**Title: Factors Influencing Smoking Cessation Among People Living with HIV In Low- And Middle-Income Countries: Theory-Guided Systematic Review and Meta-Analysis Protocol**

**Registration:** Registered with PROSPERO (Registration number: CRD42021234644)

**Authors:**

Thanh Hoang – Main author responsible for the study’s methodology and analysis.

[thanh.hoang@gu.se](mailto:thanh.hoang@gu.se)

School of Public Health and Community Medicine, University of Gothenburg, Sweden.

Van Nguyen – Second author responsible for reviewing and screening of eligible studies, and cross-checking data extraction and quality assessment.

[m.van1102@gmail.com](mailto:m.van1102@gmail.com)

Donna Shelley

Gloria Guevara Alvarez

Louise Adermark

**Amendments**

In case we need to amend this protocol, date of each amendment and description and rationale of the change will be given in this section.

**Support**

This systematic review is a paper of the author’s doctoral thesis, the doctoral position is funded by professorship grant of Professor Nawi Ng, School of Public Health and Community Medicine, University of Gothenburg, Sweden.

**INTRODUCTION**

The improved access to antiretroviral therapy (ART) has a remarkable impact on the reduction of morbidity and mortality in people living with HIV (PLWH). This treatment turns HIV transmission into a chronic condition rather than a fatal disease (Mills et al., 2011). Despite the introduction of ART, PLWH are still more vulnerable to illnesses such as cardiovascular and pulmonary disease, and cancer, compared to the general population (Petoumenos et al., 2011; Wistuba et al., 1998). A global systematic review has confirmed that tobacco smoking is more prevalent in PLWH compared to the general population (Johnston et al., 2021). Tobacco use poses a health risk to PLWH as smoking was found to be a contributor to poor ART response and adherence (O'Cleirigh et al., 2015; Shuter & Bernstein, 2008). Tobacco smoking is also likely to exacerbate conditions of PLWH as it increases the risk of HIV-related complications and greater mortality in these people (Ande et al., 2015; Feldman et al., 2006; Helleberg et al., 2015). Researchers also found a higher risk of AIDS-related deaths in smokers living with HIV (SLWH) compared to non-SLWH, and the average difference in life expectancy of these two groups was 12.3 years (Helleberg et al., 2013).

According to Global AIDS Update (2016) and a WHO global report (2018), prevalence of HIV transmission and tobacco smoking are remarkably higher in low-resource countries. A significantly high pooled prevalence of tobacco use among men living with HIV (27.1%) was estimated using Demographic and Health Survey data from 28 low- and middle-income countries (LMICs) where the burden of tobacco-related illness and death is greatest (Mdege et al., 2017; World Health Organization, 2020). Smoking cessation intervention tailored for PLWH is limited in LMICs where HIV burden related to tobacco use remains heavy. Even though a number of randomised controlled trials were carried out to examine the effectiveness of tobacco cessation interventions for PLWH, limited research has been conducted on this particular group in LMICs. Systematic reviews and meta-analyses show no evidence on long-term effectiveness, and little is known about associated factors of smoking cessation and multisession interventions for PLWH in LMICs (Mann-Jackson et al., 2019; Moscou-Jackson et al., 2014; Pool et al., 2016; Uthman et al., 2019).

Comprehensive understanding about factors influencing smoking and cessation behaviour of PLWH is vital to determine and formulate appropriate approaches and strategies for cessation interventions targeting this population. This plays a significant role in successful implementation of tobacco use treatment in order to achieve health behavioural change and to improve quality of life of PLWH. Thus, a synthesis of scientific evidence regarding factors associated with tobacco smoking and cessation among SLWH in LMICs is crucial for future tobacco cessation research and interventions for PLWH. The use of theoretical frameworks and models with respect to behavioural change is highly beneficial in evidence syntheses (Buhi & Goodson, 2007; Godfrey et al., 2010). In this review, the Integrative Model of Behavioural Prediction (IMBP) adopted from Fishbein (2000) will be employed as a guide to systematically identify associated factors of smoking and cessation behaviour among PLWH in LMICs.

**Objectives**

The aim of this systematic review is to appraise and synthesise evidence of factors influencing smoking and cessation behaviour among people living with HIV (PLWH) in low- and middle- income countries (LMICs) and to identify the statistical relationship between smoking and cessation behaviour and each construct of the IMBP. The research questions include:

* What are the factors associated with tobacco smoking among PLWH living in LMICs?
* What are the factors associated with intention to quit smoking behaviour of PLWH in LMICs?
* What are the factors associated with smoking cessation behaviour of PLWH in LMICs?
* What are the factors facilitating or hindering smoking cessation behaviour of PLWH in LMICs?

