The effect of HIV infection on the management of end-stage renal failure among patients undergoing continuous ambulatory peritoneal dialysis

PhD Thesis

By

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PREFACE

"But we have this treasure in earthen vessels, that the excellence of the power may be of God and not of us. We are hard-pressed on every side, yet not crushed; we are perplexed, but not in despair; persecuted, but not forsaken; struck down, but not destroyed—"

II Corinthians 4:7-9

It has been a long adventurous journey since 2011 when the idea of this project was first conceptualized. Like any worthwhile expedition, it has been paved with patches of good road interspersed with many instances of rocky and bumpy surface. However, I thank God for carrying me thus far. I believe that without Him none of this would have been possible. For "who shall separate us from the love of Christ? Shall tribulation, or distress, or persecution, or famine, or nakedness, or peril, or sword?" (Romans 8:35). I believe that this project was a call from God to do something of potential benefit to a group of vulnerable patients that are often discriminated against because they are too poor or too sick for anyone to try and offer them anything. Because of limited resources, HIV-positive renal failure patients with uncontrolled HIV infection are excluded from state-sponsored dialysis programme and told to fend for themselves and pay for private dialysis or go home and die. They are excluded from even peritoneal dialysis even though it is not limited by the number of available haemodialysis machines. This project was aimed at exploring the use of peritoneal dialysis particularly for indigent patients who would have otherwise not been offered anything due to their HIV infection control. Even prolonging one life for a month, a year or two would have been mission accomplished.

DECLARATION

I Kwazi Celani Zwakele Ndlovu declare that

(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

(ii) This dissertation has not been submitted for any degree or examination at any other university.

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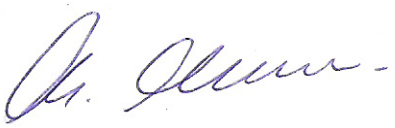
Student signature:  Date: 18 January 2017

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DEDICATION

“The ideal man bears the accidents of life with dignity and grace, making the best of circumstances.”
- Aristotle

I dedicate this thesis to the loving memory of my late father Mlamuli Mathews Ndlovu and my late grandmother Gladys Msomi, whose mental resilience and ability to rise above it all, continues to serve as a great source of motivation and inspiration. Although never having achieved great academic qualifications living in apartheid suppressive times, they made the best of what they had and had a die-hard attitude which continues to live in us today.

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List of Acronyms

AIDS	Acquired Immune Deficiency Syndrome
AIN	Acute interstitial nephritis
ATN	Acute tubular necrosis
Alb	Albumin
ART	Anti-retroviral therapy
ARV	Anti-retroviral
APOL1	Apolipoprotein L1
AC	arm circumference
BMI	Body mass index
CI	95% Confidence Interval
CPM	Calcium, Phosphate and Magnesium
CKD	Chronic kidney disease
CD4	Cluster of Differentiation 4 cell or T4 ‘helper’ lymphocyte
CAPD	Continuous Ambulatory Peritoneal Dialysis
CNS	Coagulase-negative staphylococci
CRP	C-reactive protein
ELISA	Enzyme Linked Immuno Sorbent Assay
ESRD	End-stage renal disease
ESRF	End-stage renal failure
ESR	Erythrocyte sedimentation rate
eGFR	Estimated glomerular filtration rate
ESI	exit-site infection
FGF	Fibroblast growth factor
FSGS	Focal Segmental Glomerulosclerosis
GFR	Glomerular Filtration Rate
HR	Hazard ratio
HAART	Highly active antiretroviral treatment
HD	Haemodialysis
HIV	Human immunodeficiency virus
HIVAN	HIV nephropathy
HIVIC	HIV associated immune complex disease
IRR	Incident rate ratio
IALCH	Inkosi Albert Luthuli Central Hospital
IL-1	Interleukin-1beta
IL-6	Interleukin-6
ISPD	International Society of Peritoneal Dialysis

IP	Intraperitoneal
INH	Isoniazid
KEH	King Edward Hospital
MAMC	Mid-arm muscle circumference
MRSA	Methicillin-resistant *Staphylococcus aureus*
MYH9	Myosin, heavy chain 9
NHLS	National Health Laboratory Service
NGAL	Neutrophil gelatinase-associated lipocalin
NSAIDS	Non Steroidal anti-inflammatory drugs
OR	Odds Ratio
pmp	Per million people
PD	Peritoneal dialysis
PDE	Peritoneal dialysis effluent
PDET	Peritoneal Dialysis Exchange Tubing
PEW	Protein Energy Wasting
RCT	Randomized Control Trial
RPR	Rapid Plasma Reagin (screening test for syphilis)
RRT	Renal Replacement Therapy
SES	Socio-economic status
SGA	Subjective global assessment
SSA	sub-Saharan Africa
TGF	Transforming growth factor
TB	Tuberculosis
TFT	Thyroid function test
FT3	Free Triiodothyronine
UF	Ultrafiltration
USA	United states of America
WC	Waist circumference
WHO	World Health Organisation
WBC	White Blood Cells

ABSTRACT

Continuous ambulatory peritoneal dialysis (CAPD) is cost effective, easy to learn, and requires no complex equipment, thus, is well-suited as a home dialysis modality in areas with distant or limited dialysis facilities. We aimed to evaluate the effects of HIV infection on CAPD outcomes in dialysis-requiring end-stage renal disease (ESRD) patients.

The first report (Chapter 2) evaluated the effects of HIV-infection on primary end points of mortality and catheter failure, and primary morbidity outcomes of first peritonitis and hospital admissions at one year. HIV infection was not shown to adversely influence catheter failure rates or patency; however, uncontrolled HIV infection was associated with increased relative risk of mortality, first peritonitis, and hospital admissions.

The second report (Chapter 3) evaluated the effects of HIV infection on all peritonitis episodes, including relapses and subsequent episodes at 18 months. HIV infection was associated with increased risk for overall peritonitis and peritonitis relapse. Although peritonitis was also associated with adverse catheter failure outcomes, HIV infection was not shown to result in significantly increased catheter failure rates at 18 months.

The third report (Chapter 4) evaluated the effects of HIV infection on nasal carriage of *Staphylococcus aureus*, staphylococcal peritonitis, and catheter infection rates. HIV infection was shown to be a risk factor for methicillin-resistant *S. aureus* nasal colonisation, and that it can increase the risks of coagulase-negative staphylococcal peritonitis and *S. aureus* catheter infections in association with *S. aureus* nasal carriage.

The fourth report (Chapter 5) evaluated shedding of HIV-1 particles into CAPD effluents. HIV particles were shown to be shed in detectable amounts into CAPD effluents even in patients with suppressed plasma viral load, raising concerns of a localised sanctuary site and potential infectivity of HIV-positive CAPD patients on a full complement of antiretroviral therapy.

The thesis contributes to our understanding of the morbidity and mortality associated with uncontrolled HIV infection in ESRD patients on CAPD, the shedding of HIV-1 particles into CAPD effluents, and the resistance profiles of *S. aureus* colonisers and the organism patterns that are likely to cause infection, which may assist in guiding appropriate antibiotic therapy and prophylaxis.

CHAPTER 1: INTRODUCTION

Renal failure is a recognised important contributor to mortality as well as morbidity associated with HIV infection. It can be directly related to HIV infection as in HIVAN, HIVIC, and HIV-associated thrombotic microangiopathy or it can be caused by complications of opportunistic infections, HIV-associated diseases, as well as drugs used to manage HIV infection. Furthermore, it can be caused by chronic diseases unrelated to HIV, such as diabetes, hypertension, and connective tissue diseases. HIV-associated chronic kidney disease (CKD) is particularly relevant for countries of sub-Saharan Africa (SSA) as they carry most of the global HIV burden. Epidemiological studies delineating a reliable prevalence rate of renal diseases in HIV-positive populations of SSA and South Africa are scarce. However, there is a general impression of a substantial population prevalence estimated at between 6% and 48.5% in SSA for the HIV-positive populations and 13.9% for the general populations [1-4].

1.1 HIV and renal disease

Various kidney disease manifestations have been linked to direct viral infection namely HIVAN, HIVIC and thrombotic microangiopathy. These entities result from direct interaction with HIV or immune complex deposition and result in predominantly glomerular disease [5]. They were the predominant pathologies among HIV-positive patients biopsied in the pre-ART era [6]. HIVAN, in particular, was characterised by rapid progression towards ESRD contributing substantially towards end-stage renal failure associated with HIV [7]. The second group of HIV-related renal diseases results from opportunistic infections, HIV-associated diseases, and the drugs used to manage HIV itself or associated conditions. These include disseminated infections resulting in direct renal destruction as in renal *tuberculosis* and pyelonephritis, or severe infections resulting in septicaemia and ATN [8].Various drugs used in the control of HIV infection, such as tenofovir, and those used to treat opportunistic infections/associated conditions (such as rifampin, amphotericin B, Bactrim, etc.) can result in AIN, ATN, and other tubular dysfunction [5]. All these conditions are important causes of acute kidney injury and renal failure in HIV-afflicted individuals, and without prompt diagnosis and treatment can result in permanent chronic renal dysfunction.

Introduction and widespread implementation of ART has improved outcomes associated with HIV and has turned this deadly disease into a chronic manageable condition. With longer life expectancy risk factors typically associated with CKD in the general population such as diabetes, hypertension, race and other genetic factors, family history, and hepatitis become drivers of CKD in the HIV-positive population as well. Reports have documented an increased incidence of CKD in HIV-positive patients of African ancestry in contrast to matched counterparts in the general population, and other race groups [9]. In the general population diabetes and hypertension account for 70% or more

of ESRD. In US surveys these diseases are found to be more common in African American than in age-adjusted white Americans [9]. HIV infection itself has been associated with a many-fold increase in the risk of ESRD in African Americans with HIV compared to those without HIV, a risk similar to the diabetes-associated risk [5]. Other causes of kidney disease not directly linked to virus infection include classic FSGS, IgA nephropathy, AA-amyloidosis, lupus nephritis, membranous nephropathy and post-infectious glomerulonephritis. All these non-HIV-related kidney diseases are likely to occur in the HIV population at rates approximating those of the general population [5].

1.1.1 HIV-associated nephropathy

HIV-associated nephropathy and ESRD occurs almost exclusively among patients of African descent, due to genetic susceptibilities to both development and progression of these diseases [10, 11]. Studies have shown that host factors are important determinants of susceptibility of HIV patients to the development of CKD. African ancestry has been recognised as a significant factor closely associated with the development of several renal diseases. A study by Kopp et al. [12] showed a significant association between MYH9 genetic variation and development of idiopathic FSGS, HIV-associated FSGS, and hypertensive ESRD also collectively referred to as MYH9-associated nephropathies [12]. Nelson et al. [13] identified two specific MYH9 gene variants (S-haplotype and F-haplotype) to have a very strong association to the MYH9-associated nephropathies, but no functional MYH9 gene mutation was identified [13]. Two APOL1 missense variants (termed G1 and G2 alleles) were subsequently identified to be more strongly associated with HIVAN and other MYH9-associated nephropathies than the previously reported leading MYH9 risk variants [14]. Furthermore, the APOL1 gene was neighbouring gene, located 14 kbp 3' downstream from MYH9 and showed very strong linkage disequilibrium patterns with MYH9 variants. Both APOL1 variants are common in African chromosomes but absent in European chromosomes [14, 15]. In a biopsy series from HIV-infected African-American patients, Fine et al. [16] demonstrated a strong association between APOL 1 risk alleles and non-HIVAN FSGS as well as nearly three-fold higher risk for the development of ESRD in this population group.

1.2 Treatment options

As noted above, not only is HIV a direct cause of CKD but it can also complicate the clinical course of patients with ESRD due to other causes. In the pre-ART era, the survival of most patients with HIV infection and end-stage renal failure from whatever cause was dismal. In the presence of antiretroviral treatment, dialysis-requiring kidney failure can be managed with conventional methods used to manage ESRD in the general population. Treatment options range from haemodialysis and peritoneal dialysis to renal transplantation. Studies have shown that kidney transplantation in a well-controlled HIV environment was not associated with increased infectious complications [11]. Well-controlled

HIV infection is regarded as undetectable HIV viral load and stable ARV therapy. Studies have also shown that survival of HIV-infected haemodialysis patients on ARV treatment was comparable to those of HIV negative and non-diabetic patients [17]. ARV treatment has been demonstrated to significantly increase survival rates of HIV seropositive haemodialysis patients. Factors associated with poor outcome include the following [17]:

- Low CD4 counts
- High viral loads
- HIVAN as the cause of ESRD
- Absence of ARV's
- Opportunistic infections.

However, access to the full range of RRT options is a challenge for most patients in need in low- to middle-income countries such as those of SSA where HIV infection is also most prevalent. This lack of access is more heightened among the indigent who rely substantially on the state to satisfy their basic needs and among the HIV-positive patients who often are too ill to be prioritised in resource rationing. A 2015 review by Liyanage et al. [18] estimated that between 47% and 73% of patients requiring dialysis worldwide were unable to receive it. In this analysis, Africa was estimated to have the lowest RRT access at between 9% to 16%, reflecting a significant unmet need. The prevalence of RRT was noted to be around 80 pmp in Africa compared to 1840 pmp in North America according to 2010 estimates. In South Africa, an overall RRT prevalence of 189 pmp has been reported recently consisting of 71.9 pmp in the public sector and 799.3 pmp in the private sector [19]. Although servicing about 84% of the South African population who are uninsured and poor, the public sector provided much less access compared to the private healthcare sector which services 16% of the population with healthcare insurance. These disparities in the provision of and access to RRT are typical of the difficulties faced by many low- to middle-income countries where indigent populations who rely on the state for most of their healthcare needs are too often unsatisfied due to the scarcity of resources.

1.3 Peritoneal dialysis

Peritoneal dialysis (PD) is a well-established form of dialysis used throughout the world [20]. Its' main advantage is that it is relatively easy to teach, particularly important in the South African context as there is a large rural and semi-urban population with limited educational exposure. Secondly, it is easy to travel with allowing for home dialysis therapy as it requires no complex machine. It allows for a more liberal diet as well as fluid intake. It is premised on a principle of continuous fluid and solute removal allowing for a continuous steady-state biochemical and fluid status, and it avoids see-saw fluctuations associated with intermittent haemodialysis [20]. It is also associated with

preservation of residual renal function, improved fluid and blood pressure control, reduced incidence of left ventricular hypertrophy, and less likelihood of severe cardiac arrhythmias [21].

1.3.1 Health economics of Peritoneal Dialysis

PD has been suggested to be a potentially more cost-effective option compared to HD, readily implementable in low-resource settings as it requires less infrastructure and staff complement compared to HD and can be provided easier for patients living very far from dialysis centres [22-24]. However, health economic analysis studies have painted a more complex picture. In general, PD is found to be more economical than HD as reported by many analyses from Europe, North America, South America and Asia [22-26]. In Africa, only a handful of studies have attempted to do comparative economic analyses of PD vs HD [24-27]. Furthermore, meaningful review and comparison of countries involved have been compromised by varying methodologies and limited information provided on the inputs used to estimate costs [28]. These studies have reported mixed results with some African countries such as South Africa, Sudan, and Egypt reported to have very high PD to HD cost ratios at 1.72, 1.12 and 4.55, respectively, while countries such as Kenya and Senegal were reported to have more favourable PD to HD cost ratios at 0.75 and 0.72, respectively, comparable to western countries such as the UK and USA with cost ratios of 0.52 and 0.78, respectively [24, 25]. High costs of PD fluids which often are imported is the major factor frequently credited with driving PD to HD cost ratios unfavourably [29, 30]. Lack of trained health care workers and perceived higher infective complications associated with indigent populations are other factors which impede rapid PD growth in Africa. Conditions which have been associated with favourable PD growth are PD first policies, conducive government reimbursement and import tax policies, local PD fluid manufacturing and procurement, and investment in PD research, education and training [25].

Under the right conditions, PD can potentially quickly upscale RRT access to those in desperate need. PD implementation requires far fewer resources and infrastructure costs compared with HD which is associated with very high start-up costs such as water purification systems and expensive HD machines. Furthermore, PD requires far fewer health care personnel and patient visits to maintain compared to in-centre HD which requires a lot more highly skilled health care personnel and frequent patient visits to the dialysis centre to be effective. Fewer clinic visits which can be once in one to four months, impose a far less burden on a typical CAPD patient compared to the recommended thrice weekly HD visits which can impose a tremendous financial and social burden on an indigent dialysis patient with limited resources. Socio-demographic factors, such as level of education, and availability of electricity, clean running water, and adequate sanitation system, have also been cited as hindrances to effective PD upscaling, but these factors also pose equally challenging problems to HD offerings [29]. The success of the PD first policies in Hong Kong and other parts of Asia in improving patient

survival and outcomes, such as prolonging residual kidney function, lowering infection risk, and increasing patient satisfaction, and in reducing the financial burden to the state typically posed by dialysis offerings highlights the potential of PD in expanding effective dialysis access [31, 32]. When considering all factors, the lower start-up costs, infrastructure requirements, health care personnel to patient ratios and socioeconomic demands on patients, PD seem to offer a more cost-effective option particularly for an indigent patient living far removed from a dialysis centre.

1.3.2 CAPD in Africa

Although CAPD offers great promise to increase access to RRT in the second most populous continent, that is also afflicted with enormous problems of poverty, and under development, its' countries have failed to capitalize on this potential. CAPD prevalence is estimated to be less than 20 pmp with some old estimates quoted as low as 2.2 pmp [25, 26]. Most of the continents CAPD offering is concentrated in South Africa with a prevalence rate of 26.2 pmp that is divided unequally between the public (20.9 pmp) and private (54.1 pmp) sectors [19]. Although estimated to contribute around 85% of the African PD population, the South African CAPD population only accounts for 13.9% of people on RRT in the country [19, 26]. An inclination favouring HD over CAPD that is common across the continent. Some of the impediments that have been cited to hinder growth including economic considerations such as prohibitive costs of PD fluids that are often imported and transported across rudimentary or non-existent transport infrastructure and unfavourable government policies have been noted above. However, the few studies that have been published on outcomes of CAPD in AFRICA have not shown inferior outcomes, with one South African retrospective study reported patient survival of 86.7%, 78.7% and 65.3% at 1 year, 2 years and 5 years, respectively, and technique survival of 83.3%, 71.7% and 62.1%, respectively [33]. This study is notable as it was based in a poor rural province that was not serviced by a nephrologist but was able to achieve outcomes comparable with those of highly industrialised nations [34-37]. This shows the potential of CAPD in providing adequate RRT and acceptable outcomes in a setting of underdevelopment and poverty. However, peritonitis rates vary widely with some countries such as Egypt and Senegal previously reported rates of between 0.55-0.60/patient-years well below the ISPD recommended targets at the time [38-40]. Whereas other countries such as South Africa and Sudan have reported rates above those recommended by ISPD guidelines at 0.82-0.87/year [33, 41].

1.3.3 Complications of Peritoneal Dialysis

There are several complications associated with the use of peritoneal dialysis system the major being infective, metabolic, nutritional and mechanical problems. Infective complications by far are the most important of all the complications, encompassing peritonitis, catheter exit infections, and tunnel infections. This complication depends on a delicate balance between colonisation of the PD system,

by organisms such as *Staphylococcus aureus*, and the local peritoneal defence mechanisms (chemotaxis, opsonisation, cytokine release). The main routes of infection are either through the catheter lumen resulting from touch contamination or through the outside of the catheter via exit site or tunnel contamination [20]. The other routes are through visceral micro-perforation as well as translocation of microorganisms from the intestinal lumen or urogenital organs to the peritoneal cavity [42]. This complication can in the majority of cases be managed without the need of withdrawing peritoneal dialysis, but it is also the most important complication leading to morbidity and change to haemodialysis [20].

1.3.4 CAPD associated peritonitis

Peritonitis in the setting of CAPD is defined by the presence of a cloudy PD effluent or abdominal pain and presence in PDE of more than 100 WBC/mm^3 that has more than 50% polymorphonuclear cells or a positive culture in PDE [43, 44]. Rates vary widely from country to country and between units of individual countries from rates of about 0.82 episodes/patient-years to rates as low as 0.2 episodes/patient-years published in some reports, reflecting a multiplicity of factors which contribute to the peritonitis risk [33-35, 45-47]. Gram-positive organisms account for the majority of cases of peritonitis, with *Staphylococcus* species found in about 36.8% of peritonitis episodes [43]. Gram-negative peritonitis is associated with poorer outcome and higher mortality. *Pseudomonas*, the most prominent member of this group, carries a very high mortality and is difficult to eradicate without removal of the catheter [48-50]. Furthermore, a small but significant group of peritonitis episodes are caused by fungal infections that are associated with poor outcomes and high mortality, as well as difficulty in eradication without removal of the catheter. Culture-negative peritonitis, where a positive culture result is not obtained, account for a variable 10% to 30% of peritonitis and is frequently associated with culturing techniques employed for the PD effluent [43].

1.3.5 Risk factor for CAPD associated peritonitis

Several factors have been associated with increased risk of developing peritonitis. Technical factors have been long recognised contributors to the development of peritonitis. Therefore, the developments of closed drainage systems such as the Y system and then the spikeless Ultra Twin bag system have significantly improved the incidence of peritonitis. These systems based on flush before fill principle have enhanced PD infection prevention and management [20, 43].

Exit-site and tunnel tract as identified above are prime risk factors for the establishment and spread of infection to the abdomen. Typical infections afflicting these sites are *Staphylococcus aureus* and *Pseudomonas aeruginosa* [43, 44]. Exit-site infection is characterized by the presence of a purulent drainage, with or without associated peri-catheter skin erythema. However, tunnel infection is

characterized by erythema, oedema, or tenderness over the subcutaneous pathway, and typically occurs in the presence of an exit-site infection but may occur alone. To prevent these infections aseptic techniques with nonirritating solutions and catheter immobilization are recommended by the Peritoneal Access Committee of the ISPD [43].

Antibiotic treatment is a risk factor for the development of multidrug resistant microorganisms and fungal peritonitis [43]. The latter being a serious complication associated with death in approximately 25% to 40% of episodes and failure of CAPD technique [44, 51]. It is postulated that antibiotic therapy suppresses the normal bacterial flora of the intestine and induces an overgrowth of intestinal fungi, which in turn invade across the intestinal mucosal barrier to cause an infection in the peritoneal cavity [51].

Staphylococcus aureus nasal/skin carriage is a recognised risk factor for the development of ESIs and peritonitis. A prospective cohort study by Luzar et al. [52] (1990) of 140 consecutive patients beginning CAPD at seven European hospitals enrolled over a year provided some evidence of a link between *S. aureus* nasal carriage and development of ESIs by the same organism. In this study, 63 patients (45%) were identified as *S. aureus* carriers due to a positive pre-CAPD culture of nasal swabs. *Staphylococcus aureus* carrier group had a higher rate of ESI (0.4 episodes/patient-year) than among non-carriers (0.1 episodes/patient-year, p-value 0.012). The probability of remaining free of ESI at 18 months was 92% among non-carriers and 54% among carriers. *Staphylococcus aureus* peritonitis was confined to carrier group while non-carriers had *S. epidermis* related peritonitis predominantly. No *S. aureus* peritonitis was observed in the non-carrier group during the study period. The study showed that nasal cultures were sensitive and sufficient in determining at-risk patients [52]. Bernardini et al. [53] (1996) performed a prospective RCT comparing oral cyclical rifampin (n = 41) to daily application of mupirocin to the exit site (n = 41) as prophylaxis to prevent ESIs. Both regimes were equally effective in reducing *S. aureus* PD-related infections (0.13 and 0.15/dialysis-year at risk, mupirocin vs rifampin, p = NS) compared to prospectively collected prior rates without prophylaxis (0.46/dialysis-year at risk) [43, 53, 54].

Vychytil et al. [55] (1998) performed a prospective cohort study using 76 PD patients treated in one centre in Vienna, Austria, over a three-year period. This study evaluated risk factors for the development of *S. aureus* nasal carriage and *S. aureus* catheter-related infection. The 76 study subjects were allocated to three groups. Group 1 consisted of 15 patients with diabetes. Group 2 consisted of 22 patients with chronic graft failure after renal transplantation who continued immunosuppression because of residual graft function. Group 3 consisted of 39 patients without immunosuppression or diabetes mellitus. The study results revealed a higher incidence of *Staphylococcus aureus* nasal carriage in the diabetic and immunosuppressed groups (73.3% and

72.7% respectively) compared to the non-diabetic and non-immunosuppressed group (59%). *Staphylococcus aureus* catheter infection rate was significantly higher in nasal carriers compared to non-carriers in all groups (0.71/year vs 0.41/year for group 1, 1.17/year vs 0.61/year for group 2, 0.46/year vs 0.16/year for group 3). *Staphylococcus aureus* catheter-related infection rate of immunosuppressed non-nasal carriers was even higher than the infection rate of *Staphylococcus aureus* nasal carriers of non-diabetic non-immunosuppressed Group (0.61/yr vs 0.46/yr). This result highlights the point that immunosuppression can independently escalate the risk of *S. aureus*-related infections in both *S. aureus* nasal carriers and non-carriers. The probability of *S. aureus* peritonitis was found to be significantly higher in both diabetic and immunosuppressed groups [55]. From this study, inferences can be made about the effect of other immunosuppressive conditions, such as HIV/AIDS, on *S. aureus* nasal carriage and risk of catheter-related infection among CAPD patients as literature reports in this regard is scanty.

1.4 CAPD and HIV infection

Since HIV is an immunosuppressive state, with impairment of local defence mechanism as one of many challenges, it follows that the rate of peritonitis may be adversely affected in HIV-positive patients in particular among those with low CD4 counts and uncontrolled HIV infection. CAPD may also aggravate malnutrition and hypoalbuminaemia in this population especially among those with severe wasting syndrome [20]. The presence of protein and amino-acid losses in the dialysate is also thought to potentially exacerbate the occurrence of peritonitis in this group [56]. These factors have the potential of compounding the risk of morbidity and mortality of HIV-positive peritoneal dialysis patients.

1.4.1 Outcomes of CAPD in HIV infection

Few studies have examined the outcomes of CAPD in HIV-infected patients, and all have been retrospective studies with small sample sizes. However limited, these foundational studies have shown improvements in survival and infectious complications rates with the advent of ART [57]. A pre-ART era retrospective study by Tebben et al. [58] with a sample size of 39 HIV-infected CAPD patients showed very poor outcomes. In this study, an overall peritonitis rate of 3.9 episodes/patient-year was identified in the HIV-infected patients compared to a rate of 1.5 episodes/patient-year ($P < 0.001$) among HIV-negative patients of the same unit. Technical factors were some of the factors found to influence this rate with HIV-infected patients trained on the straight system having a significantly increased rate of peritonitis compared to those trained on the Y-disconnect systems (7.1 vs 2.6 episodes/patient year, $P < 0.00$). Furthermore, the one and two-year catheter survival rates were significantly reduced in the HIV-positive population (43% vs 68% at one year and 27% vs 50%

at two years). This reduction was attributed to a high mortality rate among the HIV-positive CAPD population.

Khana et al. [59] (2005) reviewed survival experience of 53 HIV-positive CAPD patients treated at Long Island College Hospital between 1987 and 2004 covering the transition period from pre-ART to the ART era. In this retrospective study, HIV-positive CAPD patients tendered to be younger than their HIV-negative counterparts (41 years vs 56 years). African-American race, diabetes, HIV infection, lower CD4 counts were found to be independent predictors of mortality. Furthermore, HIV-positive patients had three times higher relative risk of mortality than HIV-negative patients, but survival depended very much on the clinical and immunologic stage of HIV infection. Factors such as higher serum albumin, higher CD4 count, and HIV therapy were associated with reduced risk of mortality. With each 1g/dl increase in serum albumin, there was an associated 43% reduction in relative risk of death. CD4 counts above 200 were associated with a 90% reduction in the relative risk of death compared with those with CD4 counts less than 50 cells/mm^3. The rates of hospitalization were significantly higher in HIV-positive patients than in HIV-negative patients (3.59 vs 1.63 admissions/patient years). The peritonitis rate was also found to be higher in HIV-positive population than in HIV-negative population (1.4 vs 0.84 episodes/patient years) [59].

Table 1: Survival and complication rates in different studies (Rivera et al.) [57]

	No. of patients on PD	Survival: 1-2-3 years	Mean survival (months)	Hospitalization rate	Peritonitis rate
Tebben, 1993 (1987-1992)	39	58-54-32	10	53.4 days/year	3.9 episodes/year
Kimmel, 1993 (1984-1992)	8	ND	17.9 ± 10.7	NA	2.4 episodes/year
Khana, 2005	53	ND	29.28 ± 34.4	3.59 admissions/year	1.4 episodes/year
Soleymanian, 2006 (1989-2004)	7	100-83-50	48.5 (13.5-77.1)	1.01 admissions/year	NA
Rivera, 2008 (1995-2007)	8	100-62.5-50	41.25 (12-103)	0.69 admissions/year	0.3 episodes/year

NA: Not available.

Table 1 above compares the survival data and complication rates of various studies done on HIV-infected CAPD patients. There has been a notable increase in life expectancy with survival on peritoneal dialysis of up to 9 years in some centres [57]. Mean survival rates have increased from rates between 10 to 17 months to rates above 40 months. Complication rates have also improved over the years, with peritonitis rates in HIV CAPD patients decreased from a range between 2.4 to 3.9 episodes/year in early studies to rates between 0.3 and 1.4 episodes/year in ART era studies. These studies although limited by their retrospective nature highlight the improvements in outcomes of HIV-positive CAPD patients with advances in the management of HIV infection and CAPD over the years.

1.5 HIV shedding in PD fluid

The extent of HIV shedding in PD effluents and the kind of hazards PDE and exchange equipment potentially may pose to health workers and family members assisting or living with HIV-positive CAPD patients has not been fully explored. An in-vitro experimental study by Farzadega et al. [60] (1996) assessed survival kinetics of HIV-1 in PDEs and PDET. In this study, HIV-1 was added to PDE and allowed to incubate at room temperature for 0 to 14 days. HIV-1/PDE mixture was assessed for HIV-1 P24 antigen using special mononuclear cell co-culture medium. High levels of HIV P24 antigen were recovered up to 7 days of room temperature incubation. The HIV/PDE mixture was also placed in PDET and incubated at room temperature for 10 minutes. The solution was then removed, and PDET allowed to dry for up to 168 hours. At various drying time points, the tubing was flushed with HIV culture medium, and the culture supernatant was assayed for the HIV-1 P24 antigen. HIV P24 antigen was recovered from PDET wash out up to 48 hours of drying time. Common disinfectants (Amukin and household bleach) solutions with varying dilutions were incubated with the HIV-1/PDE mixture for 10 minutes. Amukin 50% and 10% household bleach solutions were found to be effective in killing HIV-1 particles in PDE [60]. This study demonstrated the survival of HIV-1 in PDE and PDET. However, there is a general lack of reports on the shedding of HIV-1 particles into PDE in the setting of ART.

1.6 The South African HIV epidemic

The earliest HIV infection cases in South Africa were identified during the 1980's [61]. Three and half decades later the HIV epidemic still poses major challenges to the country's developmental potential. In 2012, 6.4 million South Africans were estimated to be living with HIV comprising 12.2% of the population, with some special groups such as black African females aged 20-34 and males aged 25-49 years reporting very high prevalence rates (31.6% and 25.7%, respectively) [62]. The population level prevalence has also been reported to vary according to residential area type, being highest among informal urban and rural dwellers (19.9% and 13.4%, respectively). KwaZulu-Natal has the highest estimated prevalence rate at 16.9% maintaining its status as the worst affected province in South Africa. By 2009, an estimated 1.95 million orphans and 314000 deaths were reportedly attributed to AIDS [63]. Life expectancy had reduced from 67.4 years in 1990 to 49.2 years in 2003 at the height of the HIV epidemic [64, 65]. From 2004 to 2011 when ARV treatment became available in the public sector, life expectancy increased to 60.5 years (2011), reflecting life gains due to improved ARV treatment penetration [65]. The HIV prevalence rate rose steadily from 1990 but has been relatively stable since 2004, as evidenced by statistically non-differing HIV prevalence rates among pregnant women of between 29.1% and 29.7% [63, 66]. These indicators highlight the continued threat and overall magnitude of the HIV epidemic. From all these statistics, we can deduce that advances have been made in impeding the HIV/AIDS epidemic, as demonstrated by the stabilisation of the infection rate and increased survival of those on ARV treatment. However, there are still tremendous pressures imposed by its sheer magnitude.

The greatest challenge has come from pressures the epidemic has put on budgetary processes. In 2000, the department of health spent 676 million rands on HIV/AIDS programs, increasing to 3.3 billion rands in 2007, further, increasing to 14,5 billion in the 2014/2015 financial year [61, 67]. These increases are mainly due to increased spending in laboratory services, ARV treatment expanded programs, nutritional programs, and general health system upgrades [61]. Improved laboratory services have been key in upscaling the availability of testing opportunities and in improving the clinical management of people affected by HIV/AIDS. The expanded ARV programme has prevented many deaths and has turned this deadly disease to a manageable chronic disease. In 2014, South Africa had 3.1 million people receiving ARV treatment, 47% of the number of individuals estimated to be living with HIV [67]. These statistics highlight the fact that while many lives have been affected and saved, but a considerable portion of people needing assistance have not yet been reached. In 2016, the South African government adopted the test-and-treat model advocated by WHO, thus eliminating the CD4 count threshold for accessing ART and greatly expanding the pool of HIV-infected patients qualifying for the ARV programme [68].

