Original Article

Noma and Noma-like disease in HIV/AIDS patients, a comorbid interaction: A systematic review

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Abstract

Introduction: Noma is an opportunistic polymicrobial infection that cause necrosis of the mouth and face, with high morbidity and mortality, predominantly affecting malnourished children and persons with debilitating diseases. Cases of noma-like disease in adults, although rare, have been increasingly reported in HIV/AIDS patients particularly in developing countries but also in more developed countries.

Methodology: A systematic review of the literature to assess the occurrence and clinical impact of noma and noma-like disease in HIV/AIDS patients was performed on PubMed, Virtual Health Library, Cochrane Library and Google Scholar using the keywords "HIV"[All Fields] AND "Noma"[All Fields] in December 2016 (years includead for the search: 1985 to 2016).

Results: Twenty-four published studies were identified that document the occurrence of noma or noma-like disease in a total of 133 HIV/AIDS children and adult patients in the last 22 years. Although HIV infection is not the principal risk factor for noma, in some regions may play a substantial role in its pathogenesis. The mortality rate for noma-like disease in HIV/AIDS patients was 54.3%, compared to the 15% mortality rate of treated noma patients without HIV/AIDS. Most of the cases have never been on antiretroviral therapy, and their HIV infection was discovered because of the noma-like disease.

Conclusions: The syndemic interaction between HIV/AIDS and noma-like disease adversely impacts the severity of the disease and the mortality rate. Noma-like disease, although not yet considered a specific or frequent disease associated with HIV infection, should be considered as an opportunistic infection for AIDS.

Introduction

Noma, or *cancrum oris*, is a gangrenous opportunistic polymicrobial infection that rapidly cause orofacial necrosis with high morbidity and mortality, predominantly affecting malnourished children and persons with debilitating diseases [1-4].

The actual estimated worldwide annual incidence of noma is 25,000-40,000 new cases; these statistics may underestimate the problem, since it is believed that no more than 10-15% of affected persons at acute stage reach medical care, and previously about 70-90% of these children died without receiving any care [2-6].

Noma occurs worldwide, and although the mayor incidence of noma corresponds to the geographical distribution of poverty, with most cases reported in Africa, it should not be considered as solely a disease of the developing world; the World Health Organization has received reports of sporadic cases of noma-like disease in adults, from higher-income countries, including North America and Western Europe countries, almost always associated with disorders of the immune system like AIDS in association with human immunodeficiency virus (HIV) infection [1-5,7-10]. The exact incidence of noma-like disease in adults is unknown [11-13].

The exact pathogenesis of noma is not known, but it is believed to be multifactorial, where a complex interaction between severe malnutrition and an overwhelming oral infection, frequently preceded by a viral or bacterial infection that further impairs the

immune system, results in tissue destruction via necrotizing toxins and enzymes, with secondary ischemia leading to osteonecrosis [1-3,7,10,14-16]. In many cases, the precursor for noma is acute necrotizing ulcerative gingivitis, that has been lately considered to be a marker of immune deterioration [1-3,7,15].

Noma is a polymicrobial opportunistic infection; there is no consensus regarding the causative microorganisms. The anaerobes *Fusobacterium necrophorum* and *Prevotella intermedia* have been found in the clinical sites of noma; other reported pathogens include enteric gram-negative rods, and gram-positive bacteria [2,3,7].

Clinically, three forms of the disease have been recognized: "Classic noma", "Noma neonatorum" and "Noma-like lesions of the immunocompromised or debilitated adult" [2]. Noma in its "classic" form, mainly affects female children one to four years of age; it begins as a mouth ulcer, extending to the middle and lower face, rapidly destroying the soft tissues and the bone, with a well-demarcated perimeter surrounding a blackened necrotic center that may slough spontaneously [2,7,15].

"Noma neonatorum", is a distinct identity with similarities of classic noma, but in addition to the facial lesions, necrosis of the perineal region is characteristic, mostly affecting low weight newborn and premature babies with intrauterine growth retardation; the disorder is fatal in almost all cases because of irreversible septicemia caused by *Pseudomonas aeruginosa, Escherichia coli, Klebsiella, or Staphylococci* [2,3,7].

"Noma-like lesions of the immunocompromised", is a form of the disease that occurs in immunocompromised debilitated adults, with the typical orofacial lesions seen in noma [1,2].

