BODUNRIN OLASENI OTTU

WHAT IS THE RELATIONSHIP BETWEEN HIV AND SKIN WOUND HEALING PROCESS? A SYSTEMATIC REVIEW OF CLINICAL EVIDENCE

Dissertation submitted to the Cellular and Structural Biology Graduate Program of the Universidade Federal de Viçosa in partial fulfillment of the requirements for the degree of *Magister Scientiae*.

Adviser: Reggiani Vilela Gonçalves

Co-adviser: Mariáurea Matias Sarandy Souza

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To all my friends and colleagues, whose names are too numerous to mention, thank you for your kind assistance in one way or the other.

ABSTRACT

OTTU, Bodunrin Olaseni, M.Sc., Universidade Federal de Viçosa, December, 2022. **What is the relationship between HIV and skin wound healing process? A systematic review of clinical evidence.** Adviser: Reggiani Vilela Gonçalves. Co-adviser: Mariáurea Matias Sarandy Souza

Introduction: The steady rise in the number of people living with HIV (PLHIV) all over the world confirms that HIV/AIDS is a notable global pandemic. PLHIV often have cutaneous wound infection with grave consequences, including prolonged hospitalization stay and further weakening of the immune system. Although it is known that HIV interferes with the time of the wound healing process, what remains poorly understood are the main pathways activated in this process and the relationship between these pathways, and the delay in the closure of skin wounds in infected patients. **Aim:** This systematic review aims to analyze the current evidence regarding the influence of HIV on the cellular pathways activated during the closure of skin wounds in patients infected compared to uninfected healthy humans. **Methods:** A structured search on the Pubmed/Medline, Scopus, and Web of Science databases were used to retrieve articles based on our eligibility criteria. The screening of articles that met the inclusion criteria was done using the PRISMA strategy and the risk of bias for all selected studies was assessed with the SYRCLE's tool. **Results:** A total of twelve (12) studies involving HIV seropositive patients were selected and reviewed. HIV was shown to slow the process of wound healing when compared to the control. A low $CD4^+$ count correlated with a worse healing time and increased the chance of wound infections. Despite the administration of antibiotics (n=4, 33.33, especially Cephazolin (n=2, 17%)), wound healing time in HIV+ patients were slower compared to healthy individuals and no antibiotic showed a direct influence on the wound healing process. **Conclusion:** Wound closure is impaired in HIV+ patients, probably by the release of extracellular vesicles with HIV-derived components that can modulate host immunity and promote the severity of the infection, especially CD4+, compromising the wound healing process. Thus, this study highlights the importance of preserving the immune system of HIV-positive patients to maintain a good pattern of healing, especially for skin wounds. This study is registered on the PROSPERO platform (CRD42021265199).

Keywords: Wound healing. HIV. Skin. Humans. $CD4^+$.

RESUMO

OTTU, Bodunrin Olaseni, M.Sc., Universidade Federal de Viçosa, dezembro de 2022. **Qual a relação entre o HIV e o processo de cicatrização de feridas na pele? Uma revisão sistemática de evidências clínicas.** Orientadora: Reggiani Vilela Gonçalves. Coorientadora: Mariáurea Matias Sarandy Souza.

Introdução: O aumento constante do número de pessoas vivendo com HIV (PVHIV) em todo o mundo confirma que o HIV/AIDS é uma pandemia global notável. As PVHIV frequentemente apresentam infecção de feridas cutâneas com consequências graves, incluindo internação prolongada e maior enfraquecimento do sistema imunológico. Embora se saiba que o HIV interfere no tempo do processo de cicatrização de feridas, o que permanece pouco compreendido são as principais vias ativadas nesse processo e a relação entre essas vias e o retardo no fechamento das feridas cutâneas em pacientes infectados. Objetivo: Esta revisão sistemática visa analisar as evidências atuais sobre a influência do HIV nas vias celulares ativadas durante o fechamento de feridas cutâneas em pacientes infectados em comparação com humanos saudáveis não infectados. Métodos: Uma busca estruturada nas bases de dados Pubmed/Medline, Scopus e Web of Science foi usada para recuperar artigos com base em nossos critérios de elegibilidade. A triagem dos artigos que atenderam aos critérios de inclusão foi feita usando a estratégia PRISMA e o risco de viés para todos os estudos selecionados foi avaliado com a ferramenta SYRCLE. Resultados: Um total de doze (12) estudos envolvendo pacientes soropositivos para HIV foram selecionados e revisados. O HIV mostrou retardar o processo de cicatrização de feridas quando comparado ao controle. Uma baixa contagem de CD4+ correlacionou-se com um pior tempo de cicatrização e aumentou a chance de infecções de feridas. Apesar da administração de antibióticos (n=4, 33,33, principalmente Cefazolina (n=2, 17%)), o tempo de cicatrização de feridas em pacientes HIV+ foi mais lento em comparação com indivíduos saudáveis e nenhum antibiótico mostrou influência direta no processo de cicatrização de feridas. Conclusão: O fechamento da ferida está prejudicado em pacientes HIV+, provavelmente pela liberação de vesículas extracelulares com componentes derivados do HIV que podem modular a imunidade do hospedeiro e promover a gravidade da infecção, principalmente CD4+, comprometendo o processo de cicatrização da ferida. Assim, este estudo destaca a importância da preservação do sistema imunológico de pacientes HIV positivos para manter um bom padrão de cicatrização, principalmente para feridas cutâneas. Este estudo está registrado na plataforma PROSPERO (CRD42021265199).

Palavras-chave: Cicatrização de feridas. HIV. Pele. Humanos. CD4+.

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LIST OF ABBREVIATIONS

AIDS- acquired immunodeficiency syndrome

ART- anti-retroviral therapy

CCR5- CC chemokine receptor 5

CD4- Cluster of Differentiation antigen 4 receptor

$CD4^+$- The Cluster of Difference 4 T lymphocyte

CXCR4- CXC chemokine receptor 4

ELISA- Enzyme-linked immunosorbent assay

Env- HIV envelope glycoprotein

HIV- human immunodeficiency virus

PCR- Polymerase Chain Reaction

PLHIV- people living with HIV

PRISMA- The preferred reporting items for Systematic reviews and Meta-analyses

TNF- Tumor necrosis factor

SUMMARY

OBJECTIVES

GENERAL OBJECTIVES

The study is a systematic review of literature aimed at unveiling the influence of HIV seropositivity status on the skin wound healing process of humans.

SPECIFIC OBJECTIVES

- To search current literature to know if the time to complete skin wound healing is longer in HIV patients compared to uninfected individuals based on clinical evidence.
- To elucidate the mechanism, if any, responsible for delayed wound healing time in HIV+ patients compared to HIV-negative humans.

ARTICLE

What is the relationship between HIV and skin wound healing process? A systematic review of clinical evidence

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ABSTRACT

Background: The steady rise in the number of people living with HIV (PLHIV) all over the world confirms that HIV/AIDS is a notable global pandemic. PLHIV often have cutaneous wound infection with grave consequences, including prolonged hospitalization stay and further weakening of the immune system. Although it is known that HIV interferes with the time of the wound healing process, what remains poorly understood are the main pathways activated in this process and the relationship between these pathways, and the delay in the closure of skin wounds in infected patients. **Aim:** This systematic review aims to analyze the current evidence regarding the influence of HIV on the cellular pathways activated during the closure of skin wounds in patients infected compared to uninfected healthy humans. **Methods:** A structured search on the Pubmed/Medline, Scopus, and Web of Science databases were used to retrieve articles based on our eligibility criteria. The screening of articles that met the inclusion criteria was done using the PRISMA strategy and the risk of bias for all selected studies was assessed with the SYRCLE's tool. **Results:** A total of twelve (12) studies involving HIV seropositive patients were selected and reviewed. HIV was shown to slow the process of wound healing when compared to the control. The low $CD4^+$ count correlated with a worse healing time and

increased the chance of wound infections. Despite the administration of antibiotics (n=4, 33.33, especially Cephazolin (n=2, 17%)), wound healing time in HIV+ patients was slower compared to healthy individuals and no antibiotic showed a direct influence on the wound healing process. **Conclusion:** Wound closure is impaired in HIV+ patients, probably by the release of extracellular vesicles with HIV-derived components that can modulate host immunity and promote the severity of the infection, especially CD4+, compromising the wound healing process. Thus, this study highlights the importance of preserving the immune system of HIV-positive patients to maintain a good pattern of healing, especially for skin wounds. This study is registered on the PROSPERO platform (CRD42021265199).

1. INTRODUCTION

There are two types of the human immunodeficiency virus (HIV), HIV-type 1 (HIV-1) and HIV-type 2 (HIV-2), that have been circulating in the human population for over eight decades (Eberle and Gürtler, 2012; Khalid *et al*., 2021). HIV-1 is responsible for 95% of the world's infection and is the foremost causative agent of acquired immunodeficiency syndrome (AIDS) whereas HIV-2, which is less infectious, mostly affects humans in West and Central Africa (Fanales-Belasio *et al*., 2010; Esbjörnsson *et al*., 2019). Viral entry in both types is usually initiated by the binding, activation, and subsequent fusion of the HIV envelope membrane with the plasma membrane of the host cells. This is followed by the release of the nucleocapsid into the cytoplasm, mediated by the interaction of the HIV envelope glycoprotein (Env) with the Cluster of Differentiation antigen 4 receptor (CD4) and the coreceptors [CC chemokine receptor 5 (CCR5) and CXC chemokine receptor 4 (CXCR4)] (García and Marsh, 2020).

Data availability for the prevalence of HIV and AIDS in 170 countries suggests that HIV/AIDS is a notable global pandemic. As of 2018, about 1.7 million people were newly infected with the virus and 770, 000 AIDS-related deaths were reported. The number of PLHIV globally was estimated at 37.9 million, more than half (52%) of which are women (Mahy *et al.*, 2019; UNAIDS, 2022). HIV/AIDS places a huge burden on the economic development of individuals and nations, especially in the 14 most-affected sub-Saharan countries (South Africa, Nigeria, Kenya, Mozambique, Uganda, Tanzania, Zimbabwe, Malawi, Zambia, Ethiopia, Lesotho, Botswana, Namibia, and Swaziland). Public HIV-related costs in these 14 countries are estimated to be about US$11 billion annually (Remme *et al*., 2016), and every year, the U.S government spends more than $28 billion both discretionarily and mandatorily in response to HIV (Parekh, 2019). Indeed, HIV/AIDS harms the socioeconomic development of countries

and families. The resultant effect of contracting the virus may include job loss, increased medical expenses, distress sale of possessions, poverty and low quality of life, as well as overloaded healthcare systems (Taraphdar *et al*., 2011).

