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Genetic Diversity of HIV-1 and Transfusion Safety : Systematic Review and Concepts Analysis

Christian Mangala[1,2*], Joseph Fokam[1,3,4], Denis Maulot Bangola[1,2] and Thérèse Nkoa[1,4]

[1]Catholic University of Central Africa (CUCA), Cameroon.
[2]National Public Health Laboratory (NPHL), Gabon.
[3]Chantal Biya International Reference Center (CBIRC), Cameroon.
[4]University of Yaoundé 1 (UY-1), Cameroon.

Authors' contributions

This work was carried out in collaboration among all authors. Author CM designed the study and designed it with authors TN and JF. Author CM wrote the article. All authors have reviewed, read, and accepted the final manuscript.

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ABSTRACT

Background: The genetic diversity of human immunodeficiency virus type 1 (HIV-1) is a real problem facing blood banks. This genetic diversity has a negative impact on diagnostic strategies within the transfusion chain by weakening the security of the donation. The objective of this study is to clarify the concepts emanating from the research project entitled : «Genetic diversity of HIV-1 and its effect on the residual risk in blood transfusion in Gabon».
Methods: This study was the result of a systematic review and a conceptual analysis of several studies that were systematically searched for in databases (PubMed, Google Scholar, and Medline), and whose object was focused on the genetic diversity of HIV -1 and its impact on transfusion safety. Indeed, the information relating to the concepts coming from the full articles was used. These were obtained by reading the most relevant articles. All relevant studies reporting data on HIV-1 genetic diversity and blood safety published in English between January 2012 and December 2020 have been identified for context. The method of conceptual analysis of « Walker and Avant (2005) » was used to clarify the different concepts of our study. The correlation test was used to show the relationship between the concepts.

**Corresponding author: Email: imohu2004@yahoo.fr;*

Results: This systematic review and conceptual analysis study made it possible to determine the variables and to clarify the different concepts (HIV-1, Genetic diversity, Blood transfusion, Residual risk) essential for carrying out our research project entitled: "Genetic diversity of HIV-1 and its effect on the residual risk in blood transfusion". This model made it possible to show the effect of the genetic diversity of HIV-1 on the residual risk in blood transfusion using as model variables : viral load and serological markers (Antibodies and P24 Antigen). Knowledge of molecular strains (URF, CRF, subtypes) during this study made it possible to better identify the molecular strains most involved in the residual risk. Despite its complexity, this conceptual analysis contributed enormously to the understanding of the activities and the quantifiable and non-quantifiable components that participated in our study. Statistical analysis showed that the HIV-1 concept was significantly related to the other three concepts with *P = 0.001*. Likewise for the concept of genetic diversity was also significantly linked to the two other concepts with *P = 0.003*.
Conclusion: The genetic diversity of HIV-1 in the blood transfusion environment contributes significantly to the transmission of HIV from donor to recipient. The mastery of these molecular strains is essential for the various blood banks to ensure a safe blood supply.

Keywords: HIV-1; blood transfusion; genetic diversity; residual risk.

1. INTRODUCTION

The human immunodeficiency virus (HIV) is still present in the world's population. Nevertheless, the most recent data from the World Health Organization (WHO) still show that there are annually nearly 2 million new people infected with HIV and with 36.9 million people living with this chronic infection. in 2020 [1,2].

The molecular epidemiology of HIV around the world reveals that all strains are found in Sub-Saharan Africa in general and Central Africa in particular with an overwhelming majority of non-B strains. These molecular strains could negatively impact the safety of blood donation in these endemic countries [1,3,4]. The geographic distribution of HIV strains differs from continent to continent, region to region. But population movements including immigration, tourism, and international travel are changing the molecular map of HIV every day, which is no longer static. This constitutes a health problem, especially in an African transfusion environment [5].

Blood transfusion goes a long way in improving the health of patients. It intervenes especially in anemic children due to malaria, in sickle cell disease, in pregnant women, and surgical interventions. But this intervention must be carried out within the safety standards of the blood donation throughout the transfusion chain [6].

Transfusion safety in blood banks is a major concern that concerns all stakeholders in blood donation around the world in general and in particular in countries with limited resources. Blood transfusion safety is still far from being mastered in African countries [7]. In general, in blood banks, there are more voluntary and family donors who mobilize for the donation. As a result, the risk of transmission of pathogens is higher in this category of donors [8,9]. The threat to the safety of donating blood can be linked on the one hand to the existence of different molecular strains in donors which lead to the variability of the antigens, which gives rise to the possibility of antibodies of low affinity towards “standard HIV subtype B” antigens used by screening tests [10,11].

