



Prevalence of Acute Kidney Injury and its Predictors among HIV-Positive Patients in Africa: Systematic Review and Meta-Analysis

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Abstract

Background: Acute kidney injury (AKI) is a rapid loss of the kidney's excretory function, resulting in an accumulation of end products of nitrogen metabolism. Even though there were studies that reported the prevalence of AKI among HIV-positive patients in Africa, their findings were inconsistent in terms of prevalence of AKI and its predictors across the studies. Therefore, this review study aimed to determine the pooled prevalence of AKI and its predictors. **Methods:** We searched on PubMed, Embase, Ebsco, OVID, Cochrane Library, and other supplementary search engines, including Google and Google Scholar. Articles published up to July 2023 were included in this review study. The quality of the study was assessed using the Newcastle-Ottawa Scale for cross-sectional, case-control, and cohort studies. The data were extracted using a Microsoft Excel spreadsheet and exported to Stata version 14 for analysis. A random effect meta-analysis model was used to estimate the pooled prevalence of AKI among HIV-positive patients. Heterogeneity was evaluated using Cochrane Q statistics and I squared (I^2). Furthermore, the graphic asymmetric test of the funnel plot and/or Egger's tests were computed to detect publication bias. To treat the publication bias, a trim and fill analysis was carried out. The protocol of this review has been registered in an international database, the Prospective Register of Systematic Reviews (PROSPERO), with reference number CRD42023446078. **Results:** A total of twenty-four original articles comprising 7913 HIV-positive patients were included in the study. The pooled prevalence of AKI among HIV-positive patients was found to be 23.35% (95% CI: 18.14-28.56%, $I^2 = 97.7\%$, p-value <0.001). Low hemoglobin (Hgb <8mg/dl) was found to be the determinant factor for AKI among HIV-positive patients (AOR = 2.4; 95% CI: 1.69-3.4, $I^2 = 0.0\%$, p-value = 0.40). In meta-regression analysis, sample size was the possible source of variation among the included studies (AOR = 3.11, 95%CI: 2.399-3.83). **Conclusions:** This review investigated the pooled prevalence of AKI and its predictors. Therefore, the pooled prevalence of AKI among HIV-positive patients was high. Having low levels of hemoglobin levels were associated with a higher risk of developing AKI among HIV positive patients.

Keywords: Acute kidney injury, renal dysfunction, renal impairment, HIV, Africa

Introduction

The human immunodeficiency virus (HIV) is still the leading challenge worldwide (Demberg & Robert-Guroff, 2012; Tian et al., 2023). Globally, 39 million people were living with HIV at the end of 2022. Africa remains the most severely affected region, with nearly one in every twenty-five adults living with HIV and accounting for more than two-thirds of the people living with HIV worldwide (UNAIDS, 2022).

Renal dysfunction, especially acute kidney injury (AKI), is an important cause of hospitalization and mortality among HIV-positive patients. It is a common complication in HIV-positive patients (Gameiro, Agapito Fonseca, Jorge, & Lopes, 2019). Injury or diseases, including HIV infection, can damage the kidneys and lead to kidney diseases. In people with HIV, poorly controlled HIV infection and co-infection increase the risk of AKI (Wyatt, 2017).

The exact causes of HIV-associated AKI are not well investigated, but it is associated with volume depletion, sepsis, and the intake of nephrotoxic medications (Kimweri et al., 2021). It is also associated with individual risk factors, HIV-correlated factors, and antiretroviral drug toxicity (Maggi et al., 2012). AKI can lead to life-threatening complications such as end-stage renal failure, volume overload, electrolyte disturbance, and multi-organ dysfunction (Levey & James, 2017).

AKI can affect the entire population, but its severity is higher among HIV-positive patients. The death rate of AKI among HIV-positive patients was 21.2%, 25%, and 35.3%, compared with HIV-negative individuals at 10%, 23.3%, and 16% at one, two, and five-year follow-up periods (Lopes, Melo, Raimundo, Fragoso, & Antunes, 2013). HIV-positive patients with advanced disease, advanced age, pre-existing kidney diseases, and concomitant use of nephrotoxic medication are at increased risk of adverse renal events (Boswell & Rossouw).