1.7 Renal replacement options in South African

It is now widely recommended that dialysis should not be withheld to patients based on their HIV serostatus alone. International experience has shown that HIV-positive patients can be dialyzable and transplantable [69]. However, in South Africa, renal replacement therapy (RRT) is not widely available due to limited resources. In the private sector, dialysis can be accessed if the patient can afford it or is on medical aid. However, in the public sector dialysis is reserved for those meeting the criteria for the transplant programme [70].

The criteria for renal dialysis and transplantation of HIV-positive patients in South Africa are:

- “Stability on antiretroviral therapy (ART) for at least six months.
- Adherence to ART is demonstrated, and there is a commitment to lifelong therapy.
- Absence of current AIDS-defining illness” [70]

Many patients in clinical practice present with severe dialysis-requiring renal failure at the same time they are diagnosed with HIV. In these instances, there is no time to wait for stabilisation on ARV treatment before initiating renal treatment. Without effective renal replacement treatment, these patients are condemned to uncomfortable and untimely death. The challenge is how to bridge the gap between dialysis-requiring renal failure presenting acutely before ART initiation and the stabilisation of HIV infection on ART, considering the resource constraints in the public sector. This study

evaluates the efficacy of using peritoneal dialysis in the management of HIV-positive patients in settings where HIV infection is being stabilized concurrently with the start of renal replacement.

1.8 Rationale

As noted above South Africa has several budgetary pressures impressing on the public purse. Many important imperatives compete for limited available financial resources. The HIV epidemic is a recognised strain on the county's developmental and economic potential. Its' large size and demands have challenged the budgetary processes of the last two decades. Non-communicable diseases such as CKD which can potentially affect individuals of African descent disproportionately are other worrying threats to both the health and financial wellbeing of the country. The links between HIV and renal disease also increase the complexities of challenges noted.

KwaZulu-Natal along with other provinces face a major shortage of available dialysis slots. Many patients are diagnosed with severe renal failure requiring dialysis, but not all can be accommodated in the available haemodialysis machines. Limiting the eligibility for state funded dialysis to those qualifying for transplantation has not alleviated space constraints of the haemodialysis system. Many patients in clinical practice are chronically under-dialyzed because the system cannot cope with a large number of patients accommodated by it. HIV-associated renal failure can be expected to increase in prominence as identification and diagnoses of HIV-associated renal diseases improve, and as the ageing ART era HIV population develops chronic diseases due to increased survival. Also, the inclusion of this population in the already overstretched dialysis system is a major challenge that needs innovative solutions to address it.

CAPD has the prospect of being able to alleviate the pressures imposed on the haemodialysis system. It has the potential of decanting a substantial number of patients away from the overburdened haemodialysis circuit. This study examines its' applicability and outcomes in an HIV end-stage renal failure population.

1.9 Objectives

1. To evaluate the effects of HIV positivity on outcomes of CAPD among dialysis-requiring renal failure patients.
2. To evaluate the effects of HIV positivity on risk factors, pattern and incidence of peritonitis among peritoneal dialysis patients.
3. To assess the effects of HIV positivity on the *S. aureus* nasal carriage and incidence of staphylococcal peritonitis and catheter-related infection among renal failure patients undergoing peritoneal dialysis.

4. To examine the presence and significance of HIV particles in peritoneal dialysis fluid in HIV-positive patients treated with CAPD.

1.10 Overview of Methodology

1.10.1 Study design and sample population

This prospective cohort study was carried out at KEH and IALCH, in Durban. Seventy HIV-positive and 70 HIV-negative consecutive patients meeting the inclusion criteria were recruited between September 2012 and February 2015. Participants were followed monthly for 18 months or until end points of catheter removal or death. Each objective had a specific hypothesis guiding the methodology and specific outcomes that were observed and monitored monthly during follow-up (Table 2). Detailed methodology for each objective is outlined in chapters 2 to 5 describing specific research manuscripts.

Table 2: Study design summary

	Objective 1	Objective 2	Objective 3	Objective 4
Hypothesis statement	HIV increases the risk of catheter failure, morbidity, and mortality among renal failure patients undergoing peritoneal dialysis.	HIV increases the risk of peritonitis complications among renal failure patients undergoing peritoneal dialysis	HIV increases the risk of staphylococci species peritonitis and *S. aureus* nasal carriage thereby increasing the risk of *S. aureus* peritonitis and catheter infections among renal failure patients undergoing peritoneal dialysis	HIV particles are present in the PD fluid in negligible amount and decrease even further with ARV treatment.
Study type:	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
Study population	KEH and IALCH dialysis population	KEH and IALCH dialysis population	KEH and IALCH dialysis population	HIV-positive CAPD patients
Exposures	HIV	HIV	HIV	ART
Risk factors	1. CD4 count 2. Viral load 3. ART 4. Diabetes	1. CD4 count 2. Viral load 3. ART 4. Diabetes	1. CD4 count 2. Viral load 3. ART	1. CD4 count 2. Diabetes 3. Malnutrition 4. Peritonitis

	Objective 1	Objective 2	Objective 3	Objective 4
	5. Employment 6. Level of education 7. Race 8. Malnutrition 9. Type of residence	5. Employment 6. Level of education 7. Malnutrition 8. Race 9. Type of residence		5. Employment
Outcomes	1. Catheter patency rate 2. Survival/mortality 3. First peritonitis event 4. Hospitalisation rate 5. Length of hospital stay	1. All peritonitis events	1. *S. aureus* nasal carriage 2. *S. aureus* peritonitis 3. Coagulase-negative staphylococci peritonitis 4. Exit site infections 5. Tunnel infections	1. PD fluid HIV viral level 2. Change in PDE viral level

1.10.2 Inclusion Criteria

Participants had to meet all the following inclusion criteria to be eligible for enrolment into the trial:

i). Written informed consent obtained prior to the initiation of any study procedures;

ii). Male or female subjects, younger than 60 years of age at the time informed consent is obtained;

iii). Renal Failure - as evidenced by eGFR of less than 15 ml/min

iv). Tenckhoff catheter inserted either at KEH or IALCH PD wards within two weeks before recruitment.

1.10.3 Group stratification:

Participants were stratified according to HIV infection status in into an HIV-positive group if ELISA positive or control (HIV-negative) if they were negative. Two 4th generation HIV ELISA tests performed by the NHLS were used to determine HIV infection status, screening using a HIV Ag/Ab Combo (CHIV) assay (ADVIA Centaur® XP, Siemens Healthcare Diagnostics, Tarrytown, NY, USA) and confirmation using HIV Combi and HIV Combi PT assays (Cobas e601, Roche Diagnostics, Mannheim, Germany).

1.11 Overview of the Thesis

The thesis is divided into six chapters, including this one:

Chapter 1: Outlines the background and the context of the study as well as the rationale, objectives and short overview of methodology.

Chapter 2: (Published work)
The paper entitled "**CONTINUOUS AMBULATORY PERITONEAL DIALYSIS IN PATIENTS WITH HIV AND END-STAGE RENAL FAILURE**" addresses objective 1 of section 1.11. It has been published in Peritoneal Dialysis International, the official journal of the International Society for Peritoneal Dialysis. It has been presented as published in the journal.

Chapter 3: (Published work)
The manuscript entitled "**Peritonitis outcomes in patients with HIV and end-stage renal failure on peritoneal dialysis: A prospective cohort study**" addresses objective 2 of section 1.11. It has been published in BMC Nephrology. It has been presented as published in the journal.

Chapter 4: (Manuscript Submitted and under review)
The manuscript entitled "**Staphylococcal nasal colonisation and peritoneal dialysis infective outcomes in patients with HIV and end-stage renal failure: A prospective cohort study**" addresses objective 3 of section 1.11. It has been submitted for publication in BMC infectious diseases and is under review. It has been presented in the format requested by the journal.

Chapter 5: (Published work)
The manuscript entitled "**Detection of human immunodeficiency virus-1 ribonucleic acid in the peritoneal effluent of renal failure patients on highly active anti-retroviral therapy**" addresses objective 4 of section 1.11. It has been published in Nephrology Dialysis Transplantation. It has been presented as published in the journal.

Chapter 6: Provides a general discussion and conclusion as well as proposes future work and recommendations.

CHAPTER 2: CAPD OUTCOMES IN HIV PATIENTS

Chapter 2 evaluates the effects of HIV-infection on outcomes of CAPD in end-stage renal failure patients requiring dialysis at one year. The outcomes of interest are catheter patency and failure, first peritonitis event, mortality, and hospital admissions. The paper entitled "**CONTINUOUS AMBULATORY PERITONEAL DIALYSIS IN PATIENTS WITH HIV AND END-STAGE RENAL FAILURE**" is presented as published in Peritoneal Dialysis International.

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CONTINUOUS AMBULATORY PERITONEAL DIALYSIS IN PATIENTS WITH HIV AND END-STAGE RENAL FAILURE

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♦ ***Background:*** **This study aimed to evaluate the differences in continuous ambulatory peritoneal dialysis (CAPD)-related outcomes according to human immunodeficiency virus (HIV) status of end-stage renal failure patients.**

♦ ***Methods:*** **This prospective cohort study included 70 HIV-negative and 70 HIV-positive consecutive patients with renal failure who underwent dialysis with newly inserted Tenckhoff catheters between September 2012 and February 2015. Patients were followed up monthly at a central renal clinic for 1 year or until the primary endpoints of technique failure or death.**

♦ ***Results:*** **Technique failure rates were similar (HIV-negative: 0.270 episodes/person-year; HIV-positive: 0.298 episodes/person-year; hazard ratio [HR], 1.09; 95% confidence interval [CI], 0.51 – 2.32; $p = 0.822$). However, there were fewer HIV-positive patients with complete 1-year follow-up with a patent catheter (42.9% vs 58.6% in the HIV-negative cohort; $p = 0.063$) owing to their higher all-cause mortality rate (0.55 vs 0.25 deaths/person-year, respectively; HR, 2.11; CI, 1.07 – 4.14; $p = 0.031$). Cluster of differentiation 4 count (CD4) < 200/μL (HR, 5.39; CI, 2.20 – 13.21; $p < 0.001$) and unsuppressed viral load (HR, 3.63; CI 1.72 – 7.67; $p = 0.001$) were associated with increased mortality hazards. Rates of first peritonitis were 0.616 (HIV-negative) and 1.668 (HIV-positive) episodes/person-year (HR, 2.38; CI, 1.46 – 3.89; $p = 0.001$). All-cause admission rates were 1.52 (HIV-negative) and 2.97 (HIV-positive) hospital admissions/person-year (HR, 1.66; CI, 1.12 – 2.48; $p = 0.013$).**

♦ ***Conclusion:*** **Although HIV-seropositive status of patients on CAPD did not adversely influence technique failure rates or patency at 1 year, uncontrolled HIV infection may be associated with increased relative risk of mortality and morbidity.**

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KEY WORDS: Continuous ambulatory peritoneal dialysis; CAPD; HIV; catheter patency; technique failure; mortality; hospital admission; morbidity; first peritonitis.

Renal failure is an important contributor to mortality in patients with human immunodeficiency virus (HIV) infection, which is relevant particularly to sub-Saharan Africa as it carries a disproportionate burden of the worldwide HIV epidemic (1). End-stage renal failure in patients with HIV may be directly related to HIV infection as in HIV-associated nephropathy (HIVAN), or it may be secondary to comorbidities such as diabetes, hypertension, and connective tissue diseases, among others (2–5). The presence of end-stage renal failure may contribute to additional pressure on general health budgets, since the cost of renal replacement can be prohibitive, especially in resource-constrained settings. It is widely accepted that dialysis should not be withheld from patients based on their HIV status alone. International experience has demonstrated that dialysis and transplantation are feasible in HIV-positive patients (6–9). Highly active anti-retroviral therapy (HAART) significantly increases survival rates of HIV-seropositive patients on hemodialysis (10). However, many developing countries cannot provide a wide range of renal replacement options owing to limited resources. Peritoneal dialysis (PD) is relatively cheap and easy to learn, and it requires no complex equipment. It is particularly well-suited as a home dialysis modality in areas with distant or limited dialysis facilities (11–14).

Developing countries have several important imperatives competing for limited available financial resources. South Africa, as many middle- to low-income countries, has limited hemodialysis slots, resulting in the failure to accommodate many patients with end-stage renal disease (ESRD). Consequently, South Africa limits the eligibility for state-funded dialysis to those who are suitable for transplantation and have no irreversible progressive diseases of vital organs (15). Human immunodeficiency virus-positive patients are also excluded from dialysis if their infection is not well controlled, as indicated by an unsuppressed viral load, low cluster of differentiation 4 (CD4) counts, and/or a HAART duration of less than 6 months (16). However, a significant number of patients in our clinical practice present late with both HIV and end-stage renal failure diagnosed almost simultaneously, needing the concurrent initiation of HAART and dialysis. This study aimed to evaluate the differences in continuous ambulatory peritoneal dialysis (CAPD) outcomes, primarily technique failure, mortality, and first peritonitis events, according to HIV status of ESRD patients.

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METHODS

SITES

Two sites were used for enrolment: King Edward VIII Hospital (KEH), a 799-bed regional referral hospital located in Durban, South Africa, providing regional and limited specialist services to parts of KwaZulu-Natal province, and Inkosi Albert Luthuli Central Hospital (IALCH), an 846-bed specialist referral hospital for KwaZulu-Natal province, covering a catchment area of approximately 10 million people. The renal unit based in IALCH offers CAPD (total patient population of 219), hemodialysis (150 patients), and transplantation services.

STUDY POPULATION

This prospective cohort sub-study followed up 70 HIV-negative and 70 HIV-positive patients with renal failure who underwent dialysis with a newly inserted Tenckhoff catheter at the 2 hospital sites between September 2012 and February 2015. Patients with incident CAPD between the ages of 18 and 60 years were recruited consecutively until each cohort reached the targeted 70 patients. The sample size was calculated from an anticipated effect size based on peritonitis rate differentials observed by previous similar studies (15) to achieve a power of 80% and an alpha of 0.05. The study protocol was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BE 187/11), and informed consent was obtained from study patients prior to enrolment. The status of HIV infection was determined by HIV-1 ELISA prior to enrolment, and HAART management was left to the discretion of the local clinic. The insertion of Tenckhoff catheters was performed by experienced surgeons predominantly laparoscopically (66 seronegative patients and 35 HIV-seropositive patients) at IALCH. The remaining patients underwent percutaneous Tenckhoff catheter insertion, performed by trained nephrologists at KEH (4 seronegative and 20 HIV-seropositive patients) and IALCH (15 HIV-seropositive patients). Most patients initially managed at KEH were newly diagnosed with end-stage renal failure requiring dialysis and HIV; thus they did not yet qualify for state-sponsored dialysis.

ENROLMENT AND FOLLOW-UP

On enrolment, demographic, clinical, and biochemical data were recorded. All patients were followed up at a central renal clinic in IALCH monthly for 12 months or until the endpoints of catheter removal or death. At each follow-up, vital signs, results of clinical assessment and biochemical tests, and details of complications and hospital admissions in the intervening period were recorded on predefined questionnaires. Laboratory tests for full blood count, serum urea, serum creatinine, serum electrolytes, serum albumin, C-reactive protein, erythrocyte sedimentation rate, and serum ferritin were done by the South African National Health Laboratory Service (NHLS), and results were periodically retrieved from the IALCH electronic results database.

OUTCOMES

All Tenckhoff catheters were removed centrally at IALCH. The indications for removal and the corresponding date were recorded as endpoints of study. Technique failure was defined as catheter removal due to mechanical complications or infection. In-hospital mortality at IALCH was dated, and the certified cause of death was recorded. Deaths occurring outside IALCH were recorded as home deaths, and the corresponding details were obtained via telephone interviews with the participant's relatives. This process was initiated when a participant missed a scheduled monthly clinic visit. The date of home death was not always accurate and was based on the mentioned telephone interview, the date of the last clinic visit, or the date of stoppage of delivery of CAPD fluids to the patient's home. A peritonitis event was defined as presentation with cloudy effluent and/or abdominal pain combined with an effluent white blood cell count (WCC) > 100 cells/μL and/or positive PD effluent culture. The peritonitis diagnosis was established by the CAPD nurse and the attending physician; the latter decided whether to admit the patient or treat as an outpatient depending on the severity of the clinical presentation. Initial peritonitis events were recorded via predefined questionnaires during monthly clinic visits along with the date of presentation, time interval from Tenckhoff catheter insertion to event, presenting PD WCC, and culture results retrieved from the hospital electronic record. Hospital admissions were noted during the monthly follow-up on the prescribed questionnaire. The numbers of days between date of admission and discharge for each admission episode were summed up and recorded as cumulative hospital admission days.

STATISTICAL ANALYSIS

Continuous variables were expressed as mean ± standard deviation or medians (interquartile range) and compared using Student's *t*-test or Wilcoxon Mann-Whitney test when appropriate. Proportions and categorical variables were compared using the chi-square test or Fisher's exact test, when 1 of the cell counts was below 5. Survival estimates were computed by the Kaplan-Meier method, and the log-rank test was used to compare survival curves. Univariate Cox regression survival analysis was used to estimate the association between HIV and its associated subgroups and the outcome variables. Poisson regression was used to estimate the association of HIV and cumulative hospital admission days, a count outcome. Multivariable Cox regression analysis was used to identify the independent predictors of survival. Multivariable Poisson regression analysis was used to identify independent predictors of increased cumulative hospital admission stay. All analyses were performed using STATA, version 13.1 (StataCorp LP, College Station, TX, USA). The level of significance was set at $p < 0.05$.

RESULTS

PATIENT CHARACTERISTICS

The study population of 140 CAPD patients included 70 HIV-negative and 70 HIV-positive patients. The mean age was 39.1 ± 11.7 (HIV-negative) and 37.0 ± 9.4 (HIV-positive) years, with women accounting for 42.9% and 52.9% of the 2 cohorts, respectively. There was a significant bias towards African ethnicity in the HIV-positive cohort, accounting for 100% of that group, compared to 84.3% in the HIV-negative cohort ($p = 0.003$). The prevalence of hypertension as a known comorbidity was significantly higher in the HIV-negative cohort (90% vs 74.3%, $p = 0.015$). There were significant differences between the HIV-negative group and the HIV-positive cohort in the mean baseline values of hemoglobin (9.60 ± 2.01 and 8.96 ± 1.61 g/dL, $p = 0.041$), and albumin (35.3 ± 6.7 and 31.0 ± 6.6 g/L, $p < 0.001$) levels. In the HIV-positive cohort, 51.4% of patients were either newly diagnosed with HIV or recently started on HAART (less than 6 months prior to insertion of Tenckhoff catheter). However, 57.1% of the HIV-positive patients had a suppressed viral load (less than 150 copies/mL, hospital laboratory assay limit) at the time of enrolment. While the median baseline viral load was 4,229.5 (interquartile range [IQR] 903 – 91,143) copies/mL for patients with detectable viral loads, the median dropped below the detectable limit (IQR < 150 – 2,990) on inclusion of patients with undetectable viral loads. Twenty percent of HIV patients had CD4 counts less than 200 cells/μL, 21.4% above 500 cells/μL, and the remainder (58.6%) between 200 and 500 cells/μL. Other details of the study population are outlined in Table 1.

TABLE 1
Baseline Characteristics

	HIV-negative ($n = 70$)	HIV-positive ($n = 70$)	*P* value
Age (mean±SD)	39.1±11.7	37.0±9.4	0.247[a]
Weight, kg (mean±SD)	68.9±12.6	66.1±13.7	0.213[a]
Body mass index (mean±SD)	25.1±4.7	24.5±5.4	0.436[a]
Waist circumference, cm (mean±SD)	90.5±10.9	90.0±11.5	0.822[a]
Sex			
Female, *n* (%)	30 (42.9%)	37 (52.9%)	0.236[b]
Race			
African, *n* (%)	59 (84.3%)	70 (100.0%)	0.001[c]
Indian, *n* (%)	9 (12.9%)	0 (0.0%)	
Mixed race, *n* (%)	2 (2.9%)	0 (0.0%)	
Hypertension, *n* (%)	63 (90.0%)	52 (74.3%)	0.015[b]
Diabetes, *n* (%)	4 (5.7%)	7 (10.0%)	0.532[c]
SLE, *n* (%)	4 (5.7%)	1 (1.4%)	0.366[c]
Hepatitis B, *n* (%)	7 (10.0%)	8 (12.1%)	0.737[b]
Primary residence			
Rural, *n* (%)	23 (32.9%)	24 (34.3%)	0.956[b]
Urban, *n* (%)	44 (62.9%)	45 (64.3%)	
Education level			
Primary school, *n* (%)	15 (21.4%)	13 (18.6%)	0.710[b]
High school, *n* (%)	32 (45.7%)	31 (44.3%)	
Post-grade 12, *n* (%)	20 (28.6%)	25 (35.7%)	
Employment history			
Unemployed, *n* (%)	50 (71.4%)	53 (75.7%)	0.766[b]
Employed, *n* (%)	17 (24.3%)	16 (22.9%)	
Tenckhoff catheter-insertion method			
Laparoscopic, *n* (%)	66 (94.3%)	35 (50.0%)	<0.001[c]
Percutaneous, *n* (%)	4 (5.71%)	35 (50.0%)	
Hemoglobin, g/dL (mean±SD)	9.60±2.01	8.96±1.61	0.041[a]
Albumin, g/L (mean±SD)	35.3±6.7	31.0±6.6	<0.001[a]
eGFR, mL/min/1.73 m^2 (mean±SD)	7.0±3.6	7.1±4.6	0.935[a]
Creatinine (μmol/L), median (IQR)	736.5 (542–974)	718 (598–888)	0.917[d]
CRP (mg/L), median (IQR)	19 (6–35)	56.5 (21–108)	<0.001[d]
ESR (mm/hr), median (IQR)	49 (29–66)	88 (50–129)	<0.001[d]
Ferritin (ug/L), median (IQR)	642 (370–1,049)	593 (381–973)	0.858[d]

TABLE 1 (cont'd)

	HIV-negative (n = 70)	HIV-positive (n = 70)	P value
CD4 count			
mean (cells/μL±SD)		380.7±235.4	
CD4<200 cells/μL, n (%)		14 (20.0%)	
CD4 200–350 cells/μL, n (%)		20 (28.6%)	
CD4 350–500 cells/μL, n (%)		21 (30.0%)	
CD4≥500 cells/μL, n (%)		15 (21.4%)	
Viral load			
Median, copies/mL (IQR)		4,229.5 (903–91,143)	
Suppressed (<150 copies/mL), n (%)		40 (57.1%)	
150–1,000 copies/mL, n (%)		8 (11.4%)	
>1,000 copies/mL, n (%)		22 (31.4%)	
HAART history at enrolment			
<6 months, n (%)		36 (51.4%)	
6–12 months, n (%)		9 (12.9%)	
>1 year, n (%)		25 (35.7%)	
HAART drug regimens			
3TC/EFV/ABC, n (%)		59 (84.3%)	
3TC/EFV/AZT, n (%)		2 (2.9%)	
3TC/EFV/D4T, n (%)		3 (4.3%)	
3TC/NVP/ABC, n (%)		3 (4.3%)	
3TC/Alluvia/ABC, n (%)		1 (1.43%)	
3TC/Alluvia/AZT, n (%)		1 (1.43%)	

HIV = human immunodeficiency virus; SD = standard deviation; SLE = systemic lupus erythematosus; eGFR = estimated glomerular filtration rate (MDRD equation); MDRD = modification of diet in renal disease; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; CD4 = cluster of differentiation 4; IQR = interquartile range; HAART = highly active anti-retroviral therapy; 3TC = lamivudine; EFV = efavirenz; ABC = abacavir; AZT = zidovudine; D4T = stavudine; NVP = nevirapine.

[a] T-test for comparison of means.

[b] Pearson's χ^2 test.

[c] Fisher's exact test.

[d] Wilcoxon Mann-Whitney test.

TECHNIQUE FAILURE AT 1 YEAR

The HIV-negative cohort had a higher proportion of patients with a patent catheter reaching 1 year compared to the HIV-positive group (58.6% vs 42.9%, p = 0.063). These values increased to 64.1% and 47.6% (p = 0.062), respectively, if patients who died (3 and 5 subjects, respectively) and experienced catheter loss (3 and 2 subjects, respectively) within the first month of catheter insertion were excluded. Tenckhoff catheter loss was 21.4% in both groups, with technique failure rates of 0.270 and 0.298 episodes/person-year, respectively, and HIV was associated with a non-significant Cox proportional hazard ratio of 1.09 (95% confidence interval [CI] 0.51 – 2.32, p = 0.822) for technique failure. Kaplan-Meier technique survival rates at 1 year censored for death and catheter removal not related to technique failure were 77.0% (95% CI 64.2 – 85.8%) for seronegative patients and 74.6% (95% CI 59.7 – 84.6) for HIV-seropositive patients (Figure 1) (increased to 80.6% and 76.8%, respectively, on excluding patients who did not complete the first month). Severe non-resolving bacterial peritonitis led to catheter loss in 12.9% of HIV-negative and 10.0% of HIV-seropositive patients, while fungal peritonitis was responsible for loss in 2.9% and 4.3%, respectively.

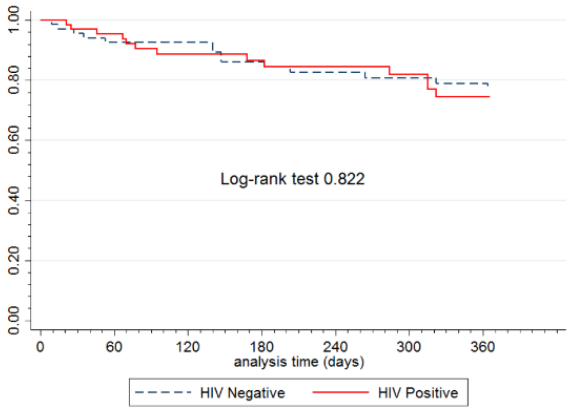

Figure 1 — Kaplan-Meier estimates for catheter patency censored for mortality, catheter loss not related to technique failure, and loss to follow-up. HIV = human immunodeficiency virus.

Mechanical complications were responsible for catheter loss in 2.9% of patients in both cohorts. One HIV-negative and 2 HIV-seropositive patients had Tenckhoff catheters removed owing to improved renal function at 92, 119, and 176 days, respectively, following insertion. Two patients were lost to follow-up: 1 in the control cohort underwent live related transplantation at 223 days, and 1 from the HIV cohort left for private hemodialysis at 138 days (Supplemental Table 1).

MORTALITY

All-cause mortality was 18.6% (13/70) in the HIV-negative cohort and 34.3% (24/70) in the HIV-positive cohort (p = 0.035), with 38% (5/13) of control group deaths occurring within 120 days of Tenckhoff catheter insertion, compared to 67% (16/24) of deaths in the HIV-positive cohort (p = 0.016). Forty-two percent (15/36) of HIV-seropositive patients that were started on HAART less than 6 months prior to Tenckhoff catheter insertion died during the follow-up period, accounting for 62.5% (15/24) of the overall mortality of this cohort. Overall mortality rates were 0.251 (HIV-negative) and 0.550 (HIV-positive) deaths/person-year, with a crude Cox univariate proportional hazard ratio of 2.11 (95% CI, 1.07 – 4.14, p = 0.031) associated with HIV (Table 2). Sudden unspecified home death was the reason of loss to follow-up of 11.4% and 17.1% patients in the control and HIV-seropositive cohort, respectively. Peritonitis with overwhelming sepsis resulted in deaths of 2.9% patients of both cohorts, while sepsis without associated peritonitis caused deaths of 2.9% patients in the control cohort and 10.0% in the HIV-seropositive cohort. Table 2 summarizes outcome rates along with corresponding unadjusted univariate Cox proportional hazard ratios or

TABLE 2
Crude Outcomes

Incidence rates per person-year	HIV-negative (n = 70)	HIV-positive (n = 70)	Hazard ratio/incidence risk ratio	P value
Technique failure rate	0.270	0.298	HR 1.09 (0.51–2.32)	0.822[a]
Mortality rate	0.251	0.550	HR 2.11 (1.07–4.14)	0.031[a]
HAART duration				
<6 months		0.714	HR 2.65 (1.26–5.58)	0.010[d]
>6 months		0.398	HR 1.57 (0.67–3.69)	0.296[d]
Baseline CD4 count				
<200 cells/μL		1.692	HR 5.39 (2.20–13.21)	<0.001[d]
200–350 cells/μL		0.673	HR 2.67 (1.14–6.26)	0.024[d]
>350 cells/μL		0.274	HR 1.08 (0.43–2.7)	0.867[d]
Baseline viral load				
>150 copies/mL		1.021	HR 3.63 (1.72–7.67)	0.001[d]
<150 copies/mL		0.311	HR 1.25 (0.53–2.92)	0.608[d]
Peritonitis rate[g]	0.616	1.668	HR 2.38 (1.46–3.89)	0.001[a]
HAART duration				
<6 months		1.768	HR 2.53 (1.43–4.48)	0.001[d]
>6 months		1.571	HR 2.29 (1.27–4.12)	0.006[d]
Baseline CD4 count				
<200 cells/μL		5.069	HR 5.16 (2.11–12.61)	< 0.001[d]
200–350 cells/μL		1.800	HR 2.58 (1.29–5.15)	0.007[d]
>350 cells/μL		1.299	HR 1.98 (1.12–3.49)	0.018[d]
Baseline viral load				
<150 copies/mL		1.337	HR 2.04 (1.17–3.54)	0.012[d]
>150 copies/mL		2.491	HR 3.48 (1.84–6.60)	<0.001[d]
All-cause admission rate[f]	1.52	2.97	HR 1.66 (1.12–2.48)	0.013[a]
HAART duration				
<1 year		3.27	HR 1.82 (1.16–2.84)	0.009[d]
>1 year		2.70	HR 1.19 (0.91–1.55)	0.209[d]
Baseline CD4 count				
<200 cells/μL		8.22	HR 3.02 (1.55–5.89)	0.001[d]
200–350 cells/μL		2.68	HR 1.49 (0.83–2.69)	0.185[d]
>350 cells/μL		2.46	HR 1.46 (0.91–2.34)	0.117
Baseline viral load				
>1,000 copies/mL		3.92	HR 2.53 (1.45–4.4)	0.001[d]
<1,000 copies/mL		2.51	HR 1.42 (0.91–2.2)	0.121[d]
Accumulative hospital admission days	14.8[c]	25.9[c]	IRR 1.47 (1.34–1.61)	<0.001[b]

TABLE 2 (cont'd)

Incidence rates per person–year	HIV-negative ($n = 70$)	HIV-positive ($n = 70$)	Hazard ratio/incidence risk ratio	P value
Baseline CD4 count				
<200 cells/μL		45.9	IRR 3.10 (2.65–3.61)	<0.0001[e]
200–350 cells/μL		27.3	IRR 1.84 (1.62–2.09)	<0.0001[e]
>350 cells/μL		21.5	IRR 1.45 (1.30–1.62)	<0.0001[e]
Catheter-related admissions	0.924	1.67	HR 1.58 (0.997–2.50)	0.051[a]

HIV = human immunodeficiency virus; HR = hazard ratio; HAART = highly active anti-retroviral therapy; CD4 = cluster of differentiation 4; IRR = incidence risk ratio.
[a] Univariate Cox proportional hazards model.
[b] Univariate Poisson regression analysis.
[c] Days hospitalized per person-year.
[d] HIV-negative control group used as the reference group.
[e] Cumulative hospital admission stay rates of each CD4 count sub-groups compared with HIV-negative rates using IR function in STATA (Poisson distribution).
[f] First hospital admission.
[g] First peritonitis episode.

Poisson incidence risk ratios. Figure 2A shows the Kaplan-Meier estimates for mortality-free days censored for catheter loss and loss to follow-up, with log-rank test ($p = 0.027$) suggesting significant differences in the patient survival curves for the 2 groups. Proportional hazard ratios (HRs) for subgroups of the HIV-seropositive cohort with CD4 count of less than 200 cells/μL (HR 5.39, 95% CI, 2.20 – 13.21, $p < 0.001$), detectable baseline HIV-1 viral load above 150 copies/mL (HR 3.63, 95% CI 1.72 – 7.67, $p = 0.001$), and HAART duration at baseline of less than 6 months (HR 2.65, 1.26 – 5.58, $p = 0.010$) were significantly higher than for the subgroups with better controlled HIV infection (Table 2), indicating much higher mortality hazards associated with HIV for these subgroups compared to the HIV-negative cohort. Figure 2B shows Kaplan-Meier estimates for patient survival based on baseline CD4 count, with groups censored for catheter loss and loss to follow-up. Log-rank test ($p < 0.001$) demonstrated a significantly increased risk for mortality with CD4 counts below 350 cells/μL. There was no difference in the survival curves of patients with CD4 count above 350 cells/μL and HIV-negative patients ($p = 0.867$). After adjusting for confounding variables, baseline serum albumin level (HR 0.85, 95% CI 0.79 – 0.92, $p < 0.001$), serum ferritin level (HR 1.001, 95% CI 1.000 – 1.001, $p = 0.009$), and HIV-1 viral load detectability (HR 2.74, 95% CI 1.03 – 7.28, $p = 0.044$) were independent predictors for mortality (Table 3).

