SYSTEMATIC REVIEW

Health risk behavior among perinatally HIV exposed uninfected adolescents: A systematic review [version 1; peer review: 2 approved with reservations]

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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

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Introduction
A high propensity for risk taking among adolescents is extensively documented\cite{1,2}. In the past, most of the research on health risk behavior (HRB) among adolescents focused on the general population\cite{3,4}, however, emerging evidence indicates that HRB such as aggressive behavior, multiple sexual partnerships, and early sexual debut, are common among HIV affected adolescents\cite{5,6}. 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\cite{7}. 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\cite{8,9}.

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\cite{10,11}. 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 subgroups. 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\cite{12}.

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\cite{13}. Although numerous health indicators such as morbidity, immunity and mortality are sub-optimal among PHEU adolescents, especially during early childhood\cite{14,15}, 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\cite{16,17}. 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\cite{18}. 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)\cite{19}. A comprehensive data base search in PubMed, PsychINFO and Applied Social Sciences Index & Abstracts was conducted for peer reviewed articles published from January 1980 up to 31st 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 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\cite{20,21}. 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\cite{22}; 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.

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Study recruitment period</th>
<th>Study characteristics</th>
<th>Participant characteristics</th>
<th>HRBs assessed</th>
<th>Study quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elkington22</td>
<td>USA</td>
<td>2003 – 2008</td>
<td>Baseline, follow-up 1 &amp; 2 of a cohort study (CASAH project)</td>
<td>134 PHEU and 206 PHIV adolescents Mean age 12.4 years and 16.7 at follow-up 2</td>
<td>Marijuana use</td>
<td>satisfactory</td>
</tr>
<tr>
<td>Mutumba23</td>
<td>USA</td>
<td>2003 – 2008</td>
<td>Baseline, follow-up 1 &amp; 2 of a cohort study (CASAH project)</td>
<td>129 PHEU and 196 PHIV adolescents Mean age for PHEU adolescents at baseline was 11.9 years and 16.7 at follow-up 2</td>
<td>Substance use (excluding nicotine)</td>
<td>satisfactory</td>
</tr>
<tr>
<td>Elkington24</td>
<td>USA</td>
<td>2003 – 2008</td>
<td>Baseline, follow-up 1 &amp; 2 of a cohort study (CASAH project)</td>
<td>129 PHEU and 195 PHIV adolescents Mean age for PHEU adolescents was 12.4 years at baseline and 16.7 at follow-up 2</td>
<td>Risky sexual behavior, Alcohol use, Marijuana use</td>
<td>satisfactory</td>
</tr>
<tr>
<td>Alperen25</td>
<td>USA</td>
<td>2007 – 2009</td>
<td>Baseline of a cohort study (AMP)</td>
<td>157 PHEU and 354 PHIV adolescents Mean age for PHEU adolescents was 12.3 years</td>
<td>Alcohol use, Cigarette use, Marijuana use</td>
<td>satisfactory</td>
</tr>
<tr>
<td>Doleza26</td>
<td>USA</td>
<td>2009</td>
<td>Follow-up 2 of a cohort study (CASAH project)</td>
<td>47 PHEU and 88 PHIV sexually active adolescents Mean age for PHEU sexually active adolescents was 18.7 years</td>
<td>Risky sexual behavior</td>
<td>satisfactory</td>
</tr>
<tr>
<td>Mellins19</td>
<td>USA</td>
<td>2007 – 2010</td>
<td>Baseline and follow-up1 of a cohort study (AMP)</td>
<td>111 PHEU and 238 PHIV adolescents Mean age for PHEU adolescents was 12.7 years</td>
<td>Risky sexual behavior, Alcohol use, Marijuana use</td>
<td>satisfactory</td>
</tr>
<tr>
<td>Bauermeister27</td>
<td>USA</td>
<td>2003 – 2007</td>
<td>Baseline of a cohort study (CASAH project)</td>
<td>127 PHEU and 195 PHIV adolescents Mean age for PHEU adolescents was 11.9 years</td>
<td>Risky sexual behavior</td>
<td>satisfactory</td>
</tr>
<tr>
<td>Elkington28</td>
<td>USA</td>
<td>2003 – 2008</td>
<td>Baseline of a cohort study (CASAH project)</td>
<td>134 PHEU and 206 PHIV adolescents Mean age for PHEU adolescents was 11.9 years</td>
<td>Risky sexual behavior, Alcohol use, Cigarette use, Marijuana use</td>
<td>satisfactory</td>
</tr>
<tr>
<td>Mellins29</td>
<td>USA</td>
<td>2003 – 2008</td>
<td>Baseline of a cohort study (CASAH project)</td>
<td>134 PHEU and 206 PHIV adolescents Mean age for PHEU adolescents was 11.9 years</td>
<td>Substance use (marijuana &amp; alcohol)</td>
<td>satisfactory</td>
</tr>
<tr>
<td>Mellins30</td>
<td>USA</td>
<td>2003 – 2008</td>
<td>Baseline of a cohort study (CASAH project)</td>
<td>127 PHEU and 193 PHIV adolescents Mean age for PHEU adolescents was 11.9 years</td>
<td>Risky sexual behavior, Alcohol use, Cigarette use, Marijuana use</td>
<td>satisfactory</td>
</tr>
<tr>
<td>Benson31</td>
<td>USA</td>
<td>2003–2008</td>
<td>Follow-up 2 and follow-up 4 of a cohort study (CASAH project)</td>
<td>105 PHEU and 178 PHIV adolescents Mean age 17 years at follow-up 2 and 19 years at follow-up 4</td>
<td>Substance use (marijuana, alcohol and other drugs)</td>
<td>satisfactory</td>
</tr>
</tbody>
</table>

