HIV group<sup>31</sup>. A more robust measure of recent unprotected vaginal sex (combining both non-use and partial condom use) during the second follow-up period of CASA cohort found a burden of 37% (compared to 23% if they only asked about non-use) among PHEU but didn't find a statistically significant differences across HIV groups<sup>26</sup>.

Multiple sexual partnership (having 2 or more sexual partners) was reported among 58.8% of sexually active PHEU adolescents and did not statistically differ from the occurrence among PHIV peers<sup>28</sup>.

### Alcohol, tobacco and other drug use behavior

Alcohol, tobacco and other drug (ATOD) use was documented among 9 of the 11 eligible studies (see [Table 1](#)). ATOD use was reported in the form of substance use disorder or substance abuse<sup>29,31</sup>, lifetime use of alcohol or marijuana or cigarettes<sup>19,24,25,28,30</sup>, use of marijuana or other substance use within the past year<sup>22,23</sup> and recent (past 3 months) substance use<sup>19</sup>.

There was an increasing trend in the burden of substance use disorder over time among PHEU, for instance an increase from 10% to 18% between second and fourth follow-up of the CASA cohort<sup>31</sup>. In this cohort, PHIV adolescents had a significantly higher burden of substance use disorder than PHEU (19% vs 10%) at second follow-up but there were no statistically significant differences found at fourth follow-up<sup>31</sup>.

Lifetime use of alcohol and marijuana was high, and increased steadily over time among PHEU. In the CASA cohort for example alcohol use increased from 15.5% at baseline (participants' mean age was 11.9 years)<sup>24,28,30</sup> to 25.6% at first follow-up (18 months later), and thereafter almost doubled (48.9%) at the second follow-up period when participants were 16.7 years on average<sup>24</sup>. Although lesser prevalent than alcohol use, marijuana use of PHEU adolescents increased by almost four times from 7.8% at the baseline to 29.6% during the second follow-up period<sup>24</sup>. Overall, there were no significant differences by HIV group (i.e. PHEU and PHIV). Results from another cohort (AMP); whose participants' mean age (12.3 years) was slightly higher than the baseline mean age of CASA participants, reported higher prevalence of lifetime use of alcohol (42%) and marijuana (19%) among PHEU adolescents<sup>25</sup> although we did not ascertain if there was a significant difference in prevalence of these two forms of behavior between the cohorts of the two studies.



Tobacco use behavior was reported by three studies that all documented lifetime cigarette use. Two of these originated from the baseline data of the CASAH cohort study, and reported the occurrence of this behavior as ranging between 6% and 7% among PHEU adolescent whose mean age was 11.9 years<sup>28,30</sup>. However, the results from the AMP cohort study reported a higher prevalence of 16% lifetime cigarette use among the PHEU adolescents who were 12.3 years on average<sup>25</sup>.

More recent use (past 3 months or past year) of alcohol or marijuana or cigarettes was much lower than lifetime substance use behavior among PHEU from both cohort studies. There were however general increasing trends in more recent use over time, but without statistically significant differences, across HIV groups.

The occurrence of substance use (excluding nicotine) within the past year was 6.9% at baseline, 4.6% at first follow-up and 10.1% at second follow-up among PHEU adolescents from the CASAH cohort<sup>23</sup>. A similar increasing trend in marijuana use by PHEU adolescents within the past year from 8.2% at baseline to 24.8% at second follow-up period of CASAH was reported<sup>22</sup>.

### Co-occurrence of HRB

Only one study from the AMP cohort explored the co-occurrence of HRB among PHEU adolescents<sup>19</sup>. In this study sexual, substance use and mental health behavioral risk factors were utilized to classify PHEU adolescents into behavioral categories corresponding to their engagement in 0, 1, 2 and all the 3 behavioral risk factors. The findings were that 11% of PHEU adolescents (16% for PHIV) reported engagement in 2

or more behavioral risk factors and there were no significant differences between HIV groups<sup>19</sup>.