PERITONITIS

Fewer HIV-negative patients experienced peritonitis during the 1-year follow-up than HIV-seropositive patients (38.6% vs 60.0%, $p = 0.011$). The peritonitis rates (first peritonitis event) were 0.616 (HIV-negative cohort) and 1.668 (HIV-seropositive cohort) episodes/person-year (HR 2.38, CI 1.46 – 3.89, $p = 0.001$), reaching 5.069 episodes/person-year when the baseline CD4 count dropped below 200 cells/μL in the HIV-seropositive cohort (HR 5.16, CI 2.11 – 12.61, $p < 0.001$). The median time from Tenckhoff catheter insertion to first peritonitis event was 137 (28 – 218) days for HIV-negative and 58 (21 – 118) days for HIV-positive cohort ($p = 0.080$), with 15.7% (11/70) of HIV-negative and 41.4% (29/70) of HIV-seropositive patients experiencing their first peritonitis event within 90 days after the insertion ($p = 0.001$). Kaplan-Meier peritonitis-free survival rates at 1 year censored for death, catheter loss and loss to follow-up were 55.4% (95% CI 41.8– 67.0%) for seronegative patients and 27.9% (95% CI 16.6 – 40.5%) for HIV-seropositive patients (log-rank test, $p = 0.0003$) (Figure 3). Furthermore, peritonitis was associated with significantly lower technique survival (59.4% vs 94.8% in the absence of peritonitis, log-rank $p < 0.0001$). The distribution of cultured microorganisms causing first peritonitis was similar in the HIV-negative and seropositive cohorts: gram-positive organisms (25.9% vs 31.0%, respectively, $p = 0.653$), gram-negative organisms (48.1% vs 38.1%, respectively, $p = 0.409$), and fungi (3.7% vs 0, respectively, $p = 0.391$) (Supplemental Table 2). Multivariable Cox proportional hazards analysis identified diabetes (HR 4.59, CI 1.85 – 11.34, $p = 0.001$) and baseline CD4 count below 200 cells/μL (HR 4.86, CI 1.63 – 14.44, $p = 0.004$) as independent predictors of first peritonitis event.

HOSPITAL ADMISSIONS

Complications requiring at least 1 hospital admission in the follow-up period were seen in 62.9% (44/70) patients of the control and 80% (56/70) of the HIV cohort ($p = 0.025$). The median time from Tenckhoff catheter insertion to first hospital admission was 34 (20 – 114.5) days for the HIV-negative cohort and 31.5 (16.5 – 97) days for the HIV-positive cohort ($p = 0.453$). The incidence of all-cause hospital admissions was 1.52 (HIV-negative) and 2.97 (HIV-positive)

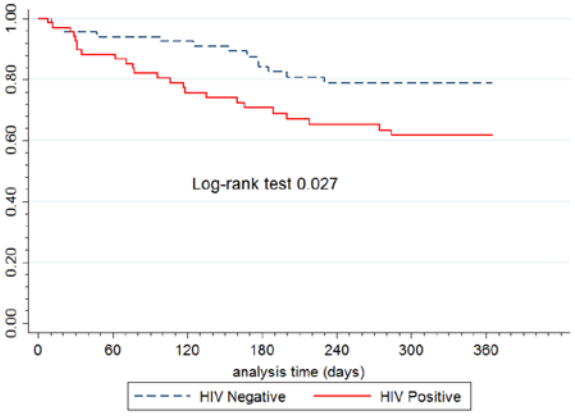

Figure 2A — Kaplan-Meier estimates for mortality outcome censored for catheter loss and loss to follow-up for all-cause mortality. HIV = human immunodeficiency virus.

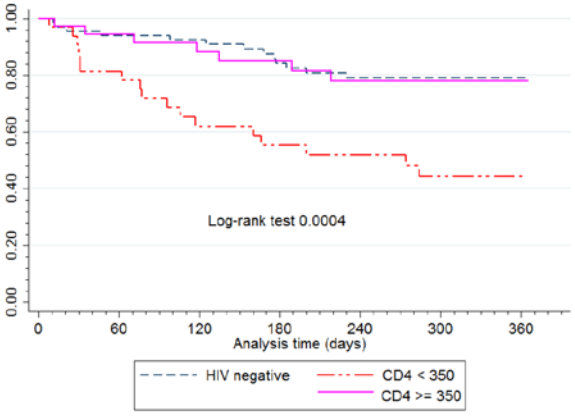

Figure 2B — Kaplan-Meier estimates for mortality outcome censored for catheter loss and loss to follow-up for all-cause mortality according to baseline CD4 count. CD = cluster of differentiation. HIV = human immunodeficiency virus.

admissions/person-year (Cox HR 1.66, 95% CI 1.12 – 2.48, $p = 0.013$), rising to 8.2 (95% CI 4.7 – 14.5) admissions/person-year when the CD4 count dropped below 200 cells/μL in the HIV-positive cohort (Table 2). The incidences of catheter associated hospital admissions (first admission), secondary to infective and mechanical complications, were 0.924 (HIV-negative) and 1.67 (HIV-positive) admissions/person-year (Cox HR 1.58, 95% CI 0.997 – 2.50, $p = 0.051$). Catheter-associated indications were responsible for 59.1% (control cohort) and 60.7% (HIV cohort) of first hospital admissions (Supplemental Table 3). Baseline viral load above 1,000 copies/mL, CD4 count less than 200 cells/μL, and HAART duration of less than a year were associated with increased hazards for all-cause hospital admission on univariate subgroups Cox regression analysis (Table 2), while race and serum ferritin level were independent predictors of all-cause hospital admissions on multivariable Cox hazard analysis (Table 3). The HIV-positive cohort had a greater number of cumulative hospitalization episodes (122 vs 82) and days spent in hospital (1,131 vs 768) and a higher cumulative rate of days spent in hospital (25.9 vs 14.8 days/person-year) compared to the control cohort (IRR 1.47, 95% CI 1.34 – 1.61, $p < 0.001$). Multivariable Poisson regression analysis identified diabetes (IRR 1.8, 95% CI 1.54 – 2.11, $p < 0.001$), systemic lupus erythematosus (IRR 1.92, 95% CI 1.54 – 2.40, $p < 0.001$), HIV-1 viral load detectability (IRR 1.23, 95% CI 1.08 – 1.40, $p = 0.002$), hemoglobin level (IRR 0.87, 95% CI 0.84 – 0.91, $p < 0.001$), and socioeconomic indicators education and employment as factors strongly associated with increased cumulative number of days spent in hospital (Table 3).

DISCUSSION

This prospective cohort study evaluated the effects of HIV on the outcomes of CAPD in patients with ESRD requiring dialysis. At 1 year, catheter patency rates were similar between the control group (77.0%) and the HIV-positive group (74.6%). However, uncontrolled HIV infection was associated with high mortality and increased peritonitis risk.

Very few studies have examined the outcomes of CAPD in HIV-seropositive patients, with most of them being retrospective studies with small sample sizes. However, these studies have demonstrated improvement in survival and reduction of complication rates concomitant with the use of HAART and advances in CAPD (17–19). There is a significant increase in life expectancy reported, with HIV patients on PD surviving up to 9 years at some centers (17). The mortality rate in our HIV cohort was significantly influenced by the status of HIV management prior to insertion of Tenckhoff catheter, as illustrated by the higher rates in patients with CD4 counts below 350 and 200 cells/μL, detectable HIV viral loads, and shorter duration of HAART prior to initiating dialysis. Further, multivariable Cox regression analysis identified the detectability of HIV viral load at baseline as the strongest independent predictor of mortality, with a hazard ratio of 2.74. This is consistent with the literature, suggesting that the immunologic and virologic state of HIV infection influences survival in patients undergoing dialysis (10,18–20). A pre-HAART era retrospective study by Tebben *et al.* also demonstrated a high mortality rate (0.604 deaths/year) associated with HIV, slightly higher than the 0.550 deaths/patient-years observed in our study. Furthermore, they reported a 33% 1-year mortality and 43% of participants reaching 1 year with a patent catheter, comparable to the 34.3% mortality and 42.9% of our HIV cohort patients reaching 1 year with a patent catheter (18). These almost identical mortality outcomes highlight some challenges faced by developing countries in exploiting advances in HAART and improved outcomes associated with the HAART era, as appreciable proportions of patients require dialysis before effective HIV infection control. A retrospective study of Khanna *et al.* identified African-American race, diabetes mellitus, HIV infection, and lower CD4 counts as independent predictors of mortality, underscoring the contributions of

TABLE 3
Multivariable Analysis

Variables	Hazard ratio/incidence risk ratio (95% CI)	*P* value
Multivariable Cox proportional hazards model		
Technique failure[a]		
HIV	HR 0.31 (0.041–2.34)	0.256
Tenckhoff catheter insertion method[b]	HR 0.73 (0.13–4.21)	0.726
Mortality[a]		
HIV	HR 0.39 (0.052–2.87)	0.354
Baseline serum albumin	HR 0.85 (0.79–0.92)	<0.001
HIV viral load[c]	HR 2.74 (1.03–7.28)	0.044
e serum ferritin	HR 1.001 (1.000–1.001)	0.009
Tenckhoff catheter insertion method[b]	HR 0.99 (0.30–3.26)	0.992
Peritonitis[d]		
HIV	HR 1.56 (0.73–3.33)	0.256
Diabetes	HR 4.59 (1.85–11.34)	0.001
Baseline CD4 count (cells/μL)		
HIV-negative	Reference	
CD4<200	HR 4.86 (1.63–14.44)	0.004
CD4 200–350	HR 1.04 (0.49–2.22)	0.918
CD4≥350	HR 1.00	
Tenckhoff catheter insertion method[b]	HR 0.68 (0.23–1.99)	0.481
All-cause admissions[a]		
HIV	HR 1.12 (0.38–3.31)	0.843
Race	HR 0.35 (0.14–0.90)	0.029
Baseline serum ferritin	HR 1.0004 (1.00003–1.00069)	0.032
Tenckhoff catheter insertion method[b]	HR 1.05 (0.46–2.40)	0.916
Multivariable Poisson regression analysis for cumulative hospital stay[e]		
HIV	IRR 0.95 (0.76–1.19)	0.649
Age	IRR 0.98 (0.97–0.98)	<0.001
Diabetes	IRR 1.80 (1.54–2.11)	<0.001
SLE	IRR 1.92 (1.54–2.40)	<0.001
Body mass index	IRR 1.02 (1.01–1.03)	0.002
Baseline hemoglobin	IRR 0.87 (0.84–0.91)	<0.001
Baseline serum albumin	IRR 1.01 (1.01–1.02)	0.003
Baseline CRP	IRR 0.999 (0.997–0.9997)	0.012
Baseline serum ferritin	IRR 1.0001 (1.000–1.0002)	0.017
Insertion site	IRR 1.23 (1.02–1.48)	0.028
Education	IRR 0.75 (0.69–0.81)	<0.001
Employment	IRR 0.79 (0.70–0.90)	<0.001
Baseline viral load[c]	IRR 1.23 (1.08–1.40)	0.002
Tenckhoff catheter insertion method[b]	IRR 1.02 (0.86–1.23)	0.784

CI = confidence interval; HIV = human immunodeficiency virus; HR = hazard ratio; CD4 = cluster of differentiation 4; SLE = systemic lupus erythematosus; CRP = C-reactive protein; IRR = incidence risk ratio.

[a] Adjusted for age, race, hypertension, diabetes, SLE, body mass index, hemoglobin, serum albumin, C-reactive protein, serum ferritin, primary residence, highest education level, employment, baseline HIV-1 viral load, Tenckhoff catheter insertion site, and Tenckhoff catheter insertion method.

[b] Tenckhoff catheter insertion method: laparoscopic vs percutaneous.

[c] Viral load groups: HIV-negative, 0; HIV viral load < 150, 1; HIV viral load > 150, 3.

[d] Adjusted for age, race, hypertension, diabetes, SLE, body mass index, hemoglobin, serum albumin, C-reactive protein, serum ferritin, primary residence, highest education level, employment, baseline CD4 count, Tenckhoff catheter insertion site, and Tenckhoff catheter insertion method.

[e] Adjusted for age, race, hypertension, diabetes, SLE, body mass index, hemoglobin, serum albumin, C-reactive protein, serum ferritin, primary residence, highest education level, employment, baseline HIV-1 viral load, Tenckhoff catheter insertion site, and Tenckhoff catheter insertion method.

comorbidity and poor HIV immunological state in determining mortality risk (19).

To our knowledge, our study is the first to evaluate prospectively the effects of HIV infection and duration of HAART on both technique failure and mortality among CAPD patients. The results suggest that patients in whom effective control of HIV infection and CAPD are initiated within 6 months of each other are at increased risk of mortality, primarily owing

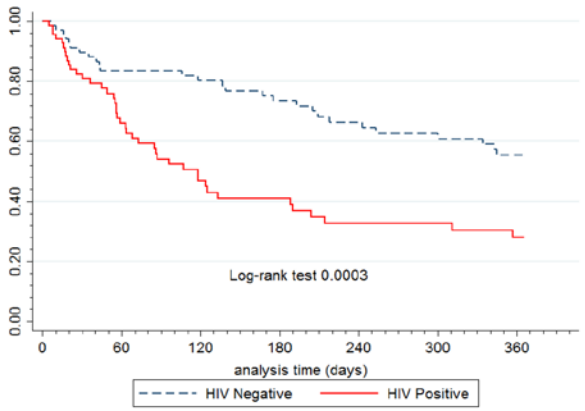

Figure 3 — Kaplan-Meier estimates for first peritonitis event censored for mortality, catheter loss, and loss to follow-up. HIV = human immunodeficiency virus.

to their uncontrolled HIV infection. The results endorse the need for early screening for both HIV and kidney disease in vulnerable populations, and early initiation of HAART in HIV patients with chronic kidney disease (CKD), well in advance of the need for renal replacement. This is especially true in resource-constrained settings where access to various options for renal replacement is limited (10).

The second independent predictor of mortality in HIV-positive patients was baseline serum albumin level (HR, 0.85). This observation is consistent with reports identifying hypoalbuminemia as an independent predictor of mortality in both HIV-seropositive (19–21) and HIV-negative ESRD patients (22–26). Serum ferritin level was another independent predictor weakly associated with mortality (HR, 1.001), an observation previously reported for hemodialysis patients (27,28). These observations probably reflect the importance of underlying malnutrition and inflammation in determining the mortality risk in patients undergoing CAPD (29).

Human immunodeficiency virus-seropositive status was associated with more than a 2-fold increase in hazards for the development of first peritonitis. This risk increased to 5-fold when the baseline CD4 count dropped below 200 cells/μL and was shown to manifest early, with a higher proportion of HIV-seropositive participants (41.4% vs 15.7%, $p = 0.001$) experiencing peritonitis within 90 days after catheter insertion. Such an increased risk of peritonitis associated with HIV and exacerbated by uncontrolled HIV infection was previously reported by Khanna *et al.* and Tebben *et al.* (18,19). Further, a baseline CD4 count below 200 cells/μL was an independent predictor of the first peritonitis event along with diabetes, underscoring the role of impaired immunological defences in determining the initial peritonitis risk. The increased risk of peritonitis raises concerns as it was also associated with lower technique survival (59.4% vs 94.8%, $p < 0.0001$) and was the leading cause of technique failure in both cohorts. Although in our study, the presence of HIV did not adversely influence technique failure at 1 year, early peritonitis exposure has been associated with poor long-term technique survival (30–32). This highlights long-term threats posed by early peritonitis associated with HIV-seropositive status.

Race (HR 0.351) and baseline serum ferritin level (HR 1.0004) were the only significant independent predictors of all-cause hospital admissions. Similar to our findings on mortality, uncontrolled HIV infection at baseline was an important factor in determining risk for all-cause hospital admissions, with baseline viral loads above 1,000 copies/mL, CD4 count less than 200 cells/μL, and HAART duration of less than a year associated with significant hazards for hospital admissions. However, diabetes, systemic lupus erythematosus, baseline HIV-1 viral load detectability, hemoglobin levels, body mass index (BMI), serum albumin, C-reactive protein level, serum ferritin level, education level, and employment status were factors independently associated with increased cumulative number of days spent in hospital, highlighting the importance of malnutrition, inflammation, socioeconomic factors, and HIV and comorbidities control in determining risk for increased morbidity. Tenckhoff insertion site was another factor influencing cumulative number of days spent in hospital, probably underscoring the influence late presentation (the majority of patients inserted at KEH) has on morbidity on dialysis.

The first major limitation of this study is the unavailability of specific causes of death for more than half of the patients, as deaths occurred outside hospital and death certificates could not be accessed. This limited our ability to assess the contribution of catheter-associated complications to mortality and verify independently the actual dates of death. However, the discrepancy in dates, which could be less than 1 month, may not have significantly affected our results. Second, regarding the assessment of technique failure, the disproportionately higher mortality rate in the HIV-seropositive cohort contributed to a dropout rate of 38.6% compared to 21.4% among seronegative patients. This may have introduced bias, resulting in a lower apparent rate of technique failure in the HIV-positive cohort. Third, the matching strategy of restricting the inclusion age to 18 – 60 years may limit the generalizability of our study to only this age group. This matching strategy was employed because HIV-positive CAPD populations are typically younger than their HIV-negative counterparts, which can be a source of confounding (18,19). Lastly, although, sample size calculations were not done in terms of expected effect sizes of technique failure and mortality, the study was adequately powered (87.8%) to assess the mortality risk associated with HIV at 1 year. The very small difference in observed technique failure outcomes (0.270 vs 0.298 failures/person-year) would have required a substantial sample size to reach the level of statistical significance, while the added clinical importance would have been doubtful. The follow-up of this cohort study is still ongoing, with the aim to evaluate broadly catheter complications associated with HIV and their effects on primary outcomes. However, a randomized controlled trial comparing hemodialysis with CAPD is needed.

CONCLUSIONS

This study suggests that HIV infection in patients on CAPD does not adversely influence technique failure rates or patency at 1 year. However, uncontrolled HIV infection may be associated with increased mortality risk, initial peritonitis risk, and hospital admissions. Morbidity and mortality in these patients can be improved with better nutrition, early CKD screening, good management of comorbidities, and timely initiation of HAART before the need for dialysis arises.

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DISCLOSURES

The authors have no financial conflicts of interest to declare.

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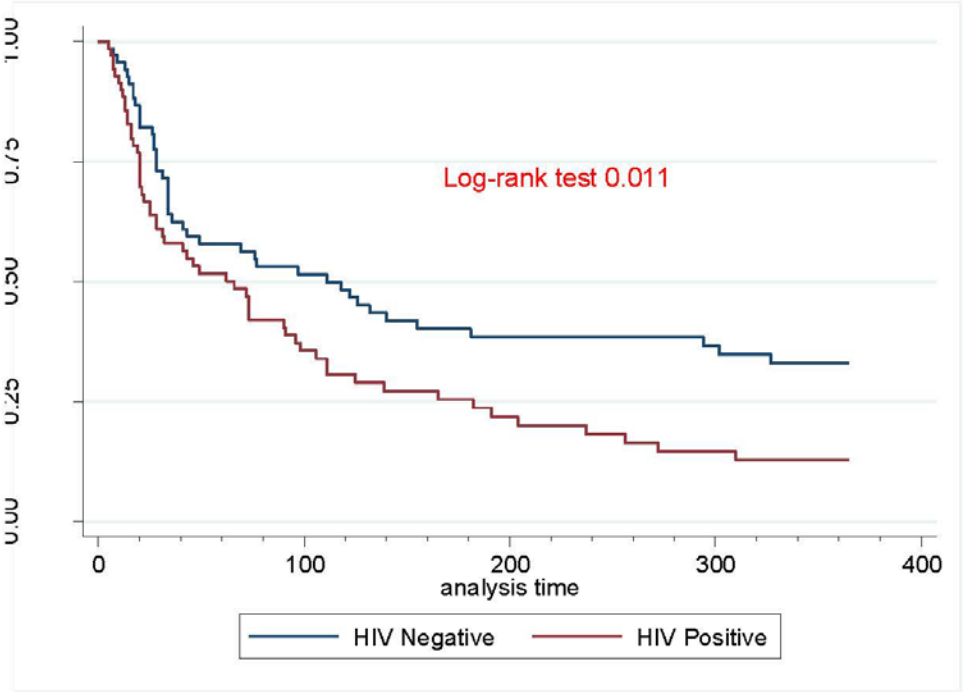
Supplemental Materials for

Continuous ambulatory peritoneal dialysis in patients with HIV and end-stage renal failure

Kwazi C. Z. Ndlovu, Alain Assounga

Supplemental Figure 1: Kaplan-Meier estimates for all-cause hospital admissions censored for mortality, catheter loss and loss to follow-up



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Supplemental Table 1: Patient outcomes at one year

One-year outcome	HIV-Negative (*n* = 70)	HIV-Positive (*n* = 70)	*P* value
Patent catheter, n (%)	41 (58.6%)	30 (42.9%)	0.063
Tenckhoff catheter removed, n (%)	15 (21.4%)	15 (21.4%)	1.000
Bacterial peritonitis, n (%)	9 (12.9%)	7 (10.0%)	0.595
Acinetobacter species, n (%)	1 (1.4%)	5 (7.1%)	0.209
Pseudomonas aeruginosa, n (%)	4 (5.7%)	1 (1.4%)	0.366
Serratia marcescens, n (%)	1 (1.4%)	1 (1.4%)	1.000
Staphylococcus aureus, n (%)	1 (1.4%)	0 (0.0%)	1.000
Stenotrophomonas maltophilia, n (%)	1 (1.4%)	0 (0.0%)	1.000
Culture negative, n (%)	1 (1.4%)	0 (0.0%)	1.000
Fungal peritonitis (Candida species), n (%)	2 (2.9%)	3 (4.3%)	1.000
TB peritonitis, n (%)	1 (1.4%)	1 (1.4%)	1.000
Mechanical complication, n (%)	2 (2.9%)	2 (2.9%)	1.000
Improved renal function, n (%)	1 (1.4%)	2 (2.9%)	1.000
Mortality, n (%)	13 (18.6%)	24 (34.3%)	0.035
Peritonitis & sepsis, n (%)	2 (2.9%)	2 (2.9%)	1.000
Sepsis, n (%)	2 (2.9%)	7 (10.0%)	0.165
Cardiovascular death, n (%)	1 (1.4%)	2 (2.9%)	1.000
Home death, n (%)	8 (11.4%)	12 (17.1%)	0.334
Others, n (%)	0 (0.0%)	1 (1.4%)	1.000
Lost to follow-up, n (%)	1 (1.4%)	1 (1.4%)	1.000

TB, Mycobacterium tuberculosis

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Supplemental Table 2: First peritonitis events

	HIV Negative (n = 27)	**HIV Positive** (n = 42)	***P* value**
Time - tenckhoff insertion to first peritonitis event			
Medians, days (IQR)	137 (28-218)	58 (21-118)	0.080[d]
Within 90 days	40.7% (11/27)	69.0% (29/42)	0.045[a]
Between 90 - 180 days	22.2% (6/27)	16.7% (7/42)	
Between 180 - 365 days	37.0% (10/27)	14.3% (6/42)	
PD WCC (cells/µl), median (IQR)	1390 (500-5020)	1335 (480-3020)	0.761[d]
Peritonitis culture results			
Gram positive	25.9% (7/27)	31.0% (13/42)	0.653[a]
MSSA	7.4% (2/27)	4.8% (2/42)	0.641[b]
MRSA	3.7% (1/27)	4.8% (2/42)	1.000[b]
MSSS	7.4% (2/27)	11.9% (5/42)	0.697[a]
MRSS	7.4% (2/27)	4.8% (2/42)	0.641[b]
Other gram positives	0	4.8% (2/42)	0.517[b]
Gram negative	48.1% (13/27)	38.1% (16/42)	0.409[a]
Pseudomonas species	14.8% (4/27)	4.8% (2/42)	0.201[b]
Klebsiella pneumoniae	7.4% (2/27)	2.4% (1/42)	0.556[b]
Acinetobacter species	3.7% (1/27)	19.0% (8/42)	0.079[b]
Other gram negatives	22.2% (6/27)	11.9% (5/42)	0.319[b]
Fungal peritonitis	3.7% (1/27)	0	0.391[b]
Culture negative	22.2% (6/27)	31.0% (13/42)	0.428[a]

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MSSA, Methicillin sensitive staphylococcus aureus; MRSA, Methicillin resistant staphylococcus aureus; MSSS, Methicillin sensitive staphylococcus species (excluding staphylococcus aureus); MRSS, Methicillin resistant staphylococcus species (excluding staphylococcus aureus)

[a]Pearson's χ^2 test

[b]Fisher's exact test

Supplemental Table 3: Indications for first hospital admission

Indication (%)	**HIV Negative (*n* = 44)**	**HIV Positive (*n* = 56)**	***P* value**
Blocked Tenckhoff catheter	15 (34.1%)	16 (28.6%)	0.554
Peritonitis	9 (20.5%)	12 (21.4%)	0.906
Tract abscess	1 (2.3%)	2 (3.6%)	1.000
Blocked Tenckhoff catheter and peritonitis	1 (2.3%)	4 (7.1%)	0.381
Pneumonia	4 (9.1%)	3 (5.4%)	0.696
Sepsis not related to catheter	3 (6.8%)	6 (10.7%)	0.727
Fluid overload	4 (9.1%)	5 (8.9%)	1.000
Others	7 (15.9%)	8 (14.3%)	0.821

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CHAPTER 3: CAPD PERITONITIS IN HIV PATIENTS

Chapter 2 outlined the effects of HIV-infection on outcomes of CAPD in end-stage renal failure patients requiring dialysis. At one-year catheter patency and failure were not demonstrated to be adversely influenced. Nevertheless, uncontrolled HIV infection was associated with increased mortality, all-cause hospital admissions, and initial peritonitis risk. The first peritonitis rates were significantly increased in the HIV-positive cohort compared to the HIV-negative cohort. Chapter 3 further explores the peritonitis risk and its' influence on catheter failure outcomes at 18 months. It examines the effects of HIV infection on all peritonitis episodes, including relapses and other subsequent episodes. It assesses the overall peritonitis rate, microorganism patterns, and risk factors associated with adverse outcome in relation to HIV infection. Chapter 3 presents a paper entitled "**Peritoneal dialysis peritonitis outcomes in patients with HIV and end-stage renal failure: A prospective cohort study**" as published in BMC Nephrology.

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RESEARCH ARTICLE Open Access

Peritonitis outcomes in patients with HIV and end-stage renal failure on peritoneal dialysis: a prospective cohort study

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Abstract

Background: Few studies have investigated the management of human immunodeficiency virus (HIV)-associated end-stage renal failure particularly in low-resource settings with limited access to renal replacement therapy. We aimed to evaluate the effects of HIV infection on continuous ambulatory peritoneal dialysis (CAPD)-associated peritonitis outcomes and technique failure in highly active antiretroviral therapy (HAART)-treated HIV-positive CAPD populations.

Methods: We conducted a single-center prospective cohort study of consecutive incident CAPD patients recruited from two hospitals in Durban, South Africa from September 2012-February 2015. Seventy HIV-negative and 70 HIV-positive end-stage renal failure patients were followed monthly for 18 months at a central renal clinic. Primary outcomes of peritonitis and catheter failure were assessed for the first 18 months of CAPD therapy. We assessed risk factors for peritonitis and catheter failure using Cox regression survival analysis.

Results: The HIV-positive cohort had a significantly increased rate of peritonitis compared to the HIV-negative cohort (1.86 vs. 0.76 episodes/person-years, respectively; hazard ratio [HR], 2.41; 95% confidence interval [CI], 1.69–3.45, $P < 0.001$). When the baseline CD4 count was below 200 cells/μL, the peritonitis rate rose to 3.69 episodes/person-years (HR 4.54, 95% CI 2.35–8.76, $P < 0.001$), while a baseline CD4 count above 350 cells/μL was associated with a peritonitis rate of 1.60 episodes/person-years (HR 2.10, CI 1.39–3.15, $P = 0.001$). HIV was associated with increased hazards of peritonitis *relapse* (HR, 3.88; CI, 1.37–10.94; $P = 0.010$). Independent predictors associated with increased peritonitis risk were HIV (HR, 1.84; CI, 1.07–3.16; $P = 0.027$), diabetes (HR, 2.09; CI, 1.09–4.03; $P = 0.027$) and a baseline CD4 count < 200 cells/μL (HR, 3.28; CI, 1.42–7.61; $P = 0.006$). Catheter failure rates were 0.34 (HIV-positive cohort) and 0.24 (HIV-negative cohort) episodes/person-years (HR, 1.42; 95% CI, 0.73–2.73; $P = 0.299$). Peritonitis (HR, 14.47; CI, 2.79–75.00; $P = 0.001$), average hemoglobin concentrations (HR, 0.75; CI, 0.59–0.95; $P = 0.016$), and average serum C-reactive protein levels were independent predictors of catheter failure.

Conclusions: HIV infection in end-stage renal disease patients managed by CAPD was associated with increased peritonitis risk; however, HIV infection did not increase the risk for CAPD catheter failure rate at 18 months.

Keywords: Continuous ambulatory peritoneal dialysis (CAPD), End-stage renal disease (ESRD), HIV, Peritonitis, Infection, Technique failure, Catheter failure

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Background

Continuous ambulatory peritoneal dialysis (CAPD) is the dialysis modality of choice for many patients with end-stage renal disease (ESRD) and a cost-effective option easily implemented in low-resource settings [1–3]. However, peritonitis presents an ongoing challenge and is a major cause of technical failure [4–6], particularly under poor socioeconomic conditions and in immunocompromised patients [7, 8]. Considerable advancement has been made in CAPD management over the last decades leading to a substantial decrease in peritonitis rates, with as few as 1 case/51 patient–months reported by some authors [9]. However, peritonitis remains an important factor influencing CAPD-associated morbidity and mortality, and certain organisms, such as fungi and Gram-negative bacteria, are associated with worse outcomes [10–12]. Although reports are inconsistent, some of the factors associated with increased peritonitis risks are age, race, sex, comorbidities (diabetes, human immunodeficiency virus [HIV]), socioeconomic status, smoking, higher body mass index (BMI), malnutrition and chronic inflammation [4, 8, 13–16].

HIV infection presents a unique challenge in patients with ESRD managed with CAPD. As HIV impairs local host defense mechanisms [16], the risk of peritonitis in this population may be influenced by the adequacy of viral control and the patient's immunologic state [8, 17]. Furthermore, the protein and amino acid losses frequently observed in CAPD may aggravate the malnutrition and hypoalbuminemia common in HIV infection, which can further compound the risk of peritonitis [18–20]. The rates of non-communicable diseases such as chronic kidney diseases (CKD) among HIV-positive populations are expected to rise significantly, as highly active antiretroviral therapy (HAART) becomes widely accessible, and life expectancy improves [21]. However, in economically disadvantaged regions such as sub-Saharan Africa where the HIV population is disproportionately concentrated, only a small percentage of those in need are expected to have access to renal replacement therapy [21–23]. CAPD is a relatively inexpensive, easily learned, and readily implemented dialysis option that does not require complex equipment [1–3, 18]. As such, it is particularly well suited as a home dialysis modality in regions where dialysis facilities are limited. However, peritonitis may complicate the use of CAPD in patients with ESRD and HIV. This study aimed to evaluate the effects of HIV infection on CAPD-associated peritonitis rates and outcomes, and to assess risk factors associated with the development of peritonitis and technique failure in HAART-treated HIV-positive CAPD populations.

Methods

The study protocol was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BE 187/11), and research was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent prior to study enrollment.

Sites

We recruited patients for a prospective cohort study from two hospitals in Durban, South Africa between September 2012 and February 2015. King Edward VIII Hospital (KEH) is a 799-bed regional referral center with limited specialist services. Inkosi Albert Luthuli Central Hospital (IALCH) is an 846-bed specialist referral hospital for KwaZulu-Natal province and covers a catchment area of approximately 10 million people. The renal unit based in IALCH offers CAPD (total patient population of 220), hemodialysis (150 patients), and transplantation services.

Study population

We enrolled 70 HIV-negative and 70 HIV-positive patients with end-stage renal failure who underwent dialysis with a newly inserted double-cuffed coiled Tenckhoff catheter at the two hospitals. Patients with incident CAPD aged 18–60 years were consecutively recruited soon after Tenckhoff insertion until each cohort reached the 70-patient target. Peritonitis rate differentials reported by previous similar studies were used to calculate the sample size required to achieve a power of 80% and an α error probability of 0.05 [8]. The HIV infection status was determined by two 4th generation HIV enzyme-linked immunosorbent assays (ELISA) performed by the South African National Health Laboratory Service (NHLS) before enrollment, screening for HIV performed using a HIV Ag/Ab Combo (CHIV) assay (ADVIA Centaur® XP, Siemens Healthcare Diagnostics, Tarrytown, NY, USA) and confirmation using HIV Combi and HIV Combi PT assays (Cobas e601, Roche Diagnostics, Mannheim, Germany). HAART management was left to the discretion of the local clinic. Tenckhoff catheter insertion was performed by experienced surgeons by laparoscopy (66 HIV-negative and 35 HIV-positive patients) at IALCH, and by trained nephrologists percutaneously at KEH (4 HIV-negative and 20 HIV-positive patients) and IALCH (15 HIV-positive patients). All CAPD patients utilized Y-sets, twin-bag systems, and conventional peritoneal dialysis (PD) solutions (Dianeal 1.5, 2.5, or 4.25% dextrose, icodextrin, or amino acid-based solutions; Baxter Healthcare, Deerfield, IL, US). They were trained predominantly as outpatients by the same nursing team, and generally performed four exchanges per day.