Differential diagnosis for noma includes clostridial or streptococcal gangrene, ecthyma gangrenosum, necrotizing fasciitis, leprosy, leishmaniasis, mucormycosis, extranodal natural killer/T-cell lymphoma and oral cancer [3,9].

The acute phase of noma is a medical emergency, its clinical course is fulminating without early recognition and timely intra-hospital intervention with broad-spectrum antibiotic treatment covering aerobes and anaerobes, correction of dehydration and electrolyte imbalance, nutritional supplementation, debridement of necrotic areas and sequestrated bone, local wound care, reversal of the immune dysfunction and specific treatment for co-existing diseases; death can occur in days or weeks, with a mortality rate without treatment of approximately 73-94% as a result of sepsis, or because of the underlying medical conditions. Prompt medical treatment has reduced the mortality to 10-15% [1-4,7,15,17,18].

Patients who survive noma suffer from its severe aesthetic and functional sequelae; once the initial stages have been overcome and a good nutritional status has been achieved, patients can be assessed for reconstructive surgical treatment [1-4,16,17].

The aim of this systematic review was to assess the occurrence and clinical impact of noma-like disease in HIV/AIDS patients.

Methodology

A systematic review of the literature was performed on PubMed, Virtual Health Library, Cochrane Library and Google Scholar using the keywords "HIV"[All Fields] AND "Noma"[All Fields] in December 2016; filters activated: Humans. The date range set for the publication search was 1985 (AIDS epidemic identified) to 2016.

From the databases search we identified 21 publications and from the references we retrieved another 14 publications. All of the authors participated in the database search and selection of articles, and at least two of the authors searched each database. A PRISMA Flow Diagram is provided. (Figure 1)

In this study, the diseases under consideration were noma or noma-like disease in HIV/AIDS patients. Cases of previous stages of noma, like necrotizing ulcerative gingivitis, were not included for this review.
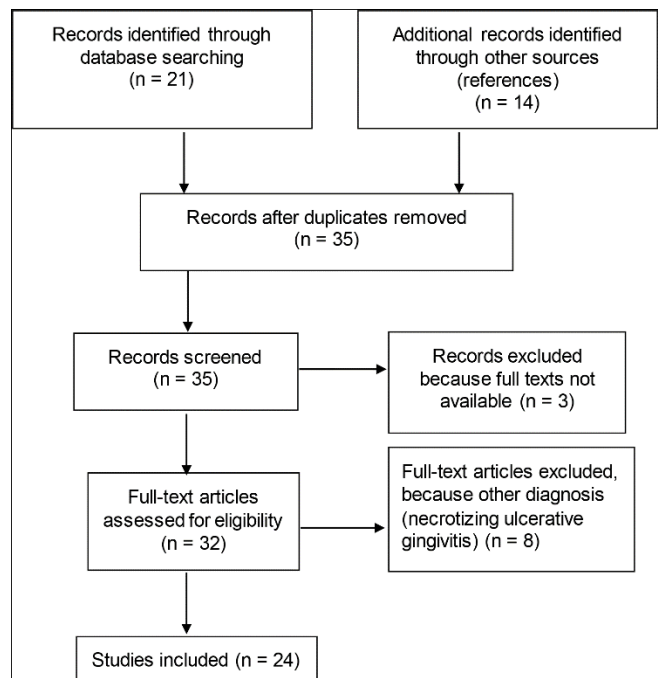
Figure 1. PRISMA flow diagram.

Table 1. Noma-like disease reports in HIV patients (1994-2016).

