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HIV Risks in Sexual Networks of Heterosexual Men in South Africa

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Abstract

Background: The interaction of HIV risks in sexual networks remains unclear in South Africa. We provide an overview of the dynamics of HIV risks in South African men through a systematic scoping review.

Methods and Analysis: Literature searches were conducted on seven online databases. Two reviewers independently screened articles against the inclusion criteria and performed a Kappa coefficient test to evaluate the degree of agreement on article selection. Thematic content analysis and a Mixed Method Appraisal Tool version 2018 were used to present the narrative account of the outcomes and to assess the risk of bias on included studies.

Results: Of the 1356 records identified, six studies reported on the dynamics of HIV infection in heterosexual men in sexual networks. All studies that were included were published between 2006 and 2016. The participants were aged 13 years and above and comprised of sero-discordant couples, HIV patients, and male and female in the general population. These studies were conducted in multiple diverse regions including South Africa, Senegal, Uganda, Malawi, Kenya, Tanzania, Botswana and Zambia. Evidence showed that age and sexual partnerships were most commonly identified attributes to either HIV infection and/or transmission risks in men. While other biological and behavioral data were reported, the results were not specific to men.

Discussion: The impact of age and sexual partnerships are poorly understood and the data available limit inferences to South African men. Limited empiric evidence of HIV risk among men impacts on the design, development and tailoring of HIV prevention interventions to alter the trajectory.

Keywords: heterosexual men, HIV transmission, sexual networks

1. Introduction

South Africa is home to the majority of HIV cases globally (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2014) and the incidence has remained unchanged over the past decades (Iwuji et al., 2018). Traditional epidemiological studies focusing primarily on individual-level risk suggest major risks in men. Majority of men remain unaware about their HIV status thus, have slow and poor linkage to care (Iwuji et al., 2018; Shisana et al., 2014; Takuva, Brown, Pillay, Delpech, & Puren, 2017), and have higher probability of progression to AIDS-defining illness compared to women (Huerga et al., 2018; Johnson, Rehle, Jooste, & Bekker, 2015). It has been argued that majority of men have low HIV risk perception, and this impacts their health-seeking behaviours to reduce risks of HIV acquisition and faster progression of HIV towards AIDS-defining illness (Shisana et al., 2014). The National Strategic Plan for 2017-2022 highlights the need to assess risk factors as drivers of HIV acquisition in order to develop multi-sectoral approaches for targeted intervention to reach at-risk populations (South African National AIDS Council [SANAC], 2017)

While many risks have been identified, the otherwise hidden epidemiological dynamics of transmission continues to resist easy characterization. Traditional methodologies are often difficult to ascertain due to the use of self-reported data and behavioural recall bias. Additional studies are required to understand men's interaction of

risks particularly within sexual networks as HIV propagates mainly through heterosexual sexual contact, and because men predominantly contribute to HIV infections in sexual partnerships (Higgins, Hoffman, & Dworkin, 2010). Combining phylogenetics, epidemiological data and serological data is essential to provide a plausible explanation for endemic transmission in sexual relationships (Chen et al., 2015) and can be used to inform real-time prevention interventions (Little et al., 2014).

Phylogenetic studies have long been used to understand the evolution of HIV and to study specific HIV transmission events but with limitations on individual transmission HIV events (Pillay & Fisher, 2007). Phylogenetic analysis has been used to understand HIV diversity and drug resistance (Bártolo et al., 2014), to understand seroconversion events (Eshleman et al., 2011), duration and concurrency of sexual partnerships in HIV transmission (Kim, Riolo, & Koopman, 2010) and to identify HIV transmissions amongst local communities and factors that may contribute to sustained transmission of the virus (Wilkinson, Engelbrecht, & de Oliveira, 2014). Understanding structural features of risks of HIV transmission, particularly in sexual networks is important as there exist minimal work focusing on characterizing these structures in South African heterosexual men.

In this review, we sought to synthesize pathways which may contribute to HIV transmission among South African men using the systematic scoping review methodology (O'Brien et al., 2016). We aimed to further map existing literature to refine future research agenda by establishing the progress of existing research towards understanding the interaction of risks to prevent HIV infection in South African men.