Enrollment and follow-up

On enrollment, demographic, clinical, and biochemical data were recorded. All patients were followed-up at a central renal clinic at IALCH monthly for 18 months or until the endpoints of catheter removal or death. At each follow-up, vital signs, clinical assessment, anthropometric measurements, and phlebotomy for biochemical tests were done by the research team, and details of peritonitis events and hospital admissions in the intervening period were recorded on predefined questionnaires. Laboratory tests for full blood count, C-reactive protein (CRP), and serum urea, creatinine, electrolytes, albumin, and ferritin were performed by the NHLS, and results were periodically retrieved from the IALCH electronic results database.

Peritonitis episodes

A peritonitis episode was defined as a clinical presentation with a cloudy effluent or abdominal pain associated with an effluent white blood cell count (WCC) of more than 100 cells/μL or a positive PD effluent culture. The diagnosis of peritonitis was made by the CAPD nurse and the attending physician. The attending physician decided whether to manage the case on an inpatient or outpatient basis depending on the severity of the clinical presentation. All patients initially received intraperitoneal vancomycin and amikacin empirically, and further therapy was modified according to culture results. Treatment duration was typically two weeks unless extended to three weeks by the attending physician due to the cultured organism or response to treatment. Episodes of peritonitis were recorded on predefined questionnaires during monthly clinic visits along with the date of presentation, whether treated as inpatient or outpatient, presenting PD WCC, and the culture result retrieved from the hospital electronic record. PD effluent WCCs were manually assessed using a 40X microscope, and PD effluent culturing was performed by the NHLS microbiology department using standard culturing techniques.

Peritonitis-associated hospital admission was defined as an admission for which peritonitis was cited as one of the indications or where peritonitis was diagnosed during the admission. The hospitalization episodes were recorded on the predefined questionnaire with the date of admission and discharge, indications for, and outcome of the admission. Catheter removal occurring during a peritonitis-associated admission episode was recorded as being related to peritonitis.

Multiple peritonitis episodes were classified as *relapsing* if occurring within 4 weeks of completion of treatment for a prior episode with the same organism or one sterile episode, *recurrent* if occurring within 4 weeks of completion of treatment for a prior episode with a different organism, or *repeat* if occurring more than 4 weeks after completion of treatment for the prior episode [24].

Endpoints

All Tenckhoff catheters were removed at IALCH. The indications for removal and the corresponding date were recorded as study endpoints. Technique failure was defined as catheter removal due to catheter malfunction or infection. The in-hospital mortality dates at IALCH and certified causes of death were recorded. Deaths occurring outside IALCH were recorded as home deaths, and the corresponding details were obtained via telephone interviews with the participants' relatives.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or medians (interquartile range [IQR]) and were compared using the Student's *t*-test or Wilcoxon-Mann-Whitney test as appropriate. Proportions and categorical variables were compared using Pearson's chi-square test or Fisher's exact test as appropriate. Survival estimates were computed using the Kaplan–Meier method, and the log-rank test was used to compare survival curves. Univariate Cox regression survival analysis was used to estimate the association between HIV, associated subgroups, and various risk factors for outcome variables. Multivariable Cox regression analysis was used to identify independent predictors of survival. All analyses were performed using Stata Statistical Software, Release 13 (StataCorp, College Station, Texas, US). The level of significance was set at $P < 0.05$.

Results

Patient characteristics

The mean patient age was 39.1 ± 11.7 (HIV-negative) and 37.0 ± 9.4 (HIV-positive) years with women accounting for 42.9 and 52.9% of the two cohorts, respectively. All patients (100%) in the HIV-positive cohort were of African ethnicity compared to 84.3% in the HIV-negative cohort ($P = 0.003$). Fifty-one percent of HIV-positive patients were either newly diagnosed with HIV or had recently started HAART (less than six months before insertion of the Tenckhoff catheter). However, 57.1% of HIV-positive patients had a suppressed viral load (<150 copies/mL, hospital laboratory assay limit) at the time of enrollment. While the median baseline viral load was 4230 copies/mL (IQR, 903–91,143) for patients with detectable viral loads, the median dropped below the detectable limit (IQR <150–2990) when including patients with undetectable viral loads. Twenty-one percent of HIV-positive patients had CD4 counts >500 cells/μL, 20.0% had <200 cells/μL, and the remainder (58.6%) had 200–500 cells/μL. Other details of the study

Table 1 Baseline characteristics

Variable	HIV-Negative (*n* = 70)	HIV-Positive (*n* = 70)	*P* value
Age (mean ± SD)	39.1 ± 11.7	37.0 ± 9.4	0.247[a]
Weight, kg (mean ± SD)	68.9 ± 12.6	66.1 ± 13.7	0.213[a]
Body mass index (mean ± SD)	25.1 ± 4.7	24.5 ± 5.4	0.436[a]
Waist circumference, cm (mean ± SD)	90.5 ± 10.9	90.0 ± 11.5	0.822[a]
Sex			
Female, *n* (%)	30 (42.9)	37 (52.9)	0.236[b]
Ethnicity			
African, *n* (%)	59 (84.3)	70 (100.0)	0.001[c]
Indian, *n* (%)	9 (12.9)	0 (0.0)	
Mixed ethnicity, *n* (%)	2 (2.9)	0 (0.0)	
Hypertension, *n* (%)	63 (90.0)	52 (74.3)	0.015[b]
Diabetes, *n* (%)	4 (5.7)	7 (10.0)	0.532[c]
SLE, *n* (%)	4 (5.7)	1 (1.4)	0.366 [c]
Hepatitis B, *n* (%)	7 (10.0)	8 (12.1)	0.737[b]
Primary residence			
City, *n* (%)	14 (20.0)	6 (8.6)	0.113[b]
Township[e], *n* (%)	30 (42.8)	39 (55.7)	
Rural, *n* (%)	23 (32.9)	24 (34.3)	
Education level			
Primary school, *n* (%)	15 (21.4)	13 (18.6)	0.710[b]
High school, *n* (%)	32 (45.7)	31 (44.3)	
Post-grade 12, *n* (%)	20 (28.6)	25 (35.7)	
Employment history			
Unemployed, *n* (%)	50 (71.4)	53 (75.7)	0.766[b]
Employed, *n* (%)	17 (24.3)	16 (22.9)	
Smoking (currently)	4 (5.71)	7 (10.0)	0.532[c]
Tenckhoff catheter insertion method			
Laparoscopic, *n* (%)	66 (94.3)	35 (50.0)	<0.001[c]
Percutaneous, *n* (%)	4 (5.71)	35 (50.0)	
Hemoglobin, g/dL (mean ± SD)	9.60 ± 2.01	8.96 ± 1.61	0.041[a]
Albumin, g/L (mean ± SD)	35.3 ± 6.7	31.0 ± 6.6	<0.001[a]
eGFR, ml/min/1.73 m^2 (mean ± SD)	7.0 ± 3.6	7.1 ± 4.6	0.935[a]
Creatinine (μmol/l), median (IQR)	736.5 (542–974)	718 (598–888)	0.917[d]
CRP (mg/L), median (IQR)	19 (6–35)	56.5 (21–108)	<0.001[d]
ESR (mm/hr), median (IQR)	49 (29–66)	88 (50–129)	<0.001[d]
Ferritin (μg/L), median (IQR)	642 (370–1049)	593 (381–973)	0.858[d]
CD4 count			
mean (cells/μL ± SD)		380.7 ± 235.4	
CD4 < 200 cells/μL, *n* (%)		14.0 (20.0)	
CD4 200–350 cells/μL, *n* (%)		20.0 (28.6)	
CD4 350–500 cells/μL, *n* (%)		21.0 (30.0)	
CD4 ≥ 500 cells/μL, *n* (%)		15.0 (21.4)	
Viral load			
Median, copies/mL (IQR)		4230 (903–91143)	
< 150 copies/mL, *n* (%)		40 (57.1)	
150–1000 copies/mL, *n* (%)		8 (11.4)	
> 1000 copies/mL, *n* (%)		22 (31.4)	
HAART history at enrollment			
< 6 months, *n* (%)		36 (51.4)	
6–12 months, *n* (%)		9 (12.9)	
> 1 year, *n* (%)		25 (35.7)	
HAART drug regimens			
3TC/EFV/ABC, *n* (%)		59 (84.3)	
3TC/EFV/AZT, *n* (%)		2 (2.9)	
3TC/EFV/D4T, *n* (%)		3 (4.3)	
3TC/NVP/ABC, *n* (%)		3 (4.3)	
3TC/Alluvia/ABC, *n* (%)		1 (1.43)	
3TC/Aluvia/AZT, *n* (%)		1 (1.43)	

SLE systemic lupus erythematosus, *eGFR* estimated glomerular filtration rate (MDRD equation), *HAART* highly active anti-retroviral therapy, *ESR* erythrocyte sedimentation rate, *CD* cluster of differentiation, *3TC* Lamivudine, *EFV* Efavirenz, *ABC* Abacavir, *AZT* Zidovudine, *D4T* Stavudine, *NVP* Nevirapine, *CRP* C-reactive protein, *HIV* human immunodeficiency virus
[a]Student's *t*-test, [b]Pearson's χ^2 test, [c]Fisher's exact test,
[d]Wilcoxon-Mann-Whitney test
[e]South African Township refers to underdeveloped urban areas created under apartheid for non-white residents

population are outlined in Table 1 and were previously described in our report on 1-year outcomes [25].

Study end points

After 18 months, 54.3% (38/70) of the HIV-negative cohort and 28.6% (20/70) of the HIV-positive cohort were alive with a patent catheter ($P = 0.002$). Technique failure occurred in 24.3% (17/70) of the HIV-negative cohort and 27.1% (19/70) of the HIV-positive cohort ($P = 0.699$), whereas 18.8% (13/70) and 40.0% (28/70), respectively, died ($P = 0.005$). One HIV-negative cohort participant and two HIV-positive participants had their Tenckhoff catheters removed due to improved renal function. One HIV-negative participant underwent kidney transplantation from a live related donor, and one HIV-positive participant left the study to undergo private hemodialysis and was lost to follow-up.

Peritonitis episodes

There were 54 peritonitis episodes observed in 44.3% (31/70) of the HIV-negative cohort and 94 episodes in 65.7% (46/70) of the HIV-positive cohort during the follow-up period ($P = 0.011$). Fifty-one percent (36/70) of

the HIV-positive cohort participants had one or more peritonitis episodes in the first 180 days following Tenckhoff catheter insertion compared to 24.3% (17/70) in the HIV-negative cohort ($P = 0.002$). Nine percent (5/54) of peritonitis episodes in the HIV-negative cohort and 13.8% (13/94) in the HIV-positive cohort were *relapse* episodes ($P = 0.602$). Eleven percent (6/54) of peritonitis episodes in the HIV-negative cohort and 7.4% (7/94) in the HIV-positive cohort were *repeat* episodes with the same organism ($P = 0.448$), while 18.5% (10/54) in the HIV-negative cohort and 23.4% (22/94) in the HIV-positive cohort were *repeat* episodes with a different organism ($P = 0.487$) (Table 2).

The HIV-negative cohort had a higher proportion of Gram-negative peritonitis episodes (44.4%, 24/54) compared to the HIV-positive cohort (27.7%, 26/94) ($P = 0.038$). Culture-negative results were seen in 18.5% (10/54) of HIV-negative and 28.7% (27/94) of HIV-positive cohort episodes ($P = 0.17$) (Table 3). The majority of the peritonitis episodes, 70.4% (38/54) in the HIV-negative cohort and 78.7% (74/94) in the HIV-positive cohort, were successfully treated without discontinuation of CAPD. Peritonitis resulted in catheter removal in 25.9% (14/54) of HIV-negative cases and 17.0% (16/94) of HIV-positive cases accounting for 82.4% (14/17) and 84.2% (16/19) of all technique failures in each cohort, respectively. A small proportion of peritonitis episodes (3.7% (2/54) in the HIV-negative group and 4.3% (4/94) in the HIV-positive group) ended in mortality during observed admissions, accounting for 15.4% (2/13) and 14.3% (4/28) of all deaths in each cohort respectively (Table 2).

Peritonitis rates and proportional hazard analysis

Overall peritonitis rates, excluding *relapse* episodes, were 0.765 (HIV-negative cohort) and 1.855 (HIV-positive cohort) episodes/person-years (1/15.7 months and 1/6.5 months, respectively), with a Cox univariate proportional hazard ratio of 2.41 (95% confidence interval (CI), 1.69–3.45, $P < 0.001$) associated with HIV infection. Kaplan-Meier peritonitis-free survival rates were 6.0% (HIV-positive cohort) and 32.3% (HIV-negative cohort) at 18 months ($P < 0.001$) (Fig. 1). When the baseline CD4 count was below 200 cells/μL, the peritonitis rate

Table 2 Peritonitis outcomes at 18 months

	HIV-Negative	HIV-Positive	*P* value
Peritonitis episodes, *n* (*n* excluding *relapse*)[a]	54 (49)	94 (81)	0.001[b]
Participants with a peritonitis episode at 180 days[e]	24.3% (17/70)	51.4% (36/70)	0.001
Participants with a peritonitis episode at 1 year[e]	38.6% (27/70)	60.0% (42/70)	0.011
Participants with a peritonitis episode at 18 months[e]	44.3% (31/70)	65.7% (46/70)	0.011
Multiple peritonitis episodes			
Time between peritonitis episodes (days), median (IQR)	75 (39–107)	55.5 (34.5–115.5)	0.503[d]
Relapse	9.2% (5/54)	13.8% (13/94)	0.602[c]
Recurrent	3.7% (2/54)	6.4% (6/94)	0.711[c]
Repeat (Same organism)	11.1% (6/54)	7.4% (7/94)	0.448[b]
Repeat (Different organism)	18.5% (10/54)	23.4% (22/94)	0.487[b]
Time - Tenckhoff catheter insertion to peritonitis episode			
Median, days (IQR)	184.5 (98–370)	144.5 (63–296)	0.124[d]
Within 180 days	50.0% (27/54)	56.4% (53/94)	0.453[b]
Between 180 – 365 days	24.1% (13/54)	27.7% (26/94)	0.634[b]
Between 365 – 550 days	25.9% (14/54)	16.0% (15/94)	0.141[b]
PD WCC (cells/μl), median (IQR)	1073 (360–2690)	979 (360–2370)	0.927[d]
Outpatient treatment	33.3% (18/54)	40.4% (38/94)	0.392[b]
Inpatient treatment	66.7% (36/54)	59.6% (56/94)	0.392[b]
Inpatient stay (days), median (IQR)	9 (7–12)	8 (7–14.5)	0.574[d]
Peritonitis episode outcomes			
CAPD continuation	70.4% (38/54)	78.7% (74/94)	0.254[b]
Catheter removal	25.9% (14/54)	17.0% (16/94)	0.195[b]
Mortality	3.7% (2/54)	4.3% (4/94)	1.000[c]

IQR interquartile range, *PD* peritoneal dialysis, *WCC* white blood cell count, *CAPD* continuous ambulatory peritoneal dialysis, *HIV* human immunodeficiency virus
[a]Peritonitis episode count excluding peritonitis relapse' [b]Pearson's χ^2 test, [c]Fisher's exact test
[d]Wilcoxon rank-sum (Mann-Whitney) test, [e]Peritonitis experience – documented 1 or more of peritonitis episodes

Table 3 Peritonitis episode culture results

	HIV-Negative	HIV-Positive	*P* value
All peritonitis episodes			
Gram-positive	33.3% (18/54)	36.2% (34/94)	0.728[a]
Staphylococcus aureus	16.7% (9/54)	7.4% (7/94)	0.082[a]
Coagulase-negative staphylococcus	16.7% (9/54)	23.4% (22/94)	0.332[a]
Other gram-positive bacteria	0.0% (0/54)	5.3% (5/94)	0.159[b]
Gram-negative	44.4% (24/54)	27.7% (26/94)	0.038[a]
Pseudomonas species	13.0% (7/54)	6.4% (6/94)	0.173[a]
Klebsiella pneumoniae	5.6% (3/54)	4.3% (4/94)	0.706[b]
Acinetobacter species	3.7% (2/54)	10.6% (10/94)	0.212[b]
Other gram-negative bacteria	22.2% (12/54)	6.4% (6/94)	0.005[a]
Mixed organisms	0.0% (0/54)	1.1% (1/94)	1.000[b]
Fungal peritonitis	3.7% (2/54)	5.3% (5/94)	1.000[b]
Mycobacterium tuberculosis	0.0% (0/54)	1.1% (1/94)	1.000[b]
Culture-negative	18.5% (10/54)	28.7% (27/94)	0.168[a]
Peritonitis *relapse* episodes			
Coagulase-negative staphylococcus	1.8% (1/54)	3.2% (3/94)	1.000[b]
Other gram-positive bacteria	0.0% (0/54)	1.1% (1/94)	1.000[b]
Pseudomonas species	1.8% (1/54)	3.2% (3/94)	1.000[b]
Other gram-negative bacteria	1.8% (1/54)	1.1% (1/94)	1.000[b]
Culture-negative	3.7% (2/54)[c]	4.3% (4/94)[d]	1.000[b]
Mycobacterium tuberculosis	0.0% (0/54)	1.1% (1/94)	1.000[b]
Peritonitis-associated catheter removal			
Staphylococcus aureus	1.8% (1/54)	0	0.365[b]
Pseudomonas species	9.3% (5/54)	1.1% (1/94)	0.025[b]
Acinetobacter species	1.8% (1/54)	6.4% (6/94)	0.423[b]
Other gram-negative bacteria	5.6% (3/54)	1.1% (1/94)	0.138[b]
Culture-negative	3.7% (2/54)	3.2% (3/94)	1.000[b]
Candida species	3.7% (2/54)	4.2% (4/94)	1.000[b]
Mycobacterium tuberculosis	0	1.1% (1/94)[e]	1.000[b]
Peritonitis-associated mortality			
Coagulase-negative staphylococcus	1.8% (1/54)	1.1% (1/94)	1.000[b]
Escherichia coli	1.8% (1/54)	1.1% (1/94)	1.000[b]
Fungal Peritonitis	0	1.1% (1/94)	1.000[b]
Culture-negative	0	1.1% (1/94)	1.000[b]

HIV human immunodeficiency virus
[a]Pearson's χ^2 test, [b]Fisher's exact test
[c]One relapse episode first presented as *Staphylococcus aureus* peritonitis then relapsed as culture-negative peritonitis
[d]Two relapse episodes first presented as *Pseudomonas aeruginosa* peritonitis then relapsed as culture-negative peritonitis
[e]First presented as culture-negative peritonitis then relapsed as *Mycobacterium tuberculosis*

rose to 3.690 episodes/person-years (HR 4.54, 95% CI 2.35–8.76, $P < 0.001$), while a baseline CD4 count above 350 cells/μL was associated with a peritonitis rate of 1.599 episodes/person-years (HR 2.10, CI 1.39–3.15, $P = 0.001$). The peritonitis *relapse* rate was 0.078 (HIV-negative cohort) and 0.298 (HIV-positive cohort) episodes/person-years (HR 3.88, CI 1.37–10.94, $P = 0.01$) (Table 4).

On multivariable analysis, HIV (HR 1.84, 95% CI 1.07–3.16, $P = 0.03$), diabetes, and a baseline CD4 count less than 200 cells/μL were found to be independent predictors of peritonitis (Table 5).

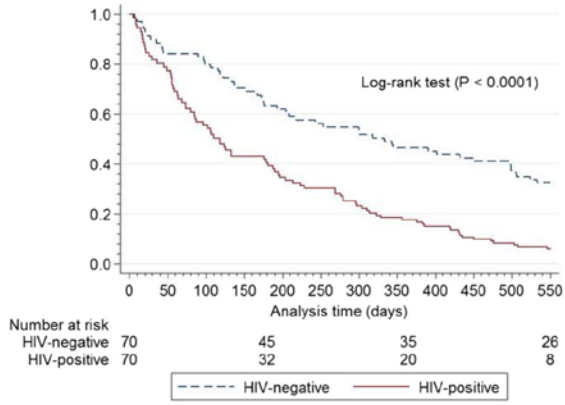

Fig. 1 Kaplan-Meier survival estimates for peritonitis episodes excluding relapses censored for mortality, catheter loss, and loss to follow-up HIV = human immunodeficiency virus

Technique failure

All-cause technique failure rates were 0.237 (HIV-negative cohort) and 0.338 (HIV-positive cohort) episodes/person-years (HR 1.42, 95% CI 0.73–2.73, $P = 0.299$). Kaplan-Meier technique survival rates at 18 months censored for death, catheter removal not related to technique failure, and loss to follow-up were 71.4% (HIV-negative cohort) and 58.2% (HIV-positive cohort), respectively ($P = 0.295$) (Fig. 2). Fifty-three percent (9/17) of technique failures in the HIV-negative cohort and 42.1% (8/19) in the HIV-positive cohort were due to gram-negative peritonitis episodes ($P = 0.516$). Fungal peritonitis was responsible for 11.8% (2/17) (HIV-negative cohort) and 21.0% (4/19) (HIV-positive cohort) of the technique failures ($P = 0.662$). Multivariable proportional hazard analysis identified peritonitis (HR 14.47, CI 2.79–75.00, $P = 0.001$), average hemoglobin concentration and average serum CRP level as independent predictors of technique failure (Table 5). Participants with one or more episodes of peritonitis during follow-up had an 18-month survival rate (Kaplan-Meier technique) of 47.5% compared to 93.9% for those who did not experience peritonitis ($P < 0.0001$) (Fig. 3).

Discussion

This prospective cohort study evaluated the effect of HIV infection on CAPD-associated peritonitis outcomes in patients with ESRD requiring dialysis. At 18 months, HIV was associated with an increased risk (HR 2.41) of developing peritonitis with rates of 1.86 episodes/person-years compared to 0.76 episodes/person-years for HIV-negative CAPD patients. Our HIV-negative peritonitis rate was higher than the target rate of 0.67/year-at-risk advocated by the 2010 International Society for Peritoneal Dialysis (ISPD) guidelines, probably reflecting a higher intrinsic risk in our patient population which is predominantly impoverished with few available choices for alternative hemodialysis [24].

The few retrospective studies that have examined the outcomes of CAPD in HIV-infected patients have demonstrated improvements in survival and reductions in peritonitis rates associated with the use of HAART and advances in CAPD [8, 17, 26]. However, to our knowledge, our study is the first to prospectively evaluate the effects of HIV infection and duration of HAART on peritonitis outcomes among ESRD patients on CAPD. Our HIV-positive CAPD-associated peritonitis rate was much lower than the 3.9 episodes/patient-year reported over 20 years ago by Tebben et al. [17], reflecting a decreased risk associated with the greater availability of HAART over the years. Further, the authors reported a decreased peritonitis rate of 2.6 episodes/patient-year for HIV-positive patients using the Y-disconnect system, highlighting improved outcomes associated with technique enhancements. Khanna et al. [8] reported a lower peritonitis rate of 1.4 episodes/patient-year at the beginning of the HAART era; however, little information was provided on the characteristics of their HIV-positive CAPD population. Our state-sponsored renal replacement program practices a "PD first" policy directing that all dialysis-requiring ESRD patients be routinely started on CAPD. Limited hemodialysis slots are thereby reserved for those who fail CAPD or have medical contraindications to CAPD. This unselective policy determining our CAPD patient population along with the low educational levels and socioeconomic status of our patients (a majority being unemployed, living in impoverished areas, and not having completed grade 12) may have contributed to an increased intrinsic peritonitis risk [14, 27, 28].

Although HIV and diabetes were identified as independent predictors of poor peritonitis outcome, the immunologic state also modified the HIV-associated risk. A baseline CD4 count <200 cells/μL increased the hazards for peritonitis more than 4-fold compared to HIV-negative CAPD patients (3.69 episodes/person-years, HR 4.54, $P < 0.001$). This probably reflects compromised host defense mechanisms against infectious organisms at lower CD4 counts. A baseline CD4 count above 350 cells/μL was associated with a 2-fold increased hazard for peritonitis (1.60 episodes/person-years, HR 2.10, $P = 0.001$), further highlighting the inherent risk associated with HIV infection even with higher CD4 counts. The peritonitis risk was demonstrated to manifest early, as within 180 days following Tenckhoff catheter insertion half of the HIV-positive cohort had at least one documented episode of peritonitis. This risk was shown to persist, as demonstrated by the peritonitis-free survival rate of only 6.0% at 18 months.

Table 4 Incidence rates and Cox proportional hazard univariate analysis

Incidence rates per person-year	HIV-Negative	HIV-Positive	Hazard ratio (95% Conf. Interval)	*P* value
All-cause peritonitis[a]	0.765	1.855	HR 2.41 (1.69–3.45)	<0.001
Baseline CD4 count				
< 200 cells/μL		3.690	HR 4.54 (2.35–8.76)	<0.001
200–350 cells/μL		1.940	HR 2.61 (1.60–4.24)	<0.001
> 350 cells/μL		1.599	HR 2.10 (1.39–3.15)	0.001
Gram-positive peritonitis	0.262	0.675	HR 2.59 (1.46–4.60)	0.001
Gram-negative peritonitis	0.353	0.512	HR 1.40 (0.80–2.44)	0.236
Culture-negative peritonitis	0.150	0.560	HR 3.64 (1.75–7.54)	0.001
Fungal peritonitis	0.028	0.089	HR 3.25 (0.63–16.79)	0.159
Peritonitis *relapse*	0.078	0.298	HR 3.88 (1.37–10.94)	0.010
Baseline CD4 count				
< 200 cells/μL		0.615	HR 10.60 (1.95–57.56)	0.006[b]
200–350 cells/μL		0.698	HR 8.82 (2.90–26.90)	<0.001[b]
≥ 350 cells/μL		0.073	HR 0.97 (0.19–5.00)	0.969[b]
Peritonitis *recurrence*	0.031	0.137	HR 4.62 (0.92–23.21)	0.063
Peritonitis *repeat* (same organism)	0.094	0.160	HR 1.81 (0.60–5.42)	0.289
Peritonitis *repeat* (different organism)	0.156	0.504	HR 3.81 (1.80–8.09)	<0.001
Multiple peritonitis[a]	0.281	0.802	HR 3.22 (1.82–5.71)	<0.001
Baseline CD4 count				
< 200 cells/μL		1.230	HR 8.41 (2.71–26.08)	<0.001[b]
200–350 cells/μL		0.931	HR 3.90 (1.86–8.18)	<0.001[b]
> 350 cells/μL		0.690	HR 2.64 (1.38–5.04)	0.003[b]
Peritonitis hospital admissions	0.815	1.814	HR 2.19 (1.44–3.35)	<0.001
Peritonitis technique failure[c]	0.195	0.285	HR 1.43 (0.69–2.93)	0.335
All-cause technique failure[d]	0.237	0.338	HR 1.42 (0.73–2.73)	0.299
Peritonitis mortality	0.028	0.071	HR 2.67 (0.49–14.60)	0.258
All-cause mortality	0.181	0.498	HR 2.53 (1.31–4.90)	0.006

HR hazard ratio, *CD* cluster of differentiation, *HIV* human immunodeficiency virus
[a] Excluding peritonitis relapse episodes; [b] HIV-positive sub-groups compared to the HIV-negative cohort; [c] Peritonitis technique failure - catheter removal due to peritonitis; [d] Technique failure - catheter removal due to catheter malfunction or infection

The HIV-positive cohort showed an increased gram-positive peritonitis rate compared to the HIV-negative cohort (0.68 vs. 0.26 episodes/person-years, HR 2.59, $P = 0.001$), possibly reflecting a greater susceptibility to touch contamination-related infection due to compromised local defense mechanisms contributing to the HIV-associated peritonitis risk. This finding suggests a role for a prophylactic antibiotic strategy, particularly in the first six months following catheter insertion when the peritonitis risk is highest and more so among patients with low CD4 counts. The HIV-positive cohort also had a significantly increased culture-negative peritonitis rate compared to the HIV-negative cohort (0.56 vs. 0.15 episodes/person-years, HR 3.64, $P = 0.001$). Culture negative cases accounted for 28.7% of the HIV-positive cohort's total peritonitis episodes; this percentage is above the 20% recommended by the 2010 ISPD guidelines. This finding could indicate a higher prevalence of fastidious organisms and mycobacteria in this group [29, 30].

Peritonitis was shown to be the predominant cause of technique failure in both cohorts and was further identified as an independent predictor of this outcome. Although HIV was associated with an increased risk of peritonitis as well as an increased risk for subsequent episodes, it was not shown to significantly influence all-cause technique failure rates (HR 1.42, $P = 0.299$) or peritonitis-associated technique failure rates (HR 1.43, $P = 0.335$). This inconsistency may be partially explained by the significantly higher proportion of gram-negative peritonitis episodes documented in the HIV-negative cohort (44.4 vs. 27.7%, $P = 0.038$); gram-negative organisms

Table 5 Cox proportional hazard univariate and multivariate analyses: risk factors vs. peritonitis and technique failure

Variable	Univariate Cox proportional hazards		Multivariable Cox proportional hazards	
	Hazard ratio (95% Conf. Interval)	*P* value	Hazard ratio (95% Conf. Interval)	*P* value
Peritonitis[d]				
HIV	2.41 (1.69–3.45)	<0.001	1.84 (1.07–3.16)	0.027
Race	0.19 (0.06–0.57	0.003	0.54 (0.05–5.66)	0.607
Catheter insertion method[a]	1.86 (1.28–2.71)	0.001	0.63 (0.28–1.42)	0.269
Catheter insertion site[b]	2.20 (1.45–3.33	<0.001	2.17 (0.84–5.58)	0.108
Diabetes	2.22 (1.35–3.66)	0.002	2.09 (1.09–4.03)	0.027
BMI	1.04 (1.00–1.08	0.033	1.01 (0.95–1.09)	0.720
Waist circumference	1.02 (1.00–1.04)	0.017	1.03 (0.99–1.06)	0.151
Baseline hemoglobin	0.85 (0.77–0.94)	0.002	1.02 (0.88–1.19)	0.786
Baseline albumin	0.95 (0.93–0.98)	0.001	0.98 (0.94–1.02)	0.298
Baseline CRP	1.00 (1.00–1.01)	0.004	1.00 (1.00–1.00)	0.652
Baseline CD4 count (cells/μL)				
HIV-negative	Reference			
CD4 < 200	4.54 (2.35–8.76)	<0.001	3.28 (1.42–7.61)	0.006
CD4 200–350	2.61 (1.6–4.24)	<0.001	1.18 (0.66–2.12)	0.577
CD4 ≥ 350	2.10 (1.39–3.15)	<0.001	1.00	
Residence				
City	Reference			
Township[c]	5.94 (2.17–16.25)	0.001	5.56 (0.82–37.50)	0.078
Rural area	6.07 (2.19–16.8)	0.001	4.68 (0.70–31.07)	0.110
Technique failure[e]				
HIV	1.42 (0.73–2.73)	0.299	0.39 (0.14–1.11)	0.077
Peritonitis	9.29 (2.84–30.36)	<0.001	14.47 (2.79–75.00)	0.001
Catheter insertion site	2.33 (1.09–4.97)	0.029	2.73 (0.49–15.21)	0.252
Catheter insertion method	1.62 (0.79–3.30)	0.185	0.69 (0.13–3.71)	0.663
Average hemoglobin	0.72 (0.59–0.88)	0.001	0.75 (0.59–0.95)	0.016
Average CRP	1.02 (1.01–1.02)	<0.001	1.02 (1.01–1.03)	<0.001

BMI Body mass index, *CD* cluster of differentiation, *CRP* C-reactive protein, *HIV* human immunodeficiency virus
[a]Catheter insertion method- laparoscopic vs. percutaneous, [b]Catheter insertion site - Inkosi Albert Luthuli Central Hospital vs King Edward VIII Hospital,
[c]South African Township refers to underdeveloped urban areas created under apartheid for non-white residents
[d]Adjusted for age, race, gender, smoking, diabetes, body mass index, waist circumference, baseline hemoglobin, baseline serum albumin, baseline C-reactive protein, primary residence, highest education level, employment, baseline CD4 count, Tenckhoff catheter insertion site, and Tenckhoff catheter insertion method (laparoscopic vs. percutaneous)
[e]Adjusted for HIV, peritonitis, age, gender, smoking, diabetes, body mass index, waist circumference, average hemoglobin, average C-reactive protein, average serum ferritin, primary residence, highest education level, employment, Tenckhoff catheter insertion site, and Tenckhoff catheter insertion method (laparoscopic vs. percutaneous)

were also the major causative organism group for technique failures in both cohorts (52.9% and 42.1%, respectively). It may be that HIV infection does not increase the risk of catheter-threatening peritonitis in the first 18 months following insertion but instead increases the risk for treatable peritonitis episodes. However, increased *relapses* and multiple episodes raise concern about the long-term risk of technique failure. Further, the disproportionately higher mortality rate in the HIV-positive cohort contributed to a dropout rate of 44.3% compared to 21.4% in the HIV-negative cohort; this may have introduced bias, resulting in a lower apparent rate of technique failure in the HIV-positive cohort.

