Antiretroviral Therapy and HIV-Associated Nephrotoxicity: A Survey

Abstract

Antiretroviral therapy (ART) has significantly improved the management of HIV, transforming it from a fatal disease to a chronic condition. However, the nephrotoxic potential of certain ART regimens, notably those containing Tenofovir disoproxil fumarate (TDF), poses a risk for renal dysfunction in people living with HIV (PLHIV). This survey explores the multifaceted issue of HIV-associated nephrotoxicity, emphasizing the pathophysiology of drug-induced kidney damage, risk factors, and prevention strategies. It highlights the interplay between direct viral effects, immune-mediated damage, and drug toxicity in the pathogenesis of nephrotoxicity. The survey underscores the importance of early detection through advanced biomarker analysis and imaging techniques, such as urinary exosome analysis, to improve diagnostic accuracy and patient outcomes. Management strategies must incorporate tailored treatment plans, preventive measures, and risk mitigation techniques, informed by risk factors like genetic predispositions and systemic conditions. The survey also identifies critical research gaps, advocating for interdisciplinary research and the development of predictive models and novel therapeutic interventions. By addressing these challenges, healthcare providers can enhance the early detection and management of renal complications, ultimately improving the quality of life for individuals affected by HIV.

1 Introduction

1.1 Significance of Antiretroviral Therapy (ARV)

Antiretroviral therapy (ARV) has fundamentally altered the landscape of HIV management, transforming it from a fatal disease into a manageable chronic condition [1]. The advent of Highly Active Antiretroviral Therapy (HAART) has markedly improved life expectancy among individuals living with HIV, contributing to an increase in chronic conditions, such as renal dysfunction, due to prolonged survival [1]. Despite these advancements, AIDS continues to pose a significant public health challenge globally, with people living with HIV (PLHIV) facing elevated risks for comorbidities like chronic kidney disease (CKD), driven by a complex interplay of immunodeficiency, chronic inflammation, aging, and antiretroviral toxicity [2].

The effectiveness of ARV is highlighted by its ability to suppress viral replication and enhance immune function, critical factors in reducing HIV-related morbidity and mortality [3]. However, persistent systemic inflammation and immune activation in PLHIV on long-term suppressive ART necessitate ongoing management to optimize patient outcomes [4]. Timely initiation of ART is crucial for improving these outcomes; however, high attrition rates between HIV diagnosis and therapy initiation present significant barriers [5].

Adherence to ART is a critical determinant of its success, with various barriers identified that hinder consistent medication adherence [6]. For instance, research in Korea has focused on estimating adherence levels and identifying factors contributing to suboptimal adherence among newly diagnosed HIV-infected individuals [6]. In Africa, socio-economic factors further complicate adherence chal-

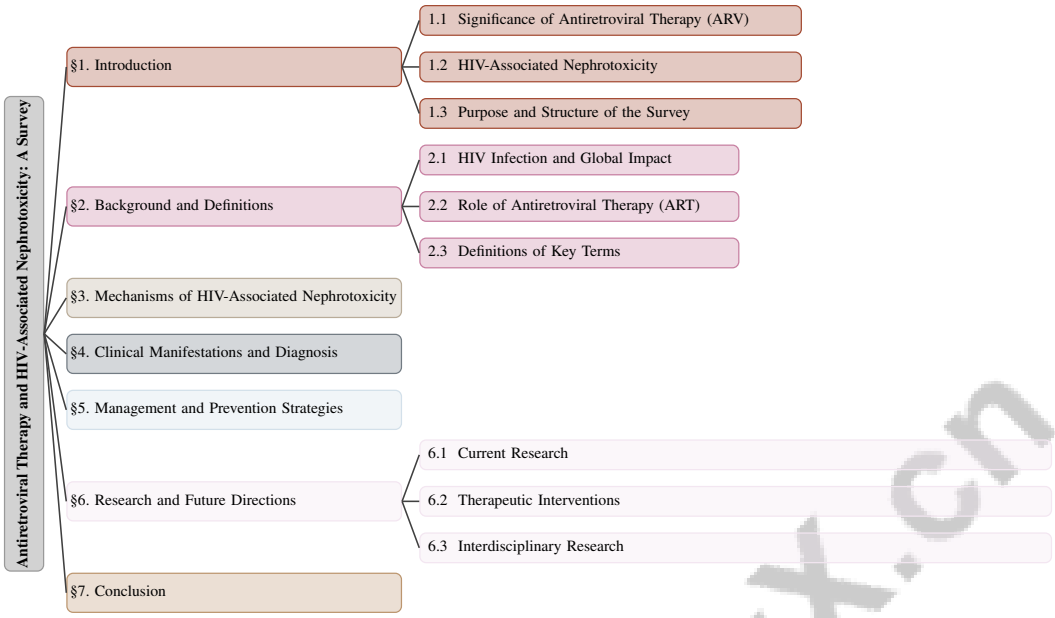


Figure 1: chapter structure

lenges, impacting the management of HIV and related conditions such as HIV-associated nephropathy (HIVAN) [7].

The ongoing evolution of ARV regimens and strategies to enhance adherence is vital in the global fight against HIV. Addressing the multifaceted challenges of adherence is essential for achieving optimal treatment outcomes and improving the quality of life for affected individuals [8]. As research continues to explore the complexities of HIV management, the significance of ARV in mitigating systemic inflammation and managing comorbidities becomes increasingly clear, underscoring its integral role in comprehensive HIV care [9].

