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## Exploring the Viral Reservoir and Certain Clinical Factors in Persons Living with Chronic HIV

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### Abstract

**Background:** People are living and thriving with a diagnosis of human immunodeficiency virus (HIV) in the chronic stage of the disease due to antiretroviral therapy. Life expectancy has increased and HIV-associated symptoms have decreased. However, antiretroviral therapy does not completely eradicate the virus so that lingering, long-living HIV proteins remain. A viral reservoir is established in the brain from these detectable HIV proteins, leading to neuroinflammation and HIV-associated symptoms. The objective of this mini-literature review is to explore the effect of this viral reservoir in the continued treatment of chronic HIV infection and neurocognitive symptoms in persons living with chronic HIV as well as the implications for nursing care.

**Methods:** A literature search was performed in the CINAHL, Elsevier, and PubMed databases for articles written in English and published on or after 2000. Keywords were HIV, AIDS, viral reservoir, neurocognition, impaired cognition, and HIV-related symptoms.

**Results:** Of the extracted 200 articles, 25 were selected. They were grouped by topics such as disease management, HIV pathogenesis, HIV-associated neurocognitive disorder (HAND), treatment of HAND, cognitive changes, and screening/assessment techniques. Viral reservoir was a common theme in all topics.

**Conclusion:** The viral reservoir is a common theme in HIV from antiretroviral therapy to the onset and progression of neurocognitive symptoms. Its presence contributes to HIV being treated as a chronic disease. A viral reservoir clinical cycle emerges where the viral reservoir results from the antiretroviral therapy and contributes to the HIV-associated symptoms. Understanding this cycle can be instrumental in the care of persons living with chronic HIV. Nurses can have a significant impact on the treatment that transcends beyond care of the traditional HIV-associated symptoms. Care involves treating the presenting clinical symptoms, the continued effects from the viral reservoir, and the emotional, social, and physical responses to the risk of advancement. Therefore, knowledge of the viral reservoir clinical cycle enhances the care delivered by nurses. This level of care will also promote the active participation of persons living with chronic HIV in their care through communication with the nurse, adherence to antiretroviral therapy, and realization of viral reservoir on quality of life.

**Keywords:** Antiretroviral therapy; Chronic HIV; HIV-associated neurocognitive disorder; Nursing care; Viral reservoir.

### Abbreviations

AD	=	Alzheimer's disease,
AIDS	=	Acquired immunodeficiency syndrome
ANI	=	Asymptomatic neurocognitive impairment
ARV	=	Antiretroviral
BBB	=	Blood brain barrier
CAN	=	Central nervous system
cART	=	Combination antiretroviral therapy
DNA	=	Deoxyribonucleic acid
HAAR	=	Highly active antiretroviral therapy
HAD	=	HIV-associated dementia
HAND	=	HIV-associated neurocognitive disorder(s)

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HIV	=	Human immunodeficiency virus
MND	=	Mild neurocognitive disorder
RNA	=	Ribonucleic acid

## Introduction

People diagnosed with the human immunodeficiency virus (HIV) are living as long as uninfected persons [1]. In 2021, 38.4 million persons were living with HIV worldwide with 28.7 million receiving antiretroviral therapy, an increase from the 7.8 million in 2010 [2]. In the United States (U.S.) during 2021, 64% of the 1.1 million persons with HIV were receiving antiretroviral therapy [3,4]. Furthermore, 51% of this 1.1 million were older adults (55 years and older) where 67% had viral suppression [5,6]. Persons with HIV are living beyond the expected years of survival due to the development, access, and adherence to antiretroviral therapy [1,7].

Antiretroviral therapy has led to unparalleled changes in the prognosis, life expectancy, and quality of life for persons living with HIV so that it is treated as a chronic disease. The therapy involves the combination of antiretroviral (ARV) drugs or medications designed to stop the virus from replication in the human body [8]. The combination antiretroviral therapy (cART) of 1996 has evolved into the Highly Active Antiretroviral Therapy (HAART) for a long-term treatment regimen. The highly active antiretroviral therapy weakens long-term the continued damage to the immune system in the 1<sup>st</sup> stage of the HIV infection and impacts the increasing viral load and decreasing CD4 count, which occur in the 2<sup>nd</sup> stage or chronic HIV infection stage [9]. By impacting the chronic HIV infection stage, also known as asymptomatic HIV infection stage, the risk of advancing to acquired immunodeficiency syndrome (AIDS) is lessened as the CD4 count increases and the viral load decreases. Persons can live in this chronic HIV stage for decades and possibly symptom-free. Consequently, persons infected with the virus can survive and even thrive as persons with chronic HIV on antiretroviral therapy [10].