The major limitation of our study is that it is a single-center observational study, which inherently limits causation inferences that can be drawn from observed associations. Statistical power, particularly relating to technique failure outcomes, was limited by the relatively small sample size and short follow-up period. The matching strategy of restricting the inclusion age to 18–60 years may limit the generalizability of

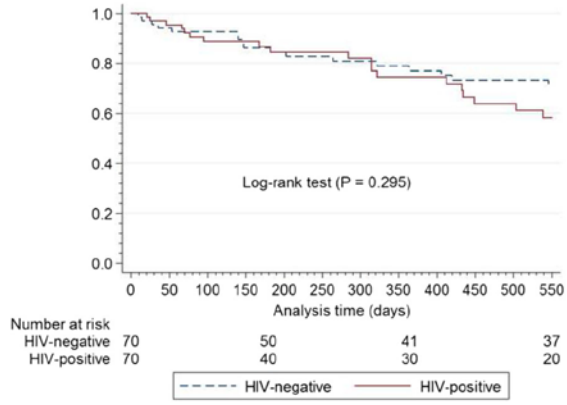

Fig. 2 Kaplan-Meier estimates for catheter patency according to HIV status censored for mortality, loss to follow-up, and catheter removal unrelated to technique failure HIV = human immunodeficiency virus

our results to only this age group. This matching strategy was employed to minimize age as a confounding factor, as HIV-positive CAPD populations are typically younger than their HIV-negative counterparts [8, 17]. More studies are needed to assess outcomes of renal replacement modalities in various HIV-positive ESRD populations.

Conclusions

Our study indicates that HIV infection can adversely influence CAPD-associated peritonitis rates, and this association is further modified by the immunological state of the infected patient. The peritonitis risk attributable to HIV infection manifests early in the course of CAPD treatment and increases the risk for subsequent episodes, but it was not shown to result in increased technique failure rates at 18 months. Early detection of CKD and HIV with the initiation of HAART before significant immunological compromise and careful management of comorbid conditions can help minimize the risk. Prophylactic antibiotics should be considered and investigated as possible strategies to help improve peritonitis outcomes.

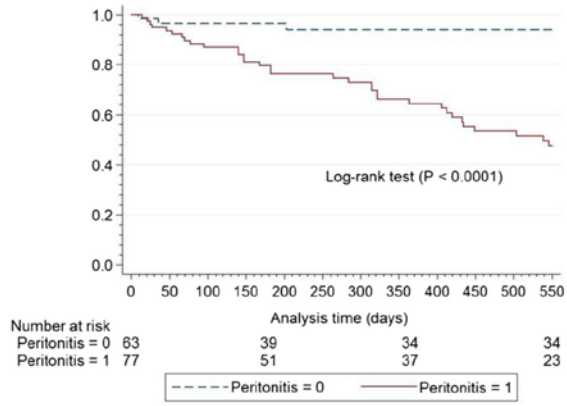

Fig. 3 Kaplan-Meier estimates for catheter patency according to peritonitis experience (1 or more peritonitis episodes during follow-up) censored for mortality, loss to follow-up, and catheter removal unrelated to catheter failure

Abbreviations

CAPD: Continuous ambulatory peritoneal dialysis; CD4: Cluster of differentiation 4; CI: Confidence interval; CKD: Chronic kidney disease; CRP: C-reactive protein; ELISA: Enzyme-linked immunosorbent assay; ESRD: End-stage renal disease; HAART: Highly active antiretroviral therapy; HIV: Human immunodeficiency virus; HR: Hazard ratio; IALCH: Inkosi Albert Luthuli Central Hospital; IQR: Interquartile range; KEH: King Edward VIII Hospital; NHLS: South African National Health Laboratory Service; PD: Peritoneal dialysis; WCC: White blood cell count

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Research idea and study design: KCZN, AA; data acquisition: KCZN; data analysis and interpretation: KCZN, WS, AA; statistical analysis: WS, KCZN; supervision and mentoring: AA. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study protocol was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BE 187/11), and research was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent prior to study enrollment.

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CHAPTER 4: *STAPHYLOCOCCUS* IN HIV AND CAPD

The early peritonitis risk associated with HIV outlined in Chapter 2 was further shown to extend beyond the initial peritonitis event in Chapter 3, as relapses and other subsequent peritonitis events were shown to be significantly higher in the HIV-positive cohort compared to the HIV-negative cohort. HIV infection was associated with increased overall peritonitis rates and the latter further modified by the immunological state of the infected patient. Furthermore, the gram-positive peritonitis rate was shown to be significantly higher in the HIV-positive cohort compared to the HIV-negative cohort. Chapter 4 explores further by examining the effects of HIV infection on *Staphylococcus* peritonitis, the predominant gram-positive organisms associated with CAPD peritonitis. Moreover, the effects of HIV infection on *Staphylococcus aureus* nasal carriage and catheter infection rates in our CAPD cohort are assessed as they are prime risk factors associated with gram-positive peritonitis. Chapter 4 is presented in a manuscript format entitled "***Staphylococcal nasal colonisation and peritoneal dialysis infective outcomes in patients with HIV and end-stage renal failure: A prospective cohort study***" as submitted for publication in BMC infectious diseases and is currently under review.

Staphylococcal nasal colonisation and peritoneal dialysis infective outcomes in patients with HIV and end-stage renal failure: A prospective cohort study

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Running title: *Staphylococcus* in HIV and CAPD

ABSTRACT

Background

Staphylococcal infective complications can cause significant morbidity in human immunodeficiency virus (HIV)-positive patients undergoing dialysis. In poorly resourced regions, such as sub-Saharan Africa, where HIV is prevalent but access to renal replacement therapy is limited, continuous ambulatory peritoneal dialysis (CAPD) can be a cost-effective option. This study evaluated the effects of HIV infection on nasal carriage of *Staphylococcus aureus*, staphylococcal peritonitis, and catheter infection rates in patients with end-stage renal failure managed with CAPD.

Methods

Sixty HIV-positive and 59 HIV-negative CAPD patients were enrolled and were followed up for up to 18 months. *Staphylococcus aureus* nasal carriage (detected by nasal swab culture), Staphylococcal peritonitis (diagnosed by clinical presentation, CAPD effluent Staphylococcal culture, and white blood cell count ≥100 cells/μL), and catheter infections (including exit site and tunnel infections) were assessed monthly. Cox regression survival analysis was used to assess the risk factors for Staphylococcal infection.

Results

At 18 months, *S. aureus* nasal carriage rates were 43.3% and 30.5% (p = 0.147) and the methicillin-resistant *S. aureus* (MRSA) nasal carriage rates were 31.7% and 13.6% (p = 0.018) for the HIV-positive and HIV-negative cohorts, respectively. *S. aureus* peritonitis rates were similar in the HIV-positive and HIV-negative cohorts at 0.136 and 0.129 episodes/person-years, respectively, (hazard ratio [HR] 0.96, 95% confidence interval [CI] 0.36–2.60, p = 0.942). The HIV-positive cohort was associated with an increased coagulase-negative staphylococcal peritonitis rate compared with the HIV-negative cohort (0.435 vs. 0.089 episodes/person-years; HR 5.27, 95% CI 2.13–13.04, p < 0.001). On multivariable analysis,

HIV (HR 3.35, 95% CI 1.20–9.36, $p = 0.021$) and diabetes (HR 3.95, 95% CI 1.18–13.30, $p = 0.026$) were prominent independent predictors of staphylococcal peritonitis. *S. aureus* catheter infection rate in the HIV-positive cohort was higher among the *S. aureus* nasal carriers (0.302 episodes/person-years) than the non-carriers (0.036 episodes/person-years) (HR 8.41, 95% CI 1.03–68.74, $p = 0.047$).

Conclusions

These findings suggest that HIV infection may be a risk factor for MRSA nasal colonisation and it may increase the risks of coagulase-negative staphylococcal peritonitis and *S. aureus* catheter infections in association with *S. aureus* nasal carriage.

KEY WORDS: Continuous ambulatory peritoneal dialysis (CAPD); HIV; peritonitis; infection; *Staphylococcus aureus*; methicillin-resistant *Staphylococcus aureus* (MRSA); nasal carriage; Coagulase-Negative *Staphylococcus*

INTRODUCTION

Infection is a major challenge in patients with end-stage renal failure who are managed with continuous ambulatory peritoneal dialysis (CAPD), and it is an important source of morbidity and technique failure. Gram-positive bacteria, most notably coagulase-negative staphylococci (CNS) and *Staphylococcus aureus(S.aureus)*, frequently cause CAPD-associated peritonitis [1-3]. Peritonitis caused by CNS infection tends to follow a benign clinical course that is easily treatable, while *S. aureus* peritonitis can be complicated with relapses and the need for catheter removal, particularly if it is associated with exit site or tunnel infections. These infections are commonly caused by touch contamination. An important risk factor for CAPD-associated exit site infections and peritonitis is *S. aureus* nasal carriage [4-6]. Immunosuppression, diabetes, previous antibiotic use, smoking, healthcare exposure, overcrowding, and intravenous drug abuse are among the factors that influence *S. aureus* colonisation [5, 7-10]. Carriage rates vary according to the geographical location, ethnicity, sex, and age [9]. Mupirocin and topical antibiotics have been associated with decreased *S. aureus* exit site infections, but not necessarily *S. aureus* peritonitis [11].

Staphylococcus aureus is a commonly isolated pathogen that causes significant morbidity and mortality among patients on dialysis, especially among those with indwelling catheters [12, 13]. The infections caused by *S. aureus* include pneumonia, bacteraemia, endocarditis, and skin and soft tissue infections. These infections present greater problems to immunocompromised patients, including those who are infected by the human immunodeficiency virus (HIV), than to those who are not immunocompromised, as immunocompromised patients are at an increased risk of infective complications caused by impaired host defence mechanisms [14-17]. An association between HIV infection and increased rates of *S. aureus* nasal colonisation in the general population has been reported, and increased likelihood of colonisation has been suggested in the advanced stages of HIV

infection [7, 18]. Infective complications in HIV-positive patients on dialysis can cause significant morbidity and mortality, and they can result in the need to transfer to haemodialysis, which gives rise to greater cost burdens to health budgets. In poorly resourced regions, such as sub-Saharan Africa, where HIV is extremely prevalent but access to renal replacement therapy is limited, CAPD can represent a cost-effective option. Indeed, CAPD can be implemented with relative ease and without the need for complex equipment, and it is well suited for areas that are remote or have limited dialysis facilities [19-21]. This study aimed to evaluate the effects of HIV infection on *S. aureus* nasal carriage, staphylococcal peritonitis, and catheter infection rates in patients with end-stage renal disease (ESRD) who were managed with CAPD.

METHODS

Study population

This prospective sub-cohort of 129 patients was drawn from a 140-patient cohort recruited from King Edward VIII Hospital and Inkosi Albert Luthuli Central Hospital, Durban, South Africa, which has been described previously [16, 22]. Consecutive patients aged 18 to 60 years who required dialysis and had newly inserted double-cuffed coiled Tenckhoff catheters were recruited between September 2012 and February 2015. Sixty HIV-positive and 59 HIV-negative patients who had at least one nasal swab sample taken during follow-up were included in this sub-study. The study protocol was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BE 187/11), and informed consent was obtained from the patients prior to enrolment. The status of HIV infection was determined by two 4th generation HIV enzyme-linked immunosorbent assays performed by the South African National Health Laboratory Service (NHLS) before enrolment; screening for HIV was performed using a HIV Ag/Ab Combo (CHIV) assay

(ADVIA Centaur® XP, Siemens Healthcare Diagnostics, Tarrytown, NY, USA) and confirmation was done using HIV Combi and HIV Combi PT assays (Cobas e601, Roche Diagnostics, Mannheim, Germany). Highly active antiretroviral therapy (HAART) was left to the discretion of the local clinic.

Y-sets, twin-bag systems, and conventional peritoneal dialysis (PD) solutions (Dianeal® 1.5%, 2.5%, or 4.25% dextrose, icodextrin, or amino acid-based solutions; Baxter Healthcare, Deerfield, IL, US) were used in all CAPD patients. They generally performed four exchanges per day. All patients received approximately 40 hours of practical and theoretical CAPD training in groups and individualised sessions conducted by the same nursing team of two senior nurses working together. A prophylactic intravenous antibiotic was administered to all patients prior to PD catheter insertion. Patients were prescribed 4% chlorhexidine Surgiscrub soap for hand washing and chlorhexidine 0.5% in ethanol 70% solution for hand rubs between hand washing. They were directed to use water and medicated soaps of their choice for exit site care.

Enrolment and follow-up

The patients' demographic, clinical, and biochemical data were documented on enrolment. The patients were followed up monthly at a central renal clinic in Inkosi Albert Luthuli Central Hospital for 18 months or until the endpoints of catheter removal and subsequent transfer to haemodialysis or death. At each follow-up assessment, nasal swabs were taken, phlebotomy was performed for biochemical tests, and the details of infective complications and hospital admissions in the intervening periods were recorded on predefined questionnaires. Full blood counts were performed and the serum concentrations of C-reactive protein, urea, creatinine, electrolytes, albumin, and ferritin were measured at NHLS, and the results were periodically retrieved from the Inkosi Albert Luthuli Central Hospital's electronic results database.

Microbiology

Swabbing of the anterior nasal vestibules with sterile swabs (Amies Agar Gel-No Charcoal Transport System; Copan Italia SpA, Brescia, Italy) was performed monthly by a research nurse, and the swabs were transported to the laboratory for processing. Colistin-nalidixic agar and mannitol salt agar media were used for the cultures. The CAPD nurse took PD effluent specimens for white blood cell (WBC) counts and culture when the patients' clinical presentations suggested peritonitis, and they were transported to the NHLS microbiology department in sterile specimen bottles for processing. The culturing was done on chocolate blood agar and brain-heart infusion broth. A Vitek® 2 system (bioMérieux, France) was used for species identification and antibiotic susceptibility testing of the nasal swab and PD effluent specimens. The PD effluent WBC counts were determined using a 40× microscope objective lens.

Definitions

A peritonitis episode was defined as a clinical presentation with a cloudy effluent or abdominal pain associated with a PD effluent WBC count of >100 cells/μL or a positive PD effluent culture. All patients were treated for at least two weeks, and they initially received intraperitoneal vancomycin and amikacin empirically, with further therapy modified according to the culture results. Episodes with culture-confirmed *Staphylococcus* growth and the date of presentation, information about whether the patient was treated as an inpatient or outpatient, and the presenting PD WBC counts were included in this analysis. The infection rates were calculated as the total number of infectious episodes with an organism during the follow-up period divided by the dialysis-years' time at risk, and they were expressed as the number of episodes per year [23].

Exit site infections were diagnosed clinically and they were defined based on the presence of purulent drainage, with or without skin erythema, at the catheter-epidermal interface. Tunnel infections were diagnosed clinically or using sonographic studies, and they were

defined based on the presence of erythema, oedema, or tenderness over the subcutaneous pathway [23]. Both infection types were referred to as catheter infections.

The participants were classified as *S. aureus* nasal carriers if at least one culture from the monthly nasal swabs was positive for *S. aureus*, and they were classified as non-carriers if none of the cultures from the monthly nasal swabs was positive for *S. aureus* during follow-up. The *S. aureus* nasal carriers were further classified as intermittent *S. aureus* carriers if only one nasal culture was positive for *S. aureus* during follow-up or as persistent carriers if more than one monthly nasal culture was positive for *S. aureus*.

Mupirocin exposure

Exposure to mupirocin during the study was determined through evaluation of the electronic hospital database at the end of the study period for instances where mupirocin was dispensed during each patient's follow-up period. The date of the first documented prescription of mupirocin and the number of months prescribed were recorded for individual patients.

Statistical analysis

The continuous variables are expressed as mean ± standard deviation (SD) or median and the interquartile range (IQR), and they were compared using Student's t-test or the Wilcoxon-Mann-Whitney test, as appropriate. The proportions and categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. The survival estimates were computed using the Kaplan-Meier method, and the log-rank test was used to compare the survival curves. Univariate Cox regression survival analysis was used to estimate the associations between HIV infection and *S. aureus* nasal carriage and the outcome variables. Multivariable Cox regression analysis was used to identify independent predictors of survival. All of the analyses were performed using Stata, version 13.1 (StataCorp LP, College Station, Texas, USA), and the significance level was set at $p < 0.05$.

RESULTS

Patients' characteristics

The study population of 119 CAPD patients included 59 HIV-negative and 60 HIV-positive patients with a mean age of 38.8 years (SD = 11.6 years) and 36.2 years (SD = 9.2 years), respectively, (p = 0.168). Women comprised 40.7% of the HIV-negative and 58.3% of the HIV-positive cohorts (p = 0.054). People of African ethnicity comprised 100% of the HIV-positive cohort and 84.8% of the HIV-negative cohort (p = 0.001). Fifty-two percent of the HIV-positive patients were either newly diagnosed with HIV or had recently been started on HAART, less than six months before Tenckhoff catheter insertion. Fifty-two percent of the HIV-positive patients had a suppressed viral load of <150 copies/mL, which was the hospital laboratory assay's limit at the time of enrolment. While the median baseline viral load was 4,229.5 copies/mL (IQR: 817–88,294.5 copies/mL) for the patients with detectable viral loads, the median fell below the detectable limit (IQR: <150–2,284.5 copies/mL) when the patients with undetectable viral loads were included. The characteristics of the study population are outlined in Table 1.

TABLE 1: Baseline Characteristics of the Patients

Study end points

After 18 months, 64.4% (38/59) of the HIV-negative patients and 33.3% (20/60) of the HIV-positive patients were alive with patent catheters (p = 0.001). Twenty-two percent (13/59) of the HIV-negative patients and 25.0% (15/60) of the HIV-positive patients (p = 0.703) had their Tenckhoff catheters removed because of malfunctions or infective complications, and 10.2% (6/59) of the HIV-negative patients and 36.7% (22/60) of the HIV-positive patients had died (p = 0.001). One HIV-negative and two HIV-positive patients had

their Tenckhoff catheters removed because their renal functions improved. One HIV-negative patient underwent live related renal transplantation, and one HIV-positive participant left the study to undergo haemodialysis and was lost to follow-up.

Staphylococcal nasal carriage

Thirty percent (18/59) of the HIV-negative patients and 43.3% (26/60) of the HIV-positive patients had detectable *S. aureus* in the nares ($p = 0.147$). The median time from Tenckhoff catheter insertion to the first *S. aureus* detection was 251 days (IQR: 97 – 377 days) for the HIV-negative patients and 67.5 days (IQR: 41 – 131 days) for the HIV-positive patients ($p = 0.002$). Twenty percent (12/59) of the HIV-negative patients and 33.3% (20/60) of the HIV-positive patients were persistent *S. aureus* carriers ($p = 0.110$). Methicillin-resistant *S. aureus* (MRSA) was found in 13.6% (8/59) of the HIV-negative patients and in 31.7% (19/60) of the HIV-positive patients ($p = 0.018$). Coagulase-negative staphylococci was detectable in the nares of 69.5% (41/59) in the HIV-negative cohort and 43.3% (26/60) in the HIV-positive cohort ($p = 0.004$). Both *S. aureus* and CNS in the nares either concomitantly or interchangeably were detected in 13.6% (8/59) of the HIV-negative cohort and 11.7% (7/60) of the HIV-positive cohort (Table 2).

TABLE 2: Patient Outcomes at 18 Months

Staphylococcal peritonitis

Staphylococcus spp. was cultured from 16 HIV-negative and 29 HIV-positive peritonitis episodes that occurred in 17.0% (10/59) of the HIV-negative and 28.3% (17/60) of the HIV-positive patients. The HIV-positive cohort was associated with a higher staphylococcal peritonitis rate (0.569 episodes/person-years) compared with the HIV-negative cohort (0.223 episodes/person-years) (hazard ratio [HR] 2.58, 95% confidence interval [CI] 1.37 – 4.85, $p =$

0.003). The staphylococcal peritonitis rate in HIV-positive patients who had baseline cluster of differentiation (CD) 4^+ cell counts of <200 cells/μL was 0.973 episodes/person-years (HR 4.44, 95% CI 1.45–13.58, $p = 0.009$), and this decreased to 0.530 episodes/person-years when the baseline $CD4^+$ cell count was >350 cells/μL (HR 2.40, 95% CI 1.18–4.86, $p = 0.015$) (Table 3). The staphylococcal peritonitis-free survival rates at 18 months were 71.7% in the HIV-negative cohort and 40.8% in the HIV-positive cohort ($p = 0.002$) (Figure 1).

TABLE 3: Incidence Rates and Cox Proportional Hazard Univariate Analysis

Figure 1: — Staphylococcal peritonitis and human immunodeficiency virus infection status. HIV = human immunodeficiency virus.

On multivariable analysis, HIV (HR 3.35, 95% CI 1.20–9.36, $p = 0.021$), diabetes, body mass index, and waist circumference were found to be independent predictors of *Staphylococcus* spp. peritonitis (Table 4).

TABLE 4: Cox Proportional Hazard Univariate and Multivariate Analyses: Risk Factors vs. Staphylococcal Peritonitis

Coagulase-negative staphylococci peritonitis rates were 0.089 episodes/person-years in the HIV-negative cohort and 0.401 episodes/person-years in the HIV-positive cohort (HR 4.80, CI 1.93–11.94, $p = 0.001$). The coagulase-negative staphylococci peritonitis rates were 0.259 episodes/person-years among CNS nasal carriers and 0.172 episodes/person-years among non-CNS nasal carriers (HR 1.45, 95% CI 0.64–3.32, $p = 0.376$).

Staphylococcus aureus was cultured in nine HIV-negative and seven HIV-positive peritonitis episodes. Four HIV-negative *S. aureus* peritonitis episodes and one HIV-positive *S. aureus* peritonitis episode preceded the detection of *S. aureus* nasal colonisation, and three HIV-negative and five HIV-positive *S. aureus* peritonitis episodes followed the detection of *S. aureus* nasal colonisation. Two HIV-negative *S. aureus* peritonitis episodes and one HIV-positive *S. aureus* peritonitis episode occurred in patients who did not have *S. aureus* nasal colonisation during follow-up. Methicillin-sensitive *S. aureus* caused 43.8% (7/16) (HIV-negative) and 10.3% (3/29) (HIV-positive) of staphylococcal peritonitis episodes ($p = 0.021$). All MRSA peritonitis episodes, comprising two in the HIV-negative cohort and four in the HIV-positive cohort, occurred in MRSA nasal carriers. The *S. aureus* peritonitis-free survival rates at 18 months were 83.7% in the HIV-negative cohort and 84.6% in the HIV-positive cohort ($p = 0.942$) (Figure 2). The *S. aureus* peritonitis rates were 0.270 episodes/person-years in the *S. aureus* nasal carriers and 0.041 episodes/person-years in the non-*S. aureus* nasal carriers (HR 6.90, 95% CI 1.97–24.25, $p = 0.003$). The *S. aureus* peritonitis-free survival rates at 18 months were 68.6% in the *S. aureus* nasal carriers and 95.8% in the non-*S. aureus* nasal carriers ($p < 0.001$) (Figure 3).

Figure 2 — *S. aureus* peritonitis and human immunodeficiency virus infection status. HIV = human immunodeficiency virus

Figure 3 — *S. aureus* peritonitis in relation to *S. aureus* nasal carriage. SA = *Staphylococcus aureus*.

Exit site and tunnel infections

Ten catheter infection episodes occurred in the HIV-negative cohort and 14 catheter infection episodes occurred in the HIV-positive cohort in 15.2% (9/59) and 18.3% (11/60) of the patients, respectively. *Staphylococcus aureus* was cultured from the exit site pus swabs or tunnel abscess aspirates in five HIV-negative and eight HIV-positive catheter infection episodes. One HIV-negative *S. aureus* catheter infection episode and none of the HIV-positive *S. aureus* catheter infection episodes preceded the detection of *S. aureus* nasal colonisation, and one HIV-negative *S. aureus* catheter infection episode and seven HIV-positive *S. aureus* catheter infection episodes followed the detection of *S. aureus* nasal colonisation. Three HIV-negative *S. aureus* catheter infection episodes and one HIV-positive *S. aureus* catheter infection episode occurred in patients who were not positive for *S. aureus* nasal colonisation during follow-up. The *S. aureus* catheter infection rates were 0.076 episodes/person-years in the HIV-negative cohort and 0.156 episodes/person-years in the HIV-positive cohort (HR 1.96, 95% CI 0.64–6.03, $p = 0.240$). The *S. aureus* catheter infection rates were 0.199 episodes/person-years for the *S. aureus* nasal carriers and 0.056 episodes/person-years for the non-carriers (HR 3.61, 95% CI 1.11 – 11.73, $p = 0.033$). The *S. aureus* catheter infection rates in the HIV-positive cohort were 0.302 episodes/person-years in the *S. aureus* nasal carriers and 0.036 episodes/person-years in the non-carriers (HR 8.41, 95% CI 1.03–68.74, $p = 0.047$) (Table 3).

Mupirocin exposure

Eighty-six percent (51/59) of the HIV-negative cohort had mupirocin ointment prescribed for exit site application compared to 60.0% (36/60) of the HIV-positive cohort ($p = 0.001$). Furthermore, mupirocin ointment was prescribed for a median 5 (2–9) months in the HIV-negative cohort compared to 3 (2–6.5) months in the HIV-positive cohort ($p = 0.140$). Fourteen percent (8/59) of the HIV-negative cohort had mupirocin nasal spray prescribed during follow-up compared to 15.0% (9/60) in the HIV-positive cohort ($p = 0.822$)

DISCUSSION

This prospective cohort study evaluated the effects of HIV infection on *S. aureus* nasal carriage and CAPD-associated staphylococcal infective outcomes in patients with ESRD who required dialysis. Our study failed to demonstrate significant differences with respect to *S. aureus* nasal colonisation, peritonitis, or catheter infection rates in relation to HIV infection. However, HIV infection was associated with significantly higher MRSA nasal carriage and staphylococcal peritonitis rates, and significantly enhanced the risk of *S. aureus* catheter infection in association with *S. aureus* nasal carriage.

Staphylococcus aureus nasal carriage rates as high as 76% have been reported for different patient populations on PD [24, 25], which underscores the variable, but high, colonisation rates among patients undergoing dialysis. The *S. aureus* nasal carriage rate of 43.3% in our HIV-positive cohort is within the wide range of rates from 20% to 63% that have been cited for different non-dialysis HIV-positive populations [7, 8, 26-31]. The difference between the HIV-positive cohort (43.3%) and HIV-negative cohort (30.5%) in relation to the *S. aureus* nasal carriage rate was not statistically significant ($p = 0.147$), which may reflect an underpowered sample size for this outcome. However, the interval between Tenckhoff catheter insertion and the first *S. aureus* nasal detection was significantly shorter in the HIV-positive cohort (67.5 days) than in the HIV-negative cohort (251 days) ($p = 0.002$), which highlights the increased underlying risk associated with HIV infection in relation to *S. aureus* nasal colonisation. To the best of our knowledge, this is the first study to prospectively evaluate the effects of an HIV seropositive status on *S. aureus* nasal colonisation rates in ESRD patients on CAPD. Our findings showed that the MRSA nasal carriage rate in the HIV-positive cohort (31.7%) was significantly higher than that in the HIV-negative cohort (13.6%) ($p = 0.018$), and that it was much higher than the pooled MRSA nasal carriage rate estimate of 6.9% (95% CI 4.8–9.3) reported in a meta-analysis of

HIV-positive non-CAPD populations [32]. This highlights the increased risk of MRSA colonies in the nares associated with HIV infection, which raises concerns about the subsequent development of more serious MRSA infections in vulnerable CAPD populations. The six MRSA peritonitis episodes in this study only occurred in the MRSA carriers, which further emphasizes the risks associated with such colonisation. Furthermore, the significantly higher proportion of episodes of methicillin-sensitive *S. aureus* peritonitis in the HIV-negative cohort (43.8%) than in the HIV-positive cohort (10.3%) ($p = 0.021$) highlights the relatively low burden of methicillin-resistant infections in the HIV-negative group. Infection with HIV has been positively linked to an increased risk of MRSA colonisation and subsequent infection in the general population [33-35]. Colonisation and infection by MRSA, which is commonly acquired through nosocomial contact, have also been associated with exposure to antibiotics, prior hospitalisation, illicit drug use, chronic skin disease, and risky lifestyle behaviours in the general population and using trimethoprim-sulfamethoxazole may confer protection from MRSA colonisation [34, 36]. Healthcare- and antibiotic-associated exposures may have increased the risk of MRSA colonisation in our CAPD cohorts. Community-associated acquisition could also have contributed to the earlier detection of MRSA colonisation in the HIV-positive cohort, as compared to the later detection of MRSA colonisation in the HIV-negative cohort (63 vs. 140.5 days after Tenckhoff catheter insertion, $p = 0.008$), which indicates a more traditional nosocomial-associated acquisition in the HIV-negative cohort [37].

The HIV-positive cohort had a higher staphylococcal peritonitis rate than the HIV-negative cohort (0.569 vs. 0.223 episodes/person-years; HR = 2.58, $p = 0.003$), because of the significantly increased CNS peritonitis incidence in the former compared with that in the latter (0.435 vs. 0.089 episodes/person-years; HR = 5.27, $p < 0.001$), which highlights the increased vulnerability of HIV-positive patients to touch contamination. This HIV-associated

risk changed with the immunological status. Compared with the HIV-negative patients, the HIV-positive patients with CD4+ cell counts <200 cells/μL had a higher risk of contracting staphylococcal peritonitis (0.973 episodes/person-years; HR 4.44, $p = 0.009$) relative to the risk of those with CD4+ cell counts >350 cells/μL contracting staphylococcal peritonitis, which was lower (0.530 episodes/person-years; HR 2.40, $p = 0.015$), and this most likely reflects an impaired local immunity [38]. Coagulase-negative staphylococci is a common skin commensal found in many parts of the body (nose, axilla, groin, etc.) to various degrees [39, 40]. It is also the most commonly isolated pathogen causing peritonitis in patients on CAPD [41]. Factors associated with the development of CNS peritonitis are access to the peritoneum via the catheter, bacterial characteristics allowing evasion of host defences, immune depression induced by conventional PD fluids, and inherent host immune system dysfunction [38, 39, 42]. In this study, HIV was found to increase the risk of developing CNS peritonitis, reflecting the immunosuppressive state of HIV and resultant impaired ability of local peritoneal immune defence mechanisms to combat the contaminating CNS organisms. Furthermore, CNS nasal carriage was found to be significantly increased in the HIV-negative cohort compared to that in the HIV-positive cohort (69.5% vs. 43.3%, $p = 0.004$), suggesting HIV-associated changes to the typical body commensal patterns favouring organisms such as MRSA, which are associated with greater healthcare exposure. However, CNS nasal carriage was not significantly associated with CNS peritonitis (HR 1.45, $p = 0.376$). Previous reports have also shown a disconnect between CNS strains colonising the body and those causing infection, as peritonitis-cultured strains tended to differ from those isolated from other body sites before infection [39, 40]. Documented mupirocin exit site exposure was significantly higher in the HIV-negative cohort than in the HIV-positive cohort (86.4% vs. 60.0%, $p = 0.001$) due to earlier recruitment of a greater proportion of HIV-negative patients when hospital policy favoured routine mupirocin exit site prophylaxis. However, chronicled

mupirocin ointment exit site exposure was not shown to have meaningful influence on the incidence of staphylococcal peritonitis both on univariate and multivariable Cox analysis (univariate HR 1.13, $p = 0.738$; multivariate HR 2.51, $p = 0.088$).

On multivariable analysis, HIV and diabetes were prominent independent predictors for the development of staphylococcal peritonitis, reinforcing the suggested risks attributed to impaired immunity. However, both cohorts responded well to the treatment, with 93.8% of the HIV-negative and 96.6% of the HIV-positive episodes of peritonitis responding to the treatment, which allowed CAPD to continue. The favourable treatment outcomes compare well with those described in previously published reports, because CNS peritonitis has a more benign course [1, 3, 43]. The *S. aureus* peritonitis rate was not affected by HIV infection status (HR 0.96, $p = 0.942$), an effect that may have been attenuated by the sporadic use of mupirocin prophylaxis that was intermittently available to the treating physicians. However, the *S. aureus* peritonitis rates were higher in both cohorts than those reported in the literature [44, 45], which probably reflects a higher intrinsic risk in our population which included patients who were poor, had low levels of secondary education, and had fewer available choices for alternative haemodialysis [46].

Compared with the HIV-negative state, HIV infection was associated with higher all-cause (0.160 vs. 0.286 episodes/person-years, HR 1.72, $p = 0.190$) and *S. aureus* (0.076 vs. 0.156 episodes/person-years, HR 1.96, $p = 0.240$) catheter infection rates. These differences were not statistically significant, which was probably a consequence of the lower numbers of these outcomes. The study's protocol did not restrict the use of mupirocin prophylaxis, either at the exit sites or the nares for ethical reasons, because these prophylactic measures significantly reduce *S. aureus*-associated catheter infections [11]. However, mupirocin was not uniformly used by the treating physicians. Concerns of resistance led to mupirocin being withdrawn from use in general CAPD by the hospital's therapeutics committee midway

through the study period, and it was reserved for nasal decolonisation of *S. aureus* thereafter. Nevertheless, the sporadic use of mupirocin likely suppressed the incidence of exit site and tunnel infections. In the HIV-positive cohort, *S. aureus* nasal carriage was associated with a very high *S. aureus* catheter infection rate compared with the non-carriers (0.302 vs. 0.036 episodes/person-years, HR 8.41, $p = 0.047$), which highlights an enhanced risk of this outcome among HIV-positive *S. aureus* nasal carriers. Seven of eight episodes of *S. aureus* catheter infection were preceded by *S. aureus* nasal colonisation, and only one episode occurred in a non-carrier, which stresses the importance of the influence of *S. aureus* nasal colonisation on catheter infection risk.