1.2 HIV-Associated Nephrotoxicity

HIV-associated nephrotoxicity poses significant clinical challenges within the context of antiretroviral therapy (ART), leading to substantial risks for both acute and chronic renal impairment among individuals living with HIV. This condition is particularly prevalent in Africa, where HIV-associated nephropathy (HIVAN) is a common complication, emphasizing the need for early detection and intervention to mitigate its progression. The interplay of persistent immune activation and systemic inflammation under effective ART contributes to the development of acute kidney injury (AKI) and chronic kidney disease (CKD), complicating patient management [1].

The risk of nephrotoxicity is heightened by the use of specific antiretroviral drugs, notably Tenofovir disoproxil fumarate (TDF), which is associated with renal toxicity, necessitating vigilant monitoring to prevent irreversible kidney damage. The clinical landscape is further complicated by the association of HIV with autoimmune conditions such as ANCA-associated vasculitis, reflecting the complex immune dysregulation in HIV-infected individuals [10]. Additionally, inadequate adherence to ART exacerbates these risks, adversely affecting treatment efficacy and long-term renal health outcomes [8].

The diverse manifestations of renal impairment in HIV-infected patients, including conditions like lupus-like membranous nephropathy, necessitate tailored treatment strategies that address both infectious and non-infectious comorbidities. This is particularly critical in regions with high HIV/TB coinfection rates, where comprehensive management approaches are needed to tackle compounded health challenges [7].

Addressing HIV-associated nephrotoxicity requires a nuanced understanding of underlying mechanisms and the implementation of individualized management strategies. Developing context-specific ART guidelines must incorporate socio-economic factors influencing treatment adherence and health

outcomes, as these significantly affect the decision-making processes of HIV-positive individuals, particularly in Africa. This approach aims to foster more effective interventions and policies tailored to the unique challenges faced by these populations [8, 6, 11]. As research delves deeper into HIV management complexities, the significance of nephrotoxicity as a critical concern in HIV care becomes increasingly apparent, highlighting the need for integrated and multidisciplinary approaches to improve patient outcomes.

1.3 Purpose and Structure of the Survey

This survey aims to comprehensively address the multifaceted issue of HIV-associated nephrotoxicity, focusing on understanding the pathophysiology of drug-induced kidney damage, identifying risk factors, and exploring prevention strategies. It seeks to bridge the knowledge gap in nephrotoxicity prediction models, particularly for HIV-positive patients undergoing Tenofovir disoproxil fumarate (TDF)-based therapy [12]. By evaluating current evidence, the survey maps the renal manifestations of HIV following the widespread implementation of antiretroviral therapy (ART), underscoring the necessity for comprehensive management strategies [13].

The survey is systematically structured to first provide a foundational understanding of HIV infection and the critical role of ART in its management. This is followed by precise definitions of key terms related to nephrotoxicity, setting the stage for an in-depth exploration of the mechanisms by which HIV and antiretroviral drugs contribute to kidney damage, including direct viral infection, immune-mediated damage, and drug toxicity [14]. The subsequent section delves into the clinical manifestations and diagnostic approaches for HIV-associated nephrotoxicity, emphasizing the importance of early recognition and the challenges inherent in accurate diagnosis.

In discussing management and prevention strategies, the survey examines tailored treatment approaches, preventive measures, and risk mitigation techniques, such as drug monitoring and regimen adjustments [15]. It also highlights the significance of rapid ART initiation in enhancing retention in care and achieving virologic suppression, particularly relevant in clinical nephrology.

Lastly, the survey reviews contemporary research on HIV-associated nephrotoxicity, identifying critical gaps in current knowledge and proposing future research directions, including the development of new biomarkers and therapeutic interventions. By covering the epidemiology, causes, detection, management, and implications of chronic kidney disease (CKD) in people living with HIV (PLWHIV), particularly in resource-limited settings, this survey aims to enhance understanding and inform clinical practice, ultimately improving patient outcomes [9].The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 HIV Infection and Global Impact

HIV infection remains a formidable global health issue, particularly in sub-Saharan Africa, where socio-economic challenges and inadequate healthcare infrastructure exacerbate the epidemic [7]. Studies from South Africa (2004-2015) highlight significant renal manifestations of HIV, underscoring the virus's extensive impact on kidney health [13]. The African Cohort Study (AFRICOS) further corroborates the epidemic's pervasive nature and associated health complications across four African nations [16]. HIV-associated nephropathy (HIVAN) is prevalent in African populations due to genetic factors and the kidney's role as a viral reservoir [17], necessitating further research for improved understanding and management. The co-epidemic of HIV and tuberculosis (TB) complicates the clinical landscape, significantly affecting kidney disease mechanisms and management strategies [18].

Globally, chronic kidney disease (CKD) prevalence among people living with HIV (PLHIV) is increasing, particularly in resource-limited settings with inadequate healthcare infrastructure [9]. PLHIV face a higher risk of CKD compared to the general population, necessitating targeted interventions [2]. Metabolic alterations persist in HIV-infected patients even after 12 months of combination antiretroviral therapy (cART), highlighting long-term health challenges [19]. Efforts to combat the HIV epidemic must prioritize not only viral management but also comprehensive care for associated comorbidities, including renal dysfunction. A multifaceted approach is essential, considering socio-economic conditions, genetic predispositions, and clinical factors such as increased drug toxicities

and kidney complications from antiretroviral therapy (ART). This is crucial for improving health outcomes for over 37 million affected individuals worldwide, especially in high-burden regions like sub-Saharan Africa, where treatment adherence and unique health risks, including a higher likelihood of CKD and acute kidney injury, must be addressed [20, 21, 22, 11, 7].

