Plasma galectin-3 is associated with decreased glomerular filtration rate in chronic HIV

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Background: People living with HIV (PLWH) have higher rates of chronic kidney disease (CKD) compared with HIV-uninfected individuals. The pathogenesis of CKD in HIV remains poorly understood but is likely from a combination of various factors, such as traditional comorbidities, prolonged antiretroviral therapy, immune dysregulation, and direct HIV effect on the kidneys. We evaluated plasma galectin-3 (Gal-3), a circulating marker of fibrosis, and its association with renal function.

Methods: Estimated glomerular filtration rate (eGFR) was assessed by CKD-EPI. Plasma galectin-3 was obtained from banked specimens by ELISA. Factors associated with eGFR were analyzed using step-wise multiple linear regression.

Results: A total of 45 PLWH and 58 HIV-uninfected participants were included with similar demographic parameters. Among PLWH, majority had undetectable plasma HIV RNA (82.2%). Gal-3 was significantly higher in PLWH than in HIV-uninfected participants (6.4 [IQR 4.0, 8.5] ng/mL and 4.5 [IQR 2.3, 6.5] ng/mL, respectively; $p = 0.020$) while a trend towards lower eGFR was found in PLWH compared to the HIV-uninfected cohort (86.8 [IQR 71.3, 91.8] and 89.0 [IQR 78.6, 97.4] mL/min/1.73 m^2, respectively; $p = 0.071$). In univariable analysis, HIV status was marginally associated with decreased eGFR (β coefficient= −0.035, $p = 0.051$). In the final multivariable regression model adjusted for traditional risk factors of CKD, Gal-3 independently predicted a decrease in eGFR (unstandardized B= −0.008, $p < 0.001$) while HIV status did not demonstrate any significant association.

Conclusion: Gal-3 was higher in PLWH compared with HIV-uninfected participants. In multivariable adjusted analyses, Gal-3, but not HIV status, was associated with decreased eGFR. The role of Gal-3 as a biomarker of kidney function needs to be further elucidated.

KEYWORDS: HIV, kidney disease, kidney fibrosis, gal-3, eGFR

Background

Chronic kidney disease (CKD) is a progressive condition associated with substantial morbidity and mortality.[1,2] CKD is characterized by a gradual loss of excretory renal function due to structural or functional abnormalities of the kidney.[3] CKD has various etiologies, including age-related nephron loss, hypertension, diabetes, toxic exposures, and various systemic inflammatory conditions.[4]

People living with HIV (PLWH) are at higher risk of developing CKD compared with HIV-uninfected individuals.[5,6] In the general population, the global prevalence of CKD is estimated to be 13.4%. While data on renal disease in PLWH varies by geographic location, the worldwide prevalence of CKD among PLWH is estimated to be as high as 48.5%.[7–9] Kidney disease in PLWH is multifactorial and may be from complications of chronic antiretroviral therapy,

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co-morbidities, co-infections, immune dysregulation, and a direct HIV effect.[10–12] Kidney damage may be exerted through viral infection of kidney cells or through immune complex deposition as a response to HIV infection.[13] Recent animal studies have suggested that kidney fibrosis may play a role in the decreased estimated glomerular filtration rate (eGFR) in CKD.[14] While acute immune activation may be beneficial in the early stages of kidney injury, a state of chronic inflammation fuels fibrosis and renal dysfunction.[15]

Galectin-3 (Gal-3), a mammalian protein that is a member of the lectin family, has been increasingly recognized for its pro-fibrotic and pro-inflammatory properties.[16–18] Gal-3 is a multifunctional beta-galactoside binding protein expressed in multiple cell types and may be excreted into the extracellular milieu, such as blood and urine.[19–21] Animal models have demonstrated an upregulation of Gal-3 in the kidneys following induced renal failure and have linked Gal-3 to renal fibrosis.[22,23] In humans, increased plasma Gal-3 is associated with a decline in estimated glomerular filtration rate (eGFR) and correlated with renal fibrosis.[24] Higher circulating Gal-3 has been associated with a higher incidence of CKD.[14,25]

Gal-3 is upregulated in HIV-infected cells and has been found to facilitate cell-to-cell transmission of HIV.[26–28] However, there is limited information about the relationship between Gal-3 and renal function in PLWH. In this study, we compared Gal-3 levels between PLWH and HIV-uninfected participants. Among PLWH, we compared Gal-3 with measured plasma biomarkers of inflammation. Finally, we determined the association of Gal-3 with eGFR adjusting for traditional CKD risk factors.