The main limitation of our study is that it was a single-centre observational study, which limits the causation inferences that can be drawn. The sample size may have been too small for differences in the *S. aureus* nasal colonisation and catheter infection outcomes to be fully appreciated. Furthermore, the disproportionately higher mortality rate in the HIV-positive cohort contributed to a significantly higher dropout rate and a significantly shorter observation time compared to the HIV-negative cohort. This may have resulted in underestimation of peritonitis and catheter-associated infection rates in the HIV-positive cohort. However, it is not expected to have meaningfully altered observed associations, such as the CNS peritonitis risk associated with HIV, as this kind of potential bias is expected to have underestimated these associations rather than enhance them. The observed differences in the *S. aureus* nasal colonisation and infection rates require further investigation with additional research in prophylactic measures.

CONCLUSIONS

This study's findings suggest that HIV infection adversely influences *S. aureus* nasal colonisation, particularly colonisation by MRSA, and that it may increase the risk of CNS peritonitis. Differences in the *S. aureus* peritonitis and catheter infection rates in relation to

HIV infection were not significant. However, HIV infection may enhance the risk of *S. aureus* catheter infections that are associated with *S. aureus* nasal carriage. These observations contribute to our understanding of the resistance profiles of *S. aureus* colonisers and the staphylococcal organism patterns that are likely to cause infection, which may assist in guiding appropriate antibiotic therapy and prophylaxis.

LIST OF ABBREVIATIONS

CAPD: continuous ambulatory peritoneal dialysis

CD4: cluster of differentiation 4

CI: confidence interval

CNS: coagulase-negative staphylococci

ESRD: end-stage renal disease

HAART: highly active antiretroviral therapy

HIV: human immunodeficiency virus

HR: hazard ratio

IQR: interquartile range

MRSA: Methicillin-resistant *S. aureus*

NHLS: South African National Health Laboratory Service

PD: peritoneal dialysis

SD: standard deviations

WBC: white blood cell

DECLARATIONS

Ethics approval and consent to participate

The study protocol was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BE 187/11), and research was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent prior to study enrolment.

Consent for publication

Not applicable

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Research idea and study design: KCZN, AA; data acquisition: KCZN, KSSH; data analysis and interpretation: KCZN, KSSH, AA; statistical analysis: KCZN; supervision and mentoring:

AA. Each author contributed important intellectual content during the manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors have read and approved the final manuscript.

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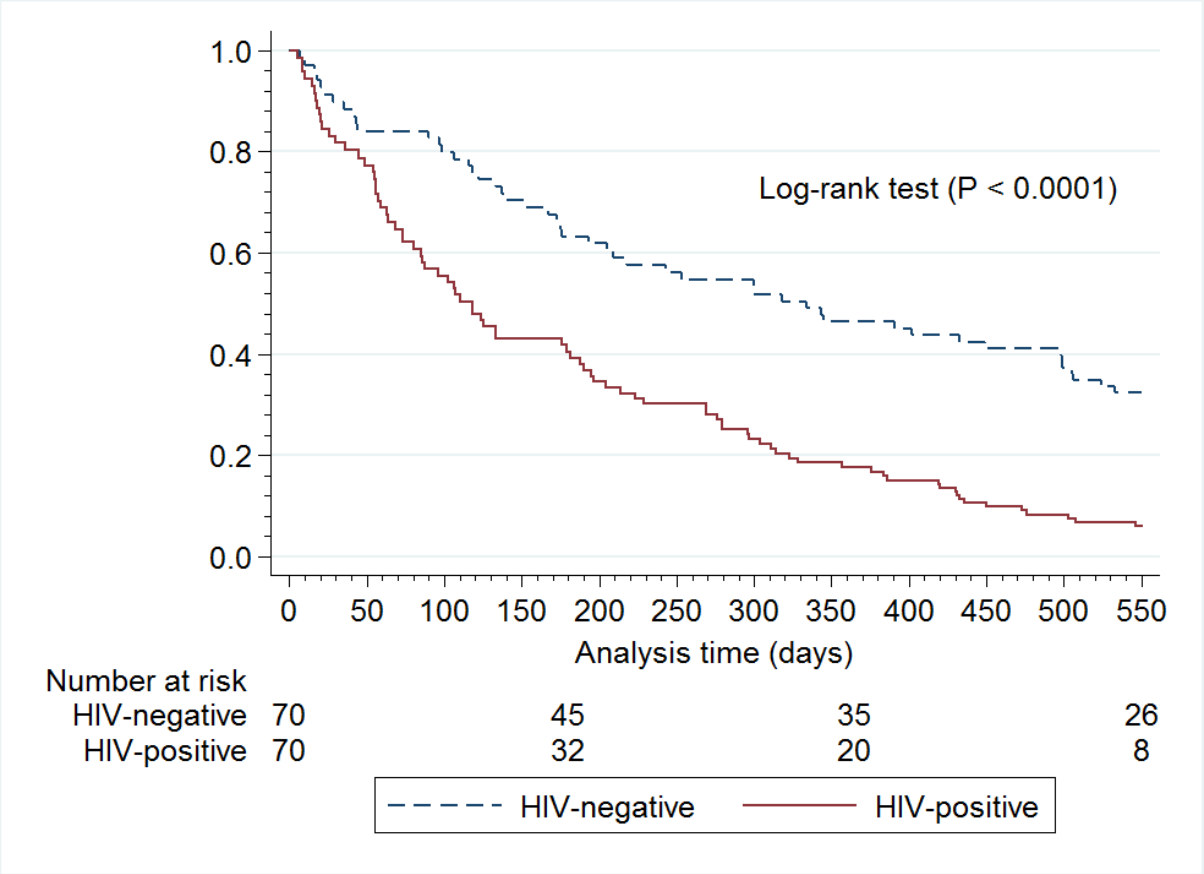
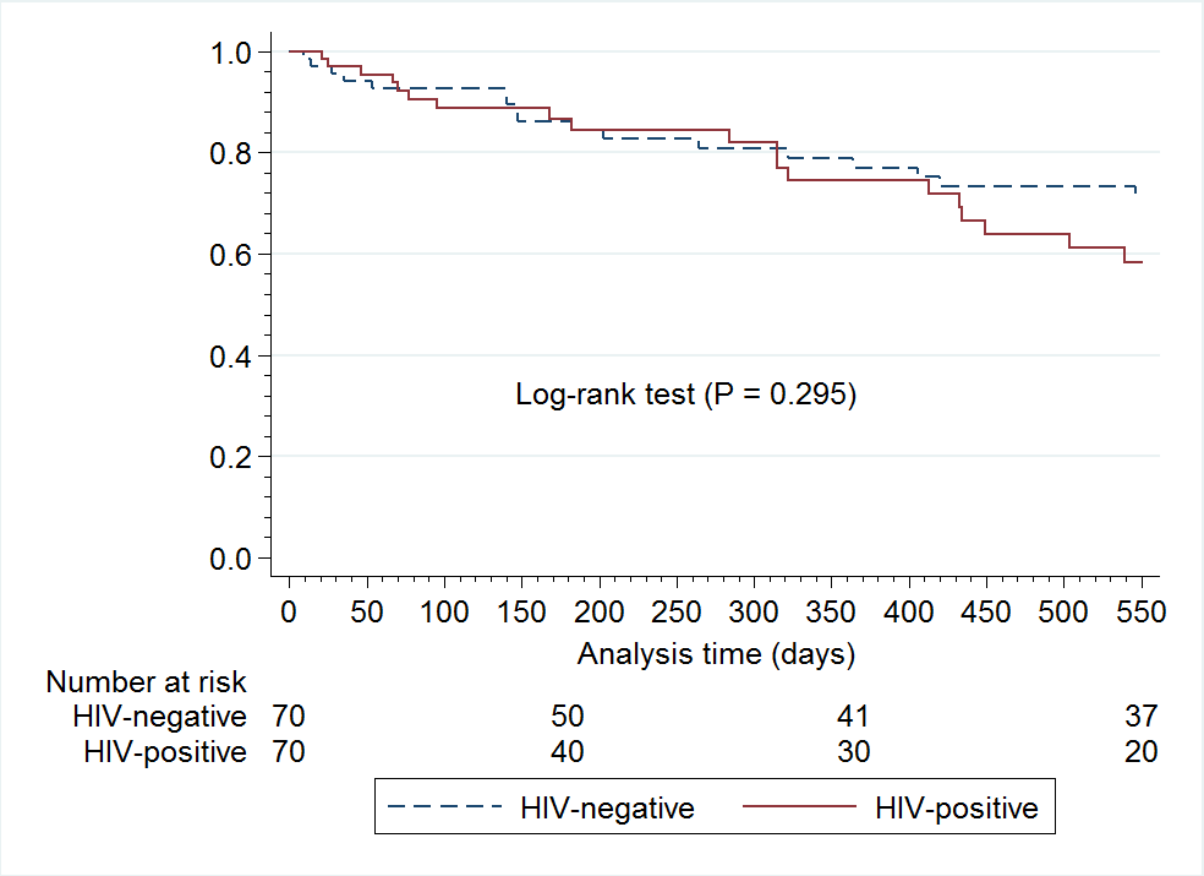
FIGURE LEGENDS

Figure 1— Staphylococcal peritonitis according to human immunodeficiency virus infection status.



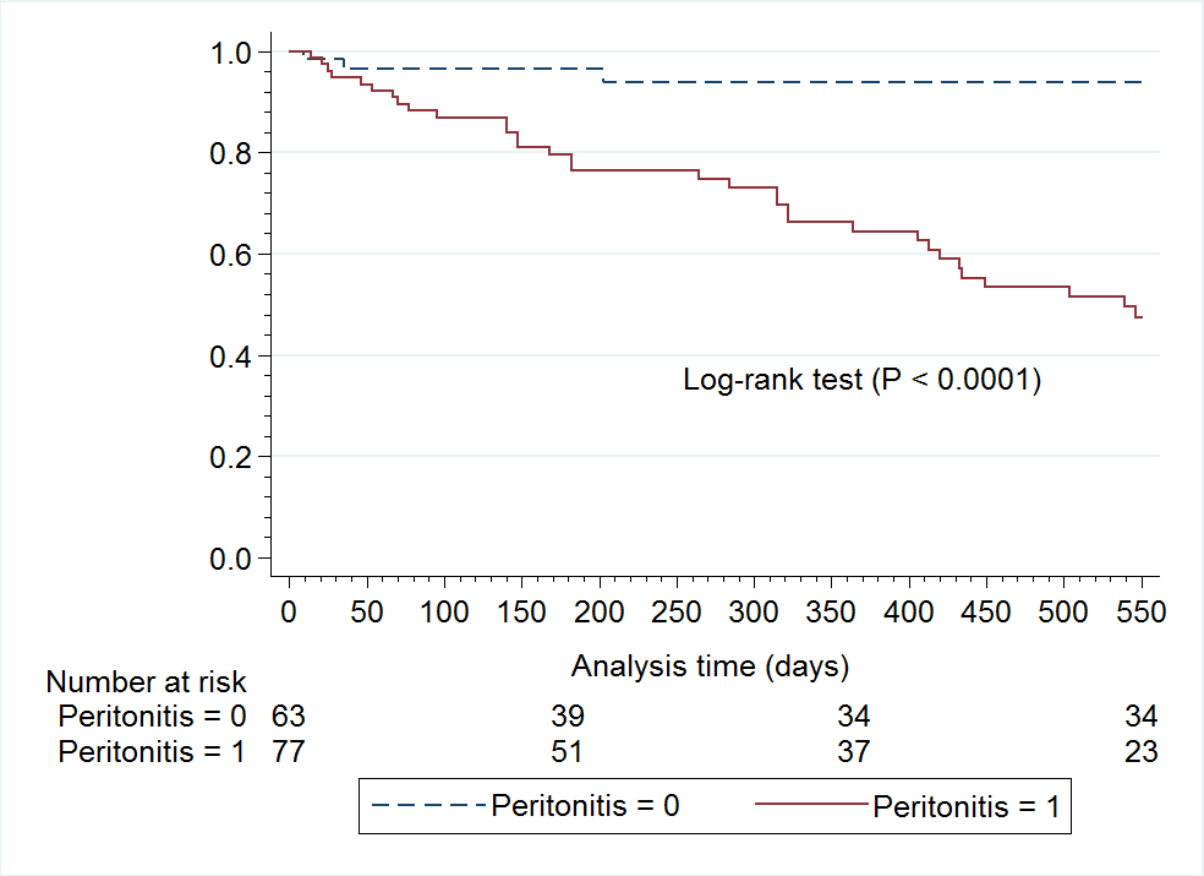
HIV = human immunodeficiency virus.

Figure 2— *S. aureus* peritonitis according to human immunodeficiency virus infection status.



HIV = human immunodeficiency virus

Figure 3— *S. aureus* peritonitis in relation to *S. aureus* nasal carriage.



SA = *Staphylococcus aureus*.

TABLES

TABLE 1: Baseline Characteristics of the Patients

	HIV negative (*n* = 59)	**HIV positive (*n* = 60)**	***p* value**
Mean ± SD age, years	38.8 ± 11.6	36.2 ± 9.2	0.168[a]
Mean ± SD weight, kg	68.6 ± 12.3	65.4 ± 13.6	0.181[a]
Body mass index, median (IQR)	23.8 (21.8–28.4)	22.8 (20.7–27.9)	0.239[d]
Mean ± SD waist circumference, cm	90.4 ± 10.4	89.6 ± 11.5	0.703[a]
Sex			
Female, *n* (%)	24 (40.7)	35 (58.3)	0.054[b]
Race			
African, *n* (%)	50 (84.8)	60 (100.0)	0.001[c]
Indian, *n* (%)	7 (11.9)	0 (0.0)	
Mixed race, *n* (%)	2 (3.4)	0 (0.0)	
Hypertension, *n* (%)	54 (91.5)	52 (75.0)	0.026[c]
Diabetes, *n* (%)	3 (5.1)	6 (10.0)	0.491[c]
SLE, *n* (%)	3 (5.1)	1 (1.7)	0.364 [c]
Hepatitis B, *n* (%)	6 (10.2)	6 (10.0)	0.974[b]
Primary residence			
Rural, *n* (%)	20 (33.9)	21 (35)	0.847[b]
Urban, *n* (%)	39 (66.1)	38 (63.3)	
Education level			
Primary school, *n* (%)	15 (25.4)	11 (18.6)	0.649[b]
High school, *n* (%)	26 (44.1)	27 (45.8)	

	HIV negative (*n* = 59)	HIV positive (*n* = 60)	*p* value
Post-grade 12, *n* (%)	18 (30.5)	21 (35.6)	
Employment status			
Unemployed, *n* (%)	43 (72.88)	47 (78.3)	0.387[b]
Employed, *n* (%)	16 (27.1)	12 (20.0)	
Tenckhoff catheter insertion method			
Laparoscopic, *n* (%)	57 (96.6)	31 (51.7)	<0.001[c]
Percutaneous, *n* (%)	2 (3.4)	29 (48.3)	
Haemoglobin (g/dL), median (IQR)	9.45 (8.2–11.2)	8.95 (7.8–9.8)	0.038[d]
Mean ± SD albumin, g/L	35.5 ± 6.8	31.06 ± 6.8	0.002[a]
eGFR (mL/min/1.73 m^2), median (IQR)	6 (4–9)	6 (5–8)	0.940 [d]
Creatinine (µmol/L), median (IQR)	728 (529–1004)	710.5 (592–880)	0.941[d]
CRP (mg/L), median (IQR)	18 (6–34)	48.5 (18.5–102.5)	<0.001[d]
ESR (mm/hr), median (IQR)	48 (29–61)	88 (50–129)	<0.001[d]
Ferritin (µg/L), median (IQR)	626 (335–1047)	565 (378.5–905.5)	0.770[d]
CD4$^+$ cell count			
Mean ± SD cells/µL		407.8 ± 238.6	
CD4$^+$ <200 cells/µL, *n* (%)		9 (15.0)	
CD4$^+$ 200–350 cells/µL, *n* (%)		18 (30.0)	
CD4$^+$ 350–500 cells/µL, *n* (%)		18 (30.0)	

	HIV negative (*n* = 59)	HIV positive (*n* = 60)	*p* value
$CD4^+$ ≥500 cells/µL, *n* (%)		15 (25.0)	
Viral load			
Median, copies/mL (IQR)		4,229.5 (817–88,294.5)	
Suppressed (<150 copies/mL), *n* (%)		31 (51.7)	
150–1,000 copies/mL, *n* (%)		8 (13.3)	
>1,000 copies/mL, *n* (%)		21 (35.0)	
HAART history at enrolment			
<6 months, *n* (%)		31 (51.7)	
6–12 months, *n* (%)		8 (13.3)	
>1 year, *n* (%)		21 (35.0)	
HAART drug regimen			
3TC/EFV/ABC, *n* (%)		50 (83.3)	
3TC/EFV/AZT, *n* (%)		2 (3.3)	
3TC/EFV/D4T, *n* (%)		3 (5.0)	
3TC/NVP/ABC, *n* (%)		3 (5.0)	
Alluvia/ABC/3TC, *n* (%)		1 (1.7)	
AZT/3TC/aluvia, *n* (%)		1 (1.7)	

SD = standard deviation; IQR = interquartile range; HIV = human immunodeficiency virus; CD = cluster of differentiation; SLE = systemic lupus erythematosus; eGFR = estimated glomerular filtration rate (Modification of Diet in Renal Disease equation); HAART = highly active antiretroviral therapy; ESR = erythrocyte sedimentation rate; 3TC = lamivudine; EFV

= efavirenz; ABC = abacavir; AZT = zidovudine; D4T = stavudine; NVP = nevirapine; CRP = C-reactive protein.

[a]t-test for comparison of means; [b]Pearson's χ^2 test; [c]Fisher's exact test; [d]Wilcoxon-Mann-Whitney test.

TABLE 2: Patient Outcomes at 18 Months

	HIV negative	HIV positive	*p* value
Staphylococcus aureus nasal carriage	30.5% (18/59)	43.3% (26/60)	0.147[a]
Intermittent *S. aureus* carrier	10.2% (6/59)	10.0% (6/60)	0.976[a]
Persistent *S. aureus* carrier	20.3% (12/59)	33.3% (20/60)	0.110[a]
Time to first *S. aureus* nasal detection (days), median (IQR)	251 (97–377)	67.5 (41–131)	0.002[c]
MRSA nasal carriage	13.6% (8/59)	31.7% (19/60)	0.018[a]
Time to first MRSA nasal detection (days), median (IQR)	140.5 (97–317.5)	63 (31–80)	0.008[c]
Coagulase-negative staphylococcal nasal carriage	69.5% (41/59)	43.3% (26/60)	0.004[a]
Dual carriage	13.6% (8/59)	11.7% (7/60)	0.756[a]
Mupirocin exit site exposure	86.4% (51/59)	60.0% (36/60)	0.001
Mupirocin exit site prescribed months, median (IQR)	5 (2–9)	3 (2–6.5)	0.140
Mupirocin nasal exposure	13.6% (8/59)	15.0% (9/60)	0.822
Mupirocin nasal prescribed months, median (IQR)	1 (1–2)	1 (1–3)	0.472

	HIV negative	HIV positive	*p* value
Staphylococcal peritonitis episodes, *n* (*n* excluding relapse[d])	16 (15)	29 (28)	0.046[a]
MSSA	43.8% (7/16)	10.3% (3/29)	0.021[b]
MRSA	12.5% (2/16)	13.8% (4/29)	1.000[b]
MSCNS	37.5% (6/16)	48.3% (14/29)	0.486[a]
MRCNS	6.3%(1/16)	27.6% (8/29)	0.127[b]
Time to peritonitis episode (days), median (IQR)	213 (67–498.5)	214 (102–357)	0.776[c]
PD WBC count (cells/μL), median (IQR)	734 (256–2,500)	988 (430–3,420)	0.366[c]
Outpatient treatment	56.2% (9/16)	58.6% (17/29)	0.878[a]
Inpatient treatment	43.8% (7/16)	41.4% (12/29)	
Inpatient stay (days), median (IQR)	10 (4–12)	10 (7–22)	0.419[c]
Episode outcome			
Continuation of PD	93.8% (15/16)	96.6% (28/29)	0.590[b]
Catheter removal	6.2% (1/16)	0	
Mortality	0	3.4% (1/29)	
Culture negative peritonitis episodes, *n* (*n* excluding relapse[d])	10 (9)	27 (24)	0.009[a]
Time to peritonitis episode (days), median (IQR)	212 (106 – 370)	143 (49 – 323)	0.432[c]

	HIV negative	HIV positive	*p* value
All-cause catheter infection, *n* episodes (*n* patients)	10 (9)	14 (11)	0.653[a]
Time to all-cause catheter infection (days), median (IQR)	112.5 (55–244)	180.5 (48–399)	0.429[c]
Exit site infection, *n* episodes (*n* patients)	9 (9)	10 (8)	0.358[b]
Tunnel infections, *n* episodes (*n* patients)	1 (1)	4 (3)	
S. aureus catheter infection, *n* episodes (*n* patients)	5 (4)	8(7)	1.000[b]
Time to *S. aureus* catheter infection (days), median (IQR)	55 (41–107)	233 (93.5–427.5)	0.092
S. aureus exit site infection, *n* episodes (*n* patients)	4 (4)	5 (4)	1.000[b]
S. aureus tunnel infections, *n* episodes (*n* patients)	1 (1)	3 (2)	

HIV = human immunodeficiency virus; IQR = interquartile range; MSSA = methicillin-sensitive *Staphylococcus aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*; MSCNS = methicillin-sensitive coagulase-negative staphylococci; MRCNS = methicillin-resistant coagulase-negative staphylococci; PD = peritoneal dialysis; WBC = white blood cell.

[a]Pearson’s χ^2 test; [b]Fisher's exact test; [c]Wilcoxon rank-sum (Mann-Whitney) test; [d]peritonitis episode count excluding peritonitis relapse.

TABLE 3: Incidence Rates and Cox Proportional Hazard Univariate Analysis

Rates - episodes/person-years	HIV negative	HIV positive	HR (95% CI)	*p* value
Staphylococcal peritonitis	0.223	0.569	2.58 (1.37–4.85)	0.003
$CD4^+$ <200 cells/μL		0.973	4.44 (1.45–13.58)	0.009[a]
$CD4^+$ 200–350 cells/μL		0.536	2.47 (1.04–5.85)	0.039[a]
$CD4^+$ ≥350 cells/μL		0.530	2.40 (1.18–4.86)	0.015[a]
S. aureus peritonitis	0.129	0.136	0.96 (0.36–2.60)	0.942
S. aureus nasal carriers	0.284	0.256	0.81 (0.27–2.42)	0.703
			7.00 (1.45–33.78)	0.015[b]
Non-carriers	0.044	0.036	0.67 (0.06–7.38)	0.742
			7.32 (0.88–60.85)	0.065[c]
CNS peritonitis	0.089	0.401	4.80 (1.93–11.94)	0.001
CNS nasal carriers	0.109	0.504	4.73 (1.70–13.16)	0.003
			2.50 (0.29–21.47)	0.402[d]
Non-CNS carriers	0.046	0.285	6.21 (0.76–50.77)	0.088
			1.58 (0.63–3.92)	0.327[e]
All-cause catheter infection	0.160	0.286	1.72 (0.76–3.90)	0.190
S. aureus catheter infection	0.076	0.156	1.96 (0.64–6.03)	0.240
S. aureus nasal carriers	0.090	0.302	3.44 (0.70–16.93)	0.129
			1.58 (0.26–9.48)	0.615[b]
Non-carriers	0.068	0.036	0.46 (0.05–4.41)	0.499
			8.41 (1.03–68.74)	0.047[c]

CI = confidence interval; HIV = human immunodeficiency virus; HR = hazard ratio; CD = cluster of differentiation; IRR = incidence rate ratio; CNS = coagulase-negative staphylococci.

[a]HIV-negative group used as the reference group; [b]*Staphylococcus aureus* nasal carriers vs non-carriers in the HIV-negative cohort; [c]*S. aureus* nasal carriers vs non-carriers in the HIV-positive cohort; [d]Coagulase-negative staphylococci nasal carriers vs non-carriers in the HIV-negative cohort; [e]Coagulase-negative staphylococci nasal carriers vs non-carriers in the HIV-positive cohort.

TABLE 4: Cox Proportional Hazard Univariate and Multivariate Analyses: Risk Factors vs. Staphylococcal Peritonitis

	Univariate Cox proportional hazards		Multivariable Cox proportional hazards[a]	
Variable	HR (95%CI)	*P* value	HR (95% CI)	*P* value
HIV	2.58 (1.37–4.85)	0.003	3.35 (1.20–9.36)	0.021
Age	0.99 (0.96–1.02)	0.480	0.98 (0.93–1.03)	0.496
Catheter insertion method	1.52 (0.78–2.97)	0.219	0.34 (0.06–1.86)	0.214
Catheter insertion site	2.34 (1.15–4.78)	0.019	3.80 (0.57–25.48)	0.169
Staphylococcal nasal carriage	2.83 (0.68–11.75)	0.152	5.88 (0.99–34.84)	0.051
Staphylococcal catheter infection	0.75 (0.23–2.44)	0.638	0.40 (0.10–1.68)	0.213
Mupirocin ointment exit site exposure	1.13 (0.54–2.36)	0.738	2.51 (0.87–7.25)	0.088
Mupirocin nasal spray exposure	2.41 (1.27–4.57)	0.007	2.08 (0.85–5.08)	0.109
Diabetes	2.80 (1.25–6.30)	0.013	3.95 (1.18–13.30)	0.026
Body mass index	0.94 (0.87–1.01)	0.108	0.80 (0.69–0.92)	0.002
Waist circumference	1.01 (0.98–1.05)	0.399	1.12 (1.05–1.21)	0.001
Baseline albumin	0.96 (0.91–1.00)	0.062	0.98 (0.92–1.04)	0.445
Baseline CD4 count				
HIV-negative	Reference			

	Univariate Cox proportional hazards		Multivariable Cox proportional hazards[a]	
Variable	HR (95%CI)	*P* value	HR (95% CI)	*P* value
CD4 <200	4.44 (1.45–13.58)	0.009	2.39 (0.53–10.89)	0.259
CD4 200–350	2.47 (1.04–5.85)	0.039	0.67 (0.20–2.26)	0.516
CD4 >= 350	2.40 (1.18–4.86)	0.015	1	

BMI, Body mass index; CI, Confidence interval; CD = cluster of differentiation; HR, Hazard ratio; HIV, human immunodeficiency virus.

[a]Adjusted for age, race, gender, smoking, diabetes, body mass index, waist circumference, baseline serum albumin, primary residence, highest education level, employment, baseline CD4 count, Tenckhoff catheter insertion site, Tenckhoff catheter insertion method (laparoscopic vs. percutaneous), staphylococci species nasal carriage, staphylococci species catheter infection, mupirocin nasal spray exposure, and exposure to topical mupirocin at exit site.

CHAPTER 5: HIV-1 IN PERITONEAL DIALYSIS EFFLUENTS

Chapters 2-4 have shown uncontrolled HIV-infection to be a significant factor for adverse mortality and morbidity outcomes. Central to this theme is peritonitis which was significantly associated with HIV infection. This HIV-associated peritonitis risk was shown to be dependent on virologic control and immunological state of the HIV-positive incident CAPD patient. Chapter 5 examines the factors associated with poor virological control, manifested by detectable plasma HIV-1 viral load, as well as evaluates the shedding of HIV particles in CAPD effluents in an HIV-positive ESRD cohort on HAART. Chapter 5 is presented in a manuscript format entitled "**Detection of human immunodeficiency virus-1 ribonucleic acid in the peritoneal effluent of renal failure patients on highly active anti-retroviral therapy**" as submitted and accepted for publication in Nephrology Dialysis Transplantation.

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Original Article

Detection of human immunodeficiency virus-1 ribonucleic acid in the peritoneal effluent of renal failure patients on highly active antiretroviral therapy

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ABSTRACT

Background. We evaluated the shedding of human immunodeficiency virus (HIV)-1 particles into continuous ambulatory peritoneal dialysis (CAPD) effluents of HIV-positive patients with end-stage renal disease (ESRD).

Methods. A total of 58 HIV-positive patients with ESRD on highly active antiretroviral therapy (HAART) who had Tenckhoff catheters inserted between September 2012 and February 2015 were prospectively reviewed and followed for 18 months. Peritoneal dialysis (PD) effluent samples from functioning CAPD catheters and plasma samples were obtained at three points during regular clinic visits on days 45 ± 37, 200 ± 19 and 377 ± 13 after catheter insertion. All specimens were stored at −20°C, and each batch was analysed by Roche quantitative HIV-1 polymerase chain reaction assay to detect HIV-1 particles. Clustered logistic regression was used to test for independent predictors of HIV-1 detection in CAPD effluents.

Results. HIV-1 RNA above 20 copies/mL assay limit was detectable in 19% (first batch), 26.3% (second batch) and 20% (third batch) of PD effluent specimens. HIV-1 RNA was detectable in PD fluid, without corresponding detection in the paired plasma in 3.4% (first batch), 5.3% (second batch) and 10% (third batch) of samples. Detection of HIV-1 in plasma sample (odds ratios 3.94; 95% confidence interval 1.14–13.55; P = 0.030), body mass index, serum albumin and HAART regimen were found to be significantly associated with HIV-1 detection in PD effluents.

Conclusions. HIV particles are shed in detectable amounts into CAPD effluents even in patients with suppressed plasma viral load, raising concerns of a localized sanctuary site and potential infectivity of HIV-positive CAPD patients on a full complement of HAART.

Keywords: continuous ambulatory peritoneal dialysis, HAART, HIV-1 RNA, PD effluents, viral load

INTRODUCTION

In 2014, an estimated 36.9 million people worldwide were living with HIV, with 25.8 million in sub-Saharan Africa (SSA), and only 15.8 million having access to antiretroviral (ARV) treatment [1, 2]. Although the incidence of new infections has been decreasing, the prevalence of people living with HIV continues to increase, mostly because of increased access to highly active antiretroviral therapy (HAART) and longer life expectancies [3–5]. As a result, non-communicable diseases such as chronic kidney disease (CKD) are expected to increase in this vulnerable population [6]. The general prevalence of CKD in SSA is estimated at approximately 13.9% and is expected to be even higher in the HIV-positive population [7]. While the incidence of HIV-associated end-stage renal disease (ESRD) has been stagnating in Western countries such as the USA [4, 8–10], the rates are expected to increase significantly in SSA in proportion to the increased availability of HAART and the subsequent increase in life expectancy. Unfortunately, only a small proportion of those affected are expected to have access to renal replacement therapy [1, 7, 11].

Continuous ambulatory peritoneal dialysis (CAPD) is a cost-effective alternative to haemodialysis, particularly in low resource settings [12–14]. Its use in HIV-infected renal failure patients has raised concerns about risks to immediate household contacts and health care providers, since HIV particles have been identified in peritoneal dialysis (PD) effluents, suggesting

potential infectivity in individuals not on a full complement of HAART [15–17]. Furthermore, HIV has been demonstrated to survive in both PD effluents and associated tubing for up to 3 days at room temperature, suggesting prolonged risk to immediate contacts if adequate disposal protocols are not followed [18]. However, with increased uptake of HAART and successful suppression of plasma HIV viral load to undetectable levels, the infectiveness of PD effluents is expected to attenuate. This study evaluated the shedding of HIV particles in CAPD effluents in patients with HIV infection-associated ESRD, who are currently on HAART.

MATERIALS AND METHODS

Hospital sites

Patients were enrolled from King Edward VIII Hospital (KEH) and Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa.

Study population

This prospective cohort sub-study was extrapolated from a 70 HIV-positive patient cohort with newly inserted Tenckhoff catheters between September 2012 and February 2015 across the two hospitals. Consecutive incident CAPD patients aged 18–60 years were recruited. A total of 58 patients, with at least one PD fluid sample collected and stored successfully during the first year of follow-up, were included. The study protocol was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BE 187/11), and all patients provided written informed consent prior to enrolment. All procedures were performed in accordance with the Helsinki Declaration. HIV status was confirmed by HIV-1 enzyme-linked immunosorbent assay prior to enrolment, and treatment with HAART was initiated by the patients' local clinic as per South African ARV guidelines. Tenckhoff catheters were inserted by experienced surgeons; the majority of catheters were inserted during laparoscopy ($n = 30$) at IALCH, while the remaining patients had percutaneous Tenckhoff catheter inserted by trained nephrologists at KEH ($n = 16$) or at IALCH ($n = 12$).

Enrolment and follow-up

Patients' demographic, clinical and biochemical data were recorded on enrolment. All patients were followed up at monthly intervals for 18 months at one central renal clinic in IALCH or until they died or their Tenckhoff catheter was removed. At each follow-up, vital signs, clinical parameters, anthropometric measurements, blood samples and PD fluid samples were obtained for all participants. Laboratory tests for full blood counts, serum levels of urea, creatinine, electrolytes, ferritin, albumin and C-reactive protein (CRP) were performed by the South African National Health Laboratory Service (NHLS), and results were periodically retrieved from the IALCH electronic results database. HIV-1 viral load at enrolment was analysed using the Abbott m2000 RealTime System by NHLS.