Coinfections of several diseases in PLHIV have been reported. PLHIV are often coinfected with tuberculosis (Gray and Cohn, 2013), Hepatitis A, B, and C (Nagu *et al*., 2008), *Toxoplasma gondii* (Wang *et al*., 2017), Schistosomiasis (Furch *et al*., 2020), cytomegalovirus (Grønborg *et al*., 2017), Covid-19 (Mirzaei *et al*., 2021) as well as cutaneous lesions (Altman *et al*., 2015). Currently, cutaneous lesions are among the most important diseases associated with HIV complications. The progression of a skin wound and consequent chronification of the lesion is determined by the inability of the host to generate an effective immune response (Wysocki, 2002). The Cluster of Difference 4 ($CD4^+$) T lymphocyte count is the most important predictive marker for monitoring immune dysfunction in PLHIV (Tinarwo *et al.*, 2019) and it has been reported that a low $CD4^+$ cell count poses a major risk factor for wound healing in HIV-infected patients (Mcmeeking *et al.*, 2014).

Cells infected with HIV normally produce extracellular vesicles that can enhance the severity of the infection and mediate the inhibition of immune response mainly by accelerating the apoptosis of immune cells. In addition, HIV infection increases the levels of cytokines and chemokines responsible for developing chronic inflammation and delay in the wound healing process (Weledji *et al.*, 2012). Additionally, factors such as the presence of infections, advanced patient age, medications, previous injuries, metabolic disorders, as well as external factors like temperature, moisture, and pressure, can cause an imbalance in the repair process, thereby impairing adequate wound closure (Han and Ceilley, 2017).

Mcmeeking *et al*. (2014) classified the wounds in HIV patients as follows; pressure, venous, post-surgical, diabetic, traumatic, ischemic, inflammatory, and unspecified. Although Clinicians generally find the evaluation of skin wounds challenging, invasive and non-invasive approaches can be used to assess the extent of healing of wounds (Wolcott *et al.*, 2010; Mcmeeking *et al.*, 2014). The invasive approach involves surgical debridement, biopsy, liquid capacity, and molds, while the non-invasive utilizes ultrasound, roentgenogram, linear measurement, acetate tracing, planimetry, visual, Kundin gauge, stereophotometry, and magnetic resonance imaging for the assessment of wounds (Lazarus *et al.*, 1994). Other reported ways of evaluating wounds include the qualitative analysis of the appearance of slough, exudate and wound edges, as well as the presence of maceration or wound infections (Wolcott *et al*., 2010). However, to establish the best therapeutic option, it is necessary to understand the main cellular mechanisms involved in skin lesion recovery as well as the main

modifications presented by the skin tissue after HIV infections. In addition, an evaluation of the socio-economic conditions of the countries is important to know if it is viable to apply a particular treatment or not. For example, in most low-and-middle-income sub-Saharan countries, where HIV/AIDS is highly prevalent, the cost of accessing antiretroviral therapy (ART), the attendant cost of transportation to and from antiretroviral clinics, as well as food and other personal costs, already places a huge financial burden on PLHIV (Nanfuka *et al*., 2019). Thus, wound healing time is of great importance to PLHIV as it can help to reduce their financial burden and this is in line with the United Nations (UN) 2030 deadline for ending the HIV/AIDS pandemic (United Nations, 2016).

Given the uncertainties and controversies surrounding the role of HIV infection in cutaneous wounds, we aimed to analyze the current evidence regarding the influence of HIV in the wound healing process of patients infected with HIV compared to uninfected humans in order to understand the main mechanisms involved in this process and to establish the best therapeutic approach that can promote recovery of the skin wounds. In this sense, we used a systematic review framework to investigate the impact of HIV on the healing of skin wounds. Thus, we analyzed the main characteristics of the experimental models, protocols of treatment, advances, and limitations of the studies, as well as the methodological quality of the studies reviewed. The risk of bias associated with the current evidence was also critically analyzed.

2. METHODOLOGY

2.1. Research question

The guiding questions for this review were: Is the closing of wounds impaired in HIV+ or AIDS patients compared to HIV(-) patients? Does the clinical stage of HIV infection affect the time of healing of wounds? What are the main mechanisms involved in the process?

2.2. Search Strategy

The preferred reporting items for Systematic reviews and Meta-analyses (PRISMA) strategy was used for the search and selection of primary and secondary studies (Page *et al*., 2021). The protocols consisted of two search levels: (i) direct searches in electronic databases, and (ii) indirect screening of reference lists from all studies identified in the direct searches. In the primary search, the databases used were PubMed/Medline (https://www.ncbi.nlm.nih.gov/pubmed), Scopus (https://www.scopus.com/home.uri), and Web of Science (https://www.webofknowledge.com). The identification of relevant studies was based on structured search filters using MeSH (Medical Subject Headings) terms developed

from the Pubmed/Medline thesaurus. In the search platform, the retrieval of relevant records was optimized by using the Title and Abstract (TIAB) algorithm for standardized and non-standardized (non-MeSH) but relevant descriptors. The same search matrix used in the Pubmed/Medline database was adopted for Scopus and Web of Science by using the search commands TITLE-ABS-KEY (Title + Abstract + Keywords) and TS= (Topic search) respectively. The search filters were combined by the Boolean connectors ‘‘[AND]’’ and ‘‘[OR]’’ in their respective platforms. To minimize the loss of relevant records, our search filters were based on four levels considering patients with: (i) skin, (ii) wound healing (clinical condition), (iii) HIV (disease) and iv) humans (Table S1). The entire process was done by two independent reviewers.

2.3. Inclusion criteria

Duplicated studies were excluded by comparing the authors' list, titles, and publication data (journal title, volume, issue, and publication date). Irrelevant studies were excluded by perusing the title and abstract. The remaining registers were recovered in full text and evaluated for eligibility. We included studies from endemic and non-endemic countries that reported the influence of HIV on wound healing in infected patients. We specifically excluded: (i) preclinical studies (non-human models), (ii) partial reports (letters, congress summaries, and commentaries) (iii) *in silico* studies, (iv) studies not involving HIV patients and (v) studies with a pathology different from skin. In addition, we scrutinized the reference lists of all relevant studies selected in the direct search to improve the retrieval of additional records (Table S1).

2.4. Data extraction

Qualitative data were extracted using structured tables constructed from basic methodological requirements and the studies were characterized according to different descriptive levels such as (i) publication characteristics [research design, authors, publication year, and countries; (ii) patient characteristics [age, sex, weight, severity of HIV disease, and other pathologies associated]; (iii) treatment characteristics [drugs and dosimetry (doses, frequency of administration, and treatment duration), and co-interventions used]; (iv) primary measure outcomes [types of wounds (incisional and excisional), cause of the wound, the method used to analyze wound healing process, wound healing time, ethical approval, or informed consent]. All types of studies indexed and retrieved in the full text were included in the systematic review. Only articles published in English language or Spanish were reviewed. No study design restrictions were adopted.

Three reviewers (BOO, ALABM and MMS) conducted the literature search, removed duplicate articles, and screened titles and abstracts based on the eligibility criteria. After initial screening, full-text articles of potentially relevant studies were independently assessed for eligibility by three reviewers (BOO, ALABM and MMS). The Kappa test was done to measure the level of agreement for the data selected by the reviewers (kappa = 0.853). All inconsistencies were resolved in consultation with two other reviewers (RVG and RDN).

2.5. Study risk of bias assessment

In the case series, the SYRCLE`s Risk of Bias (RoB) tool was applied to evaluate the reporting quality and potential risk of bias (Hooijmans *et al*., 2014). The following methodological domains based on RoB were evaluated. Consider selection bias: “Was the allocation made and applied properly?”, “Were the groups similar at baseline or were they adjusted for confounders in the analysis?”, “Was the allocation to the different groups adequately concealed?”; Consider performance bias: “Were caregivers and/or researchers blinded to each patient's HIV status?”; Consider detection bias: “Was the outcome assessor-blinded?”; Consider attrition bias: "Was there incomplete data?", "Was the incomplete results data handled properly?"; Considers reporting bias: “Are reports of the study free of selective outcome reporting?”;

Consider "Wound healing bias": "Is the healing time of holidays reported in days?". Consider "Ethical approval bias": "Does the study express the consent of the Ethics Council to carry out the research?". Consider "Statistical methods bias": "Does the study explain the methods used to perform the statistical analyses?". Consider "Outcome bias": "Are the methods used to obtain the results valid?". Consider "Applicability bias": "Is the study fully within the topic addressed by the review?". Consider other biases: “Was the study free of other issues that could result in a high risk of bias?”; The general indicators of study quality: “Was randomization at any level of the experiment indicated?” and “Was it stated that the experiment was blinded at any level?”. The items of the RoB instrument were scored “yes” (low risk of bias); “no” (high risk of bias); or “uncertain” (indicating that the item was not reported and therefore the risk of bias was unknown). The SYRCLE chart was built using the Review Manager 5.4 software system.

3. RESULTS

3.1. Characteristics of Publications

From the search on the three platforms, we retrieved 201, 215, and 129 titles from PubMed/Medline, Scopus, and Web of Science databases respectively. Thus, a total of 545 studies were identified from the search. Fifty-six (56) studies were removed because they were duplicates while the titles and abstracts of the remaining 489 articles were further perused. Only 10 studies eventually got selected because they met the inclusion criteria. Two (2) articles were included from the manual search of the references because they also met the inclusion criteria, totaling 12 studies (Figure 1- PRISMA flowchart).

These studies were carried out in 9 different countries: Uganda, Zimbabwe, France, Kenya, South Africa and Mexico (n=1, 8.33% each), United Kingdom, USA and Malawi (n=2, 16.67% each) (Table 1 and Figure 2). Twelve studies published between 1989 and 2013 were reviewed.