2.2 Role of Antiretroviral Therapy (ART)

Antiretroviral therapy (ART) is pivotal in HIV management, effectively suppressing viral replication and enhancing immune function, thereby significantly improving patient health outcomes [3]. The introduction of ART has led to a notable decline in HIV-related morbidity and mortality by reducing HIV-RNA levels, crucial for preventing disease progression [1]. However, chronic kidney disease (CKD) among PLHIV remains a pressing concern, particularly due to nephrotoxicity associated with certain ART regimens, notably those containing Tenofovir disoproxil fumarate (TDF) [3].

Managing HIV through ART is challenging, particularly with an aging cohort of PLHIV, which complicates polypharmacy and necessitates careful management of drug interactions to optimize treatment outcomes [9]. Inadequate CKD screening in this population complicates clinical management, underscoring the need for improved diagnostic and monitoring strategies [9]. Biomarkers such as cystatin C and NGAL in serum, along with KIM1 and NGAL in urine, have been identified as useful for assessing renal function and detecting early nephropathy signs in HIV-infected individuals [1].

Adherence to ART is crucial for its efficacy, with barriers affecting consistent medication intake, including treatment regimen complexity and socio-economic factors [8]. Addressing these adherence challenges is vital to prevent virologic failure and drug resistance, essential for long-term HIV management success [8]. Implementing strategic interventions, such as the RAPID model for same-day ART initiation, has shown promise in enhancing treatment uptake and retention in care, thereby improving overall patient outcomes [9].

2.3 Definitions of Key Terms

Understanding key terms is vital for comprehending the complexities of nephrotoxicity in the context of HIV and antiretroviral therapy. HIV-associated nephrotoxicity refers to kidney damage resulting from HIV infection and its treatment, often manifesting as renal dysfunction or chronic kidney disease (CKD) in PLHIV [7]. This condition is notably prevalent in African populations, frequently associated with HIV-associated nephropathy (HIVAN), characterized by low CD4 counts and high viral loads [7]. HIVAN represents a specific renal pathology linked to HIV, necessitating early detection and intervention to prevent progression to end-stage renal disease [13].

Renal dysfunction broadly encompasses any impairment in kidney function due to various etiologies, including chronic infections, systemic diseases, and drug toxicity. In HIV-infected individuals, renal dysfunction is often exacerbated by the nephrotoxic potential of certain antiretroviral drugs, such as TDF, highlighting the importance of regular kidney function monitoring [13]. Identifying sensitive biomarkers for renal dysfunction is crucial for early detection and management, with urinary exosomes explored as potential indicators of drug-induced nephrotoxicity (DIN) [23].

Drug-induced nephrotoxicity (DIN) specifically refers to renal impairment directly attributable to medication exposure, posing significant challenges in clinical nephrology due to variability in definitions and diagnostic criteria. Accurately predicting and assessing DIN is hindered by inadequate in vitro models that fail to reliably predict nephrotoxic effects, underscoring the need for improved drug safety evaluations [24]. Developing benchmarks for identifying biomarkers in vitro, such as those utilizing the RPTEC/TERT1 cell line, is essential for advancing the understanding and prevention of DIN [25]. Understanding these terms and their implications is critical for clinicians and researchers aiming to mitigate renal complications associated with HIV and its treatment [26].

In recent years, the understanding of HIV-associated nephrotoxicity has evolved significantly, revealing complex interactions between viral factors and host responses. This multifaceted condition can be attributed to various mechanisms, which are crucial for developing effective treatment strategies. Figure 2 illustrates these mechanisms, categorizing them into direct viral infection and immune-mediated damage, antiretroviral drug toxicity, pathogenic mechanisms, and biomarkers. The figure highlights the roles of genetic factors, chronic immune activation, and specific antiretroviral drugs in renal

impairment. Moreover, it underscores the importance of adherence to antiretroviral therapy (ART) in mitigating these effects. Additionally, the identification of key biomarkers and the development of innovative models for detecting nephrotoxicity are emphasized, which point to the pressing need for personalized treatment strategies and advancements in biomarker research to enhance renal health outcomes in HIV-infected patients. This comprehensive overview not only elucidates the underlying mechanisms of nephrotoxicity but also sets the stage for future research directions in this critical area of HIV care.