2. Methods

The current study is a systematic scoping review which was registered in the international prospective register of systematic reviews (PROSPERO). The registration number of the review is CRD42016039489 and is accessible via this link https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-016-0398-y (Ntombela, Mashamba-Thompson, Mtshali, Voce, & Kharsany, 2017).

2.1 Design

The purpose of the review is to highlight evidence linking the complex interaction(s) of risks of HIV infection in heterosexual South African men. The review was conducted as part of a large study, with aims to identify and characterize transmission networks of HIV in heterosexual men and to identify HIV risk factors associated with sexual networks in South Africa. We conducted this review to identify, describe and map literature with a focus on the dynamics of HIV infection in South African men and to assess the quality of the studies using a scoping review methodology. Scoping reviews are essential in comprehensive synthesis of evidence of a range of study designs (O'Brien et al., 2016), with aims to i) Assess the extent, range and nature of evidence on the literature on the topic, ii) to establish the need of conducting a systematic review, iii) to summarize and disseminate research findings and lastly iv) to identify gaps in literature on the topic. We used an amended version of a scoping review protocol described by Ntombela et al, (Ntombela et al., 2017). Briefly, we adopted a framework by Arksey, H., and O'Malley (Arksey & O'Malley, 2005). The framework involves (i) Identification of the research question, (ii) Identification of the relevant studies, (iii) Study selection (iv) Data charting and (v) Collating, summarizing and reporting the results. A quality appraisal as recommended by Levac et al, (Levac, Colquhoun, & O'Brien, 2010) was included.

2.2 Identifying the Research Question

The focus of our scoping review was to answer the question*, What is known from existing literature about the dynamics of HIV transmission among heterosexual South African men?* An amended PICOS (Population, Intervention, Comparison, Outcomes and Study setting) framework was used to determine the eligibility of the research question, as described in (Ntombela et al., 2017). To help answer our main question we asked the following questions, i) *What is the prevalence and incidence of HIV infection in heterosexual men of South Africa?* ii) *What relationships exist between social and sexual networks in HIV transmission* and iii) *what interaction exists between biological, behavioral and cultural factors of or risk in HIV sexual networks*.

2.3 Identifying Relevant Studies

We consulted with a university-affiliated librarian to draft search queries for electronic searches in seven online academic databases (PubMed, Web of Knowledge, Science Direct, EBSCOhost, Google Scholar, World Health Organization library database and UNAIDS database). The search terms were used, *HIV infection or acquisition or transmission in heterosexual men and; sex behaviors, or biological factors or cultural factors*. We limited the results by publication date (2006-2016) and language (English). Because scoping reviews allow for the inclusion of a wide range of study designs based on relevance to research questions and not the quality of study designs (Harichund & Moshabela, 2018), both qualitative and quantitative studies were included.

2.4 Study Selection

One reviewer conducted a literature search and exported all relevant results into Endnote X7 software, deleting all duplicates. Titles and abstracts were independently reviewed by two reviewers in parallel to determine eligibility for the full review. Kappa coefficient and McNemar test were used to evaluate the degree of agreement in article selection for data extraction. Any discrepancies were resolved by discussions between the reviewers. Each reviewer applied strict inclusion/exclusion. The inclusion criteria were studies that reported; i.) *biologically confirmed HIV infection as the outcome among out of school heterosexual men,* ii.) *belonging to a sexual network of any size;* iii.) *being in a current sexual partnership i.e. in the last year*. The exclusion criteria were studies that reported; HIV infection due to mother to child transmission of HIV, not biologically confirmed cases of HIV, men who have sex with men, bisexuals, gays, male sex workers, clients of sex workers, injection drug users, and transgender populations, and incarcerated men. We used the PRISMA-ScR chart to summarize the study selection procedure which captures the flow of citations reviewed in the course of this review.

2.5 Data Charting

We used a standardized data extraction sheet which was created on an Excel spreadsheet as detailed on the scoping protocol (Ntombela et al., 2017). The sheet included details on bibliography, the type of study design, the number of participants enrolled, study setting, type of intervention (s), and conclusions based on the primary and the secondary outcomes of the interventions.