Methods

Study participants

This analysis was conducted utilizing entry data from the Hawaii Aging with HIV Cardiovascular Disease Study (HAHC-CVD), a four-year longitudinal cohort study, performed to evaluate the role of oxidative stress and inflammation on cardiovascular disease in PLWH. In brief, subjects had documented HIV infection, were $\geq$40 years old and on stable antiretroviral therapy (ART) for $\geq$3 months. Subjects who were recently hospitalized, had active infection, malignancy, or AIDS-defining illness at the time of enrolment were excluded. The HAHC-CVD study was approved by the Committee on Human Studies of the University of Hawaii, and upon informed consent, participants agreed for unused specimens remaining in our repository to be used in future HIV-related studies. The details of the study design and enrollment of the PLWH cohort have been published previously.[29] HIV-seronegative participants similar in age and gender were enrolled cross-sectionally for comparison to the PLWH cohort. Similar inclusion and exclusion criteria were used, except for documented HIV-seronegative status. The details of the HIV-seronegative study were described in greater detail in a previous publication.[30] In this current analysis, inclusion was determined by the availability of stored plasma for Gal-3 assessment. It is worthy to note that there were no statistically significant differences in the clinical-demographic parameters between individuals with available plasma vs those without available plasma (i.e., similar age, gender, ethnicity, percentage with diabetes or hypertension, and levels of nadir or current CD4 T cell count).

Plasma inflammatory markers and monocyte subsets

Milliplex Human Cardiovascular Disease panels (EMD Millipore) were used to measure plasma soluble biomarkers of inflammation. Multiparametric flow cytometry was performed on cryopreserved peripheral blood mononuclear cells to measure the frequencies of monocyte subsets [classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$), non-classical ($CD14^{low/+}CD16^{++}$)], as previously described.[31]

Plasma galectin-3

Assays were performed on banked plasma that were stored at −80 °C. The human galectin-3 ELISA plates (Human Galectin-3 DuoSet ELISA, R&D Systems) were prepared according to the manufacturer's guidance. Absorbance was measured at 450/540 nm using a microplate reader (The SpectraMax® M3, Molecular Devices, San Jose, CA).

Statistical analyses

This analysis assessed Gal-3 and its association with renal function as measured by eGFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[32,33] Comparison of study parameters were calculated using Mann-Whitney U and Pearson Chi-squared tests for continuous and categorical variables, respectively, and correlations within the data were assessed by Spearman's rank sum correlation test. The significance of HIV status and Gal-3 as a predictor of eGFR were examined using stepwise multivariable linear regression models with eGFR as the dependent variable. The final multivariable model was adjusted for HIV status, Gal-3, age, hypertension, diabetes mellitus, and total monocyte count. Statistical analyses were two-tailed, and a p-value of <0.05 was considered statistically significant.

These statistical analyses were performed using IBM SPSS statistics version 29.0 (Armonk, NY).

We conducted an additional causal mediation analysis to investigate the impact of HIV on eGFR levels, with a specific focus on mediation through Galectin 3, as illustrated in Figure 1. This analysis was performed using log-eGFR as the response variable, with Gal-3 considered as the mediator, while taking into account the previously mentioned covariates. We estimated the mediation effect, direct effect, and total effect of HIV on log-EGFR, followed by corresponding inferential steps (Tingley, et al, 2014). Causal mediation analysis was performed using R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Comparisons between PLWH and HIV-uninfected group

A total of 45 PLWH and 58 HIV-uninfected participants were included in analysis. There were no significant differences in demographic and clinical parameters by HIV status, as presented in Table 1. Among PLWH, median CD4 count was 510 cells/μL and majority had undetectable plasma HIV RNA at <48 copies/mL (82.2%) and were on tenofovir disoproxil fumarate (73.3%).