PHEU- Perinataly 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 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. 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. 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 (CASAH) and the rest from the Adolescent Master Protocol (AMP).

CASAH 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 (CASAH-2) conducted each a year apart. The first phase of this second follow-up (CASAH-2) was conducted 3 years after the first follow-up.

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.

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, lifetime unprotected sex, recent (past 3 months) unprotected sex, unprotected first time sex, and multiple sexual partnerships.

In one study, the sexual debut of PHEU adolescents was 12 years, and did not statistically differ from that of PHIV peers. However, another study found a significantly higher age (13.4 years) of sexual debut among PHEU than that of PHIV adolescents (11.9 years). 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.

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 CASAH 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. 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%). 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.

Unlike lifetime unprotected sex, one study from CASAH 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. 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. A more robust measure of recent unprotected vaginal sex (combining both non-use and partial condom use) during the second follow-up period of CASAH 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.

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.

**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, lifetime use of alcohol or marijuana or cigarettes, and use of marijuana or other substance use within the past year and recent (past 3 months) substance use.

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 CASAH cohort. 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.

Lifetime use of alcohol and marijuana was high, and increased steadily over time among PHEU. In the CASAH cohort for example alcohol use increased from 15.5% at baseline (participants’ mean age was 11.9 years) 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. 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. Overall, there were no significant differences by HIV group (i.e. PHEU and PHIV). Results from another cohort (AMP); whose participants’ mean age was slightly higher than the baseline mean age of CASAH participants, reported higher prevalence of lifetime use of alcohol (42%) and marijuana (19%) among PHEU adolescents 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\textsuperscript{28,30}. 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\textsuperscript{28}.

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\textsuperscript{25}. 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\textsuperscript{22}.

Co-occurrence of HRB

Only one study from the AMP cohort explored the co-occurrence of HRB among PHEU adolescents\textsuperscript{23}. 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\textsuperscript{28}.