**METHODS**

**Eligibility criteria**

Studies will be selected based on a comprehensive set of criteria as per following:

***Study design***

We include empirical studies (including RCTs, cohort, case-control, cross-sectional, qualitative and mixed-methods studies) conducted on smoking and cessation behaviour among PLWH living in LMICs. Abstract-only studies, study protocols and grey literature such as reviews, unpublished work, editorials, and personal perspective papers will be excluded.

Studies included should empirically explore the association between predictors of tobacco smoking and cessation behaviour that can be classified as constructs of the IMBP.

***Participants***

We include studies on individuals living with HIV residing in LMICs who ever smoke regardless of their gender, smoking status (current or former smokers) and age group (youngsters/adolescences, adults or older people). Countries identified as LMICs are based on the most recent World Bank classification available from <https://data.worldbank.org/country/XO>.

***Intervention/Exposures and Comparators***

As this systematic review aims to appraise associated factors of smoking and cessation following the IMBP model, there is no intervention or comparators of interest to be considered. Thus, these elements are non-applicable. However, no search terms will be developed for the exposures or the IMBP constructs as we would like to keep the review scope wide enough so as not to overlook any relevant studies.

***Outcomes***

The included studies should report on smoking cessation, of which:

* Primary outcome: smoking cessation (abstinent or quit rates)
* Secondary outcome: current tobacco smoking status, quit attempts, intention to quit, readiness to quit, adherence to or uptake of smoking cessation aids/programmes/interventions.

In addition, studies will be restricted to Human species and English language.

**Information sources**

A systematic search for relevant studies through databases including PubMed, Scopus, PsycINFO, and Web of Science and a manual search of reference lists will be undertaken from inception until 25 September 2021 to include all relevant studies. Where full texts are unavailable, or required information is missing, study authors will be contacted.

**Search strategy**

Studies will be searched based on identified inclusion and exclusion criteria as described above. Search strategies will be developed using medical subheadings (MeSH) and text word related to HIV transmission and smoking cessation. Specific search strategies will

be developed by main author with assistance from a librarian from Biomedicine Library, University of Gothenburg, Sweden.

Search strategy employed for PubMed interface and adapted for other databases

|  |  |  |  |
| --- | --- | --- | --- |
| **PICO/PECO** | **Description** | **Search** | **Block 1 – HIV transmission & Tobacco smoking** |
| **Population** | Smokers living with HIV/AIDS | #1  #2  #3 | HIV [MeSH] OR acquired immunodeficiency syndrome [MeSH] OR HIV [Title/Abstract] OR human immunodeficiency virus [Title/Abstract] OR AIDS[Title/Abstract] OR acquired immune deficiency syndrome [Title/Abstract]  Smok\* [Title/Abstract] OR tobacco use\* [Title/Abstract] OR tobacco use [MeSH] OR smoker [MeSH] OR smoking [MeSH] OR nicotine  #1 AND #2 |
| **Interventions/**  **Exposures** |  |  | **N/A** |
| **Comparators** |  |  | **N/A** |
|  |  |  | **Block 2 – Smoking cessation behaviour** |
| **Outcomes** | *Primary outcome:*   * Smoking abstinence   *Secondary outcome:*   * Current/continued smoking * Quit attempts * Intention to quit * Readiness to quit * Adherence to/uptake of smoking cessation aids | #4 | Smoking cessation [MeSH] OR tobacco use cessation [MeSH] OR smoking cessation [Title/Abstract] OR quit\* OR abstinen\* OR stop\* OR cess\* or cease\* OR giv\* up OR intention\* OR readiness\* |
|  |  |  | **Search hits** |
|  |  | #5 | #3 AND #4 |
|  |  |  | **Limits** |
|  |  | #6 | Limit #5 to English language and Human subjects using filters |

**Study records**

***Data management***

Literature search results will be uploaded to Rayyan QCRI, an internet-based application that allows collaboration among reviewers during the study selection process. Citation extracted from databases will be imported to Endnote X9, a bibliographic citation management software, and duplicates will be removed.