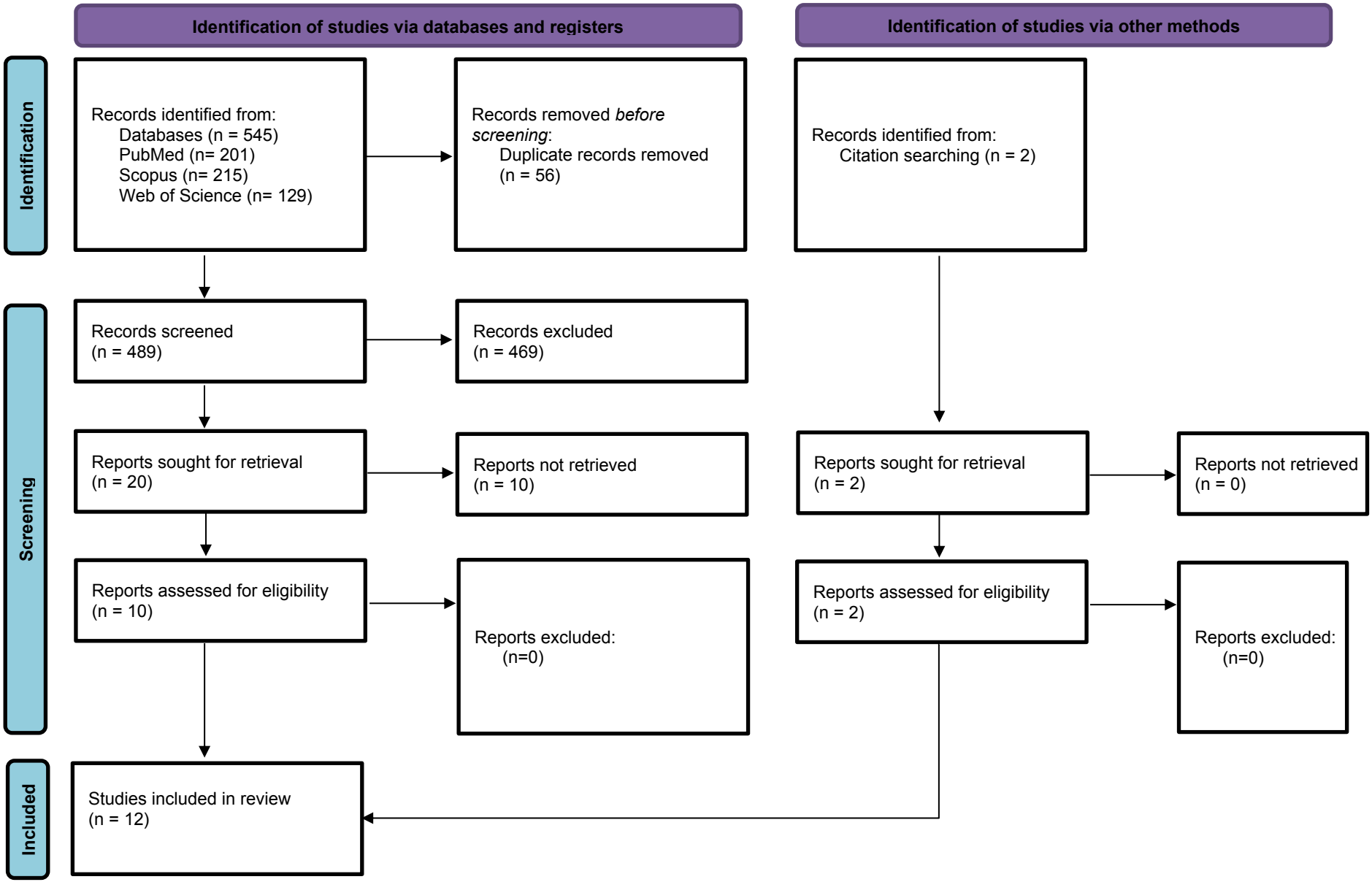
Identification of studies via databases and registers
Identification of studies via other methods
Identification
Records identified from:
Databases (n = 545)
PubMed (n= 201)
Scopus (n= 215)
Web of Science (n= 129)
Records removed *before screening*:
Duplicate records removed (n = 56)
Records identified from:
Citation searching (n = 2)
Screening
Records screened (n = 489)
Records excluded (n = 469)
Reports sought for retrieval (n = 20)
Reports not retrieved (n = 10)
Reports sought for retrieval (n = 2)
Reports not retrieved (n = 0)
Reports assessed for eligibility (n = 10)
Reports excluded: (n=0)
Reports assessed for eligibility (n = 2)
Reports excluded: (n=0)
Included
Studies included in review (n = 12)

Figure 1 | **PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram**. The flowchart indicates the research records obtained at all standardized stages of the search process required for the development of systematic reviews and meta-analyses. Based on the PRISMA statement (http://www.prisma-statement.org).

3.2.Patient characteristics

All studies involved HIV seropositive patients (100%). Male and female participants were recruited in 75% of the studies while 16.7% of the studies reported that they recruited only male participants. One study did not specify the sex of the participants (8.3%). The patients were aged between 3 months and 87 years (Table 1). Nine studies (75%) reported the study duration, with a mean duration of 14.2 months. The duration of the studies reported includes 5 years (n=1, 8.33%), 25 months (n=1, 8.33%), 18 months (n=1, 8.33%), 14 months (n=1, 8.33%), 12 months (n=1, 8.33%), 4 months (n=1, 8.33%) and 3 months (n=3, 25%), and 3 studies did not specify the duration of the studies (n=3, 25%). Only 5 of the total 12 articles directly reported the use of the informed consent forms (n=5, 41.65%) (table 1). HIV spot test (n=2, 16.67%), HIV Rapid Antibody Test (n=1, 8.33%), Enzyme-linked immunosorbent assay (ELISA) (n=2, 16.67%) and Polymerase Chain Reaction (PCR) (n=1, 8.33%) were used to screen participants for, and confirm, HIV seropositivity status. Of these, only one study reported using more than one method for confirming HIV status (n=1, 8.33%) whereas seven studies (58.31%) did not specify the methods used (Figure 2). The PCR technique was specifically used to screen children under 18 months old.

Table 1 | General characteristics of the studies, patients and methods of monitoring wound healing.

Reference	Country	Patients(n)	Wound site(s)	Sex	Age	The method used to study the wound healing process	Study duration	Informed consent
Chalya *et al*., 2011	Uganda	n= 130 n= 17 HIV+ n= 113 HIV-	Skin	M/F	3 months - 34 years	Lund-Browder Chart	4 months	Yes
Harrison *et al*., 2002	Malawi	n= 180 n= 39 HIV+ n= 141 HIV-	Ankle, forearm patella, femur, tibia, ulna, C1, C2 and phalanx .	NR	HIV+ 21 to 54 years HIV- 15 to 76 years	Asepsis scoring system	3 months	Yes

Harrison *et al*., 2004	Malawi	n= 27 n= 7 HIV+ n= 20 HIV-	Tibia	M/F	19 to 63 years.	Checketts pin track grading system	3 months	Yes
Mzezewa *et al*., 2003	Zimbabwe	n= 82 n= 39 HIV- burn patients n= 15 HIV+ burn patients Control Group n= 15 HIV+ volunteers n= 13 HIV- volunteers	Skin	M/F	HIV- burn patients; (3–51) years HIV+ burn patients; (15–45) years **Control Group** HIV+ volunteers; (19–43) years HIV-, volunteers; (20–42) years	Skin Graft survival as a measure of wound healing	Not described	Yes
Puy-Montbrun *et al*., 1992	France	n= 148 n= 0 HIV- n= 148 HIV+	Anal margin, Anal canal and Rectum	M/F	Mean of 34.2 years	Analysis of Anorectal lesions.	14 months (as calculated)	No
Rogers *et al*., 2013	Kenya	n= 323 n= 215 HIV-	Penis	M	18–35 years	Healthy scar	3 months	Yes

		n=108 HIV+				formation with no scab or opening along the incision line		
Geminiano-Martínez *et al*., 2000	Mexico	n= 46 n= 23 HIV- n= 23 HIV+	Anus	M/F	HIV- 21 - 79 years) HIV+ 24 - 57 years	Analysis of Anorectal lesions.	12 months	No
Carr *et al*., 1989	UK	n= 177 n= 161 HIV- n= 16 HIV+	Anus	M/F	Heterosexual male patients 15-83 years Heterosexual women 24-80 years) homosexual patients 22-54 years	Analysis of anorectal lesions	25 months	No
Rogers *et al*., 2008	USA	n= 3 n= 2 HIV- n= 1 HIV+	Tibia	M/F	47, 87, 52 years	Description of wounds Time to complete healing steps	Not described	No

Burke *et al*., 1991	USA	n= 52 n= 0 HIV- n= 52 HIV+	Anus	M	27 – 49 years	Analysis of Anorectal lesions.	5 years	Unclear
Davis and Wastell, 2000	UK	n= 22 n= 11 HIV- n= 11 HIV+	Scars	M/F	HIV+ 29–60 HIV- 28–84	Tensionometry	Not described	Not described
Howard *et al*., 2013	South Africa	n= 84 n= 56 HIV- n= 28 HIV+	Tibia	M/F	34.8 years.	Gustilo–Anderson grade Prospective analysis of tibial fractures and infections	18 months	Not described

For information not present in the text, it was filled in as "not described" and the sex of the patients was indicated by M and F, where M = "male" and F = "female", NR = "not reported".