The HAART, like cART, contributes to a reduction in the obvious HIV-related symptoms but does not completely eliminate the virus from the central nervous system (CNS), indicating that there is no cure for an HIV infection [5,9,11]. A viral reservoir is created in the brain from the lingering, long-living HIV proteins that are not eradicated [12,13]. This viral reservoir can potentiate the neuroinflammatory process for the translocation of replicating virions, impacting the life of persons living with chronic HIV [11-13]. The persons may experience subtle forms of symptoms such as mild to moderate HIV-associated neurocognitive disorder (HAND) with increased prevalence of these symptoms, which will significantly alter a person's quality of life, activities of daily living, medication adherence, and survival [14]. The viral reservoir influences the effectiveness of HAART in terms of addressing these subtle yet pervasive symptoms, creating a chasm regarding the care of patients living with chronic HIV. Therefore, the objective of this mini-literature review is to explore the effect of this viral reservoir in the continued treatment of chronic HIV infection and neurocognitive symptoms in persons living with chronic HIV and discuss the implications for nursing care.

## Methodology

Literature searches were performed in Elsevier, NCBI, OVID, and ProQuest databases with limitations on articles written in English and published between 2000-2022. This time range was selected to ensure the selection of foundational and historical articles as well as literature reviews that provided a thorough and concise review about the keywords. Keywords were HIV/AIDS, neurocognition, neuropsychiatry, cognitive decline, and cognitive symptoms. Two hundred abstracts were reviewed to establish the current knowledge base on cognitive changes noted in patients living with HIV/AIDS. Current assessment techniques were utilized to identify these changes. Both qualitative and quantitative articles were considered. Twenty-five articles were selected and grouped into topics related to pathogenesis (HIV infection and viral reservoir), antiretroviral therapy (cART and HAART), and symptomatology (cognitive impairment, neuropsychiatric symptoms, and HIV-associated neurocognitive disorders).

## Literature Review

### Pathogenesis

The pathogenesis of HIV infection is well documented, especially the commonly accepted Trojan horse hypothesis [15]. Briefly, the entry of the virus into the bloodstream infects the lymphocytes and monocytes, which transmigrate into the CNS compartment. Once inside, these cells promote a neuroinflammatory process with an increased transmigration of lymphocytes and monocytes, HIV-infected and non-HIV-infected cells, into the compartment. These immune cells release "proteins" and enzymes to disrupt the blood brain barrier (BBB), exposing cells in the brain. The HIV-infected cells contribute to the production of virions or HIV proteins that bind to the brain microglial cells, astrocytes, and macrophages. This binding results in the release of neurotoxins, leading to neuronal dysfunction [15]. The infected microglia, astrocytes, and macrophages cause a decrease in the CD4 count and an increase in the viral load [15].

Even though the replication of HIV proteins and neurotoxins are suppressed with antiretroviral therapy, the virus DNA is not completely eradicated, making the brain a viral reservoir [12,13]. The lingering DNA in the infected microglia, astrocytes, and macrophages creates a viral reservoir with the potential to re-seed or re-bound HIV proteins [12,13]. This re-bounding of the HIV protein can promote a neuroinflammatory process, causing the proliferation of the HIV proteins in the brain. This proliferation can lead to a disruption of neuronal transmission for the development of cognitive impairment, neuropsychiatric behavioral changes, functioning, and other symptoms [15,16]. In addition, the viral reservoir can impact cognition to the point that cognitive decline for persons living with chronic HIV and receiving antiretroviral therapy can be a significant factor in morbidity and mortality [15]. Hypothetically, the viral reservoir is regulated as long as the antiretroviral therapy is maintained. However, regulation can be compromised due to poor penetration of the antiretroviral drugs in the CNS and/or the toxic effect of the antiretroviral drugs on the brain from immediate and prolonged exposure [13]. Consequently, the viral reservoir has the potential to impact the symptoms, life expectancy, and quality of life even if receiving antiretroviral therapy.