2.6 Collating, Summarizing and Reporting the Results

We presented a narrative account of findings from the data extraction sheet through thematic content analysis. We collated various topics and themes that emerged from data extraction and synthesized and grouped them according to major themes and summarized. Evidence of whether the interaction(s) of interventions lead to HIV infection in South African men was compared to the results of heterosexual men from outside South Africa.

2.7 Quality Assessment

A tool for mixed methods obtained from Mixed Methods Appraisal Tool (MMAT) – Version 2018 (Hong, 2018) was utilized to assess the methological quality of studies included in the review. We utilized a scale to score the studies based on the following domains: How clear the research questions are, how confident researchers are in the assessment of the research question, how appropriate are the data sources collected, how suitable are the statistical analyses to address the research question, how confident are the assessments of exposure, if researcher bias is acknowledged, how appropriate are the sampling strategies utilized, the representativeness of the selected population, the confidence in measuring the outcome, and an accountable response rate. One reviewer, (D.K.), performed the quality assessment of all included studies. D.K calculated an overall percentage score for all included studies, with scores interpreted as; low quality (score ≤ 50%), average quality (score 51% to 75%), and high quality for scores 76% to 100%.

3. Results

3.1 Screening Results

We conducted electronic searches during July and August 2016. From our initial search, we identified 2028 potentially relevant records after title screening and exported them to the Endnote library X7. Of 2028, 672 were duplicates and were removed from the library. Five hundred and fifty-six (556) records were further removed during abstract screening leaving 800 records included in the screening of full text (Additional File 1). Full-text screening resulted in the exclusion of 771 articles (Figure 1). Finally, a total of 29 studies were identified to include studies only focusing on sexual networks or sexual partnerships. Twenty-three studies were ineligible for inclusion following secondary full article screening because they did not include confirmed cases of HIV sexual networks and / specific data to heterosexual men or no primary outcome of this study (Abrahams & Jewkes, 2012; Barta, Tennen, & Kiene, 2010; Beyeza-Kashesya et al., 2011; Brouwer et al., 2006; Chakrapani, Newman, Shunmugam, & Dubrow, 2010; Chen et al., 2015; De Santis, Gonzalez-Guarda, & Vasquez, 2012; Dhont et al., 2010; Dias, Marques, Gama, & Martins, 2014; Doherty, Schoenbach, & Adimora, 2009; Eaton et al., 2014; Eshleman et al., 2011; Floyd et al., 2008; Kibira, Nansubuga, Tumwesigye, Atuyambe, & Makumbi, 2014; Lin et al., 2012; Lingappa et al., 2009; Marti-Pastor et al., 2015; Patterson et al., 2012; Sgarbi et al., 2015; Simoni, Pantalone, Plummer, & Huang, 2007; Wenzel et al., 2012; Zhussupov, McNutt, Gilbert, Terlikbayeva, & El-Bassel, 2015). We identified six articles to include in our final analysis (Figure 1) which met our inclusion criteria.