Gal-3 was significantly higher in PLWH (6.4 [IQR 4.0, 8.5] ng/mL) than in HIV-uninfected participants (4.5 [IQR 2.3, 6.5] ng/mL; $p = 0.020$). Although the differences in the distribution of creatinine was statistically significant ($p = 0.016$), the differences in the range between the two groups are fairly modest: (1.0 [0.9, 1.1] for PLWH and 1.0 [0.8, 1.1] for HIV-seronegative). There was a trend in lower eGFR in PLWH than in HIV-uninfected participants (86.8 [IQR 71.3, 91.8] and 89.0 [IQR 78.6, 97.4] mL/min/1.73 m^2, respectively; $p = 0.071$), but this median difference in eGFR of 2.4 units is likely not clinically relevant. Performing correlations by HIV status, Gal-3 correlated negatively with eGFR among PLWH ($r = -0.321$, $p = 0.031$) but a significant association was not seen when the analysis was performed among HIV-uninfected participants ($r = -0.193$, $p = 0.147$).

Correlations between Gal-3 and immune parameters

The association between Gal-3 and plasma soluble biomarkers and monocytes were assessed among PLWH. HIV-specific parameters including T-cell count, monocyte subsets, cytokines and cystatin C were derived from clinical labs and banked blood and urine specimens from the Hawaii Aging with HIV study and correlated with circulating levels of Gal-3 (Table 2). Total monocyte count ($r = -0.316$, $p = 0.034$) and classical monocytes ($r = -0.329$, $p = 0.044$) were found to be negatively correlated with Gal-3 in PLWH.

Stepwise linear regression analyses

We assessed HIV status as a predictor of decreased eGFR using stepwise linear regression models adjusting for Gal-3, age, hypertension, diabetes mellitus, and total monocyte count (Table 3). In the final multivariable model, higher circulating levels of Gal-3 was associated with decreased eGFR ($\beta = -0.314$, $p = <0.001$). HIV status was associated with eGFR in univariable analysis ($\beta = -0.035$, $p = 0.051$) but was not found to be a significant in the adjusted analysis ($\beta = -0.145$, $p = 0.112$).

Causal mediation analysis

The results of the Causal Mediation Analysis (Table 4) revealed that the direct effect of HIV on log-eGFR is estimated to be −0.0288 (95% CI [-0.0553, 0.0007]; p-value = 0.064). Secondly, when examining the mediation effect of HIV on log-EGFR through Gal-3, we observe an effect of −0.0132 (95% CI [-0.03456, −0.0011]; p-value = 0.020). Combining both direct and indirect effects, the total effect of HIV on log-EGFR is −0.0420 (95% CI [-0.0716, −0.01]; p-value = 0.016). Approximately 31.43% of this total effect is mediated through Gal-3.

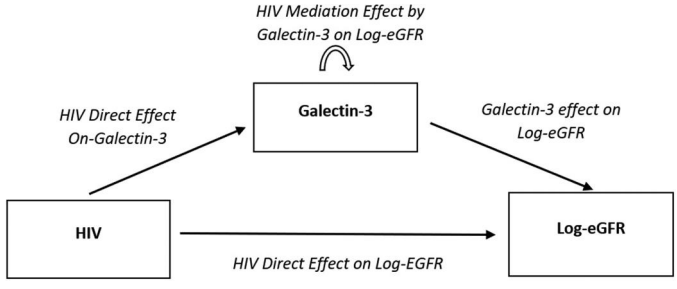

Figure 1. The analysis of HIV causal effect on estimated glomerular filtration rate (eGFR), mediated by Galectin-3.

Table 1. Comparison of demographics and clinical parameters in PLWH and HIV-negative individuals.