### **Antiretroviral Therapy**

In 1996, cART revolutionized the effort to address the growing issue of HIV infections and advancement to AIDS. The cART, a 2-or 3-medication regimen was implemented with significant results. The risk and occurrence of HIV-associated dementia (HAD) decreased and it was possible to differentiate HIV-associated cognitive impairment from other causes of the impairment [17-19]. Persons with HIV had a greater survival rate with an improved immune system as reflected by a decrease in the viral load, an increase in the CD4 count, and a decrease in opportunistic infections [17,18,20]. Importantly, cART was effective in reducing the mortality rate for persons with HIV infection [21]. In terms of quality of life, cognitive changes in persons with HIV were not associated with the use of cART [18]. These changes were related to employment, daily living, and depressive episodes [18]. Drawbacks of cART were a short-term effectiveness, the need to initiate cART as soon as possible for maximum effectiveness, and the impact on the viral load was not sustained over time [22]. The cART only addressed the severe symptoms of HAND. There is also the issue of medication adherence, which weakened the usefulness of cART [18]. Nevertheless, cART impacted the prevalence of severe HAND but not mild to moderate ([17,23], indicating the need for a more aggressive therapy.

In 2007, HAART ushered in an era of unparalleled impact on the prognosis, life expectancy, and quality of life for persons living with chronic HIV [24]. The HAART, a 3-or-more medication regimen, represents the next step in ARV therapy with an aggressive regimen that addresses symptoms and complications beyond a short-term period as well as those that cART did not. Specifically, HAART is effective in the suppression of the virion production in persons with chronic HIV for a long-term management of the viral load and CD4 count, controlling the risk of opportunistic infections [15,22,24]. This suppression impacted the long-term effect of the virus on the microglia cells, lengthening exponentially the life expectancy [4]. Persons living with chronic HIV on HAART have a lower risk and occurrence of changes in behavior(s) and cognition as well as HIV associated dementia [11,25]. The potential for HAD decreased further from the neurological-based symptoms from the HIV associated neurocognitive disorder [25]. The HAART has been useful in understanding the disorders that comprise the HIV-associated neurocognitive disorder [22,26].

However, HAART does not completely address the more subtle form of symptoms often manifested as mild to moderate HAND [11]. In addition, the neurotoxicity from long-term use of antiretroviral drugs can impact cognition and generate neuropsychiatric conditions in persons living with chronic HIV [27]. As a result, the viral reservoir influences the utility of HAART in terms of treating HAND, one of the largest factors leading to morbidity and mortality in this patient population [7].

Antiretroviral therapy, cART or HAART, is a progressive and innovative treatment in regulating the virus. The prognosis for persons with chronic HIV has significantly improved with this therapy or medication regimen. The severity of the symptoms has decreased, life expectancy has increased, socialization is encouraged, and hope has returned. Nevertheless, a viral reservoir is created from the therapy and is potentially maintained with the continual use of the therapy. This sustainability of the viral reservoir potentiates its impact, influence, and effect on the outcomes from the improved prognosis regarding the symptomatology of chronic HIV. This makes the viral reservoir an important factor in the care of persons living with chronic HIV.

### **Symptomatology**

After the introduction of antiretroviral therapy, the changes for persons living with chronic HIV were the decreased risk from life-threatening disease progression due to suppression of HIV replication, decline in mortality rate, decrease in opportunistic infections, decreased occurrence of leukopenia or thrombocytopenia, and decreased risk of HAD [11,19]. The symptoms and complications experienced are a cluster of symptoms related to cognitive, behavioral, and functional complications.

A common clinical symptom is cognitive impairment. In the early era of cART, the cognitive changes were manifested as complications in memory, executive functioning, and learning [1]. In post-cART era, poor learning continues, causing memory issues, there is less motor dysfunction with an increased occurrence of psychomotor complications [1,24]. The poor learning involves decreased processing speed of materials [24]. Memory changes are a common symptom that is impacted by the diurnal pattern [7].