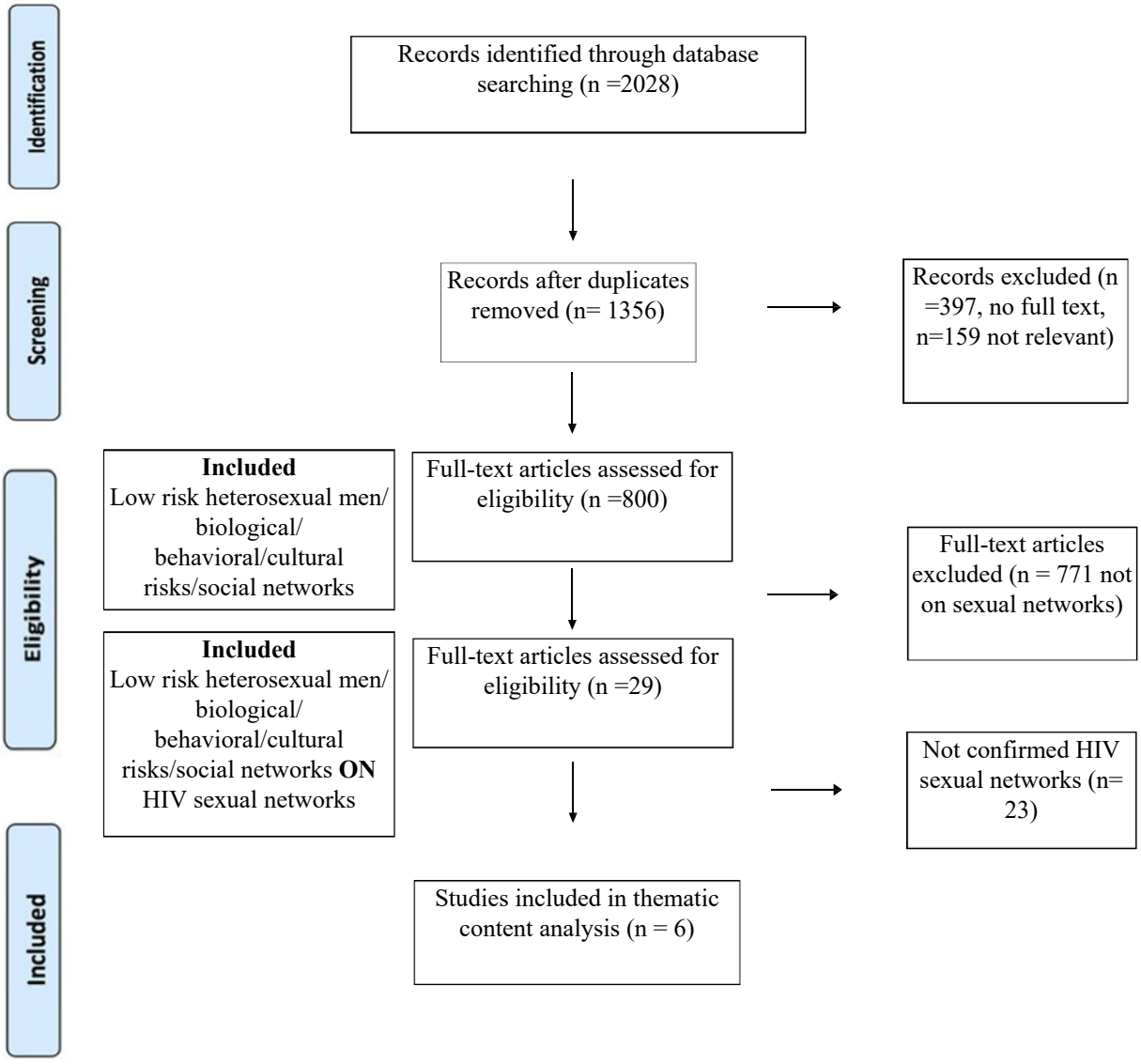

Figure 1. PRISMA-ScR chart for data extraction

The Kappa test showed that there is an 84.83% agreement versus 80.11% expected by chance which constitutes a substantial agreement (Kappa statistic = 0.24, p-value < 0.05). However, the McNemar's chi-square statistic found a statistically significant difference in the proportions of yes/no answers by the reviewers with p-value < 0.05. A third screener was invited to resolve the discrepancy between screeners results following full article screening.

3.2 Level of Bias for Included Studies

All six studies included in the review were assessed for quality (Additional File 2) using the Mixed Methods Appraisal Tool (MMAT) - Version 2018 (Hong, 2018). All six studies scored from 57 to 100%. One of the six studies scored the highest quality score of 100% (Zeh et al., 2016). Two of the included studies score 85.7% each (Hargreaves, Davey, Fearon, Hensen, & Krishnaratne, 2015; Helleringer, Kohler, Chimbiri, Chatonda, & Mkandawire, 2009). Another two included studies also scored 71.1% each (Campbell et al., 2011; Wilkinson et al., 2014), and one out of the six studies recorded a quality score of 57.1% (Jennes et al., 2012).

3.3 Characteristics of Included Studies

The summary of the characteristics of the included studies is presented in Table 1. The literature search had identified 29 studies that were reviewed. Six of these met the inclusion criteria and were included in this review.

Twenty-three studies were excluded because the HIV status of heterosexual men in the sexual networks or partnerships were not biologically confirmed. The six studies included are summarized in Table 1.