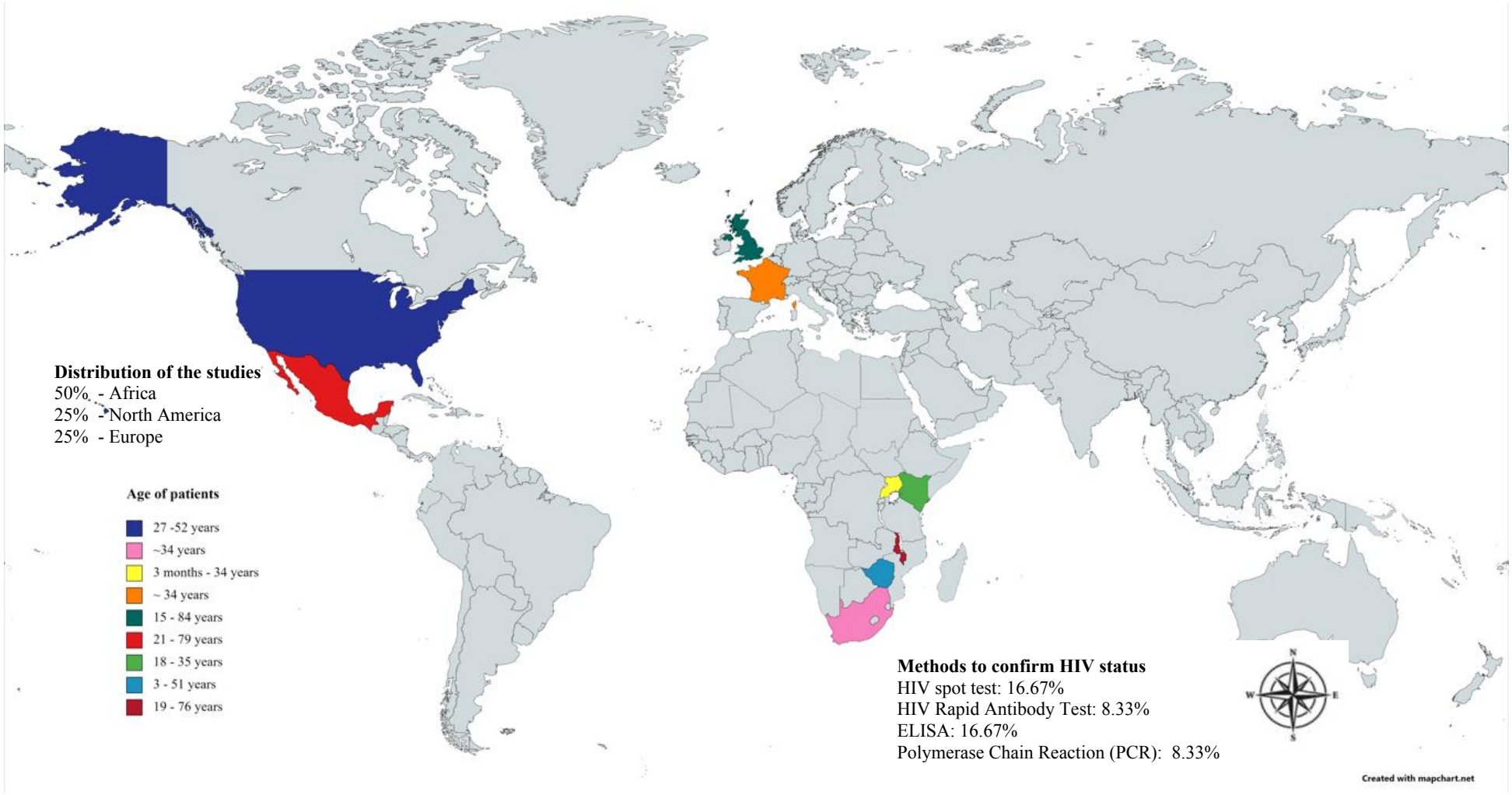

Figure 2 | **A world map showing the countries and continents where the studies included in the systematic review were conducted.**

The results of the analysis of the impact factor of the journal articles in which the studies were published show that of the 12 articles, only 1 is no longer publishing articles (8.33%), while the remaining 11 (91.66%) are still actively publishing. A more in-depth analysis of those that are still active revealed that, 9 (75%) have an impact factor above 3.0, two (16%) have an impact below 3.0 and a journal is no longer available (Figure 3).

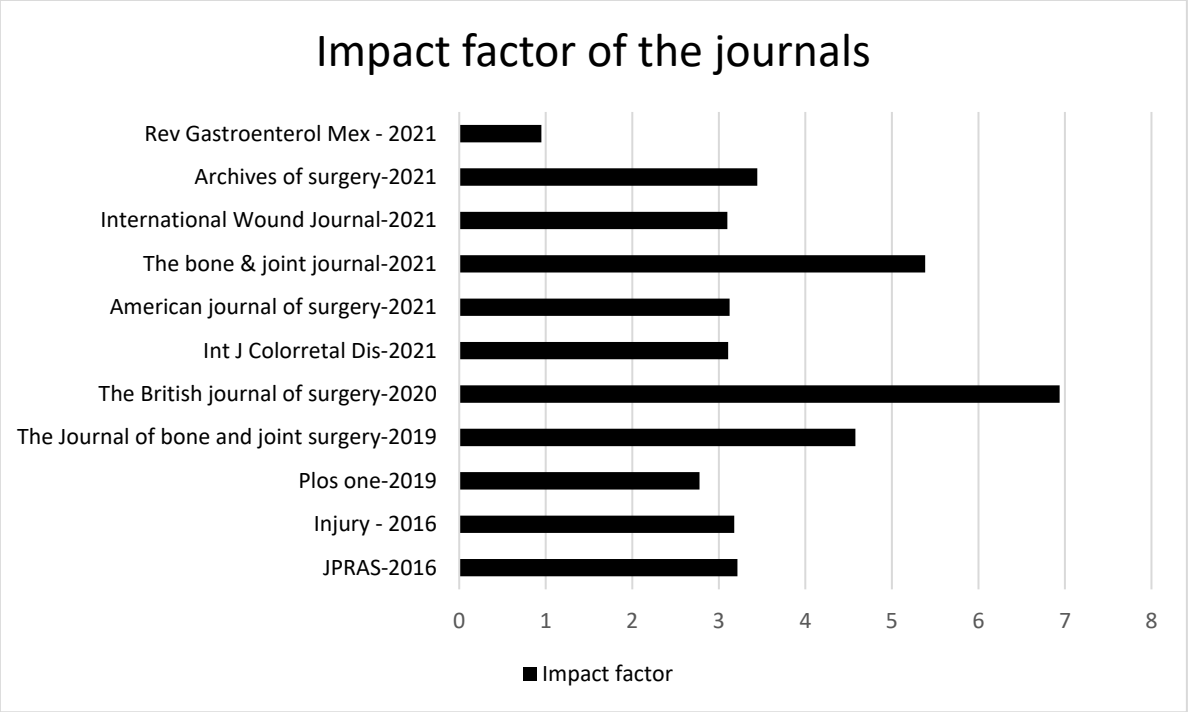

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Figure 3 | **Impact factor of the journals of the reviewed articles included in the study.**

3.3.Wound healing characteristics

The wounds were caused by anorectal lesions (n=4, 33.33%), burn injuries (n=2, 16.7%), open fractures of the tibia (n=2, 16.7%), post-circumcision in males, post-implant surgery, Charcot arthropathy of the ankle, and surgical wounds after a second surgical procedure via the old incision (n=1, 8.33% each). In addition, five studies (41.6%) reported the presence of associated pathologies, of which three were anal condyloma (60%), sexually transmitted infection, persistent lymphadenopathy, Necrotic ulcer, Visceral Kaposi's sarcoma and neurological disorders/ tumor (n=1, 20% each). Regarding co-interventions used during the research, the use of antibiotics such as cephazolin, ciprofloxacin and cloxacillin was reported (n=1, 8.16% each). Skin grafting (n=2, 16.67%), Surgical treatment, Laparotomy, and Bone marrow aspiration application (n=1, 8.16% each) were also reported (Table 2).

Table 2. **Summary of the causes of the wounds, wound healing time, other comorbidities present, medications used, HIV stage and relationship between CD4 count and scarring.**

Reference	Cause of the wounds	Other associated pathologies	Illness stage	Comparison between healing in HIV+ and CD4+ count	Co-interventions used	Wound healing time
Chalya *et al*., 2011	Severe burn injuries	None	Stage 1 to 4	HIV+ (CD4≥200Cells/uL) = HIV- (CD4≥200Cells/uL)	Skin grafting	The mean was 84% and 92% in HIV-positive and HIV-negative patients respectively.
Harrison *et al*., 2002	Wound after implant surgery	None	Stage 0 to 3	Incidence of HIV+ infections comparable to HIV- CD4 cell count did not affect the incidence of infection.	Cephazolin	Recorded the scores at 5 days, 2 and 6 weeks, and at 3 months after the operation.
Harrison *et al*., 2004	Open fractures of the tibia	None	Stage 0 to 2	HIV+ = ↓ Scar HIV- = ↑Scar	Cephazolin	HIV-positive patients: 4 months, 2 6 months HIV-negative group: 4 and 6 months

				The correlation appears weak with CD4 cell count.		
Mzezewa *et al*., 2003	Burn injuries	None	Not reported	HIV+ = ↓ CD4 HIV infection results in immune dysregulation, which may be related to impaired skin graft survival.	Skin grafting	The median length of hospital stay for early excision in 20 non-HIV-infected patients was 21 (12–53) days and for nine HIV-infected patients 41 (25–73) days. The median length of hospital stay for delayed skin grafting in 19 non-HIV-infected patients was 39 (29–123) days, and in six HIV-infected patients, it was 48 (35–86) days.
Puy-Montbrun *et al*., 1992	Anorectal lesions	Anal condylomata, suppuration, fissure, haemorrhoids	Stage 2 to 4	Not reported	Surgical treatment	Unclear, only an abnormally slow (> 3 months) wound healing was reported in 12% of the patients operated on for haemorrhoids, fissures, or suppuration.
Rogers *et al*., 2013	Male circumcision	None	HIV (WHO stage 2 and below)	At week 6	None	At week 4, 59.3% of HIV-positive men and 70.4% of age-matched HIV-negative men were healed.

				HIV+(CD4≥350Cells /uL) = HIV- (CD4≥350Cells/uL) HIV+ without ARVT (CD4<350Cells/uL) = ↓ Scar		At week 6, 93.4% of HIV-positive men and 92.6% of age-matched HIV-negative men were healed.
Geminiano-Martínez *et al*., 2000	Anorectal surgery	Anal lesions Anal condylomata Lymphadenopathy; Neurological disorders/ tumor.	Stage 0 to 4	(CD4<400Cells/uL) = ↓ Scar AIDS = ↓ Scar	Ciprofloxacin	Not exactly specified, but approximately between 9- and 65-days average in HIV (+). (Control group) = 23.21 days average.
Carr *et al*., 1989	Non-condylomatous	Condylomata Previous sexually	Stage 0, 2 and 4	HIV+ = HIV- AIDS = ↓ Scar	None	Healing of perianal wounds occurred within 6 weeks of surgery in all HIV antibody negative and all HIV

	perianal disease	transmitted infection Active sexually transmitted disease				antibody positive-asymptomatic patients but in only one of nine HIV antibody positive-symptomatic patients. Of those with delayed healing, four of the HIV antibody positive-symptomatic patients failed to exhibit healing at 2,2.5 and 3 months after surgery and were then lost to follow-up. In another four patients with symptomatic HIV infection, healing occurred at 4,9, 10 and 14 months respectively.
Rogers *et al*., 2008	Charcot arthropathy of the ankle	None	Not reported	Not rated	Skin grafting Bone marrow aspiration applied	Patient 1 - 60 days
Burke *et al*., 1991	Anorectal surgery	Persistent lymphadenopa	Stage 1, 2 and 4	Well-nourished patients = ↑Scar	None	Groups II and III 7±6 - 7±4 Group IV 12±5 - 13±12

		thy, anal condyloma, Necrotic ulcer, Visceral, Kaposi's sarcoma		Low CD4+ counts = ↑infections		
Davis and Wastell, 2000	A second surgical procedure via the old incision line.	None	Stage 4	Low CD4 = ↓ Scar	Laparotomy	Not described
Howard *et al*., 2013	Open surgically stabilized tibial fractures	None	Stage 0 to 4	No relationship was found between CD4 count and ASEPSIS wound score.	Cloxacillin	All patients were seen four weeks after discharge, 86% were seen at two months, and 76% were seen at three months.

HIV stage based on the Centers for Disease Control (CDC) table. For information not present in the text, it was filled in as "not reported" and for characteristics absent from the study, it was filled in as "none".