Parameter[a]	PLWH ($n = 45$)	HIV- ($n = 58$)	p-value
Age, years	51 [46, 56.5]	55 [47.5, 60.5]	0.125
Male, n (%)	42 (93.3%)	49 (84.5%)	0.165
Race			
Caucasian/White, n (%)	28 (62.2%)	37 (63.8%)	0.885
African American/Black	1 (2.2%)	1 (1.7%)	
Native American/Alaskan	1 (2.2%)	0 (0%)	
Native Hawaiian/Pacific Islander[b]	6 (13.3%)	6 (10.3%)	
Asian	3 (6.7%)	5 (8.6%)	
More than one race	6 (13.3%)	9 (15.5%)	
Hispanic or Latino ethnicity, n (%)	7 (15.6%)	5 (8.6%)	0.277
History of hypertension, n (%)	15 (33.3%)	15 (25.9%)	0.408
History of diabetes mellitus, n (%)	3 (6.7%)	2 (3.4%)	0.451
History of smoking n, (%)	28 (62.2%)	32 (55.2%)	0.605
$CD4^+$ T cells, cells/μL	510.0 [424.0, 686.5]	—	—
Undetectable HIV RNA, n (%)	37 (82.2%)	—	—
Current use of tenofovir disoproxil fumarate n, (%)	33 (73.3%)	—	—
Serum creatinine, mg/dL	1.0 [0.9, 1.1]	1.0 [0.8, 1.1]	0.016*
eGFR CKD-EPI[c], mL/min/1.73 m^2	86.8 [71.3, 91.8]	89.0 [78.6, 97.4]	0.071
Plasma Gal-3, ng/mL	6.4 [4.0, 8.5]	4.5 [2.3, 6.5]	0.020*

[a]Data presented as median [Quartile 1, Quartile 3] for continuous variables and n (%) for proportions.
[b]Includes any participant who indicated they are part-Native Hawaiian/Pacific Islander.
[c]Estimated Glomerular Filtration Rate was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula.
*$p < 0.05$.

Table 2. Correlation between galectin-3 and other immune parameters.[a]

	Spearman's rho	p-value
UACR	0.229	0.186
Serum cystatin C	0.059	0.701
$CD4^+$ T cells	−0.069	0.652
$CD8^+$ T cells	0.028	0.853
CD4/CD8 ratio	−0.043	0.781
Total monocyte count, cells/L	−0.316	0.034*
Classical monocytes, cells/L	−0.329	0.044*
Intermediate monocytes, cells/L	0.040	0.811
Non-classical monocytes, cells/L	−0.124	0.458
CRP	0.037	0.821
sE-Selectin	0.177	0.282
sICAM-1	0.138	0.401
IFN-γ	0.069	0.675
IL-1β	0.173	0.292
IL-6	0.005	0.978
IL-8	0.168	0.308
IL-10	−0.073	0.658
MCP-1	0.143	0.387
MMP-9	0.174	0.289
MPO	−0.101	0.540
SAA	−0.002	0.991
SAP	0.021	0.897
TNF-α	−0.013	0.939
tPAI-1	0.067	0.687
VCAM-1	−0.054	0.742
VEGF	−0.160	0.330

[a]Number of participants with available data, $n = 45$.
*$p < 0.05$.
Abbreviations: Urine Albumin/Creatinine Ratio was calculated by: UACR (mg/g) = Urine Albumin (mg/dL)/Urine Creatinine (g/dL) ≈ Albumin excretion in mg/day; CRP, C-reactive protein; sE-selectin, soluble E-Selectin; SICAM, soluble intercellular adhesion molecule-1; IFN-γ, interferon-gamma; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MMP-9, matrix metalloproteinase-9; MPO, myeloperoxidase; SAA, serum amyloid A; SAP, serum amyloid P; TNF, tumor necrosis factor; tPAI-1, tissue plasminogen activator inhibitor-1; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

Discussion

To our knowledge, this is the first study to evaluate the relationship between plasma Gal-3 concentrations and kidney dysfunction in PLWH. Some of the key findings in this paper include: higher Gal-3 among PLWH compared with HIV-uninfected participants, negative association of Gal-3 with total and classical monocytes among PLWH; and the association of Gal-3 with decreased eGFR in multivariable models adjusted for traditional risk factors for CKD. In the final linear regression model, HIV status was no longer significantly associated with eGFR. However, additional causal mediation analysis revealed that when combining both direct and indirect effects, the total effect of HIV status on log-EGFR is −0.0420. Approximately 31.43% of this total effect is mediated through Gal-3.