Cognitive impairment may be a common clinical symptom but it is not necessarily part of HAND [20,27]. It is possible to determine if the cognitive impairment is associated to HIV or a neurodegenerative condition like Alzheimer's disease (AD). Impaired amnesic memory is not reported in persons with chronic HIV even though it is observed in persons with AD [1]. The progression of the cognitive decline in HAND plateaus at mild to moderate with HAART whereas the progression continues to severe stages in AD based on age and duration of the illness [28,29]. Therefore, the cognitive changes related to memory impairment, learning challenges, and mild to moderate neurocognitive impairment.

The neuropsychiatric conditions are delirium and depression which are often observed with cognitive impairment [7]. The clinical presentation for delirium is very similar for both HIV infected and non-infected persons. It is manifested as "a waxing and waning state of inability to attend, disorganized thinking or confusion, and fluctuations in the level of consciousness" [7]. There is a high risk for delusions and hallucinations, which may be a comorbidity for HAD or depression [24,30]. The potential for major depression is extremely high from living with chronic HIV. Confronting biases and mores from social, cultural, medical, pharmaceutical, and personal influences can increase the stress and anxiety for persons living with chronic HIV, escalating susceptibility to physiological changes (i.e., CD4 count and viral load) [24]. These physiological changes can trigger depressive episodes, leading to somatic symptoms, malnutrition, wasting syndromes, GI complications, and headaches [7].

The spectrum or constellation of disorders for HAND are asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) [31]. This is also known as the Frascati criteria, where HAND is more like a chronic condition instead of an acute one where the symptoms can be asymptomatic, subjective, or mild to moderate [28]. Cognitive impairment is a common clinical symptom across the three sub-disorders of HAND [28]. The typical symptoms associated with HAND are cognitive impairment (poor attention, decreased concentration, and memory loss), behavioral disturbances (loss of motivation, depression, anxiety, and irritability), and altered motor functioning (gait issues and retarded movement) [20,24,28,30,31].

There can also be occurrences of sleep disturbances, psychosis, and mania [24,31]. These symptoms can contribute to poor quality of life, adherence to medication, and employment [20]. Adherence to HAART has impacted several aspects of HAND such as a decrease in the severity, decreased progression from ANI to MND or HAD, and progression not related to age or duration of chronic HIV [31,32]. Interestingly, a decrease in the severity has contributed to an increase in the prevalence of HAND [23,31]. There is also a high prevalence of comorbidity with the HAND since several symptoms overlap with several chronic conditions reported in both the HIV-infected persons and the non-infected persons for certain age groups [24,30]. All the symptoms can be attributed to the viral reservoir given the symptoms association to virions and HIV RNA in the CNS although the person was adhering to antiretroviral therapy [10].

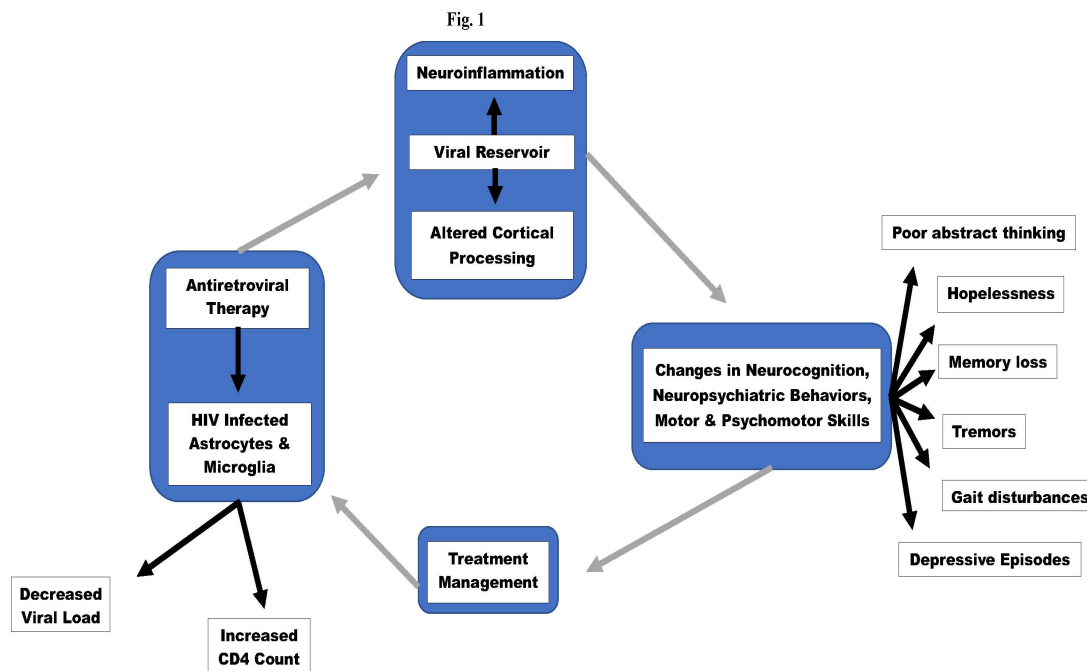
Several biomarkers (i.e., viral load and CD4 count) have been identified and related to the pathogenic process for neurocognitive and neuropsychiatric changes in persons living with chronic HIV [1,12,13]. These biomarkers can be useful in indicating the level and impact of viral reservoirs as well as assessing the risk for developing symptoms [13,19]. In particular, those with a greater viral load and lower CD4 count have an increased risk of developing cognitive impairment and symptoms related to HAND. The existence of this "dormant" reservoir may trigger and increase the severity of the symptoms [12,13]. The viral reservoir can "easily" lead to the re-bounding effect of the HIV protein from the antiretroviral therapy's neurotoxicity and decreased effectiveness, leading to possible treatment resistance [10]. Clearly, the viral reservoir can exist as a physiological risk that can trigger symptoms in persons living with chronic HIV.