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\textsuperscript{33}. 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>
<thead>
<tr>
<th>Adolescent HRB</th>
<th>Intrapersonal level</th>
<th>Interpersonal level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>-Severity of emotional and conduct problems\textsuperscript{22,25}</td>
<td>-Earlier onset of marijuana use\textsuperscript{27}</td>
</tr>
<tr>
<td></td>
<td>-Earlier onset of marijuana use\textsuperscript{27}</td>
<td>-Substance use by caregivers or close family members\textsuperscript{25}</td>
</tr>
<tr>
<td>Alcohol</td>
<td>-Severity of emotional and conduct problems\textsuperscript{25}</td>
<td>-Substance use by caregivers or close family members\textsuperscript{25}</td>
</tr>
<tr>
<td></td>
<td>-Substance use by caregivers or close family members\textsuperscript{25}</td>
<td>-Mental illness of caregiver\textsuperscript{25}</td>
</tr>
<tr>
<td>Substance use (combined)</td>
<td>-Older adolescent age\textsuperscript{3,28}</td>
<td>-Experiencing negative life events\textsuperscript{25}</td>
</tr>
<tr>
<td></td>
<td>-Experiencing negative life events\textsuperscript{25}</td>
<td>-Substance status (being PHEU)\textsuperscript{23,31}</td>
</tr>
<tr>
<td></td>
<td>-Substance status (being PHEU)\textsuperscript{23,31}</td>
<td>Mental illness of caregiver\textsuperscript{20}</td>
</tr>
<tr>
<td>Sexual risk behavior</td>
<td>-HIV status (earlier onset of sexual debut in PHIV compared to PHEU)\textsuperscript{27,31}</td>
<td>-Having behavioral disorders\textsuperscript{31}</td>
</tr>
<tr>
<td></td>
<td>-Having behavioral disorders\textsuperscript{31}</td>
<td>-Substance use (alcohol, marijuana, cigarettes)\textsuperscript{24,28,31}</td>
</tr>
<tr>
<td></td>
<td>-Substance use (alcohol, marijuana, cigarettes)\textsuperscript{24,28,31}</td>
<td>-Race (being black)\textsuperscript{24}</td>
</tr>
<tr>
<td></td>
<td>-Race (being black)\textsuperscript{24}</td>
<td>-Type of caregiver (biological mother)\textsuperscript{19}</td>
</tr>
<tr>
<td>Co-occurrence of substance use, sexual risk behavior and mental health problems</td>
<td>-Older adolescent age\textsuperscript{19}</td>
<td>-Type of caregiver (biological mother)\textsuperscript{19}</td>
</tr>
</tbody>
</table>

All reported risk factors were statistically significant (p ≤ .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 [35]. 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 [36]. 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 [37].

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 [38,39], 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 [10,30] 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 heighten 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 [39]. 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 [39].

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 [39]. 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
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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Supplementary materials
Supplementary File 1: PRISMA checklist
Click here to access the data

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Introduction
This paper seeks to review health risk behavior (HRB) among perinatally HIV exposed uninfected adolescents as this sub-population is growing given the treatment success attributed to PMTCT services. The introduction cites work that is informative and appropriate. Paragraph 3 uses an abbreviation that is undefined "EF". Given that PHEU adolescents are not actively monitored given their HRB profile is a compelling case for a public health intervention. The aims of the systematic review are clearly stated, though it is unclear what is meant by "document the burden (my italics) of HRB" in PHEU. It would be useful to clarify why HRB among PHEU's are being studied globally given that HIV prevalence rates among adolescents are largest in sub-Saharan Africa.

Methods
Restriction to three databases is not explained. At a minimum, one would expect to see EMBASE and/or CINAHL databases included as they reflect major medical and allied health-related databases. Bias is introduced into the selection process by using only English-language journals. A period of 38 years is chosen as a review period and while this seems appropriate (1980-2018), it may be useful to indicate what motivated this decision. The data extraction shows all of the data to come from the USA and is essentially from two large studies. The first aim was specifically to examine HRB among PHEU adolescents globally! This is clearly no longer the case and the study title is no longer representative of this first aim! The PRISMA search strategy should indicate how many records were extracted from each database searched.

Statistical Analysis
There is no statistical analysis to consider. Instead, the focus on the Socio-Ecological model suggests that the sub-heading be changed.
Results
Given that the review is of two studies, both based in the USA, it would be best if the review simply looked at what these two studies found in relation to HRB instead of treating them as separate studies. Table 1 could be more informative by indicating the outcomes of each study in relation to the HRB. I'm not sure that the use of the Socio-Ecological model adds anything of significance as some of the associations linked to specific HRB is imputed and doesn't always make sense. I don't believe it has much utility in this review.