There has been increased interest in Gal-3 as a biomarker of tissue fibrosis, including the heart, lungs, liver, and kidney.[16,34] In both animal models and human studies, renal injury and cardiac damage is followed by an increased expression of Gal-3, particularly in the setting of ischemia.[23,24,35] In this present study, increased circulating levels of Gal-3 was significantly associated with decreased eGFR and decreased total and non-classical monocytes in PLWH, but, interestingly, Gal-3 was not significantly associated with other plasma biomarkers of inflammation. Gal-3 has been reported to play a pivotal role in interstitial fibrosis and CKD progression in both diabetic and non-diabetic nephropathy.[36] The Framingham Heart Study also found associations between elevated Gal-3 and

Table 3. Stepwise linear regression of factors associated with eGFR*.

		Unstandardized Coefficient (B)	Standardized β-coefficient	p-value	95% Confidence Interval for B	
Model 1:	HIV status	−0.035	−0.193	0.051	−0.071	0.000
Model 2:	HIV status	−0.021	−0.114	0.227	−0.055	0.013
	Galectin-3	−0.010	−0.363	<0.001	−0.014	−0.005
Model 3:	HIV status	−0.030	−0.166	0.069	−0.063	0.002
	Galectin-3	−0.009	−0.334	<0.001	−0.013	−0.004
	Age	−0.004	−0.304	<0.001	−0.006	−0.002
Model 4:	HIV status	−0.029	−0.158	0.085	−0.062	0.004
	Galectin-3	−0.008	−0.324	<0.001	−0.013	−0.004
	Age	−0.003	−0.289	0.002	−0.006	−0.001
	Hypertension	−0.021	−0.103	0.247	−0.056	0.014
Model 5:	HIV status	−0.027	−0.149	0.101	−0.060	0.005
	Galectin-3	−0.008	−0.299	0.001	−0.013	−0.003
	Age	−0.003	−0.251	0.008	−0.005	−0.001
	Hypertension	−0.016	−0.079	0.383	−0.051	0.020
	Diabetes mellitus	−0.056	−0.132	0.170	−0.136	0.024
Model 6:	HIV status	−0.026	−0.145	0.112	−0.059	0.006
	Galectin-3	−0.008	−0.314	<0.001	−0.013	−0.003
	Age	−0.003	−0.230	0.018	−0.005	0.000
	Hypertension	−0.015	−0.075	0.404	−0.051	0.021
	Diabetes mellitus	−0.059	−0.140	0.150	−0.139	0.022
	Total monocyte count	−0.045	−0.086	0.339	−0.137	0.048

*Estimated glomerular filtration rate $\log_{10}$ transformed.

Table 4. Results of the causal mediation analysis of HIV on estimated glomerular filtration rate, mediated by galectin-3.

	Estimate	95% CI Lower	95% CI Upper	p-value
Mediation effect	−0.0132	−0.0346	−0.0011	0.020
Direct Effect	−0.0288	−0.0553	0.0007	0.064
Total Effect	−0.0420	−0.0716	−0.0100	0.016
Prop. Mediated	0.3143	0.0274	0.9200	0.028

incident CKD, suggesting that Gal-3 may serve as a biomarker especially in high-risk groups.[14] High Gal-3 levels were found to be associated with a greater prevalence of albuminuria in the Cardiovascular Health Study [37] but not in the Framingham Heart Study.[14] In the current study, we found increased Gal-3 to be independently associated with decreased eGFR in PLWH even after adjusting for diabetes and hypertension, two of the leading causes of CKD globally. No association with urine albumin/creatinine ratio was found.