And these molecular variants make screening difficult and undermine transfusion safety. This further shows the need to improve all transfusion safety conditions, at the start and the end of the transfusion chain to ensure a blood supply devoid of any pathogens.

This study based on a systematic review and an analysis of concepts, aims to clarify the different concepts of the research project entitled « genetic diversity of HIV-1 and its effect on the residual risk in blood transfusion in Gabon ».

2. METHODS

2.1 Study Design

This study is part of a research project on "the genetic diversity of HIV-1 and its effect on the residual risk in blood transfusion in Gabon". This study was the result of a systematic review and concept analysis of several studies that focused on the genetic diversity of HIV-1 and blood safety. Indeed, we used information relating to

the concepts from the full articles. These were obtained by reading the most relevant articles. All relevant studies reporting data on HIV-1 genetic diversity and blood safety published in English between January 2012 and December 2020 have been identified for context. It will be a question here of analyzing the different concepts of our study using the method of conceptual analysis of « Walker and Avant (2005) » which will allow us to clarify the different concepts. And for that, we must begin to define the concept, give the goal of the analysis, present the different uses of the concept, enumerate the attributes of the concept, the empirical referents, the antecedents, and consequences of the concept.

2.2 Research Question

The research question for our concept analysis study is : « Do HIV and blood transfusion researchers share the same concepts to describe the genetic diversity of HIV-1 ? ». This research question clarified all the different articulations of concepts related to the context of the study.

2.3 Research Strategy

Studies on the genetic diversity of HIV-1 and transfusion safety were systematically searched for in the various databases, namely PubMed, MEDLINE, Google Scholar and we carried out a manual search in the main transfusion journals. This data search was performed using the following search terms, alone or in combination : « HIV-1 », « genetic diversity », « blood transfusion », « residual risk », « blood safety » and « transfusion transmissible infections ».

2.4 Selection Criteria

The preferred reporting elements for systematic reviews and meta-analysis (PRISMA) of the 2020 guidelines served as a template for the report of this review [12]. Full articles were independently reviewed by two people from the research team for inclusion in the study. But in the event of disagreement between the two researchers, a third researcher is consulted in order to settle this situation. Out of 2106 studies (full articles) that were generated in the different databases, 1008 full articles were deleted with the reason for the presence of duplicates. The independent selection carried out by two reviewers made it possible to retain 172 full articles for a more rigorous evaluation. Then after the evaluation, 90 (52.3%) were retained for the conceptual analysis, and 82 (47.7%) full articles were excluded because they did not contain conceptual definitions of the different concepts. The studies selected met the eligibility criteria, namely published studies looking at the genetic diversity of HIV-1 and transfusion safety, and defining the different study concepts. On the other hand for non-inclusion criteria, these articles were excluded for various reasons such as studies lasting more than 10 years, not defining the concepts, non-coherent and non-exploitable information, and other reasons not allowing to combine these studies with our study (Fig. 1).

2.5 Quality of the Studies Included

The methodological quality of the included studies was assessed using the 9-point scoring system developed by Stanifer et al. [13]. The studies were assessed according to the scoring criteria. If the score was between 1-3, 4-6 or 7-9 then the quality of the studies was rated respectively as low, medium, or high. The authors counted the number of appearances of the different study concepts in each selected article. This made it possible to determine the importance of each concept. This methodology also made it possible to identify the differences and existing relationships between the concepts or between the study variables.

2.6 Data Abstraction

Data extraction was done independently to acquire relevant information contributing to the conduct of this study. And if there was a difference of opinion between the two people responsible for the extraction, a third person was invited to resolve the ambiguity to reach a consensus. All data from eligible studies were extracted. All data abstractions have been verified by all members of the research team. However, studies for which data were not obtained were simply excluded from our study.

