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ASSESSING THE IMPACT OF VARIOUS REGIMENS OF SECOND-LINE ANTIRETROVIRAL THERAPY ON THE QUALITY OF LIFE OF PEOPLE LIVING WITH HIV/AIDS, A SYSTEMATIC REVIEW

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ABSTRACT

Antiretroviral therapy (ART) has significantly improved HIV management, but some patients may require second-line regimens due to treatment failure. This systematic review explores the impact of second-line ART on quality of life (QoL) among people living with HIV/AIDS (PLHIV). PubMed/MEDLINE, Embase, Cochrane Library, and Google Scholar were searched for eligible studies, and a total of 597 records were identified. Of the total records identified, 28 articles were removed as duplicates, and 569 articles were subjected to screening. A total of 23 eligible studies from 2018 to 2022 were analyzed. It was found that various regimens such as TDF+3TC+ATV/r, AZT+3TC+ATV/r improved the QoL of PLHIV. This was influenced by factors like pill burden, age, gender, and viral load. Tailoring ART to individual needs is critical to ensure efficacy, simplicity, and improved QoL. In conclusion, the review highlighted the intricate relationship between various regimens of second-line ART and QoL. These insights aid clinicians and policymakers in enhancing care for PLHIV, especially in resource-limited settings. Further research on QoL with second-line ART is vital for better treatment outcomes and public health.

Keywords: Antiretroviral therapy, HIV/AIDS, Quality of life, PLHIV, Second-line

INTRODUCTION

HIV/AIDS remains a significant global public health issue, impacting millions of individuals across the world (UNAIDS and AIDSinfo, 2021). In 2021, approximately 38.4 million people lived with HIV, and about 28.7 million of them had received antiretroviral therapy (UNAIDS and AIDSinfo, 2021). Additionally, there were an estimated 1.5 million new HIV infections among adults aged 15 and older in 2021 (UNAIDS and AID Sinfo, 2021). The primary objectives of ART are to lower the HIV viral load to undetectable levels, rebuild and maintain the immune system, minimize the risk of opportunistic infections, and enhance the general health and quality of life of those with HIV (WHO, 2016). The effective use of ART has led to a significant shift in HIV infection management, turning it from a potentially lethal disease into a manageable chronic condition. This progress enables individuals living with HIV to enjoy longer and healthier lives (Cohen et al., 2011).

Although first-line ART regimens such as Tenofovir+Lamivudine+Dolutegravir (TDF+3TC+DTG) are typically successful, a subset of patients might encounter treatment failure due to ineffectiveness or acquire resistance from their initial treatment. When this occurs, transitioning to a second-line antiretroviral regimen becomes imperative (WHO, 2018). Selection of second-line ART regimens such as TDF+3TC+ATV/r, AZT+3TC+ATV/r is vital for sustaining viral suppression and achieving favorable outcomes. In addition to focusing on treatment effectiveness and safety, it's crucial to consider the impact of various second-line regimens on patients' quality of life. The World Health Organization (WHO) advocates for optimizing the transition from first-line to second-line regimens, aiming to minimize

side effects, reduce the number of pills, enable once-daily dosing, avoid resistance across drug classes, and prioritize regimens suitable for diverse populations (Aboud *et al.,* 2018; Vitoria *et al.,* 2013). However, progress with second-line ART hasn't been without its challenges. Some drawbacks include potential side effects associated with these newer medications, which can be more complex or have a higher burden of adherence compared to first-line treatments. Additionally, access to these regimens can be limited in resource-constrained settings, hindering their widespread use. Despite these hurdles, ongoing research continues to refine second-line ART options, aiming to strike a balance between efficacy, tolerability, and accessibility, ultimately improving the outlook for those living with HIV (Aboud *et al.,* 2018; Vitoria *et al.,* 2013).

The outcome of this study may help policymakers in adopting a better ART regimen that may lead to optimal treatment outcomes which may ultimately improve the overall QoL of such patients' population.

METHODS

Study Design

A systematic review was conducted.