Gal-3 has been reported to be a monocyte-macrophage chemoattractant that influences monocyte migration and regulates the recruitment of monocytes into inflamed tissues.[38,39] Using mouse models, Henderson et al. [23] established a profibrotic signaling axis between macrophages and tissue fibroblasts that is mediated by Gal-3, identifying macrophages as a key cell type in the pathogenesis of renal fibrosis. We hypothesize that the negative correlation found between Gal-3 and monocytes in this study is due to the relative decrease of circulating classical monocyte subsets in the blood and their migration to tissues as mediated by Gal-3.

Other galectins have been reported to play a role in HIV pathogenesis but their role in kidney disease have not been explored. Gal-1 has been shown to facilitate HIV-1 infection in monocyte-derived macrophages by promoting adsorption and early events of the virus replicative cycle [40] and through direct interaction with glycans of viral gp120 and host CD4.[41] Gal-9 has been found to be chronically elevated in HIV [42] and plays a key role in regulating the redox environment, T-cell migration, and HIV entry. [43] Gal-3 has been shown to facilitate HIV budding in Jurkat T cells. [26] However, the role of Gal-3 in HIV-associated nephropathy remains to be further elucidated.

It is interesting to note that our analyses did not show correlations between eGFR and other plasma markers of inflammation. Plasma inflammatory markers, such as TNF-alpha and IL-6, have been reported by other groups to accelerate CKD progression.[44,45] Our cohort included PLWH on ART with mostly virologically suppressed individuals. It is likely that the plasma inflammatory markers did not show any significant correlations with eGFR, as the level of inflammation may not have been significantly elevated in the setting of suppressive ART. Unfortunately, we did not have plasma biomarker data in the HIV-seronegative group to compare the levels between the two cohorts. The small sample size of the study could also have contributed to the lack of power to detect associations between the various plasma inflammatory markers and eGFR. Lastly, the relative contribution of excess plasma inflammation to eGFR may have been 'overpowered' by other factors used in the calculation of eGFR (such as age and gender).

Apart from the relatively small sample size of our cohorts, our Gal-3 analyses were further limited by the availability of stored plasma available for secondary analyses. Plasma soluble markers and monocyte analyses were also not available in the HIV-uninfected cohort. Due to the invasive nature of tissue biopsy, we also do not have renal histopathological samples to assess levels of Gal-3 and anatomical changes in our cohort. Despite these limitations, we present the first paper analyzing Gal-3 and renal function in HIV. Our PLWH cohort is well characterized and the presence of an HIV-uninfected participants with similar demographic characteristics allows for a more robust analysis.