2.7 Content Analysis

All full papers that included a conceptual definition of the approach centered on HIV-1 genetic diversity and blood safety were included in the study and submitted for subsequent conventional content analysis, to develop codes based on the actual data, ie in the definitions identified [14]. Each definition was identified and divided into meaningful units which we subsequently coded. The coding sheet was

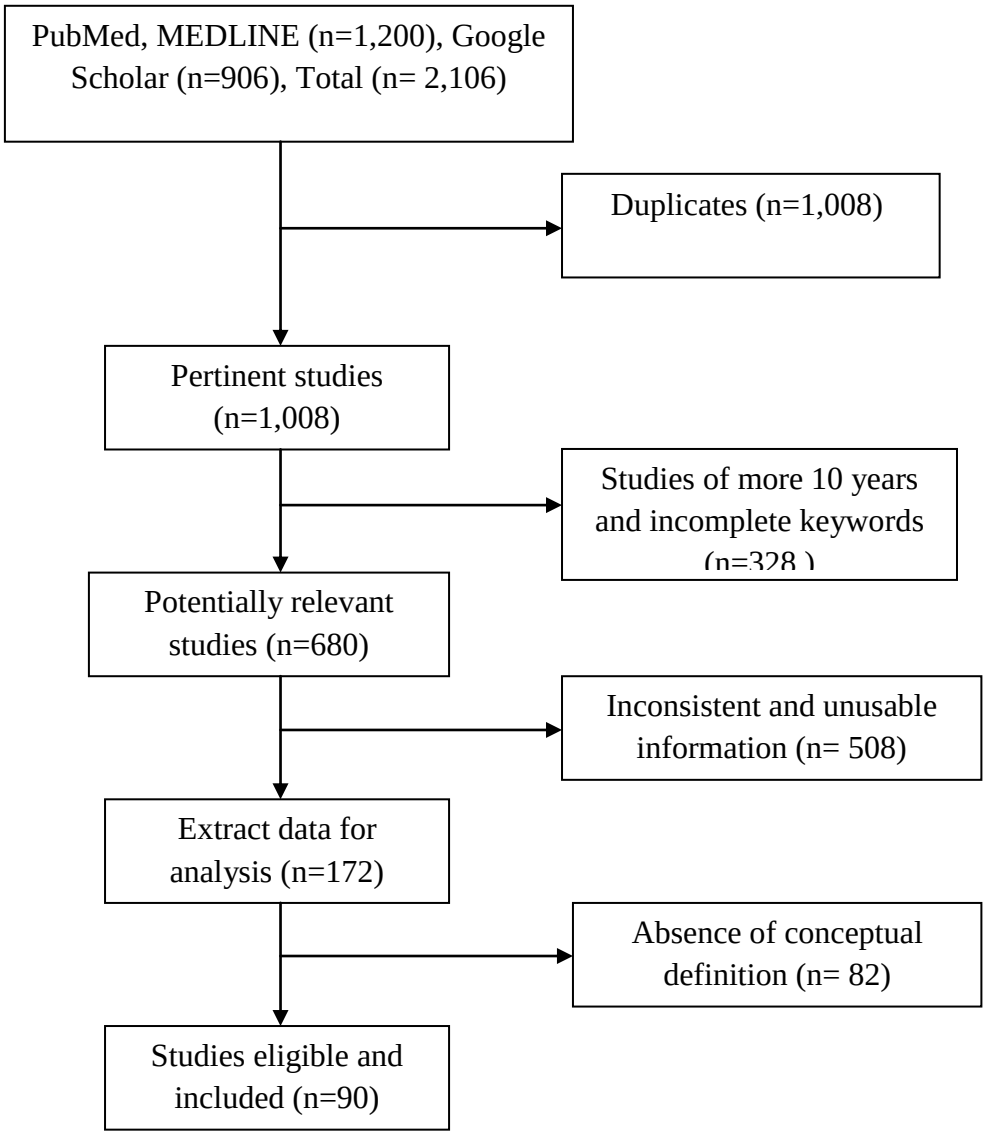

Fig. 1. Flow Diagram for the selection of studies

developed through an iterative process. One author randomly selected 50 full-length articles and initially coded the included definitions to develop a preliminary coding sheet. This process continued until the full articles were exhausted. Coding of full articles was done independently by two members of the research team. The discrepancies that emerged from these multiple coding strategies provided valuable information to refine the coding scheme and were resolved by a discussion [15]. The codes were grouped into significant groups, that is to say, were aggregated into different dimensions centered on the genetic diversity of HIV-1 and blood safety. The coding method had also made it possible to determine the number of times the concept had appeared in each full article. For the concept of HIV-1, it appeared 7,206 times in all eligible articles included in the study. 4,146 times for the concept of genetic diversity, 4,516 times for the concept of blood transfusion and 5,042 times for the concept of residual risk.