Identification and Study Selection

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were used to guide this systematic review (Page *et al.,* 2021). We systematically searched PubMed/MEDLINE, Embase, Cochrane Library, and Google Scholar to find all eligible studies. Key terms used to search the literature were "quality of life" AND "human immunodeficiency virus/acquired immunodeficiency syndrome" OR "HIV/AIDS" AND "second line antiretroviral therapy". The search included studies published between 2013 and 2023. References of identified articles were exported to Mendeley and deduplicated. This review was designed in accordance with the identified characteristics of reports on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as shown in Figure 1 (Moher *et al.*, 2009).

Eligibility Criteria Details

Primary studies that fulfilled the following criteria were considered eligible for this systematic review.

Study design: Observational studies (cross-sectional, case-control, and cohort studies) with original data reporting the impact of QoL among people with HIV/AIDS receiving various regimens of second-line ART were considered eligible to be included in this review.

Language and Publication status: Full-text articles published in English were included.

Study population: Research conducted among adult patients (equal to or age greater than 18 years) attending ART clinics were considered.

Measurements: Studies reporting the QoL using standardized measurement tools or questionnaires such as HIV/AIDS-Targeted Quality of Life instrument, SF-21 measure (ACTG SF-21), or other measurement tools were included.

Study period: Studies available online from 2013 to 2023, were included in this review.

RESULTS

A total of 597 records were identified from database search. Following the removal of 28 duplicate articles, a total of 569 articles underwent screening. After evaluating 23 articles for eligibility a total of 569 articles were subjected to screening. 23 articles were evaluated for eligibility and only 0.5% of the identified articles were included in this review. All the articles reviewed were from studies conducted in Nigeria (Biambo *et al*, 2018), South Africa (Mokgethi *et al,* 2022) and RLS (Torres *et al, 2018*). As shown in Table 1, the total number of 1677 patients were evaluated from the 3 articles. Variable comparators such as, TDF+3TC+ATV/r, AZT+3TC+ATV/r, TDF+FTC+ATV/r, LPV/r

/ DRV/r, LPV/r + RAL / LPV/r + NRTIs were used in the study.

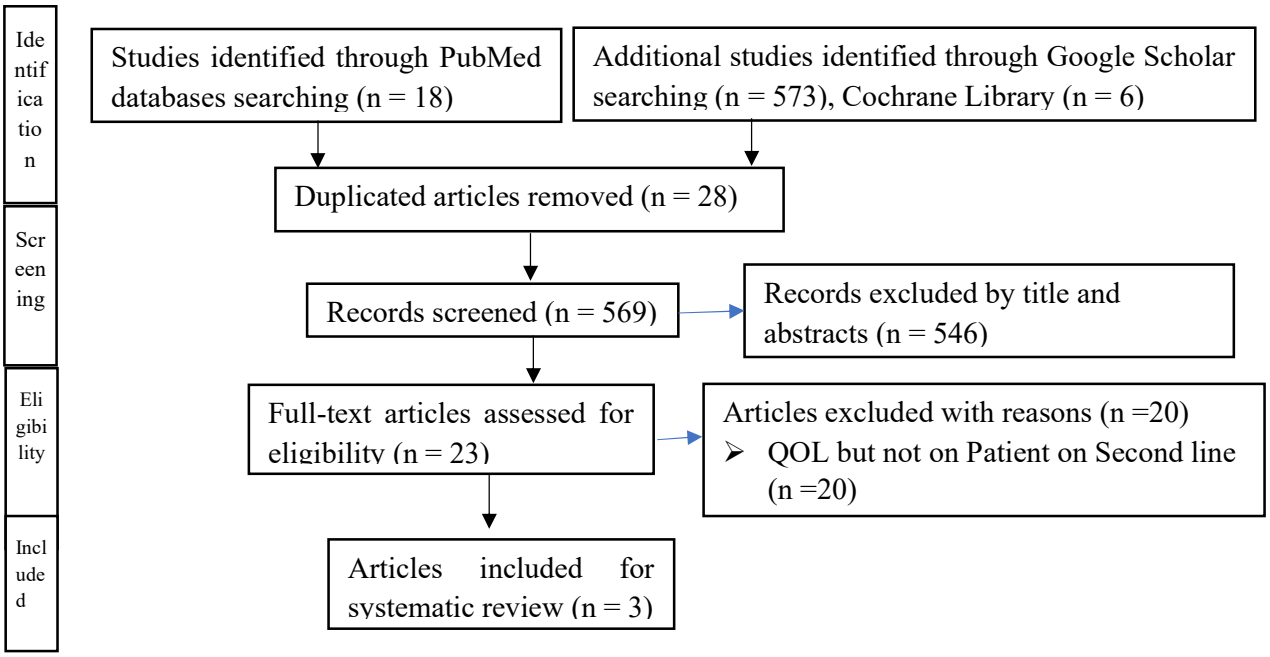

Figure 1: PRISMA Flow diagram showing paper selection process.