## Discussion

### Synthesis

Antiretroviral therapy has ushered in promising prognosis and treatment for HIV/AIDS. A positive diagnosis of HIV can result in HIV+ being a chronic condition with ART instead of an acute one that is life-threatening. Conversely, ART contributes to the development and sustainability of viral reservoirs. The current ART suppresses the replication of the virus but it does not completely eradicate the virus from the body, especially the brain. While adherence to the ART can regulate the viral reservoir, it still contributes to the symptomatology experienced by persons living with chronic HIV. The viral reservoir is an unwanted and potentially dangerous outcome from ART that can and does have an impact on the promising outcomes from ART administered to persons living with HIV.

The proposed viral reservoir cycle (Figure 1) emerges from the cyclic relationship among the antiretroviral therapy, the viral reservoir, and the symptoms where the viral reservoir is a key component. The cycle demonstrates that (1) the viral reservoir serves as a bridge between antiretroviral therapy and HIV-associated symptoms and (2) the sustainability and regulation of the viral reservoir come from the antiretroviral therapy. This creates a cycle from creation of the reservoir to stimulation of HIV-associated symptoms to treatment and back to the viral reservoir.



**Figure 1:** The Viral Reservoir Clinical Cycle.

**Caption:** The cycle demonstrates that (1) the viral reservoir serves as a bridge between antiretroviral therapy and HIV-associated symptoms and (2) the sustainability and regulation of the viral reservoir come from the antiretroviral therapy. This creates a cycle from creation of the reservoir to stimulation of HIV-associated symptoms to treatment and back to the reservoir. The blue boxes contain the specific associations and/or outcomes in the viral reservoir clinical cycle. The first box demonstrates the relationship between the antiretroviral therapy and the HIV infected brain cells. The second box show the relationship among the viral reservoir, the neuroinflammatory process, and changes in cortical processes. The third box indicates the HIV- associated symptom. The fourth and final box indicates that treatment management is delivered. The black arrows are the known information and the gray arrows related to the synthesis of the literature for the proposed viral reservoir clinical cycle.

This cycle represents the relationship between treatment (ART) and the symptoms. The viral reservoir is sustained by adherence to ART. The reservoir facilitates the symptoms and their potential to increase in severity and occurrence. As previously shared, the suppression of the replication of HIV does not eradicate all the HIV proteins, leading to the permanence of the viral reservoir. Even though a neuroinflammatory response results, there is also disruption of cortical processing, leading to symptoms such as cognitive impairment, changes in neuropsychiatric behaviors, and disruption of motor functioning. Thus, the continuation and strength of the therapy sustain and regulate the viral reservoir.