2.8 Statistical Analysis

To show the existing relationship between the different concepts, using the coding method allowed us to use the correlation test to determine the Pearson coefficient to show the existing relationship between the different concepts. All data obtained by the coding method was used in digital form. The normality test was used for all variables. Statistical analysis showed that the HIV-1 concept was significantly related

to the other three concepts (Genetic diversity, Residual risk, and blood transfusion) with *P = 0.001.* Likewise for the concept of genetic diversity was also significantly linked to the two other concepts (Residual risk and transfusion) with *P = 0.003*.

3. RESULTS

The choice of these concepts takes into account the field of interest so that the results resulting from the conceptual analysis contribute significantly to the advancement of knowledge and better clarify our research project which is entitled : « Genetic diversity of HIV-1 and its effect on the residual risk in blood transfusion in Gabon ». The conceptual terms for this study are Human Immunodeficiency Virus type 1, Blood transfusion, HIV-1 genetic diversity, and residual risk (Table 1).

3.1 Human Immunodeficiency Virus type 1 (HIV-1)

Several authors defining the concept of HIV agree that HIV is a virus belonging to the Retroviridae family and the genus Lentivirus, which attacks cells of the immune system and destroys them or renders them ineffective. The concept's history stems from animal interspecies contact, although essential to life on earth and evolution, sometimes leads to the transmission of infectious agents to a new host ill-adapted to combat this new pathogen. Indeed, before becoming HIV, this virus had as its first host the chimpanzee, the respective denomination of which is the Simian Immunodeficiency Virus (SIV). It was during a hunt that the man confronted the chimpanzee infected with SIV. During this confrontation, the chimpanzee will inflict a wound on the hunter which will be the route of transmission of the virus from the chimpanzee to humans. This virus-changing host would later be called Human Immunodeficiency Virus (HIV). The goal of the analysis of the HIV-1 concept is to clarify it in all these possible articulations that can lead to understanding the concept clearly and simply. This concept is widely used in clinical practice but also other fields. Yet the contextual basis of this concept is rarely if ever, questioned in medical disciplines. By this, we mean that the situational, relational, temporal, socio-cultural, and clinical contexts in which the concept is relevant, used effectively, and applied in various situations have not been critically examined by these disciplines. The different uses used by some authors are seropositive, AIDS, and serological status. But it is important not to confuse the concept of HIV and AIDS because HIV is a virus of the lentivirus genus while AIDS is a clinical syndrome where there is an immune deficiency in humans. For example, people living with HIV, HIV prevalence, HIV prevention, HIV testing, AIDS diagnosis, AIDS response, national AIDS program, organizations supporting people with AIDS, etc. All these terms refer populationally to HIV-1, which is the virus in question. Several authors use the concept HIV-1 to designate the disease of AIDS to better explain and be better understood by the different layers of the population, but on the other hand, others say that the use of the concept HIV-1 instead of AIDS n is not appropriate as it causes confusion among users. For them, AIDS does not mean HIV-1 and its cause is not caused only by HIV-1 because other germs can induce this syndrome in humans. Likewise, for the use of serological, seropositive, and antiretroviral status, these are uses that directly refer to the concept of HIV-1 in the medical field. Concept attributes are the main characteristics that allow us to designate or describe the concept. The information gathered from all of the selected articles was then analyzed to identify their attributes. Attributes are commonly used to describe the concept through the literature review. The attributes identified in this analysis identify situations, phenomena, experiences, and practices that fall within the concept of HIV-1 or which can be appropriately characterized using the concept of HIV-1. Conceptual analysis shows that transmission of HIV can also occur through the blood.

3.2 Blood Transfusion

Blood transfusion is a therapeutic intervention that makes it possible to reabsorb a deficiency in labile blood products (LBP) in many patients by saving their lives in certain circumstances (accidents, anemia, surgical interventions, etc.). The use of this concept is encountered in the field of transfusion medicine and allows a supply of labile blood products from a donor to a recipient. The information gathered from the literature review was then analyzed to identify the attributes of this concept. However, these attributes are commonly used to describe and designate the concept. The attributes identified in this conceptual analysis make it possible to identify situations, phenomena, and modifications directly affecting the concept as a whole. As attributes of the concept of blood transfusion, the most used are blood donation, donor, blood

bank, transfusion risk, and transfusional setting. In this specific model case, it is important to show that blood transfusion is framed by two barriers, namely medical interview and biological qualification, which ensure transfusion safety. But also to show that these different attributes make it possible to designate and describe the concept of blood transfusion in all these components. Related cases also show that a blood donor can transmit a pathogen to a recipient during the transfusion if the safety of the donation is not well ensured.