Among the studies included in this systematic review, 9 methods were used to study the wound healing process: 1) Analysis of Anorectal lesions (n=4, 33.33%), 2) Lund-Browder Chart (n=1, 8.33%), 3) Asepsis scoring system (n=1, 8.33%), 4) Checketts pin track grading system (n=1, 8.33%), 5) Skin Graft survival as a measure of wound healing (n=1, 8.33%) 6) Healthy scar formation with no scab or opening along the incision line (n=1, 8.33%), 7) Wound descriptions and time to complete healing (n=1, 8.33%) 8) Tensionometry (n=1, 8.33%) 9) Gustilo–Anderson grade Prospective analysis of tibial fractures and infections (n=1, 8.33%). Table 3 presents a general description of the methods used by the individual studies.

Table 3 | General characteristics of the methods used to study the wound healing process

Reference	Method	Description
Chalya *et al*., 2011	Lund-Browder Chart (GOMES *et al*, 2001)	Consists of a method of stipulating the affected body area in cases of burns, taking into account the patient's age and BSA (Body Surface Area).
Harrison *et al*., 2002	Asepsis scoring system (WILSON *et al*., 1986).	A method that defines scoring criteria to assess the evolution of wound healing. Among the criteria are "the presence of serous secretion, erythema, purulent exudate and separation of deep tissues, isolation of bacteria and length of hospital stay (ASEPSIS)."
Harrison *et al*., 2004	Checketts pin track grading system (Clint *et al*., 2009)	A system where the fixation pins are numbered, and then classified according to erythema, secretion and pain; with 3 grades of evaluation each: “good, bad and ugly”
Mzezewa *et al*., 2003	Skin Graft survival as a measure of wound healing	Which used the survival of skin grafts and their respective follow-ups to assess wound healing.
Puy-Montbrun *et al*., 1992	Analysis of Anorectal lesions.	Which follow-ups of the evolution of the wounds were carried out, aiming to guarantee the best results as the healing progressed.
Rogers *et al*., 2013	Healthy scar formation with no scab or opening along the incision line	Which the formation of scars was observed, evaluating the existence of crusts or reopening along the incision line
Geminiano-Martínez *et al*., 2000	Analysis of Anorectal lesions.	Which follow-ups of the evolution of the wounds were carried out, aiming to guarantee the best results as the healing progressed.
Carr *et al*., 1989	Analysis of anorectal lesions	Which follow-ups of the evolution of the wounds were carried out, aiming to guarantee the best results as the healing progressed.

Rogers *et al*., 2008	Description of wounds Time to complete healing steps	Which the wounds were monitored and evaluated in terms of wound duration, time to complete granulation, time to skin graft and time to complete healing
Burke *et al*., 1991	Analysis of Anorectal lesions.	Which follow-ups of the evolution of the wounds were carried out, aiming to guarantee the best results as the healing progressed.
Davis and Wastell, 2000	Tensionometry	Which mature scars were tensioned until rupture using a device, aiming to assess tissue resistance.
Howard *et al*., 2013	Gustilo–Anderson grade Prospective analysis of tibial fractures and infections	Which consists of a classification system for exposed or composite fractures, according to size, depth, soft tissue damage, contamination, fracture fragmentation, periosteum peeling, skin coverage, and neurovascular injuries. The method aims to guide the most appropriate way to handle each case.

It is possible that the citations do not correspond to the first records of each method described.

3.4. Primary Results

The WHO clinical staging of HIV/AIDS for adults and adolescents has been adopted for the classification of infected individuals aged 15 years and above (Table 4). Ten studies included in our review evaluated wound healing in different stages of HIV infection (83.33%) whereas two studies (16.67%) did not report the stage of infection. Of these, 3 articles (25%) reported stage 0 to 4; 2 articles (16.67%) reported stage 0 to 2; 1 article (8.33%) reported stage 0 to 3; 2 articles (16.67%) reported stage 1 to 4; 1 article (8.33%) each reported stage 2 to 4; and 1 article (8.33%) only reported stage 4 of HIV infection.

Table 4: Revised WHO clinical staging of HIV/AIDS for adults and adolescents (WHO, 2005).

Primary HIV infection
• Asymptomatic
• Acute retroviral syndrome
Clinical stage 1
• Asymptomatic
• Persistent generalized lymphadenopathy (PGL)
Clinical stage 2

- Moderate unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory tract infections (RTIs, sinusitis, bronchitis, otitis media, pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulcerations
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infections of fingers

Clinical stage 3

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

- Severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhoea for longer than one month
- Unexplained persistent fever (intermittent or constant for longer than one month)
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (TB) diagnosed in last two years
- Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Conditions where confirmatory diagnostic testing is necessary

- Unexplained anaemia (< 8 g/dl), and or neutropenia (<500/mm^3) and or
- thrombocytopenia (<50 000/ mm^3) for more than one month

Clinical stage 4

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe or radiological bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)
- Oesophageal candidiasis
- Extrapulmonary TB
- Kaposi's sarcoma
- Central nervous system (CNS) toxoplasmosis
- HIV encephalopathy

Conditions where confirmatory diagnostic testing is necessary:

- Extrapulmonary cryptococcosis including meningitis
- Disseminated non-tuberculous mycobacteria infection
- Progressive multifocal leukoencephalopathy (PML)
- Candida of trachea, bronchi or lungs
- Cryptosporidiosis
- Isosporiasis

• Visceral herpes simplex infection
• Cytomegalovirus (CMV) infection (retinitis or of an organ other than liver, spleen or lymph nodes)
• Any disseminated mycosis (e.g., histoplasmosis, coccidiomycosis, penicilliosis)
• Recurrent non-typhoidal salmonella septicaemia
• Lymphoma (cerebral or B cell non-Hodgkin)
• Invasive cervical carcinoma
• Visceral leishmaniasis

Forty-one percent of the articles (n=5) showed that there is a relationship between CD4+ levels and the effectiveness and quality of healing. However, 3 studies (25%) did not find a link between these factors and 3 articles (25%) did not consider the effect of CD4+ count on wound healing or did not report it. In addition, 2 studies (16.67%) indicated that HIV+ or HIV- status is not determinant for wound healing in patients with strong immune systems, but that healing may be compromised only for symptomatic HIV cases (when AIDS develops and the immune system is already compromised). Figure 4, discussed later, summarizes the main mechanism for the role of CD4+ in the cutaneous wound healing process through the four phases of wound healing.

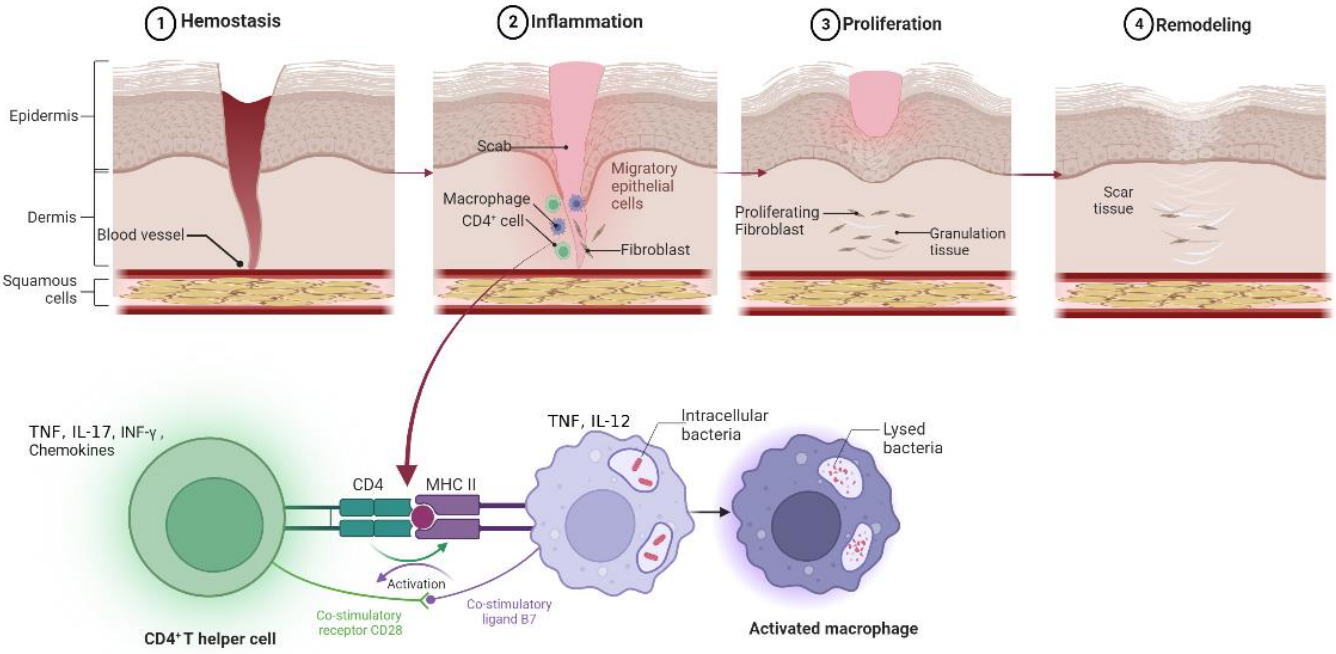
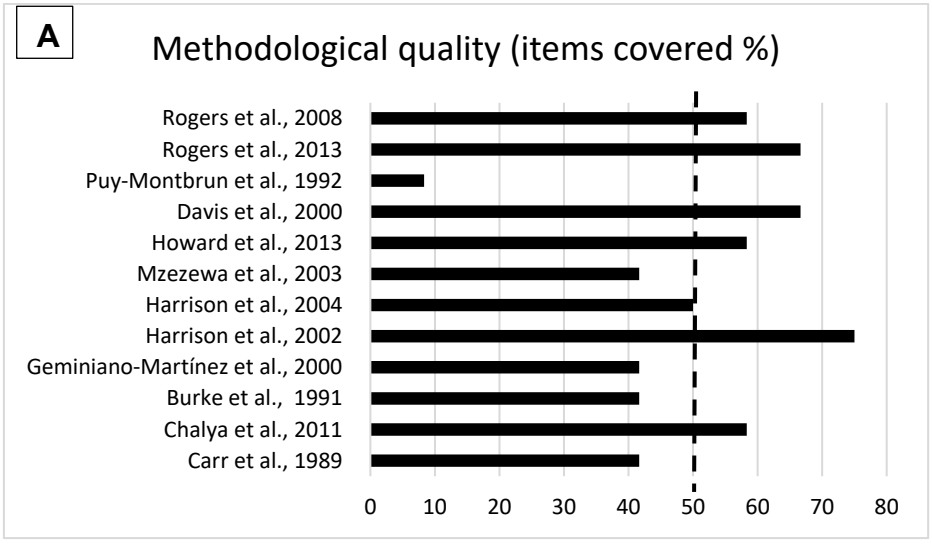


Figure 4 | **Mechanism of skin wound healing process.** A) Progression of the four phases of wound healing; Hemostasis, Inflammation, Proliferation and Remodelling. B) Activation of

macrophages by the interaction of peptide antigen with CD4 receptor and costimulatory receptor of T-helper cell.