Table 1: Comparators and Outcomes of the Selected Generic Measures extracted From the Review

Author and year	Study Setting	No. of Patients	Comparison	Outcome
Biambo *et al*, 2018	Nigeria	872	TDF + FTC + LPV/r, TDF+3TC+ATV/r, AZT+3TC+ATV/r, TDF+FTC+ATV/r, and other first and second-line regimen	Patients on TDF + FTC + LPV/r (67.58 ± 14.80) had the highest HRQoL mean score than TDF+3TC+ATV/r (52.09±11.44), AZT+3TC+ATV/r (46.15±20.66), and TDF+FTC+ATV/r (54.40±00.00)
Mokgethi *et al, 2022*	South Africa	293	LPV/r versus DRV/r	There is improved QOL of patients on DRV/r compared with LPV/r due to lower pill burden of DRV/r
Torres *et al, 2018*	Resource Limited Setting	512	LPV/r + RAL versus LPV/r + NRTIs	QoL improvements were similar after starting second-line ART of LPV/r + RAL and LPV/r + NRTIs. Mean QoL at baseline (95% Cl) for LPV/r + RAL and LPV/r + NRTIs are 66(63,69) and 68(66,71) respectively and at 48 weeks 74(72,76) for both regimens.

TDF:Tenofovir disoproxil fumarate, FTC:Emtricitabine, LPV/r:Lopinavir/ritonavir, 3TC:Lamivudine, ATV/r:Atazanavir/ritonavir, AZT:Zidovudine DRV/r:Darunavir/ritonavir RAL:Raltegravir

The key findings from the articles reviewed showed a better quality of life among patients on different regimens of second-line antiretroviral therapy. Biambo and colleagues found that patients on TDF + FTC + LPV/r (67.58 ± 14.80) had the highest HRQoL score among those on second-line regimens (Biambo *et al.,* 2018). Mokgethi and co-workers found that patients with higher pill burden, females, and older age groups had low QoL (Mokgethi *et al.,* 2022). Patients on Darunavir presented with a lower pill burden than those on lopinavir and therefore had better improvement in QoL. Torres and colleagues found that improvements in QoL were similar after starting second-line ART of LPV/r combined with either RAL or NRTIs in RLS (Torres *et al.,* 2018). Individuals with higher VL and lower CD4 at baseline were reported to have lower QoL scores at baseline but larger improvements such that the mean QoL was similar at week 48.

DISCUSSION

The result of the study by Biambo *et al.* showed better improvement in QoL for patients on LPV/r base regimen compared with ATV/r base regimen (Biambo *et al.,* 2018). This in addition to other possible reasons, could be due to higher side effects like the high risk of hyperbilirubinemia associated with ATV/r based regimens than LPV/r based cART (Tigabu *et al.,* 2020). A similar study also showed the superiority of LPV/r over ATV/r with regard to safety and effectiveness (Cohen *et al.,* 2005). On the contrary, a study by Andersson *et al.* reported a higher risk of serious adverse events in LPV/r compared to ATV/r based regimens after 144 weeks of treatment (Andersson *et al.,* 2013). Similarly, another study reported lower risk of occurrence of treatment-related grade 2-4 adverse events ATV/r compared to those in the LPV/r (Takuva & Waal, 2021). Also, Atazanavir is generally considered to have a more favorable effect on lipid (fat) levels in the blood compared to lopinavir, known to be associated with elevated levels of cholesterol and triglycerides, suggesting the use of ATV/r as first whenever there is a need to include PIs in the regimen (Tigabu *et al.,* 2020).

