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ORIGINAL ARTICLE | OBSTETRIC FISTULA REPAIR

A Comparison of Postoperative Surgical Outcomes among Women Undergoing Obstetric Fistula Repair with and without HIV

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ABSTRACT

Background and Objective: Obstetric fistula affects approximately 2 million women worldwide, predominantly in places with a high Human ImmunodeficiencyVirus (HIV) burden. In Malawi, where thousands of women live with fistulas, HIV prevalence is 11-13%. Although repair is usually successful, surgical outcomes among immunocompromised women are poorly understood. Inconsistent guidelines regarding the Cluster of Differentiation 4 (CD4) threshold necessary for repair make it difficult for surgeons to make informed decisions. This study compares the postoperative outcomes of women undergoing obstetric fistula repair with and without HIV, stratified by CD4 count.

Methods: This is a retrospective case-control study using a database of women who underwent vesicovaginal fistula repair at the Fistula Care Center from 2010-2018. HIV-positive participants, stratified by CD4<350 and CD4>350, were matched to HIV-negative controls by age within 5 years and Goh classification. Controls were matched to cases in a 3:1 ratio. Bivariate analysis and logistic regression were conducted on indicators based on HIV status and CD4 count stratification. Outcomes included dye test results, pad weights, and continence status at 2 weeks post-repair.

Results: 54 seropositive women were matched to 135 seronegative women. Of the 54 HIV positive women, 22.2% (n=12) had a CD4 count < 350. We found no statistically significant difference in surgical outcomes between HIV-positive and negative patients. 93.5% of HIV positive and 90% of HIV negative women healed completely. In our sub-analysis of 12 seropositive women with CD4<350, we found a statically significant difference in successful closure, with 25% of women with CD4<350 having a positive dye test indicating incomplete closure, compared to 2.8% of women with CD4>350 (p=0.024).

Conclusion and Global Health Implications: Our analysis confirms previous research indicating that seropositive women with a CD4>350 can safely undergo obstetric fistula repair. Further research is needed to evaluate postoperative outcomes among women with CD4<350.

Keywords: • Obstetric Fistula • Surgical Outcomes • HIV • Vesicovaginal Fistula • Fistula Repair • CD4 • AIDS • Malawi • Sub-Saharan Africa

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I. Introduction

I.I. Background of the Study

Obstetric fistula is a condition that affects approximately 2 million women, mostly in sub-Saharan Africa and parts of Asia.¹ In many countries where obstetric fistula exists, the human immunodeficiency virus (HIV) is also a health threat. In Malawi, where thousands of women have been affected by fistulas, the HIV prevalence rate is 11-13%.² Although repairs of vesicovaginal fistulas have largely been successful in 80-95% of cases, surgical outcomes among immunocompromised women are poorly understood.^{3,4}

Despite the high prevalence of HIV in countries with the highest rates of obstetric fistula, few studies have looked at the relationship between HIV status and postoperative outcomes. In a 2017 retrospective review of postoperative outcomes at the Evangel Vesicovaginal Fistula Center in Nigeria, Shepperd et al. compared rates of successful closure among women who were HIV positive with those who were HIV negative.⁵ From their sample of over 3,000 cases, of which 6% were HIV positive (n=201), they found that HIV positive patients were significantly less likely to heal after repair. More specifically, they reported that the odds of failed closure were 0.6 times as likely among HIV-positive patients compared to HIVnegative patients (95% CI 0.443-0.894).⁵ Although this did not apply for women with ureterovaginal or rectovaginal fistulas, it highlights the need for more information in optimizing outcomes for HIV-positive women. Important to note, their study did not include Cluster of Differentiation 4 (CD4) counts or viral load (VL) data, so the results cannot be stratified by severity of disease to help inform protocols for fistula centers deciding an appropriate CD4 or VL threshold at which repair might be indicated.