In Africa, even though there were different studies associated with acute kidney injury among HIV-positive patients, the findings were inconsistent in terms of prevalence of AKI and its predictors across the studies. Therefore, this study aimed to estimate the prevalence and identify predictors of AKI among HIV-positive patients in Africa.

Methods

Study Design

A systematic review and meta-analysis was used for this review study among HIV patients residing in Africa.

Study Design and Search Strategies

We searched on PubMed, Embase, Ebsco, OVID, Cochrane Library, and other supplementary search engines: Google and Google Scholar. Endnote Version 7 reference management software was used to download, organize, review, de-duplicate, and cite the articles. Our comprehensive search strategies were carried out using controlled vocabularies such as medical subject headings (MeSH) terms. Boolean logic operators “AND” and “OR” were used to combine search terms. The search string is stated as “Acute kidney injury” OR AKI OR “renal impairment” OR “renal dysfunction” OR “renal disease” AND “Human Immuno-deficiency Virus patients” OR “HIV patients” OR “HIV positive patient*” OR “Sero-positive patients” OR “Acquired Immune Deficiency Syndrome patients” OR “AIDS patients” OR “people living with HIV/AIDS” OR PLWHA AND Africa. Articles were searched by title (ti), abstract (ab), and full text (ft). Modifications of the search results were made by limiters such as study design and country. Articles published up to July 2023 were included in the study. Two reviewers (HMK and CKM) independently searched and screened articles by title, abstract, and full text. The disagreements between the reviewers were resolved through discussion. Further disagreements were solved by the involvement of the third person.

Inclusion and Exclusion Criteria

The eligibility criteria of the included studies are summarized in the table below (Table 1).

Table 1: Inclusion and exclusion criteria for included research articles

Criteria	Inclusion criteria	Exclusion criteria
Population	HIV positive patients People living with HIV/AIDS	Chronic kidney diseases prior to the exposure of HIV Patients with dialysis and/or renal dysfunction before the onset of HIV
Age	Adult (age ≥ 18 years)	Studies with no clear age reports
Design	Observational study designs (cross-sectional, cohort, case-control, and survey)	Narrative review Scoping review Systematic review and meta-analysis Qualitative studies

		Conference papers Articles with no full text
Publication status	Both published and/or unpublished studies such as preprints	
Country	African countries	
Publication year	Articles published up-to July 2023	
Language	Any language Articles with language other than English were translated to English using Google translator.	

Outcome Measurement

Acute kidney injury is defined as an increase in serum creatinine of 3 mg/dl within 48 hours and/or 1.5 times the baseline within the previous seven days, as well as urine output of < 0.5 mg/kg/hour for six hours(Makris & Spanou, 2016).

Data Extraction

The data was extracted using a Microsoft Excel spreadsheet. The format was prepared by all the authors and piloted for its clarity, aim, consistency, and depth to capture information from the included articles. Using the data extraction format, information such as author(s), year of publication, study design, country of the study, method of data collection, funding status, sample size, prevalence or incidence of AKI, and effect estimates such as OR with a 95% CI were extracted. Two reviewers (HMK and CKM) independently screened the articles by titles, abstracts, and full texts. Possible inconveniencies were solved by discussion with the reviewers and/or the involvement of the third person.

Quality Appraisal

Articles were assessed for their quality using the Newcastle-Ottawa assessment scale adapted from cross-sectional(Moskalewicz & Oremus, 2020), cohort(Wells et al., 2014), and case-control studies(Peterson, Welch, Losos, & Tugwell, 2011). A score of 6 or above was considered a high-quality article. Two reviewers (AWA and YMF) assessed the quality of the articles. The reviewers compared the quality of the appraisal scores and resolved inconsistencies before calculating the final appraisal score.

Data Analysis

The extracted data was exported to Stata version 14 for analysis. Heterogeneity was detected by Cochrane Q statistics and I^2 . The heterogeneity test statistics results of below 25%, 50%, and above 75% were declared as low, moderate, and high heterogeneity(Rücker, Schwarzer, Carpenter, & Schumacher, 2008), respectively. A random effect meta-analysis model was used to estimate the pooled prevalence of AKI (Borenstein, Hedges, Higgins, & Rothstein, 2010). The graphic asymmetry of the funnel plot test and/or Egger's test (p-value <0.005) were used to detect the publication bias(Begg & Mazumdar, 1994).