3.3 Genetic Diversity

Genetic diversity refers to the plurality, to the molecular variability of the human immunodeficiency virus type 1. But other authors define it as the major characteristic of HIV. This diversity is made up of several molecular strains which recombine over time. Genetic diversity is then the set of characteristics of a viral species in its molecular dimension. The use of genetic diversity is much more encountered in molecular biology. Some authors use words like genetic variability, variants to express the concept. The information gathered from all the articles selected was then analyzed to identify the attributes of this concept. However, these attributes are commonly used to describe and denote the concept of genetic diversity. The attributes identified in this conceptual analysis make it possible to find situations, phenomena, molecular modifications directly affecting the concept of genetic diversity as a whole. As attributes of the concept of genetic diversity, these are molecular variability, molecular variants, and molecular strains. Mutations, subtypes, and recombinant forms (CRF and URF) are also attributes of the concept of genetic diversity. The analysis of the concept of genetic diversity will make it possible to choose the best quantifiable variables that can explain the concept in all its articulations to better understand it. And these same variables of the concept will help to show the implication of genetic diversity on the residual risk in the transfusion environment. Note that knowledge of the variables of the concept has assets in the mastery of epidemiological data and virological monitoring in a patient.

3.4 Residual Risk

Some authors define residual risk as to the risk of transmission of a pathogen during a transfusion, despite the measures of donor selection and screening for biomarkers of viral infection. On the other hand, our definition is this : the residual risk is the risk of transmission of an

Table 1. Summary of the conceptual analysis

	Concepts			
Analysis tools	**HIV-1**	**Genetic diversity**	**Blood transfusion**	**Residual risk**
Attributes	HIV positive Serological statut AIDS	Molecular variability Molecular variants	Blood donation Donor	No specific attribute
Empirical referents	Anti-HIV-1 Ab AgP24 RNA (viral load)	Mutation CRF URF	Biological qualification	Negative serology Positive viral load
Consequences	Chronic infection (HIV-1)	Impact on diagnosis Therapeutic impact	Exposure of the recipient to infections	Acquisition of a chronic disease (case of HIV)
Number of concept appearances	7,206 times	4,146 times	4,516 times	5,042 times
Relationship	Blood Transfusion Genetic Diversity Residual Risk:	Blood Transfusion Residual Risk	Residual Risk HIV-1	Blood Transfusion HIV-1
Benefit of this analysis	Clarification of measurable variables and readjustment of the theme			

AIDS : Acquired ImmunoDeficiency Syndrome; AgP24 : P24 antigen; RNA : RiboNucleic Acid; CRF : Circulating Recombinant Form; URF :Unique Recombinant Form; HIV-1 : Human immunodeficiency virus type 1 ; Anti-HIV-1 Ab : Anti-HIV-1 antibodies

infectious agent from a seronegative donor and of a positive viral load to a recipient during the transfusion despite the taking into account of safety measures. In our current context, this concept is widely used in the field of transfusion. Some authors use it in transfusions of blood and human organs in transfusion medicine. The information collected from all the studies selected was then analyzed to identify no possible attribute that could describe the concept of residual risk in its entirety. The residual risk is still high in some countries around the world given the screening strategies in place that do not respond to the evolution and molecular modification of pathogens, such as HIV-1. The blood supply devoid of any infectious entity is beneficial to the recipient. The emergence of new infections transmissible by transfusion threatens the quality of blood donation, which makes sense to rigorously support screening strategies in blood banks, especially for countries with limited resources.

3.5 Relational Model

The conceptual analysis made it possible to determine the variables essential for carrying out this research project entitled : "Genetic diversity of HIV-1 and its effect on the residual risk in blood transfusion in Gabon". Speaking of variables, we can cite viral load, serological markers (anti-HIV antibodies and P24 antigen). This model has shown the effect of genetic diversity on the residual risk in blood transfusion. Knowledge of molecular strains (URF, CRF, subtypes) during this study made it possible to better identify the molecular strains most involved in the residual risk. Despite its complexity, this conceptual analysis has contributed enormously to the understanding of the activities and the quantifiable and non-quantifiable components that participate in this study.