In a retrospective cohort study looking at closure and residual incontinence after vesicovaginal fistula repair in Cameroon, Tebeu et al. found no statistically significant difference in postoperative complications among HIV-positive women (n=12) in comparison to HIV-negative women (n=40).⁶ Among HIV-negative women, the rate of vesicovaginal closure was 83% and the rate of continence was 100%, compared to 80% and 87.5% among HIV-negative women, respectively. CD4 counts were reported for 5 of the 12 seropositive patients in their sample, which ranged from 107 to 800 per cm³.⁶

Based on our review, there is a lack of guidance in the literature regarding safety thresholds for elective gynecological surgery in the presence of HIV. Conflicting research, studies with small samples, and the focus on specific operations have limited the generalizability of current information.

1.2. Objectives of the Study

The objective of this study is to compare the postoperative outcomes of obstetric fistula repair among women with and without HIV stratified by CD4 count.

1.3. Specific Aims and Hypothesis

The specific aims of this study are the following:

- Assess for differences in post-surgical complications, such as residual incontinence and incomplete fistula closure, among women who are HIV-positive with CD4 counts greater than 350, women who are HIV-positive with CD4 counts less than 350, and seronegative controls;
- Inform future clinical guidelines regarding a CD4 threshold at which it is safe to qualify for obstetric fistula repair; and
- 3) Ultimately increase the availability of fistula repair for those who qualify.

We hypothesize that there will be no statistically significant difference in postoperative outcomes among seronegative women and HIV-positive women with CD4 counts greater than 350.

2. Methods

This is a retrospective case-control study that utilizes a database of women who have undergone obstetric fistula repair at the Fistula Care Center in Lilongwe, Malawi, between the years 2010 and 2018.

2.1. Study Variables

Our independent variable is HIV status. We have chosen a CD4 count of 350 to represent mild HIV-associated immunodeficiency, which we compare to

an HIV-negative control. This CD4 threshold was selected based on the World Health Organization's immunological staging in adults, which was informed by the Malawi national HIV program.⁷ Additionally, surgery is seen as optimal when the individual's viral load is <1,000 copies/ml to reduce transmission. It is important to note that it is not always possible to obtain both a CD4 count and a viral load due to resource constraints and the removal of CD4 counts in national HIV guidelines.⁸

HIV-positive participants were matched to HIVnegative controls by age within 5 years and fistula injury based on the Goh classification, which classifies vesicovaginal fistulas based on the distance from the external urethral meatus, fistula size, and severity of vaginal fibrosis.⁹ Controls were matched to cases in a three to one ratio to gain statistical significance. When three matched controls were not available, two matched controls were used.

In a sub-analysis, we compare a cohort of seropositive women whose CD4 counts were less than 350 to those of participants with CD4 counts greater than 350, as well as to negative controls. Though most of these cases had a CD4 count above 350, some counts were lower as their repairs occurred prior to the change in policy at the Center.

Demographics and clinical assessments were compared based on HIV status and fistula characteristics. Outcomes included results of a dye test to verify fistula closure, pad weights to evaluate for residual incontinence, and post-surgical continence status at 2 weeks post-repair. Continuous variables were reported using mean and standard deviation. Categorical variables were reported as frequencies and percentages.

Women return to the Fistula Care Center at I month, 3 months, 6 months, and yearly after surgery. Therefore, any breakdown of repair and need for revision is noted in the files.

2.2. Statistical Analysis

Data were analyzed using Stata[®] 14.2.¹⁰ Bivariate analyses were performed using Welch's t-test for continuous variables and Fisher's Exact or Pearson Chi-Square for categorical variables. All p values

reported are two-sided and p < 0.05 was considered significant. Multivariable logistic regression was used to describe the effect of age, Goh classification, HIV status, CD4 count and the success of postoperative outcomes. The pad weight and continence status outcomes were dichotomized using a cut-off of 1.5 grams as a successful closure and continence status of "mild incontinence" and "no incontinence" as a success. Logistic regression models that included subsets of this model were evaluated. A posthoc power analysis was used to calculate the overall statistical power of the study based on dye test results with an effect size of 0.1.