Study Protocol Registration and Reporting

The protocol has been registered on PROSPERO with reference number CRD42023446078. The reporting of this review follows the Preferred Reporting Item for Systematic Review and Meta-Analysis (PRISMA-2020) checklist(Page et al., 2021)

Results

Study Selection and Characteristics of Included Studies

The search strategy retrieved 1071 original articles. About 493, 347, and 175 articles were removed due to duplication, not related to the topic of interest, and population variation, respectively. About 56 articles remained, and following further screening, 30 articles were removed due to variations in outcome ascertainment and not full-text. Then 26 full-text articles were assessed for eligibility, of which two articles were excluded because of poor quality and outcome interest (**Fig.1**). Finally, twenty-four articles were retrieved and included in the review, with a total of 9713 populations. Of the twenty-four studies, five were from Ethiopia(Eneyew, Seifu, Amogne, & Menon, 2016; Temesgen Fiseha & Gebreweld, 2021; Kefeni, Hajito, & Getnet, 2021; Yilma et al., 2020; YISHAK ALI, 2012), four from Tanzania(Kilonzo, Seiffudin, Bakshi, & Gunda, 2016; Mapesi et al., 2021; Mwanjala, Urrio, & Mtebe, 2022; Mwemezi, Ruggajo, Mngumi, & Furia, 2020), four from Nigeria(Emem et al., 2008; MOHAMMAD, 2011; Okafor, Unuigbo, & Chukwuonye, 2015; Sulaiman et al., 2022), two from Uganda(Kimweri et al., 2021; Nyende, Kalyesubula, Sekasanvu, & Byakika-Kibwika, 2020), one from Kenya(Karoney, Koech, Njiru, & Owino Ong'or, 2022), one from Cameroon(Alex, Carelle, Maimouna, Georges, & Enow, 2022), one from South Africa(Vachiat, Musenge, Wadee, & Naicker), one from Malawi(Struik et al., 2011), one from Senegal(Fall et al., 2017), one from Zambia(Tembo, Chirwa, Musonda, Mulenga, & Mweemba, 2017), one from Rwanda(Ndikubwimana, 2023), one from Burkina Faso(Aoua, Idrissa, Judicaël, & Gaoussou, 2023), and one from DR Congo(Ekat M.H., 2012). The pooled prevalence was calculated from the aforementioned studies, whereas for predictors of AKI, three studies for hemoglobin level(Alex et al., 2022; Aoua et al., 2023; Temesgen Fiseha & Gebreweld, 2021), six studies for CD4 count(Temesgen Fiseha & Gebreweld, 2021; Kefeni et al., 2021; Mapesi et al., 2021; MOHAMMAD, 2011; Mwanjala et al., 2022; Mwemezi et al., 2020), and three studies for WHO clinical HIV staging(Alex et al., 2022; Kefeni et al., 2021; Mapesi et al., 2021) were used. The prevalence of AKI among HIV patients ranged from 2.53% in Uganda(Nyende et al., 2020) to 56.8% in Nigeria(MOHAMMAD, 2011). The majority of the studies used lab tests as a method of data collection. All of the included studies had high-quality scores (**Table2**).