3.5. Risk of Bias

The results of the methodological quality analysis show that most of the studies that meet more than 50% of the analyzed methodological quality criteria were carried out from the 2000s onwards. None of the studies met all the methodological criteria, and the average percentage quality of all studies reviewed was 50.69% (Figure 5a). The percentage risk of bias for each item across all the studies included in the systematic review is shown in Figure 5b. The result of the risk of bias assessment of individual studies is presented in Figure 5c. No study showed a low risk of bias for all categories analyzed. Regarding selection bias, sequence generation processes were not reported or randomized in 41.67% of the studies (n=5). Regarding allocation bias, allocation processes were not reported or randomized in 100% of the studies. Nine studies (75%) did not report information on performance bias or informed that participants and patients were not blinded. Ten studies (83.33%) did not blind their outcome evaluators or did not report it. Three (3) studies (25%) did not report or did not adequately address the incomplete results. Regarding reporting bias, 25% of the studies did not present reports free of biased selections. In the wound healing category, 7 of the studies (58.33%) did not present healing periods or did so in a confusing way. Six studies (50%) did not present or did not describe ethical council approval, three studies (25%) did not present or did not describe statistical analyses and four studies (33.33%) either did not present or incompletely presented the results of all the analyses described. In terms of applicability, only 2 (16.67%) were not directly linked to the theme of this review, and 7 of the 12 articles (58.33%) had or could have other types of bias not included in this analysis.



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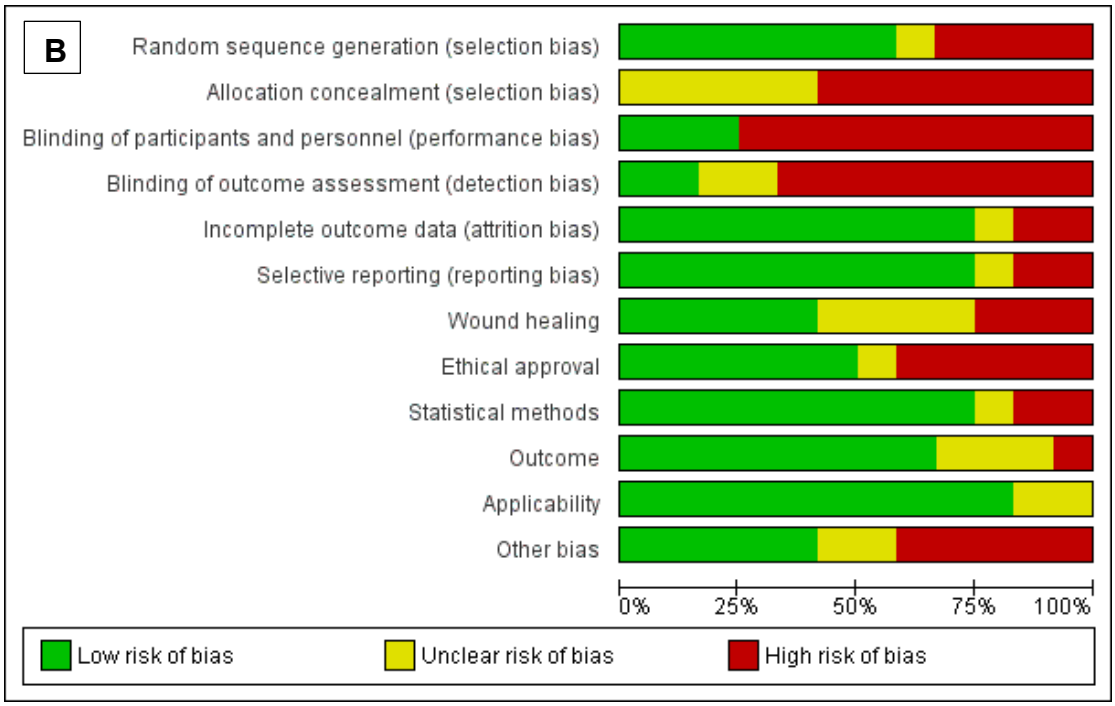

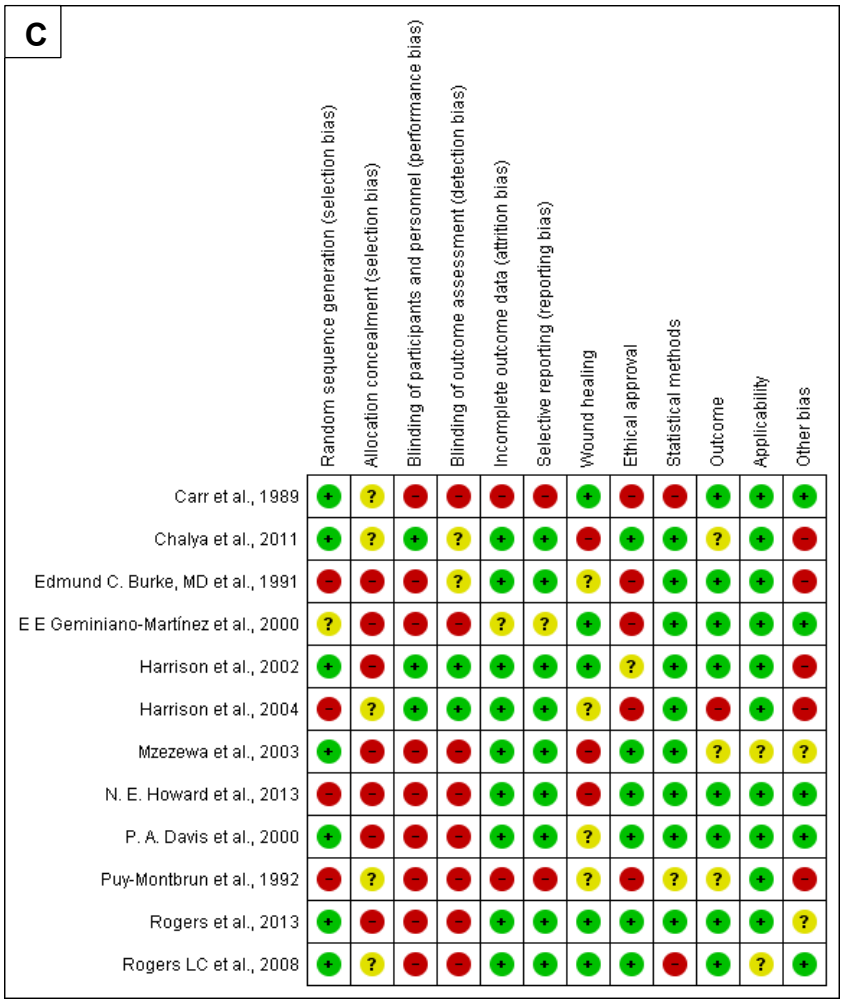

Figure 5 | **A) Methodological quality score of the articles included in the study; B) Risk of Bias (RoB) analysis for each evaluated characteristic expressed as percentages (%).** Analysis was performed using SYRCLE's Risk of Bias (RoB) technique, where absent or incomplete descriptions characterized the risk of bias. **C). Risk of bias summary of authors' judgments** about the risk of bias items for each study included in the review. Green: low risk of bias; Yellow: unclear risk of bias; and Red: high risk of bias.

4. DISCUSSION

Delayed wound healing in HIV/AIDS patients is known to cause wound infections that could increase pain, prolong the duration of stay in the hospital and further weaken an already compromised immune system. The socio-economic status of the patient is equally important because the huge financial burden of purchasing medications and managing the disease can also affect wound healing time, especially in sub-Saharan Africa (Weledji *et al*., 2012). In the present study, we investigated the effect of HIV seropositivity status on wound closure in comparison with uninfected individuals. Thus, we performed a structured search on three databases and identified 12 studies that were developed in a total of 9 countries (5 of them on the African continent, 2 on the European continent, and 2 in North America). The distribution of studies across various continents indicates a possible widespread interest in the topic of the study, as HIV infection is present in all continents and countries of the world. The strikingly high prevalence of studies on wound healing in HIV patients across the African continent observed in our study corroborates with the high prevalence of HIV in sub-Saharan Africa. The inclusion of male and female participants showed that most studies considered key populations of HIV infections including but not limited to commercial sex workers and their clients, homosexual men, drug addicts and those who have identified as transgender (UNAIDS, 2022).

Overall, despite the high global prevalence of HIV, we observed that there is a paucity of information on studies on wound care in HIV patients or underreporting of such studies as only 12 studies met our eligibility criteria. All but three studies reported entirely different methods for the assessment of wound healing among studied participants. The reason for this could be because of the broad opposing opinions of clinicians on wound care. The adoption of a universal wound assessment template in addition to the distinct observations of clinicians on wound care could lead to a more robust assessment of wounds and wound healing time (Nagle *et al*., 2022).

In our review, most wounds resulted from surgical procedures. In a recent cohort study by Chetter *et al*. (2019), a median time to healing of 86 days was reported for surgical wounds. The results from this study show a similar time of healing in HIV patients with surgical wounds. Contrarily, burn wounds took a longer time to heal in HIV patients when compared to non-HIV

patients and even resulted in significantly higher cases of mortality even though skin grafting was used as a cointervention (Chalya *et al*., 2011). This high mortality rate might be due to wound infections, septicemias, and the immunocompromised status of HIV patients with burn injuries (Tiwari, 2012). More so, because of the longer duration it takes for burn wounds to heal, and the herculean management processes involved, burn specialists recommend burn prevention, especially in HIV patients (Tiwari, 2012). Strikingly, anorectal lesions, which are more common in males than females, were reported in several studies we reviewed. The high number of anorectal wounds in HIV patients might be due to forceful sexual intercourse, anal sex in homosexual men, fisting or injuries resulting from the insertion of a foreign body. The delay in wound healing of such anorectal wounds might be due to continuous faecal soiling and difficulty in dressing such wounds because the anus has to be left open (Mittal *et al*., 2021).