4. DISCUSSION

The transmission of transfusion-transmissible infections is still a concern for those in charge of blood banks in different world countries. The genetic diversity of HIV-1 is an illustration of the threat to blood safety, especially in endemic countries (with high prevalence). Our systematic review and conceptual analysis study looked at the effect of genetic diversity in HIV-1 on residual risk in transfusion settings. Conceptual analysis revealed that the genetic diversity of HIV-1 had an impact on the residual risk in the transfusional environment. For this, it would be necessary to quantify all the variables of concept, namely : the viral load and the serological markers (anti-HIV antibodies and P24 antigen) and to determine the molecular strains in question. HIV-1 viral load has been shown by some authors to play an important role in interpreting health status, infectivity, and response to treatment [16,17,18,19]. The use of viral load allows speculation about the concept of HIV-1. Therefore, the conceptual analysis of this study made it possible to choose the viral load as the quantifiable variable par excellence of this study given its presence in several conceptual joints of viral transmission. It has also shown the involvement of the molecular components of HIV-1 on the residual risk in blood transfusion [20,21,22]. The serological markers (anti-HIV Ab, AgP24) identified as secondary variables to the concept by their presence throughout the infection would also contribute to the diagnosis of HIV-1 and the interpretation of recent or chronic infection [23]. The empirical referents were viral load and serological markers. Several authors have shown that in seropositive donors receiving antiretroviral treatment and having an undetectable viral load could have an impact on the residual risk in the transfusion environment [24,25,26]. Therefore, in such a situation, virus screening should necessarily involve detection of the viral load by molecular techniques such as RT-PCR and NAT. Transfusion safety is an approach aimed at ensuring the quality of the blood donation and protecting the recipient from any infectious intrusion [27,28,29,30,31]. Nowadays, the demand for blood donation is increasing every day in hospitals around the world, which goes without saying to improve the blood safety system, also taking into account the emergence of infectious diseases transmissible by transfusion [32,33,34,35]. Blood transfusion is one of the routes of transmission of pathogens. Therefore, the security of the donation should be ensured throughout the transfusion chain. Regarding this study, a blood transfusion would be limited to the level of risk of viral transmission of HIV-1. Viral infections threaten the safety of donation in the transfusion environment. Several factors, especially for viral infections, are thought to increase the risk of viral transmission in a transfusion environment [36,37,38,39,40]. Mutations and molecular variants could have a negative impact on the safety of the donation if the screening techniques used do not have a high sensitivity to detect the molecular strain involved. As a result, the recipient would be exposed to any viral transmission and this could

alter the vital prognosis of this recipient. Several authors have shown that the consequence of passive blood safety is exposure to infectious agents transmissible by transfusion. To estimate the efficiency of the transfusion chain, it is necessary a priori determine the transfusion risk [41-45]. Today much has been done with the aim of improving the diagnostic tests used in blood banks, but this does not exclude that these tests have limits (existence of the detection threshold) that could be caused by the genetic diversity of HIV-1 whose mutations are seen every day in infected patients. A recent study carried out in Cameroon reveals that there is a risk of the appearance of a new recombinant form of HIV-1 MO, the detection of which would require appropriate diagnostic tools [46-48]. This study would further show that the genetic diversity of HIV-1 would have an impact on the diagnosis and therefore on the residual risk in blood transfusion. Analysis of this concept would further situate the impact of molecular strains of HIV-1 on residual risk. Some studies have shown that viral load and serology (Antibodies and P2 antigens) were essential in interpreting data evaluating the effectiveness of the donation security system put in place to reduce the risk of HIV transmission in transfusion [1,49-52]. The number of times each concept appears shows its importance in the various full articles included in the study. This would explain that these concepts have been fully exploited by the various authors given their degree of importance. And the correlation test showed that the concepts in this study were significantly related (*P = 0.001*) to each other. This further confirms the importance of this study at the transfusion level.

5. CONCLUSION

The conceptual analysis of this study made it possible to better understand the research project entitled "Genetic diversity of HIV-1 and its effect on the residual risk in blood transfusion in Gabon" and to fill the existing gaps. It also allowed the readjustment of certain component of the study. The genetic diversity of HIV-1 has a considerable influence on the risk of transmission of HIV-1 in the transfusion environment. Ultimately, it should be noted that the conceptual analysis reinforced the scope of this research project in all these scientific and social connections. And also the theme does not present any ambiguity that could have a negative impact on the research activities of this project.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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