Discussion
The most important weakness of this review is that is restricted to one region and two studies! The discussion suggests that the findings are difficult to summarize because in many instances they are contradictory or no worse than that of the general population. It is neither compelling nor coherent. There are some clear findings and these should have been highlighted. For example, the statement “Third, we found that caregiver factors (like mental health and substance use,...for family-based behavioral interventions in addressing HRB for adolescents.” is a clear statement of finding. In other instances, there is contradictory evidence and these should be flagged as such. This will strengthen the discussion section.

Study strengths
There are multiple weaknesses, including bias to North America. The non-inclusion of key databases is another. The study findings are severely limited as a result and this is really a review of the CASAH longitudinal study and a more limited AMP cohort study!

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: mental health, HIV affected and infected adolescents and mental health, public mental health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 03 June 2019
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The review targets an important and reasonably narrow and very specific question.

1. Introduction
1.1. The introduction is well-written. The last sentence of paragraph two mentions some studies but refers to one study. Please revise.
1.2. There are several mentions of ‘burden’ in the paper and I was not sure if the authors are referring to Global Burden of Disease (GBD) because there is no reference to GBD.

2. Methods
2.1. Embase as the second most important medical bibliographic database is missing from the search resources with no evident justification. On the other hand, the choice of Applied Social Sciences Index & Abstracts is not clear as there is no evidence on its value for the current systematic review. In addition, searching the databases from regions with high prevalence and burden of HIV seems a reasonable idea.
2.2. There are three reported limitations for the studies: limit to peer-reviewed, and to published literature, and limitation to 1980 to 2018 while the authors have not provided the rationale for such limitations. Was the limitation because of lack or resources (time and human resources)? If so, please report these in limitation section of the paper. There is evidence that unpublished literature can contribute to and change the conclusion of the reviews, time limitation should be justified, and the value of peer-review [including mine] has not been proven.
2.3. Beside published literature bias, the authors also introduce language bias by excluding non-English literature and this should be added to the limitations of the study.
2.4. The authors have not done statistical analysis so the heading might not fit the purpose. Maybe synthesizing the finding or something like that could suit better.
2.5. The authors mentioned the tools for quality assessment of the studies in statistical analysis section while it seems to be better to mention it under quality assessment heading before the analysis heading.
2.6. Following PRISMA: unlike what has been said, the PRISMA items have not been followed. The last search date (day/month/year) and full search strategy for at least one source and preferably all sources should be reported. Without such details it is not possible to replicate the search and reproduce the same number of search results. Please also check the PRISMA items again to make sure nothing is missing.

3. Results
3.1. Study versus report: the authors list 11 reports but looking at their characteristics there seem to be two [probably multi-center or multi-report] studies: CASAH project and AMP. Salami reports of single study is very usual in biomedical/healthcare fields so I request the reviewers to check these 11 reports again to see if these are really 11 separate studies or only two studies with 11 reports. If the latter is true, then there should be only two rows in Table 1 citing all the reports. Re-organization of data in Table one could also help the authors to change the results in a better way.
referring only to two studies.

3.2. Exclusion of 15 studies for being in non-English language could raise a concern. Checking their eligibility could have been a good step before excluding them so that the readers would have known if there were other relevant studies in other languages.

3.3. The wording should change to differentiate ‘study’ from ‘report’ all over the paper. “All the 11 studies were from 2 longitudinal studies” could be “All the 11 reports/papers were from 2 longitudinal studies”.

3.4. Majority of results are written descriptively in the text. I wonder if it is possible to summarize some of the numerical data in table(s) instead or to visualize them in figure(s). Organization of the data in other formats may provide new insights.

**Discussion**

3.5. Having only two studies covering until 2010 makes me think why the research on the topic has stopped since 2010.

3.6. I also argue that limiting the language to English and not searching Embase (as a European medical database) could be another reason for geographical bias of findings towards USA.

3.7. As a good practice, the authors could have design a framework of an ‘ideal’ study that covers all they need so that the next study designers could benefit from it and design a study based on the needs of the policy and practice. Characteristics of such an ideal study could be presented in Box or Table to guide the next researchers.

I appreciate the efforts that team has put on this and I encourage them to make the requested minor revisions to the paper. I hope the findings of this team could guide the future research towards designing better studies to answer the practically and politically important questions.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

*Competing Interests*: No competing interests were disclosed.

*Reviewer Expertise*: Evidence Synthesis (including systematic reviews).

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.