Author-year	Cases	Age (years)	Gender	AIDS Stage	CD4 cells/mm³	Nutritional status / Anemia	Antiretroviral	Survive / Dead
Darie-(1994)[22]	1	20	Male	IV	Not reported	Not reported	Not reported	Dead
Barrios-(1995)[23]	1	46	Male	IV	26	Anemia	No	Survive
Chidzonga-(1996)[11]	8	30	Female	Not reported	Not reported	Severe weight loss	Not reported	Dead
		26	Male	Not reported	Not reported	Severe weight loss	Not reported	Dead
		2.5	Male	Not reported	Not reported	Not reported	Not reported	Lost, presumed dead
		1	Female	Not reported	Not reported	Failure to thrive	Not reported	Lost, presumed dead
		2	Female	Not reported	Not reported	Failure to thrive	Not reported	Survive
		2.5	Male	Not reported	Not reported	Kwashiorkor	Not reported	Lost, presumed dead
		24	Female	Not reported	Not reported	Weight loss	Not reported	Dead
		1.5	Female	Not reported	Not reported	Failure to thrive	Not reported	Lost, presumed dead
Nath-(1998)[12]	9	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Survive 1 / Dead 8
Naidoo-(2000)[24]	1	4	Female	Not reported	Not reported	Delay in growth	Not reported	Survive
Ki-Zerbo-(2001)[25]	1	40	Female	IV	Not reported	Anemia	Not reported	Dead
Tall-(2001)[26]	10	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Adedoja-(2002)[13]	2	5	Male	Not reported	Not reported	Anemia	No	Survive
		3	Male	Not reported	Not reported	Anemia	No	Survive
Mamadou-(2002)[27]	1	21	Female	Not reported	Not reported	Not reported	No	Not reported
Faye-(2003)[28]	2	37	Male	Not reported	Not reported	Not reported	Not reported	Not reported
		25	Female	Not reported	Not reported	Not reported	Not reported	Not reported
Rowe-(2004)[29]	1	2.4	Female	Not reported	Not reported	Anemia	Not reported	Not reported
Ondzotto-(2004)[30]	4	Not reported	Not reported	IV	Not reported	Not reported	Not reported	Not reported
Chidzonga-(2008)[17]	48	11 average	F=31, Male=17	Not reported	10-594	Anemia	Not reported	Lost
Danino-(2009)[31]	1	12	Male	Not reported	Not reported	Malnutrition	Not reported	Survive
Diallo-(2009)[32]	5	4	Female	Not reported	Not reported	Anemia, 4g/dl	No	Dead
		5	Female	Not reported	Not reported	Anemia, 6g/dl	No	Dead
		5	Male	Not reported	Not reported	Anemia, 6g/dl	No	Dead
		6	Female	Not reported	Not reported	Anemia, 7g/dl	No	Dead
		6	Male	Not reported	Not reported	Anemia, 7g/dl	No	Dead
Koech-(2010)[10]	1	49	Female	Not reported	Not reported	Anemia	Not reported	Survive
Pacheco-(2010)[33]	1	50	Female	IIIB	30	Anemia	Abandon	Survive
Silva-(2011)[34]	1	40	Male	Not reported	95	Severe weight loss	Abandon	Not reported
Lubala-(2012)[35]	2	3	Male	IV	6	Severe Malnutrition	Not reported	Survive
		1.6	Female	Not reported	10	Anemia	Not reported	Dead
Millogo-(2012)[36]	14	15.3 average	Not reported	Not reported	Not reported	Not reported	Not reported	Survive 9 / Dead 5
Masipa-(2013)[15]	1	6	Male	Not reported	6	Severe Malnutrition	No	Survive
vanNiekerk-(2014)[37]	1	32	Female	Not reported	118	Malnutrition	YES	Survive
Konsem-(2014)[38]	16	Not reported	Not reported	Not reported	Not reported	Anemia	Not reported	Not reported
Pedro-(2016)[16]	1	35	Female	Not reported	15	Cachectic, Anemia	Abandon	Dead
TOTAL	**133**	**13.4 average**	**Female=49 Male = 31 Not reported = 53**	**III-IV = 6 Not reported = 127**	**6-594 216 average 70% abnormal**	**Malnutrition = 124 Not reported = 9**	**No/Abandon = 13 Yes = 1 Not reported = 119**	**Dead 25 (54.3%)**

Studies were included if they reported patients with HIV infection and noma or noma-like disease and at least one of the following variables: number of patients, age, sex, AIDS stage, CD4 cell count, nutritional status, status of antiretroviral treatment, cultures, surgical reconstruction, and mortality rate.

Only reports published in English, French, or Spanish language were reviewed.

Data was extracted from the reviewed variables and the results presented with descriptive statistics.

As this literature review include only publications, informed consent of patients was not applicable.

Approval of an ethics committee was not applicable.

Results

From PubMed, the search resulted in 48 articles, from which we found 21 articles that addressed the diseases under consideration, and we retrieved 14 more articles from the other data bases and from the references, for a total of 35 articles. Three articles were not included because the full text data is not available [19,20,21], and eight articles were excluded because patients have the diagnosis of necrotizing ulcerative gingivitis and not noma. Finally, 24 publications that reported 133 cases of noma or noma-like disease in HIV/AIDS patients in the last 22 years, from 1994 to 2016, were selected and included for this review [10-13,15-17,22-38] (Table 1).