***Selection process***

Two reviewers will independently review and screen titles and abstracts following inclusion and exclusion selection criteria. Full texts of eligible studies screened by title and abstract will be obtain. Subsequently, two reviewers will continue screening the full texts and decide if the articles meet the inclusion criteria. Disagreement will be resolved through discussion and possible conflicts of interest will be declared.

***Data collection process***

Only eligible studies will proceed to the stage of data extraction. A data extraction template will be formulated and standardised in Google Form and collected data will be exported to Microsoft Excel for data management. Study reference, study design, methods, country, sample size, proportion of female participants, outcome variables, outcome definition, factors associated with smoking and cessation behaviour are the items of the eligible studies that will be reported. Main author will extract data, and second author will cross-check the data. Contact with study authors will be made if there is any uncertainty. We will resolve disagreement between authors through discussion and declare possible conflicts.

**Data items**

This study utilises the Integrative Model of Behavioural Prediction (IMBP) presented in Figure 1 as a guide to search for scientific evidence on smoking cessation behaviour (Fishbein, 2000). Proximal variables include variables that directly or indirectly influence behavioural intention and eventual behaviour. Distal variables consist of background factors influencing behavioural intention or eventual behaviour and are mediated by proximal variables.

Diagram

Description automatically generated

Figure 1. The Integrative Model of Behavioural Prediction (adapted from Fishbein, 2000).

According to the model, a given behaviour is determined by a strong intention, the absence of environmental constraints or the presence of triggers for action, necessary skills and knowledge, positive attitudes, social normative pressure, and self-efficacy towards performing the behaviour. Study findings on associated factors of the behaviour are classified into major theoretical categories guided by the IMBP constructs. This may inform researchers about logical relationships between the behaviour and potential factors, about the knowledge gap in understanding these relationship, and about which determinants contribute to a greater extent to the performance of the behaviour. For instance, a systematic review may find that factors falling into three categories including attitudes, norms, and self-efficacy are the determinants of a given behavioural intention. More examined factors fall into one category than one another may indicate either gap in literature or a weak relationship between the behaviour and the narrower category or construct. Furthermore, pool effect size identified in a meta-analysis indicates the strength of the relationship between each potential determinant or category and the behaviour.

**Outcomes and prioritisation**

In this review, smoking is defined as habitual inhalation of nicotine-containing smoke from cigarettes and other forms of combusted tobacco products such as cigars and pipes will also be considered tobacco smoking behaviour. Current smoking status was identified by the answer “Yes” to the question: “Do you currently smoke any tobacco products every day or some days?”. Smoking cessation behaviour is the primary outcome of interest, which is defined as self-reported quit rates or clinically confirmed smoking *abstinence* at six months*.* In addition to *current tobacco smoking, quit attempts*, *adherence and willingness* to engage in smoking cessation aids/programmes/interventions arethe secondary outcomes of smoking cessation behaviour*. Readiness to quit* comprising the first three stages of smoking cessation and *intention to quit* are also the secondary outcomes that indicate behavioural intention to quit (Layoun et al., 2017).

**Risk of bias in individual studies**

Two authors also independently evaluated risk of bias or quality of the eligible studies using the Critical Appraisal Skills Programme (CASP) checklist, Effective Public Health Practice Project (EPHPP) and tool for qualitative and quantitative studies, respectively (CASP, 2018; B. H. Thomas et al., 2004). The EPHPP is a standard scoring scheme that allows studies to be classified into weak, moderate and strong risk of bias. Studies that fulfilled 70% of the criteria of the CASP tool were classified as moderate-to-high quality. If agreement cannot be reached, reviewers will consult with a third reviewer to come up with consensus.

**Data synthesis**

Both narrative and statistical data syntheses will be performed. For descriptive analysis, factors associated with behavioural intention to quit and smoking cessation behaviour will be classified into categories which are the IMBP constructs.

For qualitative data, thematic analysis was employed to examine recurrent and emerging themes (J. Thomas & Harden, 2008). This is an iterative analytical approach including four stages: (1) in-depth reading; (2) line-by-line coding; (3) assembling similar codes into descriptive themes; and (4) interpreting analytical themes. NVIVO12 software was used to analyse the qualitative data (QSR International Pty, 2012).