### Risk factors

All reported risk factors underlying sexual risk behavior and alcohol, tobacco and other drug use (ATOD) were from an intrapersonal and interpersonal level (See Table 2). Some of the risk factors were cross cutting among different forms of HRB. From an intrapersonal risk factor level, underlying poor emotional and conduct behavior of PHEU adolescents (for marijuana use, alcohol use and sexual risk behavior); having early age of onset or being an older PHEU (marijuana use, multiple substance use, sexual risk behavior and co-occurrence of substance use and sexual risk behavior); and HIV status (multiple substance use and sexual risk behavior) were shared risk factors. From an interpersonal risk factor level, caregiver conditions, like substance use by caregivers or close family (marijuana and alcohol use) and mental illness of caregivers (alcohol use, substance use and sexual risk behavior) were cross cutting. There were also various behavior specific risk factors especially for sexual risk behavior and these are summarized in Table 2.

All the eligible studies were of satisfactory methodological rigor based on the New Castle-Ottawa Quality Assessment Scale<sup>33</sup>. All these studies received a star ranking for each field/criteria with exception of one item under the aspect of outcome assessment since HRB is majorly self-reported.

### Discussion

Findings from this review reveal a dearth of research on HRB of PHEU adolescents and this can have multifaceted

**Table 2. A summary of risk factors for HRB among PHEU adolescents.**

Adolescent HRB	Intrapersonal level	Interpersonal level
Marijuana	-Severity of emotional and conduct problems <sup>22,25</sup> -Earlier onset of marijuana use <sup>22</sup>	-Substance use by caregivers or close family members <sup>25</sup>
Alcohol	-Severity of emotional and conduct problems <sup>25</sup>	-Substance use by caregivers or close family members <sup>25</sup> -Mental illness of caregiver <sup>25</sup>
Substance use (combined)	-Older adolescent age <sup>23,28</sup> -Experiencing negative life events <sup>23</sup> -HIV status (being PHEU) <sup>23,31</sup>	Mental illness of caregiver <sup>30</sup>
Sexual risk behavior	-HIV status (earlier onset of sexual debut in PHIV compared to PHEU <sup>27,31</sup> , PHIV were less likely to report unprotected sex at follow-up 2 <sup>24</sup> ) -Gender (especially being male) <sup>26</sup> -Older adolescent age <sup>24,28</sup> -Having behavioral disorders <sup>31</sup> -Substance use (alcohol, marijuana, cigarettes) <sup>24,28,31</sup> -Race (being black) <sup>24</sup>	-Mental illness of caregiver <sup>30</sup> -Having a caretakers who do not promote youth autonomy <sup>28</sup> -Norms and beliefs (that peers engage in risky sexual practices, norms endorsing risky behavior) <sup>28</sup>
Co-occurrence of substance use, sexual risk behavior and mental health problems	-Older adolescent age <sup>19</sup>	-Type of caregiver (biological mother) <sup>19</sup>

**All reported risk factors were statistically significant ( $p \leq .05$ )**

implications. First, the studies emanate from one geographical context (USA), and from only two cohort studies. This potentially limits generalizability of the current evidence on HRB of PHEU to other geographic settings like sub-Saharan Africa where socio-cultural and healthcare structures are different from those in the USA. Second, the studies only document sexual risk and ATOD use behavior which leaves an evidence gap on the occurrence and underlying risk factors for other forms of HRB like violence and injury related behavior, gambling, and dietary behavior of PHEU adolescents. Nonetheless, the longitudinal design and the between group comparison (PHEU vs PHIV) of HRB outcomes in the eligible studies provides important insights on the temporal trends and group specific needs both of which are vital for public health programs.

We found that overall, the reported occurrence of risky sexual behavior such as unprotected sex among the sexually active PHEU (baseline findings) was similar to the estimated national prevalence (37–39.8%) among the general adolescent population in the USA during the period between 2003 and 2011<sup>34</sup>. However, it is important to note that results from this review indicate that lifetime occurrence of unprotected sex among sexually active PHEU adolescents increased rapidly during the mid-adolescence period (13–17 years) although the occurrence of more recent (past 3 months) unprotected sex reduced over follow-up period. Since early sexual debut (12–13 years) was also reported among the PHEU adolescents, it is plausible that their first sexual encounters are often riskier especially when initiated at an earlier age compared to older age. This may explain the varying trends between lifetime and recent condom use behavior. Indeed, similar to this explanation, other findings from a general population in the USA found that adolescents who reported having had sex by 14 years or less were less likely to have used a contraceptive method at first sex as compared to those that initiated sex later on<sup>35</sup>. However, the estimated age of first sexual debut in the USA ranges between 17.8–18.1 years which is much higher than that reported for sexually active PHEU adolescents in our review<sup>35</sup>.