The viral reservoir can also relate to the efficacy of ART. Adherence to ART hypothetically regulates the activity of the lingering, long-living HIV proteins. However, neurotoxicity and/or inadequate penetration of the drugs can lead to ‘the housing’ or ‘physiological compartmentalizing’ of the lingering, long-living HIV proteins. This reality creates the potential for re-bounding and translocation of the HIV proteins. The levels may not be substantial for the advancement to AIDs or sustained over an extended period of time due to ART. Nevertheless, these HIV proteins and neurotoxins can lead to the development and severity of the symptoms such as neurocognitive impairment and neurobehavioral complications manifested in persons living with chronic HIV. Clearly, the viral reservoir bridges the aggressive therapy to the persistent yet subtle and mild symptomatology of chronic HIV.

Recognizing this viral reservoir clinical cycle can serve as a potent guide in the care and treatment of persons living with chronic HIV for their continued adherence to ART. In addition, the viral reservoir clinical cycle may provide directions about the research on the viral reservoir, the bridging mechanism between antiretroviral therapy and HAND.

### Limitations

This mini-review has several limitations. One is that several of the selected articles were peer- reviewed literature reviews instead of peer-reviewed studies. Granted, the reviews were either systematic or integrated reviews, but it places importance on secondary sources. Another limitation was the need to select articles before 2015. Several of these articles are seminal ones given the information about HIV, especially at the time of publication. Nevertheless, the selected articles, literature reviews and studies, provide a thorough understanding about HIV, viral reservoir, and symptomatology for chronic HIV.

## **Nursing Implications**

Care from nurses can have a significant impact on the symptoms associated with persons living with chronic HIV [33]. Nurses can contribute to improved quality of life, increased functioning, and decreased stress, anxiety and depressive symptoms [33]. This outcome might be related to the care for the entire person, not the chronic disease and the individualization of the care [33]. Importantly, the care is proactive instead of reactionary, especially given the potentialities from the viral reservoir.

Adequate nursing care for persons living with chronic HIV transcends beyond care for the traditional symptoms. Adequate care includes proactive assessment for an escalation in the frequency, severity, and co-morbidity of the symptoms given the existence and sustainability of the viral reservoir from continued antiretroviral therapy [34]. This proactive care revolves around the nurses' knowledge about (1) the viral reservoir pathogenesis that contributes to the potential of infection from proliferated HIV proteins and virions, (2) the viral reservoir's relationship to the presented and possible symptoms from neurocognitive complications to neuropsychiatric challenges, and (3) the viral reservoir strengthening the association of the symptoms to HIV [20,28,33,34]. The presence of HIV proteins in the brain is more than a characterization of the neurophysiology of persons living with chronic HIV. It characterizes a high risk for exacerbation of the traditional symptoms and a potential risk for the advancement to AIDS. Persons living with chronic HIV should be screened and assessed regardless if they are symptomatic or asymptomatic given the viral reservoir and the biomarkers associated with it [10,33,34]. This approach will enhance the sensitivity in diagnosing symptoms that are HIV-associated, reducing the risk of diagnostic overestimation [10]. Medication can be useful in relieving complications from the chronic condition [10,27,16,33].

It is essential that nurses, newly licenses and veterans, receive adequate training for the needed level of specificity in treating and caring for persons living with chronic HIV. This training involves but not limited to education on (1) the viral reservoir from pathogenesis to alteration in neural transmission leading to symptoms, (2) the physiological and clinical monitoring of neuroinflammation, and (3) adequate and extensive assessment related to psychometrics, physiometrics, biomarkers, socialization, and mental health [33,35]. Communication is a key component to adequate care in terms of screening, assessing, diagnosing, and treating the neurocognitive and neuropsychiatric symptoms that easily results from the viral reservoir [10,35]. With this knowledge, the lack of continuity and confirmation in the care of persons living with HIV can be identified and addressed so that the care focuses on both the traditional symptoms and potential effects while avoiding stereotypical beliefs related to HIV, HAD, and HAND [10,34,35]. The issue of biases in the assessment can be diminished so that the impact of the viral reservoir on the symptoms can be adequately treated, avoiding the potentiality of exacerbation [35].

Consequently, nurses will have the knowledge to adequately and compassionately care for persons living with chronic HIV. Through nursing care, this vulnerable population will feel comfortable communicating, adhering to the medication regimen, informing and sharing any changes in their condition (physical, emotional, social, and mental), and being active in their care. Furthermore, nurses will continue their professional history and culture of caring for all, especially a vulnerable population like persons living with chronic HIV.

## **Conflict of Interest**

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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