For quantitative studies, only findings from adjusted analyses will be reported if a given study performed both unadjusted and statistically controlled analyses. Odds ratios (ORs) is the effect measure of interest for the meta-analysis, other effect measures such as standardised mean difference will be converted to ORs for the consistency. The effect sizes with 95% confidence intervals (CIs) will be reported together with ORs. The overall effect of each predictor is calculated using random effect meta-analysis (due to anticipated heterogeneity) with inverse variance weighting method that summarises effect sizes from individual studies by computing weighted mean of the effect sizes. The weight assigned to each study is the inverse of that study’s variance. I-square statistics and Tau-square will be used to assess heterogeneity across studies. An I-square value of 25–50% is classified as low, 50–75% as moderate and ≥75% as high heterogeneity (Higgins et al., 2003). Meta-analysis was performed using Stata 16.

**Meta-bias(es) – Publication bias**

Publication bias will be assessed by funnel plots and Egger’s test if there are at least 10 studies included in the meta-analysis of the associated factors.

**Confidence in cumulative estimate**

The quality of evidence and strength of recommendation across studies will be assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, a user friendly and widely used grading system (Gyatt et al., 2008).

**References**

Ande, A., McArthur, C., Ayuk, L., Awasom, C., Achu, P. N., Njinda, A., . . . Kumar, S. (2015). Effect of mild-to-moderate smoking on viral load, cytokines, oxidative stress, and cytochrome P450 enzymes in HIV-infected individuals. *PLoS ONE, 10*(4), e0122402. doi:10.1371/journal.pone.0122402

Buhi, E. R., & Goodson, P. (2007). Predictors of adolescent sexual behavior and intention: a theory-guided systematic review. *J Adolesc Health, 40*(1), 4-21. doi:10.1016/j.jadohealth.2006.09.027

Critical Appraisal Skills Programme. (2018). CASP Qualitative Checklist. Retrieved from <https://casp-uk.net/wp-content/uploads/2018/01/CASP-Qualitative-Checklist-2018.pdf> [Accessed: 21 February 2021]

Feldman, J. G., Minkoff, H., Schneider, M. F., Gange, S. J., Cohen, M., Watts, D. H., . . . Anastos, K. (2006). Association of cigarette smoking with HIV prognosis among women in the HAART era: a report from the women's interagency HIV study. *Am J Public Health, 96*(6), 1060-1065. doi:10.2105/AJPH.2005.062745

Fishbein, M. (2000). The role of theory in HIV prevention. *AIDS Care, 12*(3), 273-278. doi:10.1080/09540120050042918

Godfrey, C. M., Harrison, M. B., Graham, I. D., & Ross-White, A. (2010). Utilisation of theoretical models and frameworks in the process of evidence synthesis. *JBI Libr Syst Rev, 8*(18), 730-751. doi:10.11124/01938924-201008180-00001

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., . . . Group, G. W. (2008). GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ, 336(7650), 924-926. doi:10.1136/bmj.39489.470347.AD

Helleberg, M., Afzal, S., Kronborg, G., Larsen, C. S., Pedersen, G., Pedersen, C., . . . Obel, N. (2013). Mortality attributable to smoking among HIV-1-infected individuals: a nationwide, population-based cohort study. *Clin Infect Dis, 56*(5), 727-734. doi:10.1093/cid/cis933

Helleberg, M., May, M. T., Ingle, S. M., Dabis, F., Reiss, P., Fatkenheuer, G., . . . Obel, N. (2015). Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America. *AIDS, 29*(2), 221-229. doi:10.1097/QAD.0000000000000540

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ, 327*(7414), 557-560. doi:10.1136/bmj.327.7414.557

Johnston, P. I., Wright, S. W., Orr, M., Pearce, F. A., Stevens, J. W., Hubbard, R. B., & Collini, P. J. (2021). Worldwide relative smoking prevalence among people living with and without HIV: a systematic review and meta-analysis. *AIDS*. doi:10.1097/QAD.0000000000002815

Layoun, N., Hallit, S., Waked, M., Aoun Bacha, Z., Godin, I., Leveque, A., . . . Salameh, P. (2017). Predictors of past quit attempts and duration of abstinence among cigarette smokers. *J Epidemiol Glob Health, 7*(3), 199-206. doi:10.1016/j.jegh.2017.06.003

Mann-Jackson, L., Choi, D., Sutfin, E. L., Song, E. Y., Foley, K. L., Wilkin, A. M., . . . Rhodes, S. D. (2019). A Qualitative Systematic Review of Cigarette Smoking Cessation Interventions for Persons Living with HIV. *J Cancer Educ, 34*(6), 1045-1058. doi:10.1007/s13187-019-01525-2