Table 1. Studies on the dynamics of HIV infection in sexual networks of heterosexual men

Author and year	Aims	Study setting	Study design	Population	Sample size	Heterosexual men (%)
Campbell, Mary S. 2011	To evaluate the genetic linkage between HIV-1 sequences from epidemiologically linked partnerships in the trial	Kenya, Tanzania, Uganda, Botswana, South Africa, Zambia	Prospective randomized placebo-controlled trial (Quantitative)	Sero-discordant heterosexual couples enrolled from 7 countries	3404 HIV-1 sero-discordant heterosexual couples	3413 males
Clement Zeh. 2016	To identify unique characteristics of recent versus established HIV infections and describe sexual transmission networks	Western Kenya	Cross-sectional survey (Quantitative)	2674 male and female from two communities	398 HIV seropositive persons	137 (34.4%)
Grabowski Mary K. 2014	To determine the extent to which continued HIV transmission in rural communities is driven by intra-community sexual networks versus viral introductions from outside of communities	Uganda	Cohort (Quantitative)	14594 individuals from 46 communities, 6406 males	1.786 HIV seropositive	Not specified
Stéphane Helleringer 2009	To describe the context and methods of the LNS;	Malawi	Cohort (Quantitative)	923 males and females in the samples villages	Not specified	422 males
Jennes Wim 2012	To unravel intra-couple HIV1 transmission in a cohort of HIV1 concordant positive couples from Dakar, Senegal.	Senegal	Cohort (Quantitative)	HIV patients	46 concordant positives	Not specified
Wilkinson, Eduan; 2014	To uncover transmission evens of HIV amongst the infected population of Cape Town.	South Africa	Descriptive of a cohort (Quantitative)	Hospital patients	Not specified	Not specified

Most studies included study populations of community individuals, followed by heterosexual couples and HIV patients. The design in five studies was phylogenetic analysis (Campbell et al., 2011; Grabowski et al., 2014;

Jennes et al., 2012; Wilkinson et al., 2014; Zeh et al., 2016) while one study used sexual contact tracing (Helleringer et al., 2009) as methods to identify sexual networks. The main objectives were structured around describing HIV transmission events for two studies (Jennes et al., 2012; Wilkinson et al., 2014), characterize recent versus long-term infection (Zeh et al., 2016), understand drivers and sources of HIV in different communities (Grabowski et al., 2014), describe methods used for sexual contact tracing (Helleringer et al., 2009) and to understand sero-converters and their partners (Campbell et al., 2011).

3.4 Summary of Findings

3.4.1 The Prevalence and Incidence of HIV in Heterosexual Men

Three studies reported on either prevalence of HIV infection and/ or the incidence rates in men. HIV prevalence of 4.7 % was reported in Malawi and 5% in Kenya (Helleringer et al., 2009; Zeh et al., 2016). Reported incidence rates were 1.9/100pyo in men from Uganda (Grabowski et al., 2014). In three studies, the design did not allow assessments of HIV prevalence or incidence (Campbell et al., 2011; Jennes et al., 2012; Wilkinson et al., 2014). *HIV prevalence and incidence remain consistently high in African men, however, limited data on the incidence and prevalence exist in sexual networks.*

3.4.2 Risk Factors for HIV Infection in Sexual Networks

The study identified two major themes associated with HIV infection in sexual networks of heterosexual men. The two main themes were age and type of sexual partnership as presented below.

3.4.3 Age

Identified studies presented on age to be associated with HIV infection in men at baseline partner analysis or in sexual networks. Baseline data from Uganda and Western Kenya reported HIV infection to increase with increasing age (Grabowski et al., 2014; Zeh et al., 2016), further Zeh et al. (Zeh et al., 2016) segregated data to show variations in recent versus long-term infection and showed that recent infection was highest in ages 20–24 (50%, 12) years and long-term infection was higher at 30-34 years (48%, n=102) (Zeh et al., 2016). Out of 79 HIV incident infections in heterosexual men from Uganda, the incidence of HIV infection was found to increase with increasing age and highest at 25–29 (20/79) years and 30–34 (22/79) years (Grabowski et al., 2014). In sexual networks, out of 49 HIV concordant married couples from Senegal, men in sexual networks raged from 39–52 years and were older than their wives (Jennes et al., 2012). Lastly, large age differences were observed in Cape Town, South Africa, with the median age of men in clusters being 37 years of age (Wilkinson et al., 2014). *While there exists ambiguity in age risk for HIV across different countries, we acknowledge that HIV incidence is highest in the younger males and prevalence is sustained in older males, however, future research should be directed towards identifying specific age gaps in sexual networks to be targeted for HIV prevention.*