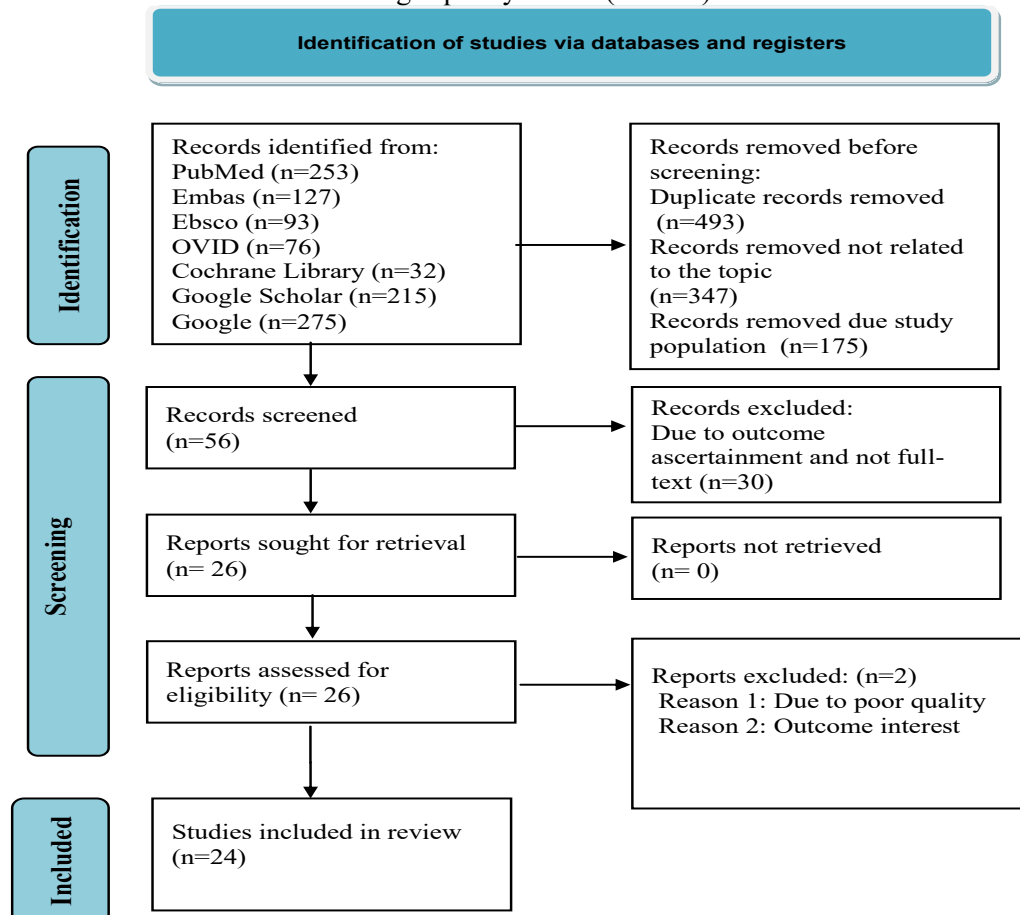


Fig. 1: PRISMA flow chart for flow of information through the phases of systematic review

Table2: Characteristics and quality status of included studies

Authors/year	Country	populat ion	Study design	Definition Basis	Data collection	Samp le size	Prevalenc e (%)	Quality score
Alex MT et al. 2022(Alex et al., 2022)	Cameroon	PLWHI V	Cohort	KDIGO - 2012	Lab test, interview	206	30.6	7
Fiseha T & Gebreweld A. 2021(Temesgen Fiseha & Gebreweld, 2021)	Ethiopia	PLWHI V	Cohort	eGFR	Record review	353	22.1	8
Karoney MJ et al.2022(Karoney et al., 2022)	Kenya	PLWHI V	Cross- sectional	eGFR	Lab test, interview	261	10	9
Kefeni BT, et al. (2021)(Kefeni et al., 2021)	Ethiopia	PLWHI V	Cross- sectional	eGFR	Record review, lab test	352	20.7	7.5
Kimweri D, et al. (2021)(Kimweri et al., 2021)	Uganda	PLWHI V	Cohort	KDIGO	Interview, record review, lab test	384	19.2	8
Mwanja MN et al. (2022)(Mwanjala et al., 2022)	Tanzania	PLWHI V	Cross- sectional	eGFR	Record review, lab test	396	20.7	8.5
Mwemezi O, et al. (2020)(Mwemezi et al., 2020)	Tanzania	PLWHI V	Cross- sectional	EGFR	Record review, lab test	287	32.8	9
Mugabo C & Ndikubwimana I. (2023)(Ndikubwimana , 2023)	Rwanda	PLWHI V	Cohort	eGFR	record review	98	24.4	8.5
Fall K et al. (2017)(Fall et al., 2017)	Senegal	PLWHI V	Cohort	eGFR	Interview, record review, lab test	248	12.9	8
Nyende L et al. (2020)(Nyende et al., 2020)	Uganda	PLWHI V	Cross- sectional	eGFR	Record review	278	2.53	7
Enyew K, et al. (2016)(Eneyew et al., 2016)	Ethiopia	PLWHI V	Cross- sectional	eGFR	lab test	60	23.3	7.5
Mapesi H, et al. (2021)(Mapesi et al., 2021)	Tanzania	PLWHI V	Cohort	eGFR	lab test	556	7.4	7
Vachiat AI, et al. (2013)(Vachiat et al.)	South Africa	PLWHI V	cross- sectional	eGFR	Record review	101	21	8
Ali Y, et al. (2012)(YISHAK ALI, 2012)	Ethiopia	PLWHI V	Cross- sectional	eGFR	Interview, record review, lab test	321	15.9	9
Semde A, et al. (2021)(Aoua et al., 2023)	Burkina Faso	PLWHI V	Cross- sectional	KDIGO	Record review	364	29.94	8.5
Emem CP, et al. (2008)(Emem et al., 2008)	Nigeria	PLWHI V	Cross- sectional	eGFR	lab test	400	38	7
Maina SM et al. (2023)(Sulaiman et al., 2022)	Nigeria	PLWHI V	Case- control	Renal Biopsy	lab test	200	10.5	7.5