Sample collection and storage

Untimed PD effluent specimens (not timed to CAPD exchanges) were collected from functioning CAPD catheters, along with corresponding blood plasma specimens. Initially, these samples were obtained soon after successfully commencing cycles, and then during regular monthly clinic visits. For patients with complicated first use (due to malfunction, infection or mechanical complications), sampling was delayed until the first monthly clinic visit with a functioning Tenckhoff catheter, defined as a combined infusion and drainage time < 30min. A research nurse collected both blood samples (4 mL), using BD K_2EDTA vacutainers and disposable needles, and PD effluent samples, using a sterile 10 mL syringe, from the Tenckhoff catheter into a sterile specimen bottle (discarding the first 10 mL of PD effluent aspirated). Both samples were transported on ice to the research laboratory where whole blood was centrifuged at 1500 RPM for 10 min, and plasma was separated in hooded benchtops. Both separated plasma and aliquoted PD effluent specimens were freeze-stored in Eppendorf tubes at $-20°$C throughout the study period.

Paired HIV-1 polymerase chain reaction analysis

The first paired specimens (PD effluent and plasma, 58 each) were withdrawn 45 ± 37 days after Tenckhoff insertion and the second specimens (38 PD effluent and 38 plasma) were obtained from participants who had a patent catheter (taken at 200 ± 19 days) for ≥ 180 days; samples were analysed at the same time in two batches when all participants had completed 6 months of dialysis. A third specimen batch (30 PD effluent and 30 plasma) was obtained at 377 ± 13 days from participants who had a patent catheter for ≥ 365 days. Samples from the third batch were all analysed simultaneously when the participants had completed 1 year of dialysis. The timing of sampling in relation to insertion of the Tenckhoff catheter varied among participants due to missed scheduled clinic visits, temporary malfunctioning of Tenckhoff catheters or due to patients presenting on a non-CAPD clinic date when the research team was not available. All polymerase chain reaction (PCR) specimens were analysed by Lancet Laboratories, using Roche quantitative HIV-1 PCR assay (COBAS® AmpliPrep/COBAS TaqMan® analysis platform) to assess for the detectability of HIV-1 RNA.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD), and medians and interquartile ranges (IQR) were used for variables that were highly skewed or contained prominent asymmetrical outliers. Categorical and ordinal variables were summarized using proportions and percentages. Proportions and categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Wilcoxon signed-rank test was used to test for differences between paired PD and plasma viral loads. One-way analysis of variance was used to compare differences among the three batches for normally distributed variables. Kruskal–Wallis rank test was used to compare differences among the three batches for non-normally distributed variables. Clustered univariate

logistic regression was used to assess the relationship between the detectability of HIV-1 particles in plasma samples and various measured variables against the detectability of HIV-1 particles in PD effluent samples. Clustered multivariable logistics regression analysis was used to identify independent predictors for detection of HIV-1 particles in PD effluent and plasma samples. All analyses were performed using Stata version 13.1 (StataCorp LP, College Station, TX, USA). The level of significance was set at $P < 0.05$.

RESULTS

Patient characteristics

We recruited 58 HIV-positive African CAPD patients, with a mean age of 35.8 ± 9.0 years and including 56.9% women. In all, 53% (31/58) of patients were either newly diagnosed cases of HIV or had recently started HAART (<6 months prior to insertion of Tenckhoff catheter). A total of 48 (82.8%) subjects were on a standard regimen of lamivudine, efavirenz and abacavir as per South African ARV treatment guidelines for patients with renal impairment. The other 10 subjects were on either modified first-line or second-line treatment regimens, depending on individual circumstances. Around 59% (34/58) of the participants had a suppressed viral load at the time of enrolment, as determined by the hospital laboratory assay limit of 150 copies/mL. The median baseline viral load for patients with detectable viral loads was 4564 copies/mL (IQR 980–88 294), but this value dropped below the detectable limit (IQR <150–3379) if patients with undetectable HIV-1 viral loads were included in the analysis. Additional baseline characteristics of the study population are outlined in Table 1.

HIV-1 PCR analysis

Approximately, 53% (31/58) of samples from the first plasma specimen batch had detectable HIV-1 particles above the 20 copies/mL assay limit, whereas only 19% (11/58) of corresponding PD effluent specimens had detectable HIV-1 particles. Around 61% (19/31) of detectable first plasma specimens and 72.7% (8/11) of detectable PD effluent specimens were from patients who had first initiated ARV therapy within 6 months of Tenckhoff catheter insertion. Roughly 26% (10/38) of the second PD effluent specimens and 20% (6/30) third PD effluent specimens had detectable HIV-1 particles (Supplementary data, Table S1).

HIV-1 viral load was detected in both paired plasma and PD fluid samples in 15.5% (9/58) of the first specimen batch, 21% (8/38) of the second specimen batch and 10% (3/30) of the third specimen batch. HIV-1 was detected in PD fluid, without being detected in the paired plasma specimen in 3.4% (2/58) of first batch specimens, 5.3% (2/38) of second batch specimens and 10% (3/30) of third batch specimens ($P = 0.417$) (Table 2). Around 3% (2/58) of subjects had at least one PD fluid specimen in which HIV-1 was detectable, while it remained undetectable in all three corresponding plasma specimens.

HIV-1 viral load logs of PD effluents were significantly lower than those of plasma for specimen batches 1 and 2 (both $P < 0.001$) and borderline significant for batch 3 ($P = 0.058$). However, there were no significant differences between individual batched viral load logs in PD effluent or plasma samples (Figure 1).

Clustered univariate and multivariable logistic regression analysis

On univariate logistic analysis, detectable plasma HIV-1 viral load was a significant factor for detection of HIV-1 particles in PD effluents in the combined batch specimen pool [odds ratios (OR) 4.21; 95% confidence interval (CI) 1.61–11.05; $P = 0.003$]. Serum albumin level (OR 0.91; CI 0.85–0.98; $P = 0.014$), body mass index (BMI) (OR 0.90; CI 0.82–0.99; $P = 0.025$) and HAART drug regimen type were significantly associated with detection of HIV-1 in PD effluents (Table 3).

A multivariable logistics regression model identified plasma HIV-1 viral load > 20 copies/mL (OR 3.44; 95% CI 1.09–10.80; $P = 0.035$), serum albumin (OR 0.86; 95% CI 0.76–0.98; $P = 0.020$), BMI (OR 0.81; 95% CI 0.68–0.98; $P = 0.031$), haemoglobin (OR 1.43; 95% CI 1.12–1.82; $P = 0.004$), nevirapine and aluvia (Lopinavir/Ritonavir)-containing HAART regimens and HAART duration >1 year at the time of study enrolment to be independent predictors for the detectability of HIV-1 viral particles in PD fluid. In a separate multivariable logistics regression analysis, we identified age (OR 0.92; CI 0.85–0.99; $P = 0.019$), HAART duration >1 year (OR 0.22; CI 0.05–0.97; $P = 0.045$), lamivudine–efavirenz–stavudine containing HAART drug regimen (OR 0.05; CI 0.00–0.66; $P = 0.024$) and having high school or higher education as significant factors associated with decreased odds of detecting of HIV-1 in the plasma (Table 3).

Peritoneal dialysis effluent white blood cell count

The median PD effluent white blood cell count (WCC) obtained around the time of PD effluent sampling for HIV-1 viral load was 8 (0–38) cells/μL. Around 9% (11/126) of sampled specimens were associated with PD WCC ≥100 cells/μL, but were without clinical features suggestive of peritonitis at the time of sampling. Three of the patients in the latter category were subsequently diagnosed with peritonitis within 15 days of PD effluent sampling, while the rest did not manifest any further clinical or microbiological culture features suggestive of peritonitis up to 1 month after sampling. HIV-1 viral load was not detected in any of the three PD effluent specimens collected near the time of the peritonitis episodes. Approximately 15% of HIV-1 detectable PD effluent specimens (4/27) were from patients with associated PD WCC ≥100 cells/μL. PD WCC was not associated with HIV-1 detection on univariate logistic regression (OR 1.00; CI 1.00–1.00; $P = 0.501$) and was not a predictor of HIV-1 detection in PD effluent on multivariable logistic regression (OR 1.00; CI 1.00–1.01; $P = 0.454$). Having a peritonitis experience (one or more peritonitis episodes) during follow-up was associated with non-significant ORs for detection of HIV-1 viral load on PD effluents on univariate and multivariate logistic regression analysis (OR 1.75; CI 0.68–4.52; $P = 0.248$ and OR 0.44; CI 0.12–1.61; $P = 0.216$, respectively).

Table 1. Baseline characteristics of study participants

Variable	$n = 58$
Age (mean ± SD)	35.8 ± 9.0
Sex	
Female, number (%) of subjects	33 (56.9)
Race	
African, number (%) of subjects	58 (100.0)
Weight, kg (mean ± SD)	66.1 ± 13.7
Body mass index (mean ± SD)	24.5 ± 5.4
Waist circumference, cm (mean ± SD)	88.4 ± 15.4
Hypertension, number (%) of subjects	44 (75.9)
Diabetes, number (%) of subjects	5 (8.6)
SLE, number (%) of subjects	1 (1.7)
Hepatitis B, number (%) of subjects	7 (12.1)
Primary residence	
Rural, number (%) of subjects	20 (34.5)
Urban, number (%) of subjects	37 (63.8)
Highest education	
Primary school, number (%) of subjects	10 (17.2)
High school, number (%) of subjects	27 (46.6)
Post-Grade 12, number (%) of subjects	20 (34.5)
Employment history	
Unemployed, number (%) of subjects	46 (79.3)
Employed, number (%) of subjects	11 (19.0)
Tenckhoff catheter insertion method	
Laparoscopic, number (%) of subjects	30 (51.7)
Percutaneous, number (%) of subjects	28 (48.3)
CD4 count	
Mean (cells/μL ± SD)	394.2 ± 241.8
CD4 < 200 cells/μL, number (%) of subjects	10 (17.2)
CD4 200–350 cells/μL, number (%) of subjects	17 (29.3)
CD4 350–500 cells/μL, number (%) of subjects	18 (31.0)
CD4 ≥ 500 cells/μL, number (%) of subjects	13 (22.4)
Viral load	
Median, copies/mL (IQR)	4564 (87 314)
<150 copies/mL, number (%) of subjects	34 (58.6%)
150–1000 copies/mL, number (%) of subjects	6 (10.3)
>1000 copies/mL, number (%) of subjects	18 (31.0)
HAART history at enrolment	
<6 months, number (%) of subjects	31 (53.4)
6–12 months, number (%) of subjects	7 (12.1)
>1 year, number (%) of subjects	20 (34.5)
HAART drug regimens	
3TC/ABC/EFV, number (%) of subjects	48 (82.8)
3TC/AZT/EFV, number (%) of subjects	2 (3.4)
3TC/D4T/EFV, number (%) of subjects	3 (5.2)
3TC/ABC/NVP, number (%) of subjects	3 (5.2)
3TC/ABC/Aluvia, number (%) of subjects	1 (1.7)
3TC/AZT/Aluvia, number (%) of subjects	1 (1.7)
Urea, mmol/L (mean ± SD)	17.8 ± 7.1
Creatinine, μmol/L (mean ± SD)	790.2 ± 289.0
eGFR, ml/min/1.73 m^2 (mean ± SD)	7.0 ± 5.0
Haemoglobin, g/dL (mean ± SD)	8.94 ± 1.59
Serum albumin, g/L (mean ± SD)	31.9 ± 6.7
CRP (mg/L), median (IQR)	48.5 (19–101)
Ferritin (μg/L), median (IQR)	578.5 (380–973)

ABC, abacavir; AZT, zidovudine; D4T, stavudine; eGFR, estimated glomerular filtration rate (MDRD equation); EFV, efavirenz; NVP, nevirapine; SLE, systemic lupus erythematosus; 3TC, lamivudine.

DISCUSSION

This prospective cohort study evaluated the shedding of HIV-1 particles in CAPD effluents of HAART-treated HIV-infected patients with ESRD. To our knowledge, this is the first study to prospectively evaluate HIV-1 viral loads in a relatively large population of HIV patients being treated with HAART while on CAPD. Our study also demonstrated a significant increase in the OR for HIV-1 particle detection in PD effluents if plasma HIV-1 viral load was not suppressed below detectable levels. This highlights the importance of optimizing HIV treatment, as uncontrolled HIV infection can increase the risk for shedding of HIV-1 particles into CAPD effluents, as observed in previous pre-HAART era studies [15–17].

A substantial proportion of our patients failed to have suppressed plasma viral load below detectable limits at 6 months (50%) and 1 year (33%) follow-up. The most likely cause of this is poor treatment adherence, although we cannot exclude the contribution of low antiviral effectiveness, pharmacokinetic properties and the development of drug-resistant strains to this observation, as these were not specifically investigated [19]. Multivariable logistic regression revealed that HAART duration of >1 year at the time of enrolment, having high school or higher education, age and a lamivudine–efavirenz–stavudine-containing HAART drug regimen were protective factors against HIV-1 detectability in plasma. Although some of these associations were not confirmed on univariate analysis, they demonstrate the importance of optimal treatment compliance and stable sustained HAART therapy on achieving virologic suppression. It has been previously demonstrated that younger age is associated with poor compliance [20]. Our study showed that age is a protective factor against HIV-1 detectability in plasma and that older age may be associated with better medication compliance and, as a result, reduced HIV-1 detectability. Plasma viral suppression has been suggested as an alternative measure of drug adherence comparable to patient self-reported estimates [21]. In their study of a rural South African adult HIV-treatment cohort, Mutevedzi *et al.* [22] demonstrated an overall virologic response rate of 86.3%, with a higher proportion of older adults showing better suppression than younger adults. This suppression rate was much higher than the 66.7% demonstrated for the ESRD CAPD population in our study, despite the fact that both sample populations were sourced from the same province and share a similar socioeconomic background. We hypothesize that psychosocial factors aggravated by the combined diagnosis of end-stage renal failure and HIV may have contributed to suboptimum compliance and the observed lower suppression rates in this special population group.

A notable proportion of patients had detectable HIV-1 particles in the PD effluents in the absence of detectable levels in corresponding plasma samples (3.4% at 45 days, 5.3% at 200 days and 10.0% at 377 days). This finding was consistent with that reported by Calcagno *et al.* [23], who demonstrated the presence of HIV-1-RNA in the peritoneal fluid of an HIV-positive end-stage liver disease patient with suppressed plasma viral load. The authors attributed this finding to the reduced penetration of some ARV drugs into the peritoneal cavity and hypothesized that active replication of HIV-1 in gut-associated lymphoid tissue or in abdominal lymph nodes may have contributed to this finding [23, 24]. HIV-1 detection in PD fluid samples of patients with undetectable plasma viral load raises concerns of a localized sanctuary site. However, whether this

Table 2. HIV-1 RNA in plasma and CAPD effluents

Variable	Batch 1 ($n = 58$)	Batch 2 ($n = 38$)	Batch 3 ($n = 30$)	P-value
Time from Tenckhoff insertion, days (mean ± SD)[a]	45 ± 37	200 ± 19	377 ± 13	
PD fluid HIV-1 viral load, >20 copies/mL	11 (19.0%)	10 (26.3%)	6 (20.0%)	0.676[b]
Plasma fluid HIV-1 viral load, >20 copies/mL	31 (53.4%)	19 (50.0%)	10 (33.3%)	0.189[b]
Paired HIV-1 PCR analysis				
Both plasma and PD fluid: HIV-1 viral load >20 copies/mL	9 (15.5%)	8 (21.0%)	3 (10.0%)	0.492[c]
PD fluid only: HIV-1 viral load >20 copies/mL	2 (3.4%)	2 (5.3%)	3 (10.0%)	0.417[c]
Plasma only: HIV-1 viral load >20 copies/mL	22 (37.9%)	11 (28.9%)	7 (23.3%)	0.352[b]
PD effluent white blood cell count				
Median, cells/μL (IQR)	10 (2–40)	6 (0–28)	3 (0–38)	0.292[d]
<100 cells/μL, number (%) of subjects	54 (93.1)	34 (89.5)	27 (90.0)	0.777[c]
≥100 cells/μL, number (%) of subjects	4 (6.9)	4 (10.5)	3 (10.0)	
Laboratory values				
Urea (mmol/L), median (IQR)	17.1 (12.6–22.6)	23.4 (14.9–31.4)	22.2 (14.6–26.5)	0.019[d]
Haemoglobin, g/dL (mean ± SD)	9.32 ± 1.81	9.78 ± 2.51	10.25 ± 2.09	0.743[e]
Serum albumin, g/L (mean ± SD)	30.1 ± 7.7	29.4 ± 6.2	29.4 ± 6.0	0.524[e]
CRP (mg/L), median (IQR)	17.5 (11–67)	12 (5–32)	12.5 (6–29)	0.080[d]

[a]Number of days from Tenckhoff insertion to taking of specimen from patient.
[b]Pearson's χ^2 test.
[c]Fisher's exact test.
[d]Kruskal–Wallis rank test.
[e]One-way analysis of variance.

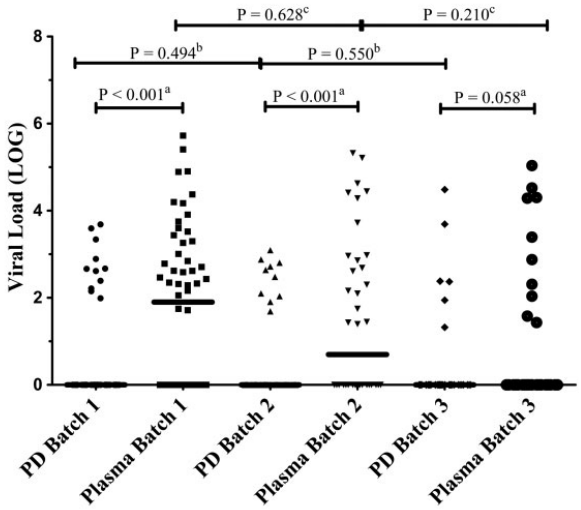

FIGURE 1: Scatter plot of viral load logs in PD fluid and plasma according to specimen batches. [a]Wilcoxon signed-rank test comparing PD effluent and plasma viral load logs in each batch. [b]Wilcoxon signed-rank test comparing PD effluent viral load logs between batches. [c]Wilcoxon signed-rank test comparing plasma viral load logs between batches. 0: undetectable viral load log (<20 copies/mL). Batch 1: 45 ± 37 mean days from Tenckhoff insertion ($n = 58$); Batch 2: 200 ± 19 mean days from Tenckhoff insertion ($n = 38$); and Batch 3: 377 ± 13 mean days from Tenckhoff insertion ($n = 30$).

detection indicates ongoing active localized viral replication requires further investigation.

Serum albumin level and BMI were identified as protective factors against HIV-1 detection in PD effluents in univariate analysis and as independent predictors in our multivariate logistic regression model. These findings suggest that malnutrition may be a factor in the shedding of HIV-1 into PD effluents. Reduced plasma levels of some ARV drugs have been reportedly associated with diarrhoea/wasting syndrome, and the latter further associated with low BMI and CD4 count [25]. Malnutrition and inflammation may induce structural and functional changes in bowel mucosa, resulting in impaired absorption of certain ARV drugs. However, small drug dosages taken by those who are underweight, particularly of efavirenz, could also have contributed to observed associations for BMI and HIV-1 detection in PD effluents. The type of HAART drug regimen was also identified as an important factor in HIV-1 detection in PD effluents, with nevirapine and aluvia (lopinavir/ritonavir) containing regimens being associated with increased odds. The majority of our patients (82.8%) were on treatment regimens containing lamivudine, efavirenz and abacavir, as per South African treatment guidelines, with abacavir serving as a substitute for tenofovir in renal failure patients [26]. Lamivudine was used by all of our study participants and has been reported to have good penetration into many body fluid compartments including the peritoneal cavity [23, 27]. Interestingly, the maximum serum concentration or the area under the serum concentration-time curve of CAPD patients is not affected by reduced renal dosing [28, 29]. A case report by Izzedine *et al.* [30] demonstrated that ritonavir (a large tightly protein bound molecule) has poor transport across the peritoneal membrane and a negligible extraction ratio (1%). Nevirapine is a smaller protein bound molecule associated with approximately 50% lower peritoneal concentrations compared with plasma [30, 31]. However, there is a general paucity of data on peritoneal penetration or stability of most ARV drugs in CAPD patients under conditions of continual peritoneal lavage by dialysis fluid. The effect of different ARV drugs and combinations in suppressing viral replication in localized peritoneal sites requires further investigation.

Table 3. Clustered univariate and multivariable logistics regression analysis for the detectability of HIV-1 viral particles in CAPD effluents and plasma

	Univariate model			Multivariable model		
	OR	95% CI	P	OR	95% CI	P
Detection of HIV-1 viral load (>20 copies/mL) in PD effluent versus plasma						
Batch 1	5.11	1.00–26.25	0.051			
Batch 2	6.18	1.10–34.70	0.038			
Batch 3	2.43	0.39–15.08	0.341			
PD effluent HIV-1 viral load >20 copies/mL[a]						
Plasma HIV-1 viral load >20 copies/mL	4.21	1.61–11.05	0.003	3.44	1.09–10.80	0.035
HAART drug regimen						
3TC/EFV/ABC	Reference					
3TC/EFV/AZT	1.00			1.00		
3TC/EFV/D4T	0.74	0.06–8.84	0.810	1.58	0.11–23.19	0.738
3TC/NVP/ABC	8.84	1.28–61.01	0.027	22.49	1.16–437.28	0.040
Aluvia/ABC/3TC	8.84	5.08–15.40	<0.001	54.67	1.31–2286.78	0.036
AZT/3TC/aluvia	2.21	1.27–3.85	0.005	28.07	0.98–803.79	0.051
Serum albumin	0.91	0.85–0.98	0.014	0.86	0.76–0.98	0.020
BMI	0.90	0.82–0.99	0.025	0.81	0.68–0.98	0.031
HAART duration[c]						
<6 months	Reference					
6–12 months	0.61	0.15–2.47	0.491	0.97	0.17–5.56	0.971
>1 year	0.73	0.25–2.07	0.550	0.08	0.01–0.59	0.013
CRP	1.00	0.99–1.02	0.517	1.00	0.98–1.01	0.685
Haemoglobin	1.01	0.84–1.22	0.912	1.43	1.12–1.82	0.004
Peritonitis	1.75	0.68–4.52	0.248	0.44	0.12–1.61	0.216
PD WCC	1.00	1.00–1.00	0.501	1.00	1.00–1.01	0.454
Plasma HIV-1 viral load >20 copies/mL[b]						
Age	0.97	0.92–1.04	0.417	0.92	0.85–0.99	0.019
HAART duration[c]						
<6 months	Reference					
6–12 months	0.51	0.12–2.11	0.350	0.24	0.04–1.26	0.091
>1 year	0.54	0.21–1.37	0.193	0.22	0.05–0.97	0.045
HAART drug regimen						
3TC/EFV/ABC	Reference					
3TC/EFV/AZT	1.10	0.25–4.87	0.898	0.94	0.18–4.85	0.938
3TC/EFV/D4T	0.44	0.22–0.89	0.021	0.05	0.00–0.66	0.024
3TC/NVP/ABC	1.10	0.38–3.18	0.857	2.10	0.27–16.38	0.478
Aluvia/ABC/3TC	1.00			1.00		
AZT/3TC/aluvia	0.55	0.33–0.91	0.020	5.94	0.61–57.78	0.124
Education						
Primary school	Reference					
High school	0.82	0.26–2.53	0.729	0.17	0.04–0.80	0.025
Post-grade 12	0.63	0.18–2.18	0.461	0.13	0.03–0.60	0.010

ABC, abacavir; AZT, zidovudine; D4T, stavudine; EFV, efavirenz; NVP, nevirapine; 3TC, lamivudine.

[a]Detectability of HIV-1 viral particles in CAPD effluents adjusted for detectability in plasma (> 20 copies/mL), ARV duration, age, HAART drug regimen, CD4 count, BMI, serum urea, serum albumin, CRP, haemoglobin, days from Tenckhoff insertion to specimen sampling, peritonitis during follow-up, PD effluent WCC, primary residence (rural versus urban), education and employment (unemployed versus employed).

[b]Detectability of HIV-1 viral particles in blood plasma adjusted for ARV duration, age, HAART drug regimen, CD4 count, BMI, serum urea, serum albumin, CRP, serum ferritin, days from Tenckhoff insertion to specimen sampling, primary residence (rural versus urban), education and employment (unemployed versus employed).

[c]Duration of HAART at enrollment.

This study has several limitations. First, PD effluent sampling was not timed to CAPD bag exchanges. Untimed samples were collected as patients arrived to the clinic and were seen by the research team. Since participants were part of a larger renal clinic community and some travelled from as far as 400 km, coordinating timed sampling was logistically difficult. However, this method did not significantly alter the associations observed for HIV-1 viral load detectability in PD effluent, as untimed sampling would have been expected to decrease the sensitivity of HIV-1 detection with the consequence of underestimating the measured effects rather than enhancing them. Secondly, the management of HAART regimens was left to the discretion and professional opinion of the local ARV clinics, which were guided by clinical treatment guidelines. Therefore, there was no strict supervision over HAART management decisions or individual exploration of underlying reasons for failure to supress. Thirdly, this was a sub-study with the overall sample size calculated according to an anticipated peritonitis-based effect size contrasted against an HIV-negative cohort, and the HAART regimens were not factored in the design or selection of patients. The small sample of patients with regimens different from the clinical standard limits the generalizability of some of these findings. Further studies are needed to evaluate the pharmacokinetics and effectiveness of commonly utilized HAART drugs

in CAPD, as well as to investigate the possible causes of failure to suppress.

This study demonstrated that HIV particles are shed in detectable amounts into the CAPD effluents of HAART-treated ESRD patients with unsuppressed, and in some instances suppressed, viral loads. This study highlights the importance of sociodemographic factors, nutritional indicators and sustained effective HAART regimens in determining successful suppression of HIV-1 in plasma and PD effluents.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org

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CONFLICT OF INTEREST STATEMENT

None declared.

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Supplementary Table 5. 1: Detection of HIV-1 RNA in Plasma and CAPD effluents

	Batch 1 (N = 58)	Batch 2 (N = 38)	Batch 3 (N = 30)	P value
PD fluid HIV-1 viral load, <20 copies/mL	47 (81.0%)	28 (73.7%)	24 (80.0%)	0.668[a]
PD fluid HIV-1 viral load, 20–199 copies/mL	3 (5.2%)	4 (10.5%)	2 (6.7%)	
PD fluid HIV-1 viral load, 200–1000 copies/mL	5 (8.6%)	5 (13.2%)	2 (6.7%)	
PD fluid HIV-1 viral load, >1000 copies/ml	3 (5.2%)	1 (2.6%)	2 (6.7%)	
Plasma fluid HIV-1 viral load, <20 copies/mL	27 (46.6%)	19 (50.0%)	20 (66.7%)	0.196[a]
Plasma fluid HIV-1 viral load, 20–199 copies/mL	5 (8.6%)	6 (15.8%)	3 (10.0%)	
Plasma fluid HIV-1 viral load, 200–1000 copies/mL	11 (19.0%)	6 (15.8%)	2 (6.7%)	
Plasma fluid HIV-1 viral load, >1000 copies/mL	15 (25.9%)	7 (18.4%)	5 (16.7%)	
Virologic rebound[b]				
PD fluid		8 (21.0%)	5 (16.7%)	0.761[a]
Plasma		8 (21.0%)	3 (10.0%)	0.323[a]
Failure to suppress[c]				

	Batch 1 (N = 58)	Batch 2 (N = 38)	Batch 3 (N = 30)	P value
PD fluid		2 (5.3%)	1 (3.3%)	1.00[a]
Plasma		11 (29.0%)	7 (23.3%)	0.783[a]

PD, Peritoneal dialysis

[a]Fisher's exact test

[b]Virologic rebound – HIV-1 viral load undetectable (<20 copies/mL) in batch 1 but detectable (> 20 copies/mL) in batch 2 or 3

[c]Failure to suppress – HIV-1 viral load detectable (>20 copies/mL) in batch 1 and batch 2 or 3

CHAPTER 6: SYNTHESIS

This prospective longitudinal study was guided by four key objectives outlined in section 1.9 of the introduction, and overall all these were satisfied. Our study has shown that uncontrolled HIV infection adversely influences mortality and morbidity outcomes early during the course of CAPD management, however, it was not shown to affect catheter patency or failure rates at 18 months. Further, HIV-1 particles were shown to be shed in appreciable amounts in CAPD effluents of patients with uncontrolled HIV infection as well as in some with suppressed plasma viral loads.

The two primary endpoints of mortality and catheter failure and key morbidity outcomes of first peritonitis and hospital admission events were addressed in Chapter 2 (objective 1). Uncontrolled HIV infection was shown to increase the mortality risk early during follow-up, with 67% of HIV-positive deaths occurring within 120 days of Tenckhoff catheter insertion compared to 38% of HIV-negative deaths ($p = 0.016$). Further, this risk was shown to be influenced by the immunological and virologic state of the HIV-positive patient. Those with CD4 counts below 350 and 200 cells/µL were associated with higher mortality rates (0.673 and 1.692 deaths/patient-years, respectively) and hazard ratios (HR 2.67, p = 0.024 and HR 5.39, p < 0.001, respectively) when compared to the HIV-negative cohort. However, those with CD4 counts above 350 cells/µL had comparable mortality rates to HIV-negative patients (0.274 vs. 0.251 deaths/patient-years, respectively, HR 1.08, p = 0.867). Moreover, those with detectable viral loads (1.021 deaths/patient-years, HR 3.63, p = 0.001) and ART commenced within 6 months of Tenckhoff insertion (0.714 deaths/patient-years, HR 2.65, p = 0.010) were associated with poor mortality outcomes. Detectable HIV viral load and baseline serum albumin and ferritin were suggested to be independent predictors of mortality, highlighting the influence uncontrolled HIV infection and malnutrition and inflammation factors in predicting mortality outcomes. These observations are in agreement with the few previously published retrospective studies [57-59]. However, to our knowledge, our study is the first to show these effects in a larger prospective cohort.

Catheter failure outcomes were not shown to be adversely influenced by HIV-infection, as reflected by non-significantly differing catheter patency (HIV-positive: 74.6% vs HIV-negative: 77.0%, p = 0.822) and failure rates (0.298 vs. 0.270 episodes/person-years, respectively, p = 0.822) documented in our cohorts at 1 year of follow-up. Further, the types and distribution of complications resulting in the removal of Tenckhoff catheters were not significantly different between the HIV-positive and HIV-negative cohorts. Infective complications were identified as the predominant cause leading to technique failure responsible for 84.6% of HIV-positive cohort catheter failures comparable to 85.7% of HIV-negative failures, while mechanical complications accounted for 15.4% and 14.3% of catheter failures, respectively.

Eighty percent of the HIV-positive cohort had complications during the first year of follow-up requiring at least one hospital admission compared to 62.9% of the HIV-negative cohort ($p = 0.025$). HIV-infection was shown to adversely influence all-cause hospital admission rates, as reflected by increased incidence rates in the HIV-positive cohort compared to the HIV-negative cohort (2.97 vs. 1.52 admissions/person-years, HR 1.66, $p = 0.013$). This morbidity risk was also shown to be influenced by the immunological state of the HIV-positive patient with baseline CD4 counts below 200 cells/µL associated with worse hospital admission outcomes (8.22 admissions/person-years, HR 3.02, $p = 0.001$). The HIV-associated morbidity risk was further demonstrated by the higher cumulative rate of days spent in hospital in the HIV-positive cohort compared to the HIV-negative cohort (25.9 vs. 14.8 days/person-years, IRR 1.47, $p < 0.001$). Tenckhoff insertion site, diabetes, systemic lupus erythematosus, baseline HIV-1 viral load detectability, hemoglobin levels, BMI, serum albumin, CRP, serum ferritin, educational level, and employment status were factors independently associated with increased cumulative number of days spent in the hospital. These associations highlight the importance of malnutrition, inflammation, socioeconomic factors, late presentation, and HIV and comorbidities control in determining risk for increased morbidity.

Peritonitis was an important morbidity outcome also shown to be adversely influenced by HIV infection. The HIV-positive cohort was associated with a two-fold higher first peritonitis rate compared to the HIV-negative cohort (1.668 vs. 0.616 episodes/person-years, HR 2.38; $p = 0.001$). Further, this rate was shown to be 5-fold higher among HIV-positive patients with CD4 counts below 200 cells/µL compared to the HIV-negative cohort (5.069 episodes/person-years, HR 5.16, $p < 0.001$), highlighting the importance of immunological control in influencing the risk for first peritonitis events. This risk was shown to manifest early, with a higher proportion of HIV-seropositive participants (41.4% vs. 15.7%, $p = 0.001$) experiencing peritonitis within 90 days after catheter insertion. The primary objective of evaluating the effects of HIV seropositivity on outcomes of CAPD among dialysis-requiring renal failure patients was realized, as the effects of HIV infection were delineated with respect to mortality and morbidity outcomes. The hypothesis that HIV infection increases the risk of catheter failure, morbidity, and mortality among renal failure patients undergoing peritoneal dialysis, was shown to be true for morbidity and mortality outcomes but not shown to be true for catheter failure outcomes.