Of the 24 reports included in this review, 12 reports were published between the years 1994 to 2004, including 41 cases, that represents 31% of the total identified cases, and 12 reports were published between the years 2008-2016, with 92 cases that represents 69% of the identified noma-like disease and HIV/AIDS cases.

We only have found case reports and case series, we couldn't find any controlled study, systematic review or meta-analysis. Level of Evidence IV.

Of the total of 133 noma or noma-like disease in HIV/AIDS patients included in this systematic review, 56 were children (70%), 24 were adults (30%), and age was not reported in 53 cases. The average age for all reported cases was 13.4 years; for the children, the average age was 5.8 years, and for the adults, the average age was 31 years.

Of the included patients, 49 were female (61.25%), 31 were male (38.75%), and gender was not reported in 53 cases.

Four patients had the antecedent of pulmonary tuberculosis, one case candidiasis, other case intravenous drug use, three cases have been previously

Table 2. Reported polymicrobial cultures in Noma-like disease HIV/AIDS patients.

	Times reported
Gram-positive	
Staphylococcus aureus	5
Group D *Streptococcus*	3
Group B hemolytic *Streptococcus*	2
Streptococcus pneumoniae	1
Gram-negative	
Klebsiella species	4
Pseudomonas aeruginosa	3
Proteus mirabilis	1
Gram-negative stain of roads and cocci	1

hospitalized for chronic diarrhea and two cases for recurrent bronchopneumonia.

The AIDS stage, was only reported in six patients as stage III and IV in this review; the stage was not reported in 127 cases.

The CD4 count was only reported in nine of the 24 publications reviewed, with counts ranging between 6 to 594 cells/mm^3 (normal 360-1500 cells/mm^3), with an average of 216 cells/mm^3; CD4 counts were abnormally low in 70% of the reported cases in this review.

Malnutrition or anemia was documented in 124 (93%) of the noma-like disease patients with HIV/AIDS included; in 9 patients, their nutritional status was not reported.

Of the 24 publications included for this review, cultures were only reported in eight publications, cultures were polymicrobial in 6 of these 8 publications (75%), revealed different bacteria species, both Gram positive (*Staphylococcus* and *Streptococcus*) and Gram-negative bacteria (*Klebsiella, Pseudomonas* and *Proteus*); in any case *fusobacterium* was isolated (Table 2).

The status of antiretroviral treatment was not reported in 119 cases, in ten cases it was documented that never have taken antiretroviral treatment, and in three cases patients abandoned their antiretroviral treatment for a mean duration of nine months, in only one case the patient was reported to be in active antiretroviral treatment.

Of the ten cases that was documented that never have taken antiretroviral treatment five died (50%), four survived (40%), and in one survival was not reported (10%); of the three cases of patients that abandoned their antiretroviral treatment one died (33.3%), one survived (33.3%), and in one survival was not reported (33.3%).

Surgical reconstruction was not reported or only soft tissue reconstruction was performed in 108 cases (81.2%), 18 cases were not reconstructed (13.5%), and only seven cases were reported to be surgically reconstructed (5.3%).

In this review of treated patients with noma-like disease and HIV/AIDS, 25 patients were reported dead (mortality rate of 54.3%) and 21 patients survived (45.7%); 52 patients were lost for follow up and were presumed dead by the authors of the reviewed publications; the mortality was not reported in 35 cases (Table 3).

Discussion

A syndemic is defined as the convergence of two or more diseases that act synergistically to magnify the burden of disease. The syndemic interaction between noma or noma-like disease and HIV/AIDS has severe consequences, similar to the AIDS and Tuberculosis syndemic [39].

This review examines the current knowledge of the impact of the noma-HIV/AIDS syndemic and reviews its epidemiological and clinical interactions.

The first report we could identify that documents the co-occurrence between noma-like disease and HIV/AIDS is from Darie [22], published in 1994, many years after the epidemic of HIV/AIDS was discovered; this may reflect that the disease to progress in this clinical scenario needs a prolonged state of immunosuppression, or that the HIV status of many patients has not been assessed until this relation has been more widely recognized.