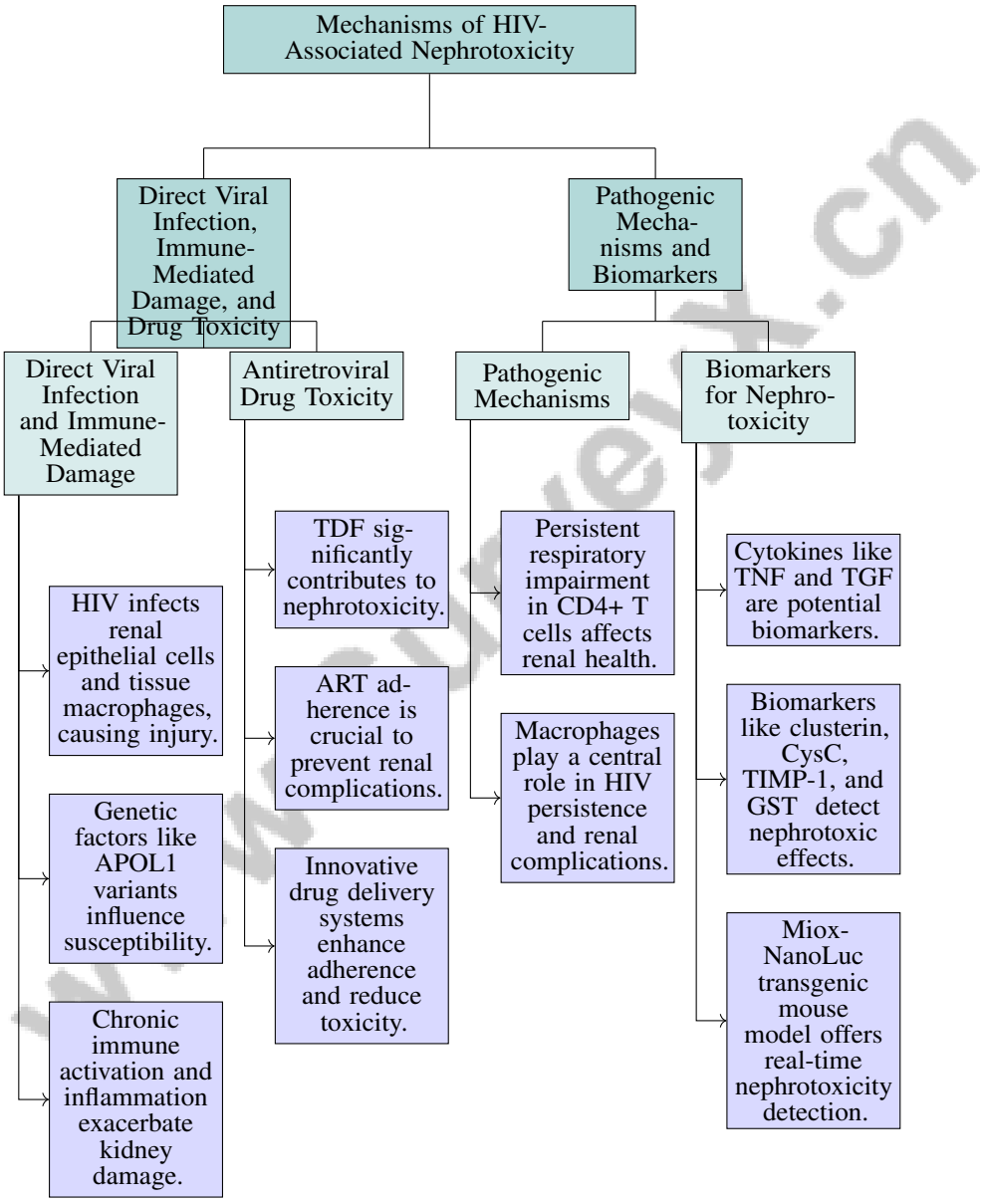


Figure 2: This figure illustrates the mechanisms of HIV-associated nephrotoxicity, categorizing them into direct viral infection and immune-mediated damage, antiretroviral drug toxicity, pathogenic mechanisms, and biomarkers. It highlights the roles of genetic factors, chronic immune activation, and specific antiretroviral drugs in renal impairment, as well as the importance of adherence to ART. Additionally, it identifies key biomarkers and innovative models for detecting nephrotoxicity, emphasizing the need for personalized treatment strategies and advancements in biomarker research to improve renal health outcomes in HIV-infected patients.

3 Mechanisms of HIV-Associated Nephrotoxicity

3.1 Direct Viral Infection, Immune-Mediated Damage, and Drug Toxicity

HIV-associated nephrotoxicity results from the interplay of direct viral infection, immune-mediated damage, and antiretroviral drug toxicity, each contributing to renal impairment in patients on ART. HIV can infect renal epithelial cells directly, persisting in tissue macrophages and causing ongoing renal injury. Genetic factors, such as APOL1 variants, further influence susceptibility, necessitating personalized treatment strategies [9]. Chronic immune activation and inflammation, driven by elevated cytokines like TNF and TGF, persist despite effective ART, exacerbating kidney damage [27]. Variability in ART response complicates renal health management [1], with HIVICK management focusing on suppressing HIV viremia [10].

Antiretroviral drugs, particularly Tenofovir disoproxil fumarate (TDF), significantly contribute to nephrotoxicity, with well-documented mechanisms necessitating improved risk assessment and management strategies [3]. Despite advancements, predicting drug-induced nephrotoxicity remains challenging due to the complexity of kidney physiology and limitations of in vitro assays [1]. Adherence to ART is crucial, as poor adherence can lead to virological non-suppression and exacerbate renal complications [8]. The Same-Day ART Initiation method addresses attrition challenges by enabling immediate ART commencement, optimizing patient outcomes and reducing nephrotoxic risks [5]. Innovative drug delivery systems, capable of administering multiple antiretrovirals in a single dose, show promise in enhancing adherence and mitigating renal toxicity.

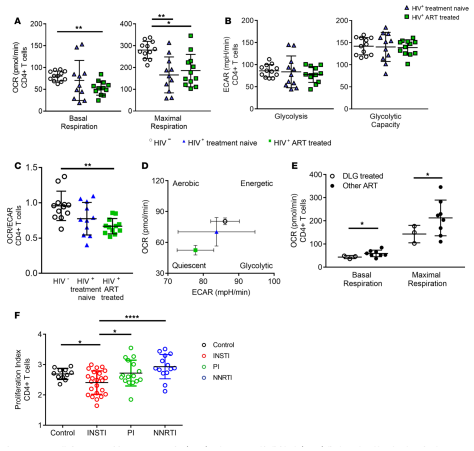
Comprehending the interactions among direct viral infection, immune-mediated damage, and antiretroviral drug toxicity is vital for managing HIV-associated nephrotoxicity, especially given the rising incidence of kidney diseases in PLHIV [20, 17, 18, 7]. Developing predictive models and biomarkers, alongside strategies to improve ART adherence and manage co-existing conditions, is essential for enhancing renal health outcomes.