Peritonitis outcomes (inclusive of relapse and subsequent episodes) were further explored in chapter 3 (objective 2). At 18 months, HIV infection was associated with an increased risk of developing peritonitis (first and subsequent episodes) with higher overall peritonitis rates reported in the HIV-positive cohort compared to the HIV-negative cohort (1.86 vs. 0.76 episodes/person-years, HR 2.41, $p < 0.001$). This risk was also shown to be modified by the immunological state of the HIV-positive patient, as those with CD4 counts below 200 cells/µL reported a 4-fold increased hazards for

peritonitis (3.69 episodes/person-years, HR 4.54, P < 0.001) compared to HIV-negative patients. The HIV-associated peritonitis risk was shown to extended to relapse episodes with the HIV-positive cohort reporting higher peritonitis relapse rates compared to the HIV-negative cohort (0.298 vs. 0.078 episodes/person-years, HR 3.88, p = 0.010). Furthermore, the peritonitis risk was shown to persist throughout follow-up, as demonstrated by the peritonitis-free survival rate of only 6.0% at 18 months compared to 32.3% in the HIV-negative cohort (p < 0.001). On multivariable analysis, HIV infection, diabetes comorbidity, and a baseline CD4 count less than 200 cells/μL were found to be independent predictors of peritonitis episodes, further, highlighting the importance of HIV-infection and associated immunological state and comorbidity in determining the peritonitis risk.

Peritonitis was shown to be the leading cause of catheter failure in both cohorts (82.4% in HIV-negative and 84.2% in HIV-positive cohorts) and was further identified as an independent predictor of this outcome (HR 14.47, p = 0.001). However, HIV infection was not shown to significantly influence all-cause catheter failure rates (0.237 and 0.338 episodes/person-years, respectively, HR 1.42, p = 0.299) and catheter patency (71.4% and 58.2%, respectively, p = 0.295) at 18 months. Associated with these observations was a lower proportion of gram-negative peritonitis episodes documented in the HIV-positive cohort (27.7% vs. 44.4%, P = 0.038) compared to the HIV-negative cohort. Furthermore, gram-negative organisms were identified as the main causative organism group for catheter failures in both cohorts (42.1% and 52.9%, respectively). Thus, it was postulated that HIV infection might not significantly increase the risk of catheter-threatening peritonitis in the first 18 months following insertion but instead preferentially increase the risk for treatable peritonitis episodes. Further supporting this hypothesis, was the documented increased gram-positive peritonitis rate in the HIV-positive cohort compared to the HIV-negative cohort (0.68 vs. 0.26 episodes/person-years, HR 2.59, P = 0.001), as these types of peritonitis episodes are typically associated with a more favourable outcome. Gram-negative organisms such as *Pseudomonas* have also been associated with very low treatment response rates and cure rates, and very high catheter failure rates compared to typical gram-positive organisms in literature reports [48, 49, 71], further supporting the notion that gram-negative organisms are the prime catheter-threatening peritonitis organisms. The second objective of evaluating the effects of HIV seropositivity on risk factors, pattern, and incidence of peritonitis among peritoneal dialysis patients was realized, as the overall peritonitis rates and associated risk factors and the types of organisms likely to cause both infection and technique failure were delineated with respect to HIV infection. The hypothesis that HIV infection increases the risk of peritonitis complications among renal failure patients undergoing peritoneal dialysis was accepted.

The effects of HIV infection on Staphylococci peritonitis, the predominant gram-positive peritonitis type, and on the rates of S. aureus nasal carriage and catheter infections, as important gram-positive risk factors, was explored in chapter 4 (objective 3). HIV infection was found to adversely influence

S. aureus nasal colonisation, particularly colonisation by MRSA, and CNS peritonitis risk. Although, no significant differences in *S. aureus* nasal colonisation rates were demonstrated in relation to HIV (30.5% in HIV-negative cohort and 43.3% in HIV-positive cohort, p = 0.147), the interval between Tenckhoff catheter insertion and the first *S. aureus* nasal detection was significantly shorter in the HIV-positive cohort (67.5 days) than in the HIV-negative cohort (251 days) (p = 0.002), highlighting an underlying HIV-associated risk for *S. aureus* nasal colonisation. Furthermore, the MRSA nasal carriage rate was significantly higher in the HIV-positive cohort (31.7%) than that in the HIV-negative cohort (13.6%) (p = 0.018), reflecting, an increased risk for the establishment of MRSA colonies in the nares associated with HIV infection. Moreover, CNS nasal carriage was found to be significantly lower in the HIV-positive cohort compared to that in the HIV-negative cohort (43.3% vs 69.5%, p = 0.004), suggesting HIV-associated changes to the usual body commensal patterns favouring organisms such as MRSA, which are associated with greater healthcare exposure.

Although, HIV infection was not shown to adversely influence *S. aureus* peritonitis rates, the HIV-positive cohort was found to have a higher overall *staphylococci* peritonitis rate than the HIV-negative cohort (0.569 vs 0.223 episodes/person-years; HR = 2.58, p = 0.003), due to significantly increased CNS peritonitis incidence in the former compared with that in the latter (0.435 vs 0.089 episodes/person-years; HR = 5.27, p < 0.001). This HIV-associated risk was demonstrated to be influenced by the immunological state of the HIV-positive patients, as those with CD4 cell counts < 200 cells/µL were associated with an even higher rate of *staphylococci* peritonitis (0.973 episodes/person-years; HR 4.44, p = 0.009) compared to the HIV-negative cohort. However, good treatment response rates were documented in both cohorts, with 93.8% of the HIV-negative and 96.6% of the HIV-positive *staphylococci* peritonitis episodes responding to treatment and allowed for CAPD to continue. HIV infection was associated with higher all-cause (0.286 vs 0.160 episodes/person-years, HR 1.72, p = 0.190) and *S. aureus* (0.156 vs 0.076 episodes/person-years, HR 1.96, p = 0.240) catheter infection rates compared to HIV-negative state, but, these differences were not statistically significant. In the HIV-positive cohort, *S. aureus* nasal carriers were associated with a significantly higher *S. aureus* catheter infection rate compared with non-carriers (0.302 vs 0.036 episodes/person-years, HR 8.41, p = 0.047), suggesting that HIV infection enhances the risk of *S. aureus* catheter infections that is associated with *S. aureus* nasal carriage. The third objective evaluating the effects of HIV seropositivity on *S. aureus* nasal carriage and incidence of *staphylococci* peritonitis and catheter-related infection among renal failure patients undergoing peritoneal dialysis was realized, as *S. aureus* nasal carriage, *staphylococci* peritonitis and catheter-related infection rates were delineated with respect to HIV infection. The hypothesis that HIV increases the risk of *staphylococci* species peritonitis and *S. aureus* nasal carriage thereby increasing the risk of *S. aureus* peritonitis and catheter infections among renal failure patients undergoing peritoneal dialysis was partially confirmed. Although HIV was not shown to increase significantly *S. aureus* nasal carriage

rates, it was associated with a significantly increased MRSA nasal colonisation rate. Furthermore, HIV was shown to increase *staphylococci* species peritonitis but not shown to significantly affect *S. aureus* peritonitis. HIV was not shown to influence significantly catheter-related infections but was shown to enhanced the risk for *S. aureus* catheter-related infections among *S. aureus* nasal carriers.

The shedding of HIV particles into CAPD effluents in HIV-positive ESRD patients on HAART and factors associated with detectability of HIV-1 viral load both in plasma and effluents were evaluated in chapter 5 (objective 4). HIV particles were demonstrated to be shed in detectable amounts into the CAPD effluents of some HIV-positive patients with unsuppressed and suppressed plasma viral loads. A consistent proportion of patients had HIV-1 particles detectable in the CAPD effluents in the absence of detectable levels in corresponding plasma samples (3.4% at 45 days, 5.3% at 200 days, and 10.0% at 377 days, p = 0.417). This finding raises concerns about a localised sanctuary site and potential infectivity of some HIV-positive CAPD patients on a full complement of HAART. The odds ratio for HIV-1 particle detection in CAPD effluents were significant increased if plasma HIV-1 viral load was not suppressed below detectable limits (OR 4.21, p = 0.003). On multivariable logistics regression, serum albumin (OR 0.86, P=0.020), BMI (OR 0.81, p = 0.031) and HAART duration >1 year (OR 0.08, p = 0.013) were identified as protective factors against the detection HIV-1 particles on CAPD effluents. Detectable plasma HIV-1 viral load (OR 3.44, p = 0.035), and nevirapine and aluvia (Lopinavir/Ritonavir)-containing HAART regimens were shown to be independent predictors for the detectability of HIV-1 viral particles in CAPD fluid. Age (OR 0.92, P=0.019), HAART duration >1 year (OR 0.22, P=0.045), lamivudine-efavirenz-stavudine containing HAART drug regimen (OR 0.05, P=0.024), and having high school or higher education (OR 0.17, p = 0.025) were identified as protective factors against detectable plasma viral loads. The fourth objective of examining the presence and significance of HIV particles in peritoneal dialysis fluid of HIV-positive patients managed with CAPD was realized, as the detectability of HIV particles was established in CAPD effluents and the potential risk for infectivity posed by these fluids to immediate family contacts was highlighted. The hypothesis that HIV particles are present in the CAPD fluids in negligible amount and decrease even further with ARV treatment was not shown to be correct. On the contrary, HIV particles were shown to be shed in detectable amounts into CAPD effluents of some HIV-positive patients on HAART and even in some patients with a suppressed plasma viral load.

The major limitation of this study was the unavailability of specific causes of death for more than half of patients, as deaths occurred outside the study hospital sites and death certificates could not be accessed. This absence limited our ability to assess the contribution of catheter-associated complications to mortality. However, the discrepancy in dates, which could be less than one month, may not have significantly affected our results. Second, regarding the assessment of technique failure, the disproportionately higher mortality rate in the HIV-positive cohort contributed to a dropout rate at

18 months of 44.3% compared to 21.4% among seronegative patients. This selectively high dropout rate may have introduced bias, resulting in a lower apparent rate of technique failure in the HIV-positive cohort. Furthermore, the short follow-up period may have also contributed to the lack of statistical power to appreciate differences in technique failure outcomes. At one year, differences in catheter failure rates between the two cohorts were negligible (0.270 vs. 0.298 episodes/person-years, HR 1.09, p = 0.822) but at 18 months the two cohorts' catheter failure rates started to separate (0.237 vs. 0.338 episodes/person-years, HR 1.42, p = 0.299) but these differences were still not statistically significant. Eighteen months may be too short a time to evaluate this outcome adequately. With a longer follow-up time and larger sample size, it is conceivable that the differences between the two cohorts in relations to catheter failures may become significant. However, the finding of comparable catheter patency rates and negligibly differing catheter failure outcomes particularly at one year is an important finding which can assist clinicians in evaluating the short-term risks of HIV-infected CAPD patients. Lastly, the matching strategy of restricting the inclusion age to 18–60 years may limit the generalizability of our results to only this age group.

Conclusion

This study suggests that HIV infection can adversely influence mortality and morbidity, most notable peritonitis, in ESRD patients on CAPD. This HIV-associated risk manifests early in the course of CAPD treatment and is modified by the immunological and virologic state of the infected patient. Socioeconomic factors, comorbidities, malnutrition, and inflammation, were also suggested to influence this risk. HIV infection was not shown to significantly affect catheter failure or patency rates at 18 months. However, increased peritonitis rates raise concerns about long-term adverse catheter failure outcomes. Furthermore, HIV infection was suggested to increase the risk for MRSA colonisation, raising concerns about subsequent drug-resistant infections. Lastly, HIV-1 particles were demonstrated to be shed in detectable amounts into the CAPD effluents of HAART-treated ESRD patients with unsuppressed, and in some instances suppressed, viral loads, with sociodemographic and nutritional factors, and sustained effective HAART regimens suggested to be important in determining successful suppression of HIV-1 in plasma and CAPD effluents.

Recommendations and future work

The current WHO-advocated policy of test-and-treat, also adopted by South Africa in 2016, which eliminates the CD4 count threshold for accessing HAART, promises to significantly improve the morbidity and mortality of HIV-positive patients including those with renal diseases. This policy will hopefully increase the number of patients who are initiated early on HAART before the need for dialysis is realized, thereby, improving both the mortality and morbidity outcomes on dialysis. Studies on outcomes of HIV-positive patients on haemodialysis also report better survival on HAART in particular among those with good HIV infection control [17, 72-74]. However, HIV-infection has

been associated with adverse haemodialysis-associated morbidity outcomes [72, 75-77], inclusive of haemodialysis catheter-related infections and hospital admissions, analogous to the poor morbidity trends observed in the HIV-positive patients on CAPD. Comparison of outcomes of CAPD vs haemodialysis in a setting of HIV infection and end-stage renal failure is limited by the fact that there is no randomised trial to date addressing the question. Inferences can only be made from observational studies of either modality. CAPD can be recommended as an acceptable dialysis modality which may be associated with adverse morbidity and mortality outcomes but also comparable short-term catheter patency outcomes. Nevertheless, a randomized controlled trial is desirable comparing haemodialysis against CAPD associated mortality and morbidity outcomes in HIV-positive ESRD patients. Such a study can assist in suggesting the best and cost-effective dialysis modality and help guide clinicians starting HIV-positive patients on renal replacement therapy.

The findings on peritonitis outcomes, recommend a role for a prophylactic antibiotic strategy, particularly in the first six months following catheter insertion when the peritonitis risk is highest and more so among patients with low CD4 counts. However, studies on types of prophylactic antibiotics and associated measures that can best help improve peritonitis outcomes are needed and would be of great potential benefit in mitigating against the HIV-associated infective risk. Lastly, the findings on shedding of HIV-1 particles into CAPD effluents of both virologically suppressed and unsuppressed CAPD effluents, suggests extra precautions be recommended to patients with regards to safe disposal of their CAPD effluents and associated tubings, as these should be considered infectious even in patients on HAART. Further studies are required to evaluate the pharmacokinetics and effectiveness of commonly utilised HAART drugs in CAPD, as well as to investigate the possible causes of failure to suppress.

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05 June 2012

Dr. KCZ Ndlovu
Department of Nephrology
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

Dear Dr Ndlovu

PROTOCOL:The effect of HIV infection on the management of renal failure among patients undergoing peritoneal dialysis. REF:BE187/11

The Biomedical Research Ethics Committee (BREC) has considered the abovementioned application.

The study was provisionally approved by a sub-committee of the Biomedical Research Ethics Committee on 24 January 2012 pending appropriate responses to queries raised. Your responses dated 16 March 2012 to queries raised have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 05 June 2012

This approval is valid for one year from **05 June 2012.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/ResearchEthics11415.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

PROFESSOR V RAMBIRITCH
Vice-Chair: Biomedical Research Ethics Committee

APPENDIX 2: INFORMATION DOCUMENT

INFORMATION DOCUMENT

Study title: The effect of HIV infection on the management of renal failure among patients undergoing peritoneal dialysis

Greetings

I Dr Kwazi C Z Ndlovu am doing research on peritoneal dialysis in renal failure in patients with or without HIV. Dialysis is type of treatment given to patients with non-functioning kidneys and it performs the cleansing function of the kidney on the body. There are two types of dialysis one called haemodialysis where blood is ran through a machine which then filters all the unwanted substances from the body. Another type is called peritoneal dialysis, where fluid is put into the abdomen (belly) for a specified period thereby allowing waste product to be removed from the body by the dialysis fluid. Research is just a tool used to learn the answer to a question. In this study we want to learn whether peritoneal dialysis can be used safely and efficaciously to help patients with renal failure and also at the same time are infected by the HIV virus.

We are asking / inviting you to participate in this research study (or asking for your permission to include your child in a research study).

We are recruiting patients who have severe kidney failure requiring dialysis. We are recruiting both patients who are HIV positive as well as those who are HIV negative. All patients in both groups will be inserted a peritoneal dialysis catheter. This is a plastic stick inserted into the abdomen (belly). A small area below the navel will be cleaned, numbed with a numbing injection and then using a small opening the dialysis catheter will be inserted into the belly. Dialysis fluid will be inserted into the belly. This process performs the cleansing function of the kidneys in the body. You will then be trained on the operation of this dialysis method. This dialysis method is used routinely in many hospitals both here in KwaZulu-Natal as well as throughout the world. This dialysis method has an advantage of allowing dialysis to be performed at home by the patient. This is particularly important since there are limited slots available in the haemodialysis system.

Like any procedure peritoneal dialysis does have uncommon complications. Very rarely internal organs can be damaged during the insertion of the dialysis catheter. Sometimes infection in the abdomen can develop later in the course of treatment. These complications are not common and every measure possible will be taken to minimize risks of such and other unforeseen complications.

If this study produces favourable results we will be able to offer more treatment options to patients presenting to King Edward hospital and surrounding hospitals with life threatening renal failure.

Alternative treatments for kidney failure such as haemodialysis are not readily available to all patients who need it due to resource constraints. This fact makes it even more important to investigate easily implementable and cost effective treatment options.

Participation in this study does not guarantee acceptance into the chronic renal programme nor will it disadvantage any of its participants. All participants will be worked-up according to local protocols and presented to the chronic renal programme committee timeously for consideration. Participation in the project will not undermine in anyway the normal care due patients with dialysis requiring renal failure. However, participants of the study will be required to answer special questionnaires which have been adapted specifically for this project to get more information about the participants that will assist in the interpretation of study results at the end of the study. This information will be kept at the strictest of confidence and will be secured in a secure room and password protected computer with access restricted to the research team. Furthermore, extra blood tests will be drawn from participants

amounting to an extra 10ml of blood withdrawn during each visit. These extra samples of blood will test for special biomarkers that are modified by renal failure and inflammation.

Participation is entirely voluntary. You may refuse to participate and that will not invoke any penalty or loss of benefits to which you are otherwise entitled. You may discontinue participation at any time without penalty loss of benefits to which you will otherwise be entitled.

You are entitled to reimbursements for any "out of pocket" expenses you may have incured as a result of participating in this study, e.g. taxi fare.

Confidentiality: Every effort will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law.
Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Biomedical Research Ethics Committee, Data Safety Monitoring Committee and the Medicines Control Council.

For further information / reporting of study related adverse events.

Contact details of researcher/s – **Dr Kwazi C. Z. Ndlovu, 0823388996**

Contact details of BREC Administrator or Chair – for reporting of complaints/ problems:
Biomedical Research Ethics, Research Office, UKZN, Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 4769 / 260 1074
Fax: +27 (0) 31 260 4609
Administrator: Ms D Ramnarain Email: BREC@ukzn.ac.za

APPENDIX 3: CONSENT DOCUMENT

Consent to Participate in Research

Greeting:

I Dr Kwazi C Z Ndlovu am doing a comparative research on peritoneal dialysis in renal failure patients with and without HIV.

You have been asked to participate in a research study to evaluate the effect of peritoneal dialysis in the treatment of severe kidney failure. You will be inserted a peritoneal dialysis catheter. This is a plastic stick inserted into the abdomen (belly). A small area below the bellybutton will be cleaned, numbed with a local numbing injection and then using a small opening the dialysis catheter will be inserted into the abdomen. Another opening will be made a few centimetres away from the first opening that will serve as an exit of dialysis catheter. Dialysis fluid will be introduced into your belly to perform the cleansing function of the kidneys. You will be trained on operation of this dialysis method and you will be expected to carry it out by yourself at home on discharge from the ward. The effect of this treatment and complications will be monitored for the next 18 months.

You have been informed that as a participant in the study you will be given required to answer special questionnaires which have been adapted specifically for this project to get more information about your background and living conditions. This information will be kept at the strictest of confidence and will be secured in a secure room and password protected computer with access restricted to the research team. Furthermore, extra blood tests will be drawn from you amounting to an extra 10ml of blood withdrawn during each visit. These extra samples of blood will test for special biomarkers that are modified by renal failure and inflammation.

You have been informed about the study by ……

You have been informed about any available compensation or medical treatment if injury occurs as a result of study-related procedures;

You may contact Dr K Ndlovu at 0823388996 any time if you have questions about the research or if you are injured as a result of the research.

You may contact the **Biomedical Research Ethics Office** on **031-260 4769 or 260 1074** or Email BREC@ukzn.ac.za if you have questions about your rights as a research participant.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to stop at any time.

If you agree to participate, you will be given a signed copy of this document and the participant information sheet which is a written summary of the research.

The research study, including the above information, has been described to me orally. I understand what my involvement in the study means and I voluntarily agree to participate. I understand that participation in this study does not guarantee acceptance into the chronic renal programme nor will it disadvantage any me in any way. I have been given an opportunity to ask any questions that I might have about participation in the study.

_____ _____

Signature of Participant **Date**

_____ _____

Signature of Witness **Date**
(Where applicable)

_____ _____

Signature of Translator **Date**
(Where applicable)

APPENDIX 4: DATA CAPTURE SHEETS

Form 1: Screening data capture sheet

Screening no	Hospital no	Base hospital	ID number

Name	Surname	Age

KEH admission date	PD ward admission date	PD stick insertion date	Medical unit	Unit Registrar

Race	Marital status	Gender	Employment status

address	Home phone
	Cell phone

HIV status	eGFR	PD contraindication	Renal programme contraindication	
		Yes / No[1]	Yes / No1	

Current problems	Medical history	Drug history

Surgical history	Social history	Smoker	Alcohol use
		Yes / No1	Yes / No1
		weight	height

BP	Pulse	Temperature	urine dipstix	urine microscopy	PD WCC

If HIV positive	Last CD4 count	Date CD4 taken	On ARV treatment	Yes / No1
If on ARV treatment	**Start date**	**ARV site**	**baseline CD4 count**	**Viral load**

Study suitability	Yes / No1	Study group	
Comments			

[1] Please circle appropriate response

Form 2: Group 1 enrolment data capture sheet

Informed Consent taken ☐ By: _____ Date signed: _____

If signed by next of kin ☐ Name: _____

Relationship to patient: _____

Group 1							
Subject_ID	**Enrolment no**	**Screening no**			**Date of enrolment**		
PD stick insertion date	**Tenckhoff insertion date**	**PD ward discharge date**			**KEH discharge date**		
Name		**Surname**			**Date of birth**		
Biometric assessment	**AC**	**MAMC**	**SGA**	**WC**	**height**	**weight**	**BMI**
BP	**Pulse**	**temperature**	**urine dipstix**		**urine microscopy**		
Initial eGFR	**Formal GFR**	**24 hr urine protein**	**24 hr urine creatinine clearance**				
Ultrasound kidneys			**Renal biopsy**				
Left		Right					

Current Problem list	Current Meds
Physical examination	

Elisa confirmation	CD4 count	Viral load	ARV naive	ARV Start date	ARV file number
☐			Yes / No		
ARV treatment site		**ARV Regimen**			

Renal programme work-up investigations							
WR		ASOT		ESR		CRP	
Complement		ANF		Hepatitis B serology			
Lipid profile				TFT and FT3			
ECG							
Echo/Muga/Mibi scan							
Chest Xray							
Additional information							

Form 3: Group 2 enrolment data capture sheet

Informed Consent taken ☐ By: _____ Date signed: _____

If signed by next of kin ☐ Name: _____

Relationship to patient: _____

Group 2							
Subject_ID	**Enrolment no**	**Screening no**			**Date of enrolment**		
PD stick insertion date	**Tenckhoff insertion date**	**PD ward discharge date**			**KEH discharge date**		
Name		**Surname**			**Date of birth**		
Biometric assessment	**AC**	**MAMC**	**SGA**	**WC**	**height**	**weight**	**BMI**
BP	**Pulse**	**Temperature**	**urine dipstix**		**urine microscopy**		
Initial eGFR	**Formal GFR**	**24 hr urine protein**	**24 hr urine creatinine clearance**				
Ultrasound kidneys			**Renal biopsy**				
Left		Right					

Current Problem list	**Current Meds**
Physical examination	

Renal programme work-up investigations							
WR		ASOT		ESR		CRP	
Complement		ANF		Hepatitis B serology			
Lipid profile				TFT and FT3			
ECG							
Echo/Muga/Mibi scan							
Chest Xray							
Additional information							

Form 4: Subject background questionnaire

Hospital no: _____ Subject no: _____ Group: _____

1. Have you ever been diagnosed with renal failure before? Yes / No
   If yes,
   i) What was the diagnosis? _____
   ii) When were you diagnosed? _____
   iii) Where were you diagnosed? _____
   iv) Was a renal biopsy done? _____
   v) Have you received hemodialysis? Yes / No If so for how long? _____
   vi) Have you received peritoneal dialysis before? Yes / No
   If yes
   When did you receive it? _____
   For how long did you receive it? _____
   Why was it stopped? _____
2. Have you been diagnosed with Hypertension (High blood pressure) ? Yes / No
   If Yes
   i) When were you diagnosed? _____
   ii) Where were you diagnosed? _____
3. Have you been diagnosed with diabetes (sugar) ? Yes / No
   If Yes
   i) When were you diagnosed? _____
   ii) Where were you diagnosed? _____
   iii) Are you on insulin? Yes / No if so for how long? _____
4. Have you been diagnosed with any connective tissue disease? Yes / No
   If Yes
   i) What is the specific diagnosis? _____
   ii) When were you diagnosed? _____
   iii) Where were you diagnosed? _____
5. Do you use pain killers (NSAIDS) such as bruffen, aspirin, or indocid? Yes / No
   i) How often do you use it?
   Every day / 2-5 times a week / once a week / occasionally
   ii) For how long have you been using it? _____
6. Do you smoke? Yes / No
   If yes
   i) When did you start smoking? _____
   ii) How many cigarettes do you smoke per day?_____
   If no
7. Have you ever smoked before? Yes / No
   If yes
   i) When did you stop? _____
   ii) When did you start? _____
   iii) How many cigarettes did you smoke per day?_____
8. Do you drink alcohol? Yes / No

If yes

i) When did you start drinking? _____
ii) What kind of alcohol do you drink? _____
iii) How often do you drink?
Every day / every weekend / occasionally

9. Have you ever used alcohol before? Yes / No
If yes

i) When did you stop? _____
ii) When did you start? _____
iii) How often do you drink?
Every day / every weekend / occasionally

10. What is your occupation?
Unemployed / scholar / student / employed / self-employed

i) Type of occupation? _____

11. What is your monthly income range?
0 – R999 / R1000 – R9999 / R10,000 – R19,999 / above R20,000

12. What was your highest education achieved?
No schooling / primary school / high school / matric / diploma / degree

13. What is your ethnicity?
African / Indian / White / coloured / other: _____

14. What is your home language?
Zulu / Xhosa / English / Afrikaans / other: _____

15. Where were you born? Township / Suburban / City / Rural area
Place:_____ Province_____

16. Where do you live now? Township / Suburban / City / Rural area
Place:_____ Province_____

17. What type of housing do you reside in?
Brick house / flat / shack / rural housing / other: _____

i) How many rooms in house? _____

18. How many people reside with you in the house? _____
19. What type of floor do you have?
concrete / tiles / carpet / wooden flooring / other: _____

20. Do you have access to water? Yes / No
In house tap / communal tap / river / other: _____

21. Do you have access to sanitation? Yes / No
In house toilet / outside toilet / pit lavatory / communal toilet / other: _____

22. What is your marital status? Single / Married / Divorced / other: _____
23. Do you have any children? Yes / No
If Yes how many: _____

Form 5:Monthly visits questionnaire

Hospital no: _____ Subject no: _____ Group: _____

1) Have you been admitted since last visit? Yes / No
If yes fill in hospital admission record form

2) Are you constipated currently? Yes / No
If Yes. For how long? _____

3) Have you suffered from constipation in the last month? Yes / No
If Yes. How often? Daily / 1-5 times a week / 1-3 times a month

4) Have you used stool softener in the last month? Yes / No
If Yes. How often? Daily / 1-5 times a week / 1-3 times a month

5) Have you suffered from diarrhoea in the last month? Yes / No
If Yes. How often? Daily / 1-5 times a week / 1-3 times a month

6) How is your appetite? Good / Poor
If Poor For how long: _____

7) Do you have abdominal pain? Yes / No

8) Have you had episodes of abdominal pain in the past month? Yes / No
If Yes. How often? Daily / 1-5 times a week / 1-3 times a month

9) What is the colour of your PD fluid? Clear / Cloudy / Bloody / Yellow

10) Are you still passing urine? Yes / No
If Yes: How much urine are you passing per day? _____

11) Do you have any problems with drainage into the PD bags?

12) How much fluid comes out from the overnight bag? _____

13) How much fluid comes out from the morning bag? _____

14) How much fluid comes out from the midday bag? _____

15) How much fluid comes out from the afternoon bag? _____

16) Have you had episodes of fever in the past month? Yes / No

17) Have you had episodes of rigors in the past month? Yes / No

18) Have you had episodes of night sweats in the past month? Yes / No

19) Have you had episodes of nausea in the past month? Yes / No
If Yes. How often? Daily / 1-5 times a week / 1-3 times a month

20) Have you had episodes of vomiting in the past month? Yes / No
If Yes. How often? Daily / 1-5 times a week / 1-3 times a month

21) Please list record of food you have eaten in the last 24 hours in next page..

B *Breakfast* **L** *Lunch* **D** *Dinner* **S** *Snack*	**Time**	**Place** **H** *Home* **R** *Restaurant (List Name)* **O** *Other*	**Food** *Be very specific, include name brands*	**Preparation** *How did you cook it* *What did you add to it*	**Serving Size**

Form 6: Monthly visit data capture sheet

Subject no: _____ Hospital no: _____

Date: _____ Visit: _____ Group: _____

Tenckhoff insertion date: _____ Membrane type: _____

Kt/v: _____ Residual renal function: _____ GFR: _____

Peritonitis episodes

Date	Microbiology	Outcome

Current PD Prescription

Time	Fluid	Duration	UF volume

Total UF volume/24hrs: _____urine dipstix: _____

weight: _____ BP: _____ Pulse: _____ Temp: _____

Current Medication

Complaints: _____

_____

_____

Appetite: _____ Constipation: _____

Examination

General: _____

_____

CVS: _____

Chest: _____

Abdomen: _____

Exit site: _____

Tract: _____

Hernia: _____

FBC: _____ CPM: _____ ALB: ____

Ue: _____ LFT:_____

PD Prescription

Time	Fluid	Duration

Medication changes

Comments

Form 7: Biochemistry data flow sheet

Hospital no: _____ Subject no: _____ Group: _____

	Enrolment	PD ward Discharge	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month	7th Month	8th Month	9th Month	10th Month	11th Month	12th Month
Sodium														
Potasium														
Chloride														
Bicarbonate														
Urea														
Creatinine														
Anion gap														
eGFR														
HB														
MCV														
MCH														
PLATELETS														
WBC														
Neutrophils														
Lymphocytes														
Albumin														
Calcium														
Phosphate														
Magnesium														
Total Protein														
Albumin														
Total Bilirubin														
ALP														
GGT														
ALT														
AST														
Cholesterol														
LDL														
HDL														

Hospital no: _____ Subject no: _____ Group: _____

	13rd Month	14th Month	15th Month	16th Month	17th Month	18th Month
Sodium						
Potasium						
Chloride						
Bicarbonate						
Urea						
Creatinine						
Anion gap						
eGFR						
HB						
MCV						
MCH						
PLATELETS						
WBC						
Neutrophils						
Lymphocytes						
Albumin						
Calcium						
Phosphate						
Magnesium						
Total Protein						
Albumin						
Total Bilirubin						
ALP						
GGT						
ALT						
AST						
Cholesterol						
LDL						
HDL						

Form 8: Biomarker data flow sheet

Hospital no: _____ Subject no: _____ Group: _____

	Enrolment	PD ward Discharge	2 Weeks	1st Month	2nd Month	3rd Month	4th Month	5th Month	6th Month	7th Month	8th Month
CRP											
ESR											
Ferritin											
Serum albumin											
serum NGAL											
serum IL-1											
serum IL-6											
serum TGF-β											
serum FGF											
serum hyaluronan											
serum β-2-microglobulin											
PDE HIV Virology*											
PDE WBC count											
PDE Total protein											
PDE Albumin											
PDE NGAL											
PDE IL-1											
PDE IL-6											
PDE TGF-β											
PDE FGF											
PDE hyaluronan											
PDE β-2-microglobulin											

Hospital no: _____ Subject no: _____ Group: _____

	9th Month	10th Month	11th Month	12th Month	13rd Month	14th Month	15th Month	16th Month	17th Month	18th Month
CRP										
ESR										
Ferritin										
Serum albumin										
serum NGAL										
serum IL-1										
serum IL-6										
serum TGF-β										
serum FGF										
serum hyaluronan										
serum β-2-microglobulin										
PDE HIV Virology*										
PDE WBC count										
PDE Total protein										
PDE Albumin										
PDE NGAL										
PDE IL-1										
PDE IL-6										
PDE TGF-β										
PDE FGF										
PDE hyaluronan										
PDE β-2-microglobulin										

Form 9: Renal function and biometric flow sheet

Hospital no: _____ Subject no: _____ Group: _____

	1st Visit	6th month	12th month	18th month
Formal GFR				
Residual renal function				
PTH				

PET test	2nd week	3rd month	6th month	9th month	12th month	15th month	18th month
kt/v							
URR							
Membrane type							

Biometric assessment				
	1st Visit	6th month	12th month	18th month
BMI				
arm circumference				
mid-arm muscle circumference				
Subjective global assessment				
waist circumference				

Seropositive Group							
	1st Visit	3rd month	6th month	9th month	12th month	15th month	18th month
Date							
CD4							
Viral load							

Form 10: Hospital admission record.

Name: _____ Surname: _____

Subject no: _____ Group: _____

Admission date	Discharge date	Hospital	CAPD related	Diagnosis	Outcome
			☐		
			☐		
			☐		
			☐		
			☐		
			☐		
			☐		
			☐		

Comments: _____

_____

_____

_____

_____