The apparent increase in the number of cases in this later period maybe due to a real increment of cases, or may reflect that more tests have been performed because of the awareness of the association of noma-like disease and HIV/AIDS. In Zambia, in the 15-year period between 1979 and 1993, the total number of admissions because of noma almost doubled every five years, reflecting at least in this region, a real increase of noma cases [12].

If we consider a conservative incidence of 25,000 new noma cases per year [2-4], then the 133 noma-like disease in HIV/AIDS patients identified in this review seems a small fraction of patients, but surely is an underestimation of its occurrence, since also only a small fraction of noma patients (with and without HIV/AIDS) are documented in published papers, and also, many of the noma patients are not routinely tested for HIV; at least until recently, the test was not readily available in all medical facilities in some countries of Africa [6,7].

Interestingly, even though immunosuppression conditions including HIV infection are known predisposing factors for noma, there are not many publications which demonstrate a corresponding increase in the incidence of the disease since the advent of the HIV epidemic in some African countries, where HIV infection is very common; particularly in South Africa and Nigeria, where noma is prevalent, most reported cases are in HIV-seronegative malnourished children [5]. This could imply therefore, that although HIV infection is a predisposing factor, it needs to be at an advanced stage, and other debilitating conditions such as malnutrition must contribute to the development of the disease, or maybe it is underdiagnosed and a changing trend of the predisposing factors is occurring [10,37,38].

Regional differences exist in the incidence of noma and AIDS; Nath [12] reported in the period between 1989-1993, a 34.6% rate (9/26) of HIV seropositive cases among the noma children tested, while apparently fewer than 5% of Nigerian children who develop noma, are HIV-seropositive. This contrasts with a recent report from Zimbabwe [17], documenting an increase in the incidence of noma that mirrors the increase in the incidence of HIV infection in that country. Tall [26] reported that, in the period from 1987-1996, the frequency of HIV among noma pediatric patients from Bobo-Dioulasso was 6%, nevertheless, testing for HIV was not systematically performed. In a later study from the same location, from 2003 to 2012, 31.37% of noma

Table 3. Noma-like disease in HIV/AIDS patient's mortality.

	Children	Adults	Age not reported	Total
Dead	6	6	13	25 /46 (54.3%)
Lost (presumed dead)	42	10	-	52
Survived	7	3	11	21 /46 (45.7%)
Not reported	1	5	29	35
TOTAL	**56**	**24**	**53**	**133**
Dead and Lost (presumed dead)	48/55 (87.3%)	16/19 (84.2%)	13/24 (54.2%)	*77/98 (78.6%)*

patients were HIV positive [38]; accordingly, Chidzonga [17] noted an increase in the number of cases seen over the years from 2002 to 2006. In the series of noma cases at Brazzaville [40], the reported rate of HIV seropositives was 90%.

Although worldwide it appears that HIV infection is not the principal risk factor for noma, the rising trend of noma-like disease in patients with HIV/AIDS appears to mirror the rise in the HIV pandemic, and at least in some countries may play a substantial role in its pathogenesis; to date, its possible relevance has not been fully investigated [8,13,16,17,29,36,37,41].

The syndemic association between HIV/AIDS and noma-like disease could have serious implications regarding its clinical impact. Millogo [36] described the characteristics of 212 noma-like disease patients with or without HIV, among them, 14 (6.6%) were HIV positive patients, in this HIV positive group he reported a male predominance, older age (mean age 15.3 vs. 4.7 years), were less frequently operated (35.7% vs. 76.3%) and their death rate was higher (37.5% vs. 5.6%). These features are consistent with the data obtained in this review.

Although noma can occur at any age, average age of cases with noma-like disease and HIV/AIDS is 13 years, that is different for the reported age of one to four years for noma patients without HIV/AIDS [29]; this also reflects a greater number of adult cases with noma-like disease and HIV/AIDS [41].

Noma incidence in adults has been reported to be increasing, and in almost all the noma-like cases reported in adults, the primary risk factors are immune deficiency associated with severe chronic malnutrition [32,35]; noma-like disease discovery in adults is a sign of poor prognosis because it may reveal an HIV infection at the AIDS stage [25,28,30,33,36].

Severe malnutrition or anemia was documented in most noma-like disease patients with HIV/AIDS (93%) in this review, like noma patients without HIV/AIDS, indicating the importance of malnutrition in the pathogenesis of this disease [2,32,35].Also, its reported that in malnourished HIV-seropositive children, the course of noma-like disease is more severe and destructive, with a reported mortality rate of 88.9% [12,15,33].