Bias was limited by de-identification of the dataset before analysis.

2.3. Ethical Approval

This study was approved by the Malawian National Health and Sciences Research Committee and by the Baylor College of Medicine Institutional Review Board.

3. Results

3.1. Sociodemographic Characteristics

Complete information was available for 54 seropositive women from 2010 to 2018 and matched to 135 seronegative women. Of the 54 HIV-positive women, 12 (22.2%) had a CD4 count < 350.The mean age for HIV-positive women was 34. I years compared to 33.0 years for matched HIV-negative women. There were no statistically significant differences in baseline characteristics (see Table 1) between HIV-positive and negative women. There were also no statistically significant differences between those with CD4 counts less than 350 and greater than 350, except for baseline levels of hemoglobin prior to surgery. This included no difference in Goh classified fistula injury, hemoglobin level, or age between HIV-positive and negative women.

3.2. Postoperative Outcome Results

We found no statistical difference in surgical outcomes between HIV-positive patients and HIV-negative patients (Table 2). There were no statistically significant differences among groups regarding the surgical outcome of incontinence

Characteristics	Among all women N (%)			Among HIV+ women only N (%)		
	HIV Neg (N=135)	HIV Pos (N=54)	p-value	CD4<350 (N=12)	CD4>350 (N=40)	p-value
Age [mean (SD)]	33.0 (9.6)	34.1 (9.1)	0.4813	35.1 (6.6)	35.6 (9.7)	0.8633
Hemoglobin [mean (SD)}	11.6 (1.9)	12.1 (1.6)	0.0850	10.7 (2.8)	12.0 (1.7)	0.0360
Location of Fistula (Goh I)			0.893			0.639
Type 1: Distal edge of fistula>3.5 cm from EUM	41 (32.0)	15 (28.8)		2 (20.0)	16 (41.0)	
Type 2: Distal edge 2.5-3.5 cm	26 (20.4)	13 (25.0)		3 (30.0)	9 (23.1)	
Type 3: Distal edge 1.5-2.5 cm	41 (32.0)	17 (32.7)		4 (40.0)	10 (25.6)	
Type 4: Distal edge<1.5 cm	20 (15.6)	7 (13.5)		I (I0.0)	4 (10.3)	
Diameter of Fistula			0.587			0.661
<1.5 cm	42 (32.8)	19 (36.5)		2 (20.0)	13 (33.3)	
1.5-3cm	44 (34.4)	20 (38.5)		4 (40.0)	15 (38.5)	
>3 cm	42 (32.8)	13 (25.0)		4 (40.0)	11 (28.2)	
Degree of Fibrosis			0.735			0.752
I: None or mild fibrosis and/or vagina length >6 cm, normal capacity	51 (39.5)	21 (40.4)		4 (40.0)	16 (41.0)	
II: Moderate or severe fibrosis and/or marked reduction in vaginal length and/or capacity	12 (9.3)	3 (5.8)		0 (0.0)	2 (5.2)	
III: Special circumstances, e.g., post-radiation, ureteric involvement, circumferential fistula, previous repair	66 (51.2)	28 (53.8)		6 (60.0)	21 (53.8)	
No special considerations	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

Table 1: Patient Characteristics

status per the patient report, pad weight, or dye test results. On follow-up visits, 93.5% of HIV-positive women and 90% of HIV-negative women had healed completely as measured by dye tests. Incontinence status reported by patients had similar outcomes for HIV positive and negative patients (continent 68.9%, mild stress 17.8% vs. continent 61.7%, mild stress 14.2%, respectively), which were similar for the dichotomized CD4 categories.