Although no study reported the role of nutrition in wound healing time, food rich in vitamins A and C are important for wound healing and immune system function and could offer tremendous benefits to HIV patients (Garcia-Prats *et al*., 2010). Administration of antibiotics such as cephazolin, ciprofloxacin and cloxacillin reported by three studies indicate the occurrence of bacterial infections, which is a characteristic feature of wounds with delayed healing (Weledji *et al*., 2012). Such antibiotics foster healing by killing or slowing the growth of the causal microorganism thereby preventing it from spreading or getting worse (Norman *et al*., 2016).

The WHO clinical stages of HIV infection are important for the baseline assessment of HIV care and for the management of HIV+ patients (Weinberg and Kovarik, 2010). Although ten studies reported wound healing in patients with different clinical stages of HIV, there was no direct relationship between any of the four clinical stages of HIV and prolonged wound healing time. However, the analyses of the selected articles demonstrate the possible existence of an influence of the $CD4^+$ count on the quality and time of wound healing in patients even though there was no agreement on the value of $CD4^+$ levels in the respective studies. Patients whose $CD4^+$ levels were between 200 and 400 cells/µl showed delayed healing compared to those with higher values except they were receiving ART. Preoperative $CD4^+$ levels were considered in HIV+ patients that underwent surgeries but there was no correlation between increased risk of infections in early wounds and low $CD4^+$ levels postoperatively. There was, however, a consensus that wound healing time was slower or worsened if the $CD4^+$ levels were extremely abnormal ($\leq$ 200 cells/µl).

Successful wound healing occurs via four sequential and overlapping phases; hemostasis, inflammation, proliferation, and remodeling (Alqatawni *et al*., 2020). A possible

explanation for how reduced $CD4^+$ levels affect wound healing is that it prolongs the inflammation phase of wound healing which allows for increased blood flow in the damaged blood vessel and leukocytes infiltration of the wound area (Berenguer-Pérez *et al*., 2019; Alqatawni *et al*., 2020). $CD4^+$ cells, which are also T- helper cells, communicate with macrophages during the inflammation phase of wound healing. Activated $CD4^+$ cells produce TNF, IL-17, and other inflammatory chemokines which stimulate macrophage migration to the wound site. The peptide antigen of the MHC class II receptor of the macrophage then binds to the CD4 receptors and this binding activates the macrophage. Simultaneously, there is a co-stimulatory interaction between macrophages and $CD4^+$ cells, mediated by the B7 ligand of macrophages and CD28, a coreceptor of $CD4^+$ cells, that further activates macrophages. Activated macrophages are important for the phagocytosis of pathogens and the secretion of inflammatory chemokines which can, in turn, activate $CD4^+$ cells, thereby enhancing the overall completion of the inflammation phase. Thus, a low $CD4^+$ count will forestall the activation of macrophages and delay the wound-healing process in HIV+ patients.

4.1 Limitation

Despite the methodological advantages present in systematic reviews that give this literary style a high level of reliability and impartiality, there are limitations and such limitations were present in our review. The present results are relevant as they demonstrate a significant relationship between the levels of CD4+ cells in the patient's blood and a better healing outcome, independent of HIV status. However, these results should be considered with some caution given the low number of articles found that met all the eligibility criteria, which makes the evidence less concise. In addition, some of the reviewed articles needed to be adapted, because even though they did not perfectly fulfill all the criteria, they proved to be relevant to the analyses carried out and were eventually included. Another relevant factor for the limitations in our review was the number of topics evaluated as "high risk of bias" in Syrcle's tool. This fact is mainly because most of the studies reviewed selected patients who sought treatment in hospitals and followed criteria different from those that would be desirable for animal models. The great difference between the dates of each study and the very variable forms of analysis methods used should also be taken into account. Part of the studies did not describe all the variables that were taken into account, which is described in tables 2 and 3 as "not described", including the absence of data on the performance of statistical analyses. Our results also point to a need for standardization of data collection methods for voluntary studies carried out with humans, since the large discrepancy between the ways each author collected data and

analyzed results was one of the main reasons for the difficulties of the analyses of the present review.

5. CONCLUSION

The clinical evidence from the studies reviewed suggests that wound closure is impaired in HIV+ patients when compared to healthy uninfected humans. A low $CD4^+$ count further worsened the wound-healing process of skin lesions. Thus, this study highlights the importance of preserving the immune system of HIV-positive patients to maintain a good pattern of healing, especially for skin wounds.

Conflicts of Interest

We declare that there are no conflicts of interest.

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6. REFERENCES

Alqatawni, A., Sharma, A.L., Attilus, B., Tyagi, M. and Daniel, R., 2020. Shedding light on the role of extracellular vesicles in HIV infection and wound healing. Viruses, 12(6), p.584.

Altman, K., Vanness, E. and Westergaard, R.P., 2015. Cutaneous manifestations of human immunodeficiency virus: a clinical update. *Current infectious disease reports*, *17*(3), pp.1-6.

Berenguer Pérez, M., López-Casanova, P., Sarabia Lavín, R., González de la Torre, H. and Verdú-Soriano, J., 2019. Epidemiology of venous leg ulcers in primary health care: Incidence and prevalence in a health centre—A time series study (2010-2014). International Wound Journal, 16(1), pp.256-265.

Burke, E.C., Orloff, S.L., Freise, C.E., Macho, J.R. and Schecter, W.P., 1991. Wound healing after anorectal surgery in human immunodeficiency virus–infected patients. *Archives of Surgery*, *126*(10), pp.1267-1271.

Carr, N.D., Mercey, D. and Slack, W.W., 1989. Non-condylomatous perianal disease in homosexual men. *British Journal of Surgery*, *76*(10), pp.1064-1066.

Chalya, P.L., Ssentongo, R. and Kakande, I., 2011. HIV seroprevalence and its effect on outcome of moderate to severe burn injuries: A Ugandan experience. *Journal of trauma management & outcomes*, *5*(1), pp.1-7.

Chetter, I.C., Oswald, A.V., McGinnis, E., Stubbs, N., Arundel, C., Buckley, H., Bell, K., Dumville, J.C., Cullum, N.A., Soares, M.O. and Saramago, P., 2019. Patients with surgical wounds healing by secondary intention: a prospective, cohort study. International Journal of Nursing Studies, 89, pp.62-71.

Clint, S.A., Eastwood, D.M., Chasseaud, M., Calder, P.R. and Marsh, D.R., 2010. The "Good, Bad and Ugly" pin site grading system: A reliable and memorable method for documenting and monitoring ring fixator pin sites. Injury, 41(2), pp.147-150.

Davis, P.A. and Wastell, C., 2000. A comparison of biomechanical properties of excised mature scars from HIV patients and non-HIV controls. *The American journal of surgery*, *180*(3), pp.217-222.

Eberle, J. and Gürtler, L., 2012. HIV types, groups, subtypes and recombinant forms: errors in replication, selection pressure and quasispecies. *Intervirology*, *55*(2), pp.79-83.

Esbjörnsson, J., Jansson, M., Jespersen, S., Månsson, F., Hønge, B.L., Lindman, J., Medina, C., Da Silva, Z.J., Norrgren, H., Medstrand, P. and Rowland-Jones, S.L., 2019. HIV-2 as a model to identify a functional HIV cure. *AIDS research and therapy*, *16*(1), pp.1-12.

Fanales-Belasio, E., Raimondo, M., Suligoi, B. and Buttò, S., 2010. HIV virology and pathogenetic mechanisms of infection: a brief overview. *Annali dell'Istituto superiore di sanita*, *46*, pp.5-14.

Furch, B.D., Koethe, J.R., Kayamba, V., Heimburger, D.C. and Kelly, P., 2020. Interactions of schistosoma and HIV in sub-Saharan Africa: a systematic review. *The American Journal of Tropical Medicine and Hygiene*, *102*(4), p.711.

García, I.L. and Marsh, M., 2020. A biophysical perspective on receptor-mediated virus entry with a focus on HIV. *Biochimica et Biophysica Acta (BBA)-Biomembranes*, *1862*(6), p.183158.

Garcia-Prats, A.J., McMeans, A.R., Ferry, G.D. and Klish, W.J., 2010. Nutrition and HIV/AIDS. HIV Curriculum, 286, pp.4-5.

Geminiano-Martínez, E.E., Ruíz-Esparza, J.P., Villanueva-Sáenz, E., JF, A.T.F. and Parrado-Montaño, J., 2000. Anorectal surgery in patients infected with human immunodeficiency virus. Revista de Gastroenterologia de Mexico, 65(4), pp.152-158.

Gomes, D., Serra, M., Souza, M., Gama, C., Pereira, M. and Serra, A., 2001. Extreme Case of Survival in Severely Burnt Patient-Case Report. Revista Brasileira de Cirurgia Plástica, 15(1), pp.73-78.

Gray, J.M. and Cohn, D.L., 2013, February. Tuberculosis and HIV coinfection. In *Seminars in respiratory and critical care medicine* 34(1): 32-43. Thieme Medical Publishers.

Grønborg, H.L., Jespersen, S., Hønge, B.L., Jensen-Fangel, S. and Wejse, C., 2017. Review of cytomegalovirus coinfection in HIV-infected individuals in Africa. *Reviews in medical virology*, *27*(1), p.e1907.

Han, G. and Ceilley, R., 2017. Chronic wound healing: a review of current management and treatments. *Advances in therapy*, *34*(3), pp.599-610.

Harrison, W.J., Lewis, C.P. and Lavy, C.B.D., 2002. Wound healing after implant surgery in HIV-positive patients. *The Journal of bone and joint surgery. British volume*, *84*(6), pp.802-806.

Harrison, W.J., Lewis, C.P. and Lavy, C.B.D., 2004. Open fractures of the tibia in HIV positive patients: a prospective controlled single-blind study. *Injury*, *35*(9), pp.852-856.

Hooijmans, C.R., Rovers, M.M., de Vries, R., Leenaars, M., Ritskes-Hoitinga, M. and Langendam, M.W., 2014. SYRCLE's risk of bias tool for animal studies. *BMC medical research methodology*, *14*(1), pp.1-9.

Howard, N.E., Phaff, M., Aird, J., Wicks, L. and Rollinson, P., 2013. Does human immunodeficiency virus status affect early wound healing in open surgically stabilised tibial fractures? A prospective study. *The Bone & Joint Journal*, *95*(12), pp.1703-1707.

Khalid, K., Padda, J., Khedr, A., Ismail, D., Zubair, U., Al-Ewaidat, O.A., Padda, S., Cooper, A.C. and Jean-Charles, G., 2021. HIV and Messenger RNA (mRNA) Vaccine. *Cureus*, *13*(7).

Lazarus, G.S., Cooper, D.M., Knighton, D.R., Margolis, D.J., Percoraro, R.E., Rodeheaver, G. and Robson, M.C., 1994. Definitions and guidelines for assessment of wounds and evaluation of healing. *Wound repair and regeneration*, *2*(3), pp.165-170.