Mdege, N. D., Shah, S., Ayo-Yusuf, O. A., Hakim, J., & Siddiqi, K. (2017). Tobacco use among people living with HIV: analysis of data from Demographic and Health Surveys from 28 low-income and middle-income countries. *Lancet Glob Health, 5*(6), e578-e592. doi:10.1016/S2214-109X(17)30170-5

Mills, E. J., Bakanda, C., Birungi, J., Chan, K., Ford, N., Cooper, C. L., . . . Hogg, R. S. (2011). Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda. *Ann Intern Med, 155*(4), 209-216. doi:10.7326/0003-4819-155-4-201108160-00358

Moscou-Jackson, G., Commodore-Mensah, Y., Farley, J., & DiGiacomo, M. (2014). Smoking-cessation interventions in people living with HIV infection: a systematic review. *J Assoc Nurses AIDS Care, 25*(1), 32-45. doi:10.1016/j.jana.2013.04.005

O'Cleirigh, C., Valentine, S. E., Pinkston, M., Herman, D., Bedoya, C. A., Gordon, J. R., & Safren, S. A. (2015). The unique challenges facing HIV-positive patients who smoke cigarettes: HIV viremia, ART adherence, engagement in HIV care, and concurrent substance use. *AIDS Behav, 19*(1), 178-185. doi:10.1007/s10461-014-0762-7

Petoumenos, K., Worm, S., Reiss, P., de Wit, S., d'Arminio Monforte, A., Sabin, C., . . . Group, D. A. D. S. (2011). Rates of cardiovascular disease following smoking cessation in patients with HIV infection: results from the D:A:D study(\*). *HIV Med, 12*(7), 412-421. doi:10.1111/j.1468-1293.2010.00901.x

Pool, E. R., Dogar, O., Lindsay, R. P., Weatherburn, P., & Siddiqi, K. (2016). Interventions for tobacco use cessation in people living with HIV and AIDS. *Cochrane Database Syst Rev*(6), CD011120. doi:10.1002/14651858.CD011120.pub2

QSR International Pty. (2012). NVIVO qualitative data software. 10th ed. In.

Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., . . . Group, P.-P. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ, 350*, g7647. doi:10.1136/bmj.g7647

Shuter, J., & Bernstein, S. L. (2008). Cigarette smoking is an independent predictor of nonadherence in HIV-infected individuals receiving highly active antiretroviral therapy. *Nicotine Tob Res, 10*(4), 731-736. doi:10.1080/14622200801908190

Thomas, B. H., Ciliska, D., Dobbins, M., & Micucci, S. (2004). A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions. *Worldviews Evid Based Nurs, 1*(3), 176-184. doi:10.1111/j.1524-475X.2004.04006.x

Thomas, J., & Harden, A. (2008). Methods for the thematic synthesis of qualitative research in systematic reviews. *BMC Med Res Methodol, 8*, 45. doi:10.1186/1471-2288-8-45

UNAIDS. (2016). Global AIDS Update 2016. Retrieved from <https://www.unaids.org/sites/default/files/media_asset/global-AIDS-update-2016_en.pdf> [Accessed: 31 January 2121]

Uthman, O. A., Nduka, C. U., Abba, M., Enriquez, R., Nordenstedt, H., Nalugoda, F., . . . Ekstrom, A. M. (2019). Comparison of mHealth and Face-to-Face Interventions for Smoking Cessation Among People Living With HIV: Meta-Analysis. *JMIR Mhealth Uhealth, 7*(1), e203. doi:10.2196/mhealth.9329

Wistuba, II, Behrens, C., Milchgrub, S., Virmani, A. K., Jagirdar, J., Thomas, B., . . . Gazdar, A. F. (1998). Comparison of molecular changes in lung cancers in HIV-positive and HIV-indeterminate subjects. *JAMA, 279*(19), 1554-1559. doi:10.1001/jama.279.19.1554

World Health Organisation. (2018). WHO global report on trends in prevalence of tobacco smoking 2000–2025, second edition. . Retrieved from <https://apps.who.int/iris/bitstream/handle/10665/272694/9789241514170-eng.pdf?ua=1> [Accessed: 31 January 2021]

World Health Organization. (2020). Tobacco. Retrieved from <https://www.who.int/news-room/fact-sheets/detail/tobacco> [Accessed: 15 Dec 2020]