3.3. CD4 Count Stratification Results

Although our current policy states that patients with a CD4 count lower than 350 do not qualify for repair, we have data from patients who received surgery prior to that clinical policy (n=12). Therefore, we compared dye tests and continence status between seropositive women whose CD4 counts were less than 350 (range: 47 - 347 cells/mm³) and above 350. In this sub-group analysis, we did detect a statically significant difference in successful closure for those with a CD4 count greater than 350, as measured by the dye test, despite the small sample (p=0.024) (Table 2). The overall statistical power for the specific

outcome of dye test results was underpowered to 0.5.

3.4. Multivariable Logistic Regression Analysis

A multivariable logistic regression analysis assessed the effect of age, Goh classification, HIV status, and CD4 count on odds of the success of postoperative outcomes (Table 3). The odds of a positive dye test, higher pad weight, and having moderate to severe incontinence were not statistically significant between positive and negative HIV status, regard to CD4 count stratification, age, or the various components of the Goh classification.

4. Discussion

4.1. Discussion

As HIV is prevalent in many countries where obstetric fistula also exists, it is important to understand clinical parameters that optimize surgical outcomes. This retrospective case-control study seeks to define a safe threshold of immunity as defined by CD4 count that will result in no differences in surgical outcomes.

Outcomes	Among all women N (%)			Among HIV + women only N(%)			
	HIV Neg (N = 135)	HIV Pos (N = 54)	p-value	CD4 < 350 (N = 12)	CD4 > 350 (N = 40)	p-value	
Dye Test Result			0.484			0.024	
Positive	12 (10.0)	3 (6.5)		2 (25.0)	I (2.8)		
Negative	108 (90.0)	43 (93.5)		6 (75.0)	35 (97.2)		
Don't know	7	4		3	2		
Pad Weight [mean (SD)]	10.3 (19.2)	8.4 (17.6)	0.5651	3.2 (6.2)	8.6 (19.5)	0.4474	
Continence Status			0.309			0.124	
Cured, continent	74 (61.7)	31 (68.9)		6 (60.0)	27 (77.1)		
Mild stress	17 (14.2)	8 (17.8)		3 (30.0)	5 (14.3)		
Moderate stress	11 (9.2)	4 (8.9)		0 (0.0)	3 (8.6)		
Severe stress	11 (9.2)	0 (0.0)		0 (0.0)	0 (0.0)		
Incontinent	7 (5.7)	2 (4.4)		1 (10.0)	0 (0.0)		

Table 2: Patient Outcomes

Table 3: Multivariable Logistic Regression Analysis of Postoperative Continence Outcomes

Variable		OR (95% CI)				
	Dye Test	Pad Weight [†]	Continence Status [‡]			
Age	0.93 (0.86 - 0.99)	1.00 (0.96 - 1.05)	1.10 (0.97 – 1.25)			
Location of Fistula	1.03 (0.75 – 1.41)	0.84 (0.66 – 1.07)	0.85 (0.48 – 1.51)			
Diameter of Fistula	0.92 (0.70 - 1.23)	0.84 (0.67 - 1.06)	0.79 (0.52 – 1.21)			
Degree of Fibrosis	0.85 (0.62– 1.17)	0.94 (0.72 – 1.23)	1.69 (0.56 – 5.08)			
HIV Status	1.99 (0.50 – 7.91)	1.09 (0.51 – 2.33)	0.79 (0.10 - 6.03)			
CD4 Count	0.92 (0.76 – 1.10)	0.96 (0.87 – 1.07)	_*			

* All of those with a recorded CD4 count had no incontinence or mild incontinence. Unable to perform logistic regression.

[†] Pad weight of <1.5 grams considered a successful outcome.

[‡] Continence status of none or mild considered a successful outcome.

We acknowledge that identifying a safe threshold is challenging. For example, it was previously thought that if the patient was on antiretrovirals for several years, immune competence could be ensured, but we now understand that this does not account for medication adherence or antiretroviral failure.