Findings on ATOD use of PHEU showed that although their substance use is not as high as that reported in the USA general adolescent population<sup>34,36</sup>, their trends of both lifetime and recent substance use especially alcohol and marijuana steeply raise and are compounded by an increasing burden of substance use disorder<sup>29,30</sup> across the adolescent period. Considering that more recent substance use is much less than lifetime substance use, we suggest that substance use may be recreational or irregular for many of the PHEU adolescents. However, amongst the substance users there is a minority with heightened vulnerability for problem substance use which is indicated by the 10–18% prevalence of substance use disorder among older PHEU adolescents. This finding highlights an urgent need for substance use intervention among PHEU adolescents and the need to identify (screen for) those at greater risk for substance use disorder so as to provide for more tailored intervention approaches.

Our findings also indicate that HRB clustering is a common phenomenon among PHEU as shown by the findings on

co-occurrence of sexual risk and substance use among 11% of PHEU adolescents in one of the studies<sup>19</sup>. This noted, only one of the 11 eligible studies investigated clustering of HRB which further highlights an increasingly documented problem of isolated analysis of HRB as opposed to use of more comprehensive approaches such as cluster analysis techniques<sup>37</sup>.

The findings from the risk factors for sexual risk behavior and substance use of PHEU adolescents have various implications. First, there was a cross-cutting effect of certain inter- and intra-personal risk factors for both forms of HRB. This is suggestive of potential co-occurrence of HRB and further highlights the need for ecological (i.e. multi-system) and comprehensive analytical approaches in the HRB research. Second, being PHEU compounded by mental and behavioral problems was predictive of certain forms of HRB. This is important because in most settings PHEU children and adolescents are not often followed up and thus miss out on vital HIV related care and services (like counseling, routine screening and mental healthcare) because health systems tend to only focus on their infected siblings and caregivers<sup>19</sup>. This means that there is a missed opportunity (or a window of opportunity) for improving health outcomes of PHEU adolescents within the HIV service delivery. Third, we found that caregiver factors (like mental health and substance use, type of caretaker, parenting behavior) play an important cross-cutting role in predisposing PHEU to HRB which may indicate a need for family-based behavioral interventions in addressing HRB of adolescents. Fourth, some of the risk factors were behavior specific or intra-personal (e.g. gender and race) which highlights the need for tailored approaches in addressing HRB of PHEU adolescents.

### Study strengths and weaknesses

The strengths of this review stem from the rigorous systematic approach we utilized to generate evidence on HRB and its underlying risk factors in an emerging adolescent sub-population, PHEU, whose longer-term health outcomes are not well understood. We also appraised the quality of the eligible studies which we found satisfactory. Nonetheless, the results from this review are limited by their origin from one geographical setting (USA) and that multiple studies are derived from same cohort studies. Although generalizability of the current findings is challenging, important findings from a temporal and within group comparison perspective are discussed thereby providing more explicit insight on HRB of PHEU adolescents.

### Conclusion

Overall, research on HRB of PHEU is scanty, originates from a single geographic context and reports few forms of HRB majorly in isolation. A substantial evidence gap on HRB of PHEU in high HIV epidemic settings (such those in SSA) where the PHEU adolescent sub-population is steadily growing. The current evidence reveals that both substance use (especially alcohol and marijuana) and sexual risk behavior (mainly early sexual debut and inconsistent condom use) are highly prevalent among PHEU and their occurrence heightens especially during mid-adolescence. These forms of HRB tend to co-occur among a minority, and many of their underlying inter- and intra-personal risk factors are cross-cutting. There is need for similar research in



settings like SSA, and more comprehensive assessment of behavioral outcomes (i.e. more forms and co-occurrence of HRB). The findings also accentuate the need for monitoring health outcomes of PHEU children and adolescents; who in most of the circumstances miss out on opportunities from healthcare systems that prioritize only the immediate needs of their HIV infected siblings and caregivers.

### Data availability

All data underlying the results are available as part of the article and no additional source data are required

### Grant information

This work was supported by the funding from the Initiative to Develop African Research Leaders (IDeAL) Wellcome Trust

award [107769/Z/15/Z] to DS as a PhD fellowship and the Medical Research Council [MR/M025454/1] to AA. The MRC award to AA is jointly funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under MRC/DFID Concordant agreement and is also part of the EDCTP2 program supported by the European Union. The funding bodies do not have any role in the design of this study, collection, analysis, interpretation and writing of this manuscript.