Most of the HIV/AIDS patients of this review who develop noma-like disease have never been in anti-retroviral therapy and some have stopped their treatment; in fact, in many cases, their HIV infection was discovered because of noma, and noma-like disease was the first manifestation of AIDS [3]. This highlights the importance of stablishing the HIV state of noma-like disease patients, especially in adults but also in children, for initiating appropriate antiretroviral therapy; other reports have also addressed the risk of stopping HIV treatment, progression of the disease and development of noma-like disease [3,16,25,27,28,33,34].

We agree with Millogo [36], Lubala [35] and others, that noma-like disease, although not yet considered a specific or frequent disease associated with HIV, since more cases are reported with this association, should be considered as an opportunistic infection for AIDS, and a possible marker of advanced stage AIDS [13,35,36].

In this review, when reported, cultures revealed different bacteria species, both gram positive and gram negative, in any case fusobacterium was isolated; cultures were not systematically performed or was specified if cultures for anaerobes were performed. This data indicates that noma-like disease in HIV/AIDS patients is associated with a nonspecific opportunistic polymicrobial oral infection [17,25].

In this systematic review of patients treated with noma-like disease and HIV/AIDS, the mortality rate was 54.3%; if also those cases lost for follow up and presumed dead by the authors of the published articles are accounted, the mortality rate increases to 78.6%. This is a very high and concerning mortality compared with the 8-15% mortality of treated noma patients without HIV/AIDS [4,5], almost approaching the mortality of untreated noma patients without HIV/AIDS [17,36,41]. Although, the mortality rate associated with noma in most patients without HIV/AIDS has reduced significantly with the advent of antibiotics [3], it is not the case in noma-like disease patients with untreated HIV/AIDS, this syndemic interaction adversely modify the course of the disease and worsens its prognosis [3,12,17,18,36,41].

No antiretroviral therapy was available for most of the patients with noma-like disease and HIV/AIDS in this review; possibly, when promptly diagnosed and treated, a more favorable evolution can be achieved. In one study, the duration of survival after a diagnosis of noma-like disease was between days and 36 months, and even if the patients survive noma, they eventually succumb to HIV/AIDS advanced stage related diseases [17]; this is specially the case for children without the possibility for access to anti-retroviral treatment in some regions [11,17,32,35].

Recurrence of noma has only been reported in five cases, one in a patient with malnutrition and HIV/AIDS with 141 CD4 cells/uL who was not on antiretroviral

therapy [41]; thus, noma-like disease does recur in AIDS patients when the risk factors are not reversed.

The high mortality rate of HIV/AIDS patients that develops noma-like disease reveals a complex scenario and a public health challenge, both in developed and developing countries. Some investigators [6,16] have advocated the inclusion of noma-like disease on the list of neglected tropical diseases to encourage more attention for this often-lethal disease. If all cases of noma-like disease were to be reported, it might be possible to characterize the clinical features and risk factors with the view to formulating evidence-based guidelines for prevention and treatment of this disease [37].

The current WHO strategy against noma include incorporating an awareness of noma into existing health education; recognition of this condition and its possible association with HIV/AIDS, may ensure timely and adequate management to reduce the morbidity and mortality that noma-like disease causes [6,16,37,38]. Because noma-like disease is rarely seen in urban centers or developed countries, its diagnosis is frequently delayed; when a debilitated or immunocompromised patient develops a precursory necrotizing ulcerative gingivitis or a stablished necrotic orofacial lesion, noma-like disease should be promptly considered as a possible diagnosis independently of the geographic location [6].

Because we could only have found case reports and case series, and we couldn't find any controlled study, systematic review or meta-analysis, the level of evidence of this study is low; also, as almost all of the patients reported also had malnutirion, the exact role of HIV infection in the pathogenesis of this syndemic interaction with noma/noma like disease is difficult to asses, although it is evident that the mortality rate is increased in those patients with noma-like disease and untreated AIDS.

Conclusion

The syndemic interaction between HIV/AIDS and noma-like disease adversely impacts the severity of the disease and the mortality rate. Noma-like disease, although not yet considered a specific or frequent disease associated with HIV infection, should be considered as an opportunistic infection for AIDS.

Acknowledgements

Authors' contributions
All authors equally contributed to this work. All authors contributed to the study design, data collection, data entry, and provided insight into the findings. All authors approved the final manuscript.

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