Because a CD4 count of 350 was previously chosen by clinicians, it was used for comparison to those who are HIV-negative. However, it is possible that 350 is an unnecessarily high threshold and might prevent a significant number of HIV-positive women with fistula from receiving much-needed repair. Although our small sub-group bivariate analysis does indicate a potential difference in rates of closure, our multivariable logistic regression did not see a difference. This difference, however, should be further evaluated in a larger sample to determine appropriate standardized guidelines given the overall low power of this study. Such guidelines might indicate clinical modifications, rather than contraindications for fistula repair, that could be applied to HIV-positive women with a CD4 count less than 350.

The complexity of the repair is another variable to consider in this discussion. For example, HIVpositive patients with lower CD4 counts whose repair requires more extensive reconstruction might warrant a longer inpatient stay than an HIV-negative patient who received the same repair or an HIVpositive patient whose repair did not require tissue grafting. Again, further research with a larger cohort stratified by CD4 count is needed to determine if a lower CD4 threshold for fistula repair is warranted. In addition, further research is required to look into how HIV VL could play a particular role in surgical outcomes. One study found that a viral load of 30,000 copies/mL or greater was associated with a threefold increased risk of complications.¹¹

CD4 count recovery is much more gradual compared to VL responses. In addition, patients with a lower nadir CD4 count have a lower likelihood of having higher or near-normal CD4 counts after years of antiretroviral therapy.^{12,13,14} Nearly 15% of persons with HIV and advanced immunosuppression (CD4 < 50) will fail to recover their CD4 count at a level greater than 200 cells/mm3 despite virological suppression.¹⁵ Therefore, guidance on what to do in the case of a patient with a CD4 count <350 and an undetectable VL is unclear. While Shepperd found a decreased rate of successful closure in HIV-positive patients, neither CD4 nor viral load was reported.⁵ Additionally, the Tebeu study found no significant difference in postoperative complications among HIV positive patients.6

4.2. Strengths and Limitations of this Study

As illustrated above, the stratification of CD4 count in our analysis was limited by the small sample size. This was complicated by changing guidelines regarding the threshold required for surgery. An aggregate study across multiple sites could be useful in further analyzing this outcome and making these results more generalizable.

Another limitation was the retrospective design of this study. Though case-control studies allow for optimal matching of cases to controls, additional research is needed to better inform future clinical guidelines. For example, a randomized control trial to confirm these findings would be particularly helpful. However, in the resource-limited settings in which obstetric fistula is most often seen, conducting a randomized-control trial can be particularly challenging.

5. Conclusion and Global Health Implications

We acknowledge that CD4 count is not readily obtainable at all facilities that offer obstetric fistula repairs. This study setting was unique in that the Fistula Care Center and Lighthouse Trust, a Public Trust and a WHO-recognized Center of Excellence for integrated HIV prevention, treatment, care, and support, are located within the same hospital compound. Lighthouse provides HIV testing and counseling, as well as CD4 and VL testing, for patients at the Fistula Care Center.

Determining optimal treatment guidelines to prepare the patient for surgery is recommended in collaboration with HIV specialists, who can also follow the patient postoperatively. Findings from other surgical specialties attempting to decrease rates of postoperative complications can help inform guidelines for obstetric fistula repair.

Compliance with Ethical Standards

Conflicts of Interest: The authors have no conflicts of interest to disclose. **Financial Disclosure:** The authors have no financial disclosures. **Funding/Support:** The authors did not receive any funding/support. **Ethics Approval:** This study was approved by the Malawian National Health and Sciences Research Committee and by the Baylor College of Medicine Institutional Review Board. **Acknowledgments:** We would like to thank the Roe Green Global Health Scholarship for their support of this work and Freedom from Fistula for the overall management of the Fistula Center. **Disclaimer:** None.

Key Messages

- Optimizing patient's surgical care in collaboration with their HIV specialist is essential for improved surgical outcomes.
- A CD4 count of 350 does not result in a statistically significant difference in surgical outcome for obstetric fistula repair.
- A CD4 count threshold is still unknown for HIV-positive women with an obstetric fistula.

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