Struik GM, et al. (2015)(Struik et al., 2011)	Malawi	PLWHI V	Cross-sectional	Cockcroft –Gault equation	lab test	526	23.3	8
Yilma D, et al. (2012)(Yilma et al., 2020)	Ethiopia	PLWHI V	Cross-sectional	eGFR	lab test	340	26.9	9
Okafor UH, et al. (2015)(Okafor et al., 2015)	Nigeria	PLWHI V	Cross-sectional	eGFR	Interview, record review, lab test	383	53.3	9
Sakajiki MA, et al. (2011)(MOHAMMAD, 2011)	Nigeria	PLWHI V	Cross-sectional	eGFR	Interview, record review, lab test	240	56.8	7.5
Kilonzo BS, et al. (2016)(Kilonzo et al., 2016)	Tanzania	PLWHI V	Cross-sectional	eGFR	Interview, record review, lab test	637	28	8
Tembo S, et al. (2017)(Tembo et al., 2017)	Zambia	PLWHI V	Cross-sectional	eGFR	lab test	360	24.76	9
Ekat MH, et al. (2012)(Ekat M.H., 2012)	DR Congo	PLWHI V	Cross-sectional	eGFR	lab test	562	8.5	8.5

Notes:- EDC: European and Developing Countries, eGFR: estimated Glomerular Filtration Rate, KDIGO: Kidney disease Improving Global Outcome, HIV: Human immunodeficiency virus; TFEL- Tanzania Field Epidemiology and Laboratory, MOH T- Ministry of Health Tanzania, FAD-Foreign affairs of Denmark

The Prevalence of Acute Kidney Injury

The pooled prevalence of AKI among HIV patients was found to be 23.35% (95% CI: 18.14-28.56%, $I^2 = 97.7\%$, p -value < 0.001)(Fig.2).

Sub Group Analysis

The subgroup analysis was computed using the study designs of the included studies. In the subgroup analysis, the level of heterogeneity is high. In the cohort designs, the level of heterogeneity was 94.3%, whereas in cross-sectional designs it was 98.2% (Fig.3). Therefore, meta-regression analyses need to be computed to identify the real source of the variations.

Meta-regression analysis

To identify the causes of the covariates, both bivariate and multivariate meta-regression analyses were computed. In the multivariate analyses, sample size was found to be the cause of the variations (AOR = 3.11, 95%CI: 2.399-3.83) (Table 3).

Table 3: Meta-regression analysis for variation of the included studies

Variables	Std.err	p-value	Coef.	95%CI
Publication year	0.584	0.174	0.82	0.39-1.203
Sample size	0.345	0.001	3.11	2.399-3.83

Notes: CI-confidence interval, Coef.-coefficient, Std.err- Standard error

Publication bias

The publication bias was assessed by the graphic asymmetry test of the funnel plot and/or Egger's tests. The funnel plot test showed that there was an asymmetrical distribution, indicating there is a publication bias (Fig. 4). Similarly, Egger's test shows that the p -value is < 0.001 , indicating there is publication

bias. Sensitivity analysis was computed to see the effect of a single study on the summary effect estimates, indicating there is no single study effect or outlier (**Fig. 5**). To treat small study effects, non-parametric trim and fill analyses were computed. As a result, eleven articles were filled, making a total of 35 articles with 34 degrees of freedom, a p-value of 1.00, and a moment-based estimate of between-study variance of 0.00 (**Fig. 6**).