3.4.4. Sexual Partnership

Five studies reported on varied responses relating to behavioral factors in HIV sexual networks (Campbell et al., 2011; Grabowski et al., 2014; Helleringer et al., 2009; Jennes et al., 2012; Wilkinson et al., 2014). Literature suggests that the type of sexual partnership is an important risk factor in HIV transmission in sexual networks (Campbell et al., 2011; Grabowski et al., 2014; Helleringer et al., 2009; Jennes et al., 2012). In heterosexual couples, majority (58%) of sero-conversions in males were reported to have a higher frequency of unlinked transmission to the sex partner enrolled with (Campbell et al., 2011); mean number of sexual partners was 2.6, 0.4 higher than that of women (Helleringer et al., 2009); In married couples, majority (82%) of husbands reported occasional sexual relationship as source of infection (Jennes et al., 2012) and husbands were found to be transmitting partners to their wives. Addition to this, one study (Grabowski et al., 2014) reported on intra and extra community sexual networks. In this study, they showed that of 79 incident male cases, 21% (CI: 17.7-22.8%) were infected by household partner, 21.5 % (CI: 12.2-32.9%) were infected by unknown partner, extra household-intra community and extra household-extra community accounted for 21.7 % (CI: 15.2-27.9%) and 16.1 % (CI: 7.8-22.3%) respectively. *HIV is frequently transmitted within sexual relationships with men being index partner, indicating that women are at risk of acquisition due to extramarital relationship status of husbands or multiple sexual partnerships.*

3.4.5 The Dynamics of HIV in Heterosexual Men of South Africa

Two studies presented data from South African men. Campbell et al. (Campbell et al., 2011) reported on 151 sero-conversions from African countries including data from South Africa and reported that the sero-converting partner was male in 58% of couples. They further reported that male sero-converters had a higher frequency of unlinked HIV transmissions and that, sex with a partner either than the HIV infected partner in which they enrolled

was reported more commonly by unlinked sero-converters. In the second study, they reported on large age differences in HIV clusters with a median age of 37 years for men and 30 years for women (Wilkinson et al., 2014). *Scarcity of data is available particularly assessing HIV transmission risks in sexual networks of heterosexual men in South Africa.*

4. Discussion

Our scoping review has identified the dynamics of HIV infection in heterosexual men in sexual networks in South Africa. Disproportionate HIV infections exist globally, this uneven distribution may be regional, national or local. Studies show the varying prevalence of HIV infection in heterosexual men is as high as 20% in some parts of Africa (Opio, Muyonga, & Mulumba, 2013). Again, South African studies also indicate similar patterns of disproportionate HIV prevalence (Jewkes et al., 2006; Wechsberg et al., 2014) and incidence rates (Baernighausen, Tanser, & Newell, 2009; Hargreaves et al., 2015; Pettifor et al., 2011) across the country. While high levels of HIV prevalence and incidence rates have been maintained without any signs of decline (Baernighausen et al., 2009; Hargreaves et al., 2015; Pettifor et al., 2011) in South Africa, the majority of available data has not linked infections to sexual networks and therefore the contribution of sexual networks and types of structures exacerbating HIV infections are not well understood.

Through this literature review, we found that evidence on the sexual network is controversial, there exist limited data characterizing sexual networks and factors associated with the transmission of HIV infections in heterosexual men. However, we can identify age and sexual partnership as having contributions to HIV infections in heterosexual men. HIV incidence was found to increase with increasing age and recent infection was highest at younger ages and long-term infections were common in older ages. These findings are consistent with many South African data which aims to understand the risk factors for HIV infection in men (Jewkes et al., 2006) and assessing sexual partnership and age pairing as a risk of HIV acquisition (Akullian et al., 2017), however, these are based on epidemiological data without the use of formal network designs. In sexual networks, the younger ages identified to be associated with HIV infection suggested that while low HIV prevalence is observed in young males, their risk to new HIV infections is similar to their female counterparts (Zeh et al., 2016).