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

### Acknowledgements

The authors would like to thank the Director of Kenya Medical Research Institute for granting permission to publish this work.

### Supplementary materials

Supplementary File 1: PRISMA checklist

[Click here to access the data](#)

### References

- Rivers SE, Reyna VF, Mills B: **Risk Taking Under the Influence: A Fuzzy-Trace Theory of Emotion in Adolescence.** *Dev Rev.* 2008; **28**(1): 107–144.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Steinberg L: **A Social Neuroscience Perspective on Adolescent Risk-Taking.** *Dev Rev.* 2008; **28**(1): 78–106.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Shrier LA, Harris SK, Sternberg M, *et al.*: **Associations of depression, self-esteem, and substance use with sexual risk among adolescents.** *Prev Med.* 2001; **33**(3): 179–189.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Brener ND, Billy JO, Grady WR: **Assessment of factors affecting the validity of self-reported health-risk behavior among adolescents: evidence from the scientific literature.** *J Adolesc Health.* 2003; **33**(6): 436–457.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Foster G, Williamson J: **A review of current literature on the impact of HIV/AIDS on children in sub-Saharan Africa.** *AIDS.* 2000; **14** Suppl 3: S275–S284.  
[PubMed Abstract](#)
- Thurman TR, Brown L, Richter L, *et al.*: **Sexual risk behavior among South African adolescents: is orphan status a factor?** *AIDS Behav.* 2006; **10**(6): 627–635.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Birdthistle IJ, Floyd S, Machingura A, *et al.*: **From affected to infected? Orphanhood and HIV risk among female adolescents in urban Zimbabwe.** *AIDS.* 2008; **22**(6): 759–766.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Tu X, Lv Y, Li X, *et al.*: **School performance and school behaviour of children affected by acquired immune deficiency syndrome (AIDS) in China.** *Vulnerable Child Youth Stud.* 2009; **4**(3): 199–209.  
[Publisher Full Text](#)
- DiClemente RJ, Hansen WB, Ponton LE: **Handbook of adolescent health risk behavior.** Springer Science & Business Media; 2013.  
[Publisher Full Text](#)
- Centres for Disease Control and prevention (CDC): **Adolescent and School Health.** Accessed 15 Aug 2018.  
[Reference Source](#)
- Currie C, Nic Gabhainn S, Godeau E, *et al.*: **The Health Behaviour in School-aged Children: WHO Collaborative Cross-National (HBSC) study: origins, concept, history and development 1982-2008.** *Int J Public Health.* 2009; **54** Suppl 2: 131–139.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Williams PL, Leister E, Chernoff M, *et al.*: **Substance use and its association with psychiatric symptoms in perinatally HIV-infected and HIV-affected adolescents.** *AIDS Behav.* 2010; **14**(5): 1072–1082.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Sherr L, Cluver LD, Toska E, *et al.*: **Differing psychological vulnerabilities among behaviourally and perinatally HIV infected adolescents in South Africa - implications for targeted health service provision.** *AIDS Care.* 2018; **30**(sup2): 92–101.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Stringer EM, Chi BH, Chintu N, *et al.*: **Monitoring effectiveness of programmes to prevent mother-to-child HIV transmission in lower-income countries.** *Bull World Health Organ.* 2008; **86**(1): 57–62.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Afran L, Garcia Knight M, Nduati E, *et al.*: **HIV-exposed uninfected children: a growing population with a vulnerable immune system?** *Clin Exp Immunol.* 2014; **176**(1): 11–22.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Filteau S: **The HIV-exposed, uninfected African child.** *Trop Med Int Health.* 2009; **14**(3): 276–287.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Sherr L, Cluver LD, Betancourt TS, *et al.*: **Evidence of impact: health, psychological and social effects of adult HIV on children.** *AIDS.* 2014; **28** Suppl 3: S251–S259.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- McNally LM, Hadingham J, Archary D, *et al.*: **HIV-exposed but uninfected children: Why are they vulnerable?** *Vulnerable Child Youth Stud.* 2006; **1**(2): 139–148.  
[Publisher Full Text](#)
- Mellins CA, Tassiopoulos K, Malee K, *et al.*: **Behavioral health risks in perinatally HIV-exposed youth: co-occurrence of sexual and drug use behavior, mental**