3.2 Pathogenic Mechanisms and Biomarkers

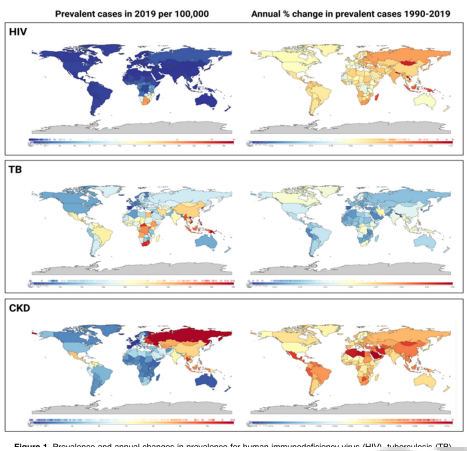
Advancing the management of renal complications in HIV patients on ART requires understanding pathogenic mechanisms and identifying biomarkers for nephrotoxicity. Persistent respiratory impairment in CD4+ T cells is a key mechanism, emphasizing the link between immune function and renal health [21]. Macrophages play a central role in HIV persistence and renal complications, necessitating targeted strategies to mitigate kidney damage [28]. Elevated cytokines, such as TNF and TGF, are potential biomarkers for nephrotoxicity and treatment effectiveness, offering insights into the inflammatory processes underlying renal impairment [27].

In drug-induced nephrotoxicity, biomarkers like clusterin, cystatin C (CysC), TIMP-1, and GST , evaluated in RPTEC/TERT1 cells, are effective in detecting nephrotoxic effects [25]. These biomarkers aid in early diagnosis and management of drug-related kidney damage, providing a foundation for improved safety evaluations of antiretroviral drugs. Innovative models, such as the Miox-NanoLuc transgenic mouse, offer real-time detection of nephrotoxicity through luminescence, identifying kidney damage prior to conventional biomarkers [29]. Advancements in biomarker research and detection technologies are crucial for enhancing nephrotoxicity assessments and optimizing therapeutic strategies for HIV-infected patients.

As shown in Figure 3, HIV-associated nephrotoxicity involves a complex interplay of pathogenic mechanisms and biomarkers essential for understanding and managing the condition. The first figure compares basal and maximal respiratory rates in HIV-positive individuals, elucidating metabolic alterations associated with HIV infection and treatment. The second figure presents a global perspective on the prevalence and annual changes in HIV, TB, and CKD as of 2019, emphasizing the broader public health implications of HIV-associated conditions. These figures underscore the multifaceted nature of HIV-associated nephrotoxicity and the importance of integrating clinical and epidemiological data to advance research and treatment strategies [21, 18].



(a) Comparison of Basal and Maximal Respiratory Rates in HIV-Positive and HIV-Positive Treatment-naive and ART-treated Individuals[21]



(b) Prevalence and Annual Changes in Prevalence for Human Immunodeficiency Virus (HIV), Tuberculosis (TB), and Chronic Kidney Disease (CKD) in 2019[18]

Figure 3: Examples of Pathogenic Mechanisms and Biomarkers

4 Clinical Manifestations and Diagnosis

4.1 Clinical Manifestations and Early Recognition

HIV-associated nephrotoxicity manifests through symptoms such as proteinuria, hematuria, and a reduced glomerular filtration rate (GFR), all of which can progress to chronic kidney disease (CKD) if not promptly addressed. Early recognition of these symptoms is crucial for preventing renal impairment and optimizing treatment outcomes. Urinary exosomes have emerged as stable biomarkers for early detection of renal dysfunction and structural injury [23]. Inflammatory biomarkers, linked to systemic inflammation, further exacerbate renal damage and contribute to age-related diseases, underscoring the importance of regular monitoring and early intervention [4].

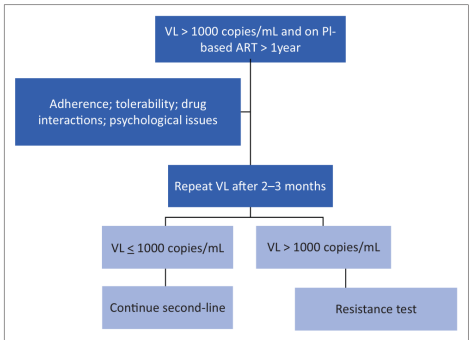
The choice of antiretroviral regimen significantly influences nephrotoxic profiles. Patients on the DCB (Dolutegravir, Cobicistat, and Bictegravir) combination exhibit lower nephrotoxicity compared to those on the DCA (Dolutegravir, Cobicistat, and Atazanavir) combination, highlighting the need for careful selection of ART regimens based on individual risk factors and renal function [3]. Early identification of nephrotoxicity is particularly vital for individuals of African ancestry, who are disproportionately affected by HIV-associated nephropathy (HIVAN) due to factors such as low CD4 counts and high viral loads. Timely interventions can significantly improve renal function and patient outcomes, addressing the increased risk of CKD and acute kidney injury in this population [20, 13, 7].