Secondly, data on sexual partnership or type of sexual partnership is important to ascertain how HIV transmission networks emerge. From the current literature, we found that there exists high concurrency which needs to be understood. In married couples, HIV is frequently transmitted within married couples, with the males being index partner indicating women are at risk of acquisition due to extramarital relationship status of husbands or concurrency (Jennes et al., 2012). Further, husbands or males are found to have the highest number of reported sexual partners and may result in higher transmission probabilities and unlinked cases are the internal source of infection and have occasional sexual relationships as an external source of infection. Current epidemiological data indicate sexual partnerships are an important risk factor for HIV infection in South Africa (Akullian et al., 2017; Beauclair, Hens, & Delva, 2015; Kalichman et al., 2013), however at this point, it is not clear whether sequential or concurrent relationships pose similar or different risks to sexual partners. In this review, we report on sexual partnerships as an important risk factor which warrants further investigation.

The extent to which social networks contribute to sexual networks or if a certain relationship exists was not answered through this review. Also, there were no specific reports on any biological factors associated with HIV infection. Research understanding social networks is essential to identify clustering behaviors and/or risk factors within individuals of linked sexual networks. Social network analysis may play an important role in understanding group norms that exist within social networks and can be used to determine the elements of sexual behavior. A recent survey found that in males, 18–24 years of age, high peer pressure and never being tested for HIV were amongst other things that promoted multiple concurrent sexual partnerships (Mlambo, Peltzer, & Chirinda, 2016). Understanding complex interactions of HIV risk behavior in social networks is important in this regard.

Of the six studies included, two were cohort study designs and the designs were primarily to understand sexual networks or HIV transmission (Helleringer et al., 2009; Jennes et al., 2012). To our knowledge, these studies are the only few studies available which were found suitable in the design to understanding HIV transmission. Although the studies provide some factors which may be regarded as contributory factors, the emphasis was not in understanding male-specific factors and therefore little is explored. Of the four studies (Campbell et al., 2011; Grabowski et al., 2014; Wilkinson et al., 2014; Zeh et al., 2016), all of them were analysis of data from bigger studies whose study design was empowered by other research questions, not tailored primarily towards understanding sexual networks and others were secondary data analysis. The four studies utilized data of all HIV positive people from the bigger studies to answer their questions and the sample sizes were based on the primary questions of the bigger studies. For these reasons, there is no clear information in terms transferability of findings

to the bigger population and in terms of the quality of these studies in classifying and understanding the interaction of risks in men.

4.1 Implication for Research

Our study has shown limited evidence that links the complex interaction of risks of HIV infection in heterosexual men in South Africa. This indicates a need for research aiming to characterize the risks of transmission or infection in sexual networks. Studies need to identify and characterize the interactions of behavioral, biological and cultural risks in the HIV epidemic of heterosexual men.

5. Conclusion

Overall this scoping review highlighted age and sexual partnership as factors associated with HIV infection in sexual networks. However, limited research in South African men prevents us from making inferences on the risks of targeted prevention for South African heterosexual men. Though the scoping review provides an insight into the risks, the data is poorly understood and incompletely documented and not targeted to understanding men. To understand the transmission dynamics in South Africa, a hyper-endemic country, it is essential that research focuses on maximizing the coverage to uncover transmissions in local communities. While one study was conducted in South Africa, the prevalence in the province is low compared to many South African provinces and to the national prevalence. Secondly, data may result in incomplete network bias due to the exclusion of many sexually active individuals below the ages of 21, and potentially miss key components of the networks that are potentially essential towards the diffusion of HIV within the general population. Locally relevant data is required to understand the dynamics and this data should be coupled with the qualitative behavioral assessment to allow for more in-depth assessment of the risks and understanding underlying issues to such behaviors.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Material

All data generated or analyzed during this study will be included in the published systematic review article.

Funding

Not applicable.

Authors' Contributions

NN contributed to conceptualizing the study and designed the data collection methods with supervision from TPM-T. NN and AM independently selected published literature for review. DK contributed to the quality assessment of included studies. NN, AM and TPM-T contributed to the writing of the first draft of the manuscript. AK contributed to the scientific review of the manuscript draft. All authors contributed to the critical review of the manuscript and to the approval of the final manuscript.

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Competing Interests Statement

The authors declare that they have no competing interests.

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