- health problems, and nonadherence to antiretroviral treatment. *AIDS Patient Care STDS*. 2011; **25**(7): 413–422.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
20. Moher D, Liberati A, Tetzlaff J, *et al.*: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009; **151**(4): 264–269, W64.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  21. World Health Organization (WHO): Health for the World's Adolescents. A second chance in the second decade. In: Geneva; 2014.  
[Reference Source](#)
  22. Elkington KS, Cruz JE, Warne P, *et al.*: Marijuana Use and Psychiatric Disorders in Perinatally HIV-Exposed Youth: Does HIV Matter? *J Pediatr Psychol*. 2016; **41**(3): 277–286.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  23. Mutumba M, Elkington KS, Bauermeister JA, *et al.*: Changes in Substance Use Symptoms Across Adolescence in Youth Perinatally Infected with HIV. *AIDS Behav*. 2017; **21**(4): 1117–1128.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  24. Elkington KS, Bauermeister JA, Santamaria EK, *et al.*: Substance use and the development of sexual risk behaviors in youth perinatally exposed to HIV. *J Pediatr Psychol*. 2015; **40**(4): 442–454.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  25. Alperen J, Brummel S, Tassiopoulos K, *et al.*: Prevalence of and risk factors for substance use among perinatally human immunodeficiency virus-infected and perinatally exposed but uninfected youth. *J Adolesc Health*. 2014; **54**(3): 341–349.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  26. Dolezal C, Warne P, Santamaria EK, *et al.*: Asking only “Did you use a condom?” underestimates the prevalence of unprotected sex among perinatally HIV infected and perinatally exposed but uninfected youth. *J Sex Res*. 2014; **51**(5): 599–604.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  27. Bauermeister JA, Elkington K, Brackis-Cott E, *et al.*: Sexual behavior and perceived peer norms: comparing perinatally HIV-infected and HIV-affected youth. *J Youth Adolesc*. 2009; **38**(8): 1110–1122.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  28. Elkington KS, Bauermeister JA, Brackis-Cott E, *et al.*: Substance use and sexual risk behaviors in perinatally human immunodeficiency virus-exposed youth: roles of caregivers, peers and HIV status. *J Adolesc Health*. 2009; **45**(2): 133–141.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  29. Mellins CA, Brackis-Cott E, Leu CS, *et al.*: Rates and types of psychiatric disorders in perinatally human immunodeficiency virus-infected youth and seroreverters. *J Child Psychol Psychiatry*. 2009; **50**(9): 1131–1138.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  30. Mellins CA, Elkington KS, Bauermeister JA, *et al.*: Sexual and drug use behavior in perinatally HIV-infected youth: mental health and family influences. *J Am Acad Child Adolesc Psychiatry*. 2009; **48**(8): 810–819.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  31. Benson S, Elkington KS, Leu CS, *et al.*: Association Between Psychiatric Disorders, Substance Use, and Sexual Risk Behaviors in Perinatally HIV-Exposed Youth. *J Assoc Nurses AIDS Care*. 2018; **29**(4): 538–549.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  32. McLeroy KR, Bibeau D, Steckler A, *et al.*: An ecological perspective on health promotion programs. *Health Educ Q*. 1988; **15**(4): 351–377.  
[PubMed Abstract](#) | [Publisher Full Text](#)
  33. Wells GA, Shea B, O'Connell D, *et al.*: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed 11 June 2017.  
[Reference Source](#)
  34. Eaton DK, Kann L, Kinchen S, *et al.*: Youth risk behavior surveillance - United States, 2011. *MMWR Surveill Summ*. 2012; **61**(4): 1–162.  
[PubMed Abstract](#)
  35. Finer LB, Philbin JM: Trends in ages at key reproductive transitions in the United States, 1951-2010. *Womens Health Issues*. 2014; **24**(3): e271–e279.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
  36. Patrick ME, O'Malley PM: The epidemiology of substance use among adolescents in the United States. In: *The Oxford Handbook of Adolescent Substance Abuse*. edn. 2016.  
[Publisher Full Text](#)
  37. Lanza ST, Cooper BR: Latent class analysis for developmental research. *Child Dev Perspect*. 2016; **10**(1): 59–64.  
[Publisher Full Text](#)