Macdonald, J.M. and Geyer, M.J. 2010. *Wound and lymphoedema management*. World Health Organization.

Mahy, M., Marsh, K., Sabin, K., Wanyeki, I., Daher, J. and Ghys, P.D., 2019. HIV estimates through 2018: data for decision-making. *AIDS (London, England)*, *33*(Suppl 3), p.S203.

McMeeking, A., Kim, I., Ross, F., Ayello, E.A., Brem, H., Linton, P. and O'Neill, D.K., 2014. Wounds in patients with HIV. *Advances in skin & wound care*, *27*(9), pp.396-403.

Mirzaei, H., McFarland, W., Karamouzian, M. and Sharifi, H., 2021. COVID-19 among people living with HIV: a systematic review. *AIDS and Behavior*, *25*(1), pp.85-92.

Mittal, K., Bora, A., Setha, A., Patel, B., Chavan, D.D., Pelleti, P.K., Shararooni, S.A. and Rathod, R., 2021. Management of Anorectal Wounds. J Indian Med Assoc, 119(5), pp.89-94.

Mzezewa, S., Jönsson, K., Sibanda, E., Åberg, M. and Salemark, L., 2003. HIV infection reduces skin graft survival in burn injuries: a prospective study. *British journal of plastic surgery*, *56*(8), pp.740-745.

Nagle, S.M., Stevens, K.A. and Wilbraham, S.C., 2022. Wound assessment. In StatPearls [Internet]. StatPearls Publishing.

Nagu, T.J., Bakari, M. and Matee, M., 2008. Hepatitis A, B and C viral co-infections among HIV-infected adults presenting for care and treatment at Muhimbili National Hospital in Dar es Salaam, Tanzania. *BMC Public Health*, *8*(1), pp.1-7.

Nanfuka, E.K., Kyaddondo, D., Ssali, S.N. and Asingwire, N., 2019. Paying to normalize life: monetary and psychosocial costs of realizing a normal life in the context of free antiretroviral therapy services in Uganda. *Journal of the International Association of Providers of AIDS Care (JIAPAC)*, *18*, p.2325958219859654.

Norman, G., Dumville, J.C., Mohapatra, D.P., Owens, G.L. and Crosbie, E.J., 2016. Antibiotics and antiseptics for surgical wounds healing by secondary intention. Cochrane Database of Systematic Reviews, (3).

Olsson, M., Järbrink, K., Divakar, U., Bajpai, R., Upton, Z., Schmidtchen, A. and Car, J., 2019. The humanistic and economic burden of chronic wounds: a systematic review. *Wound Repair and Regeneration*, *27*(1), pp.114-125.

Page, M.J., McKenzie, J.E., Bossuyt, P.M. et al. 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev., **10**: 89. https://doi.org/10.1186/s13643-021-01626-4

Parekh, 2019. Ending HIV in America - Policy and Program Insights from Local Health Agencies and Providers. Accessed 24th February 2022 via https://bipartisanpolicy.org/download/?file=/wp-content/uploads/2019/09/Ending-HIV-in-America.pdf

Puy-Montbrun, T., Denis, J., Ganansia, R., Mathoniere, F., Lemarchand, N. and Arnous-Dubois, N., 1992. Anorectal lesions in human immunodeficiency virus-infected patients. *International journal of colorectal disease*, *7*(1), pp.26-30.

Remme, M., Siapka, M., Sterck, O., Ncube, M., Watts, C. and Vassall, A., 2016. Financing the HIV response in sub-Saharan Africa from domestic sources: moving beyond a normative approach. *Social Science & Medicine*, *169*, pp.66-76.

Rogers, J.H., Odoyo-June, E., Jaoko, W. and Bailey, R.C., 2013. Time to complete wound healing in HIV-positive and HIV-negative men following medical male circumcision in Kisumu, Kenya: a prospective cohort study. *PloS one*, *8*(4), p.e61725.

Rogers, L.C., Bevilacqua, N.J. and Armstrong, D.G., 2008. The use of marrow-derived stem cells to accelerate healing in chronic wounds. *International wound journal*, *5*(1), pp.20-25.

Taraphdar, P., Guha, R.T., Haldar, D., Chatterjee, A., Dasgupta, A., Saha, B. and Mallik, S., 2011. Socioeconomic consequences of HIV/AIDS in the family system. *Nigerian medical journal: journal of the Nigeria Medical Association*, *52*(4), p.250.

Tinarwo, P., Zewotir, T., Yende-Zuma, N., Garrett, N.J. and North, D., 2019. An evaluation to determine the strongest CD4 count covariates during HIV disease progression in women in South Africa. *Infectious diseases and therapy*, *8*(2), pp.269-284.

Tiwari, V.K., 2012. Burn wound: How it differs from other wounds?. Indian journal of plastic surgery, 45(02), pp.364-373.

UNAIDS, 2022. www.unaids.org/en/resources/fact-sheet. Accessed 24th February 2022.

United Nations, 2016. Political declaration on HIV and AIDS: on the fast-track to accelerate the fight against HIV and to end the AIDS epidemic by 2030. New York.

Wang, Z.D., Wang, S.C., Liu, H.H., Ma, H.Y., Li, Z.Y., Wei, F., Zhu, X.Q. and Liu, Q., 2017. Prevalence and burden of Toxoplasma gondii infection in HIV-infected people: a systematic review and meta-analysis. *The Lancet HIV*, *4*(4), pp.e177-e188.

Weinberg, J.L. and Kovarik, C.L., 2010. The WHO clinical staging system for HIV/AIDS. AMA Journal of Ethics, 12(3), pp.202-206.

Weledji, E.P., Kamga, H.L.F., Assob, J.C. and Nsagha, D.S., 2012. A critical review on HIV/AIDS and wound care. African Journal of Clinical and Experimental Microbiology, 13(2), pp.66-73.

WHO., 2005. Clinical Staging of HIV/AIDS and HIV/AIDS Case Definitions for surveillance in Africa Region. World Health Organization.

Wilson, A.P.R., Sturridge, M.F., Treasure, T. and Grüneberg, R.N., 1986. A scoring method (ASEPSIS) for postoperative wound infections for use in clinical trials of antibiotic prophylaxis. The Lancet, 327(8476), pp.311-312.

Wolcott, R.D., Cutting, K.F., Dowd, S.E. and Percival, S.L., 2010. Types of wounds and infections. *Microbiology of wounds*, pp.219-32.

Wysocki, A.B., 2002. Evaluating and managing open skin wounds: colonization versus infection. *AACN Advanced Critical Care*, *13*(3), pp.382-397.

7. SUPPLEMENTARY MATERIAL

Supplementary Table 1 (Table S1) | Complete search strategy with search filters and number of studies recovered in the three databases (PubMed-Medline, Scopus and Web of Science).

Data base	Descriptors	Items Found	Time	Date
PUBMED	#1 Filter skin (filter PUBMED) ("humans"[MeSH Terms] OR human[TIAB])	-	-	-
	#2 Filter wound healing (filter PUBMED) ("wound healing"[MeSH Terms] OR wound healing[TIAB])	-	-	-
	# 3 Filter HIV (filter PUBMED) ("hiv"[MeSH Terms] OR HIV[TIAB] OR "acquired immunodeficiency syndrome"[MeSH Terms] OR AIDS[TIAB] OR "hiv infections"[MeSH Terms] OR hiv infections[TIAB])	-	-	-
	#4 Fillter skin (filter PUBMED) (“Skin”[MeSH terms] OR “Dermis”[MeSH terms] OR “Granulation Tissue”[MeSH terms] OR “Epidermis”[MeSH terms] OR “Keratinocytes”[MeSH terms] OR “Integumentary System”[MeSH terms] OR “Dermatology”[MeSH terms] OR “Dermoscopy”[MeSH terms] OR “Wounds and Injuries”[MeSH terms] OR “Fibrosis”[MeSH terms] OR “Skin injuries”[TIAB] OR “Skin fibrosis”[TIAB] OR “Skin scars”[TIAB] OR “Skin	-	-	-

	cicatriz"[TIAB] OR "Cicatrix"[MeSH terms])			
	Total: #1 and #2 and #3 and #4	**201**	**15:08:23**	**31/03/2021**
Data base	**Descriptors**	**Items Found**	**Time**	**Date**
SCOPUS	**#1 Filter humans (TITLE-ABS-KEY("humans"))**	**-**	**-**	**-**
	#2 Filter wound healing (TITLE-ABS-KEY("wound healing"))	**-**	**-**	**-**
	#3 Filter HIV (TITLE-ABS-KEY("hiv") OR TITLE-ABS-KEY("HIV") OR TITLE-ABS-KEY("acquired immunodeficiency syndrome") OR TITLE-ABS-KEY("AIDS") OR TITLE-ABS-KEY("hiv infections" OR TITLE-ABS-KEY("hiv infections"))	**-**	**-**	**-**

	#4 (TITLE-ABS-KEY(Skin) OR TITLE-ABS-KEY(Dermis) OR TITLE-ABS-KEY("Granulation Tissue") OR TITLE-ABS-KEY(Epidermis) OR TITLE-ABS-KEY(Keratinocyte*) OR TITLE-ABS-KEY(Integumentary System) OR TITLE-ABS-KEY(Dermatology) OR TITLE-ABS-KEY(Dermoscopy) OR TITLE-ABS-KEY(Skin wounds) OR TITLE-ABS-KEY(Skin injuries) OR TITLE-ABS-KEY(Skin fibrosis) OR TITLE-ABS-KEY(Skin scar*) OR (Skin cicatrix))	**-**	**-**	**-**
	Total: #1 and #2 and #3 and #4	**215**	**15:17:56**	**31/03/2021**
Data base	**Descriptors**	**Items Found**	**Time**	**Date**
WEB of SCIE	**#1 Filter humans TS=humans**	**-**	**-**	**-**
	#2 Filter wound healing TS=wound healing	**-**	**-**	**-**
	#3 Filter HIV TS=hiv OR TS=HIV OR TS=acquired immunodeficiency syndrome OR TS=AIDS OR TS=hiv infections	**-**	**-**	**-**

N	**#4 Filter**	**-**	**-**	**-**
C	**TS=Skin OR TS=Dermis OR**			
E	**TS=Granulation tissue OR TS=Epidermis**			
	OR TS=Keratinocyte OR			
	TS=Integumentary system OR			
	TS=Dermatology OR TS=Dermoscopy OR			
	TS=Skin wounds OR TS=Skin injuries OR			
	TS=Skin fibrosis OR TS=Skin scar OR			
	TS=Skin cicatrix			
	Total: #1 and #2 and #3 and #4	**129**	**14:13:38**	**31/03/2021**