Several studies comparing ATV/r with other PIs had demonstrated the superiority of ATV/r based cART to suppress the virus below 50 copies/ml (Gatell *et al.,* 2007). A multinational prospective observational study in high-income countries also reported a lower risk of hazard ratio for death, AIDS-defining illness, and virological failure to ATV/r than LPV/r (Cain *et al.,* 2015). Moreover, an economic evaluation from Sweden found the dominance of ATV/r based regimens over LPV/r (Thuresson *et al.,* 2011). This could be due to the simplicity of the dosing regimen (once-daily, single-pill regimen), reducing pill burden and ultimately improving adherence to treatment.

These findings suggest that the choice of specific second-line ART based regimen can play a substantial role in positively impacting patients' QoL. This reinforces the importance of personalized treatment plans to optimize patient well-being while effectively managing HIV. These findings suggest that the choice of specific antiretroviral drugs in second-line therapy can play a substantial role in positively impacting patients' QoL, highlighting the importance of tailoring ART regimens to maximize patient well-being while effectively managing HIV. This underscores the necessity for a more comprehensive study to examine and compare the effects of second-line treatment regimens in relation to QoL. This is because improvement in QoL is one of the important goals of treatment. QoL is utilized for evaluating the well-being of patients (WHOQOL-BREF, 1996). It is recognized as a fundamental element of public health (Burgoyne & Renwick, 2004), contributing to the extension of patients' lifespans (Frank *et al.,* 2019). It influences healthcare, daily routines, instills a feeling of well-being, and empowers individuals to withstand diverse aspects of illness (Sherman *et al.,* 2010).

Study conducted by Mokgethi *et al* reported several notable factors that influence QoL. They observed that patients with higher pill burdens, females, and older age groups reported lower QoL (Mokgethi *et al.,* 2022). The findings underline the importance of treatment simplicity and individualized care. For instance, patients on Darunavir presented with a lower pill burden compared to those on lopinavir, and consequently, they experienced a better improvement in QoL. This is similar to a study conducted by Langebeek *et al.* who reported that simplification of therapy to a fixed-dose regimen, ultimately lowering pill burden resulted in higher treatment satisfaction, better adherence, and better QoL (Langebeek *et al.,* 2014). This observation underscores the significance of considering not only the efficacy but also the convenience and patient experience when selecting ART regimens.

A noteworthy observation from the study conducted by Torres *et al.* was that individuals with higher viral loads (VL) and lower CD4 counts at baseline tend to have lower QoL scores initially (Torres *et al.*, 2018). However, these patients experienced more substantial improvements, resulting in similar mean QoL scores at week 48. Similar finding by Biambo and colleagues reported that patients on TDF+XTC+LPV/r regimen did not experience a significant change in annual percentage CD4 count in all the categories of baselines CD4 count (low, moderate, or high) (Biambo *et al.,* 2019). This finding highlights the resilience and adaptability of patients living with HIV and emphasizes the need for comprehensive support and monitoring, especially during the transition to second-line therapy.

These articles collectively emphasize that the choice of second-line ART regimens and their impact on QoL is a complex interplay of drug efficacy, treatment simplicity, individual patient characteristics, and the specific setting in which care is provided. The findings underscore the importance of tailoring treatment strategies to maximize QoL while effectively managing HIV and offer insights for clinicians and policymakers in optimizing care for individuals living with HIV, both in well-resourced and resource-limited settings.

CONCLUSION

This study reaffirmed second-line antiretroviral regimens have been linked to enhanced Quality of Life (QoL). Nonetheless, there is a paucity of research on individuals living with HIV receiving second-line antiretroviral treatments and being evaluated for their QoL undergoing. This dearth of research could potentially impact the comprehensiveness and robustness of the findings. Therefore, it is imperative to conduct additional studies that assess the QoL of individuals living with HIV receiving second-line antiretroviral therapy. Such investigations would not only enhance treatment outcomes but also alleviate the HIV burden, ultimately contributing to the enhancement of public health.

LIMITATIONS

There may be a risk of publication bias as only studies published in English were included, potentially excluding relevant research published in other languages. While the review acknowledges factors like age, gender, and viral load as influencers of quality of life, there may be other confounding variables not adequately addressed in the included studies that could impact the observed outcomes.

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