In conclusion, PLWH had marginally lower eGFR compared with HIV-uninfected participants. Further analysis revealed that HIV status had both direct and indirect effect on eGFR, as mediated by Gal-3. Elevated levels of circulating Gal-3 were independently associated with decreased eGFR. The correlation between Gal-3 and eGFR suggests that Gal-3 may play a role in mediating tissue inflammation and fibrosis, leading to decreased renal function. Further studies are warranted to investigate the role of Gal-3 in CKD and how it can be targeted to mitigate kidney disease among PLWH on long-term ART.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1 Ekrikpo UE, Kengne AP, Bello AK, et al. Chronic kidney disease in the global adult HIV-infected population: A systematic review and meta-analysis. *PLoS One*. 2018;13(4):e0195443.
2 Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl (2011)*. 2022;12(1):7–11.
3 Charles C, Ferris AH. Chronic kidney disease. *Prim Care.* 2020; 47(4):585–595.
4 Romagnani P, Remuzzi G, Glassock R, et al. Chronic kidney disease. *Nat Rev Dis Primers*. 2017;3(1):17088.
5 Heron JE, Bagnis CI, Gracey DM. Contemporary issues and new challenges in chronic kidney disease amongst people living with HIV. *AIDS Res Ther*. 2020;17(1):11.
6 Wyatt CM. Kidney disease and HIV infection. *Top Antivir Med*. 2017;25(1):13–16.
7 Bertoldi A, De Crignis E, Miserocchi A, et al. HIV and kidney: a dangerous liaison. *New Microbiol*. 2017;40(1):1–10.
8 Evans M, Lewis RD, Morgan AR, et al. A narrative review of chronic kidney disease in clinical practice: Current challenges and future perspectives. *Adv Ther*. 2022;39(1):33–43.
9 Naicker S, Rahmanian S, Kopp JB. HIV and chronic kidney disease. *Clin Nephrol*. 2015;83(7 Suppl 1):32–38.
10 Gameiro J, Jorge S, Lopes JA. HIV and renal disease: a contemporary review. *Int J STD AIDS*. 2018;29(7):714–719.
11 Fiseha T, Gebreweld A. Renal function in a cohort of HIV-infected patients initiating antiretroviral therapy in an outpatient setting in Ethiopia. *PLoS One*. 2021;16(1):e0245500.
12 Mwemezi O, Ruggajo P, Mngumi J, Furia FF. Renal dysfunction among HIV-infected patients on antiretroviral therapy in Dar es Salaam, Tanzania: a cross-sectional study. *Int J Nephrol*. 2020; 2020:8378947.
13 Mikulak J, Singhal PC. HIV-1 and kidney cells: better understanding of viral interaction. *Nephron Exp Nephrol*. 2010;115(2): e15–e21.
14 O'Seaghdha CM, Hwang S-J, Ho JE, Vasan RS, Levy D, Fox CS. Elevated galectin-3 precedes the development of CKD. *J Am Soc Nephrol*. 2013;24(9):1470–1477.
15 Panizo S, Martínez-Arias L, Alonso-Montes C. Fibrosis in chronic kidney disease: pathogenesis and consequences. *Int J Mol Sci*. 2021;22(1):408.
16 Li L-c, Li J, Gao J. Functions of galectin-3 and its role in fibrotic diseases. *J Pharmacol Exp Ther*. 2014;351(2):336–343.
17 Liu F-T, Hsu DK. The role of galectin-3 in promotion of the inflammatory response. *Drug News Perspect*. 2007;20(7):455–460.
18 Díaz-Alvarez L, Ortega E. The many roles of galectin-3, a multifaceted molecule, in innate immune responses against pathogens. *Mediators Inflamm*. 2017;2017:9247574–9247510.
19 Vasta GR. *Galectins as Pattern Recognition Receptors: Structure, Function, and Evolution*. New York: Springer New York; 2012:21–36.
20 Dong R, Zhang M, Hu Q, et al. Galectin-3 as a novel biomarker for disease diagnosis and a target for therapy (Review). *Int J Mol Med*. 2018;41(2):599–614.
21 Hara A, Niwa M, Noguchi K, et al. Galectin-3 as a next-generation biomarker for detecting early stage of various diseases. *Biomolecules* 2020;10(3):389.
22 Nishiyama J, Kobayashi S, Ishida A, et al. Up-regulation of galectin-3 in acute renal failure of the rat. *Am J Pathol*. 2000; 157(3):815–823.
23 Henderson NC, Mackinnon AC, Farnworth SL, et al. Galectin-3 expression and secretion links macrophages to the promotion of renal fibrosis. *Am J Pathol*. 2008;172(2):288–298.
24 Ou S-M, Tsai M-T, Chen H-Y, et al. Identification of galectin-3 as potential biomarkers for renal fibrosis by RNA-sequencing and clinicopathologic findings of kidney biopsy. *Front Med (Lausanne)*. 2021;8:748225.
25 Chen S-C, Kuo P-L. The role of galectin-3 in the kidneys. *Int J Mol Sci*. 2016;17(4):565.
26 Wang S-F, Tsao C-H, Lin Y-T, et al. Galectin-3 promotes HIV-1 budding via association with Alix and Gag p6. *Glycobiology* 2014;24(11):1022–1035.
27 Wang S-F, Hung Y-H, Tsao C-H, et al. Galectin-3 facilitates cell-to-cell HIV-1 transmission by altering the composition of