4.2 Imaging Techniques and Diagnostic Approaches

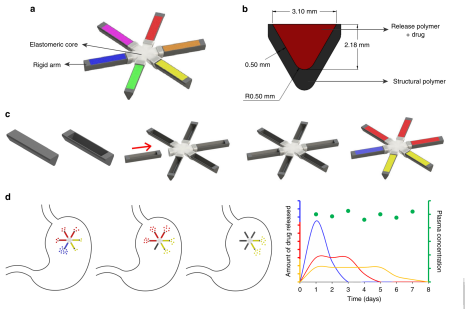
Comprehensive diagnostic approaches integrating imaging techniques are essential for detecting HIV-associated nephrotoxicity. Ultrasonography, CT, and MRI are pivotal in evaluating renal structure and function, identifying morphological changes indicative of nephrotoxicity due to medication toxicity [23, 26, 30]. While ultrasonography is a non-invasive tool for detecting changes in kidney size and echogenicity, CT and MRI provide detailed anatomical insights, crucial for distinguishing various renal pathologies, including those induced by ART [1]. However, caution is required with contrast-enhanced imaging due to the risk of contrast-induced nephropathy.

Incorporating biomarkers such as cystatin C, NGAL, and KIM-1 into diagnostic protocols enhances early detection capabilities, offering insights into renal injury before significant changes in serum creatinine levels occur [1]. Urinary exosome analysis further refines early detection, offering a non-invasive method to monitor renal function in HIV-infected patients [23]. The integration of advanced imaging with biomarker analyses, particularly in higher-risk populations, offers a robust

approach for early detection and diagnosis of HIV-associated nephrotoxicity, improving patient outcomes through tailored treatment strategies [23, 13, 1, 7].



(a) Flowchart for managing virological suppression in HIV patients[31]



(b) Concept of Oral Long Acting Antiretrovirals[32]

Figure 4: Examples of Imaging Techniques and Diagnostic Approaches

As illustrated in Figure 4, advanced diagnostic strategies and therapeutic innovations are crucial in HIV management. The first image offers a flowchart for managing virological suppression in HIV patients, emphasizing comprehensive patient management through adherence to medication and psychological considerations. The second image introduces oral long-acting antiretrovirals, highlighting innovations designed to enhance drug efficacy and compliance [31, 32].

4.3 Challenges in Nephrotoxicity Detection and Diagnosis

The detection and diagnosis of nephrotoxicity in HIV patients are challenged by the limitations of current biomarkers, such as serum creatinine, which are often insensitive and nonspecific, leading to delayed detection and irreversible renal damage [29]. The complexity of HIV-associated nephrotoxicity arises from direct viral infection of renal cells, immune-mediated injury, and antiretroviral medication toxicity, particularly in the context of polypharmacy [20, 33, 17, 18, 7]. Individual variability in responses to ART further complicates diagnosis, obscuring nephrotoxic effects attributable to specific drugs or immune responses.

Innovative biomarkers and diagnostic technologies, including urinary exosomes and advanced imaging techniques, offer opportunities for enhancing early detection and monitoring of drug-induced nephrotoxicity. Urinary exosomes effectively reflect renal injury, while in vivo models like Miox-NanoLuc transgenic mice enable real-time assessment of nephrotoxicity before conventional biomarkers indicate significant changes [23, 30, 25, 29, 26]. However, integrating these tools into clinical practice remains challenging due to the need for validation and standardization. Further research is required to establish the clinical utility of urinary exosomes in routine diagnostics.

5 Management and Prevention Strategies

5.1 Tailored Treatment Strategies, Preventive Measures, and Risk Mitigation

Managing HIV-associated nephrotoxicity requires a multifaceted approach that includes tailored treatment strategies, preventive measures, and risk mitigation. ART regimens, particularly those containing nephrotoxic agents like Tenofovir disoproxil fumarate (TDF), necessitate vigilant dose adjustments and monitoring, especially in genetically predisposed populations such as individuals of African descent [20, 17]. The RAPID program, promoting same-day ART initiation, has shown improved patient retention and virologic outcomes by minimizing therapy delays. The DCB (Dolutegravir, Cobicistat, and Bictegravir) combination is noted for its lower nephrotoxic profile, presenting a safer alternative for managing nephrotoxicity [3]. Additionally, combining tacrolimus with ART offers promising results for addressing proteinuria and renal impairment [34].

Preventive strategies emphasize regular renal function monitoring and adequate hydration [35]. Biomarkers like cystatin C, KIM1, and NGAL improve renal function assessment, aiding in the early detection of CKD [1]. The Miox-NanoLuc approach provides potential for early nephrotoxicity detection, facilitating timely interventions [29].

Risk mitigation involves managing systemic arterial hypertension and nephrotoxic antiretrovirals, both contributing to CKD in PLHIV [2]. Adherence support is crucial for high-risk groups, directly affecting ART outcomes and reducing virologic failure rates. Factors such as gender, age, and comorbidities impact adherence, necessitating targeted interventions [6]. In regions with high viraemia among HIV-infected patients on ART, adherence improvement strategies are vital for achieving virologic suppression and preventing renal complications [19].

Implementing tailored treatment strategies, preventive measures, and risk mitigation techniques is essential for managing HIV-associated nephrotoxicity. By utilizing advanced prognostic models, monitoring biomarkers, and enhancing ART adherence, healthcare providers can optimize clinical decision-making and improve health outcomes for individuals with HIV, particularly in resource-limited settings where adherence challenges are prevalent. This comprehensive approach addresses multifaceted factors influencing adherence and virological suppression, as highlighted by studies on the experiences of HIV-positive populations in Africa [8, 22, 11].