Predictors of AKI among HIV patients

Hemoglobin level

In this review study, having low hemoglobin (hgb <8mg/dl) was found to be the determinant factor of AKI among HIV-positive patients (AOR=2.4; 95% CI:1.69-3.4, $I^2=0.0\%$, p-value= 0.40). From the forest plot, the I^2 was 0.0% and the p-value was 0.40 (**Fig. 7**), indicating there is no variation across the studies.

CD4 Count

The findings of this study revealed that a low CD4 count is not a risk factor for AKI among HIV patients (AOR= 2.25; 95% CI: 0.85-5.93, $I^2= 0.0\%$, p-value=0.847). As shown in the figure below, the I^2 was 0.0% and the p-value was 0.847, meaning that there was no variation across the included studies (**Fig. 8**).

WHO clinical HIV staging

The study depicts that the WHO clinical HIV stage is not a predictor for AKI among HIV-positive patients (AOR=2.29, 95% CI: 0.49-10.74, $I^2=0.0\%$, p-value=0.955) (**Fig. 9**). From the forest plot, the I^2 was 0.00% and the p-value was 0.955, which indicates there is no variation across the study.

Discussion

The findings of this review study revealed that the pooled prevalence of AKI among HIV-positive patients in Africa was 23.35% (95% CI: 18.14-28.56%). The result of this study is lower than the studies conducted in Shanghai, China 12.5% (Shi, Chen, Lin, Ding, & He, 2022) and 0.7% Edmonton, Canada (Cooper et al., 2010). The possible reason for the discrepancy is that the Chinese study focused on incidence and used a variety of outcome measurement criteria, whereas the Canadian study focused on the effect of Tenofovir Disoproxil Fumarate (TDF) on the development of AKI and used clinical trial studies, whereas the current study used observational studies.

A low hemoglobin level was found to be the determinant factor of AKI among HIV-positive patients. HIV-positive patients who had a low hemoglobin level (hgb <8mg/dl) were 2.4 times more likely to develop AKI compared to normal hemoglobin levels. This is supported by a study in Seoul (Han et al., 2015), which stated that the odds of AKI are associated with decreased hemoglobin. The possible reasons that renal insufficiency is associated with anemia (low hemoglobin) (T Fiseha, Tamir, Seid, & Demsiss). A low hemoglobin level decreases renal tissue oxygenation and results in acute tubular necrosis.

The sample size was one of the possible sources of variation across the studies. In the meta-regression analysis, sample size is the source of the variation for the included studies. This is due to the fact that when the sample size is too small, the bias from sampling will increase the frequency of sampling (Li et al., 2015). Larger sample sizes are required to attain the desired normal power (Vallejo, Ato, Fernández, & Livacic-Rojas, 2019). Additionally, the small sample size resulted in a small effect size, which can lead to the possibility of variation.

As a strength point, the authors investigate HIV-associated AKI in Africa at large. In addition, the study investigates both the prevalence and associated factors of AKI among HIV-positive patients.

The study has the following limitations: Firstly, the study did not assess the stage of AKI, mortality, or its treatment outcome. Therefore, we recommended that further global researches which need to be carried out to estimate the global prevalence and identify other important predictors of HIV-associated AKI among HIV-positive populations.

Implications of the Study

The findings of this study provide input for healthcare workers to provide an integrated HIV care service along with routine ART services. The study gives direction for healthcare workers to emphasize on

regular monitoring of renal function tests to HIV-positive patients. Additionally, the study also helps policy makers and decision-makers focus on intervention strategies for the early detection and prevention of AKI in HIV positives.

Conclusions

This systematic review and meta-analysis revealed that the pooled prevalence of AKI among HIV-positive patients in Africa was high. HIV-positive patients with low hemoglobin levels are at risk for developing AKI. Hence, regular monitoring of kidney function tests is needed to prevent, detect, and treat AKI. Therefore, healthcare workers should provide integrated HIV-renal healthcare services such as renal function tests to prevent, detect, and treat AKI to reduce its progression to advanced stages and complications.

Abbreviations

AKI-Acute Kidney Injury, AOR- Adjusted Odds Ratio, CI-Confidence Interval, HIV- Human immunodeficiency virus, PRISMA-Preferred Reporting Item for Systematic Review and Meta-Analysis, WHO-World Health Organization.

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