membrane lipid rafts in CD4 T cells. *Glycobiology* 2022;32(9): 760–777.
28 Fogel S, Guittaut M, Legrand A, Monsigny M, Hébert E. The tat protein of HIV-1 induces galectin-3 expression. *Glycobiology* 1999;9(4):383–387.
29 Shikuma CM, Seto T, Liang CY, et al. Vitamin D levels and markers of arterial dysfunction in HIV. *AIDS Res Hum Retroviruses*. 2012;28(8):793–797.
30 SahBandar IN, Ndhlovu LC, Saiki K, et al. Relationship between circulating inflammatory monocytes and cardiovascular disease measures of carotid intimal thickness. *J Atheroscler Thromb.* 2020;27(5):441–448.
31 Chew GM, Fujita T, Webb GM, et al. TIGIT marks exhausted T cells, correlates with disease progression, and serves as a target for immune restoration in HIV and SIV infection. *PLoS Pathog*. 2016;12(1):e1005349.
32 Ibrahim F, Hamzah L, Jones R, Nitsch D, Sabin C, Post FA, UK CHIC/CKD* Study Group. Comparison of CKD-EPI and MDRD to estimate baseline renal function in HIV-positive patients. *Nephrol Dial Transplant*. 2012;27(6):2291–2297.
33 Vrouenraets S, Fux CA, Wit F, et al. A comparison of measured and estimated glomerular filtration rate in successfully treated HIV-patients with preserved renal function. *Clin Nephrol*. 2012; 77(4):311–320.
34 Sciacchitano S, Lavra L, Morgante A, et al. Galectin-3: One molecule for an alphabet of diseases, from A to Z. *Int J Mol Sci*. 2018;19(2):379.
35 Martínez-Martínez E, Brugnolaro C, Ibarrola J, et al. CT-1 (Cardiotrophin-1)-Gal-3 (Galectin-3) axis in cardiac fibrosis and inflammation. *Hypertension*. 2019;73(3):602–611.
36 Desmedt V, Desmedt S, Delanghe JR, Speeckaert R, Speeckaert MM. Galectin-3 in renal pathology: More than just an innocent bystander. *Am J Nephrol*. 2016;43(5):305–317.
37 Iacoviello M, Aspromonte N, Leone M, et al. Galectin-3 serum levels are independently associated with microalbuminuria in chronic heart failure outpatients. *Res Cardiovasc Med*. 2016; 5(1):e28952.
38 Sano H, Hsu DK, Yu L, et al. Human Galectin-3 is a novel chemoattractant for monocytes and macrophages. *J Immunol*. 2000;165(4):2156–2164.
39 Abusamra D, Anastasiou M, Panjwani NA, Alcaide P, Argueso P. Galectin-3 modulates monocyte infiltration in the injured cornea by inducing sialyl LewisX expression. *Invest Ophthalmol Visual Sci*. 2022;63(7):419–419.
40 Mercier S, St-Pierre C, Pelletier I, Ouellet M, Tremblay MJ, Sato S. Galectin-1 promotes HIV-1 infectivity in macrophages through stabilization of viral adsorption. *Virology* 2008;371(1): 121–129.
41 St-Pierre C, Manya H, Ouellet M, et al. Host-soluble galectin-1 promotes HIV-1 replication through a direct interaction with glycans of viral gp120 and host CD4. *J Virol*. 2011;85(22):11742–11751.
42 Tandon R, Chew GM, Byron MM, et al. Galectin-9 is rapidly released during acute HIV-1 infection and remains sustained at high levels despite viral suppression even in elite controllers. *AIDS Res Human Retroviruses*. 2014;30(7):654–664.
43 Bi S, Hong PW, Lee B, Baum LG. Galectin-9 binding to cell surface protein disulfide isomerase regulates the redox environment to enhance T-cell migration and HIV entry. *Proc Natl Acad Sci U S A*. 2011;108(26):10650–10655.
44 Su H, Lei CT, Zhang C. Interleukin-6 signaling pathway and its role in kidney disease: An update. *Front Immunol*. 2017;8:405.
45 Ramseyer VD, Garvin JL. Tumor necrosis factor-alpha: regulation of renal function and blood pressure. *Am J Physiol Renal Physiol.* 2013;304(10):F1231–1242.