5.2 Risk Factors, Predictive Models, and Routine Monitoring

Benchmark	Size	Domain	Task Format	Metric
VN-Benchmark[22]	100,678	Hiv Treatment	Virological Non-suppression Assessment	Odds Ratio, Proportion of Non-suppressed Patients
TDF-NB[36]	83	Nephrology	Observational Study	FEPi, uPCR
AFRICOS[16]	2,054	Hiv Treatment	Virologic Failure Assessment	Virologic Failure Rate, Viraemia Rate
RPTEC/TERT1[25]	1,000	Nephrotoxicity	Biomarker Evaluation	Protein Levels, mRNA Levels

Table 1: This table summarizes key benchmarks utilized in the study of HIV-associated nephrotoxicity, detailing their size, domain, task format, and metrics. These benchmarks are critical for understanding the effectiveness of predictive models and monitoring strategies in managing renal complications in HIV-infected individuals.

Benchmark	Size	Domain	Task Format	Metric
VN-Benchmark[22]	100,678	Hiv Treatment	Virological Non-suppression Assessment	Odds Ratio, Proportion of Non-suppressed Patients
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RPTEC/TERT1[25]	1,000	Nephrotoxicity	Biomarker Evaluation	Protein Levels, mRNA Levels

Table 2: This table summarizes key benchmarks utilized in the study of HIV-associated nephrotoxicity, detailing their size, domain, task format, and metrics. These benchmarks are critical for understanding the effectiveness of predictive models and monitoring strategies in managing renal complications in HIV-infected individuals.

Effective management of HIV-associated nephrotoxicity involves identifying risk factors, developing predictive models, and implementing routine monitoring protocols. Genetic predispositions, such as APOL1 variants, significantly influence susceptibility to renal complications in HIV-infected individuals, particularly those of African descent [17]. These genetic factors, along with systemic conditions like hypertension and nephrotoxic antiretrovirals such as TDF, increase the risk of CKD [2].

Predictive models are crucial for stratifying patients based on nephrotoxicity risk, informing clinical decisions and optimizing treatment strategies. Incorporating biomarkers like cystatin C, KIM1, and NGAL into predictive algorithms enhances renal function assessment accuracy, enabling early detection of nephrotoxic effects [1]. These biomarkers, combined with clinical parameters, inform robust predictive models that guide therapy adjustments and improve patient outcomes.

Benchmark	Size	Domain	Task Format	Metric
VN-Benchmark[22]	100,678	Hiv Treatment	Virological Non-suppression Assessment	Odds Ratio, Proportion of Non-suppressed Patients
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Routine monitoring, involving regular renal function assessments, is vital for managing HIV-associated nephrotoxicity, especially given the high prevalence of HIVAN among individuals of African ancestry. Risk factors include low CD4 counts, high viral loads, and prolonged ART use. Regular evaluations can identify complications like acute kidney injury and CKD early, allowing for timely intervention and improved outcomes [20, 13, 7]. Advanced diagnostic tools, such as urinary exosome analysis and the Miox-NanoLuc approach, offer promising avenues for non-invasive early renal injury detection, crucial for preventing progression to severe impairment.

In the context of HIV immune complex kidney disease (HIVICK), treatment options remain limited and often ineffective, particularly for managing renal inflammation from immune complex deposition [34]. This underscores the need for novel therapeutic strategies and routine monitoring to address the complex interplay between immune-mediated damage and nephrotoxicity.

Managing HIV-associated nephrotoxicity effectively relies on a holistic approach, including identifying key risk factors—such as low CD4 counts, high viral loads, and prolonged ART use—developing predictive models to assess renal function, and implementing routine monitoring strategies to detect early kidney impairment signs. This is especially crucial in high-risk populations like those of African ancestry, where HIV-associated nephropathy prevalence can reach up to 38% [20, 13, 9, 7]. By leveraging these strategies, healthcare providers can enhance early detection and management of renal complications, ultimately improving care quality for individuals living with HIV. Table 3 presents an overview of key benchmarks employed in the study of HIV-associated nephrotoxicity, highlighting their relevance to predictive modeling and routine monitoring strategies.

6 Research and Future Directions

6.1 Current Research, Identified Gaps, and Development of New Biomarkers

Recent research advancements in HIV-associated nephrotoxicity have focused on novel biomarkers and sophisticated in vitro models that mimic kidney function, providing insights into the mechanisms of nephrotoxicity and informing improved diagnostic and management strategies. Despite these advancements, understanding the role of macrophages as HIV reservoirs during ART and their nephrotoxic contributions remains incomplete, necessitating further exploration of cellular mechanisms and their renal health implications [28]. Additionally, cytokine dynamics during HAART, crucial for systemic inflammation and renal damage, are inadequately understood, highlighting the need for further studies to optimize therapeutic strategies and health outcomes [27, 4].

Future investigations should prioritize the development of new biomarkers and diagnostic tools. Urinary exosomes, promising for non-invasive renal function monitoring, require standardized isolation methods and exploration of additional biomarkers to enhance clinical applicability [23]. Incorporating tubular-specific markers in larger cohort studies could address current data limitations regarding TDF's renal effects [14]. Longitudinal studies with larger cohorts and repeated measurements are crucial for validating findings and examining factors impacting nephropathy biomarkers in HIV populations [1].

Longitudinal studies are also essential for assessing HIV drug resistance and adherence interventions, crucial for optimizing ART regimens and improving renal outcomes [2]. Research should focus on personalized adherence strategies, technology's role in monitoring compliance, and social determi-

nants of health influencing treatment adherence [8]. Investigating alternative drug combinations and long-term renal outcomes will substantiate nephrotoxicity findings [3].

To address research gaps, targeted interventions for high-risk groups and effective adherence support strategies, particularly in resource-limited settings, should be developed [11]. Concentrating on these areas will deepen understanding of HIV-associated nephrotoxicity and foster innovative diagnostic and therapeutic strategies, enhancing care quality for individuals living with HIV [20].

6.2 Therapeutic Interventions, Drug Safety, and Longitudinal Studies

Research into therapeutic interventions and drug safety is crucial for minimizing renal complications and improving outcomes for HIV patients. Future studies should enhance diagnostic tools and develop safer ART regimens, particularly for HIV and TB co-infected patients at increased kidney disease risk [18]. The metabolic dysregulation challenge in cART patients underscores the need for interventions addressing comorbidities like cardiovascular and neurocognitive disorders [19].

Longitudinal studies are vital for understanding ART's long-term renal health effects, especially in populations with high co-infection and chronic disease rates. These studies should evaluate HIV-associated nephropathy prevalence and cost-effective screening methods across diverse demographics [18]. Investigating specific ART regimens' effects on systemic inflammation and aging is critical for targeted therapeutic interventions [4].

Adherence to HIV treatment is paramount, with research identifying effective strategies such as simplified drug regimens and enhanced patient education to bolster adherence [8]. These approaches are crucial for minimizing nephrotoxicity and improving treatment efficacy. Exploring RAPID strategies across healthcare settings could provide insights into ART initiation's long-term outcomes, informing best practices and enhancing care.

Future research should optimize drug formulations and manufacturing processes to improve ART effectiveness and safety. Establishing standardized definitions and enhancing electronic surveillance for drug-induced nephrotoxicity are necessary for advancing drug safety and facilitating pharmacokinetic studies in vulnerable populations. Prioritizing research that enhances ART adherence, clarifies medication toxicity, and innovates drug delivery systems will advance therapeutic interventions and drug safety for individuals living with HIV, improving quality of life in high-burden regions like sub-Saharan Africa [20, 8, 32, 11].

6.3 Interdisciplinary Research, Future Directions, and Implementation Strategies

Advancing HIV-associated nephrotoxicity management requires an interdisciplinary approach incorporating virology, nephrology, pharmacology, and public health perspectives. Future research should focus on developing in vitro models with enhanced physiological fidelity to better replicate human renal physiology and HIV pathogenesis [24]. Such models would facilitate investigations into patient-specific responses and predictive tool creation, streamlining drug development while adhering to ethical standards.

Understanding T cell and macrophage interactions is crucial for elucidating HIV persistence mechanisms and nephrotoxicity implications [28]. Exploring these interactions may uncover novel therapeutic targets and inform interventions to mitigate renal damage in HIV-infected individuals. Investigating residual immune activation and newer ART options' anti-inflammatory properties could yield insights into reducing nephrotoxicity and enhancing patient health [37].

Implementing same-day ART initiation strategies across diverse populations presents a promising opportunity to improve retention in care and achieve virologic suppression [5]. Future studies should evaluate these strategies' feasibility and impact in various healthcare settings, particularly in resource-limited environments with significant HIVAN burden [7]. Multicenter studies examining HIVAN prevalence and risk factors across African countries, focusing on ethnicity, are essential for developing tailored interventions addressing unique challenges faced by these populations.

Interdisciplinary research should also investigate ART-associated weight gain mechanisms, as this may have implications for metabolic health and nephrotoxicity [37]. By fostering collaboration across disciplines and leveraging innovative research methodologies, the field can progress toward more

effective diagnostic and therapeutic strategies, ultimately enhancing the quality of life for individuals living with HIV.

7 Conclusion

The investigation into HIV-associated nephrotoxicity within the framework of antiretroviral therapy (ART) highlights critical challenges faced by individuals living with HIV. The substantial global HIV burden, with a pronounced impact in sub-Saharan Africa, underscores the necessity for comprehensive management strategies that address both the viral infection and its associated comorbidities, including renal impairment. Although ART has successfully transformed HIV into a manageable chronic condition, the nephrotoxic potential of specific regimens, particularly those containing Tenofovir disoproxil fumarate (TDF), demands careful monitoring and individualized treatment approaches to prevent renal damage.

The pathogenesis of HIV-associated nephrotoxicity encompasses direct viral effects, immune-mediated damage, and drug toxicity, each playing a role in renal impairment. A thorough understanding of these mechanisms is critical for the development of predictive models and the identification of biomarkers that enable early detection and management of nephrotoxic effects. The integration of advanced diagnostic techniques, such as urinary exosome analysis, offers a promising pathway for improving the precision of nephrotoxicity assessments and enhancing patient outcomes.

Comprehensive management and prevention strategies must include tailored treatment plans, preventive measures, and risk mitigation techniques. Identifying risk factors—such as genetic predispositions and systemic conditions—facilitates the development of predictive models and routine monitoring protocols essential for effective management. Furthermore, interdisciplinary research and the pursuit of novel therapeutic interventions are crucial for advancing the field and improving the quality of care for individuals living with HIV.

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